SYNTHETIC STUDIES ON TERPENOID LACTONES

A Thesis submitted for the degree of

Doctor of Philosophy

by

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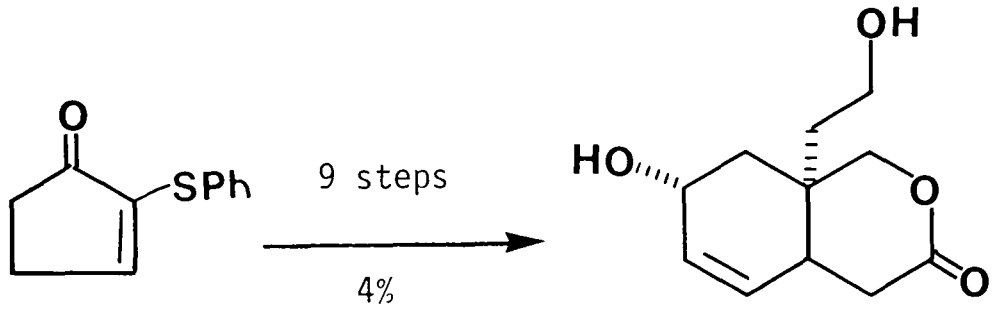
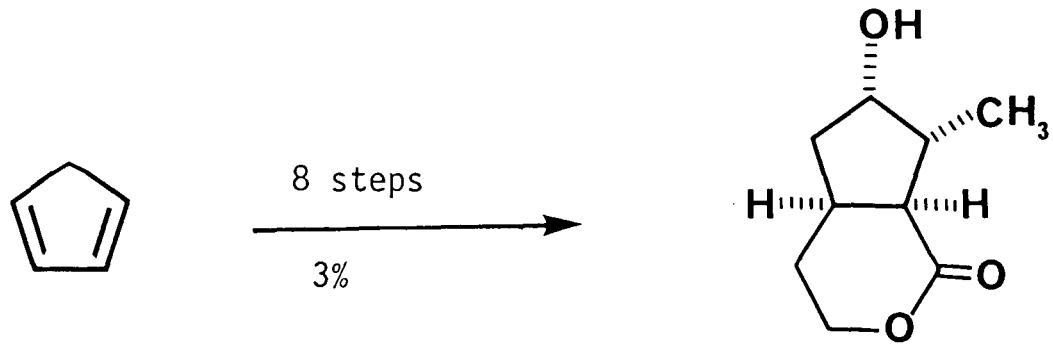
A B S T R A C T

A novel stereoselective route has been developed to a vernolepin intermediate in nine steps from 2-phenylthiocyclopentenone.



During this research, a regiospecific method for the alkylation of the $\Delta^{5,6}$ - tetrahydroindanone system has been achieved. In addition, the synthetic route demonstrates a means of differentiating between two carboxylic acid functions via a selective lactonisation.

The first total synthesis of boonein has also been completed, in 3% yield from cyclopentadiene.



This route uses a chlorine atom to direct the stereo- and regiochemical outcome of most of these reaction.

C O N T E N T S

A C K N O W L E D G E M E N T S

First and foremost, I would like to express my gratitude to my supervisor, Dr. T.V. Lee, for his guidance and enthusiasm over the last 3 years.

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I am indebted to my many colleagues at Brunel University, in particular Dr. D.A. Taylor, for his invaluable assistance during the writing up of this thesis, and Dr. S. Iddenten for our many informative discussions. Thanks also to Dr. T.H.P. Tyman for advice in the naming of some compounds, and to Dr. M.S. Alexiou, B.S. Moonga, A. Yahya, I. Economides, A. Galan, Dr. R. Middleton, Dr. J. Parrick and N. Visani, to name but a few, for their friendship during the course of my study.

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I must also mention Dr. C.J. Moody, who has kindly supplied many of the dry transfers used in this thesis, and my husband, Phil, who has put up with me during this trying period.

Finally, I would like to acknowledge the Science Research Council for the S.E.R.C. award, which enabled me to study for Ph.D.

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INTRODUCTION

Vernolepin and boonein are terpenoid lactones that have been isolated from plant sources. Although there are similarities between the two syntheses, in some respects, there is no other common linkage, and these natural products will be discussed separately herein.

CHAPTER I

VERNOLEPIN

I.A. GENERAL INTRODUCTION

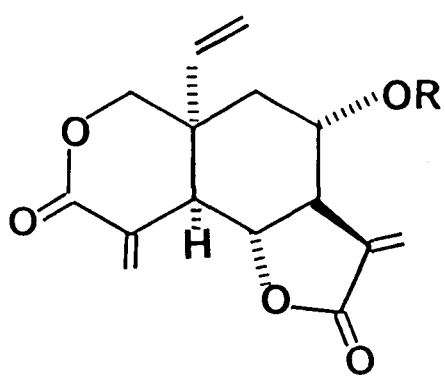
I.A.1. Discovery

With the advent of antibiotics which controlled most infectious diseases, the number of deaths due to cancer has risen sharply in the western world.[1] Some anticancer drugs[2] were already known in the 1940s, such as nitrogen mustards (derivatives of antipersonnel gases from World War I), and 5-fluorouracil, but these prototypes and various modifications of them suffered from low therapeutic indices. The need therefore existed for new templates, which could be used in the design of potentially superior chemotherapeutic agents.

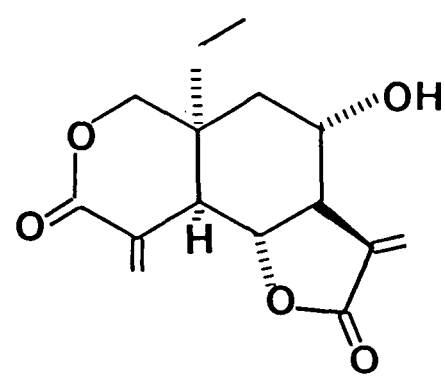
The plant kingdom has long served as a prolific source of useful drugs. An investigation of folklore resulted in the isolation of vincristine and vinblastine from the trailing periwinkle, Vinca rosea, which are currently being used in the treatment of childhood leukaemia. This, and other discoveries,[3] stimulated a worldwide survey of plant products as potential anticancer drugs, in 1959, by the Natural Products branch of the National Cancer Institute of America.[4,5]

Crude plant extracts were screened for inhibitory activity against animal tumour systems. It was during this search that Kupchan et al.[6,7] discovered that alcoholic extracts of Vernonia hymenolepis A. Rich of the family Compositae, have significant cytotoxic activity in vitro against cells derived from human carcinoma of the nasopharynx (K.B.) carried in tissue culture.

Consequently, a systematic study aimed at isolation of the active constituents was undertaken. The fractionation and isolation studies were monitored at each stage by biological assay. Kupchan found that all fractions contained the active principle, so the richest of these fractions was crystallised to give a novel elemanolide bislactone, vernolepin (1).



(1) R = H
(2) R = $COCH_3$
(3) R = $SO_2C_6H_4Br$



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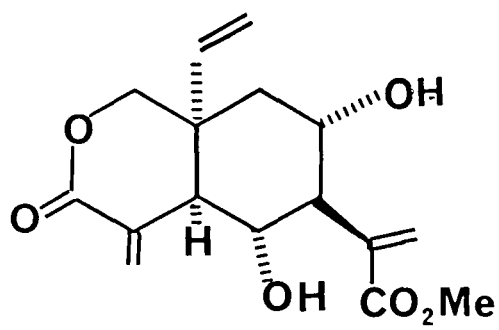
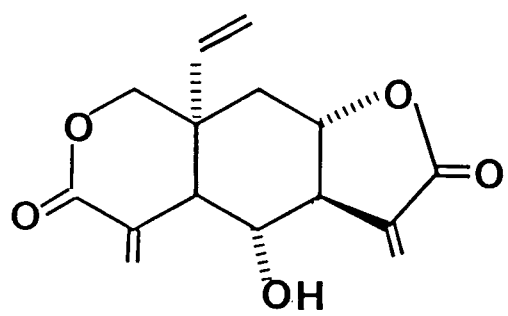


(5)

Vernolepin showed inhibitory activity in vivo against the Walker intramuscular carcinosarcoma 256, and cytotoxicity against KB cell culture.

The structure was established by normal spectroscopic examination and conversion to various derivatives (2) to (5),with final confirmation being achieved by means of X-ray crystallography.[8]

A second sesquiterpene lactone was also extracted from Vernonia hymenolepis. This was named vernomenin (6), illustrated below.



(6)

In contrast to vernolepin, this elemanolide lactone exhibited no in vivo tumour inhibitory activity.

Since its discovery, vernolepin has been isolated from other species of Vernonia. V. guineensis Benth.[9] and V. amygdalina Del.[10] have also been found to contain this sesquiterpene lactone, together with another elemanolide lactone, vernodalin.

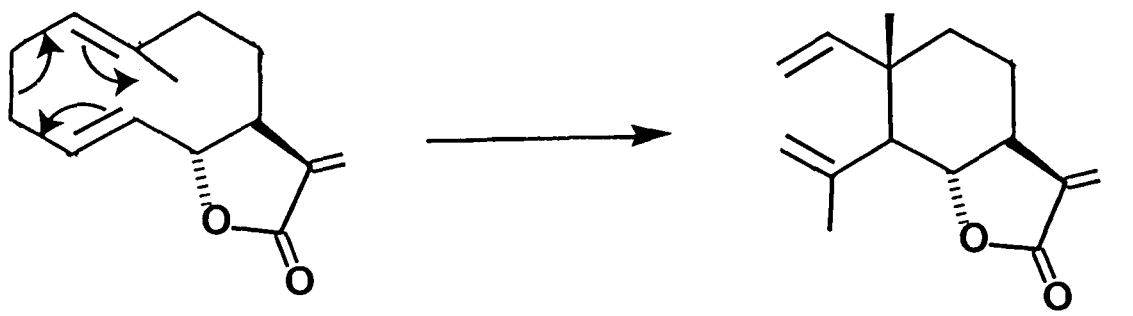
I.A.2. Nomenclature and Biogenesis

Isolation of sesquiterpene lactones began in the 1960s, with the extraction of helenalin from Helenium mexicanum.

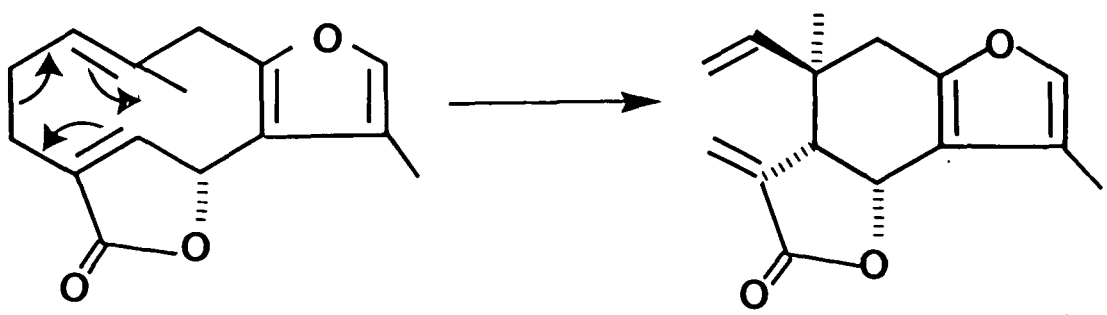
Currently over 1000 different lactones have been identified from many species of higher and lower plants, chiefly from species of Compositae.

Classification of such a vast number of compounds is based on the type of carbocyclic skeleton.[12,13,14] A few representatives of the more common classes[15] are shown in Scheme 1. Special attention has been paid to the elemanolides, as this group is of direct relevance to the research objectives discussed in a later section.

It is worth pointing out, at this stage, that some elemanolides are said to represent artifacts, which are formed by the laboratory work-up of the plant extract. This is due to the relative ease with which a group of lactones known as the germacranolides, undergo a thermal Cope rearrangement (generally >140^{o}C).



costunolide — saussurealactone [20]



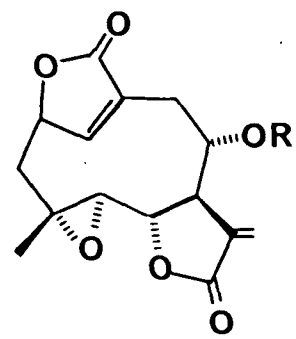
linderolactone — isolinderolactone[21]

Some Sesquiterpene Lactone representatives

Germacranolides:-

Approximately 270 known

(based on 1979 figures)

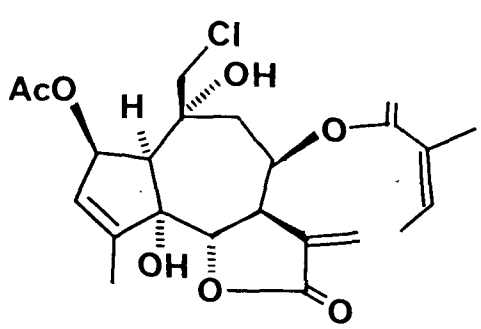


R = CH_2 = $C(CH_3)CO$ elephantopin[14]

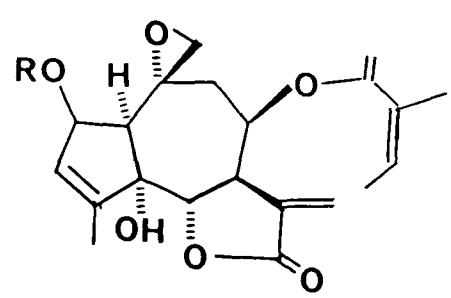
R = $(CH_3)_2$ C=CHCO elephantin

Guaianolides:-

ca 200



eupachlorin acetate [15a,b]

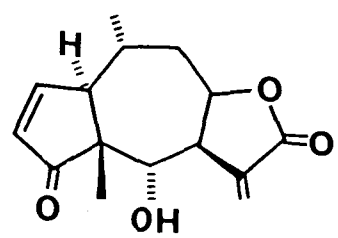


R = Ac, eupachlorin

R = H, euparotin

Pseudoguaianolides:-

ca 140

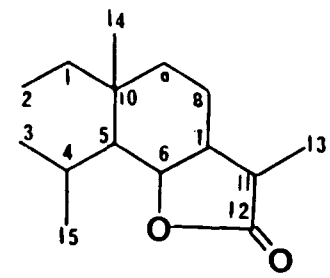


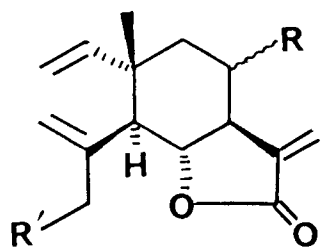
helenalin[16a,b]

Scheme 1

Elemanolides:[12] ca 30

These compounds have this basic skeleton



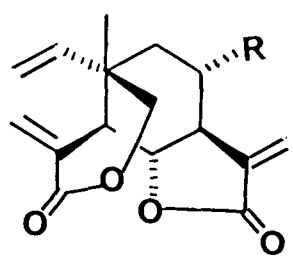


R = α-OH, R^1 = OH

11 (13)-dehydromelitensin

R = β-OAc, R^1 = H

epitulipdienolide

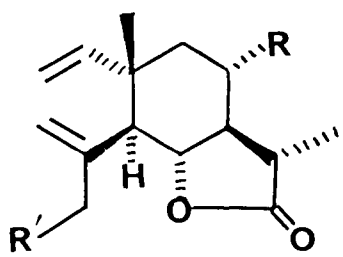


R = OH

vernolepin

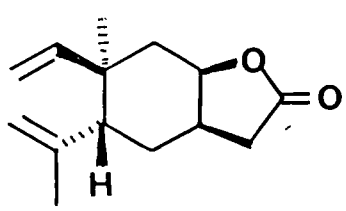
R = OCO $C(=CH_2)CH_2OH$

vernodalin



R = R^1 = H saussurea lactone

R = R^1 = OH melitensin



Callitrin

Scheme 1 cont.

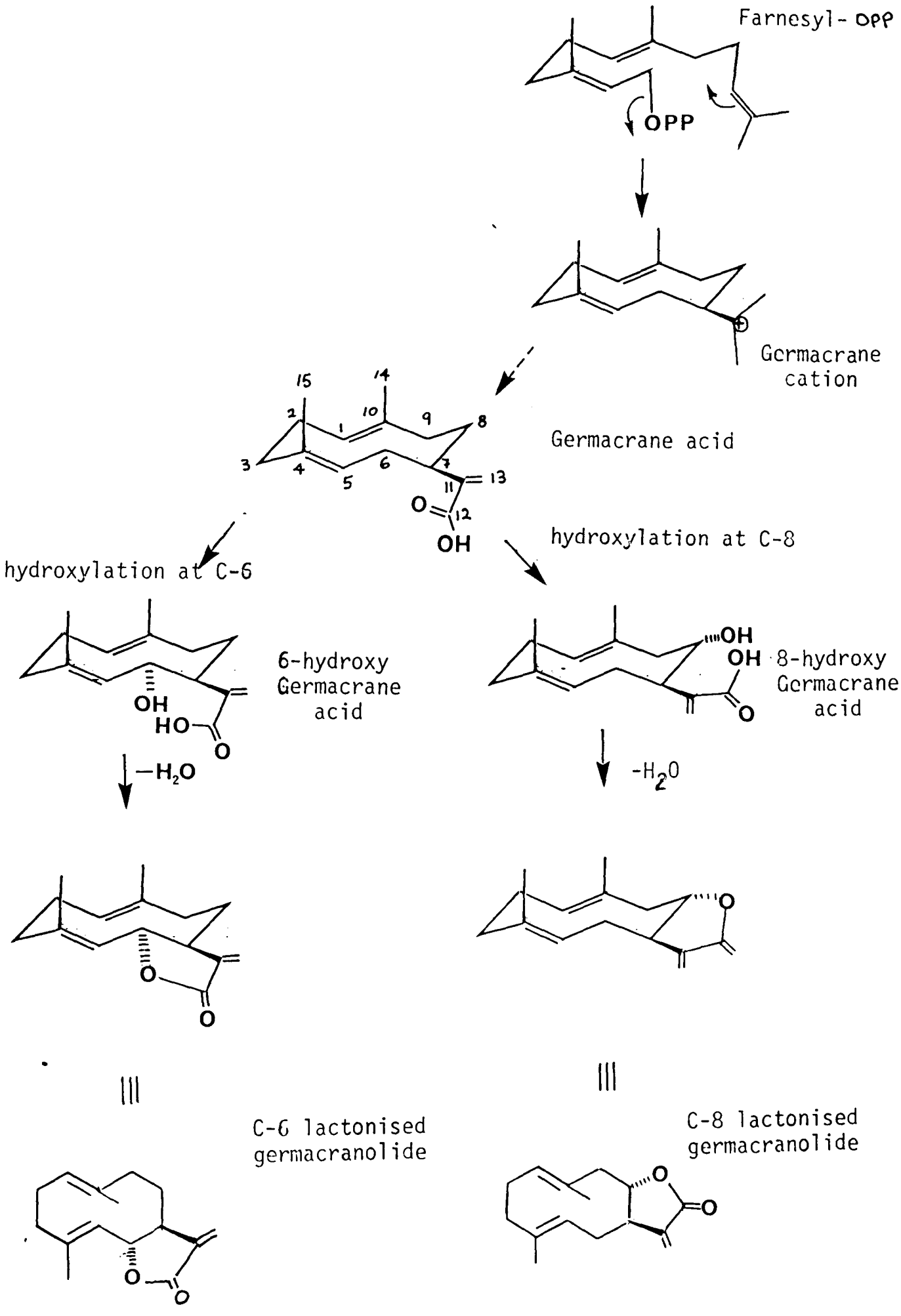
However, for the case of vernolepin and vernomenin, as their extraction did not involve the use of heat, they have been confirmed to be naturally occurring elemanolides. This is, in fact, true for most oxidatively modified divinylcyclohexane systems.

Elemanolide lactones are biogenetically derived from the germacranolides, which are in turn formed from the sesquiterpene, farnesyl pyrophosphate.[22,3]

Ring closure of trans, trans - farnesol gives rise to the family of sesquiterpene lactones[12,14,23,24] (Scheme 2). As shown, enzyme mediated cyclisation and subsequent oxidative modifications produce the C-6 and C-8 germacranolides. The suffix "olide" refers to the lactone group. The germacranolides then undergo a variety of cyclisations, ring fissions and methyl migrations to yield the other major skeletal types of sesquiterpene lactones, depicted in Scheme 3. For the sake of simplicity, only the 7,8-lactonised structures are presented. The lactones are arranged in what might be called "increasing biogenetic complexity". Therefore, the germacranolides represent the most primitive stage or stage I, elemanolides, eudesmanolides and guaianolides, stage II. Stage III is exemplified by compounds showing further modifications, such as eremophilanolides and pseudoguaianolides. The last column depicts representatives of the most highly transformed sesquiterpene lactones.

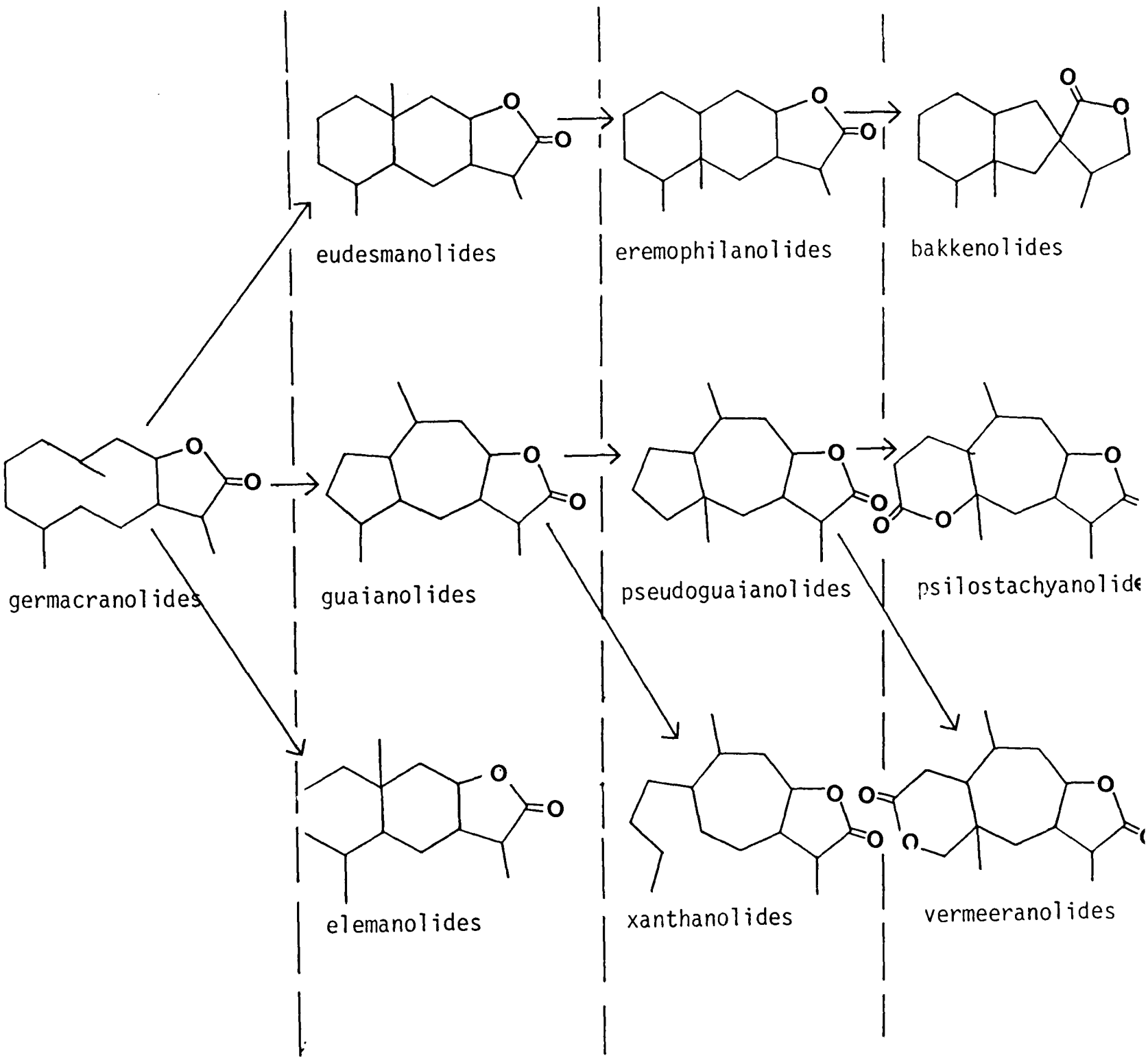
A closer examination[12] of the biosynthetic pathway to elemanolides most likely involves a Cope rearrangement of germacranolides, which occurs under laboratory conditions with great ease, as already mentioned. Whether this occurs spontaneously or is enzymatically controlled is unknown. Due to lack of experimental

Biogenesis of C-6 and C-8 germacranolides from the isoprene precursors



Scheme 2

Hypothetical biogenesis of the major sesquiterpene skeletal types



Scheme 3

evidence, the exact details of the pathway have not yet been substantiated.

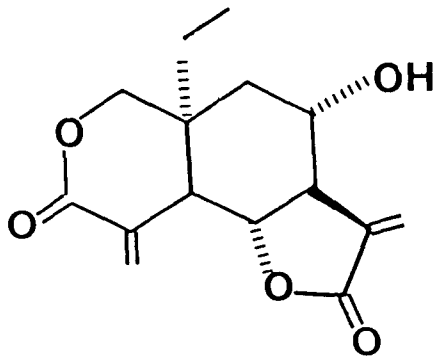
I.A.3. Biological Activity

The cytotoxicity and anti-tumour activity of vernolepin has already been mentioned. It was originally believed that this could be the result of alkylation of nucleophilic centres in the biological system. A study of reactions of tumour inhibitory α-methylene lactones, e.g. vernolepin, elephantopin and eupachlorin acetate with model biological nucleophiles[25] revealed that thiols were the most reactive of the nucleophiles investigated, and that biological activity decreased markedly with the successive addition of L-cysteine to bis unsaturated lactones.

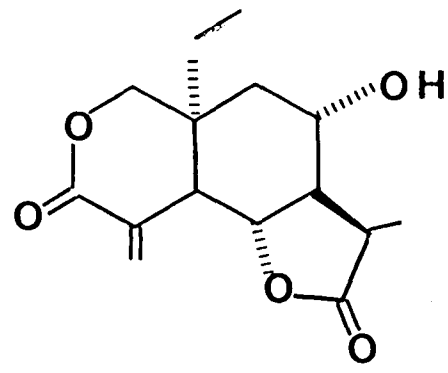
Thus, the monocysteine adducts still showed appreciable cytotoxicity, but the bis cysteine adduct was essentially devoid of all growth inhibitory activity. These findings were in agreement with the results of a survey conducted to evaluate the effects of several sesquiterpene dilactones, e.g. elephantin, vernolepin, on plant growth. These compounds were found to be strong inhibitors of the extension of wheat coleoptile[26,5] sections; (in the case of vernolepin this inhibition was reversible by the addition of indole-3-acetic acid). Again, the inhibitory effect was found to be completely blocked by the addition of a sulphydryl compound to the medium. In addition tumour inhibitory α-methylene lactones have been shown to inactivate phosophofructokinase[27], an enzyme containing many -SH groups and glycogen synthase.[28]

A survey of the structure-cytotoxicity relationship[4,5] revealed the cytotoxicity of vernolepin to be directly related to

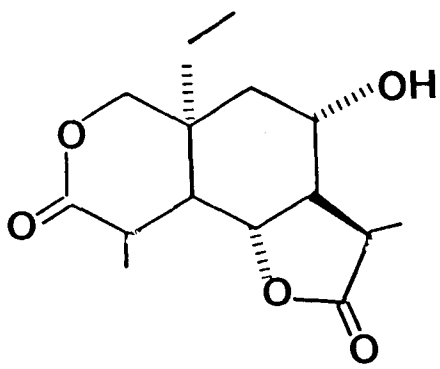
the presence of free conjugated α-methylene functions.[5] Thus, selective reduction of the ethylidene double bond to give dihydrovernolepin does not appear to affect the cytotoxicity. However, modification of the α-methylene - γ-lactone by esterification or hydrogenation results in a 10-fold diminution in cytotoxicity. Modification of both α-methylene lactone systems leads to a derivative that is essentially inactive.



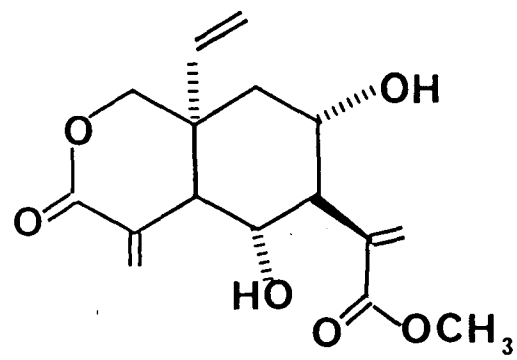
dihydrovernolepin



tetrahydrovernolepin



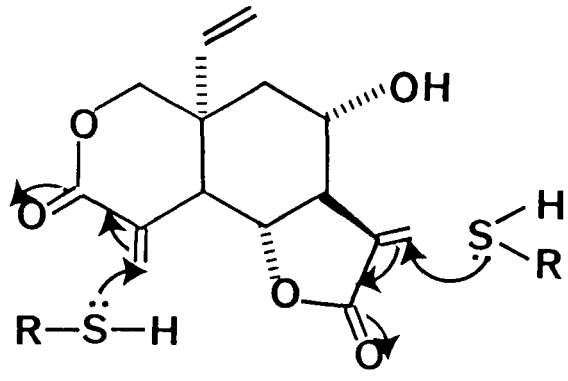
hexahydrovernolepin



acidic methanolysis product

In conclusion, these results and others,[29,30] indicate that sesquiterpene lactones act by a Michael-type addition of the conjugated α-methylene γ- and δ-lactone functions with sulphydryl bearing compounds.

viz:-



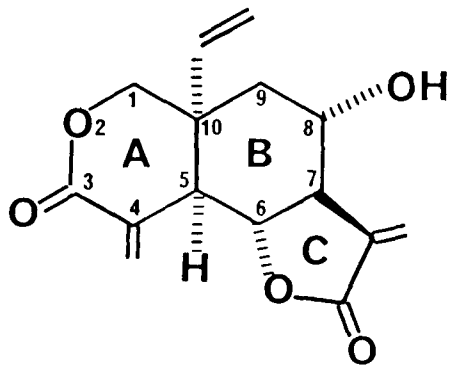
Kupchan[4] has suggested that this results in selective alkylation of key enzymes which control cell division. The selectivity may result from many factors, among which are transport of the tumour inhibitor into the cell, and the chemical nature and steric environment of the specific nucleophile to be alkylated. Alternatively, it has been suggested[30] that these compounds react with thiol groups on the cell surface.

Other biological properties of sesquiterpene lactones[10,23, 24,31] may be referred to in the bibliography.

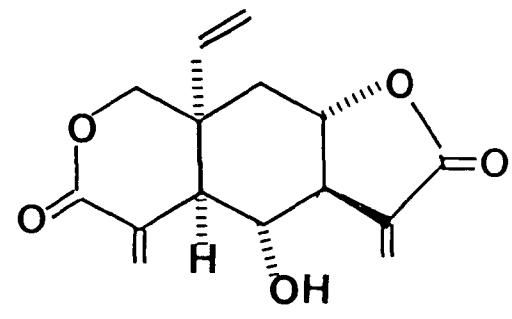
I.B. SYNTHETIC ROUTES

Vernolepin has stimulated a great deal of synthetic activity since its discovery. Interest has arisen from the novel structural and stereochemical features inherent in the molecule in addition to its physiological properties. Extensive studies have culminated in a total of five syntheses of vernolepin, plus numerous synthetic approaches. These have concentrated on the preparation of model compounds for the cis- fused α-methylene-δ-valerolactone AB ring system, possessing an angular vinyl group, and model compounds towards rings B and C of vernolepin. Many of these compounds and their analogues have been biologically tested and found to be moderately cytotoxic. As the tumour inhibitory α-methylene - γ-butyrolactone moiety has been found to exist in a rapidly expanding range of sesquiterpene lactones, a vast amount of research has been dedicated to their construction. This includes methods for cis- and trans- fusion of lactones to six, seven and ten membered rings[32] and the concomitant α-methylenation.[33,34]

I.B.1. Total Syntheses of Vernolepin



vernolepin



vernomenin

A successful stereospecific synthesis of vernolepin must be able to overcome several structural problems,[35] viz:-

(a) Construction of ring B in a stereochemical arrangement which allows for the elaboration of ring C.

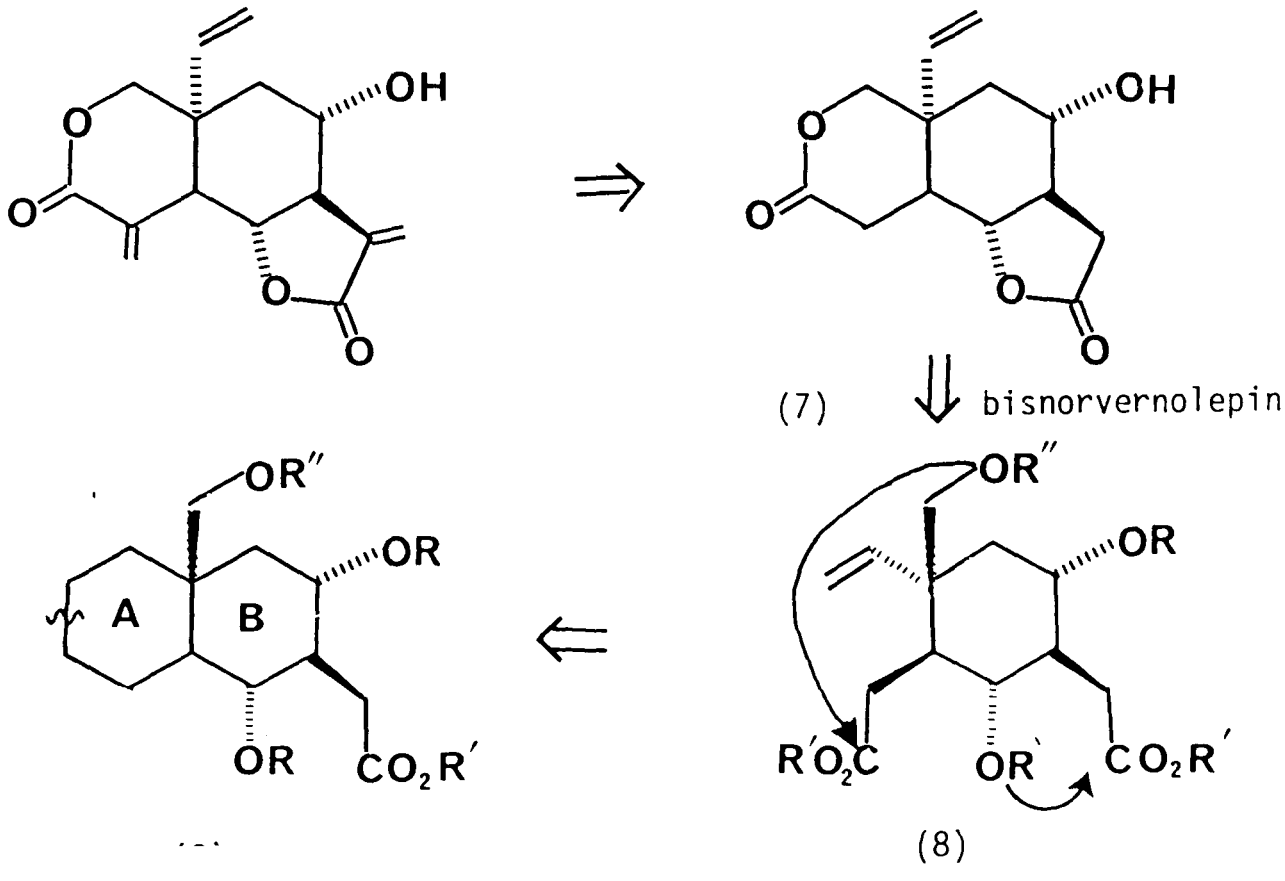
(b) Differentiation between the hydroxylactone arrangements in vernolepin and vernomenin.

(c) Bis α-methylenation of the bisnor precursor. (Grieco has shown that this may be postponed until the last stage of the synthesis).

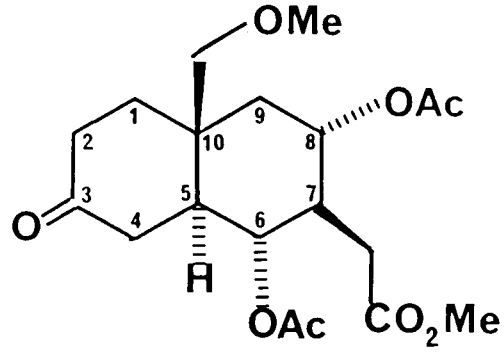
(d) Construction of the cis-fused 2-oxa-3-decalone system bearing an angular function which may be converted to a vinyl group.

(i) Grieco et al.[36,37]

The first total synthesis of (±)-vernolepin and (±)-vernomenin was reported by Grieco in 1976. The retrosynthetic strategy employed is outlined below:-



Bisnorvernolepin may be derived from the cyclohexane precursor (8) which possesses five chiral centres. The stereochemical implications associated with the construction of such a molecule are formidable. However, the problem becomes simplified by the incorporation of two of the substituents into the trans-fused decalin derivative (9). Consequently, the plan adopted by Grieco involved cleavage of the C-2, C-3 bond of a suitably functionalised ring A, with the conversion of C-1 and C-2 into a vinyl group, and formation of a carboxylic acid or its equivalent at C-3. The angular hydroxymethyl moiety would then join with C-3 to afford a cis-fused 2-oxa-3-decalone. In order to realise the synthetic scheme (10) was used as the key intermediate, (vide infra). The three chiral centres at C-6, C-7, and C-8 have the appropriate

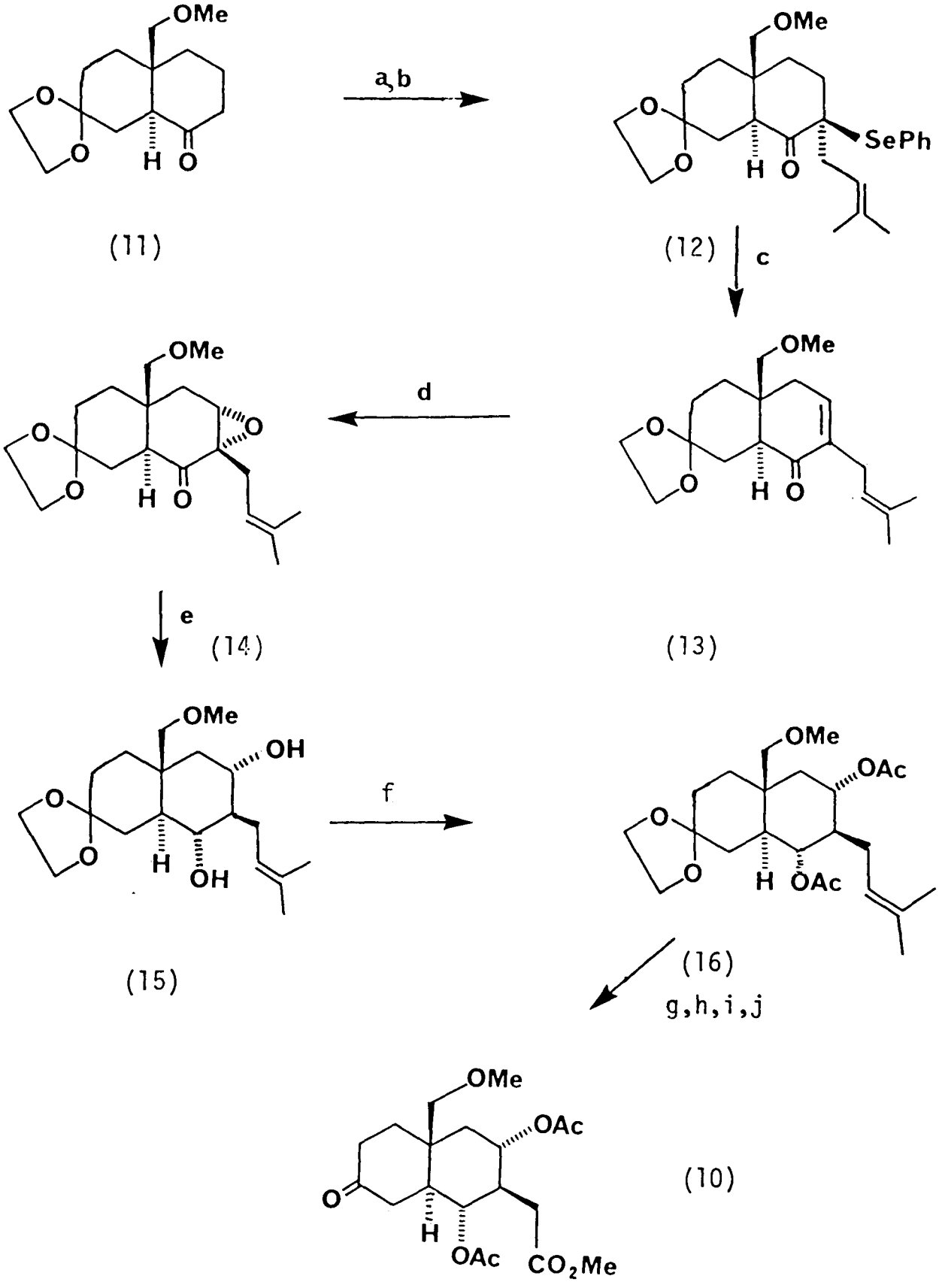


(10)

functionality for eventual conversion into bisnorvernolepin, or bisnorvernomenin.

The synthesis is shown in Schemes 4 and 5. The trans-decalone (11),obtained by equilibration of the cis-isomer with sodium ethoxide in methanol, was used as starting material. Two consecutive alkylations then occurred. The lithium enolate was initially alkylated with phenylselenyl chloride, and then, after regeneration, with prenyl bromide. The prenyl group was chosen to represent a latent

Synthesis of trans-decalone (10)



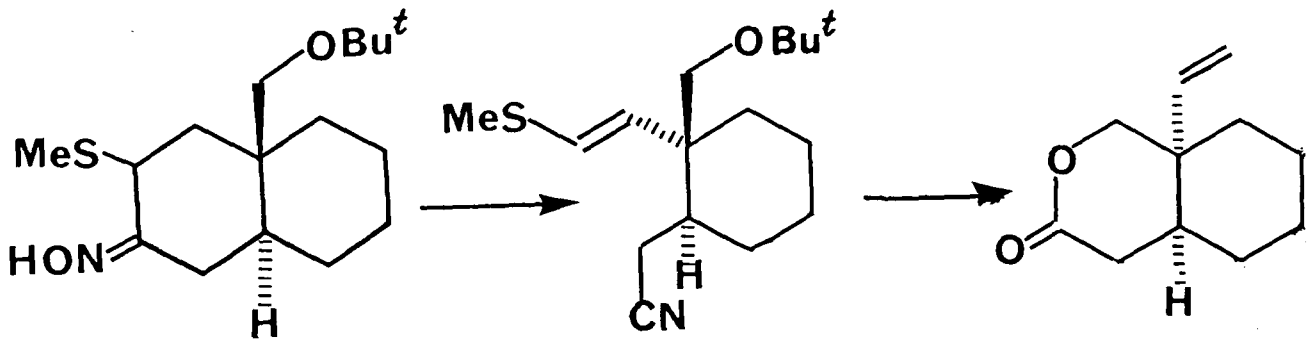
Scheme 4

a, LDA,THF, PhSeCl; b, LDA,THF, Prenylbromide; c, 30% H_2O_2; d, t-BuOOH; e, Li,NH_4Cl, NH_3, THF; f, Ac_2O,py; g, O_3, CH_2Cl_2; h, Jones reagent; i, CH_2N_2; j, HCl, THF.

acetic acid unit, as model studies had shown it to be resistant to a dissolving metal-ammonia reduction performed at a later stage in the synthesis. Treatment of the selenide (12) with hydrogen peroxide gave the selenoxide, which underwent elimination to afford the endocyclic dienone (13). Reaction with tert-butyl hydroperoxide resulted in the formation of the α-epoxide (14) exclusively. Lithium-liquid ammonia reduction, in the presence of a proton source produced the dihydroxy-decalin (15), which was converted to the diacetate derivative (16). The latent acetic acid side chain was unmasked by ozonolysis, followed by an oxidative work-up and esterification. Finally, deketalisation gave the key intermediate (10).

The next phase of the synthesis involved conversion to the 2-oxa-3-decalone system. Previous model studies on the construction of the vernolepin AB ring system had demonstrated two viable routes:[38]

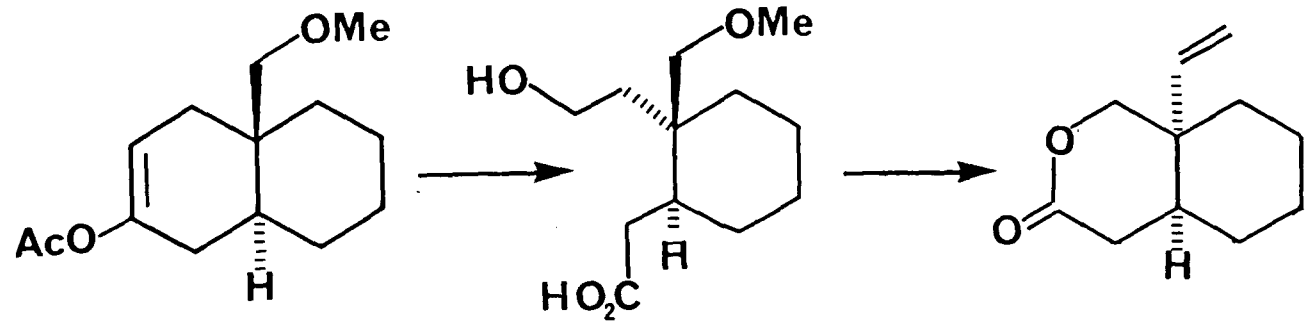
(1)



(17)

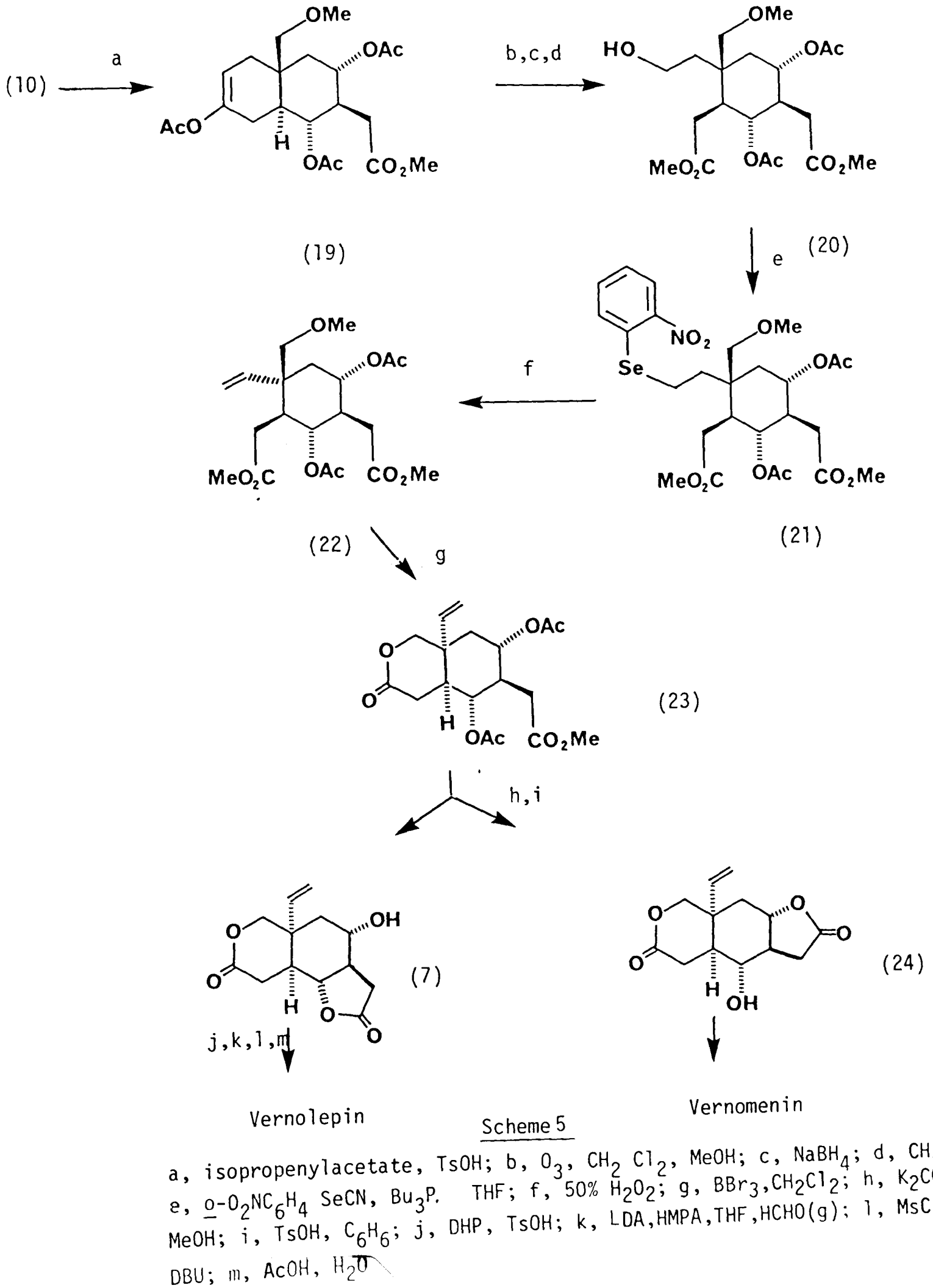
A second-order Beckmann fragmentation on the oxime (17).

(2)



(18)

Synthesis of (±) - vernolepin and (±) - vernomenin



Scheme 5

a, isopropenylacetate, TsOH; b, O_3, CH_2Cl_2, MeOH; c, $NaBH_4$; d, CH_2N_2; e, o-$O_2NC_6H_4$ SeCN, Bu_3P. THF; f, 50% H_2O_2; g, BBr_3,CH_2Cl_2; h, K_2CO_3, MeOH; i, TsOH, C_6H_6; j, DHP, TsOH; k, LDA,HMPA,THF,HCHO(g); l, MsCl,py, DBU; m, AcOH, H_2O

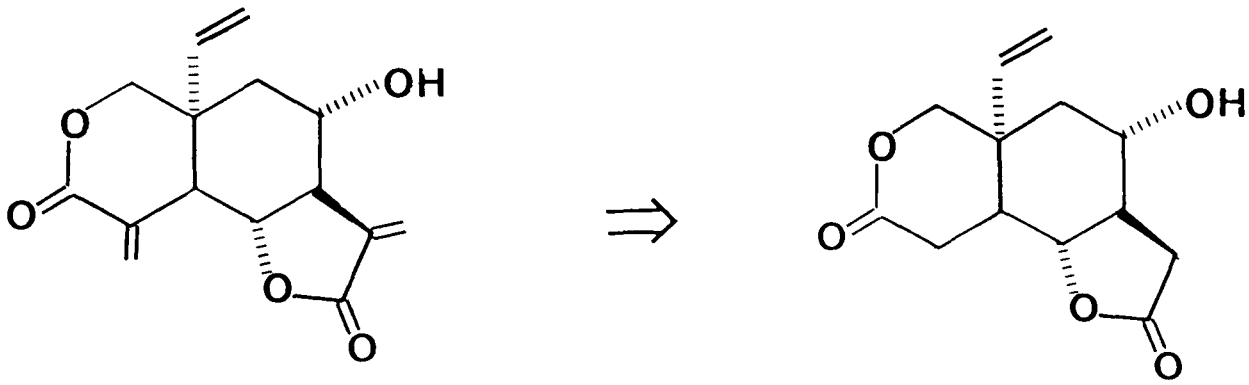
Ozonolysis,[40,41] using a reductive work-up of the enol acetate (18). This was found to be the method of choice, based on the overall yields of 2-oxa-3-decalone obtained.

Hence, ozonolysis followed by esterification of the hydroxy acid gave (20). Conversion of the hydroxyethyl function into the angular vinyl group was effected by successive oxidation and elimination of the o-nitrophenylselenide (21). Alkaline hydrolysis of the δ-lactone (23), formed by cleavage of the methyl ether with boron tribromide, followed by lactonisation gave a 2.5:1 mixture of the bisnor products, fortuitously in favour of bisnorvernolepin.

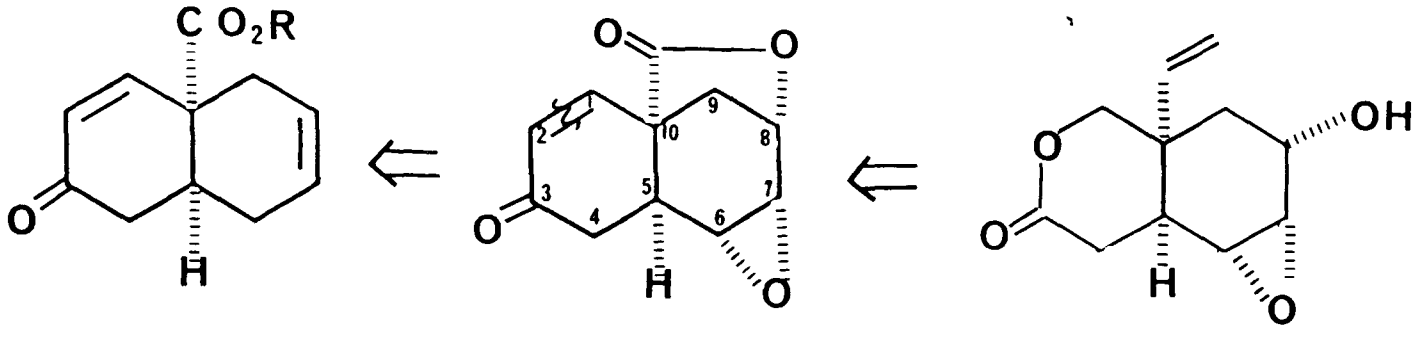
The synthesis was concluded by bis-α-methylenation. Grieco[42] had previously demonstrated the feasibility of executing the necessary steps concurrently. Thus, the dilactone enolates of both protected bisnor compounds were trapped with gaseous formaldehyde affording the crude α-hydroxymethylated lactones. These were converted into the corresponding mesylates, eliminated with diazabicycloundecene (DBU), and finally hydrolysed to afford (±) - vernolepin in a total of 23 steps from trans-decalone (6) and in an overall yield of 0.113%. (±) - Vernomenin was also obtained in 0.043% yield over 23 steps.

(ii) Danishefsky et al.[43,44]

Danishefsky et al. have adopted quite a different strategy[39] towards the synthesis of vernolepin. This is summarised below:-

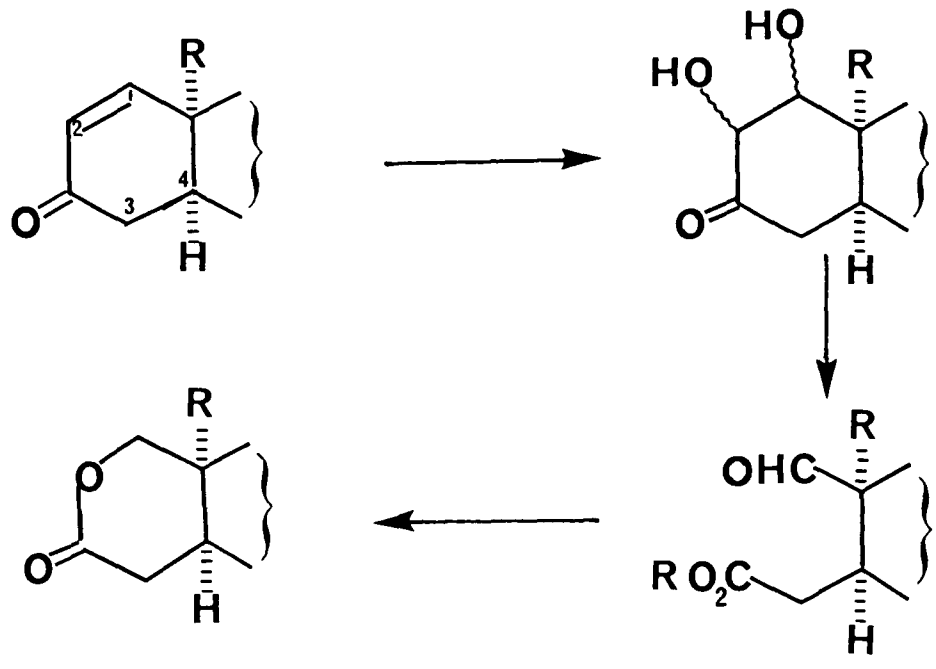


(7)



(28) (27) (26)

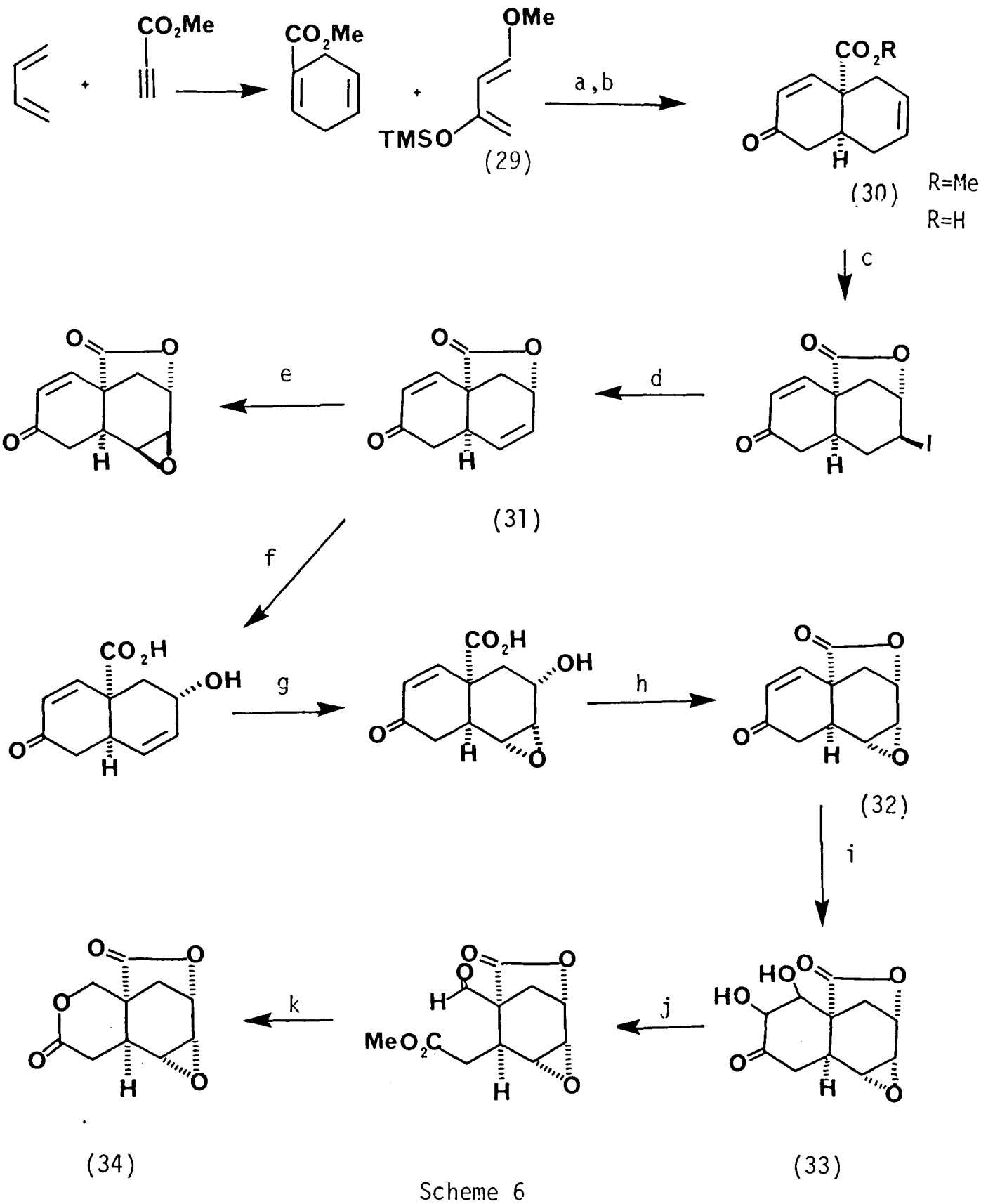
The approach was centred on the use of cis-fused hydronaphthalenes of type (28). This type of precursor would easily be available from a Diels-Alder route, and the angular functionality eventually converted into a vinyl group. Model studies[35] had indicated a feasible route to the 2-oxa-3-decalone (26) via oxidative cleavage of the C-1, C-2 bond with the excision of C-2 and formation of an acid aldehyde derivative, followed by reduction and lactonisation.



To conclude, nucleophilic attack at C-7 from the concave β side of the molecule, by a suitable 2 carbon unit, would result in the required stereochemistry for eventual conversion to bisnorvernolepin.

The synthesis (Schemes 6 and 7) was initiated by two consecutive Diels-Alder reactions. Cycloaddition of 1,3-butadiene with

Synthesis of dilactone (37)



Scheme 6

a,p-TsOH; b, NaOH, THF, H_2O; c, I_2, KI, $NaHCO_3$; d, DBU benzene; e, p-nitroperoxybenzoic acid;f, NaOH, THF, water; g, mCPBA, benzene, p-dioxane; h, NaOAc, Ac_2O; i, OsO_4, $BaClO_4$, THF, H_2O; j, $Pb(OAc)_4$, MeOH, benzene; k, $Li(Bu^tO)_3$ AlH , THF, Amberlite 1R120 (H^+ form); benzene.

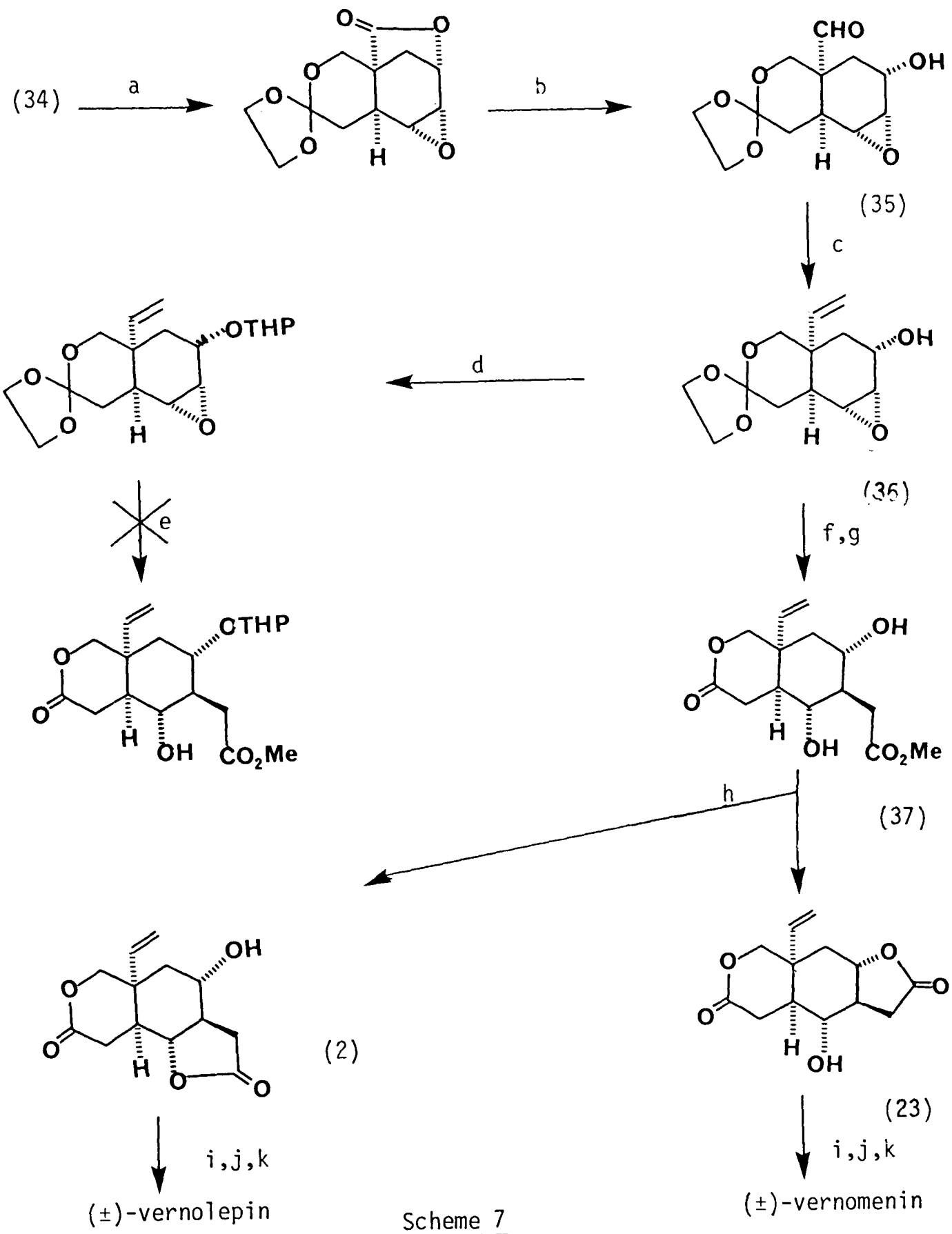
methyl propiolate gave methyl 2,5-dihydrobenzoate, which was subjected to a further reaction with diene (29). This resulted in the required cis stereochemistry for the A/B ring function. Acid treatment of the adduct afforded the enone (30) which was later saponified. This angular group was used to direct incorporation of the oxygen at C-8 into the α-configuration, by a stereoselective iodolactonisation. Treatment with DBU gave the dienone lactone (31).

The next stage of the synthesis was introduction of the 6α, 7α-oxido stereochemistry. The dienone lactone (31) proved to be resistant to attack by most peracids. Epoxidation was eventually achieved with p-nitroperoxybenzoic acid (10 days), but unfortunately gave the undesired 6β, 7β isomer. However, by initially converting the lactone to the hydroxy acid, a Henbest[45] type of stereochemical guidance could be employed to direct rapid α-epoxidation by m-CPBA. Danishefsky has suggested that the allylic hydroxy group is responsible for the strong accelerating effect. The lactone (32) was subsequently reformed by the action of anhydrous sodium acetate in hot acetic anhydride.

Construction of the A ring valerolactone was then taken in hand. Reaction of the enone with osmium tetroxide afforded the ketoglycol (33), which was cleaved by treatment with lead tetraacetate. Reduction with lithium tri-tert-butoxyaluminium hydride, followed by heating with Amberlite IR-120 afforded the dilactone (34).

As it was likely that the δ-lactone would not be stable to treatment with dilithioacetate, used at a later stage of the synthesis, it was protected. Fortunately selective orthoesterification occurred, which enabled the γ-lactone to be reduced to the hydroxyaldehyde[35] with diisobutylaluminium hydride. Wittig olefination with triphenylmethylenephosphorane gave the vinyl epoxide (36). This molecule can

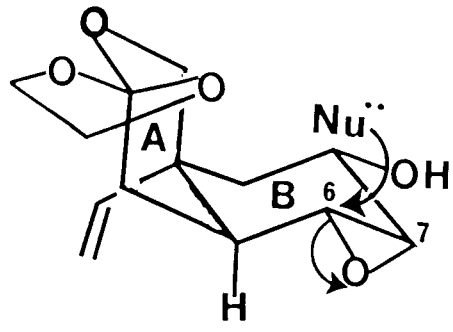
Synthesis of (±) - vernolepin and (±) - vernomenin



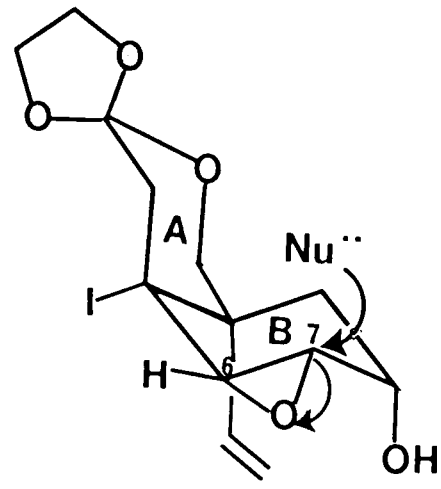
Scheme 7

a, $(CH_2OH)_2$, benzene, $MgSO_4$, Dowex SOW-X8 (H^+ form), p-TsOH;b, DIBAL, DME; c, $Ph_3P{=}CH_2$, DME; d, DHP, pTsOH; e, $LiCH_2CO_2Li$,DME; f, $LiCH_2\ CO_2Li$; g, CH_2N_2, EtOAc, acetone; h, pTsOH, benzene; i, LDA, $CH_2{=}N^+Me_2I^-$, THF, HMPA; j, MeI, p-dioxane; k, $NaHCO_3$.

exist in two chair-chair conformers, (vide infra).



I



II

Danishefsky has demonstrated the low energy conformer to be I, by a high field n.m.r. spectrum of the acetate derivative. This was expected as the substituents on the B ring are equatorial. Trans-diaxial opening by a nucleophile would result in the undesired attack at C-6. However, as the path for diaxial attack is encumbered by the axial oxygen of the ethylene orthoester linkage, the activation energy is increased. On the other hand, trans-diaxial opening of the higher energy conformer II would result in the desired cleavage at C-7. In practice,[46] treatment of the vinyl epoxide with dilithioacetate, followed by acidification and esterification gave exclusively the dihydroxyester (37). Danishefsky failed to isolate any compound resulting from attack at C-6. The diacetate derivative of (37) was found to be identical to a sample of Grieco's intermediate (23).

In order to accomplish regiospecific lactonisation of the C ring, Danishefsky planned to protect the hydroxy group of the vinyl

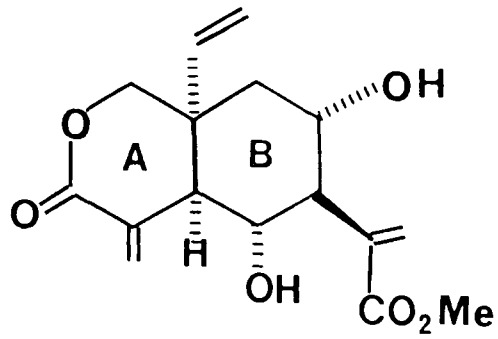
epoxide (36), until differentiation of the oxygen functions at C-6 and C-8 had been achieved. The hydroxy group was protected as the tetrahydropyranyl ether, which was then subjected to epoxide opening with dilithioacetate. Unfortunately this was not successful and only starting material was recovered. Lactone closure of the dihydroxyester (37), as expected, gave a 2:1 mixture of bisnorvernolepin and bisnorvernomenin.

The final step involved incorporation of the α-methylene groups. The "one pot" process reported earlier by Grieco[42] necessitated protection and subsequent deprotection of the hydroxy moiety. Danishefsky obviated this by utilising Eschenmoser's dimethyl (methylene) ammonium iodide. Hence, treatment of the lithium dienolate of bisnorvernolepin with Eschenmoser's salt, followed by the addition of excess methyl iodide to the crude product and treatment with aqueous sodium bicarbonate, liberated (±) -vernolepin. (±) - Vernomenin was obtained in a similar fashion.

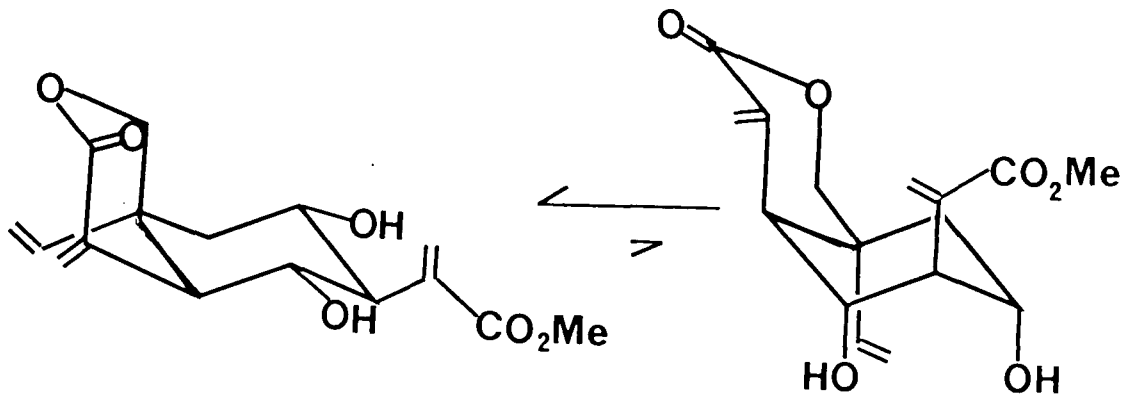
In summary (±) - vernolepin and (±) - vernomenin were prepared in 19 steps from methyl 2,5-dihydrobenzoate, and in overall yields of 1.7 and 0.5% respectively.

(iii) Isobe et al.[47-52]

The synthetic strategy of Isobe et al is based on conformational analysis of the B ring of vernolepin. Thus, the methanol adduct (38) of vernolepin could exist as two chair-chair conformers:-

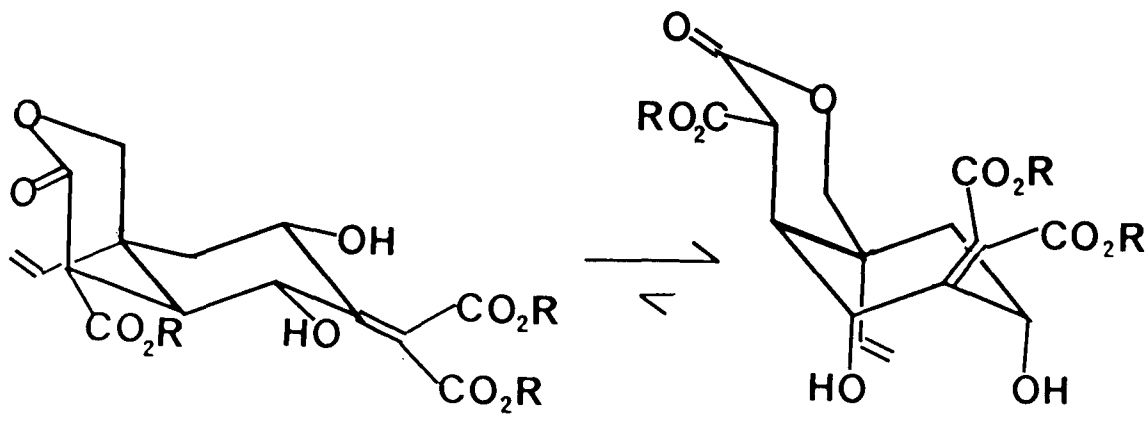


(38)



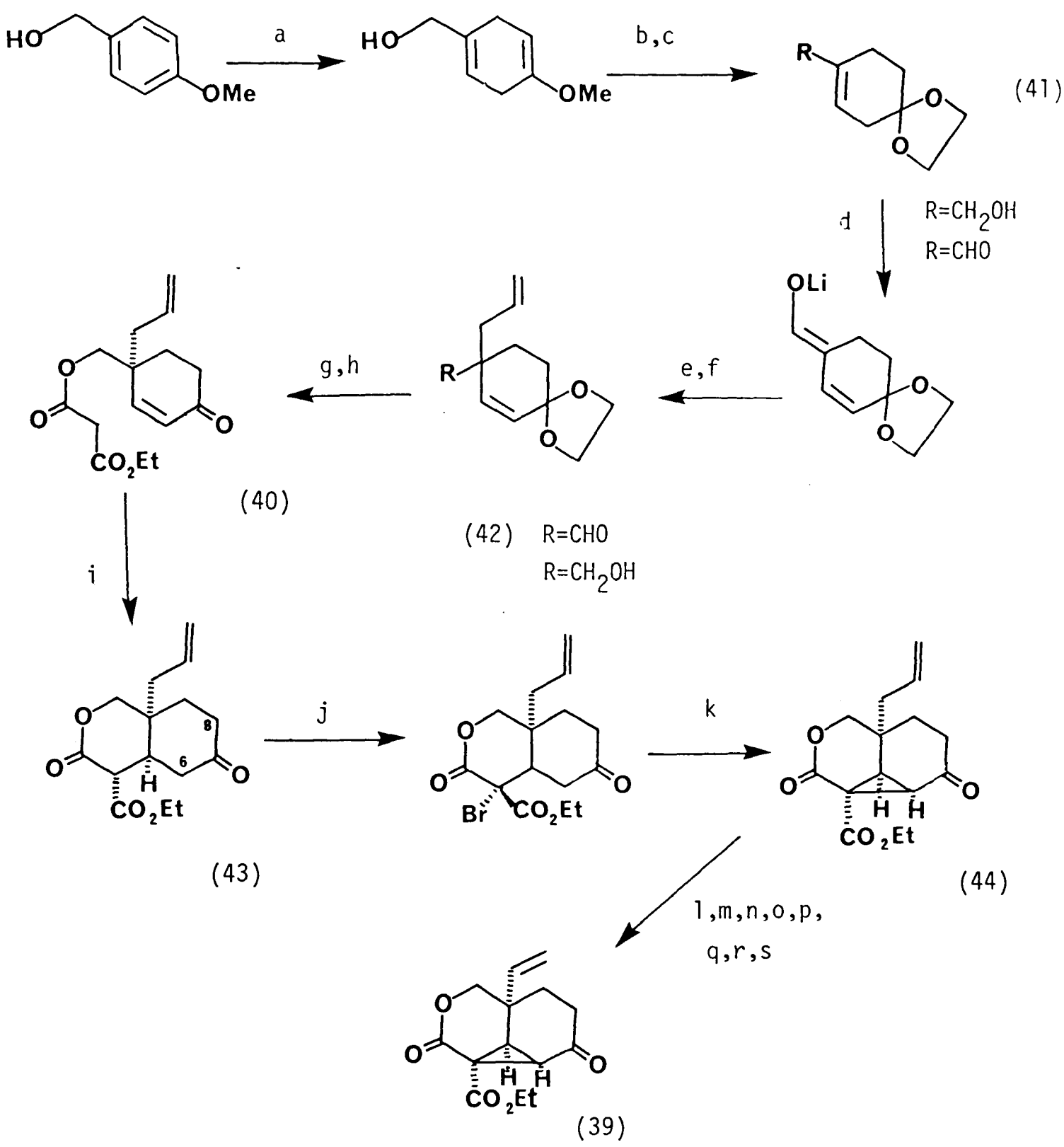
I II

Conformer I was predicted to be most stable as 5 of the 6 substituents in the B ring are equatorial. The higher energy conformer II was of synthetic interest as axial bonds may easily be introduced into a cyclohexane derivative. This is the conceptual basis for the key intermediate (39) used by Isobe. By introducing bulky substituents, as shown below, steric interference results in a shift of equilibrium to conformer IV.



III IV

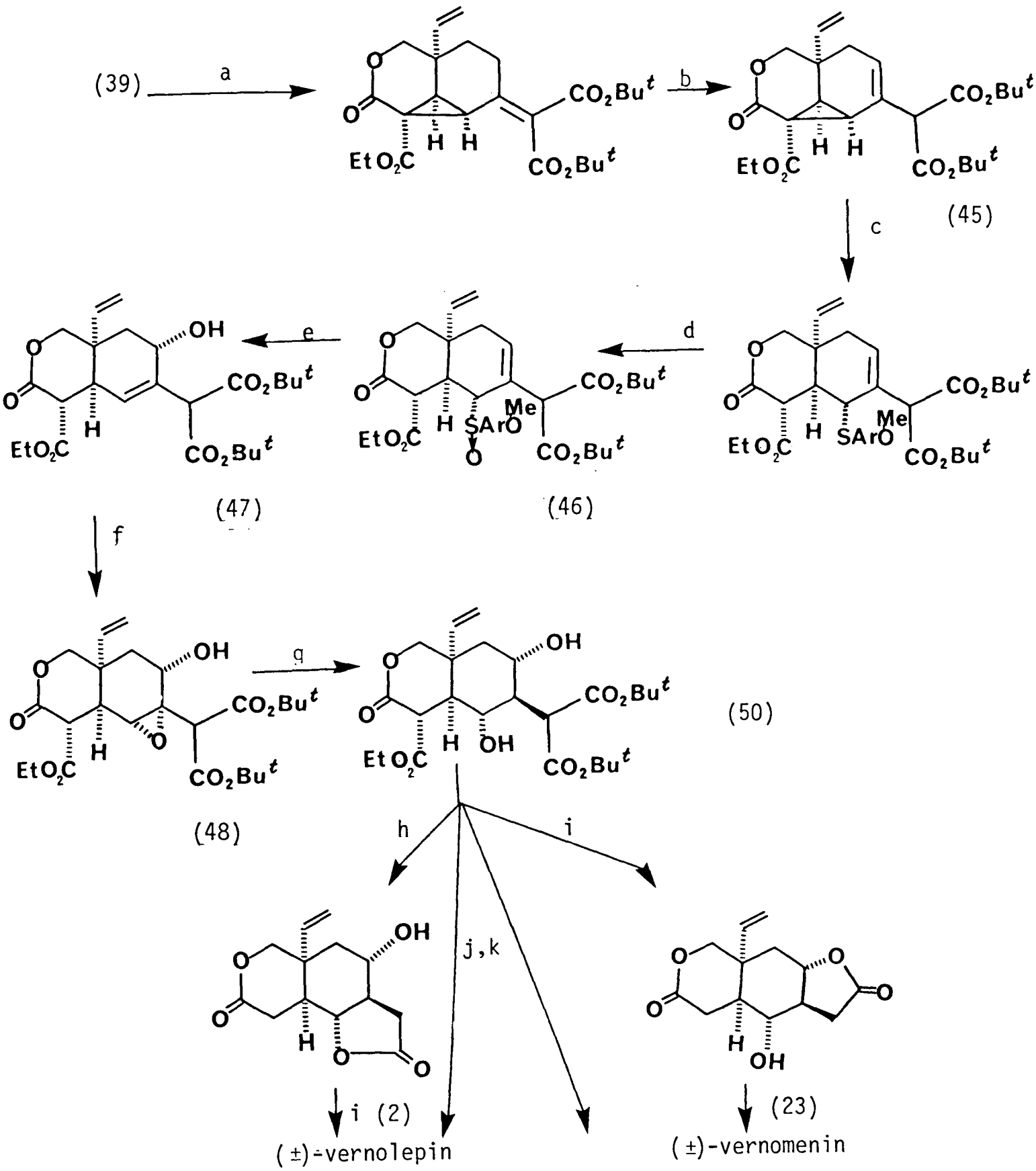
Preparation of the key synthetic intermediate



Scheme 8

a, Na, NH_3(l), THF, EtOH; b, $(CH_2OH)_2$, BF_3-etherate, THF: c, pyridinium chlorochromate, NaOAc; d, LDA, HMPA; e, CH_2CHCH_2I; f, $NaBH_4$; g, EtO_2CCH_2COCl, py; h, H_2O, HCl; i, NaH; j, NBS, THF; k, DBU; l, $(CH_2OH)_2$, BF_3-etherate, THF; m, O_3, CH_2Cl_2; n, Et_3N; o, $NaBH_4$; p, MsCl, py; q, o-$O_2NC_6H_4SeCN$, Bu_3P, THF; r, O_3, Δ; s, H_2O, HCl.

Synthesis of (±) - vernolepin and (±) - vernomenin

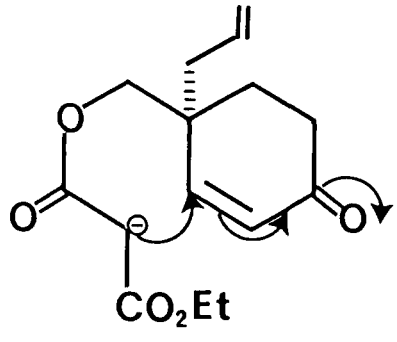


Scheme 9

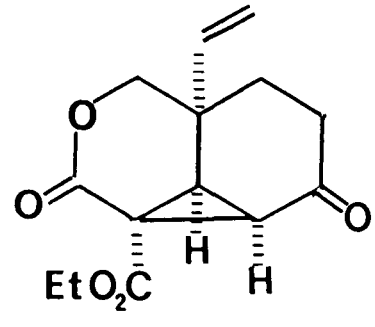
a, $CH_2(CO_2Bu^t)_2$, $TiCl_4$,py; b, DBU, THF; c, NaSAr p OCH_3, THF; d, mCPBA, CH_2Cl_2; e, $(MeO)_3P$, EtOH, Δ; f, mCPBA, CH_2Cl_2; g, $NaCNBH_3$, HMPA, B_2H_6, THF; h, Al_2O_3, dioxane, water; i, CF_3CO_2H, H_2O, Δ, dichlorobenzene; j, Amberlite IRA400 (activated with 10% NaOH), MeOH, CF_3CO_2H, H_2O; k, Et_2NH, HCHO,H_2O, NaOAc, AcOH.

In addition, the axial hydroxy groups could be used to achieve stereospecific reduction at the exo double bond, by coordination with the hydride reagent and directing attack from the α side.

The key intermediate in the synthesis is the cyclopropane derivative (39). The cis- fused 2-oxa-3-decalone system was formed



(40)

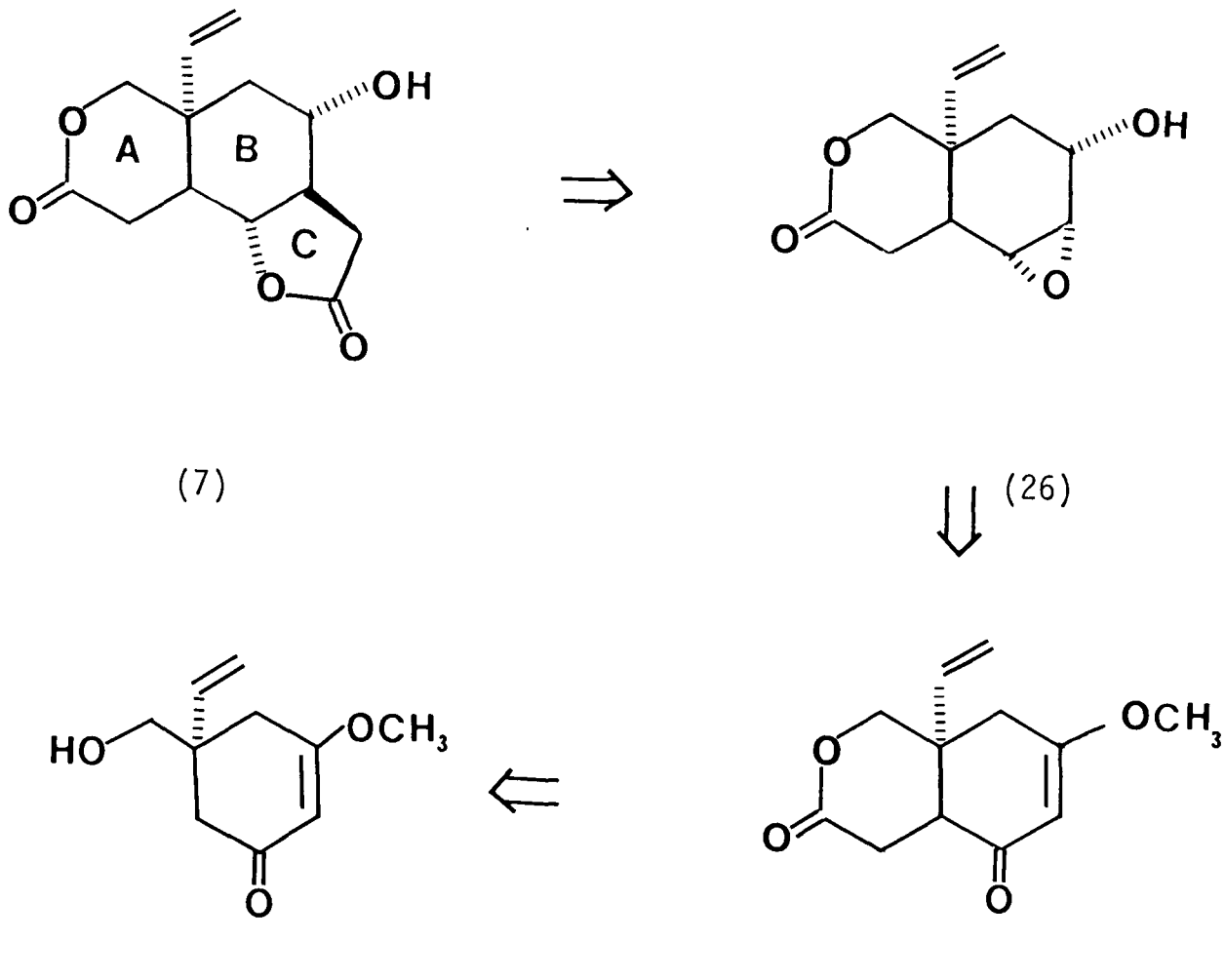


(39)

by a base catalysed intramolecular Michael-type of cyclisation of the enone malonate (40). Introduction of an angular vinyl group occurs at an early stage in the synthesis. The purpose of the cyclopropane ring is to confer sufficient rigidity to the molecule to allow further appropriate stereochemical functionalisation of the B ring. The synthesis is summarised in Schemes 8 and 9. This allowed the preparation of vernolepin in 26 steps from p-anisylalcohol and in an overall yield of 0.6%.

