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Development of Regiocontrolled Pentadienyl Indium Condensations and A Carbometallation-Intramolecular Cycloaddition Synthesis of Taxoids

Nidia Villalva

M.Sc., Universidad Nacional Autónoma de México, 1996

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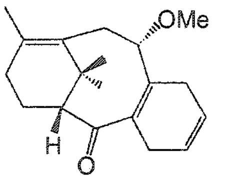
Ac	acetyl
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
BOC	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
n-BuLi	*n*-butyllithium
t-BuLi	*tert*-butyllithium
Bz	benzoyl
Cy	cyclohexyl
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DBP	dibenzoyl peroxide
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DNA	deoxyribonucleic acid
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
E	electrophile
EI	electron impact
eq.	equivalents
Et	ethyl
Ether	diethyl ether
FDA	food and drug administration
GC	gas chromatography
GTP	guanosine triphosphate
h.	hour
HRMS	high resolution mass spectrum
*i*Pr	isopropyl
IBX	2-iodoxybenzoic acid
Im	imidazole

IMDA	intramolecular Diels-Alder
IMES	*N,N'*-bis(mesityl)imidazol-2-ylidene
IR	infrared
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
MAPS	microtubule associated proteins
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
MAPH	methylaluminum bis(2,6-diphenylphenoxide)
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
[O]	oxidation
PCC	pyridinium chlorochromate
Ph	phenyl
P	protecting group
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
ppm	parts per million
Py	pyridine
RCM	ring closing metathesis
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPS	*tert*-butyldiphenylsilyl

ABSTRACT

The synthesis of the taxanes derivatives has been the major focus of this research. The efforts made towards the synthesis of these complex and successful drugs for the treatment of cancer have resulted in the development of efficient synthetic strategies. These approaches have arisen mainly from our studies in the carbometallation of propargyl alcohols and the development of stereoselective Lewis acid catalyzed IMDA. The application of these potential synthetic strategies has yielded very significant results. The synthesis of the tricyclic core of the taxanes (**2.149**) by a novel carbometallation-cycloaddition-RCM sequence was successfully achieved using readily available starting materials and mild reaction conditions. In addition, the versatile carbometallation-cycloaddition sequence allowed the synthesis of AB ring system of taxanes with different functionalities (**2.126**, **2.111** and **2.128**). The construction of a functionalized A ring (**2.84**) was also accomplished. This intermediate and some of its derivatives were employed to attempt the synthesis of B ring of taxanes by RCM. Additionally, the further functionalization of AB and ABC ring-systems of taxanes was investigated. Unfortunately, the synthesis of a biological active taxane derivative was not possible. In addition, we have studied the in situ carbonyl addition oxy-Cope rearrangement of unsaturated ketones.



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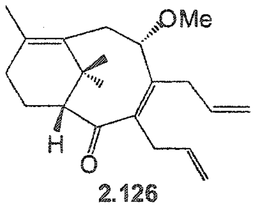

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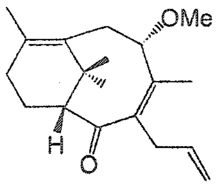

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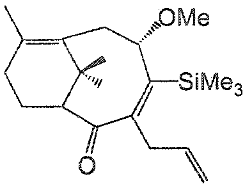

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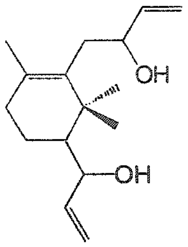

2.84

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1. INDIUM

1.1. INTRODUCTION

Carbon-carbon bond formation is an essential transformation in chemistry and an indispensable reaction in organic synthesis. In this context, the reaction of an organometallic reagent, derived from an organohalide and a metal, with a carbonyl compound is a very fundamental bond construction strategy. The use of these organometallic reagents has grown in scope and importance due to their use in the construction of complex compounds. These transformations are commonly referred to as Barbier-Grignard reactions. The reaction is a Grignard-type if generation of the organometallic is stepwise. In contrast, in a Barbier-type the organometallic is generated *in situ*. However, the use of most organometallic reagents is restricted to molecules without acidic hydrogens and the reactions are carried out under strict anhydrous conditions. In the 1980's, it was discovered that some classes of organometallics remain viable in the presence of water. Three metals in particular were the most active catalysts: Sn, Zn, and In. Tin chemistry was mainly developed by Nokami,[1] zinc chemistry by Luche[2] and Li, Chan and Araki developed the indium chemistry.[3] An appealing feature of organoindium species was their stability in water that led to numerous diverse applications. These species have a relatively low nucleophilicity; a characteristic shared by only a few organometallic reagents, which accounts for its high chemoselectivity. In addition, oxygen- and nitrogen-containing functional groups are well tolerated whereas the analogous procedures involving zinc or tin produce undesired side reactions.

Rieke[4] first initiated the study of indium for synthetic purposes in the early 1970's. Extensive investigation of indium reagents by Araki and Butsugan followed, involving their use in organic synthesis employing anhydrous solvents. They reported that metallic indium was effective in Barbier allylation[5] and Reformatsky[6] reactions of aldehydes and ketones to give homoallylic alcohols and β-hydroxy esters respectively. Indium was also used as a versatile reagent for reductions[7] and cyclopropanations.[8]

1.1.1. Indium Properties

Indium chemistry is particularly useful and attractive for several reasons. First, it is similar to the chemistry of certain transition metals and other heavier main group elements and precludes the troublesome handling of some highly toxic metals. Indium is a soft white metal, which is ductile, malleable and diamagnetic. It is stable in air at room temperature, but on heating goes to the stable indium(III) oxide. It does not react with water even at the boiling point, or with alkaline solutions. The reaction with cold dilute mineral acid is usually slow, but gentle warming with common inorganic acids will dissolve the metal. Indium (m.p. 157 °C) belongs to the series of low melting solid elements, such as gallium, cadmium, tin, bismuth and alkali metals.

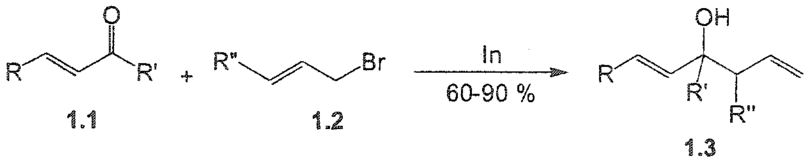
The first ionization potential of indium (5.8 eV) is much lower than that of zinc (9.4 eV) or tin (7.3 eV) and even magnesium (7.6 eV). This remarkable value is also lower than those of gallium and thallium, and closer to the first ionization potential of alkali metals like lithium or sodium (~5.0 eV).[9] The element itself is apparently without any significant toxicity, and it is claimed that none of the industrial applications of indium or its inorganic compounds produces injurious exposure for workers. Its natural occurrence in the terrestrial core is about one part in 10^5, as rare as silver, and only as a trace in some minerals, particularly those of zinc and lead. Indium has an outer electron configuration $5s^25p^1$, and it is natural to consider whether monovalent compounds exist. Indeed, indium is at the turning point for the group 13 in the periodic table of elements, since trivalent compounds dominate B, Al, Ga chemistry, and monovalent compounds are prevalent for Tl. Because of its low heterophilicity, indium is a suitable reagent for carbon-carbon bond-forming reactions. Until recently the organometallic chemistry of monovalent indium has been limited in scope by comparison to the inorganic chemistry, but recent results indicate that organometallic compounds of indium(I) will be the focus of much future research.[10]

1.1.2. Indium-Mediated Barbier-Type Reactions

The major applications of indium-mediated Barbier-type reactions are allylation of carbonyl compounds and Reformatsky-type reactions.

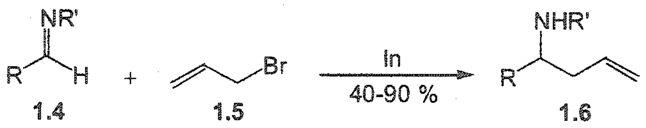
1.1.2.1. Indium-Mediated Allylation Reaction

A wide variety of aldehydes and ketones have been allylated using indium metal to afford homoallylic alcohols in good yields (Scheme 1.1). The allylation reaction has been reported[5] to proceed smoothly under very mild conditions, and even substrates having acidic hydrogens, such as ethyl acetoacetate and salicylaldehyde, were allylated in high yield. In addition, the reactions were highly regiospecific; allylic halides reacted only at the γ-position, and α,β-unsaturated carbonyl compounds gave 1,2-addition products.[11]



Scheme 1.1 Indium-Mediated Allylation

Furthermore, the allylation of carbonyl compounds was superior to existing methods with metals such as Li, Mg, Zn, Mn, Sn, Sb, Ce, Pb, and Bi. The indium-mediated allylation was successfully extended to the allylation of aldimines (Scheme 1.2) under mild conditions to afford homoallylic amines without the addition of a Lewis acid.[12,13]



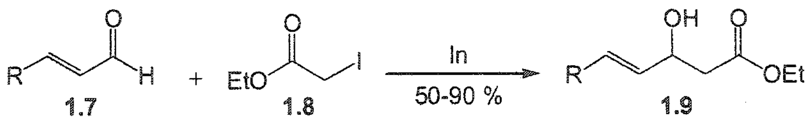
Scheme 1.2 Aldimines Allylation

The allylation of carbonyl compounds mediated by indium(I) iodide was reported to afford homoallylic alcohols in good yields.[14] However the regioselectivity of these indium(I)-mediated reactions was lower than for indium metal producing mixtures arising from both α- and γ-coupling. Different organometallic systems, such as

$InCl_3$/Al or Zn[15] and tetraorganoindium complexes, were also examined for the alkylation of carbonyl compounds.[16] These systems were less effective compared to those where indium metal was used and the rates were much slower. Additionally, Augé and co-workers[17] reported the use of manganese and TMSCl and catalytic amounts of indium to perform the allylation of carbonyl compounds.

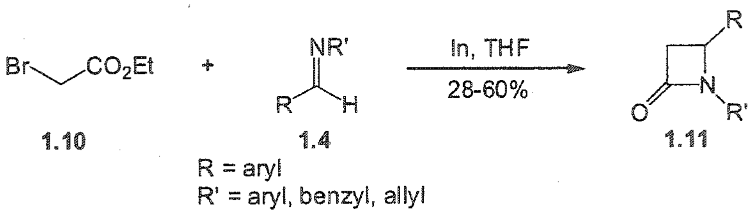
1.1.2.2. Indium-Mediated Reformatsky Reaction

The indium-mediated Reformatsky reaction of α-haloesters with a number of aldehydes and ketones gave the corresponding β-hydroxy esters in good yields[11] as shown in Scheme 1.3. Although the reactions required longer reaction times than the allylation reactions, the methodology has some advantages. When α,β-unsaturated carbonyl compounds were used, exclusive 1,2-addition was observed. In addition, hydroxyl groups did not require protection and no elimination to α,β-unsaturated esters was detected.



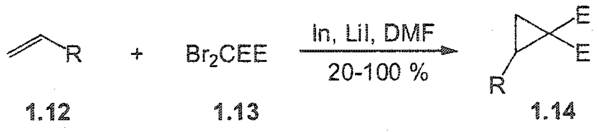
Scheme 1.3 Indium-Mediated Reformatsky Reaction

The indium-mediated Reformatsky reaction can be performed enantioselectively by adding cinchonine or cinchochidine as chiral ligands.[18] Moreover, when imines were used instead of aldehydes, the intermediates spontaneously cyclized to give β-lactams[19] as shown in Scheme 1.4.



Scheme 1.4 Synthesis of β-Lactams

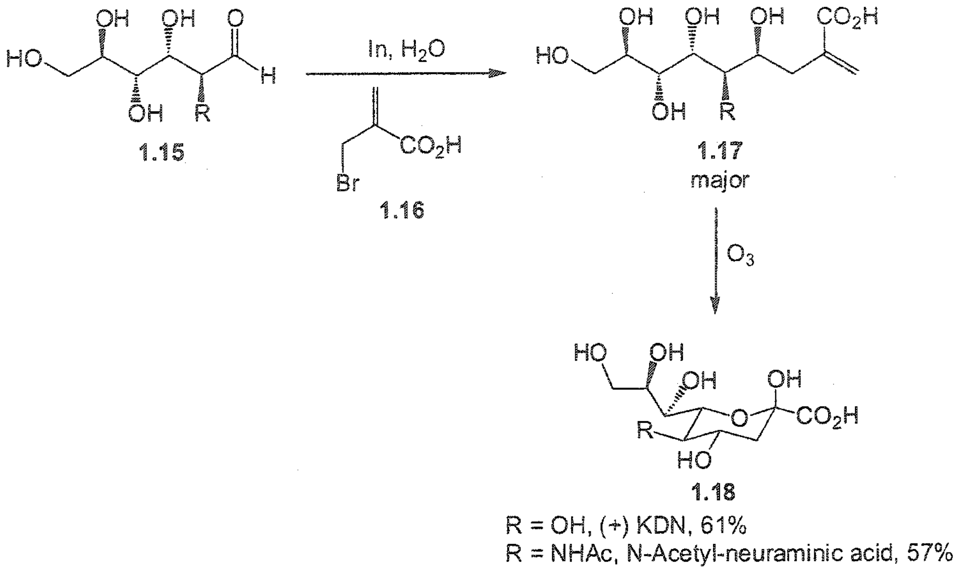
Diverse indium-mediated reactions continued to be studied and several synthetic transformations were reported illustrating potential uses for these organometallic species. Araki and Butsugan,[8] for example, performed the cyclopropanation of electron-deficient alkenes and Wideqvist-type synthesis of cyclopropanes mediated by indium metal (Scheme 1.5).



Scheme 1.5 Indium-Mediated Cyclopropanation

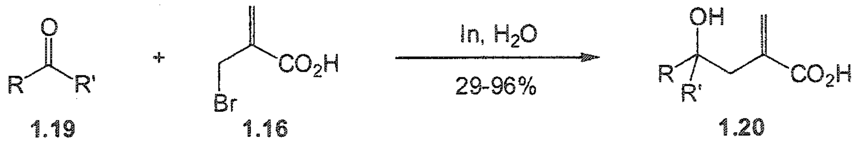
1.1.3. Synthetic Applications of Indium-Mediated Reactions

These unprecedented indium-mediated reactions in organic synthesis triggered investigations which led to the development of these reactions in aqueous media.[9,20-23] Li and Chan reported the use of indium to mediate Barbier-type allylation of aldehydes and ketones in water. The reactions were easily conducted at room temperature and in higher yields than similar reactions with zinc or tin. Furthermore, the reactions did not require heat, sonication or any promoter, and side products such as alcohols or pinacols, which were frequently observed in zinc- or tin-mediated reactions, were absent when indium was used. The reaction was later employed in the synthesis of sialic acids **1.18**, e.g. (+)-3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid (KDN), 3-deoxy-D-manno-octulosoic acid (KDO) and *N*-acetyl-neuraminic acid[24-26] (Scheme 1.6).



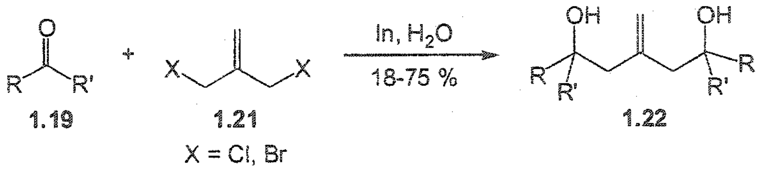
Scheme 1.6 Carbohydrate Homologation

Chan *et al.* also revealed the compatibility of carboxylic acid functionality with indium-mediated reactions. As shown in Scheme 1.7, the derivative **1.16**, 2-(bromomethyl)acrylic acid, reacted with carbonyl compounds **1.19** in the presence of indium in water to generate the corresponding γ-hydroxyl-α-methylenecarboxylic acids **1.20** in good yields.[27]



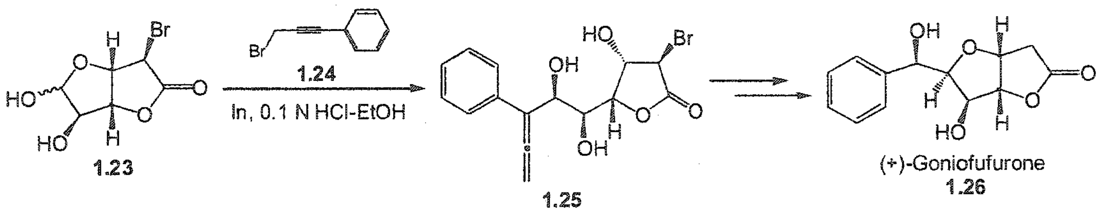
Scheme 1.7 Synthesis of Hydroxy Acids

Also, the bis-allylation reaction of various carbonyl compounds was reported by Li *et al.*[28,29] and Whitesides *et al.*[30] found that replacement of the aqueous phase with 0.1 N HCl further increased the rate of the reaction (see Scheme 1.8).



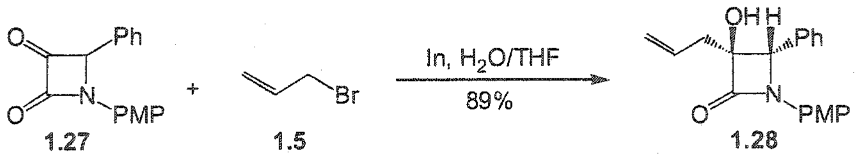
Scheme 1.8 Indium-Mediated Bisallylation

The mildness of the reaction allowed for the first study of the behavior of aldehydes with propargyl bromides.[31] This reaction was applied for the synthesis of Goniofufurone (Scheme 1.9),[32] a member of the styryl carbohydrates family that possesses anti-viral and anti-tumor activities.



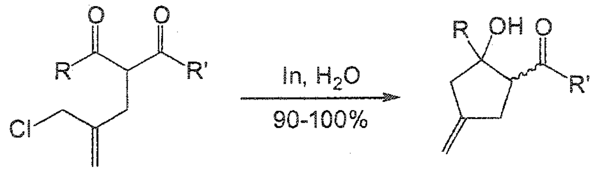
Scheme 1.9 Synthesis of Goniofufurone

The indium-mediated allylation has been also applied to carbohydrates[32-36] and for the synthesis of β-lactams.[37,38] An interesting example was reported by Bose and Paquette (Scheme 1.10) who applied the indium-mediated allylation in water to afford **1.28** as single diastereomer while zinc provides a 1:1 mixture of diastereomers.



Scheme 1.10 Stereoselective Synthesis of β-lactams

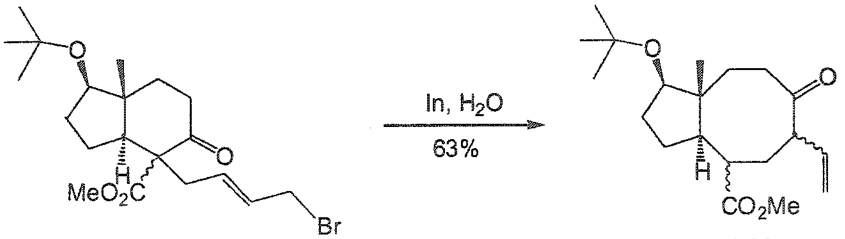
Similarly, 1,3-dicarbonyl compounds underwent efficient carbonyl allylation in an queous medium (Scheme 1.11). An intramolecular example has been used for the synthesis of carbocycles.[27,39]



1.29 **1.30**

Scheme 1.11 Synthesis of Carbocycles

A significant application of the aqueous Barbier reaction was the carbocyclic ring expansion in six-, seven-, eight- and twelve-membered rings[40] (Scheme 1.12). For instance, the five-six fused ring system **1.31** was efficiently transformed into the five-eight fused ring compound **1.32**.[9]



1.31 **1.32**

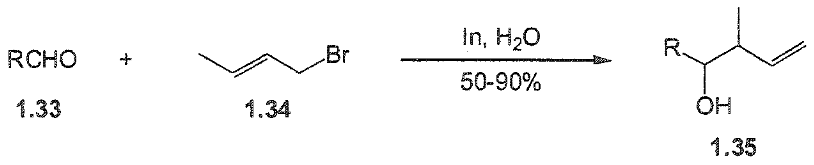
Scheme 1.12 Indium-Mediated Ring Expansion

1.1.4. Regio and Stereoselectivity

Indium-mediated organometallic reactions have elicited considerable interest not only because of their synthetic advantages but also because of the good regioselectivity, diastereoselectivity and long-range of stereoselection through chelation control. Barbier-Grignard type reactions show high chemoselectivity both in water and in organic solvents, but this is more evident when an aqueous medium is used. Generally, an aldehyde can be alkylated selectively in the presence of a ketone.

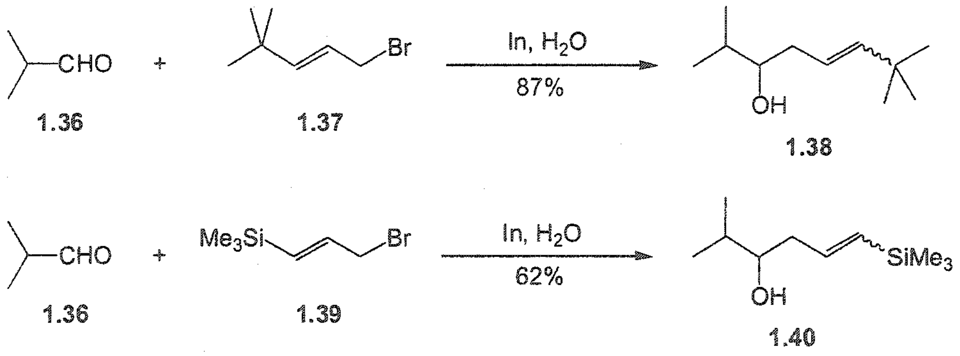
1.1.4.1. Regioselectivity

The regioselectivity of indium-mediated allylation in water involves both electronic and steric effects, as reported by Chan *et al.*[41] The reaction gave the regioisomer where the substituent is *alpha* to the carbon-carbon bond to be formed. For example, in the coupling of crotyl bromide derivatives with different aldehydes, the product was exclusively the isomer **1.35** (Scheme 1.13).



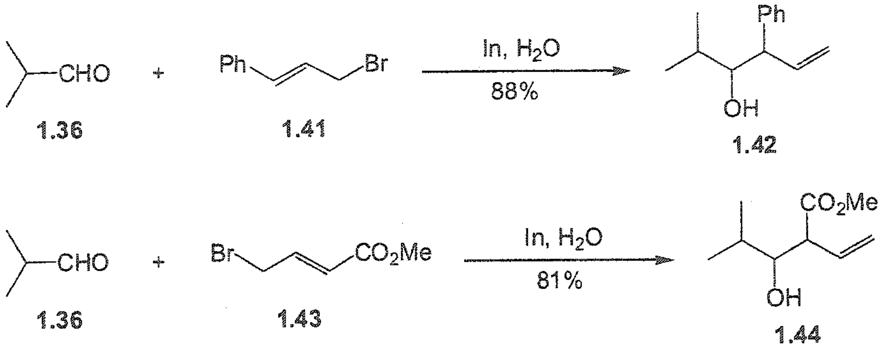
Scheme 1.13 Indium Selectivity

In addition, the regioselectivity was ruled by the steric size of the substituent but not by the degree of substitution. This was demonstrated by the reactions depicted in Scheme 1.14 where the coupling of isobutyraldehyde **1.36** with allyl bromides **1.37** and **1.39** gave **1.38** and **1.40**, respectively.



Scheme 1.14 Steric Effect in Indium Selectivity

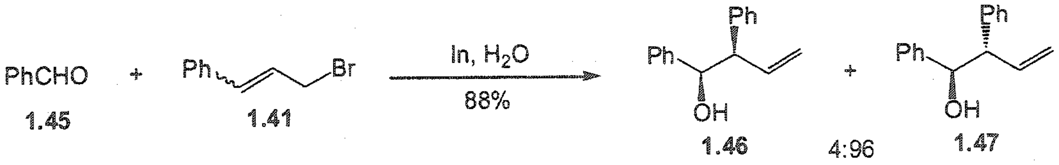
Furthermore, the presence of a conjugated double bond did not affect the regiochemistry, and the regioselectivity was independent of the geometry of the double bond or the initial location of the substituent on the double bond. This is depicted in Scheme 1.15 where isobutyraldehyde was coupled with different bromides and the non-conjugated products were obtained in both cases. In addition, **1.42** was the only product whether *E*- or *Z*-cinnamyl bromide **1.41** was used for the coupling.



Scheme 1.15 Conjugation Effect in Indium Selectivity

1.1.4.2. Diastereoselectivity

Two diastereoselective trends were observed with organoindium reagents. The diastereoselectivity depended on the substituents on both the aldehyde and the allylic halide, but not the geometry of the double bond of the allylic halide. This was revealed when both bromides *E* and *Z* **1.41** gave nearly the same diastereoselectivity (Scheme 1.16).



Scheme 1.16 Geometry Effect in Indium Diastereoselectivity

The diastereoselectivity was dependent on the size of the substituent on the aldehyde. As the size increased, the *anti*-diastereoselectivity increased as well. Chan *et al.*[41] summarized the selectivity by invoking Zimmerman-type transition states (Figure 1.1) to account for the above observations.

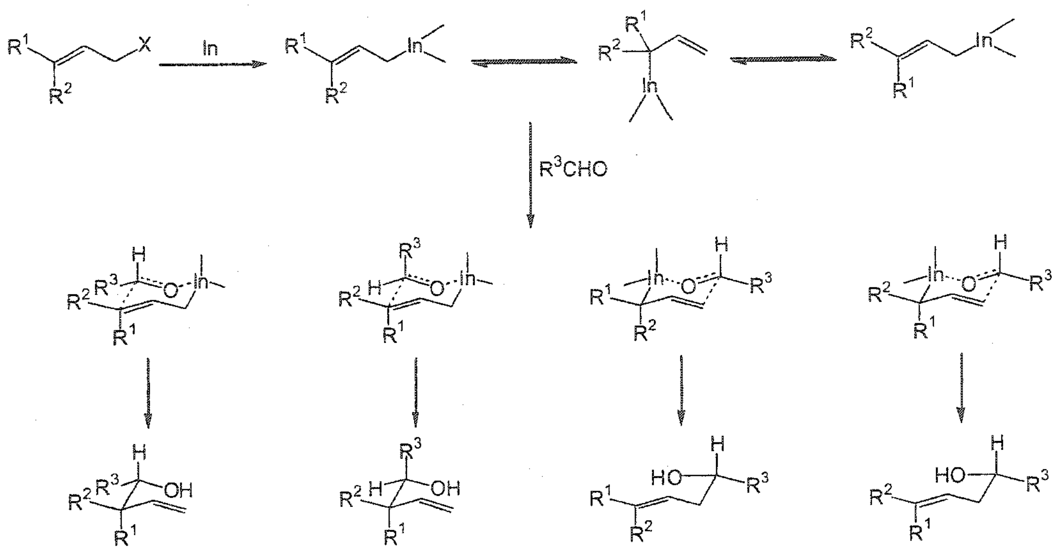


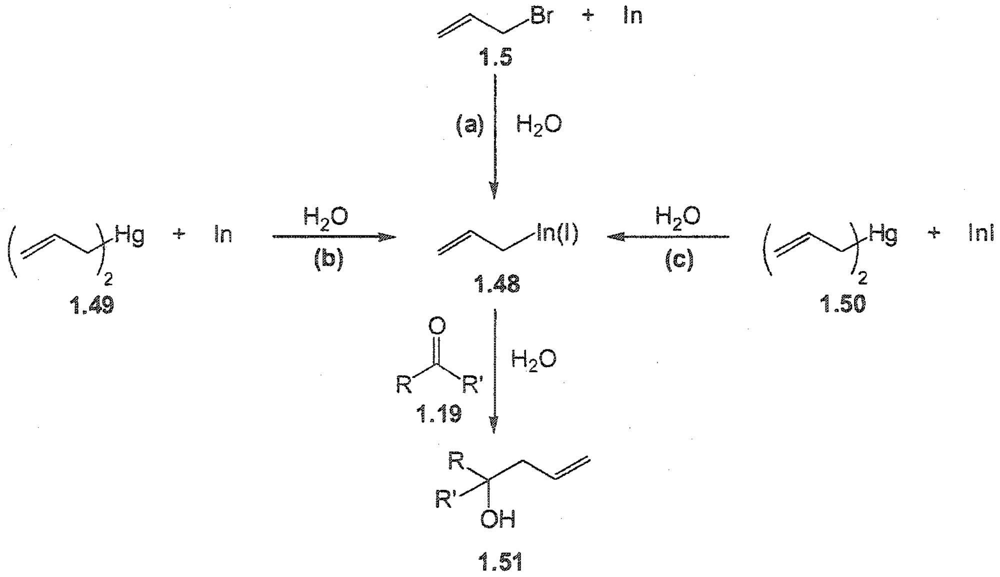
Figure 1.1 Zimmerman Type Transition States

The allyl indium species is in equlilibrium with its regioisomer causing isomerization of the doble bond. The most stable transition state will depend on the steric influence of the substituents in both the allyl group and the aldehyde.

The second trend involved the control of the *syn* or *anti* diastereoselectivity by α-substituents with the presence of a chelating group leading to *syn* products. Paquette and co-workers[42] studied the diastereofacial control of indium-mediated allylations in aqueous media and reported an improved diastereoselectivity. When both trends were combined, the indium-mediated coupling of carbonyl compounds with γ-substituted allyl bromides proceeded regio- and diastereoselectively, generating many chiral centers.

1.1.5. Mechanism

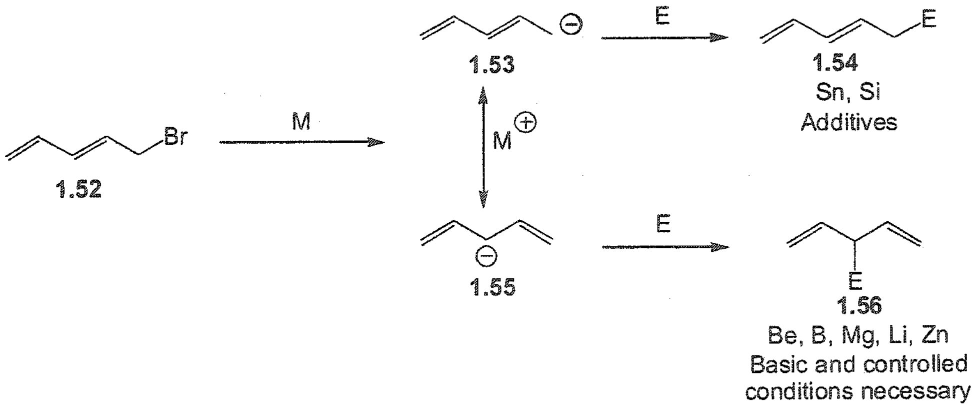
Despite the extensive chemistry developed for indium-mediated reactions, especially the allylation of carbonyl compounds, the nature of the species involved in the reaction was not clear. Initially, it was proposed that the aqueous indium-mediated allylation reaction proceeded on the metal surface, without the involvement of a discrete allylindium intermediate. Subsequently, the participation of this allylindium intermediate was postulated by Whitesides *et al.*[30] Most investigators had used the sesquihalide formulation to describe the allylindium intermediate in the indium-mediated allylation reactions in organic solvents. It had not been established whether allyl bromide reacts with indium in water to give the allylindium dibromide, allylindium bromide or allylindium sesquibromide. Chan and Yang[43] performed an important study in order to elucidate the nature of the allylindium intermediate (Scheme 1.17). Using ^1H NMR techniques they proved that a discrete allylindium intermediate is formed in the reaction of allyl bromide with indium in water (**a**). The later was confirmed by a transmetallation reaction using diallylmercury with indium halides (**c**). Subsequently, they concluded that a transient, ^1H NMR observable allylindium species in aqueous media is allylindium(I). These observations are consistent with the fact that indium has a relatively low first ionization potential but a relatively high second or third ionization potential.



Scheme 1.17 Allylindium Species in Aqueous Media

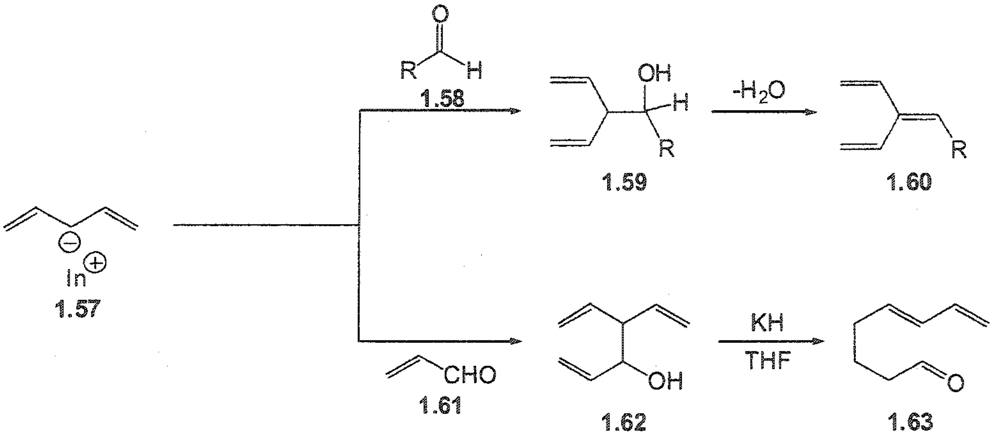
1.1.6. Indium-Mediated Pentadienylation

The indium-mediated allylation of carbonyl compounds has been extensively studied in different systems. Conversely, the use of pentadienyl bromide was considered only in the presence of others metals. The behavior of the reagent was not consistent, and the nature of the product depended on the metal (Scheme 1.18). In the presence of Sn and Si, α-addition took place preferentially and the use of additives was necessary for γ-addition.[44,45] Nishigaichi and co-workers,[46] for example, reported that $ZnCl_2$ in ether promoted the γ-selective addition of pentadienyltins to aldehydes and ketones and lithium, magnesium and calcium perchlorates favored the γ-addition of allylic tin compounds to aldehydes.[47,48] In related work, the same authors reported that *Z*-pentadienyltins reacted in the γ-position in the presence of an appropriate Lewis acid.[49] The γ-addition, on the other hand, was preferred when B,[50,51] Be,[52] Li,[53,54] Zn[55-57] and Mg[58] were used. In these cases, the nucleophiles were very unstable species that required basic and controlled conditions. In all cases the reaction was not regioselective and dimerization compounds were detected as by-products.



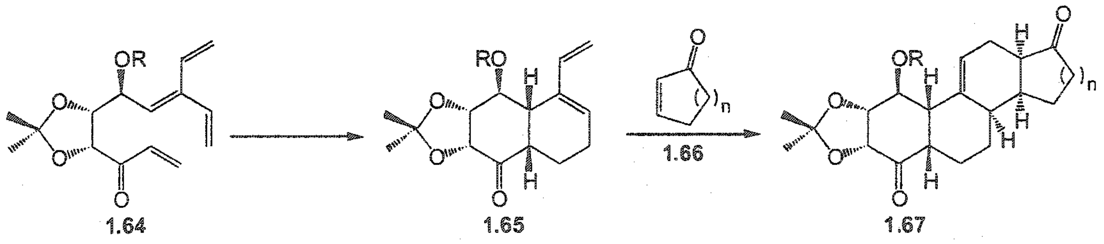
Scheme 1.18 Pentadienyl Anion

Fallis[59] and Araki [60] further extended the application of indium-mediated alkylation. Fallis and co-workers discovered that in the presence of aldehydes and cyclic ketones the pentadienyl anion **1.57** reacted in a regioselective manner, to give homoallylic alcohols as depicted in Scheme 1.19. These dienols can also undergo elimination of water to afford trienes such as **1.60**. In addition, they observed that α,β-unsaturated aldehydes afforded the 1,2-addition product **1.62** rather than the 1,4-addition product. Subsequent anionic oxy-Cope rearrangement could be employed to provide the conjugate addition product **1.63**.



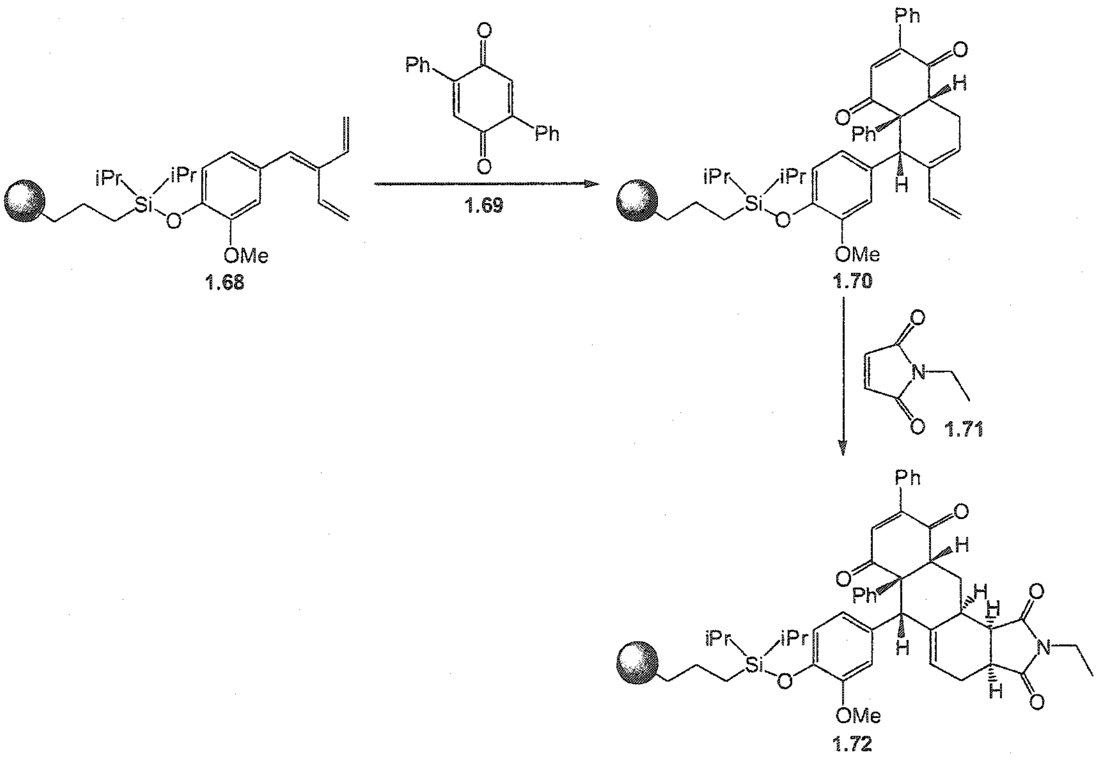
Scheme 1.19 Pentadienyl Indium Anion

This protocol to obtain cross-conjugated trienes was applied to prepare polycyclic systems (Scheme 1.20). The trienes **1.64** reacted in an intramolecular Diels-Alder reaction to afford dienes **1.65**, which reacted with dienophiles **1.66** in a tandem intermolecular Diels-Alder reaction to generate the corresponding polycyclic systems **1.67**.



Scheme 1.20 Triene Systems

In this manner, Fallis and co-workers were able to synthesize steroidal and triterpenoid skeletons by a direct and simple method.[61] The reaction was later applied as a key step for the synthesis of tetracyclic sytems.[62] The procedure was further expanded by Schreiber and co-workers to diversity-oriented synthesis (DOS)[63] for the preparation of a library composed of 29,400 multicyclic compounds.[64] Using Fallis' protocol, Schreiber and co-workers were able to obtain single diastereomers in each step (Scheme 1.21). The final products **1.72** have a central skeleton with between two and four rings and up to six stereocenters.

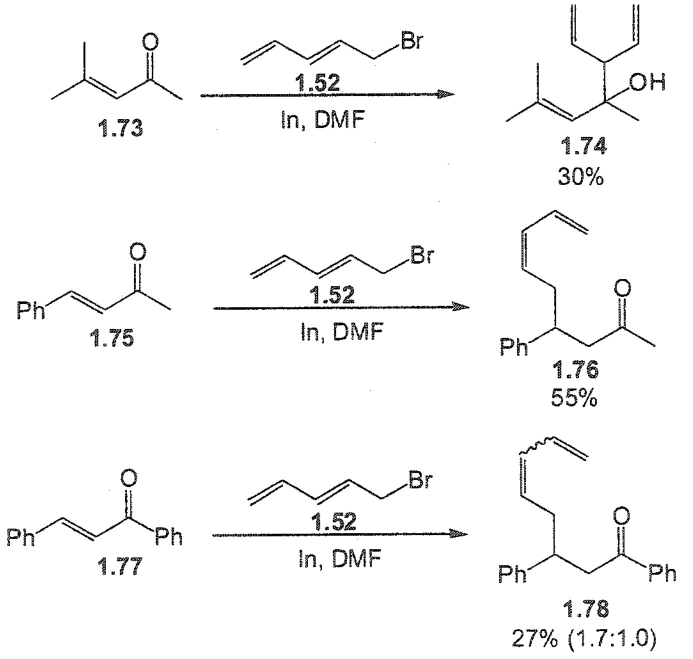


Scheme 1.21 Diversity-Oriented Synthesis (DOS)

However, neither the indium-mediated allylation nor the indium-mediated pentadienylation of α,β-unsaturated ketones has been investigated.

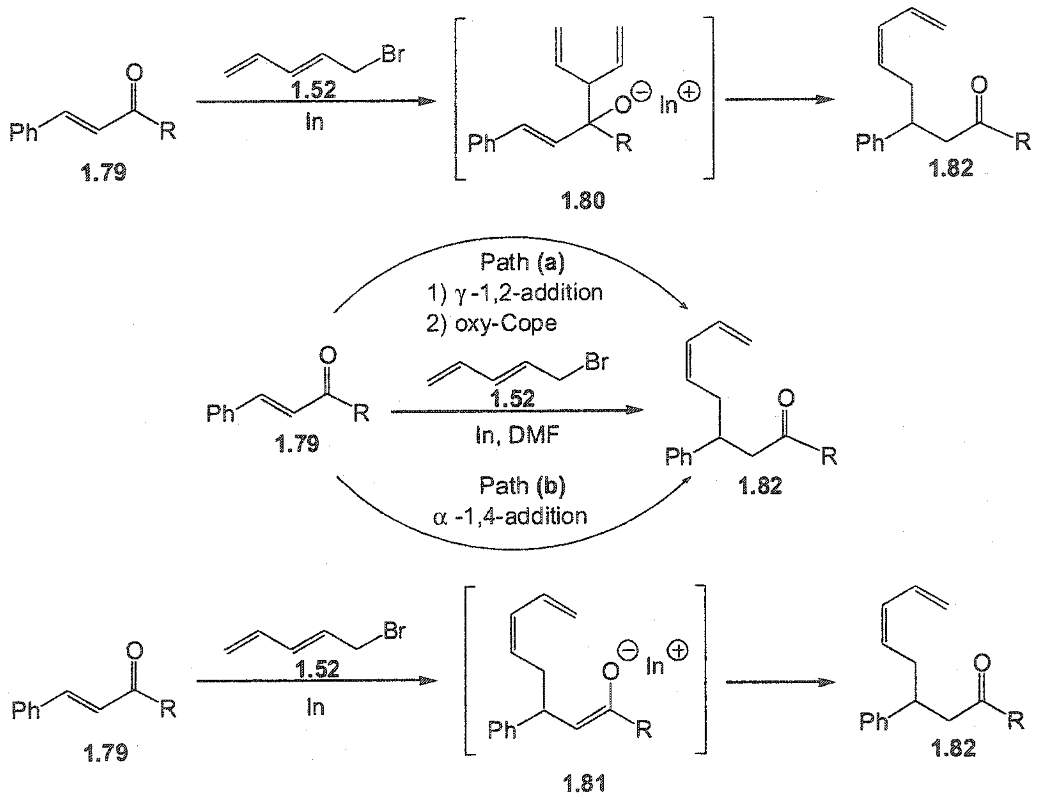
1.2. RESULTS

In order to expand the utility of this reaction, we have investigated a series of unsaturated ketones in the presence of allylbromide and pentadienyl bromide. The allylation of the carbonyl compounds has been explained by a general mechanism[41] that accounts for some of our experimental results. On the other hand, the reactivity pattern for the pentadienylation reaction was not uniform and differed from those previously reported. In some cases the 1,2-addition compound dominated and in others cases the substrates gave preferentially the 1,4-addition product from the direct conjugate addition of the α-pentadienyl anion. It was established that this is a consequence of the substitution pattern of the conjugated ketone. Methyl ketones subjected to the indium mediated-pentadienylation showed different behavior (Scheme 1.22). Mesityl oxide **1.73** afforded the 1,2 addition product **1.74.** However, phenyl substituted unsaturated methyl ketone **1.75** afforded the 1,4-addition product **1.76** with a *cis* geometry. When diphenyl ketone **1.77** was treated under the same reaction conditions, the 1,4-addition product **1.78** was also observed. Despite the lower selectivity observed, the *cis* isomer still prevailed in a 1.7:1 ratio.



Scheme 1.22 Pentadienylation of α,β-Unsaturated Ketones

At this stage, two possible addition pathways were considered to explain the results (Scheme 1.23). Path **(a)** suggested that a 1,2-addition is followed by a subsequent *in situ* indium mediated oxy-Cope rearrangement when permitted. In this case, the stereochemical divergence can be explained by competing transition states, which will lead to either the *cis* or *trans* products. Path **(b)** implicates a simple competition between the direct carbonyl and conjugated addition. The ratio of *cis*-*trans* products will depend on the transition state in the molecule in which group interactions are minimized.



Scheme 1.23 Possible Competitive Pathways for Pentadienylation

The fact that the *cis*-olefin dominates, implies that the chair conformation with the vinyl group in an axial position is preferred as depicted in Figure 1.2. It is possible that a favorable orbital interaction between the oxygen anion and the axial olefin also occurs. This could overcome the normal preference of the vinyl group for the equatorial position that leads to the *trans* product. Evidence for this conclusion was established by experiments that demonstrated a second double bond was required for this *in situ* rearrangement.

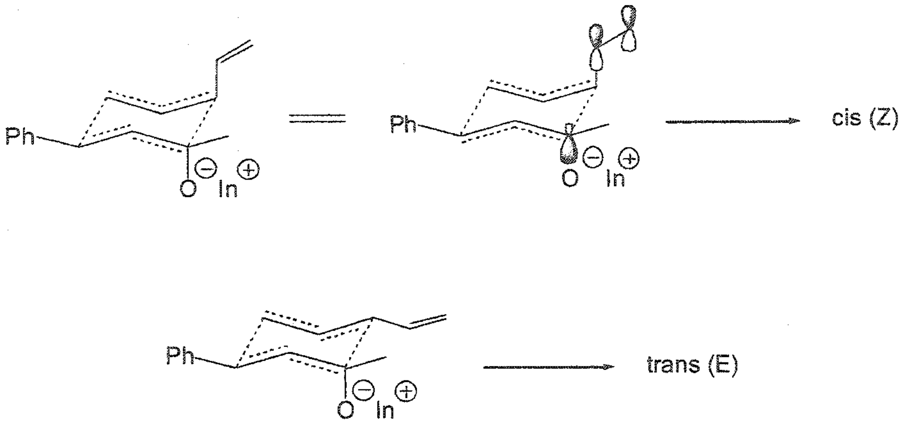
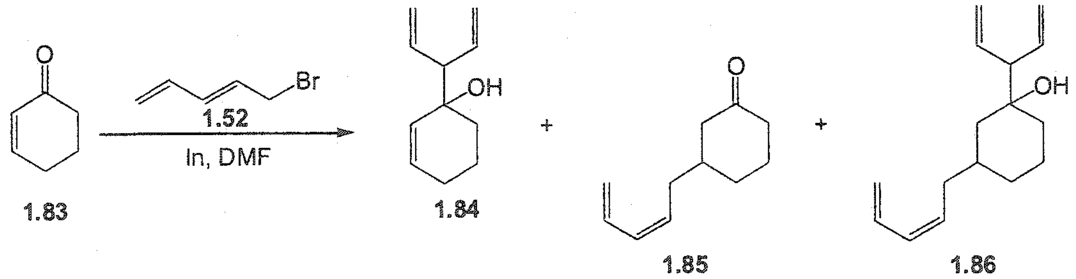


Figure 1.2 Oxy-Cope Transition States

In order to establish the factors that determined these peculiar results, the indium mediated-pentadienylation of cyclohexenone was studied (Scheme 1.24). The addition was monitored at different intervals to detect the products and their ratios.

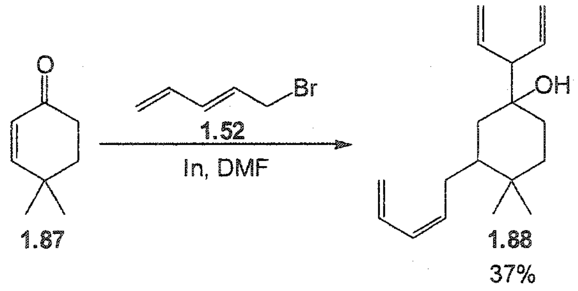


Scheme 1.24 Pentadienylation of Cyclohexenone

Time	Yield (%)		
(h)	**1.84**	**1.85**	**1.86**
24	3	16	10
48	4	8	29

Table 1.1 Product Profile

As seen in Table 1.1, after 24 hours of reaction the product **1.85** (derived from a presumed 1,4-addition) was the most abundant. This was followed by the product **1.86** corresponding to 1,2-addition and 1,4-addition. In addition, a minimal quantity of the 1,2-addition product **1.84** was identified. After 48 hours the predominant compound was **1.86,** followed by **1.85** and a small amount of the 1,2-addition product **1.84**. These results strongly suggest that these reactions proceed by an initial carbonyl addition followed by an indium mediated oxy-Cope rearrangement (path **a**). To corroborate this hypothesis, dimethyl-cyclohexenone was subjected to similar pentadienylation reaction conditions (Scheme 1.25). It was anticipated that dimethyl-cyclohexenone **1.87** would impede the 1,4-additon, providing the 1,2-addition derivative.

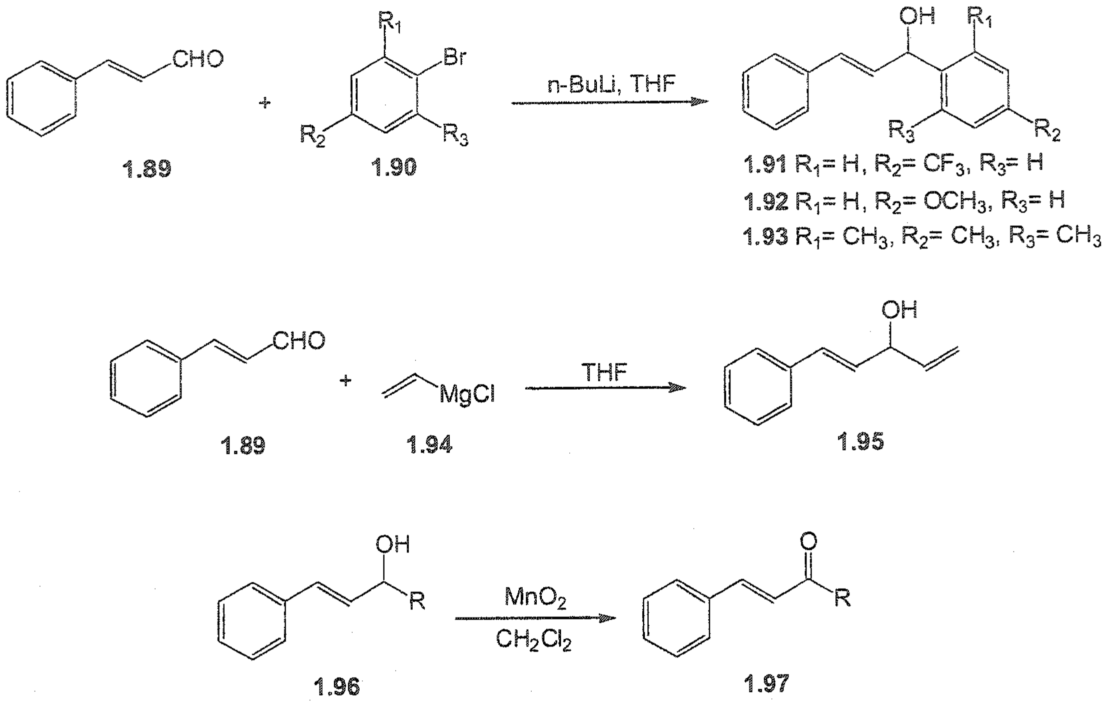


Scheme 1.25 Pentadienylation of Dimethyl-Cyclohexenone

Instead, the compound **1.88** was isolated as a major component confirming the initial assumption that the 1,2-addition product undergoes a [3,3] sigmatropic rearrangement to afford the conjugated system.

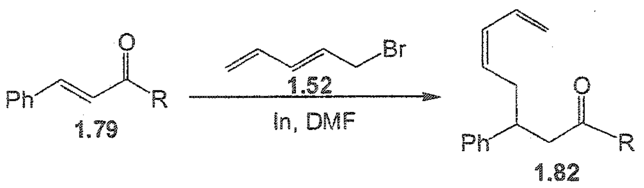
In order to determine whether different electronic and steric parameters were modulators of the product distribution for phenyl ketones, a second series of phenyl ketones with different functional groups in the aryl ring was examined. An example in which the competition between a phenyl-vinyl ketone versus a vinyl ketone could be compared, was also analyzed.

Four representative ketones were prepared by Grignard addition of **1.90** or **1.94** to cinnamyl aldehyde **1.89** followed by benzylic oxidation with manganese dioxide to afford the corresponding α,β-unsaturated systems **1.97** (Scheme 1.26).



Scheme 1.26 Preparation of Representative Ketones

The first set of experiments was performed with bromopentadienyl indium in DMF (Table 1.2). In order to observe only the influence of the reactants and to avoid any variation in the yields based on time, the reactions were examined under non-optimal but uniform conditions (DMF, 22 °C, 4h). The results tabulated below indicate that the products from a tandem carbonyl addition-oxy-Cope rearrangement were consistently observed, producing the conjugated systems. The electron-withdrawing influence of trifluoromethyl group (entry 1), favored the pentadienylation reaction. Additionally, the steric environment hinders the addition as shown in entry 3, where the 1,2-addition was clearly inhibited by the presence of methyl groups in the aromatic ring, however, the *cis* rearrangement product was still isolated in low yield. When two unsaturated systems are present in the molecule, rearrangement to the less hindered alkene is preferred as seen in entry 4.



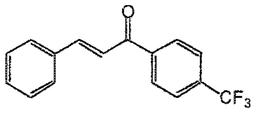
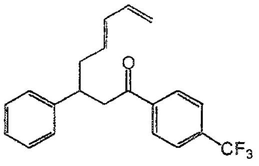
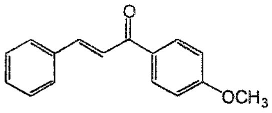
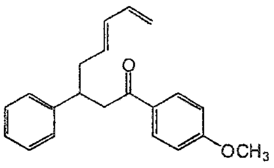
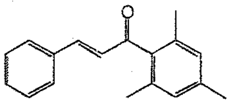
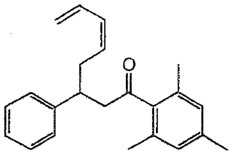
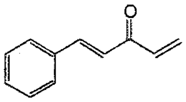
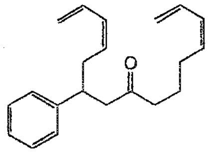
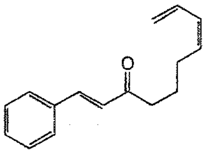
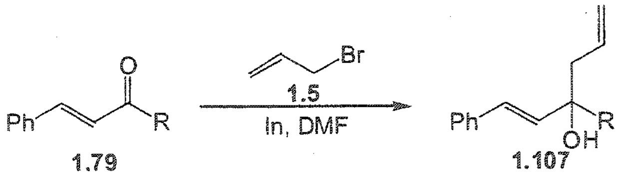
Entry	Ketone	Product	Yield (%)
1	 **1.98**	 **1.99**	20
2	 **1.100**	 (cis/trans, 1:1) **1.101**	17
3	 **1.102**	 **1.103**	6
4	 **1.104**	 **1.105**	7
		 **1.106**	6

Table 1.2 Pentadienylation of Aromatic α,β-Unsaturated Ketones

The same set of ketones (**1.98**, **1.100**, **1.102** and **1.104**) was subjected to allylation in presence of indium in DMF (Table 1.3). In contrast, as mentioned above, the indium-mediated allylation terminated at the carbonyl addition stage to generate the 1,2-addition products (**1.108** to **1.111**) and failed to undergo further rearrangement. Only in the case of a hindered environment is the 1,4-addition observed, although the product was isolated in low yield (entry 3). Electron-withdrawing groups favored the reaction (entry 1), and also demonstrated that a second double bond is required to observe a [3,3] sigmatropic rearrangement. This is confirmed in entry 4 were no rearrangement product was detected despite the presence of an unsubstituted double bond.

It is evident that steric factors strongly influence the reaction. For example, the bulky group of the mesitylene system in entry 3, hinders the 1,2-addition and a small amount of 1,4-addition product was isolated. In addition, a higher yield was obtained when no phenyl group is present in β-position as seen in entry 4.



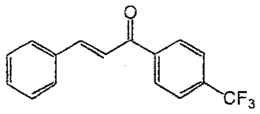
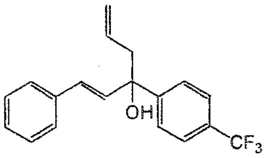
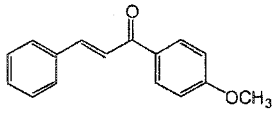
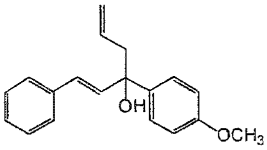
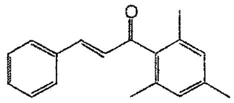
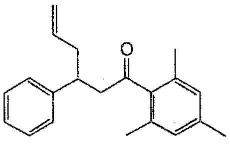
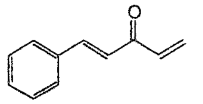
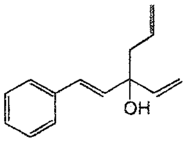
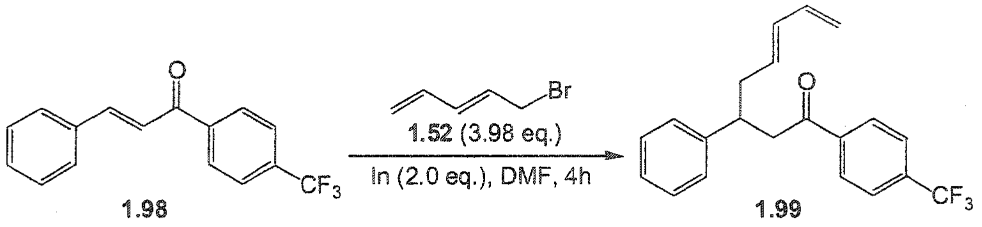
Entry	Ketone	Product	Yield (%)
1	 **1.98**	 **1.108**	37
2	 **1.100**	 **1.109**	31
3	 **1.102**	 **1.110**	8
4	 **1.104**	 **1.111**	54

Table 1.3 Allylation of Aromatic α,β-unsaturated Ketones

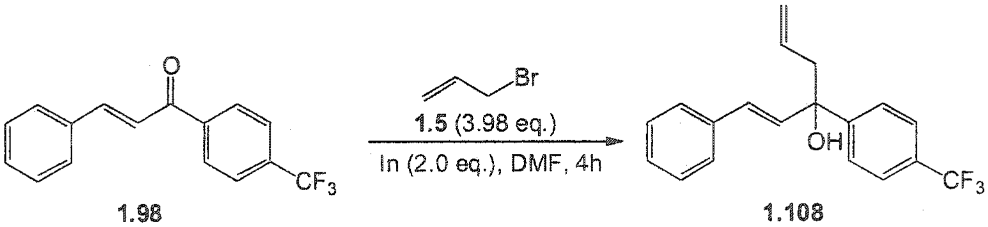
The next step was the optimization of the reaction (Table 1.4). Trifluoromethyl substituted ketone **1.98**, was chosen as a model and subjected to different reaction conditions. The temperature was increased to 60 °C and the solvent was modified. Water was used as a co-solvent and lanthanum triflate was use as an additive[65] in an attempt to increase the yield. As reflected in the yields tabulated below, the best reaction conditions were those that used water as a co-solvent in a ratio 2:1 at 60 °C. The yield was slightly increased by the addition of hydrochloric acid. The yield increased from an initial 20% (entry 1, 22 °C) to 66% (entry 7, 60 °C).



Entry	Solvent	Yield (%)	
		22 °C	60 °C
1	DMF	20	54
2	THF	2	10
3	H_2O	3	9
4	THF/H_2O, (1:1)	16	38
5	THF/H_2O, (2:1)	18	41
6	DMF/H_2O, (2:1)	-	64
7	DMF/H_2O, (2:1) 10μL HCl	-	66
8	DMF/H_2O, (2:1) La(OTf)$_3$	-	3
9	DMF, La(OTf)$_3$	-	-

Table 1.4 Optimization of Indium-Mediated Pentadienylation

The optimal reaction conditions were applied to the allylation reaction raising the yield from an initial 37% to 96%.



1.98

1.108
96%

Scheme 1.27 Optimization of Indium-Mediated Allylation

1.3. CONCLUSIONS

We have comprehensively studied the indium-mediated allylation of α,β-unsaturated ketones and provided increased understanding of dieneylindium chemistry. In addition, the indium-mediated reaction has been extended to pentadienylation of α,β-unsaturated ketones, and the unusual behavior of the reaction has been explained.

