

SYNTHESIS OF THE IONOPHORE
ANTIBIOTIC X-14547A

a thesis presented by

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ABSTRACT

The review section of this thesis deals with the recent advances in the use of the intramolecular Diels-Alder reaction in the stereo-controlled synthesis of natural products. Particular emphasis is placed upon the stereochemical consequences of detailed examination of transition state non-bonded interactions.

This thesis describes the total synthesis of antibiotic X-14547A, in 16 steps, from 2-ethyl- δ -valerolactone. The five chiral centres of the tetrahydroindan moiety of X-14547A were created by the stereo-controlled intramolecular Diels-Alder reaction of ethyl (*E,E,E*)-1-(β -methoxy)ethoxymethoxy-6-ethyl-2,4,9-undecatrienoate.

A key intermediate (1 α -ethyl-3 $\alpha\beta$,4,5,7 $\alpha\alpha$ -tetrahydroindan-4 β -carboxylic acid-5 β -methanol, γ lactone), prepared in ten steps from 2-ethyl- δ -valerolactone, was efficiently resolved and converted, in three steps, to the optically pure (-)-4(S)-[2'-N-(β -trimethylsilyl)ethoxymethylpyrrolylcarbonyl]-5(S)-phenylsulphonylmethyl-1(S)-ethyl-3 α (R),4,5,7 α (R)-tetrahydroindan.

The novel 2-lithio-N-SEM-pyrrole reagent was developed for the regiospecific incorporation of the protected 2-pyrrolylcarbonyl moiety.

The (-)-sulphone was condensed, in a stereospecific Julia reaction, with methyl α (R),5(S)-dimethyl-6(R)-(1-ethyl-1(*E*)-propenyl)tetrahydropyran-2(R)-acetate which was available from the degradation of the natural product or by total synthesis. The resulting N-SEM-X-14547A methyl ester, isolated in 53% yield, was converted in two steps, by sequential treatment with tetra-*n*-butylammonium fluoride and sodium hydroxide-methanol, in 65% overall yield, to the natural product.

A diastereomer of X-14547A methyl ester was prepared, in an analogous fashion, using the enantiomeric (+)-sulphone.

A novel and general rearrangement of antibiotic X-14547A and some closely related systems was discovered. Stereospecific electrophilic attack of the diene system of X-14547A at the C-23 position of the pyrrole moiety, with concomitant cleavage of the C-7-O bond of the tetrahydropyran moiety, in an S_N2 process, was observed for four compounds.

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Martin P. Edwards

FOR JULIE

REVIEW

RECENT DEVELOPMENTS IN THE USE OF THE INTRAMOLECULAR DIELS-ALDER REACTION IN THE STEREOCONTROLLED SYNTHESIS OF NATURAL PRODUCTS.

INTRODUCTION

In recent years, the increasing importance of the intramolecular Diels-Alder (IMDA) reaction in the stereocontrolled construction of complex polycyclic molecules, especially natural products, is reflected in the large number of reviews^{1,3} and a forthcoming book² on this subject.

The plethora of published total syntheses and synthetic approaches to natural products involving the IMDA since the last major review in 1980,^{1d} particularly in the crucial area of understanding the processes controlling the stereochemical outcome of the IMDA reaction, necessitates the present survey.

The IMDA reaction appears to be of unparalleled use in the regio-selective and stereospecific introduction of multiple asymmetric centres in polycyclic natural products or potentially useful synthons. The most powerful aspect of the IMDA reaction lies in its, increasingly predictable, control of four or more (when substituents in the chain connecting diene with dienophile are considered) centres of asymmetry.

The apparent importance of non-bonded interactions, which develop in the various diastereomeric transition states, rather than the *endo* transition state model or secondary orbital interactions, in determining the stereochemical outcome and degree of stereocontrol, in the IMDA reactions included here, is considered in detail. The important and relatively recent use of Lewis acids to enhance and even drastically change the stereocontrol in the IMDA reaction, although used in a few cases (*vide supra*), would appear to remain largely unexplored until very recently.

It is the intention in this review to particularly highlight syntheses whereby the use of the IMDA reaction as a key step led to a short and efficient synthesis. If, as is occasionally the case, the Diels-Alder substrate is only prepared by a lengthy or inefficient procedure, or the IMDA product converted to a natural product by a multistep procedure, criticism is made.

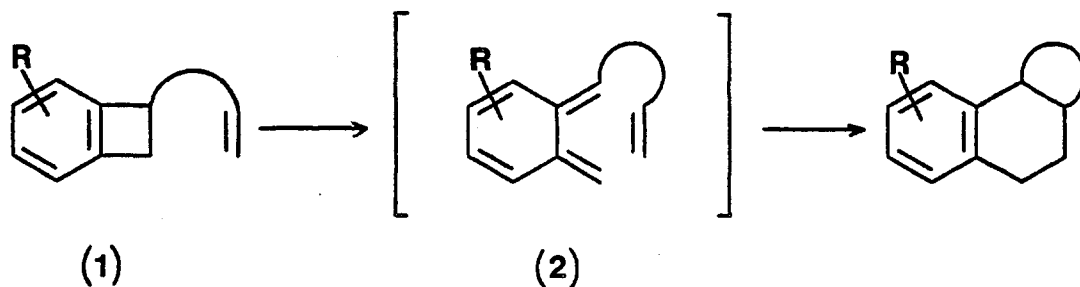
The published work considered here is conveniently split into five areas of synthetic endeavour as it is felt thus easier to gain an overall picture of the most recent developments: steroids, alkaloids, terpenoids, miscellaneous natural products, and purely stereochemical studies.

1. STEROIDS

1.1 A-Ring Aromatic Steroids

1.1.1 From Benzocyclobutene Derived *o*-Quinodimethanes (*o*-Xylylenes).

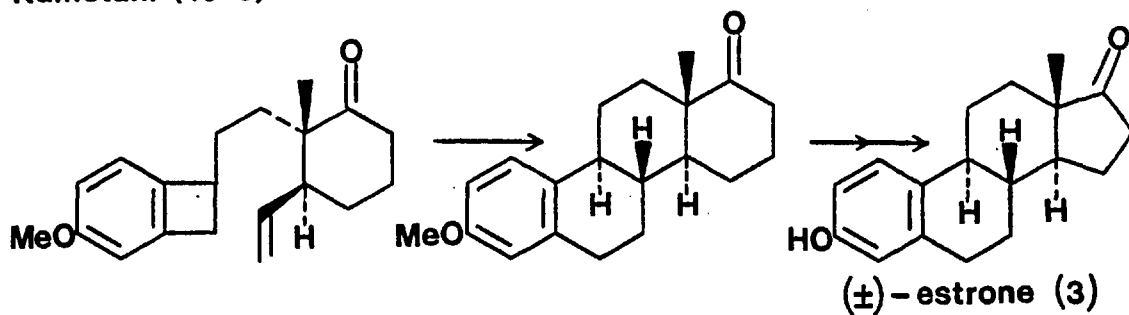
The most widely used IMDA reaction in steroid synthesis has been the cycloaddition of *o*-quinodimethanes (2), generated *in situ* by conrotatory electrocyclic opening of benzocyclobutenes (1), to internal olefins.



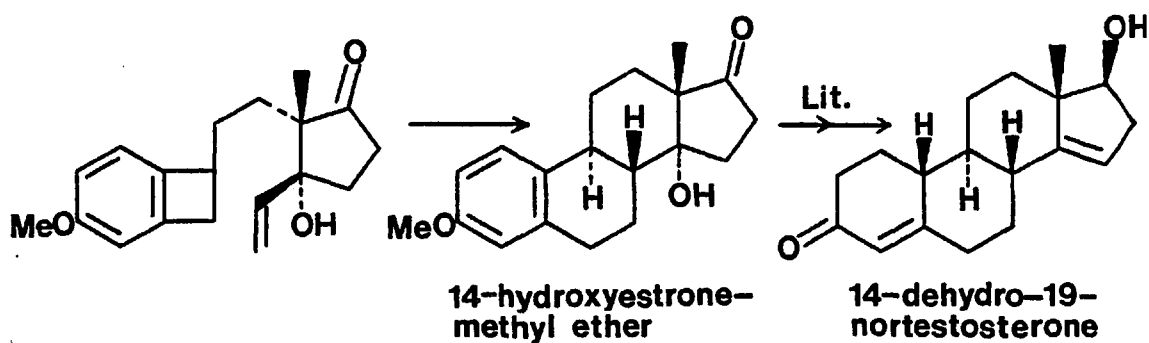
As this approach to A-ring aromatic steroids, pioneered independently by Kametani, Oppolzer, and Vollhardt, has been extensively

reviewed recently,³ the reported key IMDA reactions in each synthesis that are covered in these reviews are briefly summarised in Scheme 1.

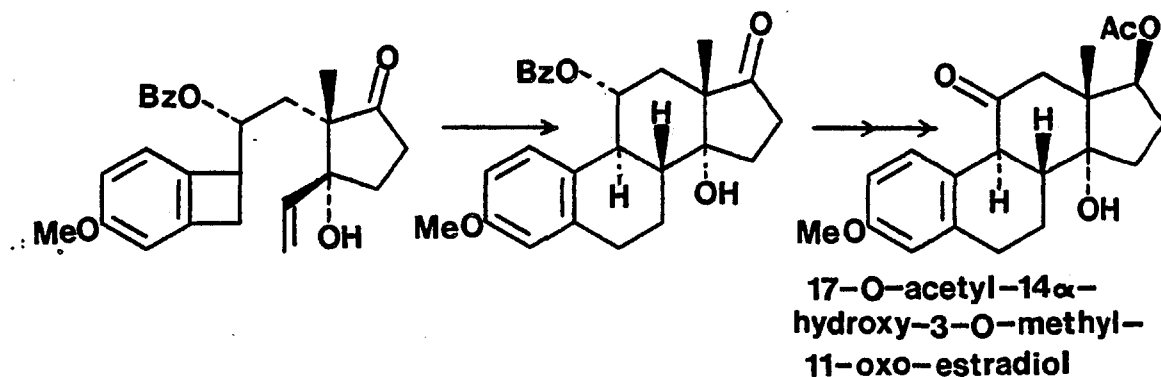
Kametani (1976)⁴



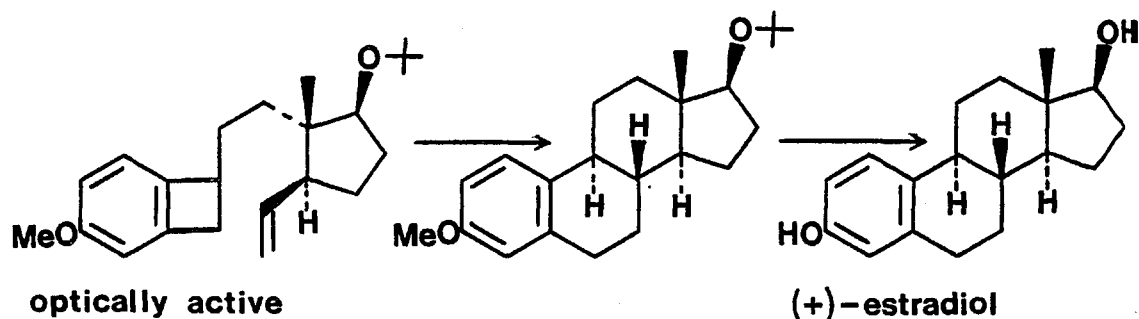
Kametani (1979)⁵



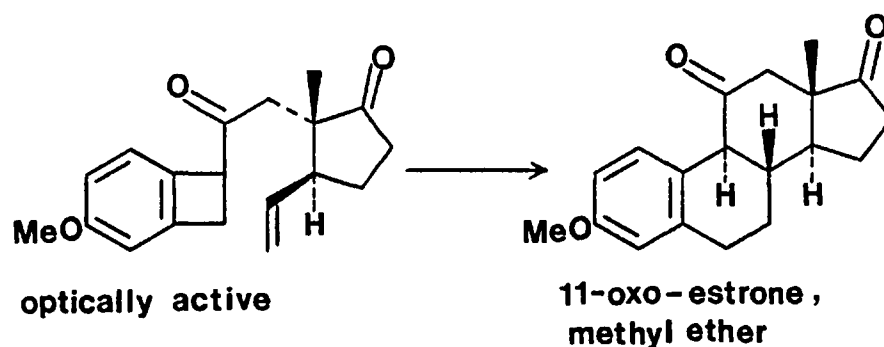
Kametani (1980)⁶



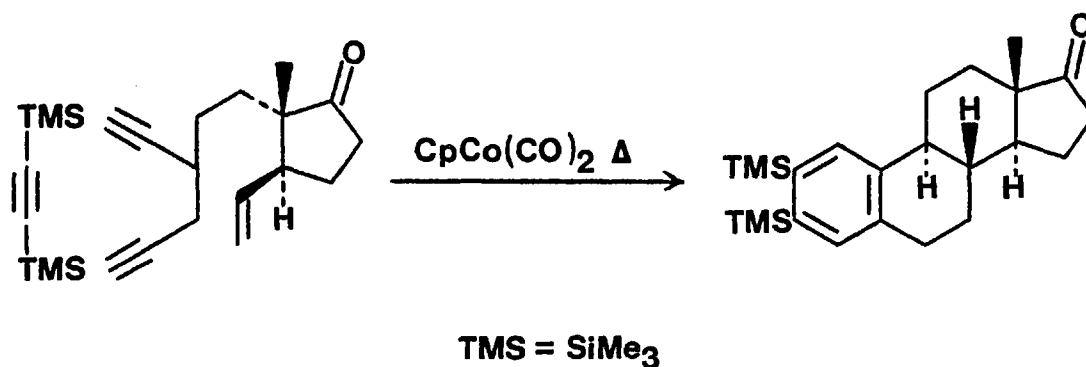
Kametani (1978)⁷



Oppolzer (1978)⁸

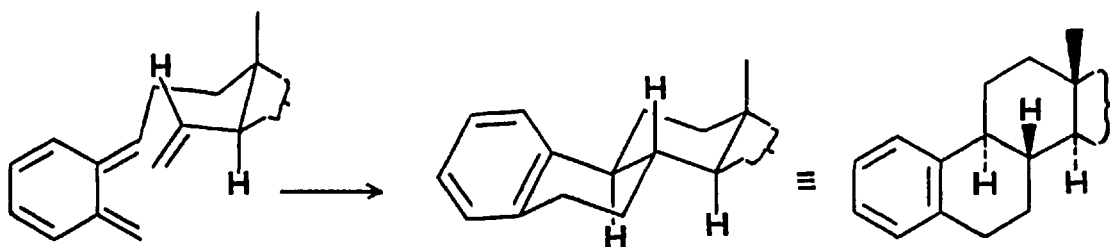


Vollhardt (1977)⁹

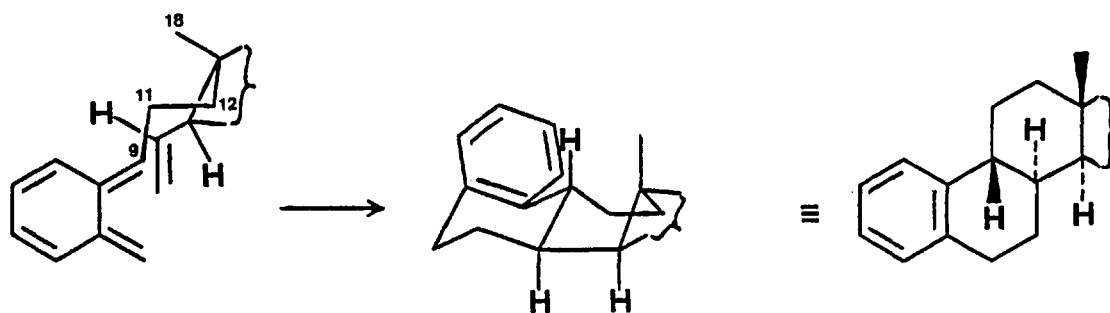


Scheme 1

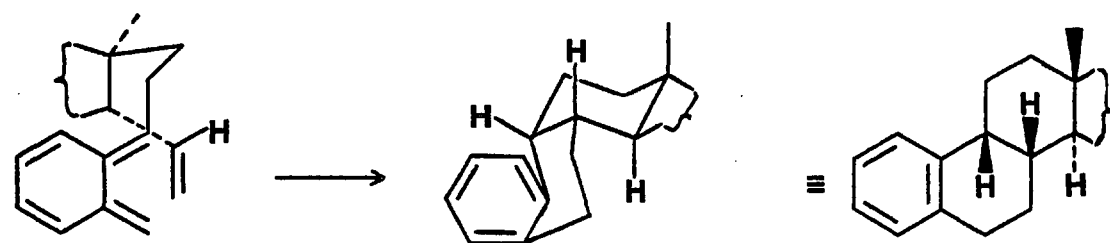
The high degree of stereoselectivity exhibited in these IMDA reactions is believed to arise through a strong preference for reaction *via* a sterically favoured *exo*- β -face chair-like transition state ((A) in diagram 1 below) to give the natural *trans-anti-trans* configuration. The alternative *exo* mode (B), to give the *trans-syn-trans* configuration, *via* a boat-like transition state, involves unfavourable steric interaction between the C-18 methyl group and the diene C-9 hydrogen as well as eclipsing of the hydrogens on the bridging methylene groups at C-11 and C-12. Either of the two diastereomeric *endo* modes (C) or (D) involve unfavourable steric interactions in the transition state. In particular, the *endo* mode involving a boat-like transition state (D) suffers a serious methyl group-*o*-quinodimethane ring steric interaction.



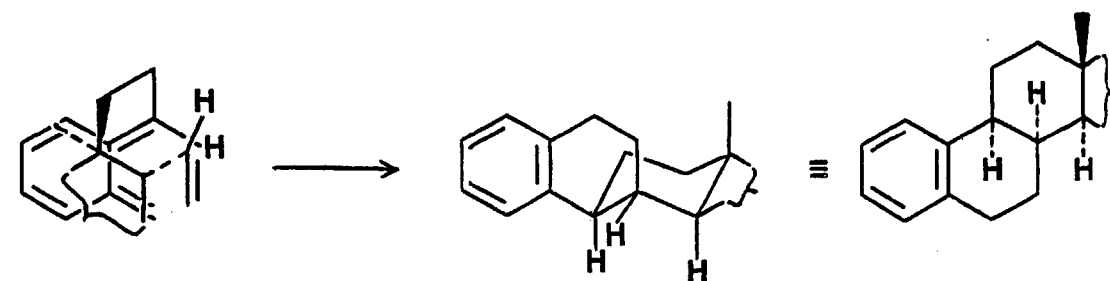
(A)



(B)



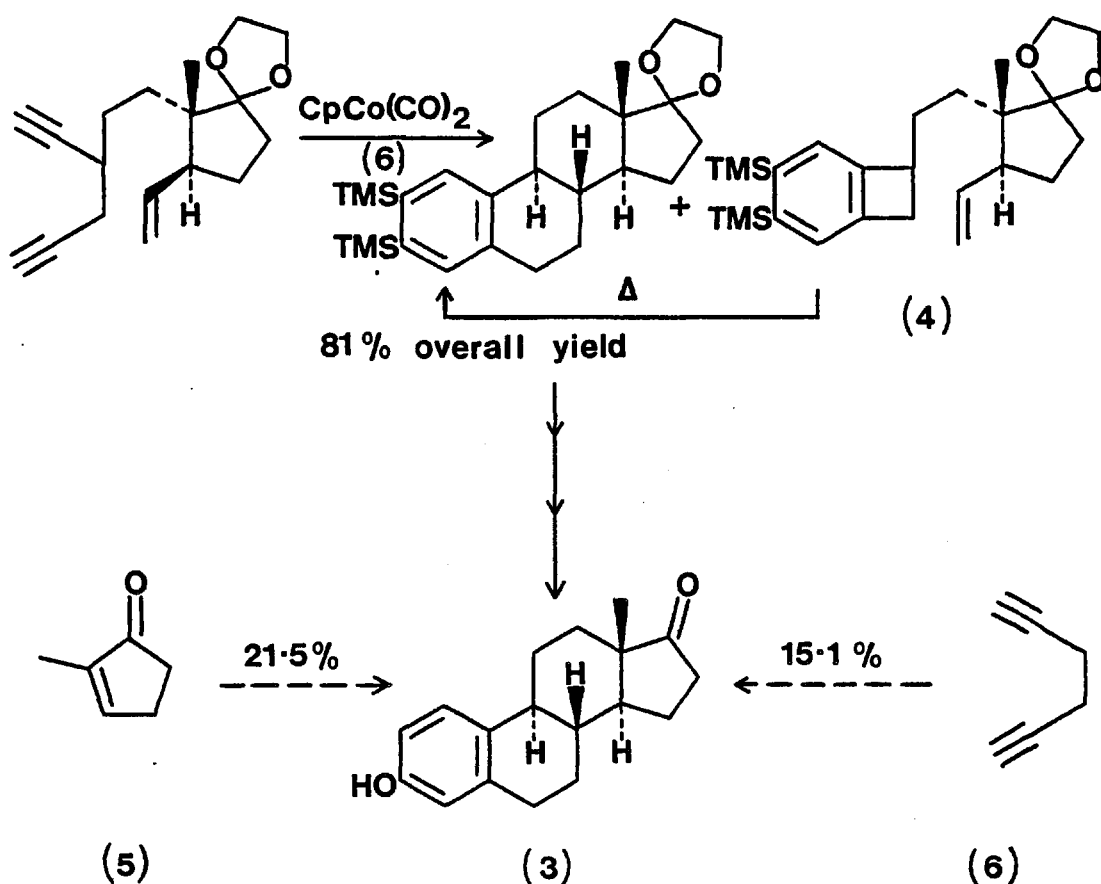
(C)



(D)

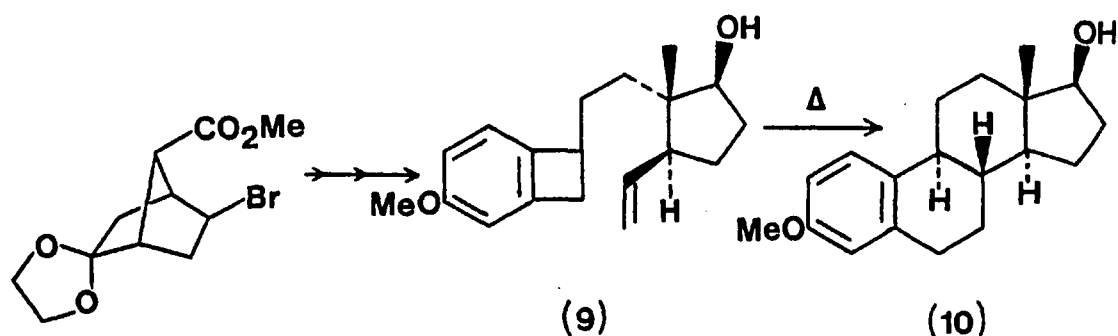
Diagram 1

Perhaps the most notable of the benzocyclobutene IMDA syntheses is the Vollhardt cobalt-mediated total synthesis of ($\pm$)-estrone.¹⁰ In sharp contrast to the multistep, low yield, preparations of the benzocyclobutene precursors employed by Kametani, more efficient in the Oppolzer work, the Vollhardt route is very concise. The total synthesis of estrone (3) using the IMDA reaction of the *in situ* formed benzocyclobutene (4) proceeds in only five steps from 2-methylcyclopent-2-enone (5) (in 21.5% overall yield) or in six steps from 1,5-hexadiyne (6) (in 15.1% overall yield).



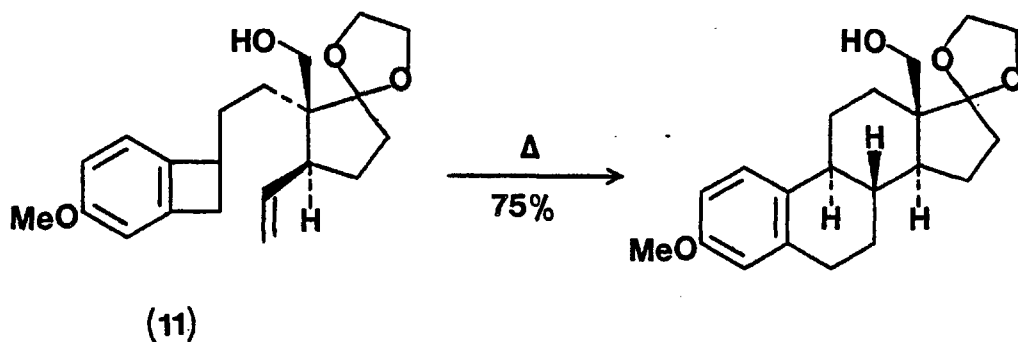
The Grieco synthesis of estrone in a racemic or optically active form *via* the IMDA reaction of the *o*-quinodimethane, derived from benzocyclobutene (9), is notable more for the novelty of the preparation of

(9) in a relatively efficient process from the readily available bromoester (8).¹¹



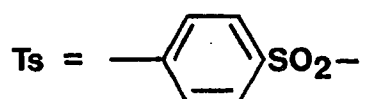
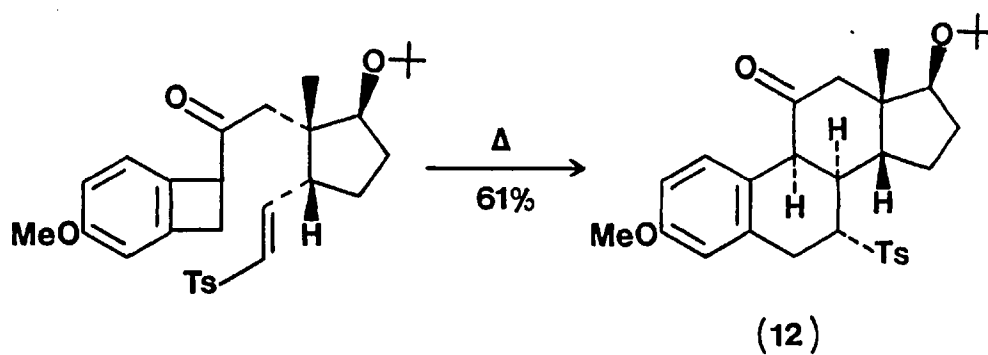
3-Methoxyestra-1,3,5(10)-triene-17β-ol (10), isolated in 78% yield, was converted to estrone (3), in two steps, in 76% overall yield.

The simple and efficient synthesis of 18-hydroxyestrone, recently reported by Tsuji and co-workers, involved the thermolysis of the benzocyclobutene (11).¹²

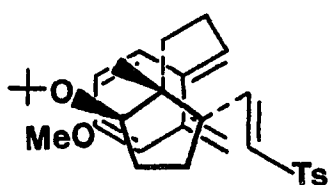


Kametani recently reported an atypical IMDA reaction in which the *cis-anti-cis* fused steroid system of (12) was created in an *endo* cyclization.

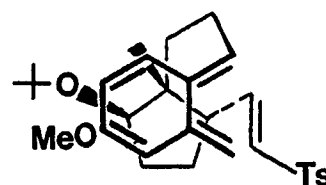
The novel *cis* fusion of the vinylcyclopentanol moiety, combined with the absence of steric repulsion between the methyl and t-butyloxy



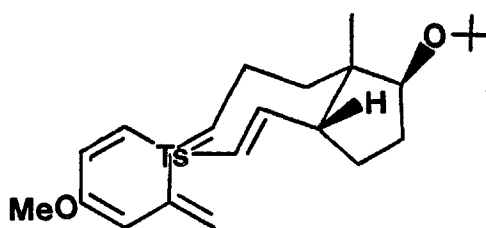
groups and the aromatic ring in the preferred *endo* transition state (A) below) compared with the alternative *endo* transition state (B), led to this stereochemical outcome.



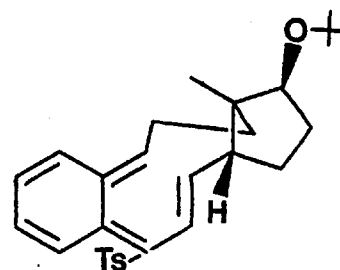
(A)



(B)



(C)



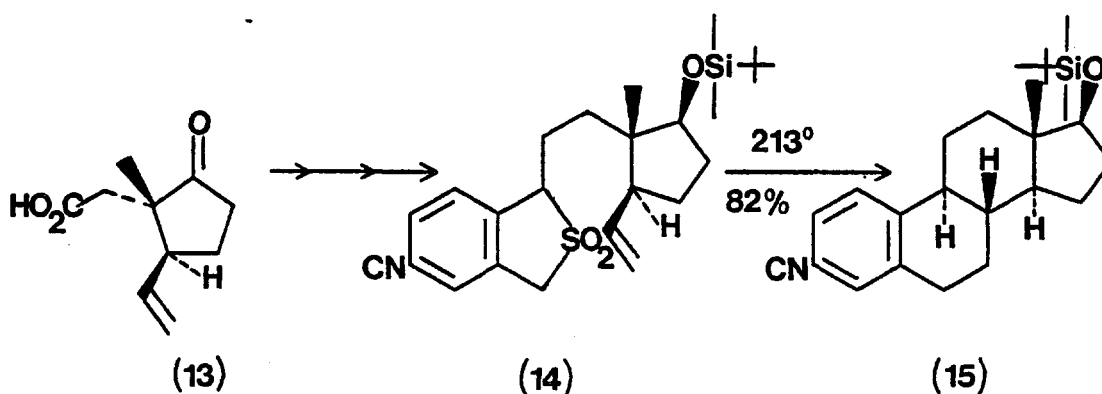
(D)

Apparently the *endo* transition state (A), with the *p*-toluenesulphonyl group *exo* is more favourable than the normal *exo* transition state (C), where the *p*-toluenesulphonyl group suffers interactions with the ring A portion of the molecule.

1.1.2 From 1,3-Dihydrobenzo[C]thiophene-2,2-dioxide derived *o*-Quinodimethanes.

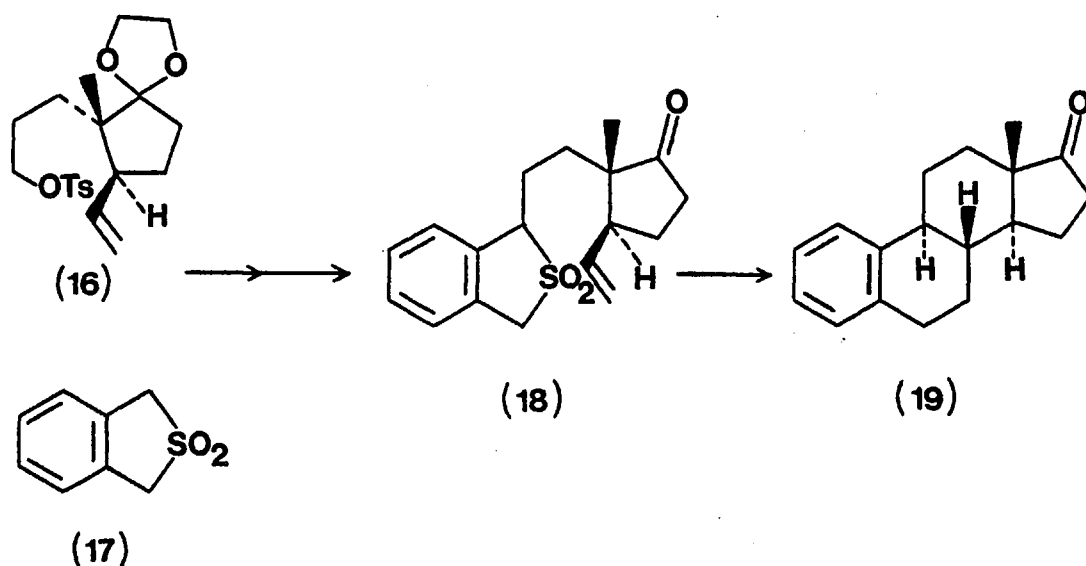
Recognising that the benzocyclobutene routes to A-ring aromatic steroids suffered, apart from in the Vollhardt cobalt-mediated route, from the multistep, low yielding, routes often necessary for preparation of the required benzocyclobutenes, Oppolzer and, independently, Nicolaou developed very short syntheses *via* an alternative method of *o*-quinodimethane generation.

Oppolzer prepared the optically pure steroid derivative (15) in seven steps (in 50% overall yield) from the readily available (+)-carboxylic acid (13) *via* the IMDA reaction of the *o*-quinodimethane formed *in situ* by thermal cheletropic extrusion of sulphur dioxide from (14).¹³



Steroid (15) was converted to (+)-estradiol, in 60% overall yield, in two steps.

Nicolaou reported an extremely concise and stereoselective synthesis of the simple steroid *estra-1,3,5(10)-trien-17-one* (19).¹⁴ The tosylate (16), prepared in four steps from 2-methylcyclopent-2-enone, was coupled with the anion of the sulphone (17) to give the requisite IMDA precursor (18) in 77% yield after ketal hydrolysis. The cyclized (19), isolated in 85% yield, was accompanied by about 5% of the *cis-anti-trans* C-9 epimer formed *via* the less hindered of the two *endo* modes (*vide supra*).

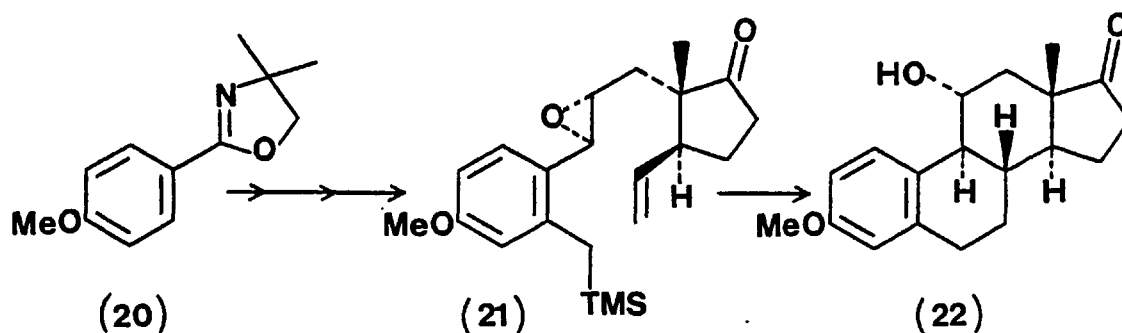


The Nicolaou synthesis, although one of the shortest steroid syntheses reported, does not have the functionality at C-3, asymmetry at C-17, or enantioselectivity of the Oppolzer application of the sulphone extrusion methodology.

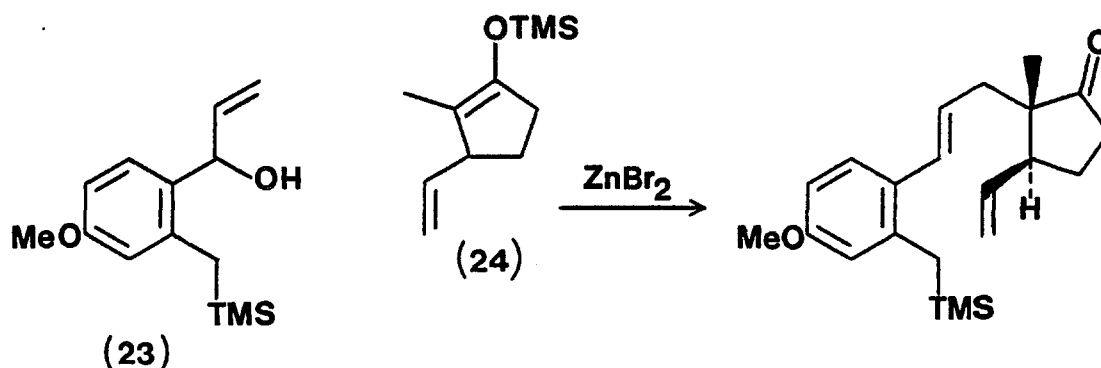
As with the benzocyclobutenes, in which conrotatory opening gives the transoid *o*-quinodimethanes, the stereochemistry in the sulphone moiety is of no consequence, as a rapid geometric isomerisation of the *o*-quinodimethane to the reactive, transoid, form occurs.

1.1.3 From Trimethylsilylmethylbenzenoid derived *o*-Quinodimethanes.

In an exceptionally short synthesis of ($\pm$)-11 α -hydroxyestrone methyl ether (22), Magnus has utilised an extremely mild novel method for generation of an *o*-quinodimethane.¹⁵ Treatment of the epoxide (21), prepared in five steps from the readily available oxazoline (20), with cesium fluoride in diglyme at room temperature gave the steroid (22) in 70% yield. The overall yield for the six step (from (20)) synthesis of (22) was 30%.

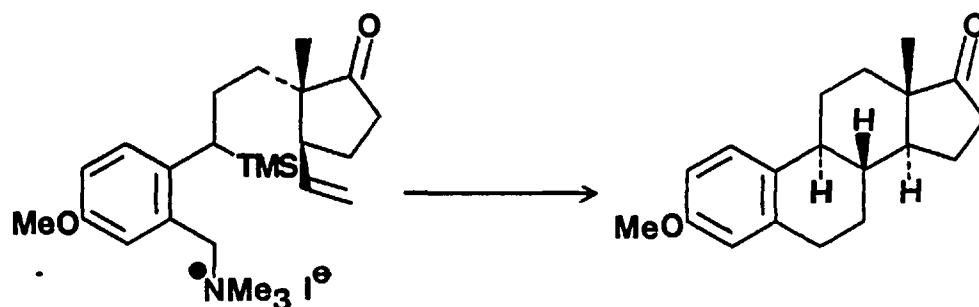


Contrary to many of the previous routes *via* benzocyclobutenes the method for coupling the *o*-quinodimethane and D-ring precursors ((23) and (24)) was efficient (88%) and stereoselective (4:1).



Using similar methodology for the preparation of steroids, Saegusa has developed a synthesis of estrone utilising the fluoride catalysed

generation of the required *o*-quinodimethane from the trimethylsilyl-methylbenzenoid (25).¹⁶

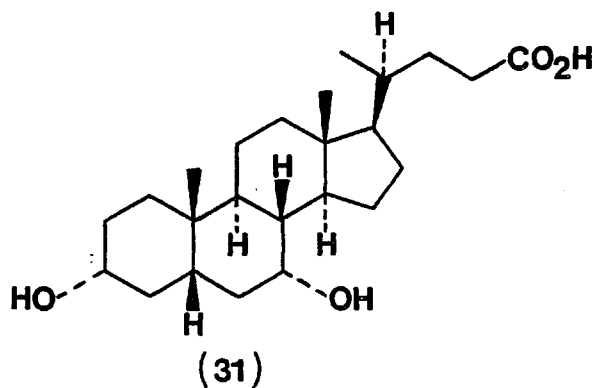
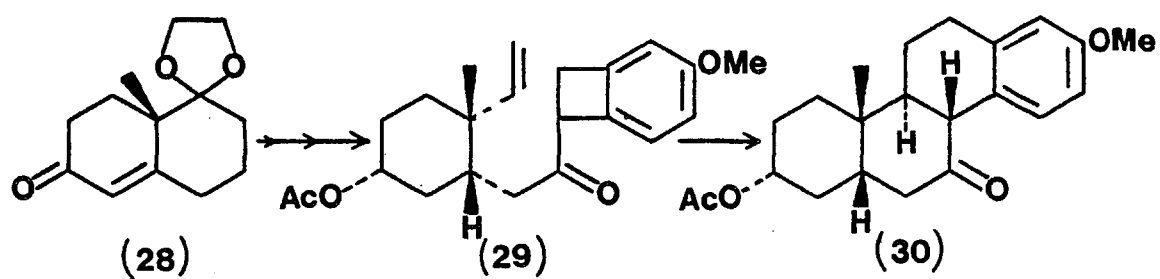
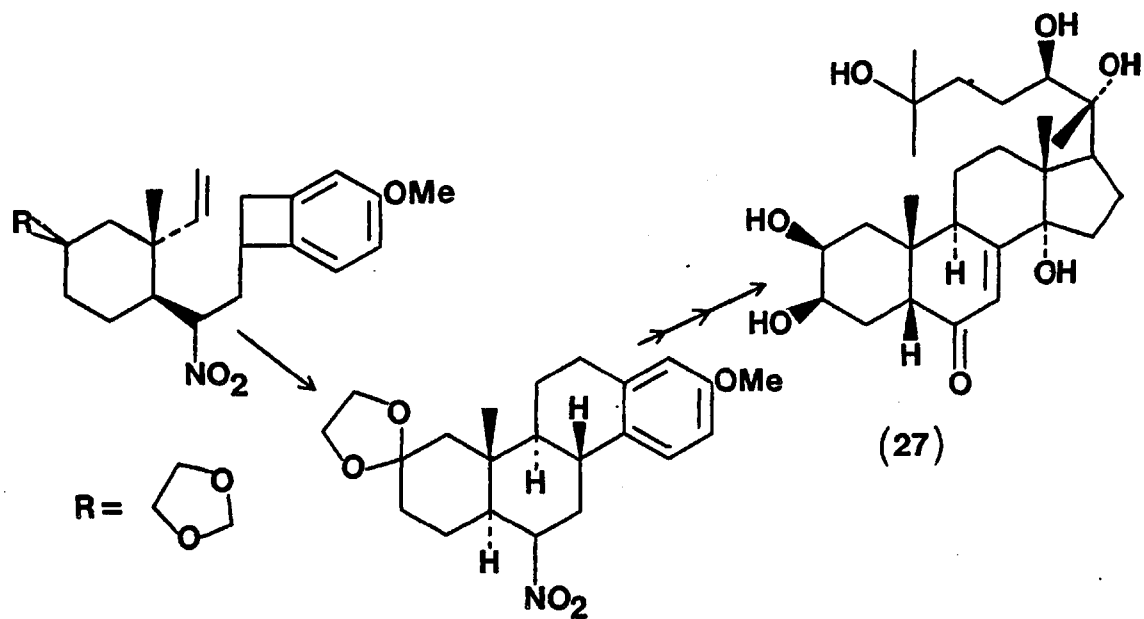
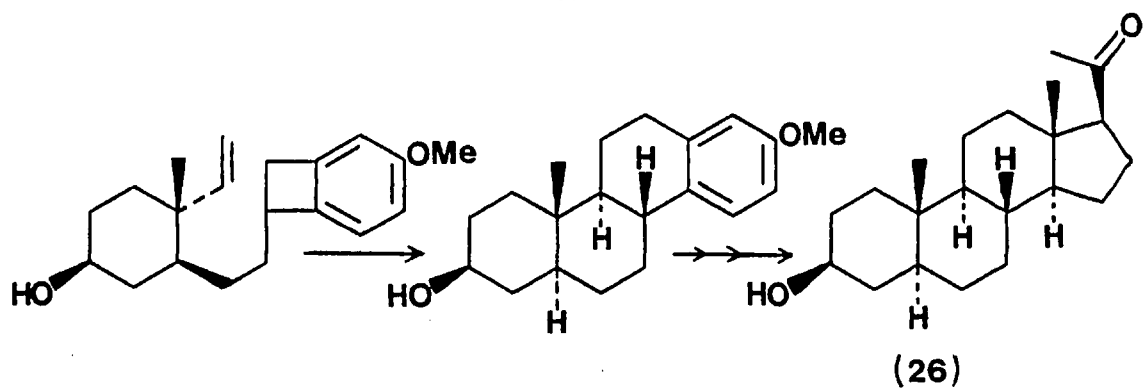


Although the conditions for *o*-quinodimethane generation and cyclization (reflux in acetonitrile with cesium fluoride) are not as mild as those used in the Magnus approach, the ease of preparation of the precursor (25) *via* silicon stabilised carbanion chemistry indicates that this may also be a generally useful method.

1.2 D-Ring Aromatic Steroids

The lengthy, rather unimpressive, Kametani syntheses of (+)-5 α -dihydropregnenolone (26) and β -ecdysone (27) *via* D-ring aromatic steroids have been reviewed elsewhere^{3b} and are only schematically summarised here.

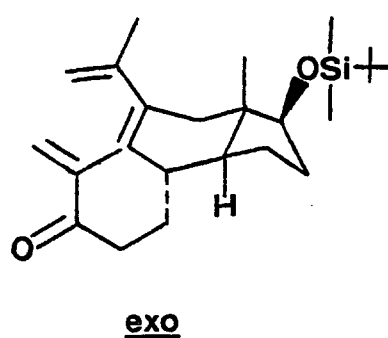
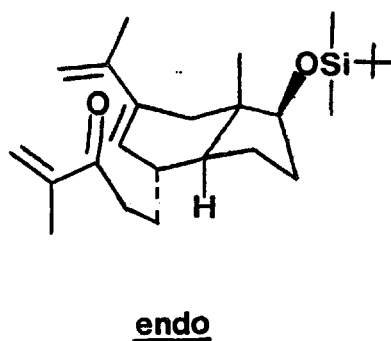
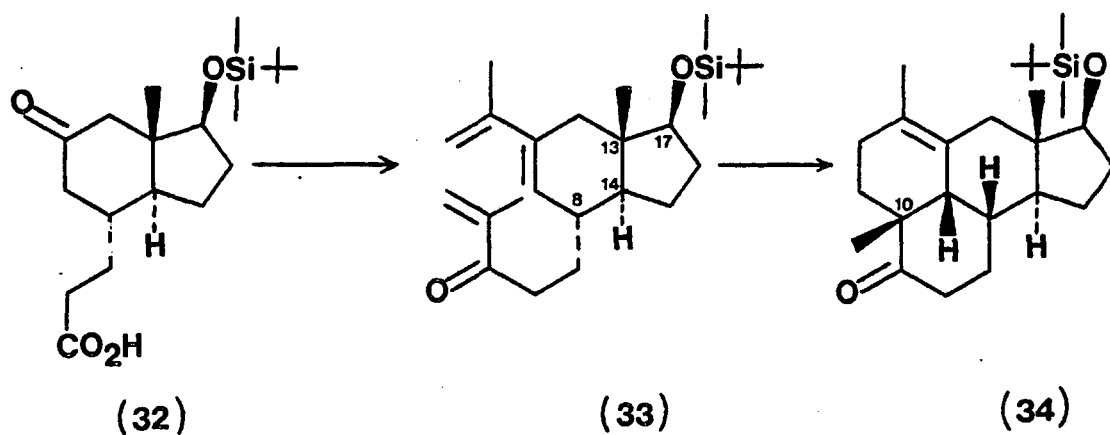
Kametani has recently published an extremely lengthy enantio-selective synthesis of (+)-chenodeoxycholic acid (31) involving IMDA reaction of the *o*-quinodimethane derived from (29), which was prepared in 20 steps (18% overall yield) from the readily available optically active enone (28).¹⁷ A further 16 steps (0.63% overall yield) were required to convert (30) to (+)-chenodeoxycholic acid.



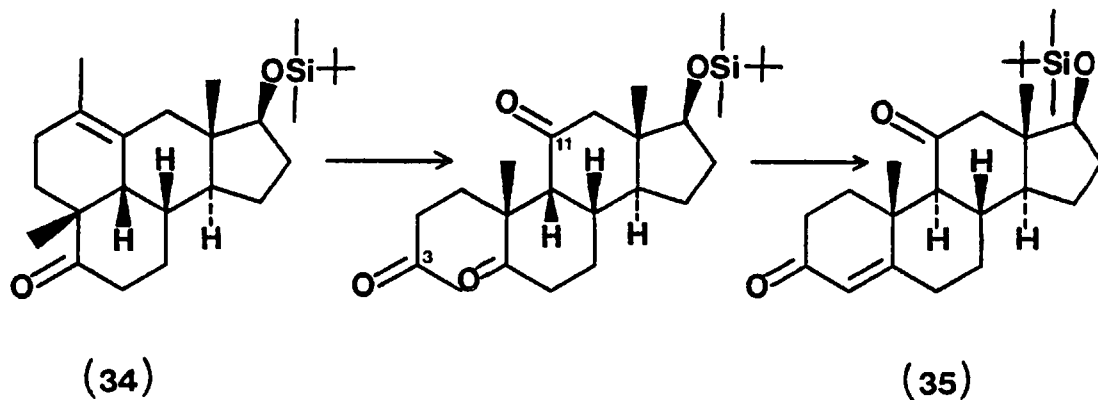
1.3 11-Oxygenated Steroids

A fine and rare example of an IMDA reaction being applied indirectly to steroid synthesis rather than the usual process of preparing a polycyclic product in which all of the formed rings are present, virtually intact, in the natural product has recently been developed by the Stork group.¹⁸

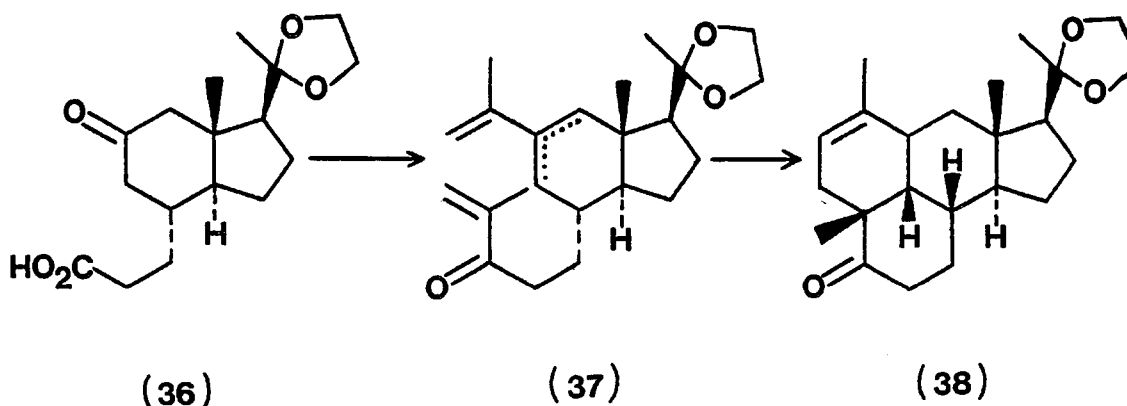
The triene (33), prepared in 81% yield from the readily available acid (32) by sequential treatment with 2-propenyl lithium (excess) and Burgess' salt, was cyclized in trifluoroacetic acid-dichloromethane at -78°C to give the tetracycle (34) in 70% yield. The ratio of *endo* to *exo* (C-10 epimer) product was 94:6 and appears to reflect the increased importance of secondary orbital interactions and the *endo* rule in low temperature Lewis-acid catalysed Diels-Alder reactions (*vide-infra*).



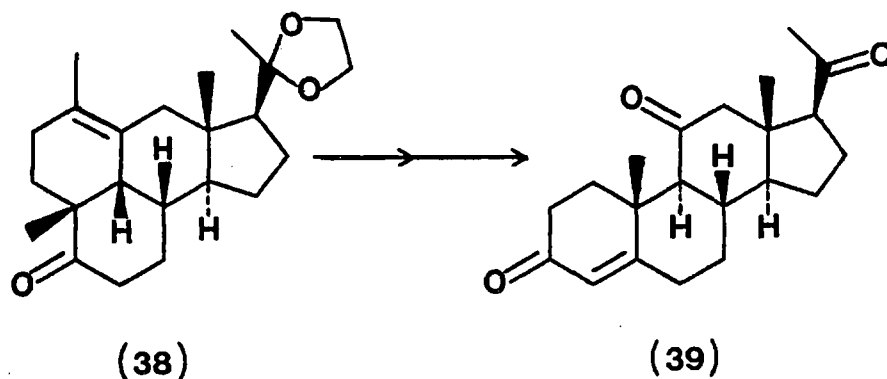
The tetracycle (34) gives the 11-ketotestosterone derivative (35), in 75% yield, upon ozonolysis and base catalysed aldol reaction. The IMDA reaction is thus used in this synthesis both to control the C-10 stereochemistry relative to the pre-existing chiral centres at C-8, C-13, C-14, and C-17 (in (33)) and to form the latent 11- and 3-keto functionalities.



A recent modification and improvement of this synthesis^{18b} involved converting the acid (36) (readily prepared, stereospecifically, in eight steps, in 28% yield, from the pyrrolidine enamine of cyclopentanone) in two steps and 40% yield to the triene (mixture of double bond isomers) (37). Refluxing this triene with rhodium chloride trihydrate in ethanol led to double bond isomerisation and isolation of the *endo* IMDA tetracyclic product (38) in 93% yield. No *exo* product was detected.



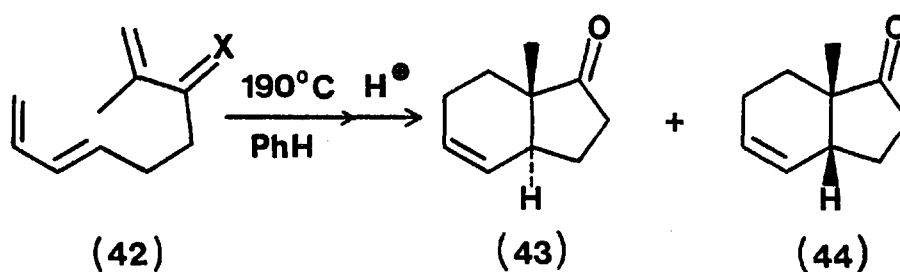
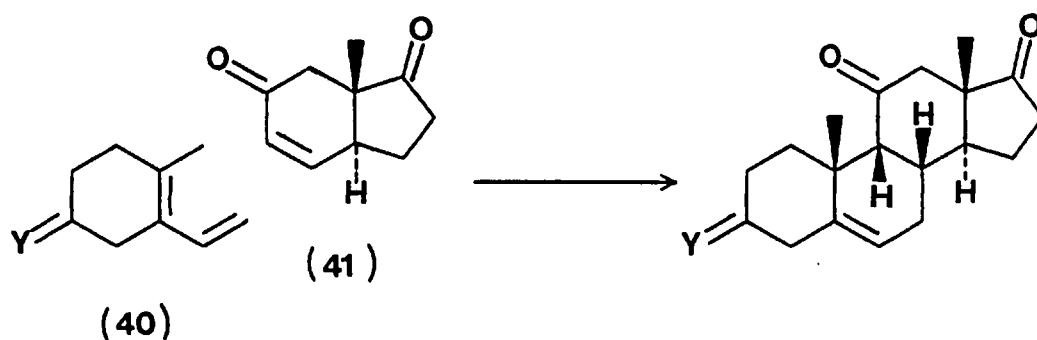
As in the previous synthesis the tetracycle (38) gave ($\pm$)-11-ketoprogesterone (39) upon ozonolysis and aldol reaction. The yield of (39) from the acid (36) was an impressive 60%.



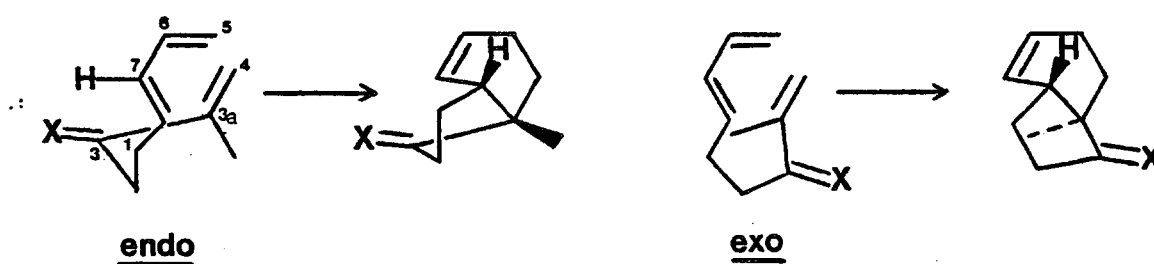
1.4 Potential Steroid Intermediates.

Jung, in anticipation of being able to construct the steroid nucleus of the corticosteroids *via* the Diels-Alder reaction of (40) with the tetrahydroindandione (41), has investigated the IMDA cyclization of trienoate (42).¹⁹

The IMDA reaction of the triene (42a) ($X = O$) unfortunately gave a 70:30 mixture with the undesired *cis*-fused tetrahydroindan (44) as the major product. However, Jung has been able to divert the stereochemical course of this IMDA reaction by preparation of ketal functionality at C-3. The ketal (42b) ($X = (OMe)_2$) gives, after acid hydrolysis, an 88% yield of a 72:28 mixture of (44):(43). This change in the stereoselectivity was explained as arising from an increase in steric destabilisation of the *endo* transition state leading to *cis*-fused (43) when an sp^3 centre replaces an sp^2 centre at C-3. It appears that the carbonyl group does not contribute much to the lowering of the activation energy of the cycloaddition due to poor overlap of the



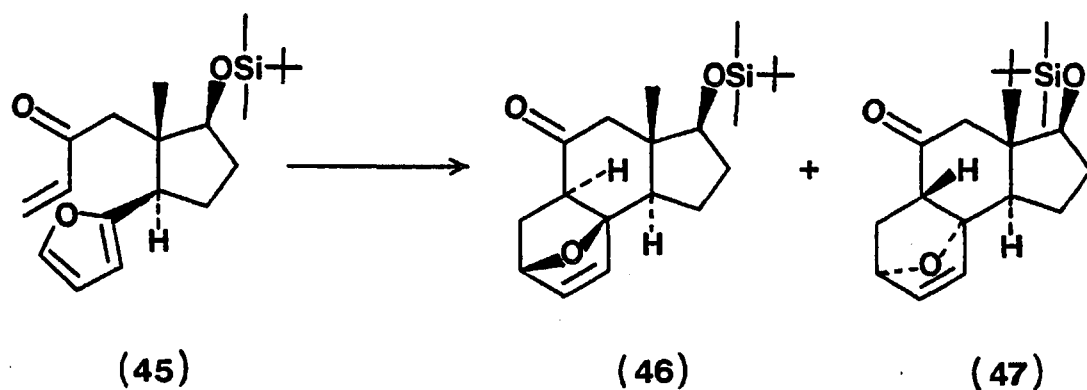
carbonyl group with the diene and the lack of planarity in the enone system (leading to 'deconjugation' and poor secondary orbital overlap) in the transition state.



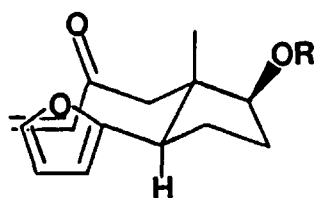
Helquist has reported similar results for the IMDA of the ketal (42c) ($X = O(CH_2)_3O$) which gives a 3:1 mixture of (43) and (44), in 85% yield after hydrolysis.²⁰ The protected alcohol derivative (42d) ($X = H, O^tBuSiMe_2$) gave only a 1:1 mixture.

It appears that more bulky groups at C-3 or even C-7 (tetrahydroindan numbering) may be needed to give sufficiently high stereoselectivity in these systems.

The potential steroid precursor (46) was prepared by IMDA reaction of (45).²¹ The reaction gave a 9:1 mixture of *exo* products (46) and (47), at 50% conversion, in refluxing benzene (six days) or a 1:8 mixture, at 61% conversion, in dichloromethane at room temperature (six days).



The formation of the *exo* product (47) at lower temperatures appears to be due to this isomer being the kinetic product, arising *via* the more stable boat-chair-boat-like conformation for the pseudo-ten-membered ring in transition state B below. The reaction is presumably reversible (only 50-60% conversion) and the thermodynamic product (46), *via* a boat-chair-chair-like transition state (A) thus predominates at higher temperatures. The authors do not report the appropriate test of this hypothesis of heating (47) in benzene.

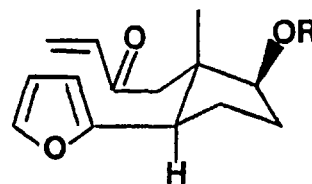


(A)

thermo



(46)



(B)

kinetic



(47)

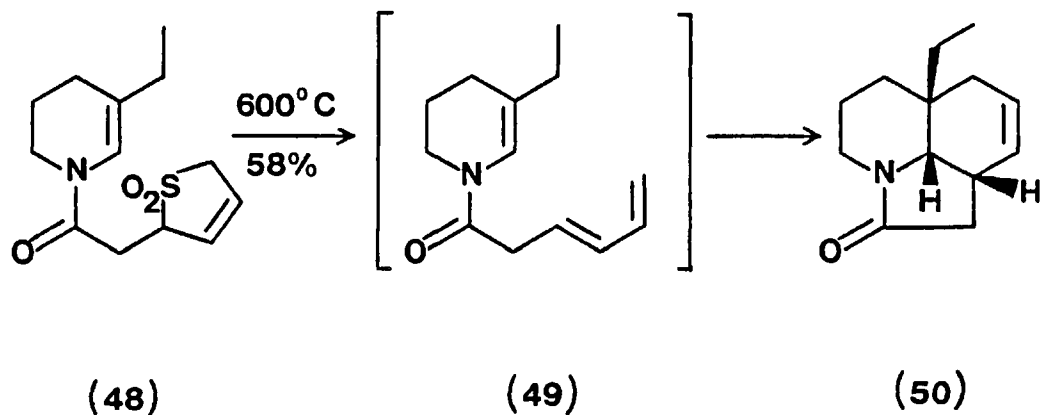
2. ALKALOIDS

Earlier syntheses of alkaloids involving the use of IMDA reactions have been reviewed elsewhere.¹⁻³ and only the very recent examples are included in this section.

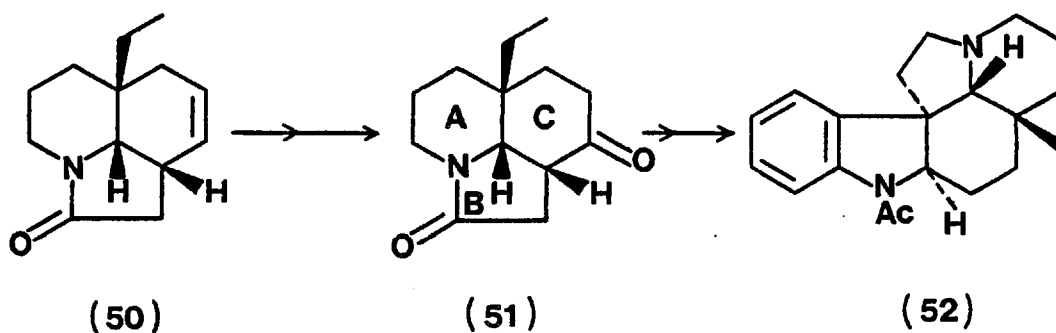
The Weinreb syntheses of the indolizidine alkaloids δ -coniceine and tylophorine are not included in this review as only one asymmetric centre is present in the IMDA products.²²

2.1 Aspidosperma Alkaloids

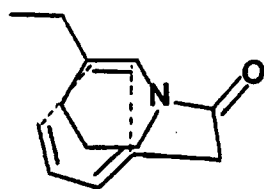
A new stereospecific approach to the synthesis of the hydrolulolidine system, that is characteristic of the Aspidosperma alkaloids, *via* the IMDA reaction of enamidodienes, is typified by the thermolysis (600°C) of the enamidosulphone (48) to give only the *endo* product (50) *via* the cheletropically formed diene (49).²³



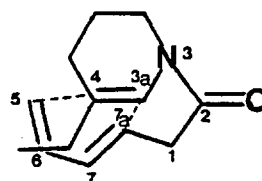
The hydrolulolidine (50) was converted, in three steps (26% yield), to (51), a key intermediate in previous syntheses of aspidospermine (52).



The *endo* transition state (A) leading to the more stable *cis*-fused 6,5 ring system must clearly be lower in energy than the alternative *exo* transition state (B), presumably due to its inherently lower strain energy.



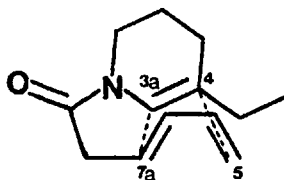
(A)



(B)

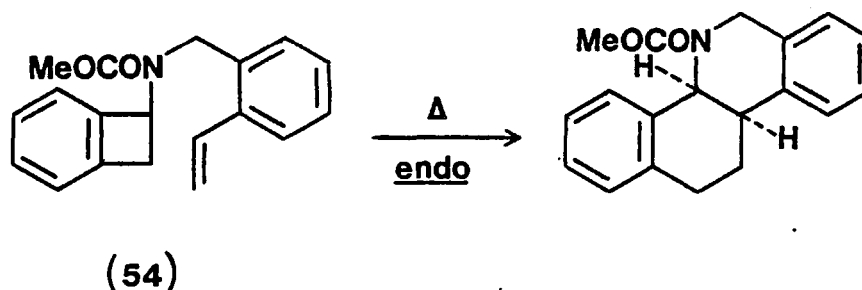
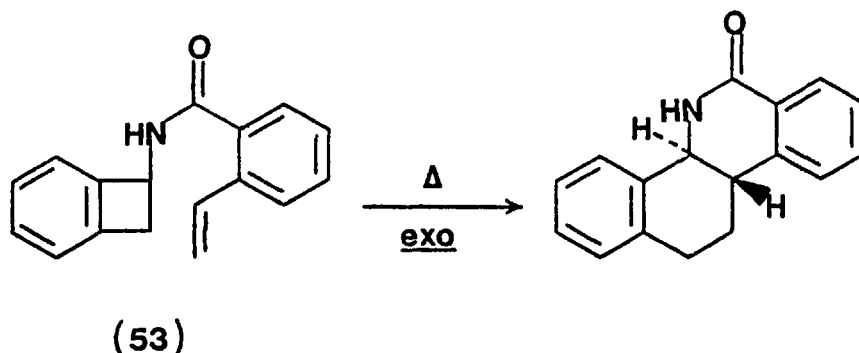
The conclusion of Martin and co-workers that the *endo* transition state is preferred not as a consequence of any favourable secondary orbital interactions agrees with the previously discussed results of Jung and Helquist and others (*vide infra*) on these 6,5-systems.

In fact, an examination of molecular models leads to the realisation that, assuming near planarity of the enamido system, the two transition states (A) and (B) above are not physically possible. A far more likely *endo* transition state is represented below. This is based on the concerted but non-synchronous transition state mechanism, discussed by Boeckman²⁴ and White²⁵ (*vide infra*), in which the C-3a - C-7a bond is more fully formed than the C-4 - C-5 bond.



The high temperature (260°C or 600°C) required for this IMDA reaction is not surprising due to the need to substantially interfere with the enamido conjugation in advanced transition state development. Although it is not easy to see why from simple molecular models, the presence of an sp^2 centre and a planar nitrogen in the bridge linking diene with dienophile in these 6,5-systems leads to the complete reversal of the usually observed *trans* preference for IMDA reactions in 6,5-systems (*vide infra*).

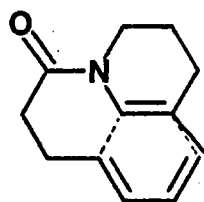
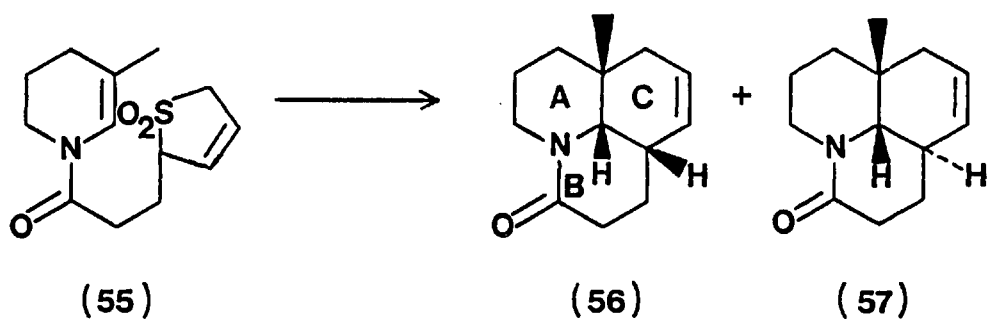
A similar reversal of stereocontrol in the reaction of the closely related urethane (53) and lactam (54) was observed in the Oppolzer studies on a chelidonine synthesis.²⁶



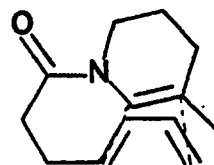
Oppolzer, in fact, concludes that it should be quite generally possible, by conformational modification of the bridge, to direct IMDA reactions completely in the direction of *trans*- or *cis*-annellated products.^{1c}

The hydrojulolidine skeleton, which is representative of the Lycopodium alkaloids, was prepared with poor stereoselectivity by thermolysis of the enamidosulphone (55). The *endo cis*-fused BC and *exo trans*-fused BC products (56) and (57) were formed in a 1:1 ratio in 43% yield.²³

The lack of stereospecificity in this reaction, as compared to the previously discussed closely related IMDA reaction of (49), was fully in accord with the expectation that the *exo* transition state leading to the *trans*-fused 6,6-BC system of (57) would be less strained than the *exo* transition state leading to the *trans*-fused 6,5-BC system of (50).



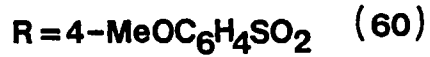
exo



endo

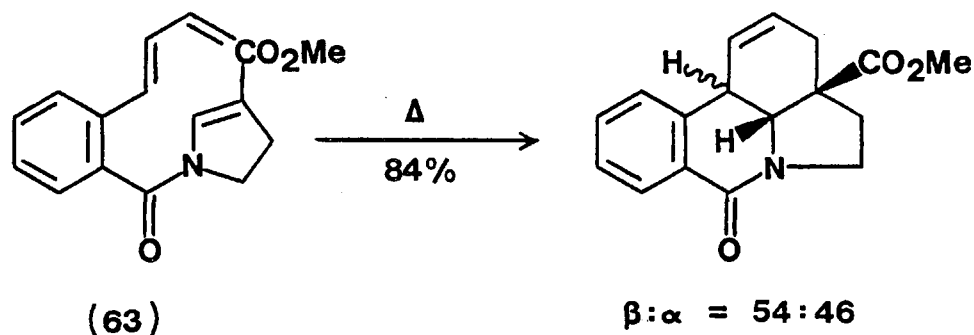
Magnus and Gallagher have developed a short, highly convergent, route to *Aspidosperma* alkaloids *via* the IMDA reaction of the novel indole-2,3-quinodimethanes.²⁷ Reaction of the imine (58) (prepared in quantitative yield from the readily available protected 3-formyl-2-methylindole) with the mixed anhydride (50) gave the tetracyclic system (60), as the only cyclization product in 33% yield, *via* the sterically favoured *exo* (*E*) transition state for the intermediate indole-2,3-quinodimethane (61).

The tetracycle (60) was efficiently converted in four steps (34% overall yield) to (±)-*Aspidospermidine* (62).



2.2 Amaryllidaceae Alkaloids

A novel "phenylbutadiene plus Δ^2 -pyrroline" IMDA reaction was used by Stork and Morgans to construct a functionalised galanthan.²⁸ The stereoselectivity of the cyclization of (63) to form the galanthan ring system, common to many Amaryllidaceae alkaloids, was, however, poor.

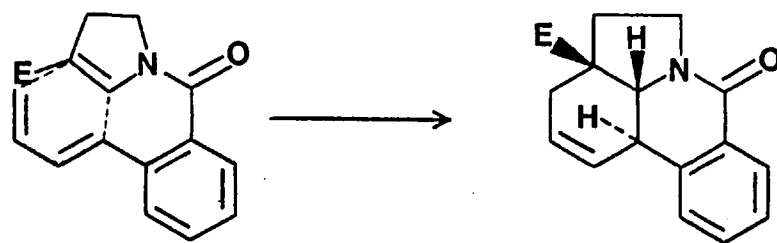


This stereochemical result was in exact agreement with the closely related IMDA reaction of (55), previously discussed. In the formation of these 6,6-systems little energy difference is apparent between the *exo* transition state, leading to the *trans*-fused product, and the *endo* transition state, leading to the *cis*-fused product.

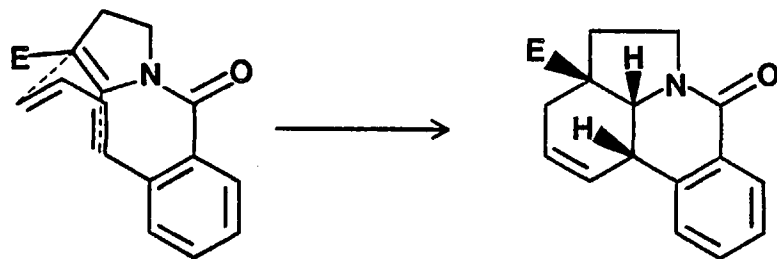
Surprisingly, the related tetrahydropyridine (64) gives a 2:1 mixture of *exo* (*trans*-fused) to *endo* (*cis*-fused) products.

Presumably, in this case, the extra methylene group present in (64) destabilises the *endo* transition state relative to the *exo* one.

A more successful IMDA approach to the galanthan system was developed by Stork and Morgans.²⁹ The galanthan (α -lycorane) system, which forms the basic skeleton of lycorine (66), the most prevalent of the Amaryllidaceae alkaloids, was constructed in a simple and stereo-specific manner.

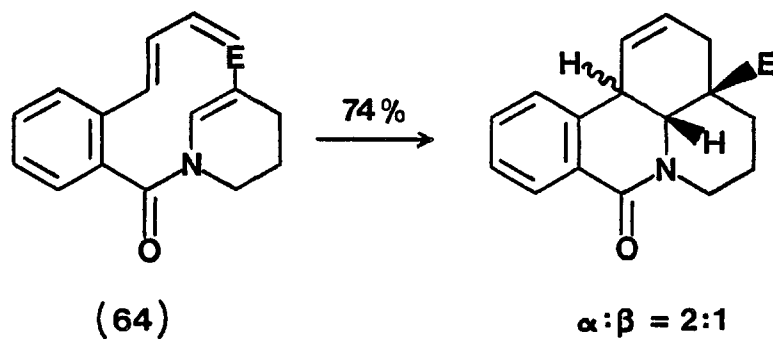


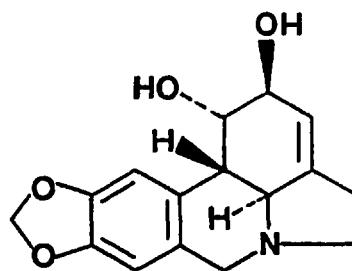
exo



endo

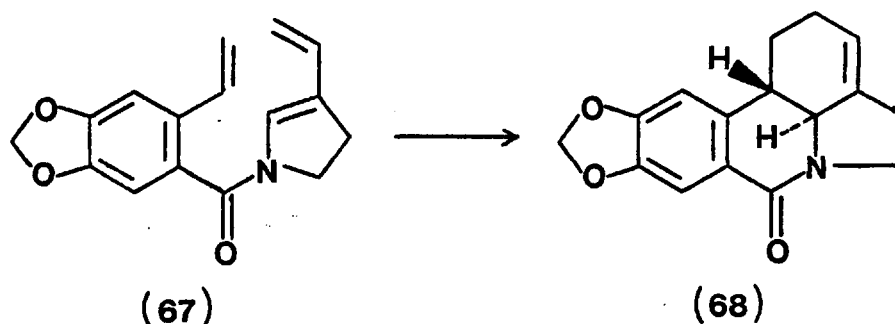
$E = \text{CO}_2\text{Me}$





(66)

The triene (67) was cyclized at 140°C (24h in chlorobenzene) to give only the *exo* (*trans*-fused) product (68) in 51% yield.



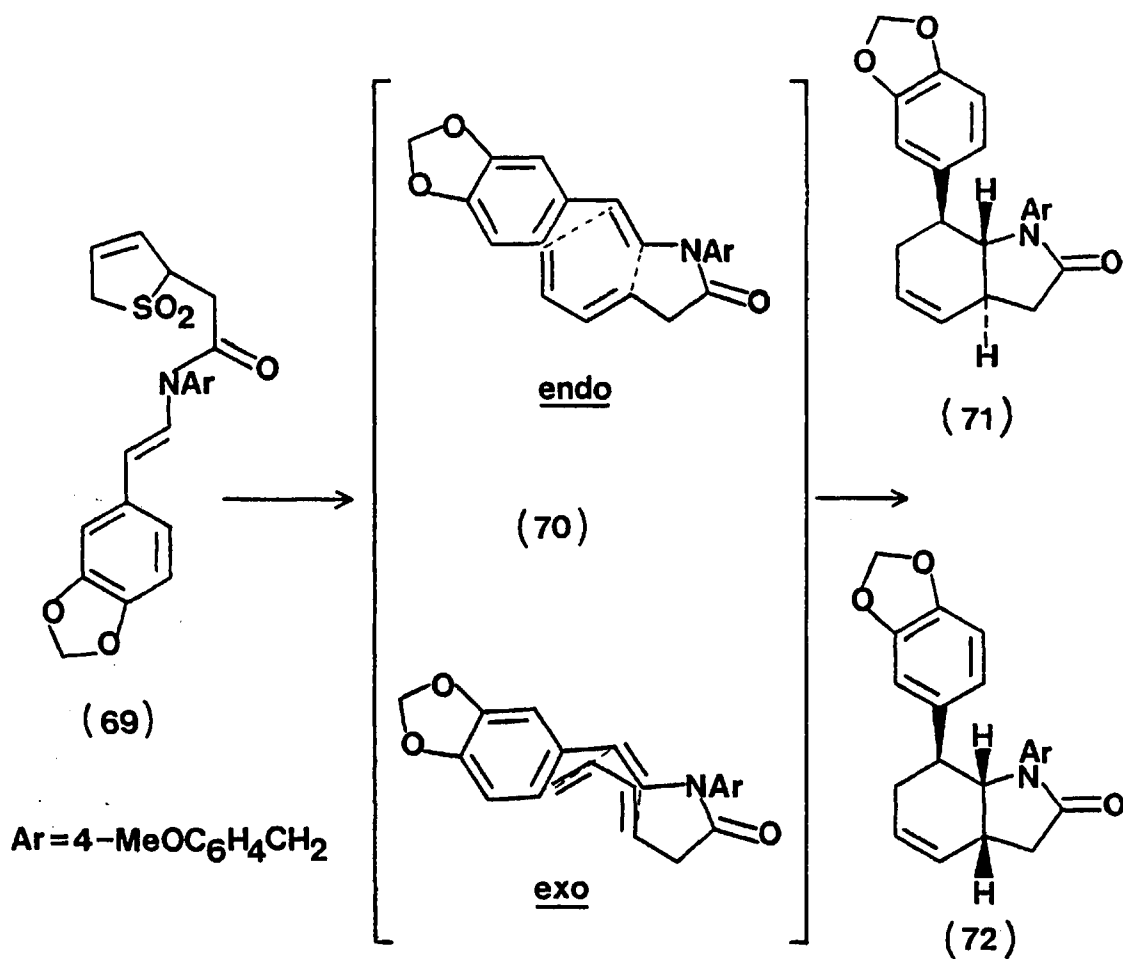
(67)

(68)

The nature of the bridge (three sp^2 centres and a planar nitrogen atom) is such as to virtually preclude reaction *via* the *endo* transition state.

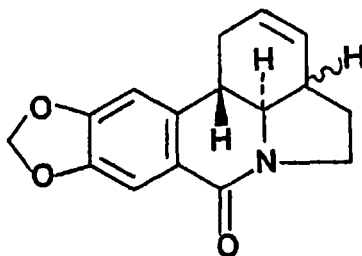
A different approach to the synthesis of lycorine, involving formation of the 6,5-ring system in an IMDA process, has been reported by Martin and Tu.³⁰ The triene (70), formed *in situ* from the sulphone (69), cyclized in a non-stereoselective manner to give a 58:42 mixture of the isomers (71) and (72), in 47% yield.

When compared with the previously discussed cyclization of the enamidodiene (49), which gave exclusively *cis* (50) *via* the *endo*



transition state, this result is initially surprising. Presumably, the fact that the enamide in (70) is not part of a constrained cyclic system (as is (49)), combined with the possible effect of the aromatic group enhancing the *endo* mode *via* secondary orbital interactions, is enough to swing the balance of the reaction away from purely *cis* product. It must be noted that the presence of the sp² centre and planar nitrogen atom is still sufficient to produce more *cis*-fused 6,5 product than in other 6,5-systems, however (*vide infra*).

After reduction to the amine, the minor and major isomers were separated and converted to α-lycorane (73) (which has been previously converted to lycorine (66)) and β-lycorane (74), both in two efficient steps.



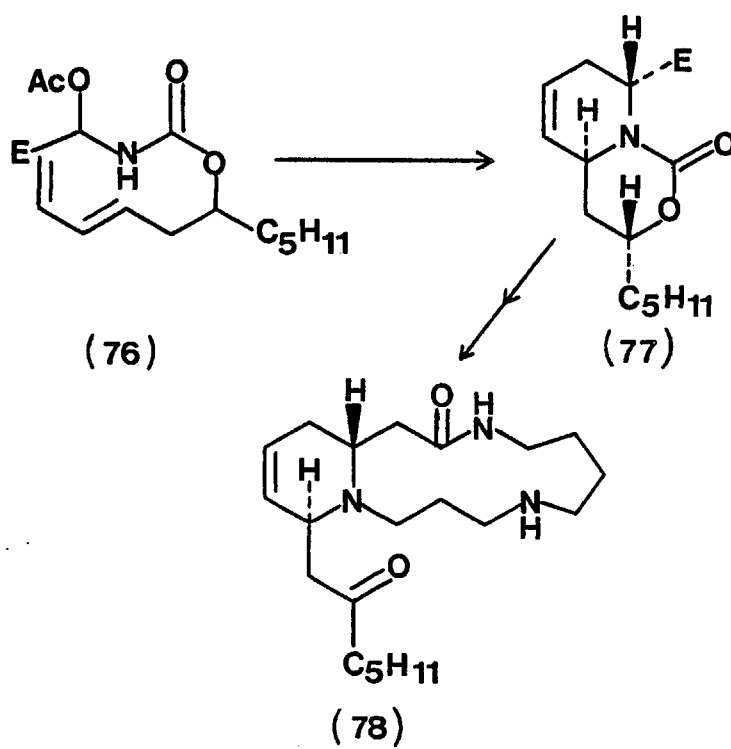
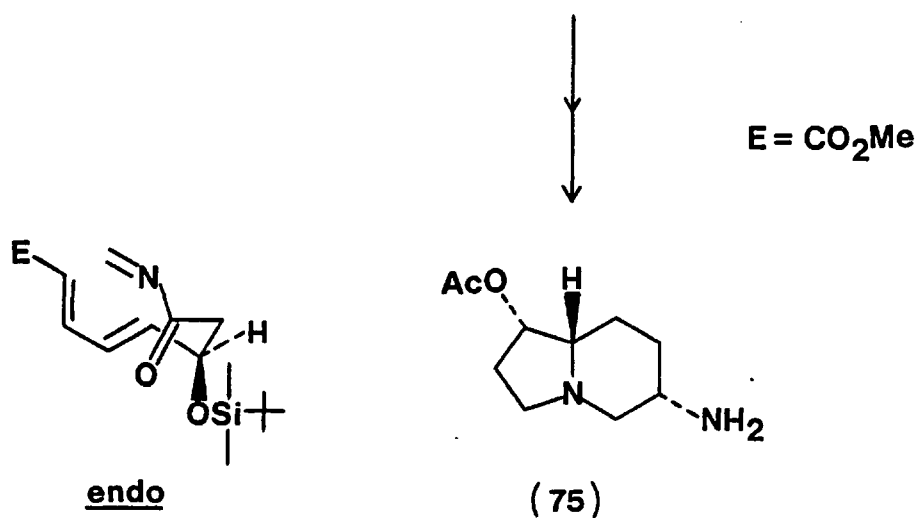
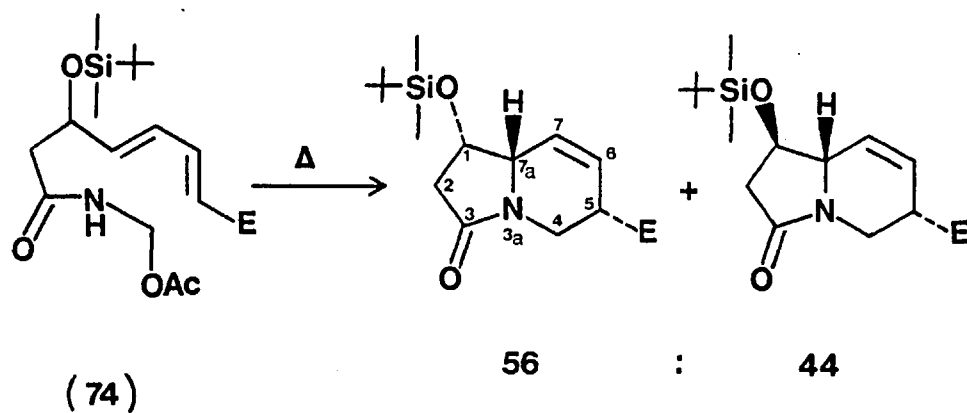
α -H (73)

β -H (74)

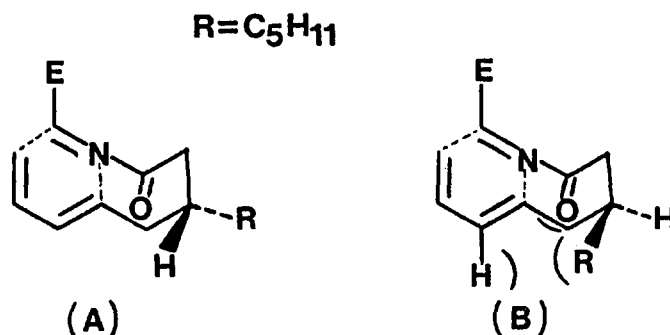
2.3 Miscellaneous Alkaloids

Weinreb has prepared the indolizidine alkaloid staframine (75) *via in situ* IMDA reaction of the imine formed from (74).³¹ The stereoselectivity of the IMDA reaction was poor, with a ratio of only 56:44 in favour of the desired stereochemistry. This small degree of stereoselection could be attributed to reaction *via* a less strained (note, only one sp^2 centre in the bridge) *endo* transition state in which there is a small preference for the protected hydroxyl substituent at C-1 (tetrahydroindan numbering) to exist in a pseudoequatorial environment. In saturated bridged 6,5 IMDA systems stereocontrol at C-1 is usually in the opposite sense due to unfavourable steric compression, particularly with the C-3a proton on the dienophile.

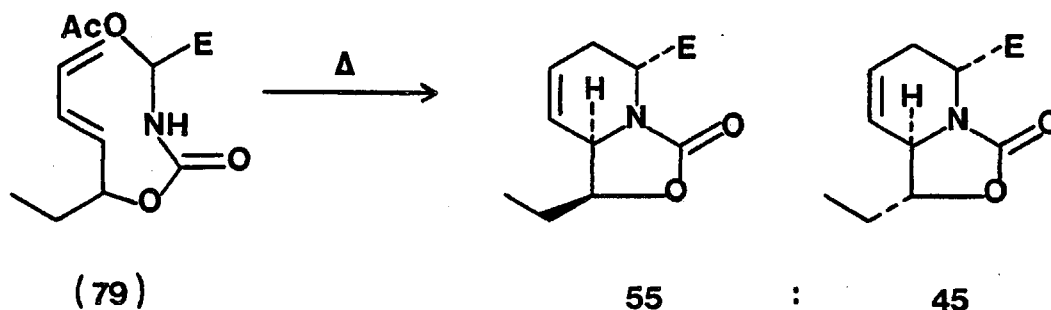
The completely stereospecific intramolecular imino Diels-Alder reaction of the (*E*)-acylimine generated *in situ* (210°C, toluene) from the diene (76) is the key step in a synthesis of anhydrocannabisativene (77) reported recently by Weinreb.³¹



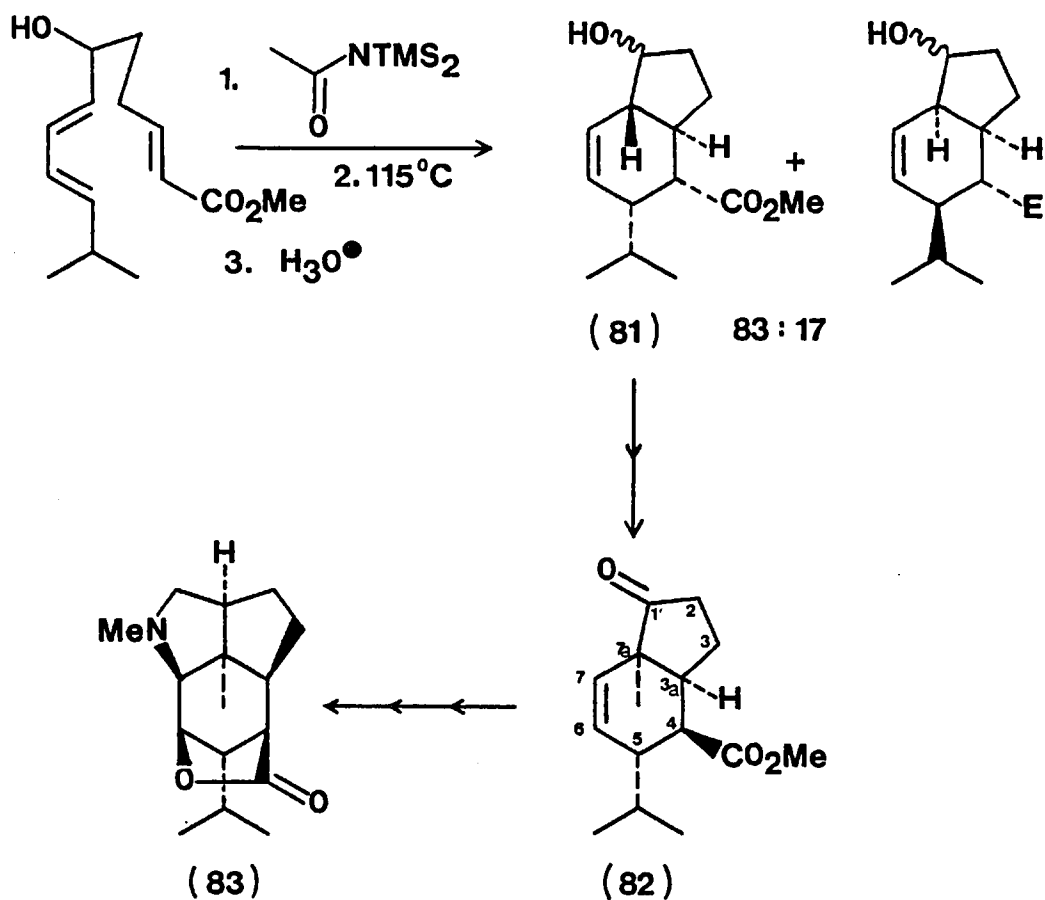
The single diastereomer (77), isolated in 77% yield, was formed *via* the less sterically crowded *endo* cyclization of an (*E*)-acylimine ((A) *vs.* (B)).



