

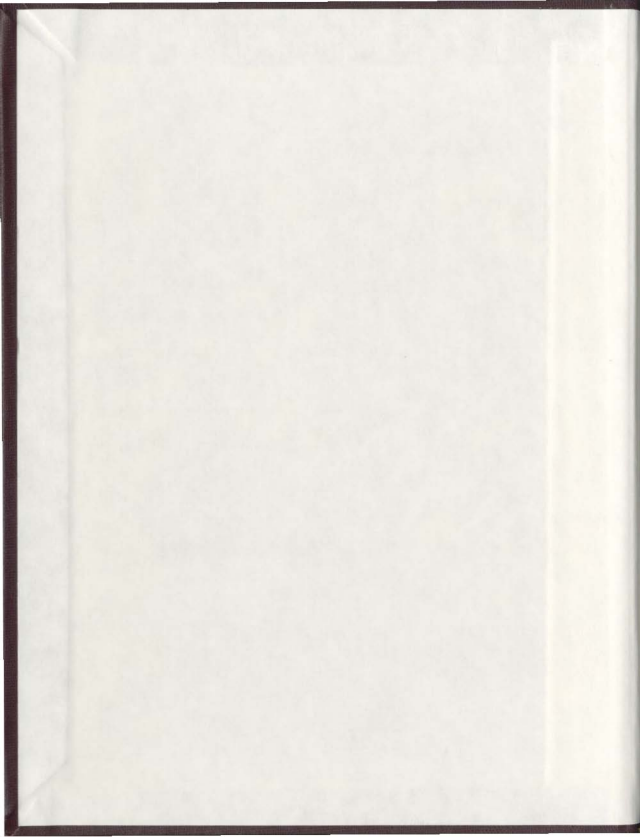
STUDIES DIRECTED TOWARD THE TOTAL
SYNTHESIS OF RETIGERANIC ACID

CENTRE FOR NEWFOUNDLAND STUDIES

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STUDIES DIRECTED TOWARD THE TOTAL
SYNTHESIS OF RETIGERANIC ACID

by

© ~~Ralph Stephen~~ Smith, B.Sc.

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

Abstract

Studies directed at the total synthesis of retigeranic acid (1) have revealed that compounds of type 81a and 87 cyclize in intramolecular fashion to give the conjoint ring systems 91 and 90 rather than the fused bicyclo [3.3.0] octanes 48 and 88. Increasing the acidity of the γ -proton did not result in alkylative cyclization.

The Wittig reagents 124, 125, and 126 have been synthesized and shown to react in normal fashion with aldehydes to give enol-ether-dienes such as 128 and α,β -unsaturated ketones 129 after hydrolysis. A route to a suitable triene 111 for the construction of the hydrindane portion of retigeranic acid has been developed, but unfortunately conditions were not found that allowed the intramolecular Diels-Alder reaction to proceed.

Acknowledgements

The author wishes to express his appreciation to Dr. Alex G. Fallis for the guidance, enthusiasm and patience he provided throughout this work.

The author would also like to thank his wife, Cheryl, for her encouragement and understanding, without which this effort would not have been possible.

Thanks are also due to Ms. Marian Baggs for recording mass spectra, and to Mr. Avery Earle who recorded the 80 MHz n.m.r. spectra.

Financial assistance from Memorial University of Newfoundland is gratefully acknowledged.

This Thesis is dedicated to the memory of

Barbara Lynn Charters

whose courage was an inspiration to
all who knew her.

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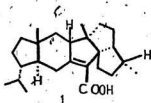
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Introduction

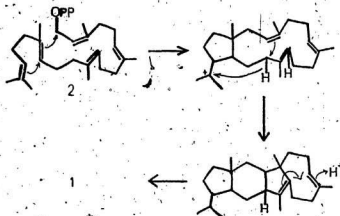
The unique sesterterpene retigeranic acid (1) was first isolated in 1965 by Seshadri et al.¹ from lichens of the Lobaria retigera group collected in the western Himalayas. In 1972 Schibata and co-workers² revised the molecular formula to $C_{25}H_{38}O_2$ based on high resolution mass spectrometry and determined the skeletal structure by means of x-ray analysis. They also proposed that the biogenetic pathway to this pentacyclic sesterterpene involved the cyclization of geranyl-farnesylpyrophosphate (2) as outlined in Scheme 1². Since then, work by Cane and Tillman³ has determined by means of enzymatic cyclization, that the biosynthesis of the structurally related triquinane skeleton compound, penetelene (3), involves a similar sequence of steps starting from farnesyl pyrophosphate (4) (Scheme 2).

Although retigeranic acid (1) does not resemble any previously known sesterterpene, its triquinane ring portion is found in many related natural products including pentalenic acid (5)⁴, isocomene (6)^{5,6}, silphinene (7)^{7,8}, and laurene (8)⁹. Structural features such as eight asymmetric carbons, three quaternary centers, a tetrasubstituted olefin and four ring junctures make retigeranic acid (1) a synthetically challenging molecule, as evident by the fact that it has yet to be totally synthesized.

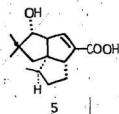
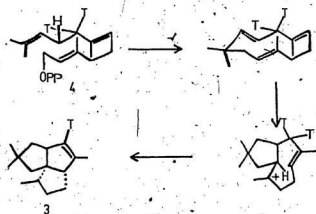
Before the early sixties there were relatively few examples of natural cyclopentanoids other than the iridoids and cedranes and the D ring of steroids. Rarer still were



Scheme 1



Scheme 2

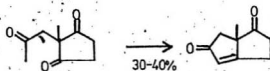
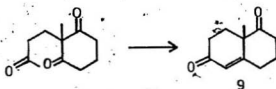


polycondensed natural products. During the mid-1970's interest in synthesizing fused cyclopentane ring systems grew rapidly as these new natural products containing di and triquinane skeletons were isolated. Since then the amount of research dealing with such polyquinane systems has increased dramatically, resulting in a number of new methods that have met the challenge of producing five membered ring systems. In particular, functionalized bicyclo[3.3.0]octane synthons have received significant attention.

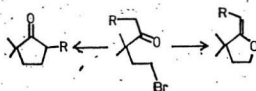
Five membered ring forming reactions include the classical Dieckman cyclization, Friedel Crafts acylation and aldol condensation. Although they may be used for a variety of ring sizes, problems arise due to the strain of five membered rings. For example, (Scheme 3)¹⁰ the analogous aldol condensation to the well known Wieland-Mieschner ketone 2 gave only 30-40% yield of the diquinane. Intramolecular alkylations show a stereoselective preference for O-alkylation over C-alkylation, which is opposite to the six membered ring case, (Scheme 4)¹². In fact, extrapolating cyclization methods that work for six membered rings to five membered rings can be "painfully deceptive"¹⁰. Representative preparative methods for condensed five membered rings are outlined below (for recent reviews see Paquette¹³, Trost¹⁰, and Demuth and Schaffner¹⁴).

Several types of annulation reactions have given fused cyclopentanoid products. Cyclodehydration procedures analogous to aldol condensations (Scheme 5) resulted in

Scheme 3



Scheme 4

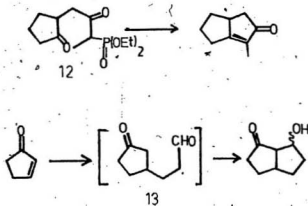
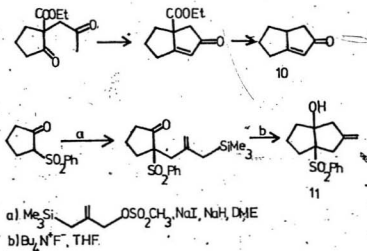


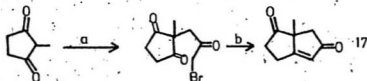
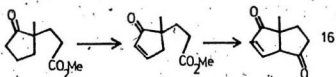
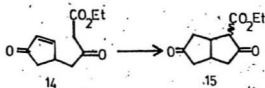
the synthesis of the elusive bicyclic enone 10¹⁵, while a modified sequence employing a vinyl silane gave 11¹⁶. The use of Wadsworth-Emmons reagents such as 12 gave desirable results¹⁷ as did aldol condensation of 13¹⁸. Intramolecular Michael additions as in the sequence 14-15¹⁹ were highly efficient, while the intramolecular Claisen condensation was used to produce highly functionalized bicyclo[3.3.0]octanes such as 16²⁰. Similarly, the intramolecular Wittig cyclization developed by Frost and Curran²¹ for the synthesis of 17 provided entry to a highly functionalized system. Some of the new techniques have involved the use of silicon containing intermediates as in the adaptations of the Nazarov cyclization outlined in Scheme 6 to produce cyclopentenone annulation²².

Ring contraction and expansion are both available to the synthetic chemist interested in these fused cyclopentane systems. The Favorskii rearrangement is an example of ring contraction that has been used as part of a sequence towards diquinanes as illustrated by the conversion of 18-19²⁴ (Scheme 7). Two types of ring expansion reactions have proved useful. One involved treating the dichlorocyclobutanone 20, resulting from dichloroketene addition to an olefin, with diazomethane to give 21²⁵; while in the other case a trimethylthio intermediate was reacted with tetrakis (acetonitrile) copper (I) perchlorate, 22-23²⁶.

The N-bromosuccinimide induced closure to bromohydrin²⁷, thiolation in the presence of Lewis acids²⁸ and the Me_2AlCl catalyzed ene reaction with formaldehyde²⁷ of 1,5-cyclo-

Scheme 5

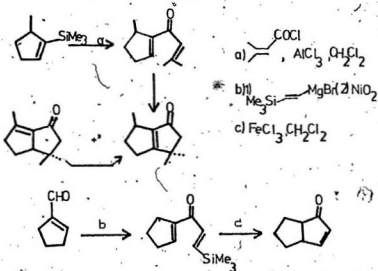




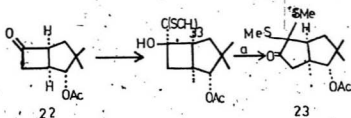
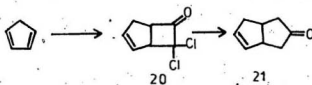
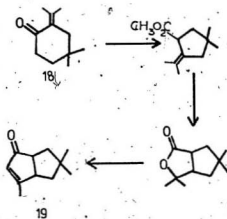
a) $\text{AcOCH}_2\text{CH}_2\text{CO}_2\text{Et}$, $\text{Pd}(\text{PPh}_3)_4$, DBU (2) NBS

b) $\text{1) Ph}_3\text{P, C}_6\text{H}_6, \Delta$ (2) $\text{K}_2\text{CO}_3, \text{H}_2\text{O}, \Delta$

Scheme 6



Scheme 7



a) $\text{CuClO}_4 \cdot 4\text{CH}_3\text{CN}$

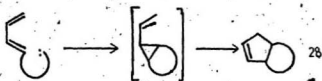
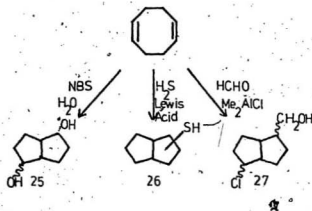
octadiene (24) are new adaptations of the well known trans-annular bond formations of eight membered rings, which gave 25, 26, and 27 respectively (Scheme 8). An analogy to a $[4 + 2]$ cycloaddition that would result in a cyclopentane ring annulation 28 has been developed by Hudlicky and models of these reactions of carbenes with conjugated dienes have been studied³⁰⁻³². Pyrolysis of the vinylcyclopropane intermediates resulted in the formation of the desired fused ring compounds (Scheme 9).

Another thermolytic vinylcyclopropane rearrangement scheme employed the condensation of cyclopentanone with a silylcyclopropyl anion followed by dehydration and pyrolysis as in the case of 29-30^{33,34}. Work by Conia et al^{35,36} has pointed out the synthetic value of the intramolecular ene reaction, 31, and a slight variation involving the pyrolysis of a diene ester has provided promising results, 32³⁷.

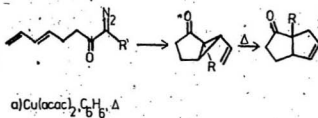
Many of these techniques for producing fused pentacyclic systems have been applied to the synthesis of both the linear and angular triquinane skeletons found in natural products. As an example, isocomene (6) has been synthesized via several routes. It was first synthesized in 1979 by three different groups concurrently. The key step in the approach of Oppolzer and co-workers^{6a,b} was an intramolecular ene reaction followed by ring contraction to give the $[6.3.0.0]^{4,8}$ triquinane skeleton as outlined in Scheme 10.

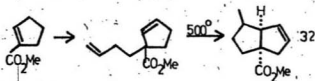
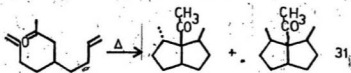
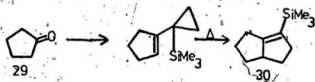
Paquette's^{6c,d} successful approach to isocomene (6) was by a stannic chloride induced cyclization and the lithium

Scheme 8

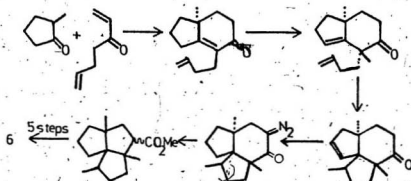


Scheme 9

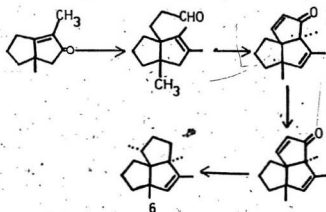




Scheme 10



Scheme 11

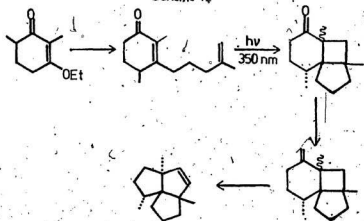


dimethylcuprate 1,4-addition of the final methyl group in the penultimate step (Scheme 11). It also involved a cuprous bromide-dimethyl sulfide complex catalyzed 1,4-conjugate addition of a ketal grignard reagent, which he has since used in several other synthetic schemes to related molecules³⁸.

