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A Thesis Entitled:

THE SYNTHESIS OF SOME CYCLOPENTANOID NATURAL PRODUCTS

By

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The synthesis of some cyclopentanoid natural products

D.T. MacPherson

Abstract

The rapidly expanding area of research into cyclopentanoid natural products is briefly reviewed by reference to some of the more important classes of such natural products. Some of the more general procedures that have been developed for the construction of cyclopentane rings are discussed.

The eight step synthesis of a highly functionalised bicyclo[3.3.0]octane derivative from readily available methyl 2-oxocyclopentanecarboxylate is described. The key feature of this synthesis involves the construction of a cyclopentane ring through intramolecular Wittig reaction using (methylthio) or (phenylthio) substituted vinyl phosphonium salts, (developed earlier in our laboratories).

This bicyclo[3.3.0]octane derivative contains useful functionality in both rings and has been used in syntheses of several natural products.

A simple three step procedure which uses the structural features of the bicyclo[3.3.0]octane unit to achieve stereocontrol led to a precursor of the beetle defensive secretion chrysomelidial.

A nine step procedure involving the conversion of a ketone to an α,β unsaturated ester and deconjugation of this ester to the β,γ-unsaturated isomer as key features led to a bicyclo[3.3.0]octane precursor to the iridoid glucoside loganin.

Two formal syntheses of hirsutene the parent hydrocarbon of the hirsutane family of natural products were developed. Both syntheses involved regiospecific α-alkylation of the anion derived from a vinyl sulphone to introduce the third ring necessary for hirsutene. Such an alkylation with 2-(2-iodoethyl)-1,3-dioxalane led to a known bicyclo[3.3.0]octane precursor to hirsutene. A similar alkylation with 5-iodo-2-pentyne led to an enyne which underwent cationic cyclization in formic acid to give a linearly fused tricyclopentanoid system. This product was converted in one step to an immediate precursor to hirsutene.

Possible further uses of this highly functionalised bicyclo[3.3.0]octane derivative are discussed.

An intermediate involved in the preparation of the key bicyclo[3.3.0]octane derivative was converted to an immediate precursor to the antitumour agent sarkomycin.

CHAPTER 1

Introduction to cyclopentanoid natural products

1.1 Historical and background

In recent years many natural products containing one or more cyclopentane rings have been isolated and characterised. Several of these natural products possess biological activity of pharmacological interest and this together with their frequently complex structure has stimulated great interest into the synthesis of such compounds. Some of the more important areas in this rapidly expanding field are outlined below.

The current interest was initiated in the early 1960's by the recognition that the prostaglandins for example PGE_1 and PGF_1 were cyclopentane containing natural products[1] (Figure 1.1).

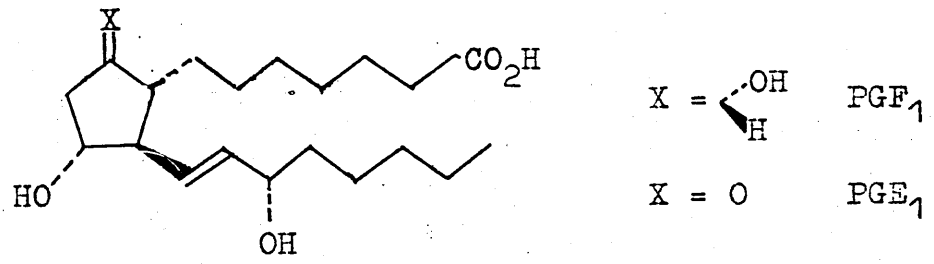


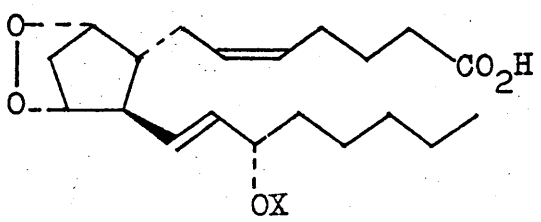
Figure 1.1

Prior to this time apart from a few classical examples such as the iridoids and jasmones, cyclopentanoid natural products and in particular di and triquinane natural products were rare.

The prostaglandins have attracted much attention from chemists and biologists largely due to their array of biological activity[2]. Since the first prostaglandin synthesis in 1967[3] the synthesis of prostaglandins and their analogues for potential therapeutic use has remained amongst the major

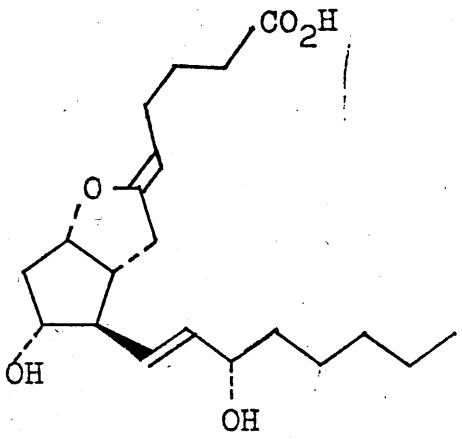
pastimes of synthetic chemists[4].

Research into prostaglandins intensified in the mid 1970's with the isolation of some unstable biosynthetic precursors to the prostaglandins, for example prostaglandin endoperoxides and prostacyclin (Figure 1.2.).



X = OH or H

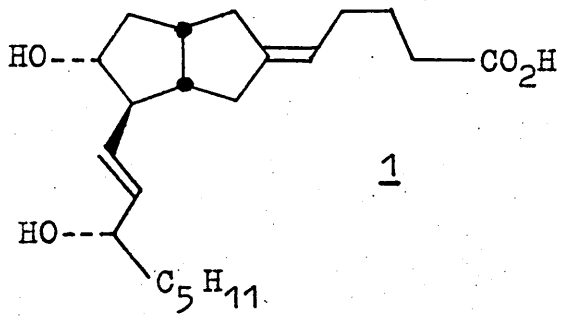
Prostaglandin endoperoxides



Prostacyclin

Figure 1.2

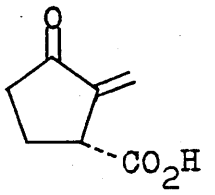
In several cases these intermediates possess more potent physiological activity than the primary prostaglandins[5]. Prostacyclin, for example is the most potent inhibitor of blood platelet aggregation known. The unstable nature of these compounds together with their remarkable activity has stimulated great efforts into the preparation of stable analogues. Among the priorities in this area is the synthesis of a stable analogue of prostacyclin for use in the prevention of thrombosis. Carbaprostacyclin 1 has attracted attention in this regard[6].



1

In general the vast amount of research effort accorded to the prostaglandins has not yet paid off in terms of useful therapeutic reagents and the search for stable prostaglandins analogues with selective biological activity looks set to continue.

The last decade has seen a growth in interest accorded to a class of novel monocyclopentanoid antibiotic/antitumour agents. The parent member of this class, sarkomycin, 2, was isolated in 1953 but has only recently attracted considerable attention as a synthetic target[7].



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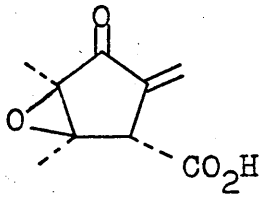
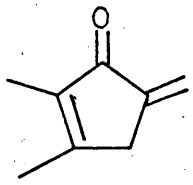
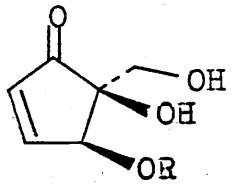
Other compounds in this class include methlenomycins A and B and pentenomycins I and II[8] (Figure 1.3).



methlenomycin A



methylenomycin B

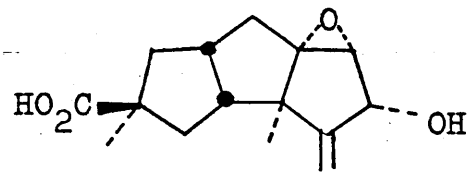


R=H
pentenomycin I

R=Ac
pentenomycin II

Figure 1.3.

The interest in polyquinane natural products began with the determination of the structure of hirsutic acid 3 in 1967[9].



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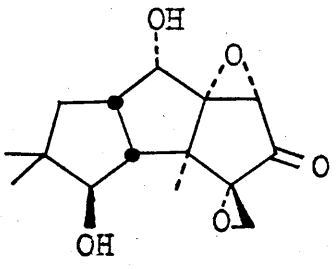
The linearly fused tricyclopentanoid framework of hirsutic acid was unique at that time but two groups of natural products containing this skeleton are now known. The most widely studied of these are the hirsutanes of which hirsutic acid is a member. Other members of this class include coriolin 4[10] and hirsutene 5[11], the proposed biogenetic precursor of the hirsutanes.



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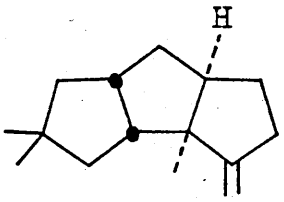

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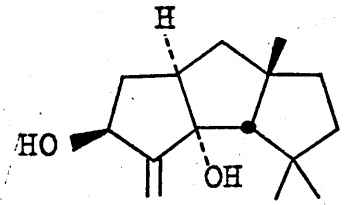
Several of the hirsutanes possess antibiotic and/or antitumour activity and thus it is not surprising that they have recently become very common synthetic targets[12].

The capnellane natural products also contain the linearly fused tricyclopentanoid system. They were isolated from marine organisms in the mid 1970's[13] and have attracted attention largely because of their similarity to the hirsutanes[14]. Examples of naturally occuring capnellanes

include $\Delta^{9(12)}$-capnellene-8β,10α-diol 6 and the parent hydrocarbon $\Delta^{9(12)}$-capnellene 7.



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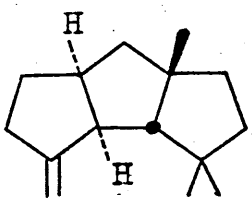

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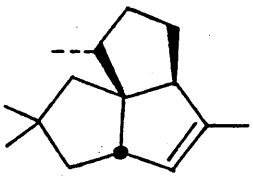
Recent biosynthetic studies by several research groups have shown that the hirsutanes are biogenetically related to the pentalenolactones, an important class of cyclopentanoid antibiotics found in Streptomyces[15]. Cane and co-workers have shown that the angularly fused tricyclopentanoid pentalenene 8, also found in Streptomyces is a biosynthetic precursor to pentalenolactone 9 and other members of this family of antibiotics[16].



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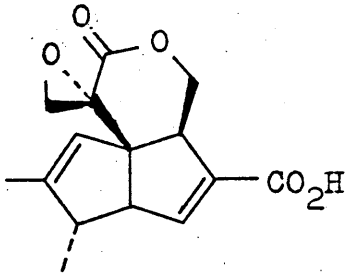

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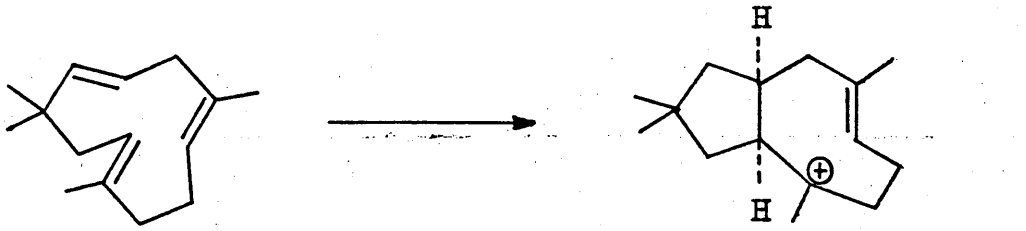
Further studies suggest that 8 is derived from humulene 10 via the so called protoilludyl cation 11[16,17]. Hirsutene is thought to be similarly derived[18] (Figure 1.4.). The capellanes may also be biosynthetically derived from humulene[19].



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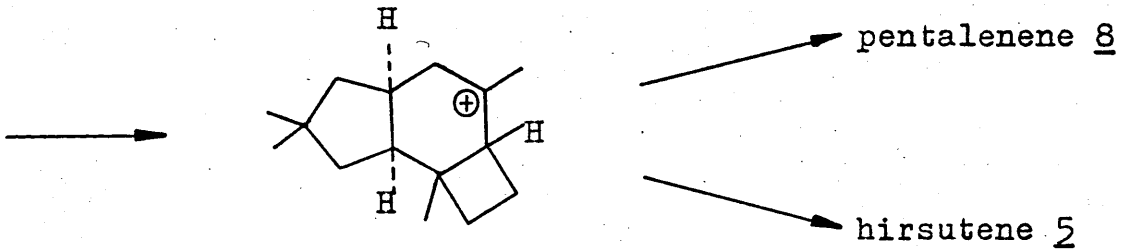

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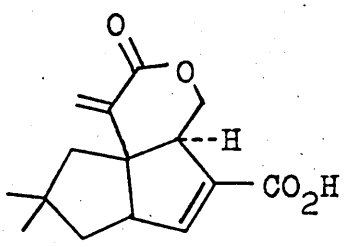
Figure 1.4.

A number of syntheses of pentalenene, pentalenolactone and other members of this group for example pentalenolactone E, 12 have been reported[20].

The structurally complex antitumour agent quadrone 13 possesses structural similarities to the pentalenolactones and has been the focus of much attention since its isolation in 1978[21].



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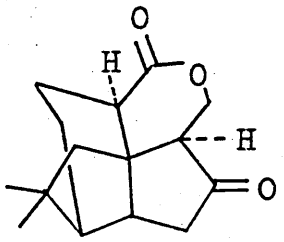
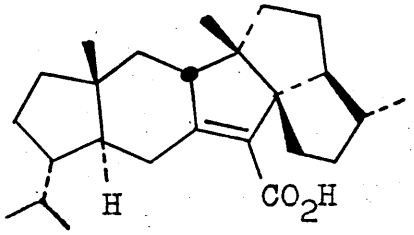


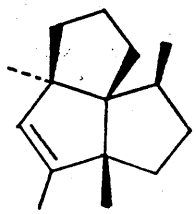
13

Angularly fused tricyclopentanoid systems structurally related to pentalenene are gaining in interest as more of

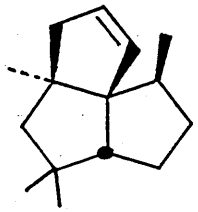
these compounds are isolated from natural sources[22]. Retigeranic acid was the first compound containing this skeleton to be isolated in 1972[23]. Other such tricyclopentanoids of synthetic interest include isocomene[24] and silphinene[25] (Figure 1.5.).



retigeranic acid



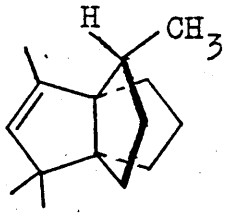
isocomene



silphinene

Figure 1.5.

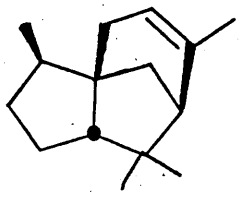
The interesting [3.3.3] propellane system modhephene 14 has also been isolated from the same source as isocomene[26].



14

Along with the recent intense interest in novel cyclopentanoid natural products there has been continual interest in the synthesis of some classical cyclopentanoid natural products. This is apparent from the number of recent syntheses of cedrene 15 and its analogues[27] and some iridoids for example loganin 16[28] and iridodial 17[29] which have been

reported.



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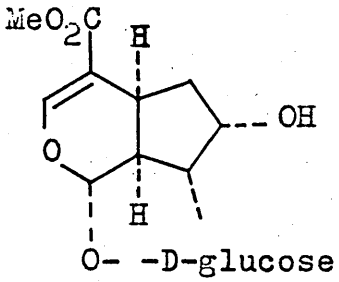

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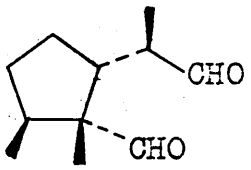


17

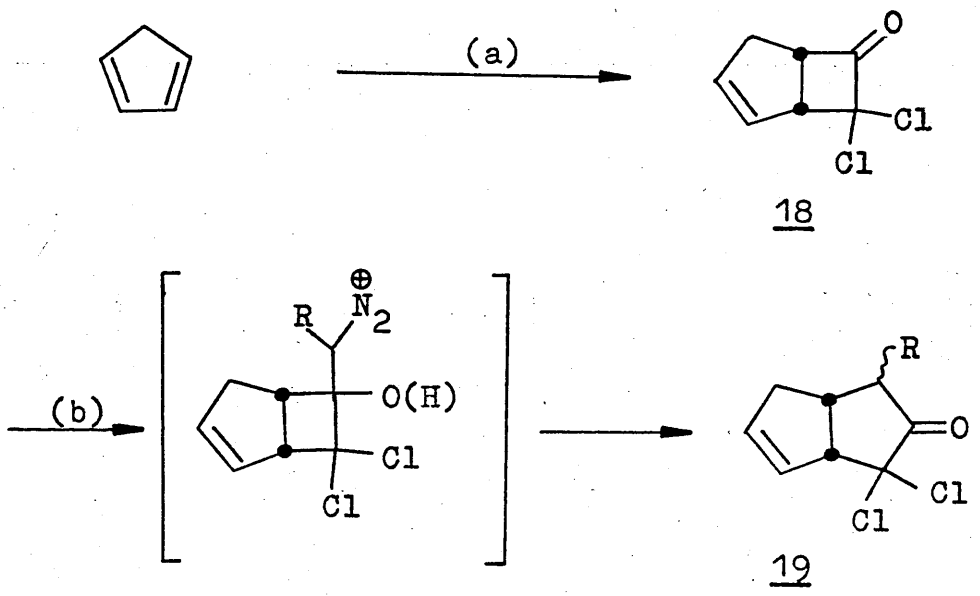
1.2 Some recent developments in the construction of cyclopentanoids.

The diversity of structure and functionality within cyclopentanoid natural products dictate the need for a broad range of procedures for the construction of such systems. Organic chemists have until recently been preoccupied with the preparation of the 6-membered ring counterparts[30] primarily because of the abundance of such a ring in natural systems. Classical ring forming reactions such as Dieckmann and intramolecular aldol condensations continue to be useful processes for cyclopentanoid formation but the need for versatility has led to the development of many novel routes to cyclopentanoids. To review all the methods now available for cyclopentanoid construction is beyond the scope of this report. However some of the more general procedures will be outlined to illustrate some of the recent developments in this rapidly developing area. Extensive review literature on this subject is available[31].

Several types of functionality have been employed in the construction of cyclopentanoids, the major ones being olefins, ketones and enones.

1.2.1 Reactions of olefins

One of the more general procedures for cyclopentanoid construction is the [2+2] cycloaddition-ring expansion method developed largely by Greene[32] (Scheme 1.1).

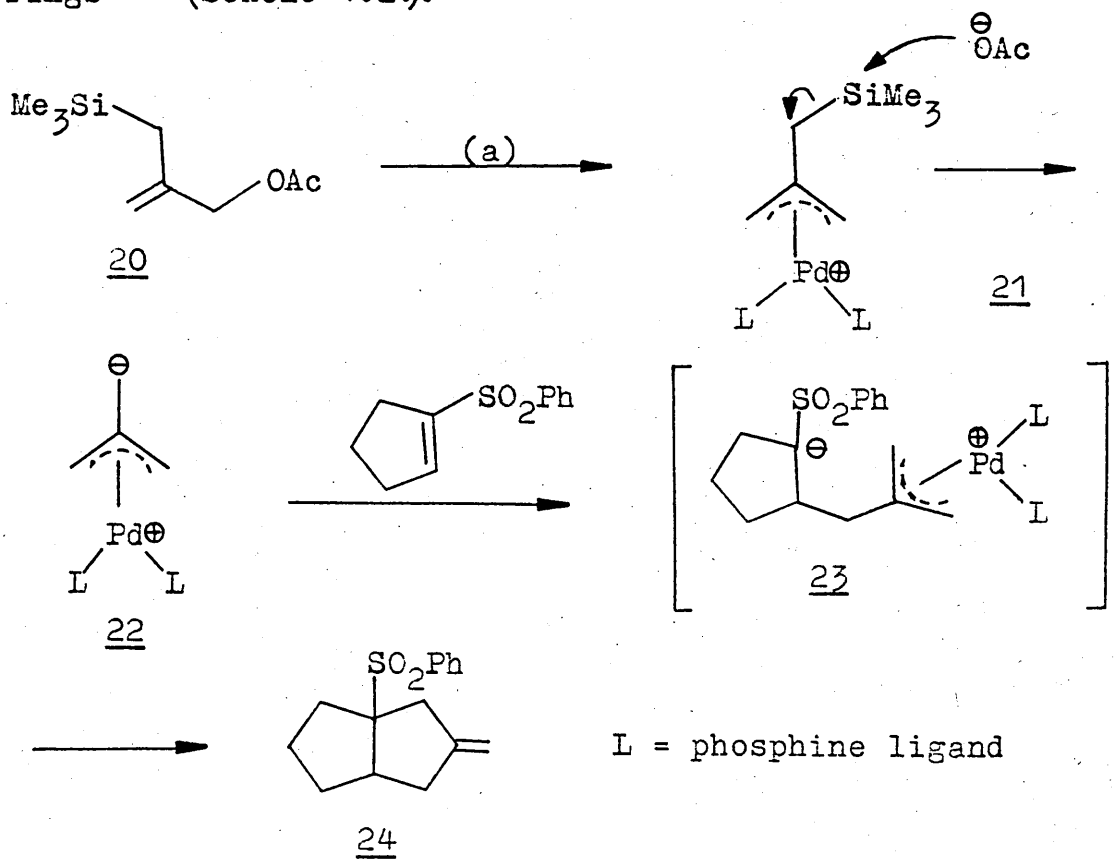


Reagents: (a) $Cl_2CHCOCl$, NEt_3, pentane; (b) $RCHN_2$.

Scheme 1.1. Cycloaddition-ring expansion approach to cyclopentanones.

The [2+2] cycloaddition of dichloroketene with olefins proceeds regioselectively due to polarisation effects. Thus cycloaddition of cyclopentadiene with dichloroketene produces cyclobutanone 18. Regioselective ring expansion with diazomethane (R=H) produces the bicyclo[3.3.0]octenone 19. The electron withdrawing effect of the α-chlorosubstituents in 18 serves to disfavour the alternative migration pathway. The chlorines can be removed by treatment with zinc in acetic acid. Alternatively a number of useful transformations of the α,α-dichlorocyclopentanones can be carried out[33]. This useful reaction has been widely employed in natural product synthesis[34].

The [3+2] cycloaddition of a trimethylenemethane palladium complex with an electron deficient olefin produces a cyclopentane ring in a process which is complementary to the Diels-Alder reaction for the formation of cyclohexane rings[35] (Scheme 1.2.).



20 21 22 23 24

L = phosphine ligand

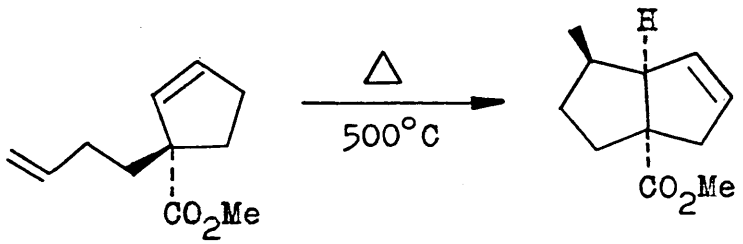
Reagents: (a) $(Ph_3P)_4Pd$, $Ph_2PCH_2CH_2PPh_2$, THF,

Scheme 1.2. [3+2] cycloaddition approach to cyclopentanes

Treatment of the allyl acetate 20 with a Pd[0] complex produces the π-allyl Pd complex 21. The extruded acetate anion acts as a silylophile to produce the reactive complex 22. When 22 is generated in the presence of an electron deficient olefin, Michael addition to produce 23 followed by charge neutralisation give cyclopentane 24. Enones,

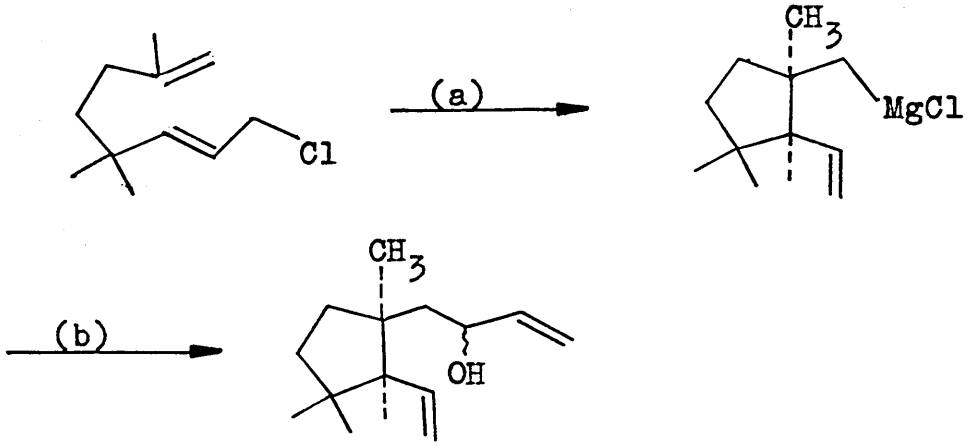
α,β-unsaturated esters, nitriles and sulphones have been used as substrates. The functionality produced is conducive to further elaboration. This procedure has been applied to the synthesis of several natural products[36].

The ene reaction is rapidly becoming an important process in the synthesis of complex natural products[37] and has found several applications in the construction of cyclopentanoids. It is highly stereoselective in common with other pericyclic reactions. The dienyl ester 25 cyclizes via an intramolecular ene reaction to produce the bicyclo[3.3.0]octane 26 as a single diastereoisomer[38].



25 26

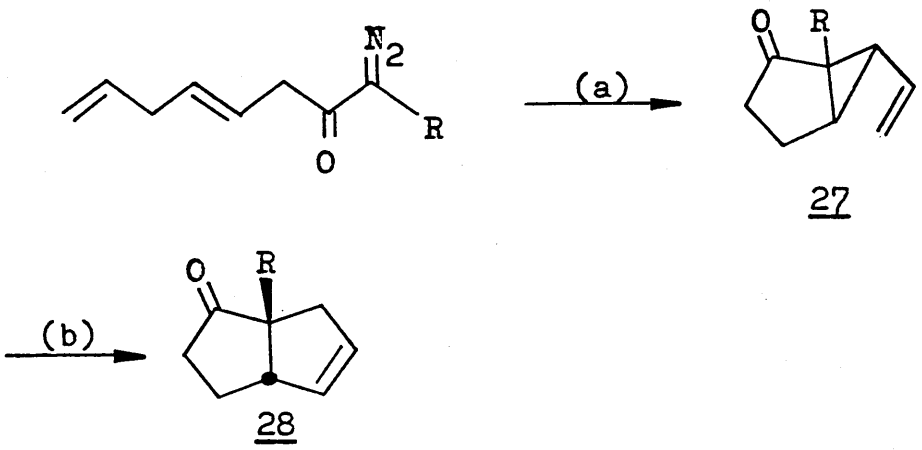
A recent modification is the magnesium ene reaction developed by Oppolzer[39]. This promises to be a highly useful reaction as the product is a Grignard reagent which can undergo the usual reactions of such organometallic reagents (Scheme 1.3.).



Reagents: (a) i. Mg, ether; ii. 60°c, 23hr; (b) i. CH_2=CHCHO; ii. H^+.

Scheme 1.3. Cyclopentanes via the magnesium ene reaction.

The thermal rearrangement of vinyl cyclopropanes has been frequently employed for the preparation of cyclopentenes. This reaction has been exploited by Hudlicky for the synthesis of di and triquinane systems[40] (Scheme 1.4).

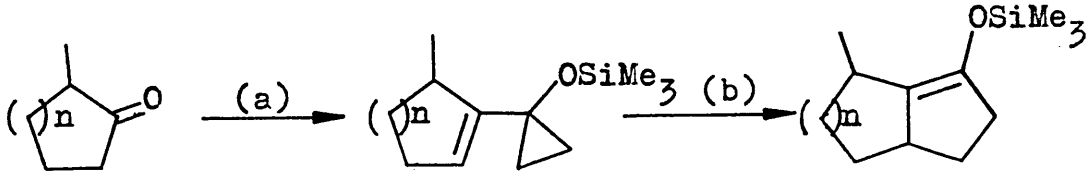


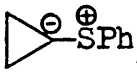
Reagents: (a) $Cu(acac)_2$, C_6H_6, Δ ; (b) Δ .

Scheme 1.4. Cyclopentenes via vinyl cyclopropane rearrangement

Intramolecular addition of a carbene to a conjugated diene produces vinyl cyclopropane 27 which is pyrolyzed to bicyclo [3.3.0] octenone 28.

The ready availability of substituted vinyl cyclopropanes from ketones extends the versatility of this rearrangement to the formation of enol derivatives, Scheme 1.5 shows one such example[41].

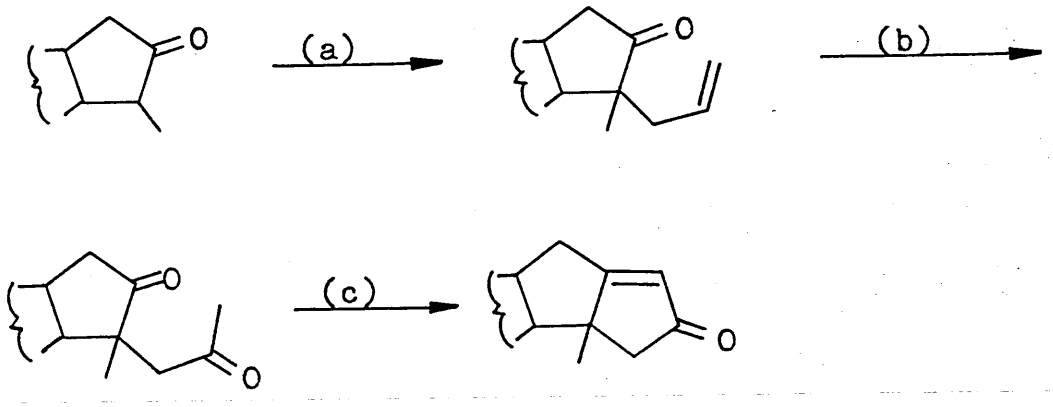


Reagents: (a) i.  ; ii. LDA, Me_3SiCl; (b) Δ .

Scheme 1.5 Functionalised cyclopentenes via vinyl cyclopropane rearrangement.

1.2.2. Reactions of ketones and enones

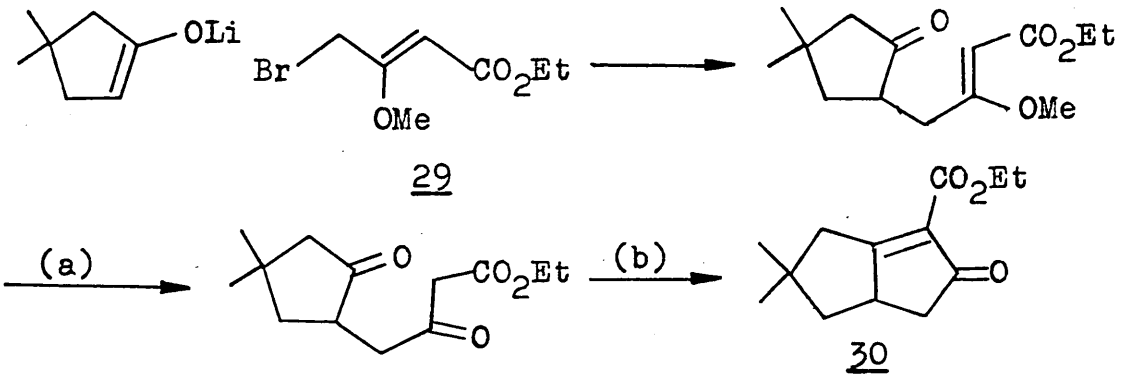
The intramolecular aldol condensation of 1,4-diketones has served as a useful reaction for the construction of cyclopentenones for many years[42]. The reaction produces functionality highly conducive to further elaboration and thus continues to be a frequently used reaction. Recent developments in this area have produced novel methods for the preparation of the necessary 1,4-dicarbonyl unit. The more useful methods are based on the alkylation of a ketone with an acetonyl equivalent[43]. The Wacker oxidation of a terminal alkene to a methyl ketone[44] allows an allyl group to serve this purpose (Scheme 1.6.).



Reagents: (a) $NaH, CH_2=CHCH_2Br$; (b) $PdCl_2, CuCl_2, O_2, DMF-H_2O$
(c) KO^tBu.

Scheme 1.6. The allyl group as an acetonyl equivalent.

A similar alkylating agent which has seen widespread application expecially in the synthesis of pentalenolactones and quadrone is 29[45] (Scheme 1.7.).

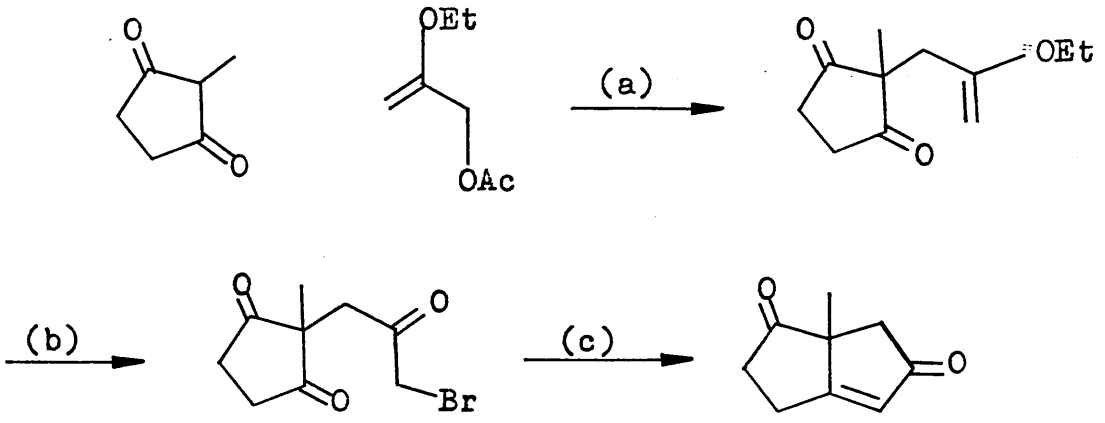


Reagents: (a) 2N HCl; (b) NaOEt

Scheme 1.7.

Annelation with this reagent produces a cyclopentenone such as 30 with the additional ester functionality.

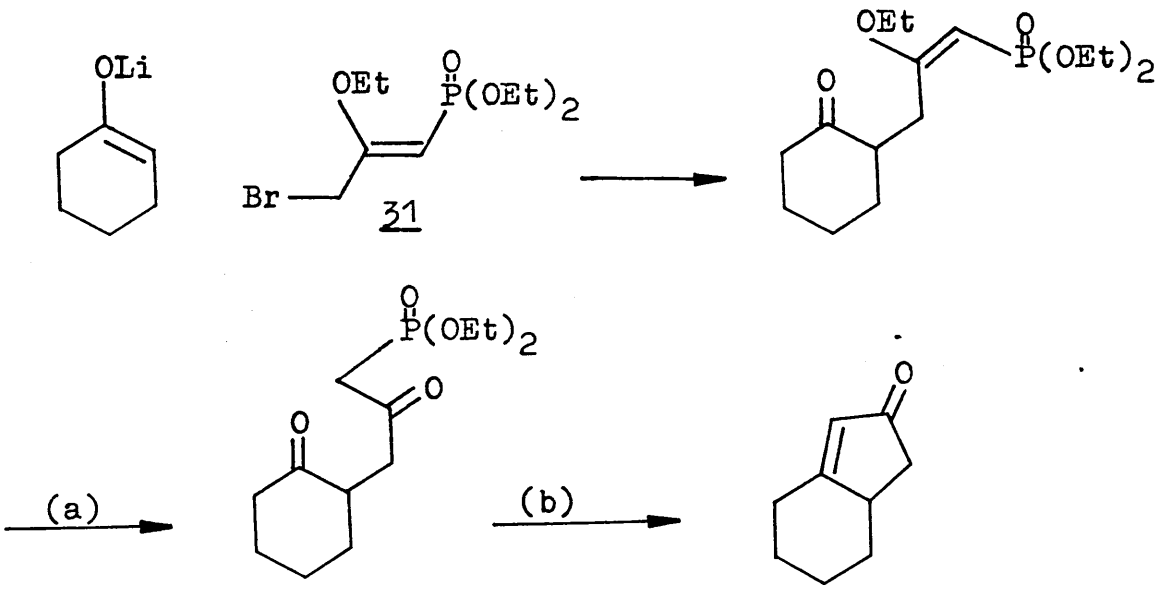
The intramolecular Wittig reaction and related olefination procedures are often useful alternatives to the aldol condensation. There have been several approaches to the development of suitable reagents for use in such reactions. Trost used an enol ether functionality as a convenient precursor to an α-keto phosphonium salt[46] (Scheme 1.8).



Reagents: (a) $Pd(Ph_3)_4$, 1-10%, DBU, toluene, 80°C; (b) NBS, H_2O; (c) i. Ph_3P, C_6H_6; ii. Aq.K_2CO_3, 40°C.

Scheme 1.8. Trost's intramolecular Wittig approach to cyclopentenones.

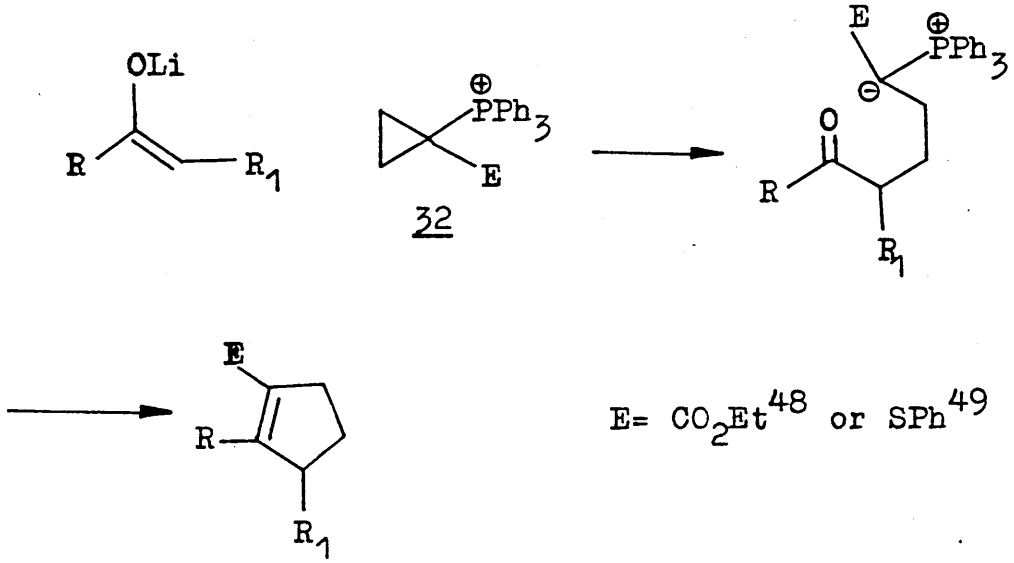
Along similar lines Piers has developed the alkylating agent 31 for cyclopentenone synthesis[47] (Scheme 1.9).