The intramolecular imino Diels-Alder reaction of the (*E*)-acylimine formed *in situ* from (79) exhibited the same poor degree of stereocontrol at C-1 as in the related example (74).³² This hints that the IMDA for cyclization of (74) was also possibly exclusively *via* the *endo* mode.

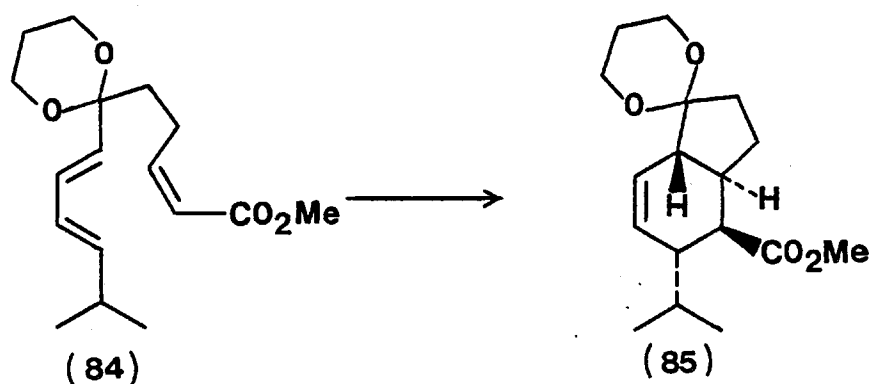


As shown in Scheme 2, Roush utilised the stereoselective IMDA of the trienoate (80) to prepare a key tetrahydroindan intermediate (81) in his synthesis of ($\pm$)-dendrobine (83).³³ The major *endo trans*-fused product (81) was converted to dendrobine by a multistep procedure *via* the doubly epimerised (C-4 and C-7a), oxidised, (C-1), and methylated derivative (82).



Scheme 2

In an improved and considerably shorter route to (82), Roush has cleverly used the (*Z*)-dienophile of (84) to establish the required stereochemistry at C-4 (thus eliminating the need for base catalysed epimerisation at this centre) in an *exo* IMDA to form, again, the *trans*-fused tetrahydroindan (85).³⁴

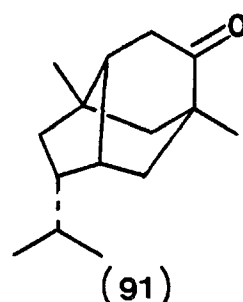
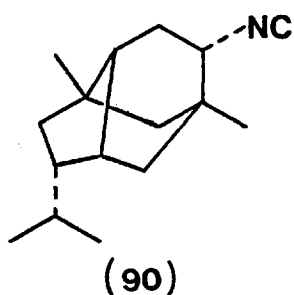
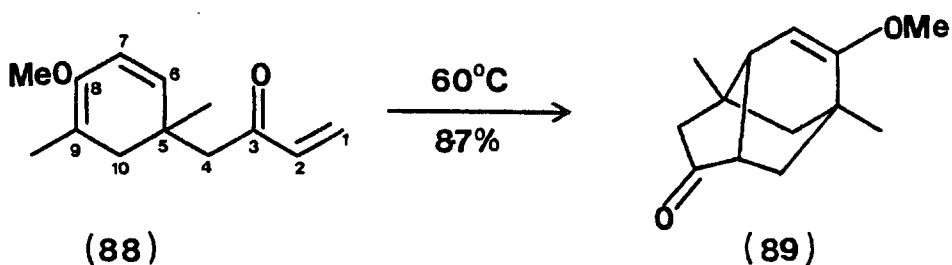
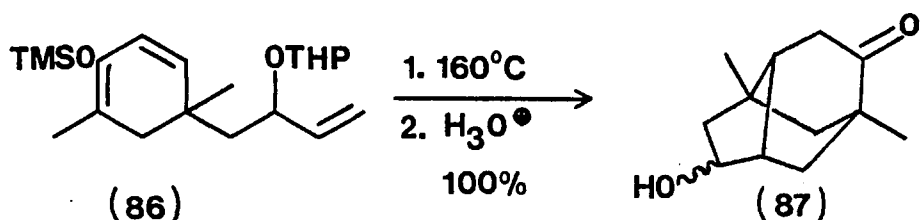


The propensity of many similar trienoate systems to preferentially form tetrahydroindan systems with a *trans* ring junction, whether *via* an *endo* ((*E*)-dienophile) or *exo* ((*Z*)-dienophile) process, has been thoroughly demonstrated by Roush.³⁵ This work is a further indication that subtle steric and stereoelectronic factors often play a far greater role in determining IMDA stereochemical outcome than does the *endo* rule or secondary orbital interactions.

3. TERPENOIDS

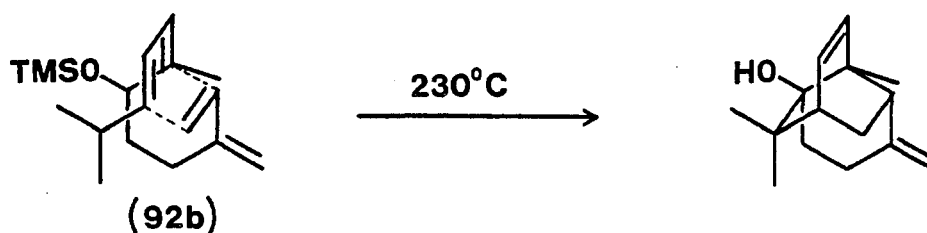
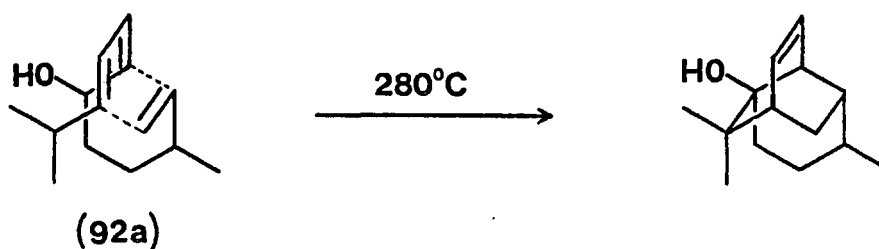
3.1 Sesquiterpenes

Yamamoto and Sham³⁶ and, independently, White³⁷ have used the IMDA reaction of the similar trienes (86) and (88) respectively, to prepare the pupukeanane skeleton of (±)-9-isocyanopupukeanane (90).



The ketones (87) and (89) were transformed into ($\pm$)-9-isocyano-pupukeanane itself and a degradation product, ($\pm$)-9-pupukeanane (91), respectively.

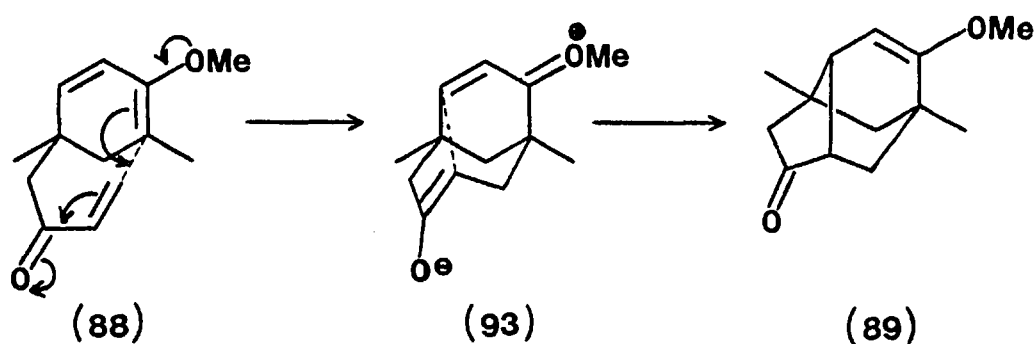
White points out that the IMDA cyclization of the triene (88) proceeds rapidly at much lower temperature (60°C) than the Yamamoto cyclization (160°C) or the two other closely related IMDA cyclizations below (92a and b).



White concluded that the ketone functionality in (88) plays a role in lowering the activation energy, although admitting that the enone moiety is considerably distorted from planarity (required for maximum secondary orbital interactions) at the point of cycloaddition. This suggestion seems unlikely in view of the previous evidence (*vide supra*) against large secondary orbital effects.

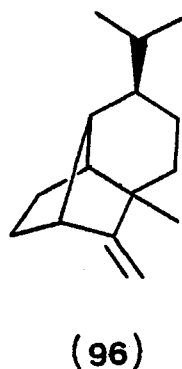
However, particularly on examination of molecular models (when it can be seen that the enone terminal carbon (C-1) can approach C-9 on

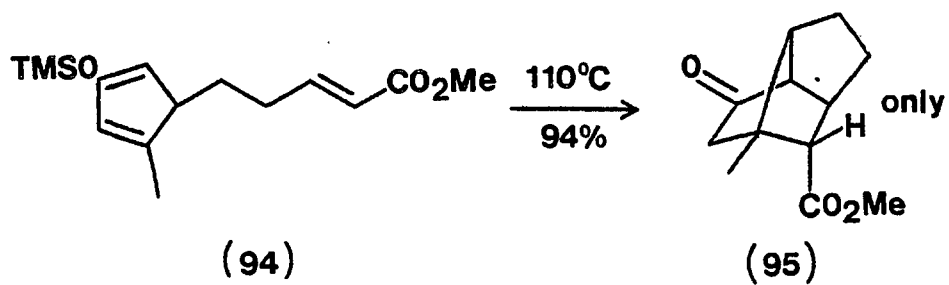
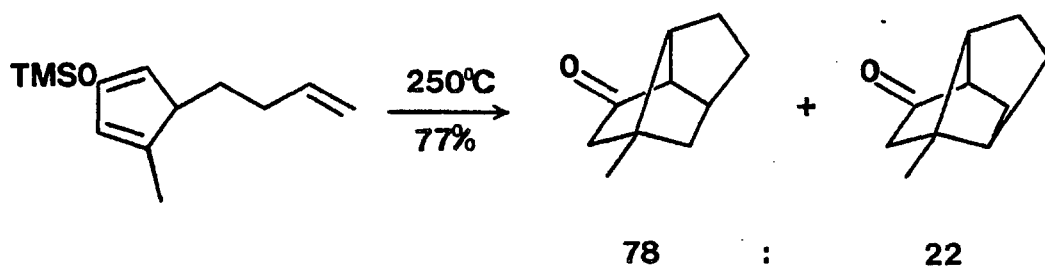
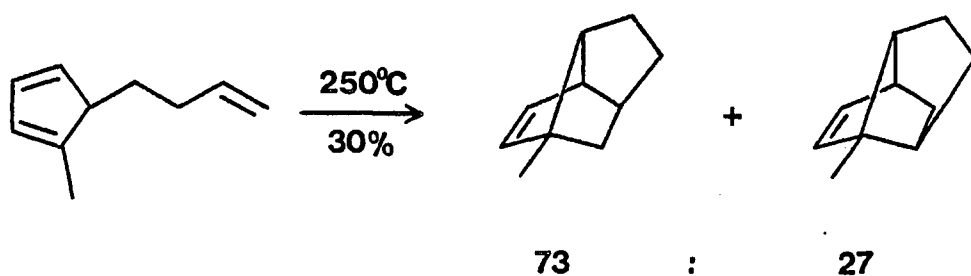
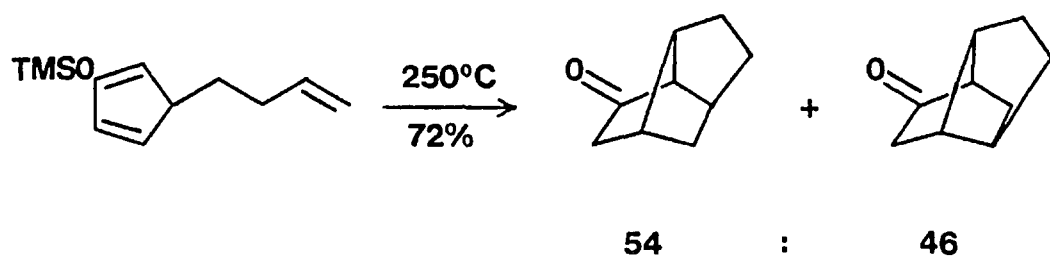
the diene moiety without any distortion of its conjugation or any unfavourable steric interactions) it seems highly likely that the cyclization of (88) is not an IMDA process at all. As shown in Scheme 3, reaction could occur in a stepwise fashion *via* the seven-membered intermediate zwitterion (93). The cyclization of (88) would thus be very likely to be an ideal candidate for low temperature Lewis acid catalysis.



The highly regiospecific cyclization of the *in-situ* prepared silyl-dienol ether (94), compared to the other examples in Scheme 3, seems highly likely, as suggested to Snowden, to involve a double Michael reaction mechanism, similar to that for cyclization of (88).³⁸

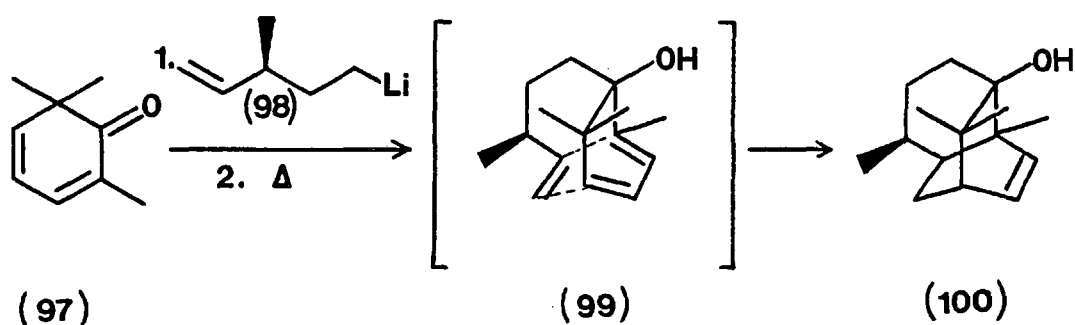
The cyclized product (95) was converted to (±)-sativene (96).³⁹



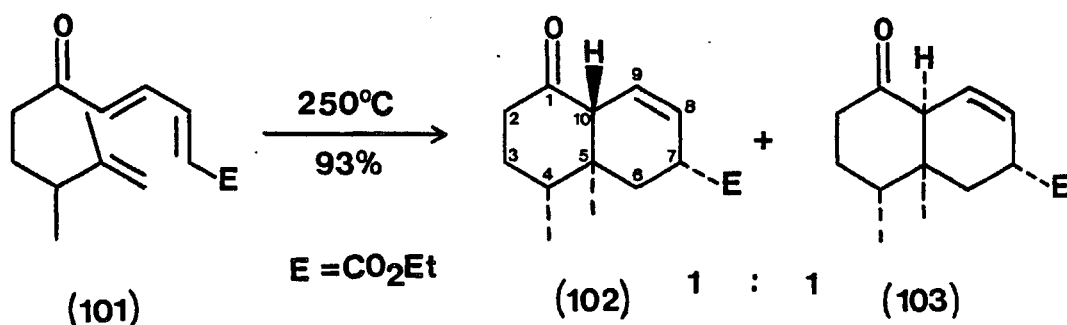


Scheme 3

Ohloff prepared (-)-patchouli alcohol, by a very short route, by hydrogenation of (100), the IMDA cyclized product of the triene (99) (prepared by addition of the optically active lithio species (98) to the dieneone (97)).



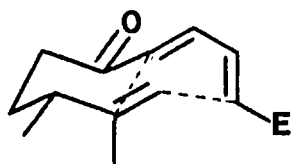
Näf and co-workers have developed a novel entry into the eremophilane and valencane sesquiterpenes *via* a stereoselective IMDA reaction of the trienoate (101).



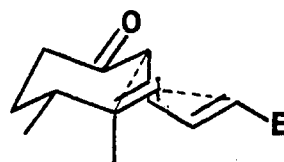
Complete stereocontrol at the important C-4, C-5, and C-7 centres was achieved through reaction *via* preferred *exo* and *endo* modes ((A) and (B) below) in which the methyl group at C-4 occupies a pseudoequatorial position.

The lack of *endo-exo* specificity is of no consequence as the majority of naturally occurring eremophilanes and valencanes do not have

a chiral tetrahedral C-10 bridgehead. Usefully, as there are examples of *cis* decalin eremophilanes, the *trans* product (102) can be rapidly epimerised to the *cis* decalin (103).

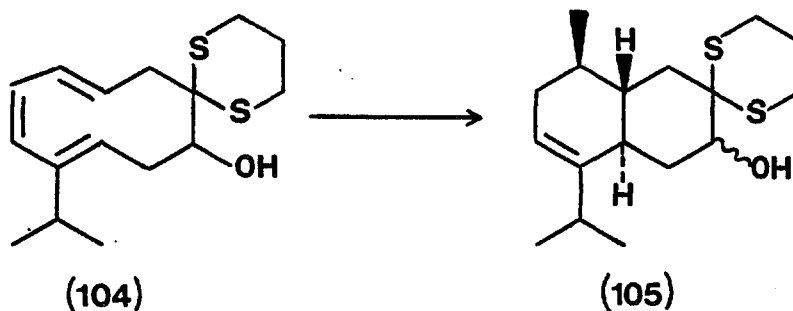


(A)



(B)

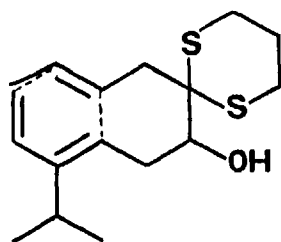
The *trans* decalin (105) is the exclusive product in the IMDA cyclization of the triene (104), used in an approach to the cadalane class of sesquiterpenes.⁴²



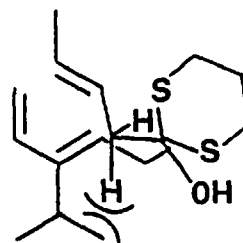
(104)

(105)

The *cis* decalin forming reaction mode (B) is disfavoured by a severe buttress interaction between the bridging methylene α to the dienophile and the isopropyl group.

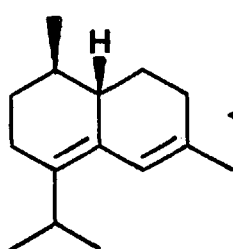


(A)

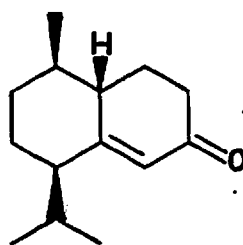


(B)

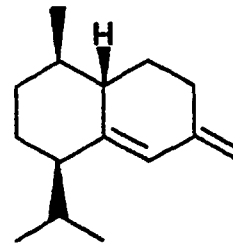
(105) was converted to the ketone (106) which had previously been converted to ($\pm$)-epizonarene (107) and ($\pm$)-epibicyclosesquiphellandrene (108).



(107)



(106)

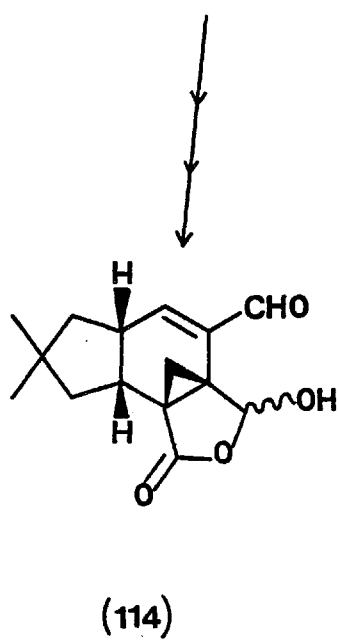
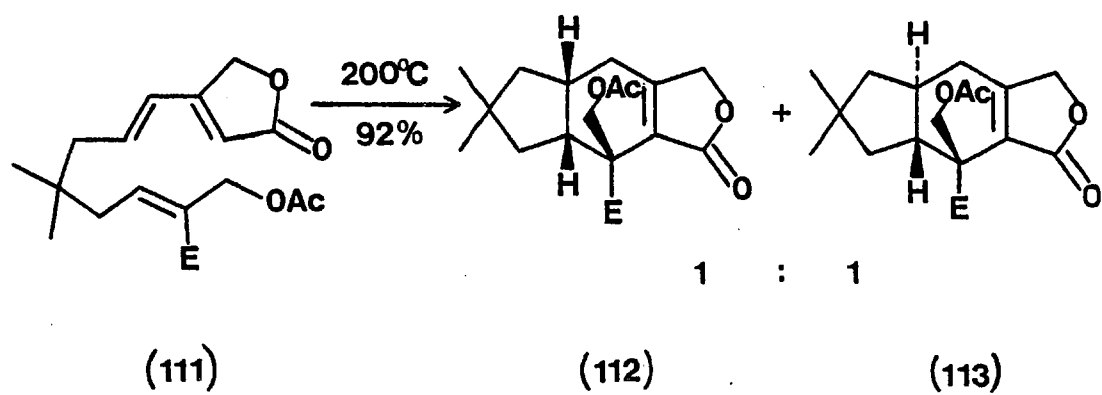
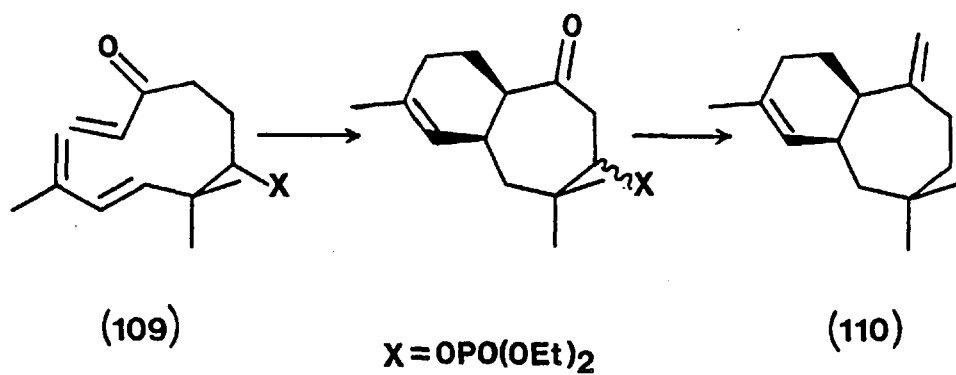


(108)

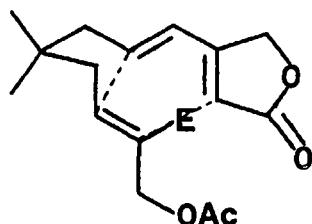
Oppolzer and Snowden prepared α -himachalene (110) by way of the facile IMDA (180°C , 19h, 90% yield) of the triene (109).⁴³ This would appear to be a relatively rare example of a genuine activated dienophile *endo* IMDA cyclization.

The key step in Boeckman's synthesis of ($\pm$)-marasmic acid (114), a unique sesquiterpene antibiotic, was the IMDA cyclization of the triene (111).⁴⁴

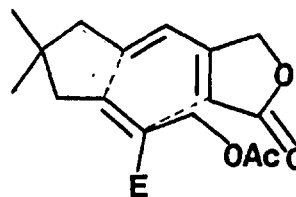
In agreement with Roush's results (*vide supra*), secondary orbital interactions in the *endo* mode were insufficient to overcome the



unfavourable nonbonded interactions in the transition state for formation of the *cis* isomer (112) and an equal proportion of *trans* isomer (113) (*via* the *exo* mode) was formed.



endo

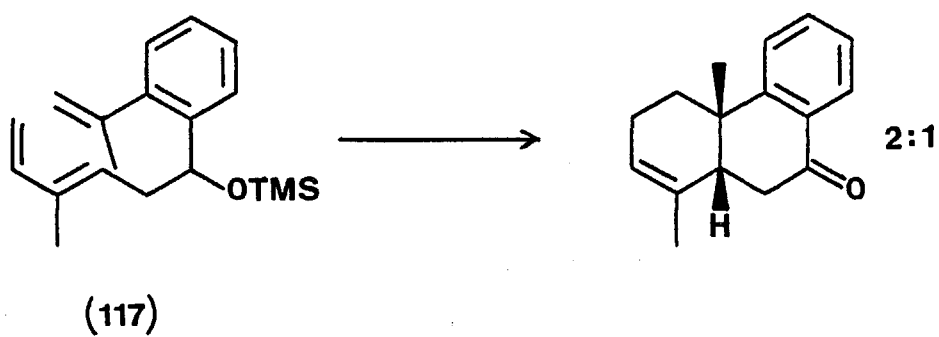
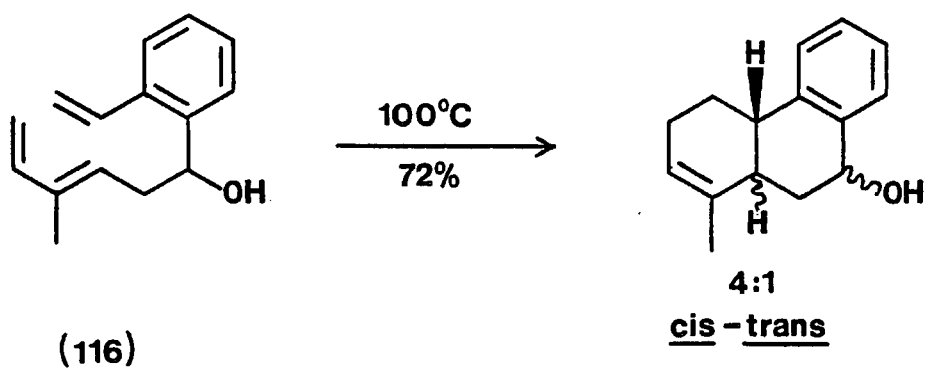
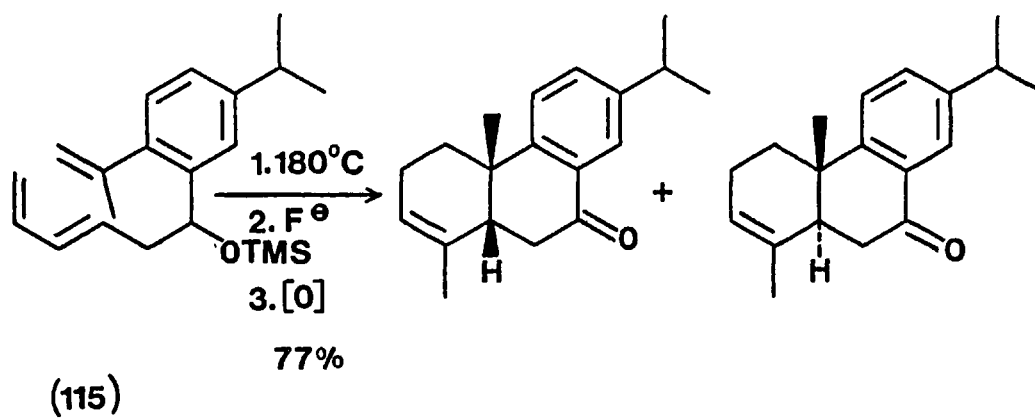


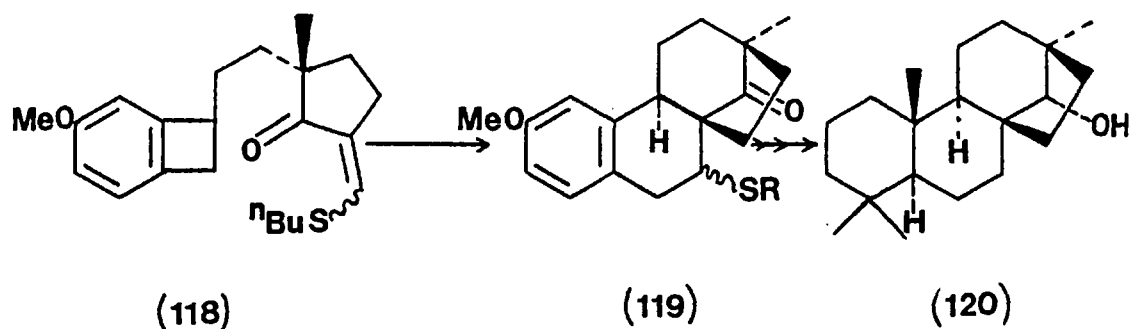
exo

3.2 Diterpenes

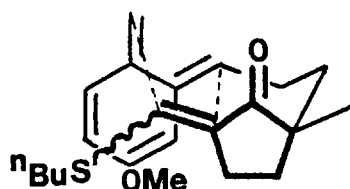
Wilson and Misra, in their studies on possible IMDA routes to tricyclic diterpenes, cyclized the triene (115) to give, after deprotection and oxidation, a 1:1 mixture of natural *cis*-fused (*endo*) and unnatural *trans*-fused (*exo*) abietane type skeleton.⁴⁵ In view of the preference for the *cis* products of the trienes (116) and (117), this result was disappointing. Although the authors point out that it is well known that subtle changes in the conformation of the bridging atoms can have dramatic effects on IMDA selectivity, it is difficult to see how the addition of a far removed isopropyl group can effect the stereochemical outcome. Electronic factors may also play a role in this case.

In an extremely lengthy synthesis of hibaoI (120). Kametani used the stereospecific *exo* IMDA reaction of the *o*-quinodimethane, formed *in situ* by thermolysis of (118), to give the intermediate (119).⁴⁶



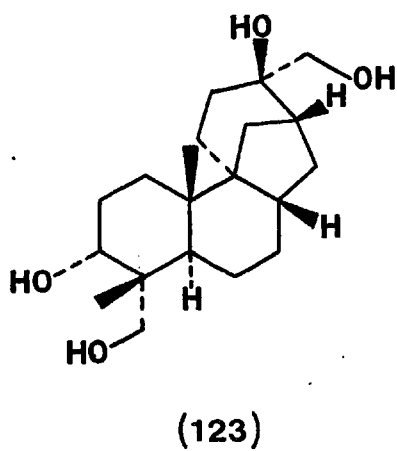
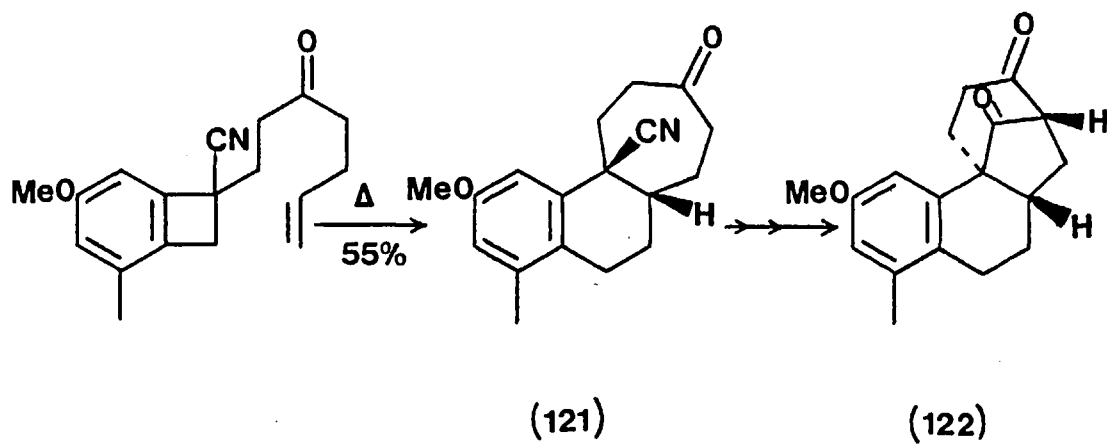


via

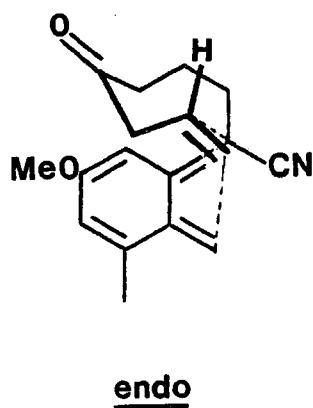


Another Kametani use, as shown in Scheme 4 below, of a benzocyclobutene generated *o*-quinodimethane is the preparation of a compound, (122), with the aphidicolin skeleton *via* the cyclized IMDA product (121), in an approach to aphidicolin (123).⁴⁷

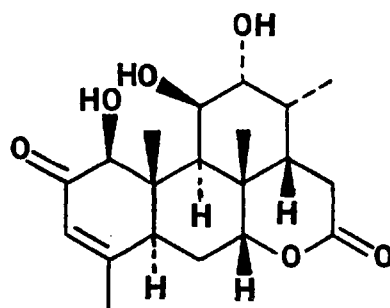
The cyclization to form (121) presumably occurs *via* the *endo* mode below, in which steric interactions between the nitrile group and the bridge are minimised.



Scheme 4

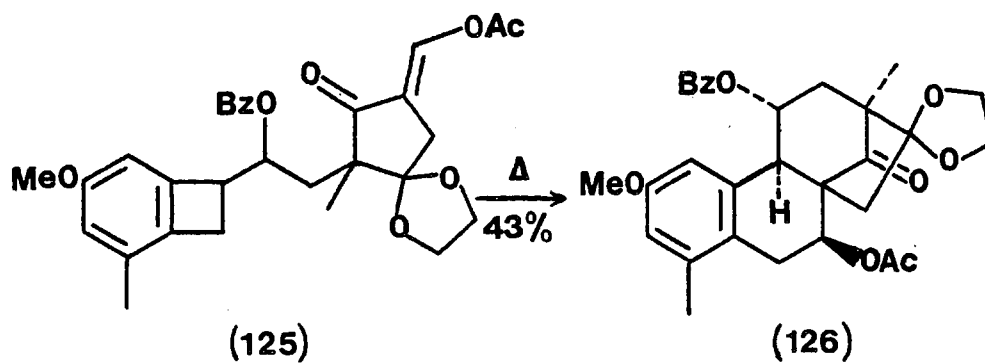


3.3 Quassinoids

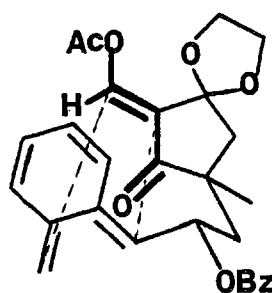


(124)

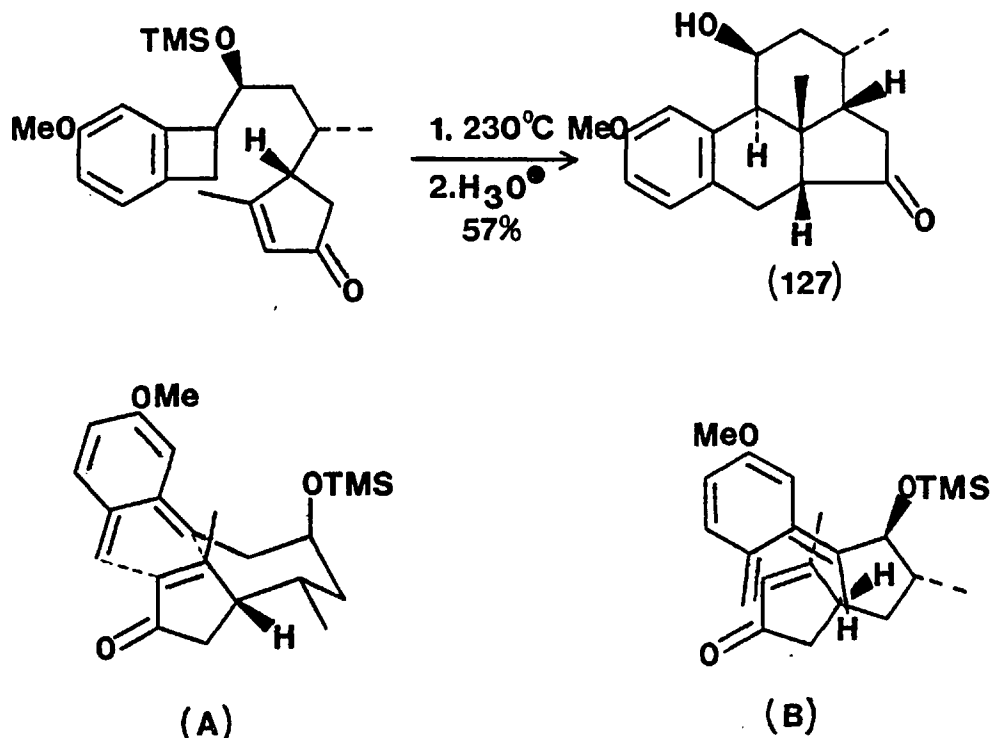
Kametani, in an approach to the highly oxygenated degraded tri-terpene quassinoid klaineane (124), originally reported the stereospecific IMDA of the *o*-quinodimethane derived from the benzocyclobutene (125).⁴⁸



via



A more likely precursor for klaineanone (124) is the IMDA product (127), recently reported by Kametani and co-workers.⁴⁹

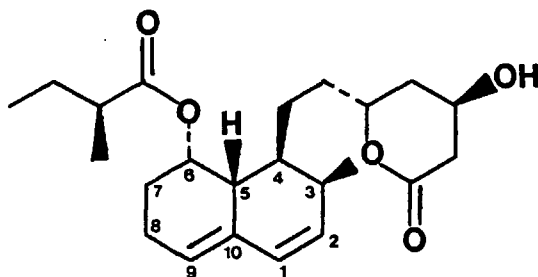


Of the two possible *exo* transition states (B) involves a non-bonding steric interaction between the diene and allylic hydrogens. The diastereomeric *endo* transition states are disfavoured because of serious interactions between the aromatic ring and the methyl group on the bridge.

4. MISCELLANEOUS NATURAL PRODUCTS

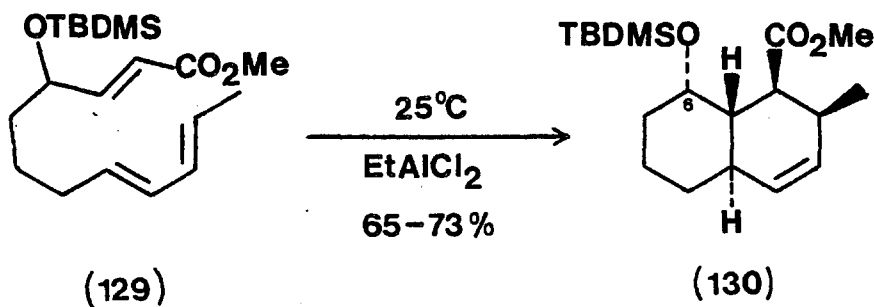
The fungal metabolite compactin (128) has attracted considerable synthetic attention due to its unusual property of being an extremely potent competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme involved in the rate limiting step of cholesterol biosynthesis. The hypocholesterolemic activity of compactin and its 8 α -methyl derivative (mevinolin) and their (9,10 α)-dihydro

analogues has been found to substantially reduce serum cholesterol levels in dogs, monkeys and humans. These drugs have, however, now been withdrawn from clinical trials.



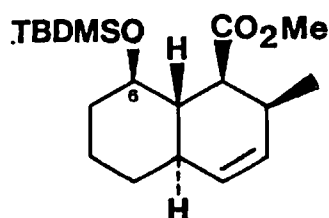
(128)

Three recent quite different IMDA approaches to compactin have recently appeared.⁵⁰⁻⁵² The first reported synthesis of the decalin portion of compactin, by Funk and Zeller, involves the stereospecific *endo* IMDA of the triene (129).⁵⁰ The degree of stereocontrol observed in this reaction was impressive, with formation of five chiral centres in a virtually completely controlled fashion (98:2 with a trace of C-6 epimer).

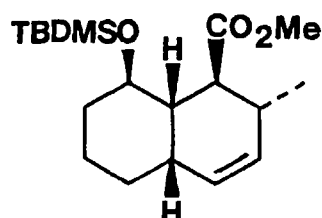


The stereochemical outcome of this cyclization was cleverly biased completely towards the *endo* mode by the use of a Lewis acid catalyst and

low temperatures to enhance secondary orbital interactions. Pioneering work in this area was reported by Roush.³⁵ Thermal cyclization (155°C) of (129) produced considerable amounts of the undesired *cis* (*exo*) isomer of (130) (65% (130) : 13% C-6 epimer (131) : 22% *cis*-fused C-6 epimer (132)).

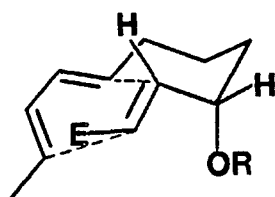


(131)



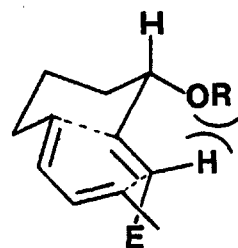
(132)

Of the two possible diastereomeric *endo* modes, (A) was favoured by the use of the bulky alcohol protecting group. The unprotected alcohol corresponding to (129) gave only a 55:45 ratio of C-6 epimers (corresponding to (130) and (131)) even with Lewis acid catalysis. An unfavourable $A^{1,3}$ -type of interaction between the pseudoequatorial protected hydroxyl group in the *endo* transition state (B) combined with better orientation of the pseudoaxial alcohol group in (A) for maximum hyperconjugative overlap ($\sigma_{C-O}^* - \pi^*$), possibly leading to a stabilising effect, were given as reasons for the preference of (A) mode reaction.



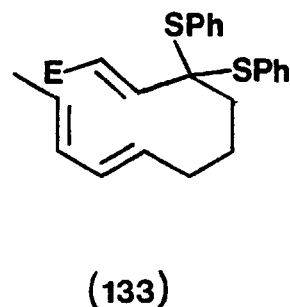
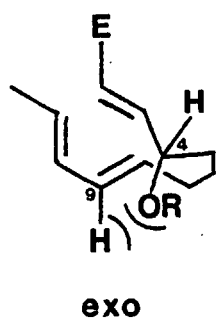
endo (A)

E = CO₂Me



endo (B)

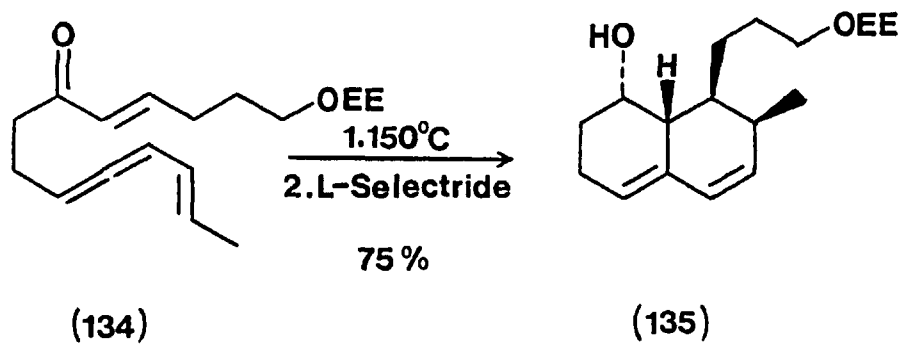
An interesting point is that the protecting group also seemed to favour reaction by the *endo* mode *vs.* the *exo* mode, as the free alcohol corresponding to (129) gave a ratio of 53:47 *trans* to *cis* and the protected (129) a 78:22 ratio, on thermal cyclization. In at least one of the two diastereomeric *exo* modes the unfavourable interaction between substituents at C-4 (decalin numbering) and the diene hydrogen at C-9 would be increased by having a more bulky substituent. Thermal cyclization of the extremely bulky derivative (133) may be expected to be strongly biased in favour of the *trans* product.



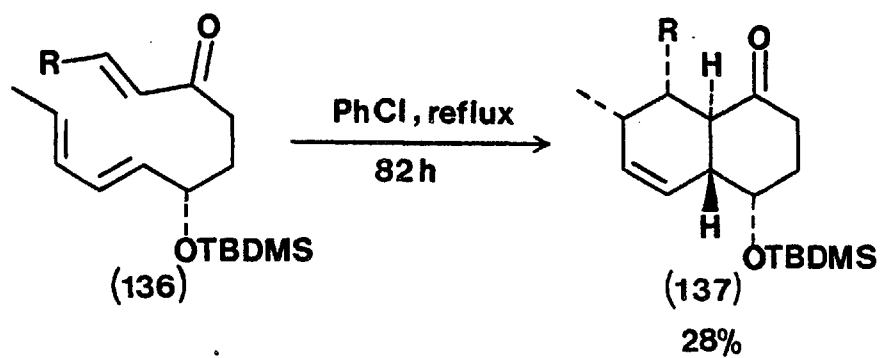
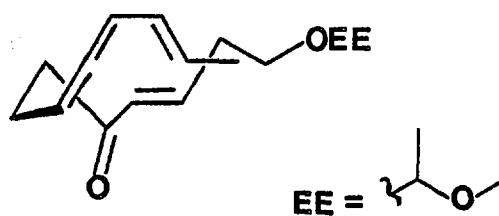
The unusual stereospecific IMDA reaction of the vinylallene (134), reported by Snider, introduces the required C-9 - C-10 unsaturation as well as the three chiral centres at C-3, C-4, and C-5.⁵¹ The *exo* product (135) is necessarily formed *via* the transition state below due to the rigidity of the allene. The fourth chiral centre is introduced stereospecifically by immediate lithium selectride reduction of the crude cyclized ketone.⁵²

The enantioselective total synthesis of (+)-compactin, reported recently by Hirama and Uei, unfortunately suffers from poor IMDA substrate triene design.

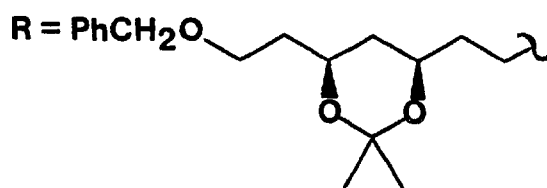
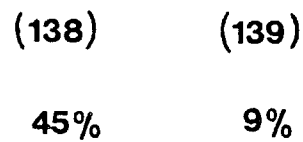
Cyclization of the optically active triene (136) was reported to give the required *trans* isomer, with complete asymmetric induction (none



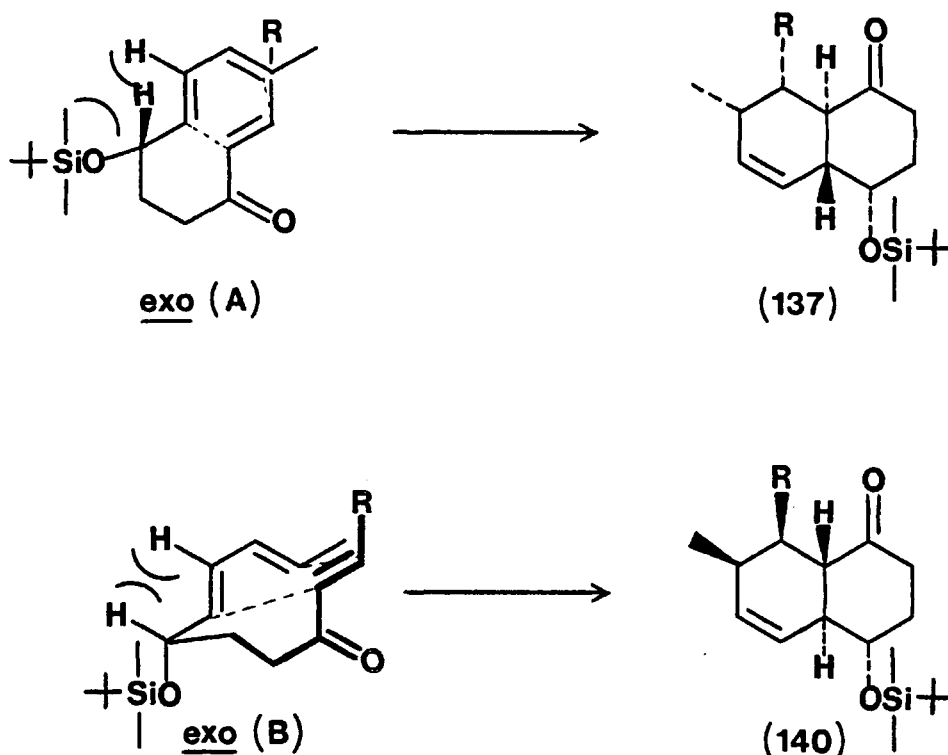
via



+ cis-fused products

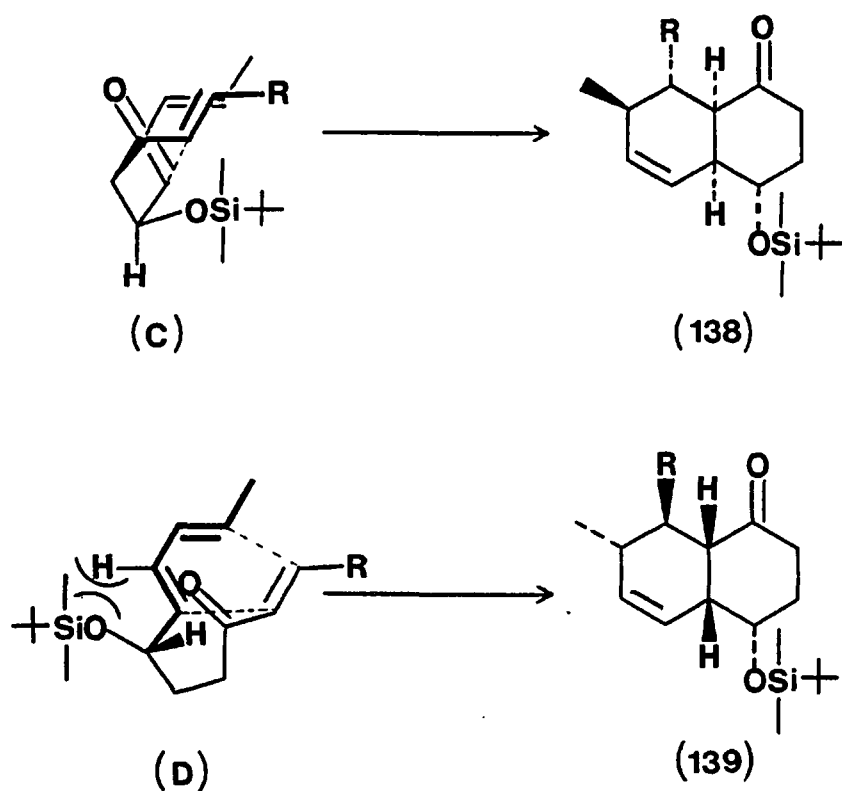


of the diastereomeric *trans* isomer) and two *cis*-fused products, in the unfortunate ratio of 28:45:9. However, of the two diastereomeric *exo* transition states, that giving rise to the isomer (137), by analogue with the previous argument of Funk and Zeller,⁵⁰ appears to be the less favoured of the two.

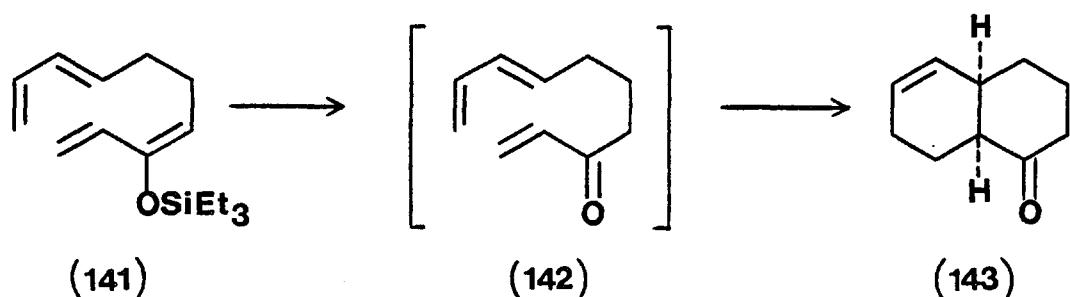


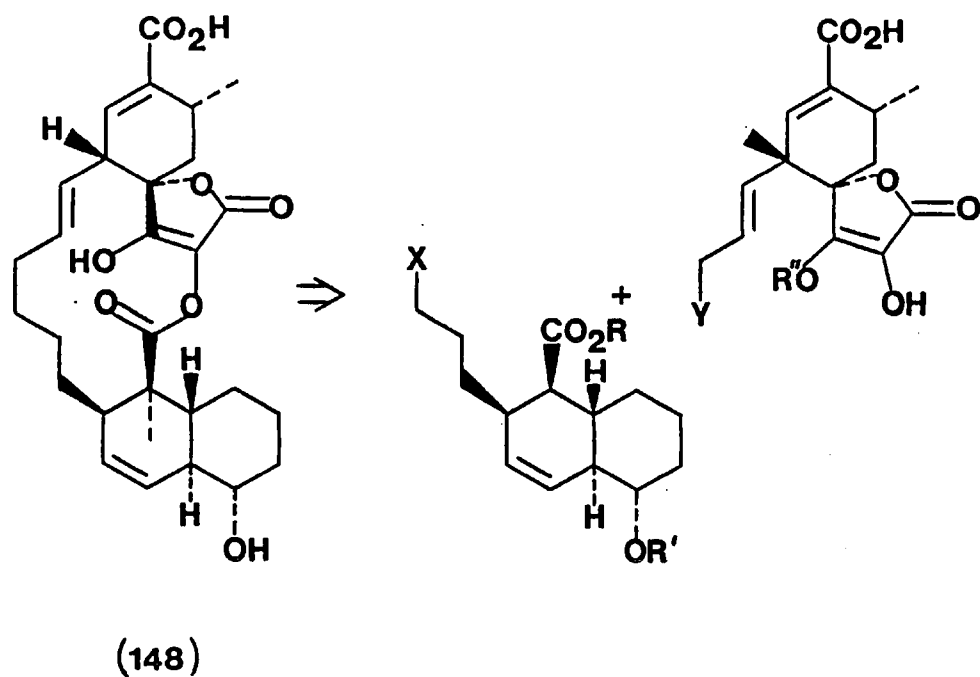
The argument for preference for isomer (137) given by the authors, that an unfavourable $A^{1,3}$ interaction between the two hydrogen atoms occurs in (B), is false. An even more unfavourable interaction between the protected hydroxyl group and the diene hydrogen occurs in (A)! The authors' statement that "the transition states in which the allylic C-OR bond is nearly perpendicular to the diene plane may be greatly stabilised" thus meaning that the two *exo* modes would be favoured over the alternative *endo* modes is erroneous and disproven by their own observation of a 28:54 ratio of *trans* (*exo*) isomers to *cis* (*endo*) isomers on thermolysis of (136).

Examination of the two *endo* transition states (C) and (D) reveals that the major and minor *cis*-fused isomers are probably (138) and (139) respectively.

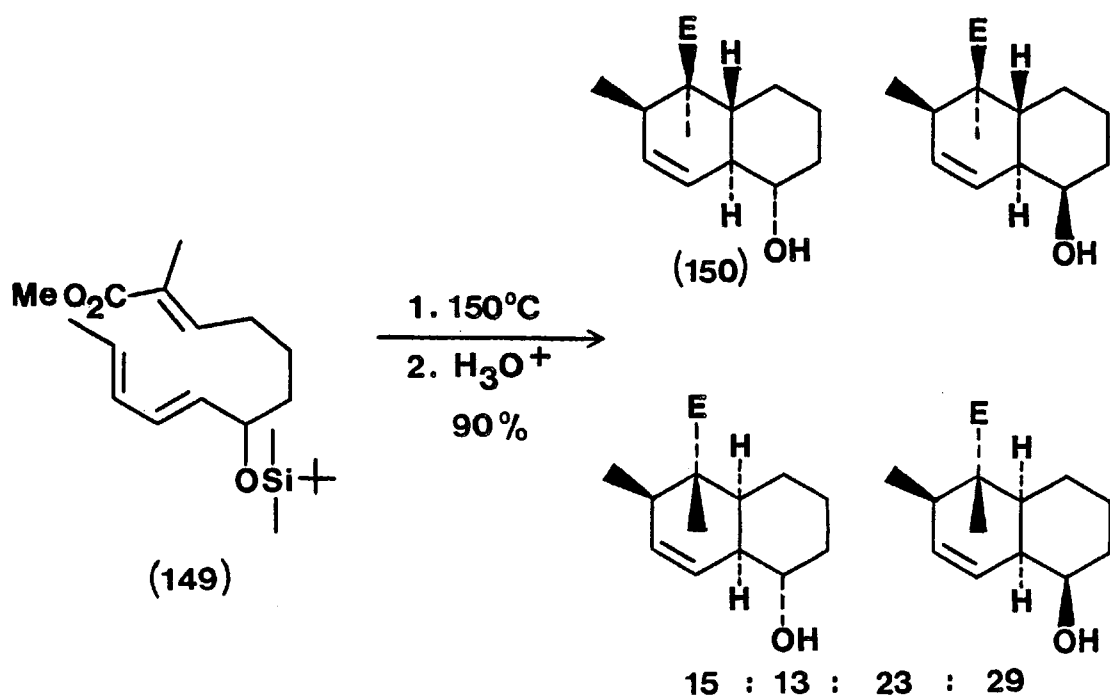


In view of the extremely facile nature of the *endo* cyclization of the closely related enone (142) (generated *in situ* from the enol ether (141) with potassium fluoride in methanol at -10°C) which spontaneously cyclized at -10°C to 0°C in 1h to give the *cis*-fused decalin (143), the unreactive nature of (136) is surprising.⁵³ Presumably the bulky substitution of the terminus of the enone and the methyl group on the diene terminus are sufficient to cause this.





Unfortunately the expected *endo trans*-fused product (150) was only the minor isomer produced along with a majority of the *cis*-fused isomers.

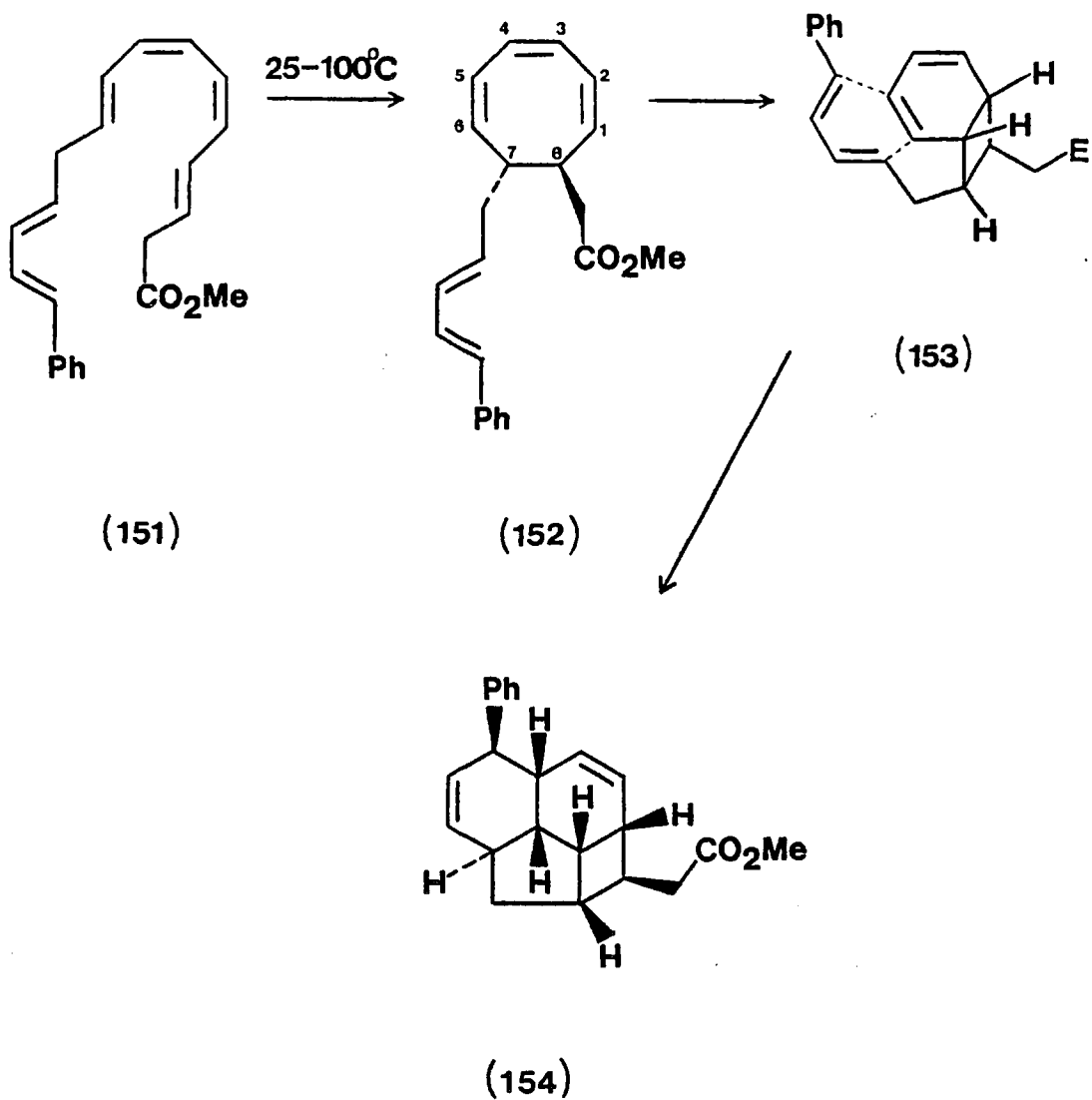


Roush discovered that the propensity to favour formation of *cis*-fused 6,6 products (in contrast to the *trans* preference in 6,5-systems) was general for these systems. Although Funk and Zeller were successful in their attempt to catalyse the IMDA of (129), Roush was unable to effect cyclization with Lewis acids and thus bias reaction towards the *endo* mode in these systems.

As with the 6,5 series Roush also found that product selectivity was independent of dienophile stereochemistry and that, generally, secondary orbital interactions do not control the stereochemical course in these IMDA reactions.

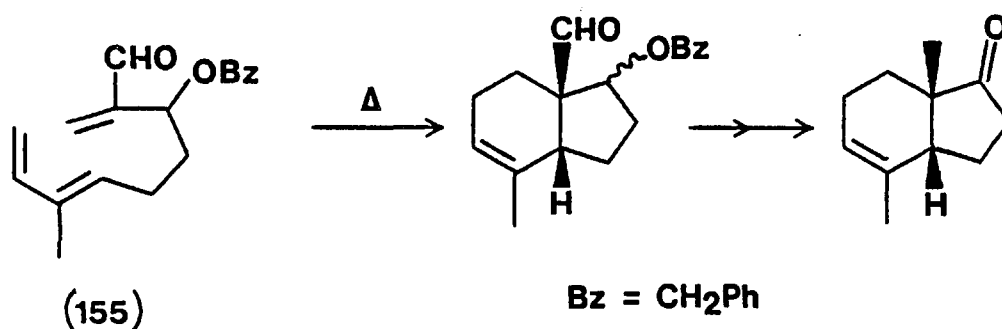
Nicolaou has recently reported a remarkable one-pot synthesis of endiandric acid A (154) from the (*E,Z,Z,E,E,E*)-hexaene (151) *via* a sequence of three stereospecific intramolecular pericyclic reactions, in 30% yield.

The hexaene (151) underwent a thermal conrotatory 8π electrocyclic reaction to form the *trans*-7,8-disubstituted cycloocta-1,3,5-triene (152). A disrotatory 6π electrocyclic process subsequently formed the *cis*-fused 6,4-system of (153) which was perfectly set up for IMDA ($2_{\pi S} + 4_{\pi S}$) reaction to give, *via* the sterically favoured *exo* transition state, the *cis, trans, cis, cis*-fused 6,6,5,4-system of endiandric acid A (154). As the endiandric acids occur in racemic form in nature, it seems likely that the Nicolaou synthesis closely follows a possible biosynthetic pathway.

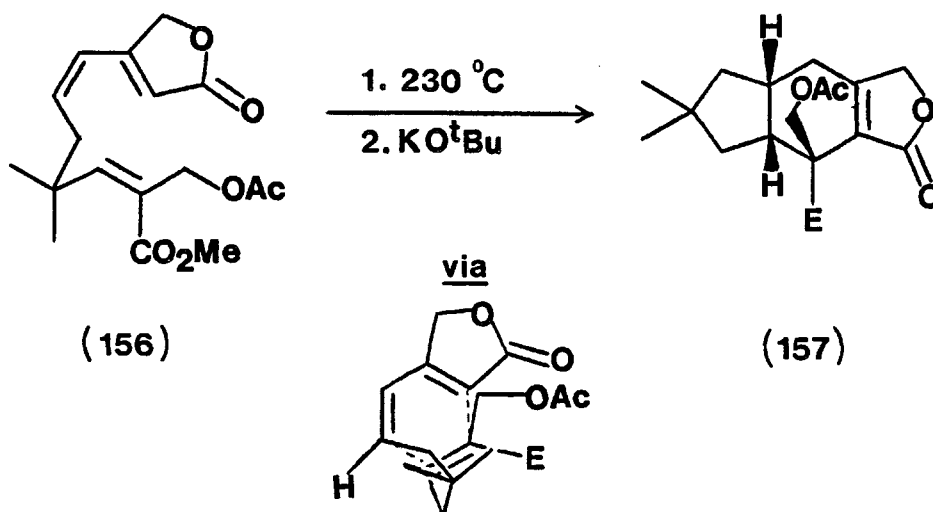


5. STEREOCHEMICAL STUDIES

As previously mentioned, White²⁵ and Boeckman²⁴ have both proposed nonsynchronous but concerted mechanisms for IMDA reactions. Taber and co-workers have also used the nonsynchronous bond formation approach to explain their observation that the acrolein dienophile in (155) leads to formation of largely the *cis*-fused 6,5-system (82:18).⁵⁶

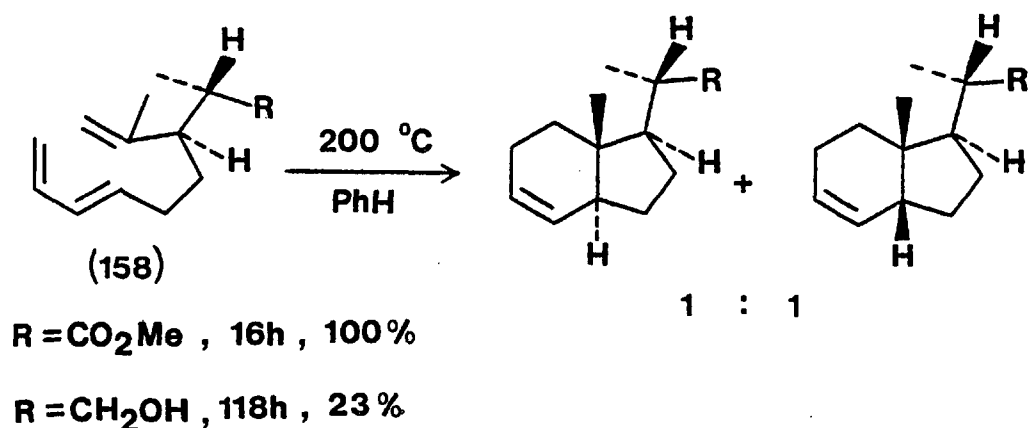


A potentially general route to *cis*-fused 6,5-systems *via* (Z)-diene units such as (156) was recently published by Boeckman.⁵⁷



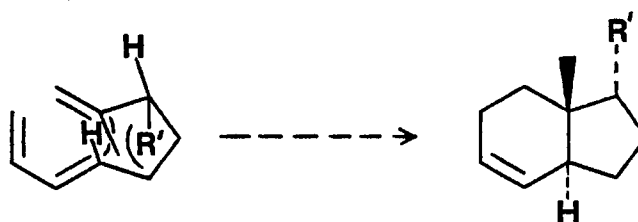
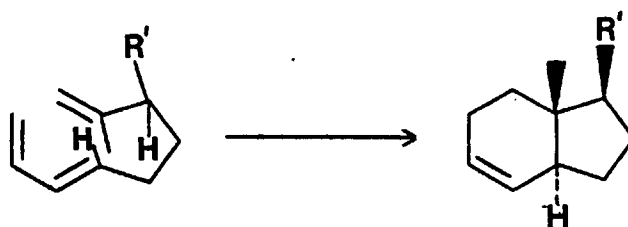
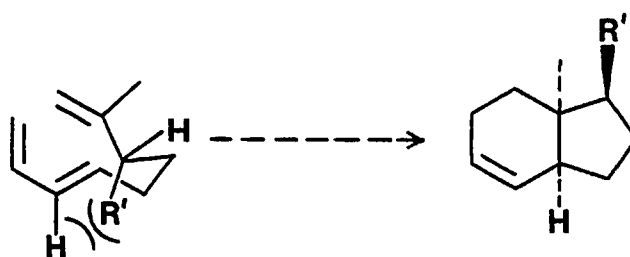
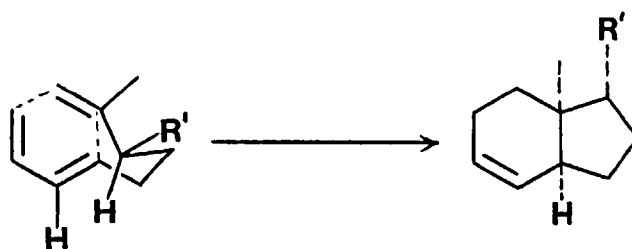
As previously discussed, (157) was converted to (±)-marasmic acid.⁴⁴

In a new approach to vitamin D metabolites, Parker recently found that the trienes (158) were cyclized with complete control of the stereochemistry at C-3 and C-3a but with no *endo-exo* preference. This was contrary to the normal *trans* preference for 6,5-systems but should be compared with the results of Taber on the cyclization of (155).



Examination of the four possible diastereomeric transition states below clearly shows that the two observed products are favoured on steric grounds.

This influence of a substituent adjacent to the dienophile controlling the stereocontrol in an IMDA is, of course, similar to that observed by Funk and Zeller.⁵⁰



REVIEW REFERENCES

1. (a) R.G. Carlson, *Annu. Rep. Med. Chem.*, 1974, 9, 270.
(b) G. Mehta, *J. Chem. Educ.*, 1976, 53, 551.
(c) W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, 1977, 16, 10.
(d) G. Brieger and J.N. Bennett, *Chem. Rev.*, 1980, 80, 63.
2. E. Ciganiek, to be published in *Org. React.*
3. (a) T. Kametani, *Pure Appl. Chem.*, 1979, 51, 747.
(b) T. Kametani and H. Nemoto, *Tetrahedron*, 1981, 37, 3.
(c) W. Oppolzer, *Synthesis*, 1978, 793.
(d) W. Oppolzer, in "New Synthetic Methods", Vol. 6, p.1, Verlag Chemie, Weinheim and New York, 1979.
(e) W. Oppolzer, *Heterocycles*, 1980, 14, 1615.
(f) R.L. Funk and K.P.C. Vollhardt, *Chem. Soc. Rev.*, 1980, 9, 41.
(g) K.P.C. Vollhardt, *Ann. N.Y. Acad. Sci.*, 1980, 333, 241.
4. (a) T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, and K. Fukumoto, *J. Am. Chem. Soc.*, 1976, 98, 3778.
(b) T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, H. Matsumoto, and K. Fukumoto, *J. Am. Chem. Soc.*, 1977, 99, 3461.
5. (a) T. Kametani, H. Nemoto, T. Tsubuki, and M. Nishiuchi, *Tetrahedron Lett.*, 1979, 20, 27.
(b) T. Kametani, H. Nemoto, M. Tsubuki, G.-E. Purvaneckas, M. Aizawa, and M. Nishiuchi, *J. Chem. Soc., Perkin Trans 1*, 1979, 2830.
6. T. Kametani, M. Aizawa, and H. Nemoto, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2793.
7. T. Kametani, H. Matsumoto, H. Nemoto, and K. Fukumoto, *J. Am. Chem. Soc.*, 1978, 100, 6218.

8. W. Oppolzer, K. Bättig, and M. Petrzilka, *Helv. Chim. Acta.*, 1978, 61, 1945.
9. R.L. Funk and K.P.C. Vollhardt, *J. Am. Chem. Soc.*, 1977, 99, 5483.
10. R.L. Funk and K.P.C. Vollhardt, *J. Am. Chem. Soc.*, 1980, 102, 5253.
11. (a) P.A. Grieco, T. Takigawa, and D.R. Moore, *J. Am. Chem. Soc.*, 1979, 101, 4380.
(b) P.A. Grieco, T. Takigawa, and W.J. Schillinger, *J. Org. Chem.*, 1980, 45, 2247.
12. T. Tsuji, H. Okumoto, Y. Kobayashi, and T. Takahashi, *Tetrahedron Lett.*, 1981, 22, 1357.
13. (a) W. Oppolzer, D.A. Roberts, and T.G.C. Bird, *Helv. Chim. Acta.*, 1979, 62, 2017.
(b) W. Oppolzer and D.A. Roberts, *Helv. Chim. Acta.*, 1980, 63, 1703.
14. (a) K.C. Nicolaou and W.E. Barnette, *J. Chem. Soc., Chem. Commun.*, 1979, 1119.
(b) K.C. Nicolaou, W.E. Barnette, and P. Ma, *J. Org. Chem.*, 1980, 45, 1463.
15. S. Djuric, T. Sarkar, and P. Magnus, *J. Am. Chem. Soc.*, 1980, 102, 6885.
16. Y. Ito, M. Nakatsuka, and T. Saegusa, *J. Am. Chem. Soc.*, 1981, 103, 476.
17. T. Kametani, K. Suzuki, and H. Nemoto, *J. Org. Chem.*, 1982, 47, 2331.

18. (a) G. Stork, G. Clark, and C.S. Shiner, *J. Am. Chem. Soc.*, 1981, 103, 4948.
(b) G. Stork and D.H. Sherman, *J. Am. Chem. Soc.*, 1982, 104, 3758.
19. M.E. Jung and K.M. Halweg, *Tetrahedron Lett.*, 1981, 22, 3929.
20. S.A. Bal and P. Helquist, *Tetrahedron Lett.*, 1981, 22, 3933.
21. L.A. Van Royen, R. Mijngheer, and P.J. De Clercq, *Tetrahedron Lett.*, 1982, 23, 3283.
22. N.A. Khatri, H.F. Schmitthenner, J. Shringarpure, and S.M. Weinreb, *J. Am. Chem. Soc.*, 1980, 103, 6387.
23. S.F. Martin, S.R. Desai, G.W. Phillips, and A.C. Miller, *J. Am. Chem. Soc.*, 1980, 102, 3294.
24. R.K. Boeckman, Jr., and S.S. Ko, *J. Am. Chem. Soc.*, 1982, 104, 1035.
25. J.D. White, B.G. Sheldon, B.A. Solheim, and J. Clardy, *J. Org. Chem.*, 1981, 46, 2273.
26. W. Oppolzer and K. Keller, *J. Am. Chem. Soc.*, 1971, 93, 3836.
27. (a) T. Gallagher and P. Magnus, *Tetrahedron*, 1981, 37, 3889.
(b) T. Gallagher, P. Magnus, and J.C. Huffman, *J. Am. Chem. Soc.*, 1982, 104, 1140.
28. D.J. Morgans, Jr. and G. Stork, *Tetrahedron Lett.*, 1979, 20, 1959.
29. G. Stork and D.J. Morgans, Jr., *J. Am. Chem. Soc.*, 1979, 101, 7110.
30. S.F. Martin and C.-Y. Tu, *J. Org. Chem.*, 1981, 46, 3763.
31. S.M. Weinreb, Reported at the 183rd A.C.S. meeting, Las Vegas, March 1982.

32. (a) B. Nader, R.W. Franck, and S.M. Weinreb, *J. Am. Chem. Soc.*, 1980, 102, 1153.
(b) B. Nader, T.R. Bailey, R.W. Franck, and S.M. Weinreb, *J. Am. Chem. Soc.*, 1981, 103, 7573.
33. W.R. Roush, *J. Am. Chem. Soc.*, 1980, 102, 1390.
34. W.R. Roush and H.R. Gillis, *J. Org. Chem.*, 1980, 45, 4283.
35. (a) W.R. Roush, *J. Org. Chem.*, 1979, 44, 4008.
(b) W.R. Roush, A.I. Ko, and H.R. Gillis, *J. Org. Chem. Chem.*, 1980, 45, 4264.
(c) W.R. Roush and H.R. Gillis, *J. Org. Chem.*, 1980, 45, 4267.
(d) W.R. Roush, H.R. Gillis, and A.I. Ko, *J. Am. Chem. Soc.*, 1982, 104, 2269.
36. H. Yamamoto and H.L. Sham, *J. Am. Chem. Soc.*, 1979, 101, 1609.
37. G.A. Schiehser and J.D. White, *J. Org. Chem.*, 1980, 45, 1864.
38. R.L. Snowden, *Tetrahedron Lett.*, 1981, 22, 97.
39. R.L. Snowden, *Tetrahedron Lett.*, 1981, 22, 101.
40. G. Ohloff, *Helv. Chim. Acta.*, 1981, 64, 1387.
41. F. Näf, R. Decorzant, and W. Thommen, *Helv. Chim. Acta.*, 1979, 62, 114.
42. S.R. Wilson and R.N. Misra, *J. Org. Chem.*, 1980, 45, 5079.
43. W. Oppolzer and R.L. Snowden, *Helv. Chim. Acta.*, 1981, 64, 2592.
44. R.K. Boeckman, Jr., and S.S. Ko, *J. Am. Chem. Soc.*, 1980, 102, 7146.
45. S.R. Wilson and D.T. Mao, *J. Org. Chem.*, 1979, 44, 3039.
46. T. Kametani, K. Suzuki, H. Nemoto, and K. Fukumoto, *J. Org. Chem.*, 1979, 44, 1036.

47. (a) T. Kametani, T. Hondo, and Y. Shiratori, *Tetrahedron Lett.*, 1980, 21, 1665.
(b) T. Kametani, T. Honda, Y. Shiratori, H. Matsumoto, and K. Fukumoto, *J. Chem. Soc., Perkin Trans 1.*, 1981, 1386.
48. T. Kametani, M. Chihiro, T. Honda, and K. Fukumoto, *Chem. Pharm. Bull.*, 1980, 28, 2468.
49. K. Fukumoto, M. Chihiro, Y. Shiratori, M. Ihara, T. Kametani, and T. Honda, *Tetrahedron Lett.*, 1982, 23, 2973.
50. R.L. Funk and W.E. Zeller, *J. Org. Chem.*, 1982, 47, 180.
51. E.A. Deutsch and B.B. Snider, *J. Org. Chem.*, 1982, 47, 2682.
52. M. Hirama and M. Uei, *J. Am. Chem. Soc.*, 1982, 104, 4251.
53. W. Oppolzer, R.L. Snowden, and D.P. Simmons, *Helv. Chim. Acta*, 1981, 64, 2002 and 2022.
54. A. Ichihara, R. Kimura, S. Yamada, and S. Sakamura, *J. Am. Chem. Soc.*, 1980, 102, 6353.
55. W.R. Roush and S.E. Hall, *J. Am. Chem. Soc.*, 1981, 103, 5200.
56. D.F. Taber, C. Campbell, B.P. Gunn, and I-C. Chiu, *Tetrahedron Lett.*, 1981, 22, 5141.
57. R.K. Boeckman, Jr. and T.R. Alessi, *J. Am. Chem. Soc.*, 1982, 104, 3216.
58. K.A. Parker and T. Iqbal, *J. Org. Chem.*, 1982, 47, 337.
59. K.C. Nicolaou, Reported at the 183rd A.C.S. meeting, Las Vegas, March 1982.

INTRODUCTION

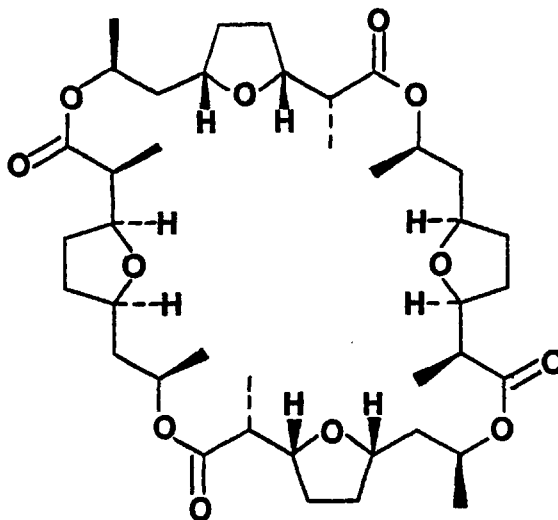
The research described in this thesis was aimed at achieving a total synthesis of the novel ionophore antibiotic X-14547A (1). A highly convergent, short and efficient, enantio- and stereoselective synthesis of X-14547A has been accomplished by a stereospecific coupling of a right hand half (*vide infra*), the synthesis of which forms the main body of this thesis, with a left hand half fragment derived from the natural product. Our total synthesis of X-14547A was recently successfully completed when this left hand half molecule was synthesised by my colleagues in these laboratories. A total synthesis of the same left hand half recently appeared in the literature.¹

Before describing the work presented in this thesis a brief introduction to the ionophore antibiotics, in particular the polyethers, and especially X-14547A itself, will be given. A section on the detailed retrosynthetic analysis of X-14547A and a consideration of the possible problems involved in any projected synthesis of this molecule completes this introductory section.

1. THE IONOPHORE ANTIBIOTICS

The ionophore antibiotics, a group of natural products of increasing biological and commercial importance, belong to the large and growing class of compounds, known as ionophores, that are able to provide a vehicle for the carriage of a variety of cations through lipid barriers by forming lipid soluble complexes.² To date, the ionophore antibiotics are composed of 4 distinct classes: the pharmaceutically important linear peptide ionophores exemplified by the gramicidins, the cyclic depsipeptide ionophores such as valinomycin, the macrotetrolide ionophores typified by nonactin (2), and the

polyether antibiotics or carboxylic acid ionophores, first isolated in 1951,³ exemplified by monensin (3) and lasalocid A (4).



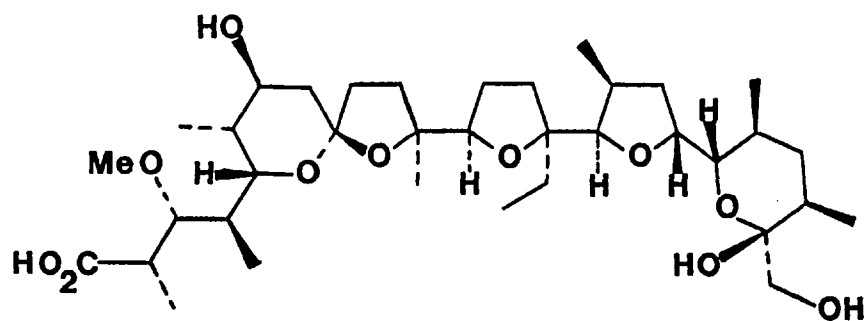
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1.1 The Polyether Antibiotics

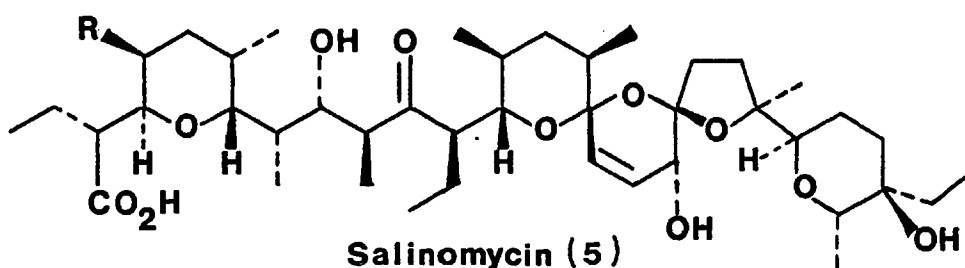
The current high level of interest in the polyether antibiotics, both biological⁴ and synthetic,^{5-10,28} began with the structure determination of monensin in 1967.¹¹

Although originally called carboxylic acid ionophores by Pressman, the preferred name of "polyether" more accurately defines this class of ionophores. The often considerable number of tetrahydropyrans and tetrahydrofurans found in these compounds is the most striking aspect of the structural features which characterise these unique polyether antibiotics.⁴

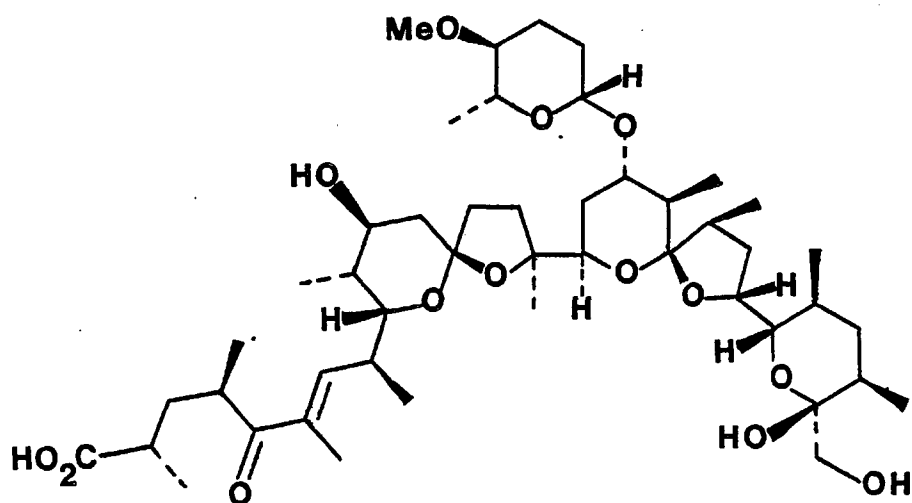
The polyether antibiotics, isolated from various *Streptomyces* species, display a variety of interesting and potentially useful activities. The ability to allow the passive diffusion of excess cations across lipid barriers *in vivo* seems to be one of the most important reasons for the many different biological activities reported.⁴ In particular, the antimicrobial activity is attributed



Monensin (3)



Salinomycin (5)



Dianemycin (6)

Some Monovalent-Cation Polyether Antibiotics

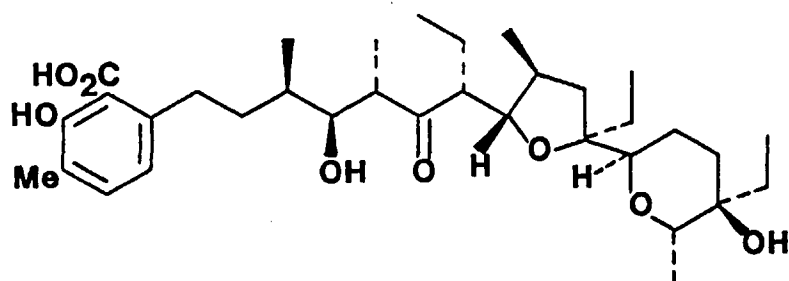
to specific effects that the polyethers have on the permeability of certain cations across cell membranes.¹² This microbial inhibition is most likely due to losses of essential monovalent cations, such as K^+ , from mitochondrial fragments leading to uncoupling of oxidative phosphorylation.⁴

The polyether antibiotics are further classified by whether or not they have the ability to transport divalent cations. By far the larger of these two classes, the polyethers not possessing this ability, is further subdivided into two classes: the monovalent polyethers such as monensin, a most important coccidiostatic agent in the poultry industry, and salinomycin (5), and the monovalent monoglycoside polyethers, typified by dianemycin (6). The distinction arises with the presence of the 2,3,6-trideoxy-4-O-methyl-D-erythrohexapyranose moiety in the antibiotics of the second class.

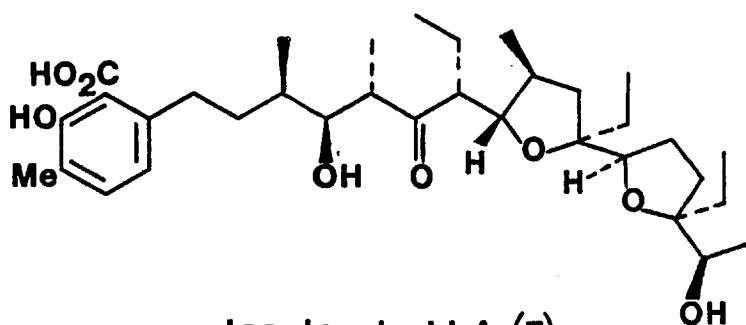
1.1.1 The Divalent-Cation Polyether Antibiotics

The third, smaller, class of polyether antibiotics, those with the ability to transport certain divalent cations, is made up of 5 major members: lasalocid A (4), iso-lasalocid A (7), lysocellin (8), antibiotic A-23187 (9), and antibiotic X-14547A (1).

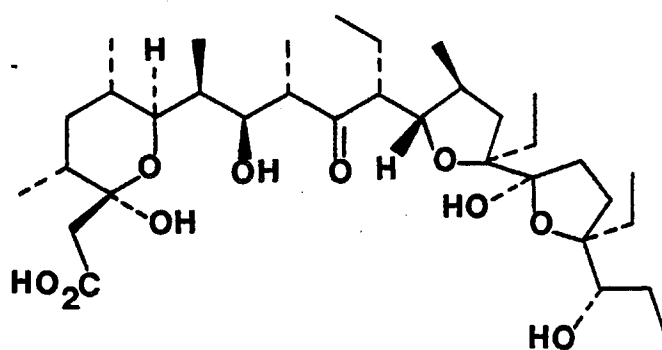
Much attention has been focussed on the biology of both A-23187 and lasalocid A since the discovery of their ability to mobilise Ca^{2+} ions.² Calcium release has been ascribed as the cause of many of the biological effects of the divalent-cation polyether antibiotics.⁴ Amongst the effects with the most potential, perhaps the most important are those associated with the cardiovascular system. In 1972 and 1973 Pressman¹³ and Levy¹⁴ discovered that, in isolated rabbit hearts and perfused working heart rat preparations, the divalent cation polyethers are very potent inotropic agents. This digitalis-like activity was



Lasalocid A (4)



Iso-lasalocid A (7)



Lysocellin (8)

Divalent-Cation Polyether Antibiotics

originally ascribed to the release of Ca^{2+} ions by A-23187 and lasalocid A leading to stimulation of myocardial contractility. However, later results, in particular the fact that monovalent cation polyether antibiotics were also found to be active, even more potent in some cases, seems to indicate a considerably more complex mechanism of action.

In the live dog a single dose of lasalocid A was found to lead to a number of interesting effects on cardiovascular function.¹⁵ However, A-23187 produced abnormal results in the dog with depression of cardiovascular functions in some cases.² It was concluded that this observation, which reinforced doubt about solely Ca^{2+} control, was connected with the greater selectivity for divalent over monovalent cations of A-23187.