(iv) Schlessinger et al.[53,54]

Bisnorvernolepin was the ultimate synthetic target for Schlessinger et al. as other research groups had demonstrated the feasibility of incorporation of the α-methylene units at the last stage of a total synthesis. Schlessinger has described a synthesis based on the retrosynthetic strategy summarised below:-

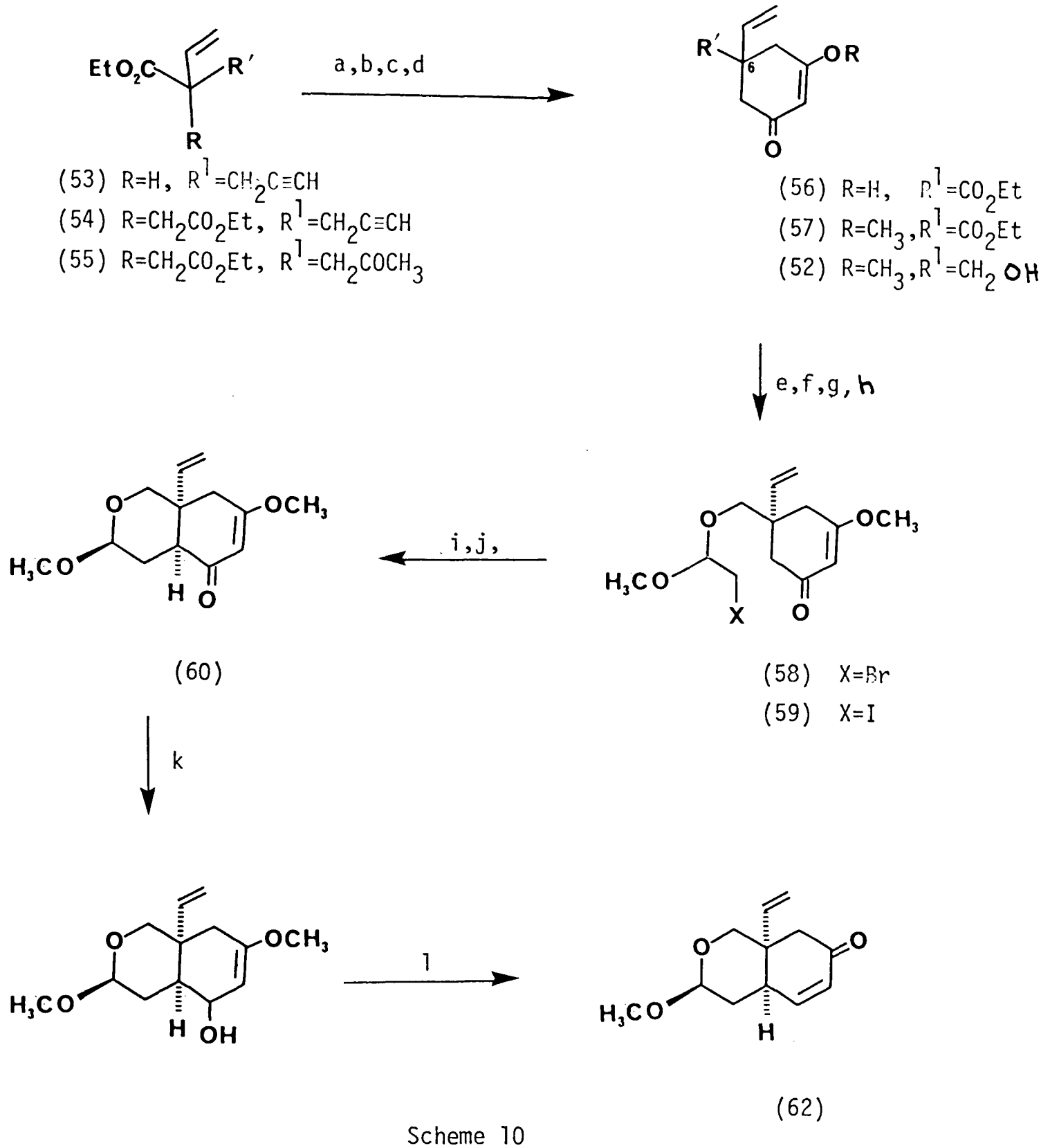


(51)

As can be seen, the synthetic intermediate (51) is a precursor of the vernolepin B ring. Again, the cis-fused oxadecaline system is constructed by the addition of a 2-carbon unit to the hydroxymethyl group. This bears a strong resemblance to the Isobe synthesis; the difference being, cyclisation is accomplished by nucleophilic attack of an enolate anion on an electrophilic centre. instead of 1,4-addition of a carbanion onto an α, β-unsaturated system.

The appropriate functionalisation of the B ring was achieved by reduction of a vinylogous ester to an enone and further stereoselective reduction of an α-alcohol, (Scheme 10). A Danishefsky type type of strategy is employed for the elaboration of the γ-lactone, viz:- Henbest α-epoxidation and nucleophilic ring opening at C-7,(Scheme 11).

Preparation of acetal enone (81)



(53) R=H, R^1=$CH_2C{\equiv}CH$

(54) R=CH_2CO_2Et, R^1=$CH_2C{\equiv}CH$

(55) R=CH_2CO_2Et, R^1=CH_2COCH_3

(56) R=H, R^1=CO_2Et

(57) R=CH_3, R^1=CO_2Et

(52) R=CH_3, R^1=CH_2OH

(60)

(58) X=Br

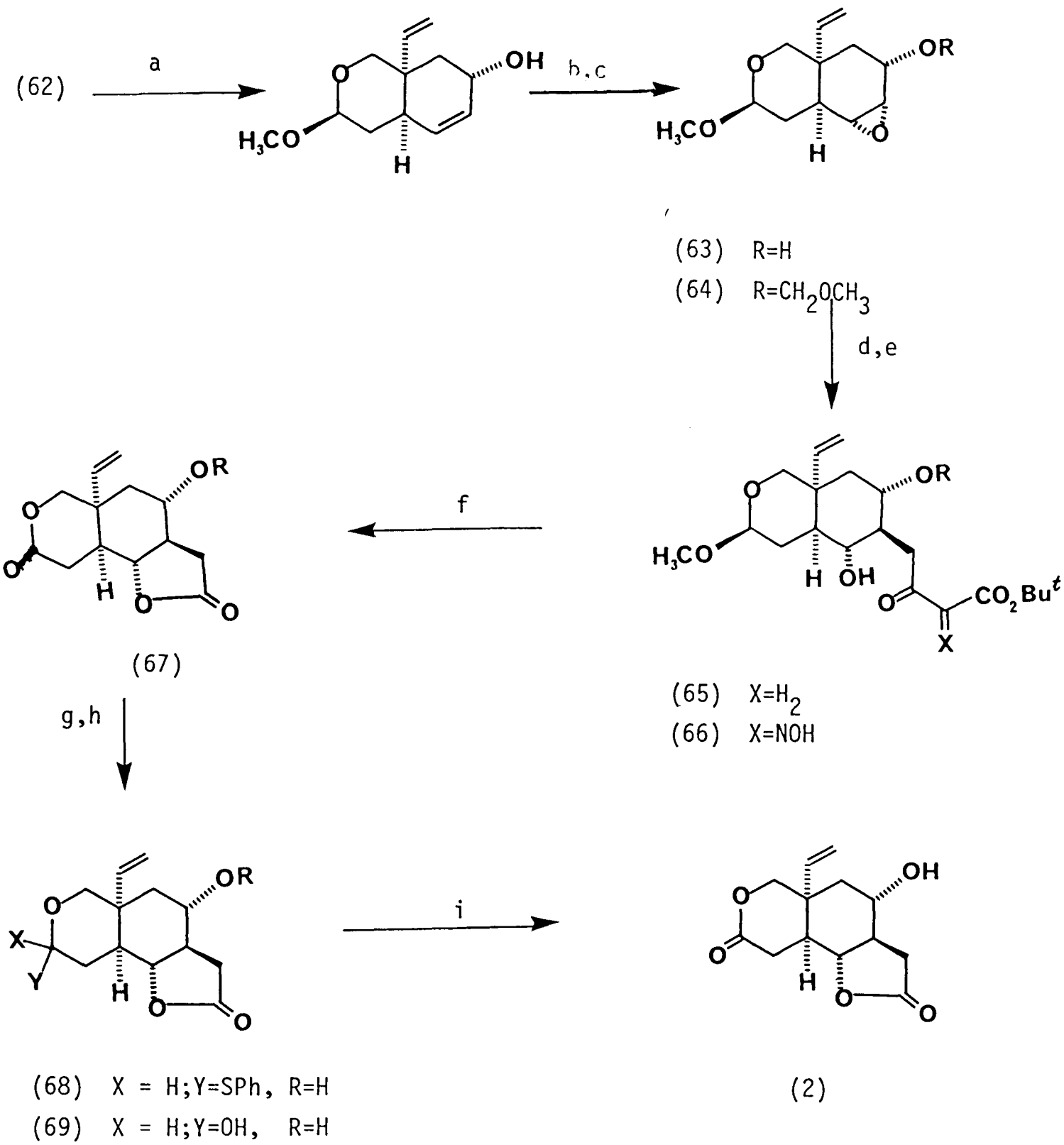
(59) X=I

(62)

Scheme 10

a, LDA, HMPA, $BrCH_2$ $C{\equiv}CH$; b, LDA, $BrCH_2CO_2Et$; c, $HgSO_4$, aq. H_2SO_4; d, Bu^tOK, Bu^tOH; e, $CH(OMe)_3$, MeOH; f, LDA, $LiAlH_4$; g, N, N-dimethylaniline, 1,2-dibromo-1-methoxyethane; h, NaI, CH_3COCH_3; i, lithium bis(trimethyl) silylamide, THF; j, DMSO, Zn, Cu, MeOH, H_2SO_4; k, $LiAlH_4$; l, I_2, THF.

Synthesis of bisnorvernolepin



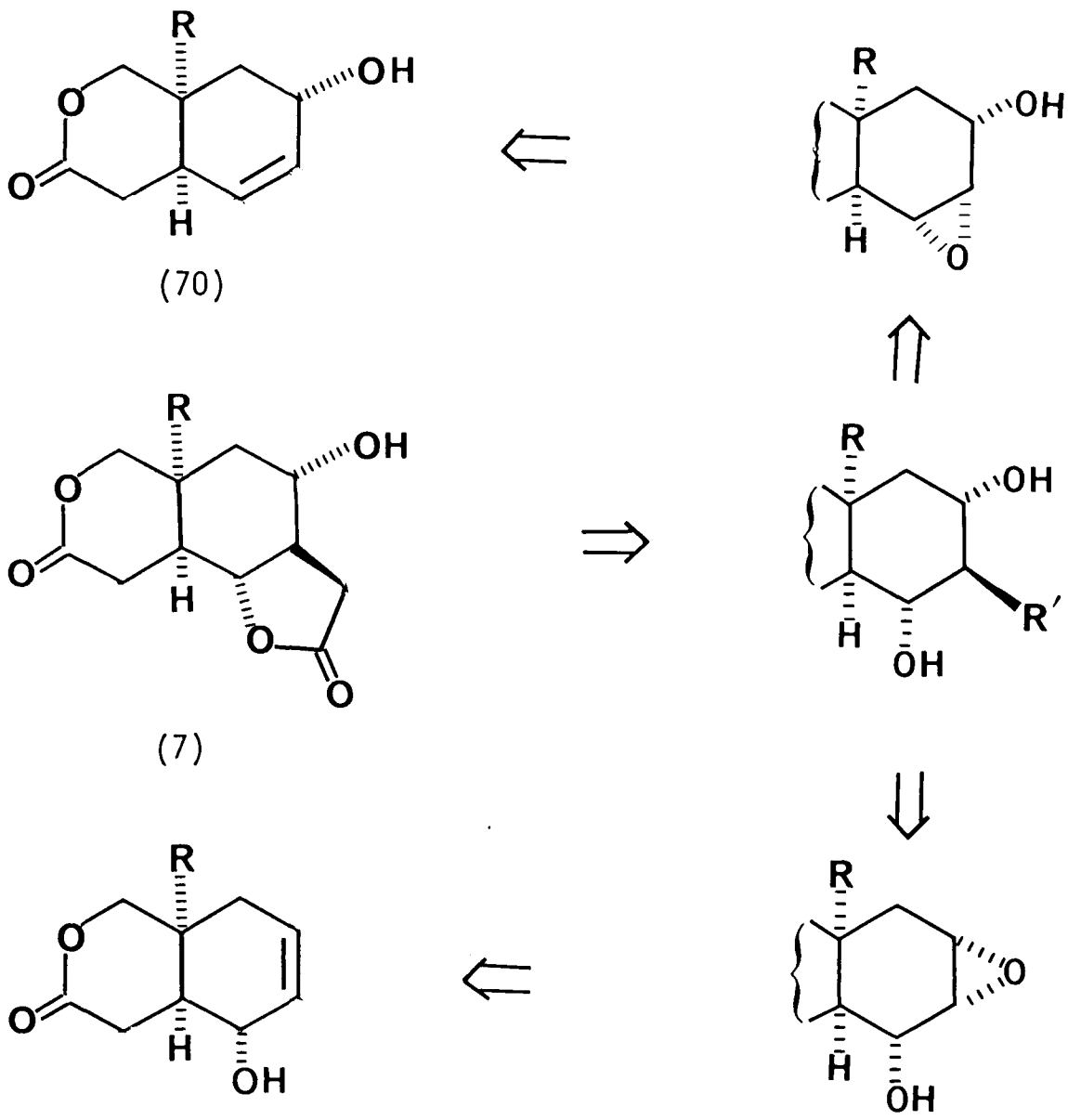
Scheme 11

a, DIBAL, hexane-toluene; b, m-CPBA, EtOAc; c, $ClCH_2OCH_3$, NaH; d, $LiCH_2COCH_2CO_2Li$, DME; e, Bu^tOK, Bu^tOH, isoamyl nitrite, THF; f, Ac_2O, AcOH; g, PhSH, BF_3-etherate, CH_2Cl_2; h, ceric ammonium nitrate; i, Jones reagent.

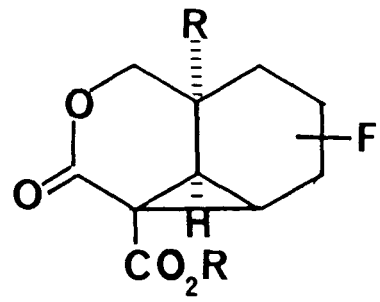
The synthesis differs from others described so far, in that lactonisation to form the C ring gave exclusively bisnorvernolepin. An overall yield of 12% was achieved in 20 steps from ethyl crotonate.

(v) Vandewalle et al.[56]

The retrosynthetic strategy employed by Vandewalle et al.is illustrated below:-



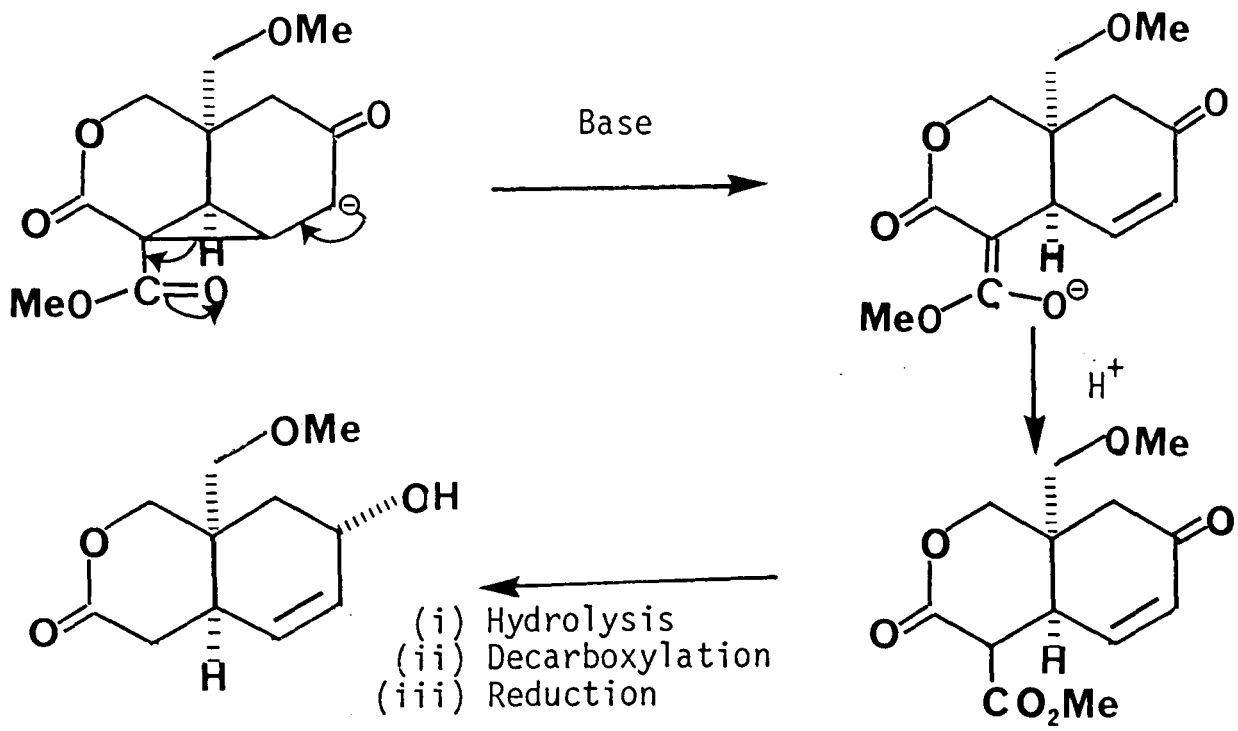
In this approach, bisnorvernolepin could be derived from two possible allylic alcohols (70) and (71). These are, therefore, the primary synthetic targets. Construction of the cis-fused 2-oxa-3-decalone system would involve intra- or intermolecular opening of a suitable tricyclic precursor of type (72), which in turn could be



(72)

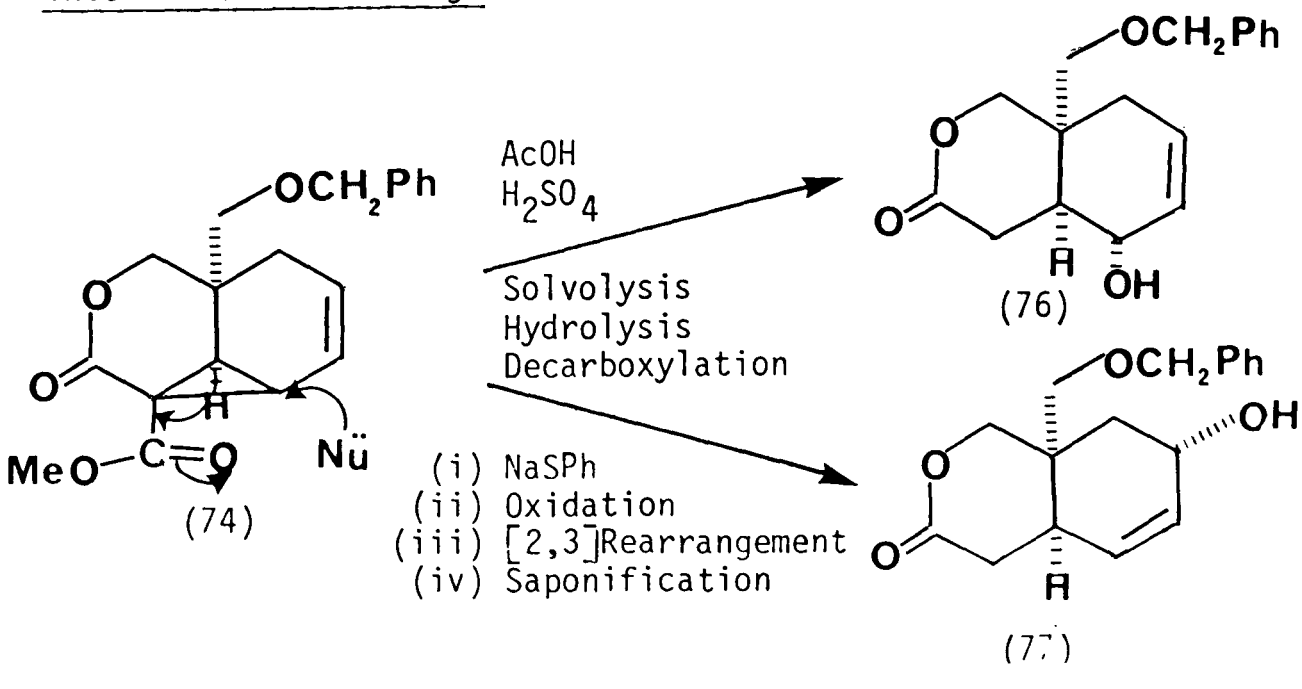
synthesised by an intramolecular carbenoid cyclopropanation reaction, (this was attempted in Isobe's synthesis). The choice of functionality F is dependent upon the mode of cyclopropane ring opening. viz:-

intramolecular cleavage[57]



(73)

intermolecular cleavage[58]

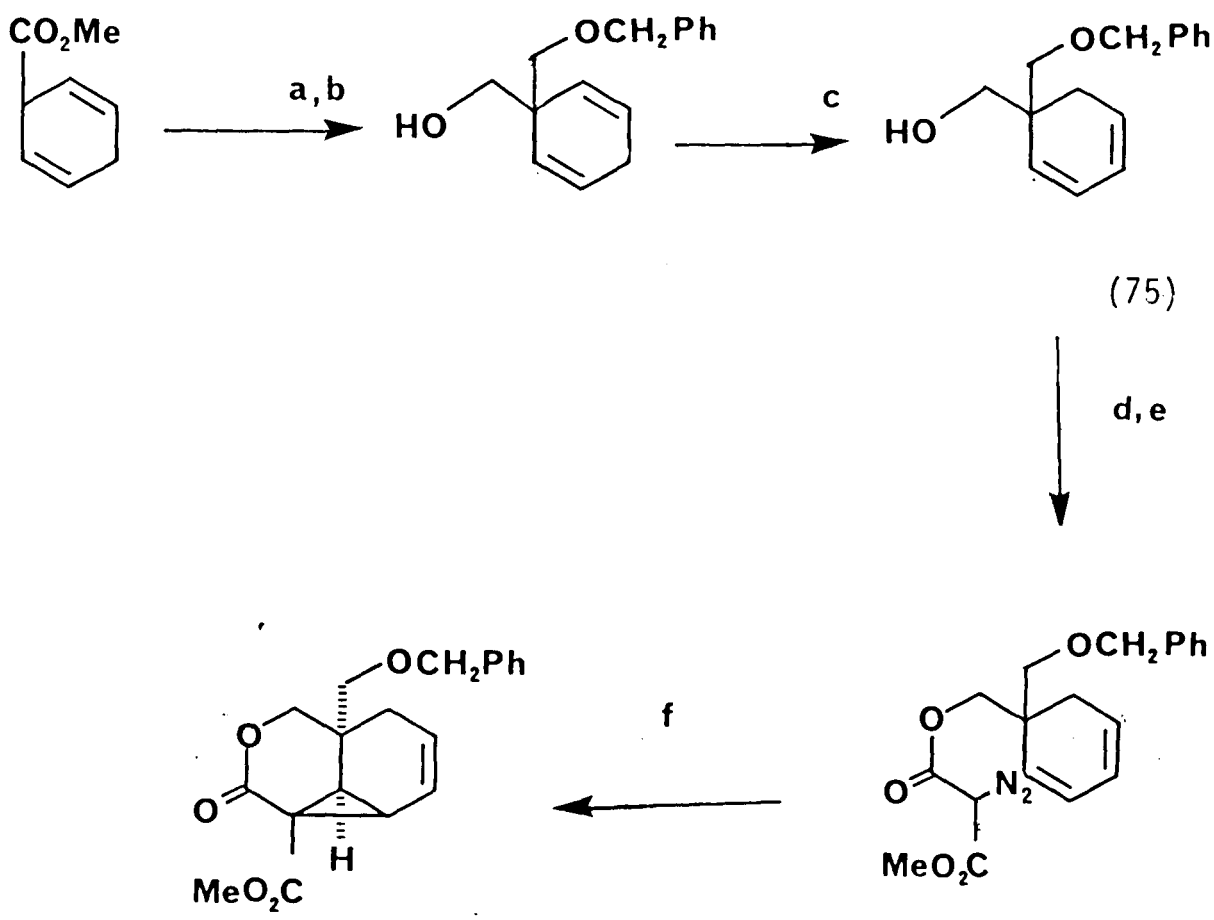


(74)

(76)

(77)

Preparation of the key synthetic intermediate (74)

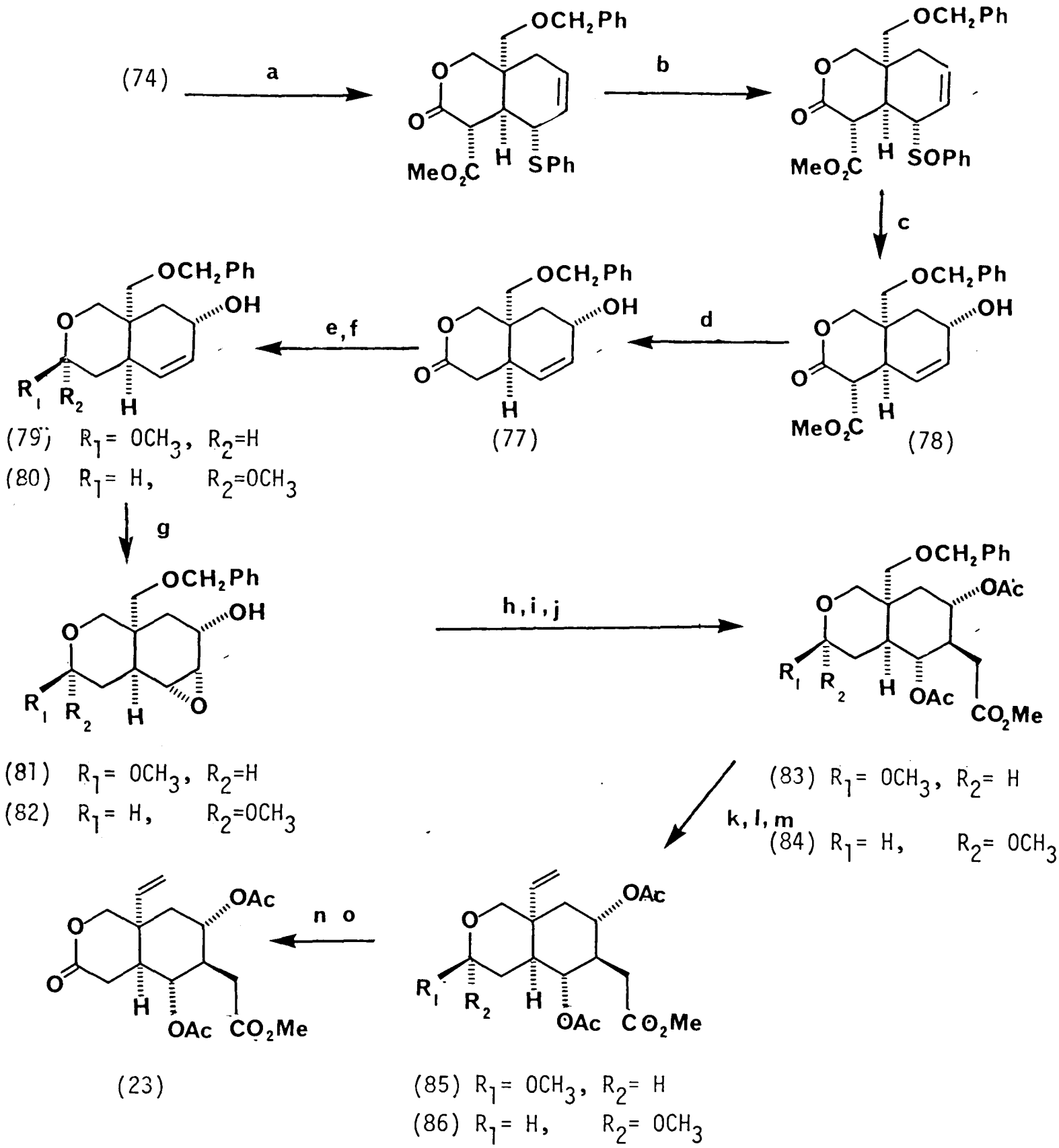


(74)

Scheme 12

a, LDA, THF, HMPA, $ClCH_2OCH_2Ph$; b, $LiAlH_4$; c, Bu^tOK, DMSO; d, $ClCOCH_2CO_2Me$, py; e, TsN_3, Et_3N, CH_3CN; f, $Cu(acac)_2$, toluene.

Synthesis of Grieco's lactone (23)



(79) R_1= OCH_3, R_2=H
(80) R_1= H, R_2=OCH_3
(77)
(78)
(81) R_1= OCH_3, R_2=H
(82) R_1= H, R_2=OCH_3
(83) R_1= OCH_3, R_2= H
(84) R_1= H, R_2= OCH_3
(23)
(85) R_1= OCH_3, R_2= H
(86) R_1= H, R_2= OCH_3

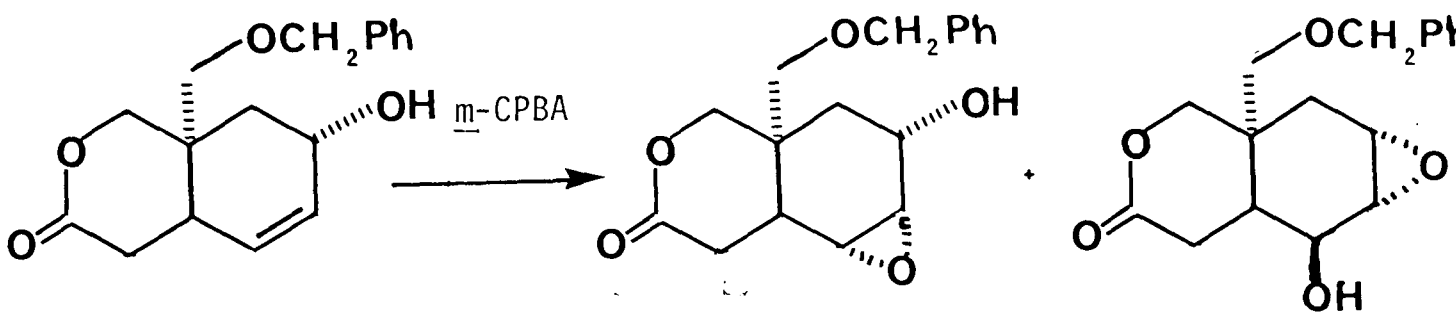
Scheme 13

a, NaSPh, DMSO; b, m-CPBA, CH_2Cl_2; c $(MeO)_3P$, MeOH; d, K_2CO_3, MeOH, H_2O; H_2SO_4; benzene; e, DIBAL, C_7H_8; f, MeOH, H_2SO_4; g, mCPBA, CH_2Cl_2; h, $LiCH_2CO_2Li$, DME; i, CH_2N_2; j, AC_2O,py; k, 10% Pd on C, H_2, EtOH; l, Collins reagent, CH_2Cl_2; m, $Ph_3P{=}CH_2$, DME; n, CH_3CN, HCl, H_2O; o, Ag_2CO_3/celite, C_6H_6.

The ultimate synthetic target of this research group was the intermediate (23) that had been previously prepared by Grieco et al. The initial approach involving intramolecular ring opening of the tricyclic derivative (73) was not successful, due to difficulties encountered in the preparation of such a compound. Vandewalle therefore turned his attention to the alternative strategy. The synthesis is summarised in Schemes 12 and 13.

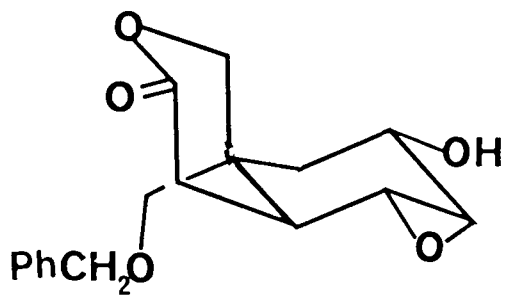
It is interesting to note that epoxidation of the allylic alcohol (77) gave a 1:1 mixture of two epoxides.

viz:-

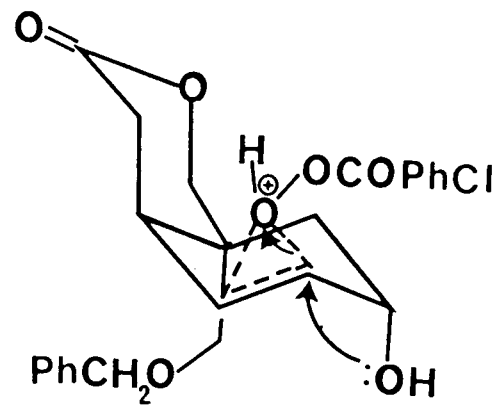


(77) 1 : 1

This was explained by oxidation of the two conformers of (77). Rearrangement of II by intramolecular displacement by the axial hydroxy group gives rise to the unexpected product.



I



II

However, Vandewalle found that by protecting the δ-lactone, a shift in the position of equilibrium towards the conformer containing the equatorial hydroxy substituent was obtained. Consequently, treatment with m CPBA resulted in exclusive α-epoxidation to afford (81) and (82).

Grieco's intermediate (23) was obtained in 23 steps from benzoic acid, and in an overall yield of 1.0%.

I.B.2. Synthetic approaches to vernolepin prototypes

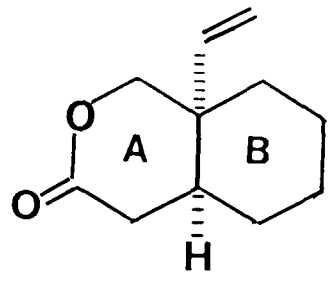
Intensive synthetic interest in the preparation of vernolepin has resulted in several approaches to prototypes of this molecule, with the eventual aim of total synthesis. These vernolepin synthons may be grouped into the following categories:- prototypes for the AB ring system, BC ring system, deoxyvernolepin and miscellaneous systems.

It must be pointed out that strategies that have been successfully employed in a synthesis of vernolepin are not discussed in this section. In addition, due to the large number of schemes developed to various vernolepin analogues, it has not been possible to include every one. Therefore, only a selection of the more viable routes to model systems directly relevant to this work, is considered

below. Others[59-69] are listed in the references.

(i) Angularly functionalised AB system

The majority of model studies have been directed towards the synthesis of the cis-fused 2 oxa-3-decalone system bearing an angular group, exemplified by (87). In addition to the synthetic benefits

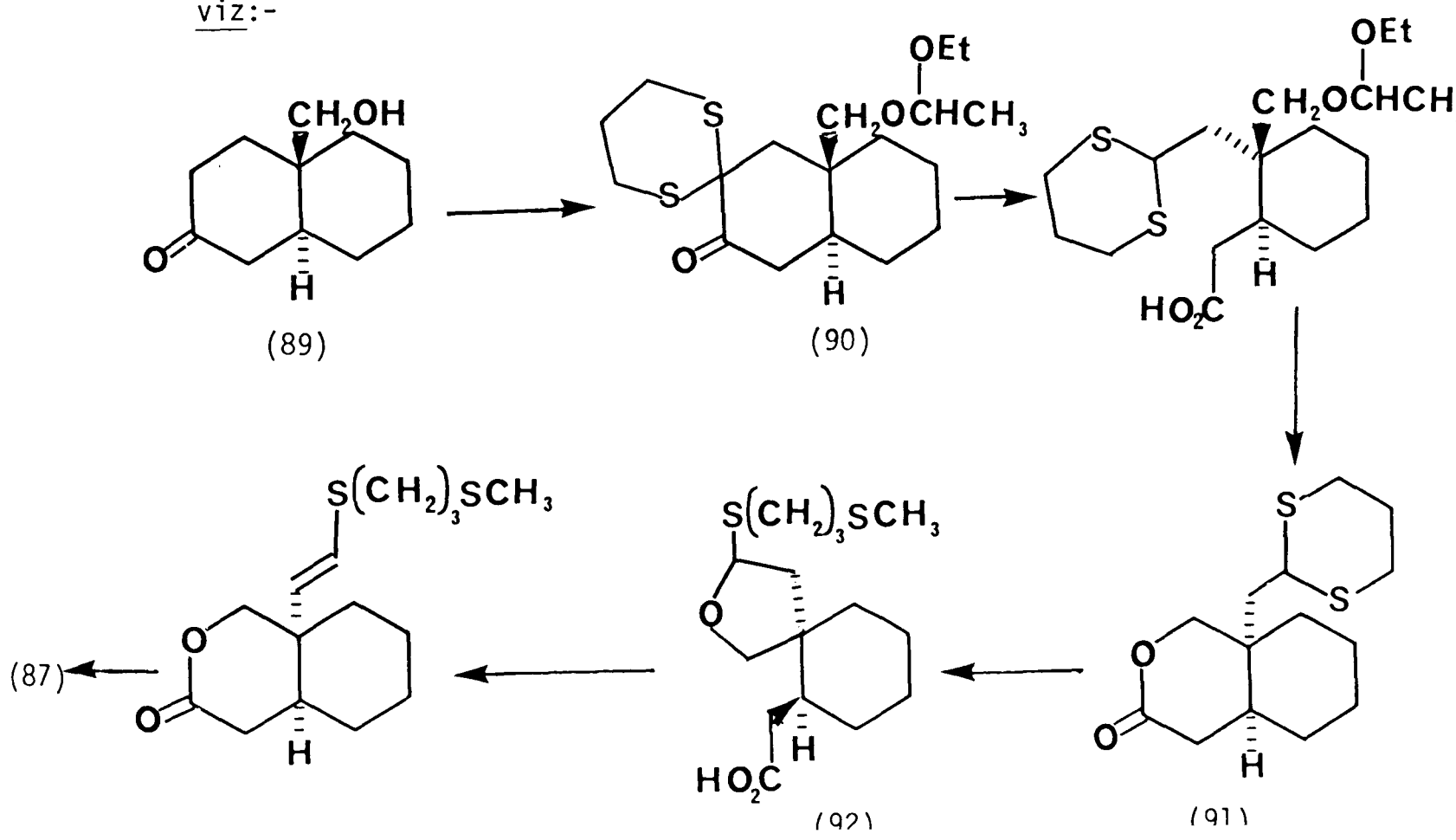


(87)

derived from construction of such a molecule, the α-methylenated derivative has been found to possess moderate in vitro cytotoxicity, consequently various analogues have been prepared for biological testing.

Various strategies have been developed for the preparation of (87). One of the most useful is that employed by Grieco in his total synthesis of vernolepin,(p 14). The approach was also adopted by Marshall and Seitz.[70,71]

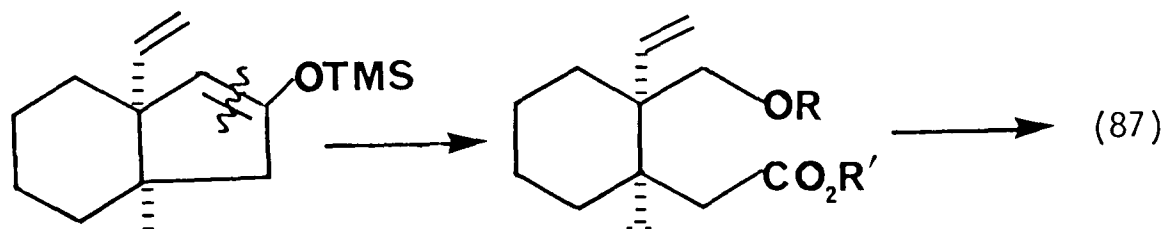
viz:-



The intermediate 3-keto-dithiane (90) was prepared by treatment of the hydroxymethyl decalinone (89) with ethyl vinyl ether, followed by hydroxymethylation and dithianylation. Base induced cleavage of the C-2, C-3 bond, followed by acid treatment afforded the cis-fused δ-lactone (91). Methylation with methyl fluorosulphate and subsequent addition of sodium hydroxide gave the cyclic hemithioacetal (92), which underwent elimination and desulphurisation to afford the target lactone (87).

Another approach involved ozonolytic cleavage of an O-silylated enolate. Using this sequence Clark and Heathcock[72-74] have devised two routes to the vernolepin prototype (87).

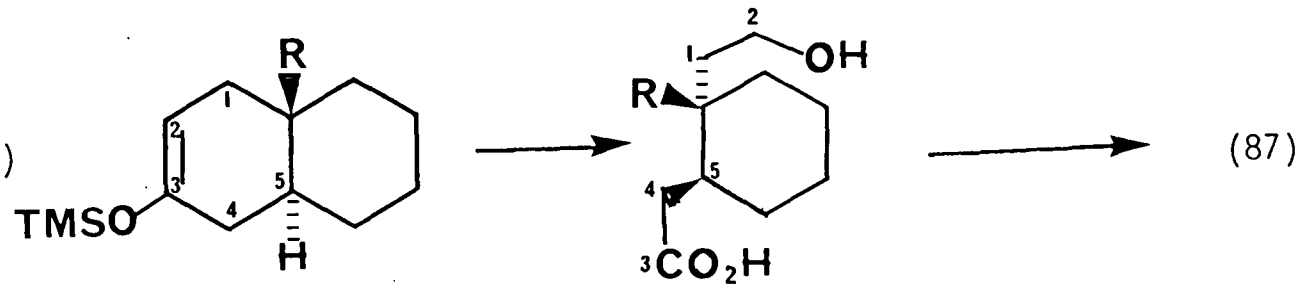
(i)



(94)

Ozonolytic cleavage of the cis-fused siloxyalkene (94), followed by a reductive work-up and cyclisation.

(ii)



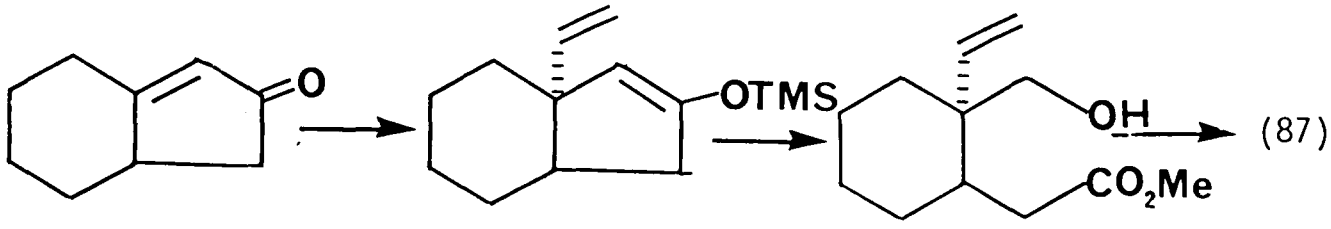
(95)

Ozonolytic cleavage of the trans-fused siloxyalkene (95) occurs with the conversion of C-1 and C-2 into a vinyl group. Cyclisation of the latent hydroxymethyl group R with the carboxylic acid moiety affords the cis-fused δ-lactone (87). This is similar to the strategy employed by Grieco and Marshall.

The former route is pertinent to both the syntheses of

vernolepin and boonein, and consequently will be discussed in more detail.

The O-silylated enolate (94) was prepared by 1,4-conjugate addition of a lithium divinyl cuprate to the enone, the intermediate enolate being trapped with trimethylsilyl chloride. Selective ozonisation of the more nucleophilic siloxyalkene linkage was acc-



(87)

(94)

omplished by the careful addition of an equivalent amount of ozone. Reduction of the intermediate methoxy hydroperoxide with sodium borohydride, and acid mediated cyclisation gave the lactone (87) in 93% yield. An advantage to this process is that analogues could be prepared in which the angular vinyl group was replaced by other groups. α-Methylenation then afforded compounds which were assessed for physiological activity.

(ii) Deoxyvernolepin

The most fully functionalised synthetic analogue, deoxy-vernolepin, was prepared by Grieco[75,76] in 1975. This prototype was synthesised by a similar strategy to that already described for vernolepin.

More recently some Japanese workers[77,78] have described a route to a deoxyvernolepin precursor from the eudesmanolide α-santonin.

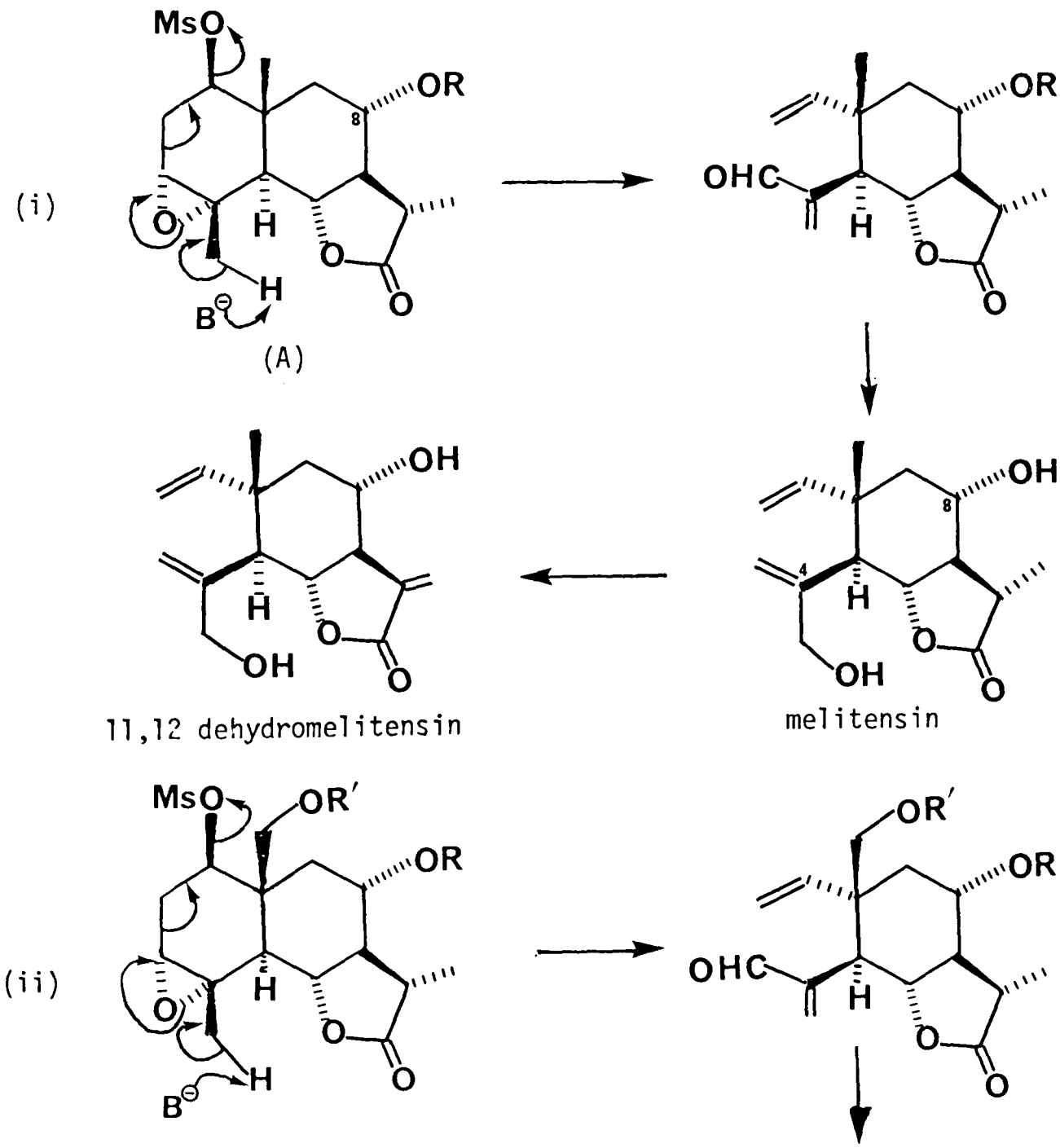
In summary, the challenge presented by the novel stereo-

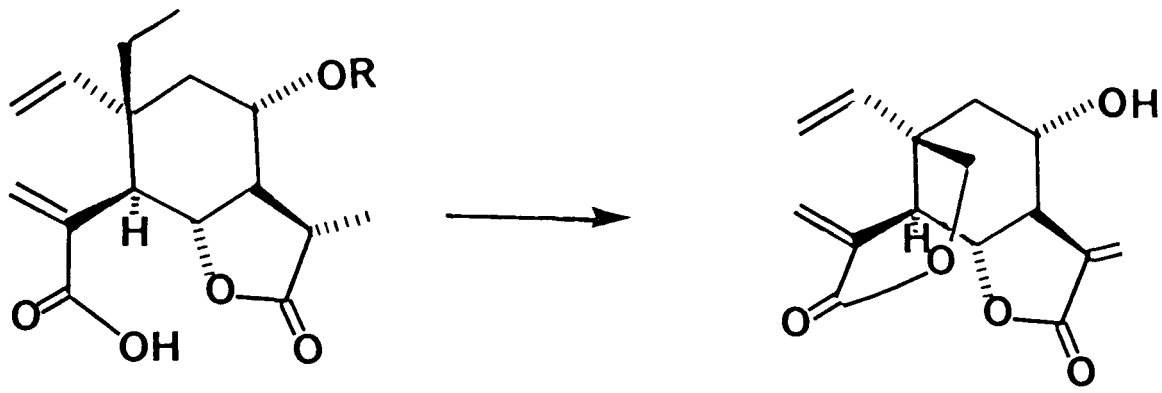
chemical features possessed by vernolepin, has led to the development of a wide range of synthetic methods, which are now available to the organic chemist.

I.B.3. General approach to elemanolides

As far as we are aware, the only reported example of a general synthetic strategy towards elemanolide lactones, has been recently published by Ando et al.[79]

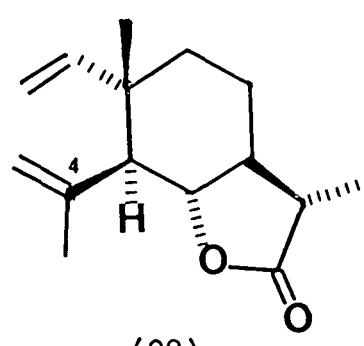
The approach was based on base mediated frag mentation of appropriately functionalised epoxy mesylates, shown below:-





vernolepin

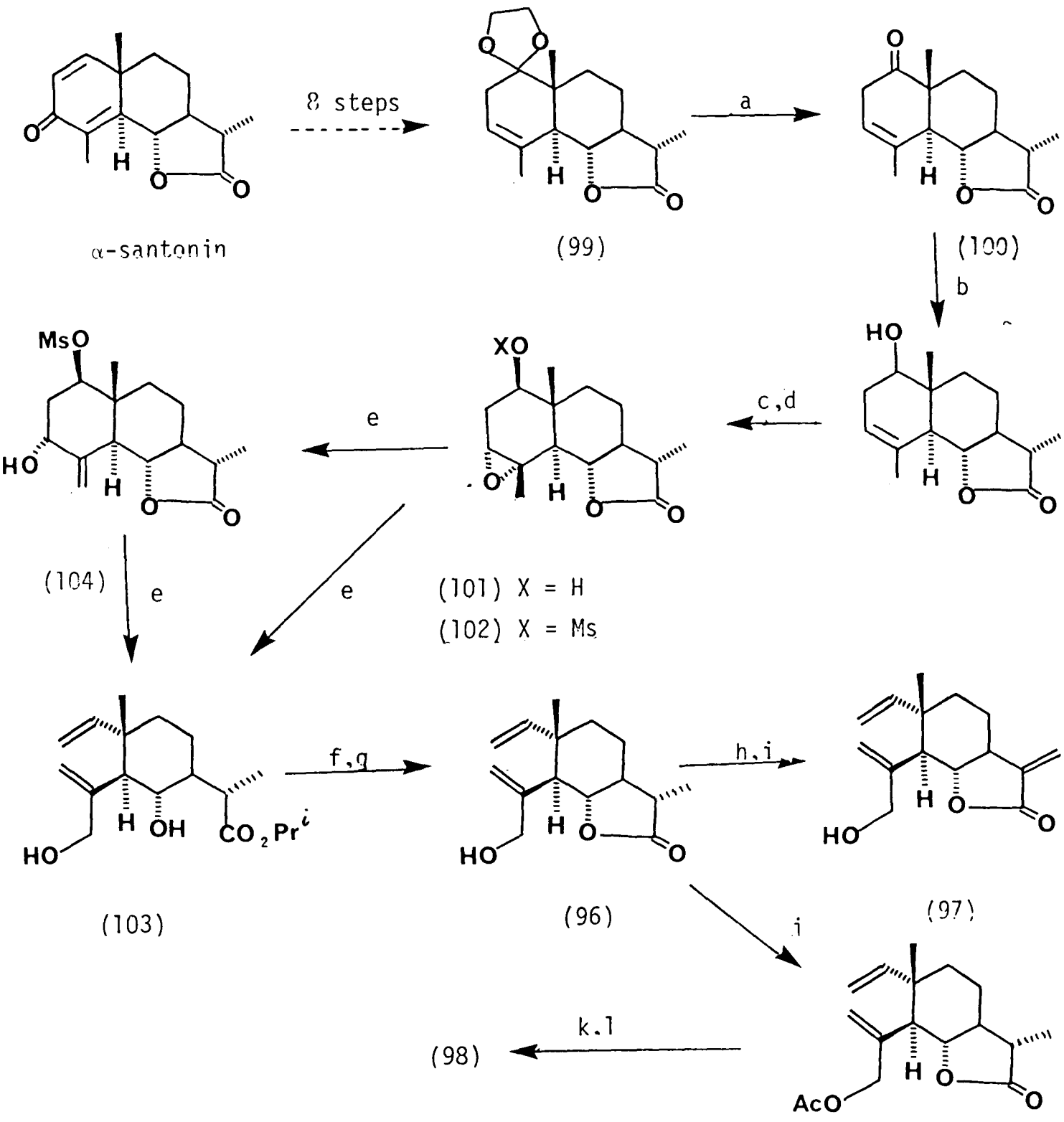
In this way, the 8-deoxymesylate of type A, has been used to prepare 8-deoxymelitensin (96), 11, 12-dehydro-8-deoxymelitensin (97) and saussurea lactone (98).



(98)

The starting material, as in the case of the previously mentioned Japanese synthesis of deoxyvernolepin, was α-santonin. This eudesmanolide was transformed in 8 steps to the acetal (99) (Scheme 14), which was treated with acetic acid to give the β, γ-unsaturated ketone (100). Reduction of the latter afforded a mixture of alcohols in which the β-epimer predominated by a ratio of 8:1. Epoxidation followed by mesylation gave the required intermediate (102). Treatment with aluminium isopropoxide gave a mixture of the desired fragmentation product (103) and the hydroxy mesylate (104), which was easily converted into (103), by the addition of a further amount of the base. The synthesis of 8-deoxymelitensin was concluded by ester hydrolysis and subsequent lactone closure. Transformation into the dehydro product (97) was

Synthesis of some elemanolide lactones from α-santonin



Scheme 14

a, 50% aq. AcOH ; b, $LiAl(Bu^tO_3)H$; c, mCPBA; d, MsCl,py; e, $Al(Pr^iO)_3$, toluene, Δ_R; f, KOH, EtOH; g, p-TsOH; h, LDA, Ph_2Se_2; i, H_2O_2, AcOH; j, Ac_2O, py k, Li, NH_3; l, Collins reagent.

effected by phenylselenylation and oxidative syn-elimination. Preparation of saussurea lactone from (96) was accomplished by reduction of the hydroxymethyl unit at C-4 into a methyl substituent.

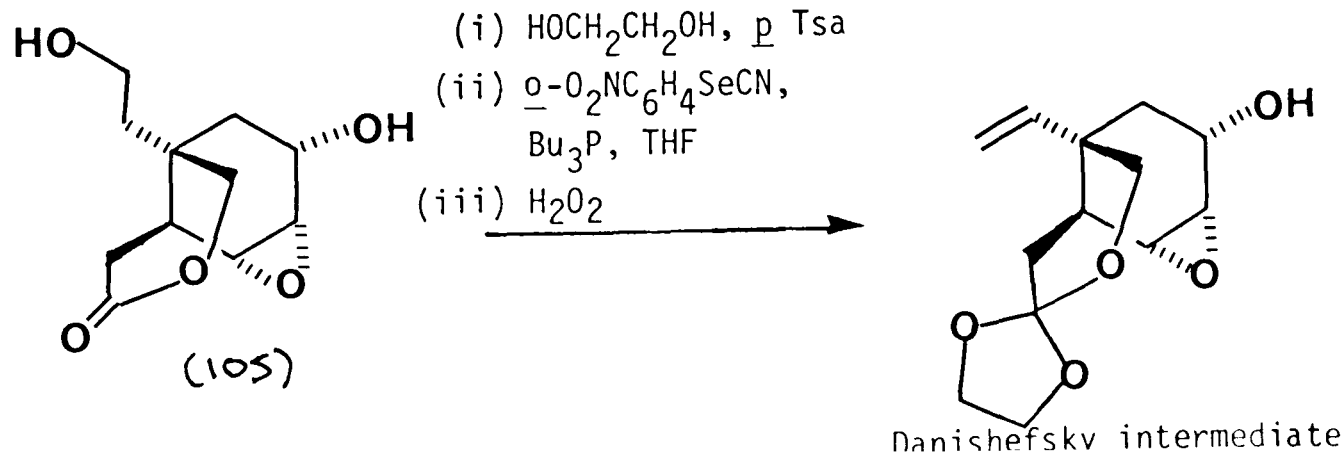
In summary, 8-deoxymelitensin, 11,12-dehydro-8-deoxy-melitensin and saussurea lactone were obtained in overall yields of 14%, 8% and 10% from α-santonin.

I.C.1. Research Objectives

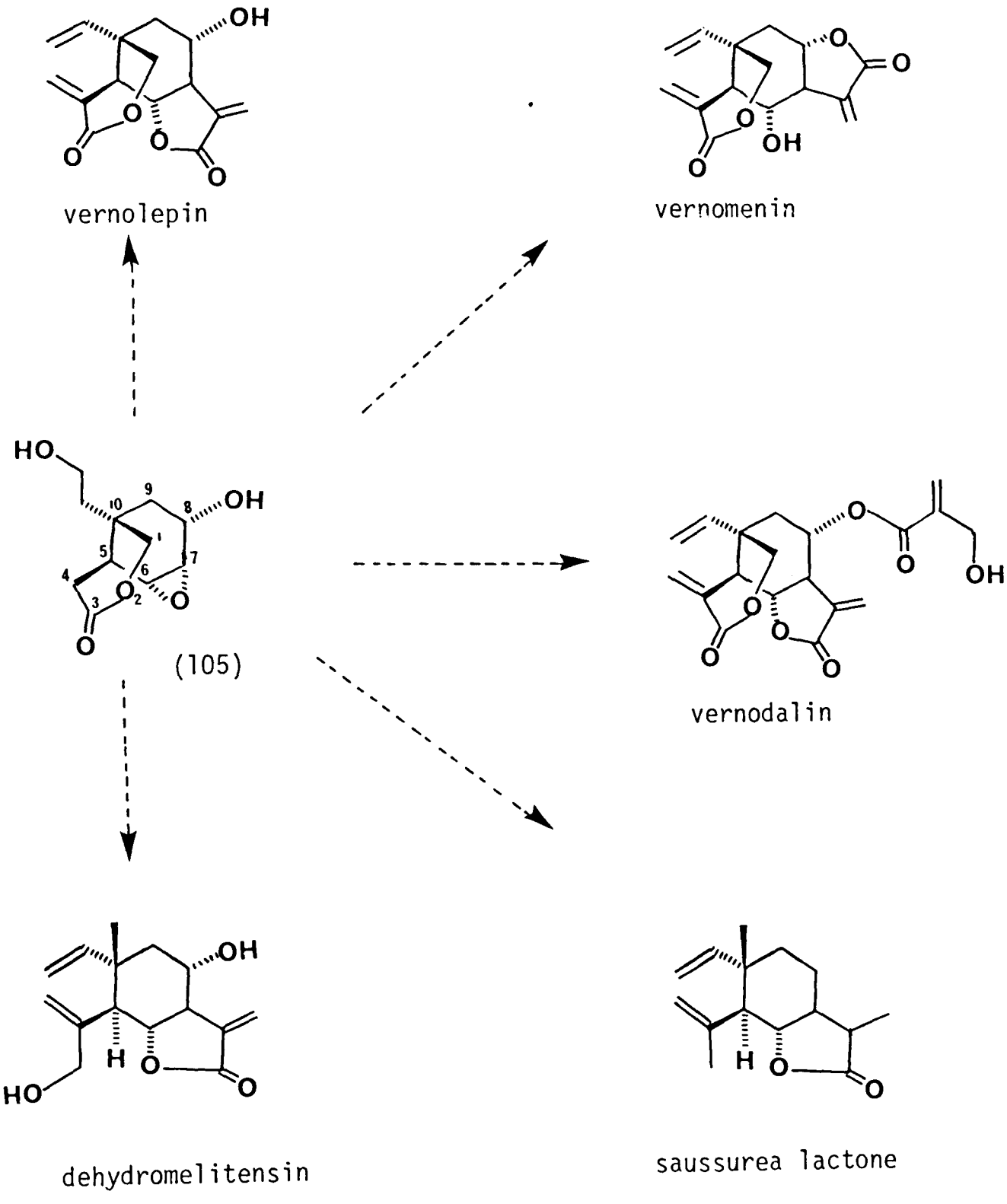
Extensive investigation into the preparation of vernolepin has led to the development of syntheses of this molecule, and often its congener vernomenin, by research groups in U.S.A., Japan and Belgium. Undoubtedly the methods used by these workers to solve the regio- and stereochemical problems posed by vernolepin are elegant, but they result in long, relatively low yielding routes to the molecule, possibly with the exception of Schlessinger et al.[54] In addition, these routes have not been applied to other sesquiterpene lactones. In fact, only one example exists to date of a general synthetic approach to lactones of the elemane class.

The purpose of this research was to develop a total synthesis of vernolepin by way of an intermediate used in Danishefsky's route. This compound could be reached via a key intermediate, which could ultimately be transformed into a range of other elemanolide lactones. Furthermore, our strategy involved the use of new chemistry, which is referred to at a later stage in this section.

The common intermediate (105) chosen is shown in Scheme 15. This cis-fused 2-oxa-3-decalone possesses all the necessary requirements for the synthesis of other elemanolides. This includes (i) a hydroxyethyl moiety at C-10, which could be readily converted into a vinyl group, (ii) a 6, 8-dioxygenated six-membered ring found in most elemanolides, (iii) elaboration of the γ-lactone by nucleophilic epoxide opening at C-7, as demonstrated by Danishefsky.

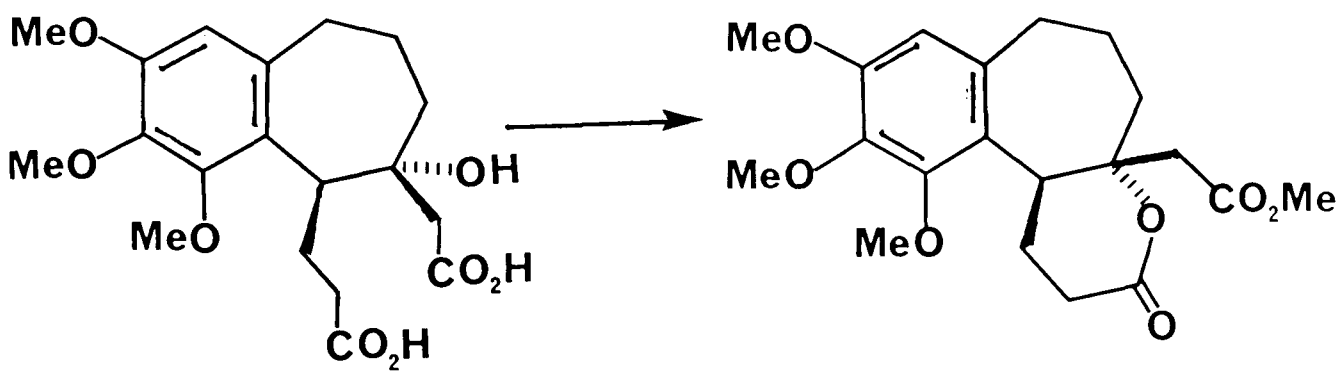


Transformation of the common intermediate (105) into other elemanolide lactones



Scheme 15

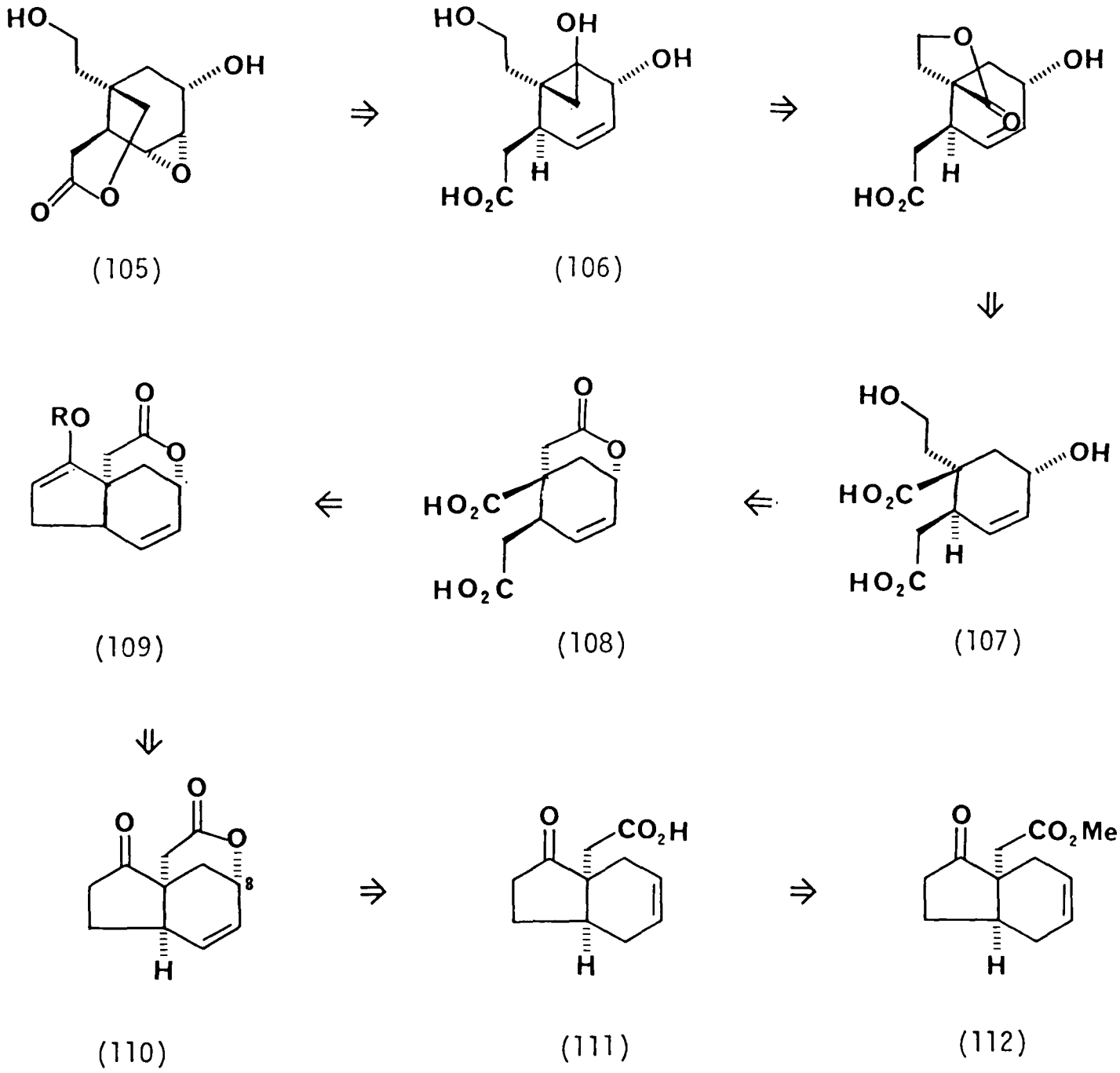
Retrosynthetic analysis of this intermediate (Scheme 16) indicates a precursor requiring a stereospecific epoxidation. It was hoped that a Henbest type of stereochemical guidance would operate, directing epoxidation in the desired fashion. However, reference to the results of Vandewalle et al.[56] under similar circumstances, would suggest the necessity of initial protection of the lactone in order to effect exclusive α-epoxidation. Consideration of the triol (106) would indicate a spirolactone precursor, which may be prepared by selective lactone formation from the corresponding dihydroxy dicarboxylic acid (107). The latter, in turn, may be derived from the dicarboxylic acid (108). Therefore, the two carboxylic acid functions in this molecule, would be chemically differentiated from each other in a novel manner, involving incorporation of one of them into a lactone followed by reduction. In some respects this chemodifferentiation is not unlike the approach used by van Tamelen[80] in his synthesis of colchicine. However, in this case differentiation was the outcome of internally



protecting the tertiary hydroxy function as the δ-lactone.

Returning to the analysis, the dicarboxylic acid (108) could be prepared by a variety of routes. For example, this transformation could be effected by cleavage of the corresponding enol (109) either ozonolytically with an oxidative workup, or perhaps

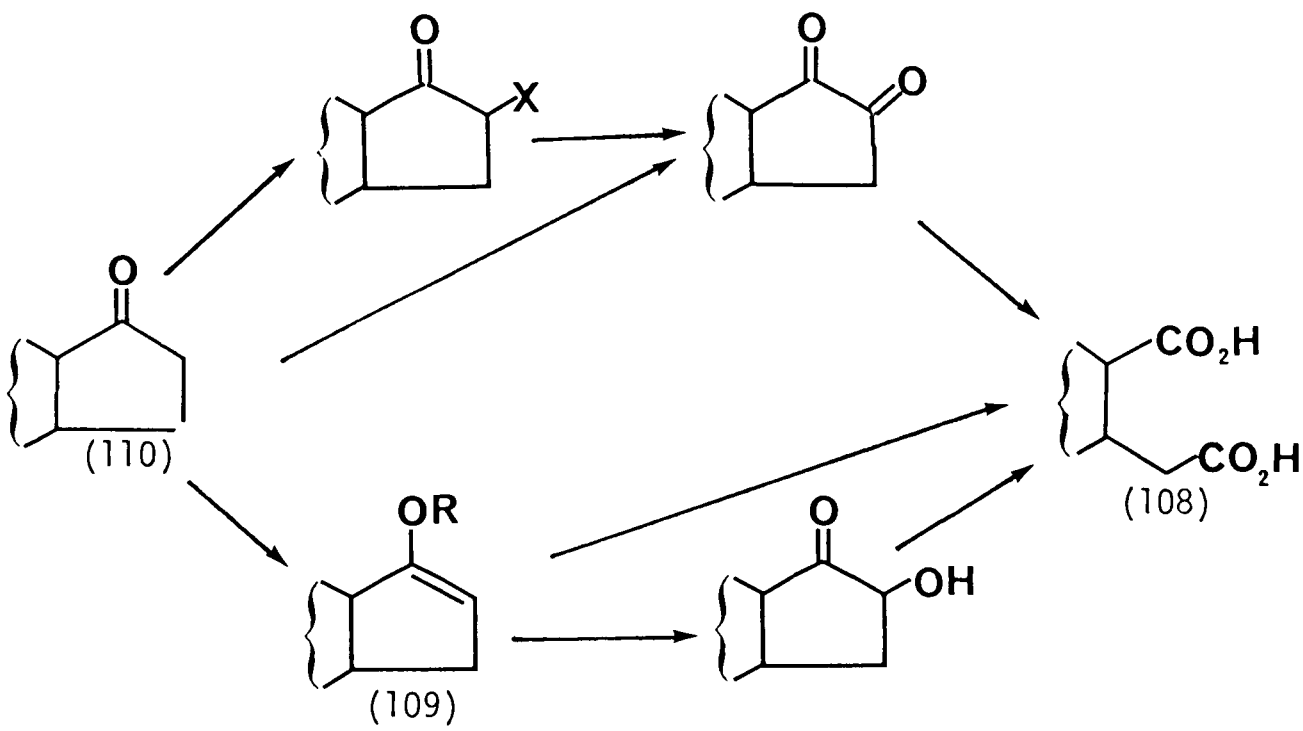
Retrosynthetic analysis of intermediate (105)



Scheme 16

using the more recently reported molybdenum acetylacetonate mediated cleavage with tert-butylhydroperoxide. An alternative route would involve alkaline hydrogen peroxide treatment of the α-diketone. Such a molecule may be formed by selenium dioxide oxidation or direct oxygenation of the precursor (110).

viz:-

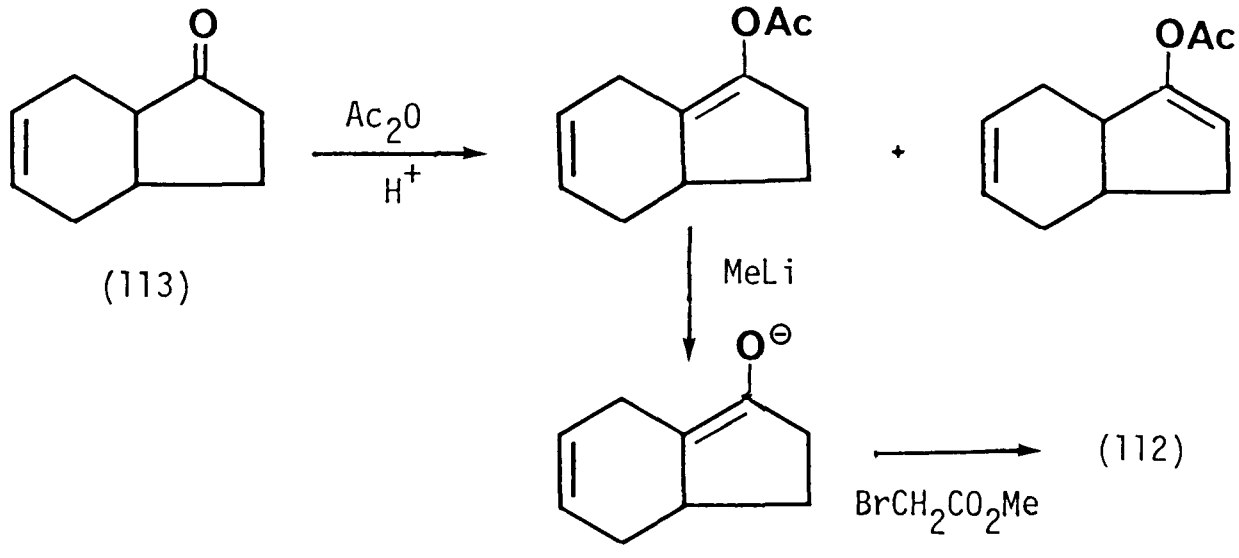


X = halogen

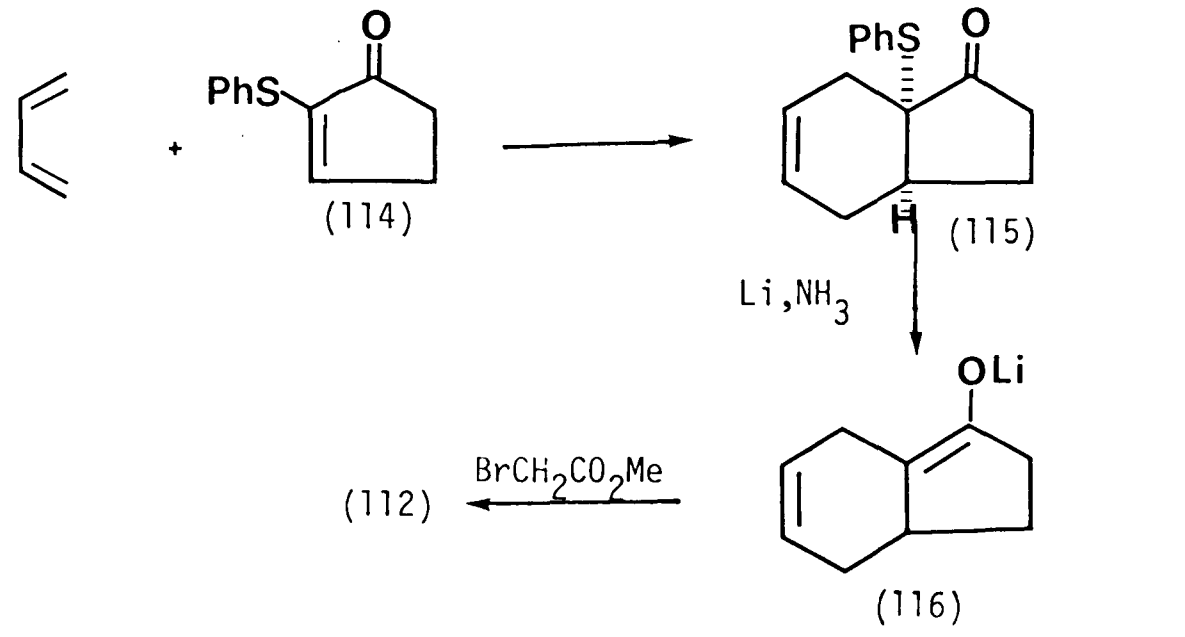
Besides, the two main approaches depicted, other modifications include functionalisation of the α-position by halogenation or possibly oxidation of the enol to form the hydroxy ketone which may subsequently be converted to the dicarboxylic acid (108).

The lactone moiety of the indanone precursor (110) could be derived from the carboxylic acid (111) using a sequence of iodolactonisation-dehydroiodination, previously employed by Danishefsky for the corresponding decalone system, so introducing the correct α-stereochemistry for the hydroxyl at C-8. Alternatively, hydrolysis to the free acid may be avoided by direct conversion of the methyl ester to the δ-lactone (110) by the analagous bromolactonisation-dehydrobromination procedure.

All that remains is a regio- and stereospecific route to the tetrahydroindanone (112). This compound has been prepared by House,[81] but the method is limited by the lengthy procedure needed to separate the isomeric enol acetates used as intermediates. Furthermore, the ketone (113) was only available in very low yields, due to the poor activity of cyclopentenone as a dienophile.

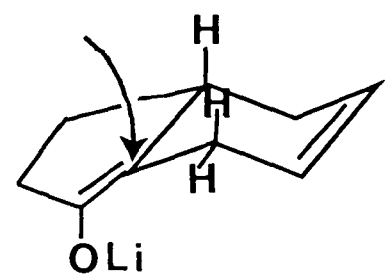


This lack of regiochemistry in alkylating tetrahydroindanones has limited their use in synthesis. However, it was planned to overcome this problem by extending the work of some American chemists,[82] who showed that the readily prepared phenylthioenone (114) undergoes Diels-Alder reaction with butadiene to form the tetrahydroindanone (115) in 85% yield. We reasoned that reductive removal of the pheny-



lthio group, in a dissolved metal reduction, would result in the formation of the enolate anion (116) exclusively, which could then be alkylated at the bridgehead position. Consequently, the phenylthio group would behave as a directing group. In addition, House has found that alkylation with methylbromoacetate occurs predominantly from an equatorial direction, thereby yielding the cis-fused product stereoselectively.

equatorial attack



Therefore, with this strategy in mind we hoped to realise our relatively short, stereospecific synthesis of the key intermediate (105).

CHAPTER II

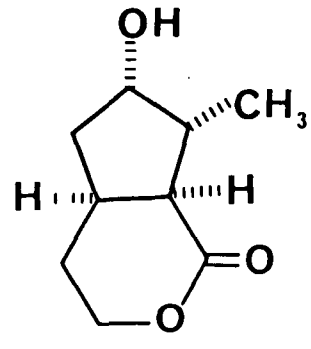
BOONEIN

II.A. GENERAL INTRODUCTION

II.A.1. Discovery

In 1925, whilst working towards the confirmation of the structure of the alkaloid echitamidine, Goodson and Henry[83] discovered a new lactone in the extract from the bark of Alstonia congensis. The molecular formula was determined to be $C_qH_{14}O_3$. However, no further attempt at structure elucidation was made.

It was not until 1983, when the lactone was again isolated, that the structure was finally established. Martini-Bettolo et al. were carrying out research into medicinal plants found in Africa. It was noted that the bark of Alstonia boonei De Wild, common to Nigeria, was widely used as an antipyretic in the treatment of malaria, and also externally applied for rheumatic pains. The latex was also used to rub on swellings caused by filaria. Given its therapeutic use, Martini-Bettolo et al. decided to investigate the aforementioned plant as a part of their programme. Two novel alkaloids,[84] N-formylechitamidine and 12-methoxy-N-formylechitamidine were isolated from the bark of A. boonei, together with the known echitamidine. The research group also reported the discovery of a new lactone,[85] corresponding to the molecular formula previously quoted by Goodson and Henry. This compound was found to be monoterpene of the iridane class, named boonein,(117) m.p. 95-96°C, $[\alpha]_D^{20}$ = 28.6



(117) boonein

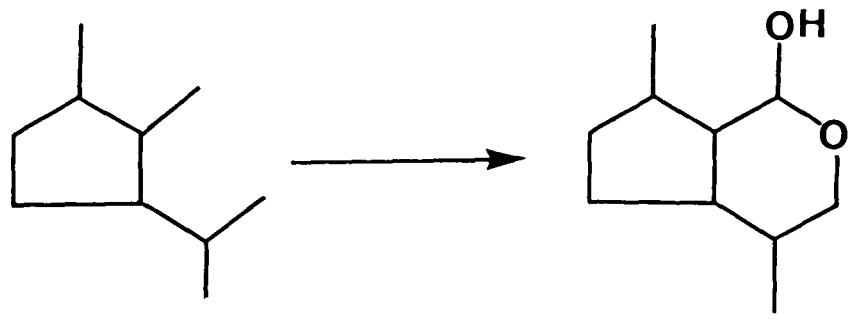
The structure of boonein was determined on the basis of spectroscopic data and conversion into various derivatives. Final confirmation was obtained by X-ray analysis.

II.A.2. Biogenesis

The structure of boonein is similar in many respects to that of the iridoid glucoside, loganin. The latter has been shown to play an important part in the biosynthesis of a major group of indole and some isoquinoline alkaloids, as well as being a precursor to secoiridoids. As boonein was discovered together with indole alkaloids, it may well be of biogenetic significance. It is therefore of some interest to consider the biogenesis of iridanes and in particular loganin, due to its role in the synthesis of alkaloids.

(a) Biogenesis of Iridanes

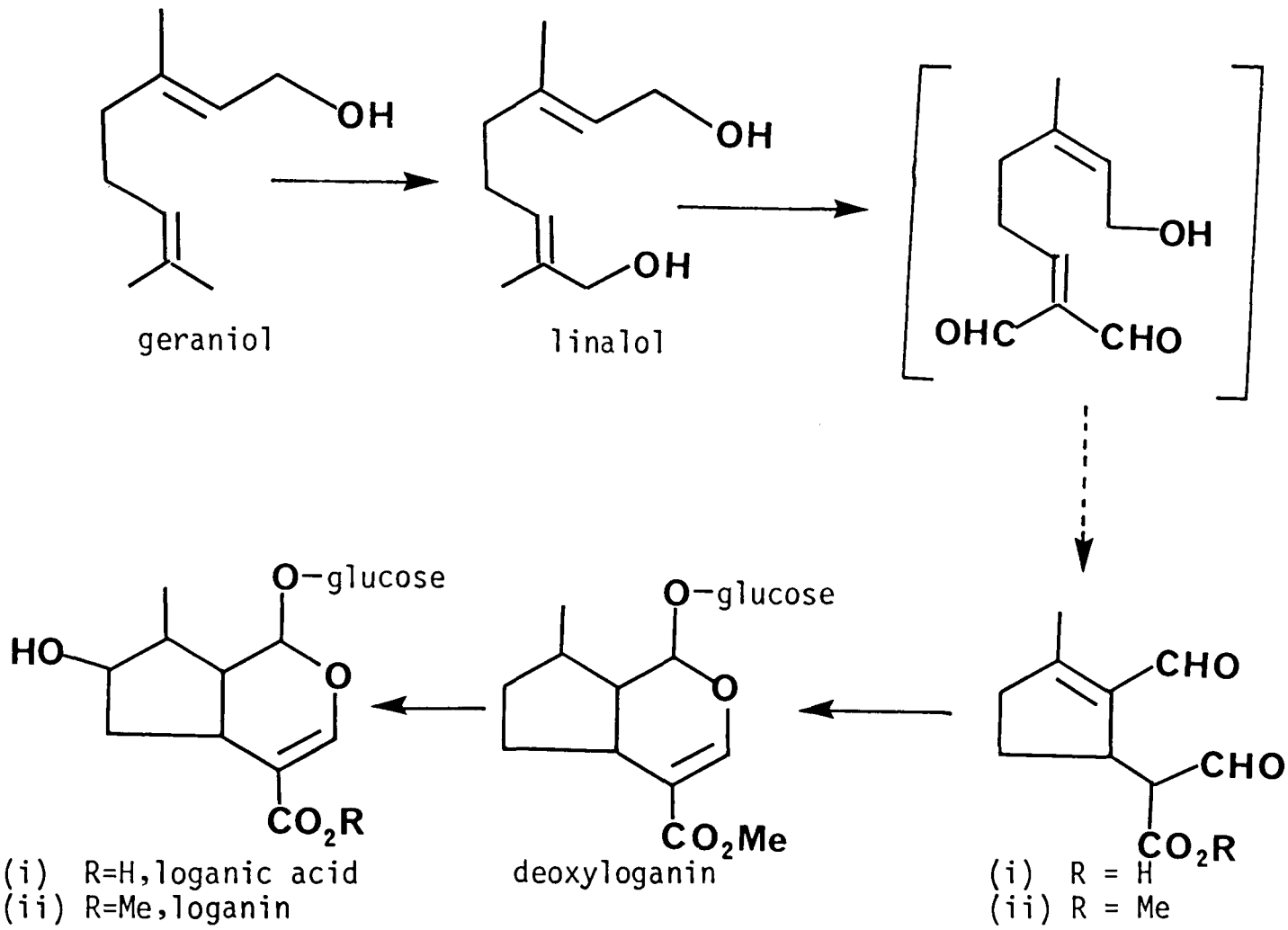
The class of monoterpene to which boonein and loganin belong is known as the iridane class. This family of compounds is based on the skeleton illustrated below, derived by cyclization of a cyclopentanoid precursor:-



iridane skeleton

These compounds often occur as their β-D-glucosides, which probably act to enhance their water solubility, and therefore the ease of transport throughout the plant.

Loganin is considered to be the parent of this class. Its biosynthetic pathway is illustrated below:-



geraniol linalol

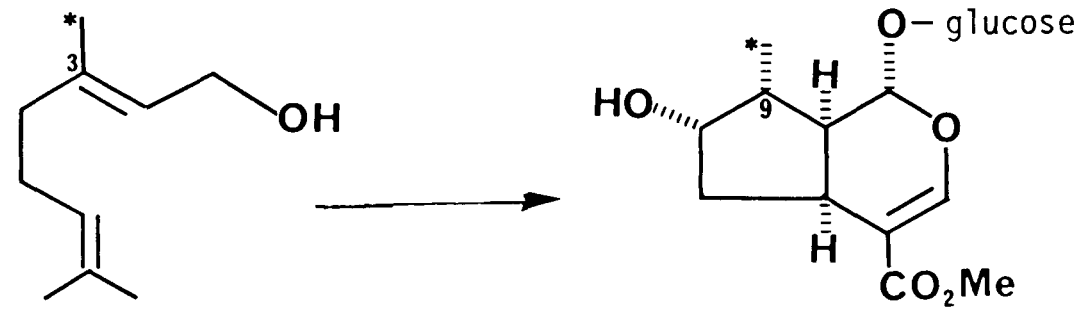
(i) R=H, loganic acid
(ii) R=Me, loganin

deoxyloganin

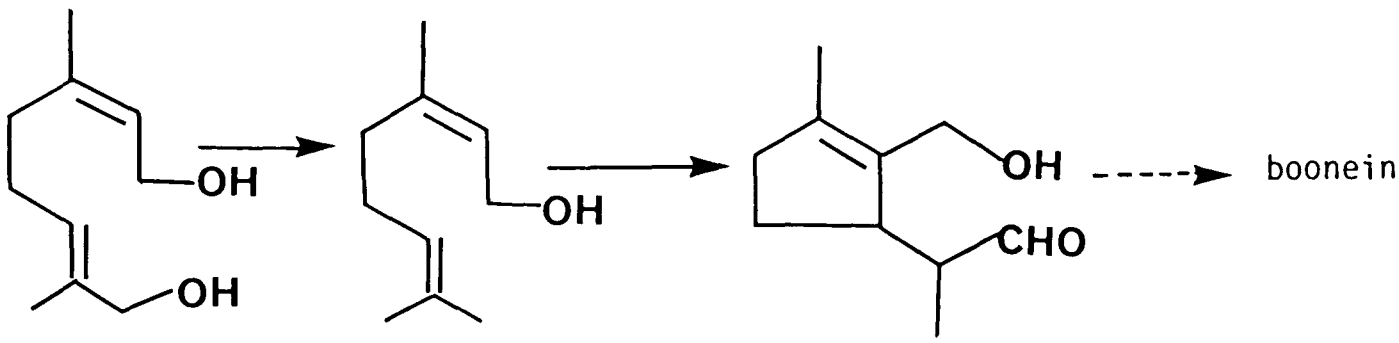
(i) R = H
(ii) R = Me

Several studies involving feeding plants, such as Vinca rosea, with labelled precursors have borne out this pathway. For example, administration of [^{14}C] - labelled geraniol at the C-3 methyl group gave [^{14}C] - loganin, in which the activity was found in the C-9 methyl substituent.

viz:-



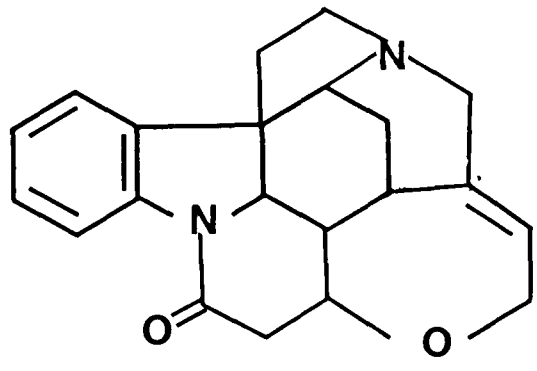
Loganin is then transformed into other iridanes. However, the closer structural resemblance between boonein and another cyclopentanoid (121) formed from linalol would suggest that the latter may be a possible precursor in this case.