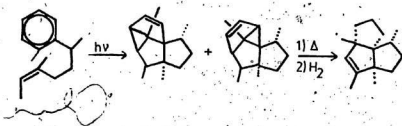
The third approach of the original trika, by Pirrung^{6e,f}, is the shortest route and featured [2 + 2] photocycloaddition and a Wagner-Meerwein rearrangement step (Scheme 12). Subsequent synthesis of isocomene (6) have been achieved by two other research groups^{6g,h}. Metaphotocycloaddition of an olefinic substituent aromatic ring followed by thermolysis and controlled hydrogenation was used by Wender and Dryer^{6h} (Scheme 13) in their novel synthesis. A synthetic scheme published by Chatterjee³⁹ has been rebuked several times in the literature and is generally considered mythical.

Although retigeranic acid has yet to be totally synthesized, a few approaches to portions of it have appeared in the literature. Paquette and co-workers^{40a,b} are working on a synthetic scheme based on two bond disconnections in the B ring (Scheme 14) which gave a functionalized angular triquinane segment 23 and a highly functionalized 1,1,2,3-tetrasubstituted cyclopentane 24 as synthons. They have described their attempts to synthesize 24 in proper enantiomeric form in an interim report on 1,2,3-trisubstituted cyclopentanes as being "more vexacious than

Scheme 12



Scheme 13

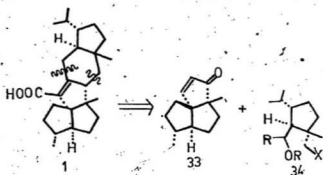


originally expected"^{40b}.

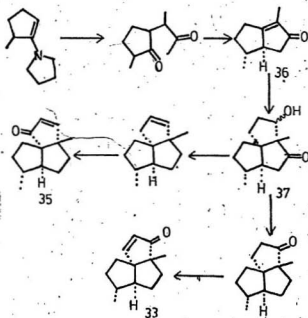
In Paquette's exhaustive review on "Recent Synthetic Developments in Polyquinane Chemistry"^{40b}, he states that the triquinane portion of retigeranic acid has been prepared by his research group in both racemic and optically active forms. Although not yet published, the racemic synthetic route is outlined in Scheme 15. Preparation of the fused bicyclic enone 36 was achieved by means of an aldol type condensation, followed by cuprous bromide-dimethylsulfide promoted conjugate addition of the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane. Acid hydrolysis permitted the formation of 37. With 37 in hand they then prepared two tricyclic enones 33 and 35 by alternate routes. Enone 35 was obtained by condensing 37 with methylphenylthiochloroformate followed by pyrolysis, Wolff-Kishner reduction and sodium chromate oxidation. The route to 33 was a little more involved requiring the protection of the alcohol function, Wolff-Kishner reduction of the ketone, deprotection, PCC oxidation of the alcohol and finally condensation with phenylselenium chloride followed by oxidative elimination.

A brief outline of the route to the optically active analogues is illustrated in Scheme 16. The chiral starting material, (+)pulegone (38), was converted to the dibromide and then underwent Favorskii rearrangement. Since the stereochemistry of the methyl substituted carbon was unaltered during the rearrangement, this stereocenter is fixed. The three additional chiral centers were then attained via

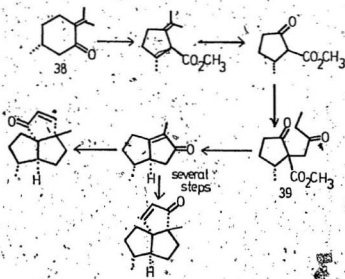
Scheme 14



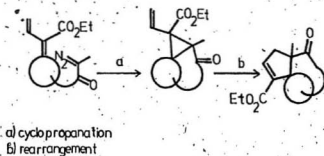
Scheme 15



Scheme 16



Scheme 17

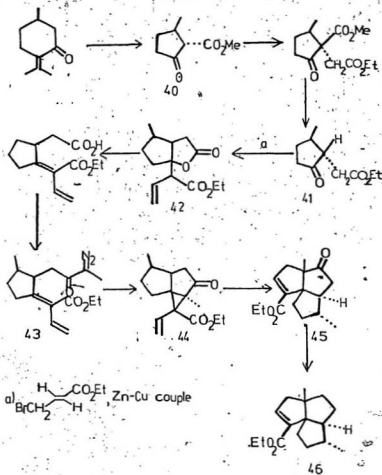


the reactions discussed in the racemic synthetic route. They hope that fusion of the final two rings will be possible now that these α,β -unsaturated ketones have been obtained.

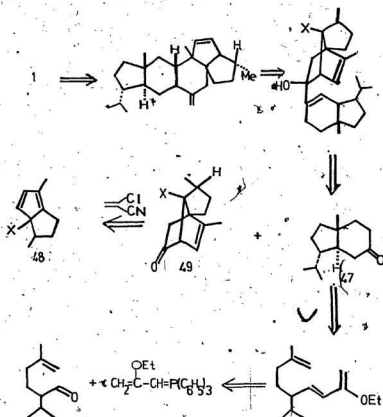
Hudlicky and Short⁴¹ have also successfully synthesized the triquinane portion of retigeranic acid by means of their general scheme, which they hope to use for several terpenic acids. This scheme centers around a carbenoid cyclopropanation and subsequent rearrangement of the resulting vinyl acrylates (Scheme 17). Their specific route to the triquinane portion began exactly like Paquette's with a Favorskii rearrangement of dibromo (+)-pulegone followed by ozonolysis to the keto-ester 40, as shown in Scheme 18. Then under Reformatsky conditions the keto-ester 41 was condensed with ethyl bromocrotonate to give the lactone 42. The acid produced by DBU elimination was converted via the acid chloride to the diazo ketone 43 which was in turn subjected to carbenoid intermediate cyclopropanation to produce 44. Flash pyrolysis over a lead carbonate treated column gave the tricyclic ketone 45 in 50% yield. This was followed by removal of the ketone functionality by way of the alcohol-xanthate which was reduced by reaction with freshly prepared $(n\text{Bu})_3\text{SnH}$ to give the tricyclic ester 46.

Our retrosynthetic scheme for retigeranic acid begins with two bond disconnections in the C-ring resulting in two pretargets distinctly different from the approaches of Paquette and Hudlicky (Scheme 19). This scheme is a major undertaking in our laboratory and is part of a general method

Scheme 18



Scheme 19

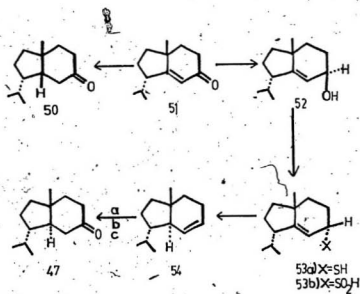


we are developing for the construction of quaternary, spiro-fused tricyclic skeletons of varying ring size which relies on a Diels-Alder: oxy-Cope rearrangement sequence. This route is highly convergent and offers good stereochemical control. The two pretargets are a substituted [4.3.0]nonane or hydrindane (left-hand piece) 47, and a bicyclo [3.3.0]octane 48 which may be transformed to a tricyclo [4.2.2.0^{4,8}]decene (right hand piece) 49.

Coincident with research in our own group, in which the hydrindanone 47, has been prepared by both an intramolecular Michael and complementary intramolecular Diels-Alder sequence (still under study, see below), Corey and Engler⁴² reported a different synthesis of this left-hand piece. They make no mention of retigeranic acid in their paper which deals with the stereospecific conversion of the hydrindenone 51 to either the trans or cis, fused hydrindanone (47 or 50 respectively) (Scheme 20).

Using the method of Snider and co-workers⁴³ they obtained 50 in two steps from 2,6-dimethyl-5-heptenal, and after LiAlH_4 reduction isolated the allylic alcohol 52 in 99% yield stereospecifically. Treatment of this alcohol with thioacetic acid, triphenylphosphine and diethylazodicarboxylate followed by LiAlH_4 reduction to the thiol and the subsequent oxidation with two equivalents of *m*-chloroperoxybenzoic acid gave the sulfinic acid 53. Thermal decomposition to the olefin 54 occurred during purification of the sulfinic acid. Conversion of the olefin to the trans fused hydrindanone 47,

Scheme 20

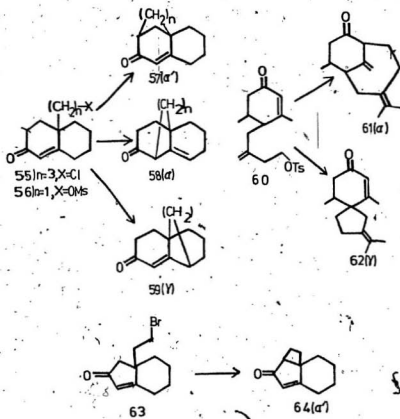


involved epoxidation with m-chloroperoxybenzoic acid, formation of an epimeric mixture of alcohols and finally sodium dichromate oxidation of the mixed alcohols.

Preliminary routes to both halves of retigeranic acid have been studied. In order to prepare the requisite bicyclo [3.3.0]octane synthon 48, a new cyclopentanone intramolecular alkylation sequence was investigated.

Previous studies⁴⁴ with $\alpha\beta$ -unsaturated ketones have established that the kinetically controlled formation of the α' enolate anion results from treatment with strong non-nucleophilic bases under aprotic conditions. Intramolecular alkylation then affords the α' alkylation product provided anion equilibration is relatively slow. In contrast, equilibrating conditions (protic solvent) favour thermodynamic control so that alkylation at the α -carbon generally results. In addition to the effect of the base-solvent combination, the balance between competing pathways in intramolecular alkylation, is influenced by the nature of the electrophile and the length of the sidechain. This is exemplified by the octalones 55 and 56 studied by Piers *et al*⁴⁵ (Scheme 21). They found that the product distribution ($\alpha' = 57$, $\alpha = 58$, $\gamma = 59$) could be partially controlled by the reaction conditions. Thus, the α' and α products predominated for $n=3$, whereas for $n=1$ only the γ and α products were encountered. Johnson and Vajs⁴⁶ found that the related cyclohexenone 60 afforded only α alkylation product 61 with potassium *tert*-butoxide (*t*-BuOH), whereas conditions which facilitated proton transfer

Scheme 21



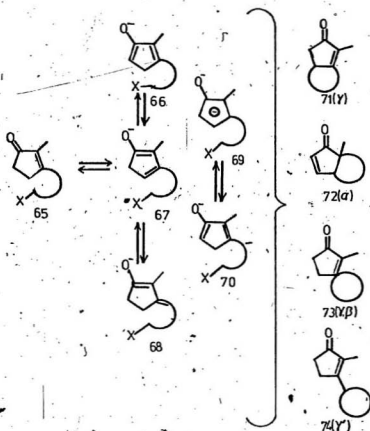
(KOH, H₂O, dimethyl sulfoxide) gave the γ alkylation product 62.

In contrast to cyclohexenones, enolate anion generation and intramolecular alkylation of cyclopentenones have received much less attention. However, Cargill and Jackson⁴⁷ demonstrated that treatment of 63 with potassium *tert*-butoxide (t-BuOH) resulted in selective formation of the α -product 64.

Clearly, substrate structure and the experimental conditions have a significant influence on the site of intramolecular alkylation of α,β -unsaturated cycloenones. As Scheme 22 illustrates, intramolecular cyclization of 65 could afford a complex product mixture. Excluding α and O-alkylated products, both of which are improbable due to the anti-Bredt olefins which would result, the most likely bicyclic systems are 71 to 74. If the initial enolate is 66 or 67 it may be regarded as a masked cyclopentadiene and treatment with a second mole of strong base should generate 69 to give a different product ratio.

A variety of dianion systems have been gainfully employed in synthesis⁴⁸ and cyclopentenones appear to satisfy the general criteria of dianion species. However, with the exception of a methoxyindanone example⁴⁹, a report of some reactions of the dianions from 3-isobutoxy-2-cyclopentenones⁵⁰ and the *in situ* generation of the dianion of 3-methyl-2-cyclopentenone in an early hydroxyferrocene preparation⁵¹, their potential as versatile synthetic inter-

Scheme 22



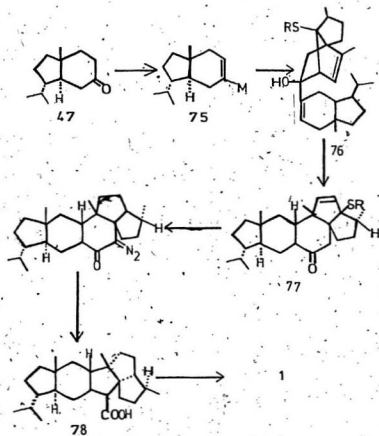
mediates remains unexplored. It was anticipated that for retigeranic acid appropriate dianions could be utilized to generate the desired diquinane skeleton.

Discussion

As outlined above, our approach to the pentacyclic sesterterpene retigeranic acid was divided into two major syntheses based on breaking two carbon-carbon bonds in the C-ring of the molecule. These two pretargets are the bicyclo [3.3.0] octane 48 which can be converted to the tricyclo [4.2.2.0^{4,8}] decene 49 (right hand piece), and the substituted bicyclo [4.3.0] nonane or hydrindane 47 (left hand piece). It was anticipated that once these two pretargets had been achieved, that the synthesis of retigeranic acid (1) could be completed by means of the route detailed in Scheme 23.

Conversion of the hydrindane 47 (left hand piece) to the Grignard or alkyllithium reagent 75 followed by reaction with the right hand piece (tricyclo [4.2.2.0^{4,8}] decene) 49, would give the alkylation product 76. Subsequent treatment with a base such as potassium hydride should provide the oxy-Cope rearrangement product 77. Hydrogenation of the olefin would then be followed by ring contraction of the C-ring from six to five carbons. This contraction could involve a diazotization followed by photochemical or thermal rearrangement to give 78. Then the final requirement, a double bond in the C-ring, could be achieved via condensation with phenylselenium chloride and subsequent oxidative elimination to produce retigeranic acid (1).