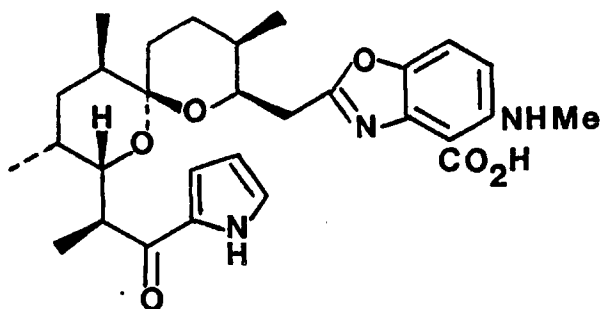
Other physiological effects of lasalocid A, possibly connected with calcium mobilisation, include coagulation of platelets, release of histamine from mast cells and fertilisation of eggs.⁴ The tenuous earlier hypotheses concerning the mode of action of these ionophores should be consolidated or modified by an increasing number of biological studies on the potentially important divalent-cation polyether antibiotics.

2. THE CARBOXYLIC ACID IONOPHORE ANTIBIOTIC X-14547A

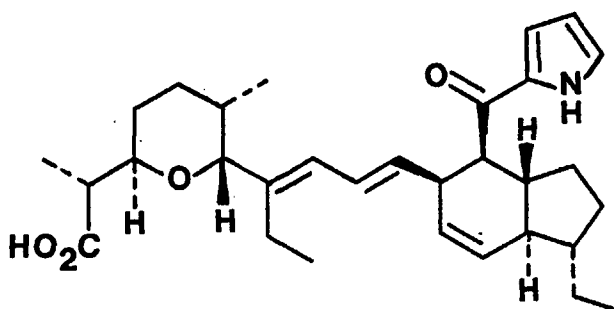
The only previously known nitrogen containing polyether, antibiotic A-23187, was the first example of a new class of divalent-cation polyethers; the divalent pyrrole ether antibiotics.¹⁶

In 1978 the second divalent pyrrole ether, antibiotic X-14547A, was reported by Westley at Hoffman-La Roche.¹⁷ This extremely interesting, novel antibiotic is produced by a new strain of *Streptomyces antibioticus*

(NRRL 8167) which was isolated from a soil sample collected in the USA in 1974.



Antibiotic A-23187 (9)



Antibiotic X-14547A (1)

The Divalent Pyrrole Ether Antibiotics

X-14547A is active *in vitro* primarily against Gram-positive bacteria, possessing a spectrum of activity similar to other polyether antibiotics.¹⁷ Other properties include antitumour and antihypertensive activity.¹⁸ The capability, shared with some other polyether antibiotics,¹⁹ to promote growth in ruminants by increasing feed utilisation in the rumen could be of commercial interest. The acute toxicity in the mouse (LD₅₀ 129 mg/kg p.o.) is in the middle of the range of polyether toxicities.⁴ X-14547A is three times less toxic than monensin (LD₅₀ 43.8 mg/kg p.o.) but slightly more toxic than the

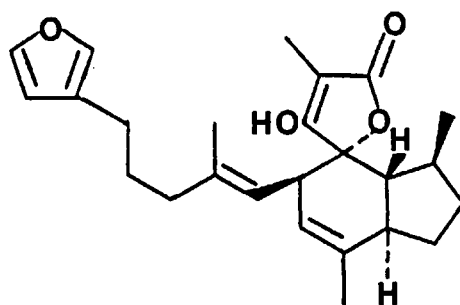
divalent-cation polyethers lasalocid A (LD₅₀ 146 mg/kg p.o.), lysocellin (LD₅₀ 350 mg/kg p.o.), and isolasalocid A (LD₅₀ 1000 mg/kg p.o.).

As befits its place in the ionophore class, X-14547A facilitates the extraction of mono- and divalent cations from an aqueous solution into a non-miscible organic solvent and transports Rb⁺ and Ca²⁺ across a solvent barrier (CHCl₃) from one aqueous phase to another.¹⁷

The ability of some polyether antibiotics to transport biogenic amines (serotonin, dopamine, norepinephrine, and epinephrine) across artificial lipid bilayers, possibly closely linked to a number of biological activities, has been demonstrated.²⁰ X-14547A forms an unusual crystalline salt complex consisting of two antibiotic molecules (one ionised) and one molecule of R(+)-1-amino-1-(4-bromophenyl)ethane where the ammonium salt is bound within a jaw-like dimer. A crystal of this complex was used in the structure and absolute configuration determination of antibiotic X-14547A.¹⁷

The novel structure of X-14547A possesses several interesting and unusual features. The (*E,E*)-1,3-butadiene system is the first example of a diene in the polyethers. The only other reported naturally occurring *trans*-fused tetrahydroindan, another feature unique in the polyether class, is ircinianin (10).²¹ The tetrahydropyran ring, more characteristic of the polyether class, differs from the analogous ring in salinomycin (5), R = H, only in possessing a methyl group, rather than an ethyl group, α - to the carboxylic acid.

In common with the other polyether antibiotics, molecular model and X-ray crystallographic studies indicate that X-14547A can adopt a cyclic conformation with, in this case, three proximal oxygens available for cation binding at the centre of the molecule (see diag. 1). The hydrophobic hydrocarbon portions of X-14547A would lie on a roughly cone shaped "outer surface" in this conformation. In direct analogy



Ircinianin (10)

to lasalocid A, whose barium and sodium salts have been shown to form dimeric complexes in solution,²² two molecules of X-14547A could be envisaged to wrap around a cation to give a hydrophobic lipid-soluble outer sphere. This sandwich structure around the mono- or divalent cation and possibly a solvating water molecule would presumably enable transport through lipid barriers.

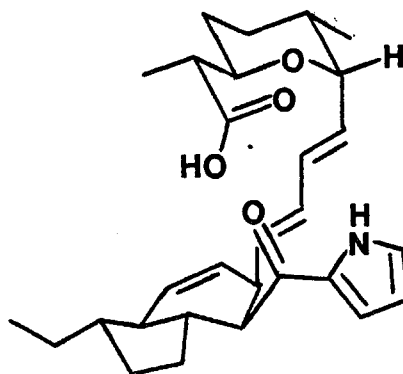


Diagram 1

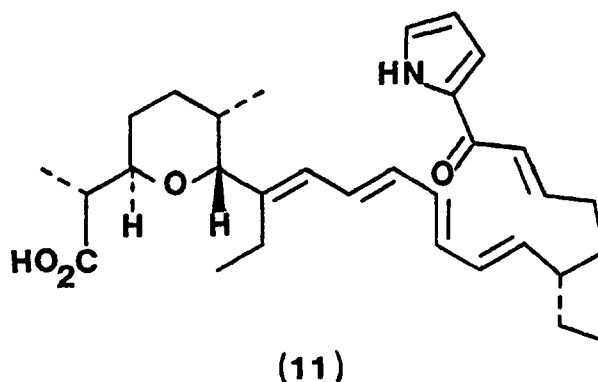
Apart from the obvious structural differences between X-14547A and the only other member of the divalent pyrrole ether antibiotics A-23187, several differences in the ability to adopt a "complexing conformation" arise on the study of molecular models. Perhaps the most obvious of these is that the structure of X-14547A incorporates only 12 atoms between the pyrrolylcarbonyl oxygen atom and either of the carboxylic acid oxygen atoms whereas the corresponding oxygen atoms in A-23187 are separated by 13 atoms. Combined with this and the presence of only 5 hetero atoms (compared with 9 in A-23187), the rigid diene backbone of X-14547A causes this ionophore to be considerably less flexible in adopting conformations for complexation. This could be expected to give rise to profound differences in the cation selectivity, entropy considerations, and binding constants of X-14547A compared with A-23187. It is thus possibly to be expected that further detailed biological studies on X-14547A may bring to light important and perhaps useful differences in biological activities for this divalent pyrrole ether.

With a view to probing structure activity relationships, possible enhancement of existing biological properties, or even development of completely new activity, a programme of X-14547A analogue study has been initiated in this laboratory by Dr. Ley.

No biosynthetic studies for X-14547A have appeared to date. However, as has been found for lasalocid A⁴ and monensin,²³ it seems likely that the biosynthesis of the tetrahydropyran moiety, at least, involves the initial formation of a polyketide chain built up from acetate, propionate, and butyrate units on a multienzyme complex.

The biosynthetic origin of the rare *trans*-fused tetrahydroindan is of considerable interest.^{17a} It seems likely, as has been speculated by Roush,²⁴ that this bicyclic system may be derived from an *in vivo*

intramolecular Diels-Alder reaction of a triene such as in (11). The biosynthesis of a number of natural products; ircinianin,²¹ the cyclopiperaceae alkaloids,²⁵ ikarugamycin,²⁶ some indole alkaloids, and others²⁷ are proposed to involve intramolecular Diels-Alder reactions.



2.1 Retrosynthetic Analysis of Antibiotic X-14547A

In recent years considerable effort has been expended in the challenging field of polyether antibiotic synthesis.^{5-10,28,29}

Although the first total synthesis of a member of these monocarboxylic acid ionophores (Kishi's lasalocid A synthesis⁵) was reported as recently as 1978, this was rapidly followed by syntheses of monensin, by Kishi,⁶ and antibiotic A-23187, by Evans, in 1979.⁷ An increasing amount of synthetic activity in the field of both the polyethers and the related polyketide macrolide and ansamycin antibiotics, particularly in the rapidly expanding area of acyclic stereocontrol,²⁹ has resulted in a large number of publications in the last 3 or 4 years. Quite a few of these have been major contributions to the field of stereocontrolled synthesis of natural products *via* stereoselective reactions.

Apart from the total syntheses of lasalocid A, monensin, and A-23187 mentioned above, a superb second synthesis of monensin by Still in 1980,⁹ second syntheses of lasalocid A and A-23187 by Ireland¹⁰ and Grieco⁸ respectively, and a non-optimised synthesis of narasin (5), R = Me, by Kishi,³⁰ no further monocarboxylic acid ionophore antibiotics had succumbed to total synthesis until the very recent syntheses of X-14547A by ourselves and Nicolaou.¹

At the outset of this project no synthetic studies on X-14547A had been reported. Only recently have the efforts of ourselves,³¹ Nicolaou,^{1,32} Roush²⁴ and Ho⁵⁵ appeared in the literature. Boeckman's group are also working on a synthesis of X-14547A.³³ These published synthetic studies will be discussed and compared with ours later in the thesis, at the end of the Results and Discussion section.

The novel antibiotic X-14547A, with its 9 chiral centres, unusual 2-pyrrolylcarbonyl group, rare *trans*-fused tetrahydroindanyl moiety, and (*E,E*)-1,3-butadienyl system, offers a stimulating challenge to the synthetic chemist.

In a retrosynthetic analysis of a complex molecule such as X-14547A the most logical strategy is one involving splitting the molecule, in an antithetical reaction,³⁴ into two or three simpler fragments or sub-targets. The most efficient convergent synthesis of such a molecule would then be a coupling of these 2 or 3 fragments in the final step. However, with such complex molecules, at the very least, sensitive functionality may need to be protected during coupling. In practice the need for maximum efficiency *via* convergence may have to be offset against the possible need to introduce sensitive functionality at as late a stage as possible after the coupling reaction.

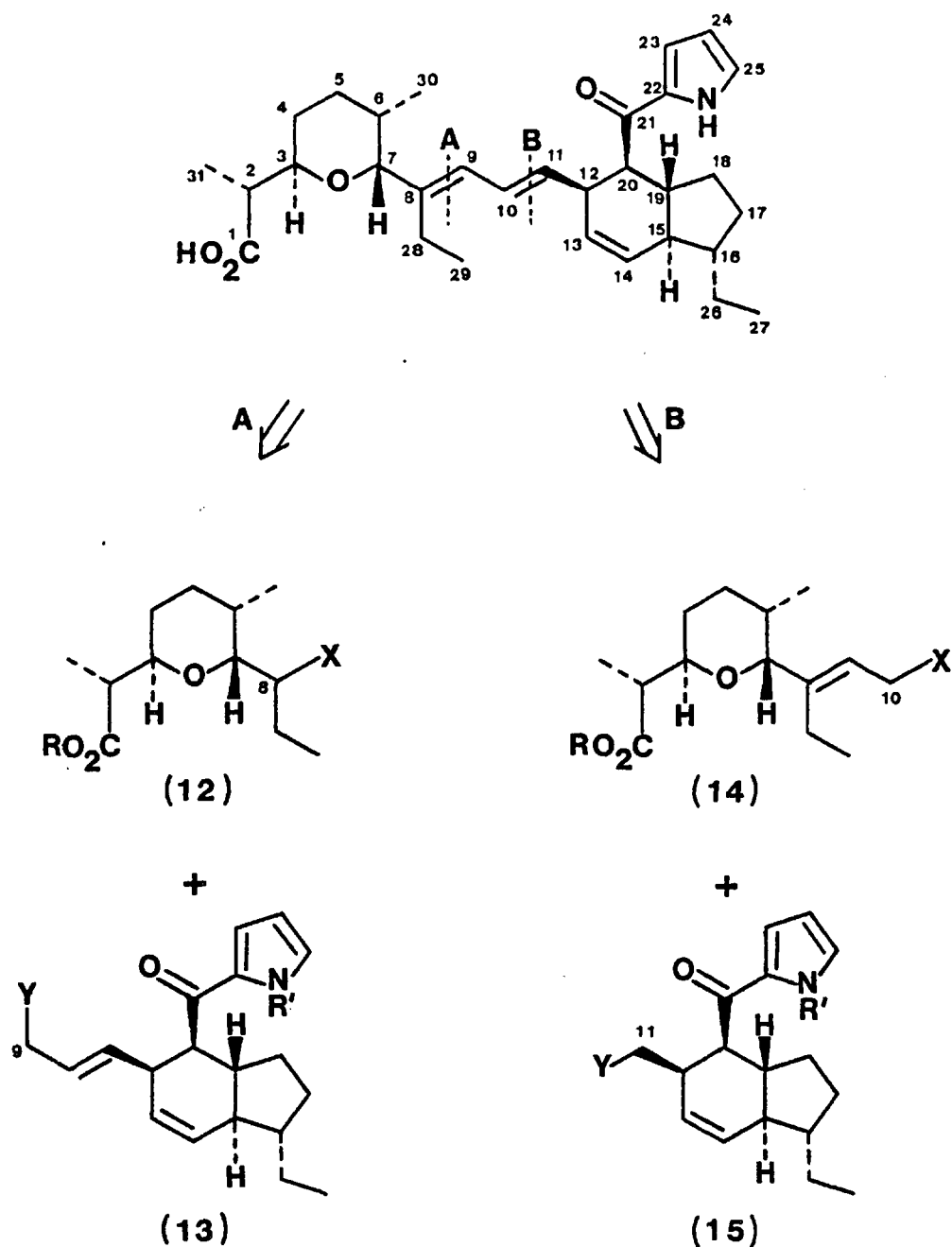
This approach to the synthesis of complex natural products is becoming increasingly prevalent and is typified by the monensin syntheses of Still⁹ and Kishi,⁶ the lasalocid A syntheses of Kishi⁵ and Ireland,¹⁰ the approach to erythronolide of Stork,³⁵ the milbemycin β_3 synthesis and approach of Smith³⁶ and Williams³⁶ respectively, and recent macrolide antibiotic syntheses of Masamune.³⁷

Two simple, potentially useful, disconnections, obvious from even only a cursory glance at the structure of X-14547A, are shown in Scheme 1. We hoped that a synthesis of X-14547A, involving the fewest possible steps subsequent to coupling, could be realised with the correct choice of a mild, selective coupling reaction and protecting groups.

Either of these two disconnections leads to a suitably protected left hand side tetrahydropyran fragment, bearing 4 of the chiral centres present in X-14547A, and a right hand side tetrahydroindan fragment containing the remaining 5 chiral centres and including a possibly protected 2-pyrrolylcarbonyl moiety.

Both of these disconnections require a regio- and stereospecific high yielding *trans* olefination reaction, with retention of *trans* olefin configuration in (13) or (14), in order to couple the two fragments and form the desired (*E,E*)-1,3-butadiene system. A mild and selective coupling reaction and subsequent deprotections would be crucial to this approach due to the problems of possible epimerisation at C-2 and C-20 (X-14547A numbering) and expected sensitivity of both the 2-pyrrolylcarbonyl moiety and the β -tetrahydropyranylacetic acid system.

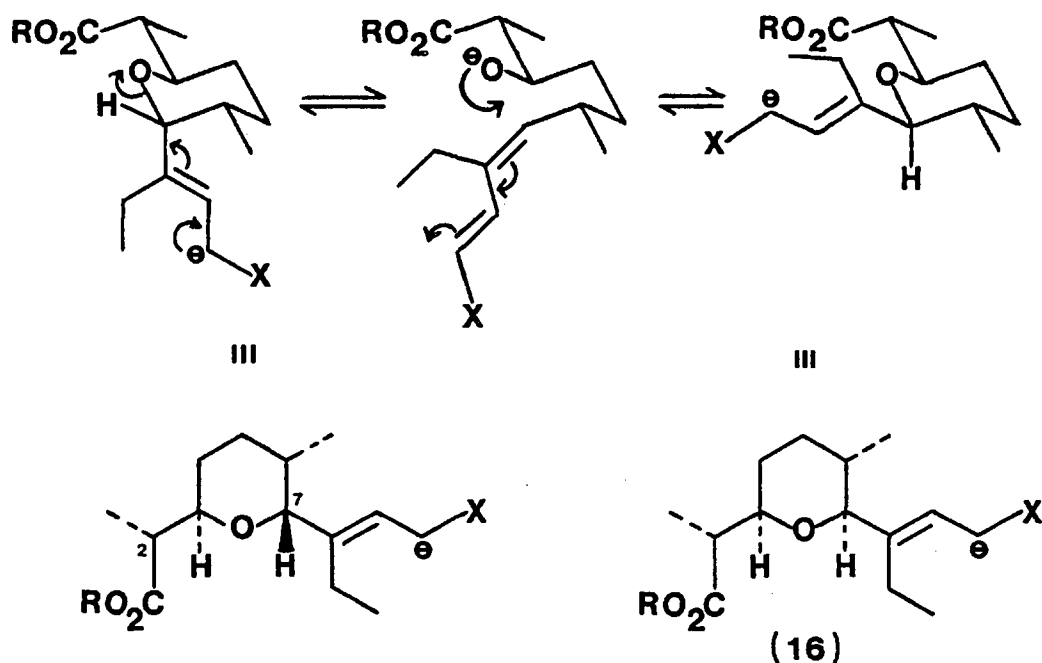
The donor and acceptor capability of the two fragments, that is whether X and Y bestow electrophilic and nucleophilic character or *vice versa*, was obviously an important initial consideration. We



Scheme 1

were extremely worried that formation of any increased electron density, in possible left hand side fragments, at C-8 in (12) or C-10 in (14) (whether in discrete anion (*eg.* X = SO₂Ph, EtO₂PO, Ph₂PO) or ylid (*eg.* X = Ph₃P[⊕]Br[⊖]) formation) might lead to ring opening *via* β-oxyelimination. Even if this were a reversible process it was

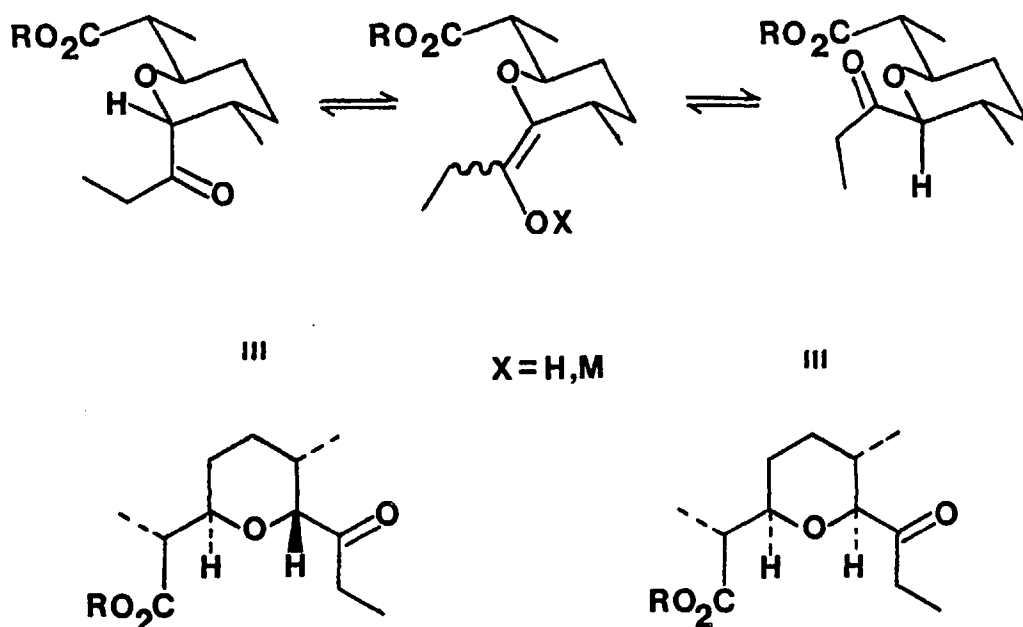
feared that epimerisation to the thermodynamically more stable all-equatorial (16) might occur as in Scheme 2.



Scheme 2

Because of these and other considerations covered below we discounted a synthetic plan involving coupling using a nucleophilic left hand fragment. In fact, although the possibility for base or acid epimerisation at C-7, as shown in Scheme 3, existed for such compounds, we decided that ketone (12), $X = =O$, or aldehyde (14), $X = -CHO$, functionality would most fit our desired criteria. We felt that by correct choice of functionality (Y) in the right hand side fragment, the desired stereospecific olefination reaction could be achieved without any accompanying epimerisation at C-2 or C-7 of the tetrahydropyranylacetic acid system.

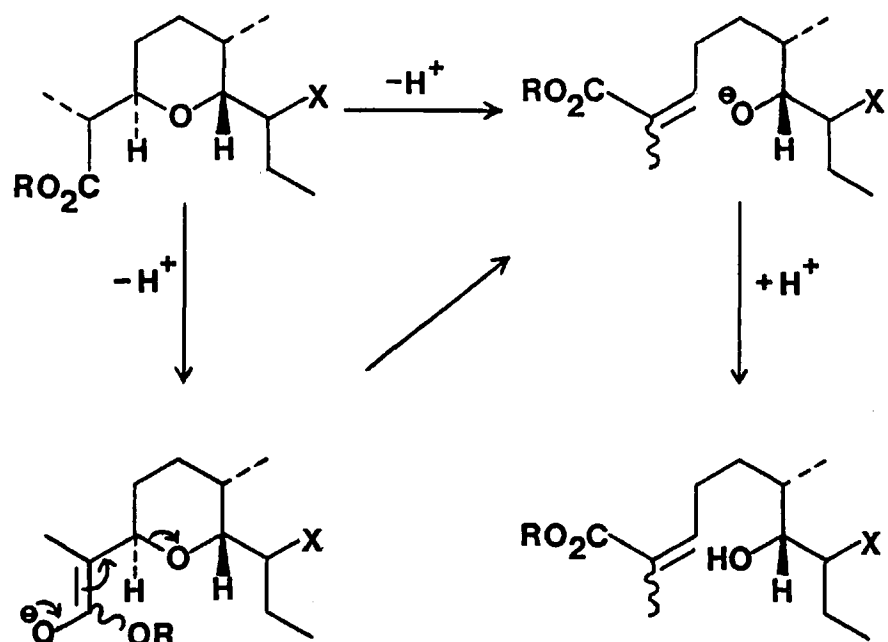
Apart from the possible epimerisation at C-2 and C-7 already mentioned, the left hand side tetrahydropyranylacetic acid system may



Scheme 3

also be expected to be susceptible to base catalysed ring opening as shown in Scheme 4. In fact, under certain strong base conditions the methyl ester, ketone (12), $X = =O$, $R = Me$, and similar compounds have been shown to undergo such a reaction in this laboratory³⁸ and the literature.⁸⁰

Epimerisation at C-12 or C-20 in right hand side tetrahydroindan fragments was not anticipated to be a problem as, in the natural configuration, the conformation (see Figure 2) is such that the pyrrolyl-carbonyl residue at C-20 is in the preferred equatorial position. Due to the unsaturation in the cyclohexene ring a pseudoaxial environment is occupied by the substituent at C-12.



Scheme 4

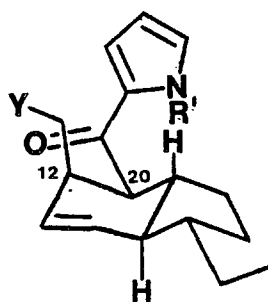


Diagram 2

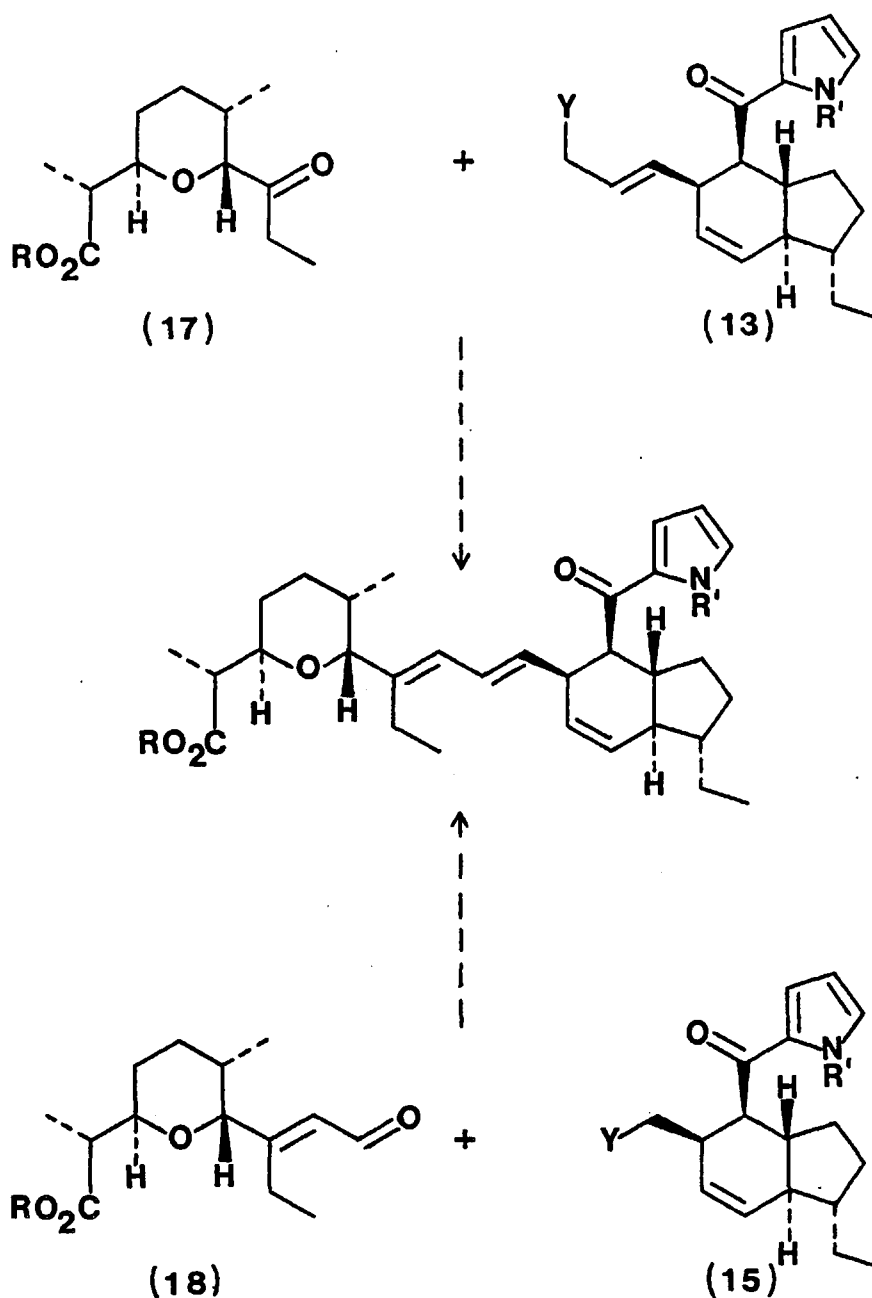
2.1.1 The Coupling Reaction

The stereospecific formation of olefins, particularly in carbon-carbon bond forming reactions, plays an extremely important role in natural products synthesis. Apart from their presence in many natural product structures, as for example in X-14547A, prostaglandins, leukotrienes, and carotenoids, geometrically defined carbon-carbon double bonds play a crucial role in most stereoselective chiral Sp^3 centre forming reactions.²⁹

In view of the large number of methods available^{39,40} we were surprised to find that really only two alternative types of olefination, the Julia sulphone-aldehyde olefination⁴¹ and the allylic phosphine oxide-ketone olefination⁴²⁻⁴³ appeared to be suitable for our desired coupling. For the reasons discussed above the required reaction was between either the left hand side ketone (17) and the suitably functionalised right hand side α,β -unsaturated anion (or ylid) from (13) or the α,β -unsaturated aldehyde (18) and the anion (or ylid) from (15), as shown in Scheme 5.

Silicon-based Peterson methodology ((13) or (15), $Y = Me_3Si$) was discounted due to probable problems in (a) regiospecific preparation of the requisite silanes, (b) stereoselectivity, and (c) the relative harshness of conditions (KH or $BF_3 \cdot Et_2O$) required for elimination of the intermediate β -hydroxysilanes.⁴⁴

Wittig olefination, between either unstabilised phosphoranylids (*eg.* (15), $Y = Ph_3P^{\oplus}$) and α,β -unsaturated aldehydes or α,β -unsaturated phosphoranylids (*eg.* (13), $Y = Ph_3P^{\oplus}$) and ketones, invariably produces mixtures of (*Z,E*) and (*E,E*)-1,3-dienes.^{39a,45} Similarly, the Horner-Emmons-Wadsworth modification of the Wittig reaction is not applicable to the preparation of the desired diene. Anions of unstabilised



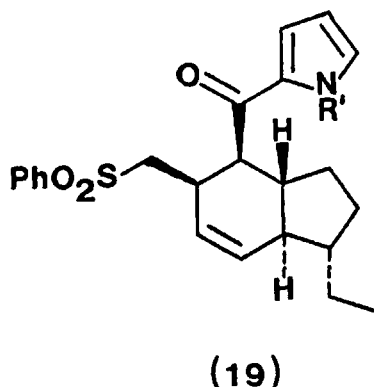
Scheme 5

phosphonates (*eg.* (15), $Y = (RO)_2PO$) do not give useful olefination reactions with ketones or aldehydes. Reactions of α,β -unsaturated phosphonate anions (*eg.* (13), $Y = RO_2PO$) with carbonyl compounds have been shown to involve problems of regioselectivity and yield and to exhibit poor stereoselection.^{35b}

However, anions derived from α,β -unsaturated diphenylphosphine oxides have been shown by Lythgoe to be effective in the preparation of (*E,E*)-1,3-dienes in reactions with ketones.⁴² Results, in a recent publication by Pattenden, seem to agree with Lythgoe's claims for high *trans*-stereoselectivity in reactions of allylic diphenylphosphine oxide anions. Yields of conjugated polyenes in reactions with α,β -unsaturated aldehydes were found to be poor though.⁴³

The most promising reaction found in the literature was the Lythgoe-Kocienski modification of the Julia olefin synthesis.⁴¹ Although the reaction had only been applied to the synthesis of non-functionalised hydrocarbons we felt that the mild conditions involved would be compatible with our planned functionality.

It was anticipated that the possibly hindered ketone (17) might be sluggish in reactions with the allylic diphenylphosphine oxide or sulphone ((13), $Y = Ph_2PO$ or SO_2Ph) anions whereas there was good precedent in the Lythgoe-Kocienski work that the anion derived from the right hand side sulphone (15), $Y = SO_2Ph$, would undergo smooth (*E,E*)-1,3-diene formation, with high stereoselectivity, with the α,β -unsaturated aldehyde (18). Combined with this, the fact that the α,β -unsaturated diphenylphosphine oxide (18), $Y = Ph_2PO$, offers a more complex synthetic problem than the sulphone (19) decided that our synthetic approach to X-14547A would be based on Julia coupling of the sulphone (19) with the α,β -unsaturated aldehyde (18).

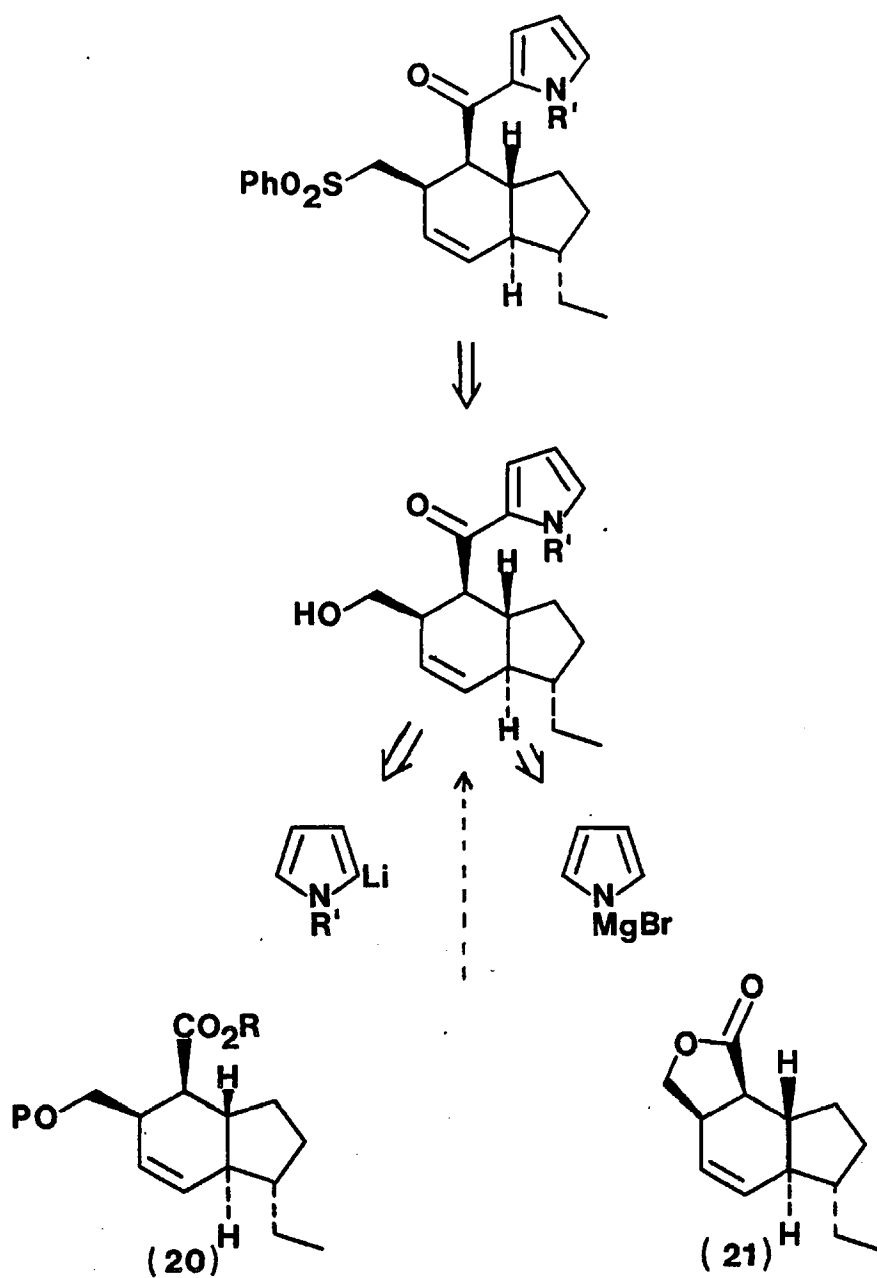


2.1.2 Synthesis of the Right Hand Side Sulphone

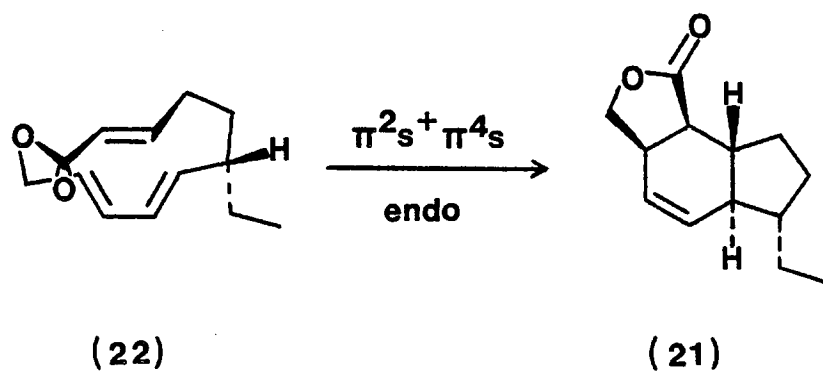
The initial strategic disconnections in our retrosynthetic analysis of the required sulphone (19), summarised in Scheme 6, were based on a report by Bean that pyrrolylmagnesium bromide reacts smoothly with esters to give, regiospecifically, the 2-acyl pyrroles.⁹⁹ As we anticipated that a free pyrrole N-H might be problematical in the later steps of our synthesis, we also considered that a protected pyrrolylcarbonyl might be formed by reaction of a 2-lithio-N-protected pyrrole with an ester or lactone.

Our original proposal for the synthesis of the lactone (21) involved the intramolecular Diels-Alder reaction of the (*E,E,E*)-macro-trienolide (22). We hoped that the required 5 relative chiral centres would be created, in one step, with correct relative stereochemistry, in an *endo* cycloaddition.

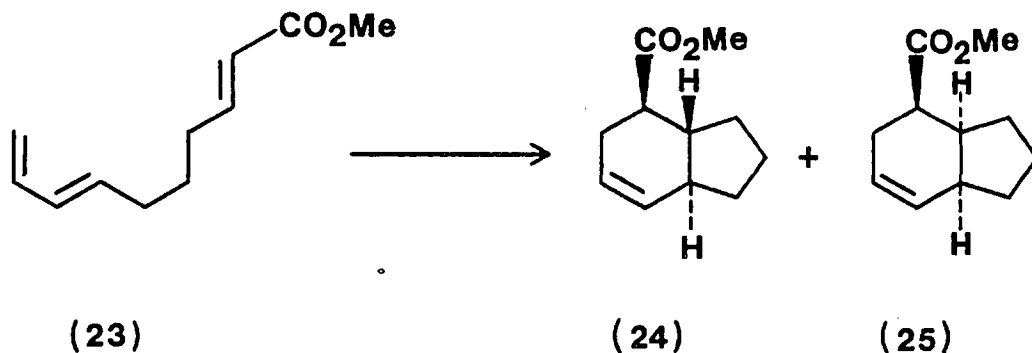
A strong precedent present in the literature was the report by House and Cronin that triene (23) cyclized exclusively to *trans*-fused (24) *via* an *endo* cycloaddition.⁴⁷ A recent reinvestigation of this



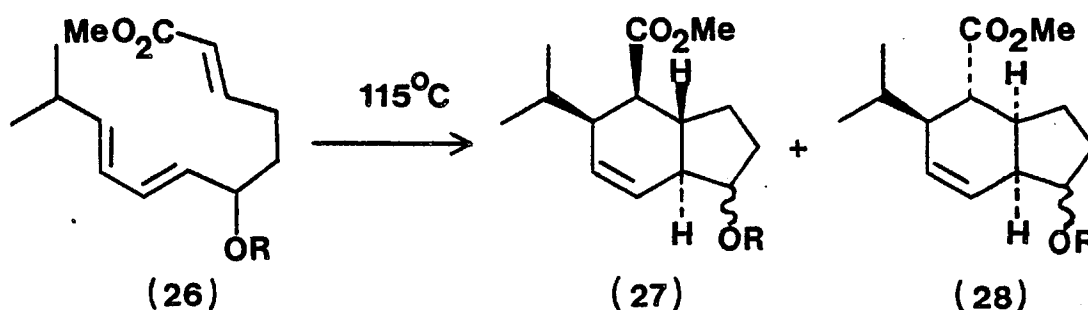
Scheme 6



reaction by Roush, however, showed that (23) cyclizes to give a 65% yield of a 60:40 mixture of (24) and *exo* product (25).^{49b}

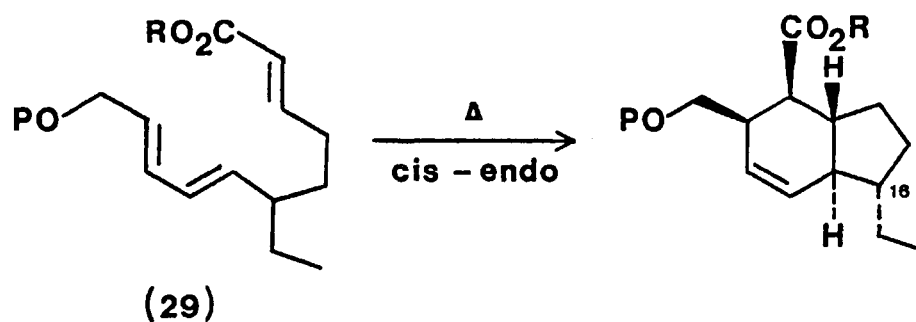


A short time after our proposal a communication on the stereochemical aspects of the intramolecular Diels-Alder reactions of a number of trienoates, for example (26), by Roush, confirmed the feasibility of our approach, if detracting slightly from its novelty.⁴⁸ Subsequently Roush has published a number of detailed studies on these and related Diels-Alder cyclizations.⁴⁹



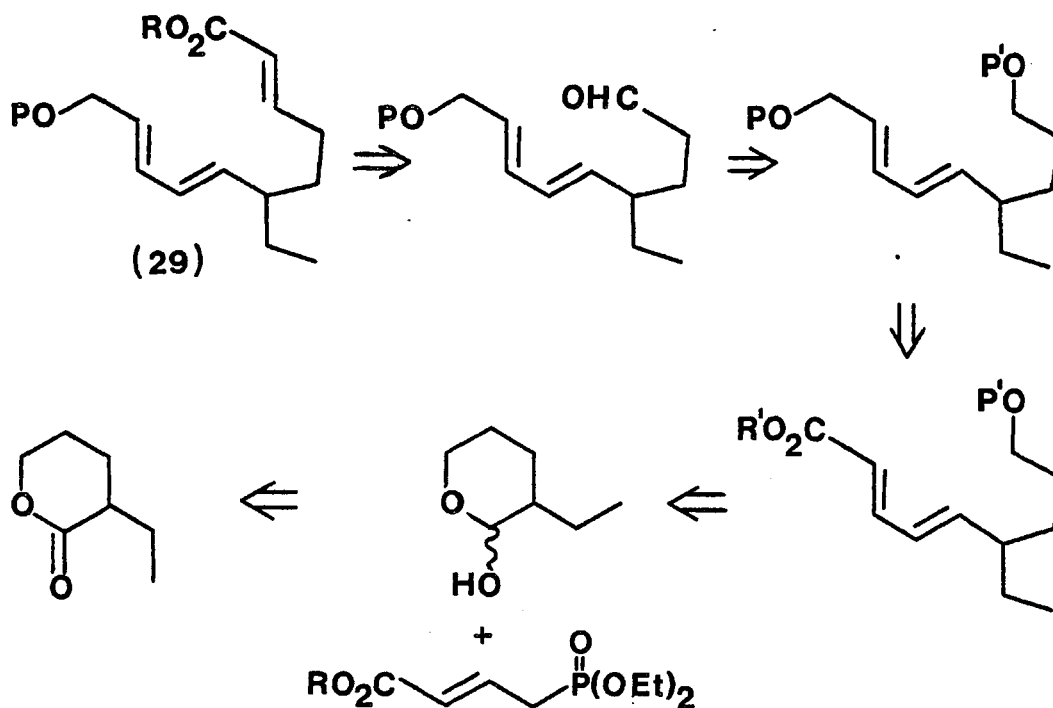
The highest ratio of *endo* to *exo* products ((27):(28)) was found to occur at lower temperatures (83:17 at 115°C, 70:30 at 150°C). We suspected that the intramolecular Diels-Alder reaction of the macro-trienolide (22) might be more facile than the acyclic cases thus requiring lower reaction temperatures and favouring higher *endo* selectivity. However, due to the more ready accessibility of the acyclic

trienoate (29) we decided to base our synthesis on the cyclization of (29).



Roush's results were not particularly encouraging as regards control of the fifth chiral centre at C-16 (X-14547A numbering) as a ratio of only 53:30 of the desired stereochemistry was observed in the *endo* products (27).

The retrosynthetic analysis, outlined in Scheme 7, of trienoate (29) was relatively straightforward and is self explanatory.



Scheme 7

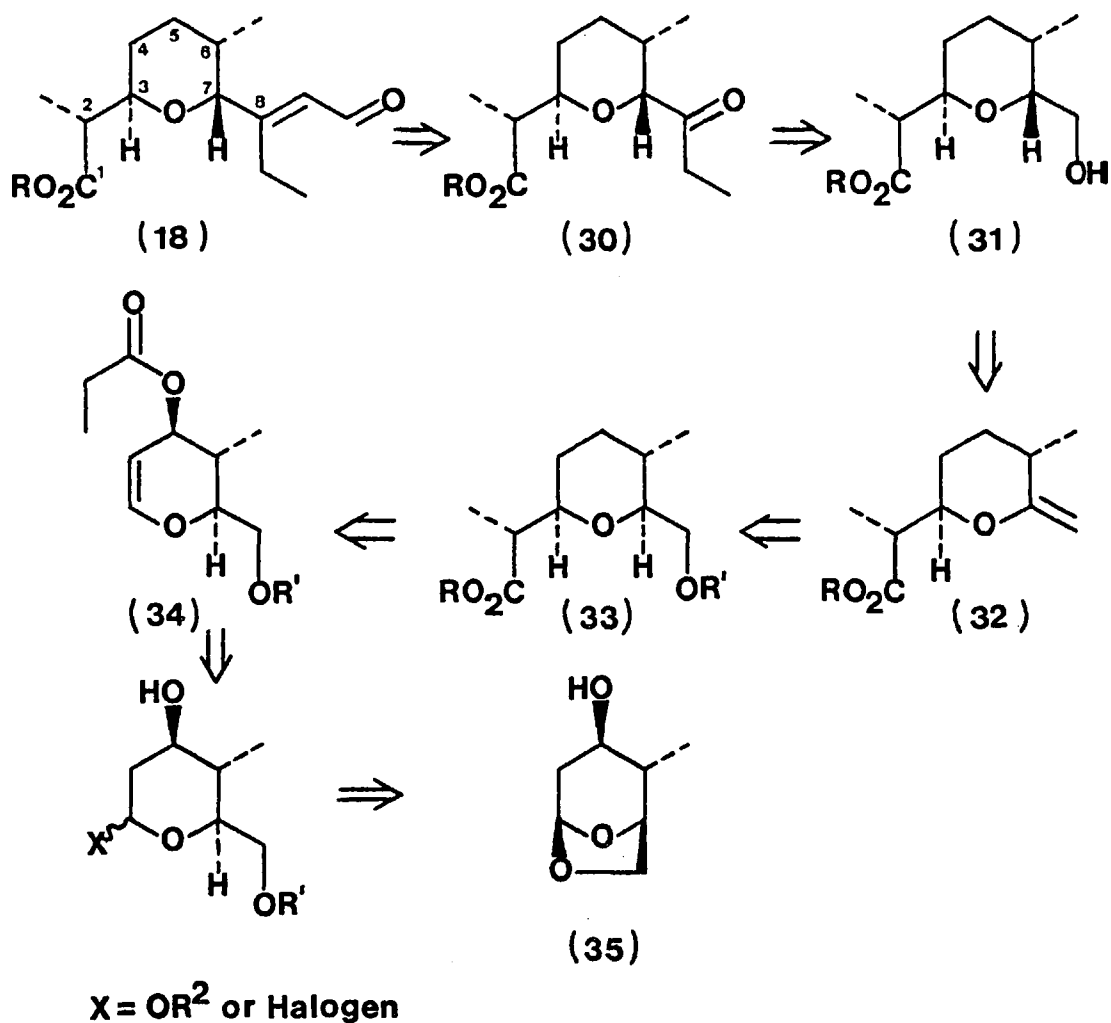
The main requirements in the synthesis of (29) were for two stereoselective *trans*-olefinations and choice of protecting groups such that P¹ could be selectively removed in the presence of P. Although it is desirable to keep the number of protecting groups in any synthesis to a minimum, in general we felt that, with modern protecting groups, if quantitative protection and quantitative selective deprotection can be achieved the efficiency of a synthesis is not reduced.

2.1.3 The Synthesis of the Left Hand Side Tetrahydropyran moiety

Although the work was performed by my co-workers S.G. Lister and B.D. Palmer, a discussion of the retrosynthesis of the left hand side tetrahydropyran moiety is included for completeness.

Two basic strategies appeared to be available for the stereoselective construction of the tetrahydropyranylacetic acid left hand half. The first and perhaps most obvious strategy would involve starting with the pyran ring intact in the form of a readily available carbohydrate starting material. Carbohydrates are finding increasing utilisation in the enantioselective synthesis of complex natural products.⁵⁰ By careful choice of stereospecific reactions involving chirality transfer we envisaged a relatively short synthesis of (31), a molecule that appeared to pose a major synthetic problem. The retrosynthetic analysis of the problem, bearing in mind that we sought a readily available optically active carbohydrate starting material, is outlined in Scheme 8.

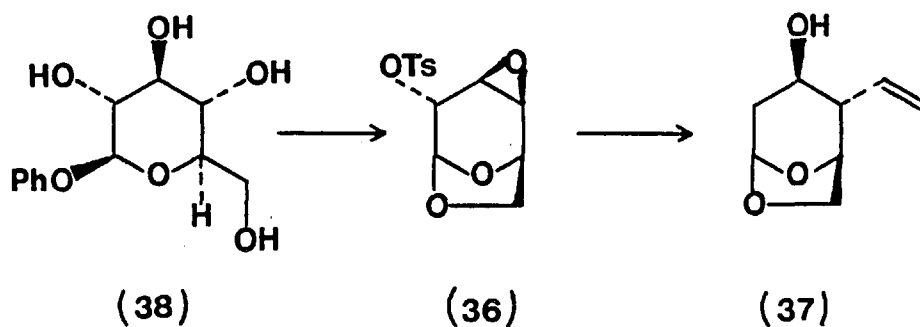
The report that the sequential treatment of the epoxy tosylate (36) with vinylmagnesium chloride/cuprous iodide and lithium triethylborohydride lead to stereospecific and high yield conversion to the alcohol (37) lead us to decide upon (36) as our starting material.⁵¹ Treatment of epoxy tosylate (36), prepared in three steps from the commercially



Scheme 8

available glucose derivative (38), with methylmagnesium chloride and a copper (I) catalyst followed by lithium triethylborohydride was expected to provide the required hydroxy anhydro sugar (35), containing the methyl group at C-6 (X-14547A numbering) with correct absolute configuration.

The chiral centres at C-2 and C-3 were planned to arise, in one step, by chirality transfer from the hydroxy group at C-5 using Ireland's stereoselective ester enolate Claisen rearrangement of the pyranoid glycal (34).⁵² After hydrogenation to remove the resulting



unsaturation between C-4 and C-5, it was hoped that the final chiral centre at C-7 could be created with the correct configuration by a dehydration-oxidative hydroboration procedure ((33) $\rightarrow$ (32) $\rightarrow$ (31)). With the construction of the four chiral centres complete it was anticipated that elaboration of (31) to the α,β -unsaturated aldehyde (18) would pose no great problem.

The second basic strategy for the preparation of the left hand side tetrahydropyranylacetic acid moiety would involve making use of the strategic disconnections A or B in Diagram 3.

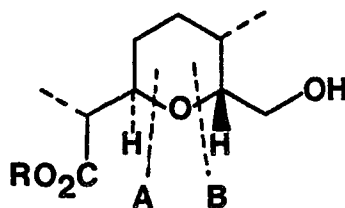
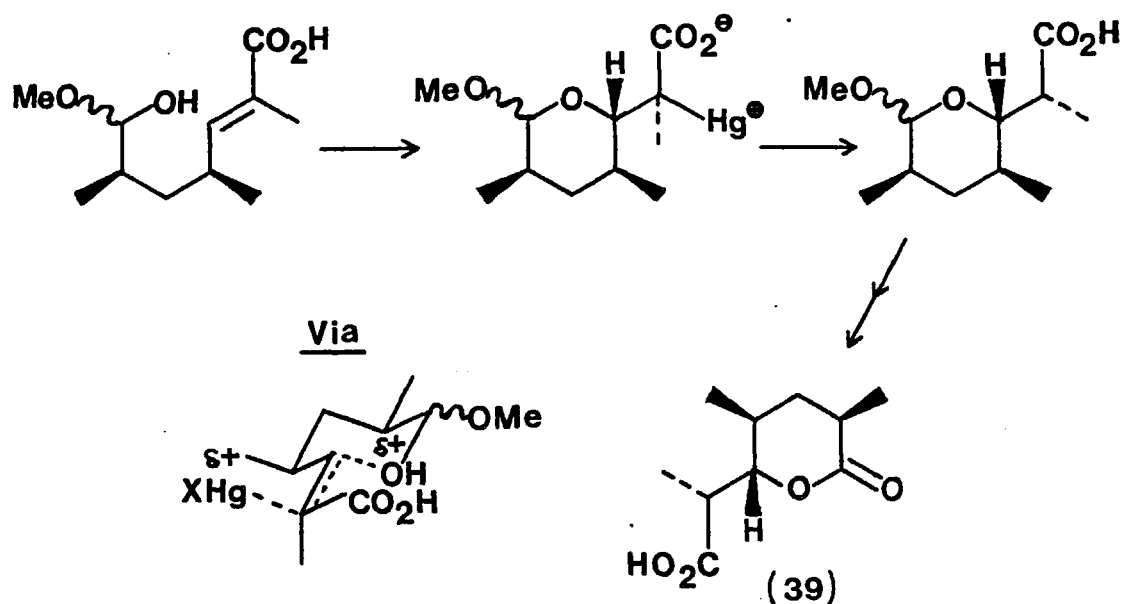


Diagram 3

Both of these disconnections require a stereospecific cyclization reaction to form the pyran ring as a key step in the strategy. A restriction to the flexibility of this approach is that both of the stereocentres at C-3 and C-7 need to be defined prior to cyclization. This is due to the orientation of the three groups at C-3, C-6, and C-7 as equatorial, equatorial, and axial respectively, in the natural

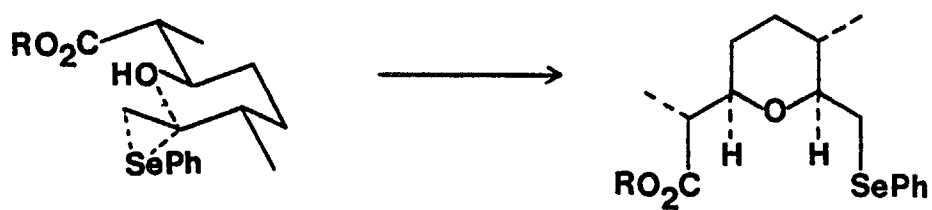
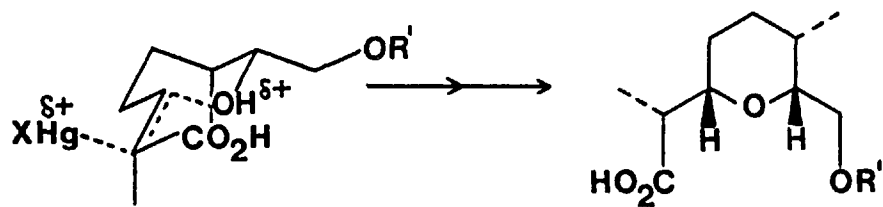
configuration. Any cyclization reaction involving addition of an oxygen nucleophile at C-3 or C-7 to a double bond at C-7 - C-8 or C-2 - C-3, respectively, would give rise to the incorrect relative stereochemistry due to the desire for the larger groups to occupy equatorial positions in the transition state. A fine example of this, shown in Scheme 9, was demonstrated in Bartlett's elegant Prelog-Djerassi Lactone (39) synthesis.⁵³



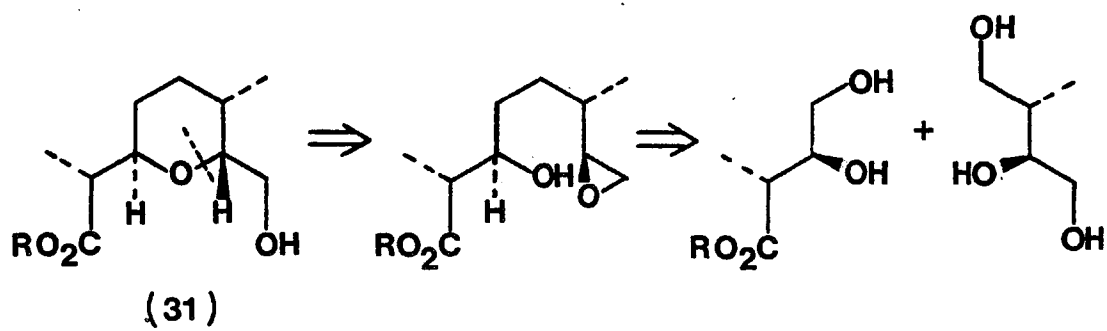
Scheme 9

Two expected examples of this principle are shown in Scheme 10. The first reaction involves analogous chemistry to Bartlett's and the second a selenium cyclization.⁵⁴

Of the two disconnections in Diagram 2 disconnection B appears to be the most useful, in synthetic terms, as the cyclization precursor resulting from this has symmetry about the C-4 - C-5 bond with respect to the chiral centres. Nicolaou and his co-workers (see Scheme 11) took advantage of the recognition of this symmetry in their recent synthesis of the X-14547A left hand side fragment (31) (*vide infra*).¹



Scheme 10



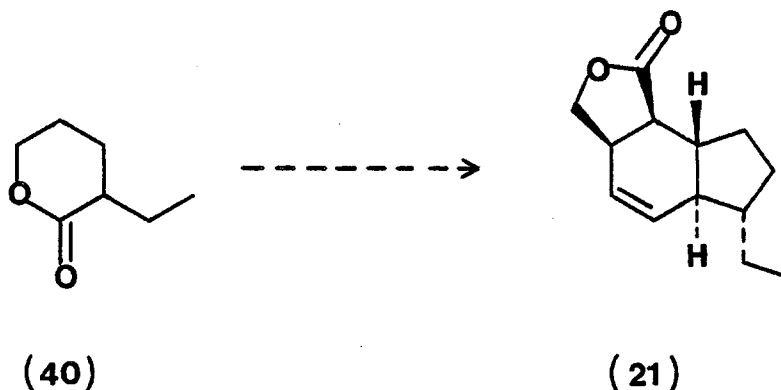
Scheme 11

RESULTS AND DISCUSSION

1. STEREOSELECTIVE SYNTHESIS OF THE TRICYCLIC TETRAHYDROINDAN LACTONE (21).

The right hand side tricyclic tetrahydroindan lactone (21), derived from X-14547A by the retrosynthetic analysis discussed in Sections 2.1.1 - 2.1.2 in the introduction section, was prepared by two similar, efficient, 10-step routes from 2-ethyl- δ -valerolactone (40). Following the retrosynthetic analysis outlined in Scheme 7 (p.), these two routes involved the stereoselective preparation and intramolecular Diels-Alder reaction of the alternative trienoates (29), R = methoxyethoxymethyl (MEM) or *t*-butyldiphenylsilyl (TBDPS). Our first route, involving the use of the MEM protecting group was published in early 1981. The second route, almost identical with a preparation of the lactone (21) reported by Nicolaou³² later that year, was tried as a comparison after a personal communication from Professor Nicolaou prior to publication, while we were in the final stages of developing our MEM route.

The two routes are compared at the end of Section 1.2.



1.1 The MEM Route to (21).

A brief communication by Schlessinger on the high yielding alkylation of lactone enolates appeared to offer the most efficient preparation of the desired starting material, 2-ethyl- δ -valerolactone (40).⁵⁶ However, in our hands, treatment of δ -valerolactone with varying amounts of lithium diisopropylamide (LDA) in THF at -78° up to -20° followed by quenching with varying amounts of ethyl iodide in hexamethylphosphoramide (HMPA), following the Schlessinger procedure, led to only inferior yields of impure material (route A below). Initially we thought this could have been due to the variable purity of the δ -valerolactone, commercially available from Aldrich Chemicals, which is very prone to polymerisation above 0°C and polymerises extensively on attempted vacuum distillation.

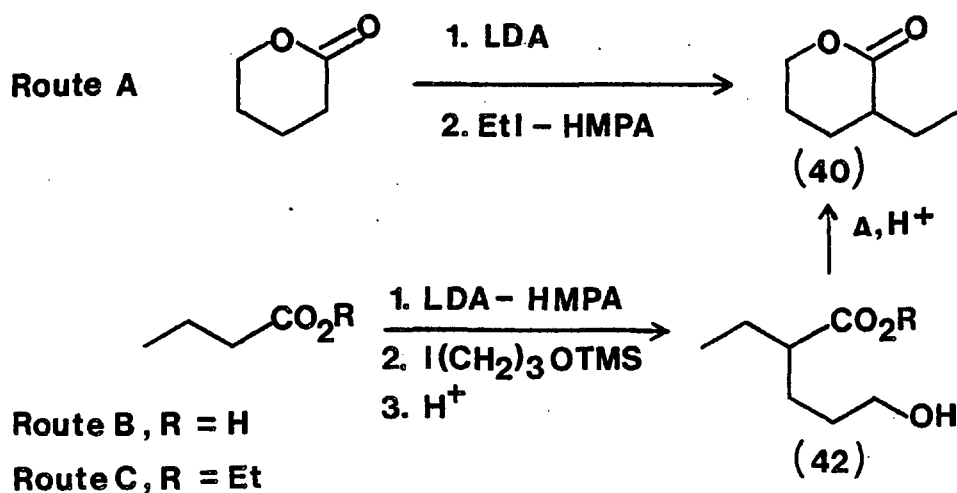
After unsuccessful attempts involving the alkylation of the dianion of butyric acid, formed using LDA-HMPA in THF, with 1-trimethylsilyloxy-3-iodopropane (41) (Route B below),⁵⁷ 2-ethyl- δ -valerolactone of high purity was prepared in high yield from ethyl butyrate (Route C below).

Using the Schlessinger procedure for the alkylation of ester enolates,⁵⁸ which involves the same conditions reported for the lactone alkylations,⁵⁶ only very poor yields of alkylated ester (42) were obtained, along with unreacted starting materials and much Claisen condensation keto-ester. However, after careful optimisation we were able to achieve yields of up to 76% for 30-40g batches of 2-ethyl- δ -valerolactone. Considerable modification to the Schlessinger procedure was required, however. In order to eradicate self condensation of the ethyl butyrate and maximise enolate formation it was necessary to use not the 1N LDA in THF proposed by Schlessinger but 0.5 to 0.6N LDA-HMPA in THF, suggested by Dubois for the alkylation of hindered

esters.⁵⁹ It was found that the highest yields, particularly on a large scale (0.4 - 0.5 mole) were obtained by dropwise slow addition of a solution of the ester in THF (*ca.* 2N) to LDA, prepared using a hexane solution of *n*-butyl lithium concentrated from the nominal 1.3 - 1.6N to about 3N. It seemed that the presence of excess hexane disfavoured both the enolate formation and alkylation steps.

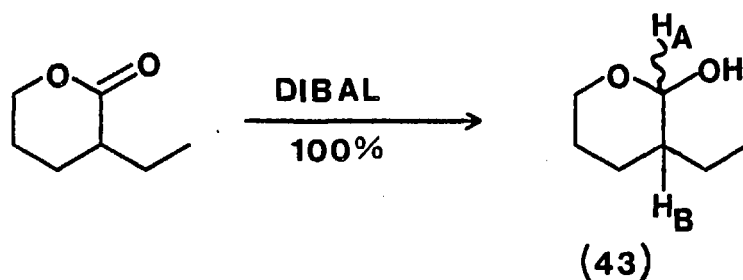
The intermediate crude hydroxy ester (42) was smoothly cyclised to the lactone (40) by heating in toluene with a trace of *p*-toluene-sulphonic acid.⁶⁰ Flash chromatography,⁶⁰ even on large scale preparations, was preferred for purification of (40), as attempted vacuum distillation led to inferior yields due to polymerisation.

The iodide (41) was simply prepared in 82% overall yield from the commercially available 3-chloropropan-1-ol by silylation of crude 3-iodopropan-1-ol⁶¹ (prepared by chloride displacement with sodium iodide in refluxing acetone) with trimethylchlorosilane and pyridine in THF.

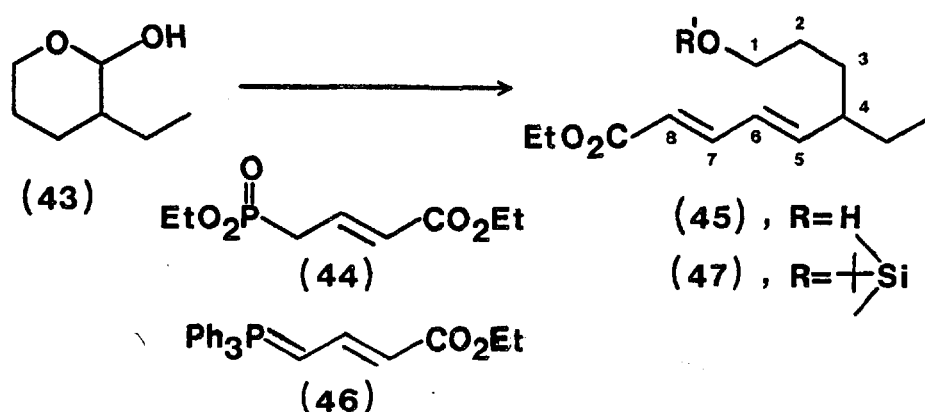


The modified alkylation procedure when applied to δ -valerolactone also gave superior results to the Schlessinger procedure, although yields of only up to 50% were achieved.

2-Ethyl- δ -valerolactol (43) was quantitatively prepared as a 1.29:1 mixture of *anti* (J_{AB} 7 Hz) and *syn* ($J_{AB} \sim 0$) diastereomers by diisobutyl aluminium hydride (DIBAL) reduction of 2-ethyl- δ -valerolactone in toluene at -78° .⁶²



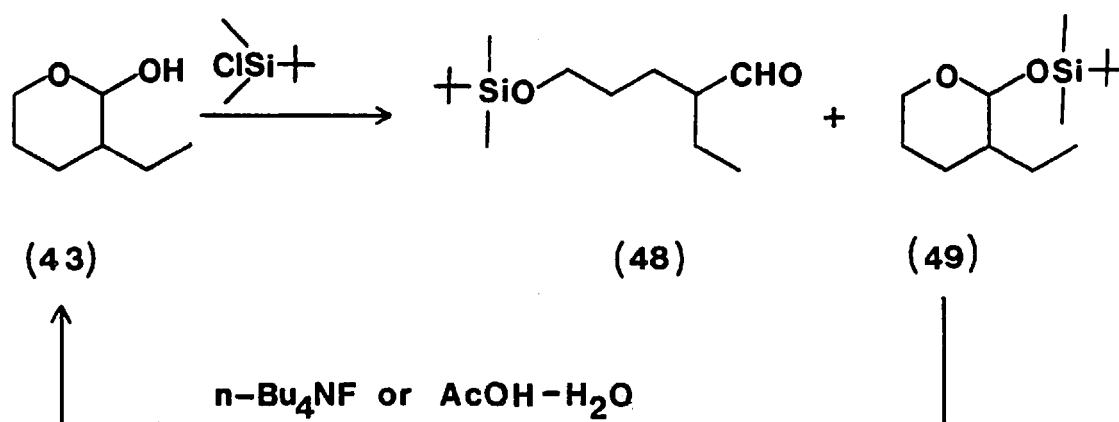
The lactols (43) were found to be remarkably unreactive towards the anion of ethyl 4-diethylphosphonocrotonate (44).⁶³ At temperatures of -78° up to 0°C only small amounts of the (*E,E*)-hydroxydienoate (45) were formed. Under forcing conditions (DMF, 60 – 120°C) up to 23% (35% based on recovered (43)) of the hydroxydienoate (45) could be prepared from the lactols (43) and the preformed ylid (3-ethoxycarbonylallylidene)triphenylphosphorane (46).⁶⁴



Although the alcohol in (45) could be quantitatively protected to give the (*E,E*)-*t*-butyldimethylsilyloxydienoate (47) by treatment with *t*-butyldimethylchlorosilane and imidazole in DMF,⁶⁵ (47) was best

obtained from the lactol (43) by reversal of the steps of olefination and protection.

The lactols (43) were quantitatively converted to a mixture of the desired aldehyde (48) and the minor lactol silyl ether (49) (ca. 2-3:1) by treatment with *t*-butyldimethylchlorosilane under either the standard conditions of Corey⁶⁵ or with triethylamine and 4-*N,N*-dimethylaminopyridine in dichloromethane.⁶⁶



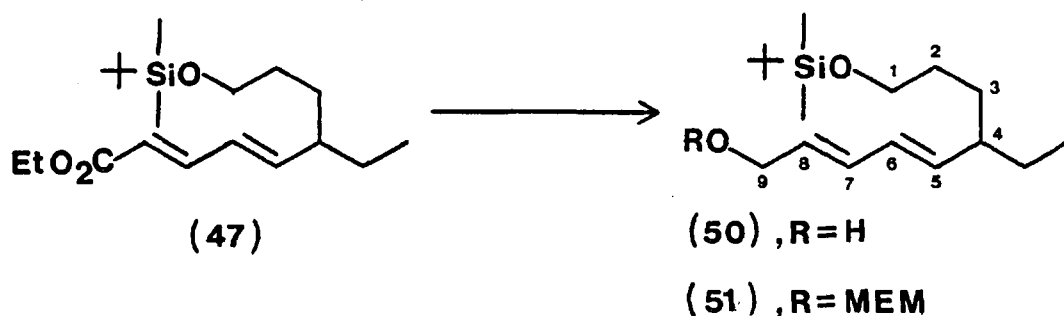
Simple flash chromatography gave yields of 67-80% of the aldehyde (48), based on the lactols (43) recovered on desilylation of (49), with tetra-*n*-butylammonium fluoride or acetic acid-water. Losses occurred due to the volatility of both (48) and (49).

Reaction of the anion formed by treatment of ethyl 4-diethylphosphonocrotonate (44) (1.2 equiv.) with LDA in THF at -78 to -40°C with the freshly prepared aldehyde (48) at -40°C gave a 97% yield of the expected (*E,E*)-dienoate (47) contaminated with 2-3% of the (*Z,E*) isomer and less than 1% of the (*Z,Z*) isomer. In large scale preparations of (47) (up to 28g, 81 mmol) yields approaching 70% of isomerically pure (*E,E*)-dienoate could be achieved after careful chromatography.

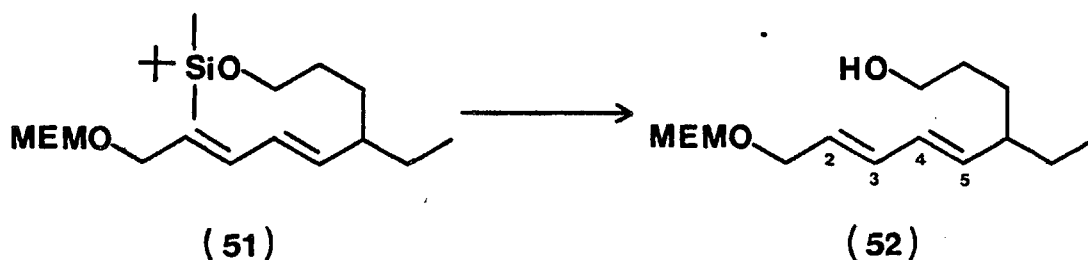
Although 60 MHz ¹H n.m.r. did not reveal details of all the olefinic protons (except H₇; J 15, 10, and 1 Hz), the (*E,E*) stereochemistry

generated in this reaction was heavily predated⁶³ and subsequently proven by high field (250 MHz) ¹H n.m.r. analysis of later diene synthetic intermediates (*vide infra*).

The (*E,E*)-dienoate (47) was smoothly reduced with 2.2 equivalents of DIBAL in toluene at 0°C to give the relatively unstable allylic alcohol (50). Immediate treatment of the crude (50) with MEM chloride and diisopropylethylamine in dichloromethane gave the diprotected (*E,E*)-dienediol (51) in 96% overall yield from the ester (47).⁶⁷



The selective monodeprotection of (51), accomplished in quantitative yield using tetra-*n*-butylammonium fluoride in THF, completed the quantitative exchange of protection from one end of the diol (in (51)) to the other (in (52)).



The *trans* olefin coupling constants $J_{2,3}$ and $J_{4,5}$ of 15.2 Hz, shown by high field (250 MHz) ¹H n.m.r. spectroscopy (see Diagram 4), clearly indicated the (*E,E*) stereochemistry of the diene.⁶⁸

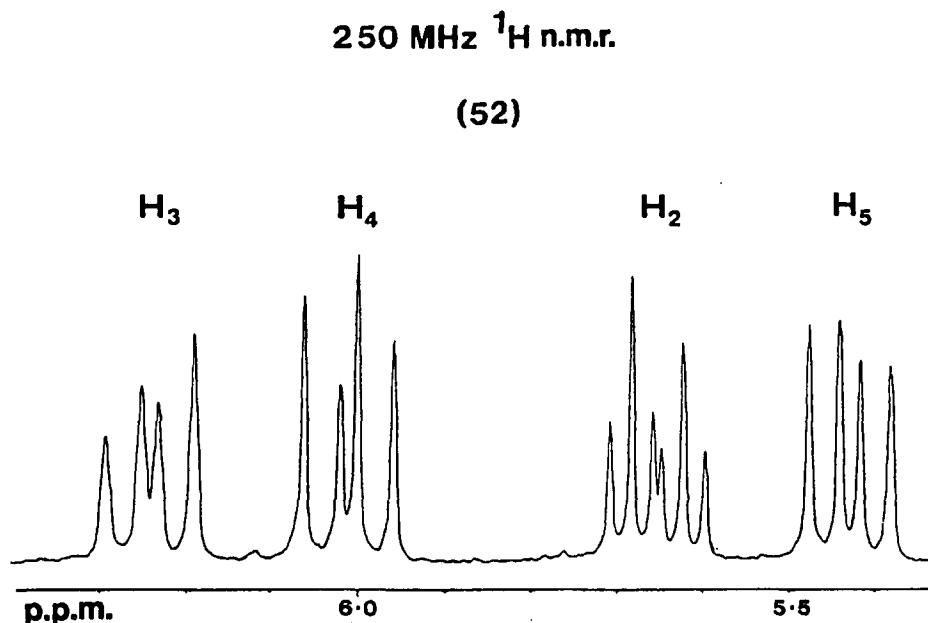
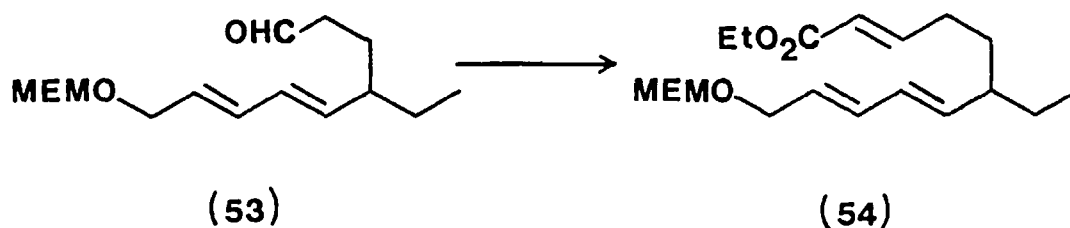


Diagram 4

The *in situ* Collins oxidation method of Ratcliffe and Rodenhurst⁶⁹ cleanly and quantitatively converted the alcohol (52) to the aldehyde (53) without any need for further purification after the normal work up.

Pyridinium chlorochromate (PCC) (1.6 equiv., 130 min) or pyridinium dichromate (PDC) (2 equiv., 20h) gave only 74 and 72% yields of the aldehyde (53) respectively.^{70,71}

The required (*E,E,E*)-trienoate (54) was stereospecifically prepared, in 95% yield after removal of triphenylphosphine oxide, by overnight reaction of the aldehyde (53) with carboethoxymethylenetriphenylphosphorane in dichloromethane.⁷² Thin layer chromatography (t.l.c.) and high field (250 MHz) ^1H n.m.r. revealed the absence of any detectable (*E,E,Z*) isomer. The coupling constant of 15.6 Hz for the olefinic protons of the α,β -unsaturated ester (54), (H_9 and H_{10}) confirmed the expected *E* stereochemistry of the newly formed double bond.⁶⁸

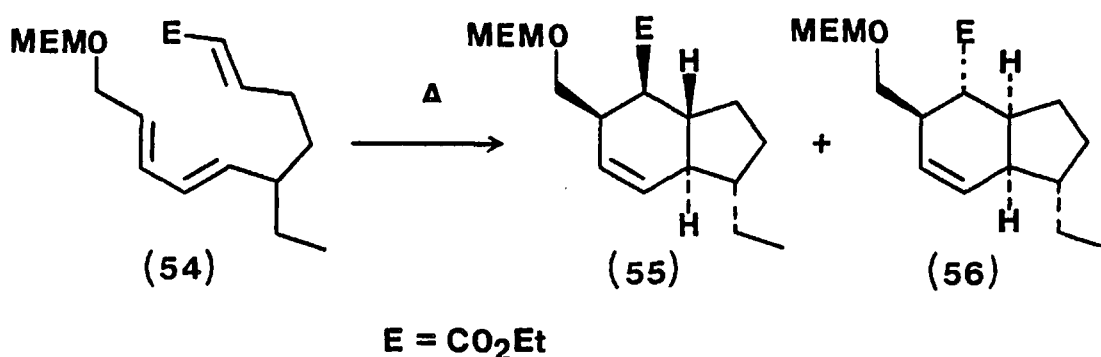


Heating of a dilute solution (*ca.* 0.01N) of the now readily available (*E,E,E*)-trienoate (54) in argon-flushed, dry toluene, at reflux, for 36-70h led to a very clean conversion of the u.v. active starting material to a single chromatographically homogeneous non-u.v. active product. 60 MHz ^1H n.m.r. showed that resonances for the six olefin protons of the trienoate (54) were absent and replaced by only two proton signals in the olefinic region of the spectrum. In a number of solvent systems the product had exactly the same R_f as the starting material. However, the reaction was conveniently followed by t.l.c. due to both the absence of u.v. activity in the product and a dark red colouration on sulphuric acid spraying, characteristic of the tetrahydroindan system.

Detailed high field (250 MHz) ^1H n.m.r. analysis of the cyclized product, isolated in quantitative yield after removal of toluene, showed that essentially one product was formed in the Diels-Alder cyclization. Not more than about 10% of other possible isomers and a trace (<5%) of the starting material were present.

Comparison of the absorptions due to H_4 , H_5 , H_6 and H_7 in the high field (250 MHz) ^1H n.m.r. spectrum of the tetrahydroindan product with the reported absorptions for the corresponding protons in the tetrahydroindan (57), prepared by an *endo* intramolecular Diels-Alder reaction

by Roush,⁴⁹ showed that the product of the intramolecular Diels-Alder reaction of trienoate (54) was indeed the *endo* product (55) as predicted (see Table 1).



A minor absorption, assignable to H_5 , at δ 5.9 (dt, J 10 and 4 Hz) (cf. (58) in Table 1 below) of a minor tetrahydroindan (<10%) product strongly indicated it to be a *cis*-fused *exo* product (56) rather than (55a) the C-1 ethyl epimer of (55).

Although providing strong evidence for the four directly involved in the ring forming reaction (C-3a, C-4, C-5, and C-7a) the high field ^1H n.m.r. gave no indication of the stereocontrol achieved at C-7 apart from showing that only one isomer was produced. At this stage, examination of molecular models showed that of the two possible diastereomeric *endo* cyclization modes, (A) and (B) in Diagram 5 below, the transition state with the ethyl group at C-1 *exo* (A), leading to the desired α configuration at C-1, would be preferred on steric grounds. Relative to transition state (A), the alternative (B), leading to the undesired β configuration involves unfavourable steric interactions between the C-1 ethyl group and both H_a and H_b .

Further implications of a detailed consideration of transition state models in this intramolecular Diels-Alder reaction are discussed in relation to other similar cases in Section 1.2 (p.120).

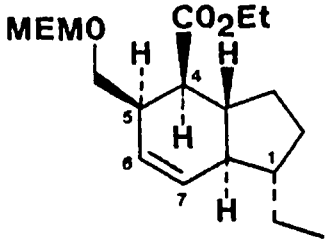
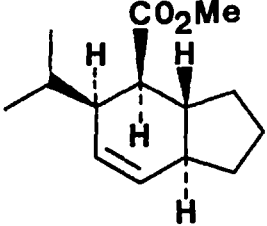
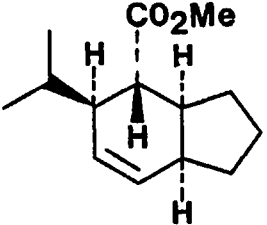
Compound	H	¹ H N.M.R. δ (p.p.m.)
 (55)	7 6 5 4	5.95 (br.d, J 10.3 Hz) 5.55 (ddd, J 10.3, 4.0, and 2.6 Hz) 2.85 (m) 2.62 (dd, J 11.2 and 6.7 Hz)
 (57)	7 6 4 5	5.95 (br.d, J 10 Hz) 5.55 (ddd, J 10, 4.4, and 2.6 Hz) 2.70 (dd, J 11.4 and 7.7 Hz) 2.60 (m)
 (58)	- - 4	5.89 (dt, J 10 and 4 Hz) 5.58 (br.d, J 10 Hz) 2.11 (dd, J 10.8 and 11.3 Hz)

Table 1

N.B. - Absorption not assigned.

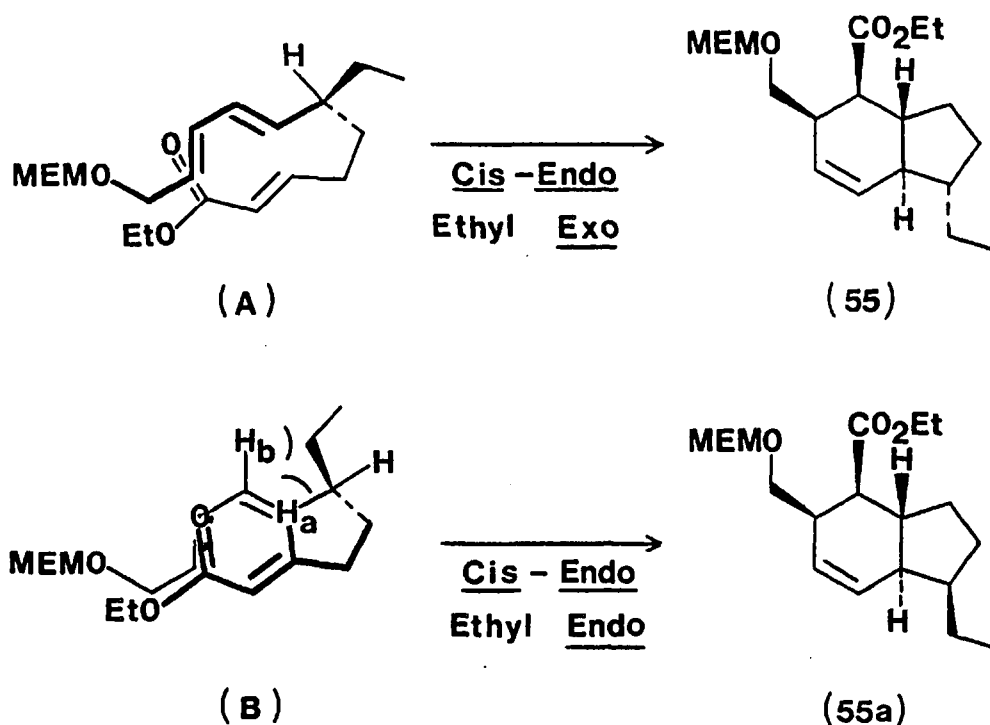
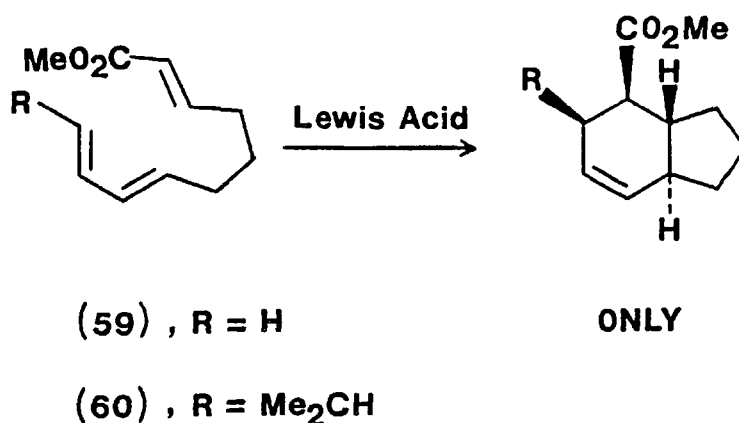


Diagram 5

This tentative but reasonable assignment of the stereocontrol at C-1 was confirmed unambiguously by X-ray crystal structure analyses of 2 subsequent tetrahydroindan synthetic intermediates (*vide infra*).

Roush recently observed dramatic effects of Lewis acid catalysis on the intramolecular Diels-Alder reaction of some methyl (*E,E,E*)-deca-2,7,9-trienoates.^{49b,d} In particular the trienoates (59) and (60) gave *trans*-fused *endo* Diels-Alder cyclization products exclusively with menthoxyaluminium dichloride, aluminium trichloride, ethylaluminium dichloride, or diethylaluminium chloride in dichloromethane, in 75-84% yields, after 18-48h at only 23°C. The corresponding thermal Diels-Alder reactions of these trienoates, at 150°C, gave 60:40 and 72:28 ratios of *trans*- to *cis*-fused tetrahydroindan for (59) and (60) respectively.⁴⁹



The increased rate and selectivity of Lewis acid catalysed Diels-Alder reactions has been rationalised in terms of frontier molecular orbitals.⁷³ Roush concluded that the increased selectivity was due to the increased secondary orbital control, caused by complexation of the Lewis acid by the ester group, reinforcing the transition state preference for the *trans* ring fusion manifested in the thermal reactions.

Although the failure to catalyse the intramolecular Diels-Alder reaction of several oxygen-containing trienoates was attributed to the complexation of the non-dienophile oxygen with the Lewis acid leading to subsequent decomposition (by Roush)⁴⁹ we were interested to see the role that the MEM protecting group might play in possible catalysis of the Diels-Alder reaction of the trienoate (54).

Roush reported that 0.1 equiv. of aluminium trichloride was sufficient for clean cyclization, with greater amounts leading to problems with triene polymerisation. Stirring the MEM trienoate (54) with 0.1 equiv. of aluminium trichloride in dichloromethane at room temperature for up to 42h led to no detectable cyclization with only traces of decomposition. Ethylaluminium dichloride, however, had an interesting

effect on (54). Apart from considerable decomposition, about 70% of the remaining material underwent cyclization in the presence of 0.9 equiv. in dichloromethane during 16h. After 28 and 47h only further general decomposition was observed. With the milder Lewis acid diethylaluminium chloride much cleaner cyclization was achieved. However, with 1 equiv. in dichloromethane at room temperature, after 42h only 75% conversion, with a small amount of decomposition, was observed. Interestingly, addition of further amounts of the catalyst led to no significant further cyclization with more general decomposition being apparent.

Although these observations were not useful from a preparative point of view, as the thermal preparation of the tetrahydroindan (55) was perfectly satisfactory, the mechanistic implications are worthy of some discussion. Although a strong Lewis acid, efficient in catalysing this type of cyclization,⁴⁹ it seems that the aluminium trichloride simply binds to the MEM protecting group. The bidentate ligand properties of the MEM protecting group are of course well known.⁶⁷ Interestingly, as an aside, samples of the MEM trienoate (55) prepared by chromatography and long periods of static evaporation under high-vacuum consistently gave inaccurate microanalytical data due to incorporation of water. Short path high-vacuum distillation was necessary to provide samples of analytical purity. This phenomenon has important implications for the deprotection of MEM ethers with anhydrous zinc bromide. The difficulty sometimes associated in these laboratories with these deprotections would seem to be most likely due to the inability of the MEM group to complex with the zinc bromide in the desired fashion for breakdown (Diagram 6) due to the presence of strongly solvated impurities in the MEM ether.