It was established that indium-mediated pentadienylation proceeds through a tandem carbonyl addition-oxy-Cope rearrangement mechanism. The predominant *cis* isomer formed for this type of reaction is due to the preferred chair conformation with a vinyl group in an axial position. This can be attributed to a favorable dipole-orbital interaction between the oxygen anion and the π-system of the adjacent axial olefin. In the indium-mediated allylation, it was observed that 1,2-addition product is preferred except when the carbonyl group is in a sterically hindered environment. No oxy-Cope rearrangement was observed with allylindium since a second conjugated double bond in the starting material is required for this transformation. Finally, the optimal reaction conditions for indium-mediated allylation and pentadienylation of α,β-unsaturated ketones have been established. These results facilitate the *a priori* behavior of this reaction and the prediction of the reaction products.

2. TAXOL

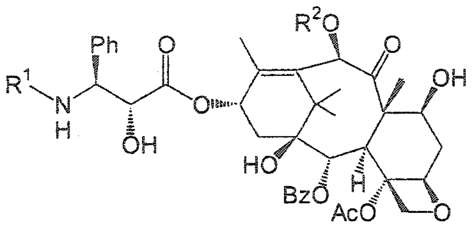
2.1. INTRODUCTION

Cancer is a group of diseases characterized by uncontrolled cell growth and the spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer is caused by both external and internal factors that can act either individually or in concert to initiate or promote carcinogenesis. It is the second leading cause of death in the USA, exceeded only by heart disease. Its overall cost is over $170 billion per year as a direct result of medical cost, lost productivity or indirect mortality cost. The American Cancer Society estimates that over 1.33 million new cancer cases will be diagnosed in 2003 in the USA and 500,000 of the afflicted are expected to die of the disease. In Canada, an estimated 140,000 new cases of cancer and 67,000 cancer related deaths will occur in 2003.[66] Cancer is generally treated with surgery, radiation, chemotherapy or a combination of these approaches.

Of the seven different classes of anticancer drugs approved for chemotherapy by the FDA, Taxol® is the most cytotoxic. This promising antitumor agent was first approved for the treatment of refractory ovarian cancer in 1992, and later in 1994 it was approved for the treatment of breast cancer. It has also proven to be extremely useful in treating various other forms of cancer, including lung, neck, bladder and cervical cancer, as well as malignant melanoma. Additionally, Taxol® may prove useful against other disorders, including polycystic kidney disease[67] and AIDS-related Karposi's sarcoma.[68] Currently, Taxol® is the largest selling cytotoxic agent in the world with sales reaching $1.6 billion in 2000.

Taxol® was discovered in the early 1960's as a part of a National Cancer Institute (NCI) screening of many plant species from around the world, conducted with the hope of discovering new cytotoxic entities. It was originally isolated from the bark of the Pacific Yew tree, a slow-growing tree found in the virgin rain forest of the Pacific Northwest United States.

The cytotoxic extract from the yew bark revealed Taxol® was the principle active compound. Its structure (Figure 2.1) was elucidated by chemical, spectroscopic and X-ray crystallographic techniques.[69]



Paclitaxel (Taxol®) R^1 = Bz, R^2 = Ac
Docetaxel (Taxotere®) R^1 = Boc, R^2 = H

Figure 2.1 Taxane Family

Taxol® is classified as an alkaloid but is a member of the taxane family of diterpenes that features a tricyclic ring nucleus. The carbon framework is architecturally complex, and a variety of polar groups is situated around its perimeter. Currently, over one hundred members of this family have been isolated from natural sources; however, Taxol® remains the most structurally complex and the most therapeutically useful.

2.1.1. Biological Profile and Supply

Despite its well documented biological activity, very little interest was shown in Taxol® until Susan Horwitz reported in 1979 that its mode of action was unique.[70] Prior to this discovery, it was believed that the cytotoxic properties of Taxol® were due to its ability to destabilize microtubules, which control the migration of chromosomes during cell division. In fact, Taxol® was found to act as a mitotic spindle poison, and to inhibit cell replication *in vitro* by promoting microtubule polymerization. It arrests eukaryotic mitosis and causes DNA fragmentation that subsequently induces apoptosis signaling: a process that initiates the destruction of proliferating tumor cells. This novel mode of action made Taxol® a prototype for a new class of anticancer drugs. Taxol's® success is due as well to its ability to work in combination with other anticancer therapeutic agents. A schematic representation (Figure 2.2) of Taxol's effect on the tubulin polymerization process is depicted below.[71]

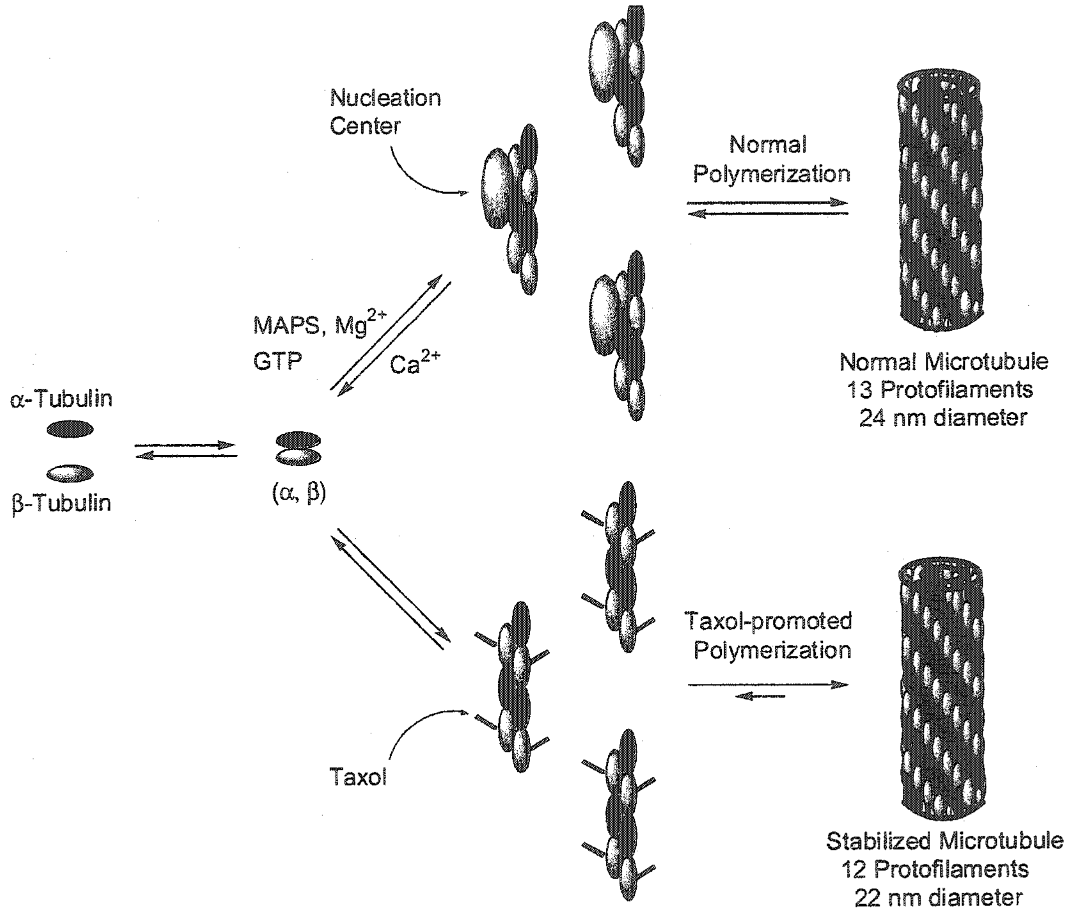


Figure 2.2 Taxol®-Promoted Microtubule Assembly

The activity of taxanes has some specific structural and substitution pattern requirements.[71-73] It is known that the presence of the side chain in Taxol® is critical for activity, as illustrated by Baccatin III[74-75] (Figure 2.4), where the lack of the side chain significantly reduces its cytotoxic and tubulin-assembly activity. However, different substituents on nitrogen 3' are tolerated. A hydroxyl substituent at C2', the phenyl group at C3', as well as their respective stereochemistries (2*R*,3*S*) are a requirement for activity (Figure 2.3). Modifications at the C3' and N3' positions have produced several analogs with excellent activity. Moreover, it has been demonstrated that removal of the 2-benzoate or the 4-acetate causes loss of activity, and these two positions seem to be required for binding to a protein site on cell microtubules. The presence of the oxetane ring is definitely a requirement for enhanced activity; likely as a hydrogen bond acceptor. Conversely, modifications at the north perimeter are well tolerated, and slight enhancement in activity can be achieved with some modifications. These positions have been employed for the attachment of different polar groups improving the solubility. Solubility was an initial obstacle in the preclinical development of Taxol®, which is highly lipophilic and insoluble in water. Fortunately, it can be formulated for clinical use in a safe, efficacious pharmaceutically acceptable form.

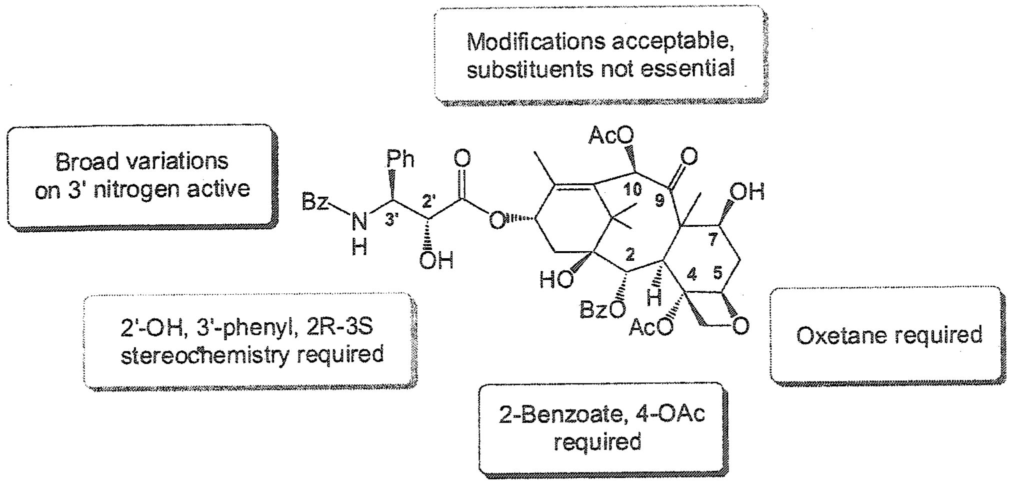


Figure 2.3 Structure-Activity Relationships of Taxol®

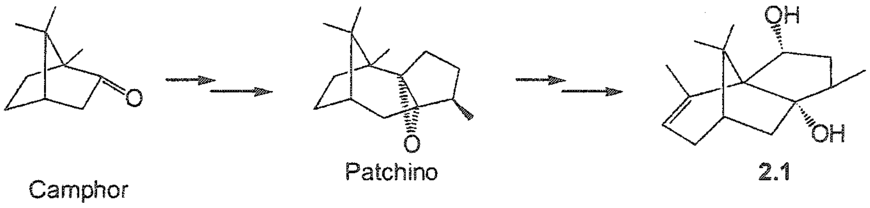
The success of Taxol® in clinical trials led to the requirement of large quantities of this material. Unfortunately, the supply of Taxol® was initially severely restricted. The natural source, the Pacific Yew tree is an environmentally protected species. It is the habitat for the spotted owl, winter food for large herbivores and a microhabitat for invertebrates. Furthermore, isolation of the compound involved killing the tree, and the quantities available by this method were pitifully small. Luckily, a closely related analogue of Taxol®, Baccatin III, was discovered in the leaves of a European species of ornamental shrub *Taxus baccata.* Although the extraction and subsequent chemical elaboration of Baccatin III to Taxol® was very laborious, the source was renewable, and sufficient quantities were obtained to carry out clinical trials, leading to the approval of Taxol® for the treatment of various cancer forms. The properties of Taxol® made it a leading drug for the treatment of cancer in the 1990s, providing an alternative to the more radical techniques of radiotherapy and surgery. The cost of producing sufficient quantities of this new super drug, however, was still a limiting factor. A possible solution to the supply problem was to develop plant cell cultures to produce Taxol®. Unfortunately, the production in this way was very difficult due to the relatively slow growth of plant cells. Alternatively, the production of Taxol® by endophytic fungi was attempted,[76] but it did not represent a rapid supply of Taxol® either. Croteau[68,77-78] has recently reported studies on the biosynthetic origin of Taxol®. However, more investigations are required.

2.1.2. Synthesis of Taxol®

Synthetic organic chemistry may provide a solution to the supply problem of Taxol®. Chemical synthesis seemed the most promising alternative source of Taxol® but represented an enormous challenge to the ingenuity and creativity of synthetic organic chemists. Six total syntheses have been carried out to date. The Holton and Nicolaou groups published their approaches in 1994, and Danishefsky and co-workers reported their route to Taxol® in 1996. Additionally, Wender and co-workers proposed an alternative synthesis in 1997, and Mukaiyama published his contribution in 1998. In 2000, Kuwajima and colleagues also reported an interesting synthesis for Taxol®.

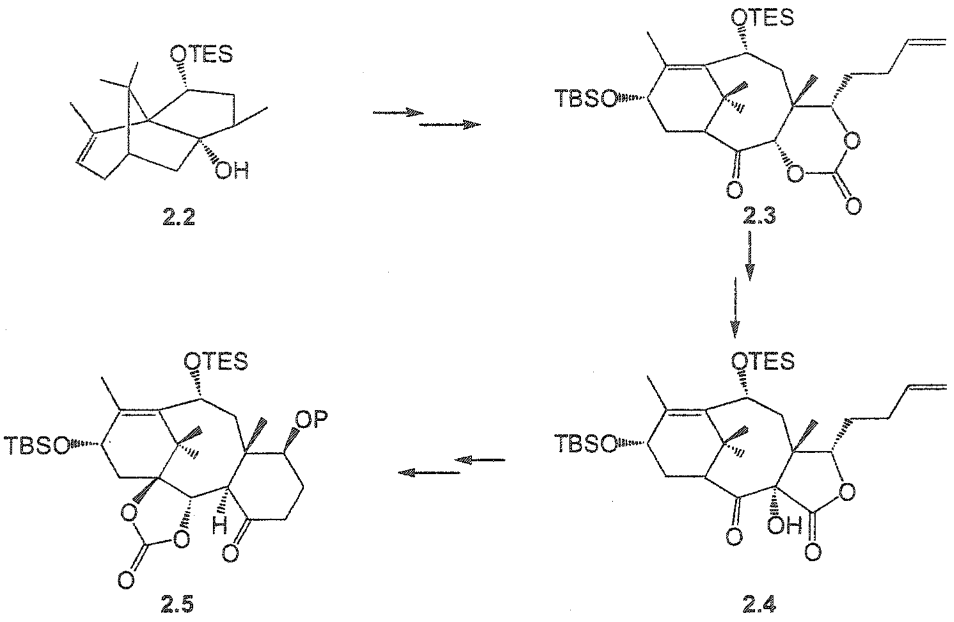
2.1.2.1. The Holton Route

Holton used camphor as a starting material, which was converted to β-patchoulene oxide[79] (patchino) following Büchi's procedure[80] (Scheme 2.1). The epoxide was converted into the allylic alcohol, and subsequently rearranged to diol **2.1**.[81]



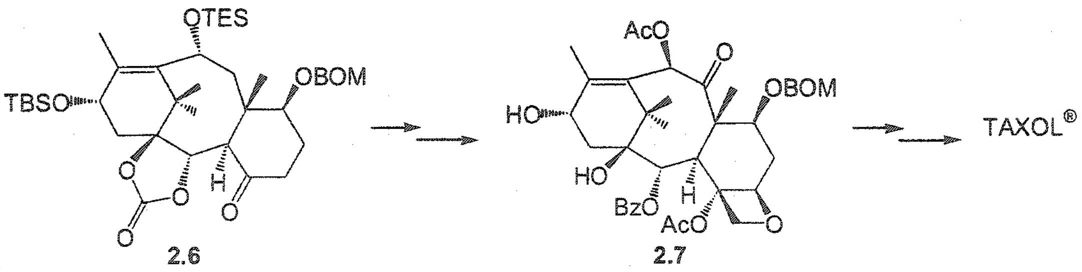
Scheme 2.1 Preparation of Diol

Silylation of **2.1** gave **2.2**, which underwent epoxy alcohol fragmentation and protection at C13 to create the bicyclo[5.3.1] skeleton of Taxol® **2.3** in 93% overall yield (Scheme 2.2). The AB system was then functionalized by an aldol condensation with 4-pentenal, followed by direct protection and hydroxylation at C2 to give carbonate **2.3**. Hydroxylactone **2.4** was obtained through the corresponding carbonate that was first oxidized and then subjected to rearrangement using LTMP.[82] The C-ring in **2.5** was effectively introduced using Dieckmann cyclization (LDA, THF, -78 °C, 93% yield), followed by decarbomethoxylation with PhSK in DMF.



Scheme 2.2 Construction of ABC Ring-System

The synthesis of Taxol® was concluded through the introduction of the oxetane D ring, oxidation at C9, and by adjustment of the regio- and stereochemistry at C9 and C10. Finally, the C13 side chain was attached to give the desired product.[83]

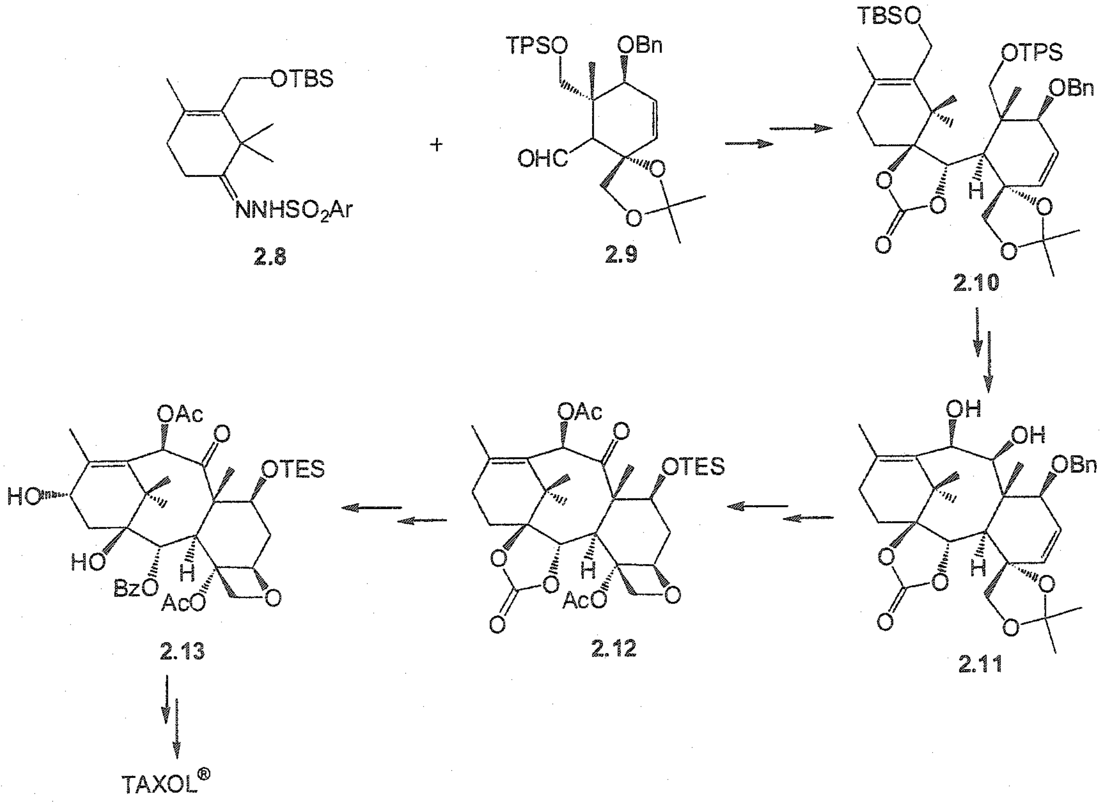


Scheme 2.3 Holton's Synthesis of Taxol®

The total synthesis developed by Holton's group is a scientific achievement. Nevertheless, it is not commercially practical, requiring 40 steps, with an overall yield of around 2%.

2.1.2.2. The Nicolaou Route

The route utilized by Nicolaou was a convergent route; the A- and C-rings were constructed separately, and then linked together using a Shapiro reaction to afford **2.10** (Scheme 2.4). In order to complete the B-ring, the cyclic carbonate was synthesized and the alcohols functionalities deprotected. The resulting alcohol underwent oxidation, followed by McMurray coupling to afford intermediate **2.11** in only 23% yield. The oxetane ring was installed by annulation of the strategically protected alcohols and successive acetylation of the tertiary alcohol. Having created the fused ABC ring system, Nicolaou then completed the total synthesis of Taxol®. Ring opening of the cyclic carbonate gave the desired C2 benzoate, and allylic oxidation with PCC afforded the alcohol **2.13** in a modest 55% yield. Introduction of the C13 side chain was achieved by the method of Ojima[84-85] and Holton. A final desilylation gave Taxol®.

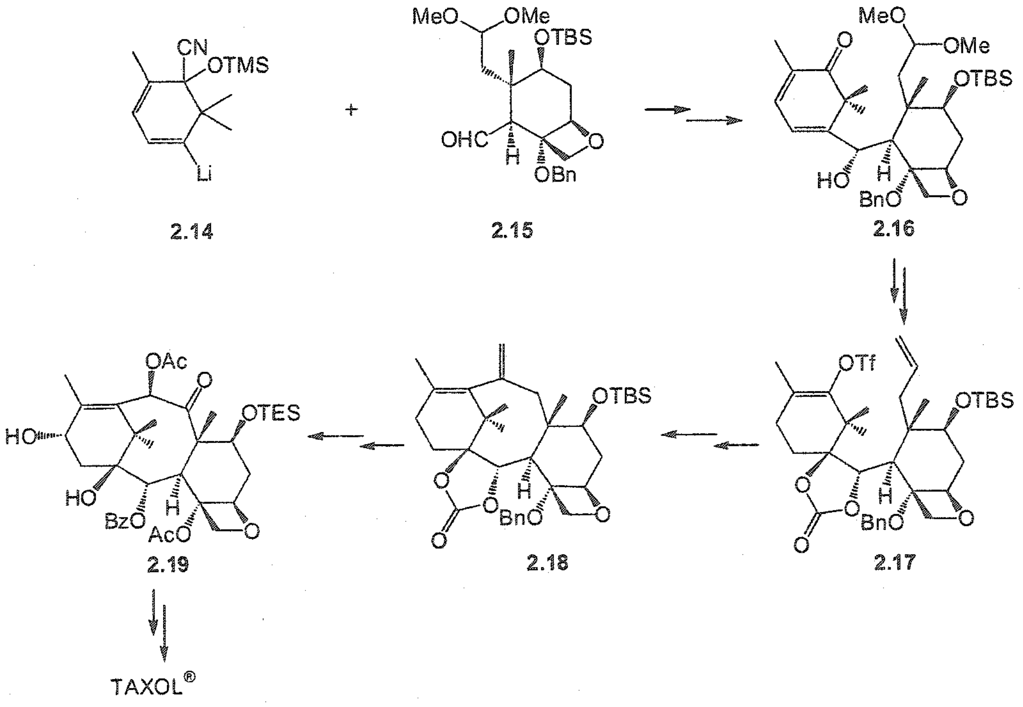


Scheme 2.4 Nicolaou's Route for Taxol®

Despite the successful completion of the total synthesis for Taxol®, application of this route for the industrial production of the compound is impractical due to the length of the route and the modest yield of various key steps (McMurry coupling 23% and oxidation of **2.12**).

2.1.2.3. The Danishefsky Route

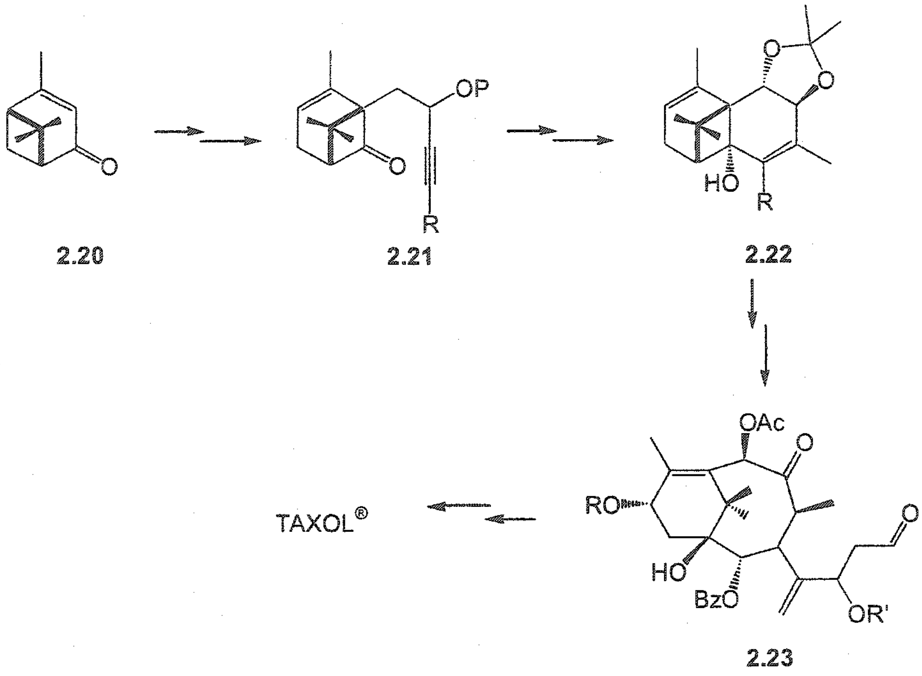
The method employed by Danishefsky[86-87] started with the Wieland-Miescher ketone, which was elaborated to a complex ketone. A ring fragmentation of this, followed by selective protections and successive ozonolylsis gave aldehyde **2.15** (Scheme 2.5). Coupling of **2.15** with the properly functionalized lithio derivative **2.14** (from trimethylcyclohexane-1,3-dione) established the C1-C2 bond of Taxol®. The intermediate was transformed to vinyl triflate **2.17** bearing an olefin for development to Taxol® core **2.18** *via* an intramolecular Heck reaction. Some transformations over the frame afforded 7-triethylsilyl Baccatin III **2.19**. The authors concluded the total synthesis of Taxol® following the Ojima protocol[84] for the introduction of the side chain.



Scheme 2.5 Danishefsky's Total Synthesis of Taxol®

2.1.2.4. The Wender Route

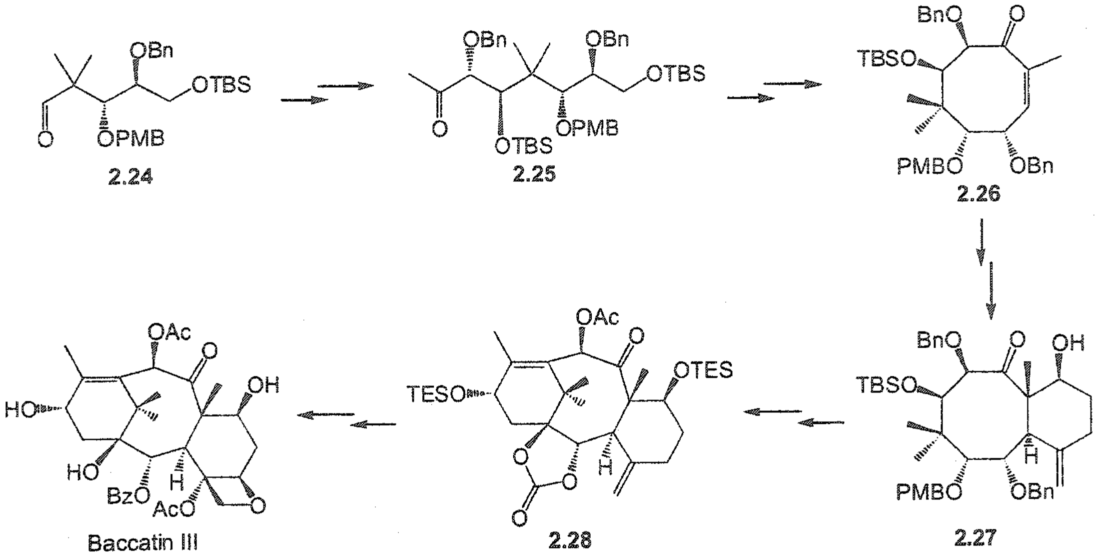
Wender introduced a different strategy[88-89] for the formation of taxanes (Scheme 2.6). He used as starting material pinene **2.20** to afford the complete A- and B-ring fragments, and used an aldol closure to establish the C-ring **2.23**. The pinene path provided Taxol® in 38 steps.



Scheme 2.6 Pinene Route for Taxol®

2.1.2.5. The Mukaiyama Route

Mukaiyama employed a synthetic plan[90-91] in which the B-ring was used as an initial scaffold for subsequent elaboration of the other rings (Scheme 2.7). The BC ring system **2.27** was formed by an intramolecular aldol reaction. The intermediate contained the necessary stereocenters and the proper functionality from which the A-ring was constructed. The ABC ring system **2.28** was formed by an intramolecular pinacol cyclization using a low-valent titanium reagent prepared from $TiCl_2$ and $LiAlH_4$. Next, the introduction of the C-13 hydroxyl group was performed, followed by formation of the oxetane ring *via* an allylic bromide. In contrast to other syntheses, Mukaiyama started the synthesis of the cyclooctene B-ring from the acyclic trialkoxy aldehyde **2.24** derived from L-serine, but required 60 steps.



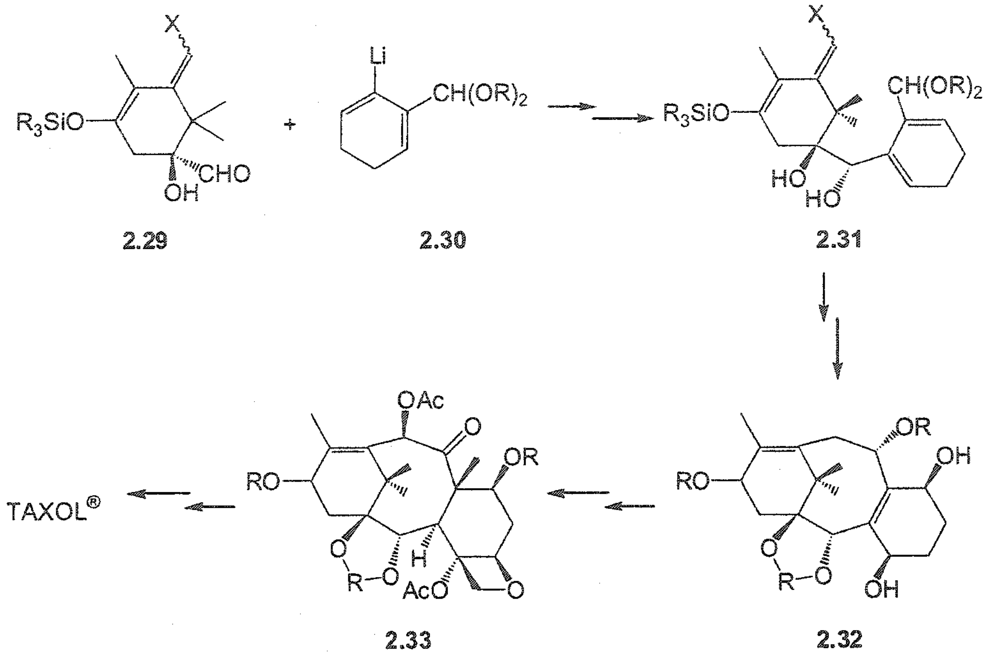
Scheme 2.7 L-Serine Route for Taxol®

The total asymmetric synthesis of Taxol® was completed by dehydration condensation between protected *N*-benzoylphenylisoserine and 7-TES Baccatin III, obtained from the above 8-membered ring enone **2.26**.

2.1.2.6. The Kuwajima Route

The Kuwajima synthesis[92] used an optically pure aldehyde **2.29** as the A-ring fragment starting material and a vinyllithium reagent **2.30** as C-ring fragment (Scheme 2.8). Coupling, followed by Lewis acid mediated B-ring cyclization gave the desired ABC endo-tricycle **2.32**. The C19-methyl group was introduced by cyclopropanation, followed by reductive cleavage. After introduction of the C10-oxygen functionality, subsequent transformations afforded the D-ring **2.33**.

Functional group manipulation and final introduction of the side chain terminated the synthesis and provided Taxol®.

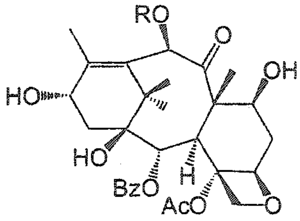


Scheme 2.8 Kuwajima's Synthesis for Taxol®

2.1.3. Semi-synthesis of Taxol®

Unfortunately, the complex structure of Taxol® does not lend itself to a rapid or simple total synthesis. One way to circumvent this problem is by semi-synthesis, starting with a more readily available precursor (Figure 2.4). The first semisynthesis of Taxol® was reported in 1988 by Potier and Greene[93] using 10-deacetylbaccatin III (10-DAB) in a four step synthesis. 10-DAB is much more abundant than Taxol®, with 0.1% for 10-DAB vs. 0.004% for Taxol®. Unfortunately, the process was still far from being commercially viable with an overall yield of only 35%. In 1989, the Holton group patented a process known as the "metal alkoxide process" (MAP) which enabled the conversion of 10-DAB into Taxol® in four steps and yields over 80%. This process was later modified and most of the Taxol® is supplied this way.[94] The currently investigated precursors for the semisynthesis of taxanes[95-97] are Baccatin

III and 10-DAB which are isolated from the needles of the *Taxus baccata* found in different locations in the Far East, Europe, Northern and Central America. Moreover, studies towards the semisynthesis of Taxol® made by Potier's group disclosed several new biologically active derivatives of Taxol®. Docetaxel was the more effective and presented some advantages over Taxol® for the treatment of some forms of cancer. Nevertheless, there is an inconvenience in the semisynthesis: taxanes isolated from the needles degrade more rapidly than Taxol® from the bark.



10-DAB, R = H
Baccatin III, R = Ac

Figure 2.4 Precursors for the Semisynthesis of Taxanes

2.1.4. Taxol Analogues

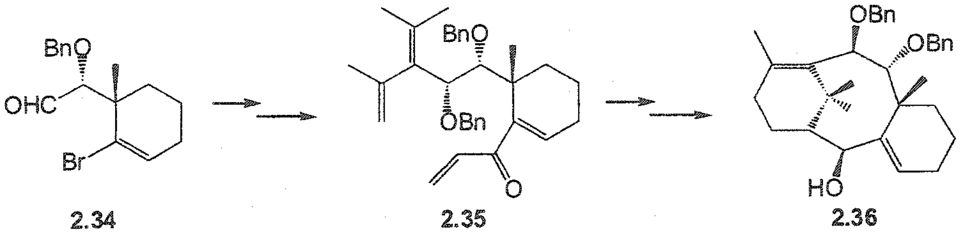
Although Taxol® is a leading drug in cancer chemotherapy and extends the lives of many people; it is not a cure. Many patients develop resistance and some tumors show minimal response to it. Therefore, the development of accessible new anticancer drugs with improved therapeutic activity, higher solubility and lower toxicity are desirable. Many groups worldwide are continuing to carry out research in this area, not only to develop newer and shorter routes to this natural product, but also to create modified structures, which may be more biologically active against various tumor types and able to overcome drug resistance. This has led to the synthesis of a large number of analogs. In this context, diverse and fascinating approaches for the synthesis of the taxane ring system have been reported. Those syntheses where the Diels-Alder and/or Ring Closing Metathesis (RCM) strategies have been applied provide particularly attractive comparisons from the perspective of this thesis.

2.1.4.1. Diels-Alder Strategy

Different groups have reported a Diels-Alder strategy for the construction of the taxane skeleton. These include the Shea researchers in California, the Winkler group at Pennsylvania, and the Fallis group at Ottawa.

2.1.4.1.1. Shea's Study

Shea and co-workers have reported successful applications of the Diels-Alder reaction for the formation of taxanes (Scheme 2.9). They have performed extensive studies, overcoming initial difficulties that included the lack of proximity of the diene-dienophile system **2.35**, and flexibility of the molecule that hampered the desired cyclization. After some failed attempts,[98] they achieved the construction of the ABC ring-system[99] of taxanes **2.36** utilizing an intramolecular cycloaddition reaction as the crucial step.

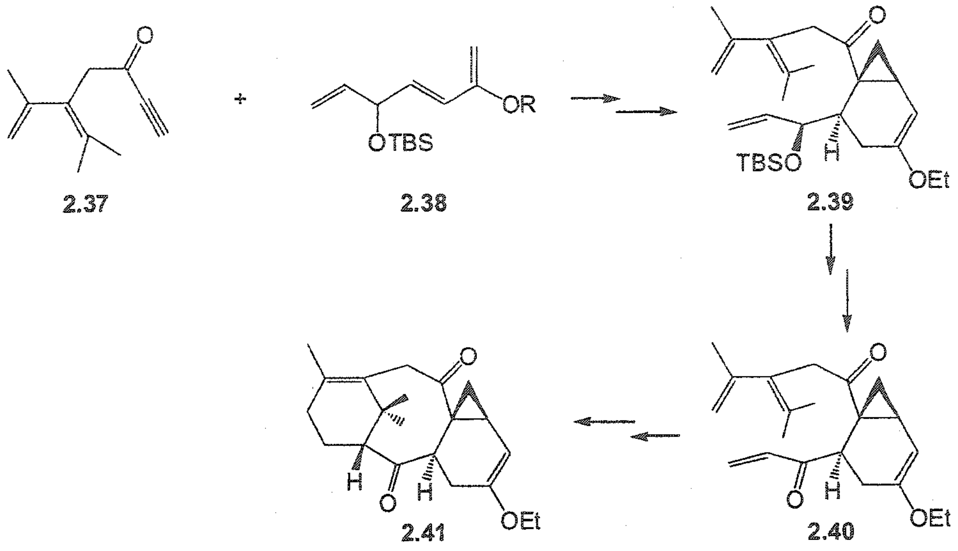


Scheme 2.9 Shea's Contribution to Taxanes

2.1.4.1.2. Winkler Strategy

Winkler and co-workers[100] demonstrated the utility of the Diels-Alder cycloaddition in the synthesis of the taxane ring system in a two-step sequence (Scheme 2.10). The starting materials were the acetylenic dienophile **2.37** and oxy diene moiety **2.38**. The reaction was carried out under high-pressure conditions to yield a mixture of diastereomers in a ratio of 2.9:1, where the *trans* isomer was the major component. Exposure of this intermediate to dimethylsulfoxonium methylide gave the cyclopropane **2.39** in the β-position with concomitant migration of the $\Delta^{4,5}$

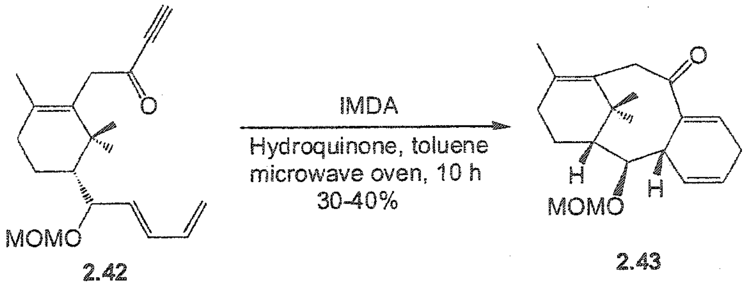
alkene. The precursor for the second cycloaddition arose from deprotection of the secondary alcohol, followed by oxidation. The double Diels-Alder strategy gives rapid access to the taxane ring system **2.41** in acceptable yields.



Scheme 2.10 Winkler's Diels-Alder Approach for Taxanes

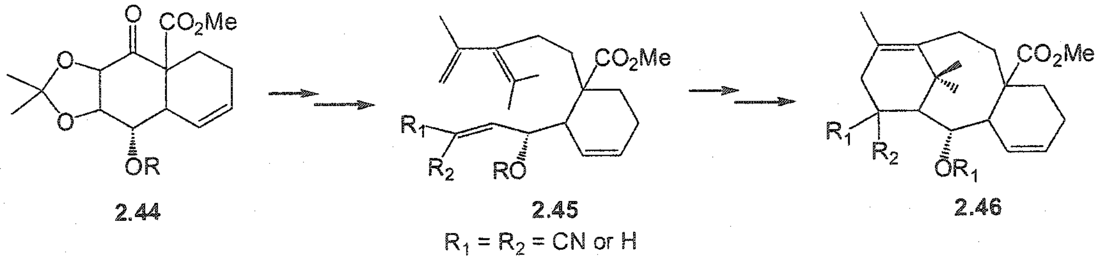
2.1.4.1.3. Fallis Approach

Fallis and co-workers have made important contributions in this field as well. In their search for synthetic strategies towards taxoids, they have developed an efficient Diels-Alder strategy for assembling the ring system of taxanes in various directions. Initially, they utilized a substituted cyclohexene as an agent to control the orientation of the reactive center. They tried the IMDA reaction using **2.42** as starting material to assemble the BC system in taxanes (Scheme 2.11).[101] The microwave-assisted thermal cyclization to form the B and C rings in the left-to-right direction provided **2.43** stereoselectively in modest yields. However, the Lewis acid catalyzed cycloaddition to generate the substituted taxane nucleus with the right relative stereochemistry at C1-C3, was not possible.



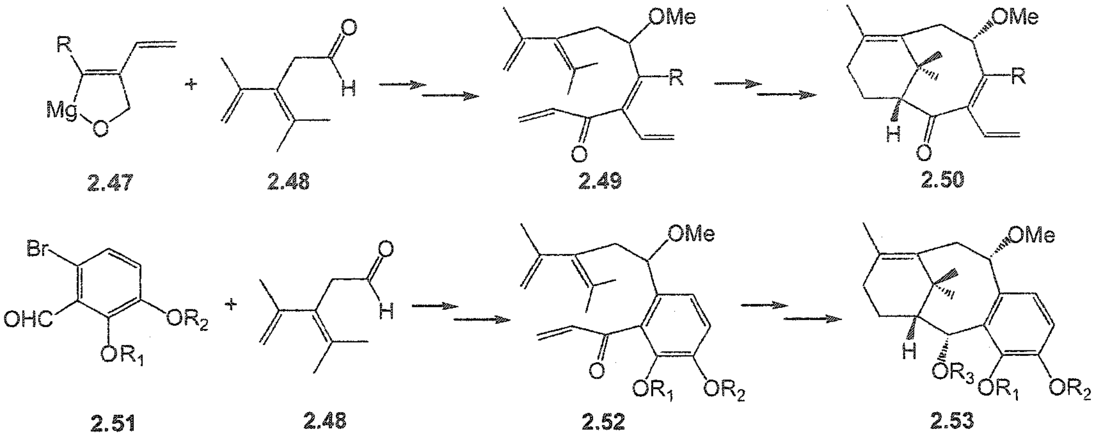
Scheme 2.11 Fallis Diels-Alder Approach to Assemble BC Rings

Subsequently, they investigated the construction of the taxane AB nucleus through a double cycloaddition to form the A and B rings in the right-to-left direction (Scheme 2.12). However, the second cycloaddition was thwarted when Lewis acid complexation between the carboxyl group and the oxygen in **2.45** failed to induce the Diels-Alder addition.



Scheme 2.12 Former Fallis Diels-Alder Approach

More research was performed before these trials culminated in an intramolecular cycloaddition that affords the AB bicycle skeleton containing either acyclic[102] **2.50** or aromatic substituents **2.53** (Scheme 2.13).[103]



Scheme 2.13 Fallis Diels-Alder Approach for Taxoids

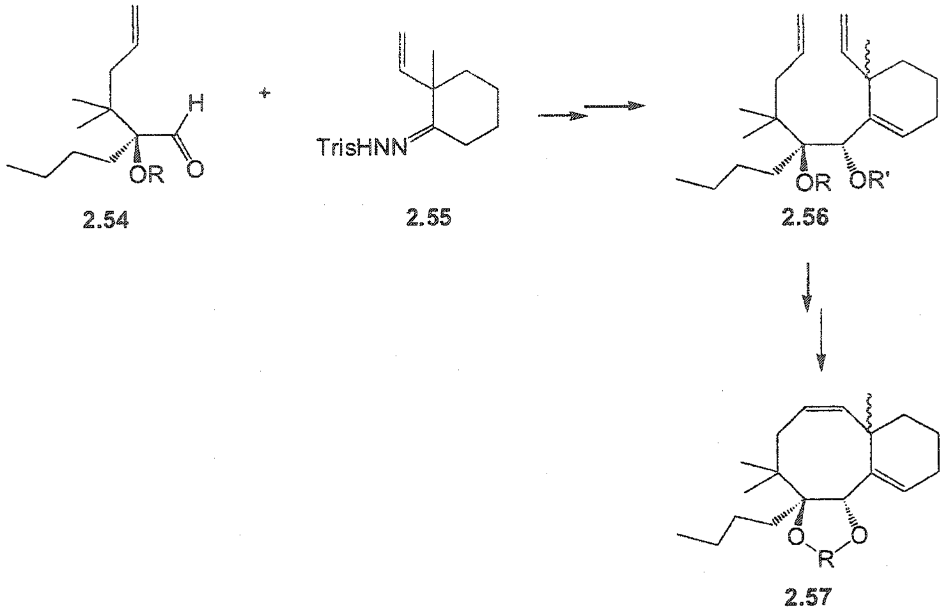
2.1.4.2. RCM Strategy

The use of RCM for the synthesis of taxanes[104-105] has received little attention. In part, this could be attributed to the dense substitution pattern in the molecule, and the assumption that only conformationally biased precursors would undergo cyclization. However, preliminary results have assessed the viability of the RCM approach to obtain taxanes derivatives. They thus provide a partial precedent for more ambitious synthetic endeavors in this area.

2.1.4.2.1 Prunet's Strategy

During the course of his research towards Taxol®, and while our research was in progress, Prunet and co-workers[106] planned a synthesis where the C9-C10 bond would be form by the metathesis reaction. The highly functionalized BC ring-system of Taxol® was then synthesized in very good yield according to Scheme 2.14, using a RCM reaction to form the eight-membered ring **2.57**. The framework contains the appropriate configuration for the C1, C2 and C8 stereogenic centers of the target molecule. In the synthetic route, the metathesis precursor **2.56** was synthesized by a

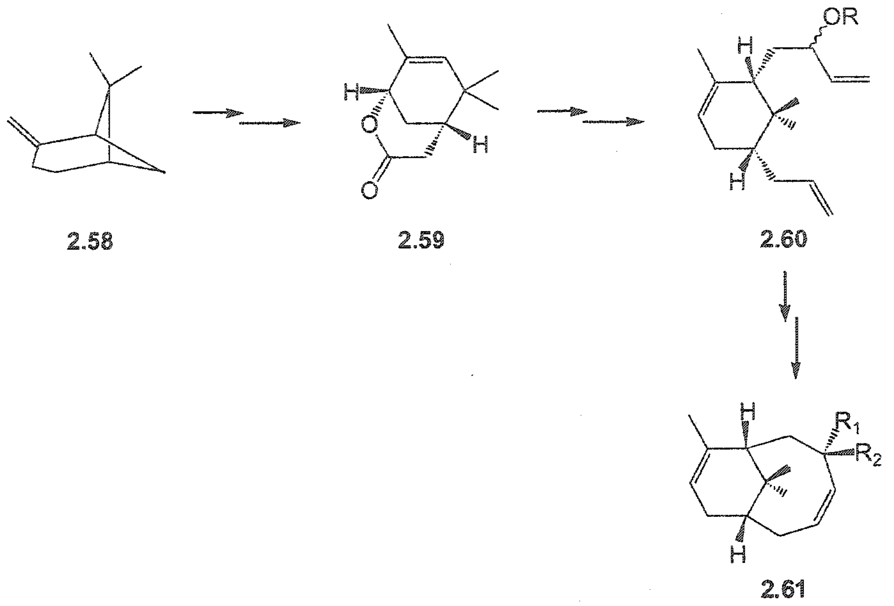
Shapiro coupling between aldehyde **2.54** and trisylhydrazone **2.55**, which was prepared in one step from the known 2-methyl-2-vinylcyclohexanone.



Scheme 2.14 BC Ring-System of Taxol® by RCM

2.1.4.2.2. Blechert's Approach

In the course of their studies concerning the synthesis of functionalized taxanes, Blechert and co-workers[105] developed the first application of RCM to elaborate the AB ring-system (Scheme 2.15). This research was also published during our investigation. They chose β-pinene **2.58** as a building block for the A ring which afforded lactone **2.59** followed by some chemical transformations that included pentacarbonyliron-mediated CO-insertion. Afterwards, two alkenic side chains were strategically attached in a *cis* configuration **2.60**. The B-ring formation of **2.61** was accomplished by RCM, confirming the relevance of this reaction. The potential of employing this strategy for a total synthesis is limited due to the known difficulty or isomerizing the alkene into the bridgehead position.



Scheme 2.15 Blechert's Approach for Taxanes

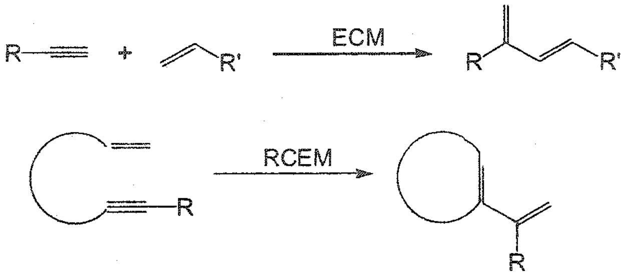
2.2. OLEFIN METATHESIS

Olefin metathesis is a versatile approach for the assembly of rings as well as acyclic systems found in many natural compounds. This transition metal catalyzed reaction is a powerful tool for both cleaving and forming C-C multiple bonds and has experienced remarkable progress through the development of efficient catalysts. Olefin metathesis reactions can be categorized into four closely related groups.[107-109]

a) Cross metathesis (CM), where two alkenes are coupled to provide a new olefin.

Scheme 2.16 Cross Metathesis

b) Enyne Metathesis (EM) is the intermolecular (ECM) or intramolecular (RCEM) coupling between double and triple bonds to afford the conjugated diene product.[110-111]



Scheme 2.17 Enyne Metathesis

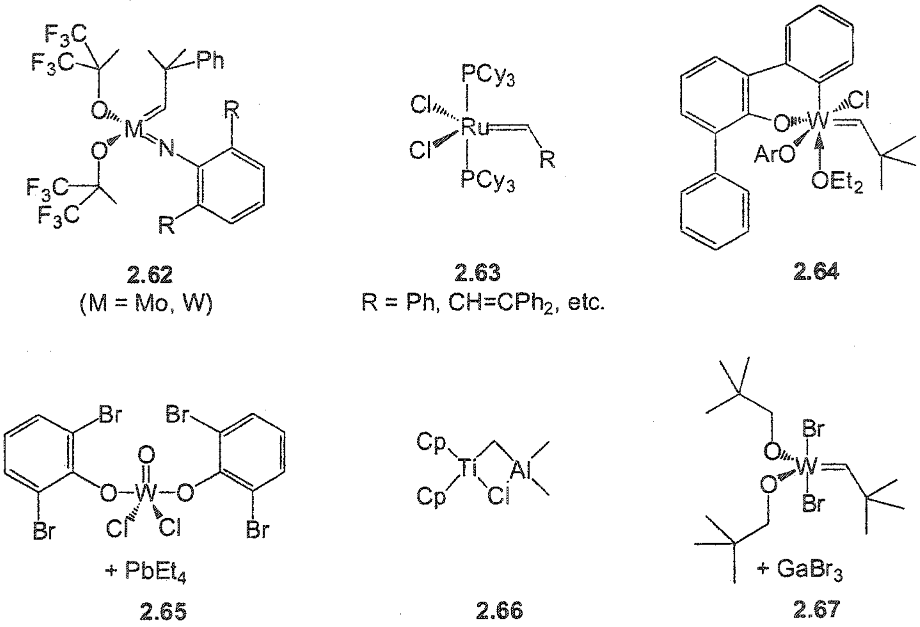
c) Ring opening metathesis (ROM) or ring-opening metathesis polymerization (ROMP) in which a cyclic alkene undergoes opening to afford polymeric compounds.

Scheme 2.18 Ring Opening Metathesis

d) Ring closing metathesis (RCM), where a diene is fused to afford two new compounds. One is a volatile olefin, and the other one is the desired cycloalkene that accumulates during the reaction.

Scheme 2.19 Ring Closing Metathesis

The mechanism in both acyclic and cyclic olefin metatheses and for all catalysts[107] is the "Chauvin mechanism"[112] which involves a sequence of metallacyclobutanes and carbene complexes. Some catalysts or catalyst precursors used for these types of reactions[113] are depicted below (Figure 2.5). The most accepted and versatile catalysts are tungsten and molybdenum allylidene complexes **2.62** that were developed by Schrock,[114] and the ruthenium carbene complexes **2.63** introduced by Grubbs.[115]



2.62 (M = Mo, W)

2.63 R = Ph, CH=CPh_2, etc.

2.64

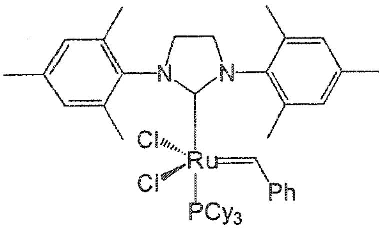
+ $PbEt_4$ **2.65**

2.66

+ $GaBr_3$ **2.67**

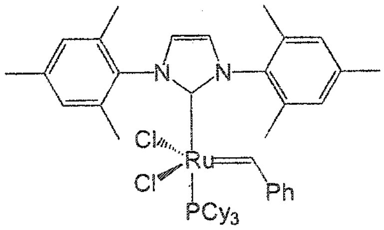
Figure 2.5 Olefin Metathesis Catalysts

RCM in particular, has evolved as a well established method for synthetic purposes. The synthesis of 5-, 6-, 7-, and 8-membered rings and macrocycles[110,116-119] has been widely reported using this protocol. At present, RCM is a recurrent strategy for the synthesis of many intermediates, and has been used as key step in several total syntheses. This robust reaction has become even more popular with the creation of a second generation of ruthenium-based catalysts[120] (Figure 2.6) that features the electron-rich σ-donating dihydroimidazolylidene carbene ligand (**2.68**, **2.69**).



2.68

(4,5-DihydroIMES)(PCy$_3$)Ru=CHPh



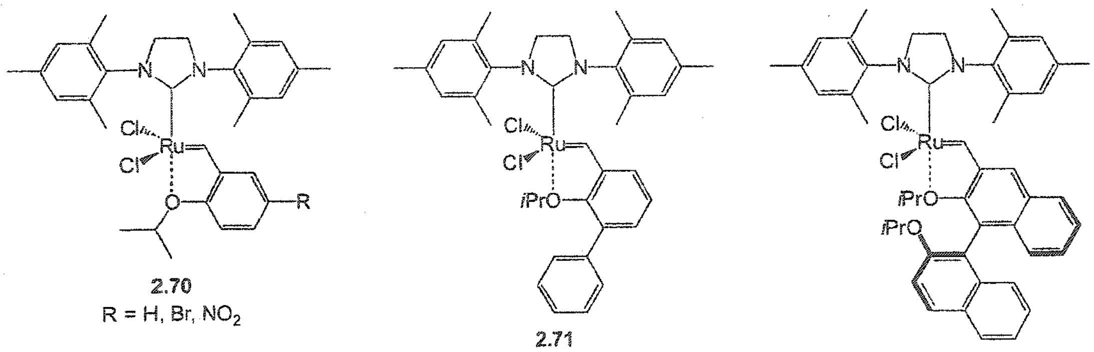
2.69

(IMES)(PCy$_3$)Cl$_2$Ru=CHPh

Figure 2.6 Second Generation Ruthenium-Based Catalysts

The new catalysts formulated by Grubbs combine enhanced reactivity, great stability and functional group tolerance. In addition, they are easy to handle because of their reasonable stability to oxygen, water and minor solvent impurities. The emergence of these *N*-heterocyclic carbene-containing ruthenium complexes has increased the scope of alkene metathesis and its applications.

Very recently, a third generation of ruthenium catalyst has been disclosed (Figure 2.7). Hoveyda and co-workers[121] synthesized a ruthenium complex **2.70** (R=H) that promotes olefin metathesis even in those olefins with electron-withdrawing functionality. The catalyst operates under very mild conditions, is stable to air and can be purified and recycled easily. Blechert and Wakamatsu elaborated a catalyst[122] with superior activity than both **2.70** and the second generation of Grubbs catalyst by replacing the isopropoxystyrene moiety in **2.70** by binol- or biphenyl-based styrene (**2.71** and **2.72**). The catalyst have been successfully applied in different types of metatheses. Amazingly, Grela and co-workers[123] prepared one more complex **2.70** (R=NO_2) with increased catalyst reactivity. The complex is very stable and tolerates various degrees of substitution of the double bonds. It is also effective for the synthesis of trisubstituted olefins, operates under very mild conditions and is applicable to all type of metathesis (RCM, CM, enyne).



2.70
R = H, Br, NO$_2$

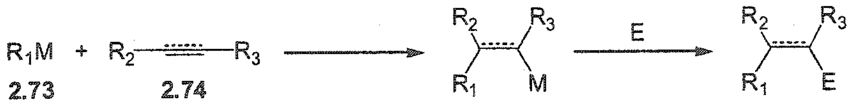
2.71

2.72

Figure 2.7 Third Generation Ruthenium-Based Catalysts

2.3. CARBOMETALLATION

Carbometallation is another powerful tool for C-C bond formation (Scheme 2.20). In this type of reactions, the C-C bond is formed by addition of an organometallic species to a carbon-carbon multiple bond, where the newly formed C-metal bond **2.75** can be used for further synthetic transformations by addition of the desired electrophile (E).[124]

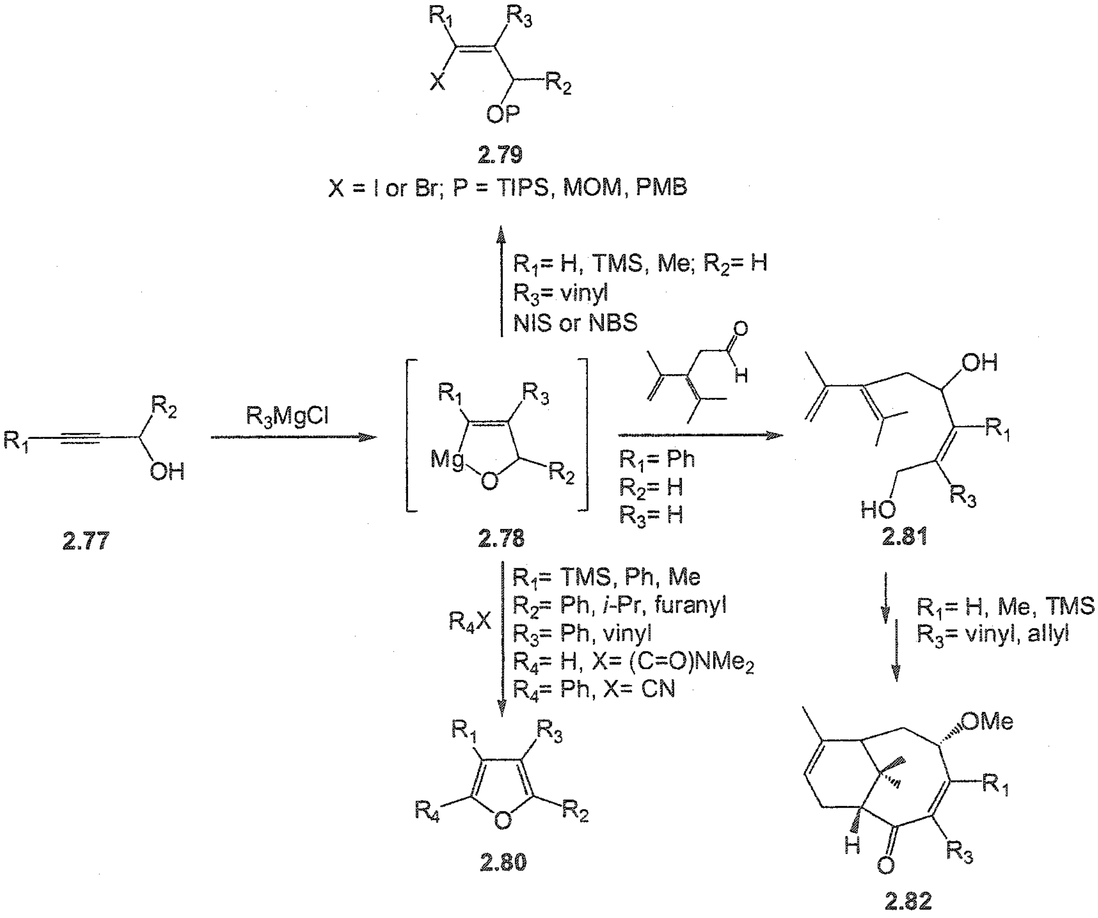


2.73 2.74 2.75 2.76

Scheme 2.20 Carbometallation

Investigations in a number of research groups during the past several years have led to the development of carbometallation as a reliable and practical method for selective transformations.[125] The reaction has been performed in the presence of diverse metals, such as Mg, Zn, Cu, Li, In, Al and Ni using alkynes alkenes, allenes and conjugated enynes as substrates.[126] Moreover, the reaction has been employed in intra- and intermolecular reactions to produce valuable compounds. Also, carbometallation has been performed enantioselectively using chiral auxiliaries.[127]

The addition of Grignard reagents to unsaturated systems containing an allylic or homoallylic heteroatom is particularly useful.[126] The presence of the heteroatom facilitates the generation of a magnesium chelate that controls the addition reaction. This reaction has been widely applied for the synthesis of allylic alcohols, dienes and butenolides. Fallis and co-workers have extensively studied this magnesium-mediated carbometallation and extended its application to a number of target molecules (Scheme 2.21). Their studies led to the synthesis of diverse building blocks utilized for the synthesis of simple (*E*) and (*Z*) halodienes[128] **2.79**, substituted furans[129] **2.80** or complicated scaffolds such as the taxane core[102] **2.82**.