Scheme 23

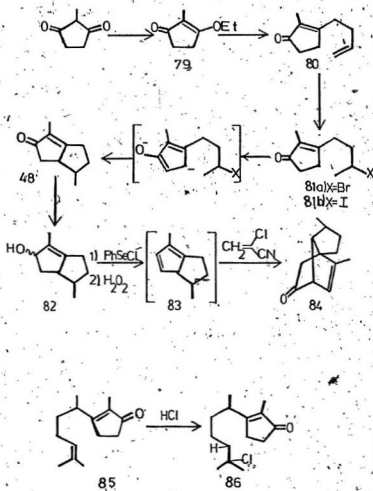


Part A: General Route to Substituted Cyclopentenones and Results of Cyclization Attempts

The complete synthetic pathway that was originally envisioned to the right hand piece of the molecule is outlined in Scheme 24. Preparation of the olefinic sidechain substituted α,β -unsaturated ketone 80 was based on analogous procedures developed by S.J. Alward in our labs. It was anticipated that the addition of hydrogen halide across the double bond in Markovnikov fashion would give the alkyl halide 81. Cyclization of the halide 81 involving a dianion intermediate seemed quite feasible based on literature precedents mentioned above, to produce the fused bicyclo [3.3.0] octane 48 as the thermodynamically favoured product. Reduction to the alcohol 82 followed by the generation of the cyclopentadiene intermediate 83 at low temperature based on work by Grieco et al⁵², should then lead to the Diels-Alder product, tricyclo[4.3.3.0^{4,8}]decene 84, using the methods of Corey⁵³.

As expected the olefin 80 was obtained by means of the 2% Na/Li alloy mediated alkylation of the enol ether 79 in an ultrasonic bath in 73%. This enol ether 79 was prepared in greater than 99% yield by refluxing 2-methyl-1,3-cyclopentanedione in acidic ethanol/benzene solution. The ultrasonic bath was employed because alkylation reactions involving a related sidechain had failed to work for a co-worker without such a device. It was later discovered that standard Grignard conditions in an ethyl ether/tetrahydrofuran solvent mixture increased the yield to 95% in

Scheme 24



this particular case where 4-bromo-1-butene was used with magnesium turnings.

With the olefin 80 in hand it appeared straight forward to convert the molecule to an alkyl halide, however this did not prove to be the case. Neither aqueous nor gaseous hydrogen chloride could be induced to add across the double bond of 80 in a number of solvents and varying reaction times, nor could hydrobromic acid or gaseous hydrogen bromide under various conditions of solvent or time, (Table 1). It was possible to add HCl across the olefin portion of the related molecule 85 under relatively mild conditions, but this is not particularly surprising as trisubstituted olefins are more reactive than terminal olefins.

In view of the difficulty of this halide addition step the synthetic route was altered slightly to epoxidize the olefin. This would result in an alcohol 88 product from the dianion intermediate cyclization reaction, but this slight inconvenience could be dealt with by converting the alcohol 88 to a methyl group by means of a zinc amalgam reduction of the tosylate 89 intermediate. The original synthetic route could then be continued after this short detour (Scheme 25).

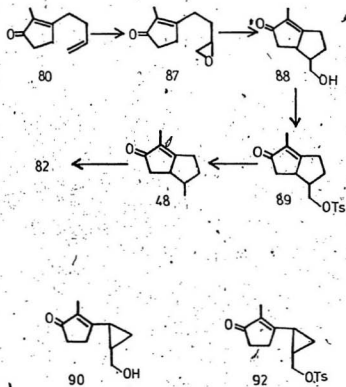
Reaction of the olefin 80 with *m*-chloroperoxybenzoic acid gave the desired epoxide 87 in 70% yield. The ^1H nmr spectrum displayed peaks between 2.6-3.0 ppm representing three protons, indicative of epoxide protons and infrared

Table 1 - Hydrogen Halide Addition Attempts

Olefin	Hydrogen Halide	Solvent	Time	Result
80	HCl (aq)	Ether	2 hrs	N.R.
80	HCl (aq)	Ether	16 hrs	N.R.
80	HCl (aq)	Ether	24 hrs	N.R.
80	HCl gas	CCl ₄	1-hr	N.R.
80	0.5M HBr/AcOH	AcOH	3 hrs	N.R.
80	0.5M HBr/AcOH	AcOH	6 hrs	N.R.
80	0.5M HBr/Benzene	Benzene	3 hrs	N.R.
80	HBr gas	Dioxane	3 hrs	N.R.
85	HCl (aq)	Ether	45 min	86
80	HCl (aq)	Dioxane	1 hr	N.R.

N.R. = no reaction

Scheme 25



bands at 1265 and 845 cm^{-1} were also consistent with an epoxide functionality.

Efforts were then begun to determine the optimum conditions for the dianion intermediate cyclization reactions. A number of bases were employed with varying results. The use of two equivalents of sodium hydride in a tetrahydrofuran solution gave a clear oil (48% yield). A broad infrared absorption between 3500-3300 cm^{-1} suggested an alcohol and bands at 1680 and 1630 cm^{-1} indicated the unsaturated ketone was still present. Inspection of the 60 MHz ^1H nmr spectrum with broad multiplet signals at 0.8-1.3, 2-2.5 and 3.6 ppm, a methyl singlet at 1.8 ppm and a possible alcohol peak at 3.2 ppm suggested that the product was either the fused system 88 or the conjoint ring system 90. Since both of these products have the same molecular weight, the high resolution mass of 166.0991 indicated only that the mass was correct for a $\text{C}_{10}\text{H}_{14}\text{O}_2$ molecule. With the aid of a 400 MHz ^1H nmr spectrum it was possible to establish the identity of the product as the conjoint ring system 90 based on the excellent resolution of the three cyclopropyl protons at 1.00, 1.14, and 1.55 ppm and the allylic cyclopropyl proton at 1.94 ppm. Also, the allylic protons and the two protons α to the carbonyl were resolved, falling at 2.18 and 2.33 ppm respectively on the 400 MHz spectrum. Changing the base to three equivalents of lithium diisopropylamide in tetrahydrofuran gave the same product in only a 13% yield. Cyclization attempts involving two equivalents of potassium

hydride gave the conjoint ring system as well in a slightly higher yield of 57%. The use of potassium amide in liquid ammonia as the base failed to give any reaction product, only recovered starting material. Since the results achieved were not the desired ones, it was decided to return to better leaving group systems.

It was found that the addition of hydrogen bromide across the double bond in the desired Markovnikov fashion could be achieved in the presence of a catalytic amount of zinc bromide. Thus, stirring the olefin 80 in a hydrogen bromide in acetic acid solution with this catalyst provided the bromide 81a in 91% yield. The distinguishing characteristics of this molecule in its ^1H nmr spectrum were the new sextet at 4.02 ppm representing one proton which identified the proton on the carbon bearing the bromide, and the absence of any olefinic signals. The proof of the structure was provided by the exact mass determination of 230.0299 which corresponds very well with the calculated value of 230.0307 for $\text{C}_{10}\text{H}_{15}\text{BrO}$.

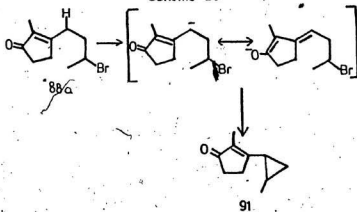
With the bromide 81a in hand studies were begun to cyclize the molecule to the desired fused ring system 48. Reacting the bromide at room temperature for fifteen hours with two equivalents of potassium hydride gave 45% yield of an oil. Unfortunately, interpretation of the ^1H nmr spectrum showed cyclopropyl protons which indicated that the conjoint ring system 91 was formed. This product resulted from the dianion intermediate formed when the base abstracts a proton

exocyclic to the ring system rather than from two points in the ring as had been hoped (Scheme 26). When the base was changed to two equivalents of sodium hydride and the reaction repeated under the same conditions of time and temperature the same results were achieved.

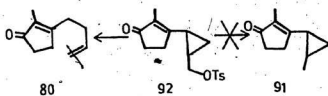
It was then felt that perhaps the desired results might be achieved if a better leaving group was employed. Thus, the bromide 81a was converted to the iodide 81b by refluxing the bromide in acetone with potassium iodide for three hours. The ^1H -nmr spectrum of the product showed that the proton attached to the halide bearing carbon was shifted downfield slightly to 4.10 ppm, and the mass spectrum showed a molecular ion at (m/z) 278 which indicated that the iodide 81b was in fact achieved in 80% yield. Attempted cyclizations of the iodide 81b with two equivalents of potassium hydride again provided the undesired conjoint ring system rather than the fused bicyclic desired product. Related studies in our laboratory have established that one mole of base also produced the conjoint ring system 91, and fused rings are only obtained when the Y(sidechain) position is blocked.

To verify that the alkylations followed a parallel course conversion of the conjoint ring alcohol 90 isolated from the epoxide cyclization reaction to the conjoint ring product 91 by way of the tosylate intermediate was attempted. As expected the alcohol 90 was readily converted to the tosylate 92 by the action of p-toluenesulfonyl chloride in pyridine in 71% yield. The infrared spectra

Scheme 26



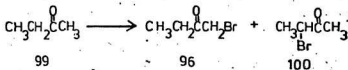
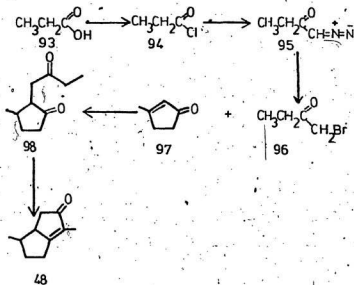
Scheme 27



of the tosylate showed the characteristic sulfonyl absorption bands at 1360 and 1170 cm^{-1} as well as an aromatic proton band at 3020 cm^{-1} . Four aromatic protons in the ^1H nmr spectrum and a peak at 320(M/z) in the mass spectra corresponding to the molecular ion were consistent with the tosylate structure. The conditions employed to reduce the tosylate to a methyl functionality however resulted in conversion of the tosylate not to the desired product, but rather reversion to the original olefinic sidechain molecule 80 (Scheme 27) by cyclopropane ring opening as a consequence of zinc promoted enolization of the ketone. These studies showed that direct cyclization of these cyclopentadienyl systems proceeded easily to conjoint ring systems but was not a viable route to fused ring systems. In view of these results, this dianion approach was abandoned in favour of a different route.

An alternate route to the bicyclo[3.3.0]octane synthon 48 was then attempted. The crucial steps of this approach were a lithium/ammonia alkylation-aldol condensation sequence as outlined in Scheme 28. The acid chloride 94 was prepared in 76% yield from propionic acid (93) by treatment with thionyl chloride on a warm water bath. The ^1H nmr spectrum showed only the ethyl peaks and the boiling point range of 76-79° C agreed with the literature value of 76-79° C. Using the method of Catch and co-workers⁵⁴ the acid chloride was converted to the α -bromoketone 96 via the diazo ketone 95 in 21% yield. The two new protons

Scheme 28



appeared as a sharp singlet at 3.87 ppm in the ^1H nmr spectrum. Diazomethane was prepared in the manner described on the bottle of Diazald (Aldrich) beginning with twenty-five grams of Diazald.

Because of the relatively poor yield of α -bromoketone acquired by this method and due to the restriction of the scale of the reaction imposed by our abiding respect for diazomethane generation, it was decided to prepare the α -bromoketone by an alternate route. This route involved a one step bromination of 2-butanone 92 based on the work of the French chemists Gaudry and Marquet⁵⁵ to give the bromides 100 and 96. Though the yield was poor, this route was preferable because the starting materials were inexpensive and the technique straight-forward.

The modified route involved an enone reduction-enolate alkylation step with lithium ammonia that was analogous to procedures developed by the research groups of Caine⁵⁶ and Stork⁵⁷ for six-membered ring cases. All attempts to alkylate 3-methyl-2-cyclopenten-1-one (97) by this method were unsuccessful. Model studies involving both 4-bromo-1-butene and benzyl chloride as the alkylating agent likewise met with disappointing results in that no reaction was observed. It would appear that this reaction is one of the cases that Paquette was referring to when he commented on the success rate of extrapolating from a six-membered ring method to a five membered ring situation.¹³

It was at this point that a different synthetic

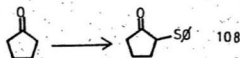
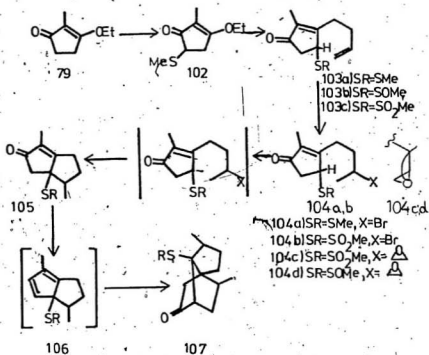
approach to the right hand piece of retigeranic acid (1) was designed.

Part B: Increasing the Acidity of the Cyclopentenone Allylic Proton and Attempted Cyclizations

This final synthetic scheme for making the fused bicyclic synthon involved increasing the acidity of the proton at the γ position in the cyclopentenone ring as outlined in detail in Scheme 29. We believed that the introduction of an alkyl- or arylthio substituent would increase the acidity of the requisite proton (γ position), such that the use of one equivalent of base would be sufficient to initiate the intramolecular alkylation reaction required to achieve the fused bicyclic system. In addition, this substituent would block the sigmatropic rearrangement of the cyclopentadiene and direct the alkenyllithium addition in the required endo direction.