Reagents: (a) H_3O^+; (b) NaH,DME.

Scheme 1.9. Piers' intramolecular Wittig approach to cyclopentenones.

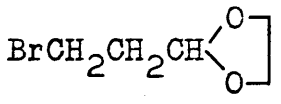
The activated cyclopropanes 32 are also useful reagents for cyclopentene formation via Wittig methodology (Scheme 1.10).



E= CO_2Et[48] or SPh[49]

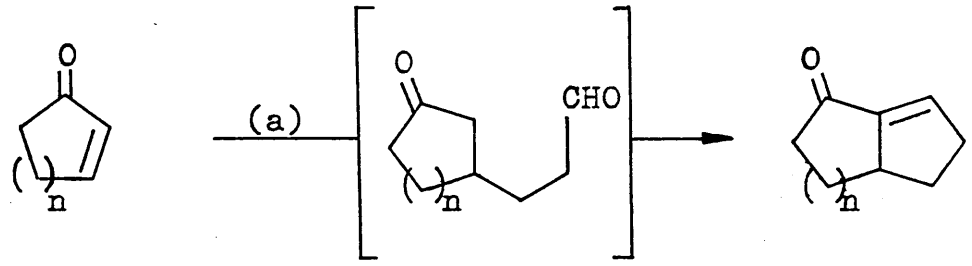
Scheme 1.10. Activated cyclopropanes in cyclopentene formation.

Rapid developments in organocopper chemistry have enabled enones to become increasingly important substrates for cyclopentane annelations via conjugate addition-intramolecular alkylation/condensation sequences. One of the more useful reagents for this type of reaction is the Grignard reagent derived from the commercially available bromo acetal 33[50]. This reagent has been developed by



33

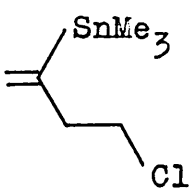
Helquist as a simple annelating reagent[51] (Scheme 1.11) and has seen widespread use in natural product synthesis[52].



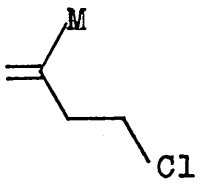
Reagents: (a) i. $BrMgCH_2CH_2CH$  , $CuBr(Me_2S)$, THF, Me_2S;
ii. HCl, H_2O, THF.

Scheme 1.11 A conjugate addition-intramolecular condensation approach to cyclopentanoids.

The vinyl tin reagent 34 has been developed by Piers[53] as a useful precursor to the cuprate annelating reagents 35.



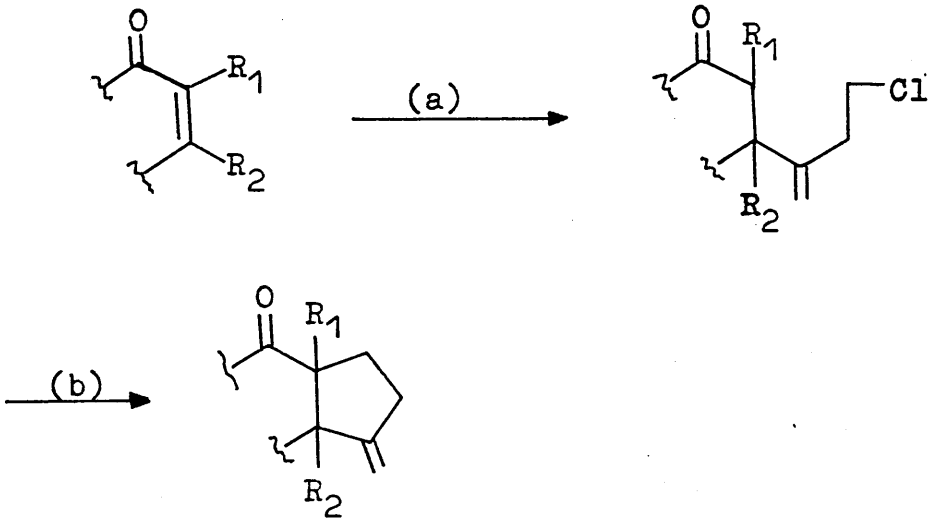
34



35 a M=Cu(SPh)Li

b M= Cu(CN)Li

Treatment of an enone with 35 followed by intramolecular alkylation of the isolated product produces a cyclopentane ring (Scheme 1.12).

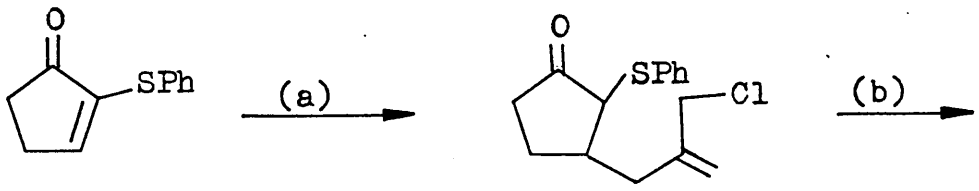


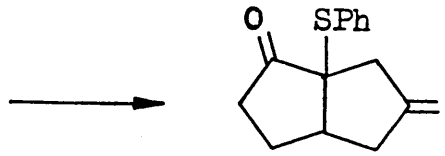
Reagents: (a) i. 35, THF,-78°C; ii. H^+; (b) KH, THF.

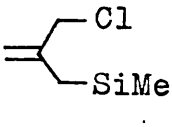
Scheme 1.12 Piers' conjugate addition-intramolecular alkylation approach to cyclopentanoids

The exo methylene group can be converted to other functionality frequently encountered in cyclopentanoid natural products.

A complementary sequence developed by Knapp places the double bond in a different position[54] (Scheme 1.13). A similar result is obtained using Trost's [3+2] cycloaddition methodology (Scheme 1.2).



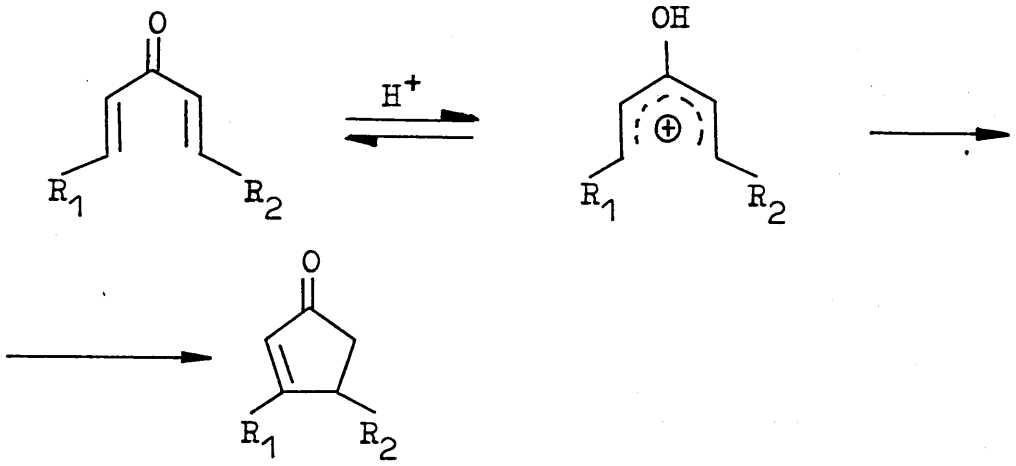


Reagents: (a) 

, $TiCl_4$, CH_2Cl_2; (b) KO^tBu, t-butanol.

Scheme 1.13. Knapp's conjugate addition-intramolecular alkylation approach to cyclopentanoids.

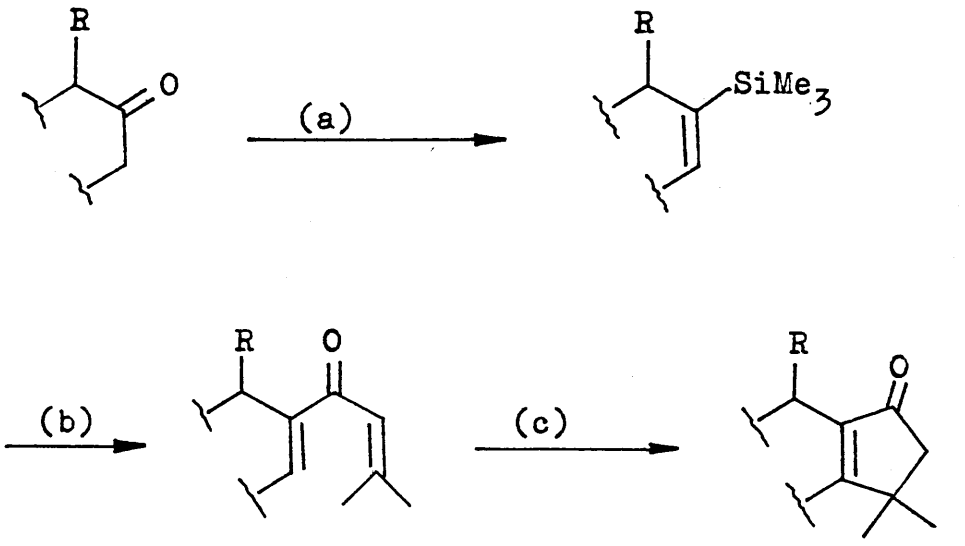
The Nazarov reaction of divinyl ketones is among the more versatile of 5-membered ring forming reactions[55], Scheme 1.14.



Scheme 1.14. The Nazarov reaction.

The versatility of the reaction stems from the variety of precursors which can be used to generate the requisite divinyl ketones. Olefins, ketones, enones and unsaturated acid halides have all served as starting materials for this reaction[55]. The more useful substrates for this reaction

are ketones. Scheme 1.15 shows a recent development in this area[56].

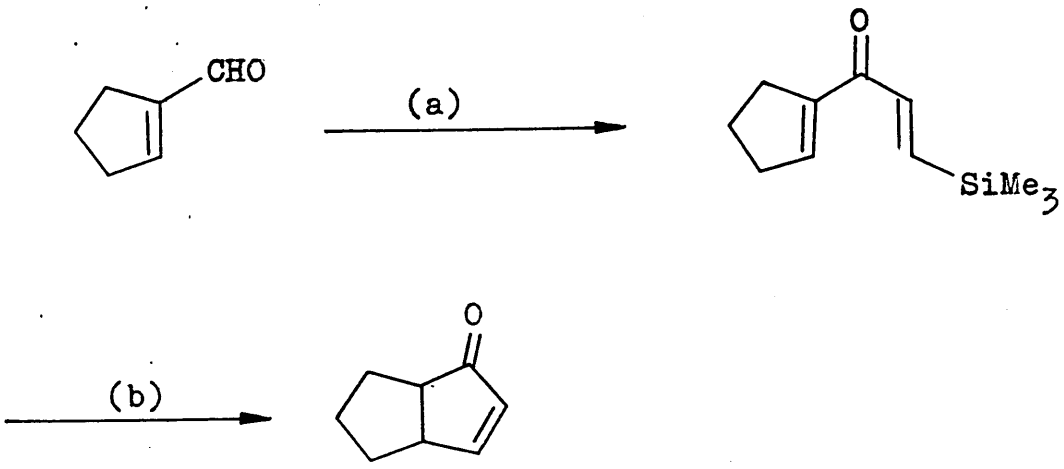


Reagents: (a) i. $PhSO_2NNH_2$; ii. n-BuLi, Me_3SiCl. (b) (b) $(CH_3)_2$ C=CHCOCl, $AlCl_3$, CH_2Cl_2; (c) i. $SnCl_4$, CH_2Cl_2, Δ ; ii. $RhCl_3$, C_2H_5OH.

Scheme 1.15. Paquette's approach to the Nazarov reaction.

Although divinyl ketones are most frequently used for this reaction, several alternative procedures for generation of the intermediate hydroxypentadienyl cation (Scheme 1.14) are available[55].

The cyclopentenone product of the Nazarov reaction normally contains the most highly substituted double bond. A recent development by Denmark involving control by silicon places the double bond in the least substituted position[57] (Scheme 1.16).



Reagents: (a) i. $Me_3SiCH = CHMgBr$, THF; ii. H^+;
iii. NiO_2/ether; (b) $FeCl_3$, CH_2Cl_2.

Scheme 1.16. Silicon controlled Nazarov reaction.

1.3 The bicyclo [3.3.0] octane framework as a structural feature in the synthesis of cyclopentanoid natural products.

The elaboration of highly functionalised bicyclo [3.3.0] - octane derivatives has become the major approach to the synthesis of di and tricyclopentanoid natural products. This is partly due to the high degree of stereocontrol which can be achieved in reactions of such systems by virtue of the partially folded structure of the cis fused bicyclo [3.3.0] - octane framework (Figure 1.6).

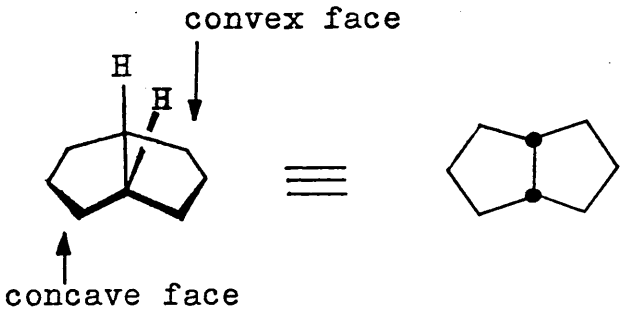


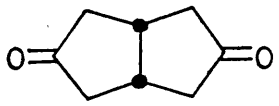
Figure 1.6.

A reagent thus prefers to approach the molecule from the convex face on kinetic grounds and a substituent will generally prefer to be on the convex face on thermodynamic grounds. Such stereocontrol has also enabled suitably functionalised bicyclo [3.3.0] octanes to be employed in stereoselective syntheses of monocyclopentanoid and non-cyclopentanoid natural products via cleavage of one or both of the cyclopentane rings[58].

The preparation of highly functionalised bicyclo[3.3.0]- octanes has thus become of major importance and has provided

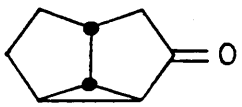
much of the impetus for developments in the area of cyclopentanoid construction[31]. Most of the procedures outlined in Section 1.2 have been applied to the construction of bicyclo[3.3.0]octanes.

Although versatile approaches towards bicyclo[3.3.0]-octane derivatives are available, particular bicyclo[3.3.0]-octanes have in general been aimed at a single target molecule from an early stage in the synthesis. There are a few exceptions to this, for example the readily available dione 36 has been used as starting material for a vide variety of natural products via selective manipulations of the two carbonyl groups[59].



36

The tricyclo[3.3.0.$0^{2,8}$]octan-3-one 37 prepared by Schaffner's group has also been converted to a number of natural products[60].



37

Recent work in our laboratories has led to the synthesis of highly functionalised cyclopentanoids through intramolecular Wittig methodology[61]. An obvious extension of this work involves the preparation of polycyclopentanoid systems. This has led to the synthesis of a highly functionalised bicyclo[3.3.0]octane which has served as a

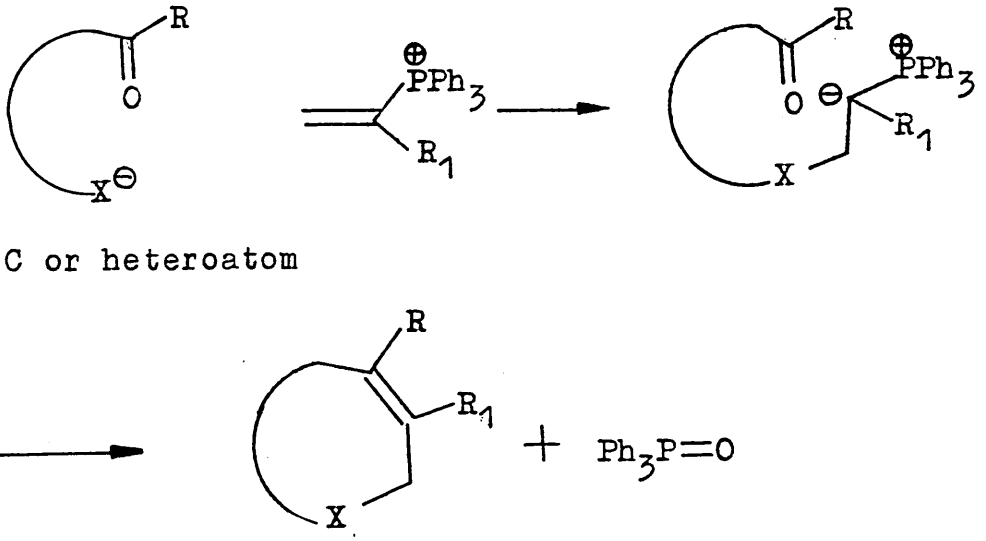
key intermediate in the synthesis of several cyclopentanoid natural products.

CHAPTER 2

The synthesis of a highly functionalised bicyclo[3.3.0]octane derivative

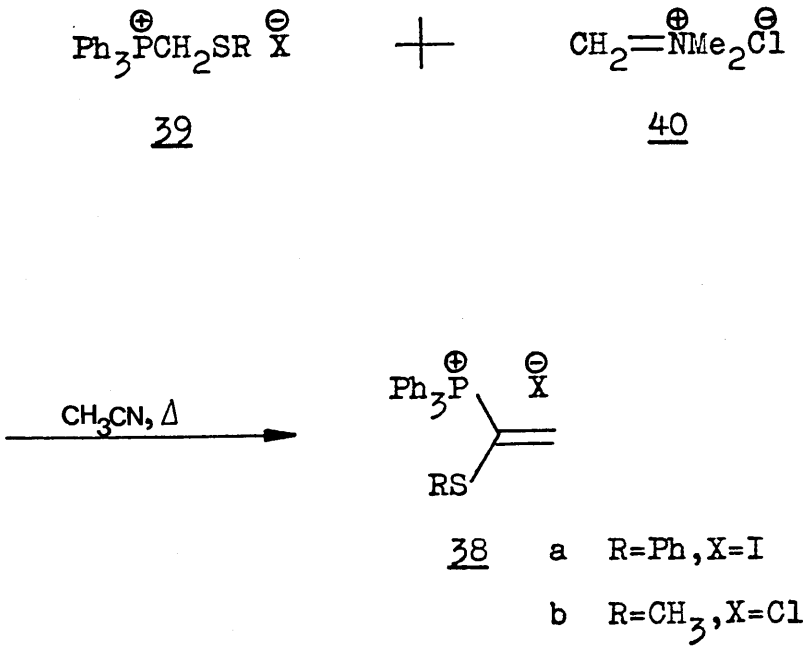
2.1 Background and synthetic strategy

Vinyl phosphonium salts have frequently been employed in the preparation of carbocyclic and heterocyclic systems[62]. Their use in the preparation of such ring systems involves attack by a nucleophile on the vinyl phosphonium salt to produce an ylid, which undergoes intramolecular Wittig reaction with a carbonyl group within the original nucleophile (Scheme 2.1).



Scheme 2.1 Ring formation using vinyl phosphonium salts.

Recent work in our laboratories has led to an efficient preparation of the substituted vinyl phosphonium salts 38 from phosphonium salts 39 and the iminium salt 40[61a] (Scheme 2.2). The formation of 38 is thought to involve base catalysis by either dimethylamine resulting from thermal decomposition of iminium salt 40 or by chloride ion which would be relatively basic in the dipolar aprotic medium.



Scheme 2.2.

The usefulness of 38 in the preparation of highly functionalised cyclopentanoids has been demonstrated[61] (Scheme 2.3).

Reagents: (a) i. NaH, THF; ii. 38.

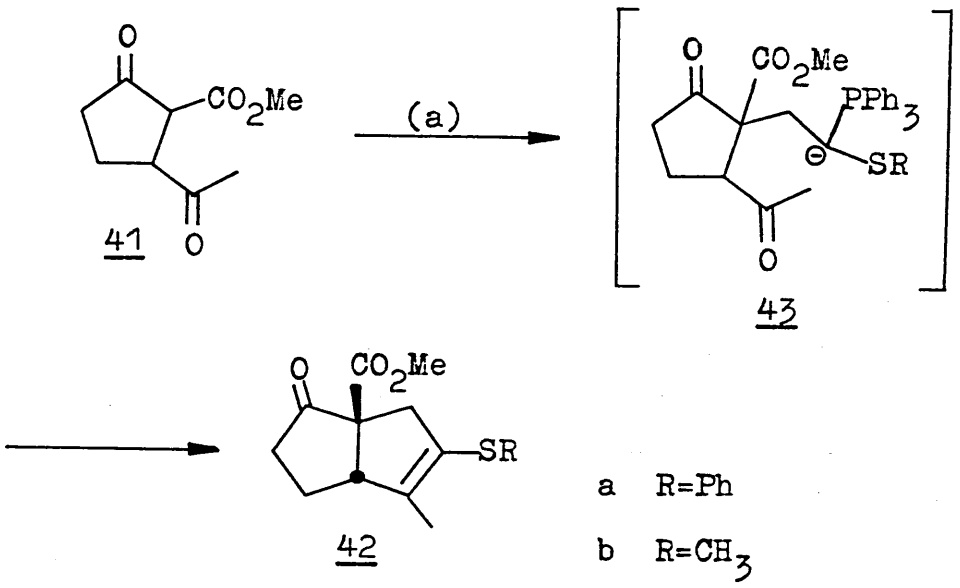
Scheme 2.3

The products of Scheme 2.3 contain three potential carbonyl groups and have been successfully applied to the syntheses of prostaglandins, jasmones and methlenomycins[61].

The recent intense interest in the preparation of di and tricyclopentanoid compounds (chapter 1) prompted us to extend the usefulness of vinyl phosphonium salts 38 to

the synthesis of such systems. As the bicyclo[3.3.0]octane unit is a key structural feature of such systems we thought the preparation of a highly functionalised bicyclo[3.3.0]-octane derivative would be a suitable starting point for our efforts.

In order to apply 38 to bicyclo[3.3.0]octane synthesis we required a suitably functionalised cyclopentanoid precursor. In accordance with previous work with 38[61] we reasoned that the diketo ester 41 would be a suitable precursor for our purposes. The successful application of our cyclopentanoid forming procedure to 41 would produce bicyclo[3.3.0]octane derivatives 42 via the intermediate ylid 43 (Scheme 2.4).



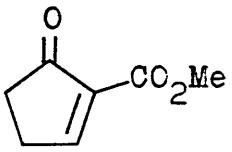
Reagents: (a) i. base; ii. 38.

Scheme 2.4.

We were further attracted to diketo ester 41 as the products of the cyclization 42 were functionalised in a way promising great potential for natural product synthesis. The

molecule contains useful functionality in both rings and a number of chemoselective and regioselective transformations including annelation reactions were foreseen. The diketo ester 41 thus became our initial target.

Retrosynthetic analysis suggested that 41 should be available via conjugate addition of an acetyl anion equivalent to the the unsaturated keto ester 44. However 44 is known to be unstable and polymerises upon reaction with many acidic and basic reagents[63]. We proposed that protection of the ketone carbonyl group as its ethylene acetal would moderate the reactivity of the double bond and thus 45 might be a more useful acceptor in conjugate addition reactions[64].



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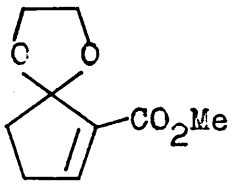
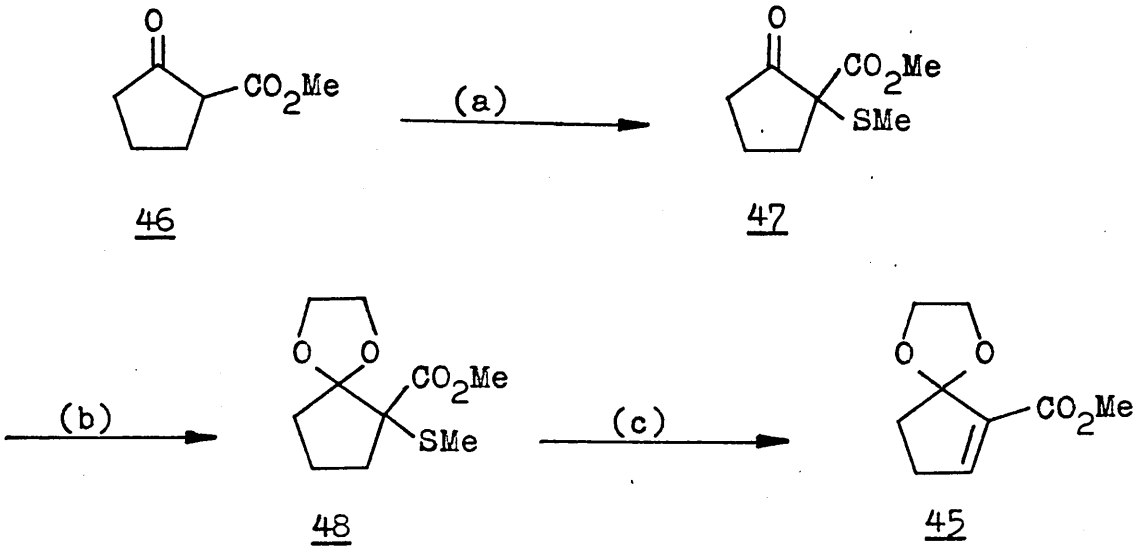


45

2.2 Results and discussion

The unsaturated ester 45 was prepared efficiently in 4 steps from readily available methyl 2-oxocyclopentane-carboxylate 46 (Scheme 2.5). Quenching of the anion of 46 with methylthiotosylate gave the α-sulphenylated product 47. The ethylene acetal of 47 was formed under standard conditions (ethylene glycol, PTSA, benzene with azeotropic water removal) to give 48 (83% from 46). Oxidation of sulphide to sulphoxide with sodium periodate (88%) followed by thermal elimination

of methylsulphenic acid[65] gave the desired intermediate 45 (87%).

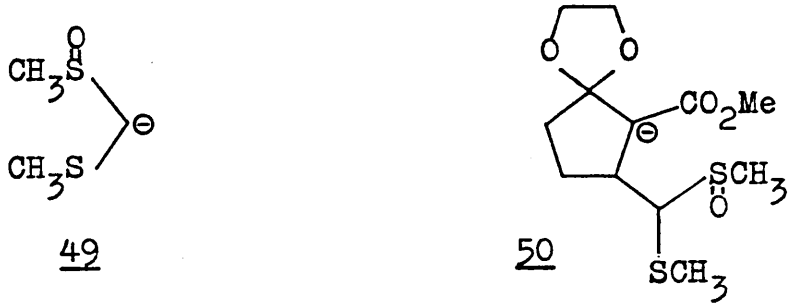


46 47 48 45

Reagents: (a) NaH, THF, -⟨O⟩-SO_2SMe; (b) $HOCH_2CH_2OH$, PTSA, benzene, Δ ; (c) i. $NaIO_4$; ii. Δ , toluene, $CaCO_3$.

Scheme 2.5

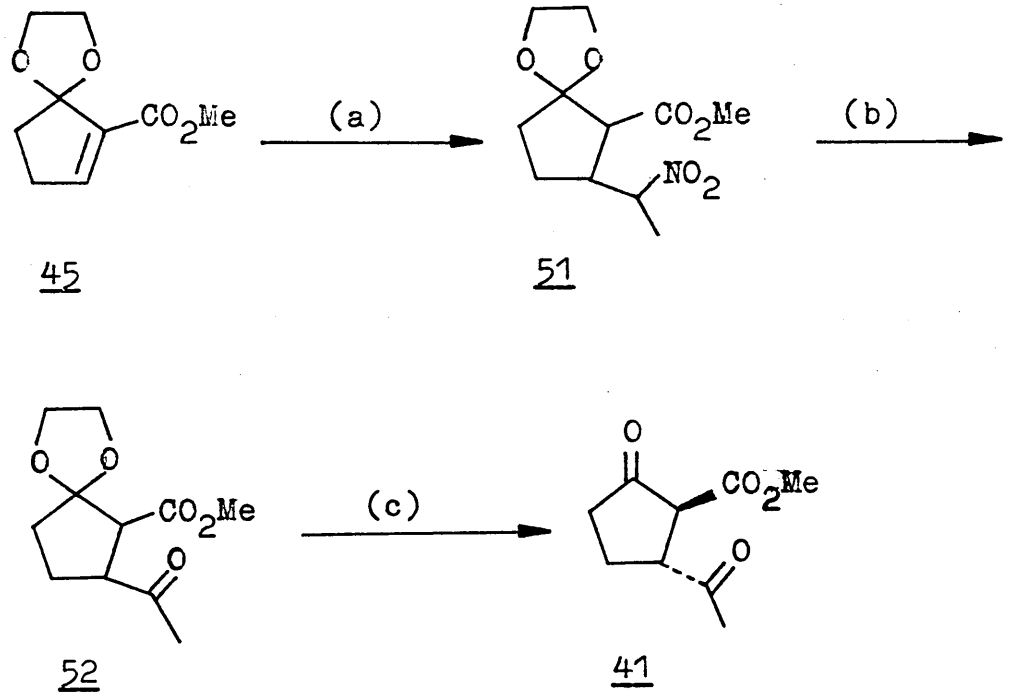
With the availability of 45 well established, its usefulness as a Michael acceptor could be investigated. The anion 49 is an acyl anion equivalent which is known to prefer the 1,4-mode of addition to conjugated systems[66]. However in a model reaction, when the unsaturated ester 45 was treated with 49 under aprotic conditions (THF) extensive decomposition of the starting material resulted. This may have been due to the intermediate enolate 50 being destroyed by ketal opening.



49 50

It was thought that this problem could be overcome by choosing an acyl anion equivalent which could be added in a solvent capable of proton donation to the intermediate enolate. Our thoughts were justified when treatment of a solution of 45 in nitroethane with catalytic tetramethylguanidine as base[67] resulted in conjugate addition of the nitronate anion to provide 51 as a mixture of two isomers (93%, 1.6:1). A similar conjugate addition to 45 with the anion of nitromethane was used in the synthesis of the antitumour compound sarkomycin (see Chapter 5).

No attempt was made to determine the stereochemistry of the two isomers of the nitroethane addition as the mixture 51 was carried through towards the desired diketo ester 41 (Scheme 2.6).



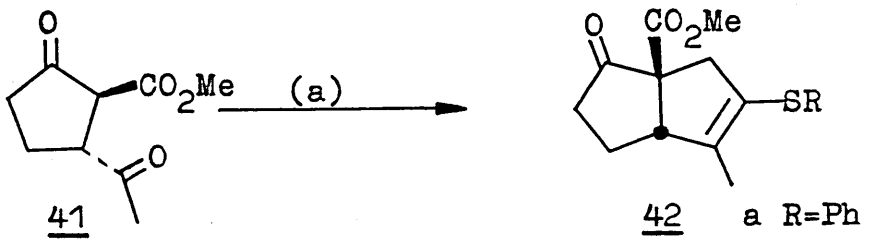
Reagents: (a) $CH_3CH_2NO_2$, tetramethylguanidine; (b) NaOMe, $TiCl_3$, NH_4OAc; (c) TFA, H_2O.

Scheme 2.6.

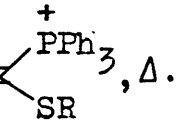
There are currently many methods available for the conversion of a nitro group to a carbonyl[68]. We investigated two methods. The more efficient method involved treatment of the nitronate anion of 51 with buffered $TiCl_3$ solution[69] to produce 52 as an inseparable mixture of isomers (77%). Treatment of the same nitronate anion with ozone followed by dimethyl sulphide[70] also produced 52 (60%). However this latter method also suffered from recovery of starting 51 thus necessitating an additional separation step. The acetal group of 52 was removed with aqueous trifluoroacetic acid to give the desired bicyclo[3.3.0]octane precursor 41 (79%) as a single product (NMR, TLC). Presumably equilibration to produce the more stable trans isomer had occurred under the acidic reaction conditions. The structure of 41 was confirmed by the presence of 3 carbonyl bonds in its infrared spectrum, C=O str.: 1760, 1735, 1705 cm^{-1} and by ^1H NMR .

We could now turn our attention to the critical bicyclo[3.3.0]octane forming reaction. Formation of the anion of 41 with sodium hydride in THF followed by addition of vinyl phosphonium salts 38 resulted in gradual disappearance of the insoluble vinyl phosphonium salts, suggesting formation of the intermediate ylid 43 (Scheme 2.4). Refluxing of the ylid solution resulted in smooth cyclization to give high yields of the desired bicyclo[3.3.0]octane derivatives 42 (42a, 83%; 42b, 97%) (Scheme 2.7).

Both 42a and 42b proved to be useful starting materials in natural product synthesis and the reasons for choosing 42a and 42b for a particular synthesis will be discussed in due course.



41 42 a R=Ph b R=CH_3

Reagents: (a) i. NaH, THF; ii.  38, Δ.

Scheme 2.7.

CHAPTER 3

Preparation of dicyclopentanoid systems

3.1 The synthesis chrysomelidial

3.2 The synthesis of loganin

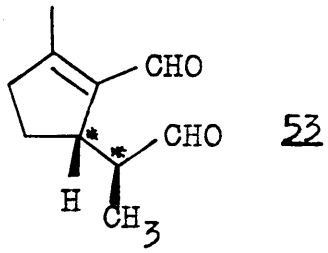
Preparation of dicyclopentanoid systems.

To get a feel for the kind of chemistry we could carry out on the bicyclo[3.3.0]octane derivatives 42 prepared as described in Chapter 2, we initially decided to prepare some known dicyclopentanoid compounds via simple functional group manipulations.

3.1 The synthesis of chrysomelidial

3.1.1 Introduction and background

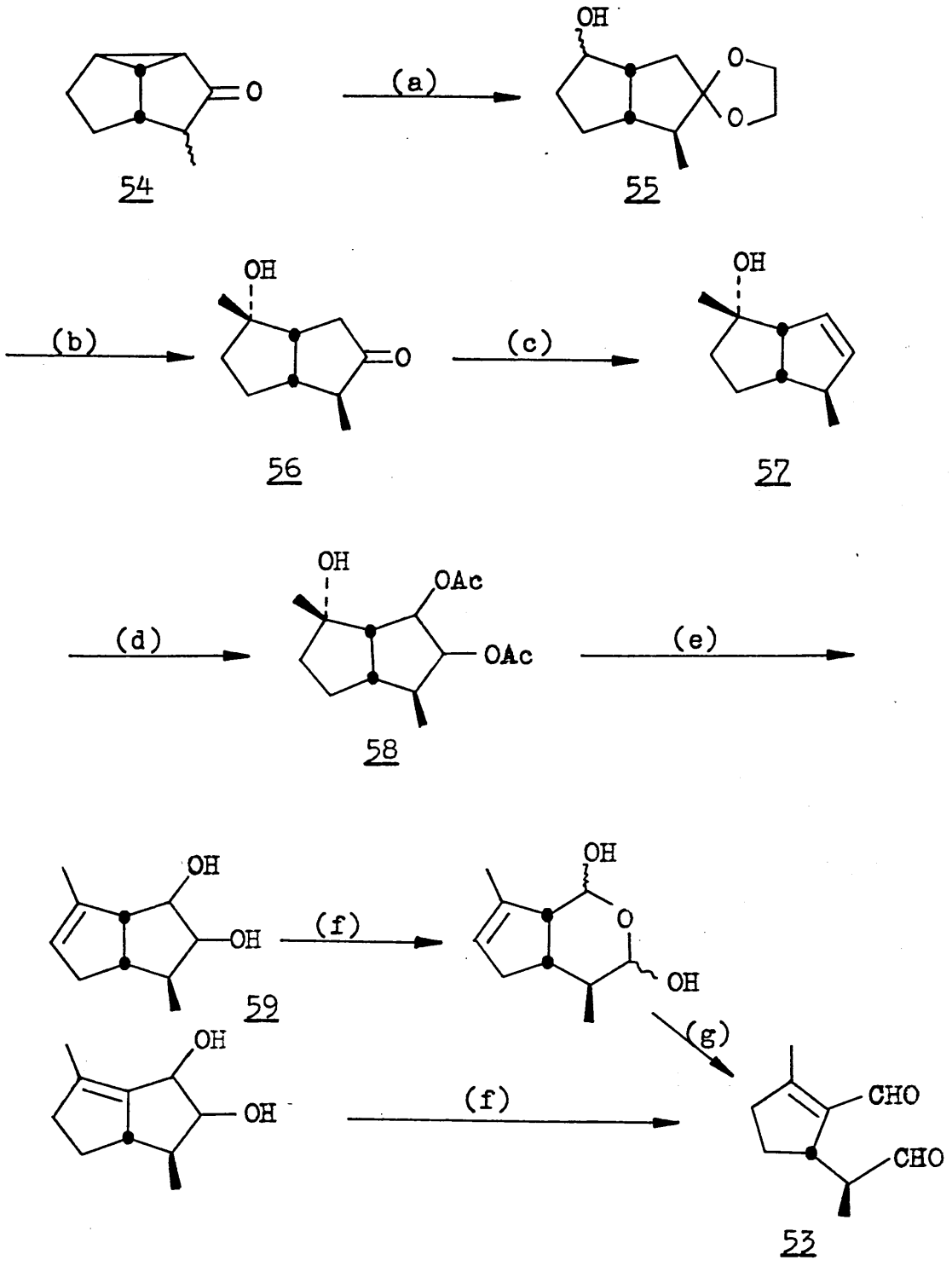
The isolation of chrysomelidial 53 from the larval defensive secretion of a chrysomelide beetle (Plagiodera versicolora) was reported in 1977[71]. The importance of 53



53

in the insect world has been studied[72].

Prior to our work three total syntheses[73] and one formal synthesis of chrysomelidial had been published. The syntheses by Meinwald and Jones[73a] and Jones and Blum[73b] were non-stereospecific and produced a mixture of chrysomelidial and its methyl epimer. Kon and Isoe in a long but high yielding synthesis of chrysomelidial used the structural features of a bicyclo[3.3.0]octane framework to advantage in order to obtain the correct relative stereochemistry at the two adjacent chiral centres in 53[73c]. Cleavage of one of the cyclopentane rings also conveniently produced the dialdehyde functionality (Scheme 3.1).

