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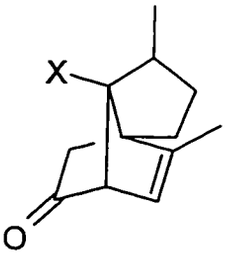
ABSTRACT

The preparation of a key synthetic intermediate for the total synthesis of retigeranic acid A (**1**) through the use an intramolecular Diels-Alder reaction is described.

Our approach to retigeranic acid A involved two key building blocks, a *trans*-hydrindane **52** and a unique tricyclic ketone **51**. The building block **52** has been successfully synthesized in the Fallis laboratory, but the synthesis of **51** by an intermolecular Diels-Alder has been difficult. A new route to **51** was devised, involving the use of an intramolecular Diels-Alder reaction. The synthesis started with the preparation of the ketone ester **76** in three steps from commercially available (R)-(+)-pulegone in a 46% yield. Alkylation of **76** with the tosylate **78**, followed by oxidative bond cleavage generated the diketone ester **80** in an overall yield of 44%. An intramolecular aldol-condensation and subsequent reduction produced the diol **72**. A selective DCC coupling with 2-chlorocrylic acid afforded the dienophile-alcohol **71** in a yield of 46%. A variety of methods were investigated for the dehydation of the alcohol to the diene **70**. In the final synthetic route, **71** was quantitatively oxidized with activated MnO_2 to the ketone **109**. The kinetic enolate of **109** was trapped using collidine and triisopropylsilyltrifluoromethanesulfonate, producing the desired diene **110** as a 1:1 mixture. This unstable compound, when heated in a refluxing 10 mole % solution of hydroquinone in benzene, underwent the desired intramolecular Diels-Alder reaction to give the adduct **112** in a yield of 64%.



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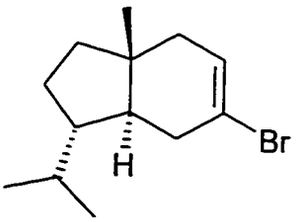

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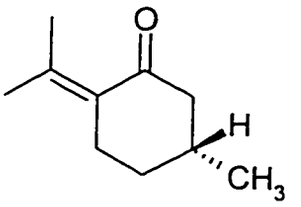
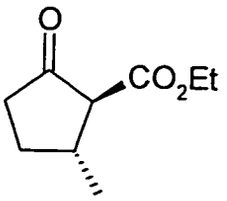


(R)-(+)-Pulegone



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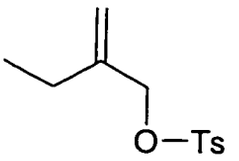

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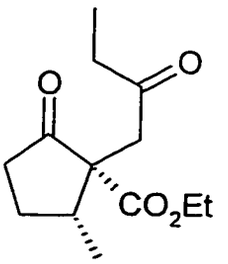

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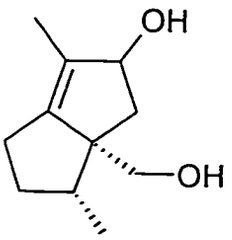

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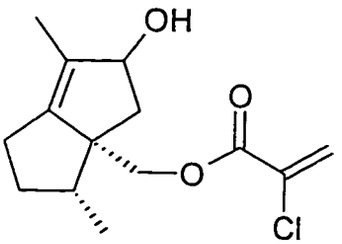

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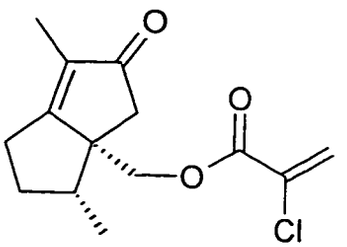

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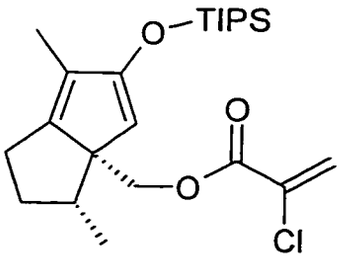

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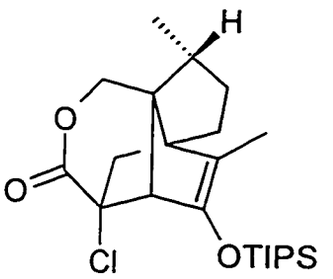

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LIST OF ABBREVIATIONS

AIBN	2,2'-azo-*bis*-(isobutyronitrile)
n-Bu	normal-butyl
calcd.	calculated
cat.	catalytic
conc	concentrated
COSY	^{1}H-^{1}H NMR correlation spectroscopy
Δ	heat
d	doublet
DCC	1,3-dicyclohexylcarbodiimide
dd	doublet of doublets
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(*N,N*-dimethylamino)pyridine
E.I.	electron impact
Et	ethyl
Et_2O	diethyl ether
FABH	Fast Atom Bombardment
g	gram(s)
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
J	coupling constant
kcal	kilocalorie(s)
LDA	lithium diisopropylamine
m	multiplet
M^+	molecular ion

Me	methyl
MHz	megahertz
mol	mole(s)
mp	melting point
NMR	nuclear magnetic resonance
q	quartet
Ph	phenyl
ppm	parts per million
R	alkyl group
s	singlet
TBS	tertiary-butyl dimethylsilyl-
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl-
TMEDA	tetramethylethylenediamine
triflate	trifluoromethanesulfonate
Ts	*para*-toluenesulfonyl-

ACKNOWLEDGEMENTS

I would first like to extend my thanks to Dr. Alex Fallis, my supervisor. He was extremely patient and understanding and I wish to thank him for the opportunity to study in his laboratory.

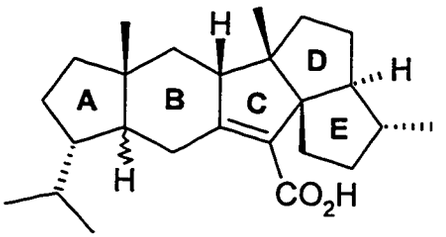
I would also thank my lab mates for all of their help and friendship during my studies at the University of Ottawa. First, I would like to thank Dr. Timothy Wong for introducing me to the worlds of "dry chemistry" and flash chromatography. Although my first project did not give the results that were expected, his help was invaluable. I want to also thank Dr. Peter Wilson. His help, ideas, and various procedures were invaluable in the retigeranic acid A project. I am sure that I would not have been able to get the results I did without him. I hope that one day he gets his own chemistry lab. I would also like to thank Dr. Simon Woo and Dr. Michael Tjepkema for their help in my research.

I believe that it was the atmosphere set in Dr Fallis' lab that made my studies at the University of Ottawa so enjoyable. I could always count on my lab mates for a good discussion. In particular, I would like to thank Jodi Lavers and Dr. Simon Woo. These adventurous souls introduced me to roller coasters and white water rafting. I will always consider them to be among my closest friends.

Lastly, I want to thank the University of Ottawa for the opportunity to do research at a wonderful institute. The labs there are probably among the best in Canada.

Chapter 1

1.1. INTRODUCTION



1: α-H = Retigeranic Acid A
2: β-H = Retigeranic Acid B

Figure 1

The total synthesis of retigeranic acid A **1** (Figure 1) is a topic of international interest. This compound is a unique pentacyclic sesterterpene that possesses complex stereochemical relationships. It has *trans*-hydrindane (A-B rings) and triquinane (C-D-E rings) subunits. These factors make retigeranic acid A a synthetic challenge.

Retigeranic acid A (**1**) and B (**2**) were isolated as a mixture in 1969 by Sheshadri from lichens of the *Lobaria retigera* group found in the Western Himalayas.[1] The structure was not completely elucidated until 1972 when the group of Shibata crystallized the *p*-bromoanilide derivative, obtaining retigeranic acid A.[2] They did not know it at the time, but they had managed to fractionally crystallize what was a 2:1 mixture of the retigeranic acids A and B, with retigeranic acid A being the minor component. By mistake, since **1** was the first form of retigeranic acid that was isolated, the minor component received the designation of retigeranic acid A. It was not until 1986 that it was discovered that retigeranic acid actually existed as a mixture of two components.[3] The syntheses published to date have therefore been of retigeranic acid A.

At present the biological activity of retigeranic acid A, if any, is unknown. The activity may be limited as other than the carboxylic acid functional group, retigeranic acid

is totally devoid of heteroatoms. Retigeranic acid does have a double bond and interesting topology, but the lack of other functionality may limit it's binding to active sites in cells. It is conceivable that functionalized derivatives of retigeranic acid A could possess some biological activity. Plants of the *genus Lobaria* have been used in perfumery and tanning and have been used in drugs for the cure of eczema and lung disorders.[4]

1.2. PREVIOUS TOTAL SYNTHESES

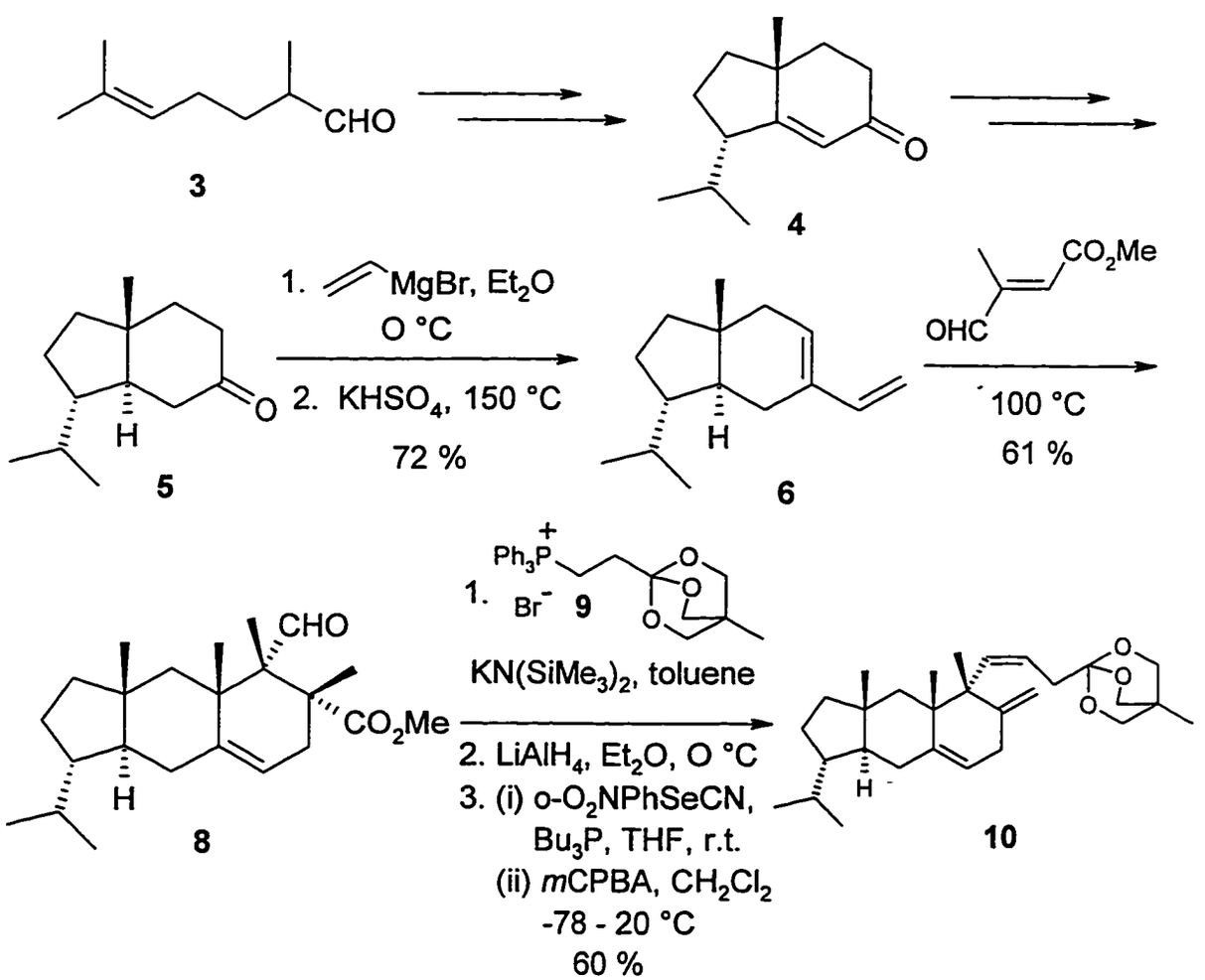
There have been several total syntheses of retigeranic acid A reported since the synthetic studies in our group were initiated. These include those from the research groups of Corey[5], Paquette[6], Hudlicky[7], and Wender[8]. Corey completed the synthesis by a Diels-Alder reaction, followed by an intramolecular ketene cycloaddition and ring expansion and contraction. Paquette performed his synthesis by conjugate additions and annulations. Hudlicky used a vinyl cyclopropane rearrangement as a key step in his synthesis for preparing the pentacycle. Wender synthesized the triquinane building block through arene photolysis and completed the pentacycle by an intramolecular Diels-Alder reaction.

1.2.1. Corey's Synthesis

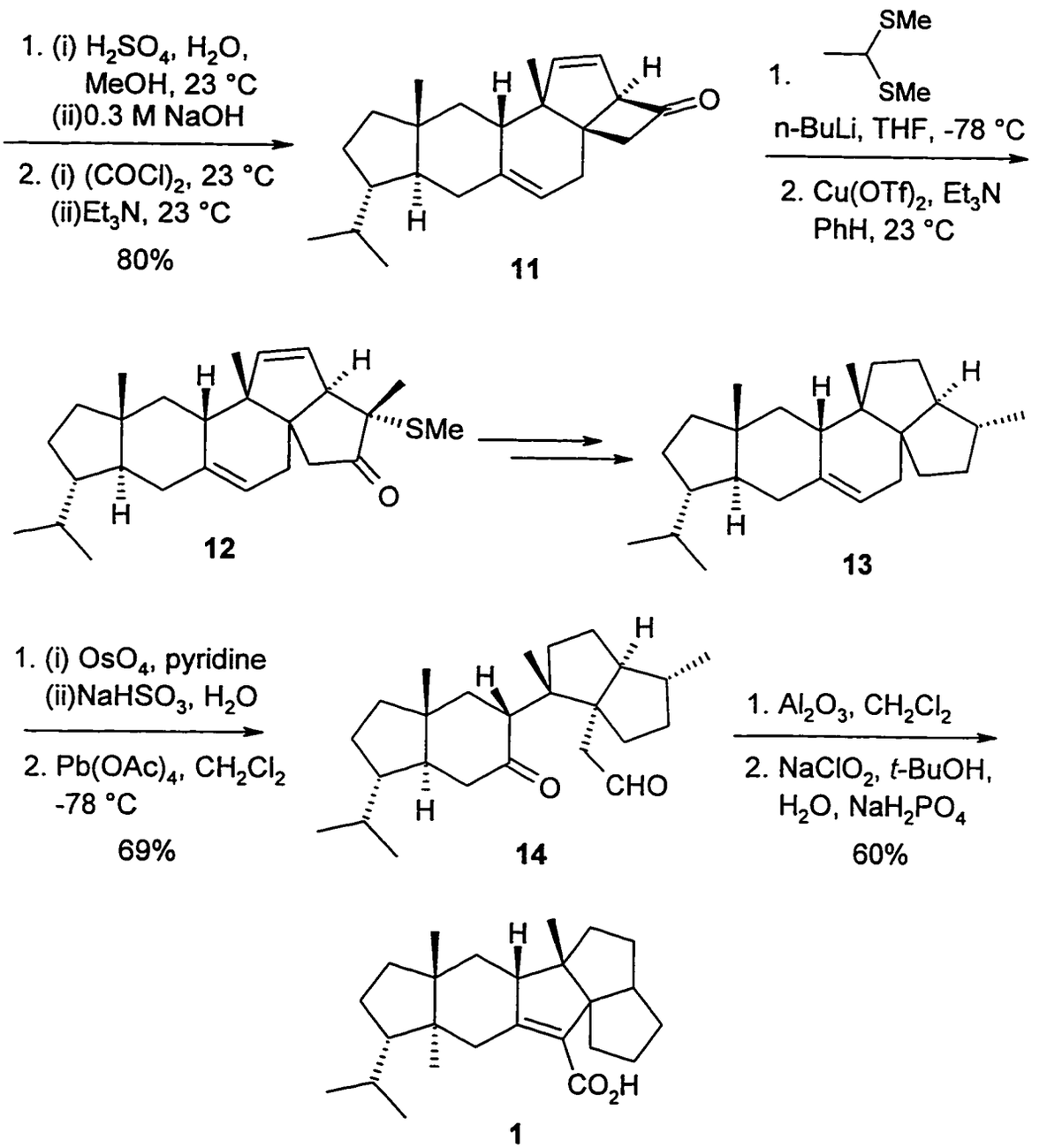
Corey and his research group were the first to synthesize retigeranic acid A. Their approach was a left to right strategy by which the A and B rings were derived from 2,6-dimethyl-5-heptenal. The C ring precursor was fashioned by an intramolecular Diels-Alder reaction and then the final D and E rings were added simultaneously (Scheme 1).[5]

After the A-B ring system was generated from **3**, the allylic ketone **4** was reduced and the stereochemistry of the resulting alcohol was inverted by Mitsunobu's procedure. This produced the trans A-B stereochemistry ring after hydrogenation. The alcohol was then oxidized to the ketone **5**. Grignard addition of vinyl magnesium bromide, followed by dehydration gave the diene **6**. A Diels-Alder reaction between the dienophile **7** and

diene **6** was used to make ring C (adduct **8**). This adduct was then subjected to Wittig olefination conditions using the phosphonium salt **9**. The ester was reduced and the alcohol eliminated to give the exo-cyclic double bond. Subsequent deprotection of **10** and formation of the ketene from the resulting acid set the stage for a [2+2] cycloaddition. This reaction generated the D ring as a cyclopentene and E ring as a cyclobutanone, as seen in **11**. After the E ring was expanded to the required cyclopentane **12**, the ring substituents were modified to give the alkene **13**. Oxidative bond cleavage was conducted using osmium tetroxide followed by treatment with lead tetraacetate. An intramolecular aldol condensation of the ketone-aldehyde **14** product gave the desired ring contracted retigeranic acid ring system. Oxidation of the α–β unsaturated aldehyde gave retigeranic acid A.



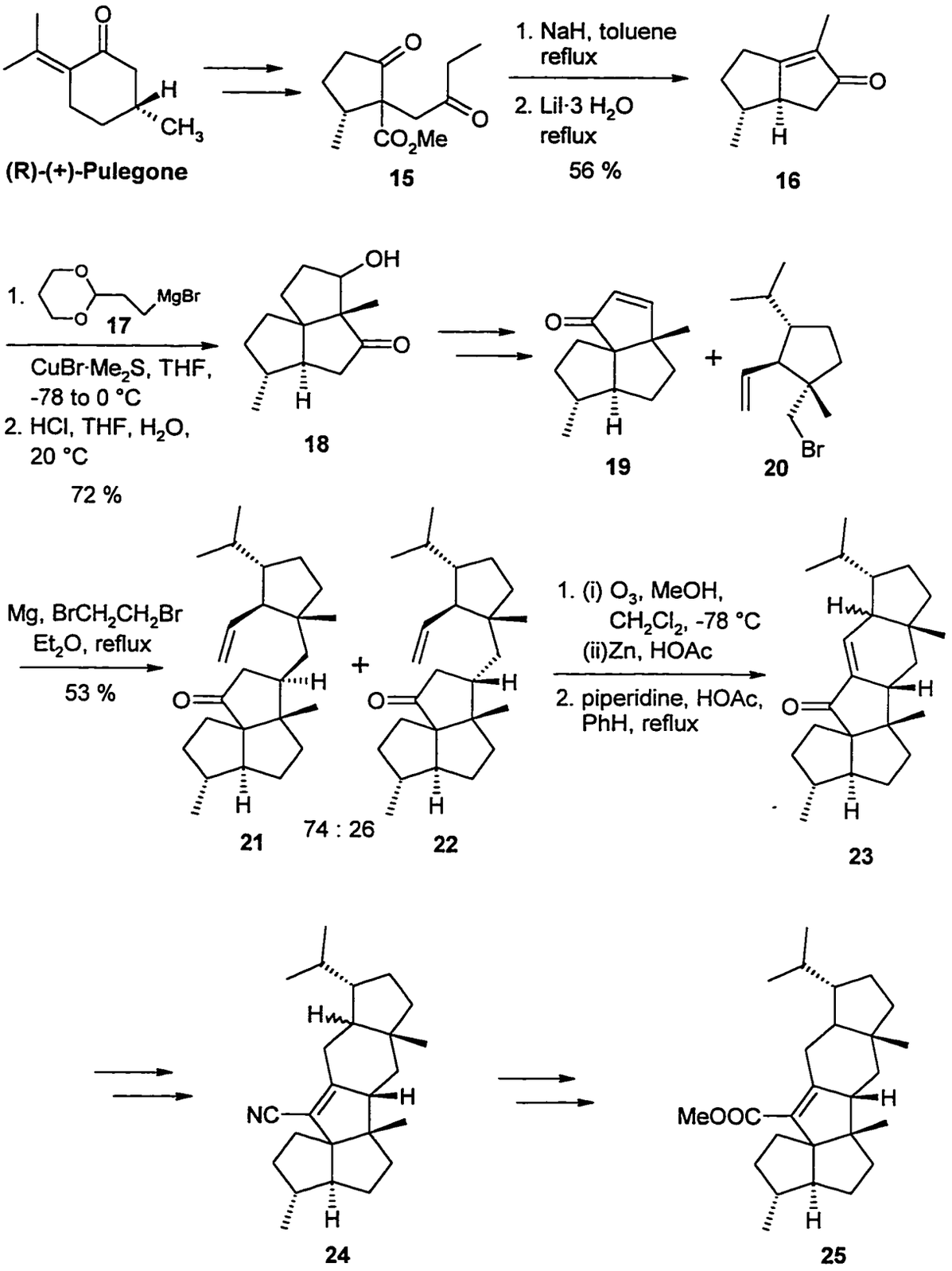
Scheme 1



Scheme 1 (continued)

1.2.2. Paquette's Approach

Paquette's group decided to use a simpler, more repetitive approach. His synthesis started with R-(+)-pulegone and, after a ring contraction reaction, started a series of addition reactions followed by cyclizations (Scheme 2).[6]

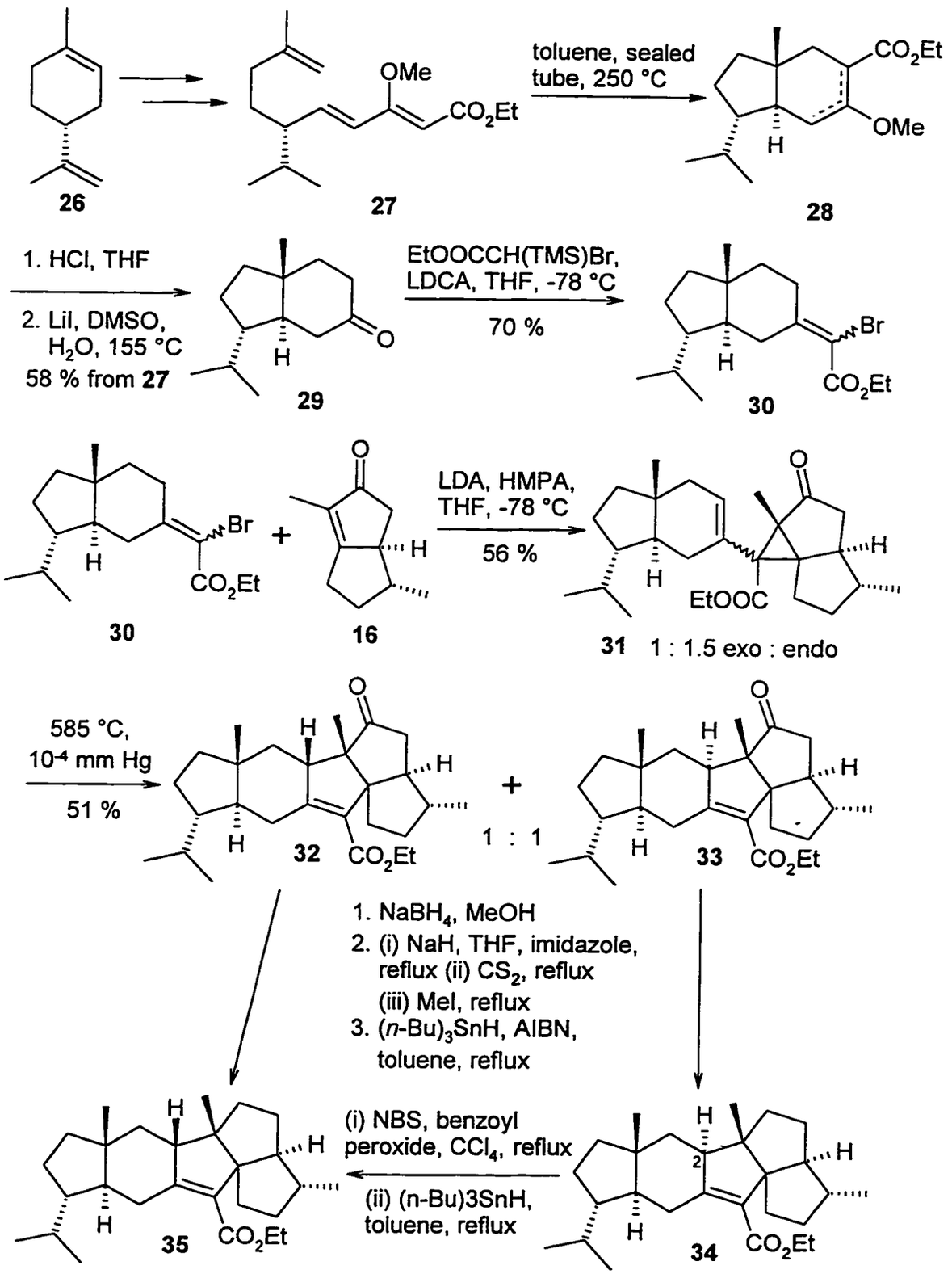

(R)-(+)-Pulegone
15
1. NaH, toluene reflux
2. LiI·3 H2O reflux
56 %
16
1.
17
MgBr
CuBr·Me2S, THF, -78 to 0 °C
2. HCl, THF, H2O, 20 °C
72 %
18
19
20
Br
Mg, BrCH2CH2Br
Et2O, reflux
53 %
21
74 : 26
22
1. (i) O3, MeOH, CH2Cl2, -78 °C
(ii)Zn, HOAc
2. piperidine, HOAc, PhH, reflux
23
24
NC
25
MeOOC

Scheme 2

The triquinane **18** was prepared initially from R-(+)-pulegone by a ring contraction reaction followed by alkylation and ozonolysis to yield the diketone-ester **15**. An aldol condensation followed by decarboxylation gave the diquinane **16**. The second annulation was performed by Grignard addition of **17**, deprotection and condensation to yield the C-D-E ring system in the triquinane **18**. Dehydration of the alcohol, Wolff-Kishner reduction of the ketone, and then allylic oxidation gave the triquinane **19**. The A-ring containing building block **20** was synthesized from (S)-limonene. The crucial coupling of the triquinane **19** and building block **20** was accomplished by reacting the Grignard reagent prepared from **20** with the ketone **19**. This addition gave a 3 to 1 mixture of **21** and **22**. The preference for addition to the β-face syn to the methyl group was attributed to steric hindrance. Ozonolysis of the vinyl group of **22** produced the aldehyde required for the third aldol condensation. The intramolecular aldol condensation gave the pentacyclic compound **23**. The double bond of **23** was hydrogenated, after which the cyanohydrin was generated from the ketone and dehydrated to the nitrile **24**. Reduction of the nitrile **24** and oxidation of the resulting alcohol gave the acid, which was esterified, to afford the retigeranic acid methyl ester **25**. This approach, however, gave a 3 to 1 mixture of the retigeranic acid methyl esters B to A.