The direct introduction of the thio group at the required γ position in compound 80 could not be achieved, based on the results of our earlier cyclization attempts which showed that the preferred anion was at the exocyclic position. Thus, the thio group was introduced α to the carbonyl function in the enol-ether 79 prior to the alkyllithium addition. After acidic workup of the alkylation reaction, the thio group would be in the desired γ position of the new α,β -unsaturated ketone product. Removal of the thio group could be conducted at a later point in the synthesis.

Scheme 29



It was decided to add a phenylthio substituent to the enol-ether 79 by treating it with one equivalent of lithium diisopropylamide and N-thiophenylsuccinimide⁵⁸. When this failed to give the desired results a series of model studies using cyclopentenone 108 were initiated (Table 2). Work by the Japanese chemist Mukaiyama and co-workers⁵⁹ suggested that N-thiophenylphthalimide might act as a better sulfur transfer reagent. The N-thiophenylphthalimide was prepared by the method of Behforuz and Kerwood⁶⁰. Eventually encouraging results were obtained when two equivalents of potassium hydride were used as the base and N-thiophenylphthalimide was used as the sulfur transfer reagent on the model compound. When these conditions were applied to the enol-ether they unfortunately did not result in the preparation of the desired product. No reaction was observed for two equivalents of potassium hydride nor for two equivalents of lithium diisopropylamide in dry dimethoxyethane.

Attempts to add a methylthio substituent α to the carbonyl of the enol-ether met with much more successful results. It was found that treating the anion, formed by the action of one equivalent of lithium diisopropylamide on the enol-ether, with dimethyl disulfide at -78°C provided ready access to the methyl sulfide enol-ether 102 in 72% yield. The distinguishing spectral feature was the appearance in the ^1H nmr of a singlet at 2.17 ppm which integrated for three protons corresponding to the methyl group

Table 2 - Thiophenyl Addition Conditions

Ketone	Base	Reagent	Solvent	Time	Result
79	LDA	a	THF	3 hrs	N.R.
cyclopentanone	NaH	a	DME	16 hrs	N.R.
cyclopentanone	NaH	b	DME	6 hrs	N.R.
cyclopentanone	LDA	b	DME/HMPA	6 hrs	N.R.
cyclopentanone	1.2 NaH	b	DME	24 hrs	N.R.
cyclopentanone	2 NaH	b	DME	24 hrs	N.R.
cyclopentanone	1.2 KH	b	DME	24 hrs	N.R.
cyclopentanone	2 KH	b	DME	72 hrs	108
79	2 KH	b	DME	24 hrs	N.R.
cyclopentanone	2 KH	b	DME	24 hrs	N.R.
cyclopentanone	2 LDA	b	THF	16 hrs	N.R.
cyclopentanone	2 LDA	b	THF	24 hrs	N.R.

a = N-thiophenylsuccinimide⁵⁸b = N-thiophenylphthalamide⁶⁰

N.R. = no reaction

attached to the sulfur atom. The exact mass of 186.0730 was in reasonable agreement with the calculated value of 186.0714 for a $C_9H_{14}SO_2$ molecule. Since then, D. Scholz⁶¹ has published a paper dealing with the addition of the methylthio substituent to a number of cyclic ketones, including the model compound worked on.

The next step in the sequence was addition of the olefin sidechain by means of an organometallic reaction. Initially, this was accomplished by means of a 2% Na/Li alloy alkylation with 4-bromo-1-butene using an ultrasonic bath. Characteristic olefin multiplet signals in the 1H nmr at 4.8-5.18 ppm and 5.48-6.02 ppm which integrated for two and one protons respectively and an exact mass of 196.0907 for a $C_{11}H_{16}SO$ molecule proved that the olefin 103a had been obtained. However, due to the abysmal yields isolated by this method (6-15%) it was decided to switch to Grignard conditions using an alkylmagnesium halide reagent, since it appeared that enolization of the thioketone was competing with the desired reaction. Model studies using methylmagnesium chloride (2.9 M in tetrahydrofuran) in varying amounts and in various solvents, indicated that two equivalents of Grignard reagent in a mixed ether/tetrahydrofuran solvent might give better results while three equivalents of Grignard reagent did not. An improved yield of 34% was achieved with 1.5 equivalents of 3-butenylmagnesium bromide.

Hydrobromination of the olefin using the technique

developed earlier was successful and the bromide product 104 had a sextet corresponding to one proton at 4.06 ppm in the ^1H nmr spectrum characteristic of a secondary bromide. A molecular ion of (m/z) 276 indicated that the correct product had been obtained. Unfortunately attempts to cyclize this bromide 104a to the corresponding fused ring system using one equivalent of potassium hydride in tetrahydrofuran and 1.5 equivalents of potassium hydride in dimethoxyethane both failed and starting material was recovered.

Not willing to surrender, we anticipated that converting the sulfide to a higher oxidation state such as the sulfoxide 103b or sulfone 103c would facilitate the desired proton abstraction. The crude spectra of the sulfoxide 103b indicated that this should indeed be the case. The proton attached to the sulfur bearing carbon appeared farther downfield than in the sulfide case as a result of deshielding effects. Attempted epoxidation of the olefin sidechain and concomitant oxidation of the sulfide 103a to the sulfoxide 104d by employing two equivalents of *m*-chloroperoxybenzoic acid gave instead the methyl sulfone with the olefin sidechain. A molecular ion of (m/z) 228 indicated that two oxygen atoms had indeed been added and the infrared spectra contained absorption bands at 1300 and 1130 cm^{-1} characteristic of a sulfone. Also, the proton at the allylic position was further deshielded and appeared as a multiplet at 4.27 ppm. Epoxidation of the sulfone 103c

was achieved when it was reacted with an additional equivalent of the oxidizing reagent. Subsequently the epoxysulfone 104c was obtained from the sulfide olefin by refluxing it with three equivalents of m-chloroperoxybenzoic acid in dichloromethane for forty-eight hours. Attempts to cyclize the epoxysulfone 104c with 1.5 equivalents of potassium hydride in dimethoxyethane, 1.1 equivalents of lithium diisopropylamide in dimethoxyethane or 1.1 equivalents of sodium hydride in tetrahydrofuran all resulted in recovering only starting material.

In a final bid to synthesize the bicyclic synthon the sulfone olefin 103c was treated with hydrogen bromide and zinc bromide to produce the bromide 104b in 21% yield. This bromide has the characteristic multiplet for a proton attached to a carbon bearing a bromide functionality. Unfortunately the use of potassium hydride as the base in either dimethoxyethane or dimethylformamide failed to achieve the desired results. All that was recovered from these attempts were decomposition products.

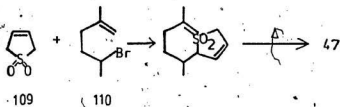
Unfortunately, it appears that the geometric requirements for this intramolecular alkylation cannot be readily achieved and that the steric bulk of the activating group may also interfere. At this point, after all these variations had proven unsuccessful, in our bid to synthesize the fused bicyclic system, it was decided to stop work on the right hand piece of retigeranic acid (1), and concentrate on the left hand piece (hydrindane portion).

Part C: Route to Hydrindanone via Wittig-Intramolecular Diels-Alder Sequence

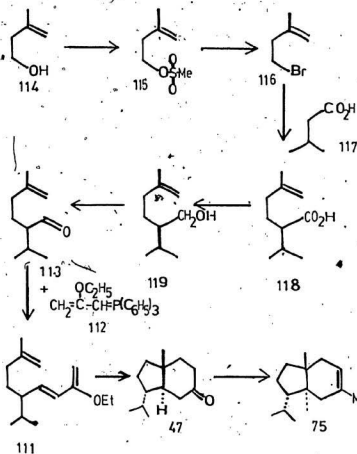
The two key steps of our initial approach to the hydrindanone 47 (left hand piece) portion of retigeranic acid involved alkylating the cyclic sulfone 109 with bromide 110, followed by an intramolecular Diels-Alder cyclization based on work by Oppolzer and co-workers⁶². The alkylation of the cyclic sulfoxide step was an extrapolation of work on linear alkyl sulfones by Kondo and Tunemoto⁶³. Several attempts to alkylate sulfone 109 with 2-bromopropane or methyl iodide using lithium diisopropylamide to form the required anion all met with failure.

An alternative route to the triene molecule necessary for the Diels-Alder reaction was then envisioned as seen in Scheme 30, which proved to be much more successful. It was anticipated that once the triene 111 had been isolated that conditions would be found for the Diels-Alder reaction to provide the hydrindane skeleton. Either acidic work up condition or subsequent reaction with dilute acid would then be sufficient to convert the vinylic ethoxy Diels-Alder product to the hydrindanone 47. This would be followed by conversion of the ketone 47 to the alkylating reagent 75 needed for the final series of steps to retigeranic acid (1) as outlined earlier in Scheme 23. The preparation of the triene molecule was divided into two sub-routes, preparation of the Wittig reagent 112 and the aldehyde 113.

A paper published by Ramirez and Dershowitz⁶⁴ indicated that the Wittig salt 122 should be easily attainable from



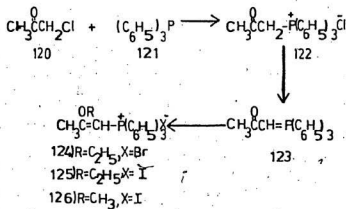
Scheme 30



chloroacetone (120) and triphenylphosphine (121) (Scheme 31). The first two steps of this sequence were in fact achieved by their methodology, but repeated attempts to form the required salt 124 using their conditions of refluxing the phosphinemethylene 123 in ethyl bromide gave only an oily sludge. We were able to successfully synthesize the required Wittig salt 124 in 93% yield by refluxing the phosphinemethylene with one equivalent of ethyl bromide for 24 hours. Subsequently this methodology was applied in the synthesis of two new Wittig salts 125 and 126.

It was necessary to convert the Wittig salt to the Wittig reagent before reacting it with the appropriate ketone. Martin and Desai⁶⁵ have used this phosphonium salt 124 for the *in situ* generation of the Wittig reagent which they then reacted with a variety of α,β -unsaturated ketones to prepare monocyclic, fused bicyclic, and spiro bicyclic ring systems. Under these conditions a two step sequence of events occurred, first an ene reaction and then intramolecular Wittig reaction. We hoped that the reagent would undergo the standard Wittig reaction only. Therefore a model study involving benzaldehyde was undertaken (Scheme 32). Addition of benzaldehyde (127) to a solution of the Wittig salt which has been treated with an equivalent of *n*-butyllithium produced the known compound *trans*-4-phenyl-3-buten-2-one (129). This product was the result of the desired Wittig reaction followed by hydrolysis of the enol ether 128 to the conjugated ketone 129 during purification by

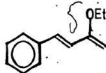
Scheme 31



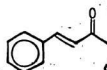
Scheme 32



127



128



129



130

flash chromatography.

Since it was known that the Wittig salt would react with an aldehyde functionality, the synthesis of the required aldehyde 113 was undertaken. An extrapolation of work done by Ireland et al⁶⁶ on ionophore antibiotic synthesis provided the means for conversion of alcohol 114 to the bromide 116 via a mesylate intermediate 115 in 90% yield. The crucial step towards the aldehyde synthesis is the alkylation of isovaleric acid (117) with a bromide. It was accomplished by a modification of a procedure developed by Pfeffer and co-workers⁶⁷ for the generation of α -anions of carboxylic acids, in 96% yield.

Once the acid 118 had been achieved it was an easy matter to reduce it with lithium aluminium hydride to the alcohol 119, and then oxidize it to the desired aldehyde 113 by stirring it in a dichloromethane solution of pyridinium chlorochromate. The aldehyde did not appear to be very stable and was used immediately for the Wittig reaction. Using the method developed for the model studies on benzaldehyde, the aldehyde was added to a tetrahydrofuran solution of the Wittig reagent. During the work up of the initial attempts the hydrolyzed product, conjugated ketone 130, was isolated as had been the case with the benzaldehyde model. This hydrolysis was believed to occur on the silica gel during flash chromatographic purification. The triene, itself 111 was isolated by vacuum distillation of the reaction mixture.

Unfortunately Diels-Alder conditions have yet to be determined that will convert the triene to the hydrindane skeleton. An attempt in refluxing toluene and a trace of pyridine in a sealed tube failed, as did an attempt with pyridine as the solvent in a sealed tube reaction. It was thought that basic conditions should be employed based on the results of a related system worked on in our labs in which conjugated trienes bearing carbomethoxy functions have been successfully cyclized.

Our work in this area is continuing. These studies have helped increase our understanding of the activity in these systems, and will ultimately facilitate the successful total synthesis of retigeranic acid.

Experimental

Melting points were determined in capillary tubes with a Thomas Hoover Uni-Melt apparatus, or a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B or 451 grating spectrometer and were calibrated against polystyrene film. Proton magnetic resonance spectra were measured at 400 MHz with a Bruker WA 400 spectrometer at the University of Alberta, at 80 MHz with a Bruker WP 80 spectrometer employing a chloroform lock or at 60 MHz with a Varian EM 360 spectrometer. Signal positions are reported in ppm downfield from tetramethylsilane (delta scale) as an internal standard, the number of protons, multiplicity, coupling constants, and proton assignments are indicated in parentheses. Mass spectra were determined on a V.G. Micromass 7070 H5 instrument using an ionization energy of 70 electron volts.

Thin layer chromatographic analyses were carried out on 7.5 x 2.5 cm glass plates coated with silica gel PF 254-360 type 60 (E. Merck) or commercial precoated silica plates with fluorescent indicator (Eastman-Kodak silica gel 13181). Flash chromatography using BDH silica gel kieselgel 60, 230-400 mesh was employed for column chromatography.

Petroleum ether refers to a fraction with boiling range 30-60° C. Anhydrous diethyl ether (ether), tetrahydrofuran (THF), dimethoxyethane (DME) and dioxane were obtained by distillation from lithium aluminium hydride or potassium/benzophenone. Absolute ethanol and methanol were dried by

distillation from magnesium. Dry hexamethylphosphoramide (HMPA), dimethylformamide (DMF) and diisopropylamine were prepared by distillation from calcium hydride. In certain cases spectrometric solvents were used without further purification; i.e. CH_2Cl_2 and acetone and sometimes just distilled. Also, for Grignard reactions the anhydrous ether was taken directly from freshly opened small cans (Fisher). Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvent with a Buchi rotary evaporator connected to a water aspirator. Unless otherwise indicated all reactions were conducted under an atmosphere of dry argon.