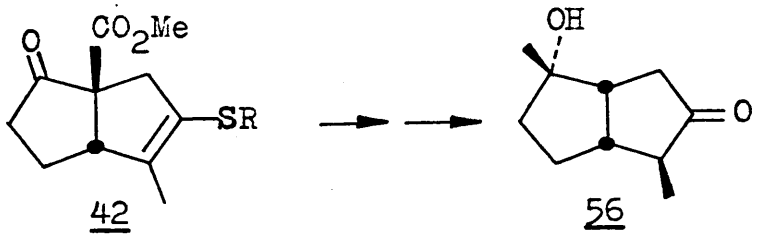


Reagents: (a) i. HCO_2H: ii. NaOMe, methanol; iii. $HOCH_2CH_2OH$, PTSA, benzene; (b) i. CrO_3, pyridine; ii. MeLi, ether; iii. PTSA; (c) i. $TsNHNH_2$; ii. n-BuLi, THF then H^+; (d) i. OsO_4; ii. $NaHSO_3$; iii. Ac_2O, pyridine; (e) i. $POCl_3$, pyridine; ii. $LiAlH_4$; (f) $NaIO_4$, Et_2O, H_2O; (g) 50% aq. AcOH.

Scheme 3.1 Kon and Isoe's chrysomelidial synthesis.

Cyclopropane ring cleavage of 54 with formic acid followed by equilibration and acetalisation produced 55 with the correct relative stereochemistry of the two adjacent chiral centres of chrysomelidial established (Scheme 3.1). The endo alcohol 56 was obtained via oxidation of 55, methyl lithium addition from the less hindered convex face of the molecule, and removal of the acetal group. Regioselective introduction of a double bond via the tosyl hydrazone of 56 gave 57. Cis hydroxylation and acetylation gave 58. Dehydration and ester cleavage gave a mixture of regio and stereoisomers 59 which could all be converted to chrysomelidial 53.

We thought that our bicyclo[3.3.0]octane 42 possessed ideal functionality for a simple preparation of 56 an intermediate in Kon and Isoe's chrysomelidial synthesis. Trost[74] has also prepared 56 via the [3+2] cycloaddition methodology mentioned in Section 1.2.1.



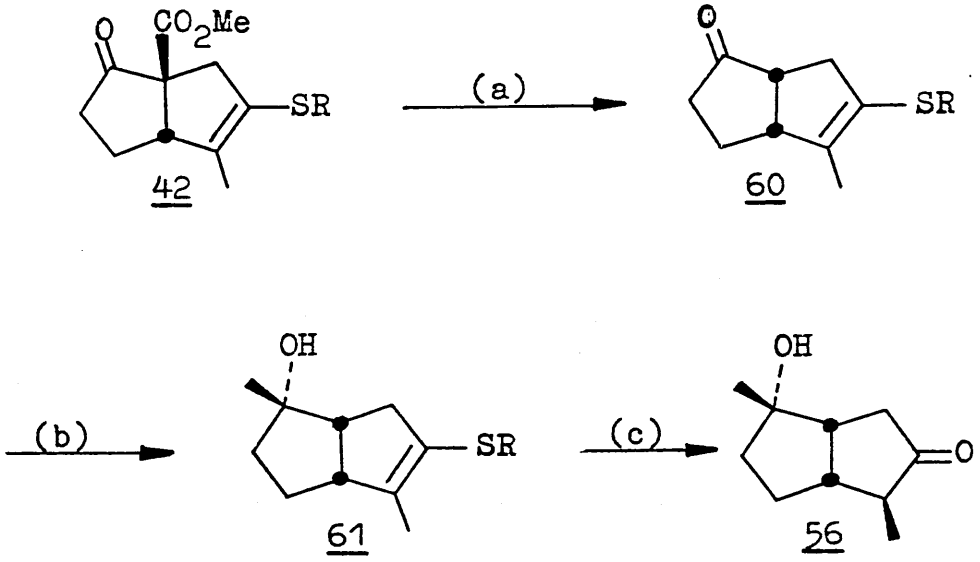
42 56

a.R=Ph, b.R=CH_3

Our proposed route to 56 involved decarbomethoxylation of 42, methyl lithium addition to the ketone and hydrolysis of the vinyl sulphide.

3.1.2 Results and discussion.

Several methods for the decarbomethoxylation of 42 were investigated. These included NaCl or LiCl in DMSO/H_2O[75], OH^-/Δ, NaCN in DMSO[76] and propane 1,2-diol/NaH[77]. However all of these methods were unsatisfactory due to the production of mixtures and/or low yields of the desired product. The one reagent which did prove suitable for this conversion was NaCN in hexamethylphosphoramide (HMPA)[78]. Although this is rather a noxious mixture it did carry out the required transformation efficiently to produce 60 (60a,79%; 60b,82%) (Scheme 3.2).



42 60 61 56

a. R=Ph, b. R=CH_3

Reagents: (a) NaCN,HMPA; (b) MeLi, ether, -78°C; (c) $HgCl_2$, H_2O, CH_3CN (with 61b).

Scheme 3.2.

We initially pursued the synthesis with the phenylthio compound 60a. Methyl lithium addition to 60a occurred stereospecifically to give a single product assumed to be endo alcohol 61a (84%) produced via approach of the nucleophile from the less hindered convex face. A similar stereospecificity was noticed in earlier chrysomelidial syntheses[73c,74].

Hydrolysis of the vinyl sulphide group of 61a to produce 56 was not without difficulty. Methods based on the use of $TiCl_4$[79], trifluoroacetic acid[80] and $HgCl_2$[81] all carried out the required release of the carbonyl group but in each case TLC analysis indicated that other products which were less polar than the starting materials were also produced in the reaction. The lack of an O-H str. band in the infrared spectra of these products suggested that dehydration of the tertiary alcohol was occurring under the acidic reaction conditions. In an attempt to overcome this problem the hydrolysis with $HgCl_2$ in acetonitrile/water was carried out in the presence of calcium carbonate or mercuric oxide[82]. This curiously gave no reaction whatsoever and only starting material was recovered. We next turned our attention to the methylthio compound 61b. We anticipated that the lower electron withdrawing effect of the alkylthio group would make the double bond of 61b more susceptible to electrophilic addition and thus 61b should be easier to hydrolyse.

Methyl lithium addition to 60b again occurred stereospecifically to produce 61b (75%) (Scheme 3.2) together with a small amount of starting 60b. The recovery

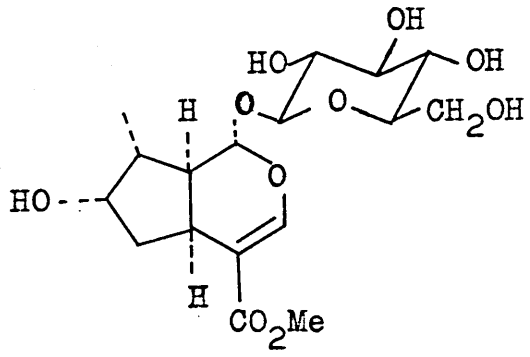
of starting material was probably due to enolisation by methyl lithium. Our first attempts to hydrolyse the vinyl sulphide of 61b involved similar procedures to those used above for the hydrolysis of 61a. Again similar results were obtained and dehydration appeared to be a competing reaction. However a careful TLC study of the reaction between 61b and $HgCl_2/H_2O$ in acetonitrile indicated that release of the carbonyl functionality occurred more readily than dehydration of the tertiary alcohol. Thus precise control of the reaction time enabled 56 to be isolated in 69% yield with the methyl group adopting the more stable exo configuration. A similar TLC study of the hydrolysis of the phenylthio vinyl sulphide 61a indicated that its hydrolysis was slower and thus the production of significant amounts of dehydration products was unavoidable.

The spectral data for our synthetic 56 were consistent with the assigned structure and the m.p. of 57.5-58.5°C compared well with the published value of 58.5-59.0°C[73c] thus confirming our stereochemical assumptions.

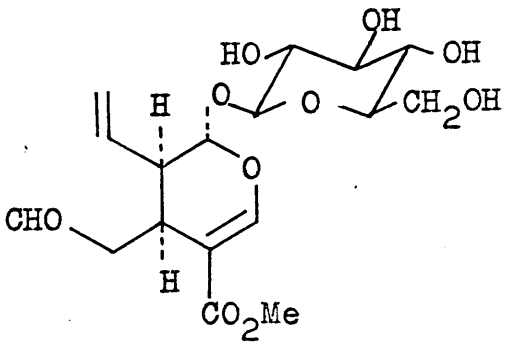
3.2 The synthesis of loganin

3.2.1 Introduction and background

The iridoid glucoside loganin 16 is a widely distributed biosynthetic intermediate in the plant world. It is a biogenetic precursor to secologanin 62 from which many indole and monoterpene alkaloids as well as iridoids are derived[83].



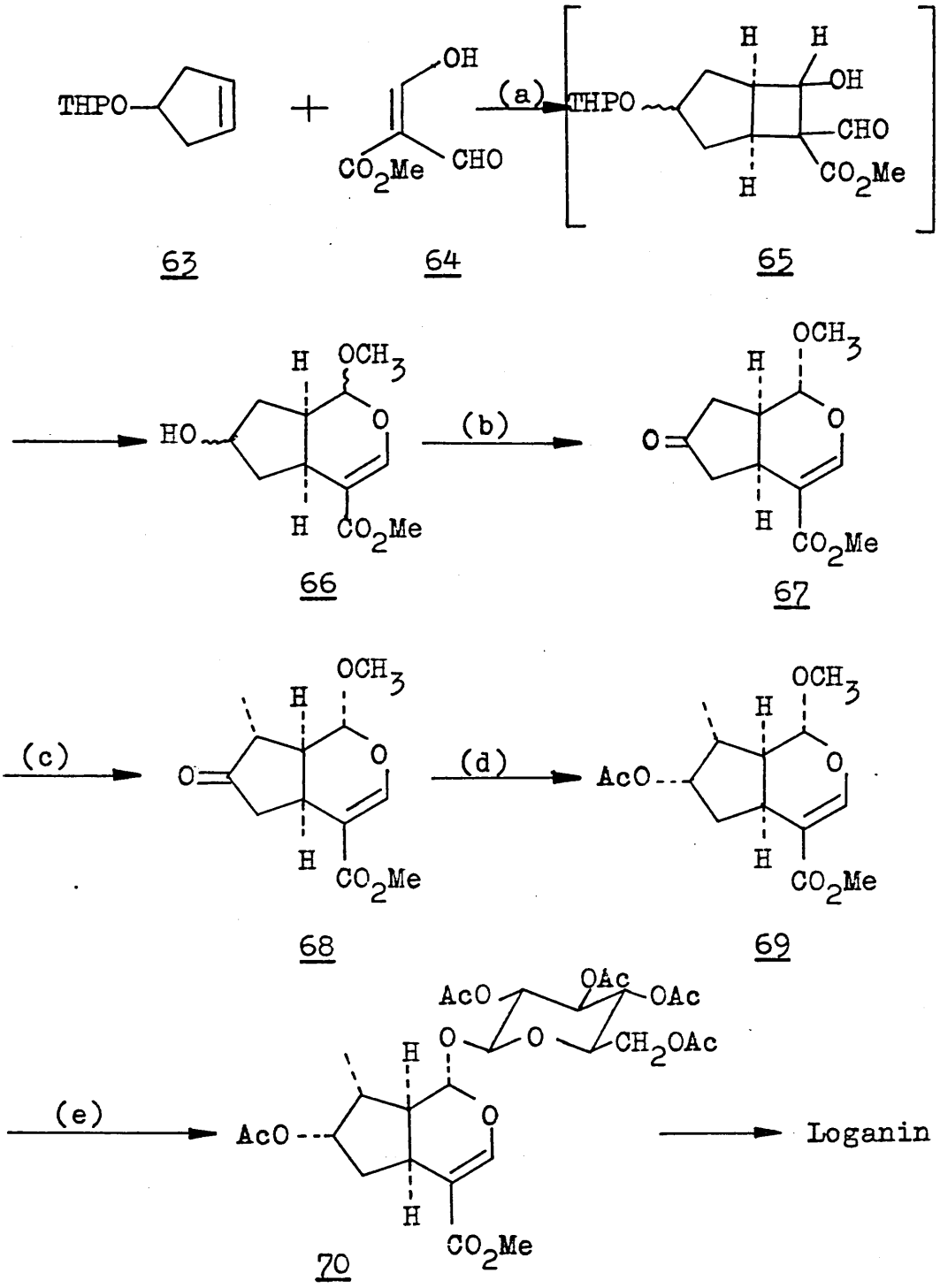
16



62

Loganin was first isolated from Strychnos nux vomica in the last century[84] but its structure and stereochemistry were only recently established by chemical means[85]. X-ray confirmation as structure 16 appeared in 1969[86].

Because of its importance and its relatively complex structure, loganin has attracted considerable attention as a synthetic target[28]. The five chiral centres present within the loganin skeleton (excluding the glucose unit) call for a number of stereoselective reactions to be carried out in order to achieve an efficient synthesis. There have been two main approaches to the synthesis of 16. The more convergent approach to the iridane skeleton was developed by Buchi and is illustrated by Buchi's total synthesis of loganin[28a] (Scheme 3.3).



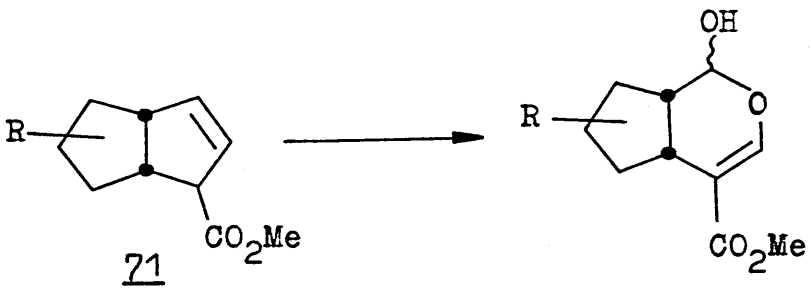
Reagents: (a) i.hν; ii.MeOH, cation exchange resin; (b) Jones reagent; (c) i.MeOCHO/NaO^{t}Am; ii.p-toluenesulphonyl chloride, pyridine, then BuSH; iii. Raney Ni; iv. NaOMe, methanol; (d) i. $NaBH_4$; ii. CH_3SO_2Cl, pyridine; iii. Et_4NOAc; (e) i. AcOH, H_2O, $HClO_4$; ii. 2,3,4,6-tetraacetyl-β-D-glucopyranose, BF_3OEt_2.

Scheme 3.3 Buchi's synthesis of loganin.

Photocycloaddition of the cyclopentene 63 with the tricarbonyl derivative 64 produced the cis-fused iridane skeleton 66 in one step presumably via retroaldol cleavage and recyclization of the initial photoproduct 65. Jones oxidation of 66 produced the desired isomer 67 as the major product. It was fortunate that methylation of 67 could be achieved regioselectively to give 68. Reduction of the ketone of 68 gave an endo-alcohol whose stereochemistry was inverted via S_N2 displacement of the derived mesylate with acetate anion to give 69. The acetate 69 contains the correct relative stereochemistry of all five chiral centres of loganin. The synthesis was completed by demethylation and glucosidation to produce loganin pentaacetate 70 which had previously been converted to loganin.

A similar approach to that of Buchi was used by Partridge's group in a short asymmetric synthesis of loganin[28b].

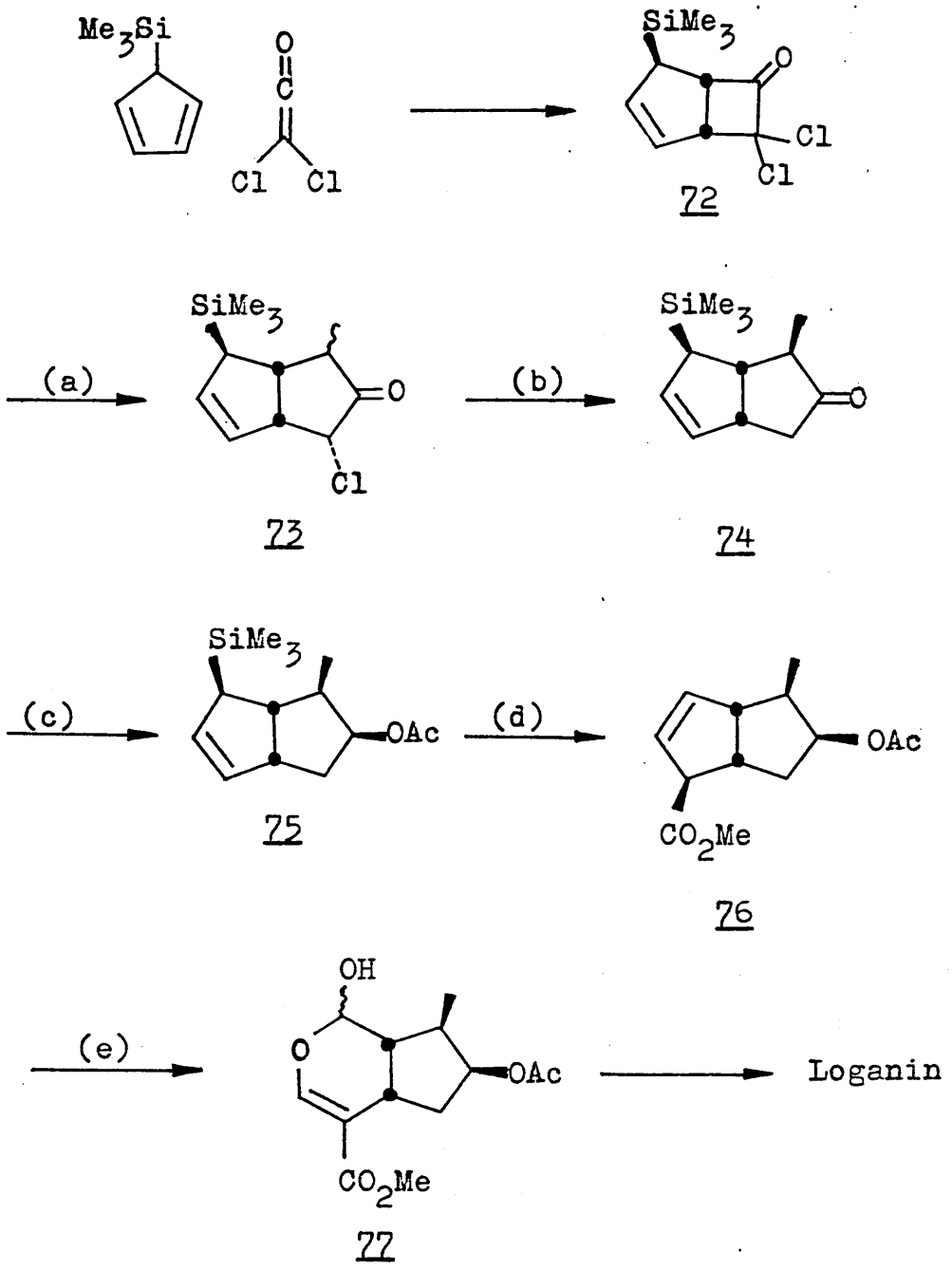
The second and more common approach to loganin involves the cleavage and recyclization of a bicyclo[3.3.0]-octene unit such as 71 (Figure 3.1). The structural features



71

Figure 3.1

of a bicyclo[3.3.0]octane system are exploited in a number of stereoselective reactions. The synthesis of loganin by Fleming[28c] typifies this approach (Scheme 3.4).



Reagents: (a) i. Zn, AcOH, H_2O; ii. $MeCHN_2$, Et_2O, MeOH; (b) i. excess Zn, AcOH, H_2O; ii. NaOMe, MeOH; (c) i. $NaBH_4$, MeOH; ii. CH_3SO_2Cl, pyridine; iii. NEt_4OAc; (d) i. $ClSO_2NCO$, CCl_4; ii. $NaNO_2$, Ac_2O, Ac_2O, AcOH; iii. NaOAc, H_2O; iv. CH_2N_2; (e) i. O_3; ii. Me_2S.

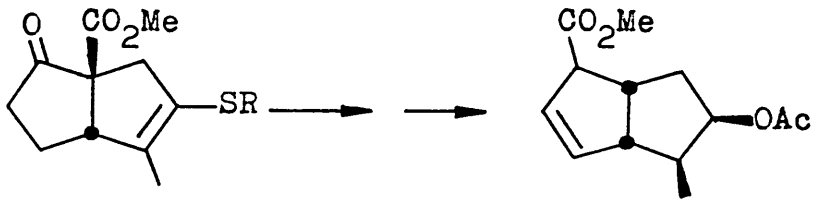
Scheme 3.4 Fleming's synthesis of loganin.

Cycloaddition of dichloroketene with trimethysilyl-cyclopentadiene produced cyclobutanone 72. Monodechlorination and regioselective ring expansion with diazoethane gave bicyclo[3.3.0]octenone 73 (Scheme 3.4). Removal of chlorine and base equilibration gave 74 with the methyl group adopting the more stable exo configuration. Reduction of the ketone of 74 occurs via approach of the hydride from the convex face of the bicyclo[3.3.0]octane system to produce the endo-alcohol. Inversion of the alcohol via S_N2 displacement of the derived mesylate with acetate anion gave 75. The propensity of allyl silanes to react with electrophiles was used to introduce the carbomethoxy group leading to 76. Cleavage of the double bond with ozone gave the hemiacetal 77 an intermediate in Buchi's loganin synthesis[28a].

Several loganin syntheses based on this approach including one asymmetric synthesis have been reported[28c-g]. An alternative stereocontrolled approach to loganin via norbornane precursors has recently been reported[28h].

The functionality present within our bicyclo[3.3.0]-octane system 42 appeared to be suited to the synthesis of loganin via a bicyclo[3.3.0]octene intermediate (Figure 3.1). In particular the bicyclo[3.3.0]octene 76 an intermediate in Fleming's synthesis (Scheme 3.4) seemed to be a promising target to aim for.

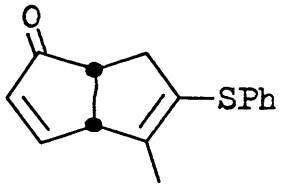
Our synthetic plan to 76 involved manipulation of the free carbonyl group to the unsaturated ester functionality, followed by hydrolysis of the vinyl sulphide. The ketone so produced could then be converted to the required exo-acetate.



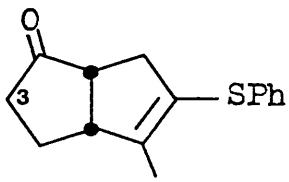
42 76

3.2.2 Results and discussion

We thought the α,β-unsaturated ester system should be available through enone 78 via homologation at the carbonyl centre.

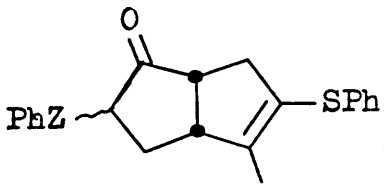


78



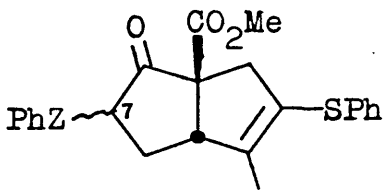
60a

The preparation of 78 was not without difficulty. Methods for introduction of the double bond based on selenoxide[87] or sulphoxide[65] elimination approaches were unsuitable for a number of reasons. Regioselective deprotonation of 60a (prepared as described in Section 3.1) was expected to occur at the 3-position on kinetic and thermodynamic grounds. However it proved difficult to isolate a satisfactory yield of monoselenated product 79 or monosulphenylated product 80 when the anion derived from 60a (LDA,THF,-78 C) was quenched with PhSeCl or PhSSPh respectively. Variations in the amount of base employed and/or the quench procedure (normal or inverse) did not improve this situation appreciably. We thought this



79 Z=Se

80 Z=S



81 Z=Se

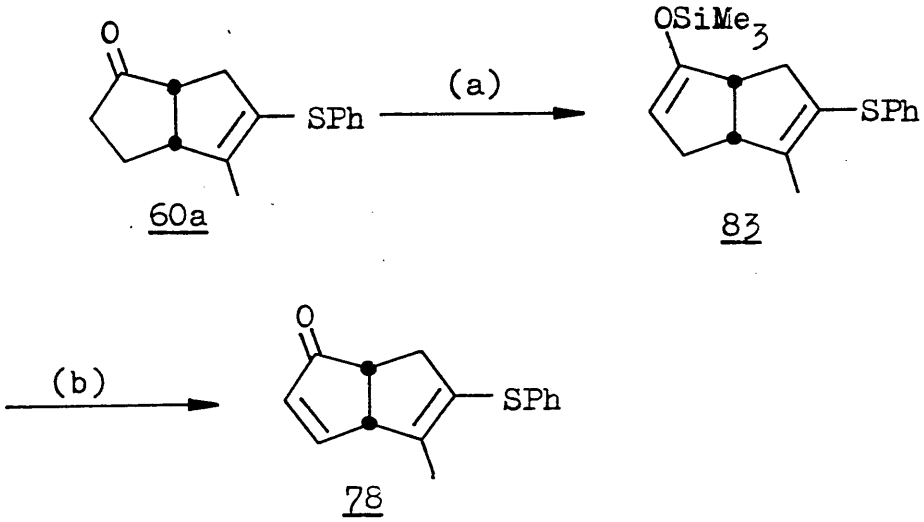
82 Z=S

problem might be overcome through the use of 42a where only one enolate can form. Quenching of the enolate anion of 42a with PhSeCl gave 81 (77%) as a mixture of two isomers (TLC, NMR). Similar quenching with PhSSPh gave 82 (42%) also as a mixture of two isomers. We decided to remove the carbomethoxy group at this stage as it was thought that the cyanide anion required to do this would react with an enone functionality.

Treatment of 81 with sodium cyanide in HMPA resulted in a low yield of isolated products. The major product showed one C=O str. ($1740cm^{-1}$) in its infrared spectrum and no OCH_3 signal in the ^1H NMR indicating decarbomethoxylation had occurred. However closer inspection of the spectral data also revealed the phenylseleno group had been lost and that the product appeared to be 60a. The product could not be separated from authentic 60a on TLC and its infrared and ^1H NMR spectral data closely matched those of 60a. Thus it appeared that the cyanide anion had removed the phenylseleno group from C-7 of 81 by attack at the metal atom. One of the other products of this reaction appeared to be PhSeSePh (TLC and IR comparison with authentic material), presumably formed

from the initial PhSeCN by-product. We thought a similar reaction might be occurring when the phenylthio compound 82 was treated with NaCN in HMPA but did not investigate this further as the desired enone 78 could be obtained efficiently via an alternative route.

Treatment of ketone 60a with DBU/trimethysilyl chloride[88] gave the silyl enol ether 83 regioselectively. The enone 78 was obtained via dehydrosilylation of 83 with palladium (II) acetate[89] (69% from 60a) (Scheme 3.5).



60a 83 78

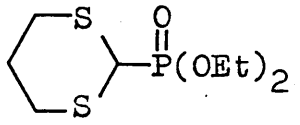
Reagents:(a) DBU,Me_3SiCl,CH_2Cl_2; (b) $Pd(OAc)_2$,p-benzoquinone, CH_3CN.

Scheme 3.5.

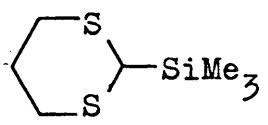
We chose to homologate the carbonyl group to the desired ester via a ketene dithioacetal. The conditions required to convert this functionality to an ester ($HgCl_2$, methanol, H_2O)[90] were also likely to hydrolyse the vinyl sulphide, a desired transformation in our planned route.

Treatment of the enone 78 with the anion derived from phosphonate 84[91] in THF at room temperature gave 1,4-addition only, as indicated by the presence of C=Ostr.

and P=O str. bands in the infrared spectrum of the product.

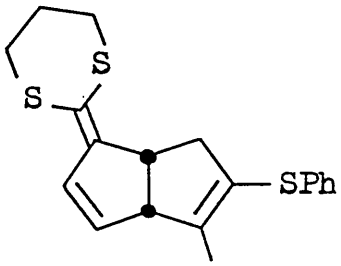


84

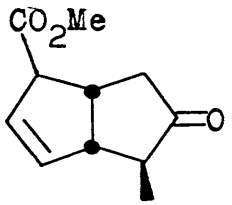


85

Treatment with the anion of 85[92] in THF at -78°C gave a mixture of 1,2 and 1,4-addition. However when this same reaction was carried out in the mixed solvent hexane/THF (1.8:1)[93], the 1,2 adduct 86 was the predominant product (58%). Unfortunately 86 appeared to be unstable probably

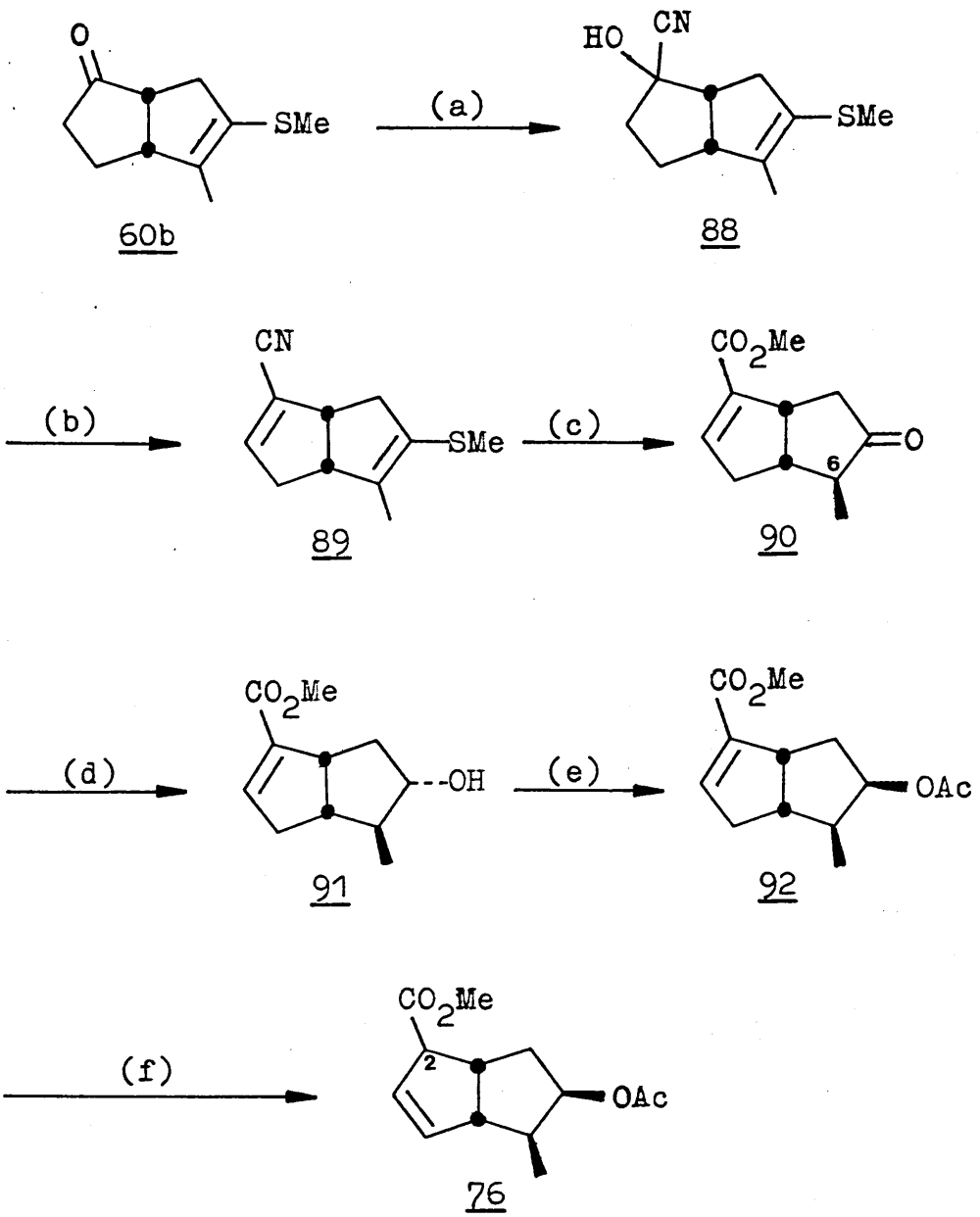


86



87

due to polymerisation of the conjugated diene system. Attempted hydrolysis of 86 ($HgCl_2$, MeOH, H_2O) gave a complex mixture of products. This result together with the possibility that the double bond of the desired β,γ-unsaturated ester 87 might move into conjugation with the ester during further manipulations prompted us to seek an alternative approach. It was decided to prepare an α,β-unsaturated ester and deconjugate this to the required β,γ-unsaturated ester at a later stage in the synthesis[94]. This led to a successful synthesis of the loganin precursor 76 (Scheme 3.6). The methylthio compound 60b was again used as starting material



Reagents: (a) NaCN,AcOH,ethanol; (b) $POCl_3$,pyridine;
(c) conc.H_2SO_4,methanol, ; (d) $NaBH_4$,methanol;
(e) i. $MeSO_2Cl$,pyridine, ii. n-Bu_4NOAc,acetone;
(f) LDA,HMPA,THF,-78°C then methanol.

Scheme 3.6.

as the vinyl sulphide was to be hydrolysed to a ketone at some stage in the synthesis.

Treatment of the ketone 60b with sodium cyanide gave the crude cyanohydrin 88 which was dehydrated regioselectively to 89 (vinyl H δ6.51,m) with $POCl_3$ in pyridine [95] (69% from 60b). A small amount of starting ketone 60b was also recovered presumably because of the reversible nature of the cyanohydrin forming reaction. Conversion of the nitrile to the methyl ester was achieved in one step by refluxing 89 in conc.H_2SO_4/methanol (1:1)[96]. This also effected hydrolysis of the vinyl sulphide functionality to produce 90 as the predominant product (48%). It was thought that some product was lost owing to decomposition under the vigorous reaction conditions. The keto ester 90 appeared to be a single isomer (TLC, 80MHz ^{1}H NMR) and the C-6 methyl group was assumed to be exo on thermodynamic grounds. To confirm this, 90 was treated with sodium methoxide in methanol, conditions which have been used to epimerise very similar systems[97]. This did not change 90 on TLC and the ^{1}H NMR of the isolated product was superimposable on that of starting material thus suggesting the C-6 methyl group was exo. A small amount of another product was isolated from the treatment of 90 with sodium methoxide. The ^{1}H NMR of this product suggested it was a methoxide conjugate addition product (OCH_3 at δ_H 3.29, MeOCH at 4.15, no vinyl CH). The conversion of 89 to 90 was not expected to produce the desired C-6 stereochemistry directly but the acidic reaction conditions would serve to equilibrate the product. A similar acid

catalysed epimerisation has been reported[98].

Completion of the synthesis was carried out using standard operations. Thus reduction of the ketone with $NaBH_4$ gave the endo alcohol 91 stereoselectively (82%). Formation of the mesylate (CH_3SO_2Cl/pyridine) followed by S_N2 displacement with acetate anion gave the exo acetate 92 (74% from 91) through inversion of configuration. This last series of reactions closely modelled those of Buchi and Fleming (Schemes 3.3 and 3.4). The α,β-unsaturated ester 92 was deconjugated by brief treatment with LDA in THF/HMPA at -78°C[28f], followed by quenching of the anion with methanol to give 76 (39%). The ester 76 appeared to be a single product on TLC but ^1H NMR indicated a 5:1 mixture of β,γ to α,β-unsaturated isomer.

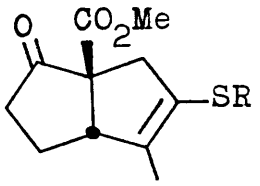
We are unsure of the stereochemistry of the carbomethoxy group of 76. We would expect the endo isomer formed via kinetic protonation. Data for both the endo and exo isomers at this centre have been published. The most noticeable difference in the the reported data of the two isomers is in the chemical shift of the vinyl protons. The endo isomer has a multiplet at δ_H 5.30 (2H)[28d] and the exo isomer has multiplets at δ_H 5.52 (1H) and 5.75 (1H)[28c]. The vinyl protons in the NMR spectrum of our 76 appeared at 5.62 and 5.81 ppm thus more closely resembling the data for the exo isomer. The ^1H NMR and infrared spectra of our 76 correlated well with spectra for the exo-carbomethoxy isomer provided by Dr.I.Fleming. However the stereochemistry of the carbomethoxy group is immaterial as the carbomethoxyl bearing carbon atom becomes sp^2 hybridised in loganin (Scheme 3.4). In the synthesis of loganin by Schaffner's

group[28d] both C-2 carbomethoxy isomers of 76 were used.

4. The synthesis of hirsutene

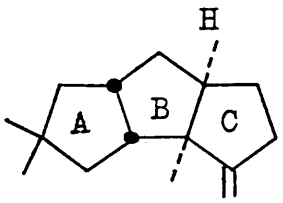
4.1 Introduction and background

After demonstrating the usefulness of our highly functionalised bicyclo[3.3.0]octane derivatives 42 in the preparation of dicyclopentanoid systems (Chapter 3) we next decided to turn our attention to the preparation of triquinane systems. The arrangement of functionality within 42 suggested that hirsutene 5 would be a suitable target to aim for.