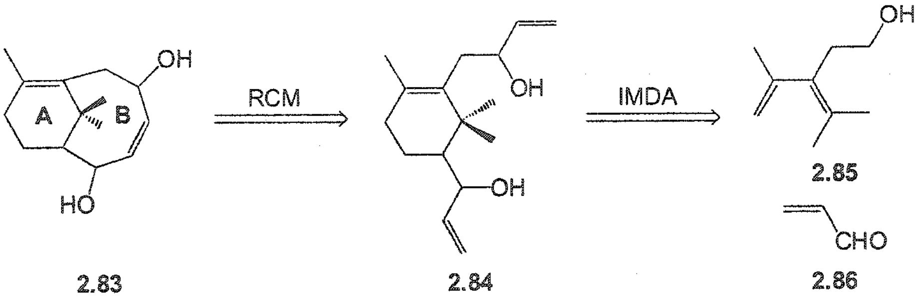
Scheme 2.21 Fallis Carbometallation Application

2.4. RESULTS

Two main issues have been identified as serious obstacles for the production of taxanes. The first of them consists in the generation of the densely oxygenated tricyclic system of taxanes in an efficient manner. The second is the synthesis of the central functionalized eight-membered ring. Our interest in overcoming these limitations and motivated by the evident need for short and efficient synthetic routes to Taxol® and its analogues, have led us to investigate RCM as a strategy for the synthesis of six- and eight- membered rings and the intramolecular Diels-Alder reaction (IMDA) as a functional tool for C-C bond formation in the taxane systems.

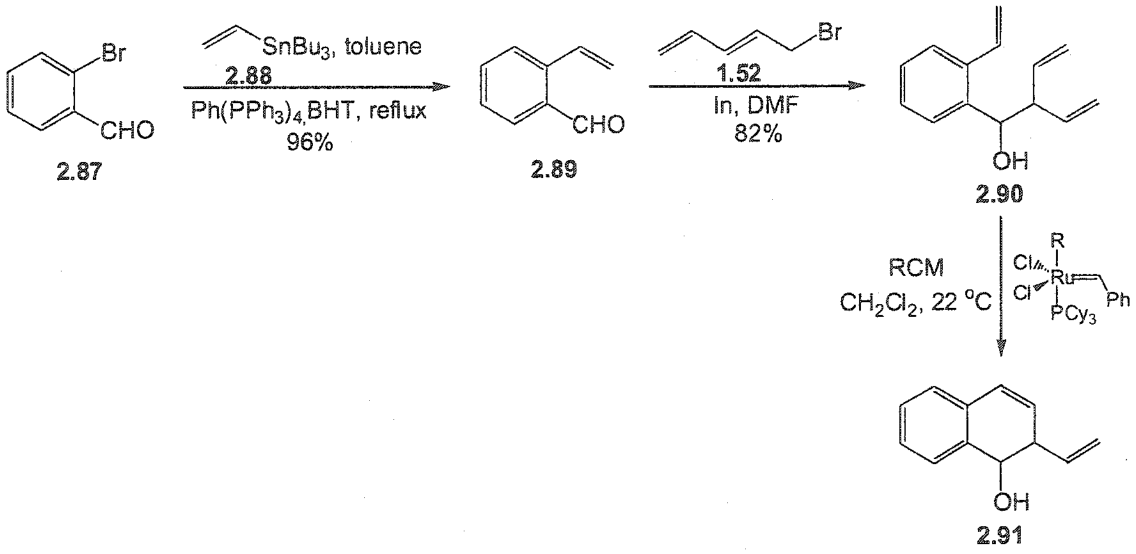
2.4.1. AB System of Taxanes by IMDA-RCM Sequence

In an attempt to develop a competent route to taxanes, a protocol that combines IMDA and RCM reactions was designed. As depicted in the retrosynthetic analysis (Scheme 2.22), the synthesis of the B ring in **2.83** would be achieved via a RCM of the properly functionalized substrate **2.84**. The A ring would be synthesized by an IMDA reaction using acrolein **2.86** as the dienophile and **2.85** as the diene.



Scheme 2.22 Strategy for AB Rings of Taxanes

Prior to the development of this strategy, some preliminary studies on RCM were carried out. Special attention was given to the second generation of Grubbs' catalysts for all the advantages that implicate the use of these ruthenium-based catalysts (**2.68** and **2.69**). However, at the time the project was initiated, these catalysts were not commercially available. Therefore, these catalysts were synthesized (Apendix **A**) following the procedures reported in the literature.[120-121,130-131] Once synthesized, the activity of the catalysts was assessed by performing RCM reactions using the model substrates displayed below in Scheme 2.23. Vinyl benzaldehyde **2.89** was synthesized via palladium-catalyzed coupling of bromobenzaldehyde **2.87**. This aldehyde was subjected to indium-mediated pentadienylation to afford the diene alcohol **2.90**. The newly-formed alcohol was treated with the three different Grubbs catalysts to afford the cyclohexenol derivative **2.91** in moderate yields (Table 2.1).



Scheme 2.23 RCM of Dienol

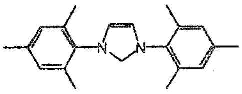
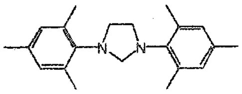
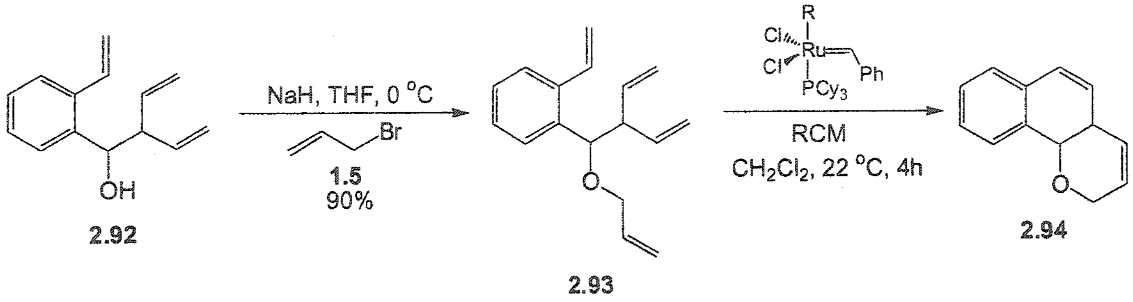
R	Yield (%)
PCy_3	31
	46
	52

Table 2.1 RCM of Diene Alcohol

In order to improve the yield, the alcohol group in **2.92** was protected (Scheme 2.24). It was anticipated that the allyl group would act as protecting group and as a building block to perform a second RCM. The double RCM was complete in short reaction times and high yields as shown in Table 2.2.



Scheme 2.24 Double RCM

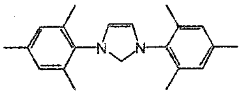
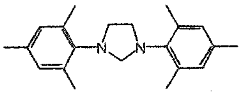
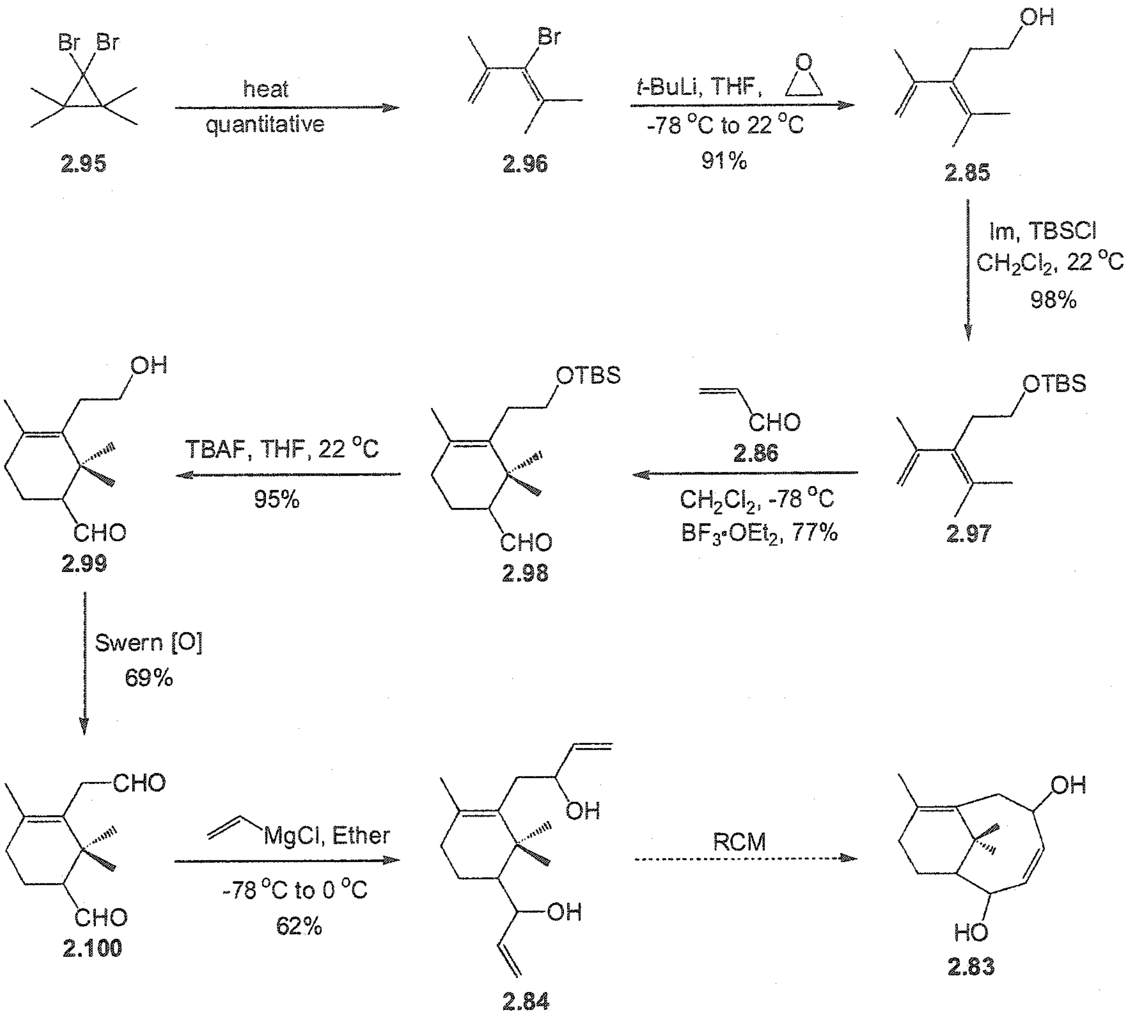
R	Yield (%)
PCy_3	72
	77
	84

Table 2.2 Double RCM of Allyl Ether

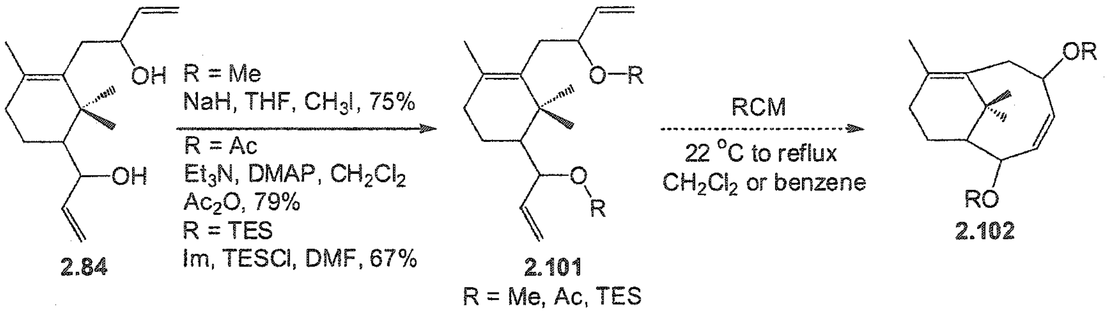
These results indicated that Grubbs' catalysts were effectively prepared and might be suitable for RCM in taxanes systems containing hydroxy groups, however higher yields can be achieved by protection of the alcohol functionality. Among the tested catalyst, **2.68** is the most active. The planned strategy for the synthesis of the B ring in taxanes by RCM was then put into practice. The synthetic route for this is shown in Scheme 2.25.



Scheme 2.25 Synthetic Route for B Ring of Taxanes by RCM

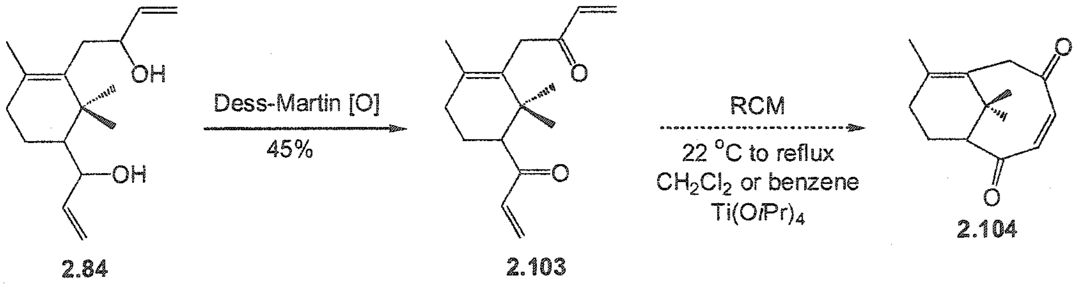
For the synthesis of the diene moiety, dibromocyclopropane **2.95** was subjected to thermal rearrangement affording bromodiene **2.96**. The diene was subjected to lithium-halogen exchange and coupled with ethylene oxide to afford diene alcohol **2.85**. The resulting alcohol was protected as a *tert*-butyldimethylsilyl (TBS) ether providing **2.97**. This silane was treated with acrolein and $BF_3 \cdot OEt_2$ in CH_2Cl_2. An intermolecular Diels-Alder reaction provided the desired A ring **2.98** as a single diastereomer in 77% yield. Treatment of **2.98** with TBAF in THF at room temperature effected deprotection of the TBS group to afford **2.99**. Oxidation of this intermediate by the Swern protocol gave the corresponding dialdehyde **2.100**. A Grignard addition was carried out using excess of vinyl magnesium chloride to ensure complete vinylation. The last step provided the required two vinyl chains that should lead to the B ring of taxanes by RCM to obtain the bicycle **2.83**.

It was suspected that the free alcohol deactivated the catalyst. Consequently, the alcohol groups were both protected and the RCM was attempted again, but the reaction did not proceed as shown in Scheme 2.26. Different protecting groups were used but all attempts were negative. The lack of reactivity could be attributed to the presence of the *gem*-dimethyl group that prevents the proximity of the chains.



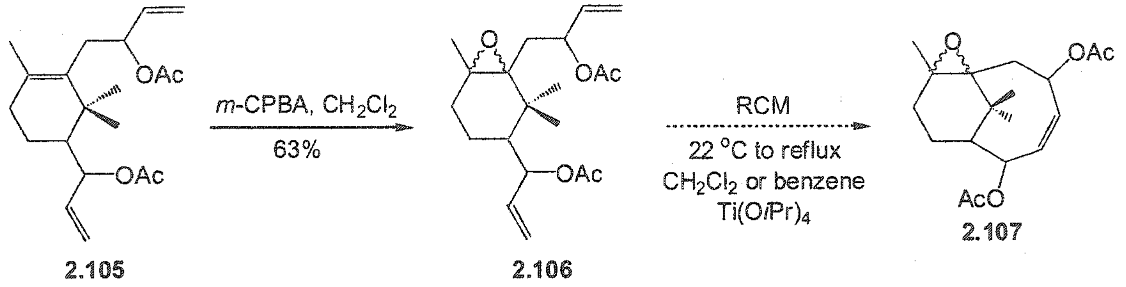
Scheme 2.26 Protecting Groups and Attempted RCM

As an alternative strategy, the oxidation of the alcohol groups to give the corresponding ketones was performed, followed by RCM using $Ti(O\textit{i}Pr)_4$ which has been reported to facilitate the ring closure reaction.[113] Nevertheless, this promoter did not work for our derivative (Scheme 2.27).



Scheme 2.27 RCM of α,β-Unsaturated Ketones

In an effort to improve the stereochemistry for the RCM, the epoxidation of the double bond in the A ring was investigated (Scheme 2.28). It was expected that the epoxidation would avoid any possible competing ROM reaction and would favor the proximity of the lateral chains. Both isomers of compound **2.106** were isolated and individually subjected to RCM, but the reaction was also unsuccessful.

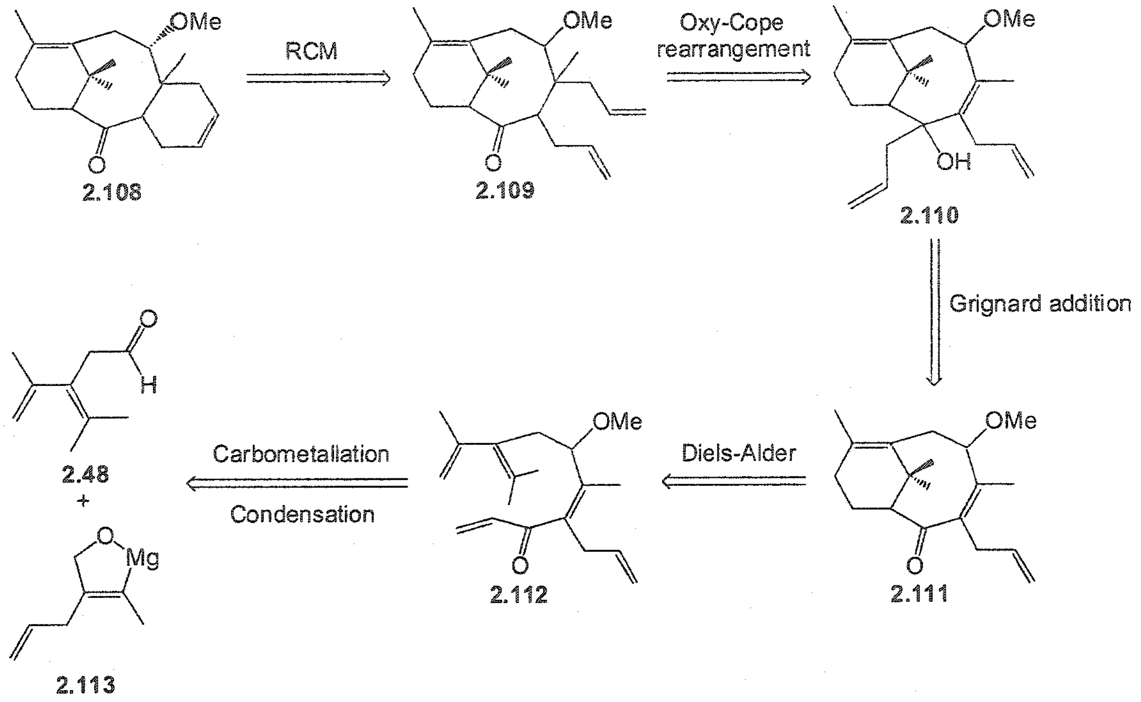


Scheme 2.28 RCM of Epoxides

Despite attempts to perform the closure of the B ring by RCM, it was not possible. The lack of reactivity in the molecule could be attributed to the functional groups present. In addition to the steric interference of the gem dimethyl groups that may prevent the close proximity of the alkenes.

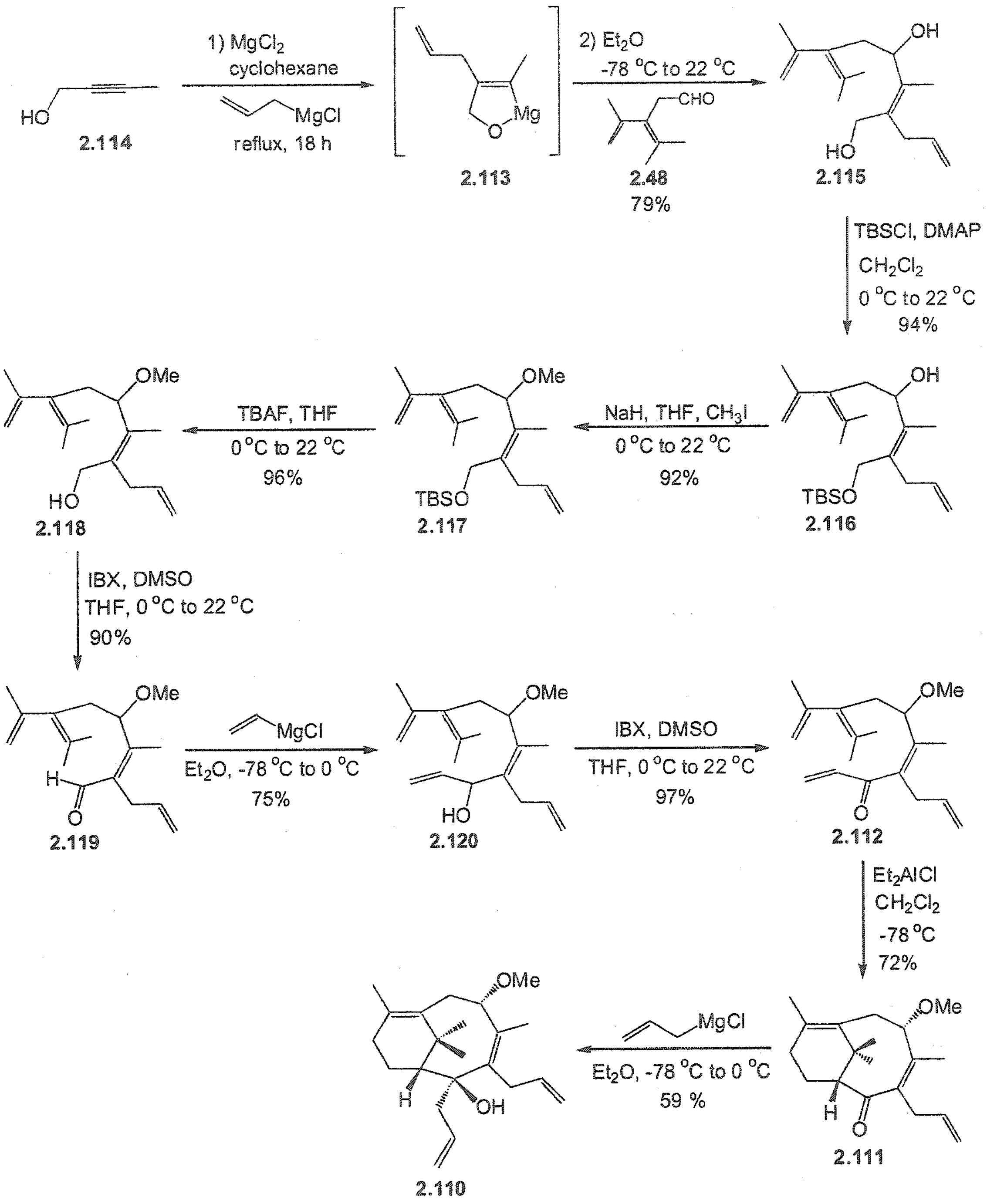
2.4.2. C Frame of Taxanes by oxy-Cope Rearrangement

A previous study of a carbometallation-cycloaddition sequence for the synthesis of the AB ring system was developed in the Fallis group.[102] We adapted this strategy for the synthesis of the ABC core system of taxanes via the AB ring system. In this version, depicted in Scheme 2.29, the six-membered ring C **2.108** would be generated by RCM. The second allyl chain in the B ring; necessary for cyclization; would be attached via an oxy-Cope rearrangement of the allylic alcohol **2.110**. The alcohol would be generated by a Grignard addition with substrate **2.111**. The IMDA reaction would be used to generate the A system, producing simultaneously the problematical eight membered-ring B. The Diels-Alder intermediate **2.112** would be generated by a carbometallation reaction and subsequent *in situ* condensation of **2.113** with aldehyde **2.48**.



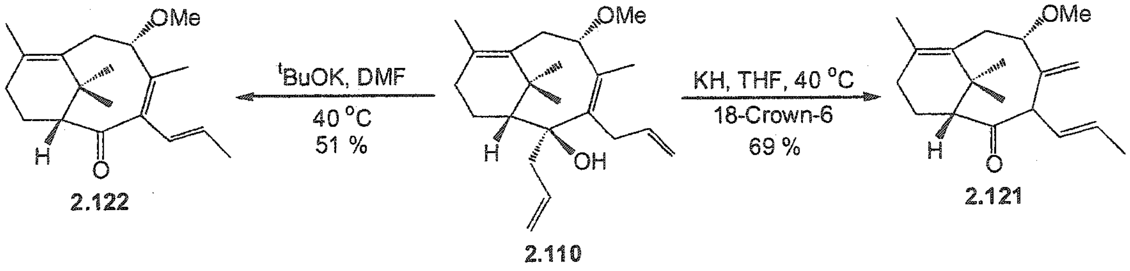
Scheme 2.29 Oxy-Cope Approach for ABC System

As shown in Scheme 2.30, the sequential combination of butynol **2.114** and allyl magnesium chloride generated a magnesium chelate **2.113**, which was subjected to an *in situ* condensation with diene aldehyde **2.48** to afford the diol **2.115** in 79% overall yield. Selective protection of the primary alcohol as its TBS ether, afforded the desired compound **2.116**. The intermediate was treated with MeI to generate the methoxy ether of the secondary alcohol **2.117**. Desilylation of **2.117** with n-Bu_4NF in THF released the primary alcohol **2.118** in 96% yield. Oxidation with IBX/DMSO afforded aldehyde **2.119** in good yield. Vinyl Grignard addition to the aldehyde furnished the vinylic alcohol **2.120**, and a second IBX oxidation provided the Diels-Alder precursor **2.112**. Exposure of this α,β-unsaturated ketone to diethyl aluminum chloride (Et_2AlCl) afforded the AB ring adduct **2.111** as a single diastereomer with the methoxy group in α position. Subsequently, the ketone was allylated by Grignard addition to produce **2.110**.



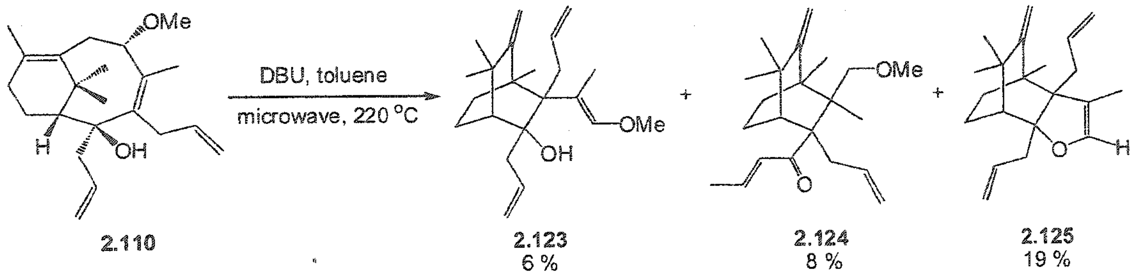
Scheme 2.30 Synthesis of Oxy-Cope Precursor

Initial investigations of an anionic oxy-Cope rearrangement were then carried out using potassium hydride and 18-crown-6 in THF (Scheme 2.31).[131-133] Unfortunately, no rearrangement was observed. Instead isomerization of the allylic chain and loss of proton in the methyl group **2.121** occurred. It was decided to survey other reported conditions for oxy-Cope rearrangements.[134-135] Potassium *tert*-butoxide, promoted the loss of allyl group, but no rearrangement was observed. Instead, the product derived from isomerization of the allylic chain **2.122**, was detected by NMR spectroscopy.



Scheme 2.31 Oxy-Cope Trials

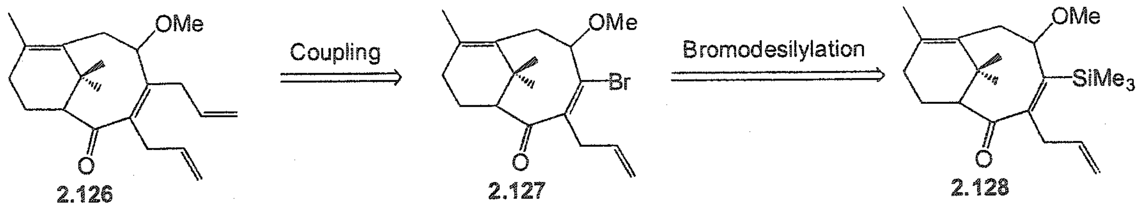
There is another feasible option for oxy-Cope rearrangement that has been effectively used.[136] This involves the use of DBU and microwave irradiation to promote the oxy-Cope rearrangement. Earlier it was discovered that the conjugated carbonyl group promoted an enone accelerated Cope rearrangement, but the reduction to the corresponding alcohol and protection as an ether inhibited the rearrangement.[102] When the reaction was performed in the presence of DBU at 220 °C in toluene (Scheme 2.32), three main compounds were isolated and characterized. Disappointingly, none of them was the desired ring system. The bicyclooctane products (**2.123**, **2.124** and **2.125**) were the result of rearrangement of the molecule without migration of the allyl group.



Scheme 2.32 DBU and Microwave in oxy-Cope Reaction

2.4.3. C Framework of Taxanes by Bromodesilylation

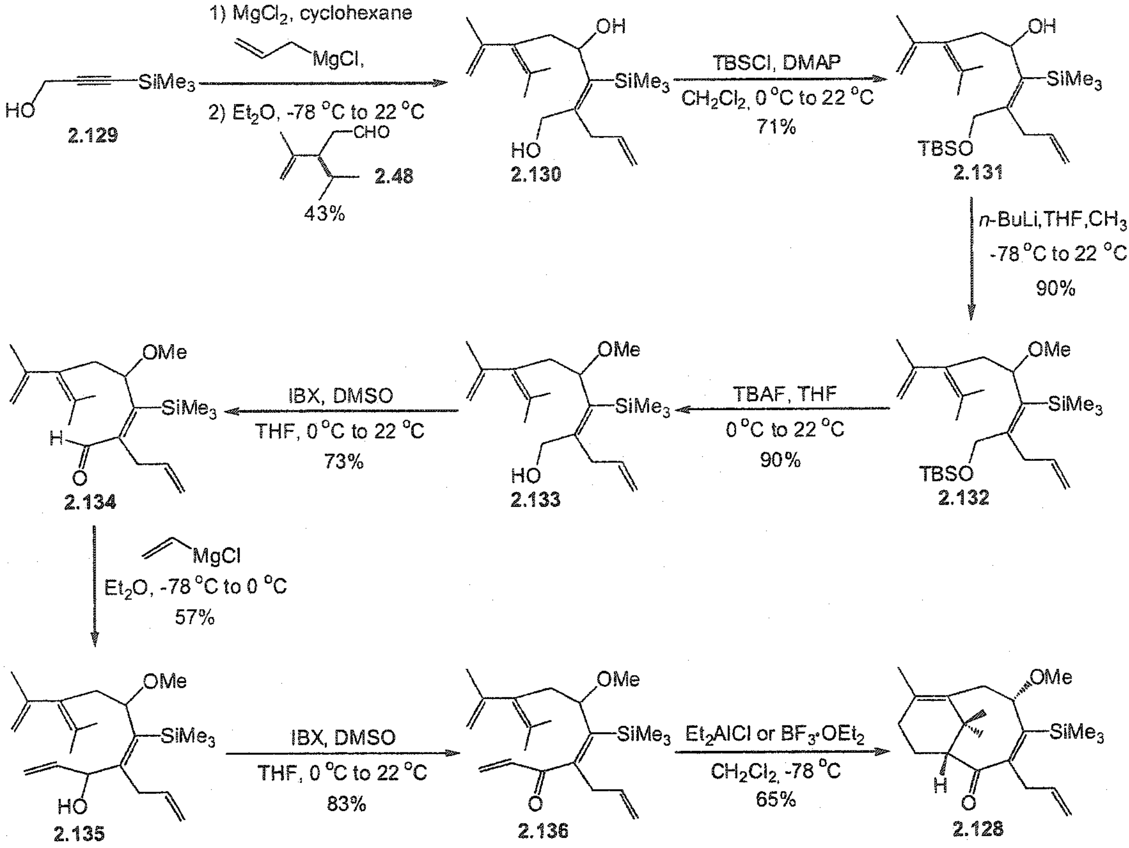
The difficulties encountered in controlling the migration of the allyl chain required a different approach. Hence, the synthetic strategy was modified in such way that the C ring would still be generated by RCM. However, the allyl group necessary for the ring closure reaction would be attached by a palladium-mediated cross coupling reaction of the bromo derivative **2.127**. This bromide would be obtained by bromodesilylation of the properly functionalized AB ring-system **2.128** (Scheme 2.33).



Scheme 2.33 Retrosynthesis for Bromodesilylation Tactic

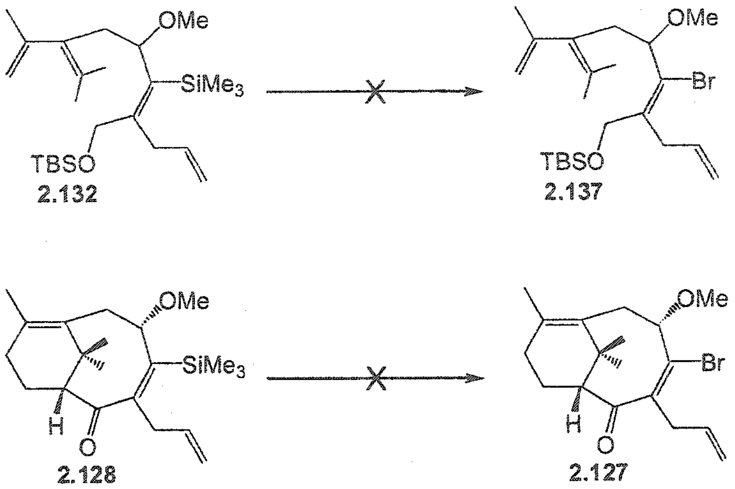
As shown is Scheme 2.34, trimethylsilyl propynol **2.129** was coupled with allyl magnesium chloride and condensed with diene aldehyde **2.48** to afford diol **2.130** in 43% overall yield. Subsequent protection and deprotection steps generated the primary alcohol **2.133**. It is pertinent to mention that the etherification reaction to generate **2.132** required the use of *n*-BuLi as a base in order to avoid any Brook rearrangement.[137-138] Oxidation of **2.133** with IBX in DMSO, followed by vinyl

Grignard addition produced the vinylic alcohol **2.135**. A second IBX oxidation provided the Diels-Alder precursor **2.136**. Exposure of this α,β-unsaturated ketone to Et_2AlCl or $BF_3 \cdot OEt_2$ in CH_2Cl_2 afforded the expected AB ring system **2.128**.



Scheme 2.34 Route to Silane Derivative

The intended bromodesilylation reaction was first tried with both primary and secondary alcohols protected (**2.132**), Scheme 2.35. Based on the literature,[139] different reagents were screened in order to perform the desilylation. In all attempts, the substrate failed to react and did not provide the desired product (Table 2.3). The bromodesilylation was also attempted on the related vinyl silane intermediate **2.128**. Regrettably, no product was observed. Direct palladium-TASF-mediated cross-coupling[140] of the organosilane **2.128** with allyl bromide was also ineffective.



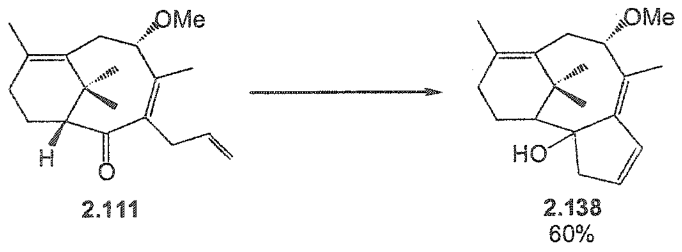
Scheme 2.35 Bromodesilylation Attempts

Entry	Reagent	Solvent	T (°C)
1	NBS	DMF	22
2	NBS	CH_2Cl_2	-10
3	Br_2	CH_2Cl_2	-10

Table 2.3 Bromodesilylation Conditions

2.4.4. Attempts Towards the Oxetane Ring

To circumvent the problems described above, it was decided to revert to the previous intermediate **2.111**. As previously mentioned, the oxetane ring is an indispensable sub-unit for the anti-cancer activity of taxanes. Thus, with a view to prepare this oxetane by functionalization of the allyl chain, a formylation reaction[141-142] was attempted. Despite the examination of various agents, the desired transformation was not observed. It is interesting to note that the anion is indeed formed, but intramolecular cyclization led to the tricycle **2.138**. In addition, the presence of the conjugated diene in the product **2.138** favors its generation (Scheme 2.36).

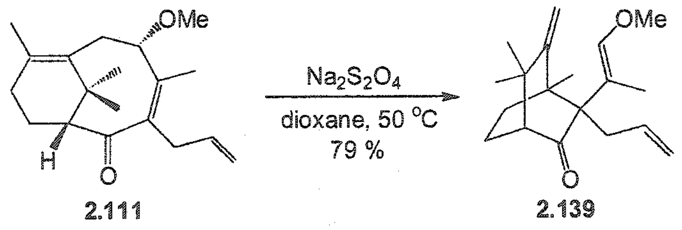


Scheme 2.36 Formylation Attempts

Entry	Reagent	Solvent	T (°C)
1	LDA, DMF	THF	-78
2	LDA, CH_2O	THF	-78
3	LDA, $CH_2O{\cdot}MAPH$	CH_2Cl_2	-78

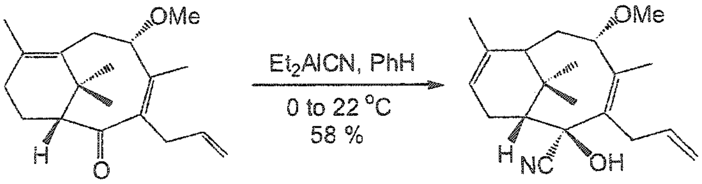
Table 2.4 Formylating Agents

In order to modify the conjugation in the system, it was decided to eliminate the conjugated double bond in the ring B by reduction, using sodium dithionite[143-144] and related reagents reported in the literature[145-146] such as trichlorosilane in the presence of $CoCl_2$ and tin hydride. The rearrangement product **2.139** was observed in high yield instead of any reduction compound (Scheme 2.37).



Scheme 2.37 Cope Rearrangement

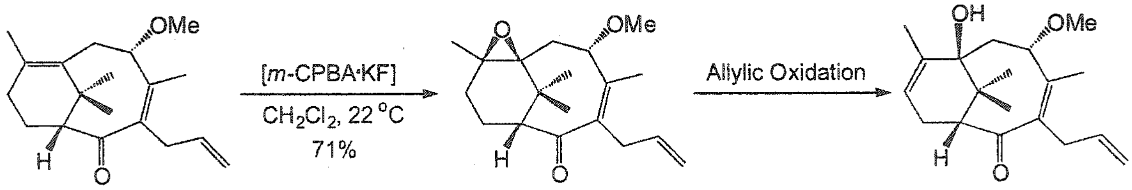
The Michael addition of cyanide was also attempted.[147-150] In this case, the 1,2-addition was preferred, and the double bond in the A ring was isomerized to give **2.140** (Scheme 2.38).



2.111 2.140

Scheme 2.38 Cyanation Approach

We hoped to functionalize the allylic chain by allylic oxidation.[151-155] In order to avoid any additional oxidation in the molecule, the double bond in the A ring of the intermediate **2.111**, was epoxidized. Normally, this alkene is completely unreactive when a C10 substituent is present. Its absence reverses the reactivity. Nevertheless, no oxidation of the allylic chain was observed, regardless of the different reagents used for this task (Table 2.5). The behavior was similar in all cases: proton abstraction causes opening of the epoxide in ring A to produce **2.142** as shown in Scheme 2.39 (the rest of the starting material decomposed).



2.111 2.141 2.142

Scheme 2.39 Allylic Oxidation in AB System

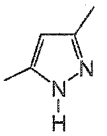
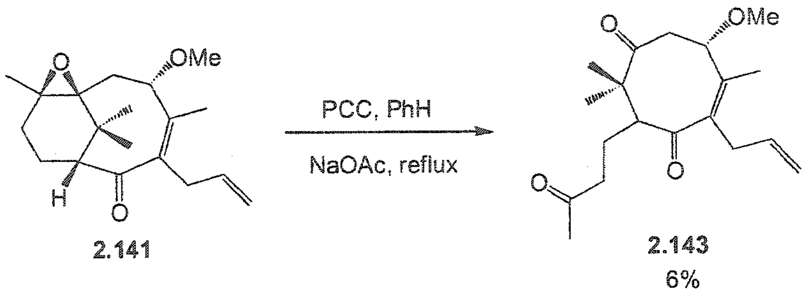
Entry	Reagent	Solvent	t (h)	T (°C)	Yield (%)
1	SeO$_2$, HOAc	Benzene	24	22	59
2	CrO$_3$·2Py	CH$_2$Cl$_2$	24	22	12
3	CrO$_3$, 	CH$_2$Cl$_2$	16	-20	21

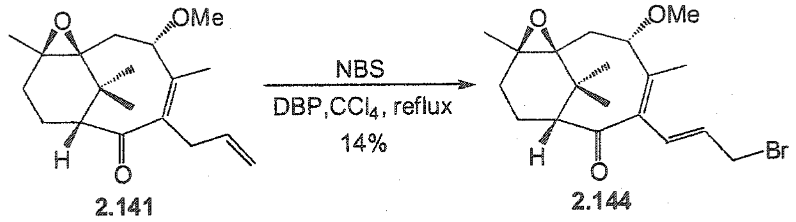
Table 2.5 Allylic Oxidation Reagents

Allylic oxidation following the procedure reported by Danishefsky[86] failed as well. The product was a cyclooctenedione **2.143** (Scheme 2.40), which resulted from the cleavage of the A ring in **2.141**.



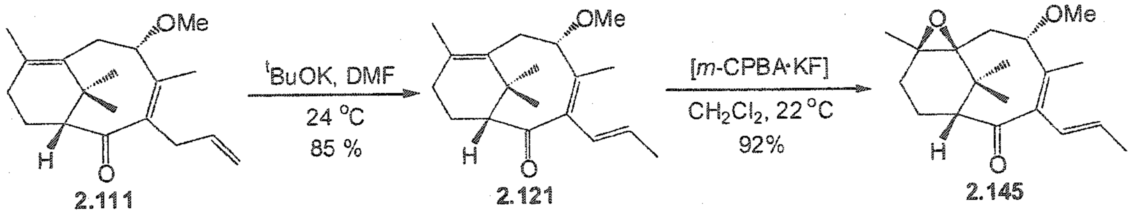
Scheme 2.40 PCC Allylic Oxidation

The allylic bromination[156] reaction was considered in order to introduce the desired functionalization of **2.141** (Scheme 2.41). The preference to maintain the very stable conjugated system dominated, and **2.144** was formed as the major product among a mixture of inseparable by-products.



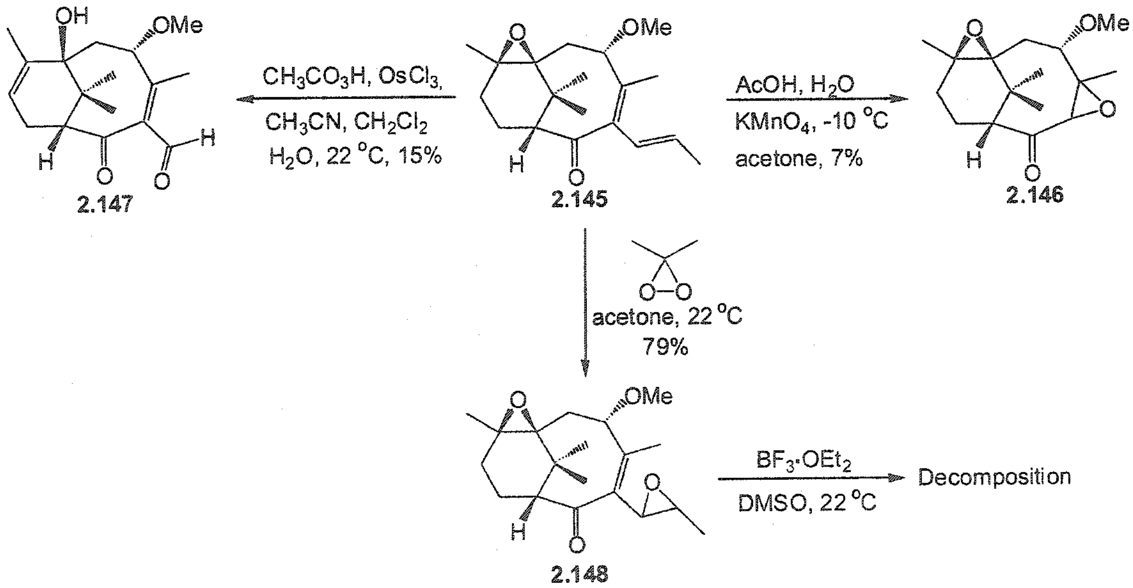
Scheme 2.41 Allylic Bromination

These results led to the investigation of other possibilities. First, the allylic double bond in **2.111** was isomerized (Scheme 2.42). The isomerization was accomplished using potassium *tert*-butoxide in DMF, under mild conditions to afford the desired intermediate **2.121**. Subsequently, the double bond in the A ring was protected to prevent further oxidation in the molecule, affording **2.145**. Performing the transformations in the specific order produced higher yields than when the epoxidation is performed followed by isomerization.



Scheme 2.42 Oxidation Precursor

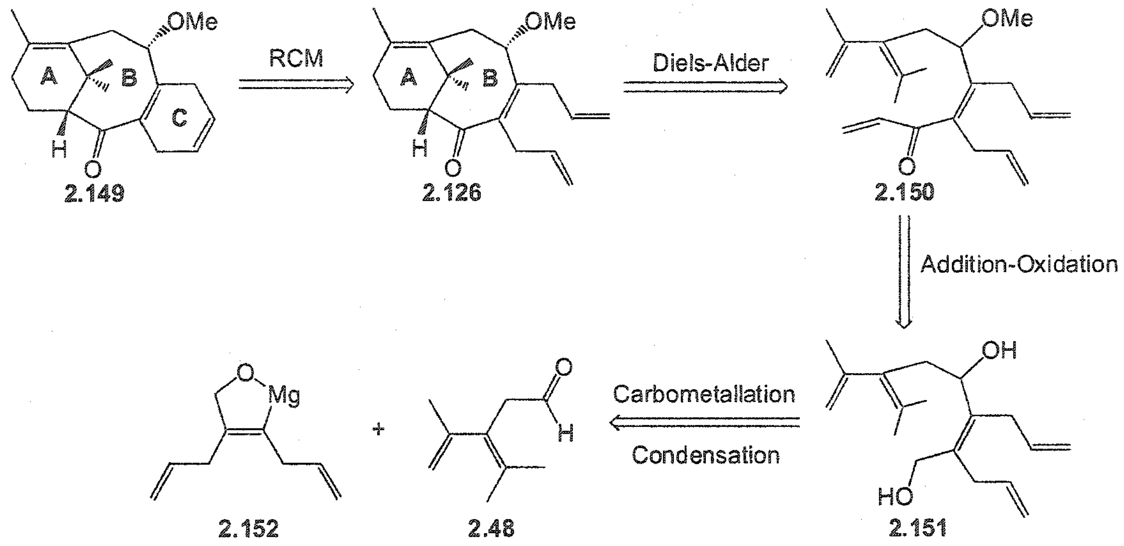
Compound **2.145** was now ready to be transformed into the corresponding α-hydroxy ketone (Scheme 2.43). Various methods for the synthesis of α-ketols were considered;[157-161] however, all attempts gave complicated mixtures of compounds. Only in two cases it was possible to isolate and characterize the oxidation products, which unfortunately were not desired (**2.146** and **2.147**), despite the use of water as a solvent to prevent cleavage of carbon-carbon double bonds.[157] The acid-catalyzed oxidation of oxirane **2.148** with $BF_3{\cdot}OEt_2$ and DMSO to give α-hydroxy ketones[162-164] was also studied with similar unsatisfactory results (Scheme 2.43).



Scheme 2.43 Attempted Synthesis of α-Hydroxy Ketones

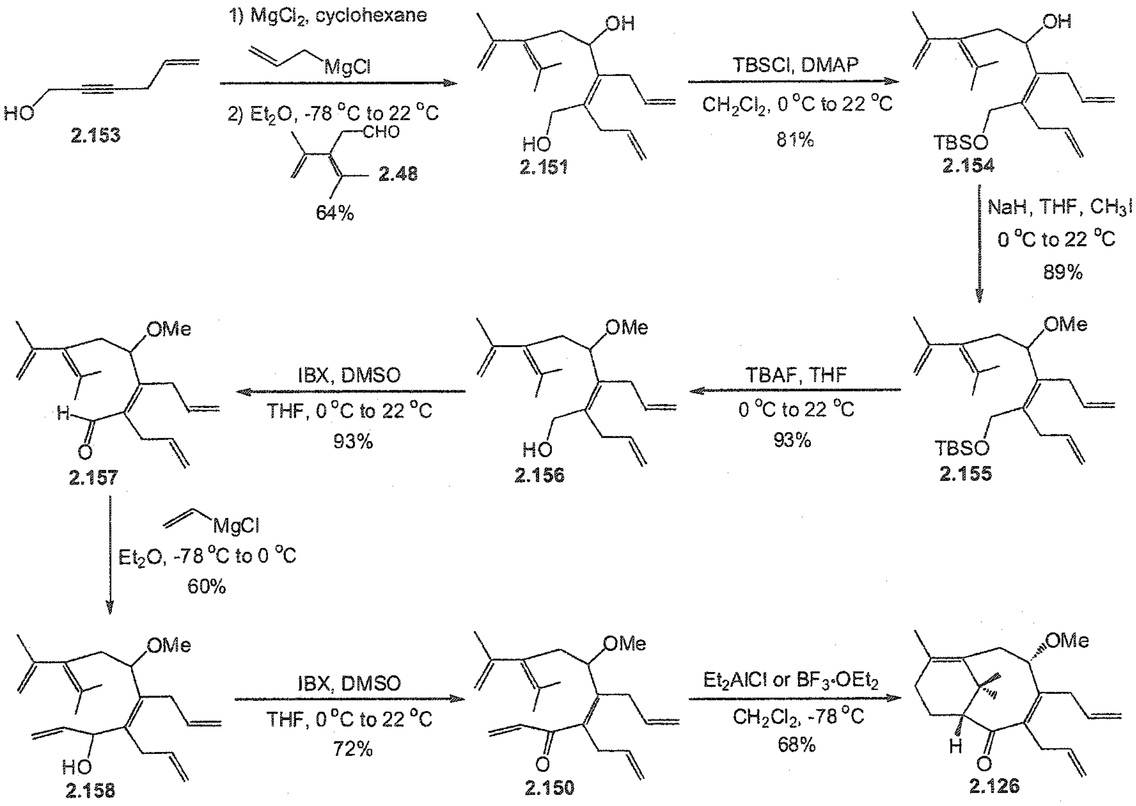
2.4.5. ABC System by Carbometallation-IMDA-RCM Sequence

The introduction of the allyl chain in an early stage of the synthesis was explored as shown in the synthetic strategy depicted in Scheme 2.44. The C ring in **2.149** would be synthesized by RCM while the AB ring system in **2.126** would be obtained by IMDA. The unsaturated ketone **2.150** would be synthesized by functionalization of the diol **2.151**, which is easily generated by sequential carbometallation-condensation reactions. In this case, the allyl group could be attached in the starting material as shown in Scheme 2.44.



Scheme 2.44 Retrosynthetic Analysis for ABC Core

The actual synthetic route for the strategy is depicted in Scheme 2.45. Hex-5-en-2-yn-1-ol **2.153**, derived from commercially available propargyl alcohol, was subjected to a carbometallation reaction promoted by $MgCl_2$. The resulting chelate reacted with diene aldehyde **2.48** in ether to yield diol **2.151** in acceptable yields. Silylation of **2.151** using TBSCl and DMAP in CH_2Cl_2 effected selective protection of the primary hydroxyl group. Treatment of alcohol **2.154** with MeI and NaH in THF provided the ether derivative **2.155** in 89% yield. Removal of the triethylsilyl group was achieved using TBAF in THF, and the resulting alcohol **2.156** was subjected to mild oxidation with IBX and DMSO in THF. The Grignard addition of vinylmagnesium chloride with **2.157**, followed by IBX/DMSO oxidation afforded ketone **2.150** in good yield. In the presence of a Lewis acid such as Et_2AlCl or $BF_3{\cdot}OEt_2$, **2.150** reacted intramolecularly to afford the Diels-Alder adduct **2.126** as a single diastereomer in good yield.



Scheme 2.45 Preparation of ABC Skeleton

Although it cannot be generalized for all Lewis acids, the observed stereoselectivity could be attributed to a complexation of the Et_2AlCl between the C2 carbonyl and C9 methoxy substituents as depicted in Figure 2.8.

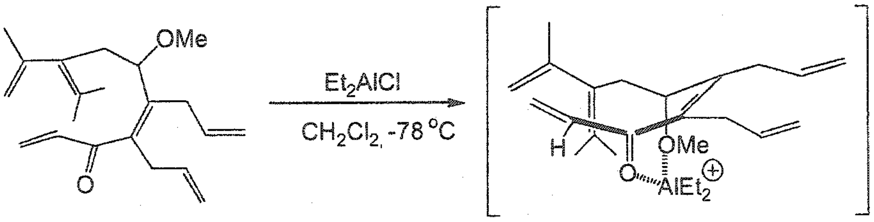
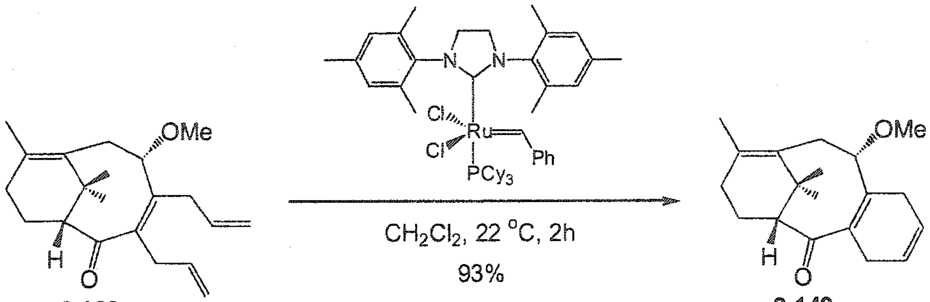


Figure 2.8 Chelation Control of IMDA Transition State

The key intermediate **2.126**, having a complete AB ring-system and bearing two allyl chains, was now ready for ring closing transformation (Scheme 2.46). Under the influence of Grubbs catalyst **2.68**, this compound underwent a RCM reaction to furnish **2.149** in 93% yield. The reaction was successful; the ABC ring system of taxanes was obtained in high yield under very mild reaction conditions and only two hours was needed for the reaction. The resulting triene was very stable and the C-ring did not aromatize even after long periods of storage.



2.126

CH_2Cl_2, 22 °C, 2h

93%

2.149

Scheme 2.46 RCM for ABC Core of Taxanes

The remarkable stability of **2.149** allowed the recrystallization of the product and a single-crystal X-ray structure of this compound was obtained. The molecular structure shows the proper arrangement of taxanes with a concave structure and the methoxy group in α configuration (Figure 2.9).

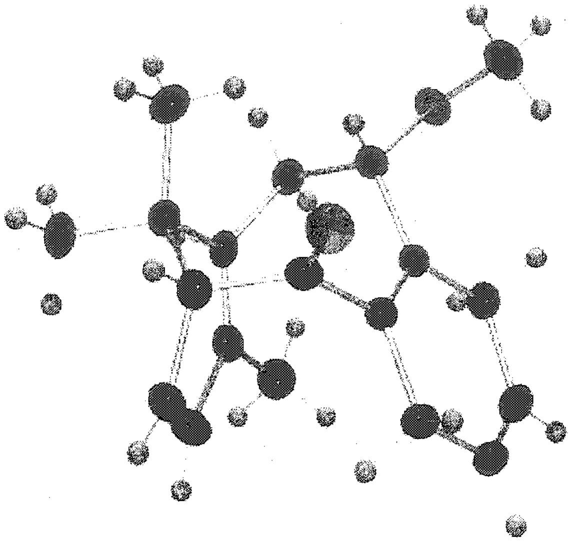


Figure 2.9 X-Ray Structure of **2.149**

2.4.6. Attempts to Functionalize the ABC System

According to this X-rays analysis, the lower face of the molecule seemed to be quite hindered. In addition, the molecule contains functional groups that could allow possible chemical modifications. Based on these observations, further functionalization of the molecule was planned in order to obtain a taxane derivative for biological testing. Several transformations were envisioned (Figure 2.10). For instance, the reduction of the ketone group in ring B **(a)** to produce the α alcohol appeared promising, since the lower face would be restricted by the concave structure. Consequently, the hydride would approach from the opposite face of the molecule, leading to the desired diastereomer. The next consideration was the functionalization of the C ring. Due to the presence of the 1,4-diene, the allylic oxidation **(b)** may have been plausible with the increased risk of potential aromatization. The epoxidation of the isolated double bond in ring C was also considered **(c)**. Finally, the alkylation of the conjugated double bond **(d)** appeared viable by a Michael addition reaction. For similar reasons, it was expected that the alkylating agent would attack on the upper face affording the desired β stereochemistry of the methyl group.

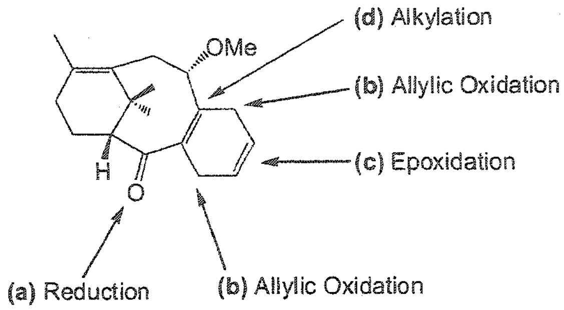
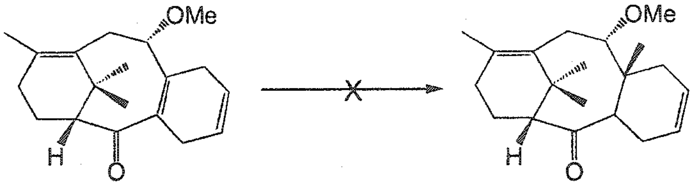


Figure 2.10 Functionalization of ABC Framework

The methylation of the α,β-unsaturated ketone was chosen for an initial attempt (Scheme 2.47). Unfortunately, the reaction did not proceed despite different alkylating agents[165] that were used (Table 2.6).



2.149

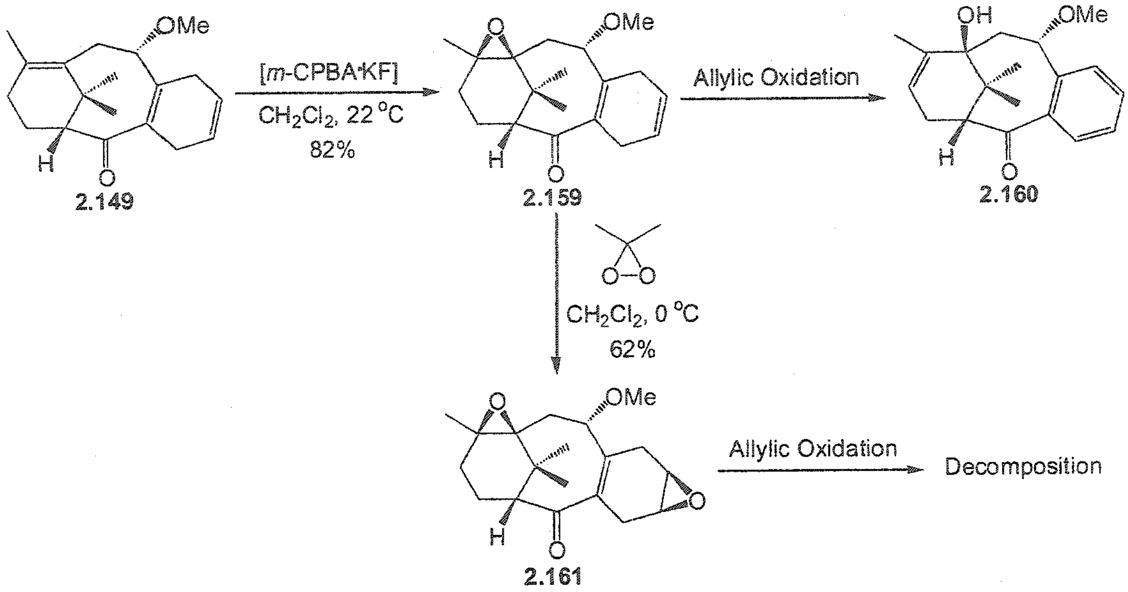
2.108

Scheme 2.47 ABC Alkylation Trials

Entry	Reagent	T (°C)
1	CuI, CH_3MgBr, Et_2O	-78
2	MeCu·BF_3, Et_2O	-78

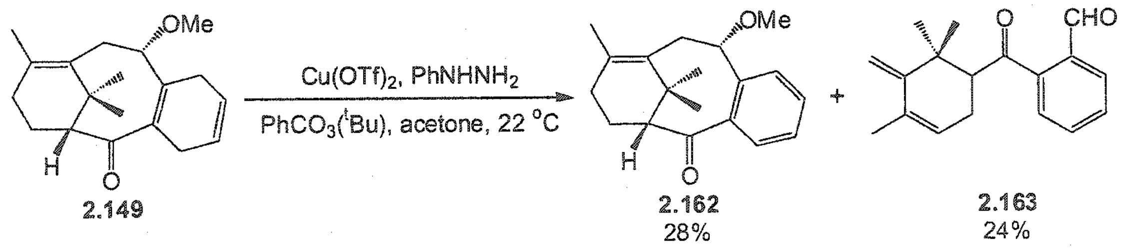
Table 2.6 Alkylation Attempts

On the other hand, the allylic oxidation[166-168] led to aromatization of the C ring and opening of the protective epoxide group in ring A of **2.159** (Scheme 2.48). In an attempt to perform the allylic oxidation on diepoxide **2.161**, the molecule underwent decomposition.