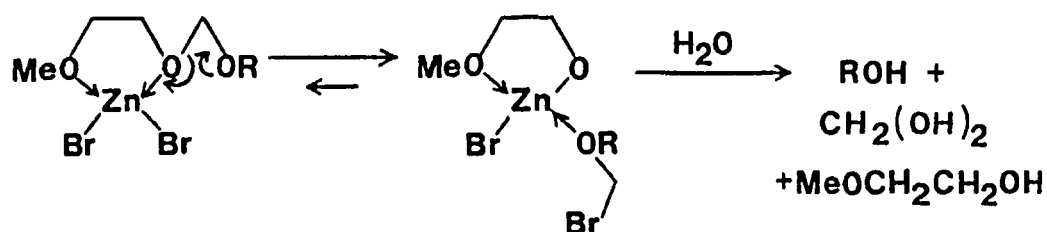
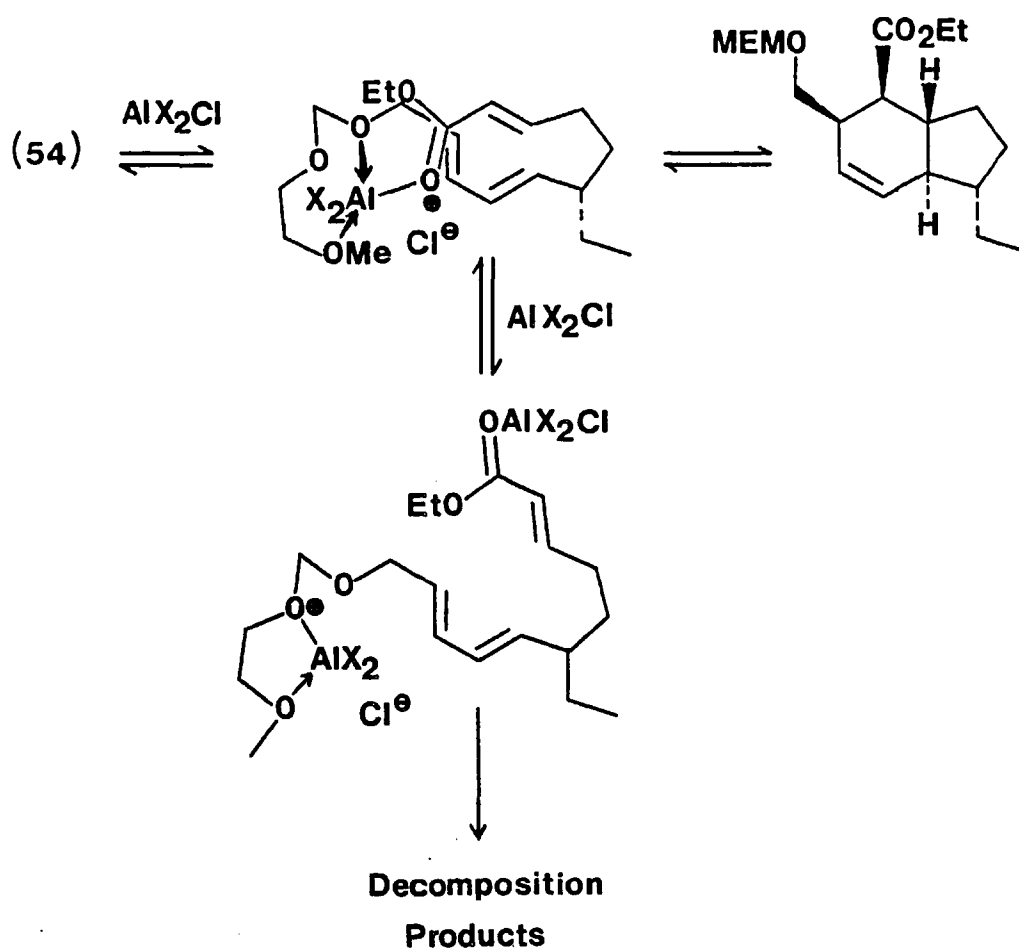


Diagram 6

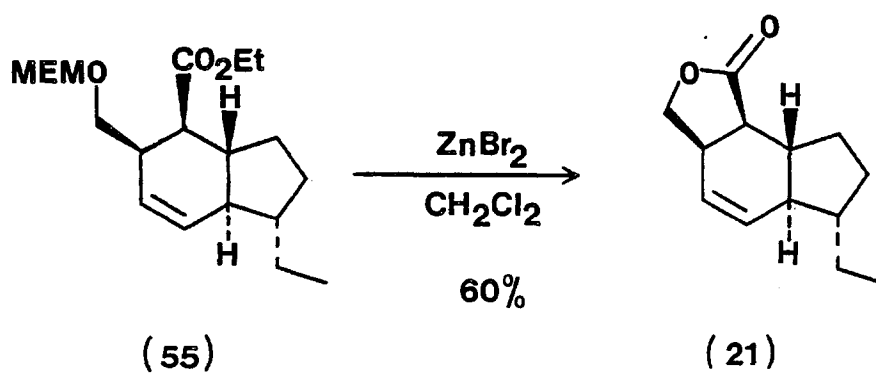
The rather vicious Lewis acid ethylaluminium dichloride apparently catalysed the cyclization of the trienoate (54) but it appears that complexation with the MEM group in the product and/or the starting material led to subsequent decomposition. The lack of any further cyclization in the presence of excess Lewis acid could be attributed to complexation by MEM and the dienophile carbonyl group of two molecules of the Lewis acid leading to repulsion between the two ends of the trienoate.

The milder Lewis acid diethylaluminium chloride was apparently involved in similar competitive equilibria with the trienoate (54), as shown in Scheme 12, with rather less decomposition occurring than with ethylaluminium dichloride.

Possibly due to the phenomenon discussed above, the removal of the MEM protecting group from the tetrahydroindan (55) with zinc bromide was an extremely capricious reaction. The occasional successful deprotections with this reagent did lead to smooth spontaneous lactonisation of the intermediate hydroxy ester to the isomerically pure (>97%) desired lactone (21) in good (60%) yield, after flash chromatography. However, on many occasions the starting MEM ether was recovered apparently untouched by the zinc bromide.

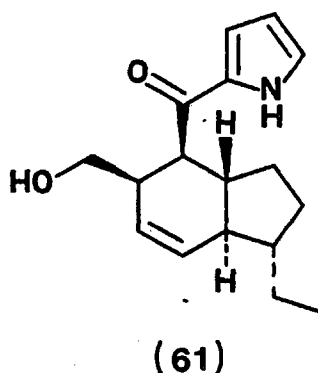


Scheme 12



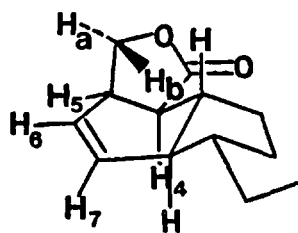
The lactone (21) thus produced (crystallised from petrol as needles, m.p. 67.5 - 68.5⁰C) was identical to the same lactone, m.p. 68 - 68.5⁰C, prepared by Nicolaou and structurally confirmed by X-ray crystallography.³²

As an independent proof of the stereochemistry of our synthetic tetrahydroindan nucleus, a crystal structure was obtained for the hydroxypyrrolylcarbonyl tetrahydroindan (61), prepared from the lactone (21) (*vide infra*).



In the high field (250 MHz) ¹H n.m.r. spectrum of the lactone (21) the protons of the cyclohexene and lactone nucleus were clearly assignable (Diagram 7).

Due to the unreliability of the zinc bromide deprotection of (55) an alternative was sought. The recommended procedure of treatment with titanium tetrachloride in dichloromethane at 0⁰C⁶⁷ led to complete disappearance of the starting material. However, none of the desired lactone (21) was observed by t.l.c. Analysis of the ¹H n.m.r. spectrum of the mixture of products showed no olefin protons, four methylenoxy protons and an intact ethyl ester. As it was useless from a synthetic standpoint, this reaction was not pursued further. On the ¹H n.m.r. evidence alone, it was clear that the major product



(21)

δ (p.p.m.)

H₇ 6.07 (d, J 10.2 Hz)

H₆ 5.58 (ddd, J 10.2, 3.8, and 2.0 Hz)

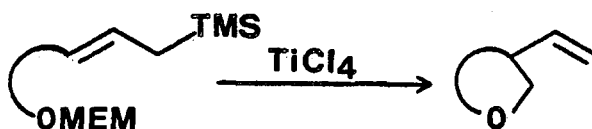
H_a 4.51 (dd, J 8.8 and 8.8 Hz)

H_b 3.90 (dd, J 8.8 and 11.5 Hz)

H₅ 3.20 (m)

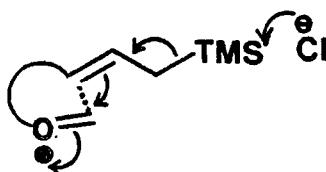
H₄ 2.54 (ddd, J 11.5, 7.6, and 6.6 Hz)

Diagram 7



Via

TMS = SiMe₃



Scheme 13

(not further characterised) was derived, as shown in Diagram 8 below, from intramolecular neighbouring group participation of the double bond in the breakdown of the MEM ether.

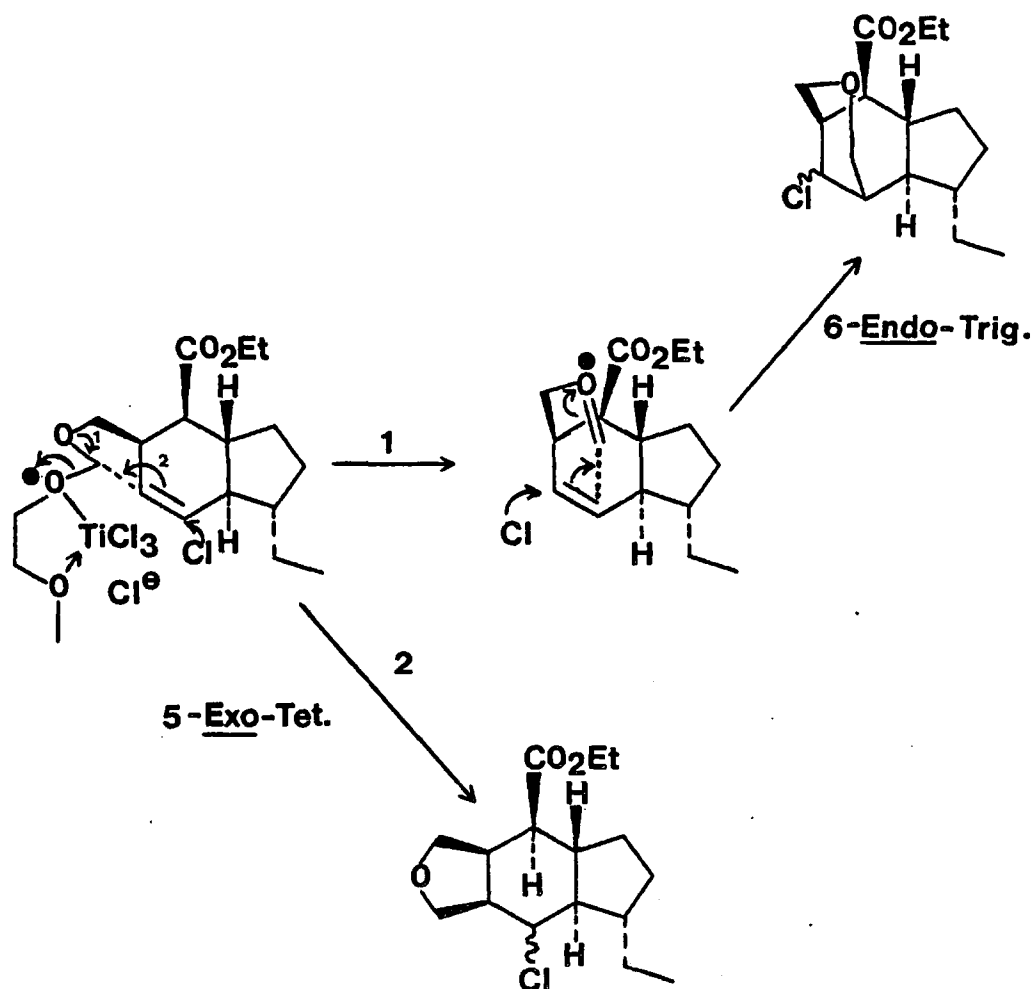


Diagram 8

A recent paper by Hoh on the intramolecular trapping of similar oxonium intermediates with allylsilanes, shown in Scheme 13, seems to lend strength to this proposed mechanism for the reaction of the trienoate (54) with titanium tetrachloride.⁷⁴

The problem of the preparation of the lactone (21) from the MEM ether (55) was conveniently solved by taking advantage of the complexing

ability of the MEM group by using a novel phase-transfer catalysed (PTC) acid deprotection procedure. Vigorous stirring of a dilute dichloromethane solution (*ca.* 0.05N) of the MEM ether (55) with concentrated hydrochloric acid in the presence of tetra-*n*-butylammonium bromide cleanly produced the lactone (21) in up to 65% yield after flash chromatography. That this was a genuine PTC process was confirmed by the observation that no deprotection was obtained in the absence of either the tetra-*n*-butylammonium bromide or the concentrated hydrochloric acid.

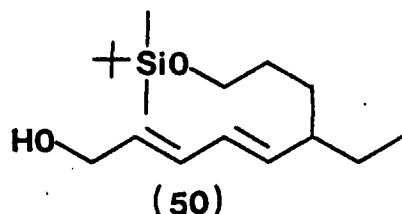
The deprotection of the MEM ether (55) completed an efficient ten-step synthesis of the important tricyclic lactone (21) in 37-44% overall yield from 2-ethyl- δ -valerolactone (40).

1.2 The TBDPS Route to (21).

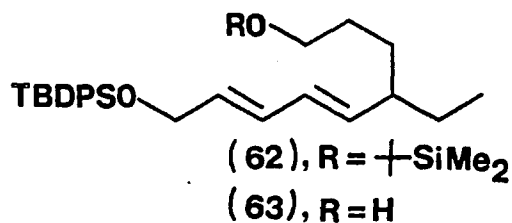
This second route, essentially the same as the MEM route just described, diverged at the alcohol (50), readily prepared in 64-76% overall yield, in four steps, from 2-ethyl- δ -valerolactone. Treatment of the allylic alcohol (50) with *t*-butyldiphenylchlorosilane (1.2 equiv.) and imidazole (2.5 equiv.) in DMF at room temperature provided a 93% yield of the diprotected (*E,E*)-dienediol (62). Selective, near quantitative (98.5%) deprotection to give the alcohol (63) was achieved by vigorous stirring with acetic acid-water-THF (2:1:1.2) for 6h at room temperature.

The overall yield of 92% for the conversion of (50) to (63) was slightly inferior to the near quantitative (98%) overall conversion of (50) to the MEM monoprotected diol (52). A significantly lower yield of 70% for the conversion of (50) to (63) was reported by Nicolaou.³² Although slightly different conditions (1.5 equiv. of *t*-butyldiphenylchlorosilane, 1.5 equiv. of imidazole in DMF then 3:2:2 acetic acid-

THF-water, 25°C, 1h) were used, it seems more likely that the allylic alcohol (50) used was not freshly prepared.



TBDPS = t-BuPh₂Si

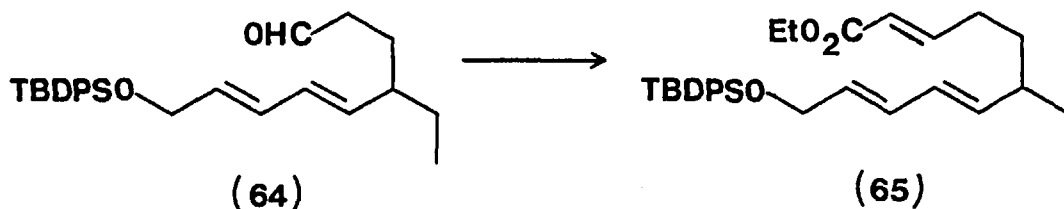


The alcohol (63) was converted to the desired ethyl (*E,E,E*)-trienoate (65) in an overall yield of 89% by sequential oxidation, using the Ratcliffe and Rodenhurst procedure⁶⁹ as before, to the aldehyde (64) (98%) and Wittig reaction with carboethoxymethylene-triphenylphosphorane in dichloromethane (91%). Nicolaou reported a similar overall yield (90%) of the corresponding methyl (*E,E,E*)-trienoate by sequential treatment of the alcohol (63) with PCC and carbomethoxymethylenetriphenylphosphorane.

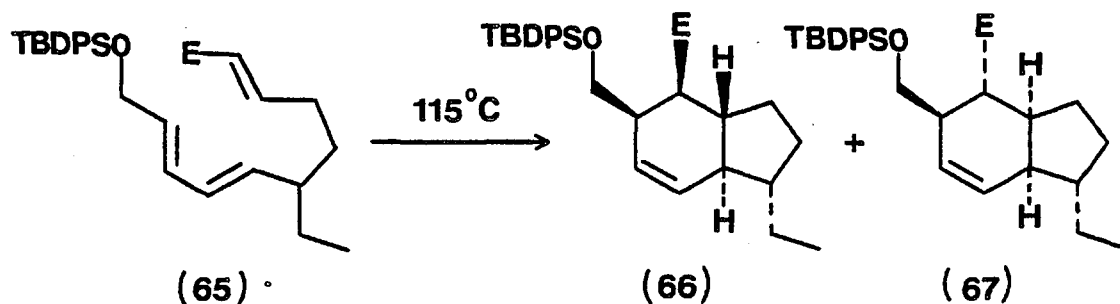
The trienoate (65) was contaminated with about 2% of the (*E,E,Z*) isomer which could be removed chromatographically, although material losses occurred on the column.

It seems likely that the complete stereospecificity observed in the Wittig preparation of the MEM trienoate (54) (no detectable (*E,E,Z*) isomer) may possibly be due to conformational and electronic effects caused by the non sterically demanding and complexing (crown ether-like) nature of the MEM protecting group compared to the extremely bulky lipophilic TBDPS protecting group.

Intramolecular Diels-Alder cyclization of the trienoate (65) was achieved, as before, by heating at reflux in dry, argon-flushed, toluene.



After 70h, careful chromatography gave recovered (65) (10%), the expected *endo* cycloaddition product (66) (64% or 71% based on recovered (65)) contaminated with only traces (<5%) of other isomers, and a mixture, containing a trace (<5%) of (66), of minor cyclization isomers (21%). On t.l.c. plates both the major and minor products showed the characteristic red colouration of the tetrahydroindan nucleus on spraying with sulphuric acid.



As in the intramolecular Diels-Alder cyclization of the MEM trienoate (54), high field (250 MHz) ^1H n.m.r. analysis of the mixture of minor tetrahydroindans revealed that the major component of this chromatographically homogeneous mixture was the *cis*-fused *exo* product (67) rather than the C-1 ethyl epimer of (66). The ^1H n.m.r. spectrum of (67) was significantly different to that of (66). In particular, the

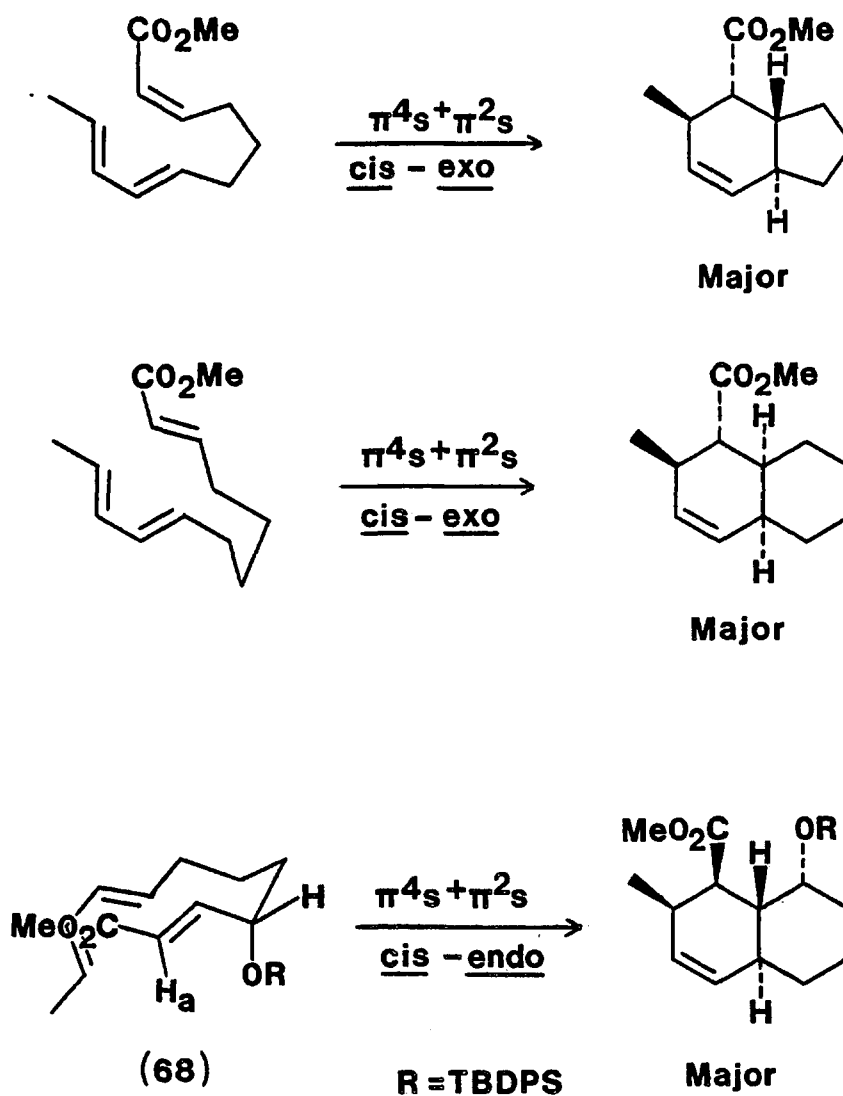
olefin protons, H₆ and H₇, at δ 5.73 (1H, ddd, J 10, 1.7, and 1.7 Hz) and 5.9 (1H, ddd, J 10, 4.2, and 3.0 Hz) were similar to the absorptions reported for the *exo cis*-fused Diels-Alder product (58) (δ 5.58 (1H, br d, J 10 Hz) and 5.89 (dt, J 10 and 4 Hz)), see Table 1, p. .

Nicolaou reported a ratio of 70% of *endo* to 15% *exo* isomers for the cyclization of the methyl ester analogue of (65).

The important difference between the intramolecular Diels-Alder reaction of the MEM and TBDPS trienoates (54) and (65) is obviously in the greater (9:1) apparent selectivity for the *endo trans*-fused tetrahydroindan product *vs.* the *exo cis*-fused tetrahydroindan product in the cyclization of the MEM trienoate (54) (*cf.* 7:2 for the TBDPS trienoate (65)).

The results of Roush and others clearly show that the stereochemical outcome of the intramolecular Diels-Alder reaction in these and related systems is often determined by a subtle interplay of a number of factors such as non-bonded interactions and electronic effects in the transition states.⁴⁹ The first two examples in Scheme 14 below show that secondary orbital interactions are not always the primary factors involved in determining preference for *exo* or *endo* modes of cycloaddition in these reactions.^{49,75} It seems, and this is particularly obvious upon examination of molecular models, that the conformational and steric effects involved in allowing attainment of the necessary bond geometries for cyclization are often the crucial deciding factors. The third example in Scheme 14 shows a case where a bulky hydroxyl-protecting group reverses the stereochemical outcome of an intramolecular Diels-Alder reaction.⁷⁶ Less bulky protected derivatives of (68) were found to give mixtures of *exo* and *endo* products. An unfavourable A-1,3 steric effect in the corresponding *exo* transition

state for cyclization of (68), between H_a and the alcohol group was the reason given for this.



Scheme 14

In view of this sensitivity of the stereochemical outcome of the intramolecular Diels-Alder reaction it is not really surprising, when one examines models for cyclizations of the MEM or TBDPS trienoates (54) or (56), to find that the cyclization of (54) is more selective for the *endo trans*-fused tetrahydroindan product. As is shown in

Diagram 9 below, an unfavourable steric interaction between the CH_2OR group attached to the diene and the ester carbonyl and ethoxy groups occurs in the *endo* transition state that is absent in the *exo* transition state. It is also apparent that the forming 5-membered ring in the *exo* transition state is more strained and involves a destabilising interaction between the C-8 methylene protons and the C-4 diene proton. It appears to be this strain in the chain bridging the diene with dienophile, rather than secondary orbital overlap that favours the *endo* cyclization.⁴⁹

Although the concerted, non-synchronous bond formation model independently proposed by White⁷⁷ and Boekmann⁷⁸ for these intramolecular Diels-Alder reactions, suggesting that early bond formation occurs between C-5 and C-9, would lead to a lessening of effects at the termini of the trienoate, it would seem fair to postulate that the much greater steric bulk of the TBDPS group compared to the MEM group would slightly disfavour the *endo* mode *vs.* the *exo* mode for (65) relative to (54). It is also possible that the effect on the diene frontier MO energies of the electron-withdrawing CH_2OMEM group plays a role in determining the outcome of the reaction.

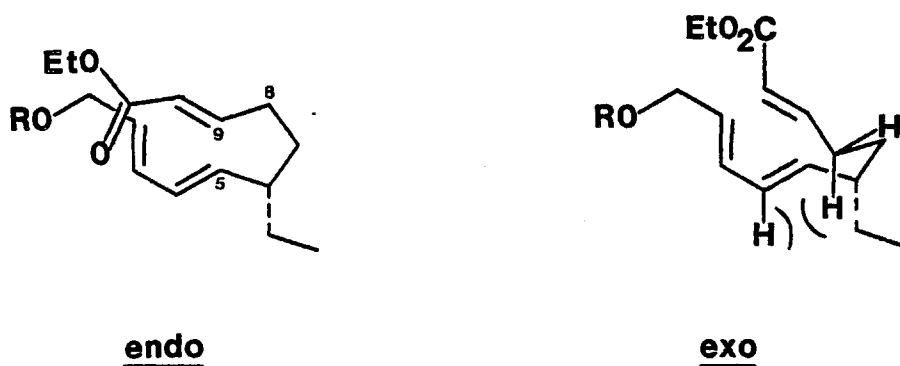


Diagram 9

Further, it seems likely that the complexing ability of the MEM group may also play a role in stabilising the *endo* transition state, in the presence of metal ion impurities, as shown in Diagram 10, or active Lewis acid sites such as are found on glassware surfaces, or particularly, on glass anti-bumping granules.

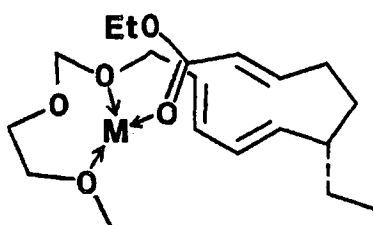


Diagram 10

The effects of Lewis acids in the catalysis of the intramolecular Diels-Alder reaction of the TBDPS trienoate (65) were investigated. As was found for the MEM trienoate (54), aluminium chloride (0.1 equiv.) had no effect on the trienoate (65) even after prolonged reaction time. Ethylaluminium dichloride lead to about 70% cyclization (by t.l.c.) accompanied by extensive decomposition. However, the milder Lewis acid diethylaluminium chloride was found to be extremely effective in catalysing the cyclization with complete conversion after 17h. In line with Roush's results for similar systems⁴⁹ only the *endo* product (66) was isolated in a non-optimised yield of 67% after flash chromatography. T.l.c. showed the complete absence of the minor component (67).

in catalysing the Diels-Alder reactions of these more useful highly functionalised trienes would vastly increase the power of the intramolecular Diels-Alder reaction in natural product synthesis.

The TBDPS route to the tricyclic lactone (21) was completed by tetra-n-butylammonium fluoride deprotection of the tetrahydroindan (66). Again, spontaneous lactonisation occurred to give an 89% yield of (21) after flash chromatography (Nicolaou reported quantitative conversion for the corresponding reaction in his synthesis.³²).

The overall yield for the ten step synthesis of (21) from 2-ethyl-valerolactone of 33-40% was very similar to the 37-44% yields for the MEM route. However, although the final MEM deprotection to prepare the lactone (21) was initially troublesome, the MEM route is to be preferred as the tricky chromatography necessary after the intramolecular Diels-Alder reactions of the TBDPS trienoate (65) is not needed in the MEM case.

2. ATTEMPTED ENANTIOSELECTIVE SYNTHESIS OF THE TRICYCLIC TETRAHYDRO-INDAN LACTONE (21).

For an enantioselective synthesis of X-14547A *via* the coupling of optically active left and right hand fragments we required a modification of our efficient synthesis of racemic (21) to produce this lactone with correct absolute as well as relative stereochemistry in high optical purity. This was particularly important as our projected synthesis of a left hand side fragment from an optically active carbohydrate starting material would produce only the required enantiomer.

In the synthesis of chiral molecules with the correct absolute configuration a number of strategies for incorporation of the desired optical activity are recognised today. Optical resolution of synthetic

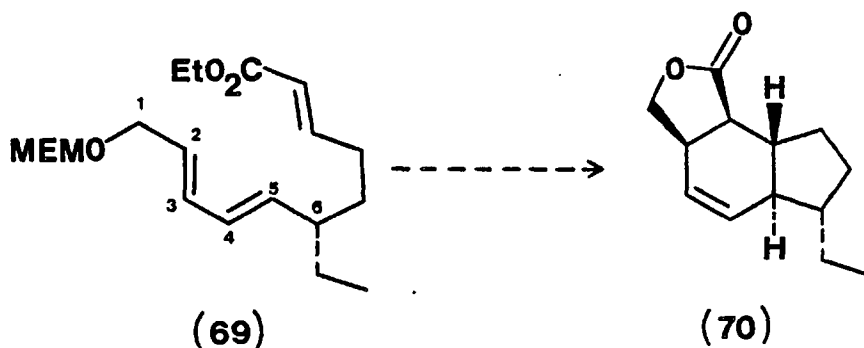
intermediates, often preferably at as early a stage in the synthesis as possible to prevent unnecessary waste of reagents, has been used throughout the history of organic synthesis.⁸¹ For the most unambiguous and highest optical purity the use of readily available optically active starting materials such as carbohydrates, terpenes, and amino acids offers perhaps the simplest solution. However, often the required chirality in desired products cannot be related to available chiral starting materials without lengthy manipulation such that syntheses from optically active starting materials are often rather lengthy.⁵⁰ Microbiological transformations are playing an important role in producing some very useful optically active chiral building blocks such as S-(+)- β -hydroxyisobutyric acid, used by Evans⁷ and Still⁹ in their calcimycin (A-23187) and monensin syntheses.⁸² In recent years asymmetric synthesis, involving the induction of absolute configuration through the use of optically active chiral reagents in reactions involving the creation of new asymmetric centres, has become increasingly important.⁸³ Early drawbacks with poor optical yields may be overcome in future years by the use of more sophisticated reagents and a greater understanding of transition state interactions.

Relatively few asymmetric syntheses produce products of necessary optical purity for natural product synthesis (>90% enantiomeric excess (ee)). Among the most generally useful today are the Sharpless enantioselective epoxidation of allylic alcohols, a powerful method capable of producing useful chiral synthons of very high optical purity;⁸⁴ the enantioselective alkylations and aldol reactions of Evans,⁸⁵ Masamune,^{86,37} and Meyers;⁸⁷ and asymmetric hydroboration using chiral boranes.⁸⁸

An important concept in enantioselective synthesis is the chiral pool,⁸⁹ the readily available optically active building blocks, whether

commercially available, conveniently prepared from commercially available materials, microbially derived, or produced by asymmetric synthesis.

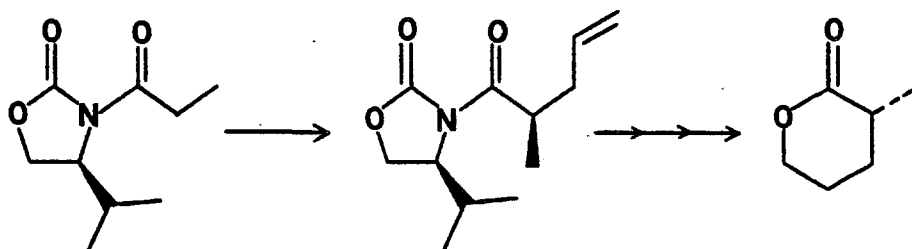
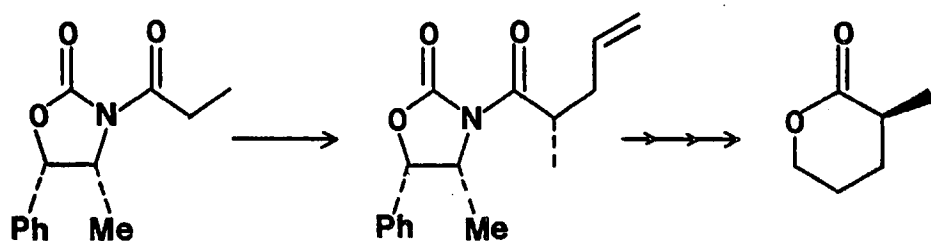
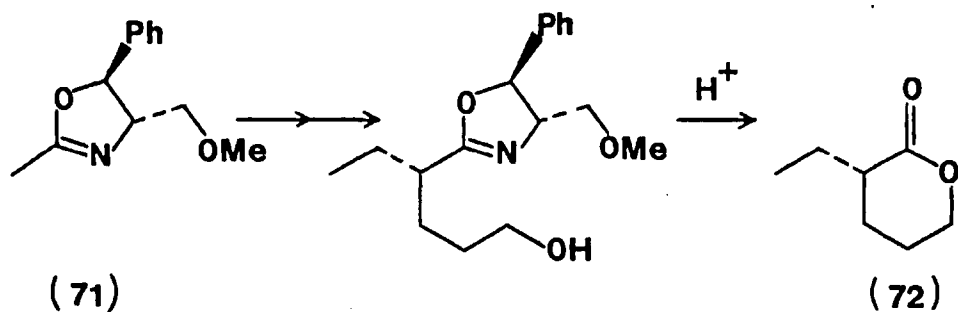
Our planned synthesis of the required enantiomer of the lactone (21) ((70)) involved using the correct absolute stereochemistry at C-6 of the optically active ethyl (*E,E,E*)-1-(β -methoxy)ethoxymethoxy-6(*S*)-ethyl-2,4,9-undecatrienoate (69) to induce the natural absolute configuration at the other 4 chiral centres formed in the stereocontrolled intramolecular Diels-Alder reaction of (69).



The problem was thus simplified to the preparation of an optically active intermediate early in the synthesis of the trienoate and carrying this intermediate through to (69) without racemisation.

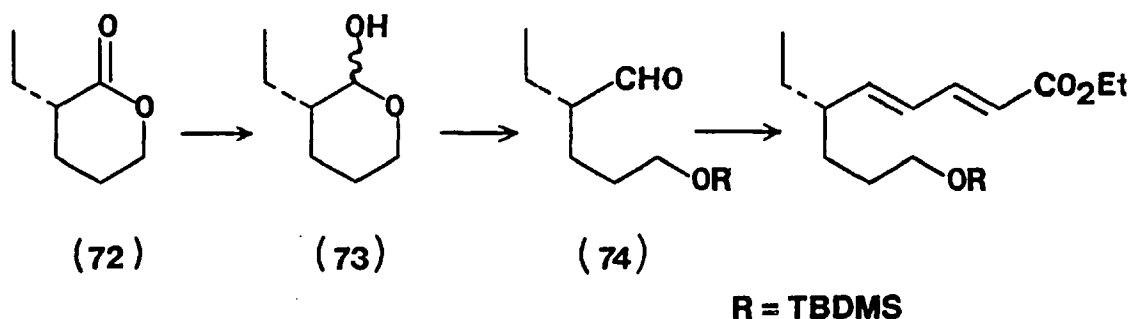
Although Meyers has reported an asymmetric synthesis of 2-substituted δ -valerolactones *via* the use of the readily available optically active chiral oxazoline (71), the reported ee's for the lactones prepared in this manner were only 52-72%.

Evans has just published an asymmetric synthesis of 2-substituted δ -valerolactones in high ee as shown in Scheme 15 below.^{85e}



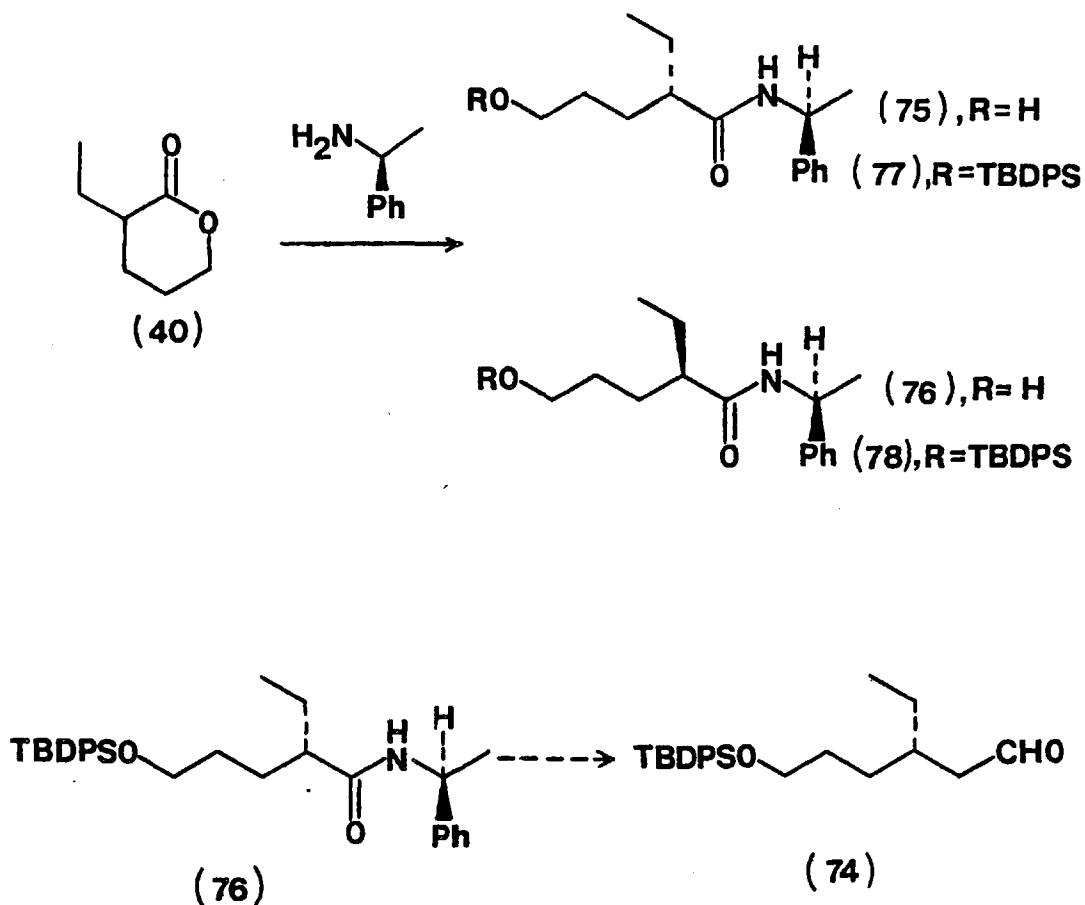
Scheme 15

Optically active 2-substituted δ -valerolactones have been reported to be very susceptible to racemisation.⁹⁰ In the synthesis of the optically active lactone (70) from (+)-2(S)-ethyl- δ -valerolactone racemisation is possible during the first four steps although there is good precedent for the use of optically active α -substituted aldehydes in Wittig type reactions without racemisation.⁹¹ Particularly in the



preparation of the aldehyde (74) from the lactols (73), it seems highly likely that the conditions (imidazole/DMF) could lead to extensive racemisation. It was thus decided that an alternative preparation of the optically active aldehyde (74) was required. For the reasons of brevity and incorporation of the maximum possible optical purity a modified resolution approach was decided.

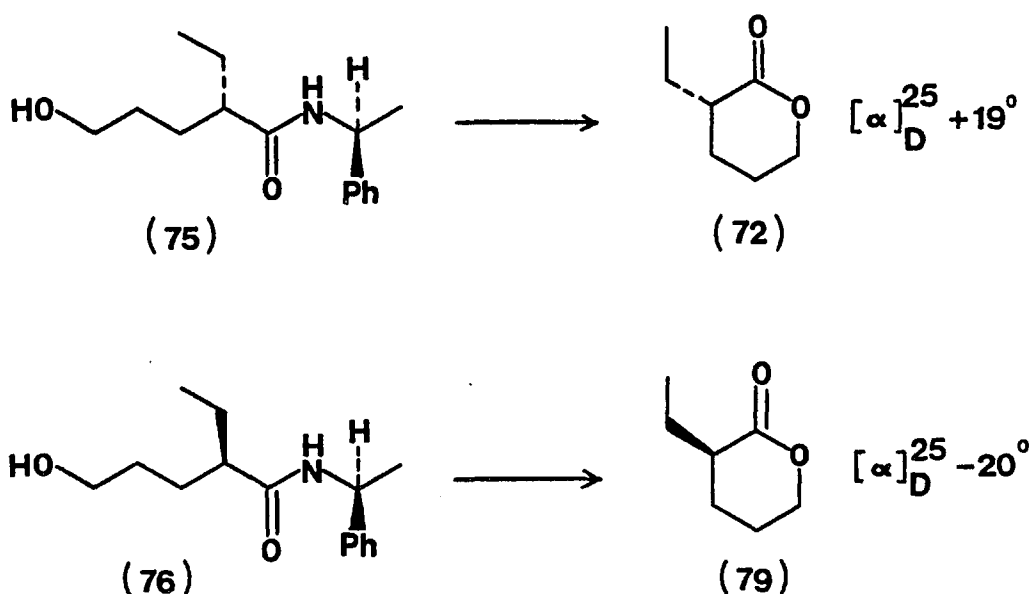
The method of Helmchen and Youssef⁹⁰ for the optical resolution of 2-substituted γ -butyrolactones *via* diastereomeric amide formation was found to give (+)-2(S)-ethyl- δ -valerolactone of very poor optical purity (*vide infra*). However, due to the ready availability of the 2-diastereomeric amides, (-)-(75) ($[\alpha]_D^{25}$ -88.9°) and (-)-(76) ($[\alpha]_D^{25}$ -119.1°) (prepared by treatment of 2-ethyl- δ -valerolactone with 1(S)-phenylethylamine and 2-hydroxypyridine in toluene at reflux and readily separated by chromatography) it was hoped that the amide (-)-(75) could be used to prepare the aldehyde (74). Reductive cleavage of the protected 4(S) amide (-)-(77) ($[\alpha]_D^{25}$ -39.4°), prepared in 82% (based on the 2(S)-ethyl- δ -valerolactone enantiomer) overall yield from 2-ethyl- δ -valerolactone, by treatment of the amide (75) with *t*-butyldiphenylchlorosilane and imidazole in DMF, was expected to give the required aldehyde (74).



High field (250 MHz) ^1H n.m.r. showed that no epimerisation occurred during the preparation of the silyl derivatives. The corresponding 4(R) amide(-)-(78) ($[\alpha]_{\text{D}}^{25} -50.4^\circ$) was prepared in the same way, also in 82% overall yield.

To ascertain which of the amides prepared from 2-ethyl- δ -valerolactone, (75) and (76), had the required 4(S) configuration, the amides were converted to the known optically active (+)-2(S)-ethyl- δ -valerolactone (72) and (-)-2(R)-ethyl- δ -valerolactone (79). Treatment with 1N sulphuric acid in 1:1 dioxan-water at 80-90 $^\circ\text{C}$, followed by heating with *p*-toluenesulphonic acid in toluene to cyclise the intermediate hydroxy acids, gave the lactones for correlation. As well as the (although non-optimised) low yields (35-55%) of optically active lactones

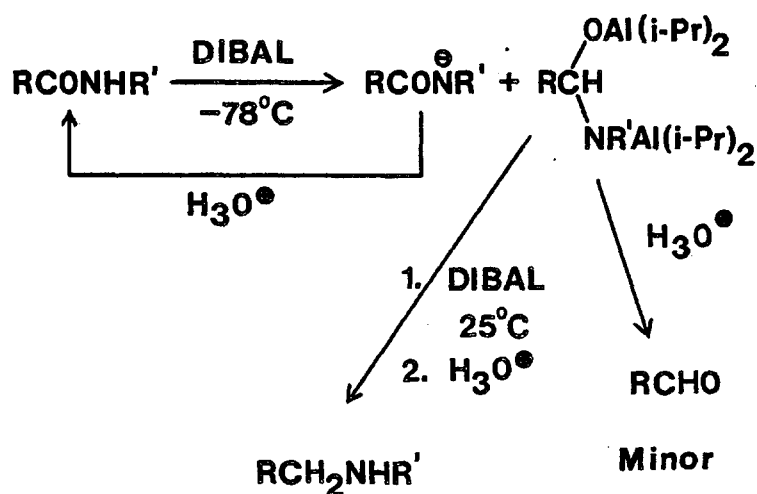
thus prepared, extensive racemisation occurred in the hydrolysis of the amides. Based on the figure of -45.3° for the $[\alpha]_D$ of 2(R)-ethyl- δ -valerolactone of 61% ee reported by Meyers,^{87b} the lactones (72) and (79) prepared by hydrolysis of (75) and (76) were of only 26-27% ee.



The advantages of effecting reductive cleavage of the amide (77) to give the aldehyde (74) would ideally be to (a) condense the two steps of amide hydrolysis and lactone reduction to the one of reductive cleavage, (b) cut out the slightly poor step of lactol silylation and separation of the recyclable minor product, and perhaps most importantly, (c) eliminate the possibility of racemisation inherent in the two steps of DIBAL reduction and silylation in the preparation of (74) from (+)-2(S)-ethyl- δ -valerolactone.

Unhindered N,N-dimethylamides are reported to be smoothly reductively cleaved to aldehydes by lithium triethoxyaluminium hydride,⁹² DIBAL,⁹³ or disiamylborane⁹⁴ in fair to good yields. Extensive searching failed to reveal a literature method for reduction of 2° amides to aldehydes, however, and attempts with 2° amides (75) and (76) showed that direct access to the aldehyde (74) was not available by such a reaction.

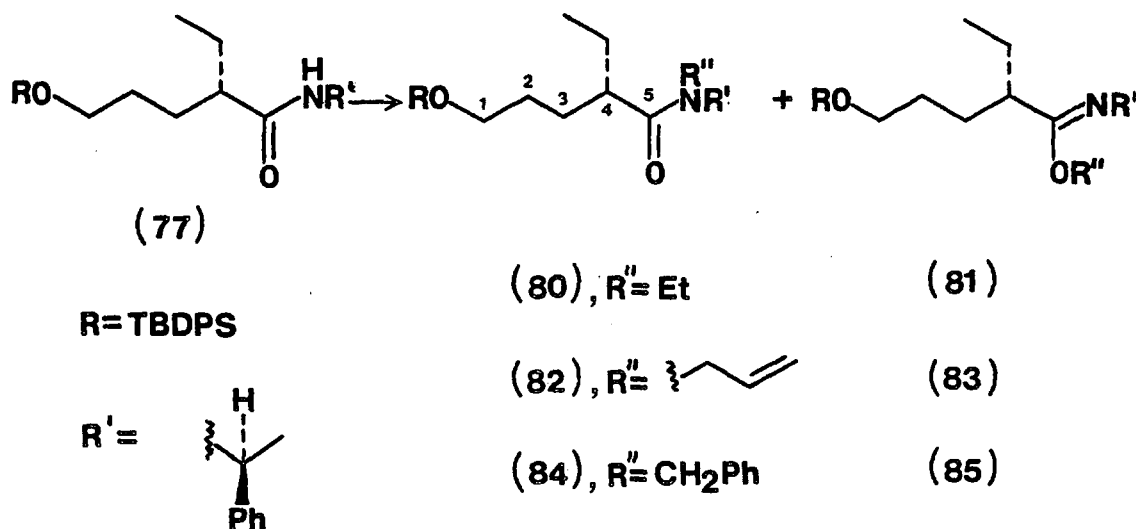
Treatment of (75) or (76) with from 1.0 to 4.0 equiv. of DIBAL in toluene at -78° gave, even after prolonged reaction times, only 10-20% of the aldehyde by t.l.c.. If the reaction mixtures were allowed to warm to room temperature the aldehyde was shown to be virtually absent on t.l.c. analysis of quenched (2N sulphuric acid) aliquots. Treatment with sodium di(β -methoxy)ethoxyaluminium hydride (RED-Al) or the RED-Al-morpholine complex⁹⁵ led, apparently, to only reaction with the amide N-H, with regeneration of starting amide only on work up. Small amounts of amine were detected on work up of the DIBAL reductions that were allowed to warm to room temperature. The problem with these 2^o amides would, as shown in Scheme 16, appear to be that any reduction of the amides was only the minor event, with the major product being the amide anion which was stable to any further reduction up to room temperature.



Scheme 16

It was hoped, however, that by eliminating the possibility of anion formation through modification of the amides, reductive cleavage, albeit in 2 steps, of (77) to (74) could be achieved as an efficient process. A mild, non-epimerising, N-alkylation procedure was thus sought.

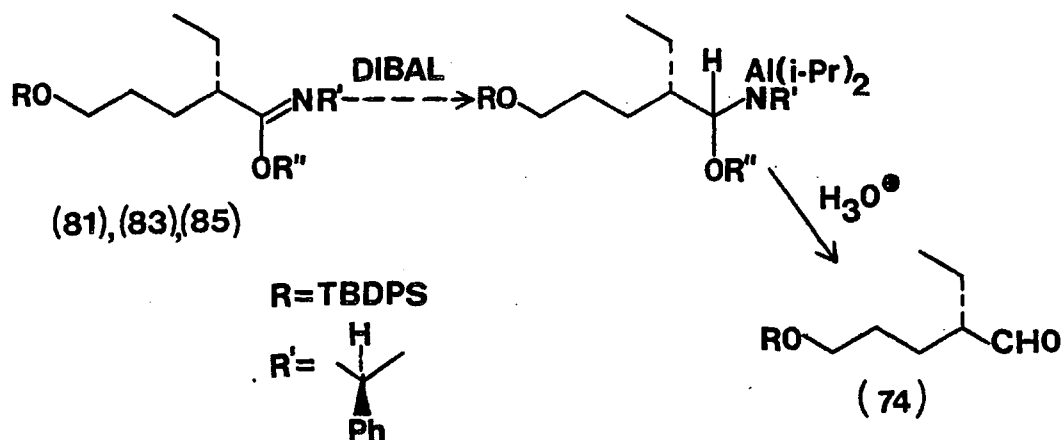
The standard literature conditions involving alkylation of the 2^o amide anion, formed by treatment with sodium hydride in refluxing xylene for long periods, with an alkyl halide in refluxing xylene for equally long periods were considered to be too harsh and would probably lead to epimerisation or worse.⁹⁶ Fortunately, a recently published method for mild PTC N-alkylation of unhindered 2^o amides was available.⁹⁷ Although the amides (77) and (78) were rather hindered, with a 3^o centre α to the amide carbonyl group and the bulky N-phenylethyl group, a series of N-alkyl derivatives of (77), as shown in Scheme 17, were prepared using this method. The amide was vigorously stirred with an alkyl halide, powdered sodium hydroxide, powdered potassium carbonate, and a catalytic amount of tetra-n-butylammonium hydrogen sulphate in refluxing benzene.



Scheme 17

With unhindered amides this method was reported to give exclusive N-alkylation.⁹⁷ However, with the hindered amide (77) ethyl bromide gave a 3:1 mixture of the inseparable N-alkyl and O-alkyl products (80) and (81) in 73% yield (96% based on recovered (77)). Methyl iodide is not a suitable electrophile for these alkylations due to

poisoning of the catalytic system by liberated iodide. Allyl bromide gave a 4:1 mixture of the inseparable (82) and (83) in 86% yield. The more bulky benzyl bromide gave a 66% yield of a 70:30 mixture of (84) and (85). The presence of these contaminating O-alkyl products, revealed by a quartet absorption corresponding to H-1' which occurred in (81), (83), and (85) at 1 ppm higher field than for the amides (80), (82), and (84) in the ^1H n.m.r. spectra, due to greater deshielding in the amides, was not expected to be a problem. It was hoped that the O-alkylated (81), (83), and (85) would give aldehydes on partial reduction and acid hydrolysis, similar to the amides. Interestingly,



this alkylation reaction was found to be a diastereodifferentiating reaction with the amides (77) and (78). Reaction of the 4(R) amide (78) with ethyl bromide, under identical conditions used for the N-alkylation of the 4(S) amide (77), gave, as the major product, the highly crystalline ethyl ether (86), in 38% yield after flash chromatography.

This totally unexpected product, resulting from an unusual preferred base catalysed desilylation rather than the desired N-deprotonation would seem to reflect a more hindered nitrogen in the 4(R) amide (78). An examination of the expected preferred conformations in solution of the amides (77) and (78), A and B in

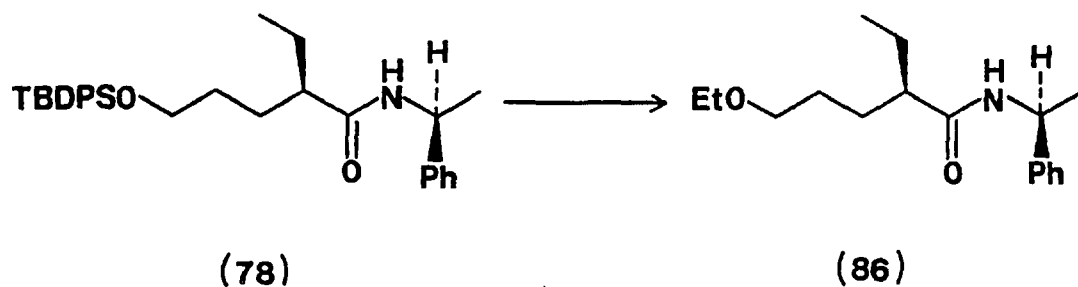


Diagram 11 below, revealed that in the 4(S) amide (77) the ethyl and methyl groups flanking the amide group lie on the same face of the molecule, leaving the other face exposed. However, in the 4(R) amide (78) one face of the amide group is shielded by the ethyl group while the other is blocked by the methyl group.

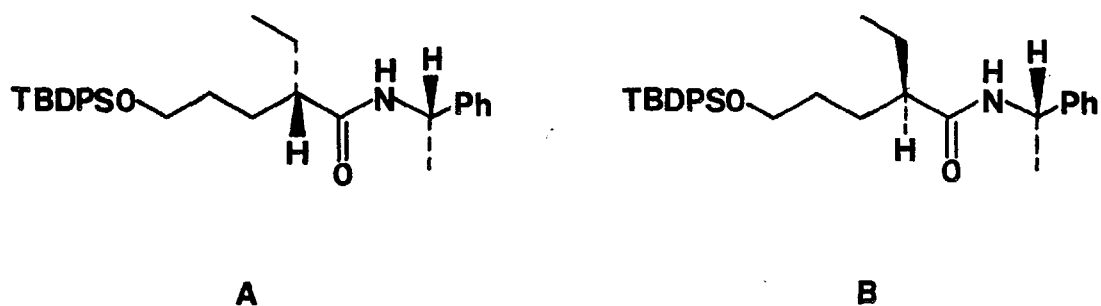
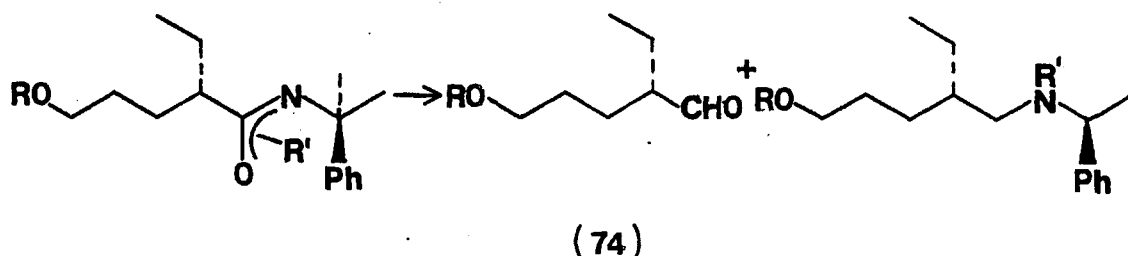


Diagram 11

This dramatic change of chemoselectivity in the alkylation of (78), in view of the apparently minor difference between A and B in Diagram 11, shows how finely balanced the reactions of these hindered amides are.

Unfortunately the alkylated derivatives (80)-(85) did not prove to be useful precursors of the desired aldehyde (74) as smooth reductive cleavage could not be achieved.

Treatment of the ethyl derivatives (80) and (81) with 1.1 equiv. of DIBAL at -78° , followed by overnight stirring at room temperature, lead to approximately 20% clean reduction to the aldehyde (74) which was isolated in 18% yield after acid work up and flash chromatography. This sample of the aldehyde gave an optical rotation of $+2.4^{\circ}$ which, by analogy with the (+)-2(S)-ethyl- δ -valerolactone, was in the right direction. However, any attempt to increase the amount of reduction by using more DIBAL or raising the initial reaction temperature to 0°C lead to increasing amounts of the over-reduction product, the amine (87). At best, with 2.2 equiv. of DIBAL at 0°C , about 50% reduction of the amide to a ca. 1:1 mixture of aldehyde and amine was produced.



$\text{R} = \text{TBDPS}$

Treatment of the allyl derivatives (82) and (83) with 2 equiv. of DIBAL at 0°C to room temperature gave a 22% isolated yield of the aldehyde (74), with no observable optical rotation, and 31% of the amine (88).

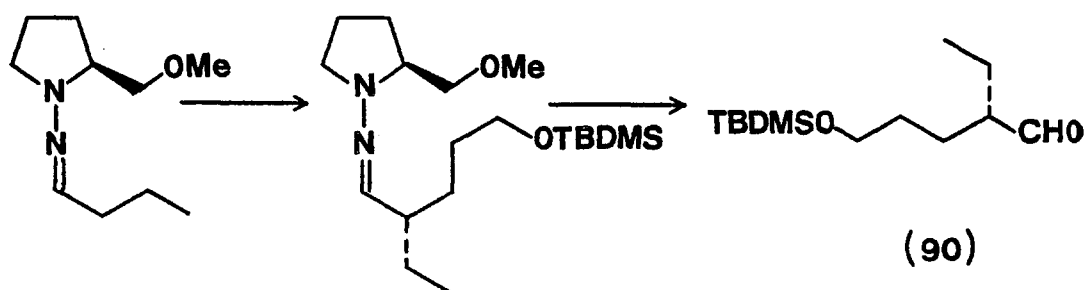
2.4 Equiv. of DIBAL at 0°C to room temperature gave an isolated yield of 26% of the aldehyde, again with no optical rotation, and 40% of the amine (89) from the benzyl derivatives (84) and (85).

All the alkylated derivatives were stable to RED-Al, even at room temperature. Due to the apparent sensitivity to steric effects of amide to aldehyde reductions, reported by Brown and co-workers^{92,94}, and in the light of our results we decided that clean reduction of these hindered amides was not a viable method for aldehyde preparation.

As the aldehyde prepared in poor yield (18-26%) by our attempts only once gave any optical rotation it seemed that rapid racemisation occurring during acid work up was also a major problem with this method.

At this time we achieved an efficient resolution of the lactone (21). Thus, as the desired lactone enantiomer (70) was now readily available (*vide infra*), further studies towards an enantioselective synthesis of the 6(S)-trienoate (69) were abandoned.

Nicolaou recently reported the preparation of the optically active aldehyde (90) *via* the Enders procedure⁹⁸ of asymmetric hydrazone alkylation outlined in Scheme 18 below.¹

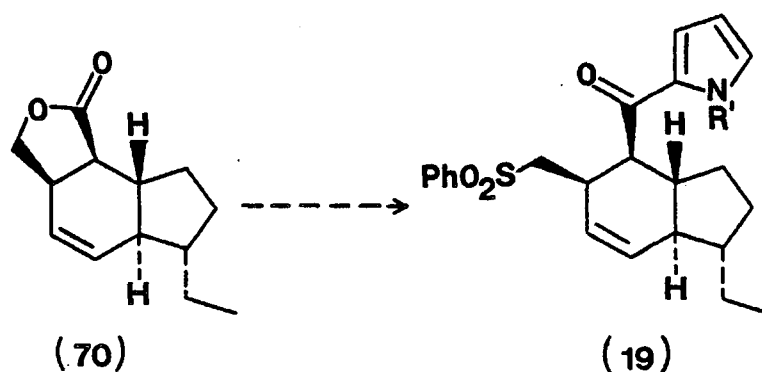


Scheme 18

The aldehyde (90) was carried through to the optically active lactone (70) ($[\alpha]_D^{25} + 113^0$) which was subsequently shown by Nicolaou to be of only 82% ee upon elaboration and coupling to optically pure left hand side fragments. Nicolaou attributed this to partial racemisation of the aldehyde (90) during handling, which was consistent with our results.

3. ENANTIOSELECTIVE SYNTHESIS OF THE RIGHT HAND SIDE SULPHONE

With the racemic tetrahydroindan lactone (21) now readily available and the attempted enantioselective synthesis (*vide supra*) of the required lactone enantiomer (70) with the correct natural configuration proving unsuccessful, methods for (a) resolving the lactone (21) and (b) converting it efficiently to the sulphone (19), required for Julia coupling with the left hand aldehyde (18), were investigated.



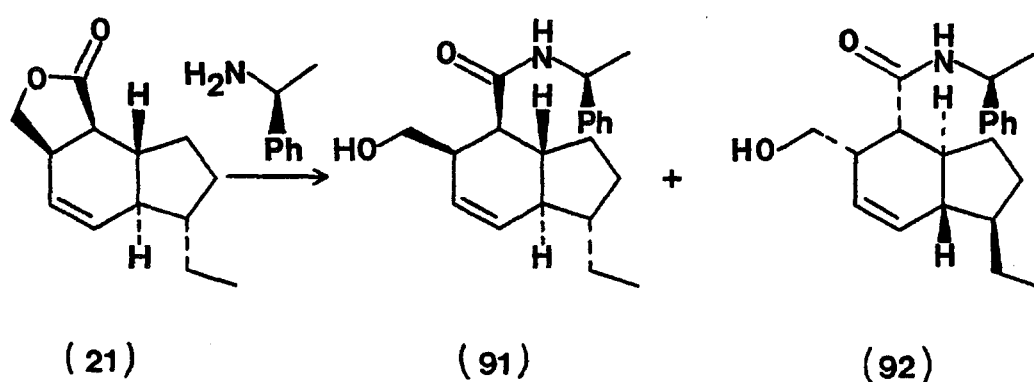
3.1 Optical Resolution of the Tricyclic Lactone (21).

As was discussed earlier in Section 2, optical resolution is often best carried out at as early a stage in a synthesis as possible. However, in our synthesis of (21), beyond the initial stages the chiral

centre is too far removed from a functional group, capable of acting as a handle for resolution, to enable separation of diastereomers.

The problems encountered in early resolution, outlined in Section 2, caused us to resort to resolution of the lactone (21) itself. As (21) is readily available in good overall yield in a relatively few number of steps, we decided that this rather 'late' resolution could be justified if it was convenient and efficient. We were also interested in studying the biology of an X-14547A diastereomer prepared using the 'wrong' right hand side enantiomer (*vide infra*). Thus the unnatural enantiomer of (21) was also required. This further justified our late resolution.

Following the procedure of Helmchen and Youssef,⁹⁰ treatment of the lactone (21) with (-)-1(S)-phenylethylamine and 2-hydroxypyridine in refluxing toluene for 6h clearly lead to about 60% conversion of the lactone to the diastereomeric amides (91) and (92). The amides were conveniently isolated in near quantitative yields (based on recovered lactone (21)) after easy flash chromatography.



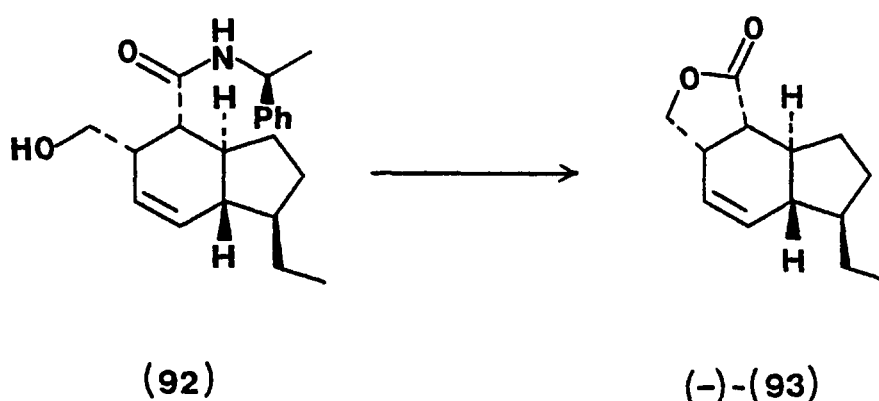
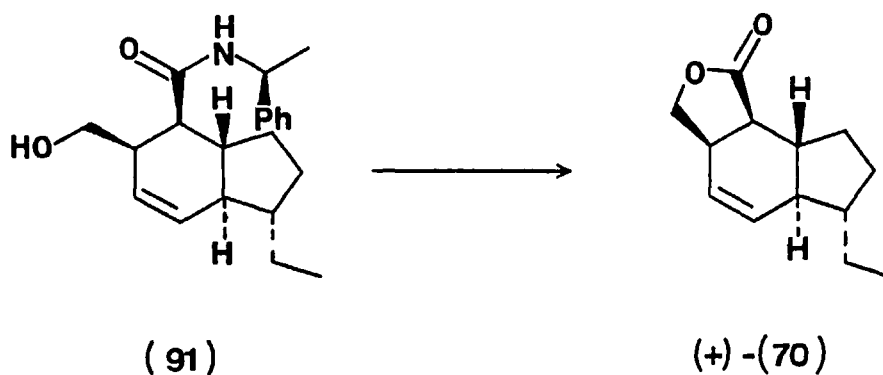
Although the δ -lactone (40) was completely converted to the corresponding amides (75) and (76) under the Helmchen and Youssef conditions, the amides (91) and (92) appeared to be at equilibrium at about 60-70%

conversion of the lactone (21). Leaving the reaction for longer periods sometimes lead to complete reversal of amide formation, particularly in smaller scale reactions when solvent loss due to evaporation was significant, with the lactone being isolated in high yield. Varying the reaction temperature or the quantities of amine or catalyst had only adverse effects on the yield of the amides. No further attempts at improving the conversion to the amides, apart from the addition of small amounts of 4-N,N-dimethylaminopyridine (up to 0.1 mole %) (which had no apparent effect on the equilibrium), were made.

Effective quantitative resolution of the lactone was completed by treatment of either of the amides with 1N sulphuric acid in 1:1 water-dioxan for 1h at 80°C. The dextrorotatory lactone (+)-(70) ($[\alpha]_D^{25} + 136^\circ$) was prepared in 98% yield from the less polar (t.l.c.) diastereomeric amide (91). The more polar amide (92) gave the laevorotatory lactone (-)-(93) ($[\alpha]_D^{25} -136^\circ$), also in 98% yield. The optically active lactones (+)-(70) and (-)-(93) were isolated as crystalline solids, m.p. 83-84°C (cf. 67.5 - 68.5°C for the racemic lactone (21)), without the need for chromatography.

Lactone (+)-(70), with the correct natural absolute configuration, prepared by Nicolaou with an ee of 82% gave a rotation of + 113°. Our samples of the resolved lactones (+)-(70) and (-)-(93) were thus, as expected, of very high optical purity (ca. 99% ee).

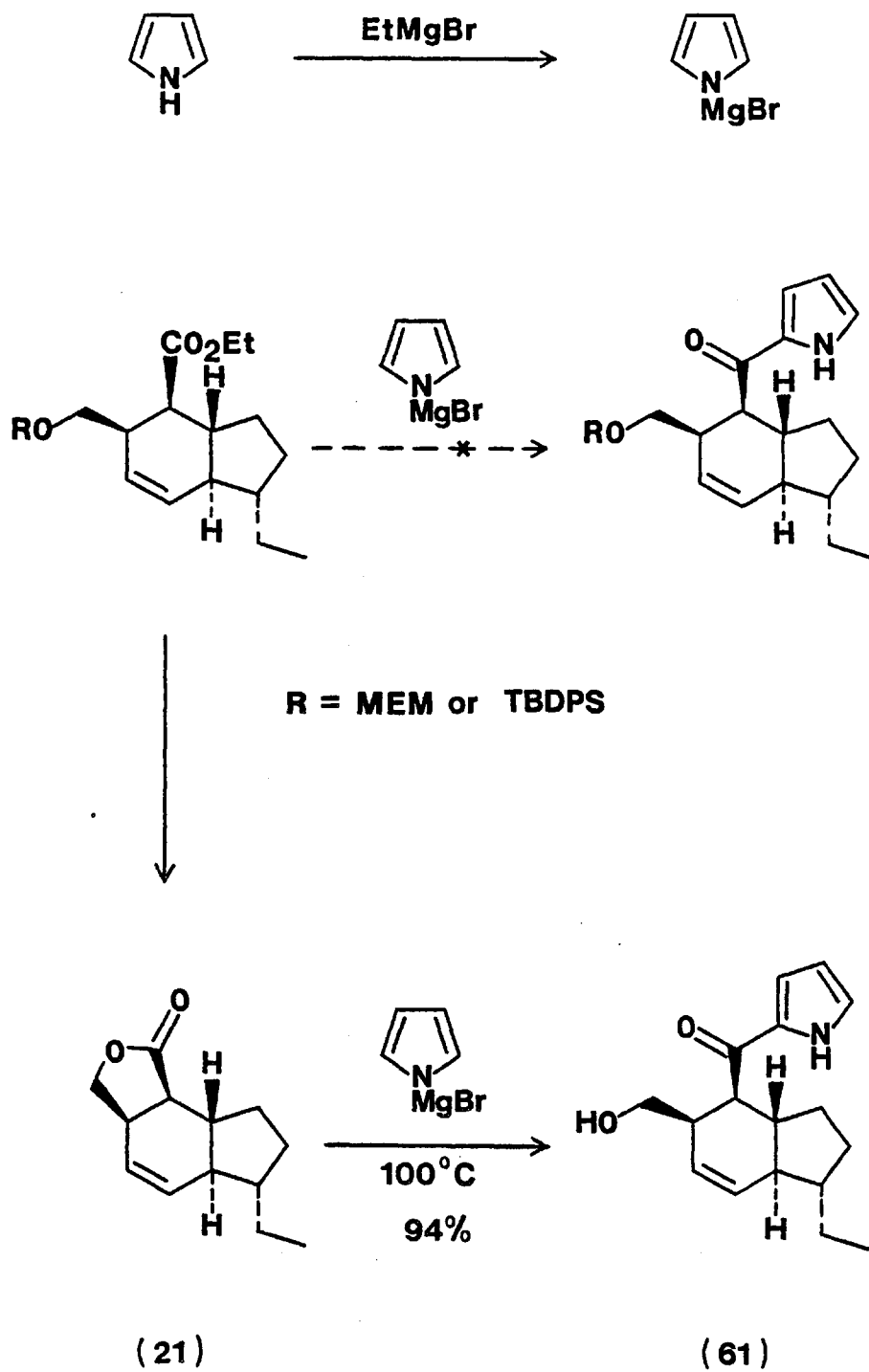
Although only 60% of the lactone (21) could be resolved during each run, due to the overall quantitative nature of the resolution, this was a very convenient method for preparing the lactones (+)-(70) and (-)-(93) of excellent optical purity.



3.2 Preparation of ($\pm$)-4 β -(2'-Pyrrolylcarbonyl)-1 α -ethyl-3 α ,4,5,7 α -tetrahydroindan-5 β -methanol (61).

Two similar routes to the desired right hand side sulphone, involving incorporation of an unprotected 2-pyrrolylcarbonyl moiety, from the tricyclic lactone (21) or its precursors the esters (55) and (66) were considered.

According to the results of Bean, pyrrolyl Grignards are smoothly regioselectively acylated at the 2 position by simple aliphatic esters in refluxing diethyl ether solutions.⁹⁹ Based on this our early plan



Scheme 19

was to introduce the 2-pyrrolylcarbonyl moiety by reaction of the esters (55) and (66) with pyrrolylmagnesium bromide, as shown in Scheme 19. However, both of the esters (55) and (66) were remarkably unreactive even after refluxing with an excess of pyrrolylmagnesium bromide in diethyl ether for extended periods. Using the forcing conditions of 100°C in toluene, recommended by Hobbs and coworkers¹⁰⁰ for the alkylation of pyrrolyl Grignards with alkyl halides, no significant reaction with either (55) or (66), before complete decomposition of the Grignard reagent, was observed.

This unreactivity of the esters (55) and (66) was perhaps not surprising in view of their hindered nature, with the bulky α -tetrahydroindan moiety and the *cis* aligned protected hydroxymethyl group.

Fortunately, the racemic lactone (21) reacted smoothly with pyrrolylmagnesium bromide, prepared by treatment of pyrrole with ethylmagnesium bromide at 0°C, in 3:1 toluene-diethyl ether at 100°C, to give the desired crystalline hydroxy pyrrolylcarbonyl (61), m.p. 88-90°C, as the only product, in 94% yield after flash chromatography.

The i.r. ($\nu_{\max}$ 1620 cm^{-1} , C=O str.) and ^1H n.m.r. data for the hydroxy pyrrolylcarbonyl (61) closely matched the data for natural X-14547A.¹⁷ As shown in Diagram 12 below, a comparison of the region δ 5 - 7.5 reveals that the absorptions corresponding to the olefinic and pyrrole C-H protons are virtually identical in X-14547A and (61).

The hydroxy pyrrolylcarbonyl (61) crystallised from petrol as well formed colourless rods. X-Ray crystallographic structure analysis confirmed the stereochemistry at all five chiral centres of (61). Both the equatorial conformation of the ethyl and 2-pyrrolylcarbonyl groups and the pseudo axial nature of the hydroxymethyl moiety was clearly shown in the X-ray structure (Diagram 13). The *syn*-planar conformation of the 2-pyrrolylcarbonyl group was also apparent.

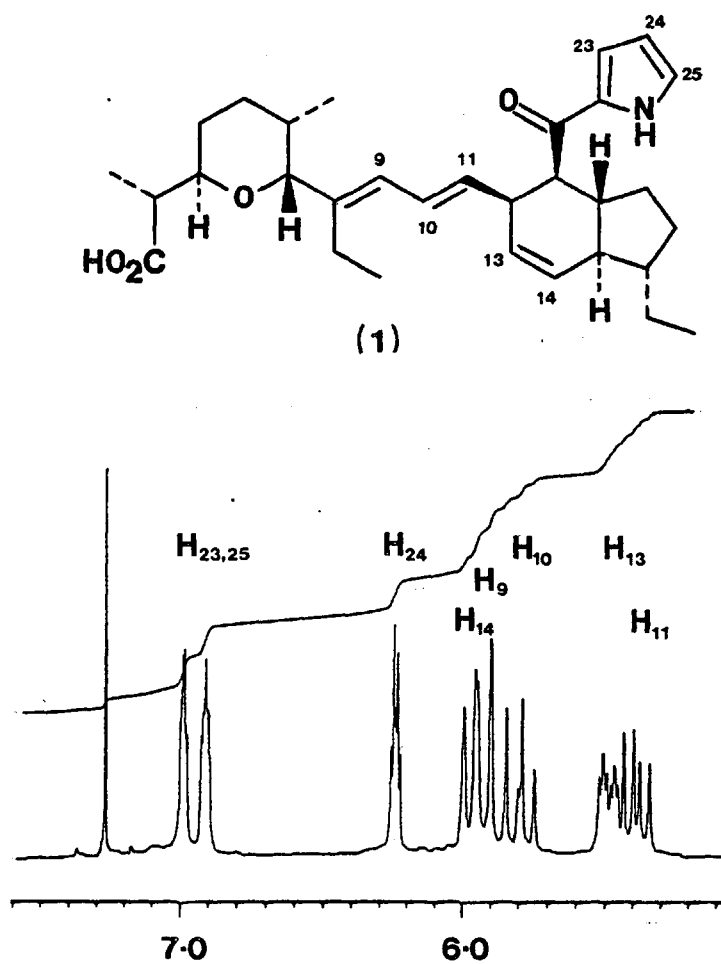
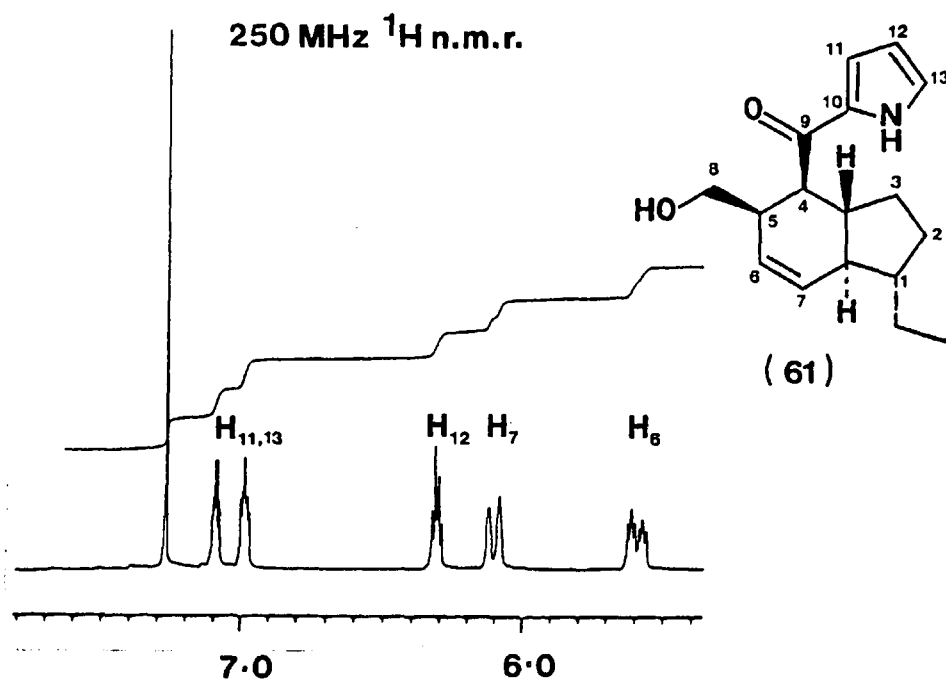


Diagram 12

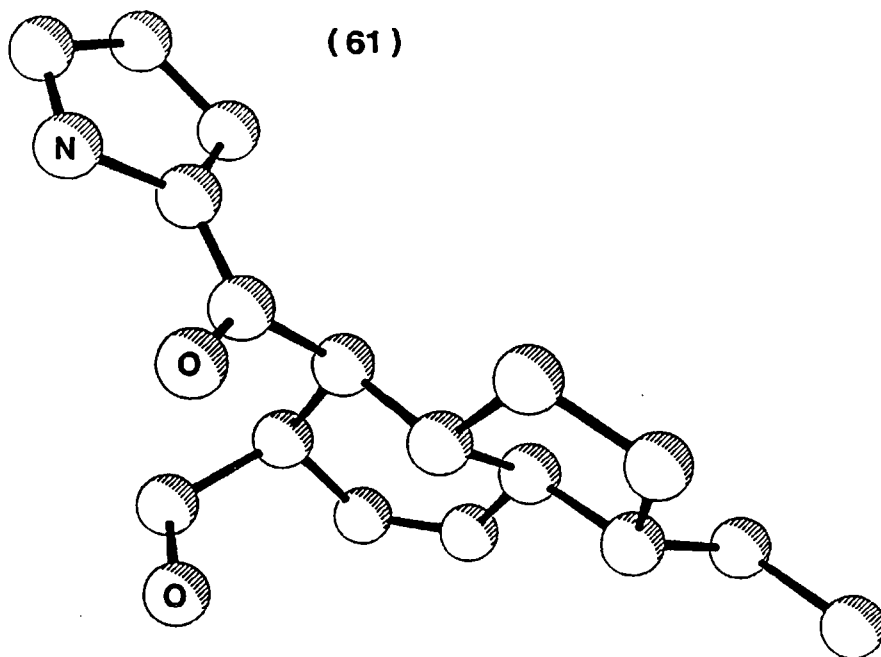
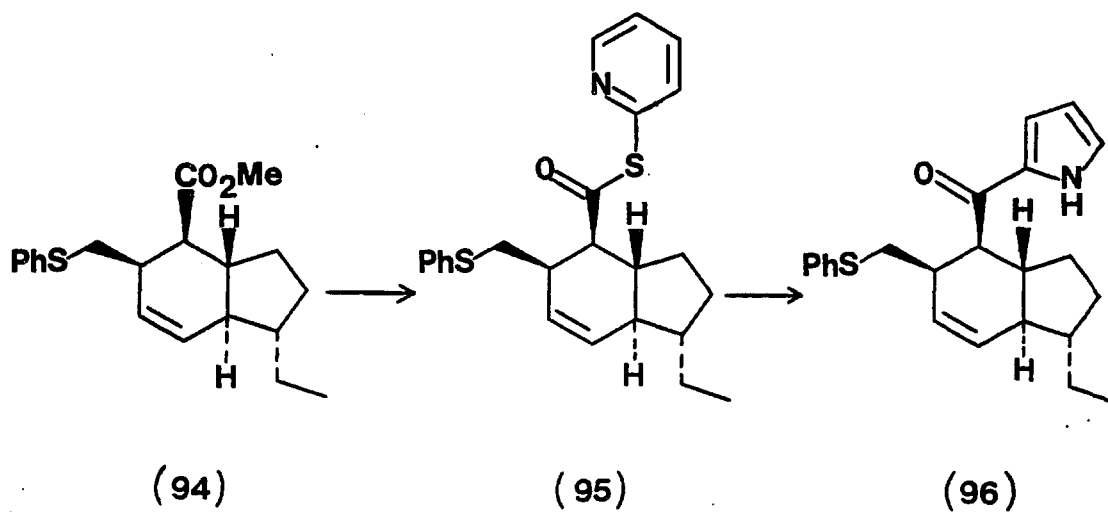
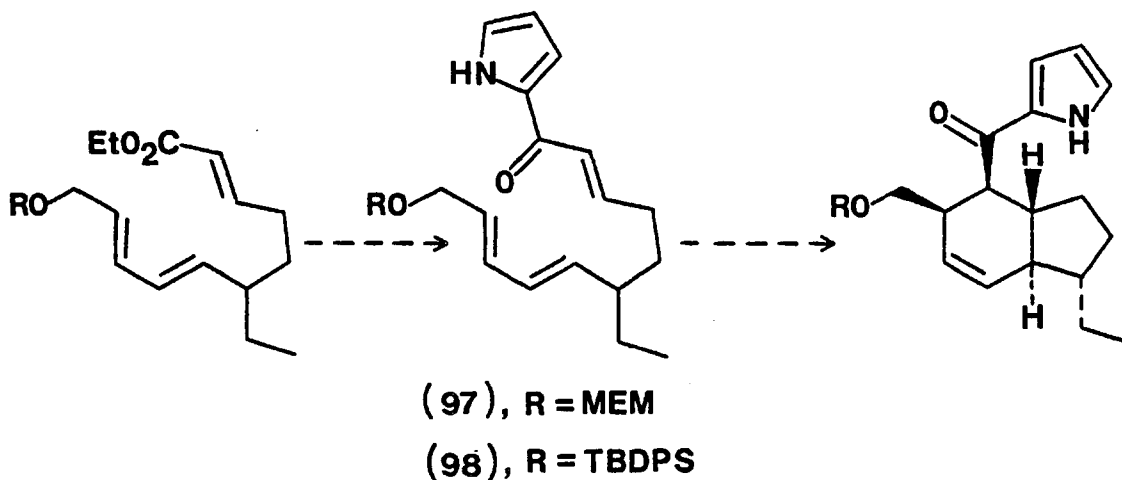


Diagram 13

Nicolaou recently published a solution to the preparation of hindered 2-pyrrolylcarbonyls by reaction of pyrrolylmagnesium chloride with the reactive 2-pyridylthioesters at -78°C .¹⁰⁹ Thus hydrolysis of the ester (94), conversion to the 2-pyridylthioester (95), and reaction with pyrrolylmagnesium chloride gave the 2-pyrrolylcarbonyl (96).¹⁰⁹



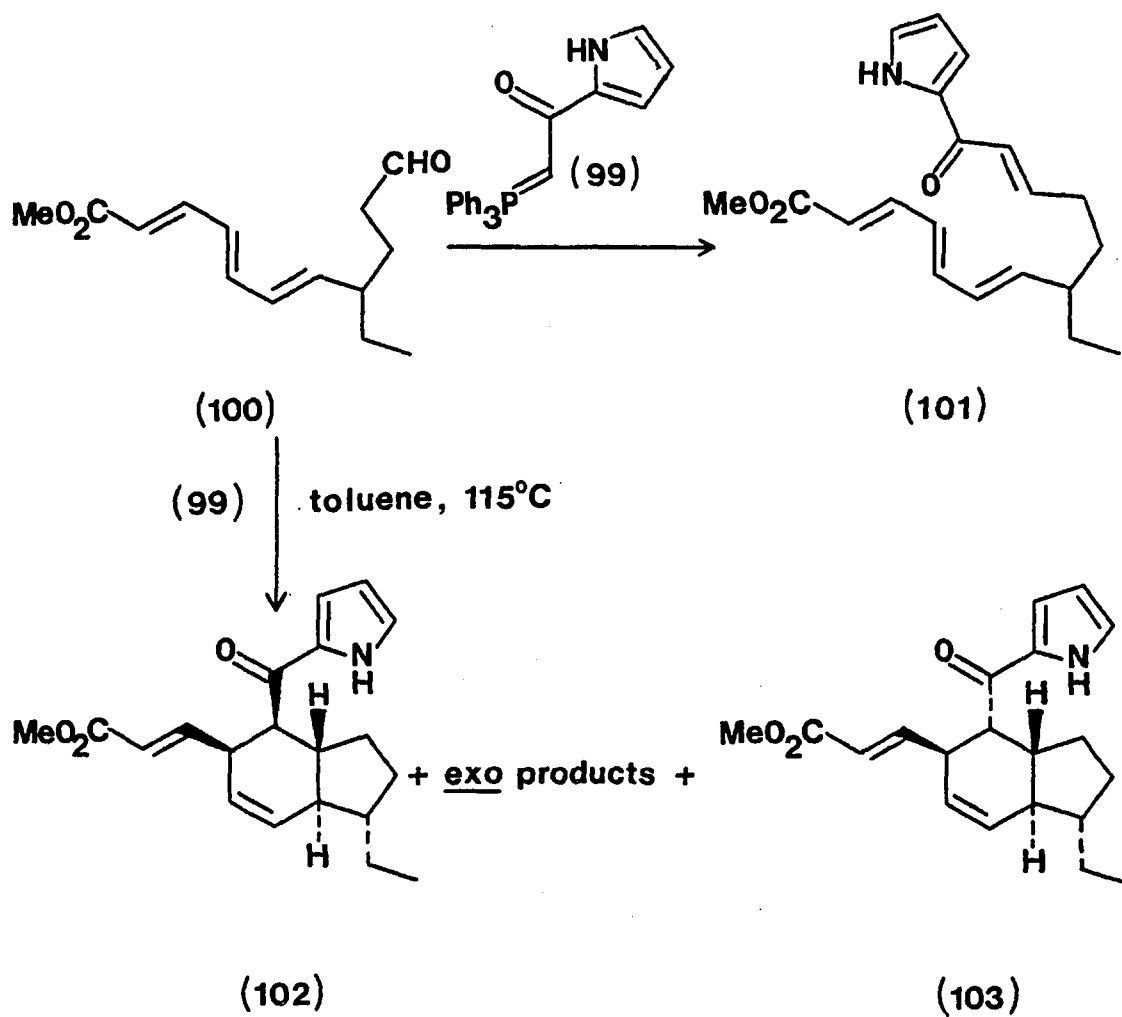
An alternative route to the hydroxy pyrrolylcarbonyl (61), involving cyclization of the α,β -unsaturated pyrrolylcarbonyl trienes (97) or (98), was not realised due to difficulties found in the preparation of (97) or (98).



Attempted reaction of the trienoates (54) and (65) with pyrrolylmagnesium bromide in diethyl ether or toluene from room temperature up to 100°C lead to, at best, mixtures of unstable (t.l.c.) products or complete decomposition. In view of the fact that this approach would not involve the optically resolvable lactone (21) no further efforts were expended.

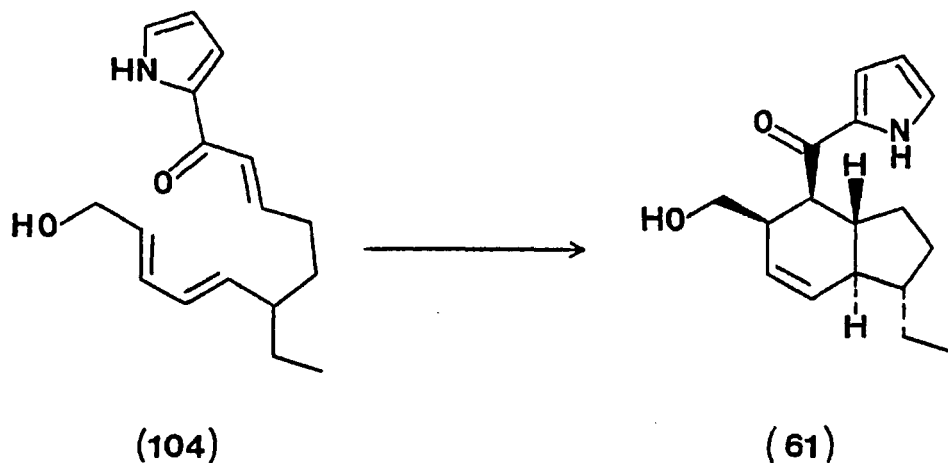
Working along similar lines, Roush obtained the phosphorane (99) by base treatment of the corresponding phosphonium salt, prepared from 2-(α -chloroacetyl)pyrrole and triphenylphosphine.²⁴ However, this ylid, possibly due to its poor solubility in organic solvents, was rather unreactive towards aldehydes. As shown in Scheme 20 below, reaction of the ylid (99) with the aldehyde (100) in dichloromethane for 4 days gave only 57% of the desired *trans* α,β -unsaturated 2-pyrrolylcarbonyl (101). Alternatively, heating the ylid (99) and the aldehyde (100) in refluxing toluene for 25h gave a 67% yield of cyclized products with a ratio of 51:11 *endo* (102) to *exo* products and 5% of the *cis*-

dienophile derived (103).²⁴



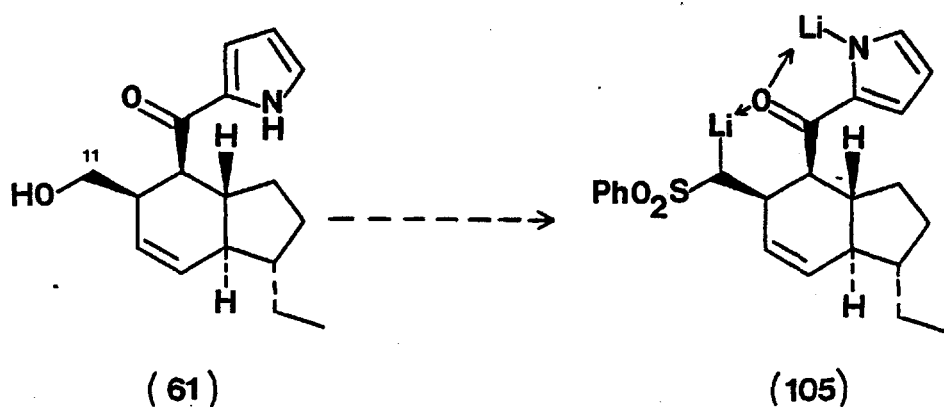
Scheme 20

Roush also found that heating of the triene (104) for 17h in toluene at reflux gave a 67% yield of a mixture of isomers of which (61) was identified as the major (>75%) product by high field (250 MHz) ^1H n.m.r..²⁴



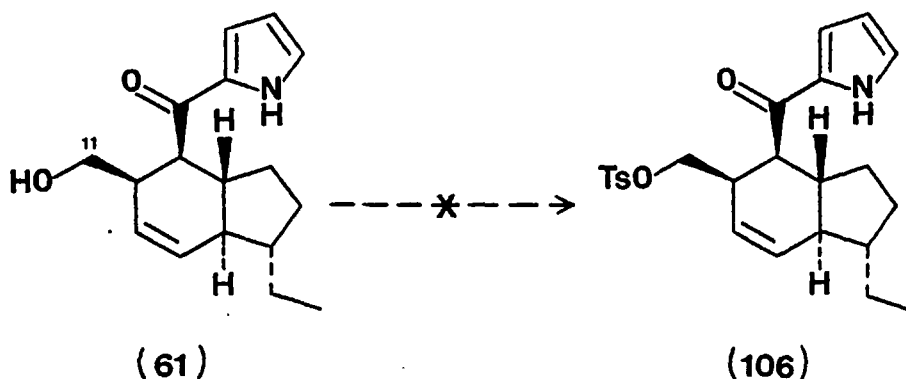
3.3 Attempted Tosylation of the Hydroxy Pyrrolylcarbonyl (61).

