To Fiona and my family, whose love and understanding have been a guidance throughout.



AN APPROACH TO THE SYNTHESIS OF THE CYTOCHALASANS

by

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AN APPROACH TO THE SYNTHESIS OF THE CYTOCHALASANS

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ABSTRACT

The cytochalasans, a group of biologically active secondary metabolites isolated from micro-organisms, are tricyclic compounds which comprise of a heavily oxygenated 11-, 13- or 14-membered ring *trans* -fused to a substituted 8-azabicyclo[4.3.0]nonane ring system.

One approach to the total synthesis of the cytochalasans involves the intramolecular Diels-Alder cyclization of a suitable 3-substituted- Δ^3-pyrrolin-2-one. As preliminary work, a synthetic route to 5S-1-acyl-5-benzyl-3-butyl- Δ^3-pyrrolin-2-ones was developed, starting from the known lactam, 5R-5-benzylpyrrolidin-2-one. However, although these dienophiles reacted stereospecifically with 2E,4E-hexadiene, the reaction conditions were harsh (200°, 30-50 h) and the sequence suffered from low overall yields.

The doubly activated dienophile, 5S-1-benzoyl-5-benzyl-3-(1-oxopropyl)-Δ^3-pyrrolin-2-one, on the other hand, was available *via* an expeditious route from the *N* -protected lactam, 5R-5-benzyl-1-(*tert*-butyldimethylsilyl)pyrrolidin-2-one. Moreover, the dienophile reacted stereoselectively with 2E,4E-hexadiene under milder conditions (100°, 8 h) to give, after deprotection, 7-benzyl-2,5-dimethyl-1-(1-oxopropyl)-8-azabicyclo[4.3.0]non-3-en-9-one. The stereochemistry of the isoindolone adduct was shown to be the same as in naturally occurring cytochalasans. The overall yield from 5R-5-benzylpyrrolidin-2-one after seven steps was 16%.

In comparative studies, the doubly activated dienophile 1-benzenesulphonyl-3-(1-oxopropyl)- Δ^3-pyrrolin-2-one was prepared and its reactions with 2E,4E-hexadiene and cyclopentadiene were studied. Although the stereoselectivity was better than for the *N*-benzoylated pyrrolin-2-one, isolated yields of cycloadducts were inferior.

Thus,as a model for an approach to the [13]cytochalasans, the diene-dienophile, 5S,12E,14E-1-benzoyl-5-benzyl-3-(1-oxohexadeca-12,14-dienyl)-Δ^3-pyrrolin-2-one, was prepared in 20% overall yield from 5R-5-benzylpyrrolidin-2-one. Regio- and stereoselective cyclization was achieved under high pressure conditions (11-13 kbar) to give a tricyclic compound in 16-35% yield. The stereochemistry of the deprotected major adduct was shown to be that required for cytochalasan synthesis. Thus, the intramolecular Diels-Alder approach to cytochalasan synthesis using diene-lactams was validated.

Acknowledgements

I should like to thank Dr. Jim Thomas for his counsel and conscientious supervision throughout the duration of this project. I am grateful also to the three generations of Part II, D. Phil. and Post-Doctoral students who provided a relaxing and amusing backdrop to the business of chemical research. In particular, many thanks are due to Liz Bish, Mick Durrant, Jon Fray, Mark Hughes, Andy Pratt, and Sunil Vather who have accompanied me throughout and offered words of encouragement and advice, or solace at appropriate times. More recently, it has been an "honour and a privilege" to work with fellow Keble-ites Tom Smith, Gareth Robinson, Simon Russell, and Charles Bingham.

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CHAPTER 1

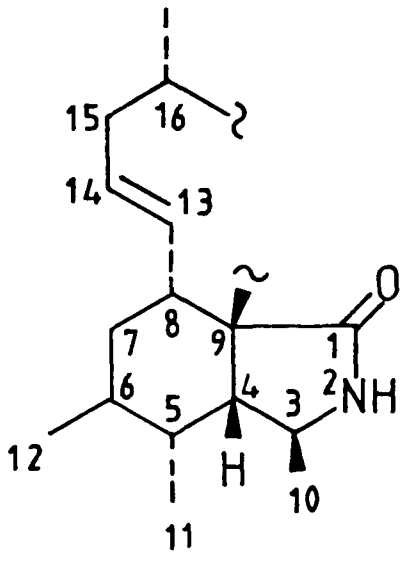
INTRODUCTION TO THE CYTOCHALASANS

This thesis describes work directed towards the total synthesis of the cytochalasans, a group of about forty biologically active secondary metabolites isolated from various moulds and micro-organisms.[1] Apart from having unique and useful effects on both mammalian and non-mammalian cells[2], the cytochalasans represent a challenging target to the synthetic organic chemist and in this regard the last decade has borne witness to the intensive efforts of several research groups (*vide infra*).

1.1 *Structural Comparison*

Since their initial discovery (1965) the number of structurally related cytochalasans has steadily increased, and several authors have written a detailed historical perspective of the story of the occurrence, isolation and structural elucidation of this group of natural products.[3] The structures of all the presently known cytochalasans are drawn in full in Appendix I. Despite the apparent bewilderment of type there are several common features (Figure 1.1) which has led to the proposal of a systematic nomenclature.[4]

Figure 1.1



i. Every cytochalasan possesses a highly substituted 8-azabicyclo[4.3.0]-nonane ring system of known absolute stereochemistry at C-3, C-4, C-8, and C-9, which is defined cytochalasan.

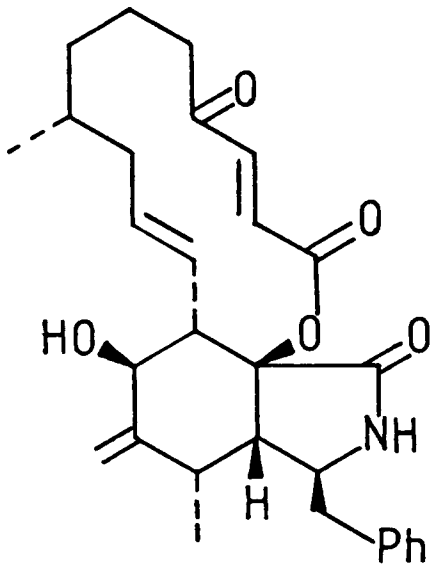
ii. *Trans* -fused to this unit across C-8 and C-9 is an 11-, 13-, or 14-membered ring which is often heavily oxygenated but which always possesses a 13E- double bond and a methyl group at C-16 of identical relative configuration (except in the aspochalasins).

There are three main types of cytochalasans, categorised by trivial names derived from their origin or on the basis of their biological activity. The cytochalasins and zygosporins are examples of [11]cytochalasans, which are all carbocyclic compounds, and of 24-oxa[14]cytochalasans which are macrolides. With the exception of cytochalasin G they all have a phenyl substituent at C-10. The chaetoglobosins on the other hand are members of the [13]cytochalasan carbocyclic family and are characterised by having an isopropyl group at C-10. Cytochalasin E is unique in possessing a 21,23-dioxa[13]cytochalasan skeleton. However, there seems to be a discrepancy between the recently reported[5] structure of cytochalasin K, which places it in the same cyclic carbonate class, and an earlier report.[6] Since the structures of both these compounds were fully elucidated at about the same time and were shown to represent new cytochalasans, the confusion of labelling probably arose from the mutual unawareness of the groups concerned.

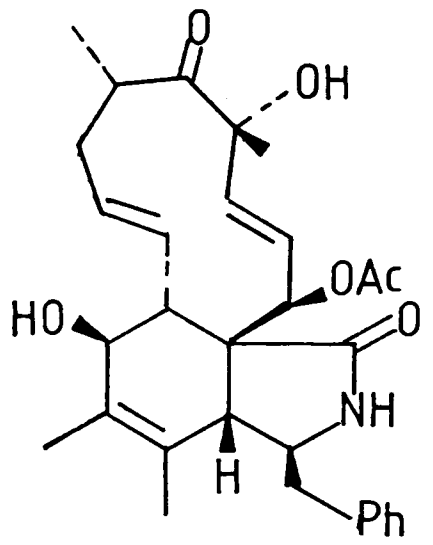
Representative examples of these structural types are illustrated in Figure 1.2. The main areas of diversity are in the variable oxidation levels of C-5, C-6, C-7, and C-12 and in the highly functionalised C-17 to C-23 portion of the macrocycle. A common feature is the exocyclic $\Delta^{6,12}$ bond in conjunction with a β-hydroxyl group at C-7 as in compounds (1) and (3). Alternatively, there may be an endocyclic $\Delta^{6,7}$ bond or a 6,7-epoxy functionality present as exemplified in metabolites (4), (5) and (6).

Figure 1.2

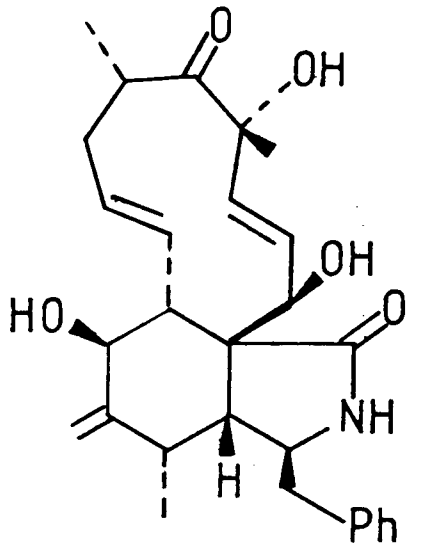
Cytochalasin A (1)



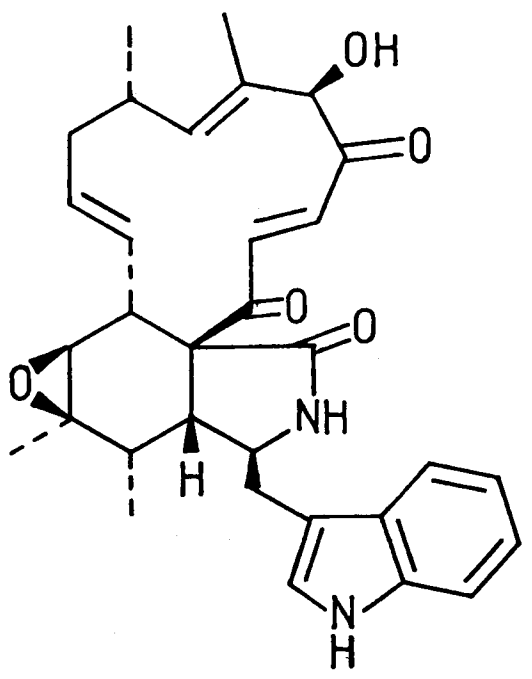
Cytochalasin C (2)



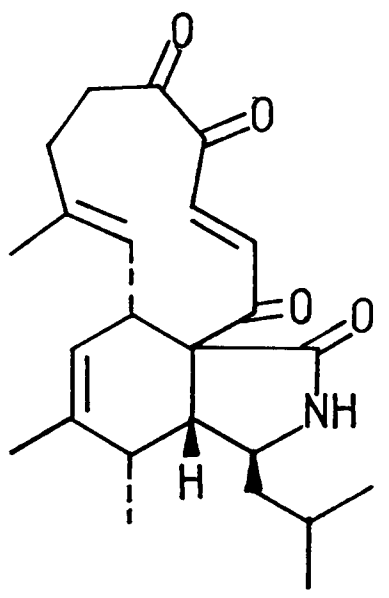
Zygosporin D (3)



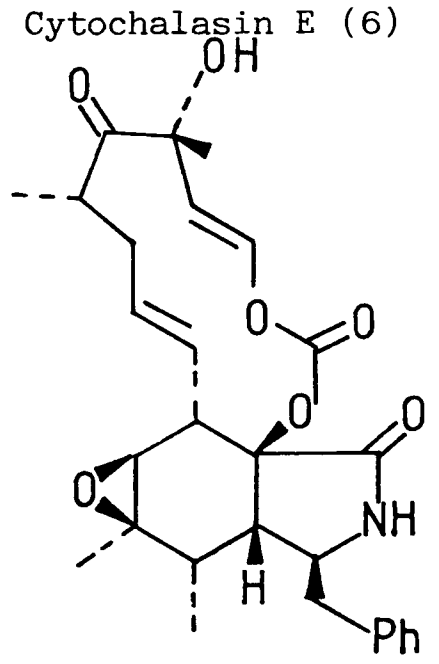
Chaetoglobosin A (4)



Aspochalasin A (5)



Cytochalasin E (6)



Finally, cytochalasin C (2) provides an example of the endocyclic $\Delta^{5,6}$ series.

1.2 *Biological Activity*

As a group the cytochalasans have remarkable effects on living cells, well described by Carter[7] and Tanenbaum.[2] In fact, the generic name describing these substances derives from one of their biological effects (Greek *cytos* ; a cell *chalasis* ; relaxation). When living cells are exposed to cytochalasin B at a concentration of 1μg/ml for several days large polynucleate cells are produced. This inhibition of cytoplasmic cleavage (cytokinesis) following the division of the nucleus (mitosis) is unique to

the cytochalasans. What is more, the effect is reversible and replacing the exposed cells in a normal culture medium results in successive cytokinesis and mononucleate cells.

At similar concentrations of cytochalasan, culture cells moving on a glass surface "freeze" and become quiescent; cell motility is, however, quickly restored once the culture medium is replaced by a normal one. This reversible interference with cell locomotion is potentially of use in helping to understand the mechanism of cell organisation and regeneration (morphogenesis) from which cancer therapy could benefit greatly.

If the cytochalasan concentration is increased to 10μg/ml, within ten minutes the nucleus of a cell may lie entirely outside the cell body, being attached only by a narrow filament. With the aid of a micromanipulator needle the nuclei can be removed quite easily to leave active enucleated cells which are useful in the study of the mechanism of gene activation and of the role of the nucleus in cell activities. Unless nuclear extrusion has proceeded too far, the effect may be quickly and completely reversed by returning the cell to a normal medium. Although the cytochalasans generally show these effects it is found that cytochalasin E (6) differs and rarely produces enucleation as well as being the only member to induce "nuclear contraction".

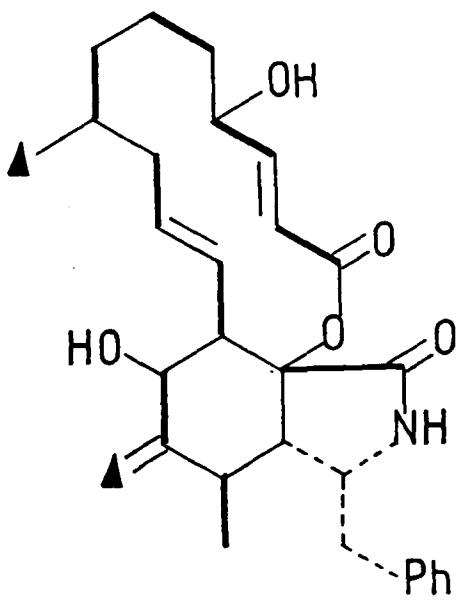
Despite the great uncertainty regarding their mode of action, the effects produced by cytochalasans at low concentrations make them useful tools in cell biology. However, the obvious sensitivity of biological systems to such chemical insults is manifested by the relatively high lethal potency to laboratory animals when exposed to high concentrations, with LD_{50} values in the range 5-200 mg/kg body weight.

1.3 *Biosynthesis*

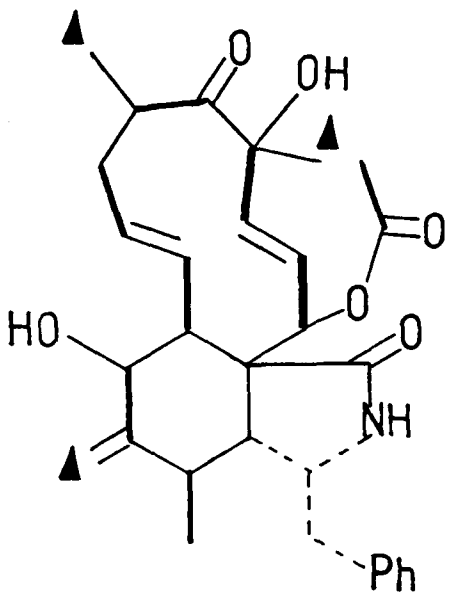
Much effort has been directed towards the elucidation of the biogenetic pathways by which cytochalasans are produced. Notable in this field is the work of Tamm *et al.* who have studied the biosynthesis of cytochalasins B (7)[8] and D (8)[9] as examples of the macrolide and carbocyclic cytochalasans, respectively. The basis of the work is to administer specifically labelled (^{3}H, ^{13}C, ^{14}C, ^{15}N) precursors (*eg.* acetate or amino acid, which are selected on the basis of a working hypothesis) to the micro-organism producing the metabolite. After isolation of the cytochalasan it is analysed for isotopic content. In the case of radioactive labels the substrate is subjected to specific chemical degradations to localize any incorporated radioactive atoms. A more convenient assay uses ^{13}C nuclear magnetic resonance (nmr) to locate carbon atoms which are isotopically enriched.

Using this methodology, the origins of all the carbon atoms in cytochalasins B and D have been established (Figure 1.3).

Figure 1.3



(7)



(8)

▲ *ex* $MeSCH_2CH_2CH(NH_2)CO_2H$

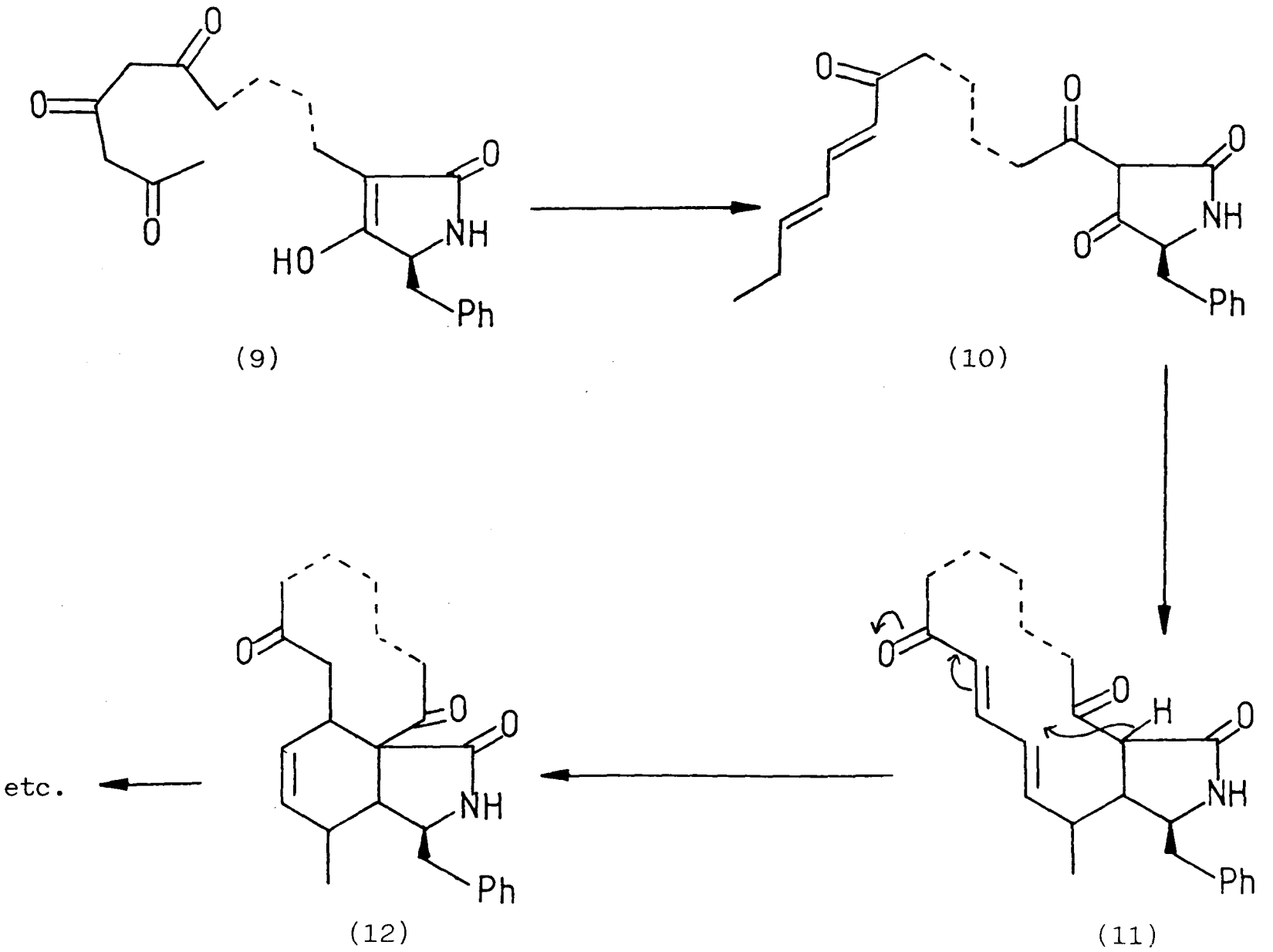
—— *ex* CH_3CO_2H

---- *ex* Phenylalanine

Thus, cytochalasin B is derived from nine acetate units, one molecule of phenylalanine and two one-carbon units from *S*-adenosyl methionine whilst cytochalasin D is made up of nine acetate units, one molecule of phenylalanine and three one-carbon units.

On the basis of these results a general biosynthetic pathway has been postulated (Scheme 1.1). A polyketide derived from the appropriate number of acetate units combines with a molecule of phenylalanine to form an intermediate amide which condenses to the lactam (9).

Scheme 1.1

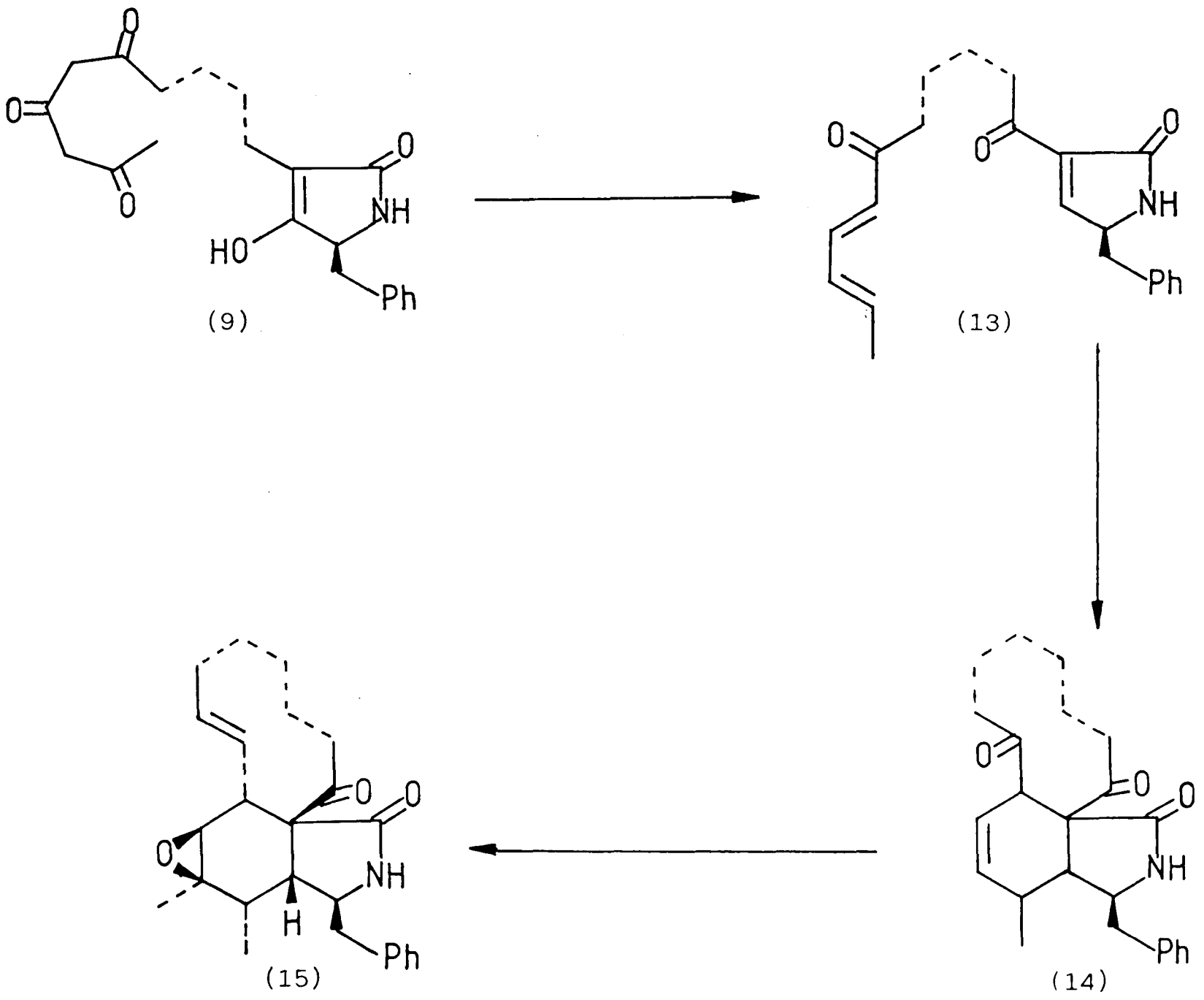


After reduction to the diene (10), the C-4,5 bond is introduced by a condensation reaction between the penultimate methylene group of the side chain, after which partial reduction and elimination of water yields the bicyclic

lactam (11). The C-8,9 bond is then formed by condensation to afford the tricyclic intermediate (12) which is transformed into cytochalasans by a sequence of methylations, reductions, eliminations, allylic oxidation and rearrangement reactions.

Turner[10] has postulated an alternative and stereochemically more attractive sequence of reactions (Scheme 1.2). From the common intermediate (9), the Δ^3-pyrrolin-2-one (13) can be envisaged to arise after reduction and dehydration. The latter can then undergo an internal Diels-Alder type cyclization to form the tricyclic intermediate (14) with the correct relative stereochemistry at C-4, C-5, C-8, and C-9 (assuming the usual *endo* transition state). After methylation and epoxidation, isoindolone (15) is produced which can undergo rearrangement to give cytochalasans with the allylic alcohol functionality.

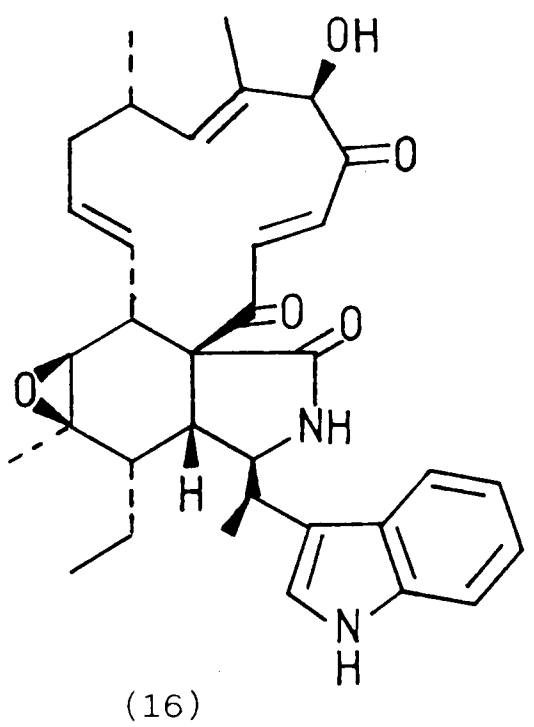
Scheme 1.2



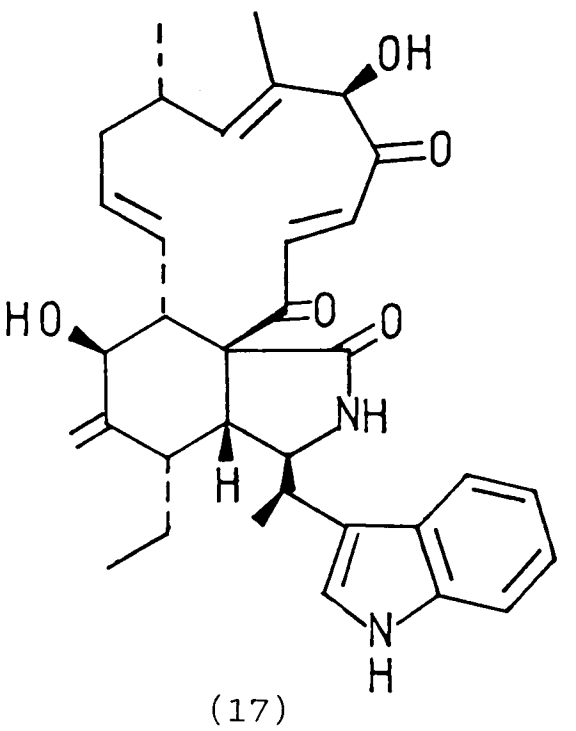
Both schemes can accommodate the biogenesis of many cytochalasans. The [11]- and [13]cytochalasans derive from octaketide and nonaketide units respectively. 24-Oxa[14]cytochalasans can be formed by Baeyer-Villiger oxidation of the corresponding [13]cytochalasans whereas the carbonate metabolite, cytochalasin E (6), is the product of two such oxidations from an [11]cytochalasan. The chaetoglobosins and aspochalasins are produced by the incorporation of the amino acids tryptophan and leucine, respectively.

However, the recent discovery of two new members of the chaetoglobosin class, K (16)[11] and L (17)[12] (Figure 1.4) has posed an interesting biosynthetic problem. Both compounds contain two extra methyl groups, at C-10 and C-11. It is likely that the former derives from methionine but the latter can be envisaged to arise from several sources. It could have come methionine, degradation and reduction of a decaketide or alternatively from a propionate starting unit on the polyketide chain, but further *in vitro* experiments are needed to test these hypotheses.

Figure 1.4



(16)



(17)

CHAPTER 2

CYTOCHALASAN SYNTHESIS

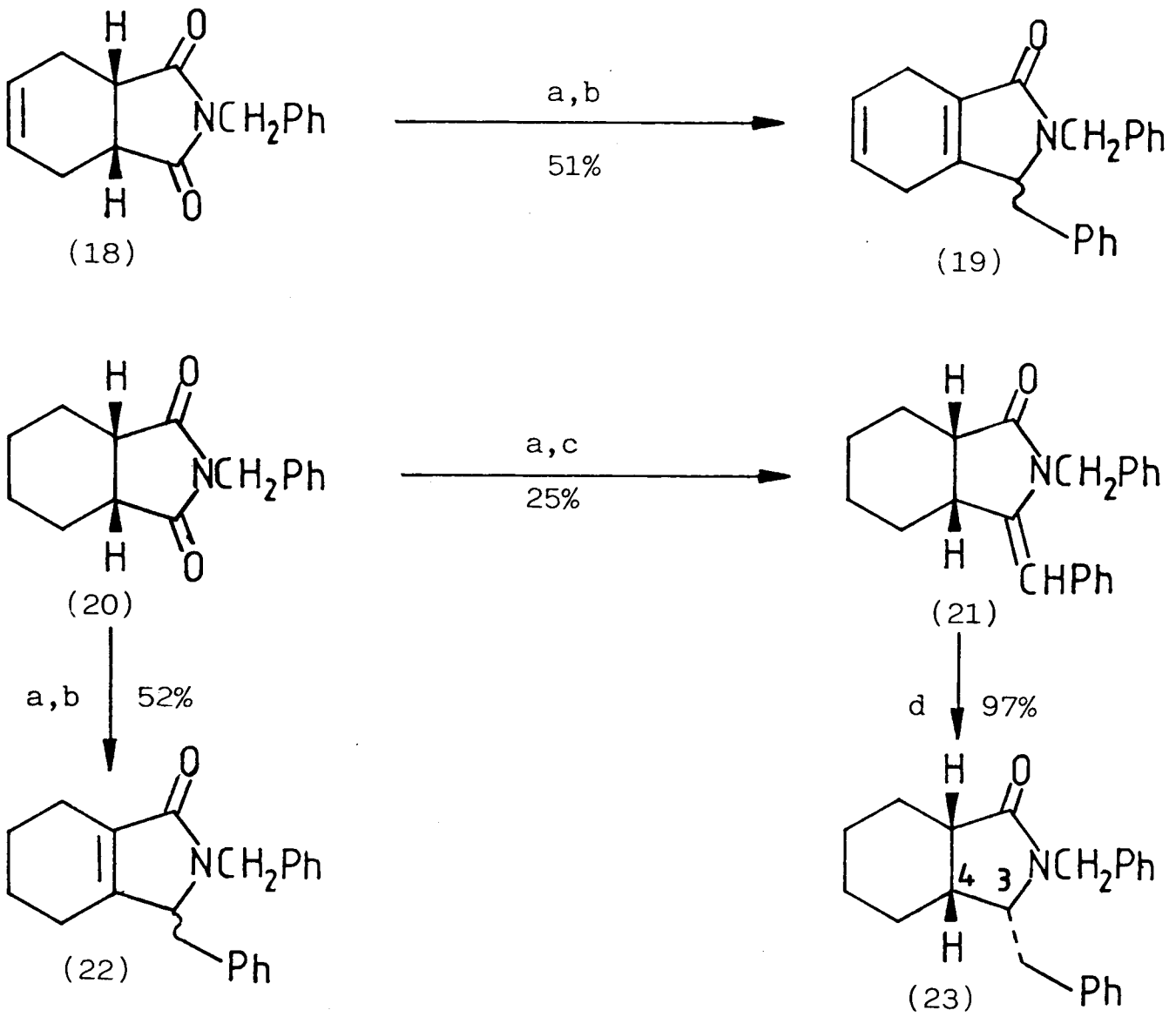
2.1 *Previous Synthetic Efforts*

The novel and imposing structures of the cytochalasans have made them attractive synthetic targets and this field of interest has been one of intense activity over the past few years. A Diels-Alder reaction in particular has been the basis of many synthetic efforts since, as mentioned earlier, this powerful reaction provides the perhydroisoindolone subunit quickly and stereospecifically. In order to put the present work into perspective it is worthwhile reviewing those studies directed towards cytochalasan synthesis, which for convenience will be divided into three sections.

2.1.1 *Use of an Intermolecular Diels-Alder Reaction*

Early work centred around the use of maleimides and maleic anhydride as the dienophilic components in these Diels-Alder approaches. Brettle and Cummings[13] have studied the reaction of some readily available 8-azabicyclo[4.3.0]non-7,9-diones with benzyl magnesium chloride (Scheme 2.1). The Grignard reaction was particularly sensitive to the work-up conditions but using a neutral procedure followed by dehydration in refluxing benzene, benzylidene compound (21) could be isolated in modest yield. Catalytic hydrogenation afforded a near quantitative yield of the dibenzyl adduct (23) which was assigned the correct C-3 stereochemistry (cytochalasan numbering) on the basis of the 5Hz coupling observed between H-3 and H-4, suggesting a *trans* -relationship. However, subsequent work[14] revealed that the actual C-3 stereochemistry is as shown, corresponding to the expected delivery of hydrogen to the least hindered, β -face of the molecule.

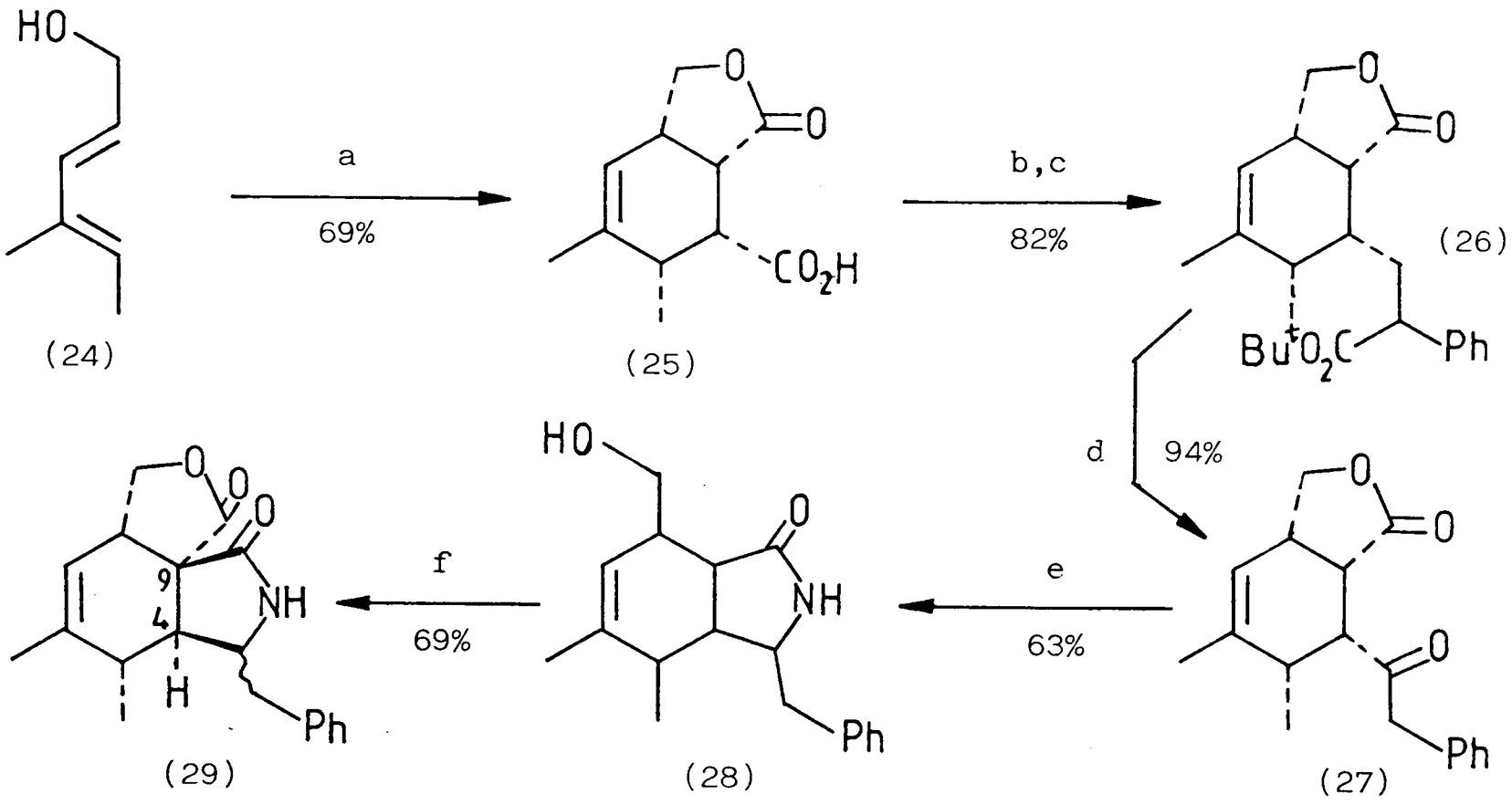
Scheme 2.1



Reagents: a BzMgCl; b H^+; c H_2O then Δ; d H_2, Pd/C.

Owens and Raphael[15] obtained the lactone acid (25) by direct reaction of maleic anhydride with dienol (24) (Scheme 2.2). The corresponding acid chloride was condensed with the lithio-derivative of *tert* -butylphenyl-acetate to give the β-ketoester (26). Subsequent hydrolysis and decarboxylation followed by reductive amination with buffered sodium cyanoborohydride gave an inseparable mixture of epimeric lactams (28). Functionalization of the tris-anion of (28) with excess dimethylcarbonate gave the tricyclic compound (29) but with the opposite cytochalasan stereochemistry. Presumably, a double epimerization at C-4 and C-9 had occurred during the reduction step.

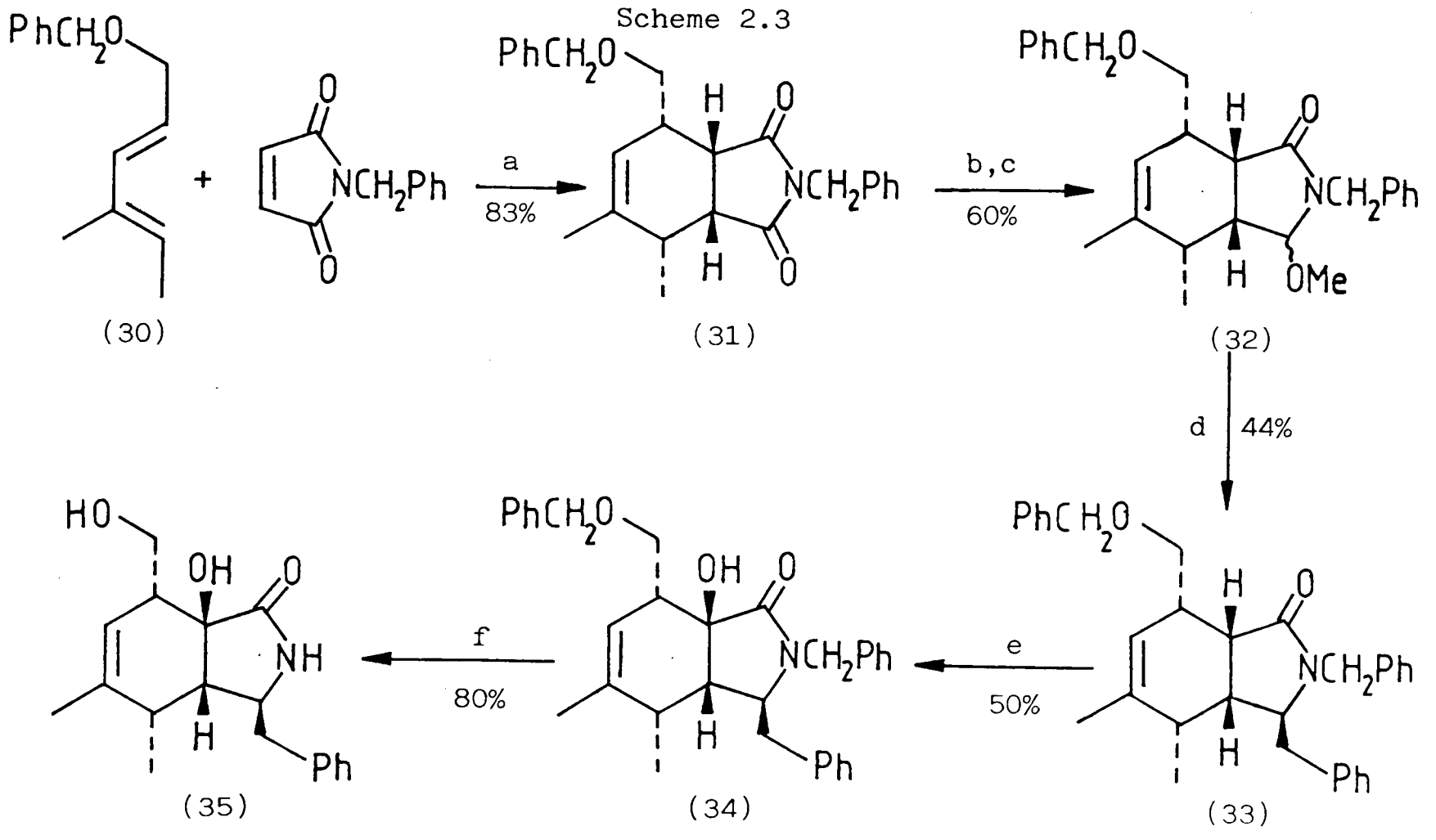
Scheme 2.2



Reagents: a $C_4H_2O_3$ 7d; b $(COCl)_2$; c $PhCH_2CO_2Bu^t$, LDA; d CF_3CO_2H, -15°, then Δ ; e $NaBH_3CN$, NH_4OAc; f LDA, $(MeO)_2CO$.

The problem of C-3 stereochemistry has been elegantly solved by Weinreb *et al.*[16] in their studies directed towards the macrolide cytochalasans. *N*-Benzylmaleimide reacted smoothly with diene (30) to give the Diels-Alder adduct (31) (Scheme 2.3).

Scheme 2.3

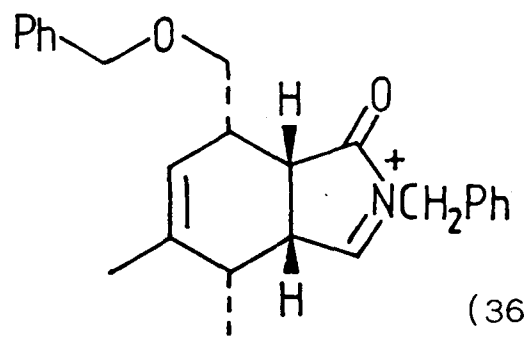


Reagents: a PhMe, 110°; b DIBAL; c HCl, MeOH; d Bz_3Al; e $LiN(TMS)_2$, O_2 then $P(OMe)_3$; f Li, NH_3.

Differentiation between the two carbonyl groups was achieved by selective reduction with di-isobutylaluminium hydride (DIBAL) followed by methanolysis to give the lactam (32) as a mixture of epimers. A possible explanation for this selectivity may be an initial complexation of the aluminium with the benzyloxy-oxygen of (31) followed by directed delivery of hydride to the C-3 carbonyl.

Treatment of methoxylactam (32) with tribenzylaluminium[16b] led stereospecifically to a single product (33), in which the C-3 benzyl group had the desired β -configuration. This alkylation is believed to occur *via* attack at the less hindered β -face of the acyliminium intermediate (36) (Figure 2.1).

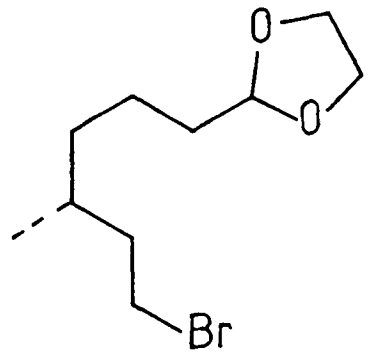
Figure 2.1



(36)

Subsequent hydroxylation and deprotection provided the functionalised isoindolone (35) which was correlated directly with a cytochalasin E degradation product. The authors also described the preparation of the α,ω - functionalised compound (37) (Figure 2.2) and the desire to join it to the isoindolone (35) and thus provide access to cytochalasins A and B.

Figure 2.2



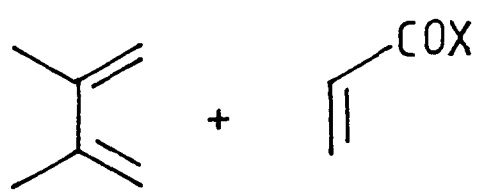
(37)

Although this strategy provides an entry into the macrolide cytochalasans it is difficult to envisage how it might be applied with great success to

the carbocyclic family since an alkylation or acylation reaction at the sterically encumbered C-9 position would be required.

In a systematic study of the intermolecular Diels-Alder reaction between α,β-unsaturated carbonyl compounds (38) and simple dienes, Vedejs and Gadwood[17] concluded thatreactivity is increased as X becomes more electron withdrawing (Figure 2.3).

Figure 2.3

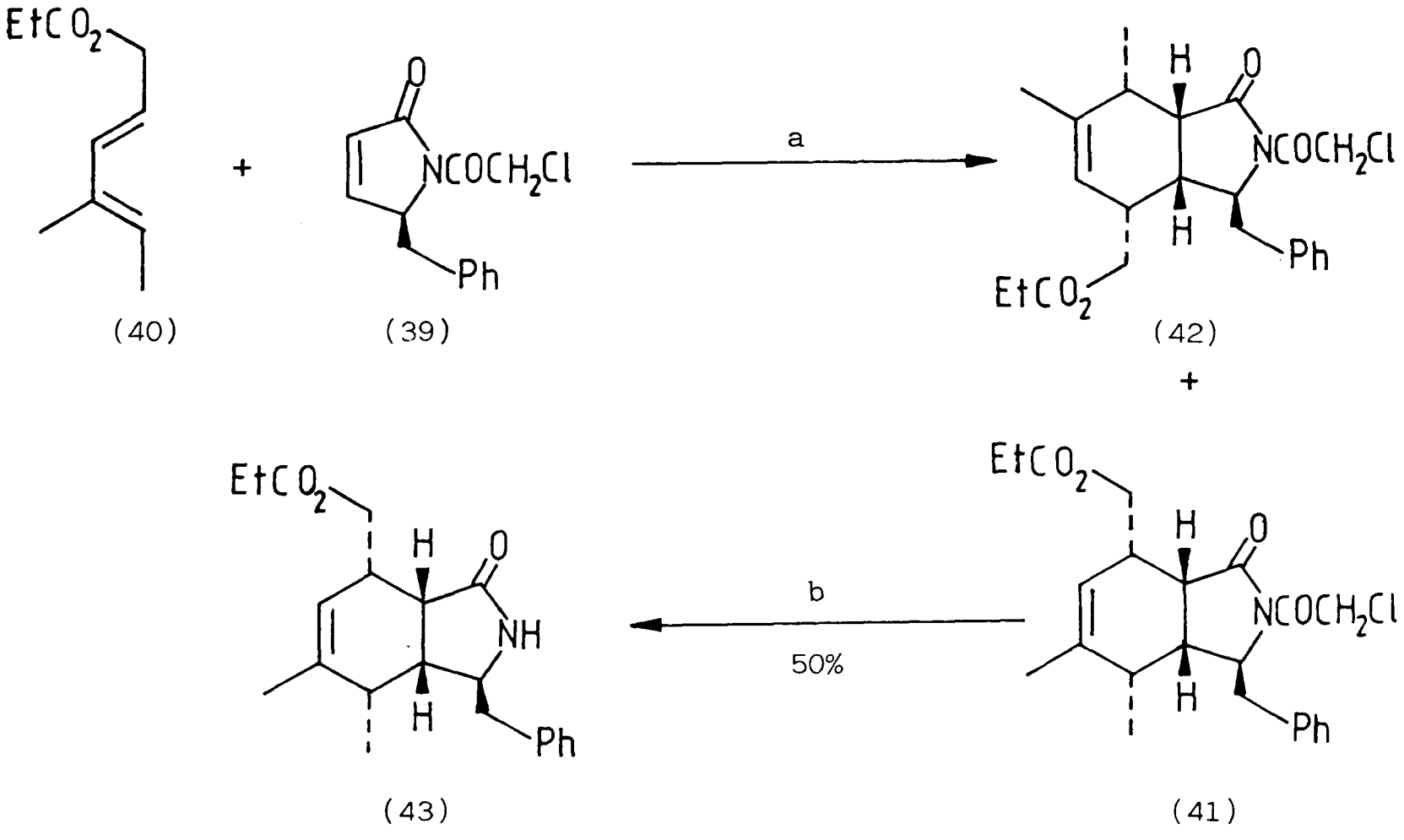


X= $N(CH_3)COCHCl_2$ > $N(CH_3)COCH_2Cl$ > $N(CH_3)COCH_3$ >> NHMe, NMe_2, OMe.

(38)

With these results in mind, cyclic imide (39) was reacted with dienyl ester (40) to give a 2:1 mixture of regioisomeric lactams (41) and (42) respectively, which were shown to have the required cytochalasan stereochemistry at C-3, C-4, C-5, C-8, and C-9 (Scheme 2.4). Subsequent deprotection with methanolic sodium carbonate furnished isoindolone (43) in about 50% overall yield.

Scheme 2.4

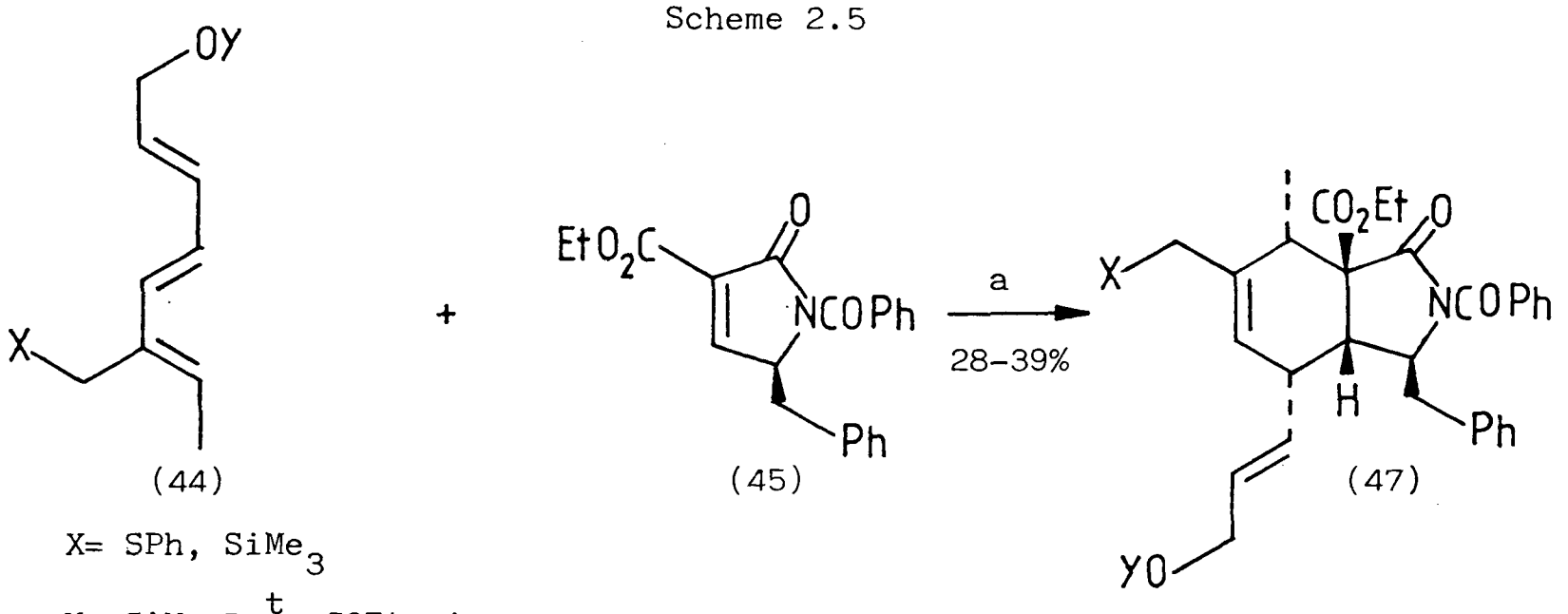


(40) (39) (42) (41) (43)

Reagents: a 120-150°; b Na_2CO_3, MeOH.

As an extension of this work,Vedejs *et al.*[18] have published their efforts on the synthesis of the isoindolone unit of cytochalasin D (49). The substituted trienes (44), obtained from a multi-step sequence of Wittig-type reactions, were reacted with the doubly activated pyrrolinone (45) at 120-130° to give the Diels-Alder adducts (46) and (47) (Scheme 2.5).

Scheme 2.5



Reagents: a C_6H_6,125°;b $NaIO_4$ then $P(OMe)_3$;c NaOH.

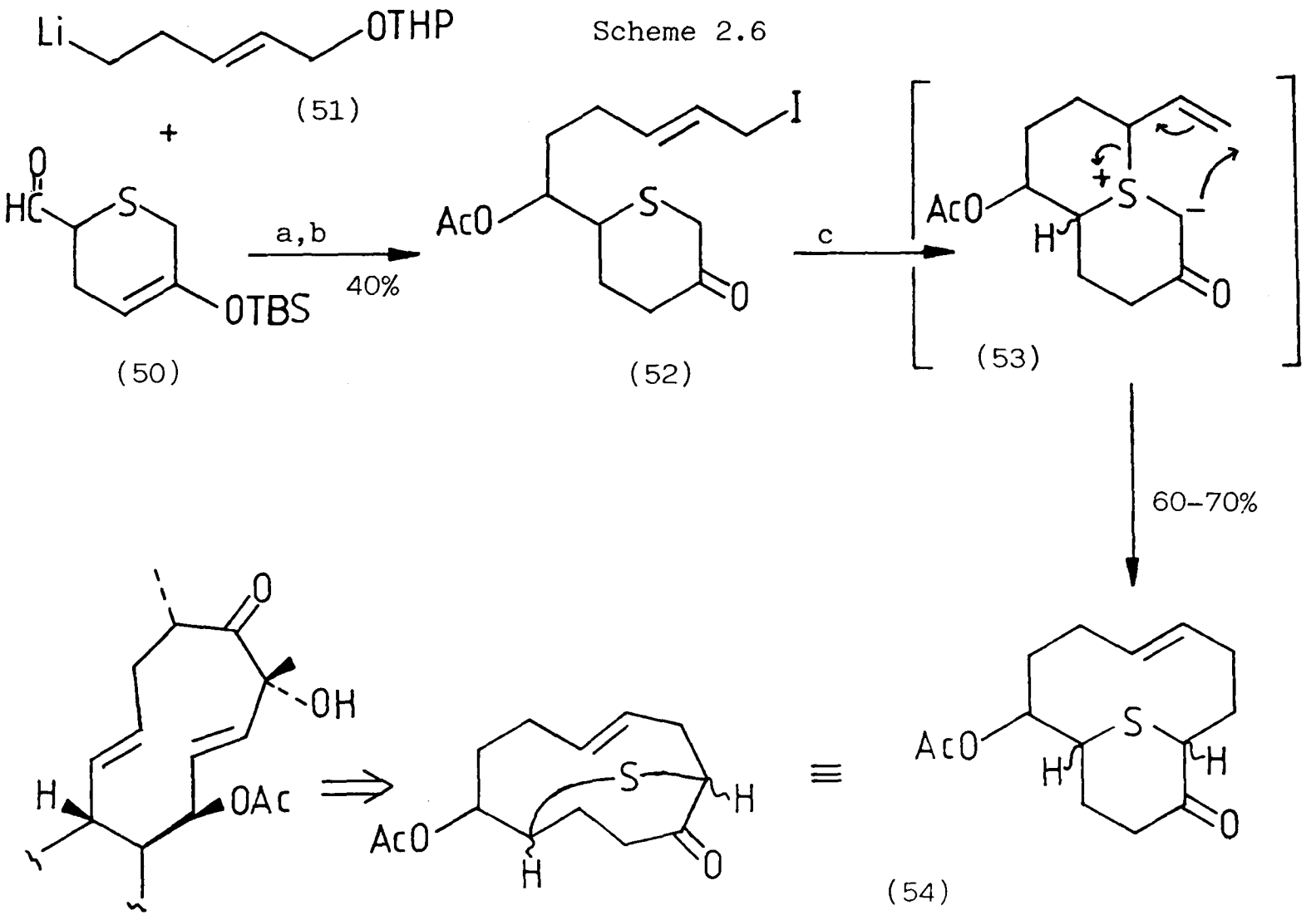
However, although the major or even exclusive products (X= SPh) were the desired regioisomers (46), the cycloadditions proceeded only in modest yields. Dienophile decomposition seemed to be the problem since trienes (44) could be recovered from the crude reaction mixture.

The exocyclic methylene/alcohol functionality present in cytochalasin D

was introduced by oxidation of the key adduct (46, X= SPh, Y= Ac), followed by allyl sulphoxide-sulphenate rearrangement with thiophilic trapping of the sulphenate. Base induced removal of the protecting groups generated the isoindolone (48) in good yield.

The problem of constructing the highly substituted cycloundecane ring of the [11]cytochalasans has also been addressed by Vedejs and co-workers, using the cyclic sulphide methodology developed in their laboratories.[19] Thus, treatment of aldehyde (50) (derived from the Diels-Alder trapping of the transient thioaldehyde, NCCSH with 2-(*tert* -butyldimethylsiloxy)-buta-1,3-diene) with organolithium reagent (51) followed by acetylation and iodination gave 3-thiacyclohexanone (52) in about 40% overall yield (Scheme 2.6). Upon heating this allylic iodide with potassium carbonate in acetonitrile, internal *S*-alkylation followed by a [2,3]- sigmatropic rearrangement of the intermediate bicyclic sulphonium ylid (53) occurred

Scheme 2.6

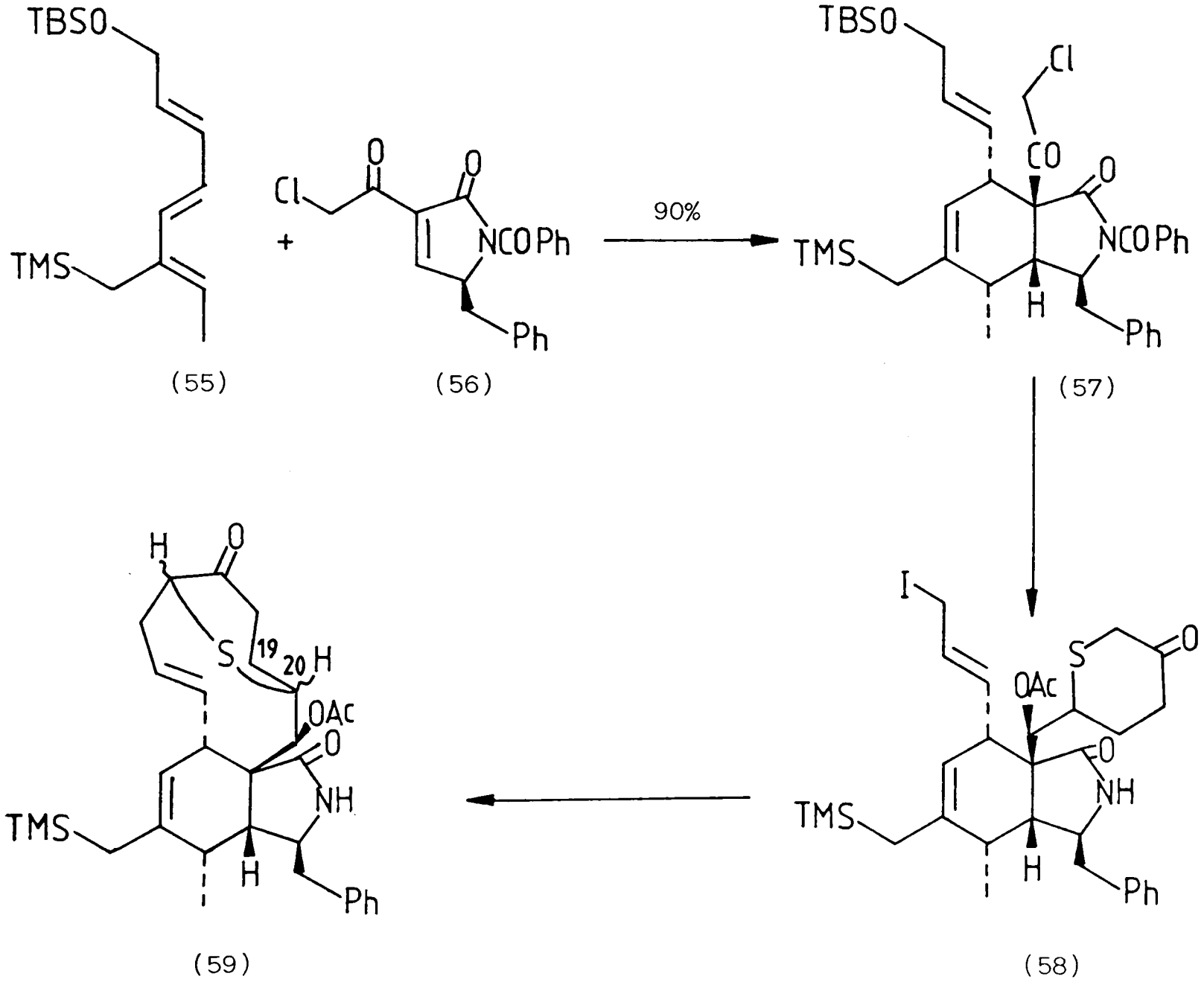


Reagents: a Ac_2O; b TMSI; c K_2CO_3.

to give the sulphur-bridged cycloundecanone (54) in 60-70% yield.

The application of this elegant chemistry to cytochalasin D synthesis has recently been disclosed[20] and is outlined in Figure 2.4. The intermolecular Diels-Alder reaction between conjugated triene (55) and the reactive pyrrolinone (56) unlike previous examples, took place at room temperature. This remarkable reaction gave an essentially quantitative yield of a *single* product (57) which was readily transformed into the tricyclic intermediate (58) in seven steps. The usual base initiated rearrangement described above generated the desired *S*-bridged cycloundecane (59). Introduction of the E-double bond between C-19 and C-20 was then accomplished by reductive cleavage of the corresponding sulphonium

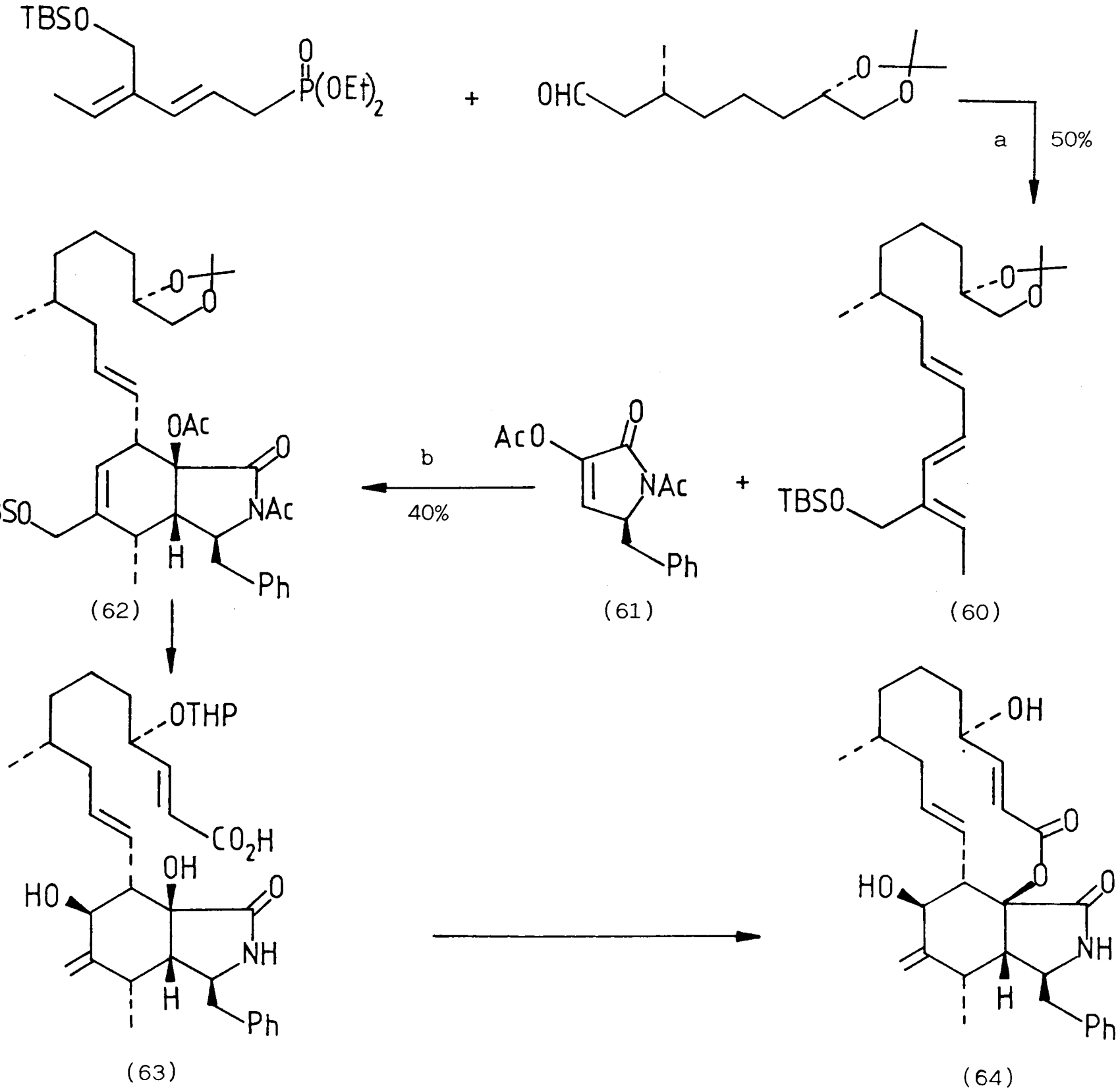
Figure 2.4



salt followed by oxidation and pyrolytic sulphoxide elimination. Clearly, the first total synthesis of a carbocyclic cytochalasan should be achieved in the near future.