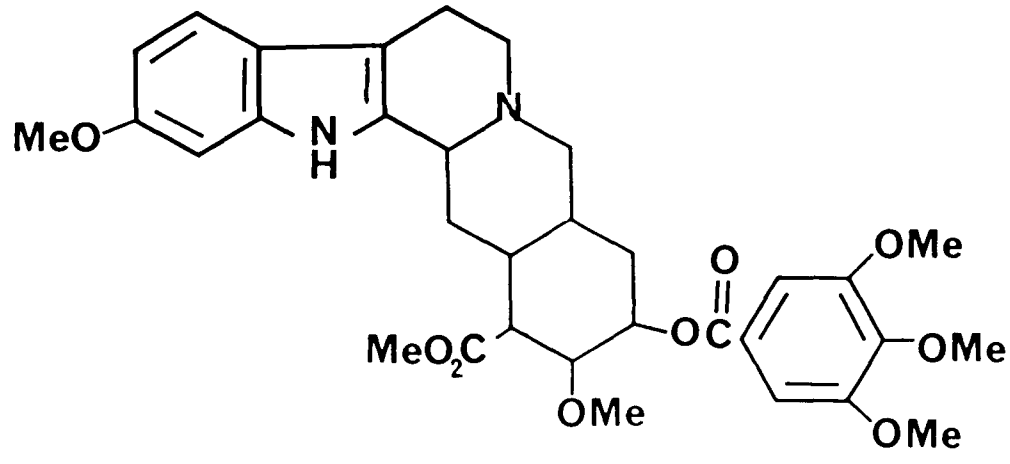
linalol (121)

(b) Loganin as a precursor to monoterpene - indole alkaloids

By far the most important role of loganin is in the biosynthesis of the large group of monoterpene-indole alkaloids.[22,86,87] This class may be exemplified by strychnine and reserpine, which are well-known for their potent physiological activities.



strychnine



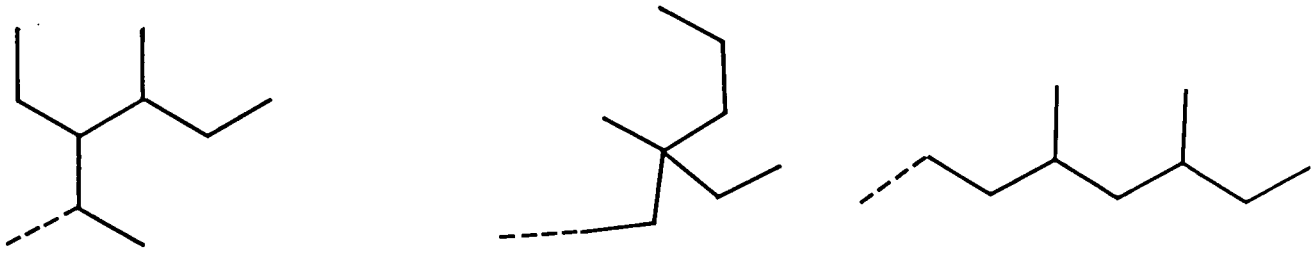
reserpine

The vast numbers of indole alkaloids currently known are, by and large, variations of a relatively few basic skeletal types.[78-81] Closer examination of these molecules reveals that they are composed of two fractions:-

(1) An indole portion which has been demonstrated to be biogenetically derived from tryptophan.

(2) A fragment consisting of 9 or 10 carbon atoms frequently referred to as the $C_{9,10}$ unit.

Inspection of the various indole alkaloids indicates the presence of three main types of $C_{9,10}$ unit:-



Type A Type B Type C

---- The C atom lost in the corresponding C_9 unit.

The biogenetic precursor of all types of this moiety has been shown to be loganin, on the basis of experiments such as feeding the [1-^{14}C] labelled iridoid to Vinca rosea. Degradation of the labelled alkaloids established that the location of activity was at the expected positions.

II.A.3. Biological Activity

In view of the fact that boonein has been only recently discovered, the full potential of its possible physiological activities has not yet been assessed. However, it is of interest to bear in mind activities of other iridoid compounds. This includes their use as antimicrobial[88] and fungicidal[89] agents, as well as possessing plant germination and growth inhibitory activity.[90]

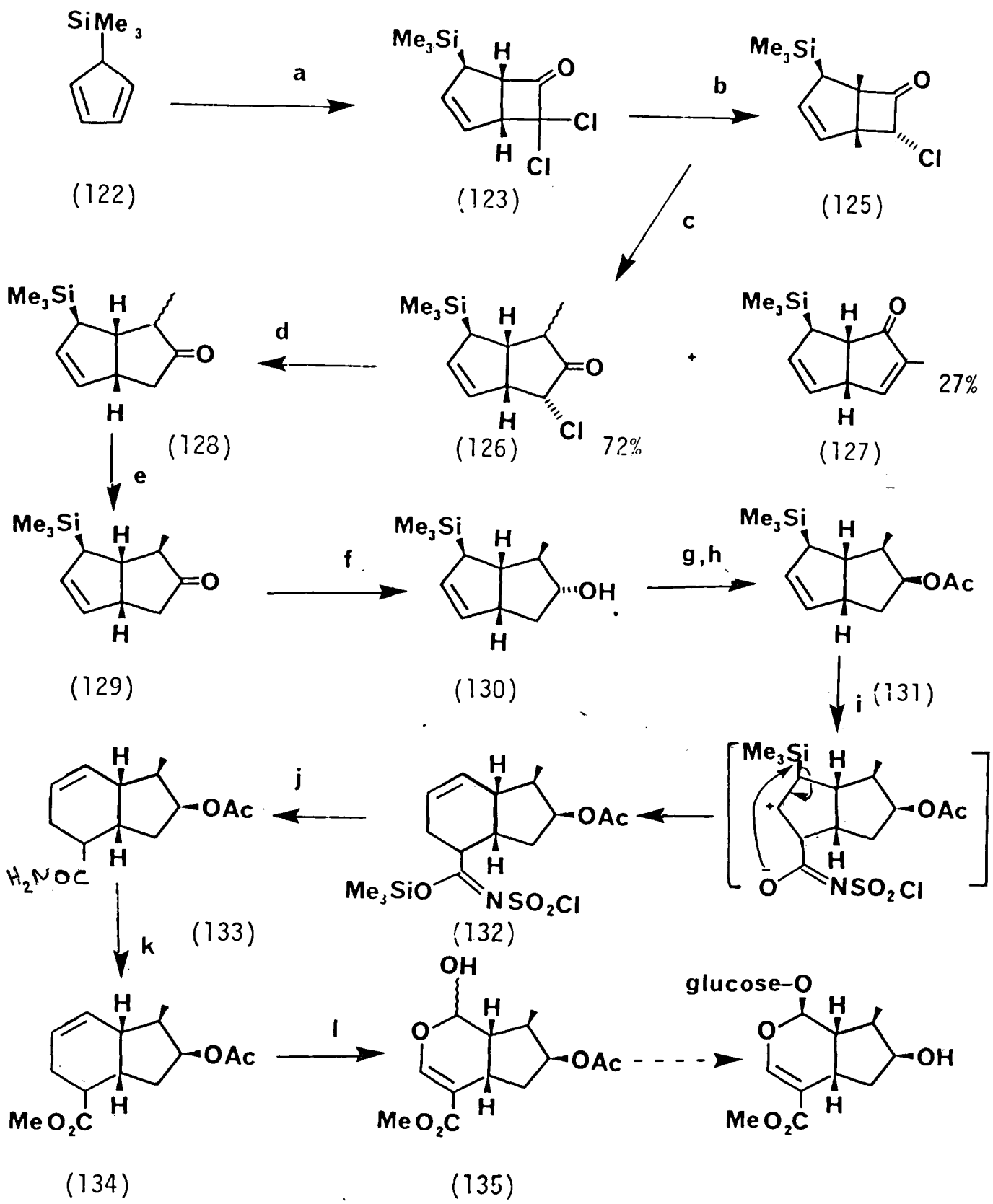
II.B.1. Synthetic Route to Boonein Analogue

As there are no existing reports to date referring to a total synthesis of boonein, it is useful to consider the strategy employed for the preparation of a related compound, such as loganin. Although this molecule has been prepared by several workers,[91-93] the route used by Fleming and Au-Yeung[94] is similar in many respects to that described later for the synthesis of boonein.

The target proposed by these authors is not, in fact, loganin, but an intermediate aglucone that has been shown by others to be easily converted to the iridoid glucoside.

The scheme adopted by Fleming and Au-Yeung is shown overleaf. The starting material was an allylsilane (122), which was subjected to a [2+2] cycloaddition with dichloroketene. Elaboration of the cyclopentane ring was performed by ring expansion of the monochlorinated derivative (125) with diazoethane. Regiochemical control by the α-chloro substituent allowed the desired product to be obtained in 72% yield. The alternative isomer (127) was also obtained but in lower yield. Dechlorination to the ketone (128) was followed by equilibration with sodium methoxide in methanol to give exclusively the exo-methyl ketone (129). Stereospecific reduction with sodium borohydride resulted in formation of the

Synthesis of loganin aglucone acetate



Scheme 17

a, $CHCl_2COCl$, Et_3N; b, Zn, AcOH; C, $MeCHN_2$, MeOH; d, Zn, AcOH; e, NaOMe, MeOH; f, $NaBH_4$, MeOH; g, MsCl,py; h, Et_4NOAc, Me_2CO; i, chlorosulphonyl isocyanate, CCl_4; j, HCl, H_2O; k, $NaNO_2$; AcOH, Ac_2O NaOAc, H_2O; CH_2N_2, Et_2O, MeOH, l, O_3, CH_2Cl_2, Me_2S or OsO_4, C_6H_6, $NaHSO_3$, EtOH, $NaIO_4$, dioxan, H_2O.

endo-alcohol (130). This functionality was inverted by conversion to the corresponding mesylate and reaction with the acetate ion to give (131). Thus, the appropriate stereochemistry in the cyclopentane ring has been established.

Formation of the left hand side of the molecule was now taken in hand.

Conversion to the ester (135) was accomplished by treatment of the allylsilane with chlorosulphonyl isocyanate. Hydrolysis of the product (132) so formed gave the amide (133) which was transformed to the ester (134) by nitrosation, hydrolysis and esterification. Two routes were developed for the formation of the δ-lactol (135). Ozonolytic cleavage of the double bond and subsequent reduction with dimethyl sulphide resulted in spontaneous cyclisation to give (135) in 47% yield. Alternatively, glycolation with osmium tetroxide and treatment with periodate gave the product in 48% yield. This was an intermediate reported in total synthesis by Büchi and Uskokovic. Remaining steps to loganin are glycosidation, and removal of the acetate group.

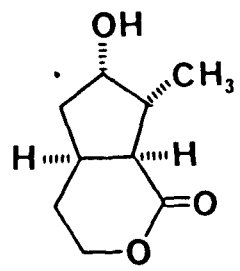
As other routes to loganin are of no particular relevance to the synthesis of boonein described later, they will not be discussed herein.

II.C.1. Research Objectives

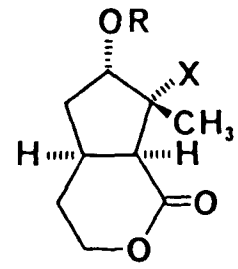
Having been only characterised last year no report on the total synthesis of boonein has appeared in the literature. In this section, I would like to draw attention to our work in this area.

The purpose of this part of the research was to develop a

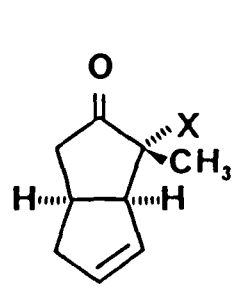
Retrosynthetic analysis of boonein



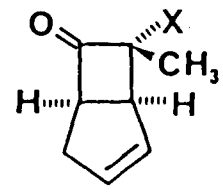
(117)



(136)



(137)



(138)

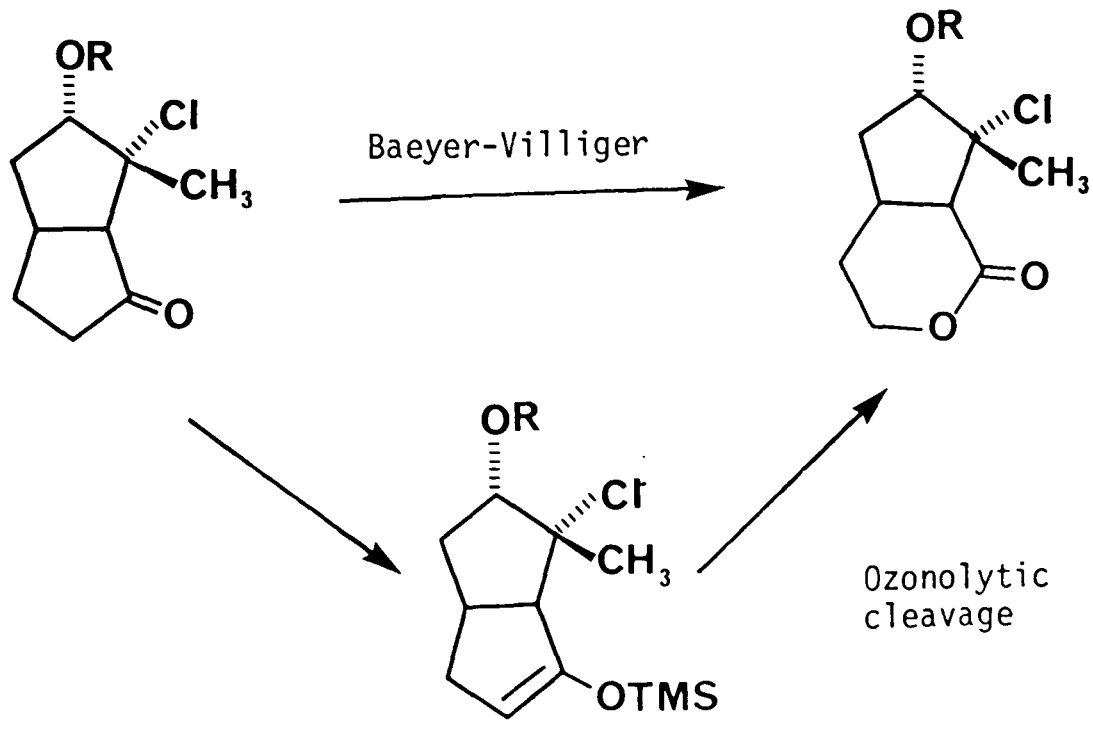
Scheme 18

R = protecting group

X = halogen

total synthesis of boonein. In addition, as interest was shown by others in the possible role of this iridoid in the biogenesis of monoterpene alkaloids, the route could eventually be adopted for the preparation of ^{14}C-labelled boonein. Feeding to Alstonia boonei, and examination of any active products formed would determine whether this molecule was of biogenetic significance.

It was hoped that the synthesis could be realised by the retrosynthetic strategy illustrated in Scheme 18. The precursor to boonein was envisaged as a protected, halogenated compound in which the stereochemistry of the methyl substituent is inverted. Hence, tributyltin hydride reduction of this molecule where R is a bulky group such as t-butyldimethylsilane, would force the reducing agent to approach from the endo face, thereby reversing the stereochemistry of the methyl group. The lactone could, in turn, be derived by oxidation of a suitable cyclopentanone precursor (136). Baeyer-Villiger reaction, or kinetic formation of the O-silylated enolate followed by ozonolytic cleavage using a reductive workup, (as reported by Clark and Heathcock[74] in a previous section, (p40)),would allow the desired transformation.



Obviously, in the case of the Baeyer-Villiger oxidation, two possible products could be formed. However, the halogen, or more specifically the chlorine atom, was expected to exert a regio-selective influence over the reaction pathway to give the desired product. Alternatively, ozonolytic cleavage would permit exclusive formation of the required lactone.

The cyclopentanoid containing compound may be formed from an olefinic precursor. Literature precedent existed for hydro-boration of a similar alkene with a diborane/THF complex to occur in mainly the desired position. If this were unsuccessful, other hydroborating agents were available or even other methods.

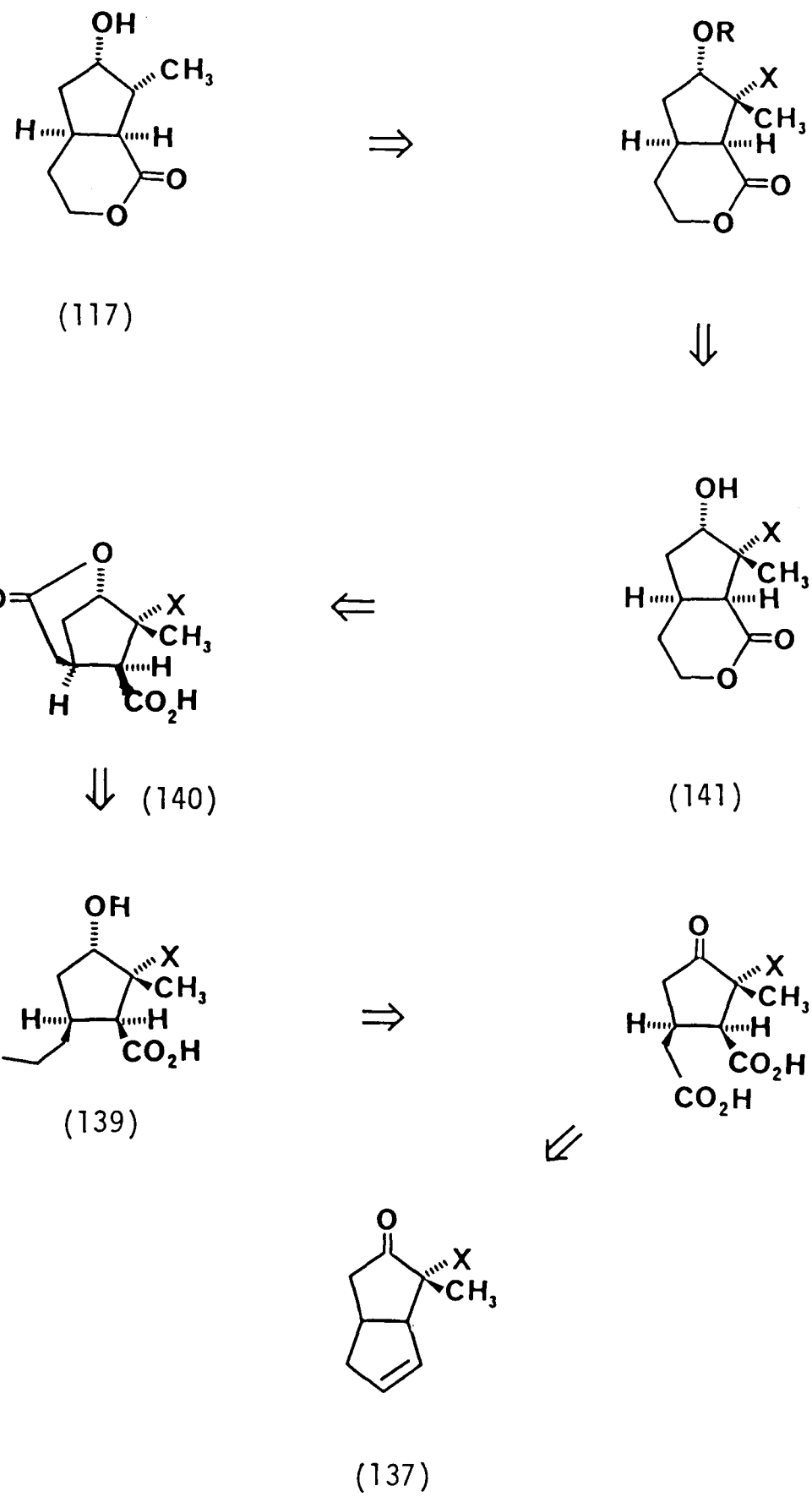
Reduction of a preceeding bicyclo [3.3.0] ketone was hoped to occur stereospecifically, or at least largely, to afford the exo-alcohol. The chlorine substituent was expected to direct attack of a reducing agent such as lithium aluminium hydride from the endo side of the molecule, so as to minimise dipole-dipole interaction.

This bicyclo [3.3.0] system could, in turn, be prepared by ring expansion of the corresponding bicyclo [3.2.0] structure (138). Again, chlorine would be used to control the regiochemistry of the reaction. This has already been referred to in Fleming's synthesis of loganin. Other workers have also exploited the α-chlorine substituent in this way.

The bicyclo [3.2.0] heptenone is the starting material of the synthesis. It was planned that this could be prepared by a well established literature route[95], involving a [2+2] cycloaddition of chloromethyl ketene and cyclopentadiene.

An alternative, potentially attractive strategy is shown

Retrosynthetic analysis of boonein



Scheme 19

in Scheme 19. It is clear that this would involve similar chemistry to that intended for vernolepin. The route again involves elaboration of a bicyclo [3.3.0] system, but in a very different way. This was envisaged to proceed via ozonolytic cleavage of the double bond of (137), followed by reduction of the ketone to afford the hydroxydicarboxylic acid (139). The latter may also be prepared by reversing the sequence, i.e. reduction, and then ozonolysis. Lactonisation would either occur spontaneously or with the aid of acid treatment to give (140).

Specific reduction of the lactone moiety by treatment with two equivalents of diisobutylaluminium hydride should successfully convert (140) into the hydroxyethyl containing molecule. Subsequent lactonisation would result in the δ-lactone portion (141) of boonein. In this way, it should again be possible to differentiate between two carboxylic acid groups, by conversion of one of them into part of a lactone ring and selective reduction.

The remaining steps would involve tin reduction and removal of the protecting group in an analogous manner to that already described.

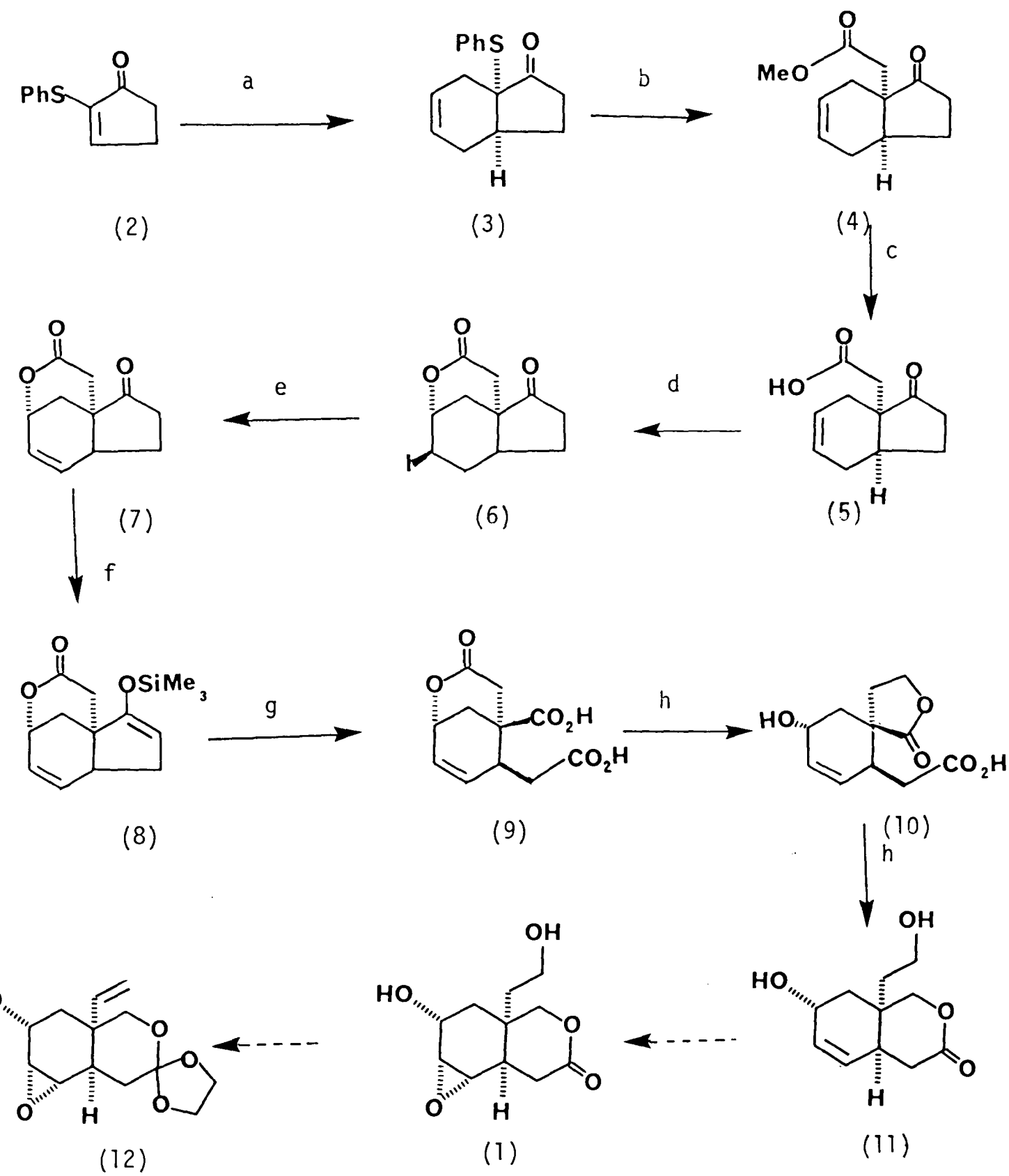
Therefore with these two schemes in mind, the boonein synthesis was embarked upon.

DISCUSSION

CHAPTER III

VERNOLEPIN

Synthesis of the cis-fused 2-oxa-3-decalone (11)



Scheme 1

a, CH_2=CH-CH=CH_2, hydroquinone, b, Li, NH_3; $BrCH_2CO_2CH_3$; c, NaOH, H_2O; d, KI, I_2; e, DBU, C_6H_6, f, LDA, $(CH_3)_3SiCl$; g, O_3, acetone; Jones reagent, h, $Bu_2^i AlH$, H^+.

The novel approach to vernolepin via the common intermediate (1) is summarised in Scheme 1. As can be seen, synthesis of the latter was completed, but for epoxidation of the double bond.

The route was initiated by a Diels-Alder reaction between the thioenone(2) and buta-1,3-diene. A high yielding, regiospecific method was developed to effect conversion of the phenylthioindanone (3) to the alkylated derivative (4). This involved lithium ammonia reduction and subsequent alkylation with methylbromoacetate. Iodolactonisation of the carboxylic acid (5) served to introduce the required α-oxido stereochemistry at C-6. Dehydroiodination gave the unsaturated lactone (7). Formation of the silyl enol ether proceeded in high yield, which in turn underwent oxidative cleavage by ozonolysis, followed by Jones oxidation. Elaboration of the cis-fused 2-oxa-3-decalone system was effected by a novel sequence of reduction, selective lactone formation and repeated reduction.

The synthetic route to the oxa-decalone (11) involves nine easy steps. In addition, each of the stereochemical features have been introduced stereoselectively, and for the most part stereospecifically.

The final epoxidation may be accomplished in one step, although protection of the allylic alcohol may be necessary to allow exclusive α-epoxidation.

Ultimate transformation into Danishefsky's vernolepin intermediate (12) would involve known functional group interconversions, namely protection of the δ-lactone moiety and Grieco's two step method for converting a hydroxyethyl function into a vinyl group.

EFFECT OF THE THIOPHENYL GROUP

Before embarking on a discussion of the thioenone (2), it is worthwhile stressing the importance of the thiophenyl group in the initial stages of the synthesis. This is outlined below:-

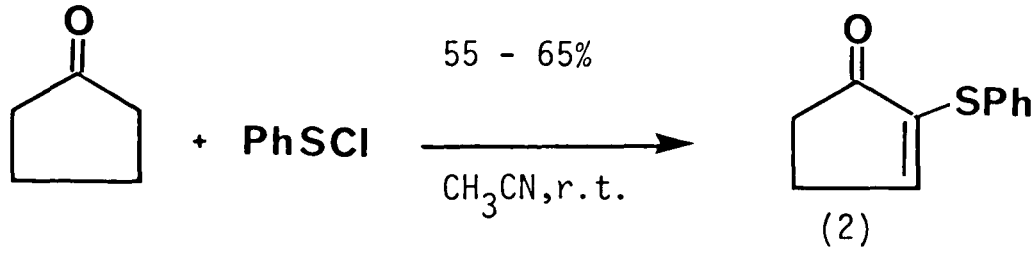
(1) The thioenone (2) may be prepared by a facile one step synthesis, in moderate yield, from cyclopentanone. In contrast, routes from the corresponding 2-cyclopentenone[96,97] are often laborious and low yielding.

(2) The electron-withdrawing nature of the moiety allows a high yield of the Diels-Alder adduct (3). In contrast, the high temperature and long time period needed to induce a similar reaction with cyclopentenone,[98] only gives a low yield of the product, which tends to isomerise under these conditions.

(3) The thiophenyl group has been used to control the direction of alkylation, enabling regiospecific production of the desired isomer. No such control is possible for the unsubstituted compound.

III.1. FORMATION OF THE THIOENONE (2)

A number of approaches have been made towards (2).[99-102] The easiest method is that reported by Monteiro,[103] based on some previous work by Oki and Kobayashi.[104] Treatment of cyclopentanone with an excess of phenylsulphenyl chloride, in dry acetonitrile gives good yields of the thioenone (2).



(2)

Phenylsulphenyl chloride was prepared by bubbling chlorine through ice-cold CCl_4, and adding a solution of thiophenol in CCl_4 in a dropwise manner. At the end of the addition, excess chlorine was removed by evaporation under reduced pressure. The success of the method was dependent on the immediate removal of excess chlorine. Any delay was found to result in decomposition of the product to diphenyldisulphide. Immediate evaporation of the solvent afforded an orange/red liquid, which was distilled under reduced pressure.

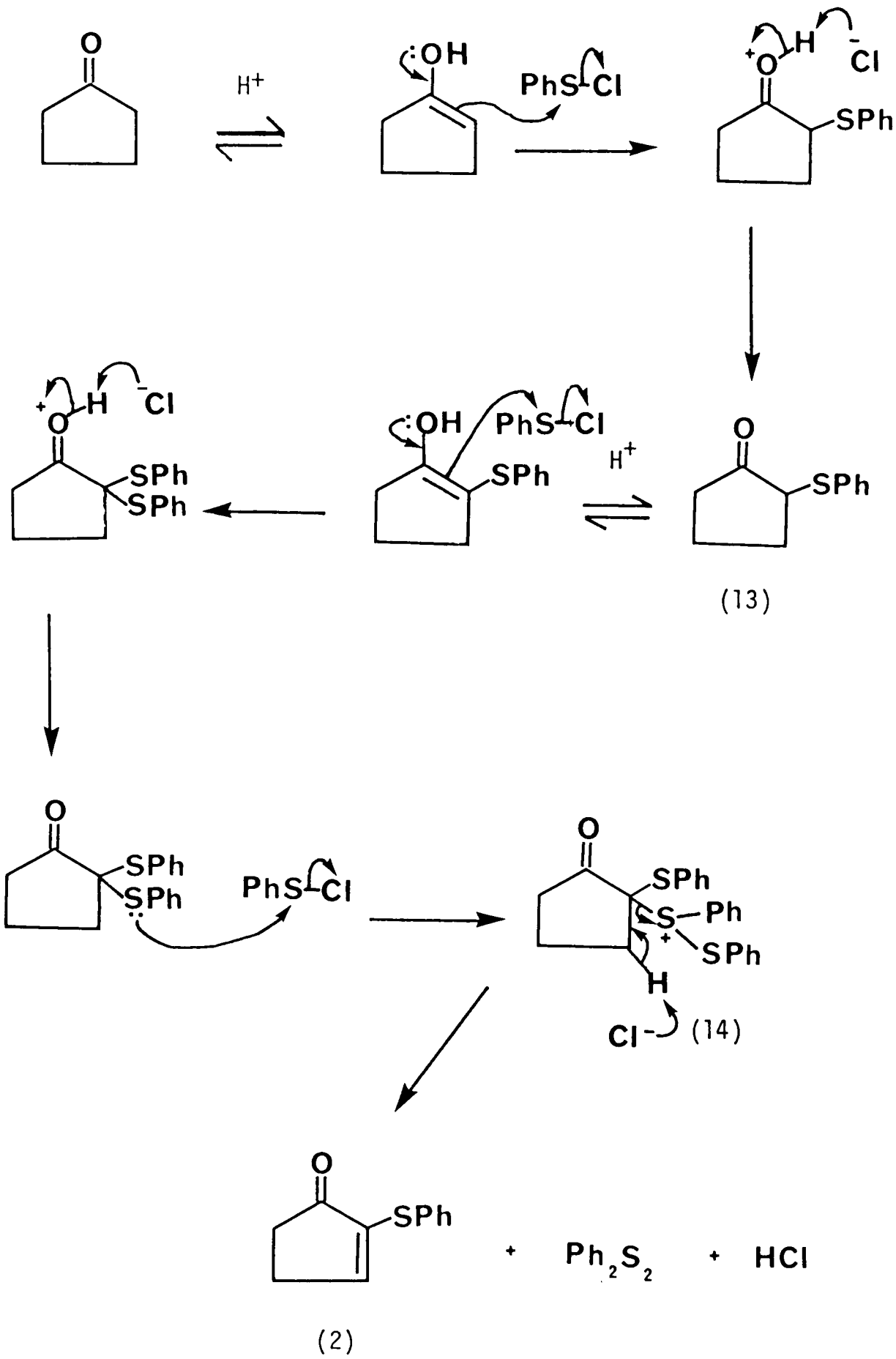
Due to the unstable nature of phenylsulphenyl chloride, storage even at sub zero temperatures in the absence of light, was not possible. The reagent had to be made in batches as required, and used directly. During the course of the research, 23 separate batches were prepared giving a sum total of approximately 1.4 kg of the compound. The yields, which ranged from 70% to being almost quantitative, were independent of batch size. The latter varied from 12 g initially to a maximum of 144g of thiophenol. This was the largest amount that

could be easily handled at any one time.

Formation of the thioenone (2) was effected simply by adding a three-fold excess of the sulphenyl chloride to a solution of cyclopentanone in acetonitrile. Hydrogen chloride, which was formed during the course of the reaction was removed by evaporation under reduced pressure. However, the large amount of diphenyl disulphide and any remaining starting material were not as easily removed. Due to unsuccessful attempts at purification by recrystallisation, sublimation and distillation, the only remaining option was chromatography. A consideration of the amounts of crude thioenone involved, shows a reaction of 317 g of phenylsulphenyl chloride with 56 g of cyclopentanone gave 310 g of crude product. Purification of portions which were small enough, for example 10 g, to allow separation by flash or gravity column chromatography, would be an extremely tedious procedure. Fortunately, this problem was overcome by the use of dry flash chromatography. Purification in 50 g batches using a large sinter funnel (diameter 15cm) afforded sufficiently pure product for the subsequent Diels-Alder reaction. In addition, this method is relatively quick, with purification taking just 30 mins.

A number of successive amounts of thioenone were prepared throughout the course of the work. The reaction was not subject to any size limitation, although for practical purposes there was no reason to make vast amounts of the product, due to the restricted batch size employed in the Diels-Alder reaction.

A proposed mechanism for the formation of the thioenone (2) is shown overleaf:

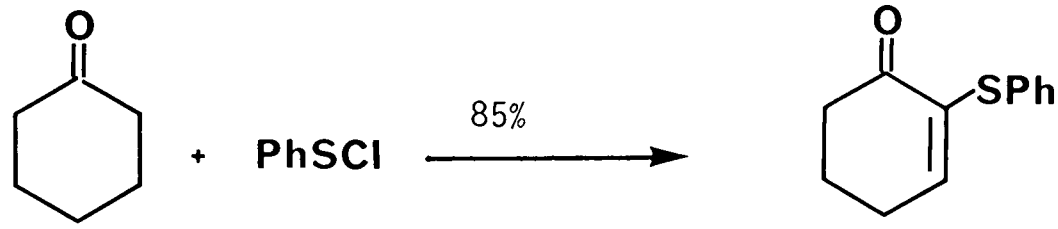


(2)

The condensation of one equivalent of each reactant gives the intermediate thioketone (13). Addition of a second and third molecule of sulphenyl chloride gives rise to the sulphonium salt (14), which then undergoes elimination to (2).

Characterisation of a pure sample of thioenone (2) by i.r. indicated a carboxyl absorption at 1710 cm^{-1}, expected for a conjugated ketone. N.m.r. analysis showed the β-H to be considerably deshielded, due to the anisotropic effect of the carboxyl group appearing as δ7.0 as a doublet of doublets, consistent with literature findings.

The generality of the method was demonstrated by reaction with cyclohexanone in an analagous manner. The product was obtained in



(15)

good yield, as yellow crystals, and characterisation was in agreement with that reported in the literature.[99] This result contradicts a recent observation by McKervey and Ratananukul,[102] who state that the procedure is peculiar to cyclopentanone alone.

III.2. DIELS-ALDER REACTION

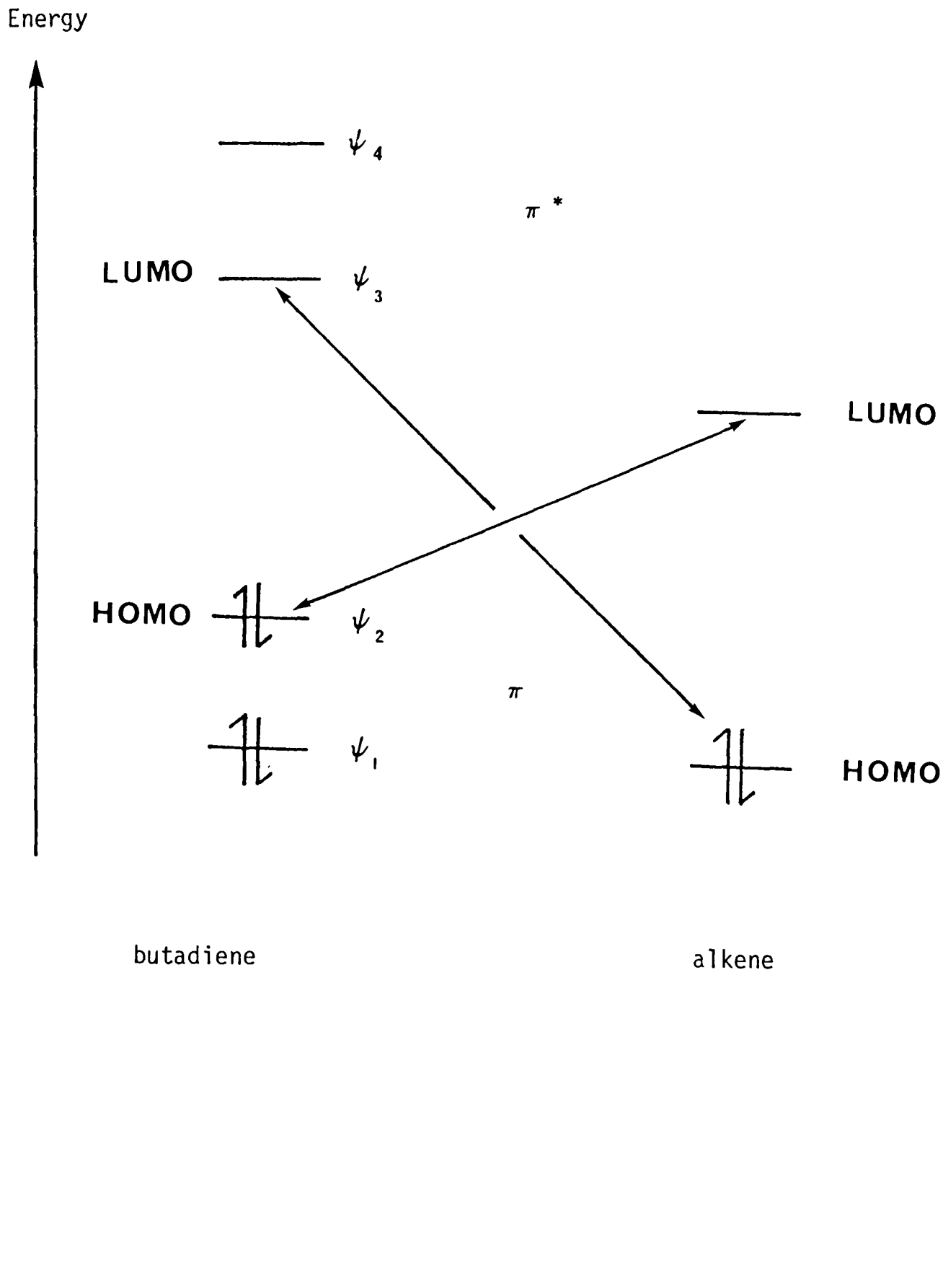
The next stage of the synthesis was accomplished via a Diels-Alder reaction[105-108] between buta-1, 3-diene and the thioenone (2). This is a thermal $[\pi 4s + \pi 2s]$ cycloaddition, in which two new σ-bonds and one π-bond are formed from the 4π-electron system of the diene and 2π-electron system of the dienophile.

Stereochemical aspects of the addition include reaction of the diene in a purely cisoid conformation. This approaches the dienophile in a strictly syn fashion, allowing the cis-fused adduct; this is known as the "cis" principle.

The generally accepted view is that the Diels-Alder reaction is a concerted cycloaddition. This is reflected by the high degree of stereospecificity of the reaction. Concerted reactions obey the Woodward-Hoffmann rules for the conservation of orbital symmetry. The rules stated that the $[4n + 2]$ reaction is an allowed process when addition occurs at the same side of the π-bonding system, i.e. supra-facially for both components. Antarafacial processes are also allowed for both participants, although these are less geometrically likely.

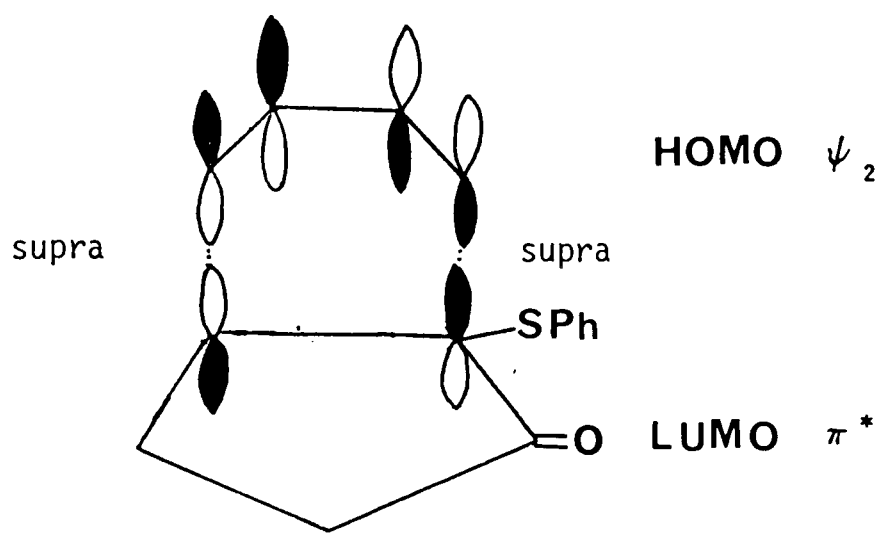
The mechanism of the process can be described in terms of the molecular orbital theory. Attention is focussed on the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of each component. The rate of reaction, in which electrons are transferred from the former to the latter, depends on the size of the energy gap between the two orbitals. The smaller the gap, the faster the process.

Π-molecular orbitals



As the diagram illustrates, in general the smallest separation is achieved between the HOMO of the diene and the LUMO of the dienophile.

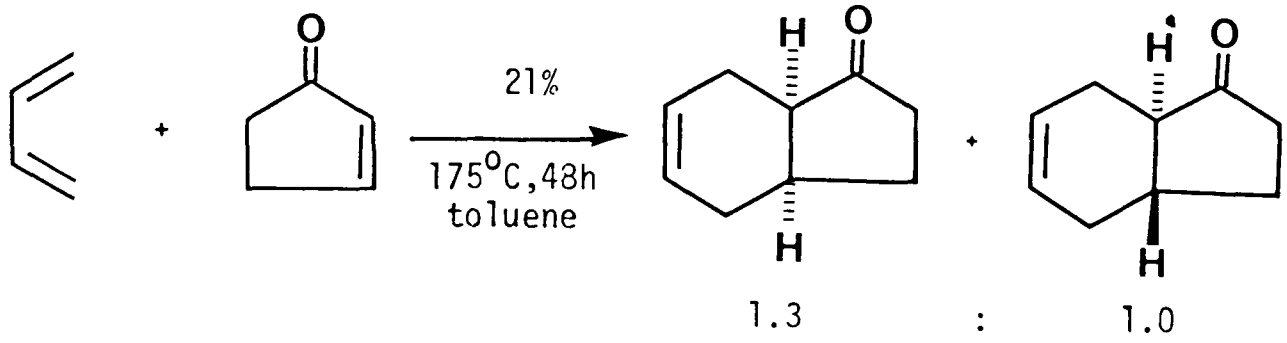
The cycloaddition between butadiene and the thioenone (2) is crudely represented:-



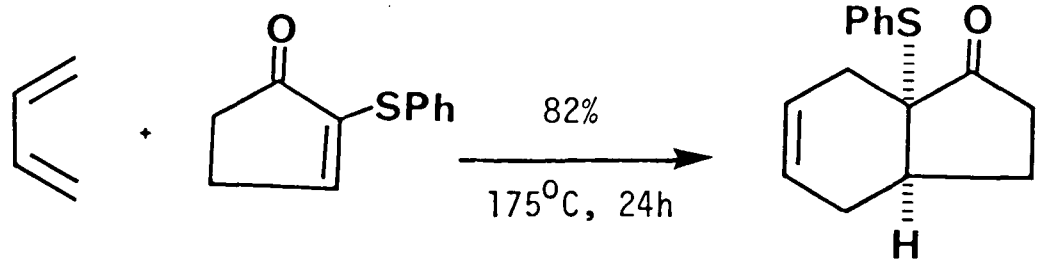
Thus, overlap brings together lobes of the same phase and bonding occurs.

The presence of an electron-withdrawing group on the dienophile serves to lower the energy of both frontier orbitals of this component. Consequently there is an enhanced interaction between the two molecules. (In contrast, electron-donating substituents on the diene have the opposite effect and also accelerate the reaction).

The effect of the thiophenyl group is exemplified by a comparison of the reaction of cyclopentenone and (2) with butadiene[82].



Cycloaddition with the unsubstituted enone afforded a 21% yield



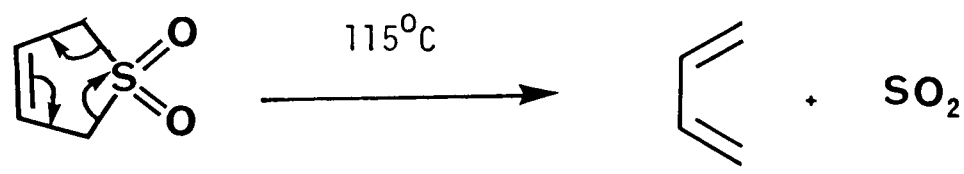
(2) (3)

of a mixture of tetrahydroindanones. Due to the long time needed to effect the transformation, the initially formed cis-fused adduct isomerised to give a mixture of products. In contrast, the electron withdrawing nature of the phenylthio group allowed 82% of the desired adduct. In addition, it would appear that the thioenone reacted twice as fast as cyclopentenone with butadiene, under the same conditions. Consequently, the phenylthio group exerts a small accelerating effect despite its larger steric bulk compared with hydrogen.

Within the context of the synthesis, Knapp's method[82] for the

preparation of (3) was followed. This involved heating a mixture of thioenone (2), butadiene and a trace amount of hydroquinone in a Carius tube, positioned in an electric oven. The function of hydroquinone was to inhibit cycloaddition of butadiene. Good yields (66%) of the desired adduct (3) were formed from reaction with pure thioenone. However,this was considerably lowered when crude thioenone was employed (vide infra). The phenylthioindanone displayed a shift in carbonyl absorption from 1710 to 1730 cm^{-1}. This was consistent with conversion of an α, β-unsaturated ketone to a cyclopentanone derivative. Furthermore, the n.m.r. spectrum was in accord with the literature values for this compound.

As butadiene is a gas, b.p.- $4^{o}C$, it had to be condensed into the Carius tube. This was rather a lengthy procedure, and so we attempted to study an alternative source of the diene. Butadiene sulphone[109] is a solid, and decomposes at $115^{o}C$ to give a mixture of butadiene and sulphur dioxide.

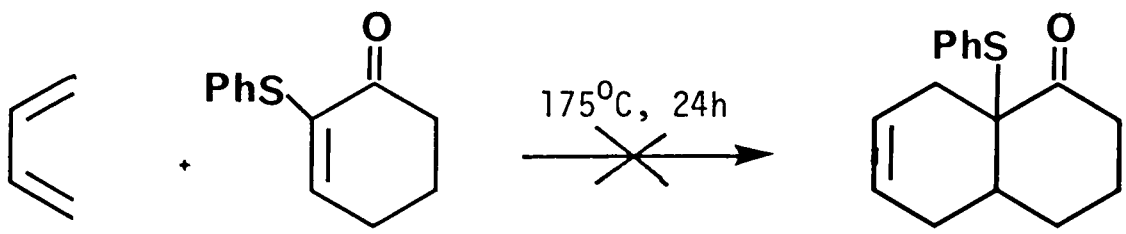


Heating a mixture of (2) and a two-fold excess of butadiene sulphone, at $115^{o}C$ for 24h, in either dibutyl ether or xylene, resulted in only trace amounts of the desired adduct. Even the application of the more stringent sealed tube conditions, with a ten-fold excess of the sulphone, afforded only an 8% yield of phenylthioindanone. The presence of substantial amounts of baseline material suggested some thermal decomposition may well have occurred. Consequently, use of this diene precursor was abandoned.

Unfortunately, the sealed tube method was not very amenable to large scale work. The electric oven employed could accommodate only four Carius tubes, which were of limited size. As it is not advisable to fill the tubes to more than half of their volume, it was discovered that a maximum of 10 g of thioenone could be used in any one tube. A total of 41 sealed tubes containing variable amounts of (2) were prepared throughout the course of the work. In order to appreciate the quantities of crude product involved, four Carius tubes, each containing 9 g of (2) afforded 100 g of the crude mixture. This was initially separated by dry flash chromatography, and subsequently purified by flash chromatography.

In general, 12.6 g of pure (3) was obtained from 50 g of impure thioenone, used in the Diels-Alder reaction.

Itseems reasonable to include, at this stage, the attempts made at preparation of the phenylthiodecalone analogue (16). On both



(15) (16)

occasions,utilisation of the normal sealed tube conditions resulted in explosions. Spectral analysis of the residue was not consistent with the desired adduct (16).

Due to the drawbacks of this method, attention was turned to the use of Lewis acid catalysed Diels-Alder reactions. This was first reported by Yates and Eaton[110] for α, β-unsaturated carbonyl compounds, with aluminium chloride. Catalysis by other Lewis acids was

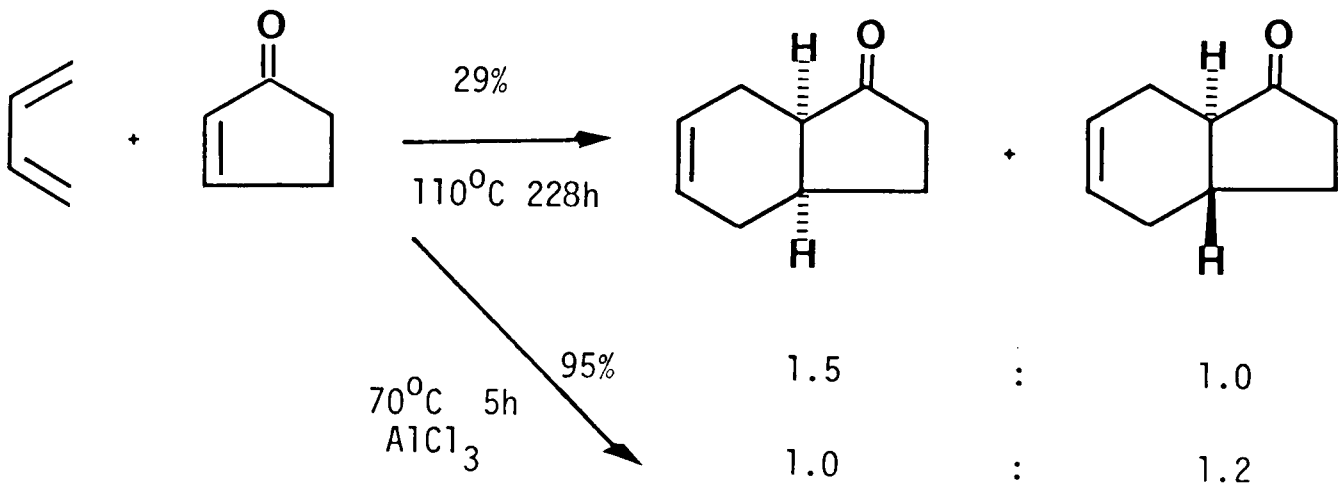
later demonstrated.[111] The catalytic effect is attributed to coordination of the Lewis acid with the carbonyl oxygen atom of the dienophile, thereby making it more electron deficient, and so more reactive.

viz:-

MX_n = Lewis acid

The mechanism of the addition is still believed to be concerted, affording cis-fused products.

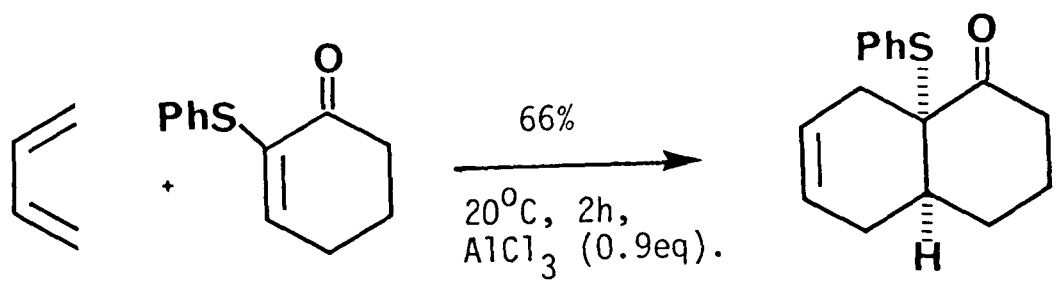
Fringuelli et al.[112] have carried out an extensive study of the aluminium chloride catalysed cycloaddition of cycloalkenones with various dienes. A comparison of the thermal and catalysed Diels-Alder



reactions reveals the dramatic accelerating effect of aluminium chloride. The difference in regio-isomer ratios is attributed to equilibration of the kinetically formed cis-isomer in the acidic medium. The cat-

alysed cycloaddition involves initial formation of an aluminium chloride-cyclopentenone complex. (The amount of Lewis acid employed is not stated in this paper). The diene is subsequently added, and the mixture heated at 70°C for the required length of time. It would appear, at first sight, that this temperature would be too high to retain butadiene, (b.p.-4°C), in the reaction mixture. Therefore the reaction was carried out with the thioenone, at -9°C. A catalytic amount of aluminium chloride was used. After 72h, the reaction was worked-up and purified to afford a 39% yield of phenylthioindanone. Substantial quantities of (2) remained.

In a previous publication, Fringuelli et al.[113] have stated that the quantity of aluminium chloride used is critical. An optimum yield is obtained using a 0.9 mole excess of the Lewis acid. This has been confirmed by some recent work, at Brunel University,[114] with the thioenone (15), (vide infra)



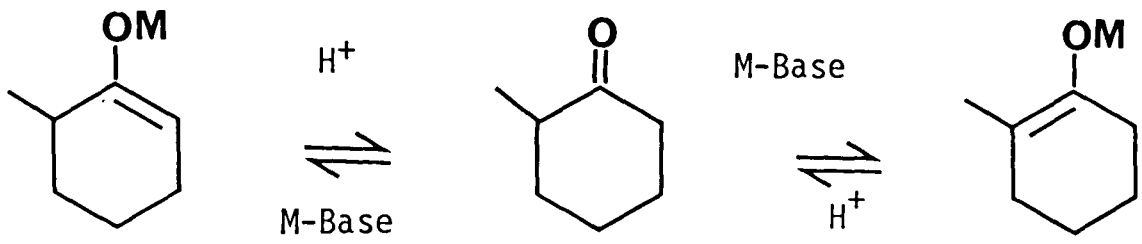
(15) (16)

Unfortunately, time did not allow application of this method to the thioenone (2). However, obviation of the sealed tube method by an analagous catalysed procedure, would greatly improve this stage of the synthesis.

III.3. REDUCTION-ALKYLATION

A considerable amount of effort has been expended in the development of a method that would allow regiospecific formation of the ketoester (4). This was accomplished by a dissolved metal reduction-alkylation sequence.

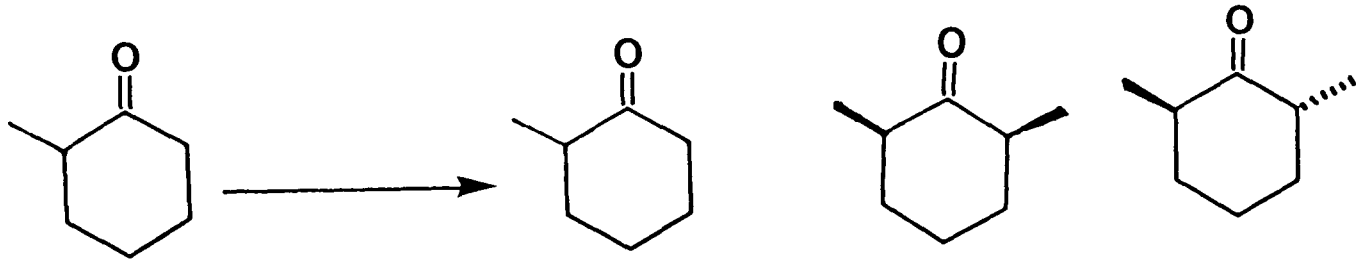
One of the main problems that limit the use of an enolate anion is their regioselective formation.[115-117] If there are two or more acidic protons present in the ketone, then in the presence of a proton donor, the formation of structurally isomeric enolate anions is possible. Alkylation may then result in a number of products. For example, equilibration of the two enolate anions of 2-methylcyclohexanone (vide infra), results in alkylation to give all the possible methylation products[118] (Scheme 2).



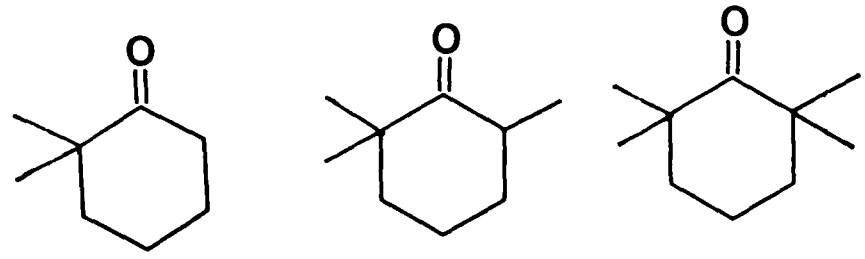
Consequently,methods have been developed for the regiospecific preparation of ketone enolates, to avoid the formation of such mixtures.[81,115-117,119-121,128]

In 1973, Coates et al.[122,123] reported that α-phenylthio ketones and aldehydes could be regiospecifically alkylated at the carbon bearing sulphur, and that the sulphide function could be reductively cleaved and alkylated by lithium ammonia reduction in a regiospecific manner.

Methylation of 2-Methylcyclohexanone

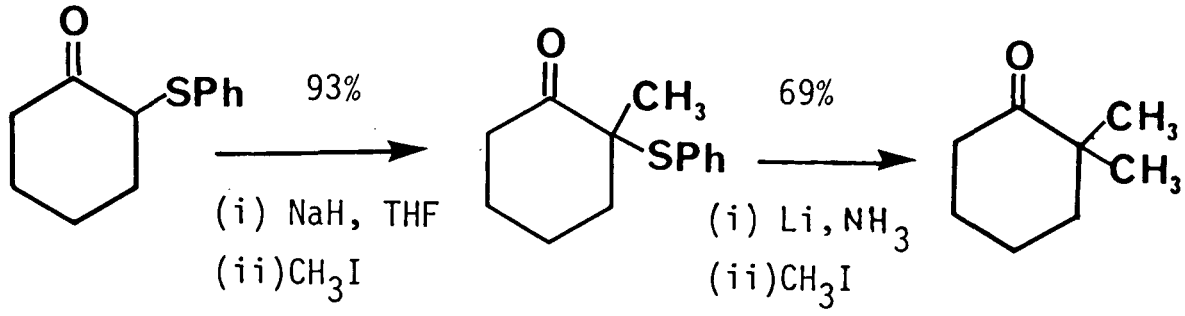


NaH, MeI	48%	13%	13%
or			
Ph_3CK, MeI	22%	9%	-



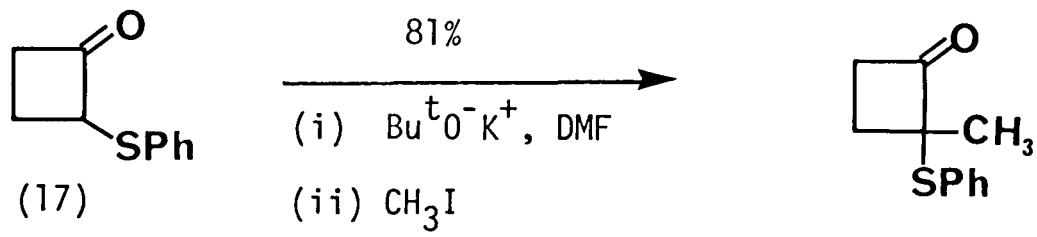
18%	8%	-
41%	21%	6%

Scheme 2



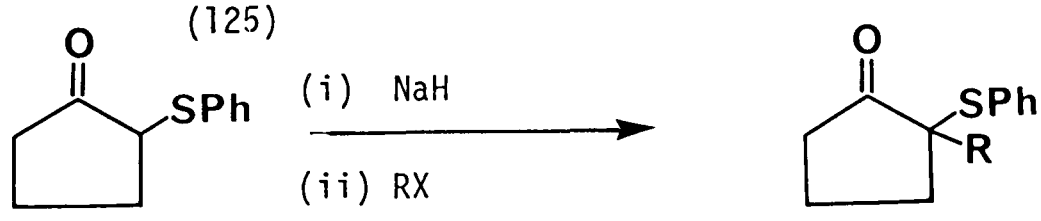
Additionally, the introduction of a sulphur substituent to the α position of a carbonyl group, enhances the acidity of an adjacent α-proton by approximately 10^3 over a simple ketone. This greatly stabilises an enolate anion at the carbon bearing sulphur. This directing effect of the thiophenyl group has also been used by many workers, for instance (17),(18) and (19).

(124)



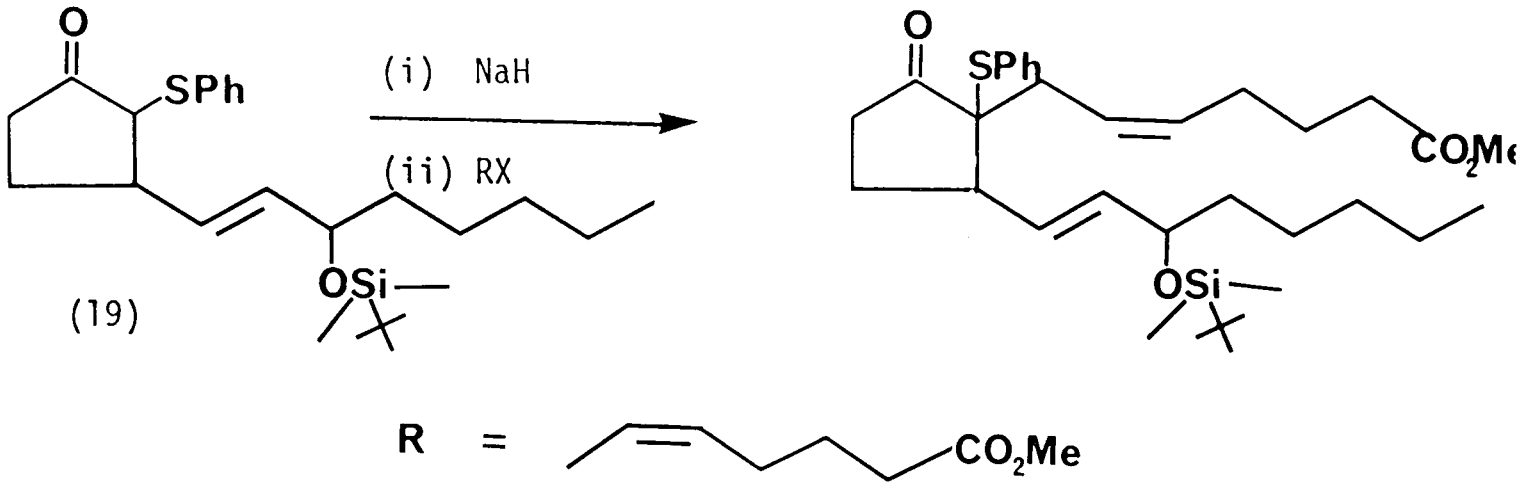
(17)

(125)



(18)

(126)



α-Tert-butylthio derivatives have been used similarly.(127)

The initial attempts at reduction-alkylation are summarised in Table 1. In all reactions, an anhydrous oxygen-free nitrogen atmosphere was maintained at all times, and the quenching agent used was saturated aqueous ammonium chloride solution. Although only three parameters are represented in the Table, in fact a number of variable factors are inherent in this complex procedure. For example, the amounts of lithium, ammonia and alkylating agent used, the volume and type of solvent, the temperature at which the electrophilic species is added, its rate of addition and the reaction time before quenching.

The original method followed the published conditions of Coates et al.(123) viz:- 10 equivalents lithium, ammonia, ether, -33°C; 15 equivalents of methyl iodide, -33°C, 30 minutes. In practice, lithium was added to liquid ammonia (20 ml) at -60°C, which dissolved giving a blue reducing system. A solution of phenylthioindanone (3) (0.5 g) in sodium dried ether was introduced at -33°C and the mixture stirred for 15 minutes. Methyl iodide was added at -33°C and the reaction mixture quenched after 30 minutes. The crude mixture obtained from workup was purified to give a number of fractions. These corresponded to methyl iodide, thioanisole, and the reduced indanone (26),(p.91). In addition, minor quantities of unknown compounds of low R_f were also isolated. It is worth pointing out that no starting material was

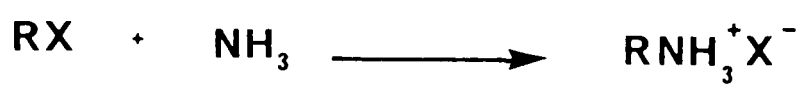
Attempts at reduction-alkylation of phenylthioindanone

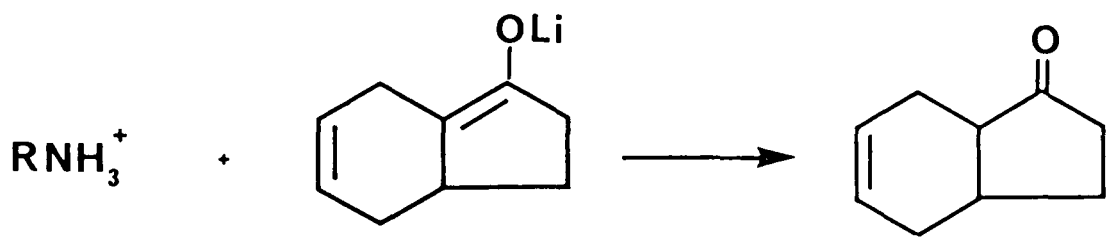
Alkylating Agent	NH_3 removed before adding alkylating agent	Solvent	Distillation of NH_3	Result
MeI	x	Ether	x	-
MeI	x	Ether	x	-
$BrCH_2CO_2Me$	x	Ether	x	-
$BrCH_2CO_2Me$	✓	Ether	x	-
$BrCH_2CO_2Me$	✓	THF	x	-
$BrCH_2CO_2Me$	✓	THF	x	-
$BrCH_2CO_2Me$	✓	THF	x	-
$BrCH_2CO_2Me$	✓	THF	x	-
$BrCH_2CO_2Me$	✓	THF	✓	-
$BrCH_2CO_2Me$	✓	THF dried with $LiAlH_4$, $Ph_3C^{\ominus}$ as indicator	✓	✓

TABLE 1

recovered. A repeat of this procedure gave similar results, as were also obtained using methylbromoacetate. (In this case a major by-product was the analogous methylphenylthioacetate).

Reference to the literature[117] indicated the possibility of a reaction of the electrophilic reagent with ammonia to form an acidic ammonium salt. This may then protonate the lithium enolate to produce the reduction product (26).



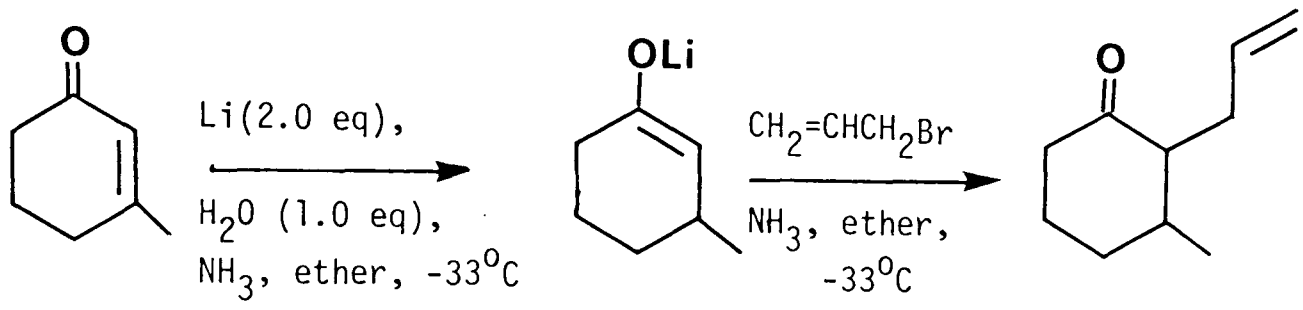


(26)

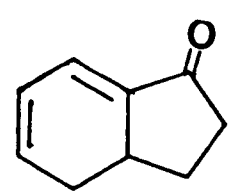
Consequently,in a subsequent attempt, ammonia was removed under reduced pressure, prior to addition of methylbromoacetate. Unfortunately, alkylated product was still not procured.

As a large proportion of ether was lost on evaporation of ammonia, it was decided to change solvents to the higher boiling THF, which was dried with calcium hydride. A repeat of the reaction still resisted all attempts at the desired transformation. Four subsequent attempts were equally unsuccessful. The fact that the reduction product (26) and no starting material was isolated, indicated that enolate anion formation must have occurred. However, this enolate anion is protonated before reaction with the electrophilic reagent.

Due to problems encountered with this reaction the reduction-alkylation of the dihydroindanones was attempted. Caine[121] has reported a detailed account of the procedure using 3-methylcyclohexenone as starting material:-



(20)



(21)

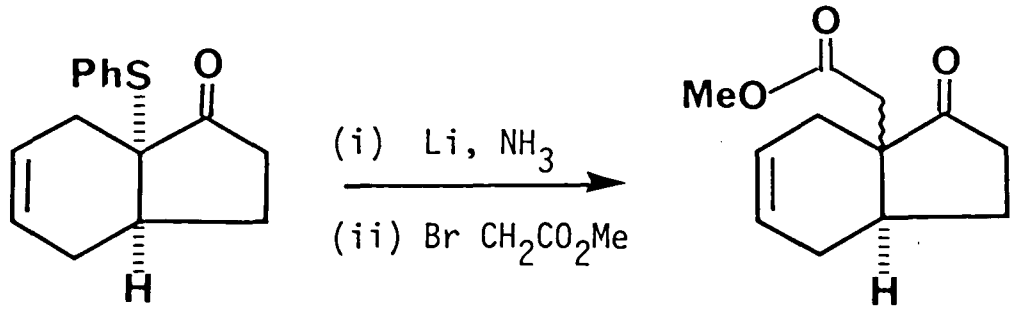
Similarly, a solution of the dihydroindanones (20) and (21) in THF and water were added to a solution of lithium in liquid ammonia. During the addition the blue colour vanished, indicating the absence of a reducing system. This was borne out by the isolation of mainly starting material from the crude product obtained after workup. Consequently, the reaction was repeated using a larger excess of lithium (2.5 equivalents). In addition, it was deemed advantageous to dry the liquid ammonia with sodium and distil it prior to use. House[115] has considered the presence of impurities in undistilled liquid ammonia, such as iron compounds, to lower the overall reducing ability of the system, by catalysing the reaction of lithium with ammonia to form hydrogen and lithium amide However, another attempt at the enone reduction-alkylation yielded mainly reduction product (26), together with unknown compounds. As this reaction did not fare much better, it was decided to return to the phenylthioindanone.

It was considered possible that the source of the troublesome proton donor may be acidic ammonium salts formed from any residual ammonia remaining from the evaporation procedure. In an effort to completely remove this, dry ether was added after the evaporation of

ammonia, and the mixture re-evaporated, unfortunately without success. The only other possible source of moisture could be from the solvent. The THF that was originally dried with calcium hydride, was further rendered anhydrous by the addition of lithium aluminium hydride with triphenylmethane being employed as indicator.

Fortunately, it was discovered that reaction with THF dried in this manner was successful. This indicates the degree to which the reaction is dependent on the rigorous exclusion of moisture.

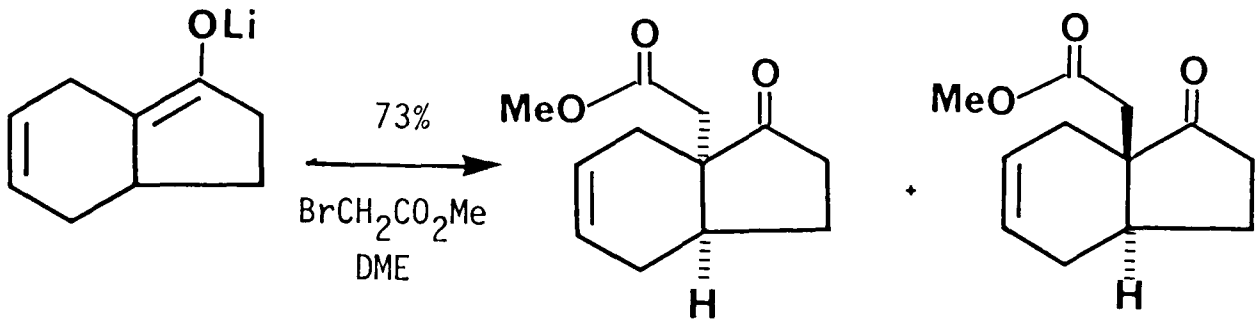
The thiophenyl group had served as an activating group[129] allowing regiospecific alkylation at the bridgehead position



(3) (4)

The ketoester (4) had i.r. absorption at 1745 cm^{-1}, for the ester and cyclopentanone derivative, and 1660 cm^{-1} indicating a double bond. The n.m.r. spectrum exhibited resonances at δ5.6 integrating to two protons, δ3.6, consistent with a methyl ester grouping, and complex absorption in the region δ2.7-1.6. These spectral characteristics are directly comparable with those reported by House[81] for the bridgehead product (4). This author had previously prepared (4) from the enol acetate as mentioned earlier. A disadvantage to preparing the lithium enolate (22) in this way was the rather

laborious procedure needed for the purification of the enol acetate. This involved distillation under reduced pressure, fractional distillation with a spinning-band column and finally redistillation. House and co-workers have reported a cis to trans ratio of 95:5 for



95 : 5

the two bridgehead isomers. This was in agreement with the ratio obtained by g.l.c. analysis of the crude alkylated product obtained by us.

The reduction-alkylation of phenylthioindanone has since been performed several times using various quantities of the starting material, (see Table 2). An optimum yield of 91% of (4) was obtained from 4 g of phenylthioindanone. Using larger batch sizes of the starting material resulted in lower yields of product. This was compounded by the long time period needed for condensation and subsequent evaporation of ammonia in large scale work. For instance this amounted to $3\frac{1}{2}$ hours when 140 ml of ammonia was employed. The temperature at which methylbromoacetate was added to the solution of lithium enolate was important. This very reactive alkylating agent typically produced a temperature rise of $30^{o}C$ when added at approximately $-20^{o}C$. This could be minimised by using more dilute solutions of enolate anion. An alternative was, of course, using a solution

Phenylthio-indanone (g)	THF/NH_3 (ml)	Li (Equiv.)	Reaction Time (min).	Yield (%)
0.5	20: 50	10	2.0	60
0.5 *	20: 50	10	2.0	38
2.0	80:200	10	2.0	62
2.0 *	80:200	10	2.0	53
1.3 *	50:130	10	2.0	38
2.0	80:200	10	2.0	48
2.4 *	95:240	10	2.0	46
2.7 +	100:270	10	2.0	48
2.5 *	90:250	10	2.0	57
2.9	100:290	10	2.0	71
3.1 *	100:310	10	2.0	59
3.5	140:350	10	2.0	80
2.6	120:260	10	2.0	87
3.3	150:330	10	1.5	70
4.0	200:400	10	2.0	91
5.9	275:590	10	2.0	63
4.8	250:480	10	2.0	69

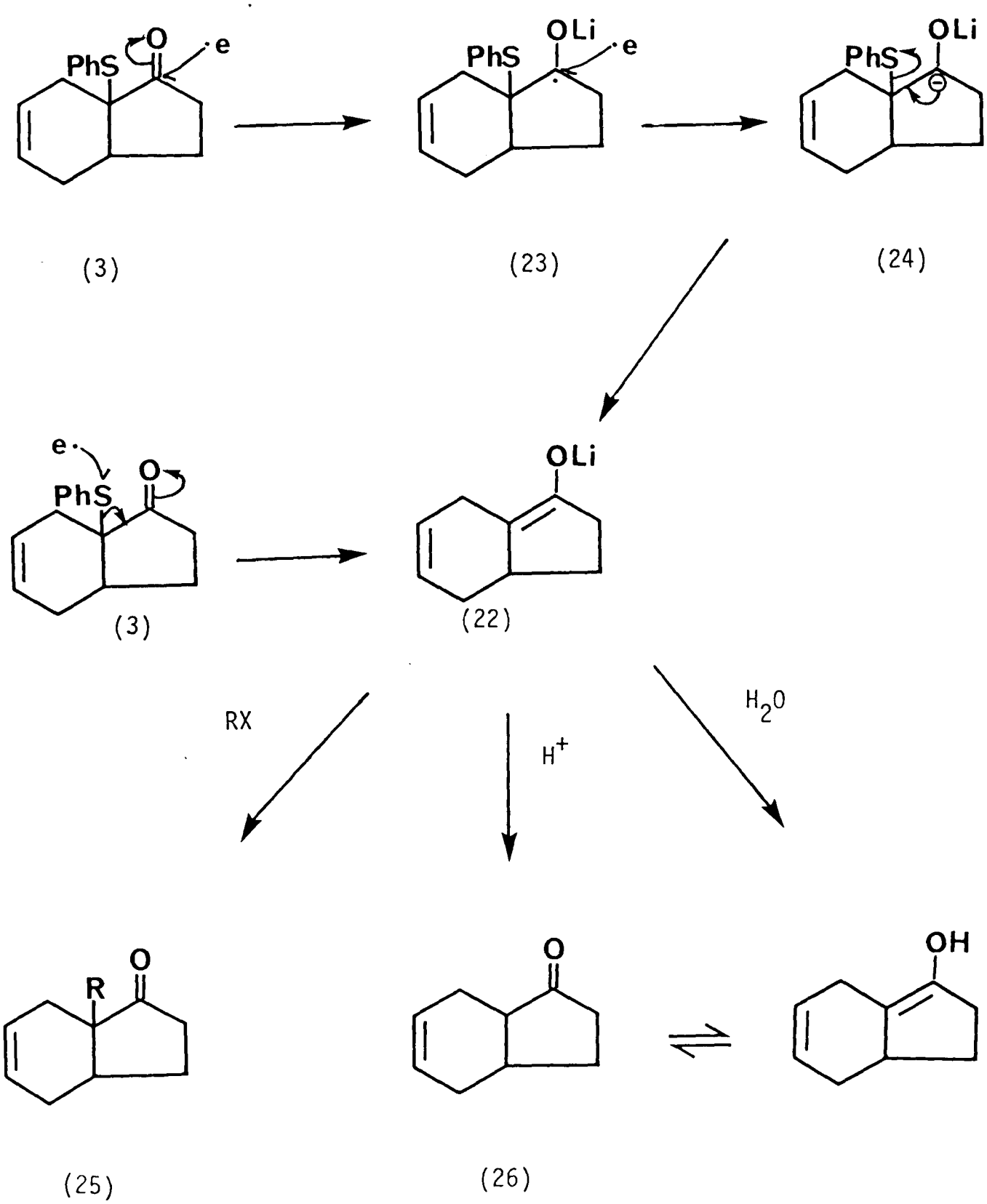
* an air leak occurred during this run.

\+ Methylbromoacetate was diluted with THF (7 ml).

Table 2

of methylbromoacetate in THF. However, this only led to a moderate yield of the desired product. Addition of precooled alkylating agent did not have much effect. A reaction time of 2 minutes was normally employed. This is very much longer than the 30 seconds used by House. However, no dialkylated product was at any time isolated.

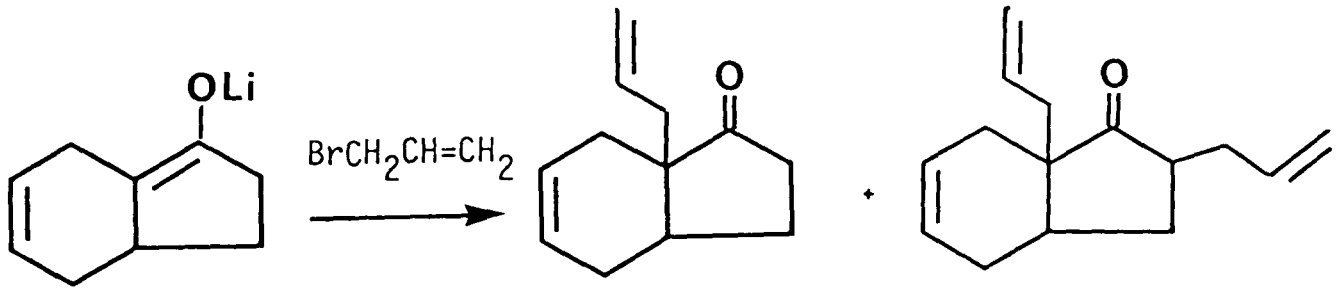
The proposed mechanism(s) for the process is illustrated below:-



(3) (23) (24) (3) (22) (25) (26)

A process is envisaged in which an electron is transferred to the carbon of the carbonyl group, followed by the addition of a second electron, thereby forming a carbanion(24). Elimination of the thiophenyl groups leads to the lithium enolate (22). Alternatively, electron transfer may occur at the sulphur moiety. Its subsequent elimination would afford (22). It is apparent that the presence of a proton donor at this stage,would result in the reduction product (26).

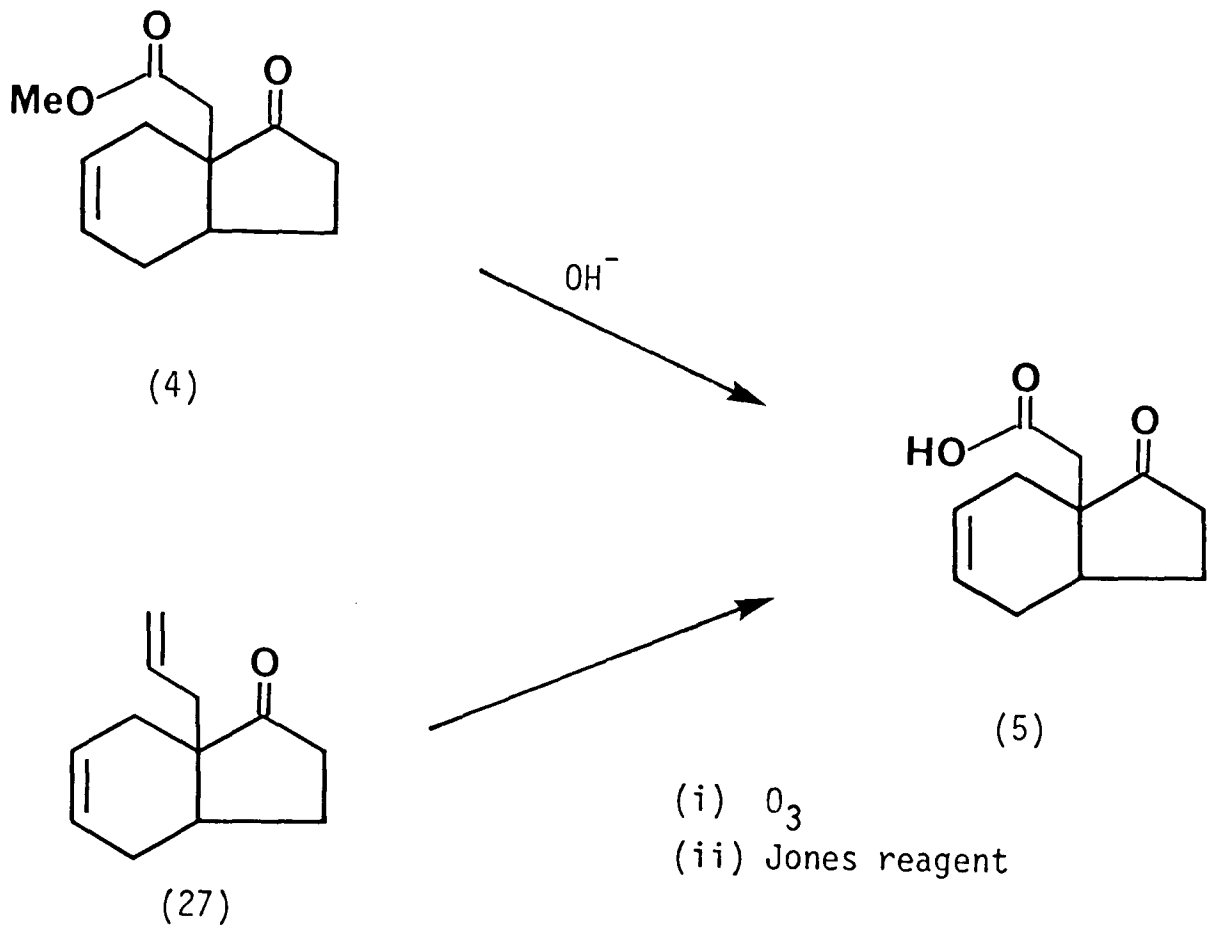
The lithium enolate has been allowed to react with different electrophilic species. Addition of allyl bromide has resulted in isolation of the allyl indanone (27) in 69% yield with 11% of the dialkylated product (28) being formed.



(22) (27) (28)

69% 11%

G.l.c. analysis of (27) gave two peaks. The ratio of these peaks in a chromatograph of the crude product was 95:5. Although no concrete proof was obtained, it is probable that this is the ratio of the cis to trans isomers at the bridgehead position, by analogy to the ketoester (4). Evidence for this assignment is planned by the following transformations:-



The carboxylic acid (5) could be obtained by alkaline hydrolysis of (4), and by selective ozonolytic cleavage of the allyl indanone (27), followed by treatment with Jones reagent. The ratio of the cis to trans isomers could then be compared from each starting material. Unfortunately, time did not permit these reactions from being carried out, but this work is under way at present.

The products obtained from alkylation with methyl iodide, were very much time dependent, as illustrated in Table 3. It was found that the best yield of monoalkylated product was achieved when the reaction time was 4½ minutes. An alkylation period of 1 minute afforded an increased quantity of the reduced indanone (26), possibly due to the fact that the lithium enolate was quenched before it had time to react with methyl iodide. In contrast a long reaction time resulted in isolation of the dimethylindanone (3) exclusively.