2-Methyl-3-ethoxy-2-cyclopenten-1-one (79)

A solution (benzene:ethanol, 13:5, 850 mL) of 2-methyl-1,3-cyclopentanedione (25 g, 0.22 mol, Aldrich) containing a catalytic amount of *p*-toluenesulfonic acid (1 g) was refluxed through molecular sieves (30 g, 4 Å) for 24 hours. The molecular sieves were exchanged for fresh molecular sieves and the refluxing continued for an additional 24 hours.

The solvent was then removed and the residual yellow oil distilled b.p. $92-105^\circ \text{C}/0.3 \text{ Torr}$, to give enol ether 79, m.p. $36-38^\circ \text{C}$, 31.1 g (100%); ir (film): 2920 (C-H), 1680 (C=O), 1625 (C=C), 1125 (C-O) cm^{-1} ; ^1H nmr (CCl_4 , 80 MHz) δ : 1.4 (t, 3H, $J=7\text{Hz}$, $\text{CH}_3\text{-CH}_2\text{-O}$), 1.51 (t, 3H, $J=1.5\text{Hz}$, $\text{CH}_3\text{-C=C}$), 2.35 (m, 2H, $\text{CH}_2\text{-C=C}$), 2.65 (m, 2H, $\text{CH}_2\text{-C=O}$), 4.15 (q, 2H, $J=7\text{Hz}$, $\text{CH}_2\text{-O}$); M.S. (m/z) 140 (M^+), 112 ($\text{M-C}_2\text{H}_4$), 83 ($\text{M-C}_2\text{H}_3\text{O}$). Exact mass calculated for $\text{C}_8\text{H}_{12}\text{O}_2$:

140.0837, found 140.0843.

3-(3-Butenyl)-2-methyl-2-cyclopentenone (80)

An ether solution (100 mL) of 4-bromo-1-butene (5.43 mL, 7.22 g, 53 mmol, Aldrich) was added dropwise (1 hour) to a solution of an anhydrous ether (200 mL) containing 2-methyl-3-ethoxy-2-cyclopenten-1-one (5.0 g, 0.036 mol) and 2% Na/Li alloy (1 g, 3 equiv.) maintained at 0° C. in an ultrasonic bath (Branson 50/60 Hz). Ultrasonic agitation initiated when addition was commenced and for a further three hours after the addition was complete. The mixture was quenched (3N HCl, 200 mL), the organic layer separated, washed with brine, extracted with ether, the combined ether extracts dried, filtered, concentrated and the product purified by chromatography (20% ethyl acetate in petroleum ether (30-60)) to give the enone olefin 80, 3.67 g (68%); ir (film): 3080 (C=C-H), 1705 (C=O), 1650 (C=C) cm^{-1} ; ^1H nmr (CCl_4) δ : 1.62 (s, 3H, $\text{CH}_3\text{-C=C}$), 2.25-2.75 (m, 8H), 4.8-5.12 (m, 2H, $\text{CH}_2\text{=C}$), 5.42-6.0 (m, 1H, -CH=C); M.S. (m/z) 150 (M^+). Exact mass calculated for $\text{C}_{10}\text{H}_{14}\text{O}$: 150.1045, found: 150.1041.

3-(3-Butenyl)-2-methyl-2-cyclopenten-1-one (80)

A tetrahydrofuran solution (25 mL) of 2-methyl-3-ethoxy-2-cyclopenten-1-one 72 (1.0 g, 7 mmol) was added dropwise to a solution of anhydrous ether (15 mL) containing 4-bromo-1-butene (1.1 mL, 1.45 g, 11 mmol, Aldrich) and

magnesium turnings (0.26 g, 11 mmol) at 23° C. The reaction mixture was allowed to stir for 30 minutes at 23° C and was then warmed to 50° C for an additional 30 minutes.

The mixture was quenched (3N HCl, excess), the organic layer separated, the aqueous layer extracted with ether (3x), and the combined ether layers washed with saturated aqueous sodium bicarbonate, dried, filtered and concentrated to give the enone olefin 80 as a yellow oil, 5.36 g (72%); ir (film): 3080 (C=C-H), 1705 (C=O), 1650 (C=C) cm^{-1} ; ^1H nmr (CCl_4) δ : 1.62 (s, 3H, $\text{CH}_3\text{-C=C}$), 2.25-2.75 (m, 8H), 4.8-5.12 (m, 2H, $\text{CH}_2\text{=C}$), 5.42-6.0 (m, 1H, CH=C); M.S. (m/z) 150 (M^+). Exact mass calculated for $\text{C}_{10}\text{H}_{14}\text{O}$: 150.1045, found: 150.1041.

3-(3-Bromobutyl)-2-methyl-2-cyclopenten-1-one (81a)

To glacial acetic acid (2 mL) containing 3-(3-butenyl)-2-methyl-2-cyclopenten-1-one (1.5 g, 10 mmol) and zinc bromide (0.3 g) was added hydrogen bromide solution (15 mL, 2.55 M in acetic acid) and the flask wrapped in aluminium foil to protect the reaction from light.

After stirring for 72 hours at 23° C the reaction mixture was poured into ice water (50 mL); extracted into ether (3 x 50 mL), washed with aqueous saturated sodium bicarbonate, washed with brine, dried, filtered, concentrated and chromatographed (40% hexane in ether) to give bromide 81a, 2.11 g (91%); ir (film), 1685 (C=O), 1640 (C=C) cm^{-1} ; ^1H nmr (CCl_4 , 80 MHz) δ : 1.67 (d, 3H, $\text{J}=7\text{Hz}$, $\text{CH}_3\text{-CH}$), 1.75 (s, 3H, $\text{CH}_3\text{-C=C}$), 2.0 (m, 2H, $\text{CH}_2\text{-CBr}$), 2.4 (m, 6H), 4.02

(sextet, 1H, $J=7\text{Hz}$, CHBr); M.S. (m/z) 232 (M^+), 230 (M^+).

Exact mass calculated for $C_{10}H_{15}BrO$: 230.0307, found: 230.0299.

3-(3-Iodobutyl)-2-methyl-2-cyclopenten-1-one (81b)

An acetone solution (30 mL) of 3-(3-bromobutyl)-2-methyl-2-cyclopenten-1-one (0.97 g, 4.2 mmol) and sodium iodide (0.63 g, 4.2 mmol) was refluxed for 3 hours.

Filtration of the reaction mixture, concentration of the resulting solution and chromatography (ether: petroleum ether, 3:2) gave the iodide 81b as an oil, 0.93g (79%); ir (film): 1680 (C=O), 1640 (C=C) cm^{-1} ; ^1H nmr (CDCl_3) δ : 1.7 (s, 3H, $\text{CH}_3\text{-C=C}$), 1.92 (d, 3H, $J=7\text{Hz}$, $\text{CH}_3\text{-CH}$) 2.15-2.75 (m, 8H), 4.10 (sextet, 1H, $J=7\text{Hz}$, $-\text{CHI}-$); M.S. (m/z) 278 (M^+).

3-(3,4-Epoxybutyl)-2-methyl-2-cyclopenten-1-one (87)

A dichloromethane solution (200 mL) of 3-(3-butenyl)-2-methyl-2-cyclopenten-1-one (8.69 g, 58 mmol) and *m*-chloroperoxybenzoic acid (13.1 g, 76 mmol, 80%, Aldrich) was stirred magnetically at 23°C for 24 hours. Then aqueous sodium bisulfite solution (100 mL, 10%) was added to destroy excess peroxy acid and the reaction mixture extracted into ether, washed with saturated aqueous sodium bicarbonate, dried, filtered, concentrated and the product purified by chromatography (ethyl acetate: pet. ether, 1:1) to give the epoxide 87 as an oil, 6.26 g (65%); ir (film): 1685 (C=O),

1640 (C=C), 1265, 845 (C-O) cm^{-1} ; ^1H nmr (CCl_4 , 80 MHz) δ : 1.60 (s, 3H, $\text{CH}_3\text{-C=C}$), 1.7 (m, 2H, $-\text{CH}_2-$), 2.45 (m, 6H, $\text{CH}_2\text{-C=C}$), 2.6-3.0 (m, 3H, epoxide protons); M.S. (m/z) 166 (M^+). Exact mass calculated for $\text{C}_{10}\text{H}_{14}\text{O}_2$: 166.0994, found: 166.1033.

3-[2-(hydroxymethyl) cyclopropyl]-2-methyl-2-cyclopentenone
(90)

A tetrahydrofuran solution (25 mL) of 3-(3,4-epoxy-butyl)-2-methyl-2-cyclopentenone (500 mg, 3 mmol) was added dropwise to a suspension of sodium hydride (0.23 g, 60% in oil, 6 mmol, Aldrich) in tetrahydrofuran (25 mL) cooled in an ice bath and stirred magnetically. After 30 minutes at 0°C , the reaction mixture was stirred at 22° for 14 hours, quenched with saturated aqueous ammonium chloride and diluted with ether. After separating the layers, the aqueous phase was extracted with ether (4 x) and the combined organic layers were dried, filtered, concentrated and the product purified by preparative layer chromatography (ethyl acetate: pet. ether, 1:1) to give the cyclized alcohol 90, 240 mg (48%); ir (film): 3300-3500 (br, OH), 1680 (C=O), 1630 (C=C) cm^{-1} , ^1H nmr (CDCl_3 , 80 MHz) δ : 0.85-1.22 (m, 7H, CH_3 and cyclopropyl H), 1.80 (t, 3H, $\text{J}=1.8\text{ Hz}$, $\text{CH}_3\text{-C=C}$), 3.60 (m, 2H, $\text{J}=6.2\text{ Hz}$, $\text{CH}_2\text{-O}$); M.S. (m/z) 166 (M^+). Exact mass calculated for $\text{C}_{10}\text{H}_{14}\text{O}_2$: 166.0994, found: 166.0991.

3-[2-(Hydroxymethyl) cyclopropyl]-2-methyl-2-cyclopentenone
(90)

A tetrahydrofuran solution (50 mL) of 3-(3, 4-epoxy-butyl)-2-methyl-2-cyclopentenone (4.7 g, 28 mmol) was added dropwise to a stirred suspension of potassium hydride (7.2 g, 35% in oil, 56 mmol, Aldrich) in tetrahydrofuran (50 mL) cooled in an ice bath. After 30 minutes at 0°C , the reaction mixture was stirred at 22°C for 12 hours, quenched with saturated aqueous ammonium chloride, and diluted with ether. The layers were separated, the aqueous layer extracted with ether (3 x), and the combined organic layers were dried, filtered, concentrated and chromatographed (3% methanol in ether) to give the cyclized alcohol 90, 2.6 g (57%); ir (film): 3300-3500 (br, OH), 1680 (C=O), 1630 (C=C) cm^{-1} ; ^1H nmr (CDCl_3 , 80 MHz) δ : 0.85-1.22 (m, 7H, CH_3 and cyclopropyl H), 1.8 (t, 3H, $J=7.8\text{ Hz}$, $\text{CH}_3\text{-C}=\text{C}$), 3.6 (m, 2H, $J=6\text{ Hz}$, $\text{CH}_2\text{-O}$), M $^+$. (m/z) 166 (M $^+$). Exact mass calculated for $\text{C}_{10}\text{H}_{14}\text{O}_2$: 166.0994, found: 166.0991.

3-[2-(Hydroxymethyl) cyclopropyl]-2-methyl-2-cyclopentenone
(90)

3-(3, 4-Epoxybutyl)-2-methyl-2-cyclopentenone (0.3 g, 1.8 mmol) in tetrahydrofuran (20 mL) was added dropwise to a tetrahydrofuran solution (20 mL) containing diisopropylamine (0.8 mL, 5.4 mmol, Aldrich), *n*-butyllithium (0.5 mL, 2.2M in hexane, Aldrich), triphenylmethane (5 mg) and hexamethylphosphoramide (1 mL) cooled to -78°C . After the addition was complete, the reaction mixture was stirred at

22° C for 16 hours, quenched with saturated aqueous ammonium chloride and diluted with ether. The aqueous layer was extracted with ether (3 x) and the combined organic layers dried, filtered, concentrated and purified by preparative layer chromatography (ethyl acetate: ether, 1:1) to give the cyclized alcohol 90, 40 mg (13%); ir (film): 3300-3500 (br.OH), 1680 (C=O), 1630 (C=C) cm^{-1} ; ^1H nmr (CDCl_3 , 80 MHz) δ : 0.85-1.22 (m, 7H, CH_3 and cyclopropyl H), 1.8 (t, 3H, $J=1.8$ Hz, $\text{CH}_3\text{-C=C}$), 3.6 (m, 2H, $J=6$ Hz, $\text{CH}_2\text{-O}$), M.S. (m/z) 166 (M^+). Exact mass calculated for $\text{C}_{10}\text{H}_{14}\text{O}_2$: 166.0994, found: 166.0991.