The only (formal) total synthesis of any cytochalasan was reported by Stork *et al.*[21] who used a [4 + 2] cycloaddition as the key reaction. An *N*-acyl pyrrolinone (61) was used by analogy with Vedejs' work[17] and upon thermolysis with the chiral triene (60) a 4:1 mixture of stereoisomers (62) was obtained (major drawn) (Scheme 2.7).

Scheme 2.7



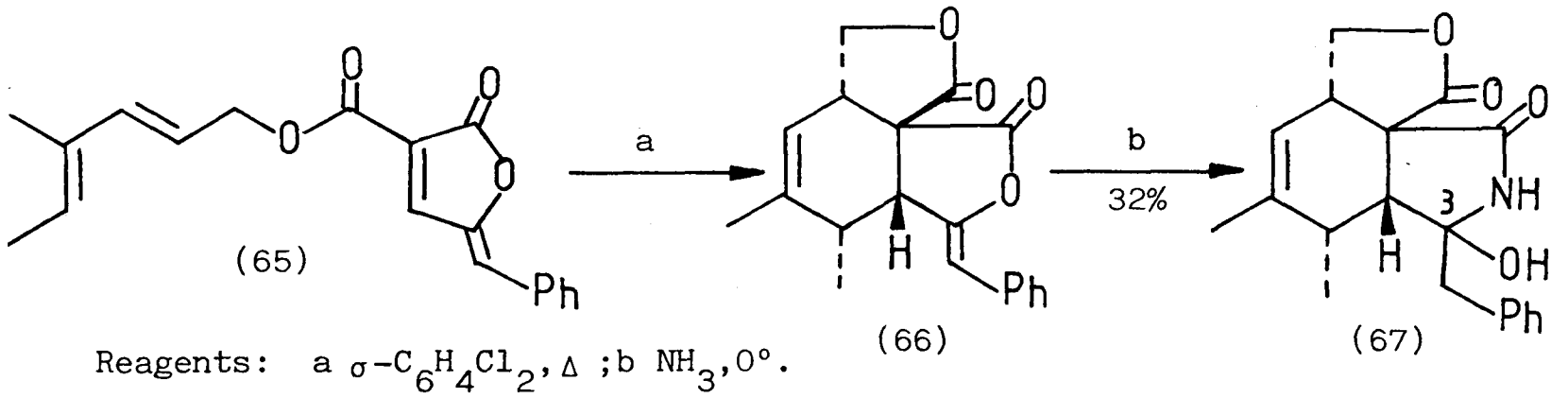
Reagents: a NaH,C_6H_6;b xylene,170°,4d.

Even under forcing conditions (170°/4 days) only a 40% conversion to the bicyclic compound was realised. Moreover, the synthesis required a further eleven steps to convert the adduct (62) into the protected *seco*-acid of cytochalasin B (63), which has been lactonized by Masamune *et al.*[22] to provide the authentic natural product in a five step sequence.

2.1.2 *Use of an Intramolecular Diels-Alder Reaction*

The first reported use[23] of an intramolecular cycloaddition in studies directed towards the synthesis of the isoindolone nucleus is depicted in Scheme 2.8. Refluxing a solution of the dienyl ester (65) in σ-dichlorobenzene gave the unstable tricyclic lactone (66) which was converted into

Scheme 2.8

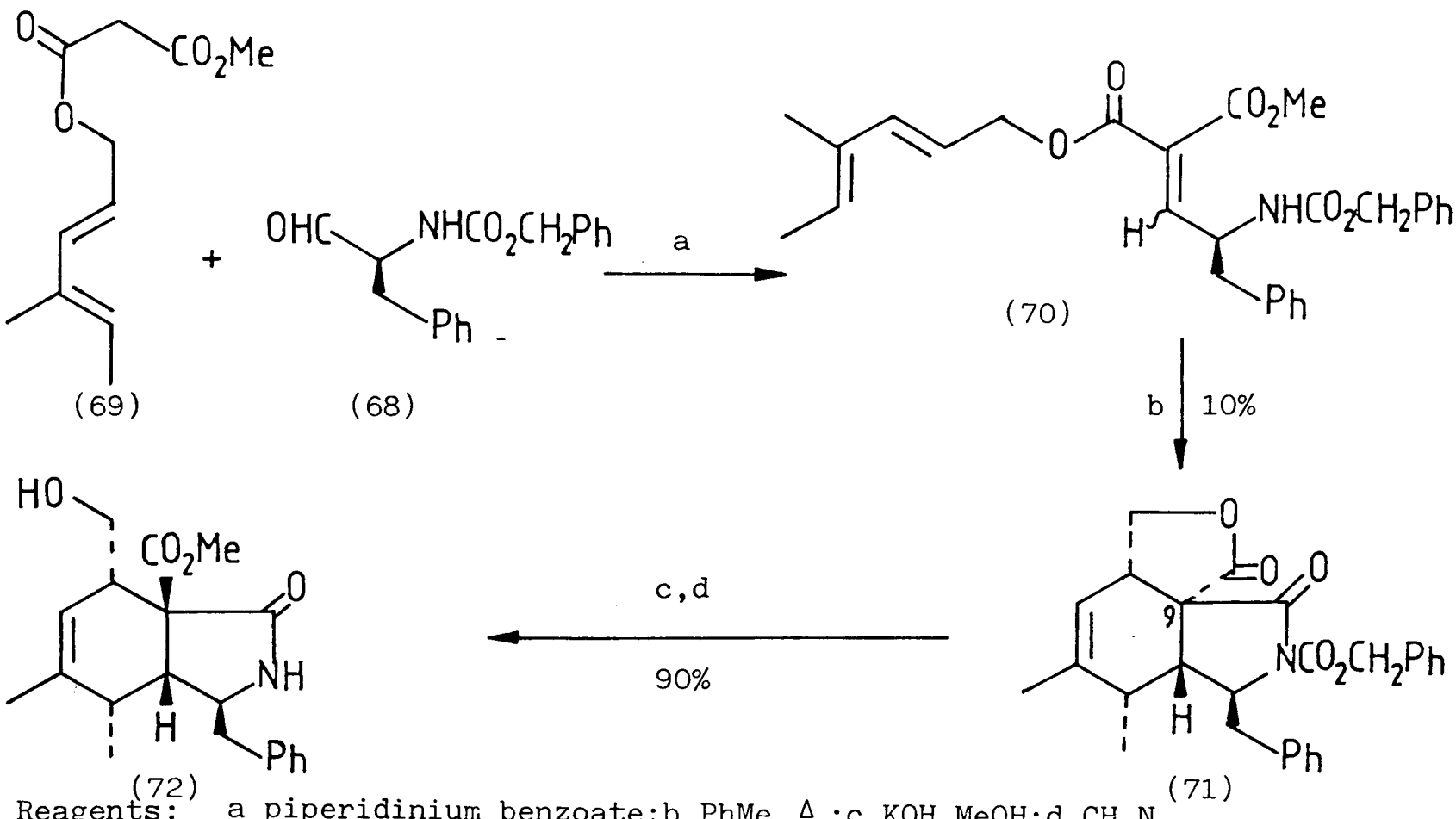


Reagents: a σ-$C_6H_4Cl_2$, Δ ; b NH_3, 0°.

lactam (67) on ammoniolysis. Although four chiral centres have been introduced stereospecifically, the modest yield and incorrect oxidation level at C-3 would appear to outweigh the convenience of this route.

Schmidlin and Tamm[24] have described the combination of a Knoevenagel-Cope reaction followed by internal cycloaddition which overcomes the problem of C-3 stereochemistry. Thus, base catalysed condensation of aldehyde (68) and malonate ester (69) gave a mixture of E- and Z- olefins (70) which was dissolved in toluene and heated for seven days. The only isoindolone product (71) was isolated in 10% yield and was shown by X-ray analysis[25] of a derivative to have the absolute configuration shown in Scheme 2.9.

Scheme 2.9

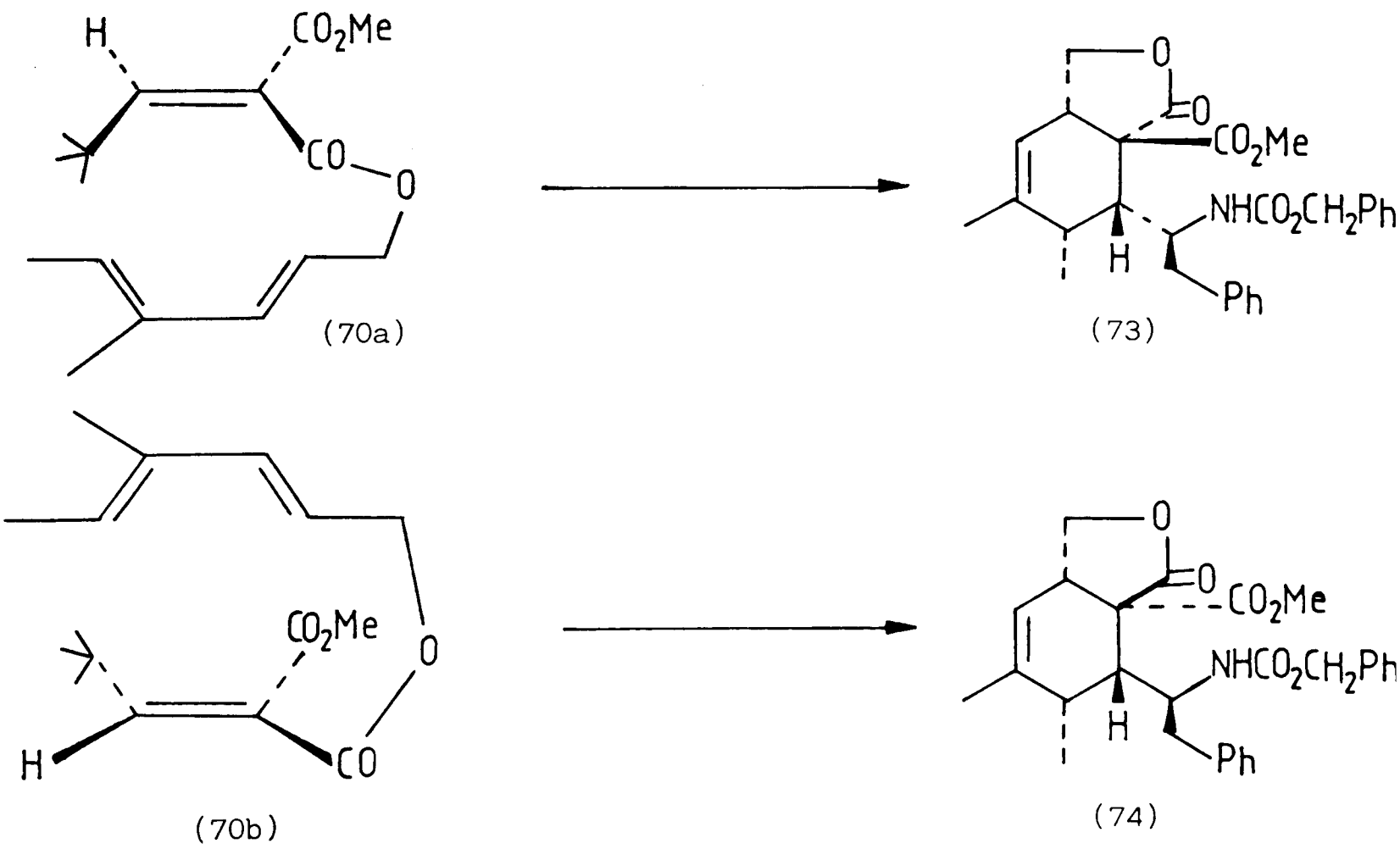


Reagents: a piperidinium benzoate;b PhMe, Δ ;c KOH,MeOH;d CH_2N_2.

The relative configurations at C-3, C-4, C-5 and C-8 are the same as in the natural products but that at C-9 is the opposite, with the lactam being *trans* -fused to the cyclohexene ring.

In order to account for the surprising formation of the *trans* -fused lactam/*cis* -fused lactone arrangement in (71), the diene-dienophile (70) is suggested to react *via* the *exo* transition state (Figure 2.5) derived from the thermodynamically less stable Z-isomer (70a).

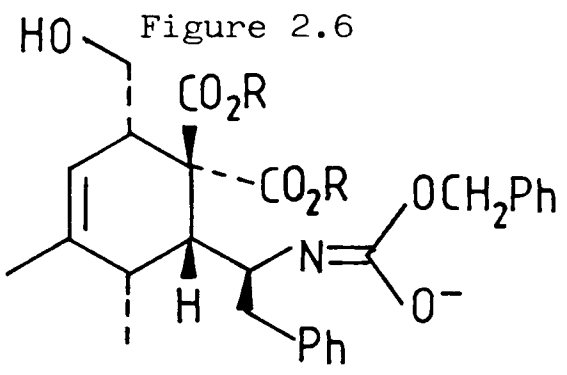
Figure 2.5



This suggests that secondary orbital interactions in the alternative *endo* transition state do not compensate for the additional strain energy required to form the *trans* -lactone. The E-isomer (70b), on the other hand, presumably does not react as expected or if it does, the adduct (74) must be unstable to either the reaction conditions or the work-up procedure.

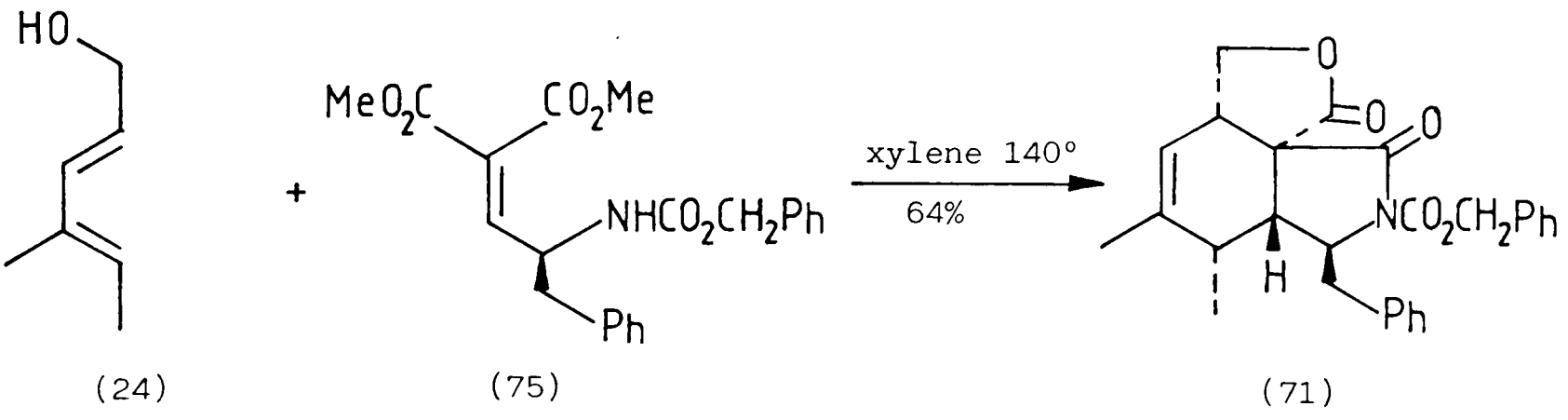
Nevertheless, when the isolated adduct (71) was treated sequentially with base and diazomethane the isoindolone produced (72) had the correct relative stereochemistry at all five chiral centres. This fact may be understood if it is assumed that the intermediate in Figure 2.6 is converted into the thermodynamically more stable *cis* -lactam by consecutive cleavage of the *N* -benzyloxycarbonyl group and ring closure.

Figure 2.6



Further evidence which supports the view that this Diels-Alder reaction issubject to thermodynamic control has been forwarded.[26] When the analogous intermolecular reaction was performed with dienol (24) and alkylidene ester (75) at 145°, adduct (71) was obtained in 64% yield (Scheme 2.10).

Scheme 2.10

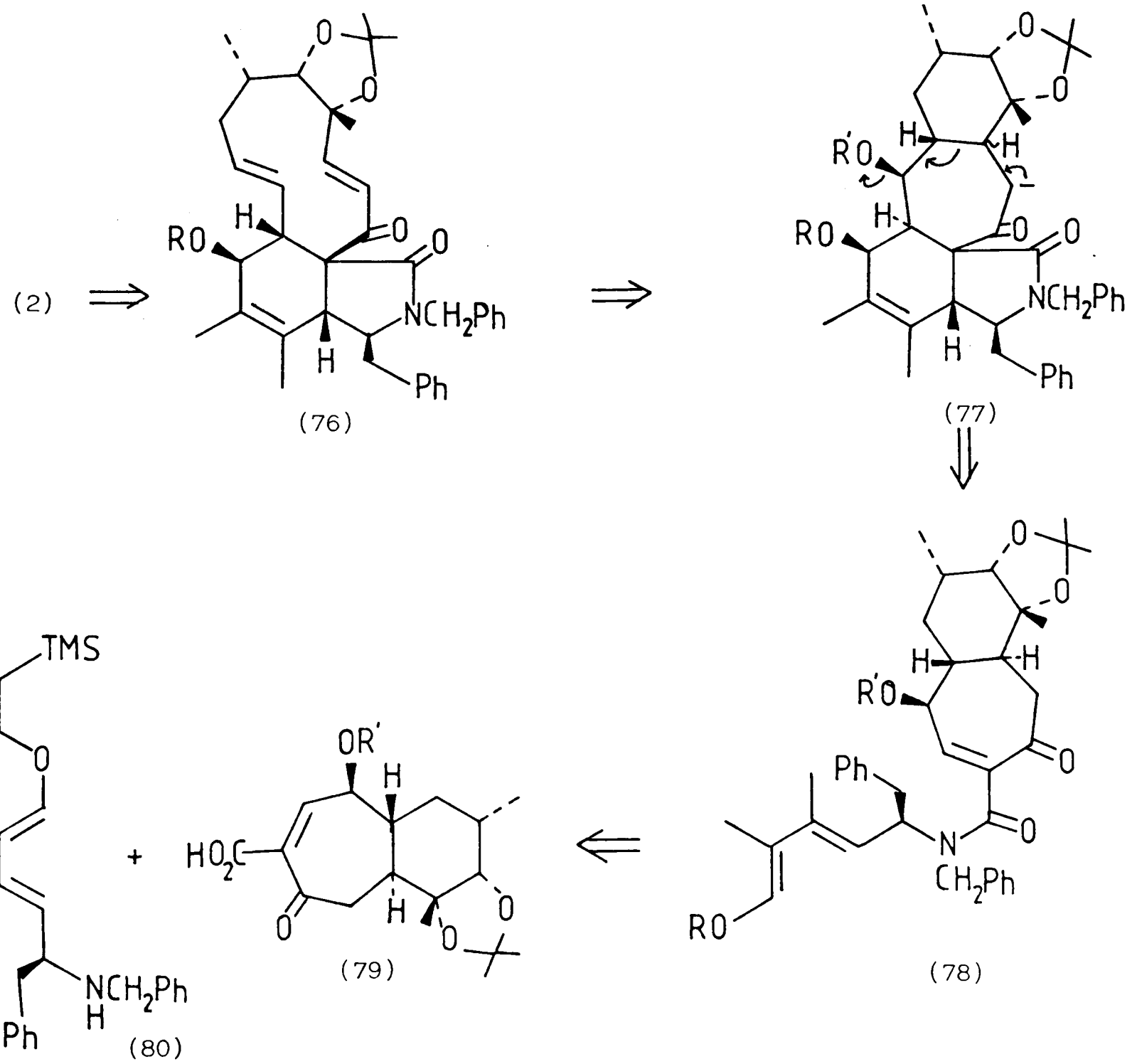


(24) (75) (71)

This demonstrates that lactone ring-closure preceeds lactam formation. The much-improved yields and ability to "epimerize" the C-9 position efficiently have made this a viable route to chiral isoindolones with different substituents at C-10. Not unexpectedly, when the hydroxyl group of dienol (24) is masked, thus preventing lactone formation, cycloaddition with (75) gives a regioisomeric mixture of adducts with the desired cytochalasan stereochemistry.[26b]

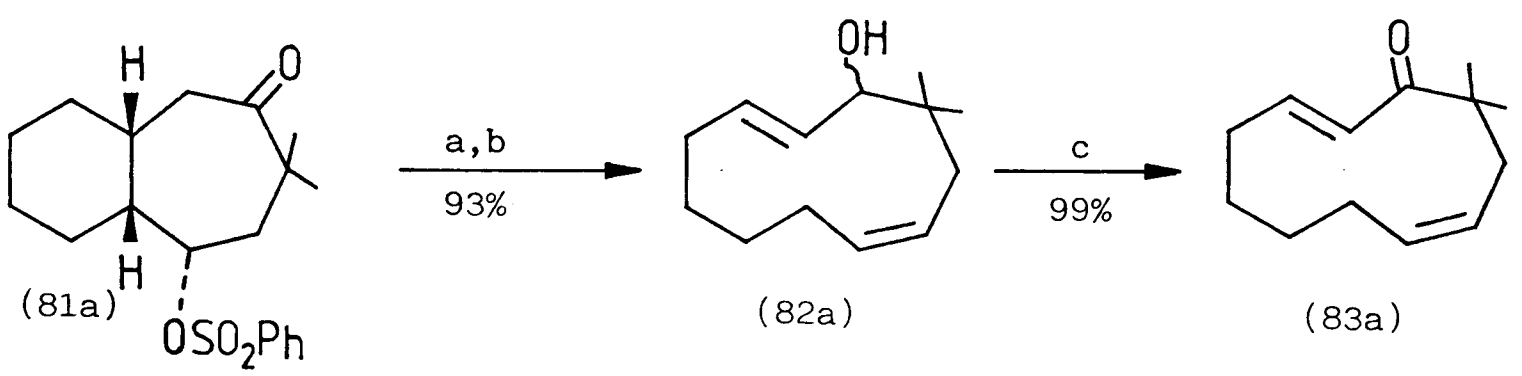
A conceptually different approach to the formation of the macrocyclic portion of the cytochalasans has been proposed by Fuchs *et al.*[27] and is illustrated in Figure 2.7.

Figure 2.7



The suitably protected cytochalasin C derivative (76) can be envisaged to arise from an enolate assisted endocyclic intra-annular 1,4-fragmentation of tetracyclic ketone (77). Extensive model studies [27a] with simple bicyclo[5.4.0]undecan-3-ones (81) established the protocol for the successful fragmentation to dienones (83) (Scheme 2.11).

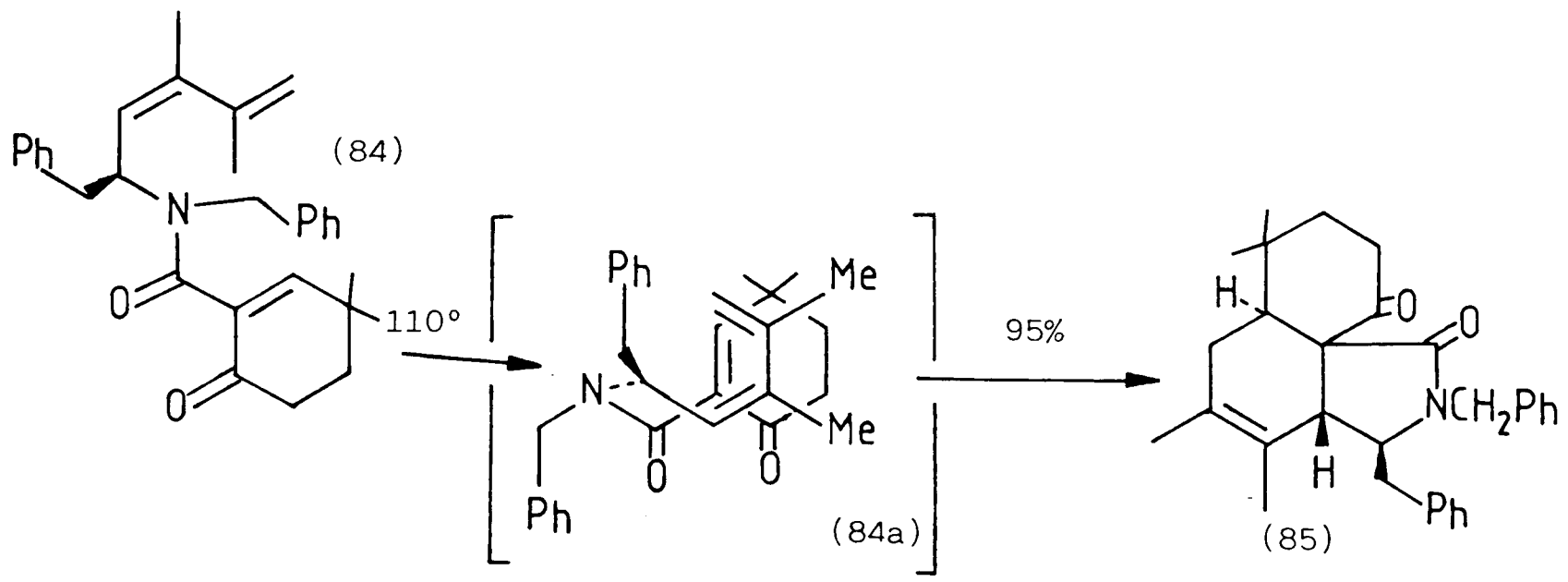
Scheme 2.11



Reagents: a LDA,-78°;b DIBAL;c MnO_2.

A stage back in the retrosynthetic analysis of tetracycle (77) is the chiral Z, Z-diene-dienophile (78). It had been shown [27b] that the model triene (84) cyclised efficiently when heated in toluene (Scheme 2.12) to

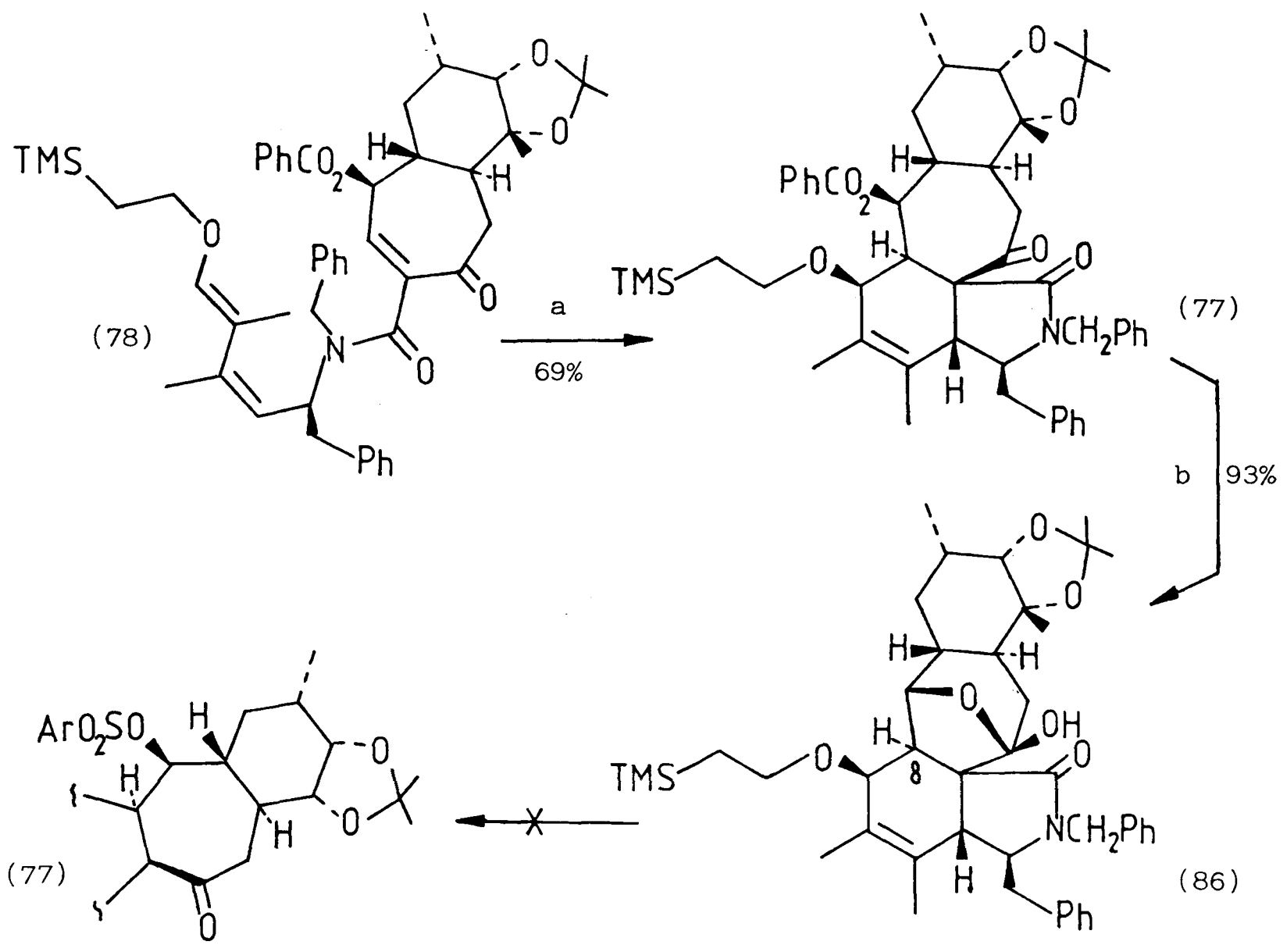
Scheme 2.12



give exclusively one product (85). The intramolecular reaction proceeded with excellent chiral induction, specifically *via* the least conjested transition state (84a).

In order to extend this finding to the desired precursor (78), much effort was expended in syntheses of the two synthons (79) and (80). After extensive but fruitless work [27c] bicyclic keto-acid (79, R= COPh) was prepared [27d] and coupled with the chiral aminodiene (80).[27d,e] Upon heating a dilute solution of triene (78, R= COPh) in toluene, a single adduct (77, R= COPh) was obtained (Scheme 2.13).

Scheme 2.13



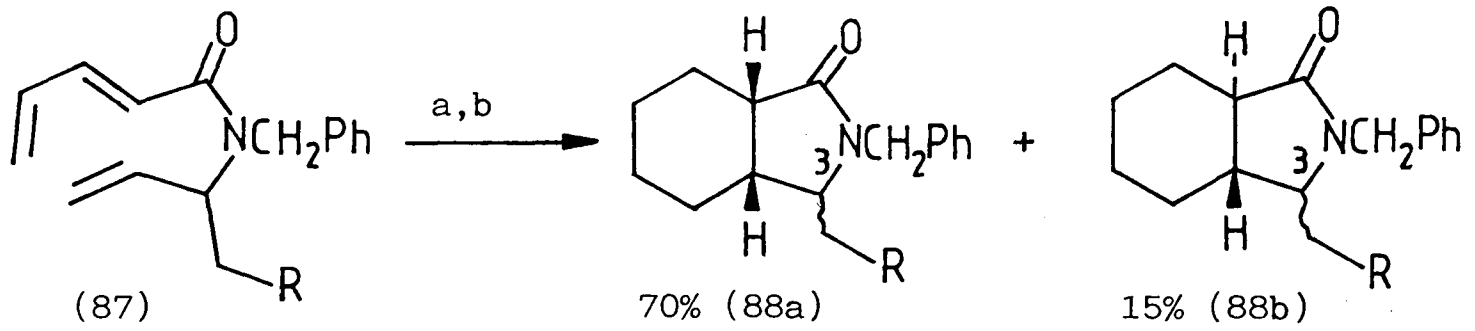
Reagents: a PhMe, Δ ;b K_2CO_3,MeOH;c Base.

Mild hydrolysis gave the closed hemiacetal (86) in 93% yield but attempts

to convert this to the prefragmentation substrate (77, R'= SO_2Ar) under basic conditions were unsuccessful. Thus the gross structure of cytochalasin C has been produced by the intramolecular cyclization of a chiral Z,Z-diene. Although the relative stereochemistry at C-3, C-4, and C-9 is correct, however, that at C-8 is "unnatural" and it remains to be seen whether this centre can be epimerized to give the natural configuration.

Brettle and Jafri[14] have recently described the intramolecular cyclization of substituted *N*-allyl-*N*-benzylpenta-2,4-dienamides (87) in refluxing dimethylformamide (DMF) (Scheme 2.14). After hydrogenation of the reaction product a mixture of all four possible isomers (88) was isolated in 85% combined yield.

Scheme 2.14



R= Ph, $CHMe_2$

		$J_{3,4}$
C-3	CH_2Ph	0Hz / 9Hz
C-3	CH_2Ph	4.5Hz / 6.8Hz

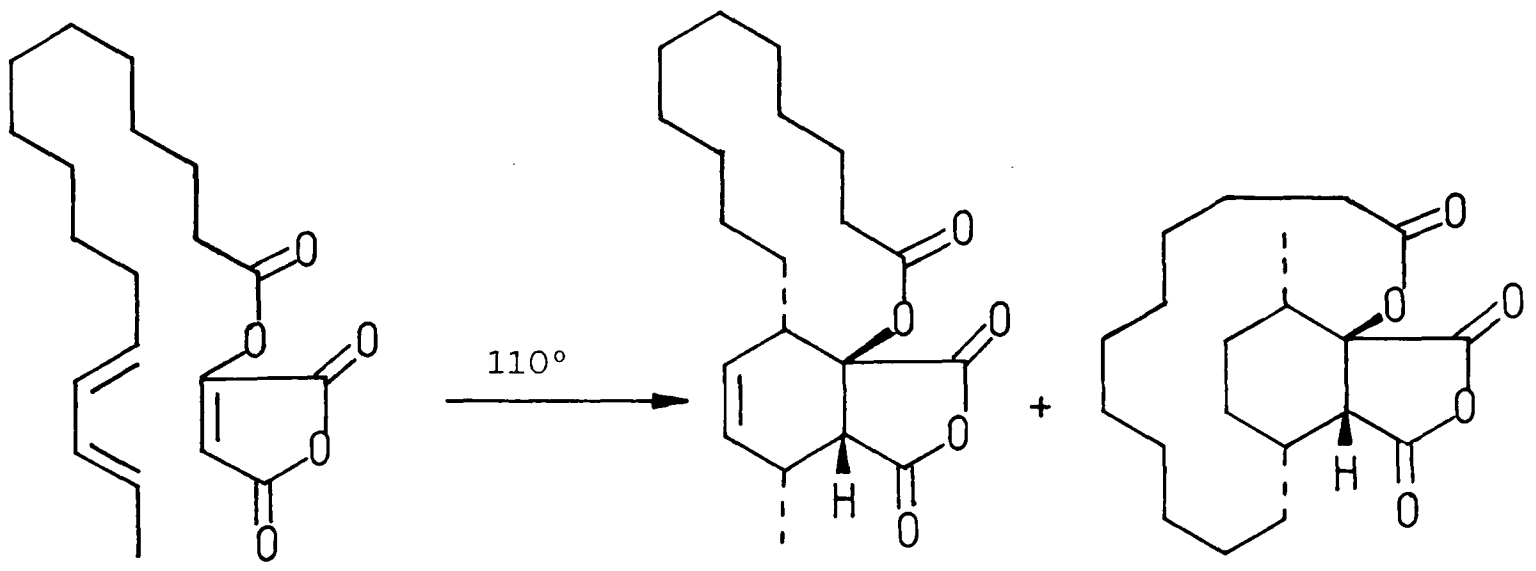
Reagents: a DMF, Δ ; b H_2,Pt.

The major isomers (88a) have *cis*-fused ring structures as would be expected if the reaction occurred *via* an *endo* transition state. However, the author suggests that when elevated temperatures are used to effect the intramolecular Diels-Alder reaction, as here, secondary orbital interactions may not be dominant in determining the transition state energies so that *endo* / *exo* mixtures are formed. Also, the number and nature of the connecting atoms between the diene and dienophile can influence the product stereochemistry in an unpredictable way.

In the present case, the relative stereochemistries of the bicyclic products were assigned on the basis of their high resolution proton (^1H) nmr spectra. From the values of the coupling constants given in Scheme 2.14 it can be seen that for product (88a, β-CH_2R), which has the desired cytochalasan stereochemistry, $J_{3,4}$= 0 Hz. Tamm[9] reports a value of 9 Hz for a similar perhydroisoindolone exemplifying the difficulty of making stereochemical assignments with any confidence on the basis of coupling constant analogies alone in these fused 5,6-ring systems.

The intramolecular Diels-Alder reaction of a long chain diene-dienophile has been shown to generate macrocyclic compounds directly.[28a] Thus, when diene-anhydride (89) was heated to 120° in toluene a 5:1 mixture of macrolides (90) and (91) was obtained in 32% combined yield (Scheme 2.15). Also isolated was 12E, 14E-hexadeca-12,14-dienoic acid (43%) due to adventitious hydrolysis.

Scheme 2.15

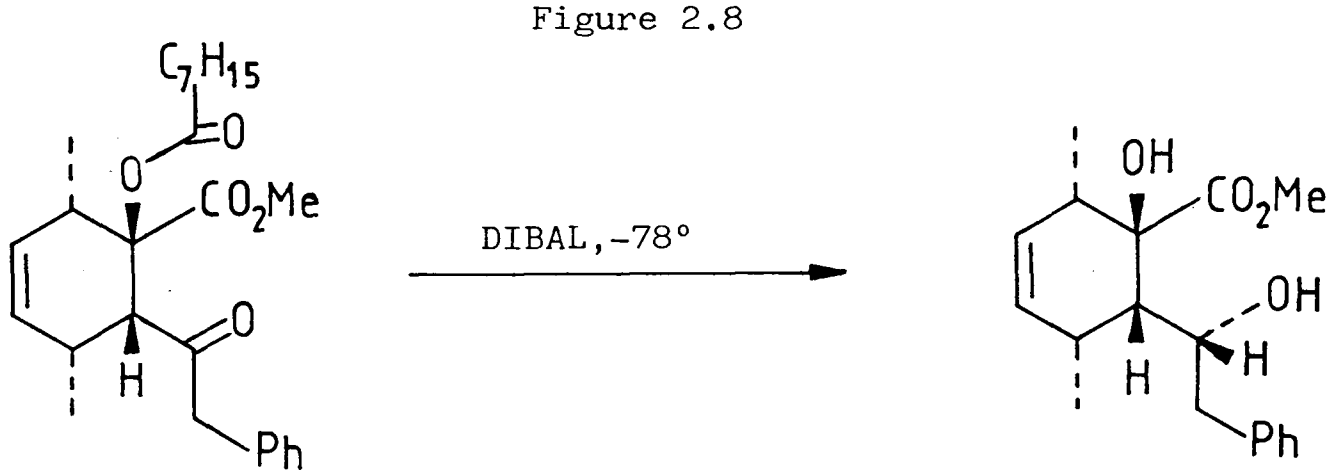


(89) (90) 27% (91) 5%

The major regioisomer (90) was shown to possess the natural cytochalasan stereochemistry but attempts to convert model anhydrides into pyrrolidin-

2-ones analogous to cytochalasans were not straightforward.[28b] For example, reduction of ketone (92) with DIBAL at -78° proceeded with concomitant ester cleavage to give, amongst other products, diol (93) (Figure 2.8). Moreover the configuration at the exocyclic position was found not to be that required at C-3 of a cytochalasan.

Figure 2.8



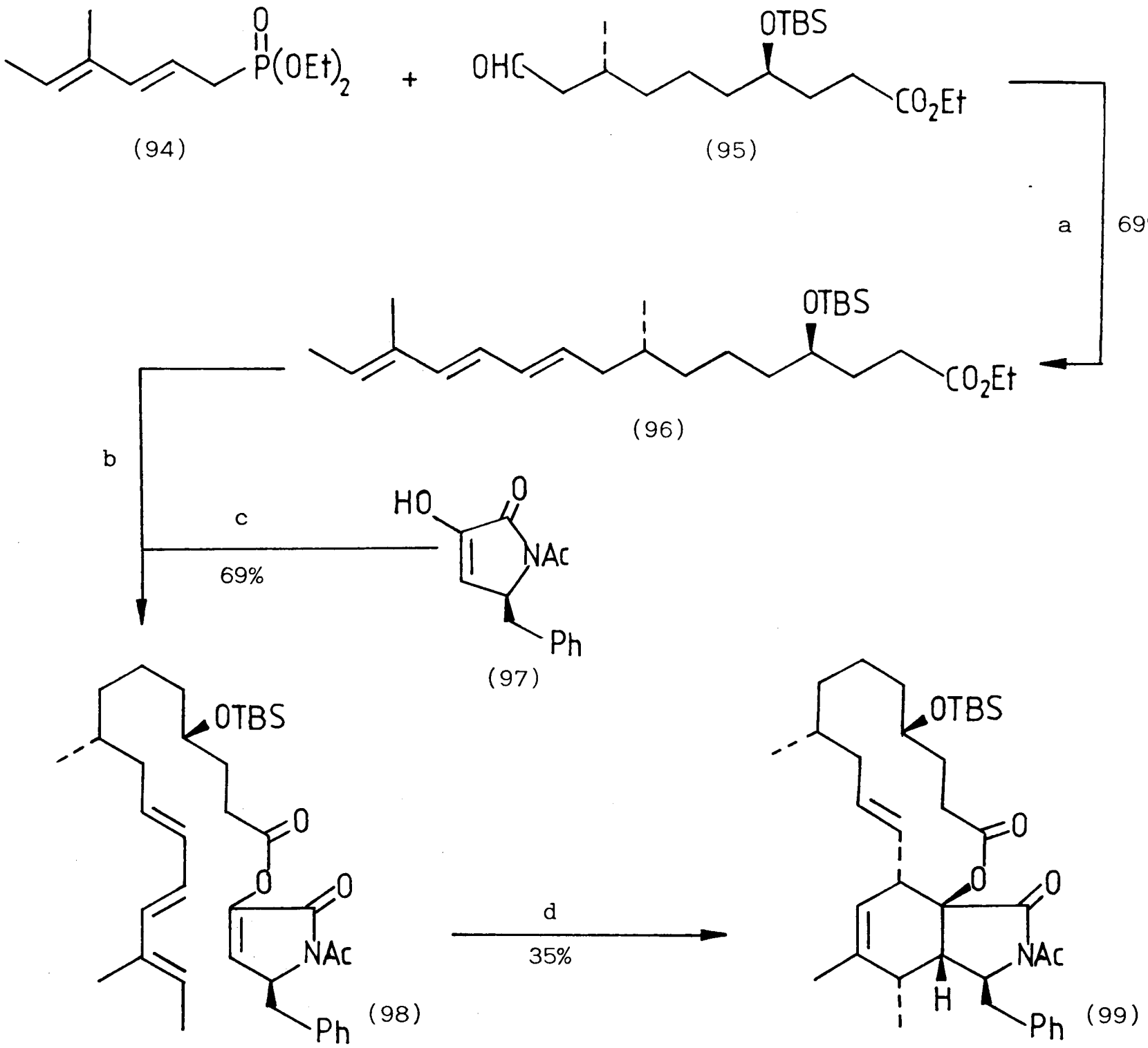
(92) (93)

After the completion of the experimental work for the present project Stork and Nakamura[29] published an improved synthesis of cytochalasin B based on a similar internal cycloaddition. Thus, triene ester (96) was prepared from phosphonate (94) and aldehyde (95) and was hydrolysed and transesterified with hydroxypyrrolinone (97) (Scheme 2.16). Cyclization of the tetraene (98) was accomplished by heating a dilute solution in mesitylene at 180-190° for six days. After one recycle the cyclization product (99) was isolated in 35% yield as a 4:1 mixture of stereoisomers. The major isomer possessed the correct stereochemistry and was converted into cytochalasin B in seven steps.

2.1.3 *Other Approaches to Cytochalasan Synthesis*

Trost[30] has recently declared an interest in cytochalasan synthesis using a palladium-assisted macrocyclization approach. The sensitive 2-ene-1,4-dione functionality depicted in Figure 2.9 is a common feature in many cytochalasans and could be envisaged to derive from allylic alkyl-

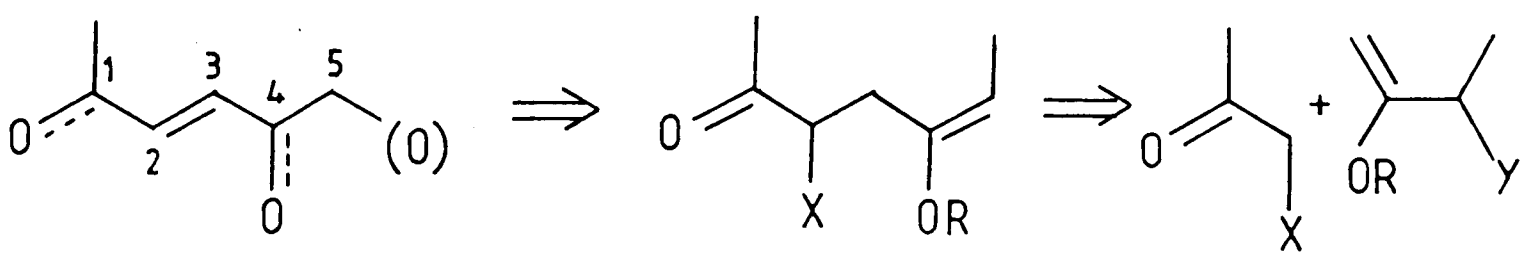
Scheme 2.16



Reagents: a LDA then HMPA;b NaOH,EtOH;c 2-chloropyridine methiodide,Et_3N, DMAP;d mesitylene, 180-190°, 6d.

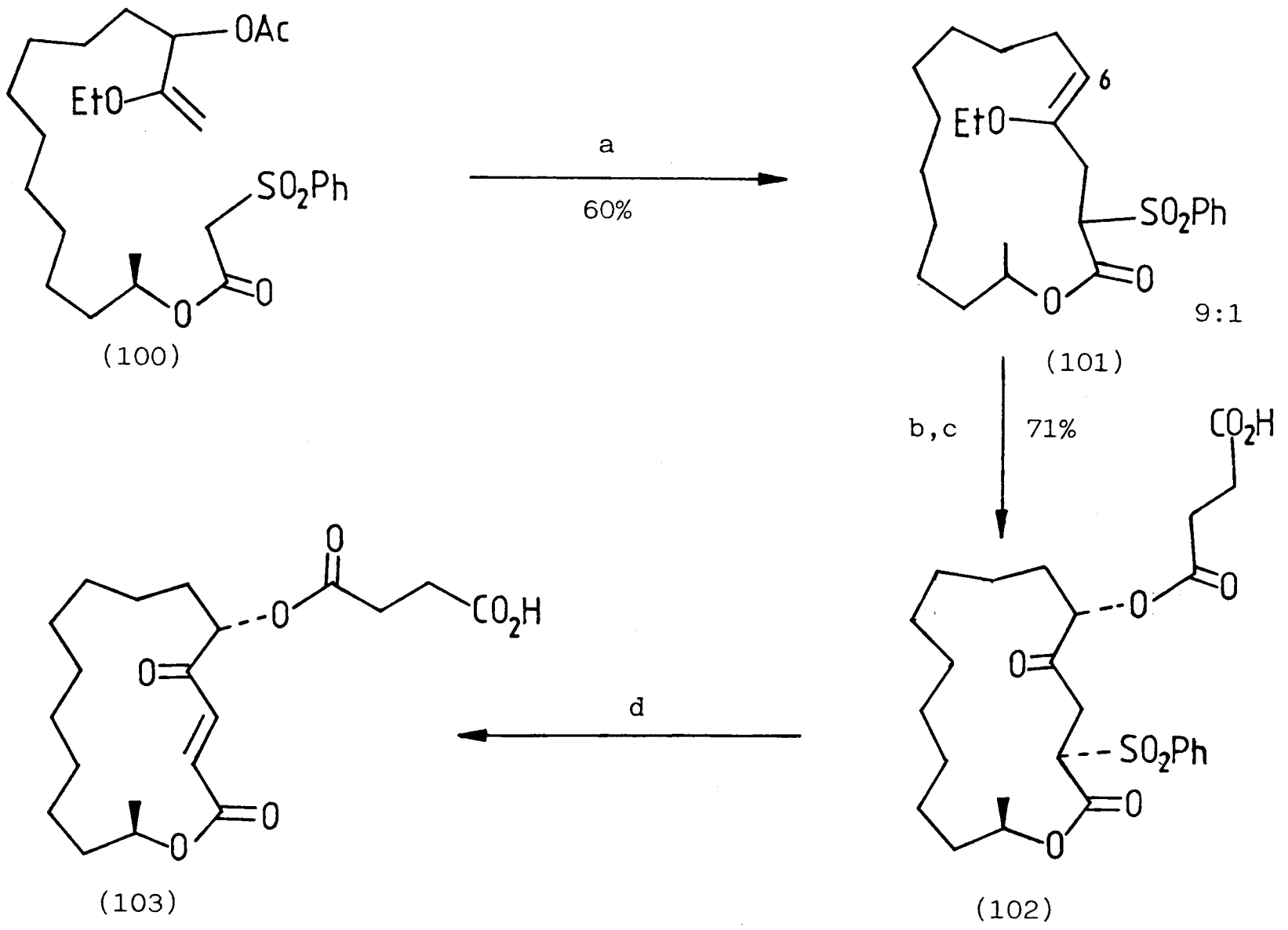
ation of a suitably chosen electrophile. Palladium templates are known to facilitate macrocyclization *via* allylic alkylation[31] and to test the feasibility of macrolide formation, model studies were conducted on the

Figure 2.9



synthesis of Antibiotic A26771B (103). Enol ether (100), available in 40% overall yield *via* an expeditious route from undec-10-enal, was cyclized in the presence of tetrakis(triphenylphosphine) palladium and *O* , *N* -bis-(trimethylsilyl)acetamide to the macrolide (101) (Scheme 2.17).

Scheme 2.17



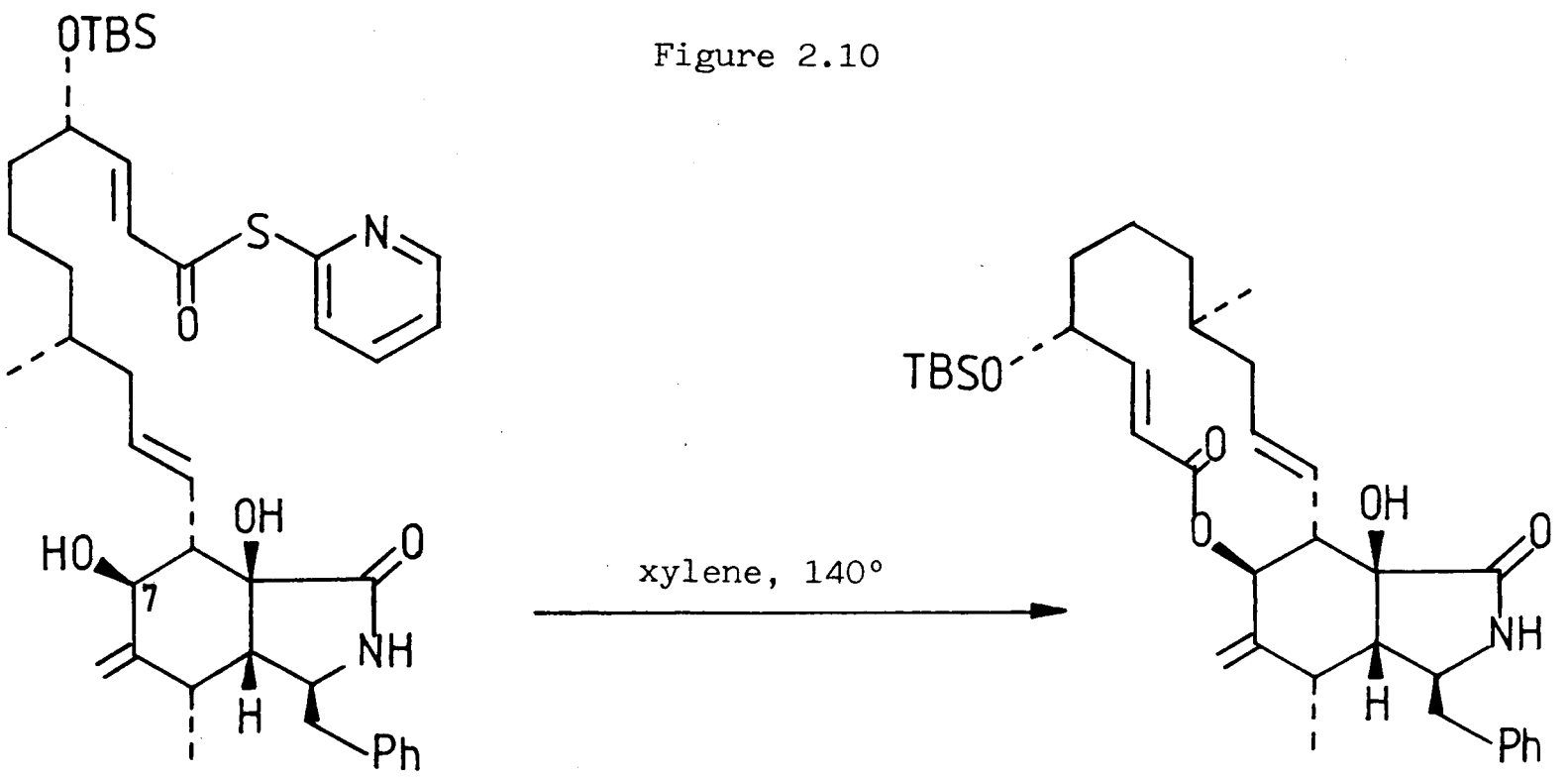
Reagents: a MeC(OTMS)=NTMS, $(Ph_3P)Pd$, $Ph_2PCH_2CH_2PPh_2$; b OsO_4, py; c succinic anhydride, DMAP; d Bu^n_4NF.

Completion of the synthesis required adjustment of the oxidation level at C-6 and elimination of the benzenesulphonyl group. The efficiency of the macrocyclization stage and general flexibility should make this strategy applicable to both macrolide and carbocyclic cytochalasan synthesis.

2.2 *The Aims of this Project*

The stereospecific and regioselective formation of fused cyclic systems by bimolecular Diels-Alder reactions has been seen to be particularly suited to the synthesis of the isoindolone unit of the cytochalasans. The Diels-Alder reaction in its intramolecular version[32] has also been the basis of several efforts. Its use in the production of five- and six-membered rings continues to be found in many programmes directed towards natural product synthesis [33] but macrocycle formation remains scarcely studied.[28,29,34] The latter would be especially attractive in cytochalasan synthesis because it would avoid the difficult functionalization of the sterically hindered C-9 position of the isoindolone unit. Typical of this, when hydroxy-2-pyridine thiol ester (104) was heated in xylene,[35] preferential cyclization with the C-7 hydroxyl group occurred to give the protected iso-cytochalasin B (105) (Figure 2.10).

Figure 2.10



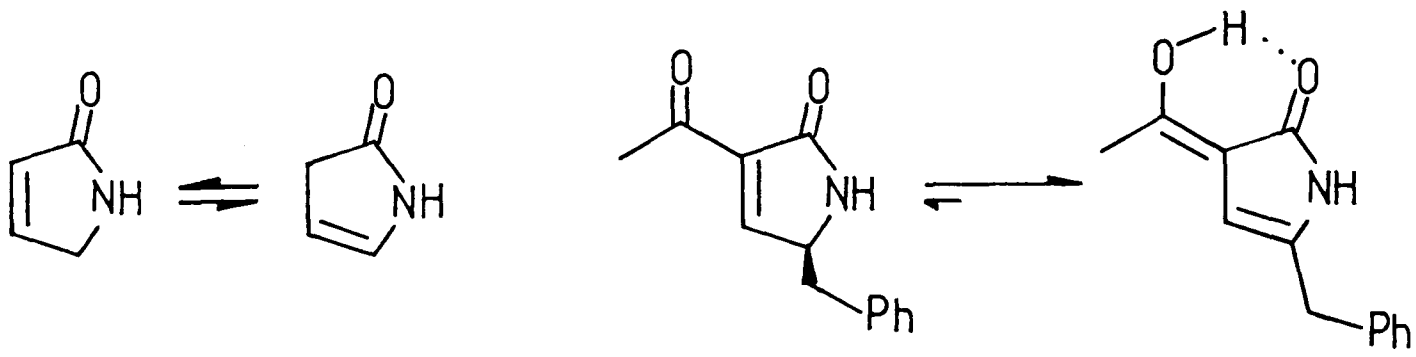
(104) (105)

The use of an intramolecular Diels-Alder reaction to provide analogues of the macrolide cytochalasans[28] has been mentioned earlier along with the

difficulties associated with transforming the anhydride moiety stereoselectively into a C-5 benzyl pyrrolidin-2-one.[28b] This prompted an investigation into the use of 3-substituted Δ^3-pyrrolin-2-ones as dienophiles.[3b]

The parent lactam (106) is known[36] to be in equilibrium with its Δ^4-isomer (107), presumably *via* the intermediacy of the 2-hydroxypyrrole and attempts to prepare the 3-acetylpyrrolinone (108) gave only the isomeric product (109)[3b,37] (Figure 2.11).

Figure 2.11



(106) (107) (108) (109)

The *N*-benzylpyrrolinone (110) could be prepared,[3b] but was found to be unreactive towards simple dienes under both thermal and Lewis acid catalysed conditions, preferring instead to tautomerize irreversibly to the unreactive benzylidene isomer (111) (Figure 2.12).

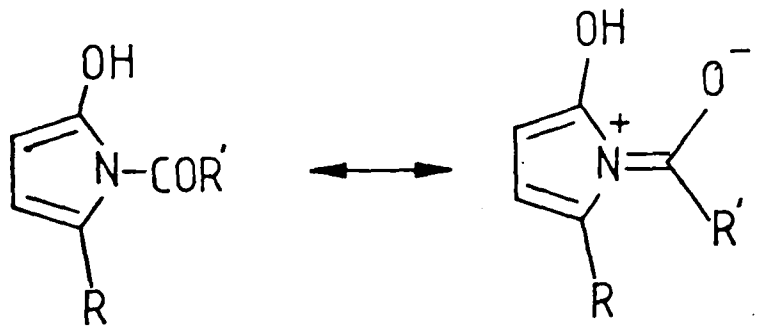
Figure 2.12



(110) (111)

In order to inhibit this undesired isomerization, Vedejs[17] has suggested the attachment of a mesomeric electron withdrawing group to the nitrogen atom to destabilize intermediate hydroxypyrroles such as (112) (Figure 2.13).

Figure 2.13

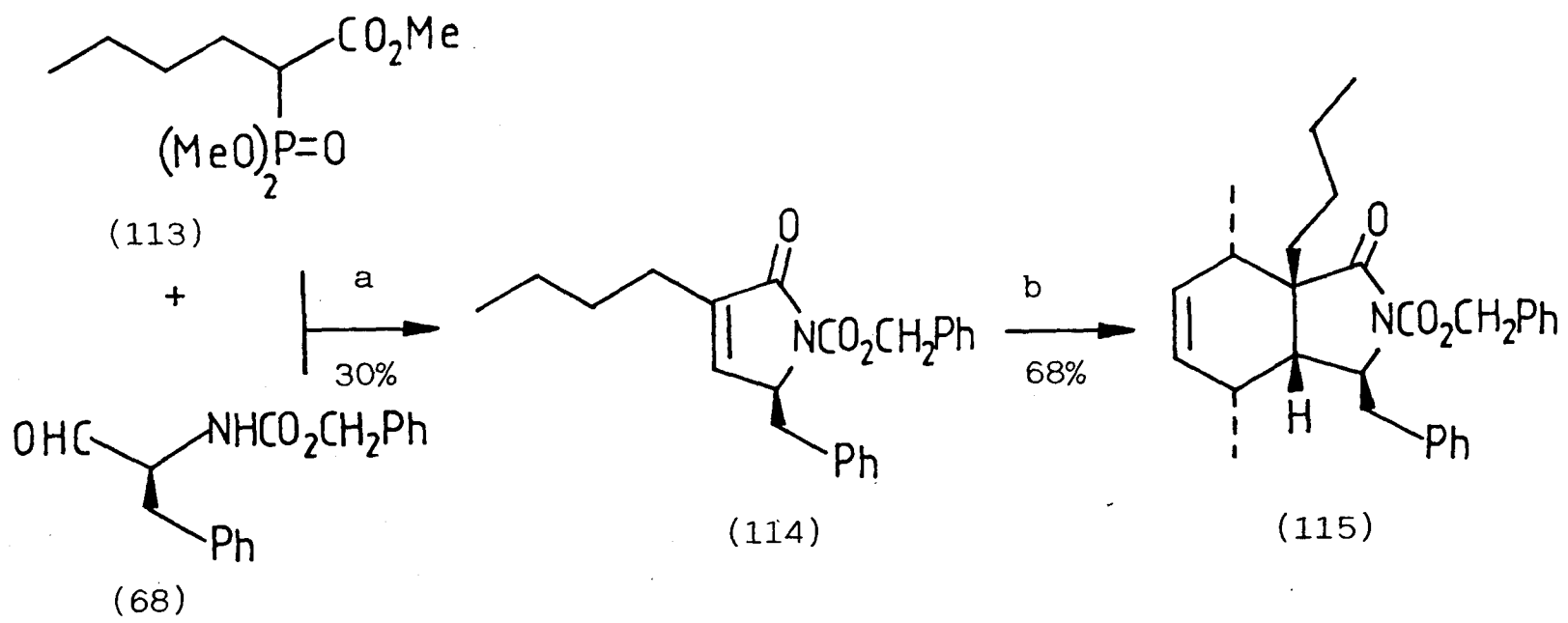


4π -antiaromatic

a (112) b

The efficacy of an *N* -acyl substituent in these systems was demonstrated by the reaction of pyrrolinone (114), available in 30% yield from the condensation of aldehyde (68) and phosphonate (113), with 2E,4E-hexadiene which provided isoindolone (115) stereospecifically [3b] (Figure 2.14).

Figure 2.14



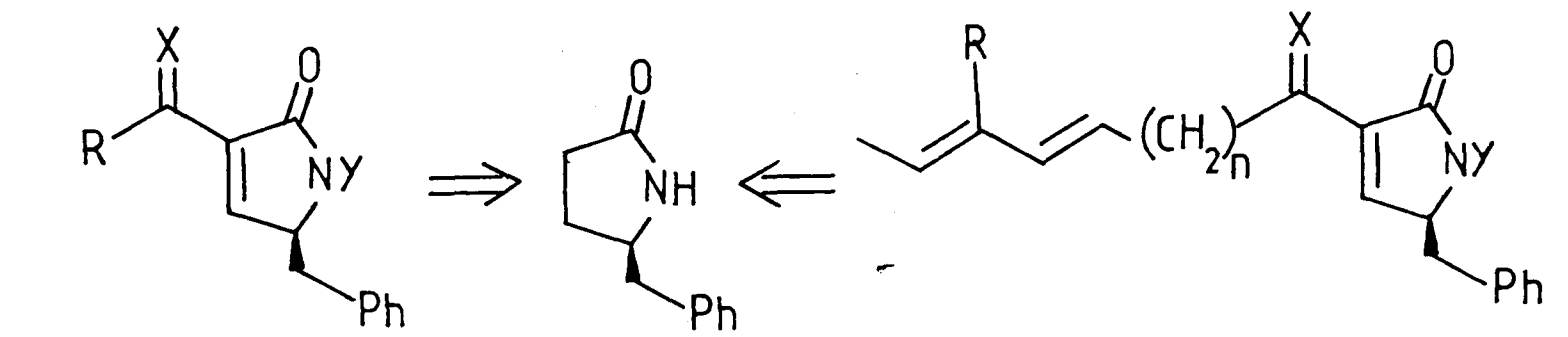
Reagents: a LDA,-40°;b 2E,4E-hexadiene, 200°,36h.

However, the modest yield of the Wadsworth-Emmons reaction and the need for forcing conditions to effect the Diels-Alder reaction prompted us to consider an alternative route to *N* -acylated pyrrolin-2-ones (117) starting from the known lactam (116)[38] (Figure 2.15). The reactivity and stereoselectivity of these systems towards simple dienes was to be investigated and if a suitable combination of functionalities X,Y could be found, model diene-lactams (118) were to be prepared in a similar fashion. The crucial intramolecular Diels-Alder reaction could then be studied to see whether this approach was viable for cytochalasan synthesis (*eg* . cyto-

chalasin D (49)).

