A THESIS ENTITLED

"STEREOCHEMICAL AND MECHANISTIC STUDIES IN BIOSYNTHETIC MODEL SYSTEMS"

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by

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Finally, I thank Professor G.W. Kirby for provision of facilities in the Chemistry Department, and the Science Research Council for financial support.

To

My Mum and Dad

... their exceptional vision, guidance and

understanding have made it all possible.

" ... all work, everywhere, is only the work of nature."

B. Gita 13.29.

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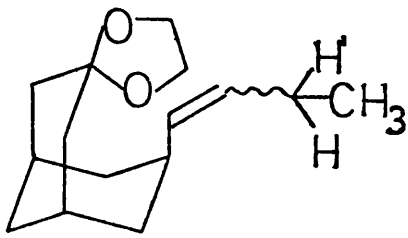

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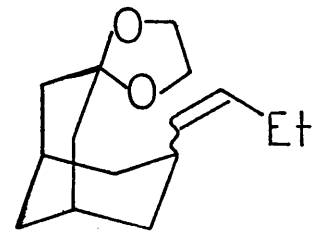

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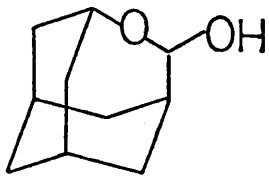

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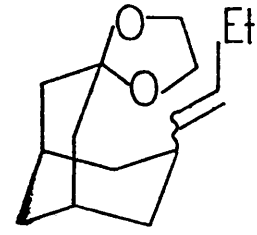

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SUMMARY

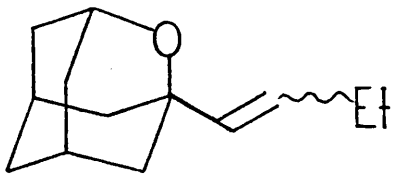
The *in vivo* isomerisation of isopentenyl pyrophosphate to dimethylallyl pyrophosphate, and the condensation of these two C-5 units, giving geranyl pyrophosphate, although formally recognisable as S_E2' processes,[28] have been explained[23] by different mechanisms, mainly because the stereochemistries of the *in vivo* transformations are different.

The stereochemical preference of the S_E' reaction, *in vitro*, unlike the much-studied S_N' process, has received little attention; only one conscious effort has been made to clarify the issue:[28] a *syn* preference was noted for this non-enzymatic S_E' reaction, in direct contrast with theoretical predictions.[24,27]

PART I

In this Thesis, the design of model systems capable of investigating the S_E' reaction, and synthetic approaches to these models, are described. The basic concept used was that of effecting S_E' cyclisation of a suitably functionalised bicyclo(3.3.1)nonane - a "seco-adamantane" - to an adamantane nucleus.

Several approaches to the first of these molecules, (29), were probed, and one, involving a Wittig reaction on lactol (105), furnished the required molecular skeleton (113), *Z*-olefin; the isomeric *E*-olefin (137) was then accessible by an olefin inversion sequence. However, in a series of experiments, it was established that aldehyde epimerisation had occurred during the Wittig reaction; these experiments uncovered some interesting chemistry, including a novel S_N'



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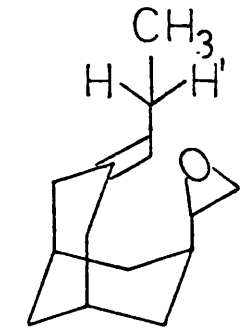

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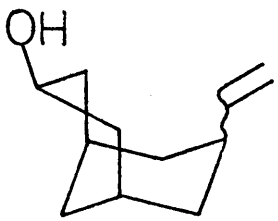

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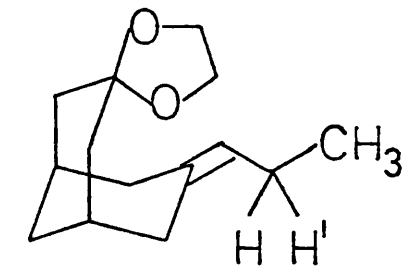

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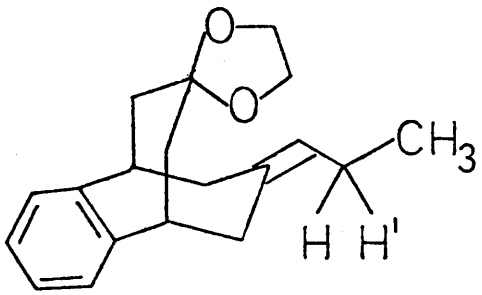

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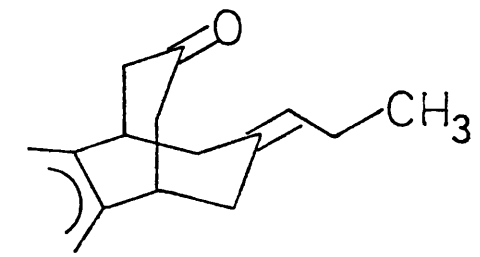

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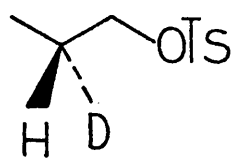

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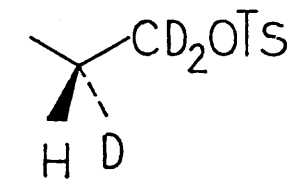

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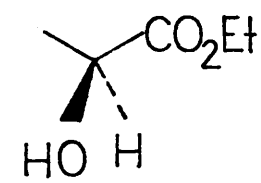


(13)

ring-closure to the oxaadamantane (129).

A second model, (155), was investigated, and considerable progress made towards it; but, spectral data (of enol (159)) suggested that an epimerisation had occurred in this route also.

Experimental difficulties with a third model, (173), resulted in modification to the closely-related benz-bicyclo (3.3.2)decane (192). Work towards this target molecule has progressed to the penultimate stage, (186).

PART II

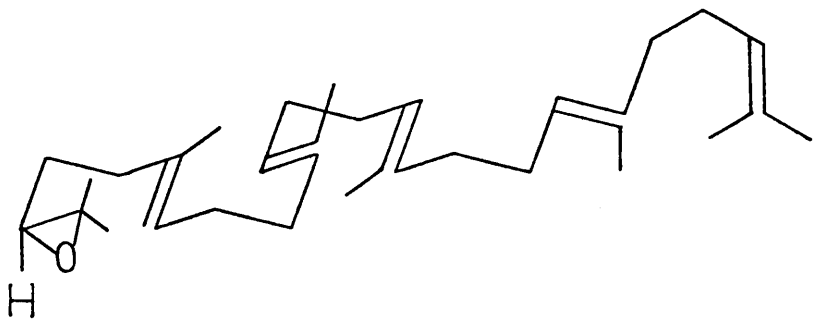
The models of Part I required specific isotopic labelling with deuterium (e.g. in (29), H or H' = D) for successful investigation of the S_E' reaction; in particular, a specifically 2-deuteriated n-propyl iodide was required.

Starting from (S)-(-)-ethyl lactate (13), routes to (R)-n-propyl-2-^{2}H tosylate (43) and (R)-n-propyl-1,1,2-$^2H_3$ tosylate (45) have been achieved.

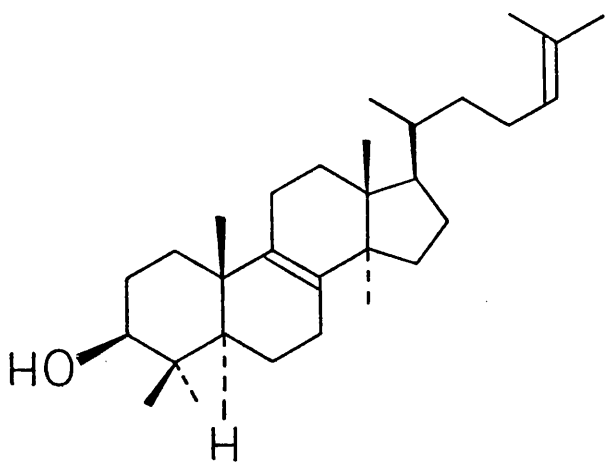
Methods for differentiating the enantiotopic protons on C-2 of n-propanol (and hence for determining accurately the optical purities of (43) and (45)) by ^{1}H.m.r. spectroscopy have been investigated.

PART I

(i) Introduction and Background



(1)



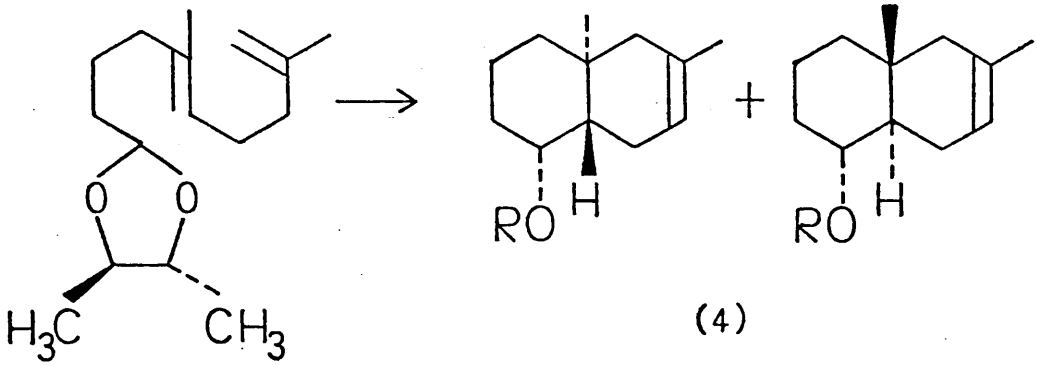
(2)

(i) Introduction and Background

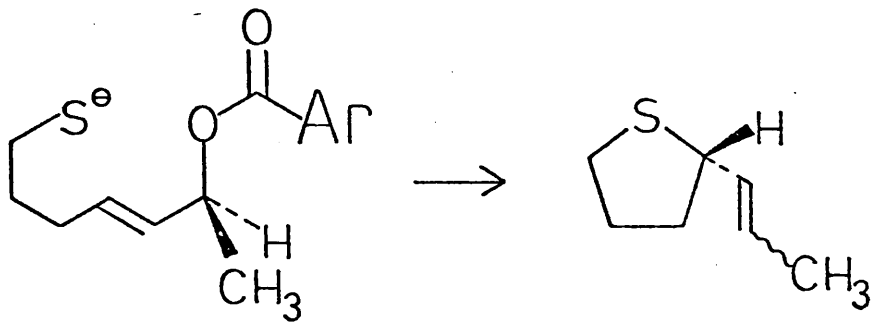
The constant demystification of biochemical transformations by detailed investigation at the molecular level has had a powerful impact on the thinking of organic chemists. Due mainly to the superb work of Cornforth[1] and Arigoni,[2] intimate details of the stereochemistry of a variety of biological processes pertaining to terpenes have been laid bare. In later studies of other biochemical systems, also, the work and results have been no less admirable - e.g. the efforts of Scott[3] and Battersby[4] in the field of porphyrins and corrins.

What is the reason for this arousal of interest in these results among organic chemists? The answer is not a simple one, but central to a consideration of the question is the stereospecificity of the transformations. The specificity observed is most often due to the involvement of chiral catalysts - i.e. enzymes - but in some cases reaction stereochemistry may be rationalized in terms of orbital symmetry or of sterically 'suitable' arrangements of atoms within molecules.

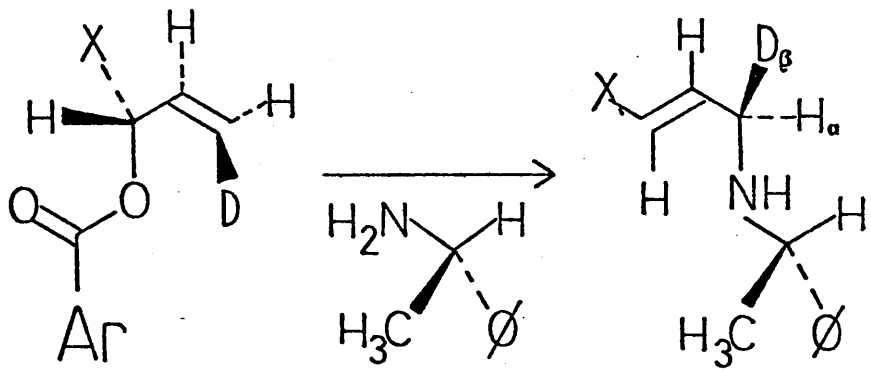
Possibly the most pertinent example of the latter is the cation-initiated cyclisation of polyene chains: the *in vivo* cyclisation of 2,3-oxidosqualene (1) to lanosterol (2) is a remarkable transformation which proceeds stereospecifically[1] to give only one of many possible isomers, and a cursory glance at the chain-extended form of squalene suggests an *in vitro* cyclisation as only a remote possibility. However, the extensive investigations of Johnson's group in Stanford[5] (but see also Ireland[6] and van Tamelen[7]) have shown that such


O
O
H3C
CH3
RO
H
RO
H

(3) (4)


O
Sθ
O
Ar
H
CH3
S
H
CH3

(5) (6)


X
H
H
H
O
O
D
Ar
H2N
H
H3C
Ø
H
Dβ
X
Hα
H
NH
H
H3C
Ø

(7) (8) (9)

in vitro cyclisations are possible, and indeed the introduction of a chiral element into the molecule results[5] in a reaction of high stereoselectivity and useful yield, e.g. (3) $\longrightarrow$ (4). The observed results may be seen in terms of a preferred folding of the polyene chain which allows the reaction to proceed, but it is doubtful if such a study would have been initiated without a knowledge of the biological counterpart.

Since, ordinarily (but see examples of the uses of enzymes in organic synthesis[8]) the chemist does not have chiral catalysts, whether enzymic or otherwise, at his disposal for everyday transformations, the probing of reaction stereochemistry is often related to the above-mentioned concepts of intrinsic electronic and conformational preferences. Indeed, a reaction labelled as being "associated with a distinctive stereochemistry",[9] the S_N2' reaction - which does not have a biochemical pedigree - has been cherished for its supposed specificity until recently, when it has become the subject of more careful investigation. Originally thought[10] to proceed unambiguously with *syn* stereochemistry, reinvestigation[11-14] has clarified the issue (particularly on the original cyclohexenyl system), revealing that the natures of the nucleophile, leaving group and solvent can radically alter the outcome of the reaction - e.g., Stork[13] finds that cyclisation of (5) to (6) proceeds almost entirely by addition of the thiolate anion *anti* to the departing mesitoate (i.e. *anti* S_N'), whereas Overton[14] shows that the strictly intermolecular aminolysis of (7) by (8), giving (9), is more delicately balanced, favouring *syn* over *anti* by the extent of 1.4-1.8(i.e. a mixture of *syn* and *anti* S_N2'). The apparent inconsistencies

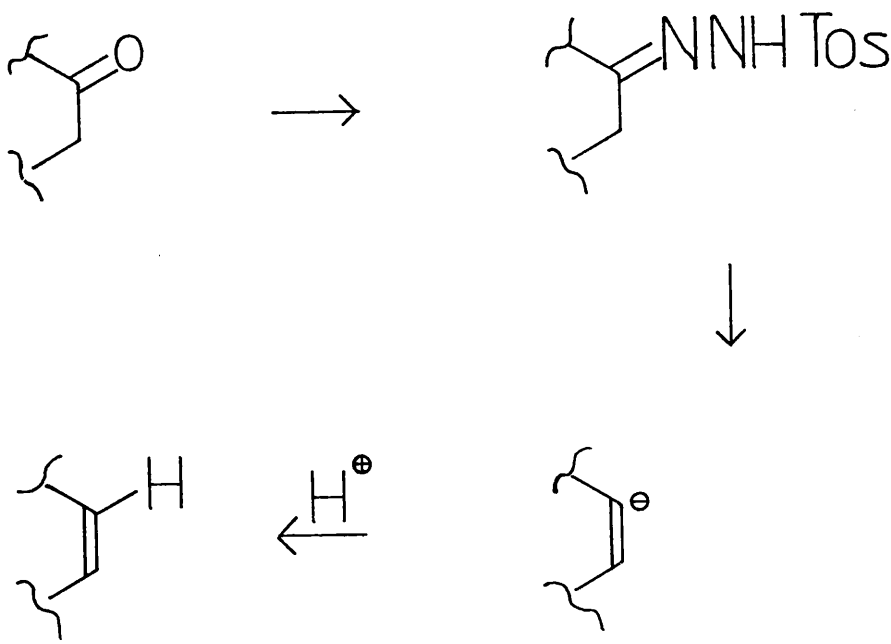


Figure (1)

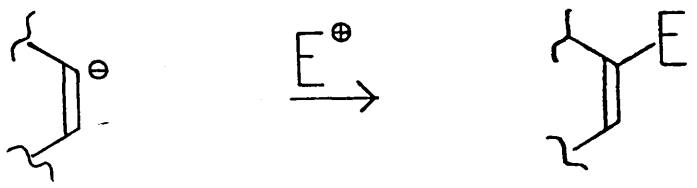
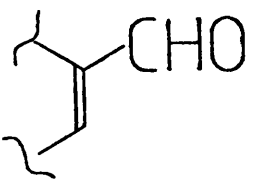


Figure (2)

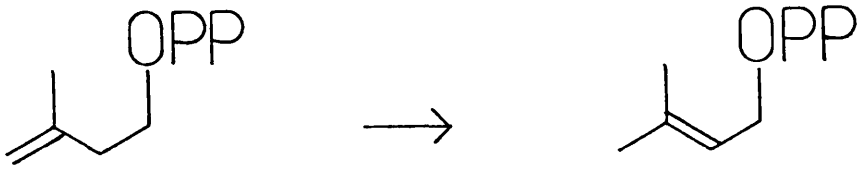


(10)

which these investigations betray serve as a warning against complacency when dealing in such matters, but conversely provide scope for obtaining a desired result in the knowledge that both stereochemistries are available. Additionally, the results can help direct theoretical studies.[15]

The search for stereoselective reactions of general applicability is apparent from the current literature; the Aldol condensation provides a good example. Impetus for a stereochemical definition of this reaction surely stems from its potential for the synthesis of macrolide antibiotics and related structures. Several of these complex molecules have yielded to inventive total syntheses[16] with the hurdle of macro-lactonisation being overcome in three or more different ways. A major obstacle now remains in the production of the contiguous asymmetric centres which adorn the periphery of many of these molecules. Initial studies mainly by Heathcock[17] within the last year have produced promising results and the recognition that, in certain cases, Z- and E- enolates will give erythro-and threo- adducts, respectively, has widened considerably the scope of this already invaluable reaction.

The translation of specific organic transformations into generalised concepts[18] has led to considerable developments in functional group interconversions, the key to this approach lying in 'loose' electrophile/nucleophile nomenclature - e.g. the Shapiro reaction,[19] a reductive olefination, is thought to proceed by the reaction pathway shown in Figure (1). Viewing the last step in general terms, as in Figure (2), has



ip-pp dma-pp

Figure (3)

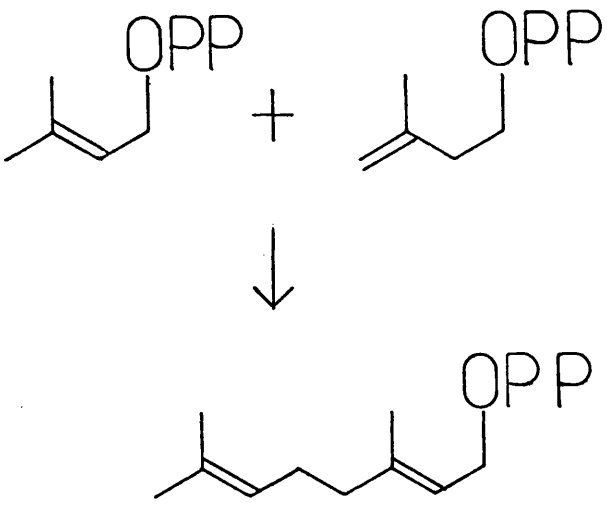
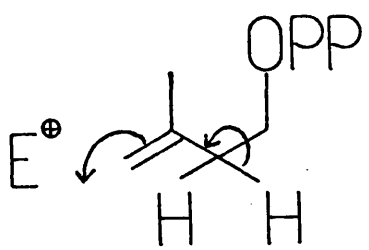


Figure (4)

Geranyl-pp



(11)

led to more interesting and potentially useful olefins - e.g. using dimethyl formamide as electrophile results[20] in the enal (10).

Extension of such methods of thinking to biological transformations could prove to be a fertile area, both with regard to functional groups and to stereochemistry. Two fundamental reactions on the biogenetic pathway to terpenes amplify this point and reveal underlying mechanistic similarities:

(a) The isomerisation of isopentenyl pyrophosphate (ip-pp) to dimethylallyl pyrophosphate (dma-pp), Figure (3).

(b) The condensation of ip-pp and dma-pp, producing geranyl pyrophosphate, Figure (4).

Formally, these processes may be represented as (11) - i.e. loss of a proton from C-2 of ip-pp, formation of a new trisubstituted olefin and addition of an electrophile (E^+) to C-4; in (a) the electrophilic component is a proton, in (b) it is dma-pp. Both processes can be described as S_E2' reactions - i.e. bimolecular electrophilic substitution with allylic displacement.

Having recognised this formal relationship, a not unreasonable expectation would be that these two processes should proceed by a similar mechanism, possibly exhibiting the same stereochemistry. But, as shown in Figures (5) and (6), Cornforth[21,22] demonstrated that the biological transformations proceed with opposite stereochemistries- namely <u>anti</u> for the

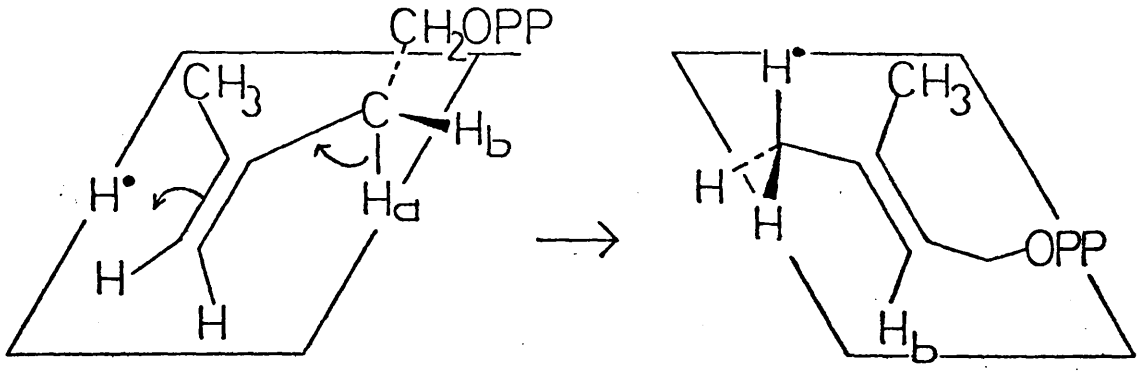


Figure (5)

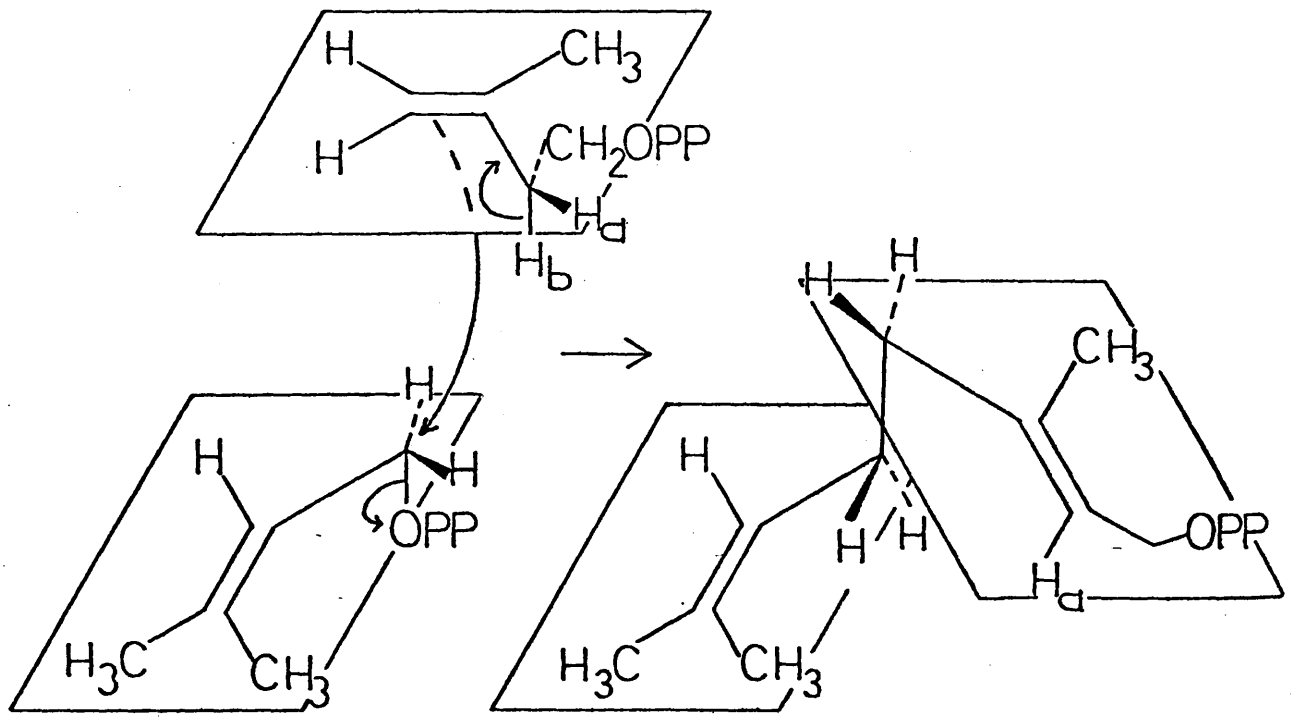


Figure (6)

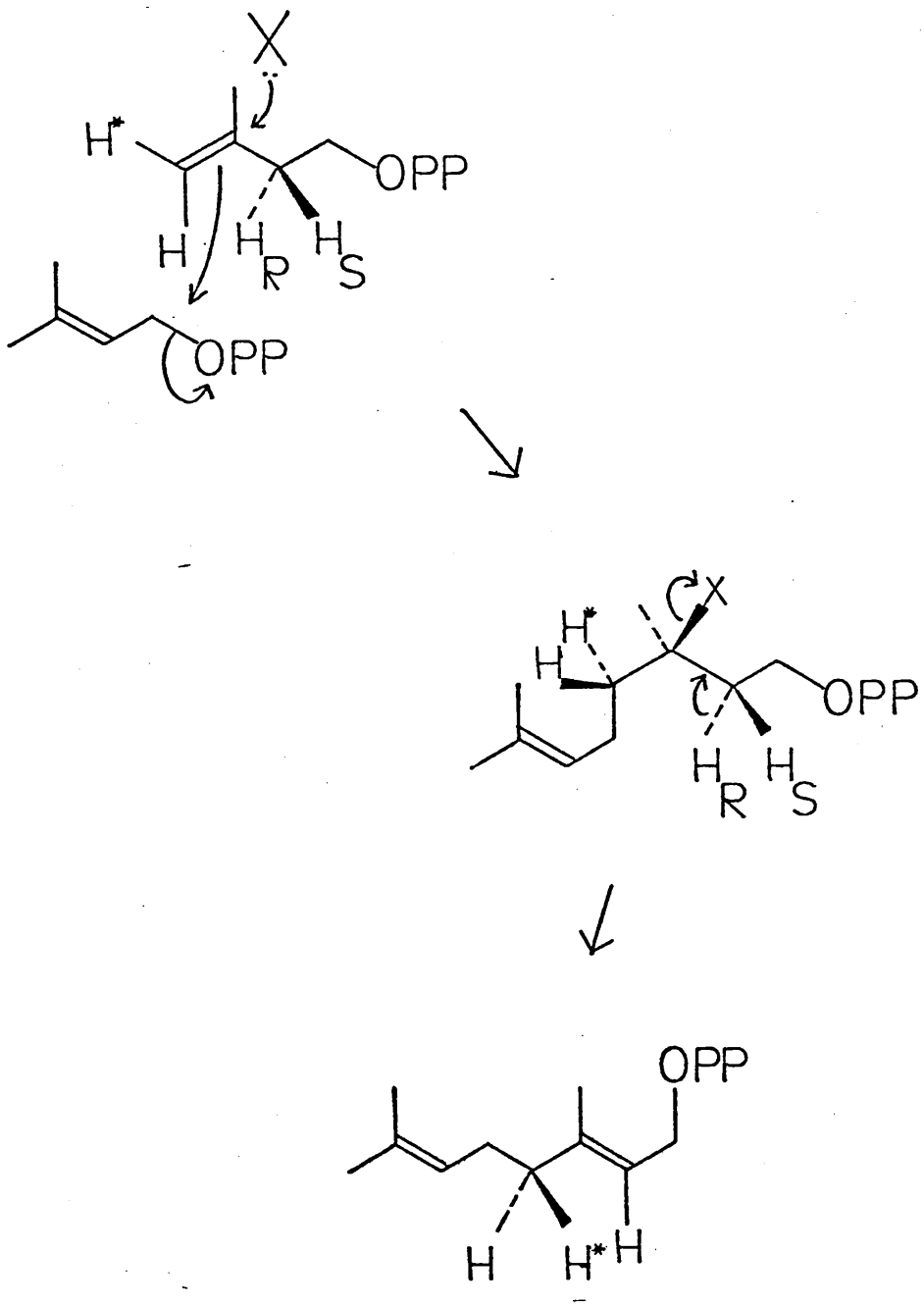


Figure (7)

isomerisation and *syn* for the coupling reaction.

How are these facts rationalised?

What predictions are there from theoretical calculations?

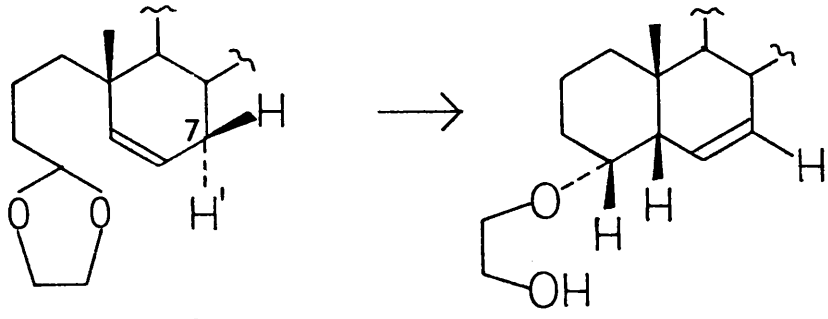
And what might be the result of an *in vitro* S_E2' reaction?

Such questions formed the background for the study described in this thesis.

The observation of *anti* stereochemistry for the ip-pp→ dma-pp isomerisation is acceptable from a stereoelectronic standpoint, since it involves maximum separation of electronic charge during the reaction - i.e. electron density from the breaking C-H bond is localised on the lower face of the molecule (as written) and electrons from the Π -bond approach the electrophile on the upper face.

Cornforth[23] uses the same empirical reasoning of charge density separation to discount formation of geranyl pyrophosphate in one step - he considers complete localisation of electron density on one face of the ip-pp molecule during reaction as energetically disfavoured - and proposes, instead, a two-step process embodied in the controversial X-group mechanism: the proposal is shown in Figure (7). A group X (unspecified, but plausibly an enzyme-bound electron donating group - e.g. water or oxygen of pyrophosphate) and dma-pp are added in an *anti* fashion across the olefin of ip-pp. This is followed by *anti* elimination of H_RX, producing geranyl pyrophosphate. If X has a formal negative charge, its binding to C-3 of ip-pp need be no more than that in a close ion-pair.

While, in general, the idea of charge-separation is



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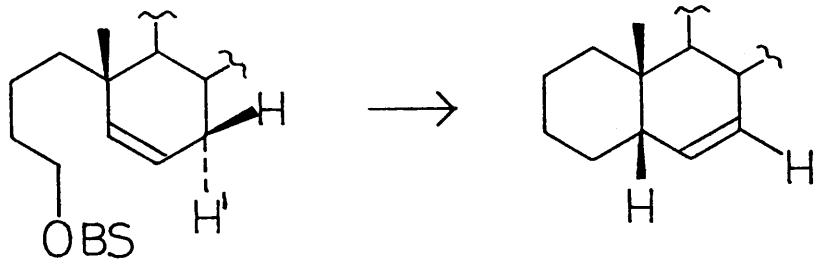


(14) (15)

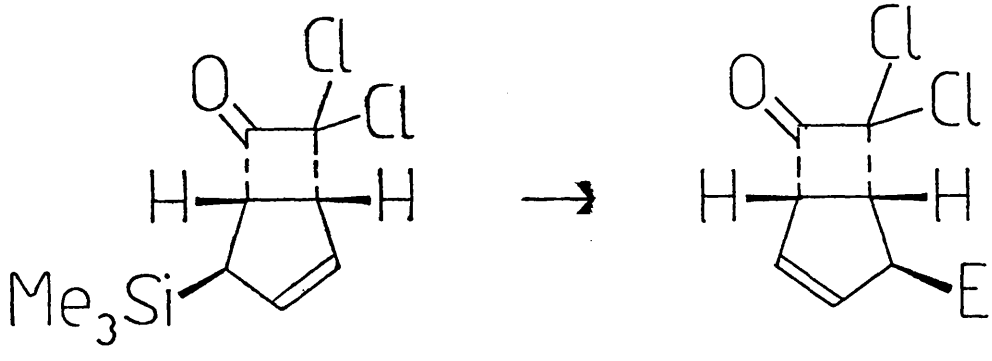
an intuitively sensible one, its application here is questionable on two grounds:

(a) In the absence of concrete evidence for the participation of a group X, pertinent mechanisms should be distinguished by the principle that "the simplest one shall be preferred". In the case in hand, the one-step syn S_E2' mechanism would be preferred.

(b) The known syn S_N' reactions[11-14] testify to the fallibility of deductions made on purely empirical notions concerning electron movement. Moreover, for the S_N2' reaction, practically all theoretical treatments to date have predicted[24-26] a syn relationship between entering and departing groups. (However, for the formally similar S_E2' process, anti stereochemistry has been predicted.[24,27])

Only one conscious effort has been made to define the stereochemical preference of the S_E2' reaction. Overton and Cunningham[28] synthesised the 4,5-secosteroids (12) and (14) (in which H or H' is deuterium) for this purpose, and, after extensive experimentation, conditions were established whereby S_E' reactions readily occurred, producing the steroids (13) and (15) respectively. The outcome was a syn preference, but, as pointed out by the authors, close investigation of the models indicated an intrinsic bias towards this result, on two accounts:

(i) The 7α- and 7β - protons are not equally disposed with respect to the Π-system in the secosteroids, the electrons of the C-7 - H_α (quasi-axial) bond being more



(16) (17)

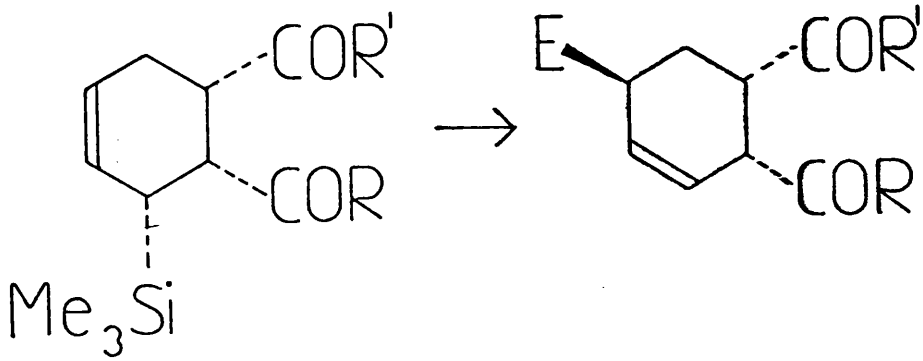
nearly aligned with the Π-orbital of the olefin. This is a known feature of cyclohexenyl rings.

(ii) The side-chain carrying the potential cationic site can approach the olefin only from the α-face of the molecule, due to steric restrictions of the 10β-methyl group.

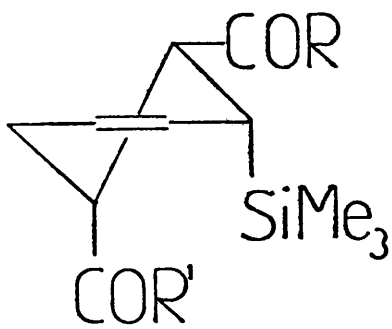
These two fixed parameters led to the not unexpected outcome of attack of the cation on the α-face of the olefin and loss of the 7α-proton. Results from the cyclisation of the 10α-methyl secosteroids would have been instructive, but synthetic difficulties curtailed this effort. However, the outcome is important regardless of limitations, since a distinctive stereochemistry - that contrary to theoretical predictions - is observed.

In addition to the above, there are several examples of reactions which may formally be categorised as S_E'. None is concerned with the S_E2' reaction or its stereochemistry but, curiously, one series of papers dealing with an aspect of silicon chemistry clearly provides examples of both <u>syn</u> and <u>anti</u> S_E2' reactions. The work in question is that of Fleming's group in Cambridge, who have shown[29] allyl silanes to be useful synthetic tools.

In the first example - a facile route to a prostaglandin synthon - treatment of the allyl silane (16) with a Lewis acid and an electrophile results in the olefin (17). This is clearly a <u>syn</u> S_E2' process, but as with the models of Overton and Cunningham[28], steric restrictions direct the electrophile to one face of the olefin - this time the "butterfly



(18) (19)



(20)

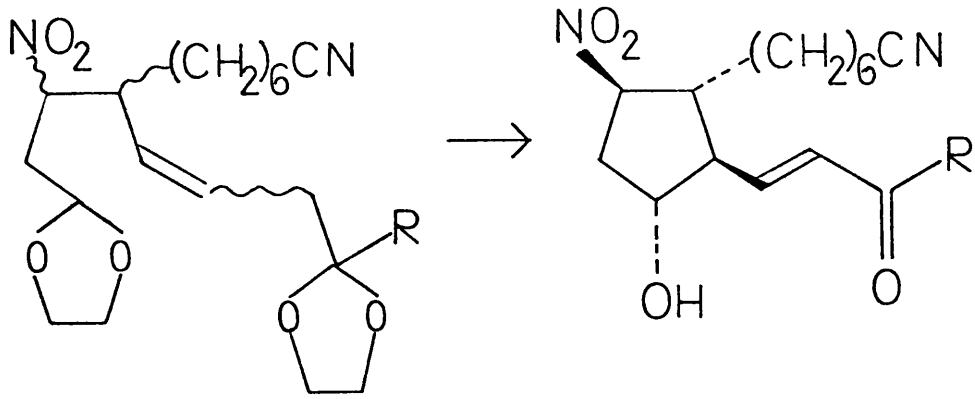


Figure (8)

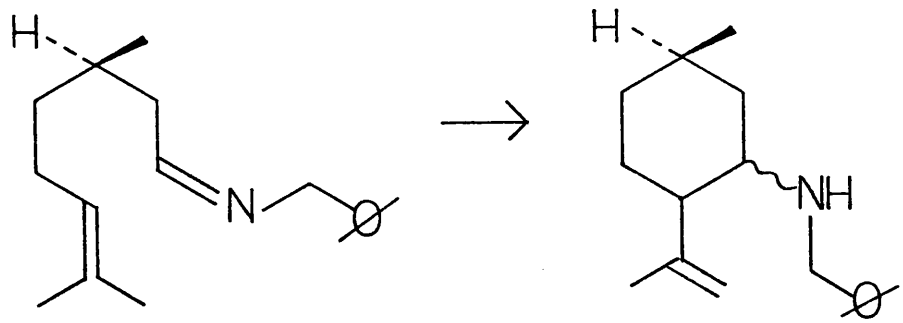


Figure (9)

shape of the bicyclo (3.2.0) skeleton allowing approach of the electrophile only to the exo face of the molecule.