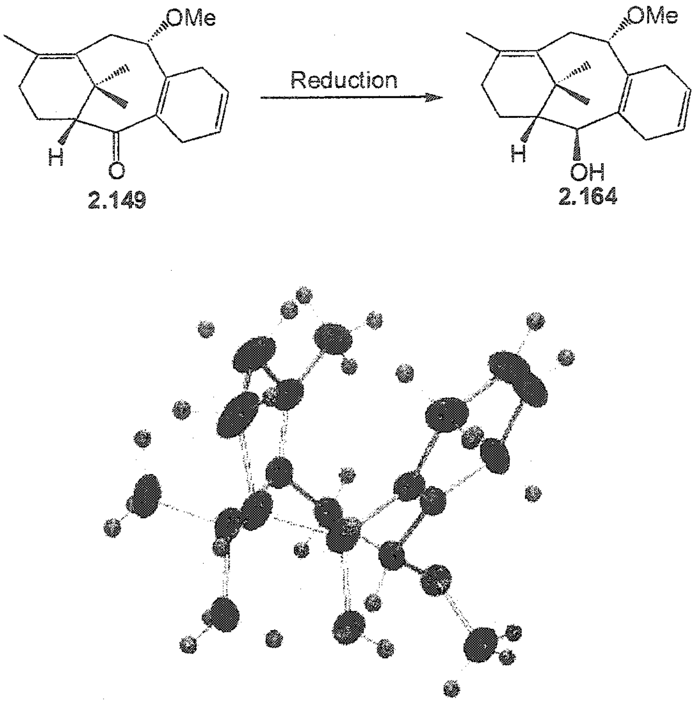
Scheme 2.48 Allylic Oxidation in ABC system

A very mild method for allylic oxidation was recently reported[169] in the literature (Scheme 2.49). Nevertheless, when the tricyclic system **2.149** was subjected to those conditions, the outcome was the aromatization of ring C (**2.162**) and ring opening of B to afford **2.163**.



Scheme 2.49 Copper-Catalyzed Allylic Oxidation

The next attempt consisted in the reduction of the ketone in B ring (Scheme 2.50). Unfortunately, the actual reduction reaction to produce the corresponding alcohol was unsatisfactory and occurred preferentially from the opposite face of the molecule. The product obtained was unlike Taxol® molecule since the alcohol is in the β position. This finding prompted the exploration of various reducing agents (Table 2.7); nevertheless, the results were equally disappointing.



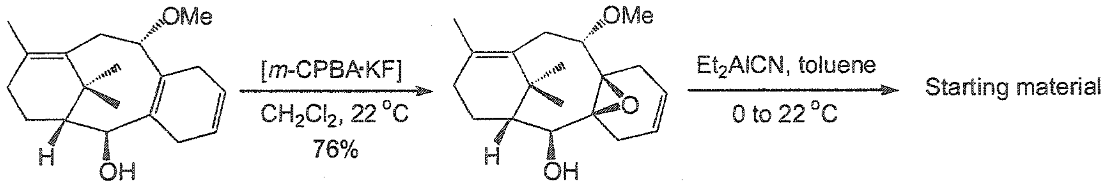
2.149 **2.164**

Scheme 2.50 Reduction of ABC System

Entry	Reagent	T (°C)	Yield (%)
1	$LiAlH_4$/THF	0 to 22	68
2	DIBAL-H/ Et_2O	22	61
3	$LiAl[OC(CH_3)_3]_3H$	0 to 22	30

Table 2.7 Reagents for Reduction

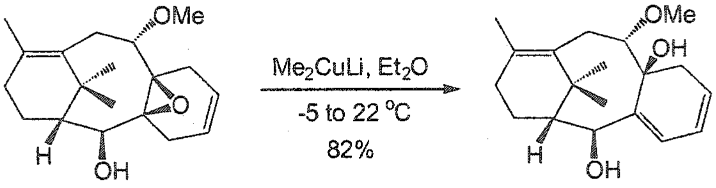
Despite the incorrect stereochemistry in **2.164**, we decided to utilize this intermediate for subsequent transformations. This decision relied on the fact that the stereochemistry might be inverted in a later steps, by Mitsunobu esterification for example. Therefore, the alcohol **2.164** was used as a directing group to perform the epoxidation in ring B (Scheme 2.51). It was planned that opening of the epoxide would provide the substituent group at C8 and would prevent aromatization of the C ring, which was observed in allylic oxidation trials. Lamentably, the opening of the epoxy alcohol at ring B did not take place upon treatment with Et_2AlCN, and methanolysis was also fruitless.



2.164 **2.165**

Scheme 2.51 Functionalization of Epoxy Alcohol

In an attempt to achieving the ring opening and simultaneously install the methyl group at the C8 position, an alternative method of alkylation was examined, as shown in Scheme 2.52. Unfortunately, when the epoxide **2.165** was treated with methyllithium, the outcome was the opening of the epoxide and formation of the diol **2.166** although in good yield.



2.165 **2.166**

Scheme 2.52 Epoxy Alcohol Opening

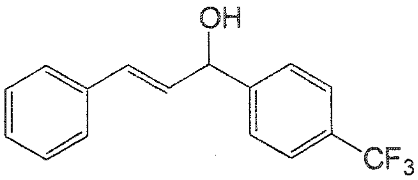
2.5. CONCLUSIONS

The carbometallation-cycloaddition sequence was successfully applied for the construction of the ABC core using readily available starting materials. This sequence has proven to be a very versatile strategy that allows the introduction of different substituents in early stages of the synthesis. The AB ring system of taxanes with different functionalities has been obtained. In an effort to overcome the inconveniences encountered during the development of this project, the initial RCM strategies for taxanes were modified.

These modifications led to the synthesis of the tricyclic core of the taxanes by a novel carbometallation-cycloaddition-RCM sequence. The skeleton had the proper taxane core and was obtained under very mild conditions in high yield. Additionally, the further functionalization of AB and ABC ring-systems of taxanes were both investigated. As it has been shown, implementation of the different methodologies for the functionalization of the tricyclic system has been challenging. This could be mainly attributed to steric factors that hampered any attack on top and north perimeter of the molecule. To circumvent these problems, the functionalization for this molecule, should be considered at an early stage to prevent the aromatization of ring C by eliminating the conjugated double bond after cycloaddition.

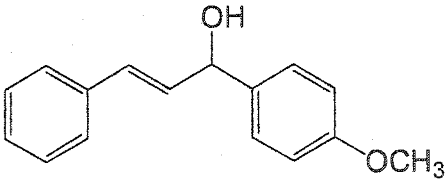
3. EXPERIMENTAL

General. Proton magnetic resonance spectra (^{1}H NMR) were obtained at 500 MHz with a Bruker AMX500, at 300 MHz with a Bruker Avance 300, or at 200 MHz with a Varian Gemini spectrometer. Carbon magnetic resonance spectra (^{13}C NMR) were obtained at 125 MHz (Bruker 500 MHz), 75 MHz (Bruker 300 MHz) and 50 MHz (Varian 200 MHz). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (δ scale). Coupling constants are reported in Hz, and the multiplicity abbreviations are reported using singlet (s), doublet (d), triplet (t), quartet (q), broad (br), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of doublet of doublet of doublets (dddd), and multiplet (m). Special analyses were performed by the first order approximations and were based on shift correlation spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC), and (DEPT) experiments. Mass spectra (MS), electronic impact (EI) were determined on a V.G. micromass 7070 HS instrument using ionization energy of 70 eV. Mass spectra, Electron Spray Ionization (ESI), was recorded on a Micromass Qualtro LC instrument having a capillary voltage of 3.5-4.5 kv, methanol was used as solvent. Elemental analyses (quantitative organic micro combustion analysis) were performed at M-H-W Laboratories, Phoenix, Arizona, USA.[170] Melting points were determined in capillary tubes with a Thomas-Hoover Unit-Melt apparatus and are uncorrected. Infrared (IR) spectra were obtained either as neat films, or as a thin film of a dichloromethane solution of the compound on sodium chloride discs. All IR spectra were recorded on a Bonem Michelson 100 Fourier transform infrared spectrometer (FT-IR) and the data are reported in reciprocal centimeters (cm^{-1}). Unless otherwise stated, all non-aqueous reactions were performed under an atmosphere of dry nitrogen in flame or oven dried glassware equipped with a magnetic stir bar and a rubber septum. Anhydrous diethyl ether (ether) and anhydrous tetrahydrofuran (THF) were freshly distilled from benzophenone/sodium. Dry benzene, toluene, dimethylformamide (DMF), dichloromethane (CH_2Cl_2), triethylamine (Et_3N) and diisopropylamine, were distilled from NaH or CaH. Cyclohexane was reagent grade stored over molecular sieves. All commercial starting materials were purchased from Aldrich Chemical Company unless otherwise stated. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Reactions were monitored by analytical thin layer chromatography (TLC) using commercial aluminum sheets pre-coated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). The TLC spots were detected using ultraviolet light and by heating the TLC after treatment with the corresponding visualization reagent. The visualization reagents used for compound detection included a 5% solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v), p-anisaldehyde staining solution (80 mL 95% ethanol, 2.9 mL sulfuric acid, 0.86 mL acetic acid, 2.1 mL *p*-anisaldehyde). The standard workup procedure involved addition of either saturated aqueous NH_4Cl solution or saturated aqueous $NaHCO_3$ solution and stirring for 20 min. The organic layer was separated and the aqueous phase extracted with either diethyl ether (ether) or dichloromethane (CH_2Cl_2). The combined organic layers were washed with brine, dried, filtered and concentrated. Solutions in organic solvents were dried over anhydrous magnesium sulphate ($MgSO_4$) or anhydrous sodium sulphate (Na_2SO_4) and solvent removed under reduced pressure using a Büchi rotary evaporator connected to air vacuum. Product purification by flash column chromatography was performed using E. Merck Silica Gel (230-400 mesh) and a mixture of petroleum ether (PE) and either diethyl ether (E) or dichloromethane (CH_2Cl_2) as eluant. Trace solvents were removed on a vacuum pump and except otherwise noted; all compounds were obtained as colourless oils.



3-Phenyl-1-(4-trifluoromethylphenyl)-prop-2-en-1-ol (1.91).
n-Butyllithium (1.98 mL, 4.9 mmol, 1.1 eq. 2.4 M in THF) was added to a solution of 4-bromobenzotrifluoride (0.6 mL, 4.4 mmol, 1.0 eq.) in THF (15 mL) at -78 °C. The solution was stirred at the same temperature for 1 h, after which cinnamaldehyde (0.6 mL, 4.4 mmol, 1.0 eq.) was added. The resulting solution was then allowed to warm to 22 °C and then was re-cooled to 0 °C. Afterwards, the standard workup with NH_4Cl, ether (2x15 mL) and Na_2SO_4 was carried out. Purification by flash column chromatography (85/15, PE/E) afforded the title compound as a colorless oil (0.96 g, 78%).

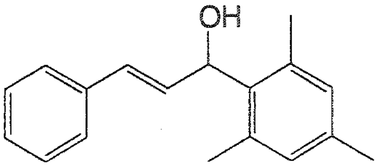
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (d, *J* = 8.2, 2H), 7.54 (d, *J* = 8.3, 2H), 7.38 (d, *J* = 7.9, 2H), 7.31 (t, *J* = 7.5, 2H), 7.25 (t, *J* = 7.5, 1H), 6.69 (d, *J* = 15.8, 1H), 6.32 (dd, *J* = 15.8, 6.9, 1H), 5.42 (d, *J* = 6.8, 1H), 2.29 (s, 1H); ^{13}C NMR δ 146.5, 136.1, 131.6, 130.7, 128.6, 128.1, 126.6, 126.5, 125.5, 125.5, 125.5, 74.6; HRMS [M^+] calcd. for $C_{16}H_{13}OF_3$ 278.0918, found 278.0922; IR (neat) 3329, 3084-2863, 1620.



1-(4-Methoxyphenyl)-3-phenylprop-2-en-1-ol (1.92).
n-Butyllithium (2.2 mL, 5.9 mmol, 1.1 eq., 2.4 M in THF) was added to a solution of 4-bromoanisole (0.7 mL, 5.4 mmol, 1.0 eq.) in THF (15 mL) at -78 °C. The solution was stirred at the same temperature for 1 h, and cinnamaldehyde (0.7 mL, 5.4 mmol, 1.0 eq.) was added. The reaction mixture was then warmed to 22 °C and was re-cooled to 0 °C. The standard workup with NH_4Cl, ether (2x15 mL) and Na_2SO_4

was then performed. The compound was purified by flash column chromatography (8/2, PE/E) and isolated as a colorless oil (1.25 g, 98%).

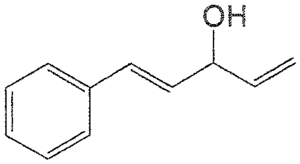
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52-7.30 (m, 7H), 7.06 (d, *J* = 7.2, 1H), 7.04 (d, *J* = 7.2, 1H), 6.75-6.70 (m, 1H), 6.55-6.47 (m, 1H), 5.23-5.16 (m, 1H), 3.89 (d, 3H), 1.75 (s, 1H); ^{13}C NMR δ 141.7, 136.9, 131.3, 130.9, 128.7, 128.6, 128.6, 126.7, 126.7, 114.1, 78.7, 55.3; HRMS [M$^+$] calcd. for $C_{16}H_{16}O_2$ 240.1150, found 240.1154; IR (neat) 3386, 3027-2836, 1610.



3-Phenyl-1-(2,4,6-trimethylphenyl)-prop-2-en-1-ol (1.93).

n-Butyllithium (2.3 mL, 5.5 mmol, 1.1 eq., 2.4 M in THF.) was added to a solution of 2-bromomesitylene (0.8 mL, 5.0 mmol, 1.0 eq.) in THF (15 mL) at -78 °C. The solution was stirred at the same temperature for 1 h, and cinnamaldehyde (0.63 mL, 5.0 mmol, 1.0 eq.) was added. The reaction mixture was allowed to reach 22 °C and was re-cooled to 0 °C. The standard workup with NH_4Cl, ether (2x15 mL) and Na_2SO_4 was then performed. Purification by flash column chromatography (9/1, PE/E) afforded the title compound as a colorless oil (1.26 g, 100 %).

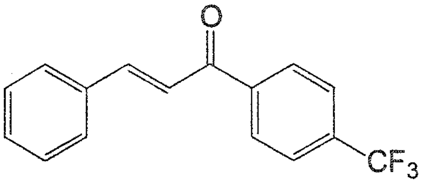
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (dd, *J* = 8.3, 1.0, 2H), 7.32 (t, *J* = 7.7, 2H), 7.24 (t, *J* = 7.6, 1H), 6.88 (s, 2H), 6.54 (t, 2H), 5.88 (d, 1H), 2.45 (s, 6H), 2.30 (s, 3H), 2.16 (s, 1H); ^{13}C NMR δ 137.1, 136.6, 135.2, 130.4, 130.1, 129.5, 128.6, 128.5, 127.4, 126.5, 71.2, 20.8, 20.6; HRMS [M$^+$] calcd. for $C_{18}H_{20}O$ 252.1514, found 252.1495; IR (neat) 3352, 3058-2860.



1-Phenylpenta-1,4-dien-3-ol (1.95).

Vinylmagnesium chloride (11.9 mL, 16.7 mmol, 1.1 eq., 1.4 M in THF.) was added to a solution of cinnamaldehyde (1.9 mL, 15.1 mmol, 1.0 eq.) in THF (10 mL) at -78 °C. The resulting solution was allowed to warm to 22 °C and then was re-cooled to 0 °C, followed by the standard workup with NH_4Cl, ether (2x15 mL) and Na_2SO_4. Purification by flash column chromatography (85/15, PE/E) afforded the title compound as a colorless oil (1.6 g, 66%).

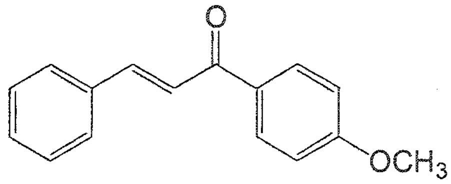
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (dd, *J* = 7.1, 1.7, 2H), 7.32 (t, *J* = 7.0, 2H), 7.26 (t, *J* = 7.3, 1H), 6.60 (d, *J* = 15.9, 1H), 6.25 (dd, *J* = 15.9, 6.5, 1H), 5.99 (ddd, *J* = 17.2, 10.4, 5.9, 1H), 5.35 (dd, *J* = 17.2, 1.4, 1H), 5.20 (dd, *J* = 10.4, 1.3, 1H), 4.80 (t, *J* = 5.8, 1H), 2.73 (s, 1H); ^{13}C NMR δ 139.4, 136.6, 130.7, 130.5, 128.6, 127.7, 126.6, 115.3, 73.7; DEPT δ -115.3; HRMS [M$^+$] calcd. for $C_{11}H_{12}O$ 160.0888, found 160.0875; IR (neat) 3355, 3082-2855.



3-Phenyl-1-(4-trifluoromethylphenyl)-propenone (1.98).

3-Phenyl-1-(4-trifluoromethylphenyl)-prop-2-en-1-ol **1.91** (0.5 g, 1.8 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (18 mL) and MnO_2 (2.0 g, 23.4 mmol, 13.0 eq.) was added. The reaction mixture was stirred at 22 °C until the reaction was complete. The reaction mixture was then filtered through a Celite pad and washed with CH_2Cl_2 (3x10 mL). After evaporation, the product was crystallized from hexane to afford the title compound as a bright yellow solid, m.p. 121-122 °C (0.26 g, 53%).

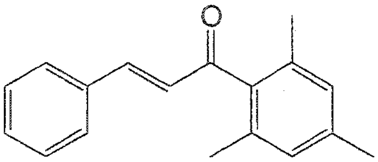
^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.08 (d, *J* = 8.1, 2H), 7.81 (d, *J* = 15.7, 1H), 7.74 (d, *J* = 7.3, 2H), 7.63 (dd, *J* = 7.5, 2,1, 2H), 7.47 (d, *J* = 15.7, 1H), 7.42-7.41 (m, 3H); ^{13}C NMR (50 MHz) δ 146.7, 131.6, 129.7, 129.4, 129.2, 126.3, 126.2, 126.2, 122.1; HRMS [M$^+$] calcd. for $C_{16}H_{11}OF_3$ 276.0762, found 276.0777; IR (neat) 3109-3034, 1666.



1-(4-Methoxyphenyl)-3-phenylpropenone (1.100).

Manganese(IV) oxide (2.35 g, 27.1 mmol, 13.0 eq.) was added to a solution of 1-(4-methoxyphenyl)-3-phenylprop-2-en-1-ol **1.92** (0.5 g, 2.1 mmol, 1.0 eq.) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at 22 °C until the reaction was complete. The suspension was then filtered through Celite pad and thoroughly washed with CH_2Cl_2 (3x10 mL). Evaporation followed by crystallization from hexane, afforded the title compound as a white solid, m.p. 105-106 °C (0.29 g, 58%).

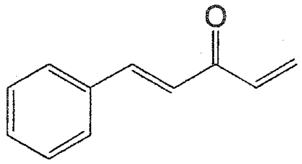
^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.01 (d, *J* = 8.0, 2H), 7.77 (d, *J* = 15.6, 1H), 7.60 (d, *J* = 3.7, 2H), 7.51 (d, *J* = 15.6, 1H), 7.36 (s, 3H), 6.93 (d, *J* = 7.9, 2H), 3.82 (s, 3H); ^{13}C NMR (50 MHz) δ 144.6, 131.5, 130.9, 129.5, 129.2, 129.0, 128.3, 127.2, 122.5, 114.5, 56.1; HRMS [M$^+$] calcd. for $C_{16}H_{14}O_2$ 238.0994, found 238.0981; IR (neat) 3078-2941, 1655.



3-Phenyl-1-(2,4,6-trimethylphenyl)-propenone (1.102).

3-Phenyl-1-(2,4,6-trimethylphenyl)-prop-2-en-1-ol **1.93** (0.5 g, 1.98 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (15 mL) and MnO_2 (2.59 g, 29.8 mmol, 15.0 eq.) was added. The reaction mixture was stirred at 22 °C until the reaction was complete. The reaction mixture was then filtered through a celite pad and washed with CH_2Cl_2 (3x10 mL). Purification by flash column chromatography (95/5, PE/E) afforded the title compound as a colorless oil (0.49 g, 100%).

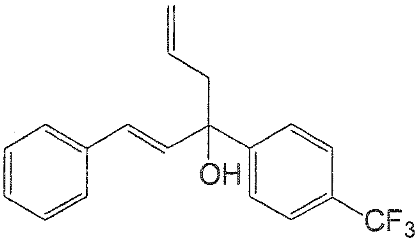
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (dd, *J* = 6.8, 2.0, 2H), 7.37-7.36 (m, 3H), 7.21 (d, *J* = 16.3, 1H), 6.94 (d, *J* = 16.2, 1H), 6.89 (s, 2H), 2.33 (s, 3H), 2.21 (s, 6H); ^{13}C NMR δ 146.5, 138.3, 137.2, 134.5, 134.1, 130.7, 128.9, 128.4, 128.4, 21.1, 19.3; HRMS [M^+] calcd. for $C_{18}H_{18}O$ 250.1358, found 250.1364; IR (neat) 3059-2859, 1644.



1-Phenylpenta-1,4-dien-3-one (1.104).

Manganese(IV) oxide (4.08 g, 46.88 mmol, 15.0 eq.) was added to a solution of 1-phenylpenta-1,4-dien-3-ol **1.95** (0.5 g, 3.13 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at 22 °C for 24 h. The suspension was then filtered through a Celite pad and thoroughly washed with CH_2Cl_2 (3x10 mL). Purification by flash column chromatography (97/3, PE/E) afforded the title compound as a colorless oil (0.38 g, 77%).

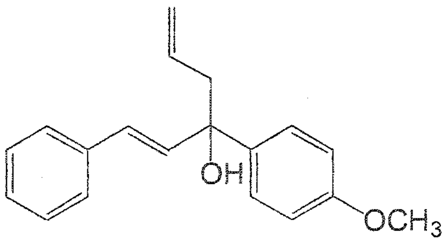
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (d, *J* = 16.0, 1H), 7.55-7.54 (m, 2H), 7.37-7.35 (m, 3H), 6.98 (d, *J* = 16.0, 1H), 6.67 (dd, *J* = 17.4, 10.7, 1H), 6.36 (dd, *J* = 17.5, 1.2, 1H), 5.85 (dd, *J* = 10.7, 1.2, 1H); ^{13}C NMR δ 189.4, 143.9, 135.4, 134.6, 130.5, 128.9, 128.4, 128.3, 124.1; DEPT δ -128.4; HRMS [M$^+$] calcd. for $C_{11}H_{10}O$ 158.0732, found 158.0720; IR (neat) 3084-3026, 1667.



1-Phenyl-3-(4-trifluoromethylphenyl)-hexa-1,5-dien-3-ol (1.108).

Allyl bromide (0.3 mL, 2.9 mmol, 3.98 eq.) was added to a solution of 3-phenyl-1-(4-trifluoromethylphenyl)-propenone **1.98** (0.2 g, 0.7 mmol, 1.0 eq.) in DMF/H_2O (2/1, 2 mL). The suspension was cooled to 0 °C and indium metal powder (0.17 g, 1.5 mmol, 2.0 eq.) was added in small portions. The reaction mixture was then warmed to 60 °C and stirred for 4 h. After cooling to 22 °C, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and poured into a flask with ether (50 mL). The suspension was then filtered through a silica gel pad, washed thoroughly with ether (2x20 mL) and purified by flash column chromatography (9/1, PE/E). The title compound was obtained as colorless oil (0.22 g, 96%).

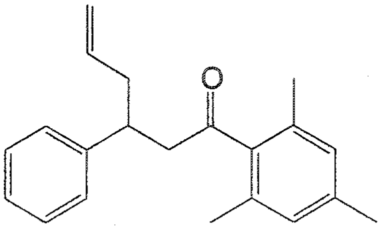
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65-7.60 (m, 4H), 7.37 (d, *J* = 7.5, 2H), 7.31 (t, *J* = 7.5, 2H), 7.24 (t, *J* = 7.3, 1H), 6.66 (d, *J* = 16.0, 1H), 6.50 (d, *J* = 16.0, 1H), 5.70 (dddd, *J* = 17.2, 10.2, 7.2, 7.2, 1H), 5.25 (d, *J* = 10.3, 1H), 5.20 (d, *J* = 17.9, 1H), 2.80 (d, *J* = 7.3 2H), 2.39 (s, 1H); ^{13}C NMR δ 149.3, 136.4, 134.3, 132.4, 129.2, 128.6, 127.8, 126.6, 125.9, 125.3, 125.2, 125.2, 120.7, 75.5, 47.1; HRMS [M$^+$-H_2O] calcd. for $C_{19}H_{15}F_3$ 300.1126, found 300.1130; IR (neat) 3553, 3463, 3081-2855.



3-(4-Methoxyphenyl)-1-phenylhexa-1,5-dien-3-ol (1.109).

Allyl bromide (0.73 mL, 8.36 mmol, 3.98 eq.) was added to a solution of 1-(4-methoxyphenyl)-3-phenylpropenone **1.100** (0.5 g, 2.1 mmol, 1.0 eq.) in DMF/H_2O (2/1, 5 mL). The suspension was cooled to 0 °C and indium metal powder (0.48 g, 4.2 mmol, 2.0 eq.) was added in small portions. The reaction mixture was stirred for 24 h at 22 °C, diluted with CH_2Cl_2 (10 mL) and poured into a flask with ether (50 mL). The suspension was filtered through a silica gel pad, washed thoroughly with ether (2x10 mL) and purified by flash column chromatography (8/2, PE/E). The title compound was obtained as colorless oil (0.18 g, 31%).

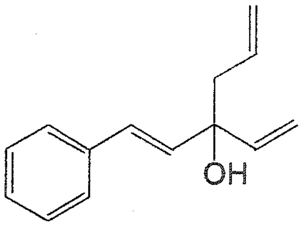
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48-7.25 (m, 7H), 6.94 (d, *J* = 8.9, 2H), 6.68 (d, *J* = 16.0, 1H), 6.55 (d, *J* = 16.0, 1H), 5.78 (dddd, *J* = 17.2, 10.1, 7.2, 7.2, 1H), 5.23 (dd, *J* = 17.0, 2.0, 1H), 5.20 (dd, *J* = 10.0, 2.0, 1H), 3.81 (s, 3H), 2.86-2.77 (m, 2H), 2.41 (s, 1H); ^{13}C NMR δ 158.6, 137.5, 136.9, 135.5, 133.4, 128.6, 128.2, 127.5, 126.8, 126.6, 119.8, 113.7, 75.5, 55.2, 47.1; HRMS [M^+-H_2O] calcd. for $C_{19}H_{18}O$ 262.1358, found 262.1368; IR (neat) 3354, 3470, 3078-2836.



3-Phenyl-1-(2,4,6-trimethylphenyl)-hex-5-en-1-one (1.110).

Allyl bromide (0.3 mL, 3.2 mmol, 3.98 eq.) was added to a solution of 3-phenyl-1-(2,4,6-trimethylphenyl)-propenone **1.102** (0.2 g, 0.8 mmol, 1.0 eq.) in DMF/H_2O (2/1, 2 mL). The suspension was cooled to 0 °C and indium metal powder (0.18 g, 1.6 mmol, 2.0 eq.) was added in small portions. The reaction mixture was stirred for 24 h at 22 °C, diluted with CH_2Cl_2 (10 mL) and poured into a flask with ether (50 mL). The suspension was filtered through a silica gel pad, washed thoroughly with ether (2x10 mL) and purified by flash column chromatography (98/2, PE/E). The title compound was obtained as colorless oil (19 mg, 8%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27-7.15 (m, 5H), 6.75 (s, 2H), 5.69 (dddd, *J* = 17.2, 10.1, 7.0, 7.0, 1H), 4.99 (d, *J* = 16.9, 1H), 4.97 (d, *J* = 10.1, 1H), 3.48-3.42 (m, 1H), 3.04 (d, *J* = 2.3, 1H), 3.02 (d, *J* = 3.7, 1H), 2.49-2.39 (m, 2H), 2.23 (s, 3H), 1.96 (s, 6H); ^{13}C NMR δ 208.8, 144.2, 139.4, 138.2, 136.2, 136.2, 132.6, 128.4, 128.3, 127.8, 126.3, 116.8, 50.7, 40.6, 39.8, 20.9, 18.8; HRMS [M^+] calcd. for $C_{21}H_{24}O$ 292.1827, found 292.1840; IR (neat) 3065-2857, 1699.

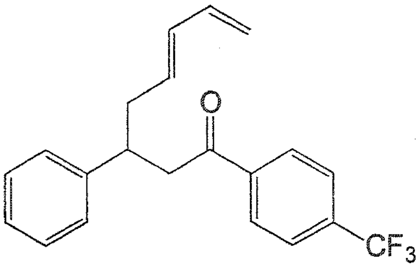


1-Phenyl-3-vinylhexa-1,5-dien-3-ol (1.111).

Allyl bromide (0.28 mL, 3.27 mmol, 3.98 eq.) was added to a solution of 1-phenylpenta-1,4-dien-3-one **1.104** (132 mg, 0.8 mmol, 1.0 eq.) in DMF/H_2O (2/1, 1.5 mL). The suspension was cooled at 0 °C and indium metal powder (190 mg, 1.6 mmol, 2.0 eq.) was added in portions. Reaction mixture was stirred for 24 h at 22 °C, diluted with CH_2Cl_2 (10 mL) and poured into a flask with ether (50 mL). The suspension was filtered through a silica gel pad washed thoroughly with ether (2x10 mL) and purified by flash column chromatography (95/5, PE/E). The title compound was obtained as a colorless oil (90 mg, 54%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, *J* = 7.8, 1H), 7.31 (t, *J* = 7.7, 1H), 7.23 (t, *J* = 7.8, 1H), 6.64 (d, *J* = 16.0, 1H), 6.30 (d, *J* = 16.0, 1H), 6.03 (dd, *J* = 17.3, 10.7, 1H), 5.83 (dddd, *J* = 16.5, 10.7, 7.4, 7.4, 1H), 5.34 (dd, *J* = 17.3, 1.1, 1H), 5.19 (d, *J* =

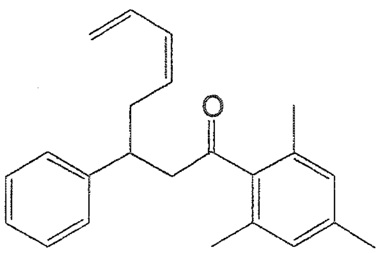
16.7, 1H), 5.16 (d, *J* = 10.1, 2H), 2.48 (d, *J* = 7.8, 2H), 2.0 (s, 1H); ^{13}C NMR δ 142.3, 137.8, 133.6, 132.9, 128.6, 128.5, 127.5, 126.5, 119.6, 113.4, 74.7, 45.9; DEPT δ -119.6, -113.4, -45.9; HRMS [M^+-H_2O] calcd. for $C_{14}H_{14}$ 182.1096, found 182.1101; IR (neat) 3557, 3446, 3079-2857.



3-Phenyl-1-(4-trifluoromethylphenyl)-octa-5,7-dien-1-one (1.99).

5-Bromopenta-1,3-diene (0.21 g, 1.4 mmol, 3.98 eq.) was added to a solution of 3-phenyl-1-(4-trifluoromethylphenyl)-propenone **1.98** (0.1 g, 0.4 mmol, 1.0 eq.) in DMF/H_2O (2/1, 1 mL). The suspension was cooled to 0 °C and 10 μL of HCl was added, followed by the addition of indium metal powder (83 mg, 0.7 mmol, 2.0 eq.) in portions. The reaction mixture was then warmed to 60 °C and stirred for 4 h. After cooling to 22 °C, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and poured into a flask with ether (25 mL). The suspension was filtered through a silica gel pad, washed thoroughly with ether (2x10 mL) and purified by flash column chromatography (98/2, PE/E). The title compound was obtained as colorless oil (82 mg, 66%).

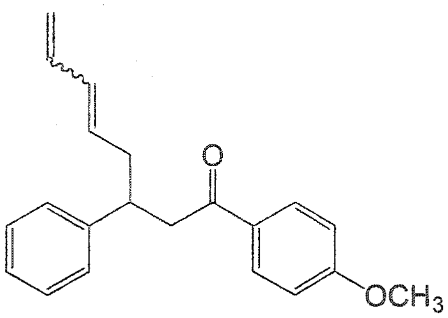
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (d, *J* = 8.1, 2H), 7.67 (d, *J* = 8.2, 2H), 7.30-7.18 (m, 5H), 6.24 (ddd, *J* = 16.9, 10.3, 10.3, 1H) 6.05 (dd, *J* = 15.2, 10.5, 1H), 5.58 (ddd, *J* = 15.0, 7.5, 7.5, 1H), 5.07 (dd, *J* = 16.9, 1.3, 1H), 5.02 (dd, *J* = 10.2, 1.3, 1H), 3.52-3.46 (m, 1H), 3.31 (d, *J* = 7.0, 2H), 2.51 (t, *J* = 7.3, 2H); ^{13}C NMR δ 197.9, 143.9, 136.8, 133.3, 129.4, 128.5, 127.5, 127.4, 126.6, 125.6, 125.6, 125.5, 125.5, 44.7, 41.1, 39.4, 34.3; MS calcd. for $C_{21}H_{19}F_3O$ 344, found [M^++NH_4]$^+$ 362 (100); IR (neat) 3086-2839, 1693.



3-Phenyl-1-(2,4,6-trimethylphenyl)-octa-5,7-dien-1-one (1.103).

5-Bromopenta-1,3-diene (0.47 g, 3.2 mmol, 3.98 eq.) was added to a solution of 3-phenyl-1-(2,4,6-trimethylphenyl)-propenone **1.102** (0.2 g, 0.8 mmol, 1.0 eq.) in DMF/H_2O (2/1, 2 mL). The suspension was cooled to 0 °C and indium metal powder (0.184 g, 1.6 mmol, 2.0 eq.) was added in portions. The reaction mixture was stirred for 24 h at 22 °C. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and poured into a flask with ether (50 mL). The suspension was filtered through a silica gel pad, washed thoroughly with ether (2x20 mL) and purified by flash column chromatography (99/1, PE/E). The title compound was obtained as colorless oil (15 mg, 6%).

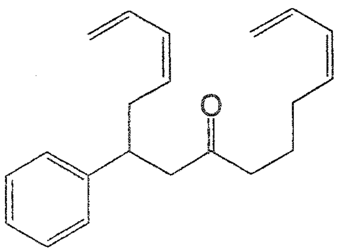
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28-7.16 (m, 5H), 6.76 (s, 2H), 6.60 (ddd, *J* = 17.0, 10.6, 10.6, 1H), 6.02 (t, *J* = 10.9, 1H), 5.35 (ddd, *J* = 10.2, 8.0, 8.0, 1H), 5.17 (dd, *J* = 16.8, 1.8, 1H), 5.08 (d, *J* = 9.8, 1H), 3.44 (t, *J* = 7.3, 1H), 3.05 (t, br, 2H), 2.73-2.67 (m, 1H), 2.46 (q, 1H), 2.24 (s, 3H), 1.98 (d, br, 6H); ^{13}C NMR δ 208.8, 132.0, 130.9, 129.59, 128.9, 128.5, 128.4, 128.4, 128.0, 127.8, 126.4, 126.4, 117.6, 50.7, 40.3, 34.3, 20.9, 18.9; MS calcd. for $C_{23}H_{26}O$ 318, found $[M^+ + NH_4]^+$ 336 (100); IR (neat) 3084-2859, 1698.



1-(4-Methoxyphenyl)-3-phenylocta-5,7-dien-1-one (1.101).

5-Bromopenta-1,3-diene (0.39 g, 2.7 mmol, 3.98 eq.) was added to a solution of 1-(4-methoxy-phenyl)-3-phenyl-propenone **1.100** (0.16 g, 0.7 mmol, 1.0 eq.) in DMF/H_2O (2/1, 2 mL). The suspension was cooled to 0 °C and indium metal powder (0.154 g, 1.3 mmol, 2.0 eq.) was added in portions. The reaction mixture was stirred for 24 h at 22 °C. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and poured into a flask with ether (50 mL). The suspension was filtered through a silica gel pad, washed thoroughly with ether (2x20 mL) and purified by flash column chromatography (97/3, PE/E). The title compound was obtained as colorless oil (35 mg, 17%).

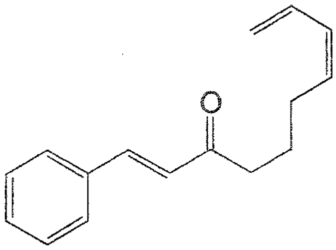
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (dd, *J* = 9.0, 3.0, 4H), 7.29-7.15 (m, 10H), 6.88 (dd, *J* = 9.0, 1.3, 4H), 6.60 (ddd, *J* = 16.8, 10.6, 10.6, 1H), 6.22 (ddd, *J* = 17.0, 10.2, 10.2, 1H), 6.05-5.97 (m 2H), 5.59-5.53 (m, 1H), 5.34 (q, 1H), 5.14 (dd, *J* = 17.7, 1.9, 1H), 5.07 (d, *J* = 17.8, 1H), 5.04 (d, *J* = 17.8, 1H), 4.93 (d, *J* = 10.2, 1H), 3.55 (s, 6H), 3.49-3.43 (m, 2H), 3.23 (q, 4H), 2.69-2.65 (m, 1H), 2.53-2.46 (m, 3H); ^{13}C NMR δ 197.4, 197.4, 144.4, 144.3, 136.9, 132.3, 132.0, 130.8, 130.3, 129.8, 128.4, 127.5, 127.5, 126.3, 126.3, 117.5, 115.3, 113.6, 55.4, 44.2, 44.2, 41.3, 41.2, 39.3, 34.2; HRMS [M$^+$] calcd. for $C_{21}H_{22}O_2$ 306.1620, found 306.1647; IR (neat) 3066-2840, 1667.



6-Phenyl-pentadeca-1,3,12,14-tetraen-8-one (1.105).

5-Bromopenta-1,3-diene (0.74 g, 5.0 mmol, 3.98 eq.) was added to a solution of 1-phenylpenta-1,4-dien-3-one **1.104** (0.2 g, 1.3 mmol, 1.0 eq.) in DMF/H_2O (2/1, 2 mL). The suspension was cooled to 0 °C and indium metal powder (0.29 g, 2.5 mmol, 2.0 eq.) was added in portions. The reaction mixture was stirred for 24 h at 22 °C. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and poured into a flask with ether (50 mL). The suspension was filtered through a silica gel pad, washed thoroughly with ether (2x20 mL) and purified by flash column chromatography (94/6, PE/E). The title compound was obtained as colorless oil (26 mg, 7%).

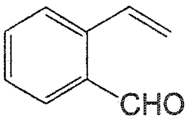
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (dd, *J* = 8.5, 8.5, 2H), 7.17 (t, 3H), 6.56-6.52 (m, 2H), 5.97 (ddd, *J* = 11.0, 11.0, 4.4, 2H), 5.34-5.26 (m, 2H), 5.16 (d, *J* = 15.8, 2H), 5.08 (d, *J* = 8.5, 1H), 5.06 (d, *J* = 8.3, 1H), 3.26-3.21 (m, 1H), 2.70 (dd, *J* = 7.3, 1.7 2H), 2.57-2.51 (m, 1H), 2.46-2.44 (m, 1H), 2.33-2.29 (m, 1H), 2.25-2.18 (m, 1H), 2.07 (q, 2H), 1.59-1.53 (m, 2H); ^{13}C NMR δ 209.4, 143.9, 132.0, 131.9, 131.5, 130.8, 130.0, 129.6, 128.5, 127.4, 126.5, 117.6, 117.2, 48.6, 42.6, 41.0, 34.3, 26.8, 23.2; DEPT δ -117.7, -117.3, -48.7, -42.6, -34.3, 26.8, 23.3; MS calcd. for $C_{21}H_{26}O$ 294, found $[M^++NH_4]^+$ 312 (100); IR (neat) 3091, 3016, 2925-2853, 1714, 999, 904, 700.



1-Phenyldeca-1,7,9-trien-3-one (1.106).

From the previous procedure, the title compound was also obtained as colorless oil (17 mg, 6%).

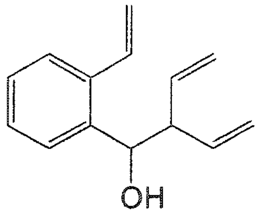
^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.54-7.51 (m, 3H), 7.39-7.36 (m, 3H), 6.71 (d, *J* = 16.2, 1H), 6.61 (dddd, *J* = 16.9, 11.1, 10.1, 1.1, 1H), 6.04 (t, *J* = 10.9, 1H), 5.43 (q, 1H), 5.18 (dd, *J* = 16.9, 2.0, 1H), 5.08 (d, *J* = 10.2, 1H), 2.66 (t, *J* = 7.3, 2H), 2.25 (ddd, *J* = 14.9, 7.5, 1.4, 2H), 1.81-1.75 (m, 2H); ^{13}C NMR δ 200.1, 142.4, 134.6, 132.1, 131.6, 130.4, 130.2, 128.9, 128.2, 126.3, 117.3, 40.0, 27.1, 24.0; DEPT δ -117.3, 40.0, 27.1, 24.0; HRMS [M$^+$] calcd. for $C_{16}H_{18}O$ 226.1358, found 226.1341; IR (neat) 3066-2840, 1717, 999, 904, 700.



2-Vinylbenzaldehyde (2.89).

Vinyltrimethylsilane (1.7 mL, 5.9 mmol, 1.1 eq.) was added to a solution of 2-bromobenzaldehyde **2.87** (0.63 mL, 5.4 mmol, 1.0 eq.), Pd(PPh$_3$)$_4$ (0.12 g, 0.11 mmol, 2 mol%) and 2,6-di-*tert*-butyl-4-methylphenol (2 mg, 0.2 mol%) in toluene (10 mL). The reaction mixture was refluxed for 4 h and then cooled to 22 °C. Pyridine (0.4 mL) was added followed by pyridinium fluoride solution (0.93 mL, 1.2 N) and the reaction mixture was stirred for 16 h at 22 °C. Afterwards the mixture was diluted with ether (20 mL) and washed with water (5 mL), 10% HCl (2x5 mL), water (5 mL) and NaHCO$_3$ (5 mL). The organic phase was dried over MgSO$_4$ and concentrated under vacuum. Purification by flash column chromatography (85/15, PE/E) afforded the title compound as a colorless oil (0.69 g, 96%).

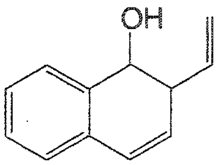
^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.25 (d, *J* = 1.3, 1H), 7.78 (dd, *J* = 7.9, 0.8, 1H), 7.52 (dd, *J* = 7.7, 1.3, 1H), 7.50 (dd, *J* = 17.1, 10.0, 1H), 7.48 (dd, *J* = 7.6, 1.3, 1H), 7.38 (ddd, *J* = 7.1, 7.1, 1.6, 1H), 5.66 (ddd, *J* = 17.4, 1.1, 1.1, 1H), 5.47 (ddd, *J* = 11.0, 1.0, 1.0, 1H); ^{13}C NMR δ 192.2, 140.4, 133.7, 133.3, 132.8, 131.1, 127.8, 127.4, 119.3; DEPT δ -119.3; HRMS [M^+] calcd. for C_9H_8O 132.0575, found 132.0590; IR (neat) 3090-3066, 1695, 1596, 1565, 1205, 1188, 773, 741.



2-Vinyl-1-(2-vinylphenyl)-but-3-en-1-ol (2.90).

5-Bromopenta-1,3-diene (2.92 g, 19.9 mmol, 3.98 eq.) was added to a solution of 2-vinylbenzaldehyde **2.89** (0.66 g, 4.99 mmol, 1.0 eq.) in DMF/H_2O (2/1, 7 mL). The suspension was cooled to 0 °C and indium metal powder (1.15 g, 9.99 mmol, 2.0 eq.) was added in portions. The reaction mixture was stirred for 1.5 h at 22 °C. After cooling to 22 °C, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and poured into a flask with ether (50 mL). The suspension was filtered through a silica gel pad, washed thoroughly with ether (2x10 mL) and purified by flash column chromatography (95/5, PE/E). The title compound was obtained as colorless oil (0.80 g, 80%).

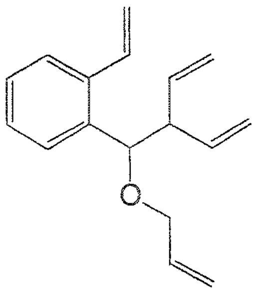
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (dd, *J* = 7.2, 1.6, 1H), 7.42 (dd, *J* = 7.0, 1.6, 1H), 7.28 (ddd, *J* = 7.4, 7.4, 1.6, 1H), 7.24 (ddd, *J* = 7.3, 7.3, 1.5, 1H), 7.04 (dd, *J* = 17.3, 10.9, 1H), 5.86 (ddd, *J* = 17.2, 10.3, 8.1, 1H), 5.72 (ddd, *J* = 17.1, 10.5, 6.8, 1H), 5.59 (dd, *J* = 17.3, 1.4, 1H), 5.31 (dd, *J* = 10.9, 1.4, 1H), 5.21 (ddd, *J* = 10.3, 1.7, 0.7, 1H), 5.13 (ddd, *J* = 17.2, 1.7, 1.1, 1H), 5.02 (q, 1H), 4.99 (ddd, *J* = 9.0, 1.5, 1.5, 1H), 4.94 (dd, *J* = 6.8, 2.6, 1H), 3.14 (q, 1H), 2.13 (t, 1H); ^{13}C NMR δ 139.0, 137.0, 136.4, 136.3, 134.6, 127.6, 127.5, 126.7, 126.2, 118.4, 116.7, 116.5, 72.3, 55.2; DEPT δ - 118.4, 116.7, 116.5; HRMS [M^+-H_2O] calcd. for $C_{14}H_{14}$ 182.1096, found 182.1074; IR (neat) 3428, 3080-2912, 1634, 1481, 1414, 1034, 997, 916, 769.



2-Vinyl-1,2-dihydronaphthalen-1-ol (2.91).

Grubbs' catalyst [(4,5-dihydroIMES)(PCy_3)Cl_2Ru=CHPh, 5 mol % in CH_2Cl_2] was added to a 0.05 M degassed CH_2Cl_2 solution of 2-vinyl-1-(2-vinylphenyl)-but-3-en-1-ol **2.90**. The solution was stirred at 22 °C for 8 h. The volatiles were removed under high vacuum, and the residue was purified by flash column chromatography (9/1, PE/E) to afford the title compound as a colorless oil (52%).

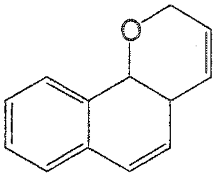
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (d, *J* = 6.8, 1H), 7.26-7.21 (m, 2H), 7.09 (d, *J* = 7.4, 1H), 6.53 (d, *J* = 9.6, 1H), 5.87 (dd, *J* = 9.5, 4.1, 1H), 5.69 (ddd, *J* = 17.4, 8.9, 8.9, 1H), 5.19 (d, *J* = 17.1, 1H), 5.11 (d, *J* = 10.2, 1H), 4.59 (d, *J* = 6.7, 1H), 3.21 (q, 1H), 2.02 (s, 1H); ^{13}C NMR δ 136.9, 135.5, 132.3, 128.4, 128.2, 127.8, 127.1, 126.8, 126.4, 117.5, 71.8, 47.8; HRMS [M^+] calcd. for $C_{12}H_{12}O$ 172.0888, found 172.0907; IR (neat) 3216, 3040-2922, 1450, 1294, 1193, 997, 918, 770.



1-(1-Allyloxy-2-vinylbut-3-enyl)-2-vinylbenzene (2.93).

Sodium hydride (0.15 g, 3.8 mmol, 1.0 eq., 60 % dispersion in mineral oil) was added to a solution of 2-vinyl-1-(2-vinylphenyl)-but-3-en-1-ol **2.92** (0.76 g, 3.8 mmol, 1.0 eq.) in THF (38 mL) at 0 °C. After 30 min allyl bromide (0.49 mL, 5.7 mmol, 1.5 eq.) and sodium iodide (0.06 g, 0.38 mmol, 0.1 eq.) were added. The solution was then stirred for 6 h at 22 °C. Standard workup with $NaHCO_3$, ether (2x10 mL) and $MgSO_4$ was performed. Purification by flash column chromatography (96/4, PE/E) provided the title compound as a colorless oil (0.59 g, 65%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (dd, *J* = 7.9, 1.6, 1H), 7.37 (dd, *J* = 7.9, 1.6, 1H), 7.29-7.23 (m, 2H), 7.06 (dd, *J* = 17.3, 10.9, 1H), 5.95 (ddd, *J* = 17.4, 10.2, 7.3, 1H), 5.88 (ddd, *J* = 16.5, 11.0, 5.3, 1H), 5.79 (ddd, *J* = 17.2, 10.2, 7.3, 1H), 5.60 (dd, *J* = 17.2, 1.0, 1H), 5.31 (dd, *J* = 10.9, 1.0, 1H), 5.23 (dd, *J* = 17.2, 1.5, 1H), 5.14 (dd, *J* = 10.4, 1.2, 1H), 5.09 (d, *J* = 10.3, 1H), 4.97 (dd, *J* = 18.0, 1.2, 1H), 4.96 (d, *J* = 17.4, 1H), 4.95 (d, *J* = 10.2, 1H), 4.68 (d, *J* = 6.3, 1H), 3.95 (dd, *J* = 13.1, 4.8, 1H), 3.72 (dd, *J* = 13.0, 6.2, 1H), 3.12 (q, 1H); ^{13}C NMR δ 137.7, 137.5, 137.0, 136.9, 134.9, 134.5, 127.5, 127.5, 127.4, 126.0, 116.7, 116.5, 116.2, 116.0, 80.1, 69.7, 54.2; HRMS [M^+-C_5H_7] calcd. for $C_{12}H_{13}O$ 173.0966, found 173.0949; IR (neat) 3080-2858, 1639, 1480, 1416, 1074, 992, 916, 773.

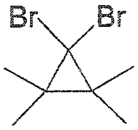


4a,10b-Dihydro-2*H*-benzo[*h*]chromene (2.94).

Grubbs' catalyst [(4,5-dihydroIMES)(PCy$_3$)Cl$_2$Ru=CHPh, 5 mol % in CH$_2$Cl$_2$] was added to a 0.05 M degassed CH$_2$Cl$_2$ solution of 1-(1-allyloxy-2-vinylbut-3-enyl)-2-vinyl-benzene **2.93**. The solution was stirred at 22 °C for 4 h. The volatiles were removed under high vacuum, and the residue was purified by flash column chromatography (94/6, PE/E). Two isomers were obtained as colorless oils (84%).

Isomer A (67%): ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.54 (d, *J* = 7.4, 1H), 7.28 (t, *J* = 7.3, 1H), 7.23 (t, *J* = 7.2, 1H), 7.10 (d, *J* = 7.3, 1H), 6.49 (dd, *J* = 9.4, 3.2, 1H), 5.95 (dd, *J* = 10.0, 1.8, 1H), 5.88 (dd, *J* = 9.5, 2.1, 1H), 5.80 (dd, *J* = 10.0, 1.9, 1H), 4.48 (dd, *J* = 16.6, 2.3, 1H), 4.47 (d, *J* = 10.6, 1H), 4.42 (ddd, *J* = 16.7, 2.2, 2.2, 1H), 3.15 (d, *J* = 11.3, 1H); ^{13}C NMR δ 136.9, 133.2, 130.1, 128.0, 127.6, 127.6, 127.0, 126.6, 125.9, 122.18, 76.5, 67.1, 37.9; HRMS [M$^+$] calcd. for C$_{13}$H$_{12}$O 184.0888, found 184.0895; IR (neat) 3030, 2823, 1171, 1124, 1088, 785, 775.

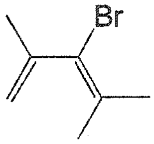
Isomer B (17%): ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.34 (d, *J* = 7.3, 1H), 7.29 (t, *J* = 7.1, 1H), 7.24 (t, *J* = 7.1, 1H), 7.11 (d, *J* = 7.3, 1H), 6.47 (dd, *J* = 9.6, 2.8, 1H), 5.97-5.94 (m, 1H), 5.86 (d, *J* = 10.2, 1H), 5.81 (d, *J* = 10.0, 1H), 4.62 (d, *J* = 5.0, 1H), 4.30 (d, *J* = 16.4, 1H), 4.18 (d, *J* = 16.3, 1H), 3.06 (s, br, 1H); ^{13}C NMR δ 133.1, 132.4, 129.5, 129.0, 128.8, 127.7, 126.8, 126.6, 125.4, 124.6, 72.6, 64.6, 35.3; HRMS [M$^+$] calcd. for C$_{13}$H$_{12}$O 184.0888, found 184.0883; IR (neat) 3032, 2929-2820, 1577, 1453, 1179, 1081, 1069, 779-754.



1,1-Dibromo-2,2,3,3-tetramethylcyclopropane (2.95).[171-172]

Bromoform (7.34 mL, 84.0 mmol, 2.0 eq.) was added dropwise to a stirred suspension of 2,3-dimethyl-2-butene (5.0 mL, 42.0 mmol, 1.0 eq.) and ^{t}BuOK (18.65 g, 77.0 mmol, 1.83 eq.) in pentane (15.0 mL) at 0 °C. The resulting mixture was stirred for 2 h at 21 °C. Water was added (200 mL) and the layers separated. The aqueous layer was extracted with hexanes (2x150 mL). The combined organic extracts were washed with brine (2x100 mL), dried over $MgSO_4$ and concentrated. The product was purified by crystallization from MeOH. Three more crops were recovered from mother liquors. The product was obtained as a cream-colored solid (9.7 g, 90%), b.p. 83 °C (24 mm).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (s, 12H); ^{13}C NMR δ 59.2, 30.1, 22.1; HRMS [M^+-Br] calcd. for $C_7H_{12}Br$ 175.0122, found 175.0137; IR (neat) 3001-2806, 1087, 960, 765.

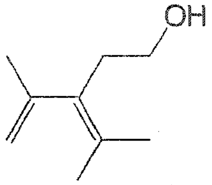


3-Bromo-2,4-dimethylpenta-1,3-diene 2.96.[173]

In a distillation apparatus equipped with a 10% NaOH solution trap, 1,1-dibromo-2,2,3,3-tetramethylcyclopropane **2.95** was heated with a propane burner until it melted. Heating was continued until a colorless liquid distilled in a range of 90 -140 °C. The distillate was subjected to a second distillation and the colorless liquid was stored at 0 °C over NaOH pellets.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.03-5.01 (m, 1H), 4.90-4.89 (m, 1H), 1.88 (s, 3H), 1.87 (t, br, 3H), 1.79 (s, 3H); ^{13}C NMR δ 144.4, 131.3, 120.5, 116.8, 24.8, 22.2, 22.1;

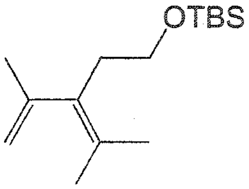
HRMS [M$^+$] calcd. for $C_7H_{11}Br$ 174.0044, found 174.0019; IR (neat) 3087, 3004-2854, 1632, 1434, 1368, 1092, 983, 907, 854.



3-Isopropenyl-4-methylpent-3-en-1-ol (2.85).[173]

t-Butyllithium (52 mL, 0.088 mol, 1.7 M in hexane, 2.2 eq.) was added to a solution of 3-bromo-2,4-dimethylpenta-1,3-diene **2.96** (7 g, 0.04 mol, 1.0 eq.) in THF (112 mL) at -78 °C. The reaction mixture was stirred at the same temperature for 30 min and then ethylene oxide (6 mL, 0.12 mol, 3.0 eq.) was added. The reaction mixture was stirred for 1 h at -78 °C, 1 h at 0 °C, and then 30 min at 22 °C. After cooling to 0 °C, the standard workup with NH_4Cl and ether (2x70 mL) was performed. Purification by flash column chromatography (75/25, PE/E) furnished the title compound (5.1 g, 91%).

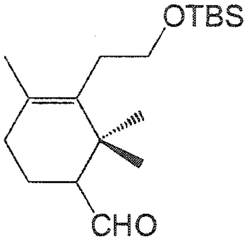
^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.93-4.91 (m, 1H), 4.54-4.53 (m, 1H), 3.57 (t, br, 2H), 2.35 (t, 2H), 1.75 (s, 3H), 1.68 (s, 3H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.7, 132.9, 128.9, 113.9, 61.6, 34.2, 22.9, 22.2, 20.2; DEPT δ -113.9, -61.6, -34.2; HRMS [M$^+$] calcd. for $C_9H_{16}O$ 140.1201, found 140.1206; IR (neat) 3347, 3075, 2963-2877, 1632, 1446, 1373, 1043-1020, 895.



***tert*-Butyl-(3-isopropenyl-4-methylpent-3-enyloxy)-dimethylsilane (2.97).**

Imidazole (4.5 g, 0.066 mol, 1.85 eq.) and TBSCl (7.5 g, 0.05 mol, 1.4 eq.) were sequentially added to a solution of 3-isopropenyl-4-methylpent-3-en-1-ol **2.85** (5 g, 0.036 mol, 1.0 eq.) in CH_2Cl_2 (155 mL) at 0 °C. The reaction mixture was stirred for 3 h at 22 °C and then cooled to 0 °C. Standard workup with $NaHCO_3$, CH_2Cl_2 (2x50 mL) and Na_2SO_4 was performed. After purification by flash column chromatography (95/5, PE/CH_2Cl_2) the title compound was obtained (8.9 g, 98%).

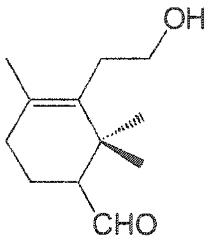
^{1}H NMR (C_6D_6, 300 MHz) δ 4.95 (s, 1H), 4.66 (s, 1H), 3.67 (t, *J* = 7.8, 2H), 2.45 (t, *J* = 7.5, 2H), 1.72 (s, 3H), 1.68 (s, 3H), 1.63 (s, 3H), 0.97 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ 146.9, 133.5, 127.3, 113.5, 62.0, 35.2, 26.2, 22.7, 21.9, 19.9, 18.5, -5.1; HRMS [M^+-(*tert*-Butyl)] calcd. for $C_{11}H_{21}OSi$ 197.1362, found 197.1358; IR (neat) 3076-2737, 1472-1463, 1255, 1100, 836, 775.



3-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-2,2,4-trimethylcyclohex-3-necarbaldehyde (2.98).

Acrolein (2.64 mL, 39.5 mmol, 6.0 eq.) was added to a solution of *tert*-butyl-(3-isopropenyl-4-methylpent-3-enyloxy)-dimethylsilane **2.97** (1.67 g, 6.59 mmol, 1.0 eq.) in CH_2Cl_2 (26.8 mL). The solution was cooled to –78 °C and $BF_3{\cdot}OEt_2$ (0.92 mL, 7.25 mmol, 1.1 eq.) was added dropwise. Reaction mixture was then stirred for 2 h at the same temperature. Afterwards, standard workup with $NaHCO_3$, ether and Na_2SO_4 was carried out. Purification by flash column chromatography (7/3, PE/CH_2Cl_2) afforded the title compound (1.6 g, 77%).

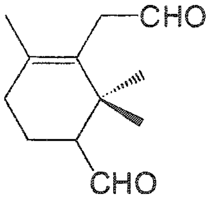
^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.60 (d, *J* = 1.9, 1H), 3.57 (t, *J* = 8.3, 2H), 2.31 (dd, *J* = 11.1, 7.5, 2H), 1.87 (d, *J* = 10.0, 1H) 1.68 (t, *J* = 6.3, 2H), 1.59-1.51 (m, 2H), 1.46 (s, 3H), 0.99 (s, 3H), 0.97 (s, 9H), 0.85 (s, 3H), 0.07 (s, 6H); ^{13}C NMR δ 204.1, 133.2, 129.4, 63.1, 57.5, 36.9, 32.5, 30.9, 27.6, 26.2, 23.3, 20.2, 19.8, 18.5, -5.0; DEPT δ -63.1, -32.5, -30.8, -19.8; HRMS [M^+-(*tert*-Butyl)] calcd. for $C_{14}H_{25}O_2Si$ 253.1624, found 253.1630; IR (neat) 2955-2857, 1721, 1472, 1255, 1093-1079, 836, 776.



3-(2-Hydroxyethyl)-2,2,4-trimethylcyclohex-3-enecarbaldehyde (2.99).

Tetrabutylammonium fluoride (46.5 mL, 0.046 mol, 1.0 M in THF, 2.0 eq.) was added to 3-[2-(*tert*-butyldimethylsilanyloxy)-ethyl]-2,2,4-trimethylcyclohex-3-enecarbaldehyde **2.98** (7.2 g, 0.023 mol, 1.0 eq.) at 0 °C. The reaction mixture was stirred for 2 h at 22 °C, water (350 mL) was added and the phases were separated. The aqueous layer was extracted with ether (3x20 mL) and the combined organic extracts were washed with brine, dried and concentrated. Purification by flash column chromatography (4/6, PE/E) afforded the pure compound (4.3 g, 95%).