The advantages of such an approach would be the efficiency of the synthesis, which becomes "doubly convergent",[39] and the general flexibility. One refinement would be to use a triene-lactam (119) since all the cytochalasans possess an E-double bond between C-13 and C-14 and Diels-Alder addition to the more substituted end of the triene unit would be expected.[21] By judicious choice of the side chain precursors an entry could be made into the [11]- and [13]cytochalasans and use of the appropriate amino acid in the synthesis of the pyrrolidinone starting material would enable derivatives of the chaetoglobosins and aspochalasins to be formed. In principle, the 24-oxa[14]cytochalasans could be derived from the carbocyclic analogues by Baeyer-Villiger oxidation for which there is precedence in cytochalasan chemistry.[40]

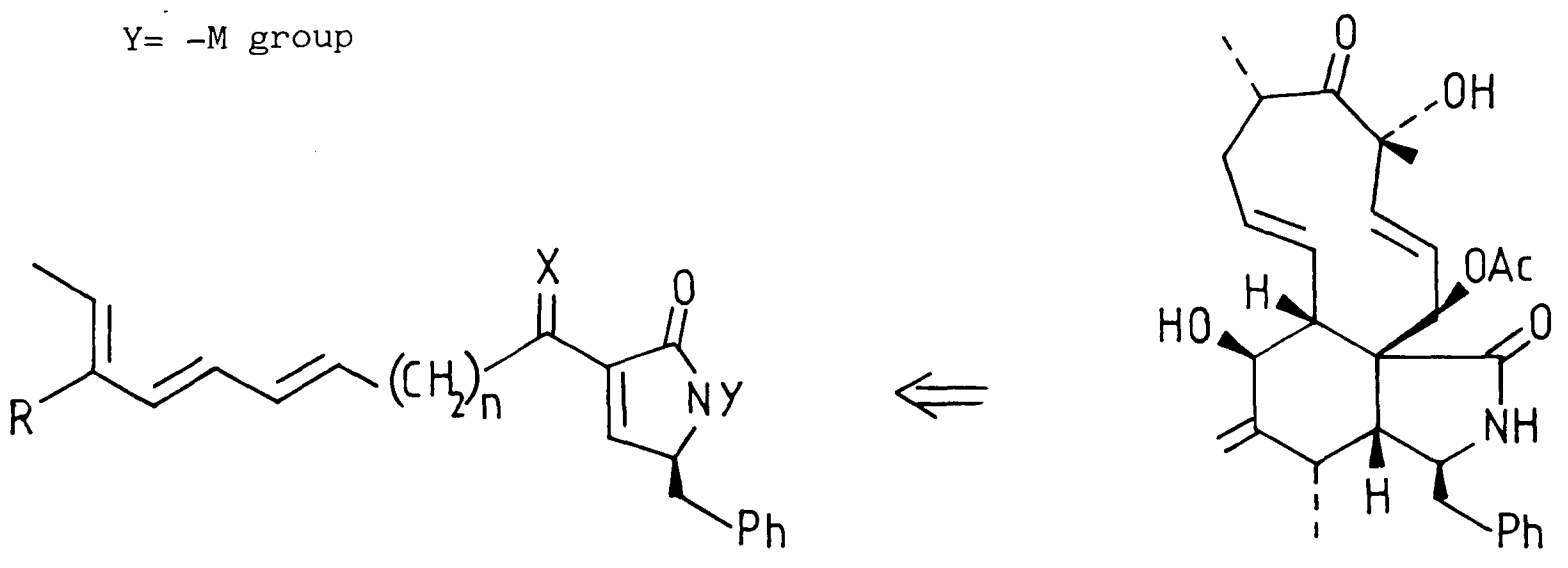
Figure 2.15



(117) (116) (118)

X= 2H, -M group

Y= -M group



(119) (49)

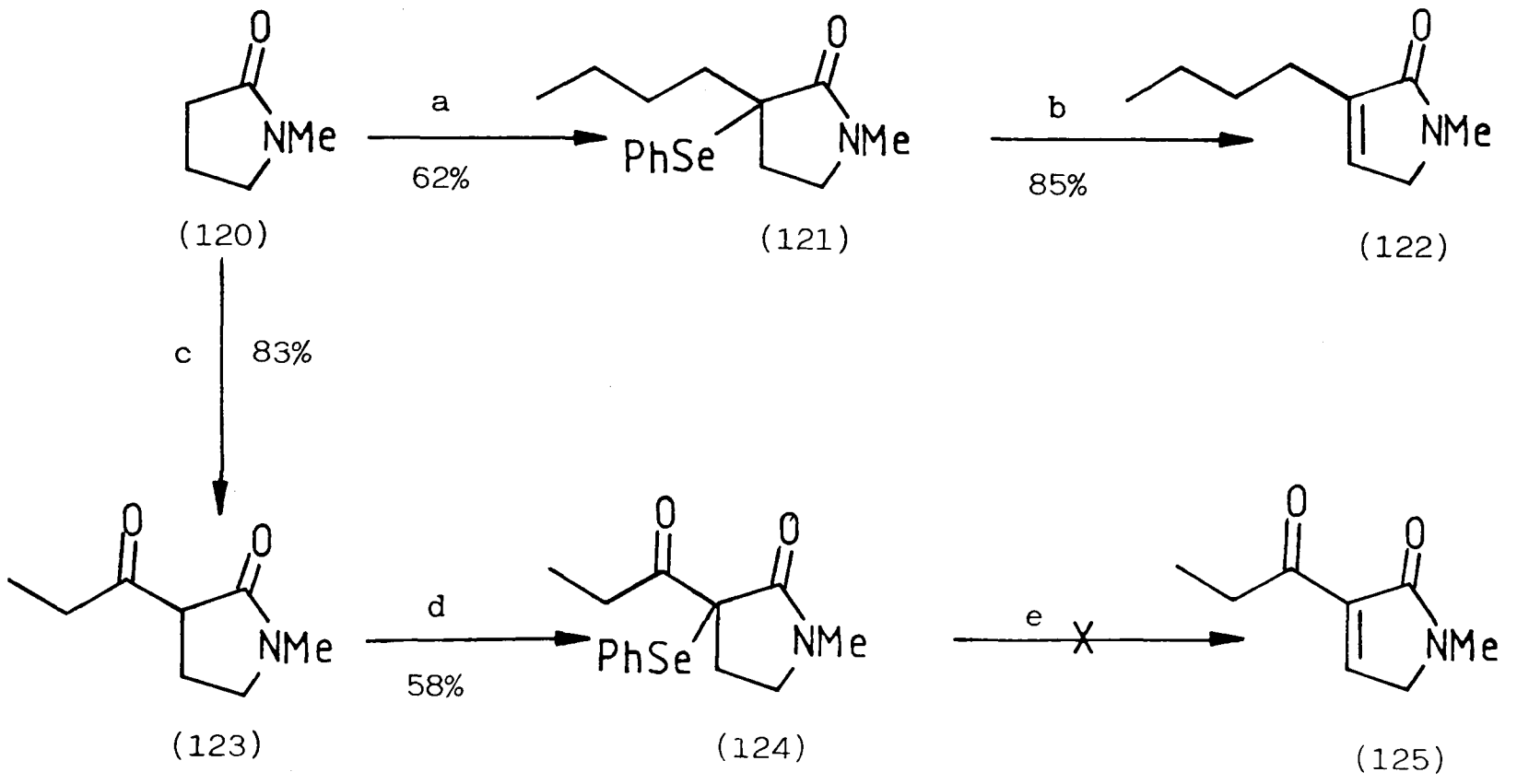
CHAPTER 3

THE SYNTHESIS OF 1-ACYL-3-ALKYL-5-BENZYL- Δ^3 *-PYRROLIN-2-ONES*

3.1 *Introduction*

The strategy proposed for the synthesis of 3-substituted-Δ^3-pyrrolin-2-ones was based on the selenoxide *syn*-elimination method for introducing unsaturation into organic molecules.[41] As preliminary work in this area, commercially available *N*-methylpyrrolidin-2-one (120) was treated with two equivalents of lithium di-isopropylamide (LDA) at -78° followed sequentially by phenylselenenyl chloride and 1-iodobutane to give selenide (121) which was subjected to the oxidative-elimination conditions of Reich *et al*.[42] (Scheme 3.1).

Scheme 3.1

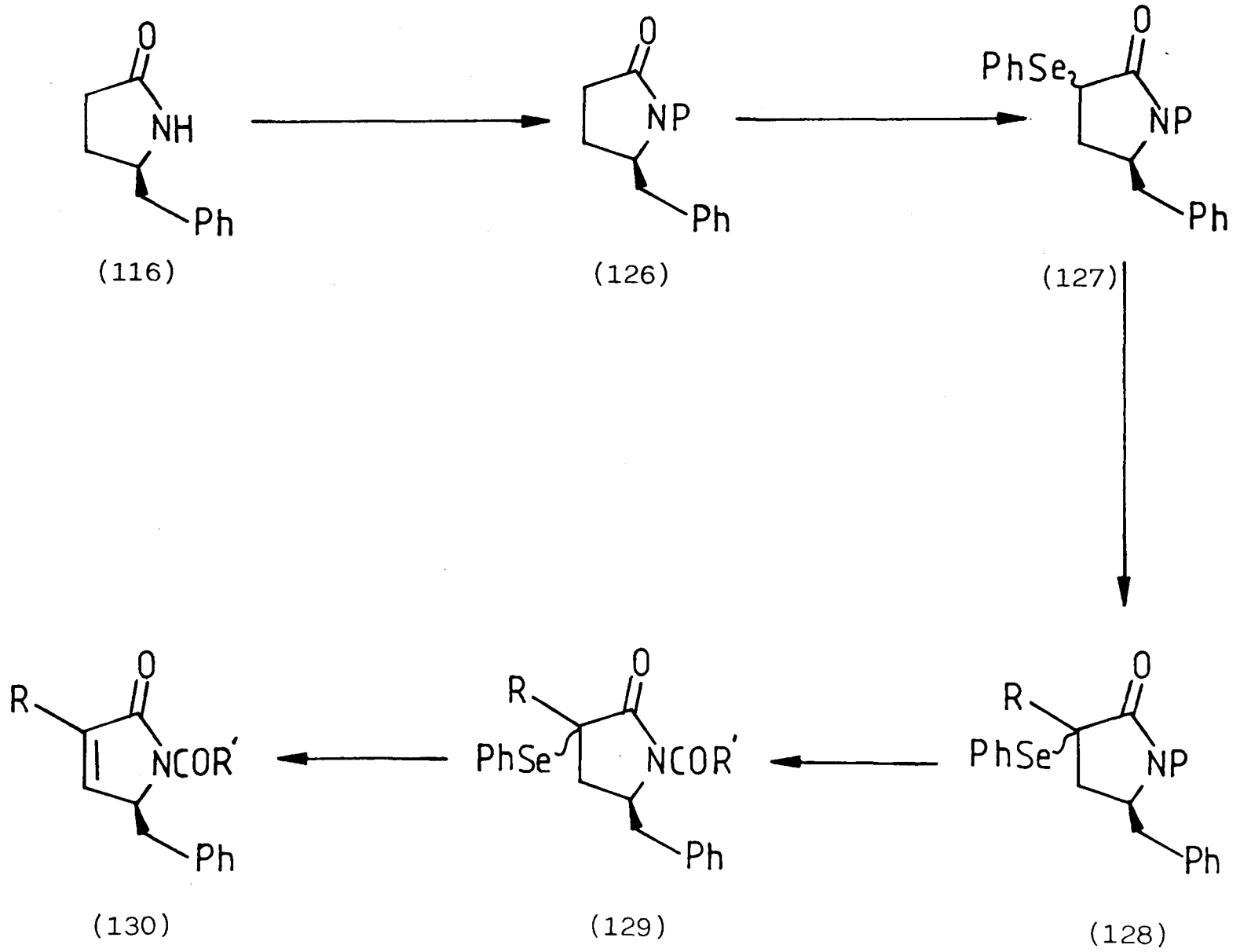


Reagents: a LDA, PhSeCl then BuI; b H_2O_2, py; c LDA, $EtCO_2Et$; d LDA, PhSeCl; e H_2O_2, chloramine-T, ArCH(O)NSO_2Ph, Bu^tO_2H.

A trial bimolecular Diels-Alder reaction with excess 2E,4E-hexadiene showed that pyrrolinone (122) was an unreactive dienophile. Formation of the 3-acylated pyrrolidin-2-one (124) was readily accomplished from (120) in a similar fashion but all attempts to prepare pyrrolinone (125) cleanly met with failure. These results confirmed the observation of Vedejs[17] that reactive but stable Δ^3-pyrrolin-2-ones required an *N*-acyl substituent.

A possible approach to *N*-acyl 3-alkylpyrrolinones was considered to utilize the stepwise protection /deprotection sequence outlined in Figure 3.1.

Figure 3.1



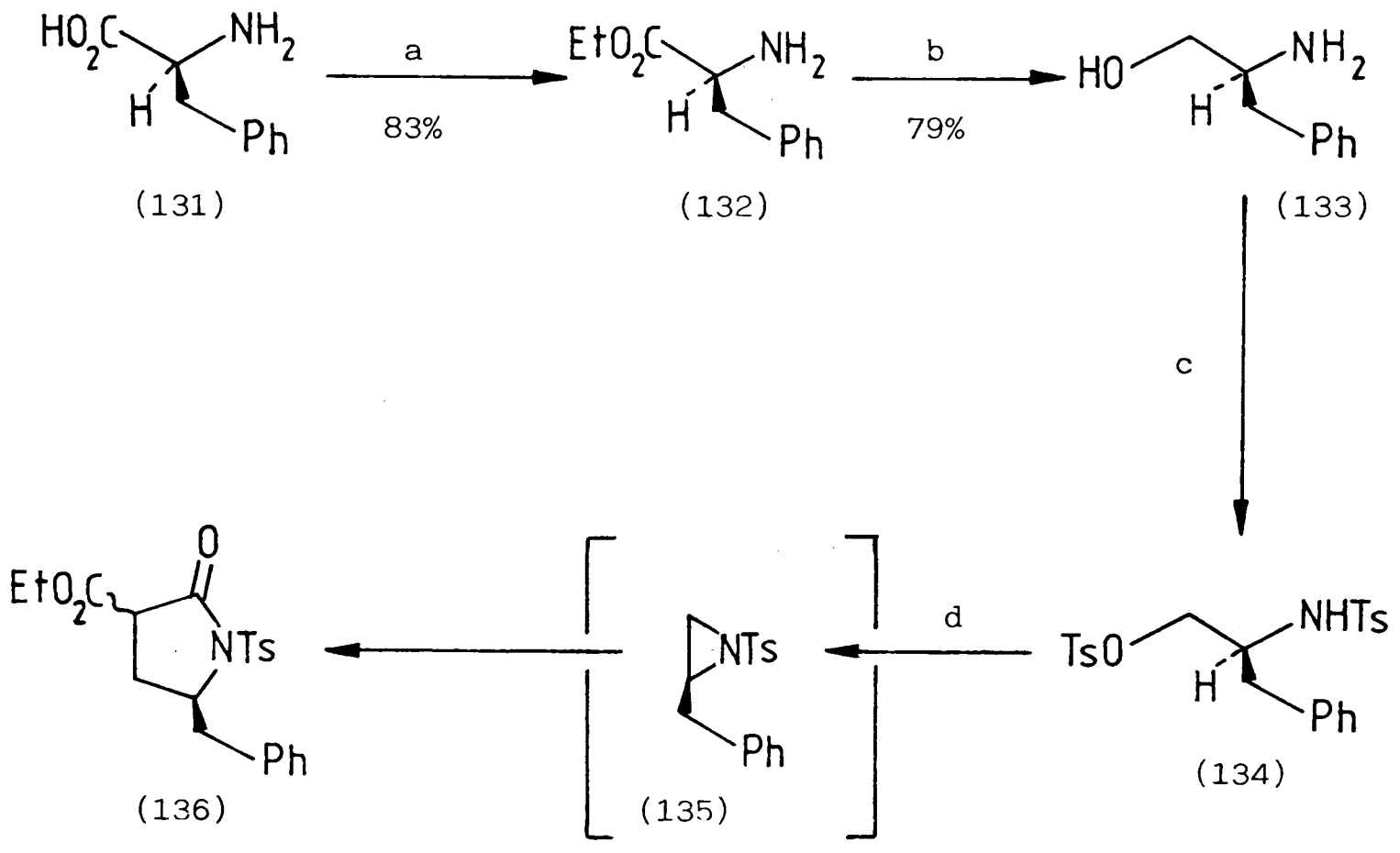
It was hoped to prepare the functionalised lactam (128) by *N*-protection of the proposed starting material (116), followed by selenenylation and alkylation. Subsequent deprotection and acylation was expected to yield the dienophile precursor (129) and thence the desired pyrrolinone (130). Acylation was believed to be desirable late in the sequence to allow for flexibility in the choice of R', and because the imide functionality present in *N*-acylated lactams was anticipated to be sensitive to nucleophiles.[43]

3.2 *Preparation of* 5R-5-*Benzylpyrrolidin-2-one*

Tseng *et al.*[38] have published a six step synthesis of the desired starting lactam in their studies of optically active pyrrolidines. The route was particularly suited to large scale work and used the commercially available L-β-phenylalanine (131) as starting material. Lithium aluminium hydride reduction of the corresponding ethyl ester (132) furnished phenylalaninol (133), which was subsequently bis-tosylated with excess tosyl chloride in pyridine (Scheme 3.2). Treatment of the bis-tosylated product (134) with three equivalents of potassio-diethyl malonate in refluxing tetrahydrofuran (THF) afforded a mixture of lactam (136) and open chain sulphonamide (137), the reaction occurring *via* the nucleophilic ring opening of the *N*-tosylaziridine (135) by malonate. Detosylation with concantrated hydrobromic acid followed by ion-exchange chromatography of the resulting hydrobromide salt gave γ-amino acid (138). Cyclization to the pyrrolidinone (116) was easily achieved by heating the amino acid in dioxan. The overall yield for the six steps on a 0.5 mole scale was typically 25%.

Although the optical yield of the product after a single low temperature crystallization was *ca* 90% as judged by optical rotation values, it was thought prudent to establish the enantiomeric excess (ee) by a chemical method. Upon quenching the lithium salt of lactam (116) with 1.1 molar

Scheme 3.2



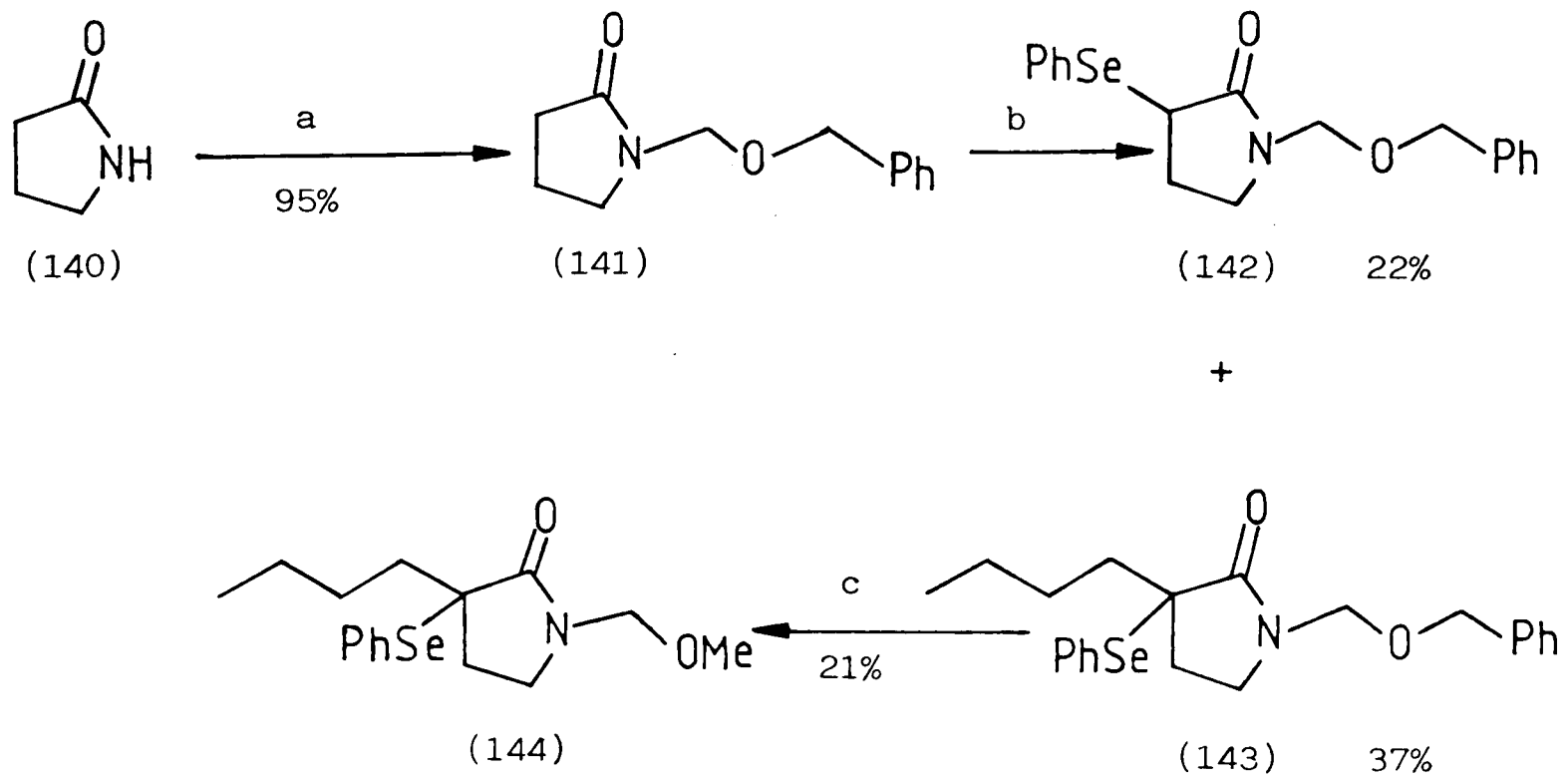
Reagents: a $SOCl_2$,EtOH;b $LiAlH_4$,Et_2O;c TsCl,py;d $KOBu^t$,$CH_2(CO_2Et)_2$;e HBr then ion-exchange column;f dioxan,100°;g BuLi then S-(-)-MTPA-chloride.

equivalents of (S)-(-)-α -methoxy-α-trifluoromethylphenylacetyl chloride ((-)-MTPA chloride)[44] a colourless oil was produced in 85% yield. The 300 MHz ^{1}H nmr spectra of lactam (116) and of this crude product are shown in Figures 3.2 and 3.3 respectively. From the relative integrals of the H-5 resonances in the latter it can be seen that the ratio of diastereoisomers is 88:12, which corresponds to a 76% ee. The major isomer was crystallized from ether-pentane to give an analytical sample of imide (139).

3.3 *Aspects of the Chemistry of* N-*Protected Pyrrolidin-2-ones*

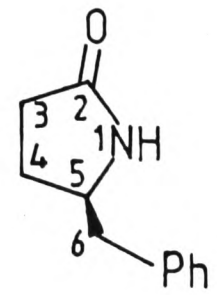
Preliminary investigations were centred around the choice of a suitable base-stable removable protecting group and for this work the model pyrrolidinone (140) was used. The benzyloxymethyl protecting group[45] of the readily prepared lactam (141) survived the alkylation reaction conditions which provided (142) and (143), but could not be removed with aqueous hydrochloric acid in refluxing THF (Scheme 3.3).

Scheme 3.3



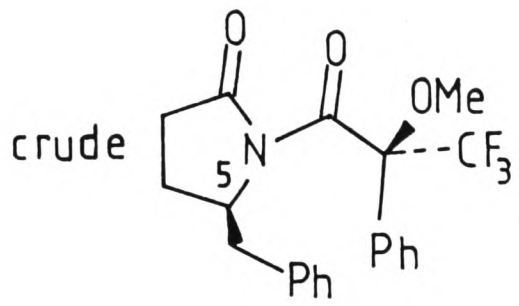
Reagents: a NaH, $PhCH_2OCH_2Cl$; b LDA, PhSeCl then BuI; c BBr_3, CH_2Cl_2.

Figure 3.2



(116)

Figure 3.3



(139)

H-5

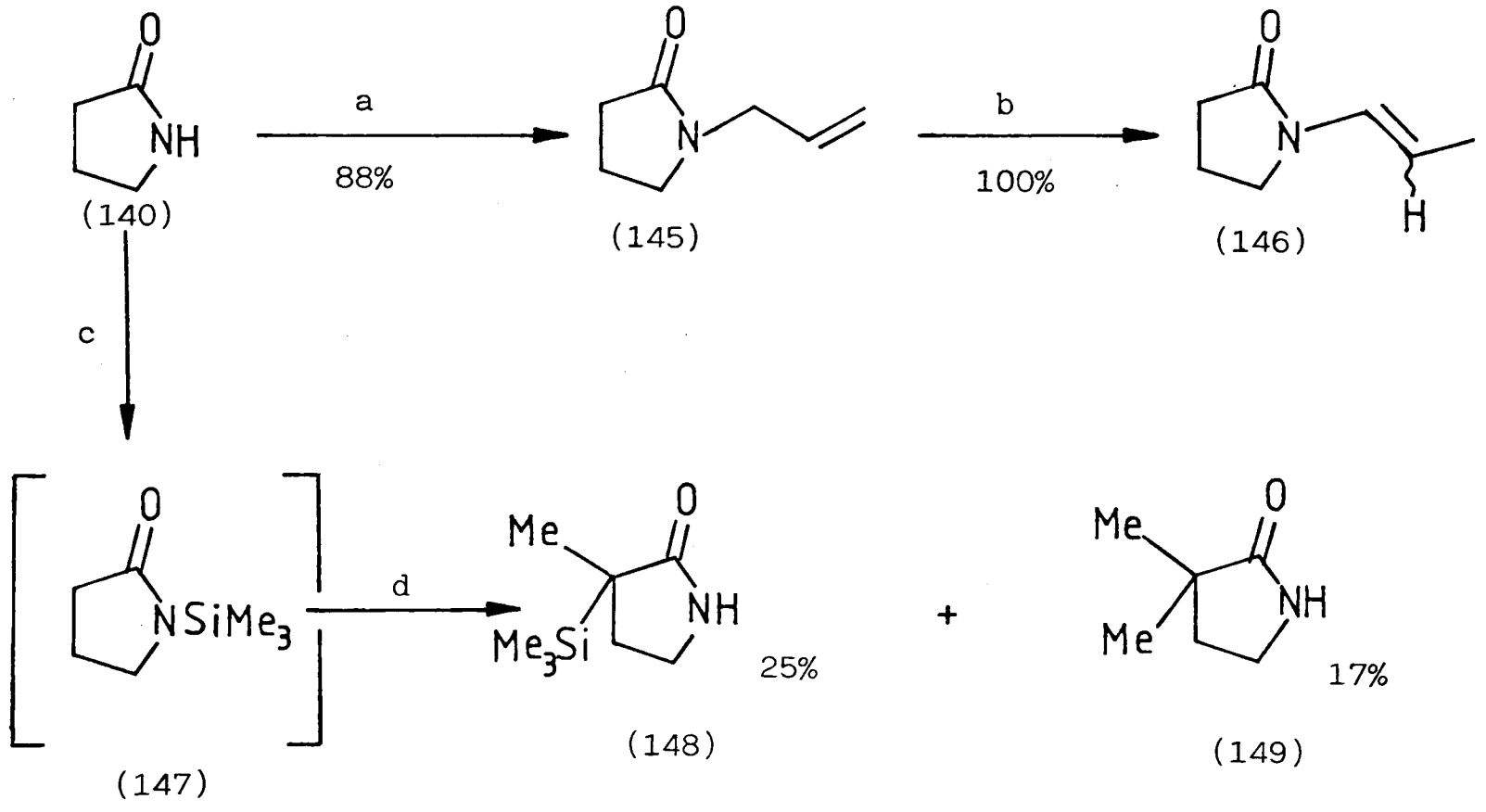
7 6 5 4 3 2 1

δ

The very electrophilic reagents boron tribromide[46] and trimethylsilyl iodide[47] on the other hand, led only to partial ether cleavage to give lactam (144), or C-Se bond cleavage products (*eg*. $PhSeCH_2Ph$).

Protection of (140) with the allyl group[48] was achieved smoothly using sodium hydride (NaH) and allyl bromide, but attempts to isomerize lactam (145) to the enamide (146) under basic conditions (*eg* . LDA, Bu^tOK) failed (Scheme 3.4). Treatment with rhodium trichloride[49] in refluxing aqueous ethanol,however, gave lactam (146) in quantitative yield as a mixture of geometrical isomers (E:Z ratio *ca* 12:1), but enamide hydrolysis[49,50] gave only a complex mixture of products.

Scheme 3.4



Reagents: a NaH, $CH_2=CHCH_2Br$;b $RhCl_3$, aq. EtOH;c TMSCl, Et_3N;d LDA, MeI.

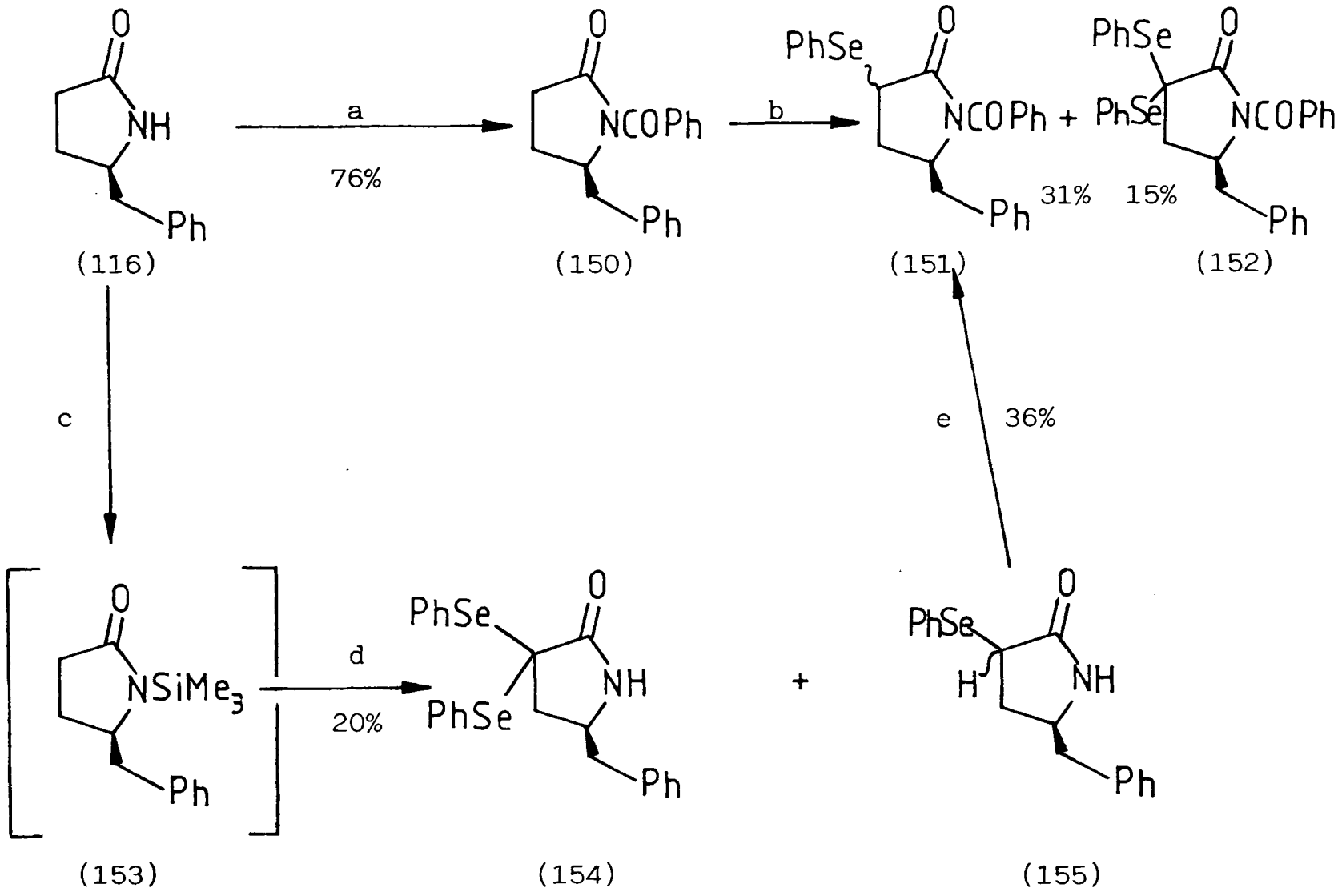
Silyl protecting groups are well established[51] and a search of the literature revealed that *N* -trimethylsilylpyrrolidin-2-one (147) was a known compound.[52] Because of the handling difficulties associated with this

moisture sensitive compound silylation was performed *in situ* and excess LDA was added to form the enolate at -78°. Methylation followed by aqueous work-up gave a complex mixture from which none of the desired 3-methyl-pyrrolidin-2-one was isolated. Instead, the C-alkylated products (148) and (149) were isolated in modest yield. Thus the balance between chemical stability and lability could not be found with those formal protecting groups studied. In addition, the conditions required to deprotect (*eg* . $RhCl_3$, H^+) would be incompatible with the conjugated diene/triene anticipated for the intramolecular cycloaddition (Figure 2.15).

The revelation by Vedejs,[18] however, that racemic *N* -benzoyl-5-benzyl-pyrrolidinone (150) could be successfully carboethoxylated and phenylselenenylated prompted us to study similar enolate reactions. Simple *N* -alkyl lactams,[53] lactones[54] and nitriles[55] have been sulphenylated and selenenylated but control of mono- or bis-substitution depended on judicious choice of the substrate: base: electrophile ratio. Treatment of the readily prepared lactam (150) with LDA at -78° followed by phenylselenenyl chloride gave, after careful work-up, a mixture of mono- and bis- selenenylated materials (151) and (152), respectively, along with recovered starting material (Scheme 3.5). Further amounts of the mono-substituted lactam could be obtained from *N* -benzoylation of the parent (155) but trial alkylation reactions with the acylated selenide gave only deprotected lactams despite cautious work-up procedures.

The *N* -trimethylsilylated lactam (153) has been used before[3b] to prepare selenide (155) but generation of this sensitive intermediate *in situ* and subsequent selenenylation gave only a mixture of the bis- and mono-selenenylated lactams (154) and (155) in low yield (*ca* 20% combined). In addition substantial amounts of starting material were recovered. Believing adventitious hydroysis of (153) to be at least partly responsible for

Scheme 3.5



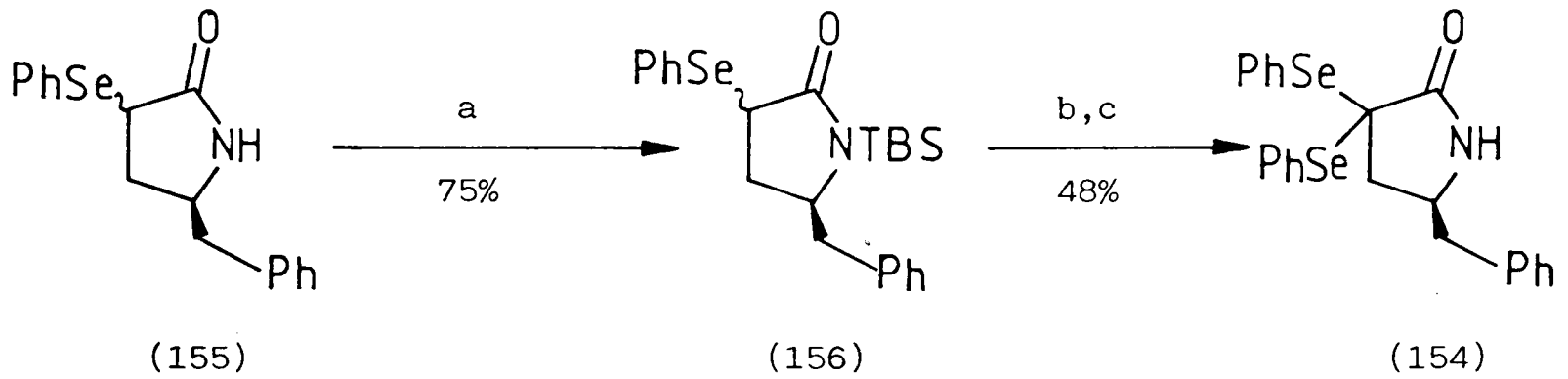
Reagents: a NaH, PhCOCl; b LDA, HMPA, PhSeCl; c TMSCl, Et_3N; d LDA, PhSeCl; e PhCOCl, Et_3N.

the low conversion, attention was turned to the use of the bulky *tert* - butyldimethylsilyl (TBS) protecting group.[56]

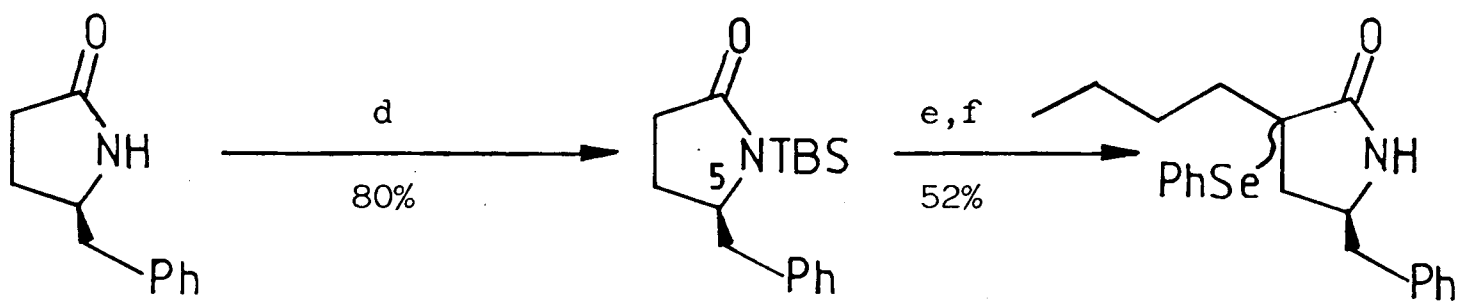
Treatment of selenide (155) with TBS-chloride in the presence of triethylamine gave the protected lactam (156) in good yield after filtration chromatography (Scheme 3.6). Selenenylation followed by fluoride ion[56] or acid induced deprotection gave the bis-selenide (154) in about 50% yield. The way was now open to a short synthesis of 3,3-disubstituted pyrrolidinones (128) (Figure 3.1).

Silylated lactam (157) was available in 80% yield as an amorphous solid after flash chromatography[57] upon treatment of starting material (116) with one equivalent each of n-butyl lithium (BuLi) and TBS-chloride at 0°. Trialkylsilylated carboxamides can have the silicon group residing

Scheme 3.6



(155) (156) (154)



(116) (157) (158)

Reagents: a TBSCl, Et_3N;b LDA, PhSeCl;c H_3O^+;d BuLi, TBSCl;e LDA, PhSeCl then BuI;f Bu^n_4NF.

on either the nitrogen or oxygen atoms.[58] In an *N*-silylated structure, amide resonance stabilization is still possible whereas in an *O*-silyl imino ether structure such a phenomenon cannot occur. In general, however, there is a subtle balance between amide resonance and the greater thermodynamic stability of the O-Si bond relative to the N-Si bond, and in some cases both structural types exist in equilibrium.[59] Evidence to support the *N*-silylated structure of (157) came from the ^1H nmr spectrum in which H-5 appeared as a multiplet at δ 3.7 [*cf.* δ 3.88 in (116) and δ 4.24 in (181)†], and from the intense lactam carbonyl stretching frequency in the infra-red (ir) spectrum ($\nu_{max.}$ 1691 cm^{-1}).

Treatment of lactam (157) with two molar equivalents of LDA at -78° followed by sequential addition of phenylselenenyl chloride and 1-iodobutane gave the functionalized lactam (158) in 52% overall yield,as a

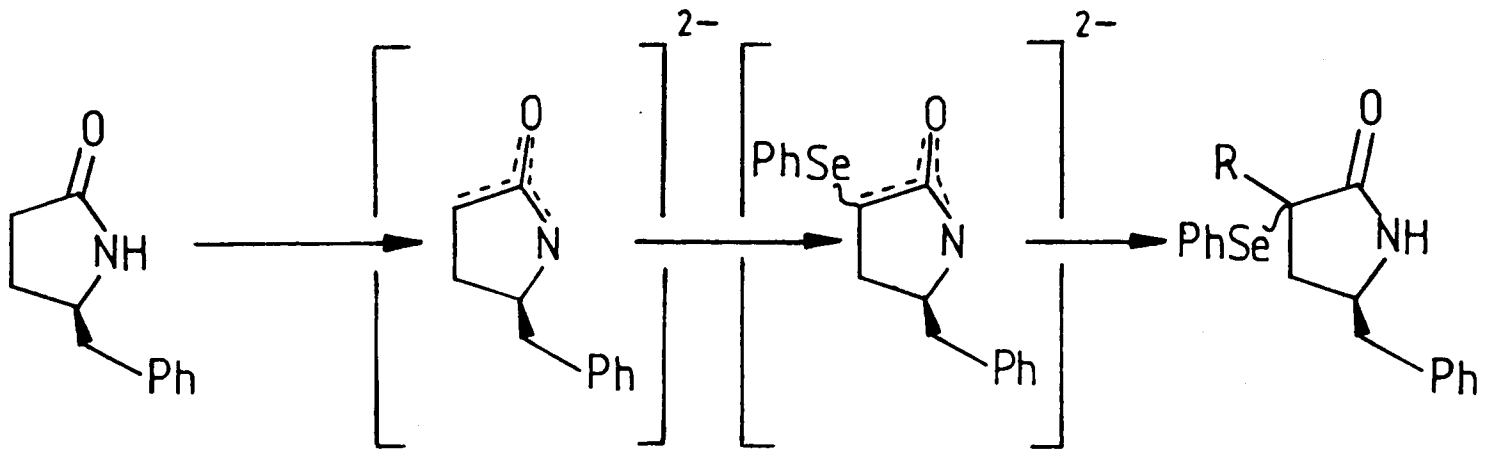
† See Scheme 3.10.

mixture of diastereoisomers (*ca* 3:1),after deprotection. However, preliminary experiments with long chain primary alkyl halides (*eg.* (183-5)) did not give C-3 alkylated products under similar conditions and mixtures of selenides (154) and (155) were isolated in low yields. Presumably in these cases the rate of alkylation was slower than the rate of proton transfer between the mono-selenide (155) and the enolate of the starting lactam (157).

3.4 *Preparation of Selenenylated Materials*

Having exposed some of the limitations of this protecting group methodology, an alternative route to substituted pyrrolidinones was considered (Figure 3.4). The rationale behind this approach derived from the review of Kaiser *et al.*[60] which illustrated the chemistry of di- and

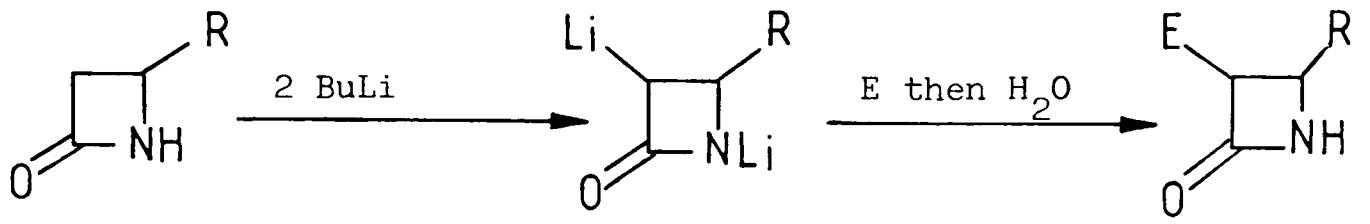
Figure 3.4



(116) (159) (160) (161)

polyalkalimetal derivatives of many functional groups. Of particular note was the preparation and selective C-3 alkylation of dimetallated carboxamides such as (163)[61] which bear a close structural similarity with pyrrolidinone (116) (Figure 3.5). If suitable conditions could be found for the generation of the 1,3-dianion (159) of starting material (116), it was hoped that selenenylation would provide mono-selenide (155) directly.

Figure 3.5



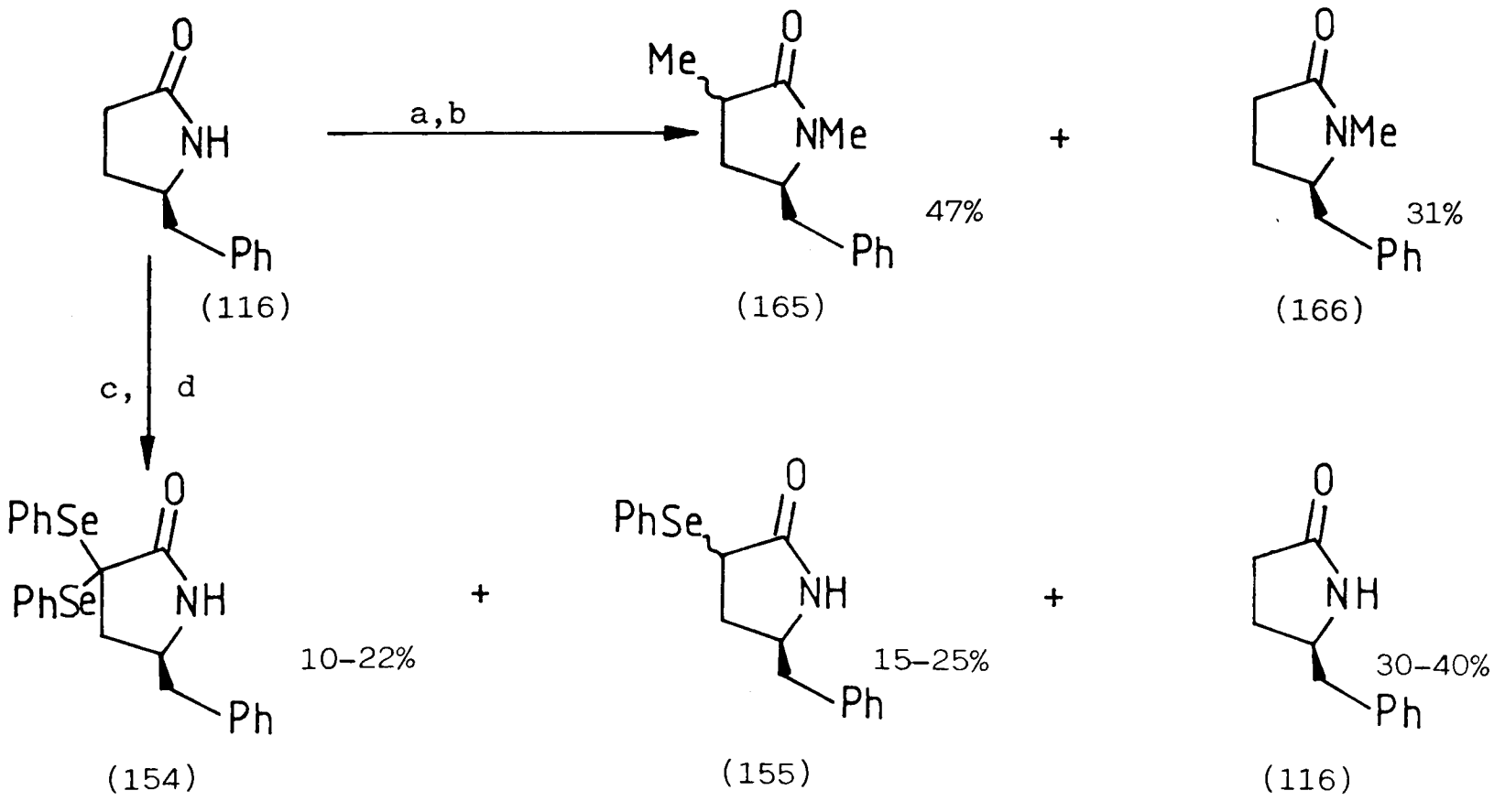
(162) (163) (164)

yields 44-88%

Generation of the corresponding dianion (160) and subsequent alkylation would then give the desired lactams (161).

To test the feasibility of this route, starting material (116) was treated with three equivalents of BuLi followed by excess iodomethane at 0° in THF to give the dimethylated and *N*-methylated products (165) and (166) in 78% combined yield after short column chromatography[62] (Scheme 3.7). However, when the dark red dianion solution was cooled to -78° and phenylselenenyl chloride was added, aqueous work-up gave a product shown

Scheme 3.7



Reagents: a BuLi (3eq.),0°;b MeI;c BuLi-TMEDA;d PhSeCl.

by thin layer chromatography (tlc) to be a mixture of five components. Careful chromatography using gradient elution enabled each product to be identified. The least polar material was diphenyl diselenide, the ubiquitous side product from selenenylation reactions, followed by the bis-selenide (154). The mono-selenenylated lactam (155) was obtained as a separable mixture of diastereoisomers and finally starting material was eluted.

Many attempts were made to optimize the reaction (Table 3.1) but mixtures of the selenenylated products were always produced in about 20-30% yield, and significant amounts of starting material were recovered (30-40%)†. The most reliable procedure for the preparation of the mono-selenide was found to involve the use of two equivalents of BuLi-TMEDA[64] (*N*, *N*, *N'*, *N'*-tetramethylethylenediamine) in THF at 0°, followed by the addition of one equivalent of phenylselenenyl chloride at -78° (Entry 2). Under these conditions the reaction could be performed on *ca* 5g scale to give selenide (155) in 15-25% yield (Entry 3). By using three equivalents of BuLi-TMEDA and excess electrophile (Entry 4) the bis-selenide (154) was formed preferentially.

Increasing the time of dianion formation (Entry 5) or lowering the temperature of reaction (Entry 6) had, if anything, a detrimental effect, while quenching the reaction at -78° with methanol prior to warming to 0° (Entry 7) gave significantly lower yields of selenenylated materials. Changing the base either made little difference (Entry 8) or gave exclusively starting material (Entry 9). Gilman and Gaj[65] have suggested -35° or below as a workable temperature for BuLi in THF to prevent decomposition of the base[66] but the use of 1,2-dimethoxy ethane as the solvent for the selenenylation reaction gave mainly starting material (Entry 10). Furthermore, an example of the use of the BuLi-TMEDA combination in THF at 0° has recently been disclosed[67] in closely related work. Thus, the dianion

† No *N*-selenenylated materials were isolated, reflecting the susceptibility of selenamides to hydrolysis.[63]

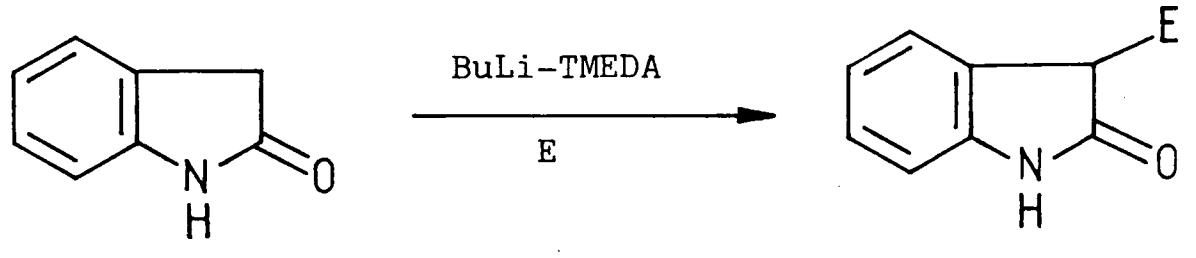
Table 3.1 Phenylselenenylation Reactions of 5R-5-Benzylpyrrolidin-2-one (116)

Entry	Conditions: Base, t (min), PhSeCl (x eq.), other	Yields % (154)	(155)	(116)
1	BuLi (2), 80, 0°, 1, THF	18	3	49
2	BuLi-TMEDA (2), 70, 0°, 1, -78° (15min) → 0°	trace	35	20
3	as 2[a]	10	25	40
4	BuLi-TMEDA (3), 60, 0°, 2.5, -78° (15 min) → 0°	22	10	34
5	BuLi-TMEDA (2), 170, 0°, 1, -78° (15 min) → 0°	trace	28	35
6	BuLi-TMEDA (2), 70, -50°, 1.1, -78° (15 min) → 0°	trace	5	64
7	BuLi-TMEDA (2), 70, 0°, 1.1, -78° (5 min), MeOH	6	12	45
8	Bu^tLi (2), -78° 0° (60 min), 1, -78° (15 min) → 0°	3	23	50
9	LDA (2), 65, 0°, 1.1, -78° (15 min) → 0°	trace	trace	> 90[b]
10	BuLi-TMEDA (2), DME[c], 70, 0°, 1, -78° (15 min) → 0°	6	trace	59

a Performed on a gram scale; b Estimated by tlc/weight of crude product; c Heterogeneous reaction.

of oxindole (167) was selectively alkylated at C-3 to give products (168) in good yield only when TMEDA was added (Figure 3.6).

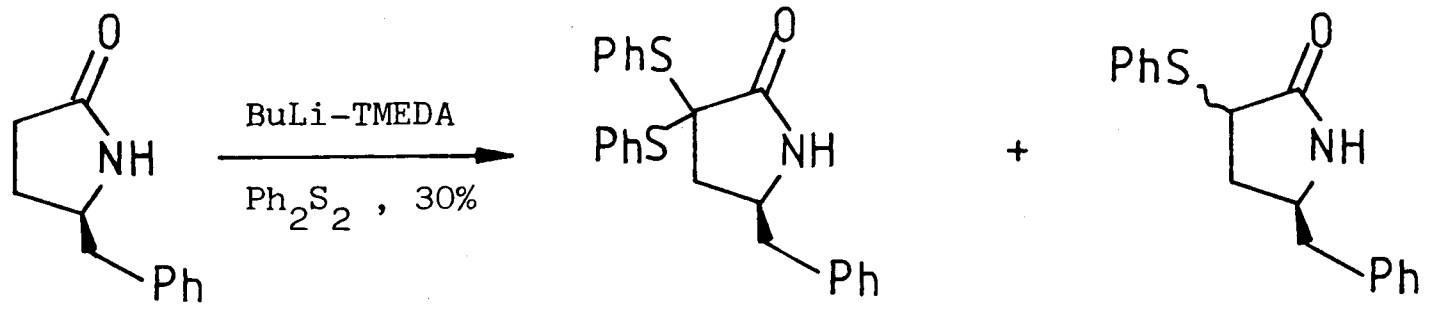
Figure 3.6



(167) (168) 40-70%

Preliminary experiments were performed with diphenyl disulphide as the electrophile but similar mixtures of mono- and bis-substitution products (170) and (169) were produced in 30% combined yield (Figure 3.7).

Figure 3.7



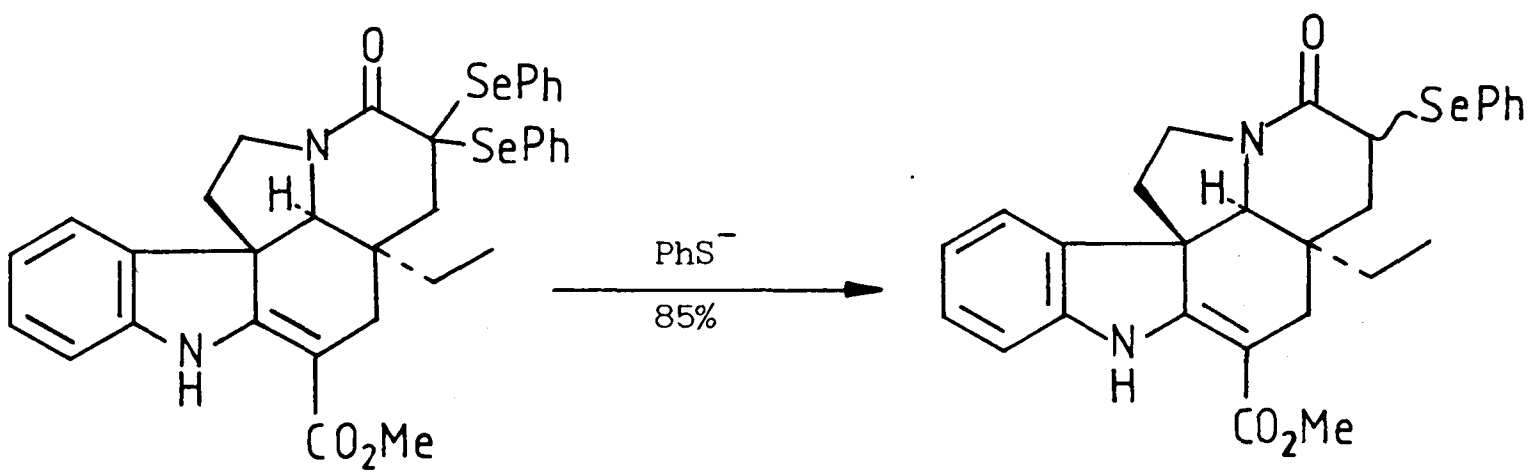
(116) (169) (170)

Although the combined yields of selenenylated lactams (154) and (155) were modest, the directness of their preparation from starting material (116) allowed their potential use in the synthesis of 3-alkylpyrrolidinones to be evaluated immediately.

3.5 *Alkylation Reactions of Selenolactams*

Treatment of selenides with strong bases is known to lead to the formation of stabilized carbanions.[68] Although there is some evidence to suggest that selenium stabilizes negative charge on neighbouring carbon slightly less effectively than does sulphur,[69] the high nucleophilicity of such carbanions once formed is unquestioned. The propensity for organolithium reagents to attack at selenium,on the other hand, has been used to advantage in the preparation of α -lithio selenides[70] and α -lithiovinyl selenides[71] from the corresponding selenoketals.† At the time however, only one method for the generation of enolates from α,α -bis-selenenylated lactams had been described in the literature. Levy *et al.*[72] treated the functionalized lactam (171) with one equivalent of sodium phenyl thiolate to provide the mono-selenenylated product (172), an intermediate in their synthesis of tabersonine (Figure 3.8).

Figure 3.8



(171) (172)

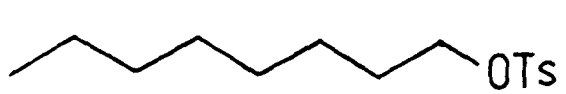
When monosubstituted lactam (155) was treated with two equivalents of BuLi followed by a primary alkyl halide at 0°,a complex mixture of products was isolated (173-6) (Scheme 3.8). The results of several variations of the reaction conditions are recorded in Table 3.2.

† The mechanism of these C-Se bond cleavage reactions may involve a concerted 'SN2' type displacement or proceed *via* an intermediate trivalent selenium species.[70]

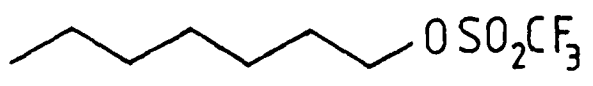
Table 3.2 Alkylation Reactions of 5-Benzyl-3-phenylselenopyrrolidin-2-one (155)

Entry	Conditions: Base, Solvent. RX (x eq.), other	Yields %						
		PhSeBu	(173)	(174)	(175)	(176)	(155)	(116)
1	BuLi, THF, MeI (20), 0°→ 25° overnight[a]	40	-	-	33	-	5	-
2	LDA, THF, MeI (6), HMPA (1.9), -20° →25°, 4h	-	12	-	26	-	5	-
3	BuLi,Et_2O, MeI (6.6), 0°→ 25°, 3h	41	-	30	-	34	-	-
4	BuLi-TMEDA, Et_2O, MeI (10.5), 0°→ 25°, 3h	44	-	23	-	42	-	-
5	BuLi, Et_2O, C_4H_9I (1.1), 0°→ 25° overnight	33	-	13	-	-	29	26
6	BuLi, Et_2O, $C_7H_{15}Br$ (1.1), 0°→ 25° overnight	52	-	27	-	6	8	28
7	BuLi, Et_2O, $C_7H_{15}Br$ (1.1), HMPA (2), 0°→ 25° overnight	26	-	12	-	10	13	27
8	BuLi, Et_2O, (177) (1.1), 0°→ 25°, 3h	b	-	-	-	-	48	-
9	BuLi, Et_2O, (178) (1.1), 0°→ 25°, 2h	40[c]	-	5	-	8	20	19

a 5% (166) also isolated; b > 90% (177) recovered; c Plus heptyl residues.



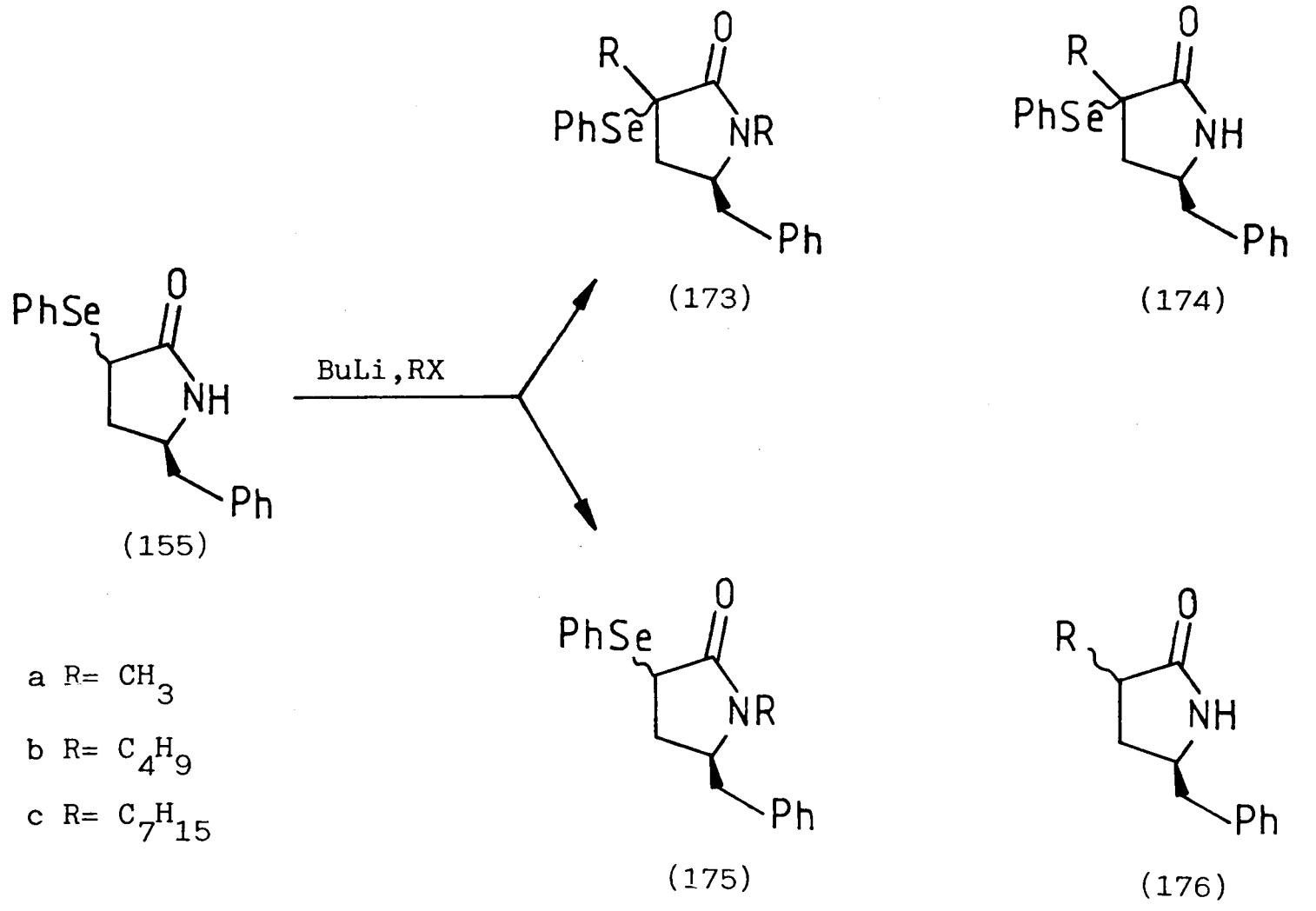
(177)



(178)

When THF was used as solvent (Entries 1 and 2) the major products were the *N*-alkylated lactams (173) and (175)† whereas selective C-3 alkylation could be achieved by using diethyl ether[73] (Entries 3-9). Nevertheless, the yields of the desired products (174) were at best 30% and in several runs substantial deselenenylation accompanied the alkylation (Entries 3 and 4). Amide bases do not generally attack at the soft electrophilic selenium and C-Se bond cleavage can be avoided[74] but when LDA-HMPA (hexamethylphosphorous triamide) was used (Entry 2) no significant improvement in the yield of alkylated products was found.

Scheme 3.8



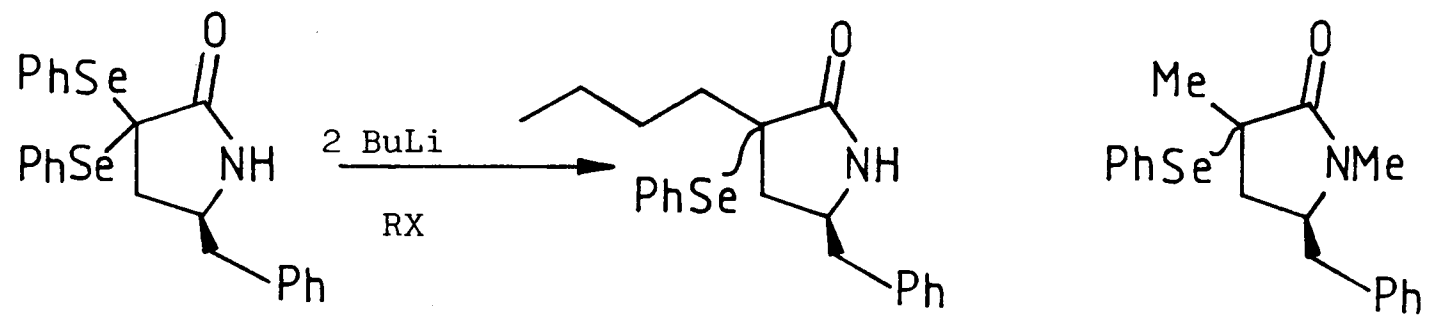
Attempts to optimize C-3 alkylation by using more reactive electro-

† In the alkylation work thus far described, the 3-substituted and 3,3-disubstituted pyrrolidin-2-one products were always isolated as mixtures of diastereoisomers. The ratios varied between 1:1 and 5:1 depending on the nature of the substituents and were often estimated from the relative integrals of the H-5 or benzylic proton resonances in the ^1H nmr spectra, which were well resolved. Although in some cases it was possible to separate the mixtures for characterization purposes, on a preparative scale the mixtures were used since ultimately the chiral centre at C-3 was to be removed by selenoxide elimination.

philes were also made, but with octyl tosylate (177) and heptyl triflate (178)[75] only small amounts of the desired products (174) were obtained (Entries 8 and 9).

From these results it would appear that,under the reaction conditions specified, C-Se bond cleavage competed effectively with alkylation. It was decided,therefore, to use this to advantage with the bis-selenide (154). Treatment with two equivalents of BuLi at 0° in THF for an hour followed by one equivalent of 1-iodobutane gave, after aqueous work-up and flash chromatography, lactam (158) in 67% yield (Scheme 3.9). When excess iodomethane was used, the dimethylated product (173a) was isolated. The efficiency of the dianion formation was apparent from the recovery of butyl phenylselenide in essentially quantitative yield.

