STUDIES   IN   RING   EXPANSION

A   THESIS   PRESENTED   TO

THE   UNIVERSITY   OF   GLASGOW

FOR   THE   DEGREE   OF   Ph.D.

BY

JAMES   O'DONNELL

CHEMISTRY   DEPARTMENT

SEPTEMBER   1976

ProQuest Number: 13804095

ProQuest 13804095

To Helen and to my parents.

CONTENTS

SUMMARY.

The work described in this thesis has been divided into three parts :

Chapter One describes several unsuccessful attempts to add dichlorocarbene to the enol-acetate derived from bicyclo[3.3.1] nonan-9-one. This was intended as a new route to the relatively inaccessible bicyclo[4.3.1] deca-2,10-dione system.

Chapter Two is concerned with investigations into the fragmentations of 4-tosyloxy bicyclo[3.2.1] and[3.3.1] alkanones as routes into specifically-substituted medium ring compounds. Two new fragmentation reactions are described, one of which has been studied in detail. Also included is a discussion of the factors affecting the hydrolysis of certain cycloheptene gem-diesters.

Chapter Three outlines synthetic approaches to a possible intermediate in the biogenesis of sesquiterpenes of the carotane family. No sesquiterpene as such has been isolated, but it is believed that with suitable modification of the reaction conditions, such a synthesis might have been achieved.
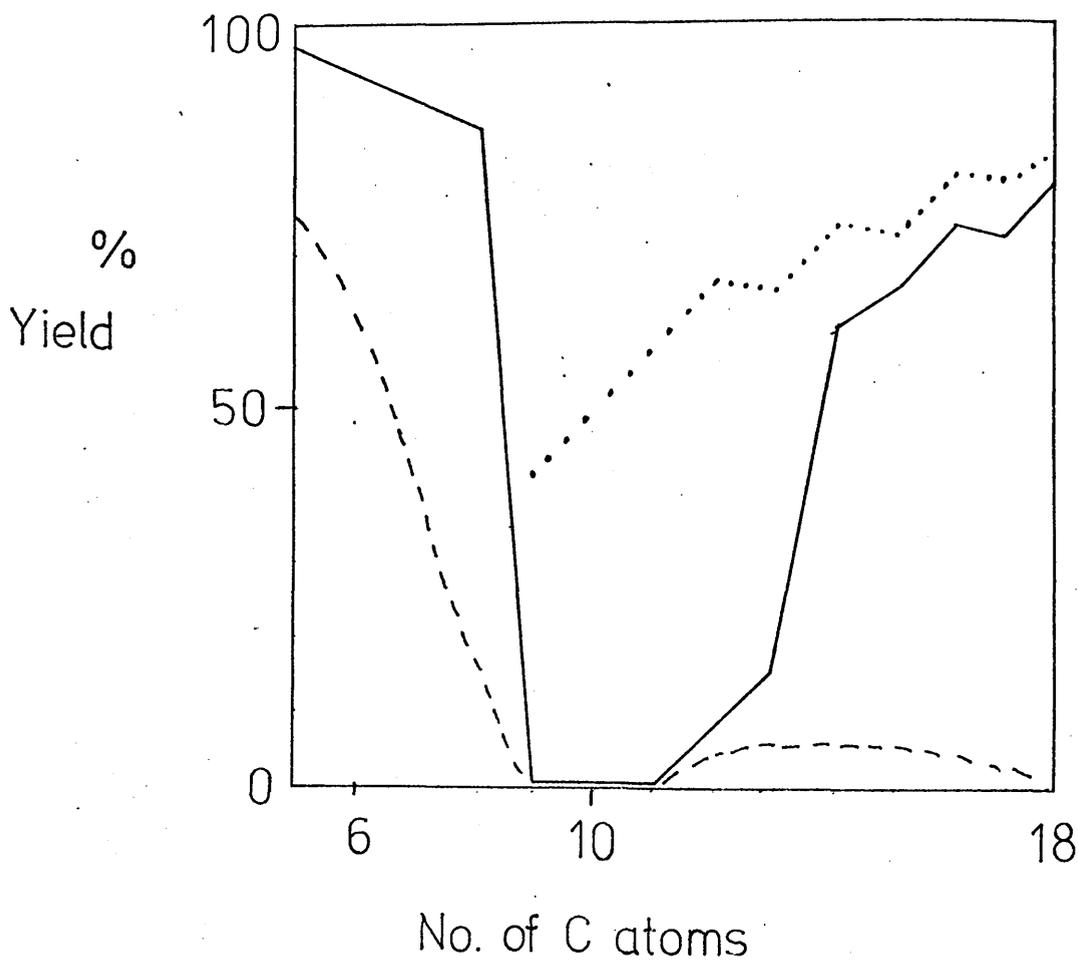
INTRODUCTION

Fig.1

Although synthetic organic chemistry is well-endowed with methods for the manipulation of functional groups and well-supplied with a variety of acyclic and 5- and 6-membered cyclic starting materials, the synthesis of medium and large rings is still underdeveloped. During the past fifty years, the rapid expansion in the field of natural product chemistry has meant that the organic chemist has had to devise many new synthetic procedures in order to keep abreast of the ever-increasing variety of chemical structures which he may be required to construct.

The earliest methods of synthesising an alicyclic compound involved a ring-closure reaction, the ease of which depended on the strain of the ring formed and the distance between the reacting centres. Three of the most general of these methods were

1) Ruzicka's distillation of the calcium and thorium salts of dicarboxylic acids, which was most successful in the preparation of 5-, 6- and 7-membered rings from adipic, pimelic and suberic acids respectively[1];

2) The Thorpe-Ziegler reaction involving an intra-molecular condensation of dinitriles under high dilution conditions[2], and

3) Prelog's acyloin synthesis, introduced in 1947[3], which provided a good route to the larger rings. Figure 1 shows the dependence of yield upon ring size for the above three methods.

Since then, many additional ring-closures (such as the Dieckmann cyclisation of diesters) have been

SCHEME 1

(1)

(2)

(3)

(4)

CH₂OTs
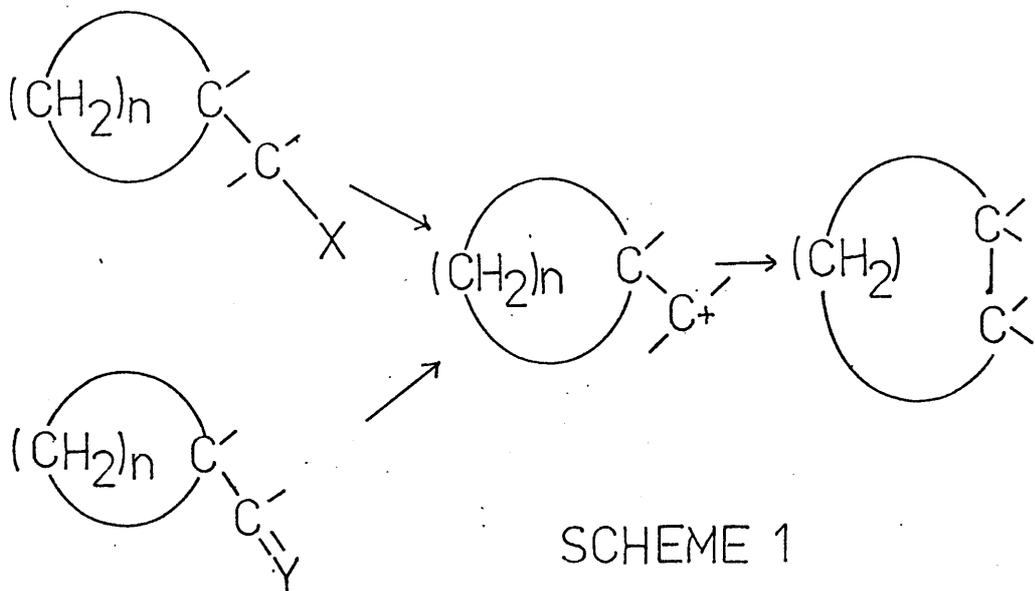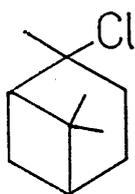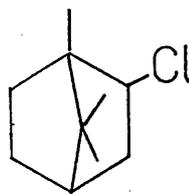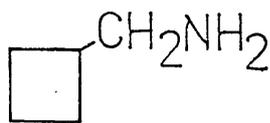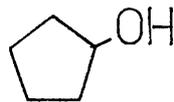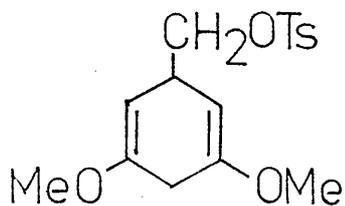
(5)
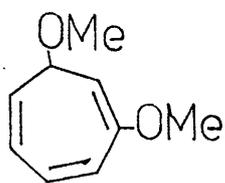
(6)
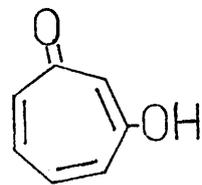
(7)

devised, but if the alicyclic rings are required to include particular substituents in particular positions, the methods presently available are less than adequate. One approach to this problem is a development of ring-expansion reactions, and this is the topic with which this thesis is concerned.

Ring expansions which increase the ring size by one carbon are well known[4]. The Wagner-Meerwein reaction (the general form of which is shown in Scheme 1) makes use of the fact that an intramolecular nucleophilic displacement may be accompanied by an enlarging of the ring system. The tendency for the intermediate carbonium ion to rearrange is directly related to the ring size and to the electronegativity of the leaving group X. Therefore, electron-withdrawing groups in the cycloalkyl portion will hinder the ring expansion, whereas electron-donating groups will facilitate it. The reaction proceeds satisfactorily for the expansion of rings from $C_3 \longrightarrow C_4$ through to $C_7 \longrightarrow C_8$, and sometimes even beyond.

Perhaps the most famous example of this type is Meerwein's conversion of pinene hydrochloride (1) to bornyl chloride (2)[5], although simpler examples had been reported earlier - the nitrous acid deamination of cyclobutyl carbinylamine (3) to cyclopentanol (4) is one[6]. More recent examples of the Wagner-Meerwein shift in the preparation of natural products include Chapman's synthesis of β-tropolone (7) from (5) via bromine oxidation of (6)[7], and Yoshikoshi's (±)-bulnesol

OTs

(8)

(9)

$(CH_2)n$ OH
C
|
C
|
X

CH_2   OH
C
|
C=Y

→

CH_2   OH
C
|
C+

→

CH_2   C=O
C

SCHEME 2

HO OTs

(10)

O
H

(11)

H

(12)

O O

HO

TsO   (13)

O O

O=
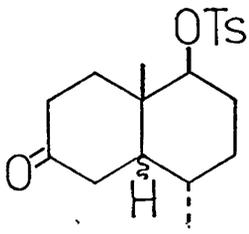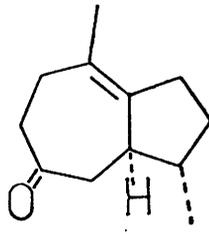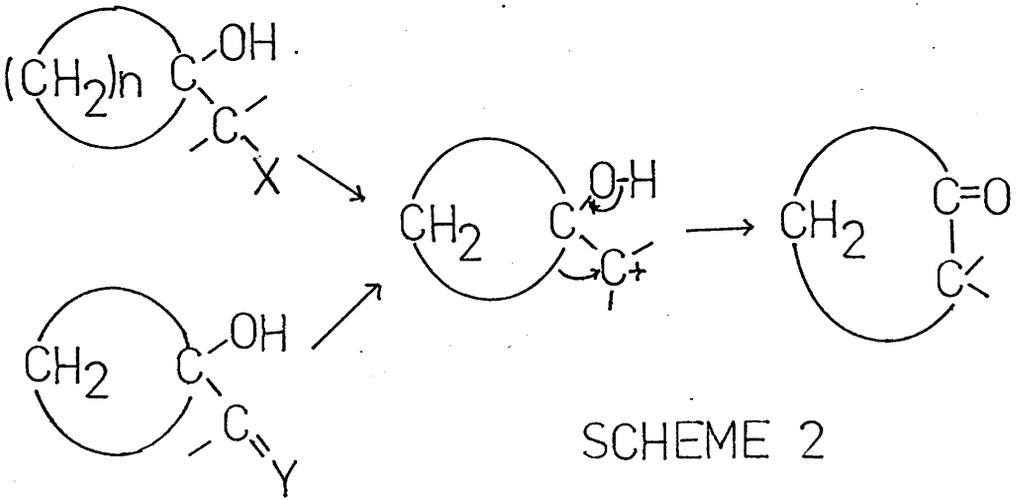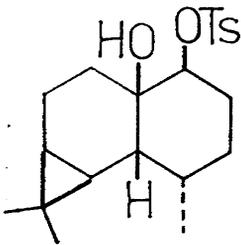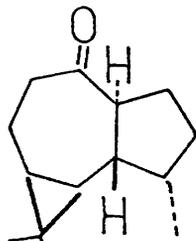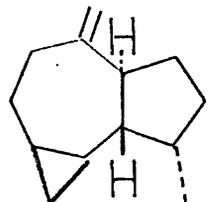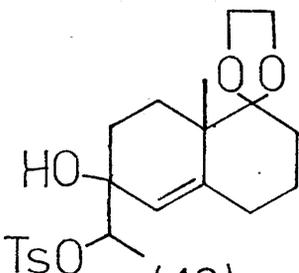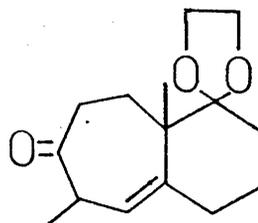
(14)

synthesis[8]. The key step in the latter, in which the
bulnesol skeleton is formed, involves the solvolytic
transformation of (8) into (9).

A very closely related ring-expansion method is
the Pinacol rearrangement, whose general form can be
seen in Scheme 2.. This can be considered as a Wagner-
Meerwein shift in which the substrate molecule has a
hydroxyl group at C(1) on the ring. This provides an
even greater driving force for the ring expansion, as
the product formed is a ketone, which is likely to be
stable. Essentially the same factors govern the use-
fulness of the Pinacol as govern the Wagner-Meerwein.
The reaction is one of the most widely-used ring
enlargement techniques, as witnessed by Buchi's
synthesis of (-)-aromadendrene (12), which involves
the rearrangement of the hydroxy-tosylate (10) to the
ketone (11) in the presence of activated alumina[9].
Similarly, Corey has utilised this transformation in
his total synthesis of longifolene, an intrinsic part
of which is the conversion of (13) into (14) in the
presence of lithium perchlorate[10].

As an example of the plethora of named reactions
in the chemical literature, the Wagner-Meerwein
rearrangement begat the Pinacol rearrangement which
in turn begat the Tiffeneau-Demjanov rearrangement.
The last-mentioned is a Pinacol in which the leaving
group is molecular nitrogen, i.e. it is essentially a
nitrous acid deamination. A simple example of its use
in the homologation of cyclic ketones is shown in

$+ \; Li\text{-}CH_2\text{-}\overset{+}{N}\equiv\overset{-}{C} \longrightarrow$

$HO\text{-}CH_2\text{-}\overset{+}{N}\equiv\overset{-}{C}$

$\longrightarrow \quad HO\text{-}CH_2\overset{+}{N}H_3\overset{-}{Cl} \quad \longrightarrow \quad HO\text{-}CH_2\overset{+}{N}_2 \quad \longrightarrow$

SCHEME 3

$\overset{+}{N}=\overset{-}{N}$

$\overset{+}{N}_2$

$CH\text{-}R$

$+ \; N_2$

$\overset{-}{\ddot{O}} \quad CH\overset{+}{N}_2 \\ R \longrightarrow$
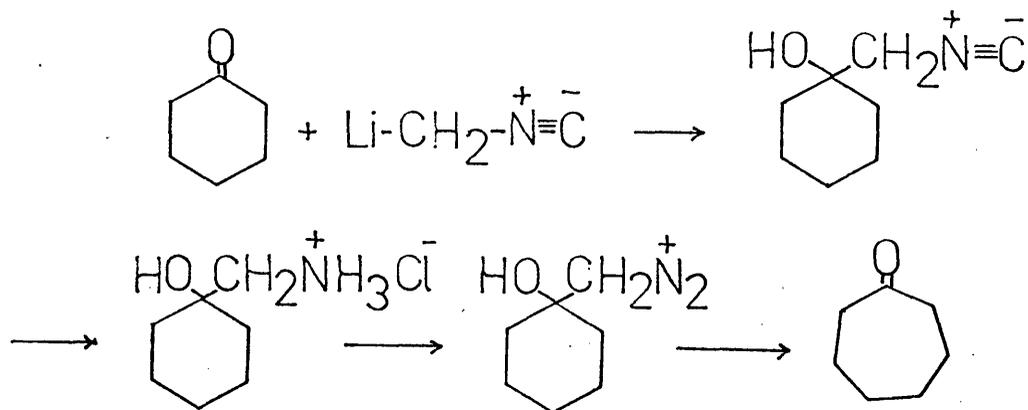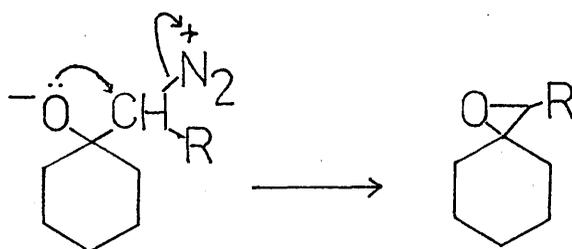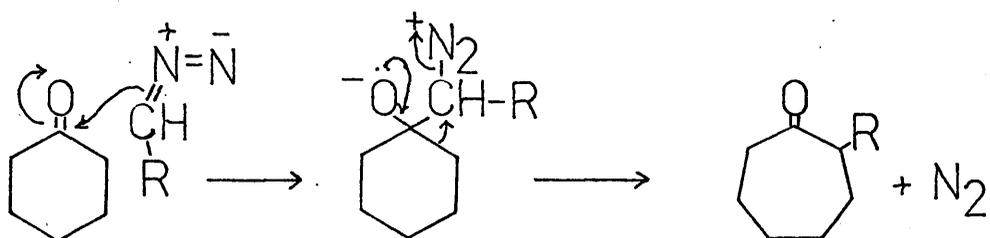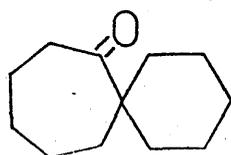
SCHEME 4

(15)

Scheme 3, in which cyclohexanone is condensed with isocyanomethyllithium to eventually produce cyclo-heptanone[11].

Another widely-used one-carbon ring enlargement process is the treatment of cyclic ketones with diazoalkanes. The overall effect of this reaction is to insert a one-carbon unit into the framework of the ring, but the regiospecificity is low, and a mixture of products will usually result when a non-symmetrical cycloalkanone is used as the substrate. The mechanism can be likened to that of the above-mentioned Tiffenaeu-Demjanov reaction, as described in Scheme 4. This also demonstrates why an almost inevitable by-product in a diazoalkane reaction is the epoxide corresponding to the starting ketone.

Most diazo ring enlargements involve diazomethane or a monosubstituted diazomethane, such as ethyl diazoacetate, N_2CH-CO_2Et. Exceptions have been reported, however, including the formation of the spiro-ketone (15) from cyclohexanone and diazocyclohexane[12], butthese tend to give an even larger number of products than usual. The expansion of larger rings $(C_7 \longrightarrow C_8$, etc.) normally proceeds in low yield, but presence of a Lewis acid catalyst can enhance this - for example, using boron trifluoride, cycloheptanone plus diazomethane yields 50% cyclo-octanone and 16% cyclononanone, while cyclo-octanone yields 44% cyclo-nonanone and 17% cyclodecanone[13]. Thus the method has its uses, but the multiplicity of products is a major
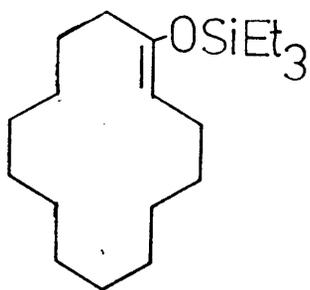
(16)
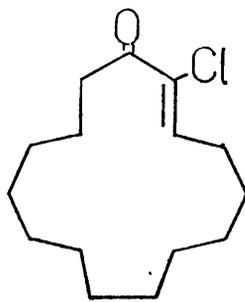
(17)
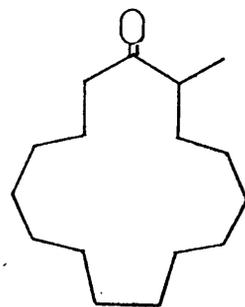
(18)
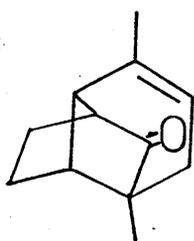
(19)

(20)
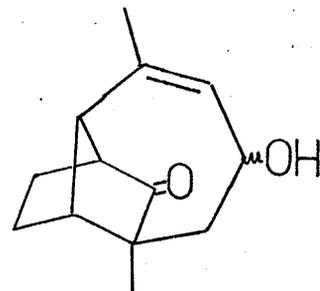
(21)
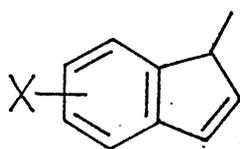
(22)
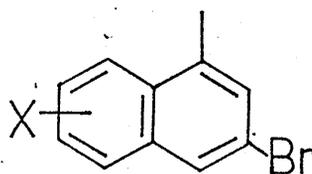
(23)

drawback.

If a ring-system contains a carbon-carbon double bond, then it is possible that a dihalocarbene, $:CX_2$, may add across it, giving a dihalocyclopropane adduct. Opening of the three-membered ring will, under the correct circumstances, lead to a ring-expanded product. For instance, in Stork's synthesis of muscone (18), dichlorocarbene generated by the thermal decomposition of sodium trichloroacetate adds to a silyl enol-ether (16) to give the homologous α-chloro enone (17)[14]. In a synthesis of longifolene, dibromocarbene from bromoform and potassium t-butoxide adds across the double bond of (19) to give the adduct (20), which undergoes a silver-ion-assisted displacement to yield the allylic alcohol (21)[15]. The above process generated the dihalocarbene by means of strong base, and this limits the applicability of the method to non-base-labile systems. However, Seyferth[16] has discovered that phenyltrihalomethyl mercury and related compounds decompose thermally to phenyl mercuric halide and dihalocarbene. This relatively mild alternative has recently been utilised in a preparation of 1-methyl-3-bromonaphthalenes from 1-methyl indenes ((22) $\longrightarrow$ (23))[17].

Turning our attention now to expansions by two or more carbons, we find that these are less common, although several standard methods do exist. An elegant pathway to seven, eight and nine membered rings involves the bridge fission of bridged bicyclic compounds. For example, a reaction developed in this department

Ph

(34)

Ph—CO₂H

$$\text{Ph}-\text{CO}_2\text{H}$$

(35)

(36)

CO₂Me

(37)

OH
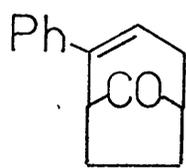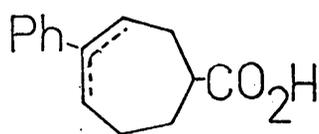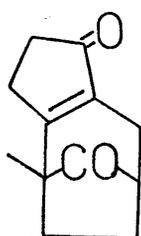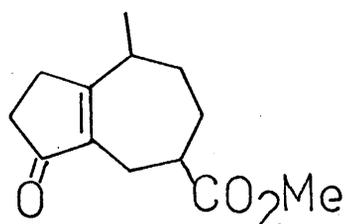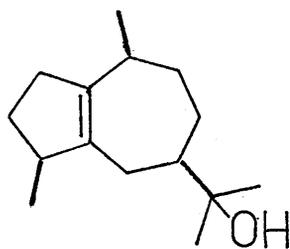
(38)
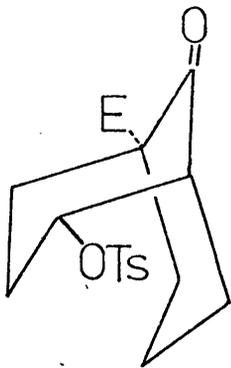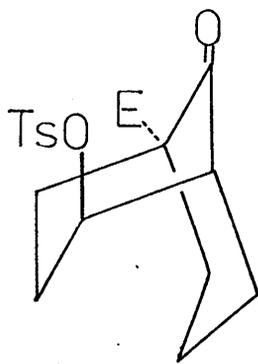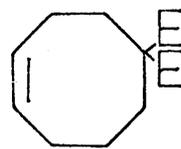
(24e)   (24a)   (25)
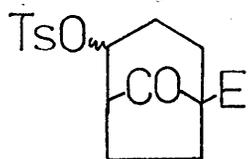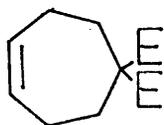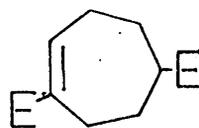
(26)   (27)   (28)
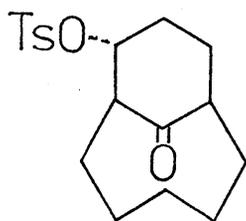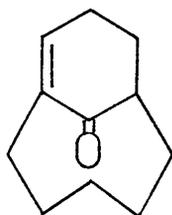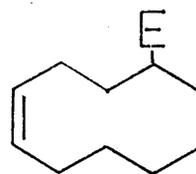
(29)   (30)   (31)

E=CO₂Et
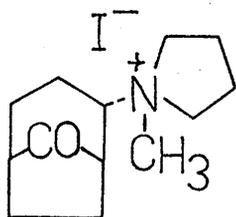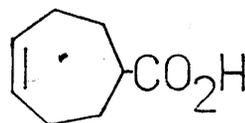
(32)   (33)

which provides a practical route to specifically-substituted medium rings is the fragmentation of 2-substituted bicyclo[3.n.1.] alkanones, as exhibited by the tosylate (24). The equatorial epimer (24e) is very readily cleaved by ethoxide ion to the cyclo-octene diester (25), while the axial epimer (24a) is unaffected[18]. The [3.2.1.] analogue, (26), opens with equal facility, giving the cycloheptene diester (27) from the equatorial, and (28) from the axial by a retro-Claisen ring-opening[19]. This method has two major drawbacks - (a) only the equatorial tosylate will fragment in the desired manner, leaving a high proportion of material unused, and (b) in the case of [n.3.1.] systems where n $\geqslant$ 5, even the equatorial tosylate does not fragment, preferring instead to undergo a β-elimination. For instance, (29) upon treatment with ethoxide yields (30) rather than (31)[20].

Tosylate need not be the leaving group in the above fragmentation. Indeed, the reaction was first dis-covered by Stork[21] who treated (32) with hydroxide and obtained cycloheptene carboxylic acid (33). There are also examples of the fragmentation in which there is no leaving group at all, but rather the driving force is the release of ring-strain. Buchanan dis-covered that the bicyclic ketone (34) opened to the cycloheptene acid (35) under acid catalysis[22]. The synthetic utility of this method is exemplified by the preparation of the sesquiterpene guaiol (38)[23]. A key step is the opening of (36) to (37) either in acidic
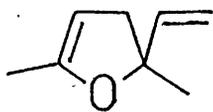
(39)
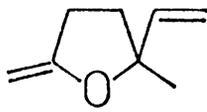
(40)
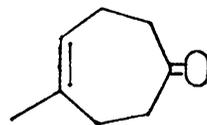
(41)
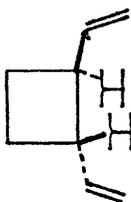
(42)

(43)

(44)
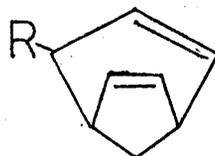
(45)
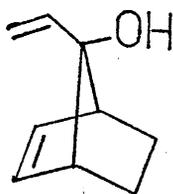
(46)

(47)

methanol or in sodium methoxide.

Sigmatropic rearrangements provide very useful alternatives to the above ring enlargement techniques. The intramolecular rearrangement of double bonds is very often a facile process, resulting in the formation of a larger ring and hence relieving ring strain. For example, the dihydrofuran (39) undergoes a [3,3] sigmatropic rearrangement to the cycloheptenone (41) via the tetrahydrofuran isomer (40)[24]. The classical Cope rearrangement has produced a wide variety of ring-expanded products, including the cyclohexene (43) from divinylcyclobutane (42)[25], and a four-carbon expansion of (44) to (45)[26]. The latter is an interesting variant of the vinylcyclopropane rearrangement. By an "oxy-Cope" rearrangement, the allylic alcohol (46) is transformed into the bicyclic enone (47)[27] in around 90% yield, and a high-yield analogue, the "siloxy-Cope" is reputed to obviate any undesired by-products[28].

These, then, are the main generalised methods of ring expansion at the present time. There are count-less other ways of enlarging a carbocyclic ring which have not been discussed in detail, and some of these are worthy of mention at this point. To correspond to the above thermal rearrangements, there are a consid-erable number of photochemical transformations which can be used[29]. Trost's research into cyclopropyl sulphur ylids is developing a method which, although young, has already found considerable use[30].

The object of the work described in this thesis was to explore further the possibilities of utilising bridged bicyclic compounds as intermediates in ring expansion reactions, and to develop new approaches to ring expansions in general.

REFERENCES.

1. L.Ruzicka, W.Brugger, M.Pfeiffer, P.Schinz and M. Stoll, Helv.Chim.Acta, 1926, 9, 499.

2. K.Ziegler, H.Eberle and H.Ohlinger, Ann.Chem., 1933, 504, 94.

3. V.Prelog, J.Chem.Soc., 1950, 420.

4. For a review, see C.D.Gutsche and D.Redmore, "Carbo-cyclic Ring Expansion Reactions" (Advances in Alicyclic Chemistry Supplement 1), Academic Press, 1968.

5. H.Meerwein and K.van Emster, Chem.Ber., 1922, 55, 2500.

6 N.Demjanov and M.Luschnikov, J.Russ.Phys.-Chem.Soc., 1903, 35, 26.

7. O.L.Chapman and P.Fitton, J.Amer.Chem.Soc., 1963, 85, 41.

8. M.Kato, H.Kosugi and A.Yoshikoshi, Chem.Comm., 1970, 185.

9. G.Buchi, W.Hofheinz and J.V.Paukstelis, J.Amer.Chem. Soc., 1966, 88, 4113.

10. E.J.Corey, M.Ohno, R.B.Mitra and P.A.Vatakencherry, ibid, 1964, 86, 478.

11. U.Schollkopf and P.Bohme, Angew.Chem.Int.Ed., 1971, 10, 491.

12. K.Heyns and A.Heins, Angew. Chem., 1956, 68, 414.

13. E.Muller and M.Bauer, Ann.Chem., 1962, 654, 92.

14. G.Stork and T.L.MacDonald, J.Amer.Chem.Soc., 1975, 97, 1264.

15. J.E.McMurry and S.J.Isser, ibid, 1972, 94, 7132.

16. D.Seyferth, J.M.Burlitch and J.K.Heeren, _J.Org.Chem._, 1962, _27_, 1491.

17. J.S.Gillespie, S.P.Acharya and D.A.Shamblee, _ibid_, 1975, _40_, 1838.

18. G.L.Buchanan, A.McKillop and R.A.Raphael, _J.Chem. Soc._, 1965, 833.

19. G.L.Buchanan and G.W.McLay, _Tetrahedron_, 1966, _22_, 1521.

20. G.L.Buchanan and G.Jamieson, _ibid_, 1972, _28_, 1129.

21. G.Stork and H.K.Landesman, _J.Amer.Chem.Soc._, 1956, _78_, 5129.

22. G.L.Buchanan, C.Maxwell and W.Henderson, _Tetrahedron_, 1965, _21_, 3273.

23. G.L.Buchanan and G.A.R.Young, _J.Chem.Soc.Perkin I_, 1973, 2404.

24. S.J.Rhoads and C.F.Brandenburg, _J.Amer.Chem.Soc._, 1971, _93_, 5805.

25. C.S.Elliot and H.M.Frey, _J.Chem.Soc._, 1965, 345.

26. C.Cupas, W.E.Watts and P.von R.Schleyer, _Tetrahedron Letters_, 1964, 2503; J.M.Brown, _Chem.Comm._, 1971, 226.

27. J.A.Berson and M.Jones, _J.Amer.Chem.Soc._, 1964, _86_, 5017, 5019.

28. R.W.Thies, _Chem.Comm._, 1971, 237.

29. P.Yates and R.O.Loutfy, _Acc.Chem.Res._, 1975, _8_, 209.

30. B.M.Trost, _ibid_, 1974, _7_, 85.

CHAPTER ONE

APPROACHES TO RING EXPANSION

VIA DICHLOROCARBENE ADDUCTS.

(5)

(6) E=CO$_2$Et

TsO — [structure: cyclohexanone with TsO and CO2Et substituents] — → [TsO — EtO / O⁻ / CO2Et intermediate in brackets]

+EtO⁻

[structure: E E cycloheptene] — Base → [structure: A A cycloheptane] — -CO₂ → [structure: A cycloheptene]

E=CO₂Et   A=CO₂H

SCHEME 1

X⟜⟜ [structure with O, A, B labels]

TsO⟜⟜ [bicyclic structure with O]

(1)   (2)

[structure (3): tricyclic with O]

[structure (4): bicyclic with CO₂H]

(3)   (4)
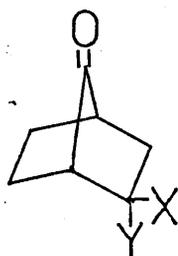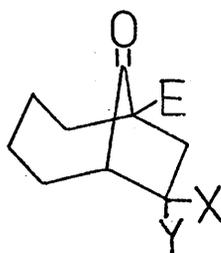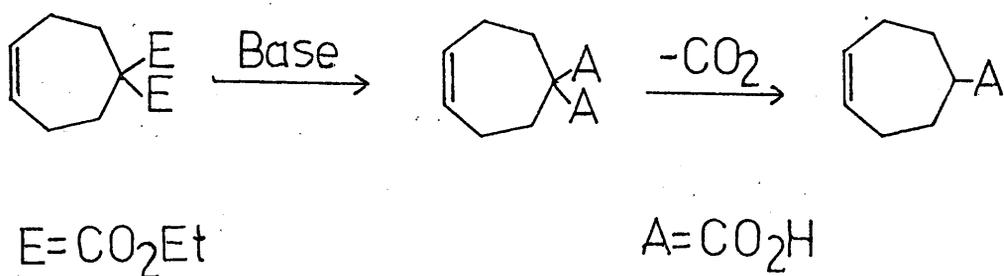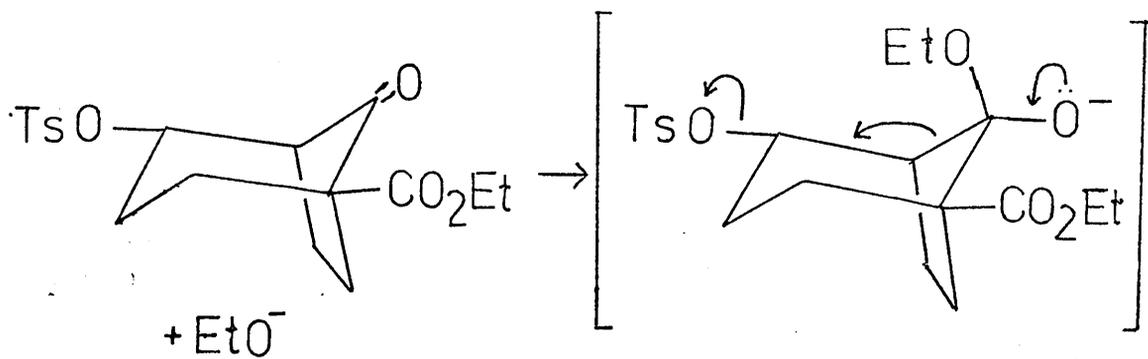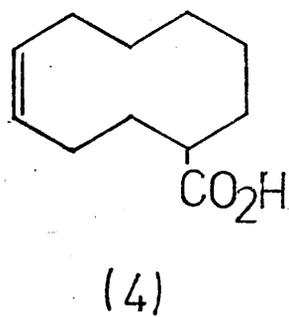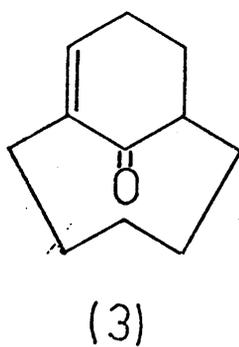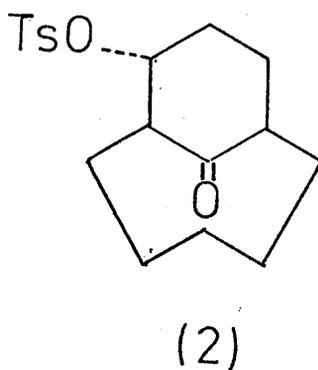
The fragmentation - elimination reaction of 2-substituted carbonyl-bridged bicyclics is developing into a useful route to specifically-substituted medium-ring compounds[1,2,3]. A typical example is shown in Scheme 1. However, the utility of the reaction is restricted by two factors : firstly, there is a limit to the size of the ring which does not contain the leaving group (ring B in (1)) - if this is larger than 7-membered, the product of a β-elimination reaction is observed. This is shown by the preferential formation of (3) rather than (4) when (2) is treated with hydroxide ion[4]. Secondly, by virtue of the normal synthetic procedure by which the carbonyl-bridgedbicyclics are prepared, i.e. Aldol condensation of a 1,5-dicarbonyl system, A has to be a six-membered ring. Moreover, in a six-membered ring, the stereo-chemistry of the equatorial tosylate is ideal (see Scheme 1) for a concerted fragmentation. If ring A is five-membered, the geometry is less than ideal, and no concerted fragmentation is observed in either of the tosylates (5)[X or Y = TsO] despite the increased ring strain[5]. Similarly, Carruthers has found[6] that neither of the tosylates (6) [X or Y = TsO] underwent fragment-ation. Thus the reaction effectively works for bicyclo[n.3.1.]alkanone systems, n $\leqslant$ 5. It has never been tested for keto-tosylates (1) in which ring A is seven- or eight-membered, although the flexibility of such systems should readily allow the anti-periplanar geometry necessary for a concerted fragmentation. It was proposed to attempt to broaden the scope of the

(14)   (15)   (16)

(17)

4. →   (18)   5. →   (19)
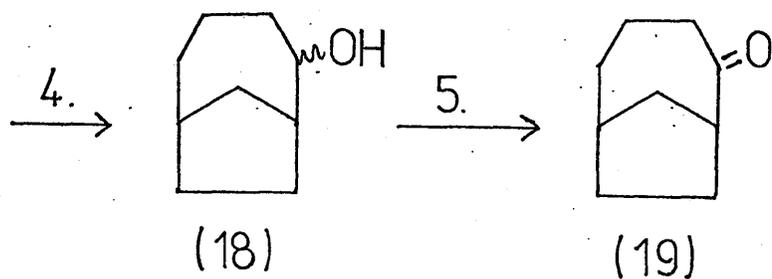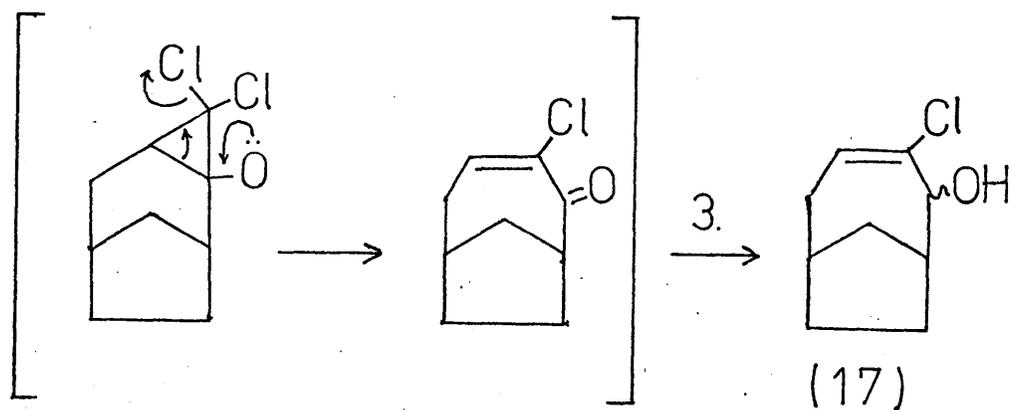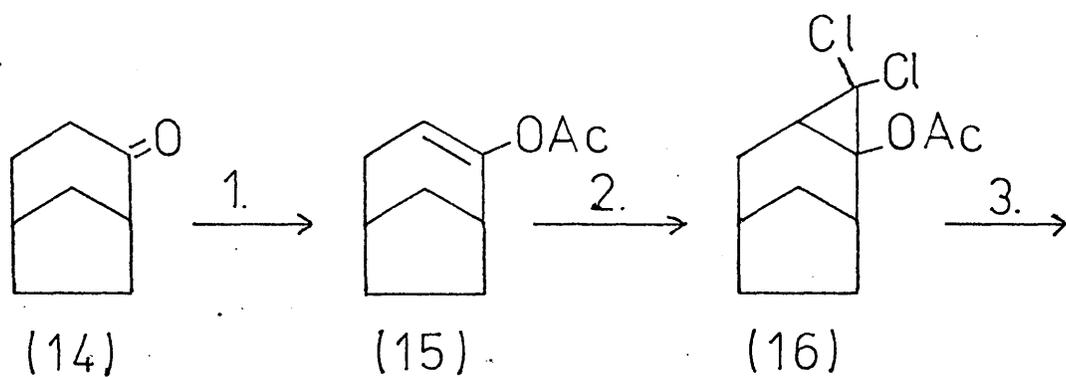
1. Isopropenyl acetate / pTSA
2. 50% aq. NaOH / CHCl₃ /TEBA Cl   3. LAH
4. H₂/Pd / NaOH/THF   5. Na₂Cr₂O₇

SCHEME 2
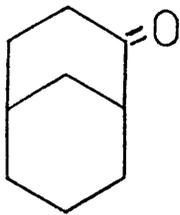
(7)
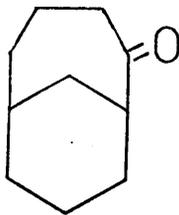
(8)

(9)
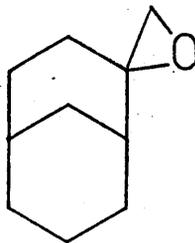
(10)
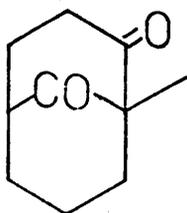
(11)
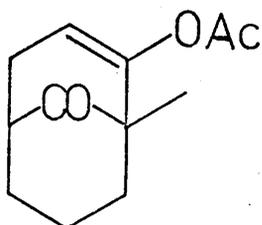
(12)
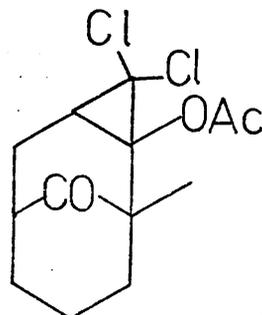
(13)

process by enlarging ring A by one or more carbons, and thereby creating a route into larger-ring compounds.