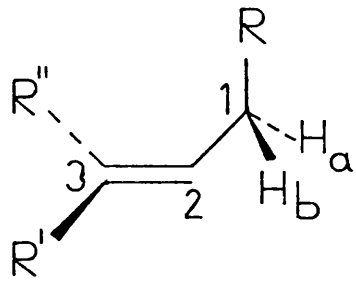
The second example, dealing with a cyclohexenyl system, proceeds with anti stereochemistry, and involves the conversion of (18) to (19). The reactive conformation of (18) is probably (20) as shown, with the silyl group quasi-axial (cf. seco-steroid models[28]), and again it is apparent that the electrophile approaches from the less hindered face, thereby avoiding steric compression with the quasi-axial - COR' group in (20).

Undoubtedly, the latter examples are non-concerted processes, and will involve the intermediacy of silicon-stablized carbonium ions,[30] but it is nevertheless relevant to the present discussion that syn and anti S_E2' products were observed.

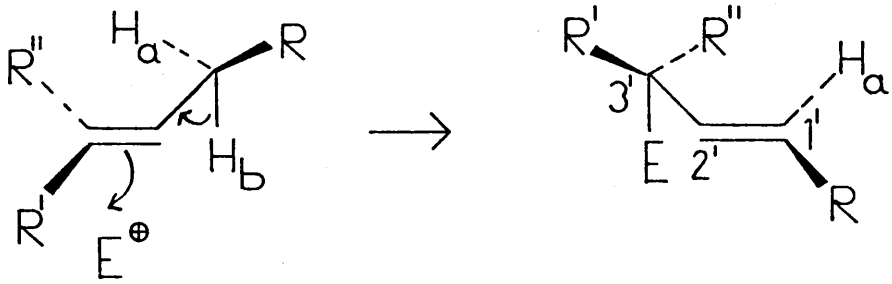
Of the other available examples of S_E' reactions, two are chosen to illustrate the potential of this reaction in ring formations, Figures (8)[31] and (9)[32].

(ii) Design of a Model System

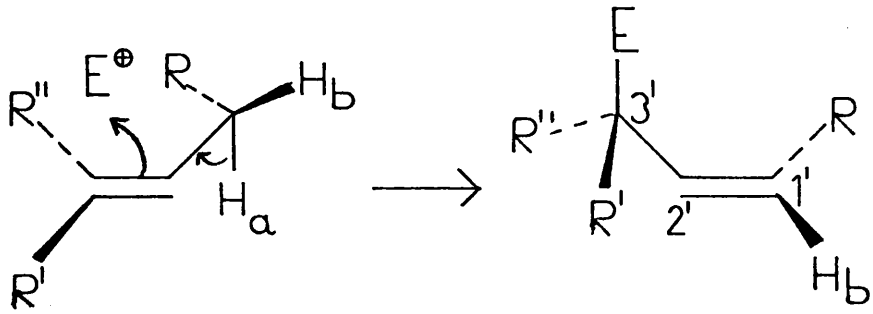
Consider the S_E2' reaction of olefin (21) with an electrophile (E^+), involving addition of the electrophile to C-3 of (21) with concomitant loss of H_a or H_b from C-1. For such a mechanism to operate, a high degree of ordering is required in the transition-state- i.e. a large entropy requirement is incurred -inasmuch as the electrophile must approach the olefin in the plane of the Π-orbital, and the C-H bond to be broken must align itself in a plane parallel to this Π-orbital. This is shown in (22) for a syn S_E2'


R
R''
1
3
2
H_a
H_b
R'

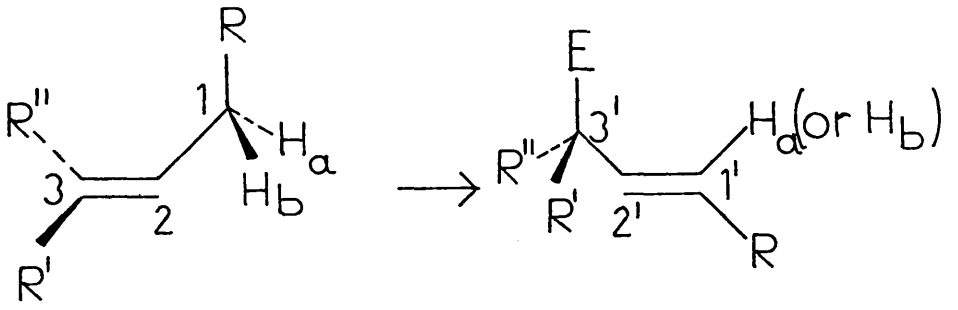
(21)


R''
H_a
R
H_b
R'
$E^{\oplus}$
R'
R''
3'
H_a
E
2'
1'
R

(22) (23)

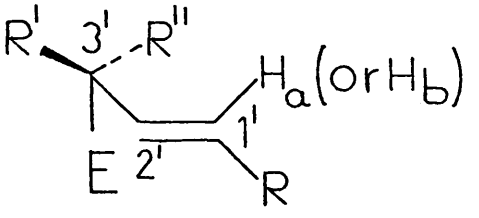

R''
$E^{\oplus}$
R
H_b
H_a
R'
E
3'
R''
R
R'
2'
1'
H_b

(24) (25)



(21) (26) , Z- or E- olefin

+



(27) , Z- or E- olefin

Figure (10)

process involving loss of H_b and addition of E^+ both from the lower face of the molecule, giving E-olefin (23), and in (24) for an anti S_E2' process involving loss of H_a from the lower face of (24) and addition of E^+ to the upper face, giving Z-olefin (25), where (23) and (25) differ

(a) in absolute configuration at C-3',

(b) in the geometry of the new olefinic linkage, C-1' - C-2', and

(c) in the identity of the proton lost from C-1.

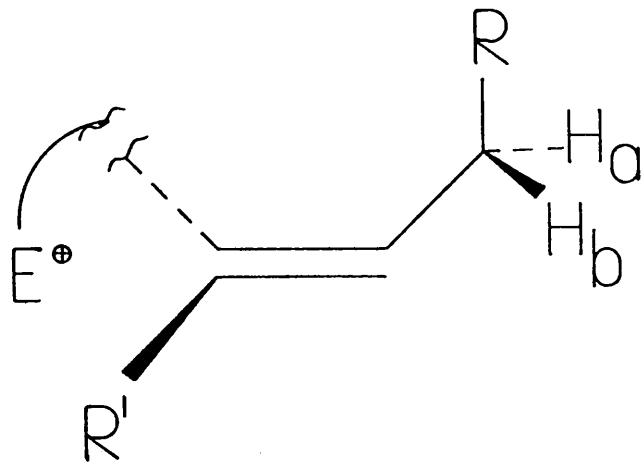
Of course, (23) and (25) are only two of eight theoretically possible products resulting from S_E2' reaction of (21) and E^+ .

Thus any model system designed to probe the stereochemistry of the S_E2' reaction must be capable of dealing with the three variables in (a) - (c), and permit a distinction between all possible products.

A formal statement of requirements may now be detailed - see Figure (10):

(i) An olefin (21), with one of the allylic protons specifically replaced by tritium at tracer level, or deuterium - i.e. either H_a or H_b of (21) must be isotopically labelled.

(ii) Interaction of this olefin with an electrophile (at C-3 of (21)) is then required, forming a new chiral centre (C-3' of (26) or (27)), the absolute configuration of which must be determined, e.g. by chemical correlation or X-ray analysis.



(28)

(iii) As the electrophile begins to interact with the Π-orbital, concomitant weakening of either C-H_a or C-H_b is mandatory to neutralize the developing positive charge at C-2 (cf. (22), (24)); the departing proton must be identified.

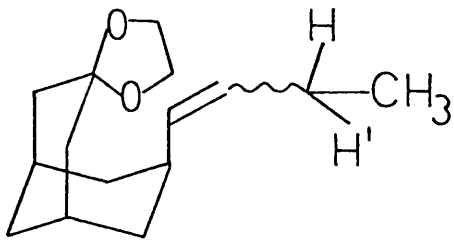
(iv) Resulting double bond isomers will require separation.

In summary, the S_E2' reaction of (21) with an electrophile, E^+ will result in products of the type (26) and (27); these products will require separation, identification and analysis for label content.

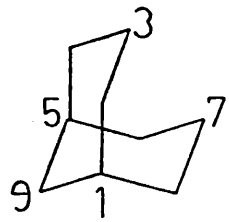
As the nucleophilic character of olefins is low, unless 'activated' towards nucleophilic reactivity by the presence of a vinyl heteroatom (e.g. enamines) or by ensuring spatial proximity of the relevant electrophile (e.g. in polyene cyclisations), it seemed prudent to incorporate the electrophilic and nucleophilic components required for an S_E2' reaction into a single molecule. This transforms the reaction into one of the S_E' type but does not, of course, affect the validity of any stereochemical deductions.

In addition, to simplify experimental procedures, deuterium was chosen as the heavy isotope for labelling.

The re-designed model should thus have the general structure (28), but it should avoid the conformational restraints of the model examined by Overton and Cunningham,[28] in particular incorporation of the olefinic linkage into a carbocylic ring.



(29)



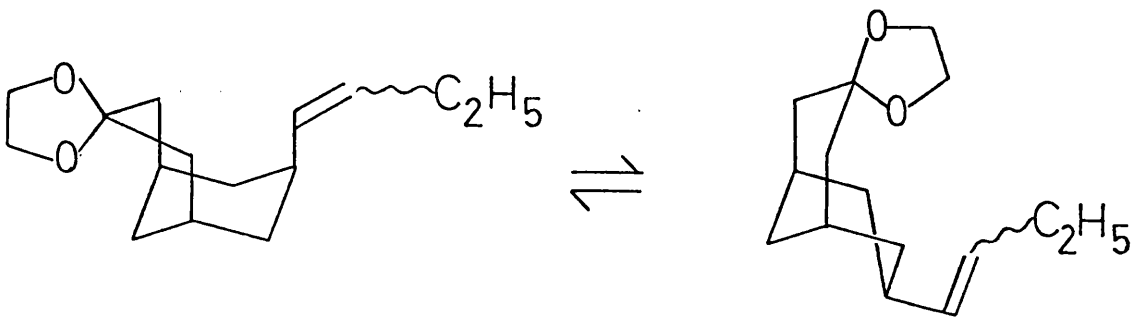
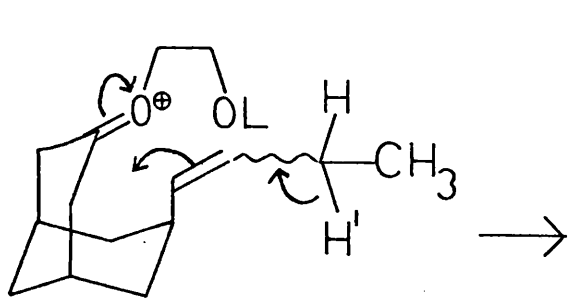
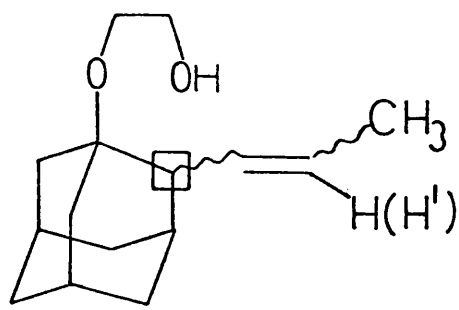


Figure (11)



(30)



(31)

(29)

L = Lewis acid

(iii) Choice of a Model System and Analysis of Products

Armed with the above requirements and being mindful of undesired constraints, several specific models were formulated; but one was pre-eminent both for its ability to align the olefin and electrophile in close proximity and its probable synthetic availability. It is (29), having an acetal as potential cationic initiator.[33]

Basically, the chosen model is a bicyclo (3.3.1) nonane skeleton with an ethylene acetal at C-3 and an endo alkenyl substituent at C-7 (numbering as shown). This system is conformationally mobile and was anticipated to exist as interconverting chair-boat/boat-chair conformations, Figure (11). However, on complexation with a Lewis acid, MX_n, formation of oxonium ion (30) should result. C-3 now being trigonal, the likelihood of a contribution from the dichair conformation is increased, at which time the stabilised carbonium ion might interact with the olefin and initiate the required S_E' reaction, as indicated by the arrows in (30). In the terminology of Baldwin,[34] this constitutes a "6-exo-trigonal" reaction, a favoured process. The product would be the very stable, 1,2-disubstituted adamantane (31).

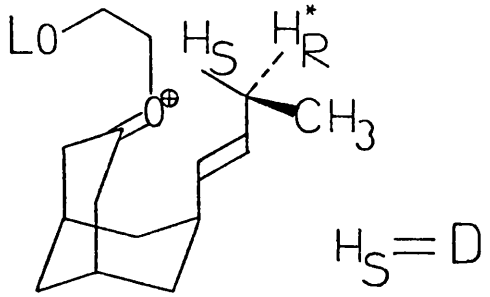
The so-formed adamantane racemates (31) posses an asymmetric centre at the required position (C-2 of the molecule, squared carbon atom), and degradation of the hydroxy-ethyl side-chain would leave an hydroxyl group adjacent to this asymmetric centre, thereby producing a convenient handle for resolution - e.g. by formation of the half phthalate esters and then treatment with a chiral base, giving separable diastereomeric salts.

An X-ray analysis on one of the enantiomers so produced would identify the absolute configuration. A prior separation of olefin isomers would be necessary.

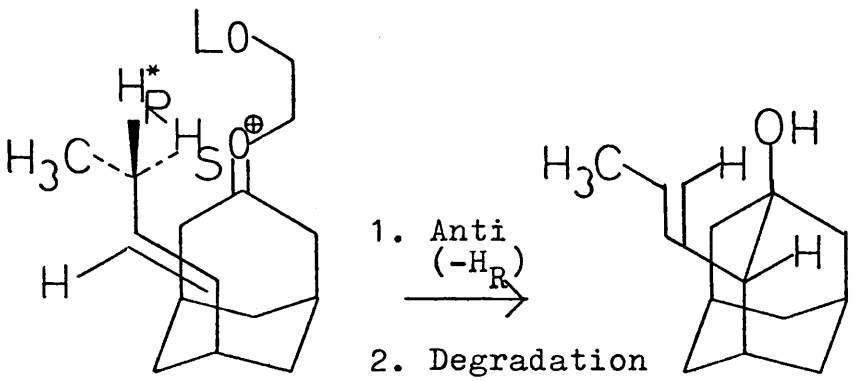
The deuterium content - found by use of mass spectrometry and ^{1}H.m.r. - of products obtained in the above ways would complete the data required for stereochemical deductions.

Availability of both enantiomers of the substituted adamantanes obviates the need for 'complementary' labelling experiments, experiments in which one cyclisation would be performed with the allylic pro-S proton replaced by deuterium, and a second having the allylic pro-R position labelled. Such twin experiments essentially provide an internal check on the validity of results obtained - e.g., if, with the pro-S position labelled, a 20% loss of label was observed, then an identical experiment with the pro-R position labelled should reveal an 80% loss of label. This type of checking procedure has found widespread use in biosynthetic investigations.[35]

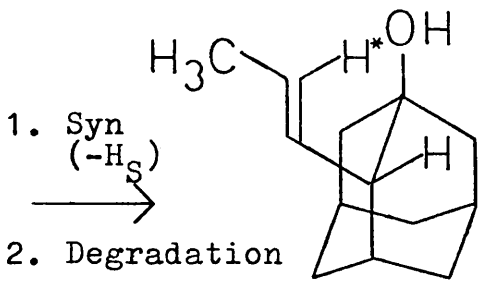
A close examination of the proposed cyclisation reaction is necessary to clarify this point. Suppose that in the cyclisation of (32), 1,2-disubstituted adamantanes are obtained as expected and E- and Z- olefin isomers can be separated. Consider the E-isomer; it is a racemate. It can be resolved via degradation of the hydroxy-ethyl side-chain to the tertiary alcohol, and use of a convenient resolving agent (see above). The enantiomers thus obtained are (34) (comprising (34') and (34"))and (36) (comprising (36') and (36")), and the absolute configuration of one (e.g. (34)) is determined by X-ray analysis, thereby also fixing the



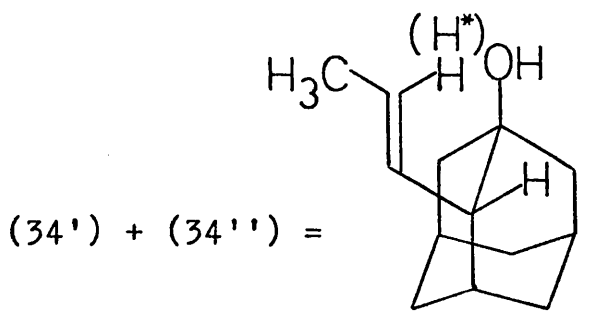
(32)



(33) (34')



(34'')



(34') + (34'') =

(34)

Figure (12)

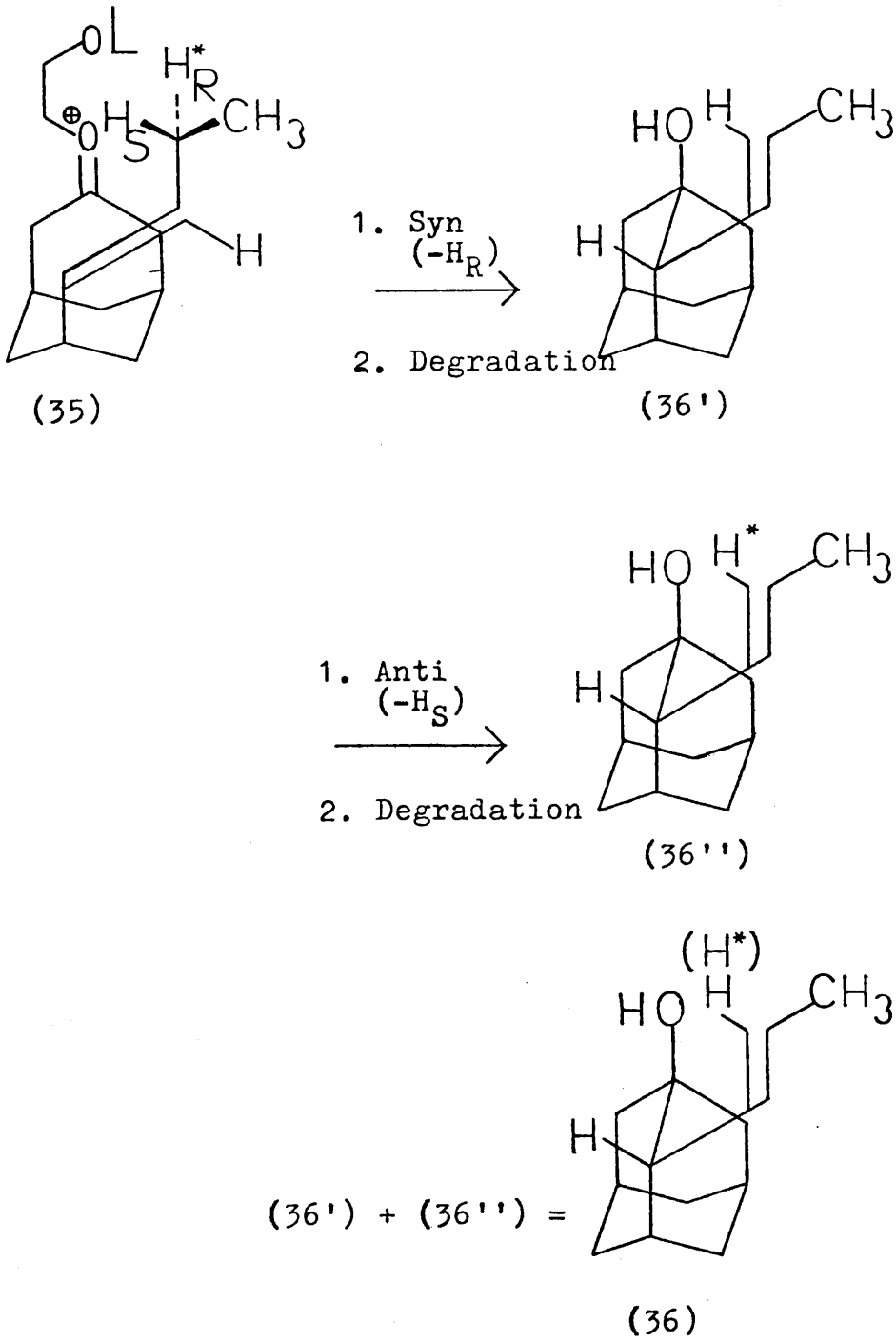


Figure (13)

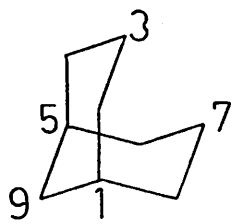
configuration of the other (as (36)).

Knowing this, one can infer that the transition states leading to (34) and (36) are related to (33) and (35), respectively. The extent to which H_R and H_S are lost thus reflects the ratio of syn and anti S_E' reaction - e.g. in (33), loss of H_S means a syn reaction, Figure (12), whereas loss of H_R means an anti reaction. In (35), Figure (13), the opposite relationship exists, remembering that in both cases only E-olefin products are being considered.

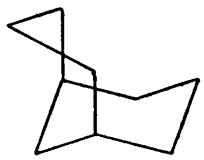
Thus in (34), if 20% label is retained, the reaction has proceeded by 80% syn, i.e., 80% loss of H_S ($\equiv$D), and 20% anti. The results obtained from (36) should substantiate this: in (36), 80% label should be retained, i.e. 20% loss of H_S ($\equiv$D), which again means 80% syn, 20% anti.

By this procedure, then, a built-in checking mechanism exists, rendering complementary labelling experiments unnecessary. Of course, a similar analysis holds for the Z-isomers of (34) and (36). (This analysis neglects the intervention of a deuterium isotope effect. In the extreme case (syn or anti S_E' mandatory) such an isotope effect could result in partial kinetic resolution.)

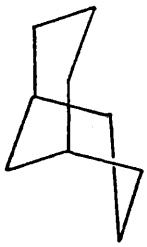
As inferred above, central to the cyclisation concept is the role of conformation, namely that for ring formation to occur, the bicyclo (3.3.1) nonane must assume a twin-chair arrangement of its cyclohexane rings, albeit only as a minor dynamic contributor. Conformational problems of bicyclo (3.3.1) nonanes have been the subject of several recent



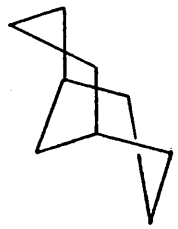
CC



bC



Cb



bb

Figure (14)

investigations, and a discussion is now given of current findings in relation to present requirements.

(iv) Conformational Analysis of Bicyclo (3.3.1) nonanes[36]

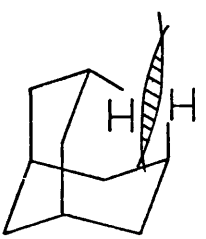
The problems of conformational analysis have challenged some of the world's finest chemical minds, and clarification of fundamental ideas culminated in the award of a Nobel Prize to Barton and Hassel in 1969. This early work dealt mainly with cyclohexanes and the results were later extended to fused carbocyclic systems such as the decalins, steroids and triterpenoids.

However, in certain respects, the bicyclo (3.3.1) nonane system offers advantages over these others:

(a) The relative positions of the two cyclohexane rings endow the system with unique flexibility. Four conformers free from angle strain are possible, shown in Figure (14) for the parent hydrocarbon. (The designations of Figure (14) will be used in this discussion, c = chair, b = boat.) Indeed boat conformations are commonplace in bicyclo (3.3.1) nonanes and since the difference in energy between chair and boat conformers is large,[37] theoretical interest is manifold.

(b) The spatial proximity of the C-3 (endo) and C-7 (endo) positions provides a sensitive handle for controlling ring geometry.

(c) Reactivity patterns of suitably functionalised systems exhibit selectivity which can be directly ascribed to conformation.



(37)

For those reasons, inter alia, bicyclo (3.3.1) nonanes have come under close scrutiny. Studies have proceeded from three general directions:

(a) Investigations by spectral methods - use of I.R., ^{1}H.m.r., ^{13}C.m.r.

(b) Investigation of chemical reactivity, in particular the study of ring-closure reactions, leading to adamantanoid and related tricyclic molecules.

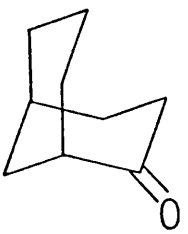
(c) Physico-chemical and theoretical studies.

Consideration of (c) is beyond the scope of the present discussion, but there are many interesting publications particularly by Allinger[38] and Schleyer.[39]

Although information gained from (a) and (b) may often be compatible, there is one fundamental difference between the two approaches: spectral data will feature mainly the most stable (thermodynamic) conformer, whereas reactivity may frequently bespeak a minor conformational contributor; physical evidence for such a short-lived species is, of course, the reaction product formed from it, although it may never exist in the ground state. The success of the proposed S_E' cyclisation rests, to a greater or lesser extent, on transient twin-chair bicyclo (3.3.1) nonanes.

(a) Spectral methods

I.R. spectroscopy found early application in the conformational analysis of bicyclo (3.3.1) nonanes; the spectrum of the parent hydrocarbon (37) shows abnormal C-H

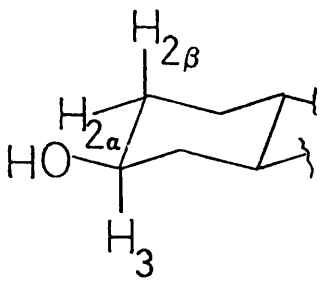


(38)

stretching and bending modes at 2990 cm^{-1} and 1490 cm^{-1} respectively, which have been attributed[40] to interactions of the C-3 (endo) and C-7 (endo) protons. It is obvious that for these to interact, the dichair conformation (or a significant contribution therefrom) must be invoked.

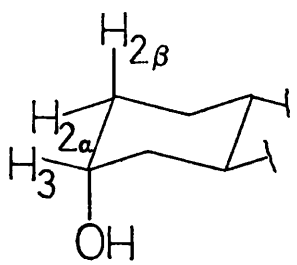
However, the use of i.r. spectroscopy in this area as a structural tool has serious limitations - e.g. the absence[41] of high-frequency bands in (38) - and it was not until the emergence of refined n.m.r. techniques at the beginning of this decade that definitive spectroscopic studies of conformation could be made. The methods of Lanthanide-Induced Shifts (LIS), variable temperatures and decoupling combined with high resolution ^{1}H.m.r. have provided information unobtainable by any other means.

The use of LIS presupposes the presence of a basic site in the molecule under consideration, to which the Lanthanide ion can complex, and most examples reported have contained either hydroxyl or ester groups for this purpose. The induced shifts are, of course, dependent on the closeness or otherwise of protons to the paramagnetic Lanthanide ion, and the overall effect is to 'expand' the spectrum, thereby allowing individual coupling constants to be extracted in pseudo first-order fashion.[42] Most important here are vicinal coupling constants, since from the Karplus equation,[43] there is a known relationship between the coupling constant of two vicinal protons and the dihedral angle between them. Casual inspection of a cyclohexane ring will reveal that as the ring geometry varies, (chair → boat → chair), so also does the



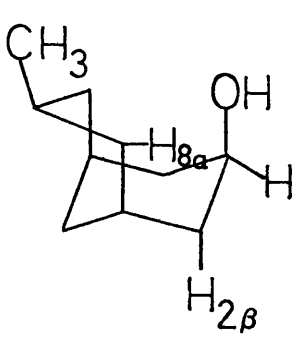
$J_{3,2\beta}$ =10 Hz

$J_{3,2\alpha}$ =5 Hz

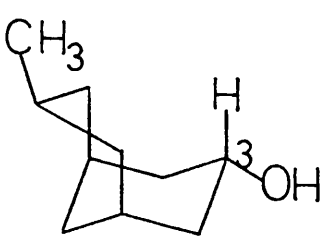


$J_{3,2\beta} = J_{3,2\alpha}$ = 3 Hz

Figure (15)



(39)



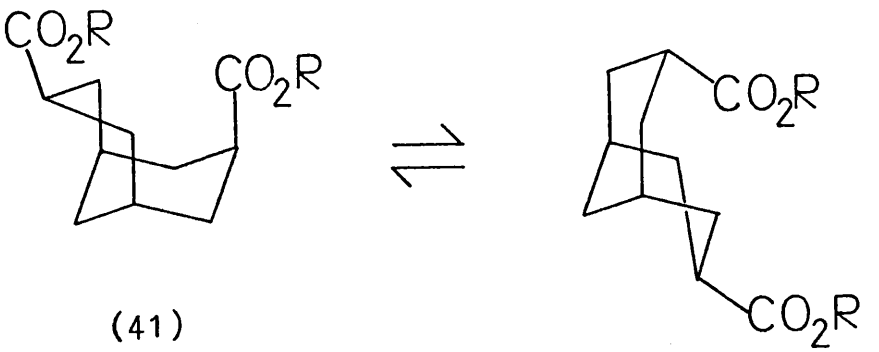
(40)

dihedral angle between vicinal protons.

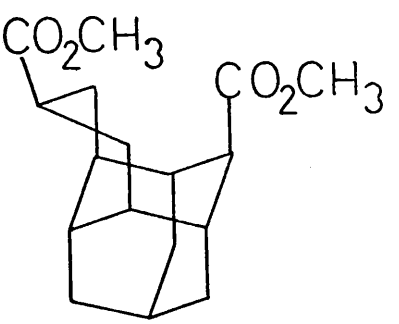
The various vicinal coupling constants thereby obtained for a particular bicyclo (3.3.1) nonane are then compared with 'expected' values. The latter are those of cyclohexane rings of known conformation - e.g. the A-rings of certain steroids are assumed to be in strict chair conformations, and can thus be used as standards, Figure (15). Having compared 'found' and 'expected' values, by reference to the Karplus relationship deviations from the steroidal values can be related to conformational changes in the bicyclic system under consideration.

It should be remembered that both cyclohexane rings of a bicyclo (3.3.1) nonane are subject to the familiar constraints[44] of six-membered carbocyclic rings - e.g. preference of chair over boat conformations as a result of bond eclipsing and flagpole interactions in thelatter - but the unique arrangement of the two rings often introducesother factors which can dominate in terms of overall molecular energy, and which may, therefore, define conformational preference.

For example the two bicyclic alcohols (39) and (40) were synthesised[45] and, using $Eu(dpm)_3$ as shift reagent, in conjunction with decouplingexperiments, relevant coupling constants were extracted. Comparison of these with steroidal values (Figure (15)) suggested that (40) had an equatorial hydroxyl group and an almost ideal chair conformation for the cyclohexanol ring. The conformation of the other ring of (40) could then only reasonably be a boat, if overwhelming interactions of the methyl group with H-3 were to be avoided.



(41) (42)



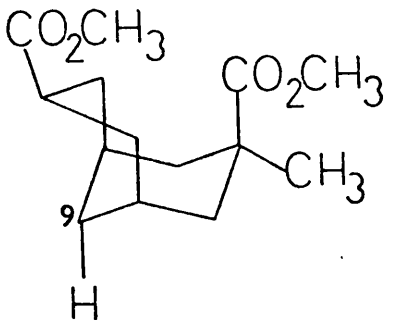
(43)

However, the situation with (39) was less obvious, although from J values, there was little doubt that the hydroxyl group was axial. By consideration of the Karplus relationship, the deviation from steroidal values could be interpreted either as a flattening of the cyclohexanol ring or as a contribution from the boat conformation. Assuming, again, a chair cyclohexanol ring, as for epimer (40), the methyl cyclohexane can only exist as a boat. Further evidence for the boat-chair conformation of (39) is gained from the fact that H-8α is more deshielded in the shifted spectrum than H-2β - i.e. H-8α must be proximate to the hydroxyl group.

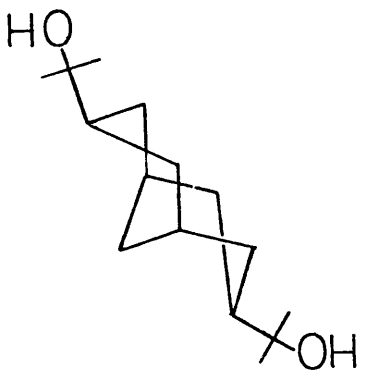
The above, then, would be a typical simple conformational analysis of substituted bicyclo (3.3.1) nonanes, and the outcome is a pronouncement of the predominant conformation. (It would remain to be shown that the conformation of the molecule did not change on complexation with the shift reagent, and this is normally done by monitoring coupling constants as the proportion of shift reagent is increased. The coupling constants should be insensitive to such changes.)

In an interesting series of papers[46-48] a Dutch group has made several important studies of other bicyclo(3.3.1) nonanes, e.g. the symmetrical di-endo diester (41) was shown[46] to exist as a rapidly equilibrating mixture of bc/cb conformers, (41) and (42), using coupling constant data similar to that outlined above.

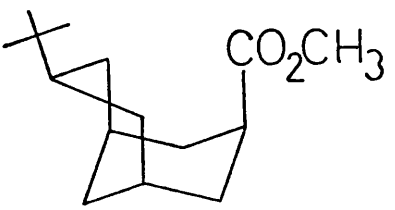
This early - and not unexpected - result was substantiated by examining[48] the fused system (43) in which that half of the



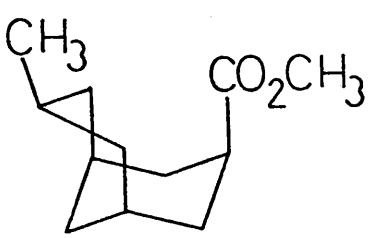
(44)



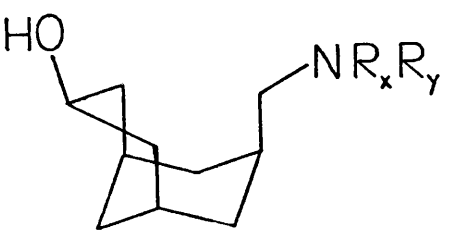
(45)



(46)



(47)



(48)

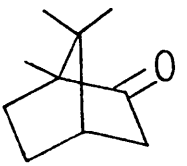
bicyclic system containing the axial ester group is locked in a chair conformation. Vicinal coupling constants indicate that the flexible three-carbon bridge exists predominantly as a boat, although there is significant flattening of the latter giving partial release from flagpole interactions.

In contrast to the rapid equilibrium (41) $\rightleftharpoons$ (42), (44) exists predominantly in the conformation shown,[48] with the methyl substituent acting as a locking group; the alternative cb form of (44) would incur prohibitive steric compression of the methyl group and proton on C-9 shown.

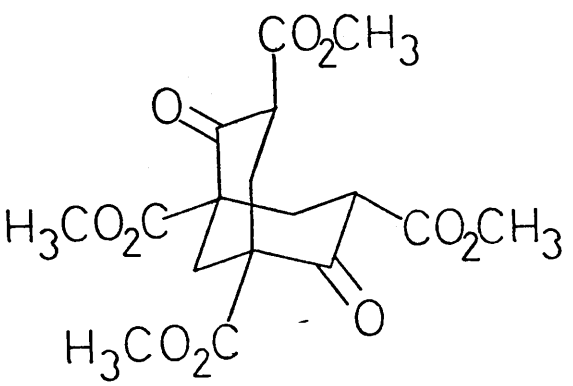
Increases in the steric bulk of endo substituents on C-3 and C-7 can enforce a double boat (bb) conformation[46] - e.g. diol (45). Further, altering[47] only one (effectively) of these substituents returns the molecule to a boat-chair, (46). Somewhat surprising is the observation[48] that the methyl analogue (47) of (46) has its ester group axial; expected flattening of the chair is noted here.

The conformations of compounds of the type (48) have been studied by Kovacic,[49] and as a rule of thumb, the populations of cb and bb conformers seem to depend on the sizes of the alkyl groups Rx, Ry.

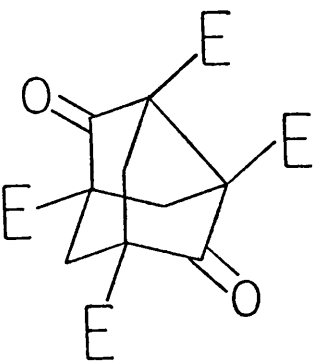
Indeed, in conclusion, this is the general trend - although there are exceptions - in bicyclo (3.3.1) nonanes with endo substituents on C-3 and C-7: the twin-chair conformation is destablised and bc or cb mainly preferred. That endo-substituent with the smaller 1,3-diaxial interactions will normally be in the chair-ring. Additionally, flattening of the rings may occur to alleviate strong steric compressions.



(49)



(50)



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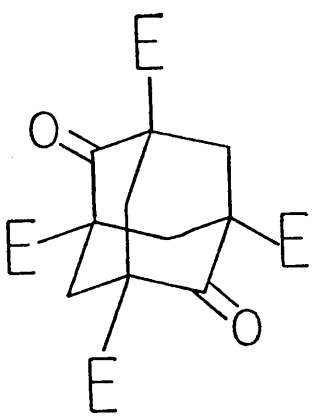
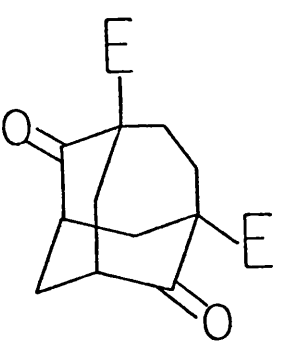
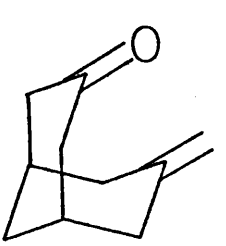


(52)



(53)

$E = CO_2R$



(54)

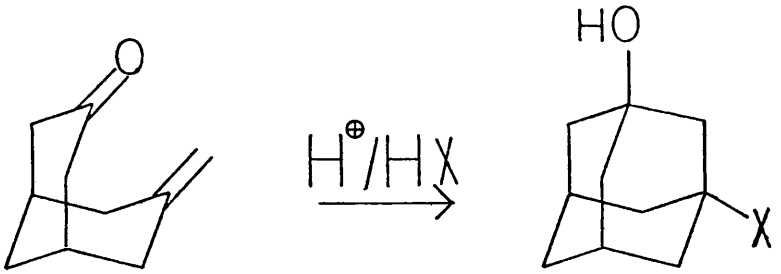
Of greater practical importance is the chemical reactivity of the bicyclic compounds, and this is now discussed.

