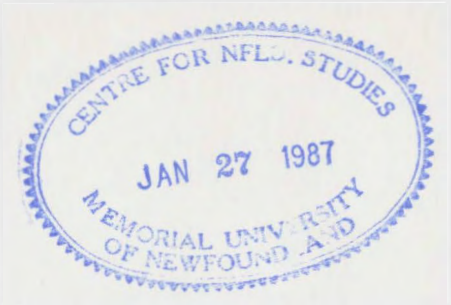
STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF LONGIFOLENE

RUDOLF ROBERT BUKOWNIK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STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF LONGIFOLENE

by

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A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

Department of Chemistry
Memorial University of Newfoundland
July 1984

St John's Newfoundland

Read not to contradict and confute, nor to believe and take for granted, nor to find talk and discorse; but to weigh and consider.

Bacon

Abstract

This thesis describes studies directed toward the total synthesis of longifolene utilising as a key step an intramolecular Diels-Alder cyclization. Different approaches for the construction of spiro[2.4]hepta-4,6-dienes have been explored and a general route involving the fulvene *63* developed. Nucleophilic addition of methlylithium to this fulvene generates a cyclopentadiene anion *in situ*, which closes to the requisite cyclopropane system by epoxide ring opening to afford *65* This cyclopentadiene unit will thus serve as the 'left-hand portion' for the approach to longifolene which is outlined. Procedures for the preparation and introduction of a suitable 'right-hand portion' have also been examined, these preliminary results have indicated the subtle blend of functionality and reactivity that will be required to generate the dienophilic unit. A suitable triene system *104* was synthesised (unfortunatly in low yield) but under the conditions examined the desired Diels-Alder cyclisation did not occur.

Acknowledgements

The author wishes to express his sincere gratitude to Samuel K. Attah-Poku for the many stimulating discussions which helped maintain his enthusiasm throughout this project; A.G. Fallis, whose guidance, enthusiasm and support permitted the completion of this project; his parents, Leo and Erna, for their unwavering faith and Memorial University of Newfoundland for financial support.

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CHAPTER 1

Introduction

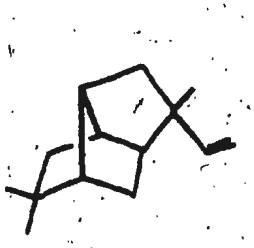
1. Structural elucidation

The first reported degradative investigations into the structure of longifolene were by Simonsen *et al*[1].

At that time they were able to identify the presence of vinyl, tertiary methyl and gem dimethyl groups. On the basis of its molecular formula, $C_{15}H_{24}$, application of the isoprene rule and the assumption that the structure contained only cyclopentane and cyclohexane rings, the following two structures *1* and *2* were postulated[2] (Chart I).

It was not until after the X-ray study of longifolene hydrochloride *3* by Moffet and Rogers[3] that the correct structure of longifolene was proposed by Ourisson and Naffa[4].

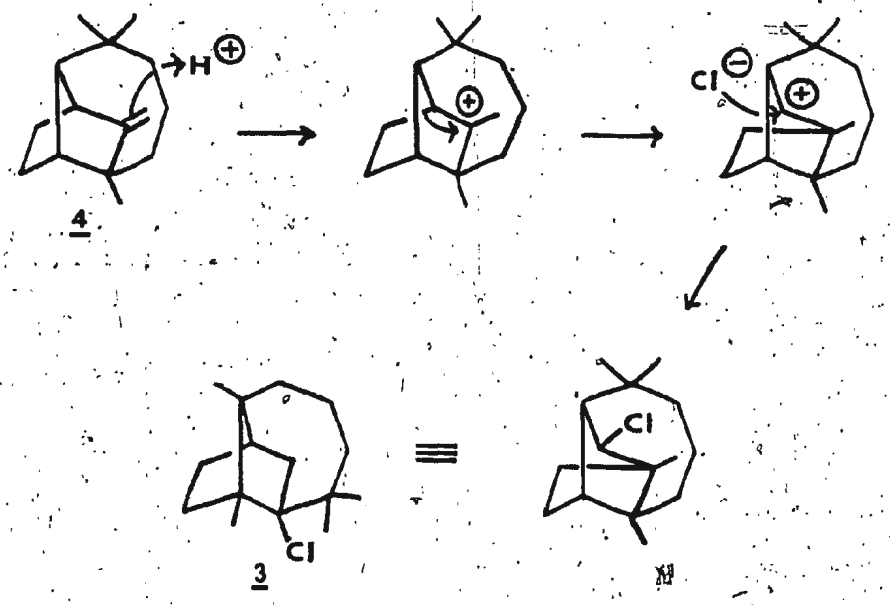
On the basis of the available chemical evidence, and the realization that upon treatment with hydrogen chloride, longifolene *4* undergoes a Wagner-Meerwein rearrangement to longifolene hydrochloride *5*, (1,2 shift, Scheme I), Ourisson arrived at the correct structure *4*.



1

2

Chart I



4 3

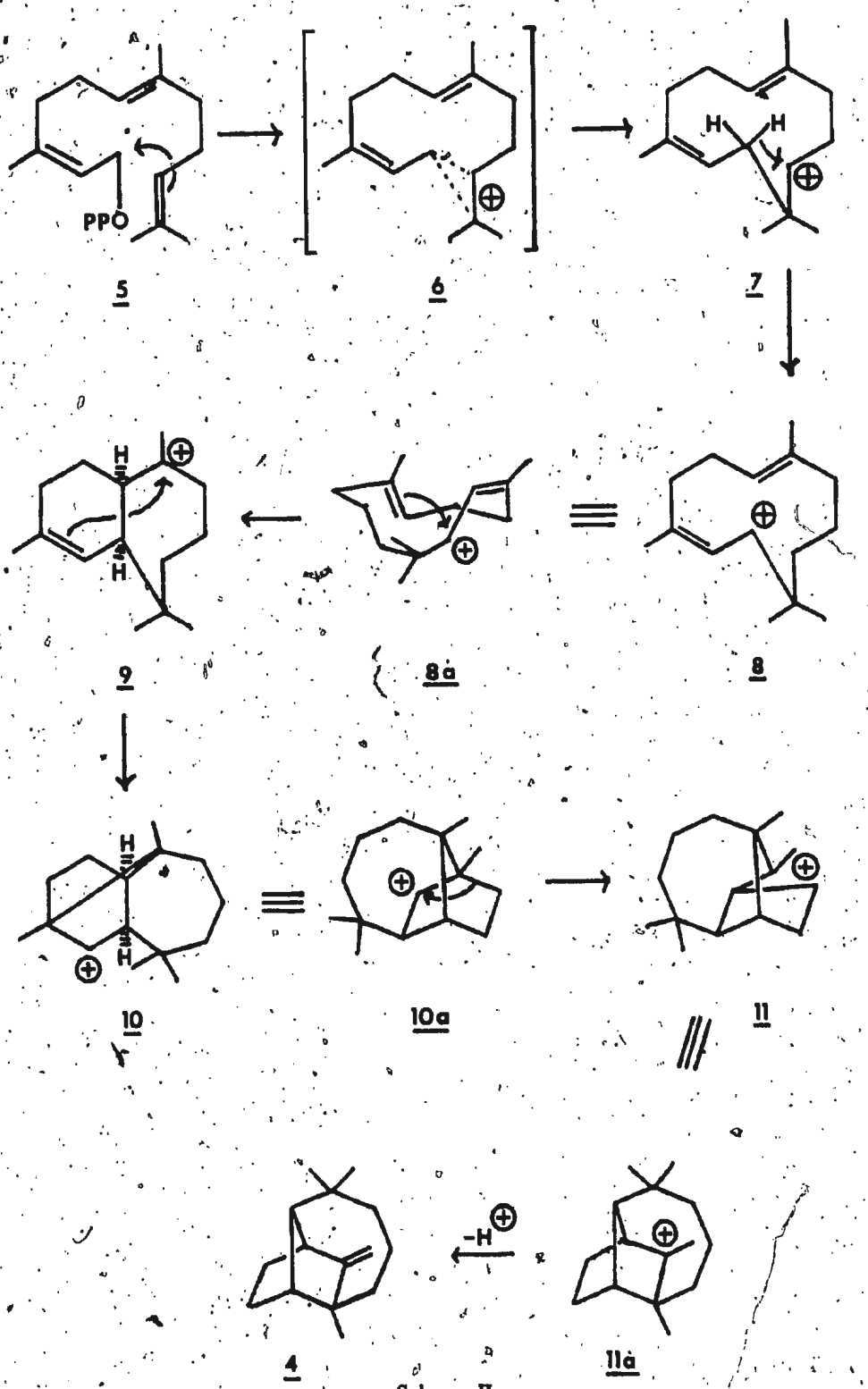
Scheme I

Further studies on the molecular rotations of a series of derivatives of longifolene and β-santalene[5] suggested that the proposed structure also represented the absolute configuration. The structure 4 has since been confirmed by several syntheses of longifolene.

2. Biosynthesis

The sesquiterpene longifolene is the major constituent in the essential oils obtained from the oleoresins of *Pinus longifolia, Pinus khasya, Pinus merkusii,*[6] and *Pinus Maritima*[7].

It has been established that sesquiterpenes arise biogenetically from the cyclization of the sesquiterpene farnesol, itself derived from the condensation of three mevalonic acid units.



5 6 7 8a 8 9 10 10a 11 11a 4

Scheme II

The biogenesis of longifolene[8] [9] involves the formation of an initial carbonium ion from *cis*-farnesyl pyrophosphate *5* (Scheme II). This carbonium ion, depending upon the pathway of rearrangement, may give rise to a variety of different sesquiterpenes. The pathway leading to longifolene begins with the formation of the secondary carbonium ion *7* via the ion *6*.

A 1,3 hydride shift gives cation *8*, whose conformation, depicted in *8a*, facilitates collapse to the *cis*-fused bicyclic ion *9*. Attack of the double bond on the cationic centre leads to cation *10* (ie. a tricyclo [2.2.1]derivative *10a*) which undergoes a facile 1,2 carbon bond migration. The resulting carbonium ion *11* (redrawn as *11a*) affords longifolene *4* by simple proton loss.

It should be noted that formal representation of the mechanism and intermediates in the preceeding manner does not necessarily reflect the actual enzymatic processes, but it does provide a useful framework for terpene classification and structure rationalization.

Preliminary experimental work has been conducted on longifolene biogenesis[9]. The feeding of (C_1-^{14}C) acetate to *Pinus longifolia roxb* resulted in the incorporation of 0.07% of the labeled acetate into longifolene. Activity in the exocyclic methylene group showed 1.8% of that expected for derivation from the carbonyl group acetate. This result is consistent with the biogenetic scheme above[10].

3. Synthetic history of longifolene

The intricate carbon network of longifolene has served as a challenging test for synthetic methodology for the past 20 years. To date there have been four published syntheses of longifolene and at least five unsuccessful attempts[11], [12].

A survey of the reported syntheses of longifolene reveals that each approach employed different strategies for the construction of the intricate bicyclo[5.4.0]undecane carbon skele-

ton.

3.1. Corey's synthesis

The first synthesis of longifolene was reported by Corey *et al*[13]. In this approach to longifolene the bridged-ring system was constructed by an intramolecular Michael addition of a homodecalin derivative *15*, as shown in Scheme III.

Precedence for this type of reaction was found in the base catalyzed cyclization of santonin to santonic acid.[14] Although santonin was smoothly transformed to santonic acid, the corresponding cyclization of homodecalin *15* to diketone *16* proved to be much less facile. Yields of only 10-20% were obtained for this crucial step.

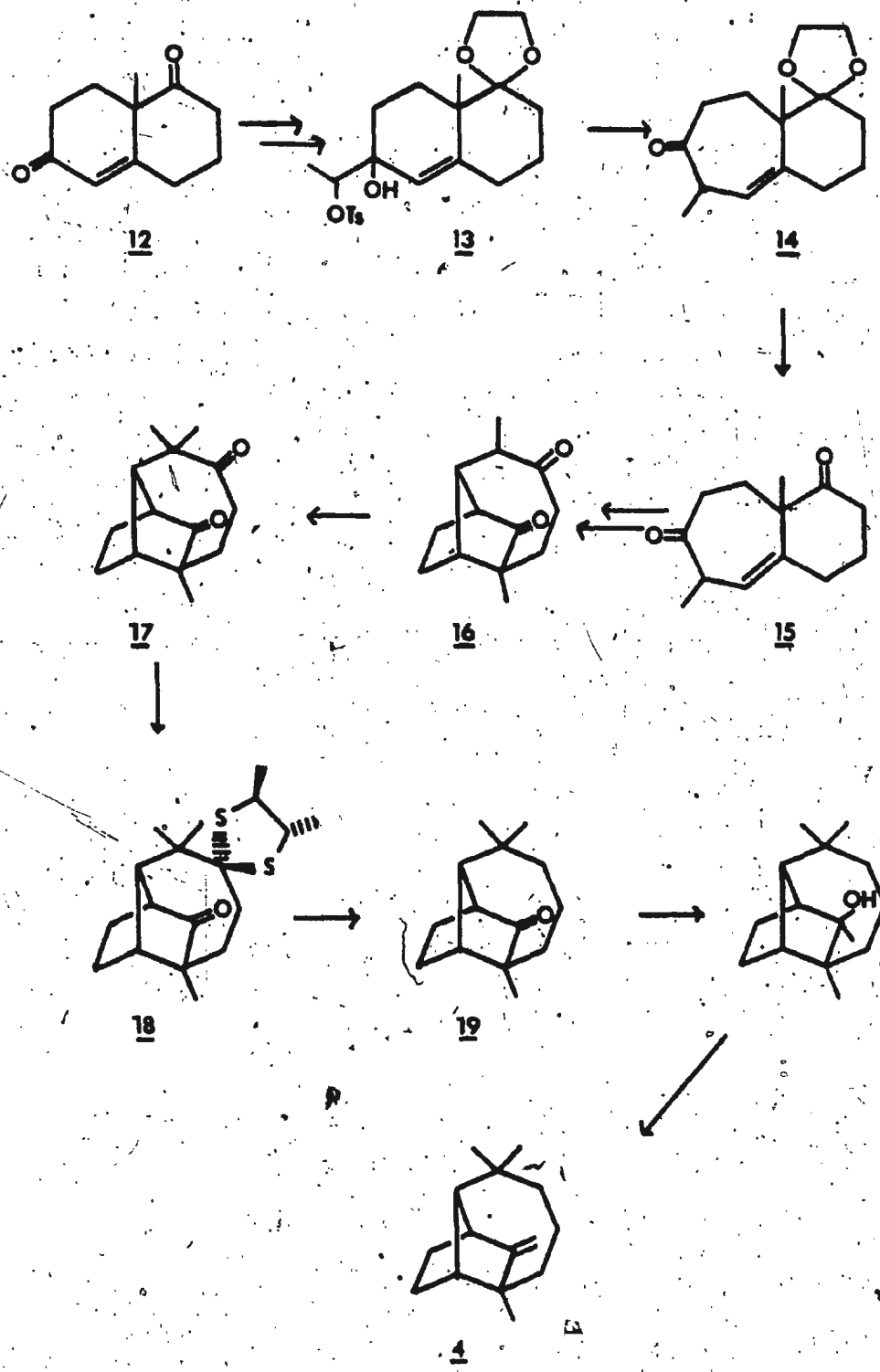
To prepare the required homodecalin *15* the Wieland-Miescher ketone *12* was converted via the tosylate *13* and then subjected to a pinacol rearrangement, which resulted in a ring expansion in 41-48% yield.