42 a R=Ph

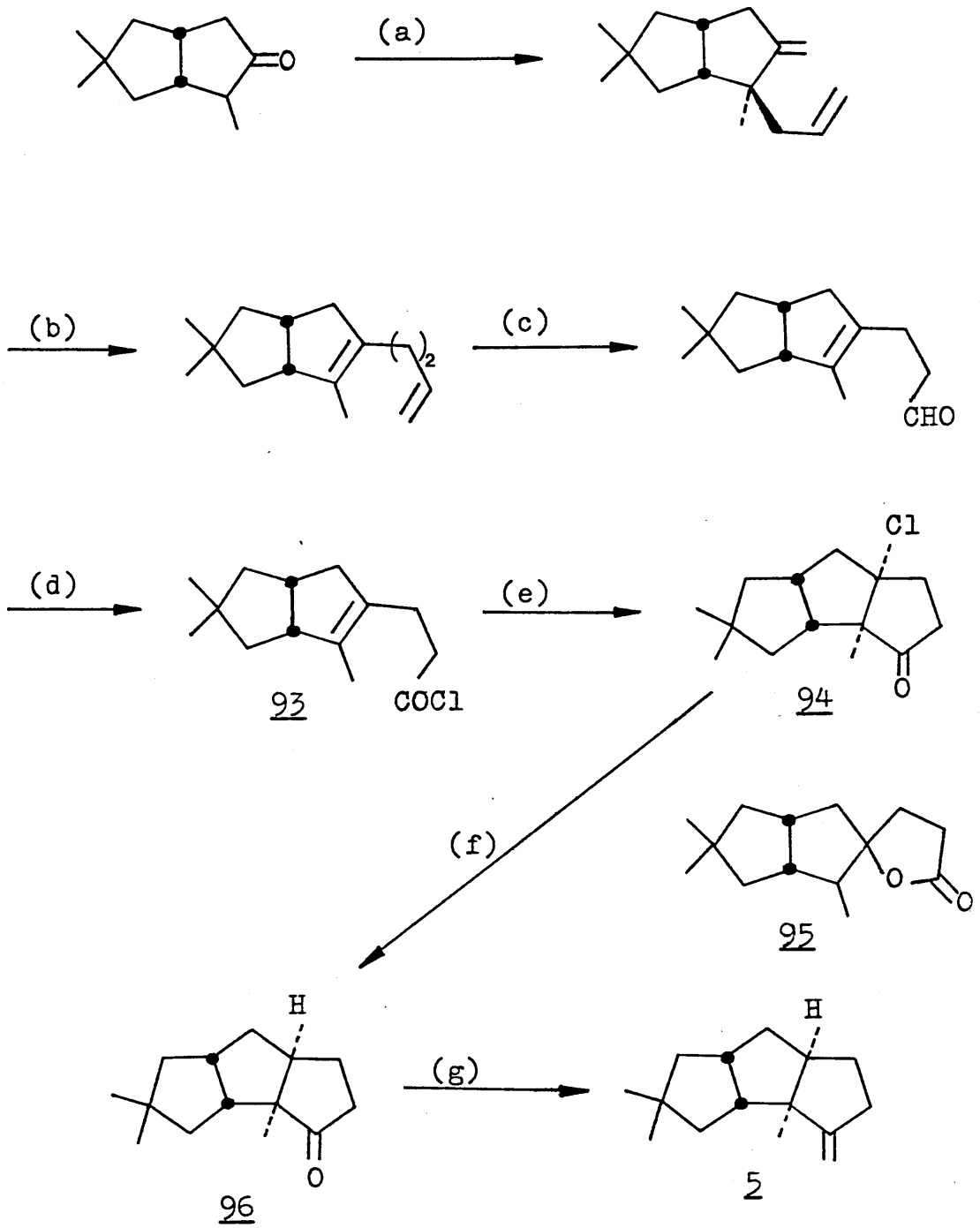
b R=CH_3



5

Hirsutene is the simplest member and proposed biogenetic precursor of the hirsutane family of natural products (Chapter 1). Since its isolation from Coriolus consors by Nozoe in 1976[11], hirsutene has become a very common synthetic target.

The first total synthesis of hirsutene was also reported by Nozoe[11] and in common with many other syntheses of the linearly fused tricyclopentanoid system[12], Nozoe's approach involved the annelation of a third cyclopentane ring onto a bicyclo[3.3.0]octane system (Scheme 4.1). The key cyclopentane forming reaction involved intramolecular Friedel-Crafts acylation of the double bond in 93 to produce the ketone 94 and lactone 95 in a 1:1 ratio. The ketone 94 was converted to 96 via dissolving metal reduction,

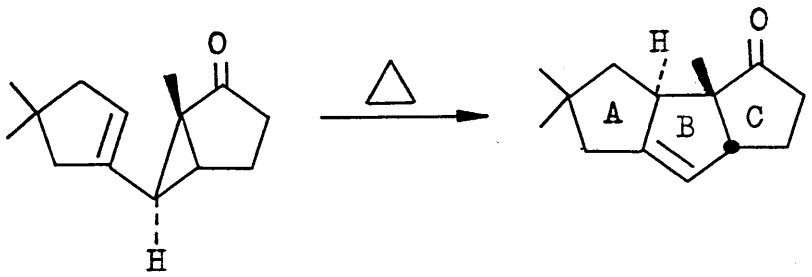


Reagents: (a) i. NaH, DME, CH_2=CH-CH_2Cl; ii. Ph_3P=CH_2;
(b) Δ, 240°C; (c) i. OsO_4; ii. $NaIO_4$; (d) i. Ag_2O;
ii. $(COCl)_2$; (e) $SnCl_4$, CS_2; (f) i. Li, NH_3, t-BuOH;
ii. CrO_3.2py; (g) Ph_3P=CH_2, DMSO.

Scheme 4.1 Nozoe's synthesis of hirsutene.

and oxidation. Wittig olefination gave hirsutene 5.

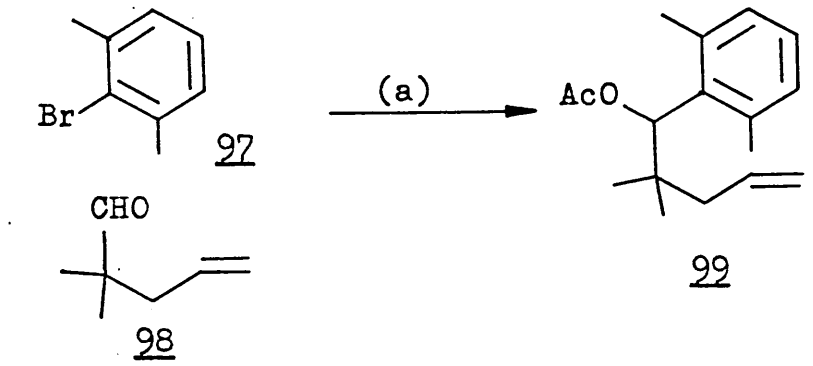
Nozoe's synthesis was followed by several syntheses which attempted to mimic the proposed biosynthesis of hirsutene from humulene[18] (see Figure 1.3). The last five years have seen the publication of numerous hirsutene syntheses by a variety of different approaches. Routes based on bicyclo[3.3.0]octane intermediates were used by Magnus[99] and Greene[100]. The syntheses of Ley[101] and Hudlicky[102] involved construction of an A-C ring system followed by intramolecular ring closure to form the central B ring. Scheme 4.2 shows Hudlicky's ring closure reaction[102].

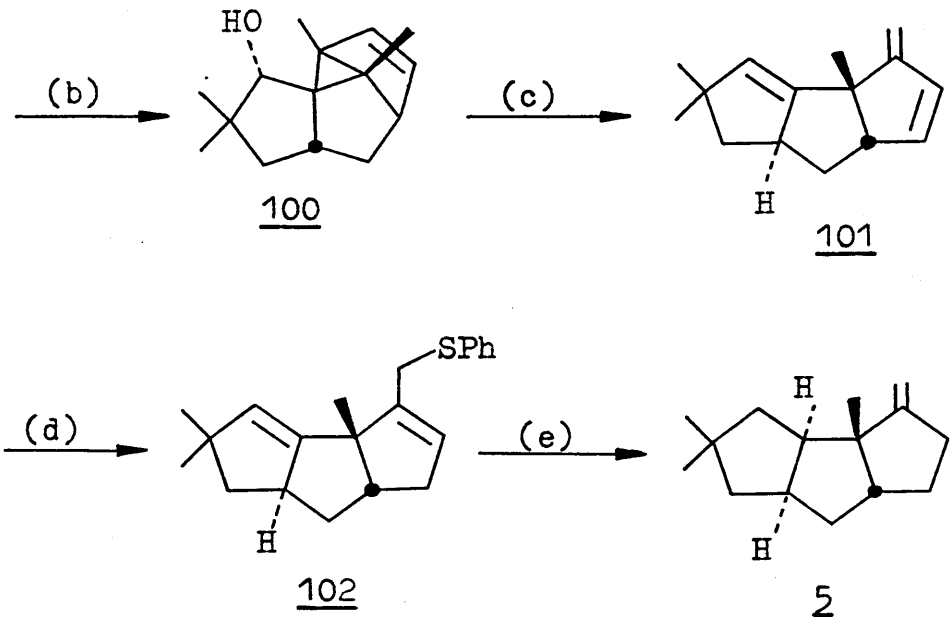


Scheme 4.2.

Other hirsutene syntheses were designed specifically to construct the linearly fused tricyclopentanoid system[103]. Most of these latter approaches were adaptable to the preparation of other members of the hirsutane family. Among the more ingenious routes of this type is the synthesis by Wender[103a] (Scheme 4.3).

Addition of the Grignard reagent of 97 to 98 followed by acetylation gave arene-olefin 99. Meta-photocycloaddition gave 100 regioselectively and stereoselectively. Cyclopropane ring opening occurred in the desired direction with acid to produce the linear tricyclopentanoid 101. The exo methylene group of 101



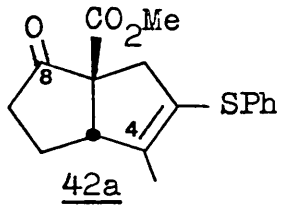


Reagents: (a) i. Mg,ether; ii. 98; iii. Ac_2O, DMAP; (b) hν; (c) 10-camphorsulphonic acid, C_6H_6; (d) 1 eq. PhSH, neat, 100°C; (e) i. H_2, $[Ir(cod)pyPCy_3]PF_6$, CH_2Cl_2; ii. $NaIO_4$; iii. Δ, C_6H_6, $(MeO)_3P$.

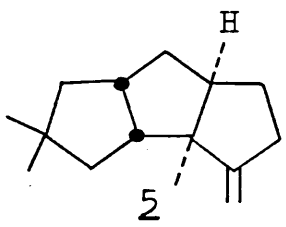
Scheme 4.3 Wender's hirsutene synthesis.

was 'protected' whilst the other double bonds were hydrogenated. Hirsutene 5 was produced via oxidation and thermal elimination of the sulphide.

We thought the annelation of a third cyclopentane ring onto our bicyclo[3.3.0]octane 42 would be a reasonable approach to hirsutene. The arrangement of functionality within 42 dictated that the vinyl sulphide be used to construct the third ring of hirsutene. We envisaged introducing the gem-dimethyl group via alkylation of the C-8 ketone of 42 and the C-4 methyl group in 42 was to become the angular methyl in hirsutene. The phenylthio compound 42a was chosen as starting material for this synthesis for reasons which will become clear.

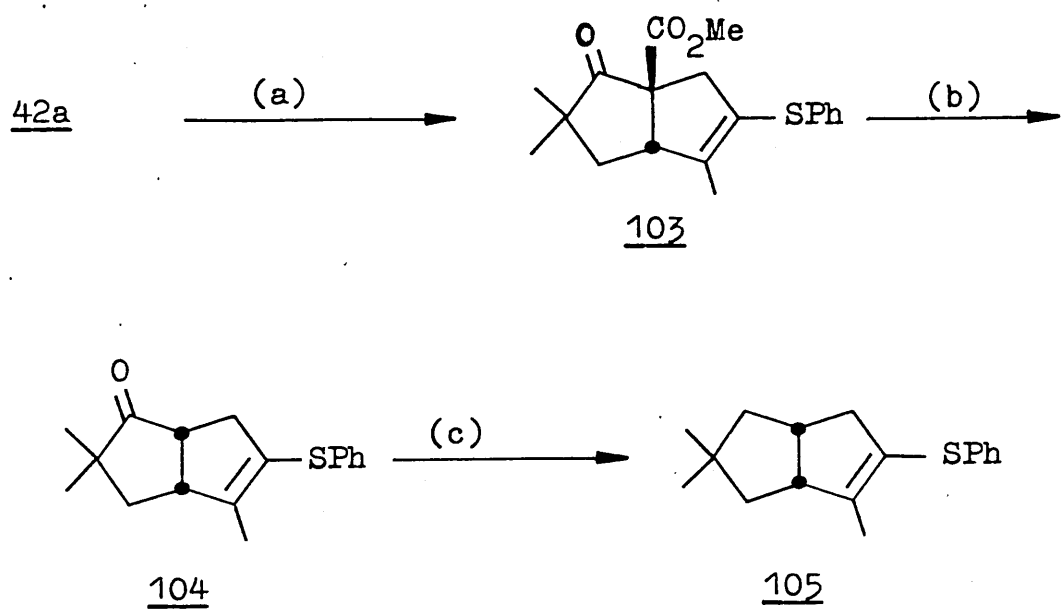


42a



4.2 Results and discussion

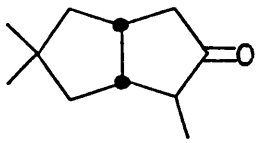
Alkylation of 42a with excess methyl iodide gave the gem-dimethylated compound 103 (83%) which was decarbomethoxylated with sodium cyanide in HMPA[78] (Section 3.1.2) to 104 (86%) (Scheme 4.4). Wolff Kishner reduction of 104 gave the vinyl sulphide 105 (94%).



Reagents: (a) KO^tBu, MeI, THF; (b) NaCN, HMPA;
(c) $NH_2NH_2.H_2O$, KOH, digol, Δ .

Scheme 4.4.

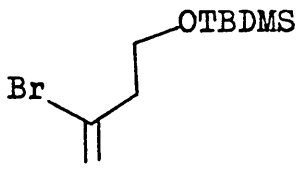
The vinyl sulphide 105 could presumably be hydrolysed to the ketone 106 an intermediate used by Nozoe in the first total synthesis of hirsutene[11] (Scheme 4.1).



106

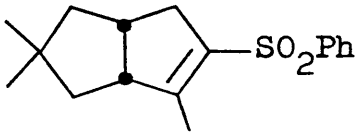
However we thought the vinyl sulphide functionality could be used to construct the third cyclopentane ring of hirsutene.

Our initial strategy involved the use of the annelating reagent 107 developed by Magnus[99]. Organocuprates are known to add to vinyl sulphones at the β position[104]. Thus we proposed to add the vinyl cuprate reagent derived

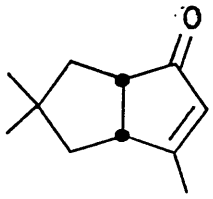


107

from 107 to the phenylsulphonyl compound 108[105] in a similar fashion to that of Magnus in his synthesis of hirsutene from enone 109[99].



108

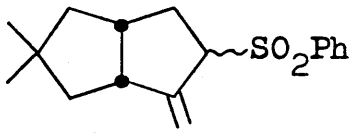


109

The vinyl sulphone 108 was obtained in nearly quantitative yield by oxidation of vinyl sulphide 105 with m-chloroperbenzoic acid.

Unfortunately model reactions of 108 with the organocuprates derived from methyl lithium and n-butyl lithium were unsuccessful under a variety of conditions. With $(n\text{-}Bu)_2CuLi$ it appeared that decomposition of the cuprate was occurring before it could react. Variations with $(n\text{-}Bu)_2CuLi/PBu_3$[106] and $n\text{-}BuCu/BF_3$[107] also gave no reaction. On one occasion when 108 was treated with Me_2CuLi a product was isolated which was not starting material. The NMR of this product showed a series of

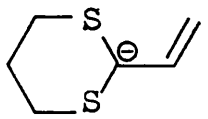
multiplets equivalent to 2 protons at δ_H 4.85-5.35 and fitted in with the structure 110 formed via deconjugation of the vinyl sulphone. In none of the above cases was



110

any of the desired conjugate addition product isolated.

We next attempted to add an acyl anion equivalent to 108. Treatment of 108 with nitroethane in the presence of tetramethylguanidine or DBU[108] as base gave clean recovery of starting material even after prolonged reaction times. Attempted addition of the anion 111[109] also returned starting materials. The apparent inertness

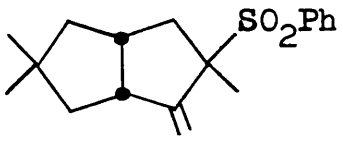


111

of 108 to nucleophilic attack at the β-carbon of the vinyl sulphone was attributed to a combination of steric hindrance and the lower activation of the β-carbon by the sulphone group relative to a ketone.

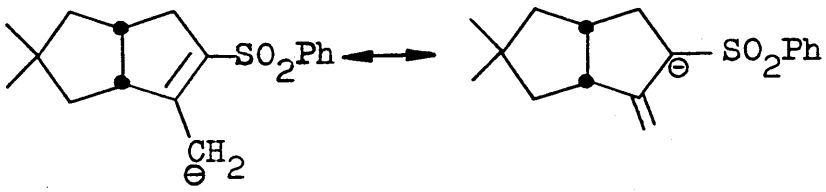
Organolithium reagents can add to vinyl sulphones in certain cases[110]. When the vinyl sulphone 108 was treated with n-butyl lithium in THF at -78°C a deep red/orange solution indicative of anion formation resulted. Quenching of this solution with methyl iodide led to the isolation of a product of slightly higher Rf value than

the starting material. The presence of one proton singlets at δ_H 5.13 and 5.50 and a three proton singlet at δ_H 1.56 in the NMR spectrum of this product indicated that it had structure 112. This must have been formed via a deconjugative



112

alkylation process involving anion 113. In accord with

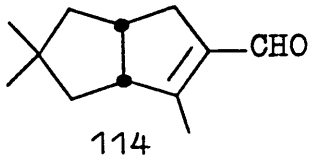


113

published work, no products of γ-alkylation were observed[111].

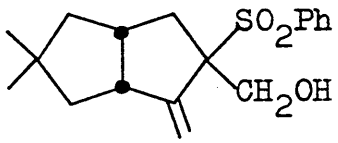
We considered that such a deconjugative alkylation reaction could be applied to the synthesis of hirsutene. To avoid competing deprotonation reactions the phenylsulphonyl compound 108 rather than its methylsulphonyl analogue must be used for such an approach.

This reaction was initially used to prepare the enal 114. It was thought that the greater electron withdrawing effect of an aldehyde relative to a sulphone group might activate the β-carbon sufficiently to allow conjugate addition to occur.

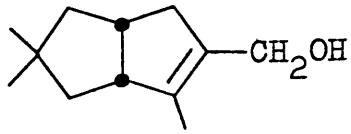


114

Quenching of the anion 113 with the formylating reagents ethyl formate or dimethylformamide gave no reaction. However quenching with gaseous formaldehyde[112] gave 115 as a mixture of two isomers (63%) whose ratio varied from



115

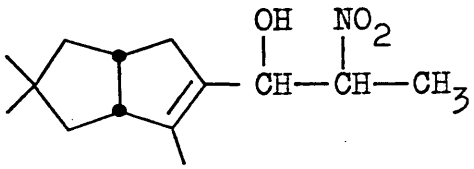


116

2:1 to 1:1 (as determined by integration of the vinyl protons in the ^{1}H NMR spectrum of the mixture). Treatment of the isomer mixture 115 with buffered 6% sodium amalgam in methanol effected desulphonylation[113] to give a single product. The disappearance of vinyl signals in the ^{1}H NMR and the appearance of a 3 proton signal at δ_H 1.61 ($CH_3C=C$), indicated that desulphonylation had fortunately occurred with migration of the double bond to produce the allylic alcohol 116 (62%). Oxidation of the primary alcohol with pyridinium chlorochromate gave the desired enal 114 (54%).

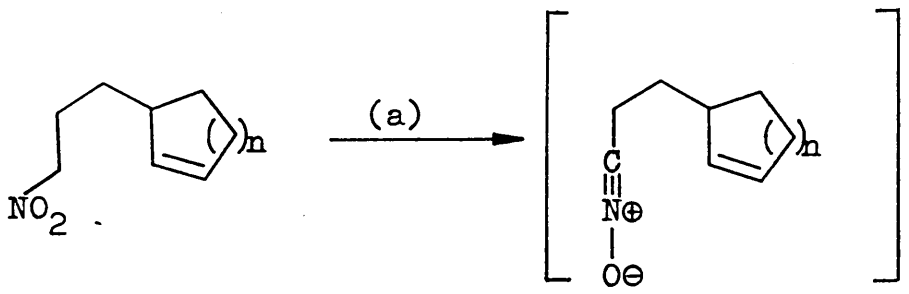
With a view to forming the C ring of hirsutene via an intramolecular aldol condensation we attempted to add the anion of nitroethane to 114 in a conjugate fashion.

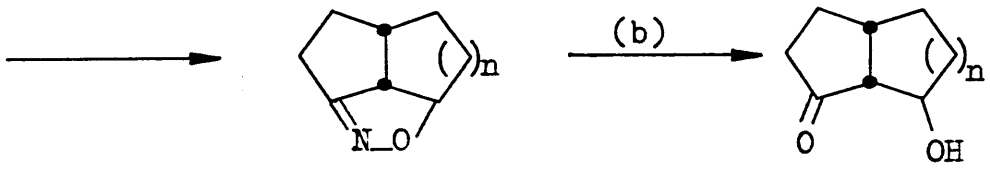
Reaction of enal 114 with nitroethane using tetramethylguanidine as base[67] for several days at room temperature produced a mixture consisting of starting 114 and two products. The infrared spectra of the two products were identical. The lack of C=O str. and the presence of OH str. and NO_2 str. bands in these spectra suggested that 1,2-addition had occurred to produce the alcohol 117 as a mixture of diastereoisomers. The ^1H NMR spectrum of the major product supported the formation of 117 (δ_H; 1.97, OH; 4.4-4.95, $CHNO_2$ and CHOH).



117

An alternative approach based on an intramolecular nitrile oxide cycloaddition (INOC) was briefly investigated. The intramolecular cycloaddition of a nitrile oxide to an olefin has been used to prepare cyclopentane rings[114]. The isoxazoline products can readily be converted to β-hydroxy ketones[114,115] (Scheme 4.5).

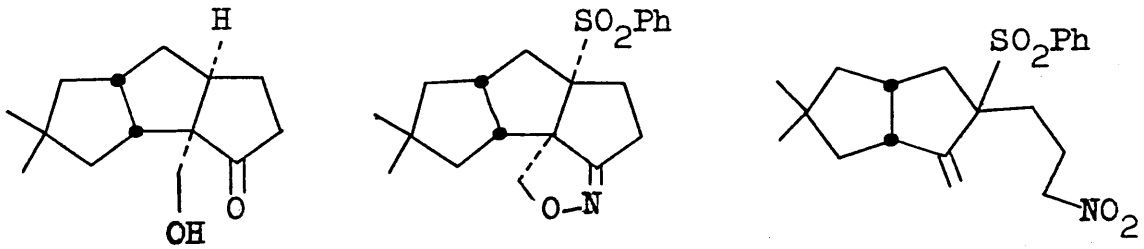




Reagents: (a) PhNCO, NEt_3, C_6H_6; (b) Raney Ni, H_2O, MeOH, buffer, H_2.

Scheme 4.5.

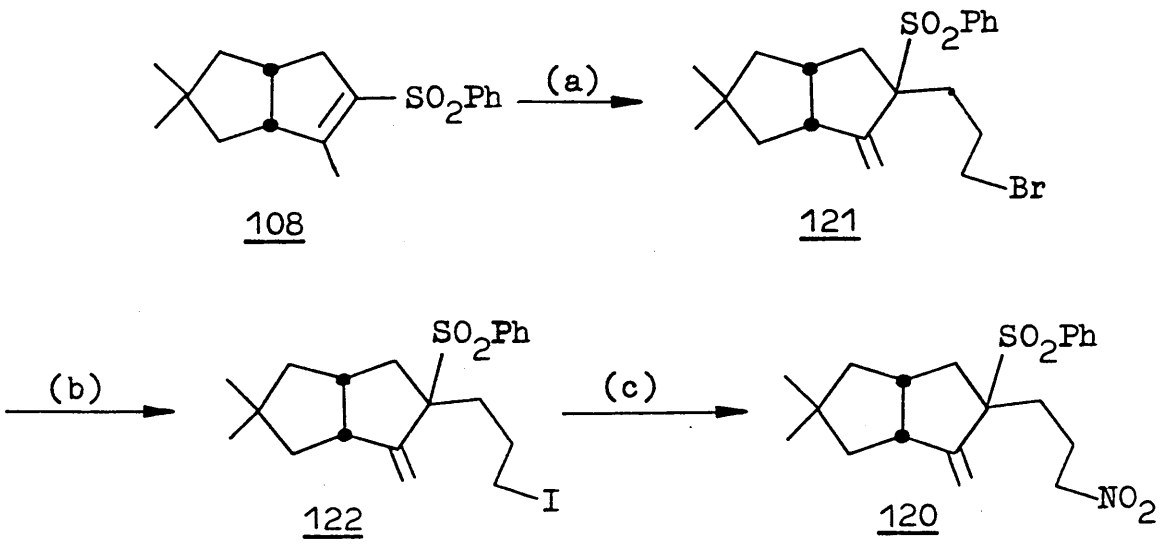
An intermediate in Ley's hirsutene synthesis[101] was the β-hydroxy ketone 118. We thought 118 should be available



118 119 120

by reduction of the isoxazoline 119 which in turn might be available from nitro alkene 120 via a INOC approach. The desired nitro alkene 120 was obtained from vinyl sulphone 108 in three steps (Scheme 4.6).

Deconjugative alkylation of 108 with 1,3-dibromopropane[116] gave 121 (83%) as a mixture of two inseparable isomers in the ratio 7:1 (NMR). The major product was assumed to be that with the bromopropyl group in the exo configuration, formed via approach of the alkylating agent



Reagents: (a) n-BuLi, THF, $BrCH_2CH_2CH_2Br$; (b) NaI, acetone; (c) $AgNO_2$, ether.

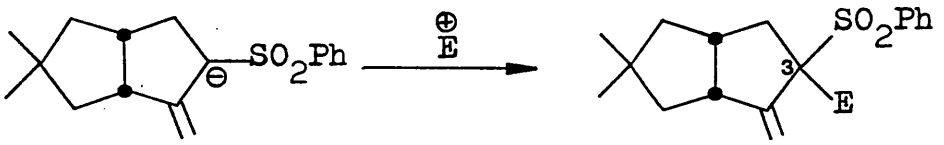
Scheme 4.6.

from the convex face of the α-sulphonyl anion. Only this isomer would produce the desired cis, anti, cis fusion of the three rings of hirsutene. However the situation may not be as simple as this.

There has been much discussion in the literature on the shape of α-sulphonyl carbanions[117]. Evidence for both planar and pyramidal arrangements at the α-carbon atom has been presented. The most recent theoretical studies on the simple model systems $\overset{\ominus}{C}H_2SO_2H$ and $\overset{\ominus}{C}H_2SO_2CH_3$ support a planar arrangement at the α-carbon[117b]. Further theoretical studies on α-lithiated sulphones indicate the most stable arrangement of such a species is an unsymmetrical chelated structure containing an intramolecular Li-O bond[117c]. It follows that reactions of such species should be stereo-

selective. The very limited experimental data are consistent with this theory[117c].

In our studies, quenching of the anion 113 with various electrophiles (see earlier examples and also later work) occurred stereoselectively in all but one case (Scheme 4.7). Ratios of isomers ranged from 100% to 6:1 (as determined by integration of the vinyl signals in the ^{1}H NMR of the products). Quenching of 113 with formaldehyde gave a more even distribution of isomers at C-3 (see earlier).



Electrophiles which reacted stereoselectively:
CH_3I, CH_3COCl, $BrCH_2CH_2CH_2Br$,
$ICH_2CH_2CH<^{O}_{O}]$, $ICH_2CH_2C{\equiv}CCH_3$.

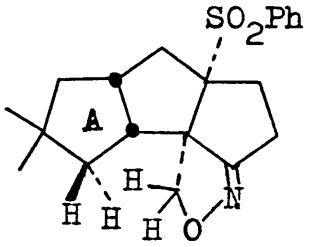
Scheme 4.7.

In our system an additional factor which is likely to have a major influence on the stereochemistry of quenching reactions of anion 113 is the structure of the bicyclo[3.3.0]octane system. The stereochemistry of the quench products of 113 has not been verified, but a planar arrangement at carbon together with the stereochemical constraints of a bicyclo[3.3.0]octane system support the exo stereochemistry for the incoming electrophile. However the poor stereoselectivity observed with the formaldehyde quench of 113 suggests some other factor may also be involved.

The presence of an intramolecular chelated structure for the α-lithiated sulphone would alter the geometry of the anion to something in between planar and pyramidal. A similar intramolecular chelated structure has been theoretically proposed for α-lithiated sulphoxides[117c]. Experimental results indicate that the stereochemistry of quenching of α-lithiated sulphoxides depends amongst other things on the nature of the electrophile[118]. Protonation (deuteration) and hydroxyalkylation of α-lithiated sulphoxides proceeds with retention of configuration whilst alkylation proceeds with inversion. A similar electrophile dependence may be present in our system. This was not investigated further as the route to hirsutene based on the INOC approach was abandoned for other reasons (see later).

The bromide 121 was refluxed with NaI in acetone to give iodide 122 (86%: 7:1 mixture of isomers) (Scheme 4.6). Nucleophilic displacement of iodide with silver nitrite[119] gave nitro alkene 120. Two isomers of 120 could be isolated in a ratio of 8:1 (total yield 37%). In a single attempt at the INOC reaction the major isomer of 120 was subjected to the normal conditions of nitrile oxide formation[115] (phenyl isocyanate, NEt_3 in benzene). Consumption of starting 120 suggested nitrile oxide formation had occurred. However it proved extremely difficult to determine exactly what was happening in the reaction. It appeared that the phenyl isocyanate and the amine and urea by-products of the reaction were masking product detection by TLC. This approach became even less attractive when a Dreiding model of the desired product 119 was examined. The model

indicated the presence of angle strain and severe steric strain between the protons in the isoxazoline ring and protons adjacent to the gem dimethyl group in the A-ring (Figure 4.1). As these steric interactions would be

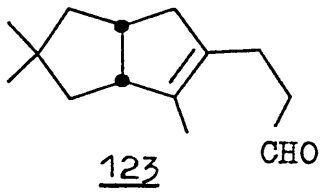


119

Figure 4.1

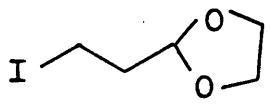
partially developed in the transition state leading to 119 a high energy of activation for the formation of 119 is likely. We did not investigate this further as other routes towards hirsutene looked more promising.

The aldehyde 123 an intermediate in Nozoe's hirsutene synthesis (Scheme 4.1) appeared to be readily available by the deconjugative alkylation-desulphonylation sequence used



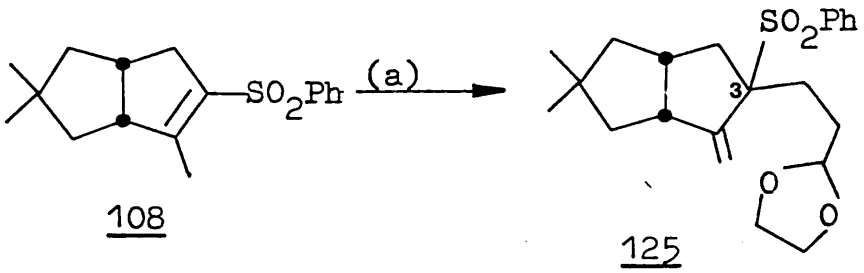
123

to prepare the allylic alcohol 116. Thus treatment of vinyl sulphone 108 with n-butyl lithium followed by quenching with the iodo acetal 124[120] introduced the necessary three carbon unit to give 125 (77%; approx. 10:1 mixture of two isomers) (Scheme 4.8). The stereochemistry at C-3 of the product 125 is immaterial

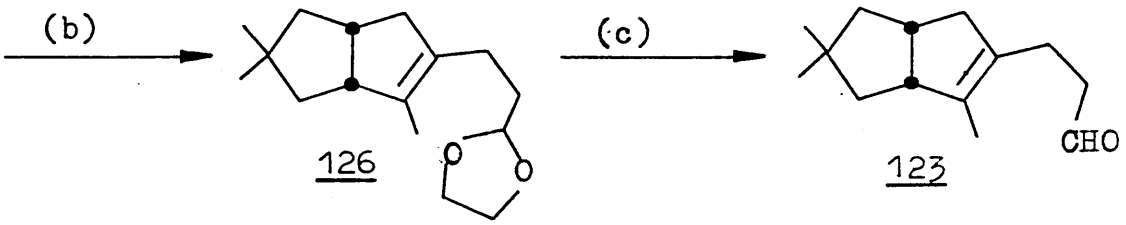


124

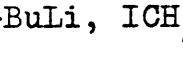
as this centre becomes sp^2 hybridised in the next step. Desulphonylation with buffered sodium amalgam[113] occurred with migration of the double bond to give 126 (90%).



108 125



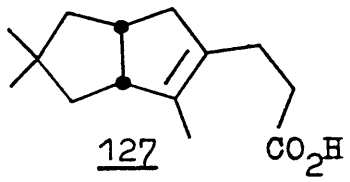
126 123

Reagents: (a) n-BuLi, ICH_2CH_2CH  , THF, -78°C; (b) Na(Hg), Na_2HPO_4, methanol; (c) PPTS, acetone, H_2O.

Scheme 4.8.

Removal of the acetal group was effected by refluxing 126 in acetone/water containing pyridinium p-toluenesulphonate (PPTS)[121] to give the desired aldehyde 123 (75%). The spectral data for 123 were consistent with the assigned structure and were in close agreement with the limited

literature data available for 123[11]. Oxidation of 123 with Jones reagent gave carboxylic acid 127 (63%) whose spectral data were also in agreement with the assigned structure.



127

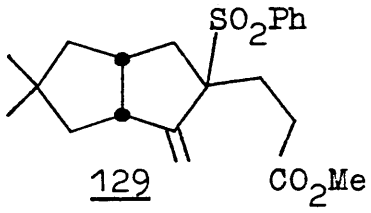
In an attempt to shorten this synthesis the anion of vinyl sulphone 108 was quenched with the halo esters 128[122]. However in both cases this resulted in low conversion to the desired product 129 probably as a result of proton transfer between the ester and the sulphonyl anion.

$XCH_2CH_2CO_2Me$

128

a X=Br

b X=I

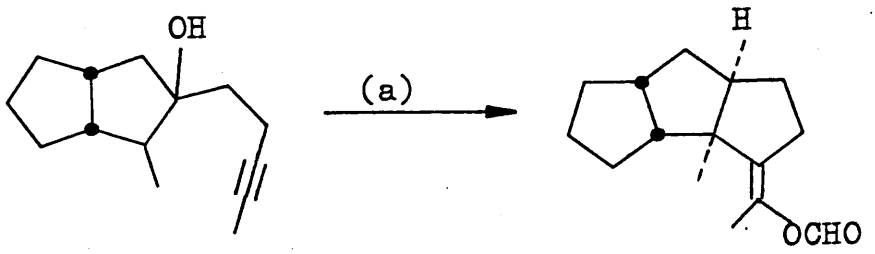


129

As 127 has been converted to hirsutene[11] the above consitutes a formal synthesis of hirsutene. However we still had not accomplished our main objective which was to build a third cyclopentane ring onto our bicyclo[3.3.0]-octane system.

In an early synthesis of a linear tricyclopentanoid skeleton, Lansbury used an intramolecular cationic cyclization procedure to build a ring onto a bicyclo[3.3.0]-

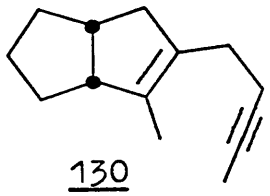
octane skeleton[123] (Scheme 4.9). This reaction must occur



Reagents: (a) HCO_2H, Δ.

Scheme 4.9.

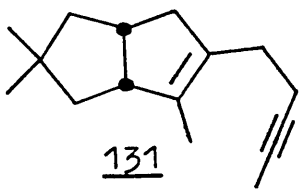
through dehydration to produce olefin 130. Reversible protonation, ring closure and trapping of the intermediate



130

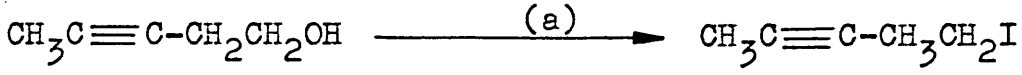
vinyl cation by formate anion give the tricyclic enol formate. Lansbury demonstrated that only the desired cis, anti, cis ring fusions form in such reactions. Adaptation of this procedure for our purposes led to a successful synthesis of hirsutene.

We thought the olefin 131 would be readily available via deconjugative alkylation-desulphonylation of vinyl sulphone 108.



131

The required alkylating agent 5-iodo-2-pentyne was prepared in two steps and 75% overall yield from commercially available 3-pentyn-1-ol[124] (Scheme 4.10). Alkylation of the

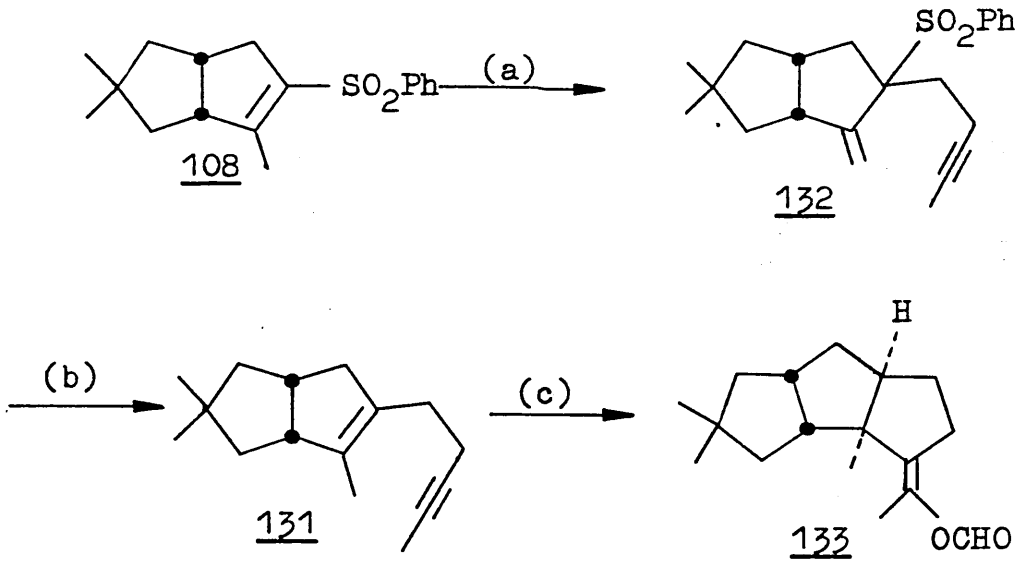


Reagents: (a) i. MsCl, NEt_3, CH_2Cl_2; ii. NaI, acetone.

Scheme 4.10.

anion of sulphone 108 with 5-iodo-2-pentyne gave 132 (72%; 6:1 mixture of isomers) (Scheme 4.11). This is in contrast to the recent findings of Clive where reaction of ketone enolates with homopropargylic halides led to elimination to produce a conjugated unsaturated system[125].