(b) Reactivity of Bicyclo(3.3.1)nonanes

As stressed above, reactivity will sometimes involve short-lived (i.e. thermodynamically disfavoured) conformers; but regio- and stereo-selective transformations can also be manifestations of the most stable molecular conformation, just as hydride attack on camphor (49) proceeds exclusively from the endo face giving[50] isoborneol.

Early recognition of the spatial proximity of C-3 and C-7 of di-chair bicyclo(3.3.1)nonanes resulted in the first ring closure reactions to both adamantane and noradamantane skeletons. Thus in 1922, Meerwein[51] succeeded in forming the noradamantane (51) by treatment of (50) (now Meerwein's salt) with bromine under basic conditions. Logical extension of this idea produced the adamantane[52] (52) and later the homoadamantane[53] (53), essentially by inserting one- and two-carbon fragments, respectively, into a bicyclic precursor.

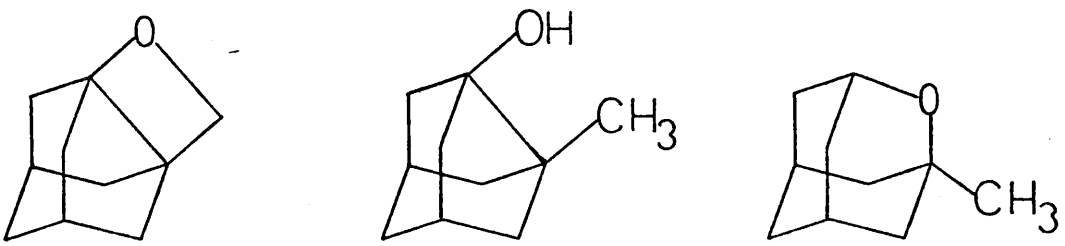
Possibly the most widely-studied ring closures of bicyclo (3.3.1) skeletons have been those possessing sp^2-hybridisation at either C-3, C-7 or both. The delightful ease with which the exomethylene ketone (54) will close to tricyclic products is readily understood when a molecular model is examined: in the twin-chair form (almost certainly the stable conformer) there is a striking alignment of carbonyl and olefin Π-orbitals making annulation of some description virtually inescapable. Hence the spectrum of reactions[54-56]



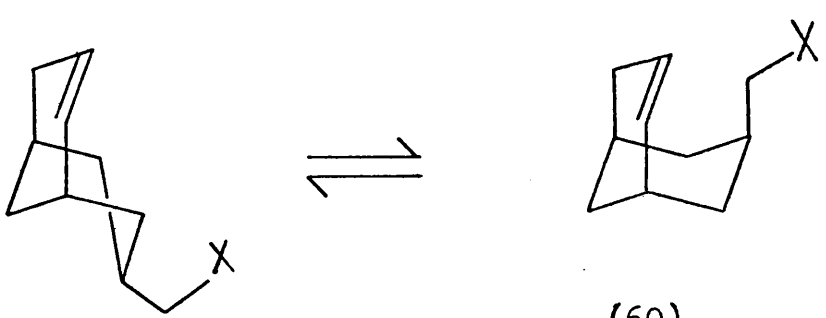
(54) (55)

X=OH, OEt, NHAc, NH_2.

Figure (16)

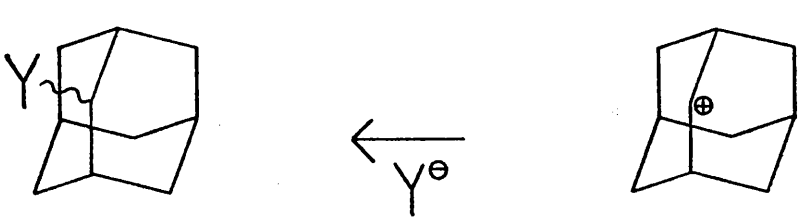


(56) (57) (58)

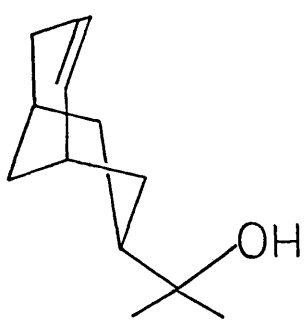


(59) (60)

Figure (17)



(62) (61)



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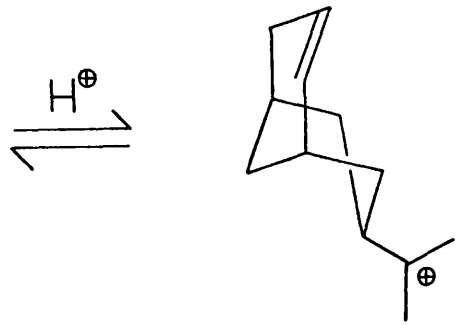
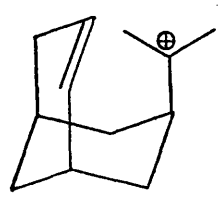
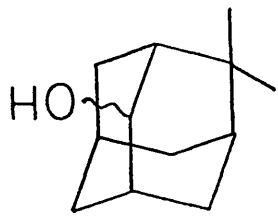


(65)



(65')



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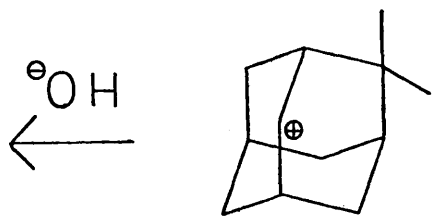


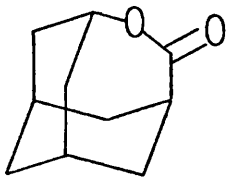
(66)

in Figure (16), all of which must involve protonation of the carbonyl group then participation by the olefin, thus constituting a ' Π -route' to adamantanes.

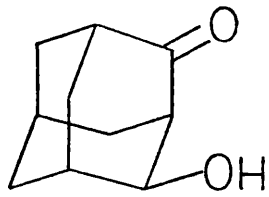
Under different conditions, other tricylic products result, all of which might reasonably be anticipated. Irradiation[57] of (54) effects a (2 + 2) cycloaddition giving oxetane (56) and the noradamantanol (57), and the latter is also the product of an attempted[57] di-imide reduction of (54). Also, after earlier reports[58] to the contrary, it now appears[59] that oxaadamantane (58) is the major product of lithium aluminium hydride reduction of (54).

Ring-closures involving Π -participation are not confined to the above types where C-3 and C-7 are both trigonal; several examples of the type shown in Figure (17) have been recorded. Regardless of the identity of X (provided it is an effective leaving group), the cb (59) is the expected[60] major conformer, and it is evident that ring closure cannot take place directly from it - i.e. dichair (60) must contribute to the conformational equilibrium. Π -participation in the displacement of X then gives rise to cation (61), the latter being captured by a nucleophile Y. As an example, the tertiary alcohol (63) is converted[61] to the epimeric alcohols (64) by such a pathway. In acid, the tertiary carbonium ion (65) may be invoked and, after a conformational flip and cyclisation, the resultant dimethyladamantyl cation (66) is quenched by addition of hydroxide ion.

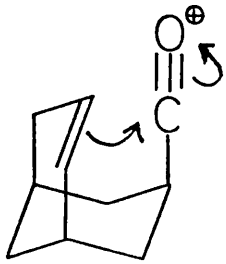
A related transformation - albeit not immediately recognisable as such - is the conversion of adamantanone



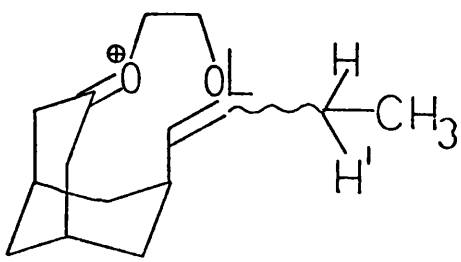
(67)



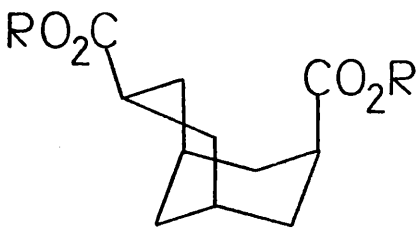
(68)



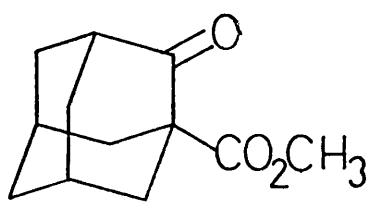
(69)



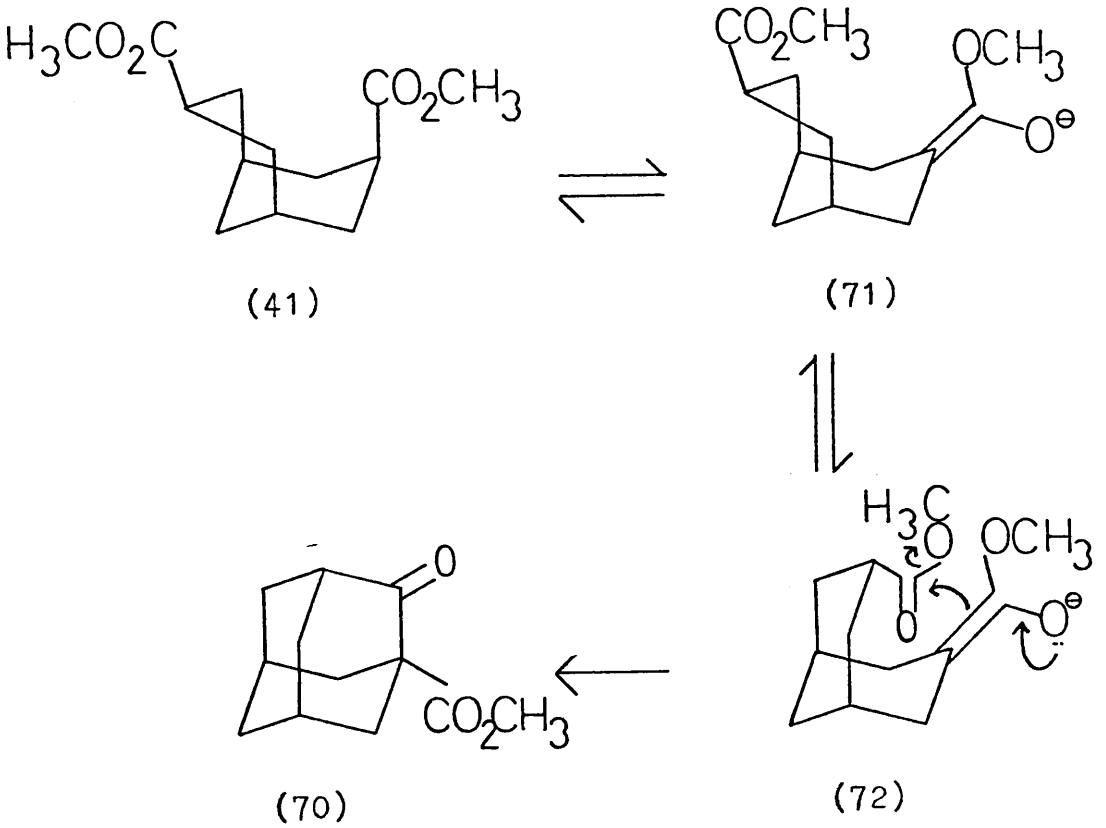
(30)



(41), R=CH_3



(70)

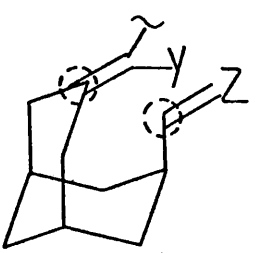


(41) (71)

(72)

(70)

Figure (18)



(73)

lactone (67) to hydroxy-ketone (68) under acid catalysis. A postulated[62,63] intermediate is the acylium ion (69) which may cyclise as indicated by the arrows, again forming a cation (cf. (66)) which is then consumed by water giving (68). The product is a single epimer, that having the hydroxyl group in the more stable axial position with respect to the cyclohexanone ring, and is thought[63] to be the product of thermodynamic control.

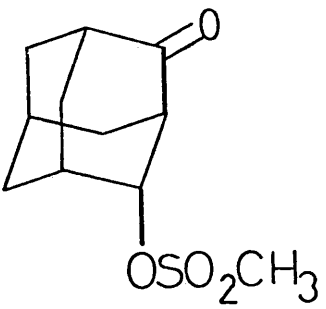
Returning to the work of Peters et al., there is found[48] a cyclisation which, formally at least, has especial significance in relation to the proposed S_E' cyclisation of (30). This concerns conversion of the symmetrical diester (41) to keto-ester (70) in the presence of methanolic sodium methoxide. A plausible mechanistic pathway is shown in Figure (18). The crucial step is that of (72) to (70) in which there is carbanion attack on an ester carbonyl, a step involving a high energy twin-chair conformer. Translation of (72) into generalised terms (e.g. (73)) reveals a fundamental relationship with (30). Thus formation of an adamantane from either (30) or (72) involves

(a) a thermodynamically disfavoured twin-chair conformer, and

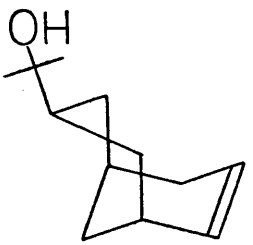
(b) interaction of two identically situated sp^2-hybridised carbon atoms (circled atoms in (73)).

- a solid analogy enforced in part by the alternative Π-route to adamantanes (cf. (69))

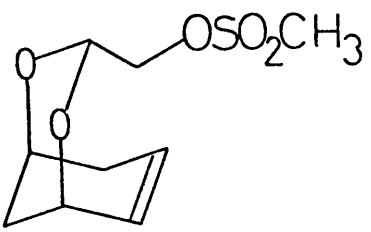
The driving force for these cyclisations is, presumably, formation of the relatively unstrained adamantane nucleus.



(74)



(63)



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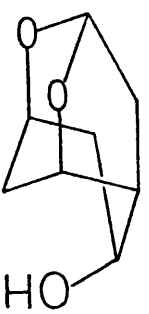
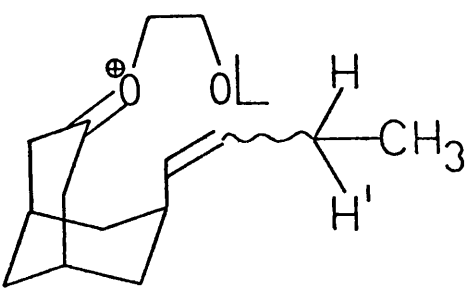


(75)

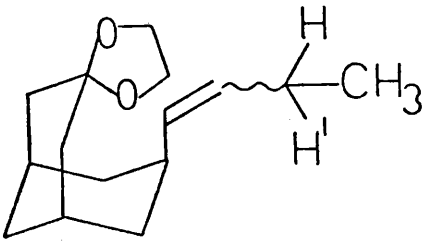


(30)

Memorable features emerge from a study of bicyclo (3.3.1) nonane-adamantane interconversions, which highlight the roles of conformation, entropy and stereoelectronic factors in chemical reactions. Indeed, with something of a poetic licence, one could describe the bicyclic systems as primitive enzymes since reacting groups are often brought into spatial proximity with correct orbital alignment, thereby effecting reactions of high specificity. This is as pertinent to the fragmentation of adamantanes to bicyclic products as to the reverse process. For example, treatment of the keto-ester (74) with methyl Grignard results[64] in formation of alcohol (63), a transformation in which parallel alignment of the heavy bonds in (74) is stereoelectronically ideal for the observed fragmentation.

And the synthetic chemist has not been slow to use the 'bridging' features of bicyclo (3.3.1) skeletons as regio- and stereo-specific control elements. In a cleverly conceived prostaglandin synthesis, involving a cyclohexane ring-contraction approach, Woodward and Ernest[65] constructed the alcohol (75) by a solvolysis of the dioxa-bicyclo (3.3.1) nonene (76). It is thought that the "three-centred electron-deficient intermediate accepts the elements of water at the most favourable location to give exclusively"[66] (75).

Briefly, then, for a suitably substituted bicyclo (3.3.1) nonane, the driving force for tricyclic product formation is evidently high and sufficient analogy exists to view the projected S_E' cyclisation of (30) in an optimistic light.



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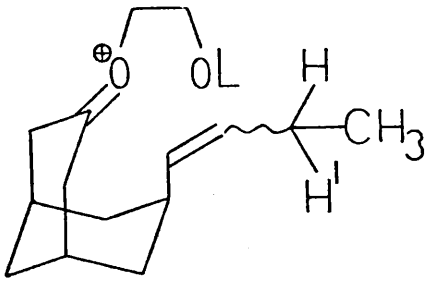

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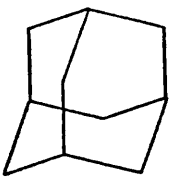

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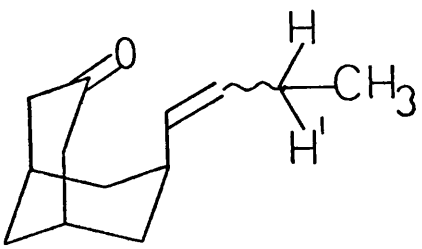
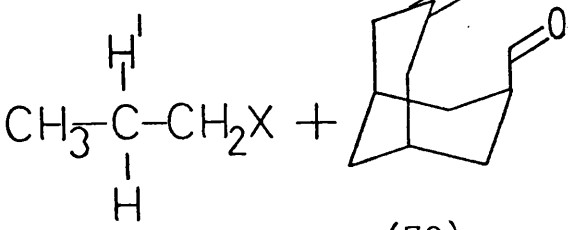
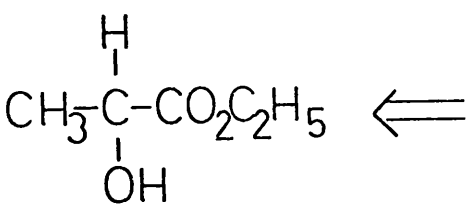


(77)



(78)

(79)



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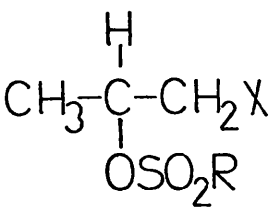

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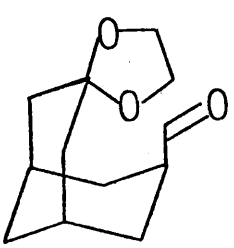


(83)

(v) Retrosynthesis of Model System

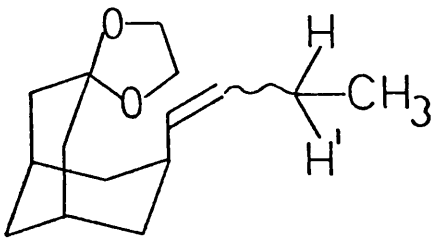
A literature search showed that bicyclo (3.3.1) nonanes with an endo-alkenyl substituent on C-7 had not been synthesized previously.

Inspection of molecular models had indicated that in the proposed transition states for the cyclisation of (30), fewer unfavourable steric interactions were incurred with E-(30); however, Z-(30) did not look prohibitive, and both isomers were sought.

Considering the acetal (29) (where H or H' is deuterium) as synthetically equivalent to enone (77), an obvious bond-disconnection at the olefin produces two synthons, a keto-aldehyde (79), and a three-carbon fragment (78). It was envisaged that the potentially vulnerable (79) would not be used as such, but more probably as a masked moiety, e.g. (83).

Recognition that the bicyclic component (79) contains the ten carbon atoms of adamantane (80) in the correct arrangement (i.e. endo-aldehyde), suggested a route to this dicarbonyl compound via fragmentation of a suitably functionalised adamantane. As noted above in the discussion of the reactivity of bicyclo (3.3.1) nonanes, the anti-periplanar alignment of certain bonds in the adamantane nucleus is favourable for fragmentations.[64]

The necessity for specific replacement of H or H', (29), by deuterium, meant that (78) would have to be a 'special' three-carbon fragment. Assuming that deuterium could be introduced by the S_N2 displacement of deuteride ion on a chiral secondary sulphonate ester,[67] (81) emerged as an



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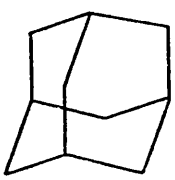
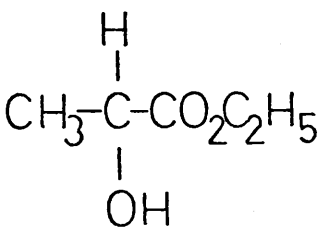


(80)



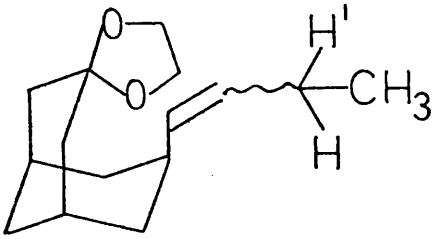
(82)

immediate precursor to (78) (where X is a group inert to deuteride ion). A convenient source of sulphonate (81) would be optically active ethyl lactate (82).

In the synthetic direction, a Wittig olefination between aldehyde (83) and (78) (where X = $^{+}PPh_3$ I^{-}) was anticipated, and available methodology[68] expected to allow specific introduction of E- and Z- olefinic bonds by choice.

To summarise, then, an adamantane nucleus and optically active ethyl lactate were chosen as basic materials for the synthesis of E- and Z- (29).

(vi) Discussion



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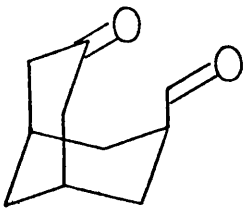

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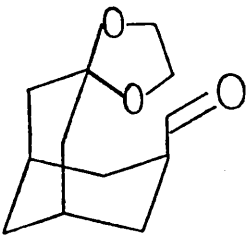

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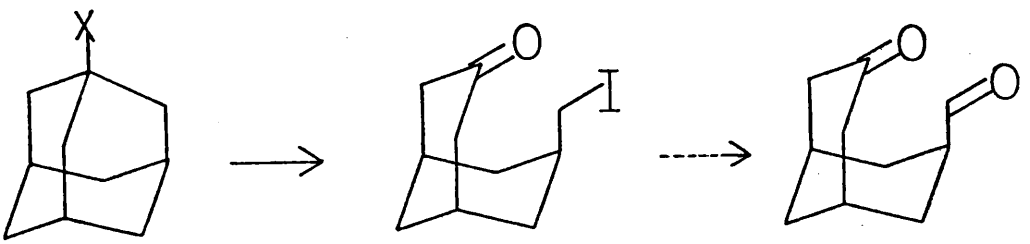
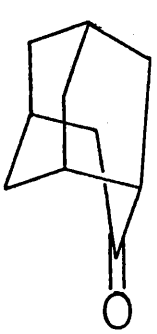


(84) , X=H
(85) , X=Br
(86) , X=OH
(87) , X=OI

(88)

(79)

Figure (19)



(89)

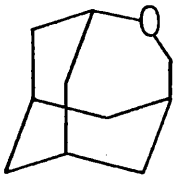
Discussion

Initial studies directed towards the synthesis of target molecule (29) did not attempt to introduce the required deuterium label - the initial target was (29) (E and Z olefins), where H = H' = proton. Unless otherwise stated, the structures of bicyclo (3.3.1) nonanes drawn do not imply any preferred conformation.

(A) Iodoketone Route

The first route chosen to synthon (79) (or (83)) was that of Figure (19). Adamantan-1-ol (86) was obtained from the parent hydrocarbon (84) via bromide (85) by standard procedures.[69] Heating (86) with iodine in the presence of lead tetraacetate produces[70,71] the reactive hypoiodite (87) which fragments under the reaction conditions giving the thermolabile iodoketone (88) as a dark and unpromising oil. Crystallization of this oil at low temperature from methanol was possible, but it was normally used as obtained.

The direct conversion of primary iodides and tosylates to aldehydes by dimethyl sulphoxide in the presence of mild base (sodium bicarbonate) is a familiar transformation,[72] but normally requires elevated temperatures, a feature seemingly incompatible with the thermolabile iodoketone (88). However, a favourable aspect was the short reaction time (generally < 5 mins) and so a small-scale oxidation of (88) to (79) was attempted. The result was a mixture of products, the ^{1}H.m.r. spectrum of which showed no aldehydic signal. Purification gave the known[70,71] tricyclic ketone (89) as major product; this arises by base-catalysed enolisation of the ketone in (88) followed by carbanion displacement of iodide



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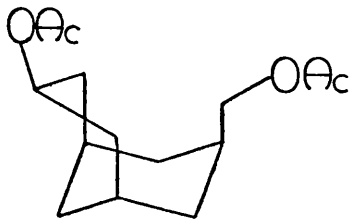

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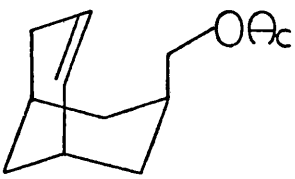
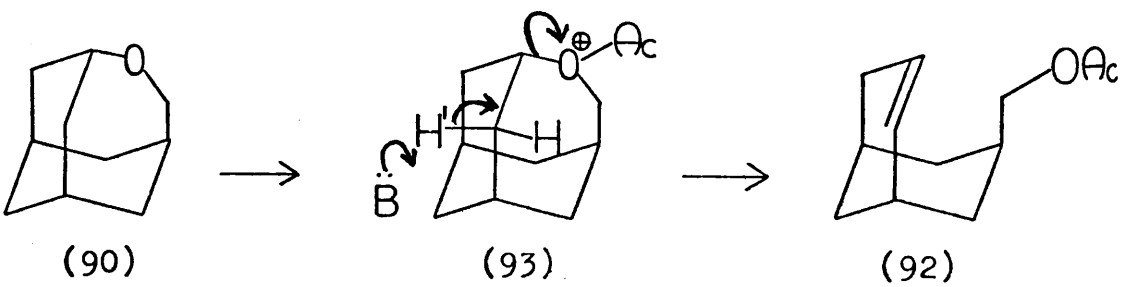
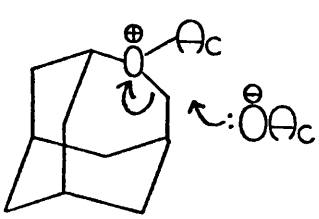


(92)



(90) (93) (92)

Figure(20)



(94)

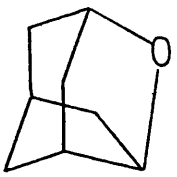
ion. An authentic sample of (89) was made[70,71] for the purpose of comparison.

An attempt to overcome the enolisation problem by prior sodium borohydride reduction of the carbonyl group also met with failure, producing only the highly crystalline ether oxahomoadamantane (90). (90) was known[73] to be the product of lithium aluminium hydride reduction of (88), and was identified by its characteristic downfield signals in the ^{1}H.m.r. spectrum, and by its I.R. spectrum (no O-H or C=O).

(90) was still potentially useful, if it could be induced to open, to give, e.g. diacetate (91), in analogy with Brun[74] and Magnus.[75] Treatment of (90) in ether with boron trifluoride diethyl etherate and acetic anhydride at 0^o produced a complex mixture of products (>5 by t.l.c.), A marked simplification of products resulted by using acetic anhydride as both solvent and reactant at low temperature (-78^o), giving the non-crystalline acetate (92) as major product (40% allowing for recovered (90)), having the expected I.R. absorptions at 3010, 1745 and 1235 cm^{-1}. The olefinic signals in the ^{1}H.m.r. spectrum were complex[76] due to multiple coupling; the doublet at 4.18 δ ($-CH_2-OAc$) had J = 6Hz, a coupling constant twice that in oxahomoadamantane (90).

A mechanism for the production of (92) is shown in Figure (20), where an anti-periplanar relationship between the C-H' bond and the breaking C-O bond in (93) facilitates the observed fragmentation.

The required diacetate (91) would arise by attack of



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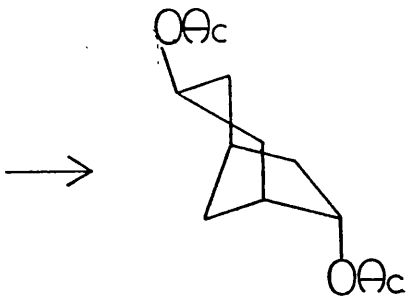
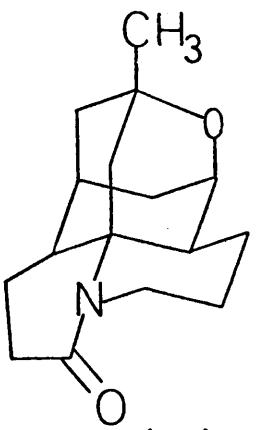


(96)



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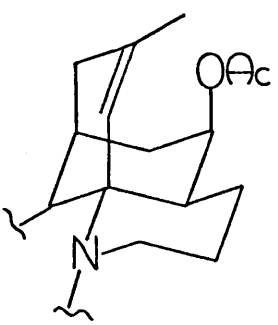

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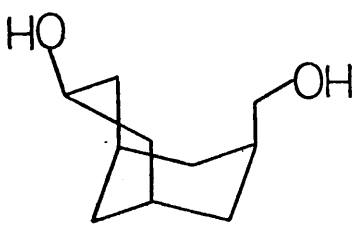

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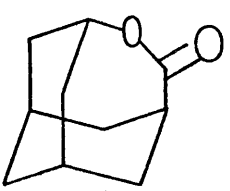
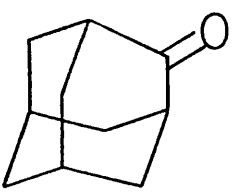


(67)



(100)

acetate ion on the oxonium ion at the kinetically favoured position, as in (94).

Failure to open (90) satisfactorily was disappointing in view of the successful cleavage of (95) to (96) by Brun,[74] in 90% yield under similar conditions. But, in contrast, Ayer[77] has noted that the lactam-ether (97), a relative of lycopodine, on treatment with boron trifluoride and acetic anhydride gave only acetate (98).

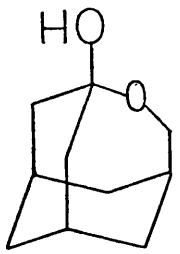
Inspection of molecular models suggested that in (92) the olefinic carbons would be equally accessible to an approaching reagent, making selective functionalisation - and hence the eventual formation of (91) - unlikely, an observation substantiated by Ourisson's work[78(a)] on a related system. Thus acetate (92) was not further investigated.

(B) Selective Oxidation Route

Having recognised that the diacetate (91) was potentially useful, a more facile route towards a molecule of this type was sought. The known[76] diol (99) was an ideal starting point in this respect, and was readily available by reduction of lactone (67), the Baeyer-Villiger oxidation product[63] of adamantanone (100).

The diol (99) was a relatively insoluble compound, and this could explain the somewhat low reported[76] yield (60%) from lactone (67). However, by continuous extraction of the aqueous layer after acidic work-up of the reduction, yields of 90-95% could be achieved routinely. The diol (99) crystallised beautifully from water.

Means were then sought to selectively functionalize (99):



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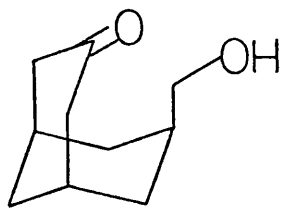
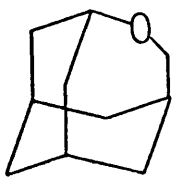


(102)



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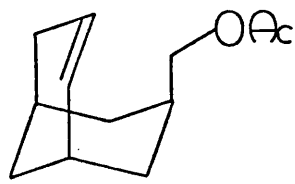

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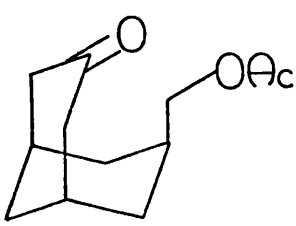

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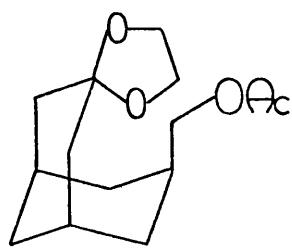

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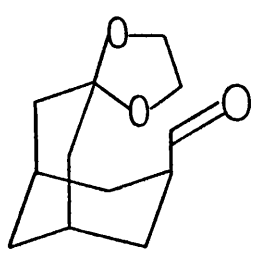
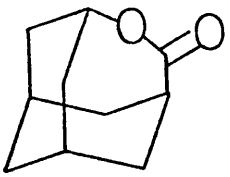


(83)

an attempt to form a monotetrahydropyranyl ether at low temperature failed, but by using a two-phase chromic acid oxidation[79] at 0°, hemiacetal (101) and keto-alcohol(102) could be obtained as an inseparable mixture, in ca. 80% yield.

The crystalline mixture was homogeneous on t.l.c. in several solvent systems, and on g.l.c.. The I.R. spectrum showed both OH (3600 cm^{-1}) and C = O (1720 cm^{-1}) absorptions. The ^{1}H.m.r. spectrum was particularly revealing, having a sharp doublet at 3.85 δ (J = 3Hz, relative integral 2H), a broad multiplet at 3.35 δ (relative integral 1H), and a sharp singlet at 2.80 δ. On D_2O exchange, the 3.85 δ doublet remained unchanged, but the upfield (3.35 δ) multiplet sharpened to a doublet, J = 6Hz; the 2.80 δ singlet disappeared (OH protons). From this, and by comparison of the $-CH_2-O$ doublets of oxahomoadamantane[73] (J = 3Hz) and acetate (92) (J = 6Hz), the doublets at 3.85 δ and 3.35 δ were assigned as the $-CH_2-O$ protons of the hemiacetal (101) and keto-alcohol (102), respectively. The ratio of (101) to (102) was ca. 2:1.

Acetylation of the mixture of (101) and (102) in the usual way gave keto-acetate (103), whose I.R. spectrum showed two carbonyl absorptions (1745, 1715 cm^{-1}) of equal intensity. The ^{1}H.m.r. spectrum showed only one doublet (at 3.80 δ) having J = 6Hz and the expected acetate methyl. Thus, apparently, the hemiacetal (101) had opened under basic conditions and was then trapped irreversibly as the ester (103).



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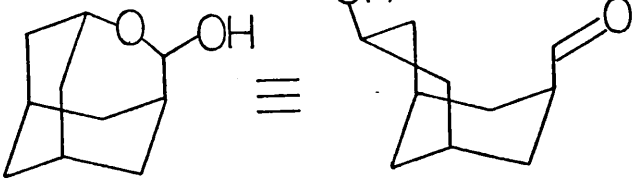
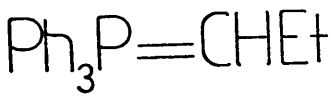
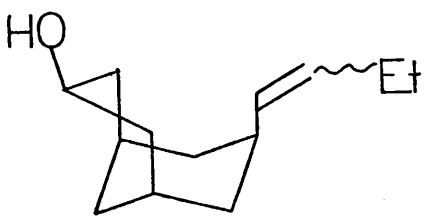


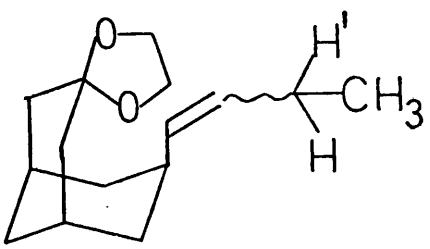
(105) ≡ (106)



(107)



(108)



(29)

The ethylene acetal (104) was obtained without incident; its relationship to the desired synthon (83) is apparent.

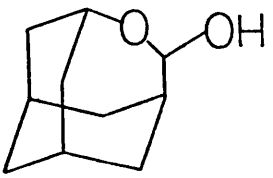
However, at this stage, this route was kept in abeyance, partly because the selective oxidation step, (99) → (101) + (102), produced significant quantities of by-products on scaling-up, but mainly because of developments regarding a more direct route to target molecule (29), as outlined below.

(C) Lactol Route

The usual lithium aluminium hydride reduction of lactone (67) to diol (99) was performed in refluxing tetrahydrofuran, over 36 hours. On one occasion, monitoring of the reaction mixture by g.l.c. revealed a transient component, intermediate in retention time between the diol (99) and the lactone (67). Logically this could only be the partial reduction product of (67) - viz. lactol (105).

Lactols, the cyclised forms of hydroxy-aldehydes (see (106)) have been utilised by Corey,[66] and subsequently others,[66] for Wittig reactions in the syntheses of various prostaglandins. A Wittig reaction on (105) using propylidenetriphenylphosphorane (107) should lead to (108), a molecule having the carbon skeleton of target molecule (29). Adjustment of the oxidation level of (108) would then give (29) itself. The use of propylidenetriphenylphosphorane is ideal for the introduction of a deuterium label (see p24).

The lactol (105) had not previously been reported, but conditions were readily established for its production:



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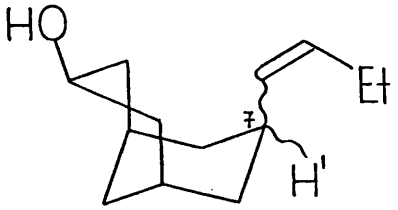
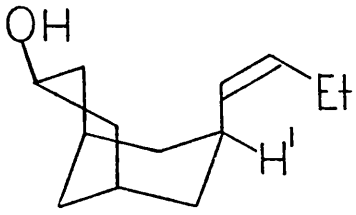


(109)

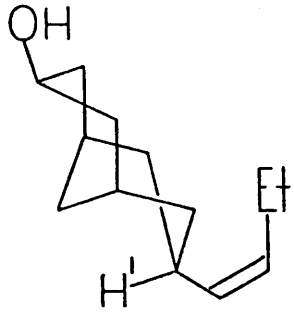
addition of a standard solution (not slurry)of lithium aluminium hydride in tetrahydrofuran to a stirring solution of lactone (67) in the same solvent at 0°, gave essentially quantitative yields. The ^{1}H.m.r. spectrum of product (105) had a low-field doublet (J = 3Hz) at 5.35 δ (O-CH-O) and a multiplet at 4.20 δ (O-CH-), but had no aldehydic signal; significant I.R. absorptions were at 3610 and 1050cm^{-1} (no C=O).