1.2.3. Hudlicky's Approach

Hudlicky's group was able to synthesize retigeranic acid ester, but they could not do it by their original method. They had originally planned to synthesis the A and B ring simultaneously by an intramolecular Diels-Alder reaction. Unfortunately, attempts to form the triene by attachment of the necessary synthon to their triquinane proved to be difficult. His new approach was just as inventive, however, as it employed an interesting vinyl cyclopropane rearrangement (Scheme 3).[7]

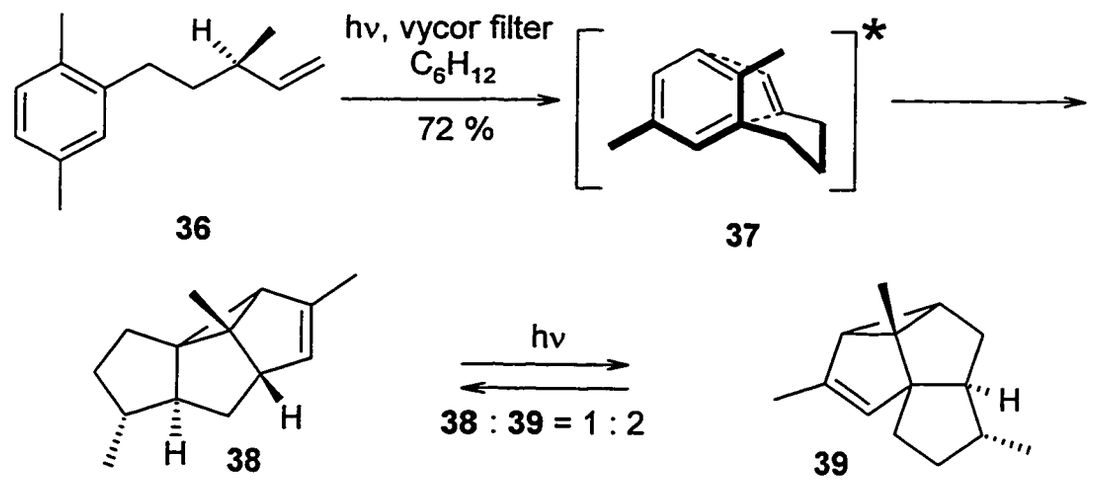

OMe
CO2Et
toluene, sealed tube, 250 °C
CO2Et
OMe
H
26
27
28
1. HCl, THF
2. LiI, DMSO, H2O, 155 °C
58 % from 27
O
H
29
EtOOCCH(TMS)Br, LDCA, THF, -78 °C
70 %
Br
H
CO2Et
30
Br
H
CO2Et
30
+
O
H
16
LDA, HMPA, THF, -78 °C
56 %
O
H
H
EtOOC
31 1 : 1.5 exo : endo
585 °C, 10-4 mm Hg
51 %
O
H
H
H
32 CO2Et
+
1 : 1
O
H
H
H
33 CO2Et
1. NaBH4, MeOH
2. (i) NaH, THF, imidazole, reflux (ii) CS2, reflux
(iii) MeI, reflux
3. (n-Bu)3SnH, AIBN, toluene, reflux
H
H
H
35 CO2Et
(i) NBS, benzoyl peroxide, CCl4, reflux
(ii) (n-Bu)3SnH, toluene, reflux
H
H
H
34 CO2Et

Scheme 3

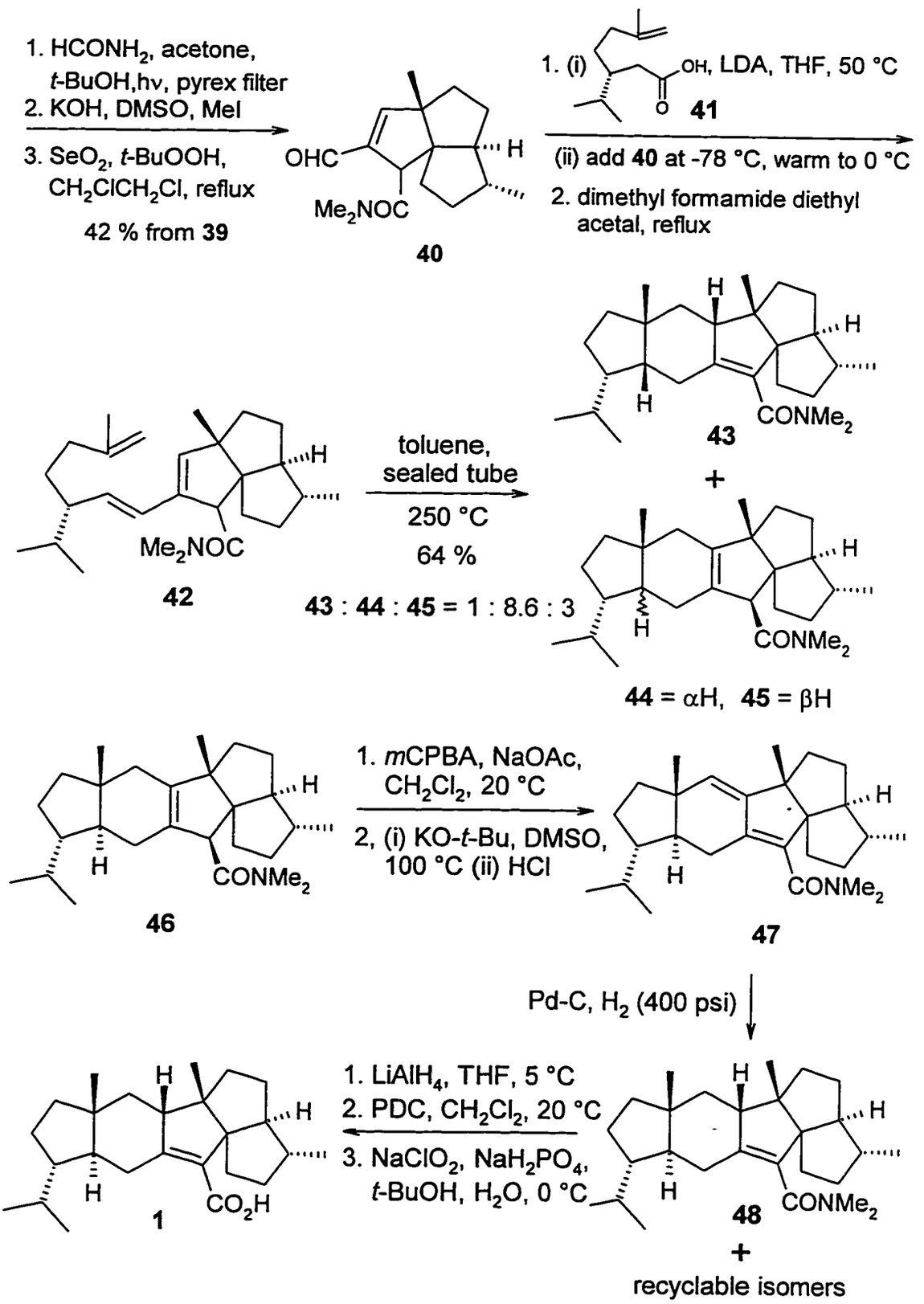
Hudlicky started his synthesis with (S)-limonene **26**. After several steps the triene **27** was prepared. This approach to **29** was previously developed by Fallis and Yadav[9] and used by Hudlicky in his synthesis. Heating **27** in toluene gave the Diels-Alder adduct **28** as a mixture of the conjugated and deconjugated enol ethers along with recovered starting material. Hydrolysis and decarboxylation of **28** gave the ketone **29**. This ketone was then reacted with ethyl (trimethylsilyl)bromoacetate to give the bromocrotonate **30**. The coupling reaction of **30** with the diquinane **16** (prepared according to Paquette's procedure) was accomplished by treating **30** with base and adding the diquinane **16** to give the vinyl cyclopropane **31**. Heating **31** under reduced pressure caused rearrangement to the epimeric pentacycles **32** and **33**. The ketone of the D ring of both epimers was removed by reduction to the alcohol followed by Barton deoxygenation to yield retigeranic acid A ethyl ester **35** and the epimer **34**. Hudlicky was able to epimerize the C-2 center of **34** to increase the yield of **35**.

1.2.4. Wender's Approach

Wender's approach was similar to Hudlicky's initial approach. Wender was able to synthesize the A and B rings simultaneouly by an intramolecular Diels-Alder reaction after successfully coupling the A and B ring precursor to his triquinane (Scheme 4).[8] The approach to the triquinane was distinct from the other approaches.



Scheme 4



Scheme 4 (continued)

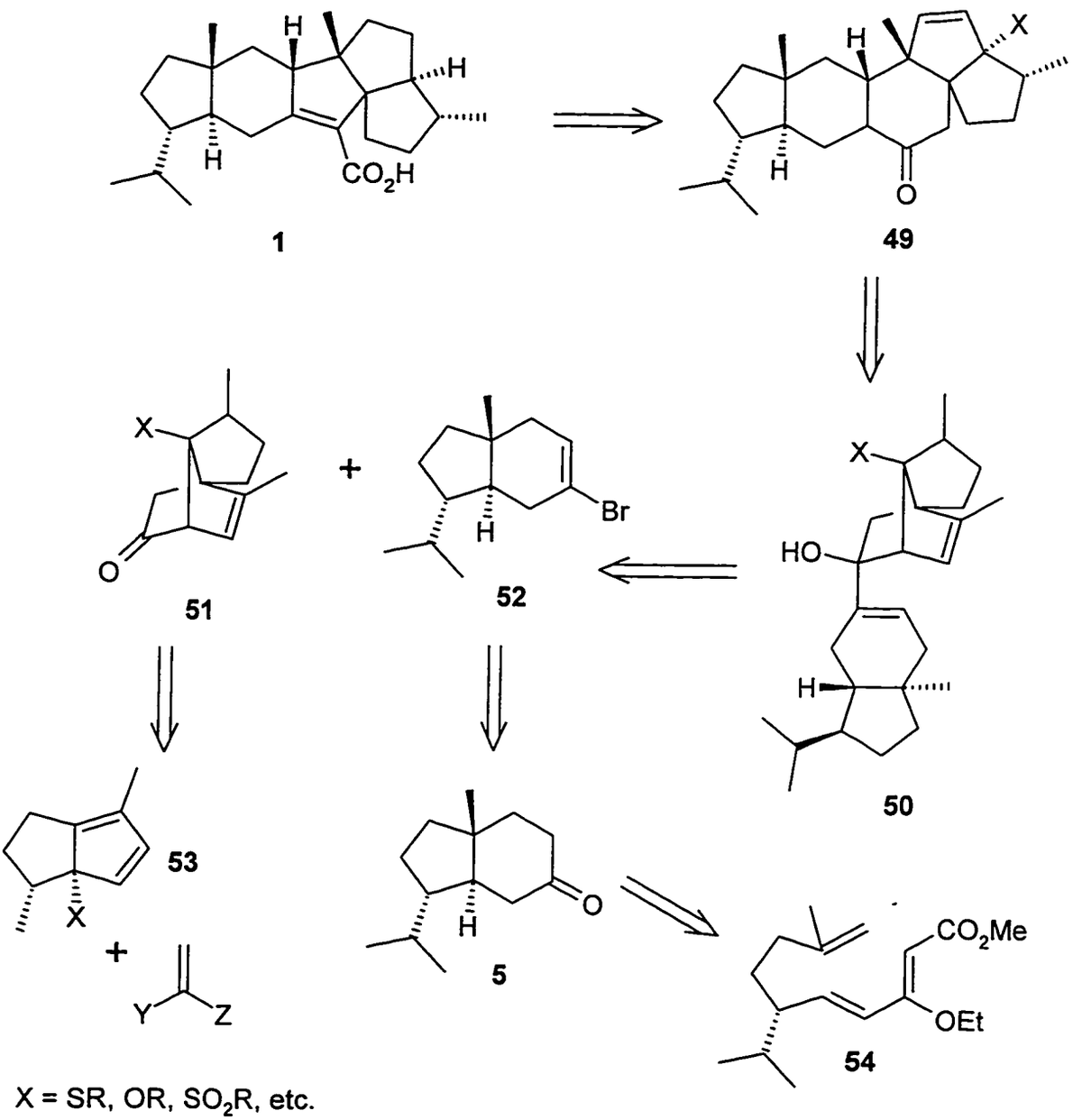
After several steps from 3-methylglutaric acid, Wender arrived at the cycloaddition precursor **36.** . The triquinane subunit was then prepared by photolysis of the arene-alkene **36**. This intramolecular cycloaddition gave a 1:2 mixture of cycloadducts **38** and **39** that existed in an interconvertible photoequilibrium. The alkene orientates itself to minimize the steric, torsional, and bond angle strain, as seen in the transition state **37***.

The vinyl cyclopropane unit of **39** was opened by the addition of photogenerated formamide radical. Subsequent allylic oxidation gave the aldehyde **40**. Condensation of the dianion generated from the acid **41** with the aldehyde **40** followed by decarboxylation gave only the alkene isomer **42**. The triene was then heated in toluene to give the Diels-Alder adducts **43**, **44** and **45** in a ratio of 1:8.6:3, respectively. Completion of the synthesis required manipulation of the functional groups. The double bond of **44** was epoxidized and then treated with base to form the diene **47**. Hydrogenation of **47** gave the desired alkene **48** along with two other isomers which could be recycled. Oxidation of the alcohol generated from the reduction of the amide gave retigeranic acid A.

1.3. Our Initial Approach

Like most of the previously described total syntheses, our approach to retigeranic acid A was convergent in nature (Scheme 5). Ring C of **1** can be made by a Favorskii diazoketone type ring contraction from the 6 membered ketone precursor **49**. As well, hydrogenation of the alkene in ring D of **49** should easily give **1**.

A key step of our synthesis involved the anionic oxy-Cope rearrangement from the diene **50** to afford **49**. Compound **50**, could in principle, be reached by the addition of the vinyl anion generated from the bromide **52** to the ketone **51**. The vinyl bromide has been be obtained from the ketone **5** via a Shapiro reaction. The tricyclic ketone **51** may be made by an intermolecular Diels-Alder reaction of the diene **53** with an appropriate dienophile.



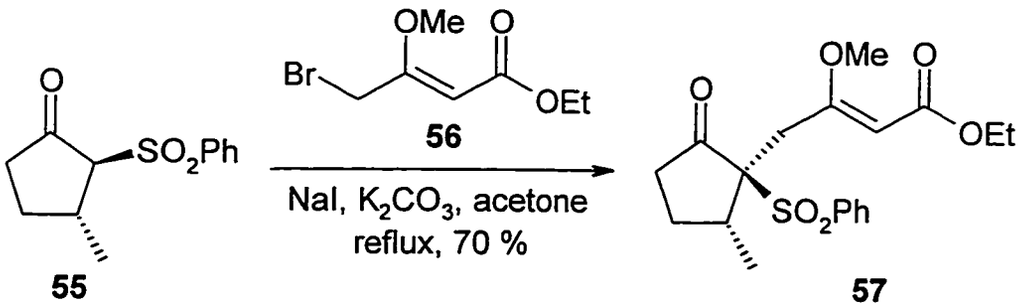
Scheme 5

The A and B ring *trans*-hydrindane **5** has been synthesized and this procedure has been used in other syntheses of retigeranic acid A.[9] Most of the recent work in the Fallis laboratory has been on synthesizing the key building block **51**. The precursor to this synthon is the annulated cyclopentadiene **53**. In order to obtain the desired stereochemistry in the final product, the dienophile must attack *syn* to the group X and the

methyl group. This is the convex face of the cyclopentadiene and should be the favored direction of addition, provided that X is not too big, or is selected to control the facial selectivity of the cycloaddition.

1.4. Dr. Tjepkema's study of 51

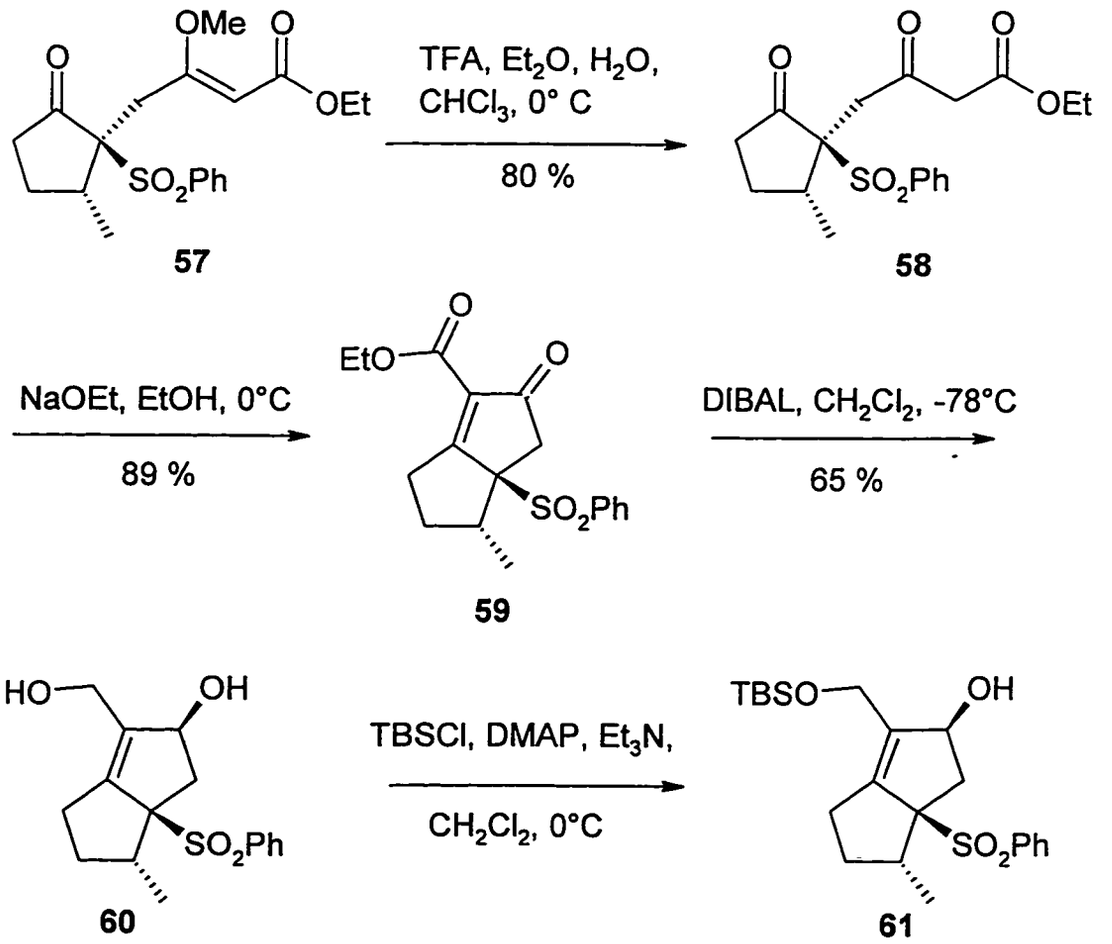
Dr. Tjepkema has completed an in-depth study of the synthesis of the tricyclic compound **51**.[10] Tjepkema started his synthesis with cyclopentanone and after several steps reached the sulfone **55**. The allylic bromide **56** needed for the coupling reaction was prepared through the formation of the methyl enol ether of ethyl acetoacetate upon treatment with NBS.



Scheme 6

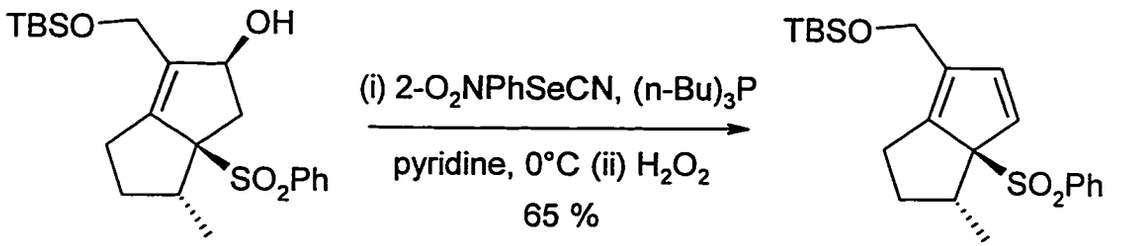
The alkylation of sulfone **55** with the bromide **56** was assisted by a Finkelstein reaction in acetone (Scheme 6), in which the more reactive iodide was generated *in situ*. X-ray crystallographic analysis of **57**, however, revealed that the sulfone and methyl groups possessed an *anti* relationship. It was expected that the bromide would approach from opposite the methyl group in the alkylation step due to steric interference, thereby giving the desired *syn* relationship between the methyl and sulfone. There are several theories to explain this observation, but the most accepted one has been developed by Cieplak.[11] This theory is based on electronic effects in which alkylation should occur *anti* to the best sigma donor. In this case the best sigma donor is the C-H bond opposite the methyl group. This anomalous alkylation has spawned a great deal of interest in our laboratory towards facial selectivity in Diels-Alder reactions.

The final result of this alkylation was that it increased the steric environment on both the top and bottom faces of the cyclopentadiene. This, however, may not affect the outcome of the Diels-Alder reaction. The placement of the sulfone in the convex face will cause the favoured addition of the dieneophile to the less hindered concave face. The Diels-Alder reaction should give the desired product, but the trans relationship between the sulfone and the methyl group will require correction of the stereochemistry in the final product. It was anticipated that this could be accomplished during the removing of the sulfone due to the significant ring strain in the unnatural isomer. Reductive cleavage of the sulfone with sodium amalgam followed by protonation should introduce the desired stereochemistry.



Scheme 7

The methyl enol ether **57** was then treated with acid to give the deprotected diketone **58** (Scheme 7).[10] This set the stage for generating the cyclopentanone. A base catalyzed aldol condensation yielded the keto-ester **59** in a crude yield of 89 %. The keto-ester **59** was then reduced using DIBAL in dichloromethane to give an average 65% yield of the diol **60**. The primary alcohol was selectively protected to produce the mono TBS ether **61**. The primary alcohol had to be protected in order to prevent side reactions when eliminating the secondary alcohol.

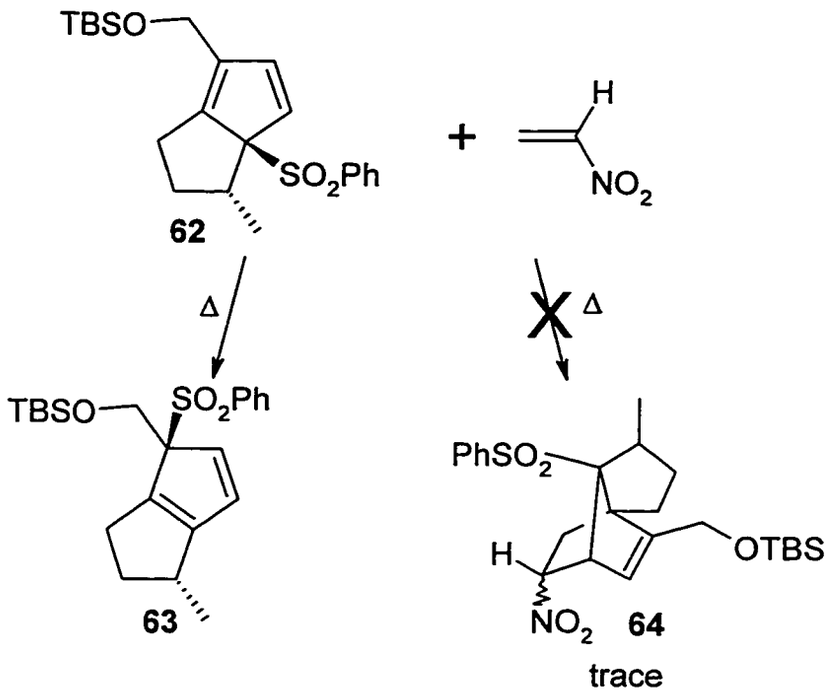


61 **62**

Scheme 8

The preparation of the diene **62** proved to be very problematic and Tjepkema tried a number of different approaches to making the diene. Several approaches gave a small amount of diene **62** or gave a mixture of dienes, but only one gave the desired diene in a good yield. The final conditions used to prepare the diene **62** employed Grieco's procedure[12] (Scheme 8).

At this point it appeared that Dr. Tjepkema was one reaction away from making the key building block **51**. A number of different dienophiles and different variations on the diene were tried, but the Diels-Alder reaction could not be performed. It appeared that the sulfone underwent a facile rearrangement above 40 °C (Scheme 9). The main product from the Diels-Alder reaction attempts was the more stable sulfone **63**, rather than the tricycle **64**.



Scheme 9

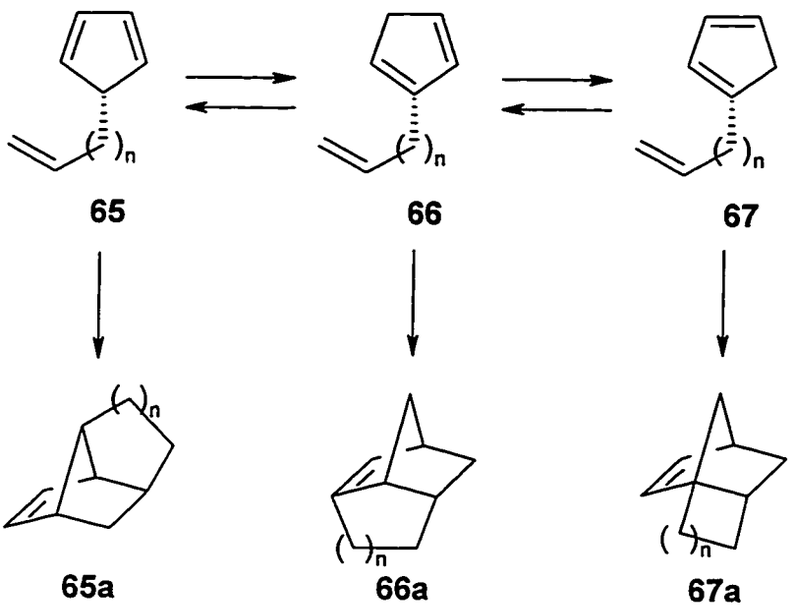
Tjepkema obtained a trace amount of the Diels-Alder adduct, however, the main products from the reactions was the rearranged diene **63**. The diene was unstable under the reaction conditions required for the cycloaddition reaction.

1.5. New Approach To 51 Via Intramolecular Diels-Alder Reaction

The failure of the intermolecular Diels-Alder reaction (Scheme 9) meant that a new approach to the formation of **51** would be required. A problem with cyclopentadienes is that the hydrogens can migrate to a form other isomers. The sulfone was supposed to prevent the migration of the double bonds, however, it was the sulfone that rearranged, resulting in **63**.

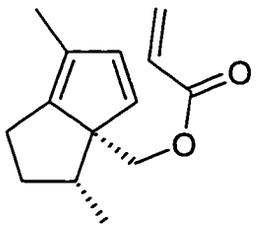
Thus a new approach to the key intermediate **51**, that involved the use of an intramolecular Diels-Alder reaction, was studied in this thesis. If a dienophile is coupled to cyclopentadiene, three different Diels-Alder adducts can be obtained from the intramolecular cyclization reaction of the diene and dienophile. This occurs because of the [1,5] sigmatropic rearrangement of the hydrogens about the cyclopentane ring

(Scheme 10). The length of the tether dictates which adduct will form. When the tether is short, **65** will be the preferred isomer for the reaction. This result is simply due to the spacial relationships that the dienophile and diene can obtain. The dienophile can only



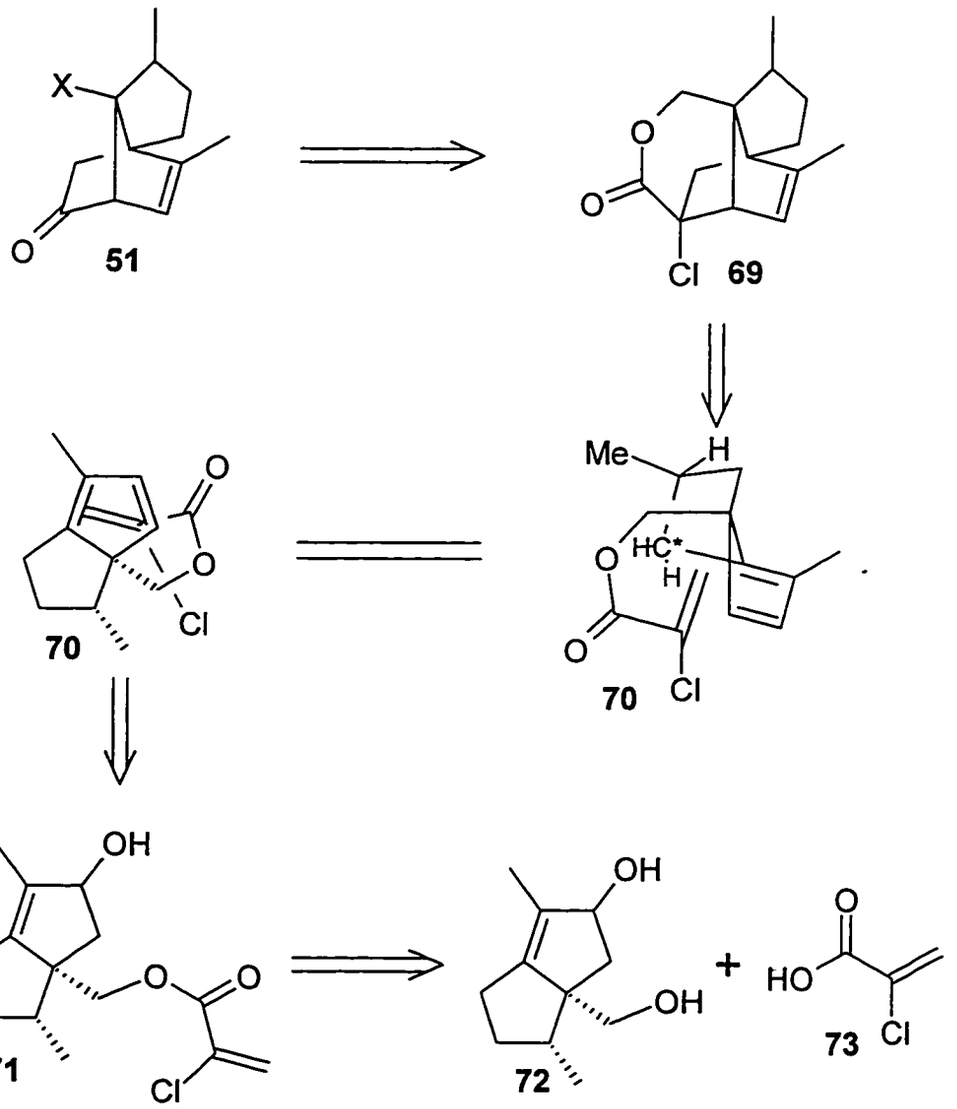
Scheme 10

reach the diene in **65** when the tether is short (n = 1, 2), giving the adduct **65a**. When the tether is longer, the diene can isomerize to **66** and **67** before going through the cycloaddition reaction, giving **66a** and **67a**.[13] The longer tether prevents close interactions of the diene and dienophile. Our new approach to the Diels-Alder reaction, should control which adduct is formed by preventing the migration of the diene. As can be seen, the position of the tether prevents the migration of the diene in **68** (Figure 2). There is now one carbon in the cyclopentadiene that is fully substituted, preventing the movement of the diene. The tether also insures that the dienophile will only attack the diene from the bottom face, as it isn't long enough to reach the top face. This system will yield only two possible isomers, but the tether is of such a length that the desired tetracycle should be the only Diels-Alder adduct.



68

Figure 2



Scheme 11

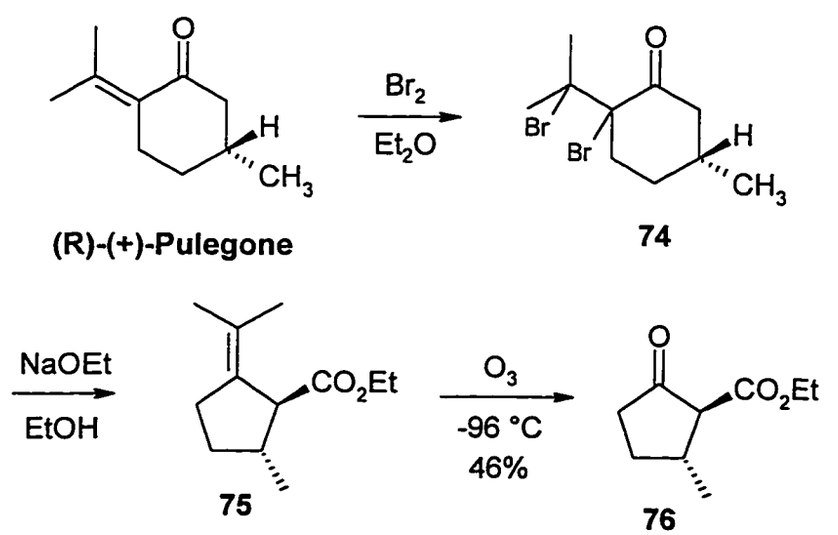
In a retrosynthetic sense, the tricycle **51** could be made from the ring opening of the chloro-lactone **69** (Scheme 11). This tetracycle could be synthesized from **70** via an the intramolecular Diels-Alder reaction. The dienophile should orient itself to minimize the steric interaction between the chlorine atom and the methylene hydrogens on the marked carbon in **70**. The diene could be made by the elimination of the alcohol of **71** following Grieco's procedure, as demonstrated by Tjepkema. The dienophile **73** can be selectively coupled to the primary alcohol in the diol **72**.

RESULTS AND DISCUSSION

Chapter 2

2.1. Synthesis of Diquinane

The synthesis of the diquinane **81** was accomplished by following Paquette's approach for the synthesis of (-)-silphiperfol-6-ene and (-)-5-oxosilphiperfol-6-ene.[6b] The preparation of both of these triquinanes used a common intermediate that was essential in our own synthesis. The synthesis of the diquinane started with technical grade (R)-(+)-pulegone. This was treated with bromine in ether to afford the dibrominated product **74** (Scheme 12).