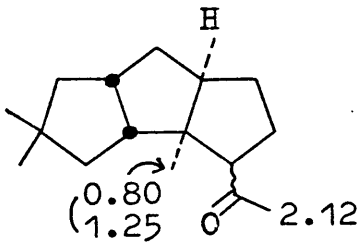
Desulphonylation of 132 with buffered sodium amalgam occurred with migration of the double bond and



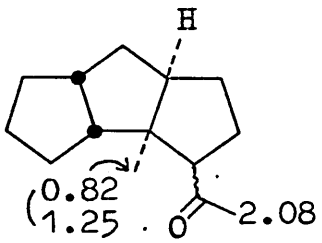
Reagents: (a) n-Butyl lithium, 5-iodo-2-pentyne, THF;
(b) Na(Hg), Na_2HPO_4, methanol; (c) HCO_2H, 50°C.

Scheme 4.11.

without affecting the triple bond to give 131 (87%). Cationic cyclization was affected in formic acid at 50°C to produce the desired tricyclic enol formate 132 (NMR δ_H 8.00, CHO) in 56% yield. Careful monitoring of this reaction was necessary to avoid decomposition of 132 to two other products. The major product was thought to be a mixture of epimers of the ketone 134 produced by hydrolysis of the enol formate. The chemical shifts of the angular



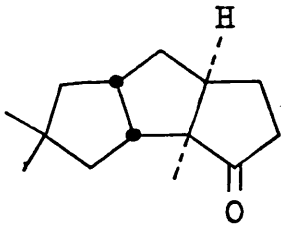
134



135

methyl group and the ketone methyl group of 134 were very close to those reported for the closely related compound 135 prepared by Lansbury[123]. The ketone 134 was also obtained when enol formate 132 was treated with KOH/methanol.

The synthesis was completed by cleavage of the double bond of 132 with excess ruthenium dioxide[126] to give the ketone 96 (42%), a known precursor to hirsutene[11].



96

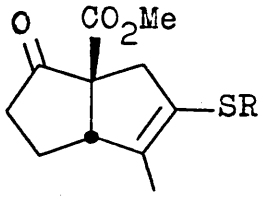
The yields of the final two stages are unoptimised. The m.p. of 42-43°C of 96 compared well with the published value of 44-45°C. The infrared data were also in agreement with published data[103b]. A 250 MHz ^{1}H NMR spectrum of our synthetic 96 was identical to a spectrum of 96 kindly supplied by Professor S.V. Ley.

CHAPTER 5

Related studies and suggestions for further work

5.1 Introduction

The range and location of functional groups within bicyclo[3.3.0]octane 42 offer further opportunities for natural product synthesis.

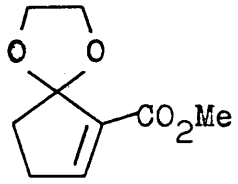


42 a R=Ph

b R=CH_3

Potential routes to $\Delta^{9(12)}$-capnellene and cedrene starting with 42 have been briefly investigated. Although these syntheses are incomplete, suggestions for their completion are outlined. Potential routes to hirsutic acid and angular triquinane systems are also presented.

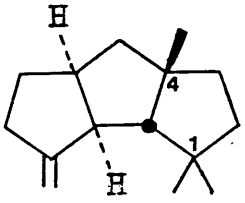
The unsaturated ester 45, one of the intermediates involved in the preparation of 42 (Chapter 2) has also proved useful as a starting material for natural product synthesis by its conversion to a precursor to the anti-tumour agent sarkomycin.



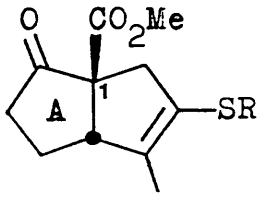
45

5.2 Towards a synthesis of $\Delta^{9(12)}$-capnellene

$\Delta^{9(12)}$-capnellene 7 is the simplest member and parent hydrocarbon of the capnellane natural products[13] (Chapter 1). Several syntheses of 7 have been reported[14]. We thought that the annelation of a third cyclopentanoid ring onto our bicyclo[3.3.0]octane system 42 would be a suitable approach to $\Delta^{9(12)}$-capnellene.

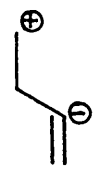


7

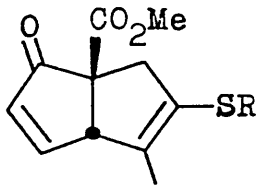


42

The location of functionality and substituents dictated that the required ring be built onto the A ring of 42. The C-1 carbomethoxy group of 42 was to become the C-4 methyl in 7 and we thought the vinyl sulphide group could be used to introduce the gem-dimethyl at C-1 (capnellane numbering) of 7. The most direct way of constructing the desired ring was to add a reagent equivalent to 136 in a 1,4-sense to the enone 137 followed by ring closure.



136

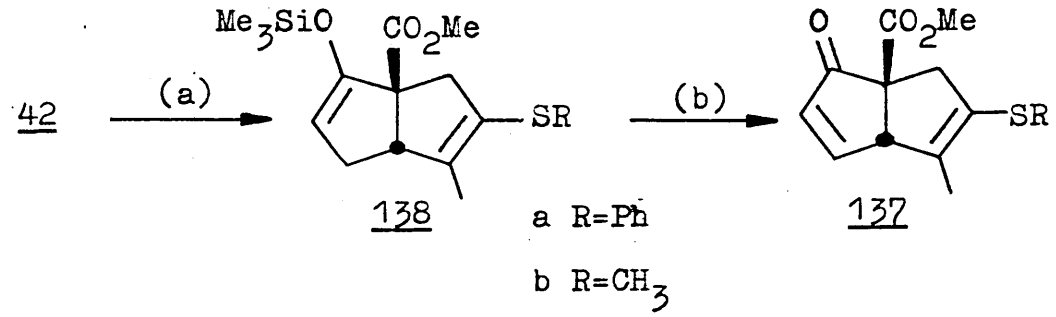


137

a R=Ph

b R=CH_3

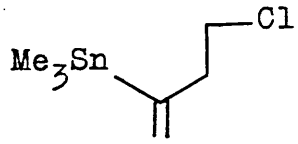
Treatment of ketone 42 with DBU, trimethylsilyl chloride[88] gave the silyl enol ether 138 which was dehydrosilylated to enone 137 (137a, 85%; 137b, 43%) with palladium (II) acetate[89] (Scheme 5.1).



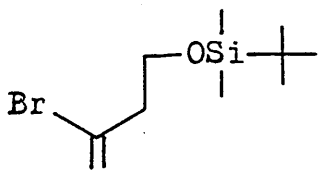
Reagents: (a) DBU, Me_3SiCl, CH_2Cl_2; (b) $Pd(OAc)_2$, p-benzoquinone, CH_3CN.

Scheme 5.1.

The annelating reagents 34 and 107 have been developed by Piers[53] and Magnus[99] respectively as equivalents to 136. We decided to use Piers' reagent 34

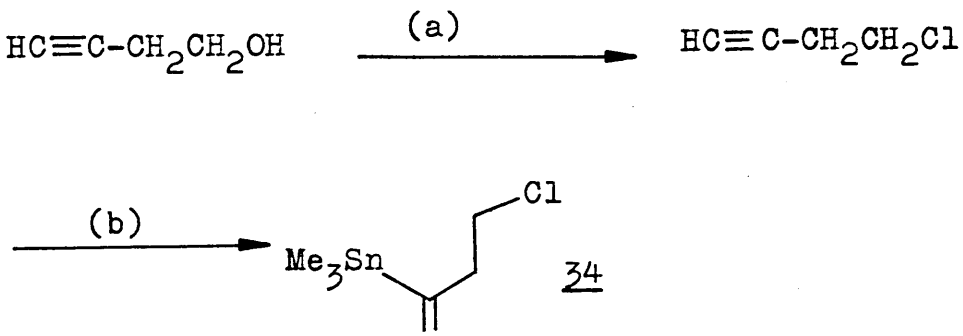


34



107

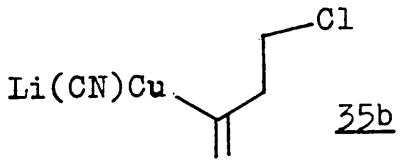
as its application involves fewer manipulations. The preparation of 34 from commercially available 3-butyn-1-ol is shown in Scheme 5.2.



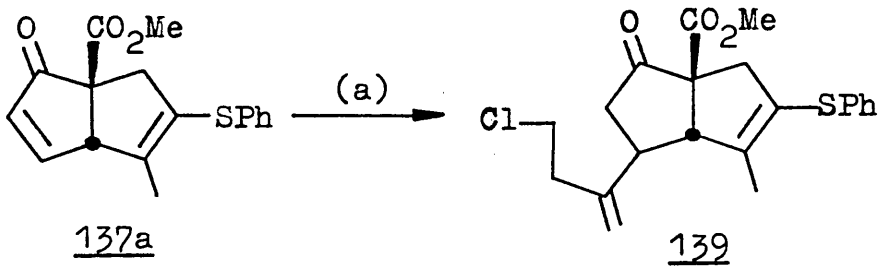
Reagents: (a) $SOCl_2$,pyridine; (b) Me_3SnLi,CuBr.Me_2S, methanol,THF.

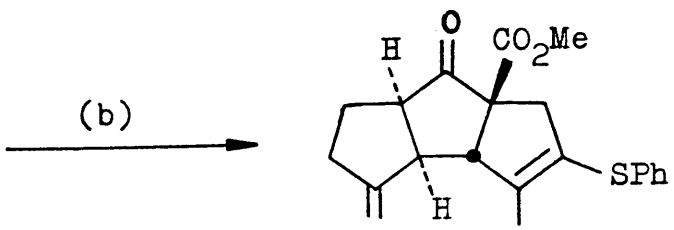
Scheme 5.2.

Transmetallation of 34 with n-butyl lithium gave the organolithium reagent which was converted to the vinyl cuprate 35b with CuCN. (Chapter 1.2). Addition of enone



137a to a solution of 35b resulted in conjugate to produce 139 (52%). It was assumed the side chain of 139 was exo, produced by approach of the cuprate from the convex face of 137a. Treatment of 139 with KH in THF[53a] gave the tricyclic product 140 (58%) (Scheme 5.3).



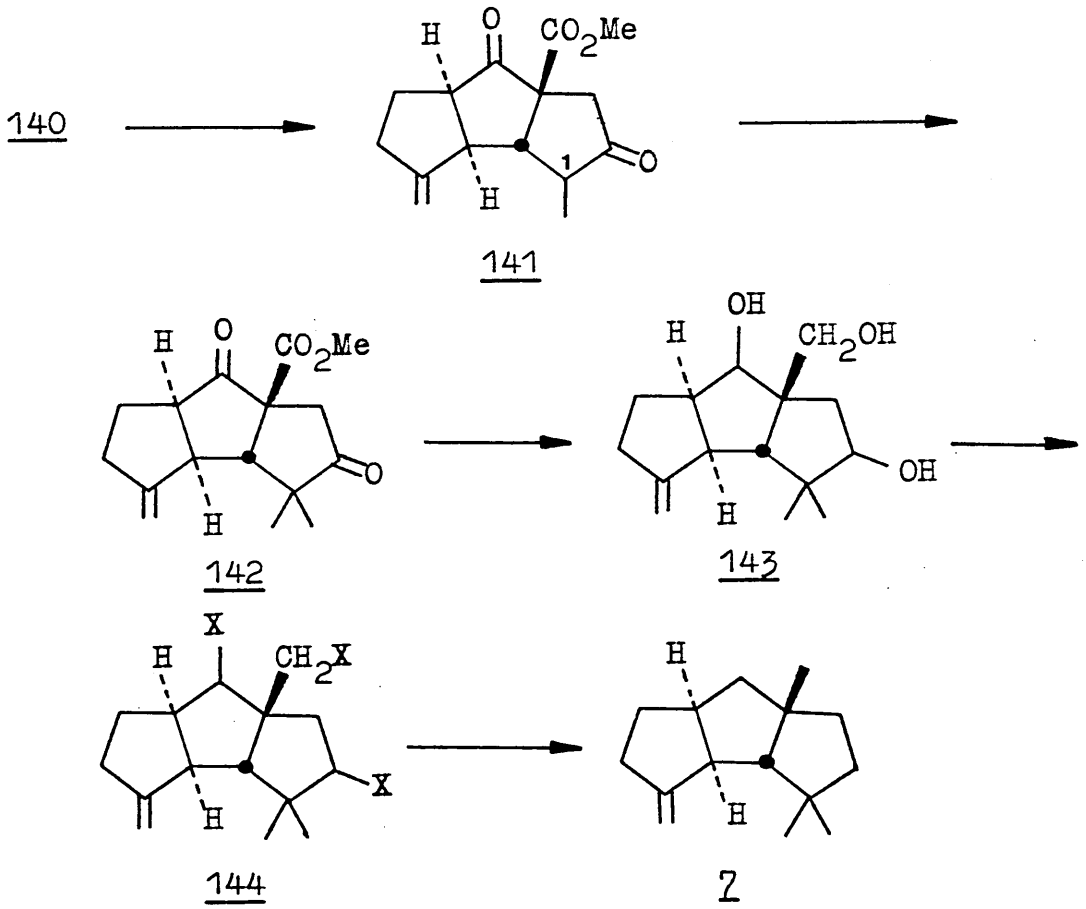


140

Reagents: (a) 35b, then NH_4Cl; (b) KH,THF.

Scheme 5.3.

When we had reached this stage Piers reported a synthesis of $\Delta^{9(12)}$-capnellene along very similar lines[14f]. A possible route for the completion of our synthesis is outlined in Scheme 5.4 .

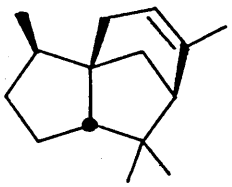


Scheme 5.4.

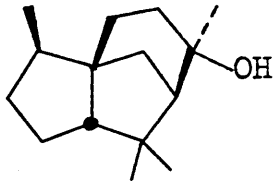
Hydrolysis of the vinyl sulphide of 140 would produce ketone 141. The methylthio vinyl sulphide analogue of 140 may prove more suitable for this synthesis as the more forcing conditions necessary to hydrolyse the phenylthio vinyl sulphide (see Chapter 3.1) would probably move the exo cyclic double bond of 141 into the ring. Regioselective methylation of 141 can be expected to occur at C-1 (capnellane numbering) to give 142 on thermodynamic grounds. All that remains is the reduction of the ketone groups to methylenes and the ester to a methyl group. It would be preferable to reduce all the carbonyl groups together. A likely method of achieving this involves complete reduction to the triol 143 with $LiAlH_4$ followed by conversion to a suitable derivate 144 which can be converted to $\Delta^{9(12)}$-capnellene via hydride reduction or dissolving metal reduction. Based on literature precedent a suitable derivative appears to be the triphosphoramidate 144 (X= $OP(O)(NMe_2)_2$) produced by quenching the trialkoxy anion of 143 with $(Me_2N)_2P(O)Cl$[127]. Treatment of 144 (X= $OP(O)(NMe_2)_2$) with $Li/EtNH_2$ in THF/t-butanol would produce $\Delta^{9(12)}$-capnellene. The free radical based deoxygenation procedures developed by Barton[128] are a possible alternative for conversion of triol 143 to $\Delta^{9(12)}$-capnellene.

5.3 Towards a synthesis of cedranoids

The tricyclic sesquiterpenes α-cedrene 15 and cedrol 145 are constituents of cedar wood oil.

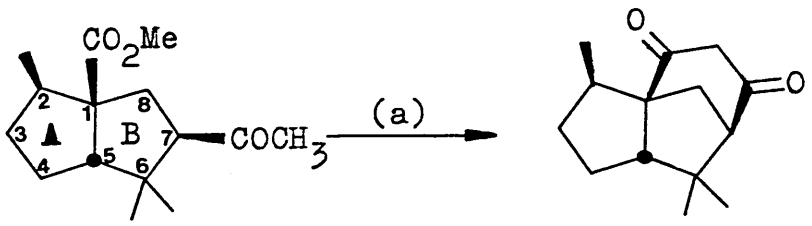


15



145

The syntheses of 15 and 145 have attracted the attention of several research groups[27] since the first total synthesis of cedrol 145 by Stork in the 1950's[27a]. Stork constructed the tricyclic cedranoid skeleton via intramolecular condensation of the keto ester 146 to produce dione 147 (Scheme 5.5). Yates and Stevens also



146 147

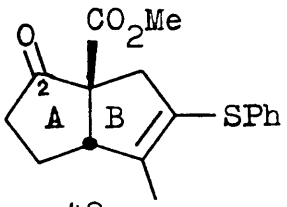
Reagents: (a) KO^{t}Bu, ^{t}butanol.

Scheme 5.5.

constructed 147 via condensation of the acetyl epimer of 146 after initial epimerisation to 146[27b].

We considered that our highly functionalised bicyclo[3.3.0]octane 42a possessed suitable functionality to be converted to 147 via one of the 7-acetyl* epimers of 146.

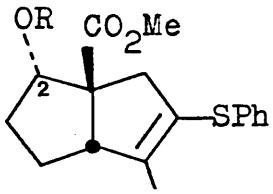
* To avoid confusion the numbering of the bicyclo[3.3.0]-octane portion of cedrene is maintained in bicyclo[3.3.0]-octane precursors to cedrene. IUPAC numbering is given in the experimental section.



42a

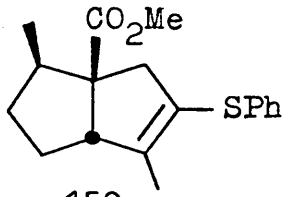
From the outset we realised that the introduction of the C-2 methyl group into ring A with the desired exo stereochemistry would be the major problem with this synthesis. Several of the published cedranoid syntheses have produced a mixture of epimers at this centre. We have not yet overcome this problem but possible solutions will be suggested.

Our initial efforts in this area involved attempted S_N2 displacement of the tosylate 148 with Me_2CuLi. Reduction of the C-2 ketone of 42a with $NaBH_4$ in methanol gave one alcohol product (80%) assumed to be endo alcohol 149 formed via approach of the hydride from the convex face of 42a. Conversion of the C-2 hydroxyl to tosylate 148 occurred slowly but efficiently (90%) with p-toluenesulphonyl chloride in pyridine.



149 R=H

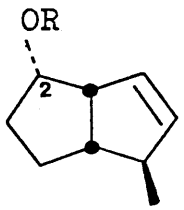
148 R=Ts



150

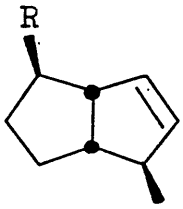
In an attempt to produce 150, treatment of 148 with Me_2CuLi in ether gave no reaction. It appeared that

the cuprate was decomposing before it reacted. Schaffner, in attempted S_N2 displacements with the similar tosylate 151 with methyl Grignard reagents or dimethyl cuprate variants noticed predominantly elimination or no reaction at all[29].



151 R=Ts

152 R=Ms



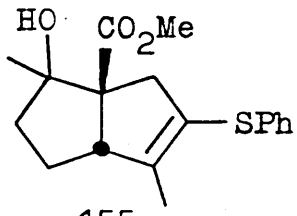
153 R=I

154 R=CH_3

Schaffner overcame this problem by treatment of the mesylate 152 with NaI in acetone to invert the configuration at C-2 to give exo iodide 153. The iodide 153 reacted with methyl Grignard reagent in the presence of CuI with retention of configuration to produce 154 with the desired exo methyl group in high yield.

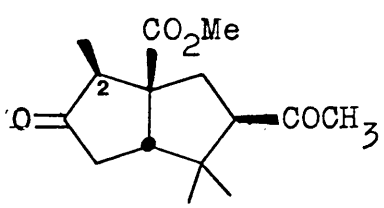
However a similar sequence on our tosylate 148 (or mesylate) may be complicated by the presence of the carbomethoxy group at the ring junction. We do not yet fully understand the steric influence of this carbomethoxy group, but several observations by us and other groups suggest that its influence on the stereochemistry at C-2 is small.

We noticed a high stereoselectivity in the reduction of 42a with $NaBH_4$. Chemoselective addition of methyl lithium to the ketone group of 42a also occurred with good stereoselectivity to produce two alcohols 155 (76%) in the ratio 7:1. In both cases the major product is assumed to

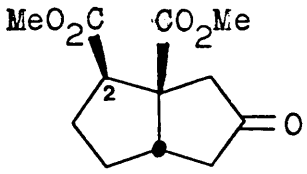


155

be the endo alcohol. Stork demonstrated that under equilibrating conditions 156 exists exclusively with the C-2 methyl group exo as shown[27a]. Yates and Stevens also



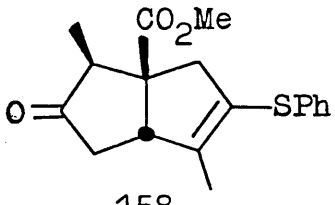
156



157

discovered that 157 with the exo carbomethoxy group at C-2 is the thermodynamically favoured product[27c].

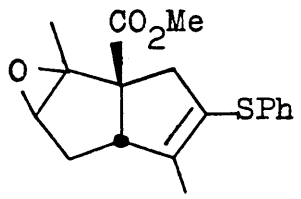
The equilibration studies of Stork on 156 suggested an alternative approach to the introduction of the C-2 methyl group of cedrene. Preparation of ketone 158 followed by equilibration and reduction of the ketone group to a methylene would produce 150.



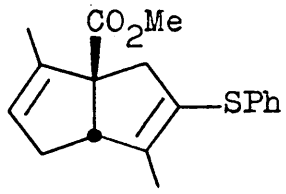
158

We considered 156 would be available via acid catalysed rearrangement of epoxide 159 which in turn

should be available from olefin 160.

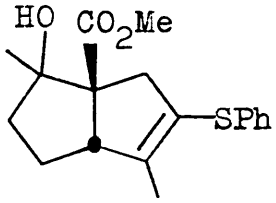


159



160

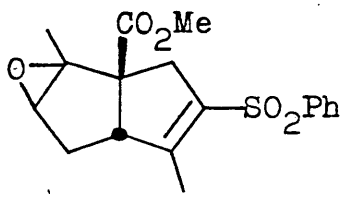
The preparation of 160 via dehydration of the alcohol mixture 155 under basic conditions has been briefly investigated.



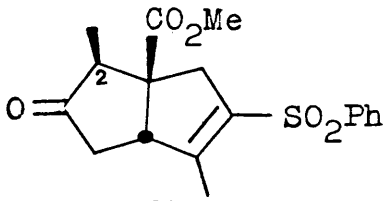
155

Treatment of the mixture 155 with $POCl_3$/pyridine resulted in the formation of a single product. The infrared spectrum of this product lacked an OH str. band, suggesting dehydration had occurred. The ^1H NMR spectrum of the product showed two signals at δ_H 1.65 and 1.83 for the methyl groups attached to the double bonds. However the vinyl region of the spectrum contained two broad singlets at δ_H 5.02 and 5.45 which corresponded to 1H in total. A similar result was obtained when the alcohol mixture 155 was treated with methanesulphonyl chloride/NEt_3/CH_2Cl_2. Although this data is not in full agreement with structure 160 we nevertheless proceeded with the epoxidation reaction. Treatment of the dehydration product with 3.5 equivalents of m-chloroperbenzoic acid (-78°C then 0°C) resulted in

disappearance of starting material to give one major product on TLC. Excess m-CPBA was required as the sulphide group was also oxidised (to a sulphone) under these conditions. Inspection of the ^{1}H NMR suggested the major product was a mixture of two compounds (1:1 ratio). The NMR lacked any signals in the vinyl region suggesting the double bond had been oxidised. The methyl signal at δ_H1.65 in the spectrum of the dehydration product (assigned to the C-2 methyl group attached to the double bond in 160) moved upfield to give two singlets (1:1 ratio) at δ_H1.28, 1.48. This upfield shift is also consistent with epoxide formation. The product could be a mixture of endo and exo epoxy sulphones 161 but further investigations to clarify this are required. Rearrangement of the epoxide of 161 to a ketone and equilibration should give 162 with the desired C-2 stereochemistry.

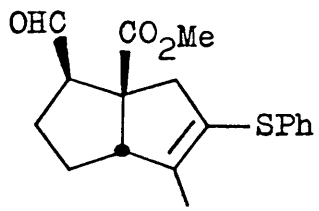


161

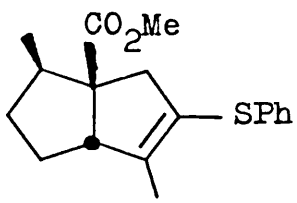


162

Yet another alternative for introduction of the C-2 methyl group of cedrene involves preparation of the aldehyde 163 via an homologation procedure[129]. Equilibration and reduction of the aldehyde to a methyl group would then produce 150.

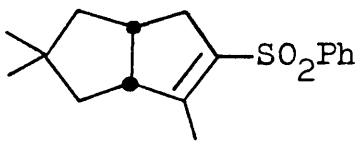


163

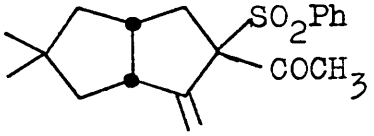


150

We believe functionalisation of the B ring of our bicyclo[3.3.0]octane system will be more straightforward. The α-acylation of the anion derived from a vinyl sulphone appeared to be a suitable method for introduction of the required C-7 acetyl group. In a model reaction, quenching of the anion derived from vinyl sulphone 108 (n-BuLi, THF, see Chapter 4) with acetyl chloride gave 164. This reaction



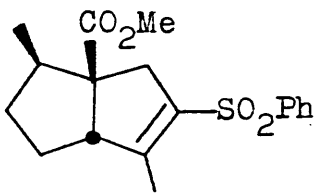
108



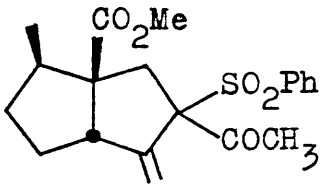
164

was also carried out using LDA as base which would be more appropriate for the synthesis of cedrene.

Thus treatment of a vinyl sulphone such as 165 with LDA/acetyl chloride should produce 166.

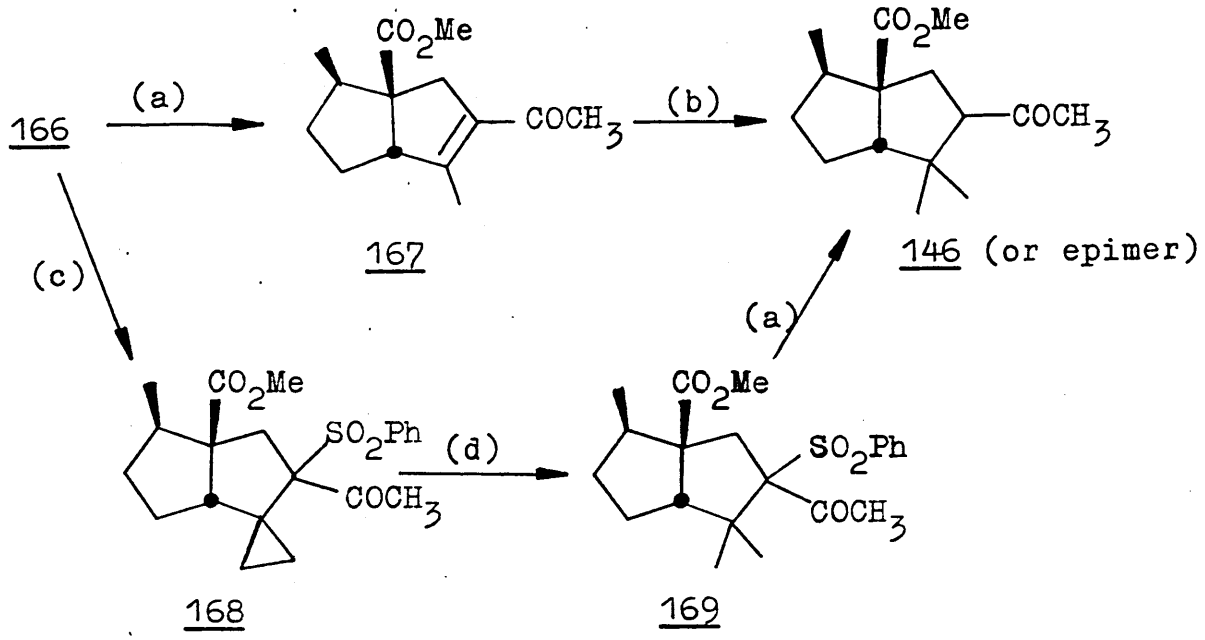


165



166

Two possibilities for the conversion of 166 to the desired product 146 are outlined in Scheme 5.6.



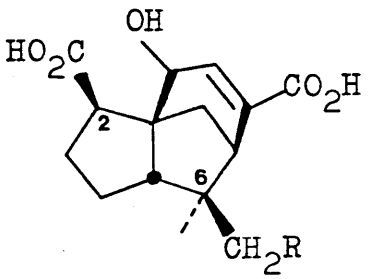
Reagents: (a) $Na(Hg)$, Na_2HPO_4, methanol; (b) Me_2CuLi;
(c) Et_2Zn, CH_2I_2; (d) H_2, catalyst.

Scheme 5.6.

Desulphonylation of 166 should produce 167 in accord with our previous work (Chapter 4). Conjugate addition of Me_2CuLi would then produce the desired product 146 (or its acetyl epimer).

Alternatively cyclopropanation[130] of the exo methylene group to produce 168 followed by hydrogenation would give 169. Desulphonylation of 169 would also produce 146 (or its acetyl epimer).

The route outlined above for the synthesis of cedranoids is potentially adaptable to the synthesis of some naturally occurring oxygenated cedranoids for example shellolic acid 170 and laccishellolic acid 171.

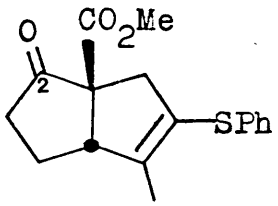


170 R=H

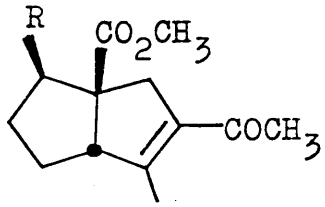
171 R=OH

These two compounds have not been synthesised but studies directed towards their synthesis have been reported[27c].

The C-2 ketone group of 42a could be used to introduce the C-2 carboxyl group of 170 and 171 via an homologation

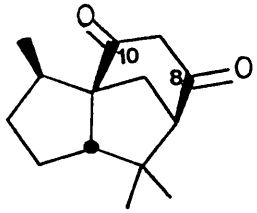


42a



172

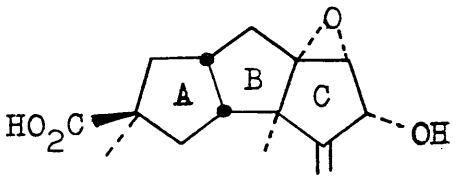
procedure[129]. The hydroxymethyl group attached to C-6 in 171 could be introduced with the correct exo stereochemistry via conjugate addition of an hydroxymethyl anion equivalent to an intermediate such as 172. The diketone 147 offers obvious potential for functionalisation at C-8 and C-10. Stork demonstrated that the C-8 ketone is less hindered than that at C-10 thus offering the potential for selective manipulation of the two carbonyl groups.



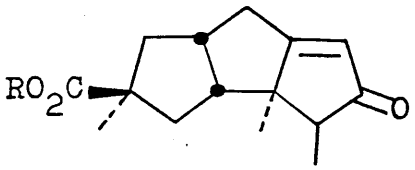
147

5.4 A possible synthesis of hirsutic acid.

Hirsutic acid 3 is a member of the hirsutane family of natural products and has been the subject of several synthetic efforts in recent years[12]. All of the reported syntheses of 3 have involved preparation of an enone such as 173 which can readily be transformed into hirsutic acid.



3



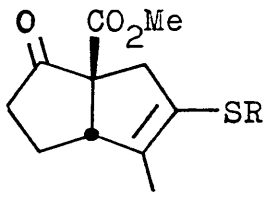
173

R=H or alkyl

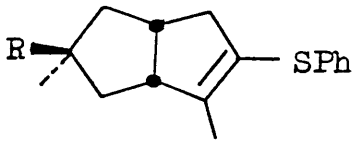
R_1=H or CH_3

Our experience with the synthesis of hirsutene (Chapter 4) suggested that a similar approach could be used to synthesize hirsutic acid via an enone such as 173. Our highly functionalised bicyclo[3.3.0]octane 42 could be used to produce the AB rings of 3 and the annelation of a third ring onto the vinyl sulphide group would lead to the linearly fused tricyclopentanoid system.

The required AB ring fragment 174 should be



42

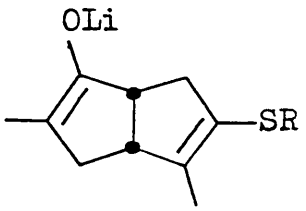


174 R=CO_2R

105 R=CH_3

available via a similar approach to that used for the preparation of the hirsutene precursor 105 (Chapter 4).

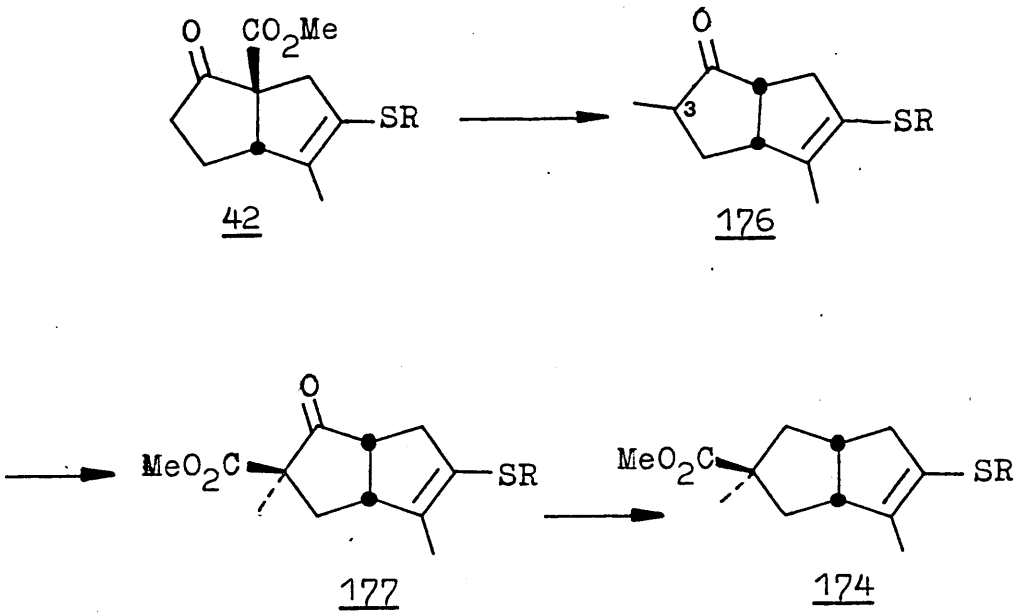
One of the major problems in the synthesis of hirsutic acid is the introduction of the methyl and carboxylic acid subsituents into ring A with the correct stereochemistry. The preparation of 174 from 42 would involve the quenching of an enolate with an alkylating reagent and an acylating reagent. The incoming electrophile is likely to finish up in the exo configuration via approach of the reagent from the convex face of the bicyclo[3.3.0]-octane system. As the carboxyl group is exo in hirsutic acid, it must be introduced after the methyl group. This would necessitate the acylation of a tertiary enolate such as 175. Acylations of tertiary enolates using classical



175

reagents such as dimethyl carbonate are unsatisfactory because of equilibrium constraints. Alternative procedures for the acylation of tertiary enolates have recently become available[131]. The procedure of Mander[131a] seems most suitable for our purposes. A possible route to the required AB ring segment 174 is outlined in Scheme 5.7.

Methylation of 42 followed by decarbomethoxylation should give 176 in accord with our previous work (Chapter 4). The acylation procedure of Mander involves reaction of a preformed enolate with methyl cyanoformate ($MeO\overset{O}{\overset{\|}{C}}-CN$).

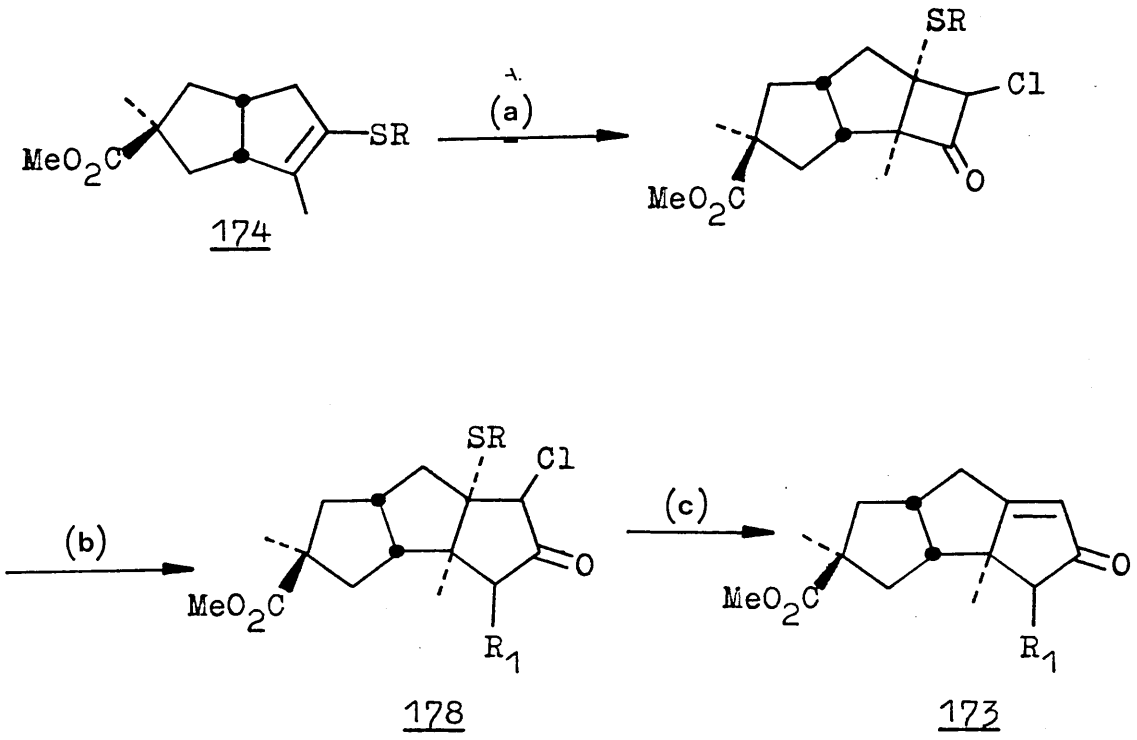


Scheme 5.7.