A Wittig reaction between (105) and (107) (two equivalents) in dimethyl sulphoxide as solvent gave an enol (109) as the only product. The olefin geometry was tentatively assumed to be Z- on the basis of literature precedent[80] and the absence of absorption between 10.3 and 10.4 μ in the I.R. spectrum.[80] The ^{1}H.m.r. spectrum showed the carbinol proton as a broad multiplet, $W_{\frac{1}{2}}$ = 30 Hz at 4.0 δ ($W_{\frac{1}{2}}$ = width of signal at half signal height), indicating that the cyclohexanol ring of (109) existed mainly in a boat conformation,[45] with the carbinol proton axial. However, of much greater importance was the configuration at C-7 of (109) - i.e. was the alkenyl side-chain endo or exo? It was conceivable that epimerisation had occurred during the Wittig reaction, and consequently that the enol product (109) had an exo alkenyl side-chain, although the short reaction time (ca. 2 hours), and high yield of a homogeneous product suggested otherwise.

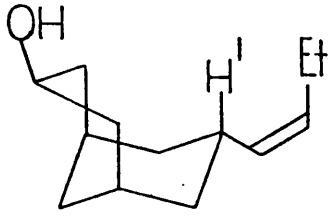
The signal from the allylic proton, H', on C-7 of (109) was an isolated multiplet at 3.10 δ, having $W_{\frac{1}{2}}$ = 28 Hz, its identity being established by double resonance experiments.



(109')



(109''')



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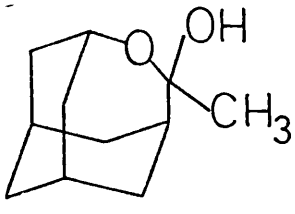
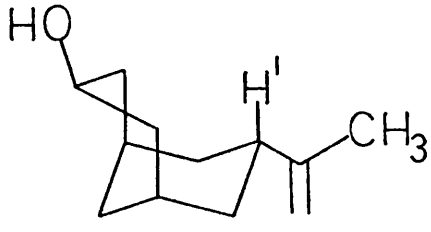
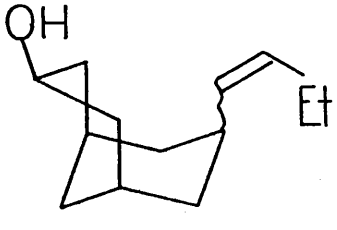


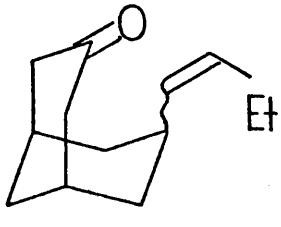
(110)



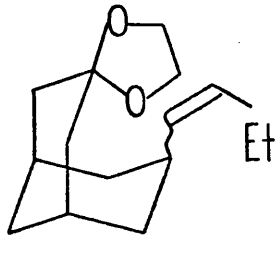
(111)



(109)



(112)



(113)

This large $W_{\frac{1}{2}}$ value suggests that H' is not equatorial, but that either

(i) in (109') there is significant flattening of the cyclohexane ring with some contribution from the twin-boat (109‴), or

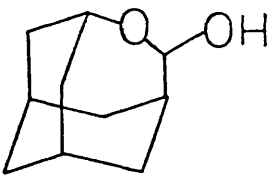
(ii) (109") is in fact the structure of the enol product.

Examination of the 90 MHz ^{1}H.m.r.spectrum in the presence of shift reagent, Eu(dpm)$_3$, was of little use since both H' and the olefinic protons experienced similar downfield shifts of about the same magnitude.

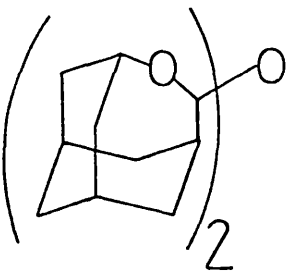
A search of the literature revealed that the hemiacetal (110) had been subjected[81] to a Wittig reaction, and that the product obtained was (111). But this sluggish conversion was incomplete even after heating for 60 hours in the presence of excess ylid, and under such conditions, epimerisation would not be unexpected. The ^{1}H.m.r. spectrum[81] of (111) did not show the allylic proton H' at low field, as was the case in (109).

One solution to the configurational problem in (109) was to convert it to acetal (113) and attempt the desired S_E' cyclisation: success would dissolve the dilemma. However, (113) proved to be inert to a variety of cyclisation attempts using various Lewis acids and solvents (see Experimental,p 63) apart from undergoing hydrolysis back to enone (112).

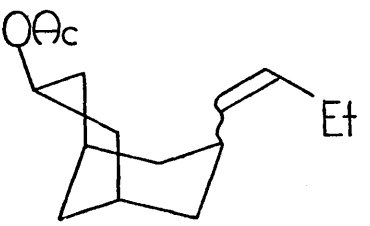
The situation regarding (109) thus remained unresolved, and attempts were now made to construct the E-isomer of target molecule (29) - recall that the S_E' cyclisation of E-



(105)



(114)



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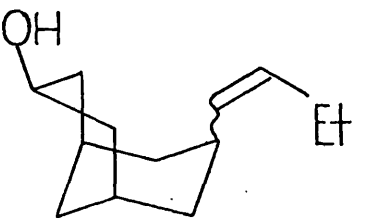
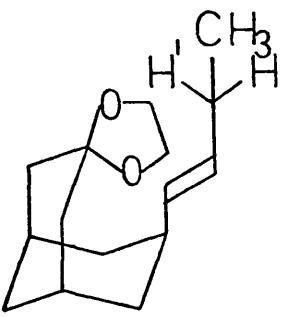
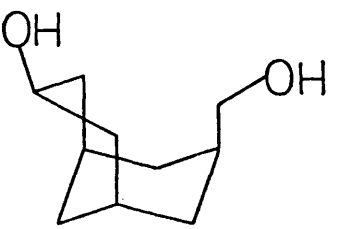


(109)



E-(29)



(99)

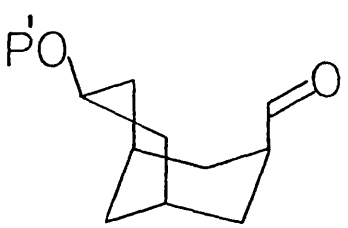
(29) had looked more promising than Z- (29), p 24 - by a fresh route.

However, a property of the lactol (105) deserves special mention at this point. Although this hemiacetal could be chromatographed and crystallised, if allowed to stand dry for 10-15 minutes, substantial quantities of the dimeric acetal (114) formed by dehydration. Similar dehydrations have been noted in other systems.[82,83] As a result of this tendency, the lactol had to be kept in solution (normally ethyl acetate) until required for the Wittig reaction, at which time the solvent would be removed rapidly on a rotary evaporator and the resulting solid dried for ca. 5 minutes on a vacuum pump before dissolution in dimethyl sulphoxide. On larger-scale runs, residual ethyl acetate could not be avoided, and varying amounts of acetate (115) resulted from the Wittig reaction, presumably by transesterification. The identity of (115) was corroborated by the conversions (115) to (109) and (109) to (115). Acid hydrolysis of the acetal (114) back to the lactol was easily accomplished.

(D) Schlosser Routes - Attempted production of E-(29)

The Schlosser modification[84] of the Wittig reaction, designed to produce predominantly E-olefins by equilibration of the intermediate betaines to the thermodynamically favoured threo-betaine, was chosen as the method for constructing E- (29).

Attempts to effect a Wittig-Schlosser reaction on lactol (105) failed, returning only starting material, and attention once again turned to the diol (99). This time an aldehyde



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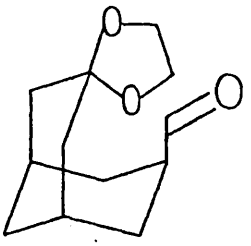
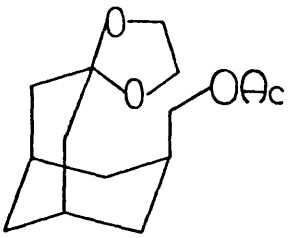
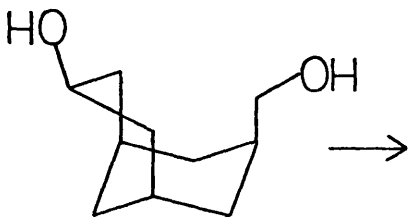


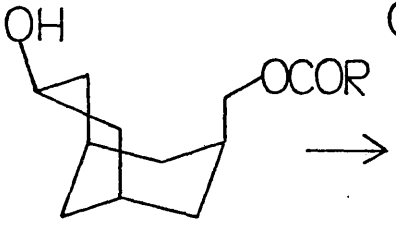
(83)



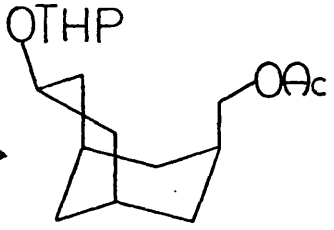
(104)



(99)

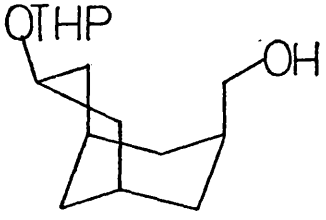


(118)
(118')

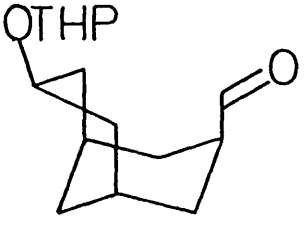


(119)

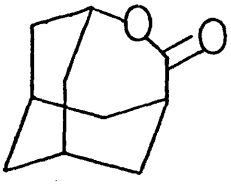
Figure(21)



(117)



(116')

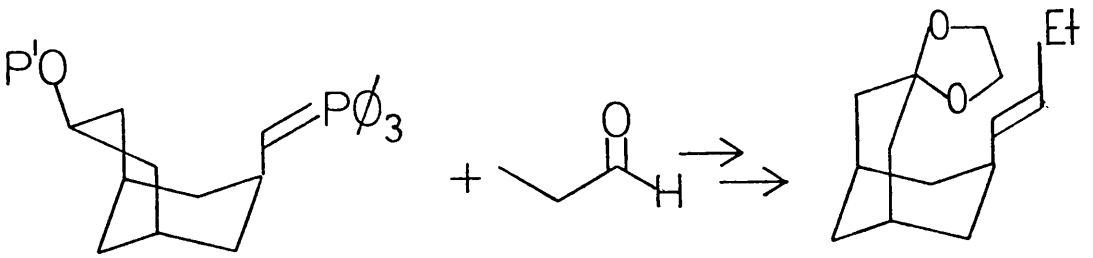


(67)

of the type (116) (P^1 = base-stable protecting group) was sought (cf. synthon (83)) by a route avoiding the technical difficulties encountered in the preparation of (104).

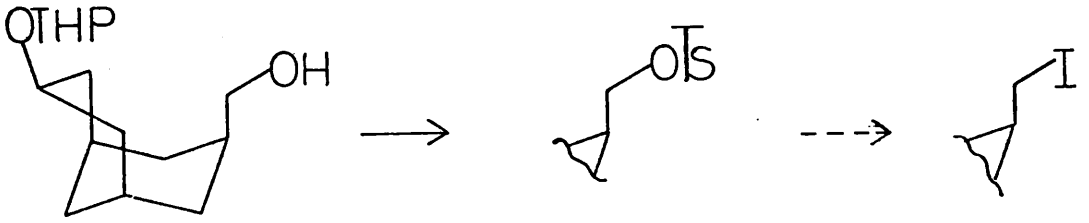
Figure (21) indicates how the alcohol (117) was made from (99). The monoacetylation was effected using one equivalent of acetic anhydride in pyridine in 90% yield (monobenzoylation to (118') was less selective); protection of the hydroxyl group giving (119) and the subsequent lithium aluminium hydride reduction to alcohol (117) were both essentially quantitative steps. The aldehyde (116') proved an elusive target: the acid-lability of the protecting group and epimerisation of the aldehyde were problems which beset the oxidation, despite attempts to use both "basic" and "neutral" oxidants - e.g., using Corey's pyridinium chlorochromate[85] with sodium acetate as buffer, at least six products showed on t.l.c., and the ^{1}H.m.r. spectrum indicated little aldehyde. Purification of this product by preparative t.l.c. (multiple elutions) yielded lactone (67) as the only recognisable product. This must have arisen by oxidation of (117) to the corresponding aldehyde (116'), hydrolysis of the THP-ether, cyclisation to the lactol and subsequent oxidation to the lactone!

Fetizon's reagent[86] in refluxing benzene did give substantial amounts (ca. 20% by ^{1}H.m.r.) of aldehyde initially, but prolonged reaction apparently caused epimerisation, indicated by the appearance of a second aldehydic signal in the ^{1}H.m.r. spectrum. But, even here, the reaction product was not clean (t.l.c.). Other methods tried were low temperature Jones (-20°),[87] modified Collins,[88] and



(120)

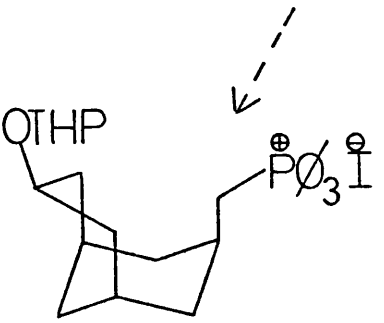
Figure(22)

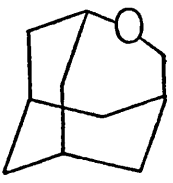


(117)

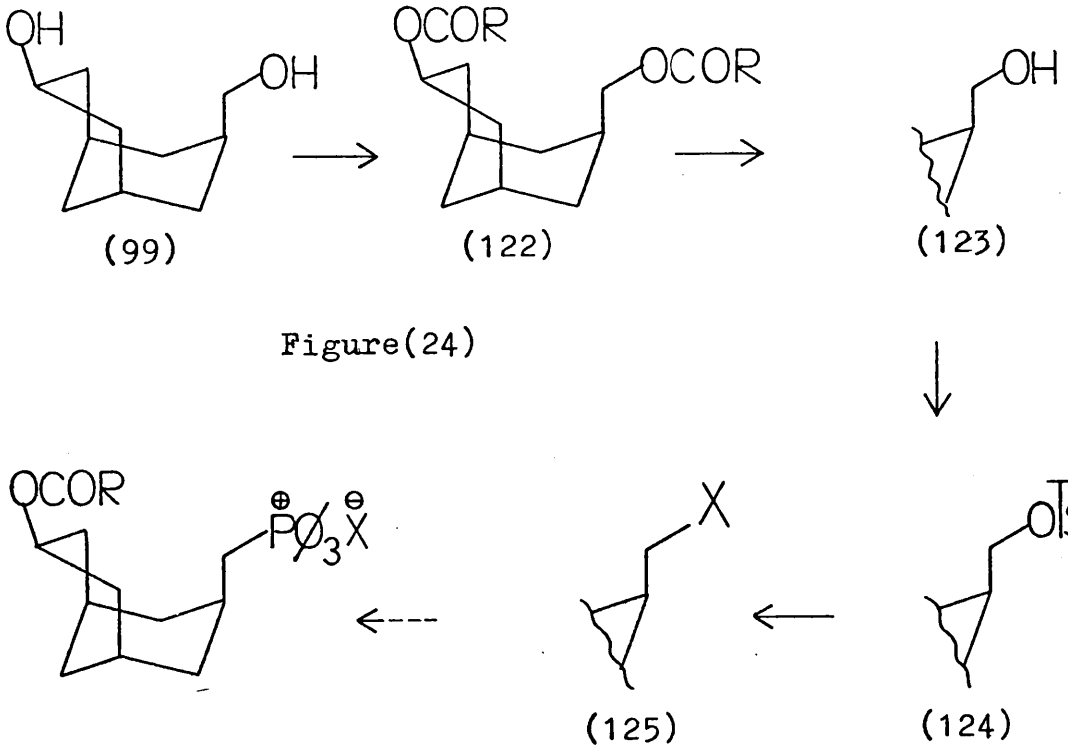
(121)

Figure(23)





(90)



Figure(24)

Figure(25)

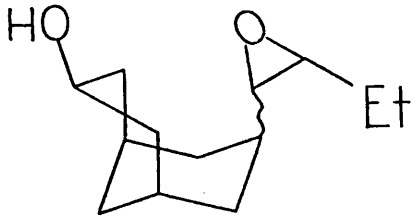
Oppenauer[89] oxidations, all of which produced small amounts of aldehyde and -apart from the Oppenauer - some lactone, but mainly what must be regarded as useless artefacts.

In an attempt to circumvent these unexpected problems, it was decided to "reverse" the components for the Wittig-Schlosser olefination - i.e. to use the bicyclononane moiety as the source of ylid and propionaldehyde as the carbonyl component (and three-carbon fragment), as in Figure (22).

The sequence outlined in Figure (23) was put into operation and tosylate (121) made, but treatment of this air-sensitive tosylate with sodium iodide in acetone at ambient temperature, and under an inert atmosphere, gave oxahomo-adamantane (90) as the major product. Its formation is rationalised by assuming hydrolysis of the THP-ether and then tosylate (or iodide) displacement by the naked secondary hydroxyl group.

With a molecule of type (120) still in mind, another sequence was probed, (Figure (24), R = CH_3 or Ph). The diol (99) was bis-acylated to diacetate (122) (R = CH_3) or dibenzoate (122) (R = Ph). Selective hydrolysis of the primary ester functions with potassium hydroxide in methanol at 0^o was effected in high yield, giving secondary monoesters (123). These were readily distinguished from their isomers (118), (118') by t.l.c. and ^{1}H.m.r. spectra. The halides (125) (X = Br, I) were then accessible via tosylates (124).

Encouraged by this success, the halides were confidently treated with triphenyl phosphine: but no phosphonium salts could be formed, even in benzene or acetonitrile at 100^o in



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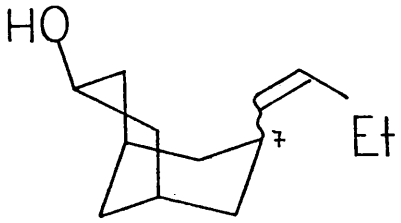


(109)

a sealed tube for extended periods - the halides appeared to be inert under most conditions. Similar treatment of the tosylates (124) failed to produce a reaction.

Such a lack of reactivity can only be attributed to steric hindrance - i.e. the large triphenyl phosphine molecule failing to approach within bonding distance of the $-CH_2X$ carbon atom, a most unexpected result.

Recognising that the only successful attempt to piece together the carbon skeleton of (29) had been that involving the Wittig reaction on lactol (105), all efforts were now channelled towards:

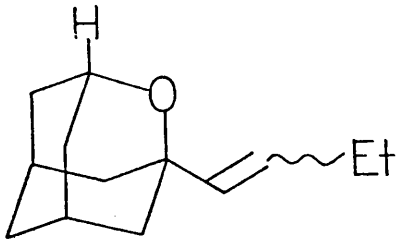
(i) Establishing, by chemical means, the configuration at C-7 of Z-enol (109), and

(ii) Producing E-enol (127) by inverting the olefin geometry of (109). Even in the event of (109) proving to have the 'wrong' (i.e. exo) configuration at C-7, it was felt that establishing methodology for an olefin inversion would still be a useful objective.

(E) Attempts to establish the configuration at C-7 of (109)

If, in fact, the alkenyl side-chain in (109) is endo, as required, then intramolecular addition of alkoxide ion to the olefin, when the latter is activated by an electrophile, should be possible, Figure (25). Three attempts were made towards this end.

(a) The epoxide (128) was made by m-chloroperbenzoic acid oxidation of (109); base treatment (butyl lithium or sodium



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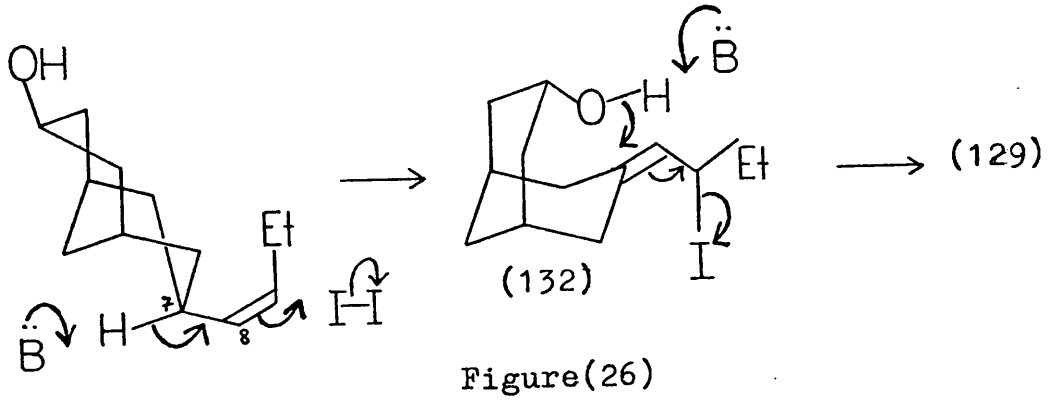
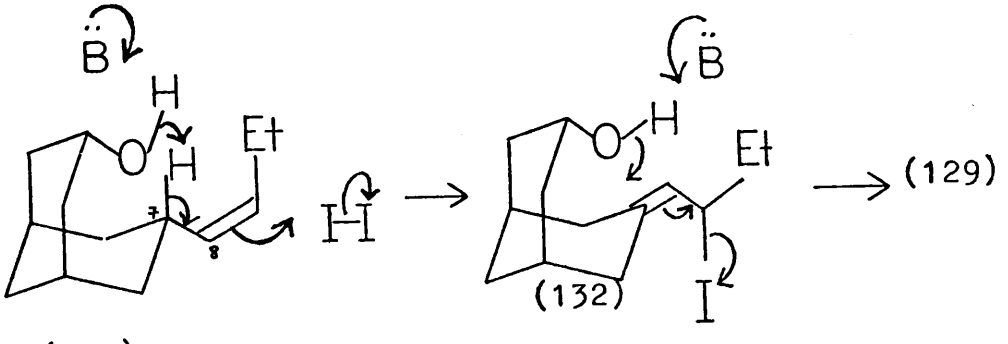


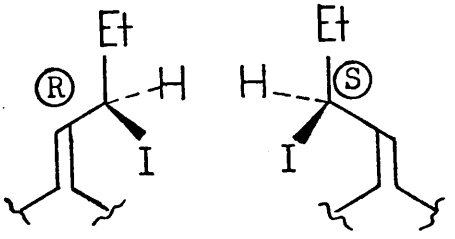
(130) (132)

Figure(26)

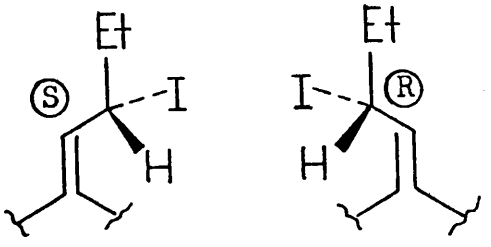


(131) (132)

Figure(27)



Figure(28)

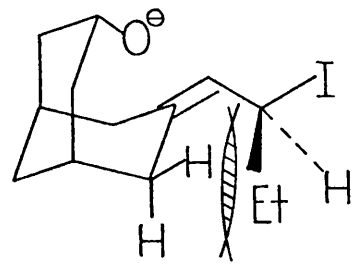


hydride) of (128) failed to produce any reaction.

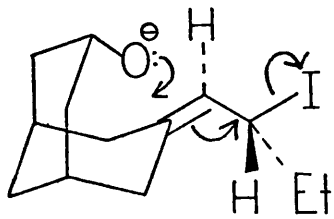
(b) Treatment of (109) in ether with iodine in the presence of dilute aqueous sodium bicarbonate - a method used[90] for converting prostaglandins to prostacyclins - produced a non-hydroxylic product, which, from the ^{1}H.m.r. spectrum still had two olefinic protons and a $-CH_2CH_3$ moiety. There was one other downfield signal, a one-proton multiplet at 4.1δ , having $W_{\frac{1}{2}}$ = 10 Hz. Structure (129) was assigned to this compound, an oxaadamantane, in which the apical proton shown is equatorial to the cyclohexane ring containing it, thus accounting for its small $W_{\frac{1}{2}}$ value of 10 Hz. Irradiation of the $-\underline{CH}_2CH_3$ protons at 2.05δ simplified the olefinic region to a clean AB quartet, J = 16 Hz, centred at 5.5δ . In the non-decoupled spectrum, the low-field limbs of the AB quartet were further split into triplets, J = 6 Hz. The ^{13}C.m.r. spectrum was in accord with (129), and the richly detailed I.R. spectrum showed intense absorption at 10.3μ . The suggestion from this was the presence of only one isomer, the E-olefin, although small amounts of the Z-isomer could not be discounted.

It is interesting to speculate on the mode of formation of (129), and pathways can be proposed starting from either epimer of (109), Figures (26),(27). The mechanisms involve an S_E2' step giving the iodoalcohols (132), and a subsequent intramolecular[59] S_N' displacement of iodide, producing (129).

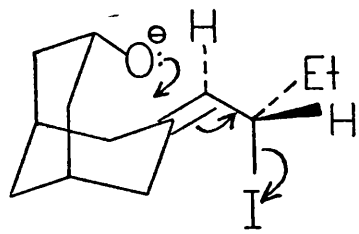
Due to the presence of two asymmetric features in iodoalcohols (132), they can exist as two diastereomeric pairs of enantiomers, represented schematically in Figure (28); and



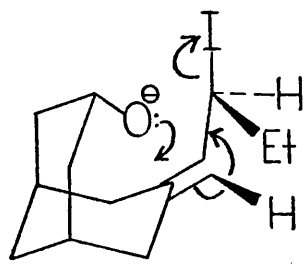
(133)



SYN → E- (129)



ANTI → E- (129)



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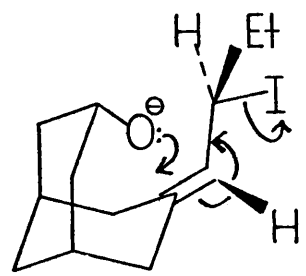
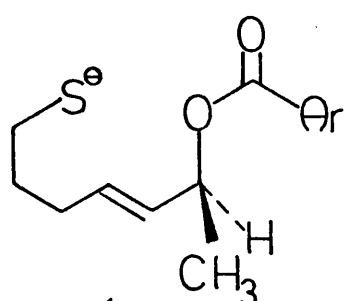


ANTI → E- (129)

Figure (29)



(5)

since in (130) and (131),

(i) the two faces of the olefin are equally accessible to iodine, and

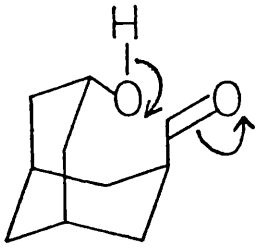
(ii) there is free rotation around the C-7-C-8 bonds, it follows that all four isomers should be formed, by syn and/or anti S_E2' mechanisms.

The subsequent transformation of (132) to (129) is, however, subject to certain steric constraints: in principle E- and Z-isomers could result, but in reality, the transition states leading to Z- (129) involve significant steric compression of the ethyl group with the bicyclononane skeleton, see (133). There is, therefore, a rationale for the preponderance of E- (129). As seen from Figure (29), syn and /or anti S_N' processes could give rise to E- (129), and there is a noteworthy similarity between these conversions and the recent S_N' model of Stork,(5).[13]

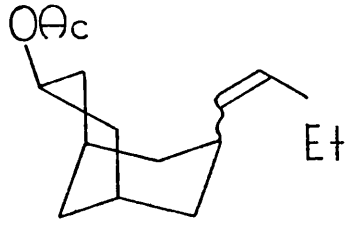
(c) Use of phenyl selenyl chloride as electrophile,[91] (Figure (25), again produced (129), but the greater complexity of the olefinic region of the ^{1}H.m.r. spectrum, and 'doubling' of some ^{13}C resonances, suggested a greater proportion of Z-isomer, than that in (b) above.

The perplexing problem of the configuration at C-7 of (109) thus still remained, although of the proposed mechanisms leading to (129), that of Figure (27) had a greater appeal.

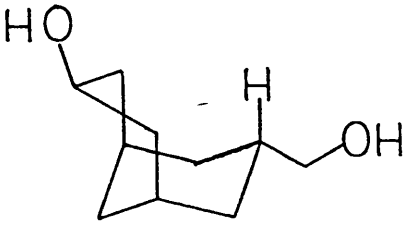
Ozonolysis of (109) (methanol and/or ethyl acetate), followed by reductive work-up using dimethyl sulphide,



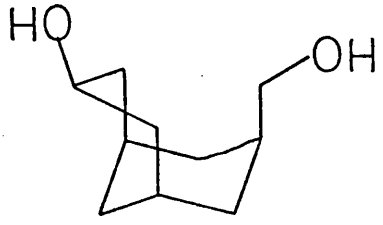
(134)



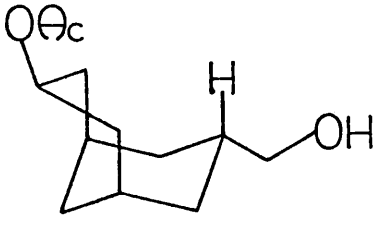
(115)



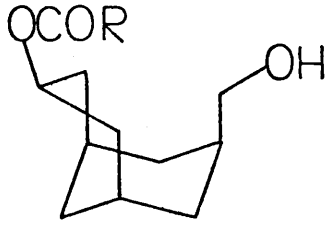
(135')



(99)



(135)



(123)

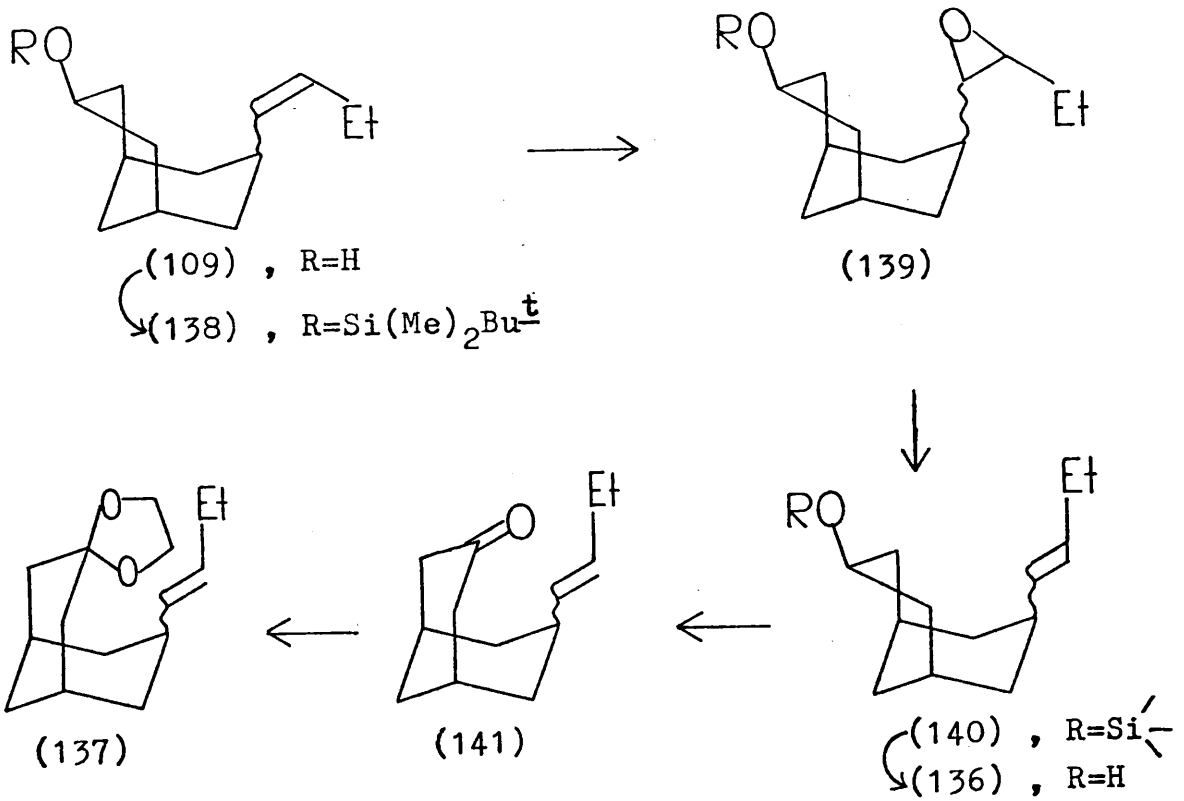


Figure (30)

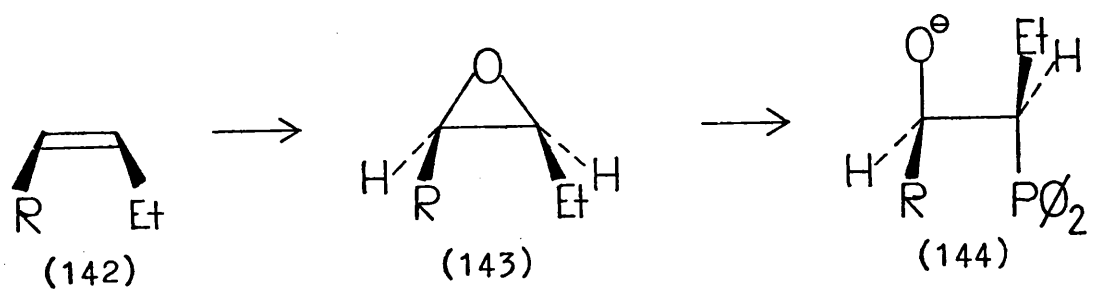
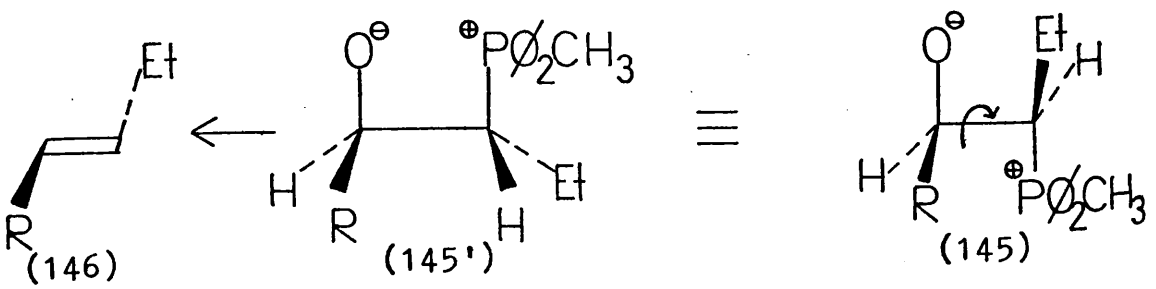


Figure (31)



repeatedly gave mixtures of products, none of which corresponded in polarity to lactol (105) - the anticipated product of closure of intermediate aldehyde (134).

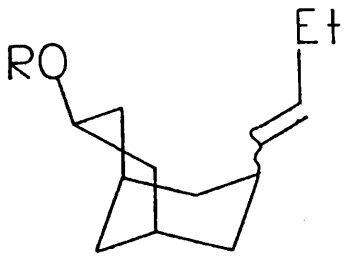
However, by using acetate (115) for ozonolysis and a lithium aluminium hydride reductive work-up, a mixture of hydroxy-acetate (135) and diol (135') could be isolated in ca. 50% yield; these products were distinguishable from their epimers (123) (R = CH_3) and (99), respectively, by t.l.c. and ^{1}H.m.r.

But the initial conclusion that the alkenyl substituent in (115) must have been exo, was tempered by the possibility that epimerisation of the intermediate aldehyde could have occurred under the basic (lithium aluminium hydride) work-up conditions.

(F) Production of E-enol (136) by an olefin inversion sequence - conclusive proof of the C-7 configuration

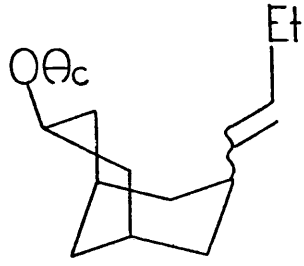
The Z $\longrightarrow$ E isomerisation of olefins can be effected either by photochemical or thermal chemical reaction.[68] The latter was selected since often the former produces only an equilibrium mixture of E and Z-isomers, which might have proven difficult to separate.

Figure (30) illustrates the route to E-enol (136), and its subsequent conversion to E- olefin acetal (137). The alcohol was protected as the tert-butyldimethylsilyl ether (138), this particular masking group[92(a)] being stable to base and to mild acid; epoxide (139) was obtained on m-chloroperbenzoic acid oxidation of (138). Sequential

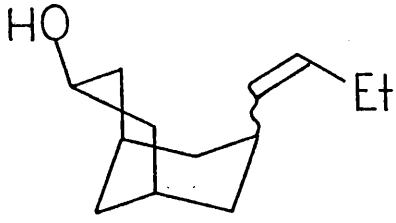


(140) , R=Si(Me)$_2$Bu^t

(136) , R=H



(147)



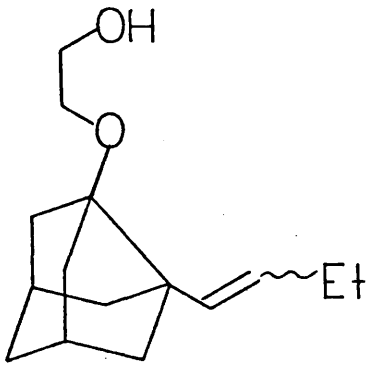
(109)

treatment of the epoxide with lithium diphenyl phosphide,[93] using tetrahydrofuran and hexamethylphosphoric triamide as solvent, followed by excess methyl iodide, gave E-enol silyl ether (140) (> 90% yield (139) ⟶ (140)). A mechanistic interpretation of this latter conversion[94] is shown in Figure (31) - the overall process may be described as '*anti* substitution' of the Z-olefin (142), followed by '*syn* elimination' to give, of necessity, the E-olefin (146).

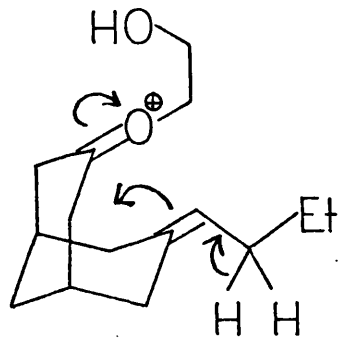
The use of hexamethylphosphoric triamide as cosolvent is absolutely essential, since in tetrahydrofuran alone, (as in the published procedure[94]) the yield of (140) from (139) was *ca.* 5%. Its function is probably two-fold, firstly promoting S_N2 attack[95] of the phosphide anion on the epoxide, and secondly facilitating phosphine oxide elimination[96] by solvating inorganic salts.