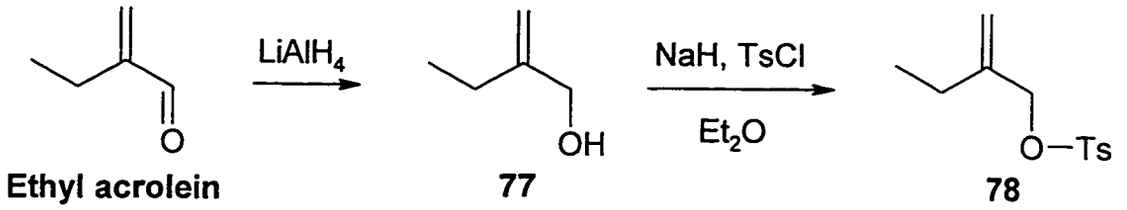


Scheme 12

The dibrominated ketone **74** was used without purification for the ring contraction reaction. Dibromo ketone **74** was added to a solution of sodium ethoxide in ethanol, which gave the ring contracted product **75** in a 71 % yield from (R)-(+)-pulegone after purification by distillation. Ozonolysis of **75** at -90 °C in ethyl acetate gave the desired ketone ester **76** in a yield of 46 % after purification by distillation.[14]

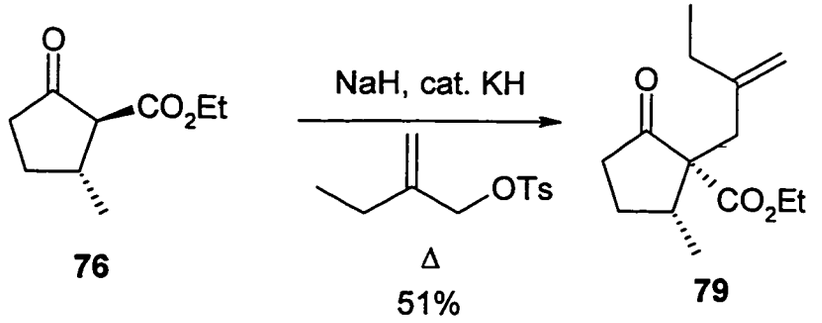
2.1.1. Alkylation of the Cyclopetanone

Prior to performing the aldol condensation, it was necessary to alkylate the cyclopentanone **76** with tosylate **78**. The alkylating agent was prepared from ethyl acrolein in two steps by following Paquette's procedure. Ethyl acrolein was reduced to the corresponding alcohol **77** in quantitative yield. The unpurified alcohol **77** was then treated with sodium hydride and *p*-toluenesulfonyl chloride in ether to give the tosylated product **78** in 50 % yield (Scheme 13).[6b]



Scheme 13

The alkylation step was carried out, again, according to Paquette's method.[6b] The keto-ester **76** was treated with sodium hydride and a catalytic amount of potassium hydride in refluxing toluene. Addition of the tosylate **78** and continued heating gave the alkylated product **79** in a yield of 51% as one isomer after purification by flash chromatography (Scheme 14). In contrast to Tjepkema's alkylation, the addition of the alkene proceeded anti to the methyl group. This alkylation gave the desired stereochemistry in **79** which was consistent with attack opposite to the adjacent methyl

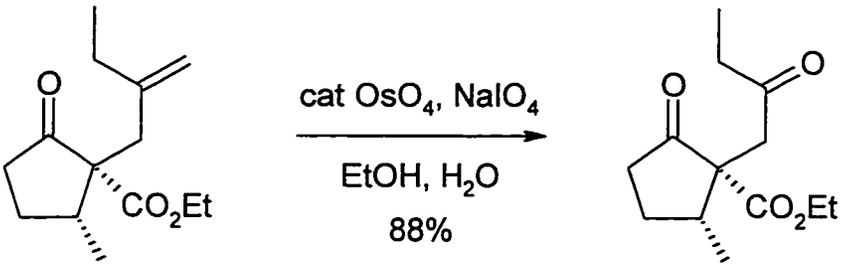


Scheme 14

substituent. The *cis* relationship between the ester and the methyl groups was confirmed in a later compound by NOE difference NMR experiments.

2.1.2 Annulation of the Cyclopentanone

In preparation for the intramolecular aldol condensation step, it was necessary to generate the second ketone from the double bond in **79**. Instead of performing the experiment as Paquette did, by ozonolysis, the Lemieux-Johnson reagent[15] was employed to perform the oxidative bond cleavage. This procedure was used because it gave much higher yields and was easier to perform. The alkene **79** was treated with a catalytic amount of osmium tetroxide in a mixture of ethanol and water. The osmium tetroxide generated the diol intermediate, and the sodium periodate regenerated the osmium



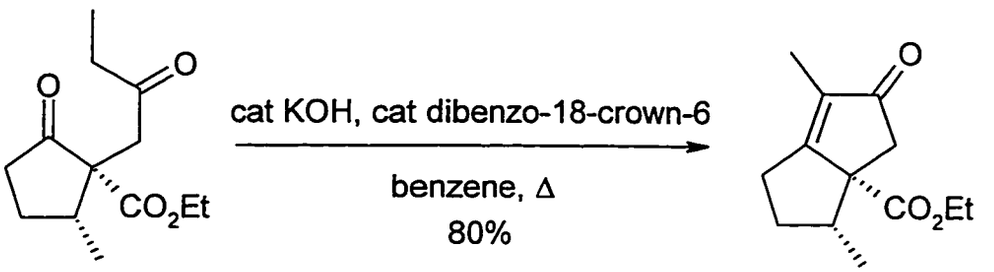
79 **80**

Scheme 15

tetroxide and further oxidized the diol to the diketone **80** and formaldehyde (Scheme 15). Typical yields for this reaction were 88%. Spectral data supported the formation of the desired product by the broad carbonyl stretch at 1729 cm^{-1} in the IR spectrum and the disappearance of the two alkene hydrogens (δ 4.77 ppm (d, J = 5.0 Hz)) in the ^1H NMR spectrum.

We again used an alternate procedure to the one Paquette used in his synthesis. He conducted the annulation with sodium hydride in refluxing toluene in a modest yield of 66 %. The decision was made to carry out the aldol condensation using a catalytic amount of potassium hydroxide and dibenzo-18-crown-6 in refluxing benzene.[16] The crown ether acted as a potassium ion sponge, thereby generating "naked" hydroxide

anions. The annulated α,β-unsaturated ketone **81** was generated from **80** in a yield of 80 % (Scheme 16). This procedure was both simpler and higher yielding than that used by Paquette. In the ^{13}C NMR spectrum a signal at 208.5 ppm was indicative of the ketone carbon and the signal at 179.8 ppm indicated the carbonyl carbon of the ester. The appearance of a singlet at 1.66 ppm representing the three hydrogens of the allylic methyl group in the ^{1}H NMR spectrum also confirmed the desired product had been produced.

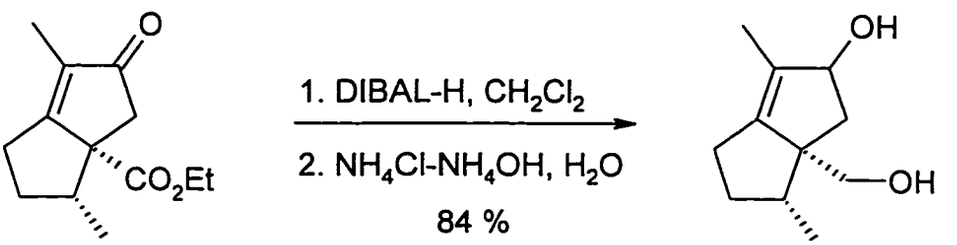


80 **81**

Scheme 16

2.2. Dienophile Attachment

The alcohol must first be generated from the ester in order to couple the desired dienophile onto the diquinane. The diol **72** was generated by the reduction of the keto-ester **81** using DIBAL-H in dichloromethane at -78 °C (Scheme 17).



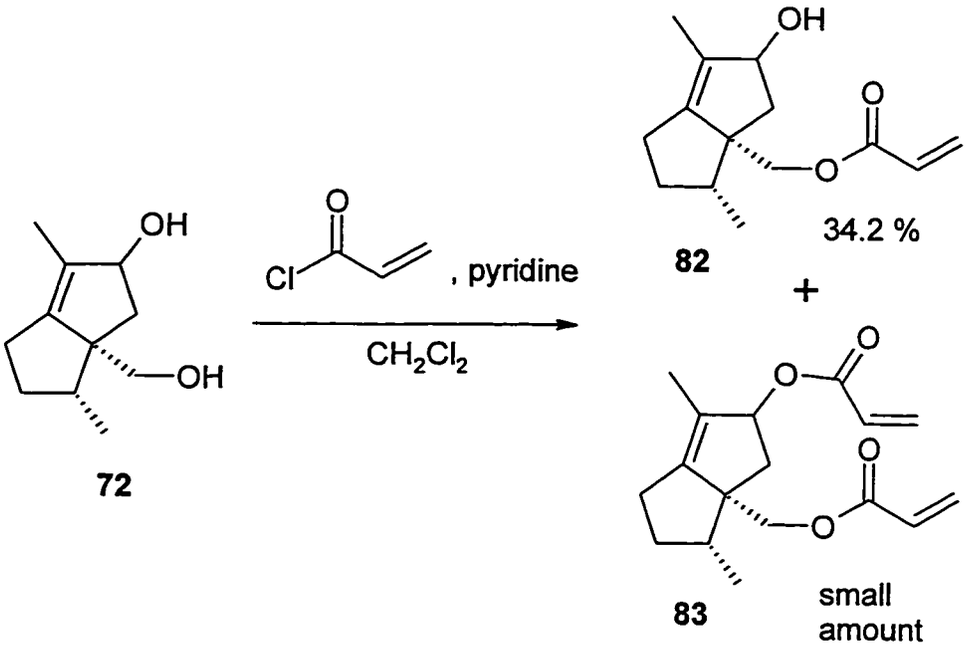
81 **72**

Scheme 17

The reaction was quenched by the addition of a pH 8 buffered solution of ammonium chloride and ammonium hydroxide in water. This resulted in a slurry that

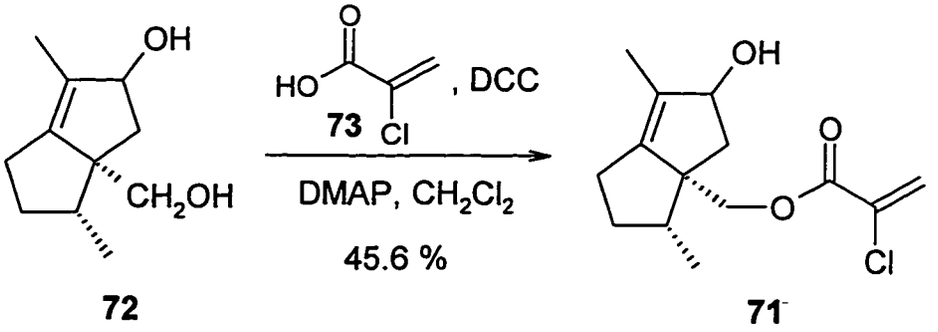
could be filtered through a bed of Celite® after adding anhydrous magnesium sulfate. This gave the resulting diol in good yield of 84%. The diol **72** was identified by the appearance of a very pronounced O-H stretch at 3412 cm^{-1} and the disappearance of C=O stretch in the IR spectrum. The primary alcohol of **72** was identified by the appearance of a multiplet at 3.44 ppm integrating for two protons in the ^1H NMR. A broad singlet at 4.99 ppm integrating for one proton was indicative of the secondary alcohol. The exact stereochemistry of the secondary alcohol was not determined as it was going to be eliminated in order to generate the diene.

The selectivity of the coupling reaction was investigated before the desired dienophile was coupled to the diol. It was important to see if the coupling reaction would favour the primary alcohol over the secondary alcohol. A large amount of acryloyl chloride was available and if there was a problem with the coupling step the reaction could be optimized before attempting it with the desired dienophile. The primary alcohol should be more available for coupling compared to the secondary alcohol, based on steric considerations. The diol **72** was treated with one equivalent of acryloyl chloride and pyridine in dry dichloromethane (Scheme 18).[18] The reaction gave two main products, the desired mono coupled alcohol **82** in 34 % yield and a trace amount of the dicoupled diester **83**, along with a small amount of starting material. This reaction showed that the acid chloride coupled to the primary alcohol selectively over the secondary alcohol, but could couple to the secondary alcohol if the primary alcohol was already esterified. The ^1H NMR spectrum of **82** revealed that the broad singlet at 4.95 ppm for the C-H of the secondary alcohol did not shift or change shape, showing that the secondary alcohol remained unreacted in the coupling reaction. The CH_2 tethering the dienophile now appeared as an AB system of two doublets, one at 3.96 ppm (J = 11.0 Hz), and one at 4.13 ppm (J = 11.0 Hz), each integrating for one hydrogen. The fact that the dienophile was incorporated was supported by three doublet of doublets in the alkene region, each integrating for one proton. The IR spectrum also showed a new C=O absorption signal at 1718 cm^{-1}.



Scheme 18

With this knowledge the proper dienophile **73** was coupled to the diol **72**. A DCC coupling was used, unlike the acid chloride coupling used in Scheme 18, as the dienophile **73** was commercially available only as the free carboxylic acid. The diol **72** was treated with 2-chloroacrylic acid and 1,3-dicyclohexylcarbodiimide along with a catalytic amount of DMAP in dichloromethane (Scheme 19).[19] This coupling gave the



Scheme 19

desired dienophile-alcohol **71** as white crystals in a 46% yield. Spectral data, both NMR and IR, supported the formation of **71**. In the ^1H NMR spectrum the CH of the secondary

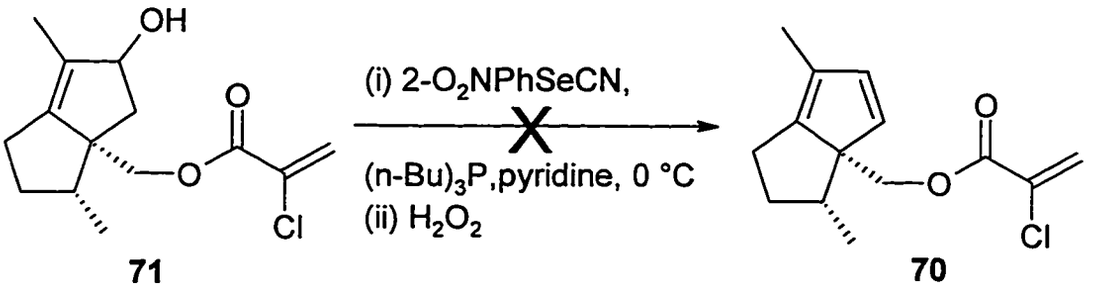
alcohol was easily identified by the characteristic broad singlet integrating for one hydrogen at 5.00 ppm. The tethered dienophile produced two sets of doublets in the ^1H NMR, one at 5.95 ppm (J = 1.4 Hz) and one at 6.43 ppm (J = 1.4 Hz), each integrating for one hydrogen. The CH_2-O of the tether was seen as two doublets representing an AB spin system, with a doublet at 4.01 ppm (J = 10.9 Hz) and a doublet at 4.18 ppm (J = 10.9 Hz). The IR spectrum of the alcohol **71** showed a broad signal at 3331 cm^{-1} for the O-H stretch and an absorption at 1718 cm^{-1} for the C=O stretching of the carbonyl of the ester.

2.3. Diene Formation

2.3.1 Grieco's Procedure

At this point it was anticipated that we were only one reaction away from trying the intramolecular Diels-Alder reaction. It was also at this stage that many surprises and difficulties were encountered. It seemed that a simple elimination reaction to remove the alcohol would generate the desired diene. Tjepkema reported that Grieco's method was useful in generating the diene in good yields.

The *o*-nitrophenylselenocyanate needed was synthesized in the lab according to a procedure used by Sharpless.[20] NMR spectrum and melting point of the selenium reagent made matched that reported in the literature. The alcohol **71** was then mixed with the selenium reagent and tributylphosphine in pyridine (Scheme 20).[12] This mixture should

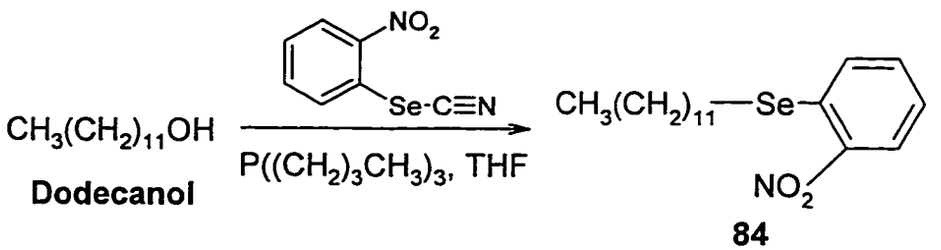


71 **70**

Scheme 20

have generated a selenium intermediate that, after oxidization with hydrogen peroxide should have eliminated to give the diene **70**.

Only starting material was recovered from the experiment. In the event, it was surprising that the elimination reaction would not proceed using Grieco's procedure. Tjepkema did report that the reactivity of the selenium reagent tended to degrade over time. It has been suggested that it may form a diphenyldiselenide. In an attempt to perform the reaction, the o-nitrophenylselenocyanate was made several times and was tested using dodecanol (Scheme 21). Even after an active batch of Grieco's reagent was made, confirmed by the generation of **84**, the dehydration to the desired diene **70** would not proceed by this route. It may be that the stereochemistry of the alcohol differs from the alcohol of **61**, which may account for it's lack of reactivity. A number of different routes towards making the proper diene were therefore examined.

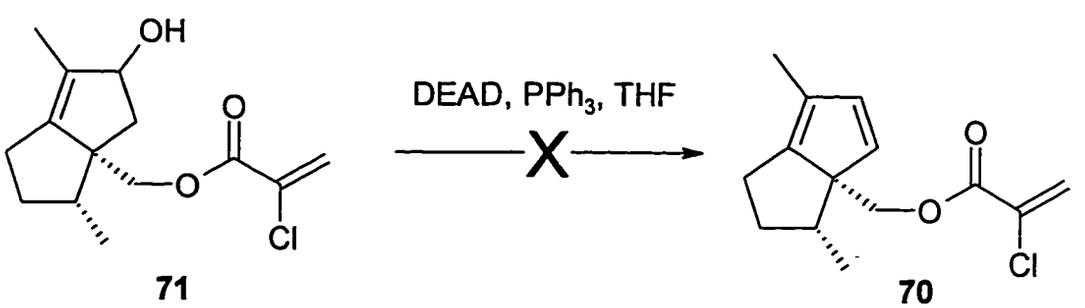


Dodecanol **84**

Scheme 21

2.3.2. Mitsunobu Elimination

At this point different avenues had to be investigated in order to carry out the



71 **70**

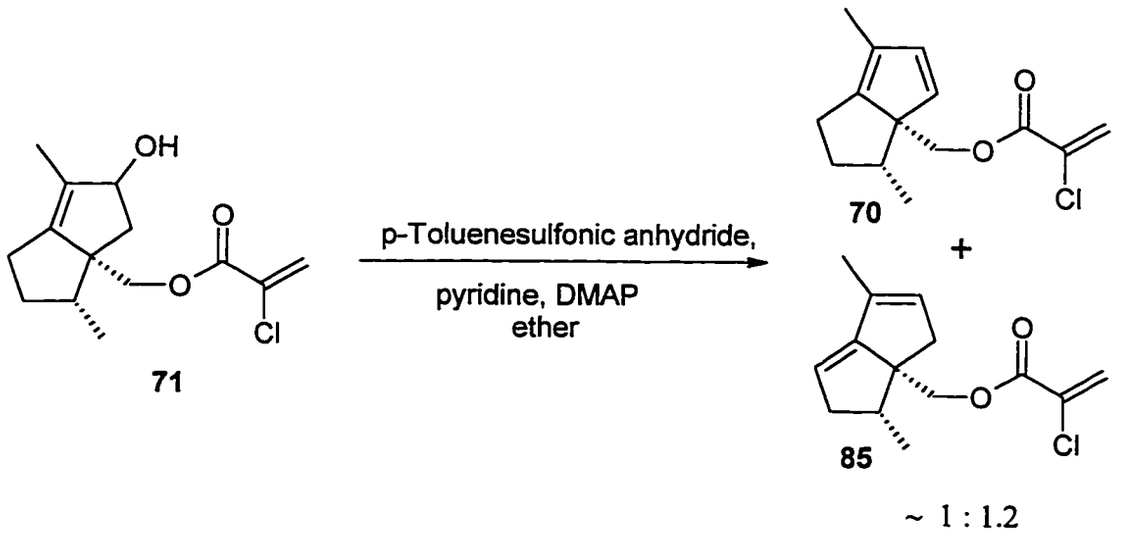
Scheme 22

elimination reaction. It was known that Mitsunobu conditions could be used to eliminate alcohols when carried out in the absence of a carboxylic acid. However, when the

alcohol **71** was subjected to these conditions, it failed to generate the diene **70** (Scheme 22).[21] Only starting material was recovered.

2.3.3. Diene Through Tosylate Elimination

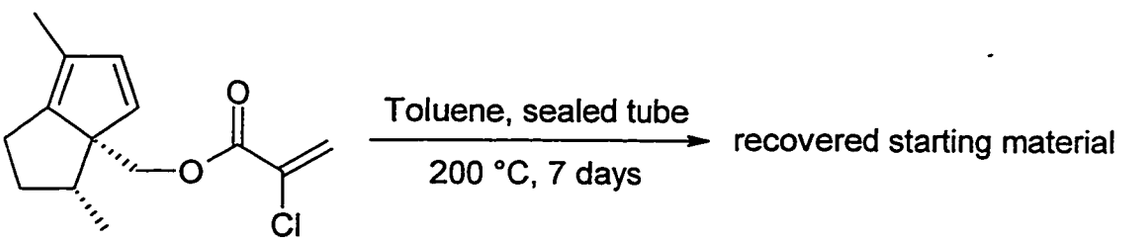
The next idea was to use a tosylate to activate the alcohol for elimination. The tosylate of the alcohol is an excellent leaving group and should only have two avenues for elimination, by 1-4 elimination or the desired 1-2 elimination. The tosylate of the alcohol was prepared by mixing the alcohol **71** with *p*-toluenesulfonic anhydride in the presence of pyridine and DMAP (Scheme 23).[22] The tosylate was never isolated, but was so reactive that it eliminated giving what was originally thought to be a 1 to 1.2 mixture of the two dienes **70** and **85** which could not be separated by column chromatography. The two dienes, designated as *trans* for undesired diene **85** and *cis* for the diene **70**, could not be separated. This gave a rather complicated ^{1}H NMR spectrum (Appendix 1). The two doublets at 5.88 ppm (J = 5.5 Hz) and 6.08 ppm (J = 5.5 Hz) matched closely those reported by Tjepkema for his diene and were initially believed to belong to the diene **70**. The other alkene peaks at 4.74, 4.87, 5.35, and 5.69 ppm were thought to be



Scheme 23

representative of **85**, as each of its alkene hydrogens should appear as two different multiplets due to coupling with neighbouring CH_2's. Two sets of dienophile chemicals shifts were seen, two overlapping at 5.95 ppm, 6.42 ppm and 6.44 ppm (J = 1.4 Hz for each), which showed of the components were not Diels-Alder adducts. The IR spectrum of the diene mixture did not show an O-H stretch.

The Diels-Alder reaction was attempted on the mixture of the two dienes since they could not be separated. The first attempt was carried out by stirring the diene mixture in refluxing toluene. On the first attempt the reaction was accidentally heated to dryness, leaving a black intractable solid. A small amount of crystals sublimed onto the reflux condenser. The crude ^1H NMR spectrum of the crystals showed what could have been a small amount of the Diels-Alder adduct based on the absence of alkene signals. The experiment was repeated, with more precautions to ensure that the reaction would not run dry. Only starting material was recovered after stirring the diene mixture in refluxing toluene. The possibility that the temperature was simply not high enough to initiate the Diels-Alder reaction was addressed by repeating the reaction in toluene in a sealed tube heated to 200 °C. Even after 7 days at 200 °C, only the starting material was recovered (Scheme 24).

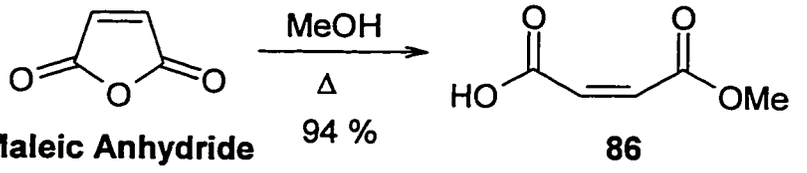


70

Scheme 24

It was believed that the dienophile was insufficiently activated since the diene-dienophile would not undergo the desired intramolecular Diels-Alder reaction. A more activated dienophile with more electron withdrawing groups was coupled to the diol in hopes of encouraging the Diels-Alder reaction.

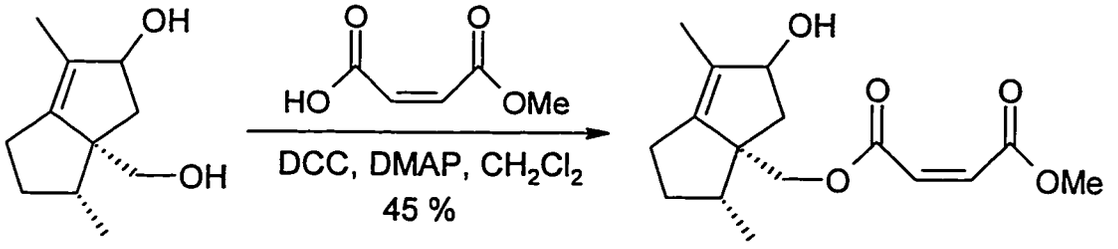
The new dienophile **86** was synthesized in high yield by refluxing a mixture of methanol and maleic anhydride (Scheme 25).[23]



Maleic Anhydride **86**

Scheme 25

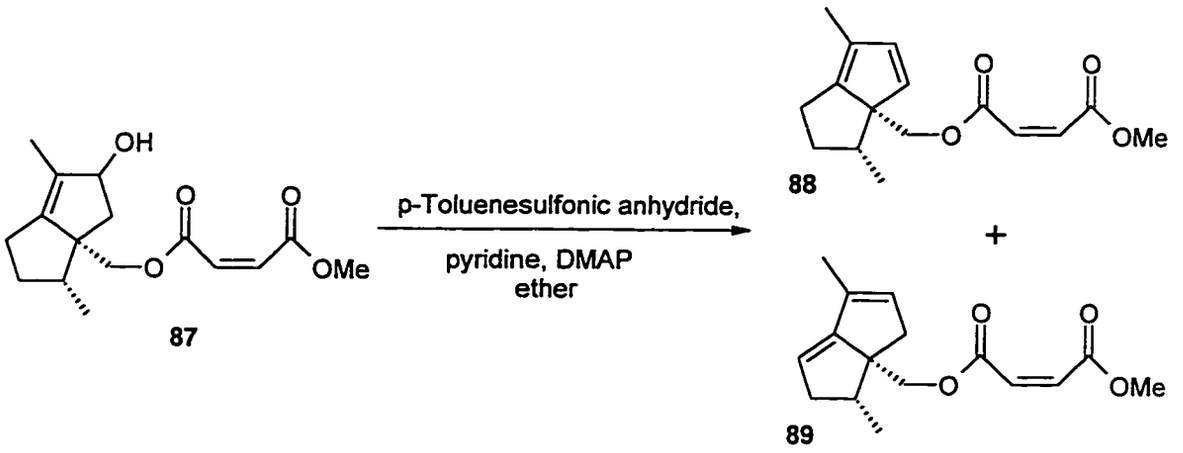
The acid **86** was again selectively coupled to the primary alcohol of the diol **72.** The coupling was carried out using 1,3-dicyclohexylcarbodiimide and DMAP in dichloromethane (Scheme 26).[19] This reaction gave the alcohol-dienophile **87** in a yield of 45%. The ^{1}H NMR spectrum of **87** closely resembled that of the alcohol-dienophile **71**. The broad singlet at 4.90 ppm integrated for the one hydrogen on the carbon bearing the secondary alcohol and confirmed the coupling occurred on the primary alcohol. The dienophile was identified by the two doublets at 6.15 (J = 12 Hz) and 6.22 ppm (J = 12 Hz), each integrating for one hydrogen. The appearance of a singlet at 3.76 ppm representing the 3 hydrogens for the methyl ester of the dienophile confirmed the structure of the product. The IR spectrum established the presence of the alcohol and carbonyl functionalities with absorptions at 1729, and 3406 cm^{-1}.



72 **87**

Scheme 26

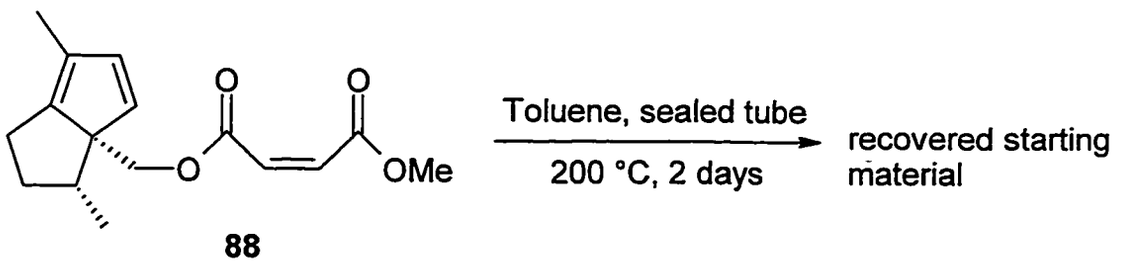
Grieco's procedure for elimination failed on the previous alcohol **71**, thus it was not attempted on the alcohol **87**. The tosylate of the alcohol was generated using *p*-toluenesulfonic anhydride and pyridine, along with a catalytic amount of DMAP (Scheme 27).[22] The tosylate was not isolated as the pyridine eliminated the tosylate to what was thought to be the dienes **88** and **89**. The IR spectrum revealed the alcohol had been



Scheme 27

eliminated by the absence of an O-H stretching signal. In the ^{1}H NMR spectrum the signal due to the secondary alcohol had disappeared and a number of signals in the alkene region had appeared. The two doublets at 5.89 (J = 5.4 Hz) and 6.07 ppm (J = 5.4 Hz) were assigned to the desired diene **88** and the other alkene shifts were assigned to the isomeric diene **89** (see spectrum in Appendix 1).

The dienes **88** and **89** could not be separated by chromatography. The mixture of dienes **88** and **89** was heated in order to effect the Diels-Alder reaction. The diene mixture was dissolved in toluene and heated to 200 °C in a sealed tube for 2 days (Scheme 28). Even with the highly activated dienophile, the compound would not undergo the intramolecular Diels-Alder reaction.



Scheme 28

The failure of these compounds to undergo the intramolecular Diels-Alder reaction was puzzling. There should have shown some reactivity in these systems, especially with the highly activated dienophile. However 2-D 500 MHz NMR experiments revealed why. COSY revealed that the signals at 4.74 ppm and 4.87 ppm for the mixture of **70** and **85** were two hydrogens that coupled to each other (J = 1.3 Hz), while HETCOR showed that these two hydrogens were on the same carbon. The two doublets at 5.88 and 6.08 ppm (J = 5.5 ppm for each hydrogen) belonged to the other alkene hydrogens. It was determined that these signals represented the diene **91a** and not **70**. The broad chemical shifts at 5.35 and 5.69 ppm represented the diene hydrogens of **85**. The actual dienes generated from both tosyl elimination reactions were not the ones initially proposed, but, unfortunately, were the diene **90** and the diene **91** with the exocyclic double bond (Figure 2).