An initial plan, involving the use of a dianion (105) derived from the sulphone (19), R'=H, in the proposed Julia coupling reaction, necessitated manipulation of the hydroxyl functionality of (61).



The intention was to create the phenylsulphone functionality, in a standard fashion, by chemoselective oxidation of a phenylsulphide, prepared by displacement of a leaving group at C-11 (X-14547A numbering) by phenylsulphide anion.¹¹⁰

Surprisingly, however, it was found impossible to prepare a compound with the desired leaving group at C-11 *via* tosylation of the hydroxyl group in (61).



Treatment of (61) with 1 - 1.5 equiv. of *p*-toluenesulphonyl chloride in pyridine at 0°C for 2h lead to clean conversion of about 55% of the alcohol to a single, less polar, product (t.l.c.). However, after an aqueous work up only about 20% of the less polar product was present. ¹H N.m.r. did not prove useful in the analysis of the crude reaction mixture due to the presence of excess *p*-toluenesulphonyl chloride. Flash chromatography gave the starting alcohol (61) only. As the starting alcohol was eluted from the column in 2 separate batches, with the first portion leaving the column much sooner than expected, it would appear that the less polar product cleanly decomposed to the starting alcohol on the column. This unexpected result was originally tentatively attributed to interference in the reaction by the pyrrole nitrogen. We suspected that an unstable N-tosyl intermediate was being formed, as a primary tosylate such as (106) would not be expected to be so labile. Later work (*vide infra*) proved this conclusion to be erroneous.

3.4 Preparation of the 2-(N-SEM-pyrrolylcarbonyl) Moiety Using 2-Lithio-N-SEM-pyrrole

In view of both our inability to prepare compounds with the desired functionality at C-11 and worries about possible complications, such as competitive N-acylation, in using the dianion (105) in a Julia reaction, we decided to turn to our alternative plan involving the use of N-protected sulphone (19), $R \neq H$.

The most efficient and elegant way of introducing the desired N-protected 2-pyrrolylcarbonyl moiety appeared to be *via* regio-selective reaction of an N-protected 2-lithiopyrrole with the tricyclic lactone (21). Any route involving protection of a preformed 2-pyrrolylcarbonyl (as in (61)) would, in any case, involve unnecessary extra steps and problems of regioselectivity in view of the results on the attempted tosylation of (61).

In view of the need to remove the protecting group from the pyrrolylcarbonyl group at a late stage in the synthesis in the presence of sensitive functionality, a selective protecting group, that could be removed under very mild conditions, was required. In view of the acid instability of pyrroles, neutral or basic conditions would be highly desirable for the removal of the strong base (for pyrrole metallation) stable protecting group.

The preparation of 2-lithio-N-alkylpyrroles and their reaction with electrophiles (most commonly carbon dioxide) has been well studied. The conditions for selective lithiation at the 2-position have been optimised.¹⁰¹ However, N-alkylpyrroles such as N-methyl and N-benzyl pyrrole, the most commonly studied, would not be suitable for our needs as no methods are available for removal of the N-alkyl group.

Studies on the optimisation of a removable protecting group suitable for N-protected-2-lithioindoles showed that the N-benzenesulphonyl and methoxymethyl groups facilitated lithiation and moderate to good yields of addition reaction with aldehydes, carbon dioxide, nitriles, ketones and acid chlorides and poor yields with esters. However, the methoxymethyl group could only be removed under the relatively vigorous conditions of boron trifluoride and lithium bromide in acetic anhydride and the benzenesulphonyl group was too labile to stand up to the aqueous work up.

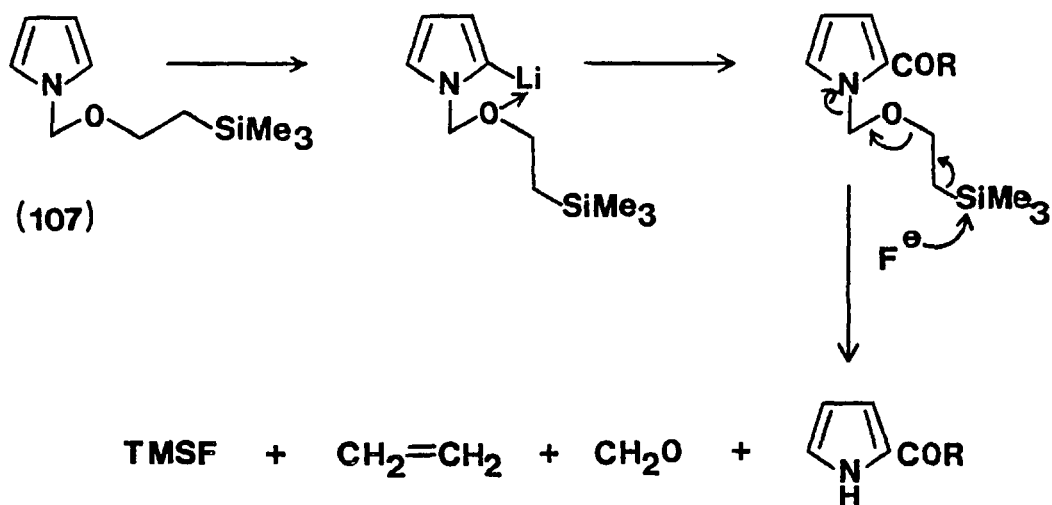
The first attempt at developing a useful 2-lithio-N-protected pyrrole appeared very recently.¹⁰³ After discovering that N-benzenesulphonyl pyrrole was not a useful candidate due to difficulty in metalation, Marinelli and coworkers found that N-t-butyloxycarbonyl pyrrole was cleanly metallated at the 2-position with lithium tetramethylpiperidide at -80°C . The 2-lithiopyrrole was quenched in fair to good yields (35-75%) with reactive electrophiles such as aldehydes and acid chlorides at -80°C . The t-butyloxycarbonyl protecting group was smoothly removed with fairly concentrated (6.5N) sodium methoxide (3 equiv.) in methanol. It would seem that because 2-lithio-N-t-butyloxycarbonylpyrrole was unstable above -45°C its reactions are limited to the more reactive electrophiles only. No previous reports of preparative reactions of 2-lithiopyrroles with less reactive electrophiles such as esters and lactones were found.

For a more generally useful reagent for 2-pyrrolylcarbonyl synthesis a suitably protected pyrrole such that C-2 carbanion formation and stabilisation would be enhanced (to allow reaction at higher temperatures with the lactone (21)) was required. It was also most important that the protecting group be removed under the mildest possible conditions.

Sundberg and Russell found that the highest yields of 2-indolyl-carbonyls were prepared using the 2-lithio-N-methoxymethylindole.¹⁰² We decided that the structurally similar (β -trimethylsilyl)ethoxymethyl (SEM) protecting group, not previously used for N-H protection, could be the ideal protecting group for our purpose.¹⁰⁴ The previously unreported, very stable, N-SEM-pyrrole (107) was readily prepared in 60-70% yield by quenching of sodiopyrrole, formed from pyrrole and sodium hydride in DMF-DMSO, with SEM-chloride. SEM-chloride is prepared by treatment of the readily available β -trimethylsilyl-ethanol and paraformaldehyde with dry hydrogen chloride.^{104a} β -Trimethylsilylethanol was readily obtained in large quantities by lithium aluminium hydride reduction of ethyl α -trimethylsilylacetate,¹⁰⁵ prepared by Reformatski reaction of ethyl α -bromoacetate with zinc and trimethylchlorosilane.¹⁰⁶ A new convenient synthesis of β -trimethylsilylethanol by reaction of trimethylsilylmethylmagnesium bromide with formaldehyde in diethyl ether has recently been published.¹⁰⁷

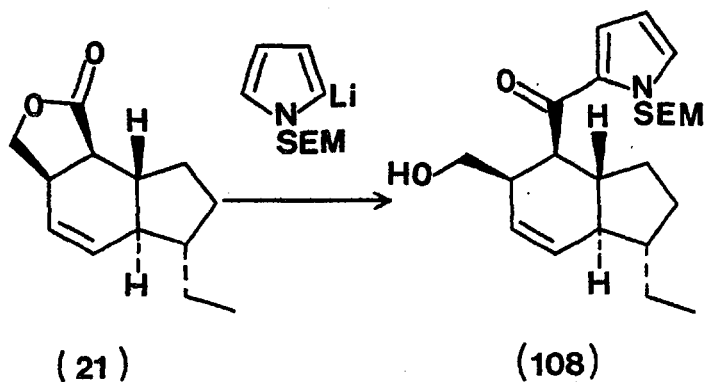
It was hoped that the SEM group would both help to direct lithiation to the 2-position and stabilise the 2-lithio anion, as shown in Scheme 21. Cleavage of the SEM group, by analogy with the SEM protected alcohols, could be expected to occur under the very mild conditions of tetra-n-butylammonium fluoride in THF.^{104a}

Using the optimised lithiation conditions recommended by Chadwick,^{101c} treatment of N-SEM-pyrrole (107) in N,N,N',N'-tetramethylethylenediamine (TMEDA) (0.5 - 0.6N) with n-butyl lithium in hexane (1.1 equiv.) at 0°C to room temperature for 30 min gave a burgundy red solution. Addition of the lactone (21) (1 equiv.) in THF, in one portion, at 0°C, followed by stirring for a further 10 min at room temperature and aqueous ammonium chloride work up gave, after flash chromatography, recovered N-SEM-pyrrole (38%), recovered lactone (21) (36%) and the desired hydroxy



Scheme 21

N-SEM-pyrrolylcarbonyl (108) (21.4% or 34% based on recovered (21)).



Attempts to raise the yield of (108) using the metallation system of nBuli-TMEDA were unsuccessful. The best yields (up to 34%) were obtained with short metallation times (5 min). Attempted metallation at -78°C led to none of the burgundy colour which was initially, erroneously, attributed to the 2-lithiopyrrole. Quenching of the pale yellow solution with (21), at -78°C, also produced none of the desired (108). Prolonged metallation times at room temperature led to less

of the alcohol (108) and greater amounts of unreacted (21). Later experiments (*vide infra*) showed that the red colour was due to N-lithio-pyrrole and polymeric products, resulting from attack of n-butyl lithium on the SEM group.

Attempted metallation of N-SEM-pyrrole with n-butyl lithium in THF at 0°C or THF-HMPA at 0°C or t-butyl lithium in THF at -78°C, followed by addition of the lactone (21), led to none of the desired (108).

Fortunately, however, treatment of N-SEM-pyrrole in dimethoxyethane (DME) with n-butyl lithium under optimised conditions gave yields of 50-62% (up to 71% based on recovered lactone (21)) of (108). Short metallation times (5-10 min) at 0-5°C were necessary to give a pale yellow solution of the 2-lithio-N-SEM-pyrrole.

High field (250 MHz) ¹H n.m.r. showed that the lithiation of the pyrrole was regiospecific for the 2-position as no regioisomers were present in (108).

A number of features of the high field (250 MHz) ¹H n.m.r. spectrum of (108) are worthy of discussion. The doublet absorptions (J 3.1 Hz) due to the pyrrole C-3 and C-5 protons were exactly equivalent and appeared as one doublet at δ 7.09. The C-4 proton absorption appeared as a doublet of doublets with both J 3.1 Hz, as expected, at δ 6.2.

Similarly to the other tetrahydroindan systems (55), (66), (21), and (61), the olefinic protons H₆ and H₇ appeared as a doublet of doubled doublets (J 10, 3.7, and 2.6 Hz) and a broad doublet (J 10 Hz) at δ 5.55 and 6.06 respectively. Apparently, the conformation of this tetrahydroindan system is such that the spatial relationship between H₇, H₅, and H_{7a} is such that any small coupling between H₇ and the other

two is unresolved at 250 MHz. However, the absorption due to H_6 exhibits coupling constants due to H_5 and H_{7a} as well as H_7 . By analogy with decoupling experiments on the tetrahydroindan ester (55), the smallest of the three coupling constants for H_6 (2.6 Hz) is due to the homoallylic H_{7a} proton. Irradiation of the multiplet absorption at δ 2.88, attributed to H_5 of the ester (55), lead to the collapse of the H_6 absorption from a doublet of doubled doublets (J 10.26, 4 and 2.56 Hz) to a doublet of doublets (J 10.26 and 2.56 Hz) due to the removal of the coupling due to H_5 .

The hydroxymethyl group and H_5 protons of (108) exhibit an interesting ABCX spin system in the high field (250 MHz) ^1H n.m.r. spectrum. Although one of the hydroxymethylene C-H proton absorptions is obscured by the absorption due to two of the methylene protons of the SEM group (those flanked by oxygen and the other methylene), the other, at δ 3.65, clearly shows coupling to the other methylene proton (J 12 Hz), the O-H proton (J 6.9 Hz), and H_5 (J 5 Hz). The O-H proton, coupled to both of the methylene protons, resonates as a doublet of doublets (J 6.9 and 6.9 Hz) at δ 3.45.

The multiplet absorption due to H_5 in (108) at δ 2.73 is obscured by the H_4 absorption. However, in the other tetrahydroindans (55), (66), (21), and (61), H_5 appears to be part of a very complex 6 spin system, as shown in Diagram 14 below, seemingly coupled to both of the methylene protons, H_6 , H_7 , and H_{7a} . No decoupling experiments, to discover true J values, were carried out on (21) and it was not considered worthwhile to try to derive first order J values from the exhibited 21 line multiplet.

250 MHz ^1H n.m.r.

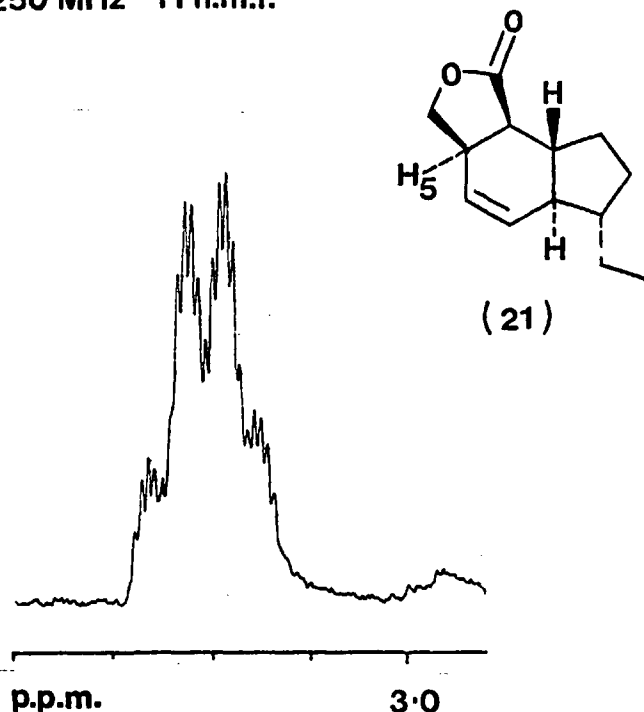
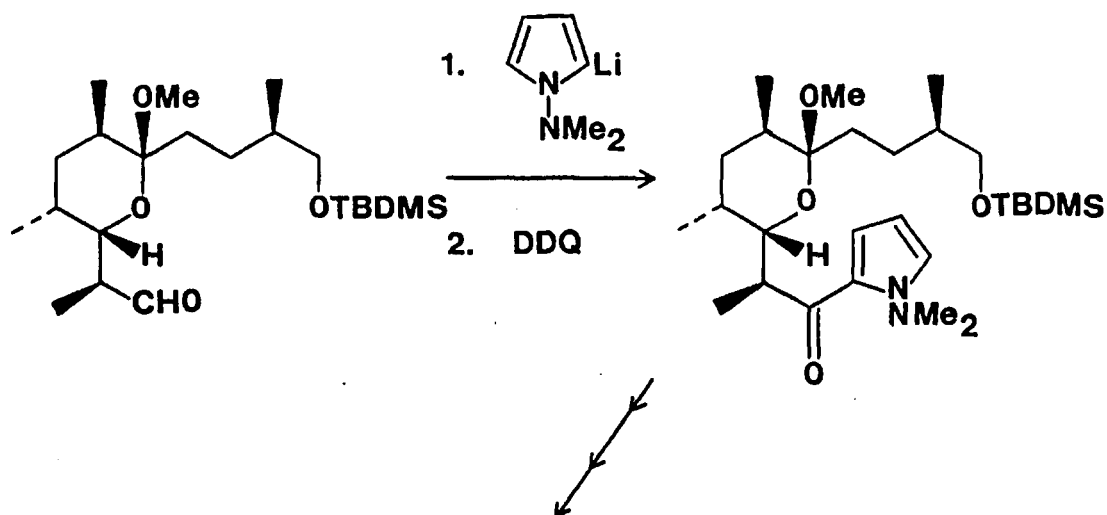


Diagram 14

Interestingly, subsequent to our work, Grieco and coworkers have recently published an alternative reagent for the preparation of 2-pyrrolylcarbonyls.¹⁰⁸ The readily available N-(N,N-dimethylamino)-pyrrole (109) was lithiated with n-butyl lithium in THF at -78°C . Quenching with tri-n-butyltin chloride gave the 2-(trimethylstannyl)-pyrrole (80%) from which the 2-lithiopyrrole could be readily regenerated by treatment with n-butyl lithium in THF at -78°C . The 2-lithiopyrrole was trapped with aldehydes in good (70-75%) yields. The 2-pyrrolylcarbonyls were prepared by oxidation of the adducts (manganese dioxide, 70%) followed by reductive cleavage (chromous acetate, ethanol) of the N-N bond. In a similar fashion to Nicolaou,¹⁰⁹ Grieco prepared 2-pyrrolylcarbonyls directly by condensation of the Grignard reagent derived by metal exchange of the 2-lithiopyrrole with magnesium bromide with reactive 2-pyridylthioesters. This reagent was used by Grieco, as shown in Scheme 22, in the total synthesis of A-23187.¹¹⁴



A-23187

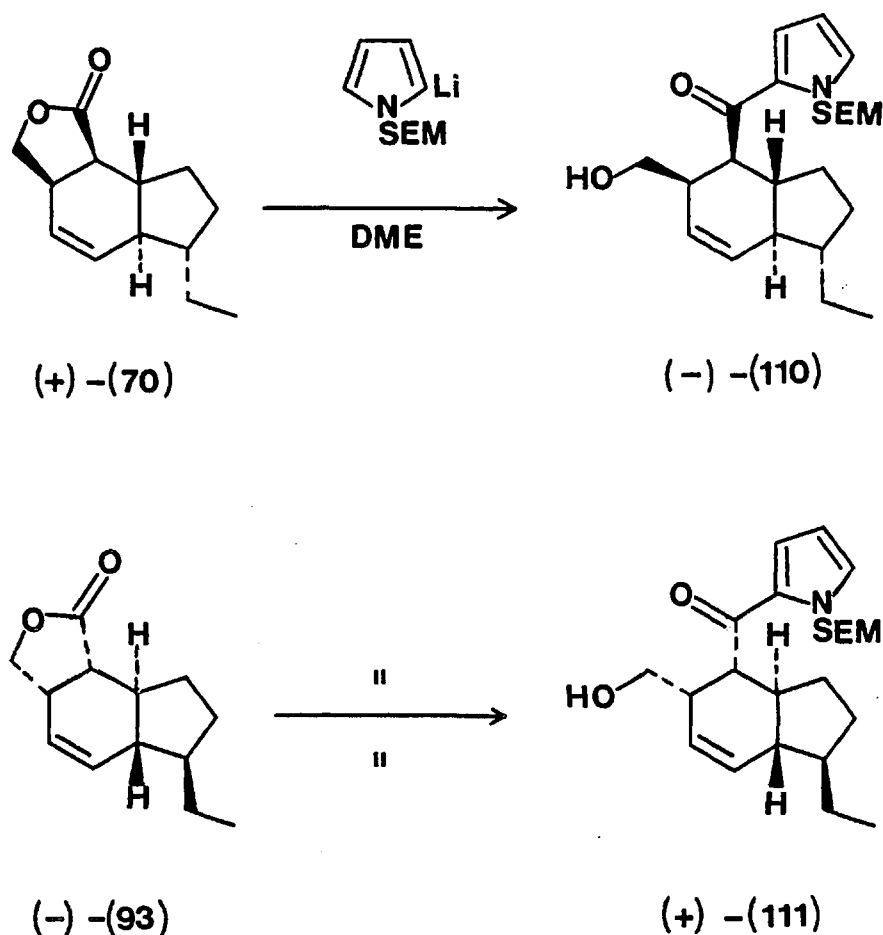
Scheme 22

We have found that the 2-N-SEM-pyrrolylcarbonyl group has proved to be remarkably stable to a variety of conditions including strong base (*n*-butyl lithium in HMPA), reductive (sodium amalgam), and oxidising (hydrogen peroxide-diphenyl diselenide) conditions, fluoride ion sufficient to remove TBDMS and TBDPS alcohol protecting groups, zinc fluoride, and lithium tetrafluoroborate in acetonitrile at 70° (*vide infra*). The SEM group thus seems to be a very useful pyrrole protecting group for systems where synthetic transformations subsequent to 2-pyrrolylcarbonyl preparation are necessary.

Further work is planned in order to increase the generality of 2-lithio-N-SEM-pyrrole by optimising its reactions with a range of electrophiles and examining possible metal exchange with magnesium bromide or zinc chloride, to modify its reactivity.¹¹⁵

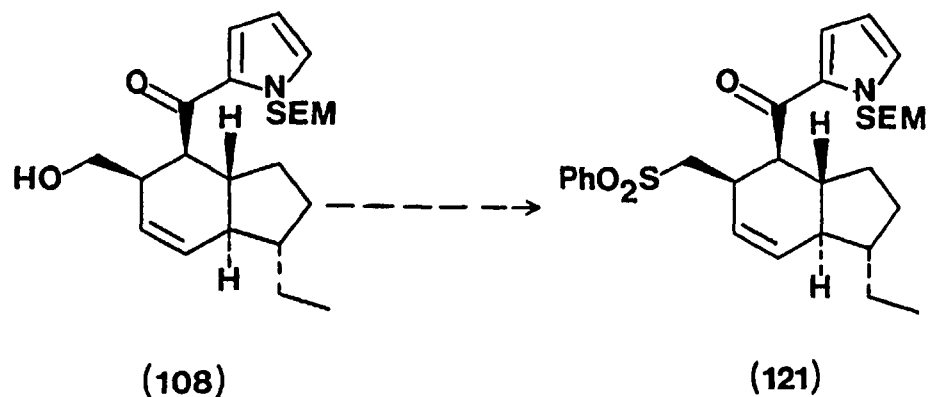
The optically pure hydroxy N-SEM-pyrrolylcarbonyl (-)-(110) ($[\alpha]_D^{25}$ - 19°), with correct absolute configuration, was prepared in 62% yield

by treatment of the lactone (+)-(70) with 2-lithio-N-SEM-pyrrole as before. The enantiomeric lactone (-)-(93) gave the antipode of (110), (+)-(111) ($[\alpha]_D^{25} + 19^\circ$) in 60% yield.



3.5 Preparation of (-)-4(S)-[2'-N-(β -trimethylsilyl)ethoxymethylpyrrolyl-carbonyl]-5(S)-phenylsulphonylmethyl-1(S)-ethyl-3a(R),4,5,7a(R)-tetrahydroindan (123).

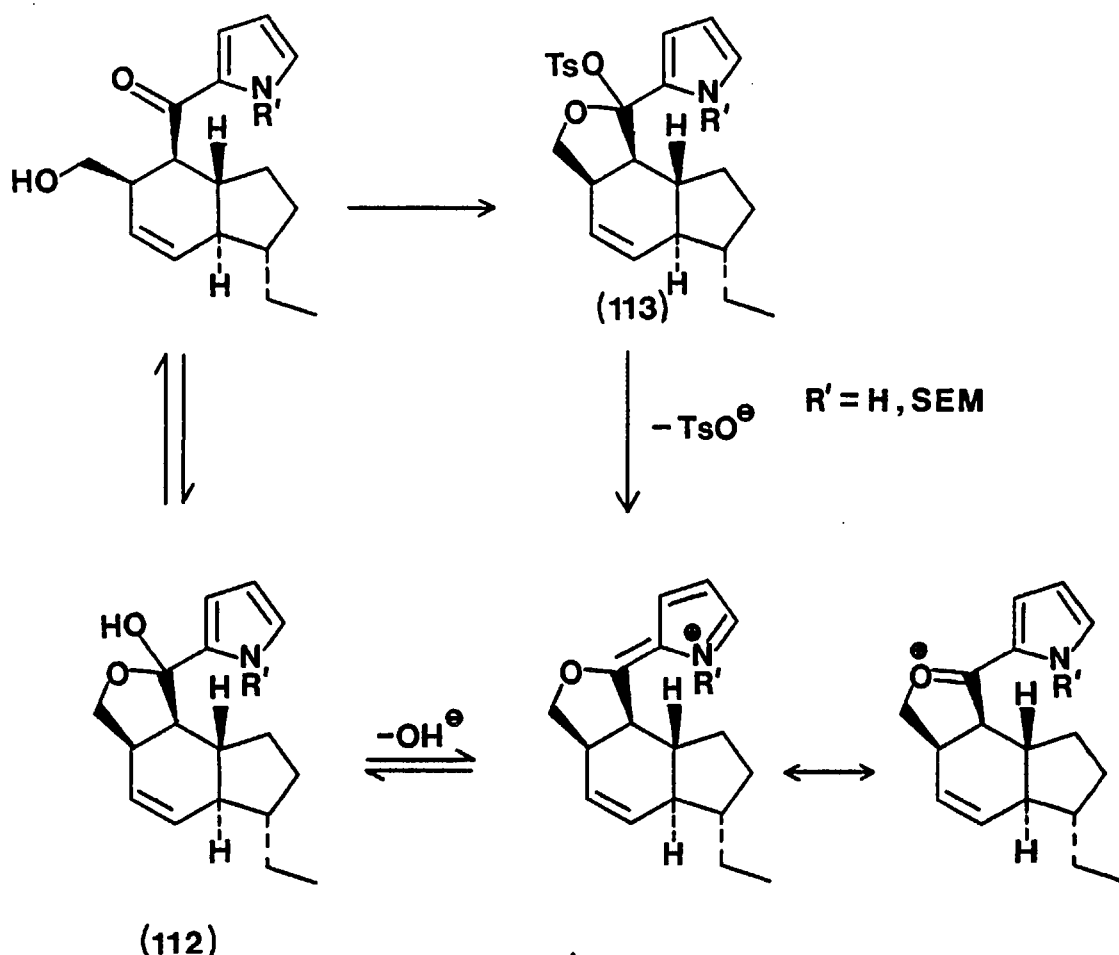
With the highly efficient preparation of either enantiomer of the hydroxy N-SEM-pyrrolylcarbonyl (108), all that was now required for preparation of the desired right hand side sulphone (121) was conversion of the hydroxyl group of (108) to the phenylsulphone moiety.



Although the transformation was ultimately achieved in a short, highly efficient manner, some interesting chemistry, apparently solving the mystery of the difficulty involved in attempts at preparing the tosylate (106) from (61), was uncovered in the initial experiments.

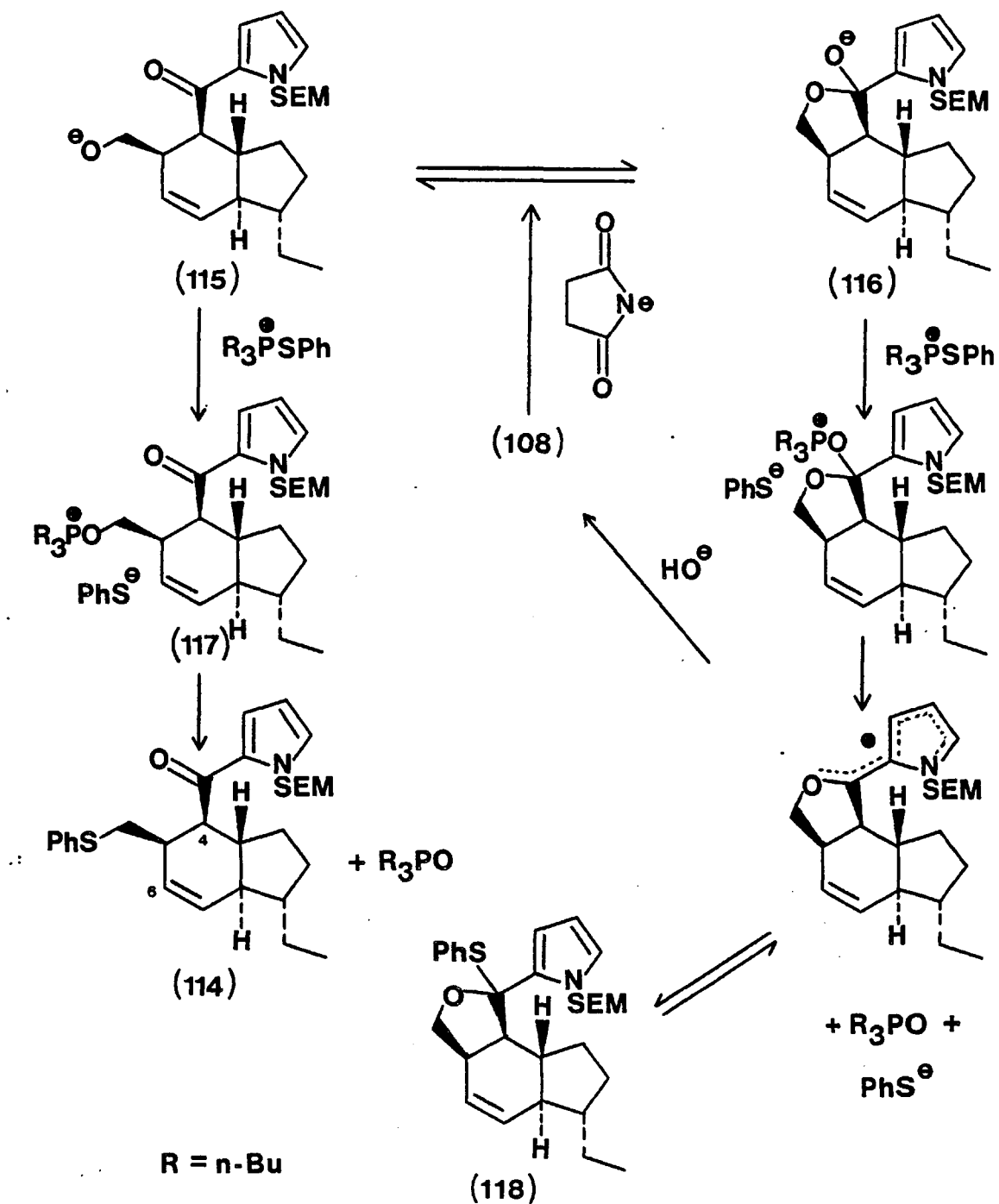
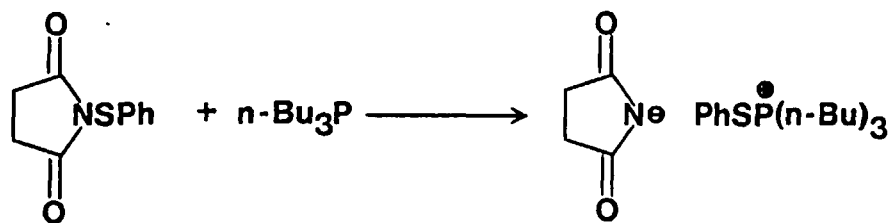
Surprisingly, attempts at preparing the tosylate or mesylate of (108) lead to exactly the same results as were observed for attempted tosylation of the unprotected pyrrolylcarbonyl (61). An initially formed less polar product (t.l.c.), formed by treatment of the alcohol (108) with *p*-toluenesulphonyl chloride in pyridine, decomposed cleanly to the starting alcohol (108) after aqueous work up. Following a non-aqueous work up, the less polar product was also cleanly converted to the starting alcohol (108) upon flash chromatography.

The only reasonable structure for this less polar product would seem to be the ketol tosylate (113), R'=SEM, resulting from base catalysed intramolecular ketalisation. The corresponding structure (113), R'=H, would also fit the observed results for the alcohol (61). As shown in Scheme 23 below, this tosylate would be expected to be extremely labile to hydrolysis *via* (112) due to the double activating effect of both the oxygen and nitrogen lone pairs.



Scheme 23

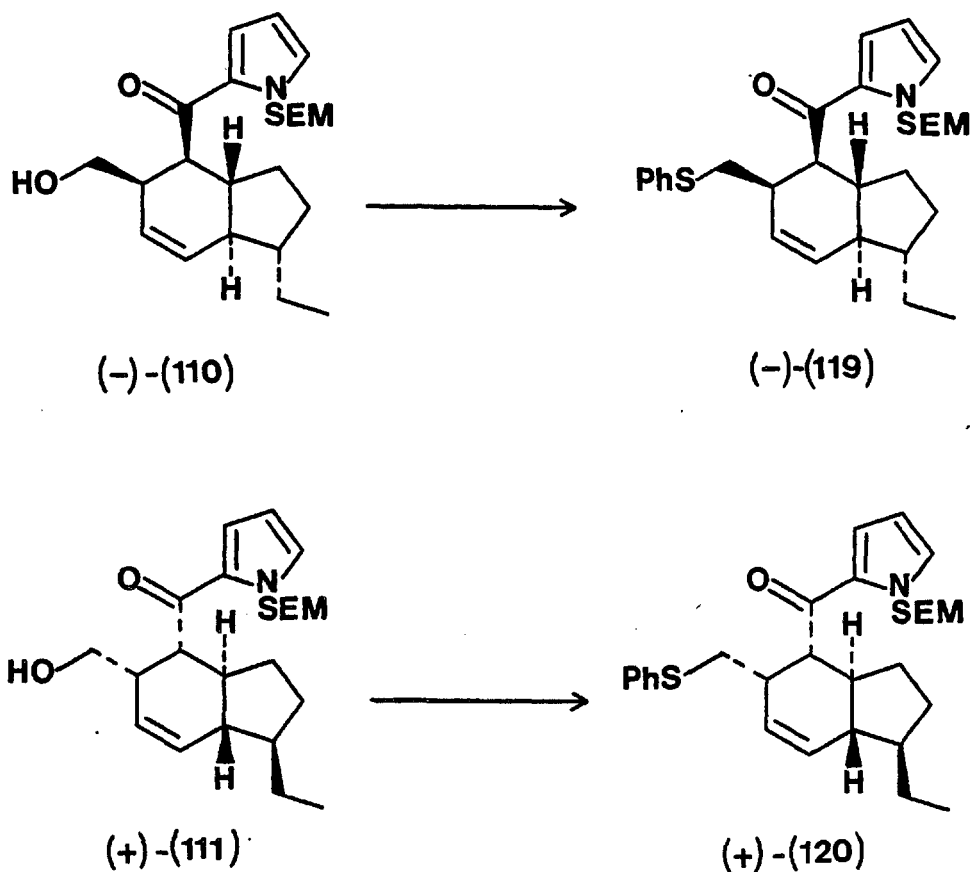
This unfortunate reactivity of the hydroxy pyrrolylcarbonyl system obviously posed a serious setback to our synthetic efforts. However, using the method of Walker, the alcohol (108) was converted, in 1 step, and in high yield, to the desired sulphide (114).¹¹⁰ Reaction of the alcohol (108) with the reagent prepared by stirring tri-*n*-butylphosphine (1.6 equiv.) with *N*-phenylsulphenylsuccinimide (1.6 equiv.) in benzene, at room temperature for 10 min, gave the sulphide (114) in 64-74% (or 72-83% based on recovered (108)). It would seem that, unlike *p*-toluenesulphonyl chloride, the tri-*n*-butylphosphonium phenylsulphide reagent preferentially reacts with an equilibrium amount of the open



Scheme 24

form of the alkoxy anion (115) to give the desired intermediate (117), being too bulky to react with the hindered quaternary system of (116). As shown in Scheme 24, a small amount of the labile (118) was apparently formed as traces of the starting alcohol (108) were eluted earlier than expected (as observed in the tosylation attempts) during flash chromatography of the crude reaction mixtures.

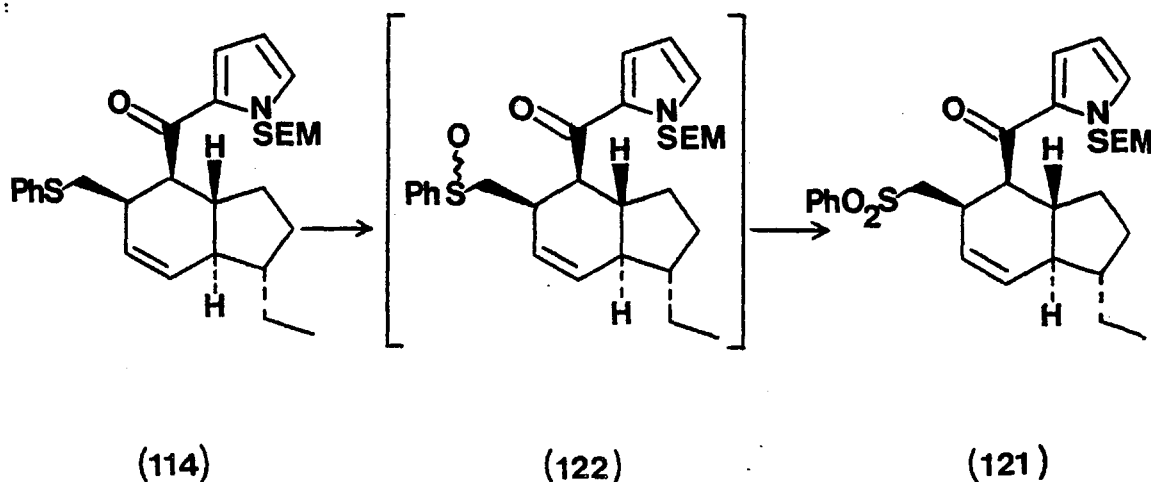
Similarly, the laevorotatory and dextrorotatory alcohols (-)-(110) and (+)-(111) gave the optically pure sulphides (-)-(119) ($[\alpha]_D^{25} -69^{\circ}$) and (+)-(120) ($[\alpha]_D^{25} + 68^{\circ}$).



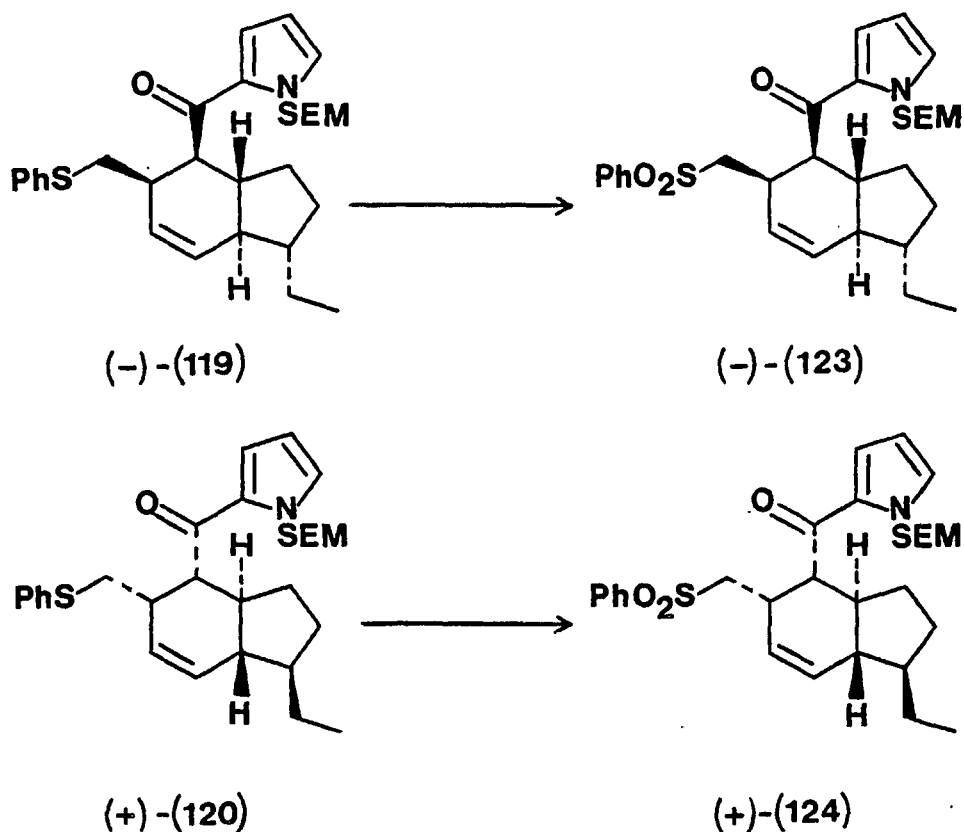
The anisotropic effect of the phenyl group in the sulphide (114) leads to deshielding of both H₆ and H₄ which resonate at σ 5.88 and 3.45 (*cf.* δ 5.55 and 2.73 in the alcohol (108)), respectively, in the high field (250 MHz) ¹H n.m.r. spectrum of (114).

The reagent often used for sulphide to sulphone oxidation, MCPBA, could not be used for preparation of the desired sulphone (121) due to the presence of the olefin in the sulphide (114).¹¹² Chemoselective oxidation of the sulphide (114) was achieved in excellent yield using the very mild procedure of Reich.¹¹¹ Reaction of the sulphide (114) with 30% hydrogen peroxide (6 equiv.) and diphenyl diselenide (1 equiv.) in 15% dichloromethane-diethyl ether, for 1h at 0°C followed by 6h at room temperature, produced the sulphone (121) *via* the intermediate diastereomeric sulfoxides (122) (t.l.c.) in 75-80% yield.

Oxidation with the recommended Reich system, with neat dichloromethane as solvent, was more rapid but much less clean. The use of diethyl ether as cosolvent, however, slowed the rate of oxidation, leading to cleaner reaction, possibly due to the effects on the solubility of the suspected oxidising species peroxybenzeneseleninic acid (PhSeO_3H). Due possibly to the acidic nature of the conditions and the acid sensitive pyrrole functionality, the Trost method for chemoselective oxidation of sulphides, using potassium hydrogen persulphate, lead to much less clean oxidation of the sulphide (114) in a small scale (t.l.c.) reaction.¹¹²



In the same way, the optically active sulphide (-)-(119) was converted to the desired right hand side sulphone (-)-(123) ($[\alpha]_D^{25} -79^0$) with the natural absolute configuration. The sulphide (+)-(120) gave, similarly, the unnatural enantiomer (+)-(124) ($[\alpha]_D^{25} + 78^0$).



As was observed for the sulphide (114) the phenyl group causes deshielding of both H_4 (δ 3.45) and H_6 in the ^1H n.m.r. spectrum. The trend of decreasing separation of the resonances of the olefin protons H_6 and H_7 on going from the alcohol (108) ($\Delta\delta = 0.51$) to the sulphide (114) ($\Delta\delta = 0.09$) is continued for the sulphone (121). In fact the signals for H_6 and H_7 coalesce ($\Delta\delta \sim 0$) in the case of the sulphone (121). In the high field (250 MHz) ^1H n.m.r. spectrum of (121) the absorption for H_6 and H_7 appears as a sharp singlet at δ 5.96. In the 400 MHz ^1H n.m.r. spectrum of (121), resolution enhanced expansion

just resolves the signals for H₆ and H₇ into a very distorted doublet and a doublet of doubled doublets with a separation of only 0.03 ppm (12 Hz), as shown in Diagram 15.

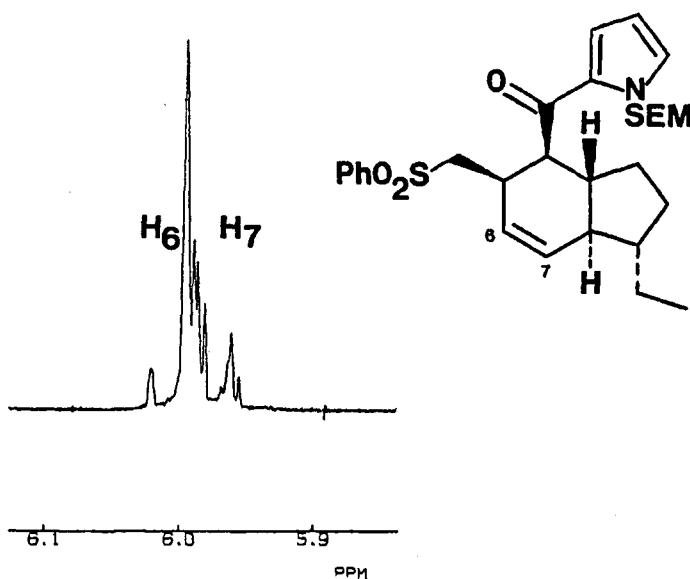


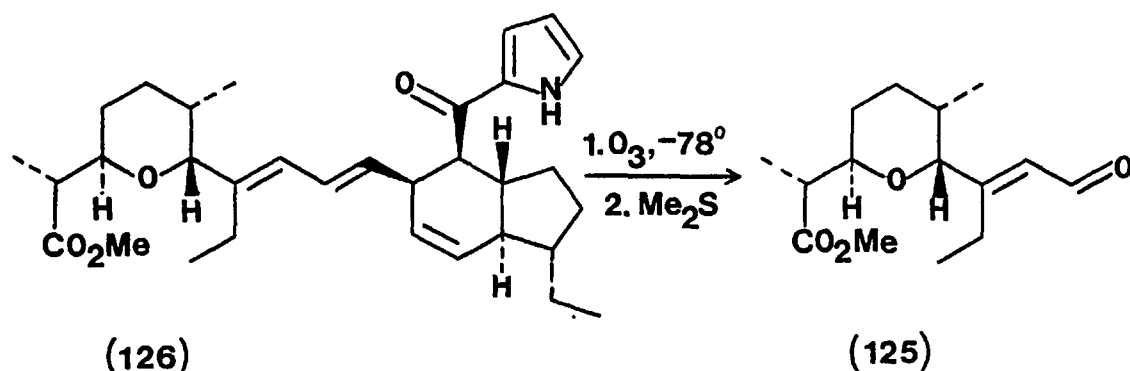
Diagram 15

The enantiomerically pure right hand side sulphone (-)-(123) was thus easily prepared from the readily available lactone (+)-(70), in an efficient three step process, in up to 47% (based on converted starting material) overall yield. The overall yield of the sulphone from 2-ethyl- δ -valerolactone was, therefore, up to 21%.

4. ENANTIOSELECTIVE SYNTHESIS OF X-14547A

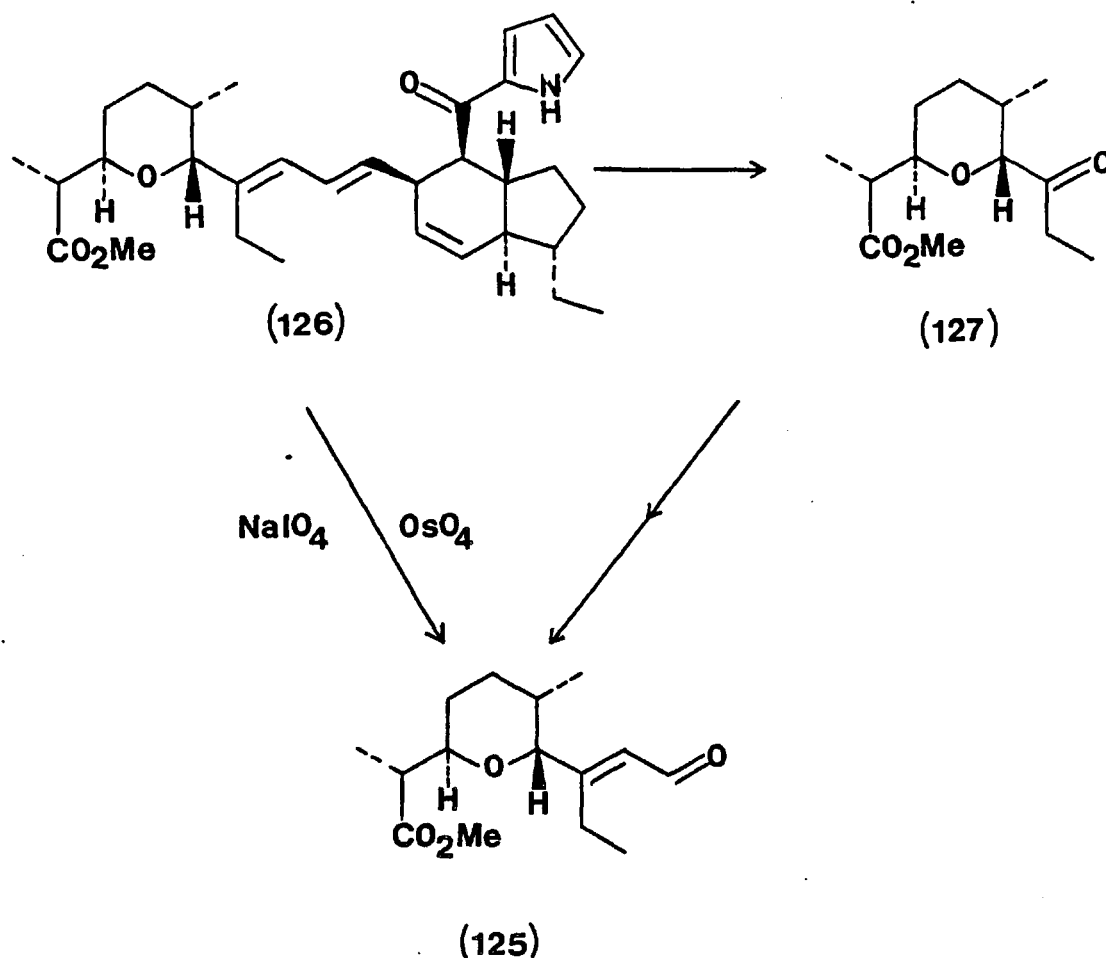
The optically active left hand side aldehyde (125) ($\equiv$ (18), R = Me), required for the projected synthesis of X-14547A *via* Julia coupling with the sulphone (-)-(123), is readily available from the natural product. Diazomethane treatment of X-14547A to give the methyl ester (126), followed by selective ozonolysis at -78⁰C, gives the aldehyde (125), after dimethylsulphide work-up, in 90% overall yield.³⁸ The surprising regioselectivity of the ozonolysis, for the least substituted double bond of (126), was presumably due to delivery of ozone *via* intramolecular

participation of the pyrrole nitrogen.



As shown in Scheme 25, Nicolaou also reported the preparation of the aldehyde *via* both osmium tetroxide catalysed sodium periodate cleavage of X-14547A methyl ester (126) (25% yield) and stereoselective conversion of the ketone (127), obtained by his group on ozonolysis of (126) (95% yield), to the aldehyde (125). Sequential treatment of the ketone (127) with vinylmagnesium bromide and pyridine chlorochromate gave the aldehyde (125), in 70% overall yield.³²

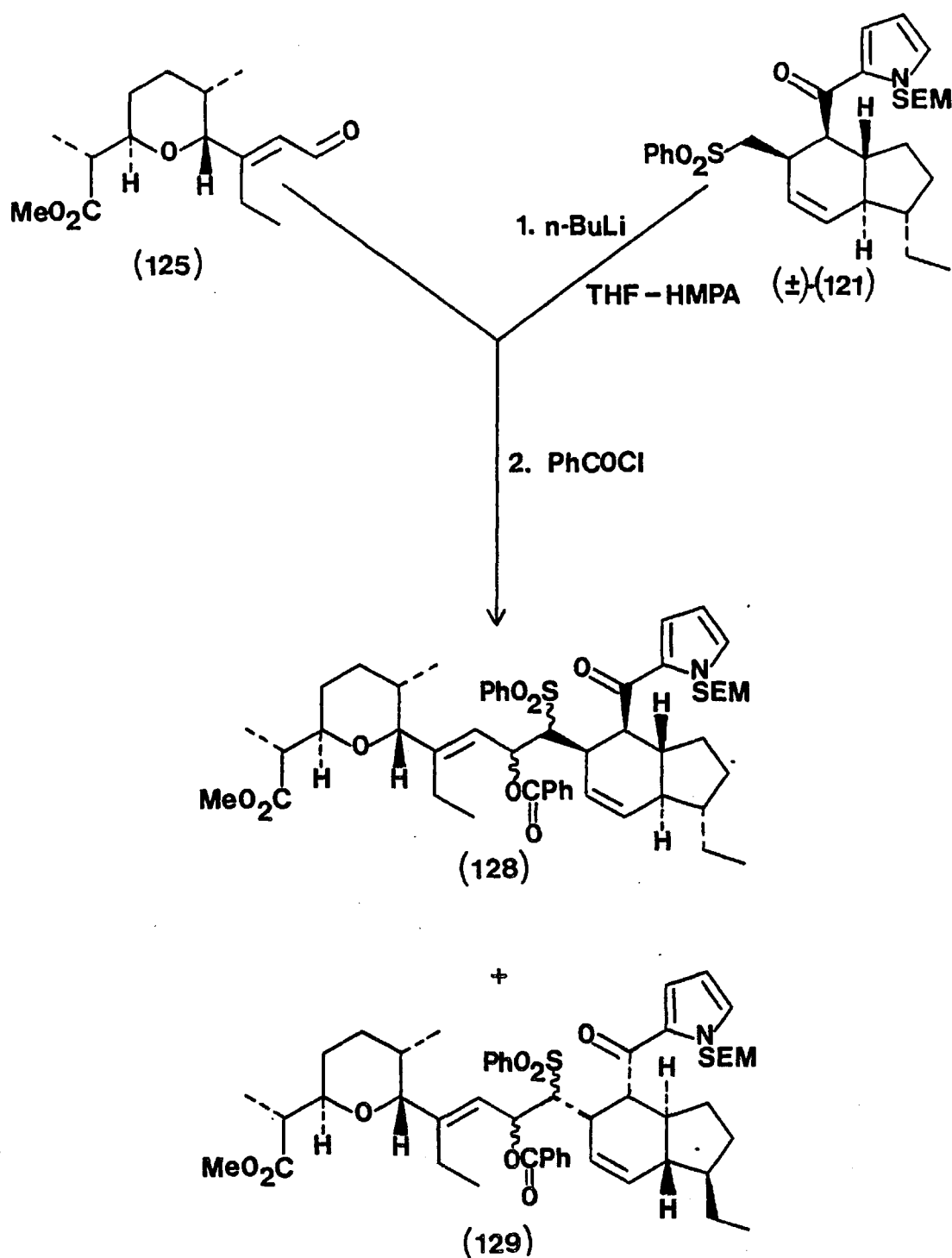
Initial attempts at the Julia coupling of the racemic sulphone (121) with the aldehyde (125), using the standard conditions developed by Lythgoe and Kocienski, were unsuccessful.⁴¹ Treatment of the sulphone (121) with *n*-butyl lithium in THF at -78°C to 0°C for up to 30 min followed by stirring with the aldehyde (125) for 45 min and quenching with excess benzoyl chloride, both at -78°C , lead cleanly to recovered starting materials, (121) and (125), only. This failure would seem to be due to the inability of the *n*-butyl lithium to effect metallation of the relatively hindered sulphone in THF alone. The addition of HMPA to the metallation system was sufficient to produce the bright orange sulphone anion rapidly, at -78°C , however. Treatment of the sulphone (121) in THF-HMPA (4:1) with *n*-butyl lithium (1 equiv.)



Scheme 25

for 15 min at -78°C followed by stirring with the aldehyde (125) for 45 min and quenching with benzoyl chloride, both at -78°C , gave, after warming up to room temperature over 2h and destruction of excess benzoyl chloride with 3-dimethylaminopropylamine, as shown in Scheme 26, a complex mixture of diastereomeric benzoyloxysulphones (128) and (129).

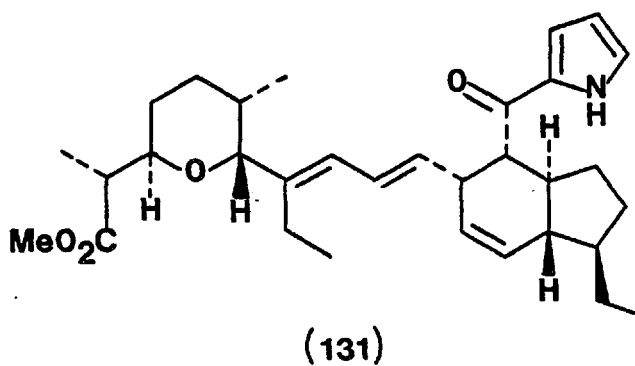
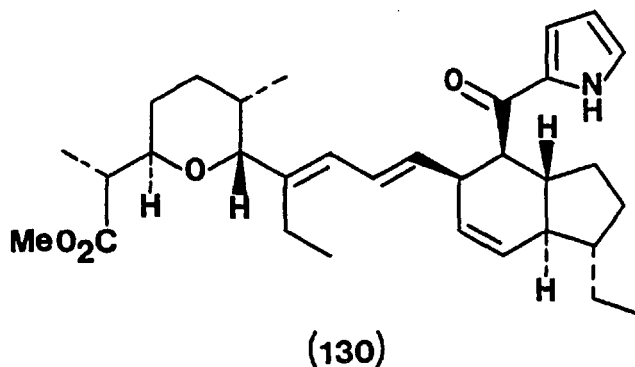
With two possible *erythro* and two *threo* diastereomers for each of the benzoyloxysulphones (128) and (129), a total of 8 diastereomers was possible from coupling the racemic sulphone (121) with the aldehyde (125). T.l.c. analysis of the crude reaction mixture indeed revealed



Scheme 26

a complex mixture of products. Although the benzoyloxysulphones could be separated from some baseline material and some excess aldehyde (125) (80% yield after flash chromatography), treatment of the complex crude mixture with sodium amalgam in methanol-THF at -20°C led to smooth

conversion of the benzyloxysulphones to apparently, a single major product (t.l.c.). As expected, the high field (250 MHz) ^1H n.m.r. spectrum of this product showed that the two diastereomeric dienes (130) and (131), unresolved by t.l.c., were in fact the major product.



Initial worries of problems arising from preferential abstraction of the possibly more acidic proton at C-4 of the sulphone, α - to the carbonyl group, proved to be unfounded.

Although the acidity of the C-4 proton could be expected to be reduced by the relatively electron rich (vinylogous amide) nature of the carbonyl group and by its tertiary status, due to its relatively unhindered α -axial environment, significant steric differentiation with the

α -sulphone protons (hindered by the presence of the *syn*-gauche 2-pyrrolylcarbonyl moiety) could not be expected. However, once formed, the hindered enolate anion would be extremely unlikely to react irreversibly with the bulky aldehyde (125). As reprotonation (from the acidic α -sulphone protons) would be expected to occur in an axial fashion, from the α -face, problems of epimerisation at C-4 (in an equilibrating process with the sulphone anion leading to irreversible reaction with (125)) would not arise. The extremely hindered (*cf.* esters (55) and (66)) carbonyl group of (121) would be expected to be stable to both *n*-butyl lithium and the sulphone anion at low temperatures. Problems arising from enolisation of the aldehyde (125) were apparently not significant.

Following the procedure developed for the model racemic sulphone (121) system, the (-)-sulphone (123) was stereospecifically condensed with the aldehyde (125) to give N-SEM-X-14547A methyl ester (130) ($[\alpha]_D^{25} -255^\circ$ (*c* 0.84, CHCl_3)) in 53% overall yield.

Close examination of the high field (250 MHz) ^1H n.m.r. spectrum of (130) revealed that the Julia product was essentially free of any diastereomeric impurities. As the only other minor products, observed by t.l.c., appeared to be merely decomposition (particularly pyrrolic) products, the Julia reaction, as expected, was stereospecific in producing only the (*E*),(*E*)-1,3-butadienyl system. Also, as expected, no epimerisation at C-2 or C-20 was apparent as all the proton signals were sharp with no doubling or shoulder peaks. Almost complete assignment of the ^1H n.m.r. spectrum was possible and many similarities with the natural product methyl ester spectrum were observed. The subsequent conversion to X-14547A (*vide infra*), provided irrefutable evidence for the structure of (130). As the ^1H n.m.r. spectrum of X-14547A methyl ester is discussed in full in this section no detailed analysis of the assignment of the ^1H n.m.r. spectrum of (130) (see the experimental section) is given.

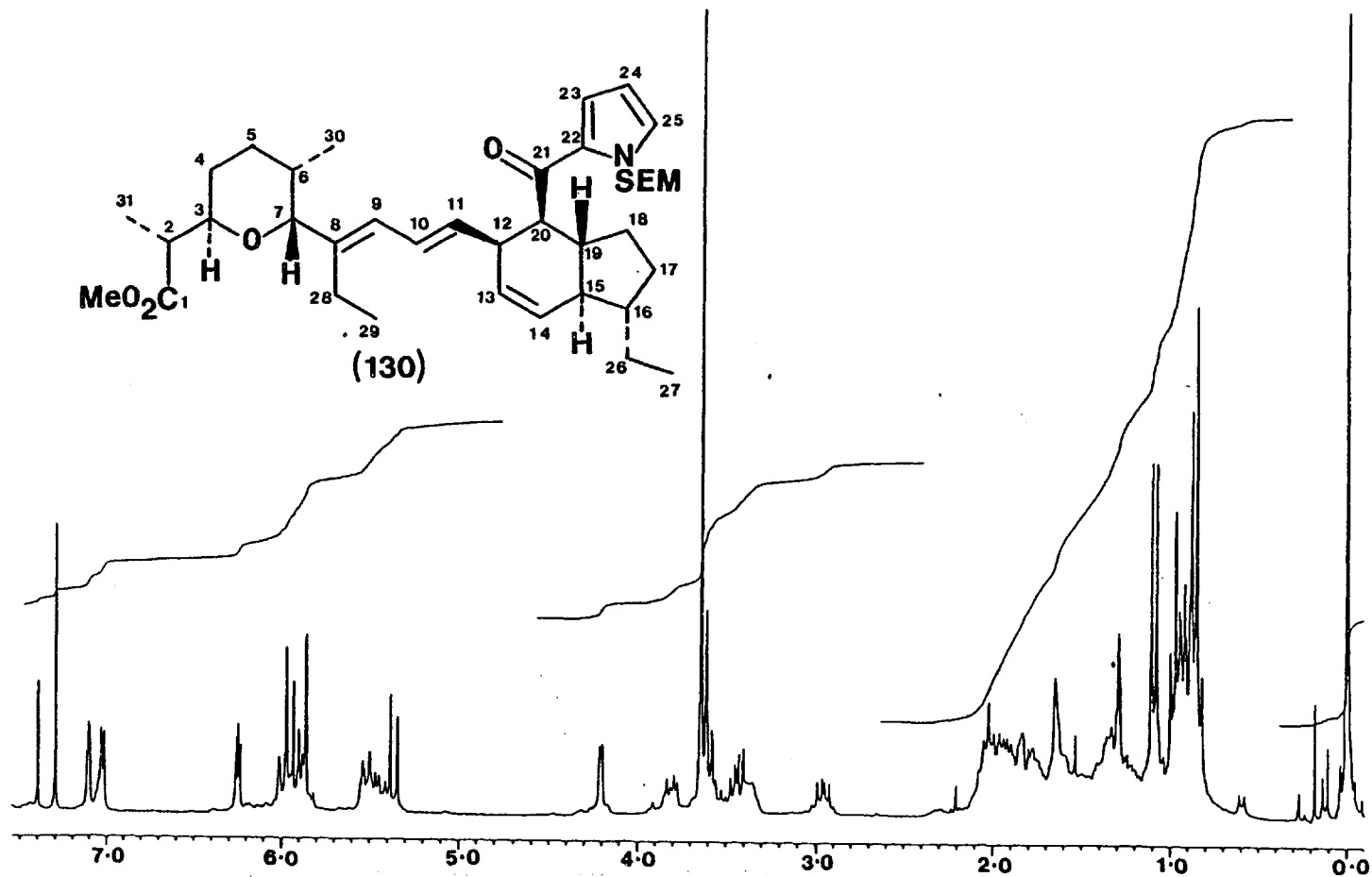
The diastereomeric Julia product N-SEM-X-14547A diastereomer methyl ester (131) ($[\alpha]_D^{25} + 190^{\circ}$ (c 1.21, CHCl_3)) was prepared, in a similar fashion, from the aldehyde (125) and the (+)-sulphone (124).

The high field ^1H n.m.r. spectrum of (131) differed from that of the diastereomeric (130) only in a change of the chemical shift of the diene protons at C-9, C-10, and C-11, which appeared as unresolved second order signals in (131). The corresponding protons of (130) were all clearly assignable (compare spectrum 1 (130) with Spectrum 2 (131) overleaf).

Attempted removal of the SEM protecting group proved initially troublesome. The N-SEM-pyrrolylcarbonyls (130) and (131) were unchanged after reaction with commercially available solutions of tetra-n-butylammonium fluoride in THF (1N) or anhydrous zinc fluoride in dry nitromethane at temperatures up to 50°C and for up to 3h. The recommended procedure of lithium tetrafluoroborate in acetonitrile at 70°C ^{104b} also failed to remove the protecting group, although an interesting reaction did occur (*vide infra*).

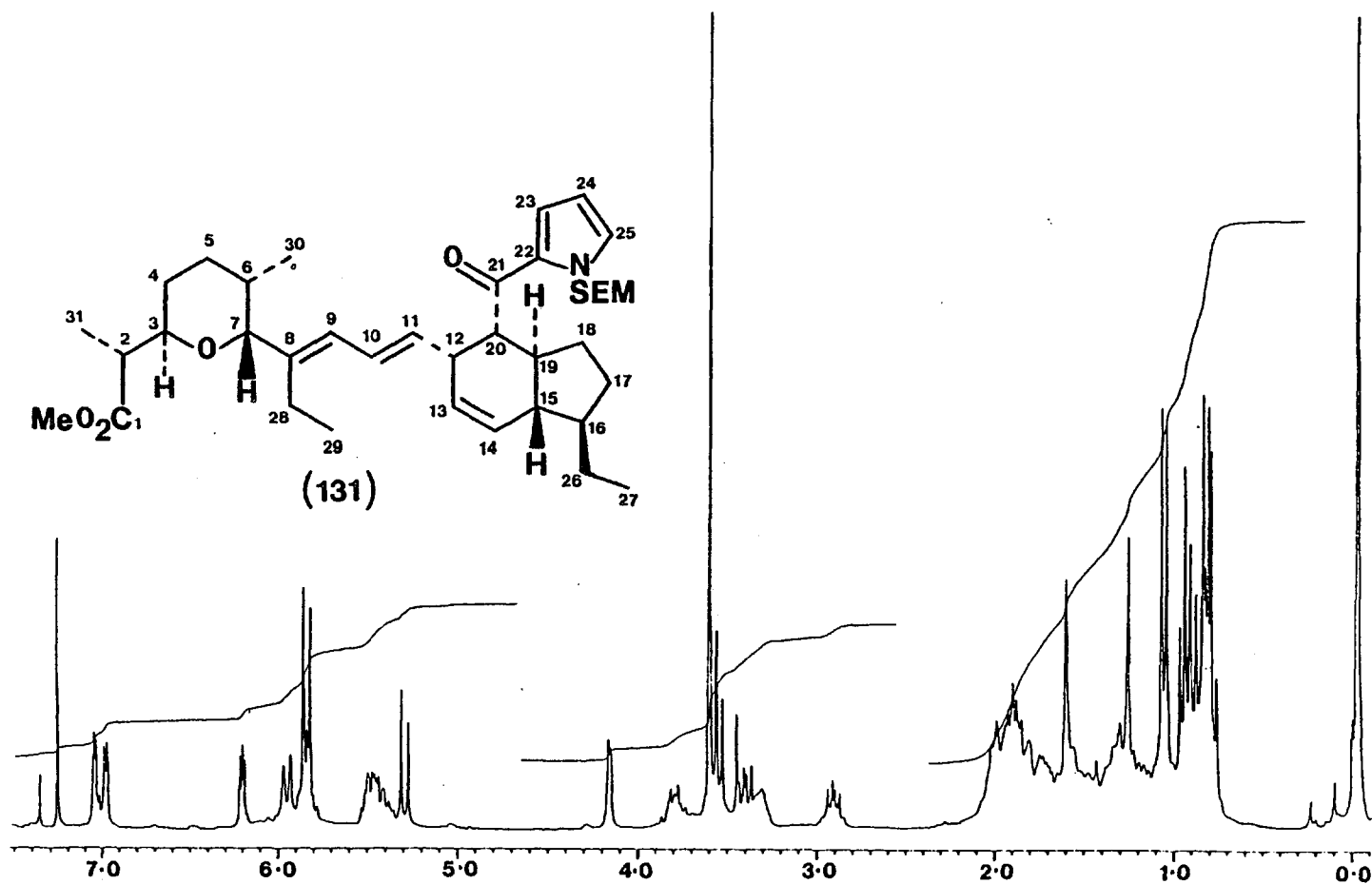
However, preparation of 'super dry' concentrated (3N) solutions of tetra-n-butylammonium fluoride in THF, by azeotropic removal of water from the commercially available trihydrate (10g benzene, rotary evaporator, ca. 5 x 80 ml azeotropes followed by heating at 50°C under high vacuum for 12h), proved to be the answer to the problem. Reaction of (130) or (131) with this solution (ca. 6 equiv.), at room temperature, produced an immediate deep red colour (possibly due to the 2-pyrrolylcarbonyl anion) which was discharged completely by addition of water after 5 min. At room temperature, complete removal of the protecting group was virtually instantaneous. However, the yields could be improved from 40-45% up to over 70% by reaction at 0°C with

250 MHz ^1H n.m.r.



Spectrum 1

250 MHz ^1H n.m.r.



Spectrum 2

a small amount of additional THF. The deprotection of the N-SEM-pyrrolylcarbonyl (130) smoothly produced, in 72% yield, the methyl ester of X-14547A (126) ($[\alpha]_D^{25} -306^0$ (c 1.3, CHCl_3)), which was identical (t.l.c., $[\alpha]_D$, i.r., ^1H n.m.r., and mass spectrum) to samples of the ester prepared from the natural product by my coworker Dr. Brian Palmer.

The five olefinic proton absorptions in the high field (250 MHz) ^1H n.m.r. spectrum of X-14547A methyl ester were first order and clearly assignable, as shown in Diagram 16.

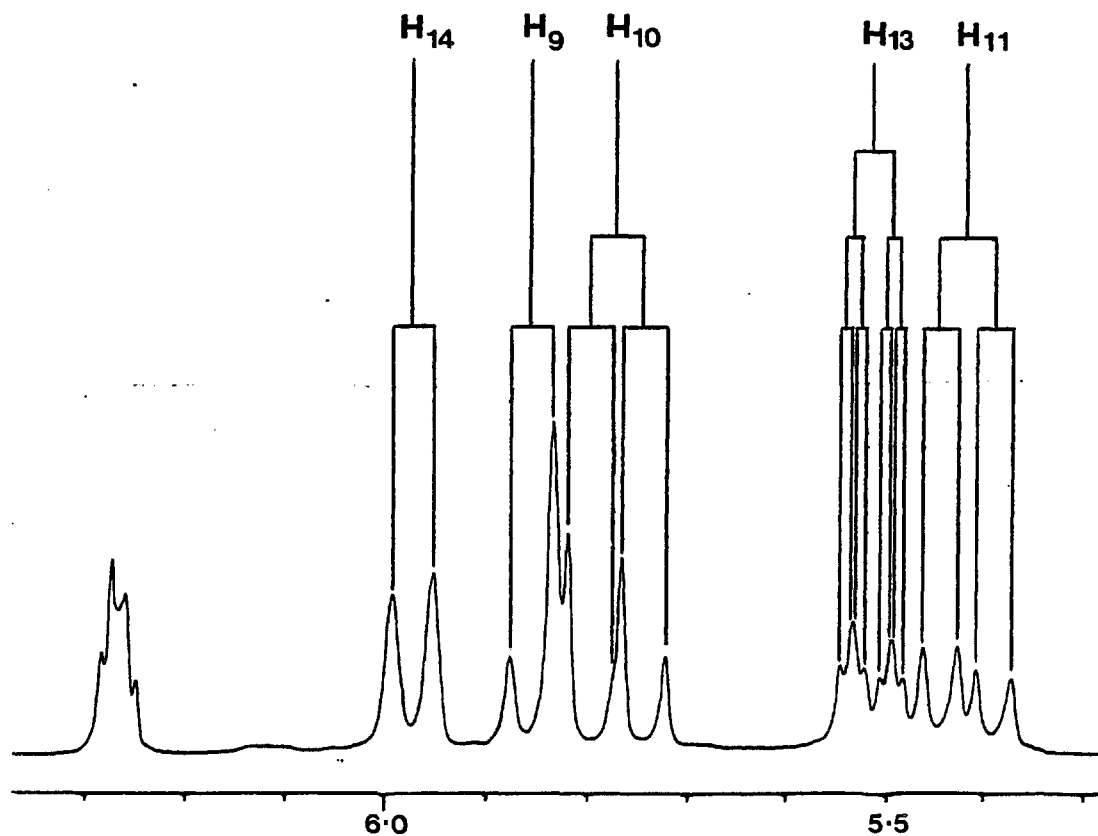
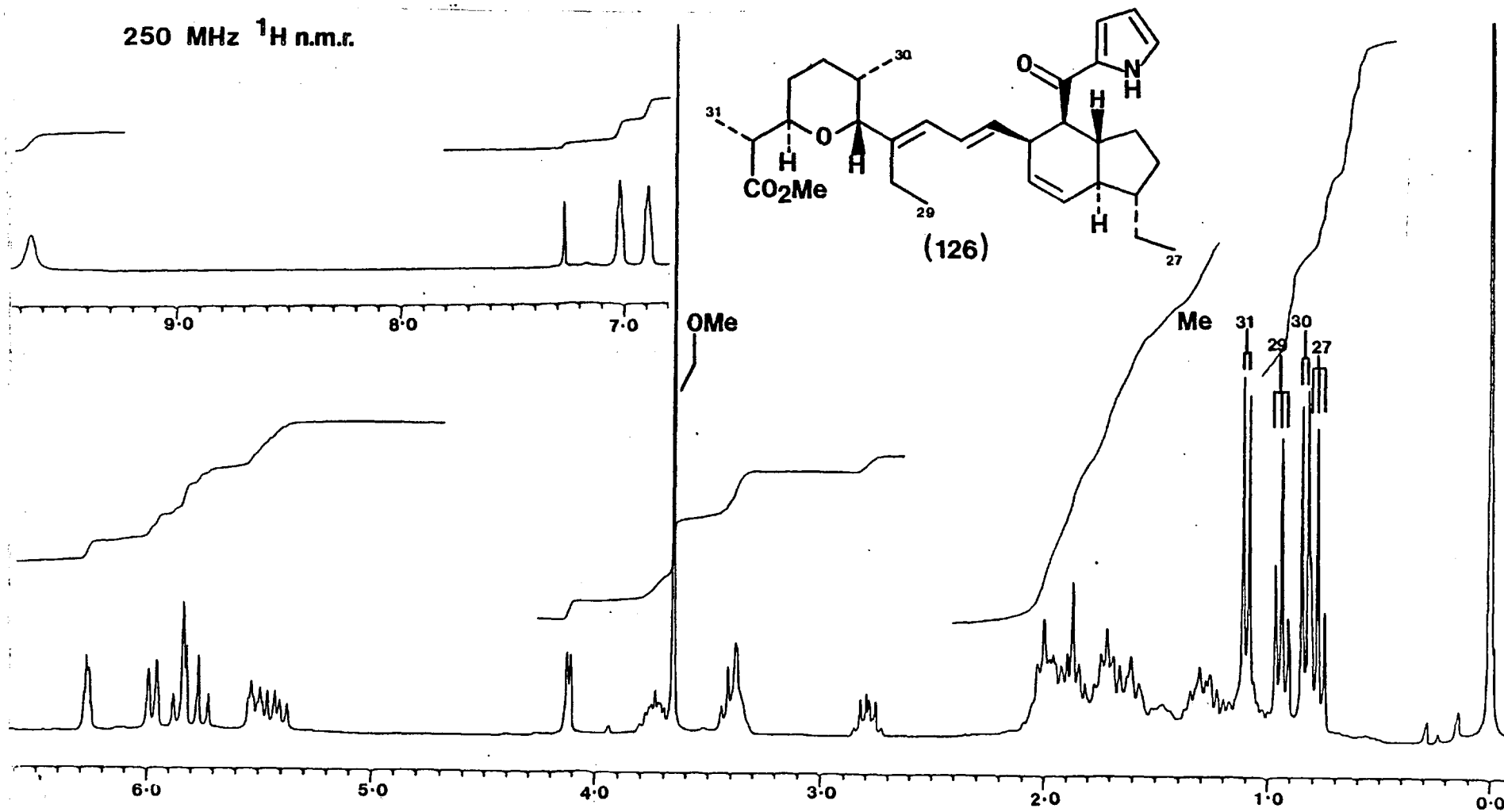


Diagram 16

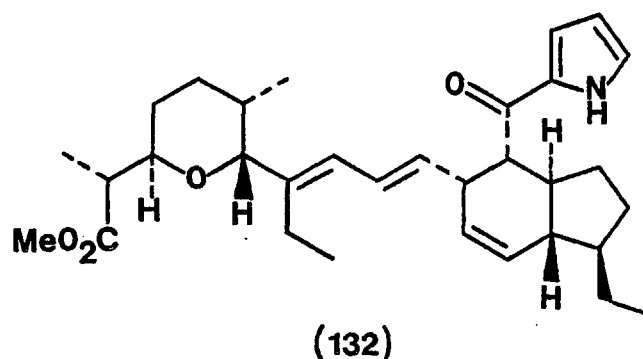
250 MHz ^1H n.m.r.



Spectrum 3

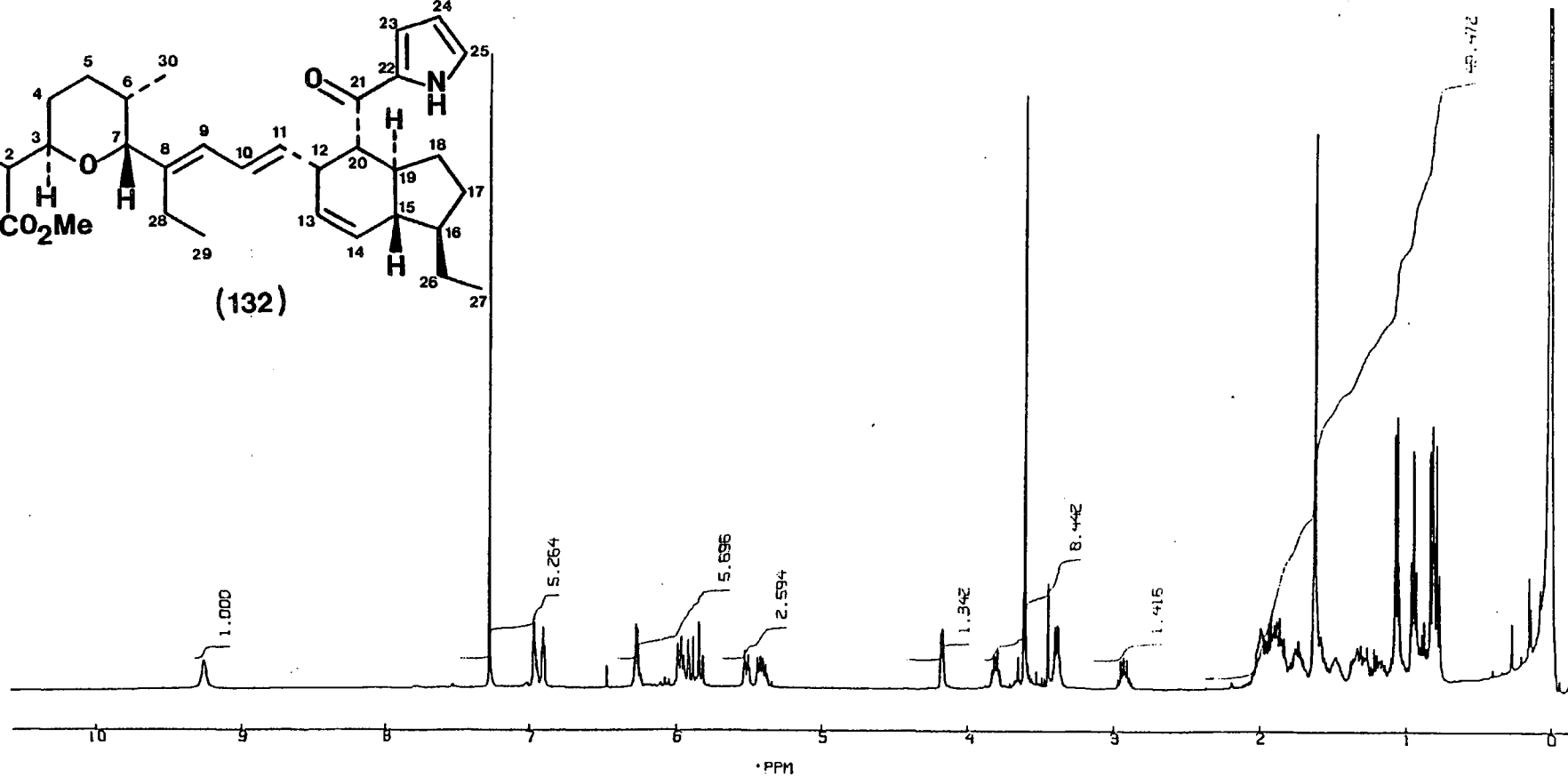
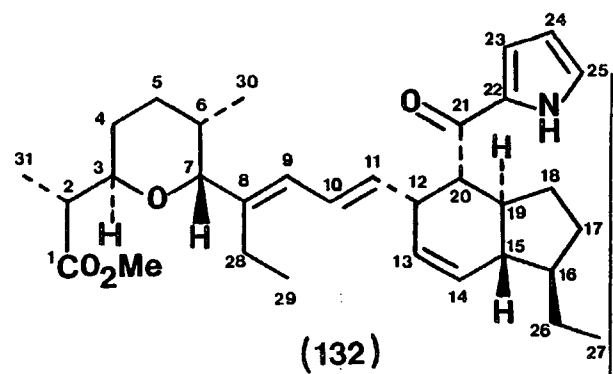
The absorptions of all five methyl groups of X-14547A methyl ester were assignable (see Spectrum 3). The absorptions of the protons flanking the oxygen of the tetrahydropyran moiety, H₃ and H₇, appeared as a multiplet at δ 3.74 and a doublet (J 4.2 Hz) at δ 4.12, respectively, as expected (H₇ deshielded relative to H₃ due to its allylic nature). H₂, H₂₀, and H₁₂ showed characteristic multiplet absorptions at δ 2.8, 3.35, and 3.4, respectively.

The diastereomeric N-SEM-pyrrolylcarbonyl (131) was also cleanly deprotected to give the X-14547A diastereomer methyl ester (132) ($[\alpha]_D^{25} + 293^0$ (c 0.37, CHCl₃)), in 63% yield. Apart from minor

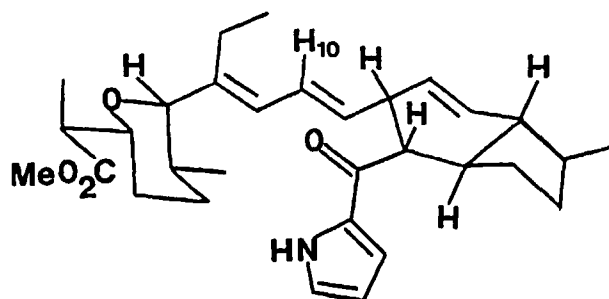


variations in chemical shifts, the only differences in the high field (400 MHz) ¹H n.m.r. spectrum of (132), compared to (126), were in the diene proton absorptions. Although the absorptions for H₁₁ were similar in (126) and (132), the H₉ and H₁₀ proton absorptions in (132) were at δ 5.82 (dd, J 11 and 0.8 Hz) and 5.92 (dd, J 15 and 11 Hz), respectively (cf. δ 5.85 (d, J 11 Hz) and 5.77 (dd, J 14 and 11 Hz) for the H₉ and H₁₀ proton absorptions in (126)). A possible explanation for this downfield shift of the H₁₀ absorption for (132) arises from consideration of the expected "globular polyether type" conformations of X-14547A methyl ester (126) and (132) in solution (see diagram 17).

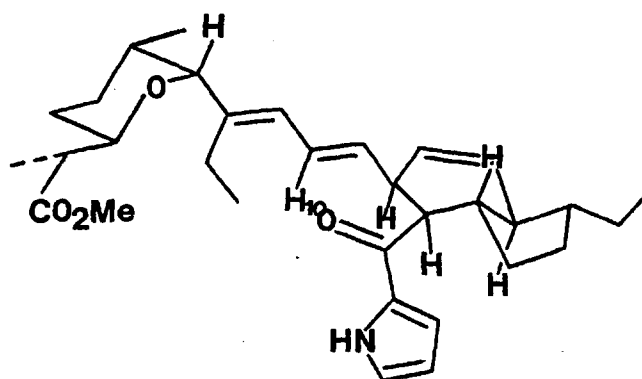
400 MHz ^1H n.m.r.



Spectrum 4



(126)



(132)

Diagram 17

Clearly, in the expected conformation for X-14547A methyl ester (126), H_{10} is quite remote from the deshielding influence of the carbonyl group of the 2-pyrrolylcarbonyl moiety. However, in the conformation for (132), H_{10} is ideally situated for the observed deshielding

due to the proximity of its environment to the carbonyl group.

Although Nicolaou has reported the clean, near qualitative, hydrolysis of X-14547A methyl ester to the natural product with lithium hydroxide (10 equiv.) in THF-water (1:1), the reaction, in our hands, was found to take longer than the seven days specified for completion by Nicolaou.³²

Our total synthesis of X-14547A was completed by the smooth hydrolysis of X-14547A methyl ester with 1N aqueous sodium hydroxide and methanol (1:3, 10-20 equiv.), at 60°C for 2h, to give the natural product (1), in 90% isolated yield. The synthetic material was identical (t.l.c., $[\alpha]_D$, i.r., ¹H n.m.r., and mass spectrum) to the natural product.

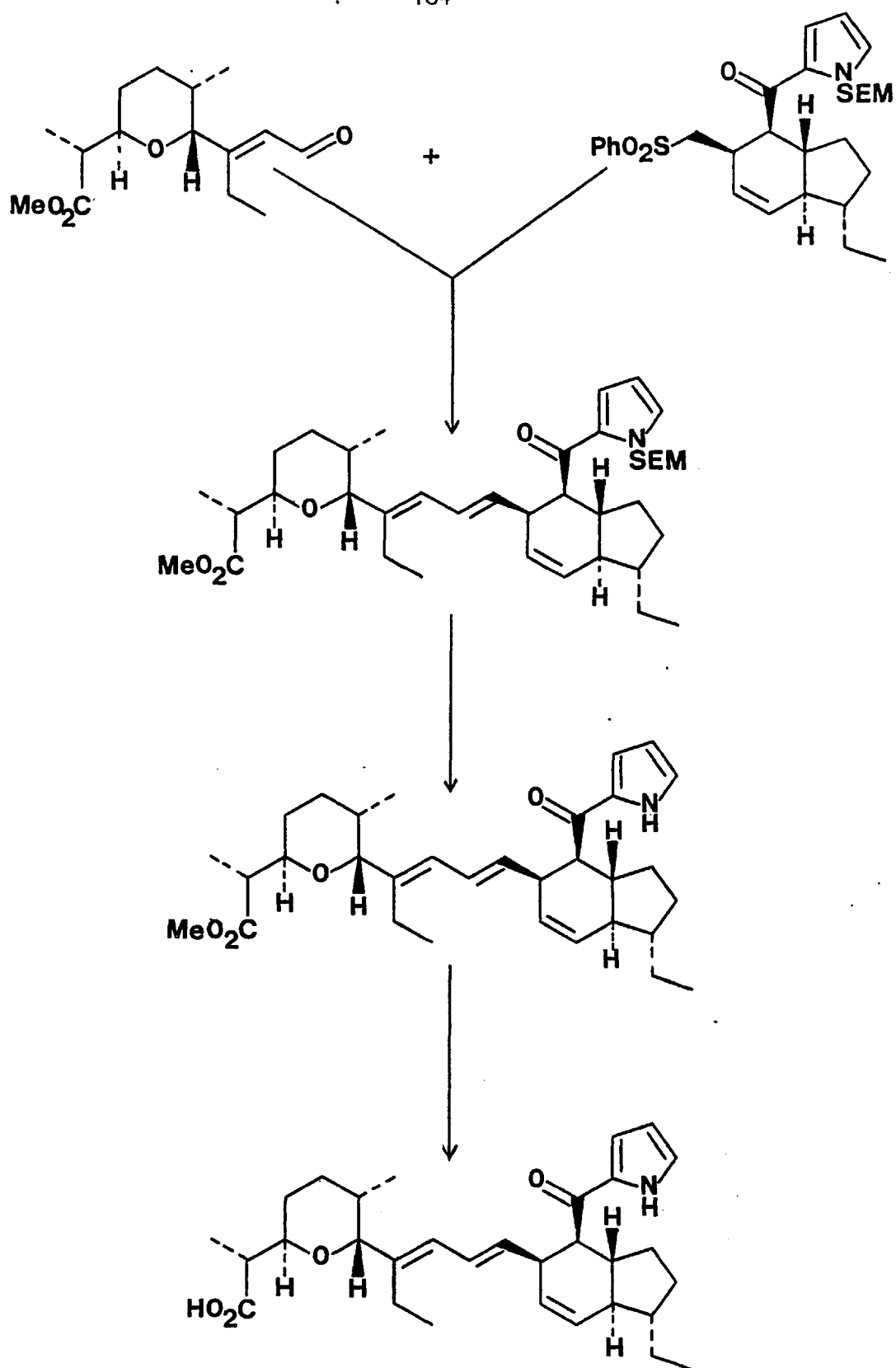
Analysis of the high field (400 MHz) ¹H n.m.r. spectrum of the synthetic X-14547A confirmed that epimerisation had not occurred during the hydrolysis of the methyl ester. Presumably, the acidity of the H-2 proton in the methyl ester (126) is sufficiently reduced by its hindered tertiary nature to preclude epimerisation under the hydrolysis conditions. There is good precedent for this in the hydrolysis of Monensin methyl ester, reported by Kishi,⁶ with sodium hydroxide (1N)-methanol (1:5) at 60°C.