One of the more common methods of expanding a cyclic ketone is to treat it with diazoalkanes. However, this was regarded as impractical due to the probable multitude of products. For example, Pietra[7] has shown that treatment of bicyclo[3.3.1]nonan-2-one(7) with diazomethane leads to both bicyclo[4.3.1]decan-2- and 3-ones(8) and (9), together with a small amount of the spiro-oxirane (10).

It was envisaged that the desired ring-expansion might be achieved by taking the known 1-methylbicyclo [3.3.1]nonan-2,9-dione (11)[8], converting it to the enol-acetate (12) and then adding dichlorocarbene across the double bond to give the tricyclic compound (13). An analogous bicyclic enol-acetate : dichlorocarbene adduct (16) has been prepared by Kraus[9] and has been shown to undergo a reductive opening of the three-membered ring to eventually give the homologous bicyclic ketone (19), as described in Scheme 2.

The starting dione (11) was prepared cleanly and in high yield from 1-N-morpholino-6-methyl cyclohexene and acryloyl chloride[8]. Conversion to its enol-acetate (12) by conventional means (isopropenyl acetate in the presence of p-toluene sulphonic acid) was found to be a very slow process, but it was discovered that if the dione (11) was treated with refluxing acetic anhydride and one drop of concentrated sulphuric acid, while slowly distilling out the acetic acid formed, the desired product could be

(12) (11)

(20)
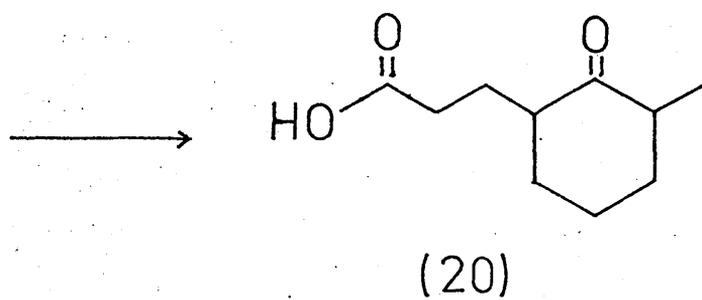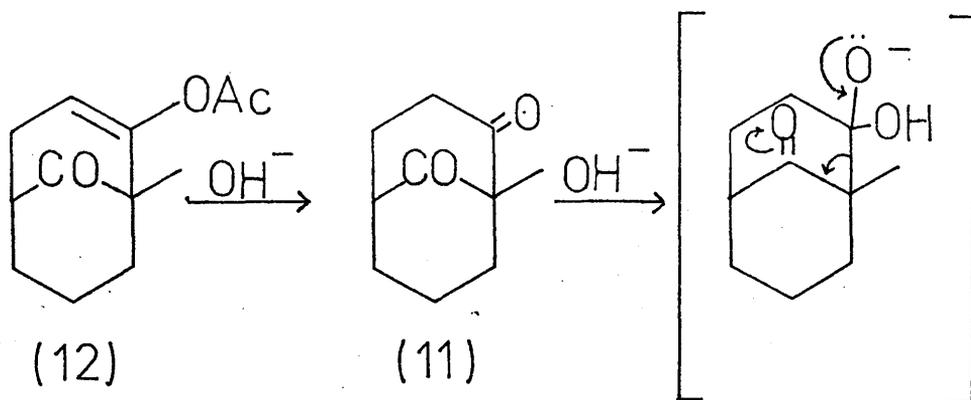
SCHEME 3

obtained quickly and in reasonable yield (49% after distillation). The enol-acetate was characterised by the appearance of the acetate methyl (2.11 δ, s) and the olefinic proton (5.55 δ, t) in the NMR spectrum. It was found that (12) could be purified by one or more methods : it sublimed readily under vacuum, it could be distilled (116-8°/0.15mm.) as a clear oil which solidified at room temperature, or it could be recrystallised from a mixture of ether and light petroleum.

The initial attempts to form the adduct (13) followed the same procedure as used by Kraus[9]: chloroform and 50% aqueous sodium hydroxide in the presence of a phase-transfer catalyst such as triethylbenzylammonium chloride[10]. However, despite altering the catalyst, the solvent and the rate of stirring of the reaction mixture, Kraus's achievement in avoiding hydrolysis of the enol-acetate could not be acomplished in our hands, and the only major product obtained from this series of reactions was the monocyclic keto-acid (20). This presumably arises from the breakdown of the bicyclic dione system formed upon hydrolysis of the enol-acetate (Scheme 3.). It has already been shown by Hickmott that acid hydrolysis of (11) leads to (20)[8]. The structure of (20) was unambiguously assigned by NMR (methyl doublet at 1.00 δ and acid proton at 9.90 δ), IR (strong O-H stretch, with two carbonyl bands at 1711 and 1754 cm^{-1}.) and microanalysis.

Attention was then turned to a well-established technique for the generation of dichlorocarbene :
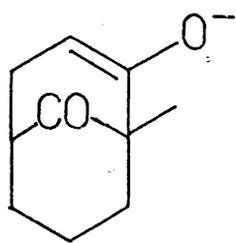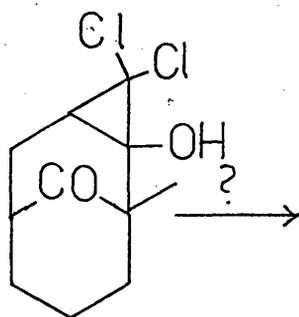
(21)   (22)
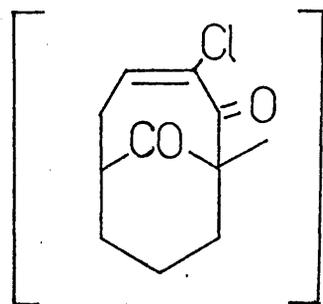
treatment of chloroform with potassium t-butoxide[11].
This has the advantage of employing a less-nucleophilic
base, thus minimising the possibility of attack on the
enol-acetate. However, despite prolonging the usual
reaction time, there was no evidence of any addition of
dichlorocarbene, and a virtually quantitative return of
unreacted enol-acetate was observed.

It is well documented that sodium trichloroacetate
decomposes thermally to produce dichlorocarbene adducts in
the presence of olefins[12,13]. Unfortunately, when the
enol-acetate (12) was treated with freshly-prepared sodium
trichloroacetate[14], the product was neither the adduct
(13) nor unreacted starting material, but the precursor
dione (11) in 96% yield. This obviously arises from
hydrolysis of (12), either because the solvent,
dimethoxyethane, was not properly dried or, more likely,
because (12) was not stable to the aqueous work-up
conditions.

Although such a reaction has not been recorded in the
literature, it was thought to be worth treating chloro-
form with sodium hydride to generate dichlorocarbene, and
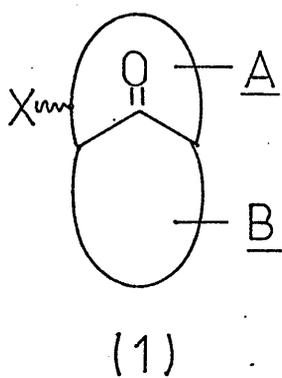if the dione (11) was present in the form of its sodium
enolate (21), there would be the possibility that the
carbene might add across the double bond to give the
adduct (22). However, when the dione was treated with
sodium hydride and chloroform in refluxing benzene, the
product obtained was the monocyclic keto-acid (20),
presumably formed by hydrolysis of unreacted dione in
the work-up, which involved 10% acetic acid. Faced with an

(23)

(24)

(25)

--Hg--CBrCl_2

(26)

$\text{CH}_2\text{=CH--OAc}$
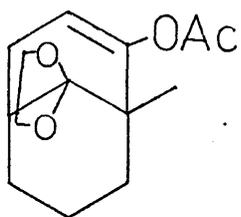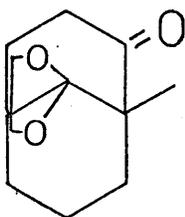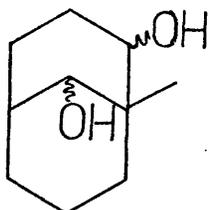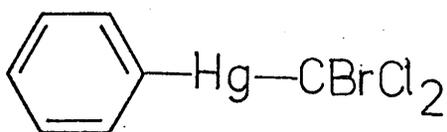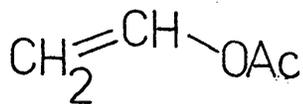
(27)
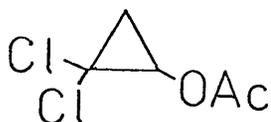
(28)

ever-growing mountain of evidence that the enol-acetate
(12) was extremely susceptible to hydrolysis and
fragmentation, the most obvious step was to protect it
in some fashion. The simplest way would be to ketalise
the ketonic carbonyl forming (23). Even if the enol-
acetate part of this molecule was hydrolysed, fragment-
ation to a monocyclic derivative would be most unlikely,
and the keto-ketal (24) produced could be utilised in
another ring-expansion reaction,or sequence. All
attempts to form (24) by selective ketalisation of the
dione (11) were singularly unsuccessful, giving an
inseparable mixture of un-, mono- and di-ketalised
products. Disappointingly, every effort to obtain (23)
in reasonable yield from (12) also failed. Even when the
enol-acetate was treated with ethylene glycol/pTSA in
refluxing benzene for eight days, only a small amount of
ketal was formed, and the bulk of the starting material
remained unchanged.

In another attempt to selectively protect one of the
carbonyl groups, the dione (11) was reduced with one
equivalent of lithium aluminium hydride. However, this
gave the diol (25) as the major product. Thus, since all
attempts at base-induced dichlorocarbene generation had
not been without their difficulties, a non-basic technique
was tried. It has been known since 1962[15] that phenyl-
trihalomethyl mercury decomposes thermally to produce
phenyl mercuric halide and dichlorocarbene. It has even
been shown[16] that phenylbromodichloromethyl mercury(26)
and vinyl acetate(27) produce 2,2-dichlorocyclopropyl

acetate(28). Initial attempts to synthesise the above
organomercurial were only partially successful, which
was not too unexpected since such syntheses are
notoriously difficult[17]. To save time, phenylbromo-
dichloromethyl mercury was obtained from a commercial
source[18], but all efforts to utilise this to effect
dichlorocarbene addition were fruitless. When the enol-
acetate(12) was treated with PhHgCBrCl$_2$ in refluxing
benzene, only unreacted (12) and PhHgBr were isolated.
Indeed, upon further investigation, our sample of
PhHgCBrCl$_2$ would not even add dichlorocarbene across
cyclohexene to produce 7,7-dichloronorcarane(29)!
It was found that the melting point of the "PhHgCBrCl$_2$"
was not 108-110° as reported by Seyferth[17] but around
280°, very close to that of PhHgBr.

At this point, since no potentially-useful route
to the dichlorocarbene adduct could be envisaged, this
approach to ring-expansion was terminated.

GENERAL EXPERIMENTAL

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Routine infra-red spectra of liquid films and nujol mulls were run on a Unicam SP1000 instrument, while solution spectra were recorded on Perkin-Elmer PE225 and PE257 spectrometers. All solutions were made up in carbon tetrachloride unless otherwise stated. Nuclear magnetic resonance were recorded on Varian T-60 and HA-100 instruments, using approximately 0.3 molar solutions with tetramethyl-silane as internal standard. Mass spectra were recorded on a AEI-GEC MS12 spectrometer.

Thin layer chromatography (TLC) was performed on silica gel, using Kieselgel GF_{254} and HF_{254} for both analytical and preparative purposes. Gas-liquid chrom-atography (GLC) was carried out on a Perkin-Elmer F.11 chromatograph equipped with a flame ionisation detector.

Drying of all organic phases was with anhydrous magnesium sulphate, and petrol refers to that fraction of petroleum ether which boils in the range 60-80°.

1-Methyl bicyclo [3.3.1] nonan-2,9-dione(11).

The above compound was prepared by the method of Hickmott and Hargreaves.[8]

A solution of 2.30g. (25.4mmoles) of acryloyl chloride in 50ml. of benzene was added dropwise, over 1 hour, to a refluxing solution of 4.50g. (24.9mmoles) of 1-N-morpholino-6-methyl cyclohexene in 75ml. of benzene, and the mixture heated under reflux for 24 hours. After cooling the reaction mixture, an equal volume of water was added, and the resulting suspension stirred for 3 hours. The two layers were then separated, and the aqueous layer extracted with 2 x 50ml. portions of ether. The combined organic layers were washed with brine and concentrated under reduced pressure to yield 3.90g. (94%) of crude dione as a reddish brown gum, which could be purified by sublimation (100° /0.05mm.), giving a white amorphous solid, m.pt. 35-6° (lit. 37.5°).

IR : ν_{co} 1723, 1708 cm^{-1}.

NMR : 1.16 δ <u>s</u> 3H.

MS : M$^+$ 166.

Found : C 72.02, H 8.48% ($C_{10}H_{14}O_2$ requires C 72.26, H 8.49%).

1-Methyl-2-acetoxy-bicyclo [3.3.1] nonan-2-en-9-one(12).

6.78g. (40.8mmoles) of dione (11) in 50ml. of AnalaR acetic anhydride was treated with one drop of conc. H_2SO_4 and the dark solution heated with partial distillation to remove the acetic acid formed. After

8 hours, the excess acetic anhydride was removed by azeotroping with toluene and the residue taken up in ether, washed with brine, dried, filtered and concentrated to yield a brown oil which was distilled (116-8°/0.15mm.) to give 4.20g. (49%) of a clear yellow oil which solidified on standing. This solid could be recrystallised from a mixture of light petroleum and ether, and further purification by sublimation (80°/0.08mm./10 minutes) gave the enol-acetate as a white solid, m.pt. 44-5°, with the following characteristics :

IR : ν_{co} 1760, 1725 cm^{-1}

NMR : 1.04 δ s 3H saturated methyl;

2.11 δ s 3H OCOCH$_3$;

5.55 δ t(J=4Hz) 1H olefinic proton.

MS : M$^+$ 208, base peak 43.

Found : C 69.37, H 7.69% (C$_{12}$H$_{16}$O$_3$ requires C 69.21, H 7.74%).

Treatment of enol-acetate (12) with sodium trichloroacetate.

A solution of 500mg. (2.40mmoles) of enol-acetate in 10ml. of dimethoxyethane was treated with 520mg. (2.80mmoles) of sodium trichloroacetate[14] and the solution heated at reflux for 19 hours, cooled and quenched with water. The product was extracted with 2 x 50ml. portions of ether, the combined ether layers washed with brine, dried, filtered and concentrated to

give 381mg. (96%) of a pale yellow oil which solidified
on standing.

IR : ν_{co} 1705, 1730cm^{-1}.

NMR : 1.05 δ s 3H bridgehead methyl.
no sign of any olefinic or acetoxy methyl
protons.

MS : M$^+$ 166.

The above data, together with TLC comparison (20%
ethyl acetate-petrol), confirmed that the above
product was the bicyclic dione (11).

Treatment of enol-acetate (12) with potassium
t-butoxide in chloroform.

A solution of 228mg. (2.00mmoles) of freshly-
prepared potassium t-butoxide[19] and 418mg. (2.00mmoles)
of enol-acetate in 8ml. of pentane, at 0° under N$_2$, was
treated with a solution of 286mg. (2.40mmoles) of dry
chloroform in 5ml. of pentane, over a period of 15
minutes. The solution was allowed to come to room
temperature and stirred for 19 hours. 25ml. of water
was added, then sufficient 6N HCl to bring to pH 7.
The layers were separated, and the aqueous extracted
with 3 x 10ml. portions of pentane. The combined
organic layers were washed with brine, dried (MgSO$_4$),
filtered and concentrated to give 406mg. of a yellow
oil which was identical by NMR, IR, MS and TLC to the
starting material.

Treatment of enol-acetate (12) with 50% NaOH and $CHCl_3$.

(a) In the presence of benzyltrimethylammonium hydroxide.

To a solution of 500mg. (2.40mmoles) of enol-acetate (12), 298mg. (2.50mmoles) of alcohol-free chloroform and 100mg. of benzyltrimethylammonium hydroxide in 10ml. of methylene chloride was added 10ml. of a 50% aqueous NaOH solution in a single portion, and the resultant solution stirred vigorously with a De Witt stirrer for 13 hours at room temperature. After dilution with water, the layers were separated, the aqueous extracted with fresh methylene chloride, and the organic portions combined. These were washed to neutrality with brine, then dried, filtered and concentrated to yield 62mg. of a yellow oil, which was shown by TLC (5% ethylacetate-petrol) to consist of at least four components.

Careful neutralisation of the above aqueous layer with 6N HCl, followed by the same work-up, led to 409mg. (92%) of a white solid, m.pt. 68-70° from benzene, the unexpected monocyclic keto-acid (20).

IR : ν_{OH} 3530cm^{-1}(free), 2300-3450cm^{-1}(bonded).

ν_{co} 1711,1754cm^{-1}.

NMR : 1.00 δ d (J=7Hz) 3H saturated CH_3.

3.50 δ q (J=7Hz) 1H.

9.90 δ s(broad) 1H exchanges with D_2O.

MS : M$^+$ 184, base peak 81.

Found : C 65.20, H 8.75% ($C_{10}H_{16}O_3$ requires C65.19, H 8.75%).

(b) In the presence of tetra-n-butylammonium bromide.

To a solution of 1.00g. (4.80mmoles) of enol-acetate, 596mg. (5.00mmoles) of alcohol-free chloroform and 200mg. of tetra-n-butylammonium bromide in 20ml. of methylene chloride was added 20ml. of a 50% aqueous solution of NaOH in a single portion. This caused spontaneous refluxing of the solvent. The reaction mixture was stirred vigorously, without external heating, for 2 hours. Following the work-up described in (a), the organic layer gave 110mg. of a multi-component oil which resisted all attempts at purification and identification, while the aqueous layer, after neutralisation and re-extraction, gave 783mg. (89%) of the keto-acid (20).

(c) In the presence of benzyltriethylammonium chloride.

When 1.00g. (4.80mmoles) of enol-acetate was treated as in (b), with the exception that benzyltriethyl-ammonium bromide, similar results were observed : the organic layer yielded 203mg. of a multi-component oil, while the aqueous layer gave 724mg. (82%) of the keto-acid (20).

Treatment of the bicyclic dione (11) with sodium hydride in chloroform.

A mixture of 500mg. (3.01mmoles) of dione, 253mg. (10.54mmoles) of NaH, as a 94% dispersion in oil, 1193mg. (10.00mmoles) of alcohol-free chloroform and 15ml. of dry benzene was stirred under reflux for 16 hours, then

treated with 20ml. of 10% AcOH. The layers were
separated and the aqueous portion extracted with
benzene. Combination of the organic layers, followed
by brine washing, drying, filtering and solvent removal
yielded 365mg. of a yellow oil, purified by prep. TLC
(20% ethyl acetate-petrol). The solid thus obtained
was identical in all respects with the previously-
mentioned keto-acid (20).

Attempted ketalisation of enol-acetate (12).

A mixture of 970mg. (4.65mmoles) of 1-methyl-2-
acetoxy bicyclo[3.3.1.] nonan-2-en-9-one (12), 620mg.
(10.00mmoles) of dry ethylene glycol and 10mg. of p-
toluene sulphonic acid in 125ml. of sodium-dried
benzene was heated under reflux in a Dean and Stark
water separator for 8 days. The reaction mixture was
cooled and washed with, successively, dilute sodium
hydrogen carbonate, water, brine and more water. After
drying (MgSO$_4$), removal of solvent under reduced
pressure gave 908mg. of a clear oil. IR (thin film)
showed the continued presence of both the bridghead and
acetate carbonyls. TLC confirmed that this product was
mainly unreacted starting material, with a trace of a
more polar compound, possibly the desired ketal-enol-
acetate (23).

1-Methyl bicyclo[3.3.1.] nonan-2,9-diol (25).

A solution of 1.15g. (6.93mmoles) of bicyclic dione
(11) in 20ml. of sodium-dried ether was added dropwise

over 5 minutes to a stirred suspension of 190mg. (5.00 mmoles) of lithium aluminium hydride in 20ml. of ether, under N_2. The reaction mixture was stirred for 25 minutes at room temperature, then quenched with 30ml. of water. The layers were separated (with difficulty), the aqueous layer extracted with ether and the combined ether layers washed with very dilute HCl, water and brine. After drying and filtering, removal of solvent gave 607 mg. (52%) of an oil which solidified of standing. Recrystallisation from a mixture of ether and light petroleum gave a fine white solid, m.pt. 155-6°, the diol (25).

IR (KBr disc) : ν_{OH} 3080-3700 cm^{-1}. Transparent in carbonyl region.

NMR : 1.05 δ s 3H saturated methyl ;

3.28 δ m 1H CH-OH ;

3.42 δ m 1H CH-OH .

MS : M$^+$ 170, base peak 41.

Found : C 70.40, H 10.68% ($C_{10}H_{18}O_2$ requires C 70.55, H 10.66%).

Treatment of enol-acetate (12) with phenylbromodichloromethyl mercury.

A suspension of 211mg. (1.01mmoles) of enol-acetate (12), 443mg. (1.00mmoles) of the organo-mercurial[18] and 20ml. of Na-dried benzene was stirred at reflux, under nitrogen, for 15 hours. Deposition of a white solid on the sides of the flask was observed after 2 hours. The reaction mixture was cooled, the white solid filtered and found to be phenyl mercuric bromide (m.pt. 284°).

Concentration of the filtrate gave 206mg. of a brown oil, identical with starting material by IR and TLC, together with a green crystalline solid which decomposed on heating.

Treatment of cyclohexene with phenylbromodichloromethyl mercury.

82mg. (1.00mmoles) of cyclohexene in 10ml. of dry benzene was treated with 450mg. (1.02mmoles) of organo-mercurial at 80° for 17 hours. Using the same work-up as described above, the only identifiable products obtained were phenyl mercuric bromide and 71mg. of unreacted cyclohexene.

REFERENCES

1. G.L.Buchanan, A.McKillop and R.A.Raphael, J.Chem.Soc., 1965, 833.

2. G.L.Buchanan, A.C.W.Curran, J.M.McCrae and G.W.McLay, Tetrahedron, 1967, 23, 4729.

3. G.L.Buchanan and G.A.R.Young, J.Chem.Soc.Perkin I, 1973, 2404.

4. G.L.Buchanan and G.Jamieson, Tetrahedron, 1972, 28, 1129.

5. P.G.Gassman and J.L.Marshall, J.Amer.Chem.Soc., 1966, 88, 2822.

6. W.Carruthers and M.I.Qureshi, J.Chem.Soc.Perkin I, 1973, 51.

7. F.Del Cima and F.Pietra, ibid, 1974, 1710.

8. P.W.Hickmott and J.R.Hargreaves, Tetrahedron, 1967, 23, 3151.

9. W.Kraus, W.Rothenwohrer, H.Sadlo and G.Klein, Angew. Chem.Int.Ed., 1972, 11, 641.

10. M.Makosza and M.Wawrzyniewicz, Tetrahedron Letters, 1969, 4659.

11. W.von E.Doering and A.K.Hoffmann, J.Amer.Chem.Soc., 1954, 76, 6162.

12. W.R.Moore, S.E.Krikorian and J.E.LaPrade, J.Org.Chem., 1963, 28, 1404.

13. S.W.Tobey and R.West, J.Amer.Chem.Soc., 1966, 88, 2481.

14. A.Winston, J.P.M.Bederka, W.G.Isner, P.C.Juliano and J.C.Sharp, J.Org.Chem., 1965, 30, 2784.

15. D.Seyferth, J.M.Burlitch and J.K.Heeren, ibid, 1962, 27, 1491.

16. D.Seyferth, J.M.Burlitch, R.J.Minasz, J.Yick-Pui Mui, H.D.Simmons, A.J.H.Treiber and S.R.Dowd, _J.Amer.Chem. Soc._, 1965, _87_, 4259.

17. D.Seyferth and R.L.Lambert, _J.Organometallic Chem._, 1969, _16_, 21.

18. Alfa Inorganics Ltd.

19. L.Skattebol and S.Solomon, _Organic Syntheses Coll. Vols._, 1973, _V_, 306.

CHAPTER TWO

RING EXPANSIONS UTILISING
BRIDGED BICYCLIC COMPOUNDS.
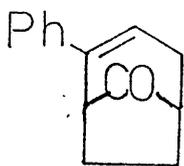
(1)
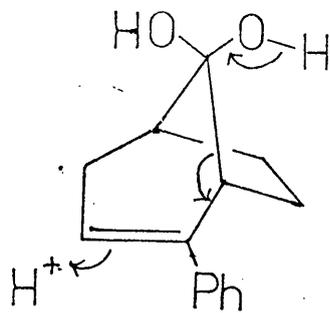
(2)
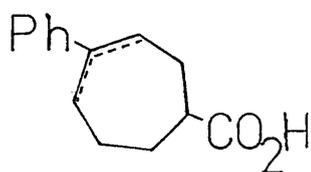
(3)
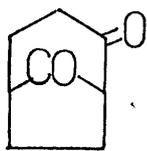
(4)
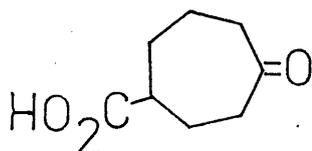
(5)
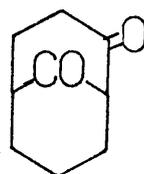
(6)
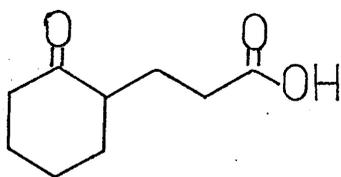
(7)
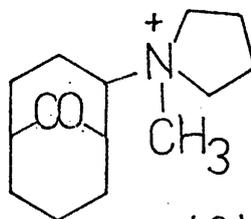
(8)
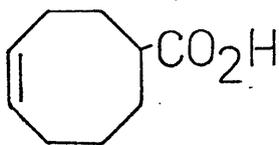
(68)
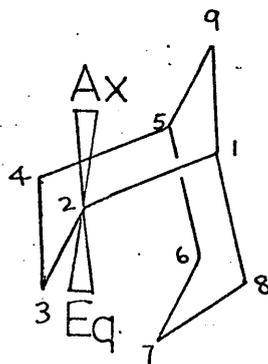
Fig. 1

The fragmentation of carbonyl-bridged bicyclics
has become a useful route to specifically-substituted
medium- and large-ring compounds[1]. Since most bicyclic
compounds are prepared from cheap and readily-available
starting materials, the method has obvious attractions.
Some examples of the fragmentation include the formation
of the cycloheptene carboxylic acids (3) from bicyclo-
octene (1) via the intermediate (2), upon treatment with
acid[2,3], and the conversion of dione (4) into cyclo-
heptanone carboxylic acid (5)[4]. It is worth noting
at this point that the bicyclo [3.3.1.] nonadione (6)
does not fragment in a similar fashion, but cleaves to
the keto-acid (7)[5]. This is an example of the import-
ance of ring-strain in the fragmentation. One of the
most interesting variants of this bridge-scission
reaction is the ability of 2-substituted carbonyl-
bridged bicyclics to fragment in a concerted fashion.
This was first demonstrated by the transformation of (8)
to cyclo-octene carboxylic acid (68)[6], but the reaction
has been studied more extensively on the analogous
tosylates. This has resulted in several restrictions
being imposed, which determine whether or not the
fragmentation will take place.

The first and perhaps major requirement is that the
2-substituent is in the equatorial position (see Fig. 1).
This geometry is necessary because the reaction is a
heterolytic fragmentation and, in order to be a
concerted process, there must be complete overlap of
the orbitals involved. Hence, as shown in Scheme 1,

(13)

TsO⋯[CO]CO₂Et ... CO_2Et — structure (33e) → NaOEt → (34)

(33e) $\xrightarrow{\text{NaOEt}}$ (34)

SCHEME 3

(14) $\xrightarrow[\substack{80° \\ 5 \text{ mins}}]{^-OEt}$ (15)

(16) $\xrightarrow[\substack{80° \\ 20 \text{ hours}}]{^-OEt}$ (17)

SCHEME 4

SCHEME 1

(9)

(10)

(11)

(12)
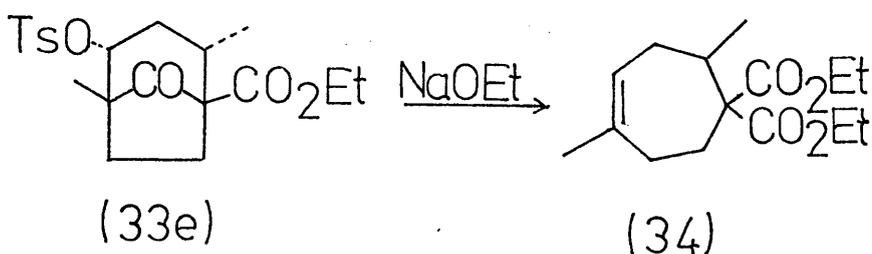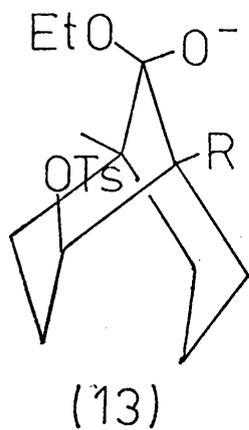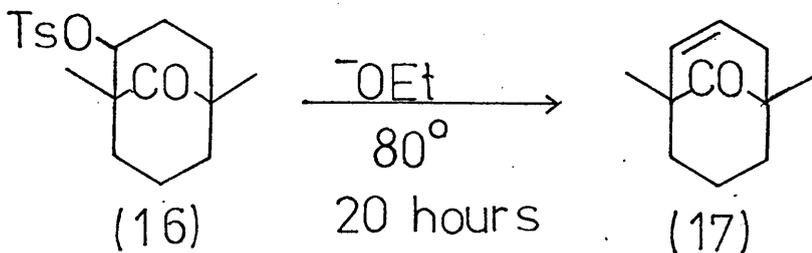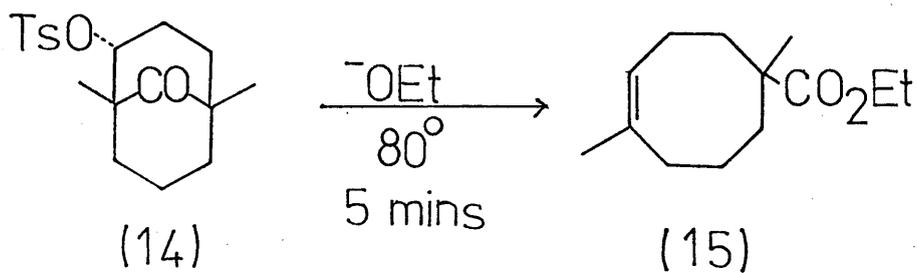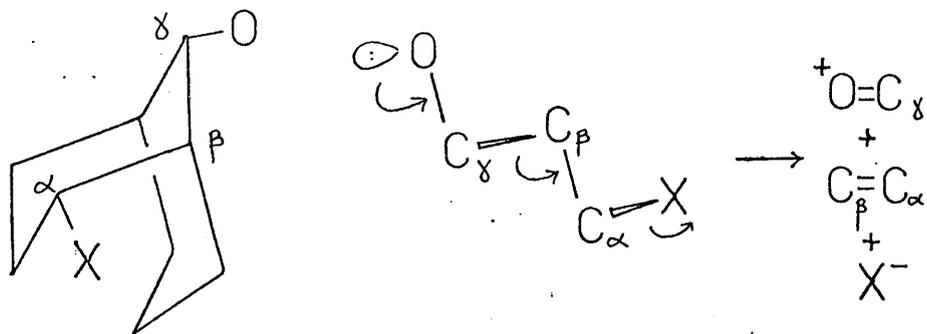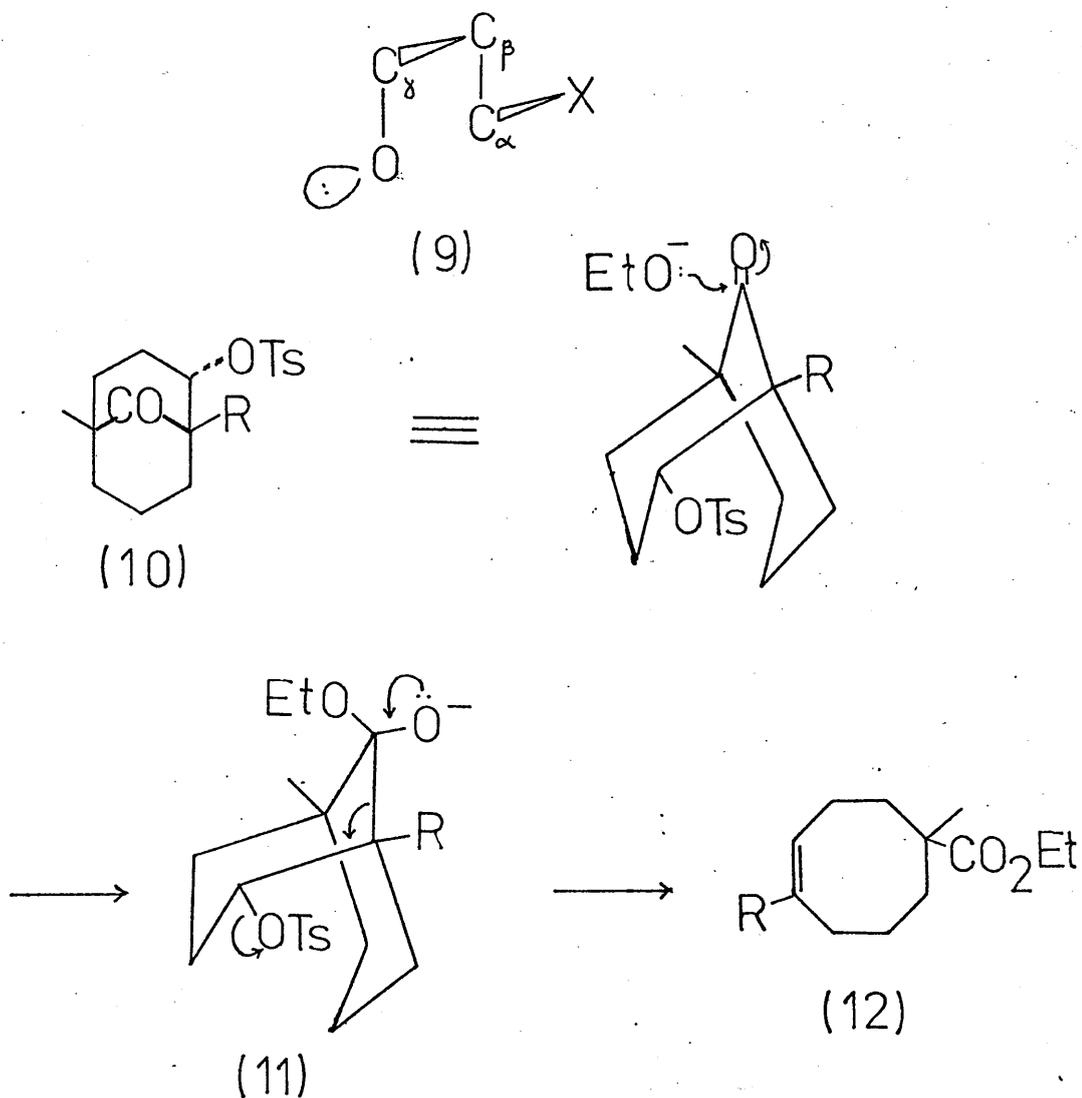
SCHEME 2

the lone pair orbital on oxygen of the bridging
carbonyl and the C_α- X bond should be anti-periplanar
to the C_β - C_γ bond. In this way, maximal orbital
overlap can occur. Rotation about the C_β - C_γ bond is
permitted, for example to give (9), as this does not
affect the overlap, but rotations about the C_α - C_β and
C_γ - 0 bonds lead to energetically less-favourable
transition states with the result that the synchronous
process is suppressed[7]. A typical fragmentation of a
carbonyl-bridged bicyclic tosylate is shown in Scheme 2.
The tetrahedral intermediate (11) has the correct
geometry for concerted breakdown, whereas its axial
epimer (13) is unable to attain such a configuration
and is unaffected by sodium ethoxide[8,9]. This becomes
a very important consideration whenever the required
tosylate is produced from a mixture of epimeric
alcohols - very often the axial (i.e. wrong) epimer may
constitute 50% of such a mixture, and therefore one half
of the total tosylate produced is useless.

The synchronous nature of the fragmentation of
equatorial tosylates can be deduced from the ease with
which such reactions occur : for example, as will be
demonstrated later, when tosylate (33) is treated with
sodium ethoxide in refluxing ethanol for 30 minutes, it
is completely converted to the gem-diester (34)
(Scheme 3). Similarly, the equatorial tosylate (14)
fragments to give (15) in only 5 minutes, whereas its
axial epimer (16) slowly eliminates the elements of
p-toluene sulphonic acid to give the bicyclo [3.3.1.]