After construction of the bicyclo[5.4.0]undecane framework, diketone *16* was elaborated to racemic longifolene in the following manner. The more reactive cycloheptane carbonyl was reduced via Raney nickel desulfurization of its thio-ketal. Addition of methyl lithium to ketone *19*, gave longifolene after dehydration of the resulting tertiary alcohol.

To prepare the optically active natural product, intermediate *17* was treated with L (+)-2,3-butanedithiol and the diastereomers were resolved. The optically active thiol *18* was then converted to optically active longifolene.

3.2. McMurry's synthesis

The second synthesis of longifolene was reported by McMurry and Isser[15]. McMurry utilised the same starting material as Corey, but his approach was to first cyclize the decalin system to a bicyclo[4.4.0]decane. Subsequent ring expansion gave the required bicyclo[5.4.0]undecane skeleton as outlined in Scheme IV.

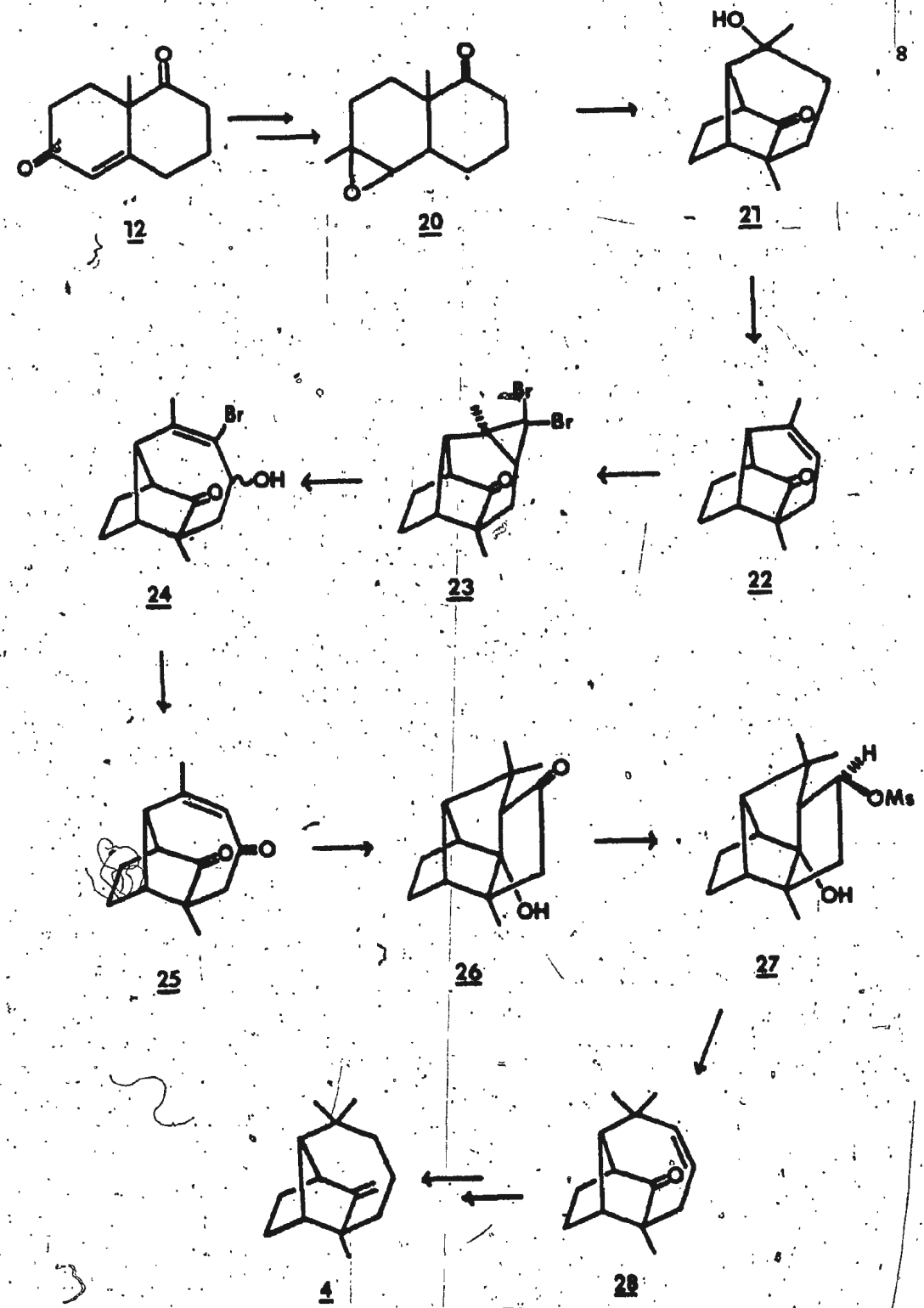


12 13 14 15 16 17 18 19 4

Scheme III

The Wieland-Miescher ketone *12* was converted to epoxy-decalin *20*, whose enolate underwent an intramolecular epoxide opening to provide the cyclized alcohol *21* in 93% yield.

Ring expansion was accomplished by solvolysis of cyclopropane *23* with silver perchlorate to yield allylic alcohol *24* quantitatively. Introduction of a methyl group by conjugate addition of lithium dimethylcuprate to enedione *25* resulted in the formation of ketone *26*, presumably by intramolecular attack of the enolate generated after conjugate addition. The bicyclo[5.4.0]undecane system was regenerated by base catalyzed rearrangement of mesylate *27* to give ketone *28* which was further elaborated to longifolene.



12 20 21 22 23 24 25 26 27 28 4

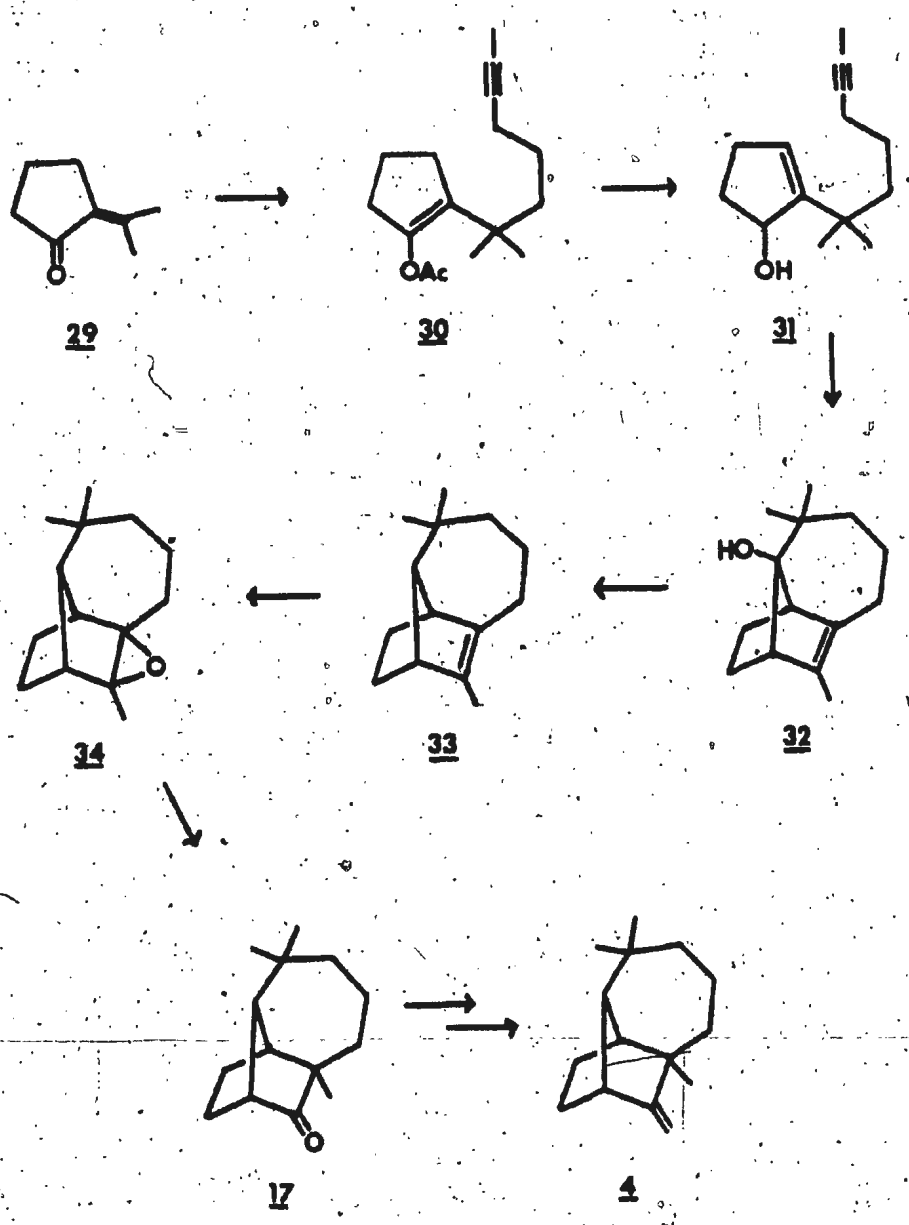
Scheme IV

3.3. Johnson's synthesis

The third synthesis of longifolene, reported by Johnson *et al*[16] utilised the acid catalyzed rearrangement of an enynol to construct the bicyclo[5.4.0]undecane framework of the longifolene skeleton.

Conjugate addition of the cuprate derived from 6-iodohex-2-yne to enone *29* and trapping of the resulting enolate with acetylchloride gave *30*. Further manipulation of this acetate yielded alcohol *31*. Treatment of alcohol *31* with trifluoroacetic acid resulted in its rearrangement to a bicyclo[5.4.0]undecene (Scheme V).

This allowed a facile entry into the longifolene framework. Completion of the synthesis was accomplished by epoxidation and rearrangement of the resulting epoxide *34*, to ketone *17*, an intermediate in both Corey's and McMurry's syntheses, thus providing longifolene in eleven steps from *29*.



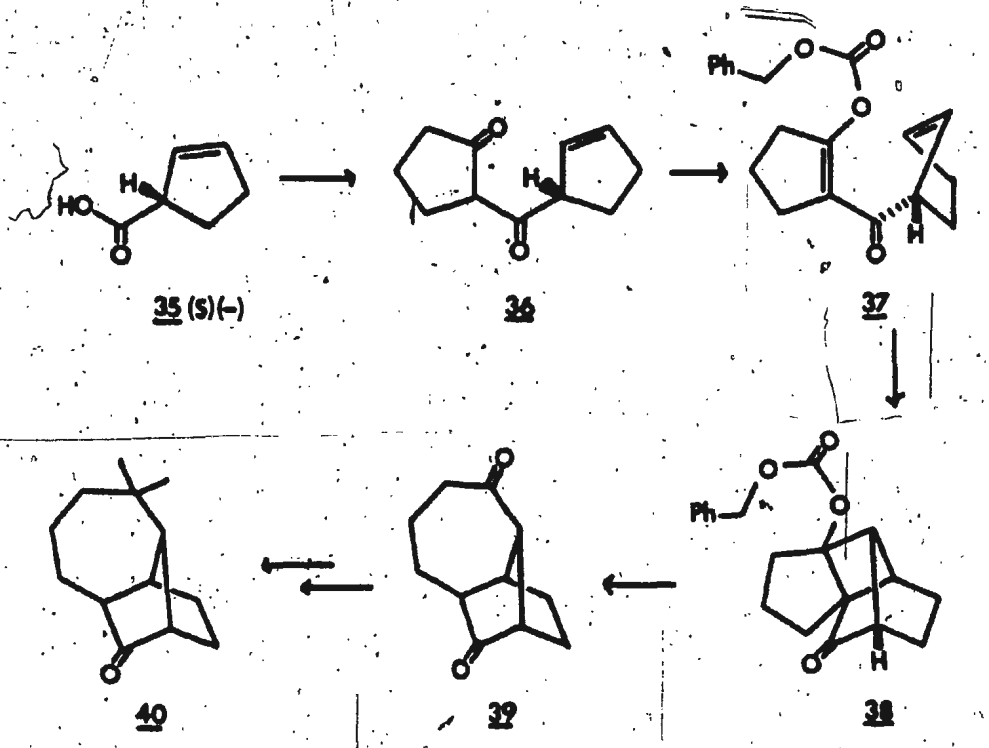
29 30 31 32 33 34 17 4

Scheme V

3.4. Oppolzer's synthesis

The fourth and most recent synthesis of longifolene was reported by Oppolzer and Godel[17]. In this synthesis an intramolecular [2+2] photoaddition-retroaldol reaction sequence (DeMayo reaction) was used to construct the longifolene skeleton (Scheme VI).

Irradiation of chiral diene *37* provided cyclobutane *38* which upon hydrogenolysis of the benzyloxycarbonyl protecting group underwent a spontaneous retroaldol reaction to yield diketone *39*. This procedure incorporated the required stereochemistry without disturbance of the chiral centre.



Scheme VI

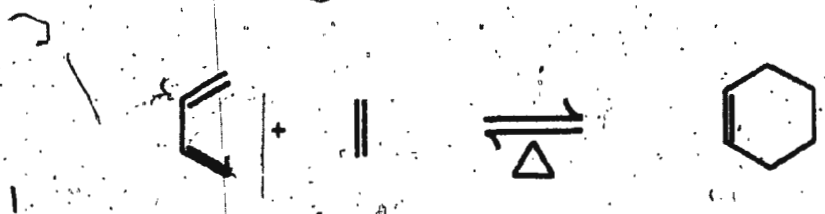
Crystallization provided the diketone in 100% optical purity. Introduction of the gem-dimethyl group was accomplished via Wittig olefination of the more reactive cycloheptanone carbonyl, Simmons-Smith cyclopropanation, and hydrogenolysis to yield ketone *40*. This intermediate was then converted to (+)longifolene in 24% overall yield from chiral acid *35*.

Such efficient construction of the intricate longifolene carbon network underscores the value of intramolecular processes for the assembly of natural product skeletons. In addition, the regio- and stereoselectivity of the requisite carbon-carbon bond formation reactions is effectively controlled.

4. The Diels-Alder reaction

The [4+2]-cycloaddition or Diels-Alder reaction has been widely applied to total synthesis. The simplest example for cyclohexene formation involves the addition of an olefin to a conjugated diene, as depicted in Equation I.

In the Diels-Alder reaction a 4-π electron system (the conjugated diene) and 2-π electron system (the dienophile) react to form two new carbon-carbon σ-bonds.