Scheme 3.9

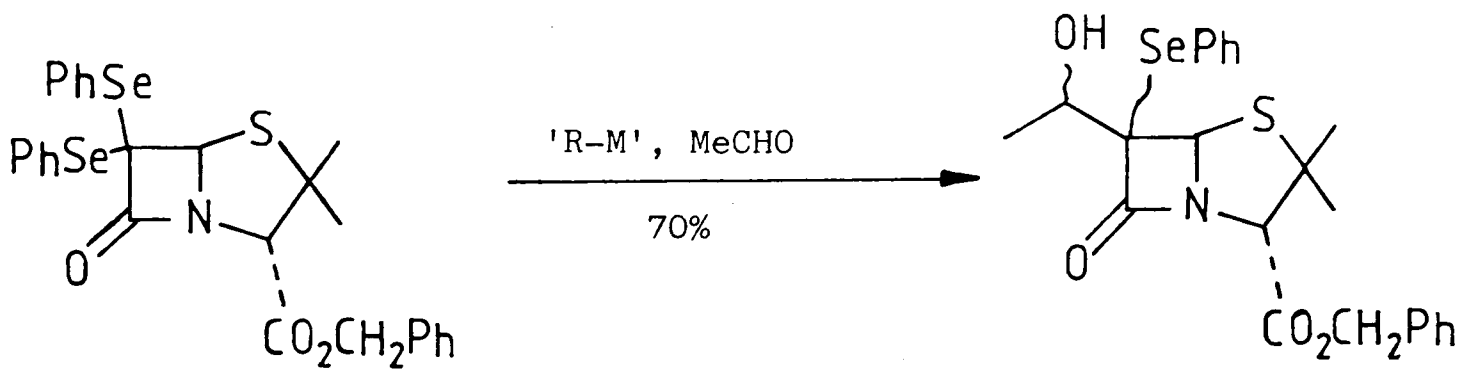


(154) (158)=(174b) (173a)

a RX= MeI, b RX= BuI 67% 61%

Some time after the completion of this work Hirai *et al*.[76] revealed a similar method of enolate generation from selenoketals (Figure 3.9). Reaction of methylmagnesium bromide or BuLi with β -lactam (179) and subsequent quenching with excess acetaldehyde afforded the selenide (180) as a mixture of diastereoisomers in 70% yield.

Figure 3.9



(179) (180)

The greater utility of the bis-selenide for the preparation of 3-alkylpyrrolidinones was offset by its formation in only modest yield from starting lactam (116). This could be alleviated to some extent by converting the mono-selenide (155) into further amounts of the bis (154) by the three step sequence outlined in Scheme 3.6.

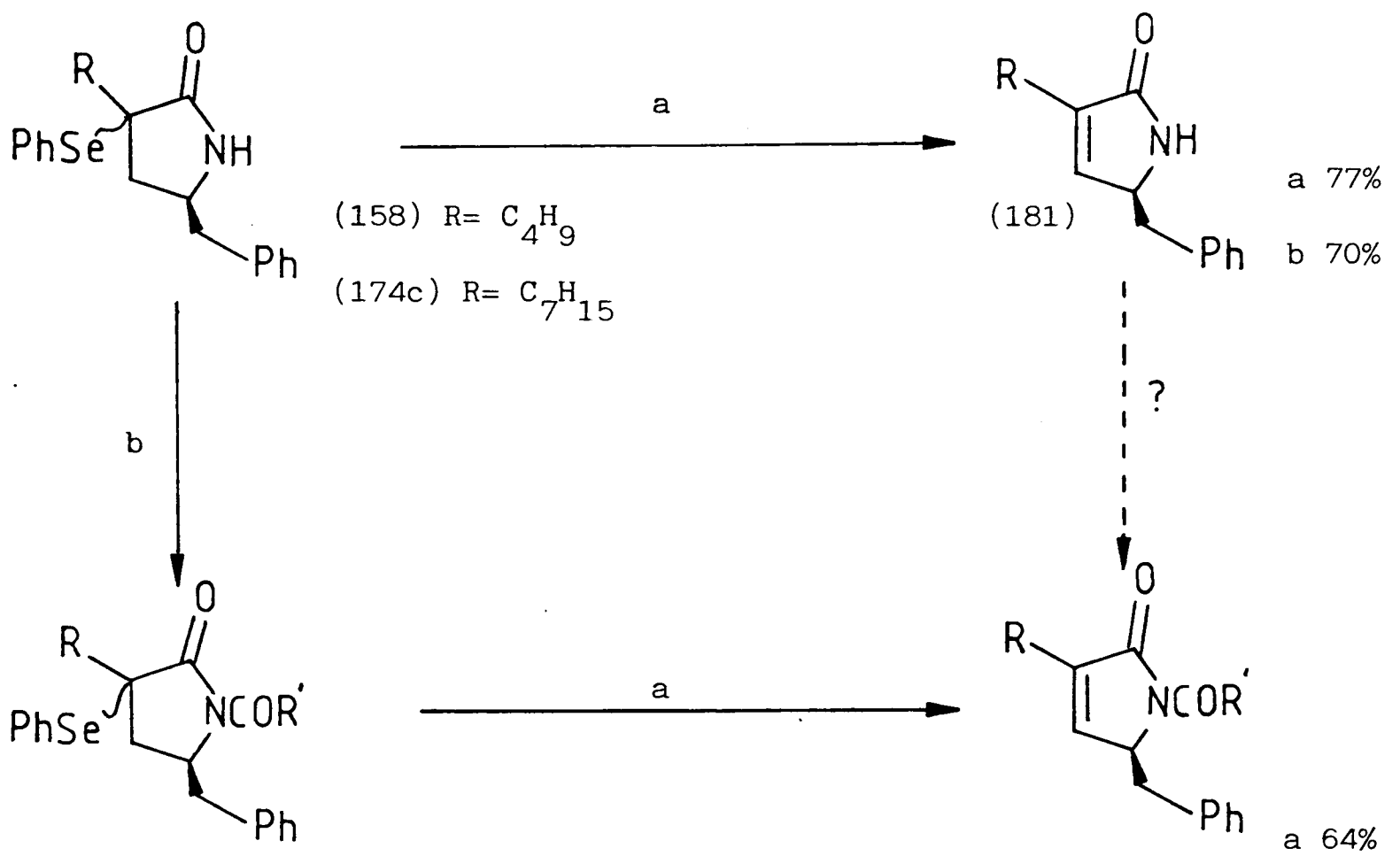
3.6 *Preparation and Diels-Alder Reactions of 1-Acyl-3-alkyl-5-benzyl-* Δ^3*-pyrrolin-2-ones*

With the requisite lactams in hand, the question of the order of the oxidation and acylation steps was next addressed. Treatment of selenides (158) and (174c) with excess hydrogen peroxide in the presence of pyridine[42] gave good yields of the desired pyrrolin-2-ones (181) (Scheme 3.10). That complete racemization at C-5 had not occurred was shown by the substantial optical rotation value of the 3-heptylpyrrolinone (181c), $[\alpha]_D^{20}$ +90.6 (c 0.46, CCl_4).

A notable feature of the high resolution ^1H nmr spectra of these compounds was the appearance of the H-5 resonance at δ 4.24, some 0.5 ppm downfield from the corresponding resonance in the selenides (δ 3.65), reflecting the deshielding effect of the double bond. Although the pyrrolinones were stable to chromatography they decomposed within a few days at room temperature to give complex purple mixtures, and trial acylation experiments with NaH as base were unsuccessful.

These difficulties could be overcome by acylating the selenides first.

Scheme 3.10



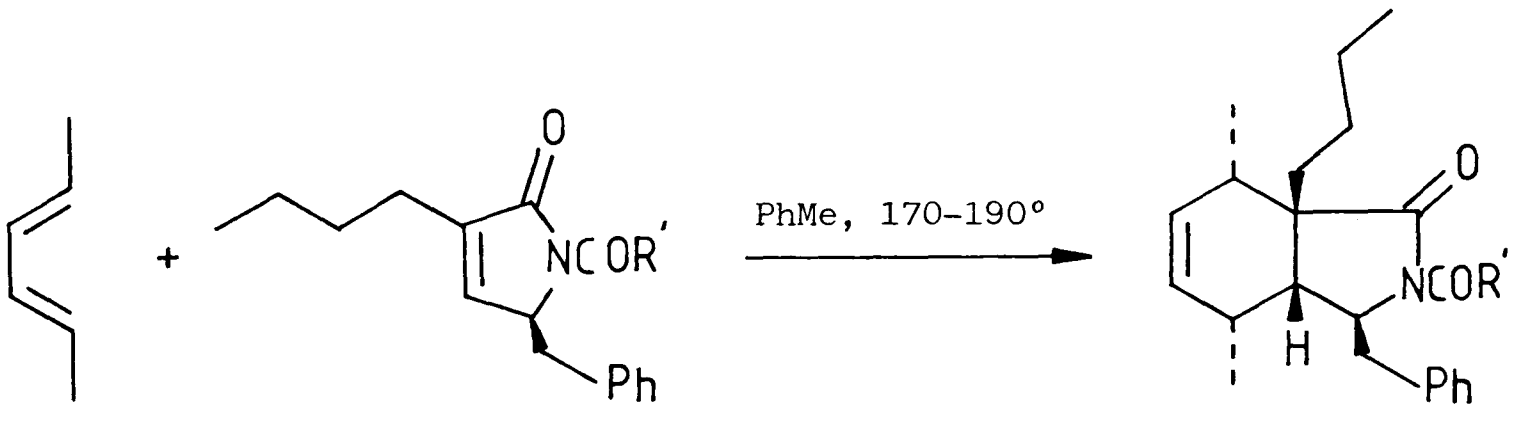
Reagents: a H_2O_2, py; b BuLi, R'COCl.

Treatment of lactam (158) with one equivalent of BuLi and a slight excess of the acid chloride (PhCOCl, AcCl) at 0°, followed by selenoxide elimination of the purified selenides (129), gave the activated pyrrolinones (130) as stable colourless oils. The increased downfield shift of the H-5 resonance upon *N* -acylation was evident from the 300 MHz ^{1}H nmr spectra, *eg* . from δ 4.68 in (129b) to δ 5.1 in (130b).

It was found that heating pyrrolinones (130) with an excess of 2E,4E-hexadiene in a sealed tube at 170-190° for 30-50 h brought about the desired Diels-Alder reactions (Scheme 3.11). However, although a single adduct (182) was isolated in each case, the yields were only modest and substantial amounts of starting material were recovered.

The gross structures of the cycloadducts were consistent with the observed spectroscopic data. In particular, the ir spectra confirmed the presence of two carbonyl groups ($\nu_{max.}$ 1720-1730 and 1680-1690 cm^{-1})

Scheme 3.11



(130) (182)

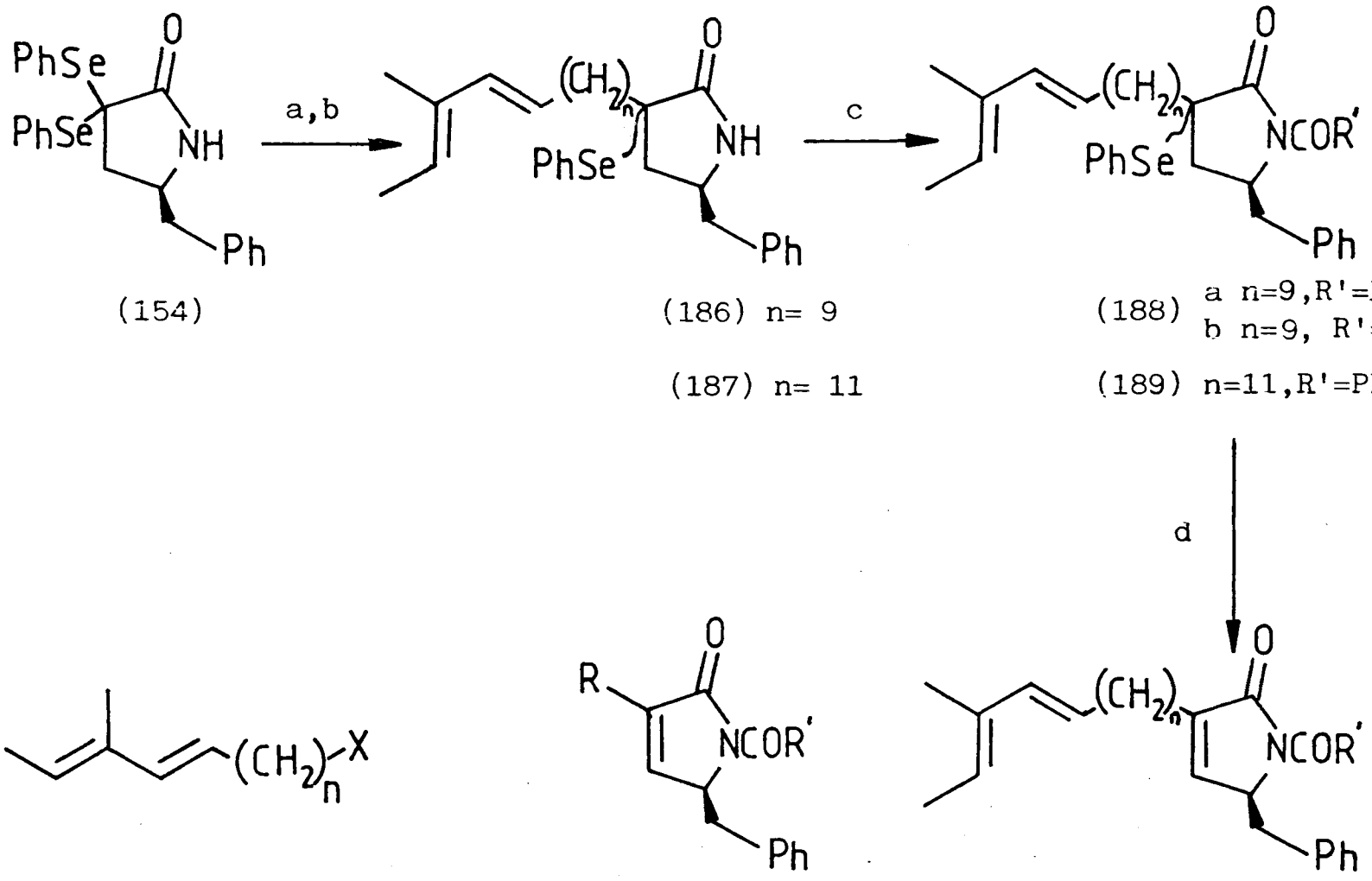
a R'=Me, b R'= Ph

and both compounds exhibited molecular ions in their mass spectra (M^++1, 354 and 416 for a and b respectively). The stereochemistry of the adducts was assigned by analogy with the closely related isoindolone (115)[3b] (see page 31) and corresponded to an *endo* selective Diels-Alder reaction in which the diene approached the dienophile from the face opposite that occupied by the C-5 benzyl group. The couplings of 4.9 Hz observed between the bridgehead proton H-4 and H-3 and H-5 were consistent with those found in natural cytochalasans and synthetic analogues (Appendix II), many of whose structures have been determined by X-ray diffraction methods.

3.7 *Preparation of Long Chain 3-Alkyl Diene-Dienophiles*

It has been mentioned that the attractive route to 3,3-disubstituted pyrrolidinones (174) *via* the *N*-silylated lactam (157) (Scheme 3.6) was not applicable to systems with alkyl chains longer than C_4. Similarly, attempts to alkylate the dianion of the monoselenide (155) with dienyl bromide (183) gave only starting materials. Fortunately however, the dianion route which used the bis-selenide (154) was found to be readily applicable to the preparation of suitable model long chain 3-alkylpyrrolidinones (186) and (187) (Scheme 3.12). Reaction of the dianion of (154) with dienyl iodide (184) gave lactam (186) in 66% yield but with iodide (185) only a 23% yield of the corresponding product (187) was obtained.

Scheme 3.12



Reagents: a 2BuLi, 0°;b (183), (184) or (185);c BuLi, R'COCl;d H_2O_2, py.

In this reaction significant amounts (51%) of mono-selenide (155) were recovered along with alkylating agent (185) (44%). Acylation and selenoxide elimination proceeded smoothly as before to give pyrrolinones (190) and (191) as stable oils.

The latter were shown by ^1H nmr spectroscopy to be contaminated with the 3-octyl- and 3-decylpyrrolinones (192) (*ca* 20% by weight). The preparation of the long chain alkyl halides (183-5)† involved[3c] a difficult copper catalysed Grignard coupling reaction (*cf.* Scheme 4.6) in which octan-1-ol and decan-1-ol were produced as side products from the Grignard, THPO-$(CH_2)_n$-MgBr, after hydrolysis. The n-alcohols could not be separated from the desired long chain dienols and were carried through as impurities in the functional group interconversion reactions which gave halides (183-5).

† Kindly prepared by Dr. M.L.Durrant in these laboratories.

Compounds (186-191),therefore, were isolated as inseparable mixtures with the 3-octylated (or decylated) lactams.

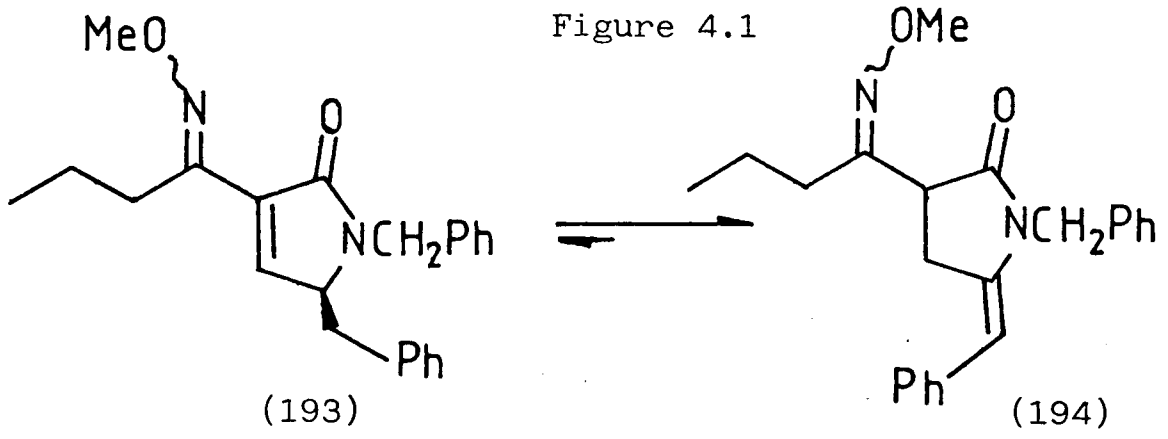
In summary, 1-acyl-3-butylpyrrolin-2-ones (130), available in rather low overall yield from lactam (116), have been shown to react stereospecifically with 2E,4E-hexadiene to give isoindolones but under harsh reaction conditions ($T > 170°$ for several days). The recovery of starting material from these Diels-Alder reactions demonstrated the efficacy of the *N*-acyl substituent but suggested that 3-alkylpyrrolinones were of insufficient reactivity to undergo the critical intramolecular cyclization. Preliminary attempts to effect these cycloadditions with trienes (190) and (191) are described in Chapter 5.

CHAPTER 4

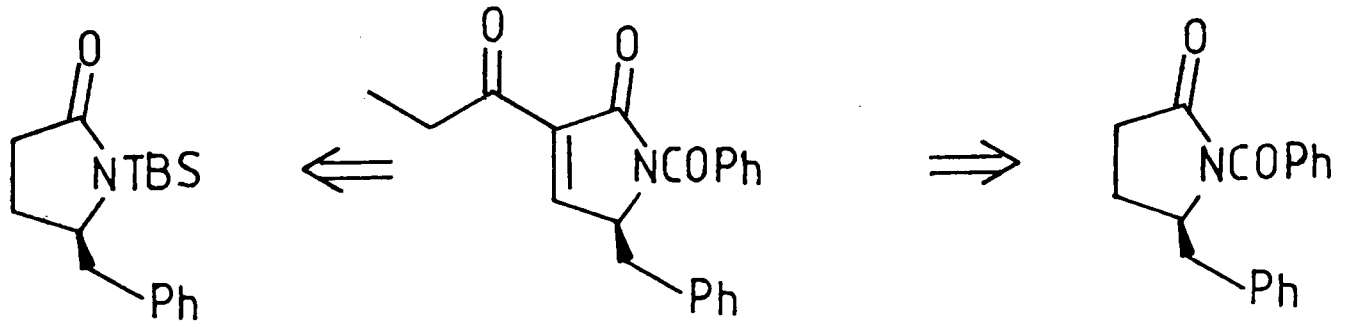
THE SYNTHESIS AND DIELS-ALDER REACTIONS OF 5-BENZYL-1,3-DIACYL-Δ^3-PYRROLIN-2-ONES

In the knowledge that 3-alkyl substituted pyrrolin-2-ones showed only moderate reactivity towards 2E,4E-hexadiene, it was decided to prepare a number of doubly activated pyrrolinones, since the introduction of an electron withdrawing group in conjugation with a double bond was known to increase its dienophilicity.[77,78] Previous work in these laboratories[3b] had shown that attempts to prepare the *O*-methyl oxime (193) were thwarted by its rapid tautomerization to the benzylidene isomer (194) (Figure 4.1).

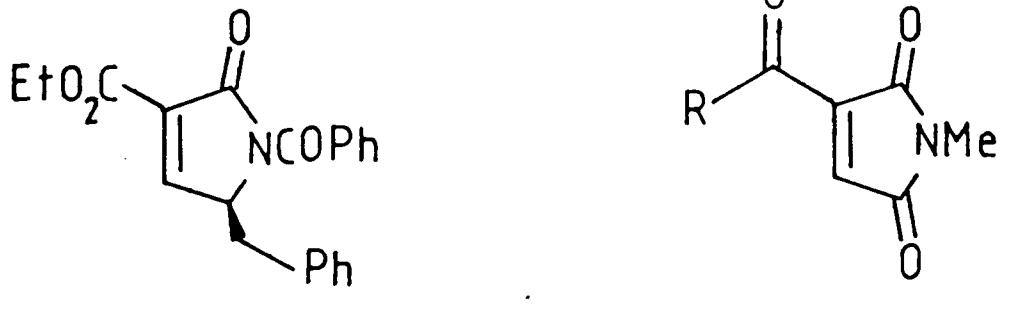
Figure 4.1



(193) (194)



(157) (195) (150)



(45) (196)

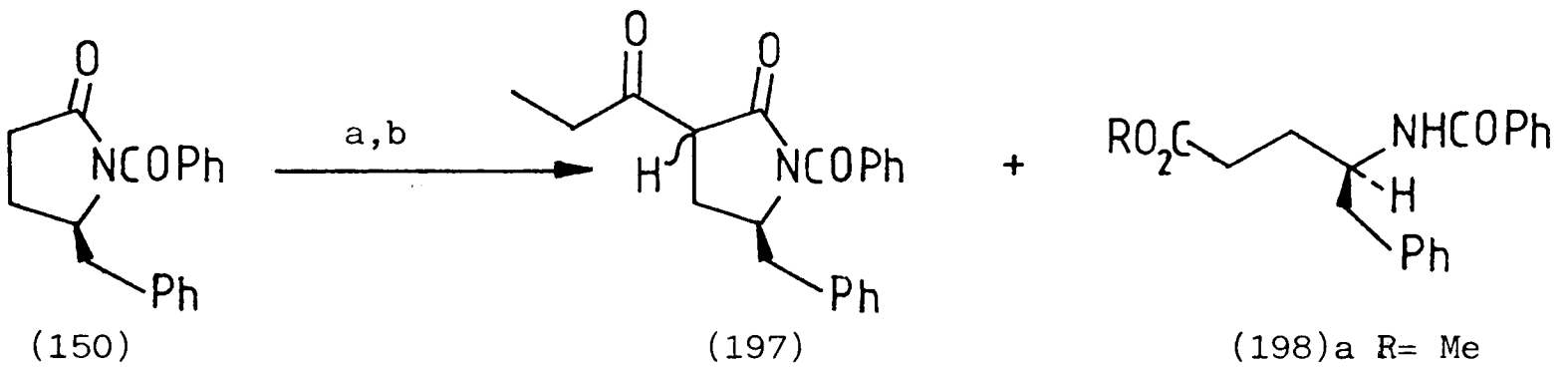
In addition, the purification and spectroscopic assignment of the precursors were complicated by the formation, at each stage of the synthesis, of diastereoisomeric *syn* and *anti* methoximes.

Based on the successful use of the reactive dienophile (45)[18] it was decided to prepare pyrrolin-2-one (195) and to investigate its Diels-Alder reactivity. Complementary work later showed that dienophiles of the maleimide type (196) were reactive towards dienes.[79] Apart from fulfilling its activating role, the acyl side chain was envisaged to provide an entry into both the carbocyclic cytochalasans (*eg*. after reduction/acylation) and the macrolides. As a method of synthesising 3-acylpyrrolinones, the route to 3-alkylpyrrolinones described in Chapter 3 was not appealing in view of the low yields of the starting material preparations and the probable incompatibility of the acyl group with organolithium reagents. Thus, it was hoped to use enolate chemistry such as that described in Section 3.3 with the *N*-benzoylated and *N*-silylated pyrrolidinones (150) and (157), respectively.

4.1 *Propanoylation of N-Protected 5-Benzylpyrrolidin-2-ones*

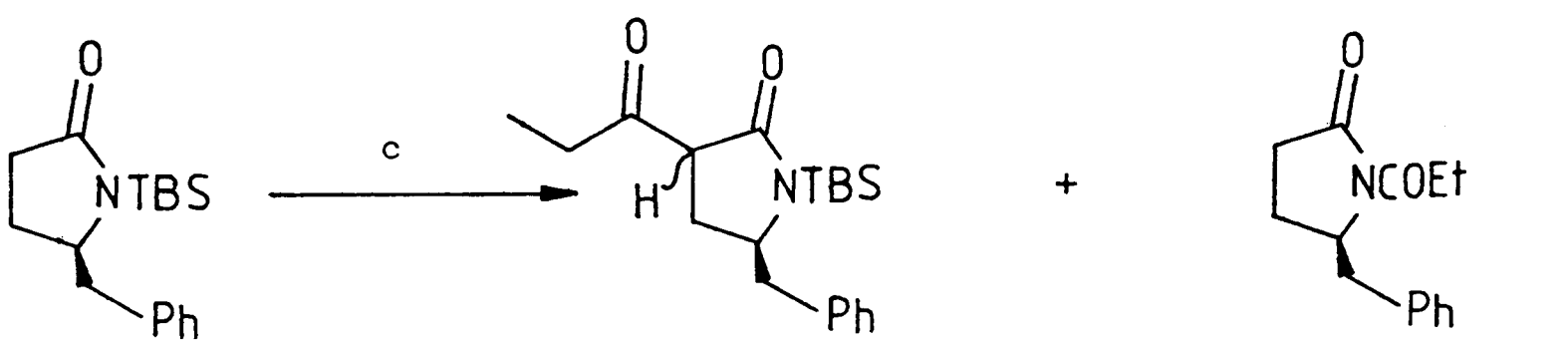
Exploratory work was concerned with the establishment of suitable conditions for the acylation of the *N*-benzoylated lactam (150). Treatment with LDA and ethyl propionate at -78°, followed by quenching with methanolic hydrogen chloride[18], gave a complex mixture of products from which acyclic methyl ester (198a) was isolated in 38% yield (Scheme 4.1). Similar acylating conditions, but with aqueous acid as the quenching agent, gave a small amount of the desired product (197) but also some open chain ester (198b) and starting material. The sensitivity of the imide functionality present in (150) towards nucleophiles has been noted previously (Section 3.2) when facile deprotection occurred during the attempted alkylation of selenide (151).

Scheme 4.1



(150) (197) (198)a R= Me

b R= Et

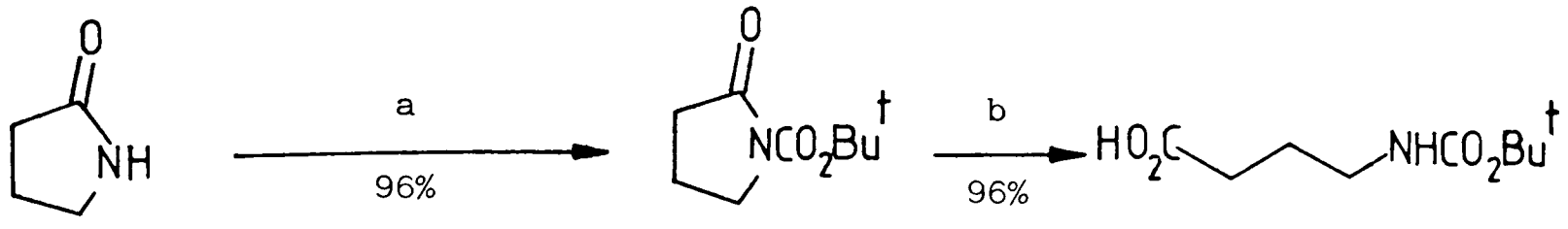


(157) (201) 74% (202) 8%

Reagents: a 2LDA, $EtCO_2Et$; b HCl, MeOH or H_3O^+; c 2LDA, inverse quench into EtCON⟨ ⟩N .

A recent publication[80] lends support to these experiences. By protecting pyrrolidin-2-one (140) as its *tert* -butyl oxycarbonyl derivative (199), the lactam C-N bond was cleaved within twenty minutes at room temperature upon treatment with lithium hydroxide to give the open chain product (200) in near quantitative yield (Figure 4.2).

Figure 4.2



(140) (199) (200)

Reagents: a $(Bu^tCO)_2O$, Et_3N, DMAP; b LiOH, THF.

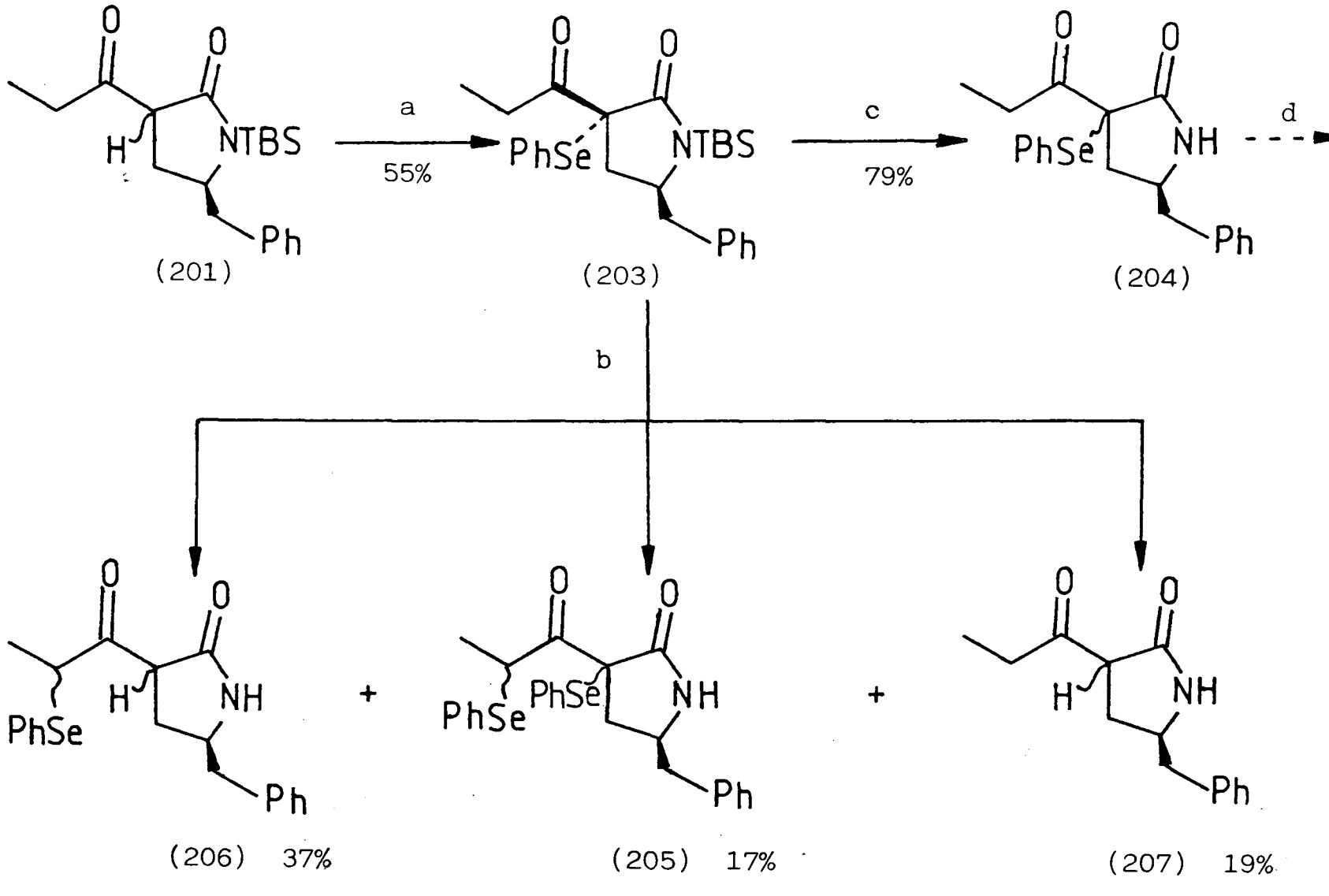
Attention was then focussed on the use of the base stable, silylated lactam (157). After trying several sets of acylating conditions (*eg*. with ethyl propionate at various temperatures), the method of choice was found to use *N*-propionyl imidazole as the electrophile.[81] Generation of the enolate of lactam (157) with two equivalents of LDA at -78° followed by an inverse quench[82] of this solution into a solution of the imidazole in THF at -78° gave the desired β -ketolactam (201) in 74% yield as a mixture of diastereoisomers.† A small amount of the *N* -acylated lactam (202) was also isolated, deriving perhaps from adventitious hydrolysis of the silylated starting material. The presence of two carbonyl groups in (201) was confirmed by the appearance of two intense absorptions in the ir spectrum ($\nu_{max.}$ 1722 and 1683 cm^{-1}). The base peak in the mass spectrum (*m /z* 288) corresponded to the loss of the EtCO fragment from the molecular ion while the 300 MHz ^1H nmr spectrum exhibited six sharp singlets at δ 0.35, 0.41, 0.44, and 0.47, (6 H) and at δ 0.97 and 1.00 (9 H) due to the TBS group.

4.2 *Preparation of Dienophile Precursors*

Several methods exist for the selenenylation of β -dicarbonyl compounds under mild conditions[63,83] but the method chosen for convenience in the present work was the use of a slight excess of LDA at -78° followed by phenylselenenyl chloride. Although the reaction was not optimized, the selenide (203) ($M^+ + 1$, 502) could be readily obtained as a white solid in 55% yield with recovery of starting material (10%) (Scheme 4.2). After a low temperature crystallization,essentially one diastereoisomer was seen in the high resolution ^1H nmr spectrum, which was tentatively assigned as having the phenylseleno moiety *trans* to the benzyl group. This material gave a satisfactory combustion analysis which established the molecular formula as $C_{26}H_{35}NO_2SiSe$.

† As before (Chapter 3), functionalization of C-3 of these chiral lactams led to the formation of diastereoisomeric mixtures (ratios 1:1 to 4:1) which could not be separated.

Scheme 4.2



Reagents: a LDA, PhSeCl; b Bu^n_4NF; c HCl, aq. THF; d Base, PhCOCl.

A stepwise deprotection/acylation sequence was now required to give the immediate dienophile precursor (204). Fluoride ion induced desilylation is an extremely widespread method for the unmasking of a range of functional groups and for carbanion generation.[56,84] A very common reagent is tetra-n-butylammonium fluoride (TBAF), although this suffers from the problem of being very hygroscopic. Nevertheless, upon treatment of silylated lactam (203) with TBAF in THF at 0°, complete desilylation occurred within an hour. Aqueous work-up gave an oil in good yield but which was shown by tlc to be a complex mixture of products. Careful short column chromatography using gradient elution allowed several components to be identified.

The least polar lactam product was a partially separable diastereoisomeric mixture of the bis-selenenylated pyrrolidinones (205), isolated

in 17% yield (M^++1 , 544). Next came the mono-selenenylated material (206) (M^+, 387) as an inseparable mixture, followed by the simple lactam (207). The presence of selenium in compounds (205) and (206) was deduced from the appearence of the $PhSe^+$ fragment (m/z , 157) and the characteristic isotope patterns† in the mass spectra. The sites of attachment of the phenylseleno groups in these rearrangement products were easily determined from the 300 MHz ^1H nmr spectra, since the methyl triplet resonance of starting material (203) at δ 1.19 had been replaced by a doublet at δ 1.5. Furthermore, the low field one-proton quartet at δ 5.0 was consistent with a C-2 selenenylated structure.

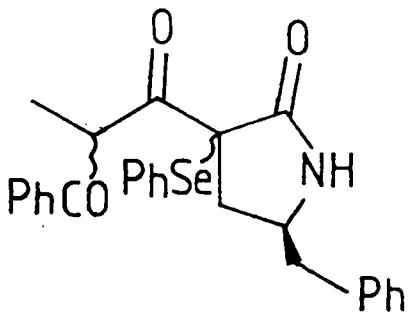
The lability of selenium groups flanked by two carbonyl groups has been noted elsewhere[85,86] and, together with the knowledge that TBAF* is a powerful nucleophile and a strong base[88], this goes some way towards rationalizing the results. Deprotonation at C-2 by fluoride ion followed by 1,3-selenium migration[86], or intermolecular selenium transfer, would give rise to the observed products. Presumably the greater acidity of the products provided the thermodynamic driving force under the basic conditions.

Fortunately,however, smooth desilylation of lactam (203) could be achieved with mineral acid in THF. After crystallization from ether, selenide (204) was obtained in 79% yield as a 1:1 mixture of diastereoisomers. However, attempted *N*-benzoylation of this material under several sets of basic conditions *eg*. with NaH, lithium isopropylcyclohexylamide (LiICA),[89] lithium 2,2,6,6-tetramethylpiperidide (LiTMP),[90] gave complex mixtures. Small amounts of *N*- benzoylated products could be isolated but C-2 benzoylation had occurred (*ca* 40-50%) to give products of the type (208) (Figure 4.3) as diastereoisomeric mixtures which were not characterized. Preliminary

† Selenium exists in several isotopic forms (atomic number 76-82) and the molecular ion of selenides often consists of seven peaks.

* It has recently been suggested that 'naked' fluoride ion is probably not the desilylating species in these reactions but that they proceed *via* hydrated F^- or the hydrogen bifluoride ion.[87]

Figure 4.3

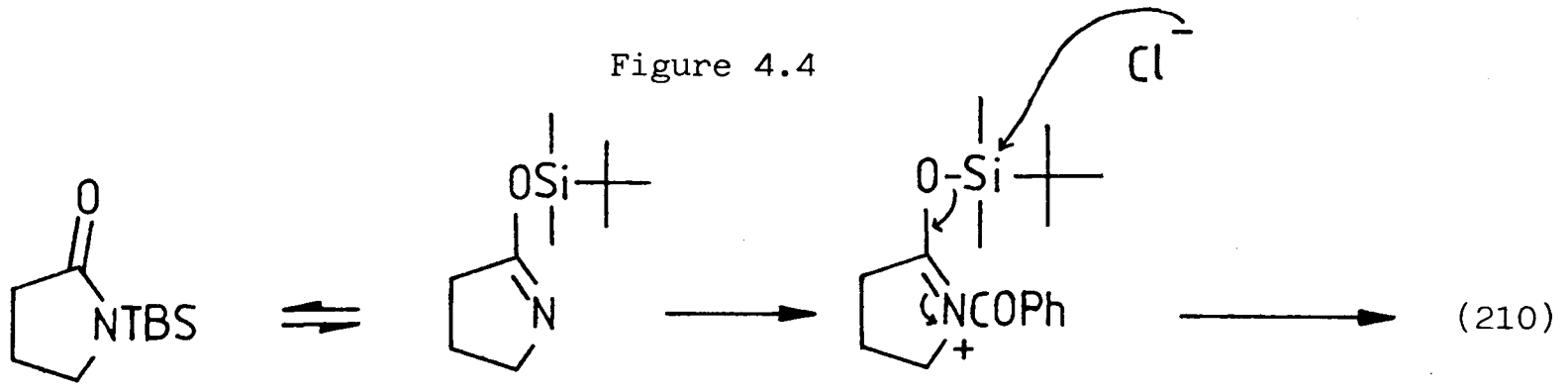


(208)

experiments using benzoyl chloride-tertiary amine combinations, with and without *N,N* -dimethylaminopyridine (DMAP) as catalyst,[91] gave only low yields of *N* -acylated products under conditions in which starting material decomposition did not compete.

Attention was then turned to the possibility of a one-step desilylation-acylation reaction. *N* -Trimethylsilylated lactams have been used previously as nucleophilic intermediates in *N*-acylation reactions.[92] To test the viability of this approach, silylated pyrrolidinone (209) was prepared and treated with benzoyl chloride in refluxing benzene (Scheme 4.3). After flash chromatography and recrystalliztion, *N*-benzoylpyrrolidin-2-one (210) was obtained in 77% yield. The mechanism of this transprotection probably involves the *O* -silylimino ether (214) (Figure 4.4).[93]

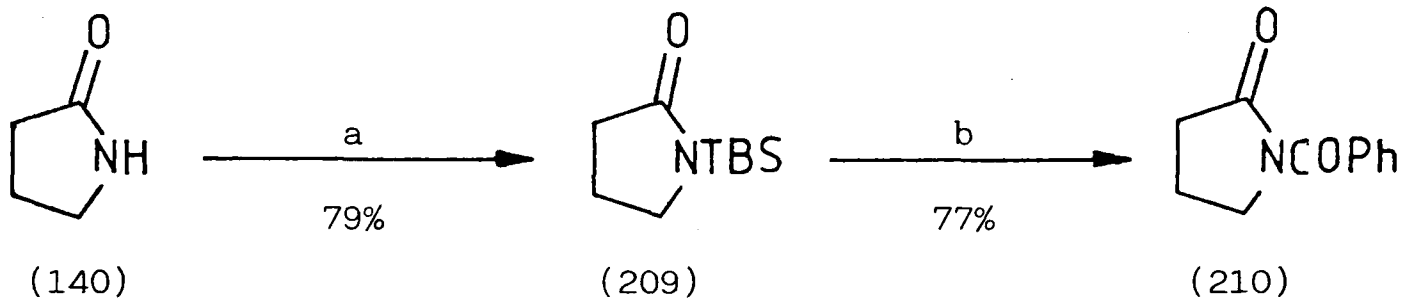
Figure 4.4



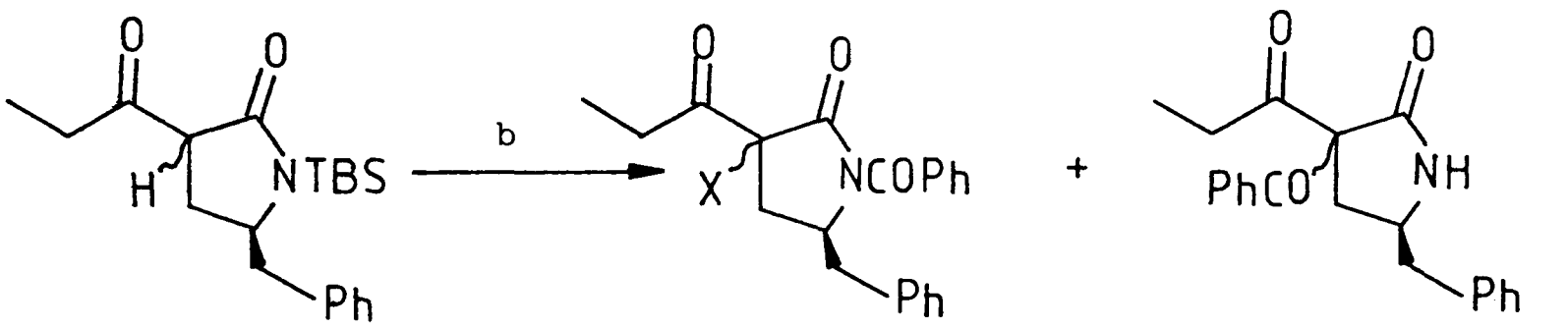
(209) (214)

Wary of the lability of α -phenylseleno- β -dicarbonyl compounds, a similar transprotection was first attempted with lactam (201). However, little *N* -benzoylation occurred to give lactams (197) and (211) and the main product was the C-3 benzoylated material (212), obtained in 48% yield.

Scheme 4.3

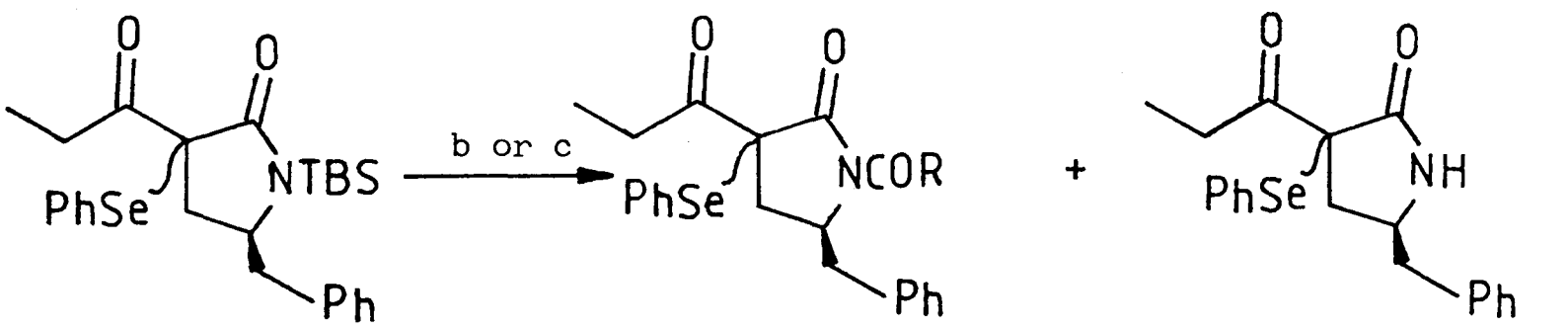


(140) (209) (210)



(201) (197) X= H, 15% (212) 48%

(211) X= COPh 9%



(203) (213) a R= Ph, 73% (204) 25%

b R= Me, 54%

Reagents: a BuLi, TBS-chloride;b PhCOCl, C_6H_6, 80°;c AcCl, C_6H_6, 60°.

The competition between enol and imino ether for electrophiles should not present a problem in the 3,3-disubstituted lactam (203), provided the selenium group is stable to the reaction conditions. Thus, freshly prepared lactam was dissolved in dry benzene and the acylating agent (PhCOCl, AcCl) was added at room temperature. After eight hours at 80°, tlc showed that no starting material remained and, after evaporation and purification by flash chromatography, the desired products (213) were obtained in good yields as diastereoisomeric mixtures. Also isolated was the desilylated lactam (204), the yield of which increased considerably when anhydrous

conditions were not maintained. Under such conditions a complex mixture of lactams (204), (213) and deselenenylated material (197) resulted.

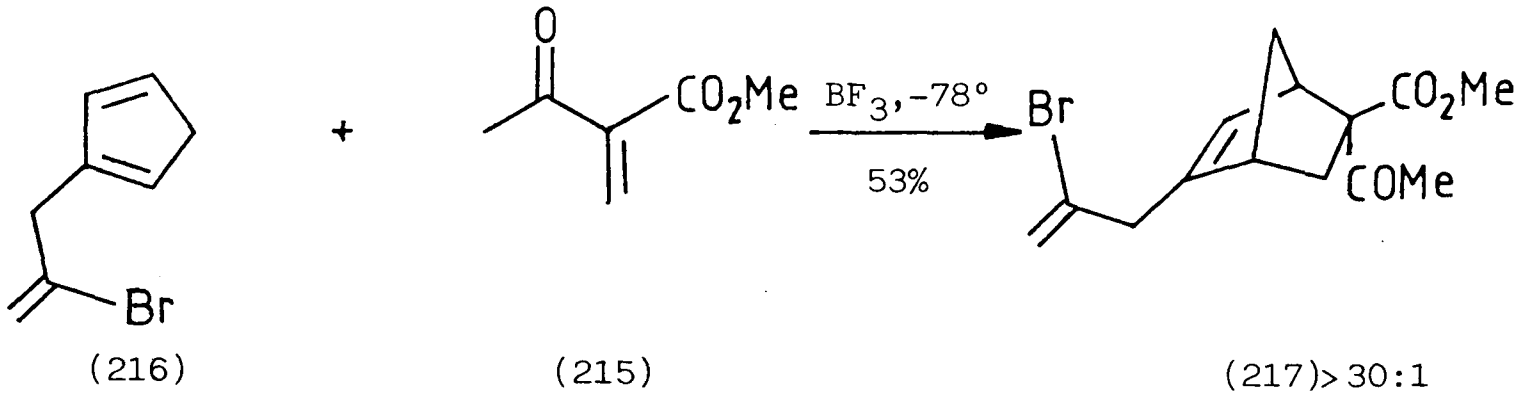
The structure of the dienophile precursor (213a) (M^+, 491) was consistent with its spectroscopic data. The carbonyl region of the ir spectrum exhibited two intense absorptions ($\nu_{max.}$ 1735 and 1695br cm^{-1}) indicative of the keto-imide functionality. Benzoylation of the nitrogen atom also caused the characteristic downfield shift of the H-5 resonance (to δ 4.65) as seen from the 300 MHz ^1H nmr spectrum.

4.3 *Preparation and Diels-Alder Reactions of 1-Benzoyl-5-benzyl-3-(1-oxo-propyl)-* Δ^3 *-pyrrolin-2-one*

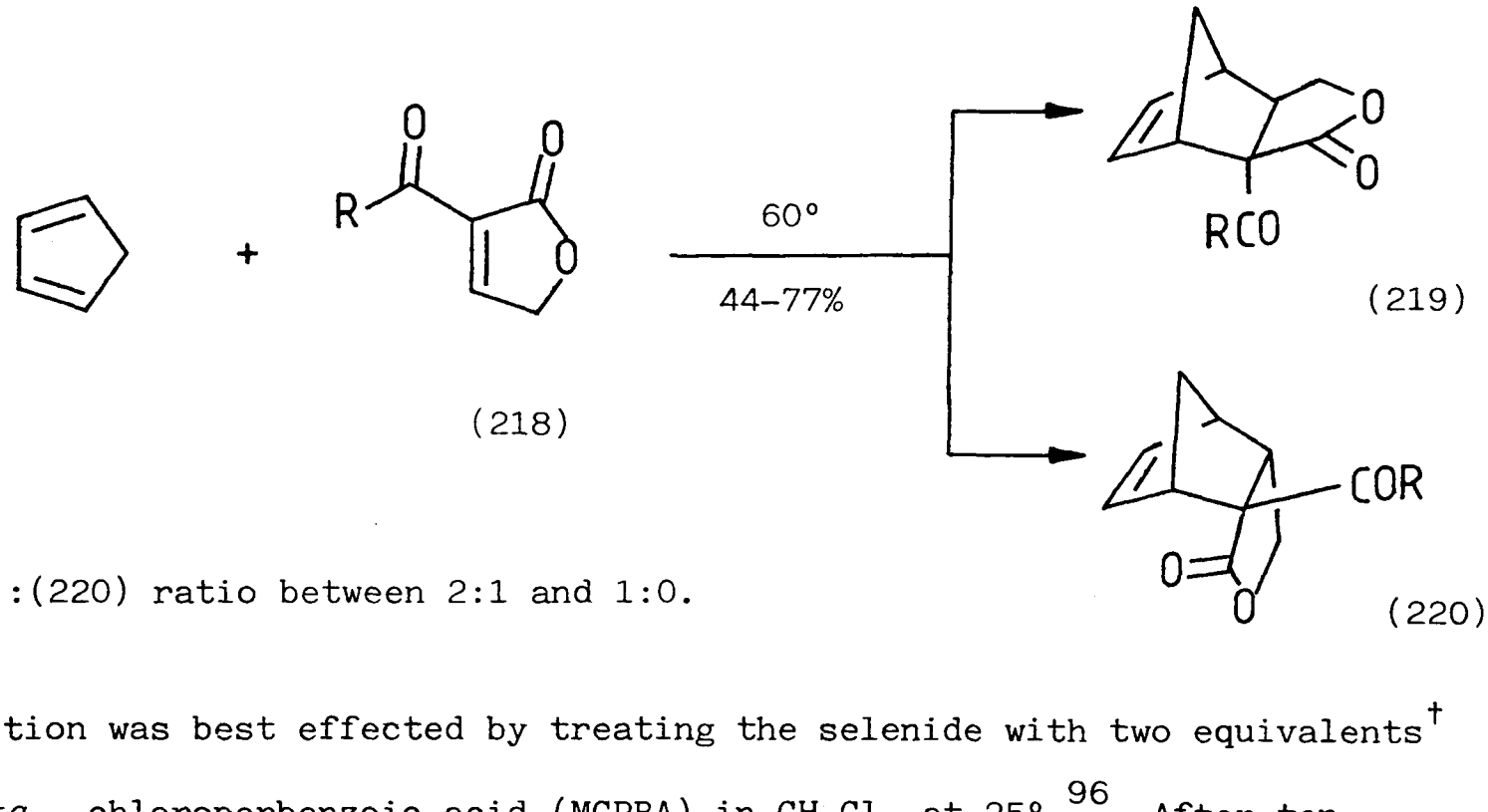
Once a reliable method for the preparation of pyrrolinone (195) had been found, it was important to discover which π-system of the dienophile dominated the *endo / exo* selectivity in Diels-Alder reactions. Recent work on the stereoselectivity of unsymmetrically substituted dienophiles further emphasised the importance of such a study. Under Lewis acid catalysed conditions acrylate (215) reacted with the substituted cyclopentadiene (216) to give essentially one adduct, (217), in which the keto group had adopted the *endo* orientation[94] (Figure 4.5). The thermal reaction between the keto-lactone(218) and cyclopentadiene gave mixtures of adducts (219) and (200) but in which the keto- *endo* isomer (219) predominated.[95] Vedejs *et al* .[18] on the other hand, had observed exclusive imide- *endo* selectivity in the Diels-Alder reactions of the 3-carboethoxypyrrolinone (45) (Scheme 2.5).

Initial attempts to prepare pyrrolinone (195) from (213a) using similar oxidative-elimination conditions as before (Section 3.6) gave only unstable green oils which produced unidentified products with 2E,4E-hexadiene. The presence of pyridine in the oxidation reaction was thought to have been detrimental by enhancing hydroxypyrrole formation. Clean pyrrolinone

Figure 4.5



(216) (215) (217)> 30:1

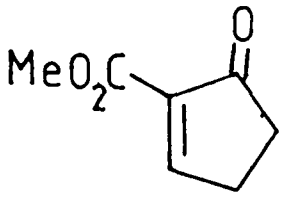


(218) (219) (220)

(219):(220) ratio between 2:1 and 1:0.

production was best effected by treating the selenide with two equivalents† of *meta* -chloroperbenzoic acid (MCPBA) in CH_2Cl_2 at 25°.[96] After ten minutes, the doubly activated pyrrolinone (195) was isolated as an unstable oil in virtually quantitative yield (Scheme 4.4). As well as the usual simplification of the ^1H nmr spectrum upon loss of the chiral centre at C-3, the vinylic proton, H-4, appeared as a fine doublet at δ 7.99. Such deshielding has also been observed in dienophile (226) (Figure 4.6) which, by virtue of the chemical shift of the vinylic proton, δ 8.38, was thought to have one of the most polarized double bonds known.[85] In addition, the ir spectrum of freshly prepared (195) confirmed the presence of three carbonyl groups ($\nu_{max.}$ 1742, 1698, 1679 cm^{-1}).

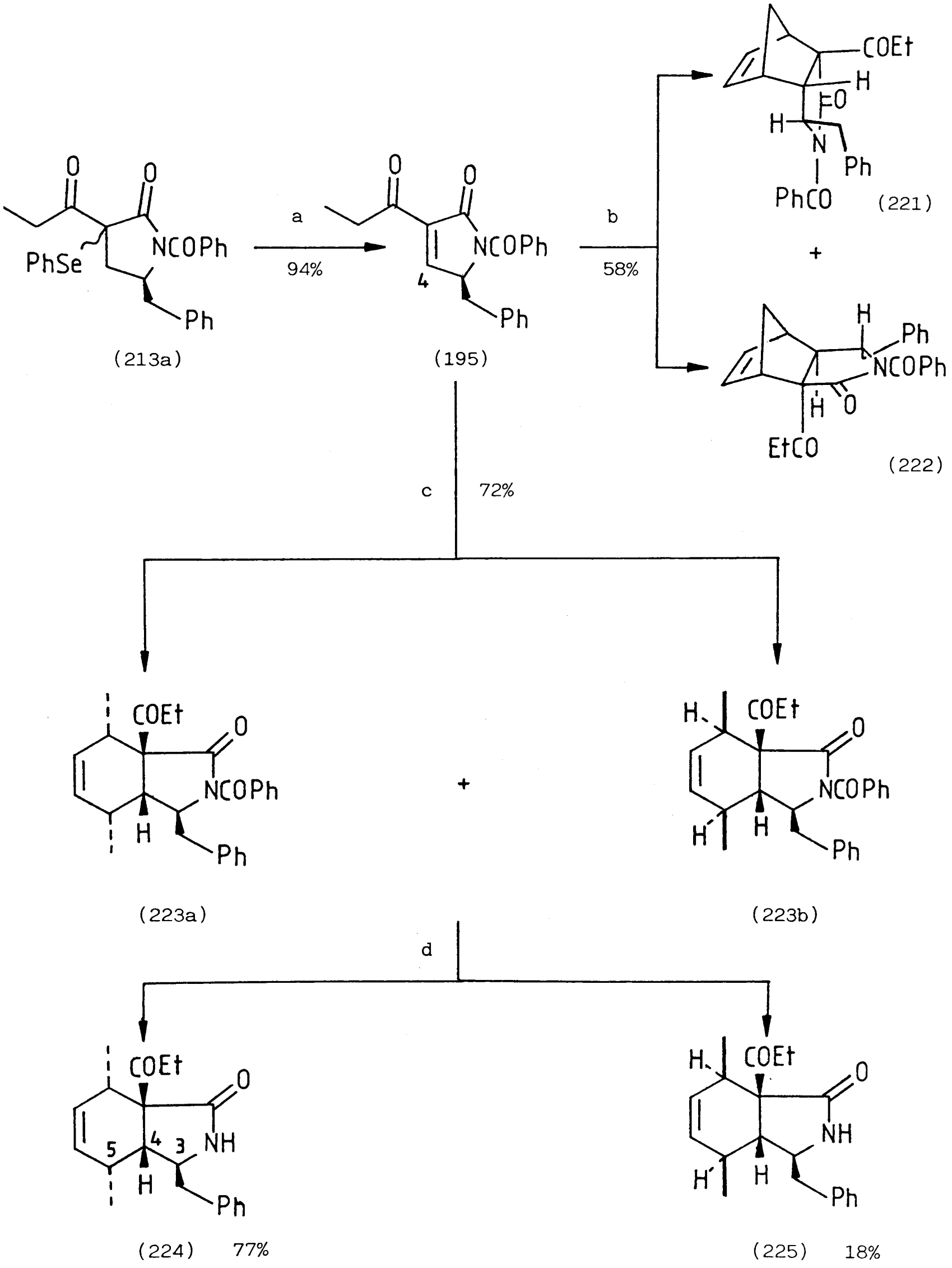
Figure 4.6



(226)

† The second equivalent oxidizes the elimination product, PhSeOH, to the seleneninic acid, $PhSeO_2H$, thus preventing side reactions with the olefinic product.

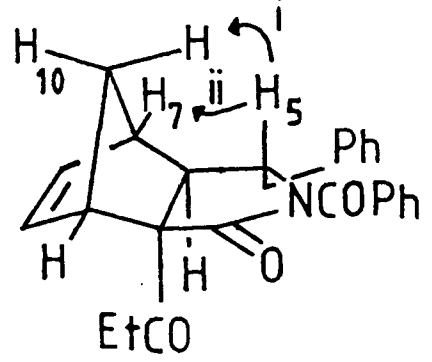
Scheme 4.4



Reagents: a MCPBA, CH_2Cl_2; b C_5H_6, C_6H_6; c 2E,4E-hexadiene, C_6H_6, 100°; d KOH, MeOH, C_6H_6.

The reactivity of pyrrolinone (195) was shown by its ready cycloaddition with cyclopentadiene at room temperature to provide a 6:5 mixture of adducts (221) and (222), respectively. Chromatography led to an enrichment of each stereoisomer in separate fractions and allowed a complete assignment of the 300 MHz ^{1}H nmr spectra by spin-decoupling experiments. The stereochemistry of the less polar, minor isomer (222) was deduced from the observation of specific nuclear Overhauser enhancements.[97] Selective irradiation of the H-5 resonance led to a 3.6% enhancement of the H-10 (*anti*) multiplet and a 7.8% enhancement of the allylic proton, H-7 (Figure 4.7). Thus the minor isomer (222) corresponded to the keto-*endo* mode of addition.

Figure 4.7



i 3.6%

ii 7.8%

(222)

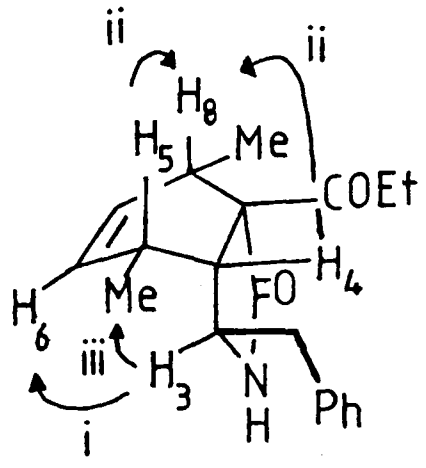
With the more discriminating diene, 2E,4E-hexadiene, pyrrolinone (195) reacted stereoselectively at 100° in benzene to give an 85:15† mixture of adducts (223) (M^{+}, 415) in 72% yield. These could not be separated by chromatography, but cleavage of the *N*-benzoyl group with base[25a] followed by short column chromatography gave the desired isoindolone (224) as the major product and the minor isomer, (225).

The structures of the adducts were assigned on the basis of their spectroscopic data. In addition, the major product (224) was obtained as a crystalline solid (needles, mp. 138.5-140°, from pentane) and gave a

† Estimated from the relative intensities of the resonances due to the protons α to the exocyclic carbonyl group, at δ 1.48 (major) and δ 1.91 (minor).

satisfactory combustion analysis. The accurate mass spectrum of the minor isomer (225) showed a molecular ion (M^+, 311.1885) which established the molecular formula as $C_{20}H_{25}NO_2$. Each isomer gave an ir spectrum in which the higher frequency carbonyl stretching band ($\nu_{max.}$ *ca* 1740 cm^{-1}) had disappeared and in which the N-H absorption appeared at ($\nu_{max.}$ 3430, 3200br cm^{-1}). The high resolution ^1H nmr spectra of each isomer are reproduced in Figures 4.8 and 4.9. The bridgehead proton, H-4 (cytochalasan numbering system), in the major isomer appeared as a multiplet at δ 2.45, but a value of 4.5 Hz was deduced for the coupling between H-4 and the methine proton H-3 from a spin-decoupling experiment. The corresponding H-4 resonance in the minor isomer appeared as a doublet of doublets at δ 2.24 for which the coupling constants were $J_{3,4}$ 3.6 Hz and $J_{4,5}$ 5 Hz. A stereochemical assignment could not be made on the basis of these results so a nuclear Overhauser experiment was performed on each isomer. In particular, the observation of a 3% enhancement of the vinylic proton resonance, H-6, upon irradiation of H-3 for the major isomer, and the absence of such an effect for the minor suggested the stereochemistries depicted in Figure 4.10. Furthermore, irradiation of H-3 in the minor isomer led to 5.5% and 5% enhancements of the allylic protons H-5 and H-8 respectively, consistent with the boat conformation shown.

Figure 4.10

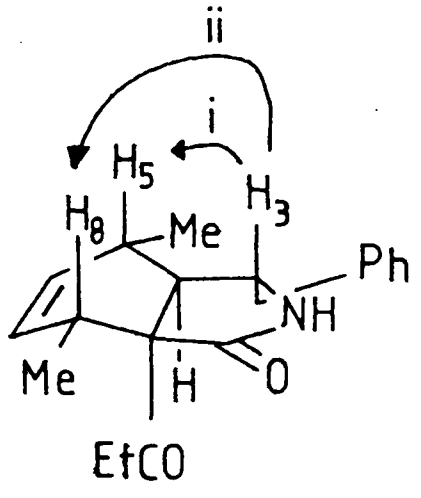


i 3%

ii 10%

iii 1.3%

(219) major

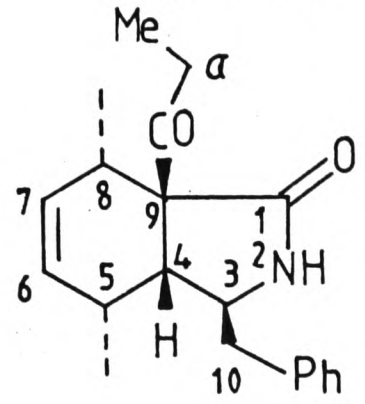


i 5.5%

ii 5%

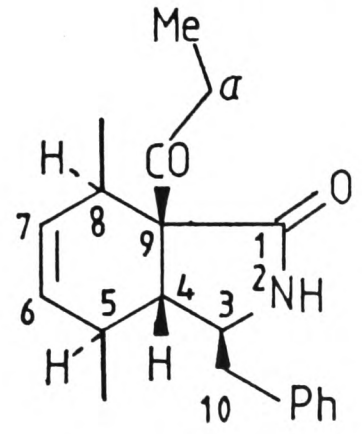
(220) minor

Figure 4.8



(224)

Figure 4.9



(225)

Thus, the 1,3-diacylpyrrolinone (195) has been shown to react stereoselectively with 2E,4E-hexadiene under milder conditions than the corresponding 3-butylpyrrolinones (130a,b), to give isoindolones in good yield. The major adduct, isolated after deprotection,has been shown to possess the structure drawn (224) and is that required for cytochalasan synthesis. The stereochemistry observed corresponded to a Diels-Alder reaction in which the constrained imide π-system dominated the *endo* / *exo* selectivity and in which the diene approached the dienophile from the face opposite that of the C-5 benzyl group.