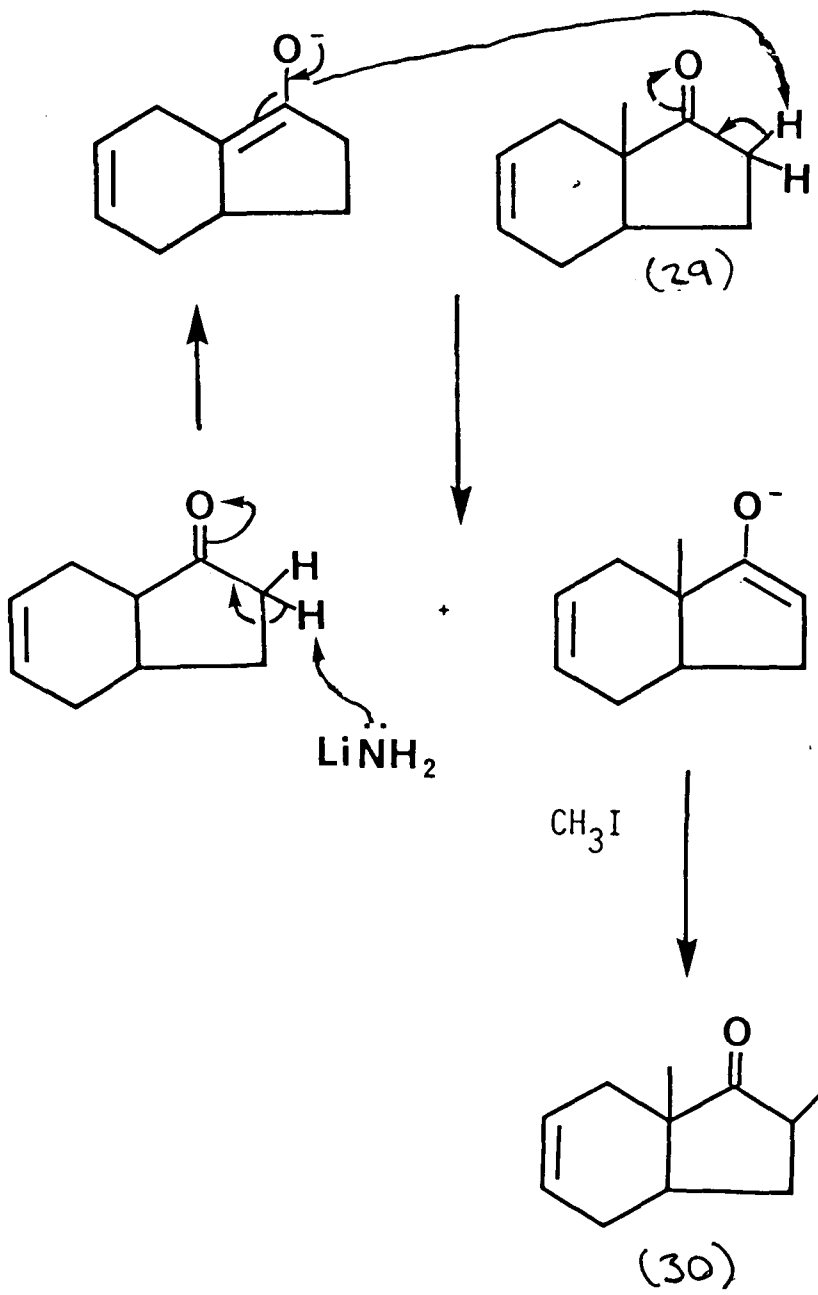
Alkylation of lithium enolate (22) with methyl iodide

Reaction Time (min.)	Methylindanone (29) (%)	Dimethylindanone (30) (%)	Reduced Indanone (26) (%)
1	37	9	37
$4\frac{1}{2}$	60	14	26
7	-	50	-

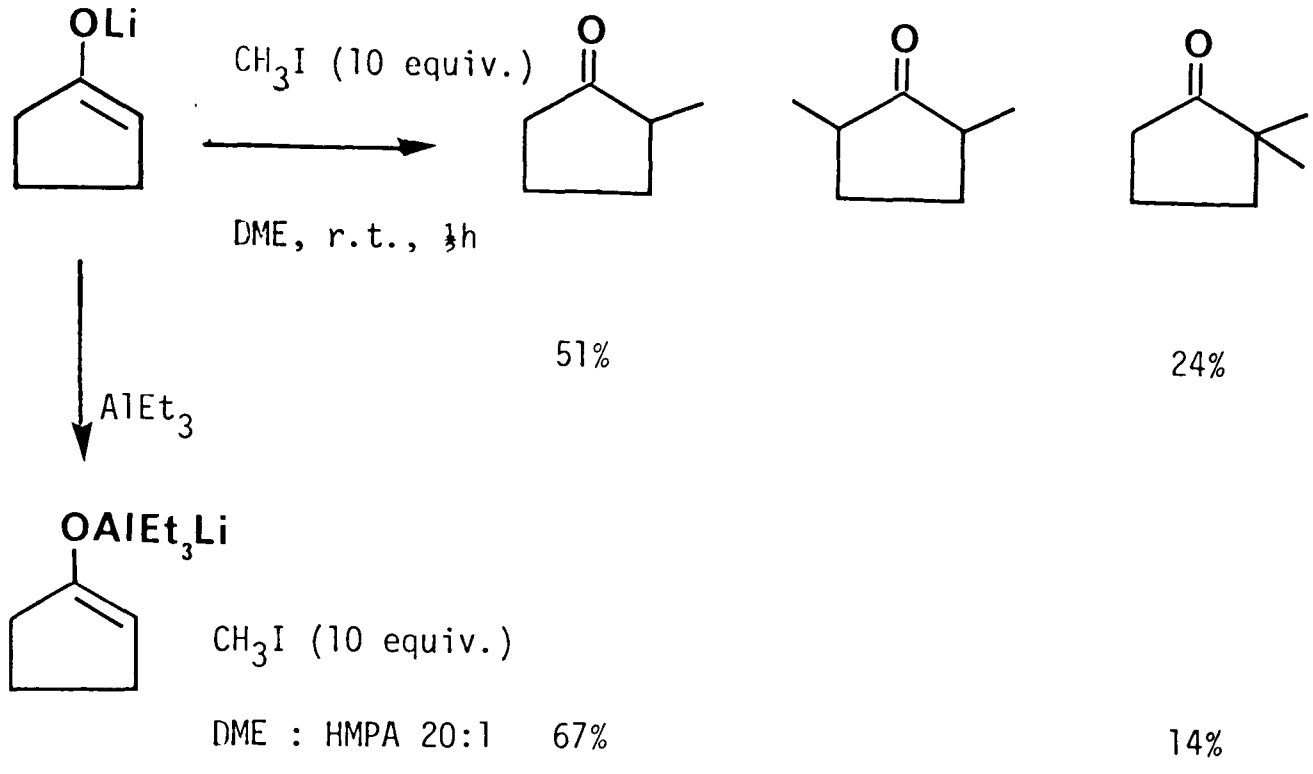
Table 3

A salient feature of the n.m.r. of the monoalkylated product included two singlets appearing at δ1.0 and δ0.8 which were attributable to the two bridgehead methyl isomers. Similarly, four singlets were displayed between the region δ1.25-0.9, integrating to six protons in the dimethyl derivative (30). G.l.c. analysis of the crude methylated product suggested a ratio of 2:1 for the two bridgehead isomers of (29). Again, although no positive evidence was obtained, literature precedent would indicate this is attributable to the cis and trans isomers respectively.

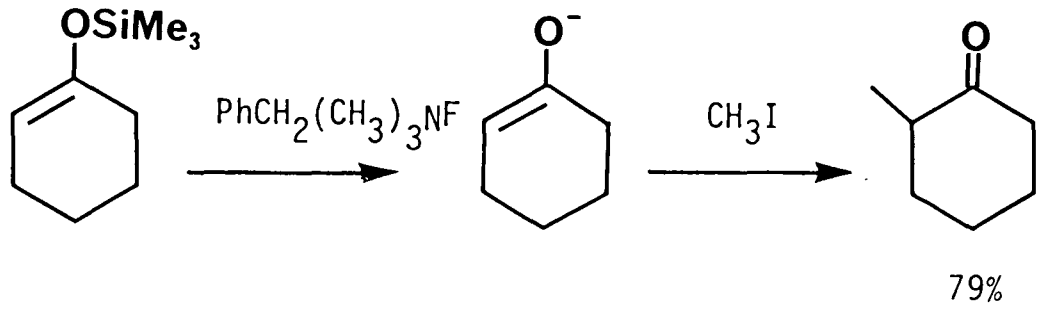
Dialkylation[117] was a particularly troublesome problem with methylation as the methyl- and dimethylindanones had very similar physical properties, making separation a difficult process. This presumably arises from proton transfer reactions between the initially formed lithium enolate and the monoalkylated product. Other bases which are present in the medium, for example lithium amide, may also lead to enolisation.



In order to minimise di- and polyalkylation, the rate of alkylation must be rapid in comparison to the competing proton transfer processes. This can be achieved by the use of highly reactive alkylating agents. The fact that dimethylindanone was isolated reflects the reduced reactivity of methyl iodide with respect to methyl bromoacetate. Various developments have been made to limit the amount of dialkylation. For example, the use of lithium triethylaluminium enolates[117] (vide infra), silyl enol ethers, enamines, blocking and activating groups, tributyltin enol



ethers and quaternary ammonium enolates.(130)



Returning to the lithium enolate (22), protonation with saturated ammonium chloride solution gave rise to the expected reduction product (26). G.l.c. analysis of the crude product afforded an area ratio of 3:1 for the two peaks corresponding to (26). As before, by analogy to the ketoester (4), this would indicate the cis to trans ratio about the bridgehead position. Table 4 summarises the observed ratios using the various electrophilic reagents.

Bridgehead ratios formed with different alkylating agents

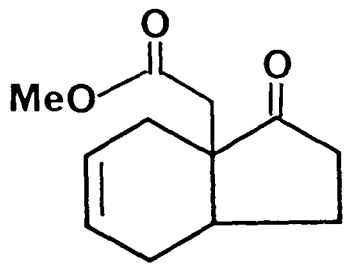
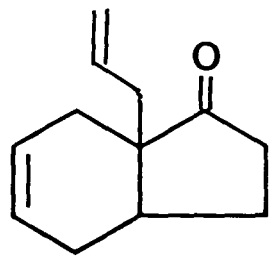
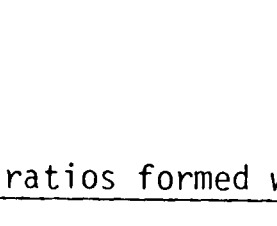
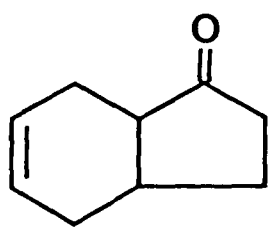
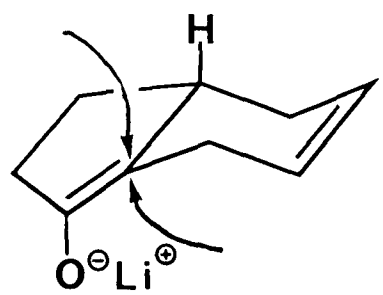
Product	cis:trans ratio
	95:5
	95:5
	2:1
	3:1

Table 4

Although a number of conformers may be used to represent the lithium enolate anion (22) House[115] has inferred that the most likely structure is represented below:-

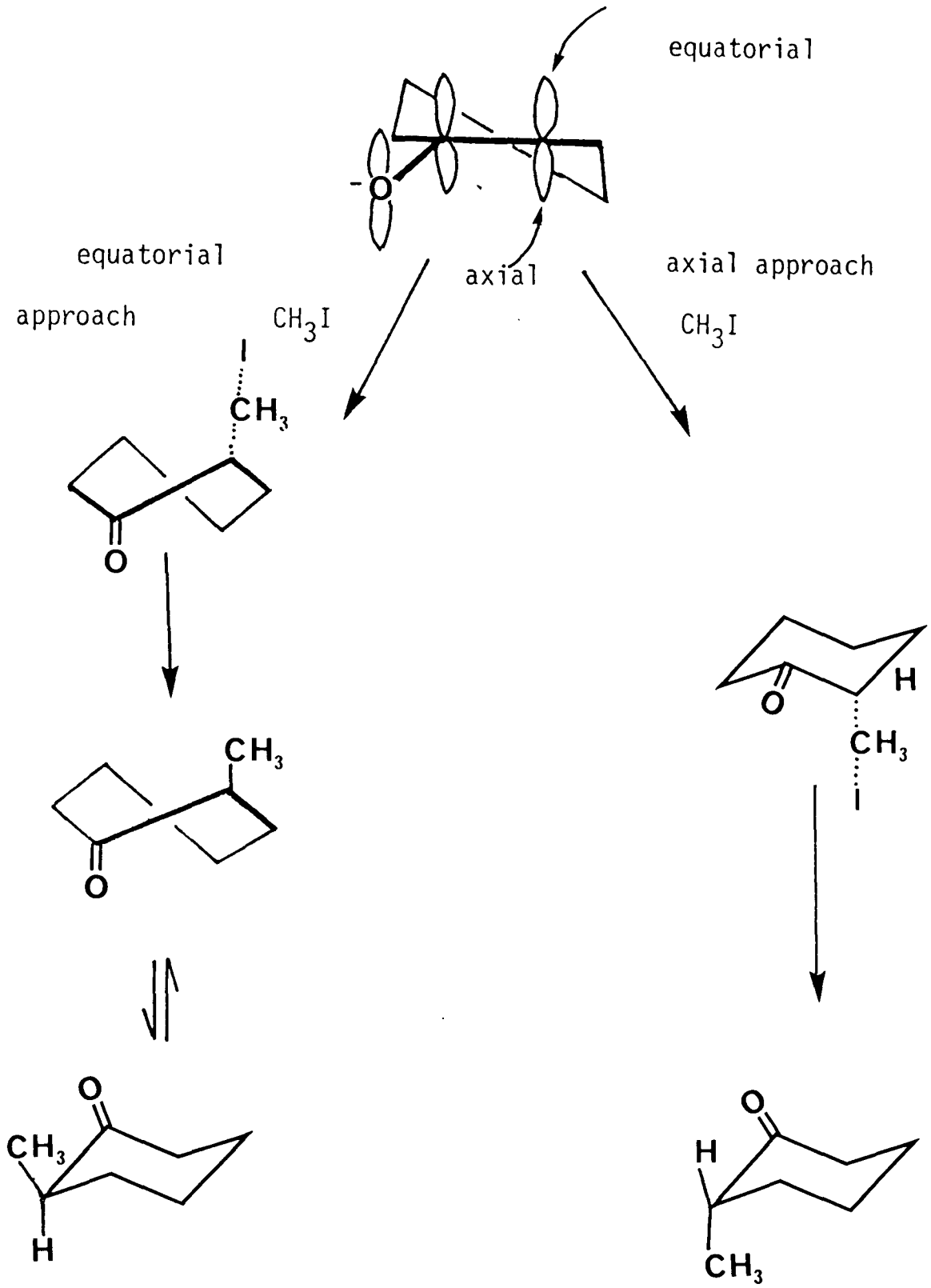
equatorial attack



axial attack

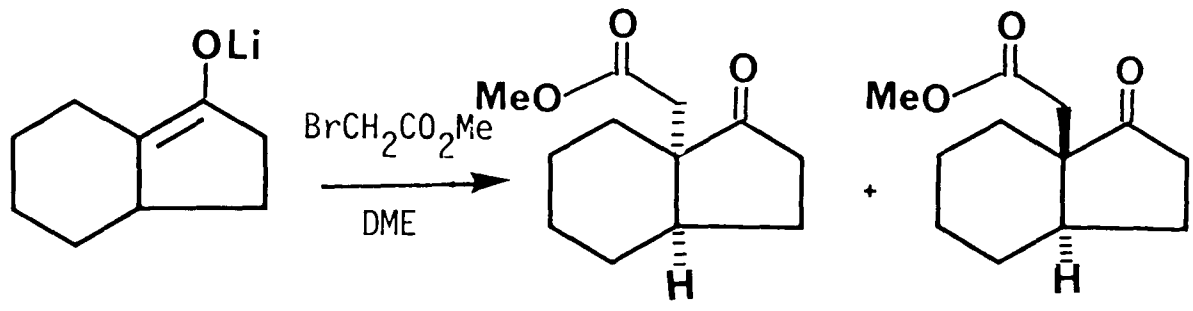
As illustrated, the molecule is susceptible to attack by an electrophilic species from both axial and equatorial directions. The alkylating agent approaches perpendicular to the plane of the enolate anion for stereoelectronic reasons. This allows maximum orbital overlap between the developing C-C bond and the π-orbital of the carbonyl group to be maintained in the transition state.

It has been suggested that axial attack of a cyclohexanone enolate[115,117] leads to a more stable chair conformation, whereas equatorial attack affords initially a twist-boat structure, (vide infra).

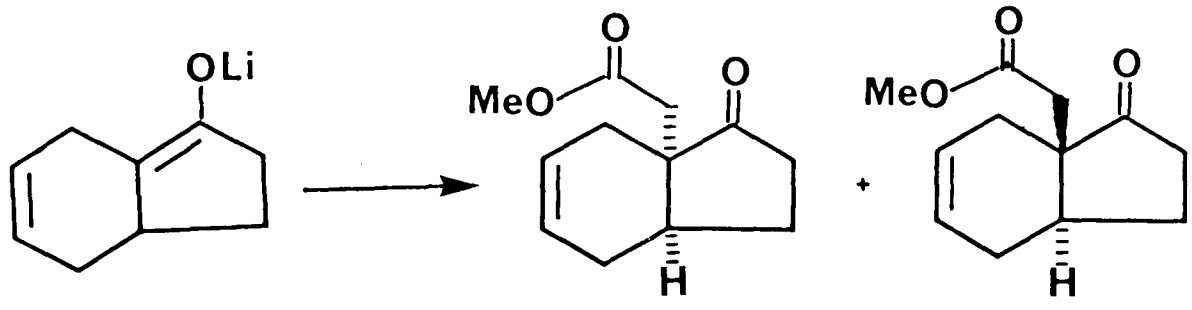


Consequently, in the absence of any other factors, stereoelectronic control would favour axial alkylation products. However, steric hindrance to the approaching electrophile must also be taken into account. Clearly, if one side of the molecule is encumbered, attack will occur from the less hindered face. Indeed, House has used steric

arguments to account for the high degree of stereoselectivity obtained upon alkylation of perhydroindanone and tetrahydroindanone enolates.

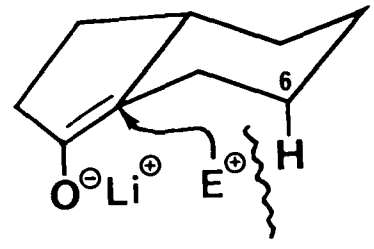


98 : 2



96 : 4

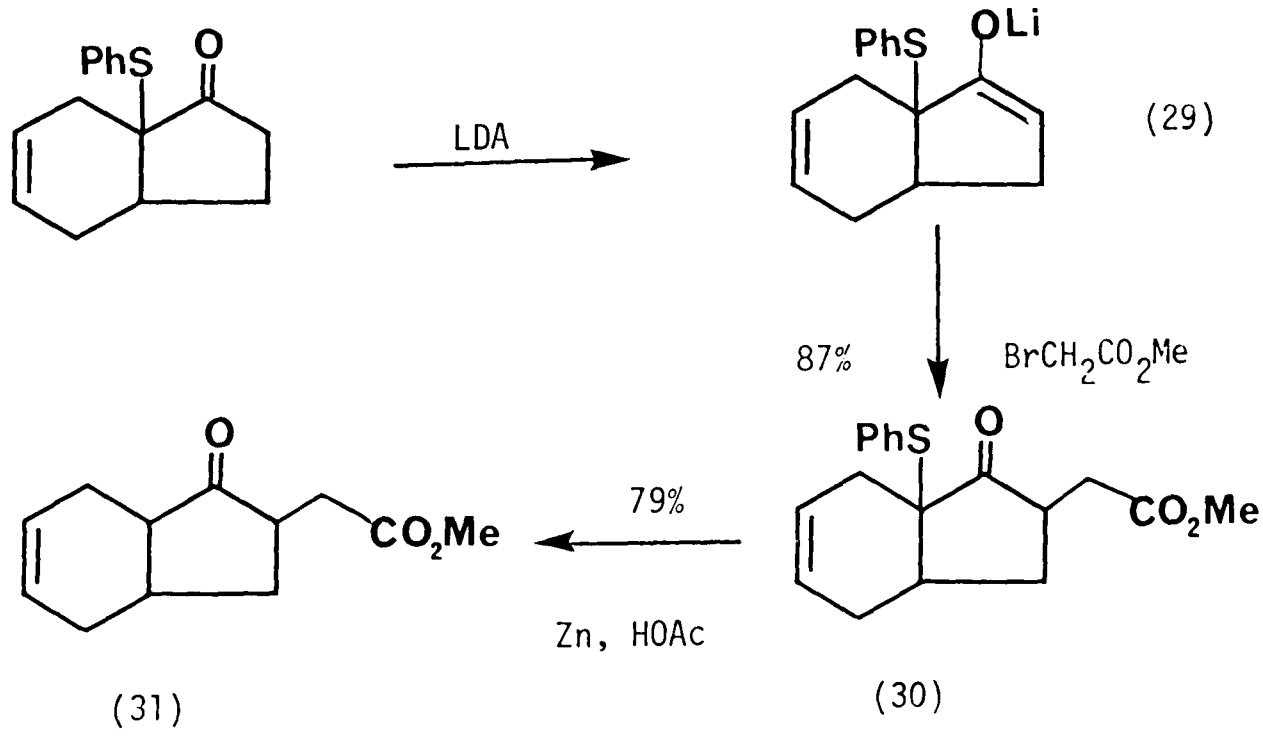
The slight increase in the propor-tion of cis-isomer observed in the first example, is believed to be the result of 1,3-diaxial interaction between H-6 and the approaching electrophile.



The result obtained from alkylation of the tetrahydroindanone enolate is directly comparable with that obtained in this work. A similar ratio was also found the allyl analogue. These results suggest that

steric hindrance to the approach of the alkylating agent is more important than stereoelectronic control in determining the direction of attack of the lithium enolate. The smaller methyl iodide molecule is more able to attack from both sides of the enolate anion, resulting in a greater proportion of the trans isomer. At first glance a ratio of 3:1 in favour of the cis isomer would appear to be extraordinarily high for protonation compared to reaction with methyl iodide. However, hydrogen bonding between water molecules may have resulted in greater steric contraint from axial approach compared to equatorial attack. But, of course, protonation[115] is equally likely to occur at oxygen, thereby forming the enol tautomer. Such an enol would have different stereochemical requirements, which means that this process is difficult to rationalise.

In the reduction-alkylation process, the phenylthio moiety has served as an activating group, allowing regiospecific alkylation at the bridgehead position. Alternatively, the opposite regiochemistry has been demonstrated, as shown below:-

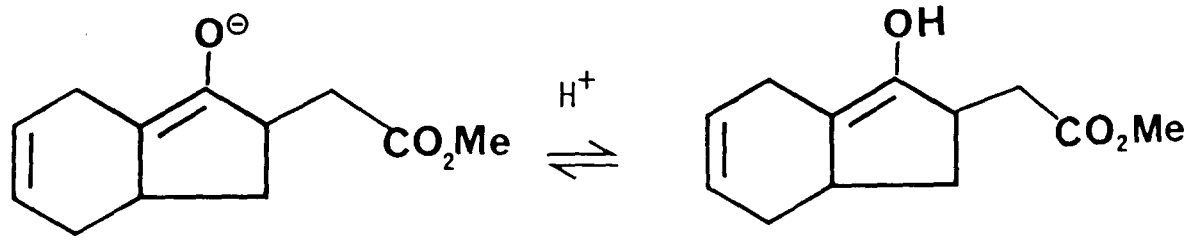


In this sequence the phenylthio group has functioned as a blocking group. Deprotonation by the hindered base lithium diisopropylamide, under kinetically controlled conditions, leads to the lithium enolate (29) exclusively. Reaction with methylbromoacetate afforded the alkylated phenylthioindanone (30) in good yield. This compound exhibited a carbonyl absorption at a slightly lower frequency of 1735 cm^{-1}. Phenyl and olefinic protons appeared as expected at δ7.4 and δ5.6, whereas the ester signal was shifted marginally downfield to δ3.7, compared to δ3.6 for the bridghead product.

Many reagents are available for desulphurisation. These include zinc and chlorotrimethylsilane, Raney nickel, sodium-mercury amalgam, aluminium-mercury amalgam and lithium ethylamine. In the event, the transformation was easily accomplished using a combination of zinc in glacial acetic acid.[131]

The ketoester (31) exhibited similar spectral data to its precursor, naturally with the exception of phenyl signals. The shift of the ester moiety was also at the slightly higher field of δ3.65.

As the reductive cleavage of the thiophenyl group was effected by a dissolved metal reduction, the mechanism is analagous to that already discussed. However, as protonation occurs under equilibrat-



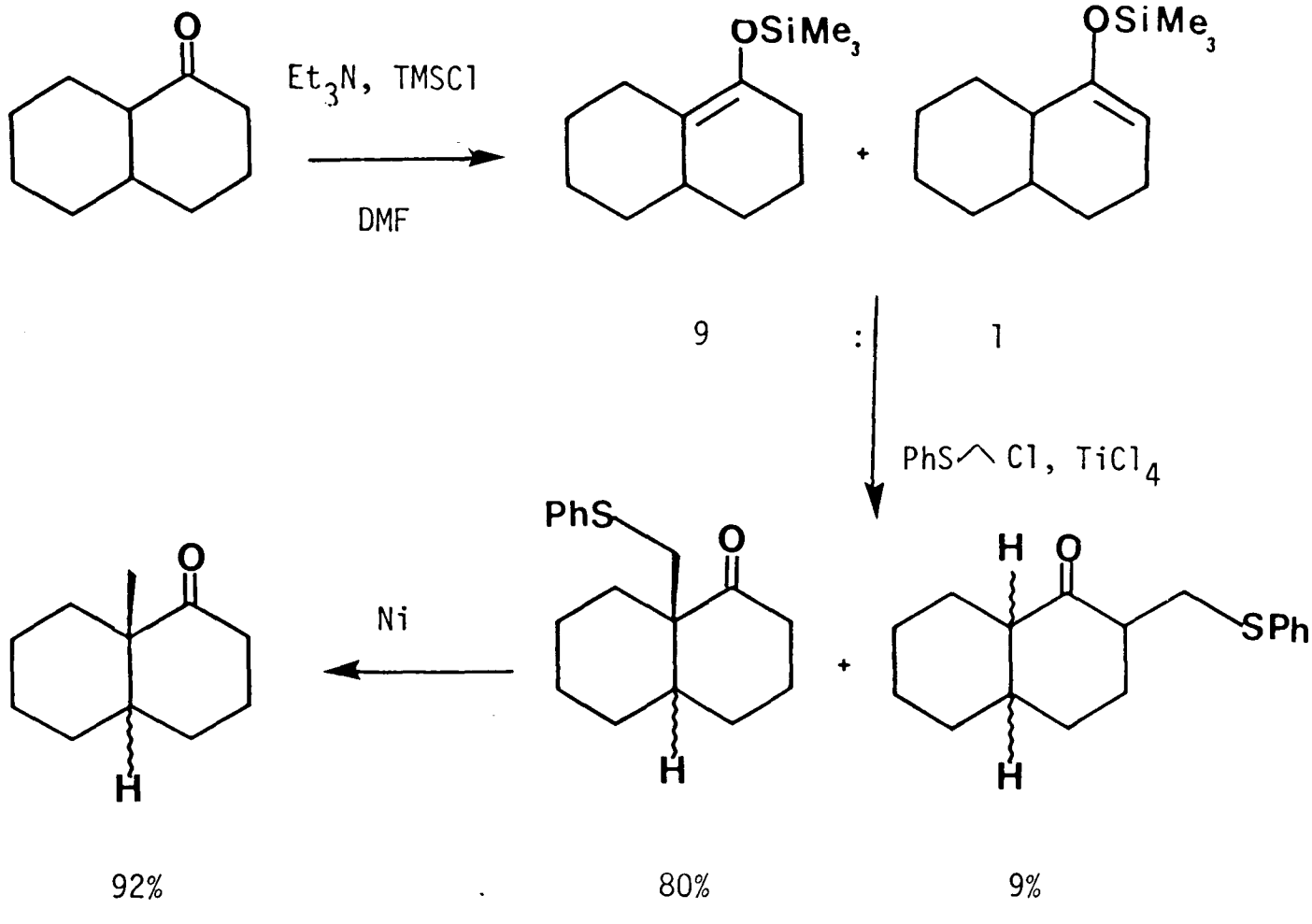
ing conditions, formation of the thermodynamic ratio of bridgehead isomers was expected. G.l.c. analysis recorded this as 3:2, which represents the proportions of cis and trans isomers respectively by literature analogy.

The stereochemistry of the ketoester (4) about the bridgehead position, formed by basic enolate chemistry had been established. It was considered possible that the ratio may be altered by introduction of the carbomethoxy methyl group under the acidic conditions of enol chemistry. Modification in favour of the trans isomer may lead to a synthetic route to the otherwise difficult to obtain trans-fused indanones.

An obvious choice of enol is the silyl enol ether,[118] as many methods are available for their formation.[132] The more or less substituted enol may be prepared directly from an unsymmetrical ketone by use of either thermodynamically or kinetically controlled conditions.[133,134]

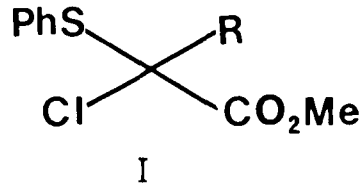
Naturally, the electrophile would have to be made more reactive,[118] but this is easily achieved by Lewis acid catalysis using titanium tetrachloride or zinc bromide.

Fleming and Paterson[135-138] have recently introduced a method of phenylthioalkylation of silyl enol ethers with primary alkyl halides. For instance:-



The alkylation process is regiospecific and often high yielding. Desulphurisation with Raney nickel affords the reduced product. Secondary and tertiary alkylation of O-silylated enolates has also been reported by Reetz.[139,140]

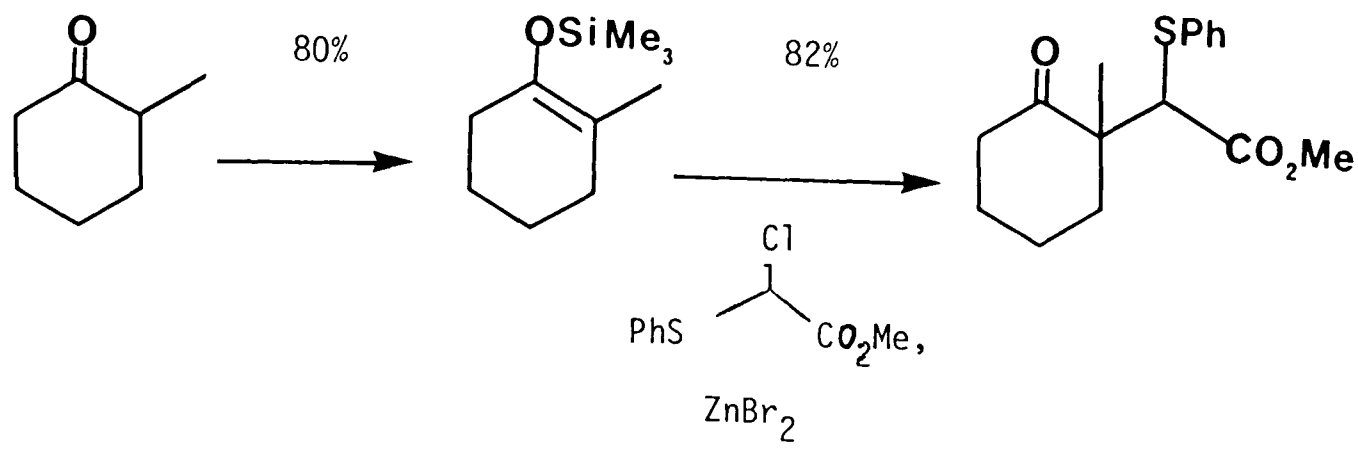
Use of phenylthioalkylating agents containing a carbonyl function was originally published by Tanikaga.[141] More recently, phenylthio (methoxy carbonyl) alkyl chlorides of type I, have been



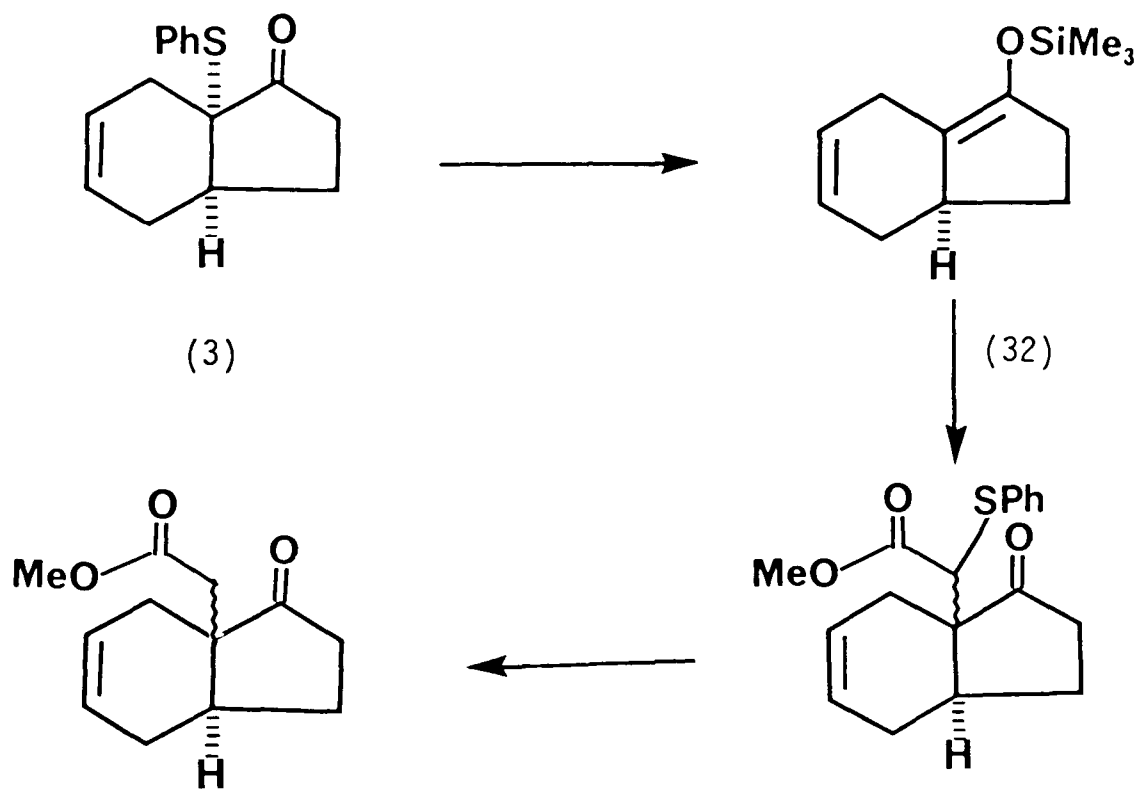
I

R = H, Me or Et

employed by two separate research groups,[142,143] allowing the formation of γ-ketoesters:-



In a similar fashion, the ketoester (4) may be obtained.



Accordingly, the first step in the sequence involved regio-specific production of the silyl enol ether (32).

The most direct approach entails trapping the lithium enolate (22), formed by the dissolved metal reduction of (3), with trimethyl-chlorosilane. Consequently, after the removal of ammonia, the enolate was quenched with a mixture of the chlorosilane and triethylamine in

THF at -10°C.[117] The resulting mixture was allowed to warm up to -5°C, and partitioned between cold aqueous sodium bicarbonate and cold hexane. Silyl enol ethers are liable to hydrolysis in the presence of aqueous, acidic or basic media, thus it is necessary to effect purification as quickly as possible after workup. As silyl enol ethers are generally fast running in t.l.c.,(R_f > 0.9) in solvents such as chloroform,one of the best ways of purification is using gravity column chromatography with a high speed of elution. Unfortunately, in this case diphenyl disulphide, a by-product of the reaction, also appeared at high R_f, occurring just above the O-silylated enolate. An attempt at separation was not successful, the main products being characterised as diphenyl disulphide and a substantial amount of reduction product (26). The latter was thought to have arisen from an inadequate reaction time. Therefore, the reaction was repeated and upon quenching, the mixture was allowed to warm up to room temperature before workup was commenced. Unfortunately n.m.r. analysis of the appropriate fraction only indicated diphenyl disulphide. On this occasion no reduction product was isolated. Thus, although t.l.c. analysis of the crude mixture indicated the presence of the silyl enol ether (32) it was proving difficult to isolate this compound.

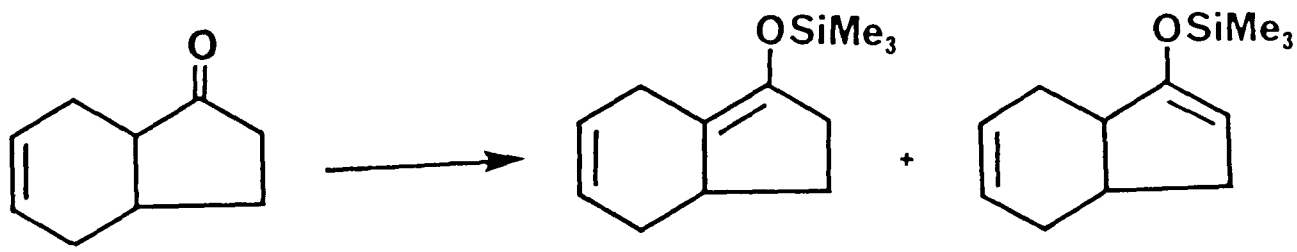
It was considered that distillation of the crude product would be a more appropriate means of purification. However, vacuum distillation of the crude product only resulted in decomposition.

One final attempt at column chromatography was judged appropriate. In this attempt the aqueous workup was replaced by a simple filtration to remove any hydrochloride salts. Fortunately, some separation was achieved, allowing a 36% yield of the desired silyl enol ether. However, after a few days, t.l.c. analysis revealed a

complex mixture of compounds, indicating decomposition had occurred. Consequently, in the next attempt it was planned to react the purified silyl enol ether immediately with methyl α-chloro-α-phenylthioacetate, in the subsequent reaction of the scheme. In the event, the silyl enol ether was only isolated as a mixture with diphenyl disulphide and use of this mixture in the following reaction was not successful, indicated by the lack of any high field signals in the n.m.r. of the crude product.

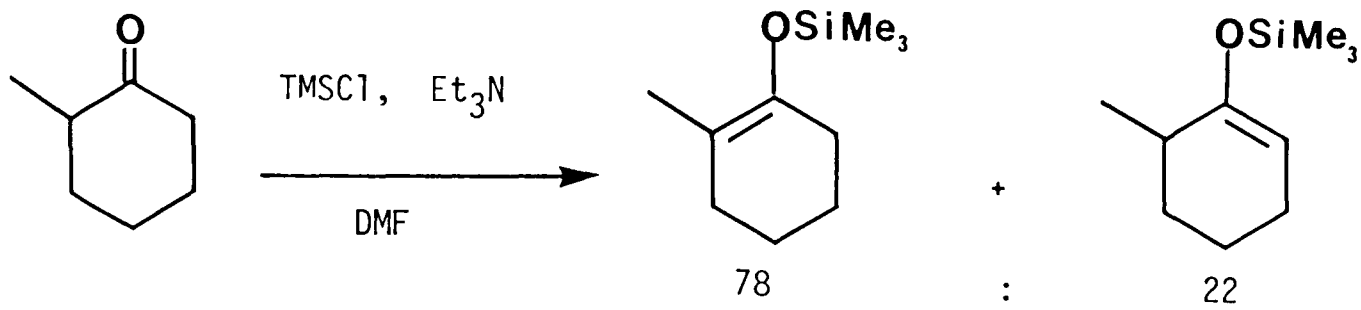
The problems encountered in purifying the crude product were largely due to the presence of diphenyl disulphide. Hence, an alternative synthesis of (32) in which diphenyl disulphide was not formed as a by-product may be more successful.

The desired silyl enol ether (32) is the more highly substituted isomer of the two possible alternatives that could be formed from the reduction product (26).

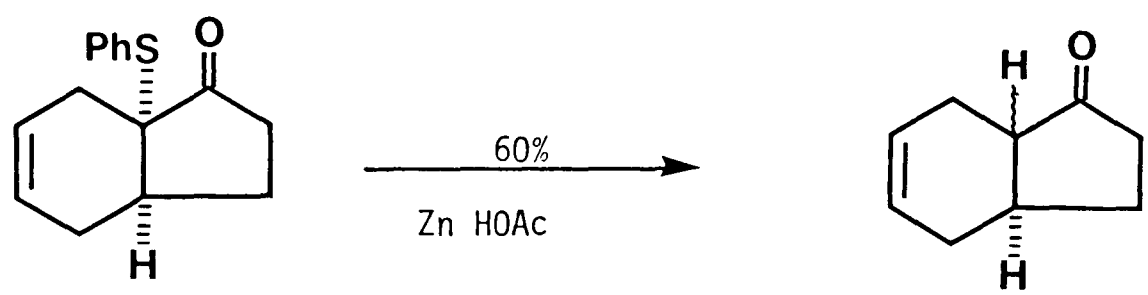


(26)

As such, it could be prepared regioselectively under equilibrating conditions. House et al.[133] have previously shown that thermodynamic control is exerted by use of triethylamine and trimethylchlorosilane in dimethylformamide under reflux (vide infra).



This obviously entailed the initial desulphurisation of the phenylthioindanone to afford the reduction product. Accordingly,



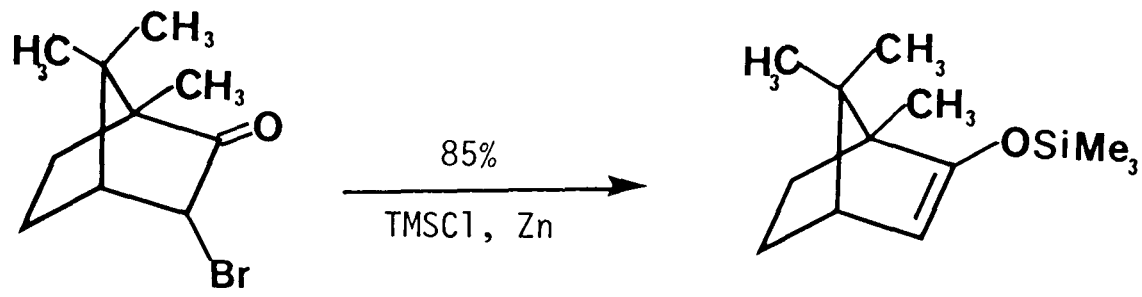
(3) (26)

reaction with zinc in glacial acetic acid afforded (26) in 60% yield, which gave spectral data, directly comparable with that recorded by House.[98]

The reduction product (26) was heated under reflux for 36 hours with the recommended reagents. However, as t.l.c. analysis indicated only trace amounts of silyl enol ether, isolation was not considered worthwhile. The situation may have been improved upon by refluxing for a longer period of time. Alternatively, this lack of reactivity may be due to moisture present in inadequately dried reagents or solvent.

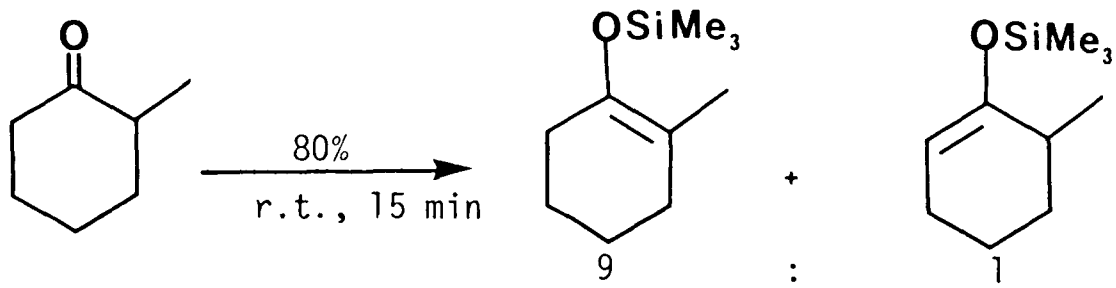
It was hoped that reaction of the phenylthioindanone (3) with

trimethylchlorosilane in the presence of zinc would be a more rewarding procedure. In point of fact, Joshi and Pande[144] have isolated the silyl enol ether in 85% yield from the corresponding α-bromo derivative:-

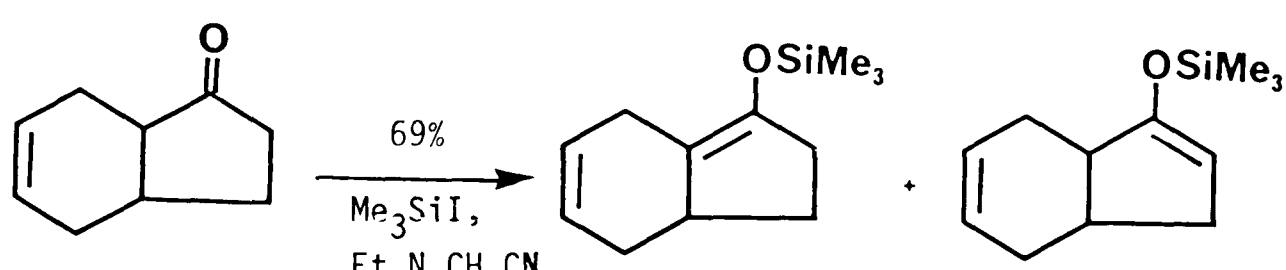


Indeed, after stirring a mixture of the ketone; zinc dust, trimethylchlorosilane, and hexamethyl phosphorous triamide in THF, at room temperature for 12 hours, t.l.c. analysis indicated almost complete conversion to the silyl enol ether. Unfortunately, an attempt at vacuum distillation resulted in decomposition of the product.

The preparation of the elusive silyl enol ether (32) appeared to be fraught with difficulties. Although the possibilities of the previous method had not been exhausted, it was decided to opt for a route recently described by some French workers.[145] An equilibrium mixture of isomers was reported to be formed by treatment of the ketone with trimethylchlorosilane, sodium iodide, and triethylamine in acetonitrile. The silylating agent is thus iodotrimethylsilane, which is generated in situ from the former two reagents. This results in silylation occurring at room temperature in remarkably short reaction times with the added bonus of high yields. For example:-

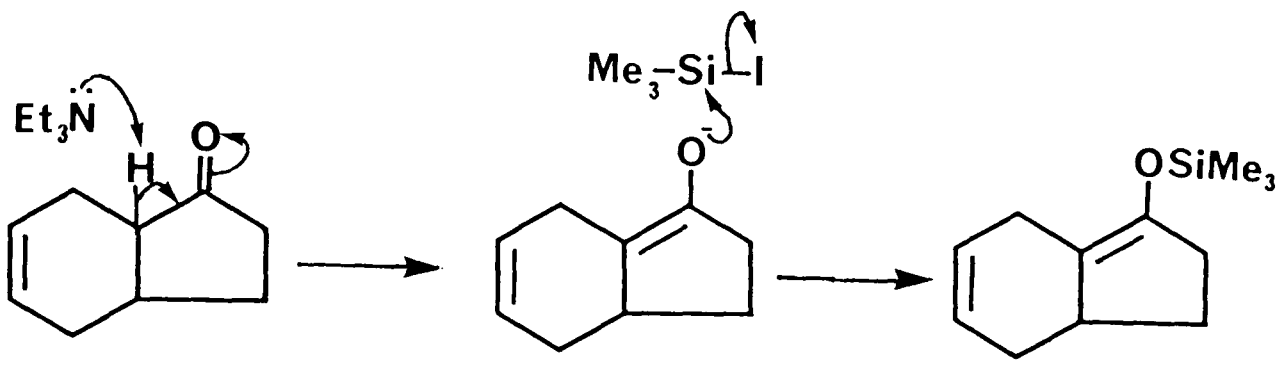


The reaction was therefore carried out in accordance with the prescribed conditions. Indeed, after 1½ hours, t.l.c. analysis revealed complete disappearance of starting material. After an aqueous workup, the crude product was purified by column chromatography, and a 69% yield of a mixture of O-silylated enolates (32) and (34) were successfully isolated. Incidentally, these compounds were shown to be stable



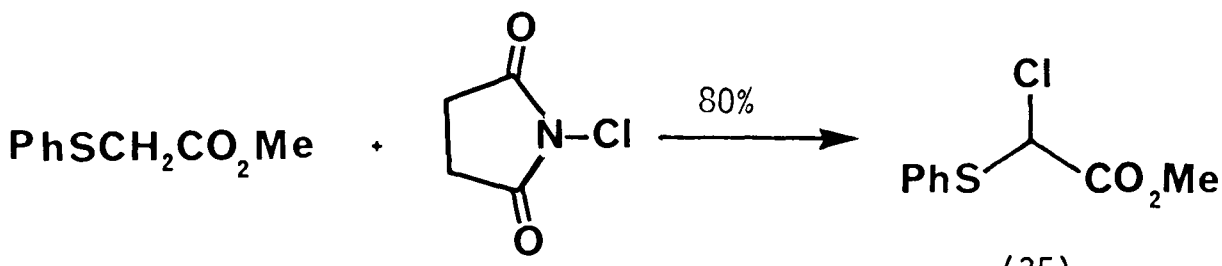
to distillation by a boiling point determination. The i.r. spectrum of this mixture exhibited two olefinic absorptions at 1690 and 1650 cm^{-1}. The former was indicative of a tetra-substituted double bond in a five-membered ring and the latter occurred at the usual position for the double bond contained in the six-membered ring. No carbonyl absorption was apparent, but a strong peak appeared at 1250 cm^{-1} suggesting a carbon-silicon bond. N.m.r. showed the appearance of only two olefinic protons, with a very small signal at δ5.0, integrating out to far less than one proton, would suggest the predominant formation of the bridgehead isomer (32). This was corroborated by g.l.c. analysis of the crude product. A ratio of 93:7, was obtained, which, by implication, must be for (32) and (34) respectively. This result was confirmed by a repeat of the method. The mechanism of

silylation is believed to proceed as follows:-



Abstraction of a proton by triethylamine at either the bridgehead position or the alternative α-position, results in enolate formation. Subsequent O-alkylation with trimethylsilyl iodide affords the silyl enol ether.

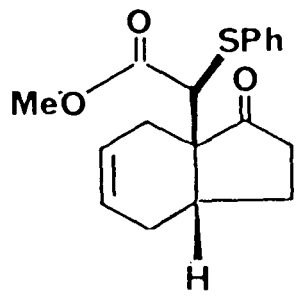
The stage was now set for phenylthioalkylation. The required methyl α-chloro-α-phenylthioacetate was readily prepared by reaction of the ester (vide infra) with N-chlorosuccinimide.[142] In this way an 80% yield of the distilled chloro ester (35) was obtained.

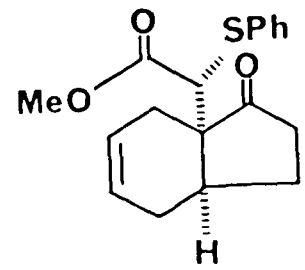


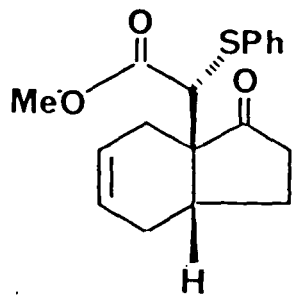
(35)

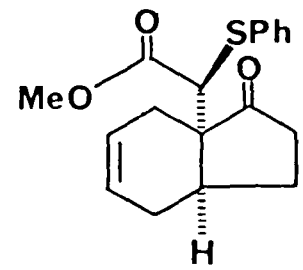
Alkylation of the O-silylated enolates with (35) in the presence of a catalytic amount of anhydrous zinc bromide proceeded without incident. As the alkylated molecule possesses three chiral centres, a total of eight isomers are possible, half of which are enantiomers. These are shown in Scheme 3. Compounds depicted on the right hand side are enantiomers of the respective diastereoisomer. Purification of the crude alkylated product resulted in

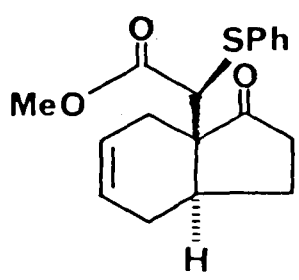
The isomers of phenylthioalkylindanone (33)

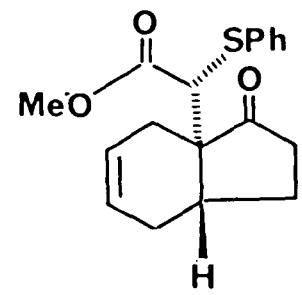


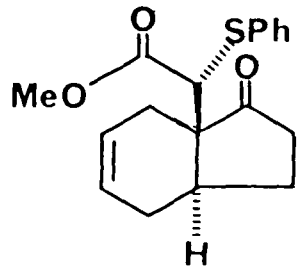


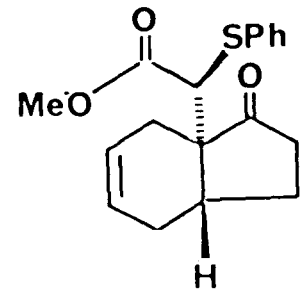












Scheme 3

the different isomers being isolated in three separate fractions. The i.r. spectrum of each fraction indicated a carbonyl absorption at 1730 cm^{-1}, and a stretching frequency of an olefin, which varied from between 1635-1660 cm^{-1}. Slight differences were observed in the chemical shifts of phenyl, olefinic and ester protons, which are summarised in Table 5. Of particular interest is the two ester signals obtained from one of the fractions indicating the presence of two isomers.

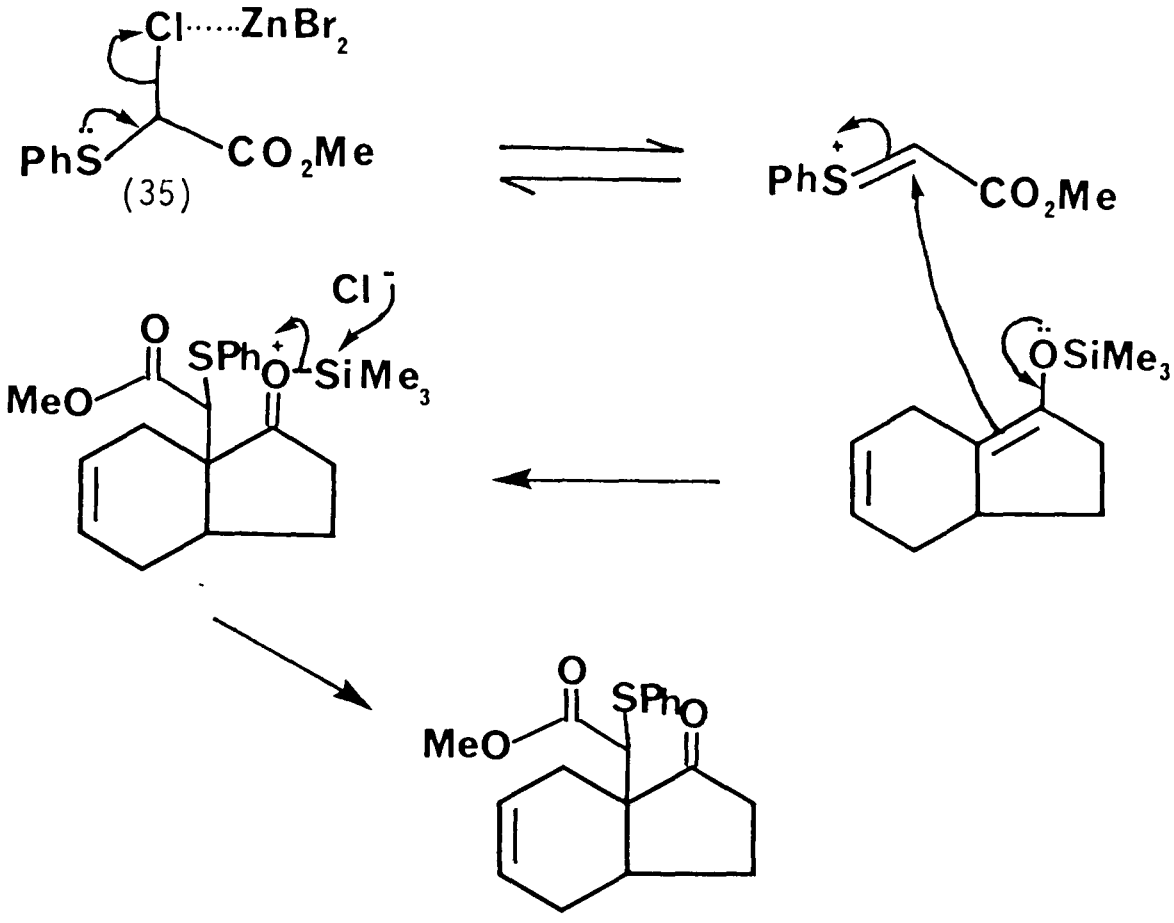
N.m.r. data for phenylthioalkylated indanones (33)

Type of signal	Fraction (δ) a	b	c
Phenyl	7.6	7.4	7.4
Olefinic	6.0	5.6	5.9
Ester	3.7	3.6 (54%) 3.5 (46%)	3.7
Alkyl	3.0-1.8	2.8-1.7	3.1-1.8

Table 5

It is thought that the process involves complexation of (35) with the Lewis acid, which brings about the formation of a stabilised carbocation. Nucleophilic attack by the silyl enol ether followed by chloride mediated cleavage of the silyl group allows the formation of the alkylated product (33).

viz:-



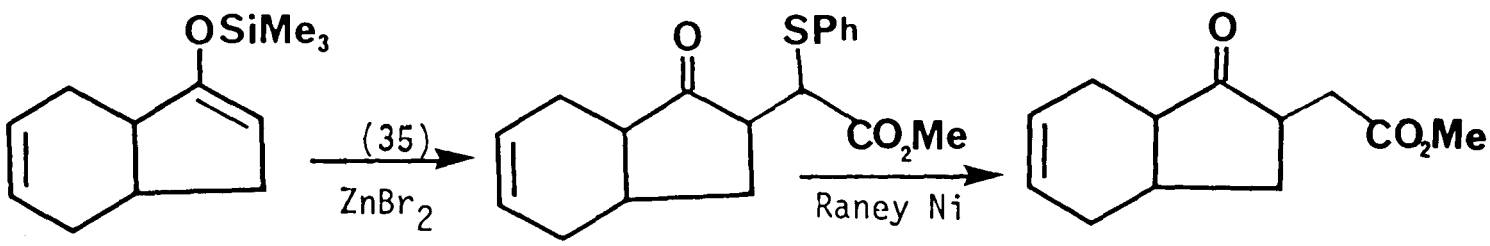
(35) 67%

Desulphurisation into the known ketoester (4) would allow a determination of the fractions containing cis or trans isomers about the bridgehead position, by a comparison of g.l.c. retention times. Consequently, each of the fractions was separately reduced with Raney nickel,[146] and the crude products analysed by g.l.c. analysis. This gave an overall ratio of 48:52 in favour of the trans isomer. The figure was corroborated by g.l.c. analysis of a desulphurised sample of crude phenylthioalkylated product. Therefore, it would appear that the phenylthioalkylation of silyl enol ethers is entirely non stereospecific. This may indicate that neither steric hindrance nor stereoelectronic control is the overriding factor in determining the stereochemical outcome of the reaction. However, the situation is as yet unclear, and research is planned to study the reaction

further, by varying the electrophile and the nature of the silyl group, in order to gain insight into the factors influencing the stereochemistry of the products formed.

Purification of the product derived by desulphurisation of the crude phenylthioindanone, resulted in isolation of the cis and trans isomers of the ketoester (4). N.m.r.and i.r. data of these compounds were directly compatible with spectra supplied by House, via a private communication. Variations between the two isomers include slight differences in the carbonyl absorption of 1745 and 1748 cm^{-1} for the cis and trans isomers, and a discrepancy of 20 cm^{-1} for the olefin stretching frequency. In addition, the ester signal of the trans iosmer occurs at a marginally higher field shift of δ3.50 compared to δ3.60 for the corresponding cis-isomer.

An additional product was isolated, which was characterised as the ketoester (31), formed in 5% yield. This compound had obviously been formed by an analogous route.



(34) (32a) (31)

The observed yield is comparable with the yield of silyl enol ether (34) found previously.

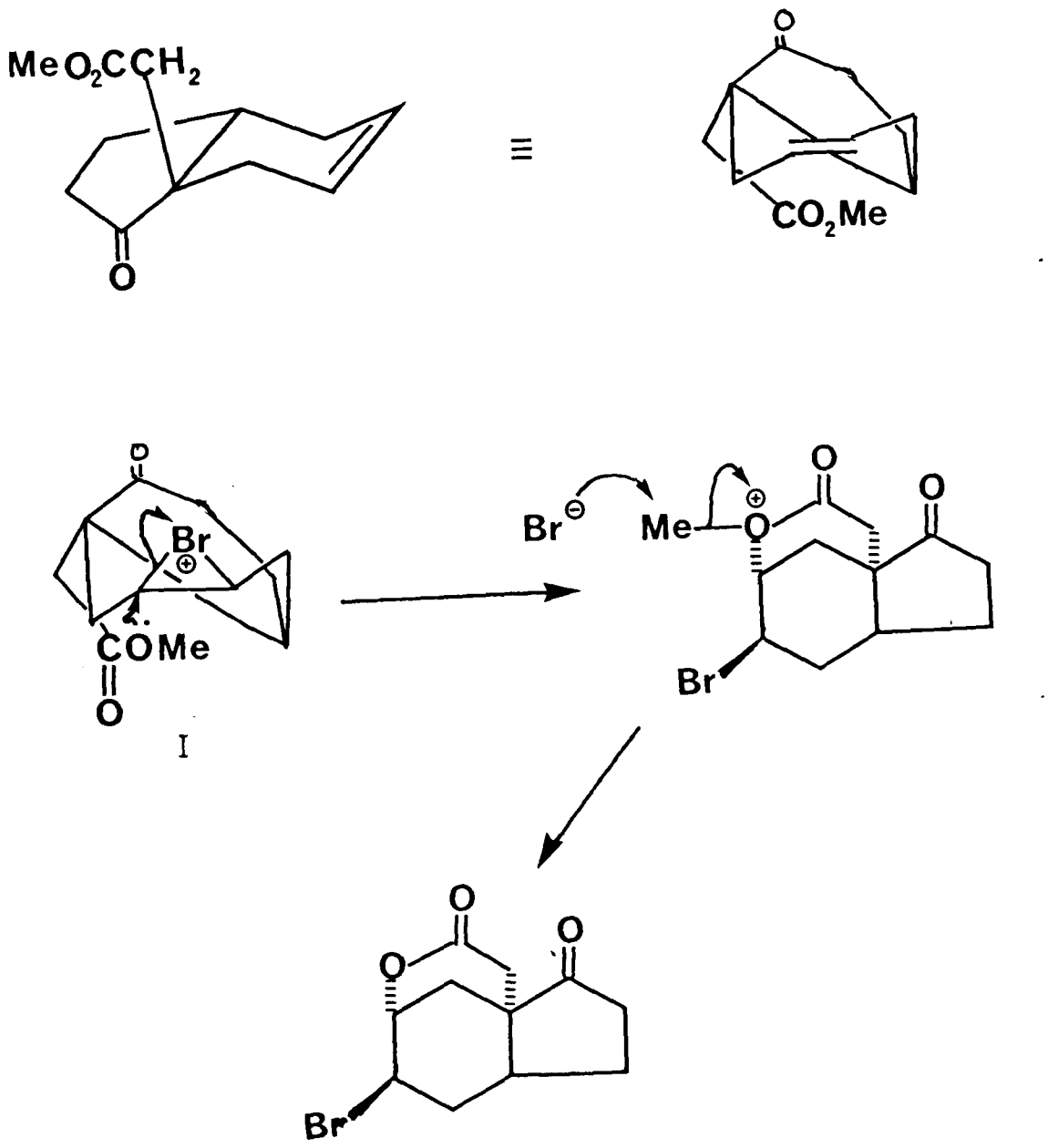
Returning to the synthesis, a regio- and virtually stereo-specific method for the generation of the ketoester (4) had been developed. This compound could now be used in the next stage of the synthesis.

III.4. HALOLACTONISATION AND DEHYDROHALOGENATION

The stage was now set for the introduction of an α-orientated oxygen functionality at C-6 of the indanone system. This was accomplished by the well established technique of halolactonisation. (147)

Initially bromolactonisation was employed as this would allow formation of the lactone directly from the ketoester (4).

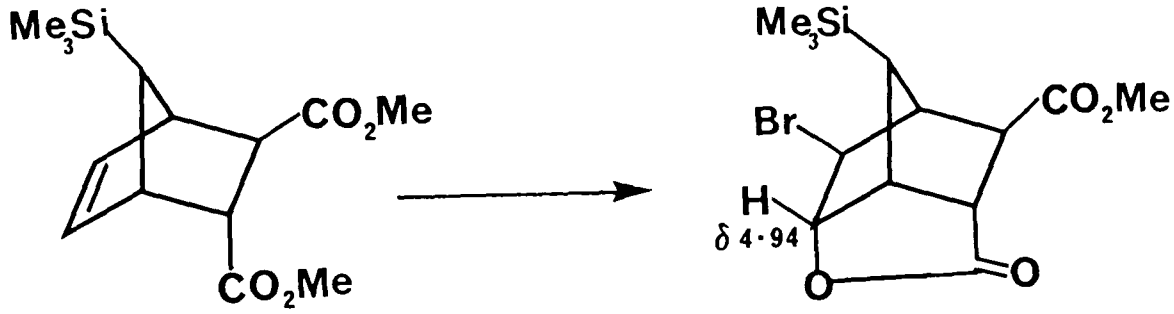
The reaction path is depicted below. Although positive bromine may attack at either side of the double bond to reversibly give two possible bromonium ions, only one will form the required and observed product.



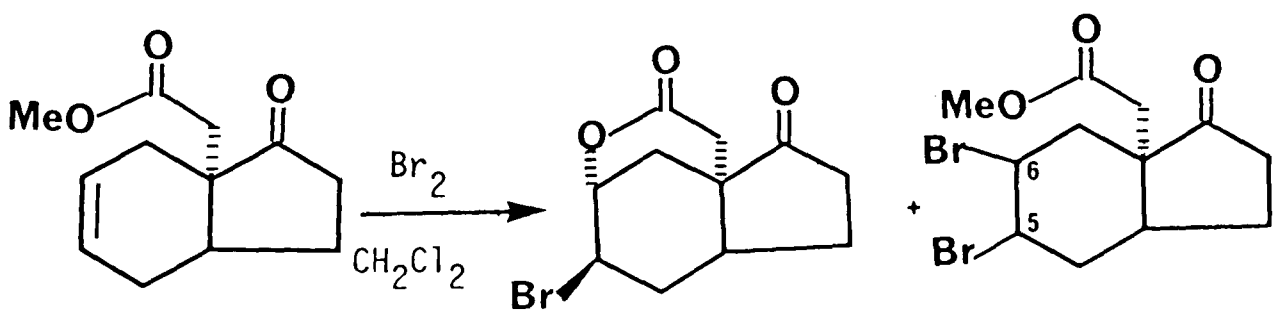
(36)

Intramolecular displacement by nucleophilic attack of the methoxy group occurs in an S_N2 fashion. This implies preferential approach of the nucleophile from the underside of the molecule, via intermediate I. Bromide mediated cleavage of the intermediate oxonium species results in the bromolactone (36). In this way the α-orientated cis-fused lactone is formed stereospecifically.

In contrast to iodolactonisation, organic solvents are commonly employed in the complementary bromolactonisation. An example of this procedure has been reported by Fleming and Michael,[148] in which the bromolactone was isolated in 53% yield.

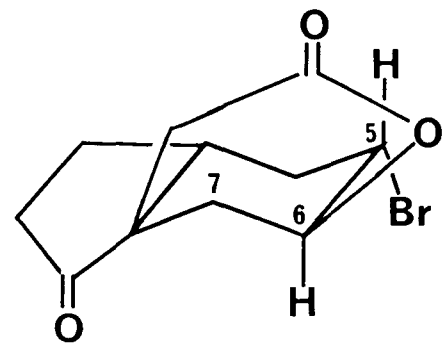


In the event, a 1.1 fold excess of bromine was added to a solution of the ketoester in dichloromethane at room temperature, and the solution stirred for one hour. Purification of the fairly complex crude mixture gave 28% of the bromolactone (36). An i.r. of the

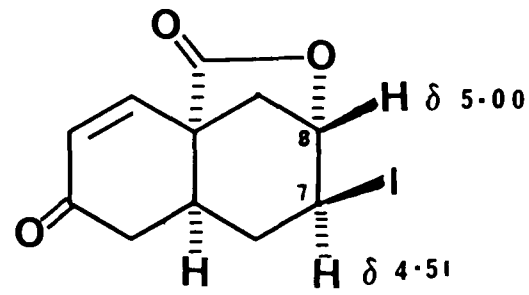


(36) (37)

latter displayed a carbonyl absorption at 1740 cm^{-1}, which is typical for δ-lactones. The proton at H-6 appeared at δ4.8.



This chemical shift is comparable with those obtained from protons in similar chemical environments in both Fleming's[148] bromolactone (δ4.94), and Danishefsky's[44] iodolactone (δ5.00). (vide infra).

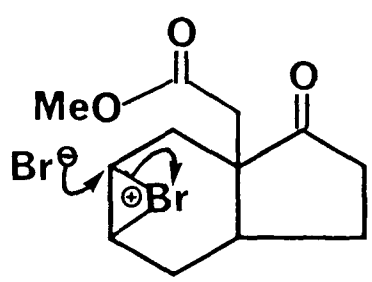


These authors have reported coupling constants of 5Hz for this methine proton, which further indicates a cis-fused lactone. Unfortunately, in (36) the proton in question appeared as a multiplet, therefore no coupling constant could be measured. However, in retrospect this may have been obtained by decoupling the two H-7 protons.

The bromolactone displays an additional multiplet at δ4.6 which is attributable to H-5. A mass spectrum gave the required molecular ion as a 1:1 pattern of the ^{79}Br and ^{81}Br isotopes.

A second compound was isolated which was tentatively assigned as the dibromo ketoester (37). This would presumably have arisen as a result of bromide attack on the bromonium ion.

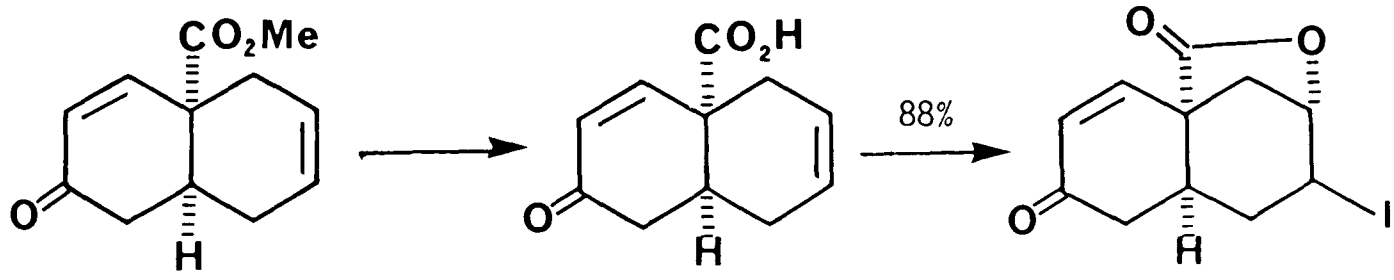
viz:-



Evidence for this product has been obtained by way of n.m.r. The signals at δ4.4 and 4.1 could be attributed to H-5 and H-6, and a singlet at δ3.6 is at an identical chemical shift to the ester signal of the starting material. Unfortunately, a mass spectrum of this compound gave inconclusive results.

In an effort to avoid this side reaction, the method was repeated at a lower temperature of -10°C. As soon as the starting material had disappeared the reaction mixture was quenched. An improved yield of 44% of the bromolactone was isolated, but the dibromoketoester was again formed.

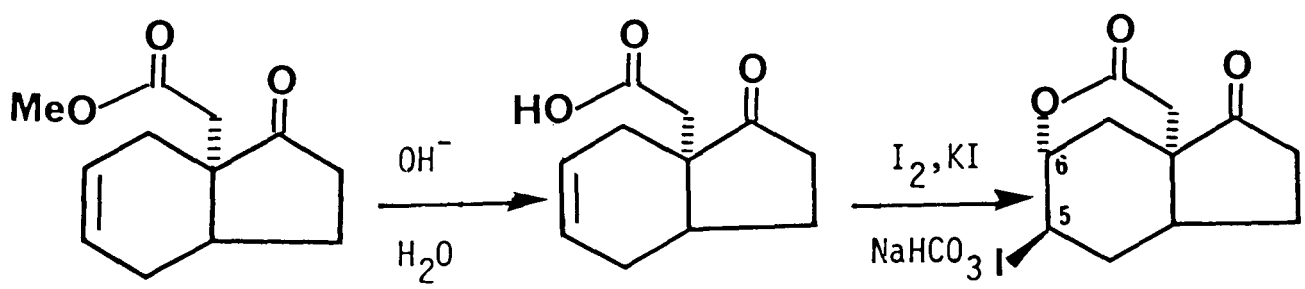
It was considered that these difficulties may possibly be circumvented by iodolactonisation. Danishefsky et al.[44] had used this procedure for the six-membered ring analogue, in which the iodolactone was isolated in 88% yield. As is apparent, this involves



the initial hydrolysis of the methyl ester. In fact, iodolactonisation generally proceeds by nucleophilic attack of a carboxylate anion as opposed to its methyl ester. This presumably reflects the fact that the larger, less nucleophilic iodide ion is less able to attack the oxonium intermediate.

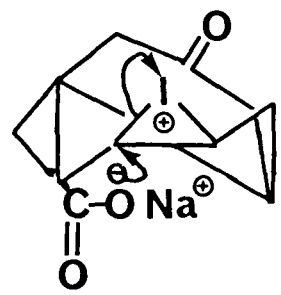
The ketoester was accordingly subjected to alkaline hydrolysis. It was found that in order to effect complete conversion to the carboxylic acid the addition of a second portion of sodium hydroxide was required. The crude product was used as such in the subsequent iodolactonisation.

The iodolactone (6) was prepared using Danishefsky's conditions. Hence, a mixture of iodine, potassium iodide and water was added to an aqueous solution of the sodium salt of the acid. The function of potassium iodide is to solubilise the iodine in water. The reaction was carried out in the dark, due to the light sensitive nature of some iodolactones. Indeed, after 64 hours 76% of the desired iodolactone (6) was formed.



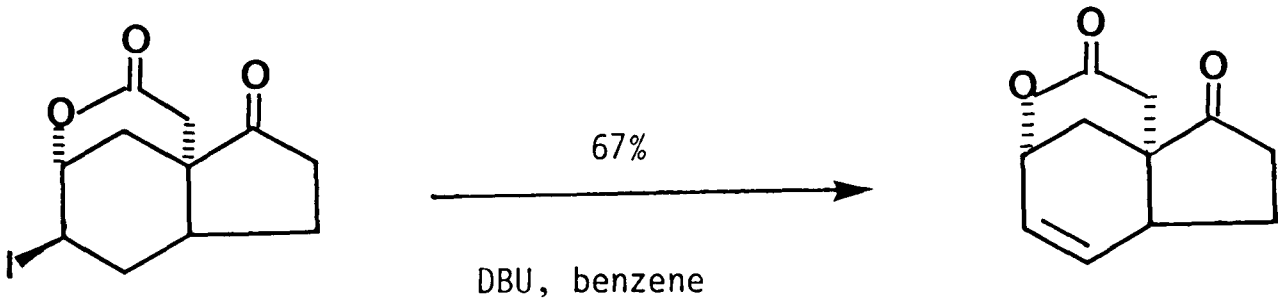
(4) (5) (6)

The mechanism of the reaction is analagous to bromolactonisation, except that intramolecular displacement involves a carboxylate anion:-



Spectral characteristics were also similar, although H-6 and H-5 occurred at the slightly higher field of δ4.65 and 4.4 respectively. Mass spectral data were in accordance with the iodolactone.

The unsaturated lactone required for further transformations in the synthetic scheme, was prepared by dehydroiodination. This is generally performed with reagents such as diazabicycloundecane (DBU) or diazabicyclononene (DBN). In this case the former was chosen, as it had been successfully employed in the elimination of Danishefsky's iodolactone. The conditions reported by this author were repeated to afford 67% of the ketolactone (7).



(6) (7)

An optimum yield was obtained using 0.25 g of iodolactone. A decrease in the product yield was observed with larger scale reactions. For example, 50% from 2 g and 42% from 8 g of starting material. The reason for this discrepancy is unknown. A total of 9 g of ketolactone was prepared during the course of the research. In general, a 3 g batch of product was synthesised from cyclopentanone intermittently over two or three months. This lengthy time period was mainly due to the chromatographical separation required at most stages of the sequence.

The ketolactone gave distinctive i.r. absorptions at 1730 cm^{-1}, for the lactone and cyclopentanone moieties, and at 1640 cm^{-1} indicating a double bond. The latter function resonates in the n.m.r. at δ6.2, with H-6 appearing downfield, with respect to the iodolactone, at δ4.8. A molecular ion and mass spectral splitting pattern confirmed the structure.

In summary, the overall transformation from the ketoester to the ketolactone was accomplished in an overall yield of 51%.

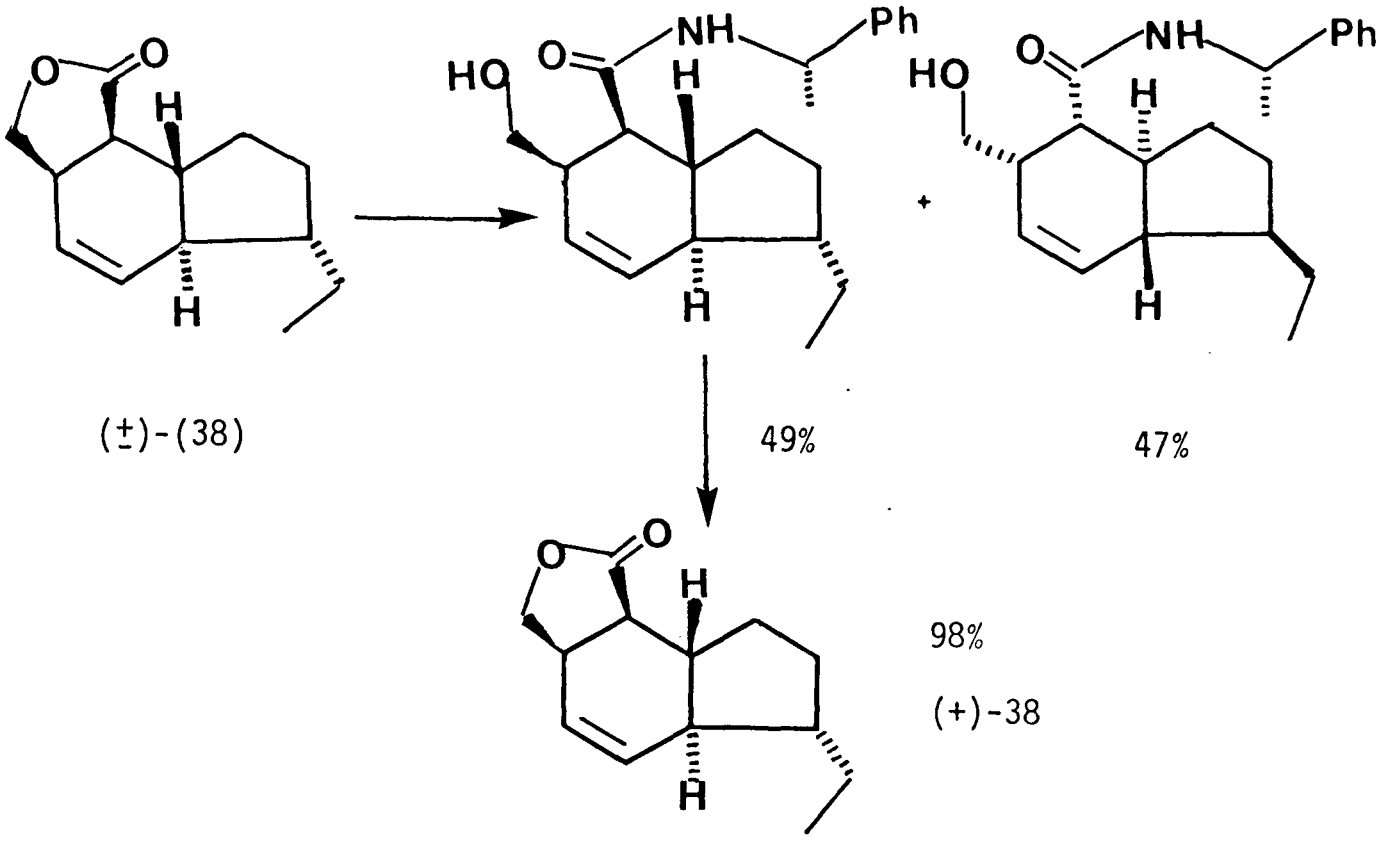
III.5. POTENTIAL RESOLUTION OF THE KETOLACTONE (7)

Natural products are generally isolated as one optically active isomer, and it is often this enantiomer alone that is physiologically active. Therefore, an added bonus to any total synthesis is the preparation of that isomer. Vernolepin was extracted as the (+)-isomer, and although there is no literature account of the biological activity of its mirror image, our target was the synthesis of the optically pure (+)-enantiomer.

There are several stages in the synthetic scheme at which resolution of the two enantiomers may be attempted. However, considering half of the compound is lost, it is generally advisable to perform this procedure at an early stage in the synthesis.

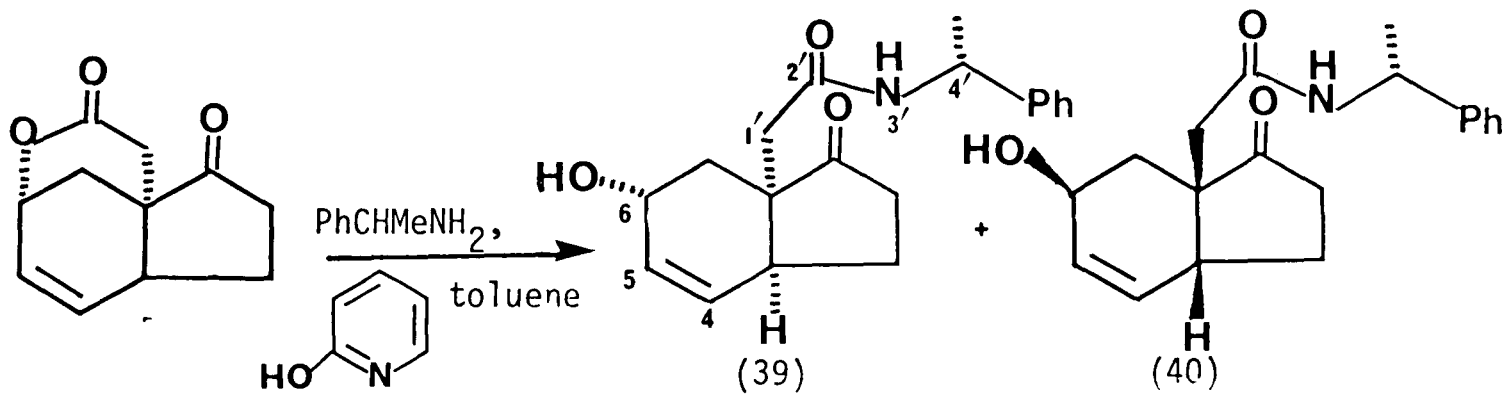
Recently, Youssef and coworkers[149] have reported a method of separating racemic δ- and γ-lactones. This involved converting the lactone into a diastereomeric mixture of amides using S-(—)- -phenylethylamine, with 2-hydroxpyridine as catalyst. The diastereoisomers were easily separated and subsequently hydrolysed to give the optically pure lactones.

This procedure has been employed by Ley et al.[150] in the total synthesis of the ionophore antibiotic X-14547A. The tricyclic lactone (38) was resolved as illustrated:-



Considering the similarities between the Ley intermediate (38) and the ketolactone (7), it was decided to attempt the Youssef resolution method.

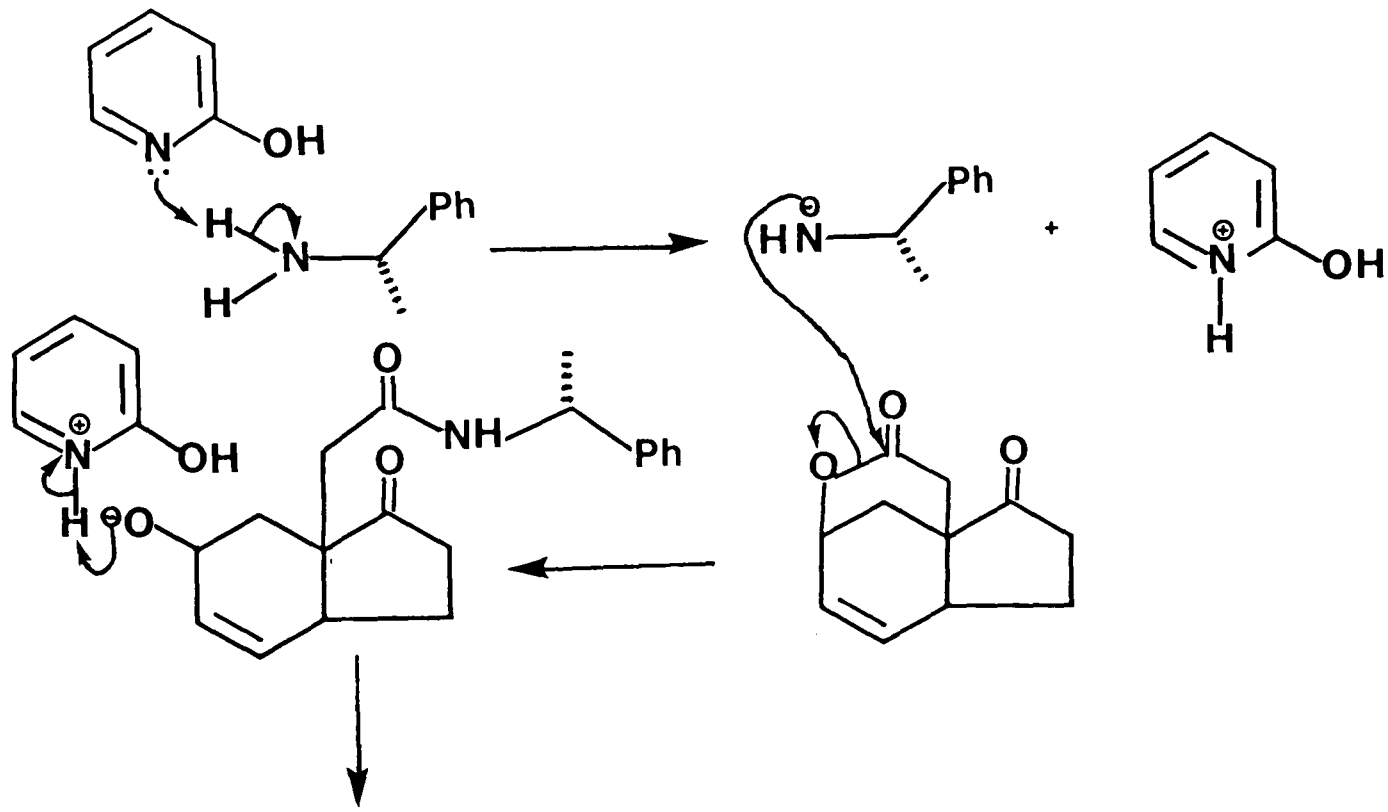
Accordingly, a mixture of the base, amine and ketolactone in toluene was heated under reflux for 20 hours. This involved heating overnight, when a marked drop in water pressure resulted in evaporation of most of the solvent, leaving a black tar. Acidic workup and purification gave the two isomeric amides in 4% and 7% yields. Positive



identification was obtained by way of amide and hydroxy stretching bands at 3440 cm^{-1} and carbonyl and amide absorptions at 1730 and 1680 cm^{-1}

respectively. The two compounds also displayed almost identical n.m.r. spectra, in which the phenyl and amide protons appeared together at δ7.2, olefinic signals at δ6.0, H-6 at δ4.7 and H-4', being α to the amido linkage, occured at δ4.35. A hydroxy signal was detected at δ1.8. Mass spectra confirmed the structures by giving accountable fragmentation patterns.

A plausible mechanism for the process would involve initial deprotonation of the amine resulting in the more nucleophilic species. Nucleophilic attack at the lactone and its concomitant cleavage, followed by protonation, would result in the observed diastereomeric hydroxyamides.

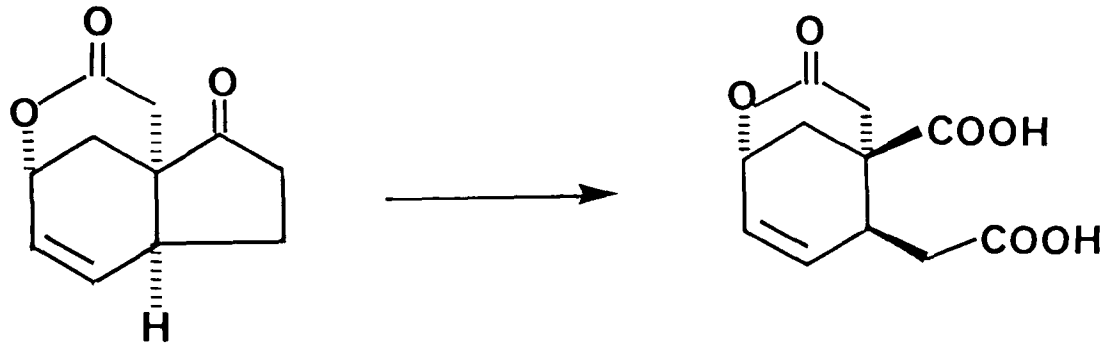


(39) + (40)

Unfortunately, due to the lack of starting material and time, this method was not repeated. In addition, the subsequent hydrolysis was not performed, as only very small amounts of the amides were available. But clearly this is a potentially very useful method for the separation of racemic lactones.

III.6. FORMATION OF THE DICARBOXYLIC ACID (9)

Several options were available for effecting the transformation of the ketolactone (7) into the dicarboxylic acid(9).

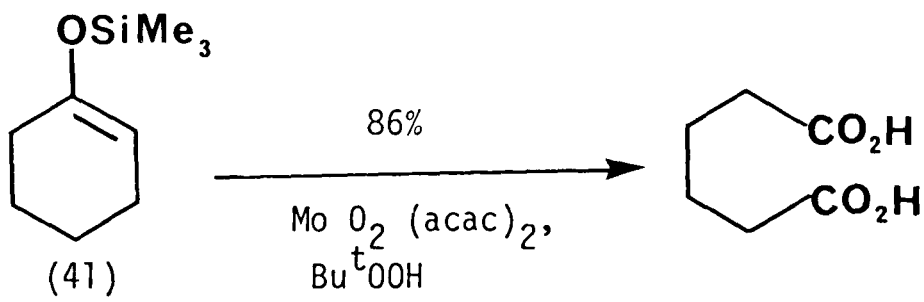


(7) (9)

A discussion is presented in this section of the various synthetic routes to this molecule, concluding with the most successful ozonolysis procedure, depicted in the overall synthetic scheme.