(44a)

EtO₂C

TsO

EtO₂C

TsO

TsO

EtO₂C

$-TsOH$

(18)

SCHEME 5

(19)

(20)

(21)

(22)
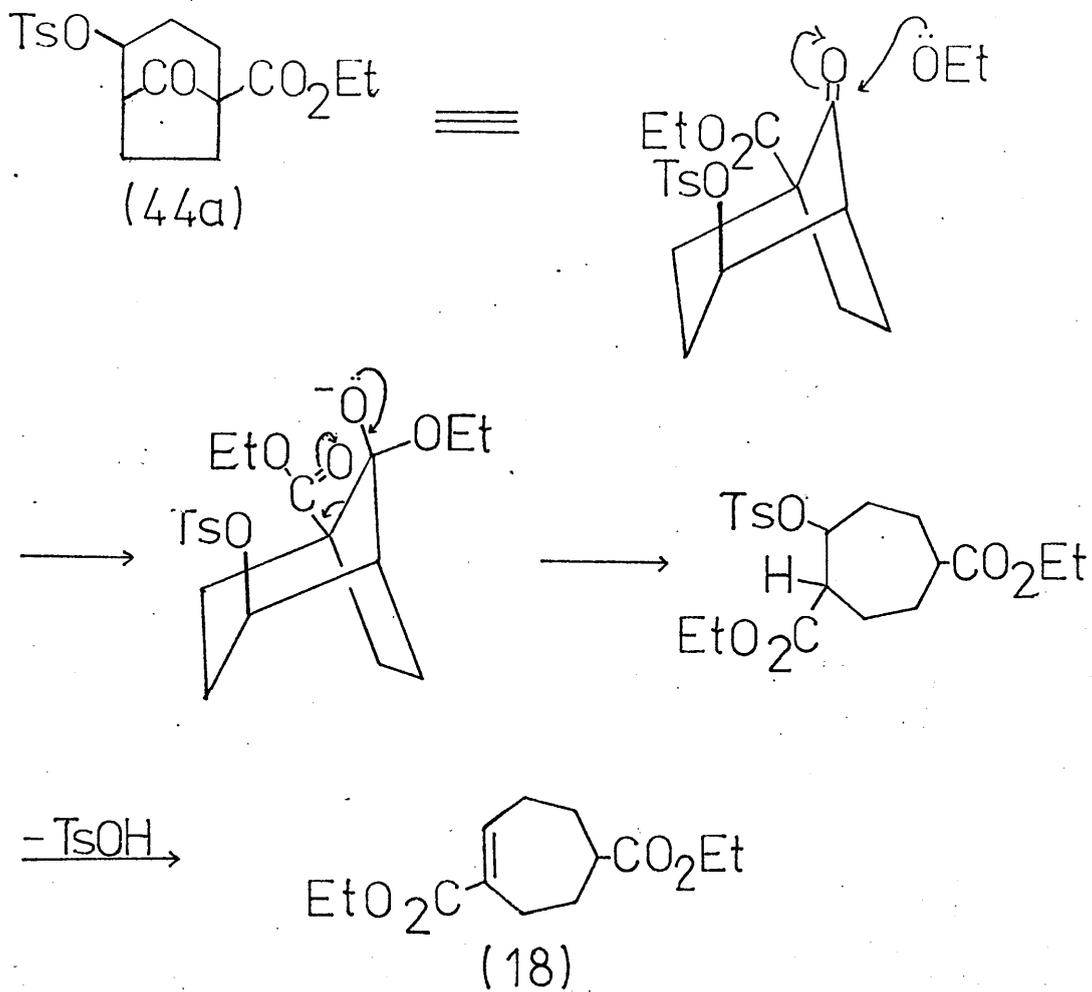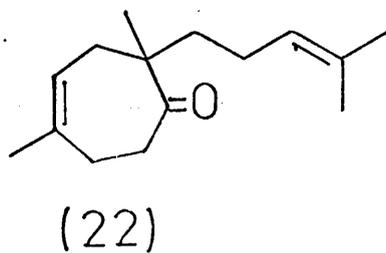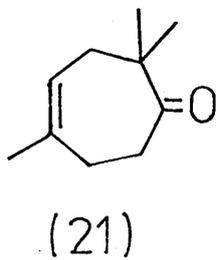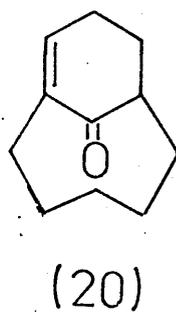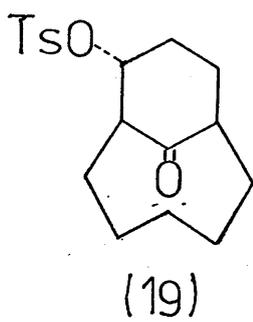
non-2-en-9-one (17), in 20 hours (Scheme 4)[8].

If there is no substituent at C (1), it is possible that even the axial tosylates will react with sodium ethoxide. This was shown by Buchanan and McLay, who treated the axial epimer of 1-ethoxycarbonyl-4-tosyloxy bicyclo [3.2.1.] octan-8-one (44a) with NaOEt and obtained the diester (13), presumably by a retro-Claisen ring-opening followed by β-elimination of the tosylate function (Scheme 5)[10].

The final restriction on fragmentation is that if the ring which does <u>not</u> contain the leaving group is larger than seven-membered, and there is no substituent at C (1), then even the equatorial tosylate will lead only to the product of β-elimination, as exemplified by the anti-Bredt enone (20) formed from tosylate (19) by treatment with hydroxide ion[11].

The initial aim of this project was to examine the possibility of utilising the fragmentation of specifically-substituted bicyclo [3.2.1.] octanone tosylates to cycloheptene derivatives with a view to the syntheses of 2,2,5-trimethylcyclohept-4-enone, karahanaenone (21), a constituent of hop oil[12], and 2,5-dimethyl-2-(4-methyl pent-3-enyl) cyclohept-4-enone (22), which could be used in a biomimetic synthesis of certain sesquiterpenes (see Chapter 3 of this thesis). The proposed route to (22) is described in Scheme 6. It was envisaged that the Michael addition of the stabilised carbanion derived from 2-ethoxycarbonyl-5-

(23) + (24)

$^-$OEt → (25) $\xrightarrow{\text{TsCl}}$ (26)

$^-$OEt → (27) $\xrightarrow{^-\text{OH}}$ (28)

$\xrightarrow{?}$ (22)   E = CO$_2$Et

SCHEME 6

(29)
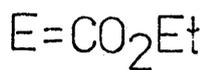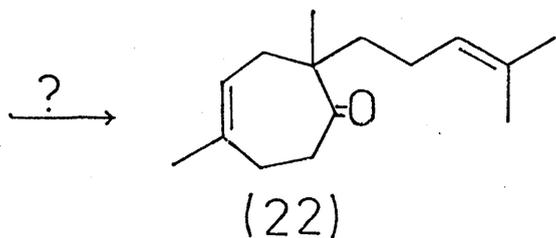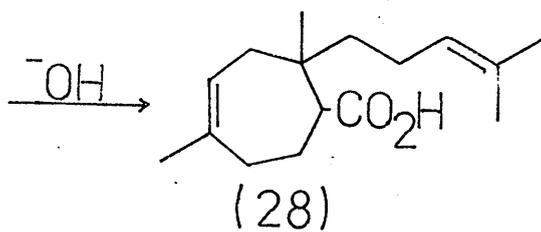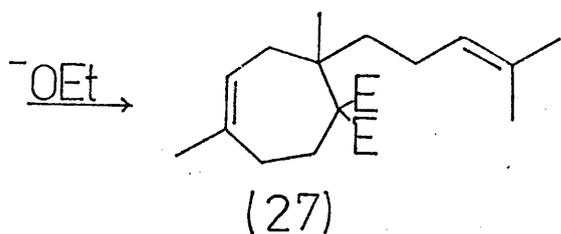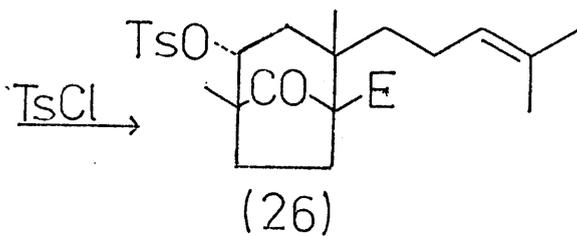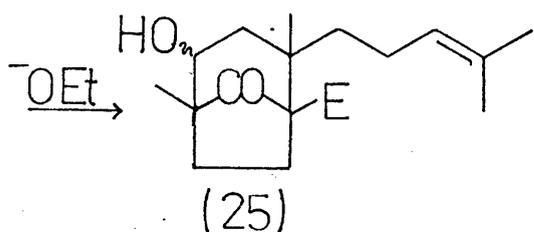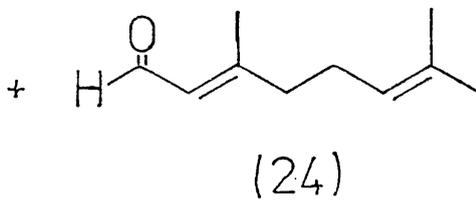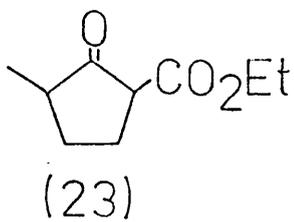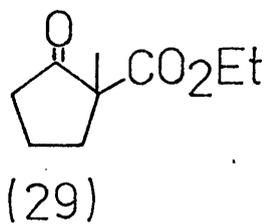
methyl cyclo-pentanone (23) onto the α,β-unsaturated enone system of citral (24) would lead to the bicyclic alcohol (25), probably as an epimeric mixture, and thence to the equatorial tosylate. This should fragment with ethoxide anion to give the trisubstituted cycloheptene diester (27), which after hydrolytic decarboxylation to the cycloheptene acid (28), might lead to (22).

The Dieckmann cyclisation of diethyl adipate, followed by alkylation with methyl iodide, gave 2-ethoxy-carbonyl-2-methyl cyclopentanone (29) in 71% yield[13]. This gave a negative ferric chloride test, and showed the C(2)-methyl as a sharp singlet at 1.24 δ in the NMR spectrum. The 2,2-disubstituted cyclopentanone was converted readily into its 2,5-isomer (23) by treatment with an equimolar amount of sodium ethoxide[14]. This product gave a positive ferric chloride test and showed the C(5)-methyl as a doublet (J=6Hz) at 1.07 δ in the NMR.

The attempted condensation of (23) with citral (24) was unsuccessful, showing only starting materials, even after four days. This result was not too unexpected, since it had been noted that in a Michael reaction, if the β-position on the enone has more than one substituent, then such a reaction proceeds either very slowly or not at all[15]. In view of this, it was decided that one of the gem-substituents in (21) and (22) would be introduced at a later stage; e.g. the synthetic approaches to karahanaenone (21) would not use 3,3-dimethyl acrolein as the Michael acceptor, since we suspected that

(30)

(31)

(32)

(33)
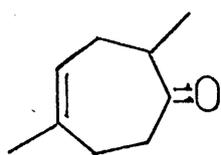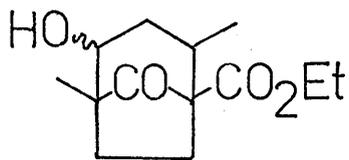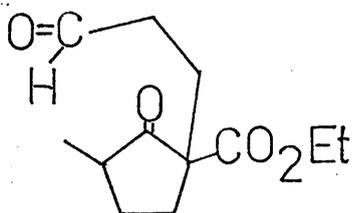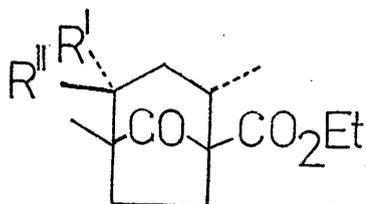
a : R^{I}=H, R^{II}= OTs

e : R^{I}=OTs, R^{II}= H

this would not react with 2-ethoxycarbonyl-5-methyl cyclopent-anone for the same reason that citral did not, but rather that crotonaldehyde would be more suitable, leading to the 2,5-dimethyl cyclohept-4-enone (30) which might be methylated specifically in the 2-position to give karahanaenone.

The condensation of (23) with crotonaldehyde in the presence of sodium ethoxide went smoothly in 75% yield, giving the bicyclic alcohol (31), presumably as a mixture of epimers. The NMR spectrum of the product showed approximately 2% of the aldehyde (32), the initial Michael adduct which undergoes an Aldol condensation under the Michael conditions. The structure of the alcohol was confirmed by IR, which showed a strong O-H stretch at 3630 cm^{-1}, plus the ester carbonyl at 1735 cm^{-1} and the bridging carbonyl at 1760 cm^{-1}, and NMR which showed the C(2) methyl as a doublet (J=8Hz) at 0.90 δ and the C(5) methyl as a sharp singlet at 1.02 δ.

The mixture of epimeric alcohols (31), purified by small-batch flash distillation, was converted into a mixture of epimeric tosylates (33e) and (33a) by treatment with p-toluene sulphonyl chloride in pyridine. The resulting crude product was separated by fractional crystallisation from hot ethanol into equatorial tosylate (33e), m.pt. 81-2°, and the axial tosylate (33a), m.pt. 161-2°. The ratio of equatorial to axial was around 2:1 and the individual epimers were identified by the half-band width ($w_{\frac{1}{2}}$) of the CH-OTs proton in the NMR spectrum. It is known that in molecules of this

CO$_2$Et
CO$_2$Et
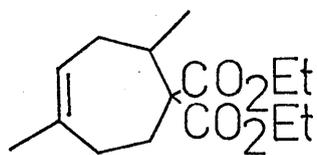
(34)

type, the axial proton (therefore equatorial tosylate) appears at higher field and shows broader coupling, and therefore a larger half-band width[16]. The equatorial tosylate showed its C(4) proton as a multiplet at 4.50 δ with $w_{\frac{1}{2}}$=16 Hz, whereas the epimeric proton on the axial tosylate appeared at 4.68 δ, with $w_{\frac{1}{2}}$=6 Hz. The remainder of the spectral details were virtually identical for both epimers, and the structural assignments made were confirmed by subsequent experiments.

An additional piece of structural information which could be gleaned from the NMR spectra of the tosylates was that the methyl group on C(2) was in the equatorial position. This must be so, as the position of the methyl doublet in both the axial and equatorial tosylates is virtually the same (around 0.90 δ). If this methyl group was axial, then its position in the spectrum of the axial tosylate would be further downfield than in the spectrum of the equatorial tosylate, since the former would give rise to a 1,3-diaxial interaction between the C(2) and C(4) substituents. This would result in the deshielding of an axial methyl group, and this is not observed[17].

Treatment of the equatorial tosylate (33e) with NaOEt went smoothly and, as predicted, gave the cycloheptene gem-diester (34), in 83% yield. This product showed only one carbonyl band, the esters, at 1735 cm^{-1} in the IR, and its NMR showed an ester methyl (1.23 δ t (J=7 Hz) 6H), a saturated methyl (0.85 δ d (J=7 Hz) 3H), an unsaturated methyl (1.67 δ s 3H) and an olefinic proton

(35)

(36)

(37)
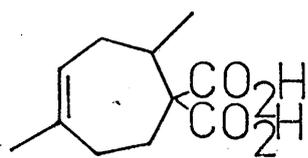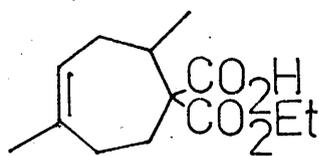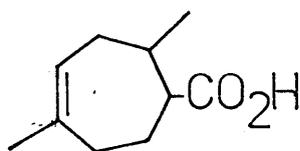
(5.34 δ s(broad) 1H). It was originally intended to hydrolyse this diester to produce the diacid (35), which would either be isolated as such, or decarboxylated to the mono-acid (37) under the hydrolysis conditions. However, in the course of a large number of experiments, whenever the diester (34) was treated with an excess of potassium hydroxide in ethanol, the product was an acid-ester (36), which was obtained as a yellow oil, showing a carbonyl O-H stretch at 2400-3400 cm^{-1} in the IR, together with two carbonyl absorptions at 1708 and 1740 cm^{-1}, the acid and ester respectively. Its NMR showed both an ester methyl (1.27 δ t(J=7Hz) 3H) and an acidic proton (11.28 δ s 1H which exchanges with D$_2$O). On only one occasion, the diacid (35) was formed (under apparently identical reaction conditions to all other hydrolyses of diester (34)); it was obtained as a white crystalline solid, m.pt.169-70°(dec.), which showed no ester signals and an acid resonance which integrated for two protons in the NMR, at 4.65 δ. Similarly, its IR spectrum showed only one carbonyl band, at 1710 cm^{-1}. When the diacid was heated in refluxing pyridine for 4 hours, it readily decarboxylated, producing the cycloheptene mono-acid (37) as a yellow oil, with ν_{co} 1708 cm^{-1} in the IR, and a one-proton acid resonance at 12.01 δ in the NMR.

Neverthless, such a hydrolysis could not be repeated, and the normal route to the mono-acid (37) was perforce through the acid-ester (36). When this was decarboxylated in refluxing pyridine, the cycloheptene

(38)

(39)

(40)
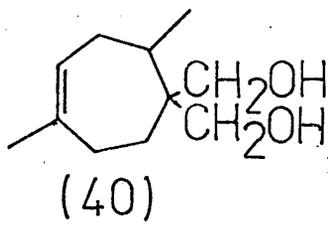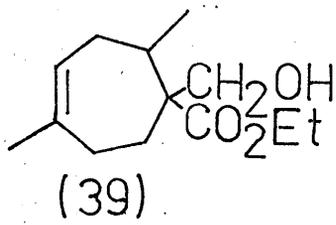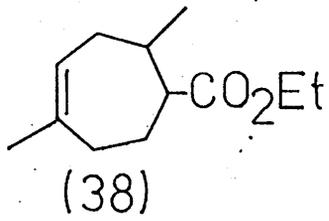
ester (38) was produced in 72% yield. The IR of this product showed no O-H stretch, and a single carbonyl absorption at 1738 cm^{-1}. The structure was confirmed by the NMR, which showed an ester methyl (1.23 δ $\underline{t}$(J=8Hz) 3H), a saturated methyl (0.87 δ $\underline{d}$(J=6Hz) 3H), an unsaturated methyl (1.70 δ $\underline{s}$ 3H) and a vinylic proton (5.50 δ $\underline{m}$ 1H), and the mass spectrum which showed M^{+}=196.

The mono-ester (38) was hydrolysed by potassium hydroxide in aqueous ethanol, by overnight reflux, and yielded the cycloheptene acid (37) (83%) as a clear viscous oil, identical to that produced by decarboxylation of the diacid (35), mentioned previously.

This discovery, that (34) could only be converted to (37) via (36) and (38), was a new and inconvenient limitation on the tosylate ring-expansion method, which merited further investigation. It seemed likely that the origin of the difficulty was steric hindrance, so the reaction of the diester (34) with a smaller nucleophile (LiAlH$_4$) was investigated, to discover whether it would reduce (34) to the hydroxy-ester (39) or to the diol (40). When the diester was treated with one equivalent of LiAlH$_4$ (i.e. a half-mole of hydride per mole of diester), the product observed was a mixture of untouched diester (34), hydroxy-ester (39) and diol (40). These were separated by prep. TLC and characterised as follows: the hydroxy-ester (39) showed 2400-3600 cm^{-1} (bonded O-H) and 1735 cm^{-1} (ester carbonyl) in the IR, and an ester methyl (1.23δ $\underline{t}$(J=7Hz) 3H) together with a hydroxyl (3.07 δ $\underline{s}$ (broad) 1H which exchanges with D$_2$O) in the

(33e)

(36)

SCHEME 8

(45)

(34)

(41)

(35)
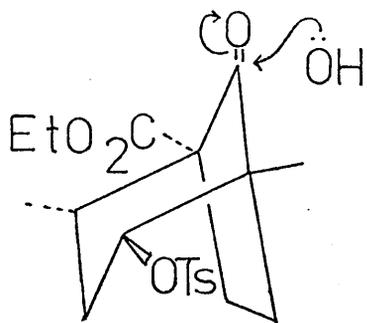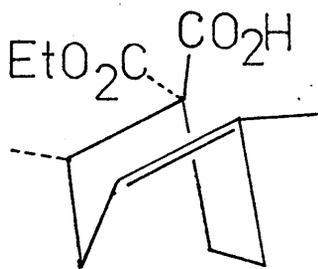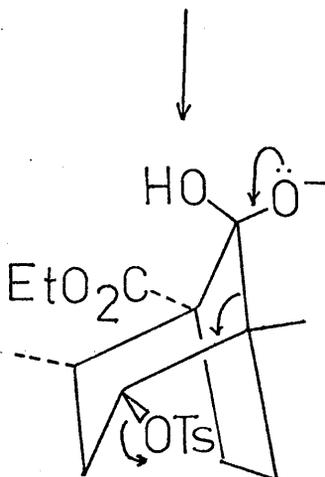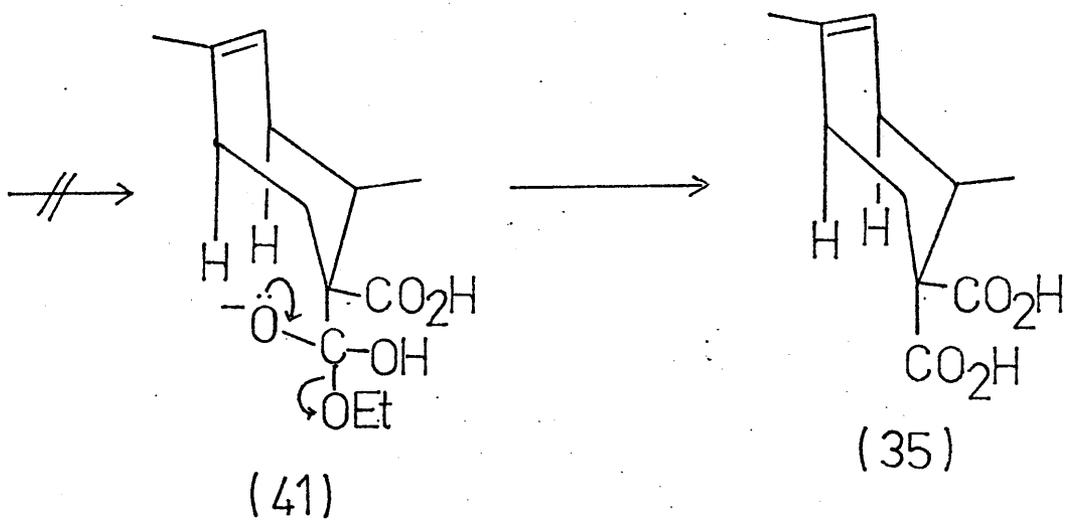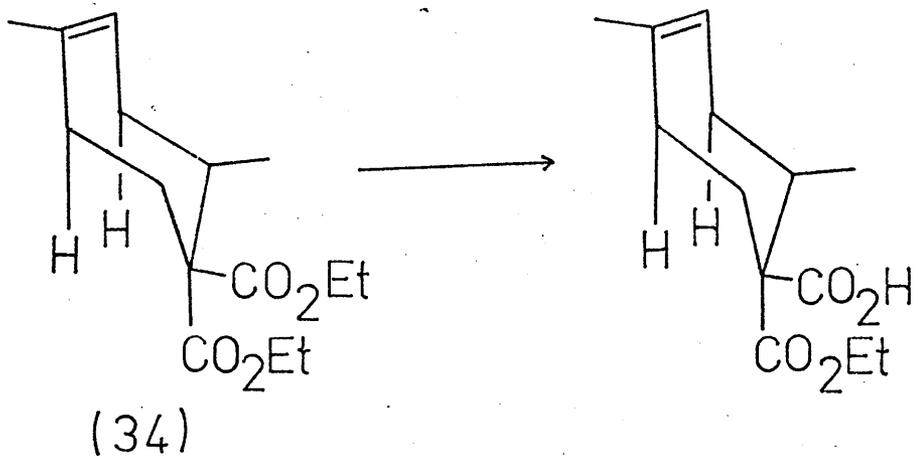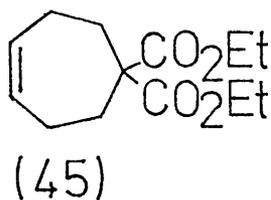
SCHEME 7

NMR. The diol (40), a white crystalline solid, m.pt. 89-90° from benzene, showed no carbonyl absorption in the IR, with a free O-H stretch at 3620 cm^{-1}, and no ester signals at all in the NMR. The hydroxyl protons appeared as a multiplet at 3.14 δ, and exchanged with D_2O. The nature of the latter product was confirmed by reduction of the diester (34) with excess lithium aluminium hydride, which gave a single product which was identical in all respects to the diol isolated by prep. TLC. Thus, even under "competitive" conditions, both ester groups are reduced, and this seems to confirm the stereochemical hypothesis. The inertness inherent in the system is probably caused by the α-methyl group, since hydrolysis of a similar cycloheptene diester (45) with no α-methyl group has been effected successfully[10]. Presumably the reactive site in the molecule must experience an increase in steric hindrance in going to the tetrahedral intermediate (41) necessary for the second hydrolysis, as shown in Scheme 7.

Interestingly, the acid-ester (36) could also be produced by treatment of the equatorial tosylate (33e) with potassium hydroxide in ethanol. Presumably this reaction follows the same path as the ethoxide-induced fragmentation, and thus this enables one to identify where the carboxyl moiety in (36) is in relation to the α-methyl group. The course of the fragmentation is shown in Scheme 8, and, if followed, results in the methyl group and the carboxyl group being <u>trans</u> to each other. As the acid-ester prepared in this fashion is identical

(81)

(82)

(83)

(84)

E=CO₂Et

TABLE 1
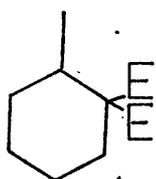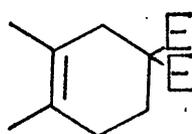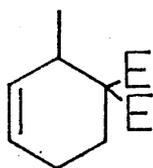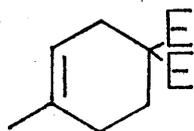
ENTRY	ALCOHOL	ALDEHYDE	TOSYLATE	DIESTER	DIACID ?	MONOACID
1	(31)	—	(33)	(34)	(36)	(37)
2	(42)	(43)	(44)	(45)	(46)	(47)
3	(48)	—	(49)	(50)	(51)	(52)
4	(53)	—	(54)	(55)	(56)	(57)
5	(58)	—	(59)	(60)	(61)	(62)
6	(63)	(64)	(65)	(66)	(67)	(68)
7	(69)	(70)	(71)	(72)	(73)	(74)
8	(75)	—	(76)	(77)	(78) (79)	(80)
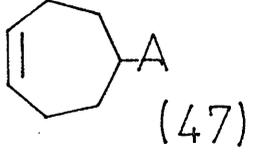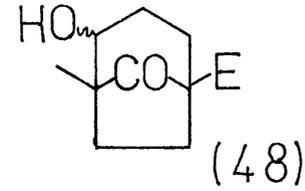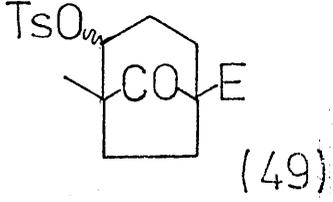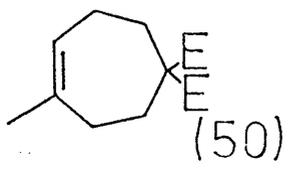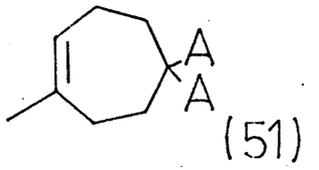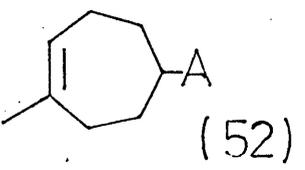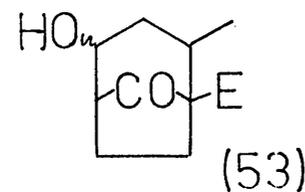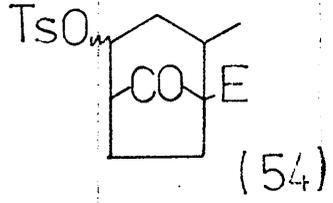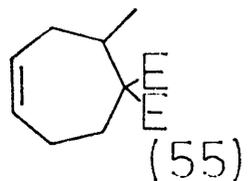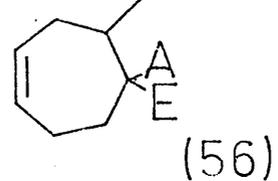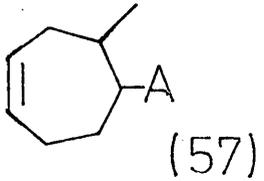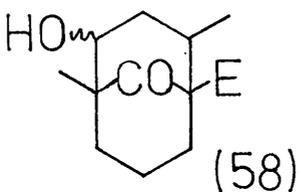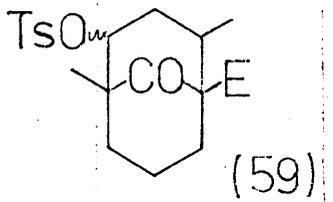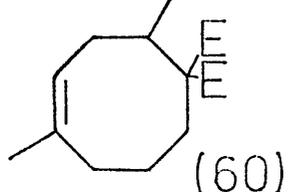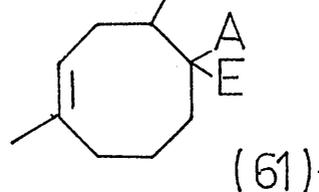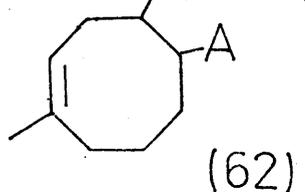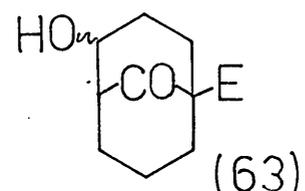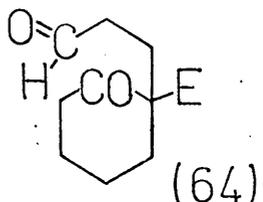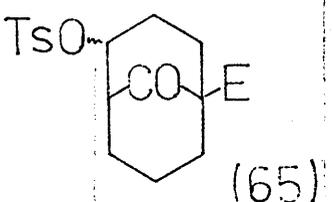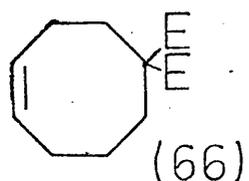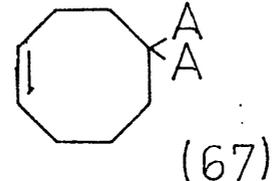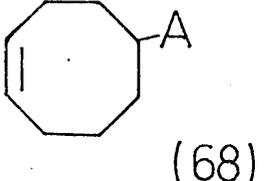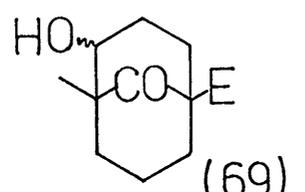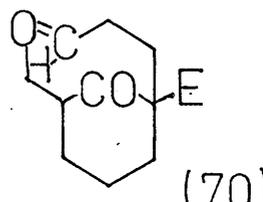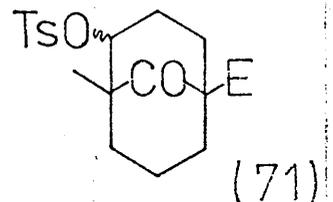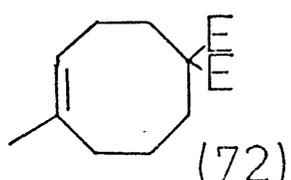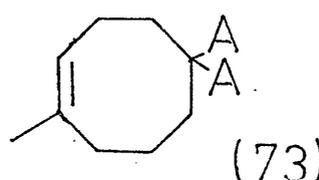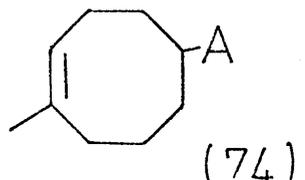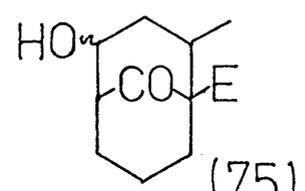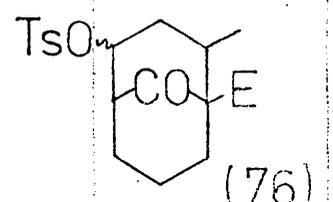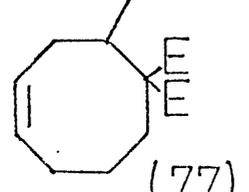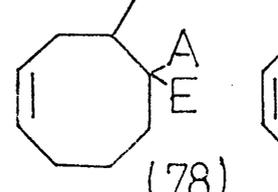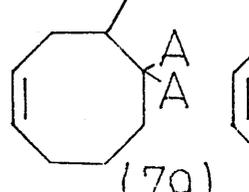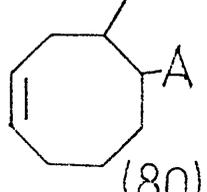
to that from the half-hydrolysis of diester (34) (by GLC
comparison of their methyl esters), it seems reasonable
to assume that they both exist in the configuration shown
in Scheme 7, rather than in the epimeric form with the
carboxyl and the ester interchanged. If we assume that
nucleophilic attack on the axial ester (c.f. (41)) is
disfavoured by 1,3-interaction with the axial hydrogens,
we must also postulate that ring inversion (which would
exchange the positions of the acid and ester functions)
is forbidden ; otherwise (45) would resist total hydrol-
ysis. This in turn leads to the surprising conclusion
that the ring is conformationally "frozen" with the
α-methyl function equatorial. This is a conclusion we
are reluctant to concede.

With a view to investigating the importance of
factors such as relative positions of methyl groups and
ring size on the hydrolysis of the medium-ring gem-
diesters such as (34), it was decided to prepare a series
of such diesters from the corresponding bicyclic [3.2.1.]
and [3.3.1.] precursors. A full list is given in Table
1. A comprehensive review of the literature produced
the conclusion that the six-membered ring analogues of
diester (34), such as (81)[18], (82)[19], (83)[20] or (84)[21],
were all readily hydrolysed with alcoholic potassium
hydroxide to give the corresponding diacids, which were
isolated and characterised. Of the seven- and eight-
membered analogues, only diesters (45) and (72) had
been previously prepared, and these were found to
hydrolyse completely[10,9].

Of all of the tosylate precursors, only one, 1-ethoxycarbonyl-4-tosyloxy-2-methyl bicyclo[3.3.1] nonan-9-one (76), was not prepared, but this omission does not affect any conclusions drawn. The parent alcohols from which the tosylates were derived, were synthesised from the appropriate 2-ethoxycarbonyl cyclo-pentarone or ʳhexanone and either acrolein or crotonaldehyde, as desired. The Michael addition was performed using either sodium ethoxide or triethylamine as base. In three cases, entries 2,6 and 7 in Table 1, the inter-mediate aldehyde was isolated as the major product, and subsequently cyclised to the required alcohol upon treatment with acid. The alcohols were converted to a mixture of epimeric tosylates by treatment with p-toluene sulphonyl chloride in pyridine, and it was found that this reaction, although slow, proceeded satisfact-orily at room temperature if given enough time. The axial and equatorial tosylates were usually separated by preparative TLC, although in certain instances fract-ional crystallisation could be used.

Entry 2 - 1-ethoxycarbonyl-4-tosyloxy bicyclo[3.2.1] octan-8-one (44) was prepared as an epimeric mixture (44e and 44a) from the corresponding alcohols (42) via the aldehyde (43). The epimers could be separated by fractional crystallisation or, more conveniently, prep. TLC, and they were both white crystalline solids with very similar melting points. Each epimer was identified by the position and half-band width of its CH-OTs proton, as mentioned previously. Treatment of the equatorial

tosylate (44e) with sodium ethoxide in ethanol produced
the expected diester (45), characterised in the IR by a
single, sharp carbonyl absorption at 1735 cm^{-1} and in
the NMR by the appearance of the ester (1.28 δ $\underline{t}$(J=7Hz)
6H) and olefinic signals (5.40 δ $\underline{s}$(broad) 2H).
Hydrolysis of the diester (45) by potassium hydroxide in
ethanol at room temperature gave the corresponding diacid
(46), in 82% yield, as a white crystalline solid, m.pt.
154-7°. Proof that both ester groups had been hydrolysed
was provided by the NMR which showed no trace of the ester
triplet at 1.28δ, but did show a two-proton resonance at
10.05 δ which disappeared when shaken with D_2O. The
diacid (46) decarboxylated readily in refluxing pyridine,
producing cyclohept   .-5-carboxylic acid (47), m.pt. 65-7°,
identical in all respects to an authentic sample[10].

Entry 3 - 1-ethoxycarbonyl-4-tosyloxy-5-methyl bicyclo
[3.2.1.] octan-8-one (49) was prepared as a mixture of
epimers (49e and 49a), separated by chromatography (the
axial being the more polar). Neither epimer was isolated
in the crystalline state, but the preparations were perf-
ormed on a very small scale and the products were there-
fore not amenable to purification by recrystallisation.
However, satisfactory spectral characterisation was
achieved. Sodium ethoxide treatment of the equatorial
tosylate (49e) furnished the expected 1-methyl-5,5-dieth-
oxycarbonyl cycloheptene (50) in 91% yield. Hydrolysis
of this diester by ethanolic KOH at reflux temperature
yielded the corresponding diacid (51), which showed no
ester signals in the NMR, but did show a two-proton acid

resonance at 12.31 δ. Decarboxylation in refluxing
pyridine gave the mono-acid (52) in virtually quantitative
yield.

Entry 4 - 1-ethoxycarbonyl-4-tosyloxy-2-methyl bicyclo
[3.2.1.]octan-8-one (54) was prepared in the normal way
from its parent alcohol (53). The tosylation product
proved to be a single epimer, the equatorial (54e), and
there was no trace in the NMR of the axial tosylate (54a).
Unusually, (54e) was an oil at room temperature (although
it solidified at -70°), and the fact that it was a single
epimer was proved by complete conversion to the diester
(55) upon treatment with NaOEt. There was no trace of any
unreacted axial tosylate (54a) in the sodium ethoxide
product. Hydrolysis of the gem-diester (55) was not easy,
as shown by the fact that the initial product was a
mixture of the acid-ester (56) and the mono-acid (57).
When this crude product was re-treated with excess KOH
in refluxing ethanol for 40 hours, the mono-acid (57) was
isolated as the only product (47% overall). IR of (57)
showed ν_{OH} 3540 cm^{-1} (free) and 2300-3400 cm^{-1} (bonded),
with ν_{co} 1705 cm^{-1} and no ester carbonyl at 1735 cm^{-1}.
The NMR confirmed the absence of the ester group, and
showed a single acid absorption at 8.60 δ.