Equation I

Although the mechanism of the reaction is still subject to controversy, the reaction proceeds in a highly stereoselective, and often stereospecific, manner. If the diene and dieneophile are connected, the regiochemistry may often be controlled completely.

This combination of high stereospecificity, regio-control and formation of two bonds in a single process under mild, neutral conditions provides the potential for efficient and facile construction of complicated carbon networks.

4.1. Brieger's attempt

Several years ago G. Brieger[12] attempted to utilise an intramolecular Diels-Alder reaction in the synthesis of longifolene. The substituted cyclopentadienes *42* and *44*, obtained by the Grignard coupling of chloride *41* with excess cyclopentadienyl magnesium bromide, were subjected to Diels-Alder reaction conditions (Scheme VII).

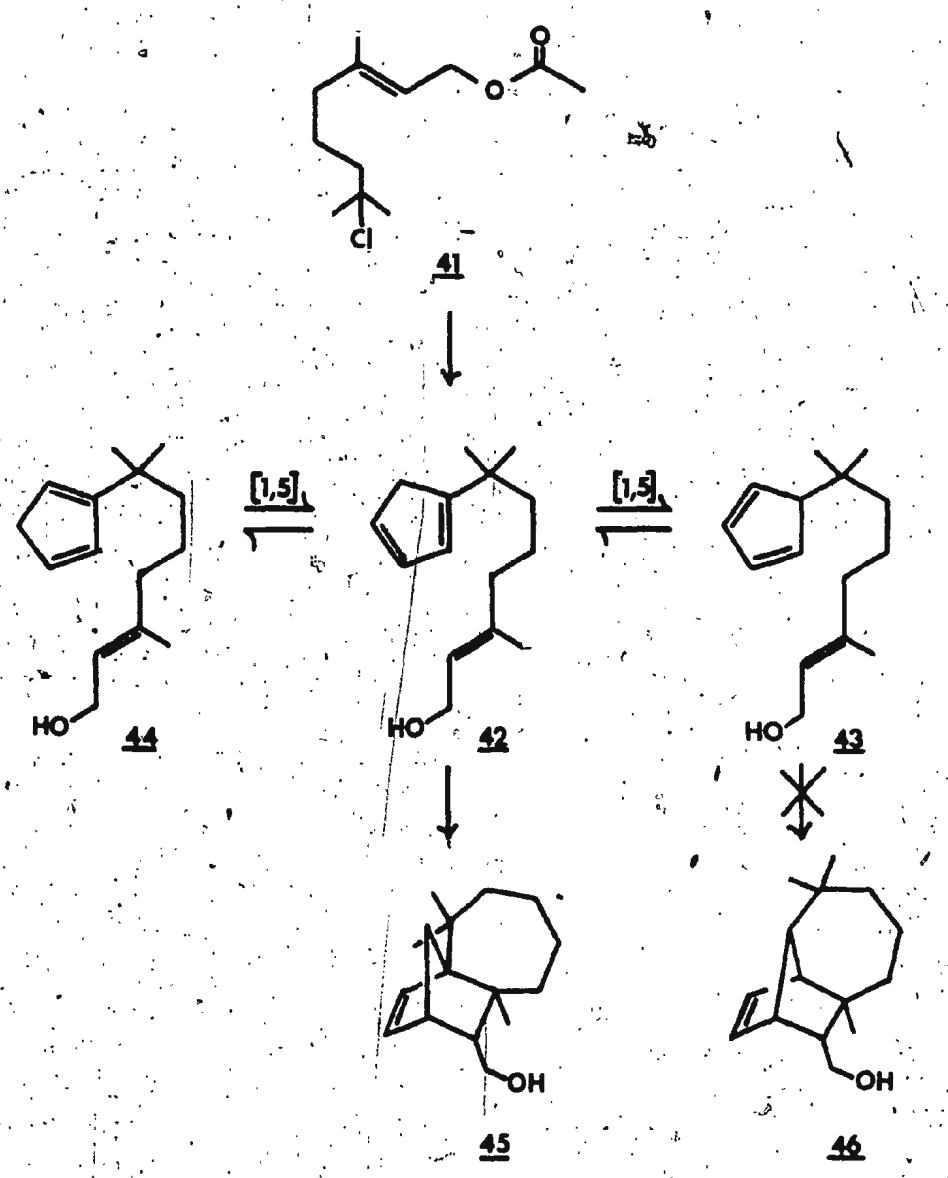
It was hoped that thermal equilibration would provide a small amount to the 5-cyclopentadienyl derivative *43* which would cyclize to the desired alcohol *46*.

In fact the product obtained in nearly quantitative yield was alcohol *45*, which corresponded to the cyclisation of the 1-substituted cyclopentadiene *42*.

It was apparent from this result that a successful internal Diels-Alder approach with 5-substituted cyclopentadienes required blocking the thermal rearrangement to the more thermodynamically stable 1-substituted isomer, or conducting the cycloaddition under mild conditions where it could compete efficiently.

4.2. Current approach

The rearrangement of 5-substituted cyclopentadienes can be prevented by dialkyl substitution of the 5 position. For example a spiro[4.2]heptadiene should block the 1,5-sigmatropic rearrangement and the cyclopropane unit may serve as a source of latent functionality.

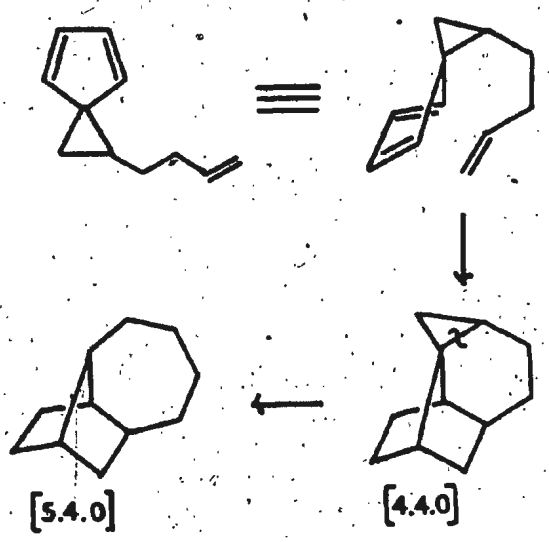


Scheme VII

The cyclization of a spiro system containing a four membered olefinic sidechain, as depicted in Scheme VIII, would generate a tetracyclo[5.4.$0^{1,7}$.$0^{2,4}$.$0^{2,8}$]undecene system. Selective cleavage of the interior cyclopropane bond should release the bicyclo[5.4.0]undecane

system required for longifolene.

A further property of this intramolecular cyclization arises from the geometric constraints imposed by the Diels-Alder transition state. Thus, only the conformation illustrated permits adduct formation. Therefore, if the cyclopropyl unit is chiral these stereochemical features will control the cyclization, resulting in an optically active product, from which chiral longifolene may be synthesized.



Scheme VIII

CHAPTER 2

Discussion

1. Longifolene retrosynthetic analysis

For this Diels-Alder approach to the synthesis of longifolene to be successful the penultimate cycloadduct must have several structural features.

(1) The penultimate cycloadduct must have suitable functionality to allow for the introduction of the exocyclic double bond of longifolene.

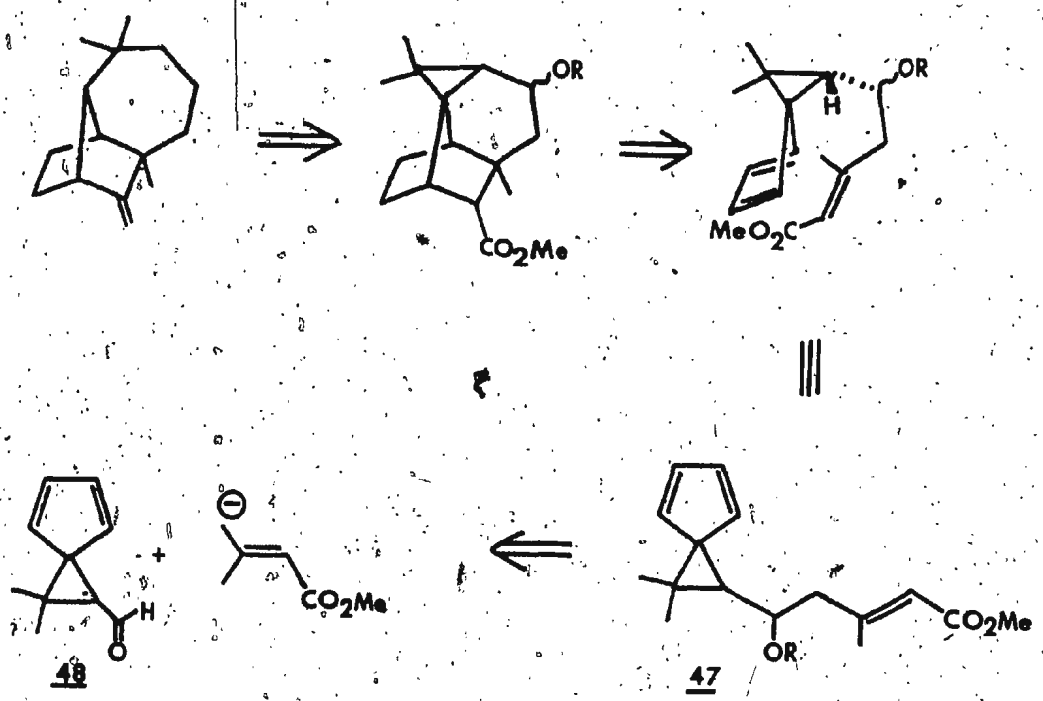
(2) Studies applying this approach to the synthesis of sinularene [18] revealed an oxygen substituent in the olefinic sidechain *alpha* to the cyclopropyl ring was essential for cyclization.

(3) A norbornene double bond was required to direct the reductive cyclopropane ring opening to the longifolene skeleton exclusively [19].

Structure *47* possessed all the necessary requirements and leads naturally to the retrosynthetic scheme shown below (Scheme IX). Thus the synthesis required construction of the cyclopropyl aldehyde *48* in both racemic and chiral form, which would then allow introduction of the olefinic sidechain through a condensation reaction.

2. Initial scheme

The condensation of cyclopentadienyl anion with epichlorohydrin[20] apparently proceeded through an epoxy-cyclopentadienyl anion intermediate, which then undergoes intramolecular nucleophilic attack to form the spirocyclopropyl-alcohol as the sole product (Equation II).



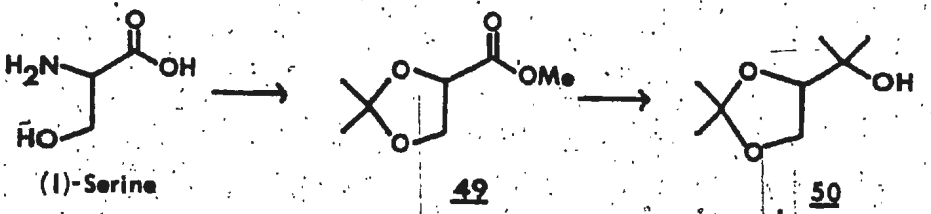
Scheme IX

This preference for spirocyclopropane formation provided the basis for the initial synthetic scheme to chiral intermediate *18* beginning with l-serine (Scheme X).

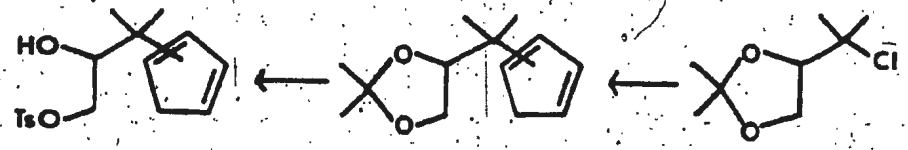
The known chiral ester *49* (prepared from l-serine), after treatment with methyl Grignard should yield the tertiary alcohol *50*. Conversion to the chloride would allow attachment of the cyclopentadienyl ring via Grignard coupling to form *51*, analogous to the scheme used by Brieger.

Deprotection to the diol and selective tosylation of the primary hydroxyl should allow preparation of the spirocyclopropyl system *53*, via intermediate epoxide *52*. Initial formation of this epoxide followed by an intramolecular S_N2 attack by the cyclopentadienyl anion would form the cyclopropyl ring with inversion of the chiral centre.

Equation II



(l)-Serine 49 50



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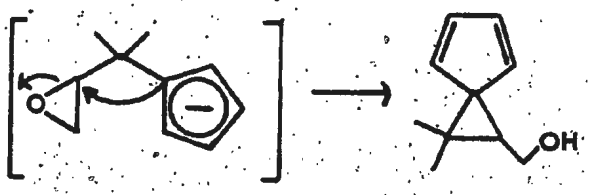


52 53

Scheme X

Treatment of *49* with methyl Grignard reagent provided alcohol *50* but the subsequent conversion to the chloride proved unsuccessful under a variety of conditions.

3. Second attempted route to the major synthon

An alternative approach (Scheme XI) required the formation of a fulvene intermediate *55* from the methyl ketone *54* and subsequent alkylation with methlylithium.

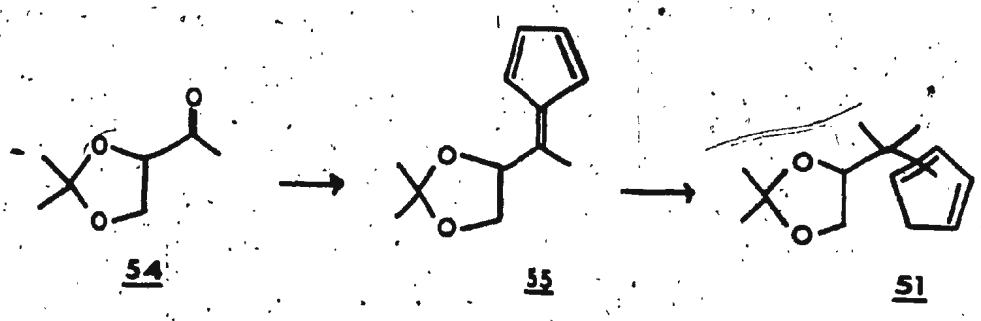
3.1. Methyl ketone preparation

Initial attempts to monoalkylate the ester *49* with one molar equivalent of methyl Grignard reagent at low temperature resulted in only recovered starting material and alcohol *50*.

The ketone synthesis of Corey and Chaykovsky[21] was investigated. This procedure involved the formation of the β-ketosulphoxide *56* from the condensation of dimethylsulphoxide anion with ester *49* and reductive hydrolysis with mercury amalgam to yield the desired methylketone *54* (Chart II). Unfortunately the intermediate β-ketosulphoxide *56* decomposed under the hydrolysis conditions.