Deprotection of (140) was somewhat sluggish under the recommended conditions[92(a)] (AcOH:H_2O = 2:1; 50°). On increasing the ratio of acid:water (to 3:1) and using a temperature of 65°, consumption of (140) was more rapid, but the product alcohol (136) was accompanied by large amounts of acetate (147). The conversions (136) to (147), and (147) to (136) were performed, using standard methods, confirming the configuration of the acetoxy group in (147). Also by subjecting alcohol (136) to the deprotection conditions, it was shown that (147) arose from a simple esterification, and not, as had been first thought, by reaction of (136) with *tert*-butyldimethylsilyl acetate.[92(b)]

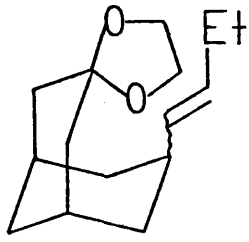
Satisfyingly the alcohol (136) was completely distinguish-



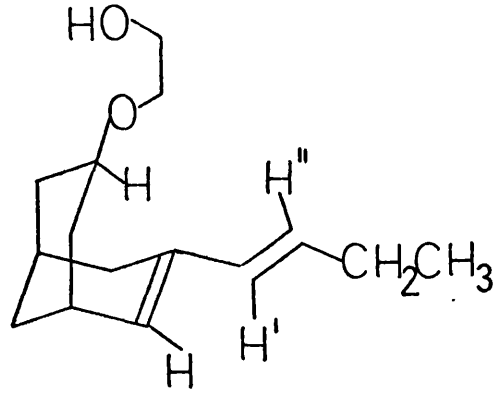
(148)



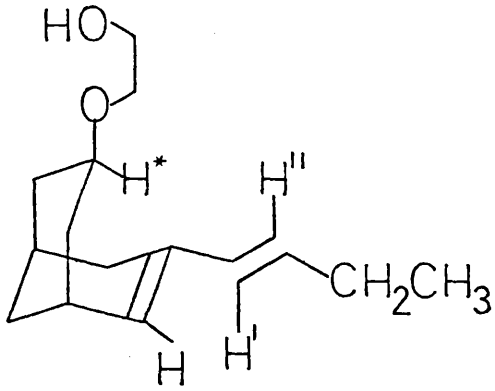
(149)



(137)



(150)

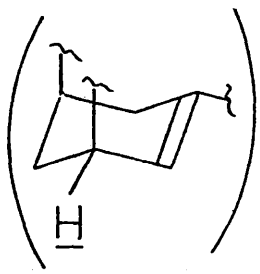


(150)

(a) Non-decoupled

(b) Irradiation at 2.05

(c) Irradiation at 2.40



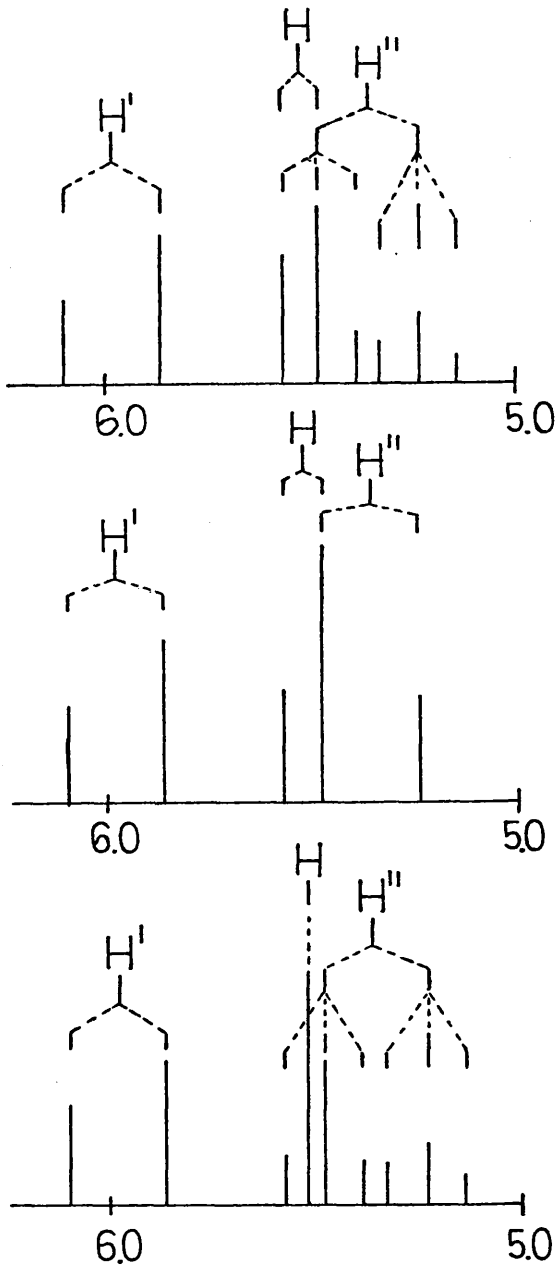


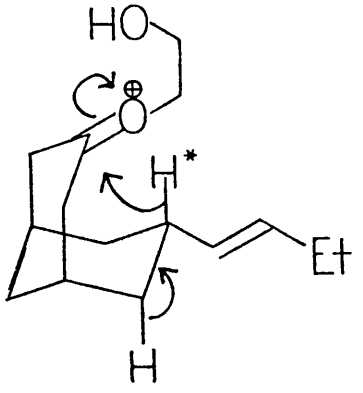
Figure (32)

able from its Z-isomer (109) on g.l.c., and had an I.R. absorption at 10.35 μ. The olefinic protons of (136) showed a marked ($\sim$ 0.5 p.p.m.) downfield shift in the ^{1}H.m.r. spectrum, compared with (109).

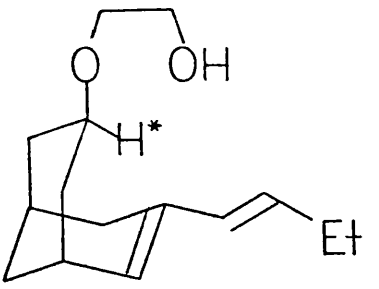
Jones oxidation of alcohol (136) at -15°, Figure (30) and acetalisation of the so-formed enone (141) under forcing conditions[97] (vast excess of ethylene glycol) gave the acetal (137). Formation of this acetal was accompanied by small amounts ($>$10%) of a hydroxylic product. At first, this compound was thought to be the mixture of noradamantanes (148). These could have arisen by an isomerisation of the olefin in (137), followed by an S_E' cyclisation as in (149). But decoupled ^{1}H.m.r. spectra (90 MHz), and especially the ^{13}C.m.r. spectrum, demolished this hope and pointed convincingly to diene (150); an intense U.V. absorption (λ_{max} = 251 nm; ε = 19,600) was in agreement.

Diagrammatic representations of the olefinic region in the ^{1}H.m.r. spectrum of (150) are shown in Figure (32). Decoupling the allylic -$\underline{CH_2}CH_3$ protons, Figure (32)(b), by irradiating at 2.05 δ, reduces the multiplicity of H" to a doublet, J = 16 Hz, centred at 5.57 δ, but has no effect on H' (doublet, J = 16 Hz, 5.98 δ), or H (doublet, J = 6 Hz, 5.6 δ). Decoupling the bridgehead allylic proton, Figure (32)(c), by irradiating at 2.40 δ, collapses H to a singlet at 5.69 δ, but has no effect on H' or H" (doublet of triplets, J_d = 16 Hz, J_t = 4.5 Hz). The non-decoupled spectrum is shown in Figure (32)(a).

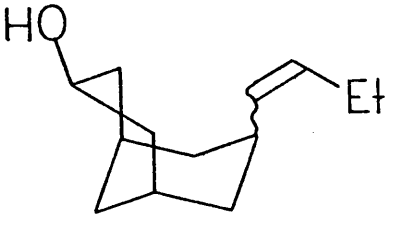
The ^{13}C.m.r. spectrum of (150) had four olefinic carbons, one of which was quarternary; in addition, there



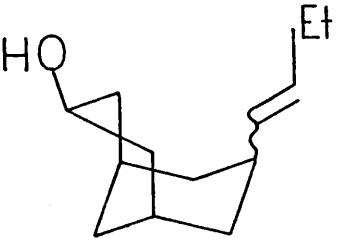
(151)



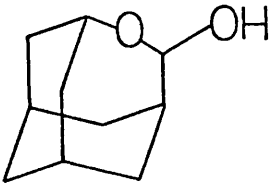
(150)



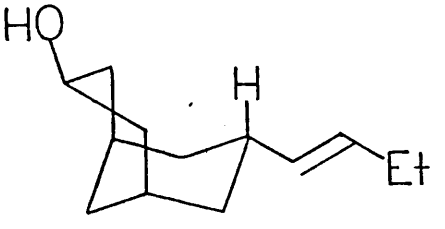
(109)



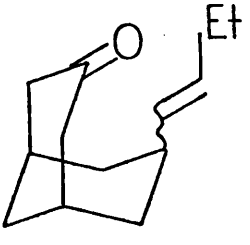
(136)



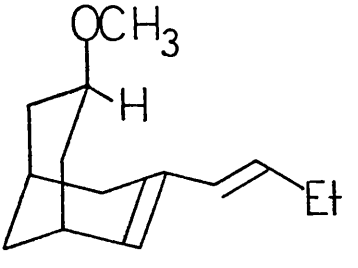
(105)



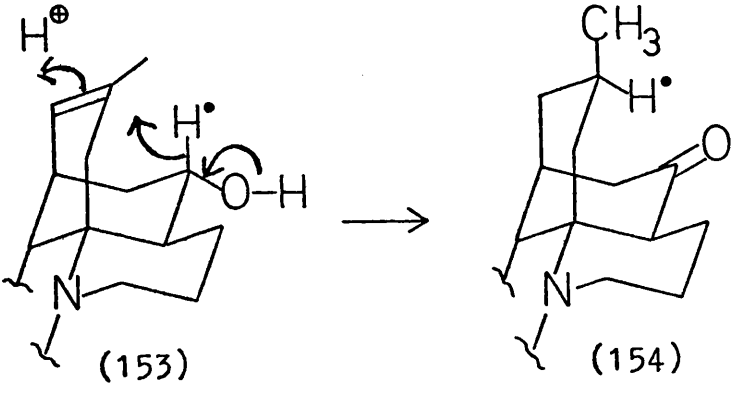
(109'')



(141)



(152)



(153) (154)

were three other downfield resonances (two triplets and one doublet, all C-O carbons, in the off-resonance decoupled spectrum).

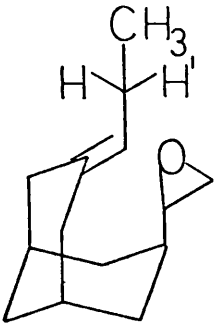
The structure of (150) in effect establishes the configuration of C-7 in (109) and (136): dienol (150) must arise by a 1,5-transannular hydride shift, (151), and for such a mechanism to operate, the alkenyl side-chain must be exo. The antiperiplanar arrangement of H and H*, (151), ensures maximum orbital overlap in the transition state leading to the new olefinic bond.

By extrapolation, then, the Wittig reaction between lactol (105) and propylidenetriphenylphosphorane had involved epimerisation, resulting in Z-enol (109'').

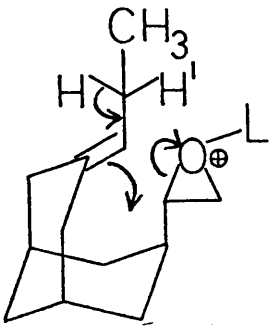
A distinction between the mechanisms of Figures (26) and (27) (see p37) may now be made, in favour of the latter.

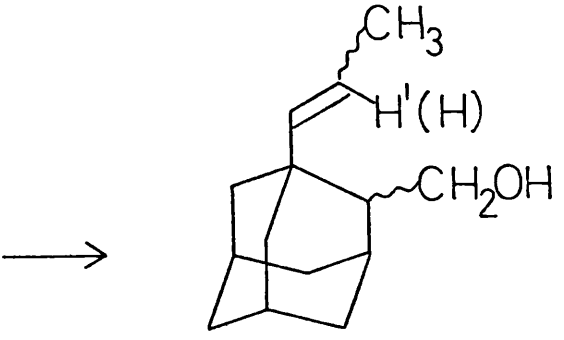
Further corroboration for the hydride shift mechanism (151) was obtained from the attempted acid-catalysed acetalisation of E-enone (141) in methanol. No acetal could be observed, even after extended periods, but methoxy-diene (152) could be isolated in small amounts (ca. 5%), Presumably a mechanism related to (151) is operative. (152) had olefinic signals in the ^{1}H.m.r. spectrum identical to those of (150).

Hydride shifts between the C-7 and C-3 positions of bicyclo (3.3.1) nonanes have been observed previously - e.g. Ayer[93] has shown that the alcohol (153) is transformed to lycopodine (154) in the presence of mineral acid.



(155)





(156)

L= Lewis acid.

Figure (33)

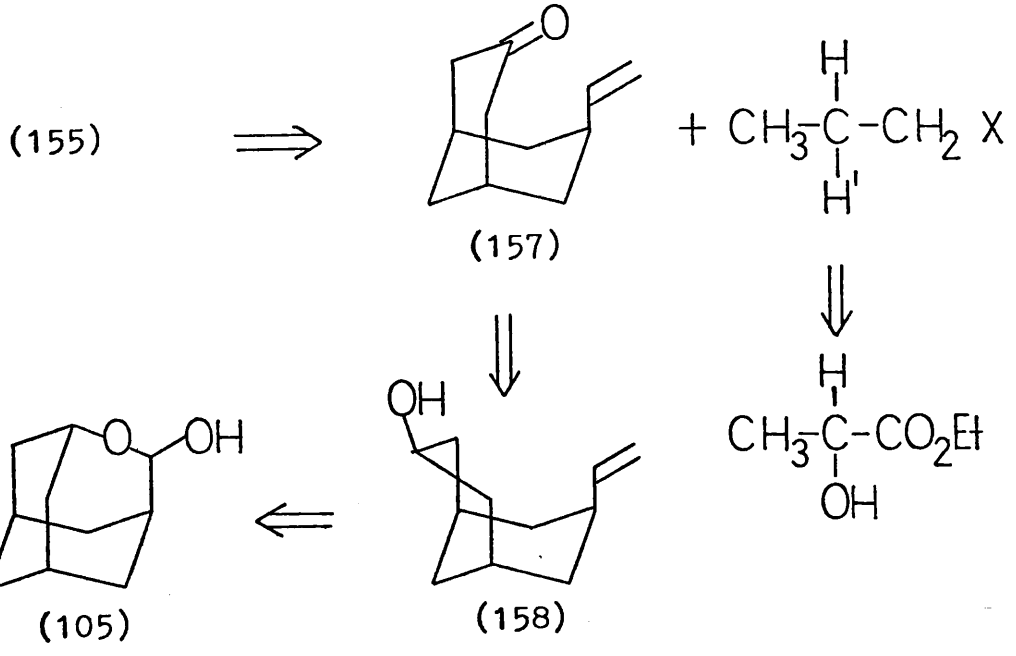
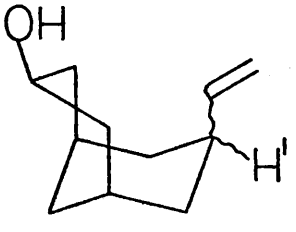
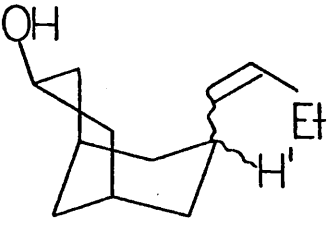


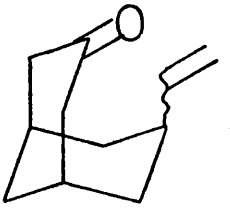
Figure (34)



(159)



(109)



(160)

(G) A Second S_E' Model - Formulation and Approaches

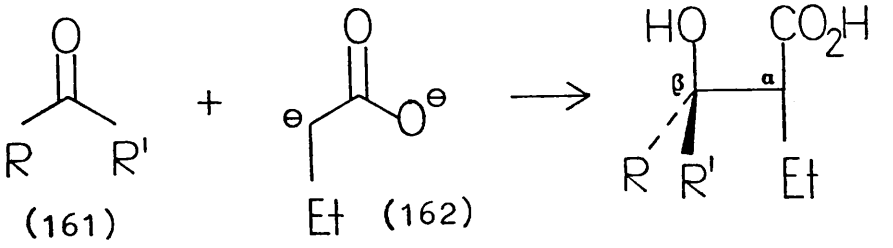
While the work of section (F) was in progress, a second model system, (155), was formulated for investigation of the S_E' reaction. Like the initial model, (155) is a 3,7-disubstituted bicyclo(3.3.1) nonane, but has an epoxide as cationic initiator.[99] The anticipated S_E' reaction on treatment of (155) with a Lewis acid, Figure (33), forms the adamantane (156).

Neither molecule (155) nor the analysis of (156) will be discussed, since the route was not followed through; however the antithetic analysis is outlined in Figure (34).

A Wittig reaction of lactol (105) with methylidene-triphenylphosphorane gave an enol (159), whose ^{1}H.m.r. spectrum showed, in addition to the characteristic $-CH=CH_2$ signals, two features in common with that of (109): the carbinol proton, and theallylic proton (H') of (159) both had large $W_{\frac{1}{2}}$ values (ca. 30 Hz), and the latter was also deshielded (3.1. δ), strong evidence that the configurations and conformations of (109) and (159) were the same.

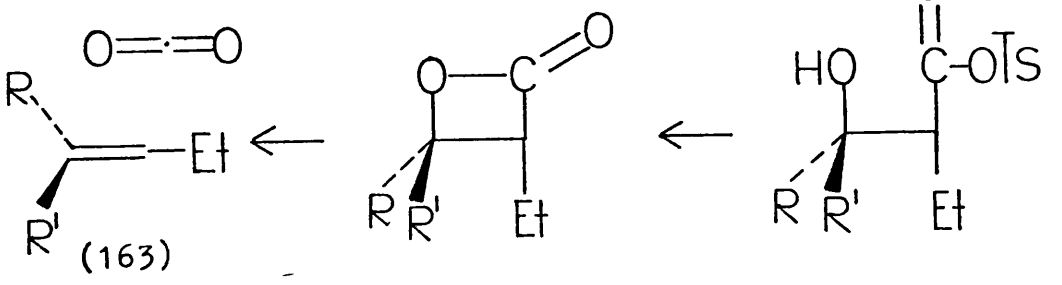
A Wittig reaction on (160) failed, returning only starting material, suggesting that the carbonyl carbon was resistant to nucleophilic attack. But although the activation energy for attack on the C-3 carbonyl group of such molecules is known[100] to be high, there is evidence from the present work - formation of ethylene acetals from (112) and (141) - that the energy barrier is not insurmountable.

An alternative method for introducing an olefin at C-3 of (160) was tried; the essence of this method is the

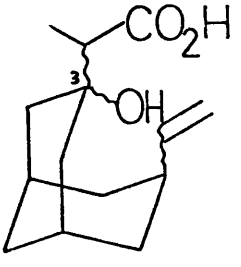


(161) (162)

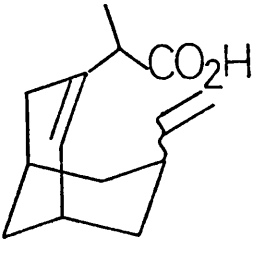
Figure (35)



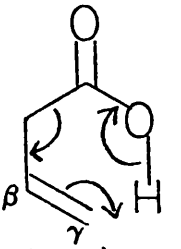
(163)



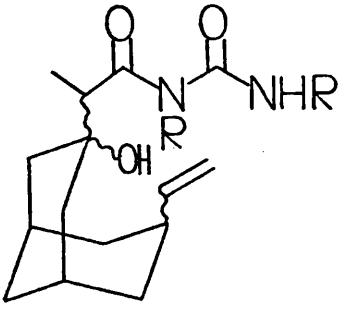
(164)



(165)

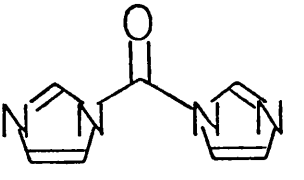


(166)

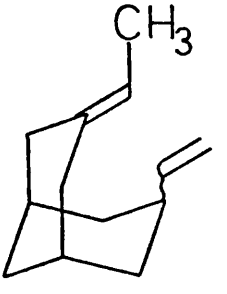


(168)

(R = cyclohexyl)



(169)



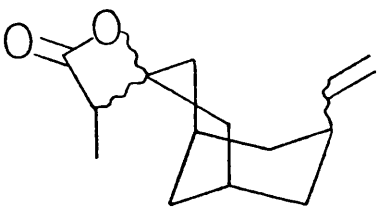
(167)

thermal decarboxylation of a β -lactone,[101] Figure (35). Since a one-carbon unit is eliminated in the decarboxylation, conversion of ketone (161) to propylidene (163) necessitates the use of butyric acid dianion (162) in the initial condensation. As a trial experiment (avoiding the pungent butyric acid), the condensation of (160) with propionic acid was pursued. Extensive experimentation was required, but moderate success (ca. 20% conversion, 80% recovery of starting material) was achieved using hexamethylphosphoric triamide as cosolvent in tetrahydrofuran, and low reaction temperatures. ^{1}H.m.r. analysis of the product, (164), showed it to be an unequal mixture of epimers at C-3.

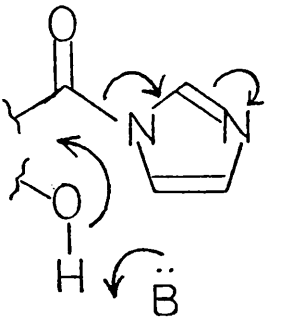
Attempted tosylation[101] did not produce any β -lactone or hydrocarbon products, but rather an acidic component (non-conjugated from the I.R. spectrum), tentatively assigned the structure (165). But thermolysis of this supposed β,γ - unsaturated acid (see (166)[102]) in refluxing quinoline[103] produced only a small amount of unidentified hydrocarbon product.

Several alternative methods[16] were then tried to effect β -lactonisation of (164). Heating either the hydroxy-acid or its methyl ester in mineral acid gave no reaction, as did base treatment (sodium hydride) of the ester. Using the peptide coupling agent dicyclohexylcarbodiimide, for carbonyl activation,[104] gave an adduct, possibly the N-acyl urea[105] (168).

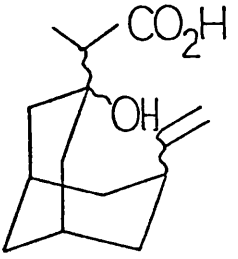
However, persistence was rewarded when, on sequential treatment of (164) with N,N'-carbonyldiimidazole (169), and diazabicyclononene (DBN),[107] hydrocarbon (167) was obtained. That the β -lactone had not been isolated came as no surprise:



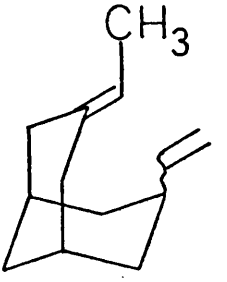
(170)



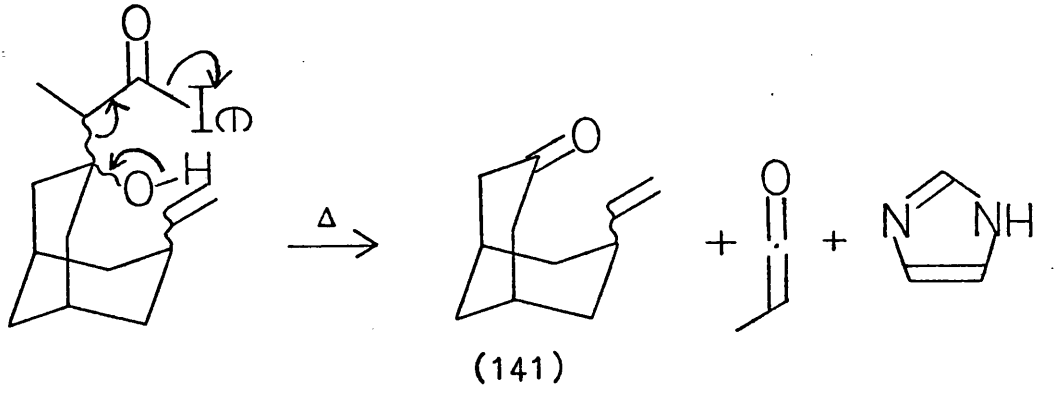
(171)



(164)



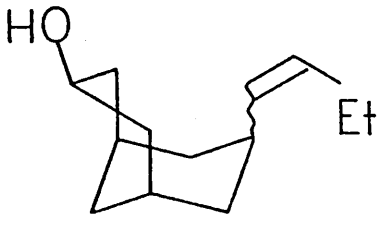
(167)



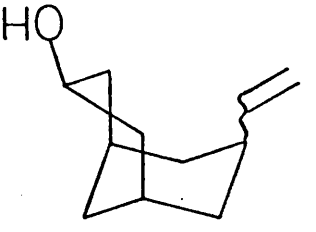
(141)

I_{Θ} = Imidazole ring

Figure (36)



(109)



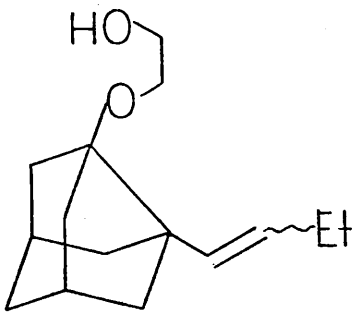
(159)

the marked preference of sp^2-hybridisation at the C-3 or C-7 positions of bicyclo(3.3.1) nonanes quite probably provides an additional driving force for decarboxylation. But, significantly, the I.R. spectrum of the crude product showed a weak 1830 cm^{-1} absorption, almost certainly residual β-lactone (170).

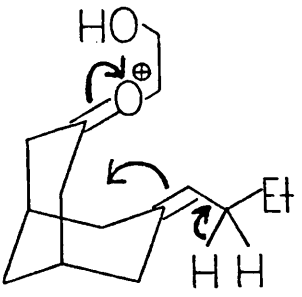
The potential of the imidazole ring for carbonyl activation was recognised by Staab,[106] and Raphael et al[107] have recently utilised an imidazolide for macrolactonisation in their elegant and very direct synthesis of pyrenophorin. (171) shows the probable mechanism for lactonisation of a hydroxy-imidazolide.

During execution of the step (164) ⟶ (167), t.l.c. monitoring indicated substantial amounts of hydrocarbon product before addition of DBN. And in an attempt to effect complete β-lactonisation/decarboxylation in the absence of base, enone (141) was generated in ca. 45% yield. A mechanistic interpretation of this result is shown in Figure (36), where carbonyl activation this time promotes formation of methyl ketene.

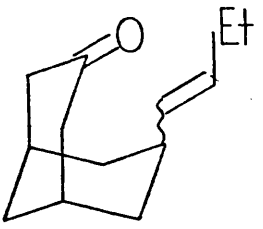
Thus a route from (141) to (167) had been forged, but investigation of model system (155) was terminated in view of the findings regarding the configuration of C-7 in (109) (and hence in (159)) discussed in section (F).



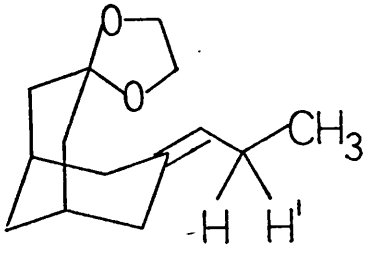
(148)



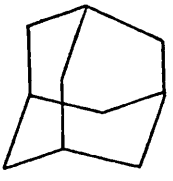
(149)



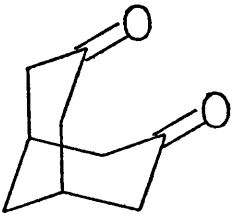
(141)



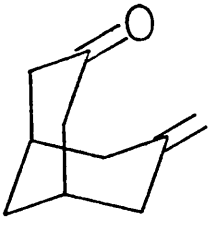
(173)



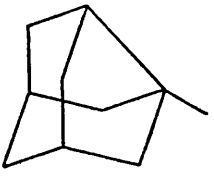
(80)



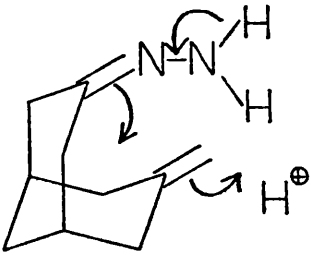
(174)



(54)



(175)



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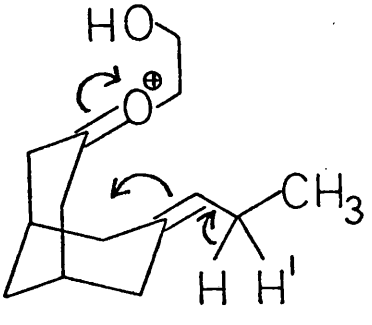
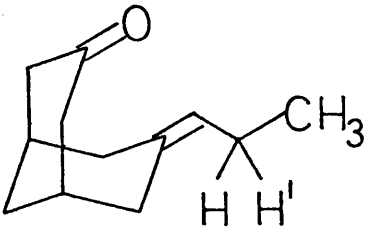


(149')



(177)

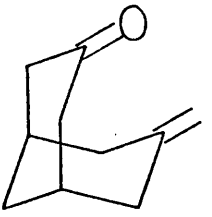
(H) A Third Model System - Formulation, Approaches and Modifications

The postulate that (148) - initially thought to be the by-product of acetalisation of (141) - could have arisen by the S_E' cyclisation of (149) (arrows), prompted the adoption of (173) as a possible S_E' model; its relation to the known[108] dione (174) looked secure, and optically active ethyl lactate could still be used as a source of labelled side-chain.

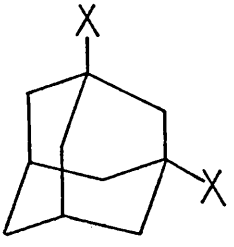
'Stimulative support' for belief in such an S_E' mechanism came unexpectedly while the synthesis of (173) was under way. In a paper subtitled "Revision of the Literature", Momose and Muraoka[109] reinvestigated a claim[110] that adamantane (80) was the sole product of attempted Wolf-Kishner reduction of enone (54). They showed[109] that, under a variety of Wolf-Kishner conditions, methyl noradamantane (175) was the major product. No adamantane was observed. The mechanism proposed[109] for the formation of (175) involves the cyclisation (176), formally an S_E' mechanism.

This result goes some way to counter the rather rash claim of Yurchenko[111] that "the noradamantane nucleus cannot be formed via intramolecular interaction of Π-electrons with a carbonium ion centre."

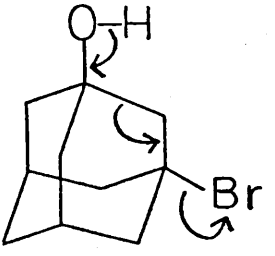
It is important to note that (173) is a dissymmetric molecule, and for investigation of the proposed S_E' reaction ((149')), would be required in optically active form. A resolution step would be most readily performed on the corresponding enone (177): for example, by formation of diastereomeric oxazolidines[112] by reaction with (d)- or (l)-ephedrine, both of which are available commercially. An



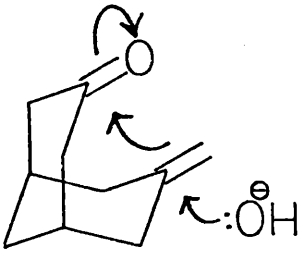
(54)



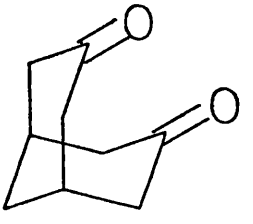
(178) , X=Br
(179) , X=OH



(180)



(180')



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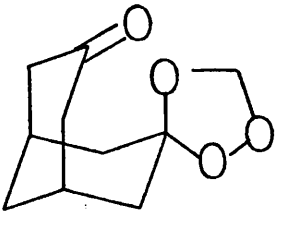


(181)

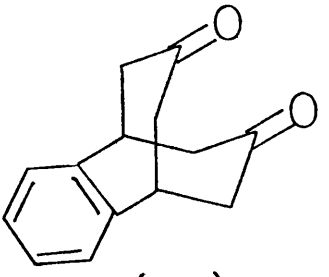
X-ray analysis would identify the absolute configuration of a particular diastereomer. This procedure has been successfully applied[112] in the resolution of prostaglandin intermediates.

The literature route to enone (54) proved, in our hands, to be fraught with difficulties. Base treatment of (178) under defined conditions reportedly gave[113(a)] high yields of (54) via fragmentation (180). But although an acceptable yield of (54) was obtained (ca. 60%) on one occasion by using a catalytic amount of ferric chloride, it was a non-reproducible result, and the reaction repeatedly gave high yields of diol (179), almost certainly by the known reclosure mechanism (180').[114]

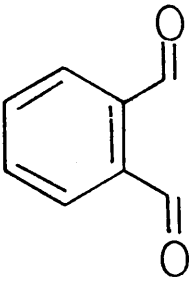
(A grain of consolation was derived from a personal communication from Professor Grob[115] in Basel, revealing that he had experienced similar difficulties with fragmentation-recombination. After consultation with the original authors,[113(a)] he discovered that the reaction temperature was absolutely critical.)

A small amount of (54) was available from the one successful attempt to prepare it, and ozonolysis followed by treatment with dimethyl sulphide gave, not (174),[116] but a crystalline product, which could be chromatographed, and which was identified as ozonide (181) by ^{1}H.m.r. (5.1 δ, 2 H singlet), ^{13}C.m.r. (208(s), 107(s), 93(t) p.p.m.) and mass spectrometry (m^{+} = 198) and by its reductive conversion (zinc, acetic acid) to dione (174),[116] in moderate yield.

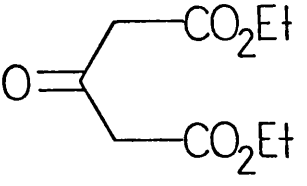
With time now at a premium, and the route to (54) of



(182)



(183)



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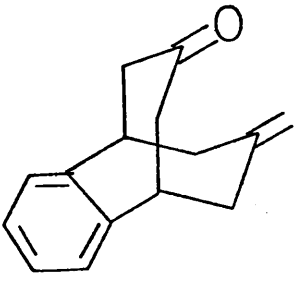
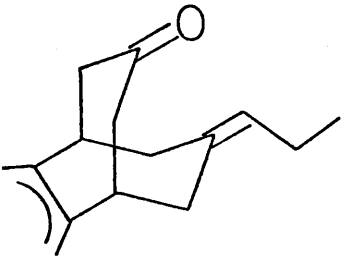


(185)



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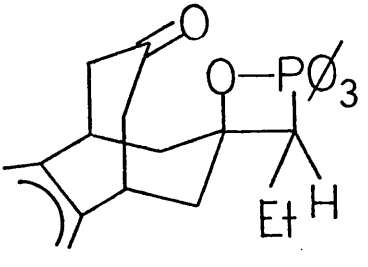
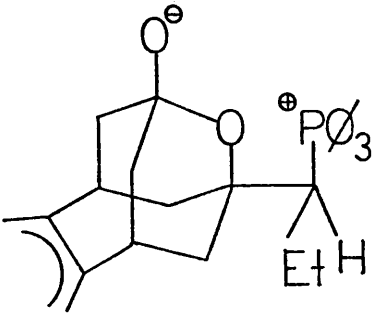


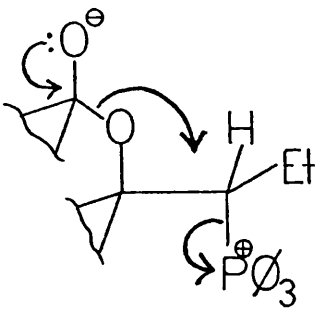
(187)



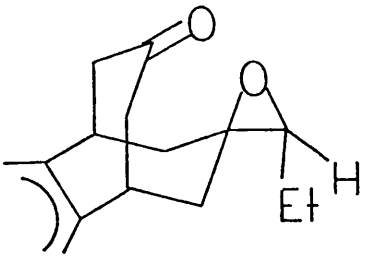
(188)

questionable viability, attention was turned to the related dione (182), a compound which also undergoes the anomalous cyclisation[117] under Wolf-Kishner conditions. By a base-catalysed double Michael condensation of phthalaldehyde (183) with diethyl-3-ketoglutarate (184), and then hydrolysis and decarboxylation of the intermediate tetra-ester, followed by purification by sublimation, dione (182) could be obtained in ca. 50% overall yield - two days' work!

A trial Wittig reaction on (182) using methylidene-triphenylphosphorane[78(b)] gave (185) in 60% yield (^{1}H.m.r. spectrum had 5.1δ , broad singlet; I.R. absorption at 1690 cm^{-1}). The yield of olefinic product (186) when propylidenetriphenylphosphorane was used in the Wittig reaction, under identical conditions, was meagre (< 10%). No starting material was recovered from this reaction, so ylid addition had in fact taken place. It was, therefore, in the formation of oxaphosphetane (187) that difficulties were being encountered, assuming that phosphine oxide elimination from the latter would be rapid. Arguing thus, and postulating zwitterion (188) as an intermediate in the reaction, the problem can be narrowed down to a failure of the C-O and C-P bonds of the impending oxaphosphetane to align in a syn-periplanar fashion, as required for (188) $\longrightarrow$ (187). CPK models substantiated this rationale, and showed that the ethyl group and P-bound phenyl groups encountered severe steric compression against the benz-bicyclo (3.3.2) decane skeleton, when attempting to attain such a syn-periplanar alignment, from either a staggered or anti-periplanar arrangement.



(189)



(190)

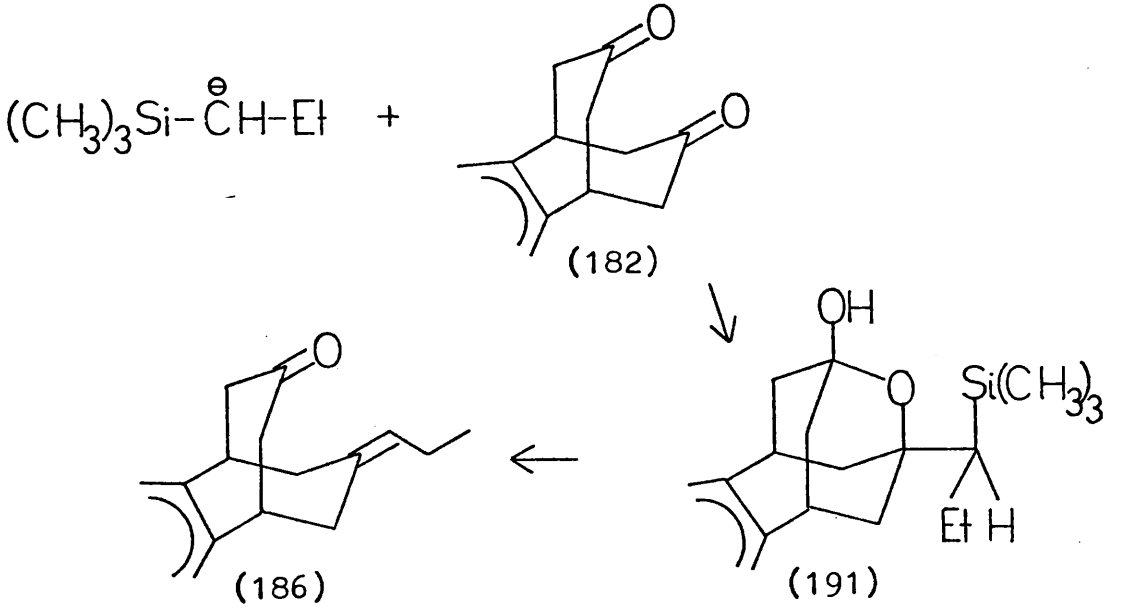
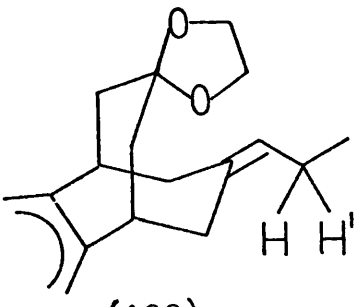
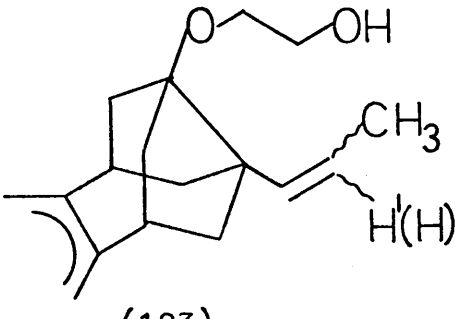


Figure (37)



(192)



(193)

However, with the ethyl replaced by a proton, in (188), steric crowding was reduced considerably, thus accounting for the good yield of (185) obtained.