The completely stereospecific synthesis of ionophore antibiotic X-14547A (Scheme 27) was accomplished in *only three steps* from the (-)-sulphone (123) in 34% overall yield. As both the Julia and de-protection step yields are expected to be increased upon further optimisation, our conversion of the sulphone (123) to X-14547A represents an extremely efficient process.

Thus the overall yield of X-14547A, for the 16 step process from 2-ethyl δ -valerolactone, was up to 7.1% (taking into account

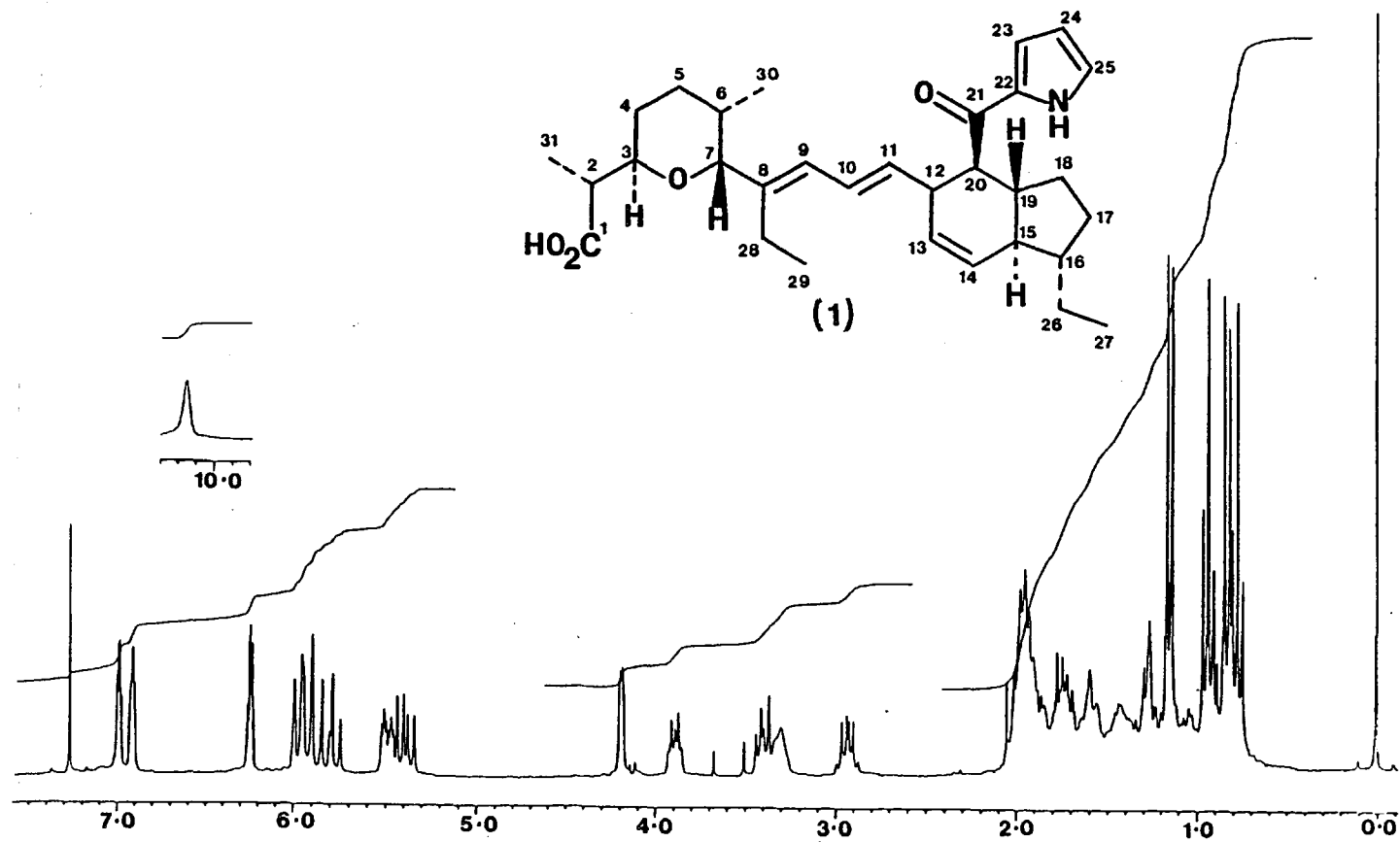
recovered starting material in a few steps) or 16% for the six steps from the (+)-lactone (70).

The complete synthesis of X-14547A, with yields, is summarised in Scheme 28.

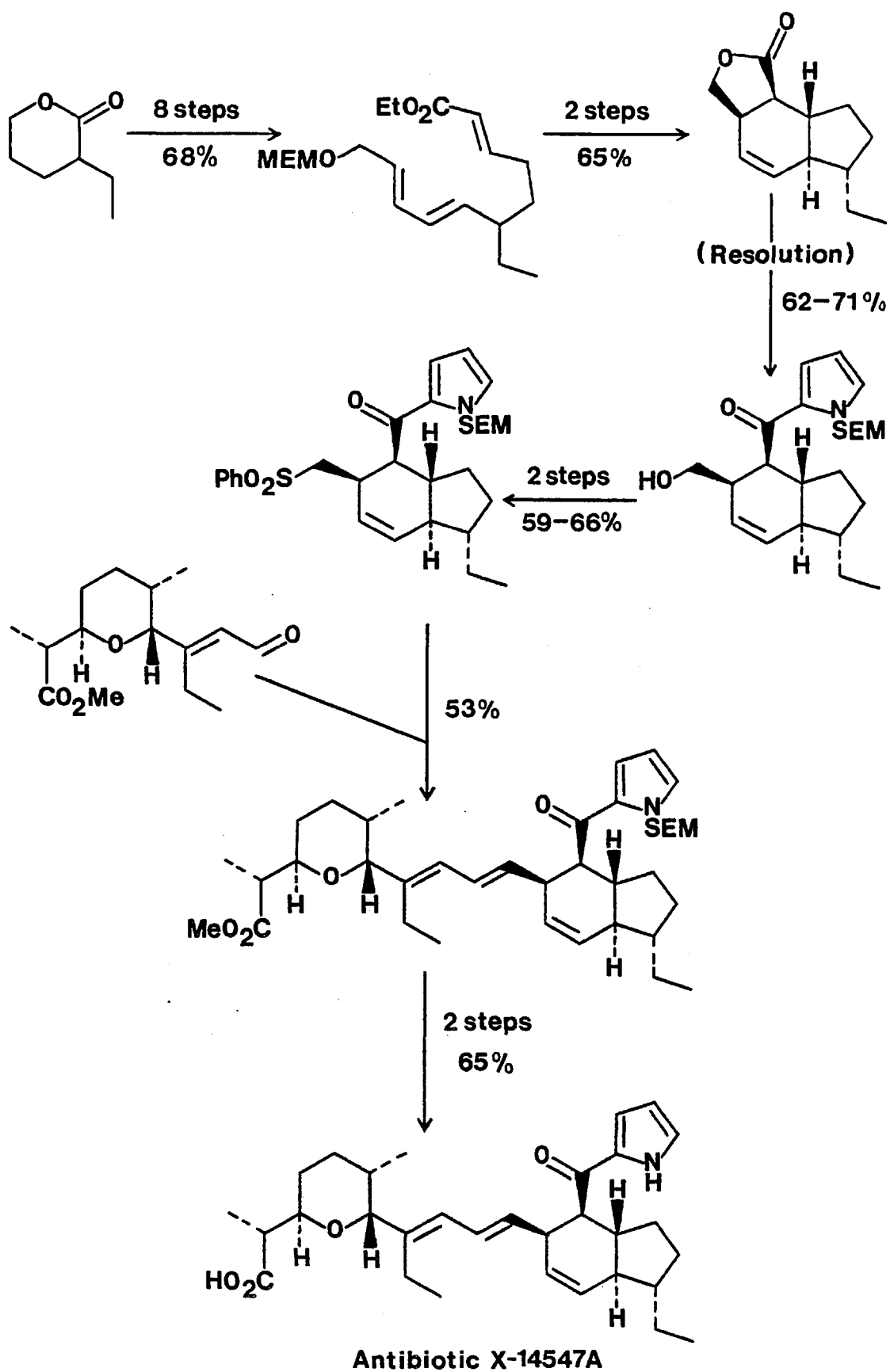


Scheme 27

250 MHz ^1H n.m.r.



Spectrum 5



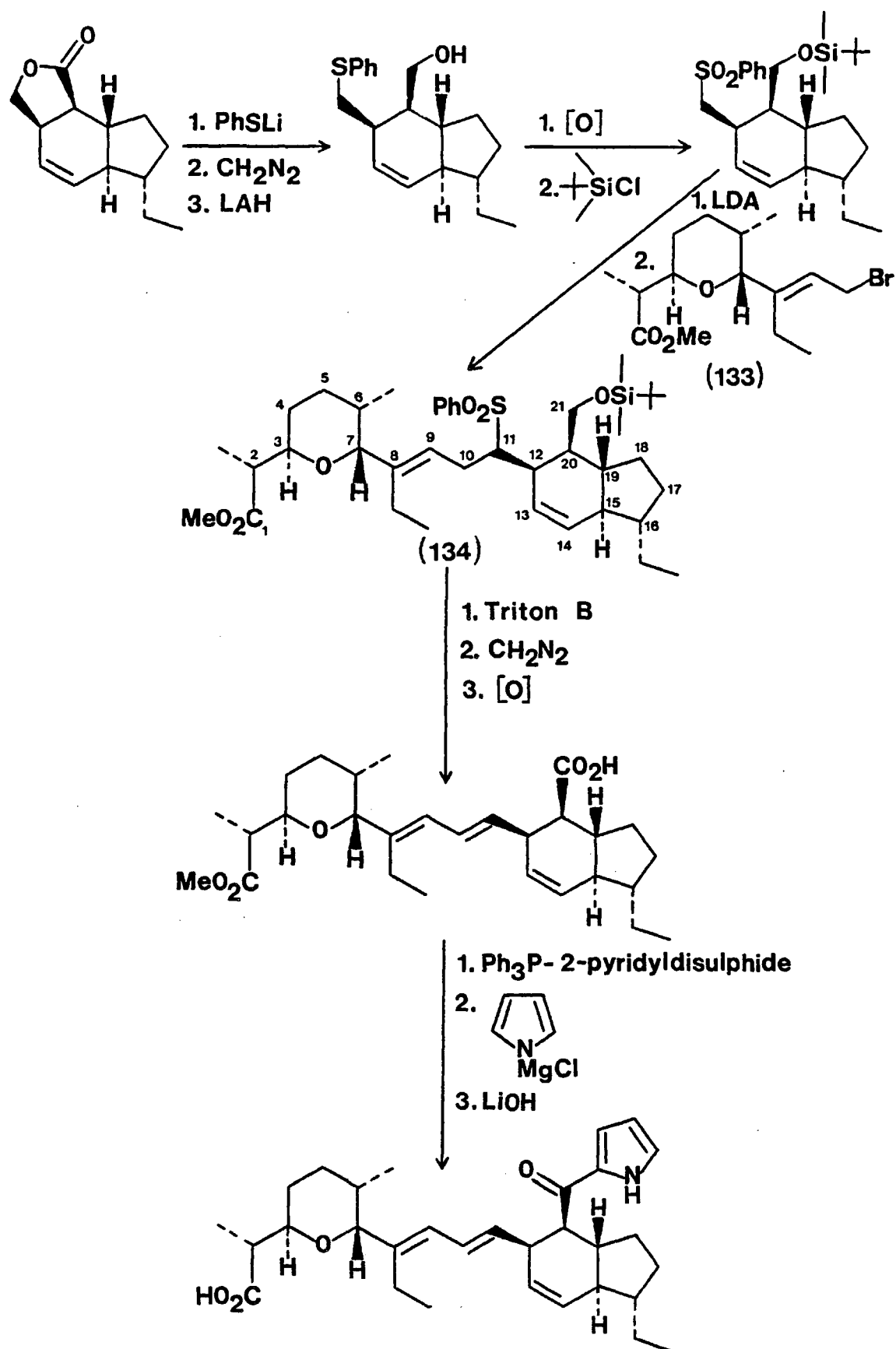
Scheme 28

4.1 A Comparison With Other Synthetic Work on X-14547A

The synthesis of antibiotic X-14547A reported by Nicolaou¹, from the lactone (+)-(70), (which was prepared with only 82% ee by an asymmetric route, see Section 2 of this thesis) is summarised in Scheme 29.

Nicolaou's 11 step conversion of (+)-(70), although characterised by impressively high yields, except for the vital coupling strategy, is almost twice as long as our synthesis. We feel that our initial aim of maximum convergency, discussed in Section 2.1 of the Introduction Section of this thesis, was achieved. It is difficult to envisage a shorter or more convergent route to X-14547A than ours, with only two steps to the natural product subsequent to coupling the left and right hand side fragments. Nicolaou's route (overall yield from the lactone (+)-(70) 18%) was somewhat less convergent than ours, requiring five further steps (counting the one pot ester activation and pyrrolyl Grignard reaction as one step) to the natural product after coupling. Although the Nicolaou route suffers from having two separate diazo-methane steps, perhaps its weakest point is the poor yield (32% or 80% based on recovered starting material) for the difficult regio- and stereospecific elimination of benzenesulphonic acid from (134). Not surprisingly, carefully defined conditions (40% triton in methanol, 45°C, 24h) were required for this tricky operation.¹ One would certainly expect problems of stereoselectivity and particularly regio-selectivity as regards possible formation of the more substituted $\Delta^{11,12}$ conjugated double bond rather than the desired $\Delta^{10,11}$ bond.

The bromide (133) was prepared by the rather lengthy route outlined in Scheme 30.



Scheme 29

steps, to the bromide (133) (6:1 (E):(Z)) in 15% yield. Ho has recently reported very similar approaches to the preparation of left hand side compounds.⁵⁵ The efforts of Roush in the area of X-14547A right hand side synthesis have been discussed earlier in this thesis.²⁴

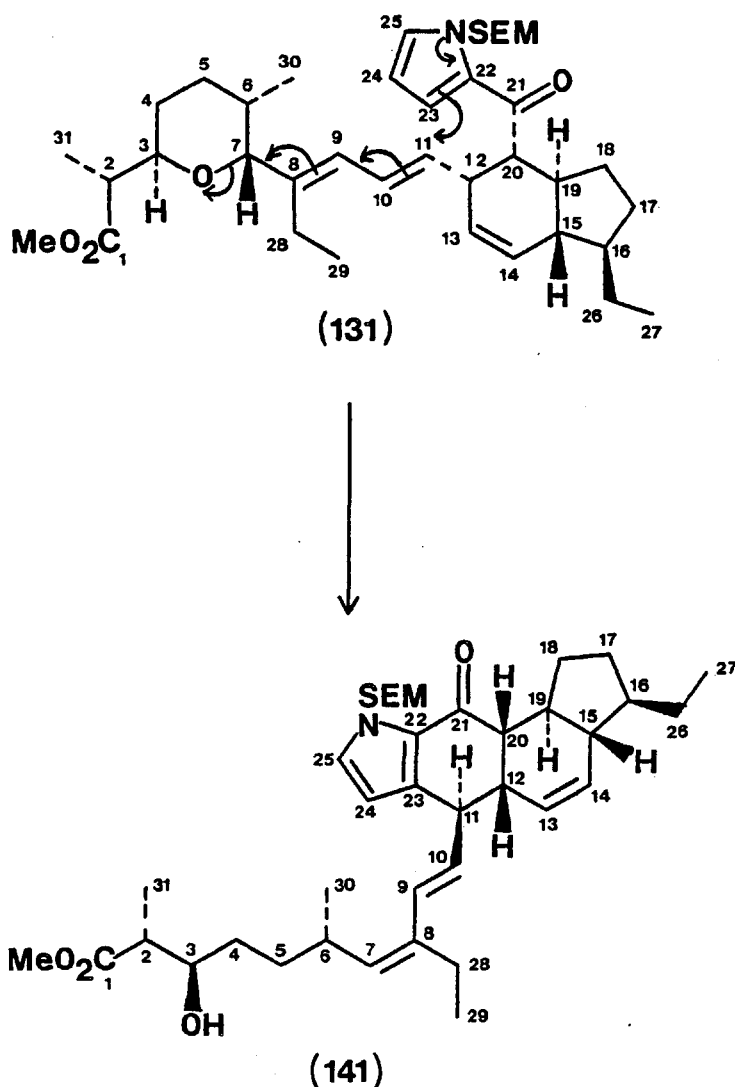
5. A NOVEL AND GENERAL REARRANGEMENT OF ANTIBIOTIC X-14547A AND SOME CLOSELY RELATED SYSTEMS.

In an attempt to remove the SEM protecting group from the N-SEM-pyrrolylcarbonyl (131), the conditions of anhydrous lithium tetrafluoroborate in acetonitrile, at 70°C, recommended by Lipshutz,^{104b} were tried. The starting material (131) was smoothly converted to a single product that was far too polar (t.l.c.) to be the desired deprotected pyrrolylcarbonyl (132). Due to the fact that the product (141), isolated in 44% yield as a colourless gum, ran at the same place as X-14547A, by t.l.c., it was initially suspected that both ester and protecting group removal had occurred. However, both i.r. ($\nu_{\max}$ 3440 (O-H Str.), 1725 (ester C=O str.), and 1645 cm⁻¹ (pyrrolylcarbonyl C=O str.)) and ¹H n.m.r. (methyl ester and SEM absorptions were both present in (141)) revealed that something quite different had happened.

Analysis of the high field (250 and 400 MHz) ¹H n.m.r. spectrum of (141) revealed several key points that led to the solution, albeit not in, as yet, a totally unambiguous fashion, of the structure. The most striking features of the ¹H n.m.r. spectrum of (141) (see Spectrum 6) were (a) the presence of only two pyrrole protons as a clean AX system (J 3 Hz) at δ 6.61 and 6.73; (b) the presence of olefinic absorptions at δ 5.5 (dd, J 16 and 9.5 Hz), 6.0 (1H, d, J 3 Hz), and 6.17 (d, J 16 Hz) that were different to those (*viz.* two dd and one d *vide supra*) in (131); (c) the presence of only one proton adjacent to oxygen, at δ 3.68 (m), with a complete absence of an absorption at the position

corresponding to the H₇ proton (the allylic proton flanking the tetrahydropyran moiety); (d) the characteristic absorptions of the two methyl groups at C-30 and C-31, the SEM protecting group, the methyl ester, and the tetrahydroindan system (see the experimental section) were all relatively unchanged as compared to those of (131).

The clear conclusion from these results was that a very unusual and stereospecific (no diastereomers were observed by t.l.c. or ¹H n.m.r.) rearrangement, involving electrophilic attack on the diene system (at C-11) by the C-23 position of the pyrrole with concomitant cleavage of the C-7-O bond in an S_N2'' process, had occurred.

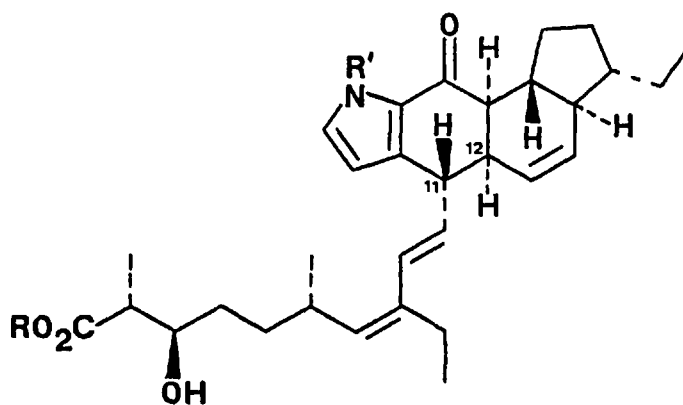


Although the $\Delta^{9,10}$ bond was clearly of the *E* configuration ($J_{9,10}$ 16 Hz) from the ^1H n.m.r. spectrum, no information about the geometry of the $\Delta^{7,8}$ bond was obtainable. However, consideration of transition states for the probable mechanism for the formation of (141) (*vide infra*) indicates that the configuration is likely to be *Z*, as depicted. It is hoped that this will eventually be confirmed by observation of a nuclear Overhauser effect between H_7 and the C-28 methylene protons.¹¹⁷

The coupling constants for the absorption attributed to the proton at the newly formed chiral centre (C-11) ($J_{11,10}$ 9.5 Hz and $J_{11,12}$ 9.5 Hz) strongly indicate a *trans* disposition of the substituents at C-11 and C-12, as depicted. The $J_{11,12}$ coupling constant would only be expected to be as large as 9.5 Hz for the *trans* coplanar conformation.⁶⁸

To our pleasure, X-14547A, X-14547A methyl ester, and N-SEM-X-14547A all underwent the same rearrangement when subjected to lithium tetrafluoroborate. Interestingly, the natural product (1) (60 min at 70°C) and its methyl ester (126) (40 min at 70°C) both rearranged faster than the SEM protected derivatives (130) and (131) (2-3h at 70°C). (1), (126), and (130) gave isolated yields of 85%, 63%, and 55% of the rearranged products (142), (143), and (144) respectively. The reaction was not completely stereospecific in these natural systems, however. A very small proportion of an uncharacterised minor diastereomer was produced in each reaction (*cf.* 100% stereospecificity for the diastereomeric (131)). Presumably this diastereomer was either a geometric isomer or the epimer at C-11.

The proton absorption attributed to H_{11} in (142), (143), and (144) also exhibited the coupling constant ($J_{11,12}$ 10 Hz) expected for the *trans* disposition of H_{11} and H_{12} .



$R = \text{Me}, R' = \text{SEM}$ (144)

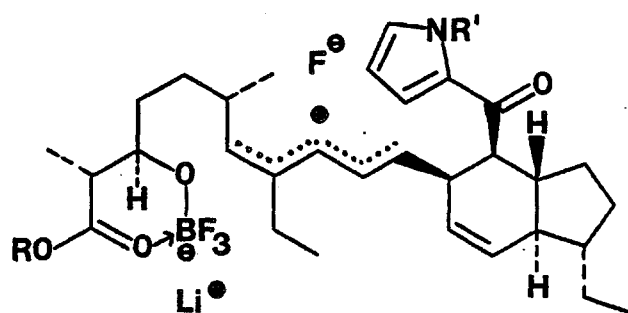
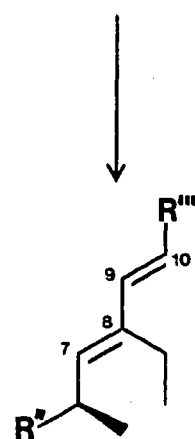
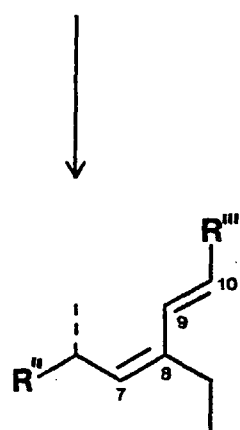
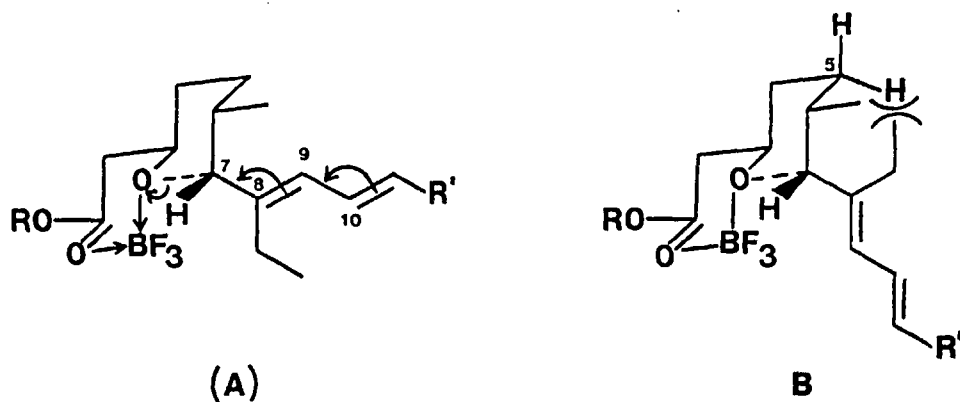
$R = \text{Me}, R' = \text{H}$ (143)

$R = \text{H}, R' = \text{H}$ (142)

The mechanism for this rearrangement presumably involves activation of the C-11 position on the diene system by strong complexation of boron trifluoride (formed by dissociation of the tetrafluoroborate), in a six membered ring, with the oxygen atoms of the tetrahydropyran moiety. Consideration of the two possible transition states for cleavage of the tetrahydropyran ring ((A) or (B) below) shows that the unfavourable interaction between the ethyl group on the diene system and the C-5 methylene group disfavors formation of the *E* olefin relative to the *Z* olefin.

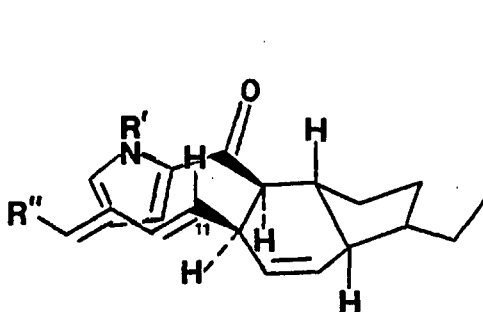
Although the reaction may be of a concerted nature it seems likely that a stepwise mechanism, involving the highly stabilised doubly allylic planar carbonium ion (145), might be involved in these rearrangements.

The activation of the tetrahydropyran system by biological systems to form (145) from X-14547A might be an extremely facile process. The interaction of the reactive carbonium ion (145) with biological nucleophiles may have considerable implications to the mechanism of many of the biological properties of X-14547A.

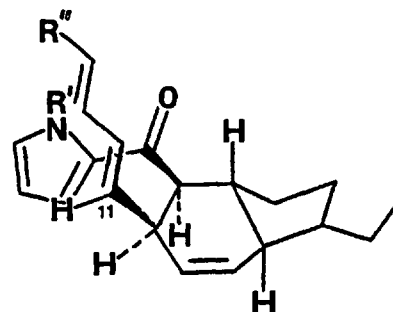


(145)

The control of the stereochemistry at C-11 in the rearrangement (assuming the previous assignment from ^1H n.m.r. evidence is correct) presumably arises *via* reaction at the α -face of the diene moiety in the extended conformation (A) rather than the more congested conformation (B).



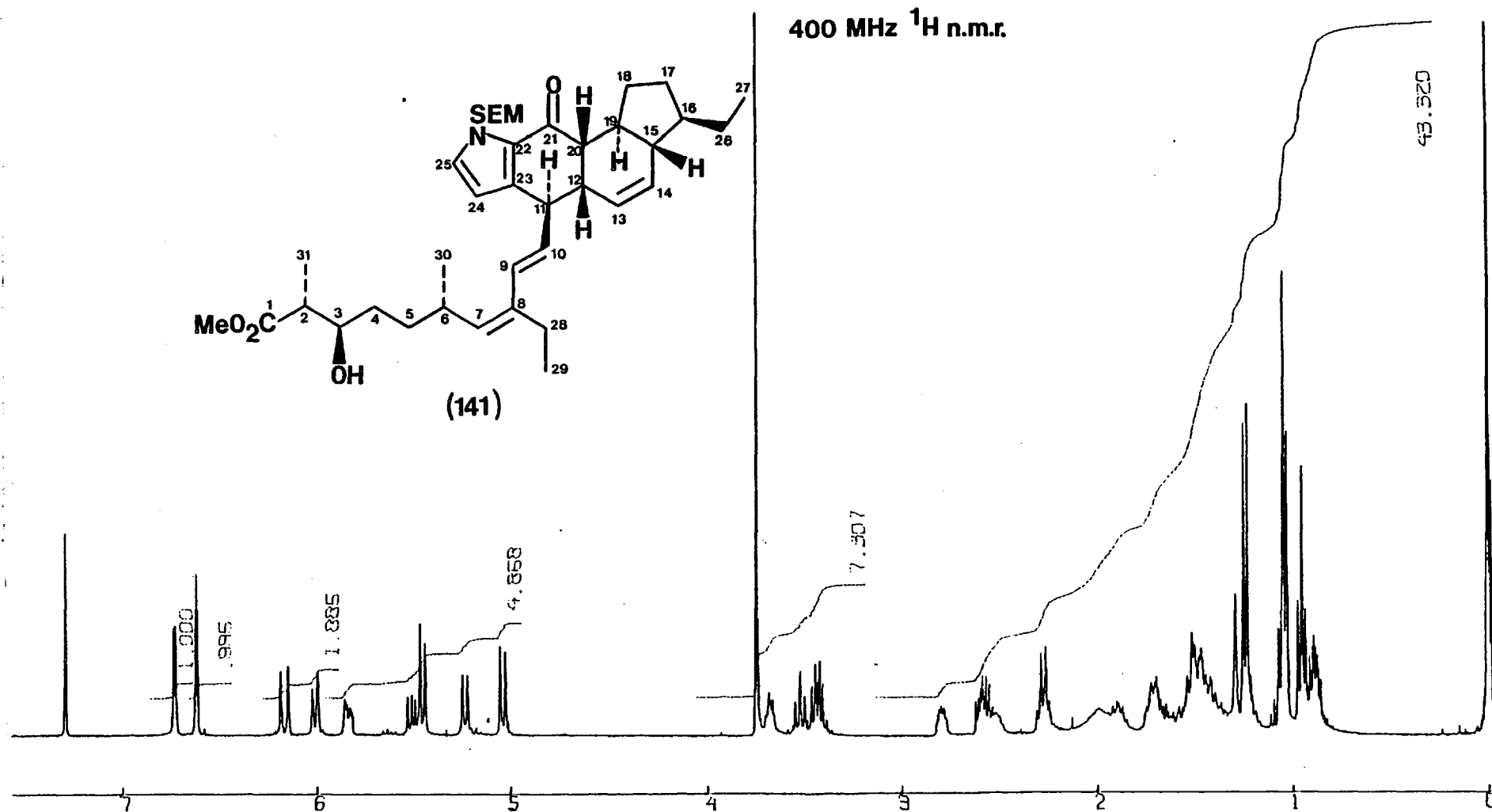
(A)



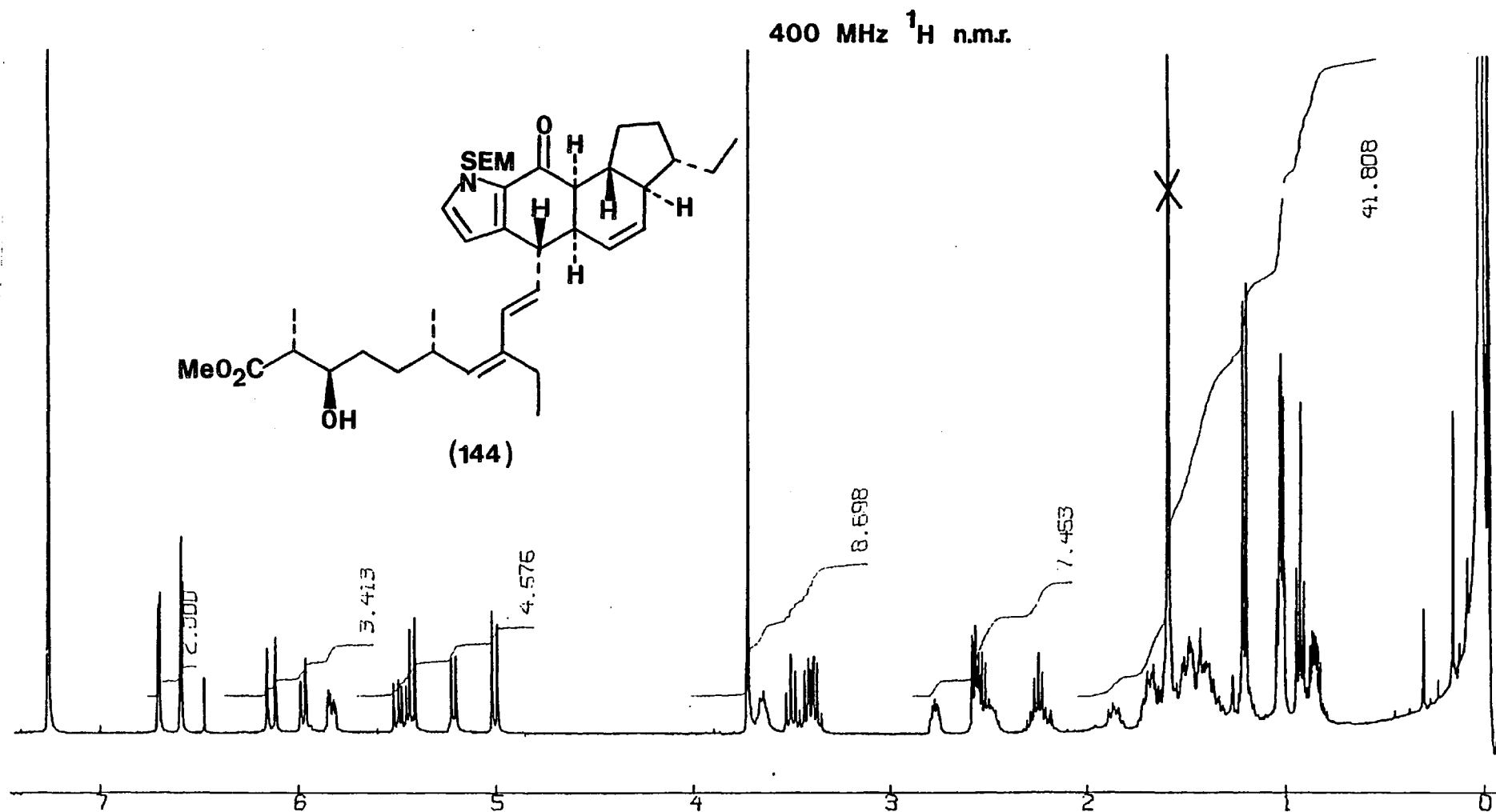
(B)

This novel and mechanistically very interesting rearrangement, with important possible biological implications, led to a strikingly unusual group of tetracyclic compounds with a lengthy (11 carbon atoms) acyclic appendage.

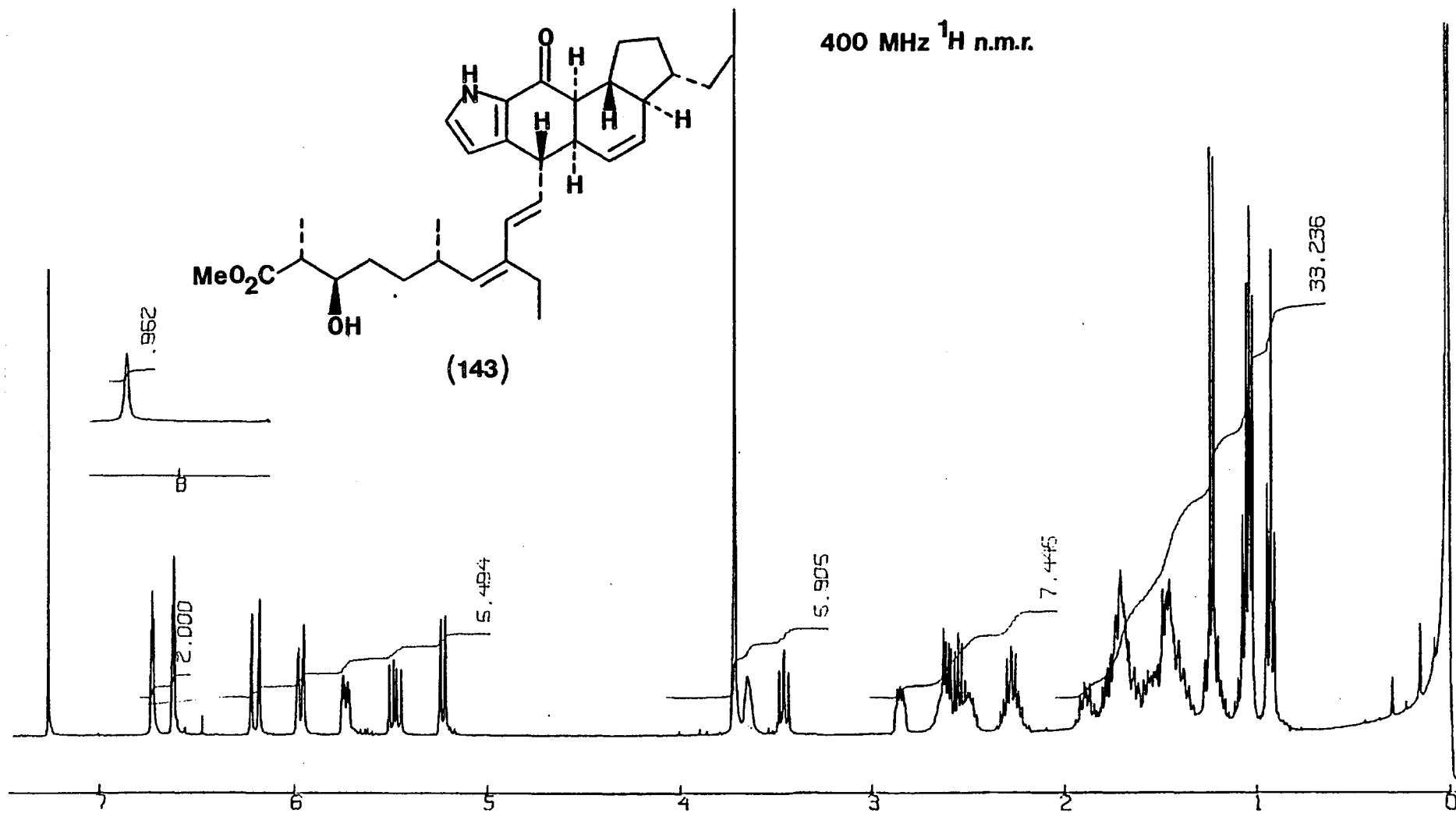
The biological properties of the compound derived from X-14547A (142) are currently under investigation by Pfizer Ltd.



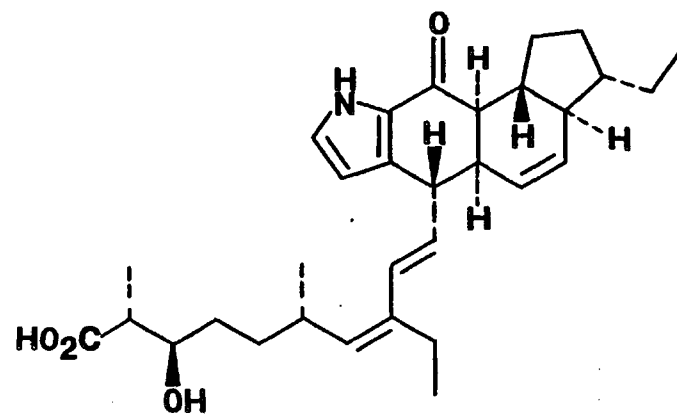
Spectrum 6



Spectrum 7

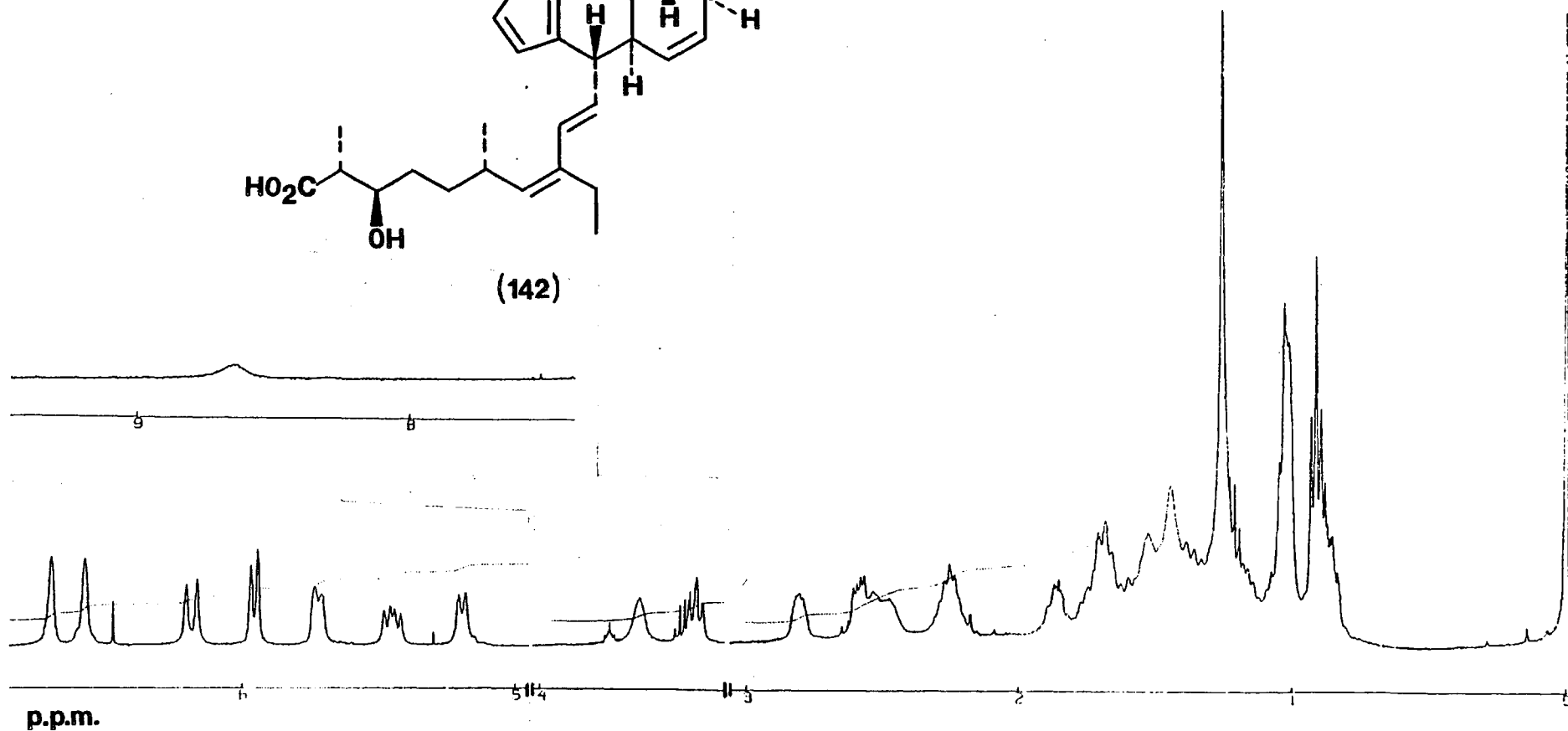


Spectrum 8



(142)

400 MHz ^1H n.m.r.



Spectrum 9

EXPERIMENTAL

Unless otherwise stated, i.r. spectra were recorded for solutions in chloroform or liquid films on a Perkin Elmer 298 machine. ^1H N.m.r. spectra were recorded at 60 MHz on a Varian EM 360A, at 250 MHz on a Bruker WM 250, and at 400 MHz on a Bruker WH 400 instrument for solutions in CDCl_3 with tetramethylsilane as internal standard. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. Mass spectra were determined with a VG Micromass 7070B instrument. Microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory.

Analytical thin layer chromatography (t.l.c.) was performed on Merck precoated silica gel F₂₅₄ plates. Preparative chromatography was carried out on columns of Merck Kieselgel H. Flash chromatography⁶⁰ was carried out on columns of Merck 9385 Kieselgel 60 or MN-Kieselgel 60 (both 230-400 mesh). For both forms of column chromatography the amount of silica, in grammes or column inches, and the column diameter are given in brackets. Except where stated, a flow rate of two column inches per minute for flash chromatography or one inch per minute for preparative chromatography was maintained using top pressure provided by a nitrogen cylinder. All solvents used for chromatography were redistilled.

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification or purified by standard means. Tetrahydrofuran (THF) was redistilled from sodium/benzophenone ketyl onto activated 4A molecular sieves and used within two days; dichloromethane was freshly distilled from phosphorous pentoxide; pyridine, diisopropylamine, trimethylchlorosilane

triethylamine, tetra-N-methylethylenediamine (TMEDA), and 1,2-dimethoxyethane (DME) were distilled from calcium hydride and stored over 4A molecular sieves or sodium hydroxide pellets; dimethylsulphoxide (DMSO) was distilled from calcium hydride and N,N-dimethylformamide (DMF) from 4A molecular sieves, both under reduced pressure; acetonitrile was dried with 4A molecular sieves and redistilled; toluene was freshly distilled from sodium wire; diethyl ether and benzene were dried over sodium wire; hexamethylphosphoramide (HMPA) was heated at 200°C with calcium hydride overnight before distillation onto 4A molecular sieves at reduced pressure; pyrrole was redistilled from calcium hydride at slightly reduced pressure immediately prior to use. All purified and dried solvents and reagents were stored under dry argon.

Anhydrous reactions were performed, under dry argon, in glassware dried at 150-200°C for at least three hours, assembled and cooled under a stream of dry argon. Reaction temperatures are reported as internal (iT) or bath (bT). Organic solutions were routinely dried with anhydrous sodium or magnesium sulphate and evaporated with a rotary evaporator, using a water aspirator, followed by static evaporation with an oil pump.

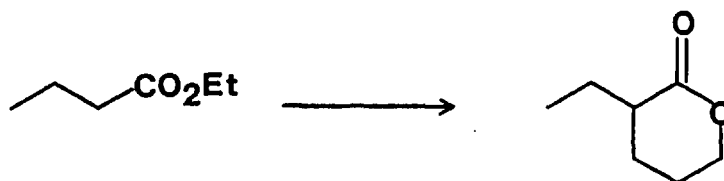
Melting points were determined with a Kofler hot stage apparatus and are uncorrected. All compounds prepared were racemic unless given a (+)- or (-)- prefix.

1. Preparation of 1-Trimethylsilyloxy-3-iodopropane (41).



3-Chloropropan-1-ol (30g, 0.317 mole) and dry sodium iodide (100g, 0.667 mole) were stirred and heated in anhydrous acetone (500 ml) at reflux in the dark for 24h. The precipitated sodium chloride was filtered from the yellow solution and the acetone removed at reduced pressure. Diethyl ether (250 ml) was added and after filtration of the remaining solids the ethereal solution was washed with 5% aqueous sodium metabisulphite (2 x 50 ml) and water before drying and concentration to a slightly discoloured oil (58.45g). Dry pyridine (58.5g, 60 ml, 0.74 mole) and trimethylchlorosilane (60.3g, 70.5 ml, 0.56 mole) were added dropwise to a vigorously stirred solution of the crude 3-iodopropan-1-ol (58.45g, 0.312 mole) in dry THF (300 ml) over 80 min at 0°C (bT). After stirring at room temperature for 1h the reaction mixture was rapidly filtered through a Celite pad. The filtrate, together with a diethyl ether (500 ml) washing of the solids on the Celite pad was concentrated at reduced pressure before addition of more diethyl ether (500 ml). After filtration through a celite pad the ethereal solution was concentrated to a pale brown oil which was distilled *in vacuo* to give 1-trimethylsilyloxy-3-iodopropane (67g, 0.26 mole, 82%) as a colourless liquid, b.p. 40-43°C at 0.2 mm Hg; ν_{max} 2960, 2900, 2870, 1250, 1100, and 840 cm^{-1} ; $\delta(\text{CCT}_4)$ 0.1 (9H, s), 1.9 (2H, m), 3.2 (2H, t, J 6 Hz), and 3.55 (2H, t, J 6 Hz).

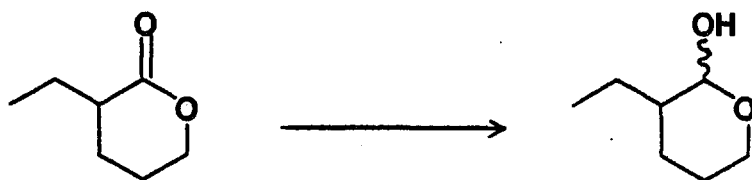
2. Preparation of 3-Ethyl-2-oxotetrahydropyran (2-ethyl- δ -valerolactone) (40).



n-Butyl lithium (292 ml of a 1.54N solution in hexane, concentrated to give an approximately 3N solution, 150 ml, 0.45 mole) was added dropwise to cooled dry diisopropylamine (63 ml, 45.5g, 0.45 mole) in dry THF (45 ml) at 0 to 3°C (iT) over 30 min. After 30 min at -10°C, dry THF (600 ml) was added before cooling to -76°C and addition of dry HMPA (156 ml, 1.03 mole) at -76--75°C in 1h. The resulting clear, pale yellow solution was stirred at -76°C for 1h before dropwise addition of dry ethyl butyrate (55.8 ml, 52.2g, 0.45 mole) in dry THF (240 ml) during 145 min at -76--74°C. After stirring the clear, pale yellow enolate solution for 80 min at -76°C dry 1-trimethylsilyloxy-3-iodopropane (61 ml, 0.35 mole) was added rapidly in one portion. After stirring at -75°C for 1h the now almost colourless solution was stirred up to 0°C in 45 min before cooling to -60°C and careful pouring onto 10% aqueous hydrochloric acid (950 ml) and ice (200g). After 10 min stirring, diethyl ether (400 ml) was added. The aqueous phase was separated and extracted with more diethyl ether (3 × 300 ml). The combined organic solutions were combined and washed successively with 5% aqueous sodium thiosulphate (200 ml), 5% aqueous sodium bicarbonate (200 ml), and brine (6 × 150 ml) before drying and concentration to a pale yellow oil (68.65g). The crude 4-ethoxycarbonylhexan-1-ol (42) was refluxed with *p*-toluenesulphonic acid (0.5g) in toluene (4000 ml) with removal of ethanol-toluene (ca. 150 ml) by distillation

for 1h. After washing with 5% aqueous sodium bicarbonate (2 × 200 ml) and brine (200 ml), the crude solution of the lactone was dried and concentrated to a mobile pale yellow oil. Multiple flash chromatography (6" silica, 50 mm dia. column) with 5:5:1 CH₂Cl₂ : 40-60 b.p. petrol: diethyl ether (t.l.c. : R_f 0.35), in ten equal portions, using the same silica for all ten elutions with a flushing of ether (7") and then the column eluant (7") between runs, gave pure 2-ethyl- δ -valerolactone (34.02g, 0.266 mole, 76% based on 1-trimethylsilyloxy-3-iodopropane) b.p. 44-46°C at 0.7 mm Hg (Lit.,^{87b} 108-112°C at 12 mm Hg); ν_{max} 1730 cm⁻¹; δ 0.95 (3H, t, J 7 Hz), 0.8 - 2.7 (7H, m), and 4.2 (2H, m) (Found: M⁺, 128.0834. C₇H₁₂O₂ requires M, 128.0837).

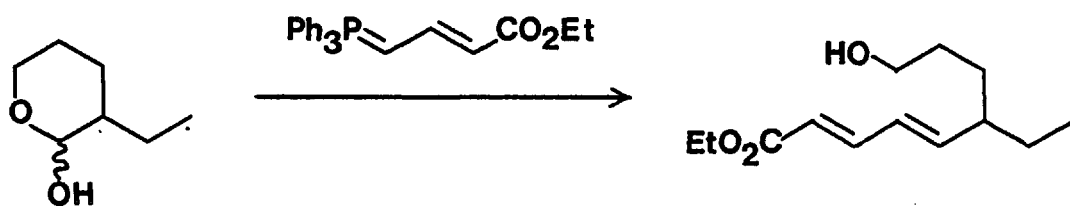
3. Preparation of 3-Ethyl-2-hydroxytetrahydropyran (2-ethyl- δ -valerolactol) (43).



Diisobutyl aluminium hydride (ca. 1.3 equiv., 150.6 ml of a 25% soln. in toluene, 0.34 mole) was added dropwise to a solution of 2-ethyl- δ -valerolactone (34.02g, 0.266 mole) in dry toluene (690 ml) at -76--74°C (iT) in 70 min. After a further 45 min at -76°C the cold solution was poured onto 10% hydrochloric acid (670 ml) and ice (100g). After vigorously shaking the mixture to destroy excess hydride the aqueous phase was separated and extracted with diethyl ether (4 × 150 ml). The combined organic solutions were washed with 5% aqueous sodium bicarbonate (2 × 150 ml), water (150 ml), and brine (150 ml) before drying and concentration *in vacuo* to give 2-ethyl- δ -valerolactol (34.6g,

0.266 mole, 100%), as a slightly pale yellow oil, as a 1.29 : 1 mixture of *anti*- and *syn*-diastereoisomers by ^1H n.m.r. (250 MHz), t.l.c. : R_f 0.35, 32% ethyl acetate - 40-60 b.p. petrol, ν_{max} 3390 cm^{-1} ; δ (for the inseparable mixture of anomers) 0.91 and 0.92 (total 3H, both t, J 7 Hz), 1.1 - 1.35 (2H, m), 1.5 - 1.8 (4H, m), 2.9 (*syn*-) and 3.32 (*anti*-) (total 1H, both br s, exchangeable, OH), 3.5 (*anti*-) and 4.0 (*syn*-) (total 2H, both m), 4.45 (0.563 H, d, J 7 Hz, *anti*- anomeric H), and 5.1 (0.437 H, s, *syn*- anomeric H); M^+ 130; (Found: C, 64.72; H, 11.04. $\text{C}_7\text{H}_{14}\text{O}_2$ requires C, 64.58; H, 10.83%).

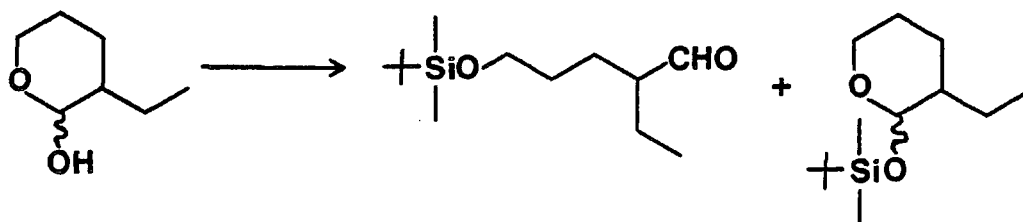
4. Preparation of Ethyl (*E,E*)-1-Hydroxy-4-ethylnona-5,7-dienoate (45).



A solution of (3-ethoxycarbonylallylidene)triphenylphosphonium bromide (2.395g, 5.0 mmol) in chloroform (19 ml) was extracted at 0°C with ice and water (11 ml) containing sodium hydroxide (0.2g, 5.5 mmol). The orange chloroform solution of (3-ethoxycarbonylallylidene)triphenylphosphorane was dried over calcium chloride before concentration, at reduced pressure, to an orange oil which was immediately covered with an argon atmosphere. After a few minutes the oil crystallised to give a solid that was dissolved in dry DMF (4 ml) by heating to 60°C. 2-Ethyl- δ -valerolactol (0.42g, 4.0 mmol) in dry DMF (1.5 ml) was added to the stirred solution at 60°C. After stirring at 60°C for 2h, 100°C for 90 min and 120°C for 1h, the brown reaction mixture was poured onto

10% aqueous hydrochloric acid (20 ml) and ice (10g) overlaid with diethyl ether (50 ml). Diethyl ether (3 × 50 ml) extracts of the aqueous phase were combined with the organic phase and washed with 10% aqueous hydrochloric acid (2 × 15 ml), 5% aqueous sodium bicarbonate (2 × 15 ml), and water (15 ml) before drying and concentration *in vacuo* to a mobile brown oil (1.65g). This was flash chromatographed (6" silica, 45 mm dia. column) with 25% ethyl acetate - 40-60 b.p. petrol to give recovered 2-ethyl- δ -valerolactol (0.18g, 1.38 mmol, 34.5% recovery) (t.l.c. : R_f 0.37, 30% ethyl acetate - 40-60 b.p. petrol), the major product, ethyl (*E,E*)-1-hydroxy-4-ethylnona-5,7-dienoate (0.21g, 0.93 mmol, 23%) as a clear, colourless oil, t.l.c. : R_f 0.31, 30% ethyl acetate - 40-60 b.p. petrol, $\nu_{\max}$ 3410, 1710, 1640, and 1618 cm^{-1} ; δ 0.8 (3H, t, J 7 Hz), 1.25 (3H, t, J 7 Hz), 1.1 - 1.8 (7H, m), 2.35 (1H, br.s, exchangeable, OH), 3.55 (2H, m), 4.15 (2H, q, J 7 Hz), 5.4 - 6.5 (3H, m), and 6.9 - 7.4 (1H, m); M^+ 226, and a mixture (ca. 1:1) of the two (40 mg).

5. Preparation of 5-t-Butyldimethylsilyloxy-2-ethylpentanal (48) and 2-t-Butyldimethylsilyloxy-3-ethyltetrahydropyran (49).



(a) Using 5-Butyldimethylchlorosilane and Imidazole in DMF.

A solution of t-butyldimethylchlorosilane (44g, 0.293 mole, 1.1 equiv.) in dry DMF (70 ml) was added dropwise over 1h to a stirred mixture of 3-ethyl-2-hydroxytetrahydropyran (34.6g, 0.266 mole) and dry

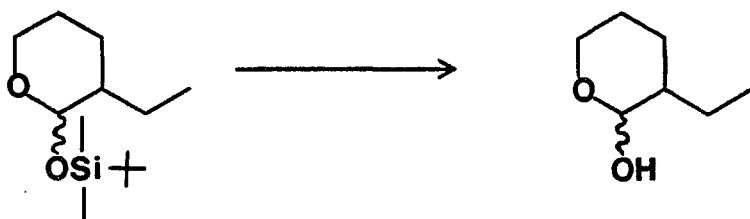
imidazole (27.13g, 0.399 mole, 1.5 equiv.) in dry DMF (20 ml) at room temperature. After stirring for 2h the reaction mixture was diluted with diethyl ether (500 ml) and water (100 ml). The organic layer was combined with a diethyl ether (4 × 50 ml) extract of the aqueous phase and washed with 0.1 N hydrochloric acid (2 × 100 ml), saturated brine (100 ml), 5% aqueous sodium bicarbonate (2 × 100 ml), and more saturated brine (100 ml) before drying and careful concentration *in vacuo* to give the mixture of (48) and (49) as a mobile, pale yellow oil (64g, 0.262 mole, 98.5%). Multiple flash chromatography (6" silica, 55 mm dia. column) with 9% diethyl ether - 40-60 b.p. petrol, in 10 × 6g portions, then 2 × 7g portions for the resulting mixed fractions (10g) and remaining crude product, and finally one 3g portion, using the same silica for all thirteen elutions with a flushing of 7" diethyl ether and then 7" of column eluant between runs, gave the pure (>98% by t.l.c.) 5-*t*-butyldimethylsilyloxy-2-ethylpentanal (31.53g, 0.129 mole, 48.5% or 67% based on recovered 2-ethyl- δ -valerolactol upon quantitative desilylation of the minor product (49)), t.l.c. : R_f 0.35, 9% diethyl ether - 40-60 b.p. petrol, $\nu_{\max}$ 2700, 1725, 1470, 1460, 1250, 1100, 840, and 775 cm^{-1} ; δ 0.05 (6H, s), 0.8 (9H, s), 0.7 - 2.3 (10H, m), 3.55 (2H, m), and 9.5 (1H, d, J 3.2 Hz); M^+ 244, and 2-*t*-butyldimethylsilyloxy-3-ethyltetrahydropyran (18g, 74 mmol, 27.8%), t.l.c. : R_f 0.55, 9% diethyl ether - 40-60 b.p. petrol, $\nu_{\max}$ 1460, 1385, 1250, 1160, 1075, 830, and 775 cm^{-1} ; δ 0.05 (6H, s), 0.8 (9H, s), 0.6 - 2.0 (10H, m), 3.3 (1H, m), 3.8 (1H, m), and 4.25 (1H, d, J 5.2 Hz); M^+ 244.

(b) Using *t*-Butyldimethylchlorosilane, Triethylamine, and 4-*N,N*-Dimethylaminopyridine in Dichloromethane

t-Butyldimethylchlorosilane (3.5g, 23.2 mmol) in dry dichloromethane (34 ml) was added dropwise to 3-ethyl-2-hydroxytetrahydropyran

(1.75g, 13.5 mmol), triethylamine (2.73g, 3.75 ml, 27 mmol), and 4-N,N-dimethylaminopyridine (0.278g, 2.27 mmol) in dry dichloromethane (34 ml) at -78° (bT). After warming to 0°C over 2h the solution was stirred at room temperature overnight and then for a further 30 min in the presence of more t-butyltrimethylchlorosilane (500 mg, 3.3 mmol). Water (50 ml) was added and the separated aqueous phase extracted with dichloromethane (3×20 ml). The combined organic layers were washed with 1% aqueous hydrochloric acid (3×20 ml), 5% aqueous sodium bicarbonate (30 ml), water (10 ml), and brine (20 ml) before drying and careful concentration *in vacuo* to a mobile pale yellow oil. Flash chromatography (6" silica, 50 mm dia. column) with 9% diethyl ether - 40-60 b.p. petrol gave a 60:40 mixture of the aldehyde (48) and (49) (1.5g, 6.15 mmol, 46%) and the pure aldehyde (48) (1.43g, 5.86 mmol, 43.4% or 79% based on recovered 2-ethyl- δ -valerolactol upon quantitative desilylation of the 60:40 mixture.

6. Desilylation of 2-t-Butyldimethylsilyloxy-3-ethyltetrahydropyran (49) : Preparation of 2-Hydroxy-3-ethyltetrahydropyran (43).



(a) Using Tetra-n-butylammonium Fluoride in THF.

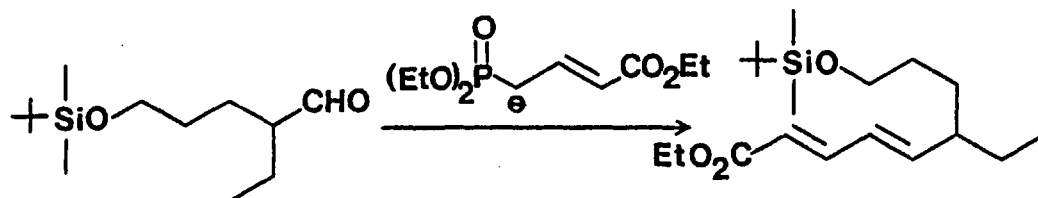
Tetra-n-butylammonium fluoride (4.51 ml of a 1.0 N soln. in THF, 4.5 mmol, 1.1 equiv.) was added to 2-t-butyl-2-dimethylsilyloxy-3-ethyltetrahydropyran (1.0g, 4.1 mmol) in dry THF (1.0 ml). After stirring

at room temperature for 1h the THF was removed *in vacuo* and the resulting viscous oil dissolved in diethyl ether (50 ml). Water (10 ml) was added and diethyl ether (3 × 10 ml) extracts were combined with the pale yellow ethereal solution and washed with water (5 ml), 1% aqueous hydrochloric acid (2 × 3 ml), and more water (5 ml) before drying and careful concentration *in vacuo* to a mobile pale yellow oil. Flash chromatography (5.5" silica, 20 mm dia. column) with 45% diethyl ether - 40-60 b.p. petrol gave 2-hydroxy-3-ethyltetrahydropyran (500 mg, 3.85 mmol, 94%).

(b) Using 2:1 Acetic acid-Water.

2-t-Butyldimethylsilyloxy-3-ethyltetrahydropyran (1.33g, 5.45 mmol) was stirred with 2:1 glacial acetic acid-water (50 ml) for 4h before addition of 40-60 b.p. petrol (100 ml). The aqueous layer was extracted with more 40-60 b.p. petrol (3 × 50 ml) and the combined organic phases washed with saturated aqueous sodium bicarbonate to remove acetic acid. After washing with 1% aqueous hydrochloric acid (20 ml) and brine (2 × 20 ml) the dried solution was carefully concentrated *in vacuo* to a colourless oil. Flash chromatography (5" silica, 20 mm dia. column) with 45% diethyl ether - 40-60 b.p. petroleum ether gave 2-hydroxy-3-ethyltetrahydropyran (680 mg, 5.23 mmol, 96%).

7. Preparation of Ethyl (*E,E*)-1-*t*-butyldimethylsilyloxy-4-ethyl-5,7-nonadienoate (47).



(a) *n*-Butyl lithium (4.3 ml of a 1.4 N solution in hexane, 6.0 mmol) was added dropwise to dry diisopropylamine (0.82 ml, 0.605g, 6.0 mmol) in dry THF (1 ml), at such a rate as to maintain the temperature at 0°C (iT), over 9 min. After 20 min at 3°C more dry THF (6.3 ml) was added to give a clear colourless solution of lithium diisopropylamide which was cooled to -78°C. Ethyl 4-diethylphosphonocrotonate (1.5g, 6.0 mmol) in dry THF (1 ml) was added dropwise over 30 min at -78- -73°C (iT) to give a clear yellow solution which was stirred at -78°C for 90 min. The solution was warmed to -48° over 10 min before addition of 5-*t*-butyldimethylsilyloxy-2-ethylpentanal (1.22g, 5.0 mmol) in dry THF (1.5 ml) during 5 min. The resulting much paler yellow solution was stirred from -45°C up to 20°C over 2h before addition of ethanol (1 ml). After the removal of THF *in vacuo* the resulting thick orange oil was diluted with diethyl ether (50 ml) and the resulting yellow solution/white solid washed with water (5 × 3 ml), 1% aqueous hydrochloric acid (2 × 1 ml), and water (3 ml) before drying and concentration *in vacuo* to a mobile pale yellow oil (1.78g). Crude flash chromatography (3" silica, 15 mm dia. column) with 5% ethyl acetate - 40-60 b.p. petrol, to remove a small amount of baseline (t.l.c.) phosphorous containing residue, gave ethyl (*E,E*)-1-*t*-butyldimethylsilyloxy-4-ethyl-5,7-nonadienoate (1.65g, 4.85 mmol, 97%), t.l.c. : R_f 0.35, 10%

diethyl ether - 40-60 b.p. petrol, $\nu_{\max}$ 1718, 1640, and 1615 cm^{-1} ; δ 0.0 (6H, s), 0.8 (9H, s), 1.2 (3H, t, J 7 Hz), 0.7 - 1.6 (9H, m), 3.45 (2H, m), 4.05 (2H, q, J 7 Hz), 5.5 - 6.0 (3H, m), and 7.2 (1H, ddd, J 15, 10, and 1 Hz); M^+ 340; (Found: C, 67.28; H, 10.76. $\text{C}_{19}\text{H}_{36}\text{O}_3\text{Si}$ requires C, 67.01; H, 10.65%), contaminated with perhaps 2-3% of a minor, presumably (Z,E), isomer (t.l.c. : R_f 0.38, 10% diethyl ether - 40-60 b.p. petrol).

(b) Preparation of Isomerically Pure (E,E)-(47) on a Multigram Scale

A solution of lithium diisopropylamide in THF (174 ml) was prepared, as in part (a) above, from diisopropylamine (20.82 ml, 0.152 mol) and n-butyl lithium (109 ml of a 1.4 N solution in hexane, concentrated to give an approximately 3N solution, 50 ml, 0.152 mole). Ethyl 4-diethylphosphonocrotonate (38.1g, 0.152 mole) in dry THF (30 ml) was added to the stirred solution of lithium diisopropylamide at -76-73°C (iT) over 100 min. The resulting yellow solution was stirred at -76°C for a further 60 min before warming to -45°C over 10 min, and dropwise addition of 5-t-butyl dimethylsilyloxy-2-ethylpentanal (30g, 0.123 mmol) in dry THF (36 ml) over 25 min at -40°C. The pale yellow solution was stirred from -45°C to room temperature 1h. After 30 min at room temperature absolute ethanol (25 ml) was added. The thick brown gummy residue remaining after removal of THF and ethanol *in vacuo* was vigorously shaken with diethyl ether (1000 ml) to give a yellow solution and white precipitate of $\text{EtO}_2\text{P}(\text{O})_2\text{H}$. The filtered (Celite pad) ethereal solution was combined with a diethyl ether (5 × 100 ml) trituration of the phosphorus residues and washed with water (5 × 100 ml), 1% aqueous hydrochloric acid (2 × 50 ml), and more water (2 × 25 ml) before drying and concentration *in vacuo* to give a mobile clear brown oil (41.0g, 120 mmol, 98% crude yield). Preparative chromatography

(100g silica, 55 mm dia. column) with 8% diethyl ether - 40-60 b.p. petrol in 6 × 6g and 1 × 5g portions, with two runs per silica column, gave, after rechromatography of resulting mixed fractions (7.27g), pure ethyl (*E,E*)-1-*t*-butyldimethylsilyloxy-4-ethyl-5,7-nonadienoate (27.56g, 81 mmol, 66%).

8. Preparation of Ethyl (*E,E*)-1-*t*-butyldimethylsilyloxy-4-ethyl-5,7-nonadienoate (47).



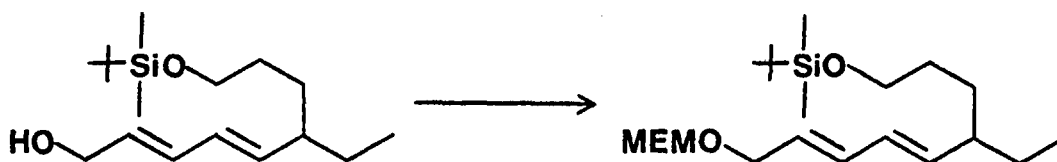
Ethyl (*E,E*)-1-hydroxy-4-ethyl-5,7-nonadienoate (277 mg, 1.23 mmol) was stirred with *t*-butyldimethylchlorosilane (223 mg, 1.48 mmol, 1.2 equiv.) and imidazole (209 mg, 3.08 mmol, 2.5 equiv.) in dry DMF (0.6 ml) for 8h at room temperature. After dilution with diethyl ether (25 ml) and water (5 ml) the organic layer was combined with a diethyl ether (3 × 10 ml) extract of the aqueous layer before washing with 0.1 N aqueous hydrochloric acid (2 × 5 ml), saturated brine (5 ml), 5% aqueous sodium bicarbonate (2 × 5 ml), and more brine (2 × 5 ml). The dried solution was concentrated *in vacuo* to a mobile pale yellow oil (475 mg) which was flash chromatographed (5" silica, 20 mm dia. column) with 5% ethyl acetate - 40-60 b.p. petrol to give ethyl (*E,E*)-1-*t*-butyldimethylsilyloxy-4-ethyl-5,7-nonadienoate (415 mg, 1.22 mmol, 99%) as a colourless oil, contaminated with perhaps 5% of the (*Z,E*) isomer (t.l.c., see Experiment 7).

9. Preparation of (E,E)-9-t-Butyldimethylsilyloxy-6-ethyl-2,4-nonadien-1-ol (50).



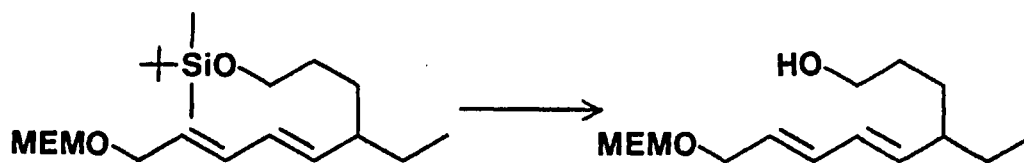
Diisobutyl aluminium hydride (18.83 ml of a 1.0 N solution in hexane, 18.83 mmol, 2.2 equiv.) was added dropwise to a solution of ethyl (E,E)-1-t-butyldimethylsilyloxy-4-ethyl-5,7-nonadienoate (2.91g, 8.56 mmol) in dry toluene (8 ml) at $-6-0^{\circ}\text{C}$ (iT) over 30 min. After stirring for a further 15 min at -5°C the colourless reaction mixture was poured onto 10% aqueous hydrochloric acid (36 ml) and ice (50g), with vigorous stirring. Diethyl ether (200 ml) was added and the aqueous phase extracted with diethyl ether (3×50 ml). The combined organic solutions were washed with water (25 ml), 1% aqueous hydrochloric acid (3×25 ml), 5% aqueous sodium bicarbonate (2×25 ml), and more water (2×25 ml) before drying and concentration *in vacuo* to give (E,E)-9-t-butyldimethylsilyloxy-6-ethyl-2,4-nonadien-1-ol (2.5g, 8.37 mmol, 98%) as a clear colourless oil, homogenous by t.l.c. (R_f 0.29, 1:1 diethyl ether - 40-60 b.p. petrol), ν_{max} 3360 and 1660 cm^{-1} ; δ 0.0 (6H, s), 0.8 (9H, s), 0.7 - 2.1 (10H, m), 2.55 (1H, br s, exchangeable, OH), 3.95 (2H, d, J 6 Hz), and 5.2 - 6.15 (4H, m); m/e: 280 (M-H₂O); 241 (M-^tBu). Flash chromatography (45% diethyl ether - 40-60 b.p. petrol) provided a sample for analysis (Found: C, 68.24; H, 11.64. C₁₇H₃₄O₂Si requires C, 68.39; H, 11.48%).

10. Preparation of (E,E)-1-(β-Methoxy)ethoxymethoxy-9-t-butyl-dimethyl-silyloxy-6-ethyl-2,4-nonadiene (51).



(E,E)-9-t-Butyldimethylsilyloxy-6-ethyl-2,4-nonadien-1-ol (2.5g, 8.37 mmol) was stirred with (β-methoxy)ethoxychloromethane (MEMCl, 1.58 ml, 13.7 mmol, 1.6 equiv.) and dry diisopropylethylamine (2.41 ml, 13.7 mmol) in dry dichloromethane (24 ml), at room temperature, for 2h. The reaction mixture was diluted with dichloromethane (250 ml) and water (50 ml). A dichloromethane (2 × 50 ml) extraction of the aqueous phase was combined with the organic phase and washed with 1% aqueous hydrochloric acid (2 × 50 ml) and water (3 × 50 ml) before drying and concentration *in vacuo* to give a yellow oil (4g). Flash chromatography (5½" silica, 55 mm dia. column) with 15% ethyl acetate - 40-60 b.p. petrol gave (E,E)-1-(β-methoxy)ethoxymethoxy-9-t-butyl-dimethylsilyloxy-6-ethyl-2,4-nonadiene (3.17g, 8.2 mmol, 98%) as a mobile colourless oil, t.l.c. : R_f 0.51, 1:1 diethyl ether - 40-60 b.p. petrol, $\nu_{\max}$ 1660 cm^{-1} ; δ 0.0 (6H, s), 0.8 (9H, s), 0.6 - 2.0 (10H, m), 3.3 (3H, s), 3.6 (6H, m), 4.0 (2H, d, J 6 Hz), 4.6 (2H, s), and 5.2 - 6.3 (4H, m), (Found: C, 65.44; H, 10.95. $\text{C}_{21}\text{H}_{42}\text{O}_4\text{Si}$ requires C, 65.23; H, 11.14%).

11. Preparation of (E,E)-1-(β-Methoxy)ethoxymethoxy-6-ethyl-2,4-nonadien-9-ol (52).



Tetra-n-butylammonium fluoride (23.9 ml of a 0.995 N solution in THF, 22.8 mmol, 1.2 equiv.) was added dropwise to a solution of (E,E)-1-(β-methoxy)ethoxymethoxy-9-t-butyltrimethylsilyloxy-6-ethyl-2,4-nonadiene (7.35g, 19 mmol) in dry THF (10 ml) over 5 min, at room temperature. After a further 15 min the THF was removed *in vacuo* and the resulting yellow oil dissolved in diethyl ether (600 ml) - water (100 ml). Diethyl ether (2 × 50 ml) extracts of the aqueous layer and a water (100 ml) wash of the organic solution were combined with the organic solution and washed with 1% aqueous hydrochloric acid (2 × 40 ml) and water (2 × 40 ml) before drying and concentration *in vacuo*, to give (E,E)-1-(β-methoxy)ethoxymethoxy-6-ethyl-2,4-nonadien-9-ol (5.12g, 18.8 mmol, 99%) as an almost colourless oil, homogeneous by t.l.c. (R_f 0.4, 60% ethyl acetate - 40-60 b.p. petrol); $\nu_{\max}$ 3380 and 1660 cm^{-1} ; δ 0.85 (3H, t, J 7 Hz), 1.2 - 2.0 (10H, m), 1.9 (1H, br s, exchangeable, OH); 3.4 (3H, s), 3.6 (4H, m), 3.7 (2H, m), 4.1 (2H, d, J 6.3 Hz), 4.75 (2H, s), 5.44 (1H, dd, J 15.2 and 8.9 Hz, H_5), 5.65 (1H, dt, J 15.2 and 6.3 Hz, H_2), 6.0 (1H, dd, J 15.2 and 10.4 Hz, H_4), and 6.25 (1H, dd, J 15.2 and 10.4 Hz, H_3), (Found: M^+ , 272.1992. $\text{C}_{15}\text{H}_{28}\text{O}_4$ requires M, 272.1987). Flash chromatography (20% ethyl acetate - 40-60 b.p. petrol) provided a sample for microanalysis (Found: C, 66.13; H, 10.67. $\text{C}_{15}\text{H}_{28}\text{O}_4$ requires C, 66.14; H, 10.36%).

12. Preparation of (E,E)-1-(β-Methoxy)ethoxymethoxy-6-ethyl-2,4-nonadien-9-ol (53).



(a) Using the *in situ* Prepared Collin's Reagent

(E,E)-1-(β-Methoxy)ethoxymethoxy-6-ethyl-2,4-nonadien-9-ol (3.0g, 11 mmol), in dry dichloromethane (3 ml), was added rapidly in one portion to the vigorously stirred, waterbath cooled, burgundy red solution resulting from stirring dry chromium trioxide (6.6g, 66 mmol) with dry pyridine (10.44g, 10.67 ml, 0.132 mole) in dry dichloromethane (170 ml) for 25 min. After 20 min vigorous stirring the brown solution was decanted and combined with diethyl ether (5 × 100 ml) triturations of the gummy black residue. The combined organic solutions were rendered virtually colourless by washing with 5% aqueous sodium hydroxide (6 × 40 ml), 5% aqueous hydrochloric acid (2 × 40 ml), 5% aqueous sodium bicarbonate (2 × 40 ml), and saturated brine (40 ml). The dried solution was concentrated *in vacuo* to give a yellow oil which was dissolved in diethyl ether (5 ml) and filtered through a pad of Kieselgel (Merck 9385) with more diethyl ether (100 ml). The resulting solution was concentrated *in vacuo* to give (E,E)-1(β-methoxy)ethoxymethoxy-6-ethyl-2,4-nonadien-9-al (2.97g, 11 mmol, 100%) as a clear colourless oil, homogeneous by t.l.c. (R_f 0.54, 60% ethyl acetate - 40-60 b.p. petrol); $\nu_{\max}$ 2720, 1760, and 1660 cm^{-1} ; δ 0.8 (3H, t, J 7 Hz), 1.1 - 2.1 (5H, m), 2.3 (2H, m), 3.3 (3H, s), 3.6 (4H, m), 4.0 (2H, d, J 6.3 Hz), 4.65

(2H, s), 5.0 - 6.3 (4H, m), and 9.15 (1H, t, J 2 Hz). Flash chromatography (25% ethyl acetate - 40-60 b.p. petrol) provided a sample for microanalysis (Found: C, 66.69; H, 9.77. $C_{15}H_{26}O_4$ requires C, 66.68; H, 9.70%).

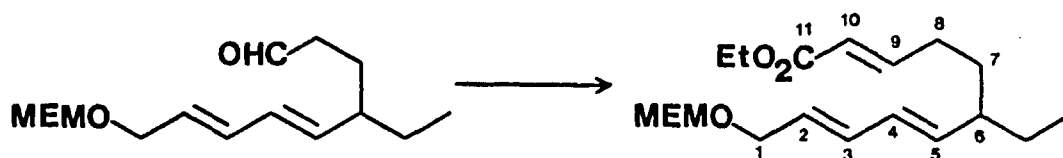
(b) Using Pyridinium Chlorochromate (PCC).

(*E,E*)-1-(β -Methoxy)ethoxymethoxy-5-ethyl-2,4-nonadien-9-ol (77.6 mg, 0.285 mmol) in dry dichloromethane (0.5 ml) was added, in one portion, to a stirred suspension of PCC (92 mg, 0.42 mmol) and anhydrous sodium acetate (7 mg, 0.086 mmol) in dry dichloromethane (0.4 ml). After 100 min, more PCC (10 mg, 0.05 mmol) was added as t.l.c. showed a trace of starting material. After a further 30 min dry diethyl ether (4.5 ml) was added. The cloudy organic solution was decanted, combined with diethyl ether (3 $\times$ 10 ml) triturations of the black solid residue, and filtered through a Celite pad. The resulting almost colourless solution was concentrated *in vacuo* to give a yellow oil which was redissolved in diethyl ether (1 ml) and passed through a Pasteur pipette containing Kieselgel (4", Merck 9385). The ethereal solution was concentrated *in vacuo* to give (*E,E*)-1-(β -methoxy)ethoxymethoxy-6-ethyl-2,4-nonadien-9-al (55.4 mg, 0.205 mmol, 72%) as a virtually colourless oil, homogeneous by t.l.c. (see part (a) above).

(c) Using Pyridinium Dichromate (PDC).

(*E,E*)-1-(β -Methoxy)ethoxymethoxy-6-ethyl-2,4-nonadien-9-ol (98.8 mg, 0.363 mmol) in dry dichloromethane (0.2 ml) was added, in one portion, to a stirred suspension of PDC (273 mg, 0.726 mmol, 2 equiv.) in dry dichloromethane (0.7 ml). After 20h at room temperature the reaction was worked up as in part b above to give (*E,E*)-1-(β -methoxy)ethoxymethoxy-6-ethyl-2,4-nonadien-9-al (72.2 mg, 0.267 mmol, 74%).

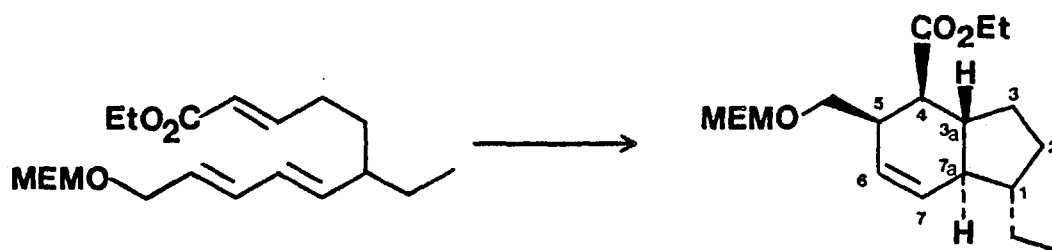
13. Preparation of Ethyl (*E,E,E*)-1-(β -methoxy)ethoxymethoxy-6-ethyl-2,4,9-undecatrienoate (54).



(*E,E*)-1-(β -Methoxy)ethoxymethoxy-6-ethylmona-2,4-dien-9-al (200 mg, 0.735 mmol) was stirred with carboethoxymethylenetriphenylphosphorane (282 mg, 0.809 mmol, 1.1 equiv.) in dry dichloromethane (1.12 ml) for 7h. The dichloromethane was removed *in vacuo* and the resulting yellow oily solid triturated with diethyl ether (3 $\times$ 5 ml). The cloudy ethereal solution was concentrated to *ca.* 2 ml before filtration (x2) through a Pasteur pipette containing Kieselgel (4", Merck 9385), to remove triphenylphosphine oxide. The ethereal solution was concentrated *in vacuo* to give ethyl (*E,E,E*)-1-(β -methoxy)ethoxymethoxy-6-ethyl-2,4,9-undecatrienoate (237.4 mg, 0.698 mmol, 95%) as a virtually colourless clear oil, homogenous by t.l.c. (R_f 0.35, 24% ethyl acetate - 40-60 b.p. petrol); $\nu_{\max}$ 1725 and 1660 cm^{-1} ; δ 0.85 (3H, t, J 7 Hz), 1.3 (3H, t, J 7 Hz), 1.2 - 1.65 (4H, m), 1.92 (1H, m), 2.15 (2H, m), 3.41 (3H, s), 3.58 (2H, m), 3.71 (2H, m), 4.1 (2H, d, J 6.3 Hz), 4.18 (2H, q, J 7 Hz), 4.75 (2H, s), 5.4 (1H, dd, J 15.3 and 9.4 Hz, H_5), 5.63 (1H, dt, J 15.3 and 6.3 Hz, H_2), 5.8 (1H, d, J 15.6 Hz, H_{10}), 6.02 (1H, dd, J 15.3 and 10.5 Hz, H_4), 6.25 (1H, dd, J 15.3 and 10.5 Hz, H_3), and 6.95 (1H, dt, J 15.6 and 6.8 Hz, H_9); (Found: M-MEM⁺, 251.1644. $\text{C}_{15}\text{H}_{23}\text{O}_3$ requires M-MEM, 251.1647). Flash chromatography

(24% ethyl acetate - 40-60 b.p. petrol) provided a sample for micro-analysis (Found: C, 66.72; H, 9.61. $C_{19}H_{32}O_5$ requires C, 67.03; H, 9.47%).

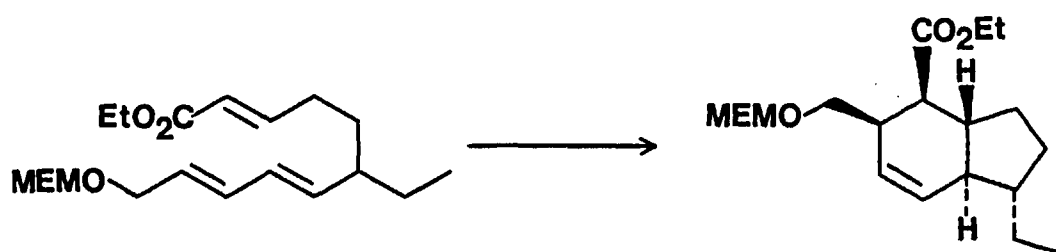
14. Preparation of ($\pm$)-Ethyl 5 β -(2'-methoxy)ethoxymethoxymethylene-1 α -ethyl-3 $\alpha\beta$,4,5,7 $\alpha\alpha$ -tetrahydroindan-4 β -carboxylate (55).



Ethyl (*E,E,E*)-1-(β -methoxy)ethoxymethoxy-6-ethyl-2,4,9-undecatrienoate (0.5g, 1.47 mmol) was heated at reflux, in dry, argon-flushed toluene (140 ml) for 80h. T.l.c. (10% diethyl ether-dichloromethane) showed clean conversion of the u.v. active trienoate (54) (R_f 0.35) to a single, non u.v. active product (R_f 0.35). The toluene was removed *in vacuo* to give, contaminated with a trace of starting material (54) and less than 10% of the other possible isomers, ($\pm$)-ethyl 5 β -(2'-methoxy)ethoxymethoxymethylene-1 α -ethyl-3 $\alpha\beta$,4,5,7 $\alpha\alpha$ -tetrahydroindan-4 β -carboxylate (0.5g, 1.47 mmol, 100%), as a clear colourless oil, ν_{max} 1730 cm^{-1} ; δ 0.91 (3H, t, J 7.2 Hz), 1.28 (3H, t, J 6.7 Hz), 1.1 - 2.05 (9H, m), 2.62 (1H, dd, J 11.2 and 6.7 Hz, H_4), 2.88 (1H, m, H_5), 3.39 (3H, s), 3.47 (2H, m), 3.5 (2H, m), 3.67 (2H, m), 4.1 (2H, qd, J 6.7 and 1.53 Hz), 4.59 (1H, d, J 6.7 Hz), 4.63 (1H, d, J 6.7 Hz), 5.55 (1H, ddd, J 10.26, 4, and 2.56 Hz, H_6), and 5.95 (1H, d, J 10.26 Hz, H_7); (Found: M-MEM $^+$, 251.1644. $C_{15}H_{23}O_3$ requires M-MEM, 251.1647). Flash

chromatography (10% diethyl ether-dichloromethane) provided a sample for microanalysis (Found: C, 66.90; H, 9.54. $C_{19}H_{32}O_5$ requires C, 67.03; H, 9.47%).

15. Intramolecular Diels-Alder Cyclization of Ethyl (*E,E,E*)-1-(β -methoxy)ethoxymethoxy-6-ethyl-2,4,9-undecatrienoate : Lewis Acid Catalysis Studies.



(a) Aluminium Trichloride

Freshly sublimed aluminium trichloride (2.08 mg, 1.56×10^{-2} mmol, 0.1 equiv.) was added to a solution of the trienoate (54) (53.2 mg, 0.156 mmol) in dry dichloromethane (5 ml) at room temperature. Even after 42h at room temperature t.l.c. analysis showed only starting material with no trace of any cyclized product.

(b) Ethylaluminium Dichloride

Ethylaluminium dichloride (69 μ l of a 25% solution in hexane, 0.135 mmol, 0.9 equiv.) was added dropwise to a solution of the trienoate (54) (51 mg, 0.15 mmol) in dry dichloromethane (5 ml) at room temperature. T.l.c. showed about 70% cyclization with much baseline material and general decomposition after 16h. After 28 and 47h, only further decomposition was indicated.

(c) Diethylaluminium Chloride

Diethylaluminium chloride (90 μ l of a 25% solution, in hexane, 0.179 mmol, 1.0 equiv.) was added dropwise to a solution of the trienoate (54) (60.9 mg, 0.179 mmol) in dry dichloromethane (5 ml) at room temperature. T.l.c. analysis showed much cleaner cyclization than with ethylaluminium chloride but even after 42h about 25% of the starting material remained. After a further 2h more diethylaluminium chloride (25 μ l, 0.05 mmol, 0.28 equiv.) was added in an attempt to achieve complete cyclization. However, even after a further 6h t.l.c. analysis showed no further significant reaction, and some decomposition.

As these results were not very promising and the thermal cyclization of (54) was very satisfactory, no further studies were carried out.