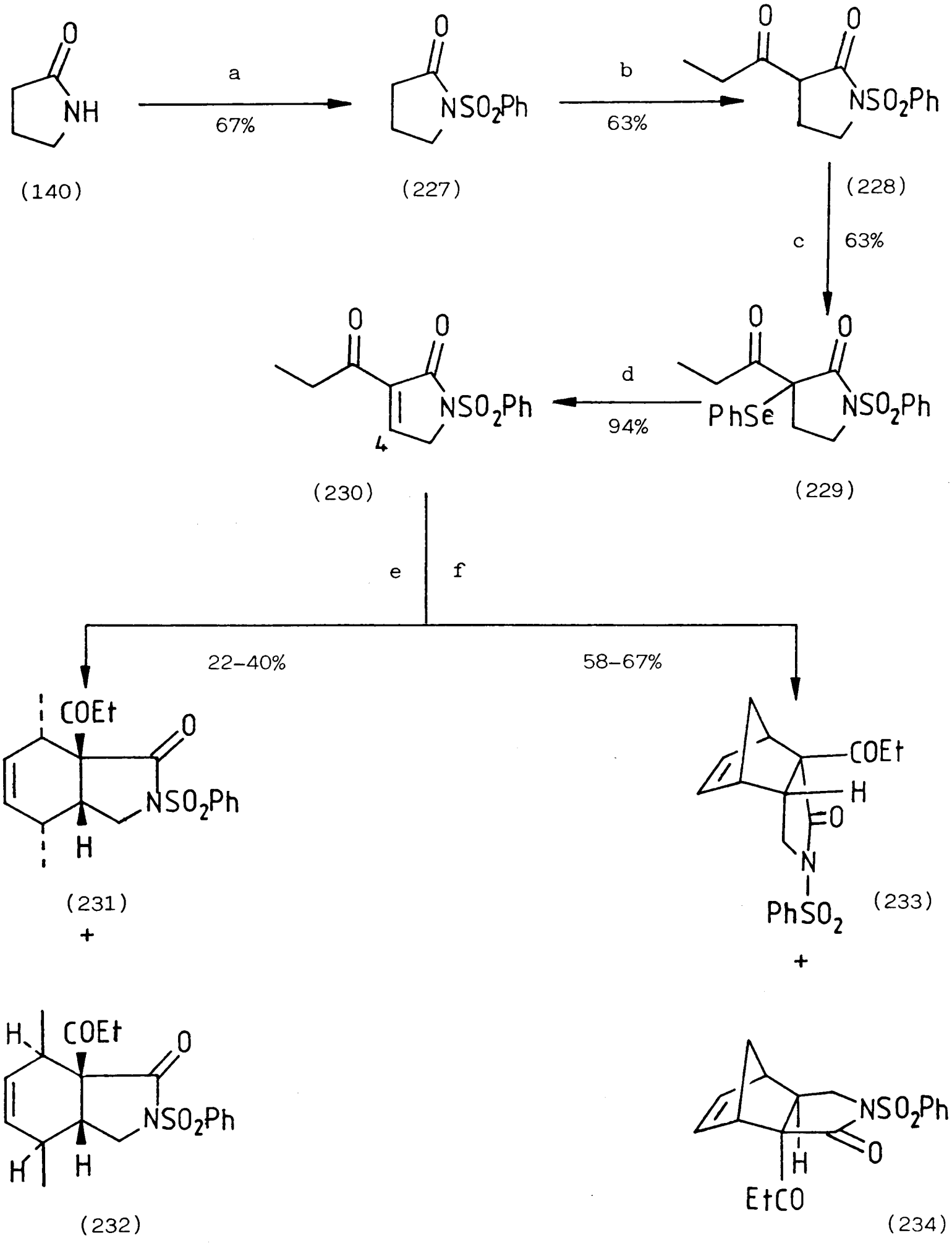
Attempts were made to determine the optical purity of the major isoindolone (224) using lithium hexamethyldisilazide-MTPA-chloride, and lanthanide chiral shift reagents[98] but these were unsuccessful. The overall yield of the isoindolones (224) and (225) in seven steps from the parent lactam (116) was 16%.

4.4 *Preparation and Diels-Alder Reactions of 1-Benzenesulphonyl-3-(1-oxopropyl)-* Δ^3*-pyrrolin-2-one*

The benzenesulphonyl group should satisfy the requirements needed for the isolation of activated pyrrolinones by being both a stable protecting group[99] and powerfully electron withdrawing.[100] In order to see how this group compared with the benzoyl group used earlier, pyrrolinone (230) was prepared according to the route outlined in Scheme 4.5.

Treatment of the lithium salt of pyrrolidin-2-one (140) with benzenesulphonyl chloride at 0° gave the protected lactam (227) as an analytical sample in 67% yield after a single crystallization. Addition of propionyl chloride to the corresponding enolate at -100° followed by a low temperature quench gave the β-ketolactam (228) smoothly,(H-3 δ 3.61, dd, J 9,7 Hz), and this was selenenylated as before to give the dienophile

Scheme 4.5



Reagents: a BuLi, $PhSO_2Cl$; b LDA, EtCOCl, -100°; c LDA, PhSeCl; d MCPBA; e 2E,4E-hexadiene; f C_5H_6.

precursor (229). Oxidative-elimination with MCPBA provided the pyrrolinone (230)as an unstable semi-solid which was used immediately in Diels-Alder reactions with 2E,4E-hexadiene and cyclopentadiene under various conditions (Table 4.1).

Table 4.1 Diels-Alder Reactions of

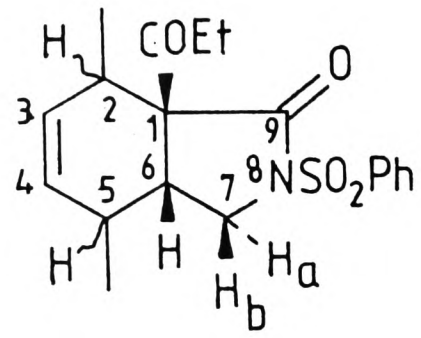
1-Benzenesulphonyl-3-(1-oxopropyl)-Δ^3-pyrrolin-2-one (230)

Entry	Conditions	Product Ratio[a]	Yield %
	2E,4E-Hexadiene	(231:232)	
1	12 eq., C_6H_6, 110°, 4 h	8:1	28
2	12 eq., C_6H_6, 110°, 8 h	9:1	22
3	28 eq., CH_2Cl_2, 115°, 8.5 h	7:1	37
4	36 eq., CH_2Cl_2, 25°, 34 h	10:1	40
	Cyclopentadiene	(233:234)	
5	27 eq., C_6H_6, 25°, 24 h	2:1	58
6	60 eq., CH_2Cl_2, 55°, 5 h	2:1	67

a Estimated from the 300 MHz ^1H nmr spectra.

The reaction was quite stereoselective in the case of the acyclic diene (Entries 1-4) but the yields were only modest. The two adducts could not be separated by chromatography but the ratio of stereoisomers could be easily estimated by measuring the relative intensities of the H-7 resonances (Figure 4.11) (8-azabicyclo[4.3.0]nonane numbering system). Protons were assigned by spin-decoupling experiments but again nuclear Overhauser differences provided stereochemical information. The most diagnostic was the 4% enhancement observed for the pseudo triplet resonance due to one H-7 proton at δ 3.42, upon irradiation of the C(2)CH_3 doublet.

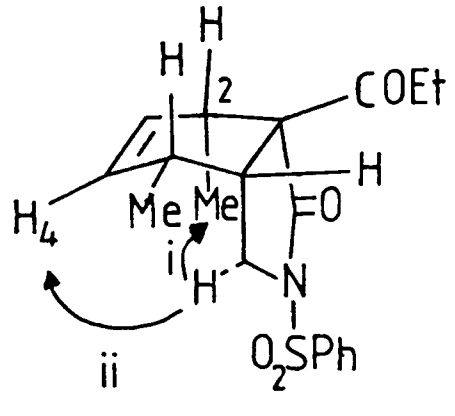
Figure 4.11



(231) and (232)

This can be rationalised if it is assumed that the lactam-*endo* product exists in a conformation in which the cyclohexene ring is virtually planar and in which the C-2 methyl group adopts a pseudo axial orientation (Figure 4.12). Although this conformation is not that expected of isoindolones[3b,101] such an enhancement is impossible in any low energy conformation of the keto-*endo* product.

Figure 4.12



i 4%

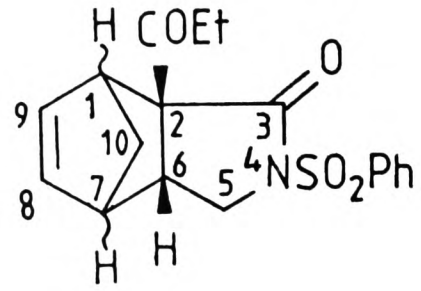
ii 1.5%

(231) major

In agreement with this, irradiation of the H-7 resonance at δ 3.42 led to small (*ca* 1.5%) enhancements of the C-2 methyl and vinylic proton resonances. Thus it would appear that the major product was, as anticipated, that derived from the lactam-*endo* mode of addition.

The cycloadditions with cyclopentadiene were, on the other hand, less stereoselective (Entries 5 and 6), but gave adducts (233) and (234) in better yield. A representative example of the high resolution ^{1}H nmr spectrum of the mixture is depicted in Figure 4.13. Of note is the appearance of the shielded multiplets between δ 1.10 and 1.46 corresponding to the bridge protons, H-10. Spin-decoupling experiments enabled an assignment to be made and it was found that the proton *syn* to the double bond resonated at lower field.[102] The major, more polar stereoisomer (233) was tentatively assigned as the lactam-*endo* product by analogy with above.

Figure 4.13



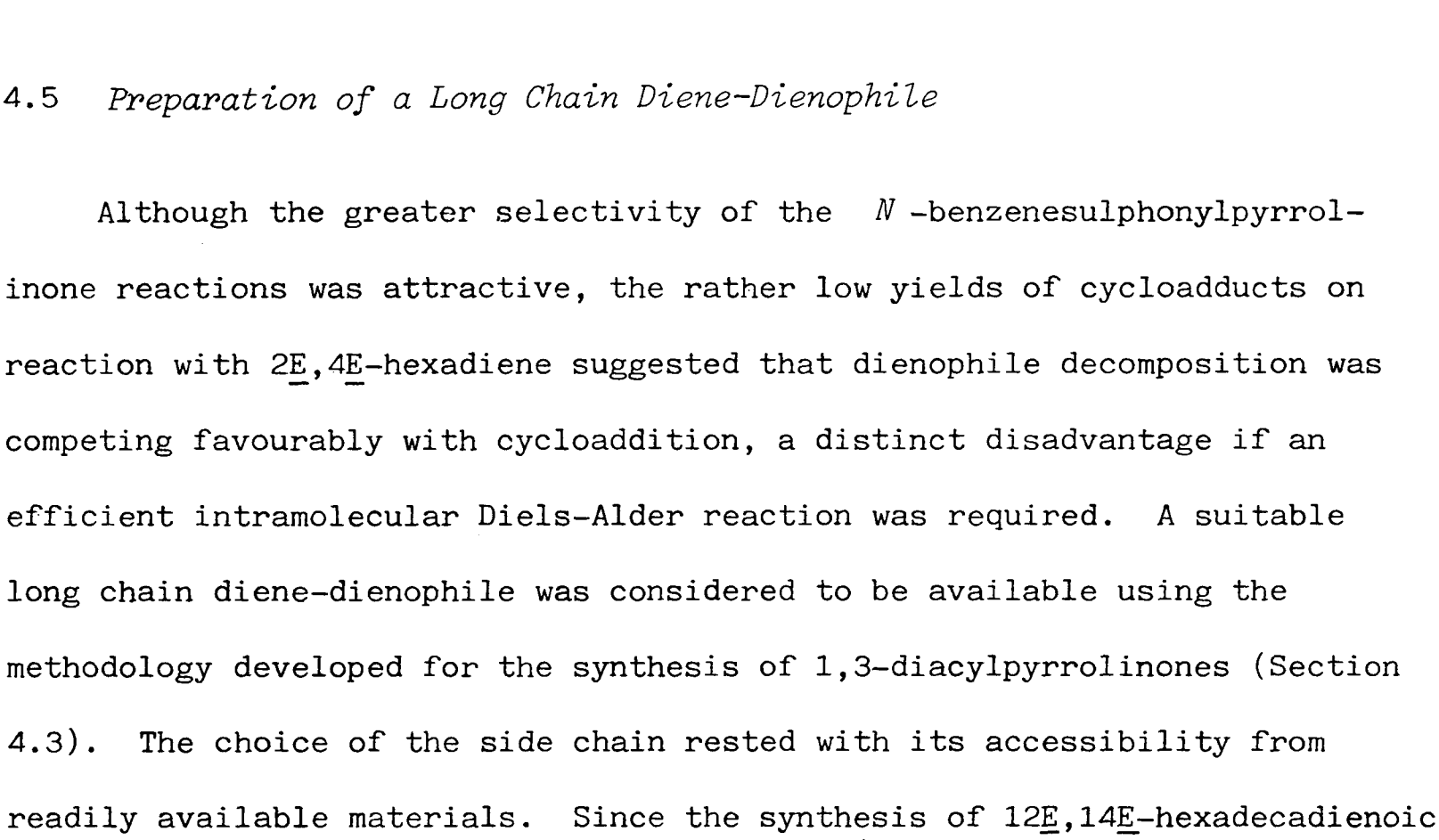
(233) and (234)

4.5 *Preparation of a Long Chain Diene-Dienophile*

Although the greater selectivity of the *N*-benzenesulphonylpyrrolinone reactions was attractive, the rather low yields of cycloadducts on reaction with 2E,4E-hexadiene suggested that dienophile decomposition was competing favourably with cycloaddition, a distinct disadvantage if an efficient intramolecular Diels-Alder reaction was required. A suitable long chain diene-dienophile was considered to be available using the methodology developed for the synthesis of 1,3-diacylpyrrolinones (Section 4.3). The choice of the side chain rested with its accessibility from readily available materials. Since the synthesis of 12E,14E-hexadecadienoic acid had been described previously[28] this was chosen to test the viability of the intramolecular Diels-Alder approach to the carbocyclic [13]cytochalasans.

Decane-1,10-diol (235) was monobrominated with hydrobromic acid to provide 10-bromodecanol (236) (Scheme 4.6). Protection of the alcohol as

Scheme 4.6

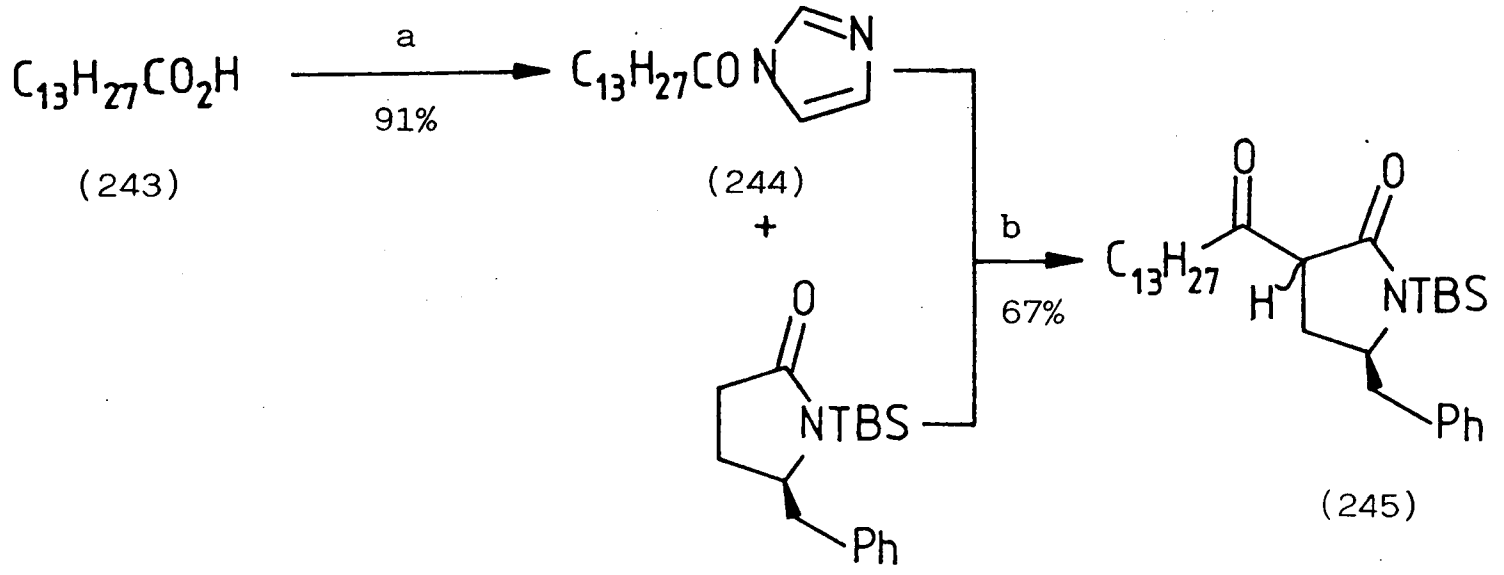


Reagents: a HBr, petrol;b DHP, TsOH;c Ac_2O, K_2CO_3;d Mg, Li_2CuCl_4, -78° → 0°; e PCC;f $AgNO_3$, NaOH, EtOH.

its tetrahydropyranyl ether (237) and subsequent copper (I) catalysed Grignard coupling with sorbyl acetate (239) gave the conjugated dienol (240) after deprotection.[103] Although the crude yield was good, crystalline alcohol could only be isolated in between 14-25% yield despite several attempts to improve the efficiency of the reaction. Fortunately, (240) was available in gram quantities, and after sequential oxidation with pyridinium chlorochromate[104] and silver oxide[105] sufficient acid (242) was in hand for the completion of the synthesis.

Nevertheless, it was thought prudent to examine the acylation of *N* -silyl lactam (157) with the *N*-acylimidazole of commercially available myristic acid (243). Treatment of (157) with two equivalents of LDA at -78° followed by *N*-tetradecanoylimidazole (244) [derived from myristic acid and 1,1'-carbonyldi-imidazole (CDI)][81] gave the β -ketolactam (245) in satisfactory yield (Scheme 4.7).

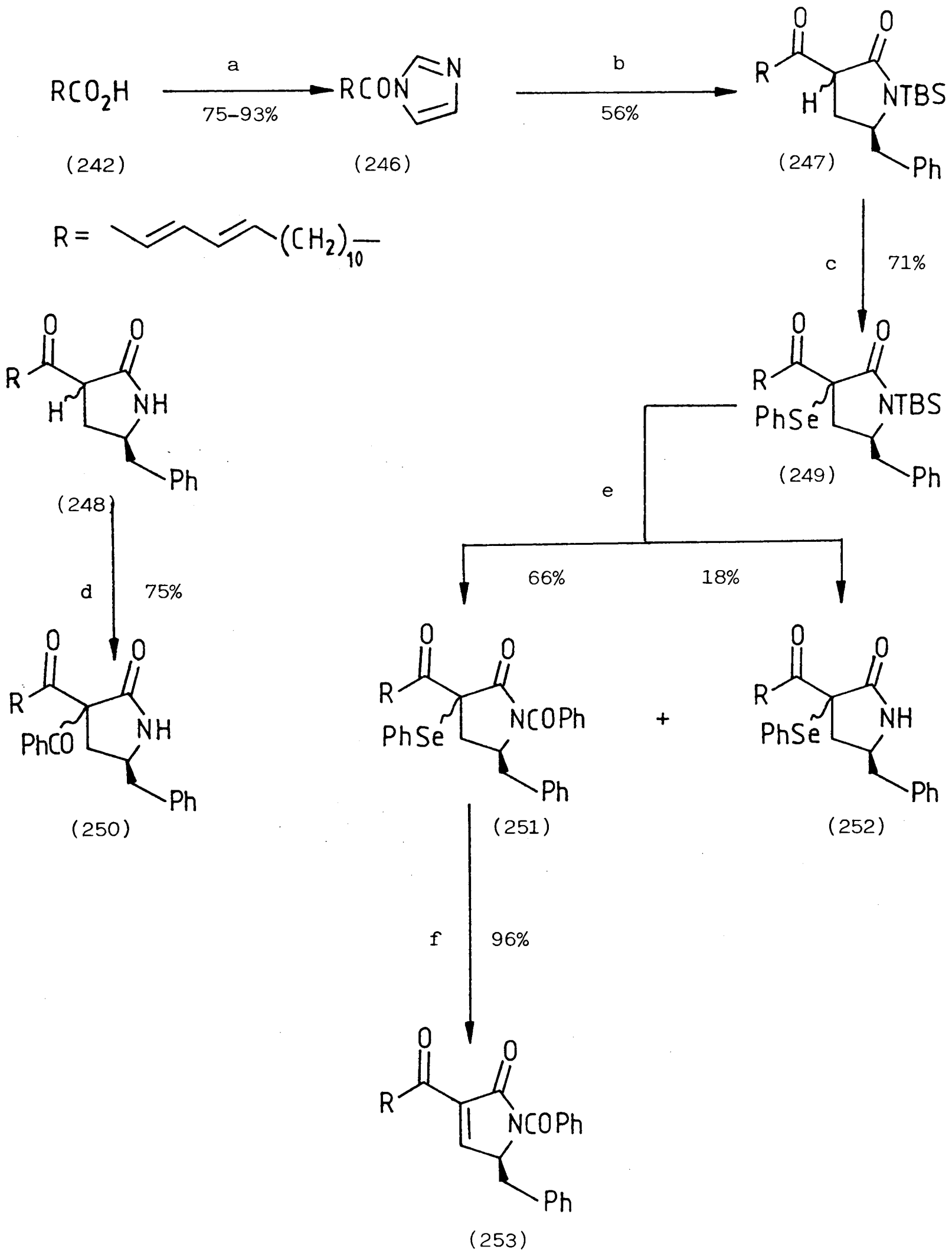
Scheme 4.7



Reagents: a CDI, THF;b LDA, -78°.

Application of this sequence to the long chain dienyl imidazole (246) provided the analogous lactam (247) (H-3, δ 3.5, dd) in slightly lower yield but with substantial recovery of acid (242) (Scheme 4.8). Adventitious silyl hydrolysis was responsible generally for about 5% of products and

Scheme 4.8



Reagents: a CDI, THF;b LDA, (157);c LDA, PhSeCl;d PhCOCl, $Pr^{i}_{2}NEt$;e PhCOCl, C_6H_6, 80°;f aq. H_2O_2, CH_2Cl_2.

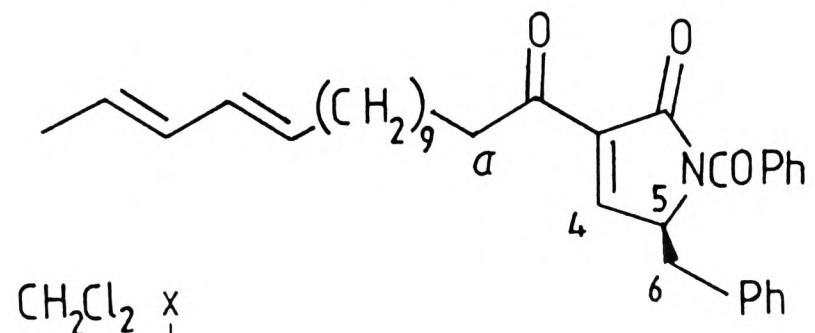
in one experiment, the acylated lactam (248) ($\nu_{max.}$ 3420 cm^{-1}) was obtained as a crystalline solid in 50% yield. Selenenylation of lactam (247) proceeded smoothly to give the selenide (249) ($M^{+}+1$, 680) which was subjected to the transprotection conditions established earlier to afford the desired acylated lactam (251). Despite rigourously anhydrous conditions the deprotected pyrrolidinone (252) was always isolated (10-20%). Attempted *N* -benzoylation of the fortuitous β -ketolactam product (248) under mild conditions led exclusively to C-3 benzoylated material (250) in 75% yield ($\nu_{max.}$ 3415, 1723, 1710, 1672 cm^{-1}).

As before, compounds (247-252) were produced as diastereoisomeric mixtures (ratios 1:1 to 3:1) which could not be separated by chromatography. Their spectroscopic features were similar to those observed in the 1-oxopropyl series (Section 4.2). It was noted, however, that during the transprotection stage, which required 12 h at 80°, partial diene isomerization occurred (E:Z ratio *ca*10:1).

The final step of the dienophile synthesis required an efficient method of selenide oxidation. Although MCPBA had been an ideal reagent in the earlier work, when selenide (251) was reacted under similar conditions a complex mixture of products resulted. In particular, the diene moiety was virtually unrecognisable in the 300 MHz ^{1}H nmr spectrum of the crude product, and the ir spectrum exhibited a strong absorption at $\nu_{max.}$ 909cm^{-1} indicative of epoxide functionality. A search of the literature revealed that selenoxide fragmentation had been performed in the presence of double bonds in several natural product syntheses[106] but not for conjugated dienes.

After some experimentation it was found that the required dienophile (253) could be cleanly and efficiently prepared simply by stirring a solution of the selenide in CH_2Cl_2 with 15-25 equivalents of aqueous

Figure 4.14



crude (253)

hydrogen peroxide. Rapid ether extraction gave the pyrrolinone as an unstable oil (average yield over many runs was 96%). The quality of the crude product was good, as judged from the 300 MHz ^{1}H nmr spectrum (Figure 4.14). As usual, H-4 appeared as a deshielded doublet, at δ 7.97, J 2 Hz, and the methine proton, H-5, was 0.8 ppm downfield (at δ 5.34) of the corresponding resonance in the starting selenide (251).

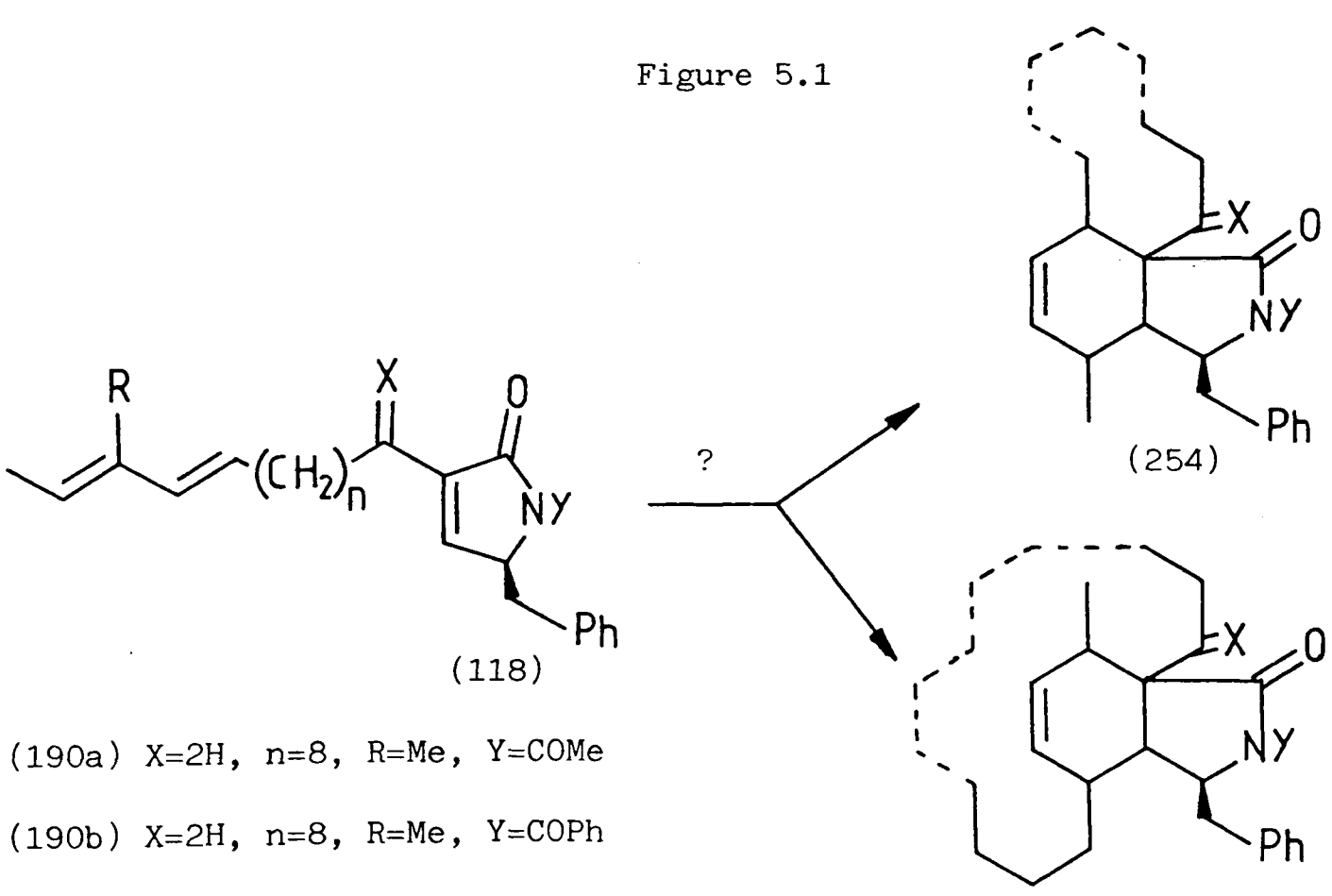
The results of the attempted intramolecular cyclization of the triene are discussed in Chapter 5.

CHAPTER 5

THE INTRAMOLECULAR DIELS-ALDER REACTIONS

Using closely related synthetic procedures it has been possible to prepare two types of triene (118) as suitable models for the critical intramolecular Diels-Alder reaction (Figure 5.1). Macrocycle formation by such reactions has not been studied in detail[32,34] and caution should be exercised in the prediction of stereo- and regiochemistry, especially at elevated temperatures[14,107] or when unfavourable steric interactions are involved.[107,108] For instance, application of Frontier Molecular Orbital (FMO) theory[109,110] to the macrocyclic system (89) (Scheme 2.15), which gave two isomeric macrolides, predicts isomer (91),which was isolated in lower yield, to be the preferred initial product.[32b †]

Figure 5.1



(190a) X=2H, n=8, R=Me, Y=COMe

(190b) X=2H, n=8, R=Me, Y=COPh

(191) X=2H, n=10, R=Me, Y=COPh

(253) X=O, n=10, R=H, Y=COPh

In the present case two regioisomeric products could result, (254) and (255), and each in principle could arise from either an *endo* or *exo* mode of addition. Moreover, this assumes that the C-5 benzyl group ascribes

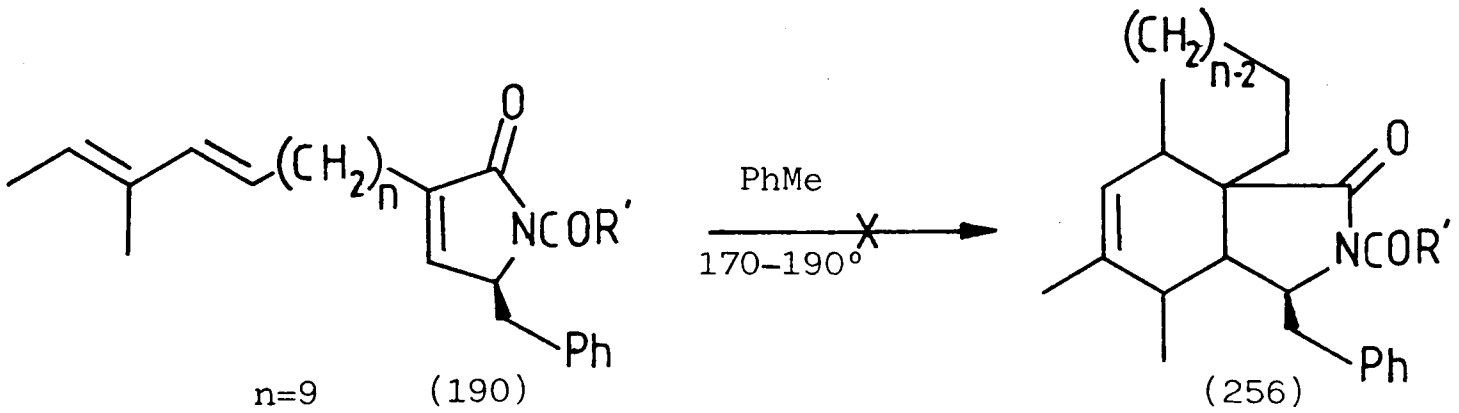
† FMO theory predicts kinetic products, and under prolonged heating cycloreversion may have occurred to give isomer (90), obtained in greater yield.

considerable diastereofacial bias to the dienophile and directs the approach of the diene to the opposite face.

5.1 *Attempted Cycloadditions of Long Chain Alkyl Diene-Dienophiles*

Dilute solutions[111] (*ca* 0.005 M) of the freshly prepared trienes (190) and (191) in triply distilled (P_2O_5) and deoxygenated toluene were heated to between 170-190° in Carius tubes for about 40 h. After removal of the solvents and short column chromatography of the residues no authentic cycloadducts (256) were isolated (Scheme 5.1). In addition, no starting materials were recovered. The only recognisable products were the unreactive 3-octyl- and 3-decylpyrrolinones (192) which had been carried through as impurities from the oxidation step. In one experiment a small amount of an unidentified material was isolated, which was homogeneous by tlc but which showed resonances in the ^1H nmr spectrum indicative of an intact Δ^3-pyrrolin-2-one structure but few vinylic protons.

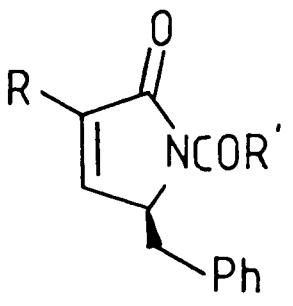
Scheme 5.1



n=9 (190)

n=11 (191)

(256)



(192)

a $R=C_8H_{17}$, R'=Me

b $R=C_8H_{17}$, R'=Ph

c $R=C_{10}H_{21}$, R'=Ph

The unreactivity of these simple alkyl model systems towards intramolecular cyclization appeared to parallel the moderate reactivity of the 3-butylpyrrolinones (130) in intermolecular Diels-Alder reactions (Section 3.6). Admittedly this conclusion was based on the results of only several intramolecular Diels-Alder attempts and a systematic investigation to find conditions under which cycloaddition occurred might have been fruitful (*eg*. by varying R', length of side chain, concentration, temperature, solvent). However, this proposal was superseded by the greater success enjoyed in Diels-Alder reactions by the doubly activated 1,3-diacylpyrrolinone (195) (Chapter 4).

5.2 *Cycloaddition of* (5S,12E,14E)-*1-Benzoyl-5-benzyl-3-(1-oxohexadeca-12,14-dienyl)-* Δ^3 *-pyrrolin-2-one*

Initial attempts to cyclize triene (253) used thermal conditions similar to those described above. Solutions of (253) in toluene or CH_2Cl_2 (*ca* 0.002 M) heated to 120° overnight did give the cycloadduct (257), as a mixture of stereoisomers (*ca*85:15) (Scheme 5.2), but the yields were low (5-10%). Attempts were also made to volatilize the triene under both flash vacuum[112] and flow pyrolysis conditions. However, in each case the compound proved to be extremely involatile (bp. > 200°/10^{-4} mmHg) and only small amounts of unidentified materials were collected.

Believing the use of high temperatures to be responsible for extensive dienophile decomposition, alternative milder conditions were sought. The effect of pressure on the rate of a reaction k, can be represented by the following equation:

$$\left(\frac{\delta \ln k}{\delta P}\right)_T = -\frac{\Delta V^{\ddagger}}{RT}$$

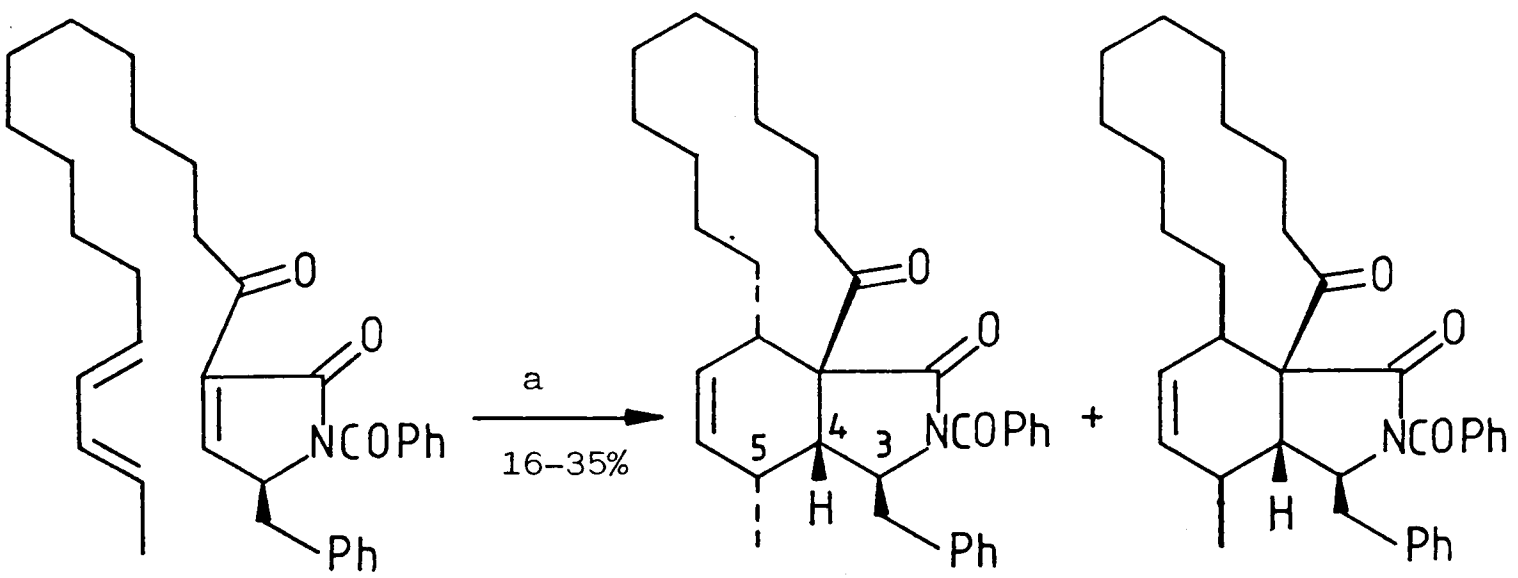
where $\Delta V^{\ddagger}$ is the difference in partial molar volumes between reagents

and transition state, known as the "volume of activation".[113] This equation predicts an increase in rate with increasing pressure for reactions in which $\Delta V^{\ddagger}$ is negative *ie.* when the volume of the transition state is smaller than the total volume of reagents. The Diels-Alder reaction,which proceeds *via* a highly ordered aromatic transition state,[78] is expected to be strongly accelerated by pressure, and indeed the effect of pressure on reactivity, regioselectivity and stereochemistry in intermolecular Diels-Alder reactions is well documented.[114] Application of high pressures to the intramolecular version has scarcely been studied[115] especially for macrocycle formation. From the little data available it seems that values of $\Delta V^{\ddagger}$ are slightly less negative than those of the well-studied intermolecular systems (for which $\Delta V^{\ddagger} < -30$ cm^3 mol^{-1}) but that an intramolecular cycloaddition will still respond well to an increase in pressure. Moreover, *endo* selectivity is enhanced because substituents located *endo* in the transition state occupy a smaller volume than when *exo* .[116] Regioselectivity is similarly affected by pressure in favour of the isomer originating from the transition state of smaller volume. It also seems reasonable to suppose that at high pressures,when solvent viscosity is great and diffusion is reduced,[113] the rate of bimolecular processes in dilute solution will be slow (*eg* . decomposition of the dienophile).

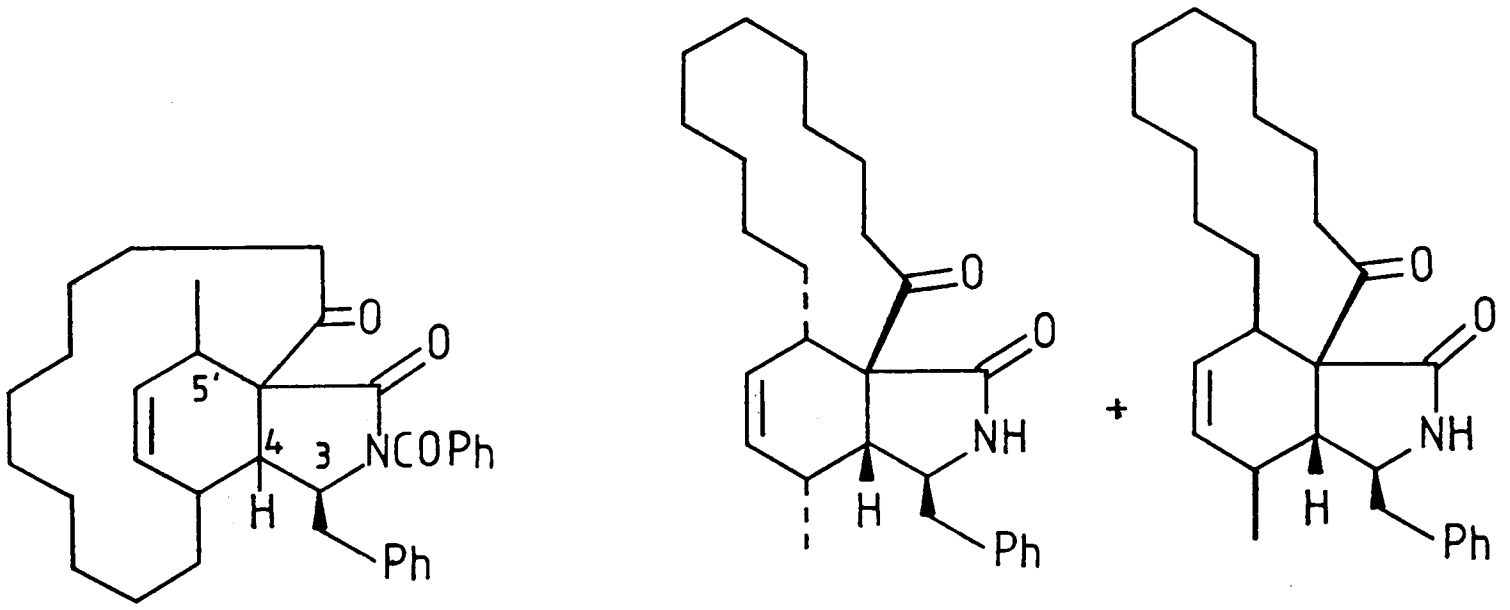
Thus, when a solution of freshly prepared triene (253) in CH_2Cl_2 † (*ca* 0.002-0.006 M) was subjected to 11-13 kbar of pressure in a piston and cylinder apparatus (Figure 5.2) at 40° overnight, improved yields of the tricyclic compound (257) were realised (16-35% after chromatography and gel filtration). The compound was isolated as an inseparable mixture (*ca* 90:10) with the desired regiochemistry, as shown by a spin-decoupling experiment. Irradiation of the methyl doublet resonance at δ 1.17 (for

† CH_2Cl_2 was an appropriate solvent because of its high freezing pressure (13 kbar at 25°).[113]

Scheme 5.2



(253) (257a) (257b)

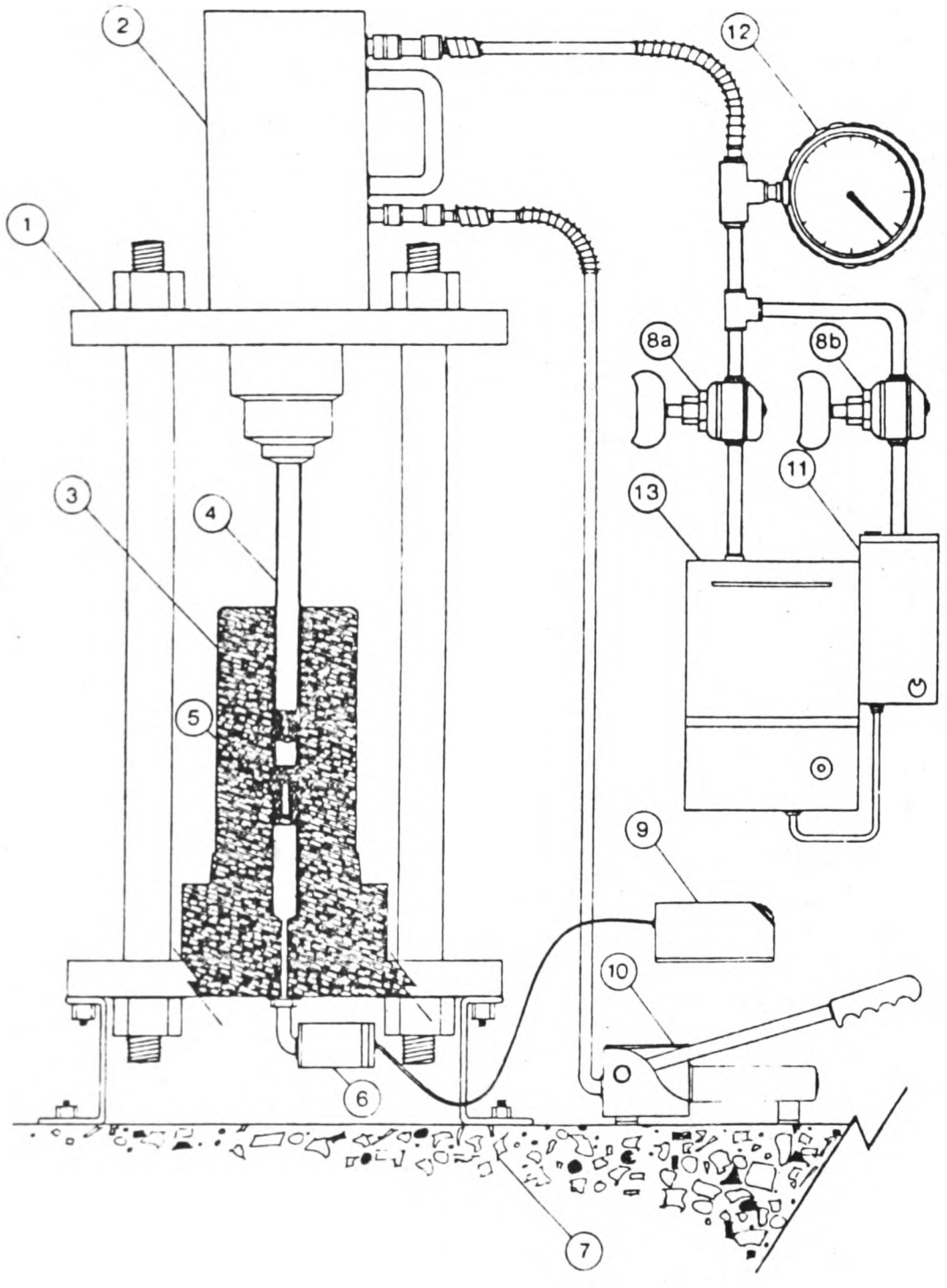


(260) (258) (259)

Reagents: a 120°, CH_2Cl_2 or toluene, or 11-13 kbar, 40°, CH_2Cl_2;

b KOH, MeOH, C_6H_6.

Figure 5. 2



Schematic Diagram for High Pressure Preparative Apparatus

Key

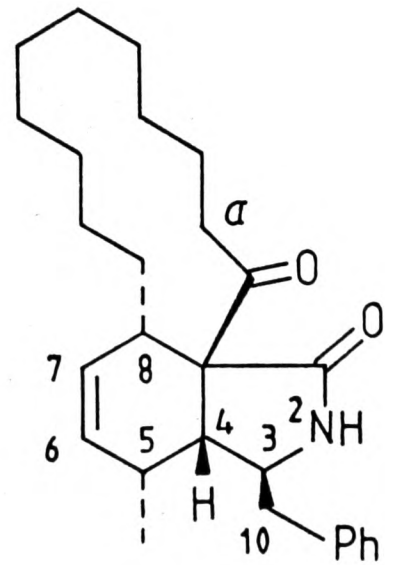
1. High Tension Frame (steel EN26).
2. Ram (100 bar capacity).
3. Bore Cylinder (steel EN26).
4. Piston (steel EN26).
5. Reaction Chamber.
6. Transducer.
7. Platform.
8. Valves.
9. Meter.
10. Hand Pump.
11. Oil Reservoir.
12. Gauge.
13 Diaphragm Pump.

the major isomer) led to a simplification of the one-proton multiplet at δ 2.51 which was thus identified as H-5 (in structure 257) or H-5' (in the regioisomer 260) (Scheme 5.2). Upon selective irradiation of the latter, the methyl doublet collapsed to a singlet *and* the overlapping doublet of doublets at δ 2.83 also collapsed, to a broad singlet. That this resonance was due to the bridgehead proton H-4 was shown by irradiation of the H-3 multiplet at δ 4.35, which led to the resonance at δ 2.83 collapsing to to a doublet. These data are entirely in agreement with structure (257). Although the yields of the cycloaddition are modest, they are comparable with those reported by Stork[29] in his improved synthesis of cytochalasin B (Scheme 2.16).

5.3 *Deprotection of the Cycloadduct*

The mixture of stereoisomers (257) was deprotected with aqueous potassium hydroxide in methanol-benzene to give a mixture of isoindolones (258) and (259) which could be separated by short column chromatography. The major isomer (74%) was identified as (258) ($M^+ + 1$, 408) on the basis of its spectroscopic data. In the ir spectrum the broad absorptions at $\nu_{max.}$ 3410, 3200 cm^{-1} and intense carbonyl absorption, $\nu_{max.}$ 1695 cm^{-1}, confirmed the presence of the deprotected lactam functionality. Extensive proton spin-decoupling experiments allowed a full assignment of the 300 MHz ^1H nmr spectrum which is reproduced in Figure 5.3. Of note is the large difference in the chemical shifts of the two protons α to the macrocyclic carbonyl group, at δ 1.92 and 3.45. Presumably one α proton is deshielded by the magnetic anisotropies of *both* carbonyl groups. The bridgehead proton H-4 appears as a pseudo triplet at δ 2.58 with values of 4.2 Hz for the couplings with H-3 and H-5, which are in the range observed for many synthetic isoindolones (Appendix II).

Figure 5.3

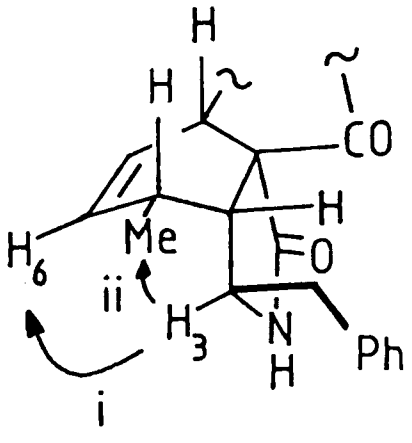


(258)

The 300 MHz ^{1}H nmr spectrum of the minor isomer (18%) (259) is shown in Figure 5.4 and the H-4 resonance is seen to be coincident with one benzylic proton H-10, at δ 2.52. However, a value of 4.2 Hz is observed for the coupling between H-4 and H-5, as in the major isomer. Similarly, the two protons α to the macrocyclic carbonyl group are well separated, at δ 2.35 and 3.17, but the conformation of the macrocycle must be such as to allow even a β-proton (δ 1.97) to be influenced by the magnetic anisotropy of the lactam carbonyl group.

The stereochemistries of the isoindolone portions of each isomer were deduced from comparative nuclear Overhauser experiments. In d_6-benzene the vinylic protons of the major isomer are quite distinct in the 300 MHz ^{1}H nmr spectrum and upon irradiation of H-3 a 1.1% enhancement was observed for H-6 (Figure 5.5). The 0.7% enhancement observed for the methyl doublet also supported regioisomeric structure (258) rather than (260). The corresponding irradiation for the minor isomer gave rise to significant enhancements of the H-5 (7%) and NH (4.2%) resonances, with no observed effect on either vinylic resonance.

Figure 5.5

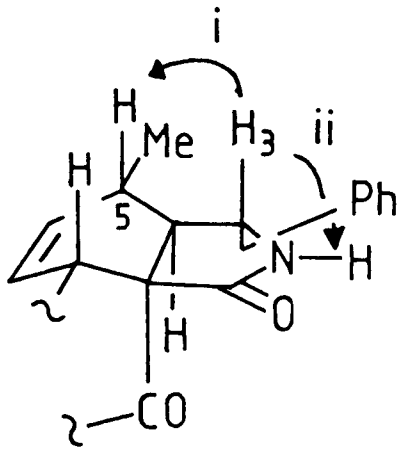


i 1.1%

ii 0.7%

i 7%

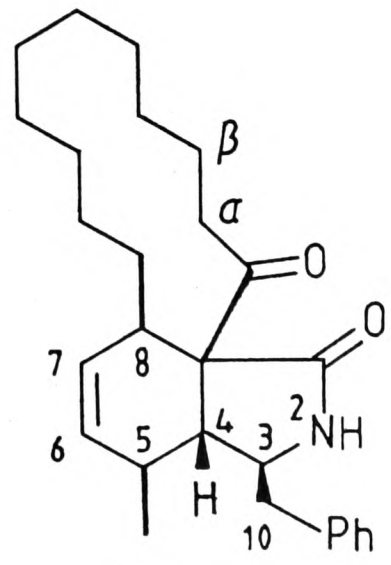
ii 4.2%



(258) (259)

These results are consistent with the boat conformations drawn above,

Figure 5.4



(259)

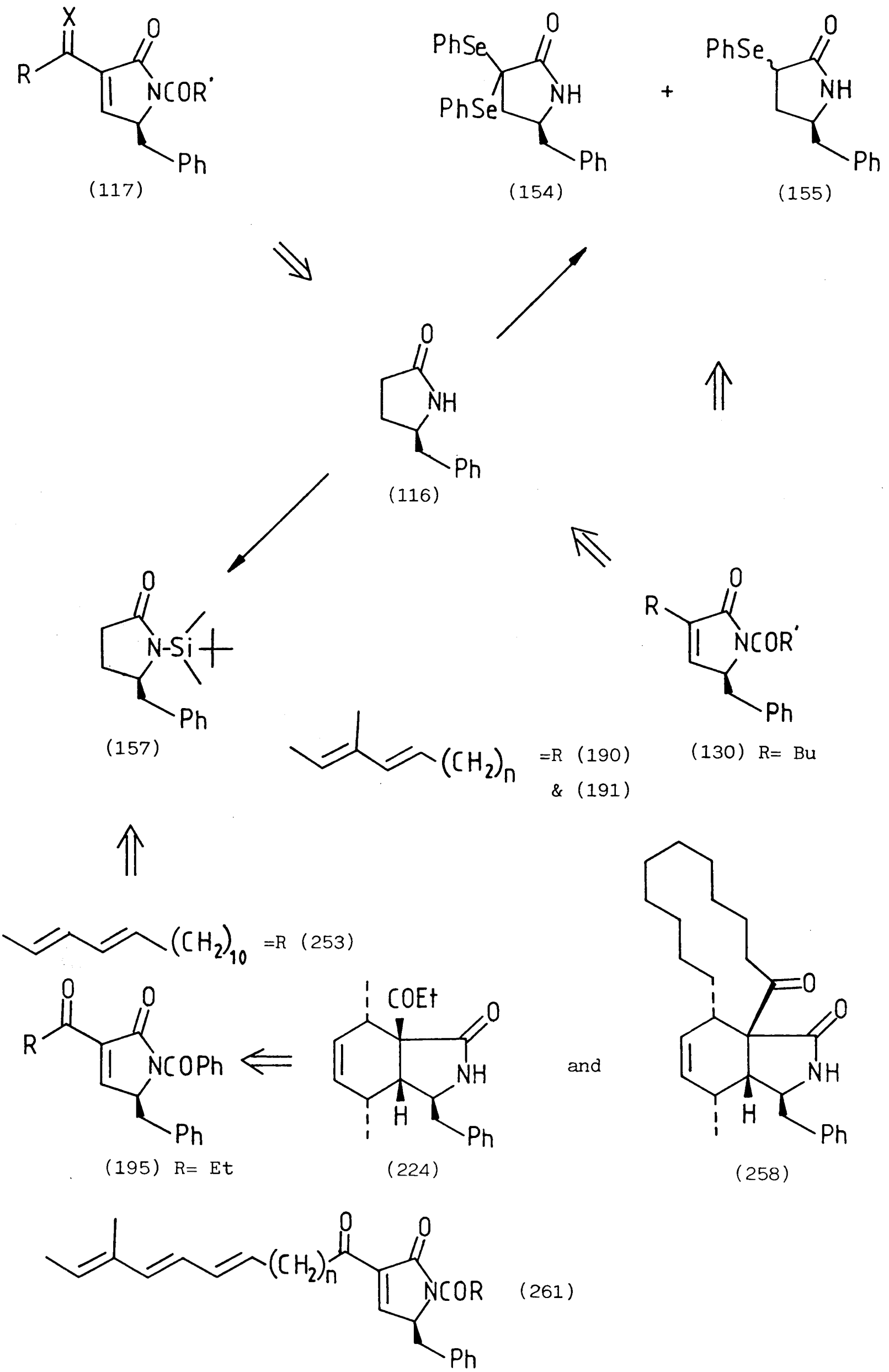
and thus the major product of the Diels-Alder cycloaddition possesses the desired cytochalasan stereochemistry,as hoped. Tricyclic compound (258) is therefore a direct analogue of the [13]cytochalasans which fulfills two of the structural criteria thought to be essential for cytotoxicity,[117] *viz* ., an intact macrocyclic ring and the presence of a C-3 benzyl group. However, (258) would not be expected to show the same level of cytotoxicity as, for example, cytochalasin D because it lacks the allylic hydroxyl group at C-7, the third structural criterion.

5.4 *Conclusion*

At the outset of this work it was decided to prepare various *N* -acylated pyrrolin-2-ones (117) from the known lactam (116) and to investigate their reactivity in Diels-Alder reactions, in model studies directed towards cytochalasan synthesis (Figure 5.6). 3-Alkylated pyrrolinones (130) were prepared in low overall yield *via* selenides (154) and (155) and were shown to react with 2E,4E-hexadiene only under harsh conditions (*ca* 200°, several days) (Chapter 3). Attempts to effect the intramolecular cyclization with long chain alkyl diene-dienophiles (190) and (191) were unsuccessful.

The doubly activated pyrrolinone (195), on the other hand, was available *via* an expeditious route from *N* -silylated lactam (157) and reacted stereoselectively with 2E,4E-hexadiene under milder conditions (100°, 8 h) to give, after deprotection, isoindolone (224) (Chapter 4). The overall yield after seven steps from lactam (116) was 16%. Long chain diene-dienophile (253) was prepared similarly in 20% overall yield and was cyclized under high pressure conditions (11-13 kbar, 40°) to give, after deprotection, the tricyclic compound (258) with the correct regiochemistry. The stereoselectivity was slightly better than for the intermolecular Diels-Alder

Figure 5.6


X
O
R
NCOR'
Ph
(117)
PhSe
PhSe
NH
(154)
+
(155)
NH
(116)
N-Si
(157)
(CH2)n
=R (190)
& (191)
(130) R= Bu
(CH2)10
=R (253)
COEt
NCOPh
(195) R= Et
(224)
and
(258)
(261)

reaction and the major adduct was shown to possess the desired cytochalasan stereochemistry (Chapter 5).

Thus, the intramolecular Diels-Alder approach to cytochalasan synthesis using chiral diene-lactams has been validated. The advantages of the strategy are the overall convergency and the simultaneous stereo- and regio-selective formation of the cyclohexene and macrocyclic rings. However, the main limitations of the route as it stands are the necessity for high pressure and high dilution conditions and consequent scaling-up problems, and the use of the transprotection step, $NSiR_3 \rightarrow NCOR'$. Even with a simple diene side chain some $\underline{E} \rightarrow \underline{Z}$ isomerization occurred during the transprotection reaction and were a conjugated triene-lactam (261) (Figure 5.6) to be prepared, such a step would be likely to lead to much decomposition. If an alternative sequence using *N* -acylated lactams could be developed, judicious selection of the diene/triene and imide reactivities should allow an efficient internal cyclization to provide the cytochalasan skeleton.

CHAPTER 6

EXPERIMENTAL SECTION

6.1 *General Directions*

All reactions were run under an atmosphere of dry nitrogen or argon at temperatures which were those of the external bath unless otherwise stated. All temperatures quoted are in degrees Celsius (°C). In most cases yields refer to unoptimised reactions.

Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on Brüker WH 300 (300 MHz) and Perkin-Elmer R24 (60 MHz) spectrometers using d_1-chloroform solutions unless otherwise indicated, with residual chloroform as internal standard. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Splitting patterns are reported as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). Additional abbreviations used are br, for broad; $^{\psi}$ for pseudo; and sh for shoulder. Nuclear Overhauser experiments were performed on Brüker WH 300 (300 MHz) or Brüker AM 250 (250 MHz) spectrometers using degassed solutions in d_1-chloroform or d_6-benzene.

Infra-red (ir) spectra were recorded on Perkin-Elmer 257 and 297 spectrometers using dilute solutions in carbon tetrachloride unless otherwise indicated; positions of absorption maxima are given in order of decreasing wavenumber (cm^{-1}).

Routine mass spectra were recorded on Varian MAT CH7, VG Micromass 16 F or ZAB-IF spectrometers; *m/z* values (followed in parentheses by the percentage abundances) are given for the molecular ion, M^+, in the electron impact (EI) mode, or for the protonated molecular ion, M^++1, in the chemical ionization (CI) mode, along with the base peak.† High resolution mass spectra were recorded on Varian Micromass 7070 or ZAB-IF spectrometers.

† For selenium containing molecules, these values refer to the ^{80}Se isotope (50% natural abundance).

Optical rotations were measured on a Perkin-Elmer 241 polarimeter by Mrs. A. Rivers and Mr. A. Howe, Oxford. Melting points were recorded on a Büchi 510 apparatus and are uncorrected. Microanalyses were performed under the supervision of Dr. F. B. Strauss, Oxford.

Short column chromatography[62] was performed using Kieselgel 60H (Merck) as the stationary phase while flash chromatography[57] was carried out using Merck silica gel 60 (40-63 μm, 230-400 mesh). The light petroleum referred to is the fraction boiling in the range 40-60°. The purity of products was checked by thin layer chromatography (tlc) using 20 x 5 cm glass plates coated with a 0.3 mm layer of Kieselgel $HF_{254+366}$ or aluminium sheets precoated with a 0.2 mm layer of Merck silica gel $60F_{254}$. Gel filtration was carried out using a Pharmacia Fraction Collector Frac-300 and was monitored by ultra-violet absorption.

All solvents and commercially available reagents were dried and purified by standard procedures[118] before use. Lithium di-isopropylamide (LDA) was prepared immediately before use according to the procedure of Reich.[42] BuLi refers to a solution of n-butyl lithium in hexane; THF is tetrahydrofuran; TMEDA is *N*,*N*,*N'*,*N'*-tetramethylethylenediamine; DMSO is dimethylsulphoxide; HMPA is hexamethylphosphoric triamide; DABCO is diazabicyclo[2.2.0]octane, and MCPBA is *meta*-choroperbenzoic acid (*ca* 80-90%). Ether refers to diethyl ether. Other common organic materials are abbreviated in the usual manner.

In the experimental text, the term "extraction" refers to the process of extracting the product into an organic solvent (specified), washing the combined extracts with water, drying over anhydrous $MgSO_4$ and evaporating under reduced pressure.

6.2 *Experiments Discussed in Chapter 3*

3-Butyl-1-methyl-3-phenylselenopyrrolidin-2-one (121)

A solution of 1-methylpyrrolidin-2-one (120) (0.2 ml, 2.08 mmol) in THF (1 ml) was added dropwise to LDA (4.64 mmol) in THF (2 ml) at -75°. The mixture was stirred for 30 min after which phenylselenenyl chloride (0.4 g, 2.08 mmol) in THF (4 ml) was added. After a further 30 min at -75° a solution of 1-iodobutane (0.24 ml, 2.1 mmol) in THF (1 ml) was added and the mixture was allowed to warm gradually to room temperature overnight. The reaction was poured into 2 M HCl and extracted with ether to give a dark oil (0.827 g) which was purified by short column chromatography using ether-petrol (1:1) as eluant. *3-Butyl-1-methyl-3-phenylselenopyrrolidin-2-one* (121) was obtained as a pale yellow oil (0.404 g, 62%), δ 0.88 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 1.26-1.36 (4H, m, $(\underline{CH}_2)_2CH_3$), 1.77-1.92 (2H, m, $\underline{CH}_2(CH_2)_2$), 2.26 (2H, m, $\underline{CH}_2CN$), 2.58 (1H, m, $\underline{CH}N$), 2.65 (3H, s, $N\underline{CH}_3$), 2.92 (1H, m, $\underline{CH}N$), 7.24-7.67 (5H, m, aromatic H); $\nu_{max.}$ 2955, 2930, 1693, 1438, 1425, 1400, 1302, 1276, and 689 cm^{-1}; *m/z* (CI) 312 ($M^+ + 1$, 27%) and 154 (100%) (Found: M^+ 311.0784. $C_{15}H_{21}NO^{80}Se$ requires M^+ 311.0788).

3-Butyl-1-methyl- Δ^3*-pyrrolin-2-one* (122)

A solution of 50% H_2O_2 (0.9 ml, 15.6 mmol) in water (10 ml) was added dropwise during 20 min to a solution of lactam (121) (1.65 g, 5.32 mmol) and pyridine (0.86 ml, 10.6 mmol) in CH_2Cl_2 (15 ml) with brisk stirring. After 50 min, the mixture was poured into 5% aqueous $NaHCO_3$ (20 ml) and CH_2Cl_2 (20 ml) and was stirred for 30 min. The organic layer was separated and washed successively with 10% HCl and brine. Concentration of the dried ($MgSO_4$) extracts gave an oil (0.81 g) which was chromatographed on silica

with ether-petrol (3:1) and then ether as eluants to give *3-butyl-1-methyl-Δ^3-pyrrolin-2-one* (122) as a pale yellow oil (690 mg, 85%), δ 0.89 (3H, t, *J* 7.4 Hz, $CH_2\underline{CH}_3$), 1.34 (2H, m, $\underline{CH}_2CH_3$), 1.50 (2H, m, $\underline{CH}_2CH_2$), 2.25 (2H, td, *J* 7.7, 1.5 Hz, $\underline{CH}_2C{=}CH$), 3.02 (3H, s, NCH_3), 3.81 (2H, d, *J* 1.5 Hz, $\underline{CH}_2N$), 6.58 (1H, t, *J* 1.5 Hz, H-4); $\nu_{max.}$ 2955, 2930, 1696sh, 1690, 1643, 1398, 1245br, and 1060 cm^{-1}; *m/z* 153 (M^+, 40%) and 112 (100%) (Found: M^+ 153.1153. $C_9H_{15}NO$ requires M^+ 153.1154).

1-Methyl-3-(1-oxopropyl)pyrrolidin-2-one (123)

Neat 1-methylpyrrolidin-2-one (120) (5.8 ml, 60.3 mmol) was added to LDA (62.4 mmol) in THF (100 ml) at -70° and the resulting solution was stirred for 30 min. Ethyl propionate (10 ml, 87.2 mmol) was then added in a continuous stream and after 5 min the cooling bath was removed. After a further 25 min, the white slurry was poured into water (100 ml), acidified with 5 M HCl to pH 4 and continuously extracted with ethyl acetate (10.5 h). The yellow oil obtained was distilled in a Kugelrohr apparatus (oven temperature 170°/0.3 mmHg) to give *1-methyl-3-(1-oxopropyl)pyrrolidin-2-one* (123) as a colourless oil (7.787 g, 83%) which quickly became yellow on standing at 4°, δ 1.05 (3H, t, *J* 7.2 Hz, $CH_2\underline{CH}_3$), 1.97-2.09 (1H, m, $\underline{CH}CN$), 2.47-2.61 (2H, m, $\underline{CH}CH_3$ and $\underline{CH}CN$), 2.82 (3H, s, $N\underline{CH}_3$), 3.06 (1H, dq, *J* 18.8, 7.2 Hz, $\underline{CH}CH_3$), 3.30 (1H, m, $\underline{CH}N$), 3.42 (1H, m, $\underline{CH}N$), 3.56 1H, dd, *J* 9.3, 5.7 Hz, $COC\underline{H}CO$); $\nu_{max.}$ 2990, 2950, 2890, 1721, 1695, 1408, 1265br, and 1108 cm^{-1}; *m/z* 155 (M^+, 25%) and 98 (100%) (Found: M^+ 155.0946. $C_8H_{13}NO_2$ requires M^+ 155.0946).