The conclusion to be drawn from the above findings has
to be that the only factor which inhibits the complete
hydrolysis of the gem-diester groups is the adjacent
methyl group. In the two instances in which such a
methyl was present, the hydrolysis gave acid-ester rather
than diacid, whereas its absence allowed the complete
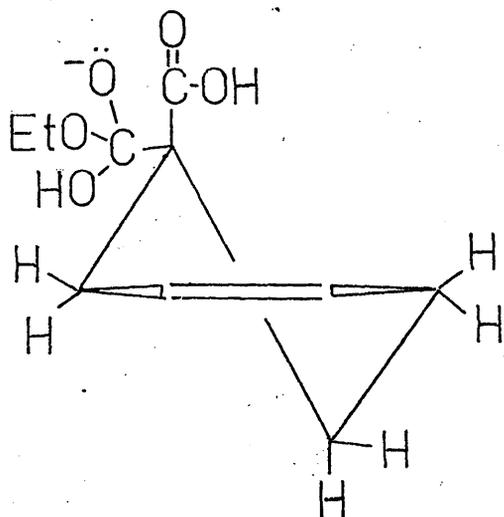
(85)

hydrolysis of both groups. This reinforces the idea of an overcrowding of the transition state for the second hydrolysis step (as depicted in Scheme 7). It is doubtful if such a situation can arise in the six-membered ring analogues quoted earlier from the literature, since the cyclohexene ring is twisted out of the "chair" configuration by a considerable amount[22]. This means that the combined effect of the α-methyl group and the 1,3-diaxial interaction of adjacent protons, as seen in (41), operates only in the cyclo-heptene case. The corresponding intermediate (85) for the cyclohexene diesters is twisted in such a way as to minimise such a steric crowding.

In an effort to discover whether this congestion of the reaction site can be reduced by enlarging the ring, and thus making the whole system more flexible, it was decided to prepare the [3.3.1.] analogues of entries 1-4, viz. entries 5-8. Unfortunately, lack of time prevent preparation of the compounds mentioned in entry 8, but as will be seen, this omission is not too vital, and in fact the products for this series of reactions can be predicted from the remainder of the results. The alcohols were prepared by condensation of either acrolein or crotonaldehyde with 2-ethoxy-carbonyl cyclohexanone (with or without a 6-methyl group) in the normal way.

Entry 5 - 1-ethoxycarbonyl-4-tosyloxy-2,5-dimethyl bicyclo[3.3.1.] nonan-9-one (59) was prepared from alcohol (58) as a single epimer, the equatorial (59).

The tosylate, a white crystalline solid, m.pt. 99-100°, showed $\underline{C}H$-OTs as a broad multiplet ($w_{\frac{1}{2}}$=18Hz) at 4.50δ in the NMR. There was no trace of any of the axial epimer (59a) in the NMR of the recrystallised reaction product, and prep. TLC of the mother liquors provided only additional equatorial tosylate and unreacted alcohol (58) in roughly equal proportions. As anticipated, (59e) fragmented readily with ethoxide ion to form 5,5-diethoxycarbonyl-1,4-dimethyl cyclo-octene (60) in 98% yield. This diester showed a sharp carbonyl absorption at 1735 cm^{-1} (ester) in the IR, with an ester methyl (1.18δ $\underline{dt}$(J=8Hz) 6H), saturated methyl (0.85δ $\underline{d}$(J=7Hz) 3H) unsaturated methyl (1.60δ $\underline{s}$ 3H) and an olefinic proton (5.45δ $\underline{t}$(J=7Hz) 1H) in the NMR. As with its cycloheptene analogue (34), the diester put up a strong resistance to hydrolysis. However, the initial overnight reflux in alcoholic KOH solution did not produce the acid-ester (61) cleanly, but seemed to be a mixture of (61) and the decarboxyl-ated-hydrolysed derivative, the mono-acid (62). When this mixture was subjected to further treatment with base, the cyclo-octene mono-acid (62) was isolated as a single compound, in 77% yield overall, a white, cryst-alline solid, m.pt. 127-8°. IR showed a free O-H at 3515 cm^{-1}, and NMR confirmed that all ester groups had been removed. The acid proton showed as a one-proton signal at 11.28δ which exchanged rapidly with D_2O.

Entry 6 - following published procedures[23,24], 1-ethoxy-carbonyl-4-hydroxy bicyclo[3.3.1] nonan-9-one (63) was

prepared from 2-ethoxycarbonyl cyclohexanone. The tosylate, prepared from (63) in the normal way, was isolated as an epimer mixture of (65e) and (65a), in the ratio 2:1, which was separated by prep. TLC, the axial epimer being the more polar. NMR characterisation of the individual epimers was straightforward : (65e) showed C$\underline{H}$-OTs as a very broad multiplet at 4.70 δ (w$_{\frac{1}{2}}$= 18Hz), whereas (65a) showed the corresponding proton as a broad singlet at 5.06 δ (w$_{\frac{1}{2}}$=8Hz). Both epimers were crystalline white solids (from ethanol) with significantly differing melting points : 88-9° for (65e) and 99-100° for (65a). The expected diester (66) was formed in 87% yield when (65e) was treated with sodium ethoxide. (66) showed a sharp carbonyl band at 1735 cm^{-1}, and its NMR featured the ester methyl (0.92δ $\underline{dt}$(J=7Hz) 6H) and the near-equivalent olefinic protons (5.63δ $\underline{m}$ 2H). Hydrolysis of (66) in alcoholic KOH solution yielded 84% of a product which showed no ester signals in the NMR, but it was not possible to integrate the acid protons, it can only be assumed that this product was the cyclo-octene gem-diacid (67) (a fairly safe guess under the circumstances). Indeed, when (67) was treated with refluxing pyridine for 3 hours, the single product obtained could be unambiguously assigned the structure (68), cyclo-octene-5-carboxylic acid. Its IR spectrum showed a broad O-H stretch between 2450-3340 cm^{-1}, with ν_{co} at 1705 cm^{-1} (acid), while its NMR had only two distinctive features : a two-proton olefinic signal at 5.70δ and a broad singlet at 6.83δ, 1H, which

exchanged in the presence of D_2O.

Entry 7 - the precursor alcohol (69) was prepared, via aldehyde (70), by the method of Parker[25]. The tosylate was prepared as a mixture of epimers, (71e) and (71a), which were separated by chromatography, and identified by the half-band width technique mentioned previously. Fragmentation of (71e) has already been performed[9], and gave the diester (72), which hydrolysed readily to the diacid (73). This was then decarboxylated to (74) in the usual way.

Entry 8 - due to insufficient time being available, this entry could not be completed, but to judge by the earlier results, the products of the hydrolysis of (77) can be predicted. It seems clear from entries 5-7 that increasing the size of the ring does not allev- iate sufficiently any steric crowding which arises from having a methyl group α to the gem-diester. In similar fashion to their [3.2.1.] homologues, the diesters without this adjacent methyl hydrolysed quite readily to their diacids, but diester (60), like diesters (34) and (55), proved more troublesome and required consid- ·erable encouragement before both ester groups were removed. Therefore, it seems reasonable to predict for entry 8 that the diester (77) would hydrolyse initially to acid-ester (78) rather than diacid (79) and subsequ- ent treatment with base would almost certainly lead to mono-acid (80).

As can be seen from the experimental details of their preparation, the tosylates are usually formed

SCHEME 9

as an epimeric mixture, and since only the equatorial
is used, a large proportion of the product, in the shape
of the axial epimer, is wasted. Therefore, efforts were
directed at means whereby these axial tosylates could
also be utilised, preferably to give similar products
to the equatorial fragmentations, in a bid to reduce
this wastage. As has been stated, the axial tosylate
has the "wrong" configuration to eliminate in a con-
certed process, but we envisaged that it might be poss-
ible to perform the fragmentation in a two-step manner,
by initial bridge-scission followed by elimination. The
bridge-scission reaction would use the electron-attract-
ing properties of the ester group at C(1) as the alter-
native to a straightforward elimination of TsO⁻, and
if the attacking nucleophile was HO⁻, rather than EtO⁻,
the initial product would be a carboxylic acid which
might decarboxylate with concomitant expulsion of the
leaving group (Scheme 9).

First attempts to induce such a fragmentation were
performed of the axial epimer of 1-ethoxycarbonyl-4-
tosyloxy-2,5-dimethyl bicyclo[3.2.1.] octan-8-one (33a).
When this was treated with a seven-fold molar excess of
potassium hydroxide in dry ethanol, the reaction went
exactly as planned and the cycloheptene mono-acid (37)
was isolated as the major product (91%), with the corres-
ponding ester (38) present in trace amounts (5%).
Obviously the reaction as depicted in Scheme 9 has not
stopped at the mono-ester (38), but this has been
hydrolysed to form (37). The acid was identical in

SCHEME 10

(90)(R=H)
(93)(R=Et)
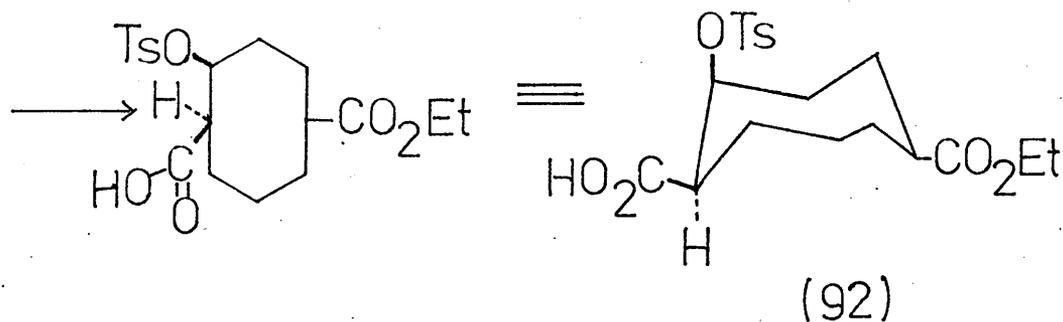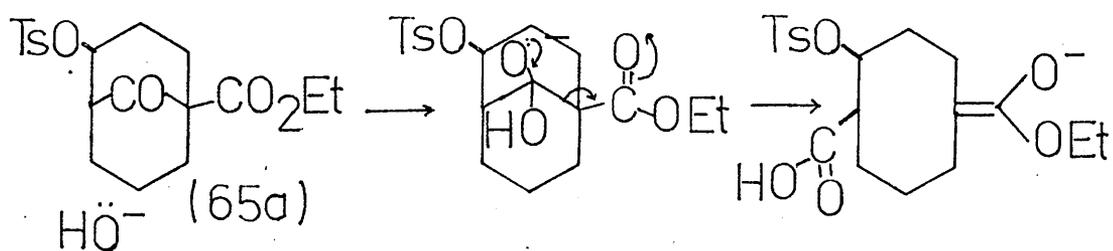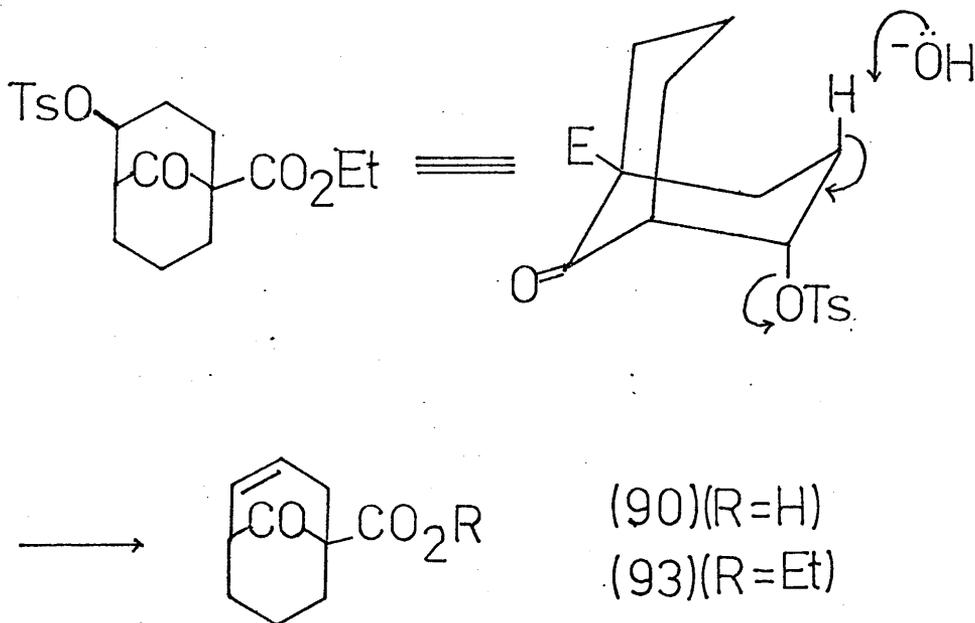
SCHEME 11

TABLE 2

AXIAL TOSYLATE	PRODUCTS
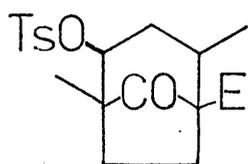
(33a)
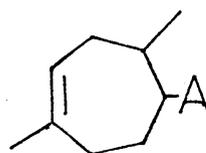
(37)
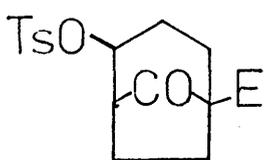
(44a)
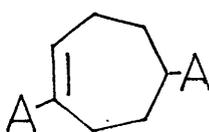
(86)
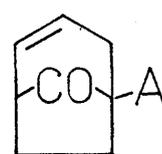
(87)
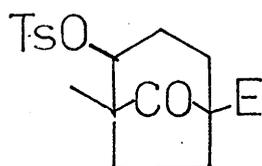
(49a)
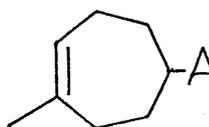
(52) ?
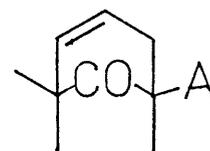
(88)
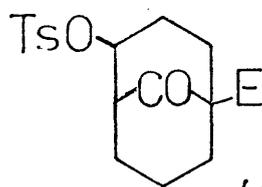
(65a)
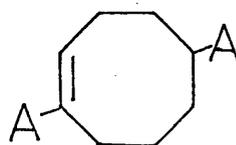
(89)
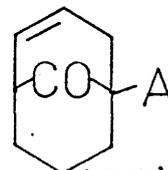
(90)
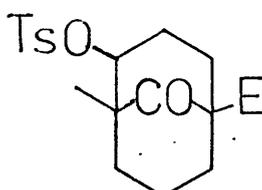
(71a)
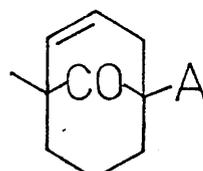
(91)

$E = CO_2Et;$ $A = CO_2H$

every respect to that produced eventually from the
equatorial tosylate (33e), and marks a substantial
increase in the yield : axial tosylate ⟶ mono-acid
in 91% in one step, compared with equatorial tosylate
⟶ gem-diester ⟶ acid-ester ⟶ ester ⟶ acid in 35%
overall, using four distinct steps. This is a new
and potentially valuable, extension of the tosylate
ring-expansion route, if it can be shown to be general.

Encouraged by this success, it was decided to use
the axial epimers prepared in the previous synthetic
sequences to investigate whether this novel reaction
could be applied to axial tosylates in general. The
result of these investigations are shown in Table 2.
This reveals immediately that the reaction is not
general, and that we had been very fortunate in choosing
the only compound which followed the predicted
sequence of events exactly! The remaining four
examples give products which must arise by alternative
pathways to that described in Scheme 9, and this we
now attempt to rationalise.

In the bicyclo[3.3.1] cases in Table 2, there are
two initial reactions which are equally feasible :

1) a retro-Claisen reaction, where the bridging
carbonyl group is attacked by hydroxide ion and the
resulting negative charge is fed through to the ester
carbonyl (Scheme 10); or

2) a β-elimination of p-toluene sulphonic acid
with retention of the basic bicyclic skeleton, as seen
in Scheme 11.

(96)

(92)

(97)

(68)

SCHEME 14

(71a)

(98)

(99)

SCHEME 15

(92)

(94)

(89)

SCHEME 12

(93)

(95)

(89)
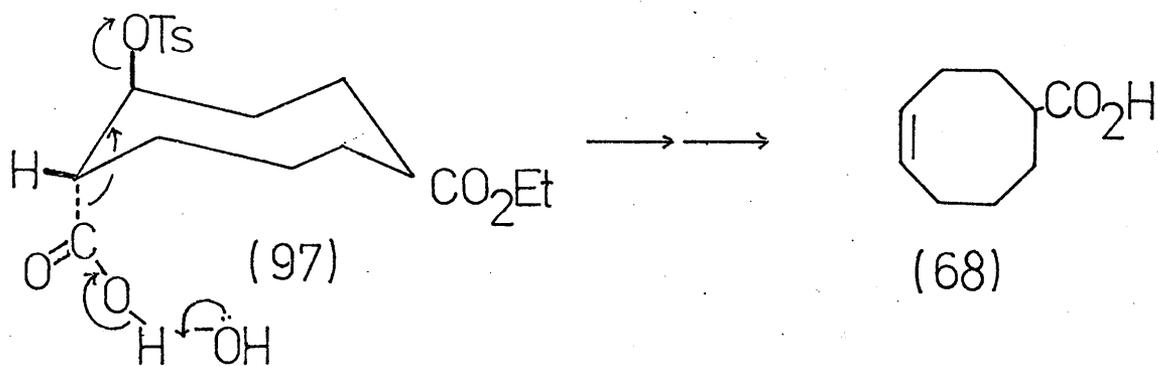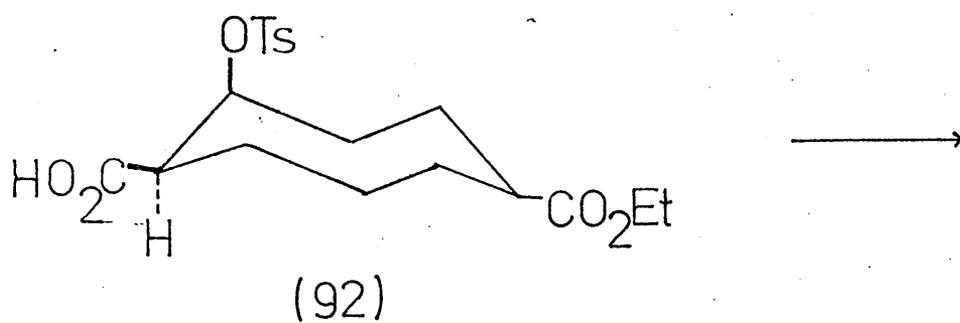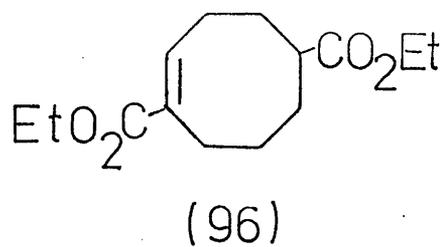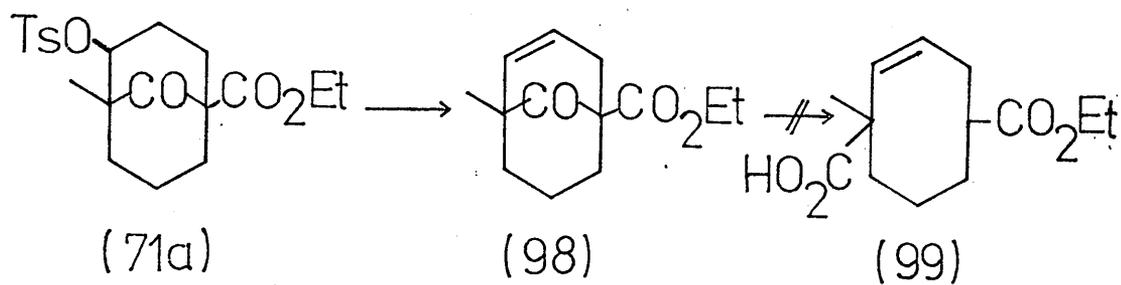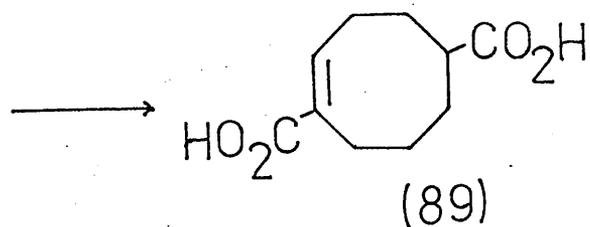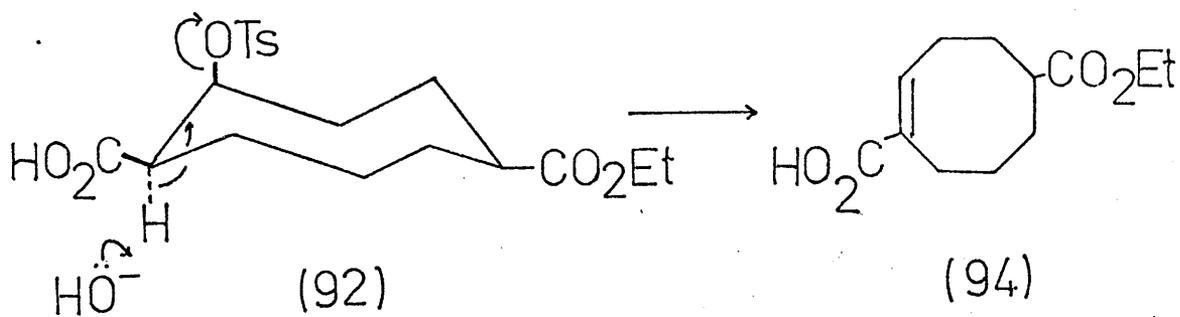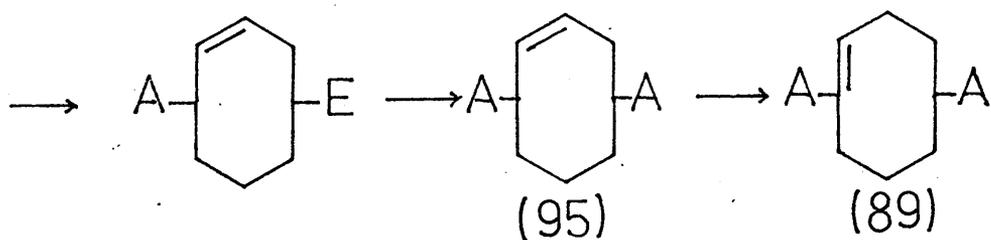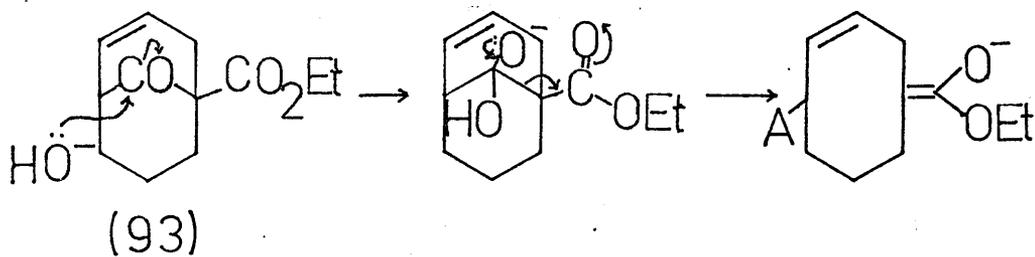
SCHEME 13

The fact that, for example, (90) is isolated from
(65a) proves that the β-elimination step depicted in
Scheme 11 actually takes place, but the question still
remains of the origin of the cyclo-octene diacid (89).
Again, there are two possibilities : the first is via
a straightforward elimination of tosylate from inter-
mediate (92) (Scheme 12), while the second involves
attack at the C(9) carbonyl of (93) by hydroxide ion
to open up the bicyclic system, giving (95), which
then shifts the double bond into conjugation (Scheme 13).
There are precedents for this type of process in the
literature : Cope has shown that treatment of (93) with
sodium ethoxide results in the formation of diester
(96)[26]. It is noteworthy that base-catalysed epimer-
isation of (92) to (97) does <u>not</u> occur, as this would
be perfectly set up for a decarboxylative elimination
to yield cyclo-octene carboxylic acid (68) (Scheme 14),
but this product is not observed.

Still in the [3.3.1.] series, when a methyl group
is present on C(5), only the product of β-elimination
is observed. The fact that in the presence of OH⁻ (98)
does not produce (99) (Scheme 15) is not surprising, as
such a retro-Claisen is known to require a better
nucleophile than HO^- (eg. NH_2^- or BuO^-)[9]. Overall then,
in this series of axial tosylates, it seems that the
β-elimination of tosylate (eg. (65a)⟶(93)) is faster
than the retro-Claisen ring opening (eg. (65a)⟶(92)).

Turning to the [3.2.1.] series of axial tosylates,
here we cannot guarantee that the same reaction paths
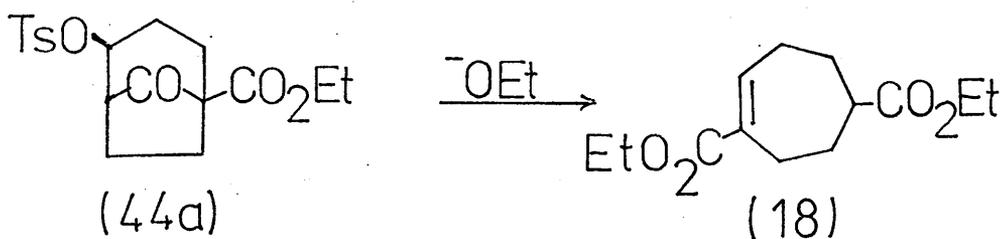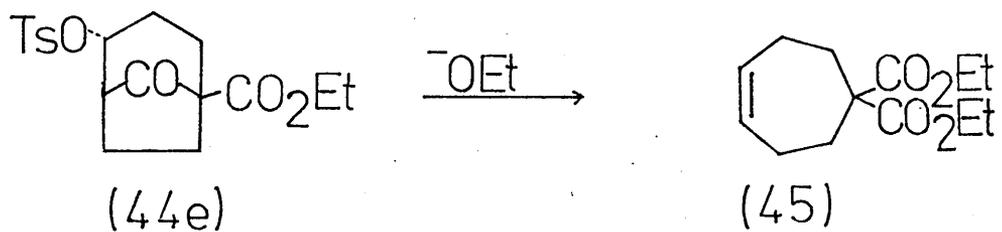
SCHEME 16
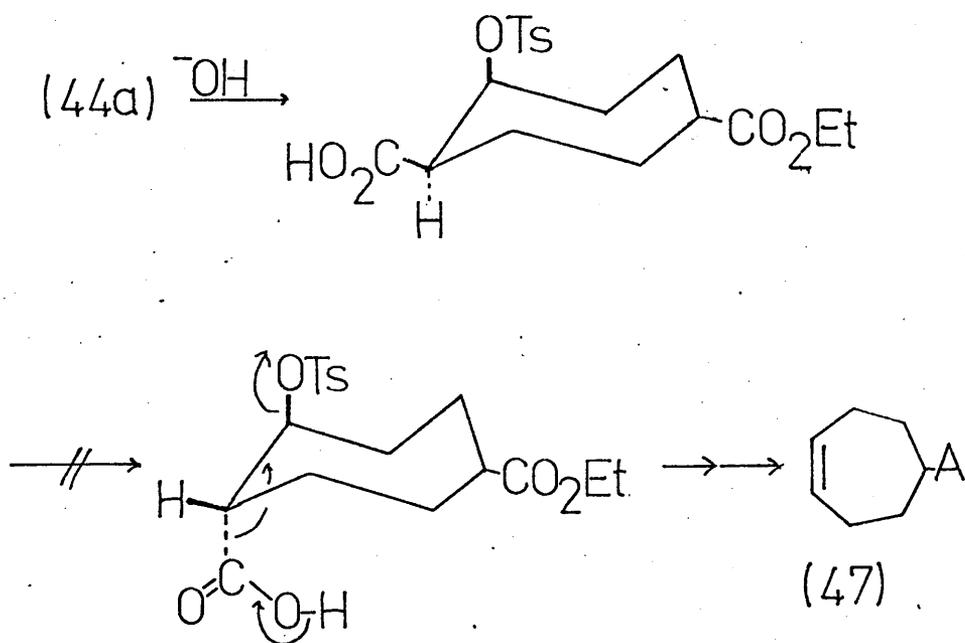
SCHEME 17

will be preferred; this is principally due to the fact
that the carbonyl bridge is more strained in the five-
membered ring case, as manifest in the IR stretching
frequency: bicyclo[3.2.1.] octan-8-one appears at
1750 cm^{-1} [27] whereas bicyclo[3.3.1.] nonan-9-one appears
at 1724 cm^{-1} [28]. Chemical evidence for this increased
strain includes the fragmentation of (4) to (5) via
attack at the bridgehead carbonyl, whereas (6) cleaves
to (7) under similar basic conditions, via attack at the
more accessible C(2) carbonyl. Similarly it is known[10]
that both the equatorial _and_ axial epimers of (44) are
opened with equal facility by ethoxide ion (Scheme 16).
This suggests that the rate of attack on the bridging
carbonyl is at least comparable with, if not greater than,
the rate of β-elimination.

Indeed, this is borne out in the case of tosylate
(44a), which, when treated with potassium hydroxide in
ethanol, gave principally the retro-Claisen product (86),
and a small amount of the β-elimination product (87).
Again it should be pointed out that there has been no
epimerisation leading to a situation where the carboxyl
group and the tosylate are trans-antiparallel (Scheme 17).
The product from the decarboxylative-elimination, (47) is
not observed. How then can we account for the unique
behavior of axial tosylate (33a)?

When the C(5) position carries a methyl group, as in
(33a) and (49a), the elimination of TsO⁻ with an anti-
periplanar H from the intermediate (100) in the retro-
Claisen opening becomes impossible (Scheme 18).

(33a)

(100)

(101)

(37)
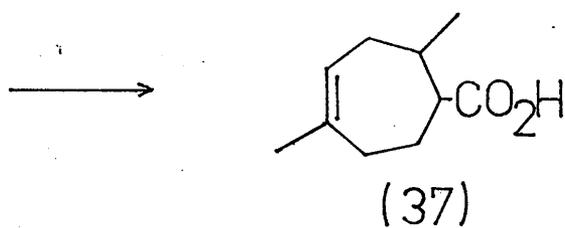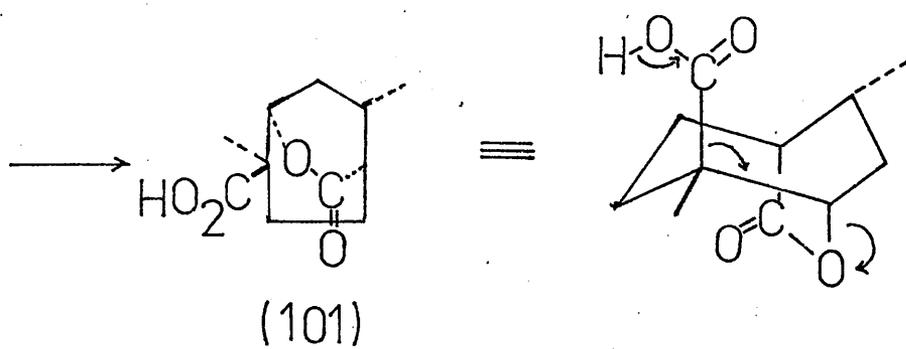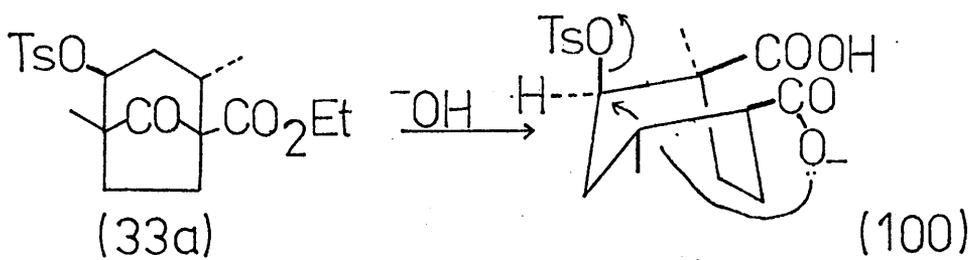
SCHEME 18

Instead, the tosylate is arguably displaced by an internal nucleophile - the C(1) carboxylate anion. Presumably the ester originally in this position is readily hydrolysable, and molecular models show that the transannular reaction is physically possible. The intermediate lactone (101) is perfectly set up for a decarboxylative-elimination of the 1,2-trans diaxial substituents, and the breakdown to produce the cycloheptene carboxylic acid (37) must proceed quite readily. There are several points worthy of note in connection with the above reactions:

(a) When sodium ethoxide is used as the base, no carboxylate anion (CO_2^-) could be formed, and hence no transannular cyclisation. This explains why Buchanan and McLay found that (44a) yielded straightforward retro-Claisen product (18)[10].

(b) In the [3.3.1.] series, since β-elimination seems to take precedence over bridge-scission, there is very little or no chance of the above reaction taking place.

(c) If the C(5) position carries a hydrogen, then the straightforward 1,2-elimination of ρ-toluene sulphonic acid appears to be more rapid than the transannular attack of the carboxylate anion.

Hence (44a) gives the diacid (86) rather than the monoacid (47). On this mechanism, the reaction would not be applicable to bicyclo[3.3.1.] nonyl tosylates, nor to bicyclo[3.2.1.] octyl tosylates lacking a bridgehead substituent. It is therefore of little general value.

It is now possible to predict that the product from
treatment of (49a) with KOH in ethanol would be the cyclo-
heptene mono-acid (52). It is a [3.2.1.] system, so
it will fragment rather than merely β-eliminate the
tosylate; and there is a C(5) substituent which results
in transannular ring-closure being the only available
method of displacing the leaving group after the retro-
Claisen has taken place. Unfortunately, when this
reaction was performed, the spectral details of the
product were ambiguous. The product is definitely an
acid, since it is soluble in base and shows a carboxyl
O-H stretch in the IR. The acid proton(s) show up
readily around 7.0 δ in the NMR, and exchange rapidly
with D_2O. The same spectrum shows a sharp singlet at
1.23 δ, presumably the one methyl group on the molecule,
but its chemical shift does not fit for a straightforward
saturated CH_3 (1.0 δ) nor an unsaturated CH_3 (1.6-1.8 δ).
The olefinic region shows only a very broad signal(s) at
5.40 δ, and the integration of this region against the
acid protons would seem to suggest that there are more of
the latter than the former in the product. Believing
the product to be possibly one of two things, (52) or
(88), the mass spectrum was run, but this gave no pos-
itive peak which could be identified as the molecular
ion, but did show significant signals at 226 (removal of
$C_7H_7SO_2H$ from the starting material?) and at 180 (mole-
cular weight of the unsaturated keto-acid (88)). As
yet, this product has not been identified, but there also
exists the possibility that it is in fact more than one

(102)

E = CO$_2$Et

SCHEME 19

(103)

(104)

(105)

(103)

(104)
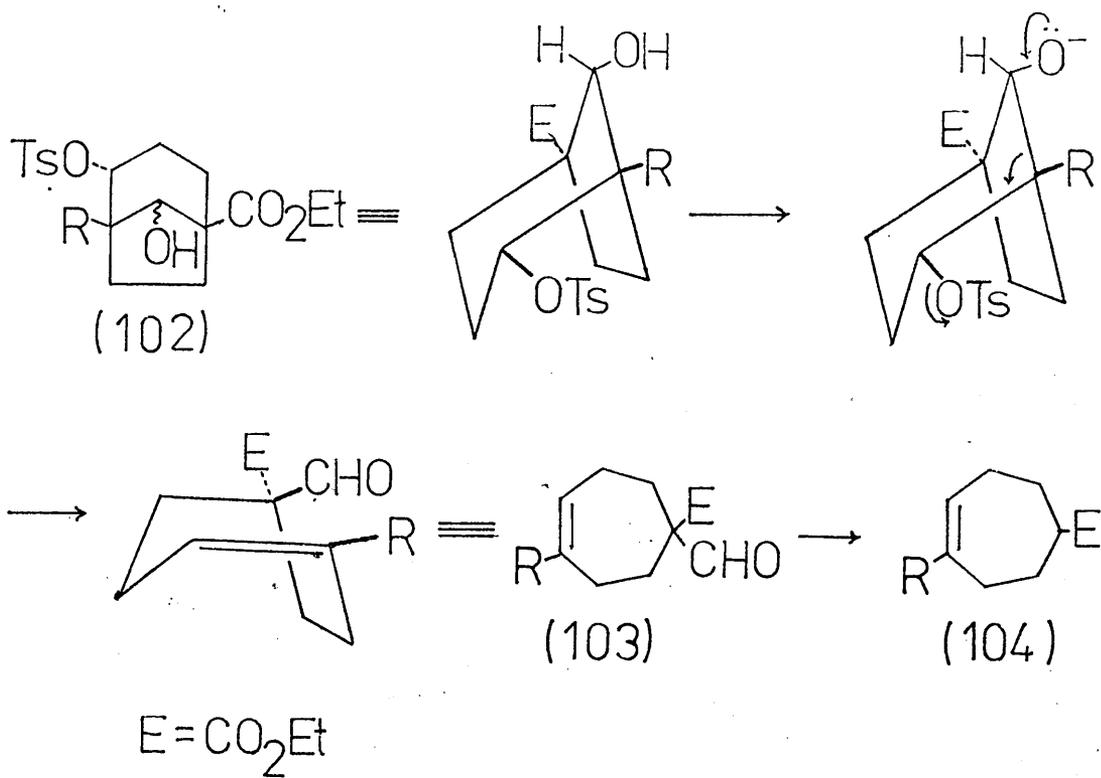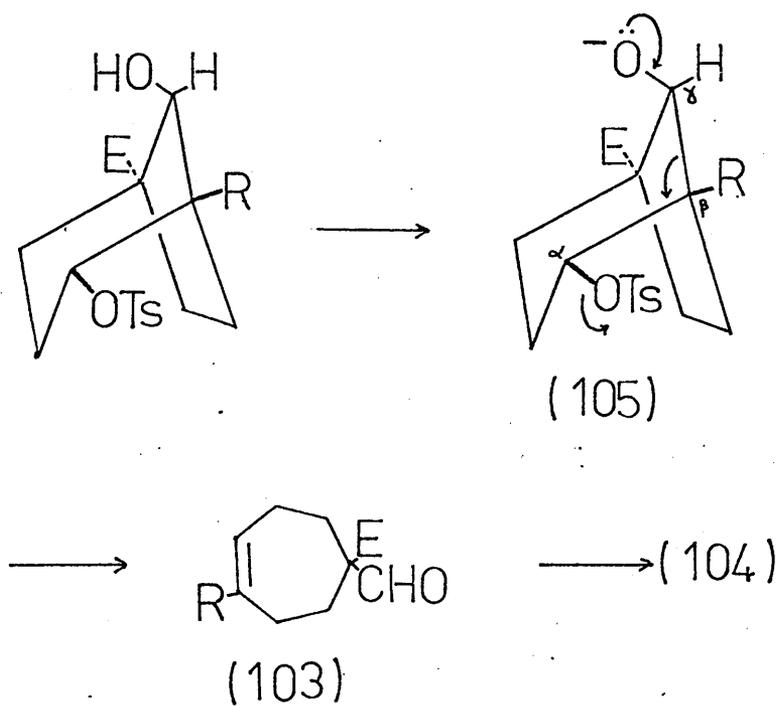
SCHEME 20

single compound. In the course of our investigations
into the unusual fragmentations of bridged bicyclic
systems, we realised that it is not always necessary to
have a carbonyl on the bridgehead if the reaction path-
way follows that described in Scheme 2. For example,
the hydroxy derivative (102) should, upon treatment with
alkoxide, fragment in a similar fashion, as in Scheme 19.
This would provide an alternative route into the cyclo-
heptene ring system, and would eliminate any problems
that might be encountered over hydrolysis of a gem-
diester, as experienced in earlier routes involving
ethoxide-induced fragmentations. The initial product in
this case would ne the non-enolisable β-aldehydo-ester
(103) which seems set up to lose t-butyl formate,
yielding the cycloheptene mono-ester (104).

There are two possible configurations for the
hydroxyl group on the bridgehead carbon: there is the
transoid arrangement whereby the hydroxyl hangs over the
ring not containing the leaving group (Scheme 19), or
there is the cisoid configuration (Scheme 20) in which
it overshadows that ring. Both possibilities are amen-
able to a concerted fragmentation process - Scheme 19
merely shows an analogy to the original fragmentation of
the carbonyl-bridged system described in Scheme 2, while
the intermediate (105) in Scheme 20 is effectively a
conformer of the intermediate from (102), produced by a
rotation around the C_β-C_χ bond. As mentioned earlier,
this is allowed under Grob's requirements for a
concerted process[7].