3-(2-Methylcyclopropyl)-2-methyl-2-cyclopenten-1-one (91)

To a magnetically stirred suspension of potassium hydride (7.1 g, 60 mmol, 35% oil suspension, Aldrich) in dimethoxyethane (50 mL) cooled in an ice bath, 3-(3-bromobutyl)-2-methyl-2-cyclopenten-1-one (6.5 g, 28 mmol) in dimethoxyethane (50 mL) was added dropwise. After stirring for 10 minutes at 0° C, stirring was continued at 22° C for 15 hours, and the reaction mixture quenched with saturated aqueous ammonium chloride and diluted with ether. The aqueous layer was extracted with ether (3 x) and the combined organic layers were dried, filtered, concentrated and chromatographed (petroleum ether: ether, 3:2) to give 91 as an oil, 1.85 g (45%), ir (film): 1690 (C=O), 1650 (C=C) cm^{-1} ; ^1H nmr (CDCl_3 , 80 MHz) δ : 0.80 (m, 1H, cyclopropyl H), 1.0-1.35 (m, 5H, cyclopropyl H and $\text{CH}_3\text{-CH}$), 1.65 (m, 1H,

cyclopropyl H), 1.7 (t, 3H, $J=1.8$ Hz, $\text{CH}_3\text{-C}=\text{C}$), 2.0-2.4 (complex, 4H). Exact mass calculated for $\text{C}_{10}\text{H}_{14}\text{O}$: 150.1044, found: 150.1044.

3-(2-Methylcyclopropyl)-2-methyl-2-cyclopenten-1-one (91)

To a magnetically stirred suspension of sodium hydride (0.54 g, 4.3 mmol, 35% in oil, Aldrich) in dimethoxyethane (5 mL) cooled in an ice bath, 3-(3-bromobutyl)-2-methyl-2-cyclopenten-1-one (600 mg, 2.2 mmol) in dimethoxyethane (5 mL) was added dropwise. After stirring for 10 minutes at 0°C , stirring was continued to 22°C for 15 hours, and the reaction mixture quenched with saturated aqueous ammonium chloride and diluted with ether. The aqueous layer was extracted with ether (3 x) and the combined organic layers were dried, filtered, concentrated and chromatographed (petroleum ether: ethyl acetate, 4:1) to give 91, 120 mg (37%), ir (CHCl_3): 1695 ($\text{C}=\text{O}$), 1650 ($\text{C}=\text{C}$) cm^{-1} ; ^1H nmr (CDCl_3): 0.75-1.0 (m, 1H, cyclopropyl), 1.0-1.35 (br s, 5H, cyclopropyl H and $\text{CH}_3\text{-CH}$), 1.65 (m, 1H, cyclopropyl H), 1.8 (br s, 3H, $\text{CH}_3\text{-C}=\text{C}$), 2.0-2.45 (m, 4H, $\text{CH}_2\text{-CH}_2$), M.S. (m/z) 150 (M^+).

3-(2-p-Toluenesulfonyloxymethylcyclopropyl)-2-methyl-2-cyclopentenone (92)

A pyridine solution (5 mL) of 3-[2-(hydroxymethyl)-cyclopropyl]-2-methyl-2-cyclopentenone (350 mg, 2.1 mmol) and p-toluenesulfonyl chloride (810 mg, 4.2 mmol) was stirred at -20°C for 22 hours. The reaction mixture was then

poured over ice water (60 mL) and extracted into ether (5 x 30 mL). The combined organic layers were washed with dilute hydrochloric acid (1N, 20 mL, 4 x), aqueous sodium bicarbonate (5%), dried over Na_2SO_4 for 6 hours, filtered and concentrated to give the tosylate 92, 0.48 g (71%), mp $87-91^\circ\text{C}$; ir (CHCl_3): 3020 (aromatic C-H), 1690 (C=O), 1630 (C=C), 1360 (S=O, assym), 1170 (S=O, sym.) cm^{-1} ; ^1H nmr (CDCl_3) δ : 0.70-1.35 (m, 4H, cyclopropyl H), 1.72 (s, 3H, $\text{CH}_3\text{-C=C}$), 2.1 (m, 2H, $\text{CH}_2\text{-C=O}$), 2.3 (m, 2H, $\text{CH}_2\text{-C=C}$), 2.44 (s, 3H, $\text{CH}_3\text{-aromatic}$), 4.0 (m, 2H, $\text{CH}_2\text{-O}$), 7.2-7.8 (m, 4H, aromatic); M.S. (m/z) 320 (M^+).

Propionyl Chloride (94)

Propionic acid (25 g, 25.2 mL, 0.337 mol) was added dropwise to thionyl chloride (50.2 g, 30.7 mL, 0.42 mol) at 22°C . After the addition was complete the mixture was warmed to 65°C for 30 minutes and then the crude product was distilled off. The crude product was purified by fractional distillation, b.p. $76-79^\circ\text{C}$ to give propionyl chloride (94), 23.6 g (76%), ^1H nmr (CCl_4) δ : 1.3 (t, 3H, $\text{J}=7\text{ Hz}$, $\text{CH}_3\text{-CH}_2$), 3.00 (q, 2H, $\text{J}=7\text{ Hz}$, $\text{-CH}_2\text{-C=O}$).

1-Bromo-2-butanone (96)

To a well stirred dry methanol solution (800 mL) of 2-butanone (50 g, 62 mL, 0.69 mol) at 0°C was added bromine (110 g, 36 mL, 0.69 mol). Stirring was continued until decolorization had occurred ($4\frac{1}{2}$ hours) and then sulfuric

acid (900 ml, 2M) was added and the stirring continued for an additional 16 hours. The reaction mixture was extracted into ether and neutralized with saturated aqueous sodium bicarbonate, the ether phase washed with water (4 x), dried over Na_2SO_4 , filtered, concentrated and the product purified by distillation, to give a clear oil, 5.54 g (6%) b.p. $105^\circ\text{C}/120\text{ Torr}$; ^1H nmr (CDCl_3) δ : 1.03 (t, 3H, $\text{J}=7\text{ Hz}$, CH_3 -), 2.62 (q, 2H, $\text{J}=7\text{ Hz}$, $-\text{CH}_2-\text{C}=\text{O}$), 3.87 (s, 2H, $-\text{CH}_2-\text{Br}$).

2-Phenylthio-1-cyclopentanone (108)

A dry dimethoxyethane solution (5 mL) of cyclopentanone (168 mg, 0.178 mL, 2 mmol) was added dropwise to a dimethoxyethane suspension (5 mL) of potassium hydride (458 mg, 4 mmol, 35% in oil, Aldrich) cooled to 0°C . The reaction mixture was allowed to warm to 22°C and a dimethoxyethane solution (40 mL) of N-thiophenylphthalimide (510 mg, 2 mmol) was added dropwise. The reaction mixture was stirred for an additional 72 hours, quenched with water, extracted into ether (4 x), washed with brine, dried, filtered, concentrated and purified by preparative layer chromatography (hexane: ethyl acetate, 4:1) to give the phenyl sulfide 108, 71 mg (81%); ir (CHCl_3): 3020 (C-H, aromatic), 1735 ($\text{C}=\text{O}$) cm^{-1} ; ^1H nmr (CDCl_3) δ : 2.2 (br m, 6H), 3.61 (m, 1H, $-\text{CH}-\text{S}-$), 7.32 (m, 5H, aromatic).

Acetyltriphenylphosphonium Chloride (122)

A benzene solution (100 mL) of triphenylphosphine (28.85 g, 100 mmol) and chloroacetone (9.25 g, 100 mmol) was refluxed for 1 hour. The reaction mixture diluted with petroleum ether and filtered under aspirator vacuum to give the phosphonium salt 122, 30.2 g (85%), m.p. 238-241° C; ir (CHCl₃): 3070 (C-H, aromatic), 1715 (C=O), 1600 and 1520 (C=C, aromatic) cm⁻¹; ¹H nmr (CDCl₃, 80 MHz)δ: 2.49 (d, 3H, J=1.5 Hz, CH₃-C=O), 6.10 (d, 2H, J=10 Hz, O=C-CH₂-P), 7.28 (m, 15H, aromatic).

Triphenylphosphineacetylmethylene (123)

A mixture of acetyltriphenylphosphonium chloride (15.7 g, 44 mmol) and 10% aqueous sodium carbonate (125 mL) was stirred at 22° C for 8 hours. Filtration under reduced pressure (water aspirator) gave the crystalline product 123, 14.1 g (91%), m.p. 203-205° C; ir (CHCl₃): 3070 (C-H, aromatic), 1525 (C=C, aromatic) cm⁻¹; ¹H nmr (CDCl₃, 80 MHz)δ: 2.07 (d, 3H, J=1.5 Hz, CH₃-C=O), 3.65 (d, 1H, J=26 Hz, HC=P), 7.45 (m, 15H, aromatic H), M.S. (m/z) 318 (M⁺).

2-Ethoxy-1-propenyltriphenylphosphonium bromide (124)

A tetrahydrofuran solution (15 mL) of triphenylphosphine acetylmethylene (1.0 g, 3.1 mmol) and ethyl bromide (0.26 mL, 3.5 mmol, Aldrich) was refluxed for 48 hours. The oily residue was crystallized (methanol: ethyl acetate, 1:20) to give the ether phosphonium bromide salt 124, 0.82 g

(61%), m.p. 165-167° C; ir (CHCl₃): 3060 (C-H, aromatic), 1600 (C=C), 1490 (C=C, aromatic), 1120 (C-O) cm⁻¹; ¹H nmr (CDCl₃, 80 MHz): 0.70 (t, 3H, J=7 Hz, CH₃-CH₂-), 2.65 (s, 3H, CH₃-C=), 4.06 (q, 2H, J=7 Hz, -CH₂-O), 5.80 (d, 1H, J=18 Hz, -CH-P), 7.73 (m, 15H, aromatic).

2-Ethoxy-1-propenyltriphenylphosphonium iodide (125)

A tetrahydrofuran solution (150 mL) of triphenylphosphineacetylmethylene (20 g, 62.4 mmol) and freshly distilled ethyl iodide (10.7 g, 69 mmol, Aldrich) was refluxed for 15 hours to give a tawny viscous oil. This oil was crystallized (methanol: ethyl acetate, 1:20) to give the ether phosphonium salt 125 as needles, 27.7 g (93%), m.p. 160-161° C; ir (CHCl₃): 3060 (C-H, aromatic), 1600 (C=C), 1485, 1440 (C=C, aromatic), 1110 (C-O, ether) 1000-870 (=CH) cm⁻¹; ¹H nmr (CHCl₃, 80 MHz): 0.69 (t, 3H, J=7 Hz, CH₃-CH₂), 2.57 (s, 3H, CH₃-C=O), 4.05 (q, 2H, J=7 Hz, CH₂-O), 5.52 (d, 1H, J=18 Hz, =CH-R), 7.6 (m, 15H, aromatic).

2-Methoxy-1-propenyltriphenylphosphonium iodide (126)

A tetrahydrofuran solution (15 mL) of triphenylphosphine acetylmethylene (1.0 g, 3.1 mmol) and methyl iodide (0.50, 3.5 mmol) was stirred at 22° C for 48 hours. Filtration under reduced pressure (water aspirator) gave the crystalline product 126, 1.13 g (78%), m.p. 138-141° C; ir (CHCl₃): 1720 (C=C), 1600 (C=C, aromatic), 1125 (C-O)

cm^{-1} : ^1H nmr (CDCl_3) δ : 2.55 (s, 3H, $\text{CH}_3\text{-C=}$), 3.63 (br s, 3H, $\text{CH}_3\text{-O}$), 5.52 (d, 1H, $J=20$ Hz, $=\text{CH-P}$), 7.75 (m, 15H, aromatic).

3-Ethoxy-2-methyl-5-methylthio-2-cyclopenten-1-one (102)

3-Ethoxy-2-methyl-cyclopenten-1-one (10 g, 71 mmol) in tetrahydrofuran (200 mL) was added dropwise to the tetrahydrofuran solution (100 mL) containing diisopropylamine (15 mL, 110 mmol, Aldrich) and *n*-butyllithium (51 mL, 2.1M in hexane, 110 mmol, Aldrich) at -78°C . After stirring the anion at -78°C for 30 minutes and at 0°C for 45 minutes, a tetrahydrofuran solution (150 mL) of dimethyl disulfide (6.44 mL, 6.74 g, 71 mmol, Aldrich) was added rapidly (1 minute).

After stirring at 23°C for 1 hour the reaction mixture was quenched with saturated aqueous ammonium chloride and the layers separated. The aqueous phase was extracted with ether (150 mL, 3 x) and the combined organic layers were dried, filtered, concentrated and chromatographed to give the sulfide 102, 9.58 g (72%); ir (film): 1680 (C=O), 1625 (C=C), 1125 (C-O) cm^{-1} ; ^1H nmr (CDCl_3 , 80 MHz) δ : 1.40 (t, 3H, $J=7$ Hz, $\text{CH}_3\text{-CH}_2$), 1.52 (t, 3H, $J=1.5$ Hz, $\text{CH}_3\text{-C=C}$), 2.17 (s, 3H, $\text{CH}_3\text{-S}$), 2.8-3.35 (br m; 2H, $\text{CH}_2\text{-C=}$), 4.2 (q, 2H, $J=7$ Hz, $\text{CH}_2\text{-Me}$); M.S. (m/z) 186 (M^+). Exact mass calculated for $\text{C}_9\text{H}_{14}\text{SO}_2$: 186.0714, found: 186.0730.

3-(3-Butenyl)-2-methyl-4-methylthio-2-cyclopenten-1-one
(130a)

A tetrahydrofuran solution (5 mL) of 3-ethoxy-2-methyl-5-methylthio-2-cyclopenten-1-one (1.32 g, 7.1 mmol) was added dropwise to a solution of anhydrous ether (5 mL) containing 4-bromo-1-butene (1.1 mL, 1.45 g, 10.7 mmol, Aldrich) and magnesium turnings (260 mg, 10.7 mmol). The reaction mixture was allowed to stir at 65° C for 15 hours.

The mixture was quenched (3N HCl, excess), the organic layer separated and the aqueous layer extracted with ether (3 x). The combined ether layers were washed with saturated sodium bicarbonate, dried, filtered and concentrated to give 103a as an oil, 312 mg (34%); ir (film): 1695 (C=O), 1635 (C=C) cm^{-1} ; ^1H nmr (CDCl_3 , 80 MHz) δ : 1.60 (s, 3H, $\text{CH}_3\text{-C=}$), 1.73 (s, 3H, $\text{CH}_3\text{-S}$), 2.06-2.8 (m, 6H), 3.77 (m, 1H, =C-CH-S-), 4.8-5.18 (m, 2H, $\text{CH}_2\text{=}$), 5.48-6.02 (m, 1H, -CH=C); M.S. (m/z) 196 (M^+). Exact mass calculated for $\text{C}_{11}\text{H}_{16}\text{S}$ 196.0922, found: 196.0907.