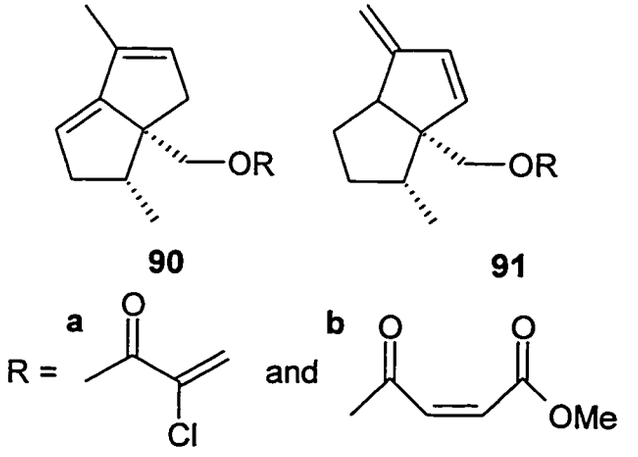
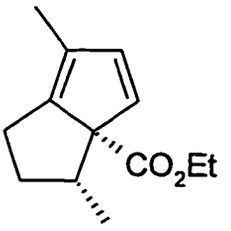


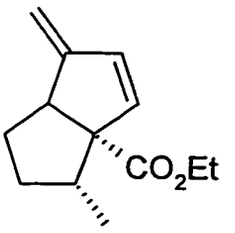
Figure 2

The generation of exocyclic double bond was surprising and disappointing. It showed that the *cis* diene was highly unstable and prone to rearrangement. MOPAC calculations performed using the CACHE molecular modeling system on a 8100/100 Power Macintosh helped explain the preference for the formation of the exocyclic double bond. These calculations showed the predicted heat of formation for the four possible



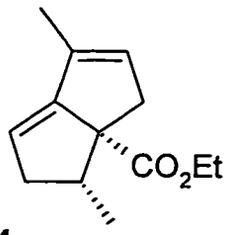
92

Heat of formation = -59.6 kcal/mol



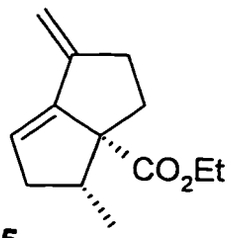
93

Heat of formation = -69.6 kcal/mol



94

Heat of formation = -61.6 kcal/mol



95

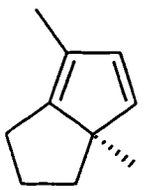
Heat of formation = -64.5 kcal/mol

Figure 3

dienes from the elimination of the tosylate (Figure 3). To simplify the calculations, the study was performed using the ethyl ester in place of the tethered dienophile.

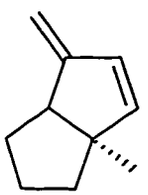
As seen in the results of the calculations, the desired diene **92** had a predicted heat of formation 10 kcal/mol higher than that of the isolated diene **93**. The CACHE program had predicted a high degree of strain in the diene **92** which could easily be understood. The diquinane had a natural concave shape. The methyl group and the ester were on the convex face of the diquinane and they close the concave face even more as they repelled each other. A bridgehead double bond would twist the to try to force a degree of planarity to the diquinane. This twist strained the diquinane as could be seen in the predicted heats of formation of the dienes **92** and **93**. In the desired diene **92**, the diene was planar. This in turn would force the diquinane to adopt a planar shape. The ester and methyl groups were at the same time repelling each other thereby forcing the concave shape. These conflicting forces, along with the tremendous strain of having two endocyclic double bonds in a 5 membered ring, must have generated a large amount of strain on the diene. The excess base present may have caused double bond migration in the desired diene **92** to form the exocyclic diene **93**. This migration obviously relieved a

significant amount of strain in the diquinane and facilitated the adoption of the favoured concave shape. The release of strain by the formation of the exocyclic double bond was also reflected in the predicted heats of formation between the diene **94** and the exocyclic diene **95**. Even between these two dienes the exocyclic double bond reduced the predicted heat of formation by 3 kcal/mol.



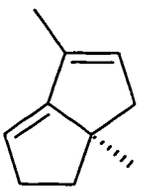
96

Heat of formation = 24.1 kcal/mol



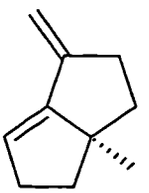
97

Heat of formation = 15.2 kcal/mol



98

Heat of formation = 22.4 kcal/mol



99

Heat of formation = 19.3 kcal/mol

Figure 4

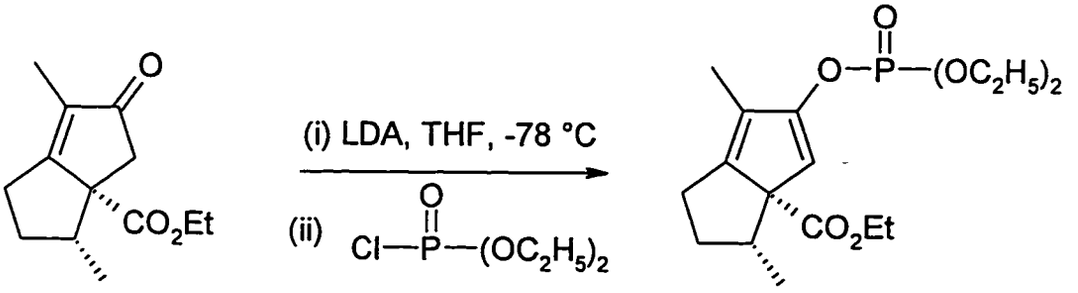
To confirm these calculations, the heats of formation were calculated for a simpler set of dienes (Figure 4). In these dienes, the ester group at the bridgehead atom was replaced with a methyl group and the E ring methyl group was removed. The dienes did have the same relationship to each other as in the previous study. The dienes **97** and **99** with the exocyclic double bond had lower heats of formation than their counterparts **96** and **98**. The exocyclic double bond obviously relieved the strain in the diquinane through the formation of the concave conformations. The *cis* diene **96** restricted the formation of the concave shape which strained the ring systems, thereby giving this diene the highest energy of formation. In the exocyclic diene **97**, the compound was free to acquire the concave shape, giving it the lowest energy.

These calculations helped to explain the formation of the exocyclic double bond. It became apparent that if the rearrangement occurred in a basic medium that a base must be avoided to preserve the diene. Attention was now directed at making the diene.

2.3.4. Diene by Enolate Formation

The diene could not be made directly from the alcohol, thus another approach was needed. One possibility would have been to block the other sites where elimination could occur. This approach was most likely why Tjepkema was able to form his diene **62**. The TBS of **61** (Scheme 8) blocked the formation of an exocyclic double bond. Armed with the knowledge that simple elimination would not work, the focus was placed on a previous compound, the keto-ester **81**. If the kinetic enolate of this compound could be trapped, this step would yield the desired diene. Subsequently the trapping agent could be removed.

This apparently straight forward strategy proved somewhat difficult to conduct. It was possible to selectively form the kinetic enolate of the ketone **81** by treating it with lithium diisopropylamide in THF at - 78 °C. The enolate was then trapped by the addition of diethyl chlorophosphate (Scheme 29)[24] to give the diene phosphate **100** in a good yield of 81 %. The formation of the product was confirmed by the disappearance of the set of doublets of the AB system of the CH_2 α to the ketone in the ^1H NMR spectrum and the appearance of a sharp singlet at 5.88 ppm. The presence of the diethyl phosphate



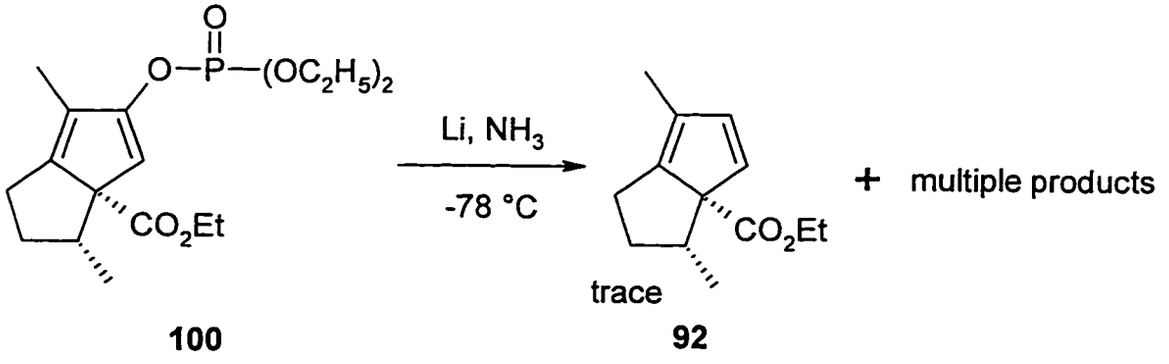
81 **100**

Scheme 29

was confirmed by the multiplet at 4.0-4.3 ppm integrating for 6 hydrogens for the three CH_2 groups of the three ethyl groups, one of which was from the ethyl ester. High resolution mass spectroscopy confirmed the exact mass of the product **100.**

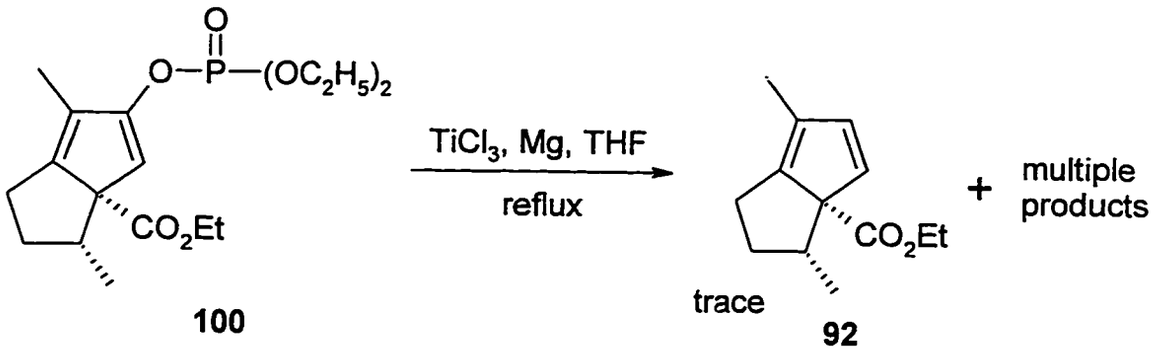
It was deemed prudent to remove the phosphate ester before trying to tether the dienophile to the diene. If it could not be easily removed now then it might also be difficult at a later stage.

Initial attempts to remove the phosphate employed lithium in liquid ammonia at -78 °C (Scheme 30).[24] The lithium in the liquid ammonia generated solvated electrons that could be identified by the bright blue colour of the reaction. The electrons remove the phosphate through a radical type reaction. The reaction did not proceed cleanly, as evident by the multiple products seen by TLC. The ^{1}H NMR spectrum of the crude product did show two small doublets at 6.5 and 6.8 ppm which may have been a trace of the diene **92**. Due to the number of products the diene **92** could not be isolated.



Scheme 30

Another route to removing the phosphate was with elemental titanium through a similar mechanism. Titanium trichloride was treated with magnesium in refluxing THF (Scheme 31).[25] This reaction generated elemental titanium which provided electrons to remove the phosphate from **100** through a radical type mechanism. In the crude ^{1}H NMR spectrum the same set of doublets were seen at 6.5 and 6.8 ppm. The diene could not be isolated from the multiple number of products generated from this reaction.



100 **92**

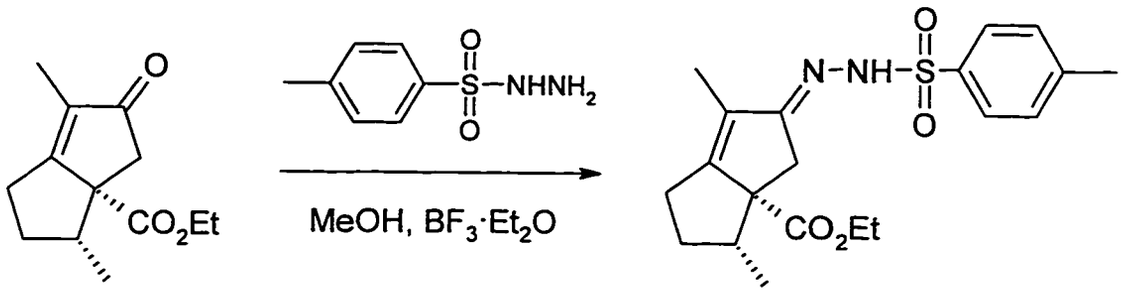
Scheme 31

The diene phosphate **100** could be generated relatively easily, thus it was hoped that the phosphate could be carried through to the Diels-Alder reaction and removed at a later stage. The phosphate group would have to be stable to the DIBAL-H reduction of the ethyl ester to the alcohol. The selective reduction of the ethyl ester did not proceed cleanly and cleavage of the phosphate ester occurred as well, destroying the diene in the process. The diene-phosphate decomposed under DIBAL-H reduction conditions, therefore another route to the diene was required.

2.3.5. Diene by Shapiro Reaction

The Shapiro reaction,[26] also known as the Bamford-Stevens reaction[27] when a base other than an organolithium is used, was investigated as another route to the diene. Aldehydes and ketones react with tosylhydrazine to form tosylhydrazones. Treatment of the hydrazone with base results in the loss of *p*-toluenesulfinate to generate the diazo compound which reacts with a second equivalent of base to generate nitrogen gas and the vinylic anion which can then be protonated. Both Grieco[28] and Shapiro[29] have used this technique to generate dienes. Literature precedent was not found for generating a diene in a five membered ring, but the Shapiro reaction generates the least substituted diene, which was desired. If the hydrazone is treated with an organolithium or LDA below 10 °C, the desired diene should be generated.[29] The low temperature prevents the migration of the double bond.

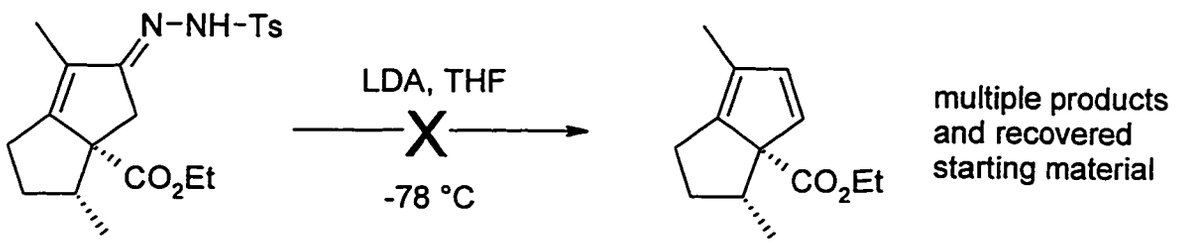
Most literature procedure found employed benzene as the reaction solvent for making hydrazones,[28] but neither the tosylhydrazine nor the product were soluble in benzene. Distilled methanol was the preferred solvent for the reaction. The tosylhydrazone **101** was made in 85 % yield by treating the ketone **81** with tosylhydrazine in dry methanol (Scheme 32).[28] The reaction was enhanced by the addition of a catalytic amount of boron trifluoride diethyl etherate.



81 **101**

Scheme 32

The formation of the tosylhydrazone was confirmed by both ^{1}H and ^{13}C NMR. In the ^{1}H NMR spectrum the toluene group presented itself in the product by the appearance of a doublet at 7.27 ppm (J = 8.1 Hz, 2 hydrogens) and at 7.84 ppm (J = 8.3 Hz, 2 hydrogens) as well as a singlet at 2.39 ppm for the methyl group. The N-H was seen as a singlet at 7.09 ppm. In the ^{13}C NMR spectrum there were 7 carbon shifts in the alkene region (128, 129, 130, 135, 143, 163, and 167 ppm) for the 9 alkene carbons. Unfortunately, the compound was not stable enough for mass spectroscopy or elemental analysis.



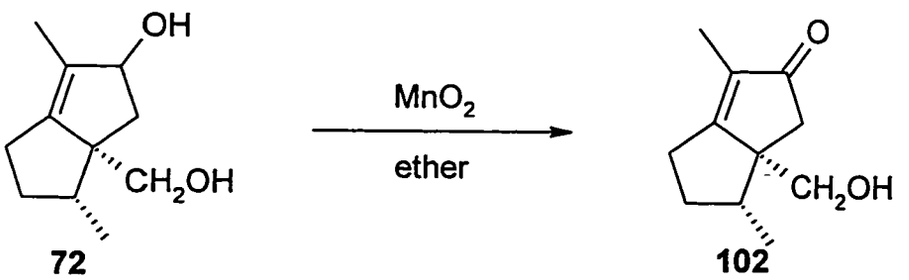
101 **92**

Scheme 33

The tosylhydrazone **101** was treated with 2 equivalents of LDA in THF at -78 °C (Scheme 33).[29] No diene **92** signals were seen in the crude ^{1}H NMR spectrum of the reaction. Only starting material was seen along with a number of unidentified side products.

There was some concern at this point that the ester of the hydrazone **101** may be affected by treatment with an organolithium base. As well, the instability of the diene **70** was already known and there was some concern whether it would be stable to a DIBAL-H reduction. This step could be avoided if the allylic alcohol of the diol **72** could be selectively oxidized. It would then be possible to generate the diene and immediately couple the dienophile for the intramolecular Diels-Alder reaction. The best oxidizing agent for this task was activated manganese dioxide. It is well documented that MnO_2 will only oxidize allylic alcohols.[30]

The activated MnO_2 was freshly made by simultaneously adding an aqueous solution of manganese sulfate and sodium hydroxide to a solution of potassium permanganate.[30a] Filtering and drying the collected solid gave the dark brown MnO_2 powder. The diol **72** was dissolved in a stirring suspension of MnO_2 and dry ether. The reaction was finished within 1 hour giving the ketone-alcohol **102** in quantitative yield (Scheme 34).[30c] The formation of the product **102** was confirmed by the appearance of a carbonyl stretch at 1671 cm^{-1} in the IR spectrum. As well, the disappearance of the signal due to the C-H of the secondary alcohol from the ^{1}H NMR spectrum and the appearance of a signal at 210.5 ppm in the ^{1}C NMR spectrum both indicated that the ketone had been formed.

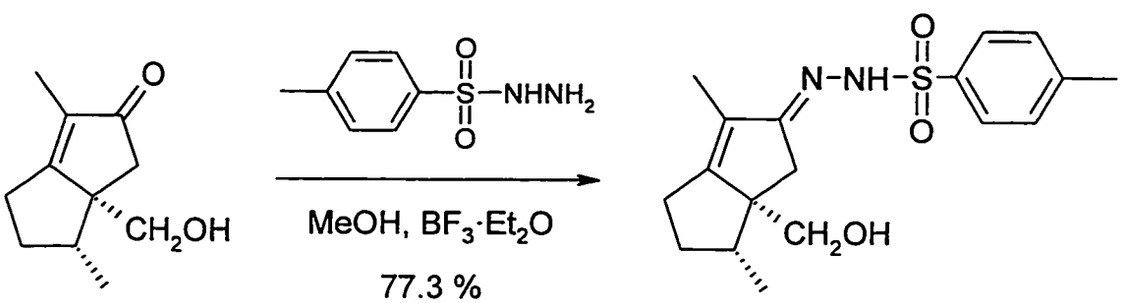


72 **102**

Scheme 34

There was some concern that the alcohol **102** would interfere with the Shapiro reaction. There is literature precedent for performing the Shapiro reaction on an alcohol containing tosylhydrazone, so these concerns were set aside.

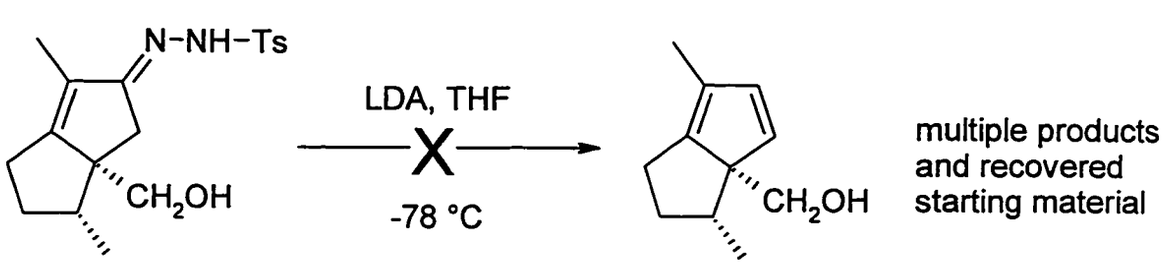
Similar to the formation of the previous tosylhydrazone, the ketone-alcohol **102** was treated with tosylhydrazine and a catalytic amount of boron trifluoride diethyl etherate in dry methanol (Scheme 35).[28] The tosylhydrazone **103** was formed as a white solid in a yield of 77%. The product was identified by ^{1}H NMR. In addition to the signals for the diquinane, the aromatic signals, appeared as two sets of doublets, 7.27 ppm (J = 8.8 Hz) and 7.83 ppm (J= 8.2 Hz) integrating for two protons each, and the signal at 2.39 ppm showed that the toluene moiety of the tosylhydrazone was present.



102 **103**

Scheme 35

The tosylhydrazone **103** was then treated with 3 equivalents of LDA in dry THF (Scheme 36).[29] The third equivalent of LDA was needed since one equivalent would react with the alcohol to form a lithium salt. Again this reaction did not yield any of the diene **104**, as only recovered starting tosylhydrazone **103** and multiple minor products were seen.



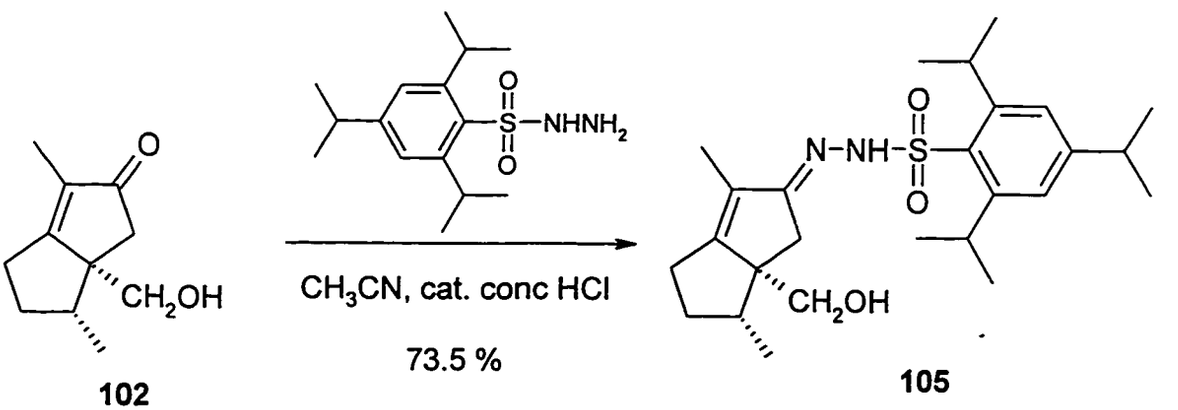
103 **104**

Scheme 36

2.3.6. Shapiro Reaction Using Trisylhydrazone

One problem that can be encountered with tosylhydrazones is their lack of reactivity. This problem stems from the fact that the sulfonyl group increases the acidity of the ortho and para hydrogens of the toluene group. The consequence of this activation is that the organolithium base can remove the protons ortho to the sulfonyl group, giving the tosyl group a negative charge. This negative charge makes the tosyl group a poor leaving group, as it must become doubly charged. A way to prevent this difficulty is to replace the ortho protons with isopropyl groups.[31]

The ketone-alcohol **104** was treated with 2,3,6-triisopropylbenzenesulfonyl-hydrazide and a catalytic amount of concentrated HCl in acetonitrile (Scheme 37).[31b] This



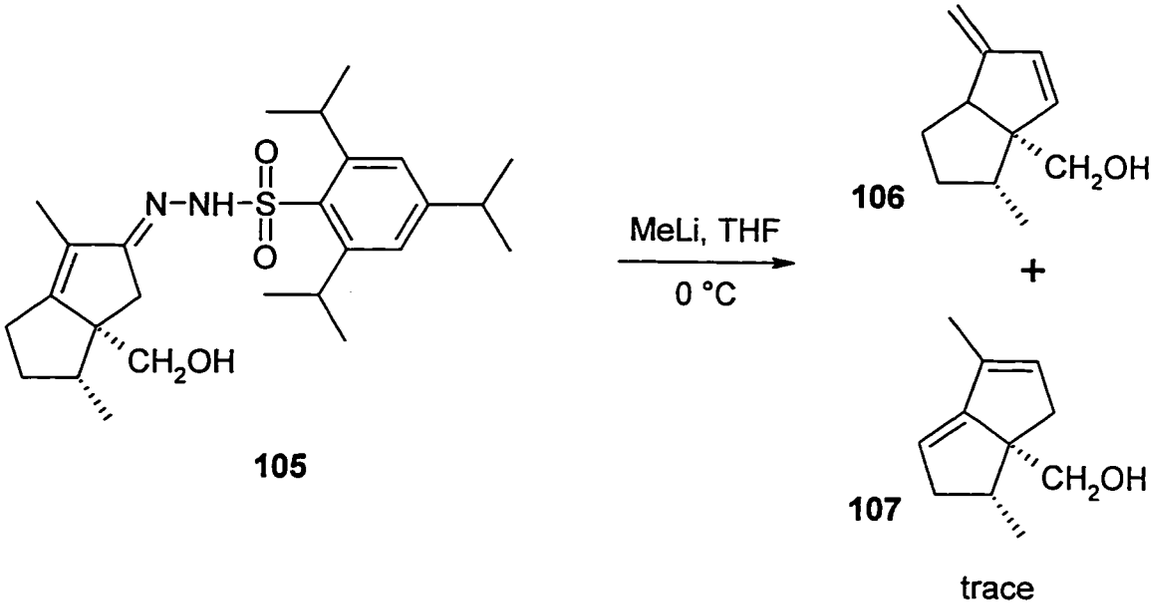
102 **105**

Scheme 37

reaction gave the trisylhydrazone **105** as a thick orange oil in a yield of 74 %. This trisylhydrazone **105** was extremely unstable. Even after purification by chromatography, the compound **105** would rapidly decompose in the NMR tube. The only reliable means of identifying the trisyl hydrazone **105** was by ^{1}H NMR. A large multiplet at 1.19-1.48 ppm integrating for 18 hydrogens supported the presence of the triisopropyl groups. The two aromatic protons appeared as a singlet at 7.13 ppm integrating for 2 hydrogens.

The trisylhydrazone **105** was treated with 3 equivalents of methyllithium in THF at 0 °C (Scheme 38).[29] Although, by TLC it appeared that the reaction did not proceed,

the crude ^{1}H NMR spectrum of the reaction revealed that the trisylhydrazone had partially undergone the Shapiro reaction. Unfortunately, the ^{1}H NMR spectrum revealed that the alkene signals were comparable to the signals of the dienes made from the alcohols



Scheme 38

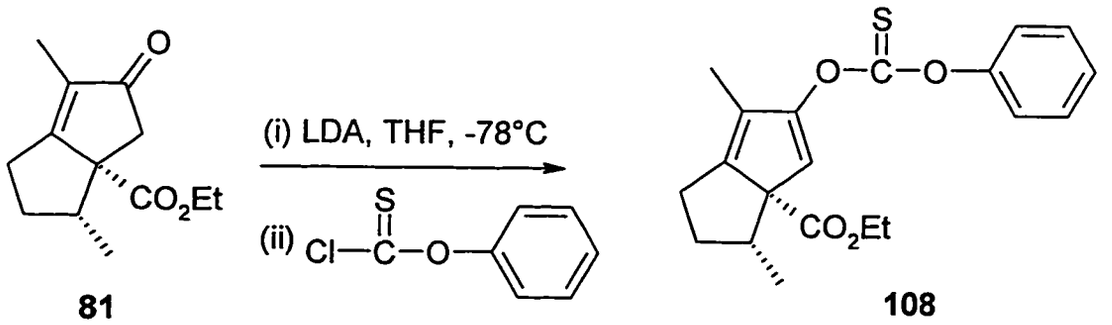
71 and **87** by tosylate elimination. The dienes made from the Shapiro reaction were the dienes **106** and **107**. It appeared that any type of base elimination would form the exocyclic double bond. The instability of the desired diene created a challenge for its synthesis.

2.3.7. Radical Cleavage

It was shown previously that the kinetic enolate can be formed from the ketone, one last attempt was made at trapping the enolate followed by deoxygenation to form the diene. This time a thiocarbonate type compound was made which could be removed by a radical reaction.

The ketone-ester **81** was treated with LDA to form the kinetic enolate. The enolate was then trapped with chlorothionoformate to form the thiocarbonate **108** in a low yield (15 %) (Scheme 39).[24] The formation of the product was confirmed by ^{1}H NMR.

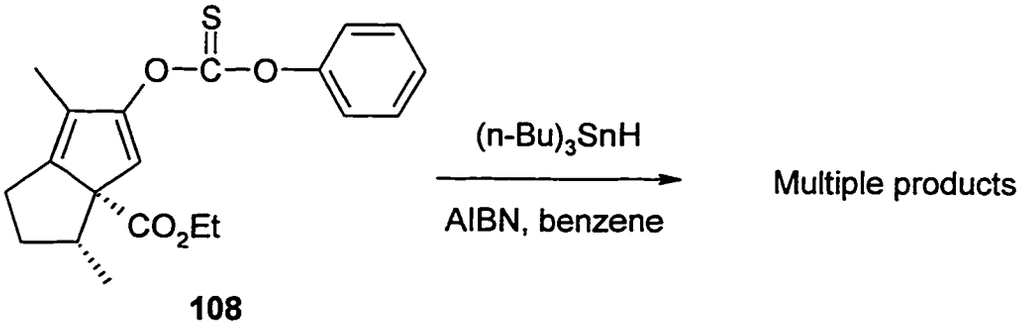
The signals for the aromatic protons for the benzene ring appeared between 7.1-7.5 ppm while the signal for the diene proton was a singlet at 6.15 ppm.



81 **108**

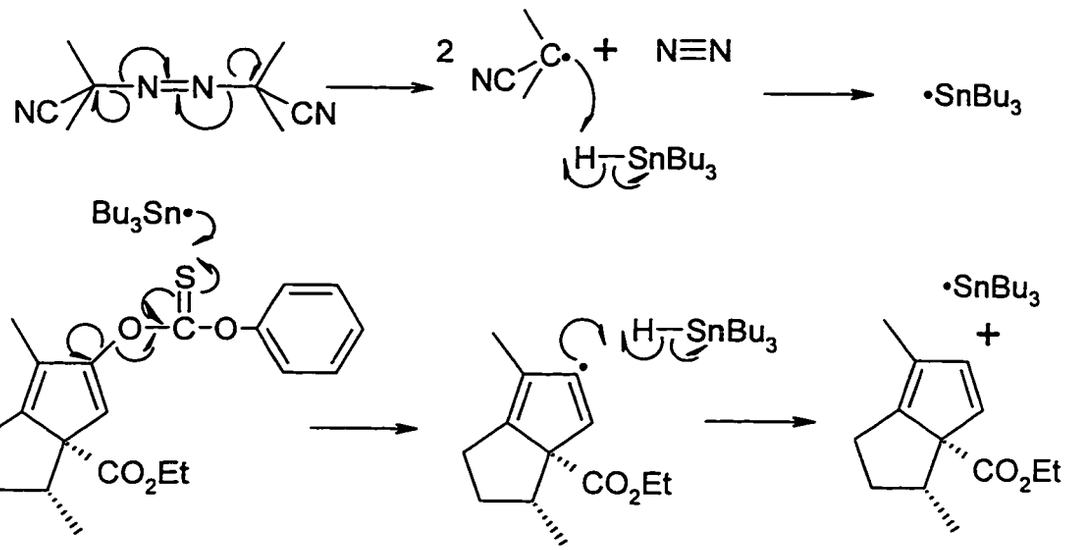
Scheme 39

A mixture of the thiocarbonate **108** and tri-*n*-butyltin hydride in benzene was heated to reflux, and a benzene solution of AIBN was added as a radical initiator (Scheme 40).[32] The radical should extract an electron from the tin hydride, to form a tin radical. The tin radical should then react with the sulfur of the thio-diene **108**, to form a vinyl radical. The vinyl radical will extract a hydrogen from the tin hydride, to regenerate the tin radical, thereby driving the reaction to completion(Scheme 41). This was the anticipated mechanism of the reaction, but the experiment did not go as predicted. The reaction gave a high number of minor products and recovered starting material.