III.6.1. Oxidative double bond cleavage with molybdenum dioxyacetylacetonate and t-butylhydroperoxide ($Mo\ O_2\ (acac)_2$, $Bu^t\ OOH$).

One of the most direct approaches to the dicarboxylic acid (9) involves a procedure that has been recently published by Kaneda et al.[151]. These workers have reported oxidative cleavage of the double bond of silyl enol ethers with the $Mo\ O_2(acac)_2$, $Bu^t\ OOH$ system. For instance:

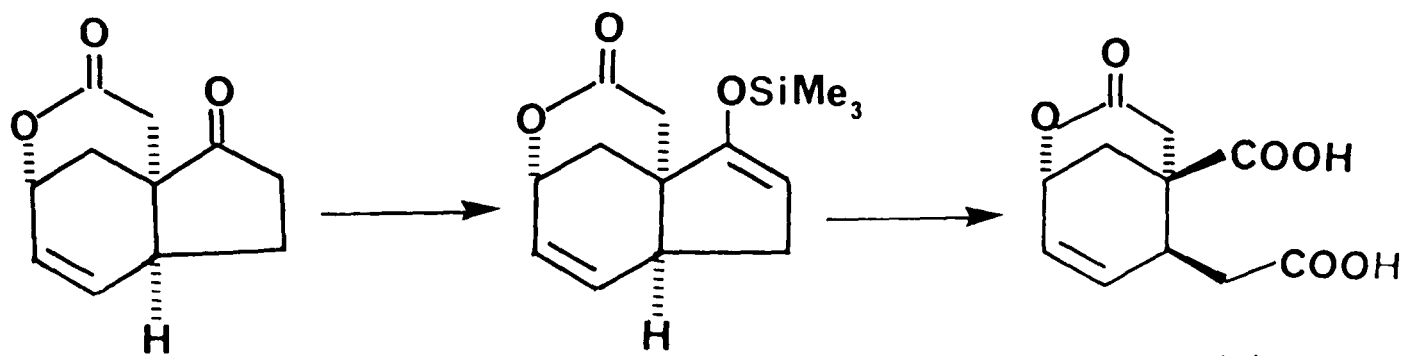


(41)

Similar, and in some cases almost quantitative yields of carboxylic acids have been found for a selection of O-silylated enolates.

The mechanism for this oxidative process is unclear. However, as molybdenum catalysed oxygenations of this nature are employed in epoxidations of isolated olefins, it is reasonable to assume an intermediate epoxide stage.

By analogy, this propitious route could be equally well applied to the silyl enol ether derivative of the ketolactone.



(8) (9)

However, due to the precious nature of the ketolactone, it was decided to attempt this procedure using cyclohexanone as a model compound.

Precise details are available for the synthesis of the molybdenum catalyst,[152] simply involving refluxing a mixture of molybdenum oxide in acetylacetone. Any unreacted oxide is removed by filtration, and the crude product crystallised to afford 61% of the compound. A solution of Bu^tOOH in anhydrous benzene was added to a solution of $MoO_2(acac)_2$ and the O-silylated enolate in benzene. The authors make no reference as to the type of Bu^t OOH used. The reagent is commercially available as:- (i) an 80% solution in di-tert-butyl peroxide, (ii) a 90% aqueous solution; and (iii) a 70% aqueous solution.

Observing that strictly anhydrous conditions were used in this reaction, the former grade was opted for. After stirring the solution at 60°C for 48 hours, a mixture of trifluoroacetic acid, THF and water was added. Crystals of adipic acid are reported to separate out from the resulting mixture over the following 24 hours. However, no crystals were observed and a dark brown liquid was obtained. The residue obtained from evaporation of the organic layer was washed with benzene affording crude adipic acid in 48% yield.

The discrepancy between the two findings may have arisen from the type of Bu^t OOH employed in the reaction. Reference to the literature[153] suggested that the presence of di-tert-butyl peroxide may present problems during the workup of a reaction mixture, in addition to its effect of greatly lowering the thermal stability of Bu^t OOH. The authors have recommended the use of anhydrous Bu^t OOH in 1,2-dichloroethane, which can be prepared from the aqueous solution by phase

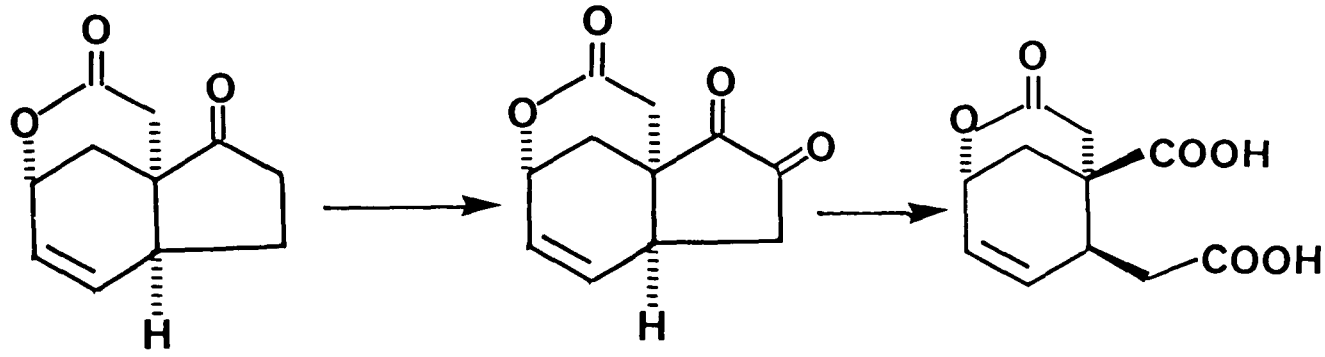
separation and azeotropic distillation.

Accordingly a 30% solution (as determined by n.m.r. analysis) of Bu^tOOH in dichloroethane was prepared. The reaction was repeated, but again no crystals separated out from the reaction medium, and a lower yield of 7% of the product was isolated by evaporation of the organic layer.

As this clearly was not a very successful procedure for the model compound, an alternative route was sought.

III.6.2. Cleavage of an α-diketone with alkaline hydrogen peroxide

A dicarboxylic acid can be prepared by alkaline cleavage of the 1,2-diketone, i.e.

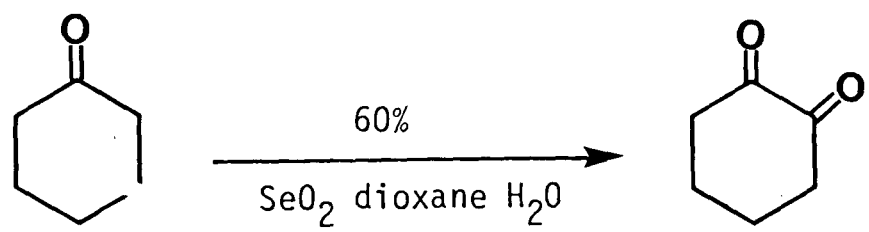


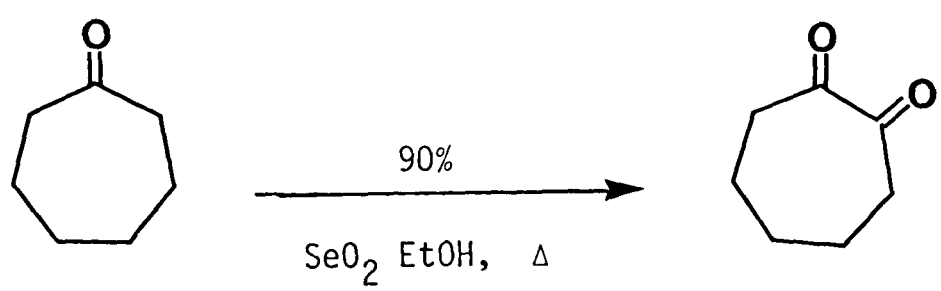
(7) (42) (9)

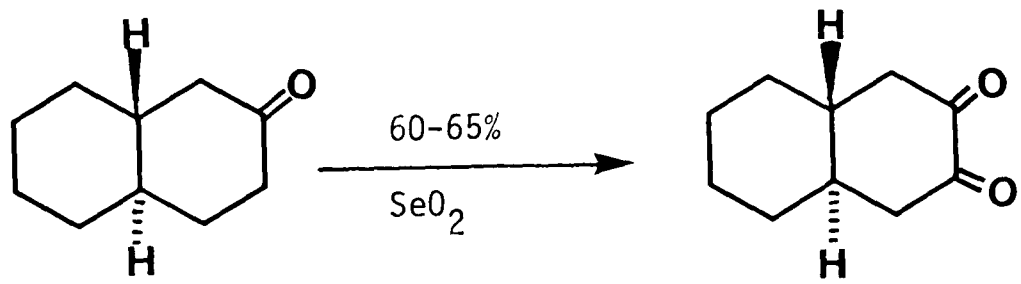
Possible routes to the dicarbonyl precursor (42) were therefore examined.

III.6.2.a Selenium dioxide oxidation

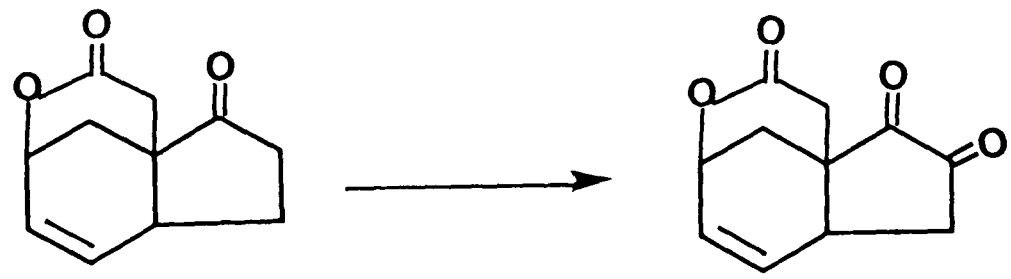
Selenium dioxide appeared to be the reagent of choice for this transformation,[154-156] as its use for the preparation of 1,2-dicarbonyl compounds is well established. In addition, products have often been isolated in good yields. For example:





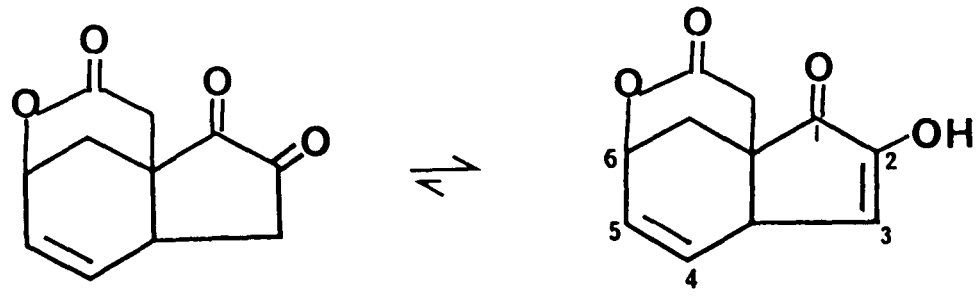


Consequently, oxidation of the ketolactone was attempted.



Originally a detailed account of the preparation of cyclohexanedione was followed. In this procedure,[157] selenious acid was used as oxidant in a mixture of dioxane and water. The authors advocate the slow addition of a solution of selenious acid (0.17 equivalents) in dioxane and water, to the ketone, as the reaction was very vigorous. Cooling is necessary to minimise any temperature rise, which is reported to have a deleterious effect on the product yield. As the reaction proceeded, red amorphous selenium was deposited. The mixture was stirred for a further 11 hours before being subjected to workup.

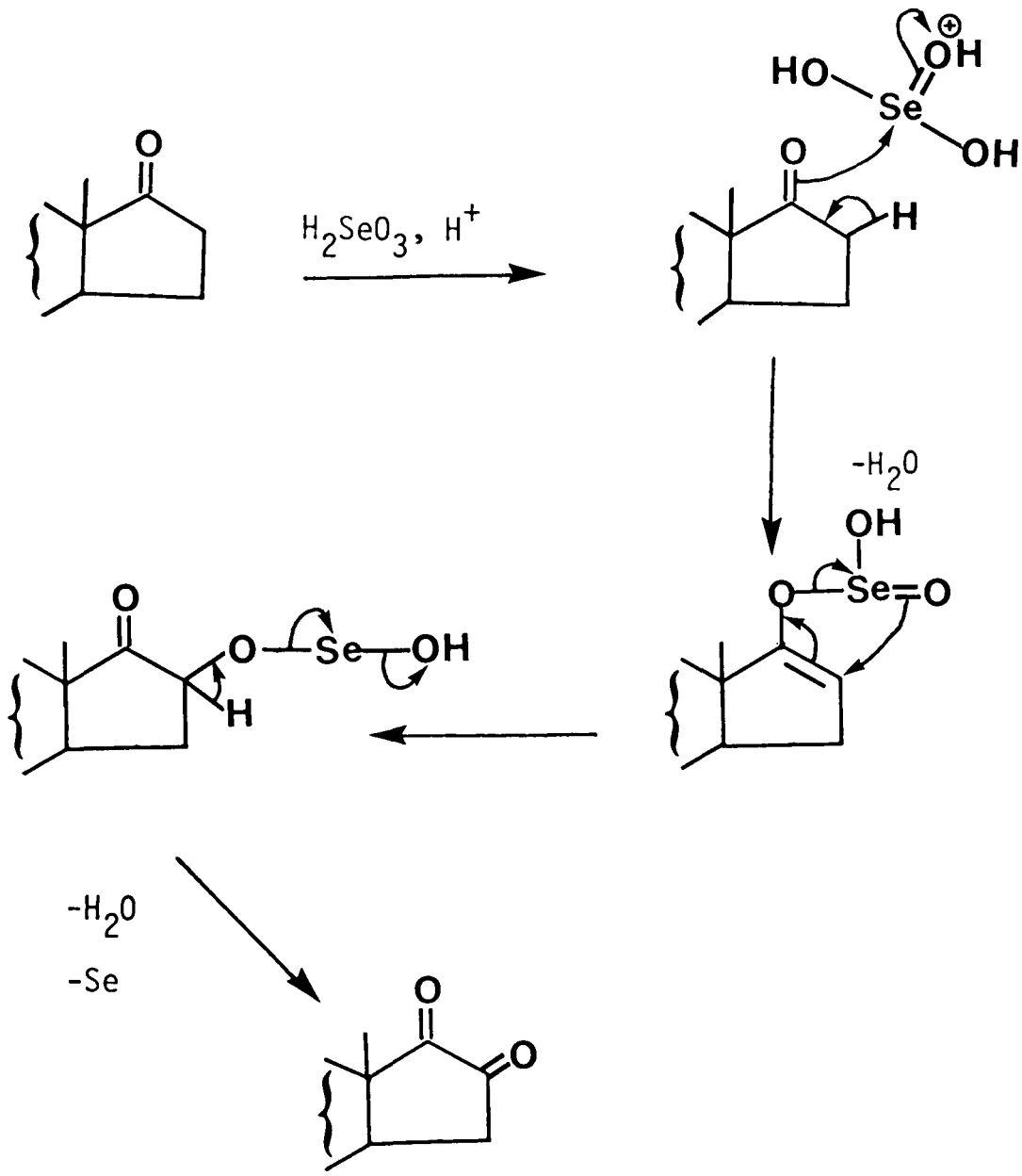
In the case in hand, no temperature rise was observed on addition of the oxidising agent and only starting material was present after 24 hours. Therefore an additional portion of selenous acid was introduced. After stirring for a further 72 hours, a trace amount of compound of lower R_f was detected by t.l.c. Additional quantities of selenious acid (to a total of 3 equivalents) were introduced and the entire mixture heated, but still appreciable quantities of ketolactone remained. Nevertheless, workup of the reaction mixture and subsequent purification afforded (42) as a 90% mixture of the enol and ketotautomers respectively, as determined by n.m.r. A 33% conversion to the desired product was thus obtained, although this only corresponded to an isolated yield of 12%.



The presence of hydroxy, carbonyl and olefinic absorptions in the i.r. were consistent with this compound. N.m.r. proved the predominance of

the enol tautomer by exhibiting hydroxy and H-3 signals each integrating to 0.9 of a proton. The remainder of the spectrum was similar to starting material. Confirmation by a mass spectrum and accurate mass accredited the structure.

The oxidation is believed to follow the reaction pathway indicated below:



The reaction is catalysed by acid in this mechanism,[115] with acetic acid frequently being used for this purpose.

In an effort to improve the yield of product, various modifications were made to the method, summarised in Table 6. Literature reports state that selenium dioxide and selenious acid may be used

Oxidation of ketolacetone (7)

Oxidant	Solvent System	AcOH Catalyst	Temperature time of reaction	Product Yield (%)
H_2SeO_3 (3eq. total)	dioxane, water	-	120h, r.t. 45°C, 3½h. 75°C, ½h.	12
SeO_2 (6eq. total)	dioxane, water	✓	5h. r.t. 90°C 1h.	6
SeO_2 purified (8eq. total)	dioxane, water	✓	50°C, 120h.	-
SeO_2 (1.25 eq.)	AcOH	-	reflux, 18h.	-
H_2SeO_3 (3 eq.)	70% AcOH	-	45°C, 5h	-
H_2SeO_3 (3 eq.)	70% MeOH	-	reflux, 5h.	-
H_2SeO_3 (3 eq.)	dioxane, water	-	60°C, 1h. 70°C 2h.	9

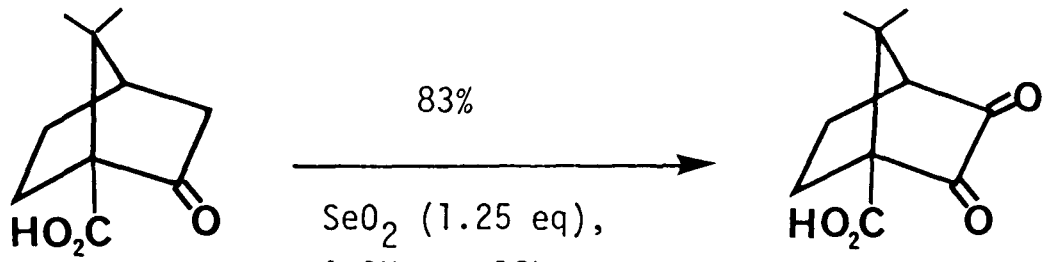
Table 6

interchangeably, therefore in the subsequent reaction selenium dioxide was employed in conjunction with an acid catalyst. No conversion to the diketone was observed after stirring the solution containing one equivalent of selenium dioxide for two hours. Further quantities of the oxidant were added totalling a 6-fold excess and t.l.c. indicated a trace amount of product. The entire mixture was heated under reflux for one hour. Unfortunately spots corresponding to both the starting material and diketone appeared weaker and substantial amounts of base-line material were visualised. Purification of the crude mixture afforded (42) in a reduced yield of 6%.

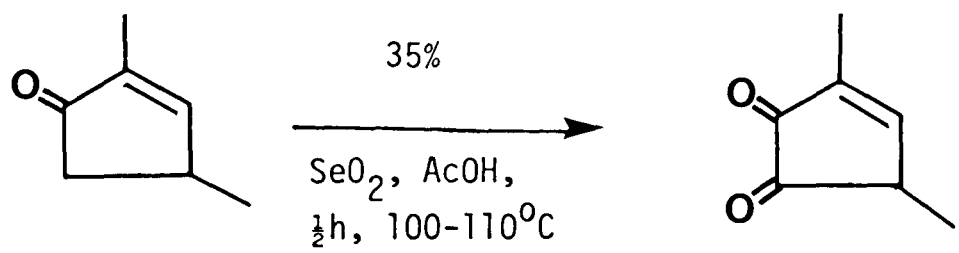
There is literature precedent[154] for freshly sublimed selenium dioxide behaving in quite a different way to the ordinary dioxide, as the latter is often contaminated with copper and other heavy metals. Accordingly, purified oxidant was employed in the next attempt. As the preceeding results would suggest the ketolactone and diketone to be unstable at high temperatures, the reaction was performed at a maximum of 50^{o}C. Although t.l.c. indicated a compound coeluting with the desired product, none of (42) was isolated from purification.

Rabjohn[156] and others have indicated that the yield of product can be influenced by the choice of reaction solvent. A great variety of solvents have been used, the most common being:- dioxane, acetic acid, acetic anhydride, water, ethanol, benzene and methanol. Combinations of solvents are frequently employed. Water is often added to enhance the solubility of selenium dioxide in nonhydroxylic media. Trachtenberg[155] has recommended oxidation of ketones or aldehydes to be carried out in acetic acid, as this solvent allows rapid conversions to product. This is exemplified by the following instances:-

(158)

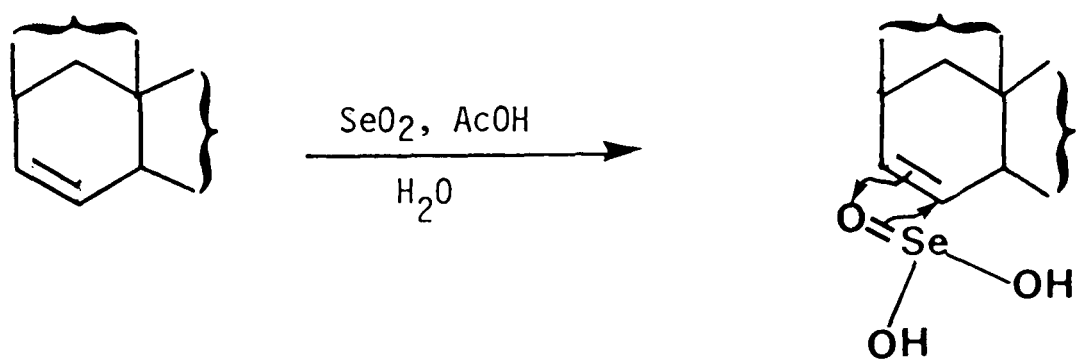


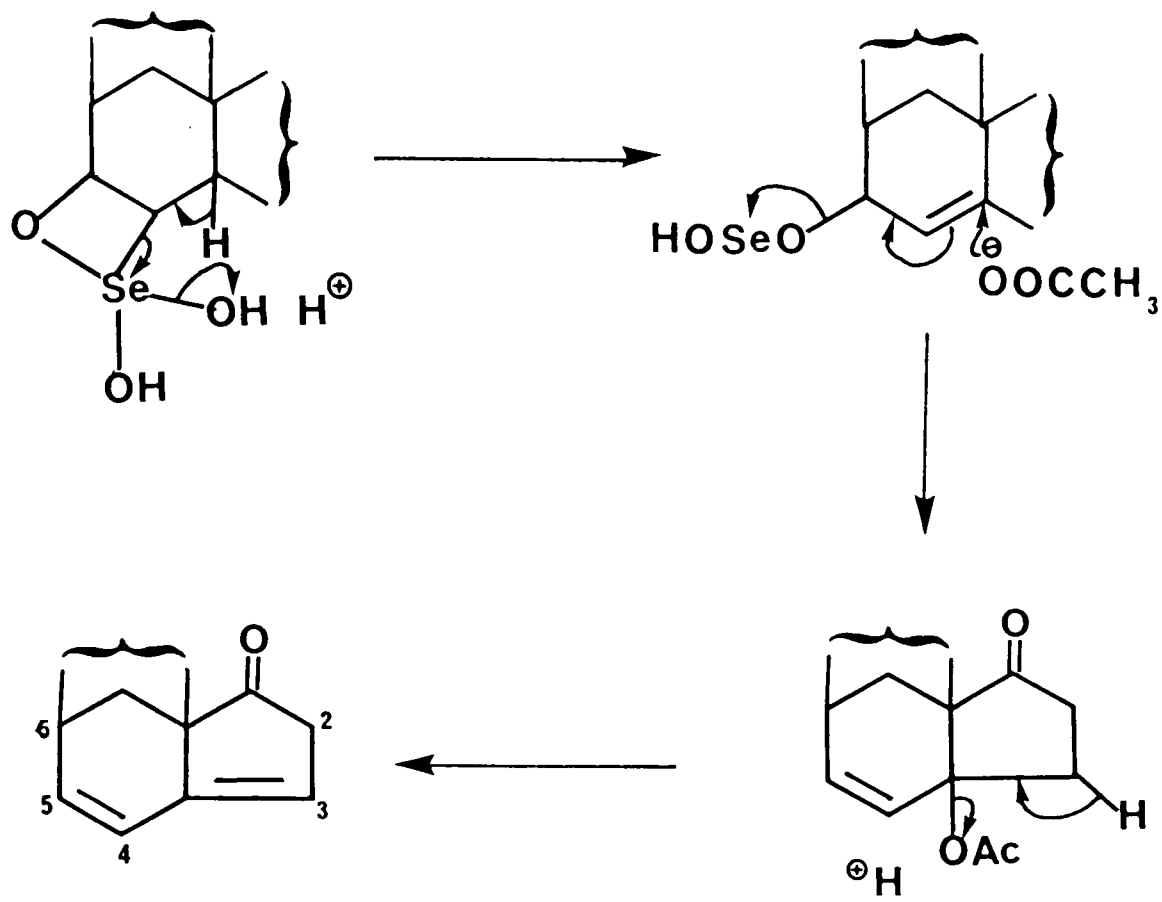
(157)



Consequently the ketolactone was heated under reflux with selenium dioxide in glacial acetic acid. None of the desired product was detected by t.l.c., and n.m.r. of the crude product tentatively indicated the diene (43). Obviously a competing reaction under these conditions is allylic oxidation. In fact, House[115] mentions that this pathway is favoured when an acetic acid-acetic anhydride solvent mixture is used.

A possible mechanism accounting for this process is given below:-





(43)

Guillemonat has shown that when allylic oxidation is at a tertiary carbon, the conjugated diene is generally obtained. This is not surprising as dehydration under the acidic conditions of the reaction should be a relatively facile process.

Evidence to the diene is based on an olefinic signal corresponding to three protons, appearing as a multiplet at δ6.1, H-6 at its usual shift of δ4.9 and two protons resonating at δ3.5. Naturally as one would expect for a crude sample, the integration of the alkyl region which occurred between δ3.2 and δ1.9 was far in excess of the calculated figure. However, as ketones are known to be slightly more activating than olefins, as illustrated by the exclusive dione formation, (vide supra), allylic oxidation was not expected.

A more favourable outcome was hoped for using a dilute acid solution. In addition, as no seemingly obvious beneficial effect was

gained by the use of selenium dioxide, selenious acid was re-employed. As noted from the entry in the Table, after heating the mixture at 45°C for 5 hours, no product or for that matter diene, was indicated by t.l.c. Decomposition of the ketolactone to baseline material was solely detected.

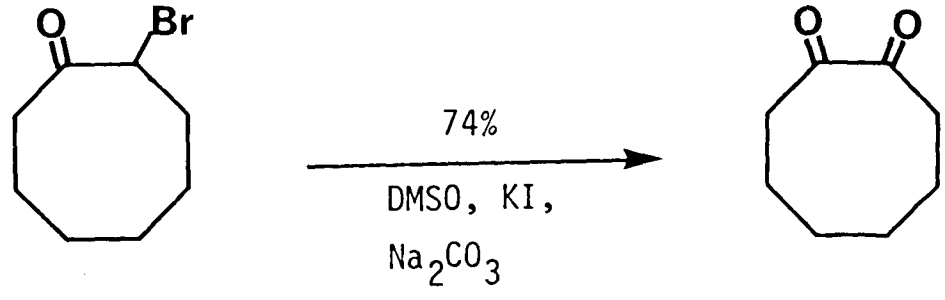
It was reasoned that methanol may be a more propitious choice of solvent. But a similar reaction conducted in this solvent fared no better.

Out of the media tested, a dioxane, water mixture gave the best results. In a final attempt to optimise the conditions, the ketolactone was heated with selenious acid in this solvent system for one hour at 60°C, and two hours at 70°C. As prolonged heating would appear to cause decomposition, although appreciable amounts of starting material remained, the mixture was allowed to cool, worked-up and purified. Only 9% of the diketone was isolated. These consistently low yields would seem to be analogous to cyclopentanone, when the dione is only obtained in 7% yield.[155] This compares unfavourably with cyclohexanone and cycloheptanone when 60% and 90% yields are isolated respectively. In conclusion, although the diketone could be prepared from this route, the yields were far from satisfactory. Consequently, an alternative method was required.

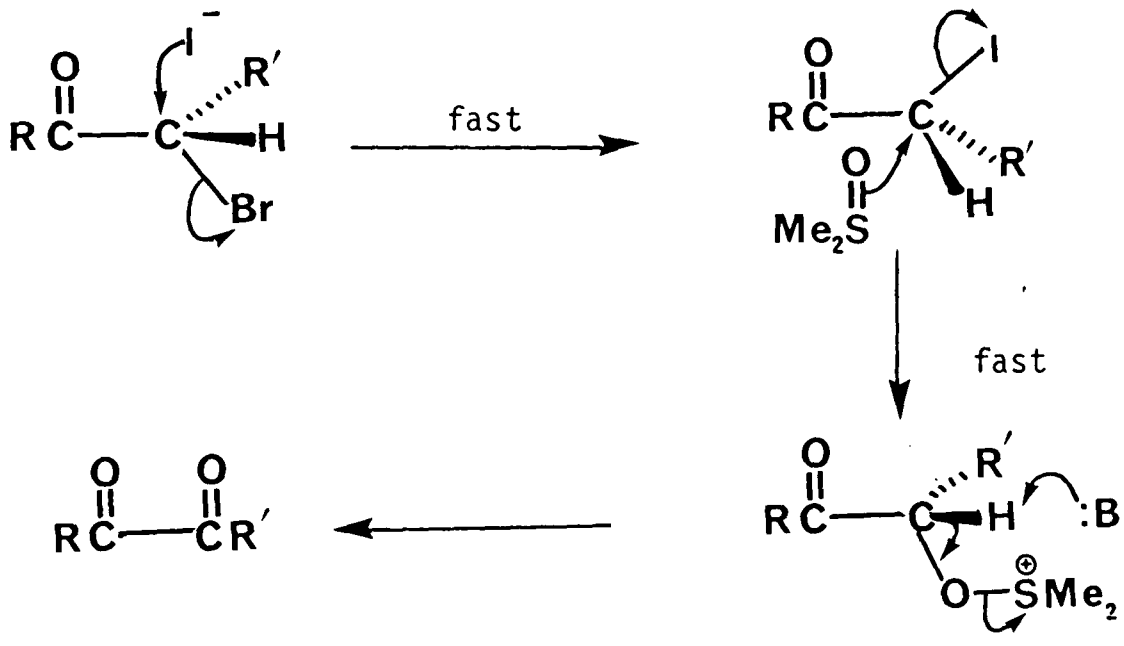
III.6.2.b <u>α-Halogenation and subsequent oxidation</u>

The reactions of primary halides and tosylates with dimethylsulphoxide in a Kornblum type of oxidation, have served as synthetic routes to aldehydes and ketones. However, the yields obtained in secondary systems are often poor.

Macomber and Bauer[159] have recently developed a high yielding process for the conversion of α-bromoketones into α-diketones.



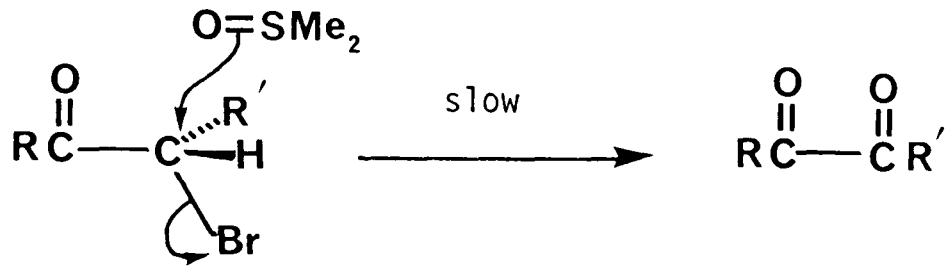
The reaction is believed to be catalysed by iodide ion in the manner indicated.



Thus, displacement of bromine, with iodine is followed by

accelerated nucleophilic attack at the α-carbon. This is accredited to the iodine behaving as a better leaving group than bromine and a stronger nucleophile than DMSO.

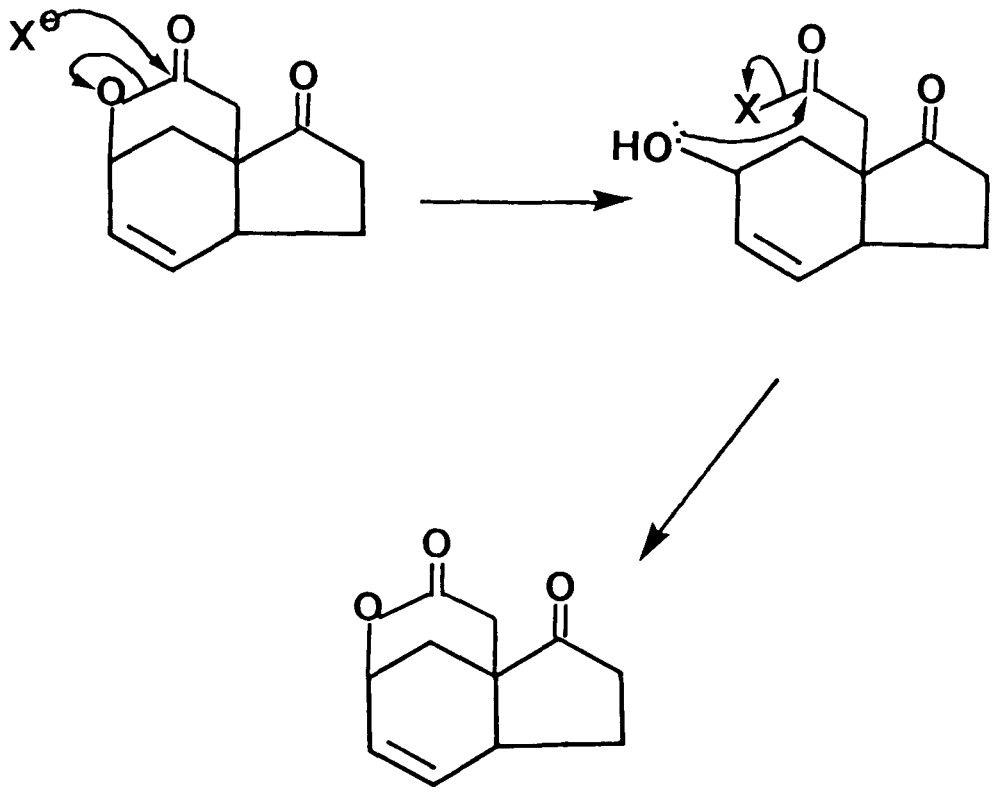
The alternative direct oxidation of the bromo derivative is a much slower process.



Therefore, the first step in this procedure involved the α-bromination of the ketolactone. Treatment with the commonly used brominating agents such as bromine, hydrogen bromide or N-bromo-succinimide would have undoubtedly afforded mixtures of products resulting from addition at the double bond or at the allylic position, as well as the intended transformation. Macomber and Bauer have recommended the use of cupric bromide in refluxing chloroform and ethyl acetate. Yields of the listed α-bromoketones range from 90 to 97%.

With this promising method in mind, the ketolactone was duly refluxed in the mixed solvents with the brominating agent. Indeed, at the end of the addition of cupric bromide, t.l.c. indicated complete disappearance of starting material. The reaction mixture was submitted to the prescribed workup which included washing the organic layer with sodium bicarbonate, and the crude product was analysed. To our disbelief, the spectra and t.l.c. were identical in every way to the starting material. A possible pathway to account

for these findings is illustrated below.



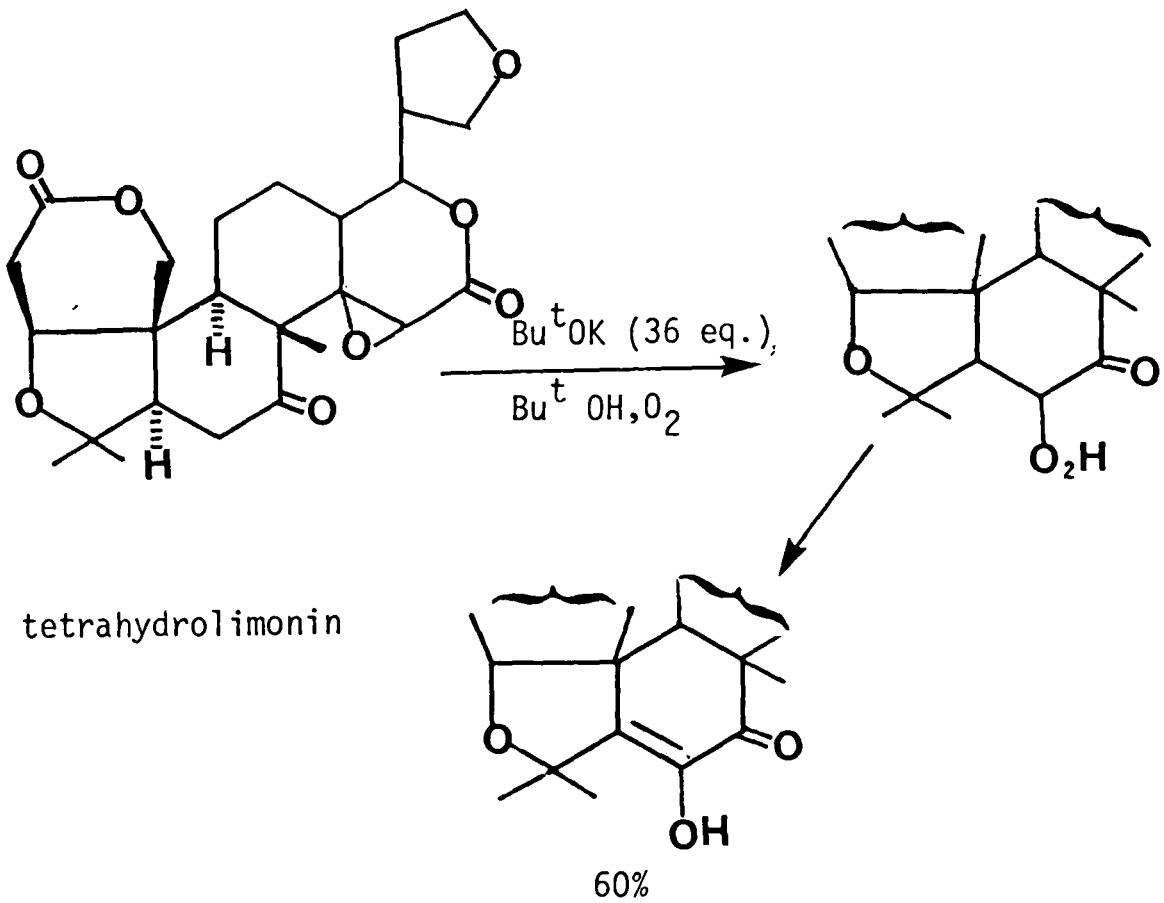
Attack at the carbonyl group by a nucleophilic species such as bromide ion results in cleavage of the lactone. This molecule would have a different R_f to the ketolactone. On workup closure of the lactone causes displacement of the anion to afford the starting material.

Although other brominating agents could have been employed, it is apparent that the ketolactone possesses several functionalities. A more gainful approach to the diketone was therefore sought elsewhere.

III.6.2.c Oxygenation

The reaction of enolate anions with molecular oxygen has been used to prepare 1,2-diketones. α-Hydroperoxyketones are intermediates in this transformation. Indeed, it is the base induced cleavage of such compounds, together with other side reactions that often result in greatly reducing the yield of the dicarbonyl compounds.

However, autoxidation of ketones can proceed without cleavage of the carbon chain, even under strongly basic conditions. This has been demonstrated for the cyclic ketones of the limonin series:[160,161]



tetrahydrolimonin

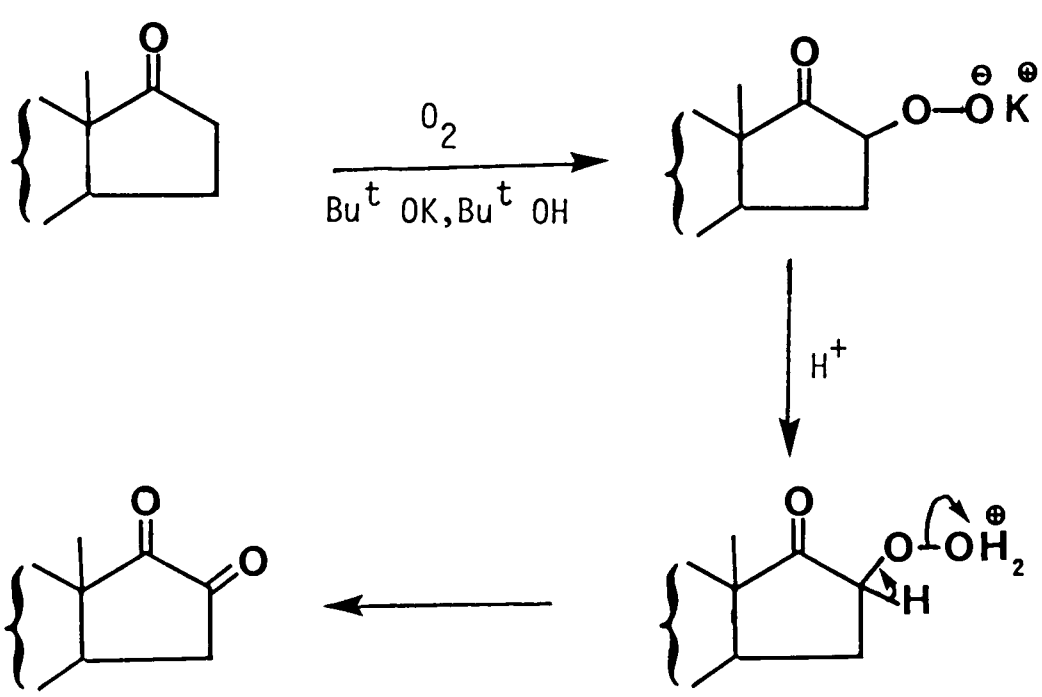
60%

Barton et al.[162] have studied the oxygenation of 20-oxo-steroids under similar conditions. The intermediate hydroperoxy derivative was isolated and subsequently reduced affording the α-hydroxyketone.

As tetrahydrolimonin would appear to be a far more sensitive molecule than the ketolactone, oxygenation of the latter was

attempted. Accordingly, a solution of potassium t-butoxide in t-butanol was saturated with oxygen. A solution of the ketone in a small volume of t-butanol was added through the side arm of the hydrogenation flask and the mixture shaken with oxygen until there was no further uptake of oxygen. At this stage the compound was thought to be present as the potassium salt of the hydroperoxide. The addition of acid should convert this into the diketone.

viz:-

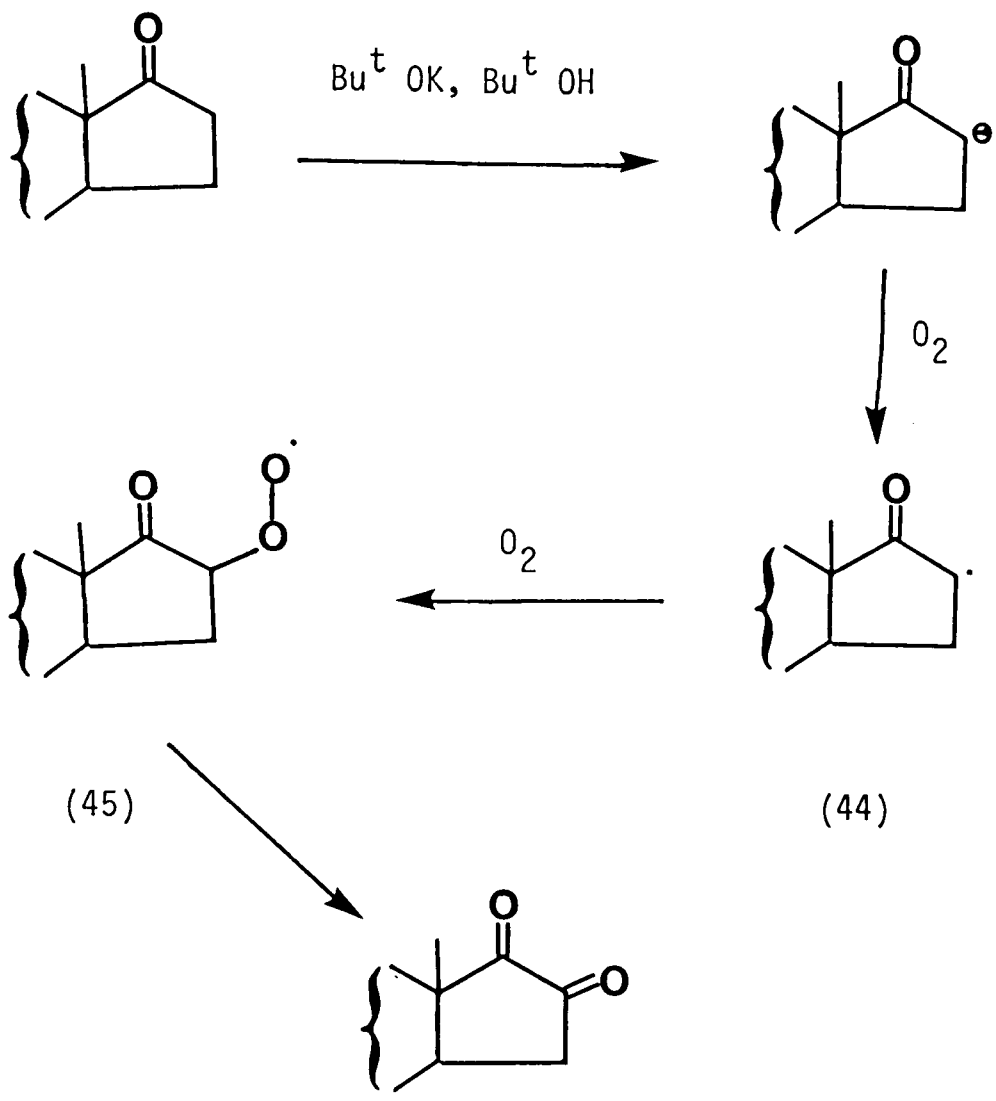


T.l.c. analysis of the crude product indicated an extremely complex mixture of compounds, including starting material and α-diketone. Attempts at purification by a variety of chromatographical techniques were, not surprisingly, unsuccessful.

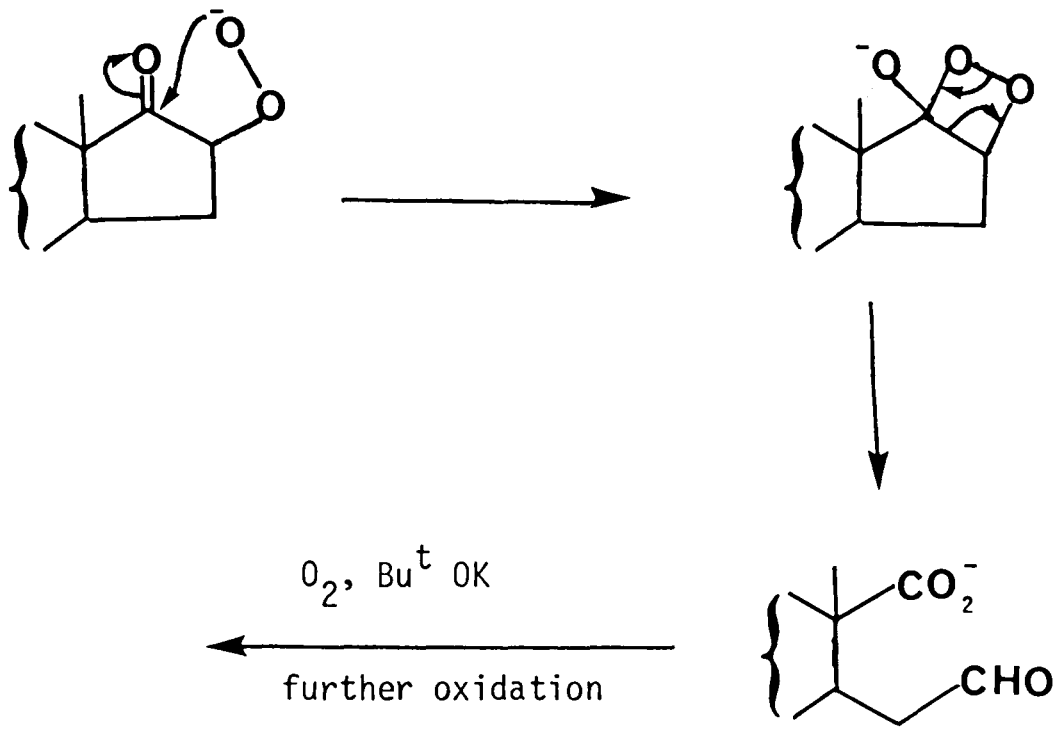
A repeat of the procedure using a smaller excess of the base (16 equivalents), as recommended by Barton et al;[162] gave similar results.

The origin of such a complex mixture becomes apparent when

the mechanism is considered.



The enolate anion reacts with oxygen to form an α-keto-radical (44), which in turn may react further to afford the α-keto hydroperoxide anion (45). In addition to this pathway α-ketohydroperoxides may undergo cleavage in the presence of base, and the product of the cleavage oxidised further. Alternatively, the initially formed α-keto radicals may couple or the α-diketone react with the enolate anion, in the absence of excess oxygen, to form semidione anion radicals.



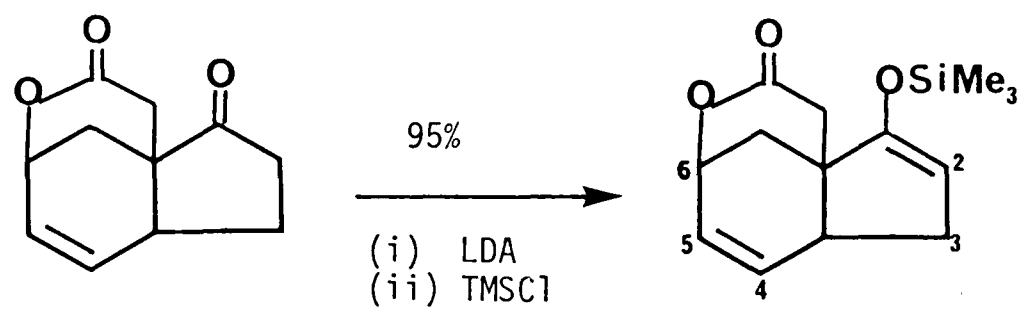
In order to minimise cleavage of the intermediate hydroperoxide, triethyl phosphite has been recommended for *in situ* reduction to the hydroxyketone.[163] Other reagents such as zinc and sodium sulphite[164] have also been used for reduction. The reaction may also be improved upon by the use of low temperatures in the region of $-25^{o}C$, with dipolar aprotic solvents. Wasserman and Lipshutz[164] have advocated the use of LDA for the generation of enolates. These authors have reported excellent yields of oxygenation products. Consequently there were many possible ways of improving the method. However, by chance, success was encountered in a different route to the dicarboxylic acid (9), thereby invalidating any further effort with this procedure.

Silylation

As efforts towards procuring the dicarboxylic acid had been so far thwarted, it was hoped that a change to enol chemistry may

prove more rewarding.

Column chromatography of the crude product, obtained by silylation of the enolate anion formed by deprotonation with LDA, afforded the O-silylated enolate in a remarkably high yield of 95%.



(7) (8)

Obviously a competing reaction in this process would theoretically be silylation of the lactone moiety. This group is well-known to be less reactive than cyclopentanone and by using only a slight excess of base (1.1 equivalents) and very low temperatures (-80^{o}C), this danger was obviated.

Salient features of the i.r. of (8) include, the δ-lactone absorption at 1740 cm^{-1} and an intense peak at 1640 cm^{-1} corresponding to both the double bond and enol functions. An absorption at 1250 cm^{-1} confirmed the presence of a silyl group. The olefinic protons, H-4 and H-5, and H-6 appeared, as in the precursor, at δ6.0 and δ4.75, in the n.m.r. An additional signal at δ4.65 was accredited to H-2. Normal alkyl resonance occurred in the region δ3.0-1.7, and a 9 proton singlet at δ0.25 indicated the trimethylsilyl moiety. A mass spectrum and accurate mass of the molecular ion were in accord with the structure of (8),

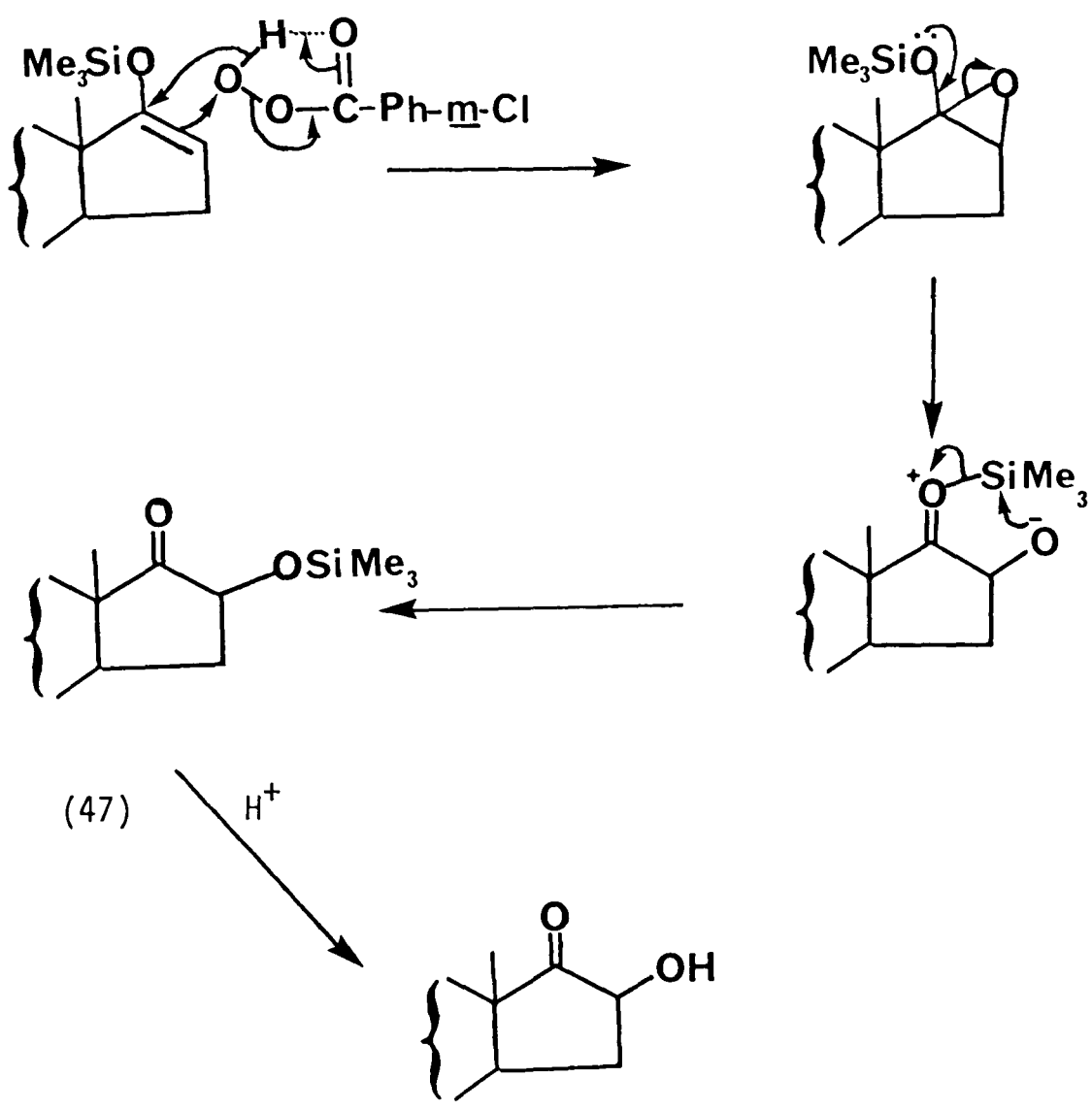
Several options were now open for conversion of the silyl enol ether into the dicarboxylic acid. The most direct approach would be oxidative cleavage of the more nucleophilic double bond, either by the molybdenum catalysed Bu^tOOH system or by ozonolysis with an oxidative workup. Alternatively, oxidation of the O-silylated enolate to afford the α-hydroxyketone, would lend a route to the α-diketone.

As an ozonizer was not initially available, it was decided to attempt the previously employed $MoO_2(acac)_2$, Bu^tOOH procedure once more. Purification of the crude product yielded the starting ketone and compounds that had obviously undergone more deep seated changes than the intended transformation.

Peracid oxidation of the silyl enol ether was subsequently explored.

III.6.2.d α-Hydroxylation

This was carried out by reaction with m-chloroperoxybenzoic acid. The crude product was subjected to a reductive workup in order to remove any excess peracid. The ketolactone (19%), a low yield of the α-hydroxyketone (46) (6%) and the lactone silane (47) (31%) were isolated from purification. The latter is believed to be an intermediate in the reaction pathway, and was probably obtained due to insufficient hydrolytic conditions.



(46)

The electron-rich enol undergoes electrophilic attack by the peracid affording the epoxide which rearranges to the lactone

silane. Hydrolysis of the silyl group leads to the desired product.

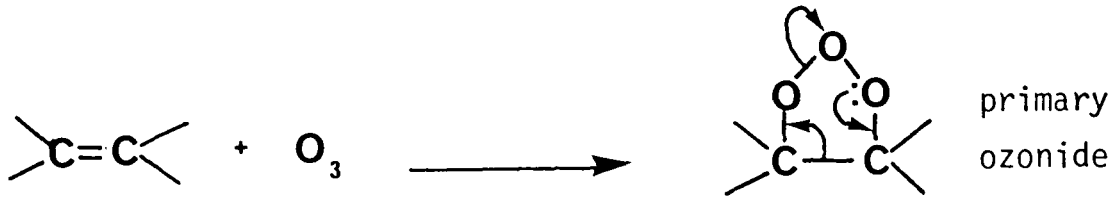
Rubottom et al.[165] have previously isolated δ-silanes under similar oxidation conditions, in which a nonaqueous workup was employed. Evidence for the lactone silane (47) is based on n.m.r. analysis. Signals at δ6.0 and δ4.8 were assigned, as before, to H-4, H-5 and H-6. H-2 appeared upfield, with respect to the starting material, at δ4.2, as expected for a proton sited geminally to a protected hydroxy group, as well as being α to a carbonyl function. Alkyl protons were displayed in the usual region and 9 protons attributed to the silyl signal appeared as a singlet at 0.1. This was confirmed by subjecting the compound to acid hydrolysis. A 9% yield of hydroxyketone was recovered. Characterisation by i.r. revealed the presence of hydroxy, carbonyl and olefinic functions. The n.m.r. spectrum was much the same as the lactone silane with, of course, the exception of the silyl protons and the appearance of an exchangeable hydroxy signal.

In summary, a total of 15% of the hydroxyketone was obtained, which obviously falls somewhat short of an acceptable yield.

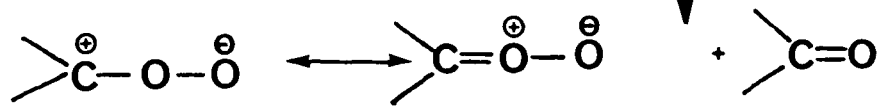
III.6.3. Oxidative cleavage of the double bond by ozone with Jones reagent

Ozone was originally discovered in the eighteenth century. Its use in the cleavage of unsaturated compounds became a standard method for the location of double bonds in molecules. Currently, with the availability of commercial ozone generators, this form of carbon-carbon bond cleavage is extensively used in organic chemistry.[166,167]

There have been several schemes relating to the mechanism of ozonolysis. Until 1966 the generally accepted reaction pathway was that proposed by Criegee.[168]

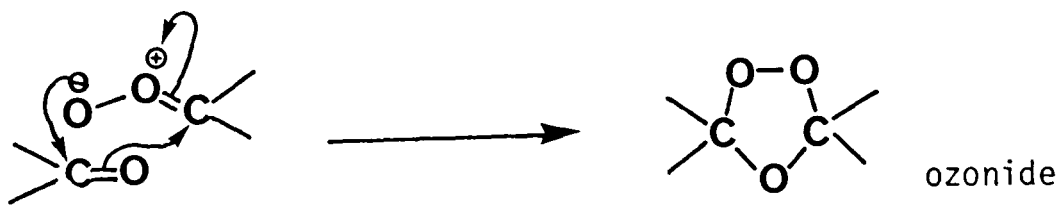


(48)



(49)

carbonyl oxide

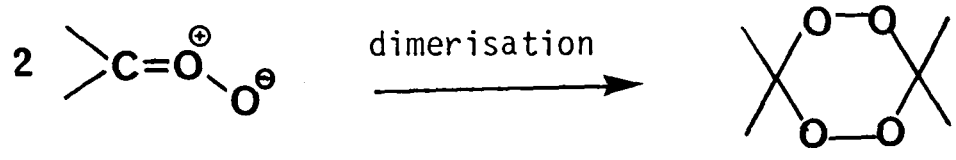


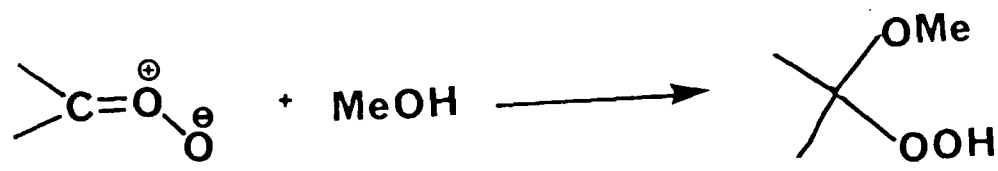
(50)

Ozone adds on to the olefin to form a 1,2,3-trioxolone, known as the primary ozonide (48). This unstable species breaks down into a ketone and a carbonyl oxide (49). The zwitterion may react

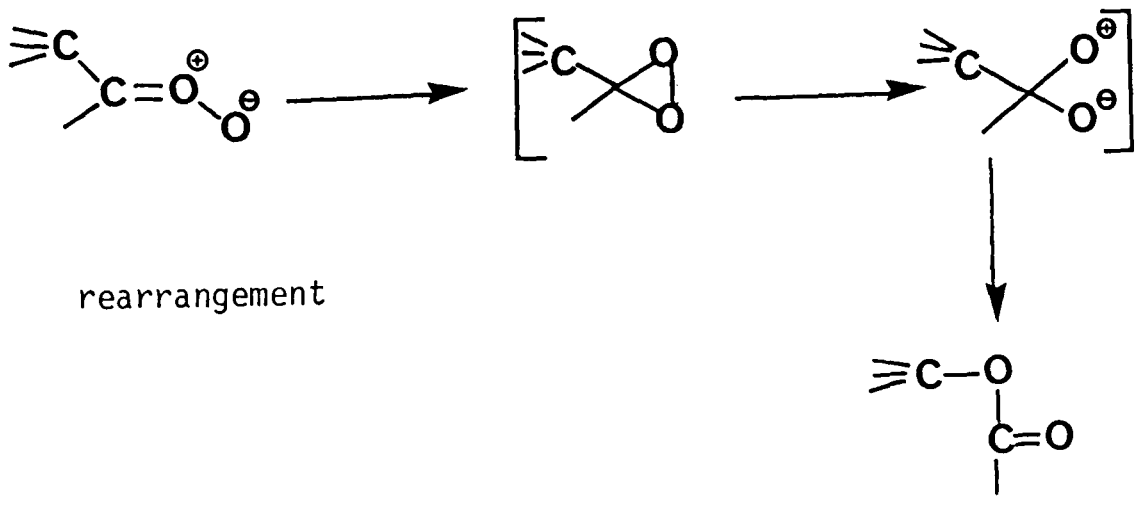
further with a carbonyl compound to give an ozonide (50). This is depicted as being monomeric, having the 1,2,4-trioxolane structure. In compounds possessing tetra-substituted double bonds, oligomeric ozonides may be formed, but little is known about such species.

The reactive carbonyl oxide may also undergo other reactions. For instance, dimerisation reaction with proton active substances such as methanol, or rearrangements in which the adjacent carbon-carbon single bond is cleaved, (vide infra).



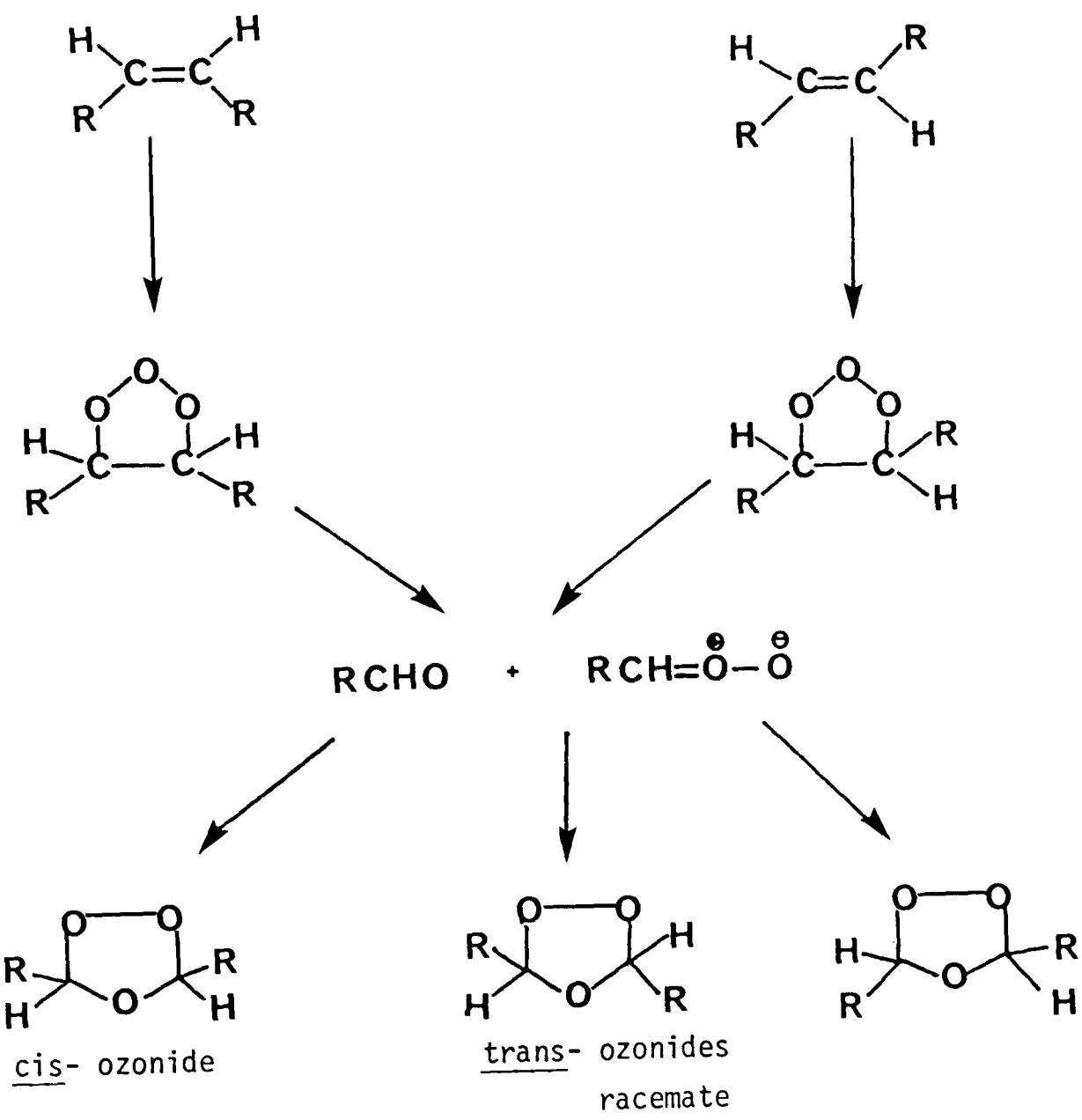


methoxyhydroperoxide



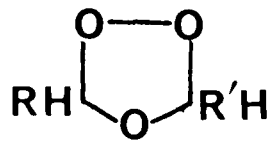
rearrangement

However, this simple Criegee mechanism was unable to explain certain stereochemical features of the resultant ozonides. More precisely, this theory would suggest that there should be no difference in the stereochemistry of ozonides whether they were derived from cis or trans olefins.

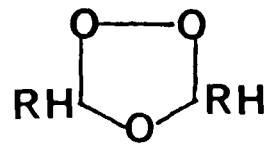


Use of unsymmetrical olefins may yield up to six different ozonides.

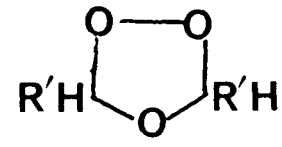
viz:-



cis and trans



cis and trans



cis and trans

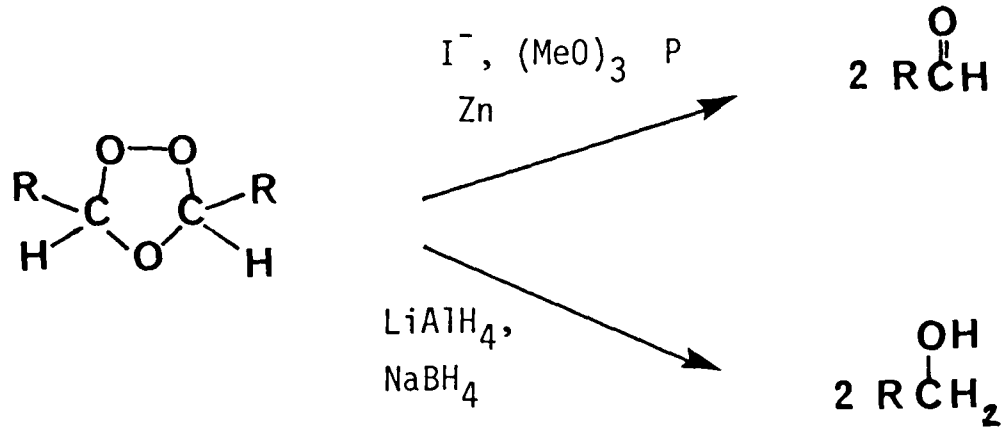
Experimental evidence[166,167] acquired by Schröder and later by Story and Murray have shown that the geometry of the olefin can exert a considerable influence on the composition of the ozonide mixture.

For this reason Story, Murray and Youssefyeh have proposed a working hypothesis or SMY mechanism. However, this has later been shown not to occur to any measurable extent. Bailey and Bauld, and Kuczkowski have forwarded alternative theories to account for these experimental results. These are based on the concept that bulky olefins yield carbonyl oxides which may exist as syn or anti forms. Unequal amounts of these isomers are afforded by the nonplanar primary ozonide precursors. In general, an axial substituent in the primary leads to a syn carbonyl oxide, which in turn affords a trans orientated ozonide.

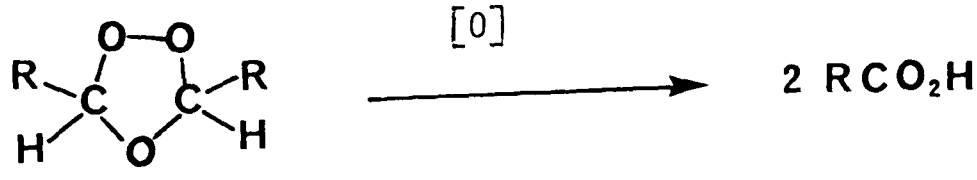
However, recent experimental results cannot be fully rationalised by this syn- and anti-carbonyl concept. Consequently, the actual mechanism of the ozonolysis procedure is believed to involve a further refinement of the Criegee mechanism.

As the exact ozonolytic pathway is unclear at this stage, the original Criegee hypothesis has been adopted in a discussion of this research.

The resultant ozonide may occasionally be stable enough to be isolated. However, more usually it is decomposed by one of the following procedures:- reductive, oxidative, hydrolytic or thermal. The choice of method is dependent upon the type of product desired. For example, reductive decomposition may lead to aldehyde or alcohol functions, depending on the type of reducing agent used.



Oxidative workup with agents such as chromic acid, nitric acid, permanganate, hydrogen peroxide or peracids, give two carboxylic acid groups.

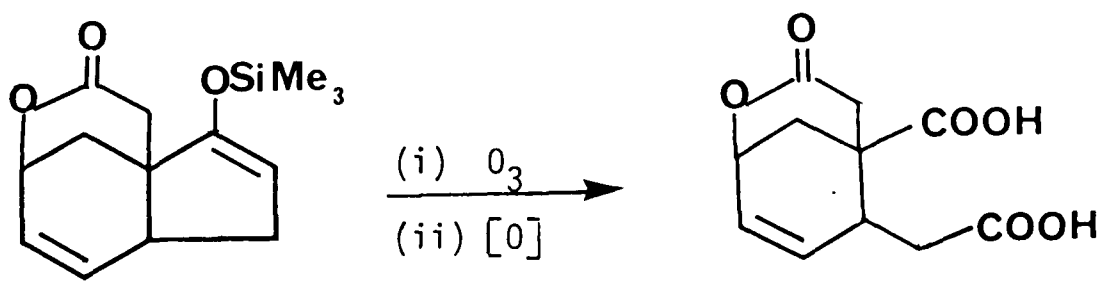


Hydrolysis yields carbonyl groups and pyrolysis may afford a mixture of aldehydes, ketones, carboxylic acids and anomalous products.

In practice, ozonolysis is carried out at low temperatures

of the region of -78°C. This tends to minimise the undesirable side reactions of the carbonyl oxides, favouring a maximum yield of ozonide. Ozone is typically produced in an ozonizer, in which dry air or oxygen is allowed to pass between two electrodes. The application of a high voltage of alternating current produces an alternating ion flow, which results in conversion to ozone.

Returning to the context of this work, the silyl enol ether contains two double bonds. Selective ozonisation of the more nucleophilic siloxyalkene was required in order to effect the transformation into the dicarboxylic acid.



(8) (9)

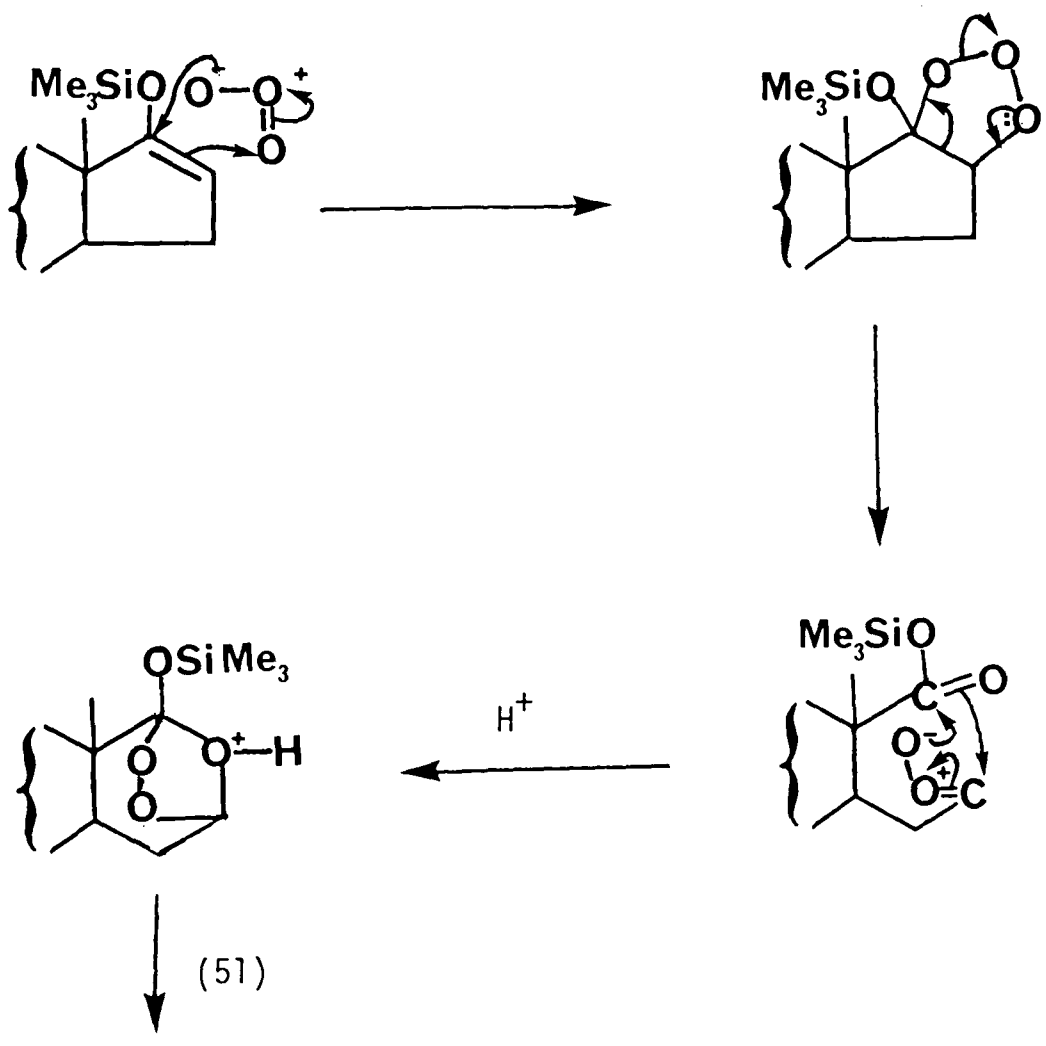
Clark and Heathcock[74] had earlier reported the feasibility of such a process, in their synthesis of the oxadecalone discussed earlier (see Chapter I p40). This was achieved by carefully monitoring the amount of ozone added.

A variety of solvents have been employed in ozonolysis ranging from pentane to water. For the first attempt at this procedure, acetone was chosen. Although it is not one of the most commonly employed solvents, there are excellent literature reports[169] of its use, and it would be a convenient medium in which to perform the subsequent Jones oxidation.

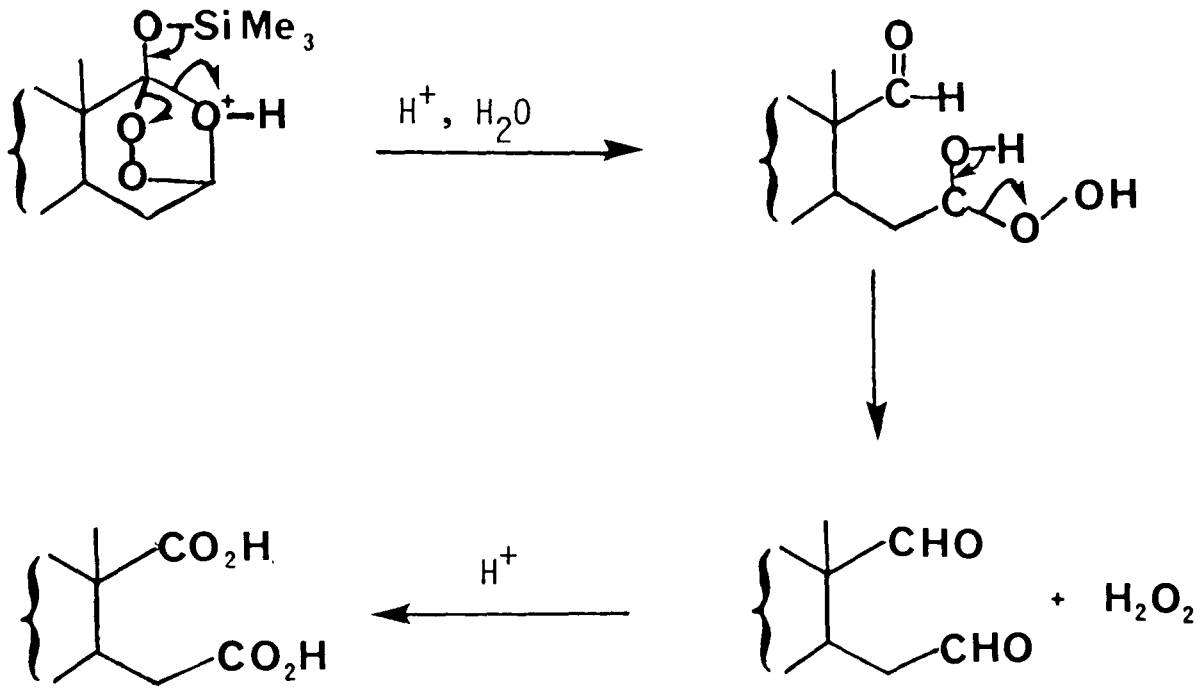
To begin with, ozonolysis was carried out with the O-sily-

lated enolate of cyclohexanone. A 76% yield of adipic acid was isolated.

With success in hand, the method was repeated with the silyl enol ether needed in the synthesis. Unfortunately in both of the fractions isolated from purification, no double bond could be located by n.m.r. Obviously cleavage of both olefinic functions must have occurred. Therefore, in the subsequent run ozone was added over one minute periods. After each addition, the reaction mixture was analysed by t.l.c. This was continued until the starting material had just disappeared. In this way it was possible to effect cleavage of the enol double bond whilst leaving the other double bond intact. Oxidative workup, followed by purification afforded the elusive dicarboxylic acid in 73% yield. In accord with Criegee's mechanism, the proposed reaction pathway is illustrated below:-



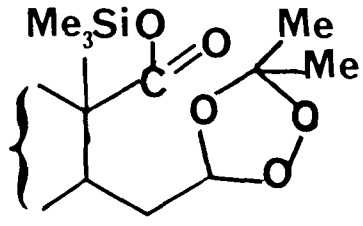
(51)



(9)

Decomposition of the ozonide (51) is believed to result from attack at the ether linkage, which is well-known under hydrolytic conditions. As is apparent, hydrogen peroxide is produced as a by-product. Consequently, during the workup procedure, when the reaction mixture was evaporated to dryness, low temperatures were employed.

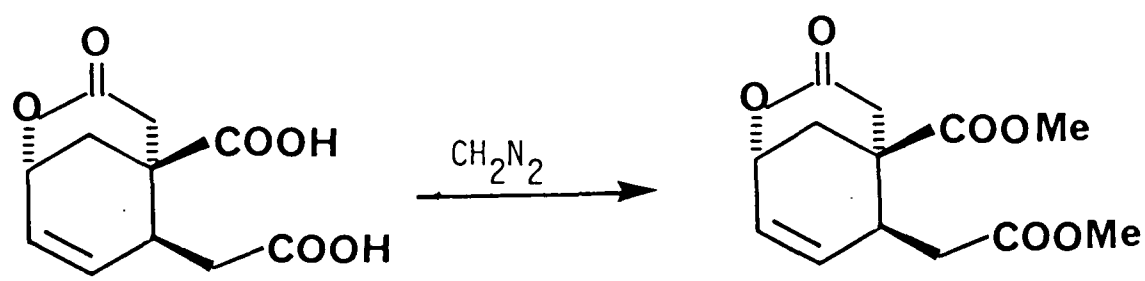
In addition, as acetone was used as solvent, this carbonyl function could theoretically compete for the carbonyl oxide moiety. Therefore, ozonides of the nature of (52) may be expected to be formed. However, Criegee[168] has stated that intramolecular reactions



(52)

are far more preferred than an intermolecular process. Indeed,this has been verified by the high yield of dicarboxylic acid obtained.

Characterisation by i.r. gave a strong, broad peak at 3500-3300cm^{-1} indicative of a carboxylic acid which was confirmed by a strong absorption at 1720 cm^{-1}. Further confirmation by n.m.r. analysis indicated two exchangeable protons at δ10.0, consistent with carboxylic acid functions, and the usual double bond and H-5 (H-6, in the precursor numbering system) signals at δ6.1 and δ4.8. Alkyl protons occurred in the range δ3.0-2.1. Although the mass spectrum tallied with the proposed structure, an accurate mass determination of the molecular ion was not possible, due to its extremely low relative abundance. Consequently, rigorous proof was obtained by conversion into the dimethyl ester.



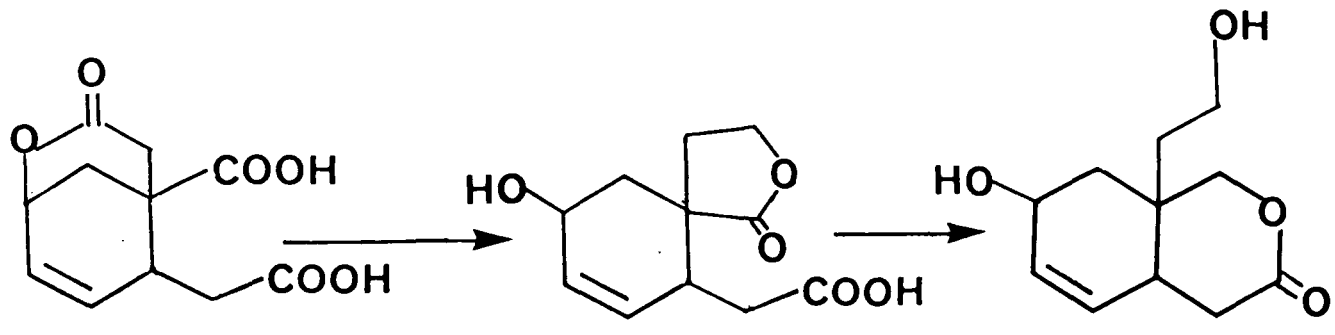
(9) (53)

This facile process simply involved the addition of an ethereal solution of diazomethane to a solution of the di-acid in THF. Although an almost quantitative yield of product would have been envisaged only 51% of the dimethyl ester was isolated. This was largely due to its thermal instability which was apparent by application of the heat involved in evaporation of the solvent. A shift in carbonyl absorption to 1742 cm^{-1} was consistent with the dimethyl ester analogue. In addition, the double bond stretch was now visible at 1648 cm^{-1}. The disappearance of the two carboxylic acid signals in the n.m.r. was met by the appearance of two ester resonances at δ3.73 and δ3.67, which integrated to a total of six protons. These

results corroborated the presence of dimethyl ester which in turn validated the dicarboxylic acid (9).

III.7. FORMATION OF THE 2-OXA-3-DECALONE (11)

The concluding phase of the synthesis constituted conversion of the dicarboxylic acid (9) into the 2-oxa-3-decalone derivative (11).

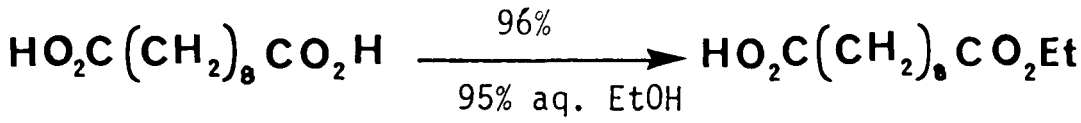


(9) (10) (11)

This involved differentiation between the two carboxylic acid functions of (9).

Carboxylic acid groups are conventionally differentiated by monoesterification. Babler and May[170] have recently optimised a procedure allowing 96% conversion to ethyl sebacate.

viz:-



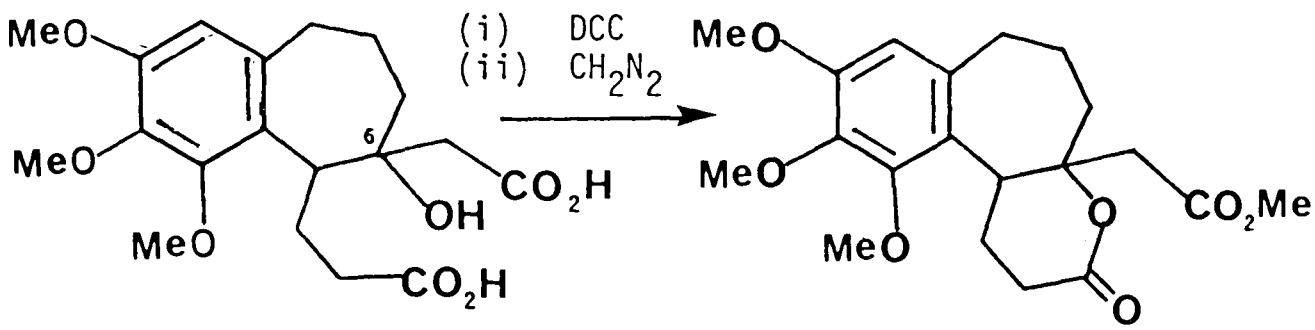
sebacic acid ethyl sebacate

The monoester was removed from the aqueous mixture by continuous extraction with cyclohexane, (in which sebacic acid is virtually insoluble), before it could be converted to the corresponding diester.

However, in the case in hand, it would be difficult to predict which of the acid groups would be more susceptible to mono-

esterification of this nature.

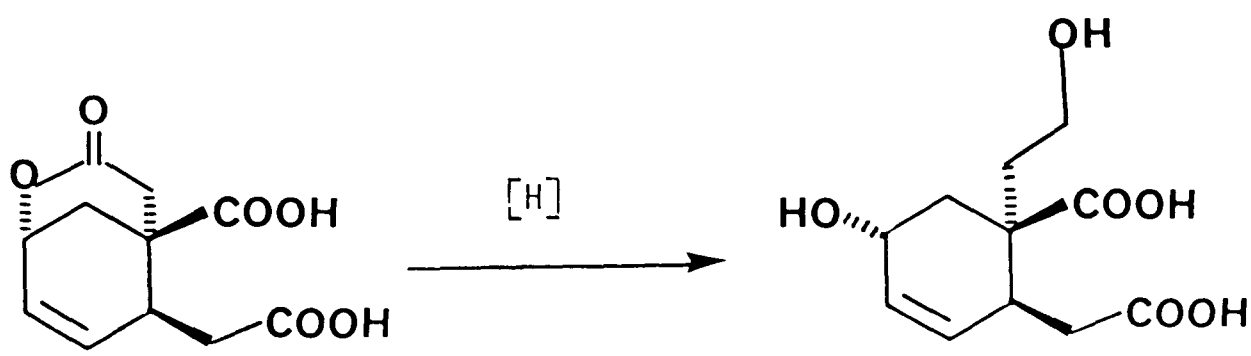
Van Tamelen et al.[80] have documented a synthesis of colchicine in which an intermediate stage involves differentiation between two carboxylic acid functions.