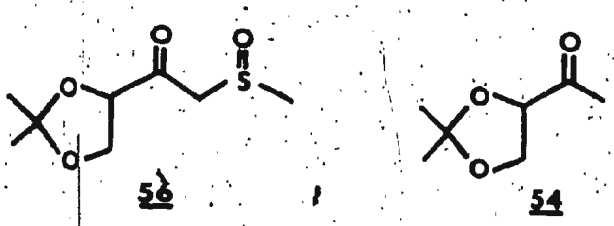
Carboxylic acids are known to react with two molar equivalents of methyllithium to produce the corresponding methylketone[22]. In initial attempts ester *49* was hydrolyzed to its potassium salt *57* and treated with ion exchange resin to produce the corresponding acid *58*. The acetonide group proved too labile for use of the acid on a preparative scale. A convenient solution was found involving hydrolysis of the methyl ester *49* directly to the lithium salt *59* and subsequent treatment with methyl Grignard reagent to provided the methlyketone *54* in 90% yield (Chart III).

After this work was complete Dumont and Pfander[23] reported an alternative preparation of *54* and its conversion to *50* in the R series as well as the synthesis of (S)-*50* from *49*.



54 55 51

Scheme XI

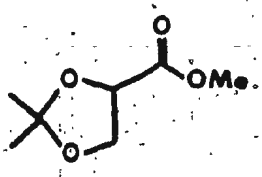


56 54

Chart II

3.2. Dioxolanylfulvene preparation

Condensation of ketone *54* with cyclopentadienyl anion gave various mixtures of the alcohol *60* and fulvene *55* resulting from direct dehydration of the alkoxy intermediate (Chart IV). The ratio of alcohol to fulvene was temperature dependent. Low temperature condensation resulted in exclusive alcohol formation, while higher temperatures favoured fulvene formation. The best results were obtained by performing the condensation in refluxing dioxane with lithium cyclopentadiene. This provided the fulvene *55* exclusively in modest yield (67%).



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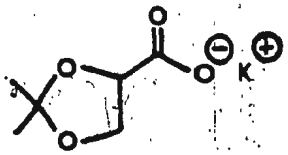

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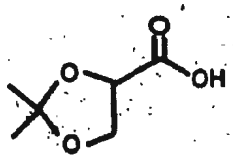

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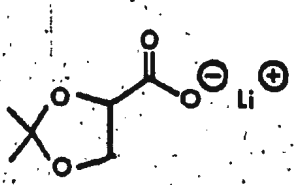

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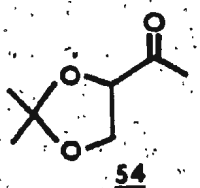

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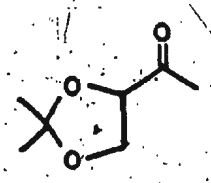
Chart III



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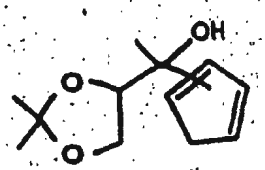

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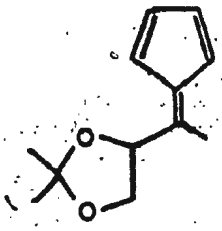
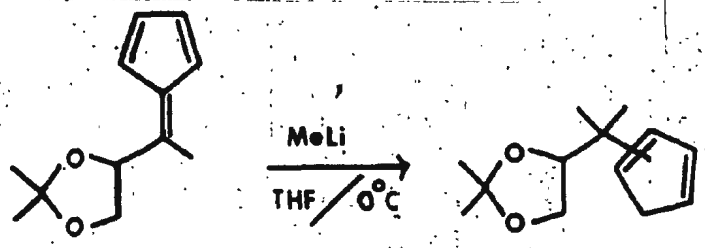


55

Chart IV

3.3. Attempted dioxolanylfulvene deprotection

The addition of methyllithium across the exocyclic double bond of fulvene *55* proceeded smoothly to give the cyclopentadienyl compound *51* in 46% yield (Equation III). Construction of the crucial spirocyclopropyl synthon *48* now entailed deprotection of the diol functionality, tosylation of the primary alcohol and cyclization.



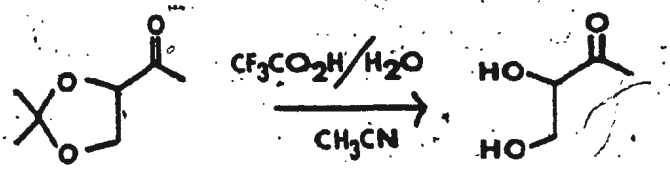
55 51

Equation III

All attempts to remove the acetonide protecting group were unsuccessful. Direct hydrolysis of the acetonide with various acid/solvent combinations was monitored by NMR. Either no reaction was observed, or when more vigorous conditions were employed the cyclopentadienyl resonances diminished, concomitant with the release of acetone, and no free diol could be isolated. Ketal exchange methods including thioketals and copper sulfate catalysis also met with failure. These methods were also tried on the fulvene *55* with similar results.

4. Major synthon preparation via epoxyfulvene

Thwarted in our efforts to construct the epoxide functionality after introduction of the cyclopentadienyl ring, we investigated the possibility of epoxide introduction at the ketone stage prior to fulvene formation. To this end the ketone *54* was smoothly hydrolysed under acidic conditions to the diol *61* (Equation IV). Conversion of *61* to a primary tosylate should allow chiral epoxide formation by intramolecular displacement of the tosylate with the alkoxide formed from the secondary hydroxyl group by base treatment.

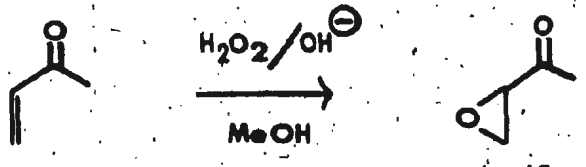


54 61

Equation IV

4.1. Epoxyfulvene preparation

To circumvent the tedious multistep preparation of the chiral epoxide *62* a convenient source of racemic epoxide was developed by a one-step epoxidation of methly vinyl ketone (30% H_2O_2, NaOH, 0°, 71%). All subsequent experiments were performed on racemic material (Equation V). The condensation with cyclopentadienyl anion was explored next. Exposure of epoxyketone *62* to the conditions employed for the formation of fulvene *55* from ketoacetonide *54* resulted in rapid decomposition of the initial adduct. Clearly milder conditions were necessary for the survival of the epoxide functionality. A systematic investigation of alkoxides as condensing agents resulted in optimum yields of *ca.* 30% utilising



62

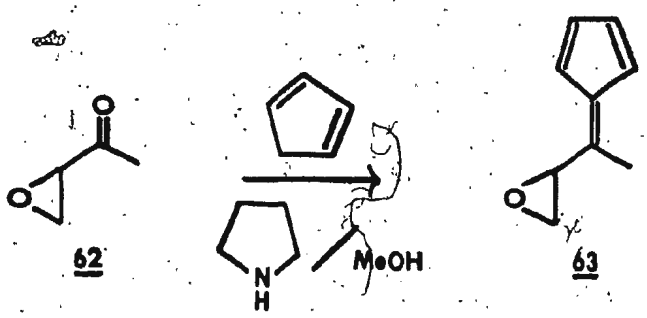
Equation V

lithiumhydroxide in methanol. The search for still milder conditions was continued with the investigation of the behavior of several amine bases as condensing agents. Tertiary amines proved ineffective, whereas secondary and primary amines afforded small quantities of fulvene *ca.* 20%, while pyrrolidine proved to be extremely effective. The exposure of cyclopentadiene and epoxyketone to 0.2 mole equivalent pyrrolidine in methanol resulted in high yields of fulvene *63* (Equation VI).

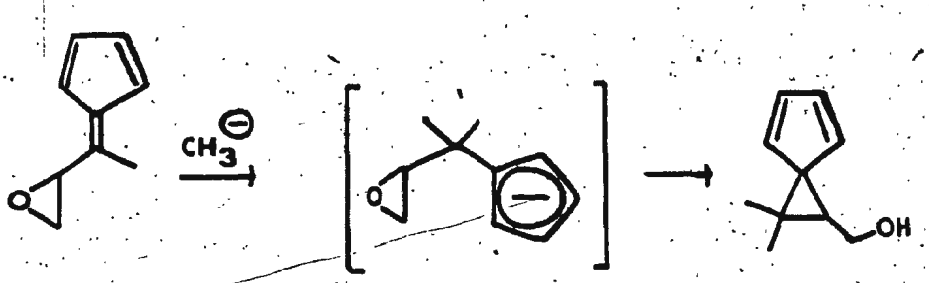
These results are in accord with a recent paper by Little and Stone[24] in which the effectiveness of pyrrolidine was similarly reported although in their examples the base was used in molar excess.

4.2. Epoxyfulvene cyclization

The treatment of epoxyfulvene *63* with methyllithium may result in nucleophilic attack on the epoxide or addition across the exocyclic fulvene double bond. The desired addition will generate an intermediate cyclopentadienyl anion *64* which could attack the epoxide, and form the required spirocyclopropyl compound *65* (Scheme XII).



Equation VI



63 64 65

Scheme XII

We were pleased to find that exposure of epoxyfulvene *63* to methyllithium resulted in formation of spiroalcohol *65* and recovery of starting material. No trace of the products that would result from initial attack on the epoxide moiety could be detected. Under optimum conditions a product/fulvene ratio of 6:1 was obtained. The products were easily separable by chromatography. The recovered fulvene may have arisen from competing formation of an allylic anion which was protonated on work-up to regenerate the fulvene.

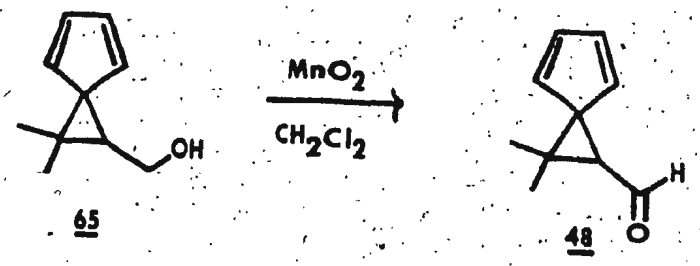
The cyclopropyl alcohol was sensitive to chromium based oxidising agents, but a good yield (73%) of the cyclopropyl aldehyde *48* was realized by manganese dioxide oxidation (Equation VII).

5. Alternative routes to the major synthon

In parallel with experiments aimed at developing a chiral route to the cyclopropyl aldehyde *48* several other racemic approaches were investigated.

5.1. Conjugate addition

One may envisage the conjugate addition of cyclopentadienyl anion to an α-bromo-α,β-unsaturated ester to form an intermediate α-bromo-β-cyclopentadienyl anion ester *67*



65 48

Equation VII

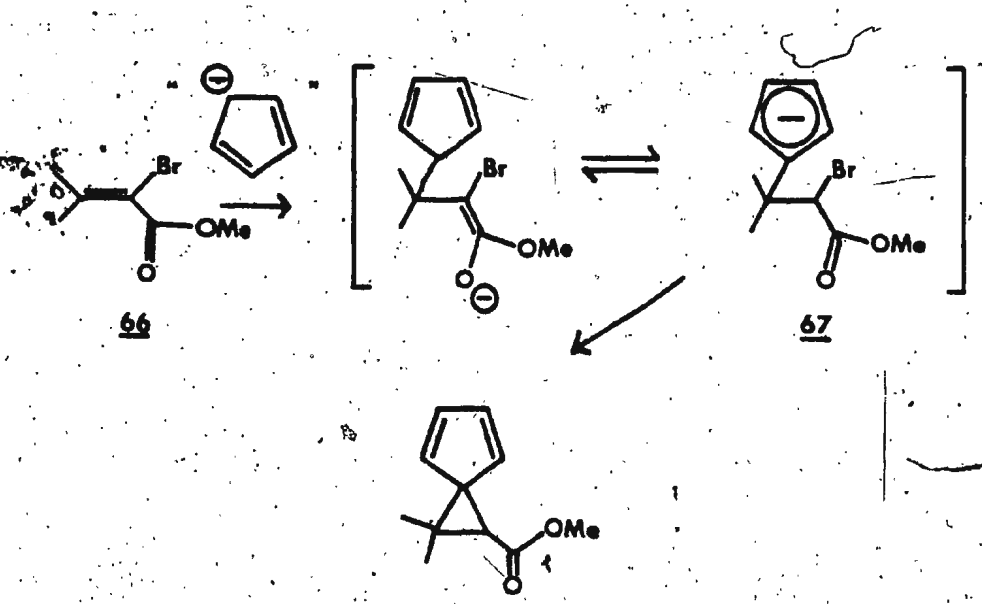
which could attack the bromide by an S_N2 displacement to provide the cyclopropyl ester *68* (Scheme XIII). Previous work had shown that this was feasible in a model system (Fallis and Wang unpublished) although a trisubstituted enone is a more demanding case (Equation VIII).

The possibility of such a conjugate addition was investigated with the preparation of α-bromoseneciate by the addition of bromine to ethyl seneciate to form *69* and subsequent elimination of hydrogen bromide with sodium ethoxide (Chart V).

Unfortunately no reaction ensued upon treatment of ethyl α-bromoseneciate *66* with dicyclopentadienylithium cuprate. Direct addition of sodium cyclopentadiene was also unsuccessful.

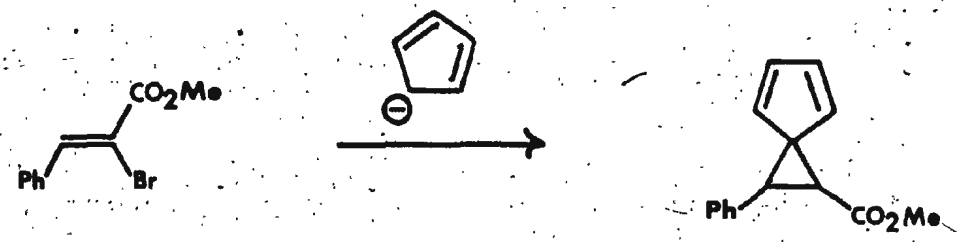
5.2. Dibromide displacement

Another approach which merited investigation entailed the consecutive displacement of a 1,2-dibromide *72* with cyclopentadienyl anion (Scheme XIV). Initial bromide displacement would yield a 1-bromo-2-cyclopentadienyl species *74*, which after regeneration of cyclopentadienyl anion could undergo an intramolecular displacement to provide the desired

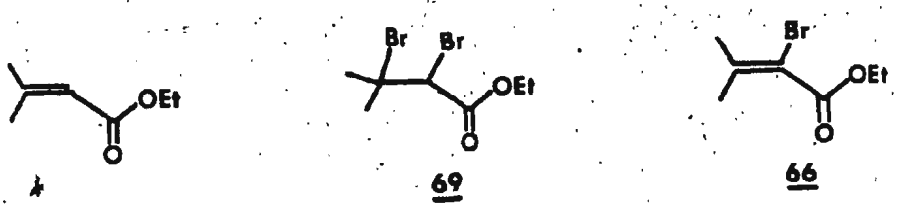


66 67 68

Scheme XIII



Equation VIII

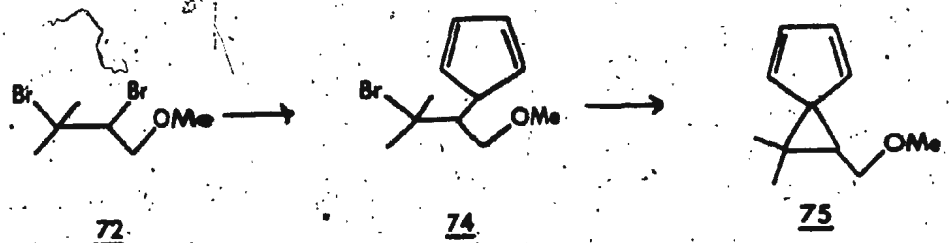


69 66

Chart V

cyclopropyl system*75*.