108

Scheme 40



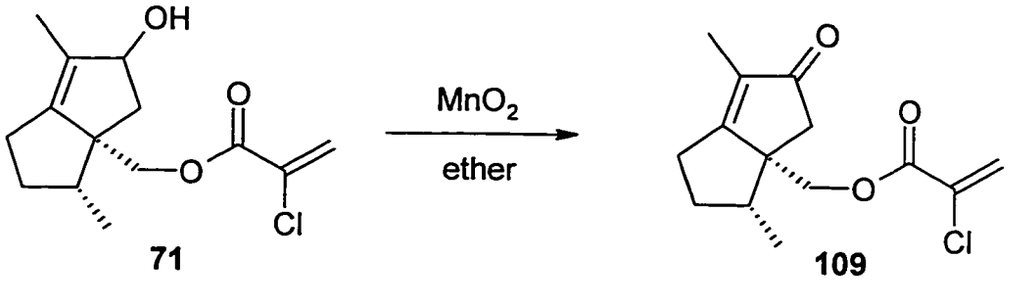
Scheme 41

2.4. Final Route to Diels-Alder Adduct

It was established that the diene could be formed by trapping the kinetic enolate, but the compound could not successfully be deoxygenated to make the diene. The only apparent strategy remaining was the formation of the diene by trapping the enolate, followed by attachment of the dienophile and subsequent Diels-Alder reaction. However, the diethyl phosphate **100** did not survive the DIBAL-H reduction conditions, thus it was apparent that the dienophile would have to be coupled before the diene was formed. As a consequence, the allylic alcohol of **71** would have to be oxidized to the ketone.

The alcohol **71** was dissolved in dry dichloromethane and was treated with 10 equivalents of activated MnO_2. Within 30 minutes the reaction was finished, yielding the ketone-dienophile **109** in quantitative yield (Scheme 42).[30] The formation of the ketone was supported by the loss of the alcohol O-H stretch and the appearance of a carbonyl stretch at 1670 cm $^{-1}$ in the IR spectrum of the product. The CH_2 alpha to the ketone changed from two doublets of doublets, an ABX spin system, to two doublets at 2.12 ppm (J = 17.4 Hz) and 2.49 ppm (J = 17.2 Hz), an AB spin system, in the ^{1}H NMR spectrum. This change was expected because the loss of the CH hydrogen of the secondary alcohol changed the spin system of the neighbouring CH_2. As well, the CH of the secondary

alcohol had disappeared from the ^{1}H NMR spectrum of **109**, further confirming the oxidation of the allylic alcohol to the ketone. The appearance of a signal at 208.7 ppm in the ^{13}C NMR spectrum of the product confirmed the presence of the ketone.



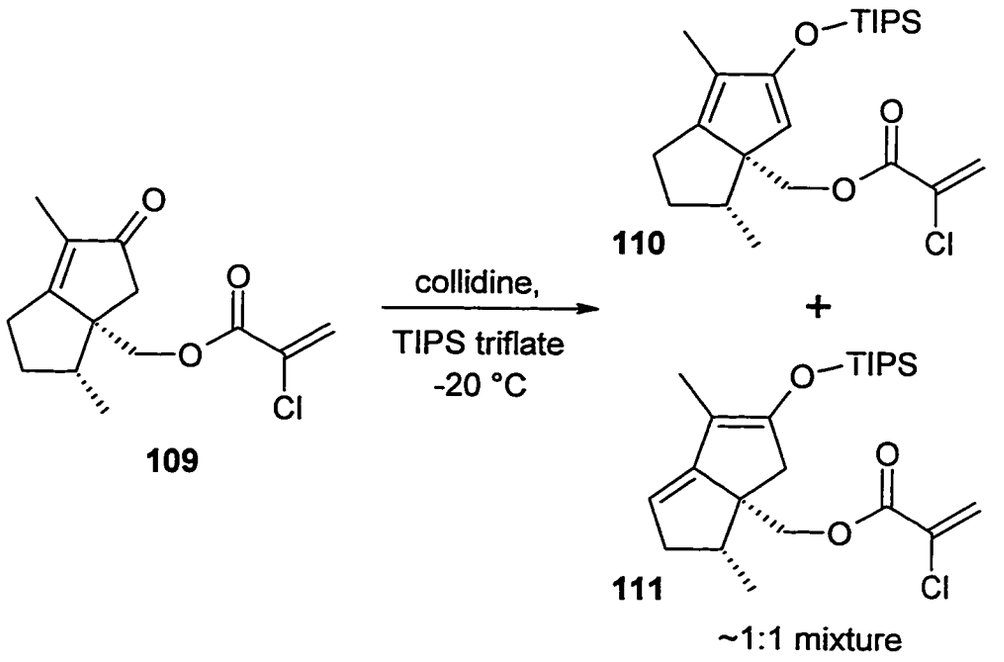
71 **109**

Scheme 42

The stability of the dienophile towards organolithium bases was unknown. It was known that the dienophile was stable to amine bases like pyridine, so a milder base was chosen to form the enolate. The diene was formed following a procedure that Tjepkema used to trap enolates with triisopropylsilyltrifluoromethanesulfonate.

The ketone-dienophile **109** was treated with collidine and triisopropyltrifluoromethanesulfonate in dichloromethane at 0 °C (Scheme 43).[33] The reaction proceeded very cleanly, giving only the *trans* diene **111** and the desired *cis* diene **110** in a one to one to a three to one ratio, with a yield for both at 74 %. The two dienes were highly unstable, which may account for the varying ratios. The products were initially isolated by flash chromatography on silica gel, but appeared to revert back to the ketone. As well, even deuterated chloroform would cause the reversion back to the ketone. This particular TIPS group appeared to be abnormally sensitive to acid as even the trace amount of acid in deuterated chloroform would cause the undesired decomposition.

The diene mixture of **110** and **111** was kept in an acid free environment in order to prevent the cleavage of the TIPS group. The products were purified by chromatography on basic alumina. As well, the ^{1}H NMR spectrum of the mixture was acquired using deuterated benzene as the solvent. The diene mixture of **110** and **111** could only be analyzed by ^{1}H NMR spectroscopy because of its unstable nature. In retrospect, it appeared that the diene underwent an acid catalyzed rearrangement to from the exo-cyclic double bond.



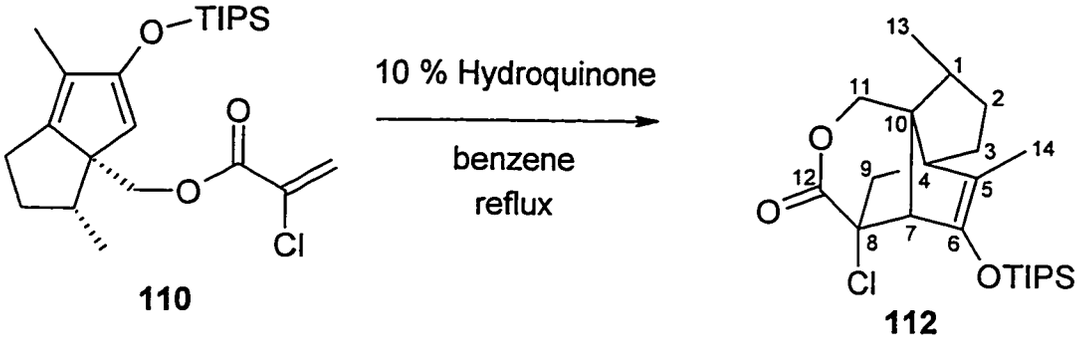
Scheme 43

In the ^{1}H NMR spectrum of the mixture the two products were easily distinguished. The alkene proton of the *cis* diene **110** was seen as a sharp singlet at 5.3 ppm, showing no coupling as expected. The alkene proton of the *trans* diene **111** appeared as a broader signal, almost a triplet, at 5.18 ppm. The overlapping triisopropyl groups of both dienes appeared as a large multiplet at 0.9-1.3 ppm.

The dienes existed as a mixture, however, it was hoped that only the desired diene would undergo the intramolecular Diels-Alder reaction and the product could be easily isolated. The Diels-Alder reaction was initially attempted by heating the diene mixture in refluxing toluene. By TLC the starting diene mixture had disappeared, but the reaction had generated a large number of products. The mixture was subjected to chromatography and different fractions of the column were studied by ^{1}H NMR spectroscopy. One fraction appeared to contain the desired Diels-Alder adduct **112**. The spectrum contained no alkene signals, but had several AB spin systems that would be expected in the product.

Initially it was believed that the high temperature was causing the unstable dienes to decompose before they had a chance to react. The intramolecular Diels-Alder reaction was repeated, but this time in refluxing benzene. The refluxing benzene should provide

sufficient energy to effect the Diels-Alder reaction, but should not, hopefully, cause the decomposition of the TIPS-diene **110**. Hydroquinone (10 mole percent) was added as a radical scavenger to discourage decomposition. On the first attempt the reaction went cleanly, giving the Diels-Alder adduct **112**. When the reaction was attempted without the hydroquinone, there was substantial decomposition of the diene mixture and only a trace amount of the Diels-Alder adduct **112** was seen. It was apparent that the hydroquinone played a vital role and prevented the decomposition of the dienes. The reaction was repeated once more with 10 % hydroquinone on a 1 to 1 mixture of the diene-dienophiles **110** and **111** to give the Diels-Alder adduct **112** in a yield of 64 %, based on the initial quantity of **110** present (Scheme 44).



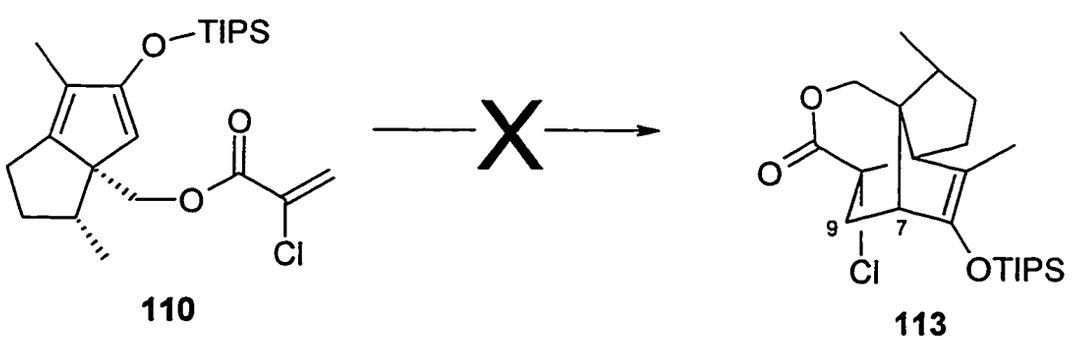
110 **112**

Scheme 44

The signal of the methyl methyl group 13 on ring E appeared as a doublet at 0.49 ppm (J = 7.2 Hz) integrating for 3 hydrogens in the ^{1}H NMR spectrum. The neighbouring hydrogen on C_1 appeared as a multiplet at 1.20 to 1.40 ppm. The COSY 2D NMR showed coupling between C_1 and for a multiplet at 1.70 to 1.77 ppm, which integrated for one hydrogen, and part of the large multiplet between 0.90 and 1.13 ppm, which integrated for 23 hydrogens. The multiplet at 1.70 to 1.77 and part of the large multiple were the two nonequivalent hydrogens of C_2. These in turn showed coupling for the multiplet at 1.29-1.40, which integrated for one hydrogen, and for a different part of the large multiplet. These were the 2 hydrogens of C_3. The other 21 hydrogens of the multiplet between 0.90 and 1.13 ppm were from the TIPS group, indicating that it remained attached during the Diels-Alder reaction.

The CH_2 at C_{11} was still an AB system seen as two doublets at 3.44 ppm (J = 12.8 Hz) and 3.85 ppm (J = 12.8 Hz), both integrating for one hydrogen each. The CH_2 of C_9 was also seen as two sets of doublets at 1.49 ppm (J = 12.8 Hz) and 1.95 ppm (J = 12.8 Hz), each integrating for one hydrogen. The COSY 2D NMR experiment showed that the CH_2's exhibited only coupling to themselves, indicating that they were isolated in the compound.

The bridgehead hydrogen at C_7 appeared as a sharp singlet at 2.72 ppm. This signal integrated for only one hydrogen and showed no coupling, indicating that the neighbouring carbons were devoid of hydrogens. This confirmed that Diels-Alder reaction occurred as desired. If the reaction followed the other possible route (Scheme 45), carbon C_7 would be right beside the CH_2 at C_9, as seen in **113**. In this case, hydrogens at both C_7 and C_9 would show coupling to each other, which would complicate the signals for both.



110 **113**

Scheme 45

The remaining unaccounted hydrogen signal was at 1.44 ppm, integrating for three hydrogens. This signal was due to the allylic methyl group at C_{14}.

There were no chemical shifts in the alkene region of the ^1H NMR spectrum. This indicated that the Diels-Alder reaction must have occurred, since the reaction was not performed under hydrogenation conditions. The presence of the double bond was confirmed in the ^{13}C NMR spectrum of the adduct **112** by the two chemical shifts at 147.0 and 120.0 ppm, for the double bond between carbons 5 and 6.

The Diels-Alder adduct **112** was extremely stable. The product was isolated by flash chromatography using silica gel, which showed that the TIPS protecting group was no longer sensitive to trace amounts of acid. As well, **112** could be analyzed by EI high resolution mass spectrometry. The calculated mass for **112** was 424.2202 and the mass found was 424.2201.

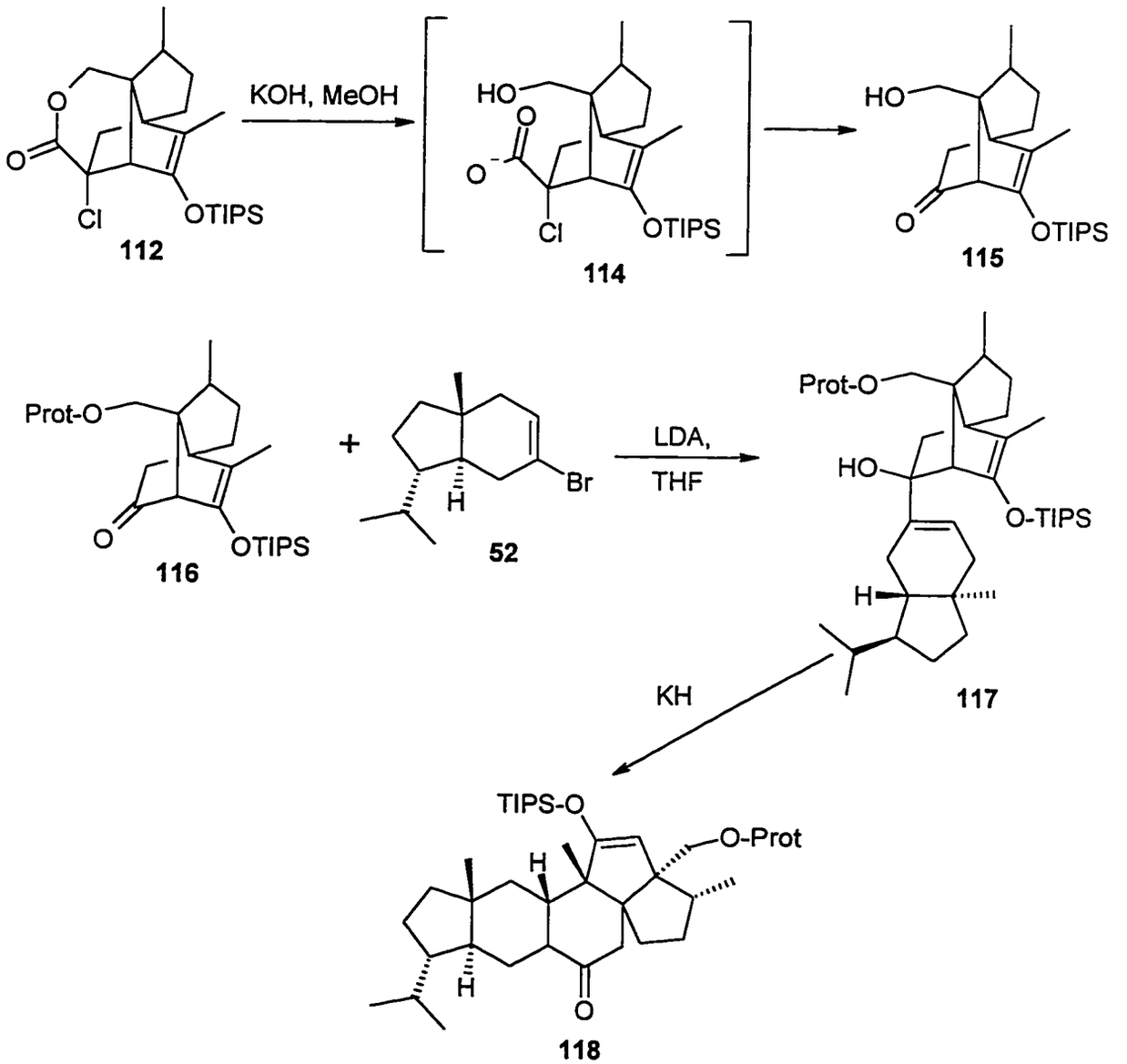
2.5. Steps to Complete the Synthesis

At this point a key step in the proposed synthetic scheme had been achieved. It was shown that the key building block **51** could be synthesized via an intramolecular Diels-Alder reaction. The diene was made by trapping the enolate, since other methods for diene formation provided the wrong isomer with an exocyclic double bond. A way to prevent the exocyclic double bond from forming would be to add a blocking group on the allylic methyl group. Our current approach will add a step later in the synthesis as the silyl ether will have to be removed. The unstable diene **110** proved to be highly reactive in the Diels-Alder reaction.

The proposed scheme to complete the synthesis of retigeranic acid A is shown in Scheme 46. The TIPS group is highly sensitive to acids, although it is very stable to bases. There is literature precedent that the TIPS group will remain unaffected when potassium hydroxide in methanol is used to saponify the lactone.[34] This ring opening step will form the intermediate **114** which should collapse, with the loss of carbon dioxide, to the ketone-alcohol **115**. The alcohol will have to be protected before the addition of the *trans*-hydrindane **52** is accomplished.

The vinyl bromide can then be treated with *s*-BuLi in THF. This reaction will generate the vinyl anion which can then be added to the ketone of the tricycle **116**. The alcohol **117** generated from this reaction is then predisposed for the oxy-Cope rearrangement. Treatment of the alcohol **117** with potassium hydride will effect the oxy-Cope rearrangement which should yield the ketone **118**. This compound then only needs to be defunctionalized and undergo a ring contraction reaction to yield retigeranic acid A.

One of the key hurdles of this ongoing project has been cleared. The successful synthesis of the Diels-Alder adduct showed that this route to retigeranic acid A is still viable. The dienophile tether prevents the migration of the diene, as long as the diene is made by trapping the enolate. The tether also controls the stereochemistry of the Diels-Alder adduct. This work has brought the Fallis laboratory one step closer to synthesizing retigeranic acid A.



Scheme 46

EXPERIMENTAL

CHAPTER 3

General Experimental

All of the compounds synthesized were analyzed by infrared, nuclear magnetic resonance, and mass spectrum analysis. The infrared (IR) spectra of various compounds were measured as a neat film on sodium chloride discs. All IR spectra were recorded on a Bomem Michelson 100 transform spectrometer (FTIR). The reference that was used was the atmospheric infrared spectrum and this was subtracted from all % transmittance spectra.

The nuclear magnetic resonance spectra (NMR) of all of the compounds were either measured in a solution of deuterated chloroform ($CDCl_3$), in a solution of deuterated benzene (C_6D_6), or in a solution of deuterated methanol (CD_3OD). The proton nuclear magnetic resonance (^1H NMR) spectra of experimental compounds were recorded either at 200 MHz on a Varian Gemini spectrometer, or at 500 MHz on a Bruker WM500 spectrometer. The chemical shifts were relative to an internal lock on the deuterium from the solvent used and were reported in parts per million (ppm) downfield of tetramethylsilane (δ scale). The multiplicity, number of protons, and coupling constants (J in Hz) were reported in parentheses after each chemical shift.

The carbon nuclear magnetic resonance spectra (^{13}C NMR) of all the compounds were recorded either at 50 MHz on a Varian Gemini spectrometer, or at 125 MHz on a Bruker WM500 spectrometer. The chemical shifts were relative to an internal lock on the deuterium from the solvent used and were reported in parts per million (ppm) downfield of tetramethylsilane (δ scale).

Elemental analyses were either performed in the chemistry department at the University of Ottawa or were done by the M-H-W Laboratories in Phoenix, Arizona.

Mass spectrum analyses and high resolution mass spectra (HRMS) were performed by the analytical services available at the University of Ottawa. Low resolution mass spectra were performed using electron impact (EI) ionization. High resolution mass spectroscopy was performed on a Kratos Concept-IIA mass spectrometer

using an electron beam with an energy of 70 eV. Unstable compounds of high molecular weight were examined by FABH (Fast Atom Bombardment) accurate mass experiments.

The melting points of crystalline products were measured on a Thomas Hoover "unimelt" oil bath melting point apparatus and are uncorrected.

Analytical thin layer chromatography (TLC) were performed using EM Separations silica gel on aluminum sheets, 60 F_{254}. Individual compounds were seen either by ultraviolet light or by staining. The stains that were used were either a 5 % solution of ammonium molybdate in 10 % aqueous H_2SO_4 or a 2.5 % solution of p-anisaldehyde in 95 % ethanol containing 3 % H_2SO_4. The TLC plates were developed by dipping the plates into the appropriate stain and then heating the plates until the spots appear. Purification of compounds were carried out by either classical distillation methods or by chromatography. Drip and flash chromatography were done with EM Science Silica Gel 60, specific size 460-520 m^2/g.

Basic alumina was used in place of silica gel in cases where the compounds were acid sensitive. Analytical TLC for these acid sensitive compounds was performed using Merck aluminum oxide 60 F_{254} neutral (Type E) sheets coated on aluminum sheets. Drip chromatography was done with Aldrich aluminum oxide, activated, basic, Brockmann I, standard grade 150 mesh.

All reactions were performed under a nitrogen atmosphere unless otherwise stated. The nitrogen was dried by passing through two columns packed alternatively with drierite and calcium hydroxide pellets. The glassware that was used for these moisture sensitive reactions was either dried overnight in an oven or flame dried with a propane torch. Disposable and oven dried syringes were used to transfer chemicals and solvents. "Drying" refers to removing the water from the organic mixture with anhydrous magnesium sulfate, if it is not stated. "Concentration" refers to the removal of solvent by roto-evaporation on a Buchi R110 Rotovapour using a water aspirator as the vacuum source.

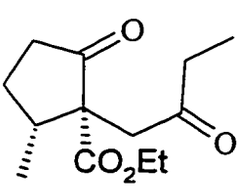
Solvents and Reagents

All moisture sensitive reactions were performed using dry, distilled solvents. Some solvents were kept in constantly maintained stills and were freshly distilled prior to use. THF and ether were distilled over a mixture of sodium and benzophenone. Dichloromethane, benzene, and toluene were distilled over calcium hydride. Other solvents were distilled and stored over activated 4 Å molecular sieves. These include methanol and acetonitrile, both which were distilled over calcium hydride.

Pyridine and tetramethylethylenediamine (TMEDA) were distilled over calcium hydride and were stored over sodium hydroxide. Diisopropylamine was also freshly distilled in a maintained still.

Petroleum ether refers to a mixture of hydrocarbons. Ether refers to diethyl ether

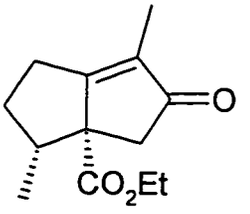
Ethyl (1S,2S)-2-methyl-5-oxo-1-(2-oxobutyl)cyclopentane-1-carboxylate (**80**)



Ethanol (95%, 180 mL) and distilled water (115 mL) were added sequential to the keto-ester **79** (6.366 g, 26.71 mmol). The stirred mixture was cooled to 0°C and sodium metaperiodate (14.282 g, 66.77 mmol) was added. Once a majority of the sodium metaperiodate was dissolved, osmium tetroxide (two small crystals) were added and the reaction allowed to warm to 21 °C. After stirring for 24 hours, TLC (30% ethyl acetate in petroleum ether) analysis indicated that the starting material was totally consumed and that the reaction consisted of a combination of the desired product and the diol intermediate. An additional allotment of sodium metaperiodate (5 g, 23.38 mmol) was added and the reaction was stirred for another 48 hours. The mixture was concentrated in vacuo to remove the majority of the ethanol. The slurry was filtered through Celite® with

CH_2Cl_2 (600 mL). The filtrate was extracted with ether (1 X 600 mL + 2 X 200 mL). The combined organic extracts were washed with distilled water (180 mL), brine (180 mL), dried, filtered, and concentrated. Flash chromatography (30 % ethyl acetate/petroleum ether) yielded the pure diketo-ester **80** (5.618g, 88 %) as a clear colourless oil.; IR (neat) 2939, 1729 (b) cm^{-1}; ^1H NMR (200 MHz) δ: 0.91-0.98 (m, 6 H), 1.17 (t, 3 H, J = 1.8 Hz), 1.75-1.88 (m, 1 H), 1.97-2.16 (m, 1 H), 2.30-2.74 (m, 5H), 2.96 (d, 1H, J = 4.0 Hz), 3.18 (d, 1 H, 4.0 Hz), 3.95-4.22 (m, 2 H); ^{13}C NMR (50 MHz) δ: 7.5, 14.1, 15.4, 28.5, 35.9, 38.1, 38.7, 44.1, 60.6, 61.2, 170.1, 208.5, 216.1; HRMS (EI) calc for $C_{13}H_{20}O_4$ 240.1362, found 240.1371; $[\alpha]_D^{30.4}$ +53.4 ° (c 23.5, $CHCl_3$).

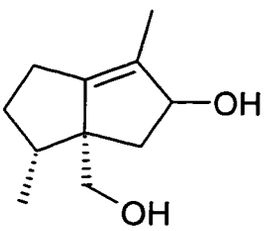
Ethyl (3S,3aS)-3,6-dimethyl-5-oxo-1,2,3,3a,4,5-hexahydro-3a-pentalene carboxylate (**81**)



The diketo-ester **80** (2.330 g, 9.70 mmol) was dissolved in dry benzene (230 mL) and dibenzo-18-crown-6 (200 mg) plus potassium hydroxide (4 crushed pellets) were added to the reaction mixture. The reaction was stirred at reflux overnight. The mixture was cooled to 21°C and filtered through a silica plug with ether (500 mL). The resulting solution was concentrated and the residual oil purified by chromatography (15% ethyl acetate in petroleum ether) to afford the bicyclic compound **81** (1.811, 84 %) as a clear colourless oil; IR (neat) 3412, 2937, 1717, 1669 cm^{-1}; ^1H NMR (500 MHz) δ: 1.073 (d, 3 H, J = 6.8 Hz), 1.223 (t, 3 H, J = 7.1 Hz), 1.66 (s, 3 H), 1.71-1.80 (m, 1 H), 1.92-2.01 (m, 1 H), 2.04-2.11 (m, 1 H), 2.11 (d, 1 H, J = 17.9 Hz), 2.49-2.55 (m, 1 H), 2.77-2.82 (m, 1

H), 3.12 (d, 1 H, J = 17.9 Hz), 4.05-4.15 (m, 2 H); ^{13}C NMR (125 MHz) δ: 8.45, 14.17, 15.32, 25.81, 32.04, 44.50, 45.43, 60.94, 61.39, 133.44, 171.47, 179.75, 208.48; Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; found: C, 70.37; H, 7.95; $[\alpha]_D^{29.2}$ -31.3 (c 12.0, $CHCl_3$).

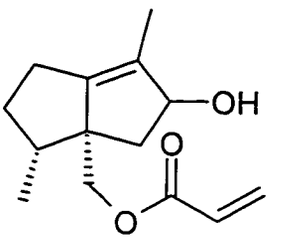
(6S,6aS)-6a-(Hydroxymethyl)-3,6-dimethyl-1,2,4,5,6,6a-hexahydro-2-pentalenol (**72**)



The keto-ester (**81**) (0.500g, 2.25 mmol) was dissolved in dry CH_2Cl_2 (22 mL) under a nitrogen atmosphere and was cooled to -78° C by an external dry ice/acetone bath. Diisobutylaluminum hydride (1.0 M in hexanes) (10.2 mL, 10.2 mmol) was added dropwise over 5 minutes. The reaction was stirred at -78 ° C for 10 minutes and cooling bath was removed to allow the reaction to warm to 21°C. After one hour the reaction was cooled to 0° C and was diluted with CH_2Cl_2 (30 mL). Aqueous NH_4Cl/NH_4OH (pH=8 buffered solution, 4 mL) was slowly added. The mixture was stirred at 0° C for 1 hour. Anhydrous $MgSO_4$ was added and the slurry was filtered though a Celite® bed, washing with excess amounts of ether. The filtrate was concentrated and the residual oil was purified by chromatography (100% ethyl acetate) to yield the diol **72** (0.342g, 84 %) as a thick oil; IR (neat) 3412, 2937, 1717, 1669 cm^{-1}; ^{1}H NMR (500 MHz) δ: 0.91 (d, 2 H, J = 7.0 Hz), 1.18 (t, 1 H, J = 7.0 Hz), 1.32 (dd, 1 H, J = 6.7, 12.7 Hz), 1.59-1.68 (m, 1 H), 1.65 (s, 1 H), 1.71-1.79 (m, 1 H), 2.01-2.12 (m, 2 H), 2.19-2.23 (m, 1 H), 2.48 (dd, 1

H, J = 6.7, 12.7 Hz), 3.44 (dt, 2 H, J = 9.7, 6.7 Hz), 4.99 (bs, 1 H); ^{13}C NMR (125 MHz) δ: 10.80, 13.83, 21.50, 33.85, 43.71, 46.49, 60.74, 63.89, 83.67, 132.52, 146.85; HRMS (EI) calc for $C_{11}H_{18}O_2$ 182.1307, found 182.1304; $[\alpha]_D^{31.8}$ -41.2 (c 38.5, $CHCl_3$).