16. Preparation of ($\pm$)-1 α -Ethyl-3 α ,4,5,7 α -tetrahydroindan-4 β -carboxylic acid-5 β -methanol, γ -lactone (21) from ($\pm$)-Ethyl 5 β -(2'-methoxy)ethoxymethoxymethylene-1 α -ethyl-3 α ,4,5,7 α -tetrahydroindan-4 β -carboxylate (55).



(a) Using zinc bromide

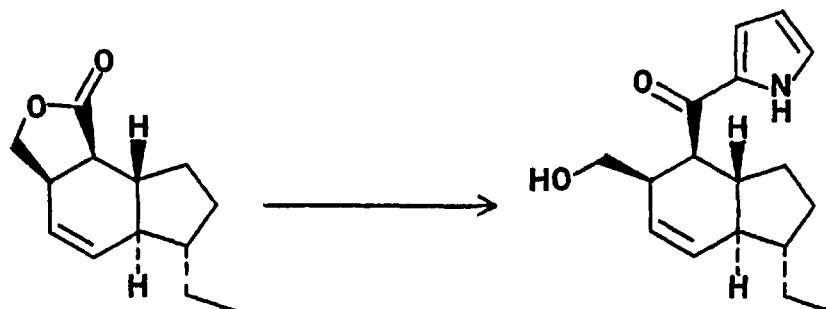
The MEM-protected hydroxy ester (55) (52.3 mg, 1.54×10^{-4} mole) in dry dichloromethane (0.3 ml) was stirred with *freshly fused* dry zinc bromide (0.35g, 1.53 mmol, *ca.* 10 equivs.) overnight. The reaction

mixture was diluted with dichloromethane (10 ml) before washing with saturated aqueous sodium bicarbonate (3 × 5 ml) and brine (5 ml). The dichloromethane solution was combined with a dichloromethane (2 × 5 ml) back extraction of the combined aqueous phases before drying and concentration *in vacuo* to a pale yellow oil. Flash chromatography (6" silica, 25 mm dia. column) with 21.5% ethyl acetate - 40-60 b.p. petrol (t.l.c. : R_f 0.35) gave the *lactone* (21) (19.1 mg, 9.27×10^{-5} mole, 60%), m.p. 67.5 - 68.5°C (40-60 b.p. petrol), $\nu_{\max}$ 1760 cm^{-1} ; δ 0.95 (3H, t, J 7.14 Hz), 1.1 - 1.8 (7H, m), 1.99 (2H, m), 2.54 (1H, ddd, J 11.5, 7.6, and 6.6 Hz, H_4), 3.2 (1H, m, H_5), 3.9 (1H, dd, J 8.8 and 11.5 Hz), 4.51 (1H, dd, J 8.8 and 8.8 Hz), 5.58 (1H, ddd, J 10.2, 3.82, and 2.03 Hz, H_6), and 6.07 (1H, d, J 10.2 Hz, H_7); (Found: M^+ , 206.1306. $\text{C}_{13}\text{H}_{18}\text{O}_2$ requires M , 206.1307; C, 75.41; H, 8.77. $\text{C}_{13}\text{H}_{18}\text{O}_2$ requires C, 75.69; H, 8.80%).

(b) Using Hydrochloric Acid with Phase-Transfer Catalysis.

The MEM-protected hydroxy ester (55) (0.620g, 1.82 mmol) was vigorously stirred with concentrated hydrochloric acid (5 ml) and tetra-*n*-butylammonium bromide (0.8g, 1.9 mmol) in dichloromethane (36 ml) for 6h, at room temperature. The reaction mixture was poured into water (50 ml) and ice (10g) over dichloromethane (100 ml). The organic layer, combined with a dichloromethane (3 × 50 ml) extraction of the aqueous layer, was washed with saturated aqueous sodium bicarbonate (2 × 30 ml) and water (50 ml) before drying and concentration *in vacuo* to a pale yellow oil. Flash chromatography (6" silica, 30 mm dia. column) with 22.5% ethyl acetate - 40-60 b.p. petrol gave the *lactone* (21) (0.244g, 1.185 mmol, 65%) as in part (a) above.

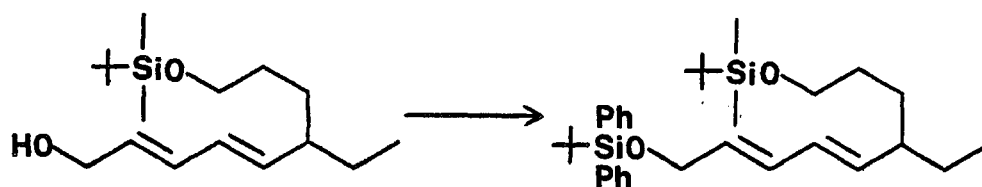
17. Preparation of ($\pm$)-4 β -(2'-Pyrrolylcarbonyl)-1 α -ethyl-3 α ,4,5,7 $\alpha\alpha$ -tetrahydroindan-5 β -methanol (61).



Freshly distilled pyrrole (1.05 ml, 1.005g, 15 mmol) was added dropwise to ethylmagnesium bromide in diethyl ether [5 ml of a 3N solution (15 mmol), prepared from magnesium turnings (1.46g, 60 mmol) in dry diethyl ether (10 ml) and ethyl bromide (4.48 ml, 6.54g, 60 mmol) in dry diethyl ether (5 ml), made up to a total of 20 ml of solution] at 0°C under dry argon. After stirring for 30 min at room temperature the solvent was removed by blowing argon through the solution. Toluene-diethyl ether (3:1) was added to give a homogeneous solution/suspension (total volume 5 ml). A portion of this 3N pyrrolyl-magnesium bromide solution (1.09 ml, 3.26 mmol, 4 equiv.) was added to a solution of the lactone (21) (0.1682g, 8.16×10^{-4} mole) in dry toluene (0.47 ml) at 100°C (bT). After 10 min stirring at 100°C the brown solution was cooled to 0°C before addition of saturated aqueous ammonium chloride (1 ml). Diethyl ether (50 ml) and water (10 ml) was added and the aqueous phase extracted with more diethyl ether (3 $\times$ 10 ml). The combined organic solutions were washed with 5% aqueous sodium carbonate (2 $\times$ 10 ml) and water (20 ml) before drying and concentration *in vacuo* to a dark oil. Flash chromatography (5.5" silica, 30 mm dia. column) with 85% diethyl ether - 40-60 b.p. petrol

(t.l.c. : R_f 0.35) gave ($\pm$)-4 β -(2'-pyrrolylcarbonyl)-1 α -ethyl-3 $\alpha\beta$,4,5,7 $\alpha\alpha$ -tetrahydroindan-5 β -methanol (0.209g, 7.65×10^{-4} mole, 94%), m.p. 88-90°C (40-60 b.p. petrol), $\nu_{\max}$ 3440, 3300, 1620, and 1535 cm^{-1} ; δ 0.92 (3H, t, J 7.35 Hz), 1.0 - 2.2 (9H, m), 2.74 (1H, dd, J 8.2 and 6 Hz, H_4), 2.94 (1H, br s, exchangeable, OH), 3.45 (1H, dd, J 12 and 7 Hz, H_5), 3.55 and 3.63 (both 1H, dd, J 12 and 4.4 Hz, CH_2OH), 5.6 (1H, ddd, J 10.1, 3.9, and 2.5 Hz, H_6), 6.1 (1H, d, J 10.1 Hz, H_7), 6.3, 6.95, and 7.1 (each 1H, m, pyrrole H), and 10.3 (1H, br s, exchangeable, NH); (Found: M^+ , 273.1732. $\text{C}_{17}\text{H}_{23}\text{NO}_2$ requires M, 273.1729; C, 74.58; H, 8.51; N, 5.13. $\text{C}_{17}\text{H}_{23}\text{NO}_2$ requires C, 74.69; H, 8.48; N, 5.12%).

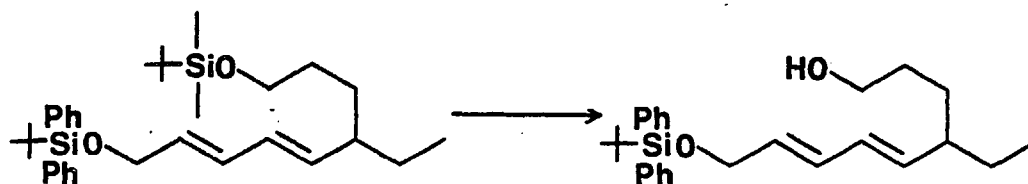
18. Preparation of (*E,E*)-1-*t*-Butyldiphenylsilyloxy-9-*t*-butyldimethylsilyloxy-6-ethyl-2,4-nonadiene (62).



(*E,E*)-9-*t*-Butyldimethylsilyloxy-6-ethyl-2,4-nonadien-1-ol (4.84g, 16.2 mmol) was stirred with *t*-butyldiphenylchlorosilane (5.1 ml, 19.4 mmol, 1.2 equiv.) and dry imidazole (2.76g, 40.5 mmol, 2.5 equiv.) in dry DMF (9 ml) at room temperature for 3h. The two phase reaction mixture was poured onto diethyl ether (250 ml) and water (50 ml) was added. The organic phase, combined with a diethyl ether (3 $\times$ 50 ml) extraction of the aqueous phase, was washed with water (50 ml), 1% aqueous hydrochloric acid (2 $\times$ 40 ml), and more water (3 $\times$ 40 ml)

before drying and concentration *in vacuo* to a clear, pale yellow, viscous oil (10.13g). Flash chromatography (5" silica, 55 min dia. column) with 20% dichloromethane - 40-60 b.p. petrol (t.l.c. : R_f 0.35) gave (*E,E*)-1-*t*-butyldiphenylsilyloxy-9-*t*-butyldimethylsilyloxy-6-ethyl-2,4-nonadiene (8.04g, 15 mmol, 93%) as a clear, colourless, viscous oil, $\nu_{\max}$ 1588, 1470, 1460, 1425, 1250, 1100, 985, 830, 770, 735, and 700 cm^{-1} ; δ 0.05 (6H, s), 0.85 (3H, t, J 7 Hz), 0.91 (9H, s), 1.09 (9H, s), 0.8 - 1.7 (6H, m), 1.9 (1H, m), 3.6 (2H, m), 4.25 (1H, d, J 4.4 Hz), 5.4 (1H, dd, 15.5 and 8.8 Hz, H_3), 5.66 (1H, dt, J 15.5 and 4.4 Hz, H_2), 6.0 (1H, dd, J 15.5 and 8.8 Hz, H_4), 6.25 (1H, dd, J 15.5 and 11.1 Hz, H_5), 7.4 (6H, m), and 7.7 (4H, m); m/e : M^+ 536. (Found: C, 73.97; H, 10.01. $\text{C}_{33}\text{H}_{52}\text{O}_2\text{Si}_2$ requires C, 73.82; H, 9.76%).

19. Preparation of (*E,E*)-1-*t*-Butyldiphenylsilyloxy-6-ethyl-2,4-nonadien-9-ol (63).



(*E,E*)-1-*t*-Butyldiphenylsilyloxy-9-*t*-butyldimethylsilyloxy-6-ethyl-2,4-nonadiene (7.63g, 14.21 mmol) was vigorously stirred with acetic acid (102 ml), water (51 ml), and THF (61 ml) at room temperature for 6h. The clear reaction mixture was diluted with 40-60 b.p. petrol (500 ml). The aqueous phase, combined with a water (200 ml) wash of the organic phase, was extracted with 40-60 b.p. petrol (3 $\times$ 100 ml). The combined organic solutions were washed with saturated aqueous sodium

bicarbonate until carbon dioxide evolution ceased. After washing with 1% aqueous hydrochloric acid (2×25 ml) and water (50 ml) the dried solution was concentrated *in vacuo* to give (*E,E*)-1-*t*-butyldiphenylsilyloxy-6-ethyl-2,4-nonadien-9-ol (5.9g, 14 mmol, 98.5%) as a clear, colourless, viscous oil, homogeneous by t.l.c. (R_f 0.46, 20% ethyl acetate - 40-60 b.p. petrol), $\nu_{\max}$ 3370 cm^{-1} ; δ 0.85 (3H, t, J 7 Hz), 1.05 (9H, s), 1.0 - 1.8 (6H, m), 3.6 (1H, br s, OH), 3.6 (2H, t, J 6.6 Hz), 4.23 (2H, d, J 4.4 Hz), 5.4 (1H, dd, 15.5 and 8.8 Hz, H_3), 5.66 (1H, dt, J 15.5 and 4.4 Hz, H_2), 6.0 (1H, dd, J 15.5 and 8.8 Hz, H_4), 6.25 (1H, dd, J 15.5 and 11.1 Hz, H_5), 7.4 (6H, m), and 7.7 (4H, m); (Found: M^+ , 422.2654. $\text{C}_{27}\text{H}_{38}\text{O}_2\text{Si}$ requires M , 422.2641). Flash chromatography (25% ethyl acetate - 40-60 b.p. petrol) provided a sample for microanalysis (Found: C, 76.94; H, 9.07. $\text{C}_{27}\text{H}_{38}\text{O}_2\text{Si}$ requires C, 76.80; H, 8.99%).

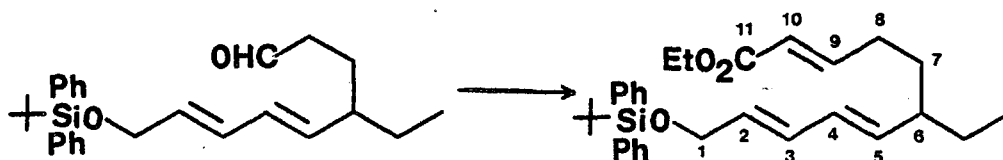
20. Preparation of (*E,E*)-1-*t*-Butyldiphenylsilyloxy-6-ethyl-2,4-nonadien-9-ol (64).



(*E,E*)-1-*t*-Butyldiphenylsilyloxy-6-ethyl-2,4-nonadien-9-ol (3.0g, 7.1 mmol) in dry dichloromethane (4 ml) was added, rapidly in one portion, to the vigorously stirred, waterbath cooled, burgundy red solution resulting from stirring dry chromium trioxide (4.36g, 43.6 mmol) and dry pyridine (7.01 ml, 6.88g, 87 mmol) in dry dichloromethane (110 ml) for 20 min at room temperature. After 15 min

vigorous stirring at room temperature the brown solution was decanted from the tarry residue which was then rigorously triturated with diethyl ether (5 × 150 ml). The combined organic solutions were washed with 5% aqueous sodium hydroxide (4 × 40 ml), 5% aqueous hydrochloric acid (2 × 20 ml), 5% aqueous sodium bicarbonate (3 × 20 ml), and saturated brine (20 ml) before drying and concentration *in vacuo* to a brown oil. This was redissolved in diethyl ether (10 ml) and filtered through a pad of Kieselgel (Merck 9385) before concentration *in vacuo* to give (*E,E*)-1-*t*-butyldiphenylsilyloxy-6-ethyl-2,4-nonadien-9-ol (2.92g, 6.95 mmol, 98%) as a viscous pale yellow oil, homogeneous by t.l.c. (R_f 0.59, 25% ethyl acetate - 40-60 b.p. petrol), $\nu_{\max}$ 2720, 1728, 1430, 1110, and 705 cm^{-1} ; δ 0.6 - 2.0 (8H, m), 1.1 (9H, s), 2.3 (2H, m), 4.2 (2H, d, J 4.4 Hz), 5.2 - 6.4 (4H, m), 7.3 (6H, m), 7.6 (4H, m), and 9.2 (1H, t, J 2 Hz); (Found: M^+ , 420.2476. $\text{C}_{27}\text{H}_{36}\text{O}_2\text{Si}$ requires M , 420.2484). Flash chromatography (15% ethyl acetate - 40-60 b.p. petrol) provided a sample for microanalysis (Found: C, 77.18; H, 8.83. $\text{C}_{27}\text{H}_{36}\text{O}_2\text{Si}$ requires C, 77.17; H, 8.63%).

21. Preparation of Ethyl (*E,E,E*)-1-*t*-butyldiphenylsilyloxy-6-ethyl-2,4,9-undecatrienoate (65).

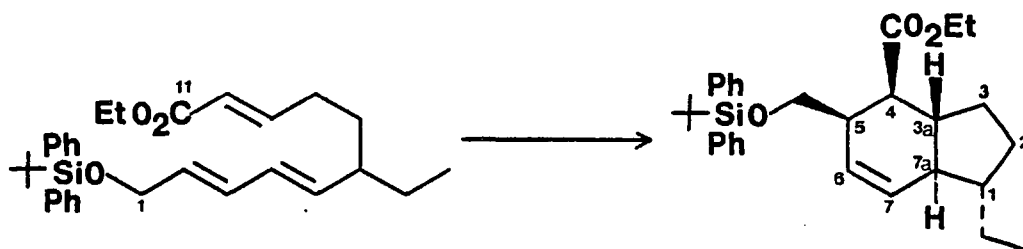


(*E,E*)-1-*t*-Butyldiphenylsilyloxy-6-ethyl-2,4-nonadien-9-ol (3.91g, 9.3 mmol) was stirred overnight with carboethoxymethylenetriphenylphosphorane (3.89g, 11.6 mmol, 1.2 equiv.) in dry dichloromethane

(17.7 ml). After removal of solvent *in vacuo* the resulting yellow oily solid was triturated with diethyl ether - 40-60 b.p. petrol (1:1) (3 × 100 ml). The resulting cloudy solution was concentrated to *ca.* 20 ml before filtration through a short pad of silica to remove the remaining triphenylphosphine oxide. The clear solution, together with a diethyl ether - 40-60 b.p. petrol (1:1) (50 ml) rinse of the silica was concentrated *in vacuo* to give *ethyl (E,E,E)-1-t-butyl-diphenylsilyloxy-6-ethyl-2,4,9-undecatrienoate* (4.15g, 8.46 mmol, 91%), t.l.c. : R_f 0.35, 8% ethyl acetate - 40-60 b.p. petrol, $\nu_{\max}$ 1720, 1655, 1590, 1430, 1265, 1110, and 705 cm^{-1} ; δ 0.88 (3H, t, J 7 Hz), 1.1 (9H, s), 1.1 - 1.7 (4H, m), 1.32 (3H, t, J 7.5 Hz), 1.95 (1H, m, H_6), 2.2 (2H, m, $\text{CH}_2\text{CH}=\text{CHCO}_2\text{Et}$), 4.2 (2H, q, J 7.5 Hz), 4.28 (2H, d, J 6.6 Hz), 5.37 (1H, dd, J 15.2 and 9.1 Hz, H_5), 5.7 (1H, dt, J 15.2 and 6.6 Hz, H_2), 5.85 (1H, dt, J 15.7 and 1.5 Hz, H_{10}), 6.05 (1H, dd, J 15.2 and 10.1 Hz, H_4), 6.27 (1H, dd, J 15.2 and 10.1 Hz, H_3), 7.0 (1H, dt, J 15.7 and 7.1 Hz, H_9), 7.42 (6H, m), and 7.72 (4H, m); (Found: M^+ , 490.2897. $\text{C}_{31}\text{H}_{42}\text{O}_3\text{Si}$ requires M, 490.2903; C, 75.68; H, 8.94. $\text{C}_{31}\text{H}_{42}\text{O}_3\text{Si}$ requires C, 75.94; H, 8.63%), contaminated with perhaps 2% of the (*E,E,Z*) isomer. Isomerically pure (*E,E,E*)-(65) (3.4g, 6.93 mmol, 75%) was obtained upon preparative chromatography (100g silica, 50 mm dia. column) with 5% ethyl acetate - 40-60 b.p. petrol and a flow rate of 80 sec per column inch (rechromatographing the mixed fractions on 85g silica on the same column with 3% ethyl acetate - 40-60 b.p. petrol at 70 sec per column inch). Pure *ethyl (E,E,Z)-1-t-butyl-diphenylsilyloxy-6-ethyl-2,4,9-undecatrienoate* (63 mg, 0.128 mmol, 1.4%), t.l.c. : R_f 0.41, 8% ethyl acetate - 40-60 b.p. petrol, $\nu_{\max}$ 1720, 1645, 1590, 1430, 1110, and 705 cm^{-1} ; δ 0.86 (3H, t, J 7.0 Hz), 1.1 (9H, s), 1.3 (3H, t, J 7.5 Hz), 1.1 - 1.65 (4H, m), 1.95 (1H, m, H_6), 2.64 (2H, m, $\text{CH}_2\text{CH}=\text{CHCO}_2\text{Et}$), 4.16 (2H, q, J 7.5 Hz), 4.25 (2H, d, J 5 Hz), 5.4 (1H,

dd, J 15.2 and 8.8 Hz, H, H_5), 5.67 (1H, dt, J 15.2 and 5 Hz, H_2), 5.75 (1H, dt, J 11.4 and 1.3 Hz, H_{10}), 6.02 (1H, dd, J 15.2 and 10.6 Hz, H_4), 6.2 (1H, dt, J 11.4 and 7.3 Hz, H_9), 6.24 (1H, dd, J 15.2 and 10.6 Hz, H_3), 7.4 (6H, m), and 7.7 (4H, m) (Found: M^+ , 490.2897. $C_{31}H_{42}O_3Si$ requires M, 490.2903), was the minor product isolated after preparative chromatography.

22. Preparation of ($\pm$)-Ethyl 5 β -t-butylidiphenylsilyloxymethylene-1 α -ethyl-3 α ,4,5,7 α -tetrahydroindan-4 β -carboxylate (66).



(a) By Thermal Cyclization of (65).

Ethyl (*E,E,E*)-1-t-butylidiphenylsilyloxy-6-ethyl-2,4,9-undecatrienoate (0.75g, 1.53 mmol) was heated at reflux, in dry, argon-flushed toluene (170 ml) for 70h. The toluene was removed *in vacuo* to give a colourless oil (0.75g). Preparative chromatography (80g silica, 55 mm dia. column) with 3% ethyl acetate - 40-60 b.p. petrol gave ethyl 5 β -t-butylidiphenylsilyloxymethylene-1 α -ethyl-3 α ,4,5,7 α -tetrahydroindan-4 β -carboxylate (0.48g, 9.8×10^{-4} mole, 64% or 71% based on recovered starting material (65)), t.l.c. : R_f 0.5, 8% ethyl acetate - 40-60 b.p. petrol, ν_{max} 1730 cm^{-1} ; δ 0.9 (3H, t, J 7 Hz), 1.05 (9H, s), 1.1 (3H, t, J 7 Hz), 1.0 - 2.1 (9H, m), 2.65 (1H, dd, J 11.4 and 7.2 Hz, H_4), 2.83 (1H, m, H_5), 3.55 (1H, dd, J 10.2 and 6.9 Hz, CH_2O),

3.65 (1H, dd, J 10.2 and 5.9 Hz, CH₂O), 4.0 (2H, m), 5.73 (1H, ddd, J 10.2, 4.5, and 2.3 Hz, H₆), 5.96 (1H, d, J 10.2 Hz), 7.4 (6H, m), and 7.66 (4H, m) (Found: M-tBu⁺, 433.2191. C₂₇H₃₃O₃Si requires 433.2199), and a minor component, homogeneous by t.l.c. (R_f 0.46, 8% ethyl acetate - 40-60 b.p. petrol), although apparently a mixture by ¹H n.m.r. (250 MHz), containing, as the major compound, ethyl 5β-t-butyldiphenylsilyloxy-methylene-1α-ethyl-3α,4,5,7α-tetrahydroindan-4α-carboxylate (67) (0.161g, 3.29 × 10⁻⁴ mole, 21%), ν_{max} 1730 cm⁻¹; δ 0.9 (3H, t, J 7 Hz), 1.05 (9H, s), 1.15 (3H, t, J 7.5 Hz), 1.2 - 2.0 (8H, m), 2.25 (1H, m), 2.35 (1H, m), 2.6 (1H, m), 3.51 (1H, dd, J 9.97 and 7.6 Hz, CH₂O), 3.6 (1H, dd, J 9.97 and 4.5 Hz, CH₂O), 4.05 (2H, m), 5.73 (1H, ddd, J 10, 1.7, and 1.7 Hz), 5.9 (1H, ddd, J = 10, 4.2, and 3.0 Hz), 7.38 (6H, m), and 7.66 (4H, m). Unreacted starting material (65) (74 mg, 1.5 × 10⁻⁴ mole, 10%) was recovered during chromatography by increasing the eluant polarity from 8 to 20% ethyl acetate - 40-60 b.p. petrol after collection of the first two components, (66) and (67).

(b) By Lewis Acid Catalyzed Cyclization of (65).

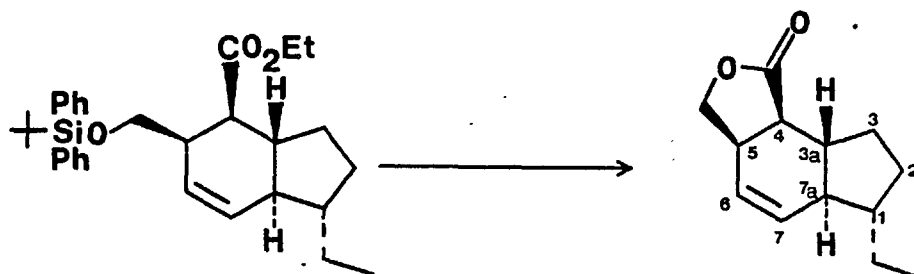
(i) Using Diethylaluminium Chloride.

Diethylaluminium chloride (70 μl of a 25% solution in hexane, 0.138 mmol, 1.0 equiv.) was added dropwise to a stirred solution of the trienoate (65) (67.9 mg, 0.138 mmol) in dry dichloromethane (5 ml) at room temperature. After 17h at room temperature the reaction mixture was poured onto water (10 ml). The dichloromethane solution, combined with a dichloromethane extract (2 × 5 ml) of the aqueous phase, was washed with 5% aqueous sodium bicarbonate (2 × 5 ml) and water (5 ml) before drying and concentration *in vacuo* to a colourless oil (75 mg), homogeneous by t.l.c. Flash chromatography (5" silica, 20 mm dia. column) gave (66) (46 mg, 9.4 × 10⁻⁵ mole, 67%) as in part (a) above. T.l.c. showed the complete absence of the minor component described in part (a) above.

(ii) Using Other Lewis Acids.

As was found for the MEM-protected trienoate (54) in Experiment 15(a) aluminium trichloride (0.1 equiv.) failed to cause any cyclization of the t-BDPS-protected trienoate (65) in dichloromethane at room temperature. Similarly, with (65) in dichloromethane, ethylaluminium dichloride (0.9 equiv.) led to about 70% cyclization with extensive decomposition, after 17h at room temperature, as was observed with (54) in Experiment 15.

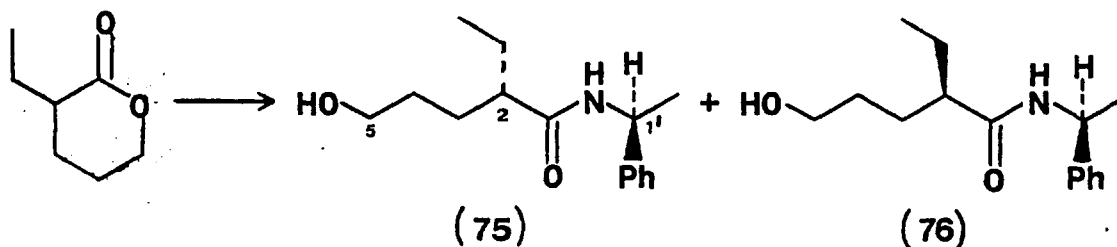
23. Preparation of ($\pm$)-1 α -Ethyl-3 α ,4,5,7 α -tetrahydroindan-4 β -carboxylate-5 β -methanol, γ -lactone (21) from ($\pm$)-Ethyl 5 β -t-butyl-diphenylsilyloxymethylene-1 α -ethyl-3 α ,4,5,7 α -tetrahydroindan-4 β -carboxylate (66).



Tetra-n-butylammonium fluoride (1.4 ml of a 1N solution in THF, 1.4 mmol, 1.5 equiv.) was added to a solution of ($\pm$)-ethyl 5 β -t-butyl-diphenylsilyloxymethylene-1 α -ethyl-3 α ,4,5,7 α -tetrahydroindan-4 β -carboxylate (0.45g, 9.18×10^{-4} mole) in dry THF (10.3 ml) at room temperature. After 1h the THF was removed *in vacuo* and the resulting yellow oil dissolved in diethyl ether (50 ml)-water (20 ml). The ethereal solution, combined with a diethyl ether (2 $\times$ 20 ml) extract of the aqueous phase, was washed with 1% aqueous hydrochloric acid (3 $\times$ 20 ml) and water

(2 × 20 ml) before drying and concentration *in vacuo* to a pale yellow oil (0.411g). Flash chromatography (5.5" silica, 30 mm dia. column) gave the lactone (21) (0.168g, 8.16×10^{-4} mole, 89%) as in Experiment 16(a) above.

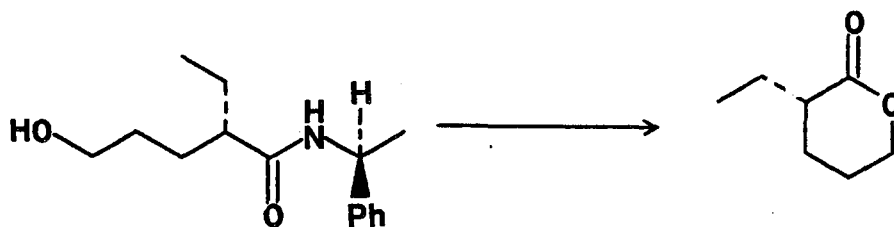
24. Preparation of (-)-N-1'(S)-Phenylethyl-5-hydroxy-2(S)-ethylpentanamide (75) and (-)-N-1'(S)-Phenylethyl-5-hydroxy-2(R)-ethylpentanamide (76).



2-Ethyl- δ -valerolactone (2.0g, 15.6 mmol) was heated at reflux with (-)-1(S)-phenylethylamine (3.79g, 31.2 mmol, 2 equiv.) and 2-hydroxypyridine (1.48g, 15.6 mmol, 1 equiv.) in dry toluene (7.9 ml) for 12h. T.l.c. (ethyl acetate) showed clean, quantitative conversion of the lactone to the amides (75) and (76) which appeared as two overlapping spots, R_f 0.32 and 0.23 respectively. Dichloromethane (50 ml) was added and the yellow solution extracted with 0.5N aqueous hydrochloric acid (3 × 20 ml). The organic solution, combined with a dichloromethane (2 × 10 ml) extract of the acidic aqueous phase, was washed with water (10 ml), 5% aqueous sodium bicarbonate (30 ml), and saturated brine (10 ml) before drying and concentration *in vacuo* to a thick yellow gum (4.0g). Preparative chromatography (100g silica, 50 mm dia. column) of this gum, in four equal portions, with 3% methanol-diethyl ether, after rechromatography of the mixed fractions

(1.05g) in the same way, gave (-)-N-1'(S)-phenylethyl-5-hydroxy-2(S)-ethylpentanamide (1.6g, 6.42 mmol, 41.2%), m.p. 70-72°C (chloroform - 40-60 b.p. petrol), $[\alpha]_D^{25}$ -88.9° (c 1.13, MeOH), $\nu_{\max}$ 3450(sh), 3280, 1630, and 1545 cm⁻¹; δ 0.9 (3H, t, J 7.5 Hz), 1.44 (3H, d, J 7 Hz), 1.3 - 1.7 (6H, m), 2.05 (1H, m, H₄), 3.3 (1H, br s, exchangeable, OH), 3.45 (2H, m), 5.1 (1H, overlapping qd, J 7 and 7.5 Hz, H₁'), 6.7 (1H, m, NH), and 7.25 (5H, m); M⁺ 249. (Found: C, 72.36; H, 9.34; N, 5.62. C₁₅H₂₃NO₂ requires 72.25; H, 9.30; N, 5.62%), and (-)-N-1'(S)-phenylethyl-5-hydroxy-2(R)-ethylpentanamide (1.6g, 6.42 mmol, 41.2%), m.p. 79-80°C (ethyl acetate - 40-60 b.p. petrol), $[\alpha]_D^{25}$ -119.1° (c 1.15, MeOH), $\nu_{\max}$ 3450(sh), 3280, 1630, and 1545 cm⁻¹; δ 0.84 (3H, t, J 7 Hz), 1.49 (3H, d, J 7.5 Hz), 1.4 - 1.75 (6H, m), 2.0 (1H, m, H₄), 2.35 (1H, br s, exchangeable, OH), 3.62 (2H, m), 5.16 (1H, overlapping qd, J 7 and 7.5 Hz, H₁'), 6.09 (1H, br d, J 7.5 Hz, exchangeable, NH), and 7.3 (5H, m); M⁺ 249. (Found: C, 72.06; H, 9.44; N, 5.72. C₁₅H₂₃NO₂ requires C, 72.25; H, 9.30; N, 5.62%)

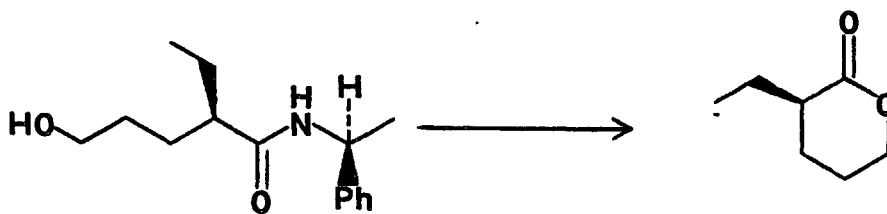
25. Preparation of (+)-2(S)-Ethyl- δ -valerolactone (72).



(-)-N-1'(S)-Phenylethyl-5-hydroxy-2(S)-ethylpentanamide (0.25g, 1.0 mmol) was stirred at 80-90°C in 1N sulphuric acid (in 1:1 water-dioxan, 2 ml) for 16h. T.l.c. (97% diethyl ether-methanol) showed no amide (75) remaining but (50% dichloromethane-diethyl ether) also none of the desired lactone (72). The reaction mixture was extracted with

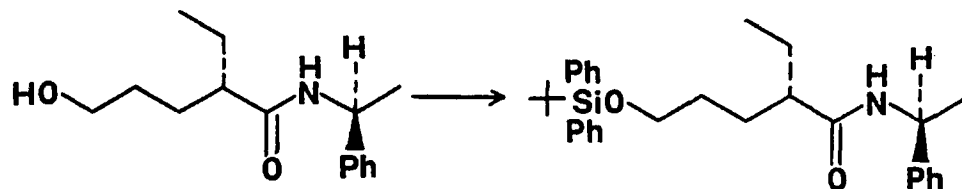
dichloromethane (5 × 10 ml) and the organic solution washed with water (10 ml) and brine (10 ml) before drying and concentration *in vacuo*. The crude product was heated at reflux in dry toluene (80 ml) with a trace of *p*-toluenesulphonic acid (*ca.* 10 mg) for 30 min. After water (2 × 20 ml) and brine (2 × 20 ml) washes, drying, and concentration *in vacuo*, the pale yellow oil was dissolved in 50% dichloromethane-diethyl ether (1 ml) and passed through a Pasteur pipette containing Kieselgel (2", Merck 9385) to remove polar impurities. The solution resulting from elution of the product with 50% dichloromethane-diethyl ether from the silica was concentrated *in vacuo* to give (+)-2(S)-ethyl- δ -valerolactone (44.6 mg, 0.35 mmol, 35%) as a virtually colourless, clear oil, $[\alpha]_D^{25} + 19^{\circ}$ (*c* 4.46, MeOH) Lit.^{87b} $[\alpha]_D^{25} + 74^{\circ}$, enantiomeric excess (ee) 26%; t.l.c., i.r., and ^1H n.m.r. as before (Experiment 2).

26. Preparation of (-)-2(R)-Ethyl- δ -valerolactone (79).



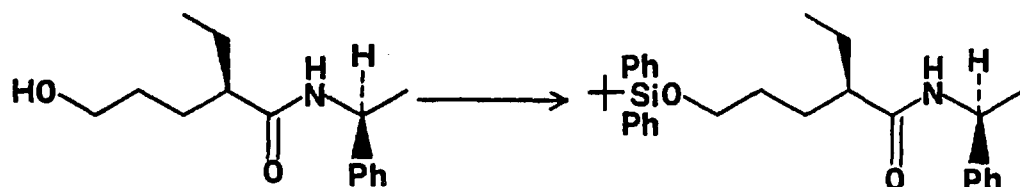
Following the procedure given in Experiment 25 above, (-)-N-1'(S)-phenylethyl-5-hydroxy-2(R)-ethylpentanamide (0.1g, 0.4 mmol) gave (-)-2(R)-ethyl- δ -valerolactone (28.2 mg, 0.22 mmol, 55%), $[\alpha]_D^{25} -20.3^{\circ}$ (*c* 2.82, MeOH) Lit.^{87b} $[\alpha]_D^{25} -74^{\circ}$, ee 27%; t.l.c., i.r., and ^1H n.m.r. as before.

27. Preparation of (-)-1'(S)-N-Phenylethyl-5-t-butyl-diphenylsilyloxy-2(S)-ethylpentanamide (77).



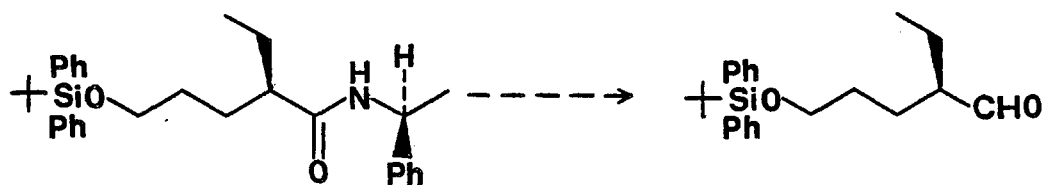
(-)-N-1'(S)-Phenylethyl-5-hydroxy-2(S)-ethylpentanamide (0.5g, 2 mmol) was stirred with t-butyl-diphenylchlorosilane (0.56 ml, 0.59g, 2.4 mmol, 1.2 equiv.) and dry imidazole (0.204g, 3 mmol, 1.5 equiv.) in dry DMF (1 ml) for 10h at room temperature. The reaction mixture was poured into diethyl ether (25 ml) and water (10 ml). The organic solution, combined with a diethyl ether (3 × 10 ml) extract of the aqueous phase, was washed with 1% aqueous hydrochloric acid (2 × 5 ml), water (5 ml), and brine (5 ml) before drying and concentration *in vacuo* to a viscous creamy oil (1.15g). Flash chromatography (6" silica, 35 mm dia. column), to remove non-polar silicon-containing impurities, with 1:1 diethyl ether - 40-60 b.p. petrol gave (-)-1'(S)-N-phenylethyl-5-t-butyl-diphenylsilyloxy-2(S)-ethylpentanamide (0.98g, 2 mmol, 100%), m.p. 99-100°C (40-60 b.p. petrol), $[\alpha]_D^{25} -39.4^\circ$ (c 1.11, MeOH), t.l.c. : R_f 0.35, 1:1 diethyl ether - 40-60 b.p. petrol, $\nu_{\max}$ 3410, 3340(sh), and 1650 cm^{-1} ; δ 0.9 (3H, t, J 7 Hz), 1.05 (9H, s), 1.46 (3H, d, J 7.5 Hz), 1.35 - 1.75 (6H, m), 1.9 (1H, m, H_4), 3.6 (2H, m), 5.16 (1H, overlapping qd, J 7.5 and 7.7 Hz, H_1), 5.6 (1H, br d, J 7.7 Hz, exchangeable, NH), 7.2 - 7.55 (11H, m), and 7.63 (4H, m); M^+ 487. (Found: C, 76.44; H, 8.50; N, 2.87. $\text{C}_{31}\text{H}_{41}\text{NO}_2\text{Si}$ requires C, 76.34; H, 8.47; N, 2.87%).

28. Preparation of (-)-1'(S)-N-Phenylethyl-5-t-butyl-diphenylsilyloxy-2(R)-ethylpentanamide (78).



Following the procedure given in Experiment 27 above, (-)-1'(S)-N-phenylethyl-1-hydroxy-4(R)-ethylpentanamide (0.5g, 2 mmol) gave (-)-1'(S)-N-phenylethyl-5-t-butyl-diphenylsilyloxy-2(R)-ethylpentanamide (0.974g, 2 mmol, 100%), m.p. 85-86°C (40-60 b.p. petrol), $[\alpha]_D^{25}$ -50.4 (c 1.17, MeOH), t.l.c. : R_f 0.35, 1:1 diethyl ether - 40-60 b.p. petrol, $\nu_{\max}$ 3410, 3340(sh), and 1650 cm^{-1} ; δ 0.5 - 2.15 (10H, m), 1.05 (9H, s), 1.2 (3H, d, J 7.5 Hz), 3.55 (2H, m), 5.1 (1H, overlapping qd, J 7.5 and 8 Hz), 6.65 (1H, br d, J 8 Hz, exchangeable, NH), and 6.8 - 7.9 (15H, m); M^+ 487; (Found: C, 76.53; H, 8.56; N, 2.94. $\text{C}_{31}\text{H}_{41}\text{NO}_2\text{Si}$ requires C, 76.34; H, 8.47; N, 2.87%).

29. Attempted Preparation of 1-t-Butyldiphenylsilyloxy-2(R)-ethylpentanal (74) via Reductive Cleavage of (-)-1'(S)-N-Phenylethyl-5-t-butyl-diphenylsilyloxy-2(R)-ethylpentanamide (78).



(a) Using Diisobutylaluminium Hydride (DIBAL).

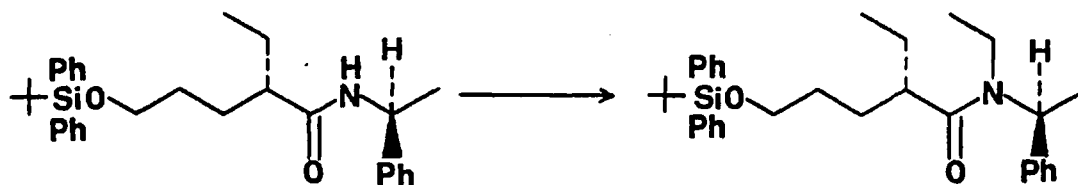
DIBAL (0.3 ml of a 25% solution in toluene, 5.26×10^{-4} mole, 1.1 equiv.) was added dropwise to a solution of the amide (78) (0.25g, 4.8×10^{-4} mole) in dry toluene (0.9 ml) at -78°C (bT) over 10 min. After stirring for a further hour at -78°C t.l.c. (1:1 diethyl ether - 40-60 b.p. petrol) showed only a trace of the desired aldehyde (74) (R_f 0.6) and unreacted (78).. The reaction mixture was stirred up to 0°C in 10 min but t.l.c. showed no further reduction. The reaction mixture was recooled to -78°C and more DIBAL (0.2 ml, 3.51×10^{-4} mole, 0.73 equiv.) added. After 1h at -78°C t.l.c. revealed no increase in the amount of aldehyde present. Sodium di-(β -methoxy)ethoxyaluminium hydride (Red-Al, 35 μl of a 3.4N solution in benzene, 1.2×10^{-4} mole, 0.25 equiv.) was added at -78°C . After a further hour t.l.c. showed no aldehyde (74) with only (78) and a trace of a polar product which smell indicated was the amine resulting from over-reduction.

Treatment of the amide (78) (0.1g, 1.91×10^{-4} mole) with a large excess of DIBAL (0.48 ml of a 25% solution in toluene, 8.36×10^{-4} mole, 4.4 equiv.) at -78°C led to no increase in the small amount of aldehyde (74) produced.

(b) Using the Red-Al-Morpholine Complex.

A portion (0.54 ml, 4.18×10^{-4} mole, 2.2 equiv.), of the solution formed by adding dry morpholine (0.53 ml, 0.53g, 6.08 mmol) in toluene (3 ml) to Red-Al (1.62 ml of a 3.4N solution in benzene, 5.5 mmol) in toluene (2 ml) at 0°C , was added dropwise to the amide (78) (0.1g, 1.91×10^{-4} mole) in dry toluene (0.4 ml) at -78°C . Stirring for 5h at -78°C and overnight at room temperature led to no observable reduction of the amide.

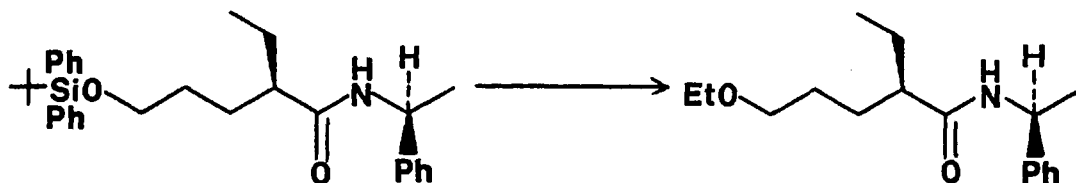
30. Preparation of 1'(S)-N-Phenylethyl-5-t-butyl-diphenylsilyloxy-2(S)-ethylpentan-N-ethylamide (80).



(-)-1'(S)-N-Phenylethyl-5-t-butyl-diphenylsilyloxy-2(S)-ethylpentanamide (0.2g, 3.82×10^{-4} mole) and dry bromoethane (1.0 ml, X.S) in dry benzene (0.6 ml) were vigorously stirred, at reflux, with powdered sodium hydroxide (54 mg, 1.35 mmol, 3.5 equiv.), powdered potassium carbonate (0.108g, 7.8×10^{-4} mole, 2 equiv.), and a catalytic amount of tetra-n-butylammonium hydrogen sulphate (13 mg, 3.82×10^{-5} mole, 0.1 equiv.) for 5h. The reaction was diluted with toluene (20 ml) and water (5 ml). The organic solution, combined with a toluene (2 × 10 ml) extract of the aqueous phase, was washed with water (4 ml), 1% aqueous hydrochloric acid (2 × 4 ml), and saturated brine (4 ml) before drying and concentration *in vacuo* to a viscous oil (0.213g). Flash chromatography (6" silica, 30 mm dia. column) gave 1'(S)-N-phenylethyl-5-t-butyl-diphenylsilyloxy-2(S)-ethylpentan-N-ethylamide (0.143g, 2.8×10^{-4} mole, 73% or 96% based on recovered starting material (77)) as a colourless viscous oil, t.l.c. : R_f 0.38, 1:1 diethyl ether - 40-60 b.p. petrol, $\nu_{\max}$ 1640 cm^{-1} ; δ 0.5 - 1.7 (14H, m), 1.3 (3H, d, J 7.8 Hz), 0.85 (9H, s), 2.9 (1H, m), 3.6 (2H, m), 5.9 (1H, q, J 7.8 Hz), and 7.1 - 7.6 (15H, m) (Found: $M^+ - t\text{Bu}^+$, 458.2509. $\text{C}_{29}\text{H}_{36}\text{NO}_2\text{Si}$ requires 458.2515), contaminated with ca. 25% of the inseparable O-alkylated product, 1'(S)-N-phenylethyl-

5-t-butyl-1,1-diphenylsilyloxy-7-ethoxy-2(S)-ethylpentanimine (81), presumably as a mixture of geometric isomers (from two minor absorptions in the ^1H n.m.r. spectrum at 2.3 and 5.1 ppm corresponding to H_4 and H_1 , respectively).

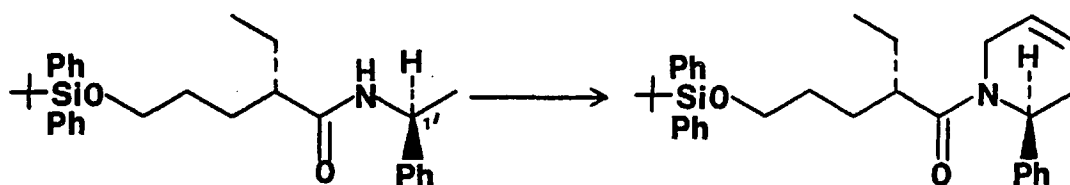
31. Preparation of (-)-1'(S)-N-Phenylethyl-5-ethoxy-2(R)-ethylpentanamide (86).



(-)-1'(S)-N-Phenylethyl-5-t-butyl-1,1-diphenylsilyloxy-2(R)-ethylpentanamide (0.625g, 1.25 mmol) and dry bromoethane (0.2 ml, 2.5 mmol) in dry benzene (2 ml) were vigorously stirred, at reflux, with powdered sodium hydroxide (0.176g, 4.4 mmol), powdered potassium carbonate (0.35g, 2.55 mmol), and tetra-n-butylammonium hydrogensulphate (42.4 mg, 9.55×10^{-5} mole) for 4h. T.l.c. (1:1 diethyl ether - 40-60 b.p. petrol) analysis showed only a trace of the desired N-ethyl product, a number of minor products, and a major, polar product. Work up as in Experiment 30 above gave a mobile, almost colourless oil (0.691g). Flash chromatography (6" silica, 20 mm dia. column) with 85% diethyl ether - 40-60 b.p. petrol gave (-)-1'(S)-N-Phenylethyl-1-ethoxy-4(R)-ethylpentanamide (0.131g, 4.7×10^{-4} mole, 38%), R_f 0.35, 85% diethylether - 40-60 b.p. petrol, m.p. 62-63°C (40-60 b.p. petrol), $[\alpha]_D^{25} -73^\circ$ (c 1.06, CHCl_3), ν_{max} 3440, 3360(br), 1660, and 1490 cm^{-1} ; δ 0.75 (3H, t, J 7 Hz), 1.15 (3H, t, J 7.5 Hz), 1.5 (3H, d, J 7 Hz), 1.2 - 2.5 (7H, m), 3.4

(2H, q, J 7.5 Hz), 3.4 (2H, m), 5.1 (1H, overlapping qd, J 7 and 7.6 Hz), 6.35 (1H, br d, J 7.6 Hz, exchangeable, NH), and 7.3 (5H, m); M^+ 277. (Found: C, 73.72; H, 9.92; N, 5.08. $C_{17}H_{27}NO_2$ requires C, 73.61; H, 9.81; N, 5.05%).

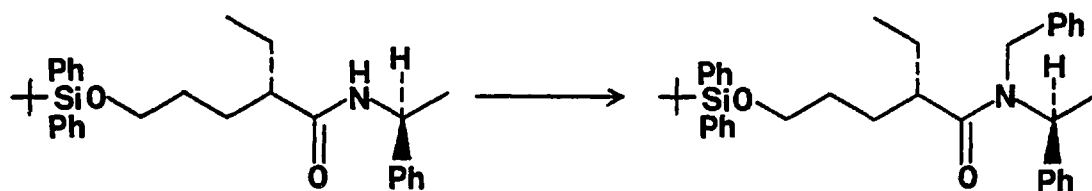
32. Preparation of 1'(S)-N-Phenylethyl-5-t-butyldiphenylsilyloxy-2(S)-ethylpentan-N-allylamide (82).



(-)-1'(S)-N-Phenylethyl-5-t-butyldiphenylsilyloxy-2(S)-ethylpentanamide (0.2g, 3.82×10^{-4} mole) and dry allyl bromide (0.1 ml, 1.15 mmol, 3 equiv.) in dry benzene (0.6 ml) were vigorously stirred, at reflux, with powdered sodium hydroxide (54 mg, 1.35 mmol), powdered potassium carbonate (0.108g, 7.8×10^{-4} mole), and tetra-n-butylammonium hydrogen-sulphate (13 mg, 3.82×10^{-5} mole) for 2h. Work up as in Experiment 30 above gave an almost colourless viscous oil (0.216g). Flash chromatography (6" silica, 20 mm dia. column) with 40% diethyl ether - 40-60 b.p. petrol gave 1'(S)-N-Phenylethyl-5-t-butyldiphenylsilyloxy-2(S)-ethylpentan-N-allylamide (0.173g, 3.28×10^{-4} mole, 86%), t.l.c. : R_f 0.35, 40% diethyl ether - 40-60 b.p. petrol, as a colourless oil, ν_{max} 1640 cm^{-1} ; δ 0.9 (3H, t, J 7.1 Hz), 1.05 (9H, s), 1.5 (3H, d, J 7.3 Hz), 1.4 - 1.8 (6H, m), 2.45 (1H, m, H_4), 3.35 - 4.15 (4H, m), 4.95 - 5.05 (2H, m), 5.55 (1H, m), 6.18 (1H, q, J 7.3 Hz, $H_{1'}$), 7.3 (11H, m), and 7.65 (4H, m); (Found: M^+ , 527.3211. $C_{34}H_{45}NO_2Si$ requires M^+ , 527.3219), contaminated with ca. 20% of the inseparable O-alkylated product,

1'(S)-N-phenylethyl-5-t-butyl-diphenylsilyloxy-5-allyloxy-2(S)-ethyl-pentanimine (83) (from minor absorptions in the ^1H n.m.r. spectrum at 2.66(m), 5.25(q), and 5.78 ppm corresponding to H_4 , $H_{1'}$, and an olefinic proton respectively).

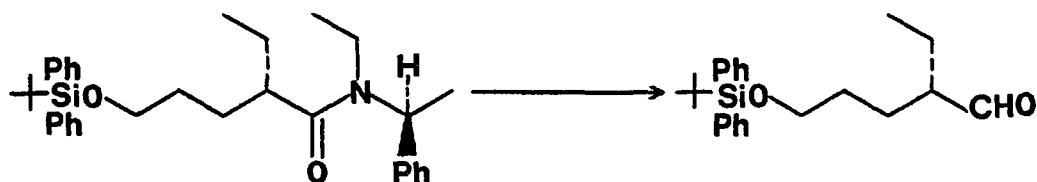
33. Preparation of 1'(S)-N-Phenylethyl-5-t-butyl-diphenylsilyloxy-2(S)-ethylpentan-N-benzylamide (84).



(-)-1'(S)-N-Phenylethyl-5-t-butyl-diphenylsilyloxy-2(S)-ethyl-pentanamide (0.610g, 1.25 mmol) and dry benzyl bromide (0.45 ml; 0.64g, 3.75 mmol, 3 equiv.) in dry benzene (1.8 ml) were vigorously stirred, at reflux, with powdered sodium hydroxide (0.165g, 4.12 mmol), powdered potassium carbonate (0.329g, 2.38 mmol), and tetra-n-butyl-ammonium hydrogensulphate (40 mg, 1.18×10^{-4} mole) for 2h. Work up as in Experiment 30 above gave a mobile colourless oil (1.03g) contaminated with benzyl bromide. Flash chromatography (6" silica, 30 mm dia. column) with 35% diethyl ether - 40-60 b.p. petrol gave 1'(S)-N-phenylethyl-5-t-butyl-diphenylsilyloxy-2(S)-ethylpentan-N-benzylamide (0.478g, 8.3×10^{-4} mole, 66%), as a colourless oil, t.l.c. : R_f 0.35, 35% diethyl ether - 40-60 b.p. petrol, ν_{max} 1640, 1605(sh), and 1590 cm^{-1} ; δ 0.75 (3H, t, J 7.5 Hz), 1.2 (9H, s), 1.45 (3H, d, J 8 Hz), 1.3 - 1.9 (4H, m), 2.25 (1H, m, H_4), 3.55 (2H, t, J 5 Hz), 4.15 and 4.4 (both 1H, d, J 18 Hz, CH_2Ph), 6.25 (1H, q, J 8 Hz, $H_{1'}$), and 7.0 - 7.7

(20H, m); (Found: $M-tBu^+$, 520.2658. $C_{34}H_{38}NO_2Si$ requires 520.2671), contaminated with *ca.* 30% of the inseparable O-alkylated product, 1'(S)-N-Phenylethyl-5-t-butyldiphenylsilyloxy-1-benzyloxy-2(S)-ethylpentanimine (85), δ 0.89 (3H, t, J 7.1 Hz), 1.08 (9H, s), 1.45 (3H, d, J 8 Hz), 1.3 - 1.9 (4H, m), 2.7 (1H, m, H_4), 3.69 (2H, t, J 5 Hz), 3.93 and 4.97 (both 1H, d, J 15.5 Hz), 5.3 (1H, q, J 8 Hz, $H_{1'}$), and 7.0 - 7.7 (20H, m).

34. DIBAL Reduction of 1'(S)-N-Phenylethyl-5-t-butyldiphenylsilyloxy-2(S)-ethylpentan-N-ethylamide (80).

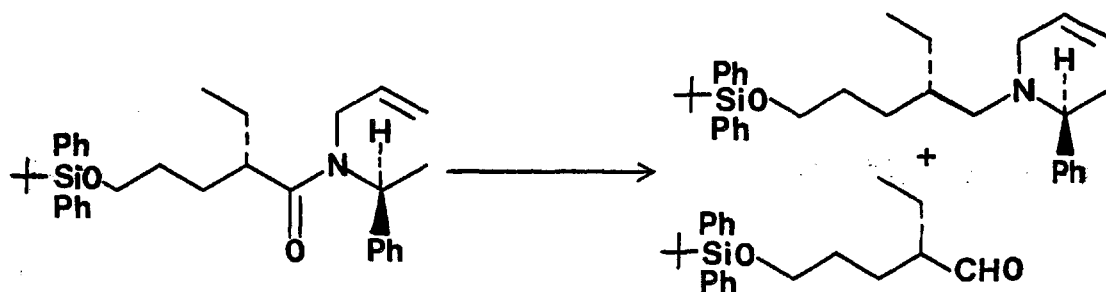


(a) DIBAL (0.16 ml of a 25% solution in toluene, 2.86×10^{-4} mol, 1.1 equiv.) was added dropwise to a solution of the amide (80) (0.134g, 2.6×10^{-4} mol) in dry toluene (0.5 ml) at $-78^{\circ}C$ (bT) over 5 min. Stirring at $-78^{\circ}C$ for 1h followed by slow warming to room temperature and overnight stirring at this temperature led to *ca.* 20% clean reduction to the aldehyde (74) (t.l.c. : R_f 0.58 1:1 diethyl ether - 40-60 b.p. petrol). The reaction mixture was vigorously shaken with 2N aqueous sulphuric acid (20 ml) before addition of diethyl ether (20 ml), separation of the two phases, and diethyl ether (2×10 ml) extraction of the aqueous phase. The combined organic solutions were washed with 2N aqueous sulphuric acid (1 ml), water (1 ml), 5% aqueous sodium bicarbonate (1 ml), and more water (1 ml) before drying

and concentration *in vacuo* to a mobile pale yellow oil (65.6 mg). Flash chromatography (5" silica, 20 mm dia. column) with 14% diethyl ether - 40-60 b.p. petrol gave (+)-1-t-butylidiphenylsilyloxy-2(S)-ethylpentanal (16.9 mg, 4.6×10^{-5} mole, 18%), as a colourless oil, $[\alpha]_D^{25} + 2.4^0$ (c 1.69, MeOH), $\nu_{\max}$ 1725 cm^{-1} ; δ 0.8 - 1.8 (9H, m), 1.03 (9H, s), 2.2 (1H, m), 3.65 (2H, m), 7.2 - 7.8 (10H, m), and 9.5 (1H, d, J 4.2 Hz); m/e: 311 ($\text{M}^+ - \text{tBu}^+$).

(b) DIBAL (0.58 ml of a 1N solution in hexane, 5.8×10^{-4} mole, 1.1 equiv.) was added dropwise, over 15 min, to a solution of the amide (80) (0.273g, 5.3×10^{-4} mole) in dry diethyl ether (1 ml) at 0°C (bT). Stirring at 0°C for 1h led to only ca. 20% reduction to the aldehyde (74) (t.l.c.) with a trace of a less polar product (R_f 0.7, 1:1 diethyl ether - 40-60 b.p. petrol). Addition of another portion of DIBAL (0.58 ml, 1.1 equiv.) followed by another 2h at 0°C showed only ca. 50% reduction of the amide to a ca. 1:1 mixture of the aldehyde (74) and the less polar product tentatively identified as 1'(S)-N-Phenylethyl-N-ethyl-5-t-butylidiphenylsilyloxy-2(S)-ethylpentanamine, by analogy with the corresponding characterised amines (88) and (89) formed by reduction of the amides (82) and (84) (see Experiments 35 and 36).

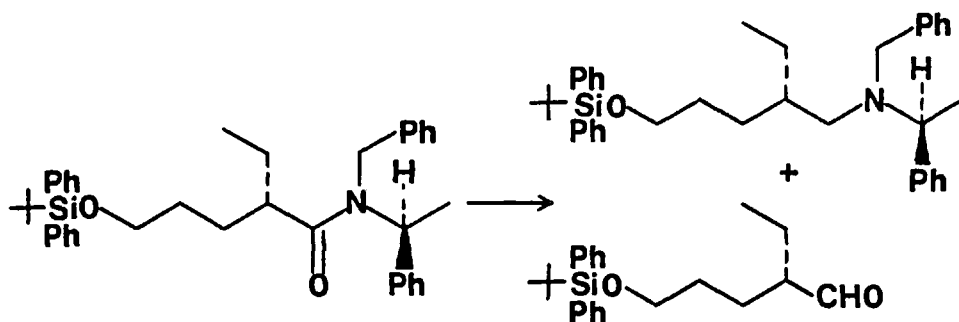
35. DIBAL Reduction of 1'(S)-N-Phenylethyl-5-t-butylidiphenylsilyloxy-2(S)-ethylpentan-N-allylamide (82).



(a) DIBAL (0.13 ml of a 25% solution in toluene, 2.24×10^{-4} mole, 2 equiv.) was stirred with the amide (82) (59.3 mg, 1.12×10^{-4} mole) in dry toluene (1.5 ml) at 0°C . After several hours only *ca.* 50% reduction was indicated by t.l.c. (40% diethyl ether - 40-60 b.p. petrol).

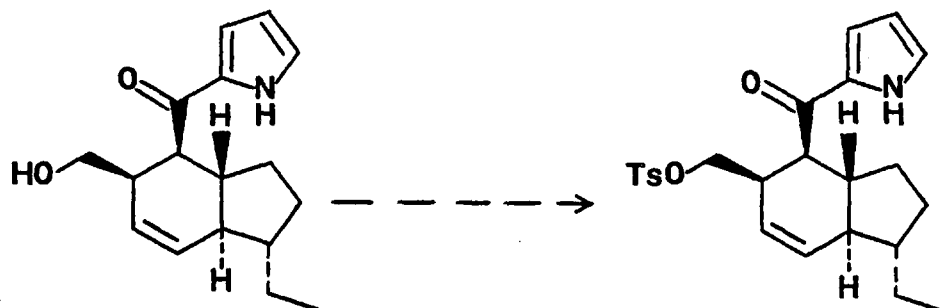
(b) DIBAL (0.27 ml of a 25% solution in toluene, 4.76×10^{-4} mole, 1.5 equiv.) was added to a solution of the amide (82) (167.3 mg, 3.17×10^{-4} mole) in dry diethyl ether (0.7 ml) at 0°C . After stirring up to room temperature for 6h, t.l.c. showed *ca.* 60% clean reduction. More DIBAL (0.1 ml, 1.76×10^{-4} mole, 0.56 equiv.) was added at room temperature. After 15 min at room temperature t.l.c. showed that reduction of the amide was complete. After work up as in Experiment 34 above, flash chromatography (6" silica, 20 mm dia. column) with 14% diethyl ether - 40-60 b.p. petrol gave the aldehyde (74) (25.7 mg, 7.5×10^{-5} mole, 22%), with no observable optical rotation, and 1'(S)-N-Phenylethyl-N-allyl-5-t-butylidiphenylsilyloxy-2(S)-ethylpentan-1-amine (88) (50.5 mg, 9.84×10^{-5} mole, 31%), t.l.c. : R_f 0.75, 1:1 diethyl ether - 40-60 b.p. petrol, ν_{max} 1600, 1425, 1110, and 700 cm^{-1} ; δ 0.7 - 1.9 (10H, m), 1.2 (9H, s), 1.4 (3H, d, J 7 Hz), 2.3 (2H, m, H_5), 3.1 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 3.7 (2H, m), 3.9 (1H, q, J 7 Hz), 5.0 - 5.3 (2H, m), 5.5 - 5.9 (1H, m), and 7.2 - 7.8 (15H, m); m/e: 311 ($\text{M}^+ - \text{tBu} - \text{CH}_2\text{CH}=\text{CH}_2 - \text{CH}_3\text{CHPh}$).

36. DIBAL Reduction of 1'(S)-N-Phenylethyl-5-t-butyl-diphenylsilyloxy-2(S)-ethylpentan-N-benzylamide (84).



DIBAL (0.49 ml of a 25% solution in toluene, 8.7×10^{-4} mole, 2 equiv.) was added, over 10 min, to the amide (84) (0.250g, 4.33×10^{-4} mole) in dry diethyl ether (1 ml) at $-6-0^{\circ}\text{C}$ (iT). After 30 min at 0°C t.l.c. (35% diethyl ether - 40-60 b.p. petrol) showed *ca.* 80% reduction of the amide to the aldehyde (74) and a less polar product (R_f 0.67). After warming to room temperature in 30 min no further change was apparent by t.l.c. More DIBAL (0.1 ml, 0.41 equiv.) was added to complete reduction and after 10 min at room temperature t.l.c. showed no amide (84) remaining. After work up as in Experiment 34 above flash chromatography (5½" silica, 20 mm dia. column) with 10% diethyl ether - 40-60 b.p. petrol gave the aldehyde (74) (42 mg, 1.14×10^{-4} mole, 26%), as before, but again with no observable optical rotation, and the less polar product 1'(S)-N-phenylethyl-N-benzyl-5-t-butyl-diphenylsilyloxy-2(S)-ethylpentan-1-amine (89) (98.7 mg, 1.75×10^{-4} mole, 40%), ν_{max} 1600, 1599, 1495, 1430, 1110, and 700 cm^{-1} ; δ 0.62 (3H, t, J 7.5 Hz), 1.05 (9H, s), 1.0 - 1.55 (7H, m), 1.35 (3H, d, J 7 Hz), 2.11 and 2.31 (both 1H, dd, J 13.3 and 6.6 Hz, CH_2N), 3.41 and 3.51 (both 1H, d, J 13.3 Hz, CH_2Ph), 3.62 (2H, t, J 6.6 Hz), 3.9 (1H, q, J 7 Hz, H_1), 7.15 - 7.4 (16H, m), and 7.89 (4H, m).

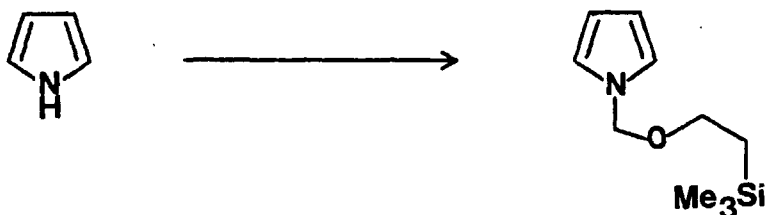
37. Attempted Preparation of ($\pm$)-4 β -(2'-Pyrrolylcarbonyl)-5 β -*p*-toluenesulphonyloxymethyl-1 α -ethyl-3 $\alpha\beta$,4,5,7 $\alpha\alpha$ -tetrahydroindan (106).



($\pm$)-4 β -(2'-Pyrrolylcarbonyl)-1 α -ethyl-3 $\alpha\beta$,4,5,7 $\alpha\alpha$ -tetrahydroindan-5 β -methanol (60 mg, 2.2×10^{-4} mole) in dry pyridine (100 μ l) was added dropwise to dry *p*-toluenesulphonyl chloride (0.105g, 5.5×10^{-4} mole, 2.5 equiv.) in dry pyridine (250 μ l) at 0 $^{\circ}$ C (bT) over 5 min. After stirring for 2h at 0 $^{\circ}$ C t.l.c. (90% diethyl ether - 40-60 b.p. petrol) showed clean, *ca.* 55%, conversion of the alcohol to a single less polar product (R_f 0.6). 85% Lactic acid (30 μ l) was added to the stirred brown suspension at 0 $^{\circ}$ C. After a further 30 min at 0 $^{\circ}$ C the now clear brown solution was poured into 10% aqueous hydrochloric acid (5 ml) overlaid with diethyl ether (25 ml). The organic solution, combined with a diethyl ether (3 $\times$ 5 ml) extract of the aqueous phase, was washed with 10% aqueous hydrochloric acid (3 $\times$ 5 ml), 5% aqueous sodium bicarbonate (2 $\times$ 5 ml), and water (10 ml) before drying and concentration *in vacuo* to a pale brown oil. T.l.c. showed a decreased amount of the less polar product (*ca.* 20%). ^1H N.m.r. did not prove useful in the analysis of the crude product due to the presence of *p*-toluenesulphonyl chloride. Flash chromatography (5 $\frac{1}{2}$ " silica, 20 mm dia. column) with 85% diethyl ether - 40-60 b.p. petrol gave the starting alcohol (61) (40 mg, 1.46×10^{-4} mole, 66% recovery) only. As the

starting material was eluted from the column in two separate batches, with the first portion leaving the column much sooner than expected, it would appear that the less polar product cleanly decomposed to the starting alcohol (61) on the column.

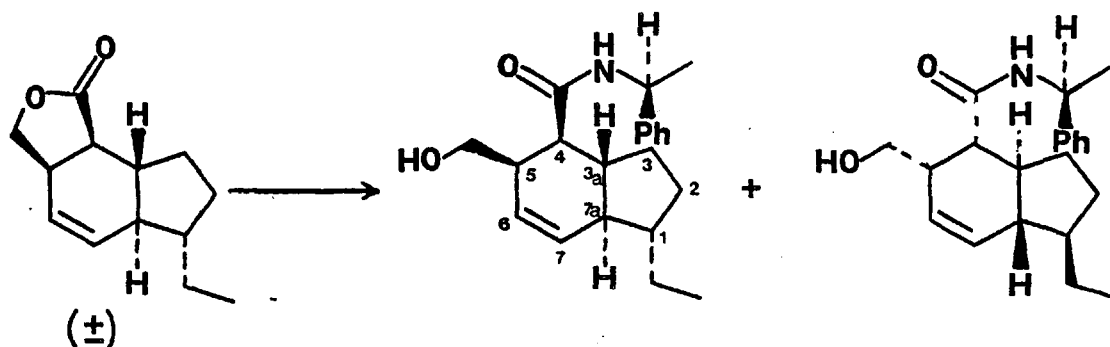
38. Preparation of 1-(β -Trimethylsilyl)ethoxymethylpyrrole (107).



Dry, freshly distilled, pyrrole (4.21 ml, 4g, 6×10^{-2} mole) was added dropwise to a cooled (ice bath), stirred, suspension of sodium hydride (4.6g of a 50% dispersion in oil, washed with dry 40-60 b.p. petrol (5 $\times$ 20 ml) to remove the oil, 9.59×10^{-2} mole, 1.6 equiv.) in dry DMF (180 ml)-DMSO (32 ml) over 15 min. After removal of the ice-bath and stirring at room temperature for 50 min, hydrogen evolution was complete. After recooling to 0°C (bT) freshly prepared β -trimethylsilylethoxymethylchloride (SEMCl, 15g, 9×10^{-2} mole, 1.5 equiv.) was added dropwise to the clear, pale yellow, solution over 5 min. The clear reaction mixture was stirred at room temperature for 30 min before careful pouring into water (200 ml) and ice (50g). The organic solution, combined with a diethyl ether (3 $\times$ 200 ml) extract of the aqueous phase, was washed with water (50 ml) 10% aqueous hydrochloric acid (2 $\times$ 50 ml), and more water (50 ml) before drying and concentration *in vacuo* to a mobile, clear, pale yellow oil (20g). Flash chromatography (6" silica, 55 mm dia column) with 5% diethyl ether - 40-60 b.p. petrol in four equal portions, using the same silica for

each 5g portion, with a 50% diethyl ether - 40-60 b.p. petrol (7 column inches) and column eluant (7") elution between each run, gave 1-(β -trimethylsilyl)ethoxymethylpyrrole (8.29g, 4.2×10^{-2} mole, 70%) as a mobile colourless liquid, b.p. 76°C at 1.5 mm Hg, t.l.c. : R_f 0.33, 6% diethyl ether - 40-60 b.p. petrol, ν_{max} 1495, 1270, 1250, 1070, 860, 835, and 720 cm^{-1} ; δ 0.0 (9H, s), 1.1 (2H, t, J 8 Hz), 3.6 (2H, t, J 8 Hz), 5.3 (2H, s), 6.2 (2H, dd, J 2.0 and 2.0 Hz), and 6.9 (2H, dd, J 2.0 and 2.0 Hz); M^+ 197. (Found: C, 61.07; H, 9.88; N, 6.85. $\text{C}_{10}\text{H}_{19}\text{NOSi}$ requires C, 60.86; H, 9.70; N, 7.10%).

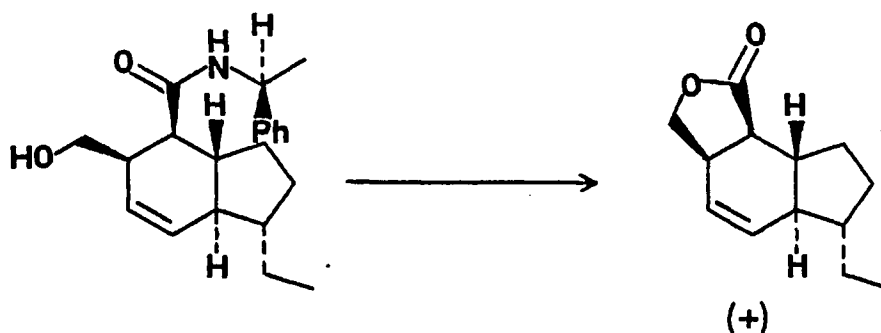
39. Preparation of (-)-5(S)-Hydroxymethyl-1(S)-ethyl-3a(R),4,5,7a(R)-tetrahydroindan-4(S)-(N-1'(S)-phenylethyl)formamide (91) and (-)-5(R)-Hydroxymethyl-1(R)-ethyl-3a(S),4,5,7a(S)-tetrahydroindan-4(R)-(N-1'(S)-phenylethyl)formamide (92).



The racemic lactone (21) (0.2g , 9.7×10^{-4} mole) was heated at 110° with (-)-1(S)-phenylethylamine ($250\text{ }\mu\text{l}$, 0.235g , 1.93×10^{-4} mole, 2 equiv.) and dry 2-hydroxypyridine (92.3 mg , 9.7×10^{-4} mole) in dry toluene ($483\text{ }\mu\text{l}$) for 6h. Dichloromethane (30 ml) was added and the solution washed with 10% aqueous hydrochloric acid ($3 \times 10\text{ ml}$). The organic solution was combined with dichloromethane ($3 \times 10\text{ ml}$) back extracts of the acidic aqueous phase and washed with water (10 ml),

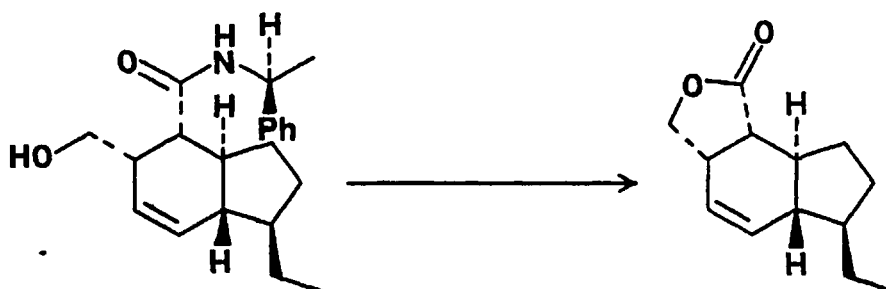
5% aqueous sodium bicarbonate (10 ml), and brine (10 ml) before drying and concentration *in vacuo* to a white solid (0.3g). Flash chromatography (6" silica, 20 mm dia. column) with 40% ethyl acetate - 40-60 b.p. petrol, after rechromatography of a mixed fraction (51.9 mg), gave unreacted lactone (21) (81.4 mg, 41% recovery), the less polar diastereomeric amide (-)-5(*S*)-hydroxymethyl-1(*S*)-ethyl-3 α (*R*),4,5,7 α (*R*)-tetrahydroindan-4(*S*)-(N-1'(*S*)-phenylethyl)formamide (91.5 mg, 2.8×10^{-4} mole, 29% or 98% based on reacted lactone enantiomer), m.p. 176-177°C (chloroform - 40-60 b.p. petrol), t.l.c. : R_f 0.4, 40% ethyl acetate - 40-60 b.p. petrol, $\nu_{\max}$ 3280, 3450, and 1630 cm^{-1} ; δ 0.85 (3H, t, J 7 Hz), 1.0 - 2.0 (9H, m), 1.45 (3H, d, J 7.5 Hz), 2.33 (1H, dd, J 11 and 7.4 Hz, H_4), 2.45 (1H, m, H_5), 3.4 (1H, s, exchangeable, OH), 3.4 and 3.55 (both 1H, m, CH_2OH) [with D_2O exchange: 3.4 (1H, dd, J 12.4 and 2.7 Hz) and 3.55 (1H, dd, J 12.4 and 5 Hz)], 5.1 (1H, overlapping qd, J 7.5 and 7.5 Hz, $H_{1'}$), 5.4 (br d, 1H, J 10 Hz, H_6), 6.95 (1H, d, J 10 Hz, H_7), 6.15 (1H, br d, J 7.5 Hz, NH), and 7.25 (5H, m); M^+ 327; (Found: C, 76.92; H, 9.00; N, 4.28. $\text{C}_{21}\text{H}_{29}\text{NO}_2$ requires C, 77.02; H, 8.93; N, 4.28%), and the more polar diastereomeric amide (-)-5(*R*)-hydroxymethyl-1(*R*)-ethyl-3 α (*S*),4,5,7 α (*S*)-tetrahydroindan-4(*R*)-(N-1'(*S*)-phenylethyl)formamide (89 mg, 2.7×10^{-4} mole, 28% or 94% based on reacted lactone enantiomer), m.p. 170-173°C (chloroform - 40-60 b.p. petrol, t.l.c. : R_f 0.27, 40% ethyl acetate - 40-60 b.p. petrol, $\nu_{\max}$ 3280, 3450, and 1630 cm^{-1} ; δ 0.85 (3H, t, J 7 Hz), 0.9 - 2.0 (9H, m), 1.45 (3H, d, J 7.5 Hz), 2.3 (1H, dd, J 11 and 6.5 Hz, H_4), 2.5 (1H, m, H_5), 3.45 (1H, dd, J 16 and 6.25 Hz, OH), 3.5 - 3.7 (2H, m), 5.1 (overlapping qd, J 7.5 and 7 Hz, $H_{1'}$), 5.4 (1H, ddd, J 10, 3.5, and 2 Hz, H_6), 5.95 (1H, d, J 10 Hz, H_7), 6.0 (1H, br s, NH), and 7.25 (5H, m); M^+ 327. (Found: C, 77.11; H, 8.92; N, 4.24. $\text{C}_{21}\text{H}_{29}\text{NO}_2$ requires C, 77.02; H, 8.93; N, 4.28%).

40. Preparation of (+)-1(S)-Ethyl-3a(R),4,5,7a(R)-tetrahydroindan-4(S)-carboxylic acid-5(S)-methanol, γ -lactone (+)-(70).



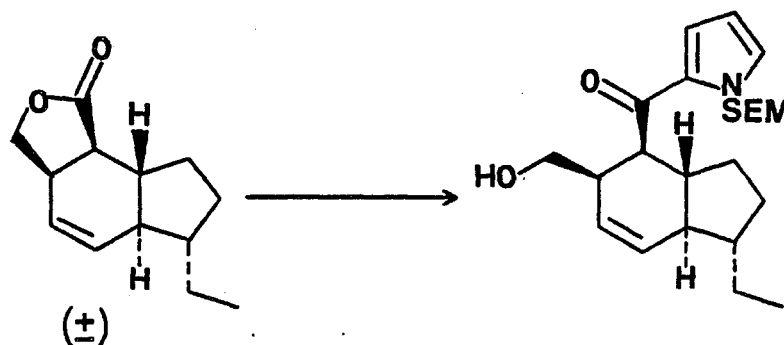
The less polar diastereomeric amide (91) (0.160g , 4.88×10^{-4} mole) was stirred in 1N sulphuric acid (in $1:1$ water-dioxan, 4 ml) for 1h at 80°C . Dichloromethane (50 ml) and water (20 ml) were added to the cooled reaction mixture. The organic phase, combined with a dichloromethane ($3 \times 20\text{ ml}$) extract of the aqueous phase, was washed with 5% aqueous sodium bicarbonate ($2 \times 20\text{ ml}$) and brine (20 ml) before drying and concentration *in vacuo* to a white solid (118 mg). The crude product was dissolved in 30% dichloromethane - $40\text{-}60\text{ b.p. petrol}$ (2 ml) and passed through a Pasteur pipette containing Kieselgel ($2\frac{1}{2}\text{''}$, Merck 9385) to remove traces of baseline impurities. Concentration *in vacuo* gave the (+)-lactone (70) (99 mg , 4.8×10^{-4} mole, 98%), homogeneous by t.l.c. (R_f 0.35 , 21.5% ethyl acetate - $40\text{-}60\text{ b.p. petrol}$), m.p. $83\text{-}84^{\circ}\text{C}$ ($40\text{-}60\text{ b.p. petrol}$), $[\alpha]_D^{25} + 136^{\circ}$ (c 1.02 , CHCl_3) (Lit.¹: $[\alpha]_D + 113^{\circ}$ (c 0.20 , CHCl_3) for lactone of 82% ee), other data as for the racemic lactone (21).

41. Preparation of (-)-1(R)-Ethyl-3a(S),4,5,7a(S)-tetrahydroindan-4(R)-carboxylic acid-5(R)-methanol, γ -lactone (-)-(93).



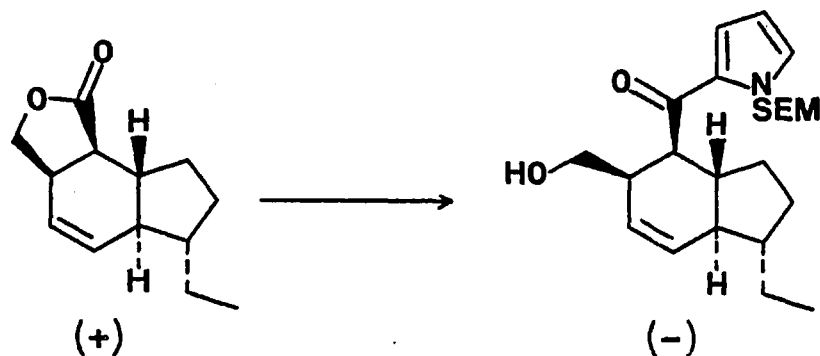
The more polar diastereomeric amide (92) (20 mg, 6.1×10^{-5} mole) was stirred in 1N sulphuric acid (in 1:1 water-dioxan, 500 μ l) for 1h at 80°C. Work up as in Experiment 40 above gave the (-)-lactone (93) (12.5 mg, 6.06×10^{-5} mole, 99%), homogeneous by t.l.c. (R_f 0.35, 21.5% ethyl acetate - 40-60 b.p. petrol), m.p. 83-84°C (40-60 b.p. petrol), $[\alpha]_D^{25} -136^\circ$ (c 0.52, CHCl_3), other data as for the racemic lactone (21).

42. Preparation of ($\pm$)-4 β -[2'-N-(β -Trimethylsilyl)ethoxymethyl-pyrrolylcarbonyl]-1 α -ethyl-3 $\alpha\beta$,4,5,7 $\alpha\alpha$ -tetrahydroindan-5 β -methanol (108).



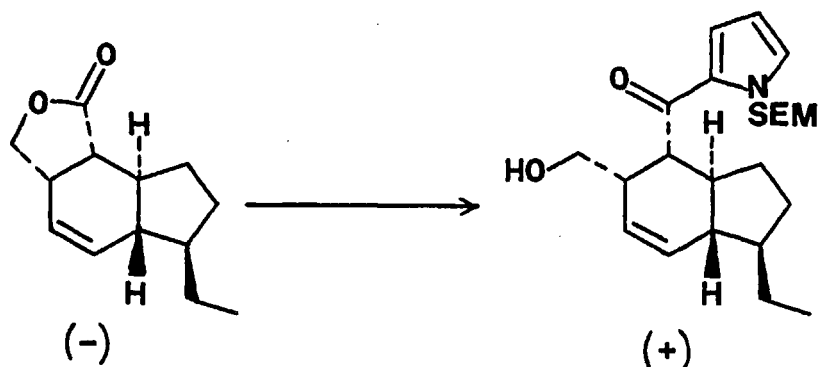
n-Butyl lithium (2.4 equiv., 0.86 ml of a 1.35N soln. in hexane) was added dropwise, over 8 min, to a stirred solution of N-(β -trimethylsilyl)ethoxymethylpyrrole (0.192g, 9.7×10^{-4} mole, 2.0 equiv.) in dry DME (1 ml) at 0°C. The pale yellow solution was stirred at 0-5°C for a further 10 min before rapid addition of the racemic lactone (21) (0.1g, 4.85×10^{-4} mole) in dry DME (400 μ l) in one portion. The reaction mixture was stirred up to room temperature over 10 min before pouring into saturated aqueous ammonium chloride (10 ml) overlaid with diethyl ether (20 ml). The yellow organic solution, combined with a diethyl ether (3 $\times$ 20 ml) extract of the aqueous phase, was washed with 5% aqueous hydrochloric acid (3 $\times$ 10 ml), 5% aqueous sodium bicarbonate (20 ml), and water (20 ml) before drying and concentration *in vacuo* to a brown oil. Flash chromatography (6" silica, 20 mm dia. column) with 25% ethyl acetate - 40-60 b.p. petrol gave ($\pm$)-4 β -[2'-N-(β -trimethylsilyl)ethoxymethylpyrrolylcarbonyl]-1 α -ethyl-3 α ,4,5,7 α -tetrahydroindan-5 β -methanol (0.117 mg, 2.9×10^{-4} mole, 60%), as a colourless oil, t.l.c. : R_f 0.28, 25% ethyl acetate - 40-60 b.p. petrol, $\nu_{\max}$ 3450, 1630, and 1520 cm^{-1} ; δ 0.0 (9H, s), 0.9 (2H, m, CH_2SiMe_3), 0.92 (3H, t, J 7 Hz), 0.9 - 2.1 (9H, m), 2.73 (1H, dd, J 8 and 6.6 Hz, H_4), 2.73 (1H, m, H_5), 3.45 (1H, dd, J 6.9 Hz and 6.9 Hz, OH), 3.48 and 3.52 (both 1H, d, J 7.8 Hz, $\text{CH}_2\text{OCH}_2\text{SiMe}_3$), 3.53 (1H, m, CH_2OH), 3.65 (1H, ddd, J 12, 6.9 and 5 Hz, CH_2OH), 5.55 (1H, ddd, J 10, 3.7, and 2.6 Hz, H_6), 5.59 and 5.89 (both 1H, d, J 10 Hz, OCH_2N), 6.06 (1H, br d, J 10 Hz, H_7), 6.2 (1H, dd, J 3.1 and 3.1 Hz, pyrrole C_4H), and 7.09 and 7.09 (both 1H, d, J 3.1 Hz, pyrrole C_3H and C_5H); M^+ 403; (Found: C, 68.32; H, 9.31; N, 3.18. $\text{C}_{23}\text{H}_{37}\text{NO}_3\text{Si}$ requires C, 68.44; H, 9.24; N, 3.47%).

43. Preparation of (-)-4(S)-[2'-N-(β -Trimethylsilyl)ethoxymethyl-pyrrolylcarbonyl]-1(S)-ethyl-3a(R),4,5,7a(R)-tetrahydroindan-5(S)-methanol (-)-(110).



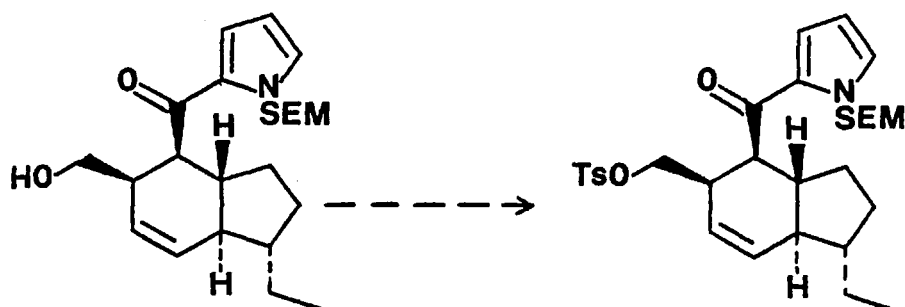
n-Butyl lithium (524 μ l of a 1.63N solution in hexane, 8.54×10^{-4} mole, 2.2 equiv.) was added dropwise, over 7 min, to N-(β -trimethylsilyl)ethoxymethylpyrrole (0.162g, 7.76×10^{-4} mole, 2 equiv.) in dry DME (1.06 ml) at 0°C (bT). After 10 min at $0-5^{\circ}\text{C}$ the (+)-lactone (70) (80 mg, 3.88×10^{-4} mole) in dry DME (200 μ l) was added rapidly in one portion. The yellow reaction mixture was stirred up to room temperature in 5 min before quenching and work up as in Experiment 42 above. Flash chromatography (5½" silica 20 mm dia. column) with 25% ethyl acetate - 40-60 b.p. petrol gave, contaminated with *ca.* 5% of the readily separable starting lactone (+)-(70), the (-)-alcohol (110) (97.1 mg, 2.41×10^{-4} mole, 62%), $[\alpha]_{\text{D}}^{25} -19^{\circ}$ (c 0.688, CHCl_3), other data as for the racemic alcohol (108).

44. Preparation of (+)-4(R)-[2'-N-(β -Trimethylsilyl)ethoxymethyl-pyrrolylcarbonyl]-1(R)-ethyl-3a(S),4,5,7a(S)-tetrahydroindan-5(R)-methanol (+)-(111).



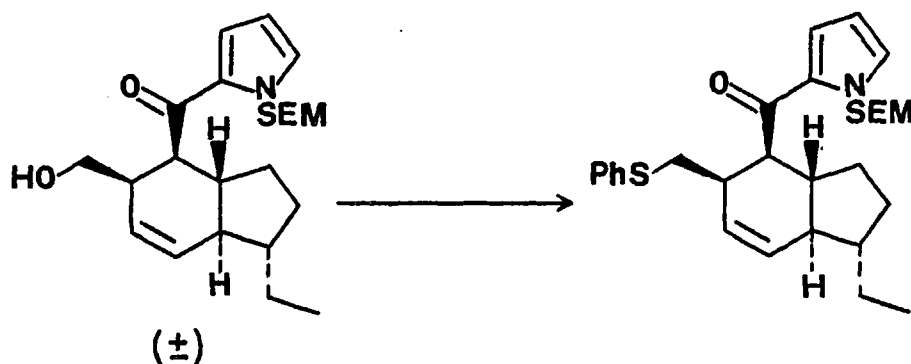
Following the procedure given in Experiment 43 above, the (-)-lactone (93) (0.1133g, 5.5×10^{-4} mole) gave, contaminated with a trace of (-)-(93) after flash chromatography (6" silica, 20 mm dia. column) with 25% ethyl acetate - 40-60 b.p. petrol, the (+)-alcohol (111) (0.134g, 3.32×10^{-4} mole, 60%), $[\alpha]_D^{25} + 19^\circ$ (c 0.92, CHCl_3), other data as for the racemic alcohol (108).