The requisite dibromide *72* was formed by reduction of ethyl seneciate, O-methylation of the resulting allyl alcohol *70* to provide ether *71* and addition of bromine. Treatment of



72 74 75

Scheme XIV

70 71

72 73

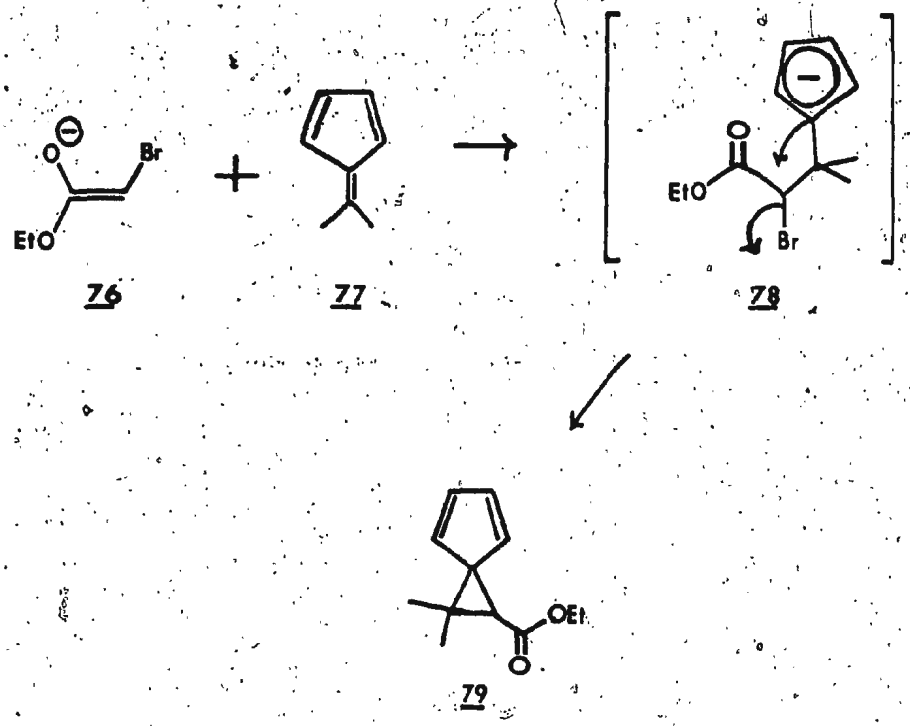
Chart VI

dibromide *72* with sodium cyclopentadiene resulted in formation of cyclopentadienyl bromide *74*. Further base treatment yielded the elimination product *79* rather than the desired cyclopropyl ether *75* (Chart VI).

5.3. Darzen type approach

In analogous fashion to the successful synthesis above the addition of ethyl bromoacetate enolate *76* to dimethylfulvene *77* would result in an intermediate cyclopentadienyl anion *78* which could then attack the bromide to form the desired cyclopropyl compound *79* (Scheme XV).

Treatment of dimethylfulvene with ethyl bromoacetate and sodium ethoxide resulted in extensive polymer formation. Similarly the treatment of dimethylfulvene with chloroacetonitrile and potassium t-butoxide resulted in extensive polymer formation and



76 77 78 79

Scheme XV

recovery of chloroacetonitrile.

6. Introduction of the isoprenyl sidechain

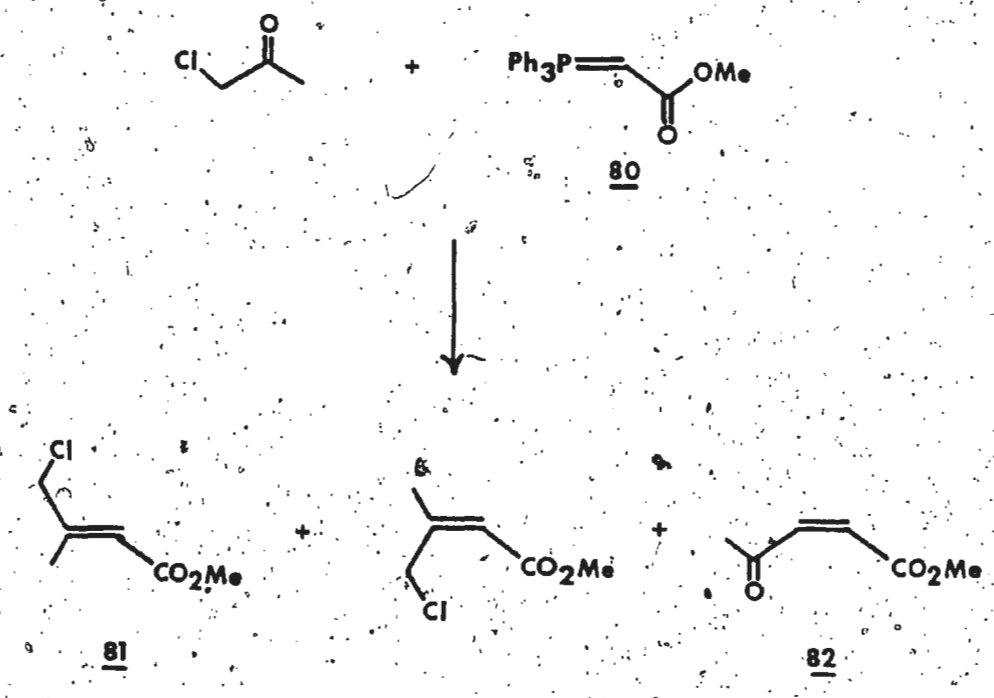
With the spirocyclopropyl ring system in hand, our attention was turned to the introduction of the olefinic sidechain. Much recent work has focused on the competition of α versus γ alkylation/condensation of crotyl units. In order to ascertain if an isoprene unit could be used for the right hand portion of longifolene *81* was synthesized as follows.

6.1. Chloro Grignard addition

Initial preparation of the desired methyl γ-chlorosenecioate was accomplished by a Wittig reaction of chloroacetone with triphenyl carboxymethyl phosphate *80* (Equation IX). The reaction gave three products in 50% overall yield, from which the desired E-methyl-4-chlorosenecioate *81* could be isolated by HPLC. The side product *82* resulted from the known reaction of stable phosphoranes and α-halo carbonyl compounds to form initially a γ-ketophosphonium salt. Elimination of halogen acid and triphenyl phosphine under the influence of additional phosphorane formed the α,β-unsaturated ketone[25]. This competing process precluded the extension of the Wittig synthesis to γ-bromosenecioate.

The Grignard addition of chlorosenecioate *81* to cyclopropanal *18* proved troublesome. In contrast to the smooth, clean addition with γ-chlorocrotonate, reactions with *81* were difficult to initiate, requiring prolonged heating and furnishing a large number of products with similar retention factor's (Rf's, by TLC), whose NMR spectra were inconsistent with the desired product.

A more reactive halogen derivative might alleviate some of these problems. Attempted chlorine/iodine exchange with sodium iodide/acetone resulted in a product which was too unstable for preparative use, thus the bromo derivative was sought.

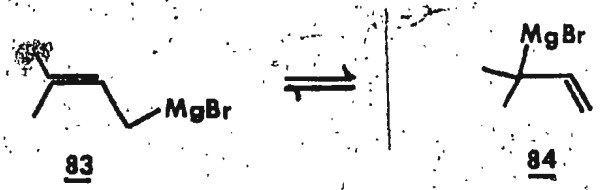


Equation IX

0.2. Bromo Grignard addition

A convenient method for the preparation of E-methyl-4-bromosenecioate was reported by Corey and Erickson[26]. Although initiation of the Grignard reaction with bromosenecioate proceeded with greater facility, a mixture of α and γ products was obtained.

A recent review by Benkeser[27] discussed the structure of γ,γ-dimethylallylmagnesium bromide. From interpretation of the temperature dependent NMR spectra a rapid equilibrium betweeen the pair of structures *83* and *84* was proposed, with the equilibrium well on the side of *83* at room temperature (Equation X). Even more interesting was the disclosure that crotyl Grignard additions to highly hindered ketones like t-butyl isopropylketone were reversible, with short reaction times the α-methylallyl adduct *85* formed in nearly



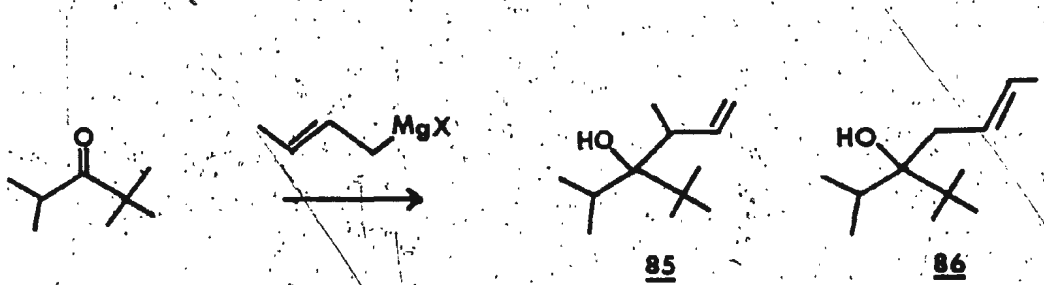
83 84

Equation X

quantitative yield, but with longer reaction times this isomer was converted almost entirely to the most thermodynamically stable carbinol *86* (Equation XI).

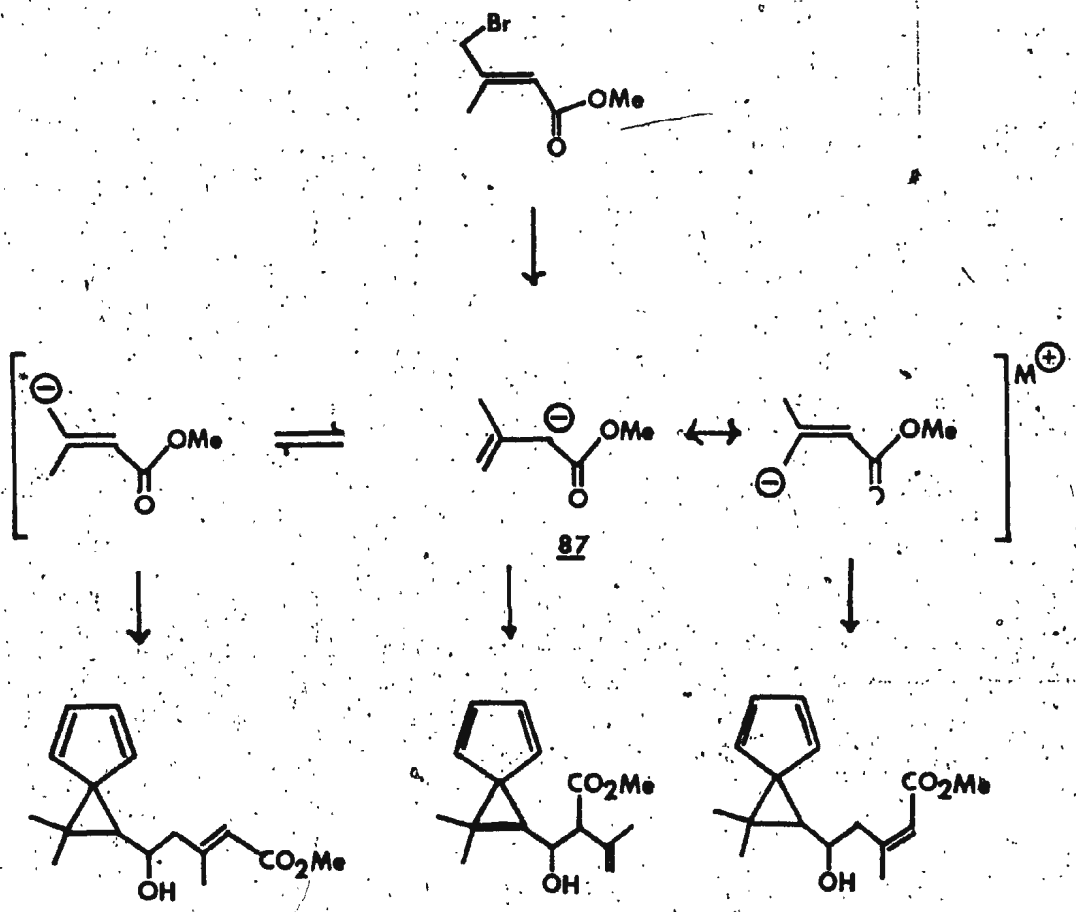
Grignard addition of γ-haloseneciоates resulted from alkylation α and γ to the carbonyl (Scheme XVI). The products obtained via anion *87* (M=MgBr) have three consecutive chiral centres which can form four possible diastereomeric pairs, gamma alkylation would result in another four possible regio/stereo isomers. Therefore the large number of products detected is not surprising.

Inspection of the NMR spectra of the product mixture revealed the absence of proton resonances at δ6 which is indicative of an olefinic proton alpha to an ester. The proton



85 86

Equation XI



Scheme XVI

resonances at δ5–4.7 suggest the presence of a terminal methylene, thus indicating the preferential formation of alpha addition products. Extended reaction times were investigated with prolonged heating at various temperatures. Although there were minor changes in the NMR spectra, decomposition was the major result.

6.3. Reformatsky addition

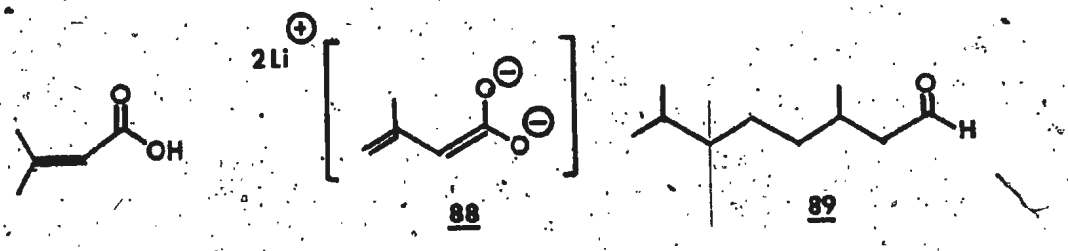
Fuson and Southwick reported the Reformatsky condensation of methyl γ-bromosenecioate with various carbonyl compounds[28] gave "normal" and "abnormal" addition products resulting from gamma and alpha addition, respectively (Scheme XVI, M=Zn). The direct reaction of zinc and bromosenecioate proved difficult to achieve on a millimolar scale. The innovation introduced by Boudjouk[29], of executing the condensation in the presence of ultrasonic waves resulted in facile condensation with aldehyde *48* at room temperature. The initial adduct composition was similar to that of the Grignard addition. Mild heating substantially changed the product distribution as monitored by TLC. NMR analysis revealed an increase in the desired proton resonances at δ6, thus indicating rearrangement to the desired γ-addition products. However the complexity of the NMR spectra indicated we were still dealing with many stereo/regio-isomers.