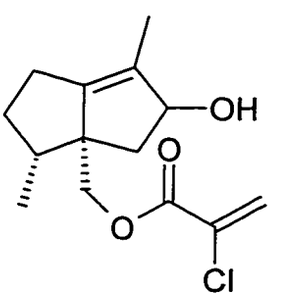
[(3S,3aS)-5-Hydroxy-3,6-dimethyl-1,2,3,3a,4,5-hexahydro-3-pentalenyl] methyl acrylate (**82**)



The diol **72** (42.8 mg, 0.235 mmol) was dissolved in dry CH_2Cl_2 (10 mL). Pyridine (28.4 μL, 0.353 mmol) and freshly distilled acryloyl chloride (21.0 μL, 0.258 mmol) were sequentially added to the reaction. The reaction, monitored by TLC (3:2 ethyl acetate/petroleum ether), was complete after 30 minutes. The reaction was diluted with ether (20 mL), washed with aqueous saturated ammonium chloride (3 X 7 mL), and aqueous saturated sodium bicarbonate (7 mL). The organic layer was dried, filtered, and concentrated. Purification by flash chromatography (3:2 ethyl acetate/petroleum ether) gave the desired product **82** (17.0 mg, 34.2 %), along with recovered starting material (3.8 mg), and di-coupled product **83** as colourless oils; IR (neat) 3331, 2915, 1718, 1192 cm^{-1}; ^{1}H NMR (200 MHz) δ: 0.96 (d, 2 H. J = 6.6 Hz), 1.33 (dd, 1 H, J = 7.2, 12.7 Hz), 1.54-1.85 (m, 3 H), 1.59 (s, 3 H), 1.99-2.32 (m, 3 H), 2.47 (dd, 2 H, J = 6.4, 12.8 Hz), 3.96 (d, 1 H, J_{AB} = 11.0 Hz), 4.13 (d, 1 H, J_{AB} = 10.9 Hz), 4.95 (bs, 1 H), 5.79 (dd, 1 H, J = 1.8, 10.3 Hz), 6.05 (dd, 1 H, J = 10.3, 17.2 Hz), 6.32 (dd, 1 H, J = 1.8, 17.2 Hz); ^{13}C NMR (50 MHz) δ: 10.68, 14.33, 21.68, 33.92, 44.16, 46.38, 58.06, 65.86, 83.57, 128.59,

130.52, 131.22, 147.27, 166.21; HRMS (EI) calc for $C_{14}H_{20}O_3$ 236.1413, found 238.1389; $[\alpha]_D^{28.6}$ -44.4 (c 12.6, $CHCl_3$).

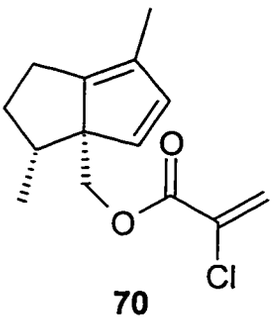
[(3S,3aS)-5-Hydroxy-3,6-dimethyl-1,2,3,3a,4,5-hexahydro-3-pentalenyl] methyl 2-chloroacrylate (**71**)



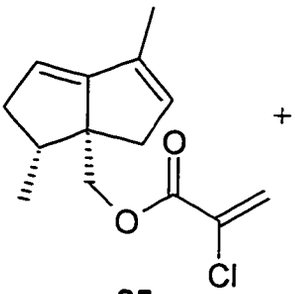
2-Chloroacrylic acid (172.2 mg, 1.617 mmol) was dissolved in cold (0°C) dry CH_2Cl_2 (10 mL) and DCC (606.6 mg, 2.94 mmol) was added. The mixture was allowed to stir at 0° C for 20 minutes. The diol **72** (267.2mg, 1.47 mmol) in CH_2Cl_2 (14 mL) containing DMAP (30 mg) was added. The reaction was stirred at 0° C for an additional 10 minutes and then at 21° C for 3 hours. The reaction was diluted with CH_2Cl_2 (10 mL) and was washed with a saturated aqueous solution of sodium bicarbonate (20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting oil/solid mixture was purified by flash chromatography (3:1 hexanes: ethyl acetate) to give the desired product **71** (0.182 g, 46 %) as white crystals; mp 62-64° C; IR (neat) 3331, 2915, 1718, 1192 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.96 (d, 2 H, J = 6.9 Hz), 1.36 (dd, 1 H, J = 7.1, 12.9), 1.60 (s, 3 H), 1.62 (s, 1 H), 1.66-1.80 (m, 2 H), 2.06-2.21 (m, 2 H), 2.47 (dd, 1 H, J = 6.5, 12.8 Hz), 4.01 (d, 1 H, J_{AB} = 10.9 Hz), 4.18 (d, 1 H, J_{AB} = 10.9 Hz), 5.00 (bs, 1 H), 5.95 (d, 1 H, J = 1.4 Hz), 6.43 (d, 1 H, 1.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.65, 14.29, 21.67, 33.88, 44.12, 46.20, 58.00, 67.95, 83.39,

125.57, 131.56, 146.86, 162.04; HRMS (EI) calc for $C_{14}H_{19}O_3Cl$ 270.1023, found 270.1023; $[\alpha]_D^{30.0}$ -68.3 (c 3.6, $CHCl_3$).

Attempted preparation of **70**; Isolation of [(3S,3aS)-3,6-dimethyl-2,3,3a,4-tetrahydro-3-pentalenyl]methyl 2-chloroacrylate (**85**) and [(3S,3aS)-3-methyl-6-methylene-1,2,3,3a,6,6a-hexahydro-3-pentalenyl]methyl 2-chloroacrylate (**91a**)

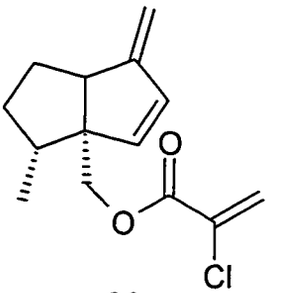


70



85

+

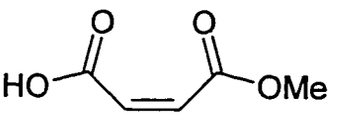


91a

The alcohol **71** (100 mg, 0.37 mmol) and pyridine (45 μL, 0.556 mmol) were dissolved in dry CH_2Cl_2 (6 mL). The stirred solution was cooled to 0° C and *p*-toluenesulfonic anhydride (182 mg, 0556 mmol) and 4 dimethylaminopyridine (~3 mg) were added to the solution. The reaction was slowly allowed to warm to 21° C overnight. The reaction was diluted with ether (15 mL), water was added (8 mL) and the layers separated. The organic layer was washed with water (8mL), brine (8mL) dried over anhydrous $MgSO_4$, filtered, and concentrated. The residual oil was purified by flash chromatography (3:1 hexanes/ethyl acetate) to yield a 1.2:1 mixture of the dienes **85** and **91a** (63.1 mg, 67.3 %) as an oil; IR (neat) 3123, 3045, 2919, 1733, 1610, 1262, 1117 cm^{-1}; Diene **91a** ^1H NMR (500 MHz, $CDCl_3$) δ: 0.98 (d, 1 H, 7.2 Hz), 1.33-1.44 (m, 2 H), 1.70-1.75 (m, 1 H), 1.93 (m, 1 H), 2.09-2.17 (m, 1 H), 2.83-2.86 (m, 1 H), 4.09 (d, 1 H, *J* = 10.9 Hz), 4.30 (d, 1 H, *J* = 10.9 Hz), 4.74 (dd, 1 H, *J* = 0.7, 1.3 Hz), 4.87 (d, 1 H, *J* = 1.3 Hz), 5.88 (dd, 1 H, *J* = 0.7, 5.5 Hz), 5.95 (d, 1 H, *J* = 1.4 Hz), 6.08 (d, 1 H, *J* = 5.5

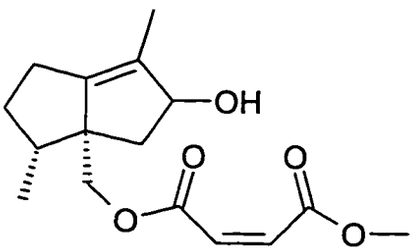
Hz), 6.42 (d, 1 H, J = 1.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.94, 32.68, 34.05, 40.57, 49.93, 62.63, 69.26, 104.56, 125.60, 131.61, 133.89, 141.83, 158.89, 162.04 ; Diene **85**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.10 (d, 3 H, J = 7.1 Hz), 1.76 (s, 3 H), 2.08 (bd, 1 H, 16.5 Hz), 2.19 (bd, 1 H, 16.5 Hz), 2.46-2.49 (m, 1 H), 2.50-2.57 (m, 2 H), 3.99 (d, 1 H, J = 11.1 Hz), 4.12 (d, 1 H, J = 11.0 Hz), 5.35 (bs, 1 H), 5.69 (bs, 1 H), 5.95 (d, 1 H, J = 1.4 Hz), 6.44 (d, 1 H, J = 1.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.08, 14.45, 38.61, 44.47, 45.43, 59.11, 67.36, 115.17, 125.34, 131.84, 134.02, 135.69, 158.54, 161.95.

(Z)-4-Methoxy-4-oxo-2-butenoic acid (**86**)



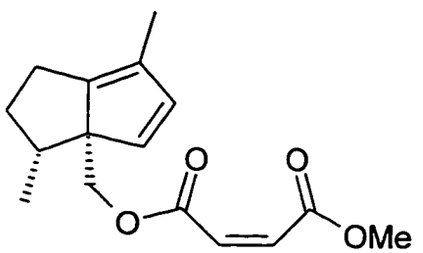
Maleic anhydride (1.316g, 13.4 mmol) was dissolved in dry methanol. The solution was stirred at reflux temperatures for 16 hours.[23] The solvent was removed under reduced pressure and the product was isolated by flash chromatography (ethyl acetate). This gave the acid **86** as a colorless oil (1.6427 g, 94 % yield). IR (neat) 3500-2600 (broad signal), 1701, 1606, 1227 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.97 (2, 3 H), 6.31 (s, 2 H), 11.83 (s, 1); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 52.84, 130.11, 132.48, 166.94, 166.99 ppm; Anal. Calcd for $C_5H_6O_4$: C, 46.16; H, 4.65; found: C, 45.88; H, 4.74.

1-{[(3S,3aS)-5-Hydroxy-3,6-dimethyl-1,2,3,3a,4,5-hexahydro-3-pentalenyl] methyl}4-methyl(Z)-2-butenedioate (**87**)



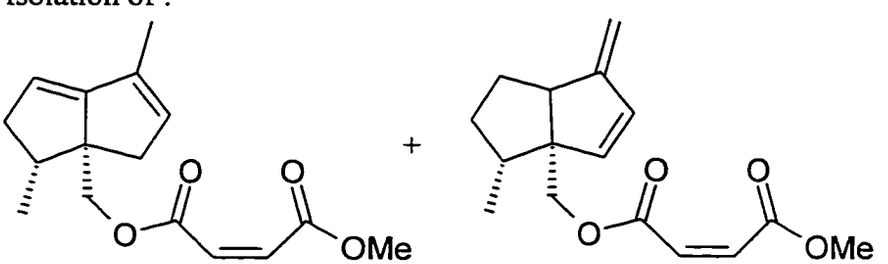
1,3-Dicyclohexylcarbodiimide (169.9 mg, 0.822 mmol) was added to a stirred solution of the acid **86** (85.2 mg, 0.655 mmol) in dry CH_2Cl_2 (4 mL) at 0° C. The mixture was allowed to stir at 0° C for 20 minutes then the diol **72** (100 mg, 0.549 mmol) in dry CH_2Cl_2 (6 mL) was added. The addition syringe was rinsed with CH_2Cl_2 (2 mL) and the solution added to the reaction, along with 4-dimethylaminopyridine (12 mg). The reaction was stirred to 0° C for an additional 10 minutes and then at 21° C for 6 hours. The reaction was diluted with ether (30 mL), washed with saturated aqueous sodium bicarbonate (8 mL), and the organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting oil/solid mixture was purified by flash chromatography (3:2 hexanes/ethyl acetate) to give the desired product **87** (72 mg, 44.6 %); IR (neat) 3406, 2919, 1729, 1644, 1224, 1014 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.93 (d, 3 H, J = 6.6 Hz), 1.32 (dd, 1 H, J = 7.2, 12.8 Hz), 1.59 (s, 3 H), 1.60-1.85 (m, 2 H), 1.96-2.25 (m, 3 H), 2.45 (dd, 1 H, J = 6.5, 12.7 Hz), 3.76 (s, 3 H), 4.01 (d, 1 H, J_{AB} = 10.8 Hz), 4.12 (d, 1 H, J_{AB} = 10.9 Hz), 4.90 (m, 1 H), 6.15 (d, 1 H, J = 12.0 Hz), 6.22 (d, 1 H, J = 12 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 10.65, 14.23, 21.54, 33.78, 44.15, 46.17, 52.17, 57.86, 66.67, 83.40, 129.71, 129.77, 131.47, 146.83, 165.28, 165.62; HRMS (EI) calc for $C_{14}H_{19}O_3Cl$ 294.1468, found 294.1463; $[\alpha]_D^{27.6}$ -86.7 (c 16.6, $CHCl_3$).

Attempted preparation of **88**; Isolation of 1-{[(3S,3aS)-3,6 dimethyl-2,3,3a,4-tetrahydro-3-pentalenyl]methyl}4-methyl (Z)-2-butenedioate (**89**) and 1-{[(3S,3aS)-3-methyl-6-methylene-1,2,3,3a,6,6a-hexahydro-3-pentalenyl]methyl}4-methyl (Z)-2-butenedioate (**91b**)



88

Isolation of :

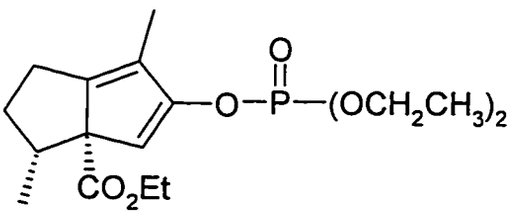


89 **91b**

The alcohol-ester **87** (14.2 mg, 0.0483 mmol) and pyridine were dissolved in dry CH_2Cl_2 (1 mL) and *p*-toluenesulfonic anhydride (17.2 mg, 0.0530 mmol) and 4-dimethylaminopyridine (catalytic amount) were added at 0° C. The reaction was allowed to slowly warm to 21° C and stirred overnight. The reaction was diluted with ether (4 mL). Water was added (2 mL) and the layers were separated. The organic layer was washed with water (2 mL) and brine (2 mL), dried ($MgSO_4$), filtered, and concentrated. The oil was purified by flash chromatography (3:1 hexanes/ethyl acetate) to yield a 1.33 to 1 mixture of dienes **89** and **91b** (11.2 mg, 84.1%); IR (neat) 3050, 2926,1733, 1642, 1445, 1396, 1164 cm^{-1}; Diene **91b** ^1H NMR (500 MHz, $CDCl_3$) δ: 0.96 (d, 1 H, 7.2 Hz), 1.29-1.36 (m, 1 H),1.37-1.43 (m, 1 H), 1.67-1.74 (m, 1 H), 1.88-1.94 (m, 1 H), 2.05-2.11 (m, 1 H), 2.78-2.81 (m, 1 H), 3.76 (s, 3 H), 4.07 (d, 1 H, J = 10.9 Hz), 4.27 (d, 1 H, J =

10.9 Hz), 4.72 (bs, 1 H), 4.86 (bs, 1 H), 5.89 (d, 1 H, J = 5.4 Hz), 6.07 (d, 1 H, J = 5.4 Hz), 6.20 (bs, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.90, 32.56, 33.81, 40.36, 49.68, 52.08, 62.46, 68.24, 104.29, 129.74, 129.78, 133.71, 142.19, 159.12, 165.24, 165.63; Diene **89.** ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07 (d, 3 H, J = 7.1 Hz), 1.76 (s, 3 H), 2.02 (bd, 1 H, 16.4 Hz), 2.20 (bd, 1 H, 16.4 Hz), 2.21-2.23 (m, 1 H), 2.41-2.55 (m, 2 H), 3.76 (s, 3 H), 3.93 (d, 1 H, J = 11.1 Hz), 4.13 (d, 1 H, J = 11.1 Hz), 5.33 (bs, 1 H), 5.68 (bs, 1 H), 6.19 (bs, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.00, 14.33, 38.44, 44.20, 45.54, 52.08, 58.97, 66.03, 114.98, 129.55, 129.58, 134.05, 135.50, 158.63, 165.54, 165.74; HRMS (EI) calc for $C_{16}H_{20}O_4$ 276.1362, found 276.13705.

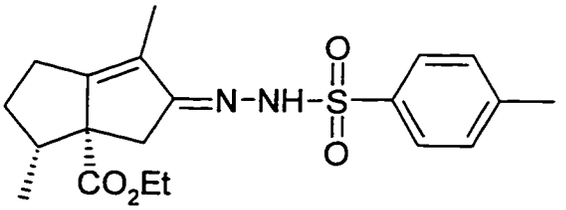
Ethyl (3S,3aS)-5-[(diethoxyphosphoryl)oxy]-3,6-dimethyl-1,2,3,3a-tetrahydro-3a-pentalenecarboxylate (**100**)



n-Butyl lithium (2.4 M in hexanes. 340 μL, 0.82 mmol) was added dropwise to a stirred solution of diisopropylamine (115 μL, 0.878 mmol) in dry THF (8 mL) at 0° C. The solution was allowed to stir at 0° C for 30 minutes and was cooled to -78° C. The keto-ester **81** (150 mg, 0.675 mmol) in dry THF (1.5 mL) was added dropwise. The reaction was allowed to stir at -78° C for 30 minutes. The freshly distilled diethyl chlorophosphate (147 μL, 0.945 mmol) and TMEDA (68 μL) were added sequentially. The reaction was allowed to warm up to 21°C. TLC analysis showed that the reaction was complete in 2 hours. The reaction was cooled to 0° C, quenched with aqueous saturated NH_4Cl (6 mL) and. transferred to a separatory funnel containing ether (25 mL).

The layers were separated and the organic layer was washed with 10% HCl (6 mL), saturated $NaHCO_3$ (2 X 6 mL), and brine (6 mL) prior to drying, filtering and concentration. The remaining oil was purified by flash chromatography (15 % ethyl acetate/petroleum ether) to yield the enol phosphate **100** as a colourless oil (0.2384 g, 81 %); IR (neat) 3510, 2947, 1721, 1576, 1285, 1206, 1042 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.03 (d, 3 H, J = 7.0 Hz), 1.19, (t, 3 H, J = 7.2 Hz), 1.92 (t, 6 H, J = 7.1 Hz), 1.40-1.60 (m, 1 H), 1.68 (s, 3 H), 2.01-2.38 (m, 3 H), 2.42-2.67 (m, 1 H), 4.00-4.30 (m, 6 H), 5.88 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 9.82, 14.19, 15.91, 16.57, 22.67, 38.91, 41.76, 60.43, 64.51, 68.75, 111.76, 127.88, 151.82, 152.43, 169.88; HRMS (EI) calc for $C_{17}H_{27}O_6P$ 358.1546, found 358.1535.

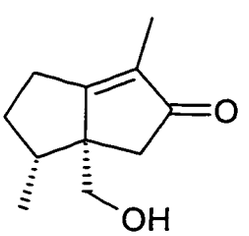
Ethyl (3S,3aS)-3,6-dimethyl-5-{(Z)-2-[toluenesulfonyl]hydrazono}-1,2,3,3a,4, 5-hexahydro-3a-pentalenecarboxylate (**101**)



The keto-ester **81** (50 mg, 0.225 mmol) and tosyl hydrazone (51.5 mg, 0.277 mmol) were dissolved in dry methanol (1.5 mL). The reaction was catalyzed by the addition of boron trifluoride diethyletherate (2 drops from a 50 μL syringe). The reaction was allowed to stir at 21°C for one hour. TLC (30 % ethyl acetate/petroleum ether) showed minor product spots. The reaction was then heated to 40° C with an oil bath for 4 hours. The reaction was recooled to 21°C and was diluted with CH_2Cl_2 (3 mL). The resulting solution was dried (anhydrous $MgSO_4$), filtered, and concentrated . The residual oil was purified by flash chromatography (30 % ethyl acetate/petroleum ether) to give the

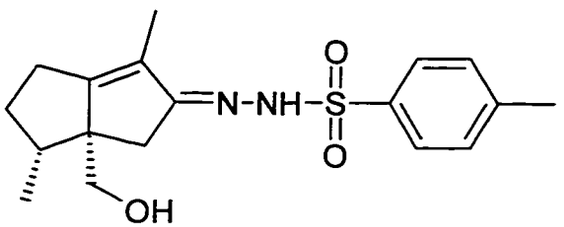
desired hydrazone **101** (75 mg, 85 %) as a thick yellow oil; IR (neat) 3213.75, 2953.32, 1720, 1625, 1342, 1171 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.97 (d, 3 H, J = 6.6 Hz), 1.21 (t, 3 H, J = 7.1 Hz), 1.54-2.15 (m, 3 H), 1.65 (s, 3 H), 2.10 (d, 1 H, J = 17.0 Hz), 2.27-2.73 (m, 2 H), 2.39 (s, 3 H), 3.15 (d, 1 H, J = 17.0 Hz), 3.99-4.25 (m, 2 H), 7.09 (s, 1 H), 7.27 (d, 2 H, J = 8.1 Hz), 7.84 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 9.76, 14.11, 15.18, 21.48, 24.37, 33.94, 44.05, 60.80, 64.61, 128.04, 129.25, 130.22, 135.27, 143.68, 163.29, 167.39, 172.12.

(6S,6aS)-6a-(Hydroxymethyl)-3,6-dimethyl-1,2,4,5,6,6a-hexahydro-2-pentaienone (**102**)



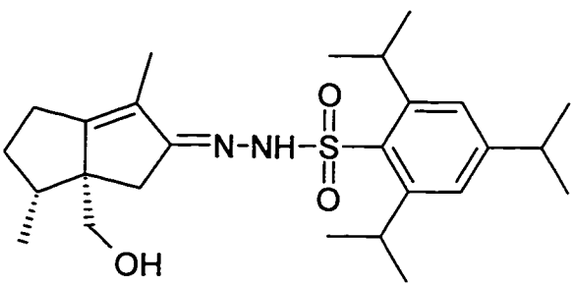
The diol **72** (108.7 mg, 0.596 mmol) was dissolved in dry ether (6 mL). Freshly prepared activated MnO_2[30] (1.087 mg) was added to the reaction solution. The suspension was stirred vigorously for 30 minutes. The reaction was filtered through Celite®, and the filter washed thoroughly with ether (200 mL). The filtrate was concentrated and the residual oil purified by flash chromatography to yield the desired ketone-alcohol **102** (100.3 mg, 93.4 %) as a colourless oil; IR (neat) 3391, 2918, 1671, 1056 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ: 1.00 (d, 3 H, J = 6.6 Hz), 1.61 (s, 3 H), 1.64-2.15 (m, 3 H), 1.94 (d, 1 H, J = 17.4), 2.35-2.86 (m, 3 H), 2.45 (d, 2 H, J = 17.3 Hz), 3.54 (d, 2 H, J = 2.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 8.5, 14.0, 24.3, 32.4, 41.5, 45.5, 55.9, 62.4, 133.6, 182.9, 210.5; $[\alpha]_D^{26.8}$ +36.5 (c 24.0, $CHCl_3$).

N'1-[(6S,6aS)-6a-(Hydroxymethyl)-3,6-dimethyl-1,2,4,5,6,6a-hexahydro-2-pentalenyliden]-toluenesulfonohydrazide (**103**)



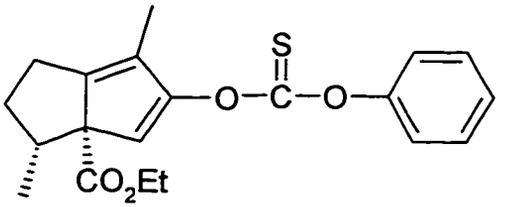
The keto-alcohol **102** (50 mg, 0.277 mmol) and tosyl hydrazone (63.4 mg, 0.340 mmol) were dissolved in dry methanol (1.5 mL). The reaction was catalyzed by the addition of boron trifluoride diethyletherate (2 drops from a 50 μL syringe). The reaction was then stirred at 40° C with an oil bath for 4 hours. The reaction was cooled to 21° C and diluted with CH_2Cl_2 (3 mL). The resulting solution was dried (anhydrous $MgSO_4$), filtered, and concentrated . The residual oil was purified by flash chromatography (40 % ethyl acetate/petroleum ether) to give the desired hydrazone **103** (74.6 mg, 77 %) as a white solid; mp 150-151 °C (dec.); IR (neat) 3429, 2936, 1613, 1597, 1445, 1149 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.96 (d, 3 H, J = 6.6 Hz), 1.54-2.15 (m, 3 H), 1.68 (s, 3 H), 2.03 (d, 1 H, J = 16.8 Hz), 2.25-2.60 (m, 2 H), 2.39 (s, 3 H), 2.58 (d, 1 H, J = 16.9 Hz), 3.49 (s, 2 H), 7.26 (d, 2 H, J = 8.8 Hz), 7.83 (d, 2 H, J = 8.2 Hz); ^{13}C NMR (50 MHz, CD_3OD) δ: 9.91, 14.25, 21.48, 23.56, 34.50, 36.98, 42.84, 60.00, 63.33, 129.07, 130.25, 137.47, 144.91, 150.02, 167.94, 171.60; FABH accurate (MH^+) calc for $C_{18}H_{25}N_2O_3S$ 349.1586, found 349.156; $[\alpha]_D^{28.0}$ -28.0 (c 7.6, MeOH).

N'1-[(6S,6aS)-6a-(Hydroxymethyl)-3,6-dimethyl-1,2,4,5,6,6a-hexahydro-2-pentalenyliden]-2,4,6-triisopropyl-1-benzenesulfonohydrazide (**104**)



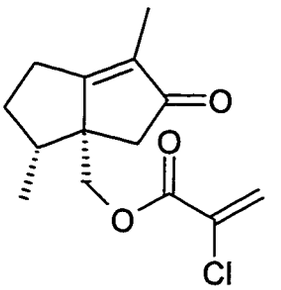
The keto-alcohol **102** (15 mg, 0.083 mmol) was dissolved in dry acetonitrile (1 mL) and 2,4,6-triisopropylbenzenesulfonylhydrazide (27 mg, 0.092 mmol) plus concentrated HCl (10 μL) were added to the stirring solution. The mixture was stirred overnight. The stirring bar was removed and the reaction concentrated. The resulting oil was purified twice by flash chromatography (75 % ethyl acetate/petroleum ether, then 30 % ethyl acetate/petroleum ether) to yield the desired hydrazone **104** (28.2 mg, 73.5 %) as a thick yellow oil; IR (neat) 3425, 2929, 2361, 1732, 1605, 1169 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.97 (d, 3 H, J = 6.5 Hz), 1.19-1.48 (m, 18 H), 1.54-2.15 (m, 3 H), 1.64 (s, 3 H), 2.03 (d, 1 H, J = 16.7 Hz), 2.25-2.42 (m, 2 H), 2.58 (d, 1 H, J = 16.5 Hz), 2.80-2.98 (m, 1 H), 3.49 (s, 2 H),4.02-4.30 (m, 2 H), 7.13 (s, 2 H); FABH accurate (MH^+) calc for $C_{26}H_{41}N_2O_3S$ 461.2838, found 461.2549 .

Ethyl (3S,3aS)-3,6-dimethyl-5-[(phenoxycarbothioyl)oxy]-1,2,3,3a-tetrahydro-3a-pentalenecarboxylate (**108**)



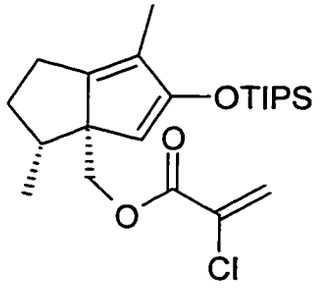
The LDA needed for this experiment was prepared by adding n-butyllithium (2.5 M in hexanes, 94 μL, 0.23 mmol) to a solution of diisopropylamine (33 μL, 0.25 mmol) in THF (1.5 mL) at 0 °C. The solution was allowed to stir for 30 minutes at 0 °C and was then cooled to -78 °C. The keto-ester **81** (40 mg, 0.18 mmol) in THF (0.5 mL) was added dropwise. The reaction was stirred at -78 °C for 30 minutes and then phenyl chlorothionoformate (37 μL, 0.27 mmol) and TMEDA (23 μL) were added sequentially to the reaction. The reaction was allowed to warm to 21°C overnight. The reaction was quenched with an saturated aqueous solution of NH_4Cl (2 mL) at 0 °C. The mixture was added to a separatory funnel containing ether (15 mL). The layers were separated and the organic layer was washed with 10 % HCl (2 mL), saturated $NaHCO_3$ (2 mL), and brine (2 mL). The organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting oil was purified by chromatography (2 % ethyl acetate/petroleum ether) to give desired product **108** as a yellow oil (10 mg, 15 %). IR (neat) 2948, 1723, 1588, 1197 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.12 (d, 3 H, J = 6.8), 1.24 (t, 3 H, J = 7.1 Hz), 1.55-1.78 (m, 1 H), 1.78 (s, 3 H), 2.13-2.38 (m, 3 H), 2.55-2.70 (m, 1 H), 4.14 (q, 2 H, J = 7.1 Hz), 6.15 (s, 1 H), 7.14 (d, 2 H, J = 8.3 Hz), 7.29 (t, 1 H, J = 8.1 Hz), 7.43 (t, 2 H, J = 8.1, 8.3 Hz) HRMS (EI) calc for $C_{20}H_{22}O_4S$ 358.1239, found 358.1213.

[(3S,3aS)-3,6-Dimethyl-5-oxo-1,2,3,3a,4,5-hexahydro-3-pentalenyl]methyl 2-chloroacrylate (**109**)

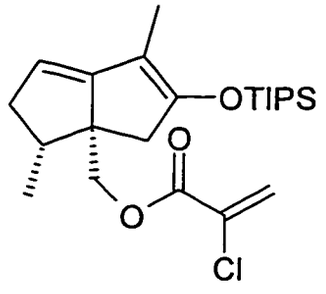


The dienophile-alcohol **71** (111.9 mg, 0.413 mmol) was dissolved in dry diethyl ether (10 mL). Manganese dioxide (activated) (1.12 g) was added to the stirred solution. After 1 hour the suspension was filtered through a Celite® bed, and the bed washed thoroughly with ether. The filtrate was concentrated and the resulting oil was purified by flash chromatography (35 % ethyl acetate/petroleum ether) to give the desired ketone **109** (95.5 mg, 86.0%) as a thick oil; IR (neat) 3120, 2928, 1721, 1609, 1263, 1114 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ: 1,10 (d, 3 H, J = 6.6 Hz), 1.65 (s, 3 H), 1.70-1.98 (m, 2 H), 2.04-2.25 (m, 1H), 2.12 (d, 1 H, J = 17.4 Hz), 2.47-2.74 (m, 2 H), 2.49 (d, 1 H, 17.2 Hz), 4.07 (d, 1 H, J = 11.0 Hz), 4.34 (d, 1 H, J = 11.0 Hz), 5.96 (d, 1 H, J = 1.7 Hz), 6.33 (d, 1 H, J = 1.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 8.4, 14.3, 24.3, 32.4, 41.9, 45.7, 53.9, 66.0, 126.3, 130.9,131.3, 161.7, 180.8, 208.7; HRMS (EI) calc for $C_{14}H_{17}O_3Cl$ 268.0867, found 268.0883.