3-(3-Bromobutyl)-2-methyl-4-methylthio-2-cyclopenten-1-one
(104a)

3-(3-Butenyl)-2-methyl-4-methylthio-2-cyclopenten-1-one (850 mg, 4.5 mmol) was added to glacial acetic acid (5 mL) containing zinc bromide (100 mg). Hydrogen bromide in acetic acid solution (5 mL, 30%) was added to the stirred reaction mixture, and the flask wrapped in aluminium foil to protect the reaction from light.

After stirring for 48 hours at 23° C the reaction mixture was poured into ice water (50 mL), extracted into ether (3 x 50 mL), washed with saturated aqueous sodium bicarbonate, washed with brine, dried, filtered, concentrated and the product purified by chromatography (ether: petroleum ether, 3:2) to give the bromide 104a as an oil, 88 mg (13%); ^1H nmr (CDCl_3) δ : 1.70 (s, 3H, $\text{CH}_3\text{-C}=\text{C}$), 1.8 (s, 3H, $\text{CH}_3\text{-S-}$), 2.02 (m, 2H, $\text{-CH}_2\text{CHBr-}$), 2.33-2.90 (m, 4H), 4.06 (sextet, 1H, -CHBr-), M.S. (m/z) 276 (M^+).

3-(3-Butenyl)-2-methyl-4-methylsulfonyl-2-cyclopenten-1-one (103c)

A dichloromethane solution (50 mL) of 3-(3-butenyl)-2-methyl-4-methylthio-2-cyclopenten-1-one (1.0 g, 5.1 mmol) and m-chloroperoxybenzoic acid (2.32 g, 10.3 mmol, 80%, Aldrich) was refluxed for 6 hours. Then 10% aqueous sodium bisulfite (20 mL) was added to destroy excess peroxy acid and the reaction mixture extracted into dichloromethane (4 x 30 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate, followed by 0.5M aqueous sodium-hydroxide (excess), then dried, filtered, concentrated and chromatographed (ether) to give the sulfone (103c), 785 mg (68%); ir (CHCl_3): 1710 ($\text{C}=\text{O}$), 1635 ($\text{C}=\text{C}$), 1300 ($\text{S}=\text{O}$) cm^{-1} ; ^1H nmr (CDCl_3) δ : 1.80 (d, 3H, $\text{J}=1.5$ Hz, $\text{CH}_3\text{-C}=\text{C}$), 2.3-2.55 (m, 2H), 2.65-3.0 (m, 7H, 4.27 (m, 1H, $\text{-CH-SO}_2\text{-}$), 4.83-5.2 (m, 2H, $\text{CH}_2\text{=}$), 5.5-6.05 (m, 1H, -CH-C=); M.S. (m/z) 228 (M^+).

3-(3-Bromobutyl)-2-methyl-4-methylsulfonyl-2-cyclopenten-1-one (104b)

3-(3-Butenyl)-2-methyl-4-methylsulfonyl-2-cyclopenten-1-one (1.4 g, 6.3 mmol) and zinc bromide (0.25 g) in glacial acetic acid (10 mL) were added to a stirred hydrogen bromide in acetic acid solution (20 mL, 30-32%) and the flask wrapped in aluminium foil to protect the reaction from light.

After stirring for 96 hours, the reaction mixture was poured into ice water (50 mL), extracted into ether (3 x 50 mL), washed with saturated aqueous sodium bicarbonate, brine, dried, filtered, concentrated, and chromatographed (ethyl acetate: hexane, 1:9) to give the bromide 104b, 400 mg (21%); ir (film): 1700 (C=C), 1640 (C=O), 1310 (S=O), 1230 (C-Br), 1130 (S=O) cm^{-1} , ^1H nmr (CDCl_3) δ : 1.71 (s, 3H, $\text{CH}_3\text{-C=C}$), 2.17 (d, 3H, $J=2$ Hz, $\text{CH}_3\text{-CHBr}$), 3.91 (m, 1H, $\text{-CH-SO}_2\text{Me}$), 5.0 (m, 1H, -CHBr-Me).

3-(3,4-Epoxybutyl)-2-methyl-4-methylsulfonyl-2-cyclopenten-1-one (104c)

A dichloromethane solution (50 mL) of 3-(3-butenyl)-2-methyl-4-methylsulfonyl-2-cyclopenten-1-one (795 mg, 3.5 mmol) and m -chloroperoxybenzoic acid (750 mg, 3.5 mmol, 80% Aldrich) was refluxed for 48 hours. Then 10% aqueous sodium bisulfite (excess) was added to destroy any residual peroxy acid and the reaction mixture extracted into dichloromethane (4 x 25 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (2 x), followed by 10% aqueous sodium hydroxide (2 x), then dried, filtered,

concentrated and chromatographed (ethyl acetate) to give the sulfone epoxide 104c, as a clear oil, 640 mg (75%); ir (film): 1700 (C=O), 1635 (C=C), 1300 (S=O) cm^{-1} ; ^1H nmr (CDCl_3) δ : 1.83 (s, 3H, $\text{CH}_3\text{-C=}$), 1.9-2.1 (m, 2H, $\text{-CH}_2\text{-}$), 2.35-3.15 (m, 10H), 4.5 (m, 1H, -CH-SO_2).

3-Methyl-3-buten-1-ol mesylate (115)

To a dichloromethane solution (100 mL) of 3-methyl-3-buten-1-ol (114) (8.61 g, 0.1 mol) at 0° C was added a dichloromethane solution (20 mL) of triethylamine (20 mL, 14.4 g, 0.14 mol) and methanesulfonyl chloride (7.6 mL, 0.1 mol). After stirring for 1 hour 0.5M aqueous sodium bicarbonate (50 mL) was added and the reaction mixture stirred vigorously for 10 minutes. The layers were separated, the aqueous layer back extracted with dichloromethane and the combined organic layers washed with brine, dried filtered and concentrated to give the mesylate (115), 13.94 g (85%); ir (CDCl_3): 1665 (C=C), 1030 (S=O) cm^{-1} ; ^1H nmr (CDCl_3) δ : 1.78 (s, 3H, $\text{CH}_3\text{-C=}$), 2.40 (t, 2H, J=7 Hz , $\text{CH}_2\text{-C=C}$), 2.95 (s, 3H, $\text{CH}_3\text{-S}$), 4.21 (t, 2H, J=7 Hz , $\text{-CH}_2\text{-O}$) 4.80 (br s, 2H, $\text{CH}_2=$); M.S. (m/z) 164 (M^+).

4-Bromo-2-methyl-1-butene (116)

An acetone solution (1000 mL) of β -methyl-3-buten-1-ol mesylate (90.0 g, 0.549 mol) and lithium bromide (52 g, 0.600 mol) was refluxed for 1 hour. Then ether (500 mL) and water (500 mL) were added, the layers separated, the aqueous layer re-extracted with ether (3 x) and the combined ether

layers washed with brine, dried, filtered, concentrated and the bromide 116 purified by distillation, b.p. $120^{\circ}\text{--}130^{\circ}\text{C}/760\text{ torr}$, 74.0 g (90%); ir (CDCl_3): $1660\text{ (C=C) cm}^{-1}$; $^1\text{H nmr}$ (CDCl_3) δ : 1.72 (s, 3H, $\text{CH}_3\text{-C=}$), 2.53 (t, 2H, $J=7\text{ Hz}$, $\text{CH}_2\text{-C=}$), 3.45 (t, 2H, $J=7\text{ Hz}$, $\text{CH}_2\text{-Br}$), 4.75 (br s, 2H, $\text{CH}_2\text{=}$).

5-Methyl-2-isopropyl-5-hexenoic acid (118)

Isovaleric acid (117) (1.53 g, 15.0 mmol, Aldrich) was added to a stirred suspension of sodium hydride (0.6 g, 15.0 mmol, 60% dispersion in oil) in dry tetrahydrofuran (15 mL) and diisopropylamine (1.53 g, 15.0 mmol). The reaction was refluxed for 10 minutes, cooled to 0°C with an external ice bath, and *n*-butyllithium (7.14 mL, 15.0 mmol, 2.1M in hexane) added. The mixture was warmed to 35°C for 20 minutes, cooled to 22°C and 4-bromo-2-methyl-1-butene (2.22 g, 15.0 mmol) added. Stirring was continued at 30°C for 24 hours, the cold reaction mixture (0°C) quenched slowly with water, acidified with 10% aqueous hydrochloric acid and extracted with ether. The combined ether extracts were washed with brine, dried, filtered and concentrated to afford the acid 118, 2.04 g (80%); ir (film): $3500\text{--}2500\text{ (OH)}$, $1700\text{ (C=O) cm}^{-1}$; $^1\text{H nmr}$ (CCl_4) δ : 1.02 (d, 6H, $J=7\text{ Hz}$, $(\text{CH}_3)_2\text{C}$), 1.72 (s, 3H, $\text{CH}_3\text{-C=}$), 4.71 (br s, 2H, $\text{H}_2\text{C=C}$), 10.90 (br s, 1H, COOH); M.S. (m/z) 170 (M^+).

5-Methyl-2-isopropyl-5-hexen-1-ol (119)

5-Methyl-2-isopropyl-5-hexenoic acid (2.04 g, 12.0 mmol)

in anhydrous ether (15 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (0.456 g, 12 mmol) in anhydrous ether (15 mL) maintained at 0° C. Stirring was continued for 1 hour at 22° C after addition was complete, additional ether (50 mL) added, followed by water (1 mL) dropwise and anhydrous sodium sulfate. The solution was dried, filtered, concentrated and the product purified by chromatography (ethyl acetate: hexane, 1:9) to give the alcohol 119, 1.8 g (96%); ir (film): 3300 (br, OH), 3060 (H-C=) cm^{-1} ; ^1H nmr (CCl_4) δ : 0.90 (d, 6H, J=7 Hz, $(\text{CH}_3)_2\text{C}$), 1.75 (s, 3H, $\text{CH}_3\text{-C=C}$), 3.50 (d, 2H, J=5 Hz, $\text{CH}_2\text{-O}$), 3.77 (s, 1H, OH), 4.64 (br s, 2H, $\text{CH}_2\text{=C}$); M.S. (m/z) 156 (M^+).

5-Methyl-2-isopropyl-5-hexen-1-ol (117)

A dry dichloromethane solution (2 mL) of 5-methyl-2-isopropyl-5-hexenol (1.7 g, 10.9 mmol) was added to a well stirred suspension of pyridinium chlorochromate (6.0 g, 27.9 mmol) and sodium acetate (0.5 g, 6.2 mmol) and the reaction stirred at 22° C for 3 hours. The reaction mixture was diluted with ether (150 mL), filtered under vacuum through a short column of silica gel, concentrated and the product purified by chromatography (2% ethyl acetate/n-hexane) to give the aldehyde 117, 1.4 g (88%); ir (film): 3060 (H-C=O), 1730 (C=O), 1670 (C=C) cm^{-1} ; ^1H nmr (CCl_4) δ : 0.89 (d, 6H, J=7 Hz, $(\text{CH}_3)_2\text{C}$), 1.63 (s, 3H, $\text{CH}_3\text{-C=C}$), 4.54 (br s, 2H, $\text{H}_2\text{C=C}$), 9.54 (d, 1H, J=1 Hz, H-C=O); M.S. (m/z) 142 (M^+).

2-Ethoxy-5-isopropyl-8-methyl-1, 3, 8-nonatriene (III)

n-Butyllithium (4.8 mL, 12.6 mmol, 2.6M in hexane, Aldrich) was added to a well stirred anhydrous tetrahydrofuran solution (30 mL) of the phosphonium salt 125 (6.0 g, 12.6 mmol) cooled to -78° C. After the addition was complete the red-orange mixture was allowed to warm to -23° C and the stirring continued for 2 hours. The reaction mixture was then recooled to -78° C and a tetrahydrofuran solution (15 mL) of 5-methyl-2-isopropyl-2-hexenal (1.30 g, 8.3 mmol), 111, was added dropwise. The reaction mixture was warmed to 23° C and stirred for 18 hours. Cold water (75 mL) was added, the layers separated, the organic layer washed with water, and the aqueous layer back extracted with ether (2 x). The combined organic extracts were dried, filtered, concentrated and distilled by Kugelrohr (90° C/0.1 torr) to give the triene 111 as an oil, 750 mg (27%); ir (film): 3080 (C=C-H, stretch), 1575, 1450 (C=C), 1080 (C-O) cm^{-1} , ^1H nmr (CCl_4) δ : 0.75-0.90 (overlapping d, 6H, $\text{J}=7$ Hz, $(\text{CH}_3)_2\text{CH}$), 1.31 (t, 3H, $\text{J}=7$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$), 1.50-2.1 (M, 6H, $-\text{CH}_2-$, $\text{R}_2\text{CH-}$), 1.69 (s, 3H, $\text{CH}_3\text{-C=C}$), 3.7 (q, 2H, $\text{J}=7$ Hz, $\text{Me-CH}_2\text{-O}$), 3.9 (s, 2H, $\text{CH}_2\text{=C-O}$), 4.6 (s, 2H, $\text{H}_2\text{C=C=Me}$), 5.69 (br s, 2H, $-\text{CH=CH-}$); M.S. (m/z) 222 (M^+). From an attempted preparative layer chromatography purification (ether: petroleum ether, 1:9) of the crude triene (500 mg), recovered the hydrolysed product, 8-methyl-5-isopropyl-3, 8-nonadien-2-one (120), 170 mg; ir (film): 3080 (C=C-H, stretch), 1689 (C=O), 1625, 1450 (C=C) cm^{-1} , ^1H nmr (CCl_4) δ : 0.87 (overlapping d,