1-Methyl-3-(1-oxopropyl)-3-phenylselenopyrrolidin-2-one (124)

A solution of lactam (123) (1.016 g, 6.55 mmol) in THF (4 ml) was added slowly to LDA (7.21 mmol) in THF (10 ml) at -78° and the resulting

mixture was stirred briskly for 75 min. Phenylselenenyl chloride (1.685 g, 8.8 mmol) in THF (7 ml) was added, the reaction was allowed to warm to 0° during 2.5 h and was then poured into saturated aqueous NH_4Cl. Ether extraction gave an oil which was purified by flash chromatography eluting with ether-petrol (1:1), to give *1-methyl-3-(1-oxopropyl)-3-phenylseleno-pyrrolidin-2-one* (124) as a pale yellow solid (1.183 g, 58%). Crystallization from ether-petrol gave needles, mp. 59-60°, δ 1.12 (3H, t, *J* 7.2 Hz, $CH_2\underline{CH}_3$), 2.02 (1H, ddd, *J* 14.4, 7.5, 3.5 Hz, $C\underline{H}CN$), 2.69 (1H, ddd, *J* 15.4, 8.4, 7.2 Hz, $C\underline{H}CN$), 2.82 (3H, s, $NC\underline{H}_3$), 2.93-3.21 (3H, m, $C\underline{H}CH_3$ and $C\underline{H}_2N$), 3.34 (1H, dq, *J* 17.8, 7.3 Hz, $C\underline{H}CH_3$), 7.25-7.55 (5H, m, aromatic H); $\nu_{max.}$ 2940, 1699, 1405, 1297, and 691 cm^{-1}; *m/z* 311 (M^+, 16%) and 174 (100%) (Found: C, 54.1; H, 5.5; N, 4.7. $C_{14}H_{17}NO_2Se$ requires C, 54.2; H, 5.5; N, 4.5%).

Attempted Preparation of 1-Methyl-3-(1-oxopropyl)- Δ^3*-pyrrolin-2-one* (125)

Method 1

2 Ml of a solution of 30% H_2O_2 (1 ml, 10 mmol) in water (9 ml) was added to lactam (124) (81 mg, 0.261 mmol) in CH_2Cl_2 (1 ml) at 0° and the mixture was stirred vigorously for 10 min. The ice-bath was removed and after 20 min tlc analysis indicated the absence of starting material. The reaction was poured into 10% $NaHCO_3$ (10 ml) and CH_2Cl_2 (10 ml) and extracted to give a yellow oil (35 mg) which was shown to be a complex mixture by ^1H nmr and tlc.

Method 2

A solution of the lactam (78 mg, 0.253 mmol) in benzene (1 ml) was added to a suspension of chloramine-T[119] (60 mg, 0.263 mmol) in water (1 ml) and the mixture was stirred vigorously. One drop of Aliquat 336 was added and after 30 min the dark green mixture was poured into water and extracted

with ether. The product obtained was shown to be a complex mixture by tlc and was not analysed further.

Method 3

2-Benzenesulphonyl-3-(4'-nitrophenyl)oxaziridine[120] (80 mg, 0.261 mmol) in $CHCl_3$ (1 ml) was added to a solution of the lactam (80 mg, 0.26 mmol) in $CHCl_3$ (1 ml).[121] The resulting bright yellow solution was stirred for 15 min by which time tlc analysis showed that starting material had been consumed. The reaction was poured into saturated aqueous $NaHCO_3$ (10 ml) and $CHCl_3$ (15 ml) and extracted to give an orange solid (125 mg) shown by ^1H nmr and tlc to be a complex mixture which was not analysed further.

Method 4

70% Aqueous *tert* -butylhydrogenperoxide (0.2 ml, 1.5 mmol) was added to a solution of the lactam (88 mg, 0.284 mmol) in THF (1 ml) at 0°. After 10 min the ice-bath was removed and the solution was stirred at room temperature. Tlc analysis at regular intervals showed that the reaction was very slow even after a further 0.5 ml of peroxide had been added. After 80 h, the yellow solution was poured into ether (30 ml) and worked-up as described[122] to give an orange oil(13 mg) shown to be selenium-containing residues by tlc and ^1H nmr.

2S-Ethyl 2-Amino-3-phenylpropanoate (132)

Following the procedure of Seki[123] with L- β -phenylalanine (131) (100 g, 0.605 mol) and $SOCl_2$ (76 ml, 1.05 mol) in ethanol (900 ml), the ester (132) was obtained as an oil (96.8 g, 83%), bp. 100°/3 mmHg (lit.,[124] 140-142°/10 mmHg), $[\alpha]_D^{20}$ +15.1 (c 1.94, EtOH), δ 1.23 (3H, t, *J* 7.3 Hz, $CH_2\underline{CH}_3$), 1.50 (2H, brs, $N\underline{H}_2$), 2.85 (1H, dd, *J* 13.5, 7.7 Hz, C<u>H</u>Ph), 3.06 (1H, dd, *J* 13.2, 5.3 Hz, C<u>H</u>Ph), 3.70 (1H, dd, *J* 7.7, 5.5 Hz, C<u>H</u>N), 4.15 (2H, q, *J* 7.1 Hz, $O\underline{CH}_2CH_3$), 7.17-7.31 (5H, m, aromatic H).

2S-2-Amino-3-phenylpropan-1-ol (133)

Amino alcohol (133) was prepared by reducing ester (132) (96.8 g, 0.5 mol) with $LiAlH_4$ (29 g, 0.764 mol) in ether (750 ml) according to the literature method.[125] Best yields were realised by washing the inorganic salts produced in the work-up with copious amounts of CH_2Cl_2. Recrystallization from ether-CH_2Cl_2 gave the alcohol (133) (59.98 g, 79%) as plates mp. 89-91°, $[\alpha]_D^{20}$ -24.0 (c 2.04, EtOH) (lit.,[126] 90-91°, $[\alpha]_D^{23}$ -24.7), δ 2.08 (3H, brs, $N\underline{H}_2$ and O$\underline{H}$), 2.51 (1H, dd, *J* 13.5, 8.6 Hz, C$\underline{H}$Ph), 2.79 (1H, dd, *J* 13.5, 5.0 Hz, C$\underline{H}$Ph), 3.11 (1H, m, C$\underline{H}$N), 3.39 (1H, dd, *J* 10.6, 7.5 Hz, C$\underline{H}$O), 3.63 (1H, dd, *J* 10.8, 3.8 Hz, C$\underline{H}$O), 7.18-7.33 (5H, m, aromatic H).

4R-4-Amino-5-phenylpentanoic acid (138)

Sequential treatment of alcohol (133) (70.63 g, 0.467 mol) with *p*-toluenesulphonyl chloride (356 g, 1.867 mol) in pyridine (500 ml), diethyl malonate (197 ml, 1.3 mol) and $KOBu^t$ (150 g, 1.34 mol) in THF (750 ml), and 48% HBr (500 ml) according to the literature procedure[38] followed by ion-exchange chromatography (Amberlite IR-120, H^+ form) gave the amino acid (138) (37.89 g, 42% overall) mp. 174-177° (EtOH-ether), $[\alpha]_D^{20}$ -30.3 (c 1.49, H_2O) (lit.,[38] 189.5-191.5°, $[\alpha]_D^{20}$ -33.8), δ (D_2O) 1.66 (2H, m, $C\underline{H}_2CH_2CO_2H$), 2.09 (2H, t, *J* 7.1 Hz, $C\underline{H}_2CO_2H$), 2.58 (1H, dd, *J* 14.2, 8.5 Hz, C$\underline{H}$Ph), 2.82 (1H, dd, *J* 14.3, 5.8 Hz, C$\underline{H}$Ph), 3.26 (1H, m, C$\underline{H}$N), 7.03-7.22 (5H, m, aromatic H).

5R-5-Benzylpyrrolidin-2-one (116)

A suspension of the amino acid (138) (37.89 g, 0.196 mol) in dioxan (450 ml) was boiled under reflux for 42 h and then treated with charcoal for 50 min. Filtration through Celite followed by evaporation under reduced

pressure gave a yellow oil (32.7 g) which was crystallized from ether at low temperature to give the lactam (116) as a pale yellow solid (29.74 g, 87%), mp. 54-55°, $[\alpha]_D^{20}$ +36.7 (c 1.2, EtOH) (lit.,[38] 58-61°, $[\alpha]_D^{20}$ +39.6); δ 1.76-1.87 (1H,m, CHCN), 2.14-2.31 (3H, m, $CHCH_2CO$), 2.70 (1H, dd, *J* 13.3, 8.4 Hz, CHPh), 2.87 (1H, dd, *J* 13.2, 5.3 Hz, CHPh), 3.88 (1H, m, CHN), 6.49 (1H, brs, NH), 7.15-7.35 (5H, m, aromatic H); $\nu_{max.}$ 3445, 3200br, 1712sh, 1706, 1456, 1412, 1293, and 697 cm^{-1}; *m/z* (CI) 176 (M^++1 , 84%) and 84 (100%).

(5R,2'S)-*5-Benzyl-1-(2'-methoxy-2'-phenyl-3',3',3'-trifluoropropanoyl) pyrrolidin-2-one* (139)

BuLi (1.5 M, 0.11 ml) was added to a solution of lactam (116) (28.5 mg, 0.1626 mmol) in THF (0.5 ml) at 0° and the resulting suspension was stirred for 15 min. (-)-2-Methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride (46 mg, *ca* 0.18 mmol) in THF (0.8 ml) was added, the mixture was stirred for 45 min at 0°, and for a further 90 min at room temperature before being poured into water (10 ml). Extraction with ether gave a colourless oil (54 mg, 85%) which was shown to be a mixture of diastereoisomers (88: 12) by ^1H nmr spectroscopy. The major isomer was crystallized from ether-pentane to give (5R,2'S)-*5-benzyl-(2'-methoxy-2'-phenyl-3',3',3',-trifluoropropanoyl)pyrrolidin-2-one* (139) as crystals mp. 136-7°, $[\alpha]_D^{20}$ -97.0 (c 0.13, $CHCl_3$), δ 1.92 (2H, m, CH_2CH_2CO), 2.33 (2H, m, CH_2CO), 2.63 (1H, dd, *J* 13.1, 9.9 Hz, CHPh), 3.38 (1H, dd, *J* 13.1, 3.2 Hz, CHPh), 3.66 (3H, q, *J* 1.5 Hz, OCH_3), 4.67 (1H, m, CHN), 7.25-7.57 (10H, m, aromatic H); $\nu_{max.}$ ($CHCl_3$) 1765, 1690, and 1180 cm^{-1}; *m/z* 391 (M^+ , 5%) and 189 (100%) (Found: C, 64.2; H, 5.2; N,3.7. $C_{21}H_{20}F_3NO_3$ requires C, 64.4; H, 5.15; N, 3.6%).

1-Benzyloxymethylpyrrolidin-2-one (141)

A solution of pyrrolidin-2-one (140) (3.8 ml, 50 mmol) in THF (8 ml) was added dropwise to a suspension of NaH (50% dispersion in mineral oil, 2.64 g, 55 mmol) in THF (20 ml) at 0°. The mixture was stirred for 30 min and benzylchloromethyl ether (7 ml, 50.5 mmol) in THF (10 ml) was then added at 0°. After removing the ice-bath, the mixture was refluxed for 17 h and the volatiles were removed under reduced pressure. Ether was added to the resulting slurry, the mixture was filtered through Celite and the solvent was removed to give *1-benzyloxymethylpyrrolidin-2-one* (141) as a pink oil (9.7 g, 95%). A portion of this oil was purified by Kugelrohr distillation (oven temperature 190-200°/0.4 mmHg) to give a colourless sample, δ 1.88 (2H, m, $C\underline{H}_2CH_2CO$), 2.30 (2H, t, J 8.2 Hz, $CH_2\underline{C}O$), 3.39 (2H, t, J 7.2 Hz, $CH_2\underline{N}$), 4.44 (2H, s, $OCH_2\underline{N}$), 4.77 (2H, s, $OCH_2\underline{Ph}$), 7.22-7.30 (5H, m, aromatic H); $\nu_{max.}$ 2935, 2880, 1704, 1493, 1461, 1422, 1380, 1284, 1264, 1066br, and 695 cm^{-1}; *m/z* (CI) 206 (M^++1 , 15%) and 98 (100%).

1-Benzyloxymethyl-3-butyl-3-phenylselenopyrrolidin-2-one (143)

A solution of lactam (141) (0.48 g, 2.01 mmol) in THF (2 ml) was added to LDA (4.42 mmol) in THF (2 ml) at -78°. After 30 min, phenylselenenyl chloride (0.38 g, 2 mmol) in THF (3 ml) was added and the resulting mixture was stirred for a further 30 min. 1-Iodobutane (0.23 ml, 2 mmol) in THF (2 ml) was then added at -78° and the mixture was allowed to warm to room temperature gradually, and was stirred overnight. The mixture was poured into 3 M HCl (20 ml) and extracted with ether to give a red oil (0.99 g) which was purified by short column chromatography using gradient elution starting with ether-petrol (3:7) as eluant. *1-Benzyloxymethyl-3-butyl-3-phenylselenopyrrolidin-2-one* (143) was obtained as a pale yellow oil (0.31 g, 37%), δ 0.82 (3H, t, J 7.1 Hz, $CH_2\underline{C}H_3$), 1.17-1.81 (6H, m, $(C\underline{H}_2)_3Me$),

2.05 (2H, m, $C\underline{H}_2CN$), 3.14 (2H, m, $C\underline{H}_2N$), 4.39 and 4.50 (2H, ABq, *J* 11.8 Hz, $NC\underline{H}_2O$), 4.57 and 4.75 (2H, ABq, *J* 10.7 Hz, $OC\underline{H}_2Ph$), 7.18-7.59 (10H, m, aromatic H); $\nu_{max.}$ 2965, 2940, 2880, 1705, 1423, 1273br, 1070br, and 696 cm^{-1}; *m/z* 417 (M^+, 4%) and 91 (100%). Also eluted was *1-benzyloxymethyl-3-phenylselenopyrrolidin-2-one* (142) as an oil (0.16 g, 22%), δ 1.96-2.08 (1H, m, $C\underline{H}CN$), 2.27-2.40 (1H, m, $C\underline{H}CN$), 3.13-3.32 (2H, m, $C\underline{H}_2N$), 3.82 (1H, dd, *J* 8,4 Hz, $C\underline{H}Se$), 4.36 and 4.41 (2H, ABq, *J* 10.5 Hz, $NC\underline{H}_2O$), 4.64 and 4.76 (2H, ABq, *J* 12.6 Hz, $OC\underline{H}_2Ph$), 7.19-7.62 (10H, m, aromatic H); $\nu_{max.}$ 2935, 2870, 1705, 1420, 1268br, 1064br, 907, and 690 cm^{-1}; *m/z* 361 (M^+, 3%) and 98 (100%).

Attempted Deprotection of 1-Benzyloxymethyl-3-butyl-3-phenylselenopyrrolidin-2-one (143)

Method 1

A mixture of the lactam (143) (140 mg, 0.34 mmol) and 1$\underline{M}$ HCl (2 ml) in THF (3 ml) was stirred at 25°. The reaction was monitored by tlc which indicated that for varying reaction times (5-40 h) either very little deprotection occurred or a complex mixture of products was formed.

Method 2

A solution of the lactam (210 mg, 0.5 mmol) in $CHCl_3$ (2 ml) was added dropwise to a solution of iodine (250 mg, 1 mmol) and hexamethyldisilane (0.1 ml, 0.5 mmol)[127] in $CHCl_3$ (11 ml) and the resulting mixture was refluxed for 6 h. Water (30 ml) was added with vigorous stirring and the mixture was extracted with ether. The combined extracts were washed with aqueous $Na_2S_2O_3$ solution, dried ($MgSO_4$) and evaporated to give a yellow oil (210 mg). Purification by chromatography using gradient elution with ether-petrol gave a mobile yellow oil (120 mg, 97%) identified as benzylphenylselenide, δ 4.00 (1H, s, $C\underline{H}Ph$), 4.32 (1H, s, $C\underline{H}Ph$), 7.05-7.45 (10H, m, aromatic H);

$\nu_{max.}$ 3065, 3035, 2930, 1494, 1478, 1454, 1439, 1162, and 690 cm^{-1}; *m/z* 248 ($^{\bullet}M^{+}$, 11%) and 91 (100%), and an oil (56 mg) shown by tlc to be a complex mixture of products.

Method 3

BBr_3 (0.2 ml, 2.1 mmol) in CH_2Cl_2 (4 ml) was added to a solution of the lactam (210 mg, 0.5 mmol) in CH_2Cl_2 (10 ml) at 0°. The resulting gelatinous mixture was stirred at 25° for 17 h, poured into water (20 ml) and extracted with ether to give a brown oil (210 mg) shown by tlc to be a complex mixture. Chromatography using ether-petrol (1:3) as eluant gave benzyl bromide fractions followed by a pale yellow oil (35 mg, 21%) tentatively identified as *3-butyl-1-methoxymethyl-3-phenylselenopyrrolidin- 2-one* (144), δ 0.83 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 1.15-1.55 (4H, m, $(\underline{CH}_2)_2Me$), 1.62-1.87 (2H, m, $\underline{CH}_2Pr$), 2.13 (2H, m, $\underline{CH}_2CN$), 2.98-3.21 (2H, m, $\underline{CH}_2N$), 3.24 (3H, s, $O\underline{CH}_3$), 4.45 and 4.61 (2H, ABq, *J* 12.6 Hz, $N\underline{CH}_2O$), 7.18-7.61 (5H, m, aromatic H); $\nu_{max.}$ 2960, 2935, 1698, 1272br, 1097, 1073, 911, and 692 cm^{-1}; *m/z* 341 (M^{+}, 7%) and 152 (100%). Finally, an unidentified yellow oil (38 mg) was eluted.

1-(Prop-2-enyl)pyrrolidin-2-one (145)

A solution of pyrrolidin-2-one (140) (7.6 ml, 0.1 mol) in THF (20 ml) was added during 25 min to a suspension of NaH (50% dispersion, washed with THF (2x20 ml)) (5.3 g, 0.11 mol) in THF (50 ml) at 0°. After stirring the mixture for a further 75 min, allyl bromide (12 ml, 0.139 mol) in THF (25 ml) was added during 30 min, the ice-bath was removed and the mixture was refluxed for 22 h. The resulting mixture was filtered through Celite and the filtrate was concentrated to give an orange oil (11.98 g). Distillation *in vacuo* gave 1-(prop-2-enyl)pyrrolidin-2-one (145) as an oil (10.66 g,

88%), bp. 52-6°/0.9 mmHg (lit.,[128] 115-120°(bath)/12 mmHg), δ 1.93 (2H, tt, *J* 7.9, 7.5 Hz, $C\underline{H}_2CN$), 2.30 (2H, t, *J* 8.1 Hz, $C\underline{H}_2CO$), 3.26 (2H, t, *J* 7.5 Hz, $C\underline{H}_2N$), 3.79 (2H, d, *J* 5.7 Hz, $NC\underline{H}_2CH$), 5.08 (2H, m, $CH=C\underline{H}_2$), 5.56-5.69 (1H, m, $C\underline{H}=CH_2$); $\nu_{max.}$ 2980, 1694, 1645, 1493, 1462, 1417, 1262, and 926 cm^{-1}; *m/z* 125 (M^+, 43%) and 70 (100%).

Attempted Isomerization of 1-(Prop-2-enyl)pyrrolidin-2-one (145)

Method 1[129]

A mixture of lactam (145) (135 mg, 1.08 mmol) and $KOBu^t$ (120 mg, 1.08 mmol) in DMSO (4 ml) was heated at 100° for 25 min and then poured into water (20 ml). Extraction with ether gave a yellow oil (51 mg) shown by tlc to be a complex mixture of products.

Method 2[130]

A mixture of the lactam (188 mg, 1.5 mmol), 10% palladium on charcoal (20 mg) and *p* -toluenesulphonic acid (20 mg) in methanol (3.5 ml) was refluxed for 24 h, filtered through Celite and evaporated to give an oil (210 mg) shown by ^1H nmr and tlc to be a mixture of starting material and *p* -toluenesulphonic acid.

Method 3[49]

A mixture of the lactam (130 mg, 1.04 mmol), rhodium(III)chloride trihydrate (18.8 mg, 0.071 mmol) and DABCO (62 mg, 0.55 mmol) in EtOH-water (9:1) (5 ml) was refluxed for 17 h, poured into water (20 ml) and extracted with ether to give a pale yellow oil (142 mg) shown by tlc and ^1H nmr to be a clean mixture of 1-(prop-1-enyl)pyrrolidin-2-one (146) (E:Z ratio *ca.* 12:1) δ (E-isomer) 1.72 (3H, dd, *J* 6.6, 1.3 Hz, $CHC\underline{H}_3$), 2.08 (2H, tt, *J* 7.5 Hz, $C\underline{H}_2CN$), 2.47 (2H, t, *J* 8.1 Hz, $C\underline{H}_2CO$), 3.49 (2H, t, *J* 7 Hz, $C\underline{H}_2N$), 4.96 (1H, m, *J* 14.1, 6.6 Hz, $C\underline{H}CH_3$), 6.87 (1H, dd, *J* 14.1, 1.3 Hz, $C\underline{H}N$);

δ (Z-isomer) 1.76 (3H, obscured dd, *J* 6.6, 1.8 Hz, $CHC\underline{H}_3$), 2.09 (2H, m, $C\underline{H}_2CN$), 2.42 (2H, obscured t, *J* 7.5 Hz, $C\underline{H}_2CO$), 3.78 (2H, t, *J* 7 Hz, $C\underline{H}_2N$), 4.95 (1H, m, $C\underline{H}CH_3$), 6.35 (1H, brd, *J* 9 Hz, $C\underline{H}N$). This crude material was dissolved in methanol (1 ml) and 3% HCl-methanol (2 ml) was added. After several days at 25° considerable starting material remained (tlc) but after a week a complex mixture of products had been formed.

Methylation of 1-Trimethylsilylpyrrolidin-2-one (147)

Trimethylsilyl chloride (1.8 ml, 14.2 mmol) was added to a solution of pyrrolidin-2-one (140) (1 ml, 13.2 mmol) and triethylamine (2 ml, 14.3 mmol) in benzene (22 ml) and the resulting mixture was refluxed for 2.5 h. THF (20 ml) was added, the mixture was cooled to -78° and LDA (42 mmol) in THF (20 ml) was added slowly. After 1 h, iodomethane (4.1 ml, 65.9 mmol) was added and the resulting mixture was allowed to warm gradually to 0° during 1.5 h. Acidification with 3M HCl (5 ml) followed by extraction with ether gave an oil (1.85 g) shown by tlc to be a complex mixture of products. Purification by flash chromatography eluting with ether-methanol (95:5), gave a pale yellow solid (563 mg, 25%) identified as *3-methyl-3-trimethylsilylpyrrolidin-2-one* (148). A portion of this solid was crystallized from $CHCl_3$ to give plates mp. 126-8°, δ 0.10 (9H, s, $Si(C\underline{H}_3)_3$), 1.24 (3H, s, $CC\underline{H}_3$), 1.92 (1H, m, $C\underline{H}CN$), 2.27 (1H, m, $C\underline{H}CN$), 3.20 (1H, m, *J* 9.3, 7.9 Hz, $C\underline{H}N$), 3.30 (1H, m, $C\underline{H}N$), 5.77 (1H, brs, NH); $\nu_{max.}$ 3455, 3200br, 2955, 1695sh, 1683, 1455, 1413, and 1249br cm^{-1}; *m/z* 171 (M^+, 34%) and 73 (100%) (Found: M^+ 171.1079. $C_8H_{17}NOSi$ requires M^+ 171.1079). Also eluted was 3,3-dimethylpyrrolidin-2-one (149) as a semi-solid (254 mg, 17%), δ 1.15 (6H, s, $C(C\underline{H}_3)_2$), 1.93 (2H, t, *J* 7.4 Hz, $C\underline{H}_2CN$), 3.29 (2H, t, *J* 7.4 Hz, $C\underline{H}_2N$), 7.20 (1H, brs, NH).

5R-1-Benzoyl-5-benzylpyrrolidin-2-one (150)

A solution of lactam (116) (780 mg, 4.45 mmol) in THF (4.5 ml) was added to a suspension of 50% NaH (washed with (2x5 ml) THF) (240 mg, 5 mmol) in THF (12 ml) at 0° and the resulting slurry was stirred for 30 min. Benzoyl chloride (685 mg, 4.87 mmol) in THF (2.5 ml) was then added and, after 35 min at 0°, the mixture was allowed to warm to 25°. Water (20 ml) was added and the product was extracted with ether to give an oil which was purified by flash chromatography using ether-petrol (9:1) as eluant. *5R-1-Benzoyl-5-benzylpyrrolidin-2-one* (150) was obtained as a viscous oil (950 mg, 76%), $[\alpha]_D^{20}$ +164.3 (c 0.375, $CHCl_3$), δ 1.89-2.18 (2H, m, CH_2CN), 2.38-2.44 (2H, m, CH_2CO), 2.90 (1H, dd, *J* 13.2,8.2Hz, CHPh), 3.30 (1H, dd, *J* 13.2, 3 Hz, CHPh), 4.73 (1H, m, *J* 4 Hz, CHN), 7.25-7.65 (10H, m, aromatic H); $\nu_{max.}$ 3040, 1752, 1680, 1453, 1350, 1300br, 1229, and 693 cm^{-1}; *m/z* 279 (M^+, 32%) and 105 (100%) (Found: M^+ 279.1262. $C_{18}H_{17}NO_2$ requires M^+ 279.1259).

Phenylselenenylations of N*-Protected Lactams*

I With 5R-1-Benzoyl-5-benzylpyrrolidin-2-one (150)

A solution of lactam (150) (490 mg, 1.77 mmol) and HMPA (0.3 ml, 1.72 mmol) in THF (10 ml) was added during 15 min to LDA (2.1 mmol) in THF (5 ml) at -78° and the resulting solution was stirred for 50 min. Phenylselenenyl chloride (410 mg, 2.14 mmol) in THF (6 ml) was then added and the mixture was allowed to warm to 0° during 2 h. 3% HCl-methanol (3 ml) was added and the mixture was poured into 10% HCl (15 ml) and extracted with ether to give a crude oil (808 mg). Short column chromatography using ether-petrol (3:7) as eluant gave *5S-1-benzoyl-3,3-bis(phenylseleno)pyrrolidin-2-one* (152) as an oil (158 mg, 15%), $[\alpha]_D^{20}$ -71.5 (c 0.36, $CHCl_3$); δ 2.30 (1H,dd, *J* 14.7, 7 Hz, CHCN), 2.40 (1H, dd, *J* 14.7, 8.2 Hz, CHCN), 2.70 (1H, dd, *J* 13.3,

8.8 Hz, CHPh), 3.21 (1H, dd, *J* 13.3, 3.3 Hz, CHPh), 4.43 (1H, qd, *J* 8.4, 3.3 Hz, CHN), 6.97-7.78 (20H, m, aromatic H); $\nu_{max.}$ 3070, 2935, 1737, 1687, 1440, 1274br, 1205br, 693, and 657 cm^{-1}; *m/z* 591 (M^+, 3%) and 105 (100%) (Found: M^+ 591.0214. $C_{30}H_{25}NO_2{}^{80}Se_2$ requires M^+ 591.0216), followed by *1-benzoyl-5-benzyl-3-phenylselenopyrrolidin-2-one* (151) as an oil (237 mg, 31%), δ (*ca* 2:1 ratio) 2.08-2.25 (1H, m, CHCN), 2.37-2.47 (0.67H, m, CHCN), 2.52-2.64 (0.33H, m, CHCN), 2.79 (0.33H, dd, *J* 13, 9 Hz, CHPh), 2.92 (0.67H, dd, *J* 13.5, 7.5 Hz, CHPh), 3.27 (0.67H, dd, *J* 13.5, 3.8 Hz, CHPh), 3.42 (0.33H, dd, *J* 13, 4 Hz, CHPh), 3.80 (0.67H, dd, *J* 7.5, 6.5 Hz, CHSe), 3.92 (0.33H, dd, *J* 8.5, 5 Hz, CHSe), 4.55 (0.67H, m, CHN), 4.69 (0.33H, m, CHN), 7.18-7.74 (15H, m, aromatic H); $\nu_{max.}$ 3070, 3035, 1743, 1681, 1453, 1349, 1290br, 1228, and 690 cm^{-1}; *m/z* 435 (M^+, 2%) and 105 (100%) (Found: M^+ 435.0738. $C_{24}H_{21}NO_2{}^{80}Se$ requires M^+ 435.0737). Starting lactam (116) was also recovered (78 mg, 16%).

II With 1-Benzoyl-5-benzyl-3-phenylselenopyrrolidin-2-one(151)

A solution of lactam (151) (200 mg, 0.46 mmol) and HMPA (0.08 ml, 0.46 mmol) in THF (3 ml) was added to LDA (0.55 mmol) in THF (2.5 ml) at -78° and the resulting solution was stirred for 1 h. 1-Bromoheptane (100 mg, 0.56 mmol) in THF (2 ml) was then added and, after being kept at -78° for 3 h, the mixture was allowed to gradually attain room temperature and was stirred overnight. The reaction was worked-up as in the previous experiment to give a crude product shown to be a complex mixture by tlc. Chromatography,using gradient elution with ether-petrol (2:3) initially, gave debenzoylated selenide (155) as the only recognisable product (78 mg, 51%).

Alternative Preparation of 1-Benzoyl-5-benzyl-3-phenylselenopyrrolidin-2-one (151)

Benzoyl chloride (0.17 ml, 1.46 mmol) was added to a solution of lactam (155) (380 mg, 1.16 mmol) and triethylamine (0.25 ml, 1.79 mmol) in CH_2Cl_2 (5 ml) at 0°. After 15 min the mixture was brought to room temperature and was stirred for 19 h, poured into water (20 ml) and extracted with ether. The crude oil obtained was purified by flash chromatography using ether-petrol (1:3) as eluant to give the desired lactam (151) (182 mg, 36%) and recovered starting material (155) (174 mg, 46%). Using a stronger base (*eg* . NaH) led to some deprotonation of the selenium bearing carbon atom and C-3 benzoylated products which were not characterized.

III With N *- Silylated Lactams*

Method 1

A solution of lactam (116) (438 mg, 2.5 mmol) in THF (4 ml) was added to a suspension of 50% NaH (132 mg, 2.75 mmol) in THF (14 ml) at 0° and the resulting mixture was stirred for 25 min. Trimethylsilyl chloride (3.2 ml, 25.2 mmol) was then added and the mixture was refluxed gently for 5 h. The volatile components were evaporated under a stream of nitrogen and THF (12 ml) was added to the residue. After being cooled to -78°, LDA (5.5 mmol) was added to the mixture which was stirred for a further 40 min before the addition of phenylselenenyl chloride (522 mg, 2.74 mmol) in THF (2 ml). The reaction was stirred for 15 min at -78° and was allowed to warm to 0° during 30 min before the addition of 3 M HCl (4 ml). Aqueous extraction with ether gave a brown oil which was purified by flash chromatography using ether-petrol (1:1) as eluant to give the bis-selenenylated product (154) (67 mg, 6%), the mono-selenenylated lactam (155) (78 mg, 9%) and starting material (116) (266 mg, 66%) (see later for data for 154 and 155).

Method 2

A solution of lactam (116) (218 mg, 1.24 mmol) in THF (4 ml) was added

to a suspension of 50% NaH (70 mg, 1.46 mmol) in THF (7 ml) at 0° and the resulting mixture was stirred for 35 min. Trimethylsilyl choride (0.32 ml, 2.5 mmol) in THF (2 ml) was then added and the mixture was allowed to warm to 25° and was stirred for 6 h. After being cooled to -78°, LDA (3.9 mmol) was added during 5 min and the mixture was stirred for a further 30 min before the addition of phenylselenenyl chloride (530 mg, 2.77 mmol) in THF (4 ml). The reaction was allowed to warm gradually to 25° during 90 min, water (3 ml) was added and the product was extracted with ether to give an oil shown by tlc to be complex mixture. Short column chromatography using gradient elution with ether-petrol mixtures gave the selenides (154) (82 mg, 14%) and (155) (59 mg, 14%) along with starting material (116) (61 mg, 28%).

*5-Benzyl-1-*tert*-butyldimethylsilyl-3-phenylselenopyrrolidin-2-one* (156)

A solution of *tert* -butyldimethylsilyl chloride (250 mg, 1.66 mmol) in benzene (2 ml) was added to a solution of lactam (155) (470 mg, 1.42 mmol) and triethylamine (0.4 ml, 2.87 mmol) in benzene (10 ml) at 10°. The mixture was allowed to warm to 25° and was then stirred for 16 h. Purification by filtration chromatography eluting with ether gave, after evaporation, 5-benzyl-1- *tert* -butyldimethylsilyl-3-phenylselenopyrrolidin-2-one (156) as a pale yellow oil (519 mg, 75%) contaminated with some *tert* -butyldimethylsilanol, δ (*ca* 3:2 ratio of diastereoisomers) 0.36, 0.41. 0.44, and 0.45 (6H, all s, $Si(C\underline{H}_3)_2$), 0.98 and 1.05 (9H, both s, $Si(C\underline{H}_3)_3$), 1.91-2.16 (1H, m, C<u>H</u>CN), 2.20-2.87 (2H, m, C<u>H</u>CN and C<u>H</u>Ph), 2.94 (0.6H, dd, *J* 13.5, 4 Hz, C<u>H</u>Ph), 3.10 (0.4H, dd, *J* 13, 2 Hz, C<u>H</u>Ph), 3.59-3.73 (0.6H, m, C<u>H</u>N), 3.76-3.96 (1.4H, m, C<u>H</u>Se and C<u>H</u>N), 7.05-7.76 (10H, m, aromatic H).

Alternative Preparation of 5<u>S</u> *-5-Benzyl-3,3-bis(phenylseleno)pyrrolidin-2-one* (154)

The foregoing lactam (156) (267 mg, 0.6 mmol) in THF (1.5 ml) was added during 6 min to LDA (0.9 mmol) in THF (2 ml) at -78°. After 35 min, phenylselenenyl chloride (145 mg, 0.76 mmol) in THF (1.5 ml) was added and the mixture was kept at -78° for 15 min, brought to -20° and was stirred for a further 15 min. After being allowed to warm to 0°, tetra n-butylammonium fluoride (1 M in THF, 1.2 ml) was added slowly and the mixture was stirred for 17 h at 25°. Aqueous work-up followed by flash chromatography using ether-$CHCl_3$ (1:4) as eluant gave the title compound (154) (140 mg, 48%).

5R-5-Benzyl-1-(tert-butyldimethylsilyl)pyrrolidin-2-one (157)

BuLi (1.6 M, 3.7 ml, 5.92 mmol) was added dropwise to a solution of lactam (116) (1.041 g, 5.94 mmol) in THF (25 ml) at 0°. After 30 min, *tert*-butyldimethylsilyl chloride (0.89 g, 5.90 mmol) in THF (8 ml) was added and the mixture was allowed to warm to 25° and was stirred overnight. The solvents were removed *in vacuo*, ether was added to the residue and the mixture was filtered through Celite. Evaporation gave a yellow oil which was purified by flash chromatography, using ether-petrol (3:1) as eluant, to give 5R *-5-benzyl-1-(tert-butyldimethylsilyl)pyrrolidin-2-one* (157) as an amorphous solid (1.374 g, 80%). A portion was crystallized from ether at low temperature to give an analytical sample, mp. 53-6°, $[\alpha]_D^{20}$ +63.6 (c 0.54, CCl_4), δ 0.25 and 0.33 (6H, both s, $Si(CH_3)_2$), 0.92 (9H, s, $Si(CH_3)_3$), 1.71-1.92 (2H, m, CH_2CN), 2.04-2.15 (1H, ddd, *J* 16.8, 8.4, 2.2 Hz, CHCO), 2.25-2.36 (1H, m, CHCO), 2.48 (1H, dd, *J* 13.3, 10.6 Hz, CHPh), 2.84 (1H, dd, *J* 13.3, 3.3 Hz, CHPh), 3.68-3.77 (1H, m, CHN), 7.05-7.27 (5H, m, aromatic H); $\nu_{max.}$ 2955, 1691, 1378, 1234, 1108br, 950, and 702 cm^{-1}; *m/z* (CI) 290 (M^++1, 5%) and 75 (100%) (Found: C, 70.2; H, 9.2; N, 5.2. $C_{17}H_{27}NOSi$ requires C, 70.5; H, 9.4; N, 4.8%).

5-Benzyl-3-butyl-3-phenylselenopyrrolidin-2-one (158)

A solution of the silylated lactam (157) (336 mg, 1.16 mmol) in THF (1.5 ml) was added to LDA (2.04 mmol) in THF (4 ml) at -78° and the resulting solution was stirred for 50 min. Phenylselenenyl chloride (280 mg, 1.46 mmol) in THF (2 ml) was added, followed by 1-iodobutane (260 mg, 1.41 mmol) in THF (2 ml) after 35 min at -78°. The resulting mixture was kept at -78° for 1.5 h and was allowed to warm gradually to room temperature overnight after which it was poured into 3 M HCl (20 ml).† This mixture was stirred for 30 min and extracted with ether to give an oil which, after flash chromatography eluting with ether-petrol (3:1), gave *5-benzyl-3-butyl-3-phenylselenopyrrolidin-2-one* (158) as an oil (231 mg, 52%), δ (*ca* 7:2 ratio) 0.92 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 1.23-1.55 (4H, m, $(\underline{CH}_2)_2$), 1.71-1.91 (2H, m, $\underline{CH}_2Pr$), 1.99 (0.22H, dd, *J* 13, 7.5 Hz, $\underline{CH}CN$), 2.12 (0.78H, dd, *J* 15, 5 Hz, $\underline{CH}CN$), 2.27-2.53 (1.78H, m, $\underline{CH}CN$ and $\underline{CH}_2Ph$), 2.47 (0.78H, dd, *J* 15, 7.5 Hz, $\underline{CH}CN$), 2.66 (0.22H, dd, *J* 13, 7 Hz, $\underline{CH}Ph$), 2.77 (0.22H, dd, *J* 13, 6 Hz, $\underline{CH}Ph$), 3.50 (0.22H, m, $\underline{CH}N$), 3.69 (0.78H, m, $\underline{CH}N$), 6.11 (0.22H, brs, NH), 6.39 (0.78H, brs, NH), 7.01-7.80 (10H, m, aromatic H); $\nu_{max.}$ 3440, 3200br, 2960, 2935, 1714, 1698, and 693 cm^{-1}; *m/z* 387 (M^+, 9%) and 91 (100%) (Found: M^+ 387.1105. $C_{21}H_{25}NO^{80}Se$ requires M^+ 387.1101).

Methylation of 5R-*5-Benzylpyrrolidin-2-one* (116)

BuLi (1.7 M, 2.3 ml, 3.91 mmol) was added to a solution of the lactam (116) (232 mg, 1.32 mmol) and TMEDA (0.6 ml, 3.98 mmol) in THF (4 ml) at 0° and the solution was stirred for 1 h. Iodomethane (1 ml, 16.1 mmol) was then added dropwise and the resulting mixture was allowed to warm to 25° during 2.5 h before being poured into water (10 ml) and extracted with CH_2Cl_2.

† Alternatively, the crude mixture was cooled to 0°, 1 M tetra n-butylammonium fluoride (1-2 eq.) was added and the mixture was stirred for several hours until desilylation was complete (tlc).

The residue was purified by short column chromatography using ether-methanol (19:1) as eluant to give *5-benzyl-1,3-dimethylpyrrolidin-2-one* (165) as an oil (125 mg, 47%), δ (*ca* 1:1 ratio) 1.09 and 1.13 (3H, both d, *J* 7 Hz, $CHC\underline{H}_3$), 1.19-1.41 and 1.56-1.70 (1H, both m, C<u>H</u>CN), 1.98-2.27 (1.5H, m, C<u>H</u>CN and $C\underline{H}CH_3$), 2.36 (0.5H, m, $C\underline{H}CH_3$), 2.53 (0.5H, dd, *J* 14, 9 Hz, C<u>H</u>Ph), 2.66 (0.5H, dd, *J* 13.5, 8.5 Hz, C<u>H</u>Ph), 2.90(3H, brs, $NC\underline{H}_3$), 2.97 (0.5H, dd, *J* 13.5, 4 Hz, C<u>H</u>Ph), 3.20 (0.5H, dd, *J* 13.5, 4 Hz, C<u>H</u>Ph), 3.58-3.76 (1H, m, C<u>H</u>N), 7.13-7.41 (5H,m, aromatic H); $\nu_{max.}$ 2970, 2935, 1697, 1455, 1428, 1400, 1310, and 695 cm^{-1}; *m/z* (CI) 204 (M^++1 , 45%) and 112 (100%) along with 5<u>R</u>-*5-benzyl-1-methylpyrrolidin-2-one* (166) as needles (78 mg, 31%), mp. 70-1° (pentane), $[\alpha]_D^{20}$ +85.0 (c 0.78, $CHCl_3$); δ 1.70-1.81 (1H, m, C<u>H</u>CN), 1.93-2.06 (1H, m, C<u>H</u>CN), 2.15-2.22 (2H, m, $C\underline{H}_2CO$), 2.65 (1H, dd, *J* 13.5, 8.1 Hz, C<u>H</u>Ph), 2.89 (3H, s, $NC\underline{H}_3$), 3.04 (1H, dd, *J* 13.7, 4.4 Hz, C<u>H</u>Ph), 3.76 (1H, m, *J* 4 Hz, C<u>H</u>N), 7.15-7.37 (5H, m, aromatic H); $\nu_{max.}$ 3035, 2930, 1705sh, 1700, 1454, 1423, 1400, 1308, 1110br, and 697 cm^{-1}; *m/z* (CI) 190 (M^++1 , 40%) and 98 (100%) (Found: C, 76.4; H, 7.9; N, 7.3. $C_{12}H_{15}NO$ requires C, 76.15; H, 8.0; N, 7.4%).

Phenylselenenylation of 5<u>R</u>-*5-Benzylpyrrolidin-2-one* (116)

General Procedure (See Table 3.1)

BuLi (2 molar eq.) was added dropwise to a solution of 5<u>R</u>-5-benzyl-pyrrolidin-2-one (116) and TMEDA (2 molar eq.) in THF at 0° (conc. *ca* 0.1-0.15 <u>M</u>). The resulting dark red solution was stirred for 1 h at 0°, cooled to -78° and phenylselenenyl chloride (1-1.2 molar eq.) in THF was added. After 15 min, the yellow mixture was brought to 0°, quenched with water and extracted with ether. The ethereal extracts were washed several times with brine, dried ($MgSO_4$) and evaporated to give an oil. Purification by short column chromatography using gradient elution starting with ether-

petrol (1:1) gave, in order of elution, diphenyl diselenide, 5S-*5-benzyl-3,3-bis(phenylseleno)pyrrolidin-2-one* (154) as a solid mp. 135.5-138° (ether-CH_2Cl_2), $[\alpha]_D^{20}$ -19.1 (c 1.06, $CHCl_3$), δ 2.15-2.27 (2H, m, CH_2CN), 2.43-2.54 (2H, m, CH_2Ph), 3.45 (1H, m, CHN), 5.60 (1H, brs, NH), 6.93-7.74 (15H, m, aromatic H); $\nu_{max.}$ 3425, 3010, 1704sh, 1699, 1478, 1439, 1409, and 694 cm^{-1}; *m/z* 487 (M^+ , 2%) and 330 (100%) (Found: C, 56.7; H, 4.5; N, 3.0. $C_{23}H_{21}NOSe_2$ requires C, 56.9; H, 4.4; N, 2.9%), *5-benzyl-3-phenylselenopyrrolidin-2-one* (155) as a separable mixture of diastereoisomeric oils, δ (less polar) 2.33 (2H, ψ t, *J* 6.4 Hz, CH_2CN), 2.66 (1H, dd, *J* 13.5, 7.9 Hz, CHPh), 2.79 (1H, dd, *J* 13.5, 5.6 Hz, CHPh), 3.65 (1H, m, *J* 6.4 Hz, CHN), 3.84 (1H, t, *J* 6.3 Hz, CHSe), 6.10 (1H, brs, NH), 7.07-7.72 (10H, m, aromatic H); $[\alpha]_D^{20}$ +41.3 (c 0.53, $CHCl_3$), $\nu_{max.}$ 3440, 3200br, 2935, 1711sh, 1700, 1479, 1442, and 692 cm^{-1}; *m/z* (CI) 332 (M^++1 , 73%) and 232 (100%); δ (more polar) 1.96 (1H, ddd, *J* 13.8, 7.6, 6 Hz, CHCN), 2.46 (1H, dd, *J* 13.4, 8.3 Hz, CHPh), 2.63 (1H, dd, *J* 13.4, 5.9 Hz, CHPh), 2.74 (1H, ddd, *J* 13.9, 9.6, 7.4 Hz, CHCN), 3.81 (1H, m, *J* 7 Hz, CHN), 3.92 (1H, dd, *J* 9.6, 7.5 Hz, CHSe), 6.10 (1H, brs, NH), 7.03-7.76 (10H, m, aromatic H); $[\alpha]_D^{20}$ +45.8 (c 1.4, $CHCl_3$); $\nu_{max.}$ 3440, 3200br, 2930, 1715sh, 1702, 1479, 1442, 1411br, and 693 cm^{-1}; *m/z* (CI) 332 (M^++1 , 38%) and 84 (100%), and starting material (116).

Phenylsulphenylation of 5R-*5-Benzylpyrrolidin-2-one* (116)

BuLi (1.7 M, 8.6 ml) was added dropwise to a solution of lactam (116) (1.23 g, 7.02 mmol) and TMEDA (2.1 ml, 13.9 mmol) in THF (50 ml) at 0°. The resulting solution was stirred for 1 h at 0° and cooled to -78° after which diphenyl disulphide (1.71 g, 7.83 mmol) in THF (15 ml) was added. The mixture was allowed to attain room temperature during 2.5 h, water (10 ml) was added and the aqueous phase was extracted with ether to give a crude

oil (2.53 g). Purification by flash chromatography using ether as eluant gave, in order of elution, diphenyl disulphide (0.74 g, 43%), 5S-*5-benzyl-3,3-bis(phenylthio)pyrrolidin-2-one* (169) as a solid (0.125 g, 4.5%), mp. 146-7° (CH_2Cl_2), $[\alpha]_D^{20}$ -43.9 (c 0.14, CCl_4); δ 2.15 (1H, dd, *J* 14.2, 7.5 Hz, CHCN), 2.32 (1H, dd, *J* 13.4, 9 Hz, CHPh), 2.42 (1H, dd, *J* 14.2, 6.6 Hz, CHCN), 2.61 (1H, dd, *J* 13.5, 5 Hz, CHPh), 3.63 (1H, m, CHN), 5.68 (1H, brs, NH), 7.03-7.72 (15H, m, aromatic H); $\nu_{max.}$ 3425, 3065, 1725, 1707sh, 1439, and 690 cm^{-1}; *m/z* (CI) 392 (M^++1, 32%) and 284 (100%) (Found: C, 70.5; H, 5.4; S, 16.3. $C_{23}H_{21}NOS_2$ requires C, 70.55; H, 5.4; S, 16.4%), *5-benzyl-3-phenylthiopyrrolidin-2-one* (170) as a separable mixture of diastereoisomers: (less polar) (0.275 g, 14%), $[\alpha]_D^{20}$ -12.0 (c 0.25, $CHCl_3$); δ 2.38-2.43 (2H, m, CH_2CN), 2.82 (1H, dd, *J* 13.2, 7.5 Hz, CHPh), 2.93 (1H, dd, *J* 13.3, 5.7 Hz, CHPh), 3.81-3.93 (1H, m, CHN), 3.85 (1H, dd, *J* 8, 6.2 Hz, CHS), 6.50 (1H, brs, NH), 7.26-7.65 (10H, m, aromatic H); $\nu_{max.}$ 3445, 3210br, 1725sh, 1707, 1484, 1443, and 692 cm^{-1}; *m/z* 283 (M^+, 38%) and 91 (100%) (Found: M^+ 283.1032. $C_{17}H_{17}NOS$ requires M^+ 283.1031); (more polar) (0.229 g, 12%), mp. 90-1° (ether-petrol), $[\alpha]_D^{20}$ -102.6 (c 0.30, $CHCl_3$); δ 1.88 (1H, ddd, *J* 13.7, 8.9, 6.7 Hz, CHCN), 2.45 (1H, dd, *J* 13.3, 8.8 Hz, CHPh), 2.67-2.78 (2H, m, CHCN and CHPh), 3.77 (1H, m, CHN), 3.83 (1H, dd, *J* 9.3, 8.8 Hz, CHS), 5.62 (1H, brs, NH), 7.08-7.56 (10H, m, aromatic H); $\nu_{max.}$ 3440, 3210br, 3065, 2935, 1721sh, 1708, 1442, 1265br, and 692 cm^{-1}; *m/z* 283 (M^+, 29%) and 82 (100%) (Found: C, 72.0; H, 6.05; N, 5.0; S, 11.5. $C_{17}H_{17}NOS$ requires C, 72.0; H, 6.05; N, 4.9; S, 11.3%), and starting material (116) (0.27 g, 22%).

Alkylation Reactions of 5-Benzyl-3-phenylselenopyrrolidin-2-one (155)

General Procedure

The base (2 molar eq.) (see Table 3.2) was added to a solution of

lactam (155) in THF (or ether) at 0° (concentration *ca* 0.1 M). After 1 h, the alkylating agent (1-20 molar eq.) was added and the resulting mixture was stirred at 0° for several hours and allowed to warm gradually to 25°. Water was added to quench the reaction and the aqueous phase was extracted with ether (or CH_2Cl_2). The crude product was purified by short column chromatography using gradient elution with ether-petrol mixtures.

With iodomethane:

5-Benzyl-3-methyl-3-phenylselenopyrrolidin-2-one (174a)

(101 mg), δ (less polar diastereoisomer) 1.59 (3H, s, CCH_3), 1.87 (1H, dd, *J* 13.7, 8.8 Hz, CHCN), 2.47 (1H, dd, *J* 13.7, 5.6 Hz, CHCN), 2.61 (1H,dd, *J* 13.7, 8.4 Hz, CHPh), 2.80 (1H, dd, *J* 13.3, 5.3 Hz, CHPh), 3.58 (1H, m, CHN), 5.65 (1H, brs, NH), 7.09-7.70 (10H, m, aromatic H); $\nu_{max.}$ 3440, 2930, 1717, 1700, 1441, 1405, and 693 cm^{-1}; *m/z* 345 (M^+, 7%) and 91 (100%) (Found: M^+ 345.0626. $C_{18}H_{19}NO^{80}Se$ requires M^+ 345.0631); δ (more polar diastereoisomer) 1.59 (3H, s, CCH_3), 2.22 (1H, dd, *J* 14.5, 5 Hz, CHCN), 2.37 (1H, dd, *J* 14.5, 7.8 Hz, CHCN), 2.47 (1H, dd, *J* 13.2, 8.4 Hz, CHPh), 2.59 (1H, dd, *J* 13.3, 6.2 Hz, CHPh), 3.76 (1H, m, CHN), 5.93 (1H, brs, NH), 7.04-7.79 (10H, m, aromatic H); $\nu_{max.}$ 3445, 1716, 1701, 1458, 1412, and 693 cm^{-1}; *m/z* 345 (M^+, 10%) and 91 (100%) (Found: M^+ 345.0626. $C_{18}H_{19}NO^{80}Se$ requires M^+ 345.0631).

5-Benzyl-1-methyl-3-phenylselenopyrrolidin-2-one (175a)

(76 mg) δ (less polar diastereoisomer) 2.05-2.26 (2H, m, CH_2CN), 2.54 (1H, dd, *J* 13.5, 8 Hz, CHPh), 2.81 (3H, s, NCH_3), 2.90 (1H, m, CHPh), 3.35 (1H, m, CHN), 3.66 (1H, dd, *J* 8.8, 5 Hz, CHSe), 7.05-7.64 (10H, m, aromatic H); $[\alpha]_D^{20}$ +41.3 (c 0.525, $CHCl_3$); $\nu_{max.}$ 3075, 3035, 2935, 1699, 1480, 1442, 1400, 1315br, 1100, and 695 cm^{-1}; *m/z* 345 (M^+, 1%) and 42 (100%); δ (more polar diastereoisomer) 1.77-1.85 (1H, ddd, *J* 14.2, 5.8, 4.9 Hz, CHCN), 2.18

(1H, dd, *J* 13.3, 10 Hz, C$\underline{H}$Ph), 2.40 (1H, ddd, *J* 14.2, 9.7, 8 Hz, C$\underline{H}$CN), 2.81 (3H, s, NC$\underline{H}_3$), 3.00 (1H, dd, *J* 13.2, 4.4 Hz, C$\underline{H}$Ph), 3.62 (1H, m, C$\underline{H}$N), 3.81 (1H, dd, *J* 9.7, 5.8 Hz, C$\underline{H}$Se), 7.00-7.69 (10H, m, aromatic H); $[\alpha]_D^{20}$ +45.8 (c 1.4, $CHCl_3$); $\nu_{max.}$ 3070, 3035, 2935, 1699, 1481, 1442, 1402, 1313br, and 694 cm^{-1}; *m/z* 345 (M^+, 7%) and 96 (100%) (Found: M^+ 345.0637. $C_{18}H_{19}NO^{80}Se$ requires M^+ 345.0631).

5-Benzyl-3-methylpyrrolidin-2-one (176a)

(62 mg), mp. 105-8° (petrol), δ (*ca* 3:2 ratio) 1.18 (1.2H, d, *J* 7.5 Hz, CHC$\underline{H}_3$), 1.20 (1.8H, d, *J* 7.1 Hz, CHC$\underline{H}_3$), 1.89 (0.6H, m, C$\underline{H}$CN), 2.12 (0.4H, m, C$\underline{H}$CN), 2.39-2.52 (1.6H, m, C$\underline{H}$CN and C$\underline{H}$CO), 2.66-2.91 (1.2H, obscured m, C$\underline{H}$CN and C$\underline{H}_2$Ph), 2.70 (0.6H, dd, *J* 13.2, 8.4 Hz, C$\underline{H}$Ph), 2.86 (0.6H, dd, *J* 13.3, 5.3 Hz, C$\underline{H}$Ph), 3.76-3.84 (1H, m, C$\underline{H}$N), 5.85 (0.6H, brs, NH), 5.96 (0.4H, brs, NH), 7.16-7.38 (5H, m, aromatic H); $\nu_{max.}$ 3445, 3200br, 2935, 1716, 1705, 1458, 1410, 1300br, and 699 cm^{-1}; *m/z* (CI) 190 (M^++1, 43%) and 98 (100%).

With 1-bromoheptane:

5-Benzyl-3-heptyl-3-phenylselenopyrrolidin-2-one (174c)

(129 mg) δ (*ca* 3:1 ratio) 0.89 (3H, t, *J* 7.5 Hz, $CH_2C\underline{H}_3$), 1.18-1.60 (10H, m, $(C\underline{H}_2)_5$), 1.74-1.90 (2H, m, $C\underline{H}_2C_6H_{13}$), 1.98 (0.25H, dd, *J* 13.5, 7.5 Hz, C$\underline{H}$CN), 2.12 (0.75H, dd, *J* 15, 5 Hz, C$\underline{H}$CN), 2.26 (0.75H, dd, *J* 14, 8.5 Hz, C$\underline{H}$Ph), 2.33 (0.25H, dd, *J* 14, 6.5 Hz, C$\underline{H}$CN), 2.42-2.57 (1.5H, m, C$\underline{H}$CN and C$\underline{H}$Ph), 2.62 (0.25H, dd, *J* 13, 8 Hz, C$\underline{H}$Ph), 2.80 (0.25H, dd, *J* 12.5, 5 Hz, C$\underline{H}$Ph), 3.54 (0.25H, m, C$\underline{H}$N), 3.69 (0.75H, m, C$\underline{H}$N), 5.71 (0.25H, brs, NH), 5.89 (0.75H, brs, NH), 7.02-7.75 (10H, m, aromatic H); $\nu_{max.}$ 3440, 3200br, 2985, 2935, 1714, 1698, 1440, 910, and 694 cm^{-1}; *m/z* 429 (M^+, 9%) and 210 (100%) (Found: M^+ 429.1574. $C_{24}H_{31}NO^{80}Se$ requires M^+ 429.1571).

5-Benzyl-3-heptylpyrrolidin-2-one (176c)

(21 mg) δ (*ca* 5:1 ratio) 0.91 (3H, t, *J* 6.5 Hz, $CH_2\underline{CH}_3$), 1.22-1.50 (10H, m, $(\underline{CH}_2)_5$), 1.76-2.24 (3.83H, m, $\underline{CH}_2$CHCO and $\underline{CH}_2$CN), 2.29-2.47 (0.83H, m, C<u>H</u>CO), 2.62-2.91 (0.34H, obscured m, C<u>H</u>CN and C<u>H</u>CO), 2.70 (0.83H, dd, *J* 13, 9 Hz, C<u>H</u>Ph), 2.82 (0.83H, dd, *J* 13, 5 Hz, C<u>H</u>Ph), 3.00 (0.17H, dd, *J* 12.5, 7 Hz, C<u>H</u>Ph), 3.21 (0.17H, dd, *J* 12.5, 3 Hz, C<u>H</u>Ph), 3.79 (0.83H, m, C<u>H</u>N), 3.92 (0.17H, m, C<u>H</u>N), 5.82 (0.17H, brs, NH), 5.90 (0.83H, brs, NH), 7.12-7.42 (5H, m, aromatic H); *m/z* (CI) 274 (M^++1, 100%).

Octyl Tosylate (177)

Octyl tosylate (177) was prepared in 85% yield according to the literature method[131] as a colourless oil, bp. 176-182°/1 mmHg, δ 0.87 (3H, t, *J* 6.8 Hz, $CH_2\underline{CH}_3$), 1.21-1.28 (10H, m, $(\underline{CH}_2)_5$), 1.61 (2H, m, $\underline{CH}_2CH_2O$), 2.45 (3H, s, $C\underline{H}_3$), 4.02 (2H, t, *J* 6.6 Hz, $\underline{CH}_2O$), 7.35 (2H, d, *J* 8 Hz, aromatic H), 7.79 (2H, d, *J* 8.4 Hz, aromatic H).

Heptyltrifluoromethane sulphonate (178)[132]

Heptan-1-ol (185 mg, 1.59 mmol) and pyridine (0.13 ml, 1.6 mmol) in CH_2Cl_2 (2.5 ml) were added during 15 min to a solution of trifluoromethane sulphonic anhydride (0.3 ml, 1.78 mmol) in CH_2Cl_2 (6 ml) at 0°. After being stirred for 2 h the mixture was poured into ice-water (30 ml) and quickly extracted with CH_2Cl_2. The volatile components were removed from the dried ($MgSO_4$) extracts at 0° to give the triflate (178) as an unstable light brown oil (350 mg, 89%) which partially solidified on standing at 4°, δ 0.92 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 1.24-1.47 (8H, m, $(\underline{CH}_2)_4$), 1.82 (2H, m, $\underline{CH}_2CH_2O$), 4.55 (2H, t, *J* 7 Hz, CH_2O); $\nu_{max.}$ 2960, 2935, 2860, 1470, 1420, 1200br, 1150, 930br, and 596 cm^{-1}; *m/z* (CI) 98 (9%) and 41 (100%).

Alkylation Reactions of 5S *-5-Benzyl-3,3-bis(phenylseleno)pyrrolidin-2-one* (154)

With iodomethane:

BuLi (1.65 M, 1.1 ml, 1.81 mmol) was added during 5 min to a solution of lactam (154) (416 mg, 0.857 mmol) in THF (5 ml) at 0°. After being stirred for 1 h at 0°, iodomethane (0.53 ml, 8.51 mmol) was added and the resulting solution was stirred for a further 75 min before water (1 ml) was added. Extraction with ether gave a yellow oil which was purified by short column chromatography using gradient elution starting with ether-petrol (2:1). *5-Benzyl-1,3-dimethyl-3-phenylselenopyrrolidin-2-one* (173a) was obtained as a partially separable mixture of diastereoisomeric oils (*ca* 5:2 ratio) (188 mg, 61%), δ (less polar) 1.51 (3H, s, CCH_3), 1.72 (1H, dd, *J* 14, 7.5 Hz, CHCN), 2.20-2.44 (2H, m, CHCN and CHPh), 2.74 (3H, s, NCH_3), 3.00-3.13 (2H, m, CHPh and CHN), 7.00-7.64 (10H, m, aromatic H); δ (more polar) 1.50 (3H, s, CCH_3), 2.02-2.15 (2H, m, CH_2CN), 2.22 (1H, dd, *J* 13, 10 Hz, CHPh), 2.86 (3H, s, NCH_3), 3.05 (1H, dd, *J* 13, 4.5 Hz, CHPh), 3.63 (1H, m, CHN), 7.07-7.73 (10H, m, aromatic H); $\nu_{max.}$ 3040, 2930br, 1698, 1487, 1400, and 675 cm^{-1}; *m/z* 359 (M^+,5%) and 110 (100%) (Found: M^+ 359.0786. $C_{19}H_{21}NO^{80}Se$ requires M^+ 359.0788).

With 1-iodobutane:

BuLi (1.65 M, 1.1 ml, 1.81 mmol) was added to a solution of lactam (154) (410 mg, 0.85 mmol) in THF (5 ml) at 0° and the resulting solution was stirred for 1 h before the addition of 1-iodobutane (220 mg, 1.19 mmol) in THF (1.5 ml). The reaction was kept at 0° for 3 h, allowed to warm to 25° and quenched with water (1 ml). Extraction with ether gave an oil which was purified by flash chromatography using ether-petrol (3:1) as eluant to give the desired lactam (158) (221 mg, 67%).

5S-5-Benzyl-3-butyl- Δ^3*-pyrrolin-2-one* (181a)

1 Ml of a solution of 50% H_2O_2 (1 ml, 17.3 mmol) in water (9 ml) was added to a briskly stirred solution of lactam (158) (204 mg, 0.528 mmol) and pyridine (0.1 ml, 1.23 mmol) in CH_2Cl_2 (4 ml) at 0°. After 5 min, the mixture was brought to 25° and was stirred for 50 min, poured into a mixture of 10% aqueous $NaHCO_3$ (5 ml) and CH_2Cl_2 (15 ml) and stirred for an additional 30 min. The organic layer was separated, washed successively with 3 M HCl (10 ml) and brine and dried ($MgSO_4$). Evaporation gave an oil which was purified by flash chromatography with ether as eluant to give 5S-*5-benzyl-3-butyl-* Δ^3*-pyrrolin-2-one* (181a) as an oil (85 mg, 70%), δ 0.92 (3H, t, *J* 7.2 Hz, $CH_2\underline{CH}_3$), 1.31-1.57 (4H, m, $(\underline{CH}_2)_2$), 2.26 (2H, t, *J* 7.2 Hz, $\underline{CH}_2C=$), 2.69 (1H, dd, *J* 13.3, 8.2 Hz, C<u>H</u>Ph), 2.90 (1H, dd, *J* 13.3, 6.1 Hz, C<u>H</u>Ph), 4.24 (1H, ψ t, *J* 7.1 Hz, C<u>H</u>N), 6.31 (1H, brs, NH), 6.65 (1H, t, *J* 1.9 Hz, H-4), 7,20-7.38 (5H, m, aromatic H); $\nu_{max.}$ 3450, 3250br, 2965, 2935, 1712br, and 700 cm^{-1}; *m/z* 229 (M^+, 33%) and 91 (100%) (Found; M^+ 229.1469. $C_{15}H_{19}NO$ requires M^+ 229.1467).

In a similar fashion, 5S-*5-benzyl-3-heptyl-* Δ^3*-pyrrolin-2-one* (181b) was prepared from lactam (174c) (105 mg, 0.245 mmol), after flash chromatography with ether-methanol (49:1) as eluant, as an oil (51 mg, 77%), $[\alpha]_D^{20}$ +90.6 (c 0.46, CCl_4), δ 0.89 (3H, t, *J* 7.1 Hz, $CH_2\underline{CH}_3$), 1.24-1.39 (8H, m, $(\underline{CH}_2)_4$), 1.46-1.59 (2H, m, $\underline{CH}_2CH_2C=$), 2.24 (2H, t, *J* 7.1 Hz, $\underline{CH}_2C=$), 2.72 (1H, dd, *J* 13.3, 8.4 Hz, C<u>H</u>Ph), 2.88 (1H, dd, *J* 13.3, 6.2 Hz, C<u>H</u>Ph), 4.24 (1H, ψ t, *J* 7.2 Hz, C<u>H</u>N), 6.53 (1H, brs, NH), 6.64 (1H, t, *J* 1.8 Hz, H-4), 7.18-7.39 (5H, m, aromatic H); $\nu_{max.}$ 3465, 3200br, 2965, 2935, 2865, 1714, 1698, 1458, and 695 cm^{-1}; *m/z* 271 (M^+, 21%) and 91 (100%) (Found: M^+ 271.1939. $C_{18}H_{25}NO$ requires M^+ 271.1936).

Acylation of 3-Alkyl-5-benzyl-3-phenylselenopyrrolidin-2-ones

General Procedure:

BuLi (1 molar eq.) was added to a solution of the unprotected lactam (174) in THF (*ca* 0.15 M) at 0° and after 10 min the acid chloride (1.2 molar eq.) was added. Stirring was continued for 30–45 min, the volatile components were removed and the residue was diluted with ether. Filtration through Celite followed by evaporation gave a crude oil which was purified by flash chromatography using ether–petrol mixtures as eluants.

In this way the following products were prepared as colourless oils:

1-Acetyl-5-benzyl-3-butyl-3-phenylselenopyrrolidin-2-one (129a)

(67 mg, 70%) δ (*ca* 3:1 ratio) 0.81–0.94 (3H, m, $CH_2\underline{CH}_3$), 1.17–1.37 (4H, m, $(\underline{CH}_2)_2$), 1.49–2.18 (4H, m, $\underline{CH}_2$Pr and $\underline{CH}_2$CN), 2.56 and 2.58 (3H, both s, $NCO\underline{CH}_3$), 2.73 (0.75H, dd, *J* 14, 8 Hz, C<u>H</u>Ph), 2.89 (0.25H, dd, *J* 12, 10 Hz, C<u>H</u>Ph), 3.13 (0.75H, dd, *J* 14, 4 Hz, C<u>H</u>Ph), 3.44 (0.25H, dd, *J* 12, 4 Hz, 4.40–4.57 (1H, m, C<u>H</u>N), 7.08–7.69 (10H, m, aromatic H); $\nu_{max.}$ 2965, 2935, 1738, 1704, 1377, 1352, 1275br, 1118, and 699 cm^{-1}; *m/z* 429 (M^+, 7%) and 43 (100%) (Found: M^+ 429.1212. $C_{23}H_{27}NO_2{}^{80}Se$ requires M^+ 429.1206).