{(3S,3aS)-3,6-Dimethyl-5-[(1,1,1-triisopropyl)oxy]-1,2,3,3a-tetrahydo-3-pentalenyl}methyl 2-chloroacrylate (**110**) and {(3S,3aS)-3,6-dimethyl-5-[(1,1,1-triisopropyl)oxy]-2,3,3a,4-tetrahydo-3-pentalenyl}methyl 2-chloroacrylate (**111**)



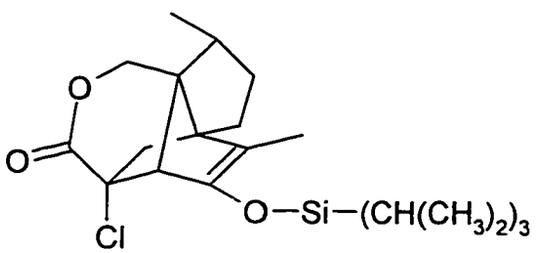
110



111

Collidine (47 μL, 0.35 mmol) and triisopropyltrifluoromethanesulfonate (63 μL, 0.23 mmol) were sequentially added to a stirred solution of the dienophile-ketone **109** (31.3 mg, 0.12 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C. The reaction was stirred at this temperature for 6 hours. The reaction was quenched by adding saturated $NaHCO_3$ solution (4 mL) and poured into a separatory funnel containing ether (20 mL). The layers were separated and the organic layer was washed with saturated $NaHCO_3$ (5 mL), brine (2 x 10 mL), dried (anhydrous $MgSO_4$), filtered, and concentrated. The resulting oil was purified by gravity chromatography (basic alumina, 4 % ethyl acetate in petroleum ether) to yield a 3:1 mixture of the dienes **110** and **111** (22.7 mg, 73.7 %) and recovered dienophile-ketone **109** (10 mg). Note: This compound was extremely unstable and was stored by freezing in benzene. Any trace of acid would cleave the TIPS group. The mixture was used as is for the Diels-Alder reaction. Note: Complete characterization was not carried out. The mixture of dienes was highly unstable, so the compound was only analyzed by ^1H NMR. Because no 2-D NMR experiments were performed, it was impossible to assign the peaks. Please refer to the spectrum of the mixture in the Appendix. As can be seen, the singlet at 5.30 ppm was due to the hydrogen of the diene **110**, while the triplet at 5.18 was due to the diene hydrogen of **111**.

(4S)-9-chloro-4,12-dimethyl-11-[(1,1,1-triisopropylsilyl)oxy]-7-oxatetracyclo [7.3.1.$0^{1,5}$.$0^{5,10}$]tridec-11-en-8-one (**112**)



An approximately one to one mixture of the diene-dienophiles **110** and **111** (22.7 mg, 0.058 mmol) and hydroquinone (1.5 mg, 0.014 mmol) were dissolved in dry benzene (13 mL). The mixture was stirred for 1 day at reflux temperature. The reaction was concentrated under vacuum and the remaining oil purified by flash chromatography (10 % ethyl acetate/petroleum ether) to yield the desired Diels-Alder adduct **112** (7.3 mg, 64 %) along with the unwanted diene-dienophile **111** and a trace amount of dienophile ketone **109**; IR (neat) 2945, 2868, 1759, 1673, 1330, 1236 cm^{-1}; ^1H NMR (500 MHz,C_6D_6) δ: 0.49 (d, 3 H, J = 7.2 Hz), 0.90-1.13 (m, 23 H), 1.29-1.40 (m, 1 H) 1.44 (s, 3 H), 1.49 (d, 1 H, J = 12.8 Hz), 1.70-1.77 (m, 1 H), 1.95 (d, 1 H, J = 12.8 Hz), 2.38-2.43 (m, 1 H), 2.72 (s, 1 H), 3.44 (d, 1 H, J = 12.8 Hz), 3.85 (d, 1 H, J = 12.8 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ: 7.65, 13.04, 15.16, 17.93, 17.99, 21.84, 30.16, 31.33, 37.41, 45.00, 56.17, 67.07, 67.39, 76.10, 120.01, 147.01, 169.69; HRMS (EI) calc for $C_{23}H_{37}O_3SiCl$ 424.2202, found 424.2202; $[\alpha]_D^{27.8}$ -1.0 (c 3.2, $CHCl_3$).

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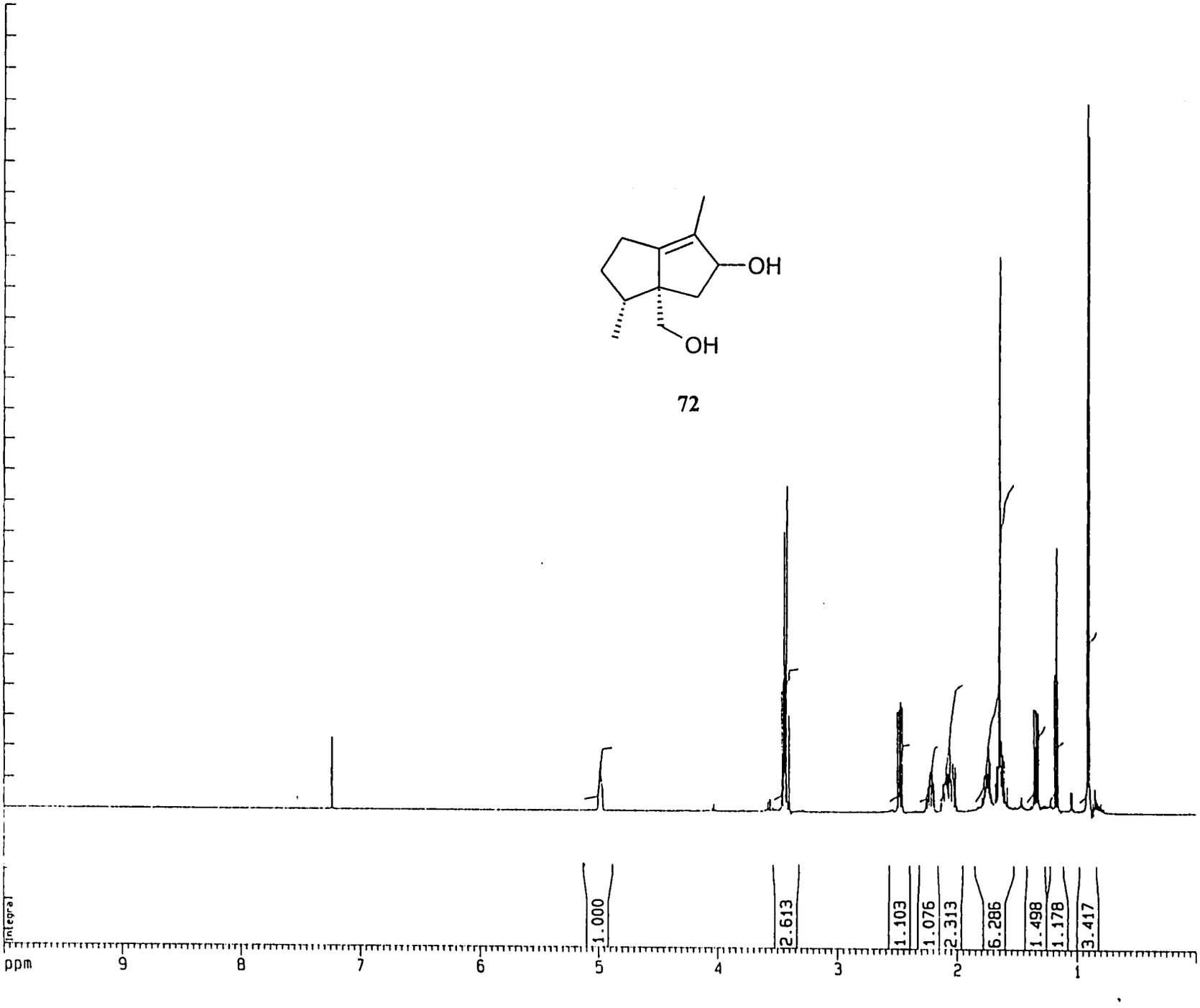
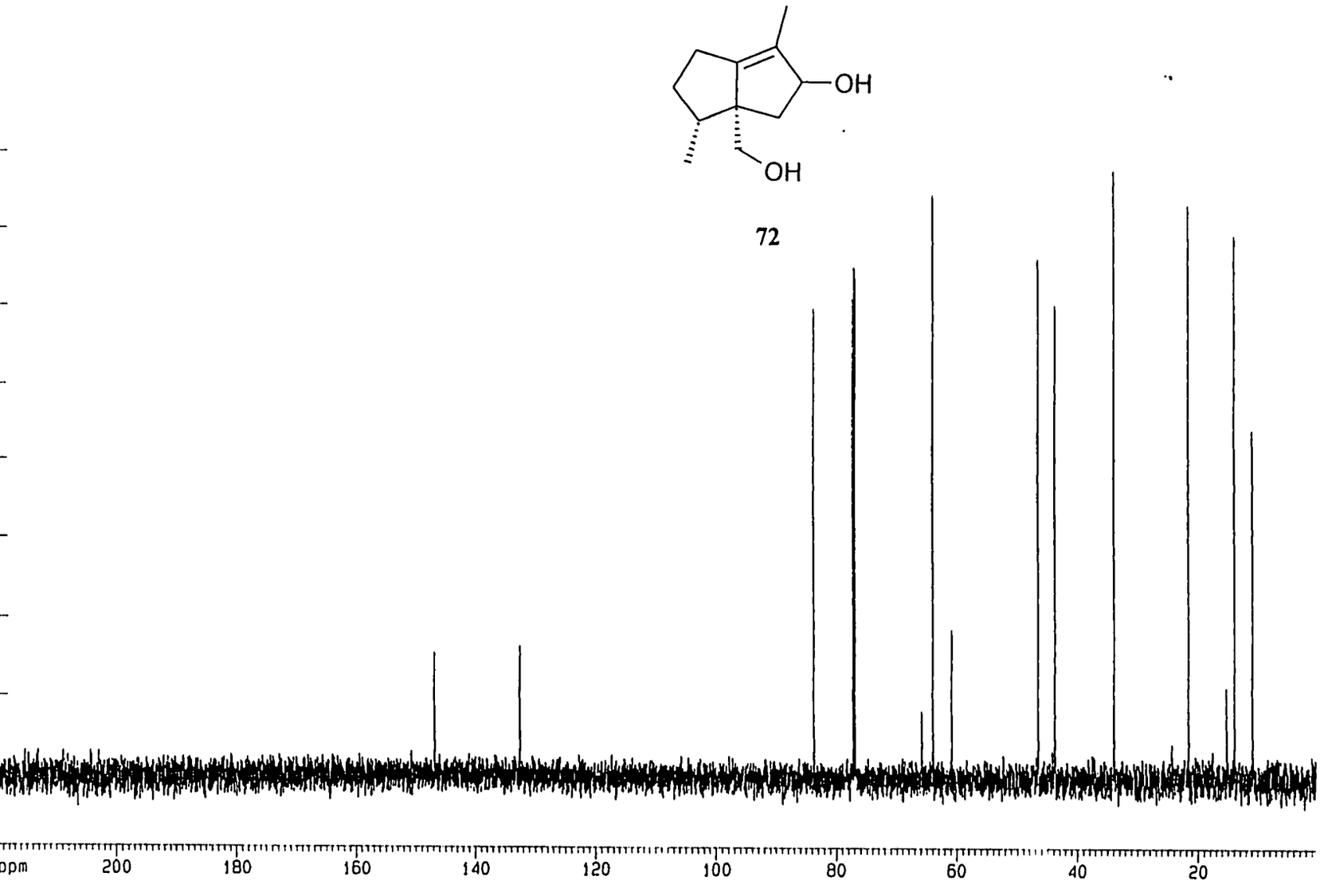
APPENDIX I

REPRODUCTION OF THE ORIGINAL SPECTRA OF SOME KEY COMPOUNDS DESCRIBED IN THIS THESIS

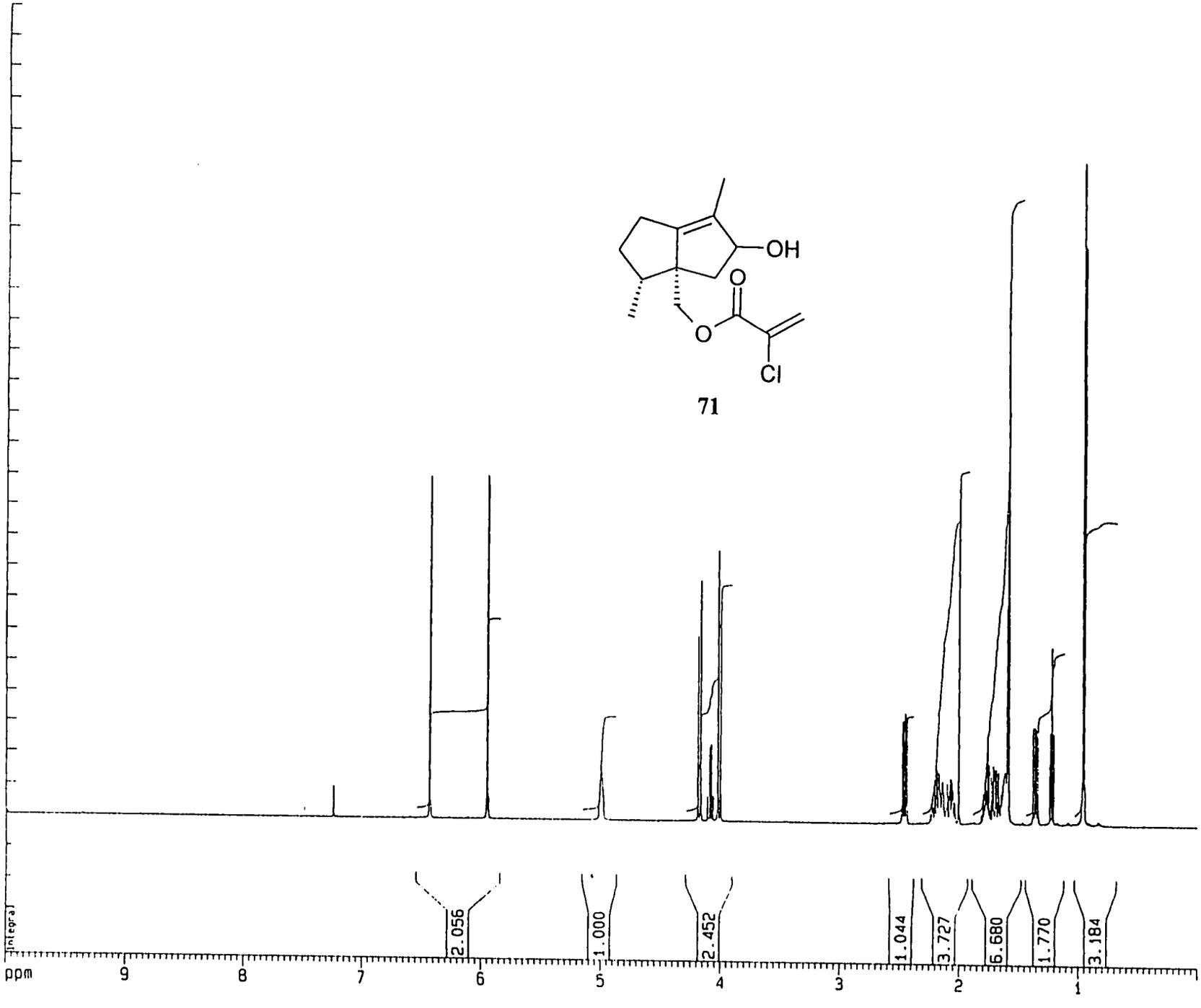


^{1}H NMR Spectrum ($CDCl_3$, 500 MHz) of **72**

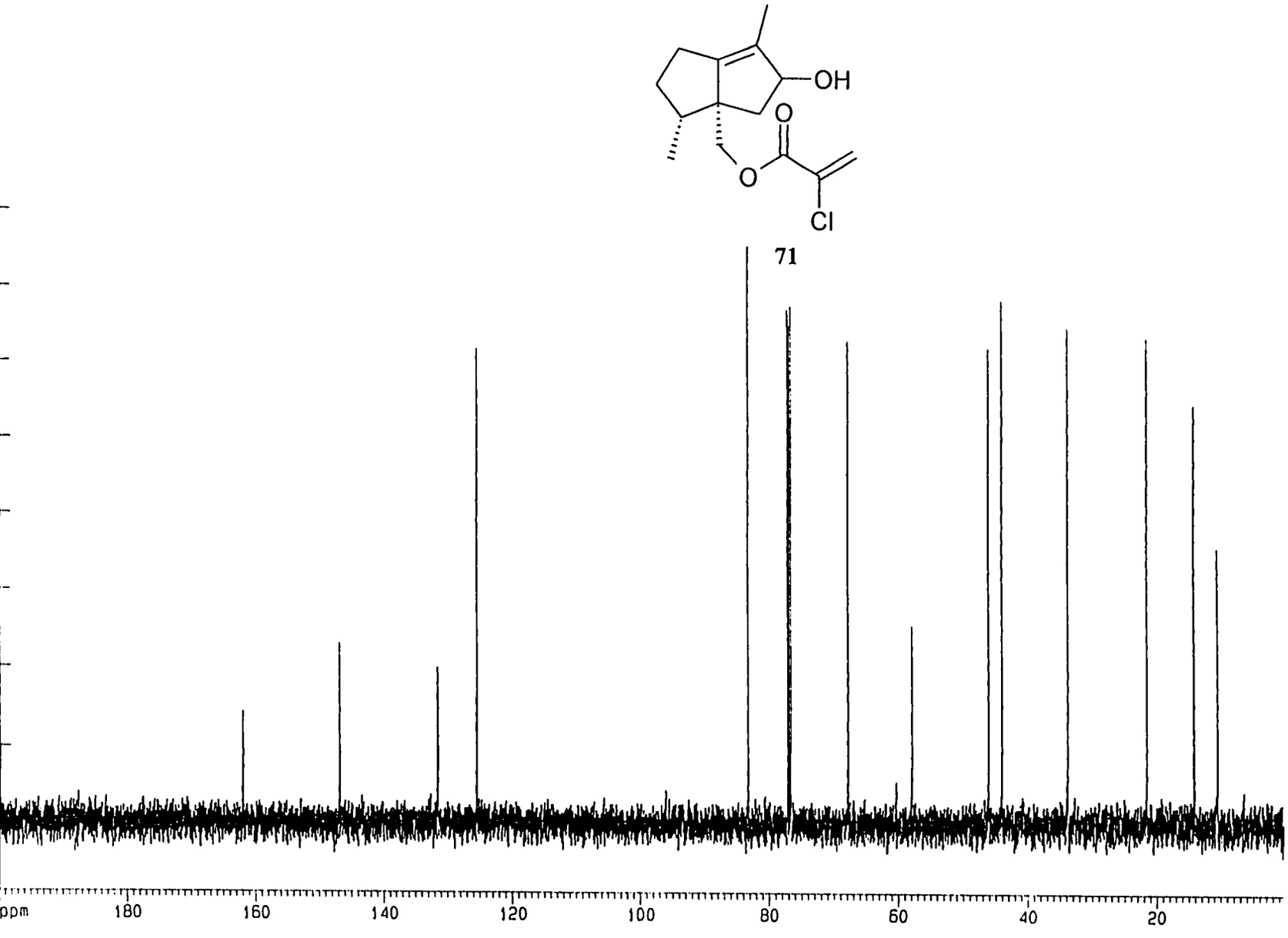


72

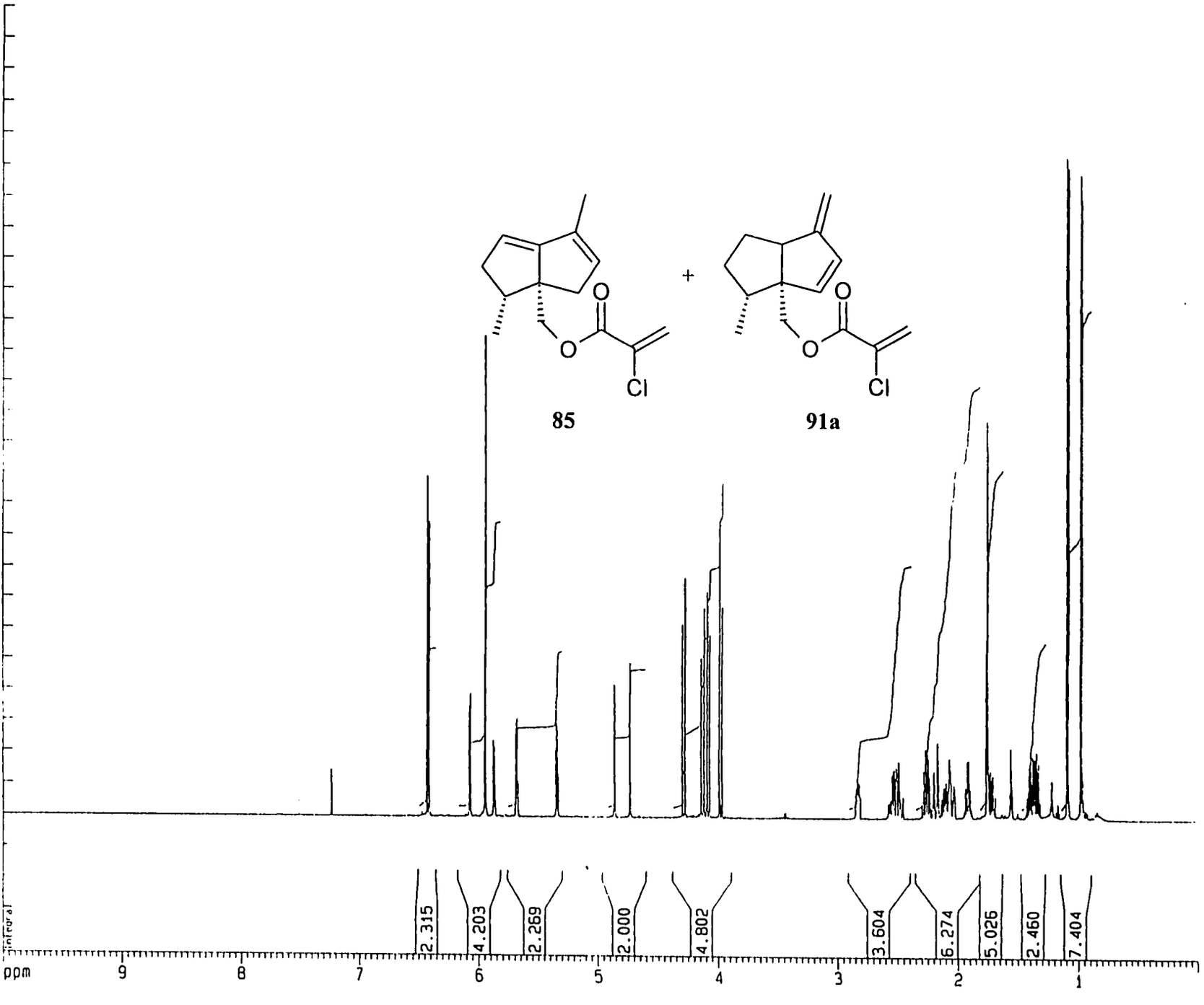
^{13}C NMR Spectrum ($CDCl_3$, 125 MHz) of **72**



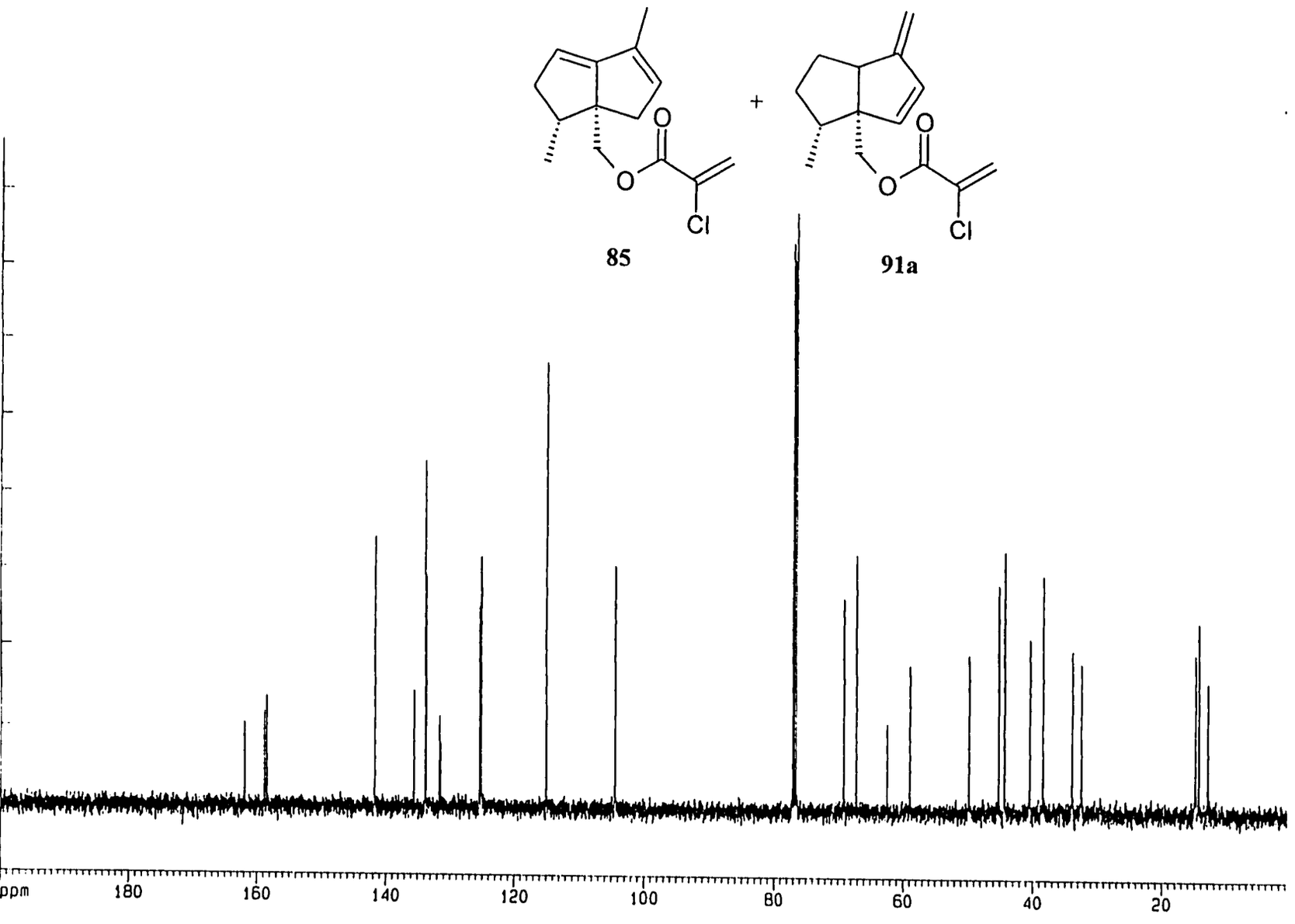
^{1}H NMR Spectrum ($CDCl_3$, 500 MHz) of **71**



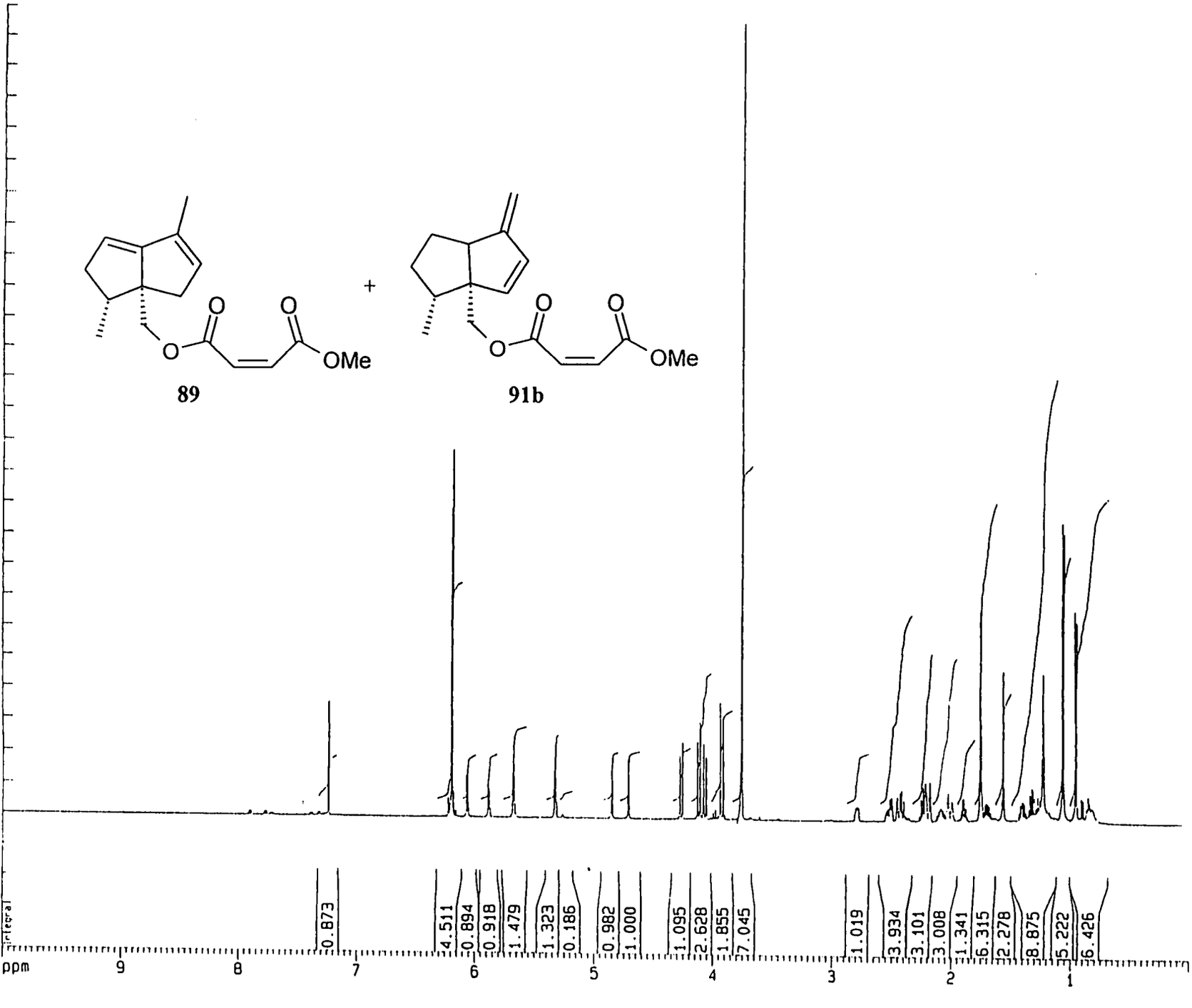
^{13}C NMR Spectrum ($CDCl_3$, 125 MHz) of **71**