Confronted with these discouraging results alternative methods for the introduction of the "isoprene" sidechain were investigated before beginning the arduous task of isolating and identifying the myriad of isomers generated by these condensations.

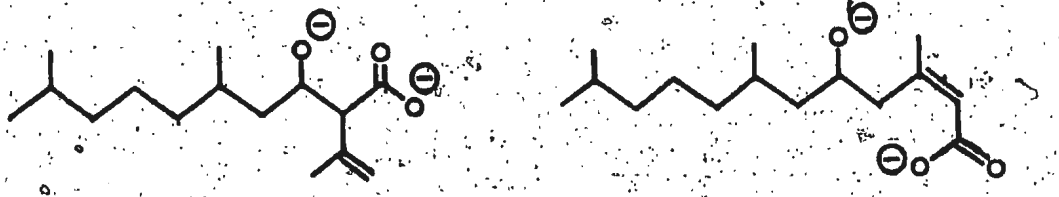
6.4. Senecioic acid condensations

Henrich *et al* reported the condensation of dimetalated senecioic acid *88* [30] with aldehyde *89* yielded an initial adduct *90* which when heated in refluxing tetrahydrofuran rearranged to isomer *91* as a mixture of *Z* and *E* isomers in the ratio 9:1, respectively (Chart VII).

Application of this method resulted in an initial product composition similar to that observed in the Grignard additions. All attempts to rearrange the initial dimetalated adduct *92* to the desired gamma addition product *93* resulted in no change, and as the temperature was raised extensive decomposition occurred (Chart VIII).

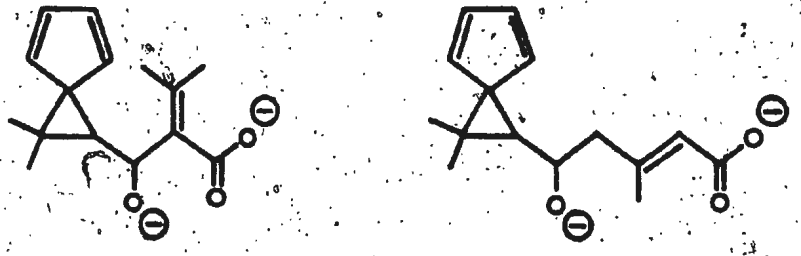


88 89



90 91

Chart VII



92 93

Chart VIII

A modification of this procedure by Cainelli *et al*[31] in which the dipotassium salt was used, reportedly gives only γ product. Attempted use of this reagent resulted in the isolation of a black tar which possesed no cyclopentadienyl resonances in the proton NMR spectra.

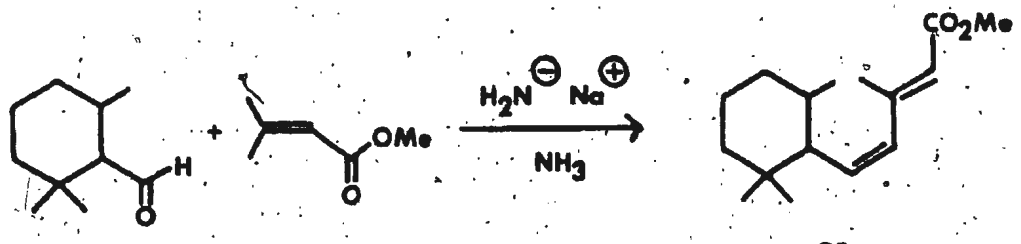
6.5. Methyl Senecioate addition attempts

Schwieter[32] reported γ addition of methyl senecioate to β-ionilideneacetaldehyde *94* with potassium amide in liquid ammonia to produce *95* (Equation XII).

Again application of the literature method resulted in recovery of methyl senecioate and decomposition of the cyclopropyl aldehyde. Evidently the spirocylopropylcyclopentadienyl system cannot withstand the vigorous conditions required for introduction of the senecioic sidechain, with the desired regiochemistry.

6.6. Seneciol addition attempts

Defeated in our attempts to introduce the senecioate ester sidechain with the appropriate regiochemistry in a synthetically useful way, a different tactic was explored.



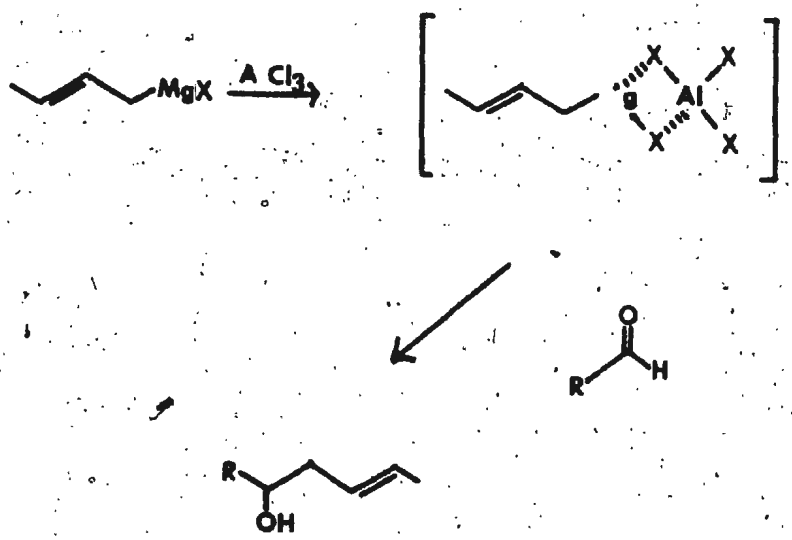
94 **95**

Equation XII

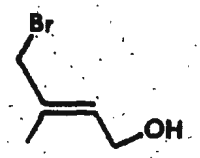
Yamamoto reported that the prior complexation of crotyl Grignard with aluminum chloride at -78° leads to high γ-regioselectivity in carbonyl addition [33] (Scheme XVII). This apparent solution to the regiochemical problem seemed well suited to our case, especially in the light of the demonstrated stability of cyclopropanal *48* to low temperature Grignard additions.

To investigate this potential solution methyl γ-bromosenecioate was reduced to the corresponding alcohol *96*. A protected seneciol should undergo addition similar to the crotonate and also contain the latent functionality for the later introduction of the exocyclic methylene of longifolene.

The tetrahydropyran and *t*-butyldimethylsilyl derivatives *97* and *98* respectively were prepared (Chart IX). In each case initial Grignard formation was sluggish and the aluminum chloride complexed addition proved unsuccessful, with recovery of starting material or loss of the tetrahydropyran protecting group.



Scheme XVII



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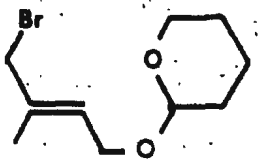

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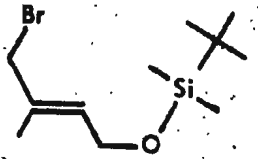


98

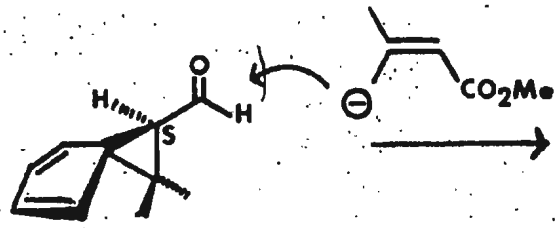
Chart IX

7. Preliminary Diels-Alder results

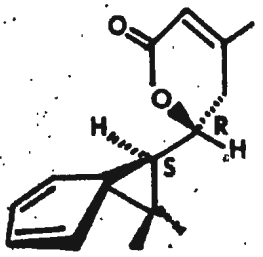
The Reformatsky condensation offered the most promise for the introduction of the sidechain and was investigated in greater detail.

Methyl bromosencioate was reacted with aldehyde *48* as previously described with prolonged heating (55 °, 8 hours). The reaction mixture was chromatographed to yield 11 products, one of which was crystalline. The crystaline product, lactone *103* arose from γ-addition *cis* to the carbomethoxy group and subsequent lactonization.

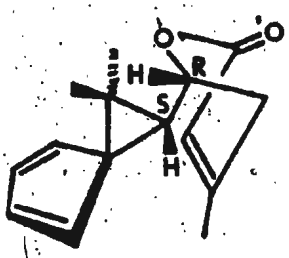
The lactone was subjected to Diels-Alder conditions (220°, xylene, sealed tube, 24 hours) but failed to cyclize. The Cram rule[34] predicts the formation of RS, SR diastereomeric pairs (*103a*, Scheme XVIII illustrated for the S aldehyde) which have the wrong relative stereochemistry needed for the Diels-Alder reaction to proceed. Caution should be exercised in the application of Cram's rule to cases with a cyclopropyl ring adjacent to the carbonyl. Since the bond angles are distorted from tetrahedral geometry to incorporate the cyclopropyl ring the outcome of addition may be affected.



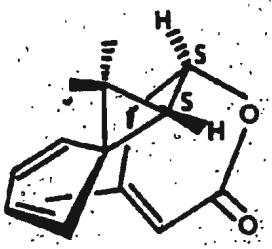
48



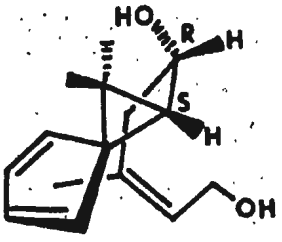
103a



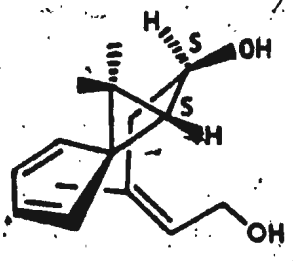
103a



103b



104a



104b

Scheme XVIII

The SS, RR diastereomeric pairs (*103b*) with the correct relative stereochemistry would be subject to a nonbonded interaction between the cyclopropyl hydrogen and the carbonyl which would be forced into close proximity.

Irrespective of the stereochemistry adjacent to the cyclopropyl ring, reduction to the diol *104* would free the olefinic sidechain to adopt the conformation required for cyclisation. To this end the lactone *103* was reduced with lithium aluminumhydride. The failure of diol *104* to cyclise under the Diels-Alder conditions previously described may be due to deactivation of the dienophile through loss of ester conjugation and the adverse steric interactions of the vinylmethyl group in the transition state.

8. Conclusion

A general route to substituted spiro[2.4]hepta-4,6-dienes has been developed, and the feasibility of constructing the 'left-hand portion' of longifolene by this method demonstrated. In spite of the failure of the preliminary attempts to generate the tetracyclo[5.4.0^{1,7}.0^{2,4}.0^{3,9}]undecene ring system the approach looks promising. Closely related spiro[2.4]hepta-4,6-dien-1-yl esters undergo Diels-Alder cyclisations[35] and lend credence to this route.

CHAPTER 3

Experimental

1. Initial Remarks

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrometer and were calibrated against the 1600 cm^{-1} and 2850 cm^{-1} bands of polystyrene film. Nuclear magnetic resonance spectra were determined with a Varian Model EM-360 or Bruker 80 spectrometer. Band positions are reported in parts per million downfield from tetramethylsilane as an internal standard. ^{13}C NMR spectra are proton decoupled unless otherwise specified. Mass spectra were recorded on a Micro-Mass 7070 HS mass spectrometer at an ionization potential of 70 eV unless otherwise specified.

Chromatographic separations were carried out using the "flash chromatography technique"[36] on Kiesegel 60 silica (230-400 mesh, Merck) using a ratio of 30:1 (wt silica gel):(wt. crude product) unless otherwise specified.

Optical rotations were recorded on a Perkin-Elmer 121 spectrometer utilizing the sodium D line at 589.9 nm. All solvents were distilled prior to use, anhydrous dimethoxyethane, ether, tetrahydrofuran and dioxane were dried and distilled from lithium aluminum hydride or potassium/benzophenone; absolute methanol and ethanol were dried and distilled from magnesium; diisoproplyamine, dimethylsulfoxide and dimethyl formamide were dried and distilled from calcium hydride; all distillations were carried out under a nitrogen atmosphere.

Reactions were conducted under an inert atmosphere of anhydrous nitrogen unless otherwise specified. Organic solutions were dried over anhydrous magnesium sulfate or anhydrous sodium sulfate and evaporated by means of a Buchi rotarary evaporator under reduced pressure.

2. S-(-)-4-Carbomethoxy-1,2-dimethyl-1,3-dioxolane (49)

Prepared by the procedure of: C.M. Lok, J.P. Ward and D.A. van Dorp[37].

B.p. 77-81° @ 10 mmHg, (lit 77-80° @ 10 mmHg), $[\alpha]_D$ -9.33 (neat), (lit -10.1 (neat))

IR (neat, ν, cm^{-1}): 2940-3020 (CH), 1740 (C=O), 1380, 1397 (CMe_2).

^1H NMR ($CDCl_3$, δ, ppm): 1.33 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.90-4.25 (m, 2H, CH_2), 4.33-4.60 (m, 1H, CH).

^{13}C NMR ($CDCl_3$, δ, ppm): 25.27 (CH_3), 51.92 (OCH_3), 67.05 (CH_2), 73.88 (CH), 111.14 (quaternary C), 171.46 (C=O).

3. S-(-)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-ol (50)

A solution of ester *49* (8.36 g, 52.25 mmol) in ether (10 ml) was added dropwise to a 0° (ice/water bath) stirred solution prepared by the reaction of iodomethane (8.14 ml, 130.8 mmol) with magnesium turnings (3.18 g, 156.9 mmol). After addition the reaction mixture was refluxed 12 hours, cooled in an ice/water bath and saturated aqueous ammonium chloride (30 ml) added. The resulting solution was extracted with ether (3x20 ml), dried, concentrated and distilled to yield *50* as a clear oil (5.80 g, 36.3 mmol, 69%).

B.p. 35-45° @ 0.7 mmHg, $[\alpha]_D$ -9.32 (neat).

IR (neat, ν, cm^{-1}): 3580 (OH), 3470 (br, OH), 1385, 1375 (CMe_2).

^{1}H NMR ($CDCl_3$, δ, ppm): 1.09 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.30 (bs, 1H, OH), 3.73-3.93 (m, 3H, -CH-CH_2).

^{13}C NMR ($CDCl_3$, δ, ppm): 24.33 (CH_3), 24.89 (CH_3), 26.03 (2 CH_3), 64.91 (CH_2), 69.61 (C-OH), 82.00 (CH), 109.00 (CMe_2).