Changes in solvent, and reaction temperature did not alleviate the difficulty. In some cases, t.l.c. indicated trace amounts of triphenyl phosphine which must have arisen as in partial structure (189), with concomitant formation of epoxide (190), but the latter could not be detected. This is attributed to the exceptionally intense staining of triphenyl phosphine in iodine vapour.

The solution to this problem could lie in reducing the bulk of the groups on phosphorus - e.g. using (R)Ph_2P=CHEt, where R = propyl, as ylid.

An alternative approach might be that of Figure (37), where condensation of the silicon-stabilised carbanion[118] with dione (182) would probably give (191), after protonation. Silanol elimination[119] - analogous to phosphine oxide elimination of the Wittig reaction - would give required enone (186). The much smaller bulk of $SiMe_3$ compared to PPh_3 should favour attainment of the syn-periplanar relationship of C-O and C-Si bonds, (191), necessary for elimination under basic conditions.[119]

Regrettably, time did not allow pursuit of either alternative - an excursion into organo-silicon chemistry would have been a most welcome experience.

The remaining objectives, then, are:

(i) To improve the yield of olefination (182) $\longrightarrow$ (186).

(ii) To obtain (192) in resolved form.

(iii) To find conditions for S_E' cyclisation (192) $\longrightarrow$ (193).

(iv) Finally to use labelled (192) (i.e. H or H' = D) in the cyclisation and interpret the results in terms of the stereochemistry of the S_E' reaction.

- - - - - -

(vii) Experimental

General Experimental Procedure

All melting points (m.p.) were determined on a Kofler hot-stage apparatus, and are uncorrected. Routine infra-red spectra were recorded, in dilute carbon tetrachloride solution (unless otherwise stated) on a Perkin-Elmer 257 spectrophotometer. Ultra-violet spectra were recorded in methanol on a Pye-Unicam 8000 spectrophotometer. ^{1}H.m.r. spectra were recorded in deuteriochloroform (unless otherwise stated), using tetramethylsilane (TMS) as internal standard, on a Varian T.60 (60 MHz) or a Perkin-Elmer R.32 (90 MHz); ^{13}C.m.r. spectra were recorded (by Dr. D.S. Rycroft) on a Varian XL100, using $CDCl_3$ and TMS as above. Mass spectra were routinely recorded using an A.E.I. M.S. 12 spectrometer; high resolution spectra were obtained on an A.E.I. M.S. 902 spectrometer, and all spectra were recorded at 70 eV.

In all cases where product was isolated "by solvent extraction", the procedure followed was to extract the aqueous layer with several portions of the indicated solvent; then the organic layers were combined and washed with water, followed by saturated brine. The organic layer was dried over anhydrous magnesium sulphate (unless otherwise stated), then filtered, and the solvent evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" and "acid wash" indicate washing the combined organic layers with saturated aqueous sodium bicarbonate, or with dilute (6N) hydrochloric acid, respectively, prior to the aforementioned washing

with water.

For reactions run using pyridine as base and/or solvent, the following work-up procedure was used: the reaction mixture was diluted with the indicated solvent, filtered, then washed sequentially with saturated aqueous copper sulphate (4X), water 2(X), and saturated brine. This was followed by drying and evaporation of solvent, as outlined above.

For lithium aluminium hydride reductions, the following work-up procedure was used: water was dropped cautiously onto the reaction mixture to quench the reaction; the gelatinous inorganic salts were coagulated by addition of moist sodium sulphate, the solution was filtered, and the precipitate washed with several portions of the indicated solvent. The combined organic layers were washed with water 2(X) and saturated brine. Drying and evaporation of solvent were as outlined above.

Unless otherwise stated, the purity of all new compounds was ascertained by t.l.c. analysis in three suitable solvent systems, and, in selected cases, by g.l.c. analysis (1% OV-1 or 1% SE-30 packings in glass columns of length six feet, using temperatures between 150^{o} and 200^{o}).

Preparative t.l.c. was run using the indicated percentages of ethyl acetate in hexane as developing solvent (d.s.); Merck Kieselgel GF_{254} was used for analytical and preparative plates. Column chromatography was run using increasing percentages of ethyl acetate in hexane as solvent, and either I.C.N. Silica gel Woelm, or Aluminium Oxide Woelm as adsorbent.

All solvents were purified and dried using standard procedures.

Standard abbreviations are used when quoting spectral data; only significant spectral characteristics are quoted.

A. Iodoketone Route

1-bromoadamantane (85)

This was prepared by the method of Stetter,[69] in 94% crude yield, and had m.p. 115 - 119° (lit.,[69] 119 - 120°). It was normally used without further purification.

1-hydroxyadamantane (86)

This was also prepared by the method of Stetter.[69] After recrystallisation of the crude product from aqueous tetrahydrofuran, followed by sublimation, (86) had m.p. 288 - 290° (lit.,[69] 288 - 290°)

Iodoketone (88)[70,71]

To a solution of 1-hydroxyadamantane (86) (3.03 g) in dry benzene (75 ml) were added rapidly lead tetraacetate (9.8 g), calcium carbonate (2.6 g) and iodine (5.6 g), and the mixture heated at 55-60° for 1.5 h. The cooled mixture was filtered, and the solid washed with benzene (30 ml) and ether (30 ml). The combined filtrate was washed with aqueous sodium bisulphite until colourless, then with water, followed by dilute aqueous sodium bicarbonate, and dried. Filtration and concentration gave a dark oil (5.16 g, crude yield ~ 95%) which could be crystallised from methanol at -78° to give (88), m.p. 75-78° (lit.,[70,71] 78-79°).

The crude product was ca. 80% pure by ^{1}H.m.r. analysis and was normally used without further purification.

Attempted oxidation of iodoketone (88)

To a stirred mixture of sodium bicarbonate (1.2 g) in dry dimethyl sulphoxide (10 ml) at 150°, under an atmosphere

of nitrogen, was added iodoketone (88) (100 mg) in dimethyl sulphoxide (1.0 ml), in one portion. After 4 mins, the solution was rapidly cooled and the product isolated by ether extraction. Preparative t.l.c. (d.s. 20%) gave ketone (89) (25 mg), having m.p. 210-212°, (lit.,[70,71] 210-212°) and $\nu_{max.}$, 1715, 1720 (sh) cm^{-1}.

This product was identical in all respects to that prepared by heating iodoketone (88) in pyridine, as described by Lunn.[71]

Attempted reduction of iodoketone (88)

To a stirred solution of iodoketone (88) (100 mg) in methanol (5 ml), was added sodium borohydride (17 mg) in one portion. After 45 mins., the reaction mixture was poured onto water and the product isolated by ether extraction, giving oxahomoadamantane (90), having m.p. 268-269° (lit.,[76] 268-269°), δ 4.25 (m, 1H), 3.85 (d, J = 3Hz, 2H).

Oxahomoadamantane (90)[73]

A solution of iodoketone (88) (1.0 g) in dry ether (18 ml) was added to a slurry of lithium aluminium hydride (250 mg) in refluxing ether, at a rate sufficient to maintain gentle reflux. After complete addition and a further 20 mins. at reflux, the reaction was quenched and worked-up, giving (90) (540 mg. 94%), essentially pure by ^{1}H.m.r. analysis.

Attempted opening of oxahomoadamantane (90)

(a) To the ether (90) (20 mg) in acetic anhydride (1.0 ml) and ether (2.0 ml) at 0^{o}, was added one drop of freshly distilled boron trifluoride diethyl etherate. After 60 mins. at 0^{o}, t.l.c. indicated $\leq$ 5 products, mostly of greater polarity than (90). The reaction mixture was not further investigated.

(b) To the ether (90) (170 mg) in acetic anhydride (2.0 ml) at -78^{o} was added a precooled (-78^{o}) solution of boron trifluoride diethyl etherate (2.0 ml). After 4 h at this temperature, water was added, and the product was isolated by ether extraction, including base wash. Preparative t.l.c. (d.s. 10%) gave oxahomoadamantane (90) (80 mg), and acetate (92) (45 mg), having ν_{max}, 3010, 1745, 1235, 1030 cm^{-1}; δ, 5.5-6.1 (m,2H), 4.1 (d, J = 6Hz,2H), sharp singlet at 2.0; M^{+} = 194. ($C_{12}H_{18}O_2$ requires M^{+} = 194.)

B. Selective Oxidation Route

4-oxahomoadamantan-5-one (67)

The procedure followed was that of McKervey,[63] and gave lactone (67) 96%) having ν_{max}, 1715 cm^{-1}; δ, 4.5 (m, 1H), 3.1 (m, 1H).

Diol (99)

A solution of lactone (67) (10.0 g) in dry tetrahydrofuran (40 ml) was added to a slurry of lithium aluminium hydride (1.5 g) in refluxing tetrahydrofuran (60 ml), at a rate sufficient to maintain gentle reflux. After complete addition, and further reflux for 36 h, water was added cautiously to quench the reaction. Dilute hydrochloric acid was then added to dissolve inorganic salts, and the product isolated by ethyl acetate extraction giving diol (99) (3.44 g).

The aqueous layer was continuously extracted with ethyl acetate for four days, yielding a second crop of diol (99) (5.9 g). Total yield[76] of (99), 94%. Crystallisation from water or ethyl acetate gave (99) as colourless plates, having m.p. 166-167° (lit., [76] 167.5-168°) and ν_{max}, (KBr disc), 3300 cm^{-1}.

Treatment of diol (99) with Dihydropyran

A solution of redistilled dihydropyran (0.1 ml) in dry dioxan (20 ml) was slowly dropped into a stirred mixture of diol (99) (100 mg) and p-toluenesulphonic acid (2.0 mg), at 15° in dioxan (2 ml). T.l.c. at regular intervals indicated

the appearance of three spots, in addition to (99). The reaction was not further investigated.

Selective oxidation of diol to hemiacetal (101) and keto-alcohol (102)

A chromic acid solution was prepared[79] by dissolving sodium dichromate dihydrate (10 g) in water (30 ml), then adding concentrated sulphuric acid (97%, 13.6 g), and diluting the mixture to 50 ml total volume.

For the purposes of this oxidation, the acid was further diluted by mixing the chromic solution (5.0 ml) with water (20 ml).

The diol (99) (250 mg) was suspended in ether (20 ml). With vigorous stirring, at 0^{o}, the dilute chromic acid solution was added slowly from a burette. After addition of ca. 20 ml of acid, t.l.c. indicated absence of (99), and one major less polar product. The reaction mixture was poured onto ice and the product isolated by ethyl acetate extraction, including base washes to neutrality. Preparative t.l.c. (d.s. 30%) gave a crystalline solid (186 mg, 81%) identified as a mixture of hemiacetal (101) and keto-alcohol (102). A sample crystallised from benzene-light petroleum (1:20) had m.p. 100-116^{o}; ν_{max}, 3600, 1720, 1135, 1095, 1065 cm^{-1}; δ, 3.85 (d, J = 3Hz, relative integral 2H), 3.35 (m, relative integral 2H, sharpens on D_2O exchange to d, J = 6Hz); M^{+} = 168. (Found C, 71.5; H, 9.6. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.55%)

Keto-acetate (103)

To the mixture of hemiacetal (101) and keto-alcohol (102) (100 mg) in pyridine (1.0 ml), was added acetic anhydride (1.0 ml). After standing at room temperature overnight, usual work-up using ether as solvent, and then preparative t.l.c. (d.s. 20%) gave keto-acetate (103) (113 mg, 95%) as an oil having ν_{max}, 1745, 1715, 1230, 1035 cm^{-1}; δ, 3.8 (d, J = 6Hz, 2H); M^+ = 210.
(Found: C, 68.6; H, 8.4. $C_{12}H_{18}O_3$ requires C, 68.6; H, 8.6%.)

Acetoxy-acetal (104)

A mixture of keto-acetate (103) (140 mg), ethylene glycol (0.5 ml), and naphthalenesulphonic acid (5 mg) in dry benzene (25 ml) was heated under reflux with azeotropic removal of water into a Dean-Stark trap charged with activated molecular sieves, for 18 h. The cooled mixture was washed with saturated aqueous sodium bicarbonate (2X), water (1X) saturated brine (1X) and dried. Filtration and concentration and preparative t.l.c. (d.s. 10%) gave acetoxy-acetal (104) (138 mg, 76%), an oil having ν_{max}, 1745, 1355, 1230, 1145 cm^{-1}; δ, 4.2-3.8 (m, 6H); M^+ = 254.
(Found M^+ = 254.15170. $C_{14}H_{22}O_4$ requires M^+ = 254.151799.)

C. Lactol Route

Lactol (105)

A standard solution of lithium aluminium hydride in tetrahydrofuran was prepared by adding the solvent (50 ml) to the hydride (1.0 g), under an atmosphere of nitrogen, and allowing the solid residue to settle.

45 ml of this solution was added slowly (over ca. 1.5 h) to a stirring solution of lactone (67) (5.0 g) in tetrahydrofuran (25 ml) at 0^{o}, under a nitrogen atmosphere. After complete addition, stirring was continued for a further 30 mins, then water was cautiously added to quench the reaction. The usual work-up using ethyl acetate as solvent, gave a white crystalline solid (5.0 g, 100%) which was ca. 95% homogeneous by g.l.c. (1% OV-1 at 160^{o}) and was normally used in the subsequent Wittig reaction without further purification.

A sample crystallised from acetone (0^{o}) had m.p. $133-135^{o}$; ν_{max} ($CHCl_3$), 3610, 1050 cm^{-1}; δ, 5.35 (d, J = 3Hz, 1H, sharpens on D_2O exchange), 4.20 (m, 1H), 3.0 (s, 1H, disappears on D_2O exchange); δ (^{13}C), 99.87(d), 72.33(d); M^+ = 168 ($C_{10}H_{16}O_2$ requires M^+ = 168). This compound could not be analysed because of its propensity fordehydration.

Z-enol (109)

(a) The anion of dimethyl sulphoxide was prepared as follows: neat sodium hydride (384 mg, 16 mmol) and dry dimethyl sulphoxide (10 ml) were stirred and heated at $75-80^{o}$ (bath temperature) under a nitrogen atmosphere for

1.5 h, then rapidly cooled to 10-15°. This dimsyl anion solution was added by syringe to a solution of n-propyltriphenylphosphonium iodide (6.46 g, 16 mmol) in dimethyl sulphoxide (20 ml), under an inert atmosphere, giving the deep-red ylid. After 5 mins, the lactol (105) (1.34 g, 8 mmol) in dimethyl sulphoxide (10 ml) was added over 5 mins; the ylid colour was discharged. After 2.5 h, the reaction mixture was poured onto a hexane-ice mixture. Precipitated triphenylphosphine oxide was filtered off and washed with hexane, then the product isolated by hexane extraction. The crude product was chromatographed on Alumina(Grade II, neutral, 100 g) giving Z-enol (109) (1.55 g, 85%), an oil having ν_{max}, 3610, 1460, 1040 cm^{-1}; δ, 5.6-5.0 (m, 2H), 4.0 (m, $W_{\frac{1}{2}}$ = 28Hz, 1H), 3.1 (m, $W_{\frac{1}{2}}$ = 26Hz, 1H), triplet at 1.0, J = 8Hz; δ (^{13}C), 135.3(d), 130.4(d), 65.2(d), 14.7(q); M^+ = 194.
(Found: C, 80.5; H, 11.1. $C_{13}H_{22}O$ requires C, 80.6; H, 11.35%)

(b) On a larger scale (14.0 g of lactol) this Wittig reaction gave, after chromatography of the product, Z-enol (109) (8.6 g) and acetate (115) (5.2 g), an oil, having ν_{max}, 1740, 1370, 1245 cm^{-1}; δ (CCl_4), 5.5-4.8 (m, 3H), 3.2(m, $W_{\frac{1}{2}}$ = 32Hz, 1H), singlet at 2.0, triplet (J = 7Hz) at 1.0; M^+ = 236.
(Found: C, 76.45; H, 10.2. $C_{15}H_{24}O_2$ requires C, 76.3; H, 10.2%.)

Acetylation of Z-enol (109)

The enol (109) (20 mg) was refluxed in pyridine (1.0 ml), acetic anhydride (1.0 ml) for 4h. Usual work-up, using ether as solvent, gave, after preparative t.l.c. (d.s. 20%)

an acetate (24 mg, 100%), identical in all respects with (115).

Reduction of Acetate (115)

The acetate (115) (100 mg) in dry ether (3 ml) was added to a slurry of lithium aluminium hydride (50 mg) in refluxing ether (5 ml). Refluxing was continued for a further 20 mins, then usual work-up gave, after preparative t.l.c. (d.s. 20%), an alcohol (76 mg, 93%), identical in all respects with Z-enol (109).

Dimeric Acetal (114)

A crystalline sample of lactol (105) (100 mg) was allowed to stand in a dessicator for 0.5h. Preparative t.l.c. (d.s. 20%) of the solid gave lactol (105) (58 mg) and acetal (114) (38 mg). A sample of the latter, crystallised from methanol, had m.p. 205-208°, ν_{max}, 1040, 1020, 975 cm^{-1}; δ 5.25 (d, J = 4Hz, 1H), 4.15 (m, 1H); δ (^{13}C), 84.29 (d), 72.21 (d); M^+ = 318. (Found: C, 75.65, H, 9.6 . $C_{20}H_{30}O_3$ requires C, 75.5; H, 9.45%.)

Hydrolysis of Acetal (114)

To the acetal (114) (20 mg) in tetrahydrofuran (2.0 ml), was added dilute hydrochloric acid (6N, 1.0 ml), and the mixture stirred at R.T. for 12 h, when t.l.c. and g.l.c. analyses showed that the product was lactol (105).

Z-enone (112)

To a stirred solution of enol (109) (1.0 g) in acetone (10 ml) at 0^{o}, was added Jones Reagent, dropwise, until the red colour just persisted. After a further 15 mins, isopropanol (1.0 ml) was added, then water and the product was isolated by ethyl acetate extraction. Preparative t.l.c. (d.s. 15%) gave enone (112) (910 mg, 91%) an oil having ν_{max}, 1715, 1215, 1115 cm^{-1}; δ, 5.6-5.0 (m, 2H); δ (^{13}C), 212.9 (s); M^{+} 192. DNP of (112) had m.p. 115-116^{o}.

(Found: C, 61.0; H, 6.45; N, 15.2. $C_{19}H_{24}O_4N_4$ requires C, 61.3; H, 6.45; N, 15.05%.)

Z-olefin acetal (113)

A mixture of enone (112) (30 mg), ethylene glycol (100 mg), p-toluenesulphonic acid (5 mg.) in dry benzene (15 ml), was refluxed with azeotropic removal of water, for 12 h. The cooled mixture was washed with saturated aqueous sodium bicarbonate (2X), water (1X), saturated brine (1X), and dried. Filtration and concentration gave, after preparative t.l.c. (d.s. 10%), olefin acetal (113) (31 mg, 81%), an oil having ν_{max}, 1135, 1105, 1085 cm^{-1}; δ, 5.5-4.9 (m, 2H), 3.9 (br s,4H), 3.45 (m, $W_{\frac{1}{2}}$ = 30Hz, 1H); M^{+} = 236 ($C_{15}H_{24}O_2$ requires M^{+} = 236).

Attempts to cyclise the Z-olefin acetal (113)

(i) To a stirred solution of the acetal (113) (50 mg) in dry methylene chloride (2ml), under a nitrogen atmosphere, at -78^{o}, was added a standard solution of stannic chloride

(10 equivalents) in methylene chloride (0.5 ml), dropwise, by syringe, over 2 mins. After 30 s, saturated aqueous sodium bicarbonate was added and the product was isolated by methylene chloride extraction, giving, after preparative t.l.c. (d.s. 10%), starting acetal (113) (28 mg) and enone (112) (18 mg).

(ii) Repetition of the above procedure, except at R.T., gave enone (112) as the only product.

(iii) To a stirring solution of the acetal (113) (50 mg) in dry benzene (5 ml), under an atmosphere of nitrogen, was added a small piece of anhydrous aluminium chloride (ca. 20 mg). The mixture was refluxed for 3 h, when t.l.c. showed only starting material. Prolonged reaction led to some hydrolysis to enone (112) (t.l.c.).

(iv) To a stirring solution of the acetal (113) (50 mg) in dry dimethylformamide (2 ml), under an atmosphere of nitrogen, was added anhydrous aluminium chloride (ca. 20mg). After 2 h, only starting material was visible (t.l.c.), but after refluxing for 24 h, complete hydrolysis to enone (112) had occurred.

(v) To a stirring solution of the acetal (113) (150 mg) in dry benzene (2 ml) under an atmosphere of nitrogen, was added freshly distilled boron trifluoride etherate (1 drop). After 30 mins, t.l.c. indicated only enone (112).

D. Schlosser Routes

Attempted Schlosser on lactol (105)

(i) To a slurry of propylidenetriphenylphosphorane (695 mg, 1.8 mmol) in dry tetrahydrofuran (5 ml), under an atmosphere of nitrogen, was added a solution of phenyl lithium in benzene-ether (1.0 ml, 2.0 mmol). The deep-red ylid was stirred at R.T. for 10 mins., then cooled to -78°. After 10 mins, a solution of the lactol (105) (110 mg, 0.73 mmol) in tetrahydrofuran (5 ml) was added dropwise by syringe; a precipitate formed almost immediately. The solution was allowed to warm to -30° over 20 mins, then a further portion of phenyl lithium solution added (0.5 ml, 1.0 mmol). After stirring at -30° for 15 mins, excess methanol was added, then water, and the product was isolated by ether extraction, giving, after preparative t.l.c. (d.s. 30%), the starting lactol (105) (80 mg), as the only product.

(ii) Repetition of this procedure, except using three equivalents of ylid, gave a similar result.

Primary Acetate (118)

To a stirred suspension of diol (99) (6.80 g) in dry pyridine (35 ml) and ether (30 ml), was added acetic anhydride (8.0 g, 1 equiv.) in ether (25 ml) over 15 mins. Stirring at R.T. was continued for 32 h, at which time the solution was homogeneous. The reaction was worked up in the usual way, using ether for extraction, and gave, after chromatography on Alumina (Grade III, 200 g) monoacetate (118) (7.15 g, 90%). The oily acetate could be crystallised from hexane, and had m.p. 67-69°; ν_{max}, 3610, 1745, 1245 cm^{-1};

δ, 4.2 (m, 1H), 3.9 (d, J = 5Hz, 2H); M^+ = 212.
(Found: C, 67.9; H, 9.4. $C_{12}H_{20}O_3$ requires C, 67.9 ; H, 9.4%.)

Some diacetate (122) (R = CH_3) was produced in this reaction, an oil having ν_{max}, 1745, 1240 cm^{-1}; δ, 5.2 (m, 1H), 3.9 (d, J = 6Hz, 2H); M^+= 254.
(Found: C, 66.1; H, 9.0 . $C_{14}H_{22}O_4$ requires C, 66.0 ; H, 8.65%.)

Primary Benzoate (118')

To the diol (99) (270 mg) in pyridine (2 ml) and ether (2 ml), at 0°, was added benzoyl chloride (250 mg, 1.1 equiv) in ether (1 ml). After 16 h at room temperature the usual work-up, using ether as solvent, gave, after preparative t.l.c. (d.s. 30%), the primary benzoate (118') (208 mg) m.p. 122.5-124.5°, having ν_{max}, 3610, 3010, 1710, 1275 cm^{-1}; δ , 8.00 (m, 2H), 7.42 (m, 3H), 4.21 (m, 3H); M^+ = 274.
(Found: C, 74.4; H, 8.3. $C_{17}H_{20}O$ requires C, 74.4, H, 8.05%)

Also isolated was dibenzoate (122) (R = Ph) (200 mg) m.p. 83-85.5°, having ν_{max}, 3010, 1710, 1275 cm^{-1}; δ , 8.11 (m, 4H), 7.52 (m, 6H), 5.45 (m, 1H), 4.10 (d, J = 6Hz, 2H); M^+ = 378.
(Found: C, 76.0 ; H, 6.85. $C_{24}H_{26}O_4$ requires C, 76.25; H, 6.9 %.)

THP-ether (119)

The acetate (118) (2.04 g), dihydropyran (2.5 g, freshly distilled), and p-toluenesulphonic acid (10 mg) were

dissolved in benzene (30 ml), and the mixture stirred at room temperature for 28 h. The reaction mixture was diluted with ether (40 ml), the solution washed with saturated aqueous sodium bicarbonate (2X), water (1X), saturated brine (1X) and dried. Filtration gave the THP-ether (119) (3.04 g,100%), a mobile oil having ν_{max}, 1745, 1245, 1035 1020, 995 cm^{-1}; δ (CCl_4), 4.65 (m, 1H), 4.10-3.35 (m, 5H); M^+ = 296.

($C_{17}H_{28}O_4$ requires M^+ = 296.)

Alcohol (117)

The THP-acetate (119) (350 mg) in ether (5 ml) was added to a slurry of lithium aluminium hydride (250 mg) in refluxing ether (10 ml). The mixture was refluxed for a further 5 h, then the product was isolated in the usual way, giving alcohol (117) (302 mg,100%), as a mobile oil having ν_{max}, 3620, 1120, 1075, 1035, 1020, 995 cm^{-1}; δ (CCl_4), 4.70 (m, 1H), 4.21-3.20 (m, 5H), 2.50 (m, 1H, exchangeable with D_2O); M^+ = 254. ($C_{15}H_{26}O_3$ requires M^+ = 254.)

Attempts to oxidise alcohol (117) to aldehyde (116')

(a) Using pyridinium chlorochromate

The reagent was prepared by the method of Corey.[85] The oxidant (258 mg) and sodium acetate (28 mg) were suspended in dry methylene chloride (3 ml) and the alcohol (117) (170 mg) in methylene chloride (2 ml) added in one portion. Immediately, the solution turned dark and a precipitate formed. After 1.75 h, t.l.c. indicated several products. The reaction mixture was diluted with ether and filtered through a short column of Celite. Removal of solvent gave,

after preparative t.l.c. (d.s. 20%), lactone (67) (43 mg) as the only identifiable product, and was identical in all respects with an authentic sample.

(b) Using Fetizon's Reagent

The reagent was prepared by the method of Fetizon.[86] To the alcohol (117) (90 mg) in dry benzene (25 ml), was added the oxidant (2.5 g, 10 equivalents). The mixture was refluxed, with azeotropic removal of water, for 3 h, then cooled, filtered and solvent removed in vacuo , giving a colourless oil (88 mg) whose ^{1}H.m.r. spectrum showed ca. 20% aldehyde (δ 9.8), and starting material, together with several minor impurities. Repetition of this experiment, under identical conditions, but for eight hours, gave a product whose ^{1}H.m.r. spectrum showed two aldehydic signals (δ 9.80, 9.55) and still some starting material. No attempt was made to isolate the aldehydes by preparative t.l.c.

(c) Using the Modified Collins Procedure[88]

Chromium trioxide (240 mg) was added to a stirred solution of dry pyridine (380 mg) in dry methylene chloride (5 ml). The resulting solution was stirred at room temperature for 45 mins, then the alcohol (117) (150 mg) in methylene chloride (2 ml) added in one portion. After 1.5 h t.l.c. analysis showed little starting material, but several other components. The reaction mixture was poured onto saturated aqueous sodium bicarbonate, and the product isolated by ether extraction. ^{1}H.m.r. analysis indicated less than 10% aldehyde; t.l.c. comparison indicated the presence of lactone (67) in the product.

(d) Using Jones Reagent at low temperature[87]

The alcohol (117) (25 mg) in acetone (5 ml), at -20°, was treated with Jones reagent (1 equivalent). After 15 mins at -20°, isopropanol (1 ml) was added, the reaction mixtured poured onto saturated aqueous sodium bicarbonate and the product isolated by ether extraction, giving an oil whose ^{1}H.m.r. spectrum showed little aldehyde. T.l.c. indicated several components, one of which was lactone (67), by comparison.

(e) Using Oppenauer Oxidation[89]

A mixture of alcohol (117) (100 mg) and cyclohexanone (0.5ml) in toluene (45 ml) was stirred and heated until 20 ml of solvent distilled. Aluminium isopropoxide (160 mg) was added and refluxing continued for 16 h. The cooled reaction mixture was washed with saturated aqueous sodium hydrogen tartrate (1X), brine (1X), and dried. Filtration and concentration gave an oil whose ^{1}H.m.r. spectrum showed a small aldehydic signal (δ 9.8), and whose t.l.c. showed some starting material and several other products.

Tosylate (121)

To the alcohol (117) (430 mg) in pyridine (10 ml), was added tosyl chloride (355 mg) in one portion. Swirling rendered the solution homogeneous, and, after standing at room temperature for 16 h, the usual work up, using ether as solvent gave the tosylate (121) (700 mg 98%) as an unstable semi-solid, having ν_{max}, 1370, 1190, 1180 cm^{-1}; δ , 7.52 (AB quartet, J = 8Hz, 4H), 4.63 (m, 1H), singlet at 2.50;

M^+ = 408 ($C_{22}H_{34}O_5S$ requires M^+ = 408.)

Treatment of tosylate (121) with sodium iodide

To a solution of sodium iodide (99 mg) in acetone (5 ml), under a nitrogen atmosphere, was added the tosylate (121) (125 mg) in acetone (1 ml). After 12 h, the reaction mixture was poured into saturated aqueous sodium bicarbonate, and the product isolated by ether extraction. Preparative t.l.c. (d.s. 10%) of the product gave oxahomoadamantane (90) (35 mg) together with starting material (15 mg).

Diacetate (122) (R = CH_3)

A mixture of diol (99) (941 mg), acetic anhydride (1.02 g) and pyridine (10 ml) was heated under reflux for 12 h. Usual work-up, using ether as solvent gave diacetate (122) (R = CH_3) (1.41 g, 98%).

Dibenzoate (122) (R = Ph)

A mixture of diol (99) (1.0g), benzoyl chloride (1.5 g) and pyridine (20 ml) was heated under reflux for 12 h. The usual work-up, using ether as solvent, followed by chromatography on Alumina(Grade II, neutral, 50 g) gave dibenzoate (122) (R = Ph) (2.10 g, 93%), m.p. 81-84°.

Secondary Acetate (123) (R = CH_3)

The diacetate (122) (R = CH_3) (1.02 g) in methanol (5 ml) at 0° was treated with a 5% solution of potassium hydroxide in methanol (10 ml). After stirring at 0° for 9.5 h, the reaction mixture was poured onto ice, and the product isolated by ether extraction, including an acid-wash, giving the

hydroxy-acetate (123) (R = CH_3) (806 mg, 96%) as an oil. A sample crystallised from ether-petroleum ether had m.p. 57-58°, ν_{max}, 3615, 1745, 1230 cm^{-1}; δ, 5.21 (m, 1H), 3.53 (d, J = 6Hz, 2H), 2.80 (s, 1H, exchangeable with D_2O): M^+ = 212.

(Found: C, 67.9; H, 9.2. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.4%).

Secondary Benzoate (123) (R = Ph)

The dibenzoate (122) (R = Ph) (50 mg) in methanol (4 ml) was treated with a 5% solution of potassium hydroxide in methanol (0.5 ml). After 14 h at room temperature, cold water was added, and the product was isolated by ether extraction, including acid-wash. Preparative t.l.c. (d.s. 30%) gave the hydroxy-benzoate (123) (R = Ph) (21 mg, 60%) and oil having ν_{max}, 3620, 1715, 1270, 1240, 1115 cm^{-1}; δ, 5.41 (m, 1H), 3.52 (d, J = 6Hz, 2H); M^+ = 274.

(Found: C, 74.1; H, 8.25. $C_{17}H_{20}O_3$ requires C, 74.4; H, 8.05%.)

Acetate-Tosylate (124) (R = CH_3)

The acetate (123) (R = CH_3) (100 mg), tosyl chloride (150 mg) and pyridine (2 ml) were mixed and allowed to stand at room temperature for 12 h. Usual work-up, using ether-benzene as solvent, and preparative t.l.c. (d.s. 20%), gave tosylate (124) (R = CH_3) (175 mg, 96%) an oil having ν_{max}, 1740, 1370, 1230, 1190, 1180 cm^{-1}; δ, 7.61 (AB quartet, J = 8Hz, 4H), 5.23 (m, 1H), 3.90 (d, J = 6Hz, 2H), 2.42 (s, 3H); M^+ = 366.

(Found: C, 62.3; H, 7.35. $C_{19}H_{26}O_5S$ requires C, 62.3;

H, 7.15%).

Benzoate-Tosylate (124) (R = Ph)

Tosylation of benzoate (123) (R = Ph) was effected exactly as described above, giving tosylate (124) (R = Ph) (96%), an oil having ν_{max}, 1720, 1370, 1270, 1250, 1190 1180, 1100 cm^{-1}; δ, 8.20-7.21(m, 9H), 5.45 (m, 1H), 3.91 (d, J = 6Hz, 2H), 2.45 (s, 3H); M^+ = 428 ($C_{24}H_{28}O_5S$ requires M^+ = 428.)

Iodo-acetate (125) (R = CH_3, X = I)

The tosylate (124) (R = CH_3) (100 mg) and sodium iodide (150 mg) were dissolved in acetone (10 ml) and the mixture refluxed for 18 h. A second portion of sodium iodide (100 mg) was added, and, after refluxing for 7 h, the cooled reaction mixture was filtered, the solvent was removed in vacuo, and the product purified by preparative t.l.c. (d.s. 10%), giving iodo-acetate (125) (R = CH_3, X = I) (80 mg, 91%). A sample crystallised from petroleum ether had m.p. 69-70°, ν_{max}, 1740, 1230 cm^{-1}; δ, 5.22 (m, 1H) 3.10 (d, J = 6Hz, 2H); M^+ = 322.
(Found: C, 44.5; H, 5.9, I, 39.45. $C_{12}H_{19}O_2I$ requires C, 44.75; H, 5.9, I, 39.5%.)

Idobenzoate (125) (R = Ph, X = I)

The tosylate (124) (R = Ph, X = I) (22 mg) and sodium iodide (40 mg) were refluxed in acetone (3 ml) for 13 h. Removal of solvent and preparative t.l.c. (d.s. 50%) gave an oil (18 mg). ^{1}H.m.r. analysis showed that this compound

was mainly iodobenzoate (125) (R = Ph, X = I), but also that it was contaminated by a small amount of starting tosylate. Absorptions due to iodobenzoate (125), δ , 5.42 (m, 1H), 3.02 (d, J = 6Hz, 2H).

The impure iodobenzoate was used in the attempted preparation of the corresponding phosphonium salt.

Bromo-acetate (125) (R = CH_3, X = Br)

Tosylate (124) (R = CH_3) (110 mg) and lithium bromide (200 mg) were dissolved in acetone (8 ml) and the mixture refluxed for 15 h. A second portion of lithium bromide (100 mg) was added and, after refluxing for a further 15 h, removal of solvent and preparative t.l.c. (d.s. 20%) gave bromo-acetate (125) (R = CH_3, X = Br), an oil having ν_{max}, 1740,1260, 1240, 1215 cm^{-1}; δ , 5.15 (m, 1H), 3.33 (d , J = 5Hz, 2H), M = 215, 217.
(Found: C, 52.4; H, 6.75. $C_{12}H_{19}O_2Br$ requires C, 52.35; H, 6.9%.)

Attempts to form phosphonium salts (126)

(a) Iodo-acetate (125) (R = CH_3, X = I)

(i) The iodo-acetate (125) (R = CH_3, X = I) (59 mg) and triphenyl phosphine (79 mg) were dissolved in benzene (5 ml) and the mixture refluxed for 48 h, at which time t.l.c. showed starting materials. No precipitate was observed.

Refluxing the mixture for 5 days gave a small amount of a precipitate, but its ^{1}H.m.r. spectrum had no acetate methyl signal. The spectrum of the product obtained from the supernatant showed that some decomposition of starting

material had occurred.

(ii) The iodo-acetate (125) (200 mg) and triphenyl phosphine (314 mg) were dissolved in benzene (4 ml) and the mixture heated at 100° in a sealed tube for 20 h. Removal of solvent gave a viscous oil whose ^{1}H.m.r. spectrum showed only starting materials.

Subjecting the same mixture to identical conditions for 4 days, produced a small amount of precipitate whose ^{1}H.m.r. spectrum showed no acetate methyl signal.

(iii) The iodo-acetate (125) (165 mg) and triphenyl phosphine (195 mg) were dissolved in acetonitrile (5 ml). After refluxing the mixture for 18 h, ^{1}H.m.r. of the product - obtained after removal of solvent - showed only starting material.

(b) Bromo-acetate (125) (R = CH_3, X = Br)

This halide was subjected to the conditions in (a) above, with similar results.

(c) Iodo-benzoate (125) (R = Ph , X = I)

This halide was subjected to the conditions in (a) above; similar results were obtained, although decomposition of starting material to unidentified artefacts was more rapid.

(d) Tosylate (124) (R = CH_3)

An attempt to form a phosphonium tosylate from (124) (R = CH_3) and triphenyl phosphine failed; conditions used were those of (a), above.

E. Attempts to establish the configuration of C-7 in Z-enol (109)

Hydroxy-Epoxide (128)

To the enol (109) (500 mg) in dry methylene chloride (8 ml) at 0^{o}, was added m-chloroperbenzoic acid (625 mg) in methylene chloride (8 ml), with stirring, over 10 mins. After a further 15 mins, methylene chloride (20 ml) was added, the solution was washed with saturated aqueous sodium bicarbonate (3X), water (IX), brine (1X), and dried. Filtration and concentration gave epoxide (128), a viscous oil having ν_{max}, 3615, 1460, 1050 cm^{-1}; δ, 4.00 (m, 1H), 3.15-2.61 (m, 2H); M^{+} = 210.
(Found: C,74.6, H, 10.45. $C_{13}H_{22}O_2$ requires C, 74.3; H, 10.4%.)