1-Benzoyl-5-benzyl-3-butyl-3-phenylselenopyrrolidin-2-one (129b)

(206 mg, 91%), δ (*ca* 5:1 ratio) 0.81 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 1.10–1.80 (6H, m, $(\underline{CH}_2)_3$), 2.14 (1H, dd, *J* 15, 3.1 Hz, C<u>H</u>CN), 2.29 (1H, dd, *J* 15, 9.3 Hz, C<u>H</u>CN), 2.79 (0.17H, dd, *J* 13, 10.6 Hz, C<u>H</u>Ph), 2.92 (0.83H, dd, *J* 13, 9.5 Hz, C<u>H</u>Ph), 3.39 (0.17H, dd, *J* 13, 3.5 Hz, C<u>H</u>Ph), 3.46 (0.83H, dd, *J* 12.8, 3.5 Hz, C<u>H</u>Ph), 4.45 (0.17H, m, C<u>H</u>N), 4.69 (0.83H, m, C<u>H</u>N), 7.25–8.23 (15H, m, aromatic H); $\nu_{max.}$ 2965, 2935, 1739, 1684, 1453, 1351, 1291br, 1213br, and 690 cm^{-1}; *m/z* 492 (M^++1, 1%) and 105 (100%).

Oxidative-Elimination of 1-Acyl-3-alkyl-5-benzyl-3-phenylseleno-pyrrolidin-2-ones

General Procedure:

Aqueous H_2O_2 (3.2-3.8 molar eq.) was added dropwise to a solution of the selenide (129) in CH_2Cl_2 (*ca* 0.1-0.15 M) containing pyridine (2.1 molar eq.) at 0°. After being stirred vigorously for 30 min, the mixture was allowed to warm to 25° and was then poured into 10% $NaHCO_3$-CH_2Cl_2 (1:3). Stirring was continued for 15 min, the organic layer was separated, washed with brine and dried ($MgSO_4$). Evaporation gave a crude oil which was purified by flash chromatography eluting with ether-petrol mixtures. In this way the following compounds were prepared as colourless oils:

5S-*1-Acetyl-5-benzyl-3-butyl-* Δ^3*-pyrrolin-2-one* (130a)

(47 mg, 64%), $[\alpha]_D^{20}$ +47.6 (c 0.25, $CHCl_3$), δ 0.89 (3H, t, *J* 7.1 Hz, $CH_2\underline{CH}_3$), 1.23-1.45 (4H, m, $(\underline{CH}_2)_2$), 2.17 (2H, t, *J* 7.1 Hz, $\underline{CH}_2C=$), 2.57 (3H, s, $NCO\underline{CH}_3$), 2.84 (1H, dd, *J* 13.3, 8.8 Hz, $\underline{CH}Ph$), 3.47 (1H, dd, *J* 13.3, 3.6Hz, $\underline{CH}Ph$), 4.81 (1H, m, $\underline{CH}N$), 6.75 (1H, d, *J* 1.8 Hz, H-4), 7.08-7.37 (5H, m, aromatic H); $\nu_{max.}$ 2965, 2935, 1730, 1700, 1455, 1378, 1355, 1290br, and 700 cm^{-1}; *m/z* 271 (M^+ , 8%) and 91 (100%) (Found: M^+ 271.1575. $C_{17}H_{21}NO_2$ requires M^+ 271.1572).

5S-*1-Benzoyl-5-benzyl-3-butyl-* Δ^3*-pyrrolin-2-one* (130b)

(81 mg, 75%), $[\alpha]_D^{20}$ +432.1 (c 0.79, $CHCl_3$), δ 0.80 (3H, t, *J* 7.1 Hz, $CH_2\underline{CH}_3$), 1.15-1.37 (4H, m, $(\underline{CH}_2)_2$), 2.07 (2H, td, *J* 7, 1.3 Hz, $\underline{CH}_2C=$), 3.00 (1H, dd, *J* 13.3, 8 Hz, $\underline{CH}Ph$), 3.30 (1H, dd, *J* 13.3, 3.1 Hz, $\underline{CH}Ph$), 5.08 (1H, m, $\underline{CH}N$), 6.79 (1H, d, *J* 1.3 Hz, H-4), 7.06-7.48 (10H, m, aromatic H); $\nu_{max.}$ 2965, 2935, 2865, 1738, 1676, 1604, 1497, 1451, 1348, 1310br, 1168, 860, and 696 cm^{-1}; *m/z* 333 (M^+ , 17%) and 105 (100%) (Found: M^+ 333.1728.

$C_{22}H_{23}NO_2$ requires M^+ 333.1729).

Intermolecular Diels-Alder Reactions

General Procedure:

A solution of the dienophile (130) and 2E,4E-hexadiene (10 molar eq.) in dried and degassed toluene (*ca* 0.1-0.6 M) was sealed under argon in a Pyrex tube (7x4 mm) and heated to between 170-190° for 30-50 h. The volatile components were removed and the crude product was purified by short column chromatography using ether-petrol (1:4) as eluant. In this way lactam (130a) (38 mg, 0.14 mmol) gave 1S,2S,5R,6R,7S-*8-acetyl-7-benzyl-1-butyl-2,5-dimethyl-8-azabicyclo[4.3.0]non-3-en-9-one* (182a) as an oil (16.8 mg, 34%), $[\alpha]_D^{20}$ +123.1 (c 0.52, $CHCl_3$), δ 0.84-1.30 (12H, m, $(CH_2)_3CH_3$ and $CHCH_3$), 1.17 (3H, d, *J* 7.4 Hz, $CHCH_3$), 1.54 (1H, m, $CHCH_3$), 2.07-2.21 (2H, m, $CHCH_3$ and H-6), 2.47 (3H, s, $NCOCH_3$), 2.90 (1H, dd, *J* 13.4, 3.2 Hz, CHPh), 3.03 (1H, dd, *J* 13.3, 6.8 Hz, CHPh), 4.03 (1H, m, CHN), 5.53-5.62 (2H, m, vinylic H), 7.08-7.35 (5H, m, aromatic H); $\nu_{max.}$ ($CHCl_3$) 2965, 2935, 1727, 1690, 1385, 1288br, and 700 cm^{-1}; *m/z* 354 (M^++1, 3%) and 43 (100%) (Found: M^+ 353.2355. $C_{23}H_{31}NO_2$ requires M^+ 353.2355), along with unreacted starting material (130a) (11.6 mg, 31%).

Similarly, lactam (130b) (38 mg, 0.114 mmol) gave 1S,2S,5R,6R,7S,-*8-benzoyl-7-benzyl-1-butyl-2,5-dimethyl-8-azabicyclo[4.3.0]non-3-en-9-one* (182b) as an oil (9 mg, 19%), $[\alpha]_D^{20}$ +207.9 (c 0.19, $CHCl_3$), δ 0.82-1.29 (6H, m, $(CH_2)_3$), 0.91 (3H, t, *J* 7 Hz, CH_2CH_3), 1.02 (3H, d, *J* 7Hz, $CHCH_3$), 1.15 (3H, d, *J* 7 Hz, $CHCH_3$), 2.13-2.28 (2H, m, $CHCH_3$ and $CHCH_3$), 2.38 (1H, ψ t, *J* 4.9 Hz, H-6), 3.08 (1H, dd, *J* 13.3, 3.1 Hz, CHPh), 3.19 (1H, dd, *J* 13.7, 6.7 Hz, CHPh), 4.25 (1H, m, CHN), 5.69 (2H, m, vinylic H), 7.13-7.57 (10H, m, aromatic H); $\nu_{max.}$ 3035, 2965, 2935, 2875, 1737, 1676,

1452, 1288br, and 695 cm^{-1}; *m/z* (CI) 416 (M^++1 , 100%) and 105 (33%), along with unreacted starting material (130b) (23.5 mg, 62%).

10E,12E *-12-Methyltetradeca-10,12-dienyl bromide* (183) *and -iodide* (184) *and* 12E,14E *-14-Methylhexadeca-12,14-dienyl iodide* (185) were prepared by Dr. M.L.Durrant in these laboratories.[3c] The 300 MHz ^1H nmr spectra of these materials showed them to be contaminated by the octyl (or decyl) halide (*ca* 20-30% by weight). (184) δ 1.34 (12H, m, $(CH_2)_6$), 1.72 (6H, m, 12-CH_3 and 13-CH_3), 1.83 (2H, m, $CH_2(CH_2)_6$), 2.10 (2H, m, CH_2CH=), 3.20 (2H, t, *J* 7.6 Hz, CH_2I), 5.45 (1H, brq, H-13), 5.55 (1H, dt, *J* 15.1, 7.6 Hz, H-10), 6.07 (1H, d, *J* 15.1 Hz, H-11).

Attempted Preparation of 10E,12E *-5-Benzyl-3-(12-methyltetradeca-10,12-dienyl)-3-phenylselenopyrrolidin-2-one* (186)

Method 1

A solution of the silylated lactam (157) (310 mg, 1.07 mmol) in THF (1.6 ml) was added to LDA (2.5 mmol) in THF (3.5 ml) at -75° and the resulting solution was stirred for 45 min. Phenylselenenyl chloride (250 mg, 1.31 mmol) in THF (2 ml) was added, and after 35 min at -75°, dienyl bromide (183)[or iodide (184)] (1.1 molar eq.) in THF (2 ml) was added. The reaction was kept at -75° for 2 h and then allowed to warm slowly to 25°. After 17 h, the mixture was poured into water (10 ml) and was extracted with ether. The crude product obtained was purified by flash chromatography eluting with ether-petrol (85:15), to give unreacted bromide (340 mg, *ca* 100%) and some bis-selenide (154) (78 mg, 15%) as the only recognisable product.

Method 2

BuLi (1.65 M, 1.6 ml, 2.6 mmol) was added to a solution of selenide

(155) (407 mg, 1.23 mmol) in ether (9 ml) at 0° and the resulting solution was stirred for 1 h. Dienyl bromide (183) (390 mg, 1.35 mmol) in ether (1.5 ml) was added dropwise and the mixture was stirred at 0° for 4 h before being allowed to warm to 25° and stirred overnight. Water (2 ml) was added and the product was extracted with ether to give an oil which was purified by short column chromatography using gradient elution with ether-petrol mixtures. Phenylbutylselenide was isolated as a yellow oil (90 mg, 34%), δ (60 MHz) 0.79-1.93 (7H, m, $(CH_2)_2CH_3$), 2.85 (2H, t, J 7 Hz, CH_2Se), 6.96-7.53 (5H, m, aromatic H); $\nu_{max.}$ 3080, 2965, 2935, 2880, 1478, 1440, 1380, 1196br, and 689 cm^{-1}; *m/z* 214 (M^+, 54%) and 158 (100%) (Found: M^+ 214.0260. $C_{10}H_{14}{}^{80}Se$ requires M^+ 214.0260), and dienyl bromide (183) was recovered (351 mg, 90%) along with starting material (155) (134 mg, 33%).

Method 3

BuLi (1.65 M, 1.15 ml, 1.9 mmol) was added during 5 min to a solution of the bis-selenide (154) (456 mg, 0.939 mmol) in THF (5 ml) at 0°, and the resulting solution was stirred for 1 h. Dienyl iodide (184) (360 mg, 1.08 mmol) in THF (1.5 ml) was then added and the solution was stirred at 0° for 3 h before water (1 ml) was added. Extraction with ether gave a crude oil which was purified by flash chromatography, eluting with ether-petrol (3:1), to give phenyl butylselenide (200 mg, 100%) and recovered iodide (184) (74 mg, 20%) along with 10E,12E-*5-benzyl-3-(12-methyltetradeca-10,12-dienyl)-3-phenylselenopyrrolidin-2-one* (186) as a colourless oil (334 mg, 66%), δ (*ca* 4:1 ratio) 1.20-1.86 (16H, m, $(CH_2)_8$), 1.67-1.75 (6H, m, 12-CH_3 and 13-CH_3), 1.91-2.17 (3.2H, m, CH_2CH= and CHCN), 2.23 (0.8H, dd, J 13, 8 Hz, CHPh), 2.47 (0.8H, obscured dd, J 13, 5 Hz, CHPh), 2.42-2.55 (0.8H, m, CHCN), 2.61 (0.2H, dd, J 13, 8 Hz, CHPh), 2.79 (0.2H, dd, J 13, 5 Hz, CHPh), 3.52 (0.2H, m, CHN), 3.67 (0.8H, m, CHN), 5.45 (1H, brq, J 7 Hz, H-13), 5.55 (1H, dt, J 15, 7.5 Hz, H-10), 5.81 (1H, brs,

NH), 6.06 (1H, d, *J* 16 Hz, H-11), 6.99 - 7.79 (10H, m, aromatic H) (10E,12E: 10E,12Z ratio *ca* 7:1), δ (Z-isomer) 5.23-5.37 and 5.65 (2H, m, H-10 and H-13), 6.45 (1H, d, *J* 16 Hz, H-11); $\nu_{max.}$ 3435, 2930, 2860, 1714, 1698, 1440, and 690br cm^{-1}; *m/z* (CI) 538 (M^++1, 15%) and 288 (100%).

Similarly, 12E,14E-*5-benzyl-3-(14-methylhexadeca-12,14-dienyl)-3-phenyl-selenopyrrolidin-2-one* (187) was prepared from selenide (154) (400 mg, 0.824 mmol) and dienyl iodide (185) (335 mg, 0.93 mmol) as an oil (105 mg, 23%) after flash chromatography using ether-petrol (3:1) as eluant, δ (*ca* 5:1 ratio) 1.20-1.54 (20H, m, $(CH_2)_{10}$), 1.64-1.80 (6H, m, 14-CH_3 and 15-CH_3), 1.92-2.13 (3H, m, CH_2CH= and CHCN), 2.19 (0.83H, dd, *J* 12.5, 7.5 Hz, CHPh), 2.32 (0.17H, dd, *J* 13, 5 Hz, CHPh), 2.41-2.63 (1.83H, m, CHPh and CHCN), 2.80 (0.17H, dd, *J* 13, 3.5 Hz, CHPh), 3.53 (0.17H, m, CHN), 3.66 (0.83H, m, CHN), 5.44 (1H, brq, *J* 7 Hz, H-15), 5.56 (1H, dt, *J* 16, 7 Hz, H-12), 5.60 (1H, brs, NH), 6.06 (1H, d, *J* 15 Hz, H-13), 6.97-7.78 (10H, m, aromatic H) (12E,14E: 12E,14Z ratio *ca* 5:1) δ (Z-isomer) 5.25-5.36 (1H, m, H-15), 5.69 (1H, m, H-12), 6.46 (1H, d, *J* 15 Hz, H-13). Also isolated were unreacted dienyl iodide (185) (147 mg, 44%) and mono-selenide (155) (153 mg, 57%).

Using the general procedure described on page 125, the following *N*-acylated lactams were prepared:

10E,12E-*1-Acetyl-5-benzyl-3-(12-methyltetradeca-10,12-dienyl)-3-phenyl-selenopyrrolidin-2-one* (188a), (261 mg, 85%), δ (*ca* 4:1 ratio) 1.13-1.59 (16H, m, $(CH_2)_8$), 1.65-1.81 (6H, m, 12-CH_3 and 13-CH_3), 1.95-2.39 (4H, m, CH_2CH= and CH_2CN), 2.59 (3H, s, $NCOCH_3$), 2.92 (1H, ψt, *J* 12.5 Hz, CHPh), 3.39-3.63 (0.2H, m, CHPh), 3.56 (0.8H, dd, *J* 13, 3 Hz, CHPh), 4.10 (0.2H, m, CHN), 4.47 (0.8H, m, CHN), 5.46 (1H, brq, *J* 7 Hz, H-13), 5.56

(1H, dt, *J* 15, 7 Hz, H-10), 6.07 (1H, d, *J* 16 Hz, H-11), 7.08-7.73 (10H, m, aromatic H) (12E:Z ratio *ca* 6:1) δ (Z-isomer) 5.24-5.39 (1H, m, H-13), 5.64-5.83 (1H, m, H-10), 6.47 (1H, d, *J* 16 Hz, H-11); $\nu_{max.}$ 2930, 2860, 1732, 1704, 1375, 1350, 1273, and 692 cm^{-1}; *m/z* (CI) 580 (M^++1 , 32%) and 91 (100%).

10E,12E-*1-Benzoyl-5-benzyl-3-(12-methyltetradeca-10,12-dienyl)-3-phenyl-selenopyrrolidin-2-one* (188b), (280 mg, 98%), δ (*ca* 4:1 ratio) 1.13-1.59 (16H, m, $(CH_2)_8$), 1.67-1.82 (6H, m, 12-CH_3 and 13-CH_3), 2.03-2.17 (2H, m, CH_2CH=), 2.13 (1H, obscured dd, *J* 15, 3 Hz, CHCN), 2.30 (1H, dd, *J* 15.5, 8.5 Hz, CHCN), 2.81 (0.2H, dd, *J* 13, 9 Hz, CHPh), 2.92 (0.8H, dd, *J* 12.5, 10 Hz, CHPh), 3.37 (0.2H, dd, *J* 13, 3.5 Hz, CHPh), 3.46 (0.8H, dd, *J* 13.5, 3.5 Hz, CHPh), 4.45 (0.2H, m, CHN), 4.68 (0.8H, m, CHN), 5.45 (1H, brq, *J* 7 Hz, H-13), 5.55 (1H, dt, *J* 15.5, 7.5 Hz, H-10), 6.07 (1H, d, *J* 16 Hz, H-11), 7.14-7.72 (15H, m, aromatic H), (12E:Z ratio *ca* 13:2), δ (Z-isomer) 5.23-5.39 (1H, m, H-13), 5.62-5.79 (1H, m, H-10), 6.45 (1H, d, *J* 15 Hz, H-11); $\nu_{max.}$ 2935, 2860, 1739, 1683, 1604, 1453, 1350, 1292br, 1217br, 692, and 658 cm^{-1}; *m/z* (CI) 642 (M^++1 , 3%) and 392 (100%).

12E,14E-*1-Benzoyl-5-benzyl-3-(14-methylhexadeca-12,14-dienyl)-3-phenyl-selenopyrrolidin-2-one* (189), (114 mg, 92%),† δ (*ca* 5:1 ratio) 1.12-1.58 (20H, m, $(CH_2)_{10}$), 1.66-1.81 (6H, m, 14-CH_3 and 15-CH_3), 2.02-2.19 (3H, m, CH_2CH= and CHCN), 2.30 (1H, dd, *J* 15, 9 Hz, CHCN), 2.79 (0.17H, dd, *J* 13, 9.5 Hz, CHPh), 2.92 (0.83H, dd, *J* 13, 3 Hz, CHPh), 3.36 (0.17H, dd, *J* 13, 3 Hz, CHPh), 3.46 (0.83H, dd, *J* 13, 3 Hz, CHPh), 4.43 (0.17H, m, CHN), 4.68 (0.83H, m, CHN), 5.45 (1H, brq, *J* 7.5 Hz, H-15), 5.55 (1H, dt, *J* 15, 7 Hz, H-12), 6.07 (1H, d, *J* 15 Hz, H-13), 7.13-7.74 (15H, m, aromatic H), (14E:Z ratio *ca* 9:1), δ (Z-isomer) 5.24-5.37 (1H, m, H-15),

† Estimated to contain 17% decylated product by ^1H nmr.

5.62-5.75 (1H, m, H-12), 6.46 (1H, d, *J* 15 Hz, H-13); $\nu_{max.}$ 3070, 3035, 2930, 2860, 1740, 1684, 1605, 1452, 1350, 1290br, 1218br, 690, and 656 cm^{-1} *m/z* (CI) 670 ($M^+ + 1$, 2%) and 105 (100%).

Using the general procedure described on page 126, the following trienes were prepared:

5S,10E,12E-*1-Acetyl-5-benzyl-3-(12-methyltetradeca-10,12-dienyl)*-Δ^3-*pyrrolin-2-one* (190a), (84 mg, 54%),† δ (12E:Z ratio *ca* 4:1) 1.18-1.47 (14H, m, $(CH_2)_7$), 1.67-1.81 (6H, m, 12-CH_3 and 13-CH_3), 2.08 (2H, brq, *J* 7 Hz, CH_2CH=), 2.17 (2H, ψt, *J* 7 Hz, CH_2C=), 2.58 (3H, s, $NCOCH_3$), 2.84 (1H, dd, *J* 13.5, 8.5 Hz, CHPh), 3.49 (1H, dd, *J* 13, 3 Hz, CHPh), 4.82 (1H, m, CHN), 5.45 (1H, brq, *J* 7 Hz, H-13), 5.55 (1H, dt, *J* 15, 7 Hz, H-10), 6.05 (1H, d, *J* 16 Hz, H-11), 6.67 (1H, d, *J* 2 Hz, H-4), 7.07-7.35 (5H, m, aromatic H), δ (Z-isomer) 5.24-5.39 (1H, m, H-13), 5.62-5.82 (1H, m, H-10), 6.45 (1H, d, *J* 15 Hz, H-11); $\nu_{max.}$ 2935, 2865, 1729, 1699, 1379, 1358, 1292, and 702 cm^{-1}; *m/z* 421 (M^+, 5%) and 91 (100%) (Found: M^+ 421.2979. $C_{28}H_{39}NO_2$ requires M^+ 421.2981).

5S,10E,12E-*1-Benzoyl-5-benzyl-3-(12-methyltetradec-10,12-dienyl)*-Δ^3-*pyrrolin-2-one* (190b), (103 mg, 59%),* $[\alpha]_D^{20}$ +272.6 (c 0.5, $CHCl_3$); δ (12E:Z ratio *ca* 6:1) 1.25-1.49 (14H, m, $(CH_2)_7$), 1.65-1.79 (6H, m, 12-CH_3 and 13-CH_3), 2.05-2.16 (4H, m, CH_2CH= and CH_2C=), 3.08 (1H, dd, *J* 13.3, 8 Hz, CHPh), 3.38 (1H, dd, *J* 13.3, 3.3 Hz, CHPh), 5.16 (1H, m, CHN), 5.45 (1H, brq, *J* 6.6 Hz, H-13), 5.55 (1H, dt, *J* 15.5, 7.1 Hz, H-10), 6.06 (1H, d, *J* 15.5 Hz, H-11), 6.87 (1H, brs, H-4), 7.14-7.56 (10H, m, aromatic H), δ (Z-isomer) 5.23-5.37 (1H, m, H-13), 5.62-5.81 (1H, m, H-10), 6.45 (1H, d, *J* 15.5 Hz, H-11); $\nu_{max.}$ 3040, 2935, 2860, 1740, 1677, 1605, 1453,

† Estimated to contain 26% octylated product by ^1H nmr.
* Estimated to contain 30% octylated product by ^1H nmr.

1349, 1310br, 1218, 964, 859, 694, and 659 cm^{-1}; *m/z* (CI) 484 ($M^+ +1$, 63%) and 390 (100%).

5S,12E,14E *-1-Benzoyl-5-benzyl-3-(14-methylhexadeca-12,14-dienyl)-* Δ^3 *-pyrrolin-2-one* (191), (38 mg, 50%); $[\alpha]_D^{20}$ +238.5 (c 0.34, CCl_4); δ (14E:Z ratio *ca* 7:1) 1.20-1.59 (18H, m, $(CH_2)_9$), 1.66-1.80 (6H, m, 14-CH_3 and 15-CH_3),2.04-2.15 (4H, m, $CH_2CH=$ and $CH_2C=$), 3.07 (1H, dd, *J* 13.3, 8 Hz, CHPh), 3.38 (1H, dd, *J* 13.4, 3.4 Hz, CHPh), 5.15 (1H, m, CHN), 5.44 (1H, brq, *J* 7.5 Hz, H-15), 5.54 (1H, dt, *J* 15, 7 Hz, H-12), 6.05 (1H, d, *J* 15.5 Hz, H-13), 6.86 (1H, d, *J* 1.9 Hz, H-4), 7.12-7.58 (10H, m, aromatic H); $\nu_{max.}$ 3040, 2935, 2860, 1740, 1678, 1606, 1452, 1222br, 1209br, 965, 860, 696, and 661 cm^{-1}; *m/z* (CI) 512 ($M^+ +1$, 72%) and 105 (100%).

6.3 *Experiments Discussed in Chapter 4*

Propanoylation of N-*Protected Lactams*

With 5R*-1-Benzoyl-5-benzylpyrrolidin-2-one* (150)

Method 1

A solution of lactam (150) (310 mg, 1.11 mmol) in THF (2.5 ml) was added to LDA (2.4 mmol) in THF (2.5 ml) at -75° and the resulting solution was stirred for 15 min. Neat ethyl propionate (0.165 ml, 1.44 mmol) was then added quickly and, after 5 min, the cooling bath was removed and the reaction was allowed to warm to 0° (35 min). 3% HCl in methanol (2 ml) was added and the mixture was poured into 3 M HCl (15 ml) and extracted with ether. The crude product was purified by short column chromatography using ether-petrol (4:1) as eluant, to give a mobile oil (111 mg) shown by ^{1}H nmr to be a mixture of methyl benzoate and Claisen products derived from ethyl propionate. Also eluted was the acyclic product 4R-*methyl 4-benzamido-5-phenylpentanoate* (198a) as flakes (131 mg, 38%), mp. 139° (CH_2Cl_2-ether), $[\alpha]_D^{20}$ +8.7 (c 0.32, $CHCl_3$); δ 1.76-2.03 (2H, m, CH_2CH_2CO), 2.32-2.55 (2H, m, CH_2CO), 2.87 (1H, dd, *J* 13.5, 7.2 Hz, CHPh), 3.03 (1H, dd, *J* 13.6, 5.4 Hz, CHPh), 3.60 (3H, s, OCH_3), 4.39 (1H, m, CHN), 6.22 (1H, brd, *J* 7 Hz, NH), 7.20-7.76 (10H, m, aromatic H); $\nu_{max.}$($CHCl_3$) 3440, 3010, 1728br, 1660br, 1516, 1488, and 700 cm^{-1}; *m/z* (CI) 312 (M^++1 , 35%) and 105 (100%) (Found: C, 73.3; H, 6.6; N, 4.5. $C_{19}H_{21}NO_3$ requires C, 73.3; H, 6.8; N, 4.5%).

Method 2

A solution of the lactam (236 mg, 0.845 mmol) in THF (1.5 ml) was added to LDA (0.935 mmol) in THF (1 ml) at -75° and the resulting solution

was stirred for 30 min. Neat ethyl propionate (0.11 ml, 0.96 mmol) was added, the reaction was allowed to warm to 0° and was then poured into 3 M HCl (15 ml). Rapid extraction with ether gave an oil (232 mg) which was shown to be a complex mixture of products. Purification by short column chromatography using ether-petrol (3:1) as eluant gave, in order of elution, *1-benzoyl-3-benzyl-3-(1-oxopropyl)pyrrolidin-2-one* (197) (20 mg, 7%), δ (*ca* 5:3 ratio) 1.02 and 1.12 (1.87H and 1.13H, both t, *J* 7 Hz, $CH_2\underline{CH}_3$), 1.97-2.23 (1.37H, m, C<u>H</u>CN), 2.35-3.03 (3.63H, m, C<u>H</u>CN, $\underline{CH}_2CH_3$ and C<u>H</u>Ph), 3.29 (0.63H, dd, *J* 13.5, 4 Hz, C<u>H</u>Ph), 3.40-3.50 (1H,m, C<u>H</u>Ph and COC<u>H</u>CO), 3.72 (0.38H, dd, *J* 9.5, 6.5 Hz, COC<u>H</u>CO), 4.62 (0.38H, m, C<u>H</u>N), 4.81 (0.63H, m, C<u>H</u>N), 7.23-7.65 (10H, m, aromatic H); $\nu_{max.}$ 2985, 1745, 1724, 1685, 1453, 1286br, 1220, 1115br, 911, and 695 cm^{-1}; *m/z* 335 (M^+, 4%) and 105 (100%) (Found: M^+ 335.1522. $C_{21}H_{21}NO_3$ requires M^+ 335.1521), starting material (61 mg, 26%) and a white solid (30 mg), mp. 141.5-143.5°, identified as a mixture (56:44) of starting lactam (7%) and 4<u>R</u>-*ethyl 4-benzamido-5-phenylpentanoate* (198b) (5%), δ 1.18 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 1.76-2.19 (2H, m, $\underline{CH}_2CH_2CO$), 2.32-2.54 (2H, m, $\underline{CH}_2CO$), 2.86 (1H, dd, *J* 13, 7.5 Hz, C<u>H</u>Ph), 3.04 (1H, dd, *J* 13.5, 5 Hz, C<u>H</u>Ph), 4.07 (2H, two overlapping q, *J* 7 Hz, $\underline{CH}_2O$), 4.40 (1H, m, C<u>H</u>N), 6.32 (1H, brd, 9 Hz, NH), 7.22-7.76 (10H, m, aromatic H); *m/z* (CI) 326 (M^++1, 39%) and 105 (100%).

*5-Benzyl-1-(*tert*-butyldimethylsilyl)-3-(1-oxopropyl)pyrrolidin-2-one* (201)

A solution of the silylated lactam (157) (2.465 g, 8.09 mmol) in THF (2.5 ml) was added during 10 min to LDA (17.85 mmol) in THF (20 ml) at -75°. After being stirred for 50 min, the solution was transferred to a separate flask containing a solution of 1-(1-oxopropyl)imidazole [formed

in situ by reacting 1,1'-carbonyldi-imidazole (1.46 g, 9 mmol) with propanoic acid (0.67 ml, 8.98 mmol) in THF (12 ml)][81] at -75° by means of a cannula and a nitrogen bubbler. The resulting mixture was stirred at -75° for 1 h and was then allowed to warm to 0° (45 min) before being poured into 2 M HCl (40 ml) and ether (50 ml). Extraction gave a yellow oil which was purified by flash chromatography using ether-petrol (1:3) as eluant, to give *5-benzyl-1-(*tert*-butyldimethylsilyl)-3-(1-oxopropyl)-pyrrolidin-2-one* (201) as an oil (2.056 g, 74%); δ (*ca* 3:2 ratio) 0.35, 0.41, 0.44 and 0.47 (6H, all s, $Si(CH_3)_2$), 0.97 and 1.00 (9H, both s, $Si(CH_3)_3$), 1.07 and 1.14 (3H, both t, *J* 7.5 Hz, CH_2CH_3), 1.83-2.02 (1H, m, CHCN), 2.40-2.71 (3H, m, CHCN, $CHCH_3$ and CHPh), 2.88-3.19 (2H, m, $CHCH_3$ and CHPh), 3.47-3.61 (1H, m, COCHCO), 3.71-3.90 (1H, m, CHN), 7.14-7.42 (5H, m, aromatic H); $\nu_{max.}$ 2960, 2935, 1722, 1683, 1375, 1230br, 1103, and 702 cm^{-1}; *m/z* 346 (M^++1, 3%) and 288 (100%). Also isolated was a colourless oil (156 mg, 8%) identified as 5R-*5-benzyl-1-(1-oxopropyl)-pyrrolidin-2-one* (202), δ 1.20 (3H, t, *J* 7.5 Hz, CH_2CH_3), 1.82-2.08 (2H, m, CH_2CH_2CO), 2.32-2.42 (2H, m, CH_2CO), 2.76 (1H, dd, *J* 14.5, 9.5 Hz, CHPh), 2.98 (2H, q, *J* 7.5 Hz, CH_2CH_3), 3.14 (1H, dd, *J* 14.5, 4 Hz, CHPh), 4.57-4.68 (1H, m, CHN), 7.20-7.41 (5H, m, aromatic H); $\nu_{max.}$ 2985, 1743, 1699, 1470, 1449, 1224, 909, and 698 cm^{-1}; *m/z* 231 (M^+, 5%) and 84 (100%) (Found: M^+ 231.1258. $C_{14}H_{17}NO_2$ requires M^+ 231.1259), and starting material (110 mg, 5%).

*5-Benzyl-1-(*tert*-butyldimethylsilyl)-3-(1-oxopropyl)-3-phenylseleno-pyrrolidin-2-one* (203)

A solution of lactam (201) (1.6 g, 4.4 mmol) in THF (2.5 ml) was added during 5 min to LDA (5.27 mmol) in THF (7 ml) at -75°. After 35 min

phenylselenenyl chloride (1.038 g, 5.42 mmol) in THF (2.5 ml) was added, the mixture was allowed to warm to -5° (90 min) and was then poured into 2 M HCl (30 ml). Extraction with ether gave a crude semi-solid which was purified by flash chromatography using ether-petrol (1:9) as eluant to give *5-benzyl-1-(*tert*-butyldimethylsilyl)-3-(1-oxopropyl)-3-phenylselenopyrrolidin-2-one* (203) as a solid (1.2 g, 55%), mp. 100-102°. Crystallization from pentane at low temperature of a small portion gave an analytical sample, mp. 109-110°; δ 0.40 and 0.44 (6H, both s, $Si(CH_3)_2$), 1.04 (9H, s, $Si(CH_3)_3$), 1.19 (3H, t, *J* 7.3 Hz, CH_2CH_3), 2.11-2.22 (2H, m, CH_2CN), 2.63 (1H, dd, *J* 13.7, 1.2 Hz, CHPh), 2.75-2.86 (2H, m, CHPh and $CHCH_3$), 3.47 (1H, dq, *J* 23, 7.3 Hz, $CHCH_3$), 3.66 (1H, m, CHN), 7.16-7.58 (10H, m, aromatic H); $\nu_{max.}$ 2960, 2935, 1685br, 1374, 1352, 1234br, 1097br, and 692 cm^{-1}; *m/z* (CI) 502 (M^++1, 45%) and 346 (100%) (Found: C, 62.4; H, 6.95; N, 3.0. $C_{26}H_{35}NO_2SiSe$ requires C, 62.4; H, 7.05; N,2.8%). Also isolated was unreacted starting material (201) (161 mg, 10%).

*Desilylation of 5-Benzyl-1-(*tert*-butyldimethylsilyl)-3-(1-oxopropyl)-3-phenylselenopyrrolidin-2-one* (203)

With fluoride ion

Tetra n-butylammonium fluoride (1 M in THF, 0.8 ml) was added dropwise to a solution of lactam (203) (187 mg, 0.373 mmol) in THF (2 ml) at 0°. After 35 min the mixture was allowed to warm to 25° and was poured into water (15 min) and ether (20 ml). Extraction gave an oil (173 mg) shown to be a complex mixture of products by tlc. Purification by short column chromatography using gradient elution with ether-petrol mixtures, gave *5-benzyl-3-(1-oxo-2-phenylselenopropyl)-3-phenylselenopyrrolidin-2-one* (205) as separable diastereoisomeric solids (9.5 mg) and (15 mg); δ (less polar) 1.52 (3H, d, *J* 7 Hz, $CHCH_3$), 2.12 (1H, dd, *J* 14, 7.5 Hz, CHCN), 2.80 (1H,

dd, *J* 14.2, 9.7 Hz, C<u>H</u>Ph), 2.90-3.02 (2H, m, C<u>H</u>Ph and C<u>H</u>CN), 3.92 (1H, m, C<u>H</u>N), 4.97 (1H, q, C<u>H</u>CH_3), 5.88 (1H, brs, NH), 7.16-7.56 (15H, m, aromatic H); *m/z* (CI) 544 (M^++1 , 2%) and 91 (100%) and δ (more polar) 1.52 (3H, d, *J* 7 Hz, $CHCH_3$), 2.32-2.42 (2H, m, CH_2CN), 2.81 (1H, dd, *J* 14.5, 10 Hz, C<u>H</u>Ph), 2.96 (1H, dd, *J* 14.5, 6 Hz, C<u>H</u>Ph), 3.92 (1H, m, C<u>H</u>N), 5.09 (1H, q, *J* 7 Hz, C<u>H</u>CH_3), 5.88 (1H, brs, NH), 7.21-7.52 (15H, m, aromatic H); *m/z* (CI) 544 (M^++1 , 18%) and 230 (100%), plus a mixed fraction (9.5 mg, 17% total). Further elution gave *5-benzyl-3-(1-oxo-2-phenylseleno-propyl)pyrrolidin-2-one* (206) as an oil (53 mg, 37%), δ (*ca* 6:5 ratio) 1.47 and 1.54 (3H, major and minor, both d, *J* 7 Hz, $CHCH_3$), 1.92 and 2.18-2.54 (1H minor and 2H, both m, CH_2CN), 2.61-3.00 (1H major and 2H, both m, CH_2CN and CH_2Ph), 3.84 and 3.97 (1H, both m, C<u>H</u>N), 4.09-4.27 (1H, m, COC<u>H</u>CO), 4.38-4.57 (1H, m, C<u>H</u>Se), 5.67 (1H, brs, NH), 7.15-7.57 (10H, m, aromatic H); *m/z* 387 (M^+ , 25%) and 84 (100%). Finally, *5-benzyl-3-(1-oxopropyl)pyrrolidin-2-one* (207) was obtained as a solid (16 mg, 19%), mp. 73.5-74° (ether-petrol); δ (*ca* 1:1 ratio) 1.07 and 1.12 (3H, both t, *J* 7.5 Hz, CH_2CH_3), 1.89 and 2.27 (1H, both m, C<u>H</u>CN), 2.39-3.18 (5H, m, CH_2CH_3, C<u>H</u>CN and CH_2Ph), 3.52 (0.5H, dd, *J* 10.5, 6 Hz, COC<u>H</u>CO), 3.59 (0.5H, dd, *J* 10.5, 8.7 Hz, COC<u>H</u>CO), 3.82 and 3.97 (1H, both m, C<u>H</u>N), 5.97 and 6.02 (1H, both brs, NH), 7.15-7.39 (5H, m, aromatic H); $\nu_{max.}$ 3440, 3200br, 2945, 1711br, 1457, 1414, 1116, and 699 cm^{-1}; *m/z* 232 (M^++1, 6%) and 57 (100%) (Found: C, 72.4; H, 7.4; N, 5.9. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%).

With mineral acid

3 <u>M</u> HCl (5 ml) was added dropwise to a solution of the lactam (310 mg, 0.62 mmol) in THF (5 ml) at 0° with efficient stirring. After being allowed to warm to 25°, the mixture was stirred for an additional 11 h, poured

into water (20 ml) and extracted with ether to give a crude solid. Purification by flash chromatography using ether-petrol (2:1) as eluant gave *5-benzyl-3-(1-oxopropyl)-3-phenylselenopyrrolidin-2-one* (204) as a yellow solid (188 mg, 79%), mp. 114° which was crystallized from ether, mp. 118.5°, δ (*ca* 1:1 ratio) 1.10 and 1.15 (3H, both t, *J* 7.2 Hz, $CH_2\underline{CH}_3$), 1.99 (0.5H, dd, *J* 13.8, 6.8 Hz, C<u>H</u>CN), 2.18 (0.5H, dd, *J* 14.6, 6.3 Hz, C<u>H</u>CN), 2.46 (0.5H, dd, *J* 14.6, 7.5 Hz, C<u>H</u>CN), 2.59 (1H, m, C<u>H</u>CN and C<u>H</u>Ph), 2.78-2.96 (2H, m, $\underline{CH}CH_3$ and C<u>H</u>Ph), 3.03 (0.5H, dd, *J* 14.3, 7.1 Hz, C<u>H</u>Ph), 3.25-3.38 (1H, m, $\underline{CH}CH_3$), 3.74 (1H, m, C<u>H</u>N), 5.59 (1H, brs, NH), 7.08-7.54 (10H, m, aromatic H); $\nu_{max.}$ 3430, 1717, 1700, 1442, 1410, and 692br cm^{-1}; *m/z* (CI) 388 (M^++1, 32%) and 232 (100%) (Found: C, 62.3; H, 5.5; N, 3.6. $C_{20}H_{21}NO_2Se$ requires C, 62.2; H, 5.5; N, 3.6%).

Attempted N *-Benzoylation of 5-Benzyl-3-(1-oxopropyl)-3-phenylselenopyrrolidin-2-one* (204)

Method 1

The lactam (204) (55 mg, 0.142 mmol) was treated with NaH (60% dispersion in mineral oil, 6.5 mg, 0.163 mmol) in THF (2.5 ml) at 0° for 90 min followed by benzoyl chloride (1 ml of a 0.164 <u>M</u> solution in THF). After quenching with 2 <u>M</u> HCl and extractive work-up, a yellow oil was obtained (69 mg) which was shown by tlc to be a complex mixture of products.

Method 2

The lactam (57 mg, 0.147 mmol) was treated with a solution of LiICA[89] (1 ml of a 0.146 <u>M</u> solution in THF) in THF (0.9 ml) at 0° for 10 min followed by benzoyl chloride (1 ml of a 0.172 <u>M</u> solution in THF). After 30 min, the reaction was worked-up as before to give an oil (75 mg) which was shown by tlc to be a complex mixture of products.

Method 3

A solution of the lactam (65 mg, 0.168 mmol) in THF (1 ml) was added slowly to LiTMP[90] (1 ml of a 0.17 M solution in THF) at -78°. After 15 min, benzoyl chloride (1 ml of a 0.17 M solution in THF) was added and the mixture was allowed to warm gradually to 25° (2.5 h). Work-up as before gave an oil (79 mg) which was shown by tlc to be a complex mixture of products.

In all three experiments chromatographic purification led to the isolation of small amounts of authentic *N*-benzoylated materials but mainly to C-2 benzoylated products (208) (40-50%) as mixtures of diastereoisomers which were not characterized, δ (partial) 1.50 (3H, d, *J* 7 Hz, $CHC\underline{H}_3$), 4.58 (1H, q, *J* 7 Hz, $COC\underline{H}CO$), 6.34 (1H, brs, NH).

Method 4

Freshly distilled acetyl chloride (0.04 ml, 0.56 mmol) was added to a stirred solution of the lactam (59 mg, 0.153 mmol) and di-isopropylethylamine (0.06 ml, 0.344 mmol) in CH_2Cl_2 (0.5 ml) at 25°. After 17 h, the mixture was poured into 3 M HCl (5 ml) and extracted with ether to give a yellow oil (56 mg). Purification by preparative tlc using ether-petrol (1:3) as eluant gave an oil (10 mg, 15%) shown by ^{1}H nmr to be *N*-acetylated lactam (213b).

Alternative Preparation of 5R*-1-Benzoyl-5-benzylpyrrolidin-2-one* (150)

Benzoyl chloride (0.36 ml, 3.1 mmol) was added to a solution of lactam (116) (109 mg, 0.622 mmol) and *N*,*N*-dimethylaminopyridine[91] (15 mg, 0.12 mmol) in pyridine (2 ml) at 25°. The mixture was heated at 55° for 17 h, poured into 3 M HCl (10 ml) and extracted with ether to give a yellow oil which was purified by flash chromatography eluting with ether-petrol(1:1) to give the title compound (150) (140 mg, 80%).

Application of these conditions to selenide (204), however, resulted in extensive decomposition.

*1-*tert*-Butyldimethylsilylpyrrolidin-2-one* (209)

BuLi (1.7 M, 5.9 ml, 10 mmol) was added dropwise to a solution of pyrrolidin-2-one (140) (0.76 ml, 10 mmol) in THF (30 ml) at 0°. After 30 min, *tert* -butyldimethylsilyl chloride (1.5 g, 10 mmol) in THF (4 ml) was added to the milky suspension and the mixture was allowed to warm to 25° during 2.5 h. The volatile components were removed and the residue was filtered through a plug of silica and was washed several times with ether. Evaporation gave *1-* tert *-butyldimethylsilylpyrrolidin-2-one* (209) as a pale yellow oil (1.576 g, 79%). An analytical sample was obtained by Kugelrohr distillation (oven temperature 150°/1 mmHg); δ 0.26 (6H, s, $Si(CH_3)_2$), 0.94 (9H, s, $Si(CH_3)_3$), 1.97-2.07 (2H, m, CH_2CN), 2.33 (2H, t, *J* 8.1 Hz, CH_2CO), 3.39 (2H, t, *J* 6.8 Hz, CH_2N); $\nu_{max.}$ 2960, 2935, 2865, 1690, 1473, 1383, 1252, 1118, and 950 cm^{-1}; *m/z* 200 ($M^+ +1$, 1%) and 142 (100%) (Found: C, 60.6; H, 10.8; N, 7.1. $C_{10}H_{21}NOSi$ requires C, 60.3; H, 10.55; N, 7.0%).

1-Benzoylpyrrolidin-2-one (210)

A solution of lactam (209) (0.417 g, 2.09 mmol) and benzoyl chloride (0.28 ml, 2.41 mmol) in benzene (5 ml) was refluxed for 7 h.[92] Removal of the solvent followed by flash chromatography using ether-petrol (9:1) as eluant gave 1-benzoylpyrrolidin-2-one (210) as a pink solid (0.306 g, 77%). Recrystallization from ether gave needles mp. 91-91.5° (lit.,[133] 89°); δ 2.15 (2H, m, *J* 7.6 Hz, CH_2CN), 2.62 (2H, t, *J* 8 Hz, CH_2CO), 3.97

(2H, t, *J* 7.1 Hz, $C\underline{H}_2N$), 7.39-7.66 (5H, m, aromatic H); $\nu_{max.}$ 1752, 1683, 1263, 1221, 1199, 1190, and 696 cm^{-1}; *m/z* 189 (M^+, 11%) and 77 (100%).

Attempted N-*Benzoylation of 5-Benzyl-1-(*tert*-butyldimethylsilyl)-3-(1-oxopropyl)pyrrolidin-2-one* (201)

Benzoyl chloride (0.5 ml of a 0.74 M solution in benzene) was added to a solution of lactam (201) (126 mg, 0.365 mmol) in benzene (1.2 ml) and the resulting solution was refluxed for 9 h. The volatile components were removed and the residue was purified by short column chromatography using gradient elution with ether-petrol mixtures. *1-Benzoyl-5-benzyl-3-(1-oxopropyl)pyrrolidin-2-one* (197) was obtained as an oil (18 mg, 15%). Also eluted were *3-benzoyl-5-benzyl-3-(1-oxopropyl)pyrrolidin-2-one* (212) as an oil (58 mg, 48%), δ (*ca* 1:1 ratio) 1.07 and 1.16 (3H, both t, *J* 7.5 Hz, $CH_2C\underline{H}_3$), 1.89 (0.5H, ddd, *J* 15, 9, 6 Hz, C<u>H</u>CN), 2.20-3.19 (5H, m, $C\underline{H}_2CH_3$, C<u>H</u>CN and C<u>H</u>Ph), 3.56 (0.5H, m, C<u>H</u>Ph), 3.77-4.03 (1H, m, C<u>H</u>N), 5.79 (1H, brs, NH), 7.15-7.62 and 8.16 (10H, both m, aromatic H); $\nu_{max.}$ 3450, 3220br, 1745, 1712, 1685, 1457, 1265br, 1205, and 700 cm^{-1}; *m/z* (CI) 336 (M^++1 , 42%) and 232 (100%) and an oil (15 mg, 9%) tentatively identified as the dibenzoylated lactam (211) on the basis of its ^1H nmr spectrum, δ (partial) 4.72 (1H, m, C<u>H</u>N), 7.26-7.66 and 8.05 (15H, both m, aromatic H).

1-Benzoyl-5-benzyl-3-(1-oxopropyl)-3-phenylselenopyrrolidin-2-one (213a)

Benzoyl chloride (0.5 ml of a 1.43 M solution in benzene) was added to a solution of selenide (203) (359 mg, 0.717 mmol) in benzene (3.5 ml) and the resulting solution was heated at 80° (oil bath) for 8 h. The volatile components were removed and the residue was purified by flash chromatography using ether-petrol (1:4) as eluant to give *1-benzoyl-5-benzyl-3-(1-oxo-*

propyl)-3-phenylselenopyrrolidin-2-one (213a) as a viscous oil (257 mg, 73%), δ (*ca* 4:1 ratio) 1.02 and 1.10 (0.6H and 0.4H, both t, *J* 7 Hz, $CH_2\underline{CH}_3$), 1.99 (0.8H, dd, *J* 14.5, 6.5 Hz, C<u>H</u>CN), 2.09 (0.2H, dd, *J* 13, 6 Hz, C<u>H</u>CN), 2.20-2.37 (1H, m, C<u>H</u>CN), 2.49 (0.8H, dd, *J* 15, 8 Hz, C<u>H</u>Ph), 2.59-2.94 (1.2H, m, C<u>H</u>Ph and $C\underline{H}CH_3$), 3.04-3.35 (2H, m, C<u>H</u>Ph and $C\underline{H}CH_3$), 4.56 (1H, m, C<u>H</u>N), 7.05-7.64 (15H, m, aromatic H); $\nu_{max.}$ 2980, 1735, 1695br, 1352, 1286br, 1220br, 908, 692, and 656 cm^{-1}; *m/z* 491 (M^+, <1%) and 105 (100%). Also eluted was the deprotected lactam (204) (69 mg, 25%).

If the experiment was not performed with freshly prepared starting lactam and dry reagents, deselenenylated products were isolated, *eg* . 1-benzoyl-5-benzyl-3-(1-oxopropyl)pyrrolidin-2-one (197) (12-20%).

1-Acetyl-5-benzyl-3-(1-oxopropyl)-3-phenylselenopyrrolidin-2-one (213b)

Acetyl chloride (0.6 ml of a 0.42 <u>M</u> solution in benzene) was added to a solution of lactam (203) (104 mg, 0.208 mmol) in benzene (1 ml) and the resulting solution was heated at 60° (oil bath) for 7.5 h.† The volatile components were removed and the residue was purified by flash chromatography using ether-petrol (1:3) as eluant to give *1-acetyl-5-benzyl--3-(1-oxopropyl)-3-phenylselenopyrrolidin-2-one* (213b) as a solid (48 mg, 54%), mp. 128-9° (ether-pentane), δ 1.13 (3H, t, *J* 7.2 Hz, $CH_2\underline{CH}_3$), 2.06 (1H, dd, *J* 14.4, 8.7 Hz, C<u>H</u>CN), 2.36 (1H, dd, *J* 12.9, 9.9 Hz, C<u>H</u>CN), 2.54 (1H, obscured dq, $C\underline{H}CH_3$),2.55 (3H, s, $NCOCH_3$), 2.60 (1H, obscured dd, C<u>H</u>Ph), 3.10 (1H, dd, *J* 12.9, 3 Hz, C<u>H</u>Ph), 3.26 (1H, obscured dq, *J* 7.2 Hz, $C\underline{H}CH_3$), 4.36 (1H, m, C<u>H</u>N), 7.15-7.50 (10H, m, aromatic H); $\nu_{max.}$ 3065, 3035, 1729, 1710, 1440, 1373, 1348, 1265br, 1181, and 692 cm^{-1}; *m/z* 429 (M^+, 11%) and 91 (100%) (Found: C, 61.75; H, 5.4; N, 3.3. $C_{22}H_{23}NO_3Se$ requires C, 61.7; H, 5.4; N, 3.3%).

† After 2 h a further 0.5 ml of the acetyl chloride solution was added.

5S-1-Benzoyl-5-benzyl-3-(1-oxopropyl)- Δ^3-pyrrolin-2-one (195)

MCPBA (85 mg, 0.42 mmol) was added in portions to a solution of the selenide (213a) (100 mg, 0.2 mmol) in CH_2Cl_2 (1.5 ml) at 25°. After 10 min, the mixture was poured into ice-cold saturated aqueous Na_2CO_3 (5 ml) and extracted rapidly with CH_2Cl_2 (2x15 ml) to give *5S-1-benzoyl-5-benzyl-3-(1-oxopropyl)- Δ^3-pyrrolin-2-one* (195) as a pale yellow oil (63 mg, 94%), δ 1.04 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 2.82 (2H, q, *J* 7 Hz, $\underline{CH}_2CH_3$), 3.18 (1H, dd, *J* 14.5, 8 Hz, C<u>H</u>Ph), 3.49 (1H, dd, *J* 14.5, 3.5 Hz, C<u>H</u>Ph), 5.34 (1H, ddd, *J* 8, 3.5, 2.5 Hz, C<u>H</u>N), 7.13-7.62 (10H, m, aromatic H), 7.99 (1H, d, *J* 2.5 Hz, H-4); $\nu_{max.}$ 1742, 1698, 1679, 1620, 1451, 1346, 1297, 1223, 693, and 664 cm^{-1}. This material was used immediately without purification.

Intermolecular Diels-Alder Reactions

4-Benzoyl-5-benzyl-2-(1-oxopropyl)-4-azatricyclo[5.2.1.$0^{2,6}$] dec-8-en-3-one (221) and (222)

A solution of the pyrrolinone (195) (49.5 mg, 0.149 mmol) and freshly distilled cyclopentadiene (0.13 ml, 1.57 mmol) in benzene (0.5 ml) was stirred at 25° for 3 h. Removal of the volatile components and purification of the residue by short column chromatography using ether-petrol (1:3) as eluant gave *4-benzoyl-5-benzyl-2-(1-oxopropyl)-4-azatricyclo[5.2.1.$0^{2,6}$] dec-8-en-3-one* (221) and (222) as a partially separated mixture of stereoisomers (*ca* 5:6) (34.4 mg, 58%), δ (less polar, 222) 1.05 (3H, t, *J* 7.1Hz, $CH_2\underline{CH}_3$), 1.48-1.60 (2H, m, 10-H_2), 2.50 (1H, dq, *J* 19.2, 7.1 Hz, $\underline{CH}_2CH_3$), 2.55 (1H, brs, H-7), 2.66 (1H, brs, H-6), 2.78 (1H, dd, *J* 12.8, 10.5 Hz, C<u>H</u>Ph), 3.02 (1H, dq, *J* 19.2, 7.1 Hz, $\underline{CH}_2CH_3$), 3.35 (1H, dd, *J* 12.8, 3.4 Hz, C<u>H</u>Ph), 3.49 (1H, brs, H-1), 4.41 (1H, dt, *J* 10, 3 Hz, C<u>H</u>N), 6.00 (1H, dd,

J 5.7, 2.8 Hz, H-9(, 6.15 (1H, dd, J 5.7, 3.1 Hz, H-8), 7.25-7.58 (10H, m, aromatic H); δ (more polar, 221) 1.05 (3H, t, J 7 Hz, $CH_2\underline{C}H_3$), 1.52 (2H, m, 10-H_2), 2.70 (2H, m, J 19, 7 Hz, $C\underline{H}_2CH_3$), 2.82 (1H, brs, H-7), 2.85 (1H, dd, J 12.5, 10.5 Hz, C<u>H</u>Ph), 3.16 (1H, dd, J 5.5, 3 Hz, H-6), 3.24 (1H, dd, J 12.5, 3 Hz, C<u>H</u>Ph), 3.35 (1H, brs, H-1), 4.22 (1H, dt, J 10, 3 Hz, C<u>H</u>N), 6.26 (1H, dd, J 5.5, 3 Hz, H-9), 6.35 (1H, dd, J 5.5, 3 Hz, H-8), 7.25-7.59 (10H, m, aromatic H); $\nu_{max.}$ 2980, 2935, 1732, 1704, 1687, 1280, 1226br, 1140, 692, and 659 cm^{-1}; *m/z* 399 (M^+, 4%) and 105 (100%) (Found: M^+ 399.1834. $C_{26}H_{25}NO_3$ requires M^+ 399.1836).

8-Benzoyl-7-benzyl-2,5-dimethyl-1-(1-oxopropyl)-8-azabicyclo[4.3.0] non-3-en-9-one (223)

A solution of the pyrrolinone (195) (205 mg, 0.62 mmol) and 2<u>E</u>,4<u>E</u>-hexadiene (0.55 ml, 4.82 mmol) in benzene (1.5 ml) was heated at 100° in a sealed Pyrex tube (13x10 mm) for 8 h. After cooling, the volatile components were removed and the residue was purified by short column chromatography using ether-petrol (2:7) as eluant to give *8-benzoyl-7-benzyl -2,5-dimethyl-1-(1-oxopropyl)-8-azabicyclo[4.3.0]non-3-en-9-one* (223) as a viscous oil (187 mg, 72%); $[\alpha]_D^{20}$ +74.7 (c 0.17, $CHCl_3$); δ (*ca* 4:1 ratio) 0.73 (0.6H, d, J 7 Hz, $CHC\underline{H}_3$), 0.89 (2.4H, t, J 7 Hz, $CH_2C\underline{H}_3$), 1.07 (0.6H, d, J 7.4 Hz, $CHC\underline{H}_3$), 1.10 (2.4H, d, J 7.2 Hz, 5-$C\underline{H}_3$), 1.13 (0.6H, t, J 7.1 Hz, $CH_2C\underline{H}_3$), 1.16 (2.4H, d, J 7.1 Hz, 2-$C\underline{H}_3$), 1.48 (0.8H, dq, J 19.1, 7 Hz, $COC\underline{H}CH_3$), 1.91 (0.2H, m, $COC\underline{H}CH_3$), 2.24-2.74 (2H, m, $COC\underline{H}CH_3$ and H-5), 2.64 (1H, dd, J 6, 5.4 Hz, H-6), 2.79 (1H, m, H-2), 2.95 (1H, dd, J 13.6, 2.9 Hz, C<u>H</u>Ph), 3.17 (1H, dd, J 13.7, 6.6 Hz, C<u>H</u>Ph), 4.36-4.42 (1H, m, C<u>H</u>N), 5.61-5.77 (2H, m, vinylic H), 7.11-7.73 (10H, m, aromatic H); $\nu_{max.}$ 2970, 2940, 1738, 1712, 1681, 1604, 1451, 1288br, 1216, 693, and 658 cm^{-1}; *m/z* 416 (M^+, 29%) and 105 (100%) (Found: M^+ 415.2147. $C_{27}H_{29}NO_3$ requires

M^+ 415.2149).

7-Benzyl-2,5-dimethyl-1-(1-oxopropyl)-8-azabicyclo[4.3.0]non-3-en-9-one (224) and (225)

50% Aqueous KOH (4 ml) was added dropwise to a solution of the isoindolone (223) (177 mg, 0.426 mmol) in benzene-methanol (1:2) (10 ml)[25a] and the resulting mixture was stirred briskly for 5 h. The reaction was poured into 3 M HCl (15 ml) and the product was extracted with ether to give a crude solid (179 mg). Purification by short column chromatography using ether-petrol (1:2) and (2:1) as eluants gave 1S,2S,5R,6R,7S-*7-benzyl-2,5-dimethyl-1-(1-oxopropyl)-8-azabicyclo[4.3.0]non-3-en-9-one* (224) as a solid (101 mg, 77%) which was crystallized from cold pentane to give needles, mp. 138.5-140°; $[\alpha]_D^{20}$ +13.1 (c 0.28, CCl_4); δ 1.03 (3H, t, *J* 7.2 Hz, $CH_2\underline{CH}_3$), 1.20 (3H, d, *J* 7.2 Hz, 2-$\underline{CH}_3$), 1.25 (3H, d, *J* 7 Hz, 5-$\underline{CH}_3$), 2.32 (1H, dq, *J* 18.6, 7.1 Hz, $\underline{CH}_2CH_3$), 2.45 (2H, m, *J* 4.5 Hz, H-6 and H-5), 2.55 (1H, dd, *J* 13.6, 9 Hz, C<u>H</u>Ph), 2.75 (1H, dq, *J* 18.5, 7.1 Hz, C<u>H</u>CH_3), 2.94 (1H, m, H-2), 3.02 (1H, dd, *J* 13.7, 3.4 Hz, C<u>H</u>Ph), 3.47 (1H, m, C<u>H</u>N), 5.57 (1H, brs, NH), 5.64 (1H, m, H-4), 5.74 (1H, dt, *J* 8.9, 3 Hz, H-3), 7.14-7.37 (5H, m, aromatic H); $\nu_{max.}$ 3430, 3190br, 2965, 2935, 1707, 1692, 1453, 1378, and 698 cm^{-1}; *m/z* 312 (M^++1, 17%) and 91 (100%) (Found: C, 76.8; H, 7.9; N, 4.6. $C_{20}H_{25}NO_2$ requires C, 77.1; H, 8.1; N, 4.5%). Also eluted was 1S,2R,5S,6R,7S-*7-benzyl-2,5-dimethyl-1-(1-oxopropyl)-8-azabicyclo[4.3.0]non-3-en-9-one* (225) as a colourless oil (24 mg, 18%), δ 1.00 (3H, d, *J* 7.1 Hz, 5-$\underline{CH}_3$), 1.06 (3H, t, *J* 7.1 Hz, $CH_2\underline{CH}_3$), 1.18 (3H, d, *J* 7.4 Hz, 2-$\underline{CH}_3$), 2.06 (1H, m, H-5), 2.24 (1H, dd, *J* 5, 3.6 Hz, H-6), 2.46 (1H, dq, *J* 18.5, 7.1 Hz, $\underline{CH}_2CH_3$), 2.49 (1H, m, H-2), 2.59 (1H, dd, *J* 13.5, 8.6 Hz, C<u>H</u>Ph), 2.78 (1H, dq, *J* 18.5, 7.1 Hz, $\underline{CH}_2CH_3$), 2.88 (1H, dd, *J* 13.5, 5.2 Hz, C<u>H</u>Ph), 3.49 (1H, m, C<u>H</u>N), 5.63 (2H, m, vinylic H),

6.08 (1H, brs, NH), 7.17-7.36 (5H, m, aromatic H); $\nu_{max.}$ 3430, 3200br, 2965, 2940, 1709br, 1458, 1382, and 699 cm^{-1}; *m/z* 312 (M^++1 , 58%) and 91 (100%) (Found: M^+ 311.1885. $C_{20}H_{25}NO_2$ requires M^+ 311.1885).

1-Benzenesulphonylpyrrolidin-2-one (227)

BuLi (2.3 M, 21.7 ml, 50 mmol) was added to a solution of pyrrolidin-2-one (140) (3.8 ml, 50 mmol) in THF (160 ml) at 0° and the resulting slurry was stirred for 35 min. Neat benzenesulphonyl chloride (7 ml, 54.8 mmol) was then added and after 50 min at 0° the solvents were removed *in vacuo* . CH_2Cl_2 was added to the residue which was triturated with ether. The mixture was filtered through Celite, the inorganic salts were washed several times with CH_2Cl_2 and the filtrate was concentrated. The crude solid product was dissolved in ethanol and treated with charcoal for 10 min. After filtering, the hot solution was allowed to cool, a small amount of pentane was added and the whole was left in a refrigerator overnight. *1-Benzenesulphonylpyrrolidin-2-one* (227) was collected as a crystalline solid (7.562 g, 67%), mp. 83.5-84°; δ 2.09 (2H, tt, *J* 7.6 Hz, CH_2CN), 2.45 (2H, t, *J* 7.7 Hz, CH_2CO), 3.92 (2H, t, *J* 7 Hz, CH_2N), 7.54-8.10 (5H, m, aromatic H); $\nu_{max.}$ ($CHCl_3$) 3030, 1742, 1360, 1174, 1123, 960, and 687 cm^{-1}; *m/z* 226 (M^++1 , 4%) and 141 (100%) (Found: C, 53.3; H, 4.95; N, 6.4; S, 14.3. $C_{10}H_{11}NO_3S$ requires C, 53.3; H, 4.9; N, 6.2; S,14.2%).

1-Benzenesulphonyl-3-(1-oxopropyl)pyrrolidin-2-one (228)

A solution of lactam (227) (1.5 g, 6.66 mmol) in THF (6 ml) was added to LDA (13.6 mmol) in THF (20 ml) at -70°. After 30 min, the solution was cooled to -100°, neat propionyl chloride (0.65 ml, 7.45 mmol) was added quickly and the mixture was stirred for 20 min. 3 M HCl (10 ml) was then

added, the slurry was poured into more acid (20 ml) and the aqueous phase was continuously extracted with CH_2Cl_2 (120 ml) for 3 h. The organic extracts were dried ($MgSO_4$) and evaporated to give an oil which was purified by flash chromatography using ether-petrol (3:1) as eluant. *1-Benzenesulphonyl-3-(1-oxopropyl)pyrrolidin-2-one* (228) was obtained as a pale yellow oil (1.171 g, 63%), δ 0.99 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 2.05-2.18 (1H, m, C<u>H</u>CN), 2.37-2.61 (2H, m, C<u>H</u>CN and $C\underline{H}CH_3$), 2.86 (1H, dq, *J* 19, 7 Hz, $C\underline{H}CH_3$), 3.61 (1H, dd, *J* 9, 7 Hz, COC<u>H</u>CO), 3.81-4.00 (2H, m, $C\underline{H}_2N$), 7.52-8.07 (5H, m, aromatic H); $\nu_{max.}$ 2985, 1742, 1721, 1685, 1453, 1381, 1217, 1177, 1094, and 688 cm^{-1}; *m/z* 281 (M^+, 4%) and 77 (100%) (Found: M^+ 281.0722. $C_{13}H_{15}NO_4S$ requires M^+ 281.0722).

1-Benzenesulphonyl-3-(1-oxopropyl)-3-phenylselenopyrrolidin-2-one (229)

A solution of lactam (228) (306 mg, 1.09 mmol) in THF (1.5 ml) was added to LDA (1.2 mmol) in THF (2 ml) at -75°. After 15 min, phenylselenenyl chloride (290 mg, 1.51 mmol) in THF (1.5 ml) was added and the mixture was stirred for 5 min before being brought immediately to 0°. Saturated aqueous NH_4Cl (25 ml) and 3 <u>M</u> HCl (10 ml) were added and the product was extracted with ether to give a crude oil. Purification by flash chromatography using ether-petrol (1:1) as eluant gave *1-benzenesulphonyl-3-(1-oxopropyl)-3-phenylselenopyrrolidin-2-one* (229) as a pale yellow solid (298 mg, 63%). A portion was crystallized from ether to give plates, mp. 90°; δ 1.04 (3H, t, *J* 7.1 Hz, $CH_2\underline{CH}_3$), 1.88 (1H, ddd, *J* 14.5, 6.6, 2.4 Hz, C<u>H</u>CN), 2.49-2.63 (1H, m, C<u>H</u>CN), 2.65-2.76 (1H, dq, *J* 18.4, 7.1 Hz, $C\underline{H}CH_3$), 2.98-3.12 (1H, dq, *J* 18.3, 7.1 Hz, $C\underline{H}CH_3$), 3.63-3.72 (1H, m, C<u>H</u>N), 3.86 (1H, brt, *J* 9.3, 8.6 Hz, C<u>H</u>N), 7.23-8.13 (10H, m, aromatic H); $\nu_{max.}^{(CHCl_3)}$ 3030, 1728, 1701, 1373, 1360, 1188, 1174, 1120, 1092, and 688 cm^{-1}; *m/z* 437 (M^+, 6%) and 77 (100%) (Found: C, 52.3; H, 4.65; N, 3.4. $C_{19}H_{19}NO_4SSe$

requires C, 52.3; H, 4.4; N, 3.2%).