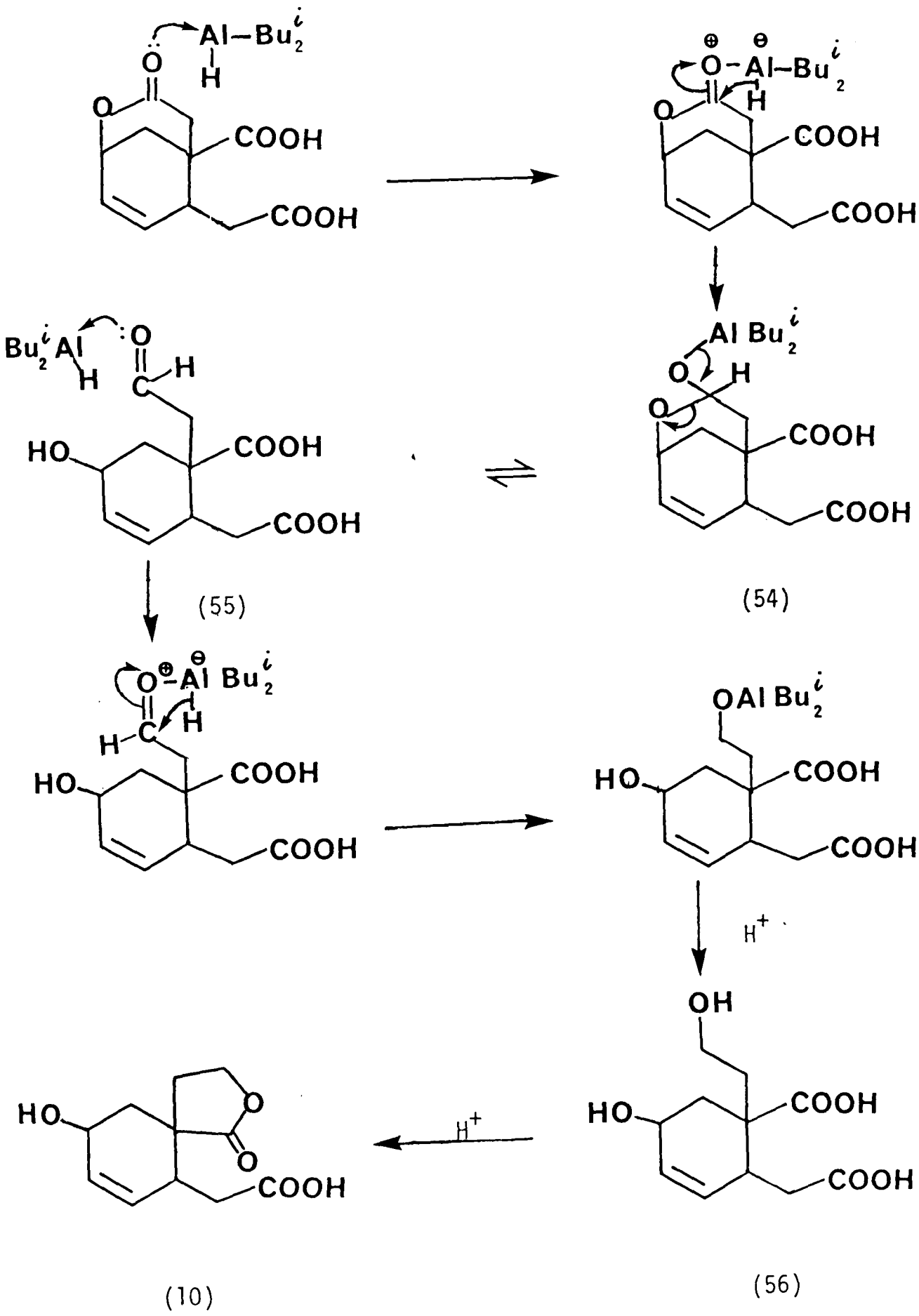
Although this was achieved, the purpose of the transformation was protection of the tertiary hydroxy function at C-6, which would otherwise interfere with the intended subsequent acyloin condensation.

Within the context of the work, chemodifferentiation was planned by similarly converting one of the acid groups into a lactone, followed by reduction.

Initially, a reagent was required that would selectively effect reduction of the δ-lactone into a primary alcohol, in the presence of carboxylic and olefinic functions.



Diisobutylaluminium hydride[171] appeared to be appropriate. It has been used extensively in natural product synthesis and is commercially available in solution with various solvents. The reaction is believed to proceed via the lactol, by electrophilic addition to the carbonyl group. The mechanism is illustrated for the case in hand.

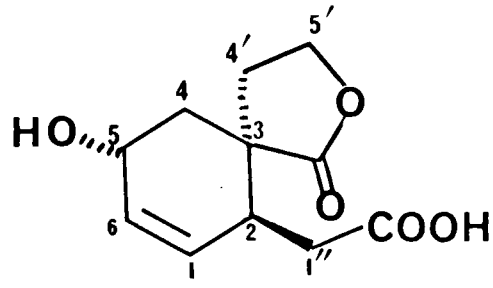


Equilibration between the lactol derivative (54) and the hydroxyaldehyde (55) is well known. This would allow attack by a second molecule of the reducing agent, and acid treatment would liberate the lactone (10) via the dihydroxydicarboxylic acid (56).

Consequently, it would appear that a two-fold excess of diisobutylaluminium hydride was required.

In the event, a solution of the hydride in THF was added to the dicarboxylic acid in THF at -78^{o}C. T.l.c. analysis indicated complete disappearance of the starting material after 45 min. The reaction mixture was, accordingly, subjected to an acidic workup. However, spectral analysis of the crude product, suggested predominantly starting material. In retrospect this is not surprising, as the carboxylic acid functions would be expected to form a complex with the aluminium species.

In the subsequent attempt, a five-fold excess of diisobutylaluminium hydride was employed to overcome the problem. The reaction was allowed to continue for five hours, whereupon the mixture was treated in the normal way. Purification of the crude product gave a compound that was tentatively assigned as the spirolactone (10). Confirmatory evidence was gained by i.r. in the appearance of an absorption at 1780 cm^{-1}, which is typical of a γ-lactone. A peak at 1720 cm^{-1} was indicative of a carboxylic acid group which also manifested itself at 3170 cm^{-1}. A weak hydroxy absorption was present at 3540 and the olefinic stretch appeared at 1650 cm^{-1}. With regard to n.m.r. analysis H-1 and H-6 were located at δ5.9.

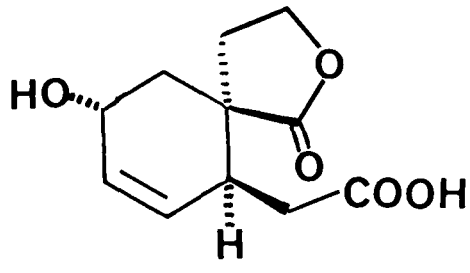


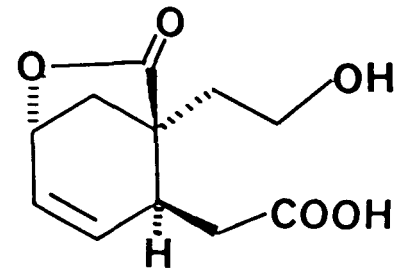
(10)

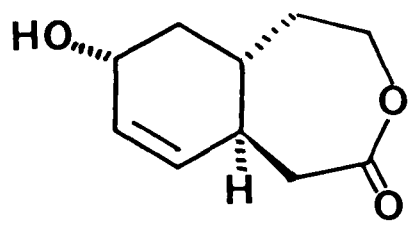
The one proton multiplet at δ4.8 was assigned to H-5 although it was expected that this proton would appear at a higher field than in the δ-lactone precursor, where it also occurs at δ4.8. On the other hand, this is the normal chemical shift for a proton sited at an allylic position, geminal to a hydroxy group. The two proton signals at δ4.15 can be accredited to the two H-5' protons in the γ-lactone moiety. A multiplet at δ3.6 is due to the allylic proton at C-2. Although this is an uncommonly low field for this type of proton, the stereochemistry of the molecule may be exerting a deshielding effect on H-5. Complex signals are observed in the range δ2.7-2.2 which could be accounted for by 2H-4, 2H-4' and 2H-1". An exchangeable proton appeared at δ2.1, which was probably due to the hydroxy proton. No carboxylic acid proton could be located in the spectrum. However,this is not unknown.

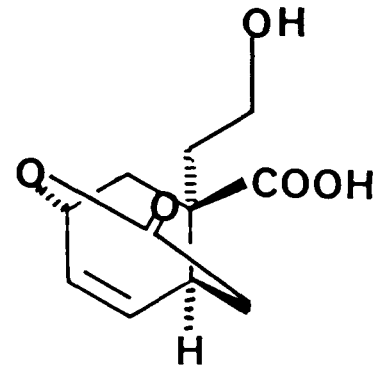
Consequently, evidence would point towards the spirolactone structure.

Acid treatment of the dihydroxydicarboxylic acid may have theoretically given a number of lactones. An examination of molecular models has indicated the spirolactone to be the least strained possibility. This reinforces the evidence for the tentative assign-





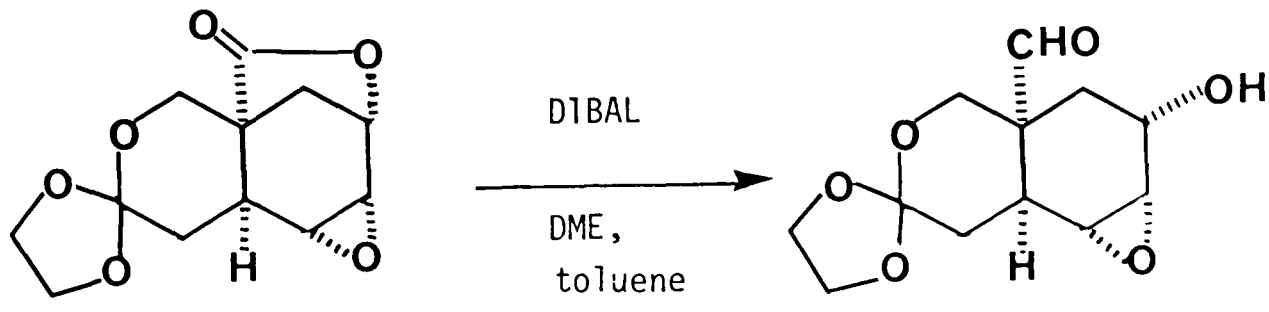




ment of (10).

Two successive attempts at this procedure were not successful, with mainly starting material being isolated in both cases.

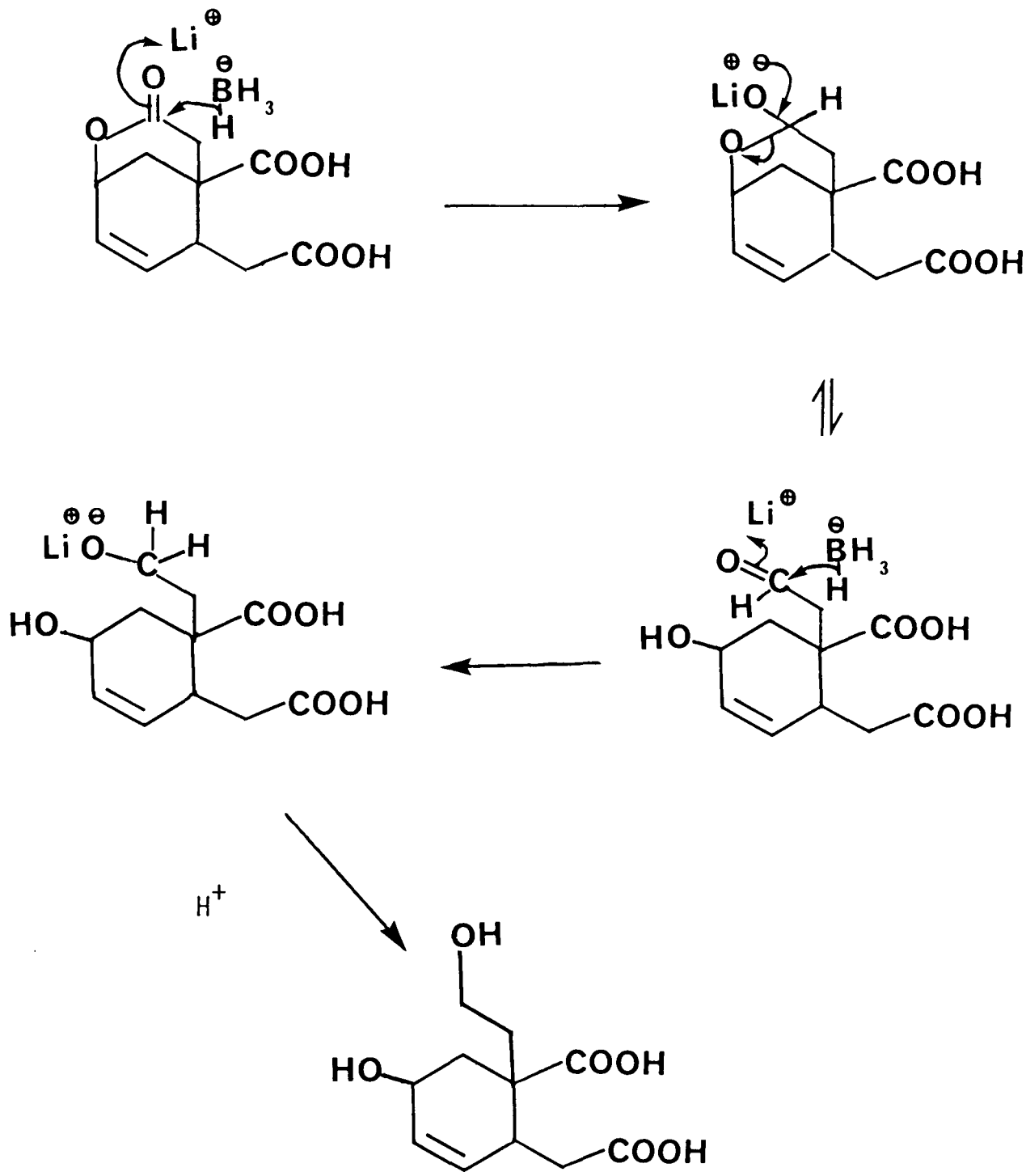
In their total synthesis of vernolepin, Danishefsky et al[44] have reported reduction of a lactone, with a diisobutylaluminium hydride, to the hydroxyaldehyde.



In this procedure the reducing agent was administered in portions over 20 minute intervals. Thus, starting with 1.5 excess of hydride, successive amounts of 0.8, 0.6 and 0.4 were added over the following hour.

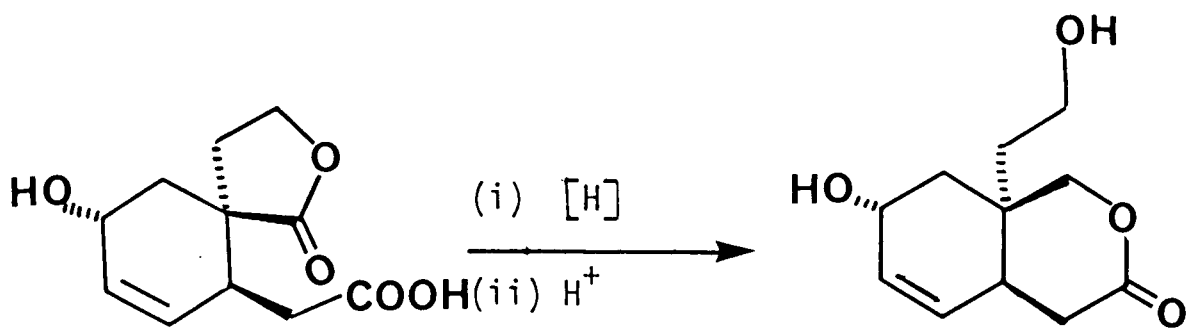
Accordingly, this method was adopted with the dicarboxylic acid. In this case the reaction was commenced with a 3.5 fold excess of diisobutylaluminium hydride, to allow for complexation with the two acid groups. After the prescribed addition a further equivalent of hydride was introduced to effect reduction to the alcohol. Acidic workup afforded a crude production which exhibited no absorption in the 1780 cm^{-1} region. Consequently the spirolactone could not have been formed. Additionally an n.m.r. was not consistent with starting material or, for that matter, hydroxyaldehyde.

Lithium borohydride[172] also selectively reduces lactones in the presence of olefinic and acid functions. Consequently, the dicarboxylic acid was reacted with this reagent. Purification of the crude product gave a compound with similar spectral characteristics to those described earlier for the tentatively assigned spirolactone (10). Confirmation of the structure was sought by conversion to the methyl ester (10a) by treatment with diazomethane. Indeed, a shift in carbonyl absorption was noted to 1735 cm^{-1}. Hydroxy, γ-lactone and olefinic peaks were still apparent. A three proton methyl ester signal was also located in the n.m.r. which occurred together with H-2, at δ3.7, as expected. Lithium borohydride functions as a nucleophilic reducing agent, and is believed to act as illustrated in the following mechanism.



(56)

Consequently, although evidence was in favour of the spirolactone, there was by no means concrete proof of the structure. One ultimate way of confirmation was by transformation into the 2 oxa-3-decalone derivative (11). The route simply entailed a repeated selective reduction of the lactone moiety, and subsequent acid catalysed cyclisation.



(10) (11)

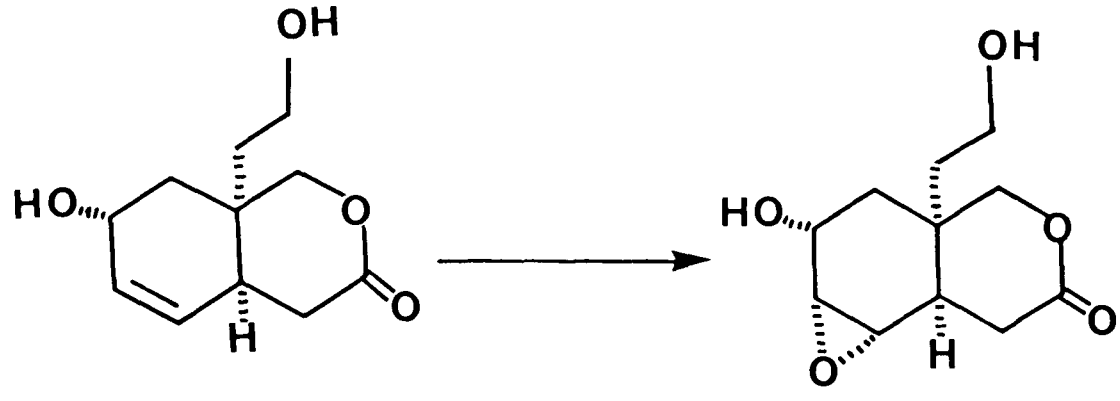
A crude mixture obtained by an analogous lithium borohydride reduction of the proposed spirolactone, was mainly composed of starting material. This was clearly demonstrated by the presence of γ-lactone and carboxylic acid absorptions in the i.r. The desired product would exhibit a characteristic δ-lactone absorption at 1740 cm^{-1}. A similar result was obtained by heating (10) under reflux with the borohydride.

The required transformation was eventually accomplished by reaction with diisobutylaluminium hydride,using the aforementioned procedure adopted by Danishefsky. A 45% yield of the desired 2-oxa-3-decalone (11) was obtained, which displayed spectral characteristics in keeping with the proposed structure.

In conclusion, a novel procedure has been developed for the differentiation between two equivalent carboxylic acid functions.

III.8. PROPOSALS FOR FURTHER WORK

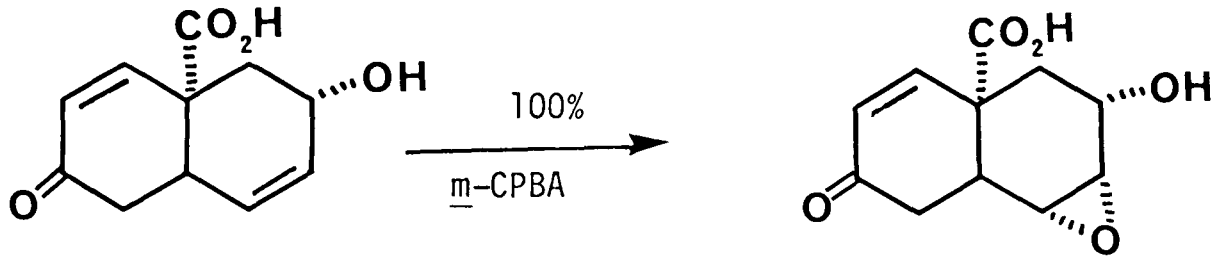
To conclude the synthesis of the common intermediate, epoxidation of the oxa-decalone derivative is required.



(11) (1)

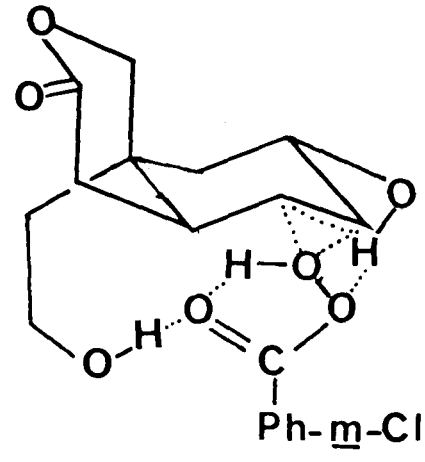
This was not attempted in the research due to a lack of starting material. The preparation of further amounts of (11) would enable this reaction to be carried out.

This step has been achieved in both Danishefsky's[44] and Schlessinger's[54] synthesis of vernolepin, described earlier. For example:-



Electrophilic attack by the peracid is believed to be directed by the allylic alcohol by hydrogen bonding. The optimum geometry for this epoxidation transition state is suggested to be one in which

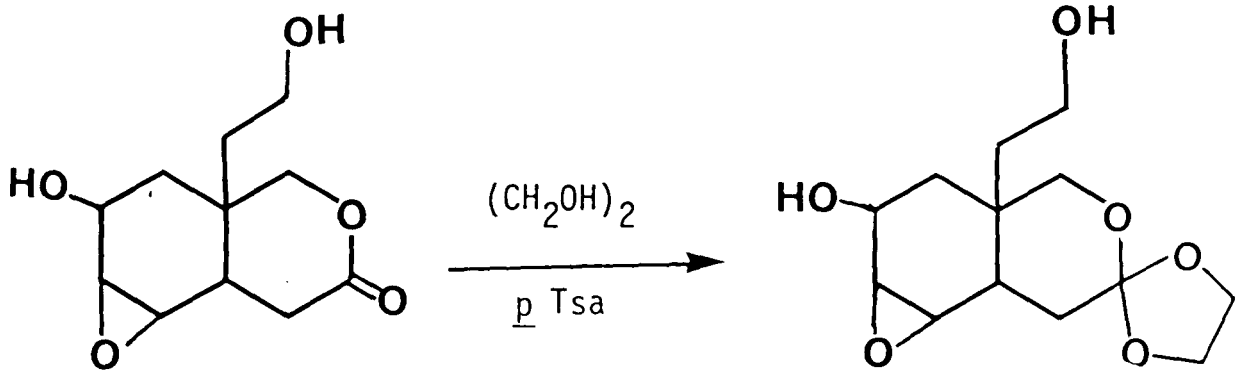
the hydroxy group has adopted a pseudoequatorial position. This conformer is illustrated for the 2-oxadecalone (11). In addition, hydrogen bonding by the hydroxyethyl function may aid this process.



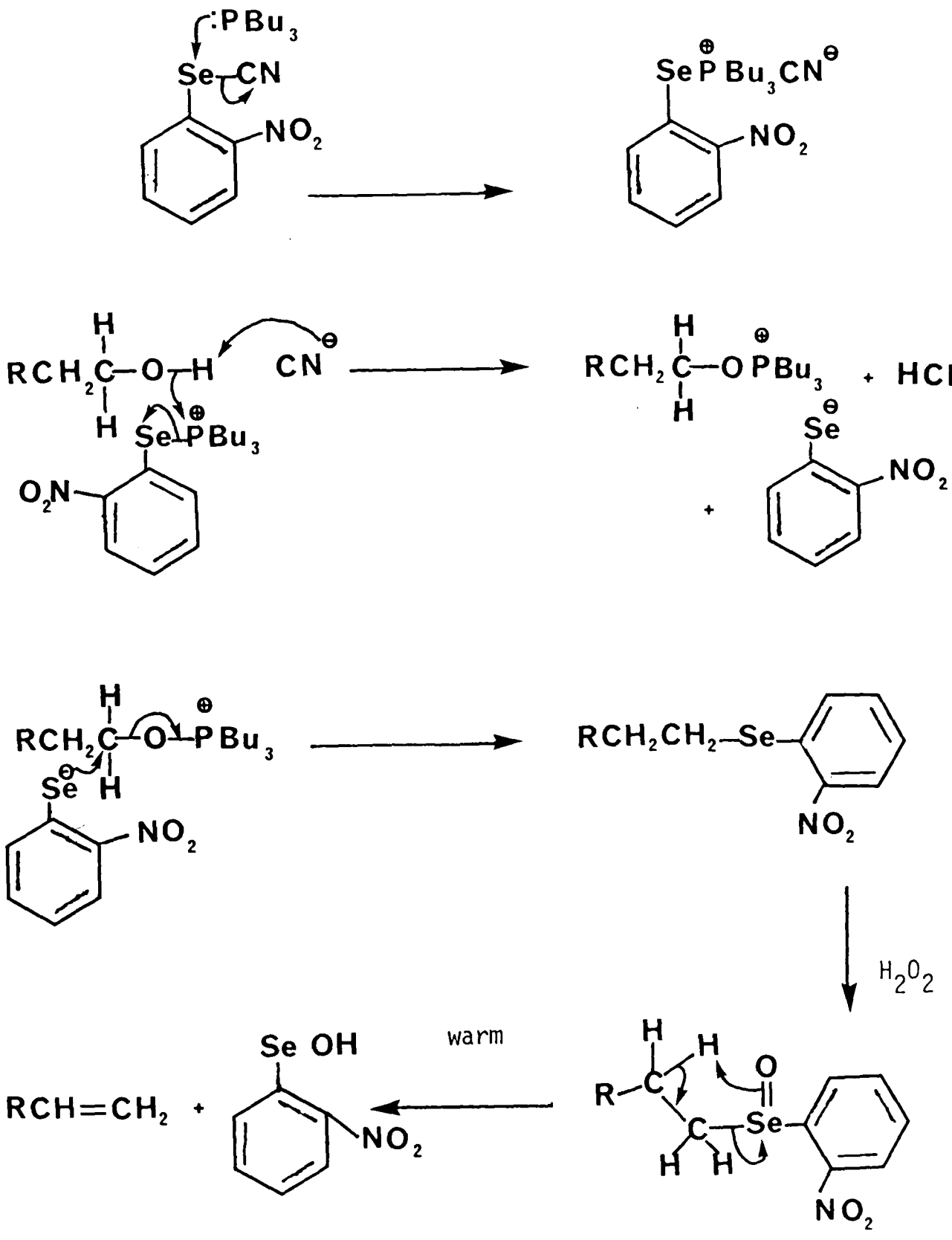
Vandewalle et al.[56] have isolated a mixture of epoxides by reaction of their intermediate with a peracid, (see Chapter I p37). However, these authors have reported that by initially protecting the δ-lactone, the desired α-epoxide may be stereospecifically obtained.

Accordingly, if a similar problem arose in the synthesis of the intermediate (1), protection would be the answer.

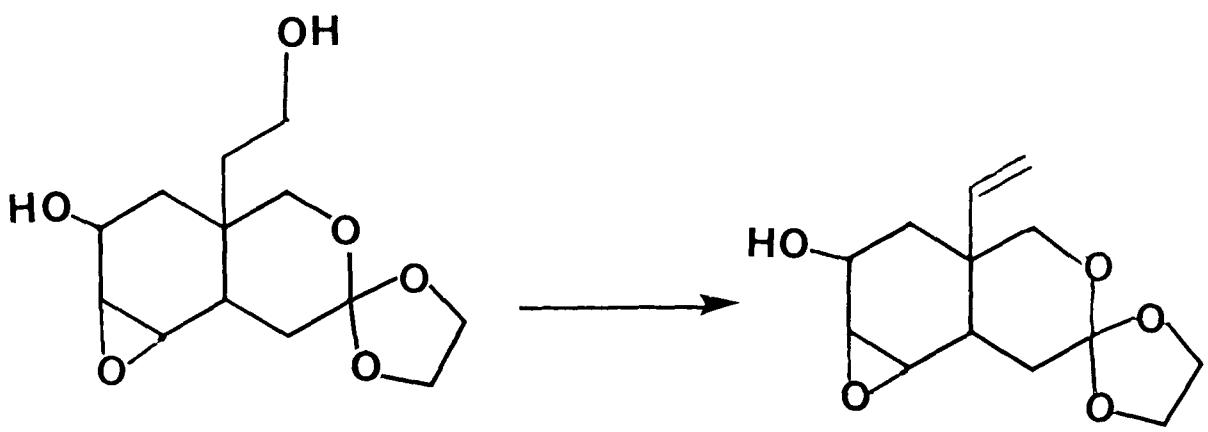
Two further transformations would be required to reach an intermediate that would tie in with Danishefsky's synthesis of vernolepin. The first step would simply involve protection of the δ-lactone as the ketal.



The second step constitutes conversion of the hydroxyethyl moiety into an angular vinyl substituent. This could be carried out by an analagous procedure to that employed by Grieco et al.[37] in their synthesis of vernolepin. This involves preparation of the o-nitrophenyl selenide, followed by oxidation and subsequent elimination. An overall yield of 81% has been reported for this process (vide infra).



Thus,



(12)

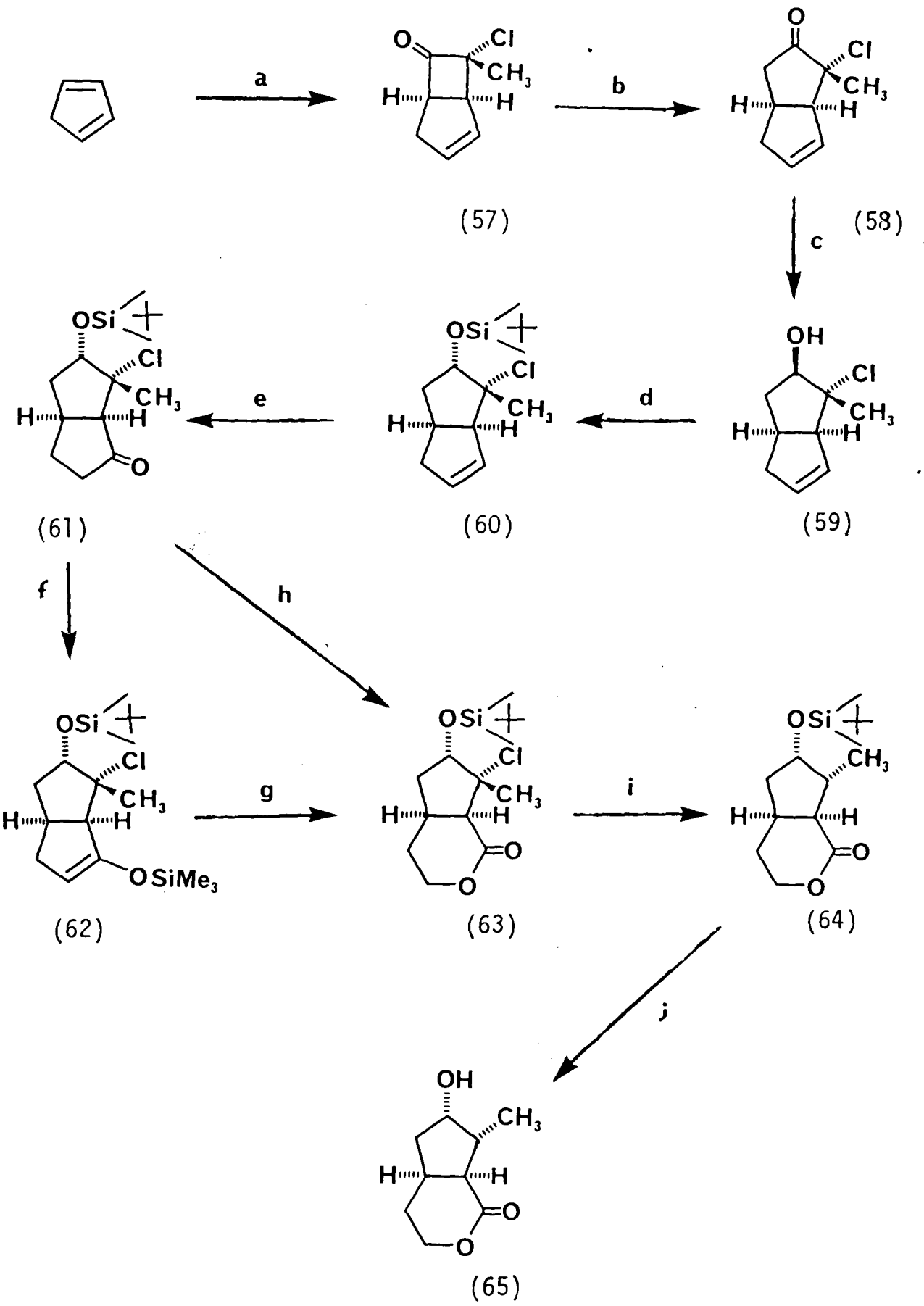
Danishefky's intermediate

The total synthesis of vernolepin would then be accomplished in a total of 18 steps, the shortest route so far reported.

CHAPTER IV

BOONEIN

Total synthesis of (±) -boonein (65)



Scheme 4

a, $Cl(CH_3)\ C{=}C{=}O$; b, CH_2N_2; c, $LiAlH_4$; d, Me_2Bu^tSiCl, $(Me_2CH)_2\ NEt$; e, BH_3, THF, H_2O_2, NaOH, Jones reagent; f, LDA, Me_3SiCl; g, O_3, $NaBH_4$; h, mCPBA; i, Bu_3SnH, azobisisobutyronitrile; j, AcOH, THF, water.

The total synthesis of boonein is summarised in Scheme 4.

A thermal [2+2] cycloaddition of methylchloroketone and cyclopentadiene formed the adduct (57), which was subjected to ring expansion to give the bicyclo [3.3.0] oct-2-en-7-one (58.) Reduction of the ketone gave predominantly the exo-alcohol, which was protected in the form of the t-butyldimethylsilyl ether. Reduction of the double bond and oxidation of the intermediate alkylborane afforded (61) regioselectively. The lactone was obtained by either Baeyer-Villiger oxidation, or via ozonolytic cleavage of the corresponding O-silylated enolate. Dechlorination and subsequent deprotection gave racemic boonein (65).

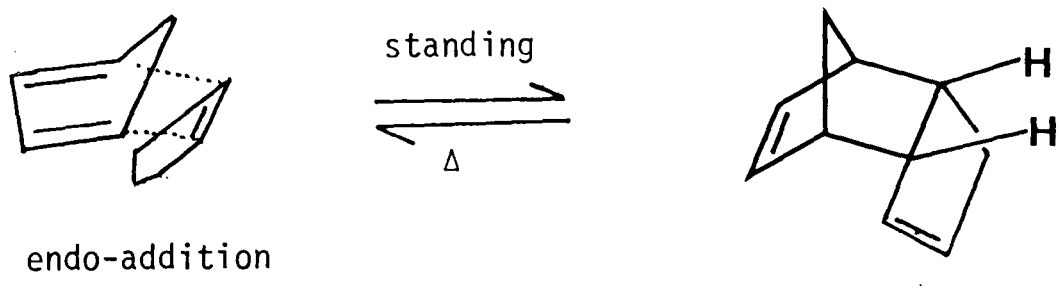
The synthetic route therefore involved eight or nine facile steps, depending on the route of oxidation. This provided boonein in overall yields of 3 or 1% respectively, from cyclopentadiene.

IV.1. FORMATION OF THE BICYCLIC [3.3.0] KETONE (58)

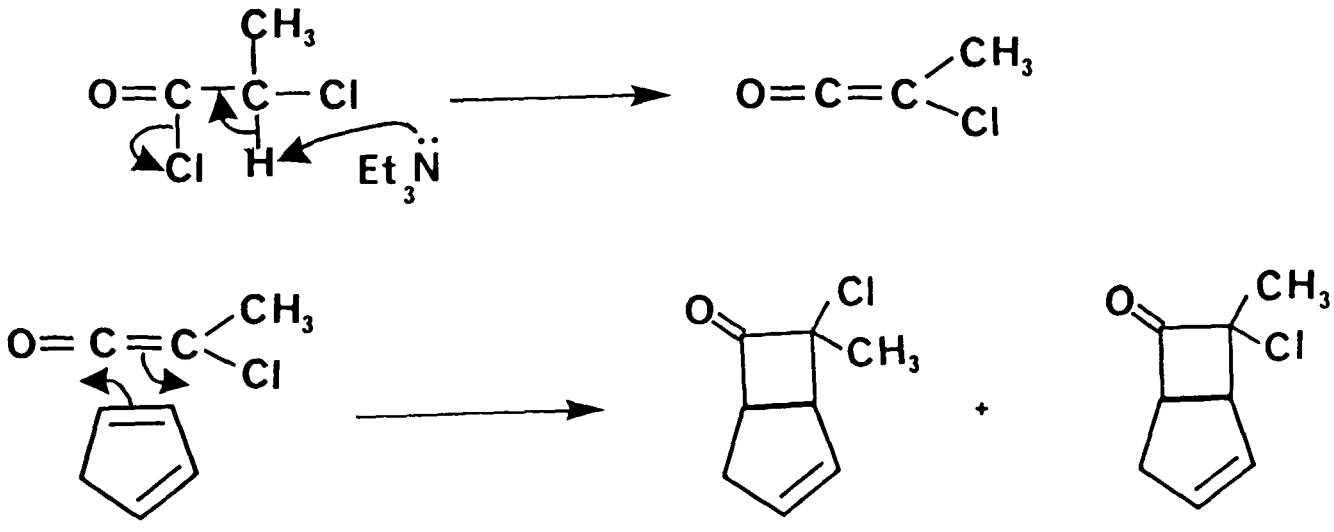
(a) [2+2] CYCLOADDITION

Cycloaddition between ketenes and olefin derivatives offers a simple route to functionally substituted four membered rings. These adducts have been used as valuable precursors in several syntheses.

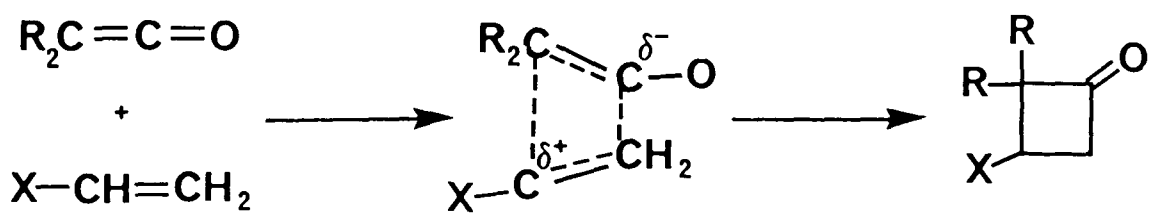
In the boonein synthesis, a cycloaddition was performed between methylchloroketene and cyclopentadiene.[95] The latter was prepared by thermally cracking the commercially available dimer. The diene must be used directly as it slowly redimerizes on standing.



Methylchloroketene was generated *in situ* from α-chloropropionyl chloride and triethylamine. The reaction was carried out in darkness so as to minimise ketene dimerization. The isomeric bicycloheptenones were isolated by distillation of the crude product.

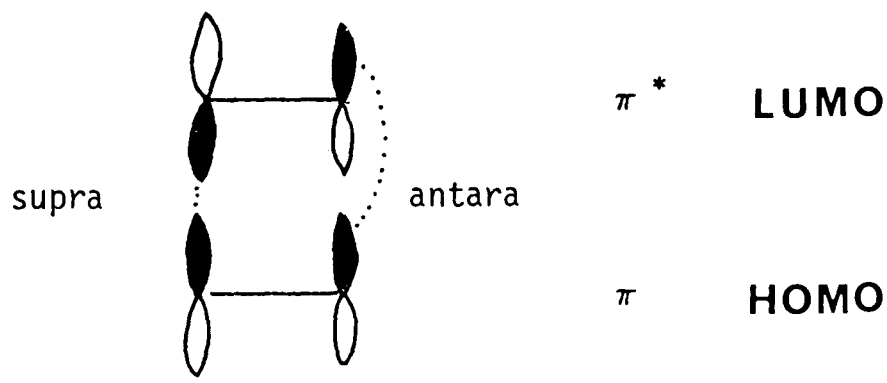


The reaction is entirely regiospecific. This can be explained as the olefin acting as a nucleophile and therefore in the transition state it must bear a partially positive charge. The maximisation of charge separation in the transition state results in only one regioisomer being formed.



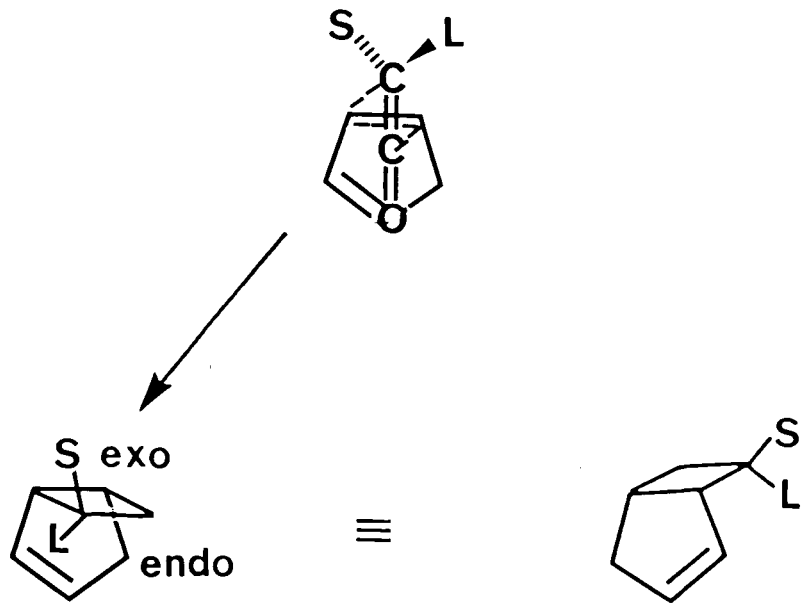
The depicted transition state assumes a concerted process. This is generally believed to be the case in the [2+2] cycloaddition. Accordingly, the Woodward and Hoffmann rules apply for the conservation of orbital symmetry. These state that the process is allowed when the addition is suprafacial with respect to one component and antarafacial to the other, (see Chapter III p73). As illustrated for the dimerization of ethene,antarafacial addition is geometrically unlikely.

Thermal [2+2] cycloaddition of ethene



However, the geometric restrictions can be overcome by ketenes in their additions to olefins. The ketene approaches cyclopentadiene (173) with its functional plane perpendicular to the π-plane of the diene.

The larger of the two ketene substituents is orientated preferentially away from the ring. Consequently, in the cycloadduct an endo-position is adopted.



As there is only a relatively small difference in the Van der Waals radius between the methyl and chlorine groups, 2.0 and 1.8 Å respectively, a mixture of stereoisomers was obtained. A 4:1 ratio in favour of the desired 7-endo-methyl isomer was recorded, in agreement with the previous findings of Drieding.[95] The two isomers were

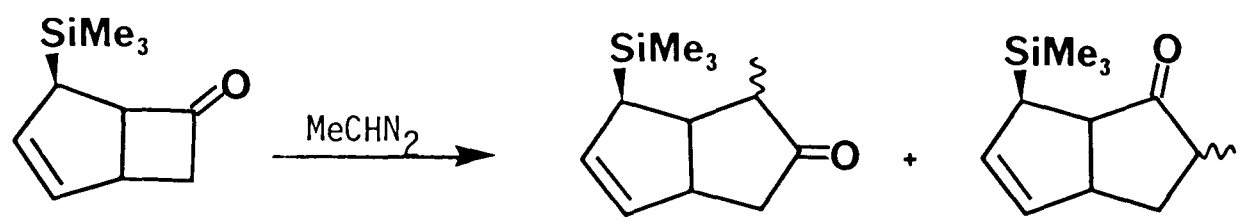
readily distinguishable as the methyl group appeared at the higher field of δ1.5 when in the endo configuration, compared to δ1.7 in the exo orientation, (66).

Spectral data, for these two compounds, were in accordance with that reported in the literature.

(b) RING EXPANSION

One of the most direct routes for the ring expansion of cyclic ketones involves using diazo compounds.

The α-chloro substituent in the bicyclo [3.2.0] system exerts a directing effect on the process, which would otherwise give a mixture of regioisomers. This is exemplified by ring expansion of an intermediate employed in Fleming's synthesis[94,174] of loganin aglucone, mentioned earlier.

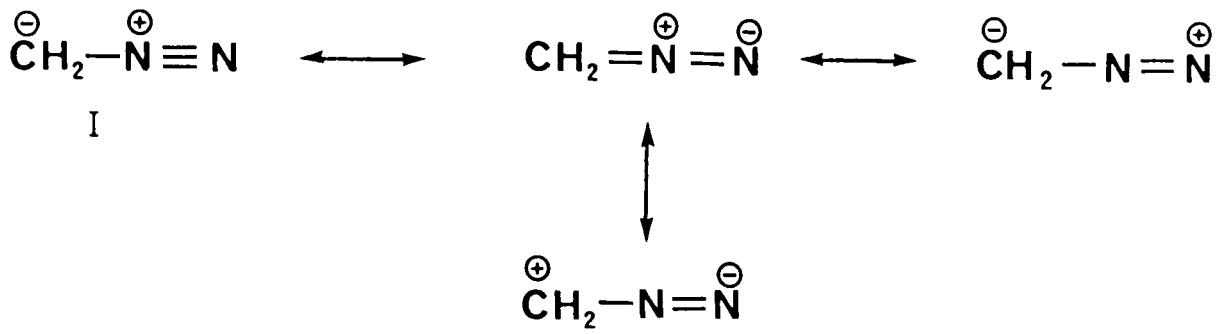


42% 37%

The mixture of isomers was only slightly in favour of migration of the more substituted carbon. However, this problem was obviated by the use of an α-haloketone in an analogous fashion to the synthesis under discussion.

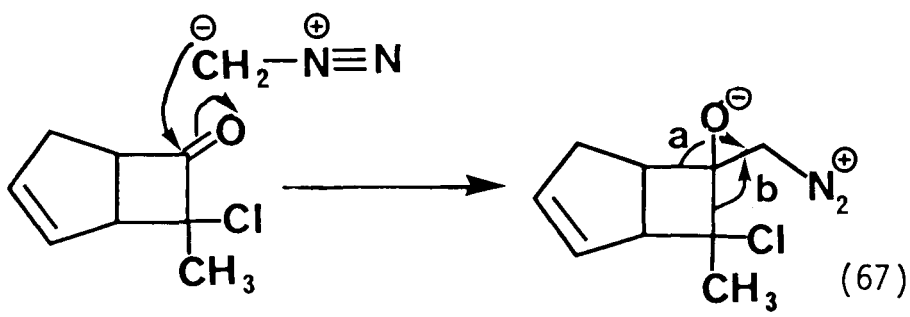
The directing influence of an α-halo substituent was also reported by Greene and Duprés.[175] These authors have found that α, α-dichlorocyclobutanones undergo highly regioselective one carbon ring expansions with diazomethane to produce α, α-dichlorocyclopentanones in good yields. This method has since been extended for α-mono-bromo and α-acetoxy ketones.[176]

The reaction is a 1,2-nucleophilic rearrangement involving a charge separated intermediate. The structure of diazomethane may be represented by the following valence tautomers.[177]

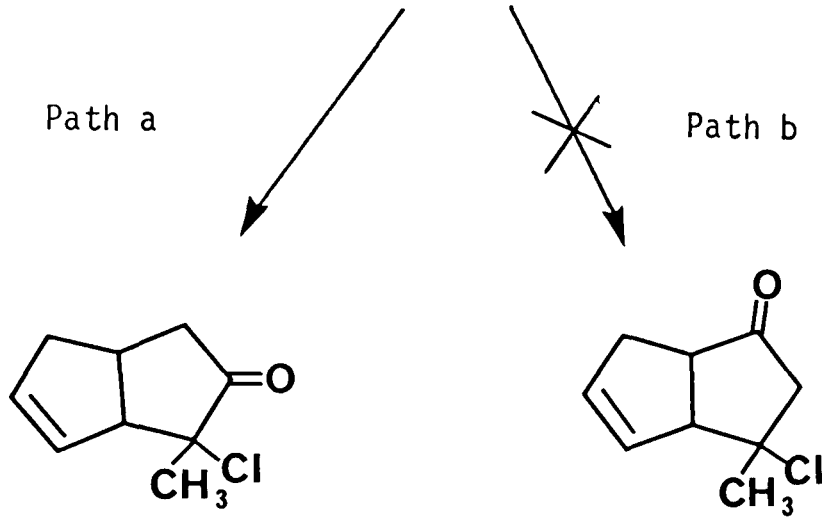


I

Structure I is best suited for the purpose in hand. Nucleophilic addition at the carbonyl group gives the intermediate (67).



(67)



Two migratory paths are then possible. The electron withdrawing effect of the α-chloro substituent was found to completely suppress migration of the carbon bearing it, thus favouring path a over path b. Indeed, none of the undesired regioisomer was isolated. The electronic effect of the halogen also serves to accelerate the reaction. From the scheme it is apparent that the oxygen atom could act as an intramolecular nucleophile, resulting in epoxidation. How-

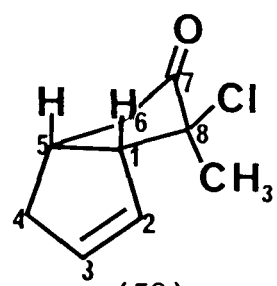
ever it has been found by others that this is inconsequential, and none of the corresponding product was obtained during the course of this work.

The reaction was carried out using the conditions reported by Greene and Duprés.[175] Thus, successive addition of a 1.6 fold excess of ethereal diazomethane and methanol to the substrate, and allowing the reaction to continue for 20 minutes gave the product. Presumably, the addition of methanol was to catalyse the diazomethane-carbonyl reaction,[178] by activating the carbonyl carbon to nucleophilic attack by the diazoalkane. Another effect of such catalysts is to reduce the amount of epoxide that is formed, by decreasing the ability of the oxygen to act as an intramolecular nucleophile.

T.l.c. analysis of the crude mixture suggested incomplete conversion to the ring expanded homologue. This was borne out by the appearance of two carbonyl absorptions at 1780 cm^{-1} and 1750 cm^{-1} in the i.r. This reflects the diminished activity of the monochloroketone compared to the dichloro analogue.

In a repeat of the above method, a substantial amount of starting material remained after a reaction time of 4 hours. Consequently, in the subsequent attempt, a 2.0 fold excess of diazomethane was employed. The reaction was quenched after 2 hours and an i.r. of the crude product exhibited three carbonyl absorptions at 1780 cm^{-1}, 1750 cm^{-1}, 1720 cm^{-1}. This would indicate formation of the bicyclo [4.3.0] (58a) homologue. Although the occurrence of higher homologues is well known in the presence of excess diazomethane, the persistent appearance of starting material in the crude product was unexplicable, as a consideration of the strained nature of the four-membered ring would suggest rapid ring expansion to the cyclopentanone adduct. I.r. analysis indicated the optimum conditions for the formation of the

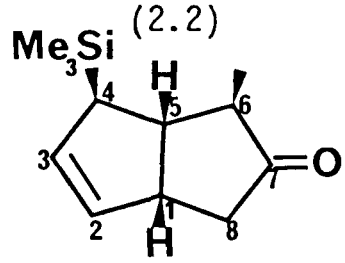
desired bicyclo [3.3.0] system were obtained by utilisation of a 1.8 fold excess of diazomethane and a reaction time of 2 hours. The crude product thus isolated contained the following yields of bicycloketones:- [3.2.0], 15%, [3.3.0], 79%, [4.3.0], 6%, as determined by g.l.c. Notable features of the n.m.r. of the adduct (58) included a considerable



(58)

upfield shift of H-5 from δ4.5 in the precursor to δ3.0. H-1 also appeared at a higher field of δ3.6. This compared with δ3.9 in the precursor. An increase in shielding is well known in ring expansion from a cyclobutanone to a cyclopentanone derivative. Confirmatory evidence for the assignment of H-1 may be obtained by a comparison with Fleming's intermediate[94] (vide infra).

(2.2)



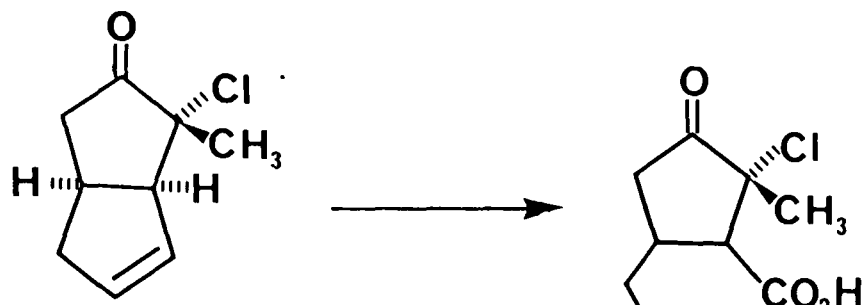
(3.2)

The bicyclic [3.3.0] ketone could now be employed as starting material in either of the synthetic schemes outlined in the research objectives.

Before embarking on a discussion of the successful route, summarised at the beginning of this chapter, the next section will be concerned with application of the alternative strategy.

IV.2. OZONOLYTIC CLEAVAGE OF THE BICYCLIC [3.3.0] KETONE

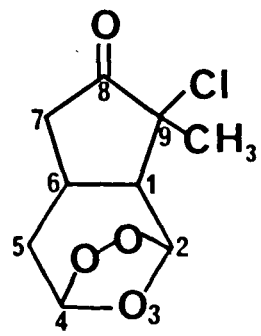
Cleavage of the double bond of (58) was originally planned by ozonolysis. Oxidative workup would then allow formation of the dicarboxylic acid (68).



(58) (68)

As good yields of the diacid (9) employed in the synthesis of vernolepin had been obtained, an analagous procedure was initially carried out with the boonein precursor (58).

Hence, ozonisation in acetone with the subsequent addition of Jones reagent lead to a mixture of components. The major compound isolated in 21% yield was tentatively assigned as the ozonide (69). Although this species was originally believed to be unstable, there are numerous literature reports of the isolation of ozonides which often have melting points of over 100°C.(166)

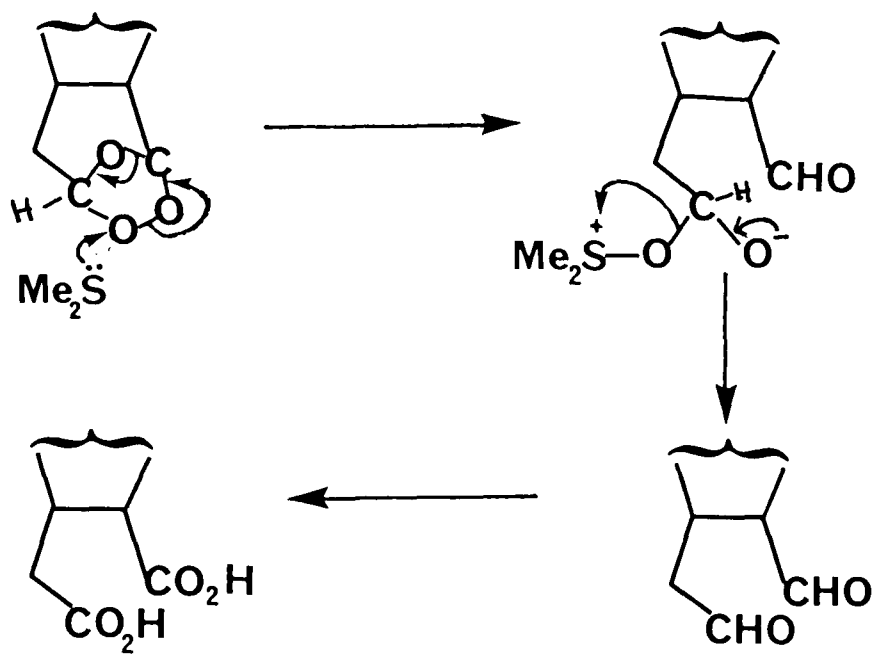


(69)

Spectral evidence for this structure included two signals at δ5.9 integrating to two protons, which could be allotted to protons H-2 and H-4, a methyl resonance at δ1.72 and complex absorption between δ3.22-1.78. The i.r. displayed carbonyl and ether moieties, and the required molecular ion was exhibited in the mass spectrum.

Assuming this molecule was isolated, it would appear to be insensitive to acidic oxidative conditions. Consequently, reduction of the ozonide was attempted, followed by oxidation of the intermediate dialdehyde.

viz:-

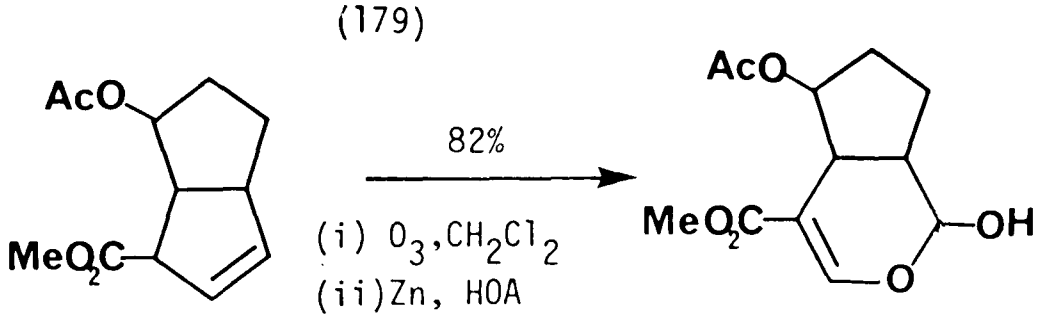


As this procedure resulted in a complex mixture of compounds, purification was not undertaken.

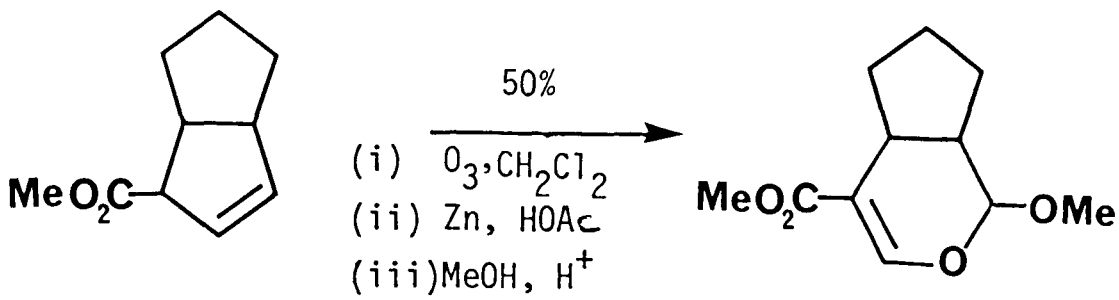
It was reasoned that reduction of the ozonide in situ followed by oxidation may prove a more advantageous method.

Reference to the literature indicated successful ozonisations of similar bicyclic systems had been achieved using dichloromethane as solvent. For example:-

(179)



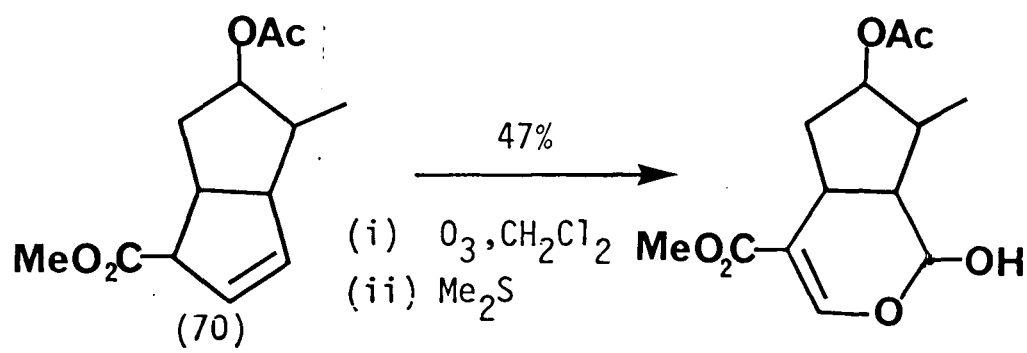
(180)



Criegee[168] has noted that the yield of products obtained from ozonolysis is often highly dependent on the medium employed. Consequently, the subsequent run was performed in dichloromethane.

In practice, a complex mixture of compounds was again recorded by t.l.c. analysis of the crude product. However, purification did allow isolation of a 9% yield of the dicarboxylic acid(68).

Fleming and Au-Yeung[94] have published precise details concerning ozonisation of (70) using a dimethylsulphide mediated reduction.

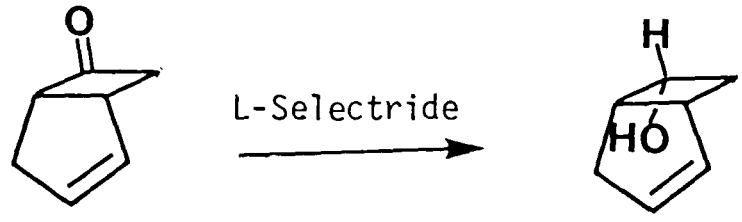


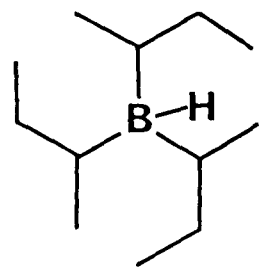
As reaction conditions are known to effect the outcome of such procedures, in an effort to improve the yield of diacid, Fleming's method was followed in the initial stage of the reaction. Unfortunately t.l.c. analysis of the crude product obtained upon oxidation, revealed an even more intricate mixture of compounds, with only a trace amount of the diacid (68) being apparent.

Naturally, ozonolysis could have been attempted in other solvents, such as pentane. Alternatively, another route[181] may have been employed for conversion to the dicarboxylic acid. However, at this stage, substantial progress was being made with the other synthetic strategy. Consequently, due to the lack of time available, efforts were directed towards the more promising scheme.

IV.3. REDUCTION

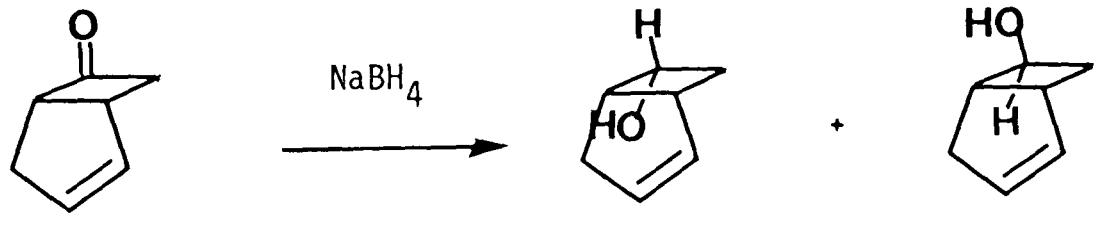
The predominant diastereoisomer that is formed upon metal hydride reduction of a carbonyl group is dependent upon many factors, such as torsional strain, steric interactions, unequal distortion of electrons about the carbonyl group, and orbital symmetry control.(182) Among these, steric hindrance to the approaching hydride carrier is well established. This has been employed to accomplish stereospecific reduction of the bicycloketone shown below:(183)



L-Selectride = 

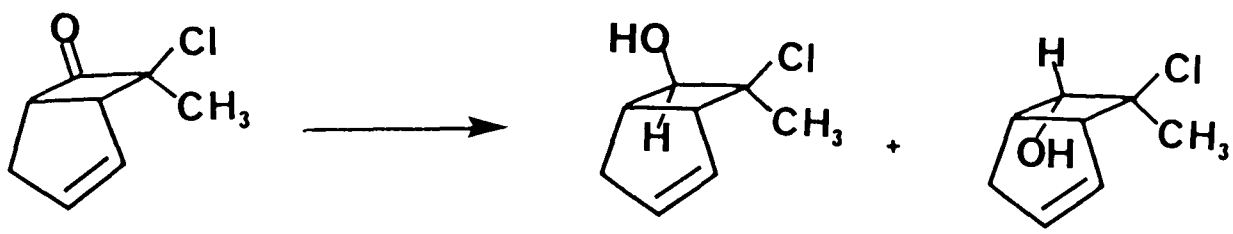
The reducing agent approaches from the less hindered exo-face of the molecule, promoting formation of the endo-alcohol. Obviously in this case, the stereoselectivity is enhanced by use of a bulky metal hydride. Indeed, utilisation of a less sterically demanding hydride, such as sodium borohydride, provides a mixture of epimers.(184)

viz:-

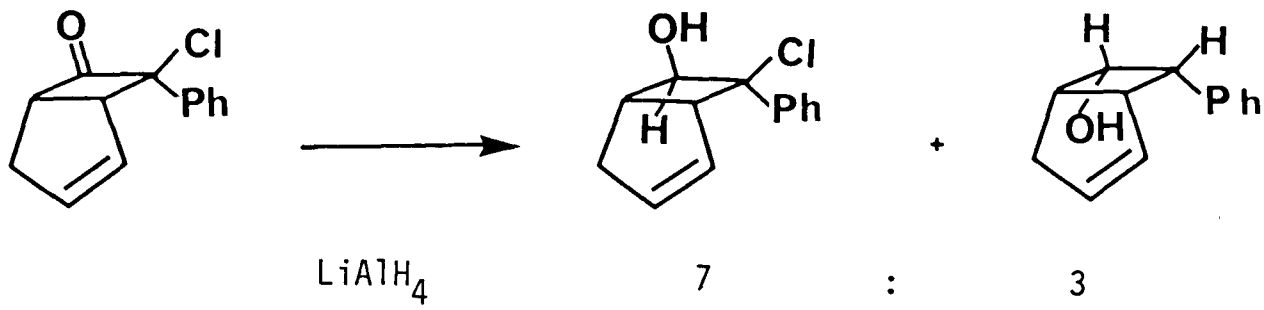


75 : 25

For ketones containing an α-chloro substituent another factor must be taken into consideration. The metal hydride approaches the carbonyl group from such a direction as to allow maximum separation between the electronegative α-substituent and the negatively charged nucleophilic reagent. Consequently this minimises the resulting dipole-dipole interaction in the transition state. Dreiding and co-workers[185] have performed reductions on a series of exo-halobicyclic ketones. These authors have found that in these instances where the



$LiAlH_4$	70%		-
$NaBH_4$ (MeOH)	78	:	22

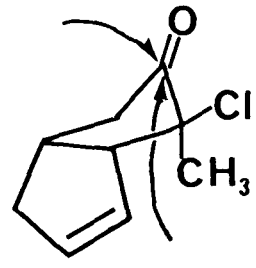


$LiAlH_4$	7	:	3

steric and dipole effects are opposed, lithium aluminium hydride and sodium borohydride reduction gave predominantly the exo-alcohol. Even the 7-endo-phenyl derivative was reduced to afford exclusively the 7-exo-chloro-alcohol. However, the dechlorinated endo-alcohol was also obtained. These results would suggest that the directive power of the carbon-halogen dipole has overcome steric interactions, thereby favouring production of the exo-alcohol.

By analogy, reduction of the homologous exo-chlorobicyclo [3.3.0] ketone should give predominantly the desired exo-alcohol. In fact, it was reasoned that owing to the less folded nature of the bicyclic ketone this would enhance production of the required alcohol.

exo-attack

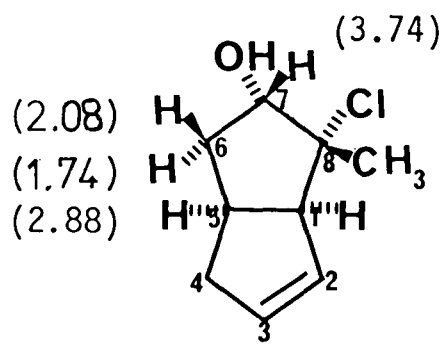


endo-attack

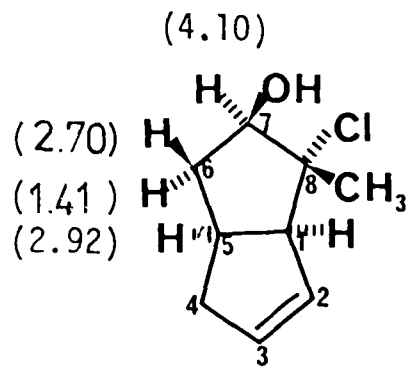
However, in practice, lithium aluminium hydride reduction of (58) with two hydride equivalents afforded a mixture of epimers, together with a compound of slightly lower R_f later characterised as the dechlorinated alcohol (71)(p.191). By reducing the hydride excess to 1.7, formation of the latter compound was eliminated. The two diastereoisomers displayed almost identical R_f values. It is therefore hardly surprising that an attempt at separation by dry flash chromatography and the chromatotron was not successful. In contrast, the compounds were well resolved by analytical g.l.c. Consequently, separation by preparative g.l.c. appeared possible. The fractions collected by this procedure were reinjected in order to assay their purity. Unfortunately a number of peaks appeared, suggesting that alcohols had low thermal stability. Even with the column and injector temperatures at 100°C and 120°C, without using the detector, decomposition of the hydroxy products still occurred. Separation was finally achieved by way of flash chromatography. A maximum of 1 g of crude product could be purified at any one time, using a column of silica 8 cm wide and 25 cm high. As is apparent,

this was a very time-consuming procedure.

The configuration of the hydroxy group in the chlorohydrins was tentatively assigned by examination of the n.m.r. spectra. Confirmation of this initial assignment was obtained by eventual conversion to boonein. It is well knownthat in the analagous bicyclo



(59)



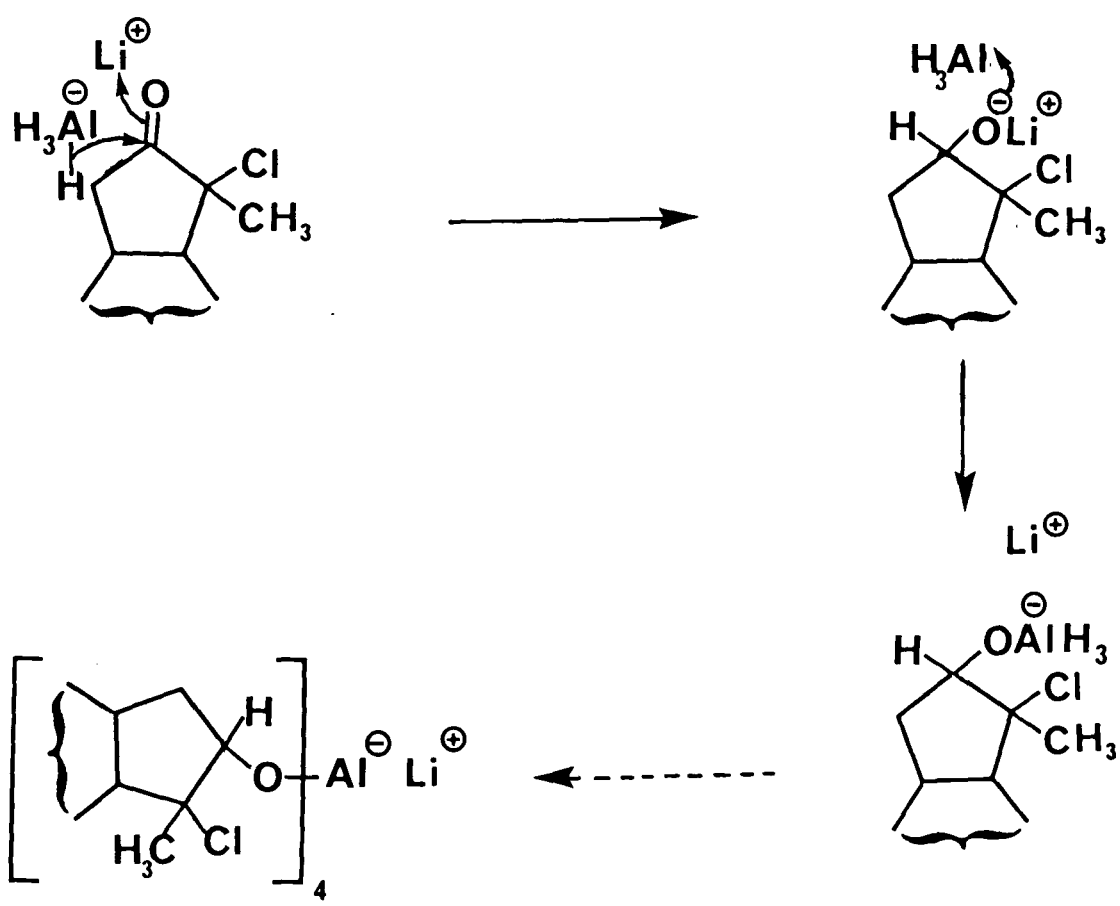
(72)

[3.2.0] system both H-7 and H-5 appear at higher field in the exo-alcohol[185] than in the corresponding endo-product. This is in agreement with the relevant chemical shifts of the assigned exo-isomer (59). Thus, H-7, presumably shielded by the anisotropic effect of the five-membered ring, occurs at δ3.74 in (59). This compares with a value of δ4.10 for the endo-alcohol (72). The bridgehead proton H-5 is marginally upfield in the exo-isomer. Additional criteria in the [3.2.0] system include higher coupling constant values between H-7, H-5 and H-7, H-1, for the endo-alcohol. Unfortunately, as H-7 appeared as a multiplet in (59) a comparison could not be made in this case.

Differences between the two alcohols also occurred towards the higher end of the spectrum, in particular with respect to the H-6 protons. The endo proton at H-6 appears at 2.08 in (59). The proximate oxygen atom in the endo-alcohol causes a marked downfield shift to δ2.70.[186] The other proton moves upfield from δ1.74 to δ1.41.

Confirmation of the structural assignment was attempted by a Nuclear Overhauser Effect. By irradiating H-7 with a secondary field this should only affect the integral of the methyl group if these moieties were syn, as in the exo-alcohol. However, in the event, no clear distinction was observed between the two chlorohydrins.

In ether, lithium aluminium hydride exists as a contact ion pair. The actual reducing agent is believed to be the $Li^{+}AlH_4^{-}$ ion pair.[115,187] Reduction by the transfer of a hydride anion from the metal atom to the carbonyl carbon atom, is assisted by the prior or synchronous association of the carbonyl oxygen atom with the lithium cation.

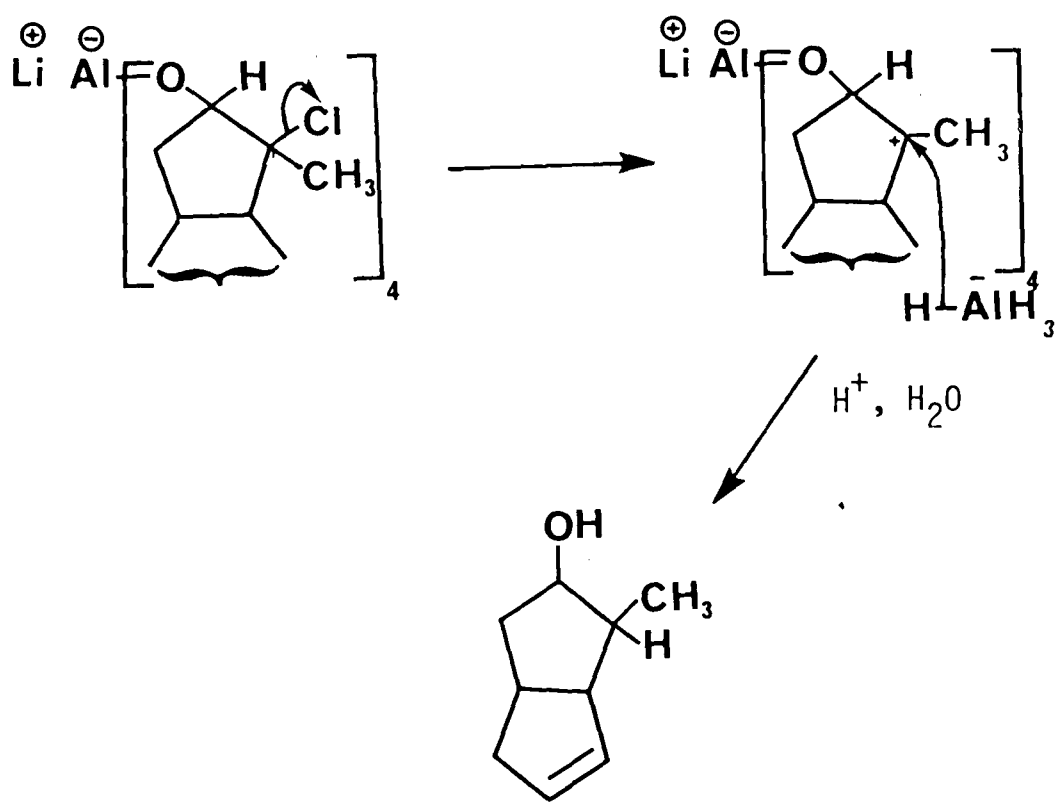


The resulting aluminium hydride-lithium alkoxide pair is rapidly converted to a lithium alkoxyaluminium hydride. Three further molecules of ketone may be similarly reduced to form a tetralkoxyaluminium anion. After each successive reduction, hydride transfer becomes a more

difficult process. However, in some cases disproportionation of the various alkoxyaluminium hydrides has been known to occur, thus regenerating the reactive tetrahydroaluminium species:-

The mechanism by which the dechlorinated alcohol is formed is uncertain. However, as chlorine is a good leaving group, nucleophilic displacement by the aluminium hydride is probable.

viz:-



(71)

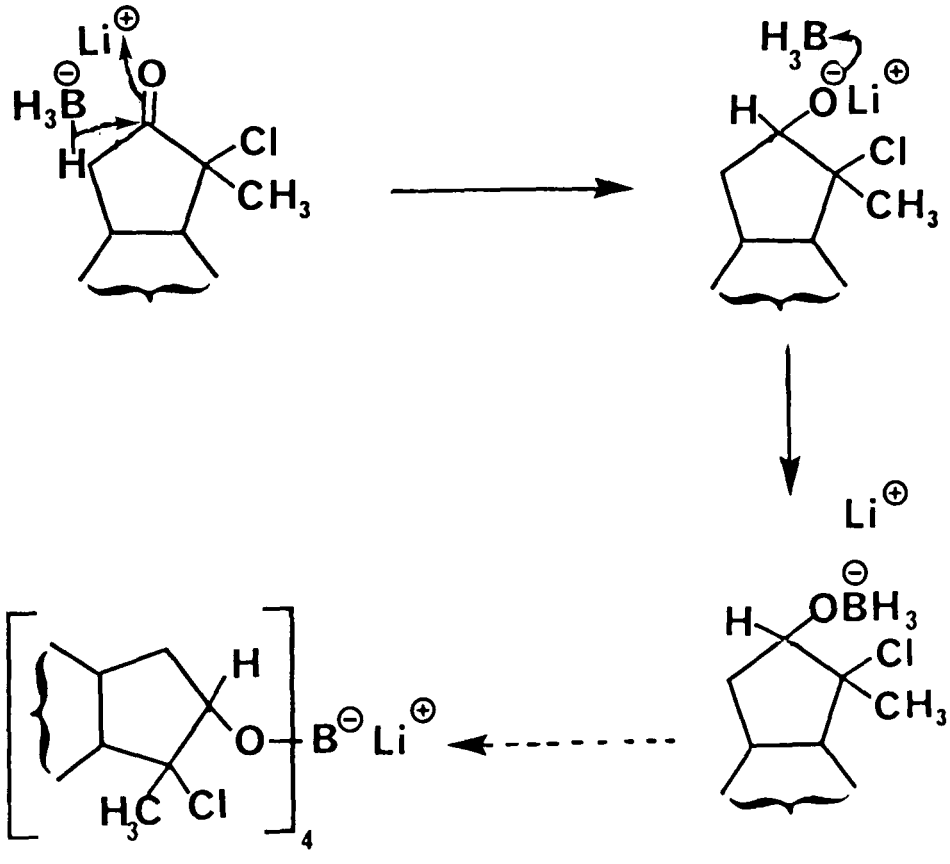
The ratio of chlorohydrins recorded by g.l.c. analysis was 61:39 in favour of the exo-alcohol. It would therefore appear that the electrostatic effect was not the predominant factor in determining the stereochemical course of the reaction.

If steric factors played a more important role in the reduct-

ion, utilisation of a smaller nucleophilic reagent would be expected to enhance attack from the more hindered side of the molecule creating a greater proportion of the exo-alcohol. Exo-attack would be discouraged by dipole interaction with the exo-chloro substituent.

As the borohydride anion is smaller than that of aluminium hydride, it should be less sensitive to steric interactions. Consequently, lithium borohydride was chosen in the subsequent reduction. The predominant product formed upon treatment with a 9.6 fold hydride excess was the dechlorinated alcohol (71). Very small amounts of both exo- and endo-chlorohydrins were isolated, which were shown to be present in a ratio of 52:48 by g.l.c. analysis of a crude sample, (see Table 8). The dechlorinated product persisted in a repeat of the reduction with 1.7 equivalents of hydride. Identical proportions of the two epimers were recorded.

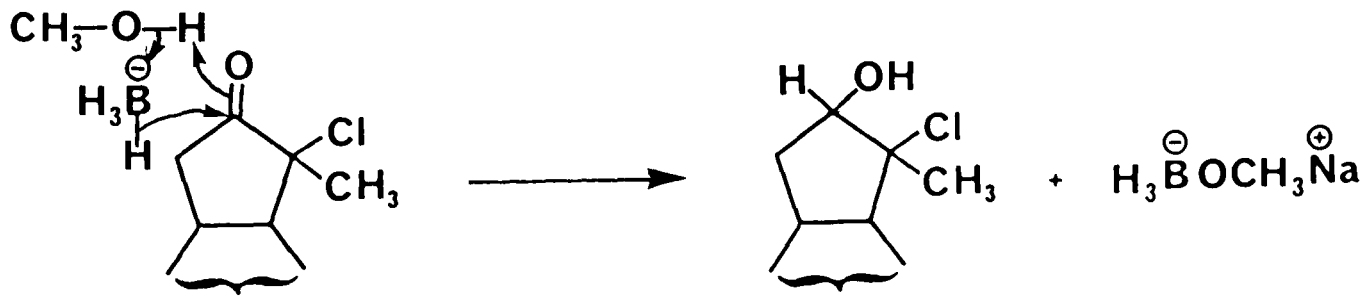
The lithium cation is believed to catalyse the reduction by polarising the carbonyl group. As in the case of lithium aluminium



hydride, reductions all four of the hydrogen atoms of lithium borohydride may be utilised in the reduction of ketone molecules. However, in contrast, the first step is rate-limiting. This is thought to either imply that reductions involving alkoxyborohydrides are much faster, or that rapid disproportionation occurs after the initial stage, so that the actual reducing agent is always the borohydride anion.

The dechlorinated alcohol may have been formed by an analagous substitution mechanism to that already discussed. It is conceivable that the quantity of this product may have been reduced by further decreasing the hydride excess. However, the proportion of exo-alcohol was far from satisfactory. In retrospect this may have been improved upon by performing the reaction in ether, as the reagent exists as solvent separated pairs in THF, and consequently has a greater steric requirement. Even so, the effective size of the borohydride anion in THF is smaller than the aluminium hydride anion in ether. This would suggest that steric hindrance to the hydride carrier was not the dominant factor involved in the reduction. Before completely discarding the steric effect, another reduction was performed, this time with sodium borohydride.

Sodium borohydride reductions require the presence of an electrophilic catalyst, such as a protic solvent,[115] for example methanol. With this exception, the mechanism of the process is analagous to that of lithium borohydride.



Alcohols formed by reductions of (58)

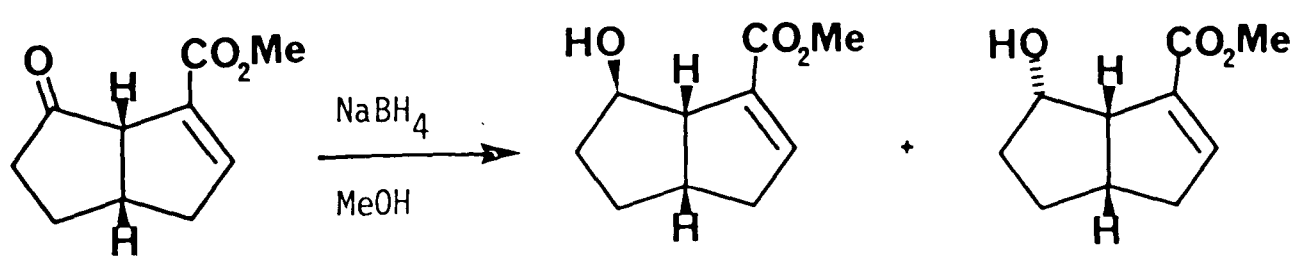
Reducing Agent	g.l.c. Ratio exo	endo	Isolated Yield exo	endo	Crude Yield
$LiAlH_4$	61	39	39	27	76
$LiBH_4$	52	48	3	3	61
$NaBH_4$	41	59	-	-	-
DIBAL	37	43	25	47	102
Na,EtOH	10	90	-	-	-

Table 8

However, it has recently been shown that the alkoxy groups on boron originate from the alcohol rather than the ketone.(188) Beckett et al.(189) have suggested that the participation of these methoxyborohydrides encourage attack from the least hindered side of the molecule, although at first sight these species would appear to be less sterically demanding than the corresponding alkoxyborohydrides derived from the ketone. This situation is further complicated by disproportionation.

In practice, the ratio obtained for the exo-and endo-alcohols was 41:59.

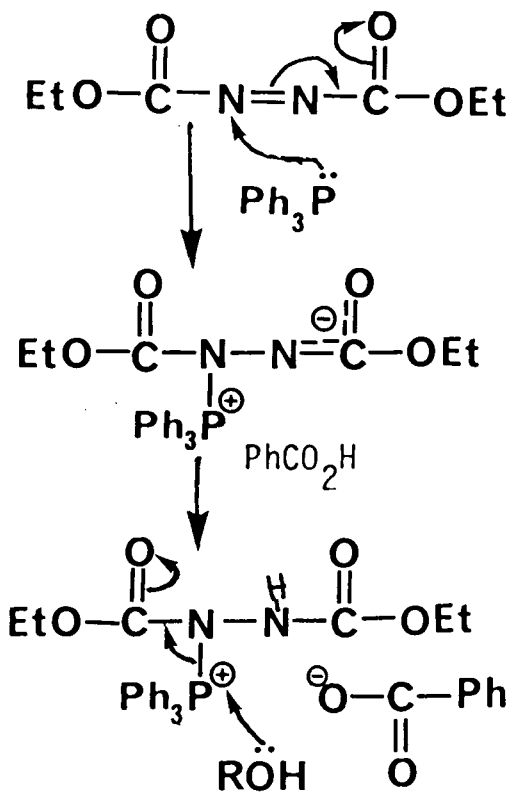
The shift in favour of the endo-epimer is in agreement with Dreiding's(185) findings mentioned earlier and also the ratio obtained bv Vandewalle et al.(179) The degree of solvation or the different



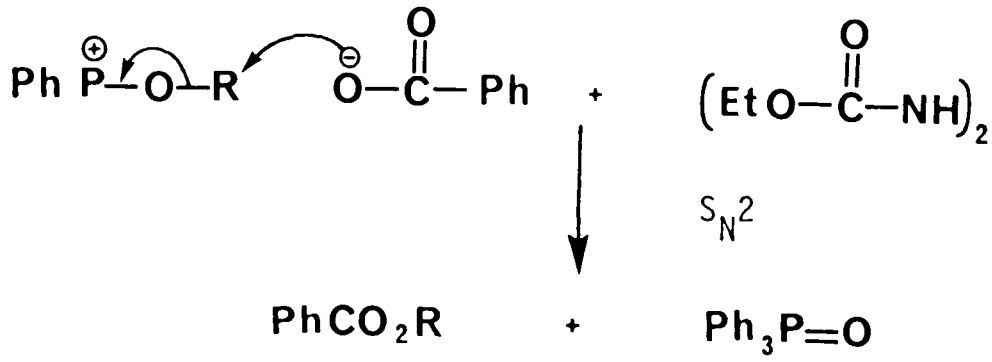
1 : 3

steric requirement of the transition state may be responsible for the promotion of exo-attack. Dechlorinated produce was also evident from the reduction.