Thus regioselective enolate generation at C-3 in 176 (either by proton abstraction or through the silyl enol ether of 176) followed by quenching with methyl cyanoformate should give 177 stereoselectively. Reduction of the ketone of 177 to a methylene would then produce 174.

Several possibilities exist to construct the third cyclopentane ring to produce enone 173[31]. One of the potentially more attractive routes because of its brevity is outlined in Scheme 5.8.

Vinyl sulphides undergo regioselective cycloaddition with chloroketenes[132]. Ring expansion of α-chlorocyclobutanones with diazoalkanes also occurs regioselectively[28c,32]. This suggests that the tricyclic system 178 should be available via a cycloaddition-ring expansion procedure. Dissolving metal reduction of 178 would then give enone 173.



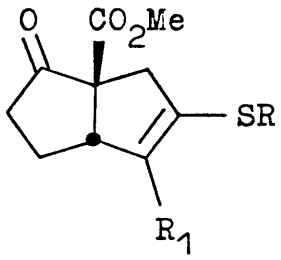
R=CH_3 or Ph, R_1=H or CH_3

Reagents: (a) Cl(H)C=C=O; (b) R_1CHN_2; (c) Zn,AcOH.

Scheme 5.8.

5.5 Potential uses of analogues of the bicyclo[3.3.0]-octane derivatives 42.

In another project in our laboratories the bicyclo-[3.3.0]octane 179 has been prepared via a similar route to that used to prepare 42[133]. The use of 179 for the



R=CH_3 or Ph

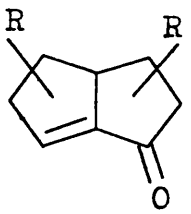
179 R_1=H

42 R_1=CH_3

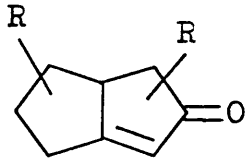
synthesis of prostacyclin analogues is currently under investigation[133].

The bicyclo[3.3.0]octane 179 also offers the potential for the preparation of angular tricyclopentanoid systems.

The most common approach employed in the synthesis of angular triquinane systems involves the annelation of a third cyclopentane ring onto a bicyclo[3.3.0]octenone such as 180 or 181[20,24,25].



180



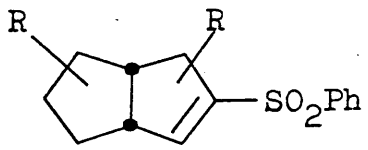
181

The synthetic utility of our bicyclo[3.3.0]octane system (179 or 42) would be greatly extended if it could

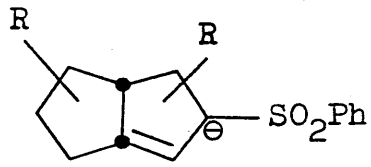
be converted to an enone such as 180 or 181. A possible route for the conversion of 179 to an enone such as 181 is outlined below.

There are several procedures available for the conversion of a sulphone to a ketone[134]. A recent method[134] involves treatment of an α-sulphonyl carbanion with $Me_3Si\text{-}O\text{-}O\text{-}SiMe_3$ to produce a ketone in good yield. This procedure has also been used to prepare an enone from the anion of an allyl sulphone.

Based on our previous work (Chapter 4) the conversion of 179 to a vinyl sulphone such as 182 should be straightforward. Treatment of 182 with a n-BuLi should produce



182



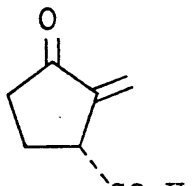
183

the anion 183 which could be converted to 181 via the procedure mentioned above[134].

5.6 The synthesis of sarkomycin.

Sarkomycin 2 is the simplest member of the cyclopentanoid family of antibiotic/antitumour agents which also includes the pentenomycins and methlenomycins (Chapter 1.1). Since its isolation in 1953[7] sarkomycin has attracted considerable attention both as a synthetic target and as an antitumour compound of pharmacological interest[7].

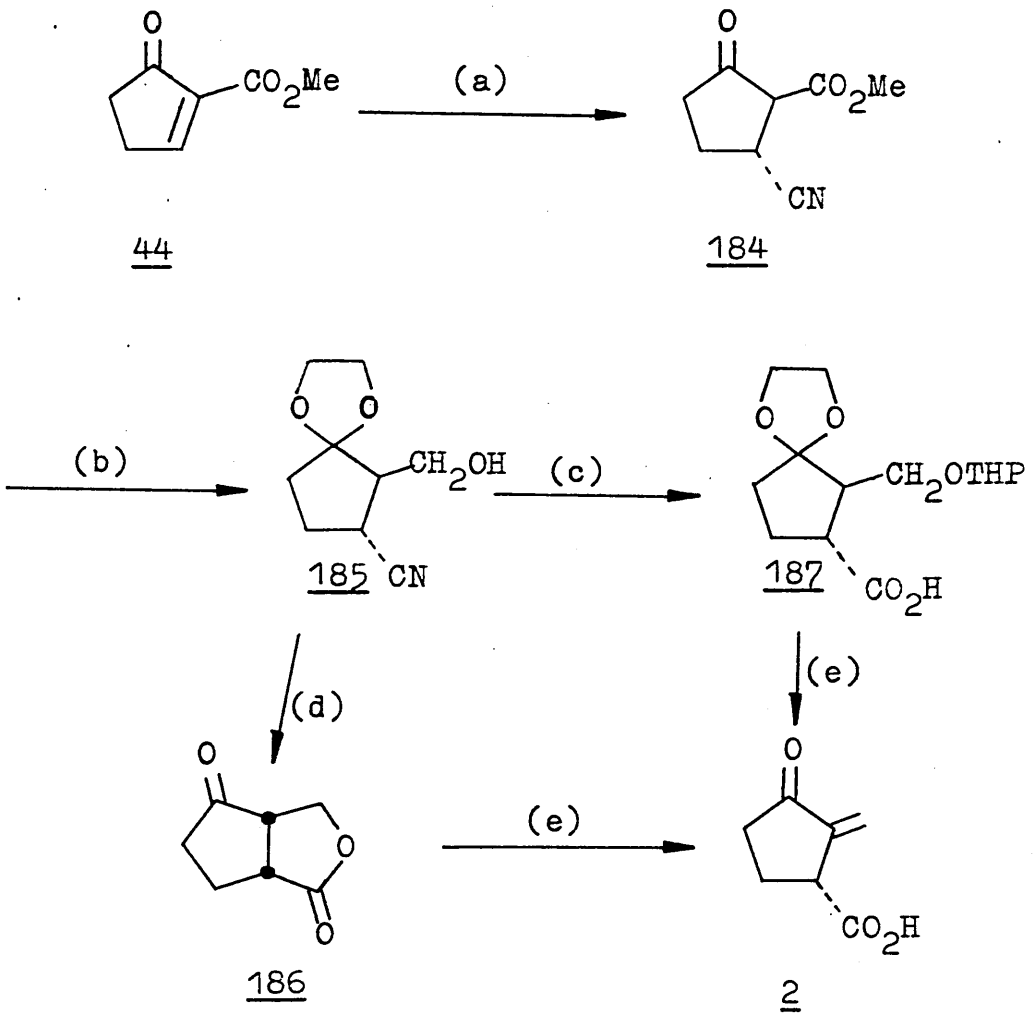
Early syntheses of sarkomycin were non regio-selective and the first regiocontrolled synthesis of 2 by Marx only appeared recently[7c].



2

Sarkomycin is rather unstable and thus synthetic efforts have been directed towards the preparation of a stable precursor which can readily be converted to the natural product.

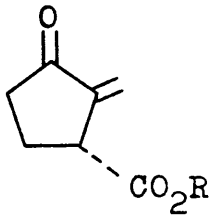
The synthesis of Marx (Scheme 5.9) involved the addition of cyanide anion to the unstable methyl 5-oxocyclo-pent-1 -enecarboxylate 44 to produce 184. Acetalisation and selective reduction of the ester gave 185. The cyano alcohol 185 was converted into two stable sarkomycin precursors. Hydrolysis of the nitrile and removal of the acetal gave the lactone 186. Alternatively conversion of 185 to its tetrahydropyranyl ether and base



Reagents: (a) Et_2AlCN; (b) i) $HOCH_2CH_2OH$,PTSA,C_6H_6; ii) $LiBH_4$,THF,H_2O,NaOH; (c) i) dihydropyran, H^+; ii) KOH; (d) i) NaOH; ii) PTSA,H_2O; (e) dil.HCl.

Scheme 5.9. Marx's synthesis of sarkomycin.

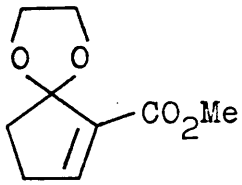
hydrolysis of the nitrile gave the acid 187. Both 186 and 187 could be converted to sarkomycin by treatment with dilute HCl. Other groups have prepared intermediates similar to those of Marx. The lactone 186 has become the most commonly prepared precursor to sarkomycin[7c-g]. Esters of sarkomycin 188 are also stable and have been prepared by several groups[7i-k].



R=Me or Et

188

Our interest in sarkomycin arose when we realised that the unsaturated ester 45, an intermediate in our bicyclo[3.3.0]octane synthesis possessed ideal functionality for a sarkomycin synthesis along similar lines to that of Marx (Scheme 5.9). The protected sarkomycin precursor 187



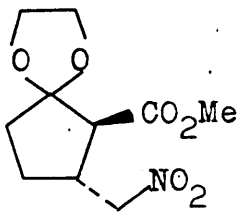
45

was chosen as a particularly suitable target.

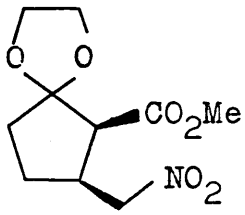
Initially we needed to add a carboxyl anion equivalent in a 1,4 sense to 45. In our bicyclo[3.3.0]octane synthesis the anion of nitroethane had proved very efficient as an acetyl anion equivalent in conjugate addition reactions to 45. As there are several methods available for the conversion of a primary nitro group to an aldehyde or carboxylic acid[68] we considered the anion of nitromethane would be a suitable carboxyl anion equivalent for this purpose.

Treatment of 45 in nitromethane with catalytic tetramethylguanidine[67] at room temperature for 4 days gave a mixture of two products (77%) in the ratio 12:1 after

column chromatography. The major product was originally thought to be the trans adduct 189 on thermodynamic grounds[135].



189



190

However we now believe that the major product was the cis isomer 190 based on two observations.

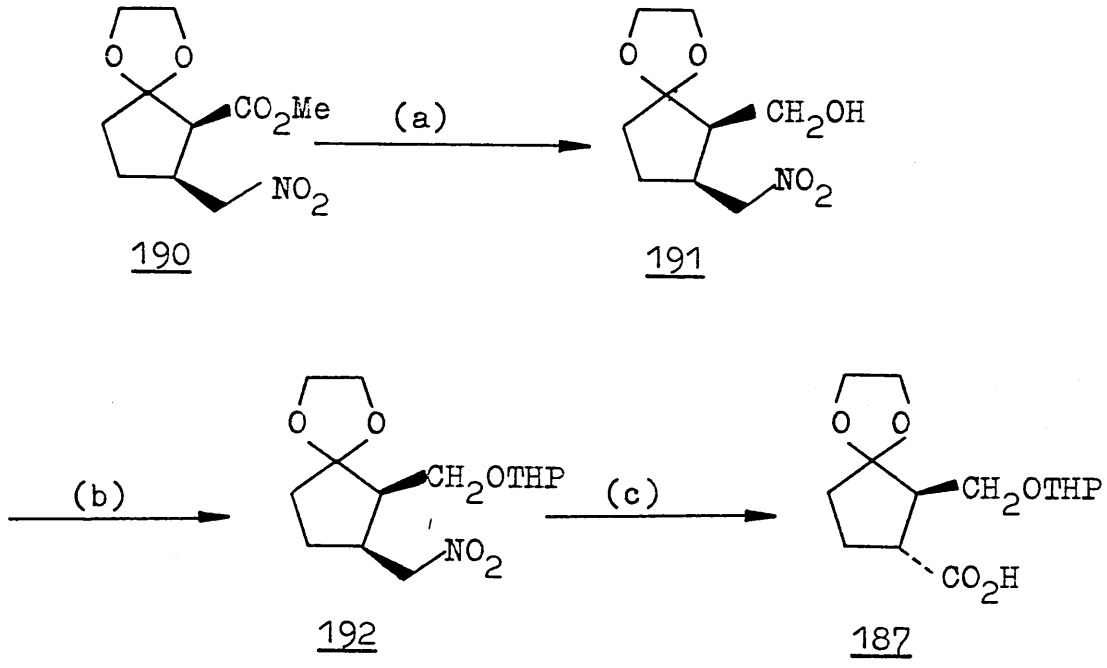
i) The ^1H NMR spectrum of the major product showed a doublet at 2.70ppm for the proton α to the ester. The observed coupling constant of 8Hz for this doublet is consistent with a dihedral angle of approximately 0° between the two protons which are coupling (cis arrangement, Karplus equation)[136].

ii) If the major product was the trans isomer then an even greater preference than 12:1 would have been expected in the analogous reaction with the larger nitroethane anion. The observed product ratio with nitroethane was 1.6:1 (Chapter 2).

The cis isomer 190 is obviously the product of kinetic protonation. The reaction is carried out in nitromethane and the most acidic proton in the product is that adjacent to the nitro group. The production of the cis product 190 must therefore reflect the inability of the carbomethoxy group to epimerise under these reaction conditions.

The major isomer was carried through subsequent steps.

The most efficient reagent for selective reduction of the ester group of 190 was aluminium hydride prepared from $AlCl_3$ and $LiAlH_4$[137]. This produced the desired alcohol 191 (85%) as a single product presumably as the cis isomer (Scheme 5.10). Surprisingly AlH_3 prepared from $LiAlH_4$ and $c.H_2SO_4$[138] proved much less efficient for this conversion. Lithium borohydride and sodium borohydride/t-butanol[138] were also less efficient. The alcohol 191 was converted to its tetrahydropyranyl ether 192 (79%) using pyridinium p-toluenesulphonate as catalyst[140].



Reagents: (a) AlH_3, ether; (b) dihydropyran, PPTS, CH_2Cl_2; (c) i) KOH, $MgSO_4$, H_2O; ii) $KMnO_4$.

Scheme 5.10.

Conversion of the primary nitro group to the desired carboxylic acid was achieved in one pot through the aldehyde by oxidation of the nitronate anion of 192 with excess potassium permanganate[141] to produce 187 (50%). Comparison of data obtained for 187 with the published data of Marx[7c], suggested that epimerisation to the trans isomer had occurred under the reaction conditions. The infrared data for 187 were identical to those of Marx. The ^{1}H NMR data for 187 were also identical to those of Marx apart from the chemical shift of the acid proton. Our acid proton appeared at δ_H 9.0 whereas Marx's appeared at δ_H 9.85ppm. This may have been due to a concentration effect. Our product melted over a broad range. The majority of crystals melted at 68-70°C which is in accord with the value of 69-71°C reported by Marx. However some crystals melted at approximately 15°C higher. This may have been a different crystal form of 187 or another diatereoisomer produced by the introduction of an extra chiral centre in the tetrahydropyranyl group. Our requests for spectra of 187 for direct comparison were unacknowledged.

As 187 has been converted to sarkomycin by Marx[7c] the above constitutes a formal synthesis of sarkomycin.

6.1 General notes.

^{1}H NMR spectra were obtained on one of the following instruments: Jeol-C60 (60MHz), Bruker WP80 (80MHz), Perkin Elmer R34 (220MHz) and Bruker AM250 (250MHz).

^{13}C NMR spectra were obtained on a Bruker WP80 instrument.

Chemical shifts are quoted in parts per million (ppm) on the δ scale using tetramethylsilane as internal reference.

Abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet.

Infrared spectra were obtained on a Pye-Unicam SP200 spectrophotometer or a Pye-Unicam SP3-100 spectrophotometer.

Frequencies (ν) are quoted in wavenumbers (cm^{-1}).

Mass spectral data were obtained on a AEI M59 or a Kratos MS25 intrument.

High resolution mass spectra (HRMS) were obtained at Sheffield University on a Kratos MS80 spectrometer (40eV).

Microanalyses were performed by Elemental Microanalyses Ltd, Beaworthy, Devon.

Column chromatography was carried out on Merck '7736' (15-50 m) or '7734' (70-230 mesh) silica gel. Eluting solvents were distilled prior to use.

Petroleum spirit refers to 40-60 petroleum spirit.

Melting points are uncorrected.

Dry tetrahydrofuran (THF) was obtained by distillation from potassium metal.

Dry diethyl ether was obtained by distillation from lithium aluminium hydride.

Dry diisopropylamine, benzene and dichloramethane were obtained by distillation from calcium hydride.

Acetone was dried over $MgSO_4$ and distilled.

Dry methanol was obtained by treating with sodium and distillation.

Pyridine was dried over potassium hydroxide.

6.2 Experimental methods.

Methylthiotosylate.

To a 1 litre 3 necked flask equipped with a mechanical stirrer and a thermometer, was added a solution of potassium hydroxide (56.1g, 1mol) in water (28ml). Hydrogen sulphide (generated with Kipp's apparatus) was bubbled through the stirred solution at 0°C for 30 minutes. The mixture was purged with nitrogen to remove excess hydrogen sulphide, diluted with water (117ml) and warmed to 55-60°C under nitrogen. p-Toluenesulphonyl chloride (90g, 0.47mol) was added portionwise to maintain the temperature at 55-60°C. After completion of the addition the mixture was warmed to 60°C for 1 hour and filtered under suction through a warm filter. Cooling of the filtrate in ice for several hours produced a mass of crystals which were filtered under suction and sucked dry. Drying was completed in a vacuum oven to produce potassium thiotosylate (62.0g, 58%) as white crystals.

To a mechanically stirred solution of potassium thiotosylate (60g, 0.27mol) in water (200ml) was added dimethyl sulphate (67g, 0.54mol). The mixture was stirred vigourously overnight at room temperature and then extracted with ether. Drying of the ether ($MgSO_4$), solvent removal and recrystallisation from benzene gave methylthiotosylate (27.0g, 50%) as white crystals m.pt. 54-55°C (lit.[142] 57.5-58.5°C).

NMR ($CDCl_3$,80MHz), δ_H : 2.47 (3H,s), 2.50 (3H,s), 7.25-7.95 (4H,m).

IR (KBr), ν : 1605, 1343 (s), 1150 (s),1083.

Methyl 6-(methylthio)-1,4-dioxaspiro[4.4]nonane-6-carboxylate (48)

A solution of methyl 2-oxocyclopentanecarboxylate (50g, 0.35mol) in THF (500ml) was added dropwise to a mechanically stirred suspension of sodium hydride (14.8g, of 60% dispersion in oil, 0.37mol, previously washed with hexane) in THF (100ml) at 0 C under a nitrogen atmosphere. After completion of the addition the solution was stirred at room temperature for 20 minutes and methylthiotosylate (73g, 0.36mol) in THF (200ml) was added over 5 minutes. The reaction mixture was stirred at room temperature for 4 hours during which time a white solid came out of solution. The mixture was filtered under suction and the filter cake thoroughly washed with ether. The solvent was removed from the filtrate and the residue partitioned between ether/water. The aqueous layer was extracted with ether and the combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed to give crude methyl 1-(methylthio)-2-oxocyclopentanecarboxylate 47 as a yellow oil (~100%).

A small portion of the sample was chromatographed on silica gel (elution with 10% ethyl acetate in petroleum spirit) to obtain an analytical sample.

NMR ($CDCl_3$,60MHz), δ_H: 2.08 (3H,s,SCH_3), 1.70-2.50 (6H, series of m), 3.70 (3H,s,OCH_3).

IR (neat) ν : 1755, 1740.

Microanalysis: Found C,51.24; H,6.54, $C_8H_{12}O_3S$ requires C,51.03; H,6.43.

A mixture of the crude product from above (65g, 0.35 mol), ethylene glycol (100ml) and p-toluenesulphonic acid (1.5g) were refluxed in benzene (600ml) under a Dean-Stark trap. After 48 hours GC analysis indicated almost complete disappearance of starting material. The cooled reaction mixture was washed once with saturated sodium bicarbonate solution and several times with water. Drying of the organic layer ($MgSO_4$), removal of the solvent and distillation gave 48 as a yellow oil (68g, 83% from 46). b.pt. 115-120°C at 5torr.

GC conditions: Column-10% Apiezon L, Temp. 200°C, carrier gas flow rate-40ml/min., retention times-starting material 4 minutes, product 9 minutes.

NMR ($CDCl_3$,60MHz), δ_H: 1.60-2.50 (9H, series of m,SCH_3 at 2.02), 3.63 (3H,s,OCH_3), 3.77-4.15 (4H,m,OCH_2CH_2O).

IR (neat) ν : 1730.

MS m/e : 232(M^+), (100%).

HRMS : Found 232.0777(M^+), $C_{10}H_{16}O_4S$ requires 232.0769.

Methyl 1,4-dioxaspiro[4.4]non-6-ene-6-carboxylate (45).

A suspension of sodium periodate (32.1g, 0.15mol) in water (200ml) was added dropwise to a mechanically stirred solution of sulphide 48 (34g, 0.15mol) in methanol (400ml) at 0°C. After completion of the addition the reaction

mixture was stirred at room temperature for 24 hours during which time a white solid came out of solution. The reaction mixture was filtered and the filter cake thoroughly washed with methanol. The solvent was removed from the filtrate at <40°C and the residue partitioned between water/dichloromethane. Extraction of the aqueous layer with dichloromethane, drying ($MgSO_4$) and removal of the solvent gave the crude product. Column chromatography on silica gel (elution with 40% ethyl acetate in petroleum spirit, changed to 10% methanol in ethyl acetate to elute product) gave a diastereomeric pair of sulphoxides as an oil (32.1g, 88%).

NMR ($CDCl_3$) δ_H : 1.65-2.75 (6H, series of m), 2.17 (3H,s, $SOCH_3$), 3.55-4.21 (4H,m,-OCH_2CH_2O-), 3.36 (3H,s,OCH_3).

IR (neat) ν : 1738, 1060.

The mixture of sulphoxides (32g, 0.13mol) was dissolved in toluene (500ml) containing powdered calcium carbonate (15g, 0.15mol) and refluxed for 16 hours. The cooled reaction mixture was filtered and the solvent removed. Column chromatography on silica gel (elution with 20% ethyl acetate in petroleum spirit containing 1% triethylamine) gave 45 as a yellow oil (20.7g, 87%).

NMR ($CDCl_3$,60MHz) δ_H: 1.90-2.52 (4H, series of m), 3.63 (s,3H,OCH_3), 3.81-4.26 (4H,m,-OCH_2CH_2O-), 6.95 (1H,t,vinyl H).

IR (neat) ν : 1725, 1638.

HRMS : Found 184.0732 (M^+), $C_9H_{12}O_4$ requires 184.0736

Methyl 7-(1-nitroethyl)-1,4-dioxaspiro[4.4]-nonane-6-carboxylate (51).

A mixture of ester 45 (6g, 32.6mmol), nitroethane (10.8ml, 150mmol) and tetramethyl guanidine (0.75g, 0.82ml, 6.5mmol) was stirred under a nitrogen atmosphere at room temperature for 3 days. The orange/red solution was acidified to pH 6 with 2N HCl and extracted with ether. The organic extracts were dried ($MgSO_4$) and the solvent removed. Column chromatography on silica gel (elution with 20% ethyl acetate in petroleum spirit) gave 51 (7.73g,92%) as a mixture of two isomers (1.6:1, stereochemistry undefined). The product could also be purified by distillation to give 51 in 90% yield. b.pt. 160-168°C at 3-4 torr.

Major isomer,high Rf, m.pt. 68-70°C (ether).

NMR ($CDCl_3$,80MHz) δ_H : 1.54 (3H,d,J=7Hz,$C\underline{H}_3CHNO_2$), 1.70-2.95 (6H, series of m), 3.71 (3H,s,$OC\underline{H}_3$), 3.95 (4H, broad s,-$OC\underline{H}_2C\underline{H}_2O$-), 4.50-4.95 (1H,m,$C\underline{H}NO_2$).

IR (KBr) ν : 1722, 1550, 1370,1078.

Microanalysis : Found C,51.01; H,6.66; N,5.36. $C_{11}H_{17}O_6N$ requires C,50.96; H,6.61; N,5.40.

Minor isomer, low Rf, m.pt. 66-68°C.

NMR ($CDCl_3$,80MHz) δ_H : 1.49 (3H,d,J=6Hz,$C\underline{H}_3CHNO_2$), 1.60-3.00 (6H, series of m), 3.74 (3H,s,$OC\underline{H}_3$), 3.95 (4H, broad s, $OC\underline{H}_2C\underline{H}_2O$-), 4.42-4.90 (1H,m,$C\underline{H}NO_2$).

IR (neat) ν : 1730, 1555, 1370.

Microanalysis: Found C, 51.51; H,6.71; N,5.34. $C_{11}H_{17}O_6N$ requires C,50.96; H,6.61; N,5.40.

Methyl 7-acetyl-1,4-dioxaspiro[4.4]nonane-6-carboxylate (52)

i) Using $TiCl_3$

To a stirred solution of sodium methoxide, (prepared from sodium (2.65g, o.115mol) in methanol (50ml)) was added a solution of nitroester 51 (29.5g, 0.11mol) in methanol (200ml). The mixture was stirred under a nitrogen atmosphere for 20 minutes. A solution of ammonium acetate (211g, 2.74mol) in water (690ml) was added to $TiCl_3$ solution (15% w/v, 456ml, 0.46mol) under a nitrogen atmosphere in a pressure equalised dropping funnel, and the mixture was rapidly added to the anion solution. After stirring for 1.5 hours at room temperature the reaction mixture was extracted several times with ether. The combined organic extracts were washed with saturated sodium bicarbonate solution (2x), and brine. Drying ($MgSO_4$) and solvent removal gave 52 as an inseparable mixture of two isomers (19.6g, 77%).

NMR ($CDCl_3$, 80MHz) δ_H : 1.52-2.50 (7H, series of m, CH_3CO at 2.15, 2.20), 2.90-3.53 (2H, series of m, $CHCO_2Me$ and $CHCOCH_3$), 3.69, 3.72 (2s, 3H, OCH_3), 3.97 (4H, broad s, $-OCH_2CH_2O-$).

IR (neat) ν : 1738, 1710, 1170.

ii) Using ozone

To a stirred solution of sodium methoxide, prepared by dissolving sodium (1.96g, 0.085mol) in methanol (50ml), was added a solution of nitro ester 51 (20g, 0.077mol) in methanol (250ml). The mixture was cooled to -78°C and O_3/O_2 was bubbled through until a pale blue colour persisted

(approx. 3 hours). The mixture was left at -78°C for 30 minutes and then purged with N_2 to remove excess O_3. Dimethyl sulphide (5ml) was added and the mixture allowed to reach room temperature overnight. The volatiles were removed on the rotary evaporator and the residue dissolved in ether. The ether was washed with water and saturated sodium chloride solution and dried ($MgSO_4$). Solvent removal and column chromatography on silica gel (elution with 20—40% ethyl acetate in petroleum spirit) gave starting material 51 (4.10g) and product 52 (10.97g, 63%). Yield based on recovered starting material = 80%.

Data-as above.

Methyl 2-acetyl-5-oxocyclopentane-1-carboxylate (41).

The acetal 52 (11.2g, 0.05mol) was stirred in a mixture of TFA-H_2O (2:1, 45ml) for 6 hours at room temperature. The bulk of the TFA was removed under vacuum and the residue partitioned between ether/saturated sodium chloride solution. The aqueous layer was extracted several times with ether and the combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 40% ethyl acetate in petroleum spirit) gave 41 as an off white solid which was washed with a small amount of ether to give pure 41 as a white solid (7.15g,79%). m.pt. 81-82°C.

NMR ($CDCl_3$,80MHz) δ_H : 1.60-2.70 (4H,series of m), 2.29

(3H,s,$C\underline{H}_3CO$), 3.55-3.90 (2H,m,$C\underline{H}COCH_3$ and $C\underline{H}CO_2Me$), 3.79 (3H,s,$OC\underline{H}_3$)

δ_C : 23.9,28.6,37.9,52.2,52.6,56.3,168.5,206.6,208.6.

IR (KBr) ν : 1760,1735,1705.

Microanalysis : Found C,58.74; H,6.62. $C_9H_{12}O_4$ requires C,58.68; H,6.57.

Methyl 4-methyl-8-oxo-3-(phenylthio)bicyclo[3.3.0]oct-3-ene-1-carboxylate (42a).

To a suspension of sodium hydride (60% dispersion in mineral oil, 598mg, 15mmol, previously washed with petroleum spirit) in THF (5ml) at 0°C under N_2 was added a solution of diketo ester 41 (2.5g, 13.6mmol) in THF (60ml). The mixture was stirred at room temperature for 15 minutes and vinyl phosphonium salt 38a (7.3g, 13.9mmol) was added. After stirring at room temperature for 20 minutes the mixture was refluxed for 1 hour. The THF was removed on the rotary evaporator and the residue partitioned between ether/2N HCl. The product was extracted with ether/ethyl acetate and the combined organic extracts were washed with water and saturated sodium chloride solution. Drying ($MgSO_4$) and solvent removal gave an oil which was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum spirit) to give 42a as a white solid (3.40g,83%), m.pt. 79-81°C.

NMR ($CDCl_3$,80MHz) δ_H : 1.88 (3H,s,$C\underline{H}_3C=C$), 2.12-2.58 (4H, series of m), 2.75 (1H,d,J=20Hz,AB system), 3.08 (1H, d,J=20Hz,AB system), 3.68 (4H,s,$OC\underline{H}_3$ and allylic C$\underline{H}$),

7.15-7.33 (5H,m,$SC_6\underline{H}_5$).

δ_C : 13.1(q),23.2(t),36.0(t),42.9(t),52.5(q),57.1(d), 63.2(s),126.8(d),127.4(s),129.0(d),130.4(d),133.7(s), 141.0(s),170.4(s),215.0(s).

IR (KBr) ν : 1750, 1715, 1635(w), 1580(w).

Microanalysis : Found C,67.49; H,6.03; S,10.33 $C_{17}H_{18}O_3S$ requires C,67.52; H,6.00; S,10.61.

Methyl 4-methyl-3-(methylthio)-8-oxobicyclo[3.3.0]oct-3-ene-1-carboxylate (42b).

Treatment of diketo ester 41 (3g, 16.3mmol) with NaH (716mg, 60% dispersion in mineral oil, 17.9mmol) and vinyl phosphonium salt 38b (7.25g, 19.56mmol) in a similar manner to that described above, followed by work up and column chromatography on silica gel (elution with 30% ethyl acetate in petroleum spirit) gave 42b as an oil (3.78g, 97%).

NMR ($CDCl_3$ 80MHz) δ_H : 1.60-1.78 (3H, unresolved m,$C\underline{H}_3C{=}C$), 2.00-2.58 (4H,series of m), 2.23 (3H,s,$SC\underline{H}_3$), 2.72-3.38 (2H, series of m, allylic $C\underline{H}_2$), 3.50-3.70 (1H, broad unresolved signal, allylic C$\underline{H}$), 3.72 (3H,s,$OC\underline{H}_3$).

δ_C : 12.6(q),14.4(q),23.1(t),35.8(t), 42.0(t),52.6(q),57.2(d),63.2(s),129.2(s),133.8(s), 170.5(s),215.9(s).

IR (neat) ν : 1745, 1722, 1620(w).

MS m/e : 240(M^+), 181(M-CO_2Me).

Microanalysis : Found C,60.15; H,6.80 $C_{12}H_{16}O_3S$ requires C,59.99; H,6.71.

6-Methyl-7-(phenylthio)bicyclo[3.3.0]oct-6-en-2-one (60a).

Finely powdered sodium cyanide (0.665g, 13.6mmol) was dissolved in HMPA (60ml) at 75°C under a nitrogen atmosphere. The -keto ester 42a (2g, 6.6mmol) in HMPA (15ml) was added dropwise to the stirred solution. After completion of the addition stirring was continued at 75°C for 1 hour. The mixture was cooled and poured into 2N HCL (300ml) and extracted with carbon tetrachloride. The combined extracts were thoroughly washed with 2N NaOH (2x, to reverse any cyanohydrim formation), dried ($MgSO_4$) and the solvent removed. Column chromatography on silica gel (elution with 10% ethyl acetate in petroleum spirit) gave 60a as a colourless oil (1.27g, 79%).

NMR ($CDCl_3$, 220MHz) δ: 1.89 (3H, s, $CH_3C=C$), 2.02-2.38 (4H, series of m), 2.50-2.73 (3H, m, allylic CH_2 and angular CH), 3.47 (1H, broad s, allylic CH), 7.10-7.30 (5H, m, SC_6H_5).

IR (neat) ν : 3060, 1740, 1627(w), 1585.

Microanalsis : Found C,73.40; H,6.69. $C_{15}H_{16}OS$ requires C,73.73; H,6.60.

6-Methyl-7-(methylthio)bicyclo[3.3.0]oct-6-en-2-one (60b)

Treatment of keto ester 42b (3.78g, 15.7mmol) with NaCN (1.54g, 31.5mmol) in a similar manner to that above followed by work up and column chromatography on silica gel (elution with 25% ethyl acetate in petroleum spirit) gave 60b as a colourless oil (2.37g, 82%).

NMR ($CDCl_3$,80MHz) δ_H : 1.82 (3H,s,$C\underline{H}_3C$=C), 1.94-2.16 (4H, m), 2.19 (3H,s,$SC\underline{H}_3$), 2.60-2.82 (3H,m,allylic $C\underline{H}_2$ and angular C<u>H</u>), 3.25-3.55 (1H,broad unresolved signal, allylic C<u>H</u>).

IR (neat) ν : 1730, 1615(w).

Microanalsis : Found C,66.08; H,7.83. $C_{10}H_{14}OS$ requires C,65.89; H,7.74.

exo-2,6-Dimethyl-7-phenythiobicyclo[3.3.0]oct-6-en-endo-2-ol (61a)

The ketone 60a (400mg, 1.64mmol) was dissolved in dry ether (8ml) and cooled to -78°C under a nitrogen atmosphere. Methyl lithium (2.1ml of 1.6M solution in diethyl ether, 3.28mmol) was added. After stirring for 10 minutes at -78°C infrared analysis indicated that the reaction had gone to completion (disappearance of C=Ostr.). The reaction was worked up by pouring into 2N HCl and extracting with ether. The combined organic extracts were washed with saturated sodium bicarbonate solution, dried ($MgSO_4$), and the solvent removed to give pure 61a as a slightly yellow oil (356mg, 84%).

NMR ($CDCl_3$,220MHz) δ_H : 1.28 (3H,s,$C\underline{H}_3COH$), 1.40-2.10 (8H,series of m,$C\underline{H}_3C$=C at 1.83, O<u>H</u> at 1.55), 2.40-2.55 (3H,m), 3.20 (1H,broad unresolved signal,allylic C<u>H</u>), 7.10-7.35 (5H,m,$SC_6\underline{H}_5$).

IR (neat) ν : 3500, 1640(w), 1595.

exo-2,6-Dimethyl-7-methylthiobicyclo[3.3.0]oct-6-en-endo-2-ol (61b)

Treatment of ketone 60b (154mg, 0.82mmol) with methyl lithium (1.54ml of 1.6M solution in diethyl ether, 2.46mmol) in a similar manner to that above, followed by work up and column chromatography on silica gel (elution with 10% ethyl acetate in petroleum spirit) gave 61b as a colourless oil (122mg, 75%).

NMR ($CDCl_3$, 80MHz) δ_H : 1.29 (3H,s,$C\underline{H}_3COH$), 1.40-2.0 (8H, series of m, O$\underline{H}$ at1.61,$C\underline{H}_3C{=}C$ at 1.70), 2.10-2.70 (3H, series of m), 2.28 (3H,s,$SC\underline{H}_3$), 3.10 (1H,broad unresolved signal, allylic C$\underline{H}$).

IR (neat) : 3440, 1625(w).

Microanalysis : Found C,66.28; H,9.41. $C_{11}H_{18}OS$ requires C,66.63; H,9.15.

endo-6-Hydroxy-exo-2,exo-6-dimethylbicyclo[3.3.0]octan-3-one. (56)

Mercuric chloride (413mg, 1.52mmol) in acetonitrile: water (3:1, 3ml) was added to a solution of alcohol 61b (100mg, 0.51mmol) in the same solvent (3ml). The mixture was refluxed for 1 hour, cooled and filtered through Hyflo super cel. The filter aid was washed thoroughly with ether and the combined filtrate and washings were poured into a separating funnel containing aqueous sodium sulphide. The aqueous layer was extracted with ether and the combined extracts were washed with water and dried ($MgSO_4$). Solvent removal and column chromatography on silica gel (elution with 20% ethyl acetate in petroleum spirit) gave 56 as white

crystals (59mg, 69%), m.pt. 57.5-58.5°C (lit[73c] 58-59°C).

NMR ($CDCl_3$, 80MHz) δ_H : 1.05 (3H,d,J=8Hz,$C\underline{H}_3CC=O$), 1.32 (3H,s,$C\underline{H}_3COH$), 1.55 (1H,broad s,O$\underline{H}$), 1.70-2.50 (9H, series of m).

IR (KBr) ν : 3500, 1735.

Methyl 4-methyl-8-oxo-7-(phenylseleno)-3-(phenylthio)-bicyclo[3.3.0]oct-3-ene-1-carboxylate (81).

A solution of diisopropylamine (37mg, 0.051ml, 0.364mmo in THF (2ml) was cooled to 0°C under nitrogen and treated with n-butyl lithium (0.238ml of 1.53M solution in hexane, 0.364mmol). After stirring at 0°C for 20 minutes the mixture was cooled to -78°C and a solution of ketone 42a (100mg, 0.331mmol) in THF (3ml) was added via a canula. The mixture was stirred for 30 minutes at -78°C and phenylselenyl chloride (190mg, 0.993mmol) in THF (3ml) was added. Stirring was continued at -78 C for 15 minutes and the mixture was poured into a separating funnel containing ether/2N HCl. The organic layer was washed successively with water, saturated sodium bicarbonate solution and saturated sodium chloride solution. Drying ($MgSO_4$), solvent removal and column chromatography on silica gel (elution with 10% ethyl acetate in petroleum spirit) gave the product 81 (116mg, 77%) as a mixture of two isomers.