1-Benzenesulphonyl-3-(1-oxopropyl)- Δ^3*-pyrrolin-2-one* (230)

MCPBA (58 mg, 0.29 mmol) was added in portions to a solution of the selenide (229) (55 mg, 0.135 mmol) in CH_2Cl_2 (1.3 ml) at 25°. After 5 min the colourless solution was poured into ice-cold 10% aqueous $NaHCO_3$ (5 ml) and the product was extracted with CH_2Cl_2 (2x10 ml) to give *1-benzenesulphonyl-3-(1-oxopropyl)-* Δ^3 *-pyrrolin-2-one* (230) as an unstable semi-solid (35.6 mg, 94%), δ 1.07 (3H, t, *J* 7.2 Hz, $CH_2\underline{CH}_3$), 2.88 (2H, q, *J* 7.1 Hz, $C\underline{H}_2CH_3$), 4.56 (2H, d, *J* 2 Hz, $C\underline{H}_2N$), 7.49-8.15 (6H, m, H-4 and aromatic H); $\nu_{max.}$ (CH_2Cl_2) 3070, 2940, 1735, 1700, 1626br, 1374br, 1227, 1189, 1179, 1091, 808, and 687 cm^{-1}. This material was used immediately without purification.

Intermolecular Diels-Alder Reactions

General Procedure

A solution of the crude pyrrolinone (230) (*ca* 50 mg/ml) and 2E,4E-hexadiene or freshly distilled cyclopentadiene (12-60 molar eq.) in CH_2Cl_2 or benzene was sealed in a Pyrex tube (13x10 mm) under argon and heated to 110-120° (or 55° for cyclopentadiene cases) for the appropriate time (see Table 4.1). After cooling, the volatile components were removed and the crude product was purified by flash chromatography eluting with ether-petrol (1:1) in the hexadiene cases, and petrol (to remove dicyclopentadiene) followed by ether-petrol (1:1) in the cyclopentadiene reactions. In this way the following adducts were isolated:

1RS*,2RS*,5SR*,6SR* *-8-Benzenesulphonyl-2,5-dimethyl-1-(1-oxopropyl)-8-aza-*

bicyclo[4.3.0]non-3-en-9-one (231) and (232), (*ca* 20 mg, 22-40%), δ (*ca* 7:1 ratio) 0.72 (0.38H, d, *J* 7.5 Hz, $CHC\underline{H}_3$), 0.75 (2.62H, d, *J* 7.5 Hz, 2-$C\underline{H}_3$), 0.82 (0.38H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 1.01 (2.62H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 1.09 (2.62H, d, *J* 7.4 Hz, 5-$C\underline{H}_3$), 1.10 (0.38H, obscured d, $CHC\underline{H}_3$), 1.70-1.87 (0.12H, m, $C\underline{H}CH_3$), 2.39-2.45 (0.88H, m, H-5), 2.55 (2H, q, *J* 7.2 Hz, $C\underline{H}_2CH_3$), 2.75-2.80 (1H, m, H-2), 2.83-2.92 (1H, m, *J* 8.7 Hz, H-6), 3.42 (0.88H, ψ t, *J* 9.8 Hz, $C\underline{H}N$), 3.55-3.72 (0.25H, m, $C\underline{H}_2N$), 3.92 (0.88H, dd, *J* 9.5, 8.5 Hz, $C\underline{H}N$), 5.20-5.41 (0.25H, m, vinylic H), 5.42 (0.88H, brdt, *J* 9.5, 2 Hz, H-3), 5.53 (0.88H, dt, *J* 9.8, 3 Hz, H-4), 7.53-8.10 (5H, m, aromatic H); $\nu_{max.}$ ($CHCl_3$) 3035, 2970, 1731, 1710, 1453, 1370br, 1188, 1175, 1091, and 688 cm^{-1}; *m/z* 361 (M^+, 7%) and 304 (100%) (Found: M^+ 361.1350. $C_{19}H_{23}NO_4S$ requires M^+ 361.1348).

1$\underline{RS}^*$,2$\underline{RS}^*$,6$\underline{SR}^*$,7$\underline{SR}^*$ *-4-Benzenesulphonyl-2-(1-oxopropyl)-4-azatricyclo-*[*5.2.1.*$0^{2,6}$]*dec-8-en-3-one* (233) and (234) as a partially separated mixture of stereoisomers, (*ca* 30 mg, 58-67%), δ (less polar, 234) 0.88 (3H, t, *J* 7 Hz, $CH_2C\underline{H}_3$), 1.10 (1H, brd, *J* 9.5 Hz, H_{anti}-10), 1.22 (1H, obscured m, H_{syn}-10), 2.32 (1H, dq, *J* 19, 7 Hz, $C\underline{H}CH_3$), 2.76 (1H, m, H-6), 2.82 (1H, brs, 10-C$\underline{H}$), 2.90 (1H, dq, *J* 18.5, 7 Hz, $C\underline{H}CH_3$), 3.34 (1H, brs, 10-C$\underline{H}$), 3.49 (1H, dd, *J* 10.5, 3.5 Hz, $C\underline{H}N$), 4.04 (1H, dd, *J* 10, 9 Hz, $C\underline{H}N$), 5.94 (1H, dd, *J* 6, 3 Hz, vinylic H), 6.17 (1H, dd, *J* 6, 3 Hz, vinylic H), 7.45-7.97 (5H, m, aromatic H); δ (more polar, 233) 1.02 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 1.38 (1H, brd, *J* 9.2 Hz, H_{anti}-10), 1.46 (1H, brdt, *J* 9.1, 1.6 Hz, H_{syn}-10), 2.67 (1H, dq, *J* 18.8, 7.2 Hz, $C\underline{H}CH_3$), 2.79 (1H, dq, *J* 18.7, 7.1 Hz, $C\underline{H}CH_3$), 3.05 (1H, brs, 10-C$\underline{H}$), 3.23 (1H, ddd, *J* 9.3, 4.1, 2.7 Hz, H-6), 3.30 (1H, obscured brs, 10-C$\underline{H}$), 3.33 (1H, dd, *J* 10.7, 2.7 Hz, C$\underline{H}$N), 3.93 (1H, dd, *J* 10.7, 9.3 Hz, C$\underline{H}$N), 5.65 (1H, dd, *J* 5.7, 3 Hz, vinylic H), 5.93 (1H, dd, *J* 5.6, 3 Hz, vinylic H), 7.53-8.02 (5H, m, aromatic H);

$\nu_{max.}$ 2985, 1731, 1712, 1483, 1451, 1382br, 1188, 1179, 1130, 1090, and 688 cm^{-1}; *m/z* 345 (M^+ , 10%) and 280 (100%) (Found: M^+ 345.1035. $C_{18}H_{19}NO_4S$ requires M^+ 345.1035).

Attempted Determination of the Optical Purity of Isoindolone (224)

Method 1

BuLi (1.5 M, 0.05 ml, 0.075 mmol) was added to a solution of hexamethyldisilazine (0.02 ml, 0.095 mmol) in THF (0.5 ml) at 0°. After 10 min, the solution was cooled to -70° and the isoindolone (224) (22 mg, 0.07 mmol) in THF (0.6 ml) was added slowly. The solution was stirred for 15 min and (-)-MTPA-chloride (27 mg, *ca* 0.1 mmol) in THF (0.6 ml) was added. After 5 min, the cooling bath was removed and the solution was stirred for 1 h, poured into 3 M HCl (10 ml) and extracted with ether to give an oil (38 mg). Tlc analysis and the 300 MHz ^1H nmr spectrum of the crude product showed it to be a mixture of both starting materials.

Method 2

Tris (3-(trifluoromethylhydroxymethylene)-*d*-camphorato) europium (III) (6 mg, 0.007 mmol) was added to a solution of the isoindolone (8.5 mg, 0.027 mmol) in $CDCl_3$ (*ca* 1.5 ml) and the 300 MHz ^1H nmr spectrum was recorded.[98] Further 6 mg portions of the chiral shift reagent were added but no well-resolved splitting of the resonances was observed.

10-Bromodecanol (236)

Decane-1,10-diol (235) (50 g, 0.287 mol) and 48% HBr (150 ml) were reacted according to the literature method.[134] After purification with

anhydrous $CaCl_2$[135] and distillation,10-bromodecanol (236) was obtained as an oil (44.9 g, 66%), bp. 120-5°/1.5 mmHg (lit.,[136] 166-9°/10 mmHg), δ 1.25-1.48 (12H, m, $(C\underline{H}_2)_6$), 1.58 (3H, m, $C\underline{H}_2CH_2Br$ and OH), 1.86 (2H, m, *J* 7.5 Hz, $C\underline{H}_2CH_2O$), 3.41 (2H, t, *J* 7 Hz, $C\underline{H}_2Br$), 3.64 (2H, t, *J* 7 Hz, $C\underline{H}_2O$).

10-Bromodecanol-OTHP-ether (237)

The O-THP ether[3a] was prepared from the alcohol (236) according to the method of Rossi[137] (> 95%) but using only 1.1 molar equivalents of dihydropyran, δ (60 MHz) 1.1-2.1 (22H, m, $(C\underline{H}_2)_8$, 3'-H_2, 4'-H_2, and 5'-H_2), 3.2-4.1 (6H, m, $C\underline{H}_2Br$, $C\underline{H}_2O$ and 6'-H_2), 4.59 (1H, brs, 2'-H).

2E,4E *-Hexadien-1-ol* (238)

The dienol was prepared in 57% yield from 2E,4E-hexadienoic acid according to the literature method[138] and using the work-up procedure of Micović,[139] bp. 76-80°/ *ca* 12 mmHg (lit.,[138] 76-7°/12 mmHg), δ (60 MHz) 1.65 (1H, brs, OH), 1.76 (3H, d, *J* 6 Hz, $CHC\underline{H}_3$), 4.16 (2H, brd, *J* 6 Hz, $C\underline{H}_2O$), 5.39-6.51 (4H, m, vinylic H).

2E,4E *-Hexadienyl Acetate* (239)

The ester was prepared in 73% yield according to the literature method,[140] bp. 76-80°/*ca* 12 mmHg (lit.,[141] 81-3°/18 mmHg), δ 1.76 (3H, d, *J* 6.7 Hz, $CHC\underline{H}_3$), 2.06 (3H, s, $COC\underline{H}_3$), 4.56 (2H, d, *J* 6.6 Hz, $C\underline{H}_2O$), 5.56-6.29 (4H, m, vinylic H).

12E,14E *-Hexadecadien-1-ol* (240)

The dienol (240) was prepared according to the literature procedure[28] but in consistently lower yields (14-25%). The modifications of adding the Grignard solution *to* the sorbyl acetate (239) and copper catalyst at -78° or -30° did not lead to any improvement in the yield of pure product. Mp. 46.5-47.5° (ether) (lit.,[28] 48-9°), δ 1.20-1.67 (19H, m, $(C\underline{H}_2)_9$ and OH), 1.73 (3H, d, *J* 6.5 Hz, $CHC\underline{H}_3$), 2.05 (2H, brq, *J* 6.9 Hz, $C\underline{H}_2CH=$), 3.65 (2H, t, *J* 6.6 Hz, $C\underline{H}_2O$), 5.51-5.63 and 5.95-6.08 (4H, both m, vinylic H); *m/z* 238 (M^+ , 19%) and 68 (100%).

12E,14E-*Hexadecadienal* (241)

The aldehyde (241) was prepared in 85-95% yield from alcohol (240) according to the literature method.[28] The simplified work-up of rapidly filtering the crude mixture through a short column of silica enabled the aldehyde to be obtained as a low melting solid, mp. 30-1°, δ 1.21-1.68 (16H, m, $(C\underline{H}_2)_8$), 1.73 (3H, d, *J* 6.4 Hz, $CHC\underline{H}_3$), 2.04 (2H, brq, *J* 6.9 Hz, $C\underline{H}_2CH=$), 2.42 (2H, td, *J* 7.3, 1.8 Hz, $C\underline{H}_2CH=O$), 5.50-5.63 and 5.94-6.07 (4H, m, vinylic H), 9.77 (1H, t, *J* 1.8 Hz, $C\underline{H}=O$).

12E,14E-*Hexadecadienoic Acid* (242)

The acid (242) was prepared from the foregoing aldehyde (241) according to the literature method[28] in 58-74% yield as an amorphous solid, mp. 63-5° (ether) (lit.,[28] 63-64.5°), δ 1.27-1.69 (17H, m, $(C\underline{H}_2)_8$ and OH), 1.73 (3H, d, *J* 6.4 Hz, $CHC\underline{H}_3$), 2.04 (2H, brq, *J* 6.9 Hz, $C\underline{H}_2CH=$), 2.36 (2H, t, *J* 7.5 Hz, $C\underline{H}_2CO_2H$), 5.50-5.63 and 5.94-6.08 (4H, m, vinylic H).

1-Tetradecanoylimidazole (244)[142]

A solution of myristic acid (243) (288 mg, 1.26 mmol) in THF (1.4 ml) was added to a suspension of 1,1'-carbonyldi-imidazole (209 mg, 1.29 mmol) in THF (4 ml) and the mixture was stirred for 75 min. The THF was removed *in vacuo* , ice-cold water and ether were added to the residue and the product was quickly extracted. *1-Tetradecanoylimidazole* (244) was obtained as a crystalline mass (319 mg, 91%), mp. 70-2°. Recrystallization from ether gave plates, mp. 77-8°, δ 0.89 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 1.23-1.48 (20H, m, $(\underline{CH}_2)_{10}$), 1.80 (2H, tt, *J* 7 Hz, $\underline{CH}_2CCO$), 2.86 (2H, t, *J* 7.3 Hz, 7.11 (1H, t, *J* 0.7 Hz, H-4'), 7.49 (1H, t, *J* 1.5 Hz, H-5'), 8.17 (1H, s, H-2'); $\nu_{max.}$ 2935, 2860, 1746, 1472, 1388, 1228br, and 650 cm^{-1}; *m/z* 278 (M^+ , 1%) and 69 (100%) (Found: C, 73.2; H, 10.9; N, 9.95. $C_{17}H_{30}N_2O$ requires C, 73.3; H, 10.9; N, 10.1%).

5-Benzyl-1- tert *-butyldimethylsilyl-3-(1-oxotetradecyl)pyrrolidin-2-one* (245)

A solution of lactam (157) (291 mg, 1 mmol) in THF (1.8 ml) was added to LDA (2.08 mmol) in THF (3 ml) at -75°. After 50 min, 1-tetradecanoyl-imidazole (244) (296 mg, 1.06 mmol) in THF (3.5 ml) was added and the resulting mixture was allowed to warm to 0° (2 h), before being poured into 3 M HCl (10 ml) and extracted with ether. The crude oil obtained was purified by flash chromatography eluting with ether-petrol (1:5), to give *5-benzyl-1-* tert *-butyldimethylsilyl-3-(1-oxotetradecyl)pyrrolidin-2-one* (245) as an oil (334 mg, 67%) which crystallized slowly at 4° into an amorphous solid, mp. 53-56.5°, δ (*ca* 2:1 ratio) 0.33, 0.39, 0.42, and 0.45 (6H, all s, $Si(\underline{CH}_3)_2$), 0.89 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 0.97 and 1.00 (9H, both s, $Si(\underline{CH}_3)_3$), 1.26 (22H, brs, $(\underline{CH}_2)_{11}$), 1.55 (1H, m, $\underline{CH}CN$), 1.87 (0.67H, m, $\underline{CH}CN$), 2.42-2.68 (2.33H, m, $\underline{CH}CN$ and $\underline{CH}_2CO$), 2.88-3.05 (2H, m, $\underline{CH}_2Ph$), 3.48 (0.67H, dd, *J* 11.1, 8.1 Hz, $COC\underline{H}CO$), 3.55 (0.33H, dd, *J* 10.4,

2.3 Hz, COCHCO), 3.82 (1H, m, CHN), 7.15-7.40 (5H, m, aromatic H); $\nu_{max.}$ 2965, 2935, 2860, 1721, 1683, 1467, 1375, 1355, 1230, 1087, and 700 cm^{-1}; *m/z* 499 (M^+ , 1%) and 442 (100%) (Found: C, 74.4; H, 10.45; N, 3.0. $C_{31}H_{53}NO_2Si$ requires C, 74.5; H, 10.7; N, 2.8%).

12E,14E-*1-(Hexadeca-12,14-dienoyl)imidazole* (246)

Using the procedure for the preparation of imidazole (244), but leaving the reaction for 1-2 h, 12E,14E-*1-(Hexadeca-12,14-dienoyl)imidazole* (246) was prepared from the acid (242) as an amorphous solid (75-93%), mp. 71-2° (ether-petrol); δ 1.24-1.47 (14H, m, $(CH_2)_7$), 1.73 (3H, d, *J* 6.7 Hz, $CHCH_3$), 1.81 (2H, m, CH_2CH_2CO), 2.05 (2H, td, *J* 7, 6.8 Hz, $CH_2CH=$), 2.86 (2H, t, *J* 7.4 Hz, CH_2CO), 5.51- 5.63 (2H, m, vinylic H), 5.95-6.08 (2H, m, vinylic H), 7.11 (1H, d, *J* 1 Hz, H-4'), 7.50 (1H, d, *J* 1 Hz, H-5'), 8.17 (1H, s, H-2'); $\nu_{max.}$ 3025, 2935, 2860, 1747, 1473, 1388, 1228br, 985, and 650 cm^{-1}; *m/z* 302 (M^+ , 2%) and 69 (100%) (Found: C, 75.3; H, 10.2; N, 9.0. $C_{19}H_{30}N_2O$ requires C, 75.45; H, 10.0; N, 9.3%).

12E,14E-*5-Benzyl-1-(* tert*-butyldimethylsilyl)-3-(1-oxohexadeca-12,14-dienyl)pyrrolidin-2-one* (247)

A solution of lactam (157) (131 mg, 0.452 mmol) in THF (1.5 ml) was added to LDA (0.928 mmol) in THF (1.5 ml) at -75°. After 50 min, 12E,14E-1-(hexadeca-12,14-dienoyl)imidazole (246) (140 mg, 0.463 mmol) in THF (1.5 ml) was added and the resulting mixture was allowed to warm gradually to 0° (1.5 h) before being poured into acidic NH_4Cl solution. Rapid ether extraction gave an oil which was purified by flash chromatography using ether-petrol (1:4) as eluant. 12E,14E -*5-Benzyl-1-(*tert*-butyldimethylsilyl)-3-(1-oxo-*

hexadeca-12,14-dienyl)pyrrolidin-2-one (247) was obtained as an oil (132 mg, 56%), δ (*ca* 1:1 ratio) 0.33, 0.39, 0.42, and 0.45 (6H, all s, $Si(C\underline{H}_3)_3$), 0.97 and 1.00 (9H, both s, $Si(C\underline{H}_3)_3$), 1.22-1.62 (16H, m, $(C\underline{H}_2)_8$), 1.73 (3H, d, *J* 6.3 Hz, $CHC\underline{H}_3$), 1.82-1.98 (1H, m, C<u>H</u>CN), 2.04 (2H, brq, *J* 7 Hz, $C\underline{H}_2CH=$), 2.42-2.68 (3H, m, C<u>H</u>CN, C<u>H</u>CO and C<u>H</u>Ph), 2.88-3.08 (2H, m, C<u>H</u>CO and C<u>H</u>Ph), 3.49 (0.5H, dd, *J* 11.1, 8 Hz, COC<u>H</u>CO), 3.55 (0.5H, dd, *J* 11, 3.5 Hz, COC<u>H</u>CO), 3.75 (0.5H, m, C<u>H</u>N), 3.84 (0.5H, m, C<u>H</u>N), 5.51-5.63 (2H, m, vinylic H), 5.95-6.08 (2H, m, vinylic H), 7.15-7.40 (5H, m, aromatic H); $\nu_{max.}$ 2935, 2865, 1720, 1682, 1465, 1373, 1230br, 1087, and 700 cm^{-1}; *m/z* 523 (M^+, 22%) and 466 (100%) (Found: M^+ 523.3857. $C_{33}H_{53}NO_2Si$ requires M^+ 523.3845), along with dienoic acid (242) (33 mg, 28%).

In most of these acylations, starting material and acid (242) were recovered in *ca* 30% combined yield. Adventitious silyl hydrolysis was also responsible for *ca* 5% products and, in one experiment, 12<u>E</u>,14<u>E</u>-*5-benzyl-3-(1-oxohexadeca-12,14-dienyl)pyrrolidin-2-one* (248) was obtained as a solid (266 mg, 50%), mp. 72-4° (ether-petrol), δ (*ca* 1:1 ratio) 1.28 and 1.52-1.65 (16H, m, $(C\underline{H}_2)_8$), 1.74 (3H, d, *J* 7 Hz, $CHC\underline{H}_3$), 1.87 (0.5H, ddd, *J* 16, 10, 6 Hz, C<u>H</u>CN), 2.05 (2H, brq, *J* 7.5 Hz, $C\underline{H}_2CH=$), 2.20-2.34 (0.5H, m, C<u>H</u>CN), 2.40-3.08 (5H, m, C<u>H</u>CN, $C\underline{H}_2CO$ and $C\underline{H}_2Ph$), 3.52 (0.5H, dd, *J* 9, 4 Hz, COC<u>H</u>CO), 3.59 (0.5H, dd, *J* 11, 9 Hz, COC<u>H</u>CO), 3.82 and 3.97 (1H, both m, C<u>H</u>N), 5.52-5.64 and 5.94-6.08 (4H, m, vinylic H), 5.67 and 5.71 (1H, both brs, NH), 7.15-7.37 (5H, m, aromatic H); $\nu_{max.}$ (CH_2Cl_2) 3420, 2935, 2860, 1698br, 1454, 1410, 1376, and 992 cm^{-1}; *m/z* 409 (M^+, 5%) and 81 (100%) (Found: C, 78.95; H, 9.6; N, 3.4. $C_{27}H_{39}NO_2$ requires C, 79.2; H, 9.6; N, 3.4%).

12<u>E</u>,14<u>E</u>-*5-Benzyl-1-(tert-butyldimethylsilyl)-3-(1-oxohexadeca-12,14-dienyl)-3-phenylselenopyrrolidin-2-one* (249)

A solution of lactam (247) (656 mg, 1.25 mmol) in THF (4 ml) was added to LDA (1.5 mmol) in THF (3 ml) at -75°. After 1 h, phenylselenenyl chloride (346 mg, 1.81 mmol) in THF (3 ml) was added and the resulting mixture was allowed to warm to 0° (1 h) before being poured into saturated NH_4Cl (20 ml). Rapid ether extraction and purification of the crude oil obtained using ether-petrol (1:20) as eluant gave 12E,14E-*5-benzyl-1-(tert-butyldimethylsilyl)-3-(1-oxohexadeca-12,14-dienyl)-3-phenylseleno-pyrrolididn-2-one* (249) as an oil (600 mg, 71%), δ (*ca* 3:1 ratio) 0.42 and 0.45 (6H, both s, $Si(C\underline{H}_3)_2$), 1.05 and 1.06 (9H, both s, $Si(C\underline{H}_3)_3$), 1.25-1.70 (17H, m, $(C\underline{H}_2)_8$ and C<u>H</u>CN), 1.76 (3H, d, *J* 7 Hz, $CHC\underline{H}_3$), 2.05 (2H, m, *J* 7.5 Hz, $C\underline{H}_2CH=$), 2.08-2.37 (2H, m, C<u>H</u>CN and C<u>H</u>CO), 2.62-3.02 (2H, m, C<u>H</u>CO and C<u>H</u>Ph), 3.08-3.40 (1H, m, C<u>H</u>Ph), 3.65 (0.75H, m, C<u>H</u>N), 3.77 (0.25H, m, C<u>H</u>N), 5.49-5.65 and 5.94-6.10 (4H, m, vinylic H), 6.96-7.54 (10H, m, aromatic H); $\nu_{max.}$ (CH_2Cl_2) 2935, 2840, 1673br, 1378, 1352, 1238br, 1097, 993, and 844 cm^{-1}; *m/z* (CI) 680 (M^++1, 6%) and 524 (100%), along with impure desilylated product (252) (126 mg, *ca* 15%).

12E,14E-*3-Benzoyl-5-benzyl-3-(1-oxohexadeca-12,14-dienyl)pyrrolidin-2-one* (250)

Benzoyl chloride (0.6 ml of a 0.56 M solution in CH_2Cl_2) was added to a solution of lactam (248) (95 mg, 0.232 mmol) and di-isopropylethyl-amine (0.07 ml, 0.4 mmol) in CH_2Cl_2 (0.6 ml) at 0°. After 1 h, the ice-bath was removed and the reaction was stirred at 25° for 24 h before being poured into 3 M HCl (5 ml) and extracted with ether. Purification of the crude product by flash chromatography, eluting with ether-petrol (1:2), gave 12E,14E-*3-benzoyl-5-benzyl-3-(1-oxohexadeca-12,14-dienyl)pyrrolidin-2-one* (250) as a viscous oil (89 mg, 75%), δ (*ca* 2:1 ratio) 1.12-1.59

(16H, m, $(C\underline{H}_2)_8$), 1.74 (3H, d, *J* 7 Hz, $CHC\underline{H}_3$), 2.04 (2H, m, *J* 7.5 Hz, $C\underline{H}_2CH=$), 2.29-2.45 (2H, m, $C\underline{H}_2CN$), 2.64 (0.67H, dd, *J* 13, 7 Hz, C<u>H</u>Ph), 2.69-3.12 (3H, m, $C\underline{H}_2CO$ and C<u>H</u>Ph), 3.30 (0.33H, dd, *J* 13, 7.5 Hz, C<u>H</u>Ph), 3.81-3.99 (1H, m, C<u>H</u>N), 5.50-5.65 and 5.97-6.08 (4H, m, vinylic H), 5.94 (1H, brs, NH), 7.13-7.87 (10H, m, aromatic H); $\nu_{max.}$ (CH_2Cl_2) 3415, 2935, 2860, 1723sh, 1710, 1672, 1599, 1582, 1450, 1239br, 993, and 910 cm^{-1}; *m/z* 513 (M^+ , 2%) and 105 (100%) (Found: M^+ 513.3257±20. $C_{34}H_{43}NO_3$ requires M^+ 513.3243).

12<u>E</u>,14<u>E</u>-*1-Benzoyl-5-benzyl-3-(1-oxohexadeca-12,14-dienyl)-3-phenylseleno-pyrrolidin-2-one* (251)

Benzoyl chloride (1.2 ml of a 0.91 <u>M</u> solution in benzene) was added to a solution of lactam (249) (623 mg, 0.918 mmol) in benzene (3.8 ml) and the resulting solution was heated at 80° for 12 h. The volatile components were removed and the residue was purified by flash chromatography using ether-petrol (1:7) as eluant to give 12<u>E</u>,14<u>E</u>-*1-benzoyl-5-benzyl-3-(1-oxohexadeca-12,14-dienyl)-3-phenylselenopyrrolidin-2-one* (251) as an oil (403 mg, 66%), (12<u>E</u>,14<u>E</u>:12<u>E</u>,14<u>Z</u> ratio *ca* 10:1), δ (*ca* 5:2 ratio) 1.20-1.68 (16H, m, $(C\underline{H}_2)_8$), 1.74 (3H, d, *J* 7 Hz, $CHC\underline{H}_3$), 1.96-2.13 (3H, m, $C\underline{H}_2CH=$ and C<u>H</u>CN), 2.33 (0.3H, dd, *J* 15, 6 Hz, C<u>H</u>CN), 2.50 (0.7H, dd, *J* 15, 7 Hz, C<u>H</u>CN), 2.60-2.83 (2.7H, m, C<u>H</u>CO and C<u>H</u>Ph), 2.95 (0.3H, dd, *J* 13, 9 Hz, C<u>H</u>Ph), 2.99-3.23 (1H, m, C<u>H</u>CO), 3.29 (0.7H, dd, *J* 14, 2.5 Hz, C<u>H</u>Ph), 3.30 (0.3H, obscured m, C<u>H</u>Ph), 4.55 (1H, m, C<u>H</u>N), 5.52-5.67 and 5.95-6.10 (4H, m, vinylic H), 7.05-7.67 (15H, m, aromatic H), δ (<u>Z</u>-isomer) 5.35, 5.69 and 6.32 (m, vinylic H); $\nu_{max.}$ (CH_2Cl_2) 2930, 2860, 1730, 1689br, 1603, 1348, 1270br, 1222, 994, and 655 cm^{-1}; *m/z* (CI) 670 (M^++1 , 1%) and 105 (100%), along with 12<u>E</u>,14<u>E</u>-*5-benzyl-3-(1-oxohexadeca-12,14-dienyl)-3-phenylselenopyrrolidin-2-one* (252) as an oil (93 mg, 18%), δ (<u>E</u>:<u>Z</u> ratio *ca* 4:1-9:1) 1.23-1.72

(16H, m, $(C\underline{H}_2)_8$), 1.76 (3H, d, *J* 7 Hz, $CHC\underline{H}_3$), 1.94-2.23 (3H, m, $C\underline{H}_2CH=$ and $C\underline{H}CN$), 2.47 (1H, dd, *J* 15, 7.5 Hz, $C\underline{H}CN$), 2.62 (1H, dd, *J* 13, 9.5 Hz, $C\underline{H}Ph$), 2.74-3.07 (2H, m, $C\underline{H}Ph$ and $C\underline{H}CO$), 3.13-3.32 (1H, m, $C\underline{H}CO$), 3.67-3.82 (1H, m, $C\underline{H}N$), 5.50-5.77 (2H, m, vinylic H), 5.91-6.10 (3H, m, vinylic H and NH), 7.07-7.59 (10H, m, aromatic H); δ (Z-isomer) 5.25-5.45 and 6.25-6.42 (m, vinylic H); $\nu_{max.}$ 3430, 3200br, 2935, 2860, 1714, 1699, 1405, 1371, 909, and 695 cm^{-1}; *m/z* (CI) 566 (M^++1, 9%) and 410 (100%).

5S,12E,14E-*1-Benzoyl-5-benzyl-3-(1-oxohexadeca-12,14-dienyl)-* Δ^3*-pyrrolin-2-one* (253)

General Procedure

A portion of a solution of 30% H_2O_2 (1 ml, *ca* 10 mmol) in water (9 ml) (15-25 molar eq.) was added dropwise to a vigorously stirred solution of the selenide (251) in CH_2Cl_2 (*ca* 30 mg/ml) and after 45-60 min, the mixture was poured into ice-cold 10% $NaHCO_3$ and extracted quickly into cold CH_2Cl_2 (x2). 5S,12E,14E-*1-Benzoyl-5-benzyl-3-(1-oxohexadeca-12,14-dienyl)-* Δ^3*-pyrrolin-2-one* (253) was obtained as an unstable yellow oil (30-50 mg, average yield 96%), δ 1.20-1.60 (16H, m, $(C\underline{H}_2)_8$), 1.76 (3H, d, *J* 7 Hz, $CHC\underline{H}_3$), 2.05 (2H, m, $C\underline{H}_2CH=$), 2.79 (2H, t, *J* 7 Hz, $C\underline{H}_2CO$), 3.17 (1H, dd, *J* 12.5, 8 Hz, $C\underline{H}Ph$), 3.47 (1H, dd, *J* 13, 3 Hz, $C\underline{H}Ph$), 5.34 (1H, m, $C\underline{H}N$), 5.50-5.65 and 5.96-6.12 (4H, m, vinylic H), 7.12-7.65 (10H, m, aromatic H); $\nu_{max.}$ (CH_2Cl_2) 2935, 2860, 1740, 1679br, 1621, 1451, 1300br, 994, 910, 843, and 664 cm^{-1}. This material was used immediately without purification.

6.4 *Experiments Discussed in Chapter 5*

Attempted Intramolecular Diels-Alder Reactions of Alkyl Diene-Dienophiles

General Procedure

A solution of the impure dienophile,(190) or (191), in degassed toluene (*ca* 0.005 M) was sealed in a Pyrex tube (14x11 mm) under argon and the whole was heated to between 170-190° in a Carius Oven. After 35-45 h, the solvent was removed under reduced pressure and the residue was purified by short column chromatography using ether-petrol mixtures.

From dienophile (190a) (20 mg) was obtained 5S-*1-acetyl-5-benzyl-3-octyl-* Δ^3*-pyrrolin-2-one* (192a) (*ca* 10 mg) as the only identifiable product, δ 0.90 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 1.18-1.50 (12H, m, $(\underline{CH}_2)_6$), 2.18 (2H, ψ t, *J* 7.5 Hz, $\underline{CH}_2C=$), 2.59 (3H, s, $NCO\underline{CH}_3$), 2.86 (1H, dd, *J* 14, 9 Hz, C<u>H</u>Ph), 3.49 (1H, dd, *J* 13.5, 3.5 Hz, C<u>H</u>Ph), 4.84 (1H, m, C<u>H</u>N), 6.77 (1H, brs, H-4), 7.08-7.35 (5H, m, aromatic H).

Similarly, dienophile (190b) (23 mg) gave 5S-*1-benzoyl-5-benzyl-3-octyl-* Δ^3*-pyrrolin-2-one* (192b) (*ca* 8 mg), δ 0.89 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 1.25-1.49 (12H, m, $(\underline{CH}_2)_6$), 2.15 (2H, ψ t, *J* 7 Hz, $\underline{CH}_2C=$), 3.08 (1H, dd, *J* 13.3, 8 Hz, C<u>H</u>Ph), 3.38 (1H, dd, *J* 13.3, 3.4 Hz, C<u>H</u>Ph), 5.16 (1H, m, C<u>H</u>N), 6.87 (1H, brs, H-4), 7.14-7.56 (10H, m, aromatic H). Also eluted was an unidentified oil (2.5 mg) which was homogeneous by tlc but which showed resonances in the ^{1}H nmr spectrum indicative of an intact Δ^3-pyrrolin-2-one structure but few vinylic protons.

From dienophile (191) (23 mg) only 5S-*1-benzoyl-5-benzyl-3-decyl-* Δ^3*-pyrrolin-2-one* (192c) was isolated, as an oil (4.2 mg), δ 0.90 (3H, t, *J* 7 Hz, $CH_2\underline{CH}_3$), 1.15-1.50 (16H, m, $(\underline{CH}_2)_8$), 2.15 (2H, ψ t, *J* 7.5 Hz, $\underline{CH}_2C=$), 3.08 (1H, dd, *J* 13, 8 Hz, C<u>H</u>Ph), 3.39 (1H, dd, *J* 13, 3 Hz, C<u>H</u>Ph), 5.18 (1H, m, C<u>H</u>N), 6.86 (1H, brs, H-4), 7.07-7.57 (10H, m, aromatic H).

Intramolecular Diels-Alder Reactions of the Doubly Activated Dienophile (253)

Thermal Reactions

A solution of the dienophile (253) in degassed toluene (or CH_2Cl_2) (*ca* 0.002 M) was sealed under argon in a flame-dried Carius tube and heated at 120° for 15-22 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography eluting with ether-petrol (1:5), to give the desired product (257) as an oil (5-10%) (*ca* 85:15 mixture).

Flash Vacuum Pyrolysis

Freshly prepared dienophile (253) (27 mg, 0.053 mmol) was heated to *ca* 200° at 10^{-4} mmHg and the volatile materials which passed through the pyrolysis tube (temperature *ca* 650°) were collected in a liquid nitrogen trap. The only isolable material was an orange oil (5 mg) which was shown by tlc to contain none of the cycloadduct (257).

Flow Pyrolysis

A solution of the dienophile (253) (29 mg, 0.057 mmol) in hexane-ether (11:1) (24 ml) was dripped into a quartz tube (30x3 cm) packed with pre-silylated Pyrex helices at *ca* 350° under a positive pressure of nitrogen. After the addition was complete, a further 25 ml of hexane was used to wash the column. The solvents were collected in a trap which was cooled to -78°, and were then evaporated under reduced pressure to give a yellow solid (5 mg). Tlc analysis showed that this material did not contain the desired product (257).

High Pressure Reactions

A solution of the dienophile (253) in CH_2Cl_2 (16 ml) (*ca* 0.002-0.006 M)

was placed in a Teflon vessel and the whole was immersed in hydraulic fluid (PLEXOL 244; Rohm and Haas (UK) Ltd.), maintained at 40°, and subjected to 11-13 kbar of pressure by means of a piston and cylinder apparatus (see Figure 5.2). After 18-24 h, the reaction was removed and the solvent was evaporated under reduced pressure. The oily residue was purified by flash chromatography as before, but hydraulic fluid (which could not be prevented from leaking into the Teflon vessel) was a major impurity. The impure mixture was thus passed through a Sephadex LH-20 column (30x2.5 cm), eluting with methanol, to give *19-benzoyl-18-benzyl-16-methyl-19-azatricyclo-*[*15.3.0.*^{1,13} *0*^{1,17}] *eicosa-14-en-2,20-dione* (257) as an oil (*ca* 10 mg, 16-35%), δ (*ca* 90:10 mixture of stereoisomers,"major" resonances reported) 1.00-1.61 (18H, m, $(C\underline{H}_2)_9$), 1.17 (3H, d, *J* 7.3 Hz, $CHC\underline{H}_3$), 1.83 (1H, ψt, *J* 12 Hz, H-3), 2.24 (1H, m, H-13), 2.51 (1H, m, H-16), 2.83 (1H, overlapping dd, *J* 6, 4 Hz, H-17), 2.85 (1H, dd, *J* 13.5, 2.5 Hz, C$\underline{H}$Ph), 3.08 (1H, m, H-3), 3.19 (1H, dd, *J* 13.5, 6.4 Hz, C$\underline{H}$Ph), 4.35 (1H, m, *J* 3.1 Hz, C$\underline{H}$N), 5.71 (1H, dt, *J* 8.8, 3.2 Hz, vinylic H), 5.80 (1H, dt, *J* 8.9, 2.8 Hz, vinylic H), 7.08-7.62 (10H, m, aromatic H); $\nu_{max.}$ (CH_2Cl_2) 2925, 2850, 1735, 1700, 1678, 1600, 1447, 1370, 1270br, 1218, and 655 cm^{-1}; *m/z* (CI) 512 (M^+*+1* , 100%).

18-Benzyl-16-methyl-19-azatricyclo[*15.3.0.*^{1,13} *0*^{1,17}] *eicosa-14-en-2,20-dione* (258) and (259)

50% Aqueous KOH (0.4 ml) was added slowly to a solution of isoindolone (257) (22 mg, 0.043 mmol) in methanol-benzene (2:1) (1.2 ml) with vigorous stirring. After 1 h the reaction was poured into 3 $\underline{M}$ HCl (5 ml) and the product was extracted with ether (3x10 ml) to give an oil (22 mg). Purification by short column chromatography using gradient elution starting with ether-petrol (1:2), gave 1$\underline{R}$,13$\underline{R}$,16$\underline{S}$,17$\underline{R}$,18$\underline{R}$-*18-benzyl-16-methyl-19-aza-*

tricyclo[*15.3.0.*^{1,13} *0* ^{1,17}] *eicosa-14-en-2,20-dione* (258) as an oil (13 mg, 74%), $[\alpha]_D^{20}$ -74.0 (c 0.53, $CHCl_3$); δ 1.10-1.83 (18H, m, $(C\underline{H}_2)_9$), 1.22 (3H, d, *J* 6.9 Hz, $CHC\underline{H}_3$), 1.92 (1H, ψ t, *J* 12 Hz, H-3), 2.28 (1H, brd, *J* 10.8 Hz, H-13), 2.46 (1H, dd, *J* 13.6, 7.9 Hz, C<u>H</u>Ph), 2.54 (1H, m, H-16), 2.58 (1H, ψ t, *J* 4.2 Hz, H-17), 2.87 (1H, dd, *J* 13.6, 3.8 Hz, C<u>H</u>Ph), 3.37 (1H, m, *J* 3.8 Hz, C<u>H</u>N), 3.45 (1H, ddd, *J* 19.5, 11.7, 2.3 Hz, H-3), 5.71 (2H, m, vinylic H), 5.85 (1H, brs, NH), 7.09-7.32 (5H, m, aromatic H); $\nu_{max.}$ (CH_2Cl_2) 3410, 3200br, 2930, 2850, 1695br, 1495, 1453br, 1302, 909, and 665 cm^{-1}; *m/z* (CI) 408 (M^++1 , 100%), and 1<u>R</u>,13<u>S</u>,16<u>R</u>,17<u>R</u>,18<u>R</u>-*18-benzyl-16-methyl-19-azatricyclo*[*15.3.0.*^{1,13} *0* ^{1,17}] *eicosa-14-en-2,20-dione* (259) as an oil (1.6 mg, 9%), δ 0.99 (3H, d, *J* 7.1 Hz, $CHC\underline{H}_3$), 1.21-1.77 (17H, m, $(C\underline{H}_2)_8$ and H-4), 1.97 (2H, m, H-4 and H-16), 2.35 (1H, m, H-3), 2.52 (2H, two overlapping dd, *J* 13.5 and *J* 4.2 Hz, C<u>H</u>Ph and H-17), 2.65 (1H, m, H-13), 2.67 (1H, dd, *J* 13.3, 6.6 Hz, C<u>H</u>Ph), 3.17 (1H, ddd, *J* 19.5, 10.2, 3.6 Hz, H-3), 3.36 (1H, m, C<u>H</u>N), 5.69 (2H, m, H-15 and NH), 5.85 (1H, ddd, *J* 9.9, 4.5, 2.1 Hz, H-14), 7.15-7.37 (5H, m, aromatic H); $\nu_{max.}$ (CH_2Cl_2) 2935, 2860, 1714br, and 1465 cm^{-1}; *m/z* 407 (M^+ , 5%) and 57 (100%) (Found: M^+ 407.2823. $C_{27}H_{37}NO_2$ requires M^+ 407.2824).

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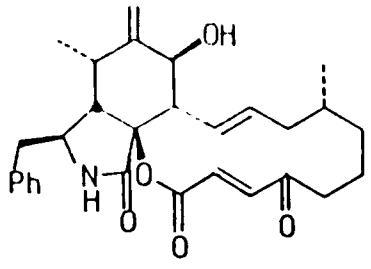
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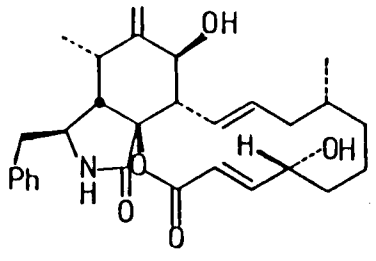
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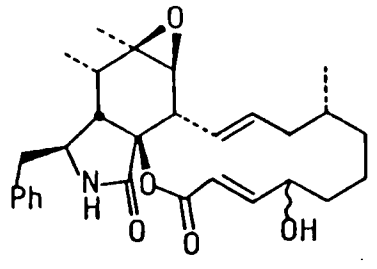
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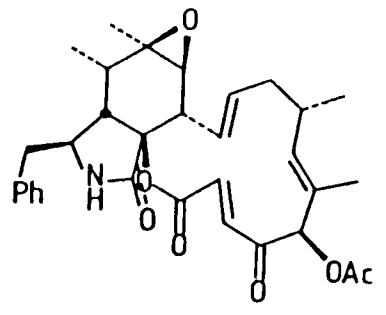
Cytochalasin A
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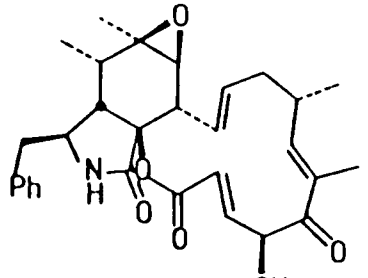
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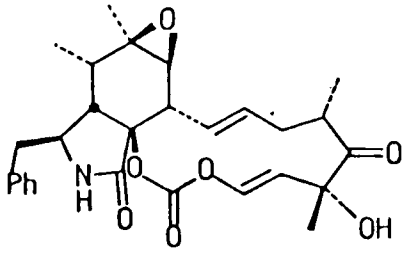
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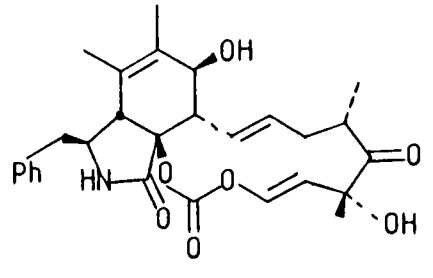
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Cytochalasin M

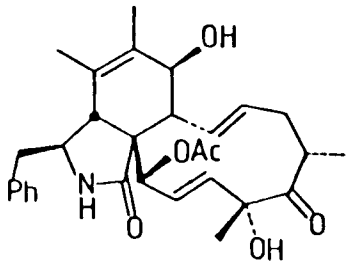


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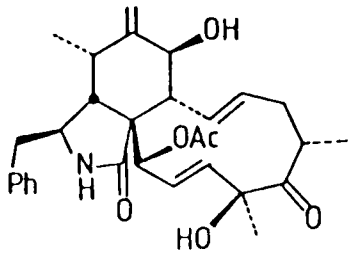


Cytochalasin K[5]

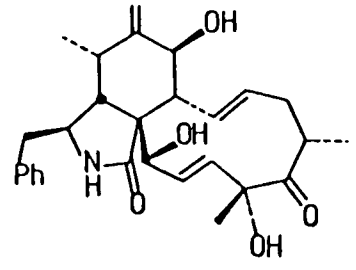
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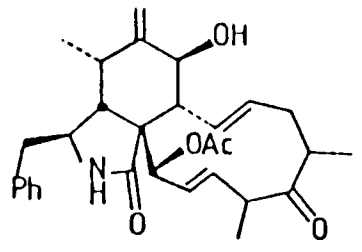
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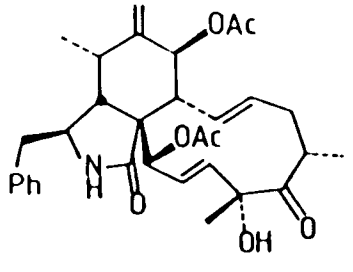
Cytochalasin D
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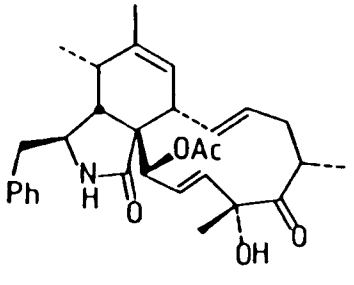
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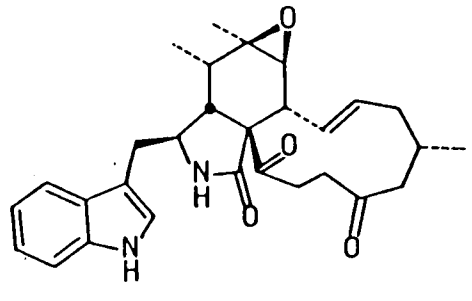
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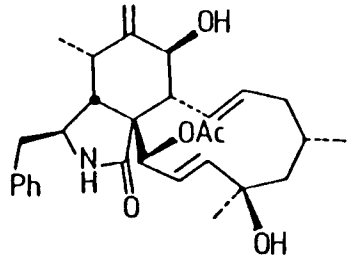
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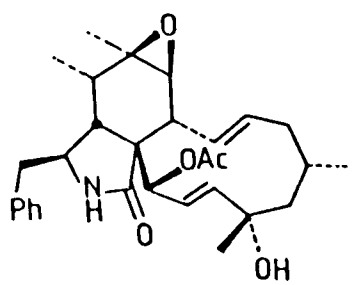
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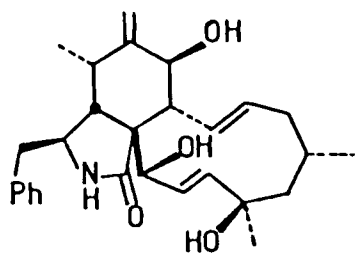
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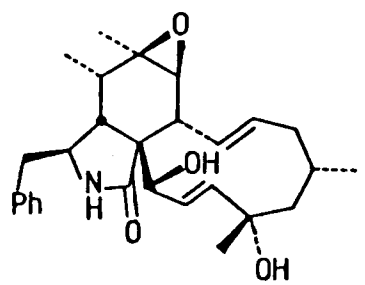
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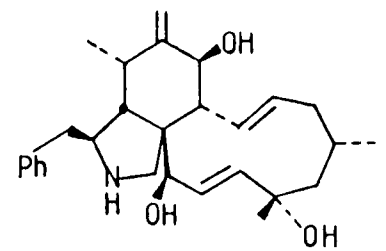
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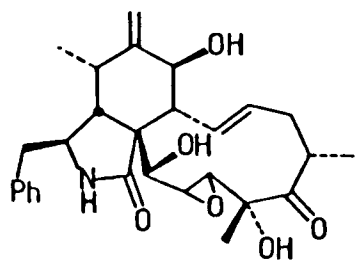
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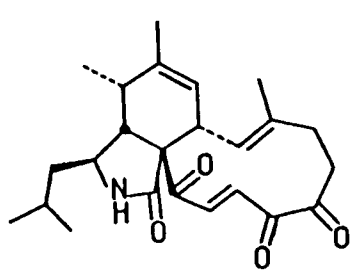
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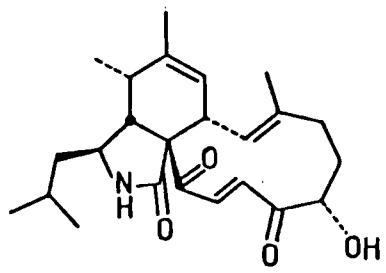
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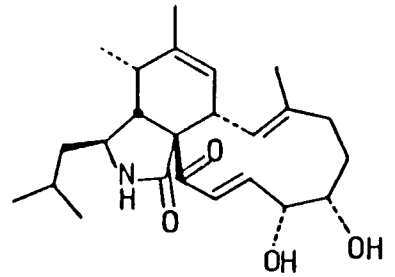
Engleromycin



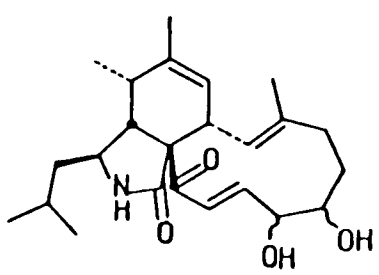
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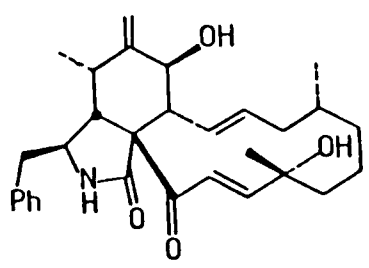
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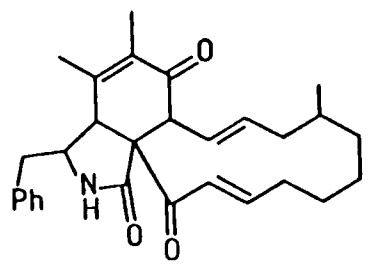
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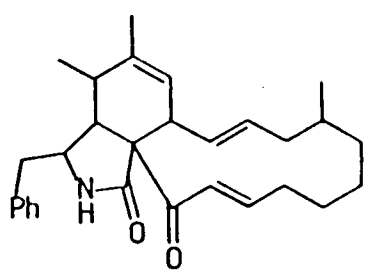
Aspochalasin D



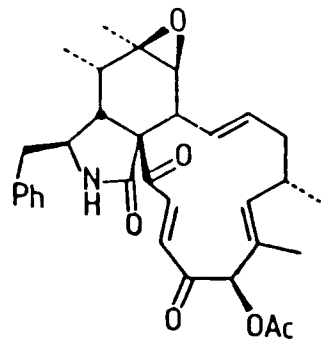
Deoxaphomin



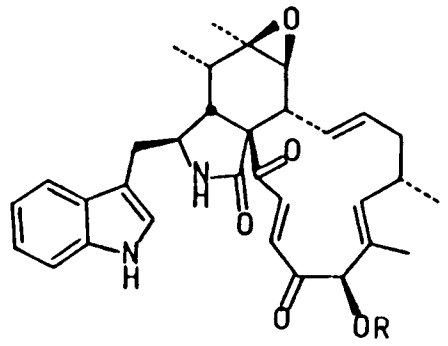
Protophomin



Proxiphomin

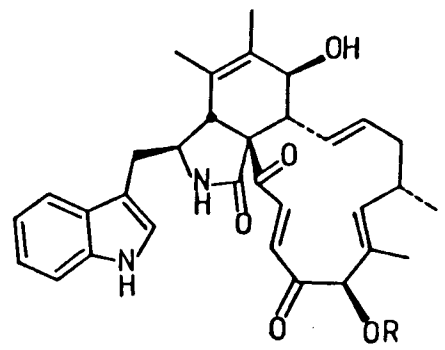


Cytochalasin K[6]



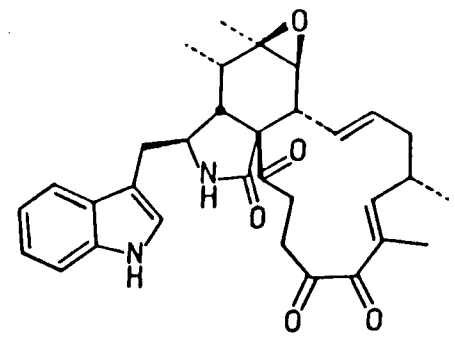
Chaetoglobosin A (R=H)

19-O-Acetylchaetoglobosin A (R=Ac)

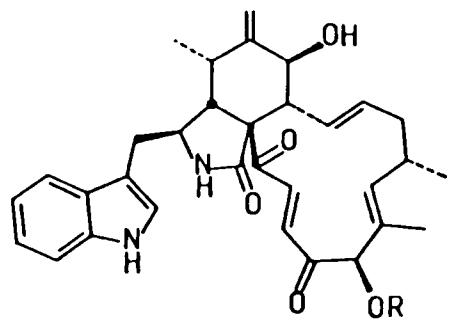


Chaetoglobosin B (R=H)

19-O-Acetylchaetoglobosin B (R=Ac)

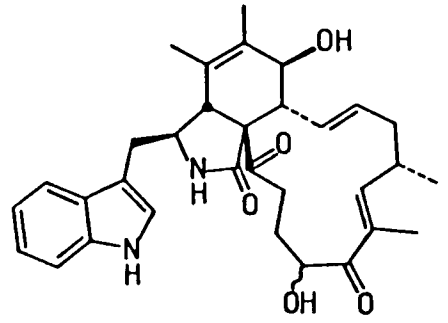


Chaetoglobosin C

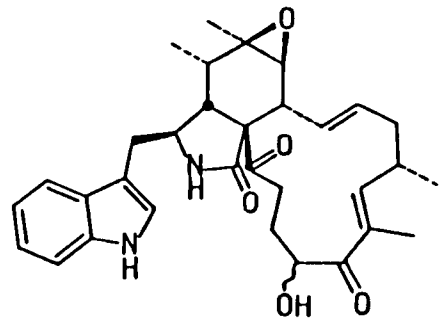


Chaetoglobosin D (R=H)

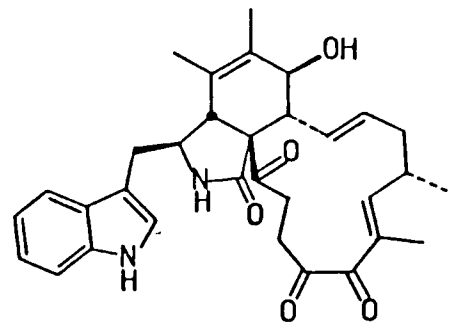
19-O-Acetylchaetoglobosin D (R=Ac)



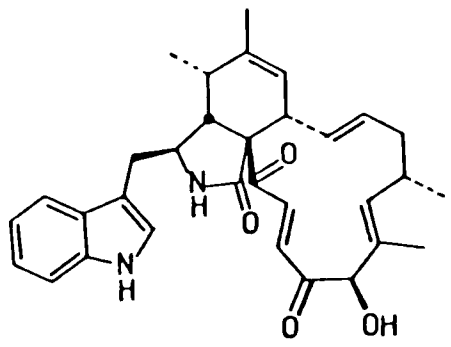
Chaetoglobosin E



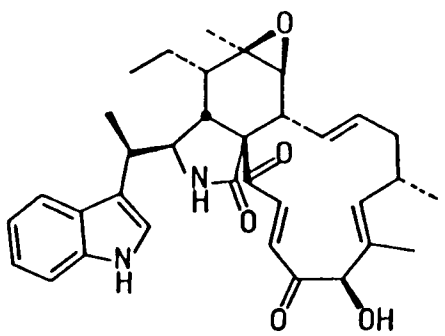
Chaetoglobosin F



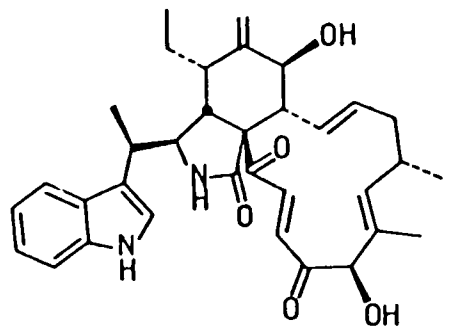
Chaetoglobosin G



Chaetoglobosin J



Chaetoglobosin K



Chaetoglobosin L

APPENDIX II

Table A Selected ^{1}H nmr data of some cytochalasans*

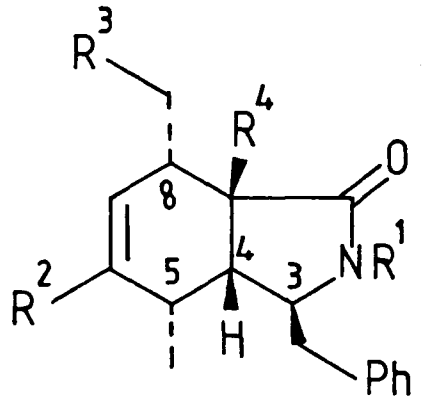
Compound in $CDCl_3$	Chemical shift(δ), multiplicity, $J_{3,4}$, $J_{4,5}$ (Hz)			
	H-3	H-4	H-5	H-8
Cytochalasin B †	3.72, m	3.19, dd, 1.5,2.5	3.63, m	4.02, ψt
Cytochalasin E	3.6-3.8, m	2.5-3.1, m		
Cytochalasin K[5]	3.38, ψt	3.75-3.87, m	-	2.5-3.0,m
Cytochalasin L	3.71, m	2.8, dd, 3.3,4.5	2.24, m	2.68, m
Cytochalasin M	3.63, m	2.53, ψt, 4	2.07, m	2.49, m
Cytochalasin D†	3.63, m	2.50, m	3.04, m	3.44, ψt
Cytochalasin K[6]	3.66, m	2.99, dd, 2.5,5.5	1.83, m	2.21, m
Deoxaphomin	2.81, ψt	3.15, dd, 2,6	3.44, m	2.50, ψt
Protophomin	3.5, ψt	3.71, brs, <1	-	3.13, d
Chaetoglobosin A	3.81, m	3.03, dd, 3,5	1.85, m	2.14, m
19-O-Acetylchaeto-globosin A	3.80, m	2.93, dd, 3,5	1.84, m	2.14, dd
19-O-Acetylchaeto-globosin D	3.84, m	2.9, ψt, 5	2.84, m	2.33, m
Chaetoglobosin K#	3.84, m	3.0-3.35, m	1.50-2.50, m	
Chaetoglobosin L#	3.5-3.75, m	3.36, ψt, 5	1.90-2.70, m	

* See references 1 to 30 and references therein.

† Solvent d_5-pyridine

Solvent $CDCl_3/D_2O$

Table B Selected ^{1}H nmr data of synthetic isoindolones*



R^1	R^2	R^3	R^4	Chemical shift(δ), multiplicity, $J_{3,4}$, $J_{4,5}$ (Hz) H-3	H-4	H-5	H-8
H	H	H	H	3.41, ddd	2.57, m, 5	2.34, m	
H	H	H	C_4H_9	3.11, ddd	2.03, m, 6.2	1.89, m	2.03, m
H	CH_3	OH	CO_2Me	3.31, ddd	2.54, m, 4.2	2.54, m	2.96, m
H	CH_3	-O-CO-		4.68, ddd	2.3-2.4,m,9.5	2.35, m	3.2, m
$COCH_2Cl$	H	H	H	4.32, ddd	2.53, brt,2,9	2.13/2.31, m	
COPh	H	H	CO_2Et	4.37, dt	2.76,dd,3.1,6	2.33/2.52, m	
COPh	CH_3	OCOEt	H	4.45, m	2.6, dd, 2,7	2.23/2.52, m	
COPh	CH_3	OCOEt	CO_2Et	4.3, m	2.78,dd,3.5,6	2.42/2.92, m	
COPh	CH_2TMS	OTBS	H	4.42, ddd	2.52,ddd,1.7,6	2.16, dq	2.39, m
COMe	H	H	C_4H_9	3.11, ddd	2.05,m,4.5	1.87, m	
Cbz	H	H	C_4H_9	4.05, ddd	2.08, ψt, 5	1.87, m	
Cbz	CH_3	OMe	CO_2Me	3.95, m	2.55,dd, 3,6	2.33, m	2.84, m
Cbz	CH_3	OCOEt	CO_2Me	3.97, m	2.56,dd, 2,6	2.25-2.4,m	2.90, m
Cbz	CH_3	OTBS	CO_2Me	3.95, m	2.53,brd,<1,6	2.2-2.4,m	2.6-2.9, m

* See references 3, 17, 18, 19, 24, 25, 26; solvent $CDCl_3$ throughout.

TMS= $SiMe_3$; TBS= $SiMe_2Bu^t$; Cbz= CO_2CH_2Ph.

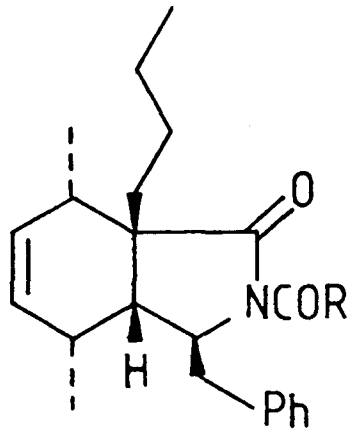
Table C Partial ^{1}H nmr data of new isoindolones*

Compound	Chemical shift (δ), multiplicity, $J_{3,4}$, $J_{4,5}$ (Hz)			
	H-3	H-4	H-5	H-8
(182a)	4.03, m	2.07-2.21, m	1.54 and 2.07-2.21, m	
(182b)	4.25, m	2.38, ψt, 4.9	2.13-2.28, m	
(221)	4.22, dt	3.16, dd, 3, 5.5	2.82, brs	3.35, brs
(222)	4.41, dt	2.66, brs	2.55, brs,	3.49, brs
(223)†	4.40, m	2.64, dd, 5.4, 6	2.24-2.74, m	2.79, m
(224)	3.47, m	2.45, m, 4.5	2.45, m	2.94, m
(225)	3.49, m	2.24, dd, 3.6, 5	2.06, m	2.49, m
(231)	3.42, ψt 3.92, dd	2.83-2.92, m	2.39-2.45, m	2.75-2.8, m
(233)	3.33, dd 3.93, dd	3.23, ddd, 2.7,4.1 9.3	3.05 and 3.30, m	
(234)	3.49, dd 4.04, dd	2.76, m	2.82 and 3.34, m	
(257)†	4.35, m	2.83, dd, 3.9, 6	2.51, m	2.24, m
(258)	3.37, m	2.58, ψt, 4.2	2.54, m	2.28, brd
(259)	3.36, m	2.52, m, 4.2	1.97, m	2.65, m

* In $CDCl_3$.

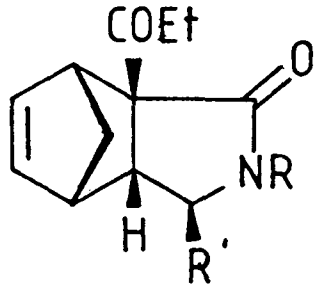
† Resonances reported are for the major isomer.

Structures of new isoindolones



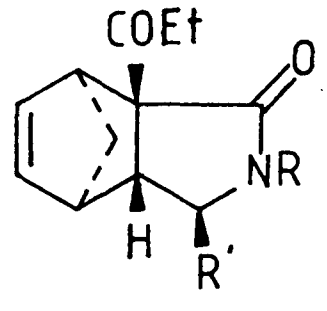
R = Me (182a)

R = Ph (182b)



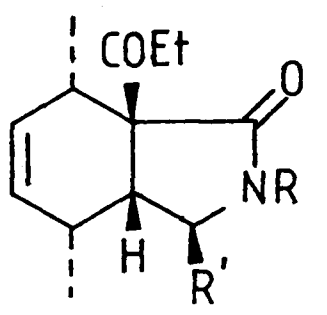
R= COPh, R'= CH_2Ph (221)

R= SO_2Ph, R'= H (233)



R= COPh, R'= CH_2Ph (222)

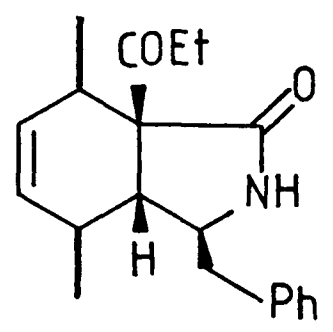
R= SO_2Ph, R'= H (234)



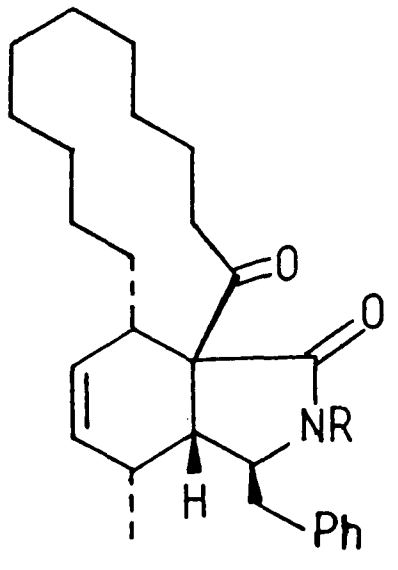
R= COPh, R'= CH_2Ph (223)

R= H, R'= CH_2Ph (224)

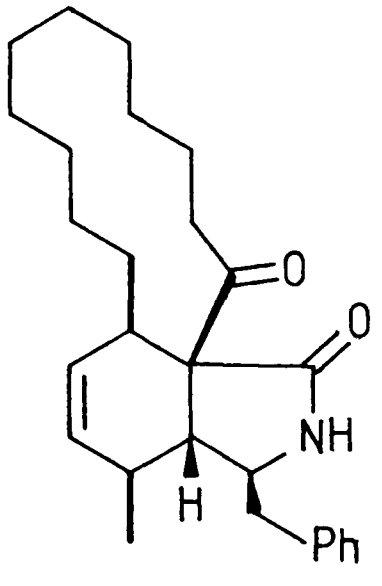
R= SO_2Ph, R'= H (231)



(225)



R= COPh (257) R= H (258)



(259)