Bu^{t}O$^-$ H-O H

EtO-C
O
OTs

(106)

EtO-C
O
O
C-H OBu^t
OTs

(107)

EtO-C
O
O-H
C-OBu^t
OTs

(108)

CO$_2$Et

(38)
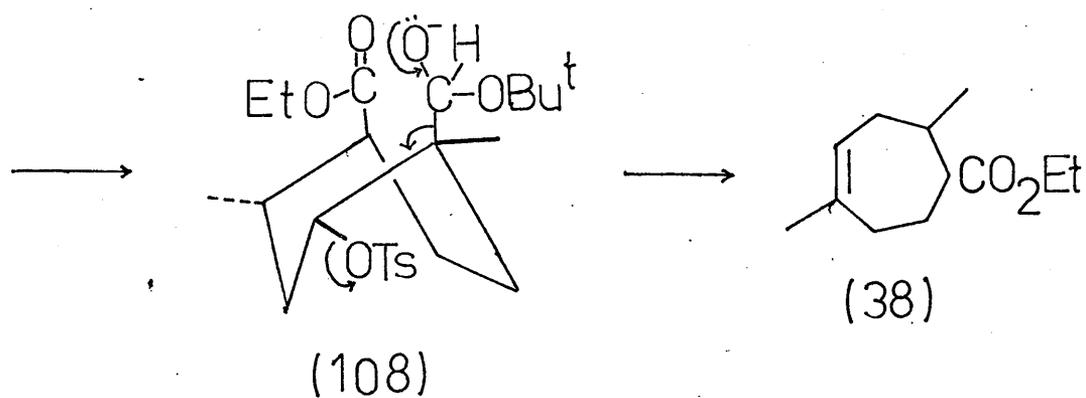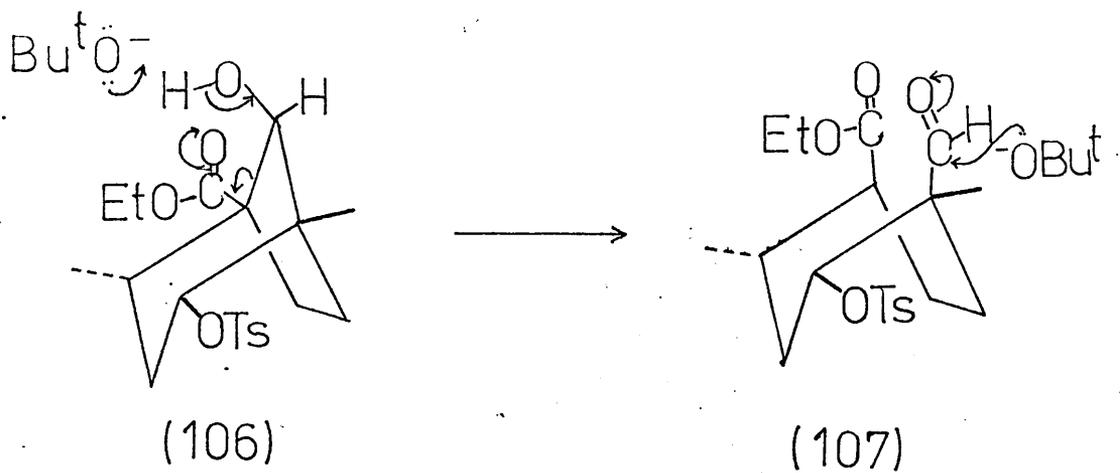
SCHEME 21

When the equatorial tosylate (33e) was treated with sodium borohydride in aqueous methanol at room temperature, the product (in 96% yield) was the hydroxy-tosylate (106) a white crystalline solid, m.pt. 135-6° (ethanol). This reduction product almost certainly has the configuration shown, as attack on the bridgehead carbonyl occurs over the face of the five-membered ring, minimising 1,3-diaxial interactions, and producing the cisoid arrangement shown. The IR spectrum of (106) showed no trace of the bridging carbonyl previously appearing at 1765 cm^{-1} in (33e), and the appearance of an O-H stretch at 3350-3630 cm^{-1}. The NMR revealed the hydroxyl group as a one-proton singlet at 3.00δ which exchanged with D_2O, and the carbinyl C$\underline{H}$-OH proton as a broad singlet at 4.00δ.

Treatment of (106) with an excess of potassium t-butoxide in refluxing benzene for 21 hours gave a mixture of starting material and a less polar product, separable by prep. TLC. When isolated, this product was shown to be identical to the mono-ester (38), prepared by decarb-oxylation of the acid-ester (36). The yield (39%) was not particularly high, but was by no means optimised, and a longer reaction time would probably have improved it. However, the fact that the reaction had not gone to completion in 21 hours would seem to indicate that it is not a concerted process, but more likely a ring-opening followed by an elimination (Scheme 21). The alternative explanation could be that insufficient base was used, for as can be seen from the scheme, at least

two moles of base are required for each mole of substrate.
The reaction pathway makes use of the C(1) ethoxycarb-
onyl group as a electron-acceptor (recall the axial tosy-
late retro-Claisen), giving an intermediate aldehyde (107)
which is attacked by $^-OBu^t$ to form the tetrahedral inter-
mediate (108) which eliminates t-butyl formate and the
tosylate leaving group, leaving the cycloheptene mono-
ester (38). It seems important from this pathway that
the base used should not be HO^-, as this would almost
certainly hydrolyse the ethoxycarbonyl group and render
it useless as an electron-acceptor.

In a similar manner to its equatorial counter-
part (33e), the axial tosylate (33a) could be readily
reduced at the bridgehead carbonyl, producing the
hydroxy-ester (109). This was achieved in virtually
quantitative yield, and gave (109) as a white cryst-
alline solid of m.pt. 139-140°. This compound now
posed an interesting question: would base treatment
produce any ring-opened material, as the equatorial
epimer had done? In this case it is impossible to
fulfil Grob's requirements for a concerted reaction. No
amount of visual twisting and rotating can achieve a
configuration in which all of the orbitals involved in
fragmentation overlap. Therefore any fragmentation
products which do arise must do so in a stepwise
fashion.

When (109) was treated in the same way as (106),
i.e. with potassium t-butoxide in refluxing benzene, the
product isolated after prep. TLC was again the cyclo-

(109)

(110)

(111)

(38)

SCHEME 22

(21)

(30)

(37)
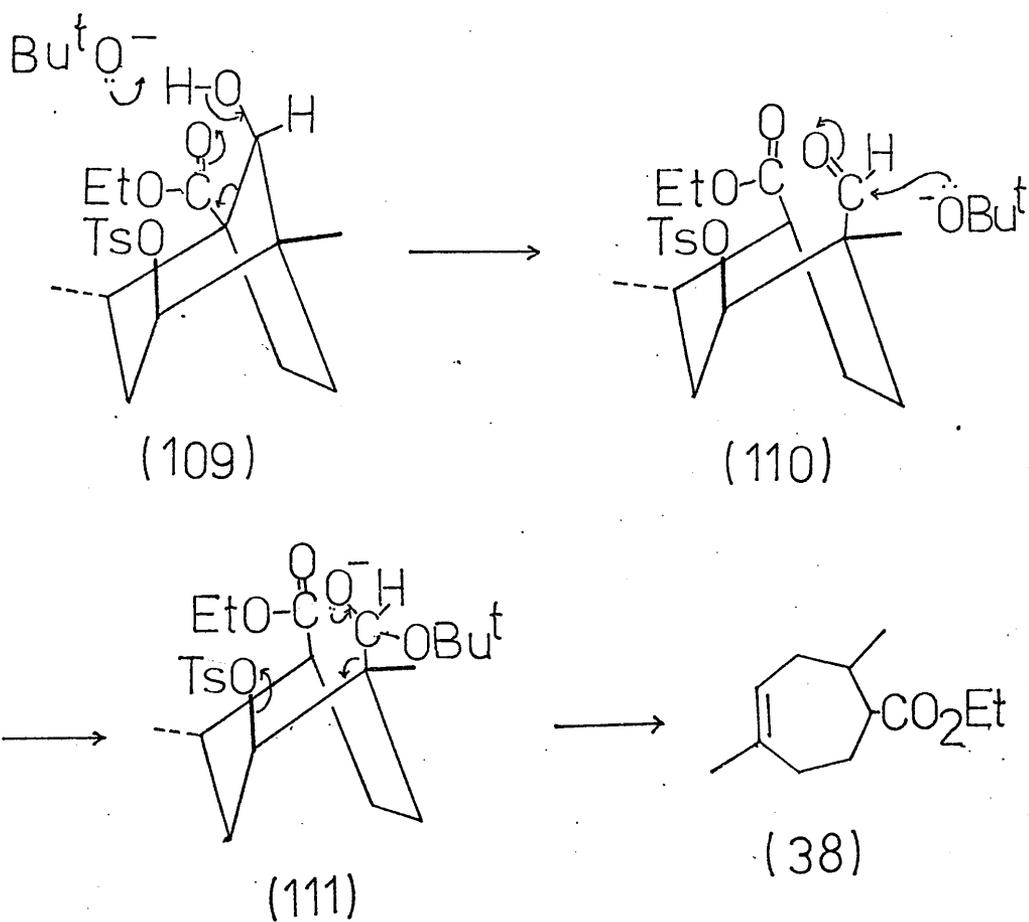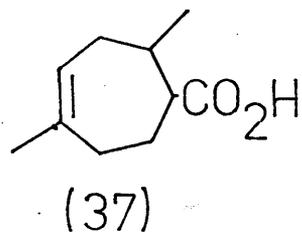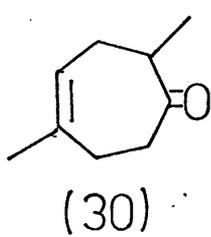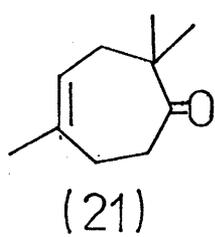
heptene mono-ester (38), in 47% yield. The identity of this material was verified by comparison with an authentic sample of (38), and the pathway by which it is produced is very similar to one of the possible pathways by which its equatorial epimer breaks down (see Scheme 22). As described in the scheme, the final step is the syn-elimination of the tosylate with simultaneous loss of t-butyl formate, and the necessary cis-coplanar configuration necessary for such an elimination can be readily attained in the flexible cycloheptane ring system. Syn-elimination promoted by potassium t-butoxide in benzene are well-known in medium- and large-ring chemisty[29,30].

This interesting conversion of an axial tosylate to a monocyclic ester is a potentially useful extension of the tosylate ring expansion method. Unfortunately, at the time of writing, the above two compounds (106) and (109) are the only substrates which have been subjected to this new fragmentation, and it would be very interesting to discover the importance of, for example, the C(5) methyl group.

Towards the end of this piece of work, several attempts were made to prepare karahanaenone (21) from the cycloheptene mono-acid (37). Overall, such a process requires an oxidative decarboxylation of (37) to give the cycloheptenone (30), which may be methylated specifically at the C(2) position to give the desired natural product. The initial attempts to bring about such a manipulation of the carboxylic acid were

(37) $\longrightarrow$ (112)

(113) $\longrightarrow$ (114)

(115) $\longrightarrow$ (116)

(117) $\longrightarrow$ (30)
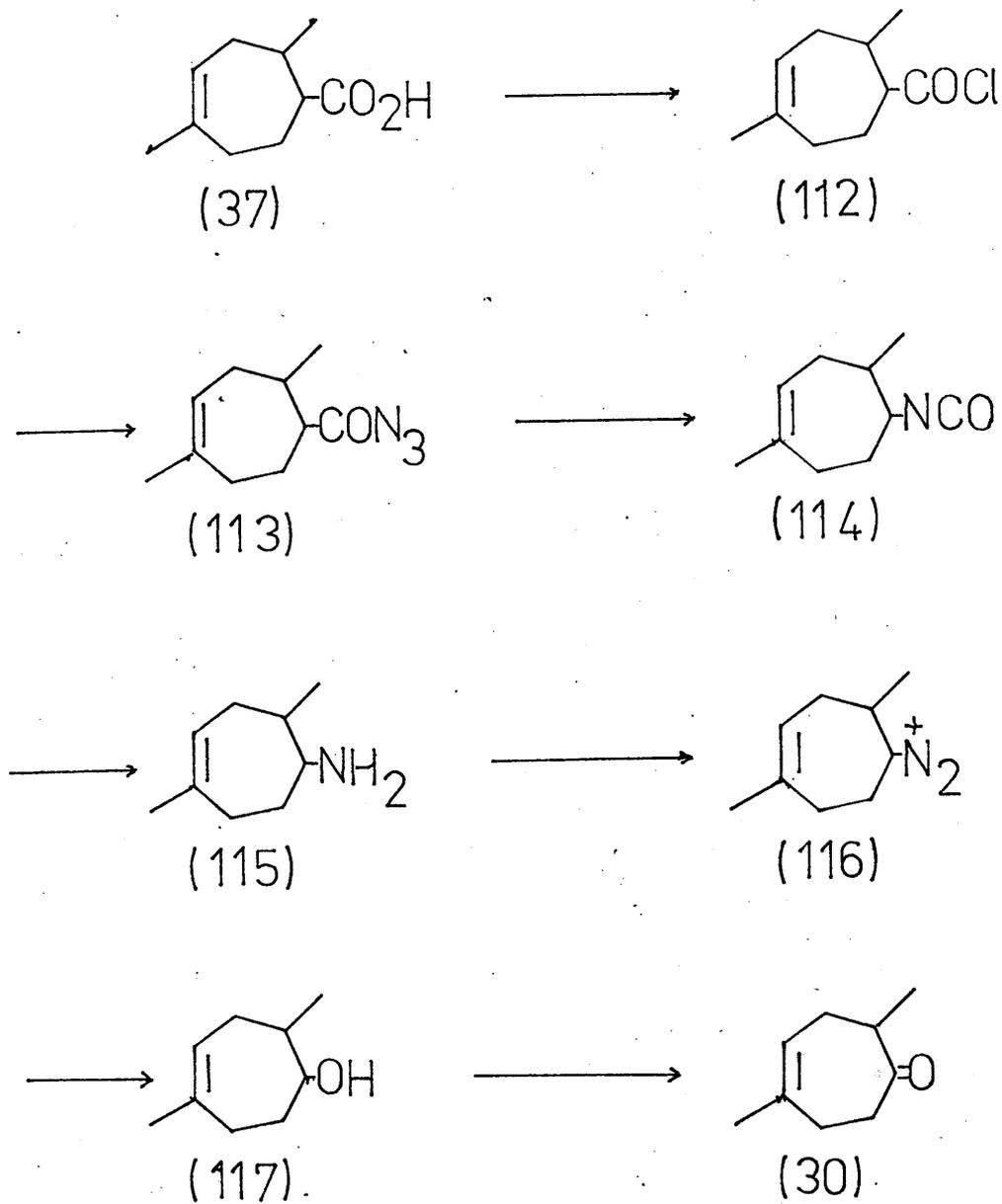
SCHEME 23

designed to follow the route described in Scheme 23.
The important features of this route are the Curtius
rearrangement of the acyl azide (113) to the isocyanate
(114), and hydrolysis of this to the amine (115).

The acid (37) was converted to its acid chloride
(112) by treatment with thionyl chloride in benzene, and
was confirmed by the disappearance of the carboxyl O-H
stretch in the IR, and the appearance of the acid
chloride carbonyl at 1785 cm^{-1}. The acid chloride in
acetone was treated with aqueous sodium azide at room
temperature, and after $3\frac{1}{2}$ hours, the IR showed no trace
of the carbonyl at 1785 cm^{-1}. Instead, the azide absorp-
tion at 2130 cm^{-1} had appeared, as well as traces of
the isocyanate peak at 2250 cm^{-1}. Clearly the azide,
once formed, was rearranging, even at room temperature.
The rearrangement was completed by refluxing the azide
in dry toluene for 12 hours, and gave a single compound
which showed only the isocyanate band at 2240 cm^{-1} in
the IR.

However, the route ran into difficulties when the
hydrolysis of the isocyanate was attempted. It is
known[31] that isocyanates are hydrolysable by heating
with aqueous or alcoholic base, giving initially the
metal carbamate, $RNHCOO^-M^+$, which is liberated as the
free carbamic acid by treatment with HCl. This is
normally accompanied by spontaneous decarboxylation to
the amine, RNH_2. When isocyanate (114) was treated with
potassium hydroxide, a brownish-white solid with a very
high melting point (230°) was isolated. The IR (KBr

(118)

(119)

SCHEME 24

$$\underset{R^I}{\overset{R}{\diagdown}}\!\!\underset{CO_2H}{\overset{H}{\diagup}} \longrightarrow \underset{R^I}{\overset{R}{\diagdown}}\!\!\underset{CO_2^-}{\overset{-}{\diagup}} \xrightarrow{(CH_3S)_2} \underset{R^I}{\overset{R}{\diagdown}}\!\!\underset{CO_2H}{\overset{SCH_3}{\diagup}}$$

$$\xrightarrow[\text{2. NCS}]{\text{1. NaHCO}_3} \underset{R^I}{\overset{R}{\diagdown}}\!\!\underset{\underset{O}{\overset{|}{C}}\!\!-O^-}{\overset{+SCH_3}{\diagup}} \xleftarrow{Cl} \longrightarrow \underset{R^I}{\overset{R}{\diagdown}}=\overset{+}{S}-CH_3$$

$$\xrightarrow{R^{II}OH} \underset{R^I}{\overset{R}{\diagdown}}\!\!\underset{OR^{II}}{\overset{SCH_3}{\diagup}} \xrightarrow{R^{II}OH} \underset{R^I}{\overset{R}{\diagdown}}\!\!\underset{OR^{II}}{\overset{OR^{II}}{\diagup}}$$

$$\xrightarrow{H^+} \underset{R^I}{\overset{R}{\diagdown}}=O$$

SCHEME 24

$$\underset{Ph}{\overset{Ph}{\diagdown}}CH-CO_2H \longrightarrow \underset{Ph}{\overset{Ph}{\diagdown}}\underset{CO_2H}{\overset{SCH_3}{\diagup}}C \longrightarrow \underset{Ph}{\overset{Ph}{\diagdown}}C=O$$

(120)
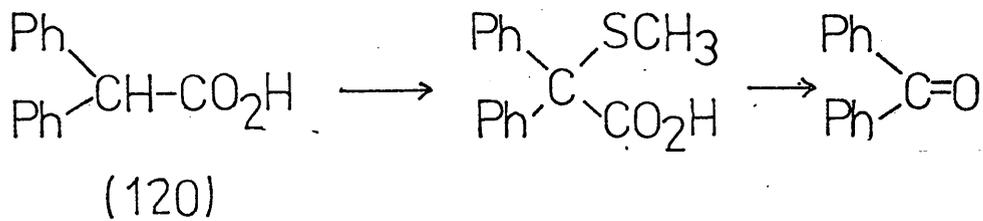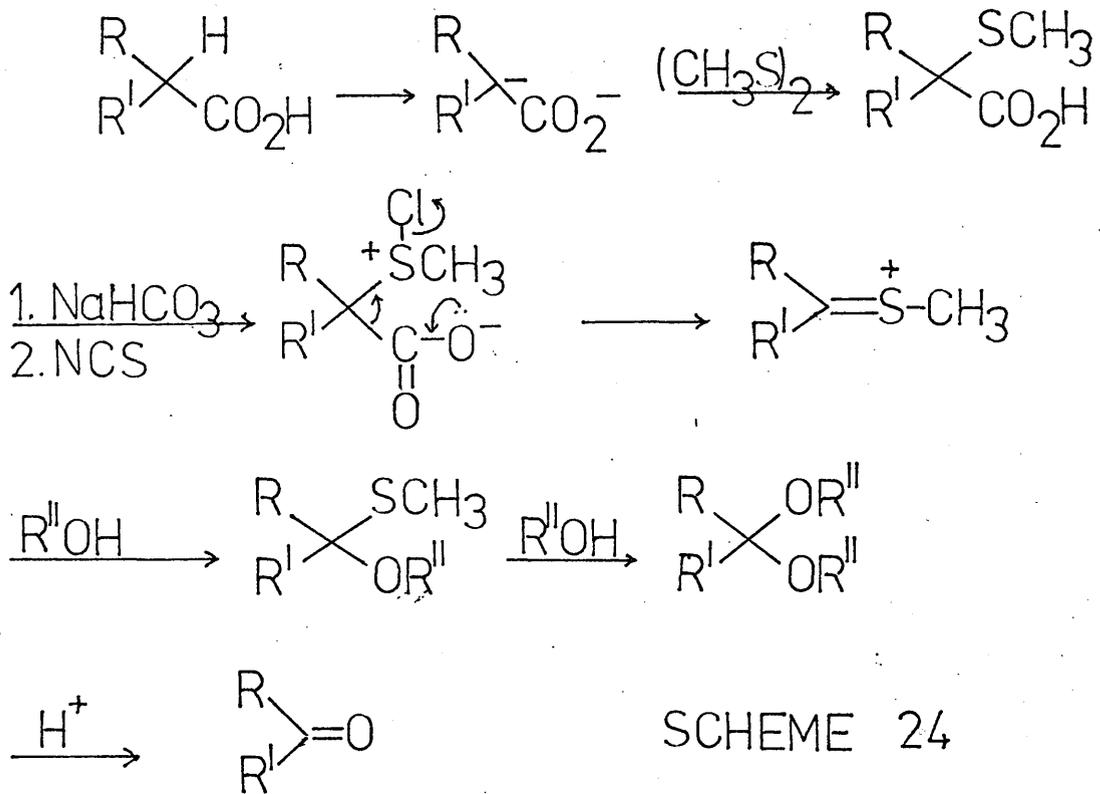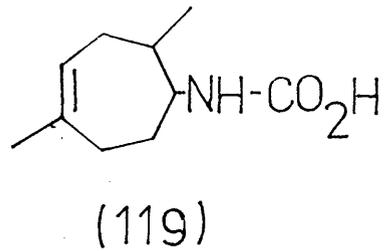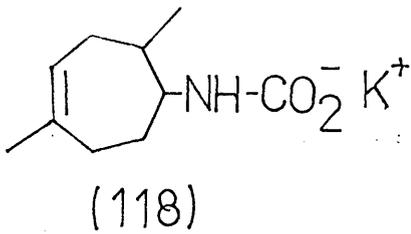
SCHEME 25

disc) of this seemed to confirm that it was the potassium carbamate (118). When this was acidified with dilute HCl, extraction with ethyl acetate gave only a trace amount of material, so the free carbamic acid must lose CO_2, liberating the amine (115) which remains in the acidic portion. Therefore this solution was taken to pH 9 with 4N sodium hydroxide and re-extracted with ethyl acetate to give a yellow-brown oil. However, this was not the desired amine (115), as its IR spectrum showed no N-H stretches, and there was a broad absorption in the carbonyl region, centered on 1720 cm^{-1}. It would seem that the hydrolysis of the isocyanate (114) was not as straightforward as expected, and this rendered the above route to cycloheptenone (30) impractical.

In the time available, one final effort was made to convert acid (37) into ketone (30). Trost[32] has shown that the dianion of a carboxylic acid carrying a proton on the α-carbon can be thiomethylated with dimethyl disulphide in this α-position. If the α-thiomethyl acid is then dissolved in base and treated with N-chlorosuccinimide, a decarboxylative-elimination occurs, leading initially to the ketal and eventually to the ketone, as shown in Scheme 24. This seemed a suitable type of reaction to perform in (37), as the corresponding sequence would lead to (30). As a test of the method, diphenyl acetic acid (120) was taken through the sequence in Scheme 25, yielding benzophenone eventually. However, despite varying the base
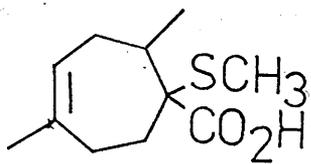
(121)

used, the solvent system and the reaction temperature, it was not possible to accomplish the conversion of (37) to the α-thiomethyl derivative (121). The only isolable reaction product in all cases was unreacted starting material.

At this point, the sands of time had run out, and further investigations in the line were impossible.

In conclusion, the original objectives, (21) and (22), have not been achieved, but this study has uncovered two new fragmentation processes, one of which has been examined thoroughly. It has also shown that the stereochemical factors associated with the cycloheptene ring system are worthy of further study.

2-Ethoxycarbonyl-2-methyl cyclopentanone (29)[33].

10.1g. (0.05moles) of diethyl adipate was added to a solution of 1.4g. (0.06gram-atoms) of sodium metal in 72ml. of dry toluene, and the solution stirred at reflux for two hours. The ethanol formed was removed by azeotroping with excess toluene. The residue (100ml.) was cooled to 0° and treated with a single portion of 16.0g. (0.113moles) of methyl iodide. This mixture was stirred under reflux overnight (15hours). After cooling, excess water was added, the layers separated and the aqueous portion re-extracted with toluene. The combined toluene layers were washed to neutrality, dried, filtered and concentrated to give a yellow oil which was distilled $(136-8^{\circ}/24\text{mm.})$ yielding 6.014g. (71%) of a clear oil, the 2,2-disubstituted cyclopentanone (29), which gave a negative ferric chloride test.

IR : ν_{co} 1755, 1735cm^{-1}.

NMR : 1.24δ s 3H saturated methyl;

1.10δ t(J=7Hz) 3H ester methyl;

4.06δ q(J=7Hz) 2H ester -CH$_2$-.

MS : M^{+} 170.

2-Ethoxycarbonyl-5-methyl cyclopentanone (23)[34].

4.689g. (27.58mmoles) of 2-ethoxycarbonyl-2-methyl cyclopentanone (29) was added dropwise to a solution of 0.635g. (27.60mgram-atoms) of sodium metal in 10ml. of dry ethanol and the solution heated under reflux for 7 hours. After cooling, the solvent was removed under reduced pressure and the residue taken up in 50ml. of toluene, poured onto 100ml. of 10% acetic acid and the

layers separated. The aqueous layer was extracted with
ether, the organic portions combined, washed to neutral-
ity with brine, dried, filtered and concentrated. This
gave 3.094g.(66%) of a pale yellow oil which was distill-
ed (115-8°/20mm.) to yield the 2,5-disubstituted cyclo-
pentanone (23) as a clear oil, which gave a positive
$FeCl_3$ test.

IR : ν_{co} 1760, 1735cm^{-1}.

NMR : 1.07δ $\underline{d}$(J=6Hz) 3H C(5) methyl;

      1.23δ $\underline{t}$(J=8Hz) 3H ester methyl;

      4.10δ $\underline{q}$(J=8Hz) 2H ester methylenes.

MS : M$^+$ 170.

Attempted condensation of 2-ethoxycarbonyl-5-methyl
cyclopentanone (23) with citral (24).

A solution of 353mg. (2.08mmoles) of the keto-
ester and 350mg. (2.30mmoles) of citral in 5ml. of dry
ethanol was added dropwise over 10 minutes to a stirred
solution of 500mg. of sodium in 25ml. of ethanol at -78°.
The reaction mixture was stirred at room temperature for
4 days then brought to pH 7 with glacial acetic acid.
The solvent was removed under reduced pressure and the
residue taken up in ether, washed with brine, dried,
filtered and concentrated to yield 573mg. of a brown-
yellow oil. Infra-red analysis showed no O-H stretch,
and three carbonyl bands at 1760cm^{-1}(cyclopentanone),
1730cm^{-1}(ester) and 1680cm^{-1}(aldehyde). NMR showed both
an aldehyde proton and the appropiate ethyl ester multi-
plets, and TLC confirmed that this product was merely a
mixture of starting materials, and that no new compound

had been formed.

1-Ethoxycarbonyl-4-hydroxy-2,5-dimethyl bicyclo[3.2.1] octan-8-one (31)[35].

A mixture of 13.3g. (7.8mmoles) of 2-ethoxycarbonyl-5-methyl cyclopentanone (23) and 6.0g. (8.6mmoles) of freshly-distilled crotonaldehyde, cooled to 0°, was added dropwise over 1 hour to a solution of 0.1g. of sodium in 50ml. of dry ethanol (containing a few crystals of hydroquinone) at -78°. On completion of addition, the cooling bath was removed, and stirring continued for two hours. The solution was neutralised with glacial acetic acid and the solvent removed under reduced pressure. The residue was taken up in ether, washed with brine, dried, filtered and concentrated to yield a brown oil which was distilled (165-7°/0.4mm.), furnishing 14.0g.(75%) of the bicyclic alcohol (31) as a clear, viscous oil.

IR : ν_{OH} 3630cm^{-1}(free), 3400-3570cm^{-1}(bonded);
ν_{CO} 1760, 1735cm^{-1}.

NMR : 0.90δ $\underline{d}$(J=8Hz) 3H C(2) methyl;

    1.02δ $\underline{s}$ 3H C(5) methyl;

    1.26δ $\underline{t}$(J=7Hz) 3H ester methyl;

    4.13δ $\underline{q}$(J=7Hz) 2H ester methylenes;

    9.60δ $\underline{s}$(broad) aldehyde proton.

Integration indicated that the product consisted of 2% aldehyde (32) and 98% bicyclic alcohol (31).

MS : M$^+$ 240.

Found : C 64.75, H 8.46% ($C_{13}H_{20}O_4$ requires C 64.98,
      H 8.39%).

1-Ethoxycarbonyl-4-tosyloxy-2,5-dimethyl bicyclo[3.2.1]
octan-8-one (33)[35].

12.48g. (5.2mmoles) of the epimeric alcohols (31)
was treated with 14.70g. (7.8mmoles) of p-toluene sulph-
onyl chloride in 50ml. of dry pyridine at 0°. The
mixture was stirred at room temperature for 4 days, then
poured onto ice-water, extracted with three portions of
ethyl acetate, and the combined organic layers washed to
neutrality with dilute HCl, brine and water. The last
traces of water were removed by azeotroping with benzene
and the solvent removed under reduced pressure (cool
water-bath), giving 19.52g.(95%) of a reddish-brown gum.
Trituration with hot ethanol gave a first crop of a white
crystalline solid. The mother liquors were further
recrystallised with the results shown (Table 3) :

Crop	Weight	M.Pt.	NMR (CH-OTs position and half-band width)		Epimer
1	1.53g.	161-2°	4.68	$w_{\frac{1}{2}}$=6Hz	Axial
2	2.21g.	74-6°	4.52	$w_{\frac{1}{2}}$=15Hz	Mixture
			4.69	$w_{\frac{1}{2}}$=8Hz	
3	4.39g.	81-2°	4.50	$w_{\frac{1}{2}}$=16Hz	Equat-orial.

Table 3

Crop 2 was further recrystallised to give 1.00g.
identical to crop 1 and 0.60g. identical to crop 3.
The assignment of stereochemistry is based on reference 16.
IR : Identical for both epimers, as follows -

ν_{CO} 1765, 1735cm^{-1};

ν_{SO_2} 1180, 1373cm^{-1}.

NMR : Identical for both epimers, with the exceptions
noted in Table 3.

0.84 δ <u>s</u> 3H C(5) methyl;

0.91 δ <u>d</u>(J=6Hz) 3H C(2) methyl;

1.25 δ <u>t</u>(J=7Hz) 3H ester methyl;

2.44 δ <u>s</u> 3H aromatic methyl;

4.18 δ <u>q</u>(J=7Hz) 2H ester -CH₂-;

7.40 δ <u>q</u>(J=8Hz) 4H aromatics.

Found : Crop 1 - C 60.88, H 6.51%

     Crop 2 - C 61.06, H 6.44%

     ($C_{20}H_{26}O_6$ requires C 60.89, H 6.64%).

<u>Treatment of the equatorial tosylate (33e) with NaOEt[35]</u>.

A solution of 5.00g. (12.70mmoles) of equatorial tosylate in 50ml. of dry ethanol was added dropwise over 10 minutes to a solution of sodium ethoxide (from 0.5g. of sodium in 60ml. of ethanol) at 60°. The mixture was stirred at reflux for 30 minutes, then cooled and poured onto 50g. of ice-water. After neutralisation with 6N HCl, the bulk of the solvent was removed on the rotary evaporator. The residue was extracted with 2 x 50ml. portions of ether and the usual work-up gave 2.81g.(83%) of the gem-diester (34) as a yellow oil. An aliquot was distilled (110-2°/0.3mm.) and had the following characteristics :

IR : Hydroxyl region transparent; ν_{co} 1735cm^{-1}(sharp).

NMR : 0.85 δ <u>d</u>(J=7Hz) 3H saturated CH₃ ;

    1.23 δ <u>t</u>(J=7Hz) 6H esters CH₃;

    1.67 δ <u>s</u> 3H olefinic CH₃;

    4.12 δ } <u>dq</u>(J=7Hz) 4H esters -CH₂-;
    4.17 δ }

    5.34 δ <u>s</u>(broad) 1H olefinic proton.

MS : M^+ 268.

Found : C 66.88, H 8.83% ($C_{15}H_{24}O_4$ requires C 67.14,
H 9.01%).

Hydrolysis of the gem-diester (34)

A solution of 2.108g. (7.87mmoles) of pure diester
in 10ml. of ethanol was treated with 1.120g. (20.00mmoles)
of potassium hydroxide, and the solution heated under
reflux overnight(16 hours). After cooling, the solvent
was removed under reduced pressure and the residue was
taken up in 30ml. of water. Any unreacted diester was
removed by washing with ether, and the aqueous layer was
neutralised with 6N HCl, extracted with 2 x 50ml. port-
ions of ether, the combined organic layers washed with
brine, dried, filtered and concentrated to yield 1.339g.
(71%) of the acid-ester (36) as a yellow oil (133-6°/
0.25mm.).

IR : ν_{OH} 2400-3400cm^{-1}(bonded), ν_{CO} 1708, 1740cm^{-1}.

NMR : $\left.\begin{matrix} 0.93\,\delta \\ 0.97\,\delta \end{matrix}\right\}$ dd(J=7Hz) 3H saturated methyl;

1.27δ t(J=7Hz) 3H ester methyl;

1.70δ s 3H unsaturated methyl;

$\left.\begin{matrix} 4.21\,\delta \\ 4.25\,\delta \end{matrix}\right\}$ dq(J=7Hz) 2H ester $-CH_2-$;

5.37δ s(broad) 1H olefinic proton;

11.28δ s 1H exchanges with D_2O.

MS : P^+ 196(M^+-CO_2), base peak 81.

Found : C 65.01, H 8.14% ($C_{13}H_{20}O_4$ requires C 64.98,
H 8.39%).

Decarboxylation of the acid-ester (36).

1.095g. (4.56mmoles) of acid-ester was dissolved

10ml. of pyridine (distilled from KOH) and the solution

refluxed for 4 hours. The solvent was removed and the

residue taken up in ether, washed with 4N NaOH to remove

any starting material, then with brine and water, dried,

filtered and concentrated to give 0.640g.(72%) of mono-

ester (38), b.pt. 85-90°/0.25mm.

IR : No O-H stretch, ν_{CO} 1738cm^{-1}.

NMR : 0.87 δ $\underline{d}$(J=6Hz) 3H saturated methyl;

  1.23 δ $\underline{t}$(J=8Hz) 3H ester methyl;

  1.70 δ $\underline{s}$ 3H unsaturated methyl;

  4.13 δ $\underline{q}$(J=8Hz) 2H ester methylenes;

  5.50 δ $\underline{m}$ 1H olefinic proton.

MS : M$^+$ 196.

Found : C 72.83, H 10.16% ($C_{12}H_{20}O_2$ requires C 73.43,

  H 10.27%).

Hydrolysis of the ester (38).

A solution of 615mg. (3.14mmoles) of ester in 15ml.

of methanol was treated with 287mg. (5.12mmoles) of KOH

in 10ml. methanol/ 3ml. water, and heated under reflux

overnight(16 hours). After cooling, the solvent was

removed under reduced pressure and the residue taken up

in water, washed with ether, neutralised with 6N HCl and

re-extracted with ether. The ether extracts were washed

with brine, dried, filtered and concentrated to yield

433mg.(83%) of the acid (37), b.pt. 120-4°/0.35mm.

IR : ν_{OH} 2340-3400cm^{-1}, ν_{CO} 1708cm^{-1}(dimer), 1740cm^{-1} (shoulder, monomer).

NMR : 0.93 δ $\underline{d}$(J=6Hz) 3H saturated CH_3;

      1.70 δ $\underline{s}$ 3H unsaturated CH_3;

      5.43 δ $\underline{m}$ 1H olefinic proton;

      12.01 δ $\underline{s}$ 1H exchanges with D_2O.

MS : M^+ 168, base peak 43.

Found : C 71.42, H 9.48% ($C_{10}H_{16}O_2$ requires C 71.39, H 9.59%).

Reduction of diester (34) with one equivalent* of LiAlH$_4$

(a) Over 16 hours :

    A solution of 100mg. (0.37mmoles) of gem-diester (34) in 5ml. of sodium-dried ether was added dropwise, under N_2, to a slurry of 8mg. (0.21mmoles) of lithium aluminium hydride in 5 ml. of ether. The heterogeneous mixture was stirred at 15° for 16 hours, then the reaction was stopped by the sequential addition of 1ml. of water, 1ml. of dilute HCl and 5ml. of water. The granular solid thusformed was easily removed by filtration, and the filtrate washed until neutral. After drying, evaporation of the solvent gave 92mg. of an oil which showed three distinct spots on TLC(15% ethyl acetate - petrol), the least polar of which corresponded to the starting material. The other two components of the mixture were separated by prep. TLC, and the middle band

*Note : equivalence is based on the assumption that one mole of lithium aluminium hydride will reduce two moles of a carboxylic ester.

shown to be hydroxy-ester (39), 22mg., by the following :

IR : ν_{OH} 2400-3600cm^{-1}(bonded), ν_{CO} 1735cm^{-1}(sharp).

NMR : 1.23δ t(J=7Hz) 3H ester methyl;

      4.20δ q(J=7Hz) 2H ester methylenes;

      5.49δ m 1H olefinic proton;

      6.42δ m 1H hydroxyl proton, exchanges with D_2O.

The most polar component from the product mixture was shown to be the completely-reduced product, the diol (40), a white crystalline solid, m.pt. 89-90°(benzene).

IR : ν_{OH}3625cm^{-1}(free), 3260-3740cm^{-1}(bonded);

      transparent in the carbonyl region.

NMR : No ester signals; 3.12δ m 2H hydroxyls, exchange

      with D_2O; 5.30δ m 1H olefinic proton.

For analysis, see later.

(b) Over 4 hours :

Using the same experimental procedure as in (a), 145mg. (0.54mmoles) of gem-diester was treated with 11mg. (0.29mmoles) of LAH for 4 hours to give 117mg. of a clear oil, identical on TLC, IR, etc. to the product from the 16 hour reaction - i.e. a three-component mixture of starting material, hydroxy-ester (39) and diol (40).

Reduction of gem-diester (34) with two equivalents of LAH

To a slurry of 15mg. (0.39mmoles) of lithium aluminium hydride in 5ml. of sodium-dried ether was added a solution of 100mg. (0.37mmoles) of 5,5-diethoxycarbonyl-1,4-dimethyl cycloheptene (34) in 5ml. of ether, and stirring under N_2 continued at room temperature for 4 hours. The reaction was worked-up as in part (a) of the previous experiment, and yielded 61mg.(89%) of the

expected diol (40), m.pt. 89-90°(benzene).
Spectral details were identical to those of the diol
isolated in the previous experiment.

MS : M$^+$ 184.

Found : C 71.50, H 10.60% (C$_{11}$H$_{20}$O$_2$ requires C 71.70
H 10.94%).

Treatment of the equatorial tosylate (33e) with a molar equivalent of potassium hydroxide in ethanol.