It was considered that a more favourable outcome may be achieved using an electrophilic reagent such as diisobutylaluminium hydride. In this case steric and electrostatic effects would be acting in unison, directing the hydride reagent to approach from the exo-face of the molecule. Accordingly, the endo-alcohol would result. Although this epimer did not have the correct configuration for further transformations in the synthesis, there are literature procedures available for inversion of the alcohol. For example, the reaction of (S)-(+)-2-octanol with benzoic acid in the presence of diethylazodicarboxylate (73) and triphenylphosphine has been reported to proceed with complete inversion of configuration to afford (R)-(−)-2-octyl benzoate.[190]

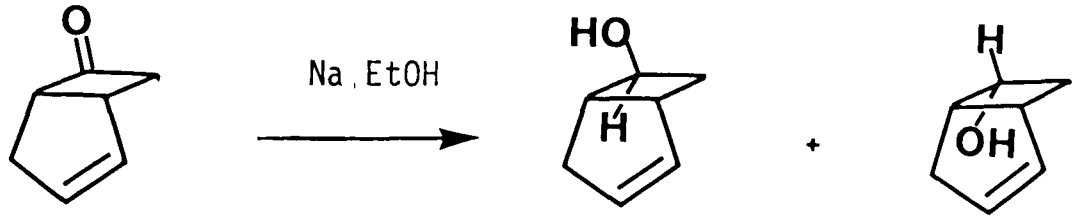


(73)



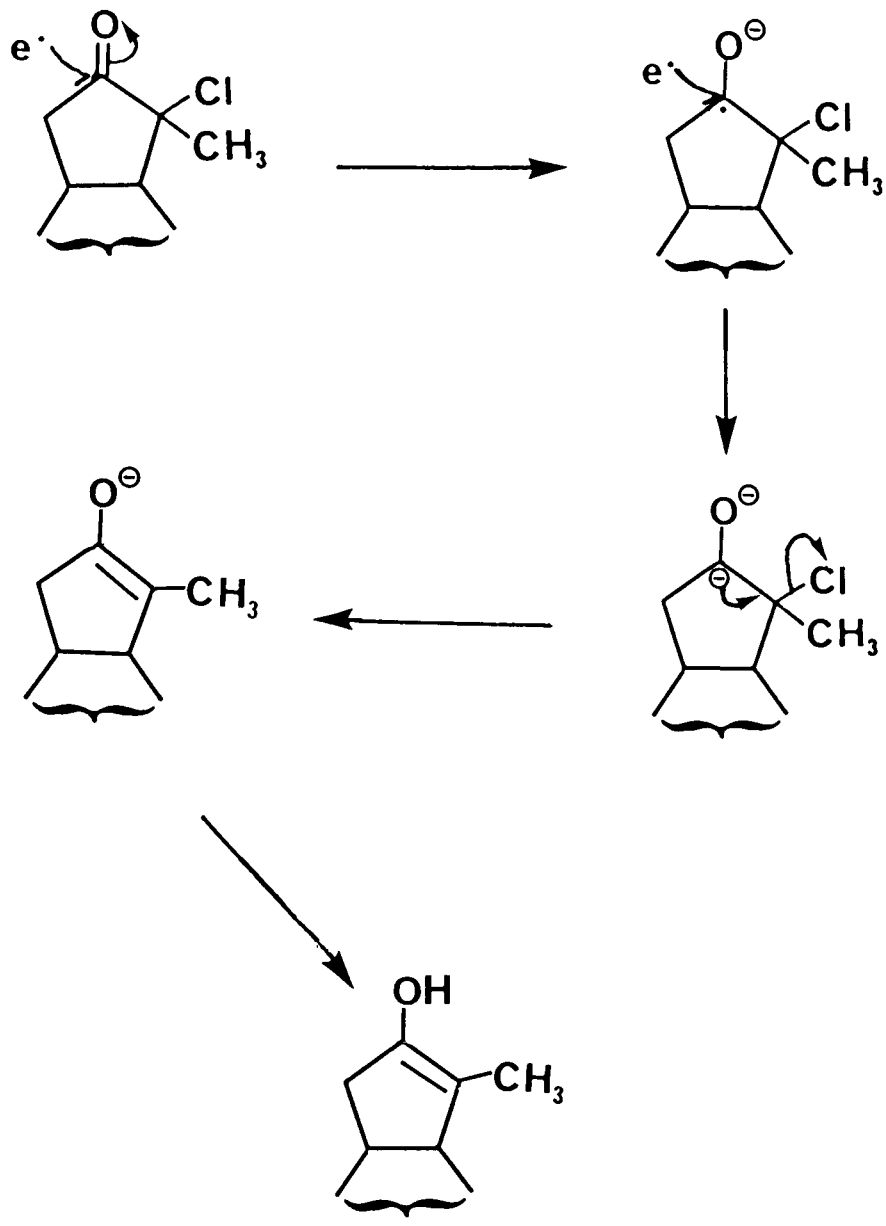
Reduction with the metal hydride did indeed produce an enhanced percentage of endo-alcohol. However, the ratio of 37:63 was not sufficiently high to warrant an attempt at inversion.

It is well known that the reduction of ketones with metals in protic solvents frequently produces the more stable alcohol. Berson and Patton[184] have found the exo-alcohol to be the more stable isomer in the bicyclic [3.2.0] system.



7 : 3

For the case in hand, the crude product obtained by treatment of sodium in ethanol, gave a complex series of peaks upon g.l.c. analysis. Identification of the chlorohydrins in the chromatogram revealed a ratio of 1:9 in favour of the endo-alcohol. This epimer would therefore appear to be the most stable product. In hindsight, the complex nature of the crude product is not surprising. As the reaction proceeds by a one electron transfer process via an enolate, dechlorination would be facile. In addition, α-halo ketones may undergo a Favorskii rearrangement.



Unfortunately, at this stage, time was becoming short, and the action of further reducing agents could not be evaluated. The most stereoselective agent recorded to date for the production of the exo-alcohol, was therefore lithium aluminium hydride. Although only a poor recovery of the crude product (76%) was isolated, this allowed the required epimer to be obtained in a yield of approximately 40%. The endo-alcohol was recycled by oxidation to the ketone and subsequent reduction. This would allow a 50% overall yield of (59).

During the course of this work, research into the microbial reduction of the bicyclic ketone by Mahon[191] has been met with some

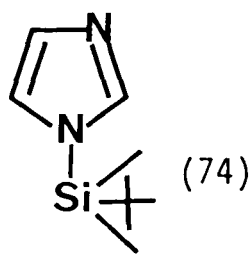
success. Hydroxylations have been carried out with Bakers yeast, Saccharomyces cerevisiae, which should allow the stereospecific production of the (S)- or in this case the exo-epimer. Unfortunately, due to problems encountered in the workup procedure, only very low crude recoveries, in the region of 30%, have been achieved. Although n.m.r., i.r. and t.l.c. analyses suggest the presence of a chlorohydrin, insufficient data is available at this stage to determine the configuration of the hydroxy group. If this process did allow stereospecific formation of the exo-alcohol in good yield, this would greatly improve the reduction step of the synthesis and provide an enantiospecific synthesis.

IV.4. PROTECTION

In order to achieve stereospecific dechlorination at the penultimate stage of the synthesis, it was necessary for the hydroxy function to be protected by a bulky group, which would shield the exo-face of the molecule.

The t-butyldimethylsilyl ether was ideally suited to this purpose. As well as being stable to basic and mildly acidic hydrolysis, it is readily cleaved by a variety of selective conditions.[192]

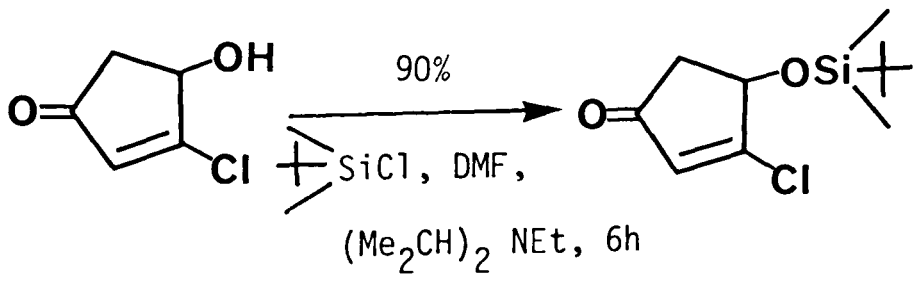
The silyl ether may be formed by several routes. It was originally prepared by Corey and Venkatswarlu.[193] The reaction was catalysed by the base imidazole and the actual 'silylating agent' was believed to be the species (74) depicted below:



(74)

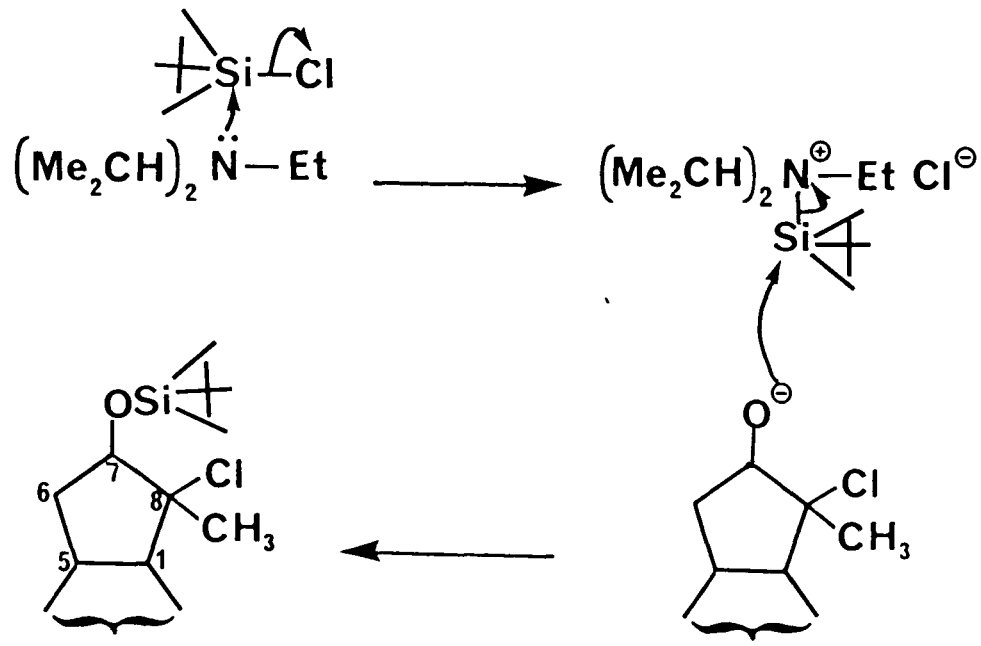
Protection was attempted using this procedure. However, no trace of the product was evident after 72 hours.

Lombardo[194] has recently published a rapid, high yielding method for procuring t-butyldimethylsilanes using diisopropylethylamine as catalyst, e.g:-



Indeed, this procedure allowed the production of the silane (60) in quantitative yield.

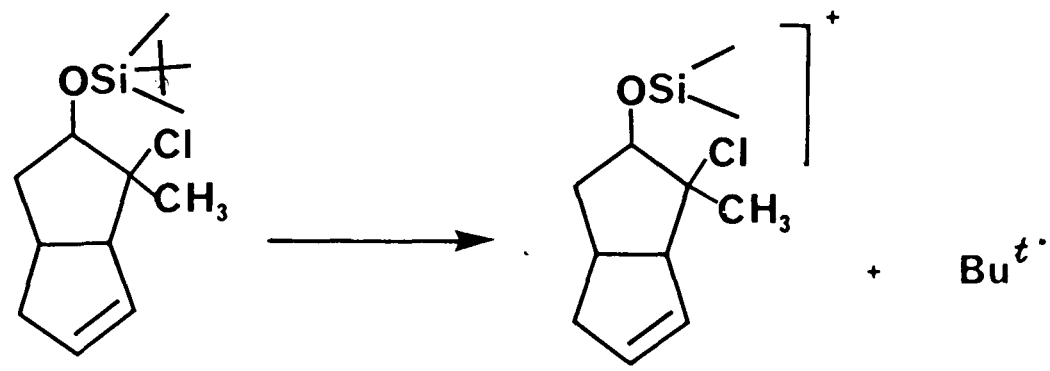
A plausible reaction pathway is illustrated (vide infra).



(60)

A salient feature of the n.m.r. includes an upfield shift of H-6 exo from δ1.74 to δ1.52, presumably due to the bulky t-butyldimethylsilyl moiety.

Loss of the t-butyl group in the mass spectrum is diagnostic for such compounds. This gives rise to a signal at 90% of the base peak. Other distinctive fragmentations include loss of the two methyl moieties.



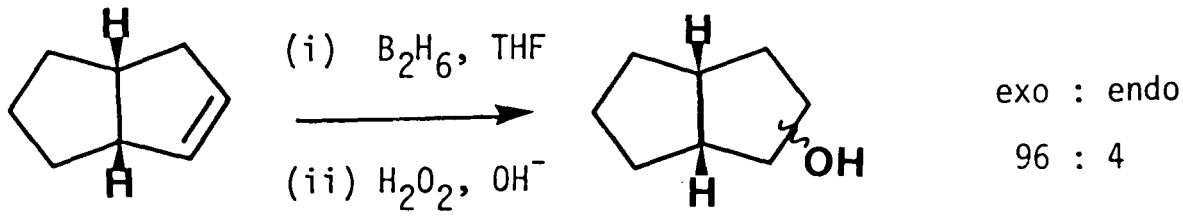
The stage was now set for the stereoselective oxidation of the olefin function.

IV.5. HYDROBORATION

A number of potential methods exist for the conversion of an olefin moiety into a ketone. Among these is the well-established Wacker process,[195] in which oxidation is carried out using palladium (II) chloride and a copper salt as catalysts under an atmosphere of oxygen. Although this procedure works well for terminal olefins, it has not yet been successfully applied to internal alkenes. Hydration of the double bond either by aqueous sulphuric acid or by an oxymercuration-demercuration sequence is another possibility. However, one of the most successful methods for effecting the desired transformation is via hydroboration and oxidation of the intermediate alkylborane.

The addition of borane to a double bond has been found to occur in a cis manner from the less hindered side of the molecule.[115] Consequently, the U-shaped cis-bicyclo [3.3.0] octene skeleton predominantly undergoes hydroboration from an exo-direction as illustrated by the following examples:-

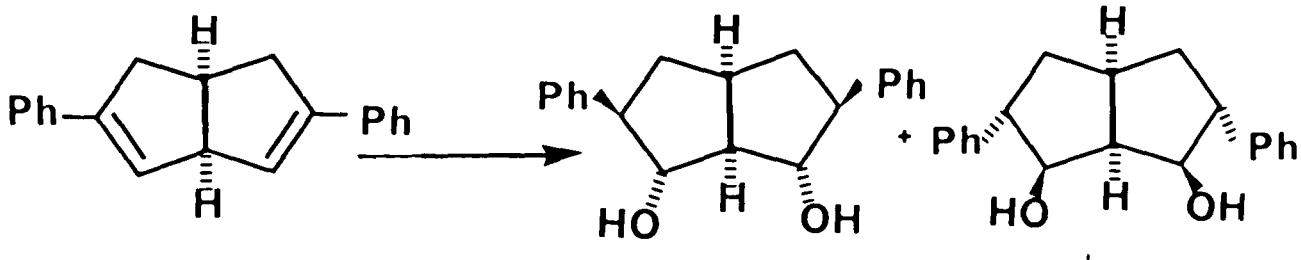
(196)



exo : endo

96 : 4

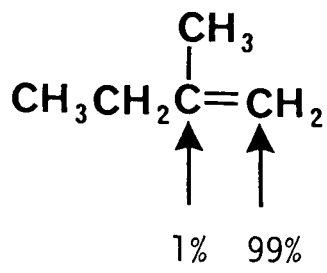
(197)

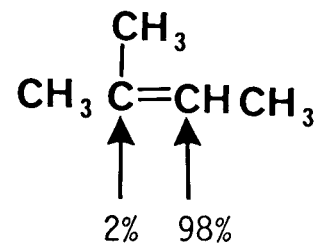


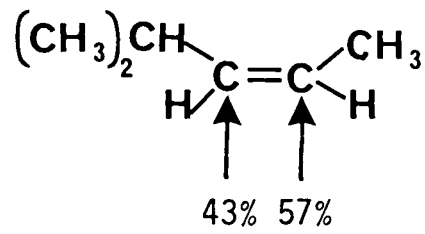
exo : endo

15 : 1

The direction of addition of borane to an unsymmetrical olefin is such that the predominant product usually has the boron atom bonded to the less highly substituted carbon atom. However, the difference is not as marked between the two positions of an internal olefin containing groups of different steric requirements (vide infra).[198]

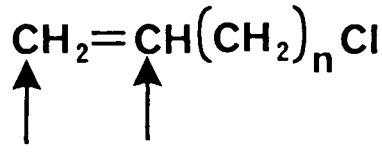






(The figures refer to the fractions of the product in which the boron atom is bonded to the carbon).

The presence of substituents, such as halo and hydroxy groups, can lead to large changes in the orientation of addition. The effect, which is attributable to the electron-withdrawing inductive effect of these substituents, is reduced when such functional groups are separated from the double bond by two or more carbons.
viz:-[199]

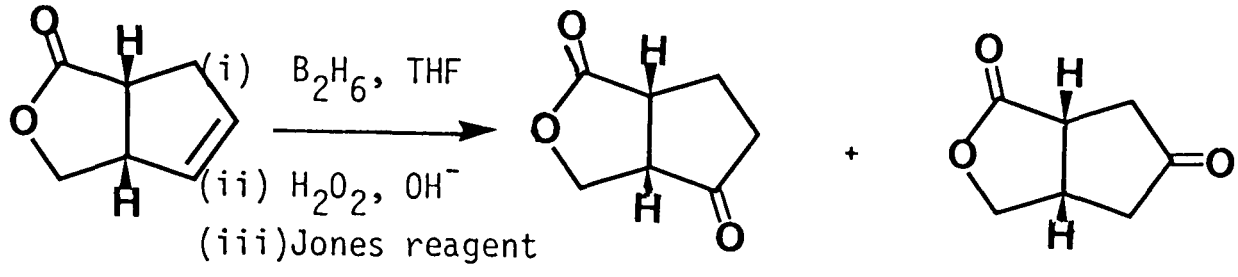


n = 1	60	:	40
n = 2	82	:	18

This directing effect may be responsible for the observed regioselect-

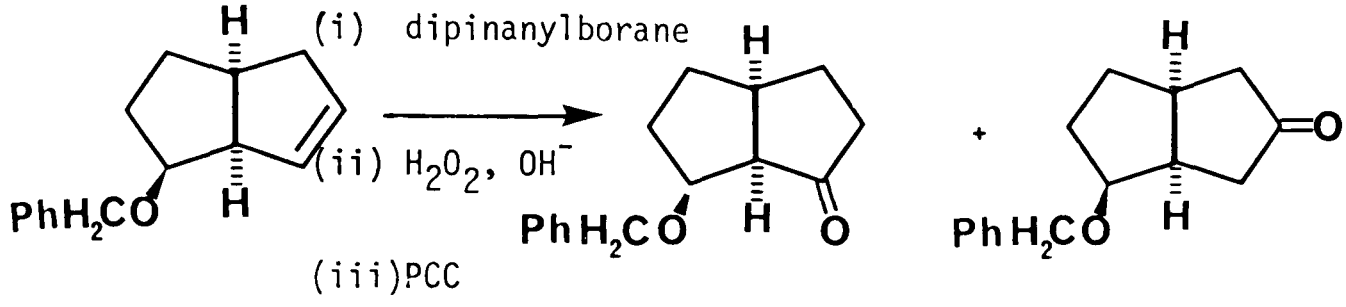
ivity in certain recently reported bicyclic systems.

(200)



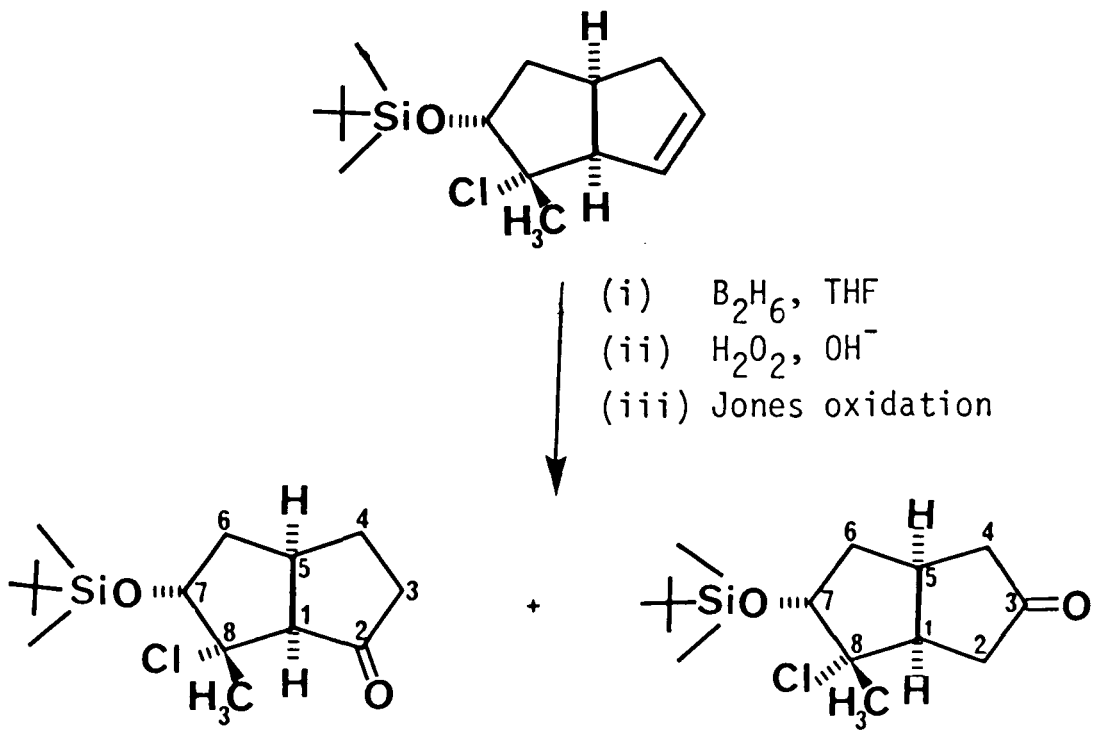
7 : 3

(201)



53 : 47

A similar result in favour of the more highly sterically hindered carbon was found within the context of this work.



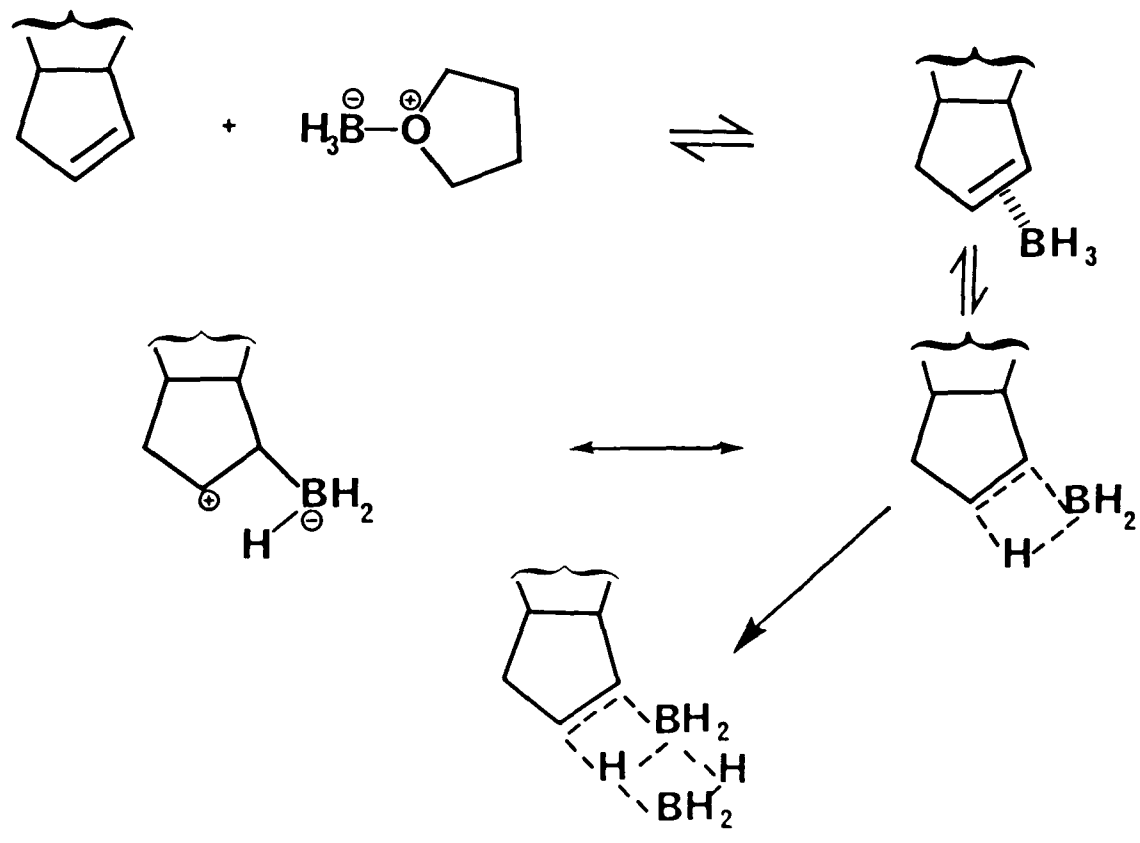
(61) (75)

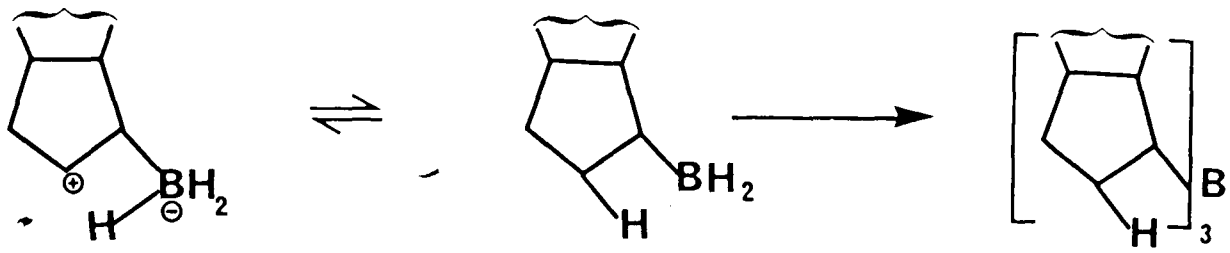
79 : 21

Thus, the desired ketone was obtained in yield of 70% by this procedure. Although the t-butyldimethylsilyl group is normally cleaved under strongly acidic conditions, by performing the Jones oxidation at $0^{o}C$ this danger was circumvented.

The two ketones were differentiated from each other by reference to n.m.r. In one compound a doublet appeared at $\delta 2.77$. This was assigned to H-1 and could obviously only be split as such in the silyl ether ketone (61). Further splitting would occur in the 3-ketone (75) by the two adjacent H-2 protons. The relatively high field resonance of H-1 in (61) is presumably attributed to shielding by the α-carbonyl function. In contrast, H-1 in (75) appeared as a multiplet together with H-5 at a lower shift of $\delta 3.11$. Differences were also observed in the chemical shifts of the remaining protons of the cyclopentanone ring, which were consistent with the postulated assignment.

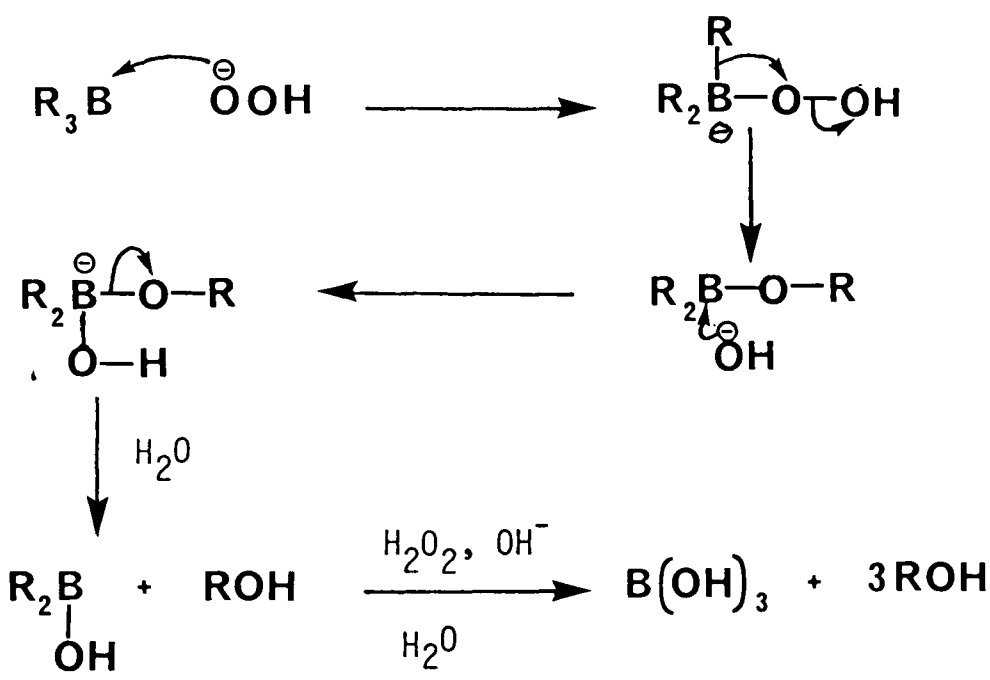
The reaction path is believed to involve a four-centred transition state formed by the addition of a borane-THF complex to the double bond.





(76)

The mechanism is complicated by the fact that monoalkylboranes tend to undergo hydrogen-bridged dimer formation as shown. However, all three hydrogens of the borane may be theoretically used in the reduction to give the species (76). Oxidation of the trialkylborane with alkaline hydrogen peroxide proceeds by successive intramolecular rearrangements of alkyl groups from boron to oxygen followed by hydrolysis.



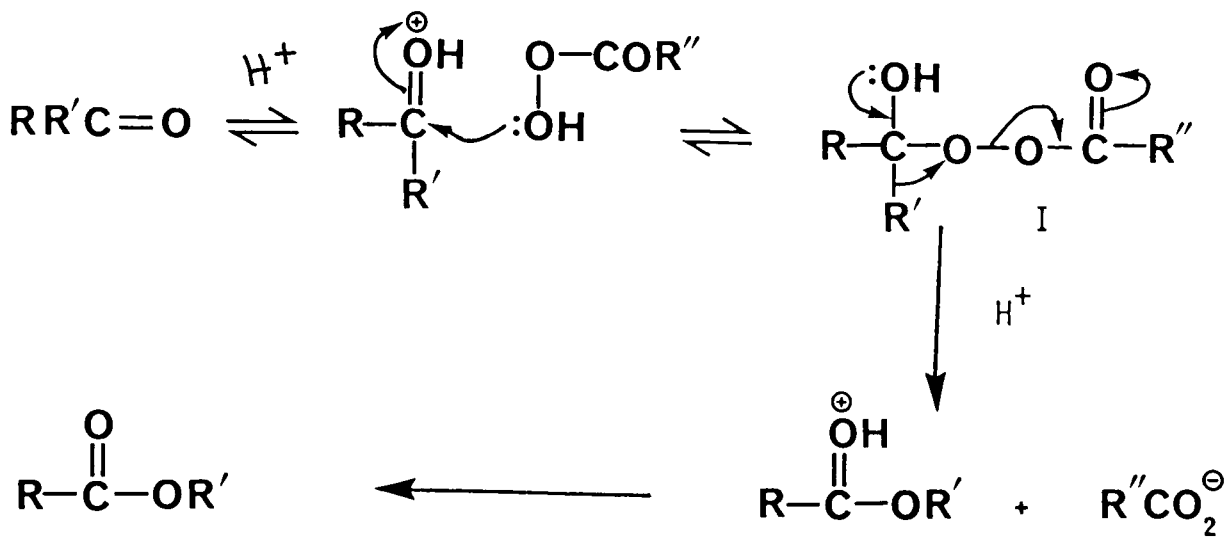
Oxidation of the diastereomeric alcohols gave the ketone (61).

IV.6. LACTONISATION

The next phase of the synthesis constituted elaboration of the δ-lactone moiety of boonein. The most direct approach to such a transformation is by a Baeyer-Villiger oxidation of the ketone.

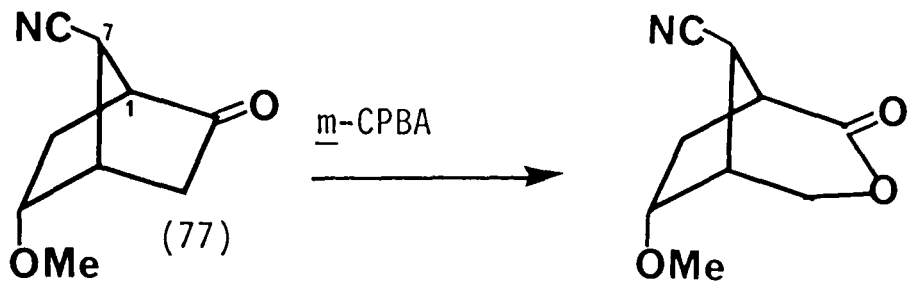
The generally accepted two-step mechanism[115] for this process was originally proposed by Criegee.

viz:-



Thus, nucleophilic addition of a peracid to a protonated carbonyl group is followed by intramolecular migration to the peroxide oxygen. It is apparent that oxidation of an unsymmetrical ketone can lead to two isomeric esters. The migratory aptitude of various alkyl groups in acyclic ketones has been found to be in the order of:- tertiary > secondary > primary. Consequently, it would appear that the migrating group is better able to support a positive charge in the transition state. However, in cyclic ketones, factors other than electronic preferences may affect the mode of ring expansion. Some workers[202-204] have suggested that the presence of a suitably substituted electron-withdrawing group influences the outcome of the Baeyer-Villiger oxidation. For example, 7-cyanonorbornanone derivatives(202)(77) were found

to result predominantly in products derived from methylene migration.

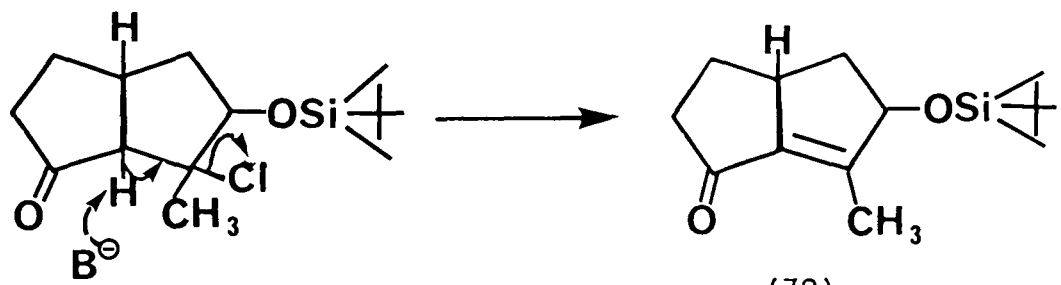


(77)

This has been explained in terms of the inductive effect of such substituents being transmitted to C-1, which is then less able to support a buildup of positive charge, as required for the migrating group in the rearrangement step.

By analogy, it was hoped that this propensity for methylene group migration could be exploited to afford the 3-oxa-lactone (63).

The oxidation was attempted with m-chloroperbenzoic acid. Sodium bicarbonate was employed to limit the acidity of the reduced acid, so as to prevent removal of the acid labile silyl ether protecting group. Unfortunately, the only product isolated corresponded to the dehydrochlorinated derivative (78). This was presumably formed by base abstraction of the bridgehead proton, mediated by sodium bicarbonate.

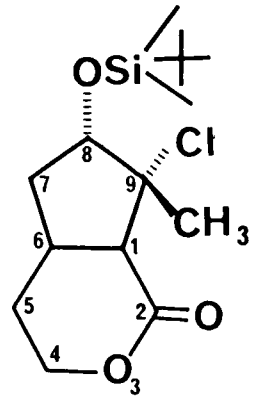


(78)

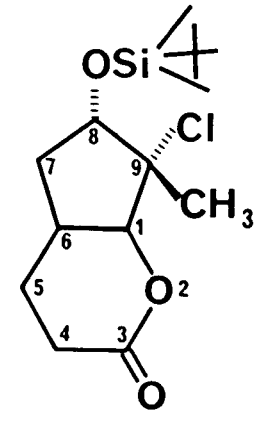
This type of compound (78) is well known to be resistant to Baeyer-Villiger oxidation. The product could equally well have arisen from an acid catalysed process. However, this was demonstrated not to

happen in a subsequent reaction using only m-chloroperbenzoic acid. An 82% conversion to a mixture of isomeric lactones was obtained, in which the 2-oxa-lactone (79) was found to predominate by a ratio of 2.8:1 based on isolated material.

The two lactones were distinguished by n.m.r. The appearance of a signal at δ4.26 integrating to two protons could clearly only originate from the two H-4 protons of the 3-oxa-lactone (63). It



(63)

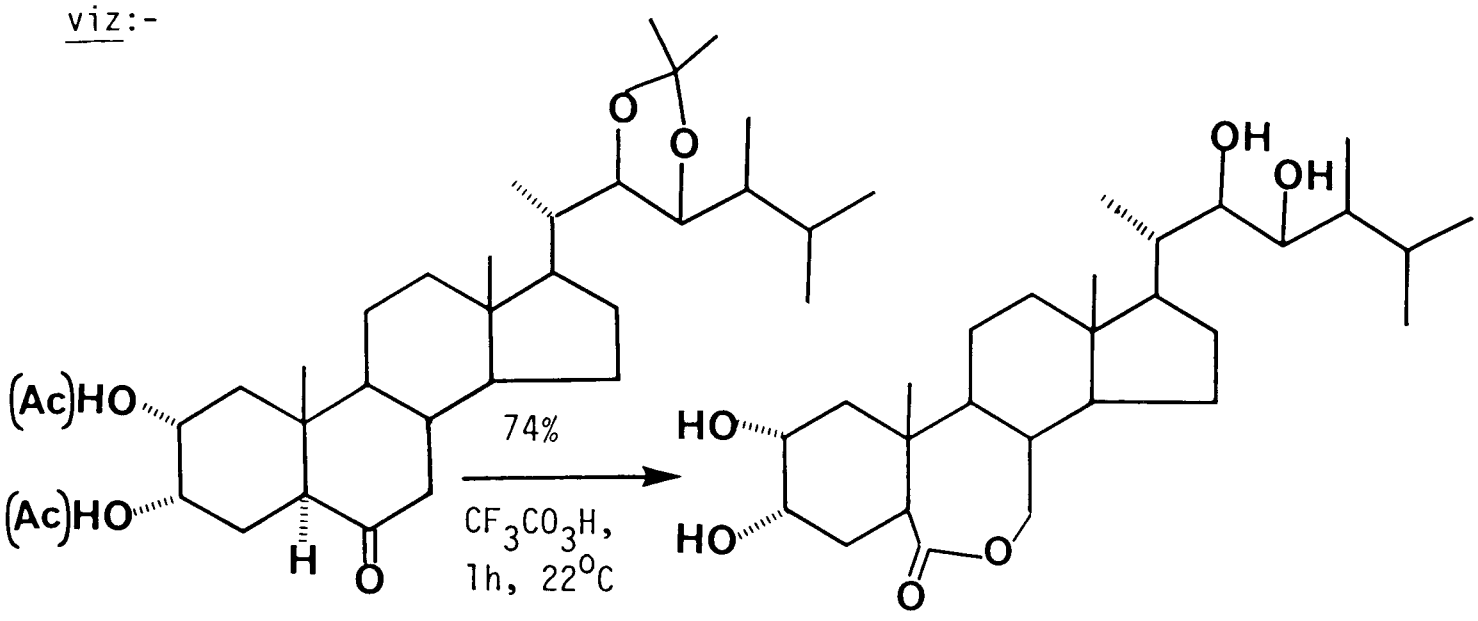


(79)

was also noted that in this spectrum the two H-3 protons α to the carbonyl group in the precursor, were replaced by higher field signals. The bridgehead proton H-1 in the 2-oxa-lactone (79) appeared as a doublet coupled to H-6, at δ4.56. An interesting feature of this n.m.r. included the downfield shift of H-8 from δ3.71 to δ4.06 which presumably must be due to the anisotropic effect of the carbonyl group.

The observed lactone ratio reflects preferential migration of the methine moiety over the methylene group. To determine whether this may be altered using a different peracid, the reaction was repeated with peroxytrifluoroacetic acid. As this is a strong acid a greater amount of the 3-oxa-lactone (63) was expected. Indeed, Siddall and Fung[205] have reported almost exclusive production of the corresponding isomer in their recently published synthesis of brassinolide.

viz:-



Simultaneous deprotection occurred on Baeyer-Villiger oxidation. Curiously, a ratio of 88:12 for the 3-oxa and 2-oxa-lactones was observed in the diacetylated derivative. This would indicate that the two hydroxy functions have a directing influence in the reaction.

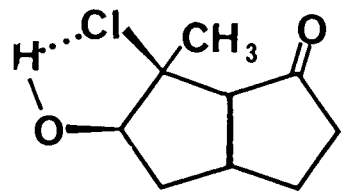
The oxidation was carried out using the conditions quoted by the aforementioned authors. In order to minimise deprotection, the reaction was initially performed at $0^{o}C$. However, as only starting material was observed after ½ hour, the mixture was allowed to warm up to room temperature. The reaction was continued for 16 hours before being subjected to workup. Trace amounts of both lactones were observed on t.l.c. analysis of the crude product, the major component being unchanged silyl ether ketone. Surprisingly, there was no evidence of deprotected material.

The oxidation was repeated with permaleic acid. An attempt to force the reaction by heating under reflux only resulted in the appearance of highly polar compounds, presumably arising from cleavage of the silyl ether. Neither lactone was observed in this case.

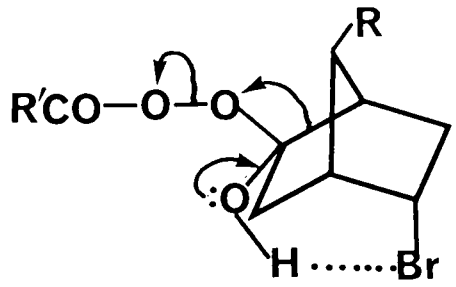
It would appear that the strength of permaleic acid was not

sufficient to effect oxidation. However, with peroxytrifluoroacetic acid, the reason for the apparent lack of activity was unclear.

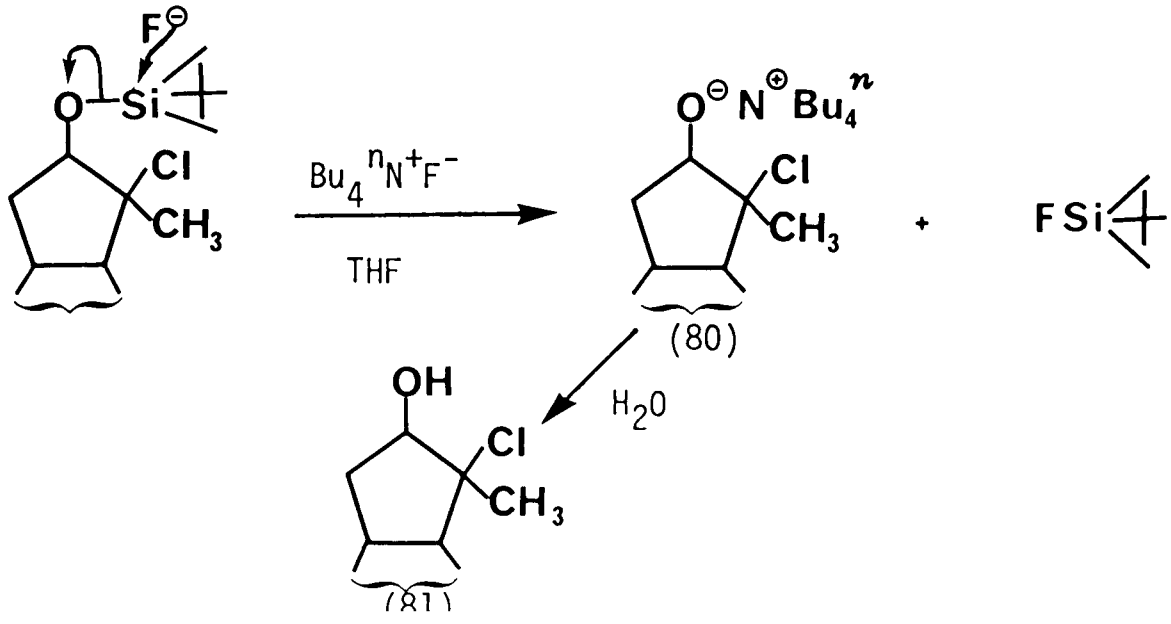
It was reasoned that the inductive effect of the chlorine substituent could be enhanced by hydrogen bonding with the deprotected alcohol. This would promote methylene migration and literature precedent[206] exists for such a surmise in that in the example shown,



hydrogen bonding favours migration of the bridgehead carbon atom.

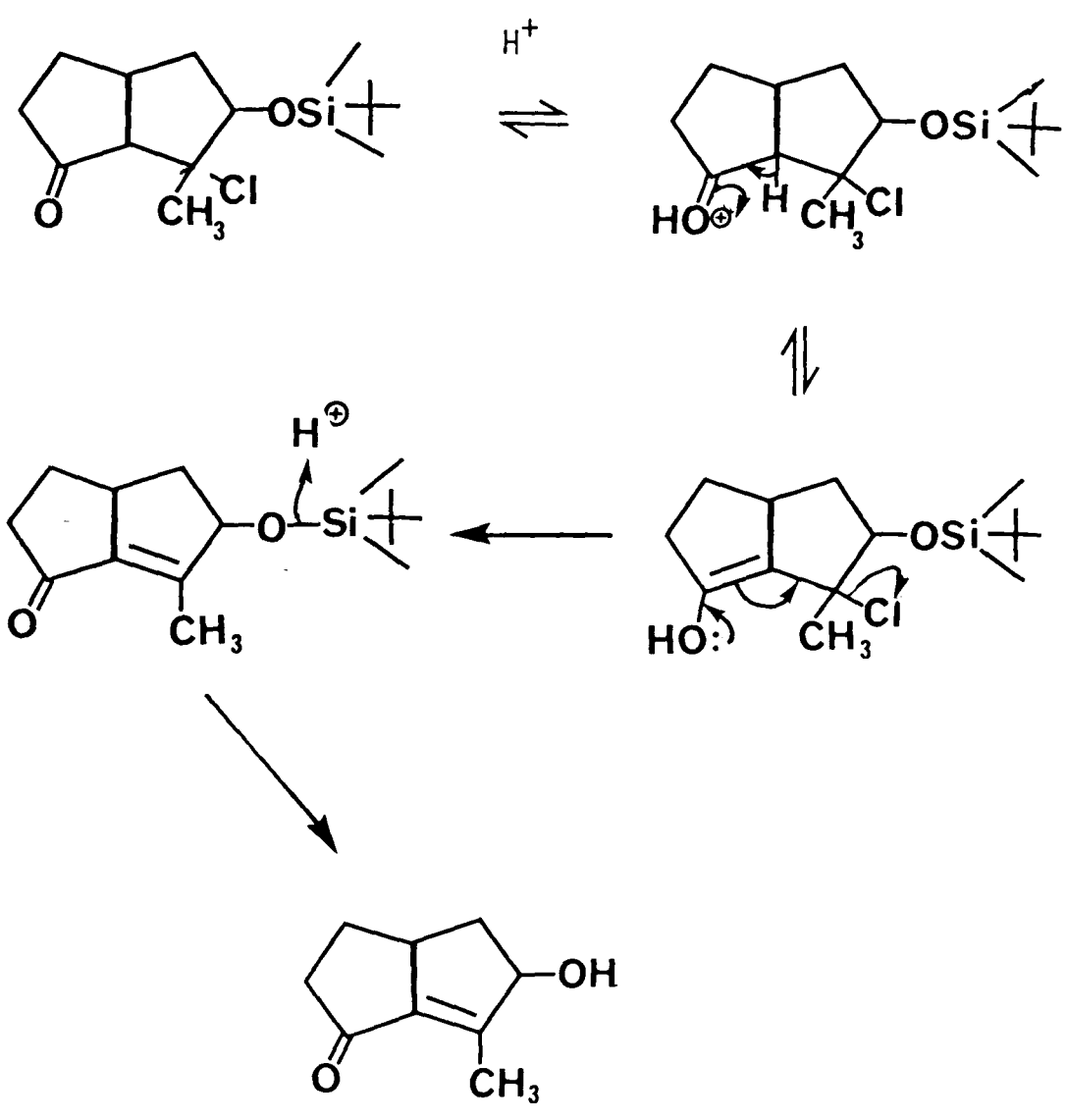


Consequently, to test this theory, deprotection was initially required. The use of tetra-n-butylammonium fluoride has been recommended[192] to effect this cleavage. This is attributable to the marked affinity of silicon for fluorine, as is apparent by the very strong Si-F bond (135 kcal).[207]



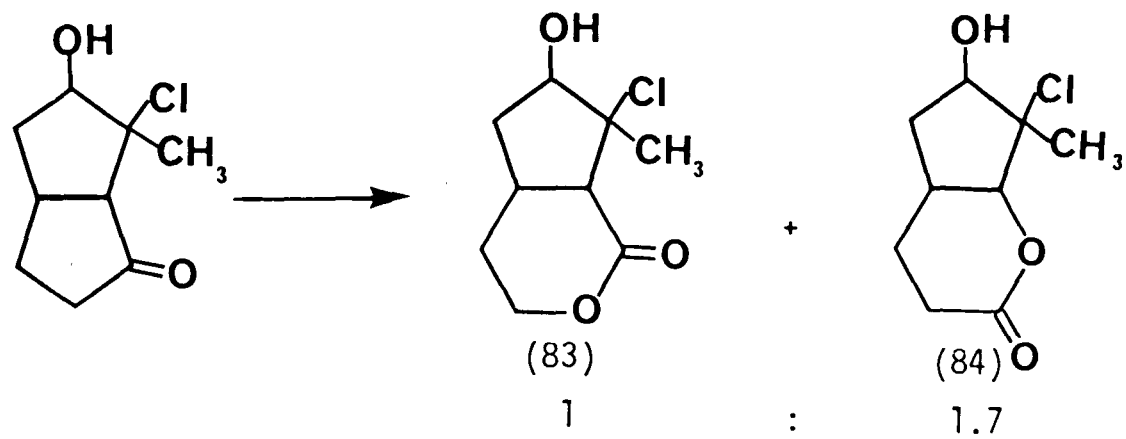
The crude product obtained from this procedure consisted of a complex mixture of compounds. Accordingly, the desired hydroxy ketone (81) was only isolated in 4% yield.

An alternative means of cleavage with aqueous acetic acid and THF proved more successful. The silyl ether was remarkably resistant to hydrolysis and complete cleavage was only achieved after heating the mixture at 60^{o}C for 5 hours, when a 48% yield was obtained. However, on this occasion another compound was isolated which was tentatively assigned as the dehydrochlorinated alcohol (82) on the basis of i.r. and mass spectral data. The accompanying mechanism provides a possible pathway for the formation of this compound:-



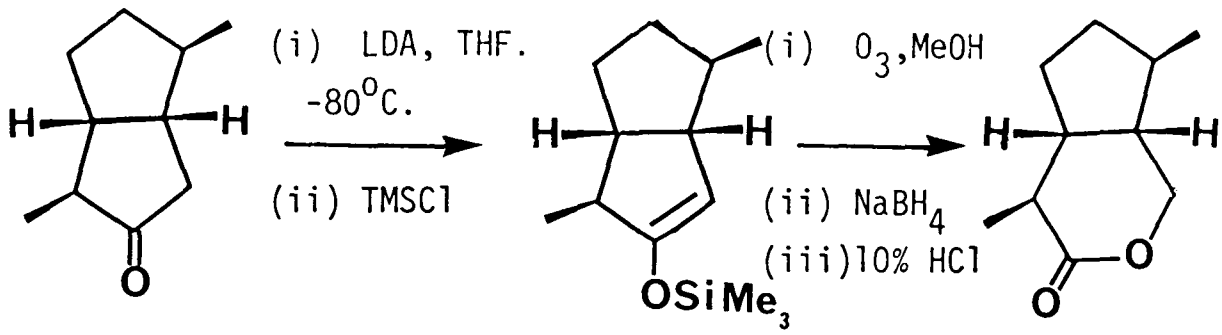
(82)

m-Chloroperoxybenzoic acid mediated oxidation of the relevant alcohol, again gave a mixture of two isomeric lactones (83) and (84).



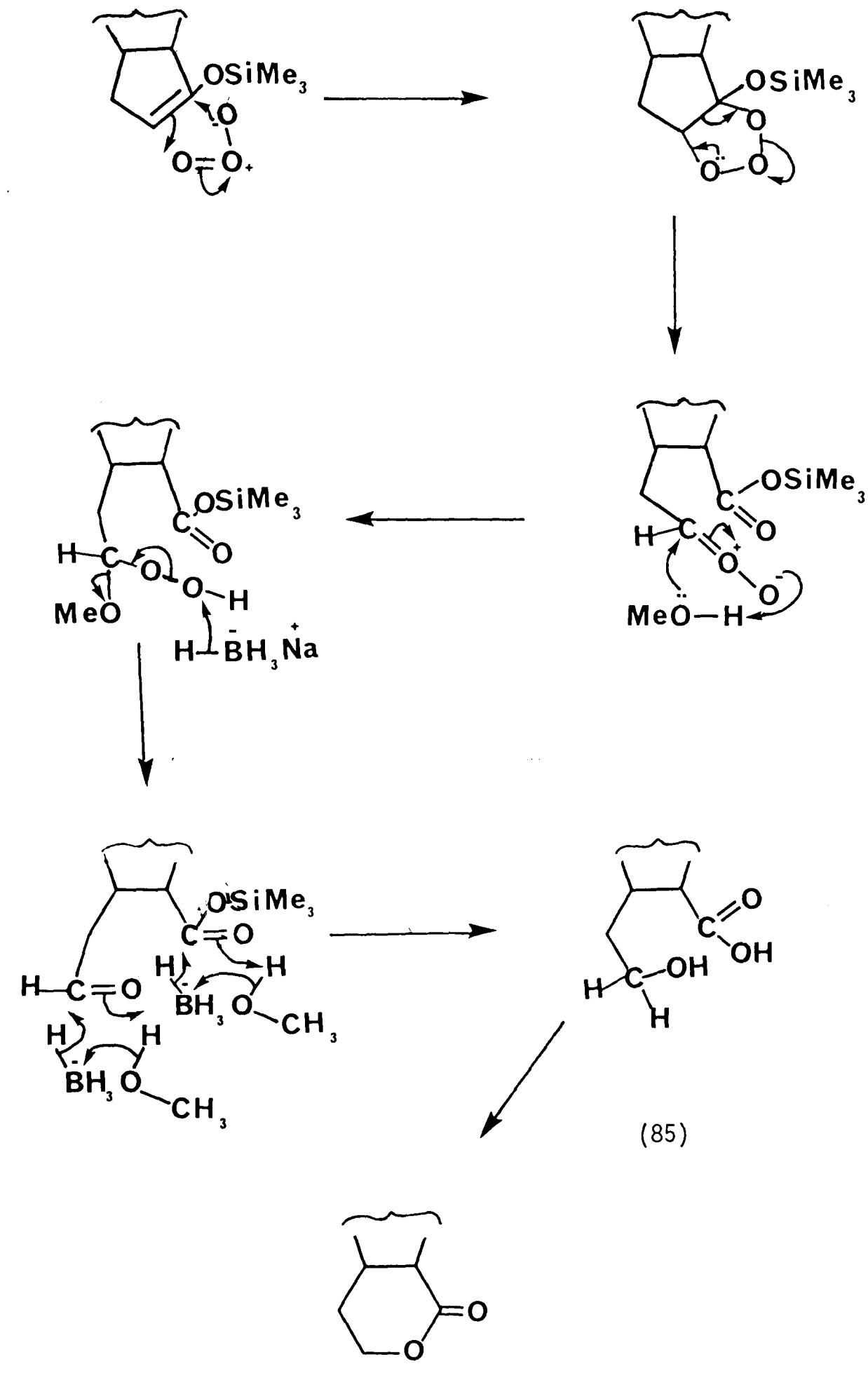
Although the proportion of the 3-oxa-lactone was increased to 1:1.7, the very small amounts of isolated product cast doubt on the accuracy of these figures, as the ratio was determined from isolated yields, as suitable g.l.c. conditions could not be found. Clearly, confirmation of this result is required by a repeat oxidation, but due to lack of time this was not possible. In any case, even allowing for a more favourable lactone ratio, the deprotection, Baeyer-Villiger oxidation and reprotection sequence would not appear to be a viable alternative to direct oxidation, unless yields of deprotected and reprotected product were very high.

A regiospecific route to the 3-oxa-lactone by ozonolytic cleavage of a siloxyalkene, originally proposed by Clark and Heathcock,[74] has already been referred to, (Chapter I,p40). This method has since been successfully employed by Whitesell and Matthews,[208] and Vandewalle et al.[209] in bicyclic [3.3.0] systems, though not in such high yields. For example:-



42% overall yield

Consequently, the procedure was applied to the silyl ether ketone (61). An almost quantitative yield of the O-silylated enolate (62) was obtained by kinetic deprotonation with lithium diisopropylamide and trapping the intermediate enolate with trimethylchlorosilane. However, the subsequent ozonolytic cleavage did not proceed as smoothly. Following Clark and Heathcock's instructions, ozone was bubbled into a solution of the enol ether (62) in methanol and dichloromethane at -78°C. The addition of ozone was carefully monitored so as to minimise any side reactions occurring from the presence of excess ozone. When t.l.c.analysis registered the disappearance of starting material, a 14-fold excess of hydride was added over 90 minutes. The mixture was allowed to warm up to room temperature, evaporated, and partitioned between 10% hydrochloric acid and ether, when the hitherto colourless solution turned orange. T.l.c. analysis of the crude product revealed an extremely complex mixture of compounds. A trace amount of a product corresponding to the desired 3-oxa-lactone was observed. Presumably the mechanism of its formation would occur along the following lines, (see Chapter III p 150).


OSiMe3
O
O=O+
OSiMe3
O
O
O
OSiMe3
C
O
H
C
O
O
H
MeO
H
BH3Na
OSiMe3
C
O
H
C
O
O
MeO—H
O
OSiMe3
C
O
H
C
O
O
H
BH3
O
CH3
H
H
BH3
O
CH3
C
O
OH
H
C
OH
H
O
C
O

(85)

Therefore, it would appear that only a 3-fold hydride excess was necessary to produce the hydroxy acid (85). Furthermore, the change in colour observed on treatment with 10% hydrochloric acid may have indicated decomposition of the molecule.

In view of the fact that sodium borohydride reduction of the ketone precursor (58) led to by-products, presumably arising through dechlorination and dehydrochlorination, a vast excess of the reagent was not desirable.

Consequently, the experiment was repeated with 4 hydride equivalents of sodium borohydride and 3.6% hydrochloric acid. On this occasion the crude mixture was less complex and 6% of the 3-oxa-lactone (63) was isolated. The presence of a large proportion of more polar compounds of very low R_f, would suggest the possibility of uncyclised hydroxy acid (85). This was substantiated by an i.r. of this fraction, where hydroxy and carboxylic acid signals were evident. As a result, in the next attempt the crude mixture was stirred with 10% hydrochloric acid for $\frac{1}{2}$ hour at $0^{o}C$, in an effort to promote cyclisation. Purification allowed a slightly increased yield of 10% of the desired lactone. However, as polar materials were still apparent by t.l.c., in retrospect, it may have been advisable to continue stirring with acid for a longer period of time. Indeed, Vandewalle et al.[209] have reported acid mediated cyclisation over 5 hours at $20^{o}C$, although in this case decomposition may have resulted. Alternatively, intramolecular dehydration may have been effected with dicyclohexylcarbodiimide, or diethyl azodicarboxylate and triphenylphosphine.[190] On a different note, the use of lithium aluminium hydride instead of sodium borohydride may have been more appropriate. Clearly, this method could be further improved, but unfortunately time did not allow this.

In conclusion, lactonisation was accomplished, albeit in low yield, by both Baeyer-Villiger oxidation and ozonolytic cleavage of the siloxyalkene. Ideally, the latter method was preferred as this provides a regiospecific route to the 3-oxa-lactone (63).

IV.7. DECHLORINATION AND DEPROTECTION

Trialkyltin hydride reduction[115,210,211] of halides proceeds via a radical mechanism which may be formulated along the following general lines:-

$$R_3SnH \longrightarrow R_3Sn\cdot + H\cdot \qquad \text{Initiation}$$

$$R_3Sn\cdot + R'Cl \longrightarrow R_3SnCl + \underset{(86)}{R'\cdot}$$

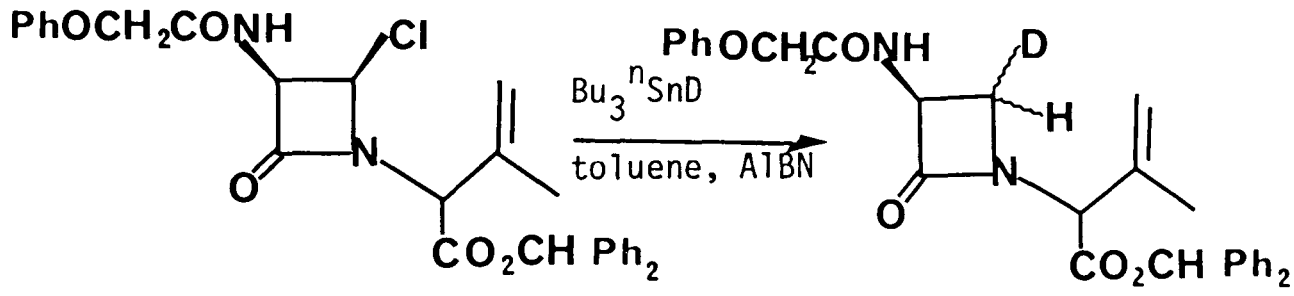
$$R'\cdot + R_3SnH \longrightarrow R'H + R_3Sn\cdot \qquad \text{Propagation}$$

$$R'\cdot + R'\cdot \longrightarrow R'-R'$$

$$R_3Sn\cdot + R'\cdot \longrightarrow R'-SnR_3$$

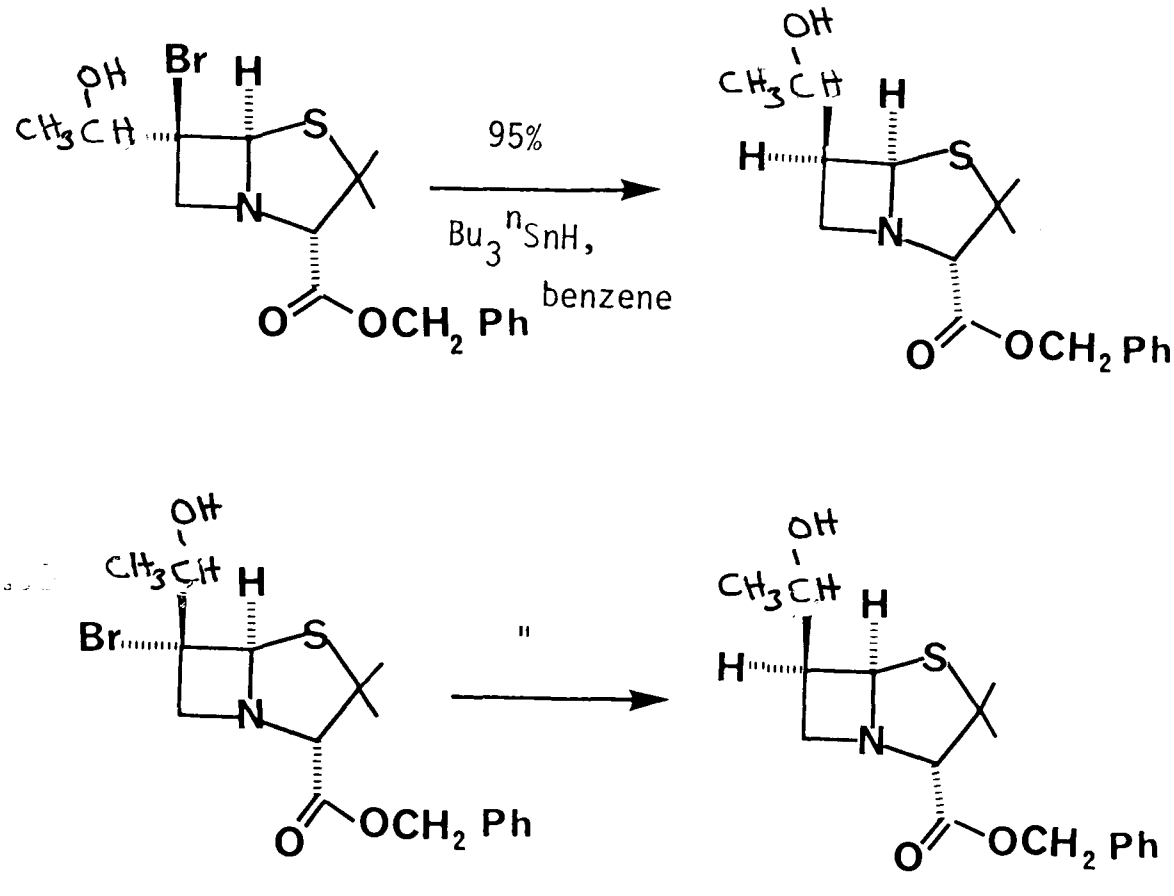
$$R_3Sn\cdot + R_3Sn\cdot \longrightarrow R_3Sn-SnR_3 \qquad \text{Termination}$$

In some cases the intermediate alkyl radical (86) may undergo inversion before donation of a hydrogen atom has had time to occur. Consequently this results in a loss of stereochemical integrity. This is exemplified by some recent work carried out by Whitesitt and Herron.[212] Reduction of chloroazetidinone with deuterated tri-n-butyl-tin hydride gave a 1:1 mixture of cis and trans isomers. viz:-

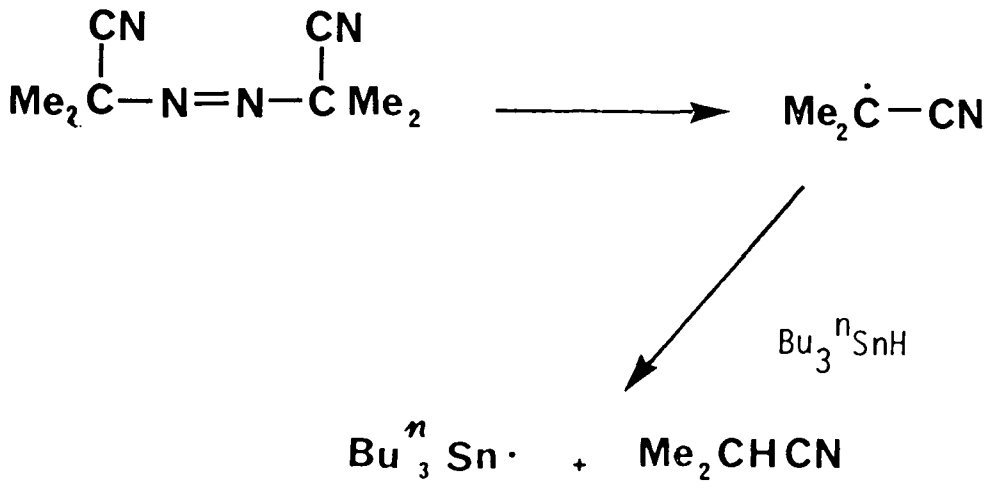


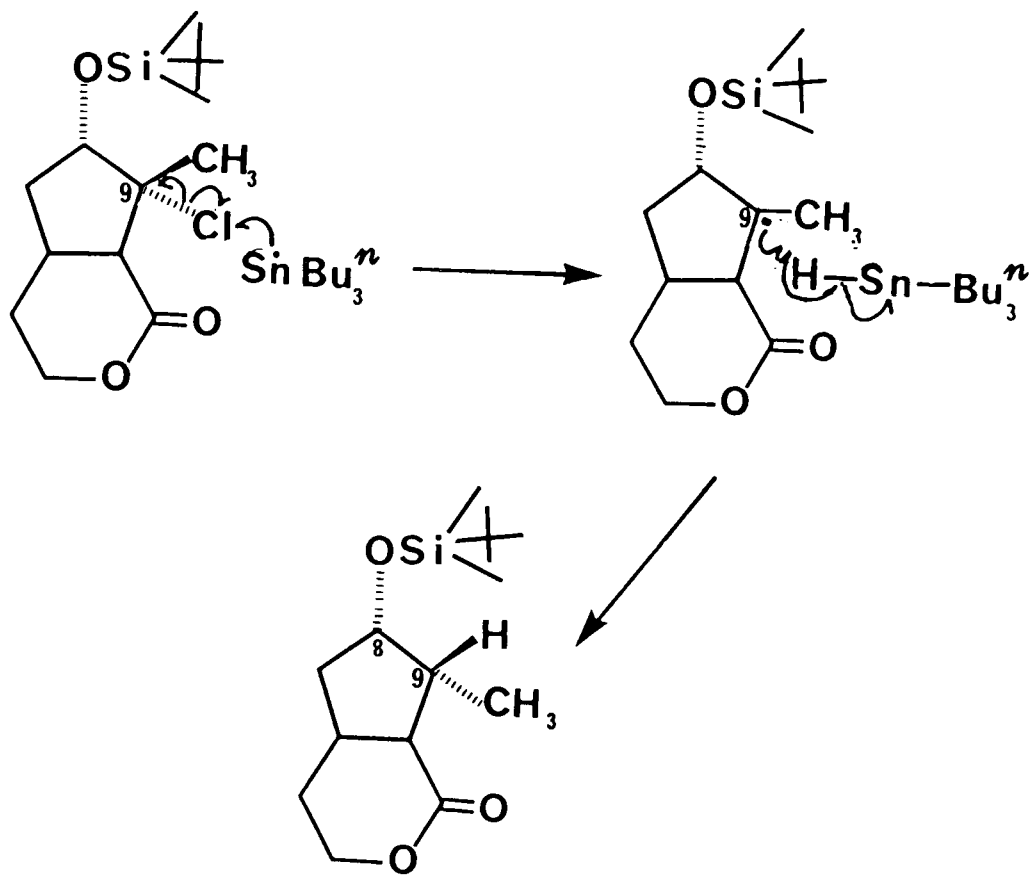
In contrast, if approach to one side of the molecule is highly encumbered, a bulky reducing agent such as tri-n-butyl-tin hydride will trap the intermediate radical from the less hindered face, allowing some measure of stereoselective control. The following examples

illustrate this point:-(213)



Similarly, as the exo-face of the 3-oxa-lactone (63) was shielded by the t-butyldimethylsilyl group, it was reasoned that access to the carbon radical would be restricted to approach from the opposite direction. This would result in inverting the methyl group at C-9, (vide infra),giving the required cis-stereochemistry exhibited in boonein.

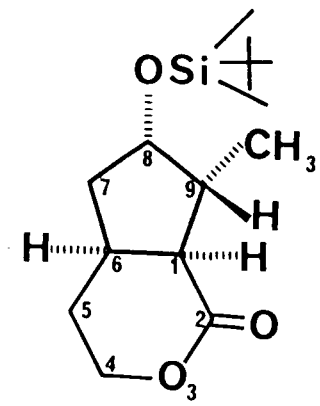




(64)

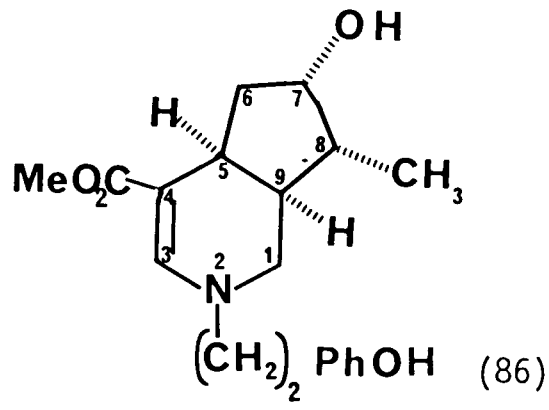
A radical initiator, such as azobisisobutyronitrile (AIBN) was required in the reaction, due to the relative lack of reactivity of alkyl chlorides with stannanes. In comparison, alkyl bromides and iodides often react readily without any initiator.

The reaction was carried out using the stannane, prepared by lithium aluminium hydride reduction of tri-n-butyltin chloride. The conditions reported by Whitesitt and Herron[212] were adopted. Accordingly, a mixture of the lactone, tin hydride, and radical initiator was heated at 65°C. After 1 hour, t.l.c. analysis registered complete disappearance of starting material, and purification of the crude product afforded 73% of a dechlorinated product. That this compound possessed the required stereochemistry at C-9 was indicated by the downfield shift of H-8 from δ3.86 in the precursor, to δ4.07. This is the region in which H-8 has been reported to resonate in boonein. Confirmation of the <u>syn</u> relationship between H-8 and the methyl group by a Nuclear Overhauser experiment was not clear-



(64)

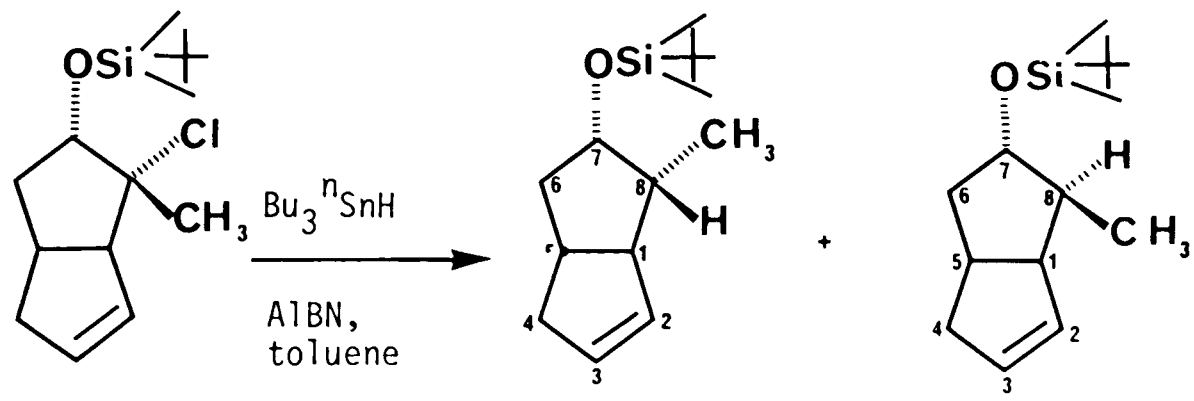
cut. The bridgehead proton H-1 appears as a doublet of doublets. A comparison of the coupling constant (J_{1-6}, 12 Hz; J_{1-9}, 9 Hz) with those quoted for a similar proton, H-9, in the recently discovered monoterpene dinklageine (86),[214] (J_{5-9}, 11 Hz; J_{8-9}, 8 Hz),



(86)

are in good agreement, thus supporting the assignment.

In order to clarify this configuration the reduction was performed on the silyl ether alkene (60), an intermediate in the synthesis. On this occasion both dechlorinated compounds were isolated.



(60) (87) : (88)

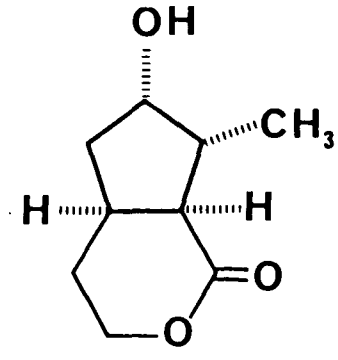
1 : 1.4

The observed ratio in favour of the endo-methyl isomer is presumably due to the folded nature of the bicyclic [3.3.0] system, discouraging attack from the concave side of the molecule.

Structural assignment was based on the chemical shift of H-7. This occurred at δ4.07 and δ3.54 for the exo- and endo-isomers respectively and the coupling constants of 8,6 and 2 Hz and 8,7 and 10 Hz for this proton were consistent with this hypothesis.

Therefore, it appeared that reduction of the 3-oxa-lactone had occurred in the desired fashion.

Final confirmation was obtained by conversion to Boonein. Cleavage of the t-butyldimethylsilyl group was only effected after heating (64) in a mixture of aqueous acetic acid and THF at 60^{o}C, for 15 hours. This extraordinarily long period of time, is at odds with the normal mildly acidic conditions employed to hydrolyse such groups. However, the reaction was successful, and purification afforded racemic boonein (65) in 89% yield. This was identical in every respect to a sample of naturally occurring d-boonein, kindly

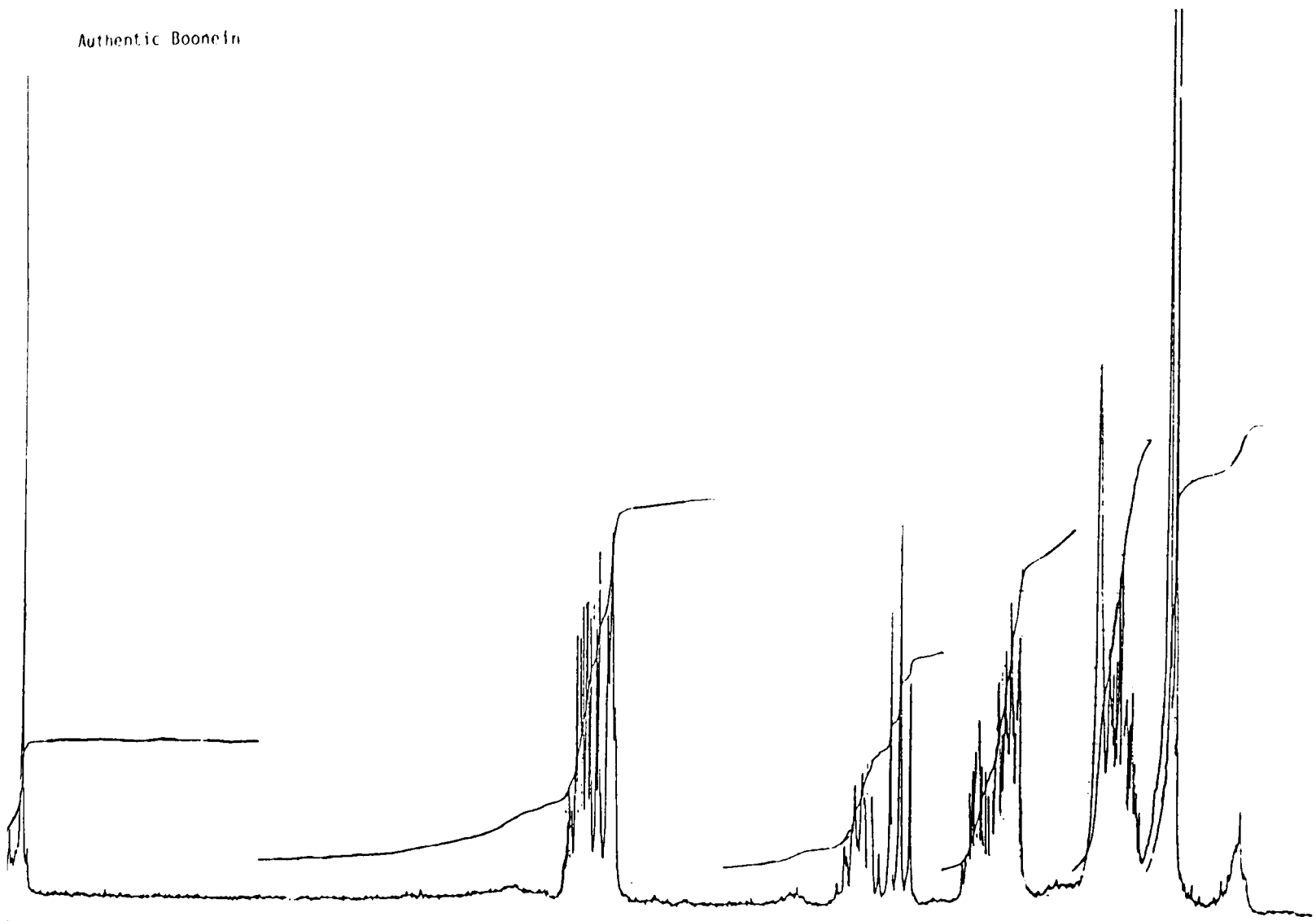


(65)

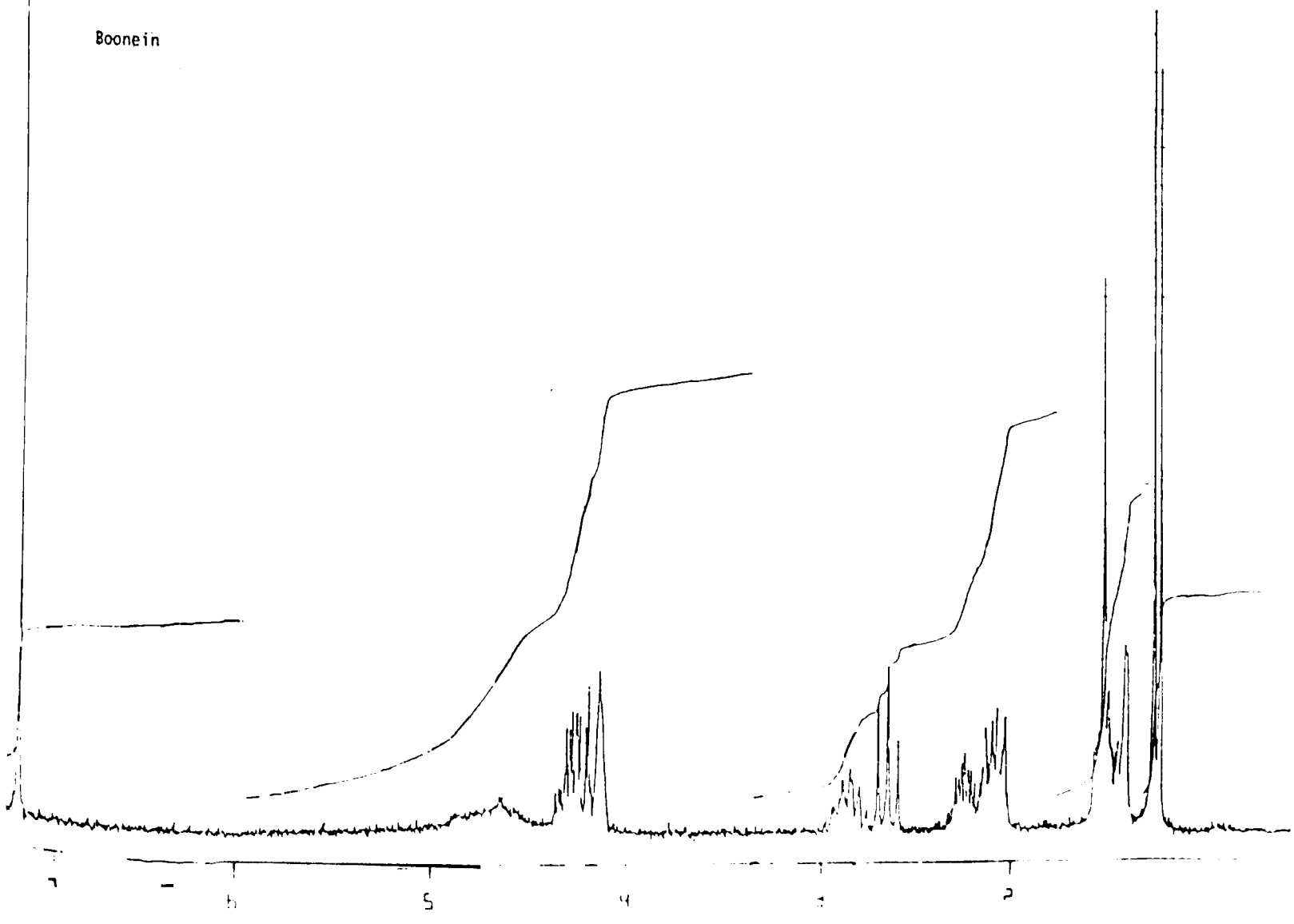
supplied by Marini-Bettolo.

This concludes the first reported total synthesis of (±)-boonein.

Authentic Boonein



Boonein



EXPERIMENTAL

N.m.r. spectra were recorded on Varian T60 (60MHz), Varian CFT-20 (80MHz) and Varian XL200 (200MHz) spectrometers; tetramethylsilane being used as internal standard in all cases. Infra-red spectra were obtained on Unicam SP3-100 and Perkin-Elmer 1420 Ratio Recording instruments. Mass spectral measurements were carried out on an A.E.I. MS902 mass spectrometer, and high resolution mass spectra were obtained from the Physico-Chemical Measurements Unit (PCMU), Harwell.

Thin layer chromatography was performed using Anachem silica gel GF_{254} analytical plates, which were developed in iodine. Flash silica (230-400 mesh) was supplied by Merck and BDH silica gel (60-120 mesh) was used for gravity column chromatography. Analytical g.l.c. analyses were carried out using a Unicam GCD chromatograph fitted with a flame ionization detector, and using nitrogen as carrier gas. The various columns and conditions used are listed below:-

(1) 10% Carbowax 20M on celite (100-120 mesh), injector and detector temperatures 250^{o}C, column (1.5m) temperature 175^{o}C, nitrogen flow rate 20ml/min; (2) as (1) but column temperature 200^{o}C; (3) 5% APL on celite, injector and detector temperatures 250^{o}C, column (2m) temperature 140^{o}C, nitrogen flow rate 20ml/min; (4) 10% OV101 on Diatomite C, injector and detector temperatures 250^{o}C, column (1.5m) temperature 110^{o}C, nitrogen flow rate 20ml/min; (5) as (4) but column temperature 150-200^{o}C at 4^{o}C/min, nitrogen flow rate 25 ml/min; (6) 5% Carbowax 20M on celite, injector and detector temperatures 200^{o}C, column (1.5m) temperature 150^{o}C, nitrogen flow rate 25ml/min; (7) 3% Dexsil 300 on Diatomite C, injector and detector temperatures 300^{o}C, column (2m) temperature 200^{o}C, nitrogen flow rate 30ml/min. Preparative g.l.c. analysis was performed using a Varian 3700 chromatograph, fitted with a Katherometer, using helium (30ml/min) as carrier gas and a 5% Carbowax 20M on celite column (1m); further conditions

are mentioned in the discussion.

Unless otherwise stated, light petroleum refers to the 40-60^{o}C boiling fraction of petroleum ether and ether refers to diethyl ether. Tetrahydrofuran (THF) and ether were dried with sodium using the benzophenone ketyl radical as indicator. In each case a persistent blue colour indicated an anhydrous state.

All organic solutions from extractions were dried over anhydrous magnesium sulphate and all melting and boiling points quoted are uncorrected. Small scale distillations were performed using a Kugelröhr bulb to bulb system, with oven temperatures being quoted.

Jones reagent was prepared by the following method:- chromium trioxide (2.72g) was dissolved in a mixture of concentrated sulphuric acid (2.3ml) and water (4.0ml). The solution was then made up to 10ml with water.

An ethereal solution of diazomethane was prepared using a Diazald kit supplied by Aldrich. A solution of p-toluenesulphonyl methylnitrosamide (Diazald) (21.4g- 0.1 mole) in ether (130ml) was added dropwise over 20 min. to a mixture of 2-(2-ethoxyethoxy)-ethanol (35ml), ether (10ml), potassium hydroxide (6g) and water (10ml) at 70^{o}C. The distillate was collected in a receiver cooled to 0^{o}C. The molarity was calculated by titration. An aliquot (5ml) was diluted with dry, distilled ether and benzoic acid (0.2$\underline{\underline{M}}$) solution in ether) added until the solution became colourless. Water and phenolphthalein were added, and the excess acid was titrated with sodium hydroxide (0.1$\underline{\underline{M}}$) solution.

Ozone was produced by passing dry compressed air through a Wallace and Tiernan BA 023 ozonator at a flow rate of approximately

25 litres/h.

The numbers adjacent to certain compounds refer to the number of the compound when quoted in the discussion.

CHAPTER V

VERNOLEPIN

V.1. FORMATION OF THE THIOENONE (2)

(a) Phenylsulphenylchloride[215,216]

A slow stream of chlorine was bubbled through carbon tetrachloride (900 ml) at 0°C, and a solution of thiophenol (144 g; 1.31 moles) in carbon tetrachloride (300 ml) added in a dropwise manner. At the end of the addition, excess chlorine was immediately removed on a rotary evaporator followed by the carbon tetrachloride. The residue was distilled under reduced pressure to afford phenyl sulphenylchloride (187 g, 99%), as an orange liquid, b.p. 46°C/0.7mm Hg (lit.[216] b.p. 73-75°C/9mm Hg), ν_{max} (thin film) 3080, 1580 (Ph) cm^{-1}, $\delta(CCl_4)$ 7.5 (5H,m,Ph).

2-Phenylthiocyclopent-2-en-1-one[103] (2)

Phenylsulphenylchloride (317 g; 2.21 moles) was added dropwise to a solution of cyclopentanone (56 g; 0.67 moles) in acetonitrile (900 ml) at room temperature (21°C). After stirring for 2½h, the solution was evaporated to give a dark brown solid (310 g). Column chromatography (on a 10 g portion of the crude product), eluting with ether and light petroleum, gave the thioenone (2) (2.4g, 59%) as orange crystals, m.p. 63-65°C (lit.[103] m.p. 64-65°C), $\nu_{max}(CCl_4)$ 3050, 2950, 2870, 1710 (C=O), 1660 (C=C) 1580 (Ph) cm^{-1}, $\delta(CCl_4)$ 7.5 (5H, m, Ph), 7.0 (1H, dd, J 2 and 3Hz, H-3), 2.7-2.4 (4H, m, 2H-4, 2H-5), m/z 190 (100%, M^+), 134 (62), 71 (60). In general, the crude mixture was roughly purified (in 50g batches) by dry flash[217] chromatography to afford the enriched product.