^{1}H NMR Spectrum ($CDCl_3$, 500 MHz) of **85** and **91a**

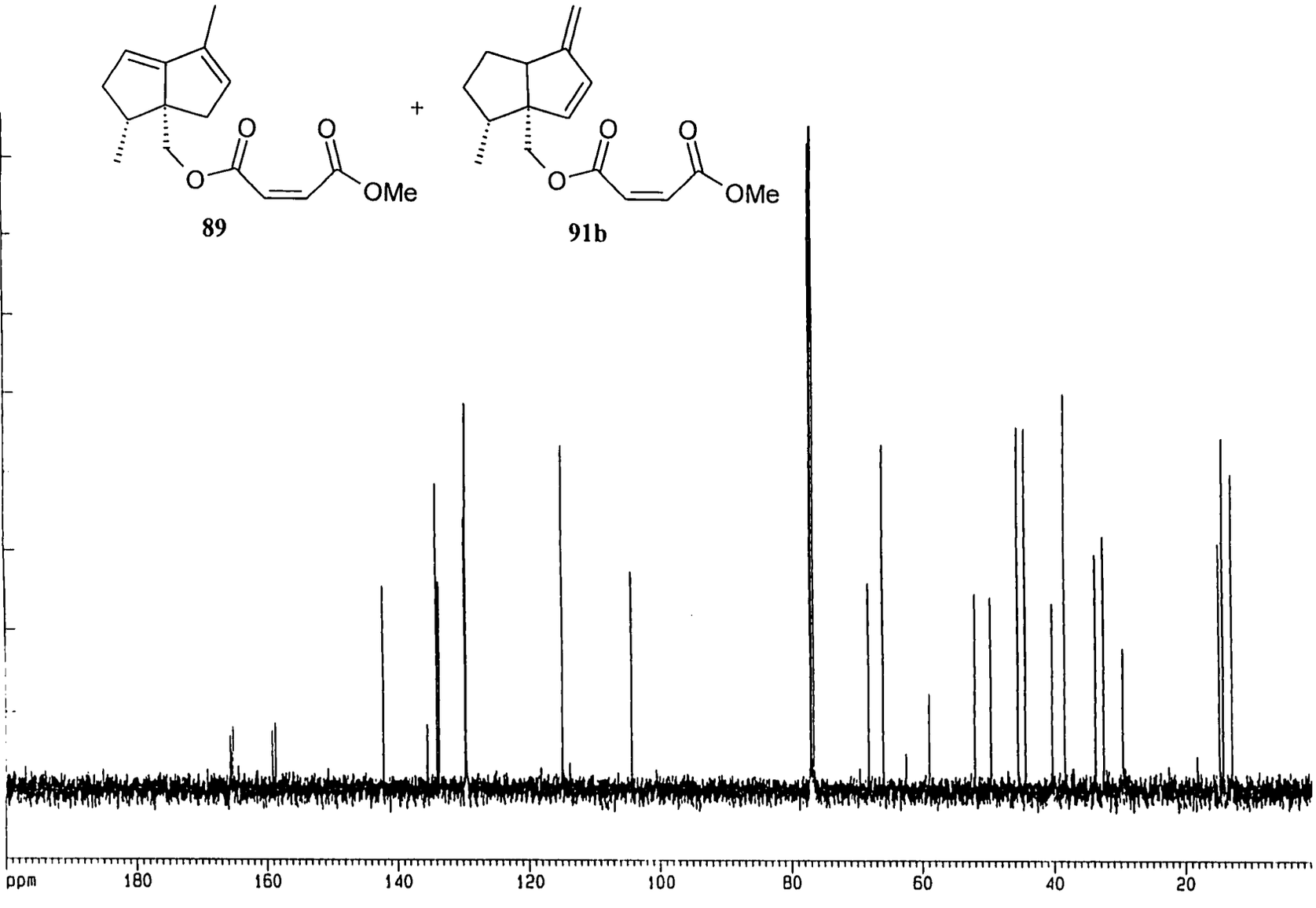


^{13}C NMR Spectrum ($CDCl_3$, 125 MHz) of **85** and **91a**

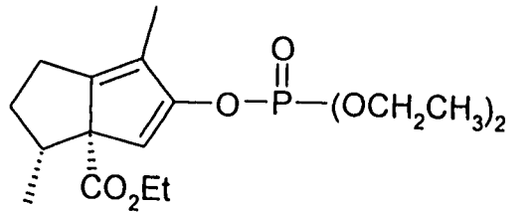


89 **91b**

^{1}H NMR Spectrum ($CDCl_3$, 500 MHz) of **89** and **91b**

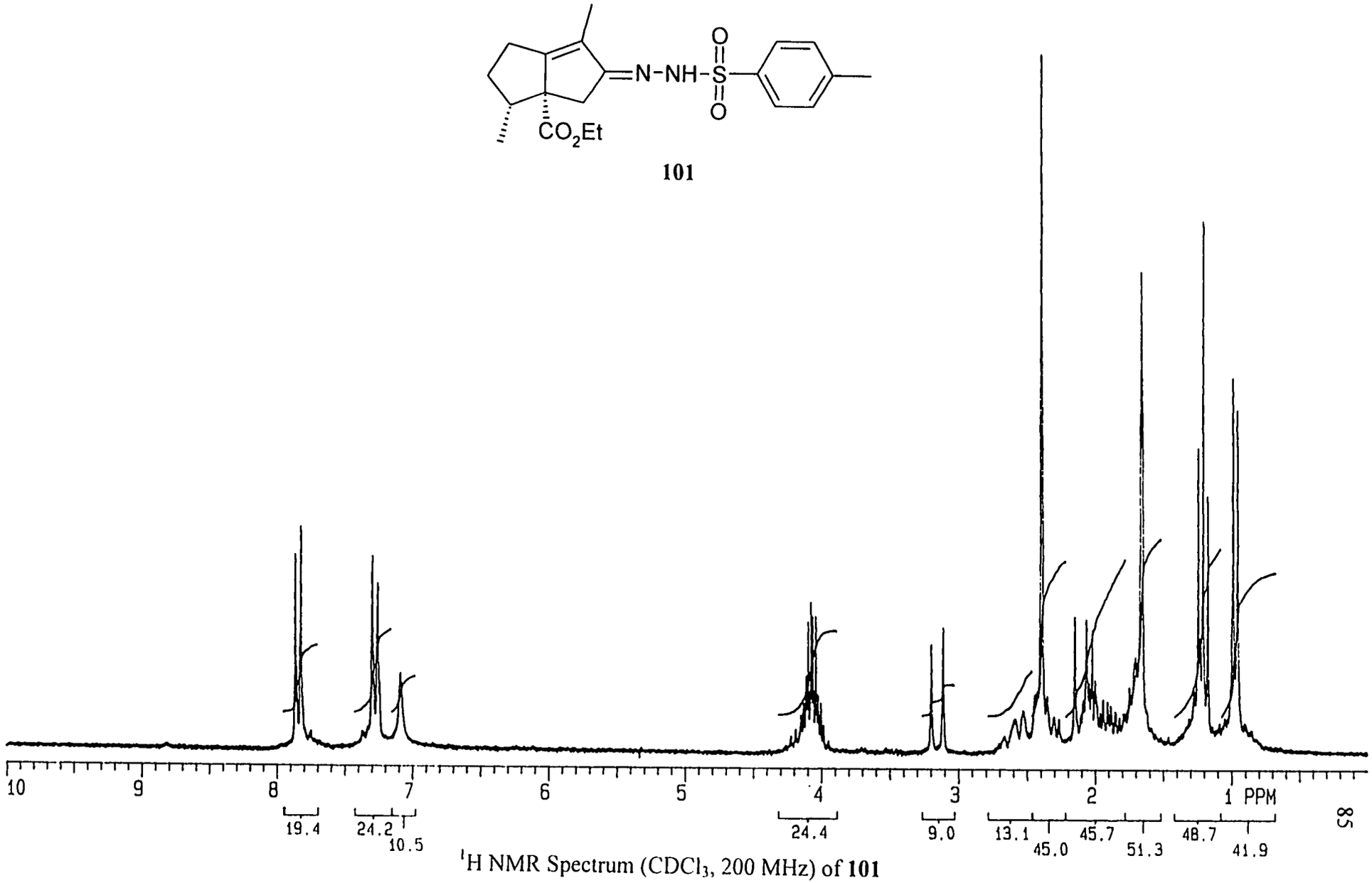


^{13}C NMR Spectrum ($CDCl_3$, 125 MHz) of **89** and **91b**



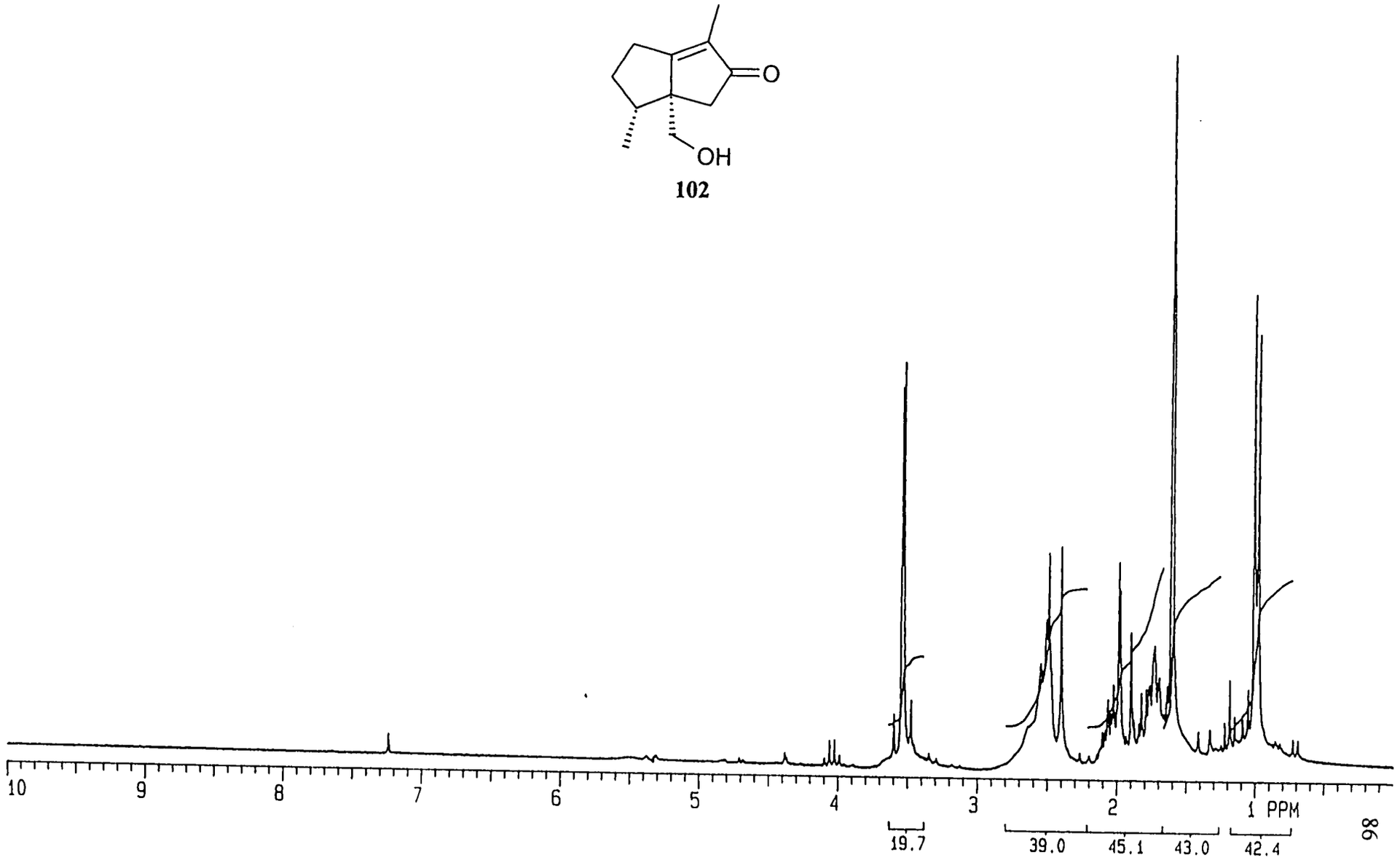
100

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **100**



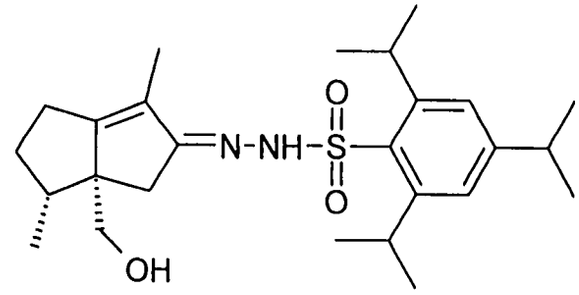
101

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **101**



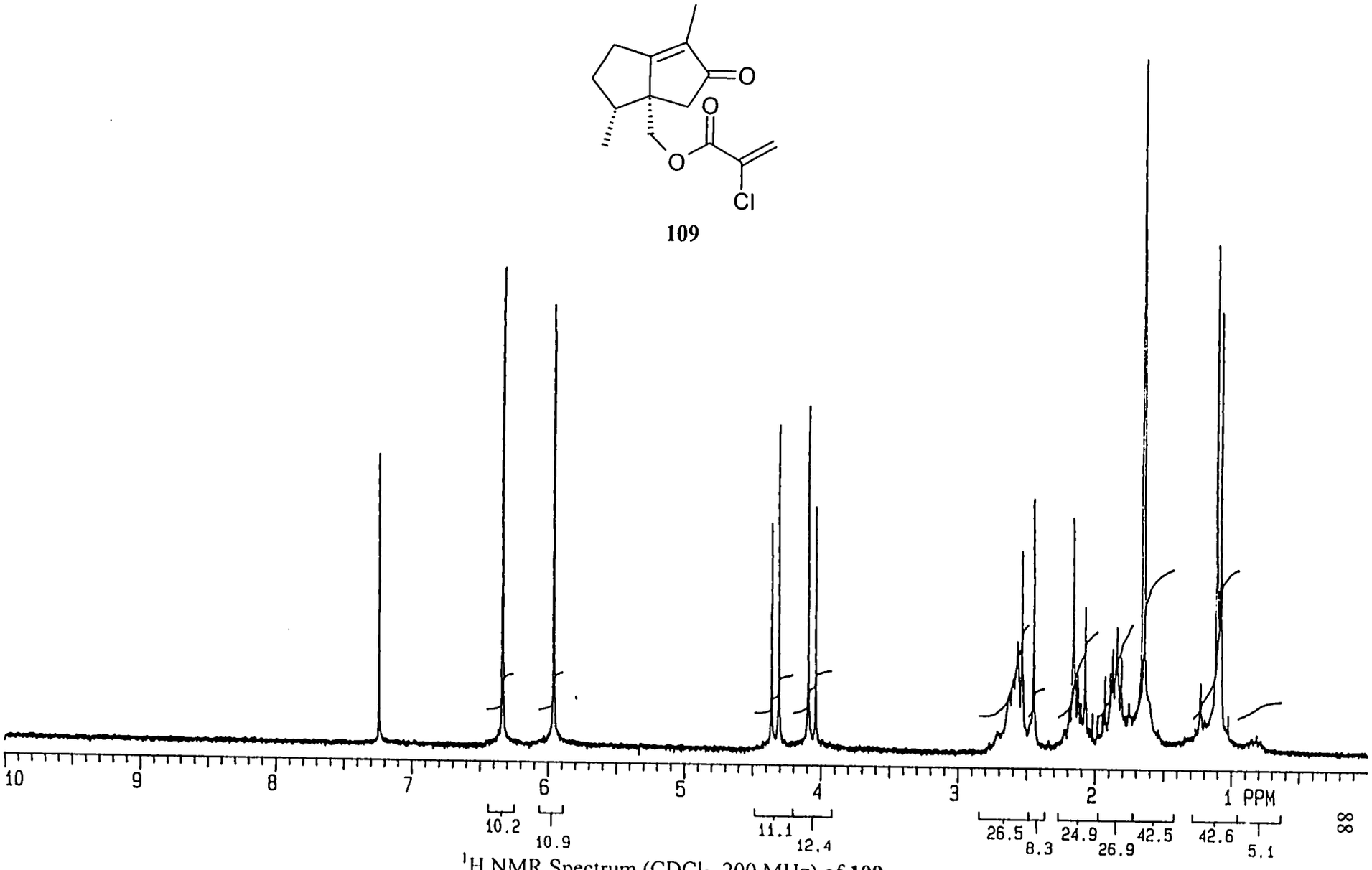
102

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **102**



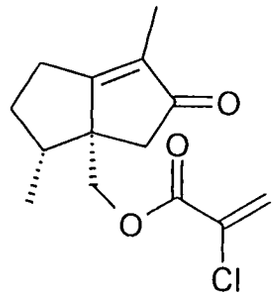
104

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **104**

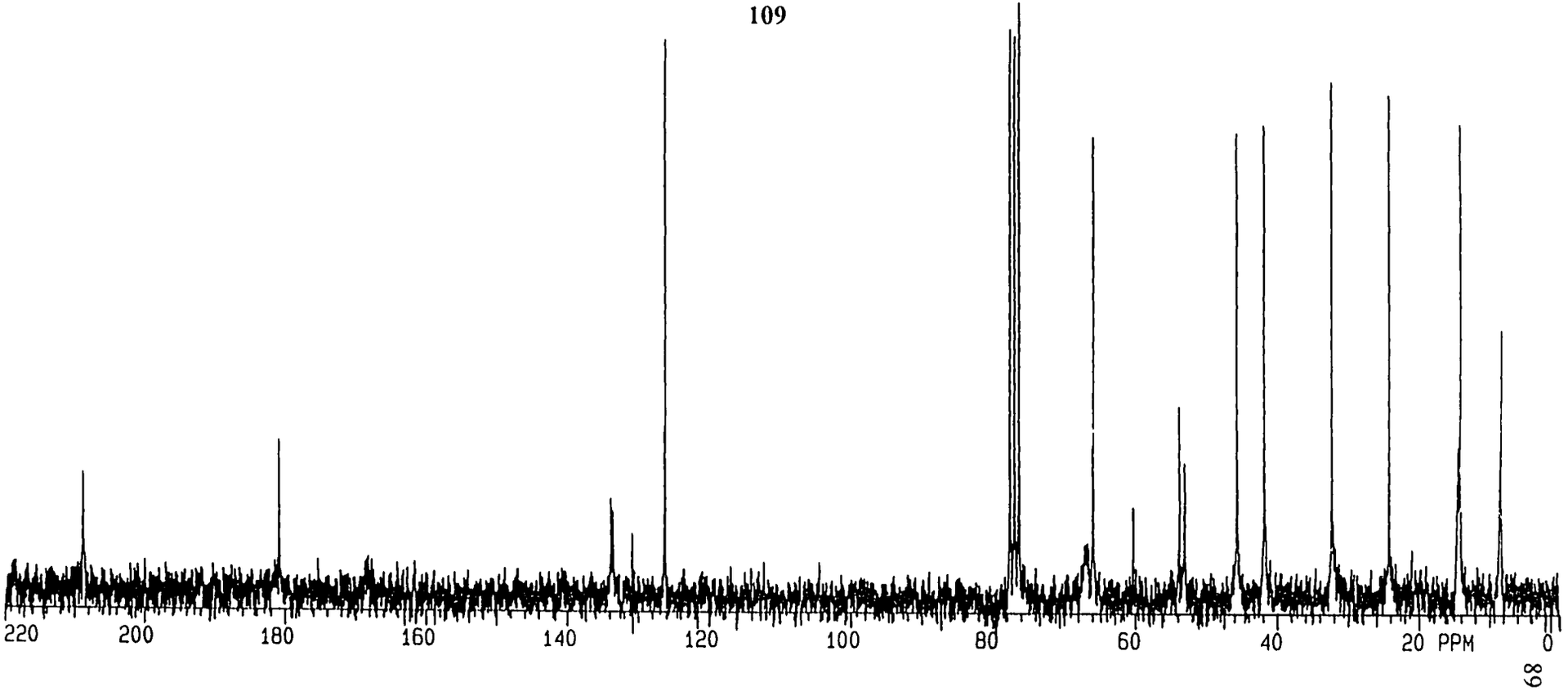


109

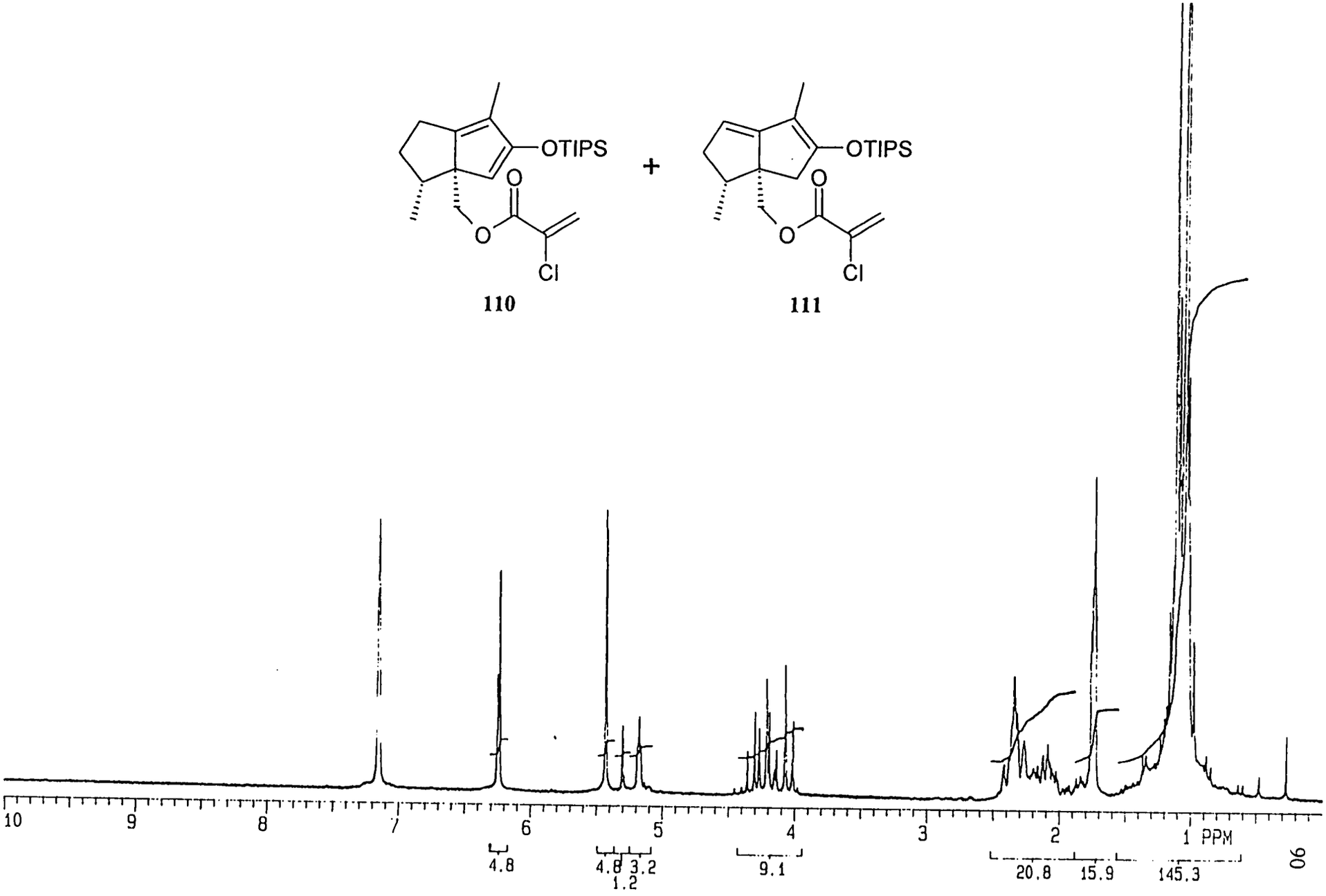
^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **109**



109

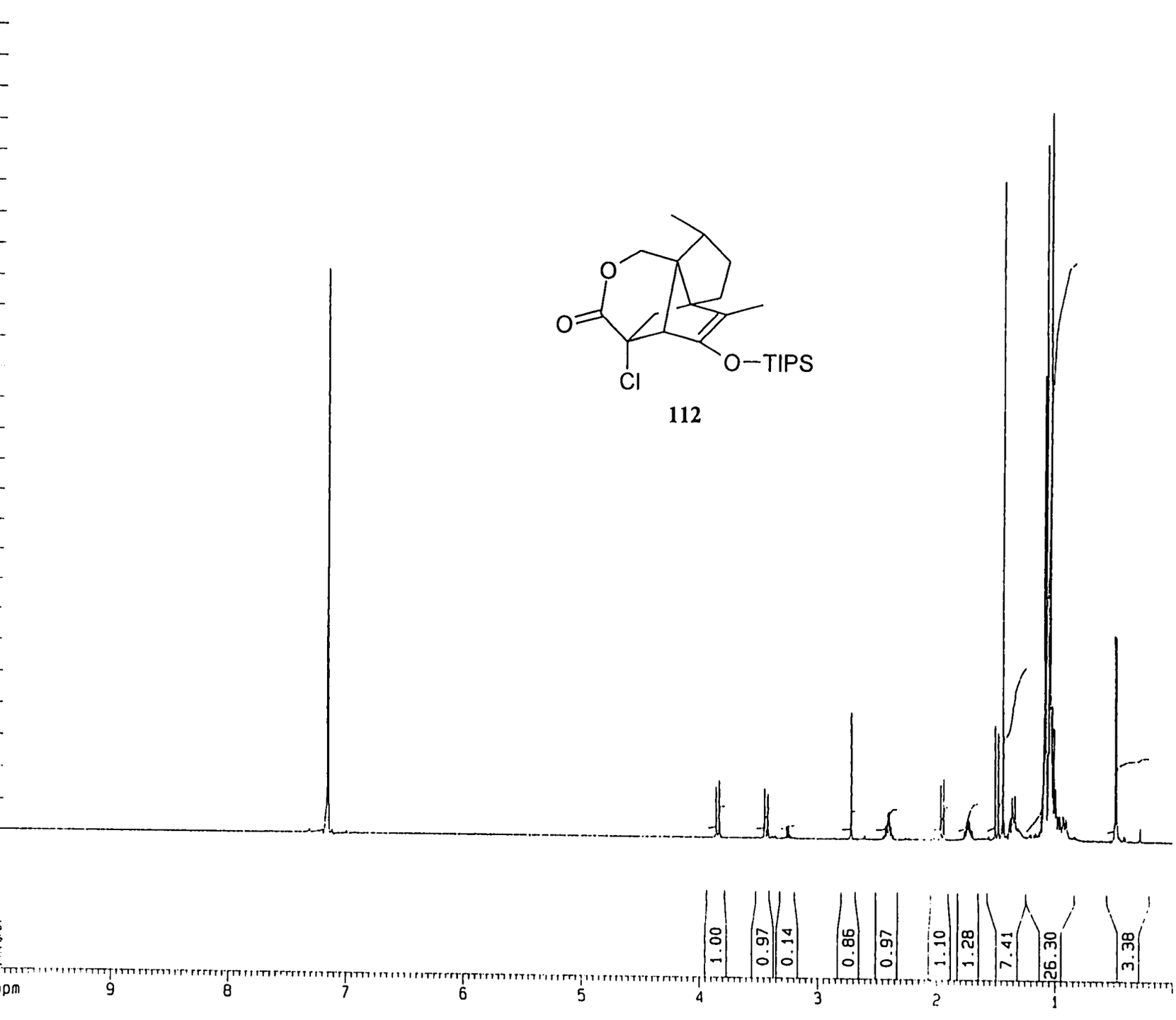


^{13}C NMR Spectrum ($CDCl_3$, 50 MHz) of **109**

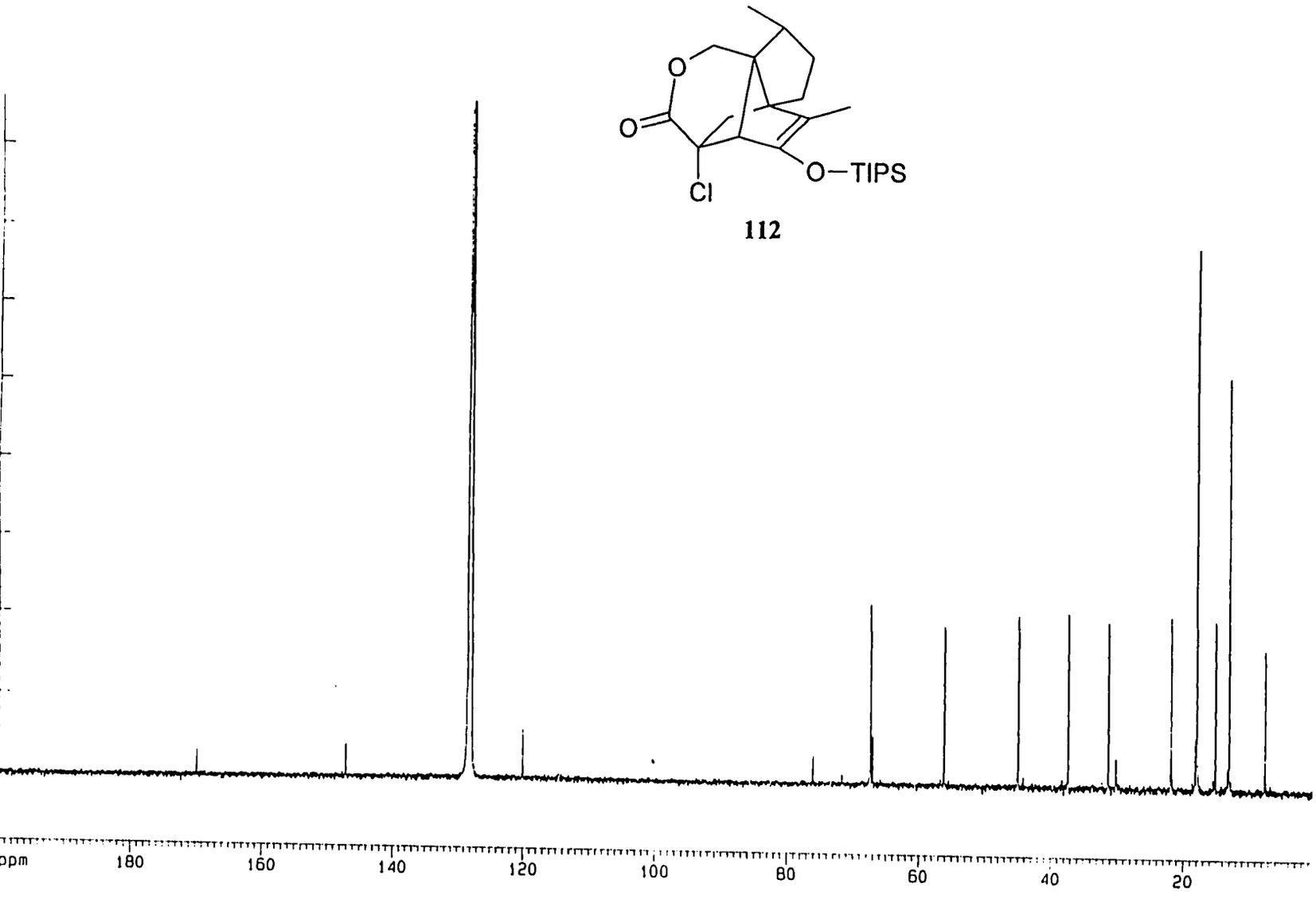


110 **111**

^{1}H NMR Spectrum (C_6D_6, 200 MHz) of **110** and **111**



^{1}H NMR Spectrum (C_6D_6, 500 MHz) of **112**



112

^{13}C NMR Spectrum (C_6D_6, 125 MHz) of **112**