2.652g. (6.73mmoles) of equatorial tosylate was
dissolved in 40ml. of dry ethanol and treated with 377mg.
(6.73mmoles) of KOH under reflux for 3 hours. The white
precipitate of p-toluene sulphonic acid formed on cooling
was filtered off and the solvent removed from the filtr-
ate under reduced pressure. This gave more unwanted acid
which was also filtered off after trituration with ether.
The ether was evaporated off to leave a white oily
residue which was dissolved in water and extracted with
two portions of ether. The usual work-up of the organic
layers gave 290mg. of a colourless oil, shown by TLC to
be a mixture of the unreacted tosylate (33e) and the
mono-ester (38), thelatter being formed presumably by
decarboxylation of the acid-ester (36). The presence of
both of these species was confirmed by NMR, which showed
an olefinic proton at 5.30δ as well as an AB quartet at
7.60δ. The ratio of mono-ester to tosylate was 3:4 by
NMR integration.

The aqueous layer from the above work-up was care-
fully neutralised with 6N HCl and re-extracted with ether.
After washing and drying, removal of the solvent yielded

360mg.(23%) of the acid-ester (36) as a viscous yellow oil which was spectroscopically and chromatographically identical to the acid-ester produced by the hydrolysis of the gem-diester (34) earlier.

Treatment of the axial tosylate (33a) with potassium hydroxide in ethanol.

A solution of 3.995g. (10.14mmoles) of axial tosylate in 150ml. of dry ethanol was treated with 3.920g. (70.00mmoles) of KOH and then heated under reflux for 16 hours. When cooled, a white precipitate had formed. Most of the solvent was removed under reduced pressure and the residue taken up in 100ml. of water. Extraction with 2 x 50ml. portions of ether, then combination of the extracts, followed by washing, drying and evaporation of solvent yielded 99mg.(5%) of 5-ethoxycarbonyl-1,4-dimethyl cycloheptene (38).

IR : ν_{co} 1735cm^{-1}.

NMR : Identical to that of the ester obtained by decarboxylation of the acid-ester (36).

MS : M$^+$ 196.

The aqueous layer from the above work-up was carefully neutralised with 6N HCl and re-extracted with ether. The usual work-up yielded 1.544g.(91%) of the acid (37).

IR : ν_{OH}3400cm^{-1}, ν_{co} 1705cm^{-1}(dimer), 1750cm^{-1}(monomer, shoulder).

NMR : 0.90 δ d(J=7Hz) 3H saturated methyl;

1.70 δ s 3H unsaturated methyl;

5.47 δ s(broad) 1H olefinic proton;

11.30 δ s 1H acid proton, exchanges with D$_2$O.

MS : M$^+$ 168, base peak 43.

Found : C 71.44, H 9.62% (C$_{10}$H$_{16}$O$_2$ requires C 71.39,

   H 9.59%).

1-Ethoxycarbonyl-4-hydroxy bicyclo[3.2.1] octan-8-one(42)[10]

A solution of 10.00g. (64.10mmoles) of 2-ethoxycar-
bonyl cyclopentanone[36] and 1ml. of freshly-distilled
triethylamine in 50ml. of sodium-dried benzene, stirred
at 0°, was treated with 3.08g. (55.00mmoles) of redistilled
acrolein and then stirred for 18 hours at room temper-
ature. The reaction mixture was neutralised with acetic
acid, washed with 2 x 100ml. portions of brine, dried,
filtered and concentrated to yield a yellow oil which, on
distillation (120-4°/0.3mm.) gave 9.10g.(67%) of a clear
oil, the aldehyde-ester (43). NMR showed the aldehydic
proton at 9.70δ.

A mixture of 8.00g. (37.74mmoles) of aldehyde-ester,
8ml. of triethylamine and 80ml. of dry benzene was
heated under reflux for 24 hours. After cooling, the
solvent was removed under reduced pressure and the
residue taken up in CHCl$_3$, washed with 4N NaOH, then
brine, dried, filtered and concentrated to give 5.96g.
(75%) of a yellow oil which was shown by NMR to be a
mixture of unreacted aldehyde-ester(10%) and the desired
bicyclic alcohol (42). The latter was separated by prep.
TLC (15% ethyl acetate - petrol) to give the pure alcohol
as a mixture of epimers.

IR : ν_{OH} 3640cm^{-1}(free), 3300-3650cm^{-1}(bonded);

   ν_{co} 1760, 1735cm^{-1}.

MS : M$^+$ 212, base peak 41.

<u>1-Ethoxycarbonyl-4-tosyloxy bicyclo[3.2.1.]octan-8-one</u>
<u>(44)</u>[10].

    4.00g. (18.87mmoles) of bicyclic alcohol (42) was
treated with a solution of 4.75g. (25.00mmoles) of p-
toluene sulphonyl chloride in 15ml. of anhydrous
pyridine at 0°, and the reaction mixture stirred at room
temperature for 4 days. It was then poured onto 50ml.
of ice-cold 6N HCl and extracted with 2 x 100ml. portions
of ether. The combined ether layers were washed with
dilute sodium hydrogen carbonate solution, and then brine
until neutral. After drying, removal of solvent gave
4.55g.(66%) of a brown gum. The epimeric tosylates
contained therein were separated either by fractional
crystallisation from hot ethanol or by preparative TLC
(40% ethyl acetate - petrol), the axial epimer being the
more polar.

The equatorial tosylate (44e), a white crystalline solid,
m.pt. $95-6^{\circ}$, showed -

IR : No O-H stretch, ν_{co} 1765, 1735cm^{-1},

     ν_{SO_2} 1375, 1175cm^{-1}.

NMR : 4.66 δ $\underline{m}$ $w_{\frac{1}{2}}$=18Hz C$\underline{H}$-OTs.

Found : C 59.26, H 5.85% ($C_{18}H_{22}O_6S$ requires C 59.16,
      H 5.80%).

The axial tosylate (44a), also a white, crystalline
solid, m.pt. $96-7^{\circ}$, showed -

IR : Identical to that of the equatorial epimer.

NMR : 5.05 δ $\underline{m}$ $w_{\frac{1}{2}}$=9Hz C$\underline{H}$-OTs.

Found : C 59.25, H 6.05% ($C_{18}H_{22}O_6S$ requires C 59.16,
      H 5.80%).

Treatment of the equatorial tosylate (44e) with NaOEt.

A solution of 2.88g. (7.87mmoles) of equatorial tosylate in 10ml. of ethanol was added dropwise to a warm solution of 200mg. of sodium in 20ml. of ethanol, and heated under reflux for 45 minutes. The reaction mixture was cooled, poured onto ice, acidified with 6N HCl and extracted with 2 x 50ml. portions of ether. The combined extracts were washed with brine, dried, filtered and concentrated to yield 1.73g.(92%) of the cycloheptene gem-diester (45) as a yellow oil (120-4°/0.5mm.).

IR : ν_{co} 1735cm^{-1}.

NMR : 1.28 δ $\underline{t}$(J=7Hz) 6H ester methyls;

   4.18 δ $\underline{q}$(J=7Hz) 4H ester methylenes;

   5.40 δ $\underline{s}$(broad) 2H olefinics.

Found : C 64.55, H 8.05% ($C_{13}H_{20}O_4$ requires C 64.98, H 8.39%).

Hydrolysis of the cycloheptene diester (45).

1.46g. (6.08mmoles) of diester and 2.80g. (50.00 mmoles) of potassium hydroxide in 25ml. of dry ethanol was allowed to stand at room temperature for 16 hours before the solvent was evaporated off and the residue quenched with water. After washing with ether to remove any unreacted starting material, the aqueous layer was neutralised with 6N HCl, re-extracted with ether and worked-up as usual to give 905mg.(82%) of the gem-diacid (46) as a white crystalline solid, m.pt. 154-7°(ethanol).

IR(CHCl$_3$) : ν_{oH} 3620cm^{-1}(free), 3300-3550cm^{-1}(bonded);

   ν_{co} 1705cm^{-1}.

NMR : 5.40 δ s(broad) 2H olefinic protons;

10.05δ s(broad) 2H acid protons, exchange with D_2O.

Found : C 58.82, H 6.69% ($C_9H_{12}O_4$ requires C 58.69,

H 6.57%).

Decarboxylation of the gem-diacid (46).

A solution of 502mg. (2.73mmoles) of diacid in 10ml. of dry pyridine was heated under reflux for 2 hours, cooled, and the pyridine removed under reduced pressure. The residue was taken up in water, neutralised with 6N HCl and extracted with ether. Usual work-up gave 351mg. (92%) of the cycloheptene mono-acid (47) as a white, crystalline solid, m.pt. 65-7° (lit. 65-7° [6]) from pet. ether.

IR(CHCl$_3$) : Identical to that of gem-diacid (46).

NMR : 5.70 δ s(broad) 2H olefinic protons;

12.03δ s(broad) 1H acid proton, exchanges with D_2O.

Found : C 68.71, H 8.72% ($C_8H_{12}O_2$ requires C 68.55,

H 8.63%).

Treatment of axial 1-ethoxycarbonyl-4-tosyloxy bicyclo [3.2.1.]octan-8-one (44a) with KOH in ethanol.

210mg. (0.57mmoles) of axial tosylate and 224mg. (4.00mmoles) of potassium hydroxide in 10ml. of dry ethanol were heated under reflux overnight(16 hours). The reaction mixture was cooled, flooded with 100ml. of water and washed with ether (washings discarded). The aqueous layer was taken to pH 7 with 6N HCl and extracted with 2 x 50ml. portions of ether. The combined ether layers were washed with brine, dried, filtered and

concentrated to yield 89mg. of a white solid. This was
shown to be a mixture of cycloheptene-1,5-dicarboxylic
acid (86) and the unsaturated bicyclic keto-acid (87),
in the ratio of 9:1, by its NMR spectrum.

IR : ν_{OH} 3600cm^{-1}(free), 3320-3620cm^{-1}(bonded),

ν_{co} 1710cm^{-1}(broad), ν_{cc} 1600cm^{-1}.

NMR : 1.0-3.0 δ broad methylene envelope;

5.80 δ m(broad) ⎫
                 ⎬ ratio 2:9
7.20 δ t(J=6Hz) ⎭

The higher field of these signals is due to the olefinic
protons of (87), whereas the enone-type signal at low-
field is due to the single unsaturated proton in (86).
This was confirmed by comparison with the spectra of
authentic samples of (86) and (87)[10].

1-Ethoxycarbonyl-4-hydroxy-5-methyl bicyclo[3.2.1]
octan-8-one (48).

A solution of 450mg. (2.65mmoles) of 2-ethoxy-
carbonyl-5-methyl cyclopentanone (23) and 0.5ml. of
triethylamine in 15ml. of dry benzene was treated with
168mg. (3.00mmoles) of freshly-distilled acrolein at
room temperature, and the mixture heated under reflux.
After 44 hours, TLC showed that all starting material
had been consumed and a more polar product formed. The
reaction mixture was cooled to room temperature, neutral-
ised with glacial acetic acid and the solvent removed
under reduced pressure. The residue was taken up in
ether, washed with brine and water, dried, filtered and
concentrated to give 513mg.(86%) of a yellow oil, the
desired alcohol (48).

IR : ν_{OH} 3635cm^{-1}(free), 3400-3660cm^{-1}(bonded);

ν_{co} 1760, 1730cm^{-1}.

NMR : 1.12 δ $\underline{s}$ 3H C(5) methyl;

1.27 δ $\underline{dt}$(J=7Hz) 3H ester methyl;

3.77 δ $\underline{m}$ 1H hydroxyl, exchanges with D_2O;

4.20 δ $\underline{dq}$(J=7Hz) 2H ester methylenes.

Downfield sweep showed no trace of an aldehyde H.

MS : M^+ 226.

1-Ethoxycarbonyl-4-tosyloxy-5-methyl bicyclo[3.2.1] octan-8-one (49).

198mg. (0.88mmoles) of 1-ethoxycarbonyl-4-hydroxy-5-methyl bicyclo[3.2.1] octan-8-one (48) at 0° was treated with a solution of 250mg. (1.31mmoles) of p-toluene sulphonyl chloride in 15ml. of dry pyridine and the reaction mixture stirred at room temperature for 7 days. It was then poured onto ice-cold dilute HCl and extracted with 2 x 50ml. portions of ether. The combined extracts were washed with dilute sodium hydrogen carbonate solution, water and brine, dried filtered and concentrated under reduced pressure at 25° to yield 173mg. of a viscous yellow oil. TLC (30% ethyl acetate - petrol) showed the presence of three compounds, which were separated by prep.TLC. The least polar component (41mg.) corresponded to unreacted alcohol (48) by IR, TLC and NMR comparisons. The middle band from the plate (62mg. of a clear oil) proved to be the equatorial tosylate (49e) by the appearance in the NMR spectrum of a broad multiplet ($w_{\frac{1}{2}}$=20Hz) at 4.70 δ ,due

to the C$\underline{H}$-OTs proton, The most polar component (29mg. of a white solid) was the axial tosylate (49a), the C$\underline{H}$-OTs proton appearing at 4.80 as a multiplet, w$_{\frac{1}{2}}$=6Hz.

IR : Identical for both epimers - no O-H stretch, and

ν_{co} 1760(shoulder), 1735cm^{-1}.

NMR : Similar for both epimers -

0.92 δ $\underline{s}$ 3H C(5) methyl;

1.27 δ $\underline{t}$(J=7Hz) 3H ester methyl;

2.45 δ $\underline{s}$ 3H aromatic methyl;

4.22 δ $\underline{q}$(J=7Hz) 2H ester methylenes;

7.57 δ $\underline{q}$(J=8Hz) 4H aromatics.

The carbinyl proton for each epimer appeared as stated above.

MS : M$^+$ 380 (both epimers).

Treatment of the equatorial tosylate (49e) with NaOEt.

Using the same technique as described previously for the preparation of 5,5-diethoxycarbonyl-1,4-dimethyl cycloheptene (34), 85mg. (0.22mmoles) of equatorial tosylate (49e) was treated with sodium ethoxide (from 100mg. of sodium in 10ml. of ethanol) to produce the cycloheptene gem-diester (50) in 91% yield.

IR : ν_{co} 1735cm^{-1}.

NMR : 1.23 δ $\underline{t}$(J=8Hz) 6H ester methyls;

1.70 δ $\underline{s}$ 3H olefinic methyl;

4.30 δ $\underline{q}$(J=8Hz) 4H ester methylenes;

5.50 δ $\underline{m}$ 1H olefinic proton.

Hydrolysis of the gem-diester (50).

51mg. (0.20mmoles) of (50) was treated with 56mg. (1.00mmoles) of KOH in 10ml. of ethanol overnight under reflux. Normal work-up yielded 33mg.(85%) of the gem-diacid (51) as a semi-solid yellow oil.

IR(CHCl$_3$) : ν_{OH} 2400-3550cm^{-1}; ν_{co} 1705cm^{-1}.

NMR : No ester signals; 1.68 δ s 3H olefinic methyl;

5.45 δ m 1H olefinic proton;

12.31 δ s(broad) 2H acid protons, exchange with D$_2$O.

Decarboxylation of the gem-diacid (51).

30mg. (0.15mmoles) of diacid was heated in refluxing dry pyridine (5ml.) for two hours. The solvent was removed under reduced pressure and the residue taken up in ether, washed with 6N HCl and brine, dried, filtered and concentrated to yield 23mg.(98%) of the cycloheptene mono-acid (52) as a yellow oil.

IR : ν_{OH} 2400-3400cm^{-1}; ν_{co} 1705cm^{-1}.

NMR : 1.67 δ s 3H olefinic methyl;

5.44 δ m 1H olefinic proton;

10.94 δ s(broad) 1H acid proton, exchanges with D$_2$O.

Treatment of the axial tosylate (49a) with KOH in EtOH.

60mg. (0.16mmoles) of axial tosylate in 12ml. of dry ethanol was treated with 116mg. (2.07mmoles) of potassium hydroxide, and the solution heated under reflux for 13 hours. The reaction mixture was cooled, poured

onto 100ml. of water and washed with ether to remove any starting material. The aqueous layer was neutralised with dilute HCl and extracted with ether. The extracts were worked-up in the usual manner to give 18mg. of a yellow-brown semi-solid oil, which as yet has not been identified beyond doubt.

IR : ν_{OH} 2420-3240cm^{-1}; ν_{co} 1705(shoulder), 1740cm^{-1}.

NMR : 1.23 δ s 3H(?) methyl group;

5.40 δ m(v.broad) olefinic signal;

7.00 δ s(broad) acid proton, exchanges with D_2O.

MS : M$^+$ unclear - gradual tailing off after 200; parent ion could be either 226 or 180.

1-Ethoxycarbonyl-2-methyl-4-hydroxy bicyclo[3.2.1] octan-8-one (53).

The above alcohol (120-5°/0.2mm.) was prepared in 78% yield from 2-ethoxycarbonyl cyclopentanone and crotonaldehyde at -78° in the presence of sodium ethoxide, using the method for the preparation of the 2,5-dimethyl counterpart (31) described earlier. Distillation of the crude reaction product was found to be most efficient if performed on a small scale (5-10g.), as this minimised the possibility of thermal decomposition.

IR : ν_{OH} 3605cm^{-1}(free), 3250-3680cm^{-1}(bonded);

ν_{co} 1750, 1720cm^{-1}.

NMR : 0.94 δ d(J=7Hz) 3H C(2) methyl;

1.24 δ t(J=8Hz) 3H ester methyl;

4.16 δ q(J=8Hz) 2H ester methylenes;

4.30 δ s(broad) 1H hydroxyl, exchanges with D_2O.

Downfield sweep revealed only a trace (1%) of
aldehyde.

MS : M$^+$ 226, base peak 41.

1-Ethoxycarbonyl-4-tosyloxy-2-methyl bicyclo[3.2.1]
octan-8-one (54).

     3.394g. (15.02mmoles) of the bicyclic alcohol (53)
was treated with a solution of 3.813g. (20.00mmoles) of
p-toluene sulphonyl chloride in 25ml. of dry pyridine
at 0°, and the reaction mixture stirred at room temper-
ature for 96 hours. It was then poured onto 80ml. of
ice-cold 6N HCl and extracted with 2 x 100ml. portions
of ether. The combined ether layers were washed with
brine until the washings were neutral, dried, filtered
and the solvent removed under reduced pressure at 25°
to yield 3.637g.(64%) of a red oil. This was purified
by prep. TLC (30% ethyl acetate - petrol) to give a
single compound as a clear, pale yellow oil.

IR : No O-H stretch; ν_{co} 1760,1735cm^{-1}.

NMR : 0.92 δ $\underline{d}$(J=6Hz) 3H C(2) methyl;

     1.22 δ $\underline{t}$(J=8Hz) 3H ester methyl;

     2.43 δ $\underline{s}$ 3H aromatic methyl;

     4.18 δ $\underline{q}$(J=8Hz) 2H ester methylenes;

     4.82 δ $\underline{m}$(w$_{\frac{1}{2}}$=22Hz) 1H C$\underline{H}$-OTs proton;

     7.57 δ $\underline{q}$(J=8Hz) 4H aromatics.

MS : M$^+$ 380.

The oil, a white solid at -70° which melted on reaching
room temperature, seemed to be a single epimer, the equa-
torial tosylate (54e), to judge from the half-band width

of the carbinyl proton signal. This was confirmed by the following experiment.

Treatment of the equatorial tosylate (54e) with NaOEt.

A solution of 220mg. (0.58mmoles) of the tosylate produced in the preceding reaction in 10ml. of dry ethanol was added dropwise over 10 minutes to a stirred solution of 0.1g. of sodium metal in 10ml. of ethanol at 60°, and the reaction mixture stirred under reflux for 30 minutes. It was poured onto 50ml. of ice-water, neutralised with 6N HCl and extracted with 2 x 30ml. portions of ether. The combined extracts were washed with brine, dried, filtered and concentrated to yield 123mg.(83%) of a yellow-brown oil which was purified by prep. TLC (30% ethyl acetate - petrol) giving the gem-diester (55) as a clear yellow oil.

IR : ν_{co} 1730cm^{-1}(sharp).

NMR : 0.98 δ d(J=6Hz) 3H saturated methyl;

1.27 δ t(J=8Hz) 6H ester methyls;

4.19 δ q(J=8Hz) 4H ester methylenes;

5.70 δ m 2H olefinic protons.

MS : M$^+$ 254.

Hydrolysis of the gem-diester (55).

A solution of 76mg. (0.30mmoles) of 4-methyl-5,5-diethoxycarbonyl cycloheptene (55) in 10ml. of ethanol was treated with 109mg. (1.94mmoles) of KOH in 3ml. of water and the solution heated under reflux overnight (20 hours). After cooling, the solvent was stripped off

on the rotary evaporator, the residue taken up in 50ml.
of water and washed with ether (washings discarded).
The aqueous layer was carefully neutralised with dilute
HCl, re-extracted with ether and the organic layers were
combined, washed with brine, dried, filtered and concen-
trated to yield 46mg.of a yellow oil. NMR showed the
presence of an ethyl ester, olefinic protons and a carb-
oxylic acid proton(s), but integration indicated that
this product was a mixture of the acid-ester (56) and
the mono-acid (57). TLC confirmed that there were two
components, so the entire reaction product was treated
again with excess KOH in ethanol for 40 hours to decarb-
oxylate and hydrolyse (56) to (57). A similar work-up
to the first one yielded 21mg.(47% overall) of the pure
cycloheptene acid (57) as a clear yellow oil.

IR : ν_{OH} 3540cm^{-1}(free), 2300-3400cm^{-1}(bonded);

   ν_{CO} 1750cm^{-1}(shoulder, monomer), 1705cm^{-1}(dimer).

NMR : 0.95 δ dd(J=5Hz) 3H methyl;

   5.72 δ m 2H olefinic protons;

   8.60 δ s(broad) 1H acid proton, exchanges with D_2O.

   There were no signals corresponding to an ethyl

   ester.

MS : M$^+$ 154, base peak 39.

2-Ethoxycarbonyl-6-methyl cyclohexanone.

The above compound was prepared from 2-methyl
cyclohexanone and diethyl oxalate using the literature
method[37] and gave satisfactory spectral analysis.

1-Ethoxycarbonyl-4-hydroxy-2,5-dimethyl bicyclo[3.3.1]
nonan-9-one (58).

The above alcohol (220-5°/0.7mm.) was prepared (in
72% yield after distillation) from 2-ethoxycarbonyl-6-
methyl cyclohexanone and crotonaldehyde at 0° in the
presence of sodium ethoxide, using the method for the
preparation of the [3.2.1] analogue (31), described
earlier. Small-batch distillation was again the pref-
erred purification technique.

IR : ν_{OH} 3610cm^{-1}(free), 3300-3700cm^{-1}(bonded);
ν_{CO} 1710-1740cm^{-1}(broad).

NMR : 1.05 $\underline{d}$(J=6Hz) 3H C(2) methyl;

1.13 $\underline{s}$ 3H C(5) methyl;

1.30 $\underline{t}$(J=8Hz) 3H ester methyl;

4.23 $\underline{q}$(J=8Hz) 2H ester methylenes;

4.85 $\underline{s}$(broad) 1H hydroxyl, exchanges with D_2O.

Downfield sweep showed no trace of an aldehyde H .

MS : M$^+$ 254.

Found : C 66.27, H 8.76% ($C_{14}H_{22}O_4$ requires C 66.12,
H 8.72%).

1-Ethoxycarbonyl-4-tosyloxy-2,5-dimethyl bicyclo[3.3.1]
nonan-9-one (59).

21.36g. (112mmoles) of tosyl chloride in 90ml. of
dry pyridine was added dropwise to 18.72g. (75.5mmoles)
of bicyclic alcohol (58) at 0° and the resulting solution
was left standing for 1 week in the refrigerator. The
reaction mixture was poured onto 100g. of crushed ice
and worked-up in the normal manner to give 17.72g. of a
golden-yellow oil. This was shown by IR and NMR to be

25% tosylate and 75% starting alcohol, and so it was re-subjected to a further 20g. of tosyl chloride in 90ml. of pyridine for 72 hours at room temperature. Work-up as before gave 19.25g. of a red oil which, on standing at room temperature for several weeks, yielded four crops (6.41g. in total) of a white crystalline solid which proved to be the equatorial tosylate (59e), m.pt. 99-100°(ethanol).

IR : No O-H stretch, ν_{co} 1730cm^{-1}(broad).

NMR : 0.90 δ s 3H C(5) methyl;

1.00 δ d(J=8Hz) 3H C(2) methyl;

1.25 δ t(J=7Hz) 3H ester methyl;

2.40 δ s 3H aromatic methyl;

4.20 δ q(J=7Hz) 2H ester -CH$_2$-;

4.50 δ m(w$_{\frac{1}{2}}$=18Hz) 1H CH-OTs;

7.55 δ q(J=8Hz) 4H aromatics.

MS : M$^+$ 408.

Found : C61.87, H 6.90% (C$_{21}$H$_{28}$O$_6$S requires C 61.74, H 6.90%).

That the equatorial tosylate (59e) was the only epimer formed was confirmed by prep. TLC of an aliquot of the mother liquors from the recrystallisation. This gave more equatorial tosylate and a large amount (about 50%) of untosylated alcohol (58), but no axial tosylate (59a).

Treatment of the equatorial tosylate (59e) with NaOEt.

404mg. (0.99mmoles) of the equatorial tosylate in 10ml. of dry ethanol was added dropwise, over 10 minutes, to a stirred solution of 100mg. of sodium in 10ml. of ethanol at 60°. The reaction mixture was stirred at

reflux temperature for a further 30 minutes and then allowed to cool. It was poured onto 50g. of ice-water, neutralised with 6N HCl and extracted with 2 x 50ml. portions of ether. The combined extracts were washed with brine, dried, filtered and concentrated to yield 275mg.(98%) of the cyclo-octene gem-diester (60) as a pale yellow oil, used without further purification.

IR : ν_{co} 1735cm^{-1}(sharp).

NMR : 0.85 δ d(J=7Hz) 3H saturated methyl;

1.18 δ dt(J=8Hz) 6H ester methyls;

1.60 δ s 3H unsaturated methyl;

4.17 δ dq(J=8Hz) 4H ester methylenes;

5.45 δ t(J=7Hz) 1H olefinic proton.

MS : M$^+$ 282, base peak 41.

Hydrolysis of the cyclo-octene gem-diester (60).

A solution of 270mg. (0.96mmoles) of diester and 300mg. (5.36mmoles) of potassium hydroxide in 10ml. of ethanol was heated under reflux for 48 hours, allowed to cool and the solvent removed under reduced pressure. The residue was taken up in water and washed with ether (which gave 8mg. of a yellow oil identical to starting material on TLC). The aqueous portion was carefully neutralised with dilute HCl and extracted with 2 x 50ml. portions of ether, which were worked-up in the normal way to furnish 175mg. of a yellow-brown oil. NMR showed the continued presence of an ethyl ester function as well as the appearance of an acidic proton at 9.2ppm. Believing this product to be a mixture of the acid-ester (61) and the mono-acid (62), it was redissolved in 10ml.

of ethanol, treated with 300mg. of KOH and the reaction mixture heated under reflux for a further 45 hours. The above work-up this time yielded 134mg.(77% overall) of a brown oil which solidified on standing at room temperature. Recrystallisation from benzene gave the cyclo-octene carboxylic acid (62) as a white crystalline solid, m.pt. 127-8°.

IR(CHCl$_3$) : ν_{OH} 3515cm^{-1}(free), 2300-3400cm^{-1}(bonded);
ν_{co} 1735cm^{-1}(dimer), 1700cm^{-1}(monomer).

NMR : 0.90 δ $\underline{d}$(J=7Hz) 3H saturated methyl;

1.72 δ $\underline{s}$ 3H unsaturated methyl;

5.37 δ $\underline{t}$(J~8Hz, poorly resolved) 1H olefinic H ;

11.28 δ $\underline{s}$(broad) 1H acid proton, exchanges with D$_2$O.

MS : M$^+$ 182, base peak 41.

Found : C 72.50, H 10.10% (C$_{11}$H$_{18}$O$_2$ requires C 72.49, H 9.95%).

1-Ethoxycarbonyl-4-hydroxy bicyclo [3.3.1] nonan-9-one(63)

This was prepared in a two-step process: the keto-aldehyde (64) was prepared by the method of Cope[23] and cyclised by the method of Horii[24], giving the bicyclic alcohol as a clear viscous oil (138-140°/0.03mm.).

IR : ν_{OH} 3620cm^{-1}(free), 3270-3600cm^{-1}(bonded);
ν_{co} 1740, 1720cm^{-1}.

NMR : 1.30 δ $\underline{t}$(J=7Hz) 3H ester methyl;

3.70 δ $\underline{s}$ 1H hydroxyl proton, exchanges with D$_2$O;

4.20 δ $\underline{q}$(J=7Hz) 2H ester methylenes.

MS : M$^+$ 226, base peak 41.

1-Ethoxycarbonyl-4-tosyloxy bicyclo[3.3.1] nonan-9-one(65)

1.15g. (5.09mmoles) of the alcohol (63) at 0° was treated with 1.43g. (7.48mmoles) of p-toluene sulphonyl chloride in 10ml. of dry pyridine and the resulting solution was stirred at room temperature for 8 days. The work-up employed for previous tosylate preparations was used to give 1.11g.(57%) of the epimeric tosylates as a colourless oil. The epimers were separated by prep. TLC (30% ethyl acetate - petrol), the axial being more polar.

The equatorial tosylate (65e), a white crystalline solid, m.pt. 88-9°(ethanol), showed -

IR : No O-H stretch, ν_{co} 1760, 1725cm^{-1}

NMR : 1.26 δ $\underline{t}$(J=8Hz) 3H ester methyl;

     2.44 δ $\underline{s}$ 3H aromatic methyl;

     4.20 δ $\underline{q}$(J=8Hz) 2H ester methylenes;

     4.70 δ $\underline{m}$(w$_{\frac{1}{2}}$=18Hz) 1H C$\underline{H}$-OTs

     7.58 δ $\underline{q}$(J=9Hz) 4H aromatics.

Found : C 60.16, H 6.44% (C$_{19}$H$_{24}$O$_6$S requires C 59.98,

     H 6.36%).

The axial tosylate (65a), also a white crystalline solid, m.pt. 99-100°(ethanol), showed -

IR : Identical to that of the equatorial epimer.

NMR : Very similar to that of the equatorial epimer, except that the C$\underline{H}$-OTs proton appeared as a broad singlet at 5.06 δ(w$_{\frac{1}{2}}$=8Hz).

Found : C 59.81, H 6.49% (C$_{19}$H$_{24}$O$_6$S requires C 59.98,

     H 6.36%).

MS : M$^+$ 380 (both epimers).

Treatment of the equatorial tosylate (65e) with NaOEt.

A solution of 335mg. (0.88mmoles) of the equatorial tosylate in 10ml. of dry ethanol was added dropwise to a stirred solution of 100mg. of sodium in 10ml. of ethanol at 65°. The reaction mixture was stirred at reflux for 45 minutes, allowed to cool to room temperature and the solvent evaporated off under reduced pressure. The residue was taken up in water, washed with ether, neutralised with dilute HCl and extracted with ether. The usual work-up of the extracts yielded 195mg.(87%) of the cyclo-octene gem-diester (66) as a yellow oil, which was used without further purification.

IR : ν_{co} 1735cm^{-1}(sharp).

NMR : 0.92 δ dt(J=7Hz) 6H ester methyls;

   4.20 δ dq(J=7Hz) 4H ester methylenes;

   5.63 δ m 2H olefinic protons.

Hydrolysis of the cyclo-octene gem-diester (66).

50mg. (0.20mmoles) of diester in 20ml. of dry EtOH was treated with 114mg. (2.04mmoles) of potassium hydroxide, and heated under reflux for 18 hours. The reaction mixture was cooled, quenched with water, neutralised with 6N HCl and extracted with ether. The usual work-up gave 39mg. of a dark-brown oil whose NMR showed no signals from an ethyl ester. Assuming that this product was the gem-diacid (67), the oil was heated in refluxing pyridine for 3 hours, cooled and the solvent taken off under reduced pressure. The residue was dissolved in ether, washed with dilute HCl and brine, dried, filtered and concentrated to yield 26mg.(84%) of cyclo-

octene-5-carboxylic acid (68) as a yellow oil.

IR : ν_{OH} 2450-3340cm^{-1}; ν_{co} 1705(dimer), 1745cm^{-1}

(monomer).

NMR : 0.8δ- 2.6δ broad methylene envelope containing

a singlet at 1.27δ;

5.70δ $\underline{m}$ 2H olefinics;

6.83δ $\underline{s}$(broad) 1H acid proton, exchanges in D_2O.

MS : M$^+$ 154, base peak 41.

Treatment of axial tosylate (65a) with KOH in ethanol.

120mg. (0.32mmoles) of the axial tosylate in 10ml.
of dry ethanol was treated with 125mg. (2.24mmoles) of
potassium hydroxide and the mixture heated under reflux
for 16 hours. After quenching with water and washing
with ether to remove any unreacted tosylate, the aqueous
layer was carefully neutralised with 6N HCl and re-extr-
acted with two portions of ether. The combined extracts
were worked-up as usual to yield 40mg. of a semi-solid
oil, which proved to be a combination of the unsaturated
bicyclic keto-acid (90) and the cycloheptene-1,5-dicarb-
oxylic acid (89).

IR : ν_{OH} 3540cm^{-1}(free), 2300-3400cm^{-1}(bonded);
ν_{co} 1710, 1740cm^{-1}.

NMR : Broad methylene envelope from 1.1δ - 3.0δ;

5.6δ $\underline{s}$(broad) olefinic protons from (90);

7.0δ $\underline{t}$(J=8Hz) α,β-unsaturated system in (89);

9.3δ $\underline{s}$(broad) acid protons, exchange with D_2O.

From the integration of the unsaturated proton peaks in
the above spectrum, the ratio of bicyclic keto-acid to
cycloheptene-1,5-diacid is approximately 1:2.

1-Ethoxycarbonyl-4-hydroxy-5-methyl bicyclo[3.3.1] nonan-9-one (69).

This was prepared by the published procedure[25] from 2-ethoxycarbonyl-6-methyl cyclohexanone and acrolein, via the aldehyde (70). A clear yellow oil (125-7°/0.06mm), it gave a negative ferric chloride test.

IR : ν_{OH} 3610cm^{-1}(free), 3010-3410cm^{-1}(bonded);

   ν_{co} 1760, 1735cm^{-1}.

NMR : 1.05 δ s 3H C(5) methyl;

   1.28 δ t(J=7Hz) 3H ester methyl;

   4.23 δ q(J=7Hz) 2H ester methylenes;

   4.90 δ s(broad) 1H hydroxyl, exchanges with D_2O.

MS : M$^+$ 240.

1-Ethoxycarbonyl-4-tosyloxy-5-methyl bicyclo[3.3.1] nonan-9-one (71).

This was prepared as an epimeric mixture from the bicyclic alcohol (69) using the published procedure[9]. The epimers were separated by prep. TLC (40% ethyl acetate - petrol) and identified by the usual NMR technique. The equatorial tosylate was not treated with NaOEt, as the product from this reaction has already been identified[9]. The axial tosylate, a white, feathery crystalline solid m.pt. 122-3°, possessed all the expected spectral characteristics.

Treatment of axial tosylate (71a) with KOH in ethanol.

A solution of 53mg. (0.13mmoles) of axial tosylate and 50mg. (0.90mmoles) of potassium hydroxide in 5ml. of dry ethanol was refluxed overnight, allowed to cool and

the solvent stripped off. The residue was taken up in water, washed with ether (washings discarded) and neutralised with dilute HCl. Re-extraction of the aqueous layer followed by the usual work-up gave 23mg.(93%) of a white solid, m.pt. 138-140°, the unsaturated bicyclic keto-acid (91).

IR(CHCl$_3$) : ν_{OH} 3520cm^{-1}(free), 2400-3600cm^{-1}(bonded); ν_{co} 1760cm^{-1}(broad).

NMR : 1.2 δ $\underline{s}$ 3H C(5) methyl;

5.4 δ $\underline{d}$(J=10Hz) 1H C(3) olefinic proton;

6.0 δ $\underline{m}$ 1H C(4) olefinic proton;

9.4 δ $\underline{s}$(broad) 1H acid proton, exchanges with D$_2$O.

This spectrum was identical to that of an authentic sample of (91)[9].

Reduction of equatorial 1-ethoxycarbonyl-4-tosyloxy-2,5-dimethyl bicyclo[3.2.1.]octan-8-one (33e) with NaBH$_4$.

373mg. (0.95mmoles) of the equatorial tosylate was treated with a solution of 38mg. (1.01mmoles) of sodium borohydride in 20ml. of 10% aqueous methanol and stirred at room temperature for 50 hours. The bulk of the solvent was removed on the rotary evaporator, leaving a 5ml. residue which was quenched with water and extracted with 2 x 50ml. portions of ether. The combined extracts were washed with brine, dried, filtered and concentrated to give 361mg.(96%) of the hydroxy-tosylate (106) as a white solid, m.pt. 135-6°(ethanol).

IR(CHCl$_3$) : ν_{OH} 3350-3630cm^{-1}; ν_{co} 1710cm^{-1}(broad).

NMR : Similar in appearance to that of the parent keto-tosylate (33e), with the addition of two signals -

3.0 δ s(broad) 1H hydroxyl, exchanges with D_2O;

4.0 δ s(broad) 1H C$\underline{H}$-OH proton.

MS : M^+ 396, base peak 91.

Found : C 60.58, H 7.14% ($C_{20}H_{28}O_6S$ requires C 60.59, H 7.12%).

Treatment of the hydroxy-tosylate (106) with KOBu^t.

A solution of 150mg. (0.38mmoles) of 1-ethoxycarbonyl-4-tosyloxy-2,5-dimethyl bicyclo[3.2.1]octan-8-ol (106) in 10ml. of sodium-dried benzene was treated with 90mg. (0.80mmoles) of potassium t-butoxide and the reaction mixture was heated under reflux for 21 hours. It was then cooled, quenched with water and the layers allowed to separate. The aqueous layer was extracted with ether, and the organic portions combined, washed twice with brine, dried, filtered and concentrated to give 93mg. of a clear oil which solidified at room temperature. TLC (40% ethyl acetate - petrol) showed the presence of both starting material and a less polar product. The latter was isolated by preparative TLC, yielding 29mg.(39% overall) of the cycloheptene ester (38) as a clear oil, identical by chromatography and by IR and NMR spectroscopy to the product of decarboxylation of the acid-ester (36).

Reduction of the axial tosylate (33a) with NaBH$_4$.

545mg. (1.38mmoles) of the axial tosylate was reduced with 53mg. (1.40mmoles) of sodium borohydride in the manner described for the equatorial epimer above. This produced 539mg.(98%) of the hydroxy-tosylate (109) as

a white, crystalline solid, m.pt. 139-140°(ethanol).

IR : ν_{OH} 3600cm^{-1}; ν_{co} 1715cm^{-1}(sharp).

NMR : Similar in appearance to that of the parent keto-
tosylate (33a), with the addition of two signals -

2.32 δ s(broad) 1H hydroxyl, exchanges with D$_2$O;

3.93 δ s(broad) 1H C$\underline{H}$-OH proton.

MS : M$^+$ 396, base peak 91.

Found : C 60.80, H 6.93% (C$_{20}$H$_{28}$O$_6$S requires C 60.59,
H 7.12%).

Treatment of the axial hydroxy-tosylate (109) with KOBu^t.

A solution of 98mg. (0.25mmoles) of (109) in 10ml.
of dry benzene was treated with 56mg. (0.50mmoles) of
potassium t-butoxide, and the reaction mixture heated
under reflux for 17 hours. Using the same work-up as
employed in the reduction of (106), the product was 51mg.
of a yellow oil which partly solidified at room temper-
ature. NMR indicated that this was a mixture of cyclo-
heptene ester (38) and p-toluene sulphonic acid. The
latter was removed by washing an ethereal solution of the
crude product with dilute sodium hydrogen carbonate,
leaving, after the usual work-up, 34mg.(47%) of pure
cycloheptene ester (38), identical in all aspects to that
produced earlier by decarboxylation of the acid-ester (36).