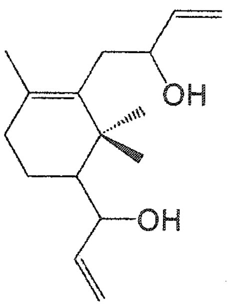
^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.77 (d, *J* = 3.0, 1H), 3.62-3.54 (m, 2H), 2.37-2.30 (m, 2H), 2.13 (dd, *J* = 10.1, 3.1, 1H) 1.98 (d, 2H), 1.83-1.78 (m, 1H), 1.73-1.65 (m, 1H), 1.63 (s, 3H), 1.17 (s, 3H), 1.02 (s, 3H); ^{13}C NMR δ 206.2, 132.4, 129.8, 62.3, 57.5, 36.8, 31.6, 30.5, 27.7, 23.5, 20.1, 19.6; DEPT δ -62.3, -31.6, -30.5, -19.6; HRMS [M^+] calcd. for $C_{12}H_{20}O_2$ 196.1463, found 196.1476; IR (neat) 3403, 2945-2835, 1718, 1473-1378, 1036.



2,2,4-Trimethyl-3-(2-oxoethyl)-cyclohex-3-enecarbaldehyde (2.100).

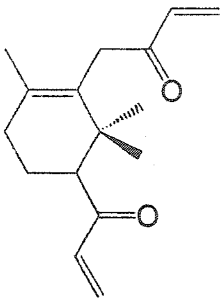
Oxalyl chloride (4.7 mL, 0.05 mol, 1.5 eq.) was added dropwise to a solution of DMSO (7.6 mL, 0.11 mol, 3.0 eq.) in CH_2Cl_2 (250 mL) at –78 °C and reaction mixture was stirred for 30 min. A solution of 3-(2-hydroxyethyl)-2,2,4-trimethyl-cyclohex-3-enecarbaldehyde **2.99** (5.0 g, 0.036 mol, 1.0 eq.) in CH_2Cl_2 (50 mL) was added and the solution was stirred 1 h at –78 °C. Triethylamine (33.9 mL, 0.24 mol, 6.8 eq.) was added and the reaction mixture was allowed to reach 22 °C and stirred for 1 h. After cooling to 0 °C, standard workup with NH_4Cl, CH_2Cl_2 (2x50 mL) and Na_2SO_4 was performed. The title compound was purified by flash column chromatography (8/2, PE/E) and isolated (3.4 g, 69%).

^1H NMR ($CDCl_3$, 500 MHz) δ 9.83 (s, 1H), 9.82 (s, 1H), 9.53 (s, 2H), 2.22 (dd, *J* = 10.6, 3.0, 1H), 2.12-2.07 (m, 2H), 1.89-1.83 (m, 1H), 1.77-1.70 (m, 1H), 1.56 (s, 3H), 1.13 (s, 3H), 0.98 (s, 3H); ^{13}C NMR δ 205.4, 200.1, 132.6, 128.2, 57.1, 43.2, 36.7, 30.7, 27.1, 22.9, 20.2, 19.5; DEPT δ -43.2, -30.7, -19.5; HRMS $[M^+]$ calcd. for $C_{12}H_{18}O_2$ 194.1307, found 194.1300; IR (neat) 2966-2834, 2726, 1719.



1-[5-(1-Hydroxyallyl)-2,6,6-trimethylcyclohex-1-enyl]-but-3-en-2-ol (2.84).
Vinylmagnesium chloride (6.6 mL, 10.58 mol, 3.0 eq., 1.6 M in THF) was added to a solution of 2,2,4-trimethyl-3-(2-oxo-ethyl)-cyclohex-3-enecarbaldehyde **2.100** (0.68 g, 3.53 mmol, 1.0 eq.) in ether (42 mL) at -78 °C. The solution was stirred for 1 h at -78 °C and 30 min at 0 °C. Standard workup with NH_4Cl, ether (2x15 mL) and $MgSO_4$ was realized. Purification by flash column chromatography (7/3, PE/E) provided the title compound (54.3 mg, 62%).

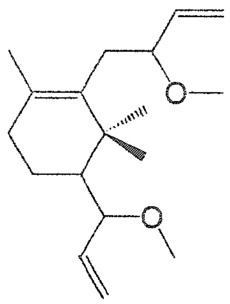
^1H NMR ($CDCl_3$, 500 MHz) δ 5.87 (ddd, *J* = 17.0, 10.7, 6.2, 2H), 5.21 (dd, *J* = 17.1, 9.4, 2H), 5.06 (dd, *J* = 17.5, 10.6, 2H), 4.5 (q, 1H), 4.28-4.24 (m, 1H), 2.41 (dd, *J* = 14.2, 9.1, 1H) 2.30 (t, 1H), 2.23 (dd, *J* = 14.3, 5.9, 1H), 2.11 (s, 3H), 1.99-1.92 (m, 1H), 1.71-1.57 (m, 2H), 1.62 (d, 3H), 1.35-1.32 (m, 1H), 1.13 (d, 3H), 1.07 (d, 3H); ^{13}C NMR δ 141.4 (2), 141.2 (2), 133.3 (2), 132.6 (2), 114.1 (2), 113.3 (2) , 72.4 (2), 72.3 (2), 49.1 (2), 37.8 (2), 36.0 (2), 32.0 (2), 29.0 (2), 24.0 (2), 21.1 (2), 17.9 (2); DEPT δ -114.1, -113.3, -36.0, -32.0, -17.9; HRMS [M^+-C_3H_4O] calcd. for $C_{13}H_{22}O$ 194.1671, found 194.1673; IR (neat) 3386, 2975-2827, 1468-1384, 991, 919.



1-(5-Acryloyl-2,6,6-trimethylcyclohex-1-enyl)-but-3-en-2-one (2.103).

1-[5-(1-Hydroxyallyl)-2,6,6-trimethylcyclohex-1-enyl]-but-3-en-2-ol **2.84** (0.114 g, 0.46 mmol, 1.0 eq.) in THF (3.0 mL) was added to a suspension of IBX (0.191 g, 0.68 mmol, 1.5 eq.) in DMSO (0.13 mL, 1.84 mmol, 4.0 eq.) at 0 °C. The solution was stirred for 3 h at 22 °C. Water (15 mL) was added and after filtration the solution was extracted with ether (2x10 mL), the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. Purification by flash chromatography (8/2, PE/E) provided the title compound (50.5 mg, 45%).

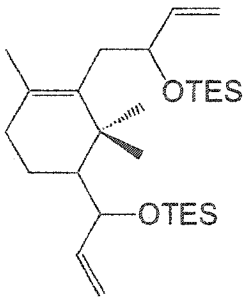
^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.43 (ddd, *J* = 17.4, 10.5, 1.9, 2H), 6.25 (dd, *J* = 17.5, 1.0, 1H), 6.19 (dd, *J* = 17.4, 1.2, 1H), 5.74 (dd, *J* = 10.6, 1.2, 1H) 5.66 (dd, *J* = 10.5, 1.2, 1H), 3.29 (s, 2H), 2.86 (dd, *J* = 11.5, 2.8, 1H), 2.16-2.09 (m, 1H), 2.02-1.97 (m, 1H), 1.90-1.82 (m, 1H), 1.68-1.63 (m, 1H), 1.47 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H); ^{13}C NMR δ 203.7, 198.2, 137.3, 135.6, 130.8, 130.5, 127.7, 127.4, 54.7, 40.0, 37.6, 31.3, 27.3, 22.7, 21.9, 20.4; DEPT δ -127.7, -127.4, -40.0, -31.3, -21.9; HRMS [M^+] calcd. for $C_{16}H_{22}O_2$ 246.1620, found 246.1619; IR (neat) 2967-2833, 1687, 1611, 1399, 1072, 979.



4-(1-Methoxyallyl)-2-(2-methoxybut-3-enyl)-1,3,3-trimethylcyclohexene (2.101a).

Sodium hydride (0.32 g, 7.98 mmol, 6.0 eq., 60 % dispersion in mineral oil) was added to a solution of 1-[5-(1-hydroxyallyl)-2,6,6-trimethylcyclohex-1-enyl]-but-3-en-2-ol **2.84** (0.33 g, 1.33 mmol, 1.0 eq.) in THF (40 mL) at 0 °C. The reaction mixture was stirred for 30 min. Iodomethane (1.33 mL, 21.28 mmol, 16.0 eq.) was added and the solution was then stirred for 5 h at 23 °C. Standard workup with NH_4Cl, ether (2x40 mL) and $MgSO_4$ was performed. Purification by flash column chromatography (95/5, PE/E) provided the title compound (0.27 g, 75%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.81-5.70 (m, 2H), 5.45 (dd, *J* = 5.0, 1.3, 1H), 5.38 (q, 1H), 5.22 (d, *J* = 17.5, 2H), 5.12 (d, *J* = 10.6, 2H), 3.04 (d, 6H), 2.43-2.36 (m, 1H), 2.27-2.20 (m, 1H), 1.96-1.93 (m, 2H), 1.68-1.66 (m, 1H) 1.63 (d, 3H), 1.54-1.50 (m, 1H), 1.42 (m, 1H), 1.08 (d, 3H), 0.82 (d, 3H); ^{13}C NMR δ 170.2, 170.0, 137.3, 137.1, 132.7, 131.0, 115.6, 114.8, 75.0, 73.0, 48.5, 38.3, 33.3, 32.9, 27.5, 27.0, 22.0, 21.4, 21.2, 18.3; DEPT δ -115.6, -114.8, -33.3, -32.9, -18.3; MS calcd. for $C_{18}H_{30}O_2$ 278.2, found $[M^{+}+NH_4]^{+}$ 296.2 (100); IR (neat) 2962-2833, 1739, 1239, 1021, 914, 544.

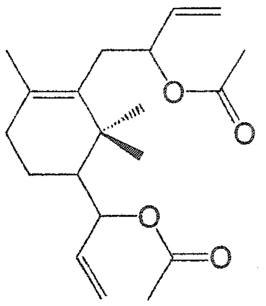


1,3,3-Trimethyl-4-(1-triethylsilanyloxyallyl)-2-(2-triethylsilanyloxybut-3-enyl)-cyclohexene (2.101b).

Imidazole (0.67 g, 9.86 mmol, 6.0 eq.) and TESCl (0.66 mL, 3.94 mmol, 2.4 eq.) were sequentially added to a solution of 1-[5-(1-hydroxyallyl)-2,6,6-trimethyl-cyclohex-1-enyl]-but-3-en-2-ol **2.84** (0.41 g, 1.63 mmol, 1.0 eq.) in DMF (8.2 mL) at 0 °C. The reaction mixture was then stirred at 22 °C for 6 h. The reaction mixture was cooled to 0 °C and standard workup with $NaHCO_3$, ether and $MgSO_4$ was carried out. The compound was obtained as a mixture of isomers that were separated by flash column chromatography (98/2, PE/CH_2Cl_2) (67%).

Isomer A (78 mg, 10%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.94 (ddd, *J* = 17.3, 10.1, 7.2, 1H), 5.82 (ddd, *J* = 17.0, 10.6, 6.2, 1H), 5.07 (dd, *J* = 17.2, 5.0, 2H), 4.98 (d, *J* = 11.0, 1H), 4.93 (d, *J* = 10.4, 1H), 4.39 (d, *J* = 7.2, 1H), 4.30 (q, 1H), 2.33 (dd, *J* = 14.3, 6.7, 1H), 2.23 (dd, *J* = 14.2, 8.0, 1H), 1.92 (t, br, 2H), 1.64-1.50 (m, 2H), 1.59 (s, 3H), 1.23 (d, br, 1H), 1.05 (s, 3H), 0.95-0.91 (m, 21H), 0.58-0.54 (m, 12H); ^{13}C NMR δ 142.9, 141.9, 134.0, 129.8, 113.1, 112.7, 74.0, 73.8, 52.2, 38.6, 37.6, 33.3, 27.8, 23.3, 21.7, 18.8, 7.0, 6.8, 5.5, 5.0; DEPT δ -113.1, -112.7, -37.6, -33.3, -18.8, -5.5, -5.0; Elemental analysis calcd. for C (70.22%), H (11.37%), found C (70.44%), H (11.29%); IR (neat) 3072-2827, 1459, 1076, 1006, 919, 742.

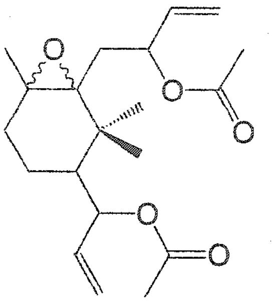
Isomer B (0.45 g, 57%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.94 (ddd, *J* = 17.3, 10.2, 7.2, 1H), 5.85 (ddd, *J* = 17.2, 10.6, 6.5, 1H), 5.09 (d, *J* = 17.0, 2H), 5.08 (d, *J* = 17.0, 1H), 4.96 (d, *J* = 10.4, 1H), 4.94 (d, *J* = 10.4, 1H), 4.39 (d, *J* = 7.1, 1H), 4.25 (q, 1H), 2.31 (d, *J* = 14.5, 8.5, 1H), 2.15 (d, *J* = 14.6, 4.8, 1H), 1.95-1.92 (m, 2H), 1.62 (s, 3H), 1.61-1.54 (m, 2H), 1.25 (d, br, 1H), 1.03 (s, 3H), 0.98 (s, 3H), 0.94-0.89 (m, 18H), 0.58-0.51 (m, 12H); ^{13}C NMR δ 143.0, 142.6, 134.4, 129.7, 113.1, 112.6, 74.5, 73.8, 52.0, 38.7, 37.4, 33.3, 27.5, 23.2, 21.5, 18.8, 7.0, 6.8, 5.5, 4.9; DEPT δ -113.1, -112.6, -37.4, -33.3, -18.8, -5.5, -4.9; Elemental analysis calcd. for C (70.22%), H (11.37%), found C (70.36%), H (11.19%); IR (neat) 3076-2830, 1459, 1116, 1075, 1006, 919, 743.



Acetic acid 1-[5-(1-acetoxyallyl)-2,6,6-trimethyl-cyclohex-1-enylmethyl]-allyl ester (2.105).

Triethylamine (0.09 mL, 0.64 mmol, 4.0 eq.) and DMAP (1 mg, 8.18x10^{-3} mmol, 0.05 eq.) were added to a stirred solution of 1-[5-(1-hydroxyallyl)-2,6,6-trimethyl-cyclohex-1-enyl]-but-3-en-2-ol **2.84** (40 mg, 0.16 mmol, 1.0 eq.) in CH_2Cl_2 (1.3 mL) at 23 °C. The reaction mixture was cooled to 0 °C and Ac_2O (45.6 µL, 0.48 mmol, 3.0 eq.) was added. Afterwards, the reaction mixture was stirred for 20 min at the same temperature and then at 23 °C for 2.5 h. Standard workup was performed and the residue purified by flash column chromatography (8/2, PE/E) to obtain the pure title compound (42 mg, 79 %).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.84-5.71 (m, 2H), 5.55 (ddd, *J* = 10.4, 5.0, 1.2, 1H), 5.45-5.38 (m, 1H), 5.19 (d, *J* = 17.5, 1H), 5.10 (d, *J* = 10.6, 2H), 5.08 (dd, *J* = 17.0, 1.6, 1H), 2.47-2.40 (m, 1H), 2.29-2.22 (m, 1H), 2.00 (t, 6H), 1.97-1.93 (m, 2H), 1.69-1.66 (m, 1H) 1.65 (d, 3H), 1.57-1.51 (m, 1H), 1.42 (d, br, 1H), 1.08 (d, 3H), 0.82 (d, 3H); ^{13}C NMR δ 170.2, 170.0, 137.3, 137.1, 132.7, 131.0, 115.6, 114.8, 75.0, 73.01, 48.5, 38.3, 33.3, 32.9, 27.5, 27.0, 22.0, 21.4, 21.2, 18.3; MS calcd. for $C_{20}H_{30}O_4$ 334.2, found $[M^{+}+NH_4]^{+}$ 352.2 (100); IR (neat) 2962-2833, 1739, 1239, 1021, 914, 544.

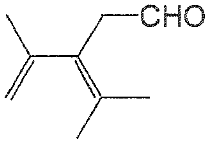


Acetic acid 1-[3-(1-acetoxyallyl)-2,2,6-trimethyl-7-oxa-bicyclo[4.1.0]hept-1-ylmethyl]-allyl ester (2.106).

3-Chloroperbenzoic acid (52 mg, 0.33 mmol, 1.1 eq.) was added to a solution of acetic acid 1-[5-(1-acetoxyallyl)-2,6,6-trimethyl-cyclohex-1-enylmethyl]-allyl ester **2.105** (100 mg, 0.299 mmol, 1.0 eq.) in CH_2Cl_2 (8 mL) at -78 °C. The reaction mixture was stirred at the same temperature for 1 h, warmed to 0 °C and stirred at that temperature for 30 min. After filtration the standard workup procedure with $NaHCO_3$, ether and $MgSO_4$ was accomplished. The compound was obtained as a mixture of isomers that were separated by flash column chromatography (75/25, PE/E) (63%).

Isomer A (37.3 mg, 36%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.80-5.73 (m, 1H), 5.70-5.63 (m, 1H), 5.53 (dd, *J* = 4.6, 1.4, 1H), 5.20 (dd, *J* = 17.2, 4.6, 1H), 5.12-5.03 (m, 4H), 2.13-2.10 (m, 1H), 2.03-2.00 (m, 6H), 1.99-1.96 (m, 1H), 1.80-1.77 (m, 1H), 1.41-1.40 (m, 2H) 1.26 (s, 3H), 1.24-1.18 (m, 2H), 1.13 (d, 3H), 0.85 (s, 3H); ^{13}C NMR δ 170.2, 169.8, 137.1, 136.8, 116.1, 114.7, 73.0, 72.1, 68.1, 63.2, 49.2, 42.5, 37.6, 34.2, 29.6, 22.8, 21.2, 20.0, 18.2, 16.2; HRMS [M^+-AcOH] calcd. for $C_{18}H_{26}O_3$ 290.1882, found 290.1854; IR (neat) 2993-2843, 1745, 1024, 933, 577.

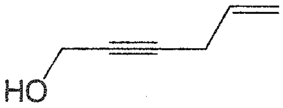
Isomer B (27.9 mg, 27%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.84 (ddd, *J* = 17.1, 10.7, 6.2, 1H), 5.65 (ddd, *J* = 17.1, 10.7, 4.7, 1H), 5.52 (dd, *J* = 4.6, 1.4, 1H), 5.30 (q, 1H), 5.25 (ddd, *J* = 17.2, 1.3, 1.3, 1H), 5.12 (ddd, *J* = 10.5, 1.3, 1.3, 1H), 5.06 (ddd, *J* = 10.7, 1.3, 1.3, 1H), 5.0 (ddd, *J* = 17.1, 1.3, 1.3, 1H), 2.03-1.97 (m, 2H), 2.01 (s, 3H), 2.00 (s, 3H), 1.67-1.64 (m, 1H), 1.82-1.77 (m, 1H), 1.44-1.38 (m, 2H), 1.33 (s, 3H), 1.09 (s, 3H), 0.83 (s, 3H); ^{13}C NMR δ 170.10, 169.74, 137.10, 136.80, 115.85, 114.67, 72.90, 72.81, 68.88, 62.85, 49.28, 41.91, 37.84, 34.54, 31.86, 29.31, 23.33, 21.14, 18.32, 16.11; HRMS calcd. for $C_{18}H_{26}O_3$ [M^+-AcOH] 290.1882, found 290.1821; IR (neat) 2983-2803, 1746, 1033, 1000, 933, 578.



3-Isopropenyl-4-methyl-pent-3-enal (2.48).[174]

3-Isopropenyl-4-methyl-pent-3-en-1-ol **2.85** (5.0 g, 0.036 mol, 1 eq.) in THF (90 mL) was added to a suspension of IBX (15 g, 0.054 mol, 1.5 eq.) in DMSO (10 mL, 0.144 mol, 4 eq.) at 0 °C. The solution was stirred then for 5 h at 22 °C. Water (60 mL) was added and after filtration the solution was extracted with ether (2x60 mL), the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. Purification by flash chromatography (75/25, PE/E) provided the title compound (4.5 g, 91%).

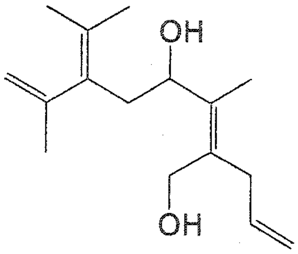
^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.48 (t, 1H), 4.92-4.91 (m, 1H), 4.61-4.60 (m, 1H), 3.11 (d, br, 2H), 1.71 (s, 6H), 1.64 (s, 3H); ^{13}C NMR δ 200.2, 146.3, 131.9, 127.4, 114.5, 47.1, 22.5, 22.1, 20.5; DEPT δ -114.5, -47.1, HRMS [M^+] calcd. for $C_9H_{14}O$ 138.1045, found 138.1052; IR (neat) 3077, 2969-2722, 1725, 1444, 1374, 899.



Hex-5-en-2-yn-1-ol (2.153).

Acetone (400 mL), propargyl alcohol (5.8 mL, 0.10 mol, 1.0 eq.), allyl bromide (10.4 mL, 0.12 mol, 1.2 eq.), potassium carbonate (27.6 g, 0.20 mol, 2.0 eq.), sodium iodide (30 g, 0.20 mol, 2.0 eq.) and cupper iodide (19 g, 0.10 mol, 1.0 eq.), were placed in a two-necked flask fitted with a magnetic stirrer. The reaction mixture was stirred at 22 °C for 5 h. The reaction mixture was then treated with 1N HCl (120 mL) and diluted with water (500 mL). After stirring the reaction mixture was filtered and the filtrate extracted with ether (5x100 mL). The organic extracts were combined, dried and evaporated. After purification by distillation (80-82 °C at 3 mmHg), the title compound was obtained (8.8 g, 92%).

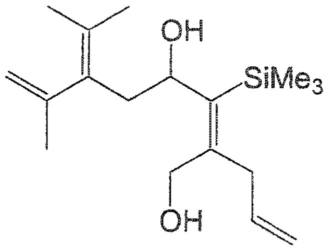
^{1}H NMR (C_6D_6, 300 MHz) δ 5.80 (dddd, *J* = 16.6, 10.6, 6.0, 5.6, 1H), 5.27 (ddd, *J* = 17.0, 3.5, 1.7, 1H), 5.07 (ddd, *J* = 10.0, 3.3, 1.6, 1H), 4.24 (t, *J* = 2.2, 2H), 2.98-2.94 (m, 2H), 2.33 (s, 1H); ^{13}C NMR δ 132.8, 116.1, 82.3, 81.9, 51.1, 23.2; DEPT δ -116.1, -51.1, -23.2; HRMS [M^+] calcd. for C_6H_8O 96.0575, found 96.0560; IR (neat) 3351, 3086-2983, 2918-2872, 1642, 1420, 1011, 918, 780.



2-Allyl-6-isopropenyl-3,7-dimethyl-octa-2,6-diene-1,4-diol (2.115).

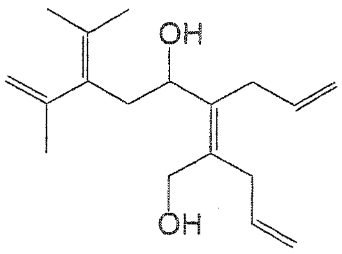
Allylmagnesium chloride (31.82 mL, 63.65 mmol, 2.5 eq.) was added to a suspension of 2-butyn-1-ol **2.114** (1.90 mL, 25.46 mmol, 1.0 eq.) and magnesium chloride (2.60 g, 28.00 mmol, 1.1 eq.) in cyclohexane (15 mL) at 22 °C. The solution was heated at reflux for 18 h, cooled to -78 °C and a solution of 3-isopropenyl-4-methyl-pent-3-enal (3.8 g, 28.00 mmol, 1.3 eq.) in ether (40 mL) was added. The solution was stirred for 1 h at -78 °C, 1 h at 0 °C and 1 h at 22 °C. The reaction was cooled to 0 °C followed by standard workup with NH_4Cl, ether (2x150 mL) and $MgSO_4$. Purification by flash column chromatography (45/55, PE/E) provided the title compound (5.0 g, 79%).

^{1}H NMR (C_6D_6, 300 MHz) δ 5.78 (dddd, *J* = 16.9, 10.2, 6.4, 6.4, 1H), 5.05 (dd, *J* = 17.1, 2.0, 1H), 5.00 (d, 1H), 4.99 (dd, *J* = 10.0, 2.0, 1H), 4.83 (dd, *J* = 8.1, 5.7, 1H), 4.69 (dd, *J* = 2.6, 0.8, 1H), 4.31 (d, *J* = 11.6, 1H), 3.93 (d, *J* = 11.6, 1H), 3.00 (s, br, 2H), 2.95 (d, *J* = 6.2, 2H), 2.6 (dd, *J* = 13.9, 8.1, 1H), 2.25 (dd, *J* = 13.9, 5.6, 1H), 1.77 (s, 3H), 1.75 (s, 3H), 1.74 (s, 3H), 1.67 (s, 3H); ^{13}C NMR δ 146.7, 137.3, 136.1, 133.6, 132.5, 128.9, 115.2, 114.3, 69.6, 60.8, 37.2, 36.3, 22.6, 22.1, 20.3, 13.0; DEPT δ -115.2, -114.3, -60.8, -37.2, -36.3; HRMS [M$^+$-H_2O] calcd. for $C_{16}H_{24}O$ 232.1827, found 232.1813; IR (neat) 3268, 2995-2859, 1447, 1010, 996, 902.



2-Allyl-6-isopropenyl-7-methyl-3-trimethysilanyl-octa-2,6-diene-1,4-diol (2.130). Allylmagnesium chloride (48.7 mL, 97.47 mmol, 2.5 eq., 2M in THF) was added to a suspension of 3-trimethylsilanyl-prop-2-yn-1-ol **2.129** (5.8 mL, 38.99 mmol, 1.0 eq.) and magnesium chloride (4.08 g, 42.88 mmol, 1.1 eq.) in cyclohexane (60 mL) at 22 °C. The suspension was heated at reflux for 18 h, cooled to -78 °C and a solution of 3-isopropenyl-4-methyl-pent-3-enal (5.93 g, 42.88 mmol, 1.1 eq.) in ether (66 mL) was added. The solution was stirred for 1 h at -78 °C, 1 h at 0 °C and 1 h at 22 °C. The reaction was cooled to 0 °C followed by standard workup with NH_4Cl, ether (2x200 mL) and $MgSO_4$. Purification by flash column chromatography (5/5, PE/E) provided the title compound (4.9 g, 43%).

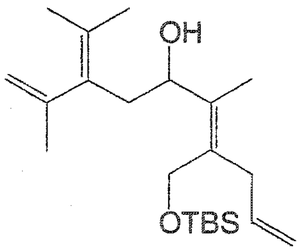
^{1}H NMR (C_6D_6, 500 MHz) δ 5.80 (dddd, *J* = 16.9, 10.4, 6.3, 6.3, 1H), 5.08 (ddd, *J* = 17.1, 3.5, 1.7, 1H), 5.03 (ddd, *J* = 10.1, 3.0, 1.5, 1H), 4.98 (dd, *J* = 2.4, 1.4, 1H), 4.74 (dd, *J* = 10.4, 3.1, 1H), 4.65 (dd, *J* = 1.8, 0.7, 1H), 4.30 (d, *J* = 11.8, 1H), 4.14 (d, *J* = 11.8, 1H), 3.14-3.04 (m, 2H), 2.76 (dd, *J* = 14.2, 10.4, 2H), 2.31 (s, br, 1H), 2.10 (d, *J* = 14.2, 1H), 1.73 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 0.31 (s, 9H); ^{13}C NMR δ 149.0, 146.7, 142.3, 137.1, 133.9, 129.2, 116.6, 114.2, 72.1, 61.7, 40.1, 39.0, 22.6, 22.0, 20.3, 2.2; DEPT δ -116.6, -114.2, -61.7, -40.1, -39.0; HRMS [M$^+$-H_2O] calcd. for $C_{18}H_{30}OSi$ 290.2066, found 290.2012; IR (neat) 3386, 3077, 2962-2852, 1442, 1250, 1088-996, 838.



2,3-Diallyl-6-isopropenyl-7-methyl-octa-2,6-diene-1,4-diol (2.151).

Allylmagnesium chloride (2M in THF, 8.46 mL, 16.93 mmol, 2.5 eq.) was added to a solution of hex-5-en-2-yn-1-ol **2.153** (0.65 g, 6.77 mmol, 1.0 eq.) in cyclohexane (6 mL) containing magnesium chloride (0.71 g, 7.45 mmol, 1.1 eq.) at 22 °C. The suspension was heated at reflux for 18 h, cooled to -78 °C and a solution of 3-isopropenyl-4-methyl-pent-3-enal (1.03 g, 7.45 mmol, 1.1 eq.) in ether (11 mL) was added. The solution was stirred for 1 h at -78 °C, 1 h at 0 °C and 1 h at 22 °C. The reaction was cooled to 0 °C followed by standard workup with NH_4Cl, ether (2x200 mL) and $MgSO_4$. Purification by flash column chromatography (5/5, PE/E) provided the title compound (1.19 g, 64%).

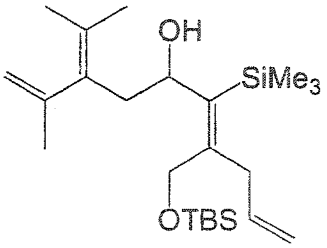
^{1}H NMR (C_6D_6, 300 MHz) δ 5.87-5.70 (m, 2H), 5.06 (dd, *J* = 5.1, 1.7, 1H), 5.02-4.98 (m, 4H), 4.61 (t, br, 1H), 4.54 (dd, *J* = 10.1, 3.5, 1H), 4.16 (d, *J* = 11.8, 1H), 4.03 (d, *J* = 11.8, 1H), 2.96-2.88 (m, 3H), 2.81 (dd, *J* = 15.6, 6.5, 1H), 2.62 (dd, *J* = 14.1, 10.2, 1H), 2.18 (s, br, 1H), 2.13 (d, br, *J* = 14.2, 2H), 1.77 (d, 3H), 1.71 (s, 3H), 1.70 (s, 3H); ^{13}C NMR δ 146.4, 138.2, 137.3, 136.3, 135.4, 133.3, 130.3, 116.1, 115.7, 114.7, 71.1, 61.4, 37.7, 36.4, 33.5, 22.9, 22.4, 20.6; DEPT δ -116.1, -115.7, -114.7, -61.4, -37.7, -36.4, -33.5; HRMS [M^+-H_2O] calcd. for $C_{18}H_{26}O$ 258.1984, found 258.1978; IR (neat) 3303, 2955-2872, 1637, 1448, 1060, 993, 890.



7-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-isopropylidene-2,6-dimethyl-deca-1,6,9-trien-5-ol (2.116).

tert-Butyldimethylsilyl chloride (2.59 g, 17.2 mmol, 1.1 eq.) and DMAP (2.10 g, 17.2 mmol, 1.1 eq.) were sequentially added to a solution of 2-allyl-6-isopropenyl-3,7-dimethyl-octa-2,6-diene-1,4-diol **2.115** (3.90 g, 15.6 mmol, 1.0 eq.) in CH_2Cl_2 (50 mL) at 0 °C. The solution was stirred for 6 h at 23 °C. Standard workup with $NaHCO_3$, ether (2x30 mL) and $MgSO_4$, followed by purification by flash column chromatography (88/12, PE/E) provided the title compound as colorless oil (5.3 g, 94 %).

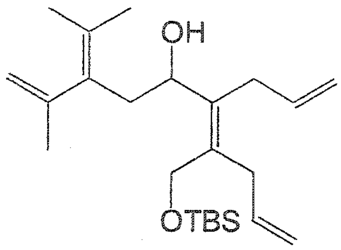
^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.73 (dddd, *J* = 17.2, 10.0, 6.5, 6.4, 1H), 4.99-4.96 (m, 1H), 4.97 (dd, *J* = 17.4, 1.9, 1H), 4.95 (dd, *J* = 10.2, 1.6, 1H), 4.70 (dd, *J* = 9.6, 4.1, 1H), 4.61 (dd, *J* = 2.0, 0.8, 1H), 4.17 (d, *J* = 11.5, 1H), 4.02 (d, *J* = 11.4, 1H), 2.87 (dd, *J* = 14.4, 6.4, 2H), 2.59 (dd, *J* = 14.0, 9.6, 1H), 2.04 (dd, *J* = 14.0, 4.0, 1H), 1.78 (s, 3H), 1.73 (s, 3H), 1.73 (s, br, 1H), 1.71 (s, 3H), 1.70 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR δ 146.2, 135.8, 135.4, 133.0, 132.0, 129.2, 114.8, 114.0, 69.0, 60.7, 36.8, 34.8, 26.0, 22.6, 21.9, 20.1, 18.4, 12.4, -5.4; DEPT δ -114.8, -114.0, -60.7, -36.8, -34.8; HRMS [M^+-H_2O] calcd. for $C_{22}H_{38}OSi$ 346.2692, found 346.2688; IR (neat) 3463, 3076, 2956-2858, 1636, 1255, 1070-1005, 837, 776.



7-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-isopropylidene-2-methyl-6-trimethylsilanyl-deca-1,6,9-trien-5-ol (2.131).

tert-Butyldimethylsilyl chloride (1.69 g, 11.07 mmol, 1.1 eq.) and DMAP (1.35 g, 11.07 mmol, 1.1 eq.) were sequentially added to a solution of 2-allyl-6-isopropenyl-7-methyl-3-trimethysilanyl-octa-2,6-diene-1,4-diol **2.130** (3.10 g, 10.10 mmol, 1.0 eq.) in CH_2Cl_2 (47 mL) at 0 °C. The solution was stirred for 6 h at 23 °C. Standard workup with $NaHCO_3$, ether (2x20 mL) and $MgSO_4$, followed by purification by flash chromatography (95/5, PE/E) provided the title compound as colorless oil (3.0 g, 71%).

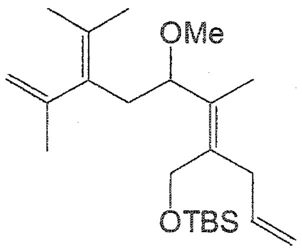
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.75 (dddd, *J* = 17.0, 10.1, 6.6, 6.6, 1H), 5.03-4.99 (m, 3H), 4.69 (dd, *J* = 10.7, 2.9, 1H), 4.63 (dd, *J* = 2.4, 0.9, 1H), 4.32 (d, *J* = 12.2, 1H), 4.10 (d, *J* = 12.2, 1H), 3.12 (dd, *J* = 14.2, 6.5, 1H), 3.00 (dd, *J* = 14.1, 6.3, 1H), 2.65 (dd, *J* = 14.3, 10.7, 1H), 1.97 (d, *J* = 12.8, 1H), 1.78 (s, 4H), 1.74 (s, 3H), 1.70 (s, 3H), 0.88 (s, 9H), 0.23 (s, 9H), 0.02 (s, 6H); ^{13}C NMR δ 148.1, 146.2, 140.3, 137.1, 133.5, 129.0, 115.8, 114.0, 71.6, 60.8, 38.6, 37.2, 25.9, 22.7, 21.9, 20.3, 18.3, 2.6, -5.4; DEPT δ -115.8, -114.0, -60.8, -38.6, -37.2; IR (neat) 2956-2857, 1251, 1073, 839, 775.



6-Allyl-7-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropylidene-2-methyl-deca-1,6,9-trien-5-ol (2.154).

tert-Butyldimethylsilyl chloride (0.20 g, 1.32 mmol, 1.1 eq.) and DMAP (0.16 g, 1.32 mmol, 1.1 eq.) were sequentially added to a solution of 2,3-diallyl-6-isopropenyl-7-methyl-octa-2,6-diene-1,4-diol **2.151** (0.33 g, 1.20 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) at 0 °C and the solution was stirred for 6 h at 23 °C. Standard workup with $NaHCO_3$, ether (2x3 mL) and $MgSO_4$, followed by purification by flash chromatography (95/5 to 92/8, PE/E) provided the title compound as colorless oil (0.38 g, 81%).

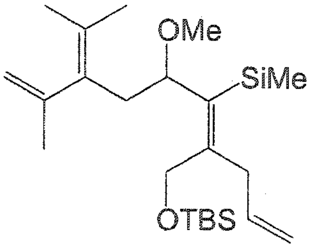
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.86 (dddd, *J* = 16.9, 10.4, 6.2, 6.2, 1H), 5.74 (dddd, *J* = 16.9, 10.3, 6.4, 6.4, 1H), 5.09-4.94 (m, 5H), 4.68 (dd, *J* = 10.3, 3.5, 1H), 4.62 (d, 1H), 4.19 (d, *J* = 11.6, 1H), 4.06 (d, *J* = 11.6, 1H), 2.96-2.81 (m, 4H), 2.60 (dd, *J* = 14.1, 10.3, 1H), 1.98 (d, 1H), 1.81 (s, 1H), 1.78 (d, 3H), 1.71 (s, 3H), 1.70 (s, 3H), 0.86 (s, 9H), 0.024 (s, 6H); ^{13}C NMR δ 146.4, 138.1, 136.8, 136.6, 134.7, 133.3, 129.8, 115.6, 115.2, 114.4, 69.8, 60.7, 37.9, 34.8, 32.2, 26.3, 23.0, 22.3, 20.6, 18.7, -5.0; DEPT δ -115.6, -115.2, -114.4, -60.7, -37.9, -34.7, -32.2; Elemental analysis calcd. for C (73.78%), H (10.84%), found C (73.67%), H (10.64%); IR (neat) 3477, 3077-2857, 1635, 1255, 1067, 837, 776.



(2-Allyl-6-isopropenyl-4-methoxy-3,7-dimethyl-octa-2,6-dienyloxy)-*tert*-butyl-dimethyl-silane (2.117).

Sodium hydride (1.61 g, 40.38 mmol, 3.0 eq., 60 % dispersion in mineral oil) was added to a solution of 7-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropylidene-2,6-dimethyl-deca-1,6,9-trien-5-ol **2.116** (4.90 g, 13.46 mmol, 1.0 eq.) in THF (50 mL) at 0 °C. After 30 min iodomethane (6.7 mL, 107.7 mmol, 8.0 eq.) was added and the solution was then stirred for 6 h at 23 °C. Standard workup with NH_4Cl, ether (2x50 mL) and $MgSO_4$ was performed. Purification by flash column chromatography (95/5, PE/E) provided the title compound (4.7 g, 92%).

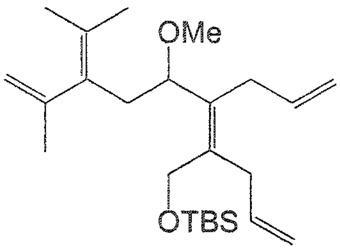
^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.74 (dddd, *J* = 16.9, 10.4, 6.3, 6.3, 1H), 4.97 (dd, *J* = 10.1, 1.7, 1H), 4.96-4.95 (m, 1H), 4.94 (dd, *J* = 16.9, 1.5, 1H), 4.56 (d, *J* = 2.7, 1H), 4.23 (d, *J* = 11.4, 1H), 4.17 (dd, *J* = 7.8, 5.7, 1H), 3.91 (d, *J* = 11.4, 1H), 2.97 (s, 3H), 2.90 (d, br, 2H), 2.52 (dd, *J* = 14.2, 7.8, 1H), 2.08 (dd, *J* = 14.3, 5.6, 1H), 1.7 (s, 3H), 1.66 (s, 3H), 1.65 (s, 3H), 1.61 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR δ 146.3, 135.9, 134.1, 133.2, 133.1, 127.3, 114.6, 113.7, 78.2, 60.3, 56.0, 35.7, 34.7, 25.9, 22.7, 21.9, 20.2, 11.9, -5.4, -5.3; DEPT δ -114.6, -113.7, -60.3, -35.7, -34.7; Elemental analysis calcd. for C (72.95%), H (11.18%), found C (73.16%), H (11.12%); IR (neat) 3077, 2956-2820, 1255, 1100-1051, 837, 775.



4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-8-isopropenyl-6-methoxy-9-methyl-5-trimethylsilanyl-deca-1,4,8-triene (2.132).

n-Butyllithium (3.4 mL, 7.82 mmol, 1.1 eq., 2.4 M in hexane) was added to a solution of 7-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropylidene-2-methyl-6-trimethylsilanyl-deca-1,6,9-trien-5-ol **2.131** (3.0 g, 7.11 mmol, 1.0 eq.) in THF (51 mL) at -78 °C. After 30 min iodomethane (2.21 mL, 35.54 mmol, 5.0 eq.) was added and the solution was then stirred for 30 min at -78 °C, 1 h at 0 °C and then 2 h at 22 °C. Standard workup with NH_4Cl, ether (2x25 mL) and $MgSO_4$ was performed. Purification by flash column chromatography (9/1, PE/CH_2Cl_2) provided the title compound (2.79 g, 90%).

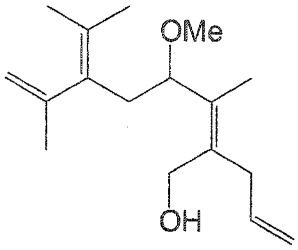
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.77 (dddd, *J* = 16.8, 10.5, 6.4, 6.4, 1H), 5.02 (d, *J* = 17.9, 1H), 5.01 (d, *J* = 9.1, 1H), 4.98 (q, 1H), 4.59 (q, 1H), 4.35 (d, *J* = 11.8, 1H), 4.14 (d, *J* = 5.3, 1H), 3.99 (s, broad, 1H), 3.12 (s, 3H), 3.10 (dd, br, 1H), 3.04 (dd, br, 1H), 2.65 (dd, *J* = 14.5, 9.3, 1H), 1.95 (dd, *J* = 14.4, 3.2, 1H), 1.76 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 0.88 (s, 9H), 0.21 (s, 9H), 0.02 (s, 6H); ^{13}C NMR δ 146.3, 136.9, 133.7, 126.8, 115.8, 113.6, 80.7, 60.3, 56.5, 37.7, 37.6, 25.9, 22.7, 21.9, 20.2, 18.2, 2.3, -5.5, -5.4; DEPT δ -115.8, -113.6, -60.3, -37.7, -37.6; IR (neat) 3077-2814, 1251, 1102, 839, 775.



tert-Butyl-(2,3-diallyl-6-isopropenyl-4-methoxy-7-methyl-octa-2,6-dienyloxy)-dimethyl-silane (2.155).

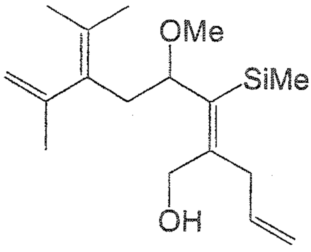
Sodium hydride (0.1 g, 2.59 mmol, 3.0 eq., 60 % dispersion in mineral oil) was added to a solution of 6-allyl-7-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropylidene-2-methyl-deca-1,6,9-trien-5-ol **2.154** (0.33 g, 0.86 mmol, 1.0 eq.) in THF (3.4 mL) at 0 °C. After 30 min iodomethane (0.4 mL, 6.89 mmol, 8.0 eq.) was added and the solution was then stirred for 6 h at 23 °C. Standard workup with NH_4Cl, ether (2x6 mL) and $MgSO_4$ was performed. Purification by flash column chromatography (97/3, PE/E) provided the title compound (0.3 g, 89%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.83-5.71 (m, 2H), 5.07-4.95 (m, 5H), 4.59 (d, br, 1H), 4.25 (d, *J* = 11.4, 1H), 4.10 (dd, *J* = 9.3, 4.1, 1H), 4.02 (d, *J* = 11.4, 1H), 3.09 (s, 3H), 2.91 (dd, *J* = 6.2, 4.8, 2H), 2.86-2.82 (m, br, 2H), 2.60 (dd, *J* = 14.5, 9.3, 1H), 1.99 (d, br, 1H), 1.75 (d, 3H), 1.66 (s, 6H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR δ 146.6, 137.8, 136.8, 136.2, 135.2, 133.7, 127.5, 115.6, 115.4, 114.1, 79.3, 60.3, 57.0, 36.8, 34.7, 32.5, 26.3, 23.1, 22.3, 20.5, 18.7, -5.0, -5.0; DEPT δ -115.5, -115.4, -114.0, -60.3, -36.8, -34.8, -32.5; IR (neat) 3077-2814, 1635, 1463-1446, 1255, 1101-1069, 837, 775.



2-Allyl-6-isopropenyl-4-methoxy-3,7-dimethyl-octa-2,6-dien-1-ol (2.118). Tetrabutylammonium fluoride (22.22 mL, 22.22 mmol, 2.0 eq., 1.0 M in THF) was added to a solution of (2-allyl-6-isopropenyl-4-methoxy-3,7-dimethyl-octa-2,6-dienyloxy)-*tert*-butyl-dimethyl-silane **2.117** (4.2 g, 11.11 mmol, 1.0 eq.) in THF (20 mL) at 0 °C. The solution was stirred for 3 h at 23 °C. Standard workup with NH_4Cl, ether (2x50 mL) and $MgSO_4$ was performed. Purification by flash column chromatography (8/2, PE/E) provided the title compound (2.8 g, 96%).

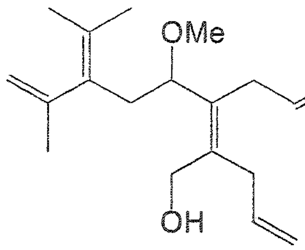
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.77 (dddd, *J* = 16.7, 10.0, 6.6, 6.4 1H), 5.00 (ddd, *J* = 11.8, 3.3, 1.6, 1H), 4.98-4.94 (m, 2H), 4.56 (d, *J* = 2.0, 1H), 4.17 (d, *J* = 6.8, 1H), 4.09 (d, *J* = 11.9, 1H), 4.00 (d, *J* = 11.9, 1H), 3.03 (s, 3H), 2.90 (t, 2H), 2.50 (dd, *J* = 14.0, 6.4, 1H), 2.19 (dd, *J* = 14.0, 7.3, 1H), 1.74 (s, 3H), 1.65 (s, 6H), 1.61 (s, 3H), 1.39 (s, br, 1H); ^{13}C NMR δ 146.5, 135.9, 135.3, 134.9, 133.7, 128.6, 115.6, 114.2, 78.7, 61.2, 56.2, 36.3, 35.6, 23.0, 22.2, 20.5, 12.4; DEPT δ -115.6, -114.2, -61.2, -36.3, -35.6; Elemental analysis calcd. for C (77.22%), H (10.67%), found C (77.36%), H (10.51%); IR (neat) 3448, 3077, 2956-2820, 1636, 1445, 1098, 996, 898.



2-Allyl-6-isopropenyl-4-methoxy-7-methyl-3-trimethysilanyl-octa-2,6-dien-1-o (2.133).

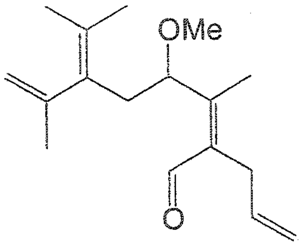
Tetrabutylammonium fluoride (4.5 mL, 4.13 mmol, 2.0 eq., 1.0 M in THF) was added to a solution of 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-8-isopropenyl-6-methoxy-9-methyl-5-trimethylsilanyl-deca-1,4,8-triene **2.132** (0.97 g, 2.06 mmol, 1.0 eq.) in THF (4.5 mL) at 0 °C. The solution was stirred for 3 h at 23 °C and standard workup with NH_4Cl, ether (2x5 mL) and $MgSO_4$ was performed. Purification by flash column chromatography (9/1, PE/E) provided the title compound (0.65 g, 90%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78 (dddd, *J* = 17.6, 9.6, 6.1, 6.1, 1H), 5.08 (ddd, *J* = 11.0, 3.6, 1.6, 1H), 5.05 (s, br, 1H), 5.02 (d, br, *J* = 18.0, 1H), 4.60 (d, *J* = 1.9, 1H), 4.18 (d, *J* = 12.7, 1H), 4.11 (dd, *J* = 8.7, 4.4, 1H), 4.08 (d, *J* = 12.7, 1H), 3.16 (s, 3H), 3.04 (dd, *J* = 6.1, 1.1, 2H), 2.71 (dd, *J* = 14.5, 8.9, 1H), 2.18 (s, br, 1H), 2.04 (dd, *J* = 14.5, 3.8, 1H), 1.75 (s, 3H), 1.68 (s, 3H), 1.65 (s, 3H), 0.19 (s, 9H); ^{13}C NMR δ 149.7, 146.6, 141.2, 137.0, 134.0, 127.9, 117.1, 114.3, 81.6, 62.2, 57.2, 40.2, 37.9, 23.1, 22.3, 20.6, 2.2; DEPT δ -117.1, -114.3, -62.2, -40.1, -37.9; IR (neat) 3433, 3076, 2963-2814, 1636, 1443, 1250, 1100, 996, 838.



2,3-Diallyl-6-isopropenyl-4-methoxy-7-methyl-octa-2,6-dien-1-ol (2.156). Tetrabutylammonium fluoride (1.5 mL, 1.49 mmol, 2.0 eq., 1.0 M in THF) was added to a solution of *tert*-butyl-(2,3-diallyl-6-isopropenyl-4-methoxy-7-methyl-octa-2,6-dienyloxy)-dimethyl-silane **2.155** (0.30 g, 0.75 mmol, 1.0 eq.) in THF (1.5 mL) at 0 °C. The solution was stirred for 3 h at 23 °C. Standard workup with NH_4Cl, ether (2x5 mL) and $MgSO_4$ was performed. Purification by flash column chromatography (8/2, PE/E) provided the title compound (0.2 g, 93%).

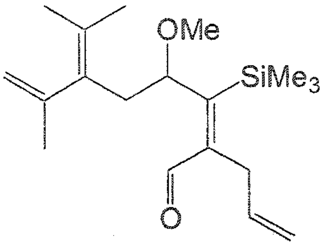
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.85-5.68 (m, 2H), 5.07-4.96 (m, 5H), 4.58 (s, 1H), 4.16 (d, *J* = 12.2, 1H), 4.07 (d, *J* = 12.2, 1H), 4.03 (dd, *J* = 8.2, 5.0, 1H), 3.17 (s, 3H), 2.94 (d, *J* = 6.1, 1H), 2.90 (d, *J* = 6.0, 1H), 2.85 (d, *J* = 5.9, 1H), 2.74 (dd, *J* = 15.2, 7.1, 1H), 2.62 (dd, *J* = 14.3, 8.3, 1H), 2.12 (dd, *J* = 14.4, 4.6, 1H), 1.88 (s, 1H), 1.79 (s, 3H), 1.63 (s, 6H); ^{13}C NMR δ 146.6, 137.1, 136.9, 136.4, 136.1, 133.7, 128.2, 116.2, 115.8, 114.3, 80.2, 61.4, 57.2, 36.6, 36.1, 33.5, 23.0, 22.3, 20.5; DEPT δ -116.2, -115.8, -114.3, -61.4, -36.6, -36.1, -33.5; Elemental analysis calcd. for C (78.57%), H (10.41%), found C (77.09%), H (9.97%); IR (neat) 3423, 3077, 2977-2814, 1635, 1446, 1100, 992, 909.



2-Allyl-6-isopropenyl-4-methoxy-3,7-dimethyl-octa-2,6-dienal (2.119).

2-Allyl-6-isopropenyl-4-methoxy-3,7-dimethyl-octa-2,6-dien-1-ol **2.118** (4.0 g, 15.15 mmol, 1.0 eq.) in THF (72 mL) was added to a suspension of IBX (6.36 g, 22.73 mmol, 1.5 eq.) in DMSO (4.3 mL, 60.60 mmol, 4.0 eq.) at 0 °C. The suspension was stirred for 3 h at 23 °C. Water (100 mL) was added and after filtration the solution was extracted with ether (2x70 mL), the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (95/5, PE/E) provided the title compound (3.6 g, 90%).

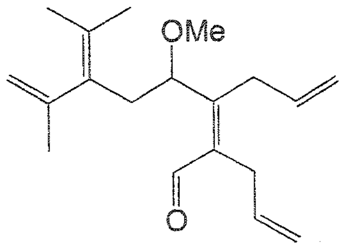
^1H NMR ($CDCl_3$, 300 MHz) δ 10.07 (s, 1H), 5.67 (ddd, *J* = 16.6, 11.0, 6.0, 1H), 4.97 (s, 1H), 4.92 (d, *J* = 10.6, 1H), 4.89 (d, *J* = 17.8, 1H), 4.78 (t, *J* = 6.8, 1H), 3.16 (s, 3H), 3.08 (dd, *J* = 15.1, 5.8, 1H), 2.95 (dd, *J* = 15.1, 5.8, 1H), 2.60 (dd, *J* = 14.1, 7.8, 1H), 2.27 (dd, *J* = 14.2, 6.8, 1H), 1.88 (s, 3H), 1.73 (s, 3H), 1.62 (s, 6H); ^{13}C NMR δ 189.4, 158.9, 145.7, 138.3, 134.8, 132.0, 129.5, 115.3, 76.8, 56.9, 35.8, 30.4, 22.8, 22.3, 20.4, 14.7; DEPT δ -115.3 (2), -35.8, -30.4; HRMS [M^+-CH_3OH] calcd. for $C_{16}H_{22}O$ 230.1671, found 230.1643; IR (neat) 3079-2820, 1671, 1443, 1100, 907.



2-Allyl-6-isopropenyl-4-methoxy-7-methyl-3-trimethysilanyl-octa-2,6-dienal (2.134).

2-Allyl-6-isopropenyl-4-methoxy-7-methyl-3-trimethysilanyl-octa-2,6-dien-1-ol **2.133** (0.698 g, 2.17 mmol, 1.0 eq.) in THF (13 mL) was added to a suspension of IBX (0.91 g, 3.25 mmol, 1.5 eq.) in DMSO (0.62 mL, 8.68 mmol, 4.0 eq.) at 0 °C. The suspension was stirred for 3 h at 23 °C. Water (20 mL) was added and after filtration the solution was extracted with ether (2x15 mL), the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (94/6, PE/E) provided the title compound (0.51 g, 73%).

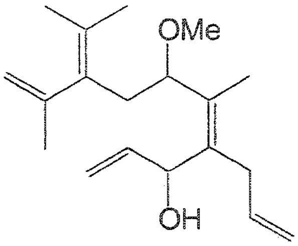
^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.19 (s, 1H), 5.77 (dddd, *J* = 16.9, 10.9, 5.6, 5.6, 1H), 4.97 (dd, *J* = 10.8, 1.3, 1H), 4.96 (s, 1H), 4.92 (dd, *J* = 17.8, 1.6, 1H), 4.58 (d, *J* = 2.0, 1H), 4.48 (dd, *J* = 8.8, 3.2, 1H), 3.17-3.11 (m, 2H), 3.15 (s, 3H), 2.71 (dd, *J* = 14.7, 9.2, 1H), 2.14 (dd, *J* = 14.7, 3.2, 1H), 1.74 (s, 3H), 1.66 (s, 3H), 1.65 (s, 3H), 0.24 (s, 9H); ^{13}C NMR δ 193.5, 147.8, 146.1, 136.3, 132.9, 128.7, 116.2, 114.8, 80.4, 57.3, 38.7, 34.4, 23.0, 22.3, 20.6, 1.5; DEPT δ -116.2, -114.8, -38.4, -34.4; IR (neat) 3077-2817, 1673, 1252, 1100, 905-841.



2,3-Diallyl-6-isopropenyl-4-methoxy-7-methyl-octa-2,6-dienal (2.157).

2,3-Diallyl-6-isopropenyl-4-methoxy-7-methyl-octa-2,6-dien-1-ol **2.156** (2.12 g, 7.131 mmol, 1.0 eq.) in THF (38 mL) was added to a suspension of IBX (3.07 g, 10.97 mmol, 1.5 eq.) in DMSO (3.1 mL, 43.86 mmol, 6.0 eq.) at 0 °C. The suspension was stirred for 5 h at 23 °C. Water (80 mL) was added and after filtration the solution was extracted with ether (2x50 mL), the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (95/5, PE/E) provided the title compound (1.96 g, 93%).

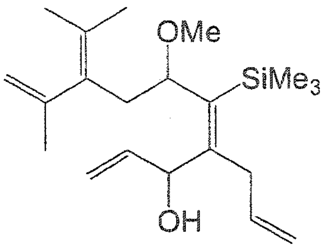
^1H NMR (C_6D_6, 300 MHz) δ 10.49 (s, 1H), 5.82 (dddd, *J* = 16.9, 10.4, 6.3, 6.3, 1H), 5.66 (dddd, *J* = 16.8, 10.2, 6.5, 6.5, 1H), 5.01 (dd, *J* = 16.7, 1.6, 2H), 4.95 (dd, br, 3H), 4.66 (d, 1H), 4.51 (dd, *J* = 8.5, 4.6, 1H), 3.24 (dd, *J* = 15.0, 6.2, 1H), 3.06 (dd, *J* = 14.3, 5.3, 1H), 2.99 (dd, *J* = 13.7, 5.1, 1H), 2.91 (s, 3H), 2.84 (dd, *J* = 14.3, 7.3, 1H), 2.73 (dd, *J* = 14.4, 8.6, 1H), 2.16 (dd, *J* = 14.4, 4.5, 1H), 1.68 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H); ^{13}C NMR δ 189.9, 157.1, 146.1, 138.3, 135.9, 134.9, 132.9, 128.8, 117.2, 115.4, 114.9, 79.0, 57.0, 37.5, 34.8, 30.6, 22.6, 22.2, 20.4; DEPT δ -117.2, -115.4, -114.9, -37.5 -34.8, -30.6; HRMS [M^+-CH_3OH] calcd. for $C_{18}H_{24}O$ 256.1827, found 256.1808; IR (neat) 3079-2821, 1671, 1637, 1446, 1101, 911.



4-Allyl-8-isopropenyl-6-methoxy-5,9-dimethyl-deca-1,4,8-trien-3-ol (2.120). Vinylmagnesium chloride (7.96 mL, 12.73 mmol, 2.0 eq., 1.6 M in THF) was added to a solution of 2-allyl-6-isopropenyl-4-methoxy-3,7-dimethyl-octa-2,6-dienal **2.119** (1.67 g, 6.37 mmol, 1.0 eq.) in ether (22 mL) at -78 °C. The solution was stirred for 1 h at -78 °C and then for 30 min at 0 °C. Standard workup with NH_4Cl, ether (2x40 mL) and $MgSO_4$, followed by purification by flash chromatography (93/7, PE/E) provided the title compound as a mixture of isomers (75%).

Isomer A (1.2 g, 65%): ^1H NMR (C_6D_6, 300 MHz) δ 5.82 (m, 2H), 5.35 (d, *J* = 17.1, 1H), 5.26 (s, broad, 1H), 5.04 (d, *J* = 17.3, 2H), 4.97 (d, *J* = 10.2, 2H), 4.78 (s, 1H), 4.35 (t, *J* = 6.7, 1H), 3.01 (s, 3H), 2.92 (dd, *J* = 15.7, 6.0, 1H), 2.81 (dd, *J* = 15.7, 5.8, 1H), 2.71 (dd, *J* = 14.1, 7.4, 1H), 2.28 (dd, *J* = 14.1, 5.9, 1H), 1.76 (s, 3H), 1.70 (s, 3H), 1.67 (s, 6H), 1.61 (s, br, 1H); ^{13}C NMR δ 146.8, 139.5, 137.3, 135.4, 135.3, 133.9, 127.6, 114.9, 114.3, 114.2, 78.6, 71.1, 56.1, 36.2, 32.8, 22.8, 22.2, 20.4, 12.8; DEPT δ -114.9, -114.3, -114.2, -36.2, -32.8; IR (neat) 3449, 3076-2816, 1635, 1445, 1100, 992, 919.

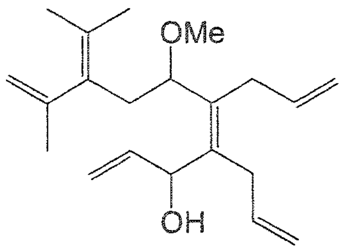
Isomer B (185 mg, 10%): ^1H NMR (C_6D_6, 300 MHz) δ 5.84 (dddd, *J* = 16.9, 10.4, 6.3, 6.2, 1H), 5.77 (ddd, *J* = 17.1, 10.5, 4.5, 1H), 5.36 (ddd, *J* = 17.1, 1.7, 1.7, 1H), 5.29 (s, br, 1H), 5.07 (d, 1H), 5.03-4.96 (m, 3H), 4.76 (d, *J* = 2.1, 1H), 4.38 (dd, *J* = 8.6, 4.6, 1H), 3.06 (s, 3H), 2.86 (d, *J* = 6.0, 2H), 2.76 (dd, *J* = 14.2, 8.6, 1H), 2.06 (dd, *J* = 14.1, 4.4, 1H), 1.76 (s, 3H), 1.71 (s, 3H), 1.69 (s, 6H), 1.60 (d, br, 1H); ^{13}C NMR δ 147.0, 139.8, 137.7, 135.5, 135.0, 133.6, 127.8, 114.9, 114.1, 114.0, 78.0, 70.8, 56.0, 36.0, 32.6, 22.9, 22.2, 20.3, 12.8; DEPT δ -114.9, -114.1, -114.0, -36.0, -32.6; IR (neat) 3449, 3076-2816, 1635, 1445, 1100, 992, 919.



4-Allyl-8-isopropenyl-6-methoxy-9-methyl-5-trimethylsilanyl-deca-1,4,8-trien-3-ol (2.135).

Vinylmagnesium chloride (2.3 mL, 3.63 mmol, 2.0 eq., 1.6 M in THF) was added to a solution of 2-allyl-6-isopropenyl-4-methoxy-7-methyl-3-trimethysilanyl-octa-2,6-dienal **2.134** (0.58 g, 1.82 mmol, 1.0 eq.) in ether (8 mL) at -78 °C. The solution was stirred for 1 h at -78 °C and then for 30 min at 0 °C. Standard workup with NH_4Cl, ether (2x10 mL) and $MgSO_4$, followed by purification by flash chromatography (9/1, PE/E) provided the title compound (0.36 g, 57%).