2-Phenylthiocyclohex-2-en-1-one (15)

The procedure described for the synthesis of the thioenone (2) was followed using cyclohexanone (2.5 g; 0.025 moles) and phenylsulphenylchloride (12 g; 0.083 moles). Flash chromatograpy,[218] eluting with

a mixture of ether and light petroleum gave the thioenone (15)(4.42 g, 85%) as yellow crystals, m.p. 30-32°C (lit.[99] m.p. 57-58°C), ν_{max} (CCl_4) 3050, 2950, 2930, 2870, 2830, 2810, 1695 (C=O), 1650 (C=C), 1580 (Ph) cm^{-1}, δ(CCl_4) 7.4 (5H,m, Ph), 6.4 (1H, dd, J 4 and 4 Hz, H-3), 2.7-1.8 (6H, m, 2H-4, 2H-5, 2H-6), m/z 204 (100%, M^+), 147 (40), 71 (38).

V.2. DIELS-ALDER REACTIONS

7a-Phenylthio-3a, 7a^{cis}-hexahydroindan-5-en-1-one (3)

(i) Method A[82]

Buta-1,3-diene (41 ml,0.474 moles) was condensed into a Carius tube containing the thioenone (2) (9.0 g;0.047 moles) and hydroquinone (0.15 g;0.0014 moles). The sealed tube was heated at 175^{o}C for 24h. The crude product (27g) was initially purified by dry flash chromatography, followed by flash chromatography, eluting with a mixture of ether and light petroleum to afford the phenylthioindanone (3) (7.6 g, 66%) as a yellow oil, (on one occasion white prisms were obtained m.p. 35^{o}C), ν_{max} (thin film) 3030, 2950, 1730 (C=O) 1660 (C=C), 1580 (Ph) cm^{-1}, $\delta(CCl_4)$ 7.35 (5H, m, Ph), 5.6 (2H, m, H-5, H-6), 2.8-1.5 (9H, m, alkyl), m/z 244 (71%, M^+), 135 (74, M - SPh), 110 (100).

(ii) Method B

A mixture of butadiene sulphone[109] (0.62 g;0.0053 moles) and thioenone (2) (0.5 g;0.0026 moles) in dibutyl ether (20 ml) was heated at 115^{o}C for 24h. T.l.c. analysis of the crude product indicated the presence of mainly starting material, with only a trace amount of phenylthioindanone (3).

(iii) Method C

The above procedure was repeated using xylene (20 ml). Similar results were obtained.

(iv) Method D

A mixture of butadiene sulphone (3.1 g;0.0263 moles), thioenone (2) (0.5 g;0.0026 moles) and hydroquinone (0.009 g;0.00008 moles) was heated in a Carius tube at 175^{o}C for 24h. The residue was washed out with ether (20 ml) and evaporated to give a brown oil. Purification by

flash chromatography gave the phenylthioindanone (3) (0.05 g,8%).

(v) Method E [112]

A solution of the thioenone (2) (0.44 g;0.002 moles) in anhydrous toluene (20 ml)was added to a catalytic amount of dry aluminium chloride, under nitrogen, at 10°C. The mixture was allowed to warm up to room temperature (21°C) and vigorously stirred for 40 min. After cooling to -78°C, buta-1, 3-diene (3.0 ml, 0.035 moles) was condensed into the flask, which was transferred to a cryogenic bath at -9°C for 72h. The resultant orange liquid was evaporated and purified by flash chromatography to afford the phenylthioindanone (3) (0.22g, 39%).

Attempted synthesis of 8a-phenylthio-3a,7a^{cis} - hexahydrodecal-6-en-1-one (16)

The thioenone (15) (0.5 g;0.0025 moles), hydroquinone (0.016 g; 0.00014 moles) and buta-1, 3-diene (4.3 ml)0.049 moles) were heated in a Carius tube at 175°C for 24h. After cooling, it was discovered that the sealed tube had exploded. T.l.c. analysis of an ether extract gave no spot corresponding to starting material and n.m.r. analysis of fractions obtained from purification did not suggest the phenylthiodecalone (16).

V.3. REDUCTION-ALKYLATION

V.3.1. Dissolved metal reduction-alkylation

7a-Carbomethoxymethyl-3a,7a *cis* -hexahydroindan-5-en-1-one(4)

The following procedure is the result of a number of attempts which are fully discussed in chapter III p 84.

Lithium (0.75 g;0.106 moles) was added to dry ammonia (100 ml at -78°C under nitrogen, to give a dark blue solution. After stirring for 10 min. a solution of phenylthioindanone (3) (2.60 g;0.01 moles) in anhydrous THF (120 ml)was added, and the mixture stirred for a further 15 min. The ammonia was removed under reduced pressure and methylbromoacetate (21.2 g;0.138 moles) was added at -20°C. After 2 min. the reaction was quenched with saturated aqueous ammonium chloride solution (30 ml)and washed with ether (3x50 ml). The combined organic layers were washed with saturated aqueous sodium bicarbonate and sodium chloride solutions, dried and evaporated to give a yellow oil. Purification by flash chromatography, using a mixture of light petroleum and ether gave the ketoester (4) (1.9 g,87%) as a colourless liquid, ν_{max} (CCl_4) 3020, 2920, 2860, 2820, 1745 (C=O), 1660 (C=C) cm^{-1}, δ(CCl_4) 5.60 (2H, m, H-5, H-6), 3.60 (3H, s, OCH_3), 2.7-1.6 (11H, m, alkyl), m/z 208 (45%, M^+), 135 (73), 134 (100), 92 (93), 91 (93). G.l.c.[1] analysis of the crude product recorded a ratio of 94:6 for the *cis* and *trans* isomers.

7a-Prop-2'-enyl-3a, 7a *cis* -hexahydroindan-5-en-1-one (27)

The previously described procedure was followed using phenylthioindanone (3) (0.5 g;0.002 moles) and allyl bromide (3.7 g;0.030 moles) to give a yellow oil. Purification by flash chromatography, eluting with a mixture of pentane and ether, gave the ketone (27) (0.25g, 69%) as a colourless liquid, b.p. 55-60°C/0.1mm Hg, (Found :

C, 81.88; H, 9.18. $C_{12}H_{16}O$ requires C, 81.77; H, 9.15%), ν_{max} (CCl_4) 3060, 3020, 2925, 2900, 2850, 2840, 1740 (C=O), 1660 and 1640 (C=C) cm^{-1}, δ(CCl_4) 5.7 (2H, m, H-5, H-6), 5.5-4.8 (3H, m, allyl) 2.7-1.7 (11H, m, alkyl), m/z 176 (10%, M^+), 135 (100, M - CH_2= CH-CH_2), 134 (90) 79 (95). G.l.c.[2] analysis of the crude product indicated a 95:5 ratio for presumably the cis and trans isomers respectively. The dialkylated ketone (28) (0.05 g,11%) was also isolated as a colourless liquid, (CCl_4) 5.7 (2H, m, H-5, H-6), 5.5-4.8 (6H, m, 2 x allyl), 2.7-1.7 (12H, m, alkyl), m/z 216 (20%, M^+), 188 (18, M - C_2H_4), 175 (94, M - CH_2 = CH-CH_2), 91 (100), 79 (86).

7a-Methyl-3a,7a cis -hexahydroindan-5-en-1-one (29)

The previous procedure for the synthesis of ketoester (4) was followed, using phenylthioindanone (3) (0.5 g;0.002 moles) and methyl iodide (4.37 g;0.030 moles). The reaction was quenched after 4½ min.to give a yellow oil. Flash chromatography using a mixture of pentane and ether gave the monoalkylated ketone (29) (0.19 g;60%) as a colourless liquid, b.p. 22°C/ 0.1mm Hg, (Found : C, 79.85; H, 9.26. $C_{10}H_{14}O$ requires C, 79.96; H, 9.39%), ν_{max} (CCl_4) 3020, 2920, 2890, 2860, 2810, 1738 (C=O), 1650 (C=C) cm^{-1}, δ(CCl_4) 5.7 (2H, m, H-5, H-6), 2.4-1.6 (9H, m, alkyl), 1.0 and 0.8 (3H, s, CH_3), m/z 150 (31%, M^+), 136 (32, M + H - CH_3), 135 (20, M - CH_3), 79 (100). G.l.c.[2] analysis of the crude product would suggest a ratio of 2:1 for the cis and trans isomers. The dialkylated ketone (30) (0.048 g, 14%) was also isolated as a colourless liquid, b.p. 21°C/0.1mm Hg, (Found : C, 80.42; H, 9.82. $C_{11}H_{16}O$ requires C, 80.44; H, 9.82%), ν_{max} (CCl_4) 3030, 2920, 2900, 2850, 2820, 1738 (C=O), 1650 (C=C) cm^{-1}, δ(CCl_4) 5.5 (2H, m, H-5, H-6), 2.6 - 1.4 (8H, m, alkyl), 1.25, 1.15, 1.00, 0.90 (6H, s, $2CH_3$) m/z 164 (82%,M^+), 149 (46, M - CH_3), 79 (100).

The experiment was repeated using different reaction times, and

the yields of monoalkylated ketone (29), dialkylated ketone (30) and indanone (26) were determined.

3a, 7a cis -Hexahydroindan-5-en-1-one (26)

The method described earlier for the synthesis of ketoester (4) was followed using phenylthioindanone (3) (0.57 g; 0.002 moles). The lithium enolate was quenched at -7°C with saturated aqueous ammonium chloride solution (10 ml) and the mixture extracted to afford a yellow oil. G.l.c. [4] analysis gave a ratio of 3:1 for presumably the cis and trans isomers respectively.

V.3.2. Lithium diisopropylamide-alkylation

2-Carbomethoxymethyl-7a-phenylthio-3a,-7a cis -hexahydroindan-5-en-1-one (31)

n-Butyl-lithium (1.54 ml of a 1.46 M solution in hexane) was added to a solution of diisopropylamine (0.32 ml; 0.0023 moles) in dry THF (10 ml) under nitrogen at -60°C. After 10 min. the phenylthioindanone (3) (0.5 g; 0.002 moles) in anhydrous THF (3 ml) was added, followed after 15 min by methylbromoacetate (0.94 g; 0.006 moles) The mixture was warmed to -12°C before quenching with saturated aqueous ammonium chloride solution (5 ml). The mixture was extracted with ether (3x20 ml) washed with saturated aqueous sodium bicarbonate and sodium chloride solutions, dried and concentrated. Flash chromatography using a mixture of chloroform and light petroleum gave the alkylated phenylthioindanone (30) (0.42 g, 87% conversion) as a yellow liquid, ν_{max} (CCl_4) 3040, 2960, 2930, 2870, 1835 (C=O), 1660 (C=C) cm^{-1}, δ(CCl_4) 7.4 (5H, m, Ph), 5.6 (2H, m, H-5, H-6), 3.7 (3H, s, OCH_3), 2.7-1.7 (10H, m, alkyl), m/z 316 (22%, M^+), 207 (46, M - SPh), 175 (83), 110 (98), 71 (100).

Starting material (0.13 g) was also recovered.

2-Carbomethoxymethyl-3a, 7a cis -hexahydroindan-5-en-1-one (31)

A solution of the alkylated phenylthioindanone (31) (0.79g; g; 0.0025 moles) in glacial acetic acid (8 ml) was added dropwise to a mixture of zinc powder (1.1 g, 0.017 moles) in glacial acetic acid[131] (10ml) and the resulting mixture was vigorously stirred at 70°C for 5h. After cooling, the zinc was removed by filtration and the filtrate diluted with chloroform (50 ml) and washed with saturated potassium carbonate solution. The organic layer was washed with water (2x50 ml), dried and evaporated to give a pale yellow liquid. Purification by flash chromatography, eluting with chloroform and subsequent dis-

tillation under reduced pressure gave the ketoester (31) (0.37 g, 79% conversion) as a colourless liquid, b.p. 120°C/0.5mm Hg, (Found : C, 69.10; H, 7.73. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74%), ν_{max} (CCl_4) 3025, 2950, 2920, 2850, 1735 (C=O), 1650 (C=C) cm^{-1}, δ(CCl_4) 5.7 (2H, m, H-5, H-6), 3.65 (3H, s, OCH_3). 2.8-1.6 (11H, m, alkyl), m/z 208 (14%, M^+), 178 (22), 177 (24), 134 (35), 116 (100).

Starting material (0.075 g) was also isolated.

A sample of the crude alkylated phenylthioindanone (30) was similarly reduced and the crude product analysed by g.l.c[1] to give a ratio of 3:2 for presumably the cis and trans isomers respectively.

V.3.3. Lewis acid catalysed alkylation of the silyl enol ether (32)

1-Trimethylsiloxy-3a,7a *cis* -hexahydroindan-1,5-diene (32)

(i) Method A

The procedure described earlier for the synthesis of ketoester (4) was followed using phenylthioindanone (3) (0.45 g; 0.0018 moles). After the removal of ammonia, triethylamine (0.11 ml 0.0008 moles) and trimethylsilyl chloride (0.46 ml 0.0037 moles) were added to the solution of lithium enolate[117] at -7°C. The mixture was allowed to warm to room temperature (21°C) and stirred for 45 min. The crude mixture was filtered through celite and evaporated. Purification by column chromatography using chloroform gave the O-silylated enolate (32) (0.16 g,36%), (see Method D for spectral data).

(ii) Attempted Method B

This involved initially preparing the reduced product (26)

3a, 7a *cis* - Hexahydroindan-5-en-1-one (26)

A solution of phenylthioindanone (3) (2 g;0.008 moles) in glacial acetic acid (15 ml) was slowly added to a mixture of zinc powder (3.6 g;0.055 moles) in glacial acetic acid (30 ml). The mixture was vigorously stirred at 70°C for 5h, and the cooled mixture was treated as described earlier. Purification by column chromatography, eluting with dichloromethane gave the indanone (26)[98] (0.66 g,60%) as a pale yellow sweet smelling liquid, ν_{max} (CCl_4),3020, 2920, 2870, 2820, 1740 (C=O), 1650 (C=C) cm^{-1}, $\delta(CCl_4)$ 5.7 (2H, m, H-5, H-6), 2.6-1.7 (10H, m, alkyl), m/z 136 (100%, M^+), 92 (81), 79 (95).

Triethylamine (3.0 g;0.03 moles) and trimethylsilyl chloride (1.4 g;0.013 moles) were added simultaneously to a solution of the indanone (26) (1.37 g;0.01 moles) in dimethylformamide (30 ml)[133] under nitrogen at room temperature, and the mixture heated under reflux for 36h. T.l.c. analysis indicated the presence of mainly starting

material, with only a trace amount of the O-silylated enolates.

(iii) Method C

A mixture of zinc powder (0.29 g;0.0045 moles, activated by washing with 5% hydrochloric acid, water, methanol, ether, and dried in vacuo), hexamethylphosphorus triamide (0.26 g;0.0015 moles) and dry THF (10 ml)under nitrogen was cooled to -10°C. A solution of phenylthioindanone (3) (0.71 g;0.0029 moles) and trimethylsilyl chloride (0.81 g;0.0075 moles) in THF was added in a dropwise manner. The mixture was stirred at room temperature (19°C) for 12h and subsequently filtered and evaporated. T.l.c. analysis of the crude product indicated the O-silylated enolate (32) to be present, but an attempt at distillation under reduced pressure resulted in decomposition.

(iv) Method D

A mixture of the indanone (26) (1.00 g;0.0074 moles) and trimethylsilyl chloride (0.99 g;0.0092 moles) in acetonitrile (15 ml) and a solution of triethylamine (0.92 g;0.0092 moles) in acetonitrile (5 ml)were simultaneously added to a solution of sodium iodide (1.37 g; 0.0091 moles) in acetonitrile (20 ml),under nitrogen at room temperature.[145] After stirring for 1½h, the reaction mixture was poured into an ice-cold water-pentane (1:1, 80 ml)mixture. The aqueous layer was washed with pentane (3x20 ml)and the combined organic extracts dried and evaporated. Column chromatography, eluting with chloroform afforded a mixture of the O-silylated enolates (32) and (34) (1.05 g,69%) as a pale yellow liquid, b.p. 110°C/6mm Hg, ν_{max} (CCl_4) 3020, 2950, 2920 2850, 1690 and 1650 (C=C) cm^{-1}, δ(CCl_4) 5.5 (2H, m, H-5, H-6) 5.0 (<< 1H, m, H-2), 2.7-0.9 (9H, m, alkyl), 0.1 (9H,s, $SiMe_3$), (Found:

$\underline{M}^+$, 208.1287 . C_{12} H_{20} O Si requires $\underline{M}$, 208.1283), $\underline{m/z}$ 208 (1%, $\underline{M}^+$), 136 (100, $\underline{M}$ + H - $SiMe_3$), 79 (97). G.l.c. [3] analysis of the crude produce indicated a ratio of 93:7 for the O-silylated enolates (32) and (34).

7a-Carbomethoxymethyl-2'-phenylthio- 3a,7a(cis)-hexahydroindan-5-en-1-one (33)

A catalytic amount of anhydrous zinc bromide was added to a stirred solution of the O-silylated enolates (32) and (34) (0.98 g; 0.0048 moles) in the presence of methyl-1-chloro-1-phenylthioacetate (35) (1.11 g;0.005 moles) in dichloromethane (20 ml), under nitrogen at room temperature (22°C).[142] Water was added after 2h and the aqueous layer was washed with dichloromethane (3x10 ml). The combined organic extracts were dried and evaporated to afford a yellow liquid, which was purified by flash chromatography using a mixture of ether and light petroleum to give the alkylated phenylthioindanone (33), the different isomers being isolated in 3 fractions:-

(a), as a white solid (0.268 g,18%), m.p. 41-44°C, ν_{max} ($CDCl_3$) 3020, 2950, 2880, 2820, 1730 (broad, C=O), 1660 (C=C) cm^{-1}, δ($CDCl_3$) 7.6 (5H, m, Ph), 6.0 (2H, m, H-5, H-6), 3.7 (3H,s, OCH_3), 3.0-1.8 (10H, m, alkyl), (Found : $\underline{M}^+$, 316.113 7. C_{18} H_{20} O_3 S requires $\underline{M}$, 316.113 3), $\underline{m/z}$ 316 (17%, $\underline{M}^+$), 207 (92,$\underline{M}$ - SPh), 135 (100, $\underline{M}$ - SPh - $CHCO_2CH_3$). (b) as a pale yellow liquid (0.32 g,21%), ν_{max} ($CDCl_3$) 3020, 2950, 2890, 2820,1730 (broad, C=O), 1660 (C=C) cm^{-1}, δ($CDCl_3$) 7.35 (5H, m, Ph), 5.6 (2H, m, H-5, H-6), 3.6 (s, OCH_3, 54% of total ester signal), 3.5 (s, OCH_3, 46% of total ester signal), 2.8-1.7 (10H, m, alkyl), (Found : $\underline{M}^+$, 316.113 5 . C_{18} H_{20} O_3 S requires $\underline{M}$, 316.113 3), $\underline{m/z}$ 316 (12%, $\underline{M}^+$), 182 (100), 135 (82). (c), as a pale yellow liquid (0.34 g,23%), ν_{max} ($CDCl_3$) 3020, 2850, 2900, 2850, 1730 (C=O), 1635 (C=C) cm^{-1},

$\delta(CDCl_3)$ 7.4 (5H, m, Ph), 5.85 (2H, m, H-5, H-6), 3.7 (3H, s, OCH_3), 3.1 - 1.8 (10H, m, alkyl), (Found : $\underline{M}^+$, 316.112 9 . $C_{18}\ H_{20}\ O_3\ S$ requires $\underline{M}$, 316. 113 3), $\underline{m/z}$ 316 (9%, $\underline{M}^+$), 182 (100), 135 (82). This constituted an overall yield of 67% for the alkylated phenylthioindanone (33).

7a-Carbomethoxymethyl-3a, 7a cis -hexahydroindan-5-en-1-one (4)

The three fractions obtained from the alkylation of the O-silylated enolates (32) and (34) were individually dissolved in acetone (1 ml) and stirred with Raney nickel at room temperature (20°C) for 2h. The mixtures were filtered, dried and evaporated. The percentage of cis- and trans-isomers of the ketoester (4) was determined by g.l.c.[1] analysis:- (a) cis (100%), (b) cis (54%), trans (46%), (c) trans (100%)- The combined weights for the two isomers gave an overall yield of cis (48%) and trans (52%).

A sample of the crude alkylated phenylthioindanone (33) (0.5 g) was similarly reduced with Raney nickel. G.l.c.[1] analysis of the crude product gave a ratio of 48:52 for the cis and trans isomers. Purification by flash chromatography, using a mixture of ether and light petroleum gave the ketoester (4). The cis-isomer (0.045 g,27%) was isolated as a colourless liquid,ν_{max} (CCl_4) 3020, 2920, 2900, 2860, 1745 (C=O), 1660 (C=C) cm^{-1}, $\delta(CCl_4)$ 5.60 (2H,m, H-5, H-6), 3.60 (3H, s, OCH_3), 2.7-1.6 (11H, m, alkyl), $\underline{m/z}$ 208 (45%, $\underline{M}^+$), 134 (100). The trans-isomer (0.053 g,31%) was obtained as a colourless liquid, ν_{max} (CCl_4) 3020, 2950, 2920, 2900, 2850, 1748 (C=O), 1640 (C=C), $\delta(CCl_4)$ 5.65 (2H, m, H-5,H-6), 3.50 (3H,s, OCH_3) 2.7 - 1.6 (11H,m, alkyl). Ths ketoester (32) (0.019 g,5%) was also isolated as a colourless liquid, ν_{max} ($CDCl_3$) 3025, 2950, 2920, 2850, 1735 (C=O), 1650 (C=C) cm^{-1}, $\delta(CDCl_3)$ 5.7 (2H, m, H-5, H-6), 3.65 (3H, s, OCH_3), 2.8-

1.6 (11H, m, alkyl), m/z 208 (14%, M^+), 116 (100).

V.4. HALOLACTONISATION AND DEHYDROHALOGENATION

5-Bromo-6, 7a cis(3'-oxa-2'-oxycyclohexa)3a,7a cis - hexahydroindan-1-one (36)

Bromine (0.25 ml;0.0044 moles) in dichloromethane (4 ml)was added to a stirred solution of the ketoester (4) (0.82 g; 0.0040 moles) in dichloromethane (15 ml),under nitrogen at -10°C.[148] After stirring for 30 min the mixture was poured into a solution of saturated sodium thiosulphate (20 ml).The aqueous layer was washed with dichloromethane (3x20 ml)and the combined organic extracts washed with brine, dried and evaporated to afford a yellow/orange semi-solid. Purification by flash chromatography, using a mixture of chloroform and ether gave the bromolactone (36) (0.47 g,44%) as a white solid m.p. 198-200°C decomp., ν_{max} ($CDCl_3$) 2970, 2915, 2850, 1740 (broad, C=O) cm^{-1}, $\delta(CDCl_3)$ 4.8 (1H, m, H-6), 4.6 (1H, m, H-5), 3.6 - 1.5 (11H, m, alkyl), m/z 273 (7%, M^+), 185 (44), 64 (97), 62 (98), 50 (100). A second fraction (0.49 g)was isolated, possibly the dibromoketoester (37), $\delta(CDCl_3)$ 4.4 and 4.1 (2H, m, H-5, H-6) 3.6 (3H, s, OCH_3), 3.2 - 2.1 (11H, m, alkyl).

7a-Carboxymethyl-3a, 7a cis -hexahydroindan-5-en-1-one (5)

Sodium hydroxide (1.96 g;0.049 moles) in water (50 ml)was added dropwise to a stirred solution of the ketoester (4) (8.47 g;0.041 moles) in THF (50 ml)at room temperature (21°C).[44] After 18h an extra portion of sodium hydroxide (0.82 g;0.021 moles) in water (20 ml)was introduced, and the mixture stirred for ½h. Acidification (pH 3), followed by extraction with dichloromethane (4x50 ml), drying and evaporation gave the acid (5) (7.5 g,102%) as a white/yellow solid, m.p. 103-107°C, ν_{max} ($CDCl_3$) 3400-3100 (broad, CO_2H), 3050, 2975, 2920, 2850, 1745 and 1715 (C=O), 1665 (C=C) cm^{-1}, $\delta(CDCl_3)$ 11.0 (1H, s, CO_2H, exchangeable on addition of D_2O), 5.7 (2H, m, H-5, H-6), 2.8 - 1.7 (m,

alkyl).

5-Iodo-6, 7a cis(3'-oxa-2'-oxycyclohexa)3a,7a cis - hexahydroindan-1-one (6)

Sodium bicarbonate (8.48 g;0.100 moles) in water (180 ml)was added to the acid (5) (7.47 g;0.042 moles), the dissolution of which was aided by agitation and gentle warming.(44) The resulting solution was cooled to $0^{o}C$ and a mixture of iodine (24.47 g;0.096 moles) and potassium iodide (80.80 g;0.487 moles) in water (160 ml)introduced. After stirring for 1h at $0^{o}C$, the mixture was warmed to room temperature ($21^{o}C$) and stirred in the dark for 64h. The brown mixture was filtered and the residue washed well with ether to give the iodolactone (6) (8.32 g,63%) as a yellow powder, m.p. 126 - $128^{o}C$ decomp. The filtrate was extracted with ethyl acetate (4x150 ml)washed with saturated aqueous sodium thiosulphate solution (150 ml),dried and evaporated to give a yellow oil. Trituration with a mixture of ether and ethyl acetate (1:1, 10 ml)gave the iodolactone (6) (1.80 g,13%) as a yellow power, ν_{max} (KBr) 2990, 2970, 2950, 2900, 2845, 1735 (broad, C=0) cm^{-1}, δ(acetone-d_6) 4.65 (1H, m, H-6), 4.4 (1H, m, H-5), 2.8 - 1.6 (1H, m, alkyl), m/z 320 (10%, M^{+}), 193 (100, M - I), 70 (78), 61 (98).

6, 7a cis(1'oxa-2'-oxycyclohexa-4',6')3a, 7a cis - hexahydroindan-4-en-1-one (7)

A solution of diazabicyloundecane (0.32 g;0.0021 moles) in dry benzene (3 ml)was added to a stirred suspension of iodolactone (6) (0.267 g;0.0008 moles) in anhydrous benzene (20 ml),under nitrogen at room temperature ($20^{o}C$).(44) The mixture was stirred for 40h and then filtered through celite, which was washed well with ethyl acetate (2x20 ml).The combined filtrates were evaporated to give a brown oil, which was purified by flash chromatography, eluting with a mixture of

chloroform and ethyl acetate. The ketolactone (7) (0.107 g,67%) was obtained as white prisms, m.p. 87 - 89°C, ν_{max} ($CDCl_3$) 3030, 2950, 2925, 2850, 1730 (broad, C=O), 1640 (C=C) cm^{-1}, δ($CDCl_3$) 6.2 (2H, m, H-4, H-5), 4.8 (1H, m, H-6), 3.4 - 1.8 (9H, m, alkyl). (Found: M^+, . $C_{11}H_{12}O_3$ requires 192.078638), m/z 192 (42%, M^+), 148 (85), 91 (100).

V.5. RESOLUTION

3a,7a^{cis},7a (N-4'-phenylethyl-2'-carbamidomethyl-1') 6-hydroxyhexahydroindan -4-en-1-one (39) and (40)

2-Hydroxypyridine (0.1 g,0.0011 moles) was added to a solution of the ketolactone (7) (0.21 g,0.0011 moles) in anhydrous toluene (20 ml) under nitrogen. A solution of S-(−)-α-phenylethylamine (0.26 g,0.0021 moles) in toluene (10 ml)was introduced and the mixture heated under reflux for 20h,[149,150] (unfortunately the mixture dried out overnight leaving a black tar). The residue was dissolved in dichloromethane (15 ml),washed with hydrochloric acid (0.5M, 5 ml),dried and evaporated. An initial purification by dry flash chromatography was followed by flash chromatography, using a mixture of chloroform and ethyl acetate to afford the two isomeric amides (39) and (40)(0.0217 g,7% and 0.0125 g, 4%), ν_{max} ($CDCl_3$) 3440 (broad, OH, NH), 3150, 3020, 2960, 2950, 2900, 2870, 1730 (C=O), 1680 (C=O), 1580 (Ph), 1540 (NH) cm^{-1}, δ($CDCl_3$) 7.2 (6H,m, Ph and NH. The integration decreases to 5H on D_2O exchange), 6.0 (2H, m, H-4, H-5), 4.7 (1H, m, H-6), 4.35 (1H, m, H-4'), 2.8 - 1.8 (9H, m, alkyl), 1.8 (1H, m, OH, disappears on D_2O exchange), 1.4 (3H, d, J 7 Hz, CH_3), m/z 295 (4%, M - H_2O), 220 (4, M - Ph - CH_3 - H), 203 (9, M - Ph - CH_3 - H_2O), 192 (21, M - Ph - Me - C - OH), 105 (100, PhCHMe)

V.6. FORMATION OF THE DICARBOXYLIC ACID (9)

V.6.1. Oxidative double bond cleavage with molybdenum dioxyacetylacetonate - t-butyl hydroperoxide

Bis (2,4-pentanedionato) dioxomolybdenum (Vl)[152]

Acetylacetone (50 ml)was added to molybdenum (Vl) oxide (10 g,0.069 moles) and the mixture refluxed for 18h. The resulting yellow slurry was filtered rapidly, and the warm solution poured into light petroleum with vigorous stirring. The mixture was chilled for 1h in an ice bath, and then filtered. The residue was washed several times with light petroleum to afford molybdenum dioxyacetylacetonate (13.9 g,61%) as an orange/brown powder, m.p. 180 - 183°C decomp. (lit.[152] 185°C decomp.).

1-Trimethylsiloxycyclohex-1-ene (41)

(i) Method A

A solution of cyclohexanone (5.0 g,0.051 moles) in dry THF (5 ml) was slowly added to a solution of lithium diisopropylamide (6.01 g;0.056 moles) in anhydrous THF (10 ml)under nitrogen at -60°C. After stirring for 30 min. trimethylsilyl chloride (7.08 ml,0.056 moles) was introduced. The white suspension was allowed to warm to 20°C and then filtered rapidly through celite and evaporated. Distillation of the crude product under reduced pressure (28mm Hg) gave two fractions: (a) (2.24g, 20-60°C); (b) (1.22g, 60-64°C), each of which contained a small amount of the O-silylated enolate (41) by t.l.c. N.m.r. analysis of the two fractions:- (a) $\delta(CCl_4)$ 4.95 (1H, dd, J 4 and 3 Hz, H-2), 3.7 (m, THF), 2.6 - 1.0 (m, alkyl), 0.3 (9H, s, $SiMe_3$), 0.2 (s, TMSCl); (b) $\delta(CCl_4)$ 4.9 (1H, m, H-2), 2.8 - 1.0 (m, alkyl), 0.2 (9H, s, $SiMe_3$), 0.1 (s, TMSCl), indicated the total amount of product in both fractions (1.02g, 12%).

(ii) Method B

Trimethylsilyl chloride (7.7 ml;0.061 moles) was added to a solution of cyclohexanone (5.0 g,0.051 moles), triethylamine (8.56 ml, 0.061 moles) and zinc bromide (0.012 g),in dry benzene under nitrogen. After refluxing for 24h the mixture was allowed to cool and then filtered through celite. Benzene was removed by atmospheric distillation, and the crude product was distilled under reduced pressure (25mm Hg). Three fractions were isolated, (0.27g, 40-50^{o}C; 0.17g, 50-60^{o}C; 5.85g, 60-70^{o}C), each of which contained some product by t.l.c. Analysis by n.m.r. indicated the total amount of O-silylated enolate (41) (4.09 g,47%).

Hexane-1,6-dioic acid

The O-silylated enolate (41) (0.51 g,0.003 moles) and molybdenum dioxyacetylacetonate (0.01 g;0.0003 moles) were dissolved in anhydrous benzene (10 ml)under nitrogen and a solution of t-butylhydroperoxide (1.35g; 0.015 moles) in dry benzene (10 ml)added dropwise.[151] The colourless solution was stirred at 60^{o}C for 48h. A mixed solution of trifluoroacetic acid, THF and water (3:1:1 20 ml) was then added, and the yellow mixture heated at 60^{o}C for a further 24h. After cooling, the organic layer was evaporated and the brown residue washed well with benzene, to afford adipic acid (0.23 g, 48%) as a fawn coloured powder, m.p. 142-146^{o}C decomp. (lit.[219] m.p. 151-154^{o}C), ν_{max} (KBr) 3400 - 3100 (broad, CO_2H), 2950, 2900, 2850, 1700 (broad, C=O) cm^{-1}, δ(acetone d_6) 7.5 (2H, m, $2CO_2H$, exchangeable on addition of D_2O), 2.5 - 1.5 (m, alkyl).

1-Trimethylsiloxy-6, 7a cis(1'-oxa-2'-oxycyclohexa-4',6'-) 3a,7a cis,hexahydroindan-2, 4-diene (8)

A solution of the ketolactone (7) (0.22 g;0.0012 moles), in

dry THF (7 ml)was slowly added to a solution of lithium diisopropylamide (0.136 g,0.0013 moles) in dry THF (20 ml),under nitrogen, at -80°C. After stirring for 45 min. trimethylsilyl chloride (0.137 g; 0.0013 moles) was introduced. The reaction mixture was allowed to warm to room temperature (20°C) and then stirred for a further 2h. The resultant yellow solution was evaporated, and the crude product purified by column chromatography, eluting with a mixture of chloroform and ethylacetate to afford the lactone O-silylated enolate (8) (0.29 g,95%) as a white solid, m.p. 77-81°C, $\nu_{max}(CCl_4)$ 3020, 2950 2900, 2850, 1740 (C=O), 1640 (C=C) 1250 ($SiMe_3$) cm^{-1}, $\delta(CCl_4)$ 6.0 (2H, m, H-4, H-5), 4.75 (1H, m, H-6), 4.65 (1H, m, H-2), 3.0 - 1.7 (7H, m, alkyl), 0.25 (9H, s, $SiMe_3$), (Found : M^+, 264.118 0. $C_{14}H_{20}O_3Si$ requires M, 264.118 2), m/z 264 (3%, M^+), 192 (28, M + H - $SiMe_3$), 91 (100).

Attempted synthesis of 3-carboxy-2-carboxymethyl-3,5 cis - (1'-oxa-2' oxycyclohexa- 4',6') cyclohex-1-ene (9)

The O-silylated enolate (8) (0.280 g;0.001 moles) and molybdenum dioxyacetylacetonate (0.0035 g;0.00001 moles) were dissolved in anhydrous benzene (10 ml)under nitrogen, and a solution of t-butyl hydroperoxide (0.382 g.0.004 moles) in dry benzene (5 ml)added dropwise. The pale yellow solution was heated at 60°C for 20h and a mixed solution of trifluoroacetic acid, THF and water (5 ml)introduced and the mixture heated at 60°C for a further 24h. The mixture was evaporated and purified by flash chromatography, using a mixture of ethylacetate and chloroform (and finally methanol) to give the ketolactone (7) (0.045 g)and two additional fractions neither of which gave n.m.r. signals corresponding to carboxylic acid, double bond (6.1) or lactone ring function (4.8).

V.6.2. Oxidation to the diketone followed by cleavage with alkaline hydrogen peroxide

6, 7a cis(1'-oxa-2'-oxycyclohexa-4',6'-) 3a, 7a cis hexahydroindan-4-en-1,2-dione (42)

(i) Method A

An aqueous solution of selenious acid (0.035 g; 0.0003 moles) in dioxane (5 ml)was added to the ketolactone (7) (0.3 g,0.0016 moles) in dioxane (5 ml)and the mixture stirred at room temperature (21^{o}C) for 24h. T.l.c. analysis showed only starting material to be present, therefore an additional portion of selenious acid (0.17 g;0.0013 moles) was introduced and stirring continued for 72h. T.l.c. showed mainly starting material with a trace amount of a lower running spot. Successive amounts of selenious acid (0.6 g in total) were added over 24h and then the reaction mixture heated to 45^{o}C for 3½h and 75^{o}C for ½h. The red/brown mixture was allowed to cool and water (20 ml)added. The aqueous layer was extracted with dichloromethane (3x20 ml),dried and evaporated to give a brown liquid. Purification by flash chromatography, using a mixture of chloroform and ethyl acetate gave (42) as a mixture of the keto and enol tautomers (0.04 g,33% conversion) as a white powder, m.p. 171-173^{o}C decomp., ν_{max} ($CDCl_3$) 3440 and 3380 (OH) 2950, 2920 1720 (C=O), 1660 (C=C) cm^{-1}, δ($CDCl_3$) 8.38 (0.9H, m, OH, exchangeable on addition of D_2O), 7.3 (0.9H, m, H-3), 6.3 (2H, m, H-4, H-5), 4.9 (1H, m, H-6), 3.4-2.0 (5H, m, alkyl), (Found : M^+, 206.057 9. $C_{11}H_{10}O_4$ requires M, 206.0579), m/z 206 (4%, M^+), 162 (10), 105 (39), 43 (10). Starting material (0.19 g was also recovered.

Oxidation with selenious acid and selenium dioxide was subsequently performed under a variety of conditions. These are referred to in the discussion.

(ii) Attempted synthesis of 2-bromo-6, 7a cis (1'-oxa-2'-oxycyclohexa-4',6'-) 3a, 7a cis, hexa hydroindan-4-en-1-one

The ketolactone (7) (0.1 g;0.0005 moles) was dissolved in a mixture of chloroform (10 ml)and ethyl acetate (10 ml)under nitrogen, and the solution heated under reflux. Cupric bromide (0.23 g,0.001 moles) was added in very small portions; each time the green colour was allowed to disappear before more reagent was added.[159] After the final addition, the solution was heated for a further 1½h. T.l.c. analysis indicated complete conversion of starting material. The mixture was allowed to cool, filtered, and the residue washed well with chloroform. The filtrate and washings were combined and and evaporated to give a yellow oil residue, which was redissolved in chloroform (20 ml),washed with water (10 ml),sodium bicarbonate solution (5%, 10 ml),brine and dried. A white solid (0.09 g)was obtained, ν_{max} ($CDCl_3$) 1730 (broad, C=O), 1640 (C=C) cm^{-1}, δ($CDCl_3$) 6.2 (2H, m, H-4, H-5), 4.9 (1H, m, H-6), 3.4 - 1.6 (m, alkyl), m/z 192 (45%, M^+), with identical spectra to starting material.

(iii) Attempted Method C

Oxygen was stored over water in the two graduated side-arms of a "hydrogenator", and was conducted to the "hydrogenation" flask through a drying tube packed with calcium chloride.

A solution of potassium t-butoxide in t-butanol (0.7 g of potassium in 20 mlof t-butanol) was introduced into the flask which was shaken in oxygen until there was no further uptake of the gas.[161] A solution of the ketolactone (7) (0.1 g;0.0005 moles) in t-butanol (2 ml)was then added, and the shaking continued for 10 min. water (20 ml)and hydrochloric acid (6M, 5 ml)were added and the mixture sub-

sequently evaporated. Water was added to the residue, and the aqueous layer extracted with chloroform (3x20 ml)and evaporated. Analysis of the crude product by t.l.c. indicated a complex mixture of compounds, and attempts at purification by either flash chromatography, preparative t.l.c. or chromatotron gave fractions which either corresponded to the ketolactone (7), or gave uninterpretable i.r. and n.m.r. spectra.

(iv) 2-Hydroxy-6, 7a $\frac{cis}{}$(1'-oxa-2'-oxycyclohexa-4',6'-)
3a, 7a $\frac{cis}{}$, hexahydroindan-4-en-1-one (46)

m-Chloroperoxybenzoic acid(0.29 g;0.0017 moles), was added in portions over 5 min to a well-stirred solution of the O-silylated enolate (8) (0.36 g;0.0014 moles) in carbon tetrachloride (30 ml), under nitrogen at room temperature (29°C). After 75 min the colourless suspension was washed with saturated aqueous sodium sulphite solution (40 ml)and saturated aqueous sodium carbonate solution (2x20 ml). The aqueous layer was subsequently back-extracted with chloroform (2x30 ml)and the combined organic layers dried and evaporated to give a colourless oil. Purification by column chromatography, eluting with a mixture of chloroform and ethyl acetate gave the following fractions:- (a), the lactone silane(47) (0.12 g,31%), $\delta(CCl_4)$ 6.0 (2H, m, H-4, H-5), 4.8 (1H, m - H-6) 4.2 (1H, m, H-2), 2.8 - 1.6 (7H, m, alkyl), 0.1 (9H, s, $SiMe_3$), (b), the ketolactone (7) (0.049 g); (c) a mixed fraction (0.172 g)which was re-purified using a chromatotron, eluting with chloroform and ethyl acetate to afford the hydroxyketone (46) (0.0177 g,6%) as a colourless liquid, ν_{max} ($CDCl_3$) 3440 (broad, OH), 2950, 2920, 2850, 1730 (C=O), 1645 (C=C) cm^{-1}, $\delta(CDCl_3)$ 6.1 (2H, m, H-4, H-5), 4.8 (1H, m, H-6), 4.2 (1H, m - H-2), 3.3 - 1.8 (7H, m, alkyl), 1.6 (1H, m, OH, exchangeable on addition of D_2O).

The lactone silane (47) (0.12 g) was dissolved in THF (10 ml), and hydrochloric acid (3M, 10 ml) added. The mixture was stirred at room temperature for 24h and then evaporated. Water (5 ml) was added to the residue and the aqueous layer extracted with ethyl acetate (3x5 ml), and the combined organic layers dried and evaporated. Purification by chromatotron, using a mixture of ethyl acetate and chloroform gave the hydroxy ketone (46) (0.0253 g, 9%).

V.6.3. Oxidative double bond cleavage with ozone-Jones reagent

Hexane-1, 6-dioic acid

Ozone was bubbled through a solution of the O-silylated enolate (41) (0.5 g;0.0029 moles) in acetone (15 ml) at -70°C, until the solution turned a faint blue colour. The freezing bath was removed, and Jones reagent added. The mixture was allowed to warm to room temperature and evaporated to dryness. Ethyl acetate (10 ml)was added to the residue and the mixture filtered through a plug of silica, which was washed well with ethyl acetate, dried and evaporated to give adipic acid (0.33 g,76%) as a white solid, m.p. 145-150°C decomp. (lit.,[219] m.p. 151-154°C), ν_{max} (KBr) 3400-3100 (broad, CO_2H), 2950, 2920, 2870, 1700 (broad, C=O) cm^{-1}, δ(acetone d_6) 7.3 (2H, m, $2CO_2H$, exchangeable on addition of D_2O), 2.6 - 1.5 (m, alkyl).

3-Carboxy-2-carboxymethyl -3,5 cis -(1'-oxa-2'-oxycyclohexa-4',6') cyclohex-1-ene (9)

Ozone was bubbled through a solution of the O-silylated enolate (8) (0.28 g;0.0011 moles) in acetone(15 ml)at -70°C until t.l.c. analysis indicated the starting material to have just reacted (9 min). The cooling bath was removed and the solution treated with Jones reagent (1.5 ml)and stirred for an additional 15 min. Excess Jones reagent was quenched with methanol, and the mixture evaporated, under reduced pressure, to dryness. The residue was dissolved in water (10 ml)and extracted with ethyl acetate (4x20 ml) dried and evaporated to give a yellow solid. Flash chromatography, eluting with a mixture of ethyl acetate and acetic acid gave the dicarboxylic acid (9) (0.19 g,73%) as a white solid, m.p. 138 - 140°C, ν_{max} (KBr) 3500 - 3300 (CO_2H), 3000, 2900, 2850, 1720 (broad, C=O) cm^{-1}, δ(acetone d_6) 10.0 (2H, m, $2CO_2H$, exchangeable on addition of D_2O),6.1 (2H, m, H-1, H-6), 4.8 (1H, m, H-5), 3.0 - 2.1 (7H, m, alkyl) m/z 240 (0.01%, M^+), 222

(2, M - H_2O), 194 (4, M - H_2O + CH_2 = CH_2), 163 (70, 222 - CH_2CO_2H) 135 (57, 163- CO).

3-Carbomethoxy-2-carbomethyoxymethyl-3,5 cis - (1 -oxa-2 -oxycyclohexa-4 ,6) cyclohex-1-ene (53)

Diazomethane (0.5 ml of a 0.364 M solution in ether) was added dropwise to a solution of the dicarboxylic acid (9) (0.0576 g; 0.0002 moles) in THF (5 ml) at room temperature (21°C) until a permanent yellow colour was obtained. After 1h, the solution was evaporated and purified by flash chromatography, using a mixture of ethyl acetate and light petroleum to afford the dimethyl ester (53) (0.033 g, 51%), as a colourless liquid, ν_{max} (CCl_4) 3040, 2990, 2950, 2920, 2840, 1742 (broad, C=O), 1648 (C=C) cm^{-1}, $\delta(CDCl_3)$ 6.02 (2H, m, H-1, H-6), 4.79 (1H, m, H-5), 3.73 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.89 - 2.14 (6H, m, alkyl).

V.7. FORMATION OF THE 2-OXA-3-DECALONE (11)

2-Carboxymethyl-3-spiro-(1'-oxa-2'-oxycyclopenta-3'-)5-hydroxycyclohex-1-ene (10)

(i) Method A

Diisobutylaluminium hydride (1.37 ml of a 1M solution in THF) was added to a solution of the dicarboxylic acid (9) (0.066 g;0.00027 moles) in anhydrous THF (10 ml) under nitrogen at -70°C, and the mixture stirred for 5h. The freezing bath was removed and the solution allowed to warm to room temperature (19°C), whereupon the reaction was quenched by the addition of water (20 ml) and sulphuric acid (1M, 10 ml), and stirred for a further 15 min. The mixture was evaporated to dryness under reduced pressure, (the crude product turned black at this stage), water (10 ml) added to the residue, and the aqueous layer extracted with ethyl acetate (3x20 ml). The combined organic extracts were washed with sulphuric acid (1M, 2x20 ml), water (20 ml), brine (20 ml), dried and evaporated. Purification by a chromatotron, eluting with a mixture of ethyl acetate, light petroleum and acetic acid gave a product, which was tentatively assigned as the spirolactone (10) (0.0039 g, 6%) as a colourless oil, ν_{max} ($CDCl_3$) 3610, 3540, (OH), 3170 (CO_2H), 3060, 2970, 2940, 2920, 2850, 1780 (C=O), 1720 (C=O), 1650 (C=C) cm^{-1}, δ($CDCl_3$) 5.9 (2H, m, H-1, H-6), 4.80 (1H, m, H-5), 4.15 (2H, m, 2H-5') 3.6 (1H, m, H-2), 2.7 - 2.2 (m, alkyl), 2.1 (1H, m, OH; disappears on the addition of D_2O).

This method could not be repeated to give the spirolactone (10).

(ii) Attempted Method B

Diisobutylaluminium hydride (1.1 ml of a 1M solution in THF) was added to a solution of the dicarboxylic acid (9) (0.076 g;0.00032 moles) in THF (2 ml) under nitrogen at -70°C. After 20 min, the follow-

ing amounts of the reducing agent (0.21 ml, 0.14 ml, 0.12 ml, 0.28 ml) were administered at 20 min. intervals. The mixture was then allowed to warm to room temperature as previously described. After acid hydrolysis, the mixture was extracted with ethyl acetate (5x50 ml), dried and evaporated. An i.r. and n.m.r. of the crude product was not consistent with the spirolactone (10), or starting material (9).

(iii) Method C

Lithium borohydride (0.0068 g; 0.00031 moles) was added to a solution of the dicarboxylic acid (9) (0.069 g; 0.00029 moles) in anhydrous THF (2 ml) under nitrogen at -60°C. The white suspension was allowed to warm to room temperature (20°C) and stirred for 2h. As t.l.c. still indicated the presence of starting material, the mixture was cooled to -50°C and a further portion of lithium borohydride (0.005 g; 0.00023 moles) introduced. The mixture was again allowed to warm to room temperature and then poured into dilute sulphuric acid (0.75 M, 30 ml) and stirred overnight. The aqueous layer was extracted with ethyl acetate (5x50 ml), dried and concentrated to give a brown oil. Purification by flash chromatography, using a mixture of ethyl acetate, light petroleum, and acetic acid gave the spirolactone (10) (0.0294 g, 45%) as a colourless oil, ν_{max} ($CDCl_3$) 3520 (broad, OH), 3300 - 3050 (broad, CO_2H), 2970, 2920, 2850, 1780 (C=O), 1715 (C=O), 1650 (C=C) cm^{-1}, δ($CDCl_3$) 6.0 (2H, m, H-1, H-6), 4.8 (1H, m, H-5), 4.2 (2H, m, 2H-5') 3.6 (1H, m, H-2), 2.7 - 2.2 (6H, m, alkyl), 2.0 (1H, m, OH, disappears on the addition of D_2O).

2-Carbomethoxymethyl-3-spiro-(1'-oxa-2'-oxycyclopenta-3'-)5-hydroxycyclohex-1-ene (10a)

Diazomethane (0.5 ml of a 0.31 M solution in ether) was added to a solution of the spirolactone (10) (0.035 g; 0.00015 moles) in

THF (2 ml). After ½h, the solution was evaporated and purified by flash chromatography to give the methyl ester (10a) (0.007 g,19%) as a white/yellow solid, ν_{max} ($CDCl_3$) 3520 and 3440 (OH), 2960, 2930, 2900, 2860, 1780 (C=O), 1735 (C=O), 1645 (C=C) cm^{-1}, δ($CDCl_3$) 5.7 (2H, m, H-1, H-6), 4.8 (1H, m, H-5), 4.2 (2H, m, 2H-5'), 3.70 (4H, m, H-2, OCH_3), 2.61 - 1.80 (m, alkyl).

8-Hydroxy- 10-hydroxyethyl-2-oxadecal-6-en-3-one (11)

(i) Method A

Method C described earlier for the synthesis of spirolactone (10) was adopted using the spirolactone (10) (0.0971 g;0.0004 moles) and lithium borohydride in the following amounts (0.0094 g;0.0004 moles initially; 0.007 g;0.0003 moles after 2h; 0.005 g;0.0002 moles after a further 2h). Work-up gave the starting material (10).

(ii) Method B

Lithium borohydride (0.008 g;0.0004 moles) was added to a solution of the spirolactone (10) (0.087 g;0.0004 moles) in dry THF (5 ml) under nitrogen, and the mixture heated under reflux for 1h. T.l.c. analysis indicated complete absence of starting material, and the mixture was allowed to cool and stirred with aqueous sulphuric acid (0.7M, 30 ml)for 2h. The aqueous layer was extracted with ethyl acetate (4x20 ml)and the combined organic layers dried and evaporated to afford a dark brown oil. Spectral analysis indicated the crude mixture to be predominantly composed of starting material (10).

(iii) Method C

Diisobutylaluminium hydride (0.5 ml of a 1M solution in THF) was added to a solution of the spirolactone (10) (0.04 g, 0.0002 moles) in dry hexane (5 ml) under nitrogen at -75°C. After 20 min, the

following amounts of the reducing agent (0.14 ml, 0.11 ml, 0.07 ml) were administered at 15 min intervals. The mixture was then allowed to warm up to room temperature as previously described. After acid hydrolysis, the mixture was extracted with ethyl acetate (5 x 30 ml), dried and evaporated. The crude product was purified by column chromatography to afford the 2-oxa-3-decalone (11), (0.017 g, 45%) as a colourless oil, ν_{max} ($CDCl_3$) 3550, 3400, 1745 cm^{-1}, δ($CDCl_3$) 5.80 (2H, m, H-6, H-7), 4.5 (1H, m, H-8), 4.30 (1H, m, OH), 4.1 (2H, dd, J 5.4 and 28 Hz, 2H-1), 3.45 (2H, m, 2H-2^1), 2.8-1.6 (m, 2H-4, 2H-9, 2H-1^1, OH), m/z 212 (15%, M^+), 194 (10%), (134, 100%).

CHAPTER VI

BOONEIN

VI.1. [2+2] CYCLOADDITION AND RING EXPANSION

7-exo-Chloro-7-endo-methylbicyclo [3.2.0] hept-2-en-6-one (57)

To a stirred solution of cyclopentadiene (76.9 g,1.17 moles) and α-chloro propionyl chloride (49.3 g,0.39 moles), in dry ether (400 ml),under nitrogen, and in the absence of light, was added triethylamine (43.2 g,0.43 moles) in a dropwise manner.[95] After the addition was complete, the mixture was stirred at room temperature for 3h. The precipitated triethylamine hydrochloride was filtered and washed with ether. The ether extracts were washed with saturated sodium bicarbonate solution (2x200 ml),water (2x300 ml),dried and evaporated to give a dark brown liquid. Purification of the crude product by distillation under reduced pressure (b.p. 84-90°C/11mm Hg. Lit.,[95] b.p. 77-90°C/11mm Hg), afforded a mixture of bicycloheptenones. Further purification by dry flash chromatography, eluting with a mixture of chloroform and light petroleum gave the 7-exo-chlorobicyclo [3.2.0] ketone (57) (35 g,58%) as a colourless liquid, ν_{max} ($CDCl_3$) 3050, 2975, 2950, 2850, 1790 (C=O), 1660 (C=C) cm^{-1}, δ($CDCl_3$) 6.35 and 6.15 (2H, m, H-2, H-3), 4.5 (1H, ddd, J 9, 9 and 4 Hz, H-5), 3.9 (1H, m, H-1), 2.9 - 2.5 (2H, m, 2H-4), 1.5 (3H, s, CH_3), m/z 156 (4%, M^+), 121 (7, M - Cl), 93 (100). The 7-endo-chloro bicyclo[3.2.0] ketone (66) (9.7 g,16%)was also isolated as a colourless liquid, ν_{max} ($CDCl_3$) 3050, 2970, 2940, 2850, 1790 (C=O), 1640 (C=C) cm^{-1}, δ($CDCl_3$) 5.8 (2H, m, H-2, H-3), 3.9 (1H, ddd, J 9, 8 and 3 Hz, H-5), 3.55 (1H,m, H-1), 2.9 - 2.5 (2H, m, 2H - 4), 1.7 (3H, s, CH_3), m/z 156 (4%, M^+), 121 (8, M - Cl), 93 (100).

8-exo-Chloro-8-endo-methylbicyclo [3.3.0] oct-2-en-7-one (58)

Diazomethane (168 ml of a 0.31 M solution in ether) and methanol

(12.7 ml) were added to the bicyclo[3.2.0] ketone (57)[175] (4.5 g, 0.029 moles), in a dropwise manner. After stirring at room temperature for 2h, the reaction was quenched with a few drops of glacial acetic acid. The solution was evaporated, redissolved in chloroform, washed with saturated sodium bicarbonate solution (2x50 ml), and the combined organic extracts dried and evaporated to afford a yellow oil. The crude product was purified by flash chromatography eluting with a mixture of ether and light petroleum to give the bicyclo [3.3.0] ketone (58) as a colourless liquid (3.78 g, 77%), b.p. 40°C/0.4 mm Hg, ν_{max} (thin film) 3060, 3010, 2960, 2920, 2850, 1750 (C=O), 1635 (C=C) cm^{-1}, $\delta(CDCl_3)$ 5.8 and 5.5 (2H, m, H-2, H-3), 3.6 (1H, m, H-1), 3.0 (1H, m, H-5), 2.6 - 2.3 (2H, m, 2H-4), 2.3 - 1.8 (2H, m, 2H-6), 1.6 (3H, s, CH_3), (Found : M^+ 170.0494. $C_9 H_{11} ClO$ requires M, 170.049838), m/z 170 (46%, M^+), 135 (83, M-Cl), 80 (100). G.l.c.[6] analysis of the crude product indicated the following yields for bicycloketones ([3.2.0] (57), 15%), ([3.3.0] (58), 79%), ([4.3.0] (58a), 6%).

VI.2. OZONOLYTIC CLEAVAGE OF THE BICYCLIC KETONE (58)

1-endo-Carboxy-2-endo-carboxymethyl-5-exo-chloro-5-endo-methylcyclopentan-4-one (68)

(i) Attempted Method A

Ozone was bubbled through a solution of the bicycloketone (58) (0.35 g;0.002 moles) in acetone (10 ml) at -78°C. After 12 min. the cooling bath was removed and Jones reagent added. Excess oxidising agent was quenched with methanol and the mixture evaporated. Water (20 ml) was added, and the aqueous layer extracted with ethyl acetate (3x20 ml), dried, and concentrated to give possibly the ozonide (69) (0.9 g, 21%), as a yellow/white solid, m.p. 95-100°C, ν_{max} ($CDCl_3$) 2990, 2965, 2940, 2850, 1755 (C=O), 1160, 1100 (C=O)cm^{-1}, δ($CDCl_3$) 5.9 and 5.8 (2H, H-2, H-4), 3.22 - 1.78 (6H, m, H-1, 2H-5, H-6, 2H-7), 1.72 (3H, s, CH_3), m/z 218 (14%, M^+), 81 (100).

The ozonide (69) was dissolved in dichloromethane (5 ml), and dimethylsulphide (5 ml) added. The mixture was stirred for 30min. evaporated, and subsequently diluted with acetone and treated with Jones reagent. T.l.c. analysis of the crude product indicated a very complex mixture of compounds.

(ii) Method B

Ozone was bubbled through a solution of the bicycloketone (58) (0.30 g;0.00176 moles) in dichloromethane (10 ml at -78°C for 11 min. The cold solution was poured onto dimethylsulphide (12 ml) at 0°C and the mixture stirred for 20 min. The solution was evaporated, dissolved in acetone (3 ml) and treated with Jones reagent. Purification of the crude product by flash chromatography, eluting with a mixture of ethyl acetate, light petroleum and acetic acid afforded the dicarboxylic acid (68) (0.31 g, 9%) as a white solid, ν_{max} ($CDCl_3$) 3500 - 3100 (CO_2H)

2990, 2940, 2870, 1755 (C=O), 1710 (C=O) cm^{-1}, $\delta(CDCl_3)$ 8.15 (2H, m, $2CO_2H$, exchangeable on addition of D_2O), 3.71 - 2.11 (6H, m, H-1, 2H-1', H-2, 2H-3).

(iii) Attempted Method C

Ozone was bubbled into a solution of the bicycloketone (58) (0.31 g;0.0018 moles) in dry dichloromethane (70 ml)at -65°C, until the solution just turned blue.(94) Excess ozone was removed by bubbling nitrogen through the solution until it became colourless. Dimethyl sulphide (3.5 ml)was added dropwise and the resulting solution stirred at -65°C for 2h and at room temperature (18°C) for 1h. The solution was evaporated and oxidised with Jones reagent. Analysis of the crude product by t.l.c. indicated a very complex mixture.

VI.3. REDUCTION

7-exo-Hydroxy-8-exo-chloro-8-endo-methylbicyclo [3.3.0] oct-2-ene (59)

(i) Method A

A solution of the bicyclic ketone (58) (2.43 g;0.014 moles) in dry ether (18 ml)was added to a vigorously stirred mixture of lithium aluminium hydride (0.23 g,0.006 moles) in anhydrous ether (40 ml),under nitrogen, at 0°C. The mixture was stirred for ½h and then quenched with wet ether (5 ml),water (5 ml),and hydrochloric acid (1M, 50 ml). After stirring for 1h, the mixture was extracted with ether (4x40 ml),washed with saturated aqueous sodium chloride solution (2x20 ml),dried and evaporated to give a yellow liquid (1.86 g). An initial attempt at purification by preparative g.l.c. [6] was unsuccessful due to decomposition at elevated temperatures. Flash chromatography, eluting with a mixture of ether and light petroleum afforded the exo-alcohol (59) (0.95 g,39%), as white needles, m.p. 53-55°C, ν_{max} ($CDCl_3$) 3560 and 3450 (OH), 3060, 2960, 2920, 2850, 1655 (C=C) cm^{-1}, δ($CDCl_3$) 5.66 (2H, m, H-2, H-3), 3.74 (1H, m, H-7), 3.46 (1H, m, H-1), 2.88 (1H, m, H-5), 2.70 (1H, m, H-4 exo), 2.08 (2H, m, H-4 endo, H-6 endo), 1.74 (1H, m, H-6 exo), 1.63 (3H, s, CH_3), (Found : M^+ 172.0660. $C_9 H_{13} ClO$ requires M, 172.0655), m/z 172 (29%, M^+), 137 (100, M - Cl), 119 (54, M - Cl - H_2O). The endo-alcohol (72) (0.65g, 27%) was isolated as a colourless oil, ν_{max} (thin film) 3550 and 3430 (OH), 3060, 2960, 2920, 2850, 1655 (C=C) cm^{-1}, δ($CDCl_3$) 5.77 (2H, m, H-2, H-3), 4.1 (1H, dd, J 4 and 5 Hz, H-7), 3.46 (1H, m, H-1), 2.92 (1H, m, H-5), 2.70 (2H, m, H-4 exo, H-6 endo), 2.23 (2H, m, H-4 endo, OH), 1.64 (3H, s, CH_3), 1.41 (1H,m, H-6 exo), (Found : M^+ 172.0652. $C_9 H_{13} ClO$ requires M, 172.0655), m/z 172 (2%, M^+), 154 (M - H_2O), 119 (100, M - H_2O - Cl). G.l.c. [6] analysis of the crude product gave a ratio of 61:39 for the exo-alcohol (59) and endo-alcohol

(72) respectively.

A Nuclear Overhauser experiment on both alcohols, irradiating H-7 with a secondary field, gave no clear distinction between the two epimers.

The endo-alcohol (72) (0.36 g,0.002 moles) was oxidised by treatment of a solution in acetone (3 ml)with Jones reagent. The resultant mixture was filtered through a plug of silica, and washed well with ether, Evaporation gave the bicycloketone (58) (0.34 g, 96%).

(ii) Method B

A solution of the bicyclic ketone (58) (0.259 g;0.0015 moles) in dry THF (3 ml)was added to a mixture of lithium borohydride (0.078 g; 0.0036 moles) in anhydrous THF (20 ml)under nitrogen at 0°C. After ½h, excess reducing agent was destroyed by the addition of water (5 ml)and sulphuric acid (1M, 20 ml). The mixture was concentrated and then extracted with ether (4x20 ml),dried, and evaporated to afford a yellow oil (0.16 g). Purification by flash chromatography gave the exo-alcohol (59) (0.007 g,3%), the endo-alcohol (72) (0.007 g,3%) and the dechlorinated alcohol (71) (0.059 g,18%) as a colourless liquid, ν_{max} ($CDCl_3$) 3620, 3540 and 3440 (OH), 3050, 2950, 2920, 2860, 1650 (C=C) cm^{-1}, δ($CDCl_3$) 5.64 (2H, m, H-2, H-3), 3.70 (1H, m, H-7), 2.68 - 2.21 (7H, m, H-1, H-5, 2H-4, 2H-6, H-8), 1.75 (1H, m, OH, exchangeable on addition of D_2O), 1.05 (3H, d, J 7 Hz, CH_3), m/z 138 (13%, M^+), 120 (97, M-H_2O), 105 (100, M - H_2O - CH_3). G.l.c. [6] analysis of the crude product gave a ratio of 52:48 for the exo-alcohol (59) and endo-alcohol (72) respectively.

The experiment was repeated using the bicyclic ketone (58) (0.20 g;0.00115 moles) and lithium borohydride (0.011g: 0.0005 moles),

the reaction being quenched after 15 min. An identical ratio was obtained for the exo- and endo-alcohols, and dechlorinated product was present.

(iii) Method C

Sodium borohydride (0.06 g;0.0015 moles) was added to a solution of the bicyclic ketone (58) (0.25 g;0.0015 moles) in methanol (20 ml)under nitrogen, at room temperature. After stirring for 15 min, water (10 ml)was introduced and the mixture concentrated. The aqueous layer was washed with chloroform (3x10 ml),the combined organic fractions dried and evaporated. Both g.l.c. [6] and t.l.c. analyses indicated complex mixtures with substantial amounts of dechlorinated product (71).

A ratio of 41:59 for the exo- and endo-alcohols was obtained.

(iv) Method D

Diisobutylaluminium hydride (20 mlof a 1.0 M solution in THF) was added to a solution of the bicyclic ketone (58) (0.97 g,0.0057 moles) in hexane (30 ml),under nitrogen, at -70°C. After stirring for 1½h, the mixture was allowed to warm up to 10°C and subsequently quenched by the addition of water (100 ml)and sulphuric acid (1M, 150 ml). The mixture was extracted with ether (3x50 ml) washed with water (2x20 ml),dried and evaporated to give a yellow liquid (1.0 g). Flash chromatography, eluting with a mixture of ether and light petroleum afforded the exo-alcohol (59) (0.25 g,25%), and the endo-alcohol (72) (0.46 g,47%). G.l.c. [6] analysis of the crude product gave a ratio of 37:63 for the exo- and endo-alcohols.

(v) Method E

Sodium (0.045 g;0.002 moles) in toluene (7ml) was added to a

solution of the bicyclic ketone (58) (0.17 g;0.001 moles) in toluene (5 ml)and ethanol (0.15 ml;0.0025 moles). The mixture was heated under reflux for 1h, cooled, and water (10 ml)introduced. The aqueous layer was washed with toluene (3x10 ml)and the combined organic extracts dried, and evaporated to give a brown liquid (0.16 g). G.l.c. [6] analysis indicated a complex mixture of products with a ratio of 1:9 for the exo- and endo-alcohols respectively.

VI.4. PROTECTION

7-exo-t-Butyldimethylsiloxy-8-exo-chloro-8-endo-methylbicyclo [3.3.0] oct-2-ene (60)

To a stirred solution of t-butyldimethylchlorosilane (0.89 g; 0.0039 moles) and diisopropylethylamine (1.08 g; 0.0084 moles) in dimethylformamide (3 ml) was slowly added a solution of the exo-alcohol (59) (0.34 g; 0.0020 moles) in dimethylformamide (3 ml) under nitrogen at room temperature.[194] After 44h, water (0.6 ml) was introduced and the mixture left for 10min. Ether (20 ml) was added and the mixture was stirred with saturated sodium bicarbonate solution (15 ml) for 15 min. extracted with ether (3x30 ml), dried and evaporated. The crude product was purified by dry flash chromatography eluting with a mixture of ether and light petroleum to afford the silylether (60) (0.56 g, 100%) as a colourless liquid b.p. 55-60°C/0.05mm Hg, ν_{max} (thin film) 3050, 2950, 2920, 2890, 2850, 1650 (C=C), 1250, cm^{-1} ($SiMe_2$), $\delta(CDCl_3)$ 5.68 (2H, m, H-2, H-3), 3.78 (1H, dd, J 8 and 10 Hz, H-7), 3.44 (1H, m, H-1), 2.9 (1H, m, H-5), 2.71 (1H, m, H-4 exo), 2.15 (2H, m, H-4 endo, H-6 endo), 1.52 (1H, m, H-6 exo), 1.57 (3H, s, CH_3), 0.90 (9H, s, Bu^t), 0.10 (6H, s, $SiMe_2$), (Found : M^+-Bu^t, 229.0807 . $C_{11}H_{18}ClOSi$ requires $M-Bu^t$, 229.0815), m/z 271 (2%, $M-CH_3$), 250 (4, $M-2CH_3$), 229 (90, $M-Bu^t$), 195 (56, $M-Bu^t$ - Cl), 93 (100).

VI.5. HYDROBORATION

7-exo-t-Butyldimethylsiloxy-8-exo-chloro-8-endo-methylbicyclo [3.3.0] oct-2-one (61)

A borane - THF complex (3.1 mlof a 1.0 M solution in THF) was added to a solution of the silylether (60) (1.76 g;0.0058 moles) in anhydrous THF (16 ml)under nitrogen, at $0^{o}C$.(200) The cooling bath was removed after the addition (2min), and the mixture was stirred at room temperature for 2h, whereupon excess borane was decomposed by the addition of water (0.34 ml). The reaction mixture was cooled in ice and dilute sodium hydroxide (3M,0.99 ml)was added followed by aqueous hydrogen peroxide (0.84 mlof a 30% solution) and the entire mixture was then warmed to $40^{o}C$ for ½h. The reaction mixture was cooled, acidified with hydrochloric acid (3M, 1.65 ml) and stirred at room temperature. After ½h, the mixture was partitioned between brine and ether and extracted. The organic layers were combined, dried and evaporated to give a mixture of the crude alcohols (2 g) ν_{max} (thin film)3370 (broad, OH), 2950, 2920, 2890, 2860, 1250 ($SiMe_2$) cm^{-1}, $\delta(CDCl_3)$ 4.3 (1H, m, OH, exchangeable on addition of D_2O), 3.8 (2H, m, H-7, H-2 or H-3) 3.1 - 1.7 (8H, m, H-5, H-1, 2H-2 or 2H-3, 2H-4, 2H-6), 1.7 (3H, s, CH_3), 0.9 (9H, s, Bu^t), 0.05 (6H, s, $SiMe_2$). The crude product was dissolved in acetone (10 ml), cooled to $0^{o}C$ and treated with Jones reagent, as described previously. The crude product was purified by flash chromatography, eluting with a mixture of light petroleum and ether, to afford the silyl ether ketone (61) (1.29 g,70%), as white rosettes m.p. 62-63^{o}C,ν_{max} (thin film) 2950, 2920, 2890, 2850, 1733 (C=O), 1250 ($SiMe_2$) cm^{-1}, $\delta(CDCl_3)$ 3.71 (1H, dd, J 12 and 8 Hz, H-7), 3.14 (1H, m, H-5), 2.77 (1H, d, J 10 Hz, H-1), 2.42 - 2.05 (3H, m, 2H-3, H-4 exo), 2.05 (1H, m, H-6 endo), 1.74 (2H, m, H-6 exo, H-4 endo), 1.66 (3H, s, CH_3), 0.94 (9H, s,Bu^t), 0.06 (6H, s, $SiMe_2$), (Found : $M^+ - Bu^t$, 245.075 1 . $C_{11}H_{18}ClO_2Si$

requires M - Bu^t 245.076 4), m/z 287 (4%, M - CH_3), 268 (4, M - Cl + H), 267 (4, M - Cl) 247 (42, M + 2 - Bu^t), 245 (100, M - Bu^t). The silyl ether ketone (75) (0.38 g,20%) was obtained as a colourless liquid, ν_{max} ($CDCl_3$) 2950, 2920, 2850, 1735 (C=O), 1250 ($SiMe_2$) cm^{-1}, δ($CDCl_3$) 3.98 (1H, dd, J 8 and 9 Hz, H-7), 3.11 (2H, m, H-5, H-1), 2.64 - 1.94 (4H, m, 2H-2, 2H-4), 1.61 (2H, m, 2H-6), 1.53 (3H, s, CH_3), 0.91 (9H, s, Bu^t), 0.07 (6H, s, $SiMe_2$),

, m/z 287 (3%, M - CH_3), 267 (3, M - Cl), 247 (30, M + 2 - Bu^t), 245 (81, M - Bu^t), 71 (100). G.l.c. [5] analysis of the crude product indicated a ratio of 79:21 for the silyl ether ketones (61) and (75) respectively.

VI.6. LACTONE FORMATION

8-exo-t-Butyldimethylsiloxy-9-exo-chloro- 9-endo-methyl-cyclopenta [1,6] hexahydropyran-2 (2H) one(63)

VI.6.1. Baeyer-Villiger oxidation

(i) Attempted Method A

Sodium bicarbonate (0.3 g;0.004 moles) and m-chloroperoxybenzoic acid (0.15 g;0.0009 moles) were added to a stirred solution of the silyl ether ketone (61) (0.16 g;0.0005 moles) in chloroform (3 ml)[202] The mixture was stirred at room temperature for 24h and heated under reflux for 17h. The cooled reaction mixture was washed with sodium sulphite solution (10%, 3x20 ml),and saturated sodium bicarbonate solution (3x20 ml). The aqueous layers were extracted with chloroform (2x30 ml)and the combined organic fractions dried and evaporated to afford a colourless oil. Column chromatography, eluting with a mixture of light petroleum and ether gave the dehydrochlorinated ketone (78) (0.049 g,65% conversion) as a colourless liquid, ν_{max} ($CDCl_3$) 2950, 2920, 2850, 1702 (C=O), 1660 (C=C), 1250 ($SiMe_2$) cm^{-1}, δ($CDCl_3$) 5.1 (1H, m, H-7), 4.2 (1H, m, H-5), 2.9 - 2.0 (6H, m, 2H-3, 2H-4, 2H-6), 1.8 (3H, s, CH_3), 0.9 (9H, s, Bu^t), 0.05 (6H, s, $SiMe_2$), m/z 266 (87%, M^+), 209 (100, M - Bu^t).

Starting material (0.077g) was also recovered.

(ii) Method B

m-Chloroperoxybenzoic acid (0.10 g;0.0006 moles) was added in portions to a stirred solution of the silyl ether ketone (61) (0.11 g; 0.0004 moles) in dichloromethane (0.8 ml). After stirring at room temperature for 24h a white suspension was obtained. Dichloromethane (10 ml)was added and the excess peracid was decomposed by washing with

sodium sulphite (10%, 3x20 ml). The organic phase was washed with saturated sodium bicarbonate solution (3x20 ml) the aqueous layers back extracted with dichloromethane (2x30 ml) and the combined organic fractions dried and evaporated. The colourless liquid was purified by flash chromatography, eluting with a mixture of light petroleum and ether to afford the 3-oxa-lactone (63) (0.025 g,26% conversion) as white rosettes, m.p. 82-84°C, ν_{max} ($CDCl_3$) 2950, 2920, 2850, 1735-1725 (broad, C=O), 1250 ($SiMe_2$) cm^{-1}, ($CDCl_3$) 4.26 (2H, m, 2H-4), 3.86 (1H, dd, J 4 and 4Hz, H-8), 3.38 (1H, d, J 15 Hz, H-6), 2.95 (1H, m, H-1), 2.09 (2H, m, H-5 exo, H-7 endo), 1.74 - 1.44 (5H, m, (including CH_3 (s) at 1.64),H-5 endo, H-7 exo), 0.90 (9H, s, Bu^t), 0.08 (6H, d, J 4 Hz, $SiMe_2$), (Found : $M^+ - CH_3$, 303.1195. $C_{14}H_{24}SiClO_3$ requires M - CH_3, 303.1183) m/z 303 (0.97%, M - CH_3), 283 (1.39, M - Cl), 263 (27.95, M + 2 - Bu^t), 261 (70.92, M - Bu^t), 57 (100, Bu^t). The 2-oxa-lactone (79) (0.0713 g,74% conversion) was also isolated as white rosettes, m.p. 56-58°C, ν_{max} ($CDCl_3$) 2950, 2920 2850, 1742 (C=O), 1250 ($SiMe_2$) cm^{-1}, δ($CDCl_3$) 4.56 (1H, d, J 6 Hz, H-1), 4.06 (1H, dd, J 10 and 8 Hz, H-8), 2.94 (1H, m, H-6), 2.54 - 2.04 (4H, m, 2H-4, H-5-exo, H-7 endo), 1.72 - 1.44 (5H, m (including CH_3(s) at 1.65), H-5 endo, H-7 exo), 0.90 (9H, s, Bu^t), 0.06 (6H, d, J 4 Hz, $SiMe_2$),

. m/z 303 (2%, M - CH_3), 263 (30, M + 2 - Bu^t), 261 (79, M - Bu^t), 151 (100, M - $OSiMe_2$ - Bu^t - Cl + H).

Starting material (0.02g) was also recovered.

(iii) Method C

Trifluoroacetic anhydride (0.44 ml; 0.0018 moles) was added dropwise to a stirred suspension of hydrogen peroxide (30% in water, 0.21 ml)in dichloromethane (5 ml)at 0°C, and the mixture stirred for

½h. A portion of the resultant trifluoroperacetic acid solution (1.25 ml of a 0.7M solution) was added to the silyl ether ketone (61) (0.075g; 0.00025 moles) in dichloromethane (5 ml).[205] The mixture was stirred for ½h at 0°C and at room temperature (25°C) for 16h. Dichloromethane (10 ml)was added and the organic layer washed with saturated sodium bicarbonate solution (3x10 ml). The aqueous layers were back-extracted with dichloromethane (2x10 ml)and the combined organic fractions dried and evaporated. T.l.c. analysis indicated the presence of mainly starting material with trace amounts of both lactones (63) and (79).

(iv) Method D

Maleic acid (0.6 g)was dissolved in dimethylformamide (1 ml) and hydrogen peroxide (30% in water, 0.2 ml)added. After 5h at room temperature, the silyl ether ketone (61) (0.037 g;0.0001 moles)in dichloromethane (1.5 ml)[202]was added and the solution stirred at room temperature (21°C) for 72h, and heated under reflux for 4h. Dichloromethane (10 ml)was added to the cooled solution and the organic layer washed with saturated sodium sulphite solution (10 ml) saturated sodium bicarbonate solution (10 ml)and water (3x5 ml). The aqueous washings were back-extracted with dichloromethane (2x10 ml) and the combined organic extracts dried and evaporated. T.l.c. analysis of the crude product indicated the presence of starting material and more polar compounds of very low R_f. Spots corresponding to either lactone were not observed.

VI.6.2. Deprotection and Baeyer-Villiger oxidation

7-exo-Hydroxy-8-exo-chloro-8-endo-methylbicyclo [3.3.0] oct-2-one (81)

(i) Method A

Tetra-n-butylammonium fluoride (1.22 ml of a 1.0 M solution in THF) was added dropwise to a solution of the silyl ether ketone (61) (0.12 g; 0.0004 moles) in anhydrous THF (2 ml) under nitrogen at room temperature. After stirring for 40h, water (5 ml) was added, and the aqueous layer extracted with ether (3x20 ml), dried and evaporated to give a yellow oil. Flash chromatography, eluting with a mixture of ether and light petroleum afforded the hydroxy ketone (81) (0.003 g, 4%) as a colourless liquid, ν_{max} ($CDCl_3$) 3600 and 3350 (OH), 2950, 2920, 2850, 1730 (C=O) cm^{-1}, δ($CDCl_3$) 3.7 (1H, m, H-7), 3.1 - 2.0 (9H, m, H-1, 2H-3, 2H-4, H-5, 2H-6, including OH at 2.0, exchangeable on addition of D_2O), 1.7 (3H, s, CH_3).

A higher running fraction of two inseparable spots (0.020 g) was also isolated, of indeterminable nature.

(ii) Method B

Acetic acid (3 ml), water (1 ml), THF (1 ml) and the silyl ether ketone (61) (0.15 g; 0.0005 moles) were stirred at room temperature (25°C) for 48h, and then at 60°C for 5h. Ether (20 ml) was added to the cooled solution which was then neutralized with saturated aqueous potassium carbonate solution. The aqueous layer was extracted with ether (3x20 ml) and the combined organic fractions washed with water (30 ml) dried and evaporated. Purification by flash chromatography, eluting with a mixture of light petroleum and ether afforded the hydroxy ketone (81) (0.045 g, 48%) as a colourless

liquid, ν_{max} (thin film) 3450 (broad) (OH), 2950, 2930, 2870, 1730 (C=O) cm^{-1}, $\delta(CDCl_3)$ 3.7 (1H, m, H-7), 3.1 - 2.0 (9H, m, H-1, 2H-3. 2H-4, H-5, 2H-6, OH), 1.7 (3H, s, CH_3) m/z 188 (6%, M^+), 153 (29, M - Cl), 152 (100, M - HCl). A second fraction, possibly the dehydrochlorinated hydroxy ketone (82) (0.003g, 3%) was obtained as a colourless liquid, ν_{max} ($CDCl_3$) 3600 and 3450 (OH), 2960, 2920, 2860, 1733 (C=O), 1660 (C=C) cm^{-1}, m/z 152 (46%, M^+), 134 (9, M - H_2O), 124 (100).

8-exo-Hydroxy-9-exo-chloro-9-endo-methylcyclopenta [1,6] hexahydropyran-2 (2H) one (83)

m-Chloroperoxybenzoic acid (0.02 g;0.0001 moles) was added to a solution of the hydroxy ketone (81) (0.013 g;0.00007 moles) in dichloromethane (0.4 ml)at room temperature (25°C), and the solution stirred for 24h. Dichloromethane (10 ml)was added and the solution treated as described previously. Purification by flash chromatography, using light petroleum and ethyl acetate as eluant gave the 3-oxa-hydroxy lactone (83) (0.0031 g,35% conversion) as white crystals, ν_{max} ($CDCl_3$) 3540 (OH), 2960, 2920, 2850, 1732-1725 (broad, C=O) cm^{-1}, m/z 186 (9%, M - H_2O), 169 (52, M - Cl), 168 (26, M - HCl), 151 (50, M - Cl - H_2O), 149 (21), 55 (100). The 2-oxa-hydroxy lactone (84) (0.0055 g,58% conversion) was also obtained as white crystals, ν_{max} ($CDCl_3$) 3560 (OH) 2960, 2920, 2850, 1738 (C=O) cm^{-1}, $\delta(CDCl_3)$ 4.6 (1H, m, H-1), 4.0 (1H, m, H-8), 2.9 - 1.7 (m, 2H-4, 2H-5, H-6, 2H-7, including OH at 2.3, exchangeable on addition of D_2O), 1.7 (3H, s, CH_3), m/z 186 (36% M - H_2O), 169 (49, M - Cl), 168 (48, M - HCl), 151 (100, M - Cl - H_2O).

Starting material (0.004g) was also recovered.

VI.6.3. Reductive double bond cleavage with Ozone-Sodium borohydride

2-Trimethylsiloxy-7-exo-t-butyldimethylsiloxy 8-exo-chloro-8-endo-methylbicyclo [3.3.0] oct-2-ene (62)

A solution of the silyl ether ketone (61) (0.061 g;0.00020 moles) in dry THF (2 ml) was slowly added to a solution of lithium di isopropylamide (0.024 g;0.00022 moles) in dry THF (2 ml) under nitrogen at -60°C. After stirring for 45 min trimethylsilylchloride (0.024 g;0.00022 moles) was introduced. The reaction mixture was allowed to warm up to room temperature (22°C) and then stirred for a further ½h. The resultant yellow solution was evaporated, and the crude product purified by column chromatography, eluting with a mixture of light petroleum and ether to afford the silyl enol ether (62) (0.074 g, 99%) as a colourless liquid, ν_{max} (thin film) 3060, 2950, 2920, 2850 1640 (C=C), 1250 ($SiMe_2$) cm^{-1}, $\delta(CDCl_3)$ 4.57 (1H, dd, J 2 and 2Hz, H-3), 3.65 (1H, dd, J 12 and 8 Hz, H-7), 3.20 (1H, m, H-1), 2.83 (1H, m, H-5), 2.62 (1H, m, H-4 exo), 2.22 (2H,m, H-4 endo, H-6 endo), 1.62 (3H, s, CH_3), 1.56 (1H, m, H-6 exo), 0.90 (9H, s, Bu^t), 0.20 (9H, s, $SiMe_3$), 0.06 (6H, s, $SiMe_2$), (Found : M^+ 374.1858 . $C_{18}H_{35}ClO_2Si_2$ requires M,374.186402), m/z 359 (4%, M - CH_3), 340 (7, M - Cl + H), 338 (8, M - Cl - H), 319 (37, M + 2 - Bu^t), 317 (89, M - Bu^t), 73 (100).

8-exo-t-Butyldimethylsiloxy-9-exo-chloro-9-endo-methylcyclopenta [1, 6] hexahydropyran-2 (2H) one (63)

Ozone was bubbled through a solution of the silyl enol ether (62) (0.15 g;0.0004 moles) in methanol (2.5 ml) and dichloromethane (0.5 ml) for 12 min. at -78°C. Sodium borohydride (0.015 g;0.0004 moles) was added, and the mixture stirred at -78°C for 15 min. After warming

to room temperature (22^{o}C) and evaporation, the residue was dissolved in ether (30 ml). The solution was cooled to 0^{o}C, hydrochloric acid (3M, 10 ml) added, and stirred for ½h. The aqueous layer was then extracted with ether (3x20 ml) and the organic layers dried and evaporated to afford a yellow oil. Purification by flash chromatography gave the 3-oxa-lactone (63) (0.013 g, 10%). This was confirmed by g.l.c. [7]

VI.7. DECHLORINATION AND DEPROTECTION

(i) 8-exo-t-Butyldimethylsiloxy-9-exo-methylcyclopenta [1, 6] hexahydropyran-2 (2H) one (64)

A solution of tri-n-butyltin chloride (0.5 g; 0.0015 moles) in dry ether (5 ml) was added dropwise to a mixture of lithium aluminium hydride (0.5 g; 0.013 moles) in anhydrous ether (10 ml). The mixture was stirred at room temperature for 20 min. and then the reaction quenched by the careful addition of wet ether (2 ml) water (5 ml), and dilute hydrochloric acid (3M, 10 ml). The aqueous layer was extracted with ether (3x30 ml) dried and evaporated to give tri-n-butyltin hydride as a colourless liquid.

A mixture of tri-n-butyltin hydride (0.104 g; 0.00036 moles), azobisisobutyronitrile (0.053 g; 0.00030 moles) and the 3-oxa-lactone (63) (0.103 g; 0.00030 moles) in dry toluene (3 ml) was heated at 65°C, under nitrogen, for 1h.[212] The cooled solution was evaporated, and the resultant white solid purified by flash chromatography, eluting with a mixture of ether and light petroleum, to give the dechlorinated lactone (64) (0.067 g, 73%) as white crystals ν_{max} ($CDCl_3$) 2960, 2920, 2870, 2850, 1725 and 1712 (broad, C=O), 1250 ($SiMe_2$) cm^{-1}, δ($CDCl_3$) 4.26 (2H, m, 2H-4), 4.07 (1H, m, H-8), 2.80 (1H, m, H-6), 2.65 (1H, dd, J 9 and 12 Hz H-1), 2.06 (3H, m, H-5-exo, H-7-endo, H-9), 1.44 (2H, m, H-5-endo, H-7-exo), 1.17 (3H, d, J 7Hz, CH_3), 0.90 (9H, s, Bu^t), 0.06 (6H, s, $SiMe_2$), (Found : M - Me, 269.159 2 . $C_{14}H_{25}O_3Si$ requires M - Me, 269.157 3), m/z 269 (1.6%, M - Me), 227 (100, M - Bu^t).

A Nuclear Overhauser Effect performed by irradiating H-8 with a secondary field gave no firm evidence for the stereochemistry of the methyl group at C-9.

(ii) 7-exo-t-Butyldimethylsiloxy -8-exo-methylbicyclo [3.3.0] oct-2-ene (87)

A mixture of freshly prepared tri-n-butyltin hydride (0.19 g; 0.0007 moles), azobisisobutyronitrile (0.099 g;0.0006 moles) and the silyl ether (60) (0.17 g;0.0006 moles) in dry toluene (5 ml)was heated under nitrogen, at 65°C, for 1½h. The solution was subsequently evaporated to afford a white solid (0.51 g). Purification by flash chromatography, eluting with heptane gave the dechlorinated alkene (87) (0.063 g,41%), as a colourless liquid, b.p. 52°C/0.3 mm Hg, ν_{max} (thin film) 3040, 2950, 2920, 2850, 1615 (C=C), 1250 ($SiMe_2$) cm^{-1}, $\delta(CDCl_3)$ 5.60 (2H, m, H-2, H-3), 4.07 (1H, ddd, J 8, 6 and 2 Hz, H-7), 2.82 (2H, m, H-1 and H-5), 2.58 (1H, m, H-4-exo), 1.99 (2H, m, H-4 endo and H-6 endo), 1.6 (1H, m, H-8), 1.3 (1H, m, H-6-exo), 1.01 (3H, d, J 8 Hz, CH_3), 0.90 (9H, s, Si-Bu^t), 0.04 (6H, s, $SiMe^2$), Found : M - m/z 252 (21%, M^+), 237 (2, M - Me), 195 (81, M - Bu^t), 75 (100). The dechlorinated alkene (88) (0.085 g,56%) was also obtained as a colourless liquid, b.p. 52°C/0.3mm Hg, ν_{max} (thin film) 3050, 2950, 2920, 2850, 1635 (C=C), 1250 ($SiMe_2$) cm^{-1}, $\delta(CDCl_3)$ 5.60 (2H, m, H-2, H-3), 3.54 (1H, ddd, J 10, 8 and 7 Hz H-7), 3.09 (1H, m, H-1), 2.66 (2H, m, H-5 and H-4-exo), 2.04 - 1.50 (4H, m, H-4 endo, 2H-6, H-8), 0.94 (3H, d, J 8 Hz, CH_3), 0.87 (9H, s, Si-Bu^t), 0.015 (6H, s, $SiMe_2$), (Found : M -

m/z 252 (15%, M^+), 237 (3, M - Me), 195 (93, M - Bu^t), 75 (100).

(±) 8-exo-Hydroxy-9-exo-methylcyclopenta [1,6] hexahydropyran-2 (2H) one (65)

A stirred mixture of the dechlorinated lactone (64) (0.044 g; 0.00016 moles), acetic acid (3 ml) water (1 ml)and THF (1 ml)was heated at 60°C for 15h. Chloroform (10 ml)was added to the cooled

solution, which was then made alkaline (pH 8)with saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with chloroform (4x15 ml)and the combined organic extracts dried and evaporated to give a pale yellow oil. Purification by flash chromatography, eluting with a mixture of ethyl acetate and light petroleum gave boonein (65) (0.023 g,89%) as white needles m.p. 95-97°C (lit.[85] m.p. 95-96°C; m.p. of authentic sample 96-97°C), ν_{max} ($CDCl_3$) 3610, 3440, (broad OH), 2960, 2925, 2870, 2850, 1725 and 1715 (broad C=O) cm^{-1}, δ($CDCl_3$) 4.40 (1H, m, OH), 4.28 (2H, m, 2H-4), 4.15 (1H, m, H-8), 2.86 (1H, m, H-6), 2.66 (1H, dd, J 10 and 12 Hz, H-1), 2.18 (3H, m, H-5 exo, H-7 endo, H-9), 1.42 (2H, m, H-5 endo, H-7 exo), 1.24 (3H, d, J 6Hz, CH_3), m/z 170 (23%, M^+), 152 (10, M - H_2O), 141 (36), 99 (100), 55 (97). T.l.c. analysis in 4 different solvent systems: (ethyl acetate, light petroleum; ethyl acetate, chloroform,chloroform; ether), demonstrated co-elution with an authentic sample of (+)-boonein.

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