4. S-(-)-2,2-Dimethyl-4-(methyl sulfonlyacetyl)1,3-dioxolane (56)

Dimethyl sulfoxide (5 ml) was added to a sodium hydride (0.25 g, 6.26 mmol, 50% oil dispersion previously washed with petroleum ether, 3x5 ml), heated (70-75°) with stirring until hydrogen evolution ceased (45 minutes). The solution was cooled (ice/water bath), tetrahydrofuran (5 ml) added, followed by ester *49* (0.50 g, 3.13 mmol) dropwise, the ice/water bath removed and stirring continued (30 minutes). The solution was diluted with saturated aqueous ammonium chloride (30 ml) and extracted with chloroform (3x20 ml). The combined chloroform extracts were washed with water (2x20 ml), dried and concentrated. The resulting oily-solid was triturated with cold ether (3x5 ml) and recrystallized from ether to give *56* (0.155 g, 0.76 mmol, 24%) as colourless prisms.

M.p. 102-104°

^{1}H NMR ($CDCl_3$, δ, ppm): 1.34 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.67 (s, 3H, SCH_3), 3.90-4.60 (m, 5H, SCH_2, CH_2, CH).

5. S-(-)-N,N-Dimethyl-4-carbamyl-2,2-dimethyl-1,3-dioxolane (98)

Ester *49* (0.22 g, 1.38 mmol) was dissolved in dimethylamine (1.0 ml) at -78° (solid CO_2/acetone bath), the solution was sealed in a glass tube and stored (58°, 15 days). The sealed tube was cooled to -78° (solid CO_2/acetone bath) opened, warmed to room temperature and the excess dimethylamine allowed to escape to yield *98*.

IR (neat, ν, cm^{-1}): 2850-2960 (CH), 1650 (C=O).

^1H NMR (CCl_4, δ, ppm): 1.20 (s, 6H, 2 CH_2), 2.74 (s, 3H, N CH_3), 2.94 (s, 3H, N CH_3), 3.80-4.20 (m, 2H, CH_2), 4.57 (t, 1H, J=6 Hz, CH).

6. S-(-)-4-Carboxy-1,2-dimethyl-1,3-dioxolane (58)

The potassium salt of *49* (100 mg, 0.54 mmol) dissolved in ether:ethanol (5:1, 2 ml) was added dropwise to a stirred suspension of pretreated ion exchange resin (Dowex 50W-X8, 1.1 g) in ether (5 ml), stirred 10 minutes and filtered. The filtrate was passed through a silica plug (ether eluent) and concentrated to yield *58* (0.046 g, 0.31 mmol, 58%) as a clear oil.

The ion exchange resin was pretreated by stirring with four normal aqueous hydrogen chloride (10 minutes), washing with deionized water (5x5 ml) and ether (5x5 ml).

IR (neat, ν, cm^{-1}): 3500-2500 (b, COOH), 1730 (C=O).

^1H NMR ($CDCl_3$, δ, ppm): 1.39 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 4.15 (d, 1H, J=6.6 Hz, CH), 4.19 (d, 1H, J=6.6 Hz, CH), 4.53 (d of d, 1H, J=6.6, 6.6 Hz, CH), 9.85 (bs, 1H, COOH).

7. Lithium Salt of S-(-) 4-Carboxy-1-dimethyl-1,3-dioxolane (59)

Methanolic lithium hydroxide (6.25 ml, 6.25 mmol, 1 M) was added to a 0° (ice/water bath), stirred solution of ester *49* (1.0 g, 6.25 mmol) in methanol (5 ml). Stirring was continued for 20 minutes after addition was complete and the reaction mixture concentrated. The residual material was triturated with ether (3x10 ml) and the remaining salt dried (100°, 0.1 mmHg, 24 hours) to yield *59* (0.90 g, 5.94 mmol, 95%) as a white powder.

M.p. 211-250° (dec); $[\alpha]_D$ -44.00 (MeOH, 0.123 g/ml).

^1H NMR ($CDCl_3$, δ, ppm): 1.35 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.70-4.55 (m, 3H, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, δ, ppm): 25.12 (q, J=130 Hz, CH_3), 25.46 (q, J=130 Hz, CH_3), 67.67 (t,

J=151 Hz, CH_2), 75.96 (d, J=151 Hz, CH), 111.25 (s, CMe_2), 78.49 (s, C=O).

8. S-(-)-2,2-Dimethyl-4-acetyl-1,3-dioxolane (54)

A solution of methylmagnesium chloride (3.31 ml, 9.89 mmol, 2.99 M in tetrahydrofuran) was added dropwise to a stirred suspension of lithium carboxylate *59* (1.00 g, 6.95 mmol) in tetrahydrofuran (10 ml). The reaction mixture was stirred until solution effected (0.5 hours) and added dropwise via "cannula" to a rapidly stirred aqueous ammonium chloride/ice slurry. The resulting solution was extracted with ether (3x20 ml), dried and concentrated to yield *54* (0.854 g, 5.93 mmol, 90%) as a clear oil.

B.p. 35-40° @ 0.5 mmHg; $[\alpha]_D$ -16.0 ($CHCl_3$, 0.134 g/ml).

IR (neat, ν, cm^{-1}): 2880-3000 (CH), 1725, 1440 (COOMe).

^1H NMR ($CDCl_3$, δ, ppm): 1.38 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.21 (s, 3H, OCH_3), 3.75-4.63 (m, 3H, CH_2CH).

^{13}C NMR ($CDCl_3$, δ, ppm): 24.75 (CH_3), 25.61 (CH_3), 25.78 (OCH_3), 66.19 (CH_2), 80.09 (CH), 110.88 (CMe_2), 208.73 (C=O).

9. R-(-)-6-Methyl-6-(2,2-dimethyl-1,3-dioxolane-4-yl)fulvene (55)

n-Butyllithium (0.69 ml, 2.45 mmol, 2.45 M) was added dropwise to a solution of cyclopentadiene (0.14 ml, 1.70 mmol, freshly distilled) in dioxane (5 ml). The reaction vessel was immersed in a preheated oil bath (120°). Upon attainment of reflux ketone *54* (0.2028 g, 1.14 mmol) was quickly added (10 sec) and the reaction solution immediately poured into a saturated aqueous ammonium chloride/ice slurry, extracted with ether (3x10 ml), dried concentrated and filtered through a short (5 cm) silica column (ether eluant) to yield *55* (0.1818 g, 0.947 mmol, 67%), as an orange oil.

IR (neat, ν, cm^{-1}): 3100, 3060, 2860-2980 (CH), 1640 (C=C), 1370, 1380 (CMe_2).

^1H NMR ($CDCl_3$, δ, ppm): 1.38 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.54 (t, 1H, J=5.7 Hz, CH), 6.31 (s, 4H, CH).

Mass Spec (m/e): 192 (M^+), 177 (40), 101 (40), 91 (28), 43 (base).

10. R-(-)-Cyclopentadien-2-yl-2-(2,2-dimethyl-1,3-dioxolane-4-yl)propane (51)

Methyllithium (1.84 ml, 2.85 mmol, 1.55 M in ether) was added dropwise to a 0° (ice/water bath), stirred solution of fulvene *55* (0.4977 g, 2.59 mmol) in tetrahydrofuran (5 ml) over a one minute period. The reaction was stirred a further five minutes and poured into a cold saturated aqueous ammonium chloride solution, extracted with ether (3x10 ml), dried, concentrated and chromatographed (10:1 hexane:ethyl acetate eluant) to yield *51* (0.246 g, 1.18 mmol, 46%) as a clear oil.

$[\alpha]_D$

IR (neat, ν, cm^{-1}): 2960-2850 (CH), 1450 (CH_3), 1370 (gem CH_3).

^1H NMR ($CDCl_3$, δ, ppm): 1.13 (s, 6H, 2 CH_3), 1.26 (s, 6H, 2 CH_3), 2.82 (bs, 2H, CH_2), 3.22-4.05 (m, 3H, $CHCH_2$), 5.80-6.60 (m, 3H, CH=CH-CH=).

11. S-(-)-4,3-Dihydroxy-2-butanone (61)

Aqueous trifluoroacetic acid (1 ml, 1M) was added to a solution of ketone *54* (0.519 g, 3.60 mmol) dissolved in acetonitrile (5 ml), stirred (2 days), pyridine (0.5 ml) added and the solution filtered through a short (5 cm) silica column (1:1 hexane:isopropanol eluant) and concentrated to yield *61* as a clear oil.

IR (neat, ν, cm^{-1}): 3350 (OH), 1675 (C=O).

^1H NMR (CD_3CN, δ, ppm): 2.12 (s, 3H, CH_3), 3.70 (d, 2H, J=4.0 Hz, CH_2), 4.10 (t, 1H, J=4.0

Hz, CH).

12. 2-Acetyloxirane (62)

Aqueous sodium hydroxide (1 N, 200 ml, 0.20 moles) was added dropwise to a solution of hydrogen peroxide (30% aqueous, 115 ml, 1.01 moles) and 3-butenone (32.5 ml, 0.325 moles) in methanol (400 ml), over a one hour period maintaining the temperature between 15-20° by use of an ice/water bath. After addition was complete the solution was stirred an additional three hours maintaining the temperature between 20-25°, poured into brine (200 ml), extracted with dichloromethane (4x150 ml) and dried. The resulting solution was concentrated to *ca.* 50 ml (maintaining the evaporator bath at room temperature) and distilled to yield *62* (24.345 g, 0.283 moles, 71%) as a colourless liquid.

B.p. 28-30° @ 8 mmHg.

IR (neat, ν, cm^{-1}): 3000 (CH), 1710 (C=O), 860 (oxirane).

^1H NMR ($CDCl_3$, δ, ppm): 1.95 (s, 3H, CH_3), 2.90 (m, 2H, CH_2), 3.20 (m, 1H, CH).

Mass Spec (m/e): 86 (M^+), 85 (5), 71 (7), 43 (base).

13. 6-Methyl-6-oxiranylfulvene (63)

Pyrrolidine (0.25 ml, 0.30 mmol) was added to a stirred solution of oxirane *62* (1.00 g, 11.6 mmol) and cyclopentadiene (1.00 ml, 12.1 mmol, freshly distilled) in methanol (5 ml) maintained at 0° (ice/water bath). The solution was stirred for a further two hours and extracted with hexane (3x10 ml). The combined extracts were washed with dilute acid (10 ml, 0.1 N HCl), saturated aqueous bicarbonate (10 ml), dried and concentrated to yield *63* (1.323 g, 10.0 mmol 86%) as an orange oil.

IR (neat, ν, cm^{-1}): 2900-3100 (CH), 1630 (C=C).

^{1}H NMR ($CDCl_3$, δ, ppm): 1.95 (s, 3H, CH_3), 2.90 (m, 2H, CH_2), 4.00 (m, 1H, O-CH), 6.50 (m, 4H, C_6H_4).

Mass Spec (m/e): 134 (M^+) 130 (64), 91 (base), 78 (59).

14. 1,1-Dimethyl-2-hydroxymethylspiro[2.4]hepta-4,6-diene (65)

Methyllithium (34.2 ml, 52.8 mmol, 1.55 M in ether) was added dropwise to a stirred, 0° (ice/water bath) solution of fulvene *63* (5.925 g, 44.0 mmol) in dimethoxyethane (100 ml). After addition was complete the solution was warmed to room temperature, poured into saturated aqueous ammonium chloride (100 ml) and extracted with ether (3x30 ml). The combined extracts were washed with brine (30 ml), water (30 ml), dried concentrated and the crude product chromatographed on florisil (100 g, 4:1 hexane:ether eluant, 100-200 mesh, Fisher) to yield recovered *63* (0.587 g, 4.40 mmol, 10%) and *65* (3.849 g, 25.7 mmol, 58%), the major fraction as a colourless oil.

IR (neat, ν, cm^{-1}): 3100-3600 (OH), 2920 (CH), 1375 (CMe_2).

^{1}H NMR (CCl_4, δ, ppm): 1.38 (s, 3H, CH_3), 1.40 (s, 3h, CH_3), 2.22 (t, 1H, J=7 Hz, CH_2), 6.30 (m, 4H, C_6H_4).

15. 1,1-Dimethyl-2-formylspiro[2.4]hepta-4,6-diene (48)

Spiro alcohol *65* (1.084 g, 7.23 mmol) was added to a refluxing, stirred suspension of active manganese dioxide[38] (20 g) in dichloromethane (100 ml). Reflux was continued for fifteen hours, the resulting suspension was filtered through a bed of celite/magnesium sulfate and concentrated to yield *48* (0.775 g, 5.24 mmol, 73%) as a colourless oil.

IR (neat, ν, cm^{-1}): 2910 (CH), 1700 (C=O).

^{1}H NMR (CCl_4, δ, ppm): 1.48 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 2.80 (d, 1H, J=6 Hz, CH) 6.1-6.8 (m, 4H, C_6H_4), 9.65 (d, 1H, J=6 Hz, CHO).

16. Ethyl-3-methyl-2,3-dibromobutanoate (69)

A solution of bromine (0.2 ml, 3.90 mmol) in dichloromethane (5 ml) was added dropwise to a 0° (ice/water bath) stirred solution of ethyl 3,3-dimethylacrylate (0.500 g, 3.90 mmol) and n-bromosuccinimide (*ca* 0.020 g) in dichloromethane (10 ml). The ice/water bath was removed and the solution stirred a further two hours at room temperature, aqueous sodium sulfite (20 ml) was added, the mixture extracted with dichloromethane (3x10 ml), dried and concentrated to give a crude product which was dissolved in carbon tetrachloride (5 ml), filtered and concentrated to yield *69* (0.931 g, 3.23 mmol, 83%) as a clear oil.

IR (neat, ν, cm^{-1}): 2975 (CH), 1745 (C=O).

^1H NMR (CCl_4, δ, ppm): 1.3 (t, 3H, J=7 Hz, CH_3), 1.95 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 4.20 (q, 2H, J=7 Hz, OCH_2), 4.25 (s,1H,

17. Ethyl-2-bromo-3-methyl-2-butenoate (66)

Dibromide *69* (8.60 g, 30.0 mmol) was added dropwise to a stirred and cooled (ice/water bath) solution of sodium (1.0 g, 43.5 mmol) dissolved in absolute ethanol (50 ml). The solution was stirred for 0.5 hours and poured into a dilute hydrochloric acid/ice mixture (100 ml, 1N), extracted with hexane (3x50 ml), dried, concentrated and distilled to yield *66* (5.90 g, 28.5 mmol, 95%) as a clear oil.

B. p. 34-35° @ 0.08 mmHg.

IR (neat, ν, cm^{-1}): 2975, 2925 (CH), 1710 (C=O), 1610 (C=C).

^1H NMR (CCl_4, δ, ppm): 1.30 (t, 3H, J=8.0 Hz, CH_3), 2.00 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 4.10 (q, 2H, J=8.0 Hz, OCH_2).

Mass Spec (m/e): 206, 208 (M^+) 178, 180 (31), 161, 163 (34), 45 (base).

18. 3-Methyl-2-buten-1-ol (70)

A solution of ethyl 3,3-dimethylacrylate (12.8 g, 0.10 moles) in ether (30 ml) was added dropwise to a stirred suspension of lithium aluminumhydride (2.30 g, 0.06 moles) in ether (200 ml) at such a rate as to maintain reflux. Stirring was continued for a further 1.5 hours, ethyl acetate (20 ml) added and the solution poured into dilute sulfuric acid (10%, 100 ml). The separated organic layer was washed with aqueous sodium bicarbonate (saturated, 50 ml), brine (50ml), dried, concentrated and distilled to yield *70* (7.119 g, 0.083 moles, 83%) as a clear liquid.