NMR ($CDCl_3$, 80MHz) δ_H : 1.87 (3H,broad s,$C\underline{H}_3C=C$), 2.02-3.25 (4H,series of m), 3.50-3.85 (4H,m,O$C\underline{H}_3$ at 3.57 and 3.69), 3.87-4.10 (1H,m,C$\underline{H}$SePh), 7.00-7.75 (10H,m, $SC_6\underline{H}_5$ and $SeC_6\underline{H}_5$).

IR (neat) ν : 1755, 1730, 1590.

MS m/e : 458(M^+,^{80}Se), 456(M^+,^{78}Se), 301(M-SePh).

Methyl 4-methyl-8-oxo-3,7-bis(phenylthio)bicyclo[3.3.0]-oct-3-ene-1-carboxylate (82).

A solution of diisopropylamine (203mg, 0.281ml, 2mmol) in THF (4ml) was cooled to 0°C under N_2 and treated with n-butyl lithium (1.31ml of 1.53M solution in hexane, 2mmol). After stirring at 0°C for 20 minutes the mixture was cooled to -78°C and a solution of ketone 42a (302mg, 1mmol) in THF (4ml) was added. The mixture was stirred for 30 minutes at -78°C and then transferred via a canula into a solution of diphenyl disulphide (240mg,1.1mmol) in HMPA (2ml) at -78°C under nitrogen. After stirring at -78°C for 1 hour the mixture was poured into ether/2N HCl. The aqueous layer was extracted with ether and the combined organic extracts were washed with 2N HCl and saturated sodium bicarbonate solution. Drying ($MgSO_4$), solvent removal and column chromatography on silica gel (elution with 5% ethyl acetate in petroleum spirit) gave 82 (172mg, 42%) as a mixture of two isomers, (approx. 1:1 ratio).

NMR ($CDCl_3$,220MHz) δ_H : 1.88 (3H,broad s,$C\underline{H}_3C$=C), 2.00-3.15 (4H,series of m), 3.30-4.05 (5H,series of m,$OC\underline{H}_3$ at 3.55 and 3.68), 7.10-7.70 (10H,m,$SC_6\underline{H}_5$).

MS m/e : 410(M^+).

Attempted preparation of 6-methyl-3-(phenylseleno)-7-(phenylthio)bicyclo[3.3.0]oct-6-en-2-one (79) : Treatment of 81 with NaCN.

Finely powdered NaCN (32mg, 0.66mmol) was dissolved in HMPA (5ml) at 75°C under N_2. The keto ester 81 (150mg, 0.33mmol) in HMPA (1ml) was added and the mixture was stirred at 75 C for 1.5 hours. After cooling the mixture was poured into 2N HCl and extracted with CCl_4. The organic extracts were washed with 2N NaOH, dried ($MgSO_4$) and evaporated. The major product was isolated by column chromatography on silica gel (elution with 10% ethyl acetate in petroleum spirit) to give a yellow oil.
Data - as for 60a

6-Methyl-7-(phenylthio)bicyclo[3.3.0]octa-3,6-dien-2-one (78)

To a solution of ketone 60a (500mg, 2.05mmol) in dry dichloromethane (8ml) was added freshly distilled trimethylsilyl chloride (0.39ml, 3.08mmol) and DBU (0.52ml, 3.49mmol). The mixture was refluxed for 1.5 hours under nitrogen, cooled and diluted with pentane (10ml). The organic solution was washed with 1% HCl, saturated sodium bicarbonate solution, dried (Na_2SO_4) and the solvent removed to give the crude siyl enol ether 83 (630mg).

To a solution of crude 83 (630mg, 2 mmol) in dry acetonitrile under a N_2 atmosphere was added palladium acetate (225mg, 1mmol) and p-benzoquinone (109mg, 1mmol). After leaving overnight at room temperature the reaction mixture was filtered and the solvent removed. Column chromatography on silica gel (elution with 4% diethyl ether

in petroleum spirit) gave 78 as a pale yellow oil (496mg, 69% from 60a.

NMR ($CDCl_3$, 80MHz) δ_H : 1.97 (3H,s,CH_3C=C), 2.45-3.15 (3H, m,allylic CH_2 and angular CH), 3.92 (1H,broad s, allylic CH), 6.15 (1H,dd,J=6Hz,2Hz), 7.22 (5H,s,SC_6H_5), 7.85 (1H,dd,J=6Hz,3Hz).

IR (neat) ν : 3110(w), 1720, 1645(w), 1595.

Microanalysis : Found C,74.25; H,6.02. $C_{15}H_{14}OS$ requires C,74.34; H,5.82.

6-[2-(1,3-dithianylidene)]-2-methyl-3-(phenylthio)bicyclo[3.3.0] octa-2,7-diene. (86)

A solution of 2-trimethylsilyl-1,3-dithiane (85mg, 0.43mmol) in THF (2ml) was cooled to 0°C under N_2 and treated with n-butyl lithium (0.31ml of 1.48M solution in hexane, 0.45mmol). After stirring at 0°C for 15 minutes, dry hexane (3.5ml) was added and the solution cooled to -78°C. The enone 78 (100mg, 0.41mmol) in hexane/THF (1.8:1, 3ml) was added and stirring was continued at -78°C for 2 hours. Work up involved adding saturated brine to the reaction mixture and extraction with ether. Drying $MgSO_4$) and removal of the solvent, followed by column chromatography on silica gel (elution with petroleum spirit) gave the product 86 as a white solid (83mg, 58%) which turned brown after standing at room temperature for a few days.

NMR ($CDCl_3$, 80MHz) δ_H : 1.90 (3H, broad s, $C\underline{H}_3C{=}C$), 2.00-2.50 (2H, m), 2.35-2.50 (1H, m), 2.70-3.20 (5H, series of m), 3.45-3.80 (1H, m), 3.80-4.05 (1H, m), 6.27 (1H, dd, J=6Hz, 2.5Hz), 6.55 (1H, dd, J=6Hz, 2Hz), 7.20 (5H, s, $SC_6\underline{H}_5$).
IR (KBr) ν : 1645, 1585.

6-Methyl-7-(methylthio)bicyclo[3.3.0]octa-2,6-diene-2-carbonitrile (89)

A solution of ketone 60b (495mg, 2.69mmol) in ethanol (10ml) was cooled in ice and treated with powdered sodium cyanide (784mg, 16mmol) and acetic acid (0.5ml). The mixture was stirred at 0°C for 30 minutes and then at 40-50°C for 4 hours. Work up involved adding 3 drops of conc. HCl to the reaction mixture and allowing it to stand for 10 minutes. Dilution with water and extraction with ether followed by washing of the organic extracts with dil. HCl, drying ($MgSO_4$) and removal of the solvent gave crude 88 which was used directly in the next stage.

The crude cyanohydrin mixture 88 from above was dissolved in pyridine (5ml) and treated with $POCl_3$ (1ml). The mixture was stirred at 50°C for 3 hours, cooled and poured into ice/water containing conc. HCl. The aqueous mixture was extracted with ether and washed successively with water, saturated sodium bicarbonate solution and brine. Drying ($MgSO_4$) and solvent removal gave a brown oil. Column chromatography on silica gel (elution with 5% ethyl acetate in petroleum spirit) gave 89 as a white solid (358mg, 69%), m.pt. 68-70.5°C (ether).

NMR ($CDCl_3$,80MHz)δ_H : 1.68 (3H,broad s,$C\underline{H}_3C{=}C$), 2.12 (3H, s,$SC\underline{H}_3$), 2.45-2.90 (4H,series of m, allylic $C\underline{H}_2$'s), 3.20-3.65 (2H,broad unresolved signal,angular C<u>H</u>'s), 6.50 (1H,m,vinyl C<u>H</u>).

IR (KBr) ν : 2220, 1633, 1617.

Microanalysis : Found C,69.30; H,6.79; N,7.32.

$C_{11}H_{13}NS$ requires C,69.06; H,6.85; N,7.32.

Methyl exo-6-methyl-7-oxobicyclo[3.3.0]oct-2-ene-2-carboxylate (90).

To a solution of 89 (358mg, 1.87mmol) in methanol (5ml) was added conc.H_2SO_4 (2ml). The mixture was refluxed for 8 hours, cooled, poured into water and extracted with ether. Washing of the combined organic extracts with saturated sodium bicarbonate solution, drying ($MgSO_4$) and solvent removal gave the crude product. Column chromatography on silica gel (elution with 10% ethyl acetate in petroleum spirit) gave 90 as an oil (175mg,48%).

NMR ($CDCl_3$,80MHz) δ_H : 1.10 (3H,d,J=6Hz,$C\underline{H}_3CCO$), 1.75-2.20 (1H,m), 2.25-3.10 (5H,series of m), 3.50 (1H,broad unresolved signal), 3.75 (3H,s,$OC\underline{H}_3$), 6.80 (1H,m, vinyl CH).

IR (neat) ν : 1740, 1715, 1630.

HRMS : Found 194.0950, $C_{11}H_{14}O_3$ requires 194.0943.

Treatment of 90 with sodium methoxide.

The ketone 90 (26mg, 0.13mmol) was stirred in a solution of sodium methoxide in methanol (0.5M, 2ml) at room temperature overnight. The mixture was acidified with 2N HCl and extracted with ether. The organic layer was washed with water and saturated sodium chloride solution, dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 10% ethyl acetate in petroleum spirit) gave 90 (12mg) whose NMR spectral data were identical to that above. There was also eluted 3mg of a minor product.

Minor product : NMR ($CDCl_3$,80MHz) δ_H : 1.06 (3H,d,J=6Hz, CH_3CO), 1.60-3.00 (9H,series of m), 3.26 (3H,s,OCH_3), 3.70 (3H,s,ester OCH_3) 4.0-4.30 (1H,m,CHOMe).

Methyl 7-endo-hydroxy-6-exo-methylbicyclo[3.3.0]oct-2-ene-2-carboxylate (91).

A solution of ketone 90 (610mg, 3.14mmol) in methanol (10ml) was cooled in an ice/salt bath and $NaBH_4$ (178mg, 4.72mmol) was added. After stirring for 10 minutes the reaction mixture was poured into ether/2N HCl and extracted with ether. The organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed. Column chromatography on silica gel (elution with 10-20% ethyl acetate in petroleum spirit) gave 91 as a colourless oil (505mg, 82%).

NMR ($CDCl_3$, 80MHz) δ_H : 1.06 (3H,d,J=6Hz,CH_3), 1.15-1.65 (2H,m), 1.95 (1H,s,OH), 2.00-2.95 (4H,series of m), 3.00-3.35 (1H,m), 3.45-3.85 (1H,m), 3.73 (3H,s,OCH_3), 6.65 (1H,vinyl CH).

IR (neat) ν : 3450, 1710, 1630.

Microanalysis : Found C,67.04; H,8.52. $C_{11}H_{16}O_3$ requires C,67.32; H,8.22.

6-Carbomethoxy-exo-2-methylbicyclo[3.3.0]oct-6-en-exo-3-yl acetate. (92)

To a solution of alcohol 91 (409mg, 2.09mmol) in pyridine (5ml) was added methane sulphonyl chloride (0.244ml, 3.13mmol). The mixture was stirred at room temperature for 1 hour and poured into ether/0.5N HCl. The aqueous layer was extracted with ether and the combined extracts were washed with 0.5N HCl (3x) and brine. Drying ($MgSO_4$) and solvent removal gave the crude mesylate (539mg) which was used directly in the next stage.

To a solution of the crude mesylate (539mg, 1.97mmol) in dry acetone under a nitrogen atmosphere was added tetra n-butyl ammonium acetate (1.8g, 6mmol) and the mixture was refluxed overnight. The acetone was removed on the rotary evaporator and the residue partitioned between ether/water. The aqueous layer was extracted with ether and the combined extracts were washed successively with water and brine. Drying ($MgSO_4$), solvent removal and column chromatography on silica gel (elution with 5% ethyl acetate in petroleum spirit) gave 92 as a colourless oil (368mg, 74% from 91).

NMR ($CDCl_3$,80MHz) δ_H : 0.98 (3H,d,J=7Hz,$C\underline{H}_3$), 1.45-2.90 (6H,series of m), 2.05 (3H,s,$C\underline{H}_3C$=O), 3.30-3.60 (1H, unresolved m), 3.72 (3H,s,$OC\underline{H}_3$), 5.02 (1H,m,C<u>H</u>OAc), 6.64 (1H,m,vinyl C<u>H</u>).

IR (neat) ν : 1740, 1720, 1635.

Microanalysis : Found C,65.72; H,7.99. $C_{13}H_{18}O_4$ requires C,65.53; H,7.61.

6-Carbomethoxy-exo-2-methylbicyclo[3.3.0]oct-7-en-exo-3-yl acetate (76).

A solution of diisopropylamine (187mg, 0.259ml, 1.85mmol) in the THF (5ml) was cooled to 0°C under N_2 and treated with n-butyl lithium (1.28ml of 1.44M solution in hexane, 1.85mmol). After stirring at 0°C for 15 minutes the mixture was cooled to -78°C and added via a canula to a solution of the ester 92 (110mg, 0.46mmol) and HMPA (331mg, 0.322ml, 1.85mmol) in THF (3ml) also maintained at -78°C. The resulting yellow solution was stirred at -78°C for 10 minutes and quenched by adding methanol (1ml) and stirring for a further 15 minutes at -78°C. The reaction mixture was poured into water and extracted with ether. The organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed. Column chromatography on silica gel (elution with 5% ethyl acetate in petroleum spirit) gave 76 as an oil (43mg, 39%), and as a 5:1 mixture of starting material: product.

Data for product :

NMR ($CDCl_3$,80MHz) δ_H : 0.99 (3H,d,J=7Hz,$C\underline{H}_3$), 1.35-2.30 (3H,series of m), 2.02 (3H,s,$C\underline{H}_3C$=O), 2.70-2.90 (3H,

series of m), 3.68 (3H,s,$OC\underline{H}_3$), 5.13 (1H,q,$C\underline{H}OAc$), 5.62 (1H,m), 5.81 (1H,m).

IR (neat) ν : 1740, 1640(w).

Methyl 4,7,7-trimethyl-8-oxo-3-(phenythio)bicyclo[3.3.0]oct-3-ene-1-carboxylate (103).

To a stirred suspension of potassium t-butoxide (3.42g, 30.5mmol) in THF (20ml) at -78°C under nitrogen was added a solution of ketone 42a (4g, 13.3mmol) in THF (60ml). After stirring the deep yellow solution at -78°C for 10 minutes, iodomethane (18.5g, 130mmol) was added via a syringe and stirring was continued at 0°C for 1 hour. The reaction mixture was poured into a separating funnel containing ether/saturated ammonium chloride solution. Drying ($MgSO_4$) of the organic layer and solvent removal gave the crude product. Column chromatography on silica gel (elution with 5% ethyl acetate in petroleum spirit) gave 103 as a colourless oil (3.62g, 83%).

NMR ($CDCl_3$,80MHz) δ_H : 1.04 (3H,s,$C\underline{H}_3$), 1.19 (3H,s,$C\underline{H}_3$), 1.87 (3H,broad s,$C\underline{H}_3C=C$), 2.00-2.42 (2H,m), 2.57-3.26 (2H,m), 3.40-3.65 (1H,m,allylic $C\underline{H}$), 3.69 (3H,s,$OC\underline{H}_3$), 7.22 (5H,s,$SC_6\underline{H}_5$).

IR (neat) ν : 1740,1730,1587.

MS m/e : 330(M^+,100%), 271(M-CO_2Me), 214.

HRMS : Found 330.1279 $C_{19}H_{22}O_3S$ requires 330.1289.

3,3,6-Trimethyl-7-(phenylthio)bicyclo[3.3.0]oct-6-en-2-one (104).

To a stirred solution of powdered sodium cyanide (1.47g, 30mmol) in HMPA (120ml) at 75°C under nitrogen was added a solution of -keto ester 103 (4.67g, 14.2mmol) in HMPA (30ml). The mixture was stirred at 75°C for 2 hours, cooled and poured into a separating funnel containing 2N HCl (500ml) (fume hood!). The product was extracted into carbon tetrachloride and the organic extracts were thoroughly washed with 2N sodium hydroxide (2x). Drying ($MgSO_4$), solvent removal and column chromatography on silica gel (elution with 10% ethyl acetate in petroleum spirit) gave 104 as an oil (3.31g, 86%).

NMR ($CDCl_3$, 80MHz) δ_H : 1.02 (3H,s,CH_3), 1.10 (3H,s,CH_3), 1.75-2.10 (5H,m,$CH_3C{=}C$ at 1.87), 2.50-3.10 (3H,series of m), 3.14-3.55 (1H,broad unresolved signal, allylic CH), 7.21 (5H,s,SC_6H_5).

IR (neat) ν : 1730, 1580(w).

MS m/e : 272(M^+,100%), 188, 57.

HRMS : Found 272.1228 $C_{17}H_{20}OS$ requires 272.1235.

2,7,7-trimethyl-3-(phenylthio)bicyclo[3.3.0]oct-2-ene (105)

Ketone 104 (3.20g, 11.8mmol), potassium hydroxide (1.99g, 35.4mmol) and hydrazine hydrate (1.18g, 23.6mmol) were refluxed together in diethylene glycol (20ml). After 1 hour the condensor was removed and the reaction temperature allowed to reach 200°C. Refluxing was continued for a further 3 hours. The cooled reaction mixture was acidified

with conc. HCl and extracted with benzene. The combined organic extracts were washed with saturated sodium chloride solution dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 10% ethyl acetate in petroleum spirit) gave 105 as a colourless oil (2.85g, 94%).

NMR ($CDCl_3$, 80MHz) δ_H : 0.98 (3H,s,$C\underline{H}_3$), 1.05 (3H,s,$C\underline{H}_3$), 1.0-2.30 (8H,series of m, $C\underline{H}_3C{=}C$ at 1.80), 2.49-2.90 (2H,m), 2.95-3.40 (1H,m,allylic C$\underline{H}$), 7.22 (5H,s,$SC_6\underline{H}_5$).

IR (neat) ν : 1590, 1475, 1450.

Microanalysis : Found C,78.87; H,8.62 $C_{17}H_{22}S$ requires C,79.01; H,8.58.

2,7,7-trimethyl-3-(phenylsulphonyl)bicyclo[3.3.0]oct-2-ene (108)

To a stirred solution of sulphide 105 (2.77g, 10.7mmol) in dichloromethane (80ml) at -78°C was added m-chloroperbenzoic acid (95%, 4.88g, 26.8mmol). The reaction mixture was stirred at -78°C for 15 minutes and at 0°C for 2 hours and then poured into a separating funnel containing 10% aqueous sodium sulphite. The aqueous layer was extracted with ether and the combined organic extracts were washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Solvent removal and column chromatography on silica gel (elution with 20% ethyl acetate in petroleum spirit) gave 108 as a colourless oil (3.05g, 98%).

NMR ($CDCl_3$) δ_H : 0.90(3H,s,$C\underline{H}_3$), 0.98 (3H,s,$C\underline{H}_3$), 1.0-1.90 (4H,series of m), 2.12 (3H,broad s,$C\underline{H}_3C{=}C$), 2.20-2.90 (3H,series of m), 3.0-3.35 (1H,m,allylic C$\underline{H}$), 7.40-7.97 (5H,m,$SO_2C_6\underline{H}_5$).

IR (neat) ν : 1630, 1304(s), 1150(s).

Microanalysis : Found C,70.39; H,7.77 $C_{17}H_{22}OS$ requires C,70.30; H,7.64.

Attempted addition of Me_2CuLi to 108.

Copper(I) iodide (657mg, 3.45mmol) was placed in a 3 necked round bottom flask which was flame dried under N_2. Dry ether (10ml) was added and the mixture cooled to 0°C. Methyl lithium (4.31ml of 1.6M solution in diethyl ether 6.90mmol) was added. After stirring for 5 minutes at 0°C, vinyl sulphone 108 (100mg, 0.35mmol) in dry ether (1ml) was added. The reaction mixture was stirred at 0°C for 3 hours and then overnight at room temperature. The mixture was poured into saturated ammonium chloride solution. Extraction with ether, drying ($MgSO_4$) and solvent removal gave the crude product. Column chromatography on silica gel (elution with 5% ethyl acetate in petroleum spirit) gave a product with the following spectral data:

NMR ($CDCl_3$,80MHz) δ_H : 0.90,0.94,0.98,1.01 (6H,4 s), approx. 0.80-3.40 (8H,series of m), 3.95-4.30 (1H,m), 4.85-5.35 (2H,series of m), 7.45-8.05 (5H,m).

IR (neat) ν : 1655(w), 1310(s), 1145(s).

3,7,7-Trimethyl-2-methylene-3-(phenylsulphonyl)bicyclo[3.3.0]octane (112)

To a solution of vinyl sulphone 108 (100mg, 0.36mmol) in THF (6ml) at -78 C°under nitrogen was added n-butyl lithium (0.273ml of 1.44M solution in hexane, 0.39mmol).

The deep orange solution was stirred for 10 minutes at -78°C and methyl iodide (0.07ml, 1.07mmol) was added. After stirring for a further 10 minutes at -78°C the reaction mixture was poured into saturated NH_4Cl solution. Extraction with ether, drying ($MgSO_4$) and solvent removal gave the crude product. Column chromatography on silica gel (elution with 5% ethyl acetate in petroleum spirit) gave 115 as an oil (82mg, 79%).

NMR ($CDCl_3$, 80MHz) δ_H : 0.90 (6H,s,CH_3CCH_3), 1.0-1.48 (4H, series of m), 1.56 (3H,s,CH_3), 1.70-2.70 (3H,series of m), 2.80-3.50 (1H,m,allylic CH), 5.13 (1H,s,vinyl CH), 5.50 (1H,s,vinyl CH), 7.30-8.10 (5H,m,$SO_2C_6H_5$).

IR (neat) ν : 1640(w), 1582(w), 1300(s), 1145(s).

Microanalysis : Found C,71.53; H,8.25 $C_{18}H_{24}O_2S$ requires C,71.01; H,7.95.

7,7-Dimethyl-2-methylene-3-(phenylsulphonyl)bicyclo[3.3.0] oct-3-yl methanol (115)

To a solution of vinyl sulphone 108 (539mg, 1.86mmol) in THF (10ml) at -78°C under nitrogen was added n-butyl lithium (1.24ml of 1.58M solution in hexane 1.95 mmol). The dark coloured solution was vigourously stirred at -78°C for 15 minutes and formaldehyde gas (prepared by heating p-formaldehyde to 160°C) was passed into the reaction flask via a side arm tube. After 1 hour 2N HCl was added and the mixture stirred vigourously. The aqueous layer was extracted with ether and the combined organic extracts were washed with saturated aqueous sodium chloride, dried

($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 25% ethyl acetate in petroleum spirit) gave starting vinyl sulphone 108 (128mg) and the title compound 115 (375mg, 63%) as a mixture of two isomers. Yield based on recovered starting material = 83%.

NMR ($CDCl_3$,80MHz) δ_H : 0.85,0.92,1.01 (6H,3 s,gem CH_3), 0.50-3.40 (9H,series of m,OH at 2.78), 3.45-4.20 (2H, series of s,diastereotopic CH_2OH), 4.55-5.43 (2H,series of signals; 4.55(d,J=2Hz), 5.06(d,J=2Hz), 5.68(s), 5.43 5.43(s), vinyl CH_2 for both isomers), 7.35-8.20 (5H, m,$SO_2C_6H_5$).

IR (neat) ν : 3550(br), 1460, 1300(s), 1145(s).

2,7,7-Trimethylbicyclo[3.3.0]oct-2-en-3-yl methanol (116)

The alcohol mixture 115 (374mg, 1.17mmol) and Na_2HPO_4 (667mg, 4.68mmol) were stirred at 0°C in dry methanol and treated with 6% sodium amalgam (2.4g). After 1 hour at 0°C another portion of 6% sodium amalgam (2.4g) was added and stirring was continued for a further hour. The reaction mixture was carefully poured into water and the product was extracted into ether. The combined organic layers were washed with saturated aqueous sodium chloride,dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 15% ethyl acetate in petroleum spirit) gave 116 as a colourless oil (131mg, 62%).

NMR ($CDCl_3$,80MHz) δ_H : 0.93 (3H,s,gem CH_3), 1.02 (3H,s, gem CH_3), 0.80-1.35 (2H,m), 1.40-1.90 (6H,m,OH at 1.56, $CH_3C=C$ at 1.61), 1.95-2.35 (1H,m), 2.45-3.33 (3H,m, allylic CH_2 and CH), 4.13 (2H,s,CH_2OH).

IR (neat) ν : 3370(br), 2960, 2880.

Microanalysis : Found C,79.27; H,11.30 (best obtained)

$C_{12}H_{20}O$ requires C,79.94; H,11.18.

2,7,7-Trimethylbicyclo[3.3.0]oct-2-ene-3-carbaldehyde (114)

The alcohol 116 (130mg, 0.72mmol) was stirred at room temperature in dichloromethane (3ml) and treated with pyridinium chlorochromate (388mg, 1.8mmol). After stirring at room temperature for 2.5 hours, ether (approx. 5ml) was added and the mixture was stirred for several minutes. The solution was decanted off and the chronium salts were washed with several small portions of ether. The combined ether solution and washings were evaporated, and chromatographed on silica gel (elution with 5% ethyl acetate in petroleum spirit) to give the aldehyde 114 as an oil (69mg, 54%) which appeared to be unstable to storage at room temperature.

NMR ($CDCl_3$,80MHz) δ_H : 0.92 (3H,s,gem CH_3), 1.04 (3H,s, gem CH_3), 0.80-1.40 (2H,m), 1.60-3.00 (8H,series of m, $CH_3C{=}C$ at 2.06), 3.10-3.45 (1H,m,allylic CH), 9.97 (1H,s,CHO).

IR (neat) ν : 2920, 2740, 1660(s), 1625(w).

Attempted conjugate addition of nitroethane to 114

To a solution of aldehyde 114 (69mg, 0.39mmol) in nitroethane (0.5ml) under nitrogen was added tetramethylguanidine (12mg, 0.013ml, 0.1mmol). After stirring for two days at room temperature TLC analysis indicated that starting material was the major component of the reaction

mixture. Another portion of tetramethylguanidine (0.02ml, 0.15mmol) was added and stirring was continued for a further 24 hours. The reaction mixture was partitioned between ether/2NHCl and the aqueous layer was extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated Column chromatography on silica gel (elution with 5% ethyl acetate in petroleum spirit) gave a small amount of starting material together with two products thought to be diastereo-isomers of the 1,2 addition product 117, High Rf (15mg, 15% and low Rf (27mg, 28%).

Major product:

NMR ($CDCl_3$,80MHz) δ_H: 0.94 (3H,s,gem CH_3), 1.03 (3H,s, gem CH_3), 0.70-1.30 (2H,m), 1.36 (3H,d,J=5Hz,CH_3CHNO_2), 1.47-2.10 (6H,m,OH at 1.96,$CH_3C=C$ at 1.70), 2.40-3.35 3H,m,allylic CH_2 and CH), 4.35-4.95 (2H,m,CHOH and $CHNO_2$).

IR (neat) ν : 3550(br), 1555(s), 1458, 1390, 1365.

Minor product:

IR (neat) ν :3520(br), 1555(s), 1458, 1393, 1368.

3-(3-Bromopropyl)-7,7-dimethyl-2-methylene-3-(phenylsulphonyl) bicyclo[3.3.0]octane (121).

To a solution of vinyl sulphone 108 (0.500g, 1.72mmol) in THF (10ml) at -78°C under nitrogen was added n-butyl lithium (1.21ml of 1.57M solution in hexane, 1.90mmol). The deep orange anion was stirred at -78°C for 15 minutes and 1,3-dibromopropane (695mg, 0.35ml, 3.44mmol) was added via a syringe. The mixture was stirred at -78°C for 2 hours

and poured into a separating funnel containing saturated aqueous ammonium chloride and ether. The aqueous layer was extracted with ether and the combined organic layers were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 10% ethyl acetate in petroleum spirit) gave 121 as a white solid (588mg, 83%) which appeared to be a 7:1 mixture of isomers by NMR, m.p. 85-87°C (from ether).

NMR ($CDCl_3$, 80MHz) δ_H : 0.86 (6H,s,gem CH_3), 0.60-2.80 (11H,series of m), 2.90-3.30 (1H,m,allylic CH), 3.37 (2H,t,J=5Hz,CH_2Br), 5.23 (1H,d,J=2Hz,vinyl CH), 5.50 (1H,d,J=2Hz,vinyl CH), 7.35-8.05 (5H,m,$SO_2C_6H_5$), small signals at 4.74 and 5.16 for vinyl CH of minor isomer.

IR (KBr) ν : 1643(w), 1583(w), 1290(s), 1138(s).

Microanalysis : Found C,58.48; H,6.76 $C_{20}H_{27}O_2SBr$ requires C,58.38; H,6.62.

3-(3-Iodopropyl)-7,7-dimethyl-2-methylene-3-(phenylsulphonyl) bicyclo[3.3.0]octane (122).

The bromide 121 (350mg, 0.852mmol) and sodium iodide (645mg, 4.3mmol) were refluxed in dry acetone (6ml) for 2.5 hours. The acetone was removed on the rotary evaporator and the residue partitioned between ether/water. The aqueous layer was extracted with ether and the combined organic layers were washed with saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 10% ethyl acetate in petroleum spirit) gave the iodide 122 as a white solid (337mg, 86%) which appeared to be a 7:1 mixture of isomers by NMR.

m.p. 103-104°C (from ether).

NMR ($CDCl_3$, 80MHz) δ_H : 0.60-2.90 (18H, series of m, gem CH_3 at 0.85), 3.15 (2H, t, J=5Hz, CH_2I), 5.25 (1H, d, J=1Hz, vinyl CH), 5.51 (1H, d, J=1Hz, vinyl CH), 7.35-8.00 (5H, m, $SO_2C_6H_5$), small signals at 4.70 and 5.15 for vinyl CH of minor isomer.

IR (KBr) ν : 1635(w), 1575(w), 1289(s), 1132(s).

Microanalysis : Found C,52.53: H,5.95 $C_{20}H_{27}O_2SI$ requires C,52.40; H,5.94.

7,7-Dimethyl-2-methylene-3-(3-nitropropyl)-3-(phenylsulphonyl) bicyclo[3.3.0]octane (123).

The iodide 122 (336mg, 0.734mmol) in dry diethyl ether (5ml) was added dropwise to a stirred suspension of silver nitrite (282mg, 1.83mmol) in ether (3ml) at 0°C in a flask which was protected from the light. After stirring at 0°C for 16 hours and at room temperature for 2 days, more silver nitrite (141mg, 0.91mmol) was added. Stirring was continued for a further 3 days at room temperature. Filtering of the reation mixture and evaporation of the filtrate gave the crude product. Column chromatography on silica gel (elution with 20% ethyl acetate in petroleum) gave 123 as two isomers, major (low Rf, 90mg, 33%) and minor (high Rf, 11mg, 4%).

NMR ($CDCl_3$, 80MHz) δ_H : for mixture; 0.84 (6H, s, gem CH_3), 0.60-3.40 (12H, series of m), 4.39 (2H, t, J=3Hz, CH_2NO_2), 5.26 (1H, d, J=1Hz, vinyl CH), 5.55 (1H, d, J=1Hz, vinyl CH),

7.40-8.00 (5H,m,$SO_2C_6\underline{H}_5$), small signals at 4.75 and 5.15 for vinyl C<u>H</u> of minor isomer.

<u>IR</u> (neat) ν : major isomer; 1555(s), 1450, 1390, 1370, 1310(s), 1148(s).

minor isomer; 1558(s), 1455, 1390, 1375, 1300(s), 1145(s).

<u>3- 7,7-Dimethyl-2-methylene-3-(phenylsulphonyl)bicyclo[3.3.0] oct-3-yl propanal ethylene acetal</u> (<u>125</u>).

To a solution of vinyl sulphone <u>108</u> (843mg,2.91mmol) in THF (15ml) at -78°C under nitrogen was added n-butyl lithium (2.03ml of 1.58M solution in hexane, 3.20mmol). The deep orange solution was stirred at -78°C for 15 minutes and quenched with 2-(2-iodoethyl)-1,3-dioxalane[120] (1.06g, 4.66mmol) in THF (5ml). After stirring at -78°C for 1.5 hours the reaction mixture was poured into a separating funnel containing ether/saturated aqueous ammonium chloride. The aqueous layer was extracted with ether and the combined organic layers were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 20% ethyl acetate in petroleum spirit) gave <u>125</u> as a white solid (873mg, 77%), m.p. 121.5-122°C (from ether).

<u>NMR</u> ($CDCl_3$,80MHz) δ_H : 0.89 (6H,s,gem $C\underline{H}_3$), 0.60-1.95 (6H,series of m), 1.95-2.78 (5H,series of m), 2.85 -3.40 (1H,m,allylic C<u>H</u>), 3.70-4.05 (4H,m,$OC\underline{H}_2C\underline{H}_2O$), 4.84 (1H,t,J=4Hz,OC<u>H</u>O), 5.25 (1H,s,vinyl C<u>H</u>), 5.51 (1H,s,vinyl C<u>H</u>), 7.32-8.10 (5H,m,$SO_2C_6\underline{H}_5$).

<u>IR</u> (KBr) ν : 1640(w), 1585(w), 1285(s), 1138(s).

Microanalysis : Found C,67.87; H,7.88 $C_{22}H_{30}O_4S$ requires C,67.78; H,7.74.

3-(2,7,7-Trimethylbicyclo[3.3.0]oct-2-en-3-yl)propanal ethylene acetal (126).

To a mixture of sulphone 125 (820mg, 2.1mmol) and Na_2HPO_4 (1.21g, 8.5mmol) in dry methanol (20ml) at 0°C was added 6% sodium amalgam (4.2g). After stirring at 0°C for 1.5 hours a further 2.5g of 6% sodium amalgam was added and stirring was continued at 0°C for a further 1.5 hours. The reaction mixture was carefully poured into water and extracted with ether. The combined organic extracts were washed with saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 10% ethyl acetate in petroleum spirit) gave 126 as a colourless oil (476mg, 90%).

NMR ($CDCl_3$,80MHz) δ_H : 0.92 (3H,s,gem CH_3), 1.02 (3H, s,gem CH_3), 0.75-1.20 (2H,m), 1.55 (3H,broad s,CH_3C=C), 1.40-1.92 (4H,series of m), 1.92-2.26 (3H,series of m), 2.30-2.80 (2H,m), 2.82-3.25 (1H,m,allylic CH), 3.75-4.05 (4H,m,OCH_2CH_2O), 4.83 (1H,t,J=5Hz,OCHO).

IR (neat) ν : 2950(s), 2860(s), 1135(s).

Microanalysis : Found C,76.70; H,10.51 $C_{16}H_{26}O_2$ requires C,76.75; H,10.47.

3-(2,7,7-Trimethylbicyclo[3.3.0]oct-2-en-3-yl)propanal (123).

Ketal 126 (538mg, 2.14mmol), pyridinium p-toluenesulphonate (320mg, 1.28mmol) and water (2ml)

were refluxed together in acetone (10ml) for 40 hours. The acetone was removed on the rotary evaporator and the residue was dissolved in ether and washed with saturated aqueous sodium bicarbonate. The ether layer was dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 3% diethyl ether in petroleum spirit) gave 123 as a sweet smelling oil (334mg, 75%) together with recovered starting material (48mg). Yield based on recovered starting material = 83%.

NMR ($CDCl_3$, 80MHz) δ_H : 0.92 (3H,s,gem CH_3), 1.00 (3H,s, gem CH_3), 0.80-1.32 (2H,m), 1.54 (3H,broad s,$CH_3C{=}C$), 1.50-1.90 (2H,m), 1.92-2.13 (1H,m),2.15-2.80 (6H,series of m), 2.85-3.28 (1H,m,allylic CH), 9.75 (1H,s,CHO).

IR (neat) ν : 2930(s), 2850, 2710, 1722(s).

3-(2,7,7-Trimethylbicyclo[3.3.0]oct-2-en-3-yl)propionic acid (127).

A solution of aldehyde 125 (100mg, 0.49mmol) in acetone (3ml) was cooled to 0°C and treated dropwise with Jones reagent until the orange colour persisted. The mixture was maintained at 0°C for 10 minutes and then transferred to a separating funnel containing saturated aqueous sodium chloride. The aqueous layer was extracted with ether and the combined ether extracts were washed with 15% aqueous sodium carbonate solution. The sodium carbonate layer was reacidified with 2N HCl and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel

(elution with 15% ethyl acetate in petroleum spirit) gave the acid 127 as a pale yellow oil (68mg, 63%).

NMR ($CDCl_3$, 80MHz) δ_H : 0.92 (3H,s,gem CH_3), 1.00 (3H,s, gem CH_3), 0.70-1.30 (2H,m), 1.55 (3H,s,$CH_3C{=}C$), 1.50-1.90 (2H,m), 1.95-2.13 (1H,unresolved signal), 2.20-2.83 (6H,series of m, sharp signal at 2.38), 2.85-3.30 (1H,m,allylic CH), 10.63 (1H,broad s,CO_2H).

IR (neat) ν : 3000(br), 1710(s).

5-Iodo-2-pentyne.

A mixture of 3-pentyn-1-ol (2g, 23.8mmol) and triethylamine (4.33g, 6.0ml, 42.8mmol) in dry dichloromethane (100ml) was cooled in an ice/salt bath and treated dropwise with methanesulphonyl chloride (3.28g, 2.23ml, 28.6mmol). After stirring at -10°C for 2 hours the reaction mixture was washed successively with ice/water, cold 2N HCl, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$) and evaporated to give the crude mesylate of 3-pentyn-1-ol (3.74g).

To a solution of the crude mesylate (3.74g, 23.1mmol) in dry acetone (40ml) was added sodium iodide (10.8g, 72mmol). The mixture was stirred overnight at room temperature and refluxed for 2 hours. The acetone was removed on the rotary evaporator and the residue partitioned between ether/water. The aqueous layer was extracted with ether and the combined organic extracts were washed with water and saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 10%

diethyl ether in petroleum spirit) gave the title compound as an oil (3.44g, 75%).

NMR ($CDCl_3$, 80MHz) δ_H : 1.79 (3H, t, J=3Hz, $C\underline{H}_3$), 2.50-2.90 (2H, m), 3.20 (2H, t, J=6Hz).

IR (neat) ν : 1438, 1255(s), 1177(s).

7,7-Dimethyl-2-methylene-3-(3-pentynyl)-3-(phenylsulphonyl) bicyclo[3.3.0]octane (132).