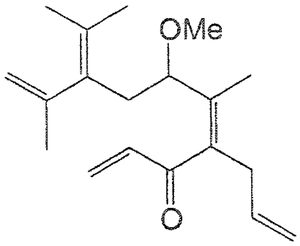
^1H NMR (C_6D_6, 300 MHz) δ 5.98 (ddd, *J* = 17.2, 10.4, 5.4, 1H), 5.88 (dddd, *J* = 17.0, 10.5, 6.1, 6.1, 1H), 5.37 (d, *J* = 17.1, 2H), 5.12-5.04 (m, 3H), 4.98 (ddd, *J* = 10.2, 1.7, 1H), 4.81 (d, *J* = 2.0, 1H), 4.36 (s, br, 1H), 3.11-2.96 (m, 3H), 3.07 (s, 3H), 2.17 (d, *J* = 14.0, 1H), 1.80 (s, 6H), 1.73 (s, 3H), 0.31 (s, 9H); ^{13}C NMR δ 146.9, 140.1, 139.2, 134.2, 128.4, 128.1, 127.8, 116.2, 114.7, 114.3, 81.2, 73.6, 57.3, 38.3, 37.2, 23.0, 22.2, 20.5, 2.6; DEPT δ -116.2, -114.7, -114.3, -38.2, -37.2; IR (neat) 3445, 3076-2814, 1635, 1584, 1443, 1250, 1100, 851-839.



4,5-Diallyl-8-isopropenyl-6-methoxy-9-methyl-deca-1,4,8-trien-3-ol (2.158). Vinylmagnesium chloride (0.7 mL, 0.97 mmol, 2.0 eq., 1.6 M in THF) was added to a solution of 2,3-diallyl-6-isopropenyl-4-methoxy-7-methyl-octa-2,6-dienal **2.157** (0.14 g, 0.49 mmol, 1.0 eq.) in ether (2 mL) at -78 °C. The solution was stirred for 1 h at -78 °C and then for 30 min at 0 °C. Standard workup with NH_4Cl, ether (2x5 mL) and $MgSO_4$, followed by purification by flash chromatography (9/1, PE/E) provided the title compound as a mixture of isomers (60%).

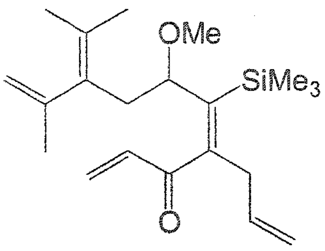
Isomer A (64.5 mg, 42%): ^{1}H NMR (C_6D_6, 300 MHz) δ 5.90 (ddd, J = 17.2, 10.3, 4.7, 1H), 5.84-5.74 (m, 2H), 5.39-5.32 (m, 2H), 5.11 (dd, J = 11.9, 1.8, 1H), 5.08-5.02 (m, 3H), 4.99 (dd, J = 9.2, 1.8, 2H), 4.78 (d, br, 1H), 4.18 (dd, J = 9.3, 3.8, 1H), 3.06 (s, 3H), 3.01-2.93 (m, 3H), 2.90-2.78 (m, 1H), 2.85 (s, 1H), 2.22 (dd, J = 14.3, 3.1, 1H), 1.93 (d, br, 1H), 1.79 (s, 3H), 1.74 (s, 3H), 1.73 (s, 3H); ^{13}C NMR δ 146.9, 139.9, 137.9, 137.1, 136.8, 136.6, 134.0, 128.0, 115.8, 115.2, 114.4, 114.2, 80.3, 72.0, 57.1, 37.3, 34.1, 33.0, 22.9, 22.2, 20.4; DEPT δ -115.8, -115.2, -114.4, -114.2, -37.3, -34.1, -32.9; IR (neat) 3421, 3077-2819, 1636, 1444, 1100, 992, 909.

Isomer B (27.7 mg, 18%): ^{1}H NMR (C_6D_6, 300 MHz) δ 5.90 (ddd, J = 16.7, 10.4, 6.1, 1H), 5.81 (ddd, J = 16.0, 10.3, 7.3, 2H), 5.42 (s, br, 1H), 5.35 (ddd, J = 18.0, 1.7, 1.7, 1H), 5.06-4.95 (m, 5H), 4.79 (d, br, 1H), 4.28 (dd, J = 10.0, 3.3, 1H), 3.06 (s, 3H), 3.05-2.94 (m, 4H), 2.92 (dd, J = 14.4, 10.0, 1H), 2.06 (d, J = 14.4, 1H), 1.79 (s, 3H), 1.75 (s, 3H), 1.74 (s, 3H), 1.38 (d, J = 3.6, 1H); ^{13}C NMR δ 146.9, 139.9, 137.9, 137.2, 136.8, 136.6, 134.0, 128.0, 115.8, 115.2, 114.4, 114.2, 80.3, 72.0, 57.1, 37.3, 34.1, 33.0, 22.9, 22.4, 20.3; DEPT δ -115.8, -115.2, -114.4, -114.2, -37.3, -34.1, -33.0; IR (neat) 3421, 3077-2819, 1636, 1444, 1100, 992, 909.



4-Allyl-8-isopropenyl-6-methoxy-5,9-dimethyl-deca-1,4,8-trien-3-one (2.112). 4-Allyl-8-isopropenyl-6-methoxy-5,9-dimethyl-deca-1,4,8-trien-3-ol **2.120** (2.6 g, 8.96 mmol, 1 eq.) in THF (47 mL) was added to a suspension of IBX (3.77 g, 13.45 mmol, 1.5 eq.) in DMSO (3.8 mL, 53.79 mmol, 6.0 eq.) at 0 °C. The suspension was stirred for 3 h at 23 °C. Water (80 mL) was added and after filtration the solution was extracted with ether (2x50 mL), the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (94/6, PE/E) provided the title compound (2.5 g, 97%).

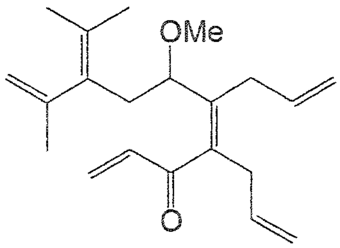
^{1}H NMR (C_6D_6, 300 MHz) δ 6.30 (dd, J = 17.5, 10.4, 1H), 5.95 (dd, J = 17.5, 1.5, 1H), 5.66 (dddd, J = 16.8, 10.3, 6.4, 6.4, 1H), 5.33 (dd, J = 10.4, 1.5, 1H), 5.03 (dd, J = 16.5, 1.0, 1H), 5.01 (t, 1H), 4.94 (dd, J = 10.1, 1.5, 1H), 4.76 (d, 1H), 4.10 (ddd, J = 9.2, 4.0, 1.6, 1H), 3.05 (s, 3H), 2.82 (d, J = 6.5, 2H), 2.72 (dd, J = 14.1, 9.3, 1H), 2.18 (dd, J = 14.1, 2.6, 1H), 1.83 (s, 3H), 1.73 (s, 3H), 1.72 (s, 3H), 1.63 (s, 3H); ^{13}C NMR δ 197.6, 146.7, 139.9, 137.3, 136.1, 134.5, 133.6, 129.0, 127.7, 116.2, 114.2, 80.3, 56.4, 35.8, 34.9, 22.8, 22.2, 20.3, 11.9; DEPT δ -129.0, -116.2, -114.2, -35.8, -34.9; HRMS [M^+-CH_3OH] calcd. for $C_{18}H_{24}O$ 256.1827, found 256.1837; IR (neat) 3077-2820, 1656, 1638, 1443, 1399, 1099, 992.



4-Allyl-8-isopropenyl-6-methoxy-9-methyl-5-trimethysilanyl-deca-1,4,8-trien-3-one (2.136).

4-Allyl-8-isopropenyl-6-methoxy-9-methyl-5-trimethylsilanyl-deca-1,4,8-trien-3-ol **2.135** (0.186 g, 0.53 mmol, 1.0 eq.) in THF (3 mL) was added to a suspension of IBX (0.22 g, 0.80 mmol, 1.5 eq.) in DMSO (0.23 mL, 3.2 mmol, 6.0 eq.) at 0 °C. The suspension was stirred for 3 h at 23 °C. Water (5 mL) was added and after filtration the solution was extracted with ether (2x5 mL), the combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (94/6, PE/E) provided the title compound (0.15 g, 83%).

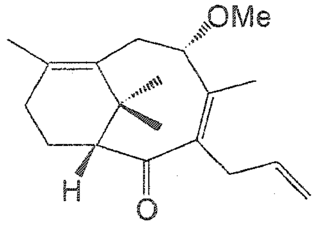
^{1}H NMR (C_6D_6, 300 MHz) δ 6.23 (dd, *J* = 17.6, 10.4, 1H), 5.91 (dd, *J* = 17.0, 1.1, 1H), 5.69 (dddd, *J* = 16.9, 10.2, 6.7, 6.7, 1H), 5.34 (dd, *J* = 10.4, 1.1, 1H), 5.05-4.94 (m, 3H), 4.75 (d, *J* = 2.3, 1H), 4.01 (dd, *J* = 10.4, 2.9, 1H), 3.11 (d, br, 2H), 3.04 (s, 3H), 2.88 (dd, *J* = 14.3, 10.5, 1H), 2.13 (d, *J* = 14.0, 1H), 1.82 (s, 3H), 1.78 (s, 3H), 1.74 (s, 3H), 0.31 (s, 9H); ^{13}C NMR δ 199.5, 150.3, 146.7, 142.5, 137.5, 134.7, 134.0, 128.9, 127.4, 117.5, 114.2, 83.0, 57.0, 38.7, 37.6, 22.9, 22.2, 20.5, 2.0; DEPT δ -128.9, -117.5, -114.2, -38.7, -37.6; IR (neat) 3075-2821, 1664, 1251, 1102, 852, 840.



4,5-Diallyl-8-isopropenyl-6-methoxy-9-methyl-deca-1,4,8-trien-3-one (2.150).

4,5-Diallyl-8-isopropenyl-6-methoxy-9-methyl-deca-1,4,8-trien-3-ol **2.158** (1.17 g, 3.70 mmol, 1.0 eq.) in THF (21 mL) was added to a suspension of IBX (1.56 g, 5.55 mmol, 1.5 eq.) in DMSO (1.6 mL, 22.2 mmol, 6.0 eq.) at 0 °C. The suspension was stirred for 3 h at 23 °C. Water (50 mL) was added and after filtration the solution was extracted with ether (2x30 mL), the combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (94/6, PE/E) provided the title compound (0.84 g, 72%).

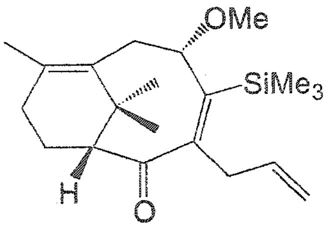
^{1}H NMR (C_6D_6, 300 MHz) δ 6.38 (dd, *J* = 17.6, 10.4, 1H), 6.10 (d, *J* = 17.5, 1H), 5.89 (d, *J* = 10.4, 1H), 5.93 (dddd, *J* = 17.1, 10.5, 6.7, 6.7, 1H), 5.69 (dddd, *J* = 17.1, 10.5, 6.9, 6.9, 1H), 5.11 (d, *J* = 17.2, 1H), 5.05 (d, *J* = 9.8, 1H), 5.04 (d, *J* = 16.9, 1H), 4.99 (d, *J* = 9.6, 1H), 4.91 (s, 1H), 4.51 (d, *J* = 2.4, 1H), 3.73 (dd, *J* = 10.0, 3.1, 1H), 3.10-2.90 (m, 2H), 3.03 (s, 3H), 2.89 (d, *J* = 6.6, 2H), 2.59 (dd, *J* = 14.5, 10.0, 1H), 1.98 (d, *J* = 14.5, 1H), 1.69 (s, 3H), 1.62 (s, 6H); ^{13}C NMR δ 199.9, 146.3, 139.5, 138.0, 137.3, 136.3, 134.5, 133.4, 130.2, 127.8, 117.2, 116.4, 114.2, 81.0, 57.3, 36.1, 35.3, 31.9, 22.9, 22.3, 20.4; DEPT δ -130.2, -117.2, -116.4, -114.2, -36.1, -35.3, -31.9; HRMS [M^+] calcd. for $C_{21}H_{30}O_2$ 314.2246, found 314.2261; IR (neat) 3077-2823, 1662, 1637, 1445, 1399, 1102, 991, 897.



3-Allyl-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,7-dien-2-one (2.111).

Diethylaluminum chloride (1.0 mL, 1.03 mmol, 1.1 eq., 1 M in hexane) or $BF_3 \cdot OEt_2$ (0.13 mL, 1.03 mmol, 1.1 eq.) was added to a solution of 4-allyl-8-isopropenyl-6-methoxy-5,9-dimethyl-deca-1,4,8-trien-3-one **2.112** (0.27 g, 0.937 mmol, 1.0 eq.) in CH_2Cl_2 (14 mL) at -78 °C. The solution was stirred at -78 °C for 2 hours, followed by standard workup with $NaHCO_3$, ether (2x10 mL) and $MgSO_4$. Purification by flash chromatography (9/1, PE/E) provided the title compound (0.194 g, 72%).

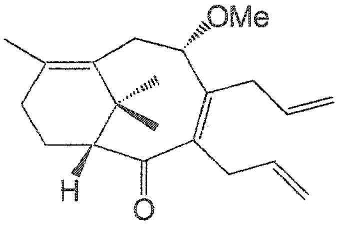
^{1}H NMR (C_6D_6, 300 MHz) δ 5.83 (dddd, *J* = 16.8, 10.2, 6.5, 6.5, 1H), 5.06 (ddd, *J* = 17.0, 3.5, 1.7, 1H), 4.98 (ddd, *J* = 10.0, 3.3, 1.6, 1H), 4.05 (dd, *J* = 11.1, 6.3, 1H), 3.06 (s, 3H), 2.87 (dd, *J* = 15.8, 6.6, 1H), 2.64-2.52 (m, 2H), 2.51-2.43 (m, 2H), 2.23-2.12 (m, 1H), 1.82-1.74 (m, 1H), 1.69-1.61 (m, 2H), 1.58 (s, 3H), 1.35 (s, 3H), 1.22 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 213.4, 138.8, 135.2, 134.0, 132.2, 131.5, 115.8, 82.3, 63.0, 57.6, 37.9, 36.4, 35.6, 28.8, 28.5, 25.1, 21.6, 19.2, 12.1; DEPT δ -115.8, -36.4, -35.6, -28.5, -19.2; HRMS [M$^+$] calcd. for $C_{19}H_{28}O_2$ 288.2089, found 288.2078; IR (neat) 3077-2824, 1669, 1464, 1103.



3-Allyl-5-methoxy-8,11,11-trimethyl-4-trimethylsilanyl-bicyclo[5.3.1]undeca-3,7-dien-2-one (2.128).

Diethylaluminum chloride (0.4 mL, 0.38 mmol, 1.1 eq., 1 M in hexane) or $BF_3 \cdot OEt_2$ (0.05 mL, 0.38 mmol, 1.1 eq.) was added to a solution of 4-allyl-8-isopropenyl-6-methoxy-9-methyl-5-trimethysilanyl-deca-1,4,8-trien-3-one **2.136** (0.12 g, 0.35 mmol, 1.0 eq.) in CH_2Cl_2 (6 mL) at -78 °C. The solution was stirred at the same temperature for 2 hours, followed by standard workup with $NaHCO_3$, ether (2x10 mL) and $MgSO_4$. Purification by flash chromatography (93/7, PE/E) provided the title compound (78 mg, 65%).

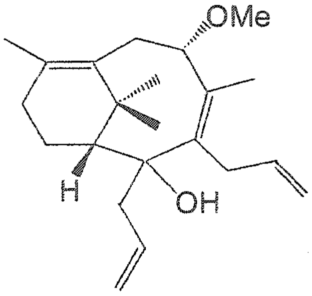
^{1}H NMR (C_6D_6, 300 MHz) δ 5.89 (dddd, *J* = 17.0, 10.1, 6.9, 6.9, 1H), 5.09 (ddd, *J* = 17.1, 3.4, 1.7, 1H), 5.00 (ddd, *J* = 10.1, 3.2, 1.6, 1H), 4.15 (dd, *J* = 11.4, 5.7, 1H), 3.25 (dd, *J* = 16.1, 6.0, 1H), 3.06 (s, 3H), 2.65-2.56 (m, 2H), 2.43 (d, *J* = 5.9, 1H), 2.32 (t, *J* = 11.8, 1H), 2.22-2.16 (m, 1H), 1.76-1.63 (m, 2H), 1.47 (s, 3H), 1.34 (s, br, 1H), 1.22 (s, 3H), 0.92 (s, 3H), 0.36 (s, 9H); ^{13}C NMR δ 213.8, 152.7, 136.2, 135.5, 133.4, 133.2, 116.4, 86.1, 63.0, 57.5, 38.4, 37.6, 35.8, 28.9, 28.7, 24.9, 22.4, 19.1, 3.4; DEPT δ -116.4, -38.4, -35.8, -28.7, -19.1; HRMS [M^+] calcd. for $C_{21}H_{34}O_2Si$ 346.2328, found 346.2339; IR (neat) 3074-2819, 1667, 1464, 1245, 1128-1095, 841.



3,4-Diallyl-5-methoxy-8,11,11-trimethyl-bicyclo[5.3.1]undeca-3,7-dien-2-one (2.126).

Diethylaluminum chloride (1.1 mL, 1.05 mmol, 1.1 eq., 1 M in hexane) or $BF_3 \cdot OEt_2$ (0.13 mL, 1.05 mmol, 1.1 eq.) was added to a solution of 4,5-diallyl-8-isopropenyl-6-methoxy-9-methyl-deca-1,4,8-trien-3-one **2.150** (0.30 g, 0.96 mmol, 1.0 eq.) in CH_2Cl_2 (15 mL) at -78 °C. The solution was stirred at -78 °C for 2 hours, followed by standard workup with $NaHCO_3$, ether (2x30 mL) and $MgSO_4$. Purification by flash chromatography (9/1, PE/E) provided the title compound (0.25 g, 68%).

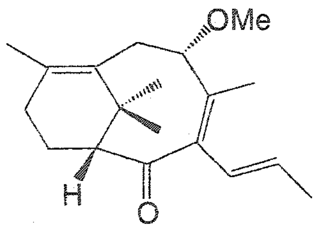
^{1}H NMR (C_6D_6, 300 MHz) δ 5.98-5.81 (m, 2H), 5.14 (d, *J* = 17.3, 1H), 5.03-4.99 (d, br, 2H), 4.97 (d, *J* = 10.5, 1H), 4.08 (dd, *J* = 11.0, 6.1, 1H), 3.11 (s, 3H), 3.07-3.05 (m, 2H), 2.70 (d, *J* = 6.0, 1H), 2.63 (d, *J* = 6.7, 1H), 2.59 (d, *J* = 6.8, 1H), 2.44 (d, *J* = 6.4, 1H), 2.35 (t, *J* = 11.8, 1H), 2.20-2.13 (m, 1H), 1.80 (s, br, 1H), 1.75-1.67 (m, 2H), 1.34 (s, 3H), 1.21 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 214.5, 141.0, 137.1, 135.7, 134.0, 132.4, 131.8, 116.4, 115.1, 82.2, 63.0, 58.6, 37.9, 36.3, 35.9, 31.7, 28.6, 28.6, 25.0, 21.6, 18.8; DEPT δ -116.4, -115.1, -36.3, -35.9, -31.7, -28.6, -25.0; HRMS [M$^+$] calcd. for $C_{21}H_{30}O_2$ 314.2246, found 314.2255; IR (neat) 3076, 2934-2827, 1672, 1637, 1448, 1098, 911.



2,3-Diallyl-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,7-dien-2-ol (2.110).

Allylmagnesium chloride (1.3 mL, 2.6 mmol, 2.0 eq., 1.6 M in THF) was added to a solution of 3-allyl-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,7-dien-2-one **2.111** (0.376 g, 1.3 mmol, 1.0 eq.) in ether (20 mL) at -78 °C. The solution was stirred for 1 h at -78 °C and then for 30 min at 0 °C. Standard workup with NH_4Cl, ether (2x30 mL) and $MgSO_4$, followed by purification by flash column chromatography (75/25, PE/E) provided the title compound (0.254 g, 59%).

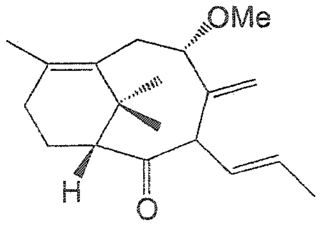
^{1}H NMR (C_6D_6, 300 MHz) δ 5.93 (dd, *J* = 11.0, 6.3, 1H), 5.87 (dddd, *J* = 17.2, 10.2, 7.6, 5.8, 1H), 5.73 (dddd, *J* = 16.7, 10.4, 6.1, 4.8, 1H), 5.05 (dd, *J* = 9.6, 2H), 4.99 (dd, *J* = 17.3, 2H), 3.30 (s, 3H), 2.90-2.74 (m, 2H), 2.70-2.58 (m, 2H), 2.51 (dd, *J* = 17.3, 5.7, 1H), 2.33 (dd, *J* = 14.0, 6.2, 1H), 2.18 (dd, br, 1H), 1.84-1.79 (m, 1H), 1.76 (s, 3H), 1.69-1.67 (m, 2H), 1.64 (s, 3H), 1.43 (s, 3H), 1.35-1.27 (m, 1H), 1.04 (s, 3H), 0.99 (s, 1H); ^{13}C NMR δ 138.5, 137.7, 135.8, 135.6, 133.2, 131.2, 119.1, 115.1, 82.4, 81.1, 57.3, 52.3, 45.8, 39.9, 38.0, 36.5, 32.8, 29.3, 28.3, 21.3, 20.8, 15.0; DEPT δ -119.1, -115.1, -45.8, -37.9, -36.5, -29.3, -20.8; HRMS [M^+] calcd. for $C_{22}H_{34}O_2$ 330.2559, found 330.2559; IR (neat) 3458, 3052-2814, 1637, 1463, 1093, 995, 911.



5-Methoxy-4,8,11,11-tetramethyl-3-propenyl-bicyclo[5.3.1]undeca-3,7-dien-2-one (2.122).

Potassium *tert*-butoxide (20.5 mg, 0.182 mmol, 1.5 eq.) was added to a solution of 3-allyl-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,7-dien-2-one **2.110** (35 mg, 0.122 mmol, 1.0 eq.) in DMF (1.0 mL). The solution was stirred for 6 h at 22 °C. The resulting suspension was filtered, neutralized with NH_4Cl and extracted with ether (2x30 mL). The combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (8/2, PE/E) afforded the title compound (29.7 mg, 85%).

^{1}H NMR (C_6D_6, 300 MHz) δ 6.24 (dd, J = 15.8, 1.7, 1H), 5.51 (dd, J = 15.8, 6.7, 1H), 4.15 (dd, J = 10.9, 6.6, 1H), 3.04 (s, 3H), 2.62 (dd, br, 1H), 2.57-2.53 (m, 2H), 2.17 (t, br, 1H), 1.97-1.81 (m, 2H), 1.80-1.66 (m, 1H), 1.70 (s, 3H), 1.52 (s, 3H), 1.51 (d, J = 6.5, 3H), 1.40 (s, 3H), 1.29 (s, 3H), 0.94 (s, 3H); ^{13}C NMR δ 212.8, 141.2, 134.5, 132.0, 131.8, 128.4, 126.7, 82.4, 63.3, 57.7, 38.0, 35.6, 29.2, 28.2, 25.2, 21.7, 19.9, 18.7, 12.2; DEPT δ -35.6, -28.2, -19.9; HRMS [M^+] calcd. for $C_{19}H_{28}O_2$ 288.2089, found 288.2076; IR (neat) 3025-2819, 1663, 1456-1438, 1101, 961.



5-Methoxy-8,11,11-trimethyl-4-methylene-3-propenyl-bicyclo[5.3.1]undec-7-en-2-one (2.121).

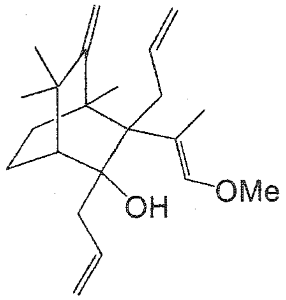
Potassium hydride (240 mg, 2.10 mmol, 5.0 eq., 35 % suspension in mineral oil) was washed with pentane (3 x 1.0 mL) and suspended in THF (2.0 mL). The resultant mixture was treated with iodine (53 mg, 0.21 mmol, 0.5 eq.) in THF (0.5 mL). After 15 min, 18-crown-6 (554 mg, 2.10 mmol, 5.0 eq.) and 2,3-diallyl-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,7-dien-2-ol **2.110** (120 mg, 0.42 mmol, 1.0 eq.) in THF (1.0 mL) were sequentially added and the resultant mixture was stirred for 1 h at 23 °C. The reaction was then cooled to -78 °C and quenched with ethanol (2 mL). Standard workup with NH_4Cl, ether (2x10 mL) and $MgSO_4$ was performed. Purification by flash chromatography (83/17, PE/E) provided the title compound (83 mg, 69%).

Similar results were obtained when 3-allyl-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,7-dien-2-one **2.111** was used instead of 2,3-diallyl-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,7-dien-2-ol **2.110**, under similar reaction conditions.

^{1}H NMR (C_6D_6, 300 MHz) δ 6.17 (ddd, *J* = 15.1, 9.9, 1.7, 1H), 5.47 (s 1H), 5.27 (dddd, *J* = 14.5, 7.0, 7.0, 7.0, 1H), 4.88 (s, 1H), 4.37 (d, *J* = 9.8, 1H), 3.50 (dd, *J* = 4.9, 1.6, 1H), 2.95 (s, 3H), 2.91 (s, br, 1H), 2.66 (dd, *J* = 9.8, 1.7, 1H), 2.35 (dd, *J* = 14.5, 5.2, 2H), 1.97 (s, 3H), 1.91 (dd, *J* = 9.3, 1.6, 1H), 1.82-1.70 (m, 1H), 1.68-1.54 (m, 1H), 1.52 (dd, *J* = 6.5, 1.6, 3H), 1.11 (s, 3H), 0.95 (s, 3H); ^{13}C NMR δ 210.4, 148.9, 134.3, 133.6, 131.7, 124.2, 118.6, 87.3, 63.1, 56.0, 50.5, 37.2, 33.9, 29.3, 29.1, 28.9, 23.4, 19.2, 17.7; DEPT δ -118.6, -33.9 -28.9 -19.2; HRMS [M$^+$] calcd. for $C_{19}H_{28}O_2$ 288.2089, found 288.2089; IR (neat) 2950, 1705, 1640.

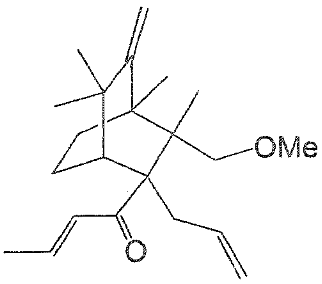
2,3-Diallyl-3-(2-methoxy-1-methyl-vinyl)-4,6,6-trimethyl-5-methylene-bicyclo[2.2.2]octan-2-ol (2.123), 1-(2-Allyl-3-methoxymethyl-3,4,6,6-tetramethyl-5-methylene-bicyclo[2.2.2]oct-2-yl)-but-2-en-1-one (2.124), and 2,6-Diallyl-5,7,9,9-tetramethyl-8-methylene-3-oxa-tricyclo[5.2.2.$0^{2,6}$]undec-4-ene (2.125).

A solution of 2,3-diallyl-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,7-dien-2-ol **2.110** (0.36 mmol, 1.0 eq.) and DBU (0.72 mmol, 2.0 eq.) in dry, deoxygenated toluene (10 ml) was heated in a quartz tube for 60 minutes at 220 °C. The solution was then cooled to 23 °C and concentrated. The residue was purified by flash column chromatography (9/1, PE/E) to afford compounds **2.123** (10.4 mg, 7.4%), **2.124** (22.1 mg, 15.7%) and **2.125** (24 mg, 19.0%).



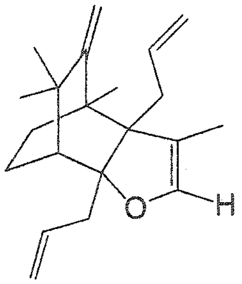
2,3-Diallyl-3-(2-methoxy-1-methyl-vinyl)-4,6,6-trimethyl-5-methylene-bicyclo [2.2.2]octan-2-ol (2.123).

^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.96 (dddd, *J* = 18.4, 8.8, 8.8, 6.5, 1H), 5.81 (dddd, *J* = 18.0, 10.3, 7.0, 7.0, 1H), 5.22 (dd, *J* = 8.4, 5.5, 1H), 5.20 (d, *J* = 9.6, 1H), 5.17 (dd, *J* = 15.7, 5.6, 1H), 5.08 (dd, *J* = 17.1, 1.5, 1H), 5.01 (dd, *J* = 10.2, 1.1, 1H), 4.80 (s, 1H), 4.70 (s, 1H), 3.19 (s, 3H), 2.66 (dd, *J* = 14.6, 6.5, 1H), 2.41 (dd, *J* = 14.5, 8.1, 1H), 2.38 (ddd, *J* = 14.5, 7.4, 7.4, 1H), 2.12-2.06 (m, 1H), 2.02 (s, 1H), 1.83-1.78 (m, 1H), 1.72-1.69 (m, 2H), 1.68 (s, 3H), 1.37 (s, 3H), 1.27 (s, 3H), 1.26 (s, br, 2H), 1.18 (s, 3H); ^{13}C NMR δ 163.3, 144.6, 136.0, 134.5, 133.6, 119.4, 116.0, 101.5, 78.8, 78.1, 55.7, 49.5, 47.7, 44.1, 38.6, 38.6, 36.6, 33.6, 30.4, 25.6, 19.5, 13.7; DEPT δ -115.0, -108.4, -72.7, -40.3, -35.1, -23.9; Elemental analysis calcd. for C (79.95%), H (10.37%), found C (76.62%), H (9.57%); IR (neat) 3559, 3076-2827, 1637, 1467, 1098, 998, 883.



1-(2-Allyl-3-methoxymethyl-3,4,6,6-tetramethyl-5-methylene-bicyclo[2.2.2]oct-2-yl)-but-2-en-1-one (2.124).

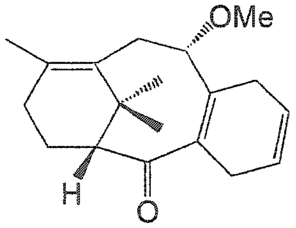
^{1}H NMR (CDCl$_3$, 500 MHz) δ 6.80 (ddd, *J* = 15.5, 13.8, 6.8, 1H), 6.14 (dd, *J* = 15.6, 3.4, 1.6, 1H), 5.76 (dddd, *J* = 17.2, 10.1, 7.1, 5.4, 1H), 5.09 (d, *J* = 6.5, 2H), 5.03 (dd, *J* = 17.2, 1.6, 1H), 4.99 (dd, *J* = 10.1, 1.3, 1H), 4.16 (d, *J* = 10.7, 1H), 3.90 (d, *J* = 10.7, 1H), 3.24 (s, 3H), 3.16-3.12 (m, 1H), 3.03 (dd, *J* = 15.9, 7.2, 1H), 2.57 (dd, *J* = 12.3, 3.7, 1H), 2.27 (dd, *J* = 14.5, 3.4, 1H), 2.07 (dd, *J* = 12.4, 3.4, 1H), 1.86 (dd, *J* = 6.9, 1.6, 3H), 1.69 (s, 3H), 1.48 (dd, *J* = 13.9, 3.6, 1H), 1.29 (s, 3H), 1.14 (s, 3H), 1.04 (dd, *J* = 13.9, 4.2, 1H), 0.93 (s, 3H); ^{13}C NMR δ 202.3, 162.7, 141.9, 139.1, 137.9, 133.3, 130.9, 115.1, 108.4, 72.7, 58.9, 58.1, 46.2, 41.1, 40.3, 35.1, 32.0, 30.1, 23.9, 23.1, 18.8, 18.2; DEPT δ -119.3, -116.0, -101.5, -47.7, -38.6, -36.6, -19.5; HRMS [M$^+$] calcd. for $C_{22}H_{34}O_2$ 330.2559, found 330.2555; IR (neat) 3072-2813, 1690, 1660.7, 1625, 1442, 1095, 906.



2,6-Diallyl-5,7,9,9-tetramethyl-8-methylene-3-oxa-tricyclo[5.2.2.0^{2,6}]undec-4-ene (2.125).

^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.94-5.80 (m, 2H), 5.90 (d, *J* = 1.3, 1H), 5.08 (d, *J* = 8.8, 1H), 5.02 (d, *J* = 17.9, 1H), 5.00 (d, *J* = 15.9, 1H), 4.98 (d, *J* = 9.8, 1H), 4.78 (d,

J = 8.3, 2H), 2.64-2.62 (m, 1H), 2.60-2.55 (m, 1H), 2.44 (dd, J = 16.3, 8.1, 2H), 1.81-1.70 (m, 1H), 1.65-1.56 (m, 2H), 1.50 (d, J = 1.5, 3H), 1.47-1.42 (m, 1H), 1.32-1.21 (m, 1H), 1.28 (s, 3H), 1.10 (s, 3H), 1.07 (s, 3H); ^{13}C NMR δ 163.6, 140.3, 138.6, 135.9, 117.1, 115.3, 114.1, 103.8, 94.2, 57.6, 44.3, 43.7, 42.5, 37.4, 35.2, 32.7, 31.7, 28.8, 21.6, 19.1, 11.2; DEPT δ -117.0, -115.3, -103.8, -42.4, -32.7 -28.8, 19.1; HRMS [M$^+$] calcd. for $C_{21}H_{30}O$ 298.2297, found 298.2305; IR (neat) 3068, 3032-2867, 1671, 1631, 1154, 1120, 1002, 921, 888, 859.

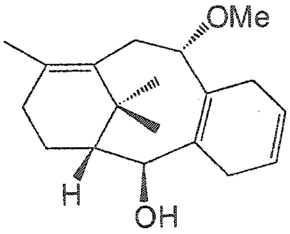


9-Methoxy-12,15,15-trimethyl-tricyclo[9.3.1.0^{3,8}]pentadeca-3(8),5,11-trien-2-one (2.149).

Grubbs' catalyst [(4,5-dihydroIMES)(PCy$_3$)Cl$_2$Ru=CHPh, 5 mol % in CH_2Cl_2] was added to a 0.02 M degassed CH_2Cl_2 solution of 3,4-diallyl-5-methoxy-8,11,11-trimethyl-bicyclo[5.3.1]undeca-3,7-dien-2-one **2.126**. The solution was stirred at 22 °C for 2h. The volatiles were removed under high vacuum, and the residue was purified by flash column chromatography (9/1, PE/E) to afford the title compound as a white solid, m.p. 90-91 °C (93%).

^{1}H NMR (C_6D_6, 300 MHz) δ 5.58 (dd, J = 10.1, 2.9, 1H), 5.47 (dd, J = 9.8, 2.2, 1H), 4.07 (dd, J = 10.9, 6.4, 1H), 3.03 (s, 3H), 2.90 (dd, br, 1H), 2.85-2.71 (m, 2H), 2.63 (ddd, J = 12.4, 6.3, 2.1, 1H), 2.50-2.42 (m, 3H), 2.14 (t, br, 1H), 1.82 (dd, J = 10.3, 3.8, 1H), 1.78-1.63 (m, 1H), 1.54 (dd, J = 10.4, 3.2, 1H), 1.42 (s, 3H), 1.21(s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 214.5, 136.5, 134.6, 131.9, 127.5, 124.4, 123.4, 82.4, 63.3, 57.9, 37.6, 35.5, 30.6, 28.8, 28.1, 25.3, 24.9, 21.3, 20.3; DEPT δ -35.5, -30.6, -28.1, -24.9, -20.3; HRMS [M$^+$] calcd. for $C_{19}H_{26}O_2$ 286.1933, found 286.1906; IR (neat) 3031-2822, 1665, 1465, 1103, 1072, 949. X-ray structural analyses: Crystal size 0.20 x 0.20 x 0.20 mm, monoclinic, space group P2(1)/c, scan range

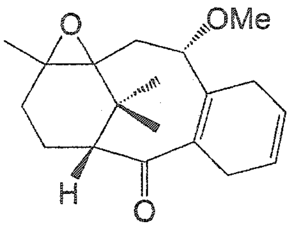
$2.27<2\theta<28.91°$, a=9.3046(10), b=11.2837(12), c=15.3871(16) Å, V =1558(3) $Å^3$, Z=4, r_{calcd}=1.221 mg/m^3, u=0.077 mm^{-1}, 3701 unique reflections at 203°K, [I_o>2.00δ(I)], R=0.0417, R_w=0.1088. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-197022.



9-Methoxy-12,15,15-trimethyl-tricyclo[9.3.1.0^{3,8}]pentadeca-3(8),5,11-trien-2-ol (2.164).

Lithium aluminum hydride (2.8 mg, 6.993x10^{-2} mmol, 1.0 eq.) was added to a solution of 9-methoxy-12,15,15-trimethyl-tricyclo[9.3.1.0^{3,8}]pentadeca-3(8),5,11-trien-2-one **2.149** (20 mg, 6.993x10^{-2} mmol, 1.0 eq.) in THF (4.2 mL) at 0 °C. The solution was warmed to reach 22 °C and stirred for 2 hours, after which time a saturated aqueous solution of sodium potassium tartrate was added dropwise until bubbling ceased. The solution was extracted with ether (3x2 mL), washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (75/25, PE/E) furnished the title compound as a white solid, m.p. 42-43 °C (15 mg, 68%).

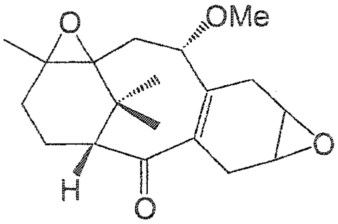
^{1}H NMR (C_6D_6, 300 MHz) δ 5.70 (dd, *J* = 10.0, 1.8, 1H), 5.55 (dd, *J* = 10.1, 1.7, 1H), 4.74 (d, *J* = 9.0, 1H), 3.27 (dd, *J* = 5.0, 2.3, 1H), 3.23-3.07 (m, 1H), 3.03 (s, 3H), 2.97 (dd, *J* = 13.9, 4.8, 1H), 2.61-2.41 (m, 2H), 2.40-2.21 (m, 3H), 2.17 (dd, *J* = 10.0, 4.5, 1H), 2.00 (dd, *J* = 10.3, 1.9, 2H), 1.86 (s, 3H), 1.44 (dd, *J* = 9.0, 5.7, 1H), 1.15 (s, 3H), 1.07 (s, 3H), 0.94 (s, 1H); ^{13}C NMR δ 137.5, 133.3, 132.4, 128.0, 125.0, 123.4, 86.6, 72.5, 55.7, 51.1, 38.1, 34.0, 33.8, 31.3, 29.3, 26,3, 26.1, 22.6, 20.7; DEPT δ -34.0, -33.8, -29.3, -26.1, -20.7; HRMS [M^+] calcd. for $C_{19}H_{28}O_2$ 288.2089, found 288.2075; IR (neat) 3399, 3026-2865, 1458, 1094, 1011, 963; X-ray structural analyses: Crystal size 0.23 x 0.15 x 0.12 mm, orthorhombic, space group Pbca, scan range $2.5<2\theta<28.81°$, a=11.070(9), b=15.1223(12), c=19.7554(16) Å, V =3308(5) Å^3, Z=8, r_{calcd}=1.158 mg/m^3, u=0.073 mm^{-1}, 4012 unique reflections at 203°K, $[I_o>2.00\delta(I)]$, R=0.0513, R_w=0.1170.



3-Methoxy-14,16,16-trimethyl-15-oxa-tetracyclo[9.4.1.0^{1,14}.0^{4,9}]sextadeca-4,6-dien-10-one (2.159).

The complex [*m*-CPBA·KF] (0.2 g, 8.75 x 10^{-4} mol, 5.0 eq.) was suspended in 4 mL of CH_2Cl_2 and stirred for 30 min at 22 °C. Then 9-methoxy-12,15,15-trimethyl-tricyclo[9.3.1.0^{3,8}]pentadeca-3(8),5,11-trien-2-one **2.149** (50 mg, 1.75 x 10^{-4} mol, 1.0 eq.) was added, and the reaction mixture stirred at 22 °C. When the reaction was complete (3h), the solids were removed by filtration and washed thoroughly with CH_2Cl_2 and the combined filtrates were dried over Na_2SO_4. The crude compound was purified by flash chromatography (76/24, PE/E) affording the title compound as a white solid, m.p. 103-104 °C (43 mg, 82%).

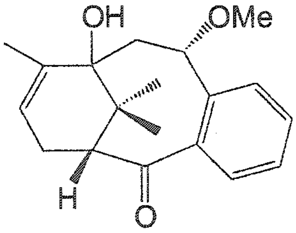
^{1}H NMR (C_6D_6, 300 MHz) δ 5.54 (dd, *J* = 11.2, 1.4, 1H), 5.43 (dd, *J* = 11.0, 1.5, 1H), 4.28 (dd, *J* = 12.4, 5.8, 1H), 2.92 (s, 3H), 2.86 (dd, br, 1H), 2.74-2.63 (m, 2H), 2.57 (d, *J* = 5.9, 1H), 2.52 (d, *J* = 5.8, 1H), 2.31 (d, br, 1H), 1.74-1.59 (m, 2H), 1.44-1.36 (m, 3H), 1.29 (s, 3H), 1.20 (s, 3H), 0.82 (s, 3H); ^{13}C NMR δ 213.6, 135.4, 130.7, 124.4, 123.2, 78.8, 63.0, 61.2, 61.0, 57.6, 37.3, 36.0, 30.4, 27.9, 25.2, 25.2, 24.9, 24.2, 19.1; DEPT δ -36.0, -30.4, -25.2, -24.9, -19.1; HRMS [M$^+$] calcd. for $C_{19}H_{26}O_3$ 302.1882, found 302.1891; IR (neat) 3029-2821, 1662, 1106.



3-Methoxy-15,17,17-trimethyl-7,16-dioxa-pentacyclo[10.4.1.0^{1,15}.0^{4,10}.0^{6,8}]septadeca-4(10)-en-11-one (2.161).

3-Methoxy-14,16,16-trimethyl-15-oxa-tetracyclo[9.4.1.0^{1,14}.0^{4,9}]sextadeca-4,6-dien-10-one **2.159** (50 mg, 0.182 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. A solution of dimethyldioxirane in acetone (0.56 mL, 1.2 eq., ~0.05 M) was added dropwise. The reaction mixture was stirred at 0 °C until the reaction was complete, at which time the solvent was evaporated. Purification by flash column chromatography (6/4, PE/E) afforded the title compound (32.6 mg, 62%).

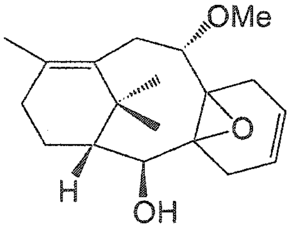
^{1}H NMR (C_6D_6, 300 MHz) δ 4.20 (dd, *J* = 12.8, 5.9, 1H), 2.88 (s, 3H), 2.81 (d, *J* = 13.9, 1H), 2.64-2.60 (m 1H), 2.49 (dd, *J* = 13.6, 5.7, 1H), 2.30-2.28 (d, *J* = 7.3, 1H), 2.0 (t, br, 2H), 1.77-1.67 (m, 1H), 1.51 (t, 1H), 1.39-1.29 (m, 2H), 1.25 (s, 3H), 0.94 (s, 3H), 0.78 (s, 3H); ^{13}C NMR δ 213.1, 133.0, 128.1, 78.1, 63.0, 60.9, 60.8, 57.5, 49.7, 49.5, 37.2, 36.4, 29.6, 27.8, 25.2, 25.0, 25.0, 23.0, 18.8; DEPT δ -36.4 -29.6, -25.2, -23.0, -18.8; HRMS [M$^+$] calcd. for $C_{19}H_{26}O_4$ 318.1831, found 318.1812; IR (neat) 3029-2821, 1662, 1106.



11-Hydroxy-9-methoxy-12,15,15-trimethyl-tricyclo[9.3.1.0^{3,8}]pentadeca-3(8),4,6,12-tetraen-2-one (2.160).

A solution of 3-methoxy-14,16,16-trimethyl-15-oxa-tetracyclo[9.4.1.0^{1,14}.0^{4,9}]sextadeca-4,6-dien-10-one **2.159** (47 mg, 1.56 x 10^{-4} mol, 1.0 eq.) in benzene (0.7 mL) and acetic acid (0.2 mL) was treated with SeO_2 (43 mg, 3.89 x 10^{-4} mol, 2.5 eq.). After 23 h at 22 °C the reaction mixture was filtered through cotton and washed with ether to remove the bulk of the precipitate. The solution was washed (3x1 mL) with water, brine, dried over Na_2SO_4 and the solvent was evaporated. Purification by flash column chromatography (5/5, PE/E) afforded the title compound as a white solid, m.p. 160-161 °C (22 mg, 47%).

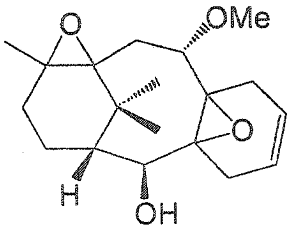
^{1}H NMR (C_6D_6, 300 MHz) δ 7.37 (d, J = 7.5, 1H), 7.05 (dddd, J = 7.6, 7.6, 1.1, 1.0, 1H), 6.87 (dd, J = 7.4, 1.0, 1H), 6.71 (d, J = 7.3, 1H), 4.62-4.54 (m, 2H), 2.96 (s, 3H), 2.54 (d, J = 5.0, 1H), 2.33-2.28 (m, 2H), 1.97 (d, br, 1H), 1.67 (d, br, 1H), 1.27 (s, 3H), 1.22 (s, 3H), 0.85 (s, 3H), 0.58 (s, br, 1H); ^{13}C NMR δ 211.3, 142.2, 137.6, 128.5, 128.0, 126.4, 123.9, 122.4, 77.1, 74.7, 61.5, 56.6, 44.3, 41.3, 30.3, 28.5, 24.9, 22.5, 17.6; DEPT δ -44.3, -24.9; HRMS [M^+] calcd. for $C_{19}H_{24}O_3$ 300.1725, found 300.1706; IR (neat) 3475, 2988, 2923, 1673, 1385, 1097, 1031, 976.



9-Methoxy-6,16,16-trimethyl-15-oxa-tetracyclo[8.4.0^{1,10}.1^{3,7}]sextadeca-6,12-dien-2-ol (2.165).

The complex [*m*-CPBA·KF] (70 mg, 0.31 mmol, 1.1 eq.) was suspended in CH_2Cl_2 (6.5 mL) and stirred for 30 min at 22 °C. 9-methoxy-12,15,15-trimethyl-tricyclo[9.3.1.0^{3,8}]pentadeca-3(8),5,11-trien-2-ol **2.164** (81 mg, 0.28 mmol, 1.0 eq.) was added, and the reaction mixture stirred at 22 °C. When the reaction was complete (12h) the solids were removed by filtration and washed thoroughly with CH_2Cl_2 and the combined filtrate was dried over anhydrous Na_2SO_4. Purification by flash chromatography (6/4, PE/E) afforded the title compound as a white solid, m.p. 159-160 °C (65 mg, 76%).

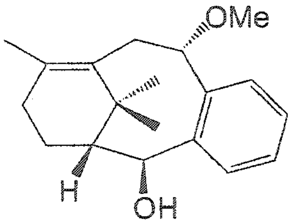
^{1}H NMR (C_6D_6, 300 MHz) δ 5.45 (d, *J* = 10.5, 1H), 5.30 (d, *J* = 10.2, 1H), 3.66 (dd, *J* = 9.1, 3.1, 1H), 3.33 (s, 3H), 3.07 (d, *J* = 3.5, 1H), 2.88 (d, br, 1H), 2.77 (dd, *J* = 14.3, 4.9, 1H), 2.37-2.30 (m, 2H), 2.22-1.97 (m, 4H), 1.92-1.79 (m, 1H), 1.75 (s, 3H), 1.67 (d, *J* = 4.0, 1H), 1.58-1.53 (m, 1H), 1.02 (s, 3H), 0.95 (s, 3H); ^{13}C NMR δ 134.1, 131.6, 123.5, 121.2, 83.9, 72.7, 66.5, 64.6, 59.2, 49.6, 37.4, 37.4, 31.1, 29.3, 29.0, 27.5, 26.2, 22.5, 21.3; DEPT δ -31.8, -29.3, -29.0, -26.2, -21.3; HRMS [M$^+$] calcd. for $C_{19}H_{26}O_3$ 304.2038, found 304.2046; IR (neat) 3406, 2942-2865, 1584, 1461, 1114,-991, 766.



3-Methoxy-14,16,16-tetramethyl-15,17-dioxa-pentacyclo[9.4.1.0^{1,14}.0^{4,9}]hepta decan-6-en-10-ol (2.165b).

As by product from the previous reaction, the title compound was obtained as a colorless oil (9.9 mg, 11 %).

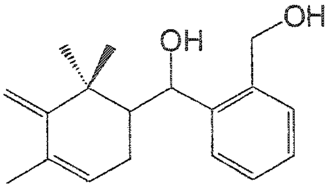
^{1}H NMR (C_6D_6, 300 MHz) δ 5.43-5.39 (m, 1H), 5.30-5.25 (m, 1H), 3.82 (dd, *J* = 10.4, 3.7, 1H), 3.24 (s, 3H), 3.05-3.03 (m, 1H), 2.70 (d, br, 1H), 2.29-2.08 (m, 3H), 2.02-1.82 (m, 4H), 1.74-1.64 (m, 2H), 1.51-1.45 (m, 1H), 1.33 (s, 3H), 0.96 (s, 3H), 0.87 (s, 3H); ^{13}C NMR δ 123.1, 121.1, 80.4, 73.1, 66.1, 64.5, 64.4, 60.5, 59.5, 46.2, 37.0, 33.3, 31.5, 29.3, 27.5, 26.3, 25.4, 25.1, 19.7; DEPT δ -33.3, -31.5, -25.4, -25.1, -19.7; HRMS [M$^+$] calcd. for $C_{19}H_{28}O_4$ 320.1988, found 320.2002; IR (neat) 3455, 23039-2827, 1455-1386, 1092, 965, 867, 676.



9-Methoxy-12,15,15-trimethyl-tricyclo[9.3.1.0^{3,8}]pentadeca-3(8),4,6,11-tetraen-2-ol (2.162).

Phenylhydrazine (0.14 µL, 1.38x10^{-3} mmol, 0.012 eq.) was added to a solution of Cu(OTf)$_2$ (4 mg, 1.15x10^{-3} mmol, 0.01 eq.) in acetone (0.1 mL). The mixture was stirred at 22 °C for 10 min. Then, 9-methoxy-12,15,15-trimethyl-tricyclo[9.3.1.0^{3,8}]pentadeca-3(8),5,11-trien-2-one **2.149** (33 mg, 0.12 mmol, 1.0 eq.) was added, followed by the dropwise addition of *tert*-butyl peroxybenzoate (4.4 µL, 2.30x10^{-2} mmol, 0.2 eq.). After the reaction was complete the solvent was evaporated under vacuum. The residue was dissolved in CH$_2$Cl$_2$ (5 mL), washed successively with NaHCO$_3$, brine and water and dried over MgSO$_4$. This gave an inseparable mixture of compounds, which was subjected to reduction in order to elucidate their structure. Hence, a solution of crude reaction mixture in ether (14 mL) was treated with 1.5 M DIBAL-H (0.16 mL, 2.33x10^{-4} mol) at 0 °C until the reduction was complete. Standard workup with NaHCO$_3$, ether and Na$_2$SO$_4$ was performed. Evaporation followed by purification by flash column chromatography (55/45, PE/E) afforded the pure title compound as a white solid, m.p. 129-130 °C (9.2 mg, 28%).

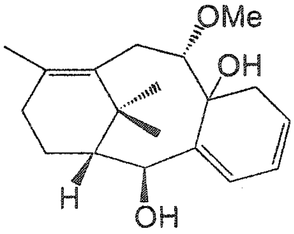
^{1}H NMR (C$_6$D$_6$, 300 MHz) δ 7.86 (d, *J* = 7.6, 1H), 7.07 (t, *J* = 7.5, 1H), 6.93 (ddd, *J* = 7.4, 7.4, 1.3, 1H), 6.71 (d, *J* = 7.4, 1H), 5.62 (dd, *J* = 10.7, 6.3, 1H), 4.28 (d, *J* = 2.6, 1H), 3.36 (s, 3H), 3.03 (dd, *J* = 11.7, 6.3, 1H), 2.60 (t, *J* = 11.3, 1H), 1.95-1.86 (m, 3H), 1.69 (s, 2H), 1.37-1.22 (m, 3H), 1.12 (s, 1H), 1.04 (s, 3H), 0.63 (s, 3H); ^{13}C NMR δ 142.0, 141.4, 132.6, 132.0, 129.3, 127.3, 126.1, 125.8, 86.5, 80.4, 57.6, 50.9, 38.6, 38.4, 32.0, 28.4, 28.1, 22.7, 20.3; DEPT δ -38.4, -28.4, -22.7; HRMS [M$^+$-MeOH] calcd. for C$_{18}$H$_{22}$O 254.1671, found 254.1661; IR (neat) 3428, 2981-2827, 1455, 1384, 1103-973, 752.



(2-Hydroxymethyl-phenyl)-(4,6,6-trimethyl-5-methylene-cyclohex-3-enyl)-methanol (2.163).

As by product from the previous reaction, the title compound was also isolated as a colorless oil (7.5 mg, 24%).

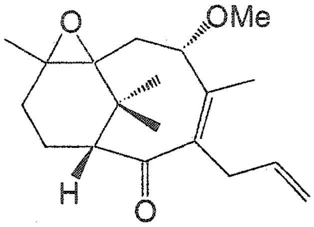
^{1}H NMR (C_6D_6, 300 MHz) δ 7.19-7.17 (m, 1H), 7.07-7.00 (m, 3H), 5.17 (s, 1H), 5.10 (s, 1H), 5.05 (s, br, 1H), 4.59 (d, *J* = 8.0, 1H), 4.57 (d, *J* = 12.4, 1H), 4.37 (d, *J* = 12.3, 1H), 2.63 (s, br, 2H), 2.01 (m, 1H), 1.76 (s, 3H), 1.43-1.37 (m, 1H), 1.34 (s, 3H), 1.27 (m, 3H), 1.26-1.13 (m, 1H); ^{13}C NMR δ 153.3, 143.2, 139.2, 132.5, 130.2, 129.2, 128.4, 127.9, 125.1, 108.0, 76.0, 63.8, 49.3, 39.0, 29.3, 28.1, 26.1, 20.6; HRMS [M^+-H_2O] calcd. for $C_{18}H_{22}O$ 254.1671, found 254.1683; IR (neat) 3387, 2981-2827, 1455, 1082, 973, 752, 731.



9-Methoxy-12,15,15-trimethyl-tricyclo[9.3.1.03,8]pentadeca-3,5,11-triene-2,8-diol (2.166).

Methyllithium (0.9 mL, 1.31x10^{-3} mol, 16.0 eq.) was added to a solution of CuI (125 mg, 6.58x10^{-4} mol, 8.0 eq.) in ether (0.5 mL) over 30 min at -5 °C. A solution of 9-methoxy-6,16,16-trimethyl-15-oxa-tetracyclo[8.4.0^{1,10}.1^{3,7}]sextadeca-6,12-dien-2-ol **2.165** (25 mg, 8.22x10^{-5} mol, 1.0 eq.) in ether (0.5 mL) was then added to this solution over 30 min. The reaction was stirred at -5 °C overnight and warmed to 22 °C for completion. Standard workup procedure with NH_4Cl, ether and Na_2SO_4 was performed. Purification by flash column chromatography (4/6, PE/E) afforded the title compound as a white solid, m.p. 137-138 °C (20.5 mg, 82%).

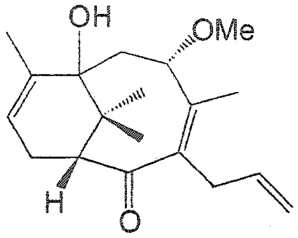
^{1}H NMR (C_6D_6, 300 MHz) δ 6.27 (d, *J* = 4.7, 1H), 6.05-6.01 (m, 1H), 5.94-5.89 (m, 1H), 4.05 (d, *J* = 6.4, 1H), 3.71 (t, *J* = 8.0, 1H), 3.35 (s, 3H), 2.82-2.71 (m, 2H), 2.45 (dd, *J* = 14.0, 8.0, 1H), 2.31 (s, 1H), 2.23-2.20 (d, br, 1H), 2.12-2.02 (m, 3H), 1.98-1.94 (d, br, 1H), 1.71(s, 3H), 1,60 (t, 1H), 1.50 (s, br, 1H), 1.20 (s, 3H), 0.93 (s, 3H); ^{13}C NMR δ 148.5, 136.4, 130.8, 126.8, 125.9, 125.0, 80.2, 77.2, 71.1, 58.0, 54.5, 37.0, 35.0, 32.0, 31.1, 28.8, 27.6, 24.3, 20.3; DEPT δ -35.0, -32.0, -31.1, -24.3; HRMS [M^+-H_2O] calcd. for $C_{19}H_{26}O_2$ 286.1933, found 286.1920; IR (neat) 3432, 3302, 2917, 1094, 1037.



5-Allyl-3-methoxy-4,10,12,12-tetramethyl-11-oxa-tricyclo[5.4.1.0^{1,10}]dodec-4-en-6-one (2.141).

The complex [*m*-CPBA·KF] (100 mg, 4.34x10^{-4} mol, 3.5 eq.) was suspended in CH_2Cl_2 (4 mL) and stirred for 30 min at 22 °C. 3-Allyl-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,7-dien-2-one **2.111** (50 mg, 1.74x10^{-4} mol, 1.0 eq.) was added, and the reaction mixture stirred at 22 °C. When the reaction was complete (18h) the solids impurities were removed by filtration and washed thoroughly with CH_2Cl_2 and the combined filtrates were dried over Na_2SO_4. The crude compound was purified by flash chromatography (75/25, PE/E) affording the title compound (37.3 mg, 71%).

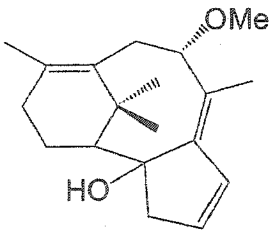
^{1}H NMR (C_6D_6, 300 MHz) δ 5.83 (dddd, *J* = 17.0, 10.2, 6.5, 6.5, 1H), 5.05 (d, *J* = 18.3, 1H), 4.99 (d, *J* = 11.3, 1H), 4.27 (dd, *J* = 12.4, 5.6, 1H), 2.97 (s, 3H), 2.87 (dd, *J* = 15.6, 6.4, 1H), 2.52 (dd, *J* = 13.3, 5.6, 2H), 2.28 (d, *J* = 7.4, 1H), 1.79-1.69 (m, 1H), 1.59 (t, 1H), 1.54 (s, 3H), 1.47-1.32 (m, 3H), 1.29 (s, 3H), 0.81 (s, 3H); ^{13}C NMR δ 212.5, 137.6, 134.7, 134.3, 116.1, 79.2, 63.0, 60.9, 60.7, 57.4, 37.6, 36.3, 36.0, 28.2, 25.6, 25.0, 23.9, 18.2, 12.7; DEPT δ -116.1, -36.3, -36.1, -25.6, -18.2; HRMS [M$^+$] calcd. for $C_{19}H_{28}O_3$ 304.2038, found 304.2020; IR (neat) 3078-2820, 1669, 1642, 1462, 1288, 936, 913, 767.



3-Allyl-7-hydroxy-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,8-dien-2-one (2.142).

A solution of 5-allyl-3-methoxy-4,10,12,12-tetramethyl-11-oxa-tricyclo[5.4.1.0^{1,10}]dodec-4-en-6-one **2.141** (34 mg, 0.11 mmol, 1.0 eq.) in benzene (0.5 mL) and acetic acid (0.2 mL) was treated with SeO_2 (25 mg, 0.22 mmol, 2.0 eq.) in acetic acid (0.7 mL). After 24 h at 23 °C the reaction mixture was filtered through cotton and washed with ether to remove the bulk of the precipitate. The organic solution was washed with water (3x1 mL), washed with brine, dried with Na_2SO_4 and the solvent was evaporated. The compound was isolated by flash column chromatography (45/55, PE/E) affording the title compound as a white solid, m.p. 69-70 °C (20 mg, 59%).

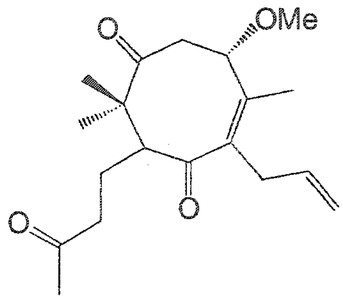
^{1}H NMR (C_6D_6, 300 MHz) δ 5.88 (dddd, J = 16.8, 10.32, 6.7, 6.7, 1H), 5.14-5.13 (m, br, 1H), 5.05 (dd, J = 17.9, 1.8, 1H), 4.98 (dd, J = 10.1, 1.8, 1H), 4.02-4.01 (m, 1H), 3.0 (s, 3H), 2.87 (dd, J = 16.2, 6.2, 1H), 2.52 (dd, J = 15.9, 6.5, 1H), 2.33 (d, J = 5.4, 1H), 2.16 (t, J = 13.2, 1H), 1.96 (dd, J = 14.0, 4.8, 2H), 1.58 (s, 3H), 1.44 (s, 3H), 1.40-1.35 (m, br, 1H), 1.24 (s, 3H), 0.84 (s, 3H), 0.53 (s, br, 1H); ^{13}C NMR δ 211.5, 138.4, 135.2, 132.9, 128.0, 121.8, 116.1, 78.1, 74.7, 61.6, 56.7, 41.6, 40.1, 36.2, 30.5, 28.8, 23.3, 21.9, 17.9; DEPT δ -116.1, -41.6, -36.2, -28.8; HRMS [M$^+$] calcd. for $C_{19}H_{28}O_3$ 304.2038, found 304.2064; IR (neat) 3504, 3076-2930, 1708, 1676, 1450, 1353, 1099, 1048.