B.p. 53-54° @ 15 mmHg, (lit 47-49° @ 11 mmHg).

IR (neat, ν, cm^{-1}): 3300 (OH), 2900 (CH), 1675 (C=C).

^1H NMR (CCl_4, δ, ppm): 1.55 (s, 3H, CH_3); 1.61 (s, 3H, CH_3), 3.50 (s,1H, OH), 3.92 (d, 2H, J=7 Hz, CH_2), 5.20 (t, 1H, J=7 Hz, =CH-).

19. Methyl-3-methyl-2-buten-1-yl ether (71)

Alcohol *70* (1.00 g, 12.0 mmol) was added dropwise to a suspension of sodium hydride (0.530 g, 18.0 mmol, 60% oil dispersion, previously washed with 3x5 ml hexane) in tetrahydrofuran (30 ml). The reaction mixture was heated (50°, oil bath) until hydrogen evolution ceased and iodomethane (1.5 ml, 24.0 mmol) added. The solution was stirred for fourteen hours at room temperature, poured into saturated aqueous ammonium chloride/ice mixture (100 ml), extracted with ether (3x50 ml), dried, concentrated and distilled to yield *71* (0.475 g, 4.80 mmol, 40%) as a colourless liquid.

B.p. 52-60° @ 1 atm.

IR (neat, ν, cm^{-1}):2800-2950 (CH), 1675 (C=C).

^{1}H NMR (CCl_4, δ, ppm): 1.65 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 3.18 (s, 3H, OCH_3), 3.76 (d, 2H, J=9.0 Hz, CH_2), 5.20 (t, 1H, J=9.0 Hz, CH).

20. Methyl-3-methyl-2,3-dibromobutan-1-yl ether (72)

A solution of bromine (1.00 ml, 19.4 mmol) in dichloromethane (10 ml) was added dropwise to a 0° (ice/water bath), stirred solution of ether *71* (1.935 g, 19.4 mmol) in dichloromethane (50 ml), stirring was continued (0.3 hours) and saturated aqueous sodium sulfate (50 ml) added. The mixture was extracted with dichloromethane (3x50 ml), dried, concentrated and distilled to yield *72* (3.286 g, 12.6 mmol, 65%) as a colourless liquid.

B.p. 97-99° @ 11 mmHg.

^{1}H NMR (CCl_4, δ, ppm): 1.81 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 3.60-4.33 (m, 3H, -CH-CH_2).

Mass Spec (m/e): 227, 229 (M^+-15), 179, 181 (3), 147, 149 (25), 45 (base).

21. Methyl cyclopentadien-2-yl-3-methyl-2-butenyl ether (73)

Cyclopentadiene (0.42 ml, 5.10 mmol, freshly distilled) was added dropwise to a stirred, 0° (ice/water bath) suspension of sodium hydride (0.340 g, 8.50 mmol, 60% oil dispersion, previously washed with 3x5 ml hexane) in tetrahydrofuran (20 ml). Stirring was continued until hydrogen evolution ceased (30 minutes) and a solution of dibromide *72* (0.870 g, 3.40 mmol) in tetrahydrofuran (5 ml) was added dropwise, the ice/water bath removed and the solution left to stir. After three days saturated aqueous ammonium chloride (10 ml) was added, solution extracted with ether (3x20 ml), dried, concentrated and filtered through a short (*ca* 5 cm) silica column (ether eluant) to yield *73* (0.279 g, 1.70 mmol, 50%) as a brown oil.

^{1}H NMR (CCl_4, δ, ppm): 1.82 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 2.82 (bs, 2H, CH_2), 3.20 (s, 3H, O-CH_3), 4.08 (s, 2H, CH_2), 6.00-6.35 (bm, 3H, 3CH).

22. Methyl (E)-4-chloro-3-methyl-2-butenoate (81)

A solution of chloroacetone (6.0 ml, 75.0 mmol) and methyl (triphenlyphosphoranylidene)acetate (17.0 g, 50.0 mmol) in dioxane (100 ml), was refluxed for eighteen hours, the solution concentrated and the residual gum triturated with hexane (4x10 ml). The combined hexane triturates were cooled (-40°, 12 hours), filtered, concentrated and distilled to yield a mixture of three products (3.505 g): *81*, Methyl (Z)-4-chloro-3-methyl-2-butenoate and methyl-3-acetyl-2-propenoate in an approximate ratio of 4:1:1 (by NMR). The desired compound was isolated utilising medium pressure liquid chromotography (column 30x4 cm, 20 psi, 230-400 mesh silica, eluant hexane:ethyl acetate 30:1) to give *81* (2.45 g, 16.5 mmol, 33%) as a colourless liquid.

B.p. 46-48° @ 0.01 mmHg.

IR (neat, ν, cm^{-1}): 2940 (CH), 1710 (C=O), 1650 (C=C).

^1H NMR (CCl_4, δ, ppm): 2.24 (s, 3H, CH_3), 3.70 (s, 3H, O-CH_3), 4.06 (s, 2H, CH_2Cl), 5.98 (bs, 1H, CH).

23. Ethyl 4-chloro-3-hydroxy-3-methylbutyrate

Prepared by the procedure of Epstien and Sonntag[39] except ethyl bromoacetate was used in place of methyl bromoacetate.

B.p. 58° @ 0.01 mmHg.

IR (neat, ν, cm^{-1}): 3425 (b, OH), 2950 (CH), 1712 (C=O).

^1H NMR ($CDCl_3$, δ, ppm): 1.35 (t, 3H, J=8 Hz, CH_3), 1.47 (s, 3H, CH_3), 2.65 (s, 1H, CH), 2.71 (s, 1H, CH), 3.61 (s, 2H, CH_2Cl), 3.88 (s, 1H, OH), 4.21 (q, 2H, J=8 Hz, CH_2).

24. Methyl (E)-4-hydroxy-3-methyl-2-butenoate

Procedure adapted from: Epstein and Sonntag[39]

Chlorohydrin *98* (1.00 g, 5.54 mmol) was added dropwise to a 0° (ice/water bath), stirred solution of methanolic potassium hydroxide (3.53 M, 3.17 mL, 11.08 mmol). The mixture was stirred for two hours and methanolic hydrogen chloride added until the mixture became neutral to litmus (1M, *ca.* 6 mL). The mixture was poured into ether (20 ml), filtered, concentrated and distilled to yield *100* (0.504 g 3.88 mmol, 70%) as a clear oil containing a small amount (*ca.* 10% by NMR) of the ethyl ester.

B.p. 80-82° @ 0.01 mmHg (Lit: 70-90° @ 0.5 mmHg).

^{1}H NMR (CCl_4, δ, ppm): 2.08(s, 3H, CH_3), 3.72 (s, 3H, O-CH_3), 4.10 (bs, 3H, CH_2 and OH), 5.98 (bs, 1H, CH).

25. (E)-Methyl 4-bromo-3-methyl-2-butenoate (101)

Prepared by the procedure of: Corey and Erickson[26].

B.p. 89° @ 10 mmHg (Lit 82-83° @ 10 mmHg).

IR (neat, γ, cm^{-1}): 2860-2950 (CH), 1720 (C=O), 1645 (C=C).

^{1}H NMR (CCl_4, δ, ppm): 2.29 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 3.92 (s, 2H, CH_2Br), 5.91 (bs, 1H, CH).

26. 2-Cyclopentadienyl-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (60)

n-Butyllithium (0.70 ml, 1.72 mmol, 2.45 M in hexane) was added dropwise to a solution of cyclopentadiene (0.15 ml, 1.82 mmol, freshly cracked) in tetrahydrofuran (5 ml), stirred (10 minutes) and cooled (-78°, solid CO_2/acetone bath). Ketone *54* (0.200 g, 1.40 mmol) dissolved in tetrahydrofuran (1 ml) was added dropwise, solution stirred (1 hour),

saturated aqueous ammomium chloride added (5 ml), the mixture warmed to room temperature, extracted with ether (3x10 ml), dried and concentrated to yield *60* (0.243 g, 1.20 mmol, 82%) as a clear oil.

IR (neat, ν, cm^{-1}): 3450 (OH), 2850-2975 (CH).

^1H NMR (CCl_4, δ, ppm): 1.18 (s, 3H, CH_3), 1.25 (s, 6H, 2 CH_3), 2.54 (bs, 1H, OH), 2.80 (bs, 2H, CH_2), 3.48–4.05 (m, 3H, CH_2), 6.15 (bs, 3H, 3 CH).

Mass Spec (m/e): 177 (M^+-33), 109 (34), 101 (56), 43 (base).

27. 2-Cyclopentadienyl-2-oxiranylethanol

Cyclopentadiene (0.11 ml, 1.32 mmol, freshly distilled) was added dropwise to a stirred suspension of sodium hydride (0.53 g, 1.32 mmol, 60% oil dispersion previously washed with 3x5 ml hexane) in tetrahydrofuran (5 ml), stirred (10 minutes), cooled (-78° solid CO_2/acetone bath) and oxirane *62* (0.100 g, 1.20 mmol) added dropwise. The solution was stirred (0.5 hours), the cooling bath removed and the solution allowed to warm to room temperature, poured into saturated aqueous ammonium chloride (20 ml), extracted with ether (3x10 ml), dried and concentrated to give a crude oil which was chromatographed (3:1 Hexane:ethyl acetate eluant) to yield *102* (0.076 g, 0.50 mmol, 17%) as a clear oil.

IR (neat, ν, cm^{-1}): 3400 (OH), 2850-3000 (CH).

^1H NMR ($CDCl_3$, δ, ppm): 1.42 (s, 3H, CH_3), 2.25 (bs, 1H, OH), 2.60-2.90 (bm, 2H, CH_2), 3.00-3.25 (bm, 3H, CH, CH_2), 6.15-6.40 (bm, 3H, 3 CH).

28. (E)-4-Bromo-3-methyl-2-butene-1-ol (96)

Diisobutyl aluminumhydride (8.64 ml, 8.3 mmol, 1M in toluene) was added dropwise to a -78° solution (solid CO_2/acetone bath) of ester *101* (0.834g, 4.32 mmol) in toluene (5 ml). The solution was stirred one hour, aqueous hydrogen chloride added (2 ml, 1 M) and the

cooling bath removed. The crude reaction mixture was filtered through a short silica column (ether eluant) to yield *96* (0.429 g, 2.60 mmol, 60%) as a clear oil.

IR (neat, ν, cm^{-1}): 3300 (OH), 2860 (CH).

^1H NMR ($CDCl_3$, δ, ppm): 1.80 (s, 3H, CH_3), 2.90 (s, 1H, OH), 4.01 (s, 1H, CH_2Br), 4.23 (d, 2H, J=7Hz, CH_2OH), 5.85 (t, 1H, J=7Hz, CH).

29. (E)-4-Bromo-3-methyl-2-butene-1-yl-2-tetrahydropyranyl ether (97)

4-Toluenesulfonic acid (*ca.* 0.1 g) was added to a cold (ice/water bath) solution of alcohol *96* (2.050 g, 12.4 mmol) and dihydropyran (1.25 ml, 13.6 mmol) in ether (20 ml). The cooled solution was stirred overnight, washed with water, dried and concentrated to yield *97* (2.544 g, 10.2 mmol, 82%) as a clear oil.

IR (neat, ν, cm^{-1}): 2920, 2850 (CH).

^1H NMR ($CDCl_3$, δ, ppm): 1.69 (bm, 6H, 3 CH_2), 1.88 (s, 3H, CH_3), 3.30-4.35 (bm, 6H, $CH_2Br+2CH_2O$), 4.62 (bs, 1H, OCHO), 5.80 (t, 1H, J=7Hz, CH).

30. (E)-4-Bromo-3-methyl-2-butene-1-yl t-butyldimethylsilyl ether (98)

Prepared by the procedure of Kandil and Slessor[40].

IR (neat, ν, cm^{-1}): 2960, 2840 (CH).

^1H NMR ($CDCl_3$, δ, ppm): 0.0 (s, 6H, $2SiCH_3$), 0.85 (s, 9H, $SiCMe_3$), 1.51 (s, 3H, CH_3), 4.12 (d, 2H, J=6Hz, OCH_2), 4.38 (s, 2H, CH_2Br), 5.40 (t, 1H, J=6Hz, CH).

31. 1,1-Dimethyl-2-(4-methyl-5,6-dihydro-1,2-pyrone-6-yl)spiro[2.4]hepta-4,6-diene (103)

Zinc dust previously treated sucessively with dilute HCl, methanol, ether and vacuum dried was added to a solution of aldehyde *18* (.500 g, 3.4 mmol), bromo ester *101* (0.780 g,

4.08 mmol) and iodine (0.17 g, 0.68 mmol) in dioxane (5 ml). The solution was immersed in a preheated (55°) ultrasonic bath for 6 hours. The ultrasonic bath was replaced by an oil bath and the solution was heated at 70° for 2 hours. Saturated aqueous ammonium chloride was added, solution extracted with ether, dried and concentrated to give a crude oil, which was chromatographed (silica, 10:1 hexane:ethyl acetate eluant) to yield *103* as white needles. M.p. 138-140 °.

IR (neat, ν, cm^{-1}): 2820 (CH), 1710 (CO).

^1H NMR ($CDCl_3$, δ, ppm): 1.40 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.32 (d, 2H, J=10Hz, CH_2), 2.00 (d, 1H, J=6Hz, CH), 4.53 (d of t, 1H, J=10, 6Hz, CH), 5.82 (bs, 1H, CH), 6.1-6.7 (m, 4H, 3CH).

32. 1,1-Dimethyl-2-(Z-1,5-dihydro-3-methyl-2-pentene-5-yl)spiro[2.4]hepta-4,6-diene (104)

The lactone *103* (*ca.* 0.50 g) was added to a cold (ice/water bath) suspension of lithium aluminumhydride (*ca.* 0.50 g) in ether, stirred for 4 hours and water was added until hydrogen evolution stopped. HCl was added (1 M) until the aluminates dissolved (1 ml), the solution was extracted with ether (3x5 ml) with salting out of the aqueous layer. The organic layer was dried and concentrated to yield *104* as an oil.

IR (neat, ν, cm^{-1}): 3350 (OH), 2900 (CH).

^1H NMR ($CDCl_3$, δ, ppm): 1.42 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.73 (bs, 4H, CH CH_3), 2.20 (d, 2H, J=10Hz, CH_2), 3.30 (bs, 1H, OH), 3.70-4.20 (m, 3H, CH CH_2), 5.7 (t, 1H, J=7Hz, CH), 6.1-6.7 (m, 4H, 4CH).

33. Procedure for Diels-Alder attempts

A solution of the triene in xylene was sealed in a glass tube fitted with a teflon needle valve. The tube was immersed in an oil bath at 220° for 24 hours and removed. After the tube had cooled the solution was removed and passed through a short silica column (ether eluant) to remove the xylene, and concentrated to yield the crude product.

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