To a solution of vinyl sulphone 108 (779mg, 2.69mmol) in THF (10ml) at -78°C under nitrogen was added n-butyl lithium (1.85ml of 1.60M solution in hexane, 2.95mmol). The orange/red solution was stirred at -78°C for 15 minutes and 5-iodo-2-pentyne (784mg, 4.04mmol) in THF (5ml) was added via a canula. After stirring at -78°C for 1.5 hours the reaction mixture was poured into saturated aqueous ammonium chloride. The aqueous layer was extracted with ether and the combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 15% diethyl ether in petroleum spirit) gave 132 as a white solid (687mg, 72%) which appeared to be a 5:1 mixture of isomers from NMR. m.p. 92-94°C (from ether).

NMR ($CDCl_3$, 80MHz) δ_H : 0.88 (6H, s, gem $C\underline{H}_3$), 0.65-1.90 (9H, series of m, $C\underline{H}_3C{\equiv}C$ at 1.75), 1.95-3.40 (6H, series of m, sharp signal at 2.21), 5.24 (1H, d, J=1Hz, vinyl C$\underline{H}$), 5.48 (1H, d, J=1Hz, vinyl C$\underline{H}$), 4.43, 5.65 (small doublets, vinyl C$\underline{H}$'s of minor isomer), 7.35-8.00 (5H, m, $SO_2C_6\underline{H}_5$).

IR (KBr) : 1640(w), 1585(w), 1290(s), 1144(s).

Microanalysis : Found C,74.03; H,8.04 $C_{12}H_{28}O_2S$ requires C,74.12; H,7.92.

2,7,7-Trimethyl-3-(3-pentynyl)bicyclo[3.3.0]oct-2-ene (131).

To a mixture of sulphone 132 (475mg, 1.33mmol) and Na_2HPO_4 (758mg, 5.34mmol) in dry methanol (10ml) at 0°C was added 6% sodium amalgam (4.0g). The mixture was stirred at 0°C for 1.5 hours and then poured carefully into water. The product was extracted into ether and the combined ether extracts were washed with saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 5% ethyl acetate in petroleum spirit) gave 131 as a clear oil (250mg, 87%).

NMR ($CDCl_3$,80MHz) δ_H : 0.92 (3H,s,gem CH_3), 1.01 (3H,s, gem CH_3), approx. 0.70-1.34 (2H,m), 1.55 (3H,s, $CH_3C{=}C$), 1.76 (3H,s,$CH_3C{\equiv}C$), approx. 1.50-1.93 (2H, m), 1.95-3.35 (8H,series of m, sharp signal at 2.17).

δ_C : 3.4,12.4,17.4,27.5,28.3,29.0,38.7, 40.8,41.7,46.1,49.8,55.4,75.3,79.3,130.9,135.8.

IR (neat) ν : 2920(s), 2825(s), 1573, 1440.

Microanalysis : Found C,89.17; H,11.18 $C_{16}H_{24}$ requires C,88.82; H,11.18.

1-(2,10,10-Trimethyl-cis,anti,cis-tricyclo[6.3.3.$0^{2,6}$]-undec-3-ylidene)ethyl methanoate (133).

The acetylene 131 (81mg, 0.037mmol) was vigorously stirred with dry formic acid (1ml) (2 phase system) at 50°C for 16 hours. The cooled reaction mixture was poured into ether/water and the aqueous layer was extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 5% diethyl ether in petroleum spirit) gave enol formate 133 as an oil (55mg, 56%).

NMR ($CDCl_3$,80MHz) δ_H : 0.70-2.90 (25H,series of m, sharp signals at 0.94,1.07,1.12,1.52,1.93), 8.00 (1H,s,OC<u>H</u>O).

IR (neat) ν : 2970(s), 2890, 1760(m), 1740(s), 1700(m).

Microanalysis : Found C,77.90; H,10.15 $C_{17}H_{26}O_2$ requires C,77.81; H,9.99.

Prolonged treatment of 131 with formic acid produced two other products. One was thought to be ketone 134 and possessed the following spectral data.

NMR ($CDCl_3$,80MHz) δ_H : 0.70-3.20 (26H,series of m, gem C<u>H</u>$_3$ at 0.94,1.05, C<u>H</u>$_3$C=O at 2.12, sharp signals also at 0.80,1.25.

IR (neat) ν : 1700(s).

2,10,10-Trimethyl-cis,anti,cis-tricyclo[6.3.0.$0^{2,6}$]undecan-3-one (96)

i) Preparation of ruthenium tetroxide solution:[126a]

To a stirred suspension of $RuO_2.xH_2O$ (Aldrich, 0.2g) in carbon tetrachloride (25ml) at 0°C was added sodium

periodate (1.6g) in water (25ml). After stirring at 0°C for 1 hour the mixture was filtered into a separating funnel and the aqueous layer was discarded. The yellow CCl_4 layer containing the ruthenium tetroxide was shaken with a fresh solution of sodium periodate (0.5g) in water (25ml), and the two phase mixture was stored in the refrigerator.

ii) Cleavage of enol formate 133:

A stirred solution of enol formate (54mg, 0.21mmol) in CCl_4 (6ml) was covered with water (approx 1ml) and treated with ruthenium tetroxide solution (CCl_4 layer) at room temperature until TLC indicated consumption of starting material (approx 10ml). Excess ruthenium tetroxide was destroyed by the addition of a few drops of isopropanol. The mixture was filtered into a separating funnel and the organic layer was washed with water, dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 5% diethyl ether in petroleum spirit) gave the product 96 as an oil which gradually crystallised (17mg, 42%) m.p. 42-43°C (from 40:60 petrol).

NMR ($CDCl_3$, 250MHz) δ_H : 0.90 (3H,s), 0.93 (3H,s), 1.03 (3H,s), 0.84-1.50 (5H,m), 1.53-1.80 (3H,m), 1.90-2.60 (4H,m), 2.73-2.86 (1H,q).

IR (neat) : 2940(s), 2860, 1735(s), 1470, 1370.

Methyl 6-methyl-2-oxo-7-(phenylthio)bicyclo[3.3.0]octa-3,6-diene-1-carboxylate (137a)

To a solution of β-keto ester 42a (677mg, 2.24mmol) in dry dichloromethane (8ml) was added DBU (580mg, 0.57ml, 3.81mmol) and freshly distilled trimethylsilyl chloride (365mg, 0.426ml, 3.36mmol). The mixture was refluxed under nitrogen for 1 hour, cooled and diluted with pentane (15ml). The organic solution was washed successively with 1% aqueous HCl and saturated aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated to give the crude silyl enol ether 138a (827mg).

A mixture of palladium acetate (274mg, 1.22mmol) and p-benzoquinone (132mg, 1.22mmol) were stirred in acetonitrile (5ml) at room temperature under nitrogen until a clear red solution was obtained. The crude silyl enol ether 138b (827mg, 2.21mmol) in acetoniltile (10ml) was added via a canula. After stirring overnight at room temperature further amounts of palladium acetate (55mg, 0.240mmol) and p-benzoquinone (26mg, 0.240mmol) were added and stirring was contineued for a further 15 hours. The mixture was filtered and the solvent evaporated. Column chromatography on silica gel (elution with 10% diethyl ether in petroleum spirit) gave the enone 137a as a white solid (575mg, 85%).

m.p. 89-90°C (from ether)

NMR ($CDCl_3$, 80MHz) δ_H : 1.99 (3H,broad s,$C\underline{H}_3C$=C), 2.50 (1H,d,J=18Hz,part of AB system), 3.32 (1H,d,J=18Hz, part of AB system), 3.67 (3H,s,$OC\underline{H}_3$), 4.30 (1H,unresolved signal, allylic C$\underline{H}$), 6.20 (1H,dd,J=6Hz,2Hz), 7.30 (5H,s,$SC_6\underline{H}_5$), 8.21 (1H,dd,J=6Hz,3Hz).

IR (KBr)ν: 1750, 1703, 1590.

Microanalysis : Found C,67.83; H,5.37 $C_{17}H_{16}O_3S$ requires C,67.97; H,5.37.

Methyl 6-methyl-7-(methylthio)-2-oxobicyclo[3.3.0]octa-3,6-diene-1-carboxylate (137b).

Treatment of β-keto ester 42b (500mg, 2.08mmol) with DBU (563mg, 0.553ml, 3.55mmol) and trimethysilyl chloride (339mg, 0.396ml, 3.12mmol) in dichloromethane (10ml) as described above gave the crude silyl enol ether 138b (629mg).

A mixture of palladium acetate (233mg, 1.04mmol) and p-benzoquinone (112mg, 1.04mmol) were stirred under nitrogen in dry acetonitrile (3ml) until a clear solution was obtained. The silyl enol ether 138b (629mg, 2.02mmol) in acetonitrile (4ml) was added via a canula. After stirring for 20 hours at room temperature the reaction mixture was filtered and the solvent evaporated. Column chromatography on silica gel (elution with 20% ehtyl acetate in petroleum spirit) gave starting β-keto ester (122mg) and the α,β-unsaturated ketone 137b (211mg, 43%). Yield based on recovered starting material = 56% m.p. 75.5-77°C (from ether).

NMR ($CDCl_3$,80MHz) δ_H : 1.80 (3H,s,CH_3C=C), 2.25 (3H,s,SCH_3), 2.80 (1H,d,J=17Hz, part of AB system), 3.48 (1H,d,J=17Hz, part of AB system), 3.34 (3H,s,OCH_3),4.10 (1H, unresolved signal, allylic CH), 6.14 (1H,d of d,J=6Hz,2Hz), 7.89 (1H,d of d,J=6Hz,2Hz).

IR (KBr) ν : 1738, 1718, 1645, 1608.

Microanalysis : Found C, 60.50; H, 5.92 $C_{12}H_{14}O_3S$ requires

C, 60.48; H, 5.92.

4-Chloro-2-(trimethylstannyl)-1-butene (34)

i) 4-chloro-1-butyne

Thionyl chloride (13.6g, 8.3ml, 0.114 mol) was added dropwise with occasional swirling to an ice cooled mixture of 3-butyn-1-ol (8g, 0.114mol) and pyridine (5 drops). After completion of the addition the mixture was refluxed for 30 minutes. Fractional distillation of the reaction through a short column packed with glass helices gave 4-chloro-1-butyne (5.1g, 51%) b.p. 86-87°C.

NMR ($CDCl_3$, 80MHz) δ_H : 2.10 (1H, t, J=3Hz, C C-H), 2.67 (2H, m, C C-CH_2), 3.64 (2H, t, J=7H_2, CH_2Cl).

IR (neat) ν: 3350(s), 2130(w).

ii) Freshly pressed lithium wire (1.27g, 0.20mol) was placed in a dry round bottomed flask which was sealed with a rubber septum. Trimethyltin chloride (7.25g, 0.04mol) in THF (100ml) was added via a canula. After completion of the addition the mixture was stirred vigourously at room temperature for 20 minutes. The green solution of trimethyltin lithium was rapidly suction filtered into a 3-necked round bottom flask via a glass sinter with two male Quickfit joints. The solution was cooled under nitrogen to -63°C and copper bromide-dimethyl sulphide complex (7.5g, 0.04mol) was added. After stirring at -63°C for 20 minutes 4-chloro-1-butyne (1.61g, 0.02mol) in THF (20ml) was added followed by dry methanol (44ml). The mixture was stirred at -63°C for 10 hours and then allowed to reach room temperature and left overnight. The THF was

removed on the rotary evaporator and the residue partioned between ether/water. The aqueous layer was extracted with ether and the combined organic extracts were washed with saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with petroleum spirit) gave 34 as a clear colourless oil (1.49g, 32%). It was thought some product was lost due to its low volatility.

NMR ($CDCl_3$, 80MHz) δ_H : 0.18 (9H,s,$(CH_3)_3Sn$), 2.72 (2H,t,J=7Hz), 3.66 (2H,t,J=7Hz,CH_2Cl), 4.90-6.10 (2H,m,vinyl H).

IR (neat) ν : 3035, 2890-2810, 1598(w), 1440, 923(s),770(s).

Methyl 3-methyl-11-methylene-7-oxo-4-(phenylthio)-cis,anti,cis-tricyclo[6.3.0.$0^{2,6}$]undec-3-ene-6-carboxylate (140).

A solution of 4-chloro-2-(trimethylstannyl)-1-butene 34 (110mg, 0.433mmol) in THF (5ml) was cooled to -78°C under nitrogen and treated with n-butyl lithium (0.33ml of 1.58M solution in hexane, 0.52mmol). After stirring at -78°C for 30 minutes, CuCN (47mg, 0.52mmol) was added, and after a further 5 minutes enone 137a (100mg, 0.333mmol) in THF (2ml) was added. Stirring was continued at -78°C for 3.5 hours. Saturated ammonium chloride solution was added to the cold reaction mixture and the product was extracted into ether. Drying ($MgSO_4$) of the organic extracts and evaporation of the solvent gave the crude product. Column chromatography on silica gel (elution with 10% ethyl acetate in petroleum spirit) gave 139 (68mg, 52%) as an oil together with recovered starting material (25mg).

139 NMR ($CDCl_3$,80MHz) δ_H : 1.91 (3H,s,$C\underline{H}_3C$=C), 2.40-3.30 (7H,series of m), 3.40-3.90 (6H,m,$OC\underline{H}_3$ at 3.70), 5.00 (1H,s,vinyl C$\underline{H}$), 5.08 (1H,s,vinyl C$\underline{H}$), 7.25 (5H,s,$SC_6\underline{H}_5$).

The ketone 139 (53mg,0.136mmol) in THF (2ml) was added to a stirred suspension of KH (approx. 40mg of 35% dispersion in mineral oil, approx. 3 equivalents) in THF (2ml) at room temperature. After stirring overnight the mixture was poured into ether/saturated NH_4Cl solution. The aqueous layer was extracted with ether and the combined organic layers were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 5% ethyl acetate in petroleum spirit) gave 140 as a white solid (28mg, 58%). m.p. 84-86°C

NMR ($CDCl_3$,80MHz) δ_H : 1.50-3.60 (12H,series of m, $C\underline{H}_3$ C=C at 1.93), 3.62 (3H,s,$OC\underline{H}_3$), 5.03 (2H, broad s,vinyl $C\underline{H}_2$), 7.22 (5H,s,$SC_6\underline{H}_5$).

IR ($CDCl_3$ solution) ν : 1720(br).

Methyl endo-8-hydroxy-4-methyl-3-(phenylthio)bicyclo[3.3.0]-oct-3-ene-1-carboxylate (149).

A solution of keto ester 42a (400mg, 1.33mmol) in methanol (10ml) was cooled in an ice/salt bath and treated with $NaBH_4$ (101mg, 2.65mmol). The mixture was stirred for 20 minutes and then poured into ether/2N HCl. The aqueous layer was extracted with ether and the organic extracts were washed with brine and dried ($MgSO_4$). Solvent removal and column chromatography on silica gel (elution with 30%

ethyl acetate in petroleum spirit) gave 141 as an oil (324mg, 80%).

NMR ($CDCl_3$, 80MHz) δ_H : 1.25-2.0 (7H, m, broad s at 1.84, $CH_3C=C$), 2.20 (1H, broad unresolved signal, OH), 2.40-3.20 (2H, series of m, allylic CH_2), 3.25-3.45 (1H, broad unresolved signal, allylic CH), 3.70 (3H, s, OCH_3), 4.25-4.55 (1H, m, CHOH), 7.24 (5H, s, SC_6H_5).

IR (neat) ν : 3460(br), 1725(s), 1643(w), 1585.

Microanalysis : Found C, 66.85; H, 6.87 $C_{17}H_{20}O_3S$ requires C, 67.07; H, 6.62.

Methyl 4-methyl-3-(phenylthio)-endo-8-(p-toluenesulphonyloxy) bicyclo[3.3.0]oct-3-ene-1-carboxylate (148).

The alcohol 149 (192mg, 0.63mmol) in dry pyridine (3ml) was cooled in ice and treated with p-toluenesulphonyl chloride (241mg, 1.26mmol). The reaction mixture was left in the refrigerator for 1 week and then poured into ice/water. The product was extracted into ether and the organic extracts were washed with 1N HCl and brine. Drying ($MgSO_4$), solvent removal and column chromatography on silica gel (elution with 15% ethyl acetate in petroleum spirit) gave 148 as an oil (289mg, 90%) which crystallised out when cooled.

NMR ($CDCl_3$, 80MHz) δ_H : 1.60-2.20 (7H, series of m, $CH_3C=C$ at 1.78), 2.42 (3H, s, CH_3Ph), 2.70-2.95 (2H, m), 3.15-3.35 (1H, broad unresolved signal, allylic CH), 3.59 (3H, s, OCH_3), 5.05-5.30 (1H, m, CHOTs), 7.10-7.80 (9H, m, aromatic CH's).

IR (KBr) ν : 1735(s), 1605, 1590, 1375(s), 1160(s).

Methyl 8-hydroxy-4,8-dimethyl-3-(phenylthio)bicyclo[3.3.0] oct-3-ene-1-carboxylate (155).

A solution of β-keto ester 42a (500mg, 1.66mmol) in diethyl ether (10ml) was cooled to -78°C under N_2 and treated with methyl lithium (1.16ml of 1.74M solution in diethyl ether, 1.74mmol). After 15 minutes more methyl lithium (0.58ml, 0.87mmol) was added and stirring continued for a further 15 minutes. 2N HCl was added to the cold reaction mixture and the product was extracted into ether. The combined organic extracts were washed successively with water and saturated sodium chloride solution. Drying ($MgSO_4$), solvent removal and column chromatography on silica gel (elution with 20% ethyl acetate in petroleum spirit) gave 155 as a mixture of two products thought to be isomers. On one occasion the products were isolated in a 7:1 ratio.

Data for major product:

NMR ($CDCl_3$,80MHz) δ_H : 1.10-2.30 (11H,series of m, CH_3COH(s) at 1.24, $CH_3C{=}C$(s) at 1.85, OH at 2.05), 2.40-3.30 (2H,series of m, allylic CH_2), 3.70 (3H,s,OCH_3), 3.35-approx.3.70 (1H,broad unresolved signal, allylic CH), 7.24 (5H,s,SC_6H_5).

IR (neat) : 3560, 1730(s), 1650(w), 1595.

Dehydration of 155.

i) using $POCl_3$/pyridine:

To a solution of the mixture of alcohols 155 (399mg, 1.25mmol) in pyridine (6ml) was added $POCl_3$ (1.15g, 0.69ml, 7.5mmol). After stirring overnight at

room temperature more $POCl_3$ (0.20ml) was added and stirring was continued at 40°C for 6 hours. The cooled reaction mixture was poured into 2N HCl and the product was extracted into ether. The combined organic extracts were washed successively with 2N HCl, saturated sodium bicarbonate solution and brine. Drying ($MgSO_4$), solvent removal and column chromatography on silica gel (elution with 5% ethyl acetate in petroleum spirit) gave a single product (317mg) with the following spectral data:

NMR ($CDCl_3$, 80MHz) δ_H : 1.65 (3H,m), 1.83 (3H,s), 2.0-approx.3.70 (5H,series of m), 3.70 (3H,s,$OC\underline{H}_3$), 5.02,5.45 (1H in total, 2 singlets), 7.23 (5H,s,$SC_6\underline{H}_5$).

IR (neat) ν : 1740(s), 1650(w), 1600.

ii) An identical product to that above was obtained when the alcohol mixture 155 was treated with methanesulphonyl chloride (2 equivalents) and triethylamine (3 equivalents) in dichloromethane at 0°C for 2 hours.

Oxidation of above dehydration product

A solution of the above dehydration product (100mg) in dichloromethane (2ml) containing Na_2HPO_4 (412mg, 2.90mmol) was cooled to -78°C and treated with m-chloroperbenzoic acid (213mg, 1.17mmol). After stirring at -78°C for 10 minutes the mixture was maintained at 0°C for 48 hours. The reaction was worked up by pouring into 10% aqueous sodium sulphite solution and extraction with ether. The combined extracts were washed with saturated sodium bicarbonate solution and brine. Drying ($MgSO_4$),

solvent removal and column chromatography on silica gel (elution with 30% ethyl acetate in petrolwum spirit) gave the major product as a white foam (89mg).

NMR ($CDCl_3$,80MHz), δ_H : 1.28,1.48 (3H,2 singlets,1:1 ratio), 2.15 (3H,s), 1.50-3.55 (approx. 6H, series of m),3.62, 3.72 (3H, 2 singlets,1:1 ratio), 7.40-8.20 (5H,m).

IR (neat) ν : 1720(s), 1630, 1300, 1145(s).

1-(7,7-Dimethyl-2-methylene-3-(phenylsulphonyl)-bicyclo[3.3.0] oct-3-yl)ethanone (164).

i) Using BuLi

To a solution of vinyl sulphone 108 (100mg, 0.345mmol) in THF (4ml) at -78°C under N_2, was added n-butyl lithium (0.264ml of 1.44M solution in hexane, 0.38mmol). The orange solution was stirred at -78°C for 10 minutes and freshly distilled acetyl chloride (90mg, 0.081ml, 1.14M) was added. After stirring for 2 hours at -78°C the cold reaction mixture was poured into a separating funnel containing ether/saturated NH_4Cl solution. The product was extracted into ether and the combined extracts were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (elution with 5% ethyl acetate in petroleum spirit) gave 164 as an oil (86mg, 75%).

NMR ($CDCl_3$80MHz) δ_H : 0.89 (3H,s,gem CH_3), 0.96 (3H,s,gem CH_3), approx. 0.80-3.50 (11H, series of m, CH_3CO is at 2.56), 5.43 (1H,s,vinyl CH), 6.14 (1H,s,vinyl CH), 7.35-8.20 (5H,m,$SO_2C_6H_5$).

IR (neat) ν : 1715(s), 1640, 1315(s), 1150(s).

Microanalysis : Found C,68.71; H,7.40 $C_{19}H_{24}O_3S$ requires C,68-64; H,7.28.

ii) Using LDA

A solution of diisopropylamine (21mg, 0.03ml, 0.206mmol) in THF (2ml) was cooled to 0 C and treated with n-butyl lithium (0.13ml of 1.60M solution in hexane, 0.206mmol). After 15 minutes the solution was cooled to 0 C and the vinyl sulphone 108 (50mg, 0.172mmol) in THF (3ml) was added. The orange/red solution was stirred for 15 minutes and quenched with freshly distilled acetyl chloride (41mg, 0.037ml, 0.52mmol). After stirring for a further 30 minutes at -78 C the reaction mixture was worked up as above to give 164 (27mg, 47%) as a white solid. m.p. 68-71 C.
Data- as above.

Methyl 7-(nitromethyl)-1,4-dioxaspiro[4.4]nonane-6-carboxylate (190).

To a solution of unsaturated ester 45 (2.44g, 13.3mmol) in nitromethane (3.5ml, 66mmol) was added tetramethylguanidine (0.340ml, 2.7mmol). The deep orange solution was stirred under a nitrogen atmosphere for 3 days at room temperature. The reaction mixture was acidified to pH 6 with 2N HCl and extracted with ether. Drying of the organic extracts ($MgSO_4$) and solvent removal gave the crude product which was purified by column chromatography on silica gel (elution with 20% ethyl acetate in petroleum spirit) to give 190 as a colourless oil (2.30g, 71%) together with a small amount of the trans isomer 189 (210mg, 6%).

Cis isomer 190

NMR ($CDCl_3$,80MHz) δ_H : 1.15-2.25 (4H,series of m), 2.69 (1H,d,J=7Hz,C<u>H</u>CO_2Me), 2.90-3.35 (1H,m,C<u>H</u>CH_2NO_2), 3.62 (3H,s,OC<u>H</u>$_3$), 3.7-3.92 (4H,m,OC<u>H</u>$_2$C<u>H</u>$_2$O), 4.30 (2H,d, J=7Hz,C<u>H</u>$_2NO_2$).

IR (neat) ν : 1740(s), 1560(s), 1380.

MS m/e : 245(M^+,weak), 186(M-CO_2Me).

Microanalysis : Found C,48.93; H,6.07; N,6.17 $C_{10}H_{15}O_6N$ requires C,48.97; H,6.17; N,5.71.

Trans isomer 189

NMR ($CDCl_3$,80MHz) δ_H : 1.05-2.30 (4H,series of m), 2.70-2.30 (1H,m), 3.05-3.25 (1H,m), 3.58 (3H,s), 3.70-3.95 (4H,m), 4.0-4.55 (2H,m).

IR (neat) ν : 1735(s), 1560(s), 1380.

MS M/e : 245(M^+,weak), 186(M-CO_2Me).

(7-(Nitromethyl)-1,4-dioxaspiro[4.4]non-6-yl)methanol (191).

A suspension of $LiAlH_4$ (104mg, 2.75mmol) in dry ether (5ml) was stirred at 0°C under a nitrogen atmosphere and anhydrous $AlCl_3$ (122mg, 0.92mmol) was added. The mixture was stirred at room temperature for 30 minutes and recooled at 0°C. Nitro ester 190 (300mg, 1.22mmol) in ether (5ml) was added to the solution dropwise via a canula. Stirring was continued at 0°C for 30 minutes and the reaction mixture was then carefully poured into water, and the pH adjusted to 6 via addition of 2N HCl. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were washed with water and brine. Drying ($MgSO_4$) and solvent removal gave 191 which was purified by column

chromatography on silica gel (elution with 40% ethyl acetate in petroleum spirit) to give 191 as an oil (227mg, 85%).

NMR ($CDCl_3$, 80MHz) δ_H : 1.20-2.25 (5H, series of m), 2.45-2.90 (2H, m, OH at 2.67), 3.52 (2H, d, J=5Hz, CH_2OH), 3.78 (4H, s, OCH_2CH_2O), 4.20-4.70 (2H, m, CH_2NO_2).

IR (neat) ν : 3500(br.), 1562(s), 1395.

Microanalysis : Found C,49.97; H,7.22; N,6.96 $C_9H_{15}O_5N$ requires C,49.76; H,6.96; N,6.45.

7-(Nitromethyl)-6-[(tetrahydropyranyloxy)methyl]-1,4-dioxaspiro[4.4]nonane (192).

A mixture of alcohol 191 (423mg, 1.95mmol), dihydropyran (491mg, 5.85mmol) and pyridinium p-toluenesulphonate (98mg, 0.39mmol) was stirred in dichloromethane (6ml) for 4 hours at room temperature. The mixture was diluted with ether (20ml), washed once with ½saturated brine, dried ($MgSO_4$) and the solvent removed. Column chromatography on silica gel (elution with 30% ethyl acetate in petroleum spirit containing 1% triethylamine) gave 192 as an oil (447mg, 79%).

NMR ($CDCl_3$, 60MHz) δ_H : 1.25-1.90 (10H, series of m), 2.20-2.90 (2H, m), 3.15-3.80 (8H, series of m, sharp signal at 3.73), 4.05-4.90 (3H, m, CH_2NO_2 and OCHO).

IR (neat) ν : 1720(w), 1555(s), 1390.

MS m/e : 301(M^+), 200.

Microanalysis : Found C,55.58; H,7.79; N,4.83 $C_{14}H_{23}O_6N$ requires C,55.80; H,7.69; N,4.65.

6-[(Tetrahydropyranyloxy)methyl]-1,4-dioxaspiro[4.4]nonane-7-carboxylic acid (187).

The nitro compound 192 (245mg, 1mmol) was added to a vigourously stirred solution of KOH (560mg, 10mmol) in water (100ml). Stirring was continued until the nitro compound had dissolved (approx. 1 hr.) and $MgSO_4$ (5.5g) in water (15ml) was added. The reaction mixture was cooled in ice and treated with $KMnO_4$ (316mg, 2mmol) dissolved in the minimum amount of water. Stirring was continued for a further 5 hours at room temperature. Work up involved acidifying the reaction mixture to pH 6 and extraction with ether. The ether extracts were washed with saturated sodium bicarbonate. The aqueous layer was reacidified and extracted with ether. Drying ($MgSO_4$) and solvent removal gave 187 as a white solid (116mg, 50%). The product melted over a broad range (see text), the majority of the crystals melted at 68-70°C (ether).

NMR ($CDCl_3$, 80MHz) δ_H : 1.35-2.25 (10H, series of m), 2.50-3.00 (2H, m), 3.25-4.15 (8H, m, singlet at 3.92), 4.65 (1H, s), 9.0 (1H, broad s).

IR (KBr) ν : 3050(br), 1735, 1710(s).

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Research Study Programme

As part of the research programme the author has attended the following lecture courses at Sheffield University:

Modern Organic Synthesis

Protecting Groups in Organic Chemistry

Asymmetric Synthesis

Frontier Molecular Orbitals in Organic Chemistry

Organoiron Complexes in Organic Synthesis

The audio course 'Modern Organic Synthesis', by B.M.Trost, E.Vedejs has also been studied.

The author has also presented a research colloquium on this work at the sponsoring establishment.

The author has attended symposia on:

Stereochemistry (Sheffield 1982, 1983)

Organic Chemistry (Nottingham, 1982; Leicester, 1983)

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CONJUGATE ADDITION TO THE ETHYLENE KETAL OF 2-CARBOMETHOXY-2-CYCLOPENTENONE A SYNTHESIS OF SARKOMYCIN

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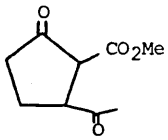
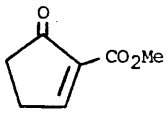
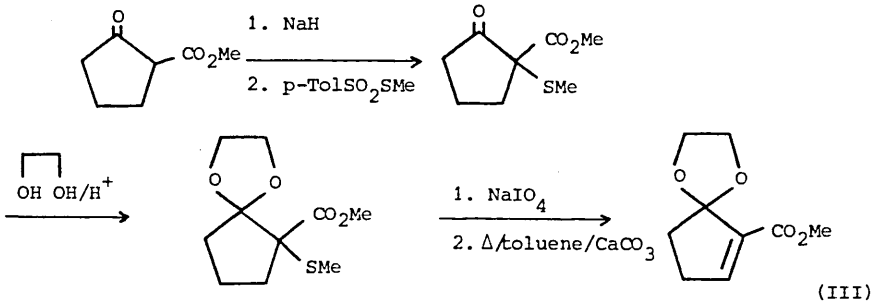
Summary: 1,4-addition of nitronate anions to the title ketal ester (III) is described; one of the adducts is converted to sarkomycin.

During work aimed at the synthesis of bicyclo[3.3.0]octanes we required a source of the diketo ester (I).[1]

(I)   (II)

Retrosynthetic analysis suggests that (I) should be available from keto ester (II) by 1,4-addition of an acyl anion equivalent. The unstable nature of (II) has been described, although it has recently been shown that cyanide ion can be added in a 1,4 sense.[2] We decided to investigate the use of the potentially more stable ketal (III)[3] which was readily obtained as shown below.

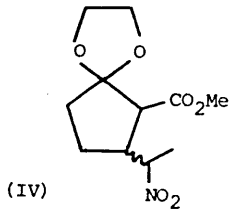


(III)

In this manner 2-carbomethoxycyclopentanone was converted to (III) in 64% overall yield (IR (neat) 1725, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.9-2.5, m, 4H; 3.6, s, 3H; 3.75-4.15, m, 4H; 6.9, t, 1H).

Reaction between (III) and the acyl anion equivalent $CH_3SOCH(Li)SCH_3$, under aprotic conditions, resulted only in extensive decomposition of (III). This failure could be a result of the intermediate anion in the addition being destroyed by ketal opening. Thus it was felt that use of an acyl anion equivalent which could be used in a solvent capable of acting as a proton donor might overcome this problem. Reaction of (III) with

excess nitroethane in the presence of tetramethylguanidine[4] resulted in the production of (IV) (92%; 5:3 mixture of isomers). The mixture (IV) was directly treated with sodium methoxide followed by buffered $TiCl_3$[5] to give the mixture (V) (95%) which was converted with aqueous TFA into (I) (79%; m. 81-82 °; IR (KBr) 1760, 1735, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7-2.6, m, 7H; 3.5-4.0, m, 2H; 3.20, s, 3H).



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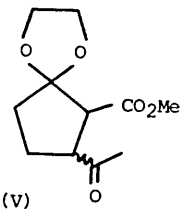

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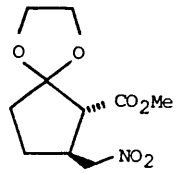

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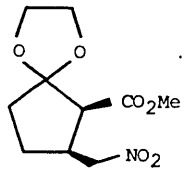
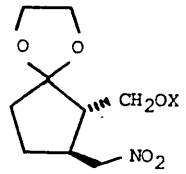


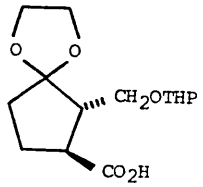
(VII)

We have also used a similar method in a synthesis of sarkomycin, an antibiotic-antitumour agent.[2,6] Reaction of (III) with excess nitromethane in the presence of tetramethylguanidine afforded (VI) (71%; IR (neat) 1730, 1555, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2-2.0, m, 4H; 2.68, d, 1H; 2.95-3.4, m, 1H; 3.62, s, 3H; 3.7-3.95, m, 4H; 4.3, d, 2H), together with a small quantity of the cis compound (VII). Reduction of (VI) with AlH_3 afforded the alcohol (VIII) (69%) which was protected as its THP ether (IX) (79%). Oxidation of (IX) with alkaline $KMnO_4$ gave the acid (X) (50%; m. 68-70 °, lit.[2] 69-72 °) whose spectral data were identical with those described. Sarkomycin (XI) was obtained by treatment of (X) with HCl as described by Marx.

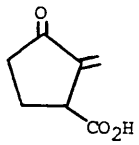


(VIII), X = H

(IX), X = THP



(X)



(XI)

Acknowledgement

We thank SERC for a grant to DTM.

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SYNTHESIS OF A HIGHLY FUNCTIONALISED BICYCLO[3.3.0]OCTANE

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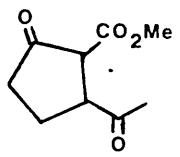
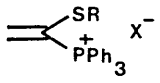
Summary: The bicyclo[3.3.0]octanes 4 and 5 are prepared by making use of vinyl phosphonium salts, and 4 is used in formal total syntheses of chrysomelidial and loganin.

There has been a surge of interest in recent years in the area of cyclopentane chemistry. This interest, prompted largely by work on prostaglandins, has now been extended to polyquinanes. A recent review has discussed developments in the latter area.[1]

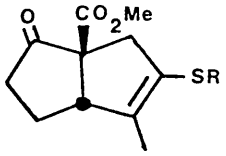
We have previously described syntheses of the diketoester 1 [2] and the vinyl phosphonium salts 2 and 3 [3]. We now report the use of these compounds in the synthesis of a bicyclo[3.3.0]octane which is highly functionalised in a way promising great potential for the synthesis of natural products.



1



2 ; R = Me , X = Cl
3 ; R = Ph , X = I

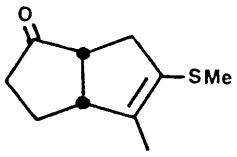


4 ; R = Me
5 ; R = Ph

Treatment of a THF solution of 1 with sodium hydride, followed by addition of the phosphonium salt 2 gave the bicyclo[3.3.0]octane 4 (97%; oil; IR (neat) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7, m, 3H; 2.1-2.3, m, 4H; 2.2, s, 3H; 3.0-3.2, m, 2H; 3.5-3.7, m, 1H; 3.7, s, 3H). Similarly, use of phosphonium salt 3 gave 5 (82%, m. 79-81 °C). Decarbomethyoxylation of 4 was readily achieved by use of sodium cyanide in HMPA[4] affording 6 (82%; oil; IR (neat) 1730, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72, s, 3H; 2.1, m, 4H; 2.2, s, 3H; 2.75, m, 3H, 3.4, broad unresolved signal 1H).

Treatment of 6 with methyl lithium in ether gave stereospecifically the alcohol 7 (75%; oil; IR (neat) 3430 cm^{-1}) whose hydrolysis ($HgCl_2/CH_3CN/H_2O$) gave the keto alcohol 8 (69%; m. 57.5-58.5 °C; lit. [5]m. 58.5-59.0 °C). This latter compound has previously been converted to chrysomelidial, 9, the defence secretion of a chrysomelide beetle.[5]

The approach to loganin also began with the bicyclo[3.3.0]octane 6. Cyanohydrin formation (NaCN/EtOH/AcOH), followed by dehydration ($POCl_3$/pyridine) gave the unsaturated nitrile 10 69%; m.67-69°; IR (KBr) 2220 cm^{-1}) which afforded the unsaturated ketoester 11 (48%; oil; IR (neat) 1740, 1720 cm^{-1}) with MeOH/c. H_2SO_4.



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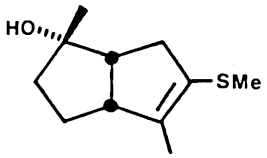

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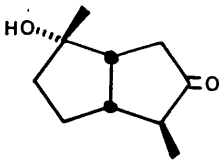

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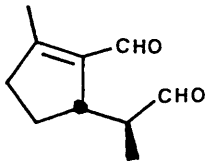
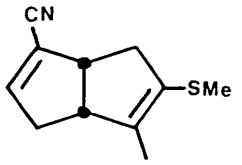
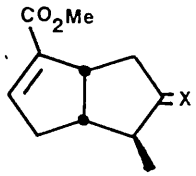


9

Stereospecific reduction of 11 with $NaBH_4$ gave the alcohol 12 (82%; IR (neat) 3450, 1710, 1630 cm^{-1}). Inversion of stereochemistry at the hydroxyl bearing carbon was then achieved via mesylation (MsCl/pyridine) followed by S_N2 displacement (Bu_4NOAc) to give the acetate 13 (74%; oil; IR (neat) 1740, 1720, 1640 cm^{-1}; ^1H NMR δ 6.6, m, 1H; 1.5-2.8, m, 6H; 2.05, s, 3H; 1.0, d, 3H).



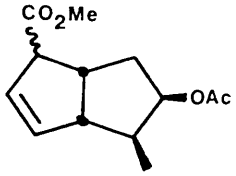
10



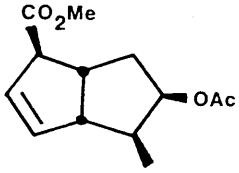
11 ; X = O

12 ; X = H, OH

13 ; X = OAc, H



14



15

Deconjugation of the α,β-unsaturated ester was achieved[6] by treatment of 13 with four equivalents of LDA in THF/HMPA at -78°, and quenching of the anion with methanol. The product 14 (39%) appeared from its NMR spectrum to be a single compound, although the stereochemistry of the carbomethoxy group is not definitely known. However, the IR and ^1H NMR spectra of 14 were identical with those of 15 prepared by a different route.[7] In terms of the conversion of 14 to loganin the stereochemistry of the carbomethoxyl bearing carbon is of no consequence since that centre becomes sp^2 hybridised.[7]

Acknowledgements

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