Conversion of the cycloheptene acid (37) to the corresp-
onding isocyanate (114).

A solution of 506mg. (3.01mmoles) of the acid and
1.631g. (13.71mmoles) of thionyl chloride in 20ml. of
sodium-dried benzene was heated under reflux for 18 hours,

cooled and the excess thionyl chloride removed under reduced pressure to yield an unweighed brown oil, the acid chloride (112). IR(thin film) showed no trace of the carboxyl O-H stretch and the appearance of an acid chloride carbonyl band at 1785cm^{-1}. This material was used without further purification.

The acid chloride in 10ml. of acetone was treated with 325mg. (5.00mmoles) of sodium azide in 1.2ml. of water (0°, dropwise addition over 15 minutes, with stirring),and the solution stirred at room temperature for 3$\frac{1}{2}$ hours. The reaction mixture was then quenched withwater and extracted with benzene. The extracts were washed with brine until the washings were neutral, then dried thoroughly, filtered and most of the solvent removed under reduced pressure at 25°. This gave the azide (113), 2130cm^{-1} in the IR, plus traces of the isocyanate (114), 2250cm^{-1}. The azide was converted completely to the isocyanate by refluxing in dry toluene for 12 hours. When the solvent was stripped off, the brown oil which remained showed a very strong isocyanate peak in the IR (2240cm^{-1}), and only a trace of azide at 2120cm^{-1}.

Attempted hydrolysis of the isocyanate (114).

The isocyanate (114) prepared as above was dissolved in 10ml. of AR dioxan and treated with 560mg. (10.00 mmoles) of potassium hydroxide in10ml. of water. The reaction mixture was heated under reflux for 2$\frac{1}{2}$ hours, cooled and concentrated under reduced pressure. The last traces of water were removed by azeotroping with benzene, leaving a brown oil which, on trituration with

ethanol, gave a whitish-brown solid. The melting point
of this compound was found to be greater than 230°,
which points to its being a salt. IR(KBr disc) showed
a very broad O-H at 2500-3740cm^{-1}, and a broad carbonyl
centred on 1650cm^{-1}. NMR was impossible as the product
would not dissolve in any of the common organic solvents.
MS showed no molecular ion, only a gradual tailing off
of peaks.

This product is postulated as being the potassium
carbamate (118). However, when it was treated with dil-
ute HCl to liberate the free carbamic acid, extraction
with ethyl acetate yielded only 4mg. of material. Pres-
uming that the carbamic acid had been decarboxylated to
the amine (115) _in situ_, the aqueous layer was basified
with 4N NaOH and re-extracted with ethyl acetate to give
18mg. of a yellow-brown oil. However, the IR of this
compound exhibited no N-H stretches, but did show a very
broad carbonyl absorption centred on 1720cm^{-1}. Hence
this cannot be the desired amine.

Treatment of the cycloheptene acid (37) with dimethyl
disulphide.

A solution of 909mg. (9mmoles) of di-isopropylamine
in 5 ml. of dry THF, under N$_2$, was treated with 8mmoles
of n-butyl lithium and stirred at 0° for 10 minutes. A
solution of 593mg. (3.53mmoles) of the acid (37) in 4ml.
THF/1ml.HMPA was added, and the solution stirred at 0°
for 1½ hours. It was then poured onto an ice-cold
solution of 470mg. (5mmoles) of dimethyl disulphide in
5ml. of THF, then stirred for 40 minutes at 0°. The

reaction mixture was poured onto 100g. of ice-water, acidified with 6N HCl and extracted with ethyl acetate. The usual work-up of the extracts gave 638mg. of a brown oil. Prep. TLC (30% ethyl acetate - petrol) gave 101mg. of unreacted starting material as the only identifiable product. No trace was found of the α-thiomethylated acid (121).

REFERENCES.

1. For a review, see G.L.Buchanan in "Topics in Carbo-
   cyclic Chemistry, Volume 1" Logos Press, 1969, p199.

2. G.L.Buchanan, C.Maxwell and W.Henderson, Tetrahedron,
   1965, 21, 3273.

3. G.L.Buchanan, A.C.W.Curran, J.M.McCrae and G.W.McLay,
   ibid, 1967, 23, 4729.

4. C.A.Grob and J.Hostynek, Helv.Chim.Acta, 1963, 46,
   2209.

5. J.R.Hargreaves and P.W.Hickmott, Tetrahedron Letters,
   1966, 4173.

6. G.Stork and H.K.Landesman, J.Amer.Chem.Soc., 1956,
   78, 5129.

7. C.A.Grob, Angew.Chem.Int.Ed., 1969, 8, 535.

8. J.Martin, W.Parker and R.A.Raphael, J.Chem.Soc.,
   1964, 289.

9. G.L.Buchanan, A.McKillop and R.A.Raphael, ibid,
   1965, 833.

10. G.L.Buchanan and G.W.McLay, Tetrahedron, 1966, 22,
    1521.

11. G.L.Buchanan and G.Jamieson, ibid, 1972, 28, 1129.

12. Y.Naya and M.Kotake, Tetrahedron Letters, 1968, 1645.
    For a synthesis of karahanaenone, see E.Demole and
    P.Enggist, Helv.Chim.Acta, 1971, 54, 456.

13. L.Nicole and L.Berlinguet, Canad.J.Chem., 1962, 40,
    353.

14. K.Sisido, K.Utimoto and T.Isida, J.Org.Chem., 1964,
    29, 2781.

15. E.D.Bergmann, D.Ginsburg and R.Pappo, Organic React-

ions, 1959, X, 179.

16. A.Hassner and C.Heathcock, J.Org.Chem., 1964, 29, 1350.

17. C.f. R.F.Zurcher, Helv.Chim.Acta, 1963, 46, 2054; K.Tori and E.Kondo, Tetrahedron Letters, 1963, 645.

18. V.P.Gol'mov, Zhur.Obs.Khim., 1953, 23, 1162 (from Chem.Abs. 1953, 47, 12255g).

19. G.B.Bachmann and H.A.Tanner, J.Org.Chem., 1939, 4, 493.

20. R.Ya.Levina, N.N.Godovikov and F.K.Velichko, Zhur. Obs.Khim., 1955, 25, 2522 (from Chem.Abs., 1956, 50, 9430c).

21. E.E.Schweizer and G.J.O'Neill, J.Org.Chem., 1965, 30, 2082.

22. W.G.Dauben and K.S.Pitzer, "Steric Effects in Organic Chemistry" (ed.M.S.Newman), Wiley New York, 1956, (chapter 1).

23. A.C.Cope and M.E.Synerholm, J.Amer.Chem.Soc., 1950, 72, 5228.

24. Z.-I.Horii, T.Imanishi, S.-W.Kim and I.Ninomiya, Chem.Pharm.Bull., 1968, 16, 1918.

25. R.D.H.Murray, W.Parker, R.A.Raphael and D.B.Jhaveri, Tetrahedron, 1962, 18, 55.

26. A.C.Cope, E.S.Graham and D.J.Marshall, J.Amer.Chem. Soc., 1954, 76, 6159.

27. C.S.Foote, ibid, 1964, 86, 1853.

28. C.S.Foote and R.B.Woodward, Tetrahedron, 1964, 20, 687.

29. B.Capon in "Organic Reaction Mechanisms" (ed. B. Capon and C.W.Rees), 1968, Interscience, p.143.

30. M.Svoboda, J.Zavada and J.Sicher, <u>Coll.Czech.Chem. Comm.</u>, 1968, <u>33</u>, 1415.

31. P.A.S.Smith, <u>Organic Reactions</u>, 1946, <u>III</u>, 379.

32. B.M.Trost and Y.Tamaru, <u>J.Amer.Chem.Soc.</u>, 1975, <u>97</u>, 3528.

33. L.Nicole and L.Berlinguet, <u>Canad.J.Chem.</u>, 1962, <u>40</u>, 353.

34. K.Sisido, K.Utimoto and T.Isida, <u>J.Org.Chem.</u>, 1964, <u>29</u>, 2781.

35. H.L.Brown, Ph.D. thesis, University of Glasgow, 1968.

36. P.S.Pinkey, <u>Organic Syntheses Coll.Vols.</u>, 1943, <u>II</u>, 146.

37. H.R.Snyder, L.A.Brooks and S.H.Shapiro, <u>ibid</u>, 531.

CHAPTER THREE

APPROACHES TO AN INTERMEDIATE

IN SESQUITERPENE BIOGENESIS.

In recent years, whenever the chemical synthesis of a natural product is planned, one of two major pathways is normally used. The first, and for many years the more important, road is through total synthesis, using the classical techniques of functional group manipulation to bring about structural and stereo-chemical control. This method has resulted in many elegant synthetic sequences producing such important natural products as cortisone[1], onocerin[2], longifolene[3], strychnine[4] and colchicine[5]. The modern variation of the "grand synthetic scheme" involves viewing the final product as a "jigsaw" of two, three or more pieces, each of which is synthesised independently, with the components being put together in the final step(s). Examples of this convergent approach include tetrodotoxin by Kishi[6], Erythron-olide B and prostaglandin E_1 by Corey[7,8] and, perhaps the ultimate in natural product synthesis, Vitamin B_{12} by Woodward, Eschenmoser and a host of others[9]. The second road, which is becoming more and more widely utilised today, is that of the biogenetic-type or biomimetic synthesis[10].

Biogenetic-type synthesis can be defined as an organic synthesis designed to follow in at least its major aspects, either a biosynthetic pathway proved or presumed to be used in the natural construction of the end-product, or chemical analogues of such a pathway. Thus non-biological or non-enzymic substrates and reaction conditions can be used in such a synthesis.

(1)   (3)

(18)   (7)
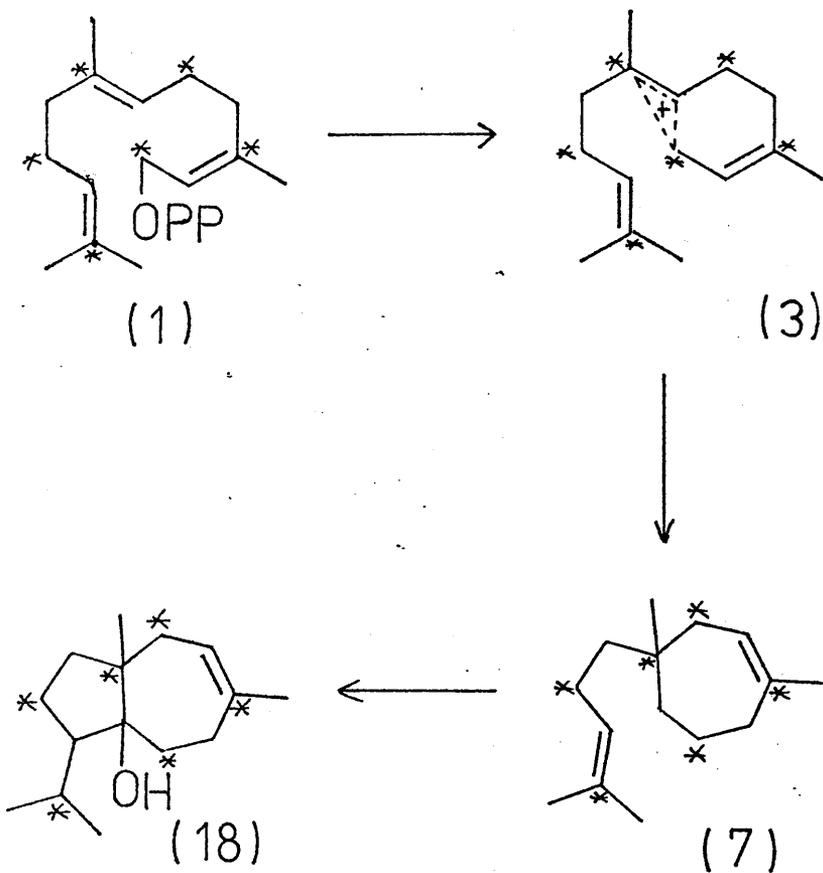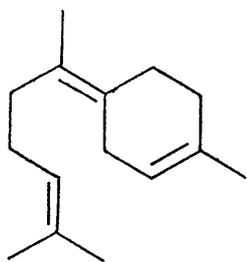
SCHEME 2

(12)
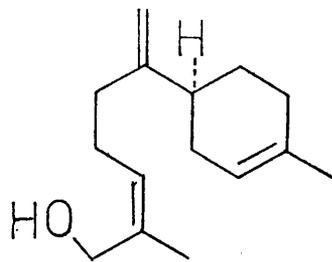
(13)

(14)

15)

(9)

(16)

(17)

(18)

(19)

(20)

(3)

(6)

(7)

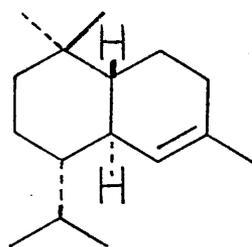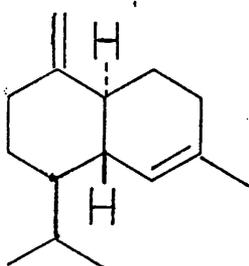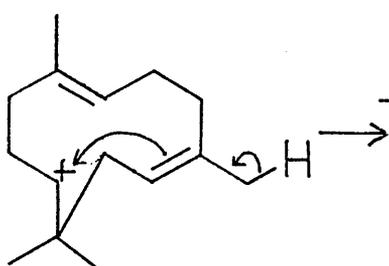(1)

(4)

(8)

(9)

(2)

(5)

(10)

(11)
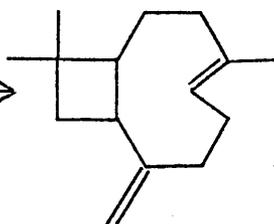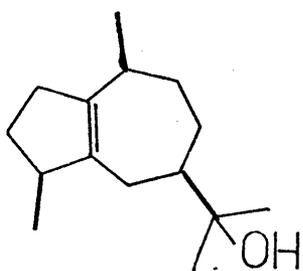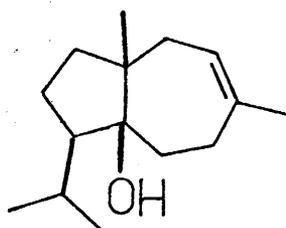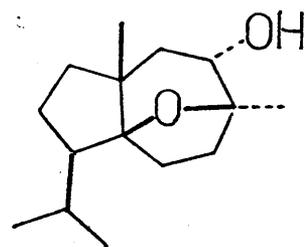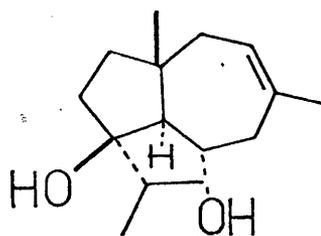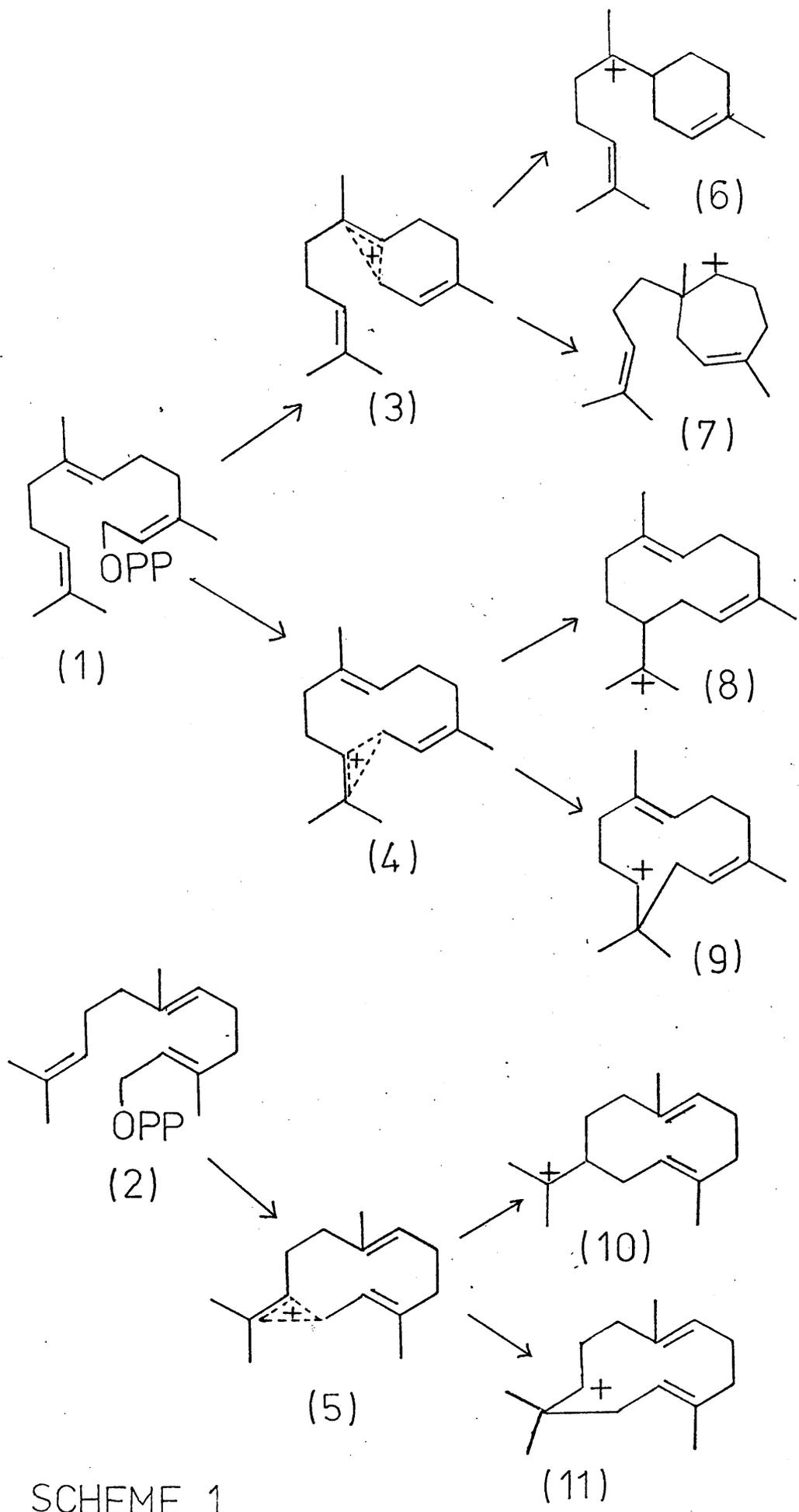
SCHEME 1

The biosynthesis of the vast majority of sesqui-
terpenes can be understood in terms of cyclisations of
the carbonium ions derived from either cis,trans-
farnesyl pyrophosphate (1) or trans,trans-farnesyl
pyrophosphate (2), as shown in Scheme 1[11,12] (for the
sake of clarity, classical carbonium ions are shown in
preference to non-classical). For example, carbonium
ion (6) is the biogenetic precursor of monocyclic sesqui-
terpenes such as γ-bisabolene (12) and lanceol (13), as
well as the bicyclic counterparts α-cadinol (14) and
γ_2-cadinene (15). Similarly, carbonium ion (9), in
which the endocyclic double bonds are not held closely
enough together to permit an internal cyclisation, leads
to caryophyllene (16), as shown.

In this area, the principal subject of interest to
the Buchanan group has been the synthesis of bicyclo
[5.3.0.]-type sesquiterpenoids, such as guaiol (17)[13].
The specific aim of this work was to investigate the
possibility of the intermediacy of the cation (7) in
the biogenesis of sesquiterpenes with the unusual
carotane skeleton, for example carotol (18)[14],
daucol (19)[14] and jaeschkanadiol (20)[15]. Evidence for the
participation of (7) in the biosynthetic pathway was
provided by Soucek[16], who degraded carotol produced from
[1-14C]-acetate and showed that C-6 and its attached
methyl group had one-sixth of the total activity
incorporated, which is consistent with the pathway shown
in Scheme 2. This result is not consistent with the
alternative pathway, described in Scheme 3, which
involves a [1,3] hydride shift in cation (8) to give

(28)

(23)

[3+3]

SCHEME 5

E = CO₂Et → $E = CO_2Et$

R =

SCHEME 4

(26)

(27)

(1)   (4)   (8)

(21)   (22)

(18)

SCHEME 3

(23)   (24)

(25)
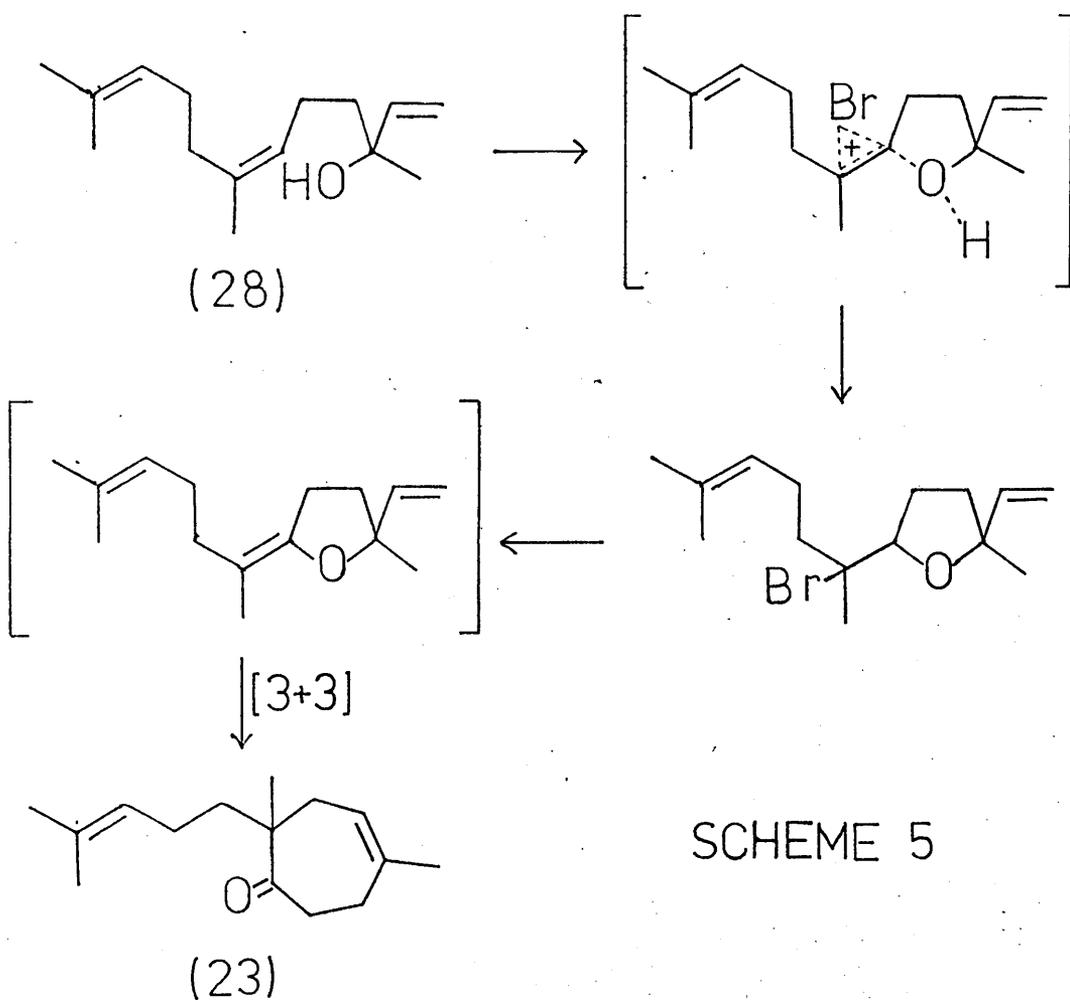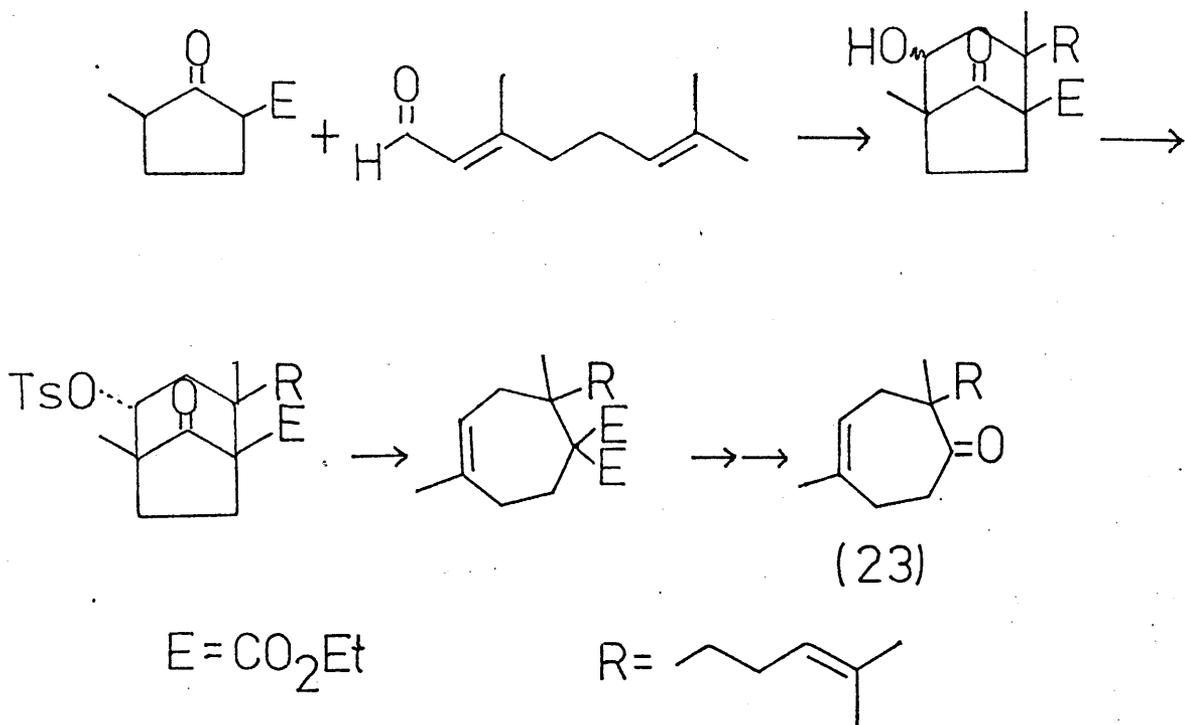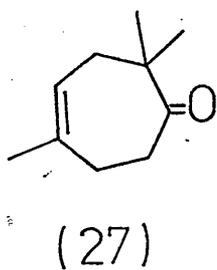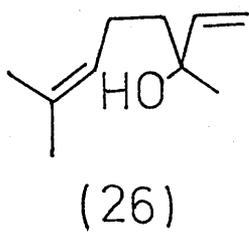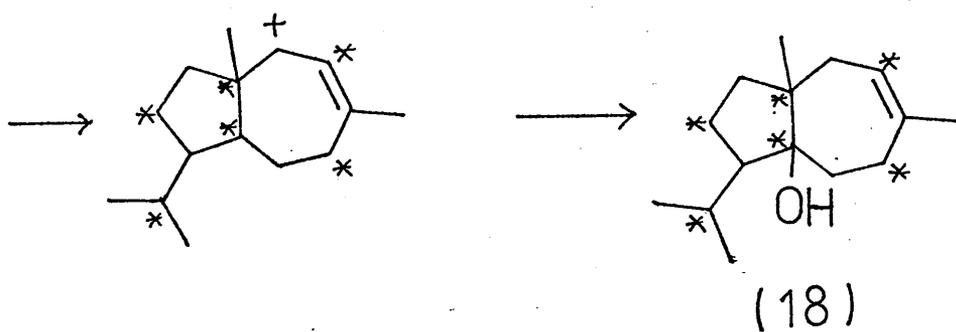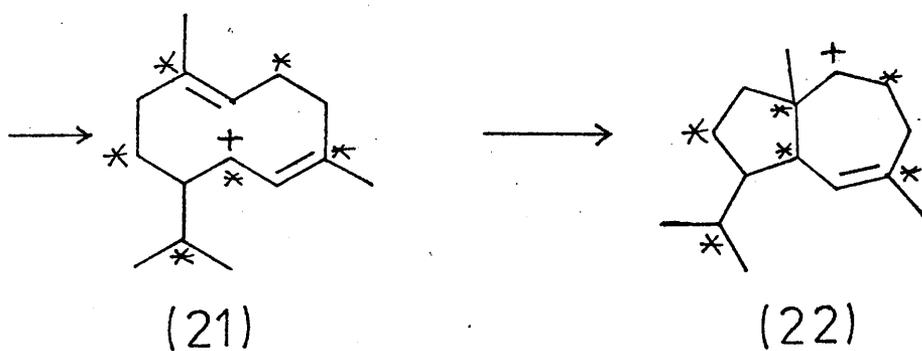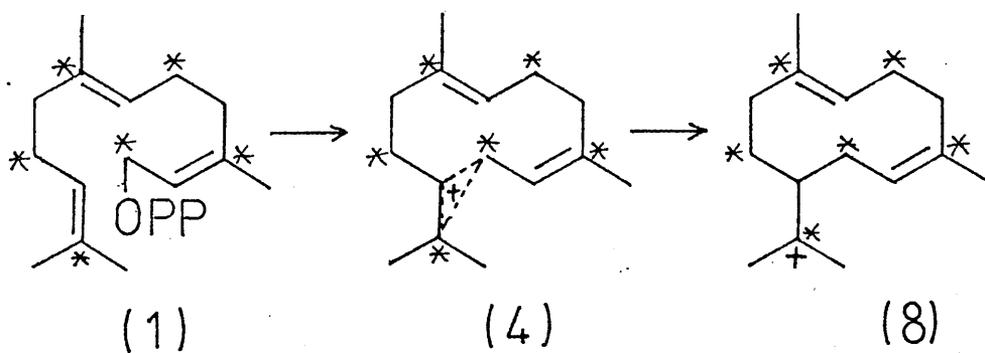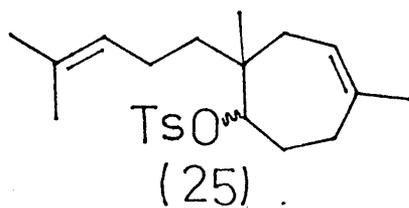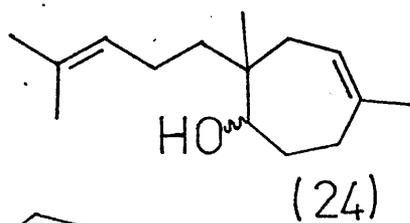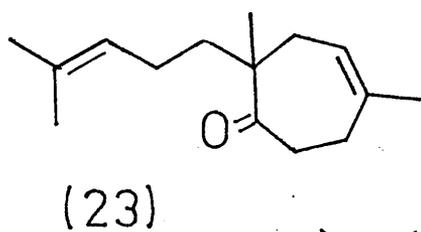
(21), which then would have to undergo cyclisation to (22) and subsequent methyl migration and hydroxylation producing carotol with the label in the positions indicated.

Generation of the carbonium ion at the correct position on the cycloheptene ring should be possible via the solvolysis of the appropriate tosylate (25), derived from the cycloheptenone (23) and its corresponding alcohol (24). In theory at least, it should be feasible to synthesise the cycloheptenone (23) by a bridge-scission reaction of the tosylate of the alcohol produced by condensation of 2-ethoxycarbonyl-5-methyl cyclopentanone and citral, with subsequent modification of the gem-diester. This is described in Scheme 4. However, as mentioned in chapter 2 of this thesis, the above condensation failed and the sequence could not be put to the test. It was fortunate that an alternative route to (23) was available.

Using a completely different approach, Demole[17] prepared (23) by a two-step process (Scheme 5) from nerolidol (28), utilising an allylic bromination-dehydrobromination technique first developed on linalool (26) to produce karahanaenone (27)[18]. In our hands, initial attempts to repeat this procedure met with only partial success, since GLC indicated that while the desired ketone (23) was being produced, it was contaminated with two impurities of shorter retention time. Careful high vacuum distillation was insufficient to separate these impurities, whose presence was

(23)

(24)

(31)

SCHEME 7

(29)

(30)

(a) B

(b) B

H

HO H

(a) (b)

(a) (b)

(29) (30)   SCHEME 6

(31)

O

X

(32)

OH
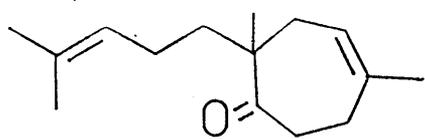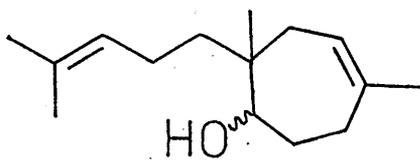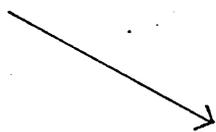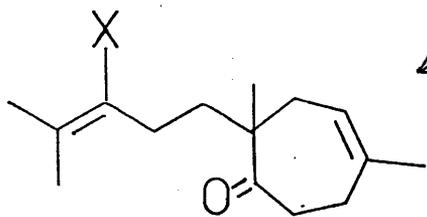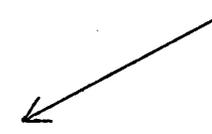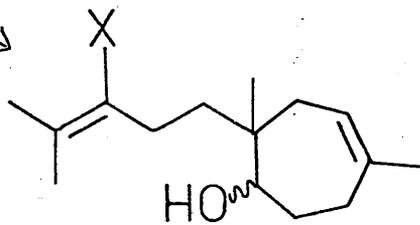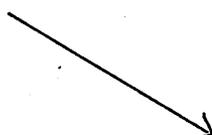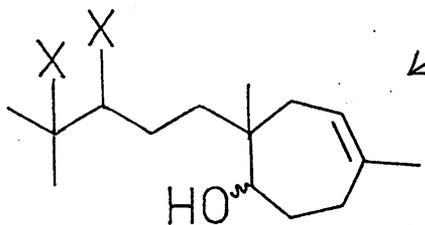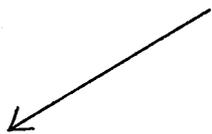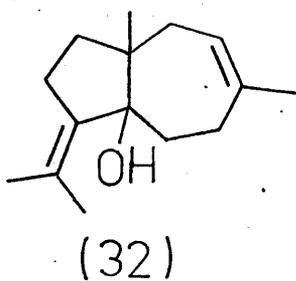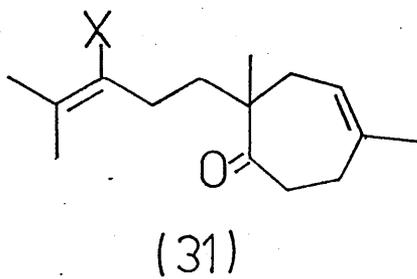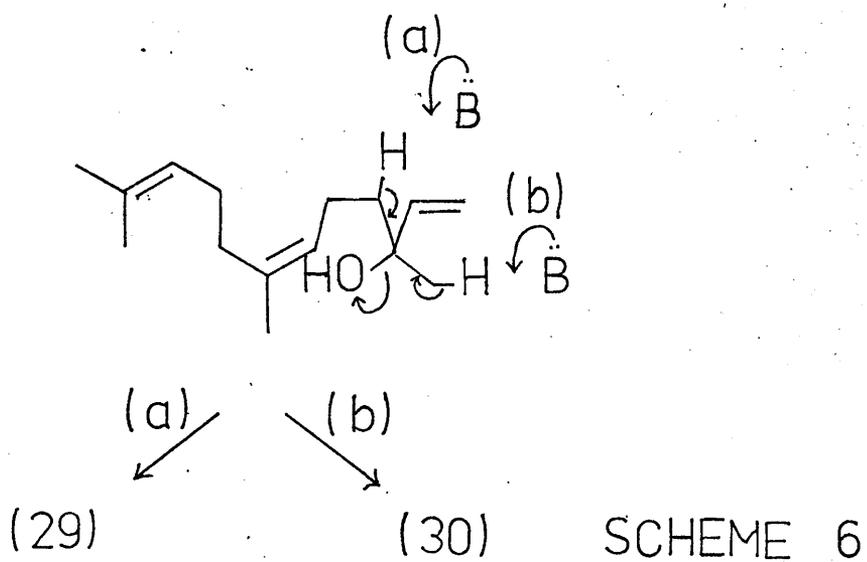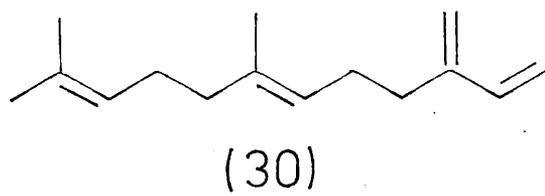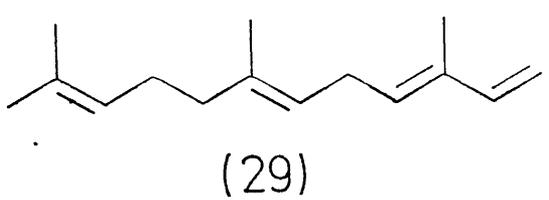
confirmed by the appearance in the ^{1}H NMR spectrum of a series of signals similar to those found in a terminal vinyl system ($-CH=CH_2$). The identity of the contaminants was brought to light using gas chromatography / mass spectrometry (GCMS), which showed that each impurity had $M^+=204$ and base peak = 43, but slightly differing breakdown patterns. A survey of the literature confirmed that these spectra fitted for α- and β-farnesene, (29) and (30), previously isolated from the natural coating of Granny Smith apples[19]. The farnesenes almost certainly arise from unreacted nerolidol being dehydrated at the refluxing collidine stage (Scheme 6). Although the impurities had been identified, it still remained necessary to remove them in order to have pure cycloheptenone with which to work. This was achieved using the technique of dry-column chromatography and gave ketone of purity $>98\%$ by GLC.

Prior to investigations into the possibility of cyclisation of the carbonium ion (7), an attempt at a purely chemical ring-closure was made. Corey[20] has shown that vinylic δ- and ε-halo ketones can be cyclised to form pentenols and hexenols respectively, using lithium di-n-butyl copper to bring about the intramolecular reaction. It was believed that if the δ-halo cycloheptenone (31) [X=Br or I] could be prepared, using the route described in Scheme 7, it would serve as a suitable cyclisation precursor, giving dehydrocarotol (32) upon treatment with a lithium dialkyl copper. Reduction of the ketone (23) to its corresponding alcohol (24) with

SCHEME 8

(33)

(34)
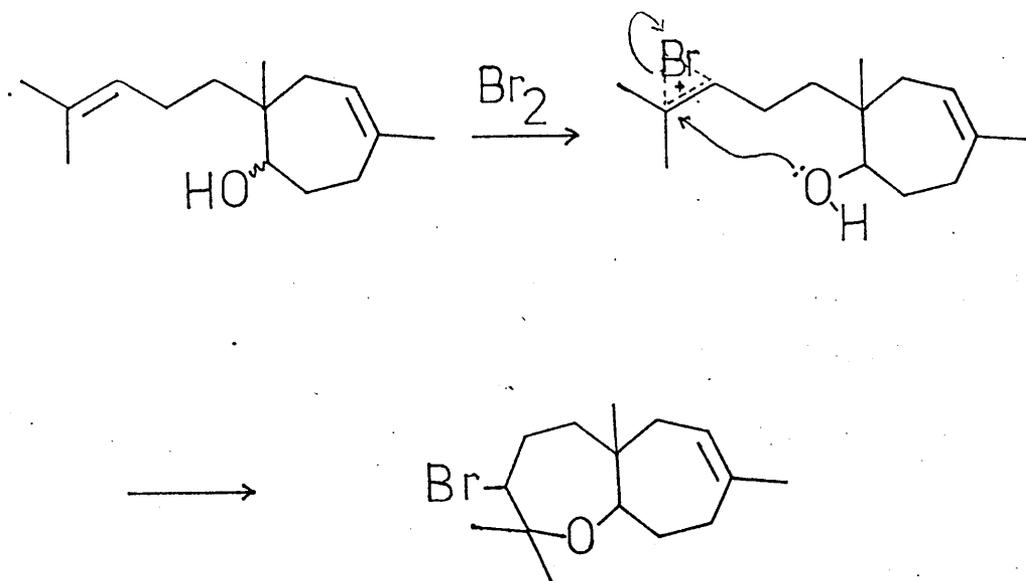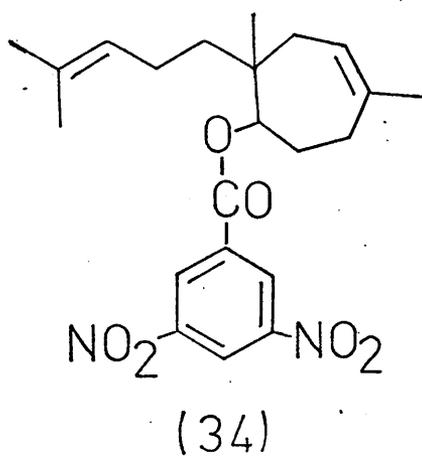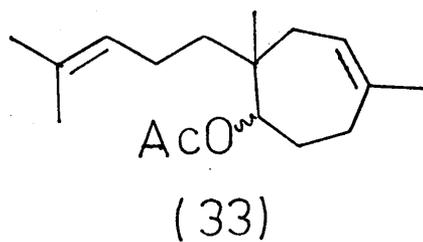
lithium aluminium hydride proceeded cleanly and in
virtually quantitative yield. However, attempts to
selectively add the elements of Br_2 across the exocyclic
double bond gave only a multi-component product from
which no single species could be isolated cleanly. It
was believed that this might have arisen from interfer-
ence by the lone pair of electrons on the hydroxyl
oxygen, as shown in Scheme 8. In an attempt to reduce
the nucleophilicity of the oxygen, the alcohol was
converted to its acetate (33) by treatment with acetic
anhydride and pyridine, but the acetate also failed to
give a dibromide, even at low temperature.