6H, $J=7$ Hz, $(\text{CH}_3)_2\text{-C}$), 1.69 (s, 3H, $\text{CH}_3\text{-C}=\text{C}$), 2.02 (s, 3H, $\text{CH}_3\text{-C}=\text{O}$), 4.60 (br s, 2H, $\text{H}_2\text{C}=\text{C}$), 5.88 (d, 1H, $J=16$ Hz, $\text{C}=\text{CH}-\text{C}=\text{O}$), 5.45 (dd, 1H, $J=9, 16$ Hz, $\text{HC}=\text{C}-\text{C}=\text{O}$), M.S. (m/z) 195 ($M + 1$).

trans-4-Phenyl-3-buten-2-one (benzalacetone) (129)

n-Butyllithium (4.4 mL, 11.3 mmol, 2.6M in hexane, Aldrich) was added slowly to a well stirred anhydrous tetrahydrofuran suspension (20 mL) of the phosphonium iodide salt 125 (5.35 g, 11.3 mmol) at -78°C . After the addition was complete, the dark red mixture was allowed to warm to -23°C and the stirring continued for 2 hours. The reaction mixture was recooled to -78°C and a tetrahydrofuran solution (10 mL) of benzaldehyde (1.0 g, 9.4 mmol, Aldrich) was added dropwise. The resulting reddish-brown mixture was quenched with water (30 mL), extracted into dichloromethane (3 x), and the combined organic layers dried, filtered, concentrated and purified by preparative layer chromatography (petroleum ether: ether, 9:1) to give the aromatic unsaturated ketone 129, 0.210 g (15%) m.p. $35-38^\circ\text{C}$, (purification required 3 columns and a preparative plate, contributing to low yield); ir (film): 1670 ($\text{C}=\text{O}$), 1610 ($\text{C}=\text{C}$), 1495, 1450 ($\text{C}=\text{C}$, aromatic) cm^{-1} ; ^1H nmr (CCl_4) δ : 2.23 (s, 3H, $\text{CH}_3\text{-C}=\text{O}$), 6.52 (d, 1H, $J=16$ Hz, $-\text{C}=\text{CH}$), 7.36 (d, 1H, $J=16$ Hz, $-\text{C}=\text{CH}$), 7.29 (s, 5H, aromatic); M.S. (m/z) 146 (M^+).

Bibliography

1. (a) P.S. Rao, K.G. Sharma, and T.R. Seshadri. *Curr. Sci.* 34, 9 (1965); (b) P.S. Rao, K.G. Sharma, and T.R. Seshadri. *Curr. Sci.* 35, 147 (1966).
2. M. Kaneda, R. Takahashi, Y. Iataka, and S. Shibata. *Tetrahedron Lett.* 4609 (1972).
3. D.E. Caine and A.M. Tillman. *J. Am. Chem. Soc.* 105, 123 (1983).
4. H. Seto, T. Sasaki, T. Ozawa, and S. Takemchi. *Tetrahedron Lett.* 4411 (1978).
5. Isolation: (a) F. Bohlmann, N. LeVan, and J. Pickhardt. *Chem. Ber.* 10, 3777 (1977); (b) L.H. Zalkow, R.M. Harris III, D. Van Derveer, and J.A. Bertrand. *J. Chem. Soc., Chem. Commun.* 456 (1977); L.H. Zalkow, R.M. Harris III, and N.I. Burke. *J. Nat. Prod.* 42, 96 (1979).
6. Synthesis: (a) W. Oppolzer, K. Battig, and T. Hudlicky. *Helv. Chim. Acta.* 62, 1493 (1979); (b) W. Oppolzer, K. Battig, and T. Hudlicky. *Tetrahedron*, 37, 4359 (1981); (c) L.A. Paquette and Y.K. Han. *J. Org. Chem.* 44, 4014 (1979); (d) L.A. Paquette and Y.K. Han. *J. Am. Chem. Soc.* 103, 1835 (1981); (e) M.C. Pirrung. *J. Am. Chem. Soc.* 101, 7130 (1979); (f) M.C. Pirrung. *J. Am. Chem. Soc.* 103, 82 (1981); (g) W.G. Dauben and D.M. Walker. *J. Org. Chem.* 46, 1103 (1981); (h) P.A. Wender and G.B. Dreyer. *Tetrahedron*, 37, 4445 (1981).
7. F. Bohlmann and J. Jakupovic. *Phytochemistry*, 19, 259 (1980).
8. L. A. Paquette and A. Leone-Bay. *J. Am. Chem. Soc.* 105, 7352 (1983).
9. F. Bohlmann, N. LeVan, T.V. Cuong Pham, T. Jakupovic, A. Shuster, V. Zabel, and W.H. Watson. *Phytochemistry*, 18, 1831 (1979).
10. B.M. Trost. *Chem. Soc. Review.* 11, 141 (1982).
11. W.G. Dauben and D.J. Hart. *J. Org. Chem.* 42, 3787 (1977).
12. (a) J.E. Baldwin and L.I. Kruse. *J. Chem. Soc., Chem. Commun.* 233 (1977); (b) H.O. House, W.V. Phillips, T.S.B. Sayer, and C.C. Yau. *J. Org. Chem.* 42, 700 (1978).
13. L.A. Paquette. *Top. Curr. Chem.* 119 (1984).

14. M. Demuth and K. Schaffner. *Angew. Chem. Int. Ed.* (Engl.) 21, 820 (1982).
15. D.K. Klipa and H.J. Hart. *J. Org. Chem.* 46, 2815 (1981).
16. B.M. Frost and J.E. Vincent. *J. Am. Chem. Soc.* 102, 5680 (1980).
17. (a) M.J. Begley, K. Cooper, and G. Pattenden. *Tetrahedron Lett.* 257 (1981); (b) M.J. Begley, K. Cooper, and G. Pattenden. *Tetrahedron*, 37, 4503 (1981).
18. A. Marfat and P. Helquist. *Tetrahedron Lett.* 4217 (1978).
19. A. Barco, S. Bernetti, P. Pollini, and G. Gandolfi. *J. Org. Chem.* 45, 4776 (1980).
20. C.M. Tice and C.H. Heathcock. *J. Org. Chem.* 46, 9 (1981).
21. B.M. Frost and D.P. Curran. *J. Am. Chem. Soc.* 102, 5699 (1980).
22. T.H. Chan, A. Baldassarre, and D. Massuda. *Synthesis*, 801 (1976).
23. E. Denmark and T.K. Jones. *J. Am. Chem. Soc.* 104, 2642 (1982).
24. L.A. Paquette, E. Farkas and R. Galemmo. *J. Org. Chem.* 46, 5434 (1981).
25. A.E. Greene and J.P. Depres. *J. Am. Chem. Soc.* 101, 4003 (1979).
26. S. Knapp, A.P. Trope, and R.M. Orna. *Tetrahedron Lett.* 4301 (1980).
27. G. Haufe, E. Kleinpeter, M. Muhlstadt, and J. Graffe. *Monatsh. Chem.* 102, 575 (1978).
28. G.A. Tolstikov, F.Y. Kanzafarov, U.M. Dzlemilev and Y.A. Sangalov. *Neflekhimiya*, 20, 674 (1980).
29. B.B. Snider, D.J. Rodini, T.C. Kirk, and R. Cordova. *J. Am. Chem. Soc.* 104, 555 (1982).
30. T. Hudlicky, J.P. Sheth, V. Gee, and D. Barnvon. *Tetrahedron Lett.* 4889 (1979).

31. T. Hudlicky and F.J. Koszyk. *Tetrahedron Lett.* 2487 (1980).
32. T. Hudlicky, F.J. Koszyk, T.M. Kytchen and J. P. Sheth. *J. Org. Chem.* 45, 5020 (1980).
33. L.A. Paquette, G.J. Wells, K.A. Horn, and T.H. Yan. *Tetrahedron Lett.* 263 (1982).
34. L.A. Paquette, G.J. Wells, K.A. Horn, and T.H. Yan. *Tetrahedron*, 29, 913 (1983).
35. J. Drouin, F. Leyendecker, and J.M. Conia. *Tetrahedron*, 26, 1195 (1980).
36. J. Drouin, F. Leyendecker, and J.M. Conia. *Tetrahedron*, 36, 1203 (1980).
37. F. Plavac and C.H. Heathcock. *Tetrahedron Lett.* 2115 (1979).
38. (a) G.D. Amis and L.A. Paquette. *J. Am. Chem. Soc.* 104, 4304 (1982); (b) G.D. Annis and L.A. Paquette. *J. Am. Chem. Soc.* 105, 7358 (1983); (c) A. Leone-Bay and L.A. Paquette. *J. Org. Chem.* 47, 4179 (1982); (d) A. Leone-Bay and L.A. Paquette. *J. Am. Chem. Soc.* 105, 7352 (1983).
39. S. Chatterjee. *J. Chem. Soc. Chem. Commun.* 620 (1979).
40. (a) R.A. Roberts, V. Schull, and L.A. Paquette. *J. Org. Chem.* 48, 2076 (1983); (b) L.A. Paquette. *Top. Curr. Chem.* 112 (1984).
41. T. Hudlicky and R.P. Short. *J. Org. Chem.* 47, 1522 (1982).
42. E.J. Corey and T.A. Engler. *Tetrahedron Lett.* 25, 149 (1984).
43. B.B. Snider, D.J. Rodini, and J. van Straten. *J. Am. Chem. Soc.* 102, 5872 (1980).
44. (a) R.A. Lee, C. McAndrews, K.M. Patel, and W. Reusch. *Tetrahedron Lett.* 965 (1973); (b) K.M. Patel and W. Reusch. *J. Org. Chem.* 40, 1504 (1975); (c) M.L. Quesada, R.H. Schlessinger, and W.H. Parsons. *J. Org. Chem.* 43, 3968 (1978); (d) J. D'Angelo. *Tetrahedron*, 32, 2979 (1976); (e) N.W. Atwater. *J. Am. Chem. Soc.* 82, 2847 (1960); (f) H.J. Ringold and G. Rosenkrantz. *J. Org. Chem.* 22, 602 (1957); (g) G. Stork and R.L. Danheiser. *J. Org. Chem.* 38, 1775 (1973); (h) G. Stork, G.A. Krans, and G.A. Garcia. *J. Org. Chem.* 39, 3459

- (1974); (i) L. Nedelec, J.C. Gase, and R. Bucourt. *Tetrahedron*, 30, 3263 (1974).
45. E. Piers, M. Zbonzy, and D.C. Wigfield. *Can. J. Chem.* 57, 1064 (1979).
 46. A.P. Johnson and V.Vajs. *Chem. Commun.* 817 (1979).
 47. R. L. Cargill and T.E. Jackson. *J. Org. Chem.* 38, 2125 (1973).
 48. J.C. Stowell. *Carbanions In Organic Synthesis*. Wiley, New York, N.Y. 1979. p. 10.
 49. B.M. Trost and L.H. Latimer. *J. Org. Chem.* 42, 3212 (1977).
 50. (a) M. Koreeda, Y. Liang, and H. Akay. *Chem. Commun.* 449 (1979); (b) M. Koreeda and S.G. Lislankar. Abstract ORGN 182, 185th American Chemical Society National Meeting, Seattle, Washington. March 20-25, 1983; *J. Am. Chem. Soc.* 105, 7203 (1983).
 51. R.E. Benson and R.V. Lindsey. *J. Am. Chem. Soc.* 79, 5471 (1957).
 52. P.A. Grieco, J.Y. Jaw, D.A. Clareman, and K.C. Nicolaou. *J. Org. Chem.* 46, 1215 (1981); (b) P.A. Greico, S. Gilman, and S. Nishizawa. *J. Org. Chem.* 41, 1485 (1976).
 53. (a) E.J. Corey, U. Koelliker, and J. Neuffner. *J. Am. Chem. Soc.* 93, 1489 (1971); (b) E.J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T.K. Schaaf. *J. Am. Chem. Soc.* 93, 1490 (1971); (c) E.J. Corey, T. Ravindranathan, and S. Terashima. *J. Am. Chem. Soc.* 93, 4326 (1971).
 54. J.R. Catch, D.F. Elliot, D.H. Hey, and E.R.H. Jones. *J. Chem. Soc.* 278 (1948).
 55. M. Gaudry and A. Marquet. *Tetrahedron*, 26, 5611 (1970).
 56. D. Caine, S.T. Chao, and H.A. Smith. *Org. Synthesis*, 56, 62.
 57. G. Stork, P. Rosen, N. Goldman, R.V. Coombs and J. Tsujui. *J. Am. Chem. Soc.* 87, 275 (1965).
 58. W. Groebel. *Chem. Ber.* 93, 284 (1980).
 59. T. Mukaiyama, T. Adachi, and T. Kummoto. *Bul. Jap. Chem. Soc.* 44, 3155 (1971).

60. M. Behforuz and J.E. Kerwood. J. Org. Chem. 34, 51 (1969).
61. D. Scholz. Synthesis, 945 (1983).
62. W. Oppolzer, D.A. Roberts, and T.G.C. Bird. Helv. Chimica Acta, 62, 2017 (1979).
63. K. Konda and D. Tunemoto. Tetrahedron Lett. 1007 (1975).
64. F. Ramirez and S. Dershowitz. J. Org. Chem. 22, 41 (1957).
65. S.F. Martin and S.R. Desai. J. Org. Chem. 42, 1664 (1977).
66. R.E. Ireland, R.C. Anderson, R. Badoud, B.J. Fitzsimmons, G.J. McGarvey, S. Thaisrivongs, and C.S. Wilcox. J. Am. Chem. Soc. 105, 1988 (1983).
67. P.E. Pfeffer, L.S. Silbert, and John M. Chirinko, Jr. J. Org. Chem. 37, 451 (1972).