Base treatment of hydroxy-epoxide (128)

The epoxide (128) (150 mg) in dry tetrahydrofuran (3 ml) under an atmosphere of nitrogen, was treated with neat sodium hydride (25 mg), and the mixture refluxed for 10h. T.l.c. analysis after this time showed only starting material.

Oxaadamantane (129)

(i) Using iodine and sodium bicarbonate[90]

To the enol (109) (140 mg) in ether (10 ml), was added a solution of sodium bicarbonate (500 mg) in water (5 ml). The heterogeneous mixture was cooled to 0^{o}, and, with vigorous stirring, a solution of iodine (380 mg) in ether (8 ml) was added dropwise over 20 mins. The reaction mixture was allowed to warm to room temperature over 3h,

and stirring continued at room temperature for a further 43 h. Excess iodine was then decomposed by cautious addition of saturated aqueous sodium bisulphite and the product isolated by ether extraction, giving, after preparative t.l.c. (d.s. 10%), oxaadamantane (129) (65 mg, 59%) a colourless oil having ν_{max}, 1465, 1445, 1375, 1345, 1330, 1200, 1095, 1085, 1015, 970, 915 cm^{-1}; δ , 5.90-5.25 (m, 2H), 4.15 (m, $W_{\frac{1}{2}}$ = 10Hz, 1H), 1.00 (t, J = 7Hz, 3H); δ , (^{13}C), 135.9 (d), 129.9 (d), 70.9 (s), 68.9 (d), 13.5 (q); M^+ = 192.

(Found: C, 81.45; H, 10.6. $C_{13}H_{20}O$ requires C, 81.15; H, 10.45%.)

(ii) Using phenyl selenyl chloride[91]

To a solution of enol (109) (388 mg) in ethyl acetate (5 ml, distilled from phosphorus pentoxide) at -78°, under an atmosphere of nitrogen, was added a solution of phenyl selenyl chloride (385 mg) in ethyl acetate (3 ml), dropwise over 10 mins, with stirring. After 15 mins at -78°, the cooling bath was removed and after 41 h at room temperature, the solvent was removed from the reaction mixture, and the residue purified by preparative t.l.c. (d.s. 10%) to give starting material (100 mg) and a second component (75 mg). Preparative t.l.c. (d.s. 5%, 2 elutions) of this latter component gave oxaadamantane (129) (60 mg), identical to that obtained above, on the basis of t.l.c., I.R. and m.s. comparisons; the ^{1}H.m.r. spectrum was similar, but the olefinic region was more complex. The ^{13}C.m.r. spectrum showed doubling of some peaks: δ , 135.8 (d), 135.6 (d), 130.2 (d), 129.9 (d), 70.9 (s), 68.9 (d), 68.0 (d).

Ozonolysis of Z-enol (109)

The enol (109) (150 mg) in methanol-ethyl acetate (25ml, 1:1) was cooled to -78° and, with stirring, treated with an oxygen-ozone stream until the blue colour persisted (ca. 3 mins). Excess ozone was removed at this temperature by a stream of nitrogen gas. Dimethyl sulphide (0.5 ml) was added in one portion, the cooling bath was removed, and stirring was continued at room temperature for 24h. T.l.c. analysis of the product showed several components, none of which corresponded to the lactol (105), by comparison. The mixture was not further investigated.

Ozonolysis of Acetate (115)

The acetate (115) (225 mg) in methylene chloride-methanol (40 ml, 1:1) was cooled to -78°, and, with stirring, treated with an oxygen-ozone stream until the blue colour persisted (ca. 5 mins). Excess ozone was removed, at this temperature, by a stream of nitrogen gas, then dimethyl sulphide (0.5 ml) added in one portion, and the mixture allowed to warm to 0° over 60 mins. The solvent was removed in vacuo, the residue dissolved in ether (3 ml), and added to a slurry of lithium aluminium hydride (100 mg) in refluxing ether. After 15 mins, the usual work-up, followed by preparative t.l.c. (d.s. 25%) gave the hydroxy-acetate (135) (25 mg), an oil having ν_{max}, 3615, 1740, 1230, 1035cm^{-1}; δ, 5.12 (m, 1H), 3.52 (d, J =6Hz, 2H), and a sharp singlet at 2.0; M^+ = 212, ($C_{12}H_{20}O_3$ requires M^+ = 212), and the diol (135') having ν_{max} ($CHCl_3$), 3610, 1040 cm^{-1};

δ , 4.02 (m, 1H), 3.43 (d, J = 5Hz, 2H); M = 152 ($M^+ = -H_2O$).

(Found: C, 71.45; H, 9.3. $C_{10}H_{16}O_2$ requires C, 71.45; H, 9.55%)

F. Production of E-enol (136) by olefin inversion.

Z-enol silyl ether (138)

To the enol (109) (7.5 g) and imidazole (6.65 g) stirring in dimethylformamide (30 ml), under an atmosphere of nitrogen, was rapidly added tert-butyldimethylsilyl chloride[92] (7.15 g) in dimethylformamide (30 ml). After 20 h water was added and the product was isolated by petroleum ether extraction. Chromatography on silica (50 g) gave Z-enol silyl ether (138) (11.00g, 92.5%) as a mobile oil having ν_{max}, 1475, 1465, 1260, 1095, 1085, 865, 835 cm^{-1}; δ (CCl_4, no TMS), 5.21-5.05 (m, 2H), 4.15-3.65 (m, 1H), 3.35-2.81 (m, 1H), 0.05 (s, 6H); M^+ = 309. (Found: C, 73.9; H, 11.8. $C_{19}H_{36}OSi$ requires C, 73.8, H, 11.55%.)

Epoxide (139)

To the olefin (138) (3.0 g) in methylene chloride (20 ml) at 0^o, was added m-chloroperbenzoic acid (1.90 g) in methylene chloride (20 ml), dropwise over 20 mins, with stirring. After a further 20 mins at 0^o, the reaction mixture was diluted with methylene chloride, and the precipitate filtered off and washed. The combined organic phase was washed with saturated aqueous sodium bicarbonate (2X), water (1X), brine (1X), and dried. Filtration and concentration gave epoxide (139) (3.3 g, 100%) as a colourless oil having ν_{max}, 1475, 1460, 1255, 1095, 870, 840 cm^{-1}; δ (CCl_4, no TMS), 4.21-3.70 (m, 1H); M = 209 ($M^+ - C_6H_{15}Si$). (Found: C, 72.2; H, 11.65. $C_{19}H_{36}O_2Si$ requires C, 72.4; H, 11.4%.)

E-enol silyl ether (140)

A mixture of lithium metal (0.42 g, 60 mmol, freshly scraped free of dark deposits under petroleum ether) and triphenyl phosphine (7.86 g, 30 mmol) in dry tetrahydrofuran (45 ml), was stirred under an argon atmosphere at room temperature for 20 h, by which time all the lithium had been consumed, and the solution was deep-red in colour.[93,94] The solution was cooled to 0°, tert-butyl chloride (2.78 g 30 mmol) in tetrahydrofuran (2 ml) was added (to react with the phenyl lithium present) and the solution allowed to warm to room temperature over 45 mins. The resulting lithium diphenyl phosphide solution was bright-red in colour.

The epoxide (139) (3.5 g, 11 mmol), in tetrahydrofuran (20 ml) and hexamethylphosphoric triamide (5 ml), was then added to the phosphide solution, over ca. 10 mins. Ninety minutes later, methyl iodide (5.68 g, 40 mmol, 2.5 ml) was added, with cooling at 0°. The colour was discharged, and a precipitate formed. After 24 h at room temperature, the reaction mixture was poured onto water and the product isolated by ether extraction.

The crude product was dissolved in a small volume of petroleum ether and filtered through a short column of silica (20 g), using 240 ml of petroleum ether. Removal of solvent gave silyl ether (140) (3.1g, 93%) as a mobile oil having ν_{max}, 1475, 1465, 1250, 1095, 1090, 870 cm^{-1}; δ (CCl_4, no TMS), 5.45-5.20 (m, 2H); M^+ = 309.
(Found: C, 73.8; H, 11.6. $C_{19}H_{36}O$ requires C, 73.8; H, 11.65%.)

E-enol (136) by deprotection of (140)

A solution of silyl ether (140) (1.1 g) in an acetic acid-water mixture (15 ml, 2:1)[92(a)] was stirred, and heated at 50° for 40 h. Water was added and the product isolated by ether extraction, including base-wash, giving E-enol (136) (608 mg, 95%), having ν_{max}, 3610, 1465, 1055, 965 cm^{-1}; δ (CCl_4), 5.42-5.15 (m, 2H), 4.21-3.41 (m, $W_{\frac{1}{2}}$ = 30Hz, 1H), 2.96-2.42 (m, $W_{\frac{1}{2}}$ = 26Hz, 1H); M^+ = 194.
(Found: C, 80.7; H, 11.55. $C_{13}H_{22}O$ requires C, 80.45; H, 11.35%.)

Acetate (147)

(i) A solution of silyl ether (140) (240 mg) in acetic acid - water (8 ml, 3:1) was stirred, and heated at 65° for 20 h. Water was added and the product was isolated by ether extraction, including base-wash. Preparative t.l.c. (d.s. 10%) gave E-enol (136) (90 mg) and the acetate (147) (35 mg), an oil having ν_{max}, 1745, 1245 cm^{-1}; δ (CCl_4), 5.45-5.20 (m, 2H), 5.15-4.60 (m, 1H), and a singlet at 2.0; M^+ = 236.
(Found: C, 76.3; H, 10.35. $C_{15}H_{24}O_2$ requires C, 76.3; H, 10.2%.)

(ii) The E-enol (136) (100 mg) and acetic anhydride (0.5 ml) were refluxed in pyridine (5 ml) for 10 h. Usual work-up, using ether as solvent, gave an acetate, identical in all respects with (147).

(iii) A sample of E-enol (136) (100 mg) was subjected to the deprotection conditions (acetic acid-water (3:1);

65°; 20 h). Preparative t.l.c. (d.s. 10%) gave starting material (64 mg) and acetate (147) (41 mg).

E-enol (136) from acetate (147)

The acetate (147) (50 mg) in dry tetrahydrofuran (3 ml) was added to a slurry of lithium aluminium hydride (20 mg) in refluxing tetrahydrofuran (8 ml). After refluxing for 30 mins, the usual work-up, using ether for extraction gave enol (136) (39 mg), identical in all respects to that obtained in the deprotection of silyl ether (140).

E-enone (141)

A stirring solution of enol (136) (1.0 g) in acetone (15 ml) at -15°, was treated dropwise with Jones reagent, until the red colour persisted. Stirring was continued for a further 30 mins at -15°, then isopropanol (1.0 ml) added, followed by saturated aqueous sodium bicarbonate, and the product isolated by ethyl acetate extraction, giving E-enone (141) (908 mg, 91%), an oil having ν_{max}, 1710, 1230, 970 cm^{-1}; δ (CCl_4), 5.61-5.02 (m, 2H); δ (^{13}C), 212.6(s); M^+ = 192. (Found: C, 81.4; H, 10.2. $C_{13}H_{20}O$ requires C, 81.2; H, 10.4%.)

Acetal (137) and Dienol (150)

A mixture of E-enone (141) (240 mg), ethylene glycol (5.0 ml, distilled from sodium), and naphthalenesulphonic acid (5 mg) in dry benzene (30 ml), was refluxed with azeotropic removal of water, for 48 h. The cooled mixture was washed successively with saturated aqueous sodium bicarbonate (2X), water (2X), brine (IX), and dried. Filtration and concentra-

tion, followed by preparative t.l.c. (d.s. 10%), gave acetal (137) (234 mg, 79%), an oil having ν_{max}, 1460, 1440, 1135, 1085, 965 cm^{-1}; δ (CCl_4), 5.45-5.30 (m, 2H), 3.91 (s, 4H); M^+ = 236.
(Found: M^+ = 236.1775. $C_{15}H_{24}O_2$ requires M^+ = 236.177620.); together with dienol (150) (18 mg) an oil having ν_{max}, 3610 1465, 1115, 1060, 965 cm^{-1}; δ, 6.21-5.42 (m, 3H), 3.81-3.40 (m, 5H), 2.72-0.82 (m, 16H, including t, J = 7Hz at 0.95); δ (^{13}C), 136.8(s), 131.6(d), 130.5(d), 129.2(d), 73.8(d), 69.10(t), 62.1(t), 13.83(q); λ_{max} = 251 nm, ε = 19,600 (EtOH); M^+ = 236.

3,5-dinitrobenzoate of (150)

A mixture of dienol (150) (23 mg), 3,5-dinitrobenzoyl chloride (25 mg) and pyridine (1.0 ml), was allowed to stand at room temperature for 24 h. The usual work-up, using ether for extraction, followed by preparative t.l.c. (d.s. 20%) gave starting material (18 mg) and the 3,5-dinitrobenzoate of (150) (5 mg), a yellow oil having ν_{max}, 3100, 1740, 1630, 1345, 1275, 925 cm^{-1}; δ (CCl_4), 9.21 (m, 3H), 6.10-5.55 (m, 3H), 4.51 (m, 2H), 3.75 (m, 3H); M^+ = 430.
(Found: M^+ = 430.17381. $C_{22}H_{26}N_2O_7$ requires M^+ = 430.17396.)

Methoxy-diene (152)

A mixture of the enone (141) (150 mg), p-toluenesulphonic acid (20 mg), and methanol (10 ml), was heated under reflux for 48 h. Removal of solvent in vacuo, followed by preparative t.l.c. (d.s. 10%) gave starting material (130 mg),

and methoxy-diene (152) (9 mg), an oil having ν_{max}, 1465, 1105, 965 cm^{-1}; δ, 6.21-5.40 (m, 3H), 3.19 (s, 3H superimposed on m, 1H); M^+ = 206 ($C_{14}H_{22}O$ requires M^+ = 206.)

This labile diene (152) partially decomposed while recording the ^{13}C.m.r. spectrum ($CDCl_3$, 25°, accumulating data over 72 h) and signals in the spectrum could not be assigned unambiguously. However, the olefinic region of the ^1H.m.r. spectrum was exactly superimposable on that of hydroxy-diene (150).

G. A Second Model System

Enol (159)

The Wittig procedure used to produce Z-enol (109) was utilized here, except that the phosphonium salt used was methyltriphenylphosphonium iodide.

After chromatography, (159) could be obtained in 71% yield, having m.p. 44-46°; ν_{max}, 3620, 3090, 1640, 1055, 915 cm^{-1}; δ , 6.02-5.41 (m, 1H), 5.13-4.70 (m, 2H), 3.92 (m, $W_{\frac{1}{2}}$ = 28 Hz, 1H), 2.80 (m, $W_{\frac{1}{2}}$ = 28Hz, 1H); δ (^{13}C), 144.8(d), 111.9(t),65.11(d); M = 148(M^+ - 18).

(Found: C, 79.75; H, 10.75. $C_{11}H_{18}O$ requires C, 79.5 ; H, 10.85%.)

Enone (160)

The enol (159) (560 mg) in acetone (5 ml) at 0°, was treated with Jones reagent, dropwise with stirring, until the red colour persisted. Stirring was continued for 15 mins at 0°, then isopropanol (1.0 ml) added, followed by saturated aqueous sodium bicarbonate, and the product was isolated by ethyl acetate extraction, giving enone (160) (533 mg, 100%), m.p. 63.5-65°, having ν_{max}, 3095, 1715, 920 cm^{-1}; δ , 5.95-5.41 (m, 1H), 5.11-4.80 (m, 2H); δ (^{13}C), 212.7(s); M^+ = 164.

(Found: C, 80.5; H, 10.0 . $C_{11}H_{16}O$ requires C,80.5; H, 9.75%.)

Attempted Wittig reaction on enone (160)

A Wittig procedure identical to that used to produce Z-enol (109), was attempted here. Only starting material was recovered.

Hydroxy-acid (164) and its methyl ester

To a stirring solution of diisopropylamine (242 mg, 2.4 mmol) in dry tetrahydrofuran (5 ml) at 0^{o}, under an atmosphere of nitrogen, was added n-butyl lithium in hexane (1.0 ml, 2.4 mmol). After cooling the mixture to -78^{o}, propionic acid (90 mg, 1.2 mmol) in tetrahydrofuran (3 ml) was added, followed (after a lapse of 1 h), by hexamethylphosphoric triamide (1.0 ml). The enone (160) (164 mg, 1 mmol) in tetrahydrofuran (5 ml) was then added dropwise over 3 mins. The temperature was maintained at -78^{o} for 40 mins, then the reaction quenched by pouring onto water, and the non-acidic components isolated by ethyl acetate extraction, giving starting enone (160) (91 mg).

The aqueous layer was acidified with dilute (6N) hydrochloric acid and the product isolated by ether extraction, giving hydroxy-acid (164) (30 mg), an oil having δ, 6.50 (m, 2H, exchangeable with D_2O), 6.00-5.52 (m, 1H), 5.21-4.70 (m, 2H), 3.90-3.22 (m, $W_{\frac{1}{2}}$ = 30Hz, 1H), 2.62-1.00 (m, 16H, including d, J = 7Hz at 1.25; slight shoulder on the latter, suggesting unequal mixture of epimers); M^{+} = 238.

(Found: M^{+} = 238.15687. $C_{14}H_{22}O_3$ requires M^{+} = 238.156885.)

Exposure of (164) to ethereal diazomethane, gave, after

preparative t.l.c. (d.s. 10%) the corresponding hydroxy-ester, an oil having ν_{max}, 3615, 1725, 1170 cm^{-1}; δ, 5.90-5.41 (m, 1H), 5.08-4.62 (m, 2H), 3.80-3.20 (s, 3H superimposed on m, 1H), 3.00 (s, 1H, exchangeable with D_2O); M^+ = 252.

(Found: M^+ = 252.17244. $C_{15}H_{24}O_3$ requires M^+ = 252.172534.)

Tosylation of hydroxy-acid (164)

To hydroxy-acid (164) (35 mg) in pyridine (3 ml) at 0°, was added tosyl chloride (110 mg) in one portion.[101] After swirling to effect dissolution, and allowing to stand at 0° for 15 h, the reaction mixture was poured onto dilute (10%) aqueous sodium carbonate and the non-acidic components isolated by ether extraction, giving only small amounts of tosyl chloride.

The aqueous layer was acidified (6N hydrochloric acid) and the product isolated by ether extraction giving an acidic product (20 mg) having ν_{max}, 3400-3100 (br), 1755 (sh), 1710, 1220, 915 cm^{-1}; δ, 8.50 (m, 1H, exchangeable with D_2O), 6.10-5.42 (m, 2H), 5.05-4.61 (m, 2H), 3.41-2.90 (m, $W_{\frac{1}{2}}$ = 30Hz, 1H); M^+ = 220. The structure of this acid is tentatively assigned as (165).

(Found: M^+ = 220.14632. $C_{14}H_{20}O_2$ requires M^+ = 220.146321.)

Decarboxylation of (165)

The acid (165) (20 mg) was dissolved in quinoline (3 ml) and, under an atmosphere of nitrogen, the mixture was heated at reflux[103] for 2 h. The cooled reaction mixture was

poured onto water, and the product isolated by ether extraction, giving only 4 mg of an oil, having ν_{max}, 3060, 1260, 1100,1010 cm^{-1}; the ^{1}H.m.r. spectrum and the m.s. were of little diagnostic value.

Attempts to β-lactonise the methyl ester of hydroxy-acid(164)

(i) To the ester (30 mg) in dry tetrahydrofuran (8 ml) under a nitrogen atmosphere, was added neat sodium hydride (ca. 25 mg). The mixture was refluxed for 16 h, but t.l.c. analysis showed only starting material, by comparison.

(ii) To the ester (30 mg) in dry benzene (3 ml), was added p-toluenesulphonic acid (5 mg). The mixture was refluxed for 24 h, but t.l.c. analysis showed only starting material, by comparison.

Attempts to β-lactonise the hydroxy-acid (164)

(i) To the hydroxy-acid (164) (20 mg) in benzene (5 ml), was added p-toluenesulphonic acid (5 mg), and the mixture was refluxed for 24 h. Removal of solvent returned only starting material, as shown by ^{1}H.m.r. analysis.

(ii) To the hydroxy-acid (164) (30 mg) in dry pyridine (1.0 ml), under an atmosphere of nitrogen, was added dicyclohexylcarbodiimide (32 mg) in pyridine (2 ml). The mixture was heated at 80° for 40 mins, then stirred at room temperature for 24 h. No precipitate (an insoluble urea is expected)was visible.

The mixture was then heated at 80° for a further 20 h, but no precipitate formed. The mixture was diluted with

ethyl acetate and washed with dilute hydrochloric acid, water, brine and dried. Filtration and concentration gave a semi-solid mass (66 mg) which, from t.l.c. analysis, was clearly not starting material. Preparative t.l.c. (d.s. 30%) gave a clear oil (39 mg), having ν_{max}, 3600-3300 (br), 1715, 1645, 1390 cm^{-1}, clearly neither the β-lactone (170) nor diene (167). The product was not further investigated.

(iii) Diene (167)

A solution of hydroxy-acid (164) (60 mg) and N,N'-carbonyldiimidazole (169) (48 mg) in tetrahydrofuran (1.0 ml), was protected from the atmosphere and stirred at room temperature for 21 h. Benzene (5 ml) and diazabicyclononene[107] (1 drop, ca. 15 mg) was added, and stirring continued for 24 h at room temperature.

The solvent was removed in vacuo, the residue taken up in benzene and filtered through a short column of alumina (Grade III, neutral). Removal of solvent from the filtrate gave a colourless oil (20 mg,54%), the diene (167), having ν_{max}, 3090, 1830 (weak, C = O of residual β-lactone), 1640, 1440, 910, 860 cm^{-1}; δ (CCl_4), 5.81-4.55 (m, 4H, including typical pattern for $-CH = CH_2$), 3.05-0.85 (m, 16H upfield limb of vinyl methyl doublet visible at 1.55 δ); M^+ = 176. ($C_{13}H_{20}$ requires M^+ = 176).

(iv) Re-formation of enone (141) from hydroxy-acid(164)

A solution of hydroxy-acid (164) (60 mg) and N, N'-carbonyldiimidazole (169) (80 mg) in tetrahydrofuran (3.0 ml) was refluxed for 1 hr. The solvent was removed in vacuo

and preparative t.l.c. (d.s. 10%) gave enone (141) (28 mg, 67%), identical in all respects to an authentic sample. A small amount of diene (167) (5 mg) was also recovered.

H. The Third S_E' Model System

1,3-dibromoadamantane[113(b)] (178)

Bromine (50 ml), boron tribromide (2.5 ml) and aluminium bromide (ca. 20 mg), were placed in a dry three-necked flask equipped with a mechanical stirrer, efficient condenser and a stopper. With stirring, adamantane (13.6 g) was added portion-wise, by removal of the stopper from the flask. After complete addition, the mixture was refluxed for 90 mins, cooled, diluted with carbon tetrachloride (200 ml), and poured carefully onto water (300 ml). Then, with cooling in an ice-bath, saturated sodium bisulphite solution (200 ml) was added to destroy excess bromine. The organic layer was washed with water (2X), then dried (over calcium chloride). Filtration and concentration gave 1,3-dibromoadamantane (178) (26 g, 88%), m.p. 110-113° (lit.[113(b)] 112-113°). This compound was easily distinguished from 1-bromoadamantane (85) on t.l.c.

Attempted fragmentation of 1,3-dibromoadamantane (178)[113(a)]

A mixture of dibromide (178) (1.0 g), dioxan (10 ml) and sodium hydroxide solution (1N, 10 ml), was heated at 180° for 18 h in a sealed glass tube. The vessel was allowed to cool over 3 h in the furnace, then the reaction mixture was poured onto water and the product isolated by n-butanol extraction. Crystallisation of the crude product from chloroform gave 1,3-dihydroxyadamantane (179) (450 mg, 75%), having ν_{max} ($CHCl_3$, saturated solution), 3610 cm^{-1}; δ (d_6-DMSO: $CHCl_3$ (1:1)), 4.11 (s, 2H), 2.20 (m, 2H), 1.52 (m, 12H); M^+ = 168.

(Found: C, 71.5; H, 9.7. $C_{10}H_{16}O_2$ requires C, 71.45; H, 9.55%.)

The mother liquor from the crystallisation did not have any carbonyl-containing compounds.

The above procedure carried out in either a sealed silica tube, or a steel autoclave* at 180° gave similar results.

Successful fragmentation of 1,3-dibromoadamantane (178)

To a mixture of 1,3-dibromoadamantane (178) (1.0 g), sodium hydroxide (1N, 10 ml) and dioxan (10 ml) in a silica tube, was added ferric chloride (27.6 mg) in water (1 ml). The sealed tube was heated at 180° for 18 h, cooled over 4 h, then the contents poured onto water and the product isolated by ether extraction. Preparative t.l.c. (d.s.20%) gave enone (54) (320 mg, ca. 60%), m.p. 160-163° (lit.[113(a)] 160-164°), having ν_{max}, 3080, 1720, 1700 (sh), 1225, 920, 895 cm^{-1}; δ (CCl_4), 4.80 (br s, 2H), 2.32 (m, 10H), 1.91 (br s, 2H).

Further attempts to reproduce this fragmentation were uniformly unsuccessful, giving only diol (179).

Ozonide (181)

A solution of enone (54) (124 mg) in ethyl acetate (30 ml), was cooled to -78° and, with stirring, was treated with an oxygen-ozone stream until the blue colour persisted (ca 5 mins). Nitrogen gas was bubbled through the solution

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* We thank Organon Laboratories, Newhouse, for the use of a steel autoclave.

to remove excess ozone and the temperature allowed to rise to room temperature over 60 mins. After 4 h at room temperature, dimethyl sulphide (0.3 ml) was added in one portion and, after 2.5 h, the solvent was removed in vacuo and the semi-crystalline product purified by preparative t.l.c. (d.s. 30%), giving ozonide (181) (65 mg, 45%), as a crystalline solid having ν_{max} ($CHCl_3$), 1735, 1710, 1380, 1350, 1345, 1140, 1065, 1000 cm^{-1}; δ, 5.00 (s, 2H), 2.51 (br s, 6H), 2.21-1.80 (m, 6H); δ (^{13}C), 208.4(s), 107.5(s), 93.2(t) $M^+ = 198$. ($C_{10}H_{14}O_4$ requires $M^+ = 198$).
Ozonide (181) gave a deep-brown colouration when placed on acidified (aqueous acetic acid) starch-iodide paper.

Dione (174)

To a solution of ozonide (181) (68 mg) in glacial acetic acid was added freshly activated zinc dust (30 mg). After stirring at room temperature for 3.5 h, a second portion of zinc (30 mg) was added, and after 12 h, water was added and the product was isolated by ethyl acetate extraction, including base wash, giving, after preparative t.l.c. (d.s. 50%), the dione (174) (20 mg, ca. 30%), m.p. 252-256° (lit.[108] 254-256°), having ν_{max} ($CHCl_3$), 1720, 1340, 1105 cm^{-1}; δ, 2.84 (m, 2H), 2.20-2.71 (m, 10H).

Benz-bicyclo (3.3.2)decan-3,7-dione (182)

The procedure followed was that of Föhlisch.[117]
To a solution of phthalaldehyde (183) (8.0 g) and diethyl-3-ketoglutarate (184) (24.24 g) in dry ethanol (120 ml), was added diethylamine (0.3 ml). The mixture was swirled, became

slightly hot, and was allowed to stand at 0° for 18 h. The crystals which formed were filtered off (13.0 g) and washed with ice-cold ethanol. Two successive crystallisations of the mother liquors (from ethanol at 0°) gave further crops of crystals (10.5 g, 0.68 g). The total yield of tetraester was 24.18 g (75%), m.p. 137-141° (lit.[177] 139-141°).

A solution of the tetraester (23.5 g) in glacial acetic acid (129 ml) and concentrated hydrochloric acid (35.5 ml), was refluxed for 12 h. The solvents were then removed in vacuo and the residue triturated with ether. The crude dione was purified by sublimation (1.0 g portions): impurities were removed by subliming the crude product at 60° and 0.5 torr, for 2 h; the cold finger was removed and any sublimed material washed off. The solid which then sublimed between 60° and 110° (at 0.5 torr) was pure dione (182). Total yield 16.0 g (75% from tetraester), m.p. 195-197°. (lit.[177] 196-199°); having ν_{max} ($CHCl_3$), 1705 cm^{-1}; δ, 7.18 (s, 4H), 3.22 (m, 2H), 2.85 (d, J = 4Hz, 8H).

Exo-methylene ketone (185)

Sodium hydride (500 mg) was heated in dry dimethyl sulphoxide (10 ml), under an atmosphere of nitrogen, at 75-80° (bath temperature) for 1.5 h. 0.25 ml of the cooled dimsyl anion solution was added to methyltriphenylphosphonium iodide (203 mg, 0.5 mmol) in dimethyl sulphoxide (3 ml). After 10 mins, a solution of the dione (182) (107 mg, 0.5 mmol) in the smallest possible volume[78(b)] of dimethyl sulphoxide was added, slowly, over 10 mins. After 20 h at room temperature, the reaction mixture was poured onto ice and the

product isolated by ether extraction. Preparative t.l.c. (d.s. 30%) gave the exo-methylene ketone (185) (61 mg, 57%), having ν_{max}, 3090, 3015, 1690, 1455, 1200, 1035, 915 cm^{-1}; δ , 7.25 (s, 4H), 5.00 (s, 2H), M^+ = 212. ($C_{15}H_{16}O$ requires M^+ = 212).

Enone (186)

Using a procedure identical to that above, enone (186) could be isolated in 8% yield, having ν_{max}, 3015, 1695, 1195, 1050 cm^{-1}; δ , 7.08 (s, 4H), 5.21 (t, J = 7Hz, 1H), 0.96 (t, J = 6Hz, 3H); M^+ = 246.
(Found: M^+ = 240.15168. $C_{17}H_{20}O$ requires M^+ = 240.151407.)

Variations of the above procedure included simply extending the reaction time or heating the ylid-dione mixture (80^o, sealed tube). In both these cases, no olefin was produced.

Further attempts to improve yield of enone (186)

(i) To a suspension of n-propyltriphenylphosphonium iodide (648 mg, 1.5 mmol) in dry tetrahydrofuran (2.0 ml) under an atmosphere of nitrogen, was added n-butyl lithium in hexane (1.0 ml, 1.5 mmol). The resulting red ylid solution was stirred for 40 mins at room temperature then hexamethylphosphoric triamide (0.5 ml) added. The mixture was cooled to 0^o, and the dione (182) (150 mg, 0.75 mmol) in tetrahydrofuran (2.0 ml) and hexamethylphosphoric triamide (0.5 ml), added slowly. After 24 h at room temperature, the reaction mixture was poured onto water and

the product isolated by ethyl acetate extraction. T.l.c. analysis of the product (staining in iodine vapour) showed a heavy base-line and some triphenyl phosphine, but no enone (186), by comparison with authentic samples.

(ii) Repeating this procedure using hexamethylphosphoric triamide as sole solvent, gave a similar result.

(iii) Repeating (ii), but heating the ylid-dione mixture in a sealed tube at 110^{o} for 18 h, gave similar results.

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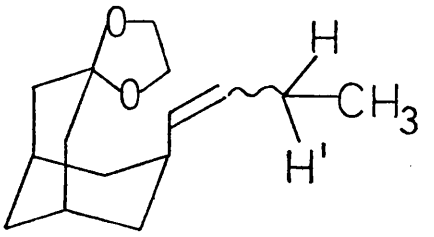
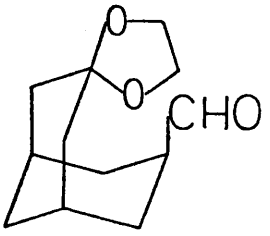
PART II

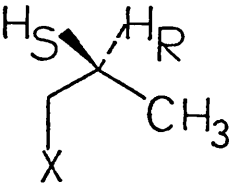
(i) Introduction


O
O
H
CH3
H'

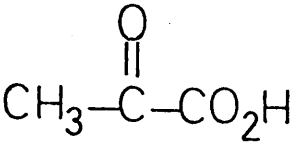
(1)


O
O
CHO

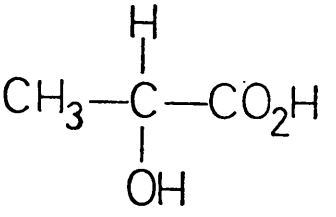
(2)


HS
HR
CH3
X

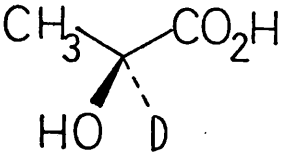
(3)


O
CH3—C—CO2H

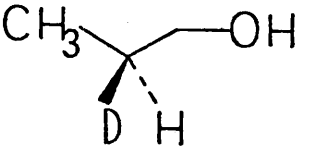
(4)


H
CH3—C—CO2H
OH

(5)


CH3
CO2H
HO
D

(6)


CH3
OH
D
H

(7)

(i) Introduction

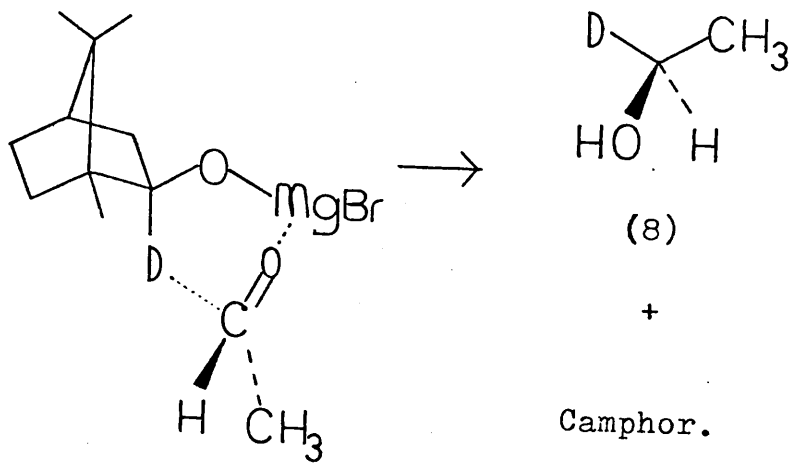
Recalling the retrosynthesis of target molecule (1) (see Part I of thesis), a proposal was made to combine - by a Wittig olefination - a bicyclic component (e.g. (2)) and a three-carbon fragment (3), the latter having either H_R or H_S specifically replaced by deuterium, and being ultimately derived from an optically active lactic acid derivative.

Methodology for obtaining the bicyclic portion has been outlined (see p. 24). The labelled unit((3), H_R or H_S = D) might be synthesised by one of several methods:

(a) By an enzyme-mediated process. The capacity of enzymes to catalyse stereospecific transformations is well-known, and successful attempts[1] have been made to harness this potential for use in certain laboratory transformations.

The chemical relationship between pyruvic acid (4) and lactic acid (5), and a detailed knowledge[2] of their interconversion in vivo, makes the transformation (4) → (5) of use for the introduction of isotopic labels: thus incubation of pyruvic acid (4) with liver alcohol dehydrogenase (LAD) in the presence of the deuteriated coenzyme NAD-D, results[3] in the formation of (S)-(+)-lactic-2-^{2}H acid (6). A sequence involving protection of the acid, tosylation of the alcohol and S_N2 displacement of this tosylate with lithium aluminium hydride, followed by deprotection and reduction of the acid, would lead to the deuteriated propanol (7) (cf. (3)).

The limitation of this method would be the expense of the enzyme and coenzyme which would severely limit the scale of reactions.

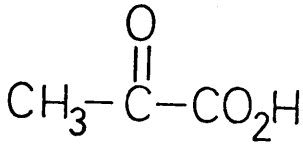


(8)

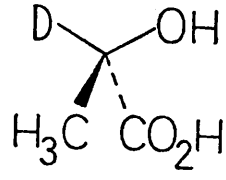
+

Camphor.

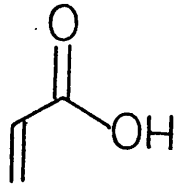
Figure (1)



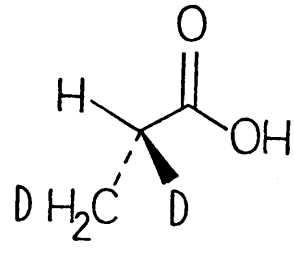
(4)



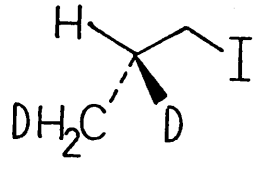
(9)



(10)



(11)



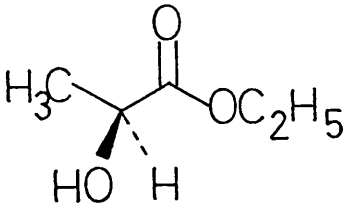
(12)

(b) By chemical asymmetric induction. The underlying concept here is the use of a chiral (non-enzymic) component to induce chirality in another (achiral) molecule. For example, the enantiotopic faces of unsymmetrical carbonyl compounds can be differentiated by isobornyloxymagnesium bromide; thus on reaction of acetaldehyde and 1-deuteriated isobornyloxymagnesium bromide[4], Figure (1), (S)-(-)-ethanol-1-^{2}H(8) results.

The extent of differentiation will depend on the relative energies of the two possible diastereomeric transition states, a reflection, inter alia, of the relative bulk of the substituents flanking the carbonyl group.

With pyruvic acid (4) as substrate in this reduction, a preponderance of (9) might be expected on the basis of the above rationalisation - i.e. assuming that CO_2H is more bulky than $-CH_3$. (9) could be transformed, in similar fashion to its enantiomer (6), into a suitable form.

A more direct approach could be the asymmetric deuteriation of acrylic acid (10), or an ester, utilising a convenient catalyst; the product of cis-addition of D_2 gas to the upper face of (10), as written, would be (11). The presence of an extra deuterium atom might cause some complication of spectra, but, in principle, (11) would be useful and could easily be converted to a convenient form, e.g. (12). However, understanding of such asymmetric reactions is not well developed,[5] and considerable exploratory work might be necessary to secure a high enantiomeric excess.



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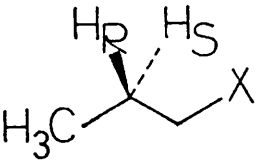

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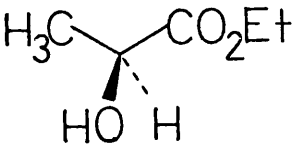

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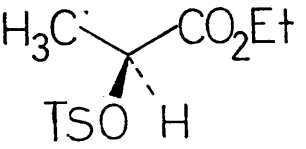

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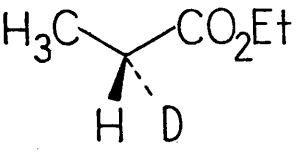

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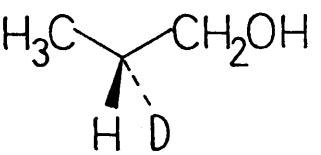
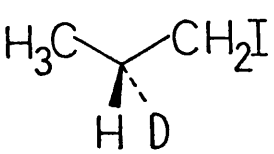


(16)



(17)

Figure (2)

(c) Starting with an optically active molecule. The availability of optically pure compounds, at low costs, from major chemical companies, can obviate the need for the - frequently unpredictable - asymmetric transformations of achiral molecules. The range of such materials is ever-increasing as enzyme-technology gains momentum, and even now, company catalogues offer a surprising variety of chemicals in optically active form.