8-Methoxy-7,11,14,14-tetramethyl-tricyclo[8.3.1.0^{2,6}]tetradeca-4,6,10-trien-2-ol (2.138).

3-Allyl-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,7-dien-2-one **2.111** (25 mg, 0.88 mmol, 1.0 eq.) in THF (0.2 mL) was added to a solution of LDA in THF (0.98 mmol, 1.1 eq.) at -78 °C. The solution was stirred for 30 min at the same temperature, DMF (0.17 mL, 1.76 mmol, 2.0 eq.) was added and the reaction mixture was stirred for an additional 2 hours. The reaction mixture was quenched with MeOH, diluted with brine and filtered through celite pad. The filtrate was extracted with ether (4x1 mL), washed with brine and dried over Na_2SO_4. Evaporation followed by purification by flash column chromatography (7/3, PE/E) afforded the title compound as a white solid, m.p. 119-120 °C (15 mg, 60%).

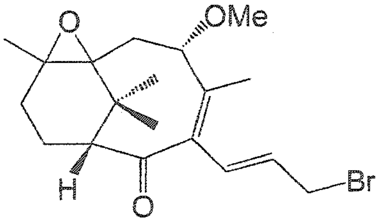
^{1}H NMR (C_6D_6, 300 MHz) δ 6.16 (ddd, *J* = 6.2, 2.6, 1.3, 1H), 5.54 (ddd, *J* = 6.0, 2.8, 2.8, 1H), 5.38 (dd, *J* = 10.8, 6.5, 1H), 3.29 (s, 3H), 2.85 (ddd, *J* = 11.9, 6.5, 2.6, 1H), 2.61 (t, *J* = 11.4,1H), 2.49 (dd, *J* = 17.7, 1.8, 1H), 2.21-2.12 (m, 2H), 1.83 (s, 3H), 1.81-1.68 (m, 2H), 1.66 (s, 3H), 1.56 (d, *J* = 8.2, 1H), 1.44 (s, 3H), 1.41-1.31 (m, br, 1H), 1.09 (s, 3H), 0.77 (s, 1H); ^{13}C NMR δ 143.6, 133.6, 133.5, 132.5, 130.6, 128.4, 87.5, 80.0, 57.5, 56.0, 54.1, 39.9, 34.7, 32.7, 29.6, 28.2, 21.4, 21.0, 14.9; DEPT δ -54.1, -34.7, -29.5, -21.0; HRMS [M$^+$] calcd. for $C_{19}H_{28}O_2$ 288.2089, found 288.2070; IR (neat) 3445, 3052-2859, 1461-1442, 1091, 978.



5-Allyl-7-methoxy-2,2,6-trimethyl-3-(3-oxo-butyl)-cyclooct-5-ene-1,4-dione (2.143).

A solution of 5-allyl-3-methoxy-4,10,12,12-tetramethyl-11-oxa-tricyclo[5.4.1.0^{1,10}]dodec-4-en-6-one **2.141** (0.2 g, 6.58x10^{-4} mol, 1.0 eq.) in benzene (99 mL), was treated with NaOAc (1.62 g, 1.97x10^{-2} mol, 30.0 eq.), celite (2 g) and PCC (4.25 g, 1.97x10^{-2} mol, 30.0 eq.). The resulting mixture was heated to reflux for 1 h. After cooling to 22 °C the reaction mixture was diluted with benzene/ether (9/1) (4 mL) and the crude reaction mixture was flushed through a plug of silica gel. Purification by flash column chromatography (7/3, PE/E) afforded the title compound (13 mg, 6.2%).

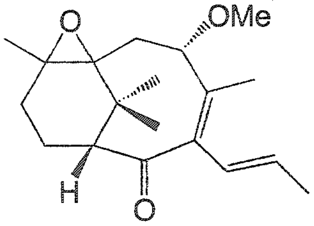
^{1}H NMR (C_6D_6, 300 MHz) δ 5.70 (dddd, *J* = 16.2, 9.8, 6.0, 6.0, 1H), 5.02 (dd, *J* = 17.4, 1.6, 1H), 4.96 (dd, *J* = 10.4, 1.6, 1H), 4.64 (dd, *J* = 10.2, 7.6, 1H), 3.08 (dd, *J* = 10.3, 1.9, 1H), 2.97 (s, 3H), 2.92-2.83 (m, 2H), 2.79-2.76 (m, 1H), 2.24-2.23 (m, 1H), 2.08-1.92 (m, 2H), 1.70 (s, 3H), 1.58 (s, 3H), 1.30-1.29 (m, 1H), 1.02 (s, 3H), 0.98 (d, 1H), 0.88 (s, 3H); ^{13}C NMR δ 209.7, 206.9, 205.0, 143.6, 136.3, 134.9, 116.1, 78.7, 58.7, 56.7, 51.7, 43.5, 41.6, 34.5, 29.5, 24.6, 20.0, 18.9, 15.5; DEPT δ -116.1, -43.5, -41.6, -34.5, -20.0; HRMS [M$^+$] calcd. for $C_{19}H_{28}O_4$ 320.1988, found 320.1998; IR (neat) 3078-2927, 1706, 1655, 1462-1442, 1114-1093, 915.



5-(3-Bromo-propenyl)-3-methoxy-4,10,12,12-tetramethyl-11-oxa-tricyclo [5.4.1.0^{1,10}]dodec-4-en-6-one (2.144).

N-Bromosuccinimide (0.16 mg, 0.88 mmol, 1.33 eq.) and benzoyl peroxide (1 mg, 4.13x10^{-3} mmol, 6.3x10^{-3} eq.) were added to a solution of 5-allyl-3-methoxy-4,10,12,12-tetramethyl-11-oxa-tricyclo[5.4.1.0^{1,10}]dodec-4-en-6-one **2.141** (0.2 g, 0.66 mmol, 1.0 eq.) in CCl_4 (1.0 ml). The reaction mixture was refluxed for 2 h and then cooled. NBS was removed by filtration and washed with CCl_4 (2x1 mL). After evaporation, the compound was purified by flash column chromatography (7/3, PE/E) to afford the title compound as a white solid, m.p. 135-136 °C (35 mg, 14%).

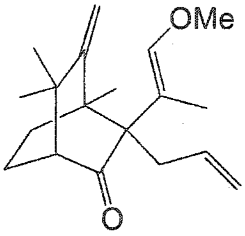
^{1}H NMR (C_6D_6, 300 MHz) δ 6.22 (d, *J* = 15.6, 1H), 5.57 (ddd, *J* = 15.6, 9.0, 6.6, 1H), 4.28 (dd, *J* = 12.4, 5.8, 1H), 3.52-3.41 (m, 2H), 2.90 (s, 3H), 2.52 (dd, *J* = 13.4, 5.9, 1H), 2.32 (d, *J* = 7.4, 1H), 1.90-1.70 (m, 2H), 1.63-1.58 (m, 1H), 1.57 (s, 3H), 1.50-1.33 (m, 2H), 1.30 (s, 3H), 1.00 (s, 3H), 0.83 (s, 3H); ^{13}C NMR δ 211.5, 138.9, 138.5, 128.7, 127.8, 79.5, 62.7, 60.9, 60.8, 57.5, 37.7, 36.4, 33.1, 28.2, 25.1, 25.0, 24.0, 18.5, 12.9; DEPT δ -36.4, -33.1, -25.1, -18.5; HRMS [M$^+$-Br] calcd. for $C_{19}H_{27}O_3$ 303.1960, found 303.1982; IR (neat) 3009-2898, 1670, 1458, 1120, 977.



3-Methoxy-4,10,12,12-tetramethyl-5-propenyl-11-oxa-tricyclo[5.4.1.0^{1,10}]dodec-4-en-6-one (2.145).

The complex [*m*-CPBA·KF] (0.56 g, 2.43 mmol, 7.0 eq.) was suspended in CH_2Cl_2 (8 mL) and stirred for 30 min at 22 °C. 5-Methoxy-4,8,11,11-tetramethyl-3-propenyl-bicyclo[5.3.1]undeca-3,7-dien-2-one **2.121** (0.1 g, 0.35 mmol, 1.0 eq.) was added, and the reaction mixture was stirred at 22 °C. After 45 min the solids were removed by filtration and washed thoroughly with CH_2Cl_2. The combined filtrates were dried over Na_2SO_4. Concentration and purification by flash chromatography (75/25, PE/E) afforded the title compound (97 mg, 92 %).

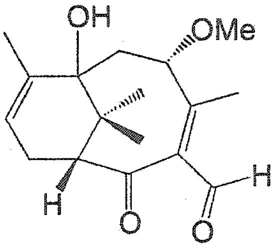
^1H NMR (C_6D_6, 300 MHz) δ 6.23 (dd, *J* = 15.8, 1.6, 1H), 5.49 (ddd, *J* = 15.7, 14.4, 6.7, 1H), 4.33 (dd, *J* = 12.4, 5.7, 1H), 2.95 (s, 3H), 2.55 (dd, *J* = 13.4, 5.8, 1H), 2.35 (d, *J* = 7.5, 1H), 1.86-1.71 (m, 2H), 1.64 (s, 3H), 1.68-1.59 (m, 1H), 1.50 (d, br, 3H), 1.46-1.37 (m, 2H), 1.34 (s, 3H), 1.07 (s, 3H), 0.86 (s, 3H); ^{13}C NMR δ 212.1, 139.8, 133.6, 128.6, 126.4, 79.5, 62.8, 60.9, 60.9, 57.5, 37.7, 36.6, 28.4, 25.3, 25.1, 24.0, 18.9, 18.7, 12.6; DEPT δ -36.6, -25.3, -18.9; HRMS [M^+] calcd. for $C_{19}H_{28}O_3$ 304.2038, found 304.2012; IR (neat) 3029-2821, 1738, 1662, 1459, 1358, 1242, 1166-1105, 1043.



3-Allyl-3-(2-methoxy-1-methyl-vinyl)-4,6,6-trimethyl-5-methylene-bicyclo[2.2.2] octan-2-one (2.139).

A solution of 3-allyl-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,7-dien-2-one **2.111** (50 mg, 0.17 mmol, 1.0 eq.) in dioxane (0.6 mL) was added to water (0.6 mL) containing $NaHCO_3$ (95 mg, 1.13 mmol, 6.5 eq.). Sodium dithionite (43 mg, 0.25 mmol, 1.44 eq.) was added and the reaction mixture was stirred at 50 °C for 18 h. The reaction mixture was then cooled to 22 °C and water was added until the solution became clear. Afterwards the reaction was extracted with ether (3x2 mL), dried over Na_2SO_4 and the solvents were evaporated. Purification by flash chromatography (93/7, PE/E) afforded the title compound (39.4 mg, 79%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.38-6.25 (m, 1H), 5.79 (s, 1H), 5.04 (d, *J* = 10.1, 1H), 4.97 (d, *J* = 17.3, 1H), 4.79 (d, *J* = 6.5, 2H), 3.16 (s, 3H), 2.51 (dd, *J* = 15.6, 7.3, 1H), 2.35 (dd, *J* = 15.5, 5.4, 1H), 1.99 (s, 1H), 1.78 (s, 3H), 1.64 (dd, *J* = 12.2, 3.3, 1H), 1.48 (d, *J* = 9.3, 2H), 1.23-1.17 (m, 1H), 1.12 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H); ^{13}C NMR δ 214.5, 160.3, 149.9, 136.7, 115.8, 110.7, 106.8, 59.0, 58.7, 56.6, 46.6, 37.3, 36.6, 30.9, 29.7, 29.5, 20.3, 19.8, 13.7; DEPT δ -115.8, -106.8, -36.6, -29.5, -19.7; HRMS [M^+] calcd. for $C_{19}H_{28}O_2$ 288.2089, found 288.2089; IR (neat) 3075-2834, 1713, 1660, 1459, 1226, 1133, 905.

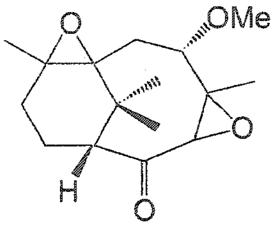


7-Hydroxy-5-methoxy-4,8,11,11-tetramethyl-2-oxo-bicyclo[5.3.1]undeca-3,8-diene-3-carbaldehyde (2.147).

A 30% solution of peracetic acid (0.66 mmol, 2.0 eq.) was added dropwise to a mixture of 3-methoxy-4,10,12,12-tetramethyl-5-propenyl-11-oxa-tricyclo$[5.4.1.0^{1,10}]$ dodec-4-en-6-one **2.145** (0.1 g, 0.33 mmol, 1.0 eq.), $OsCl_3 \cdot H_2O$ (10 mg, 3.29×10^{-3} mmol, 1.0 eq.), acetonitrile (0.33 mL), water (0.33 mL), and CH_2Cl_2 (0.33 mL) at 22 °C, over a period of 30 min. After stirring for 2 h the reaction was poured into a 5% Na_2SO_3 solution and extracted with CH_2Cl_2. The combined extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent and flash column chromatography (7/3, PE/E) afforded the title compound as a white solid, m.p. 139-140 °C (14 mg, 15%).

^{1}H NMR (C_6D_6, 300 MHz) δ 9.90 (s, 1H), 5.45-5.44 (m, 1H), 4.07 (dd, *J* = 10.9, 7.6, 1H), 3.20 (s, 3H), 2.49 (d, *J* = 5.6, 1H), 2.30-2.21 (m, 1H), 2.13 (t, *J* = 2.7, 1H), 2.05 (s, 3H), 1.98 (d, *J* = 5.3, 1H), 1.95 (d, *J* = 1.7, 1H), 1.70-1.69 (m, 3H), 1.43 (s, br, 1H), 1.20 (s, 3H), 1.06 (s, 3H); ^{13}C NMR δ 209.0, 188.1, 158.2, 142.8, 137.1, 124.4, 78.1, 75.0, 61.3, 57.7, 41.8, 37.7, 28.7, 23.1, 21.9, 17.9, 10.8; DEPT δ -37.7, -23.1;

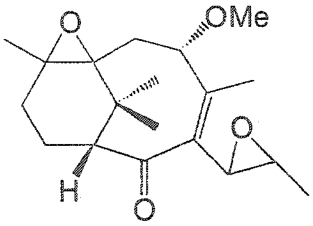
HRMS [M$^+$] calcd. for $C_{17}H_{24}O_4$ 292.1675, found 292.1664; IR (neat) 3478, 2988-2846, 1689, 1662, 1446, 1384, 1315, 1102, 979.



3-Methoxy-4,11,13,13-tetramethyl-5,12-dioxa-tetracyclo[6.4.1.0^{1,11}.0^{4,6}]tridecan-7-one (2.146).

A solution of $KMnO_4$ (42 mg, 0.26 mmol, 1.4 eq.) in water (0.2 mL) was added dropwise to a solution of 3-methoxy-4,10,12,12-tetramethyl-5-propenyl-11-oxa-tricyclo[5.4.1.0^{1,10}]dodec-4-en-6-one **2.145** (58 mg, 0.19 mmol, 1.0 eq.), in acetone (1.74 mL), water (0.42 mL), and acetic acid (0.03 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. Filtration, extraction and evaporation yielded the crude compound. Purification by flash column chromatography (65/35, PE/E) afforded the title compound as a white solid, m.p. 143-144 °C (4 mg, 7%).

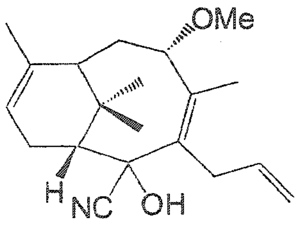
^{1}H NMR (C_3D_6O, 300 MHz) 4.14 (s, 1H), 3.33 (s, 2H), 3.27 (s, 3H), 2.98 (dd, *J* = 12.0, 5.7, 1H), 2.35-2.24 (m, 2H), 2.12-2.05 (m, 1H), 1.96-1.89 (m, 2H), 1.46 (s, 3H), 1.31 (s, 3H), 1.07 (s, 3H), 0.83 (s, 3H); ^{13}C NMR δ 206.9, 81.6, 65.7, 64.0, 62.7, 62.0, 57.8, 57.7, 37.3, 34.8, 29.1, 25.9, 25.3, 25.1, 18.0, 17.7; DEPT δ -34.8, -25.9, -17.7; IR (neat) 3013-2833, 1693, 1094, 1011, 827.



3-Methoxy-4,10,12,12-tetramethyl-5-(3-methyl-oxiranyl)-11-oxa-tricyclo [5.4.1.0^{1,10}]dodec-4-en-6-one (2.148).

Freshly prepared dimethyl-dioxirane solution (10 mL, 2.0 eq., ~0.04 M) was added to a solution of 3-methoxy-4,10,12,12-tetramethyl-5-propenyl-11-oxa-tricyclo[5.4.1.0^{1,10}] dodec-4-en-6-one **2.145** (64 mg, 0.21 mmol, 1.0 eq.) in acetone (1 mL). The reaction was stirred for 8 h at 22 °C and the solvents were removed. The crude mixture was purified by column chromatography (7/3, PE/E) and the title compound isolated as a colorless oil (53.2 mg, 79%).

^{1}H NMR (C_6D_6, 300 MHz) δ 4.23 (dd, *J* = 12.3, 6.0, 1H), 3.10 (s, br, 1H), 3.01-2.98 (m, 1H), 2.91 (s, 3H), 2.52 (dd, *J* = 13.6, 6.0, 1H), 2.28 (d, *J* = 8.0, 1H), 1.80 (s, 3H), 1.77-1.69 (m, 1H), 1.66-1.54 (m, 2H), 1.47-1.38 (m, 2H), 1.27 (s, 3H), 1.05 (s, 3H), 0.97 (d, *J* = 1.0, 3H), 0.81 (s, 3H); ^{13}C NMR δ 210.5, 141.4, 136.1, 79.0, 62.8, 60.9, 60.2, 57.6, 56.5, 53.8, 37.6, 36.2, 28.2, 25.8, 25.0, 23.9, 17.4, 17.3, 13.9; HRMS [M$^+$] calcd. for $C_{19}H_{28}O_4$ 320.1988, found 320.1997; IR (neat) 2929, 1727, 1677, 1455, 1379, 1104, 979.



3-Allyl-2-hydroxy-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,8-diene-2-carbonitrile (2.140).

Diethylaluminium cyanide (1N, 0.69 mL, 0.69 mmol, 1 M in toluene, 4.0 eq.) was added dropwise to a stirred solution of 3-allyl-5-methoxy-4,8,11,11-tetramethyl-bicyclo[5.3.1]undeca-3,7-dien-2-one **2.111** (50 mg, 0.17 mmol, 1.0 eq.) in benzene (3.4 mL) at 22 °C. The mixture was stirred at the same temperature for 3 h and then 2 M HCl was added under ice bath cooling. The product was extracted with ether (3x5 mL) and washed with brine, $NaHCO_3$, water and dried over Na_2SO_4. After evaporation and purification by flash column chromatography (75/25, PE/E) the title compound was obtained as a colorless oil (32 mg, 58%).

^{1}H NMR (C_6D_6, 300 MHz) δ 5.71-5.57 (m, 1H), 5.47 (s, 1H), 5.19 (dd, *J* = 17.9, 1H), 4.85 (d, *J* = 10.0, 1H), 2.96 (s, 3H), 2.92 (t, br, 1H), 2.48-2.42 (m, 2H), 2.20-2.14 (m, 2H), 1.87 (s, 3H), 1.55-1.49 (m, 1H), 1.46 (d, *J* = 3.1, 2H), 1.33 (s, 3H), 1.17 (d, *J* = 5.6, 1H), 1.07 (s, 3H), 0.70 (s, 3H); ^{13}C NMR δ 142.0, 137.5, 129.8, 128.6, 128.3, 127.9, 120.5, 118.3, 89.6, 58.8, 58.8, 57.9, 57.1, 41.1, 32.7, 32.5, 28.6, 25.6, 20.0, 16.2; DEPT δ -118.3, -41.2, -32.7, -32.6; HRMS [M^+] calcd. for $C_{20}H_{29}NO_2$ 315.2198, found 315.2118; IR (neat) 3425, 2930, 2241, 1719, 1635, 1455, 1371, 1089.

Claims to Original Research

1. Established that addition of γ-pentadienylindium(I) to unsaturated ketones proceeds via a tandem *in situ* carbonyl addition-oxy-Cope rearrangement mechanism providing better understanding of [3,3] sigmatropic rearrangements in these substrates.

2. Established the optimal reaction conditions for indium-mediated allylation and indium-mediated pentadienylation of α,β-unsaturated ketones to facilitate the *a priori* behavior of this reaction and the prediction of the reaction products.

3. Preparation of various functionalized AB ring systems of taxanes by improved carbometallation-cycloaddition sequences.

4. Synthesis of the tricyclic core of the taxanes in high yield by a novel carbometallation-cycloaddition-RCM sequence using readily available starting materials and very mild conditions.

5. The investigation of further functionalization of AB and ABC ring-systems of taxanes.

6. Publications:
    a) Villalva-Servín, N. P.; Melekhov, A.; Fallis, A. G. *Synthesis* **2003**, 790-794.
    b) Villalva-Servín, N. P.; Laurent, A.; Fallis, A. G. *Synlett* **2003**, 1263-1266.
    c) Villalva-Servín, N. P.; Laurent, A.; Fallis, A. G. *Can. J. Chem.* **2003**, *in press.*
    d) Laurent, A.; Villalva-Servín, N. P.; Forgione, P.; Wilson, P. D.; Smil, D. V.; Fallis, A. G. *Can. J. Chem.* **2003**, *in press.*

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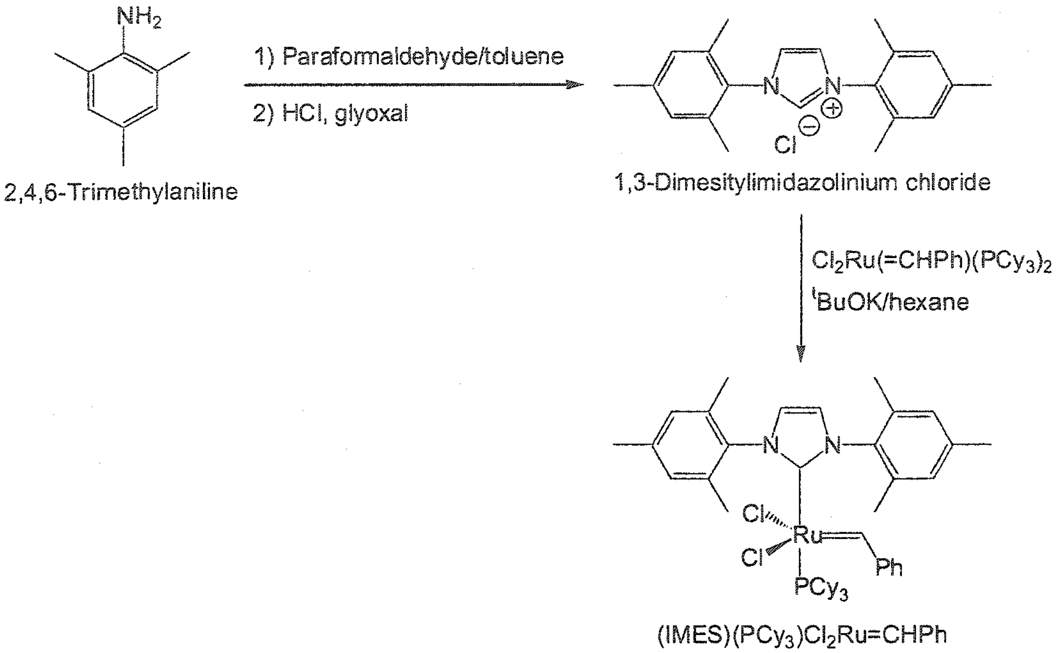
APPENDICES

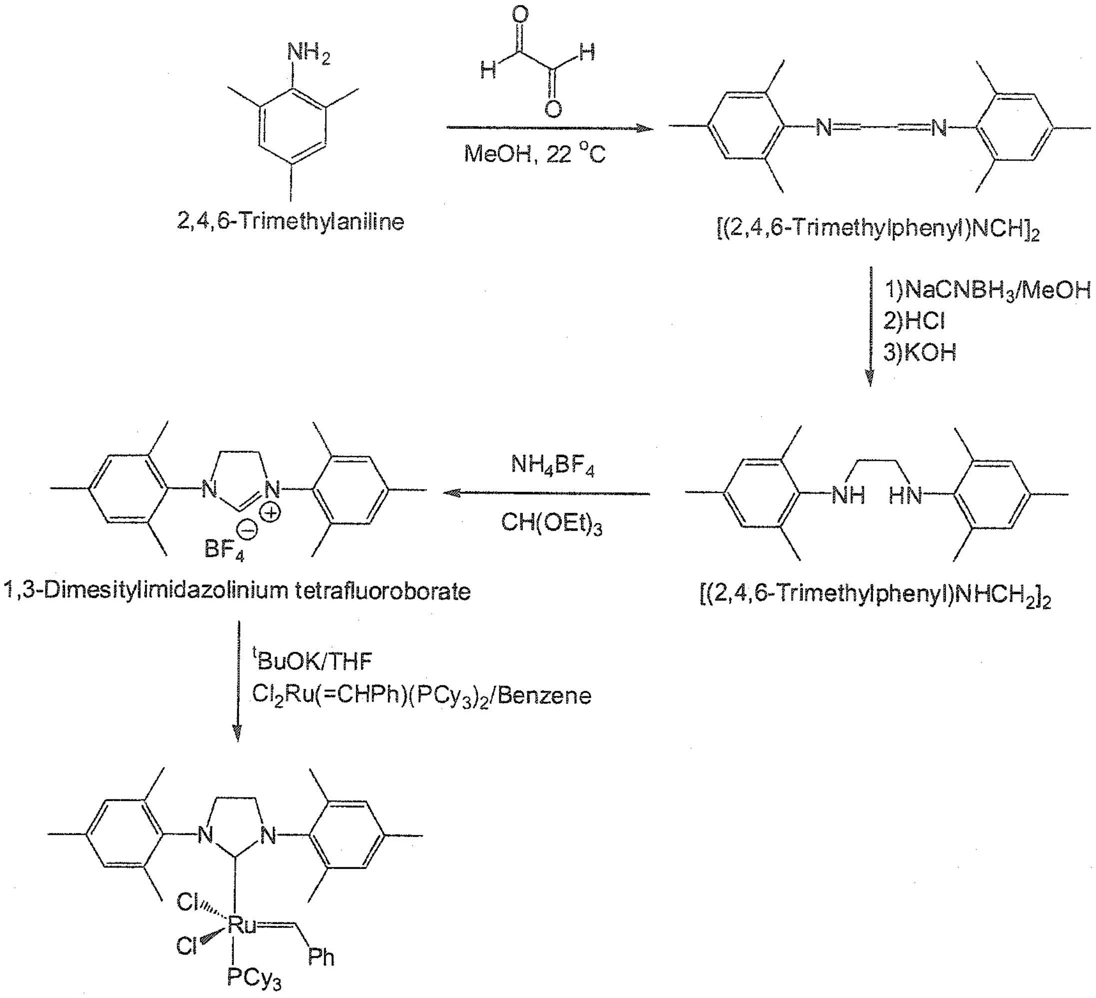
APPENDIX A

Grubbs Catalysts

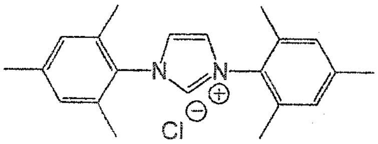
(IMES)(PCy_3)Cl_2Ru=CHPh



(4,5-DihydroIMES)$(PCy_3)Cl_2Ru=CHPh$

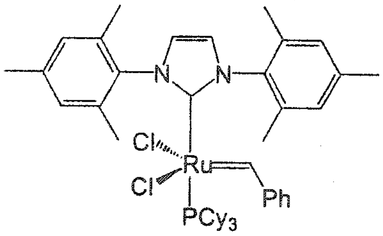


(4,5-DihydroIMES)$(PCy_3)Cl_2Ru=CHPh$



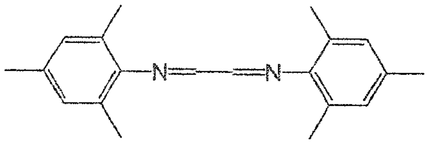
1,3-Dimesitylimidazolinium chloride.[130]

2,4,6-Trimethylaniline (10.7 g, 100 mmol, 1 eq.) in toluene (15 ml), was added dropwise to a suspension of paraformaldehyde (1.5 g, 50 mmol, 0.5 eq.) in toluene (15 ml). The reaction mixture was heated to 100 °C to dissolve all the solids, then the reaction mixture was cooled to 40 °C and aqueous 6N HCl (50 mmol, 0.5 eq.) was slowly added. The mixture was stirred for 5 minutes and glyoxal (7.25 g, 50 mmol, 0.5 eq., 40% aqueous) was added. The reaction mixture was stirred for 5 minutes at 22 °C and then heated to 100 °C. The temperature was maintained for 2 hours to afford a dark solid. The reaction mixture was allowed to cool to 22 °C and the volatiles were removed under vacuum. The brown solid was triturated in acetonitrile and filtered off to yield the title compound (58.3% yield).



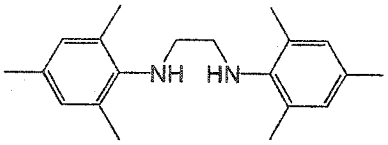
(IMES)(PCy_3)Cl_2Ru=CHPh.[131]

A 50 ml Schlenk flask was charged with $(PCy_3)_2Cl_2$Ru=CHPh (1.0 g. 1.22 mmol, 1 eq.), 1,3-dimesitylimidazolinium chloride (0.621 g, 1.82 mmol, 1.5 eq.), ^{t}BuKO (0.31 g, 2.74 mmol, 2.24 eq.) and hexane (10 ml). The reaction mixture was heated to 50 °C for 5 h and allowed to cool to 22 °C. The suspension was filtered and the precipitate was then washed with degassed water and rinsed with hexane. The precipitate was dried under vacuum to yield a pink-brown solid (76.8% yield).



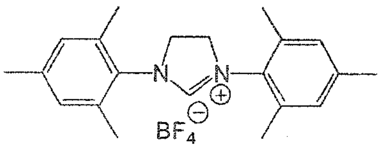
[(2,4,6-Trimethylphenyl)NCH]$_2$.[121]

Glyoxal (3.73 ml, 32.5 mmol, 40% aqueous) was dissolved in 325 ml of reagent-grade methanol. 2,4,6-Trimethylaniline (8.25 ml, 58.8 mmol, 1.81 eq.) was added dropwise and the mixture was stirred for 12 h at 22 °C as a bright yellow precipitate slowly formed. The mixture was diluted with CH_2Cl_2 and the resulting yellow solution was dried over $MgSO_4$, filtered and concentrated to a yellow-orange solid residue. The product was recrystallized from anhydrous methanol. After cooling to 22 °C the sample was storaged at –20 °C for 12 h. The title compound was obtained as long canary yellow crystals in 86% yield.



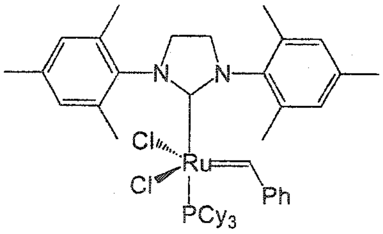
[(2,4,6-Trimethylphenyl)NHCH$_2$]$_2$.[121]

[(2,4,6-Trimethylphenyl)NCH]$_2$ (7.3 g, 25 mmol, 1 eq.) was suspended in 250 ml of MeOH. Several crystals of bromocresol green were added as a pH indicator, and the mixture was cooled to 0 °C. $NaCNBH_3$ (10.0 g, 159 mmol, 6.4 eq.) was added and the reaction mixture turned a deep blue-green color (alkaline pH). After 10 min. concentrated HCl was added dropwise restoring its original yellow color. Additional reduction slowly occurred, causing the mixture to again become basic. The acidification process was repeated until yellow color persisted. The reaction mixture was warmed to 22 °C and stirred for 1 h. A solution of 2M KOH was added dropwise until the mixture was weakly alkaline (pH=8-9). The reaction mixture was the diluted with water (300 ml) and washed three times with Et_2O (500 ml). The combined organic layers were washed with 800 ml of a saturated solution of sodium chloride, dried over $MgSO_4$, filtered and concentrated to a yellow oil. Silica gel chromatography (PE/E, 8:2) afforded the product as a colorless oil (96.5%).



1,3-Dimesitylimidazolinium tetrafluoroborate.[121]

A 25 ml round-bottom flask was charged with $[(2,4,6\text{-trimethylphenyl})NHCH_2]_2$ (7.8 g, 26.4 mmol, 1eq.) and ammonium tetrafluoroborate (2.77g, 26.4 mmol, 1 eq.). Triethylorthoformate (4.39 ml, 26.4 mmol, 1 eq.) was added and the reaction mixture was refluxed for 3 h and cooled to 22 °C. This mixture was recrystallized from hot anhydrous ethanol. The resulting bright white crystals of product were filtered, washed with pentane and dried under high vacuum to yield 64.2% of product.

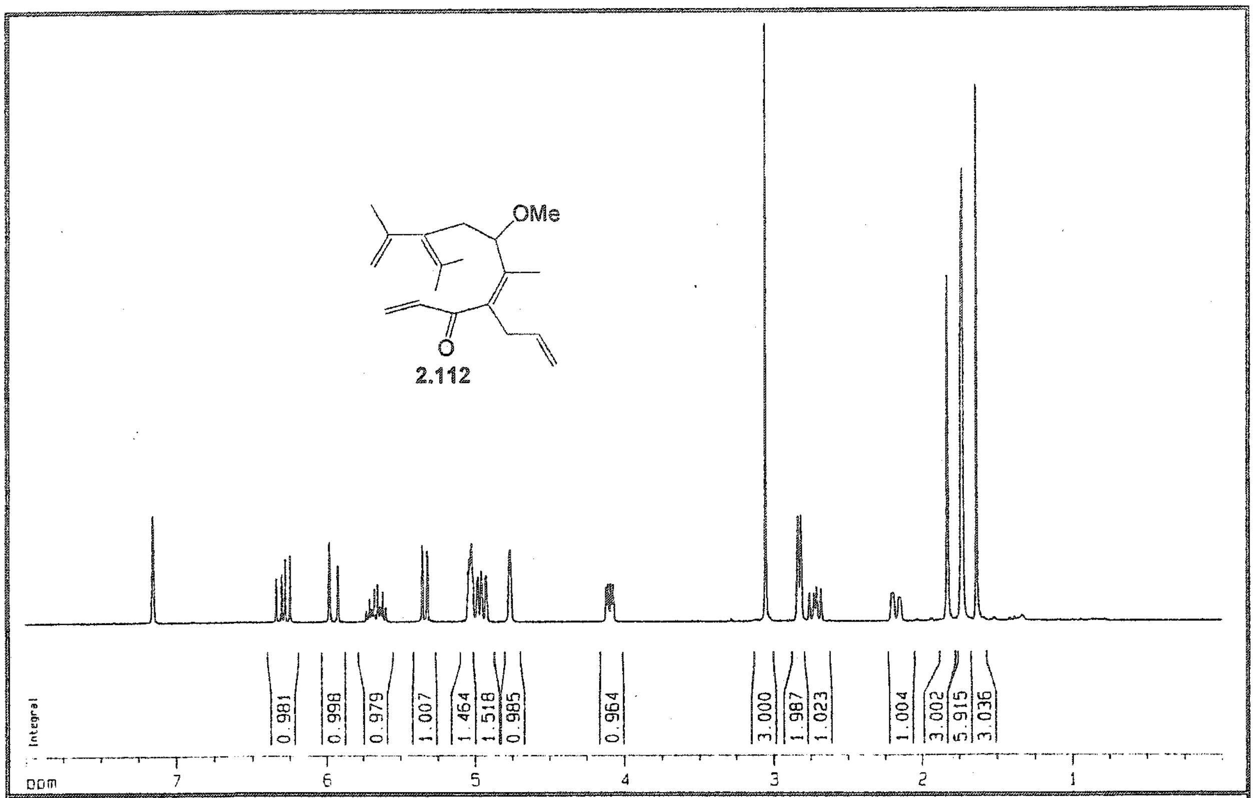


(4,5-DihydroIMES)(PCy_3)Cl_2Ru=CHPh.[120]

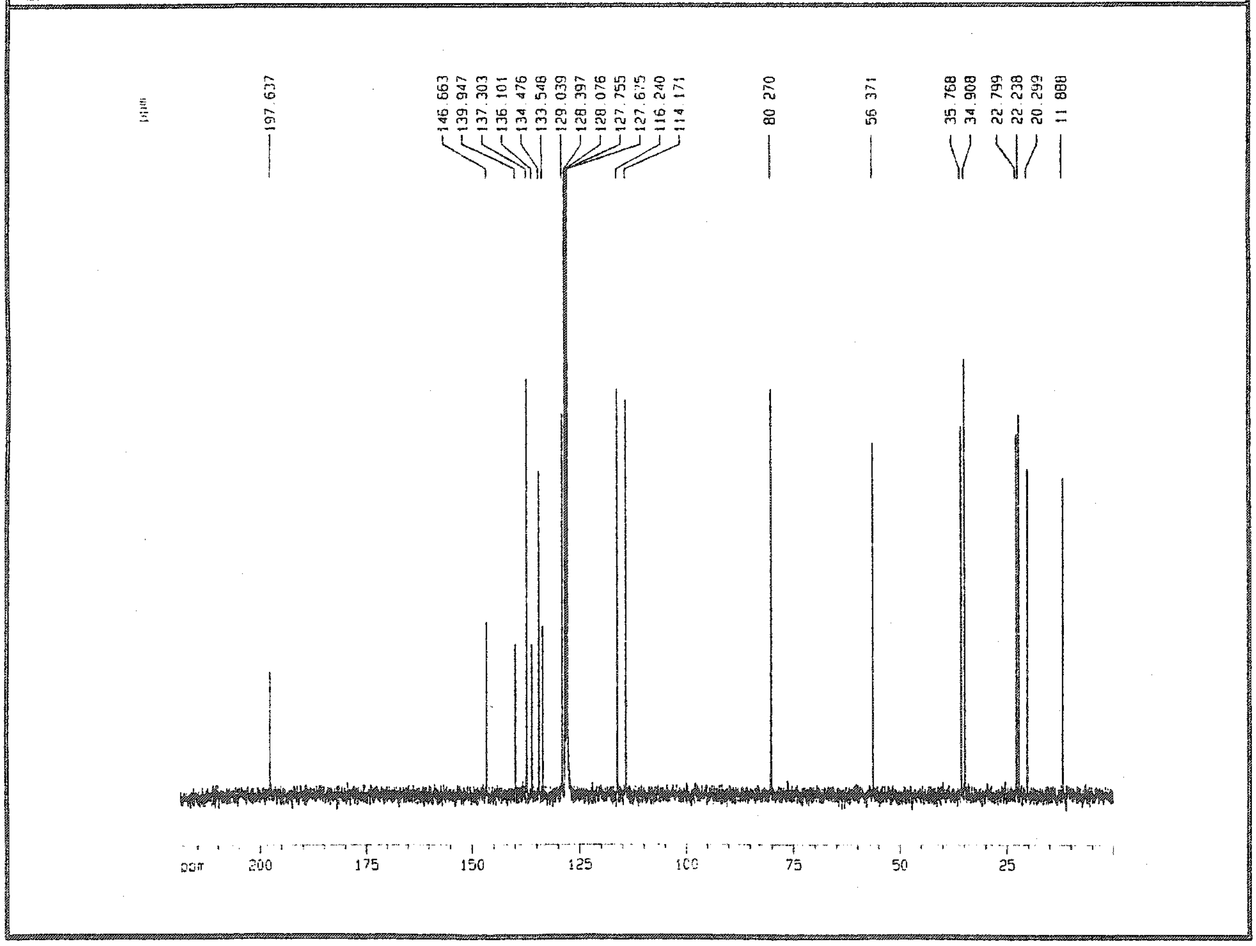
A 50 ml flame-dried Schlenk flask was charged with 1,3-dimesityl-4,5-dihydroimidazolium tetrafluoroborate (0.402 g, 1.02 mmol, 1.4 eq.) and dry THF (10 ml) under a nitrogen atmosphere. A solution of potassium *tert*-butoxide (0.125 g, 1.02 mmol, 1.4 eq.) in dry THF (20 ml) was added slowly at 22 °C. The reaction mixture was stirred at 22 °C for 1 h, followed by cannula transfer to a 100 ml flame-dried Schlenk flask under argon. Dry benzene (40 ml) and $(PCy_3)_2Cl_2Ru$=CHPh (0.600 g, 0.73 mmol, 1.0 eq.) were added. The reaction mixture was heated at 80 °C for 30 min. The volatiles were removed under vacuum and the residue was washed with anhydrous methanol (4x10 ml) to give a pinkish-brown solid (75% yield).

APPENDIX B

^{1}H NMR and ^{13}C NMR Selected Spectra


OMe
O
Integral
0.981
0.998
0.979
1.007
1.464
1.518
0.985
0.964
3.000
1.987
1.023
1.004
3.002
5.915
3.036
ppm
7
6
5
4
3
2
1

2.112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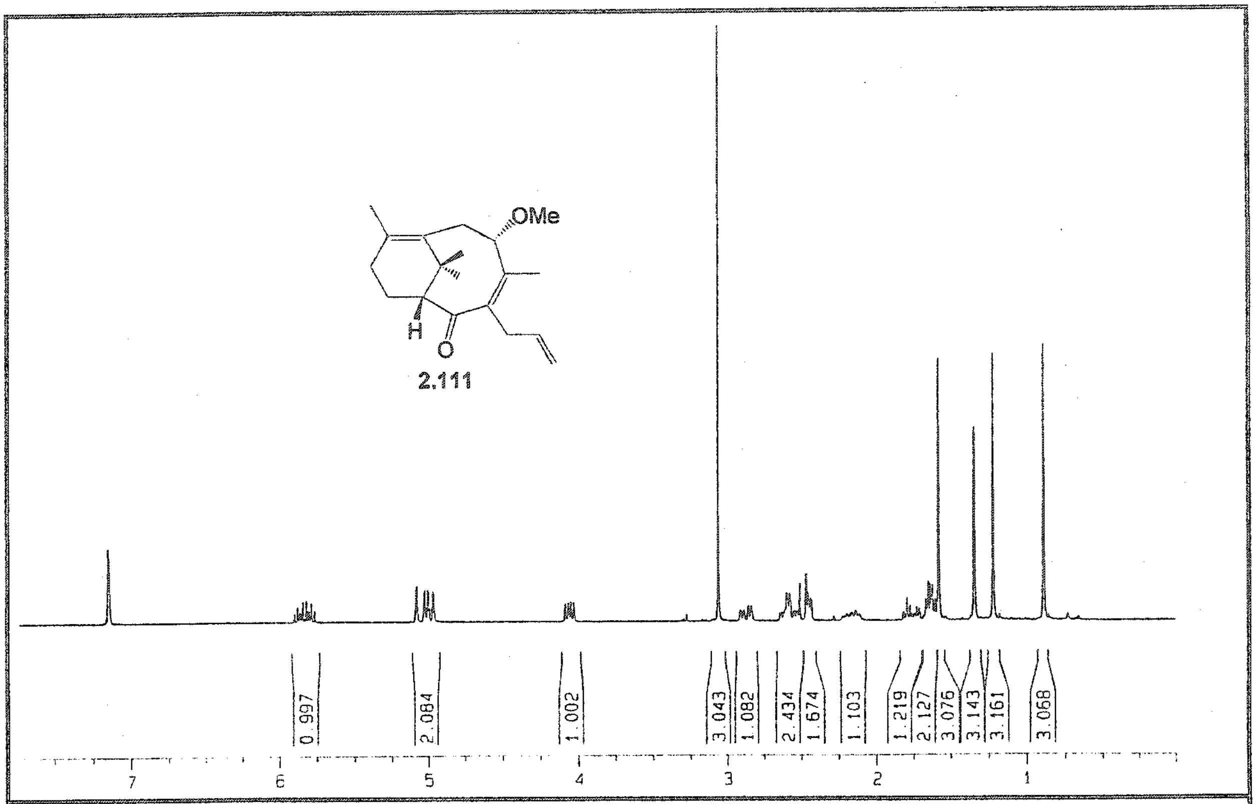
146.663
139.947
137.303
136.101
134.476
133.548
129.039
128.397
128.076
127.755
127.675
116.240
114.171
80.270
56.371
35.768
34.908
22.799
22.238
20.299
11.888
ppm
200
175
150
125
100
75
50
25


OMe
H
O
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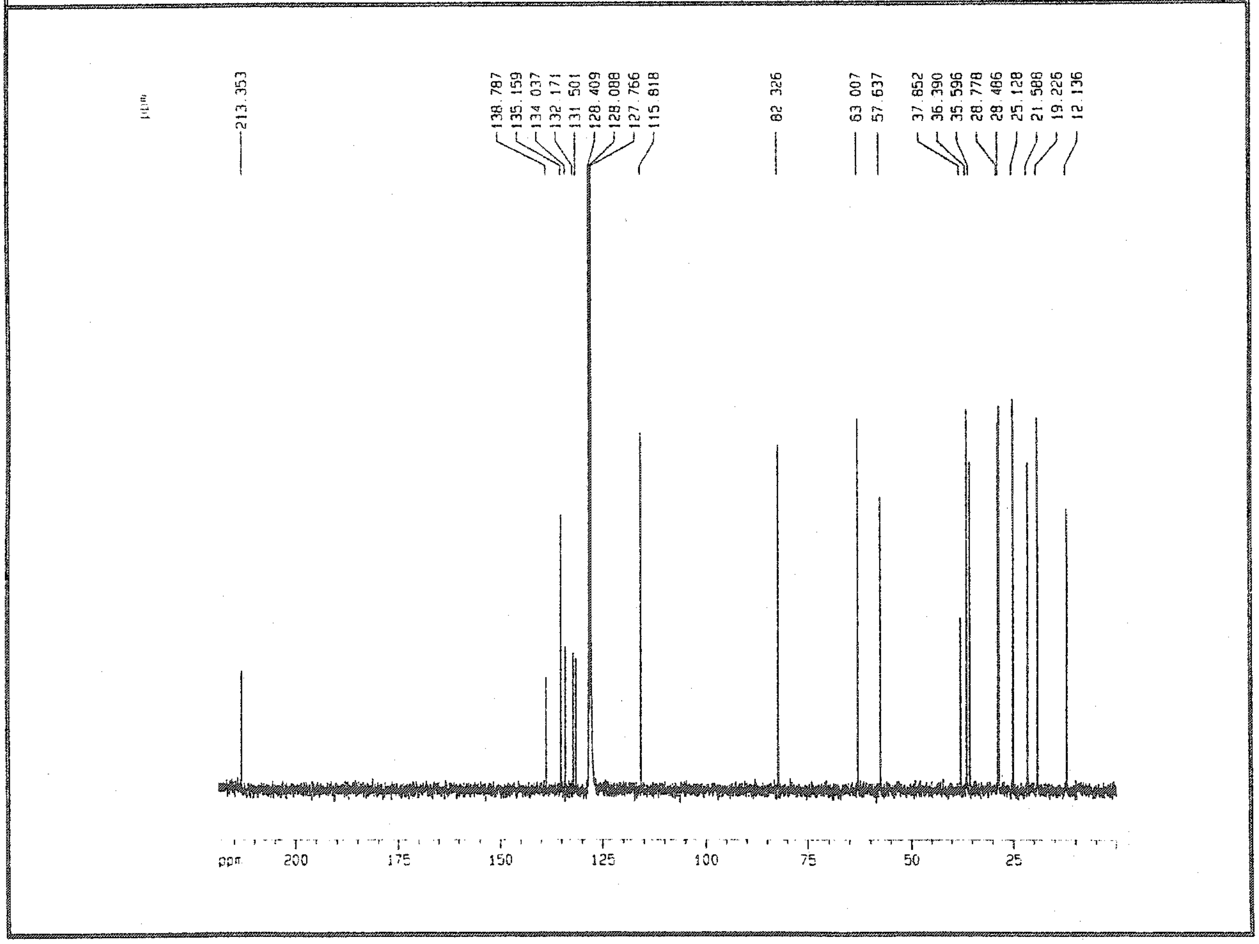
2.084
1.002
3.043
1.082
2.434
1.674
1.103
1.219
2.127
3.076
3.143
3.161
3.068
7
6
5
4
3
2
1

2.111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135.159
134.037
132.171
131.501
128.409
128.088
127.766
115.818
82.326
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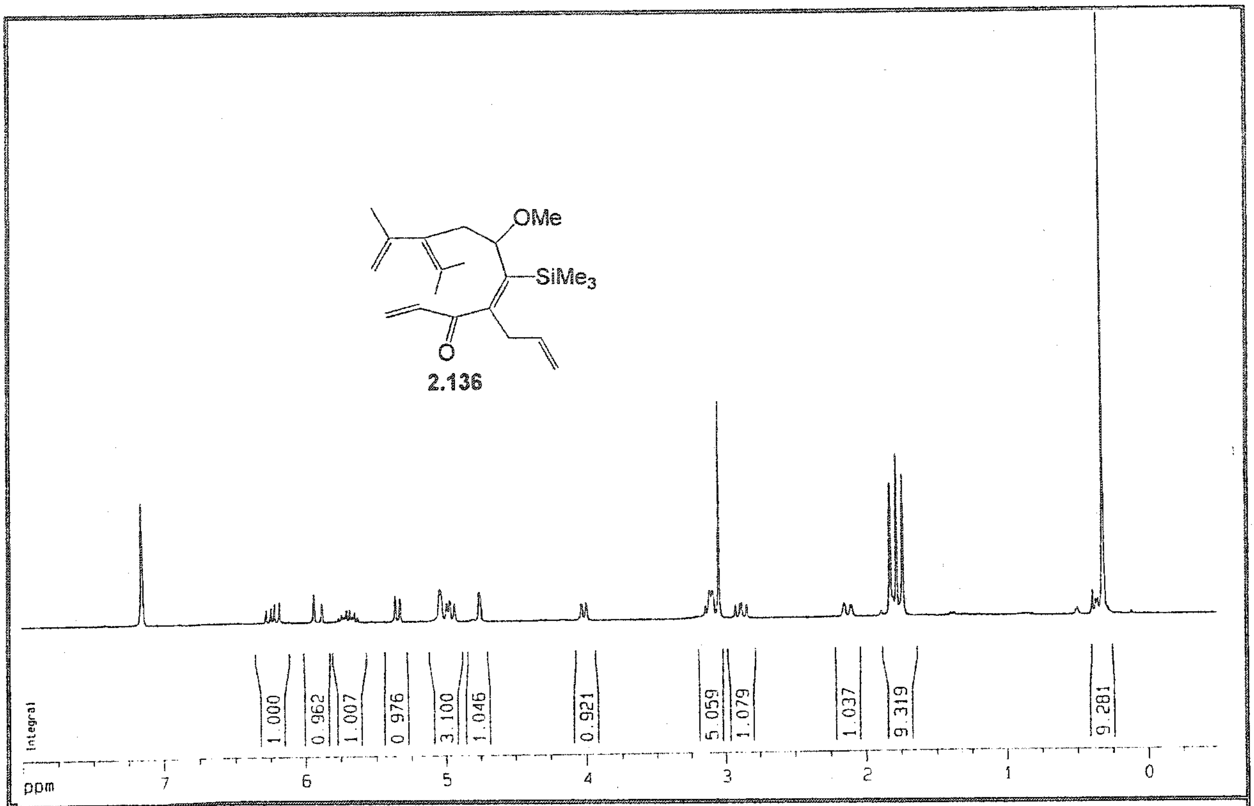
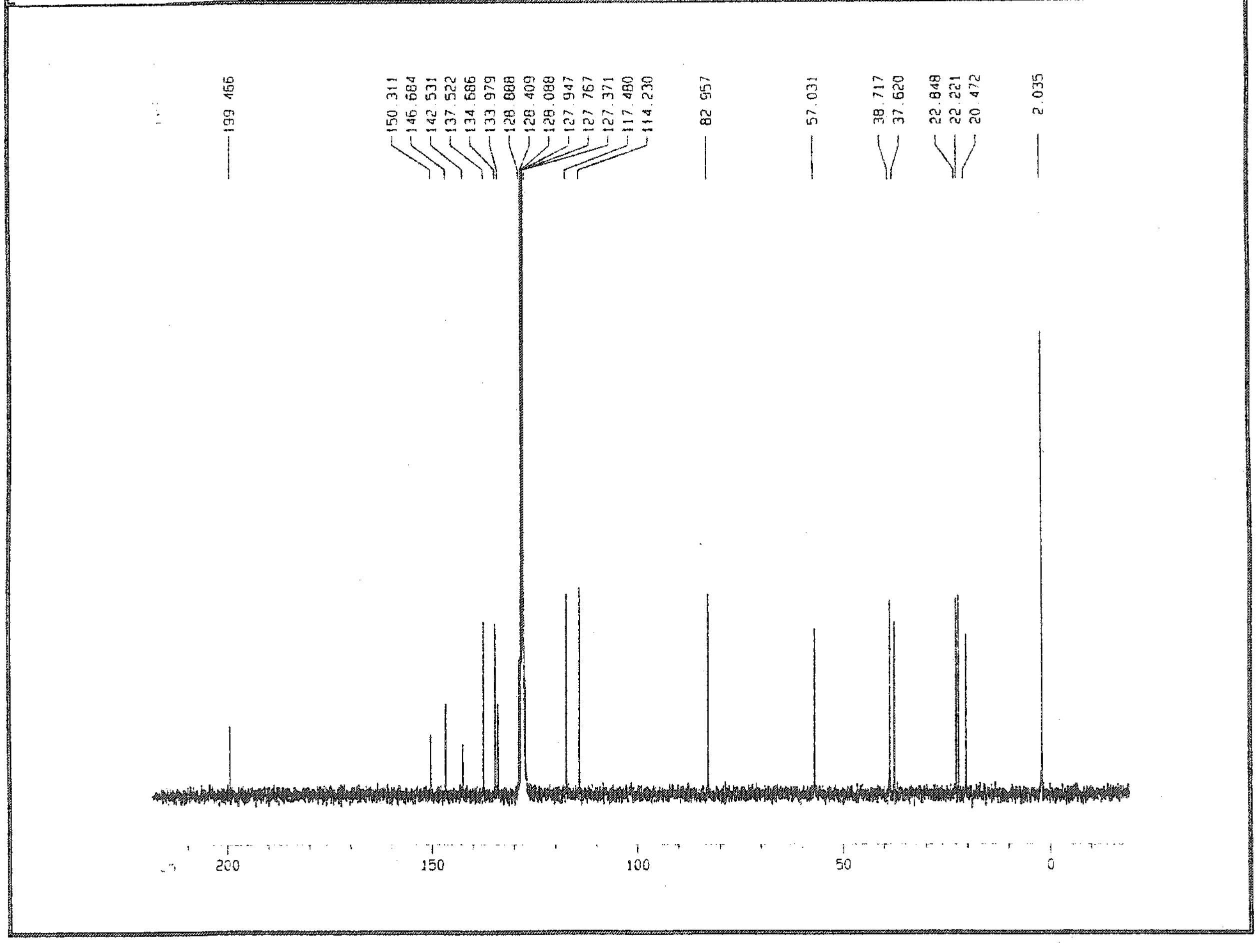
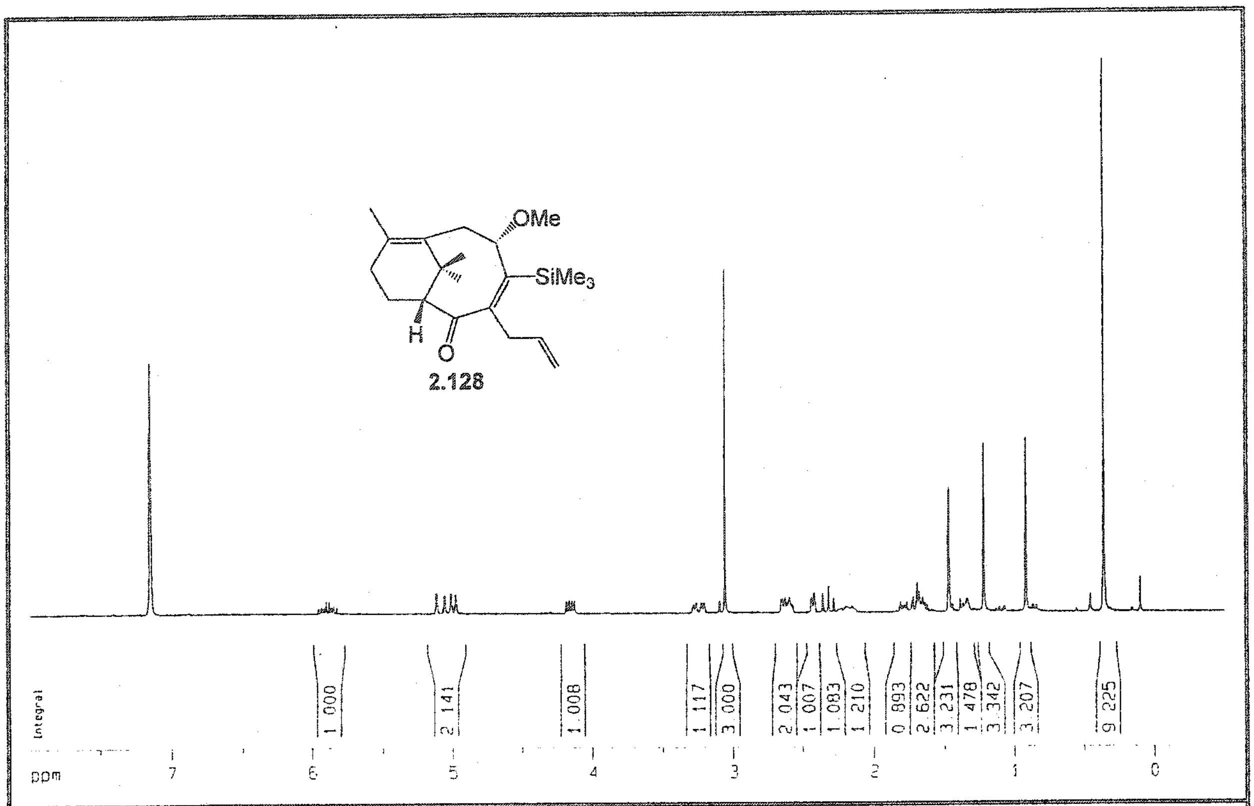
57.637
37.852
36.390
35.596
28.778
28.486
25.128
21.588
19.226
12.136
ppm
200
175
150
125
100
75
50
25

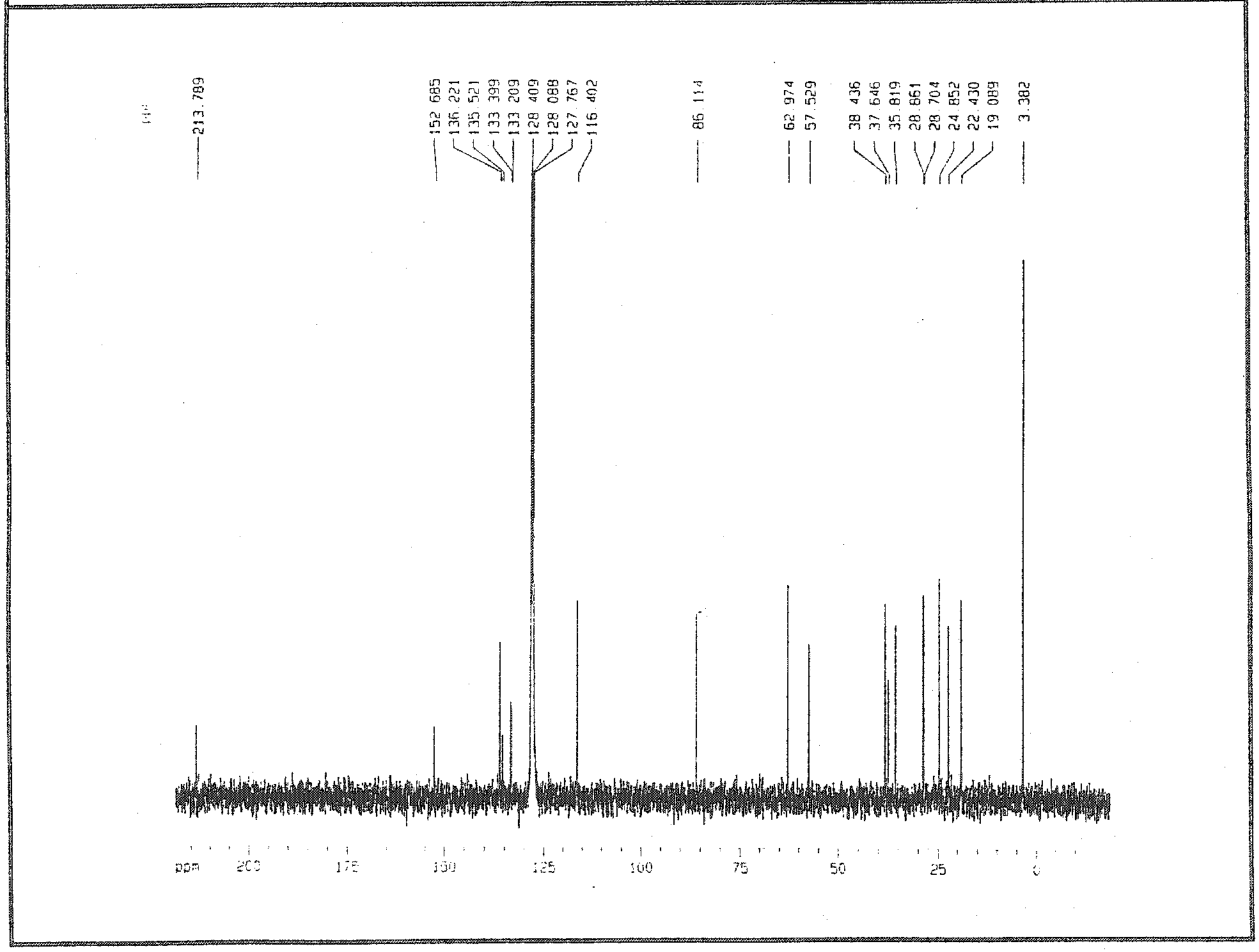

OMe
SiMe3
O
2.136
1.000
0.962
1.007
0.976
3.100
1.046
0.921
5.059
1.079
1.037
9.319
9.281
Integral
ppm
7
6
5
4
3
2
1
0