45. Attempted Preparation of ($\pm$)-4 β -[2'-N-(β -Trimethylsilyl)ethoxymethylpyrrolylcarbonyl]-5 β -*p*-toluenesulphonyloxymethyl-1 α -ethyl-3 α ,4,5,7 α -tetrahydroindan



p-Toluenesulphonyl chloride (10.9 mg, 5.7×10^{-5} mole, 1.5 equiv.) in dry pyridine (25 μ l) was added dropwise to a stirred solution of the racemic alcohol (108) (15.3 mg, 3.8×10^{-5} mole) in dry pyridine (10 μ l) at 0°C (bT). After 2h t.l.c. seemed to indicate clean conversion of the alcohol (108) to one less polar product (R_f 0.67, 20% ethyl acetate - 40-60 b.p. petrol). After work up as in Experiment 37 above t.l.c. showed only a trace of the less polar product with a majority of the starting alcohol (108). In an identical run the reaction was worked up in a non aqueous fashion involving azeotropic removal of pyridine with dry toluene (3 $\times$ 1 ml) at reduced pressure. Flash chromatography (5.5" silica, 10 mm dia. column) with 20% ethyl acetate - 40-60 b.p. petrol gave the starting alcohol (108), contaminated with *p*-toluenesulphonyl chloride, only. As the starting alcohol was eluted from the column in two separate batches, with the first portion leaving the column much sooner than expected, it would appear that the less polar product cleanly decomposed to the starting alcohol (108) on the column.

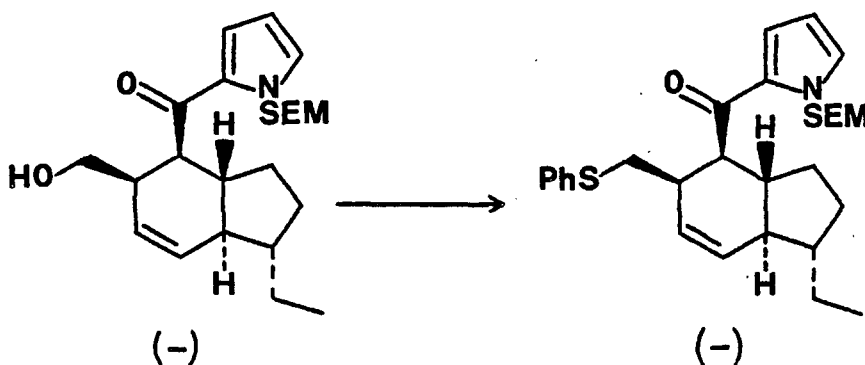
46. Preparation of ($\pm$)-4 β -[2'-N-(β -Trimethylsilyl)ethoxymethyl-pyrrolylcarbonyl]-5 β -phenylsulphenylmethyl-1 α -ethyl-3 α ,4,5,7 α -tetrahydroindan (114).



The racemic alcohol (108) (0.138g, 3.42×10^{-4} mole) in dry benzene (300 μ l) was added, rapidly in one portion, to the pale mauve solution resulting from stirring N-phenylsulphenosuccinimide (0.123g, 5.4×10^{-4} mole, 1.6 equiv.) with tri-n-butylphosphine (149 μ l, 5.4×10^{-4} mole, 1.6 equiv.) in dry benzene (1.4 ml) for 10 min at room temperature. After stirring for 2.75 h the reaction mixture was diluted with diethyl ether (40 ml) and washed with water (20 ml). The organic solution, combined with a diethyl ether (10 ml) back extract of the aqueous phase, was washed with 1% aqueous hydrochloric acid (10 ml), 5% aqueous sodium bicarbonate (15 ml), and brine (10 ml) before drying and concentration *in vacuo* to give a pale brown oil. Flash chromatography (6" silica, 20 mm dia. column) with 5% ethyl acetate - 40-60 b.p. petrol gave ($\pm$)-4 β -[2'-N-(β -Trimethylsilyl)ethoxymethylpyrrolylcarbonyl]-5 β -phenylsulphenylmethyl-1 α -ethyl-3 α ,4,5,7 α -tetrahydroindan (0.110 mg, 2.2×10^{-4} mole, 64% or 72% based on recovered starting alcohol (108),) as a colourless oil, t.l.c. : R_f 0.38, 10% ethyl acetate - 40-60 b.p. petrol, $\nu_{\max}$ 1645 cm^{-1} ; δ -0.1 (9H, s), 0.85 (2H, m, CH_2SiMe_3), 0.9 (3H, t, J 7.3 Hz), 0.9 - 2.1 (9H, m), 2.73 (1H, dd, J 12.4 and 9.4 Hz,

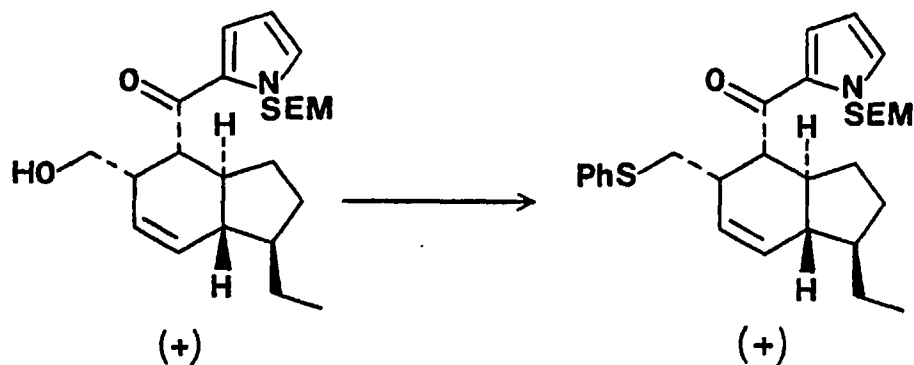
CH_2SPh), 2.85 (1H, m, H_5), 3.03 (1H, dd, J 12.4 and 4.4 Hz, CH_2SPh), 3.45 (1H, dd, J 11 and 6.3 Hz, H_4), 3.55 (2H, m, $\text{CH OCH}_2\text{SiMe}_3$), 5.7 and 5.85 (both 1H, d, J 10 Hz, NCH_2O), 5.88 (1H, ddd, J 10, 3.8, and 2.5 Hz, H_6), 5.97 (1H, d, J 10 Hz, H_7), 6.2 (1H, dd, J 3.8 and 2.5 Hz, pyrrole C_4H), 6.95 - 7.15 (5H, m), and 7.1 (2H, overlapping m, pyrrole C_3H and C_5H); M^+ 495. (Found: C, 70.20; H, 8.37; N, 3.03. $\text{C}_{29}\text{H}_{41}\text{NO}_2\text{SSi}$ requires C, 70.25; H, 8.34; N, 2.83%). Some unreacted starting alcohol (108) (15.5 mg, 3.8×10^{-5} mole) was recovered by further elution with 25% ethyl acetate - 40-60 b.p. petrol.

47. Preparation of (-)-4(S)-[2'-N-(β -Trimethylsilyl)ethoxymethyl-pyrrolylcarbonyl]-5(S)-phenylsulphenylmethyl-1(S)-ethyl-3a(R),-4,5,7a(R)-tetrahydroindan (-)-(119).



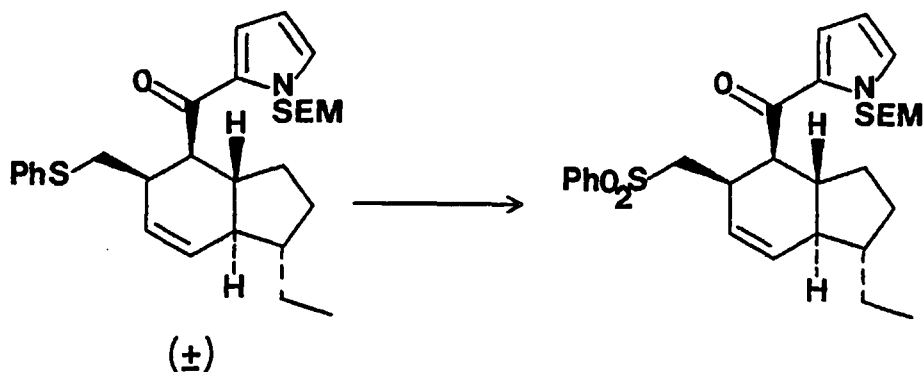
Following the procedure given in Experiment 46 above, the (-)-alcohol (110) (82.2 mg, 2.04×10^{-4} mole) in dry benzene (181 μl) was converted, using N-phenylsulphenosuccinimide (73 mg, 3.2×10^{-4} mole, 1.6 equiv.) and tri-n-butylphosphine (88 μl , 3.2×10^{-4} mole, 1.6 equiv.) in dry benzene (0.82 ml), to the (-)-sulphide (71 mg, 1.43×10^{-4} mole, 70% or 77% based on recovered alcohol), $[\alpha]_D^{25} -69^0$ (c 3.8, CHCl_3), other data as for the racemic sulphide (114). As before a small amount of starting alcohol (110) (7.7 mg, 1.9×10^{-5} mole) was recovered.

48. Preparation of (+)-4(R)-[2'-N-(β -Trimethylsilyl)ethoxymethyl-pyrrolylcarbonyl]-5(R)-phenylsulphenylmethyl-1(R)-ethyl-3a(S),-4,5,7a(S)-tetrahydroindan (+)-(120).



Following the procedure given in Experiment 46 above, the (+)-alcohol (111) (0.1084g, 2.69×10^{-4} mole) in dry benzene (280 μ l) was converted, using N-phenylsulphenosuccinimide (0.113g, 4.97×10^{-4} mole, 1.8 equiv.) and tri-n-butylphosphine (136 μ l, 4.97×10^{-4} mole, 1.8 equiv.) in dry benzene (1.26 ml), to the (+)-sulphide (98.3 mg, 1.98×10^{-4} mole, 74% or 83% based on recovered alcohol), $[\alpha]_D^{25} + 68^{\circ}$ (c 1.4, CHCl_3), other data as for the racemic sulphide (114). As before a small amount of starting alcohol (111) (12 mg, 2.98×10^{-5} mole) was recovered.

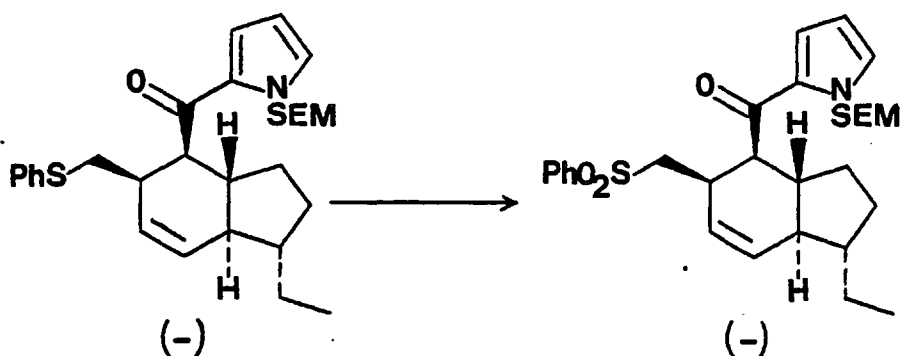
49. Preparation of ($\pm$)-4 β -[2'-N-(β -Trimethylsilyl)ethoxymethylpyrrolyl-carbonyl]-5 β -phenylsulphonylmethyl-1 α -ethyl-3 α ,4,5,7 α -tetrahydroindan (121).



30% Hydrogen peroxide (82.1 μ l, 7.26×10^{-4} mole, 6 equiv.) was added dropwise to a stirred solution of the racemic sulphide (114) (60.2 mg, 1.21×10^{-4} mole) and diphenyldiselenide (37.3 mg, 1.21×10^{-4} mole, 1 equiv.) in 15% dichloromethane - diethyl ether (550 μ l), at 0°C (bT), in 3 min. After 1h the cooling bath was removed and stirring continued at room temperature for 6h. The reaction mixture was diluted with dichloromethane (50 ml) before washing with saturated aqueous sodium bicarbonate (2×10 ml), 5% aqueous sodium metabisulphite (10 ml), and brine (10 ml). The dried organic solution was concentrated *in vacuo* to give a gum contaminated with a trace of diphenyl diselenide. Flash chromatography (6" silica, 10 mm dia. column) with 28% ethyl acetate - 40-60 b.p. petrol gave ($\pm$)-4 β -[2'-N-(β -trimethylsilyl)ethoxymethylpyrrolylcarbonyl]-5 β -phenylsulphonylmethyl-1 α -ethyl-3 α ,4,5,7 α -tetrahydroindan (48.6 mg, 9.2×10^{-5} mole, 76%), as a colourless gum, t.l.c. : R_f 0.43, 30% ethyl acetate - 40-60 b.p. petrol, ν_{max} 1635 and 1520 cm^{-1} ; δ -0.2 (9H, s), 0.85 (2H, m, CH_2SiMe_3), 0.9 (3H, t, J 7 Hz), 0.9 - 2.0 (9H, m), 3.1 (1H, m, $\text{CH}_2\text{SO}_2\text{Ph}$), 3.13 (1H, m, H_5), 3.43 (1H, m, $\text{CH}_2\text{SO}_2\text{Ph}$), 3.44 (1H, m, H_4), 3.52 (2H, m, CH_2O), 5.55

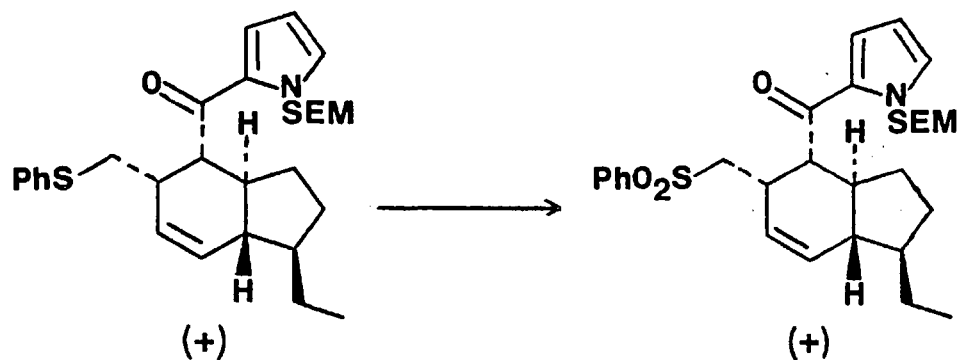
and 5.73 (both 1H, d, J 9.8 Hz, NCH₂O), 5.96 (2H, m, H₆ and H₇), 6.13 (1H, dd, J 4.3 and 2.4 Hz, pyrrole C₄'H), 6.88 (1H, dd, J 4.3 and 1.2 Hz, C₃'H), 7.08 (1H, dd, J 2.4 and 1.2 Hz, C₅'H), and 7.35 - 7.55 (5H, m); M⁺ 527. (Found: C, 66.08; H, 7.73; N, 2.45. C₂₀H₄₁NO₄Si requires C, 66.00; H, 7.83; N, 2.65%).

50. Preparation of (-)-4(S)-[2'-N-(β-Trimethylsilyl)ethoxymethyl]-pyrrolylcarbonyl]-5(S)-phenylsulphonylmethyl-1(S)-ethyl-3a(R),-4,5,7a(R)-tetrahydroindan (-)-(123).



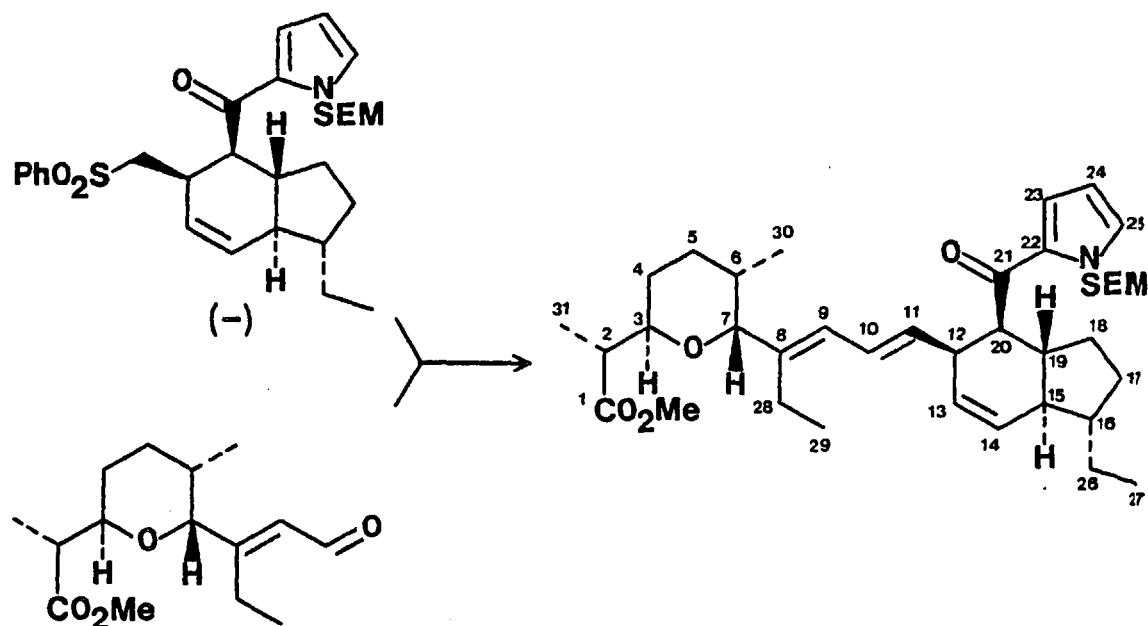
Following the procedure given in Experiment 49 above, the (-)-sulphide (119) (38 mg, 7.66×10^{-5} mole) was converted, using 30% hydrogen peroxide (51.9 μ l, 5.5×10^{-4} mole, 7.2 equiv.) and diphenyl-diselenide (23.6 mg, 7.66×10^{-5} mole, 1 equiv.) in 15% dichloromethane-diethyl ether (411 μ l), to the (-)-sulphone (123) (32.1 mg, 6.1×10^{-5} mole, 80%), $[\alpha]_D^{25} -79^0$ (c 1.05, CHCl₃), other data as for the racemic sulphone (121), after microchromatography of the crude product on a Pasteur pipette containing Kieselgel (2", Merck 9385) with 10% diethyl ether - 40-60 b.p. petrol (5 ml), 20% diethyl ether - 40-60 b.p. petrol (5 ml), and finally a gradient elution up to neat diethyl ether (total of 6 ml).

51. Preparation of (+)-4(R)-[2'-N-(β -Trimethylsilyl)ethoxymethyl-pyrrolylcarbonyl]-5(R)-phenylsulphonylmethyl-1(R)-ethyl-3a(S), 4,5,7a(S)-tetrahydroindan (+)-(124).



Following the procedure given in Experiment 49 above, the (+)-sulphide (98.3 mg, 1.8×10^{-4} mole) was converted, using 30% hydrogen peroxide (134.3 μ l, 1.08×10^{-3} mole, 6 equiv.) and diphenyldiselenide (61 mg, 1.8×10^{-4} mole, 1 equiv.) in 15% dichloromethane-diethyl ether (1.1 ml), to the (+)-sulphone (124) (71.4 mg, 1.35×10^{-4} mole, 75%), $[\alpha]_D^{25} + 78^{\circ}$ (c 1.15, CHCl_3), other data as for the racemic sulphone (121), after flash chromatography (5" silica, 20 mm dia. column) with 28% ethyl acetate - 40-60 b.p. petrol.

52. Preparation of (-)-Methyl α (R),5(S)-dimethyl-6(R)-{1-ethyl-4-[4(R)-(2'-N-(β -trimethylsilyl)ethoxymethylpyrrolylcarbonyl)-1(S)-ethyl-3a(R),4,5(R),7a(R)-tetrahydroindan-5-yl]-1(E),3(E)-butadienyl} tetrahydropyran-2(R)-acetate, N-SEM-X-14547A Methyl Ester (130).

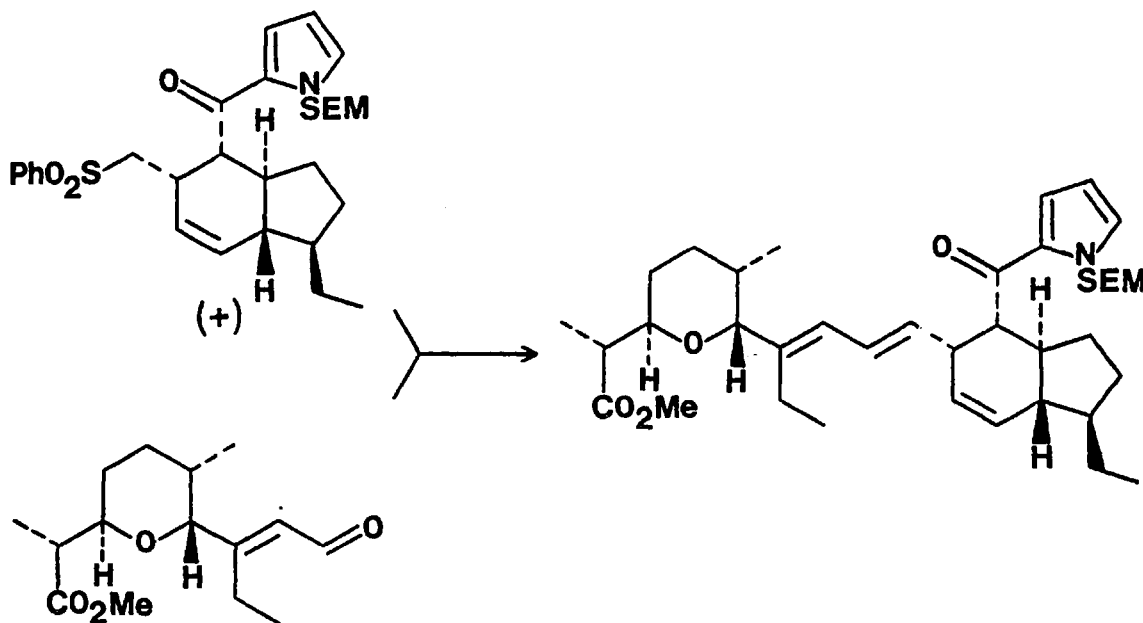


n-Butyl lithium (0.101 ml of a 1.6N solution in hexane, 1.62×10^{-4} mole, 1.2 equiv.) was added dropwise, during 5 min, to a solution of the (-)-sulphone (123) (71 mg, 1.35×10^{-4} mole) in THF (0.43 ml) and HMPA (0.11 ml) at -78°C . After 10 min at 78°C , methyl α (R),5(S)-dimethyl-6(R)-(1-ethyl-1(E)-propenyl)tetrahydropyran-2(R)-acetate (125) (43.3 mg, 1.62×10^{-4} mole, 1.2 equiv.) in THF (0.2 ml) was added, over 4 min, also at -78°C . After a further 45 min, benzoyl chloride (32.5 μl 2.7×10^{-4} mole, 2 equiv.) was added in one portion. The reaction mixture was allowed to warm to room temperature, during 2h, before addition of 3-N,N-dimethylaminopropyl-1-amine (34.7 μl , 2.7×10^{-4} mole, 2 equiv.) in one portion. The reaction mixture was diluted with diethyl ether (50 ml) and water (20 ml). The organic solution, combined with a diethyl ether (3 $\times$ 10 ml) extract of the aqueous phase, was washed with 10% aqueous hydrochloric acid (10 ml), 5% aqueous sodium bicarbonate (10 ml), and saturated brine

(20 ml) before drying and concentration *in vacuo* to a colourless gum (0.116g). T.l.c. (25% ethyl acetate - 40-60 b.p. petrol) showed a trace of the aldehyde (125) (R_f 0.32) and a number of components between R_f 0.48 and 0.76. The i.r. spectrum confirmed the presence of the 2-pyrrolylcarbonyl system (1640 cm^{-1} , C=O str.) and a particularly strong absorption at $1710 - 1740\text{ cm}^{-1}$ (C=O str.) showed that ester functionality (RCO_2Me , $\text{R}'\text{CO}_2\text{Ph}$) was present.

The crude benzoyloxysulphones (128) were stirred with sodium amalgam (0.33g of a 4% sample, *ca.* 6.8×10^{-4} mole, *ca.* 5 equiv.) in THF (1.1 ml) and methanol (0.36 ml) at -20°C for 2h. More sodium amalgam (0.2g, *ca.* 3 equiv.) was added and the reaction poured into 40-60 b.p. petrol (100 ml) and water (10 ml) after a further hour at -20°C . The organic solution, combined with a diethyl ether (10 ml) extract of the aqueous phase, was washed with saturated brine (15 ml) before drying and concentration *in vacuo*. Flash chromatography (5½" silica, 10 mm dia. column) with 22% diethyl ether - 40-60 b.p. petrol gave N-SEM-X-14547A methyl ester (130) (46 mg, 7.22×10^{-5} mole, 53%), homogeneous by t.l.c. (R_f 0.58, 50% diethyl ether - 40-60 b.p. petrol), $[\alpha]_D^{25} -255^\circ$ (c 0.84, CHCl_3), ν_{max} 1725 and 1640 cm^{-1} ; δ 0.0 (9H, s), 0.85 (3H, t, J 7 Hz, C-27 methyl), 0.88 (3H, d, J 7 Hz, C-30 methyl), 0.9 (2H, m, CH_2SiMe_3), 0.98 (3H, t, J 7 Hz, C-29 methyl), 1.0 - 2.1 (16H, m), 1.1 (3H, d, J 7 Hz, C-31 methyl), 2.95 (1H, m, H_2), 3.35 (1H, m, H_{12}), 3.45 (1H, dd, J 10.5 and 6.4 Hz, H_{20}), 3.6 (2H, m, $\text{CH}_2\text{CH}_2\text{O}$), 3.65 (3H, s, CO_2CH_3), 3.8 (1H, m, H_3), 4.2 (1H, d, J 3.3 Hz, H_7), 5.38 (1H, d, J 10.5 Hz, CH_2N), 5.45 (1H, dd, J 13.7 and 9.3 Hz, H_{11}), 5.52 (1H, ddd, J 10, 4.4, and 2.5 Hz, H_{13}), 5.9 (1H, d, J 10.5 Hz, CH_2N), 5.9 (1H, m, obscured, H_{10}), 5.95 (1H, d, J 10.6 Hz, H_9), 6.0 (1H, d, J 10 Hz, H_{14}), 6.25 (1H, dd, J 4.4 and 2.5 Hz, H_{24}), 7.02 (1H, dd, J 4.4 and 1.5 Hz, H_{25}), and 7.1 (1H, dd, J 2.5 and 1.5 Hz, H_{23}); (Found: M^+ , 637.4145. $\text{C}_{38}\text{H}_{59}\text{NO}_5\text{Si}$ requires M, 637.4159).

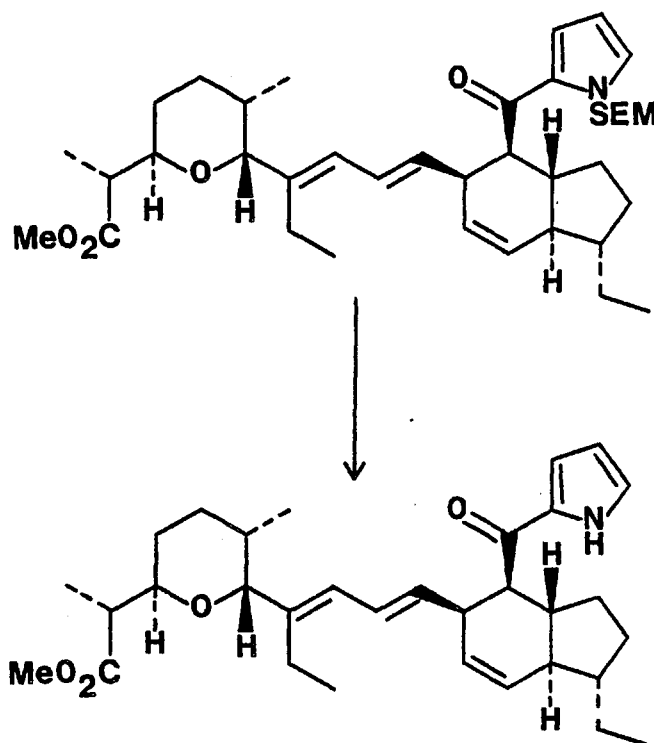
53. Preparation of (+)-Methyl $\alpha(R),5(S)$ -dimethyl-6(R)-[1-ethyl-4-{4(S)-(2'-N-(β -trimethylsilyl)ethoxymethylpyrrolylcarbonyl)-1(R)-ethyl-3a(S),4,5(S),7a(S)-tetrahydroindan-5-yl}-1(E),3(E)-butadienyl]tetrahydropyran-2(R)-acetate, N-SEM-X14547A Diastereomer Methyl Ester (131).



Following the procedure of Experiment 52, the (+)-sulphone (124) (67.8 mg, 1.29×10^{-4} mole), and methyl $\alpha(R),5(S)$ -dimethyl-6(R)-(1-ethyl-1(E)-propenyl)tetrahydropyran-2(R)-acetate (125) (38 mg, 1.42×10^{-4} mole) gave N-SEM-X-14547A diastereomer methyl ester (131) (33.4 mg, 5.24×10^{-5} mole, 41%), t.l.c.: R_f 0.58, 50% diethyl ether - 40-60 b.p. petrol, $[\alpha]_D^{25} + 190^0$ (c 1.21, CHCl₃), ν_{max} 1725 and 1640 cm⁻¹; δ 0.0 (9H, s), 0.78 (3H, t, J 7.5 Hz, C-27 methyl), 0.8 (3H, d, J 7 Hz, C-30 methyl), 0.9 (2H, m, CH₂SiMe₃), 0.94 (3H, t, J 7.5 Hz, C-29 methyl), 1.0 - 2.1 (16H, m), 1.05 (3H, d, J 7.2 Hz, C-31 methyl), 2.9 (1H, m, H₂), 3.3 (1H, m, H₁₂), 3.4 (1H, 10.4 and 6.7 Hz, H₂₀), 3.55 (2H, m, CH₂CH₂O), 3.6 (3H, s, CO₂CH₃), 3.8 (1H, m, H₃), 4.15 (1H, d, J 3.2 Hz, H₇), 5.3 (1H, d, J 10 Hz, CH₂N), 5.4 (1H, m, H₁₁), 5.48 (1H, m, H₁₃), 5.85 (1H,

d, J 10 Hz, CH_2N), 5.85 (2H, m, H_9 and H_{10}), 5.95 (1H, d, J 10 Hz, H_{14}), 6.2 (1H, dd, J 4 and 2.7 Hz, H_{24}), 6.98 (1H, dd, J 4 and 1.7 Hz, H_{25}), and 7.05 (1H, dd, J 2.7 and 1.7 Hz, H_{23}); (Found: M^+ 637.4132. $\text{C}_{38}\text{H}_{59}\text{NO}_5\text{Si}$ requires M, 637.4159).

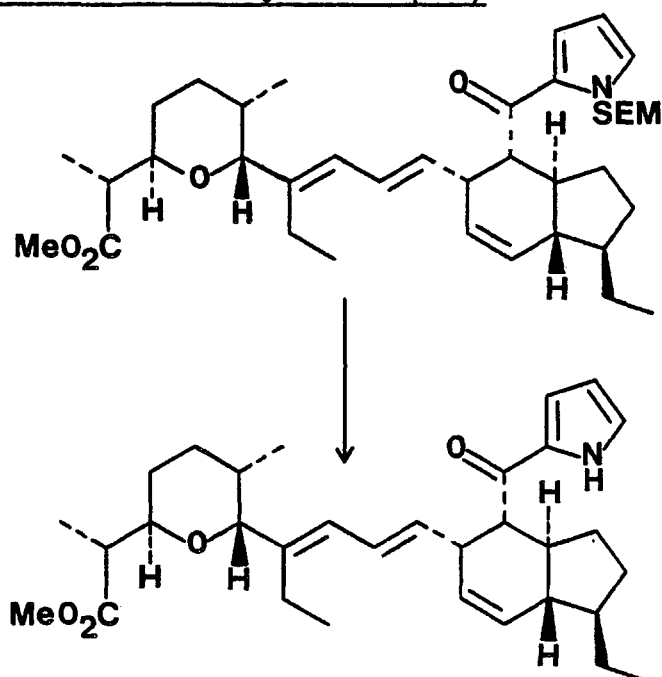
54. Preparation of (-)-Methyl $\alpha(R)$,5(S)-dimethyl-6(R)-[1-ethyl-4-{4(R)-(2'-pyrrolylcarbonyl)-1(S)-ethyl-3a(R),4,5(R),7a(R)-tetrahydroindan-5-yl}-1(E),3(E)-butadienyl]tetrahydropyran-2(R)-acetate, X-14547A Methyl Ester (126).



Anhydrous tetra-*n*-butylammonium fluoride (0.104 ml of a 3N solution in THF, 3.12×10^{-4} mole, *ca.* 10 equiv.) was added dropwise during 5 min to N-SEM-X-14547A methyl ester (130) (20 mg, 3.13×10^{-5} mole) in THF (30 μl) at 0°C . After 10 min at 0°C the reaction was warmed to room temperature in 5 min. After 30 min at room temperature the blood red reaction mixture was poured into diethyl ether (50 ml). After washing with water (5 ml), the organic solution was dried and concentrated *in vacuo* to a pale yellow viscous oil. Microchromatography on

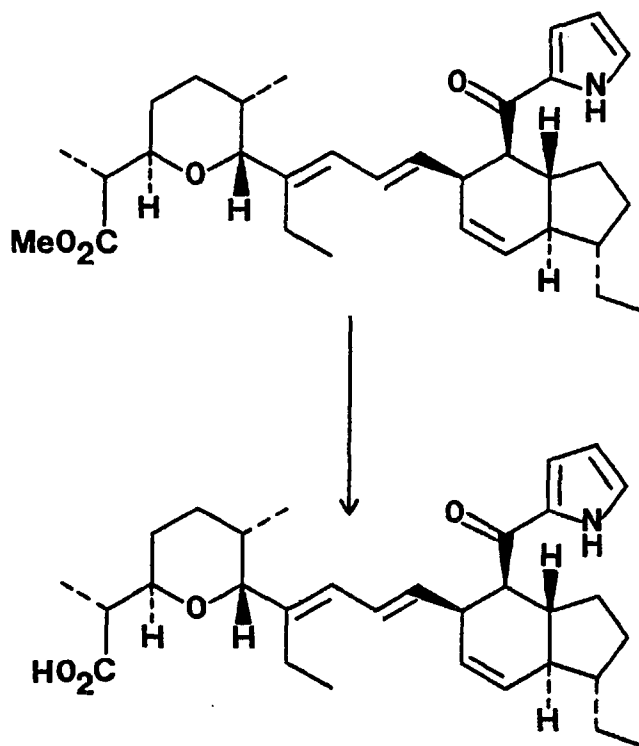
a Pasteur pipette containing Kieselgel (2½", Merck 9385) with a gradient elution of 10% up to 50% diethyl ether - 40-60 b.p. petrol (total of 15 ml) gave X-14547A methyl ester (11.4 mg, 2.25×10^{-5} mole, 72%), identical to naturally derived X-14547A methyl ester, t.l.c.: R_f 0.4, 50% diethyl ether - 40-60 b.p. petrol, $[\alpha]_D^{25} -306^0$ (c 1.3, CHCl_3), ν_{max} 3460, 1735, and 1645 cm^{-1} ; δ 0.78 (3H, t, J 7.5 Hz, C-27 methyl), 0.84 (3H, d, J 7 Hz, C-30 methyl), 0.95 (3H, t, J 7.5 Hz, C-29 methyl), 1.1 (3H, d, J 7 Hz, C-31 methyl), 1.0 - 2.1 (16H, m), 2.8 (1H, m, H_2), 3.35 (1H, m, H_{12}), 3.4 (1H, m, H_{20}), 3.65 (3H, s, CO_2CH_3), 3.74 (1H, m H_3), 4.12 (1H, d, J 4.2 Hz, H_7), 5.42 (1H, dd, J 14 and 8.7 Hz, H_{11}), 5.52 (1H, ddd, J 10, 4, and 2.5 Hz, H_{13}), 5.77 (1H, dd, J 14 and 11 Hz, H_{10}), 5.85 (1H, d, J 11 Hz, H_9), 5.97 (1H, d, J 10 Hz, H_{14}), 6.27 (1H, m, H_{24}), 6.9 (1H, m, H_{25}), 7.02 (1H, m, H_{23}), and 9.65 (1H, br.s, N-H); (Found: M^+ , 507.3336. $\text{C}_{32}\text{H}_{45}\text{NO}_4$ requires M, 507.3346).

55. Preparation of (+)-Methyl $\alpha(R),5(S)$ -dimethyl-6(R)-[1-ethyl-4-{4(S)-(2'-pyrrolylcarbonyl)-1(R)-ethyl-3a(S),4,5(S),7a(S)-tetrahydroindan-5-yl}-1(E),3(E)-butadienyl]tetrahydropyran-2(R)-acetate, X-14547A Diastereomer Methyl Ester (132).



Following the procedure of Experiment 54, (+)-methyl α (R),5(S)-dimethyl-6(R)-{1-ethyl-4-[4(S)-(2'-N-(β -trimethylsilyl)ethoxymethyl-pyrrolylcarbonyl)-1(R)-ethyl-3a(S),4,5(S),7a(S)-tetrahydroindan-5-yl]-1(E),3(E)-butadienyl}tetrahydropyran-2(R)-acetate (131) (33 mg, 5.2×10^{-5} mole) gave X-14547A diastereomer methyl ester (132) (17 mg, 3.3×10^{-5} mole, 63%), t.l.c.: R_f 0.33, 50% diethyl ether - 40-60 b.p. petrol, $[\alpha]_D^{25} + 293^\circ$ (c 0.37, CHCl_3), ν_{max} 3460, 1735, and 1645 cm^{-1} ; δ (400 MHz) 0.79 (3H, t, J 7.5 Hz, C-27 methyl), 0.82 (3H, d, J 7 Hz, C-30 methyl), 0.94 (3H, t, J 7.5 Hz, C-29 methyl), 1.6 (3H, d, J 7 Hz, C-31 methyl), 0.9 - 2.05 (16H, m), 2.92 (1H, m, H_2), 3.37 (1H, m, H_{12}), 3.39 (1H, dd, J 14 and 6.5 Hz, H_{20}), 3.61 (3H, s, CO_2CH_3), 3.8 (1H, m, H_3), 4.17 (1H, d, J 4 Hz, H_7), 5.4 (1H, dd, J 15 and 8 Hz, H_{11}), 5.51 (1H, ddd, J 10, 4, and 3 Hz, H_{13}), 5.82 (1H, dd, J 11 and 0.8 Hz, H_9), 5.92 (1H, dd, J 15 and 11 Hz, H_{10}), 5.97 (1H, d, J 10 Hz, H_{14}), 6.27 (1H, m, H_{24}), 6.9 (1H, m, H_{25}), 6.96 (1H, m, H_{23}), and 9.2 (1H, br.s, NH); (Found: M^+ , 507.3342. $\text{C}_{32}\text{H}_{45}\text{NO}_4$ requires M, 507.3346).

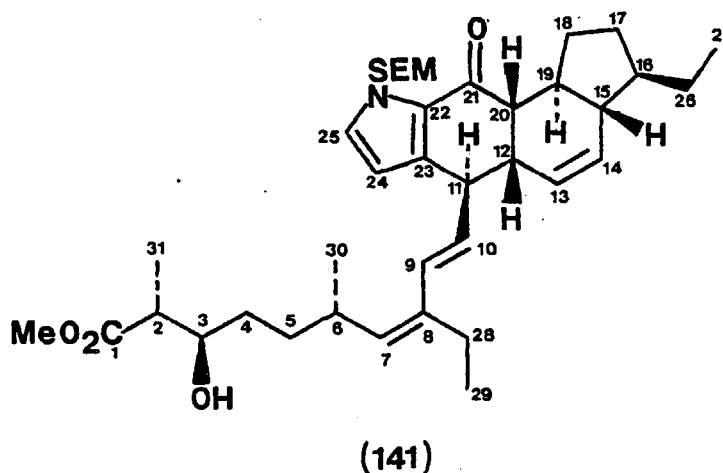
56. Preparation of (-)- α (R),5(S)-dimethyl-6(R)-[1-ethyl-4-(4(R)-(2'-pyrrolylcarbonyl)-1(S)-ethyl-3a(R),4,5(R),7a(R)-tetrahydroindan-5-yl]-1(E),3(E)-butadienyl]tetrahydropyran-2(R)-acetic acid, X-14547A (1).



X-14547A Methyl ester (126) (22 mg, 4.33×10^{-5} mole) was stirred with 1N aqueous sodium hydroxide (0.433 ml, 4.33×10^{-4} mole, 10 equiv.) and methanol (2.2 ml) at 60°C for 2.5h. More 1N aqueous sodium hydroxide (0.433 ml, 4.33×10^{-4} mole, 10 equiv.) was added and stirring continued at 60°C for a further 0.75h before dilution of the reaction mixture with diethyl ether (250 ml) and 5% aqueous hydrochloric acid (25 ml). The organic solution, combined with a diethyl ether (3 $\times$ 20 ml) extract of the aqueous phase, was washed with 5% aqueous hydrochloric acid (10 ml) and water (20 ml) before drying and concentration *in vacuo* to a colourless semi-solid. Microchromatography on a pasteur pipette containing Kieselgel (2½", Merck 9385) with a gradient elution of 50% diethyl ether - 40-60 b.p. petrol up to neat diethyl ether (total ca. 25 ml) gave X-14547A (1) (19.3 mg, 3.9×10^{-5} mole, 90%), identical to the

natural product (kindly supplied by J.W. Westley of Hoffman La Roche), t.l.c.: R_f 0.44, diethyl ether, $[\alpha]_D^{25} -324^0$ (c 0.94, $CHCl_3$) (Lit.¹⁷ $[\alpha]_D -328^0$ (c 1, $CHCl_3$), ν_{max} 3460, 3200 (br.), 1720 and 1645 cm^{-1} ; δ (400 MHz), 0.76 (3H, t, J 7.5 Hz, C-27 methyl), 0.82 (3H, d, J 7 Hz, C-30 methyl), 0.95 (3H, t, J 7.5 Hz, C-29 methyl), 1.13 (3H, d, J 7 Hz, C-31 methyl), 0.85 - 2.0 (16H, m), 2.95 (1H, m, H_2), 3.3 (1H, m, H_{12}), 3.4 (1H, dd, J 12 and 7 Hz, H_{20}), 3.89 (1H, m, H_3), 4.2 (1H, d, J 4 Hz, H_7), 5.41 (1H, dd, J 15 and 10 Hz, H_{11}), 5.5 (1H, ddd, J 10, 4 and 2.5 Hz, H_{13}), 5.78 (1H, dd, J 15 and 11 Hz, H_{10}), 5.92 (1H, d, J 11 Hz, H_9), 5.96 (1H, d, J 10 Hz, H_{14}), 6.25 (1H, m, H_{24}), 6.9 (1H, m, H_{25}), 6.99 (1H, m, H_{23}), and 10.2 (1H, br.s, NH) (CO_2H proton not assignable); (Found: M^+ , 493.3188. $C_{31}H_{43}NO_4$ requires M, 493.3189).

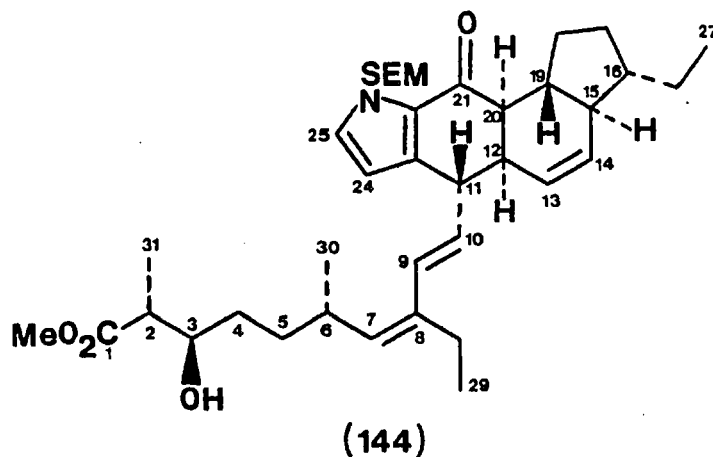
57. Rearrangement of N-SEM-X-14547A Diastereomer methyl ester:
Preparation of the Tetracycle (141).



(+)-Methyl $\alpha(R)$,5(S)-dimethyl-6(R)-[1-ethyl-4-{4(S)-(2'-N-(β -tri-methylsilyl)ethoxymethylpyrrolylcarbonyl)-1(R)-ethyl-3a(S),4,5(S),7a(S)-tetrahydroindan-5-yl}-1(E),3(E)-butadienyl]tetrahydropyran-2(R)-acetate (131) (12.1 mg, 1.9×10^{-5} mole) was stirred with anhydrous lithium

tetrafluoroborate (18 mg, 1.9×10^{-5} mole, 10 equiv.) in dry acetonitrile (0.25 ml) at 70°C for 3h. The reaction mixture was poured into diethyl ether (50 ml) and washed with water (2×10 ml) before drying and concentration *in vacuo* to a dark brown gum. Microchromatography on a Pasteur pipette containing Kieselgel (2½", Merck 9385) with 90% diethyl ether - 40-60 b.p. petrol gave the tetracycle (141) (5.3 mg, 8.3×10^{-6} mole, 44%), as a colourless gum, t.l.c.: R_f 0.44, diethyl ether, $[\alpha]_D^{25} + 33^\circ$ (c 0.5, CHCl₃), $\nu_{\max}$ 3440, 1725, and 1645 cm⁻¹; δ (400 MHz) 0.0 (9H, s), 0.89 (2H, m, CH₂SiMe₃), 0.95 (3H, t, J 7.5 Hz, C-27 methyl), 1.14 (3H, t, J 7.5 Hz, C-29 methyl), 1.14 (3H, d, J 7 Hz, C-30 methyl), 1.25 (3H, d, J 7.5 Hz, C-31 methyl), 1.0 - 2.1 (14H, m), 2.28 (2H, q, J 7.5 Hz, C-28 methylene), 2.47 - 2.62 (3H, m, H₂₀, H₁₂, and H₆), 2.8 (1H, m, H₂), 3.43 (2H, m, CH₂O), 3.52 (1H, dd, J 9.5 and 9.5 Hz, H₁₁), 3.68 (1H, m, H₃), 3.75 (3H, s, CO₂CH₃), 5.04 (1H, d, J 10 Hz, CH₂N), 5.23 (1H, d, J 10 Hz, H₇), 5.45 (1H, d, J 10 Hz, CH₂N), 5.5 (1H, dd, J 16 and 9.5 Hz, H₁₀), 5.83 (1H, ddd, J 10, 4.5, and 2.5 Hz, H₁₃), 6.0 (1H, d, J 10 Hz, H₁₄), 6.17 (1H, d, J 16 Hz, H₉), 6.61 (1H, d, J 3 Hz, H₂₄), and 6.73 (1H, d, J 3 Hz, H₂₅); (Found: M⁺, 637.4179. C₃₈H₅₉NO₅Si requires 637.4159).

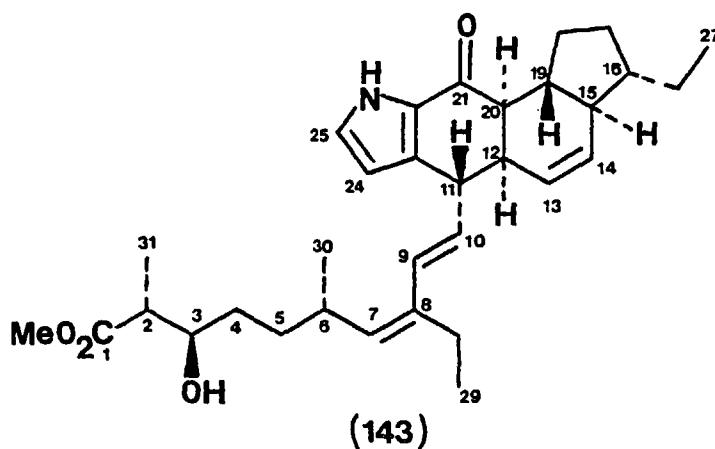
58. Rearrangement of N-SEM-X-14547A Methyl Ester: Preparation of the Tetracycle (144).



(-)-Methyl α (R),5(S)-dimethyl-6(R)-[1-ethyl-4-[4(R)-(2'-N-(β -tri-methylsilyl)ethoxymethylpyrrolylcarbonyl)-1(S)-ethyl-3a(R),4,5(R),7a(R)-tetrahydroindan-5-yl]-1(E),3(E)-butadienyl]tetrahydropyran-2(R)-acetate (130) (16 mg, 2.5×10^{-5} mole) was stirred with anhydrous lithium tetrafluoroborate (24 mg, 2.5×10^{-4} mole, 10 equiv.) in dry acetonitrile (0.263 ml) at 70°C for 2h. Work-up and microchromatography, as in Experiment 57, gave the tetracycle (144) (8.8 mg, 1.38×10^{-5} mole, 55%), as a colourless gum, t.l.c.: R_f 0.16, 90% diethyl ether - 40-60 b.p. petrol, $[\alpha]_D^{25} \sim 0^{\circ}$ (c 0.88, CHCl_3), ν_{max} 3480, 1725 and 1645 cm^{-1} ; δ (400 MHz) 0.0 (9H, s), 0.85 (2H, m, CH_2SiMe_3), 0.92 (3H, t, J 7.5 Hz, C-27 methyl), 1.1 (3H, t, J 7.5 Hz, C-29 methyl), 1.1 (3H, d, J 7 Hz, C-30 methyl), 1.2 (3H, d, J 7 Hz, C-31 methyl), 1.15 - 1.9 (13H, m), 2.25 (2H, m, C-28 methylene), 2.48 (1H, m), 2.51 (1H, m), 2.55 (1H, dd, J 3 and 2.5 Hz), 2.57 (1H, d, J 6 Hz), 2.77 (1H, m, H_2), 3.4 (2H, m, CH_2O), 3.5 (1H, dd, 10 and 9.5 Hz, H_{11}), 3.64 (1H, m, H_3), 3.71 (3H, s, CO_2CH_3), 5.0 (1H, d, J 10 Hz, CH_2N), 5.2 (1H, d, J 10 Hz, H_7), 5.42 (1H, d, J 10 Hz, CH_2N), 5.48 (1H, dd, J 16 and 9.5 Hz, H_{10}), 5.82 (1H, ddd, J 10, 4.5, and 2.5 Hz, H_{13}), 5.97 (1H, d, J 10 Hz, H_{14}), 6.13 (1H, d,

J 16 Hz, H_9), 6.58 (1H, d, J 3 Hz, H_{24}), and 6.69 (1H, d, J 3 Hz, H_{25}); (Found: M^+ , 637.4157. $C_{38}H_{59}NO_5Si$ requires 637.4159).

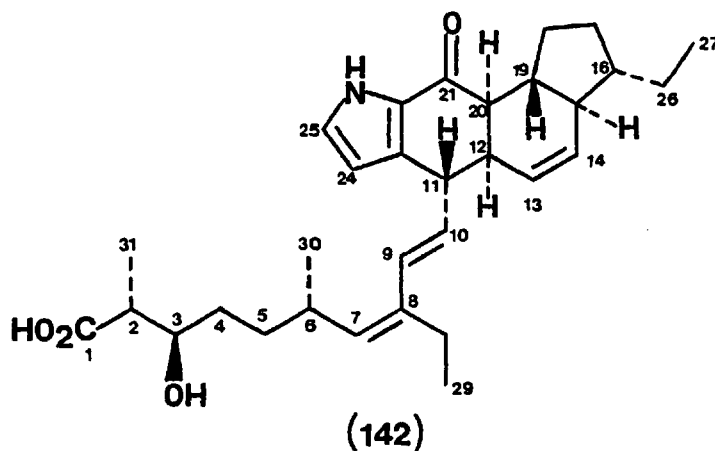
59. Rearrangement of X-14547A Methyl Ester: Preparation of the Tetracycle (143).



X-14547A Methyl ester (20 mg, 3.94×10^{-5} mole) was stirred with anhydrous lithium tetrafluoroborate (37.3 mg, 3.94×10^{-4} mole, 10 equiv.) in dry acetonitrile (0.415 ml), at 70°C , for 40 min. Work-up as in Experiment 57 and microchromatography on a pasteur pipette containing Kieselgel ($2\frac{1}{2}$ ", Merck 9385) with 50% ethyl acetate - 40-60 b.p. petrol gave the tetracycle (143) (12.6 mg, 2.48×10^{-5} mole, 63%), as an almost colourless gummy glass, t.l.c.: R_f 0.3, diethyl ether, $[\alpha]_D^{25}$ - 36.1 $^\circ$ (c 1.26, CHCl_3), ν_{max} 3440, 3380, 1725, and 1645 cm^{-1} ; δ (400 MHz) 0.92 (3H, t, J 7.5 Hz, C-27 methyl), 1.02 (3H, d, J 7 Hz, C-30 methyl), 1.05 (3H, t, J 7.5 Hz, C-29 methyl), 1.22 (3H, d, J 7 Hz, C-31 methyl), 1.15 - 1.93 (13H, m), 2.27 (2H, m, C-28 methylene), 2.5 (1H, m, H_{12}), 2.54 (1H, qd, J 7 and 6 Hz), 2.6 (1H, dd, J 11 and 5.5 Hz), 2.64 (1H, br.s, OH), 2.85 (1H, m, H_2), 3.45 (1H, dd, J 10 and 9 Hz, H_{11}), 3.65 (1H, m, H_3), 3.72 (3H, s, CO_2CH_3), 5.23 (1H, d, J 10 Hz, H_7), 5.47 (1H, dd, J 16 and 9 Hz, H_{10}), 5.73 (1H, ddd, J 10, 4.5 and 2.5 Hz, H_{13}),

5.97 (1H, d, J 10 Hz, H_{14}), 6.2 (1H, d, J 16 Hz, H_9), 6.61 (1H, dd, J 3 and 2.5 Hz, H_{24}) and 6.72 (1H, dd, J 3 and 2 Hz, H_{25}), and 8.3 (1H, br.s, NH); (Found: M^+ , 507.3336. $C_{32}H_{45}NO_4$ requires 507.3346), contaminated with a trace (<2%) of a minor, unidentified diastereomer (t.l.c.: R_f 0.32, diethyl ether).

60. Rearrangement of X-14547A: Preparation of the Tetracycle (142)



X-14547A(1) (0.1g, 2.03×10^{-4} mole) was stirred with anhydrous lithium tetrafluoroborate (0.192g, 2.03×10^{-3} mole, 10 equiv.) in dry acetonitrile (2.1 ml), at 70°C, for 1h. The reaction mixture was diluted with dichloromethane (350 ml) and water (50 ml). The organic solution, combined with a dichloromethane (2 x 25 ml) extract of the aqueous phase, was washed with 10% aqueous hydrochloric acid (50 ml) and brine (50 ml), before drying and concentration *in vacuo* to a pale yellow glassy solid. Flash chromatography (5" silica, 10 mm dia. column) with a gradient of 5% methanol-diethyl ether up to 90% methanol-diethyl ether, followed by filtration of a dichloromethane (5 ml) solution of the concentrated fractions through sodium sulphate (1") on a Pasteur pipette to remove methanol dissolved silica, gave the tetracycle (142) (85 mg, 1.72×10^{-4} mole, 85%), as a pale yellow glass that resisted

recrystallisation attempts, t.l.c.: R_f 0.39, 5% methanol-diethyl ether, $[\alpha]_D^{25} - 10^0$ (c 1.0, CHCl_3), ν_{max} 3460, 3300, 1710, and 1645 cm^{-1} ; δ (400 MHz) 0.85 (3H, t, J 7.5 Hz, C-27 methyl), 0.8 - 1.9 (22H, m), 2.25 (2H, m, C-28 methylene), 2.4 - 2.6 (3H, m), 2.8 (1H, m, H_2), 3.42 (1H, dd, J 10 and 9.5 Hz, H_{11}), 3.64 (1H, m, H_3), 5.2 (1H, d J 10 Hz, H_7), 5.45 (1H, dd, J 16 and 9 Hz, H_{10}), 5.73 (1H, br.d, J 10 Hz, H_{13}), 5.97 (1H, d, J 10 Hz, H_{14}), 6.2 (1H, d, J 16 Hz, H_9), 6.6 (1H, br.s, H_{24}), 6.7 (1H, br.s, H_{25}), and 8.65 (1H, br.s, NH) (CO_2H proton not assignable); m/e: no molecular ion, plus a minor unidentified diastereomer (7 mg); t.l.c., R_f 0.46, 5% methanol-diethyl ether.

X-Ray Crystallographic Data for (61)

Crystals of (61) $C_{17}H_{23}NO_2$ are monoclinic $a = 14.546(2)$, $b = 5.734(1)$, $c = 19.187(2)$ Å, $\beta = 105.60(1)^\circ$, $V = 1541$ Å³, space-group $P2_1/n$, $Z = 4$.

Data were measured using monochromatised $Cu-K_{\alpha}$ radiation (graphite monochromator) on a Nicolet R3m diffractometer. A total of 1602 independent reflections were measured ($\theta \leq 50^\circ$) using the ω - 2θ scan technique, and of these 1531 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. The hydrogen atoms, with the exception of the OH hydrogen which was refined isotropically and the methyl group which was refined as a rigid body, were placed at calculated positions and allowed to ride on their parent carbons. Refinement was by block-cascade full-matrix least-squares to $R = 0.044$.

Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.

REFERENCES

1. (a) K.C. Nicolaou, D.P. Papahatjis, D.A. Claremon, and R.E. Dolle, III, *J. Am. Chem. Soc.*, 1981, 103, 6967.
(b) K.C. Nicolaou, D.A. Claremon, D.P. Papahatjis, and R.L. Magoïda, *J. Am. Chem. Soc.*, 1981, 103, 6969.
2. B.C. Pressman, *Annu. Rev. Biochem.*, 1976, 45, 501.
3. (a) J. Berger, A.I. Rachlin, W.E. Scott, L.H. Sternbach, and M.W. Goldberg, *J. Am. Chem. Soc.*, 1951, 73, 5295.
(b) R.L. Harned, P. Harten, C.J. Corum, and K.L. Jones, *Antibiot. Chemother. (Washington, D.C.)*, 1951, 1, 594.
4. J.W. Westley, *Adv. Appl. Microbiol.*, 1977, 22, 177.
5. (a) T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, *J. Am. Chem. Soc.*, 1978, 100, 2933.
(b) T. Fukuyama, B. Vranesic, D.P. Negri, and Y. Kishi, *Tetrahedron Lett.*, 1978, 20, 2741 and 2745.
6. (a) G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.*, 1979, 101, 259.
(b) T. Fukuyama, C-L.J. Wang, and Y. Kishi, *J. Am. Chem. Soc.*, 1979, 101, 260.
(c) T. Fukuyama, K. Akasaka, D.S. Katanewsky, C-L.J. Wang, G. Schmid, and Y. Kishi, *J. Am. Chem. Soc.*, 1979, 101, 262.
7. D.A. Evans, C.E. Sacks, W.A. Kleschick, and T.R. Tabet, *J. Am. Chem. Soc.*, 1979, 101, 6789.
8. (a) P.A. Grieco, K. Kanai, and E. Williams, *Heterocycles*, 1979, 12, 1623.
(b) P.A. Grieco, E. Williams, H. Tanaka, and S. Gilman, *J. Org. Chem.*, 1980, 45, 3537.

9. D.B. Collum, J.H. McDonald, III, and W.C. Still, *J. Am. Chem. Soc.*, 1980, 102, 2117, 2118, and 2120.
10. (a) R.E. Ireland, S. Thaisrivongs, and C.S. Wilcox, *J. Am. Chem. Soc.*, 1980, 102, 1155.
(b) R.E. Ireland, G.J. McGarvey, R.C. Anderson, R. Badoud, B. Fitzsimmons, and S. Thaisrivongs, *J. Am. Chem. Soc.*, 1980, 102, 6178.
11. A. Agtarap, J.W. Chamberlin, M. Pinkerton, and L. Steinrauf, *J. Am. Chem. Soc.*, 1967, 89, 5737.
12. E.F. Gale, E. Cuncliffe, R.E. Reynolds, M.H. Richmond, and M.J. Waring, "The Molecular Basis of Antibiotic Action", Chapter 4, Wiley, New York, 1972.
13. B.C. Pressman, "The Role of Membranes in Metabolic Regulation", p.149, (eds., M.A. Mehlman and R.W. Hanson), Academic Press, New York, 1972.
14. J.V. Levy, J.A. Cohen, and G. Inesi, *Nature (London)*, 1973, 242, 461.
15. B.C. Pressman and N.T. de Guzman, *Ann. N.Y. Acad. Sci.*, 1975, 264, 373.
16. M.O. Chaney, P.V. Demarco, N.D. Jones, and J.L. Occolowitz, *J. Am. Chem. Soc.*, 1974, 96, 1932.
17. (a) J.W. Westley, R.H. Evans, Jr., C-M. Liu, T. Hermann, and J.F. Blount, *J. Am. Chem. Soc.*, 1978, 100, 6786.
(b) C-M. Liu, T.E. Hermann, M. Liu, D.N. Bull, N.J. Palleroni, B.L.T. Prosser, J.W. Westley, and P.A. Miller, *J. Antibiot.*, 1979, 32, 95.
(c) J.W. Westley, R.H. Evans, Jr., L.H. Sello, N. Troupe, C-M. Liu, and J.F. Blount, *J. Antibiot.*, 1979, 32, 100.

17. continued
 - (d) J.W. Westley, and C-M. Liu, *U.S. Patent*, 4,100,171, 1978.
18. J.W. Westley, personal communications to K.C. Nicolaou and W.R. Roush.
19. A.P. Raun, *U.S. Patent*, 3,937,836, 1976.
20. H. Schadt and G. Haeusler, *J. Membr. Biol.*, 1974, 18, 277.
21. W. Hofheinz and P. Schönholzer, *Helv. Chim. Acta*, 1977, 60, 1367.
22. D.J. Patel and C. Shen, *Proc. Natl. Acad. Sci. U.S.A.*, 1976, 73, 1786.
23. L.E. Day, J.W. Chamberlin, E.Z. Gordee, S. Cheu, M. Gorman, R.L. Hammill, T. Wess, R.E. Weeks, and R. Strostrane, *Antimicrob. Agents. Chemother.*, 1973, 410.
24. W.R. Roush and A.G. Myers, *J. Org. Chem.*, 1981, 46, 1509.
25. B.S. Joshi, N. Viswanathan, D.H. Gaurad, V. Balakrishnan, and W.V. Philipsborn, *Helv. Chim. Acta*, 1975, 58, 2295.
26. S. Ito and Y. Hirata, *Tetrahedron Lett.*, 1972, 13, 2557.
27. W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, 1977, 16, 10.
28. W. Wierenga, in "The Total Synthesis of Natural Products", Ed. J. ApSimon, Wiley, New York, 1981.
29. P.A. Bartlett, *Tetrahedron*, 1980, 36, 2.
30. Y. Kishi, *Aldrichimica Acta*, 1980, 13, 23.
31. M.P. Edwards, S.V. Ley, and S.G. Lister, *Tetrahedron Lett.*, 1981, 22, 361.
32. K.C. Nicolaou and R.L. Magolda, *J. Org. Chem.*, 1981, 46, 1506.
33. R.K. Boeckman, Jr., personal communication.

34. E.J. Corey, W.J. Howe, H.W. Orf, D.A. Pensak, and G. Peterson, *J. Am. Chem. Soc.*, 1975, 97, 6116.
35. G. Stork, reported at the R.S.C. 7th International Synthesis Symposium, Oxford, July 1981.
36. (a) A.B. Smith, III, and D.R. Williams, independently reported at the 183rd A.C.S. Meeting, Las Vegas, March 1982.
(b) A.B. Smith, III, S.R. Schour, J.D. Bloom, A.S. Thompson, and K.N. Winzenburg, *J. Am. Chem. Soc.*, 1982, 104, 4015.
37. (a) S. Masamune, M. Hirama, S. Mori, SK. Asrof Ali, and D.S. Garvey, *J. Am. Chem. Soc.*, 1981, 103, 1568.
(b) T. Kaiho, S. Masamune, and T. Toyoda, *J. Org. Chem.*, 1981, 47, 1612.
38. B.D. Palmer, personal communication.
39. (a) I. Gosney, chapter 2 and
(b) A.G. Rowley, chapter 3 in "Organophosphorous Reagents in Organic Synthesis, Ed. J.I.G. Cadogan, Acad. Press, New York, 1979.
40. D.J. Faulkner, *Synthesis*, 1971, 175.
41. (a) P.J. Kocienski and B. Lythgoe, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1400.
(b) P.J. Kocienski, B. Lythgoe, and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1045.
(c) B. Lythgoe and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2429.
(d) P.J. Kocienski, B. Lythgoe, and D.A. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1978, 834.
(e) P.J. Kocienski, B. Lythgoe, and S. Ruston, *J. Chem. Soc., Perkin Trans. 1*, 1978, 829.

42. (a) B. Lythgoe, T.A. Moran, M.E.N. Nambudiry, and S. Ruston, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2386.
(b) B. Lythgoe, T.A. Moran, M.E.N. Nambudiry, J. Tideswell, and P.W. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1978, 590.
(c) A.H. Davidson and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1976, 639.
(d) M. Schlosser and H.B. Tuong, *Chimia Switz.*, 1976, 30, 197.
43. J.M. Clough and G. Pattenden, *Tetrahedron*, 1981, 37, 3911.
44. E. Colvin, p.141, "Silicon in Organic Synthesis", Butterworths, London, 1981.
45. L. Barlow and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1029.
46. G.P. Bean, *J. Heterocycl. Chem.*, 1965, 2, 473.
47. H.O. House and T.C. Cronin, *J. Org. Chem.*, 1965, 30, 1061.
48. W.R. Roush, *J. Org. Chem.*, 1979, 44, 4008.
49. (a) W.R. Roush, *J. Am. Chem. Soc.*, 1980, 102, 1390.
(b) W.R. Roush, A.I. Ko, and H.R. Gillis, *J. Org. Chem.*, 1980, 45, 4264.
(c) W.R. Roush and H.R. Gillis, *J. Org. Chem.*, 1980, 45, 4267.
(d) W.R. Roush, H.R. Gillis, and A.I. Ko, *J. Am. Chem. Soc.*, 1982, 104, 2269.
50. (a) S. Hanessian, D.M. Dixit, and T. Liak, *Pure Appl. Chem.*, 1981, 53, 129.
(b) S. Hanessian, *Acc. Chem. Res.*, 1979, 12, 159.
(c) S. Hanessian, *Pure Appl. Chem.*, 1977, 49, 1201.
(d) B. Frazer-Reid and R.C. Anderson, *Fortschr. Chem. Org. Naturst.*, 1980, 39, 1.
(e) B. Frazer Reid, *Acc. Chem. Res.*, 1974, 8, 192.

51. A.G. Kelly and J.S. Roberts, *J. Chem. Soc., Chem. Commun.*, 1980, 228.
52. (a) R.E. Ireland, S. Thaisrivongs, N. Vanier, and C.S. Wilcox, *J. Org. Chem.*, 1980, 45, 48.
(b) R.E. Ireland and J.P. Daub, *J. Org. Chem.*, 1981, 46, 479.
(c) R.E. Ireland, P.G.M. Wuts, and B. Ernst, *J. Am. Chem. Soc.*, 1981, 103, 3205.
53. P.A. Bartlett and J.L. Adams, *J. Am. Chem. Soc.*, 1980, 102, 337.
54. K.C. Nicolaou, *Tetrahedron*, 1981, 37, 4097.
55. P-T. Ho, *Can. J. Chem.*, 1982, 60, 90.
56. J.L. Hermann and R.H. Schlessinger, *J. Chem. Soc., Chem. Commun.*, 1973, 711.
57. P.L. Creger, *Org. Synth.*, 1970, 50, 58.
58. R.J. Cregge, J.L. Hermann, C.S. Lee, J.E. Richman, and R.H. Schlessinger, *Tetrahedron Lett.*, 1975, 16, 2425.
59. J.A. MacPhee and J-E. Dubois, *J. Chem. Soc., Perkin Trans. 1*, 1977, 694.
60. W.C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, 43, 2923.
61. Dictionary of Organic Compounds, Vol. 3, p.1878, Eyre and Spottiswoode, London, 1965.
62. G. Saucy and R. Borer, *Helv. Chim. Acta.*, 1971, 54, 2121.
63. (a) K. Sato, *J. Org. Chem.*, 1967, 32, 177.
(b) R.S. Burden and L. Crombie, *J. Chem. Soc., (C)*, 1969, 2477.
(c) F. Bohlmann, *Chem. Ber.*, 1973, 106, 3779.

64. (a) R.K. Howe, *J. Am. Chem. Soc.*, 1971, 93, 3457.
(b) L.D. Bergelson, E.V. Dyatlovitskaya, and M.M. Shemyakin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1963, 388.
65. E.J. Corey and A. Venkateswarthy, *J. Am. Chem. Soc.*, 1972, 94, 6190.
66. S.D. Larsen and S.A. Monti, *J. Am. Chem. Soc.*, 1977, 99, 8015.
67. E.J. Corey, J-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 1976, 17, 809.
68. D.H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry", McGraw-Hill, London, 1973.
69. R. Ratcliffe and R. Rodenhurst, *J. Org. Chem.*, 1970, 35, 4000.
70. E.J. Corey and J.W. Suggs, *Tetrahedron Lett.*, 1975, 16, 2647.
71. E.J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 20, 399.
72. (a) O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta.*, 1957, 40, 1242.
(b) G. Pattenden, J.E. Way, and B.C.L. Weedon, *J. Chem. Soc.*, (C), 1970, 235.
73. (a) K.N. Houk and R.W. Strozier, *J. Am. Chem. Soc.*, 1973, 95, 4094.
(b) K.N. Houk, *Acc. Chem. Res.*, 1975, 8, 361.
(c) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, New York, 1976.
74. H. Nishiyama and K. Itoh, *J. Org. Chem.*, 1982, 47, 2496.
75. W.R. Roush and S.E. Hall, *J. Am. Chem. Soc.*, 1981, 103, 5200.
76. R.L. Funk and W.E. Zeller, *J. Org. Chem.*, 1982, 47, 180.
77. J.D. White and B. Sheldon, *J. Org. Chem.*, 1981, 46, 2273.

78. K.R. Boeckmann, Jr. and J.S. Ko, *J. Am. Chem. Soc.*, 1980, 102, 7146.
79. K.A. Parker and M.R. Adamchuk, *Tetrahedron Lett.*, 1978, 19, 1689.
80. (a) D. Seebach and M. Pohmakotr, *Helv. Chim. Acta.*, 1979, 62, 843.
(b) D. Seebach, M. Pohmakotr, C. Schregenberger, B. Weidman, R.S. Mali, and S. Pohmakotr, *Helv. Chim. Acta.*, 1982, 65, 419.
81. W.H. Wilen, A. Collet, and J. Jaques, *Tetrahedron*, 1977, 33, 2725.
82. K. Kieslich, *Bull. Soc. Chim. Fr.*, 1980, II-9.
83. (a) J.W. ApSimon and R.P. Seguin, *Tetrahedron*, 1979, 35, 2797.
(b) A.I. Meyers, *Pure Appl. Chem.*, 1979, 51, 1255.
(c) D. Valentine, Jr. and J.W. Scott, *Synthesis*, 1978, 329.
(d) "Asymmetric Reactions and Processes in Chemistry", Eds. E.E. Eliel and S. Otsuka, ACS Symposium Series No. 185, New York, 1982.
84. (a) T. Katsuki and K.B. Sharpless, *J. Am. Chem. Soc.*, 1980, 102, 5974.
(b) B.E. Rossiter, T. Katsuki, and K.B. Sharpless, *J. Am. Chem. Soc.*, 1981, 103, 464.
(c) V.S. Martin, S.S. Woodward, T. Katsuki, Y. Yamada, M. Ikeda, and K.B. Sharpless, *J. Am. Chem. Soc.*, 1981, 103, 6237.
(d) T. Katsuki, A.W.M. Lee, P. Ma, V.S. Martin, S. Masamune, K.B. Sharpless, D. Tuddenham, and F.J. Walker, *J. Org. Chem.*, 1982, 47, 1373.

84. continued

- (e) P. Ma, V.S. Martin, S. Masamune, K.B. Sharpless, and S.M. Viti, *J. Org. Chem.*, 1982, 47, 1378.
 - (f) A.W.M. Lee, V.S. Martin, S. Masamune, K.B. Sharpless, and F.J. Walker, *J. Am. Chem. Soc.*, 1982, 104, 3515.
85. (a) D.A. Evans and J.M. Takacs, *Tetrahedron Lett.*, 1980, 21, 4233.
- (b) D.A. Evans and T.R. Taber, *Tetrahedron Lett.*, 1980, 21, 4675.
- (c) D.A. Evans, J. Bartroli, and T.L. Shih, *J. Am. Chem. Soc.*, 1981, 103, 2127.
- (d) D.A. Evans and L.R. McGee, *J. Am. Chem. Soc.*, 1981, 103, 2876.
- (e) D.A. Evans, M.D. Ennis, and D.J. Mathre, *J. Am. Chem. Soc.*, 1982, 104, 1737.
86. (a) S. Masamune, W. Choy, F.A.J. Kerdesky, and B. Imperiali, *J. Am. Chem. Soc.*, 1981, 103, 1566.
- (b) W. Choy, P. Ma, and S. Masamune, *Tetrahedron Lett.*, 1981, 22, 3555.
87. (a) A.I. Meyers, R.K. Smith, and C.E. Whitten, *J. Org. Chem.*, 1979, 44, 2250.
- (b) A.I. Meyers, Y. Yamamoto, E.D. Mihelich, and R.A. Bell, *J. Org. Chem.*, 1980, 45, 2792.
- (c) A.I. Meyers, D.R. Williams, G.W. Erickson, S. White, and M. Druelinger, *J. Am. Chem. Soc.*, 1981, 103, 3081.
- (d) A.I. Meyers, D.R. Williams, S. White, and G.W. Erickson, *J. Am. Chem. Soc.*, 1981, 103, 3088.
- (e) A.I. Meyers and Y. Yamamoto, *J. Am. Chem. Soc.*, 1981, 103, 4278.
88. J.J. Partridge, N.K. Chadha, and M.R. Uskoković, *J. Am. Chem. Soc.*, 1973, 95, 532.

89. (a) D. Seebach and H.O. Kalinouski, *Nachr. Chem. Tech.*, 1976, 24, 415.
(b) D. Seebach and E. Hungerbühler, "Modern Synthetic Methods 1980", Ed. R. Scheffold, Säuerländer, Aaray, 1980.
90. G. Helmchen, G. Nill, D. Flockerzi, and M.S.K. Youssef, *Angew. Chem., Int. Ed. Engl.*, 1979, 18, 63.
91. See, for example, H. Nagaoka and Y. Kishi, *Tetrahedron*, 1981, 37, 3873.
92. H.C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, 1964, 86, 1089.
93. K. Psotta and A. Wiechers, *Tetrahedron*, 1979, 35, 255.
94. H.C. Brown, D.B. Bigley, S.K. Arora, and N.M. Moon, *J. Am. Chem. Soc.*, 1970, 92, 7161.
95. R. Kanazawa and T. Tokoroyama, *Synthesis*, 1976, 526.
96. W.S. Fones, *J. Org. Chem.*, 1949, 14, 1099.
97. A. Koziara, S. Zawadzki, and A. Zwierzak, *Synthesis*, 1979, 527.
98. D. Enders and H. Eichenhauer, *Chem. Ber.*, 1979, 112, 2933.
99. G.P. Bean, *J. Heterocycl. Chem.*, 1965, 2, 473.
100. C.F. Hobbs, C.K. McMillin, E.P. Papadopoulos, and C.A. Van der Werf, *J. Am. Chem. Soc.*, 1962, 84, 43.
101. (a) D.A. Shirley and A.P. Roussel, *J. Org. Chem.*, 1955, 20, 225.
(b) H.W. Gschwend and H.R. Rodriguez, *Org. React.*, 1979, 26, 21.
(c) D.J. Chadwick and I.A. Cliffe, *J. Chem. Soc., Perkin Trans 1*, 1979, 2845.
102. R.J. Sundberg and H.F. Russell, *J. Org. Chem.*, 1973, 38, 3324.
103. I. Hasan, E.R. Marinelli, L-C.C. Lun, F.W. Fowler, and A.B. Levy, *J. Org. Chem.*, 1981, 46, 157.

104. (a) B.H. Lipshutz and J.J. Pegram, *Tetrahedron Lett.*, 1980, 21, 3343.
(b) B.H. Lipshutz, J.J. Pegram, and M.C. Morey, *Tetrahedron Lett.*, 1981, 22, 4603.
105. H. Gerlach, *Helv. Chim. Acta.*, 1977, 60, 3039.
106. R.J. Fessenden and J.J. Fessenden, *J. Org. Chem.*, 1967, 32, 3535.
107. M.L. Mancini and J.F. Honek, *Tetrahedron Lett.*, 1982, 23, 3249.
108. G.R. Martinez, P.A. Grieco, and C.V. Srinivasan, *J. Org. Chem.*, 1981, 46, 3760.
109. K.C. Nicolaou, D.A. Claremon, and D.P. Papatijatjis, *Tetrahedron Lett.*, 1981, 22, 4647.
110. K.A.M. Walker, *Tetrahedron Lett.*, 1977, 18, 4475.
111. (a) H.J. Reich, F. Chow, and S.L. Peake, *Synthesis*, 1978, 299.
(b) K.C. Nicolaou, R.L. Magolda, W.J. Sipio, W.E. Barnette, Z. Lysenko, and M.M. Joullie, *J. Am. Chem. Soc.*, 1980, 102, 3784.
112. B.M. Trost, and D.P. Curran, *Tetrahedron Lett.*, 1981, 22, 1287.
113. See, for example, ref. 41d.
114. P.A. Grieco, reported at the 183rd A.C.S. Meeting, Las Vegas, March 1982.
115. A. Minato, K. Tamao, T. Hayashi, K. Suzuki, and M. Kumada, *Tetrahedron Lett.*, 1981, 22, 5319.
116. H.O. House, *Modern Synthetic Reactions*, chapter 9, Benjamin, London, 1972.
117. J.H. Noggle and R.E. Shirmer, "The Nuclear Overhauser Effect", Acad. Press, New York, 1971.

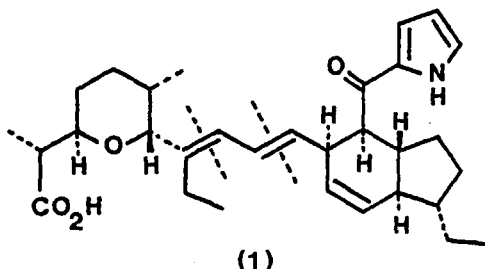
AN INTRAMOLECULAR DIELS-ALDER APPROACH
TO THE SYNTHESIS OF THE RIGHT HAND HALF OF THE IONOPHORE ANTIBIOTIC X-14547A

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ABSTRACT: Starting from ethylbutyrate, an efficient synthesis of the right hand half of the antibiotic X-14547A has been achieved in which the desired five relative chiral centres were created by an intramolecular Diels-Alder reaction.

The recently isolated novel ionophore X-14547A (1) has been shown to possess interesting biological properties¹. Although its total synthesis has not yet been achieved, it is the subject of considerable current effort.

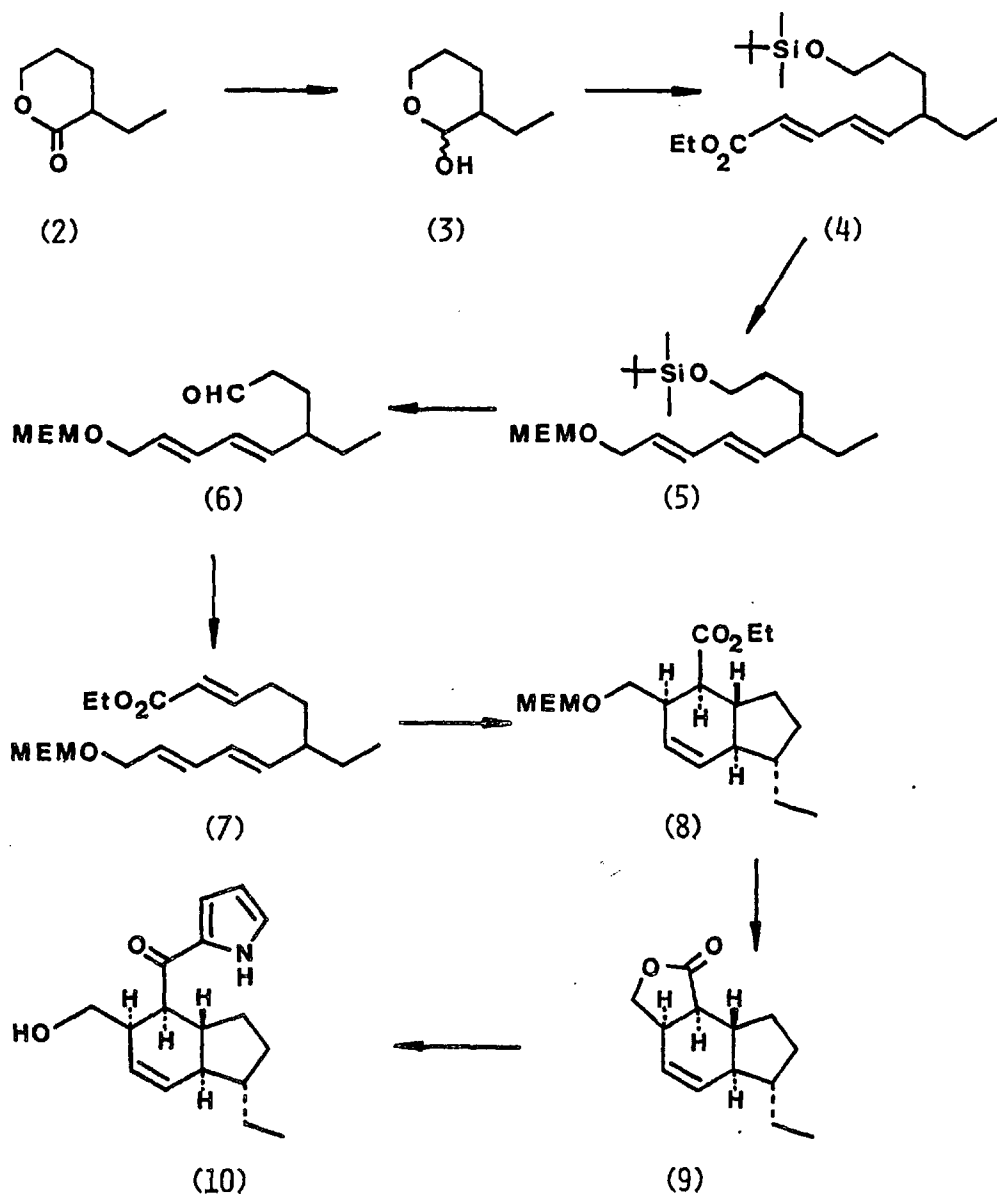
Here we report our progress towards the construction of a suitably functionalised right hand portion of this important molecule.



A retrosynthetic analysis suggests that (1) might be constructed by coupling between two appropriately protected fragments derived from either of the two disconnections in (1) above. The tetrahydroindan fragment is most logically derived by an intramolecular Diels-Alder approach^{2,3} as discussed in this letter.

2-Ethyl- δ -valerolactone (2) was conveniently prepared from ethylbutyrate by alkylation of the enolate with 1-trimethylsilyloxy-3-iodopropane followed by hydrolytic work up and cyclisation in warm toluene/P.T.S.A. Direct alkylation of δ -valerolactone was less satisfactory in our hands, particularly on a large scale.

The lactone (2) was converted, in quantitative yield, to a mixture of lactols (3)⁴ by treatment with DIBAL in toluene at -78°C . While (4) could be prepared in low yield, by Wittig reaction of the surprisingly unreactive lactols (3) with 3-(ethoxycarbonylallylidene)triphenyl-



phosphorane followed by protection, it was best obtained by silylation of (3) with *t*-butyldimethylsilyl chloride/imidazole and subsequent reaction with ethyl-4-diethylphosphonocrotonate/L.D.A. to give (4) in 72% overall yield. The *E,E*-dienoate (4) was smoothly reduced with 2.2 equiv. of DIBAL in toluene at 0°C to the corresponding alcohol which was protected as its MEM ether (5) by reaction with MEM-chloride and diisopropylethylamine in CH₂Cl₂ in 96% overall yield from (4). Removal of the *t*-butyldimethylsilyl group with 2.5 equiv. of

tetra-n-butylammonium fluoride in T.H.F followed by oxidation of the resulting alcohol with CrO_3 /pyridine in CH_2Cl_2 gave the aldehyde (6), again in 96% overall yield.

Reaction of (6) with carboethoxymethylenetriphenylphosphorane in CH_2Cl_2 at 25°C cleanly gave the E,E,E-trienoate (7) in 95% yield after removal of triphenylphosphine oxide.

With (7) now readily available, its intramolecular Diels-Alder cyclisation was investigated. Molecular models indicated that, of the two possible cis-endo cyclisation modes⁵, the one involving the sterically least hindered transition state would provide the required five relative chiral centres of the desired tetrahydroindan moiety. On heating (7) in argon-flushed toluene at reflux for 36-70 h, the cyclised product (8) was obtained as a chromatographically homogeneous compound in near quantitative yield. A detailed high field (250 MHz) ^1H n.m.r. examination of this product showed that only small amounts (<10%) of the other possible isomers were present. Removal of the MEM protecting group with freshly fused ZnBr_2 in CH_2Cl_2 led to spontaneous lactonisation to the crystalline tricyclic lactone (9), m.p. $67.5-68.5^\circ\text{C}$ in 60% overall yield from (7).

Contrary to the results of Bean⁶ on the acylation of pyrrol Grignards, the ester (8) was remarkably unreactive to pyrrol magnesium bromide even under forcing conditions but reaction of the lactone (9) with pyrrol magnesium bromide in toluene⁷ at $100-105^\circ$ gave the desired hydroxypyrrolicarboxyl compound (10) in 73% yield.

We are currently investigating synthetic routes to the left hand portion of X-14547A together with refinements to the above synthesis.

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REFERENCES:

1. J.W. Westley and C.-M. Liu, U.S. Patent, 4,100,171; J.W. Westley, R.H. Evans, Jr., C.-M. Liu, T.E. Hermann and J.F. Blount, J. Amer. Chem. Soc., 1978, **100**, 6784; C.-M. Liu, T.E. Hermann, M. Liu, D.N. Bull, N.J. Palleroni, B.L.T. Prosser, J.W. Westley, and P.A. Miller, J. Antibiot., 1979, **32**, 95; J.W. Westley, R.H. Evans, Jr., L.H. Sello, N. Troupe, C.-M. Liu, and J.F. Blount, J. Antibiot., 1979, **32**, 100.
2. For recent reviews of intramolecular Diels-Alder reactions see W. Oppolzer, Angew. Chem. Internat. Edn., 1977, **16**, 10 and G. Brieger and J.N. Bennett, Chem. Rev., 1980, **80**, 63.
3. Professors K.C. Nicolaou and W.R. Roush have each independently employed an intramolecular Diels-Alder reaction approach to the synthesis of the tetrahydroindan portion of X-14547A; we thank them for their kind exchange of information prior to publication. Prof. Nicolaou has also confirmed the structural assignment of the same lactone (9) by X-ray crystallography.
4. All new compounds were fully characterised by spectroscopic methods, acc. mass and/or microanalysis. ^1H n.m.r. data (250 MHz), δ /ppm (CDCl_3):
Compound (8): 5.95 (1H, d, J 10.26 Hz), 5.55 (1H, ddd, J 10.26, 4, 2.56 Hz), 4.63 (1H, d, J 6.7 Hz), 4.59 (1H, d, J 6.7 Hz), 4.1 (2H, dq, J 6.7, 1.53 Hz), 3.67 (2H, m), 3.5 (2H, m),

3.47 (2H, m), 3.39 (3H, s), 2.88 (1H, m), 2.62 (1H, dd, J 11.2, 6.7 Hz), 2.05-1.1 (9H, m), 1.28 (3H, t, J 6.7 Hz), and 0.91 (3H, t, J 7.2 Hz).

Compound (9): 6.07 (1H, d, J 10.2 Hz), 5.58 (1H, ddd, J 10.2, 3.82, 2.03 Hz), 4.51 (1H, q of dd, J 17.17, 4.5, 1.4 Hz), 4.51 (1H, m), 3.9 (1H, m), 3.2 (1H, m), 1.99 (2H, m), 1.8-1.1 (7H, m) and 0.95 (3H, t, J 7.14 Hz).

Compound (10): 10.03 (1H, brs, D₂O exch.), 7.1 (1H, m), 6.9 (1H, m), 6.3 (1H, m), 6.1 (1H, d, J 10.1 Hz), 5.6 (1H, dt, J 10.1, 3.2 Hz), 3.65 (2H, m), 3.46 (1H, dd, J 10.5, 7.01 Hz), 2.94 (1H, brs, D₂O exch.), 2.74 (1H, m), 2.2-1.0 (9H, m), and 0.92 (3H, t, J 7.35 Hz).

5. W.R. Roush, J. Org. Chem., 1979, 44, 4008 and references therein.
6. G.P. Bean, J. Heterocyclic Chem., 1965, 2, 473.
7. C.F. Hobbs, C.K. McMillin, E.P. Papadopoulos and C.A. Van der Werf, J. Amer. Chem. Soc., 1962, 84, 43.

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