Ethyl (L)-(+)-lactate (13) is one such compound[6] and has potential in the present context. Conversion of the alcohol to a good leaving group (tosylate or mesylate) and displacement by deuteride ion in S_N2 fashion would give a three-carbon fragment with a specific deuterium label at C-2, as required.

Assuming that the required form for this unit is the iodide (i.e. (3), X = I) - which is suitable for conversion to a phosphonium salt for a Wittig reaction - then the exact chemical constitution of this iodide will depend upon the source of deuteride ion employed in the S_N2 displacement:

(a) Treatment of (14) with sodium cyanoborodeuteride[7] or lithium triethylborodeuteride,[8] Figure (2), will exchange tosylate for deuterium with inversion of configuration[7,8] at C-2, giving (15), which can then be readily converted to (17). The latter, when used in the construction of target molecule (1) labels the pro-$\bar{R}$ position with deuterium.

(b) Use of the less selective reducing agent lithium aluminium deuteride for tosylate displacement in (14), Figure

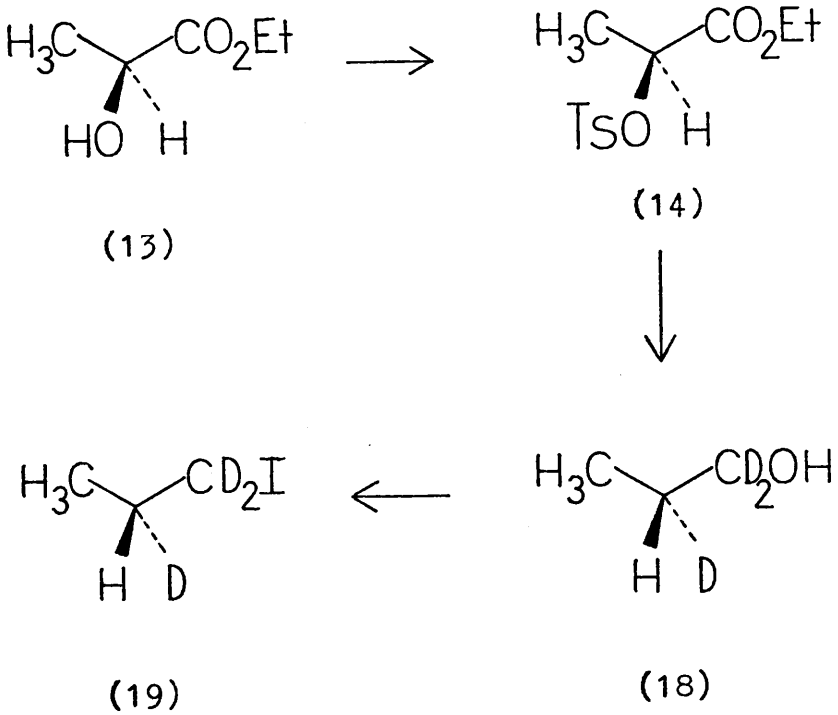
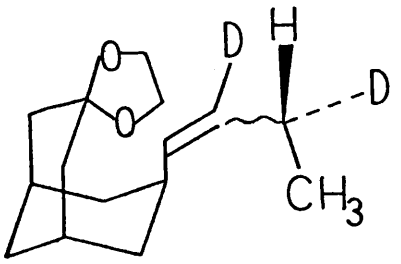
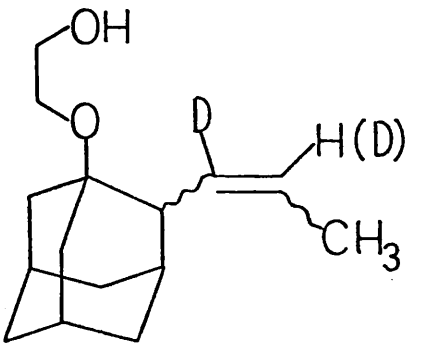


Figure (3)



(20)



(21)

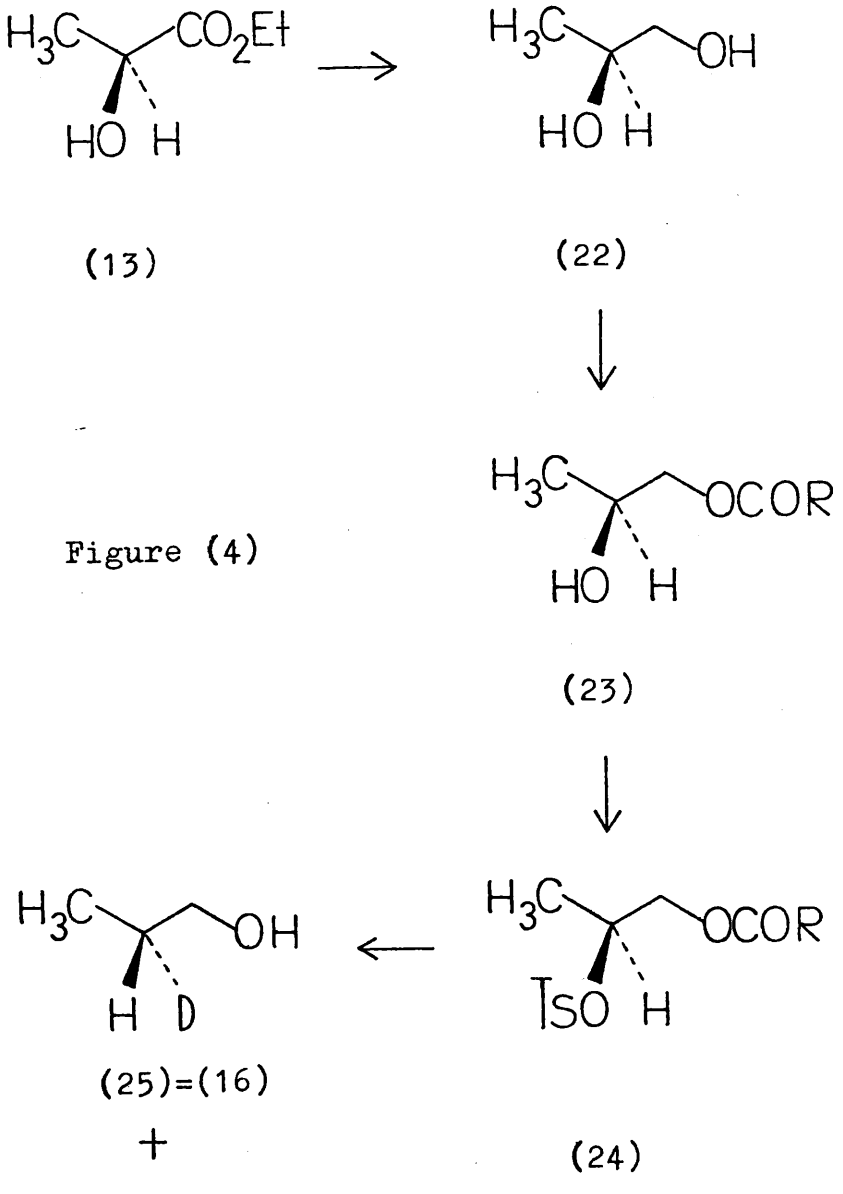

H3C
CO2Et
HO H
(13)
H3C
OH
HO H
(22)
H3C
OCOR
HO H
(23)
H3C
OCOR
TsO H
(24)
H3C
OH
H D
(25)=(16)
+
RCD2OH
(26)

Figure (4)

(3) will result in trideuterioalcohol (18), and thence the trideuteriopropyl iodide (19).

The model for cyclisation when (19) is the source of phosphonium salt would be (20) in which there is a vinyl deuterium atom in addition to the required label. Cyclisation of (20) to (21) maintains the vinylic character of this 'extra' deuterium atom, and its presence could simplify analysis of the ^{1}H.m.r. spectrum: in the products, (21), the vinylic proton content could be measured directly. In addition, the signal for the vinylic proton would be much simplified. Further, determination of the optical purity of alcohol (18) would be facilitated. As such, then, the presence of 'extra' deuterium atoms would not constitute a difficulty.

There is a further method by which the required label could be introduced, which, like (a) above, would result in only one deuterium atom in the three-carbon unit. It is shown in Figure (4). Reduction of ethyl-(L)-(+)-lactate (13) to 2-(S)-propan-1,2-diol (22) by treatment with lithium aluminium hydride followed by selective acylation of the primary hydroxyl, tosylation of the secondary hydroxyl, and then lithium aluminium deuteride reduction of (24) gives the required alcohol (25), together with an equivalent of dideuterioalcohol (26). (25) could then be utilised as in Figures (2), (3).

The advantage of the routes shown in Figures (3) and (4) over that in Figure (2) is the avoidance of the very expensive reducing agents used therein.

Thus the routes outlined in Figures (3) and (4) were

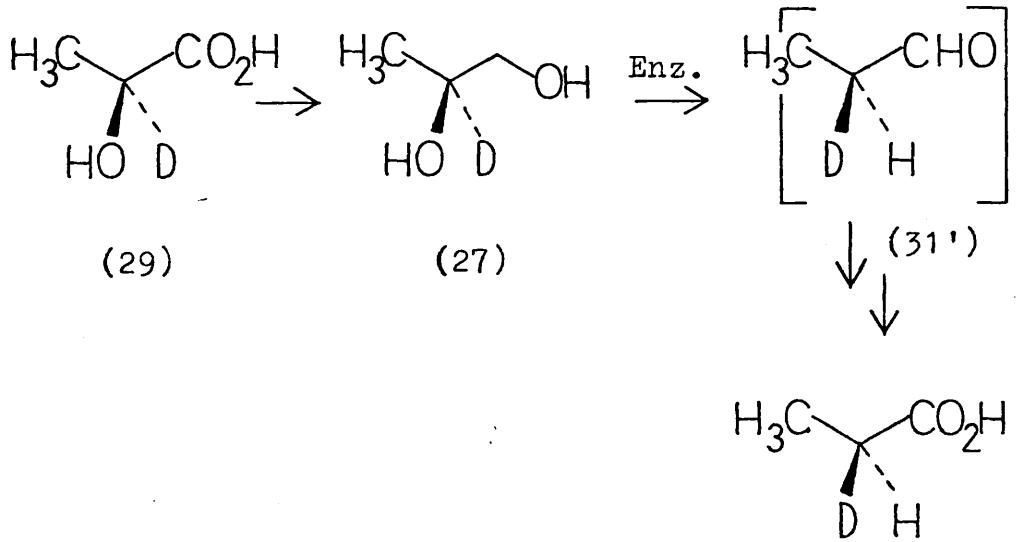

H3C
CO2H
HO D
(29)
H3C
OH
HO D
(27)
Enz.
H3C
CHO
D H
(31')
H3C
CO2H
D H
(32)
H3CO2C
CH3
HO H
(30)
HO2C
CH3
HO H
(28)
Enz.
H3C
CDO
D H
(31)

Figure (5)

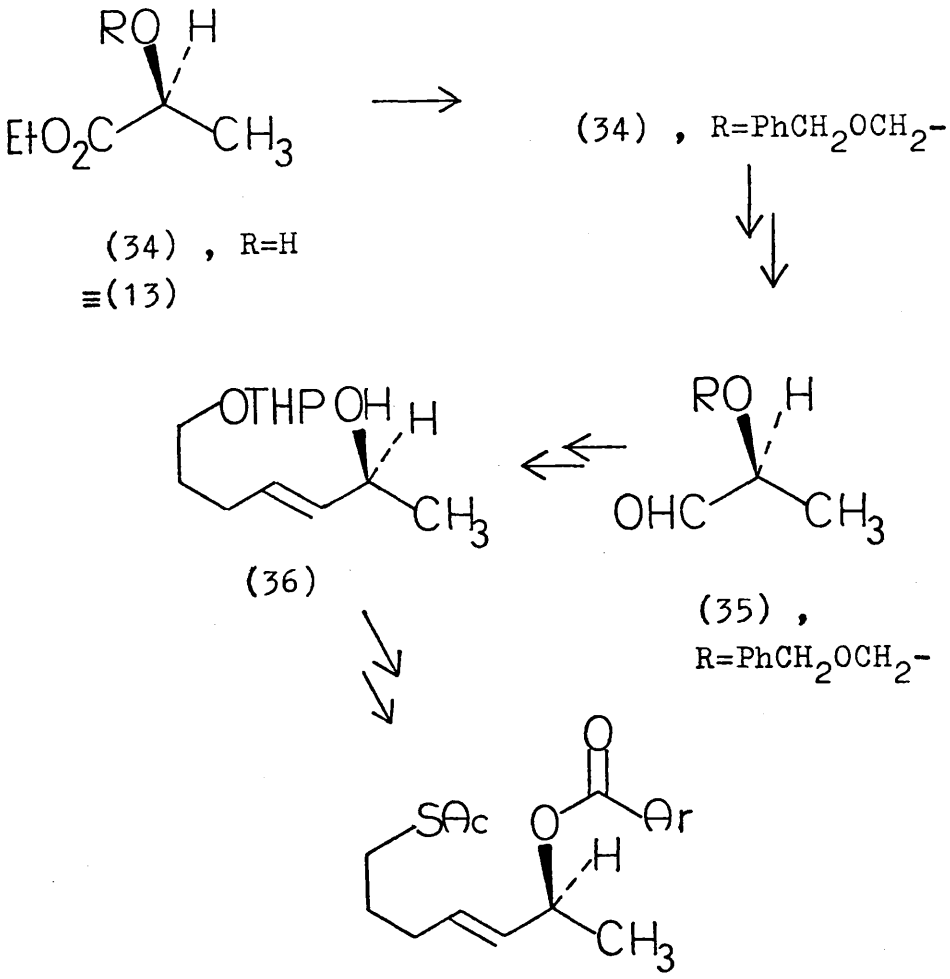

RO H
EtO2C
CH3
(34) , R=H
≡(13)
(34) , R=PhCH2OCH2-
OTHP OH H
CH3
(36)
RO H
OHC
CH3
(35) ,
R=PhCH2OCH2-
O
SAc
O
Ar
H
CH3
(33)

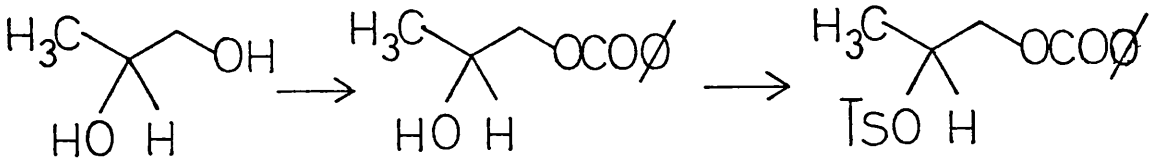
Figure (6)

selected for investigation.

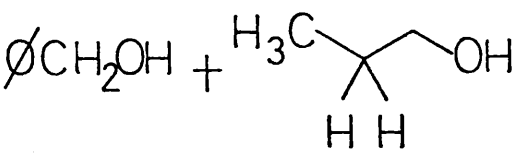
A literature search revealed that optically active lactate esters had been used in mechanistic investigations of both enzymic and non-enzymic reactions. Arigoni and co-workers[3,9] have investigated the steric course of the conversion of propan-1,2-diols to propionaldehyde in the presence of propanediol dehydrase and a B_{12}-coenzyme, and for this purpose required specifically deuteriated propane diols. (S)-(+)-propan-1,2-diol-2-^2H (27) and (R)-(-)-propan-1,2-diol-1,1-$^2H_2$ (28), were obtained from (S)-(+)-lactic-2-^2H acid (29) and methyl-(R)-(+)-lactate (30), respectively, as shown in Figure (5). These diols were then incubated with the enzyme preparation, and, after enzymic reduction of the propionaldehydes (31), (31') obtained, and then oxidation of the so-formed propanols to a common propionic acid, (32), it was established that the propane diol rearrangement involves inversion of configuration at the migration terminus - see Figure (5).

But the use of lactate esters has not been confined to the introduction of isotopic labels. Stork,[10] in his recent reinvestigation of the stereochemical preference of the S_N2' reaction, prepared substrate (33) from ethyl-(L)-(+)-lactate, (34) (R = H), as outlined in Figure (6), in a series of stereoselective transformations. The optical purity of the alcohol (36) was found to be ca. 76% using ^{19}F.m.r. by Mosher's method[11] (vide infra), and the route illustrates the synthetic utility of small chiral molecules.

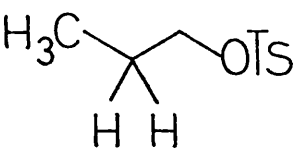
(ii) Discussion



(37) (38) (39)

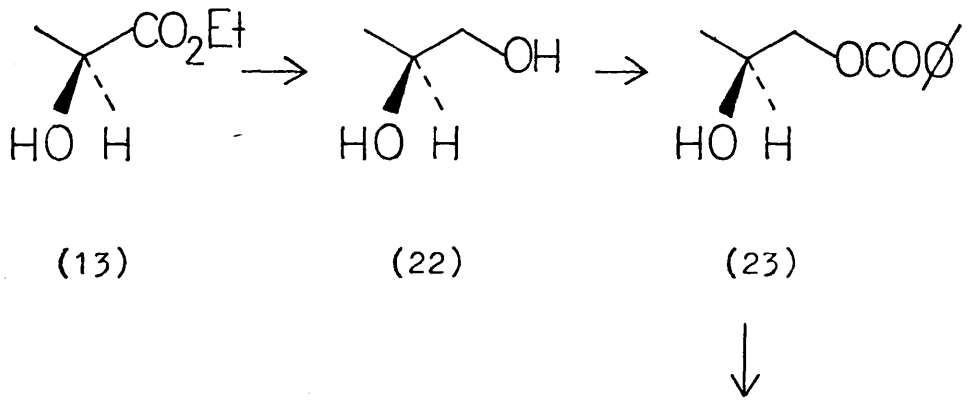


(41) (40)



(42)

Figure (7)



(13) (22) (23)

(43) (25) (24)

Figure (8)

Discussion

(A) A route to (R)-propan-1-ol-2-^{2}H (25)

The scheme of Figure (4) was first of all investigated using racemic materials - i.e., starting from (±)-propan-1, 2-diol, (37), Figure (7). Thus (37) could be selectively benzoylated using one equivalent of benzoyl chloride in pyridine; tosylation of (38) gave the crystalline tosylate (39), and subsequent lithium aluminium hydride reduction produced a mixture of n-propanol (40) and benzyl alcohol (41). Manipulation of (40) proved difficult, due to its volatility, but by an 'in situ' tosylation of the intact lithium aluminium hydride reduction product of (39), using pyridine and tosyl chloride at 0°, reasonable yields (⩾ 30%) of the much less volatile n-propyl tosylate (42) could be obtained. Under these conditions, even in an excess of tosyl chloride, no benzyl tosylate formed, making chromatographic separation of (41) and (42) a routine matter. n-Propyl tosylate (42) obtained in this manner was identical to an authentic sample.

Having shown this route to be viable, attention was turned to optically active materials. Hydride reduction of (S)-(-)-ethyl lactate (13), Figure (8), gave 2-(S)-propan-1, 2-diol (22) which, without isolation, was selectively benzoylated to (23); subsequent tosylation at 0° gave the crystalline tosylate (24).

The optical purity of (23) was ascertained by examining the ^{1}H.m.r. spectrum in the presence of the chiral shift reagent Eu(hfc)$_3$[6*], while simultaneously decoupling the -C$\underline{H}_2$-OCOPh protons by double irradiation. The optical purity

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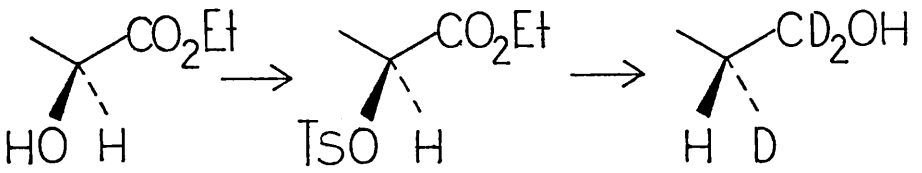
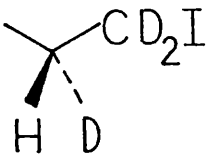
* (hfc) = 3-(heptafluoropropylhydroxymethylene)-d-camphorato.

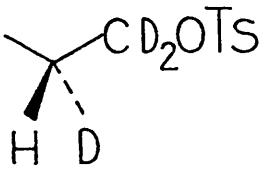


(13) (14) (18)

Figure (3)



(19)



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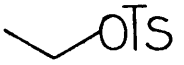

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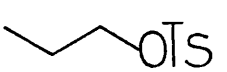


(42)

was >95%. (Identical double resonance experiments on the racemate (38) had shown that the enantiomeric carbinol proton resonances were distinguishable by this method.)

With the chiral benzoate-tosylate (24) in hand, the scheme of Figure (3) was next investigated.

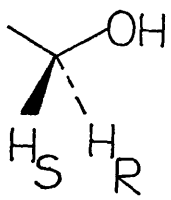
(B) A route to (R)-propan-1-ol-1,1,2-$^2H_3$ (18)

(S)-(-)-ethyl lactate (13) was tosylated in the usual manner, Figure (3), the tosylate (14) reduced by lithium aluminium deuteride in refluxing tetrahydrofuran, and the intact reduction product treated, as above, with tosyl chloride in pyridine at 0°, giving a mixture of (R)-n-propyl-1,1,2-$^2H_3$ tosylate (45) and ethyl tosylate (44); these could be separated by repeated preparative t.l.c.

The ^{1}H.m.r. spectrum of (45) showed, in addition to the expected aromatic and aryl methyl resonances, an unresolved multiplet at δ 1.5 and a broadened doublet at δ 0.9. Undeuteriated propyl tosylate, (42), shows a resolved multiplet at δ 1.65 and a triplet at δ 0.9. The mass spectrum of (45) showed an intense parent ion at M = 217.

(C) Attempts to distinguish the enantiotopic protons on C-2 of propanol (40), by ^{1}H.m.r. spectroscopy

Although the displacement of tosylate by a nucleophile is generally considered to proceed by an S_N2 mechanism[12] - i.e. with inversion of configuration - it has been shown that, in some cases, hydride ion displacement of tosylate may be accompanied by as much as 20% racemisation[13]. The chiral



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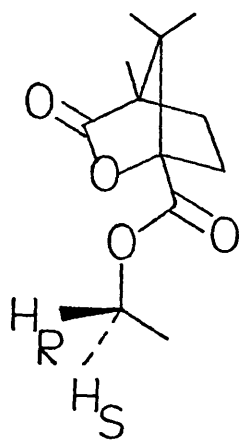


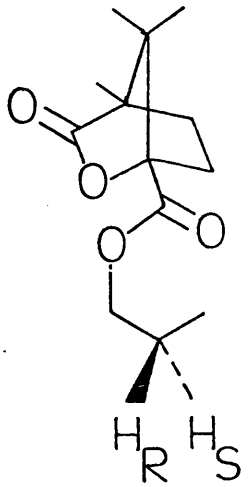
(47)

deuteriated tosylates (43) and (45) arise by such displacements, and it was therefore necessary to establish the optical purity of these compounds, if they were to serve as labelled side-chain precursors for the S_E' model (1).

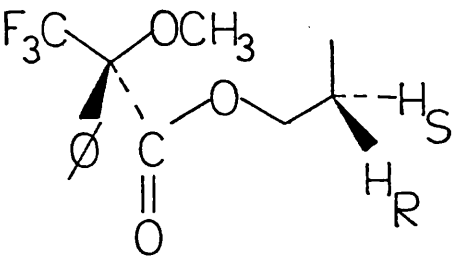
Compounds which are chiral by virtue of isotopic differences (e.g. tosylates (43) and (45)) have low optical rotations,[14] and so other methods have been sought as probes for such chirality. Enzymatic methods for determination of enantiomeric excess (ee) are sensitive, but limited to a small number of compounds. Of the physical methods available, ^{1}H.m.r. spectroscopy offers a convenient tool for some molecules of the type CHDR'R".

Since magnetic resonance is a non-chiral phenomenon, it cannot be used to investigate optical activity directly - i.e. it cannot differentiate between enantiomeric or enantiotopic atoms or groups, but it can, in theory, distinguish diastereomeric or diastereotopic atoms or groups. For example, Gerlach[15] has shown that the enantiotopic protons (H_R, H_S) of ethanol (46) can be distinguished by making the ethyl ester (47) of (-) camphanic acid, and examining its ^{1}H.m.r. spectrum at 100 MHz in the presence of the non-chiral shift reagent $Eu(dpm)_3$. Thus the optical purity of chiral 1-deuteriated ethanol samples may be determined.[15]

With a view to determining the optical purity of tosylates (43) and (45), three chiral esters of n-propanol were made, and their ^{1}H.m.r. spectrum were examined in the presence of shift reagent, to see if the enantiotopic protons



(48)



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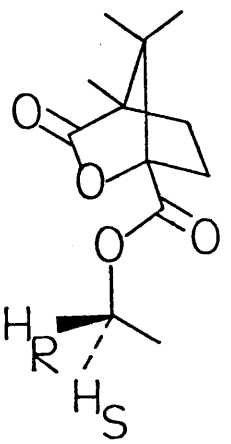


(47)

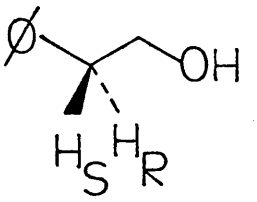
on C-2 (of n-propanol) could be distinguished; the availability of only deuteriated n-propyl tosylates (and not the corresponding alcohols, due to their volatility) necessitated that the chiral esters be formed, not by the usual method of "alcohol + acid chloride", but by tosylate displacement by carboxylate anion:

(a) Treatment of n-propyl tosylate (42) with an excess of the sodium salt of (-) camphanic acid in dimethyl sulphoxide at 80°, gave n-propyl camphanate (48). However, the diastereotopic protons of interest, H_R and H_S, overlapped with the multiply-split signals of those protons belonging to the chiral acid moiety.

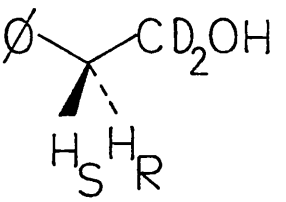
(b) The n-propyl ester (49) of (+)-2-methoxy-2-trifluoromethylphenylacetic (MTPA) acid[11] was made in analogous fashion to camphanate (48). Its ^{1}H.m.r. spectrum showed the expected phenyl and methoxyl signals; unexpectedly, the OCH_3 signal was split, presumably by long-range coupling to ^{19}F nuclei, since the splitting was evident in the parent acid also. The 90 MHz spectrum of (49) in the presence of the bulky chiral shift reagent $Eu(hfc)_3$ showed only marginal shifts of H_R and H_S, and substantial shifts for both the methoxyl and o-phenyl protons.

(iii) The n-propyl ester of (-)-MTPA acid[11] was made, as above, but again the ^{1}H.m.r. spectrum showed no useful shifts.

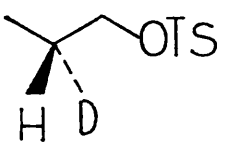
That H_R and H_S of ethyl camphanate (47) are distinguishable, but H_R and H_S of (48) are not, is probably due to two factors:



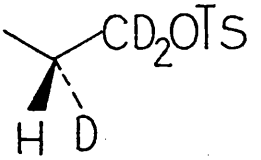
(50) , H_R or H_S = D



(51) , H_R or H_S = D



(43)



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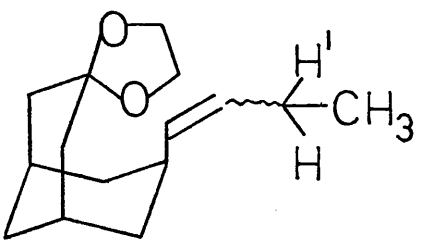
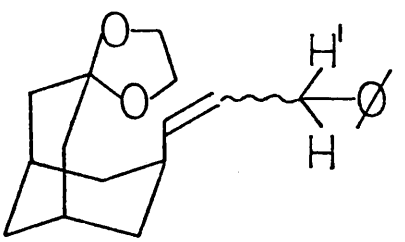
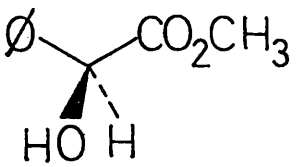


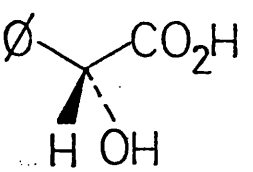
(1)



(52)



(53)



(54)

(i) Proximity of H_R, H_S of (47) to the molecular functionality, and, therefore, to the central metal ion of the shift reagent used.

(ii) H_R and H_S of (47) are 'isolated' in the ^{1}H.m.r. spectrum - i.e. there is no overlap with protons belonging to the acid-derived part of the ester, as was the case for (48).

This latter factor could be eliminated in the case of (48) by, for example, using a chiral perfluorated camphanic acid for ester formation, in which case the ^{1}H.m.r. spectrum of the ester would be free from unwanted resonances.

But, it might be more prudent to side-step the problem completely by using chiral deuteriated 2-phenylethanols (50) and (51) as replacements for n-propyl tosylates (43) and (45) as labelled side-chain precursors ; this would modify the original S_E' model (1), to (52). The adoption of these aromatic alcohols would have several distinct advantages:

(a) 2-phenylethanols are easily handled - cf. the volatile n-propanol.

(b) The benzylic protons H_R and H_S of (50) and (51) are readily distinguished by ^{1}H.m.r. spectroscopy of the alcohols in the presence of Whitesides'[16] chiral shift reagent Eu(dcm)$_3^*$.

(c) (50), H_R=D (>95% ee) and (51), H_S=D (> 70% ee) have been reported in recent literature; they are derived, respectively, from (S)-(-) methyl mandelate (53)[7], and

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* (dcm) = d,d-dicampholylmethanato.

(R)-(-)-mandelic acid (54).[17]

In summary, routes to the desired chiral deuteriated tosylates (43) and (45) were achieved; however, the optical purities of these compounds could not be determined using presently available techniques - although, from literature analogy,[18] they may be estimated at not less than 80%, and possibly significantly higher. To circumvent this problem, it is suggested that chiral deuteriated phenylethanols (50) and (51) could be used.

(iii) Experimental

Experimental (For general directions see p 51)

A. (i) n-propyl tosylate (42) from (±)-propan-1,2-diol (37)

(±)-[2-hydroxypropyl] benzoate (38)

To the diol (37) (1.0 g) in pyridine (10 ml) at 0°, was added benzoyl chloride (1.85 g, 1 equiv, redistilled) in pyridine (10 ml), dropwise, with stirring, over 10 mins. After 17.5 h at 0°, dilution with ether, and the usual work-up gave a pale-yellow oil, which, after column chromatography (silica gel, 25 g), gave monobenzoate (38) (2.08 g, 84%) as an oil having ν_{max}, 3615, 1730, 1605, 1245, 1105 cm^{-1}; δ 8.05 (m, 2H), 7.45 (m, 3H), 4.20 (m, 4H), 3.8 (s, 1H, exchangeable with D_2O), 1.20 (m, 3H); M^+ = 180.
(Found: C, 66.7; H, 6.45. $C_{10}H_{22}O_3$ requires C, 66.6; H, 6.65%.)

(±)-[2-tosyloxypropyl] benzoate (39)

To the benzoate (38) (540 mg) in pryidine (6 ml) at 0°, was added tosyl chloride (665 mg) in pyridine (6 ml), dropwise over 30 mins. After 48 h at 0°, dilution with ether-benzene and the usual work-up, gave a crystalline solid. Crystallisation from hexane gave (39), m.p. 99-102°, having ν_{max}, 1730, 1605, 1370, 1160-1260, 1105 cm^{-1}; δ, 8.0-7.15 (m, 9H), 5.00 (m, 1H), 4.35 (m, 2H), 2.35 (s, 3H), 1.45 (d, J = 7Hz, 3H); M^+ = 334.
(Found: C, 61.1; H, 5.15. $C_{17}H_{18}O_5S$ requires C, 61.1; H, 5.4%)

n-Propyl tosylate (42)

To a slurry of lithium aluminium hydride (100 mg) in refluxing tetrahydrofuran (10 ml), was added benzoate-tosylate (39) (200 mg) in tetrahydrofuran (5 ml), over 5 mins. The mixture was refluxed for 48 h, while being protected from atmospheric moisture.

The reaction mixture was cooled to 0^{o} and, with stirring, a solution of tosyl chloride (500 mg) in pyridine (5 ml) was added slowly. After 30 h at 0^{o}, the usual work-up gave, after preparative t.l.c. (d.s. 20%), benzyl alcohol (41) (65 mg) and n-propyl tosylate (42) (20 mg), the latter having δ (CCl_4), 3.95 (t, J = 7Hz, 2H), 2.45 (s, 3H), 1.65 (m, 2H), 0.90 (t, J = 7Hz, 3H); M^{+} = 214. (42) was identical to an authentic sample of n-propyl tosylate, prepared by tosylation of n-propanol.

(ii) (S)-[2-tosyloxypropyl] benzoate (24) from (S)-(-)-ethyl lactate (13)

(S)-propan-1,2-diol (22)

To a slurry of lithium aluminium hydride (2.0 g) in refluxing tetrahydrofuran (40 ml), was added (S)-(-)-ethyl lactate (13) (10.0 g) in tetrahydrofuran (40 ml), over 2h. After 30 h under reflux, the reaction was quenched by adding drops of saturated aqueous ammonium chloride, until a white precipitate formed. Chloroform (300 ml) was added and the solution filtered through a pad of celite and potassium carbonate. Removal of solvent from the filtrate gave crude diol (22) (5.94 g, 90%) which without further purifica-

tion, was selectively benzoylated, as below.

(S)-[2-hydroxypropyl] benzoate (23)

To the crude diol (22) (ca. 250 mg) in pyridine (10 ml) at 0°, was added a solution of benzoyl chloride (420 mg, 0.9 equiv.) in pyridine (10 ml), over 15 mins. After 18 h, dilution with ether-benzene and the usual work-up, gave, after column chromotography (silica gel, 25 g), (23), R = Ph, as an oil whose spectral (I.R., ^{1}H.m.r., m.s.) characteristics and t.l.c. behaviour were identical to those of racemate (38).

(S)-[2-tosyloxypropyl] benzoate (24)

Tosylation of (23) by the usual procedure, gave, after crystallisation, (24), R = Ph, whose spectral (I.R., ^{1}H.m.r., m.s.) characteristics and t.l.c. behaviour were identical to the racemate (39).

(B) (R)-n-propyl-1,1,2-$^2H_3$ tosylate (45) from (S)-(-)-ethyl lactate (13)

(S)-ethyl-2-tosyloxypropionate (14)

To (S)-(-)-ethyl lactate (13) (2.36 g), in pyridine (8 ml), at 0°, was added tosyl chloride (4.0 g) in pyridine (8 ml), over 15 mins. After 18 h at 0°, dilution with ether-benzene and usual work-up gave (14) as an oil having ν_{max}, 1745, 1370, 1150-1235 cm^{-1}; δ (CCl_4), 7.65 (AB quartet, J = 8 Hz, 4H), 4.82 (q, J = 7Hz, 1H); M^+ = 272. (Found: C, 53.25; H, 5.85. $C_{12}H_{16}O_5S$ requires C, 53.0; H, 5.9%)

(R)-n-propyl-1,1,2-$^{2}H_{3}$ tosylate (45)

To a slurry of lithium aluminium deuteride (160 mg) in refluxing tetrahydrofuran (8 ml), was added the tosylate (14) (816 mg) in tetrahydrofuran (10 ml), over 15 mins. After refluxing for 42 h, the reaction mixture was cooled to 0° and, with stirring, tosyl chloride (1.14 g) in pyridine (8 ml) was added slowly over 10 mins. After 24 h, dilution with ether and the usual work-up gave an oil. Preparative t.l.c. (d.s. benzene) separated residual tosyl chloride from a mixture of ethyl tosylate (44) and (45). The latter was separated by preparative t.l.c. (4X, d.s. 5%), giving (45) (65 mg), an oil having ν_{max}, 1600, 1370, 1190, 1180, 965 cm^{-1}; δ, 7.5 (AB quartet, J = 8Hz, 4H), 2.45 (s, 3H), I.65 (m, 1H), 0.90 (d, J = 7Hz, 3H); M^{+} = 217. (Calculated for $C_{10}H_{11}D_{3}O_{3}S$, M^{+} = 217). The ethyl tosylate (44) (80 mg) isolated had δ, 7,55 (AB quartet, J = 8Hz), 4.18 (q, J = 7Hz, 2H), 2.45 (s, 3H), 1.15 (t, J = 7Hz, 3H).

(C) Preparation of chiral esters of n-propanol

(i) n-Propyl ester of (-)-Camphanic acid

A mixture of the sodium salt of (-) camphanic acid (220 mg, 2 equiv.) and n-propyl tosylate (42) (105 mg, 1 equiv.) in dimethyl sulphoxide (3 ml), was heated at 80° for 30 mins, then ice added and the product isolated by ether extraction, giving, after preparative t.l.c. (d.s. 15%), n-propyl camphanate (48) as a viscous oil having ν_{max}, 1795, 1750, 1745, 1270, 1165, 1100, 1055 cm^{-1}; δ, 4.25 (distorted triplet, J = 6Hz), 2.62-1.55 (m, 8H), 1.2-0.80 (m, 12H); M^{+} = 240

(Calculated for $C_{13}H_{20}O_4$, $M^+ = 240$).

(ii) n-Propyl ester of (+)-2-methoxy-2-trifluoromethyl-phenylacetic (MTPA) acid

The procedure of (i), above, was used, except with the sodium salt of (+)-MTPA acid (2 equiv.). Preparative t.l.c. (d.s. 20%) gave the propyl ester (49), an oil having ν_{max}, 1755, 1450, 1250, 1185, 1120, 1020 cm^{-1}; δ, 7.55 (m, 5H), 4.35 (t, J = 7Hz, 2H), 3.60 (m, 3H), 1,80 (m, 2H), 0.95 (t, J = 7Hz, 3H); $M^+ = 276$.
(Calculated for $C_{13}H_{15}O_3F_3$, $M^+ = 276$.)

(iii) n-propyl ester of (-)-MTPA acid

The procedure of (i) above was used, except using the sodium salt of (-)-MTPA acid (2 equiv.). Preparative t.l.c. (d.s. 20%) gave the oily n-propyl ester, whose spectral (I.R., ^{1}H.m.r., m.s) characteristics and t.l.c. behaviour were identical to those of its enantiomer, (49).

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