Returning to the original idea, attempts were made
to convert the alcohol (24) to its tosylate (25), but
this only gave 10% tosylate at best, the remainder of the
alcohol being unchanged, This can be attributed to a
comparative lack of acidity of the hydroxyl proton (in
which case a stronger base than pyridine would have been
more successful) or the relative ease with which the
tosylate may dissociate to alcohol (24) and tosic
acid following initial formation. Efforts to prepare
other substituted benzene sulphonate derivatives of (24)
were equally unsuccessful.

Although the benzene sulphonates are probably the
most suitable substrates for solvolysis, alternatives
have been used in the past. These include nitro-
benzoate[21] and dinitrobenzoate[22] esters, and since we
had been able to prepare the 3,5-dinitrobenzoate (34)
as a characteristic derivative of alcohol (24), this
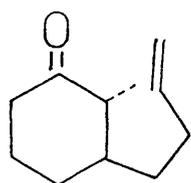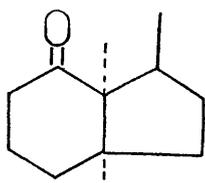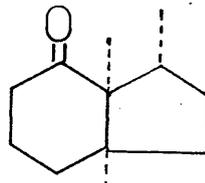
(35) (36) (37)
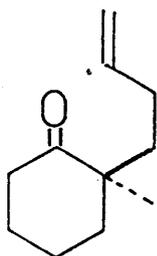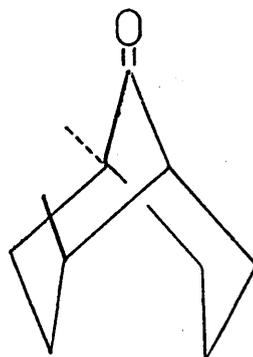
(38) (39)

(23)
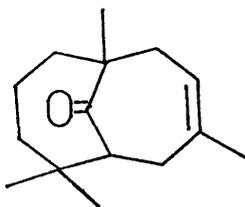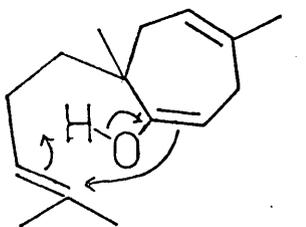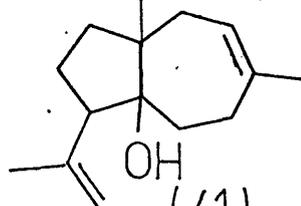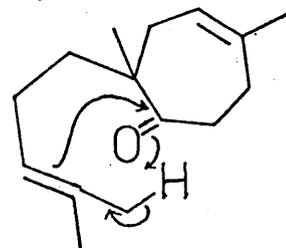
(40) (41)

SCHEME 9

was chosen as the subject for a solvolysis study.
Prepared in the normal way from (24) and 3,5-dinitro-
benzoyl chloride in pyridine, the dinitrobenzoate was
stirred in 70% aqueous acetone at 43° for 190 hours.
However, work-up produced only starting material, and
TLC showed no trace of any other products. Raising the
solvolysis temperature did not encourage the reaction
to proceed, as shown by a quantitative return of
starting material from 75% aqueous dioxan at 130° for
96 hours.

It is well-known that carbonyl compounds containing
"remote" ethylenic double bonds are capable of under-
going a thermal cyclisation[23]. For example, Conia and
co-workers have shown that both spiro compounds (e.g.
(36) and (37) from (35)[24]) and carbonyl-bridged bicyclic
compounds (e.g. (39) from (38)[25]) can be produced
thermally from the appropriate substrates. With this
in mind, it seemed reasonable to subject ketone (23)
to the thermal conditions, hoping that it would cyclise
either through its enol form to produce a bicyclo
[4.4.1] undecenone (40) or through its keto tautomer
to form a dehydrocarotol (41), as seen in Scheme 9.
First attempts to utilise Conia's technique[25] of
introducing the unsaturated carbonyl compound into a
pre-heated and evacuated system produced no change in the
starting material, but this may well have been due to
technical difficulties, principally the inability of
the system to maintain a sufficiently high vacuum.
This was unfortunate, as this method minimises the amount

(23)

(18)

SCHEME 10

(42)
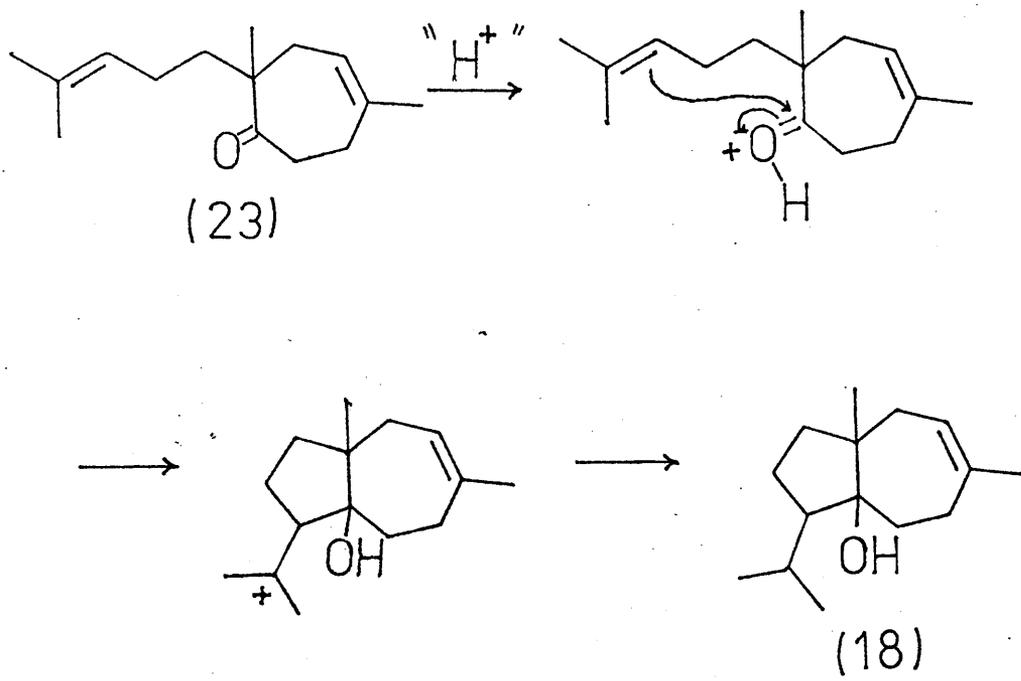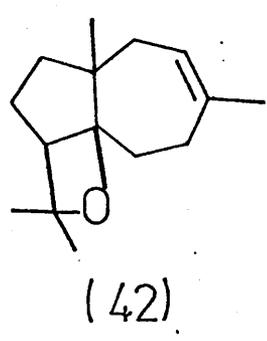
of polymerisation which inevitably occurs in such a reaction, since the substrate is effectively introduced in the vapour phase. When the ketone (23) was heated in a pyrolysis tube at 330° for 4 hours under high vacuum, the major part of the product was unreacted starting material, but both GLC and TLC showed the presence of an additional, less polar component. Clearly, this could not be the alcohol (41), which one would expect to be more polar than starting ketone, and, after purification by preparative TLC, infra-red analysis confirmed this, showing no sign of either hydroxyl or carbonyl functions. The ^{1}H NMR spectrum of this non-polar product was not particularly helpful, showing only that the original vinyl proton signals around 5.4 δ had been replaced by an almost symmetrical signal at 7.0 δ. The product also showed $M^+ = 202$ in the mass spectrum. This corresponds to a loss of 18 mass units from the parent ketone (23) and suggests a "dehydration" product. However, no structure can be drawn which accommodates this loss of H_2O and at the same time explains the ^{1}H NMR signal at 7.0 δ. We are therefore unable to formulate this thermolysis product.

In a final attempt to bring about a satisfactory cyclisation of the unsaturated side-chain in (23) onto the carbonyl group, a series of experiments were conducted, designed to proceed as described in Scheme 10. Demole[17] has shown that the cycloheptenone can undergo cyclisation in the presence of a Lewis acid catalyst, $SnCl_4$ in nitromethane, to give the "carotol-ether" (42).

ACID TREATMENT OF (23)

CONDITIONS	PRODUCTS (%)			
	A	B	C	D
$BF_3.Et_2O$/RT	70	30	–	–
HCO_2H/100°	4	–	10	86
conc.H_2SO_4/RT	90	10	–	–

TABLE 1

Therefore a variety of different forms of acid catalyst was employed. One of the mildest methods of introducing such a catalyst is to use an acidic ion-exchange resin, such as Amberlite IR-120(H)[26], but this method proved to be too mild, even at elevated temperature, and the ketone (23) remained unchanged.

It was discovered that when the proton source was changed to a fairly strong acid, cyclisation did occur, and the nature of the products obtained depended upon the acid used (see Table 1). When a fairly concentrated sulphuric acid solution was added to the cycloheptenone (23) in hexane, the reaction mixture became very dark-coloured immediately, and after being stirred vigorously overnight at room temperature, TLC showed that a very non-polar product had been formed. This was isolated by preparative TLC and shown by GLC to consist of two components, labelled (A) and (B), in the ratio 9:1. The major product, (A) (RI 1385 on 1% OV1 at 100°), gave $M^+ = 202$ by GCMS analysis, while the minor product, (B), (RI 1515) showed $M^+ = 218$. The infra-red spectrum of the above inseparable mixture showed neither hydroxyl nor carbonyl absorptions, while the ^{1}H NMR revealed two olefinic protons, four unsaturated and four saturated methyl groups.

The same two products, (A) and (B), were also produced by treatment of the ketone with boron tri-fluoride etherate. This reaction gave similar results in dry benzene at room temperature or under reflux. As previously, they were isolated as an inseparable mixture

(23)

H⁺ →

(32)

− H₂O →

(43)

→

(44)
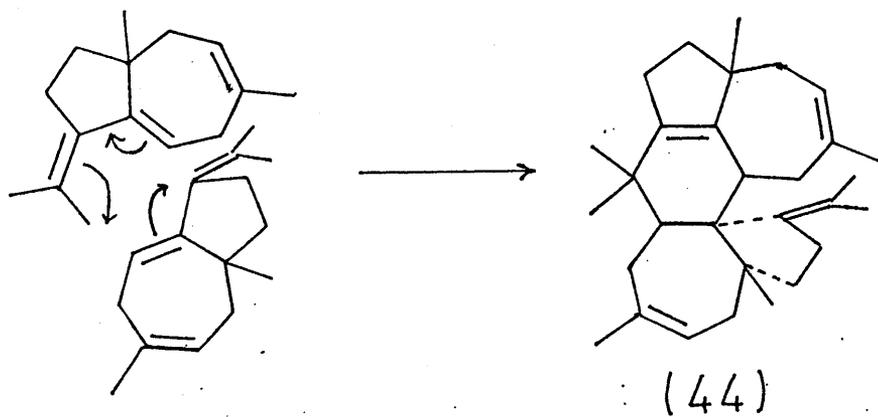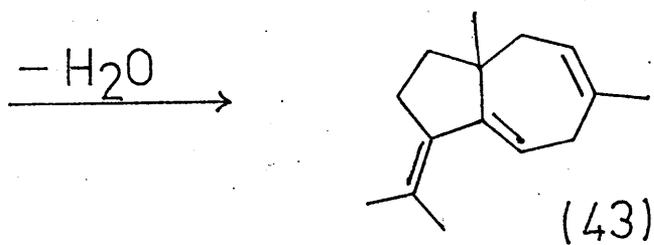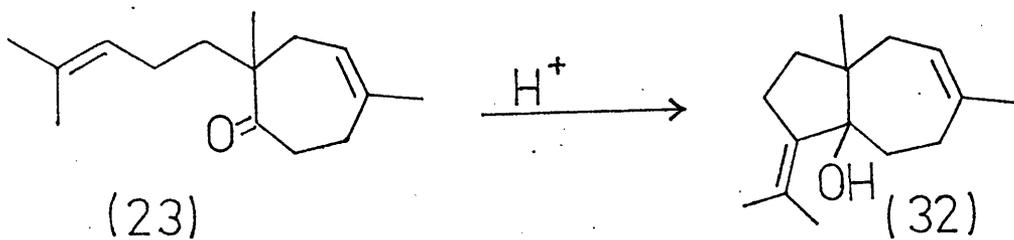
SCHEME 11

by preparative TLC, but this time in the ratio 7:3. Since it was not possible to isolate even the major component in the pure state, further investigation was severely limited. However, in contrast to the GCMS data, the mass spectrum of the 9:1 mixture of (A) and (B) gave $M^+ = 404$, with no further peaks until $^m/e$ 202. This suggests that (A) is a dimer which is reconverted to monomer under GC conditions (around 270°), and the most likely mechanism is a Diels-Alder retrogression. If we now assume that the ^{1}H NMR signals given by the mixture originate from a dimer which arises from a cyclisation-dehydration product of (23) , (A) can only have structure (44); no other dimer gives the required ratio of two vinyl hydrogens,four olefinic methyls and four saturated methyls (Scheme 11).

An attempt was made to confirm structure (44) by ^{13}C NMR, but the spectral resolution was poor, and the spectrum was more complex than expected. This, together with the fact that the dimer (unexpectedly) did not solidify, suggests that it is a mixture of stereo-isomers. Nevertheless, it seems fairly certain from these results that the expected cyclisation to the carotol skeleton has been accomplished, but the inter-mediate alcohol (32) is readily dehydrated.

Some attempts were now made to trap the diene inter-mediate (43) with maleic anhydride, but these were not sucessful. Of the two sets of cyclisation conditions described, that using H_2SO_4 seemed the more useful since the acid strength could be adjusted, hopefully, to
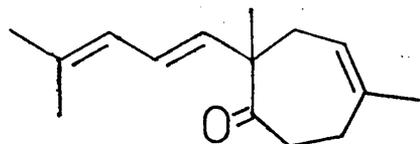
(45)
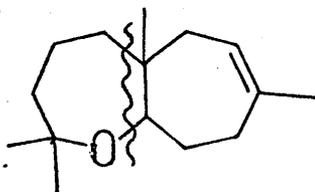
(46)

the point where dehydration of (32) to (43) was inhibited.
However, no suitable set of intermediary conditions could
be found that would stop the reaction at the alcohol
intermediate (?2).

The minor component (B) of the above mixture showed
$M^+ = 218$, which corresponds to a dehydro derivative of
the parent ketone (23). The cracking pattern showed the
loss of 28 mass units ($C = O$) but no evidence of loss of
18 (H_2O) or 82 ($M^cLafferty$ rearrangement leading to the
loss of the side-chain), which is the base peak in the
mass spectrum of (23). These facts are consistent with
structure (45), but because no pure sample could be
isolated from the mixture, this hypothesis could not be
tested further.

When a solution of the cycloheptenone (23) in
dioxan was treated with 90% formic acid and heated under
reflux, in an attempt to reduce the severity of the
above reaction conditions, a similar non-polar product
was formed, isolated by prep. TLC and shown by GLC to
consist of three components in the ratio 4:10:86. The
least abundant component was identical by GCMS to (A),
the major product from the sulphuric acid and $BF_3.Et_2O$
reactions, i.e. (44), whereas the other two products
both had $M^+ = 222$. The major product (D) has a similar
mass spectral breakdown pattern to the alcohol (24), and
shows a loss of 18 mass units, but the absence of a
hydroxyl stretch in the IR would seem to rule out the
possibility of a reduction of (23) to (24) by formic
acid. So far, no structure can be suggested for this

substance. The third component (C), which also showed $M^+ = 222$, differed from (D) in showing no loss of 18 mass units, but instead a loss of 100 mass units. A possible structure for (C) is (46). Once more, our inability to isolate pure single substances from the mixture made it impossible to carry out a rigorous structure investigation.

In conclusion, it appears to be possible to bring about ring-closure of Demole's ketone (23) in the expected fashion, but in our hands no single, pure product could be isolated which might have been utilised in a biomimetic synthesis of carotol or a related terpene.

Preparation of 2,5-dimethyl-2-(4-methyl pent-3-enyl)
cyclohept-4-enone(23).

The cycloheptenone was prepared using a slightly
modified version of a literature procedure .

A mixture of 10.12g. (46mmoles) of nerolidol
(a mixture of the cis and trans isomers), 8.30g.(52
mmoles) of N-bromosuccinimide and 90ml. of CCl_4 was
stirred at room temperature for 5 days. 100ml. of
40-60 petrol was added, and the precipitated succinimide
filtered off. The filtrate was treated with 22.82g.
(188mmoles) of freshly-distilled collidine and the
solution concentrated under reduced pressure. The
residue was heated under reflux (160-170°) for 16 hours
in an atmosphere of nitrogen, poured onto 150ml. of
ice-cold 6N HCl and extracted with two portions of
ether. The combined ether extracts were washed to
neutrality with brine and saturated $CuSO_4$ solution,
dried, filtered and concentrated to yield 7.93g. (78%)
of a dark brown oil. Distillation (80-81°/0.1mm.)
gave a clear yellow oil with the following spectral
characteristics:

IR : Transparent in the hydroxyl region.

ν_{co}1705 cm^{-1}(sharp).

NMR : 1.05 δ s 3H saturated methyl;

1.58 δ s 3H unsaturated methyl;

1.67 δ s 6H unsaturated methyls;

5.05 δ m 1H olefinic proton;

5.50 δ m 1H   "

Vinyl-like series of signals between 5.60 δ and 6.30δ.

GCMS investigation of the impurities present in cyclo-
heptenone(23).

Using a 1% SE 30 column at 100°, the above dist-
illation product was shown to consist of one major(70%)
component, retention index 1610, and two minor (30%)
components, RI 1520 and 1550. The GCMS results were as
follows:

1610 component	M^{+} 220	base peak 138
1550 component	M^{+} 204	base peak 43
1520 component	M^{+} 204	base peak 43

The breakdown pattern of the 1610 component was
consistent with that of the desired ketone , including
the McLafferty rearrangement of the sidechain (M^{+}-82).
Comparison of the spectra of the 1550 and 1520 components
with authentic versions confirmed that they arose from
α- and β- farnesene respectively.

Pur ification of the cycloheptenone(23) by dry-column
chromatography.

240g. of Grade I alumina was deactivated to Grade
III by mixing with 14.4ml. of distilled water for three
hours on a rotary evaporator. This was then used to
prepare a 20" x 1" nylon column, on which was loaded
approximately 3g. of the impure ketone, followed by a
single elution with benzene as solvent. After develop-
ment, the column was divided into ten equal sections,
and GLC (1%SE 30, 110°) showed that pure ketone had
"R_f" 0.6-0.8. The compound obtained in this manner was
more than 99% pure by GLC. Each section of column was

treated as follows: afterallowing the solvent to evap-
orate off at room temperature in a fume-cupboard, the
alumina was stirred with approximately 100ml. of dry
ether for 1 hour, the alumina filtered off and the filt-
rate concentrated at reduced pressure. These results,
giving around 65% recovery of pure ketone, were found
to be consistent, and in the case of subsequent columns
only the section 0.6-0.8 needed to be treated in this
way.

2,5-dimethyl-2-(4-methyl pent-3-enyl)cyclohept-4-enol(24)

To a stirred suspension of 456mg. (12mmoles) of
LiAlH$_4$ in 100ml. of sodium-dried ether, under nitrogen,
was added a solution of 5.06g. (23mmoles) of pure cyclo-
heptenone(23) in 50ml. of ether, dropwise over 10 mins.
The mixture was stirred overnight at room temperature,
and excess LiAlH$_4$ destroyed by the successive addition
of 1) 1ml. of water, 2) 1ml. of 4N NaOH and 3) 3ml. of
water . The resulting white granular precipitate was
filtered off and the filtrate washed to neutrality with
very dilute HCl, brine and water. After drying(MgSO$_4$),
removal of the solvent under reduced pressure furnished
5.03g. (98%) of the required alcohol as a clear oil.
IR(Thin film) : ν_{OH} 3200-3700 cm^{-1}

No absorbance in the carbonyl region.

NMR : 0.83 δ $\underline{s}$
0.99 δ $\underline{s}$ } 3H epimers of saturated methyl;

1.63 δ $\underline{s}$ 3H unsaturated methyl;

1.70 δ $\underline{s}$ 3H

1.74 δ 3H unsaturated methyl;

3.50 δ 1H C$\underline{H}$-OH

5.10 δ 1H olefinic proton;

5.30 δ 1H   "   .

MS : M$^+$ 222.

Attempted bromination of the cycloheptenol(24).

A solution of 715mg. (4.47mmoles) of Br$_2$ in 10ml. of chloroform was added dropwise to a stirred solution of 995mg. (4.47mmoles) of the alcohol in 10ml. of CHCl$_3$ over a period of 40 minutes. The colour of the solution changed from pale yellow to very dark brown through the course of the addition. After stirring for a further hour, the reaction mixture was washed with 2 x 20ml. portions of water, dried, filtered and concentrated to yield 1.31g. of a dark brown oil. TLC(20% ethyl acetate-petrol) showed that this product was a multi-component mixture which did not warrant further investigation.

1-Acetoxy-2,5-dimethyl-2-(4-methyl pent-3-enyl)cyclo-hept-4-ene(33).

3.00g. (13.5mmoles) of cycloheptenol(24) in 3.00g. (29.4mmoles) of AnalaR acetic anhydride was treated with 5 drops of dry pyridine and the solution left to stand at room temperature overnight. The acetic anhydride was removed by azeotroping with several portions of toluene under reduced pressure, yielding 3.48g. (97%) of a yellow-brown oil which was purified by chromatography on 50g. of silica gel. The resulting

acetate, a clear oil, was characterised as follows:

IR : Complete absence of any O-H stretch.

ν_{co} 1730cm^{-1}.

NMR : 0.90 δ $\underline{s}$

0.96 δ $\underline{s}$ } 3H epimers of saturated methyl;

.1.65 δ $\underline{s}$ 3H unsaturated methyl;

1.74 δ $\underline{s}$ 3H   "

1.78 δ $\underline{s}$ 3H   "

2.08 δ $\underline{s}$ 3H acetate methyl;

4.70 δ $\underline{t}$(J=6Hz) 3H C$\underline{H}$-OAc;

5.09 δ $\underline{m}$ 1H olefinic proton;

5.25 δ $\underline{m}$ 1H   "

MS : M$^+$ 264.

Bromination of the cycloheptene acetate(33).

(a) At room temperature:

A solution of 82mg. (0.51mmoles) of Br$_2$ in 10ml. of chloroform was added dropwise over a period of 5 minutes to a stirred solution of 135mg. (0.51mmoles) of the acetate in 10ml. of CHCl$_3$ at room temperature. Stirring was continued for a further two hours, then the solvent removed under reduced pressure, to give 187mg. of an olive-green oil which, after purification by prep. TLC (5% ethyl acetate-petrol), gave starting material as the only recognisable product.

(b) At -50°:

A solution of 278mg. (1.73mmoles) of Br$_2$ in 10ml. CHCl$_3$ was added dropwise over a period of 30 seconds to a stirred solution of 456mg. (1.73mmoles) of the acetate in 10ml. of CHCl$_3$ at -50°. Stirring was continued at

this temperature for 45 minutes, during which time TLC showed only the presence of starting material. The cooling bath was removed and stirring continued at room temperature for a further 36 hours. TLC now showed a multi-component mixture which could not be cleaned up by column chromatography.

Attempted conversion of the alcohol(24) to its tosylate.

281mg. (1.27mmoles) of 2,5-dimethyl-2-(4-methyl pent-3-enyl)cyclohept-4-enol(24) was treated with 380mg. (2.00mmoles) of p-toluene sulphonyl chloride in 5ml. of dry pyridine at 0°. The reaction mixture was allowed to come to room temperature and then stirred for 7 days. It was then poured onto a 20g. mixture of ice/6N HCl and left to stand overnight. After extraction with 2 x 50ml. portions of ether, the organic layers were combined, washed successively with i) very dilute HCl, ii) three portions of brine, and iii) water, dried over MgSO$_4$, filtered and concentrated to yield 258mg. of a viscous yellow oil. NMR showed that the alcohol had been converted to its tosylate only to the extent of 10%. Even prep.TLC (10% ethyl acetate-petrol) failed to produce pure tosylate.

Conversion of (24) to its 3,5-dinitrobenzoate(34).

A mixture of 0.90g. (4.1mmoles) of the alcohol(24) and 1.15g. (5.0mmoles) of 3,5-dinitrobenzoyl chloride in 20ml. of dry pyridine was heated under reflux for 7 hours, after which time TLC (5% ethyl acetate-petrol) indicated that all of the starting material had been

consumed. The reaction mixture was allowed to cool to room temperature, and, after acidification, was extracted with 3 x 50ml. portions of ether. The combined ether extracts were washed with very dilute sodium hydrogen carbonate solution, water and brine, dried, filtered and concentrated to give the dinitrobenzoate (1.36g.,80%) as a semi-solid oil. Recrystallisation from hot ethanol gave a fine white solid, m.pt. 132-3°.

IR(Nujol mull) : Transparent in O-H region, ν_{co} 1695 cm^{-1}.

NMR : 1.02 δ $\underline{s}$ 3H, 1.60 δ $\underline{s}$ 3H, 1.70 δ $\underline{s}$ 3H and

      1.82 δ $\underline{s}$ 3H, one saturated and three unsaturated

      methyl groups respectively;

      3.58 δ $\underline{t}$(J=6Hz) 1H C$\underline{H}$-OCOAr;

      5.00 δ $\underline{m}$ 1H, 5.36 $\underline{m}$ 1H, olefinic protons;

      9.03 δ $\underline{d}$(J=3Hz) 2H ortho aromatic protons;

      9.13 δ $\underline{t}$(J=3Hz) 1H para aromaric proton.

MS : M^{+} 416

Found : C 63.55, H 6.90% (C$_{22}$H$_{28}$N$_2$O$_6$ requires C 63.45,

    H 6.78%).

Attempted solvolysis of the dinitrobenzoate (34).

The solvolysis conditions used were those employed by Traylor for p-nitrobenzoate solvolysis .

A solution of 18mg. (0.04mmoles) of the dinitro-benzoate in 70% aqueous acetone was stirred at 43$\pm$2° for 190 hours, allowed to cool and the acetone removed under pressure. The aqueous residue was diluted with 50ml. of water, basified with 4N NaOH, extracted with 2 x 50ml. portions of ether, and the organic extracts combined.

These were washed with brine until neutral, dried over
MgSO$_4$, filtered and concentrated to yield 15mg. of a
white solid material which was identical by TLC (10%
ethyl acetate-petrol), NMR and melting point to the
starting material.

Pyrolysis of cycloheptenone (23).

(a) At 275° for 2 hours under partial vacuum :

The apparatus used is described in Ref. 23 .
The entire set-up was heated until the temperature of
the heating-bath (thermometer 1) reached 440°. The
system was then evacuated to 1.0mm. and 102mg. (0.46
mmoles) of pure ketone was introduced in a single
portion. At this point the internal temperature of the
flask was 275°. Heating was continued, and this
temperature maintained for 2 hours. After allowing to
cool for 4 hours, the vacuum, which had gradually
deteriorated, was released, and the entire contents of
the reaction vessel were taken up in 30ml. of anhydrous
ether. After filtration to remove polymeric/carbonised
material, the solvent was taken off under reduced
pressure to yield 58mg. of a yellow oil which was
identical to starting material by IR and GLC.

(b) At 330° for 4 hours under high vacuum :

689mg. (3.13mmoles) of pure ketone was placed at
the bottom of an 85 cm. Pyrex pyrolysis tube, and the
system degassed at 10^{-6}mm. under liquid N$_2$ temperature.
The degassing was repeated three times and then the
system was sealed at the above pressure. The tube was

heated in a Carius oven at 330° for 4 hours, frozen in liquid nitrogen and carefully opened. The entire contents were taken up in 50ml. of ethyl acetate. TLC (5% ethyl acetate-petrol) showed, in addition to unconsumed starting material, the presence of a very non-polar product, which was separated out from an aliquot of the reaction mixture by preparative TLC. NMR showed a complex series of multiplets around the saturated methyl region (1.0δ), with only two other distinctive features - the appearance of a sharp singlet a 2.3δ and the replacement of the original olefinic signals at 5.4δ by a symmetrical multiplet at 7.0δ.

IR (liquid film) showed complete transparency in both the hydroxyl and carbonyl regions, with strong ν_{C-H} 2950 and $\nu_{C=C}$ 1630 cm^{-1}.

Treatment of the cycloheptenone (23) with various acidic ion-exchange resins.

Pure ketone (23) was treated with a variety of resins in hexane at room temperature or at 69° (reflux). The resins used were Dowex 50X-8, Amberlite IR-120 (both strongly acidic resins) and Amberlite IRC-50(H) (a weakly acidic resin). Typically, 100mg. of ketone and 500mg. of resin would be stirred in hexane at the required temperature for periods of up to two weeks, monitoring by TLC(5% ethyl acetate-petrol). In all cases, this showed only the presence of starting material, with no sign of any other products being formed.

Treatment of cycloheptenone (23) with sulphuric acid in
hexane at room temperature.

(a) Dilute H_2SO_4.

A mixture of 140mg. (0.64 mmoles) of ketone, 5ml.
of hexane and 5ml. of dilute H_2SO_4 was stirred
vigorously at room temperature for 24 hours. The layers
were separated, and the aqueous layer extracted with a
further 5ml. of hexane. The combined hexane portions
were washed to neutrality with water, then dried,
filtered and concentrated to yield 120mg. of a pale
yellow oil which was shown to be starting material by
TLC, IR and NMR comparisons.

(b) Concentrated H_2SO_4.

To a solution of 120mg. (0.55mmoles) of ketone in
5ml. hexane at room temperature was added a mixture of
2.5ml. conc. H_2SO_4 and 3.0ml. of water. Immediately
upon addition, the lower layer became dark-coloured. The
mixture was stirred vigorously at room temperature
overnight (16 hours) and then a further 5ml. of hexane
was added. Work-up as in (a) above gave 91mg. of a
brown oil which was shown by TLC (5%ethyl acetate-
petrol) to be considerably less polar than the starting
ketone. After purification by preparative TLC,
analysis by GLC (1%SE30,100°) showed a single major
component (84%) with R.I. 1385. GCMS details are given
later.

NMR : saturated methyl groups at 0.95 δ(s), 1.05 δ(s)
and 1.25 δ(s) unsaturated methyls at 1.55 δ
(s-broad) and 1.70 δ (s broad), and a series of

broad multiplets 4.75-5.75 δ.

Treatment of cycloheptenone (23) with 90% formic acid.

(a) At room temperature.

To a solution of 220mg. (1.00mmole) of pure
ketone in 15ml. of AnalaR dioxan was added 15ml. of
90% formic acid and the mixture stirred at ambient
temperature for 8 days. The reaction mixture was then
poured onto 50ml. of water, extracted with ether, and
the extracts worked-up in the usual way to give a pale
yellow oil, which was purified by prep. TLC, yielding
91mg. of an oil with identical spectral characteristics
to those of the starting material.

(b) At 100° (reflux temperature).

A homogeneous mixture of 162mg. (0.74mmoles) of
ketone, 10ml. of 90% formic acid and 10ml. of AnalaR
dioxan was heated under reflux. Although TLC (2%
ethyl acetate-petrol) after 5.5 hours showed almost
complete disappearance of starting material and
concomitant formation of a less polar material, heating
was continued overnight (18 hours in total). After
cooling, the solvent system was removed at reduced
pressure to yield 147mg. of a brown oil, which was
purified by prep. TLC to give a yellow oil with the
following characteristics :

NMR : A complex series of broad multiplets around 1.0 δ,
    1.5 δ and 2.1 δ, with two downfield multiplets at
    5.1 δ and 6.8 δ.

IR : ν_{CH} 2960,2940,2870 cm^{-1}.

No absorption in carbonyl region.

GLC(1% SE30 100°) :- Three components, with retention
        indices as follows - 1400 (5%), 1525 (9%), and
        1650 (86%). For GCMS analysis, see later.

Attempted ketalisation of cycloheptenone (23).

Method (A) :   A mixture of 418mg.(1.90mmoles) of
ketone, 136mg.(2.20mmoles) of dry ethylene glycol and
25mg. of p-toluene sulphonic acid in 50ml. of sodium-
dried benzene was heated at reflux using a Dean and
Stark water separation apparatus for 48 hours. After
cooling, the solution was washed with water, dried,
filtered and concentrated to yield a very dark oil.
Preparative TLC revealed that the major component of this
oil was polymeric material, and very little, if any,
ketal could be prepared in this way.

Method (B) :   As a milder alternative to (A), the
procedure described below was used in an attempt to
prepare the desired ketal[30].

        A solution of 120mg. (0.54mmoles) of ketone in
5ml. dry acetonitrile was added to a mixture of 350mg.
(3.89mmoles) AnalaR oxalic acid and 900mg. (14.52mmoles)
of dry ethylene glycol in 5ml. of acetonitrile, and
the resulting solution allowed to stand at room temper-
ature overnight. It was then poured onto excess water,
extracted with ether, dried, filtered and concentrated to
yield 110mg. of a yellow oil which corresponded to
starting material by TLC, IR and NMR.

Comparison of the results of GCMS analysis of the
products from reaction of cycloheptenone (23) with
various strong acids.

The results are given in Table 2 below :

ACID	RI	M$^+$	BASE PEAK	OTHER PEAKS
H$_2$SO$_4$	1385 (90%)	202	159	145, 134, 131, 119, 105, 91, 81, 41.
	1515 (10%)	218	43	203, 175, 149, 133, 119, 105, 93, 91, 79, 77, 43.
HCOOH	1400 (4%)	202	159	187, 145, 134, 131, 119, 109, 105, 91, 41.
	1525 (9%)	222	41	122, 109, 107, 95, 85, 83, 81, 79, 43.
	1650 (87%)	222	41	204, 135, 122, 119, 109, 107, 91, 81, 43.
BF$_3$.Et$_2$O	1400 (70%)	202	159	187, 145, 134, 131, 119, 105, 91, 41.
	1500 (30%)	218	43	203, 175, 149, 147, 133, 119, 93, 91, 41.

1. (a) G.Rosenkranz, J.Pataki and C.Djerassi, _J.Amer._
   Chem.Soc., 1951, _73_, 4055.

   (b) R.B.Woodward, F.Sondheimer and D.Taub, _ibid_,
   1951, _73_, 4057.

2. G.Stork, A.Meisels and J.E.Davies, _ibid_, 1963,
   _85_, 3419.

3. E.J.Corey, M.Ohno, R.B.Mitra and P.A.Vatakencherry,
   ibid, 1964, _86_, 478.

4. R.B.Woodward, M.P.Cava, W.D.Ollis, A.Hunger, H.U.Daen-
   iker and K.Schenker, _Tetrahedron_, 1963, _19_, 247.

5. (a) J.Schreiber, W.Leimgruber, M.Pesaro, P.Schudel,
   T.Threlfall and A.Eschenmoser, _Helv.Chim.Acta_, 1961,
   _44_, 540.

   (b) E.E.van Tamelen, T.A.Spencer, D.S.Allen and
   R.L.Orvis, _Tetrahedron_, 1961, _14_, 8.

6. Y.Kishi, M.Aratani, T.Fukuyama, F.Nakatsubo, T.Goto,
   S.Inoue, H.Tanino, S.Sugiura and H.Kakoi, _J.Amer._
   Chem.Soc., 1972, _94_, 9217, 9219.

7. E.J.Corey, K.C.Nicolaou and L.S.Melvin, _ibid_, 1975,
   _97_, 654.

8. E.J.Corey, N.H.Andersen, R.M.Carlson, J.Paust,
   E.Vedejs, I.Vlattas and R.E.K.Winter, _ibid_, 1968,
   _90_, 3245.

9. R.B.Woodward, _Pure and Appl.Chem._, 1973, _33_, 145, and
   references therein.

10. For a recent review, see D.Goldsmith in _Fortschritte_
    der Chemie Organischer Naturstoffe, 1971, _XXIX_, 363.

11. W.Parker, J.S.Roberts and R.Ramage, _Quart.Revs._, 1967,
    _21_, 331.

12. G.Rucker, _Angew.Chem.Int.Ed._, 1973, _12_, 793.

13. G.L.Buchanan and G.A.R.Young, J.Chem.Soc.Perkin I, 1973, 2404.

14. For a synthesis of (+)-carotol and (-)-daucol, see H.De Broissia, J.Levisalles and H.Rudler, Chem.Comm., 1972, 855.

15. M.C.Sriraman, B.A.Nagasampagi, R.C.Pandey and S.Dev, Tetrahedron, 1973, 29, 985.

16. M.Soucek, Coll.Czech.Chem.Comm., 1962, 27, 2929.

17. E.Demole, P.Enggist and C.Borer, Helv.Chim.Acta, 1971, 54, 1845.

18. E.Demole and P.Enggist, ibid, 1971, 54, 456.

19. K.E.Murray, Austr.J.Chem., 1969, 22, 197.

20. E.J.Corey and I.Kuwajima, J.Amer.Chem.Soc., 1970, 92, 395.

21. I.Rothberg and R.L.Garnick, J.Chem.Soc.Perkin II, 1974, 457.

22. T.Shono, I.Nishiguchi and R.Oda, J.Org.Chem., 1970, 35, 42.

23. J.-M.Conia and P.Le Perchec, Synthesis, 1975, 1.

24. J.-M.Conia and P.Beslin, Bull.Soc.Chim.Fr., 1969, 483.

25. F.Leyendecker, G.Mandville and J.-M.Conia, ibid, 1970, 549.

26. R.D.Allan and R.J.Wells, Austr.J.Chem., 1970, 23, 1625.

27. B.Loev and M.M.Goodman, Progress in Separation and Purification, 1970, 3, 73,

28. V.M.Micovic and M.L.J.Mihailovic, J.Org.Chem., 1953, 18, 1190.

29. R.S.Brown and T.G.Traylor, J.Amer.Chem.Soc., 1973,

_25_, 8025.

30. N.H.Andersen and H.-S.Uh, <u>Synthetic Comm.</u>, 1973, _3_, 125.