199.466
150.311
146.684
142.531
137.522
134.686
133.979
128.888
128.409
128.088
127.947
127.767
127.371
117.480
114.230
82.957
57.031
38.717
37.620
22.848
22.221
20.472
2.035
200
150
100
50
0

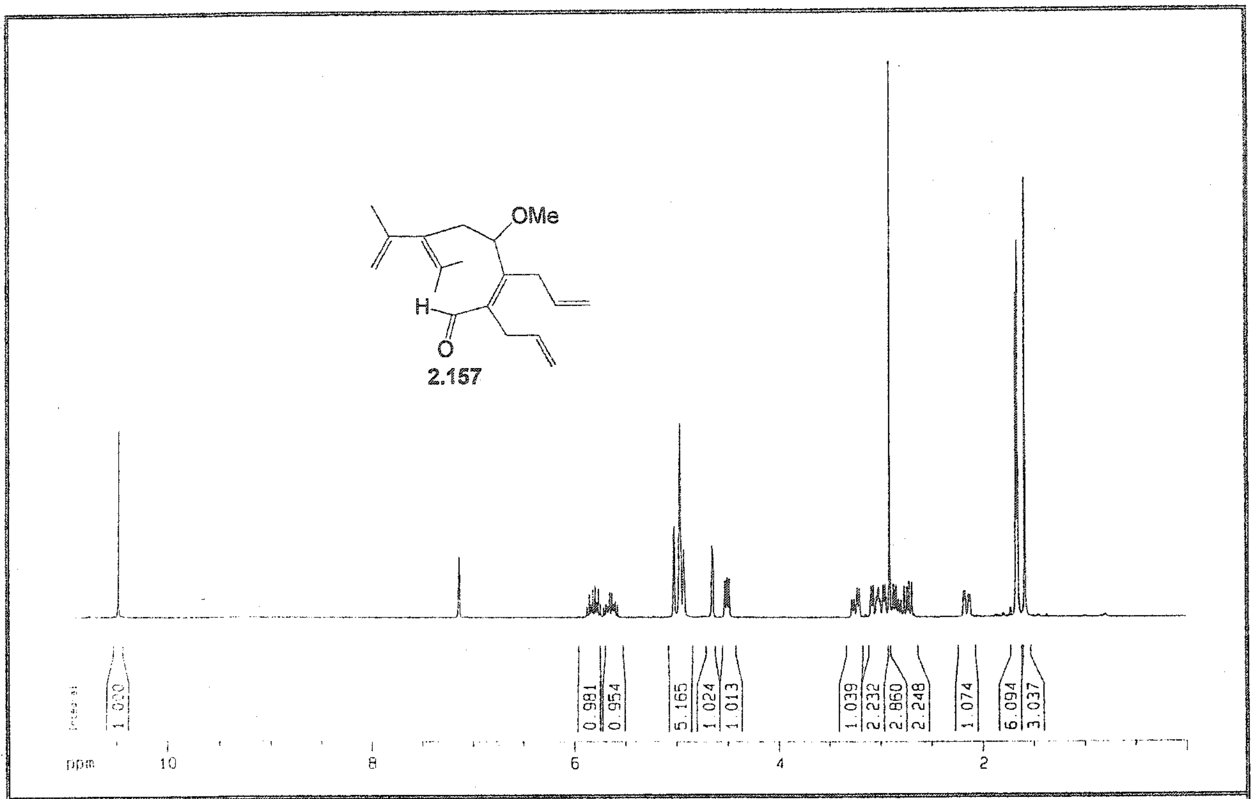


2.128

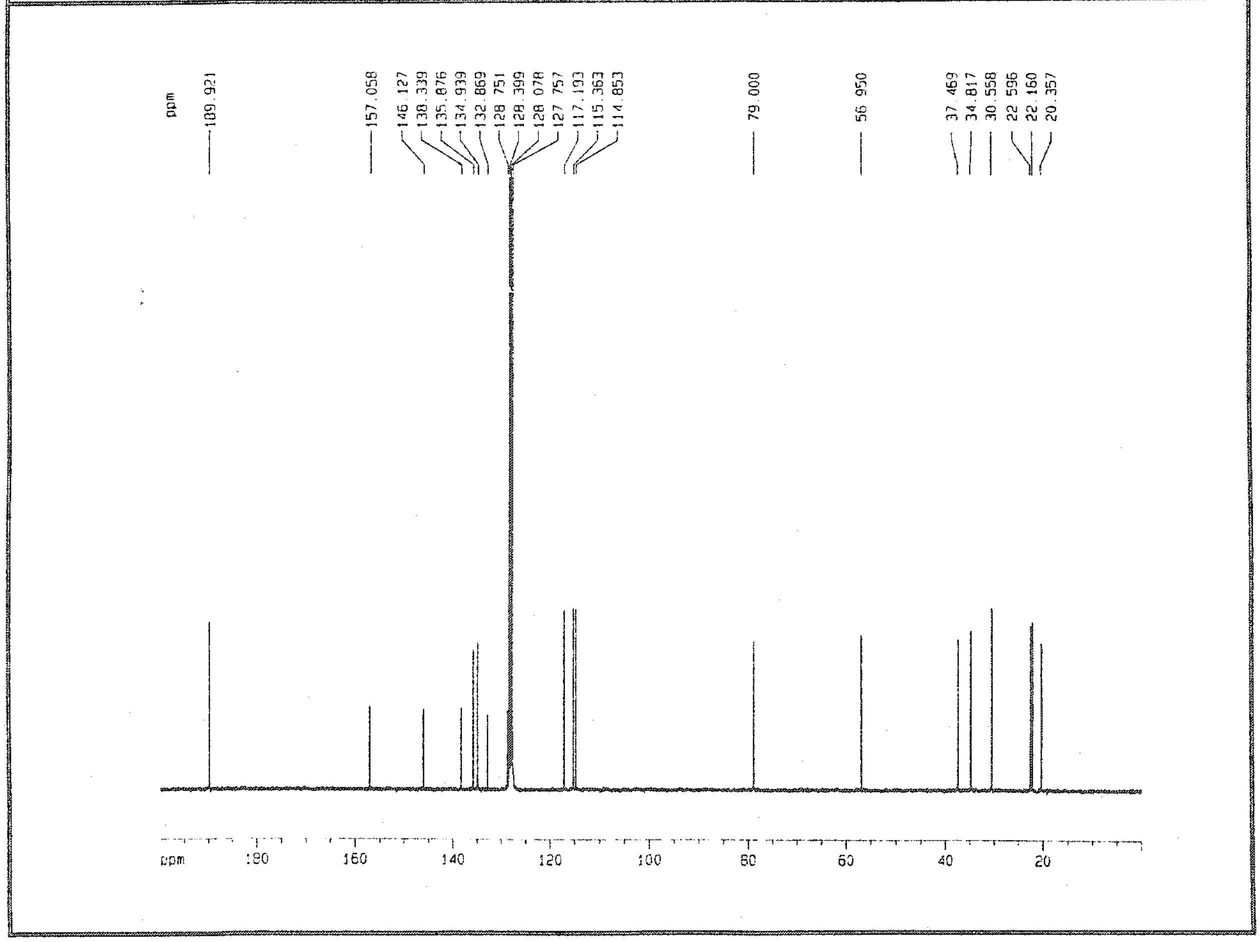
OMe
SiMe3
H
O
Integral
1.000
2.141
1.008
1.117
3.000
2.043
1.007
1.083
1.210
0.893
2.622
3.231
1.478
3.342
3.207
9.225
ppm
7
6
5
4
3
2
1
0



213.789
152.685
136.221
135.521
133.399
133.209
128.409
128.088
127.767
116.402
86.114
62.974
57.529
38.436
37.646
35.819
28.861
28.704
24.852
22.430
19.089
3.382
ppm
200
175
150
125
100
75
50
25
0


OMe
H
O
1.020
0.981
0.954
5.165
1.024
1.013
1.039
2.232
2.860
2.248
1.074
6.094
3.037
ppm
10
8
6
4
2

2.157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135.876
134.939
132.869
128.751
128.399
128.078
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115.363
114.853
79.000
56.950
37.469
34.817
30.558
22.596
22.160
20.357
ppm
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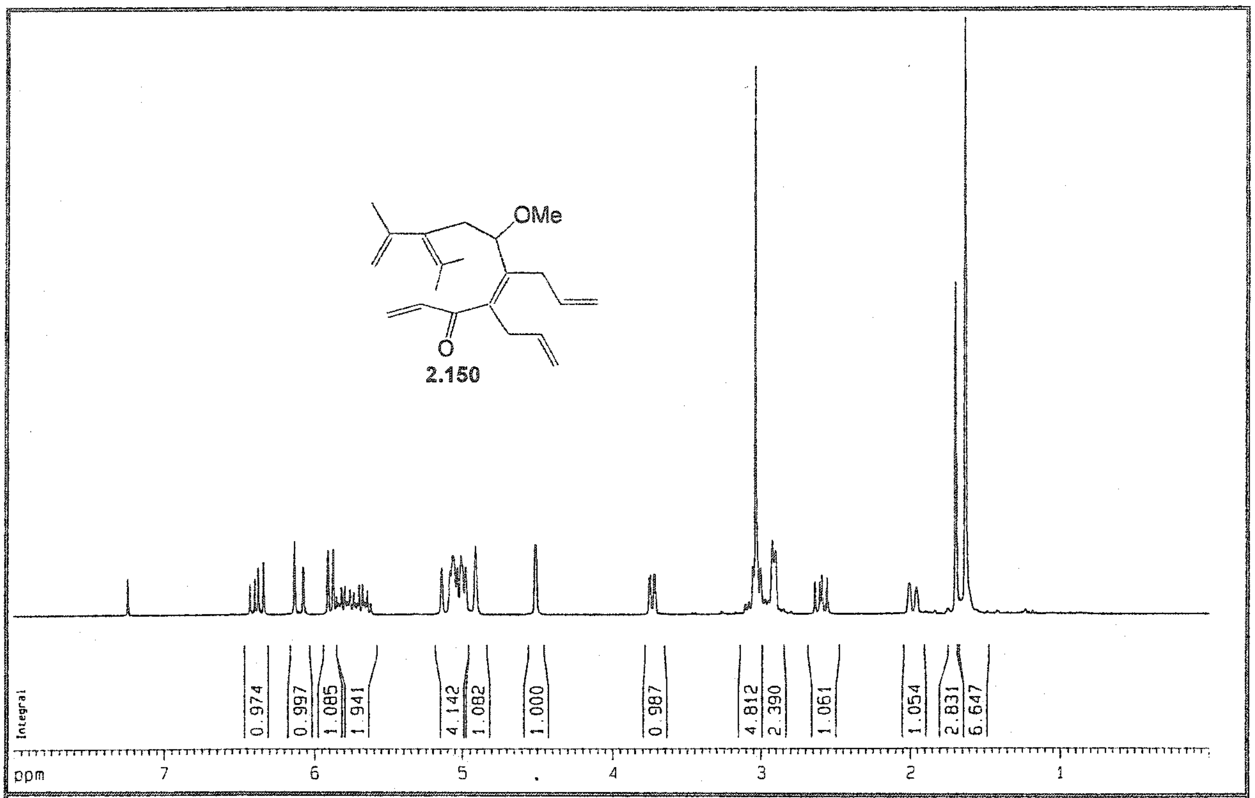
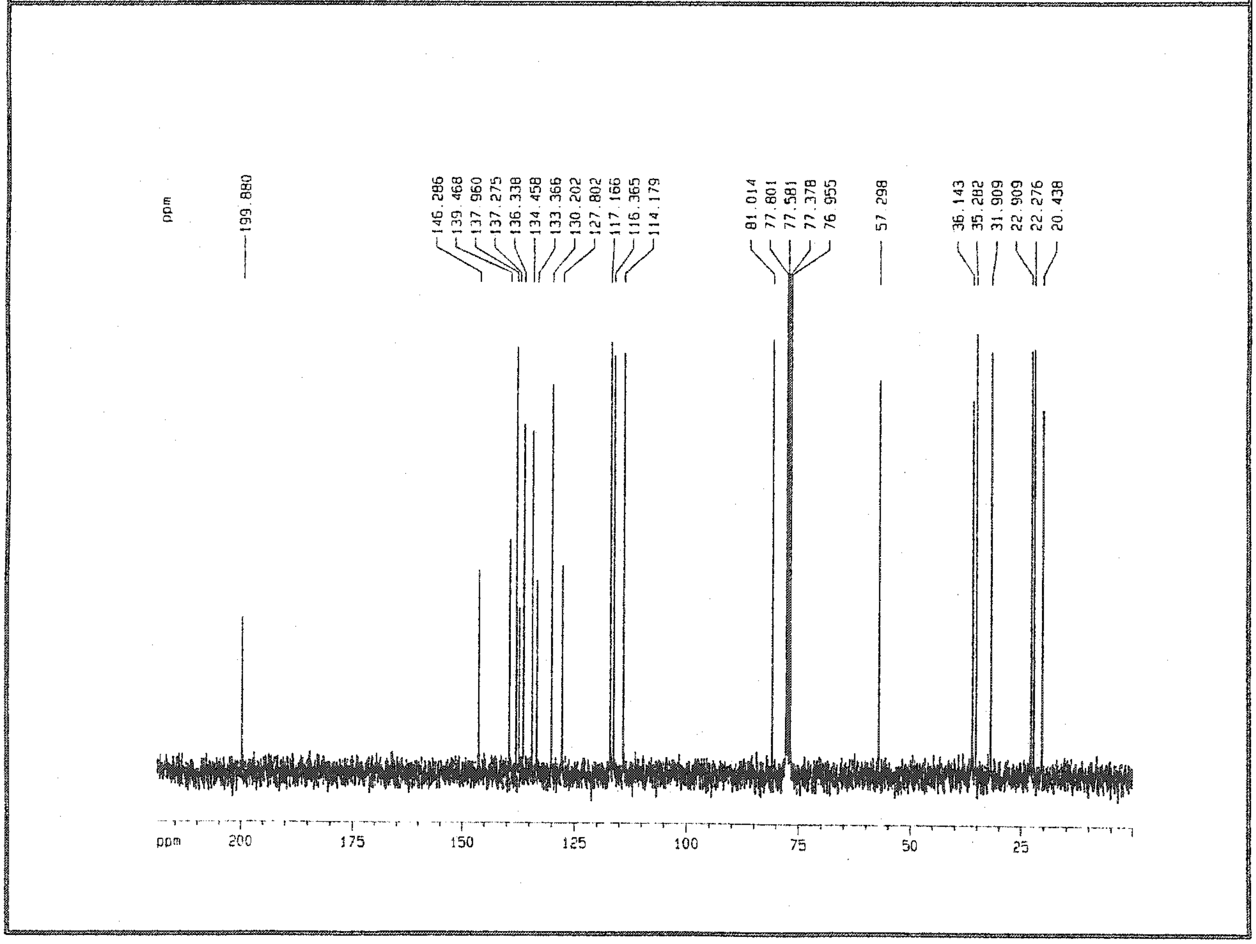
160
140
120
100
80
60
40
20



2.150

OMe
O
Integral
0.974
0.997
1.085
1.941
4.142
1.082
1.000
0.987
4.812
2.390
1.061
1.054
2.831
6.647
ppm
7
6
5
4
3
2
1



ppm
199.880
146.286
139.468
137.960
137.275
136.338
134.458
133.366
130.202
127.802
117.166
116.365
114.179
81.014
77.801
77.581
77.378
76.955
57.298
36.143
35.282
31.909
22.909
22.276
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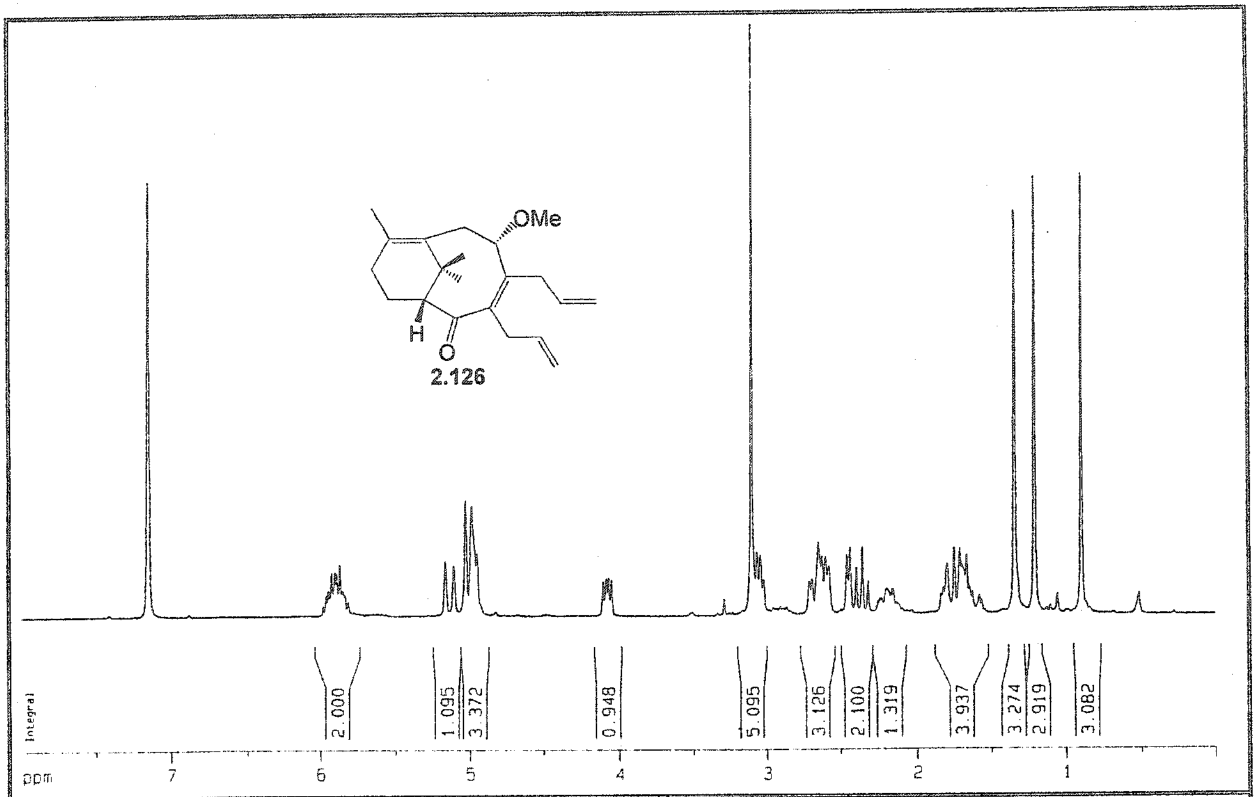
150
125
100
75
50
25


OMe
H
O
Integral
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3.372
0.948
5.095
3.126
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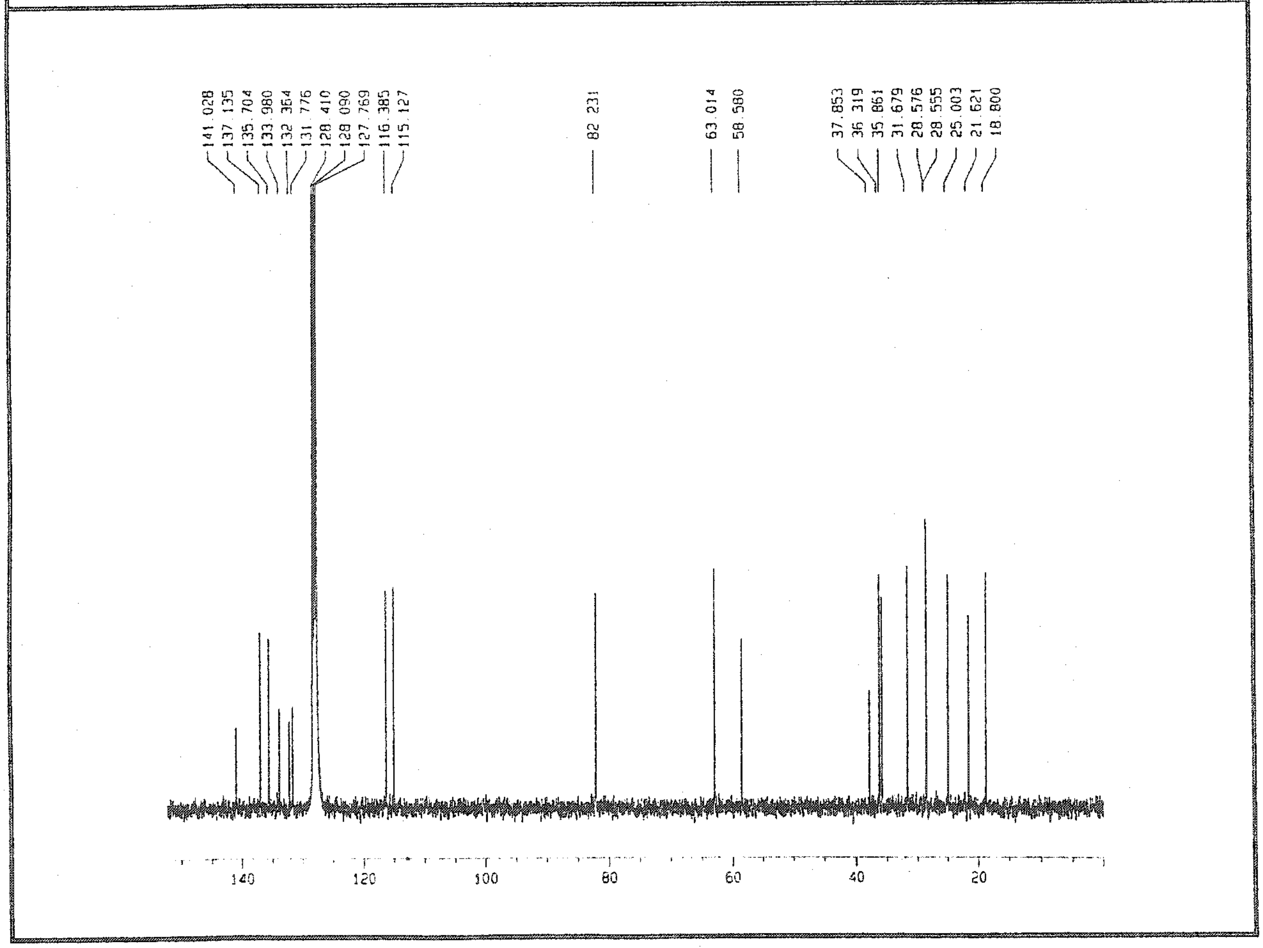
1.319
3.937
3.274
2.919
3.082
ppm
7
6
5
4
3
2
1

2.126


141.028
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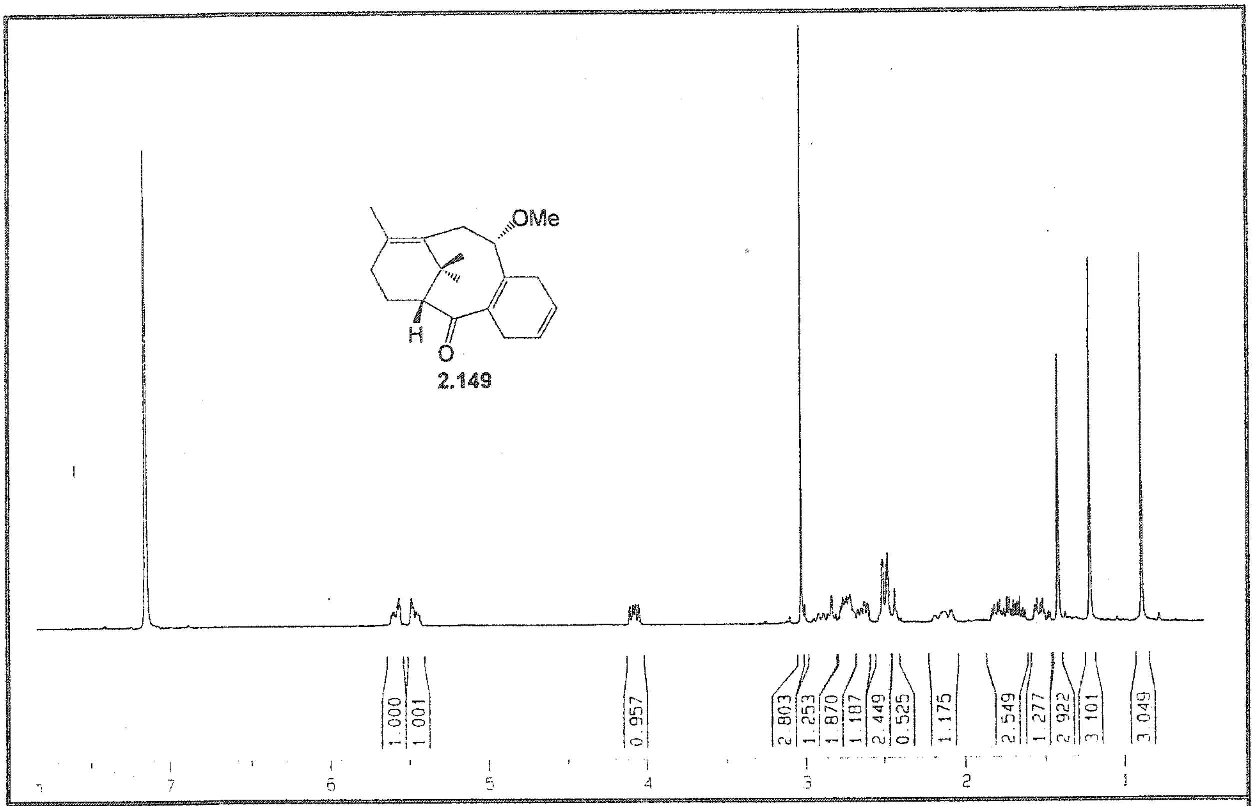
135.704
133.980
132.354
131.776
128.410
128.090
127.769
116.385
115.127
82.231
63.014
58.580
37.853
36.319
35.861
31.679
28.576
28.555
25.003
21.621
18.800
140
120
100
80
60
40
20


OMe
H
O
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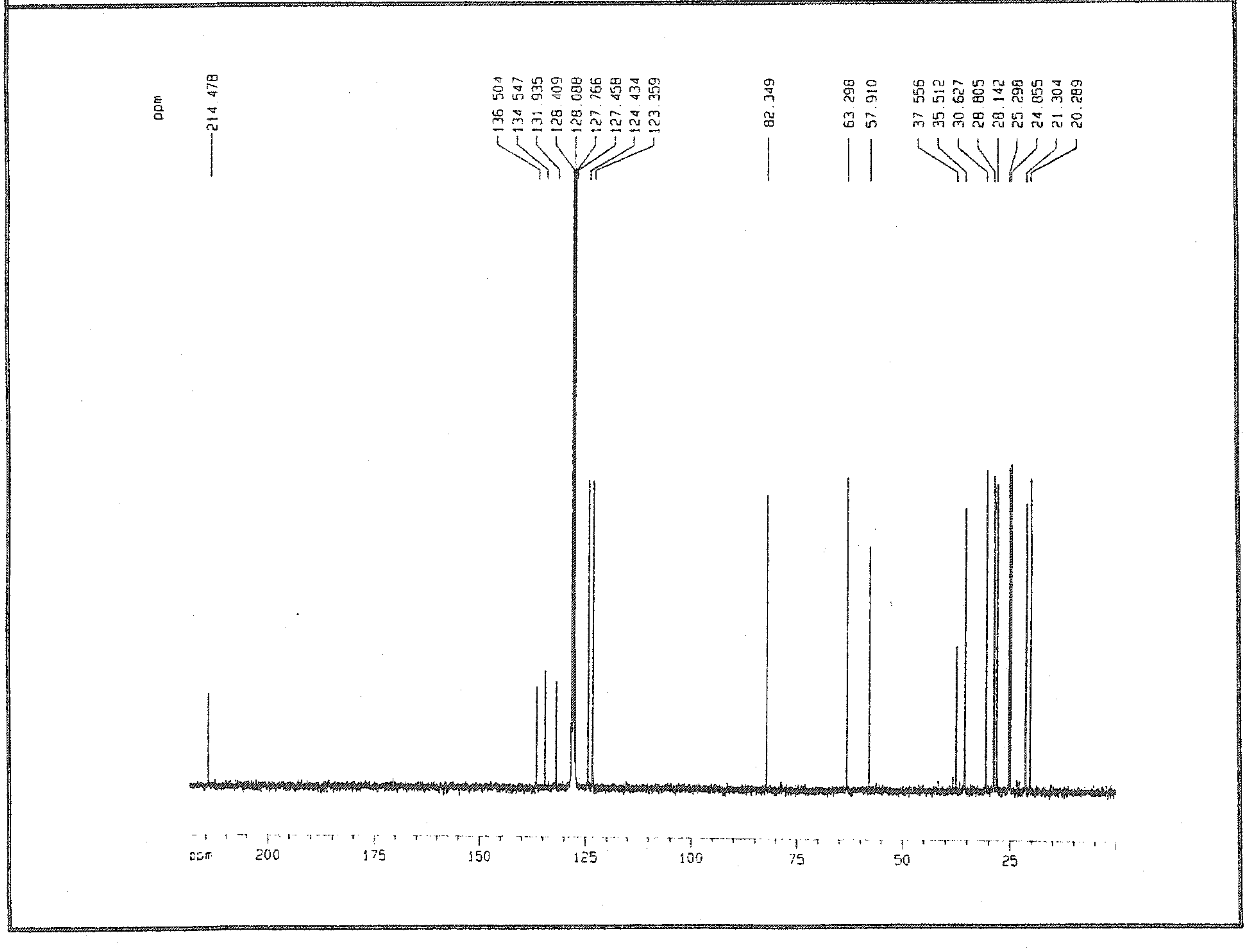
1.001
0.957
2.803
1.253
1.870
1.187
2.449
0.525
1.175
2.549
1.277
2.922
3.101
3.049
7
6
5
4
3
2
1

2.149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124.434
123.359
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57.910
37.556
35.512
30.627
28.805
28.142
25.298
24.855
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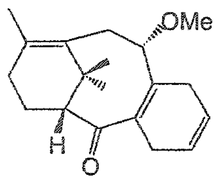
20.289
ppm
200
175
150
125
100
75
50
25

APPENDIX C

X-Ray Structures



2.149

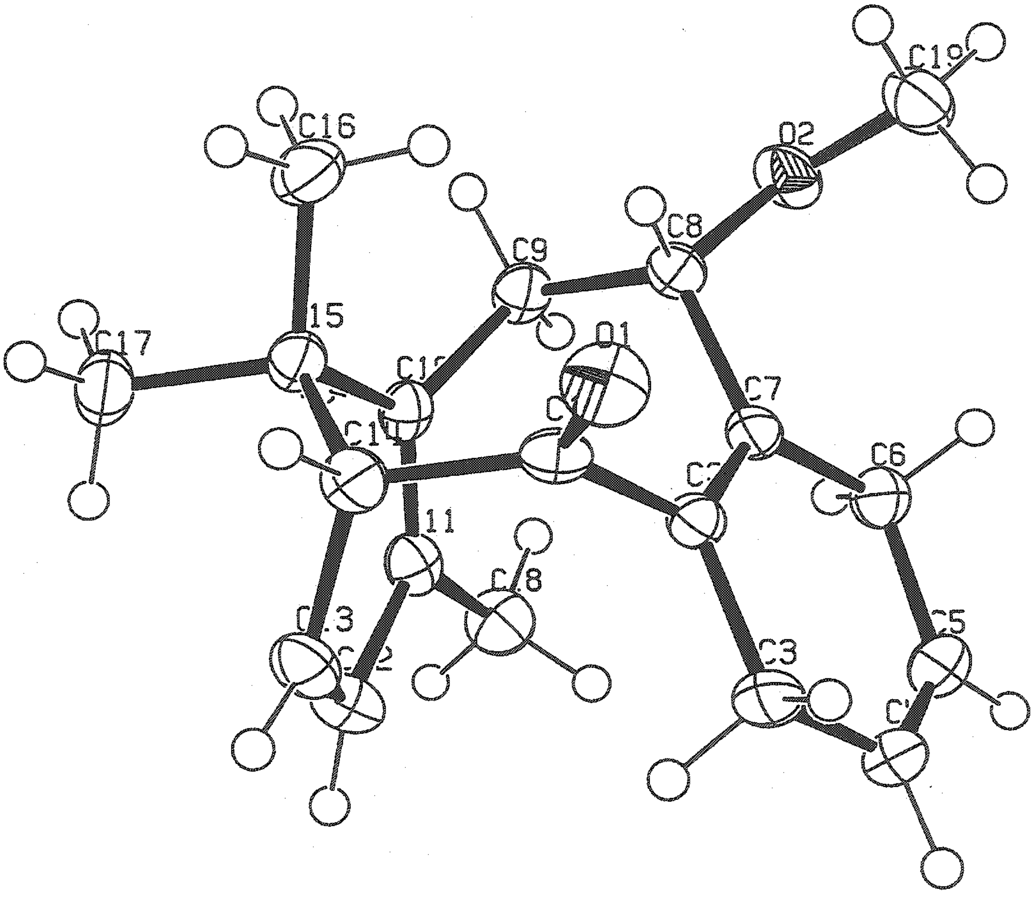


Table 1. Crystal data and structure refinement for af2006.

Identification code	af2006
Empirical formula	C19 H25 O2
Formula weight	285.39
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 9.3046(10) A alpha = 90 deg. b = 11.2837(12) A beta = 105.329(2) d c = 15.3871(16) A gamma = 90 deg.
Volume	1558.0(3) A^3
Z, Calculated density	4, 1.217 Mg/m^3
Absorption coefficient	0.077 mm^-1
F(000)	620
Crystal size	0.20 x 0.20 x 0.20 mm
Theta range for data collection	2.27 to 28.91 deg.
Limiting indices	-12<=h<=11, 0<=k<=15, 0<=l<=20
Reflections collected / unique	11592 / 3701 [R(int) = 0.0223]
Completeness to theta = 28.91	90.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000000 and 0.935436
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3701 / 0 / 190
Goodness-of-fit on F^2	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0602, wR2 = 0.1839
R indices (all data)	R1 = 0.0705, wR2 = 0.1950
Largest diff. peak and hole	0.714 and -0.911 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for af2006.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	5986(2)	5187(1)	3763(1)	37(1)
O(2)	8999(2)	2765(1)	2411(1)	30(1)
C(1)	6181(2)	4155(2)	3999(1)	23(1)
C(2)	7771(2)	3720(2)	4385(1)	22(1)
C(3)	8383(2)	4018(2)	5377(1)	28(1)
C(4)	9934(2)	3573(2)	5769(1)	33(1)
C(5)	10719(2)	3012(2)	5294(1)	34(1)
C(6)	10164(2)	2774(2)	4301(1)	28(1)
C(7)	8587(2)	3191(2)	3894(1)	22(1)
C(8)	7900(2)	2869(2)	2911(1)	24(1)
C(9)	7063(2)	1660(2)	2807(1)	26(1)
C(10)	6039(2)	1645(2)	3425(1)	23(1)
C(11)	6480(2)	1197(2)	4266(1)	25(1)
C(12)	5789(2)	1580(2)	5013(1)	31(1)
C(13)	4847(2)	2725(2)	4840(1)	29(1)
C(14)	4816(2)	3353(2)	3949(1)	25(1)
C(15)	4624(2)	2415(2)	3180(1)	25(1)
C(16)	4268(2)	3045(2)	2256(1)	33(1)
C(17)	3251(2)	1611(2)	3144(2)	35(1)
C(18)	7812(2)	390(2)	4605(1)	34(1)
C(19)	9528(2)	3887(2)	2208(1)	36(1)

Table 3. Bond lengths [A] and angles [deg] for af2006.

O(1)-C(1)	1.219(2)
O(2)-C(19)	1.422(2)
O(2)-C(8)	1.438(2)
C(1)-C(2)	1.522(2)
C(1)-C(14)	1.545(3)
C(2)-C(7)	1.344(2)
C(2)-C(3)	1.519(2)
C(3)-C(4)	1.496(3)
C(4)-C(5)	1.324(3)
C(5)-C(6)	1.501(3)
C(6)-C(7)	1.511(2)
C(7)-C(8)	1.522(2)
C(8)-C(9)	1.557(3)
C(9)-C(10)	1.514(2)
C(10)-C(11)	1.348(3)
C(10)-C(15)	1.539(2)
C(11)-C(12)	1.520(2)
C(11)-C(18)	1.516(3)
C(12)-C(13)	1.544(3)
C(13)-C(14)	1.537(3)
C(14)-C(15)	1.562(2)
C(15)-C(16)	1.546(3)
C(15)-C(17)	1.555(3)

C(19)-O(2)-C(8)	112.48(15)
O(1)-C(1)-C(2)	118.54(17)
O(1)-C(1)-C(14)	119.24(16)
C(2)-C(1)-C(14)	122.12(15)
C(7)-C(2)-C(3)	123.07(16)
C(7)-C(2)-C(1)	124.01(15)
C(3)-C(2)-C(1)	112.80(14)
C(4)-C(3)-C(2)	113.34(15)
C(5)-C(4)-C(3)	123.55(17)
C(4)-C(5)-C(6)	123.73(18)
C(5)-C(6)-C(7)	113.71(16)
C(2)-C(7)-C(6)	122.41(16)
C(2)-C(7)-C(8)	120.86(15)
C(6)-C(7)-C(8)	116.43(15)
O(2)-C(8)-C(7)	112.28(14)
O(2)-C(8)-C(9)	106.30(14)
C(7)-C(8)-C(9)	112.32(14)
C(10)-C(9)-C(8)	109.00(14)
C(11)-C(10)-C(9)	121.63(16)
C(11)-C(10)-C(15)	118.04(15)
C(9)-C(10)-C(15)	118.70(15)
C(10)-C(11)-C(12)	122.46(16)
C(10)-C(11)-C(18)	124.74(16)
C(12)-C(11)-C(18)	112.41(16)
C(11)-C(12)-C(13)	116.23(15)
C(14)-C(13)-C(12)	114.53(15)
C(13)-C(14)-C(1)	113.85(15)
C(13)-C(14)-C(15)	109.51(15)
C(1)-C(14)-C(15)	111.30(14)
C(10)-C(15)-C(16)	116.49(15)
C(10)-C(15)-C(17)	108.73(16)
C(16)-C(15)-C(17)	105.16(15)

C(10)-C(15)-C(14)	106.15(13)
C(16)-C(15)-C(14)	109.77(16)
C(17)-C(15)-C(14)	110.55(15)

Symmetry transformations used to generate equivalent atoms:

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for af2006.

	x	y	z	U(eq)
H(3A)	8373	4881	5450	34
H(3B)	7726	3676	5714	34
H(4A)	10374	3699	6386	39
H(5A)	11680	2747	5595	41
H(6A)	10215	1920	4198	34
H(6B)	10826	3169	3991	34
H(8A)	7181	3495	2632	28
H(9A)	6481	1554	2180	31
H(9B)	7783	1009	2963	31
H(10A)	5515	913	3160	28
H(12A)	5928	1145	5549	37
H(13A)	4334	3014	5247	35
H(14A)	3922	3867	3797	30
H(16A)	4173	2460	1782	49
H(16B)	5067	3591	2242	49
H(16C)	3340	3480	2164	49
H(17A)	3161	1023	2672	52
H(17B)	2357	2093	3018	52
H(17C)	3381	1215	3719	52
H(18A)	8205	159	4105	51
H(18B)	7508	-312	4874	51
H(18C)	8577	805	5053	51
H(19A)	10265	3772	1872	54
H(19B)	9978	4305	2764	54
H(19C)	8702	4347	1849	54

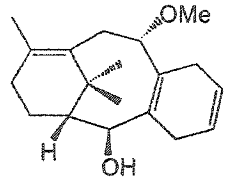
Table 4. Anisotropic displacement parameters (A^2 x 10^3) for af2006. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	42(1)	25(1)	43(1)	4(1)	10(1)	6(1)
O(2)	33(1)	35(1)	29(1)	-5(1)	18(1)	-1(1)
C(1)	30(1)	22(1)	19(1)	-3(1)	9(1)	3(1)
C(2)	25(1)	21(1)	20(1)	-1(1)	7(1)	-2(1)
C(3)	34(1)	31(1)	20(1)	-5(1)	8(1)	-5(1)
C(4)	34(1)	40(1)	21(1)	0(1)	2(1)	-10(1)
C(5)	24(1)	46(1)	28(1)	4(1)	1(1)	-3(1)
C(6)	23(1)	34(1)	28(1)	0(1)	7(1)	0(1)
C(7)	23(1)	23(1)	21(1)	-1(1)	7(1)	-3(1)
C(8)	23(1)	29(1)	21(1)	-3(1)	9(1)	1(1)
C(9)	25(1)	29(1)	25(1)	-8(1)	8(1)	-1(1)
C(10)	22(1)	22(1)	26(1)	-7(1)	7(1)	-3(1)
C(11)	27(1)	21(1)	29(1)	-3(1)	10(1)	-2(1)
C(12)	40(1)	27(1)	28(1)	2(1)	16(1)	0(1)
C(13)	31(1)	32(1)	29(1)	-3(1)	16(1)	1(1)
C(14)	22(1)	28(1)	27(1)	-2(1)	9(1)	4(1)
C(15)	21(1)	29(1)	24(1)	-4(1)	6(1)	0(1)
C(16)	27(1)	43(1)	26(1)	1(1)	2(1)	5(1)
C(17)	23(1)	43(1)	38(1)	-8(1)	8(1)	-6(1)
C(18)	34(1)	31(1)	37(1)	4(1)	9(1)	6(1)
C(19)	39(1)	41(1)	33(1)	2(1)	17(1)	-4(1)

Table 6. Torsion angles [deg] for af2006.

O(1)-C(1)-C(2)-C(7)	-94.1(2)
C(14)-C(1)-C(2)-C(7)	89.5(2)
O(1)-C(1)-C(2)-C(3)	82.1(2)
C(14)-C(1)-C(2)-C(3)	-94.34(19)
C(7)-C(2)-C(3)-C(4)	-5.0(3)
C(1)-C(2)-C(3)-C(4)	178.82(15)
C(2)-C(3)-C(4)-C(5)	2.3(3)
C(3)-C(4)-C(5)-C(6)	1.2(3)
C(4)-C(5)-C(6)-C(7)	-2.4(3)
C(3)-C(2)-C(7)-C(6)	4.1(3)
C(1)-C(2)-C(7)-C(6)	179.83(16)
C(3)-C(2)-C(7)-C(8)	177.57(16)
C(1)-C(2)-C(7)-C(8)	-6.7(3)
C(5)-C(6)-C(7)-C(2)	-0.3(3)
C(5)-C(6)-C(7)-C(8)	-174.07(16)
C(19)-O(2)-C(8)-C(7)	-75.19(19)
C(19)-O(2)-C(8)-C(9)	161.63(15)
C(2)-C(7)-C(8)-O(2)	156.74(16)
C(6)-C(7)-C(8)-O(2)	-29.4(2)
C(2)-C(7)-C(8)-C(9)	-83.5(2)
C(6)-C(7)-C(8)-C(9)	90.35(18)
O(2)-C(8)-C(9)-C(10)	172.01(14)
C(7)-C(8)-C(9)-C(10)	48.85(19)
C(8)-C(9)-C(10)-C(11)	-92.9(2)
C(8)-C(9)-C(10)-C(15)	72.22(19)
C(9)-C(10)-C(11)-C(12)	155.22(16)
C(15)-C(10)-C(11)-C(12)	-10.0(3)
C(9)-C(10)-C(11)-C(18)	-17.0(3)
C(15)-C(10)-C(11)-C(18)	177.75(17)
C(10)-C(11)-C(12)-C(13)	-15.1(3)
C(18)-C(11)-C(12)-C(13)	158.04(17)
C(11)-C(12)-C(13)-C(14)	-3.2(2)
C(12)-C(13)-C(14)-C(1)	-82.5(2)
C(12)-C(13)-C(14)-C(15)	42.8(2)
O(1)-C(1)-C(14)-C(13)	-126.50(18)
C(2)-C(1)-C(14)-C(13)	49.9(2)
O(1)-C(1)-C(14)-C(15)	109.15(18)
C(2)-C(1)-C(14)-C(15)	-74.4(2)
C(11)-C(10)-C(15)-C(16)	172.24(16)
C(9)-C(10)-C(15)-C(16)	6.6(2)
C(11)-C(10)-C(15)-C(17)	-69.2(2)
C(9)-C(10)-C(15)-C(17)	125.07(17)
C(11)-C(10)-C(15)-C(14)	49.7(2)
C(9)-C(10)-C(15)-C(14)	-115.97(16)
C(13)-C(14)-C(15)-C(10)	-64.88(18)
C(1)-C(14)-C(15)-C(10)	61.88(18)
C(13)-C(14)-C(15)-C(16)	168.43(15)
C(1)-C(14)-C(15)-C(16)	-64.81(18)
C(13)-C(14)-C(15)-C(17)	52.86(19)
C(1)-C(14)-C(15)-C(17)	179.62(15)

Symmetry transformations used to generate equivalent atoms:


OMe
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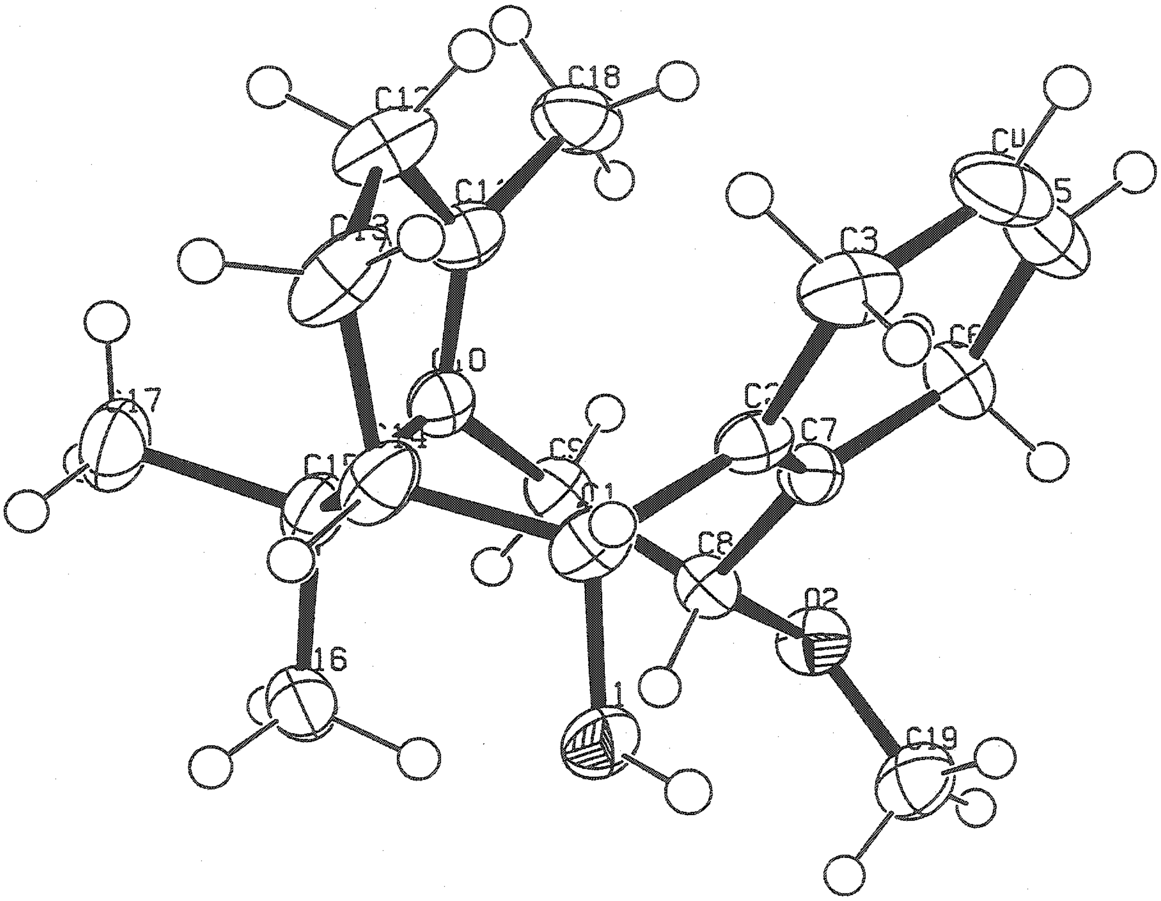
2.164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C18
C11
C13
C3
C4
C5
C6
C17
C10
C9
C2
C7
C15
C14
C1
C8
O2
C16
O1
C19

Table 1. Crystal data and structure refinement for af2007.

Identification code	af2007
Empirical formula	C19 H28 O2
Formula weight	288.41
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, Pbca
Unit cell dimensions	a = 11.0730(9) A alpha = 90 deg. b = 15.1223(12) A beta = 90 deg. c = 19.7554(16) A gamma = 90 deg.
Volume	3308.0(5) A^3
Z, Calculated density	8, 1.158 Mg/m^3
Absorption coefficient	0.073 mm^-1
F(000)	1264
Crystal size	0.23 x 0.15 x 0.12 mm
Theta range for data collection	2.50 to 28.81 deg.
Limiting indices	0<=h<=14, 0<=k<=20, 0<=l<=26
Reflections collected / unique	22173 / 4012 [R(int) = 0.0392]
Completeness to theta = 28.81	92.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000000 and 0.899619
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4012 / 0 / 190
Goodness-of-fit on F^2	1.016
Final R indices [I>2sigma(I)]	R1 = 0.0513, wR2 = 0.1170
R indices (all data)	R1 = 0.0818, wR2 = 0.1327
Largest diff. peak and hole	0.272 and -0.234 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for af2007.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	6998(1)	1774(1)	6435(1)	33(1)
O(2)	10000(1)	1543(1)	7717(1)	31(1)
C(1)	7453(1)	2613(1)	6194(1)	30(1)
C(2)	8152(1)	3132(1)	6743(1)	26(1)
C(3)	7807(2)	4109(1)	6764(1)	39(1)
C(4)	8451(2)	4641(1)	7288(1)	45(1)
C(5)	9240(2)	4304(1)	7714(1)	46(1)
C(6)	9583(2)	3346(1)	7719(1)	36(1)
C(7)	8970(1)	2799(1)	7174(1)	25(1)
C(8)	9486(1)	1871(1)	7095(1)	25(1)
C(9)	10528(1)	1848(1)	6564(1)	29(1)
C(10)	10133(1)	2290(1)	5914(1)	28(1)
C(11)	10375(1)	3147(1)	5788(1)	33(1)
C(12)	9654(2)	3675(1)	5274(1)	46(1)
C(13)	8361(2)	3322(2)	5126(1)	47(1)
C(14)	8044(1)	2444(1)	5490(1)	35(1)
C(15)	9176(2)	1829(1)	5470(1)	33(1)
C(16)	8886(2)	859(1)	5665(1)	40(1)
C(17)	9648(2)	1751(2)	4728(1)	49(1)
C(18)	11282(2)	3706(1)	6172(1)	44(1)
C(19)	9112(2)	1193(1)	8168(1)	40(1)

Table 3. Bond lengths [A] and angles [deg] for af2007.

O(1)-C(1)	1.445(2)
O(2)-C(19)	1.429(2)
O(2)-C(8)	1.4424(18)
C(1)-C(2)	1.545(2)
C(1)-C(14)	1.558(2)
C(2)-C(7)	1.342(2)
C(2)-C(3)	1.527(2)
C(3)-C(4)	1.493(3)
C(4)-C(5)	1.316(3)
C(5)-C(6)	1.499(2)
C(6)-C(7)	1.517(2)
C(7)-C(8)	1.523(2)
C(8)-C(9)	1.559(2)
C(9)-C(10)	1.514(2)
C(10)-C(11)	1.347(2)
C(10)-C(15)	1.542(2)
C(11)-C(18)	1.516(2)
C(11)-C(12)	1.518(3)
C(12)-C(13)	1.556(3)
C(13)-C(14)	1.550(3)
C(14)-C(15)	1.562(2)
C(15)-C(16)	1.549(3)
C(15)-C(17)	1.561(2)

C(19)-O(2)-C(8)	112.85(12)
O(1)-C(1)-C(2)	112.94(12)
O(1)-C(1)-C(14)	107.21(14)
C(2)-C(1)-C(14)	119.90(13)
C(7)-C(2)-C(3)	120.94(15)
C(7)-C(2)-C(1)	126.38(14)
C(3)-C(2)-C(1)	112.68(13)
C(4)-C(3)-C(2)	114.91(15)
C(5)-C(4)-C(3)	123.51(16)
C(4)-C(5)-C(6)	123.15(17)
C(5)-C(6)-C(7)	114.15(15)
C(2)-C(7)-C(6)	123.29(14)
C(2)-C(7)-C(8)	122.21(14)
C(6)-C(7)-C(8)	114.00(13)
O(2)-C(8)-C(7)	112.14(12)
O(2)-C(8)-C(9)	105.83(11)
C(7)-C(8)-C(9)	111.59(12)
C(10)-C(9)-C(8)	110.30(12)
C(11)-C(10)-C(9)	121.66(15)
C(11)-C(10)-C(15)	117.82(15)
C(9)-C(10)-C(15)	118.77(14)
C(10)-C(11)-C(18)	125.12(16)
C(10)-C(11)-C(12)	121.73(16)
C(18)-C(11)-C(12)	112.92(16)
C(11)-C(12)-C(13)	115.34(15)
C(14)-C(13)-C(12)	114.56(15)
C(13)-C(14)-C(1)	111.65(16)
C(13)-C(14)-C(15)	108.46(14)
C(1)-C(14)-C(15)	117.22(14)
C(10)-C(15)-C(16)	115.45(14)
C(10)-C(15)-C(17)	109.74(13)
C(16)-C(15)-C(17)	103.35(15)

C(10)-C(15)-C(14)	105.54(14)
C(16)-C(15)-C(14)	113.03(14)
C(17)-C(15)-C(14)	109.72(15)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for af2007.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	25(1)	43(1)	33(1)	-2(1)	7(1)	-9(1)
O(2)	31(1)	33(1)	29(1)	6(1)	-8(1)	2(1)
C(1)	20(1)	40(1)	30(1)	7(1)	-1(1)	0(1)
C(2)	20(1)	26(1)	31(1)	5(1)	4(1)	2(1)
C(3)	29(1)	31(1)	56(1)	11(1)	7(1)	7(1)
C(4)	37(1)	23(1)	77(2)	-6(1)	14(1)	1(1)
C(5)	45(1)	30(1)	63(1)	-18(1)	2(1)	-3(1)
C(6)	39(1)	33(1)	36(1)	-8(1)	-4(1)	-1(1)
C(7)	24(1)	24(1)	26(1)	-1(1)	2(1)	0(1)
C(8)	25(1)	24(1)	25(1)	0(1)	-5(1)	2(1)
C(9)	24(1)	28(1)	34(1)	-3(1)	-1(1)	5(1)
C(10)	20(1)	34(1)	29(1)	-2(1)	4(1)	0(1)
C(11)	26(1)	37(1)	35(1)	3(1)	8(1)	-3(1)
C(12)	42(1)	50(1)	46(1)	21(1)	9(1)	-2(1)
C(13)	38(1)	69(1)	35(1)	23(1)	2(1)	3(1)
C(14)	25(1)	56(1)	25(1)	7(1)	-3(1)	-6(1)
C(15)	29(1)	47(1)	23(1)	-2(1)	4(1)	-7(1)
C(16)	42(1)	44(1)	35(1)	-12(1)	8(1)	-12(1)
C(17)	46(1)	72(1)	29(1)	-9(1)	10(1)	-15(1)
C(18)	37(1)	37(1)	59(1)	-2(1)	8(1)	-10(1)
C(19)	43(1)	48(1)	30(1)	10(1)	-4(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for af2007.

	x	y	z	U(eq)
H(1A)	6406	1860	6684	50
H(1B)	6725	2973	6099	36
H(3A)	7970	4369	6319	46
H(3B)	6936	4154	6845	46
H(4A)	8283	5250	7316	55
H(5A)	9605	4683	8031	55
H(6A)	9381	3095	8162	43
H(6B)	10460	3299	7661	43
H(8A)	8834	1467	6947	29
H(9A)	11237	2153	6747	35
H(9B)	10754	1233	6473	35
H(12A)	10107	3688	4848	55
H(12B)	9588	4286	5436	55
H(13A)	7774	3773	5262	57
H(13B)	8276	3234	4637	57
H(14A)	7420	2152	5209	42
H(16A)	9622	512	5655	60
H(16B)	8312	615	5344	60
H(16C)	8542	843	6116	60
H(17A)	10357	1375	4719	74
H(17B)	9856	2334	4560	74
H(17C)	9023	1495	4445	74
H(18A)	11726	3334	6485	67
H(18B)	10860	4164	6421	67
H(18C)	11839	3976	5854	67
H(19A)	9505	981	8576	61
H(19B)	8693	707	7950	61
H(19C)	8538	1652	8285	61

Table 6. Torsion angles [deg] for af2007.

O(1)-C(1)-C(2)-C(7)	43.9(2)
C(14)-C(1)-C(2)-C(7)	-84.0(2)
O(1)-C(1)-C(2)-C(3)	-135.22(14)
C(14)-C(1)-C(2)-C(3)	96.90(17)
C(7)-C(2)-C(3)-C(4)	0.4(2)
C(1)-C(2)-C(3)-C(4)	179.62(14)
C(2)-C(3)-C(4)-C(5)	-1.4(3)
C(3)-C(4)-C(5)-C(6)	0.2(3)
C(4)-C(5)-C(6)-C(7)	1.7(3)
C(3)-C(2)-C(7)-C(6)	1.6(2)
C(1)-C(2)-C(7)-C(6)	-177.46(15)
C(3)-C(2)-C(7)-C(8)	-169.79(14)
C(1)-C(2)-C(7)-C(8)	11.1(2)
C(5)-C(6)-C(7)-C(2)	-2.7(2)
C(5)-C(6)-C(7)-C(8)	169.37(15)
C(19)-O(2)-C(8)-C(7)	81.48(16)
C(19)-O(2)-C(8)-C(9)	-156.62(13)
C(2)-C(7)-C(8)-O(2)	-159.85(14)
C(6)-C(7)-C(8)-O(2)	28.01(18)
C(2)-C(7)-C(8)-C(9)	81.61(17)
C(6)-C(7)-C(8)-C(9)	-90.54(16)
O(2)-C(8)-C(9)-C(10)	-172.69(12)
C(7)-C(8)-C(9)-C(10)	-50.44(17)
C(8)-C(9)-C(10)-C(11)	94.81(17)
C(8)-C(9)-C(10)-C(15)	-69.82(17)
C(9)-C(10)-C(11)-C(18)	15.1(2)
C(15)-C(10)-C(11)-C(18)	179.84(15)
C(9)-C(10)-C(11)-C(12)	-159.03(15)
C(15)-C(10)-C(11)-C(12)	5.7(2)
C(10)-C(11)-C(12)-C(13)	23.7(3)
C(18)-C(11)-C(12)-C(13)	-151.04(17)
C(11)-C(12)-C(13)-C(14)	-4.2(3)
C(12)-C(13)-C(14)-C(1)	90.65(19)
C(12)-C(13)-C(14)-C(15)	-40.0(2)
O(1)-C(1)-C(14)-C(13)	169.89(13)
C(2)-C(1)-C(14)-C(13)	-59.65(19)
O(1)-C(1)-C(14)-C(15)	-64.14(17)
C(2)-C(1)-C(14)-C(15)	66.3(2)
C(11)-C(10)-C(15)-C(16)	-176.74(15)
C(9)-C(10)-C(15)-C(16)	-11.5(2)
C(11)-C(10)-C(15)-C(17)	67.0(2)
C(9)-C(10)-C(15)-C(17)	-127.77(16)
C(11)-C(10)-C(15)-C(14)	-51.15(18)
C(9)-C(10)-C(15)-C(14)	114.07(15)
C(13)-C(14)-C(15)-C(10)	66.51(17)
C(1)-C(14)-C(15)-C(10)	-61.02(18)
C(13)-C(14)-C(15)-C(16)	-166.42(15)
C(1)-C(14)-C(15)-C(16)	66.05(19)
C(13)-C(14)-C(15)-C(17)	-51.66(19)
C(1)-C(14)-C(15)-C(17)	-179.19(15)

Symmetry transformations used to generate equivalent atoms: