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SYNTHESIS OF THROMBOXANE A_2 ANALOGUES

BY

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ABSTRACT

Synthesis of thromboxane A_2 analogues

by

Elizabeth H Evans

The aim of the project was to synthesize novel thromboxane A_2 analogues which would be potential thromboxane A_2 antagonists.

Three thromboxane A_2 analogues were synthesized, methyl 7-[-5-(3-hydroxy-1-(E)-octenyl)-2-methylbicyclo[3.3.1]non-2-en-9-yl]-[syn]-($\pm$)-5-(Z)-heptenoate, methyl 7-[-5-(3-hydroxy-1-(E)-octenyl)-2,2-dimethylbicyclo[3.3.1]non-9-yl]-[syn]-($\pm$)-5-(Z)-heptenoate and methyl 7-[-5-(3-hydroxy-1-(E)-octenyl)-2,2-dimethylbicyclo[3.2.1]oct-8-yl]-[syn]-($\pm$)-(Z)-heptenoate from a common functionalised bicycloalkane.

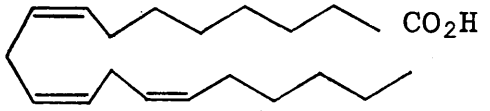
During the synthesis of these functionalised bicycloalkanes several unexpected products were observed. These included the formation of methyl 5-methyl-6-oxa-7-oxobicyclo[3.2.2]-nonanecarboxylate during the sulphuric acid catalysed cyclisation of methyl 2-oxo-1-(3'-oxobutyl)cyclopentane-carboxylate which was contrary to the work of W G Dauben and J W McFarland and the formation of ethyl 4-methyl-bicyclo[4.4.0]dec-4,6-dienecarboxylate from the treatment of ethyl 1-(3'-methylbut-2'-ene)-2oxocyclohexanecarboxylate with stannic chloride. Another interesting rearrangement reaction was the formation of methyl 2-methine-5-oxohexanoate as well as methyl 4-oxo-3-(3'-oxobutyl)-3-tetrahydrothio-phenecarboxylate during the Michael reaction of methyl vinyl ketone with methyl 4-oxo-3-tetrahydrothiophene-carboxylate. Methyl 2-(2-methylbut-3'-en-2-yl)-3-oxo-tetrahydrothiophenecarboxylate was also an unexpected product from the alkylation of methyl 3-oxo-tetrahydrothio-phenecarboxylate with 1-bromo-3-methylbut-2-ene.

CHAPTER 1

INTRODUCTION

1.1 ARACHIDONIC ACID CASCADE

The term eicosanoids introduced in 1979 [1] conveniently encompasses the widening number of biologically active compounds formed from carbon-20 unsaturated fatty acids [2], dihomo-γ-linolenic acid (eicosa-8,11,14-trienoic acid) (1), arachidonic acid (eicosa-5,8,11,14-tetraenoic acid) (2), and all-cis-eicosa-5,8,11,14,17-pentaenoic acid (3). The essential fatty acid, arachidonic acid (2) occupies a central position as precursor of the widest variety of eicosanoids.



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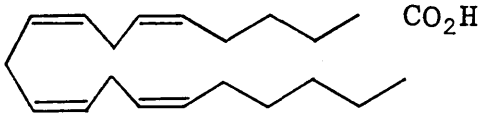

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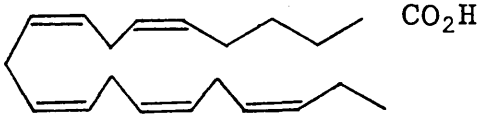
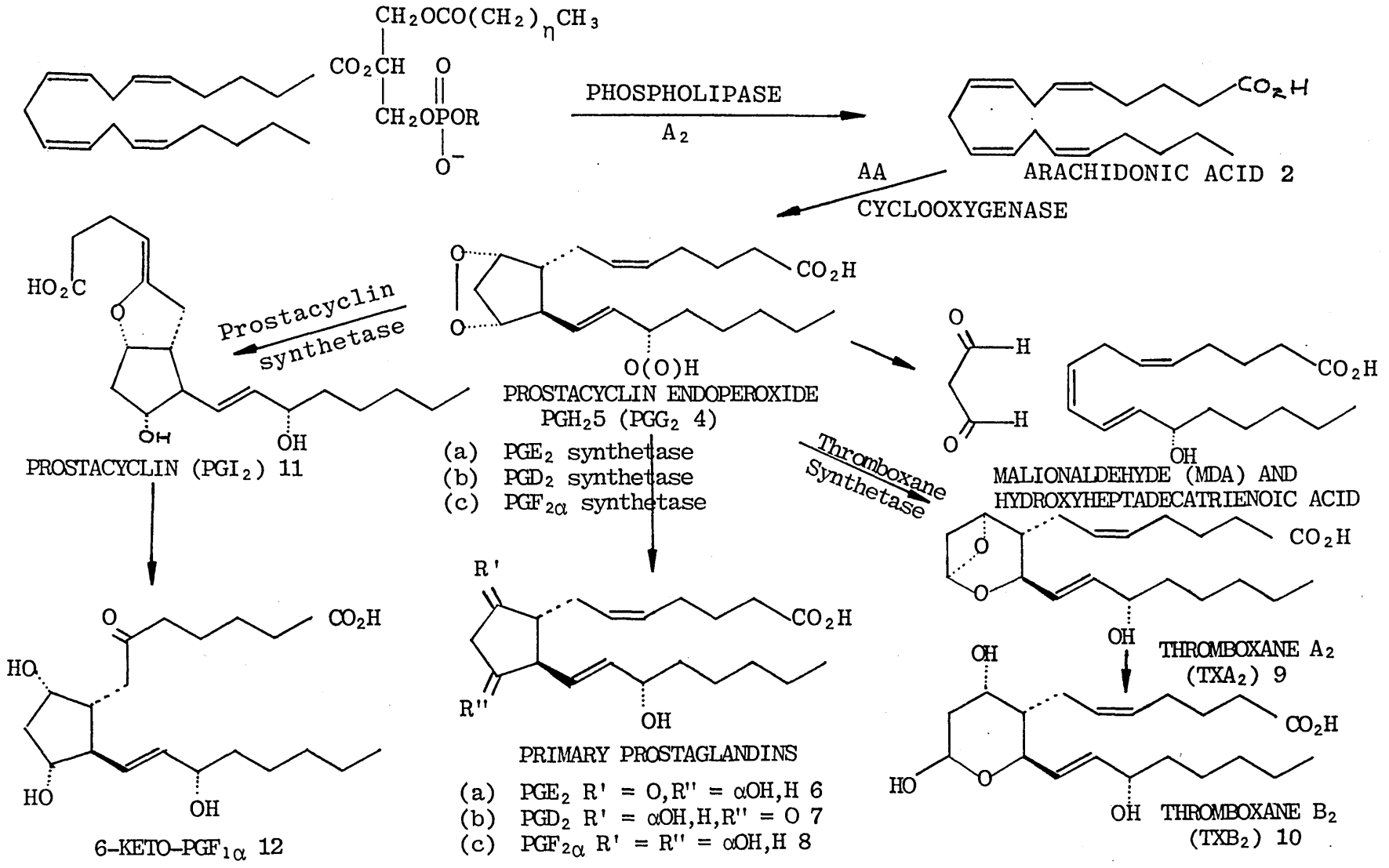


3

The cascade of compounds biosynthesized from arachidonic acid (2) in the presence of cyclooxygenase enzyme is illustrated in Scheme (1). [3]

SCHEME 1


CH2OCO(CH2)ηCH3
CO2CH
CH2OPOR
O−
PHOSPHOLIPASE
A2
CO2H
ARACHIDONIC ACID 2
AA
CYCLOOXYGENASE
HO2C
Prostacyclin
synthetase
OH
OH
PROSTACYCLIN (PGI2) 11
CO2H
O(O)H
PROSTACYCLIN ENDOPEROXIDE
PGH25 (PGG2 4)
(a) PGE2 synthetase
(b) PGD2 synthetase
(c) PGF2α synthetase
H
H
CO2H
OH
MALIONALDEHYDE (MDA) AND
HYDROXYHEPTADECATRIENOIC ACID
Thromboxane
Synthetase
CO2H
OH
THROMBOXANE A2
(TXA2) 9
HO
HO
OH
6-KETO-PGF1α 12
R'
R''
CO2H
OH
PRIMARY PROSTAGLANDINS
(a) PGE2 R' = O,R'' = αOH,H 6
(b) PGD2 R' = αOH,H,R'' = O 7
(c) PGF2α R' = R'' = αOH,H 8
OH
CO2H
HO
OH
THROMBOXANE B2
(TXB2) 10

The prostaglandins are the oldest members of the family discovered in the early 1930's [4] in human seminal plasma and eventually purified and structurally identified some 30 years later. [5] In recent years, a powerful stimulus for research has been the discovery of short-lived very potent metabolites such as thromboxane A_2 (TXA_2), [6] prostacyclin I_2 (PGI_2) [7] and another group of eicosanoids named leukotrienes. [8]

There is no evidence that eicosanoids are stored in the body and it is likely that these compounds are synthesized "on demand" following a variety of mechanical, hormonal, chemical or immunological stimuli. It has been found that 95% of arachidonic acid in any organ is bound in the membrane phospholipids. The first obligatory step in eicosanoid formation must therefore be hydrolysis of these phospholipids by phospholipase A_2 [9] to release free arachidonic acid. Once released from the cell membrane arachidonic acid is rapidly oxygenated by molecular oxygen in the presence of cyclooxygenase enzyme to yield unstable endoperoxides [10] called PGG_2 (4) [11][12] and PGH_2 (5) [11][13]. Despite their considerable biological activity, endoperoxides are now believed to be simply percursors for even more active and less stable eicosanoids.

The action of isomerase enzymes on PGH_2 (5) leads to PGE_2 (6) and PGD_2 (7) whereas a reductase gives $PGF_{2\alpha}$ (8). These are termed the classical prostaglandins. They have been studied for the last 50 years and have a wide

distribution throughout the animal kingdom. They affect gastrointestinal, reproductive, respiratory and vascular smooth muscle. They modulate the activity of other hormones in regulating autonomic neurotransmitters, inflammation and in maintaining renal flow. [14]

The endoperoxides are also converted enzymatically by platelets and certain other tissues into thromboxane A_2 (TXA_2) (9). Thromboxane A_2 [6] is a highly unstable substance ($t_{\frac{1}{2}}$ = 32 secs) with potent thrombotic and vasoconstricting properties. It is much more potent in this respect than the classical prostaglandins. Thromboxane A_2 undergoes spontaneous breakdown to stable thromboxane B_2 (TXB_2) (10) which exhibits only very weak biological activity.

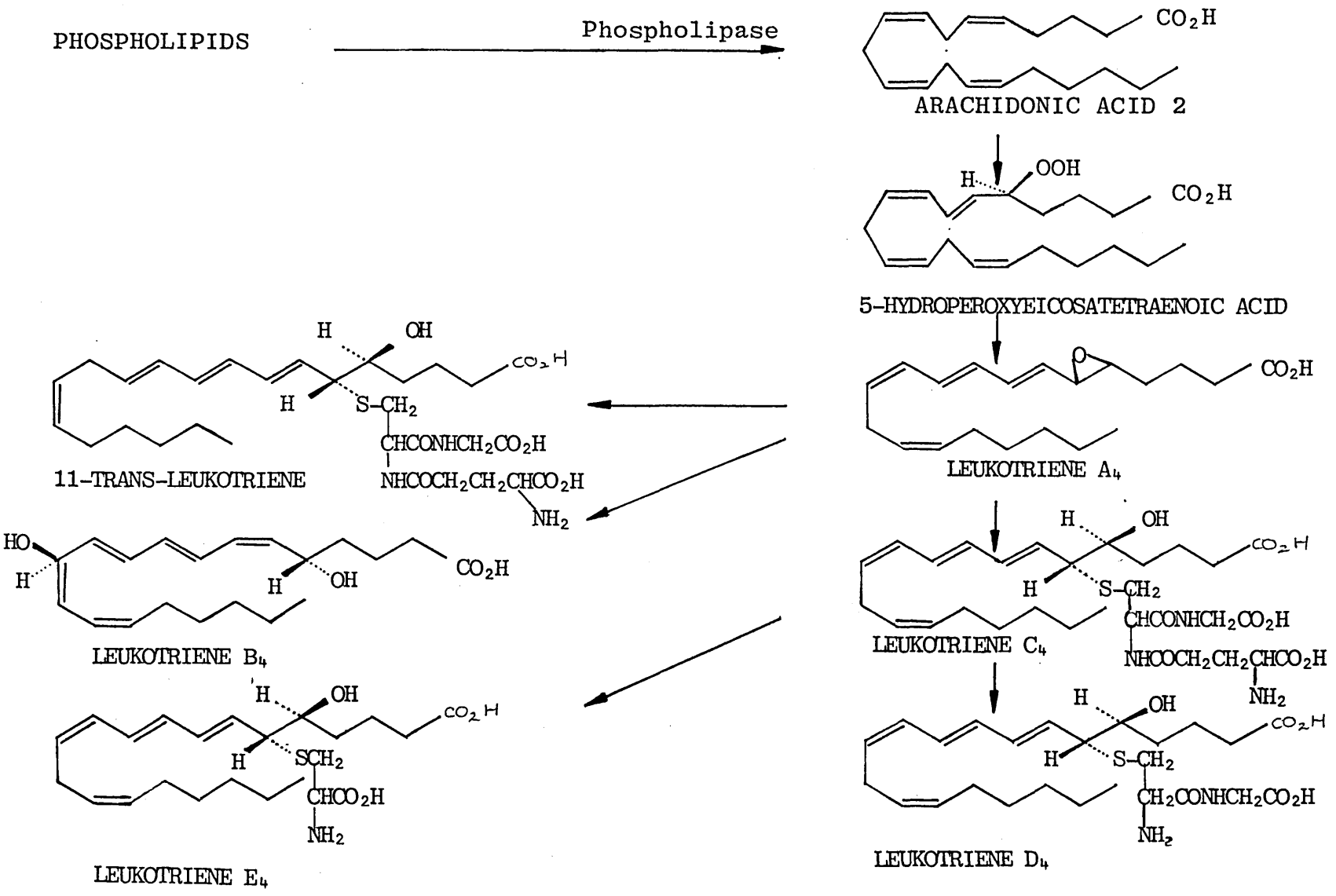
The biological profile of TXA_2 is opposite to that of prostacyclin, [7] (PGI_2) (11), a substance also derived from PGH_2 (4). Prostacyclin (11) relaxes smooth muscle both in vivo and in vitro and is the most potent inhibitor of platelet aggregation yet discovered. Like thomboxane A_2, prostacyclin is chemically unstable and is spontaneously broken down to 6-keto-$PGF_{1\alpha}$ (12).

The biological opposing effects of thromboxane A_2 (9) and prostacyclin (11) are of crucial importance to normal health and an imbalance in their production may lead to disorders such as abnormal blood pressure, artherosclerosis, stroke and heart attack.

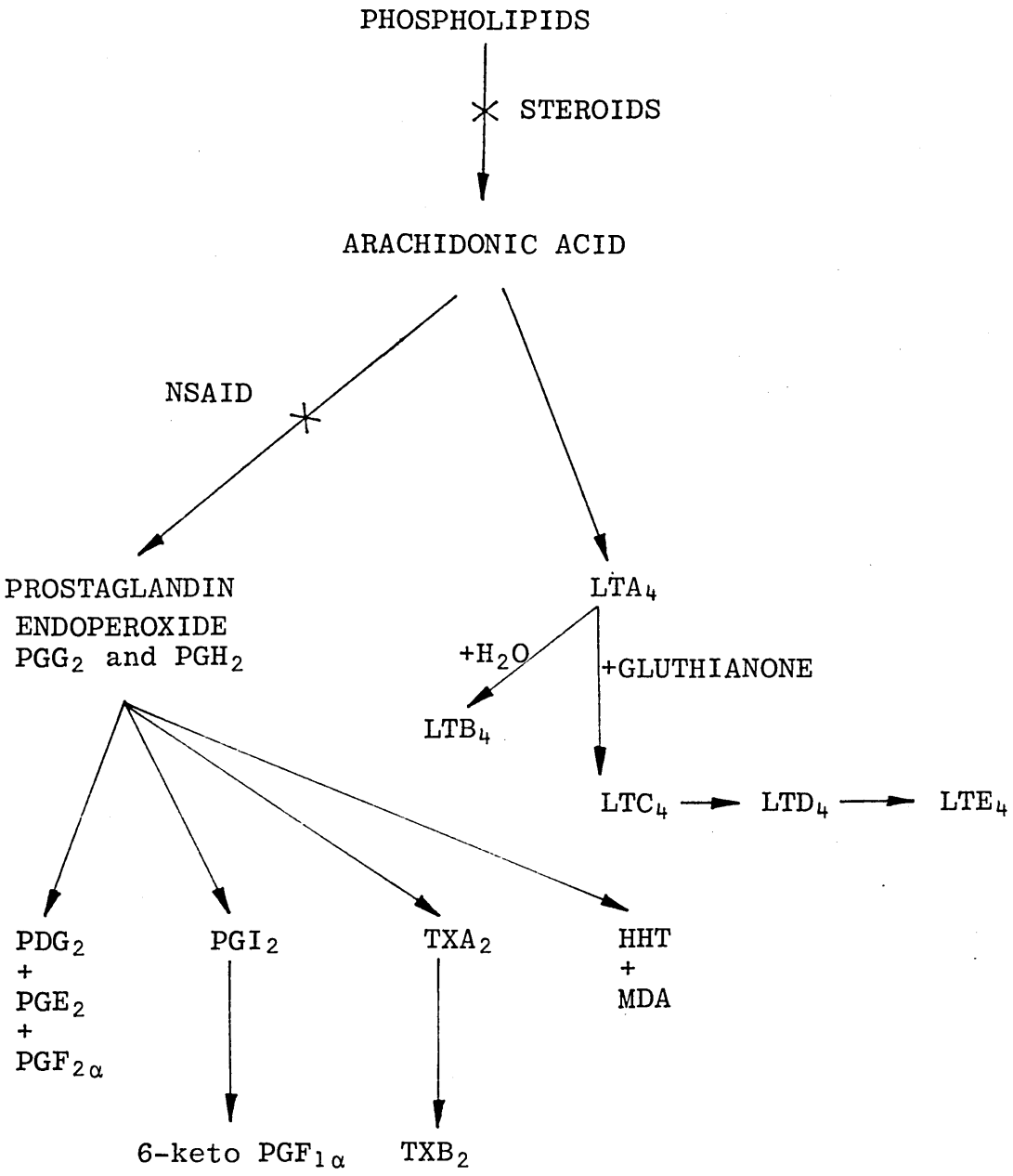
The most recent addition to the arachidonic acid peroxidation pathway has been the leukotrienes [8]. Unlike the previously mentioned metabolites of arachidonic acid, the leukotrienes are not derived from the cyclooxygenase conversion of arachidonic acid to endoperoxide (PGH_2) (5) but rather from the lipoxygenase path of metabolism. This alternative biosynthetic route (Scheme 2) may explain the presence of several unique structural features (amino acids, epoxides). This class of eicosanoids are thought to be important as mediators in such host defence mechanisms as immediate hypersensitivity reactions and acute inflammatory reactions.

The biochemical interrelationships between the cyclooxygenase pathway (yielding prostaglandins and thromboxanes) and the leukotriene pathway is illustrated in Scheme (3). Anti-inflammatory steroids prevent the release of the precursor arachidonic acid, [15] whereas cyclooxygenase inhibitors such as aspirin block the transformation of this acid into prostaglandins and thromboxanes. [16] It has recently been proposed that anti-inflammatory steroids act by stimulating the synthesis of an inhibitor of phospholipase A_2. By inhibiting the release of arachidonic acid, steroids prevent formation of not only prostaglandins and thromboxanes but also leukotrienes and other oxygenated derivatives. The inhibition of leukotriene formation might be responsible for some of the therapeutic effects

SCHEME 2


PHOSPHOLIPIDS
Phospholipase
ARACHIDONIC ACID 2
5-HYDROPEROXYEICOSATETRAENOIC ACID
LEUKOTRIENE A4
11-TRANS-LEUKOTRIENE
LEUKOTRIENE B4
LEUKOTRIENE C4
LEUKOTRIENE D4
LEUKOTRIENE E4

SCHEME 3



NSAID = Non steroidal anti-inflammatory drugs

of the steroids which are not shared by aspirin type drugs.

It is evident that arachidonic acid has a central role as a precursor of biologically active compounds. The increased knowledge about the biochemistry of the arachidonic acid derived mediators seems to offer many new possibilities of exploring the role of this system in physiological and pathophysiological processes.

1.2 RELATIONSHIP BETWEEN THROMBOXANE A_2 AND PROSTACYCLIN

The most active area of prostaglandin research at present concerns prostacyclin PGI_2 (11) and thromboxane A_2 TXA_2 (9). They have an important physiological role in normal haemostasis, i.e. the tonus of blood vessels and the aggregation of platelets. Prostacyclin inhibits platelet aggregation by stimulating adenylate cyclase and thus increasing the intracellular concentration of cyclic-3',5'-adenosine monophosphate (cAMP). [17] Prostaglandin endoperoxides (4 and 5) and thromboxane A_2 (9) produce platelet aggregation and reduce a raised platelet cAMP concentration. It would seem that the balance between cAMP inhibiting activity of the thromboxane system and the cAMP stimulating activity of prostacyclin controls human platelet aggregation. [18] [19]

Prostacyclin generated locally at the blood vessel wall or alternatively circulating freely in the blood stream may protect the vessel wall against deposition of

platelets. [20] Such a mechanism may explain the inability of platelets to adhere to healthy blood vessel walls. Damage to the vessel wall would be expected to reduce prostacyclin formation in the affected region allowing thromboxane A_2 synthesis and aggregation to proceed unchecked. The continued formation of prostacyclin by adjacent healthy parts of the vessel wall prevent the thrombus from spreading either up or down the vessel wall or from occluding the vessel entirely.

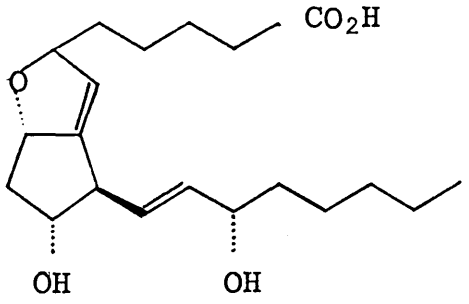
The balance between prostacyclin PGI_2 and thromboxane A_2 is important to normal health. A disturbance in this balance towards platelet aggregation may be a factor in thrombotic disease. [21][22]

Increased platelet aggregation is observed in many clinical conditions including arteriosclerosis, hypertension, angina, diabetes mellitus and following myocardial infarction. In each of these conditions, there is evidence for increased platelet thromboxane A_2 and/or reduced vascular PGI_2 formation. For example, prostacyclin production by the heart and blood vessels of rabbits made artherosclerotic by a fat-rich diet is considerably reduced compared with tissue from normal healthy animals. [23] Human artherosclerotic blood vessels similarly make only very small amounts of prostacyclin. Both lipid peroxides and low density lipoprotein are potent inhibitors of vascular

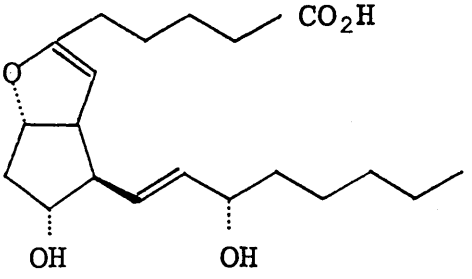
prostacyclin PGI_2 [24][25] (11) formation and are found in high concentrations in artherosclerotic plagues and plasma respectively. [26][27] These biochemical changes may therefore underlie the deficiency in prostacyclin production in this disease. In addition, platelets from rabbits with artherosclerosis exhibit increased sensitivity to aggregating agents and in the process generate more thromboxane A_2 when compared with those from healthy, artherosclerosis-free animals. Increased platelet thromboxane A_2 production has also been demonstrated in patients with hypertension, Prinzmetal's angina, thrombocytopaenic purpura and in those who have survived myocardial infarction. All of these diseases are associated with elevated platelet reactivity. Thus, it seems that diseases which predispose to thrombosis are associated with a swing of the normal TXA_2/PGI_2 balance in favour of aggregation. Conversely, patients suffering from uraemia exhibit reduced platelet TXA_2 and increased vascular PGI_2 formation. [28] Uraemia is associated with platelet hypoaggregability and increased bleeding tendency. Experiments carried out on patients with various thrombotic diseases do support the concept of a TXA_2/PGI_2 balance and highlights its importance for regulating platelet formation in vivo.

Therefore, it would seem that drugs which prevent TXA_2 or increase PGI_2 production may well have great clinical potential for the treatment of thrombosis.

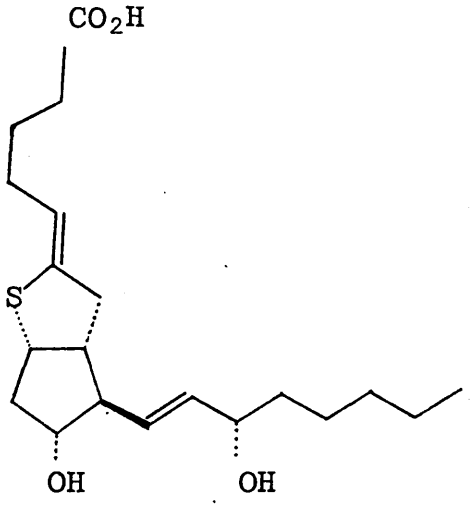
A large number of prostacyclins have already been synthesized in the search for stable, therapeutically useful mimics. In most of these analogues, the readily hydrolysed enol-ether grouping of prostacyclin has been replaced or stabilised. [29] A few examples are given below.



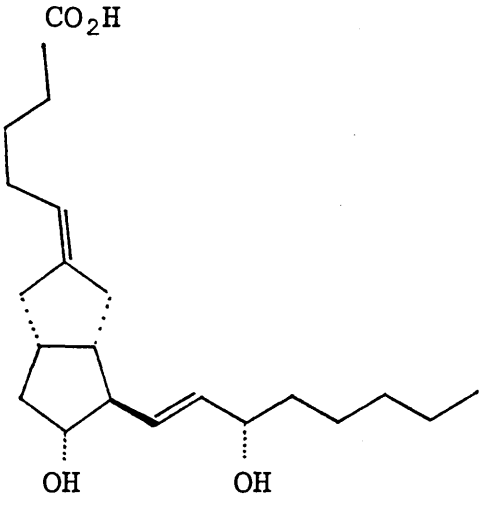
Ref [30]



Ref [31]



Ref [32]



Ref [33]

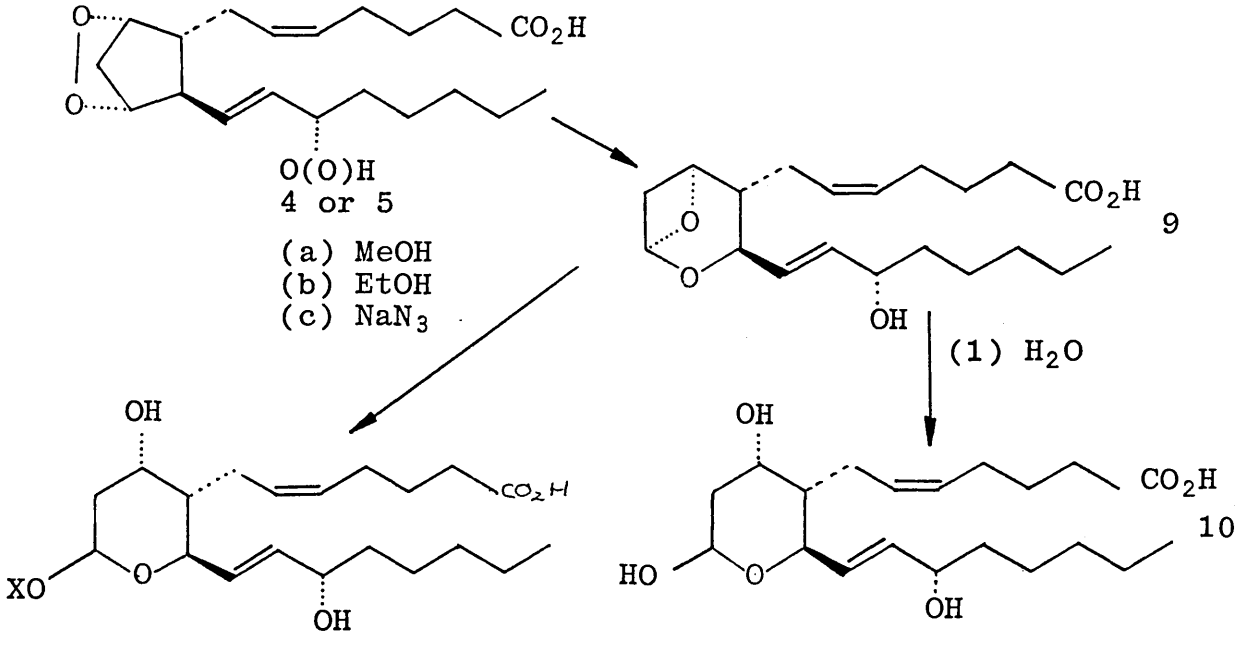
In contrast to the prostacyclin area, however, thromboxane A_2 analogues have been rare and started to appear only recently.

1.3 THROMBOXANE A_2 AND ITS SYNTHETIC ANALOGUES

Thromboxane A_2 has a short biological half-life, it has only been obtained as a biological extract and has not yet been isolated and characterised. Samuelsson's group first showed that incubation of endoperoxides (4) and (5) with human platelets gave rise to several products. [34] The most important of these was thromboxane A_2 which was rapidly hydrolysed to thromboxane B_2.

The proposed bicyclic acetal structure was consistent with the labile nature of the compound and with the fact that hydrolysis gave the hemiacetal TXB_2. Additional proof was obtained by generating thromboxane A_2 in the presence of various nucleophiles. [35] (Scheme 4)

Scheme 4



Reagents (a) MeOH Product X = OMe
(b) EtOH Product X = OEt
(c) NaN_3 Product X = N_3

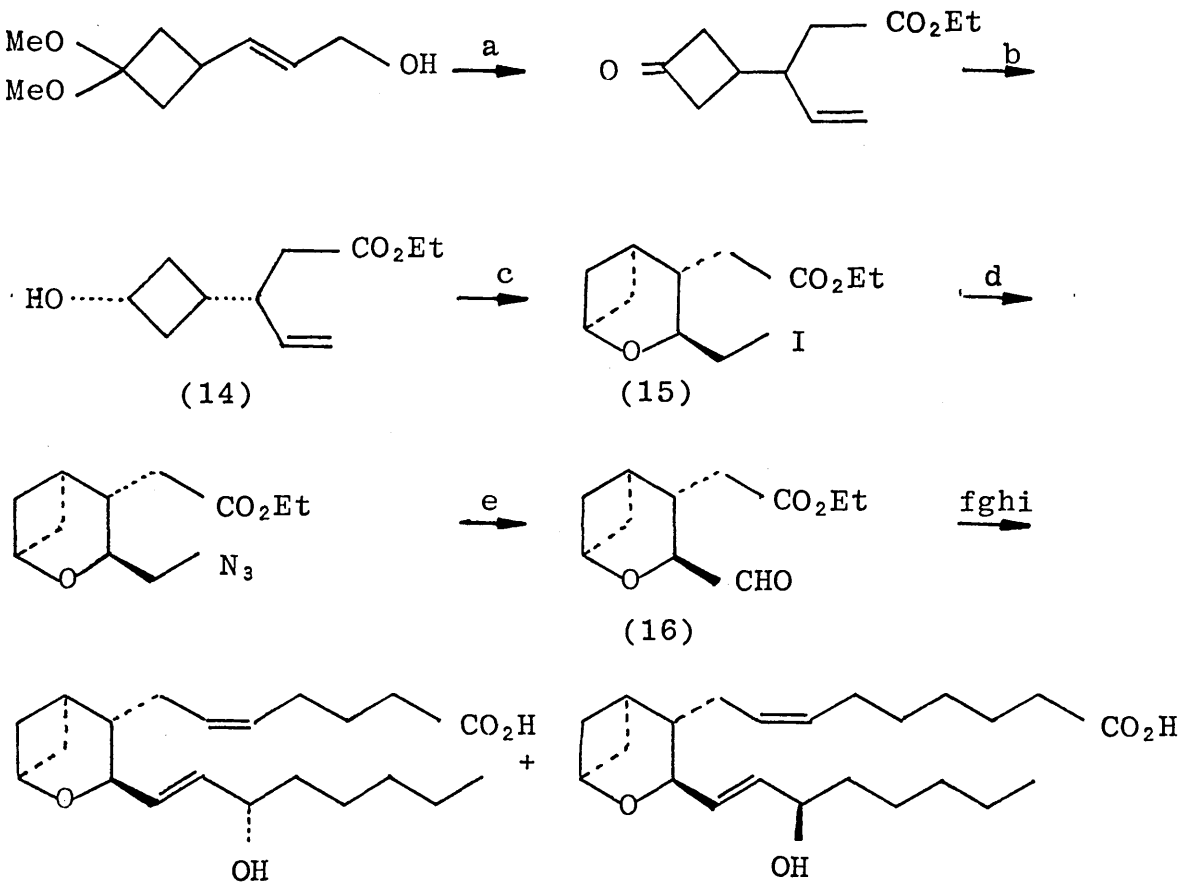
The products were in accord with nucleophilic attack occurring at the acetal carbon leading to the opening of the strained oxetane ring. Mechanistic considerations and and radio-labelling experiments [35][36] are also in agreement with TXA_2, being the bicyclic acetal (9) but this structural assignment must be regarded as tentative until a full characterisation has been carried out.

As previously mentioned, stable analogues of thromboxane A_2 are of use in biological investigations to evaluate the role of the parent molecule and also may prove to be of therapeutic value. A stable TXA_2 antagonist would have potential applications in the treatment of thrombosis and related cardiovascular diseases.

The most logical analogues for scrutiny are obviously those which are closest structurally but also stable, for example those in which one of the oxygens in the bicyclic network is replaced by another atom.

Corey [37] has been successful in the synthesis of a stable analogue (13) of thromboxane A_2 (9) with methylene replacing the 9,11 bridging oxygen, (Scheme 5). The key step in this synthesis is the stereospecific intramolecular cyclisation of (14) to (15). Treatment with iodine under a variety of conditions failed to produce (15), and intramolecular oxymercuration using standard reagents also failed. However, oxymercuration of (14) was achieved with mercuric trifluoroacetate when benzene was employed as solvent, and subsequent replacement of mercury by iodine gave the iodo-ether (15). Molecular models indicated that cyclisation should preferentially lead to the product in

SCHEME 5



Reagents

(a) *$(EtO)_3CMe$, $EtCO_2H$ 142°C then IM HCl (ca 74%)*

(b) *$NaBH_4$, EtOH, -60°C (96%)*

(c) *$Hg(OCOCF_3)_2$, benzene, 23°C then I_2 (40%)*

(d) *NaN_3, DMF, 100°C (80%)*

(e) *FSO_3Me, 23°C*

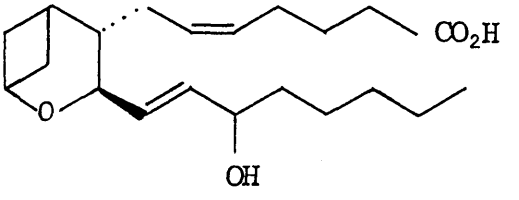
(f) *$(MeO)_2P(O)\bar{C}HC(O)C_5H_{11}Na^+$*

(g) *$Zn(BH_4)_2$, DME, 23°C*

(h) *Bu^i_2AlH*

(i) *$Ph_3P{=}CH(CH_2)_3CO_2Na$, DMSO*

which the side chains are in a trans relationship and this was confirmed when the aldehyde (16), prepared from (15) in two steps, was found not to undergo epimerisation on treatment with base.

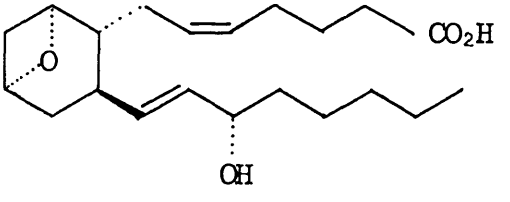


13

13a 15α OH 13b 15β OH

Both components (13a) and (13b) are reported to show interesting biological properties. The OH is designated the 15 position in direct comparison with the classical prostaglandins.

11a carba thromboxane A_2 (17), the other ether analogue of thromboxane A_2 was synthesized from PGA_2 in twelve steps by Bundy. [38]



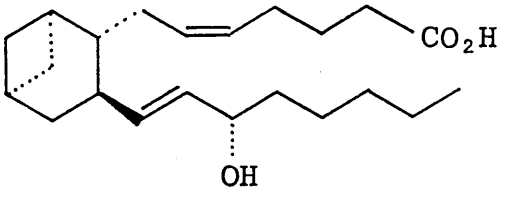
17

The analogue (17) inhibits the aggregation of human platelets.

Carbocyclic thromboxane A_2 (18) and its C-15 epimer are stable at ambient temperature in solution and have been

successfully synthesized by three independent groups. [38][40][41] In 1979, Hayashi [39] et al published the synthesis shown in Scheme (6). The bicyclic ketone (19) was prepared by a modification of a literature procedure and then annulated to give the enone (20). Lithium in ammonia reduction followed by Jones oxidation gave predominantly the trans-fused bicyclic ketone (21). Conversion into the alternative enone (22) followed by glycol formation and oxidative cleavage with lead tetraacetate gave the aldehyde ester (23). The synthesis was completed using standard conditions.

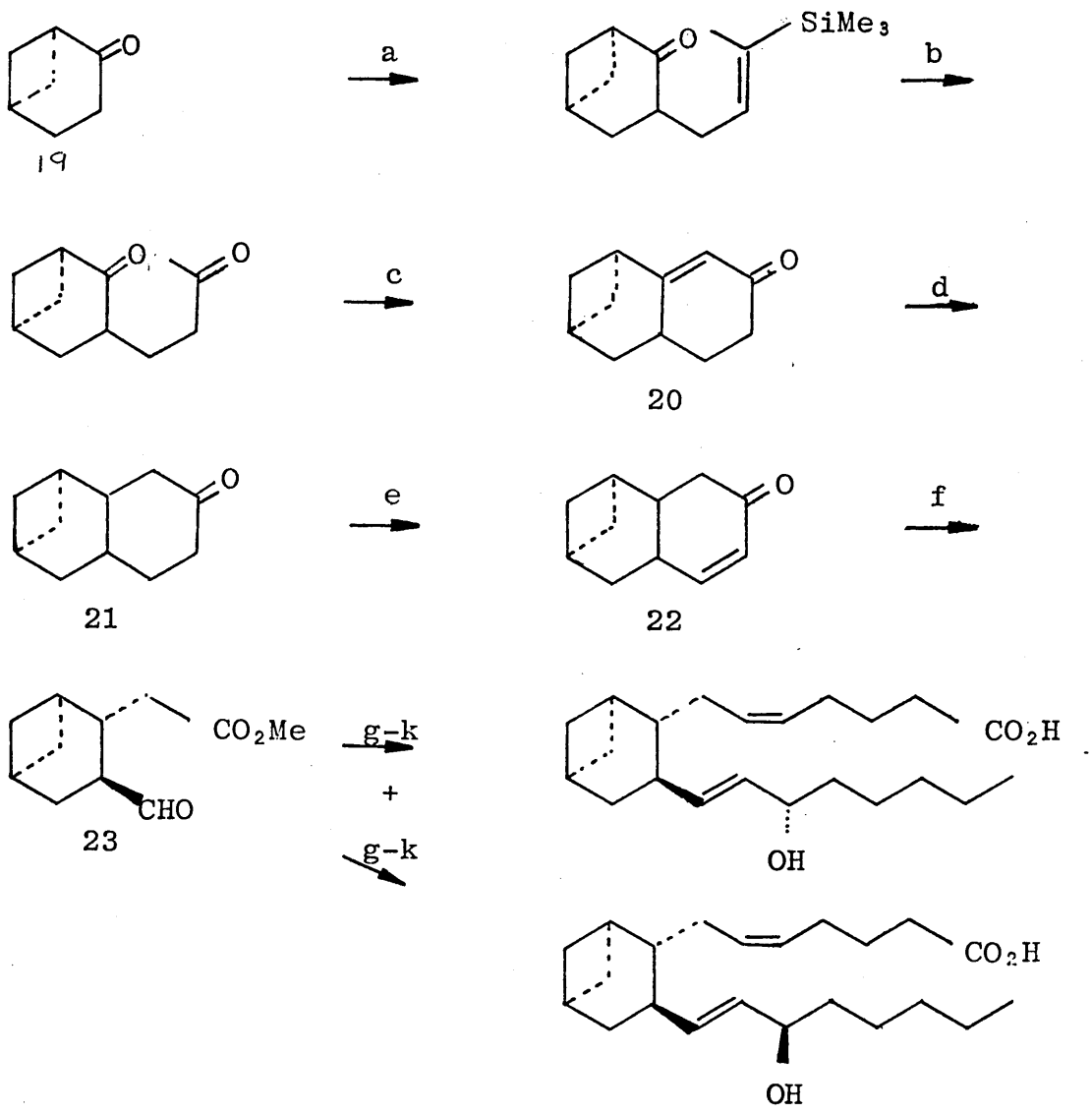
A shorter synthesis of the carbocyclic thromboxane (18) (Scheme 7) was published by Nicolaou's group. [40] The key step in the synthesis was the organocupiate conjugate addition to the α,β unsaturated aldehyde (24). Conjugate addition gave a mixture of products, with both cis and trans relationship between the side chains. However, equilibration with base led to the thermodynamically most stable trans product (25) which was readily homologated to give the aldehyde (26).



18

The carbocycle analogue exhibited extremely potent vasoconstricting activity mimicking TXA_2 in this regard. However, it behaved as a potent TXA_2 antagonist, rather

SCHEME 6



Reagents

(a) *LDA (2 equiv), THF, -78°C then $ICH_2CH=C(Me)SiMe_3$ (48%)*

(b) *MCPA (1.5 equiv), CH_2Cl_2 then HCO_2H (87%)*

(c) *10% aq KOH, MeOH (85%)*

(d) *Li-NH_3(liq) - Bu^tOH, then Jones oxidation (51%)*

(e) *$Ph_3\overset{+}{P}CH_2CH_2CO_2H\,Br_3^-$, THF, 0°C 30 min then LiBr, Li_2CO_3, DMF, 125°C 1 hour (53%)*

(f) *OsO_4, pyridine, 25°, 2 hr, then $NaHSO_3$, then $Pb(OAc)_4$ (3 equiv) in MeOH-benzene (62%)*

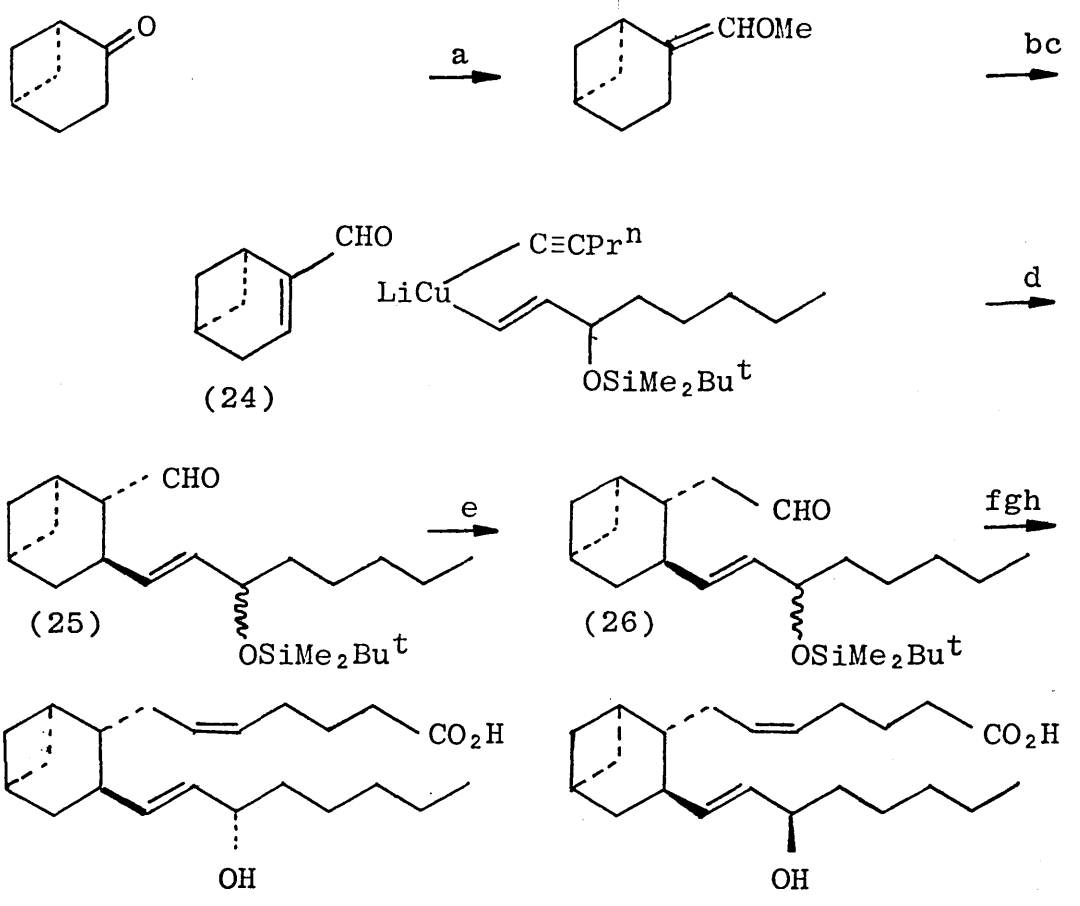
(g) *$Bu_3P=CHCOC_5H_{11}$, ether, then $NaBH_4$, MeOH (80%)*

(h) *DHP then $Bu^i{}_2AlH_4$, then SO_3 pyridine, Et_3N, DMSO (84%)*

(i) *$Ph_3P\,CH(CH_2)_3CO_2Na$, DMSO, then CH_2N_2 (83%)*

(j) *H^+, chromatography, then 5% aq NaOH, MeOH (60% α-epimer, 40% β-epimer)*

SCHEME 7



Reagents

(a) *$Ph_3PCHOMe$, THF - toluene, 0^oC*

(b) *PhSeCl (excess), K_2CO_3, CH_2Cl_2 - toluene, -78^oC*

(c) *MCPBA, CH_2Cl_2, -78^oC then $Pr^n{}_2NH$ (55% a + b + c)*

(d) *ether, -78^oC (53%)*

(e) *$Ph_3PCHOMe$, toluene - THF, 0^oC then $Hg(OAc)_2$ H_2O - THF, 25^oC then 7% aq KI (79%)*

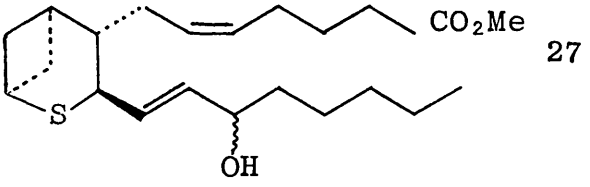
(f) *$Ph_3PCH(CH_2)_3CO_2Na$ DMSO, 25^oC then CH_2N_2, 0^oC (74%)*

(g) *AcOH-THF-H_2O (3:2:2), 45^oC then chromatography (65%, α-epimer, 33%, β-epimer)*

(h) *IM LiOH, THF-H_2O (95-97%)*

than an agonist on platelet aggregation. Furthermore, CTA_2 (18) selectively inhibited the biosynthesis of thromboxane without comprising PGI_2 production. This dual antagonist-agonist activity strongly suggests that the TXA_2 receptors on platelets and blood vessels are of different sub-classes.

Both the TXA_2 analogues (27) and (28) in which the two oxygens are replaced by a methylene and sulphur atom have been synthesized by Hayashi and his colleagues for the Ono pharmaceutical company. [42][43]

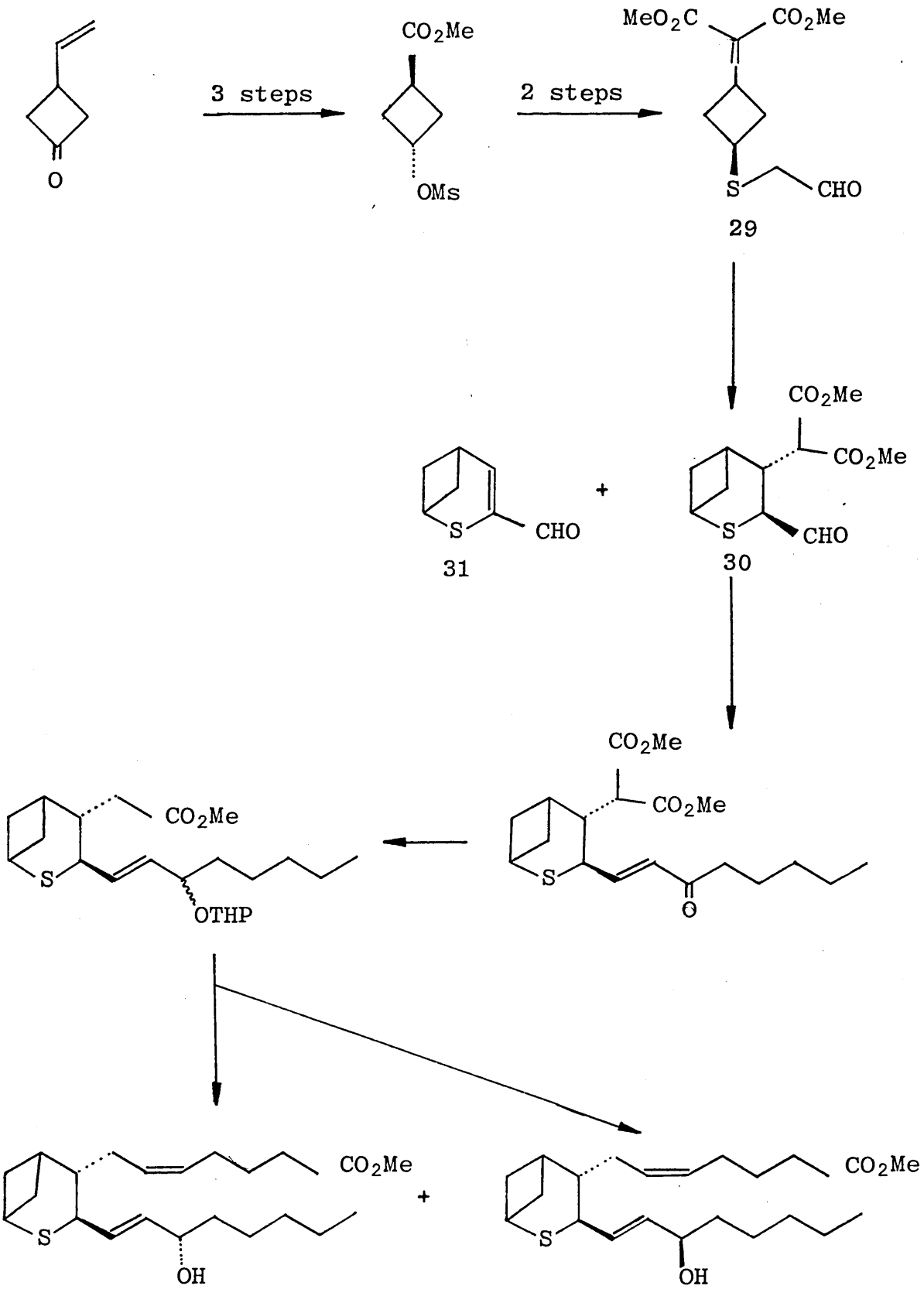


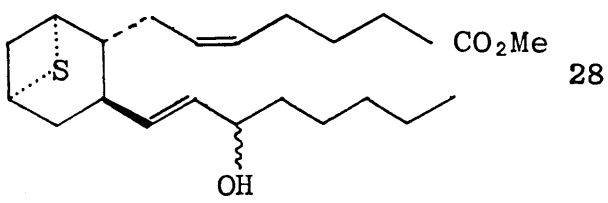
27

Both the C-15 epimers of (27) showed moderate contractile activities. However, neither compound showed aggregation activity. The synthesis is shown in Scheme (8). The crucial step was the intramolecular Michael reaction of the aldehyde. This cyclisation was unsuccessful under several conditions. However, stirring of (29) with a catalytic amount of pyrrolidin-AcOH (2:3) in benzene at room temperature gave the bicyclic compound (30) in 36% yield, together with the compound (31) in 14% yield.

The other methylene-sulphur analogue (28) shows more interesting biological activity. [43]

SCHEME 8


3 steps
2 steps
CO_2Me
OMs
MeO_2C
CO_2Me
S
CHO
29
CO_2Me
CO_2Me
S
CHO
31
+
CO_2Me
CO_2Me
S
CHO
30
CO_2Me
CO_2Me
S
O
CO_2Me
S
OTHP
CO_2Me
S
OH
+
CO_2Me
S
OH



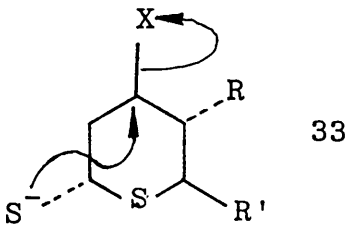
28

28a 15α OH

28b 15β OH

Both compounds (28a) and (28b) showed potent contractile activities. Additionally (28a) induced the aggregation of human-platelets.

The two oxygens in the bicyclic framework of TXA_2 have been replaced by two sulphur atoms to give an analogue (32) which has potent agonist activity. [44] The most difficult problem in the synthesis was construction of the 2,6-dithiabicyclo[3.1]heptane skeleton. Two possible intermediates (33) and (34) were the obvious precursors of the desired framework.



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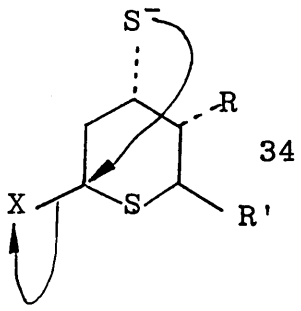
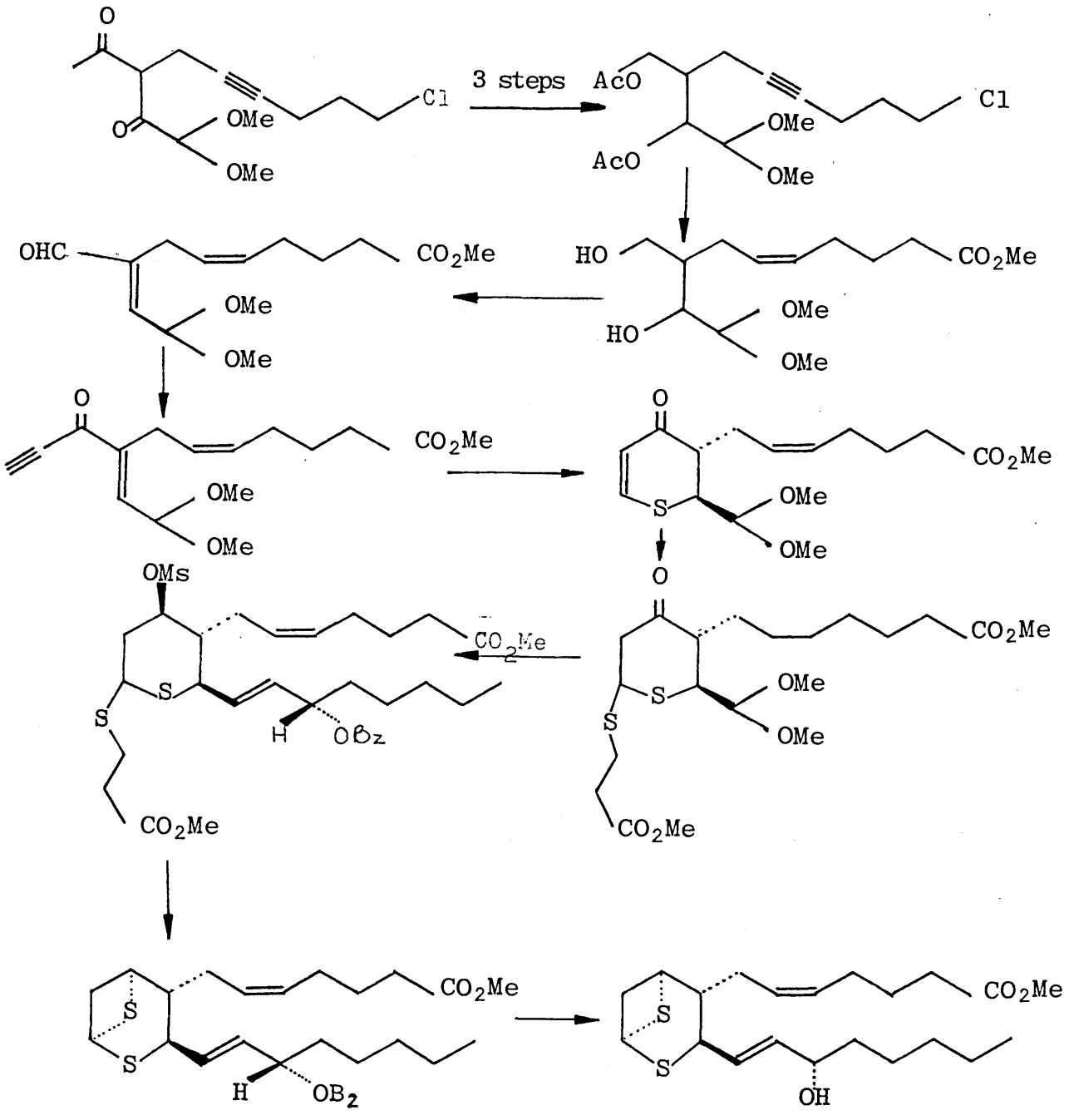


34

After model experiments, it was found to be easy to control stereochemistry of the substituents on the six membered ring, starting from the intermediate (34). The synthesis is shown in Scheme (9) and was designed such that the two sulphur atoms were introduced into the system

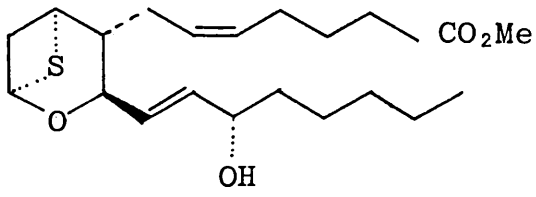
SCHEME 9



32

by different conjugate addition reactions.

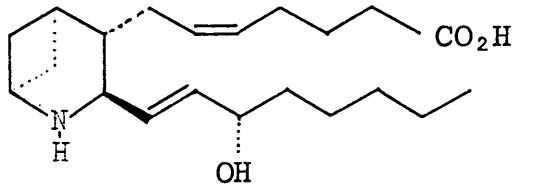
The synthesis of the analogue (35) in which the oxygen in the oxetane ring of TXA_2 has been replaced by sulphur has been accomplished. [45]



35

Preliminary experiments show that analogue (35) possesses potent biological activity.

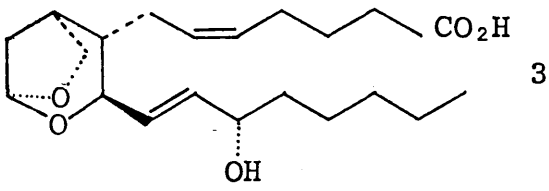
A synthesis of nitrogen containing thromboxane A_2 analogue (36) has been published. [46]



36

The analogue (36) shows contractile activity but shows no aggregation effect.

The synthesis of a stable, chiral analogue of TXA_2 (37) as well as a positional isomer (38), in which the labile oxetane ring of TXA_2 is replaced by a stable tetrahydrofuran moiety have been prepared by a group at Pfizer using conventional procedures. [47]



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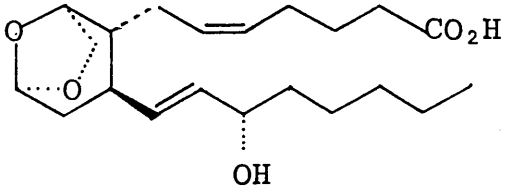
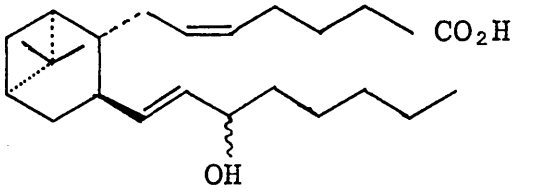


38

Initial pharmacological evaluation indicates that analogue (37) exhibits agonist activity.

A commercially available pinane derivative was elaborated to give the thromboxane analogue (39).

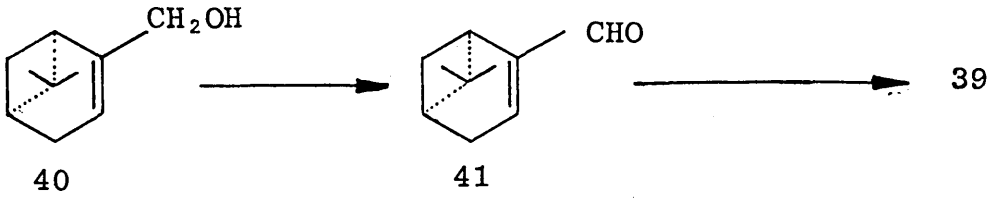


39

39a 15α OH

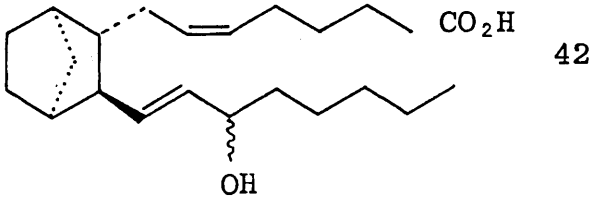
39b 15β OH

Nicolaou's group [48] and a group from May and Baker [49] reported the synthesis of this analogue (39). Nicolaou prepared the α,β unsaturated aldehyde (41) by manganese dioxide oxidation of commercially available (-)-myrtenol (40), and using the sequence of reactions already shown in Scheme (7) went on to prepared pinane-TXA_2 (39) and its 15β epimer.



Both C-15 epimers of (39) showed activity as thromboxane A_2 antagonists. (39) has been found to be an antagonist with respect to vasoconstriction and platelet aggregation. It inhibits thromboxane synthetase without comprising prostacyclin synthetase. It has been suggested that analogue (39a) has a suitable biochemical profile for use as an antithrombotic agent.

Other miscellaneous thromboxane A_2 analogues include the carbocyclic analogue (42) which was prepared by a simple synthetic route from ($\pm$) norcamphor. [50]

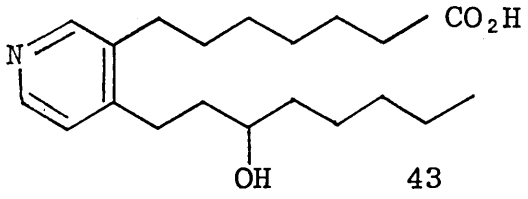


42

The individual C-15 epimers of (42) were separated and were found to be only weak inhibitors of platelet aggregation and TXA_2 synthetase.

It has been known for a long time that imidazole and pyridine are weak inhibitors of thromboxane A_2 biosynthesis, [51] perhaps because they are capable of binding to a proton donor associated with a catalytic

site. Many monosubstituted imidazoles and pyridines have been tested as thromboxane A_2 biosynthesis inhibitors, [52] some of which show interesting activity. In view of this biological activity, Corey decided to synthesize and test the pyridine prostanoids (43), (44) and (45). [53]



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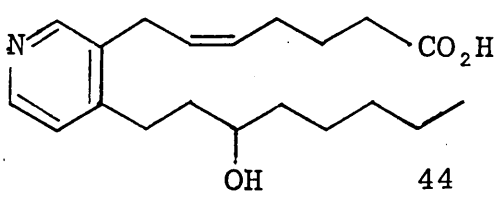
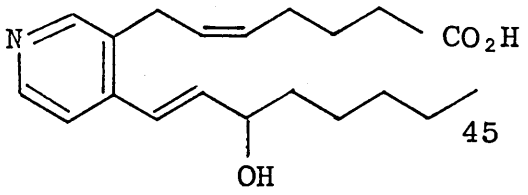


44



45

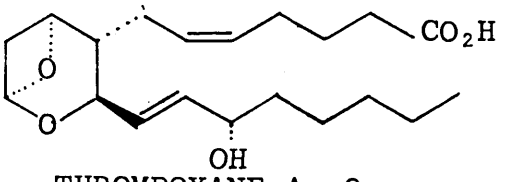
All three pyridine prostanoids (43), (44) and (45) showed inhibition of thromboxane A_2 biosynthesis, the pyridine prostanoids (43) and (44) being most potent in this regard.

The analogues mentioned are summarised in Scheme (10).

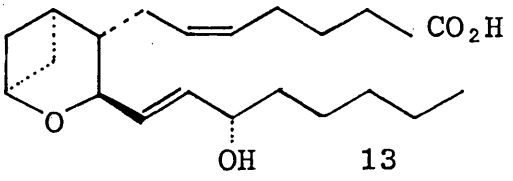
1.4 SYNTHETIC PROGRAMME

The pinane derivative (39) was of particular interest to us because of its biological profile. [48][54] We aimed to synthesize compounds in which the 6-membered carbocyclic ring and the bridging gem-dimethyl was varied. We then hoped to gain information about the nature of the receptor such as whether it required a suitable cyclic material which had a lipophilic group (in the case of (39) CMe_2) bridging the α-face of the ring.

SCHEME 10



THROMBOXANE A_2 9



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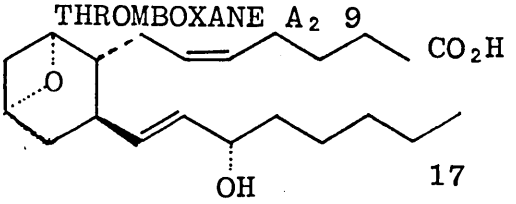

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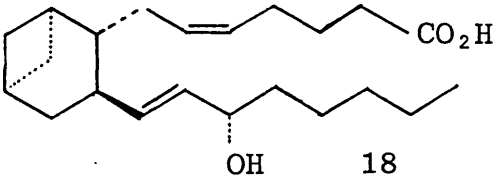

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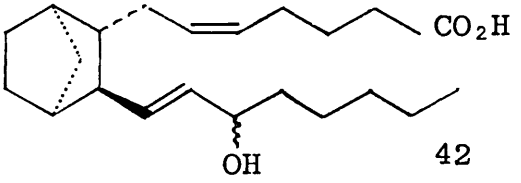

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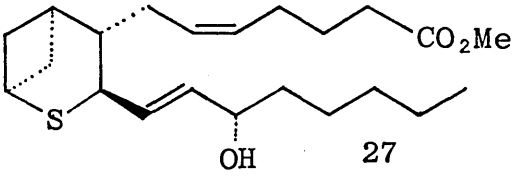

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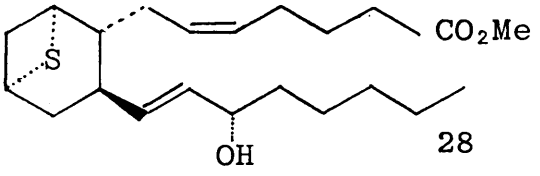

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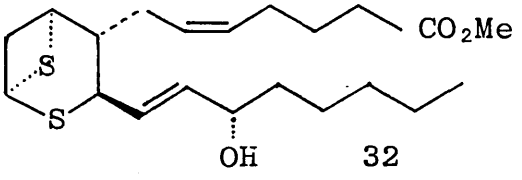

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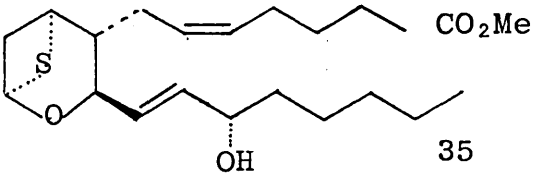

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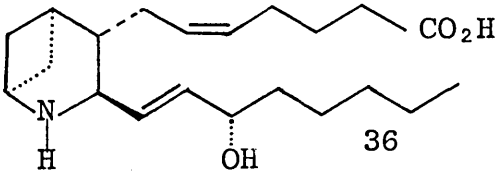

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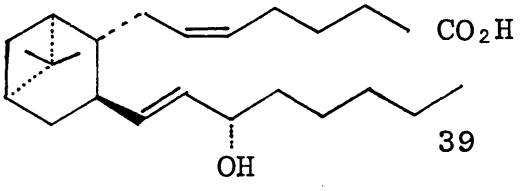

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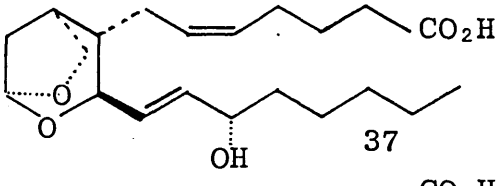

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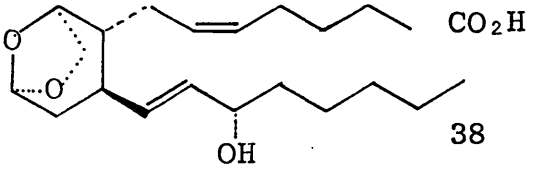

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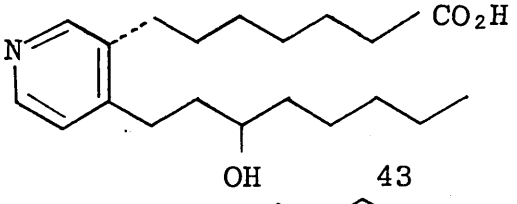

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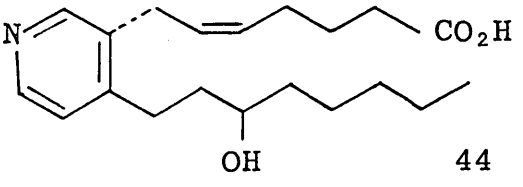

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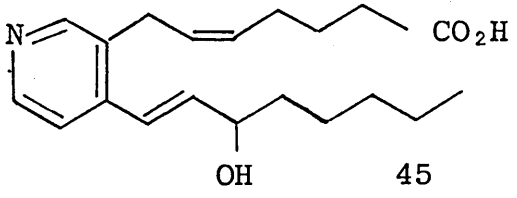
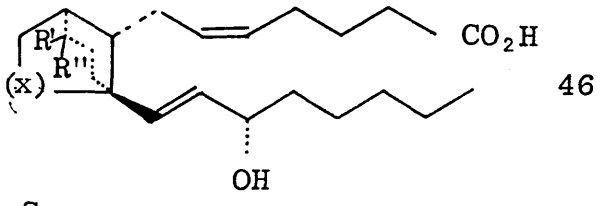


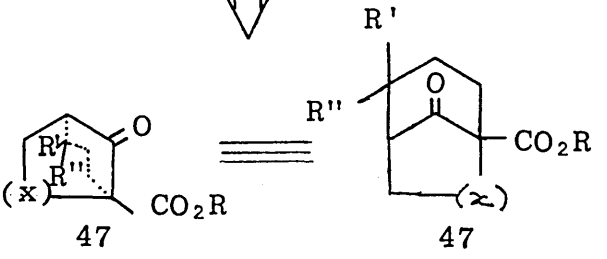
45

Initial interest was focused on compounds of the type (46). These compounds would be derived from the bicyclic ketoesters (47), key intermediates in the proposed synthetic pathway Scheme 11.



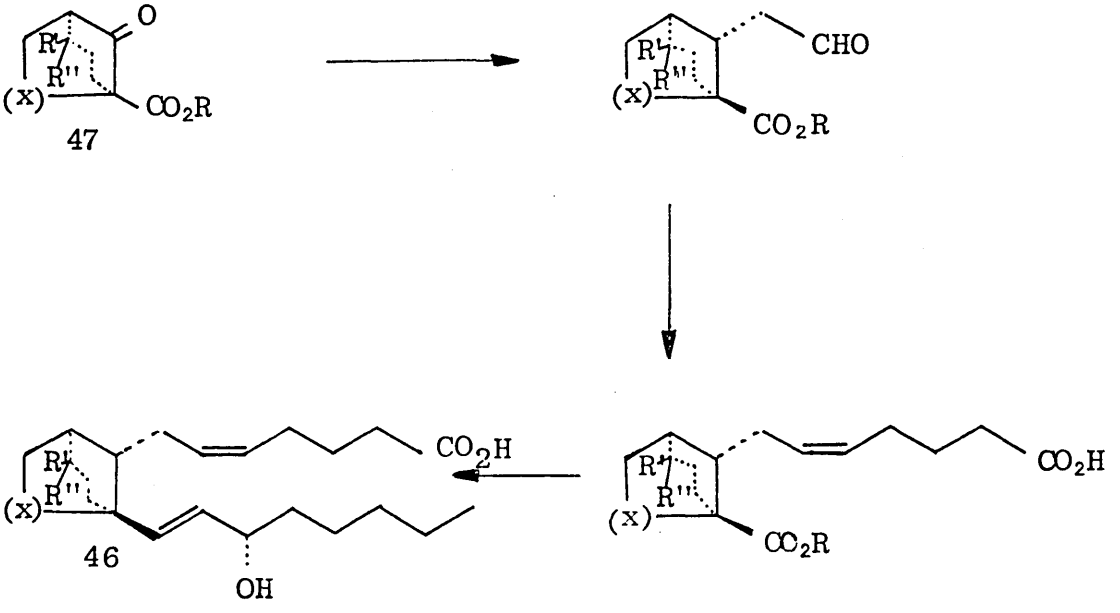
46

x = CH_2, CH_2CH_2, S



47 47

Scheme 11



47 46

Several methods directed towards making the bicyclic ketoesters were examined. These included:

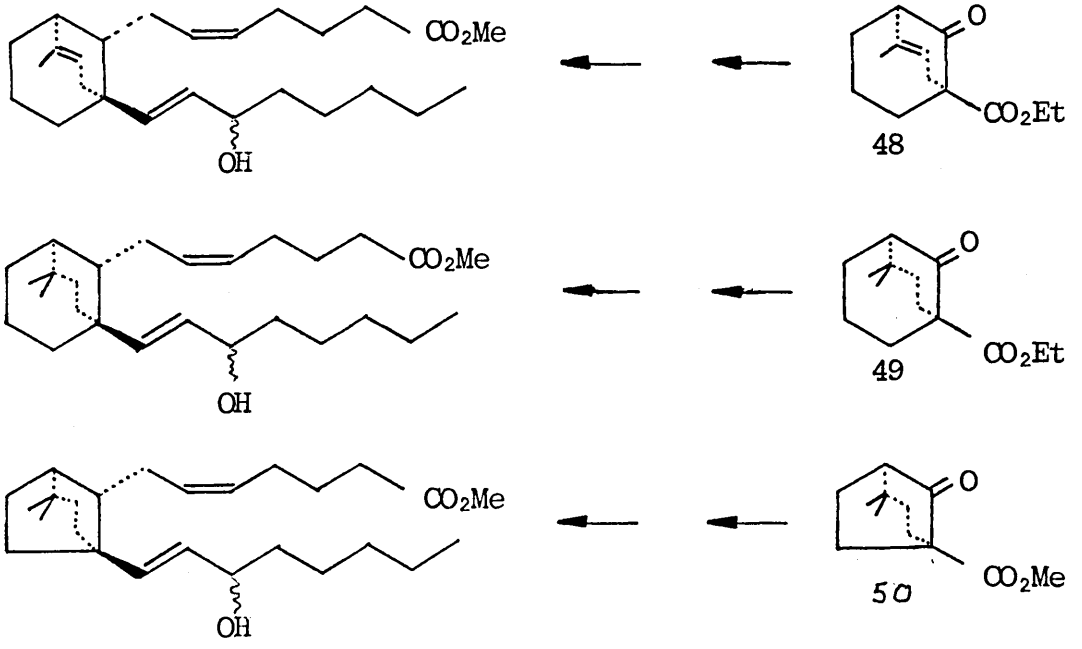
(a) Intramolecular base catalysed alkylation which is described in Chapter 2.

(b) Intramolecular aldol condensation described in Chapter 3.

(c) Acid catalysed intramolecular α-tertiary alkylation discussed in Chapter 4.

During these preparations, a number of unexpected rearrangement products were isolated and characterised. These are described in Chapters 2 and 3.

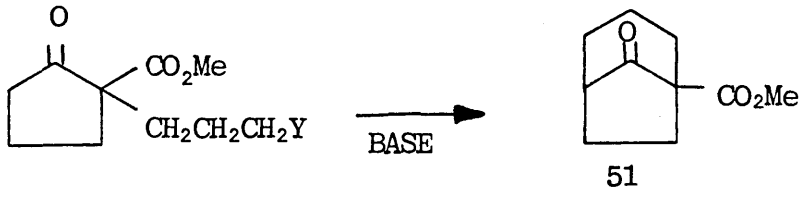
Three ketoesters (48), (49), (50) were transformed into thromboxane analogues and these form the basis for the discussion in Chapters 5 and 6.



CHAPTER 2

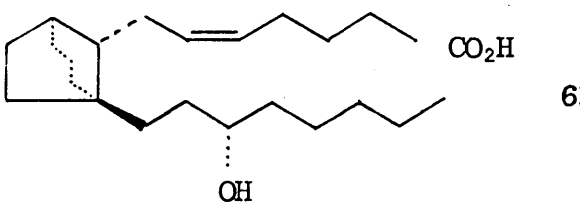
INTRAMOLECULAR BASE-CATALYSED ALKYLATION REACTIONS

Our first approach towards these bicyclic ketoesters (47) involved simple base-catalysed alkylations as shown below:-



51

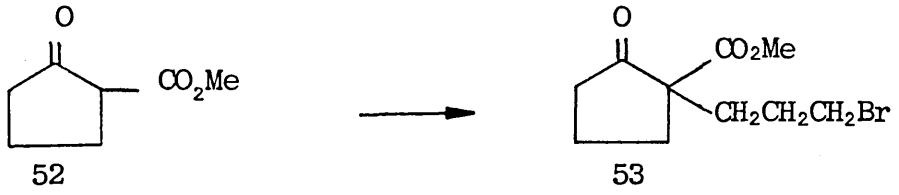
It was hoped that this reaction would provide a readily available intermediate (51), so that the methodology for the transformation of bicyclic ketoesters (47) to thromboxane analogues (46) could be worked out.



61

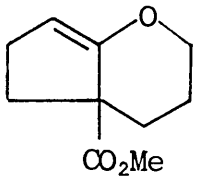
The corresponding thromboxane analogue (61) as well as being a novel and potentially interesting compound would also hopefully provide some information on the necessary nature of the lipophilic bridge.

Methyl 2-oxocyclopentanecarboxylate (52) was the starting material that was used. Condensations of one end of a dihalide with this β-ketoester (52) are well known [55] and it was readily alkylated with dibromopropane to give the bromo compound (53).



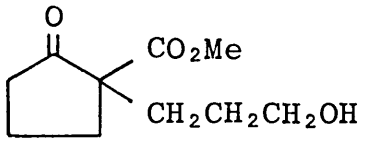
52 53

In an attempt to form the bridged system (51), the bromo compound (53) was treated with a range of bases under a variety of reaction conditions. These included sodium hydride in dimethylformamide, sodium hydride in tetrahydrofuran, potassium tert-butoxide in tetrahydrofuran and lithium diisopropylamide in tetrahydrofuran. In all cases there was one major product which was shown to be the O-alkylated product (54). 'H NMR in $CDCl_3$ shows an alkene proton at S5.15.



54

This O-alkylated product (54) on treatment with dilute acid produced as expected the alcohol (55).



55

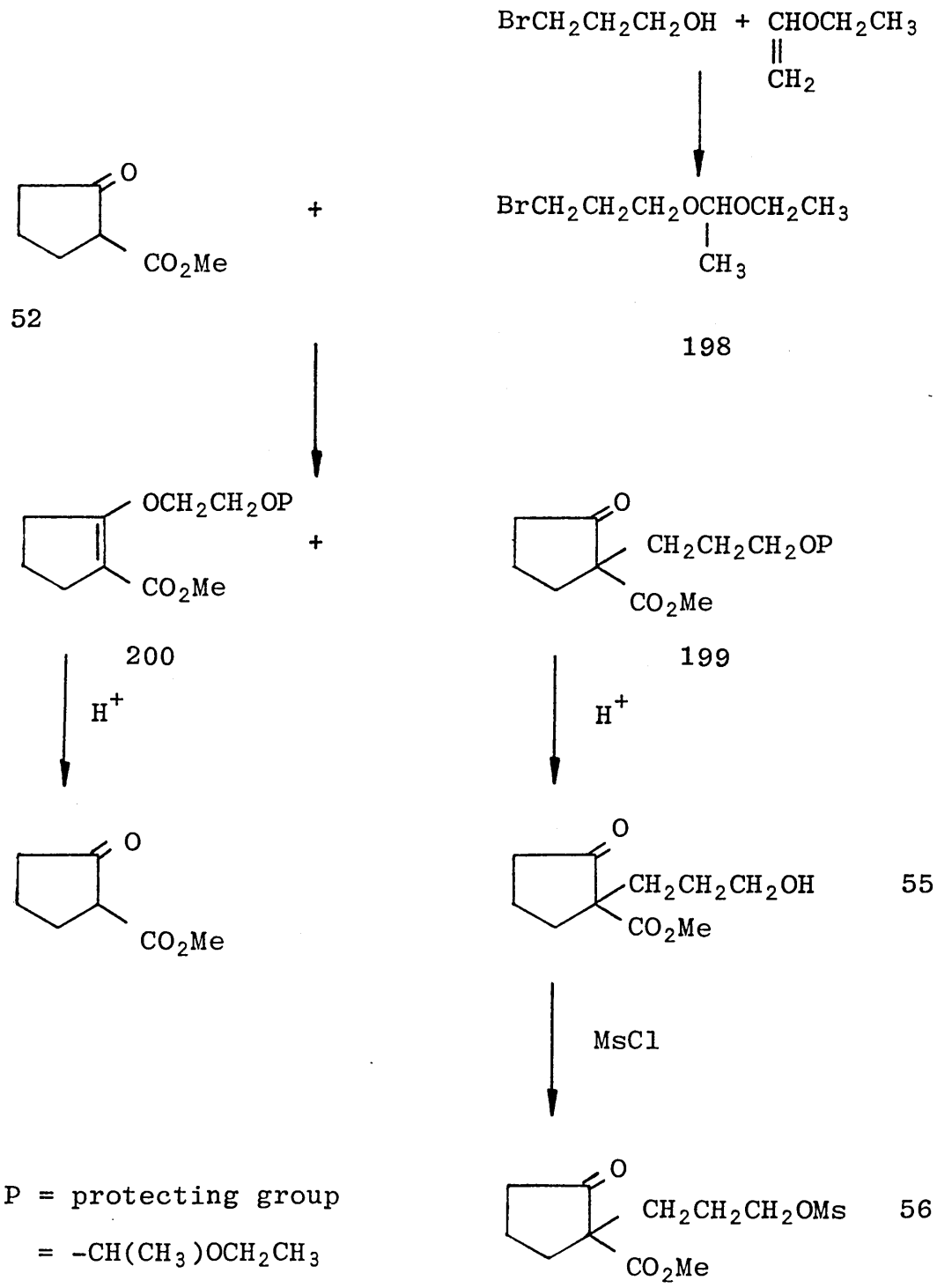
It was thought that a different leaving group, for example mesylate, might influence the amount of O-alkylation. Thus the alcohol (55) was prepared by the route outlined in Scheme (12).

The mesylate (56) was then synthesized from the alcohol (55) and on treatment with sodium hydride in dimethyl-foramide, two products were isolated, the O-alkylated product (54) and a polymer.

The competing O-alkylation product preventing the formation of the required bridged system posed a very difficult problem. Conditions favouring C-alkylation and minimising O-alkylation needed to be sought.

In general, O-alkylation competes significantly with C-alkylation only when the active methylene compounds involved are relatively acidic. In such cases, the equilibrium concentration of the enol-tautomer is often high. C-alkylation usually increases with significant decreases in the acidity of the active methylene compound. Presumably in the strongly acidic compounds, the negative charge is extensively delocalised on atoms other than

SCHEME 12



P = protecting group

= $-CH(CH_3)OCH_2CH_3$

carbon, so that the localisation of the electron pair at carbon-carbon bond is associated with a loss of a significant amount of resonance energy.

Various observations [56] suggest that the reaction in solution of a particular enolate anion with a particular alkylating agent will give the greatest proportion of O-alkylation when reaction conditions (solvent, cation, temperature) are chosen which allow the maximum amount of free enolate to be present. Presumably the greatest fraction of the negative charge in the enolate anion is located on oxygen, the most electronegative atom present, and the maximum opportunity for O-alkylation exists when the oxygen atom is not shielded or associated with a metal cation or a hydrogen-bonding solvent. Therefore alkylation at oxygen rather than carbon for an enolate anion is usually favoured by the use of polar aprotic solvents, and the presence of large ($R_4N^+ > K^+ > Na^+ > Li^+$) cations which have the tendency to dissociate from the anion.

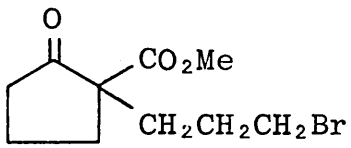
In cases when the metal enolate is not in solution and heterogeneous reaction of an alkylating agent with the solid enolate will necessarily involve reaction with an anion in which the oxygen is shielded by the metal atom, C-alkylation is favoured.

Variations in the leaving group of the alkylating agent are usually found to favour C-alkylation in the order $R\text{-}I > R\text{-}Br > R\text{-}Cl > R\text{-}OSO_2R > R\text{-}OSO_2Ar > R_3\text{-}O^{\oplus}BF_4^{\ominus}$.

As mentioned previously the degree of reactivity of an enolate is often influenced by the nature of the cation

present. Some enolate anions exist as ion pairs with cations; the lithium cation forms more tightly associated ion pairs than sodium or potassium. Usually the free enolate anions are more reactive as nucleophiles than are associated ion pairs, so the lithium cation as an ion pair should form more C-alkylated product.

Overall, some of the required bridged species (51) should be formed with the lithium enolate of the bromo compound (53) in an inert solvent, or when it forms a dissociated anion in a hydrogen bonding solvent because the dissociated anion will be selectively solvated at oxygen.



53

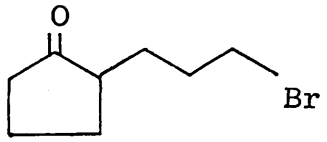
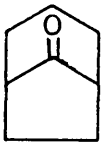
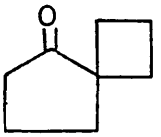
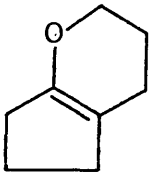
The lithium enolate was generated by treatment of lithium diisopropylamide in anhydrous tetrahydrofuran with the bromo derivative (53) at -78°C for twenty minutes. The tetrahydrofuran was then evaporated on the high vacuum and toluene was added. The reaction mixture was refluxed for two days. Gas liquid chromatography indicated a mixture of starting material (53), O-alkylated product (54) and a polymer as major products.

The above method was repeated with the mesylate derivative (56) to give similar results.

The competing O-alkylation reaction has previously been

encountered during the synthesis of spiro-ketones [57][58] (see Table (1))

TABLE 1

			
57	58	59	60
B^- ⟶			
*aq KOH	6%	13%	15%
*KO^{t}Bu/Benzene	19%	30%	22%
KOH/Benzene	2%	37%	61%
NaOMe/Benzene	-	32%	32%

*These results indicate that all three possible products are formed. In these reactions, the route to the enol-ether formation (60) involves a relatively strain-free-six-membered transition state. Formation of the bridged ketone (58) also involves a six-membered transition state, but an axial conformation of the side chain is required and considerable non-bonded interactions are built up in the transition state.

The carbomethoxy group present in our system (53) will prevent the formation of the spiro-ketone and it does not seem to be able to interfere in the transition state leading to the bridged product.

Both the bromo compound (53) and the mesylate derivative (56) were treated with potassium tert-butoxide and

refluxed in benzene in an attempt to synthesize the bridged intermediate (51). Gas liquid chromatography of both reaction mixtures indicated starting material, O-alkylated product and polymer.

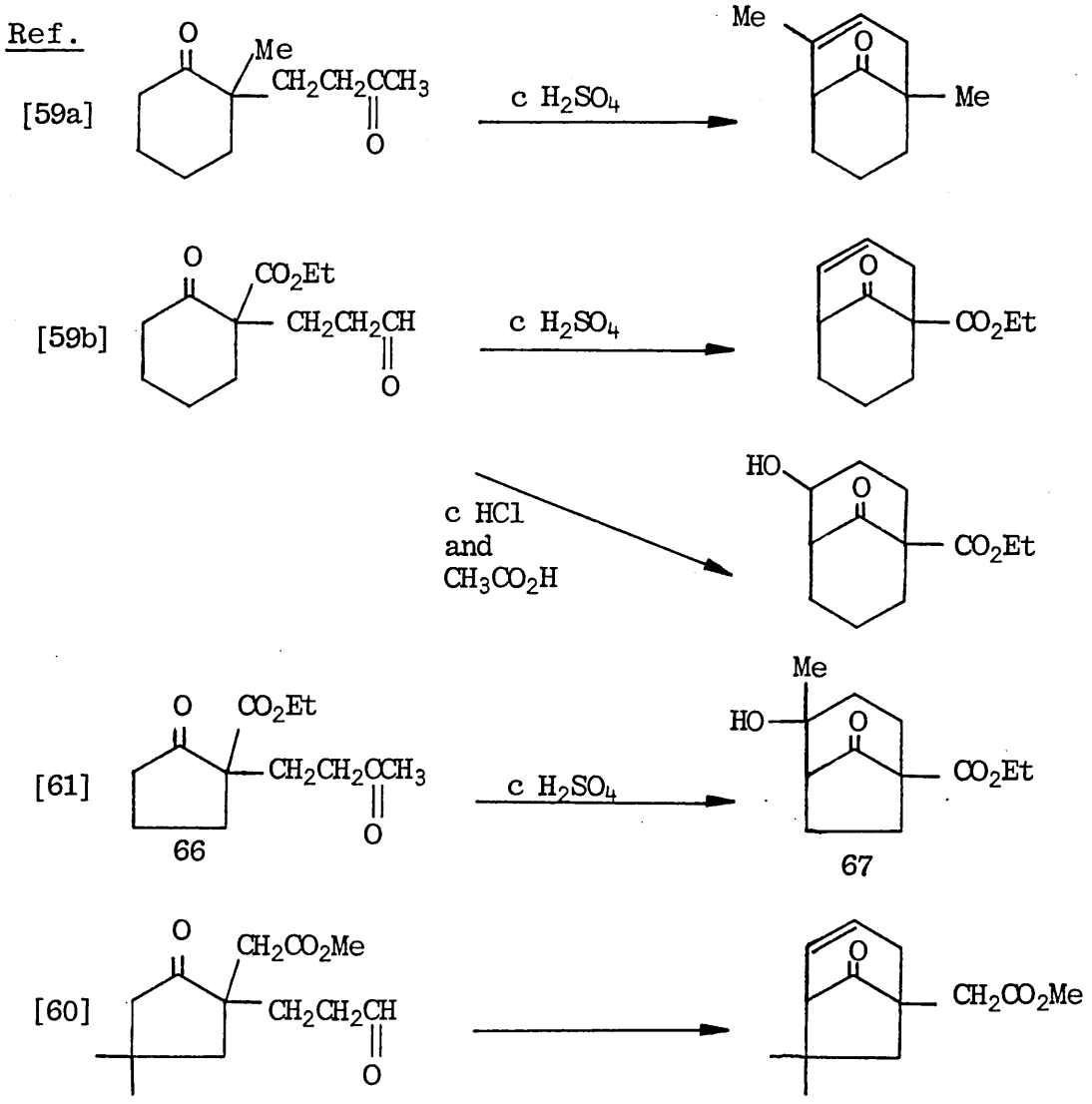
These particular type of reactions did not seem to be successful, therefore this approach was given up.

CHAPTER 3

INTRAMOLECULAR ALDOL CONDENSATIONS

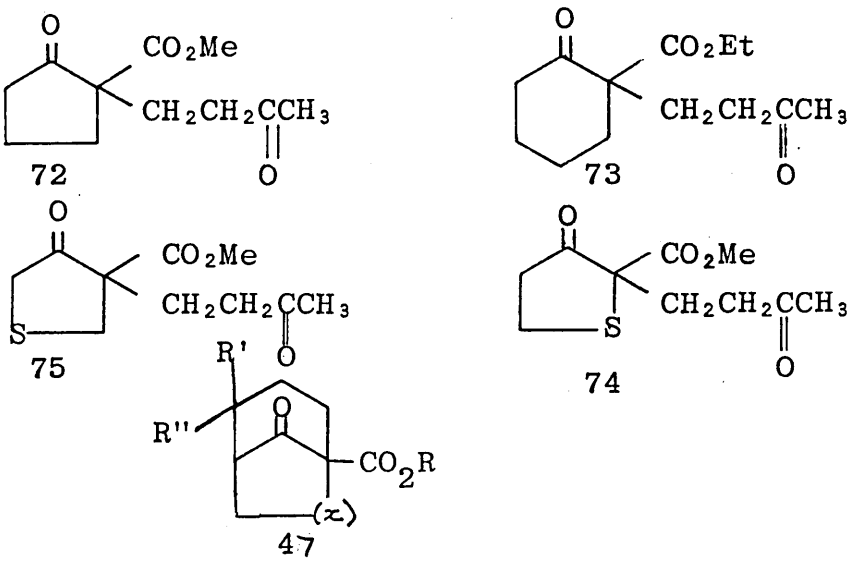
There are many examples in the literature of bicyclic ketones produced by the aldol condensation. Some of these are summarised in Scheme (13).

SCHEME 13

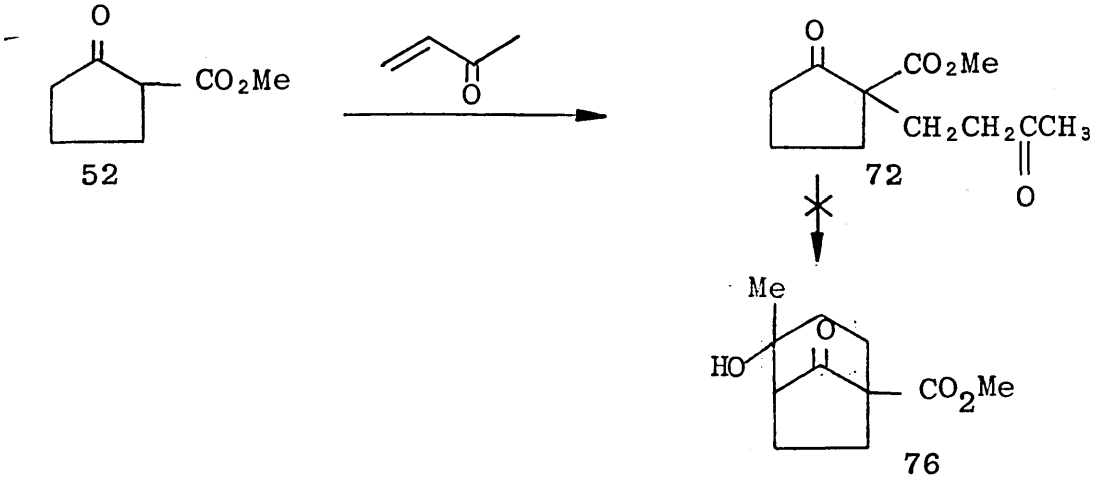


These reactions provided the basis for our study of aldol condensations with the 5-membered carbocycle (72), the 6-membered carbocycle (73) and the 5-membered sulphur heterocycles (74) and (75). These reactions could give bicyclic ketoesters which would be structurally similar to

our initial target (47), R' = Me, R'' - OH.



The cyclisation of the diketone (66) was known [61] and the preparation was repeated but using the methylester (72).



Methyl 2-oxocyclopentanecarboxylate (52) readily reacted with anhydrous methyl vinyl ketone in the presence of triethylamine to give the diketone (72). When the diketone was allowed to react with concentrated sulphuric acid, a solid product was formed. However, its properties did not seem to be consistent with the proposed structure (76) in that:

I It did not form a derivative with dinitrophenyl-hydrazine.

II Attempts to protect the supposed hydroxyl group with a wide range of protecting groups were unsuccessful.

III It did not undergo a Wittig reaction with $Ph_3P{=}Ch_2$, $Ph_3P{=}CH_2OCH_3$, $Ph_3P{=}CHCH_3$ or $Ph_2P(O)\overset{(-)}{C}HCH_3$ whilst using a variety of based and solvents.

Although these observations could be explained in terms of steric effects on the ketone and hydroxyl groups, in order to firmly verify the structure an X-ray analysis was undertaken. The X-ray study showed the product from the cyclisation to be the lactone (77) and not the expected bicyclic ketone (76). A postulated mechanism is shown in scheme (14).

SCHEME 14

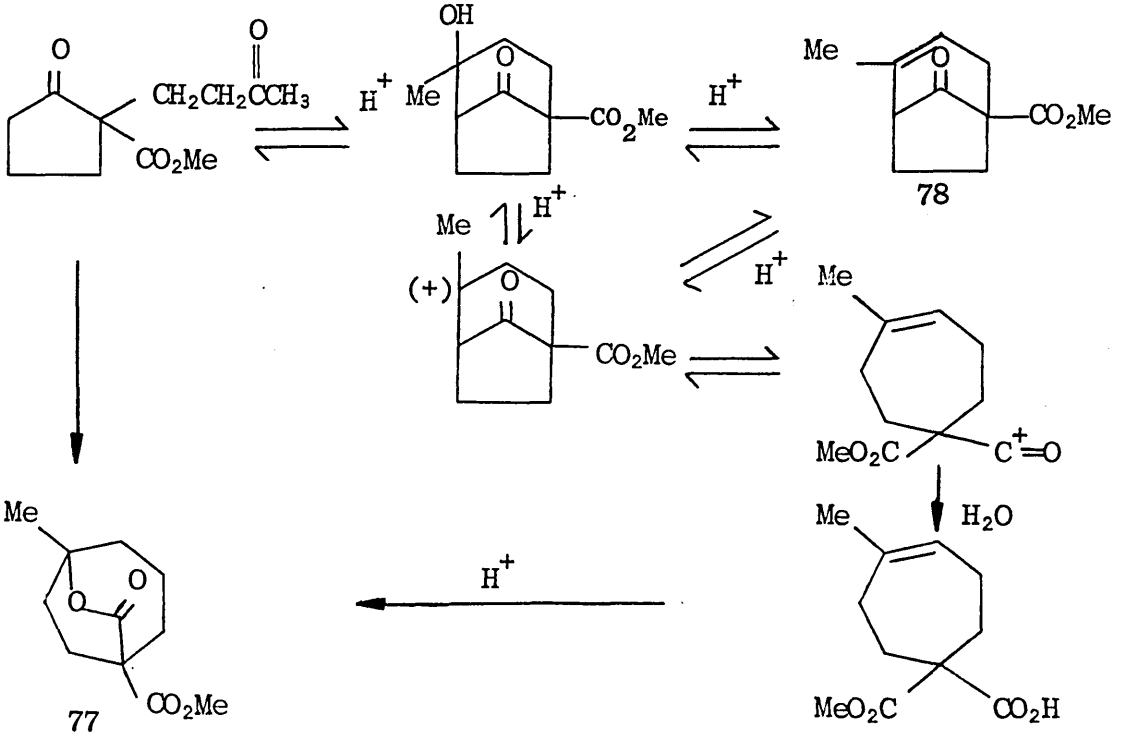
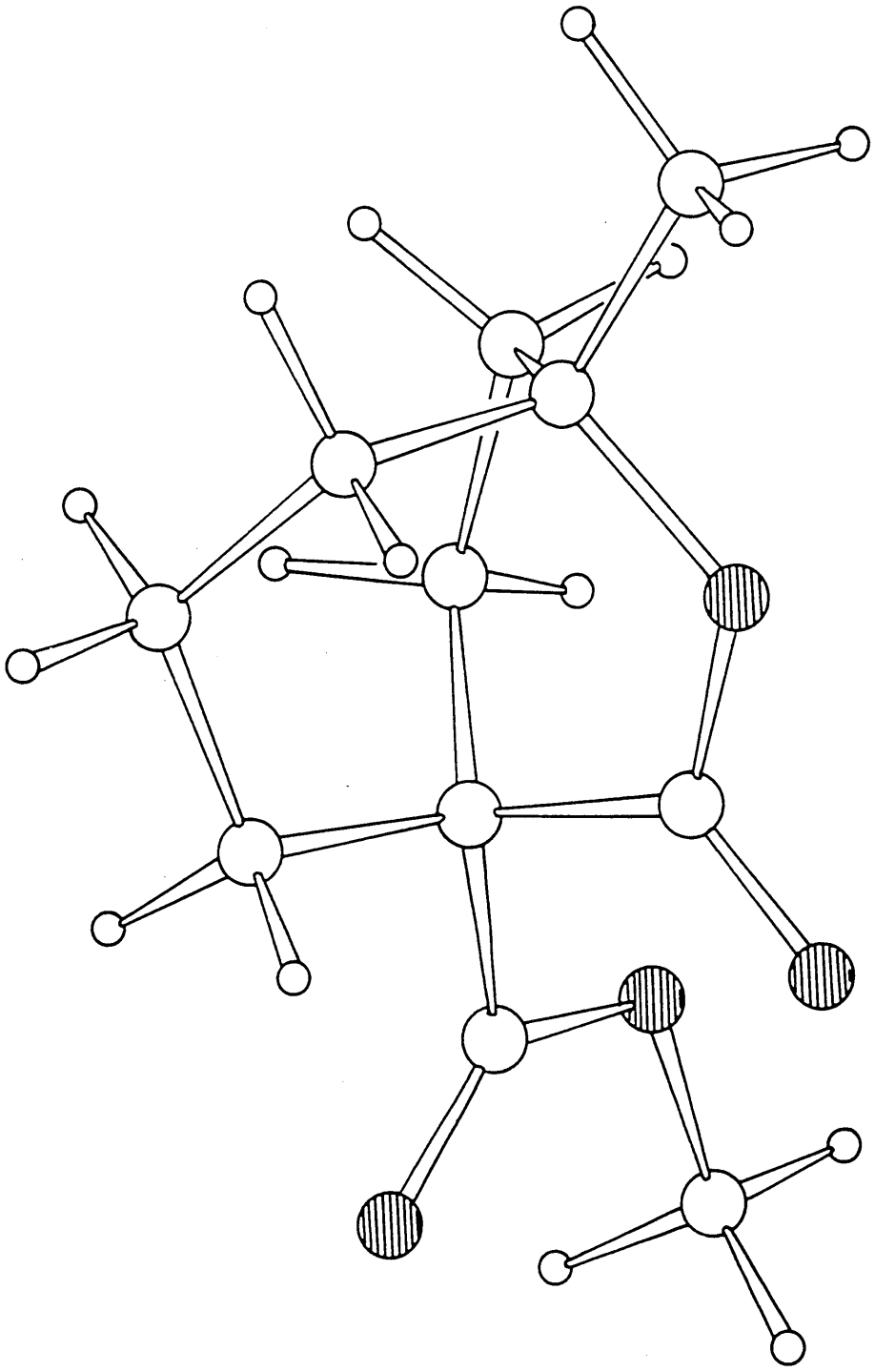
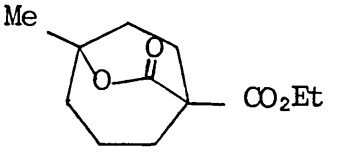


Diagram of lactone (77) obtained from the X-ray analysis data.



The 'H and ^{13}C spectra were found to be concordant with this lactonic structure. The literature reaction of the ethyl ester (66) was repeated and it was found that the 'H and ^{13}C spectra of the product were very similar to those of lactone (77) apart from the differences associated with the change from methyl to ethyl ester. The similarity between the spectra and melting point data given for alcohol (67) and that found for lactone (79), leave little doubt that the reported structure (67) is incorrect. [61]



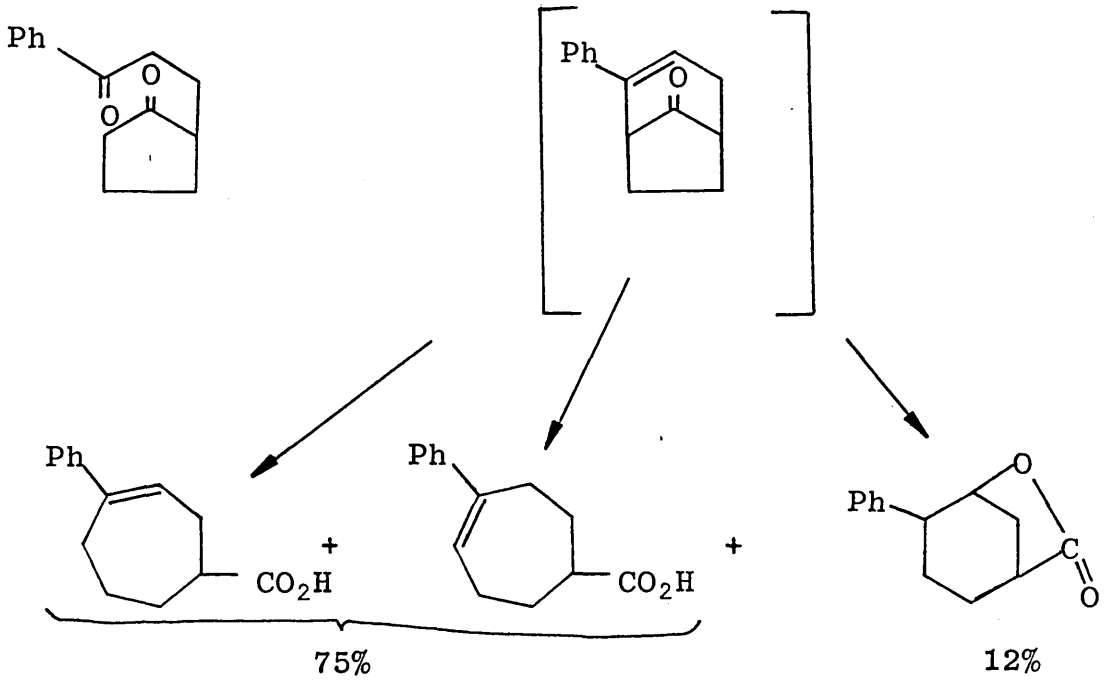
79

When shorter reaction times were used for the cyclisation, the alkene (78) was isolated along with the lactone (77) and starting material (72). The results are summarised in Table (2). Further treatment of the alkene (78) with concentrated sulphuric acid led to its conversion into the lactone (77).

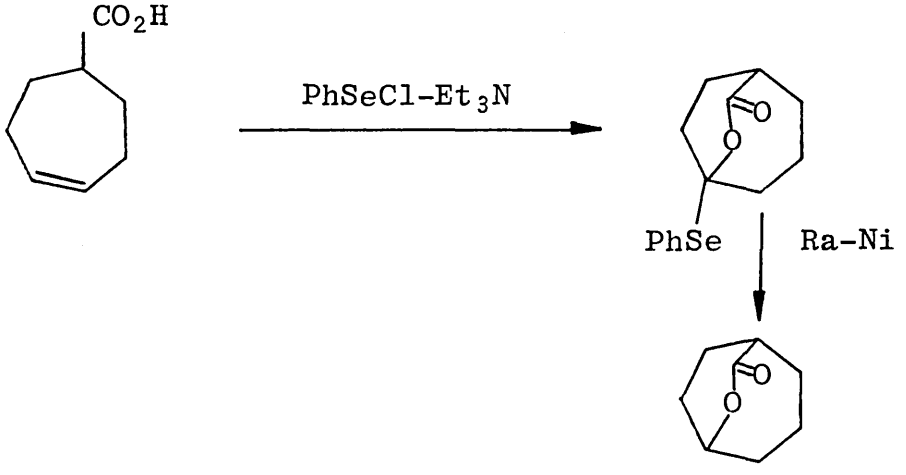
TABLE 2

Reaction Times	Lactone (77)	S.M. (72)	Alkene (78)
30 minutes	18.5%	23.9%	31.4%
1 hour	47%	5%	14.5%
14 hours	60%	-	-

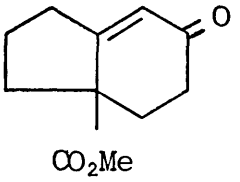
Rearrangements leading to similar cycloheptane systems have been observed previously, although lactones obtained in those systems were ɣ-lactones whereas (77) is a δ lactone. An example is shown below. [62]



The same ring system has also been obtained by phenylselenyl or phenylsulphenyl lactonisation of a cycloheptene-carboxylic acid as shown below. [63]

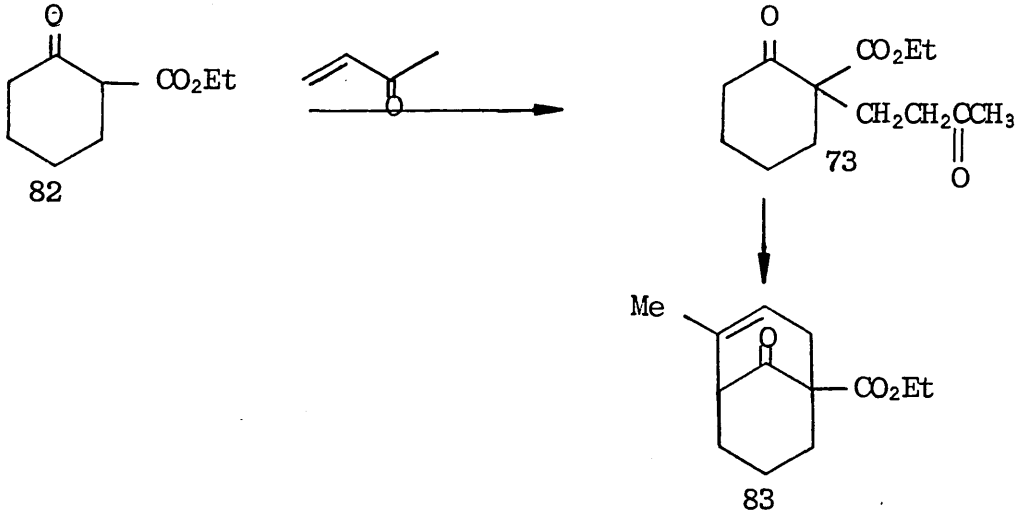


Milder acidic conditions, i.e. stannic chloride in benzene or borontrifluoride in dichloromethane on the diketone (72) gave the Robinson annulation product (80).



80

The six-membered diketone (73) of the β-ketoester (82) was synthesized in a similar manner to that just described for the five-membered carbocycle (72). Thus the β-ketoester was treated with methyl vinyl ketone and triethylamine to give the diketone (73) in 98% yield.



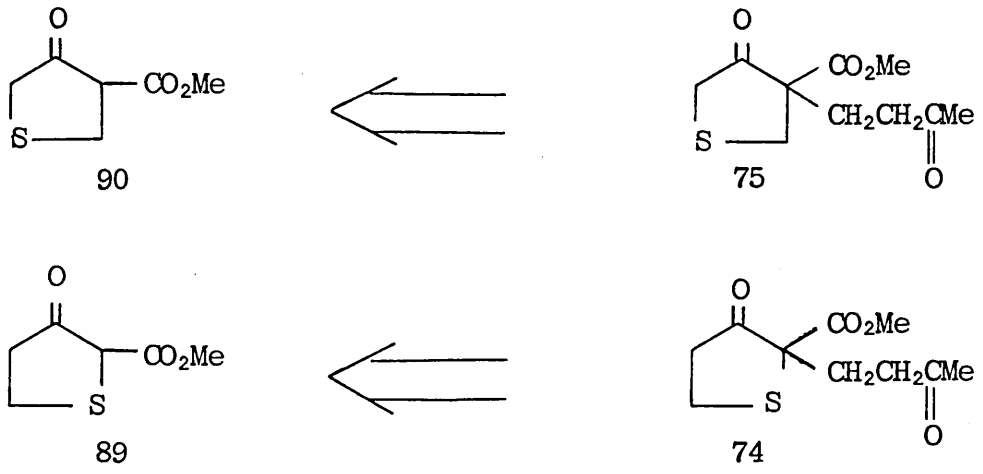
The bridged alkene (83) was the only product obtained when the diketone (73) was treated with concentrated sulphuric acid at $0^{o}C$ for 30 minutes. The alkene (83) was prepared in good yield and was used for transformation into a thromboxane A_2 analogue.

Since the alcohol (84) [64] can be isolated from the related cyclisation of diketone (85), we attempted the

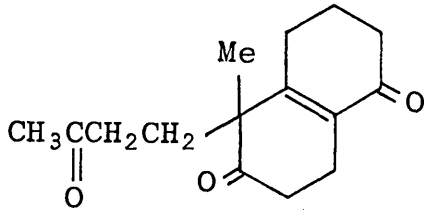
isolation of tertiary alcohol (86), (Scheme 15), since it should be an intermediate in the synthesis of the bridged alkene (83) from the diketone (73).

When different concentrations of sulphuric acid were used, the only major products were starting material (73) and the dehydration product (83). In contrast, the Robinson annulation product (87) was the only product obtained on treatment of the diketone (73) with concentrated hydrochloric acid and glacial acetic acid, stannic chloride in benzene or boron trifluoride in dichloromethane. The bridged alkene (83) was heated with formic acid in an attempt to produce the formate ester (88) but after a prolonged period, it did not react.

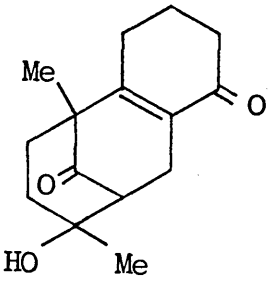
The aldol condensations with the sulphur heterocycles (74) and (75) were also explored. These diketones (74) and (75) were be derived from the heterocyclic β-ketoesters (89) and (90) respectively.



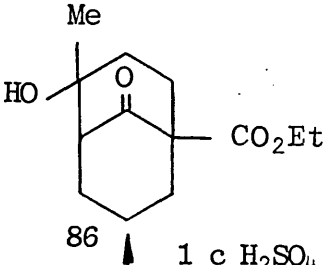
SCHEME 15



85

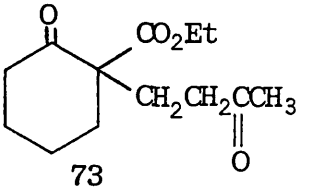


84



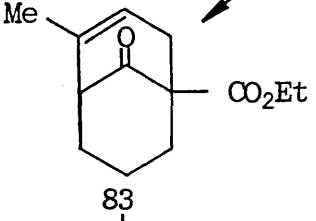
86

1 c H_2SO_4
2 H_2O



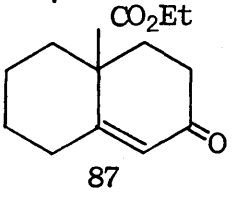
73

c HCl, CH_3CO_2H
and
$SnCl_4$ in benzene

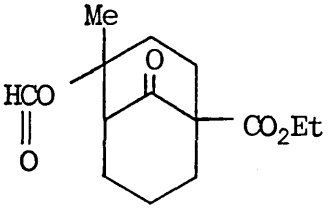


83

X HCO_2H

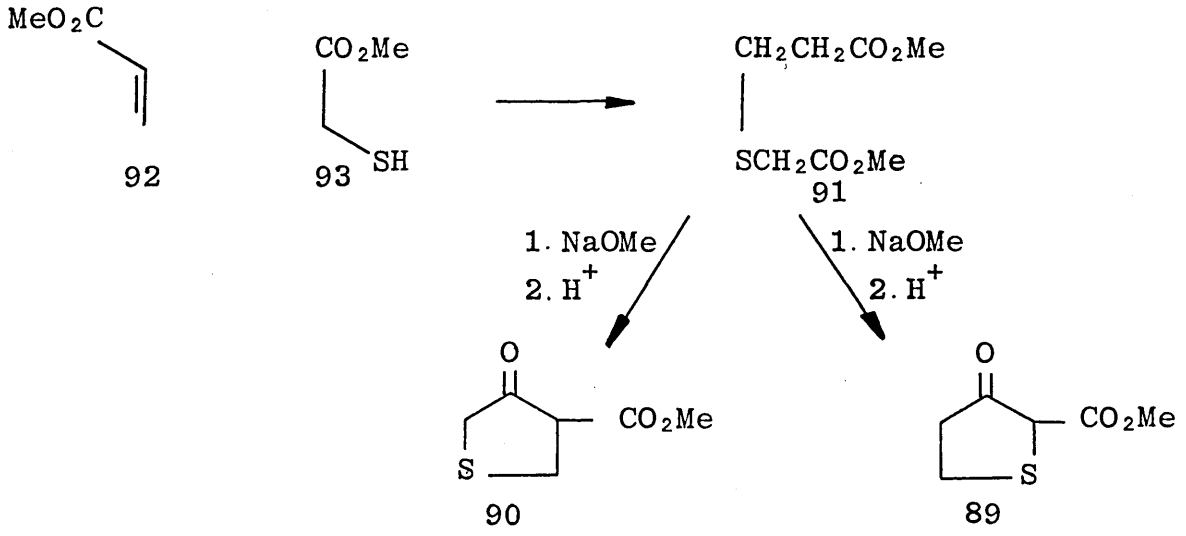


87



88

The heterocyclic β-ketoesters (89) and (90) were synthesized from the unsymmetrical sulphide (91). Methyl thioglycolate (92) and methyl acrylate (93) readily reacted together in the presence of piperidine to give this unsymmetrical sulphide (91). [65]



The unsymmetrical sulphide (91) undergoes the Dieckmann condensation to give two possible products depending on the reaction temperature. The product can be varied from mostly methyl 3-oxo-2-tetrahydrothiophenecarboxylate (89) to exclusively methyl 4-oxo-3-tetrahydrothiophenecarboxylate (90) by raising the temperature from the boiling point of diethylether to the boiling point of toluene. Woodward and Eastman [65] interpreted the formation of (89) in terms of kinetically controlled reaction course. Several years later, Hromatka and his co-workers [66], on the basis of experimental evidence concluded that the formation of (90) depends on the ability of the isomer (89) to

undergo temperature dependent retro-Claisen cleavage, anion isomerisation and alternative recyclisation.

Both isomers were synthesized. The method described by Hromatka [66] was used for methyl 4-oxo-3-tetrahydrothiophenecarboxylate (90) since it quotes a higher yield than the method outlined by Woodward and Eastman. [65] The method involved refluxing the unsymmetrical sulphide (91) with three equivalents of sodium methoxide in methanol. Both of the tautomeric forms of this isomer (90) were recognisable in the ^{1}H NMR spectrum, which displayed a double set of ester group proton signals and a broad enolic hydroxyl proton signal at approximately δ11. The ^{13}C NMR spectrum in $CDCl_3$ clearly showed the presence of both tautomers. The prevalence of the enol form was indicated by the I.R. spectrum.

The I.R. spectrum exhibited their most intense absorption bands in the carbonyl olefin stretching region at 1670 cm^{-1} (chelated, conjugated ester carbonyl group stretchings) and at 1620 cm^{-1} (conjugated C=C stretching). The general appearance of a broad less intense band at 3000-3050 cm^{-1}, unambiguously assignable to a chelated enolic O-H stretching vibration, confirmed the presence of significant equilibrium concentrations of the enol form. The above observations were in agreement with the recent work of

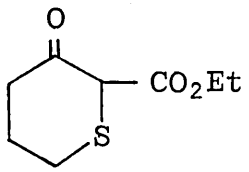
F. Duus [67] on the tautomerism of this system.

Two methods were investigated to produce methyl 3-oxo-2-tetrahydrothiophenecarboxylate (89). Using the Woodward method, this isomer (89) was the predominant product when the unsymmetrical sulphide (91) was refluxed with sodium methoxide in ether. This kinetic isomer (89) could be purified by column chromatography. A mixture of products, one of which was the required isomer (89), was obtained when the unsymmetrical sulphide (91) was treated with lithium diisopropylamide in anhydrous tetrahydrofuran. The former Woodward [65] method gives a much cleaner method and was the method of choice for the kinetic isomer (89).

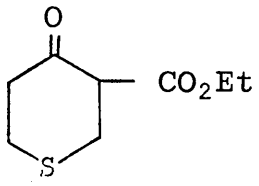
In contrast to the thermodynamic isomer (90) which exists as a tautomeric mixture in $CDCl_3$, the kinetic isomer exist almost exclusively in the keto form. The 'H NMR in $CDCl_3$ shows a very minor amount of a second ester group and the ^{13}C NMR spectrum in $CDCl_3$ shows only the presence of the keto form. The I.R. however shows the presence of the enol tautomer, besides the dominating strong bands in the carbonyl region at around 1760 cm^{-1} (ketonic C=O stretching) and around 1740 cm^{-1} (ester C=O stretching), there were also medium intensity bands at around 1660 cm^{-1} (chelated conjugated ester C=O stretching) and around 1610 cm^{-1} (conjugated C=C stretching). The apparent absence of distinct IR enolic O-H stretching vibration bands in the region above 3000 cm^{-1} is not unexpected owing to the relatively low enol concentrations and the fact that hydroxylic stretching vibration bands of

enols engaged in intramolecular hydrogen-bonding with a carbonyl group usually are broad and of low intensity.

It seems that the position of the sulphur atom in the 5-membered heterocyclic ring relative to the ketone and ester functionalities influences the degree of enolisation. This is not easily explained since in the six-membered heterocyclic series (94) and (95) enolise to a similar extent approximately 75% in carbon tetrachloride [67] and do not seem to be affected by the relative positions of the functional groups.

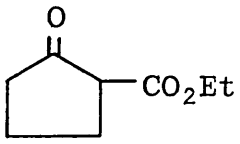


94

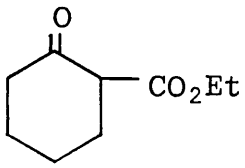


95

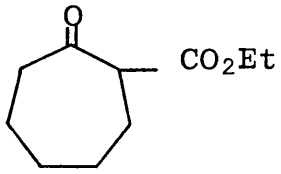
Ring size is known to affect the extent of enolisation in the homocyclic series. [68] The 5-membered carbocycle (52) in a solution of carbontetrachloride enolises to an extent of 11.5%, the 6-membered carbocycle (82) and the 7-membered carbocycle (96) to 85% and 31% respectively.



52



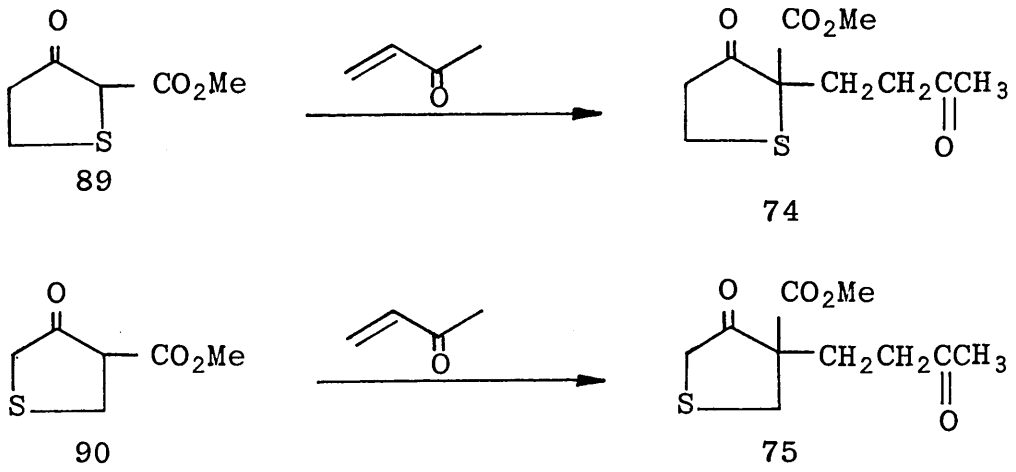
82



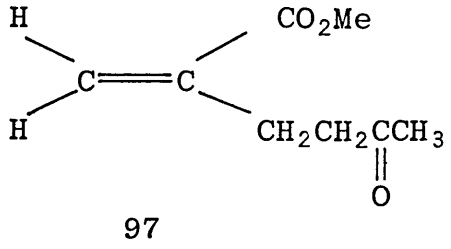
96

The two heterocyclic ketoesters (89) and (90) were obtained cleanly and in good yield. Methyl vinyl ketone in the presence of triethylamine underwent a Michael reaction

with both sulphur heterocycles (89) and (90) to give the diketones (74) and (75) respectively.

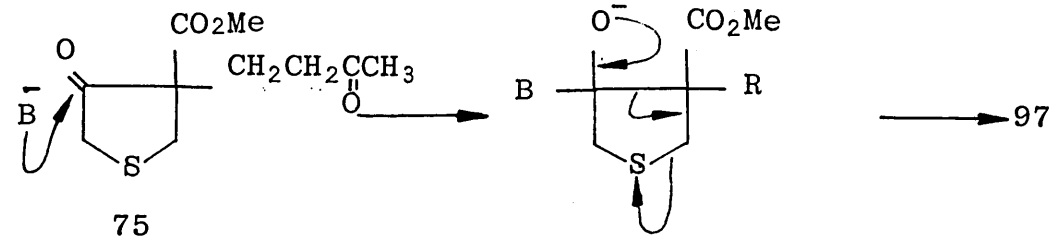


In the case of the sulphur heterocycle (75), during the Michael reaction another product was isolated. Spectral evidence suggested it was the α-substituted acrylic ester (97).

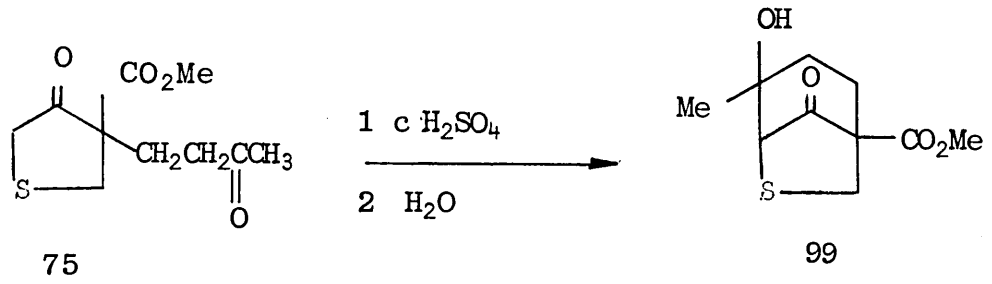


97

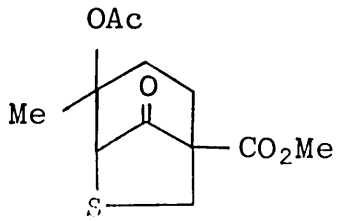
When similar methyl 3-alkyl-4-oxo-3-tetrahydrothiophene-carboxylates (98) have been treated with sodium hydroxide under biphasic reaction conditions, α-substituted acrylic esters have been obtained as products. [69] The postulated mechanism is as follows:



When our sulphur heterocycle (90) was subjected to the same biphasic reaction conditions, the same α-substituted acrylic ester (97) was obtained.

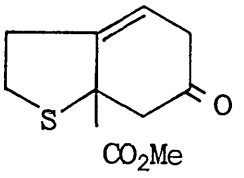


In an attempt to form the required bridged species, the diketone (75) was treated with concentrated sulphuric acid. Under these conditions, the diketone (75) cyclised to give the bridged alcohol (99) as the major product. The alcohol has been converted to the acetate (97) with acetic anhydride in the presence of one equivalent of 4-dimethyl-aminopyridine [70]. Lack of time prevented a study of the conversion of the acetate (100) to a thromboxane analogue.



100

In complete contrast, the other diketone (74) has failed to cyclise to give any bridged compounds. A Lewis acid catalysed reaction with stannic chloride in benzene of the diketone (74) gave polymeric material with a small amount of the Robinson annulation product (101).

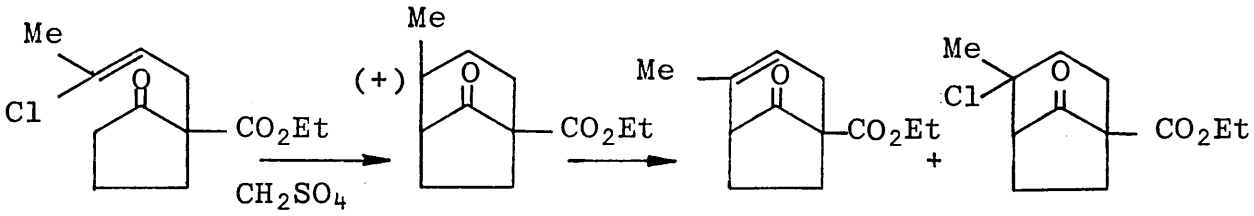


101

CHAPTER FOUR

ACID CATALYSED INTRAMOLECULAR α-TERTIARY ALKYLATION

Studies by W. G. Dauben et al on the cyclisation of (102) with concentrated sulphuric acid suggested that a carbocation (103) was involved in the mechanism because of the appearance of the tertiary chloride (104) as a minor product.



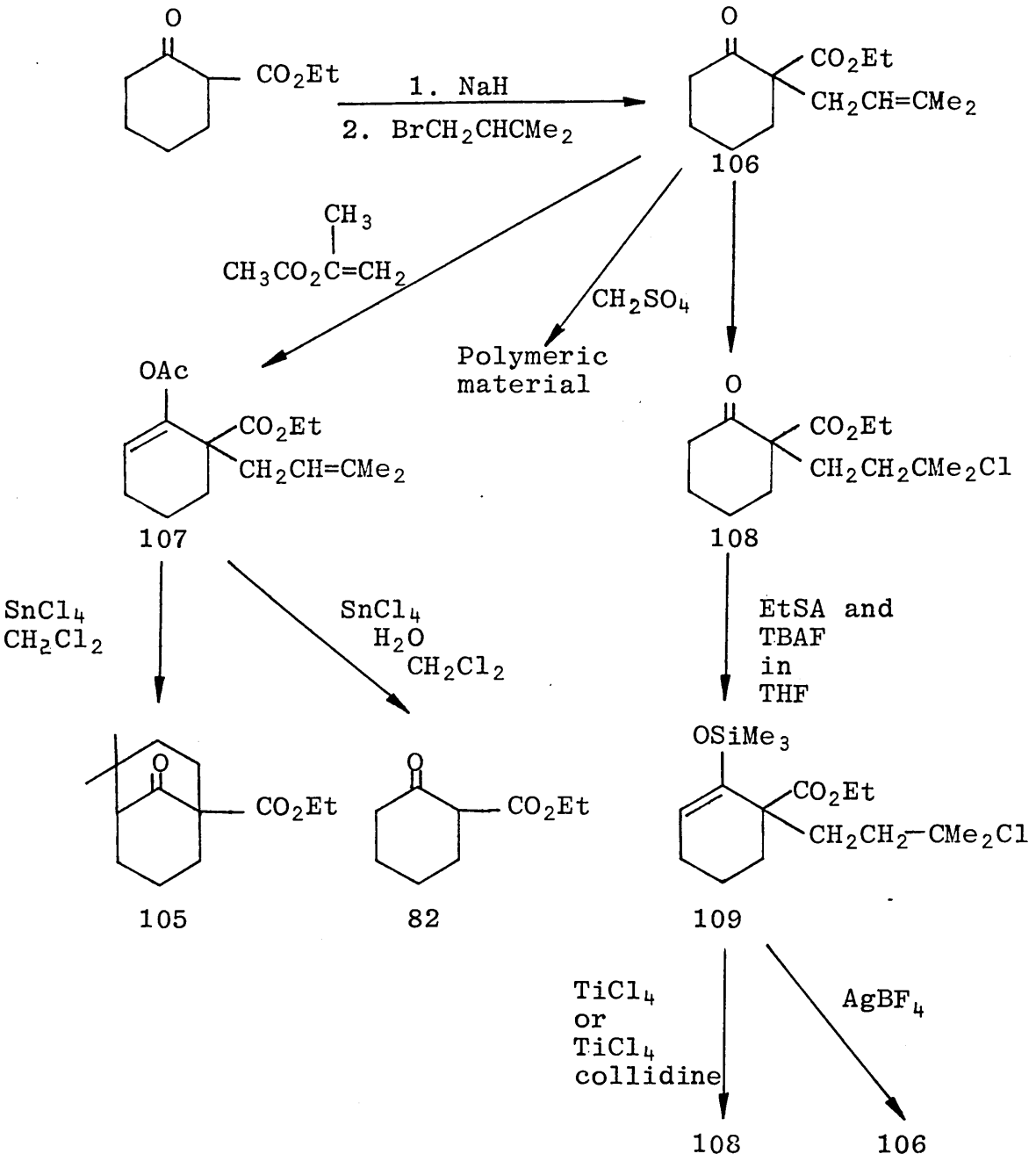
102 103 104

This work prompted us to realise the possibility of synthesizing the gemdimethyl intermediate (105) from the readily available prenyl compound (106).

106 105

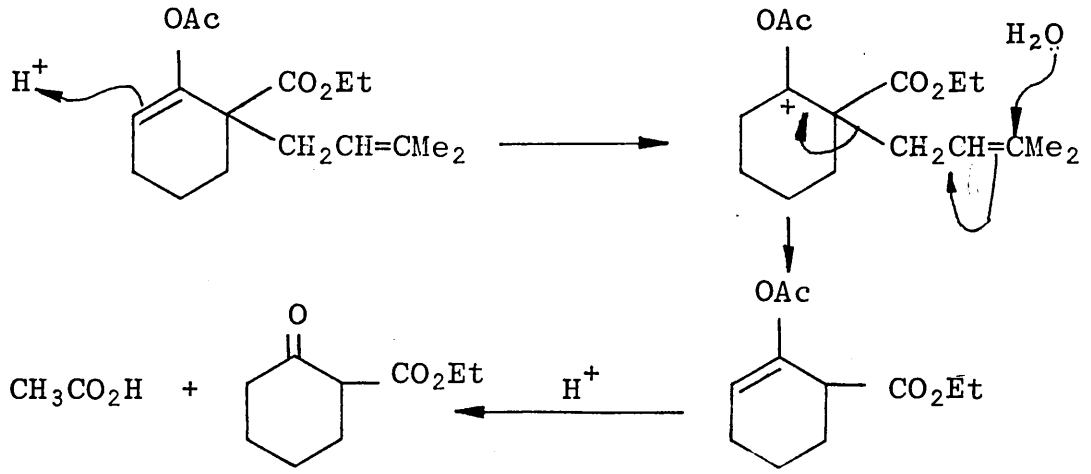
The prenyl compound (106) was easily prepared by the reaction of the sodium enolate of ethyl 2-oxocyclohexane-carboxylate (82) with 1-bromo-3-methyl-2-butene (prenyl bromide) in dimethylformamide.

SCHEME 15

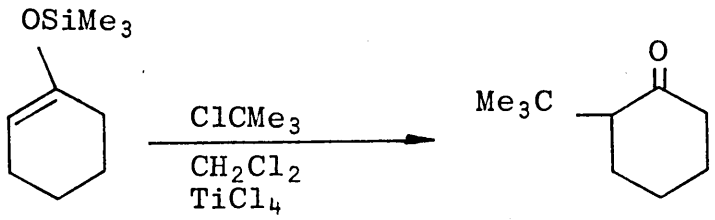

1. NaH
2. BrCH2CHCMe2
106
CH3CO2C=CH2
CH2SO4
Polymeric material
107
108
SnCl4 CH2Cl2
SnCl4 H2O CH2Cl2
EtSA and TBAF in THF
105
82
109
TiCl4 or TiCl4 collidine
AgBF4
108
106

Several potential routes to the preparation of the gemdimethyl analogue were investigated. In the successful route, (scheme 15), the enol-acetate (107) was prepared by treatment of the prenyl compound (106) with isoproprenyl-acetate in the presence of toluene-4-sulphonic acid. [71] This enol-acetate underwent smooth intramolecular α-tertiary alkylation with stannic chloride in dichloro-methane to give the required gemdimethyl compound (105) in 96% yield. [72]

If the dichloromethane was excessively wet, then ethyl 2-oxocyclohexanecarboxylate (82) appeared as a product. A possible mechanism is shown below. When the prenyl compound (106) was subjected to the same reaction conditions no ethyl 2-oxocyclohexanecarboxylate (82) was obtained.

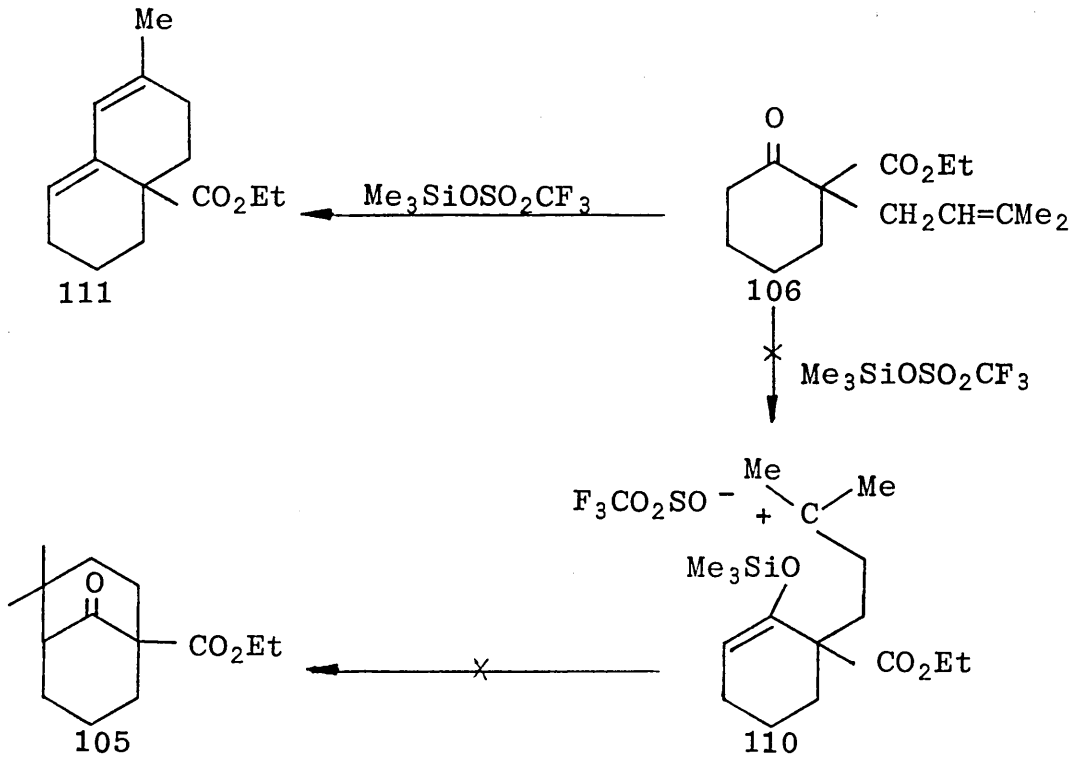


A possible intramolecular α-tertiary alkylation using the tertiary chloride (109) was also studied, (scheme 15). Intermolecular reactions of this type are known [73] for example:



The tertiary chloride (108) was synthesized by treating the prenyl compound (106) with hydrogen chloride. The trimethylsilyl group was then introduced under mild conditions with ethyl trimethylsilylacetate in the presence of tetra-n-butylammonium fluoride giving the silylenol-ether (109) [74]. Treatment of the silylenol-ether (109) with the Lewis acid titanium tetrachloride resulted in the loss of the silyl group giving (108). Since this might have been caused by traces of moisture producing hydrochloric acid, the experiment was repeated with the addition of collidine. The same product (108) was obtained. The silylenol-ether (109) when treated with a different Lewis acid, silver tetrafluoraborate, yielded the prenyl compound (106).

Another method using a Lewis acid involved treating the prenyl compound (106) with a catalytic amount of trimethylsilyltrifluoromethanesulphonate. This did not cause reaction via the anticipated intermediate (110) but gave instead the transoid diene (111), see below.

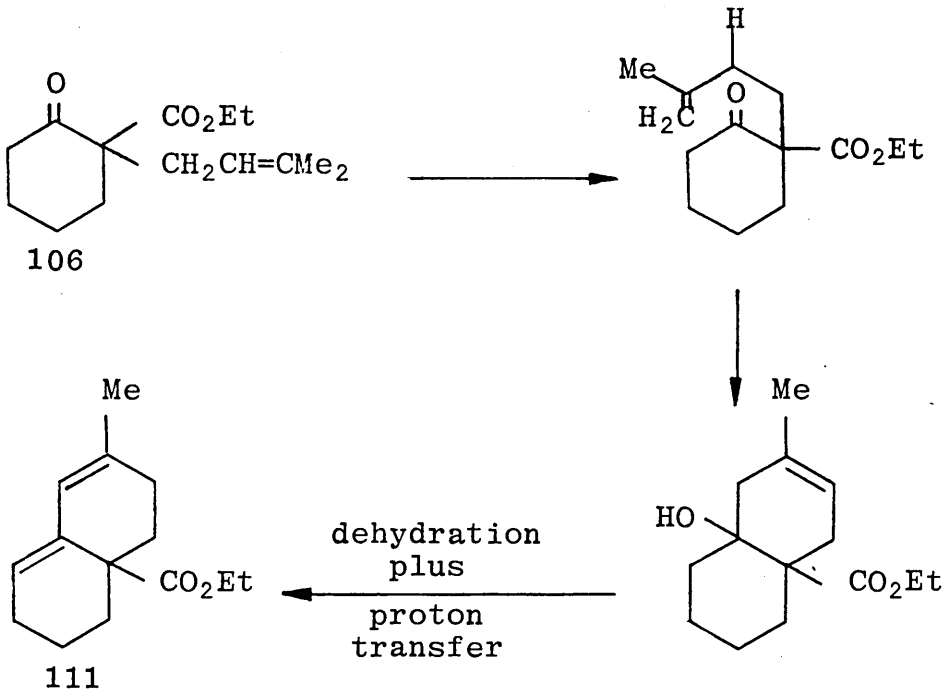


These and other similar conditions, giving rise to the diene (111), are shown in Table 3.

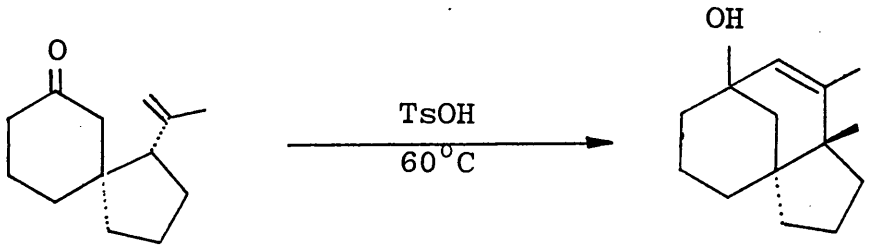
Table 3

S.M	Reaction Conditions	Yield
106	Catalytic amount of $Me_3SiOSO_2CF_3$	64%
106	1 equivalent of $HOSO_2CF_3$	Not recorded
106	1 equivalent of $SnCl_4$	68%
112	1 equivalent of $HOSO_2CF_3$	Not recorded

A possible mechanism is shown below:



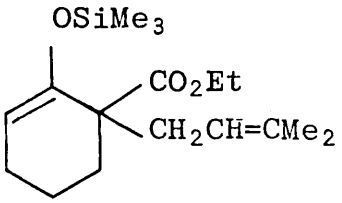
The formation of the diene seems to be an example of the ene reaction, [75] similar reactions are known for example [76].



The structure of the diene (111) was confirmed by examination of the decoupled and coupled ^{13}C spectra. Application of the Fieser-Woodward [77] rules to the UV spectrum of the diene shows it to be the transoid isomer (111) and not the cisoid isomer.

Another possible route to the bridged ketone (105) involves

the Cope rearrangement of the silylenol-ether (112) to give the rearranged product (113).



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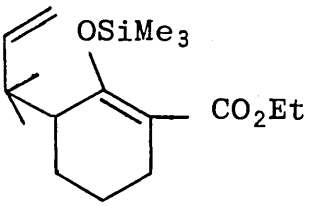
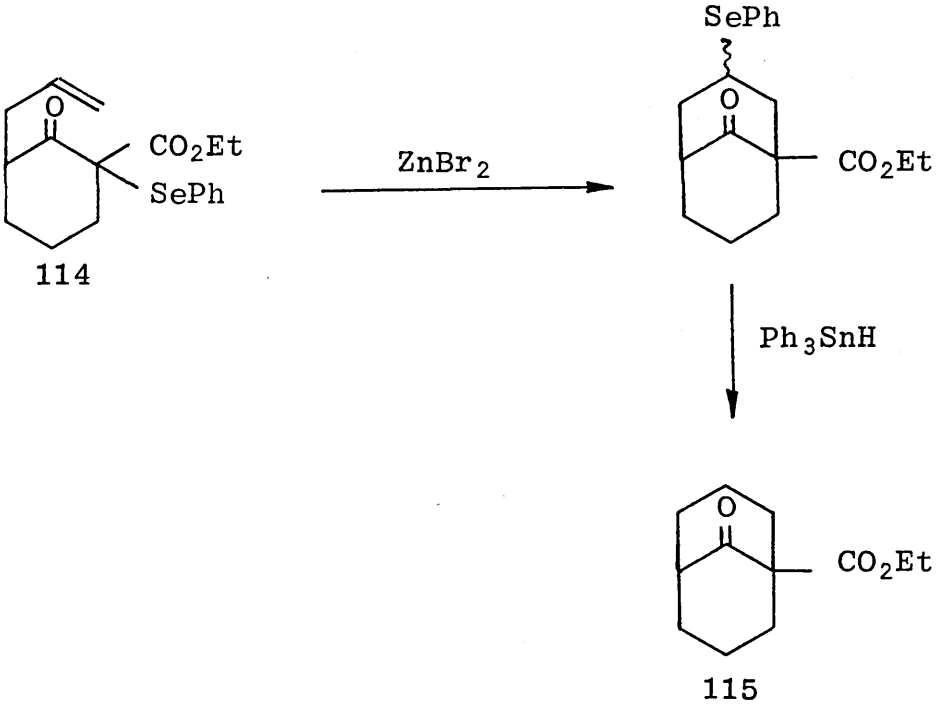


113

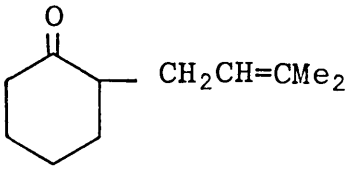
This rearranged product would be a useful intermediate for the preparation of the gemdimethyl compound (105) by analogy with the work of Ley [78] who converted (114) to (115) as shown below:



114

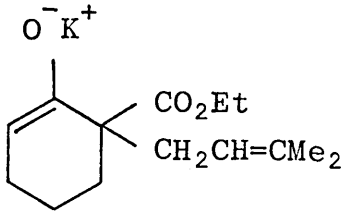
115

However, the silylenol-ether (112) did not change on heating in solution, in an autoclave at high temperatures. On pyrolysis, neat under nitrogen, the decarbethoxylated product (116) and desilylated starting material (106) were the only compounds isolated.

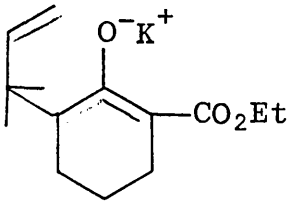


116

In addition, the attempted Cope rearrangement using the potassium enolate (117) of the ketone (106) did not give any of the required rearranged product (118).



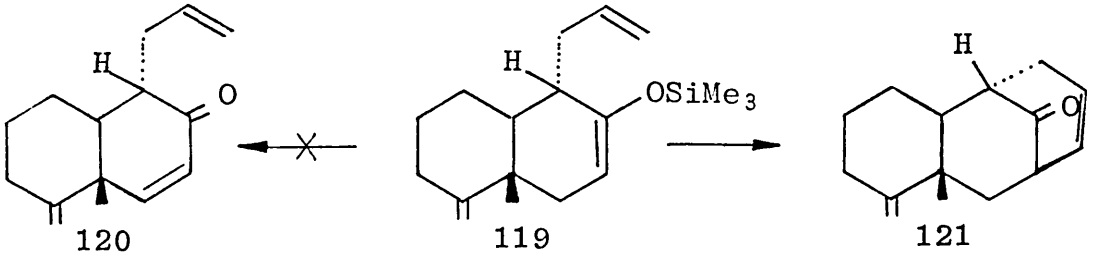
117



118

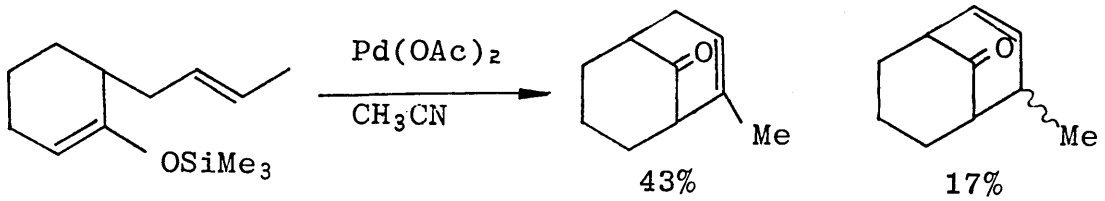
The reaction of the prenyl compound (106) with sulphuric acid yielded a mixture of polymeric material which could not be identified.

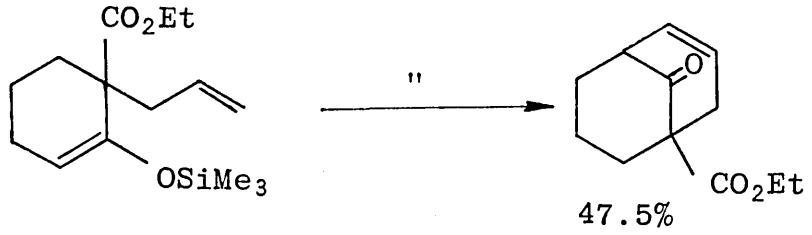
The reaction of silylenol-ethers with palladium acetate ($Pd(OAc)_2$) in acetonitrile has been shown by Ito et al [79] to be a valuable route to α,β-unsaturated carbonyl compounds. Kende et al [80] noticed that during their application of this procedure to the ajugarin precursor (119), they isolated, instead of the enone (120), the bicyclic ketone (121) in 80% yield.



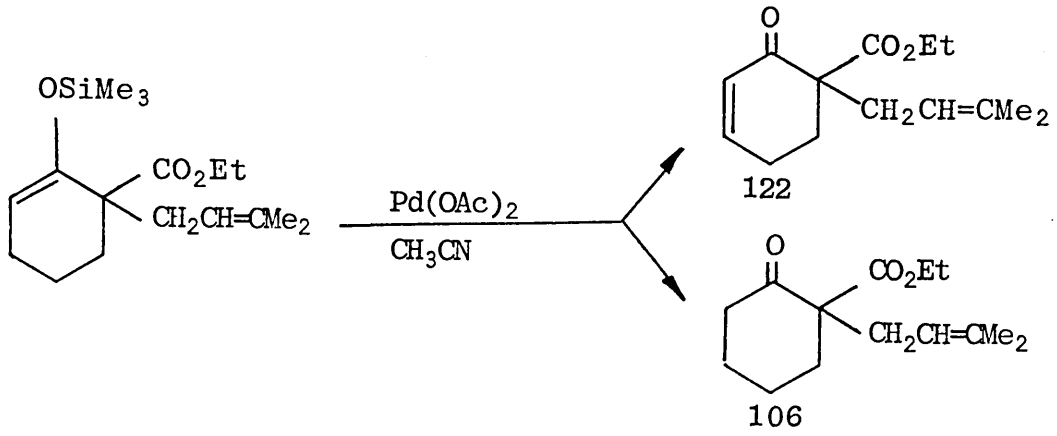
120 119 121

In order to further study this reaction, a variety of cyclopentanones and cyclohexanones bearing unsaturated side chains α or λ to the carbonyl group were converted to trimethylsilyl enol-ethers and these were subjected to reaction with $Pd(OAc)_2$ under standard conditions. Some of the pertinent cyclohexanone examples are shown below.



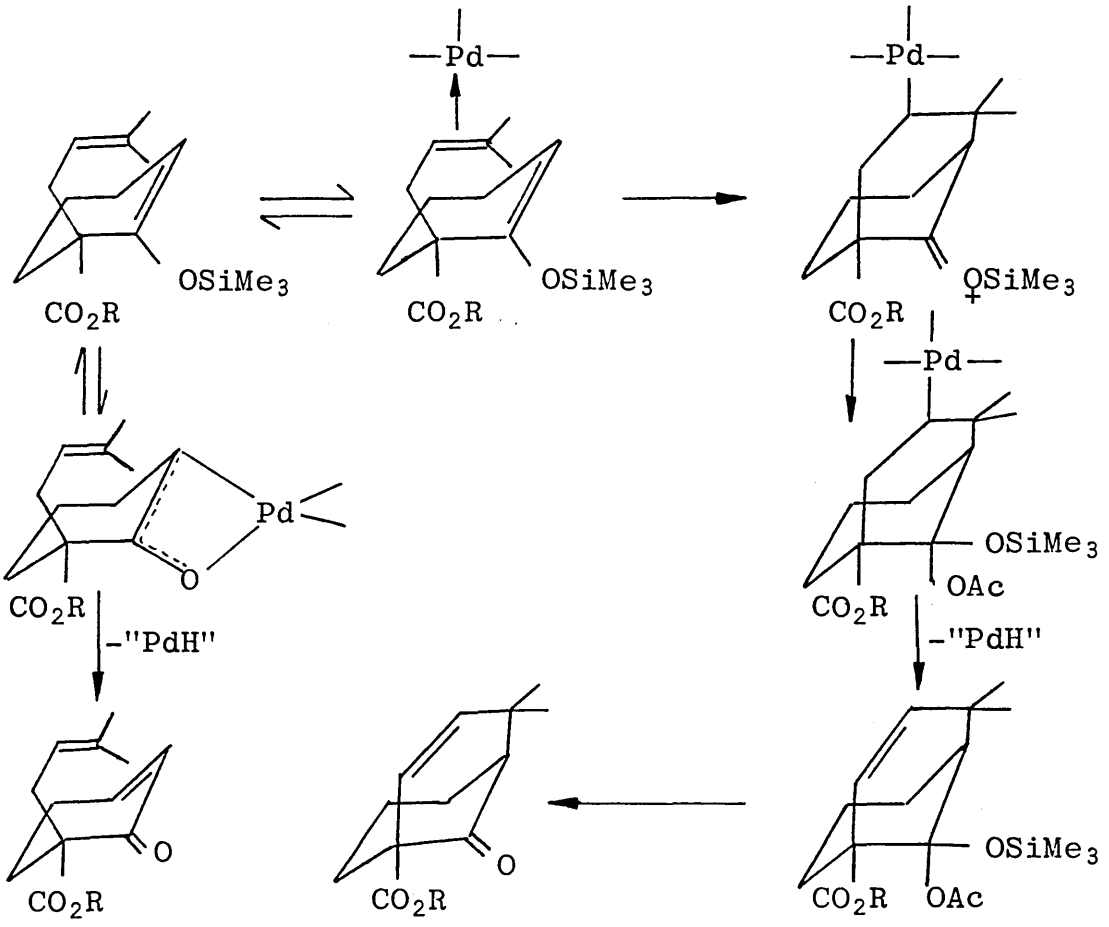


When these conditions were applied to our silylenol-ether (112), the products obtained were the α, β-unsaturated ketone (122) and the desilylated product (106).



The examples reported by Kende et al did not include a tertiary substituted alkene. It seems from our result that it is more favourable for the palladium acetate to

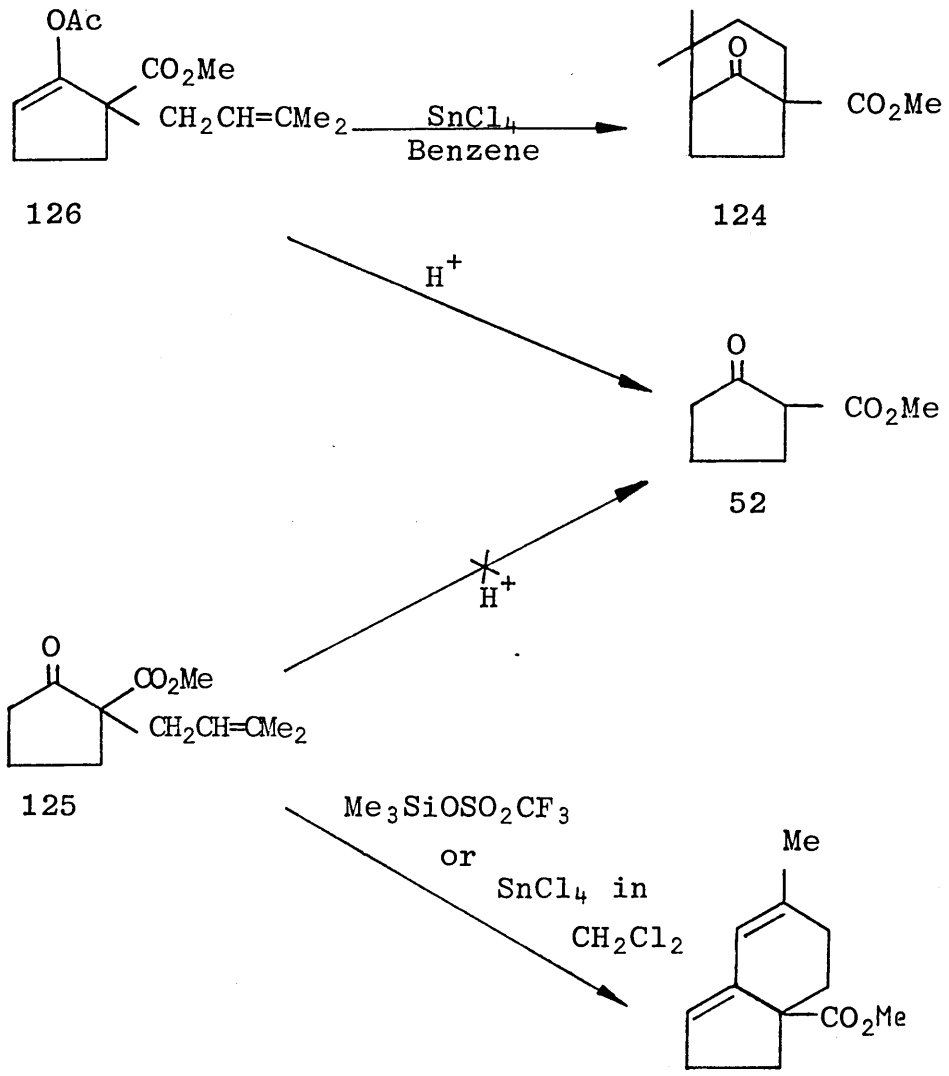
co-ordinate to the enol-ether double bond to give the α,β-unsaturated ketone than to co-ordinate to the tertiary substituted alkene to give the bicycle (123). The postulated mechanism leading to both products is shown below.



The investigative reactions to synthesize the gemdimethyl intermediate (105) were carried out exclusively on the 6-membered prenyl compound (106). The preparation of the corresponding 5-membered-gemdimethyl intermediate (124) was then immediately possible and some of the more interesting reactions were also repeated with the

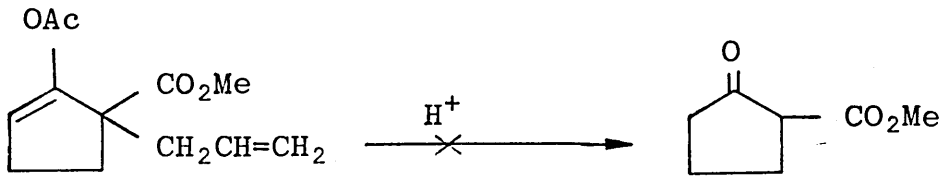
5-membered prenyl compound (125). These results are summarised in scheme 16.

Scheme 16



In order to investigate the generality of the dealkylation reaction mentioned previously on page (56) and seen in scheme 16 (126) → (52). The enol-acetate of the allyl compound (127) was prepared but it failed to dealkylate

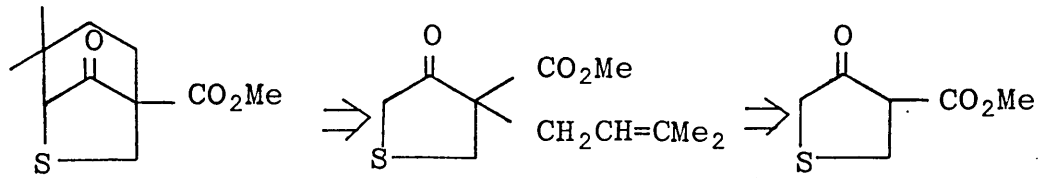
under similar conditions to that of the prenyl enol-acetate compound (126).



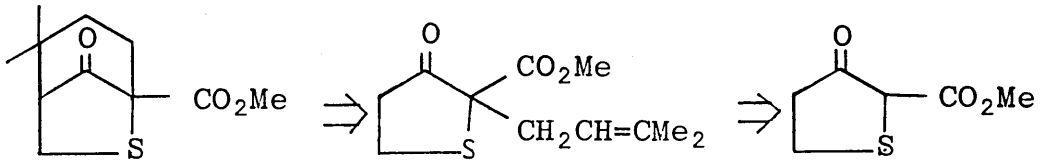
127 52

It may be that the dealkylation reaction is dependent on the stability of the carbocation formed. The dimethylallyl cation is more stable than the allyl cation.

In order to extend our work to heterocyclic thromboxane analogues, we investigated the synthesis of (128) and (129) which could afford (130) and (131).

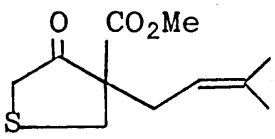


130 128 90

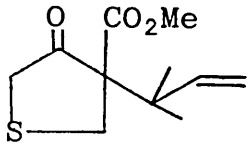


131 129 89

When the sulphur heterocycle (90) was alkylated with prenyl bromide under the same conditions as had been used in the carbocyclic series, two products were isolated. They were identified as the prenyl product (132) and the rearranged product (133).

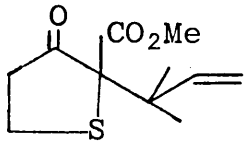


132



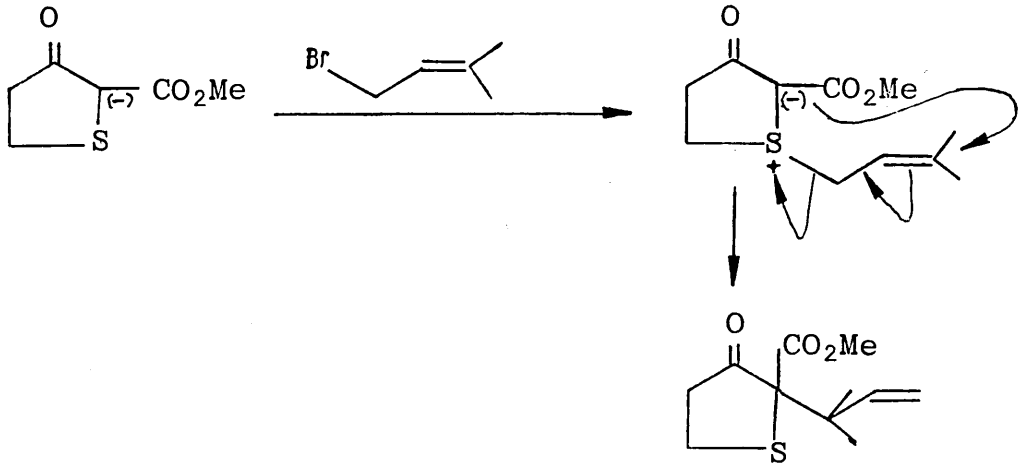
133

Using similar conditions, the other sulphur heterocycle (89) gave exclusively the rearranged product (134).



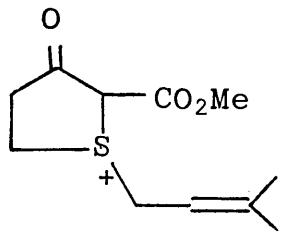
134

A possible mechanism is postulated below:



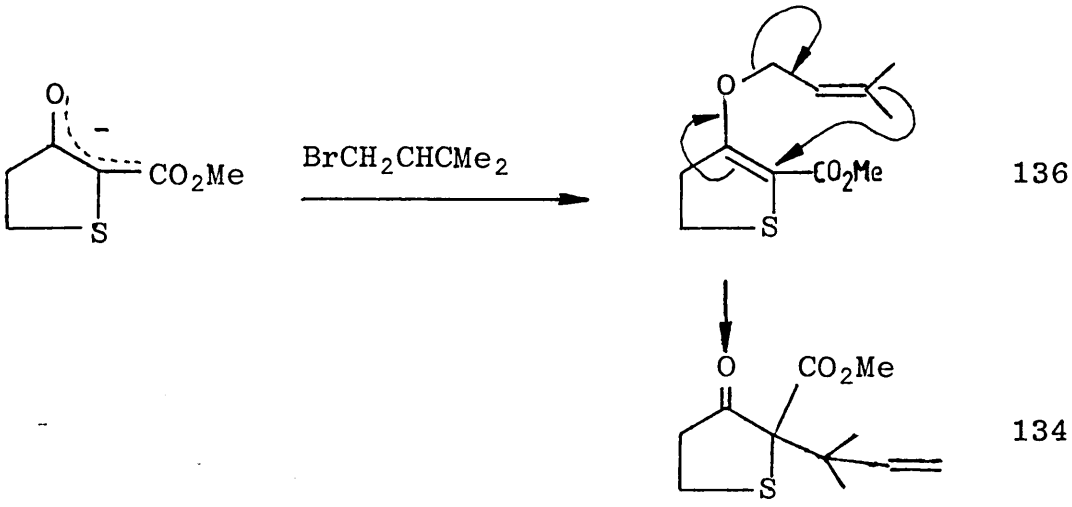
134

This mechanism could be supported if the sulphonium salt (135) was isolated and then treated with sodium hydride. Unfortunately several attempts at synthesizing and isolating the sulphonium salt were unsuccessful.



135

Another possible mechanism might involve an O-alkylation followed by a Claisen rearrangement as shown below.

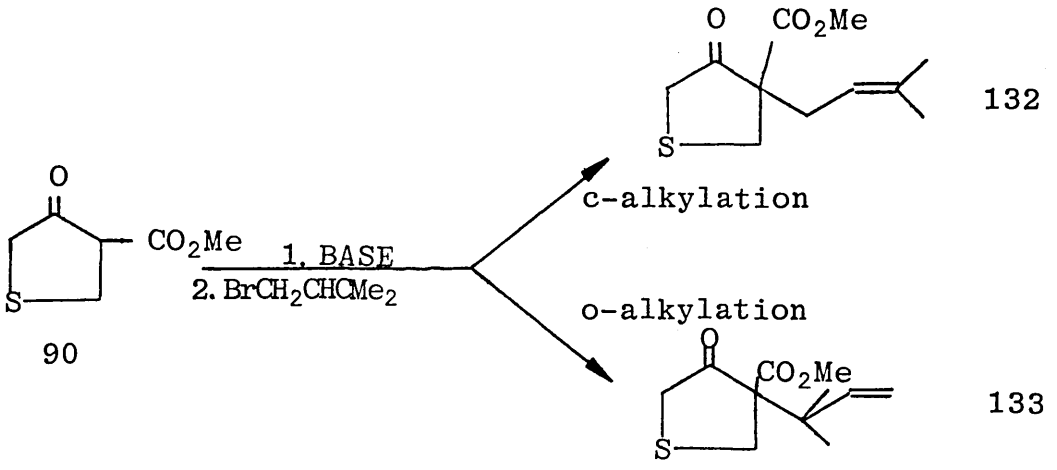


136

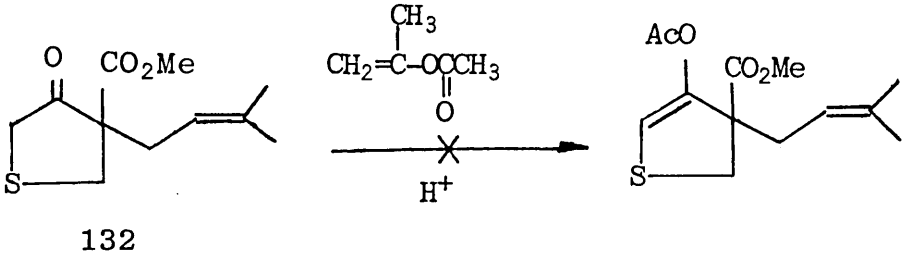
134

This is not easily explained since it does not account for the fact that the rearranged product is not seen in the alkylation with either the five or six membered carbocyclic systems (52) and (82) respectively and only to a lesser extent with the other sulphur heterocycle (90). The reaction with (89) was complete after 20 minutes at room temperature, but the Claisen rearrangement [81] is not usually so facile. Lack of time prevented further study

of this mechanism. The mechanism could be supported by isolating the O-alkylated product (136) but this seems unlikely if this is the reaction course because of the very facile rearrangement. Another possibility would be to vary the base and solvent in order to influence the C and O alkylation ratio and then monitor the amounts of the two products (132) and (133) from the alkylations of the heterocycle (90).

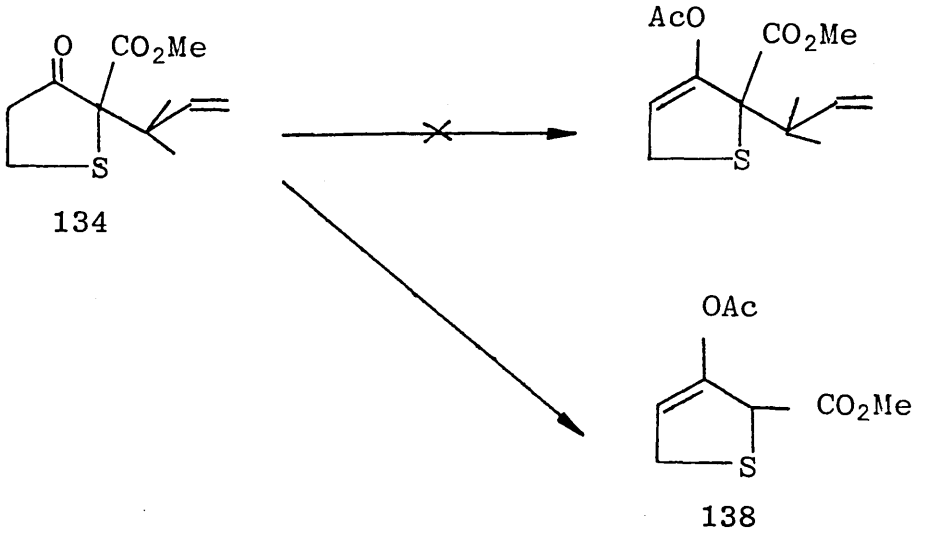


A further reaction investigated with the sulphur heterocycles (132) and (134) was the enol acetate formation. Both sulphur heterocycles (132) and (134) were treated with isoproprenylacetate in the presence of toluene-4-sulphonic acid. The prenyl compound (132) decomposed under the reaction conditions.



132

During the preparation of the enol acetate of the rearranged product (134), the only product isolated under the reaction conditions was the enol acetate of the dealkylated product (138). It seems that dealkylation has occurred under the acidic conditions of the reaction medium.



134

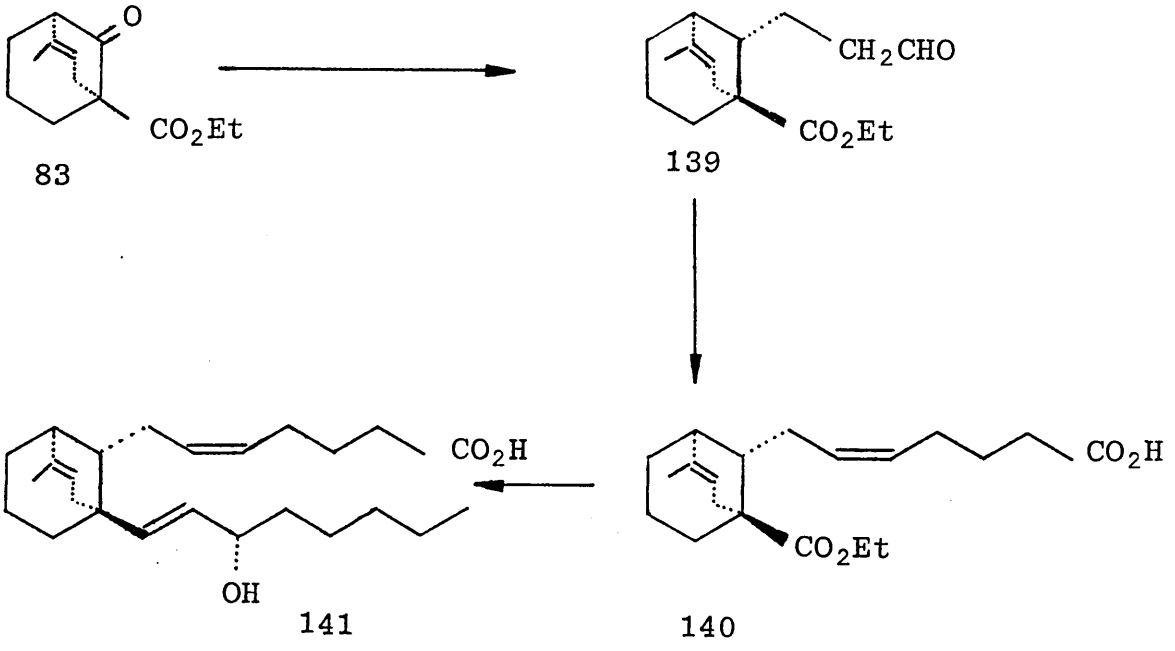
138

If time had allowed further study in this area, other methods towards the enol acetates of (132) and (134) would have been explored.

CHAPTER 5

SYNTHESIS OF A THROMBOXANE A_2 ANALOGUE FROM ETHYL 4-METHYL-9-OXOBICYCLO [3.3.1] NON-3-ENYLCARBOXYLATE

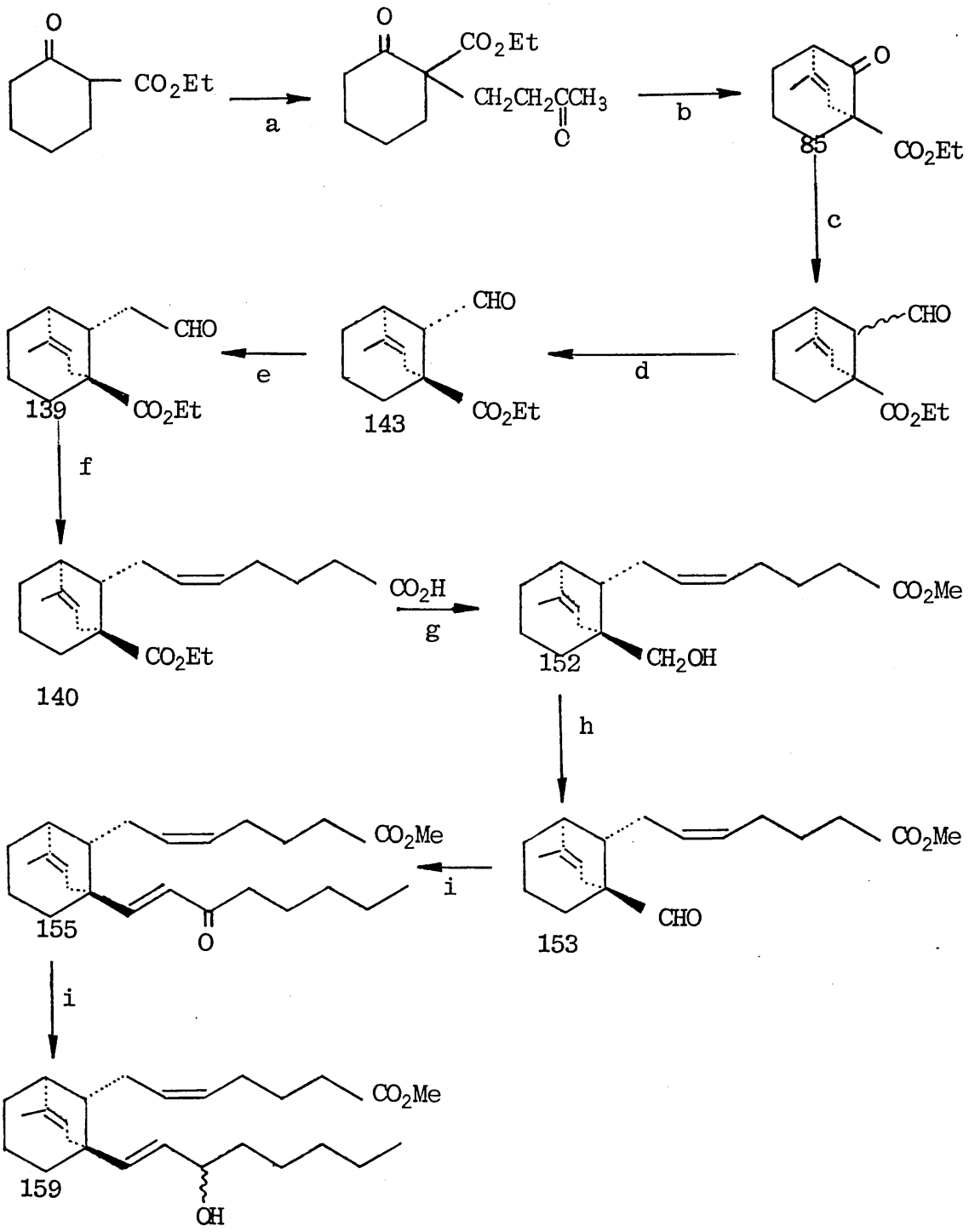
The bicyclic ketoester (83) has the necessary functionalities for transformation to a thromboxane analogue (141). The keto-function at C-9 could be elaborated to the α chain and the ester functionality to the β chain.



The successful route for the conversion of ethyl 2-oxocyclohexanecarboxylate (82) to a thromboxane A_2 analogue, with yields, is summarised in scheme 17.

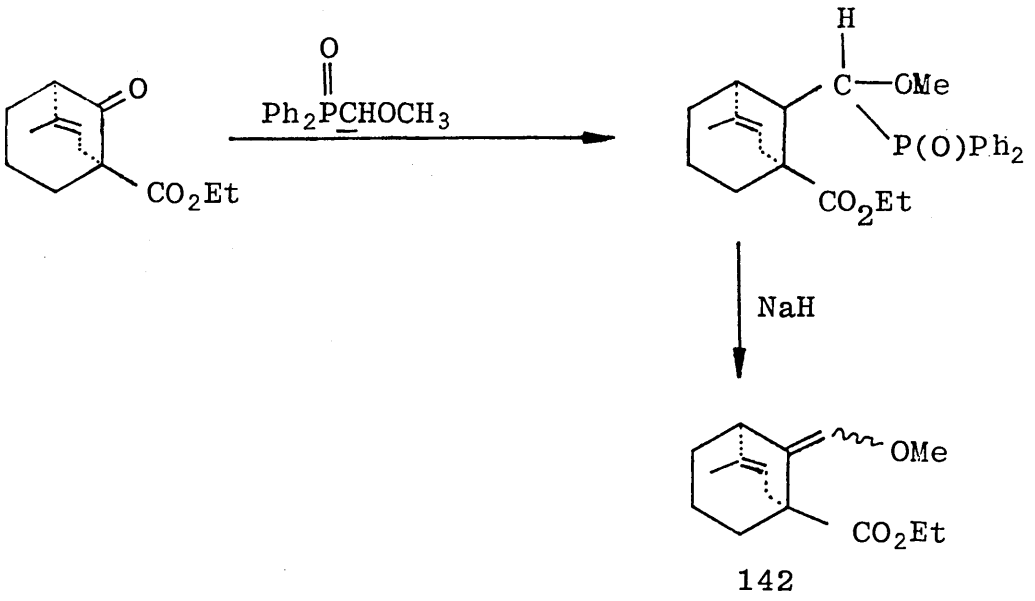
The first step from the bicyclic ketoester (83) was the stereospecific two carbon homologation to the aldehyde (139). Several Wittig reactions with various phosphonium salts under varying conditions failed. However, a Wittig-Horner reaction to give a one carbon homologation using

SCHEME 17



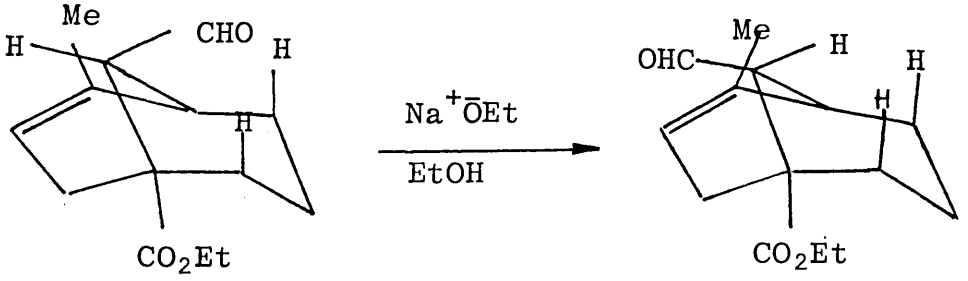
Reagents (a) methyl vinyl ketone and Et_3N in benzene, (97%) (b) CH_2SO_4, (60%), (c) $Ph_2P(O)\bar{C}HOCH_3$ then NaH followed by H_3O^+ (91%), (d) NaOEt in EtOH, (96%), (e) $Ph_3P{=}CHOCH_3$ then $Hg(OAc)_2$ followed by KI (75%), (f) $Ph_3P{=}CH(CH_2)_3CO_2^-K$, (87%) (g) Dibal, CH_2N_2, (87%), (h) P.C.C. (92%), (i) $MeO)_2P(O)\bar{C}HC(O)C_5H_{11}Na^+$ (87%), (j) $NaBH_4$ (90%)

methoxymethyldiphenylphosphine oxide [82] was successful and gave a geometric mixture of enol ethers (142) in good yield.



142

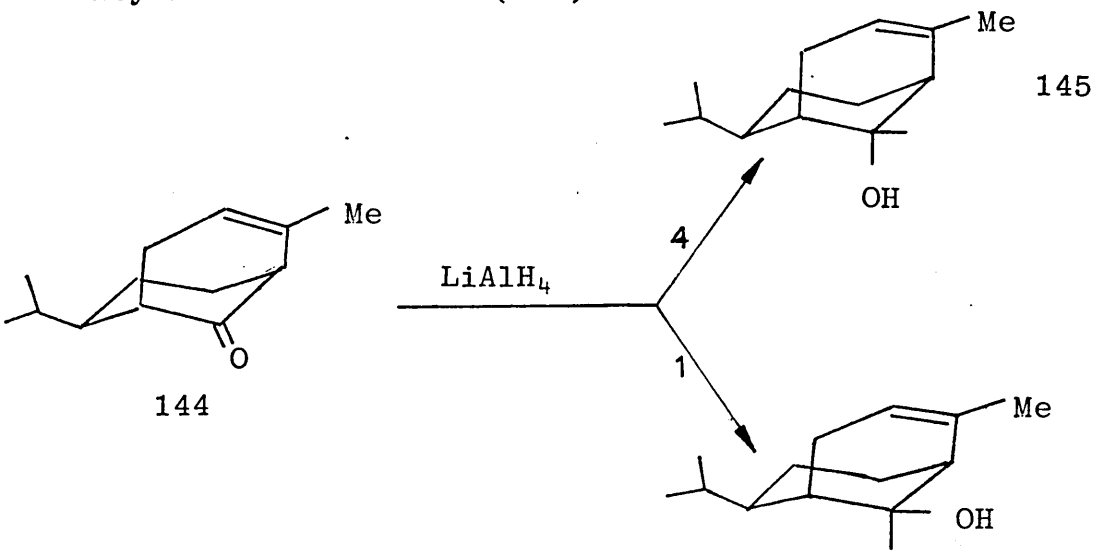
The enol ethers (142) were hydrolysed with a catalytic amount of acid in acetone to give an epimeric mixture of aldehydes. The proton n.m.r. of this mixture showed there to be a 2:1 ratio of epimers. On treatment with a catalytic amount of sodium ethoxide in ethanol, the mixture epimerised to one aldehyde (143), the previous major component.



143

Studies using Dreiding models suggest that the thermodynamically favoured epimer is in the required stereochemical conformation for the thromboxane A_2 analogue (141). This assumes that the 1,3-diaxial interactions of the axial hydrogens on C2 and C4 have more of a steric effect on the aldehyde than the π-electrons of the double bond.

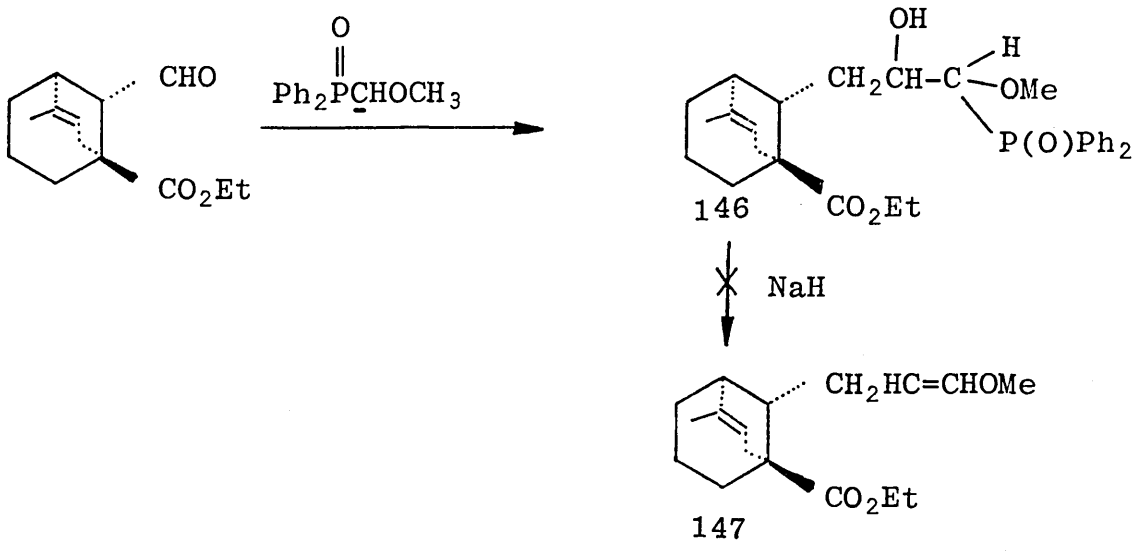
This is in agreement with the work of Corey [83] on the synthesis of helminthosporal which involved a similar bicyclic intermediate (144).



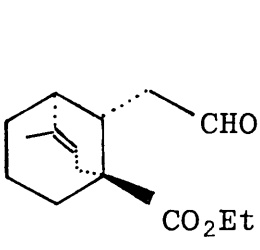
Corey showed that the reduction of the ketone group at C-9 with the bicyclic ketone (144) gave predominantly the alcohol (145) with an axial orientation with respect to the cyclohexane ring. This infers that there is more steric hindrance to the reducing agent from the axial hydrogens on C2 and C4 than there is from the π-electrons on the double bond.

Another one carbon homologation was now necessary. The Wittig reagent methoxymethyldiphenylphosphine oxide was not

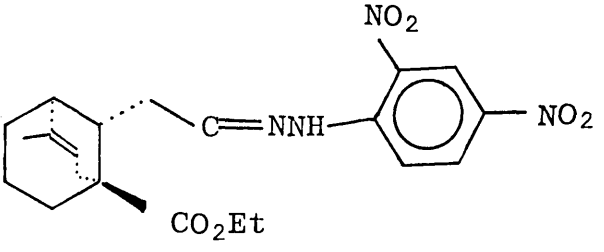
successful in preparing the second aldehyde (139) because of the very slow collapse of the initial intermediate (146) with sodium hydride to give the enol ether (147).



However, condensation of the aldehyde (143) with methoxymethyltriphenylphosphorane [84] in toluene and tetrahydrofuran solution at $0^{\circ}C$ gave the enol ether (147). The aldehyde (139) was liberated from the enol ether (147) in good yield by treatment with mercuric acetate followed by potassium iodide. The stereochemistry of the aldehyde (139) was confirmed by X-ray analysis of its dinitrophenylhydrazone (148). This shows clearly the trans (E) arrangement of the side chains. The X-ray structure is shown overleaf.

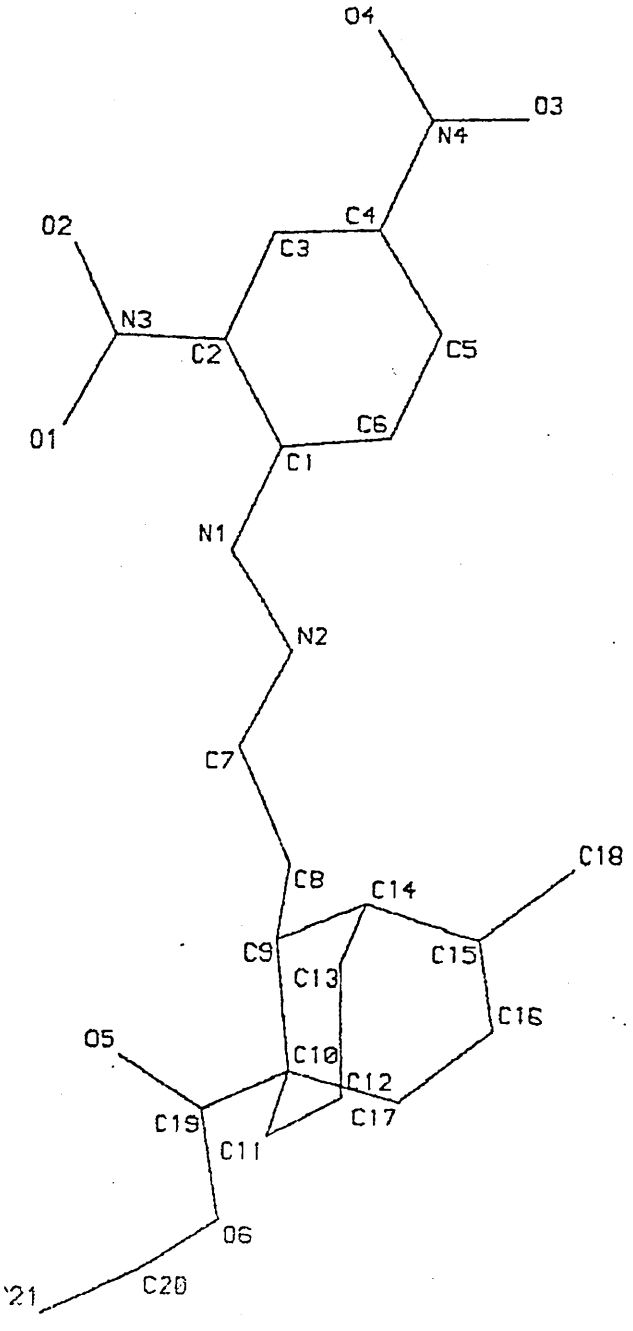


139

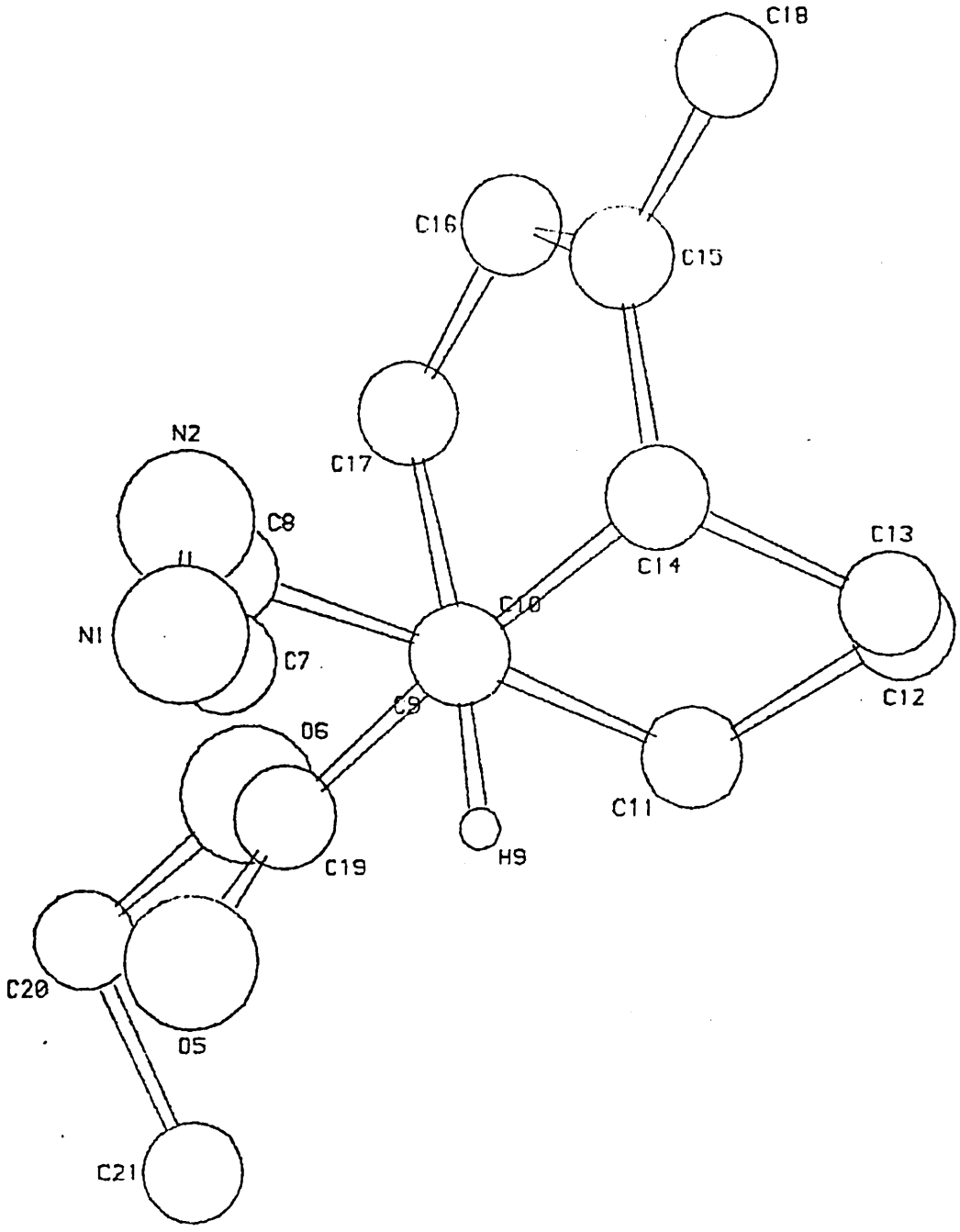


148

Diagram of the dinitrophenylhydrazone (148) obtained from the X-ray analysis data.

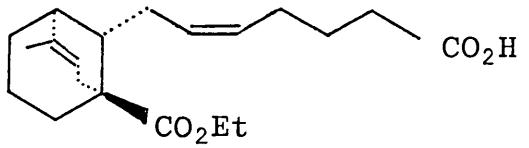


A view along C9 to C10 as numbered in the previous X-ray diagram. (Viewed along C5 to C9 as numbered in text.)



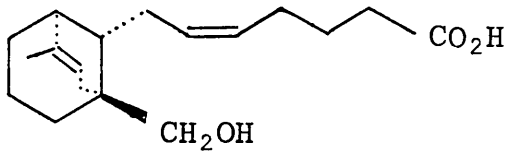
The α side chain was completed to give the acid (140) by treating the aldehyde (139) with the potassium salt of 4-carboxybutyltriphenylphosphorane (149) in tetrahydrofuran and furnished a cis (Z) double bond. [85]

$Ph_3P = CHCH_2CH_2CH_2CO_2^-K^+$ 149

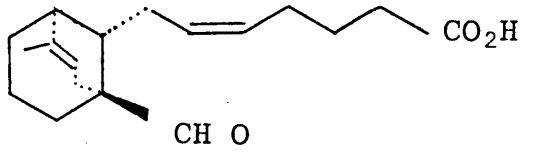


140

The ester group now needed to be modified to complete the synthesis. It had been reported that ester groups could be reduced selectively to aldehydes in the presence of an acid group with di-isobutylaluminium hydride (dibal). [86] When this was attempted on acid (140), a mixture of alcohol (150), aldehyde (151) and starting material (140) was obtained.



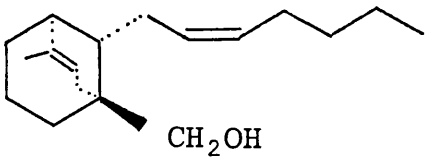
150



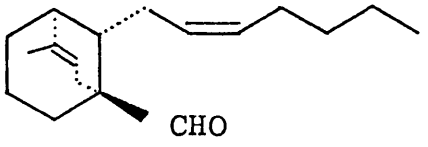
151

By using one extra equivalent of dibal, the ester was reduced completely to the alcohol (150) in almost quantitative yield. Oxidation of the acid-alcohol (150)

with pyridinium chloro chromate [87] resulted in clean conversion in low yield to the aldehyde (151). However, when the acid-alcohol (150) was treated with diazomethane to give the methyl ester (152), the latter was oxidised with pyridinium chloro chromate to give the corresponding aldehyde (153) cleanly and in high yield.

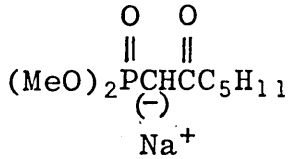


152

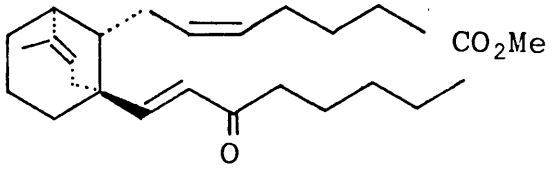


153

The β side chain was introduced by using the Wadsworth-Emmons modification of the Wittig reaction which established a trans (E) double bond. [88] This was readily accomplished by reacting the aldehyde (153) with the sodium derivative of dimethyl-2-oxoheptylphosphonate (154) in tetrahydrofuran and gave the α,β-unsaturated ketone (155).

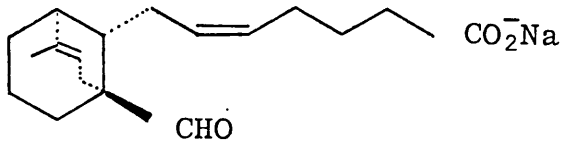


154

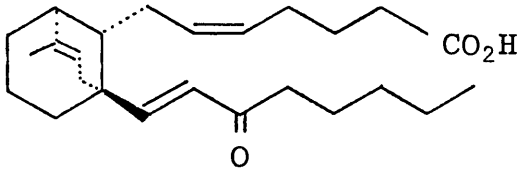


155

The β side chain has also been introduced by treating the sodium salt of the aldehyde acid (156) with the sodium derivative of dimethyl-2-oxoheptylphosphonate (154) to give the α,β unsaturated ketone (157).

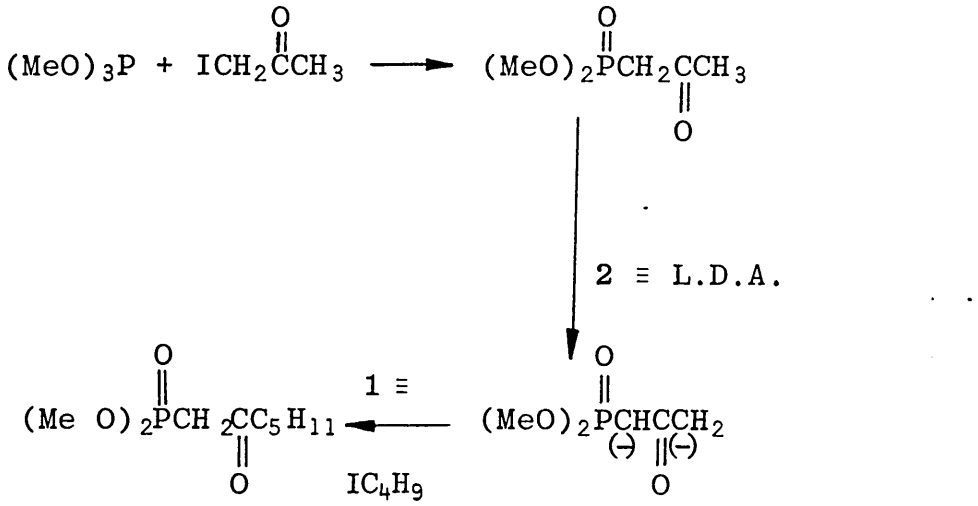


156



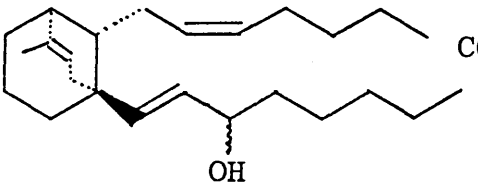
157

Dimethyl-2-oxoheptylphosphonate (158) was prepared using established conditions as shown below. [89]



158

Reduction of the α,β unsaturated ketone (155) with sodium borohydride gave as expected an epimeric mixture of alcohols (159). [90]



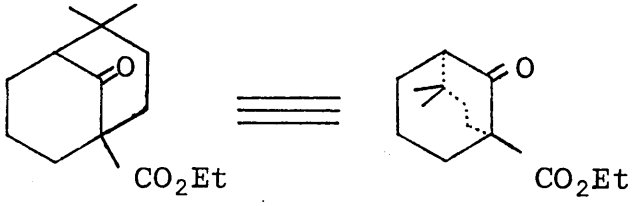
159

The epimeric alcohols were not separated because of the very difficult separation and the fact that the individual epimers were not required for the biological testing.

The preliminary pharmacology results indicated that there was no activity as a thromboxane A_2 antagonist.

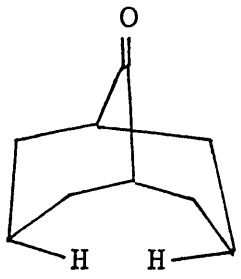
CHAPTER 6

6.1 TRANSFORMATION OF ETHYL 4,4-DIMETHYL-9-OXOBICYCLO [3.3.1] NONANECARBOXYLATE TO A THROMBOXANE A_2 ANALOGUE

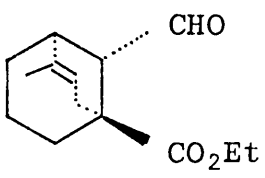


105 105

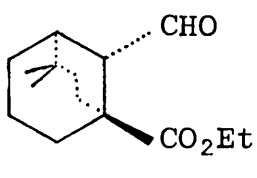
Previous workers in the area of bicyclo[3.3.1] nonane systems have shown that the molecule is in the twin-chair conformation, [91] despite the unfavourable interaction between the endo hydrogens on C3 and C7.



We therefore assumed that our bicylic ketone (105) was also in the same conformation. Dreiding models suggest that the required aldehyde (160) is not the thermodynamically favoured isomer as was the case with the previous analogue (143).

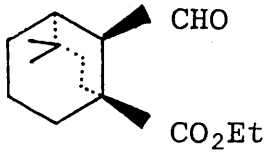


143

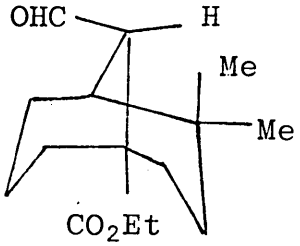


160

The axial methyl on C4 imparts more hindrance on the aldehyde than do the axial hydrogens on C6 and C8. The thermodynamically favoured isomer is therefore (161) with the cis (Z) configuration of the side chains.



161



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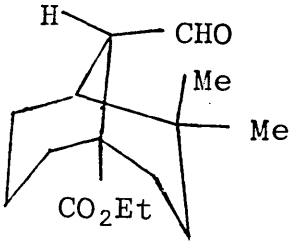
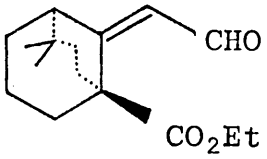
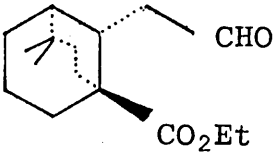


160

However, studies using Dreiding models suggested that the reduction of the α,β-unsaturated aldehyde (162) would give the required isomer (163) by addition of the hydrogen to the least hindered side.

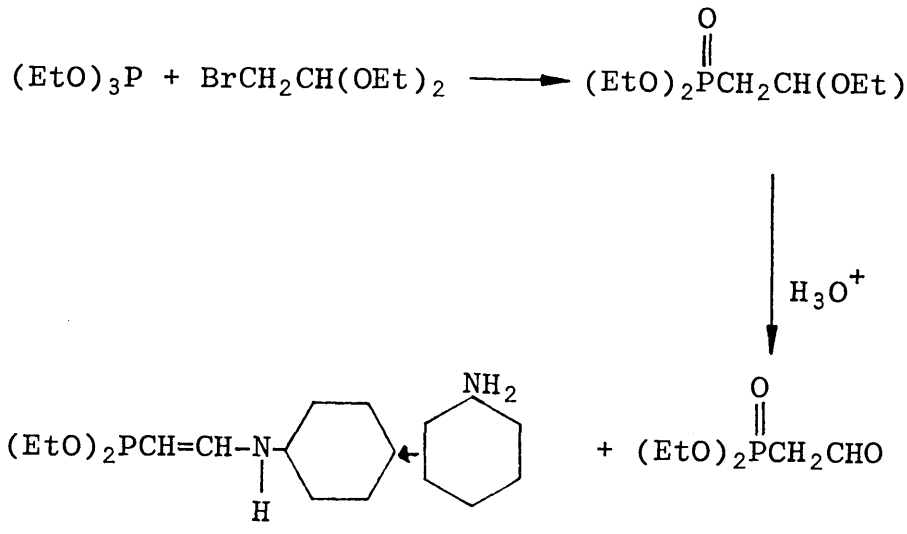


162



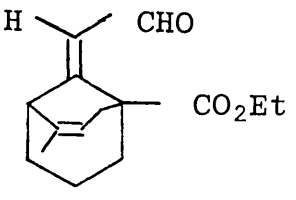
163

Diethyl 2-(cyclohexylamino)vinyl phosphonate (164) would seem to be an ideal Wittig reagent [92] for the preparation of this α,β-unsaturated aldehyde (162). This phosphonate was prepared using established conditions.

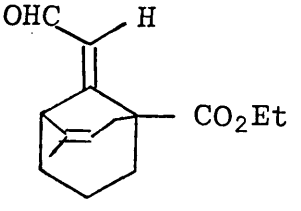


164

The olefin (83) was used as a model compound for the Wittig reaction. Treatment of the olefin (83) with the anion from diethyl 2-(cyclohexylamino)vinyl phosphonate (164) gave the unsaturated imine which was hydrolysed to two isomeric aldehydes (165) and (166).



165



166

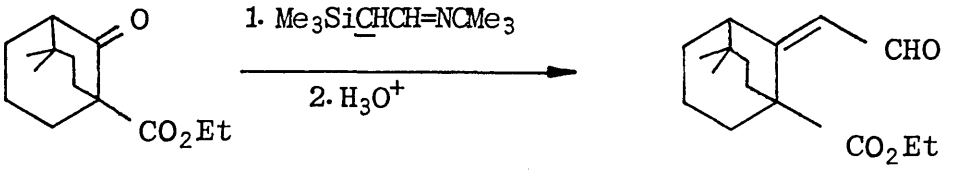
However, when the reaction was repeated with the gemdimethyl intermediate (105), no reaction was apparent.

An alternative method which has been developed by Corey [93] for the two carbon homologation of ketones and aldehydes to α,β-unsaturated aldehydes involves the use of the silylaldimine (167):

$Me_3SiCH_2CH = NCMe_3$ 167

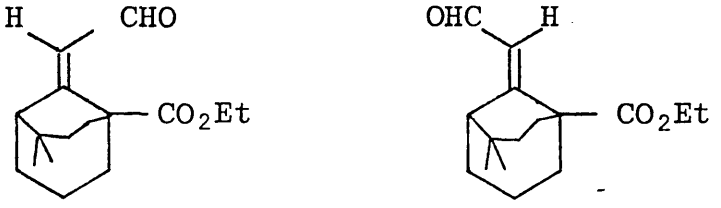
This method was attempted and our α,β-unsaturated aldehyde

(162) was successfully synthesized. The gemdimethyl intermediate (105) was treated with the anion of the silylaldimine (167) followed by treatment with aqueous acid in tetrahydrofuran to give the α,β-unsaturated aldehyde (162). 2.6 equivalents of the silylaldimine anion were required before the reaction went to completion.



105 162

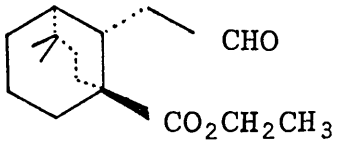
A chromous sulphate reduction, [94][95] which is highly selective for conjugated alkenes, was the first method of reduction attempted. Under these conditions our α,β-unsaturated aldehyde isomerised from the Z isomer (168) to the E isomer (169) without any reduced product being produced.



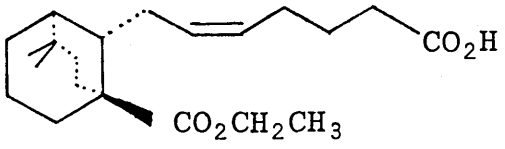
168 169

Catalytic hydrogenation [95] with palladium on carbon of the α,β-unsaturated aldehyde (168) in ethyl acetate and hexane gave cleanly the required saturated aldehyde (163). The α side chain was completed by treatment of the aldehyde (163) with the potassium salt of 4-carboxybutyltri-

phenylphosphorane to give the acid (170).

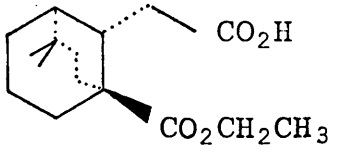


163



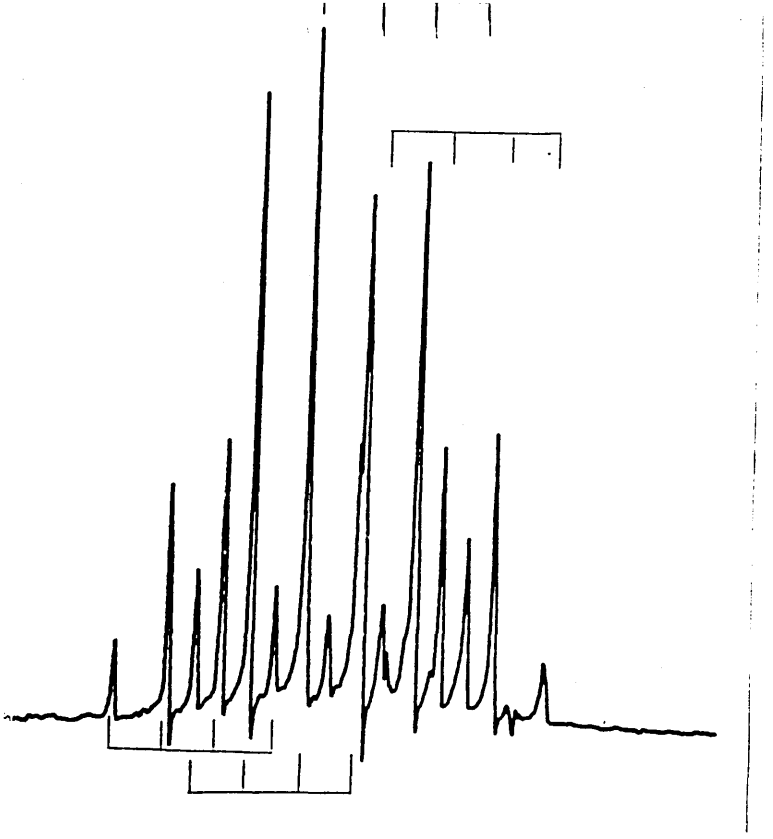
170

Low resolution proton n.m.r. showed the methylene protons of the ester in both the aldehyde (163) and the acid (170) to be a complex pattern. The signal for the aldehyde proton was however a clean triplet. The aldehyde (163) was rapidly oxidised to the acid (171) in deutrochloroform. The aldehyde (163) would therefore not be suitable for extensive n.m.r. studies and for this reason (171) was used.

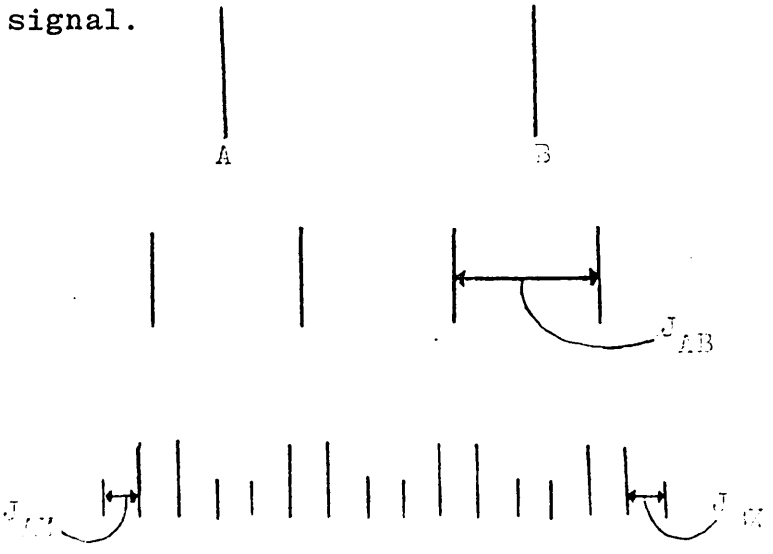


171

A 400 MHz proton n.m.r. spectrum was run on both the acids (170) and (171). The methylene protons of the ester in both spectra appeared as 16 lines as shown overleaf.

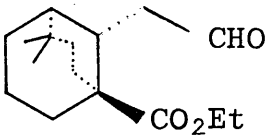


This can be explained in terms of prochiral geminal anischronicity because the ester group is attached to a chiral centre. The geminal protons of the methylene are therefore not equivalent and the n.m.r. multiplet can be seen as 4 quartets. This arises from the geminal protons being split by each other into two doublets and then each signal being split by the adjacent methyl protons into a quartet as shown below. It can be thought of as an ABX signal.

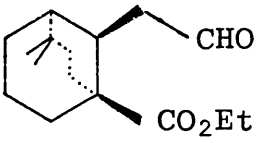


The ^{13}C spectra of the acids (170) and (171) showed only one set of carbons. It was therefore assumed that the reduction had given only one product, the required trans (E) aldehyde (163).

The synthesis of the cis (Z) aldehyde (172) was attempted as additional evidence for the identity of the trans (E) aldehyde (163).

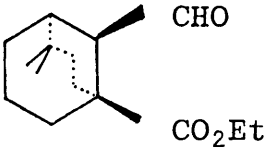


163

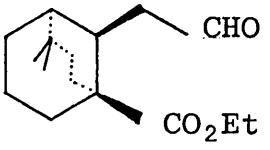


172

As discussed earlier, Dreiding models suggested that the cis (Z) aldehyde (161) would be the thermodynamically favoured isomer. The synthesis of the cis (Z) aldehyde (161) would be attempted and it was hoped that it could be converted into (172) and be shown to be different from aldehyde (163).



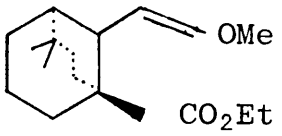
161



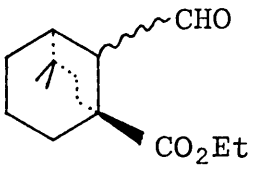
172

Several attempts to convert the gemdimethyl intermediate (105) to the aldehyde (161) using the Wittig-Horner reagent methoxymethyldiphenylphosphine oxide were inconsistent and unsatisfactory. At best 5% yields of the enol ether (173) were isolated and only an impure sample of an aldehyde (174)

was obtained.

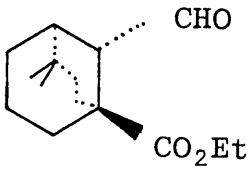


173



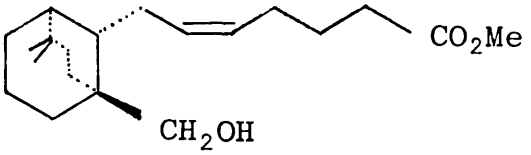
174

An experiment on t.l.c. scale showed that one aldehyde was formed on hydrolysis which was epimerised to another aldehyde with sodium ethoxide in ethanol. This has not been rigorously proven because of the low yield. The results of the t.l.c. experiment imply that the cis (Z) isomer (161) was obtained upon epimerisation of the trans (E) isomer (160) which is in agreement with the trans (E) isomer (163) being obtained from the reduction.



160

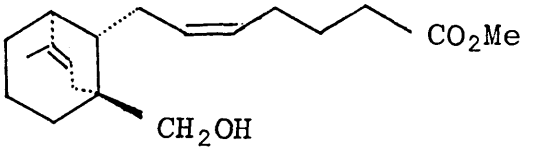
The dibal reduction of the ester group in the acid (170) followed by treatment with diazomethane gave the alcohol (175).



175

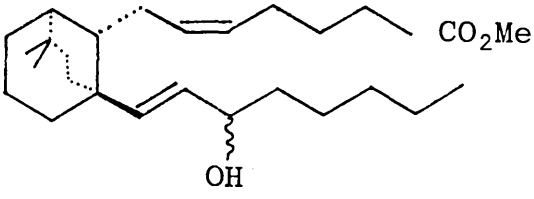
The methylene adjacent to the alcohol also shows prochiral geminal anischronicity. The methylene protons occur as two doublets with a J value of 13Hz.

This was also observed with the alcohol (152) during the synthesis of the previously discussed analogue (159).



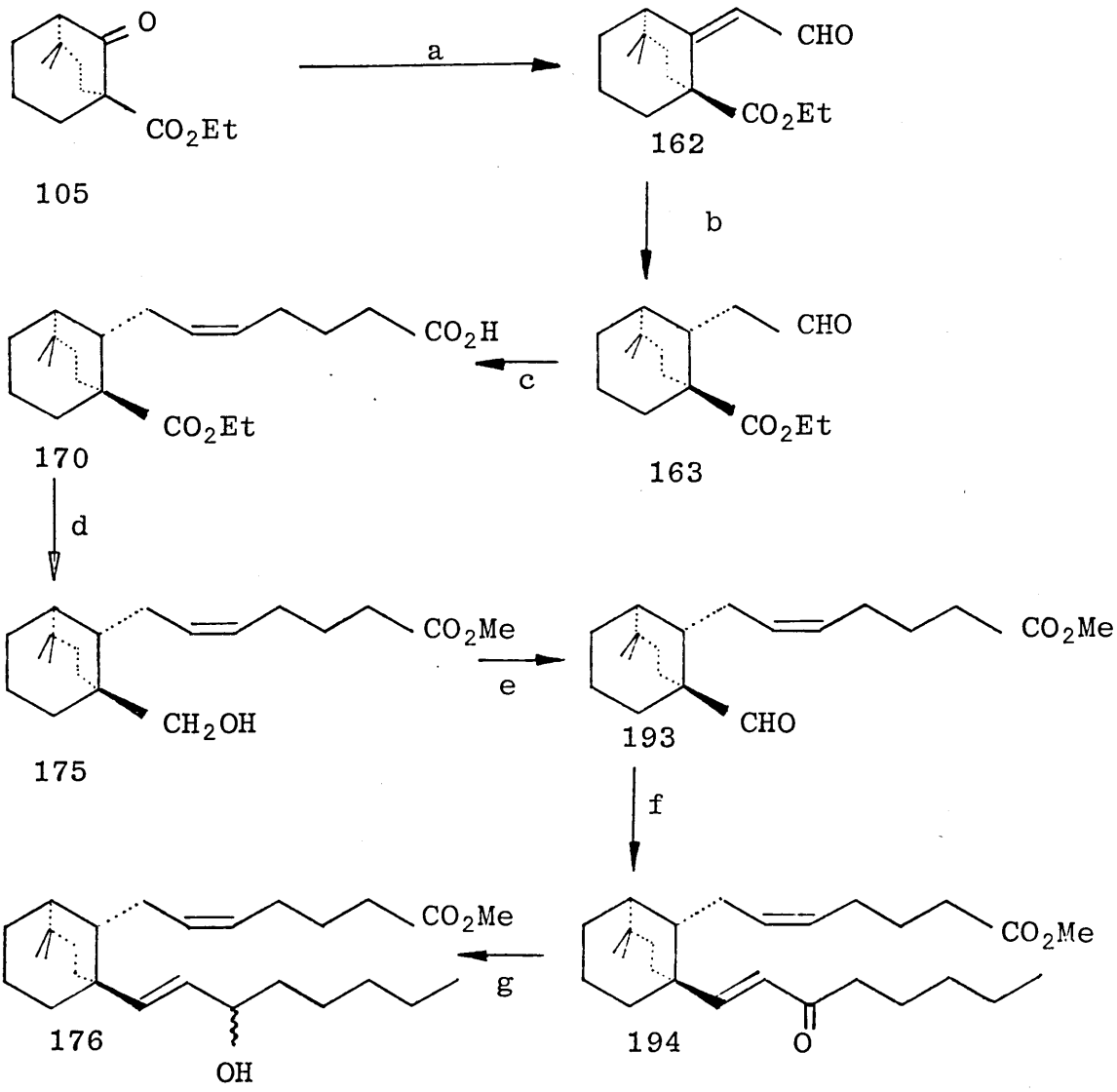
152

The completion of this synthesis to the thromboxane analogue (176) proceeded as expected and is summarised in scheme 18 overleaf.



176

SCHEME 18



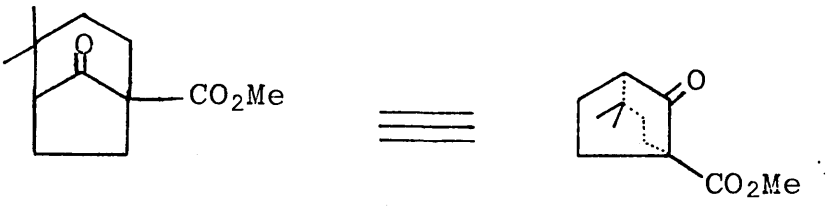
Reagents : (a) $Me_3Si\bar{C}HCH{=}N{-}CMe_3Li^+$ then H_3O^+, (69%)

(b) Pd/C, H_2, (98%), (c) $Ph_3P{=}CH(CH_2)_3CO_2^-K^+$ (74%)

(d) Dibal then CH_2N_2 (74%), (e) PCC (100%)

(f) $(MeO)_2P(O)CHC(O)C_5H_{11}$ Na , (79%), (g) $NaBH_4$ (90%)

6.2 TRANSFORMATION OF METHYL 4,4-DIMETHYL-8-OXOBICYCLO [3.2.1] OCTANECARBOXYLATE TO A THROMBOXANE A_2 ANALOGUE



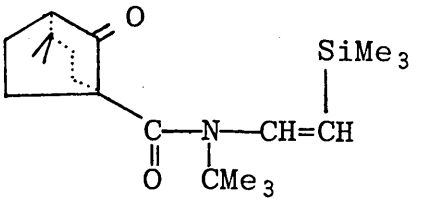
124 124

It is more obvious with this bicyclo [3.2.1] intermediate (124) that the gemdimethyl imparts steric hindrance on its side of the molecule. As with the previous bicyclo [3.3.1] intermediate (105), reduction of the α,β-unsaturated aldehyde (178) should give the trans aldehyde (179).

178 179

When the bicyclic ketoester (124) was treated with the silylaldimine (167) only a small amount of the required α,β-unsaturated aldehyde was formed. The major product seemed to be the amide (180).

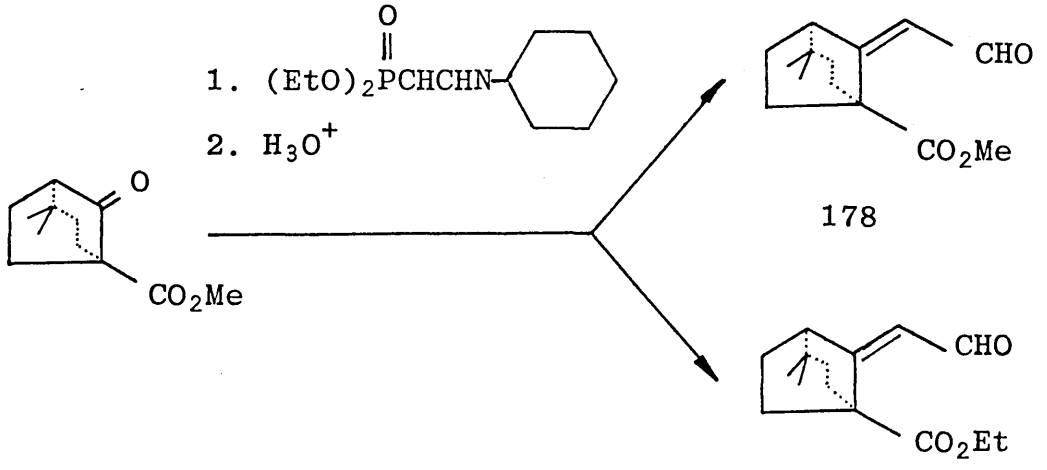
$Me_3SiCH_2CH = NCMe_3$ 167



180

The proton n.m.r. is in agreement with this structure (180) and the accurate mass of the molecular ion agrees with the empirical formula. However, the i.r. does not have any strong carbonyl stretches at 1700-1750 cm^{-1}, but does show stretches at 1680 cm^{-1} and 1645 cm^{-1}. The ^{13}C n.m.r. does not seem to show the presence of any carbonyl groups.

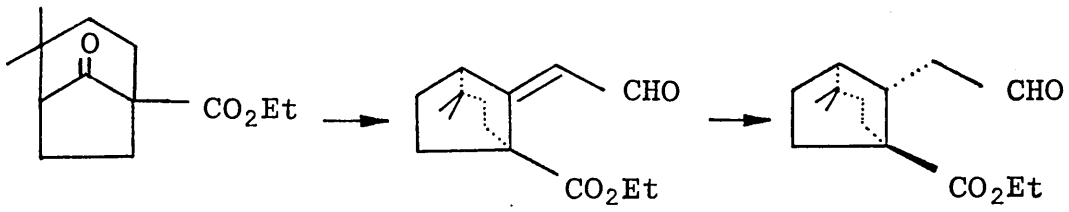
The α,β-unsaturated aldehyde (178) was however synthesized by treatment of (124) with diethyl 2-(cyclohexylamino)-vinyl phosphonate (164). The α,β-unsaturated aldehyde produced by this reaction was a mixture of methyl and ethyl esters in about 40% yield.



178

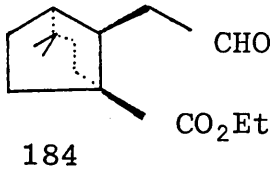
181

When the α,β-unsaturated aldehyde (181) was prepared using the ethyl ester (182) and then reduced using hydrogen with palladium on carbon in ethyl acetate in hexane, only one product was apparent by t.l.c. and n.m.r. It was presumed to be the required trans (E) isomer (183).



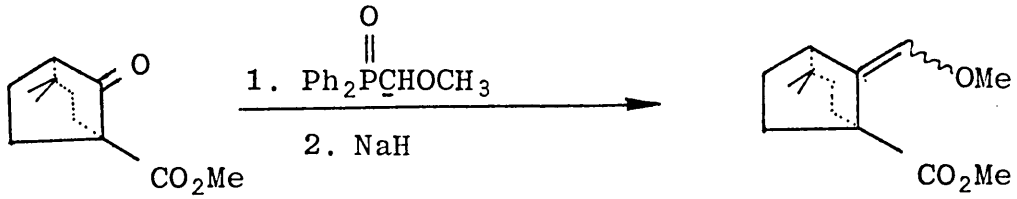
182 181 183

The synthesis of the cis aldehyde (184) was attempted as additional evidence for the identity of the trans (E) aldehyde (183).



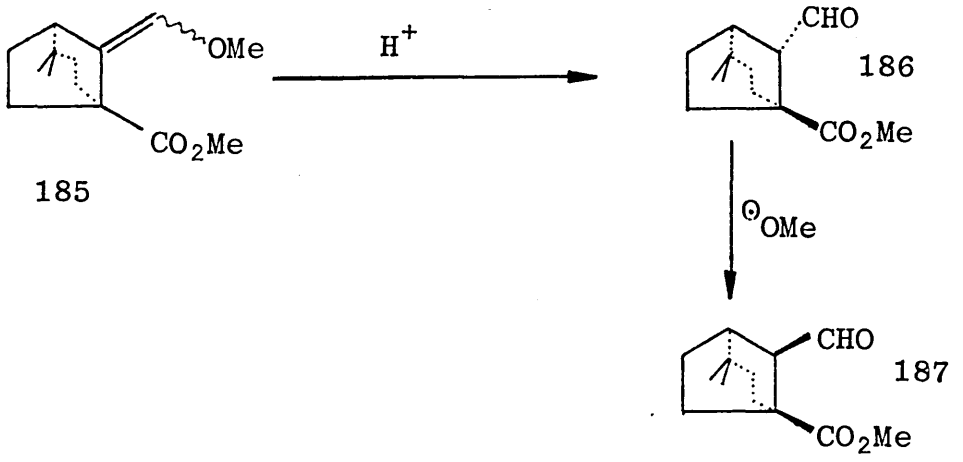
184

Trial reactions were initially carried out on the methyl ester (124). The bicyclic ketone (124) was treated with methoxymethyldiphenylphosphine oxide. This gave a mixture of enol ethers (185) in good yield.



124 185

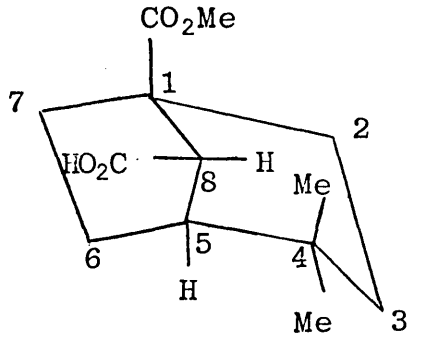
When the enol ethers (185) were treated with a catalytic amount of hydrochloric acid in acetone, they hydrolysed to give exclusively one aldehyde (186). This aldehyde could be epimerised by treatment with sodium methoxide in methanol to give another aldehyde (187).



Studies using Dreiding models suggest that the first aldehyde (186) was the trans (E) isomer and the thermodynamically favoured aldehyde (187) the cis (Z) isomer. It appears that the protonation occurred from the least hindered side and that the aldehyde (186) was isolated before it could be epimerised to the more stable aldehyde (187).

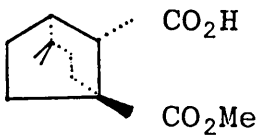
Both aldehydes (186) and (187) oxidised in deutrochloroform solution to give the acids (188) and (189) respectively. High resolution proton n.m.r. were obtained on the acids in an attempt to prove the stereochemistry. An extensive decoupling experiment was carried out on acid (189). The results are summarised in Table 3 overleaf.

TABLE 3

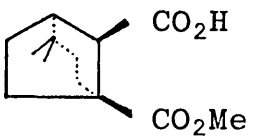


189

Resonance δ	Appearance	Inference and Apparent Coupling Constants
3.7	s	$-CO_2C\underline{H}_3$
3.1	s	C(8)H
2.25	m	C(7)H exo
2.05	t	C(5)H J with C(6)H = 3.5 Hz
1.81	tdd	C(2)H exo J with C(2)H endo = 13 Hz, J with C(3)H exo = 13 Hz, J with C(3)H endo = 6 Hz W coupling with C(7)H exo = 2 Hz
1.6	m	C(7)H endo
1.55	ddd	C(2)H endo J with C(2)H exo = 13 Hz, J with C(3)H endo = 6 Hz. W coupling with C(7)H endo = 2 Hz
1.4	tdd	C(3)H endo J with C(3)H exo = 13 Hz, J with C(2)H exo = 13 Hz, J with C(2)H endo = 6 Hz
1.25	m	C(3)H exo
1.05	s	$-C\underline{C}H_3$
0.95	s	$-C\underline{C}H_3$

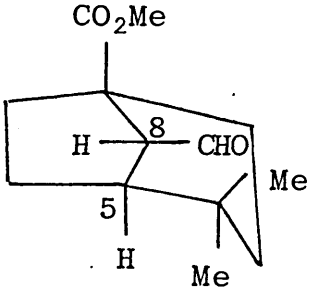


188

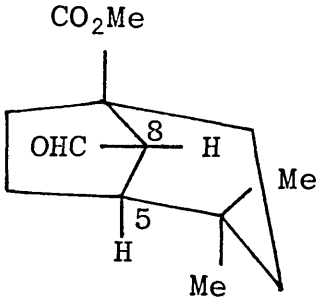


189

It is interesting to note that the proton on C8 in both the spectra of the trans (E) aldehyde (186) and trans (E) acid (188) is a doublet whereas in the spectra of the cis (Z) aldehyde (187) and trans (Z) acid (189) it is a singlet.



186



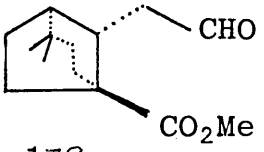
187

This is because the dihedral angle between the bridgehead proton on C5 and the proton on C8 is approximately 45°C for the aldehyde (186), the value of 45° being predicted from molecular models. The Karplus equation [96] predicts a coupling constant of 4.5 Hz for this arrangement which is in good agreement with observed coupling constant of 5 Hz.

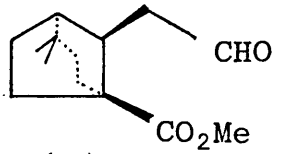
The dihedral angle between the bridgehead proton on C5 and the proton on C8 is approximately 90° for the cis (Z) aldehyde (187). The Karplus equation predicts that there will be no coupling and this is in agreement with the observed singlet.

The decoupling experiment on the acid (189) showed that when the protons on C8 and C5 were irradiated, a nuclear Overhauser effect [97] was observed at the C4 methyl frequencies. This is additional proof for the cis (Z) configuration since no nuclear Overhauser effect should be seen on irradiation of the C8 proton with the trans (E) isomer (188).

Both aldehydes (186) and (187) were homologated to give the second aldehydes (179) and (191).



179

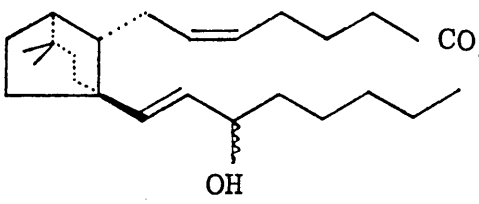


191

This was necessary to ensure that the trans (E) isomer (186) did not epimerise under the basic reaction conditions of the Wittig reaction. Proton n.m.r. showed that the aldehydes (179) and (191) were different and not contaminated by each other.

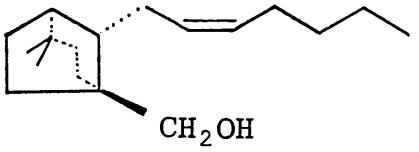
The two carbon homologation from the ketone (124) to the trans (E) aldehyde (179) gave a better overall yield than the method via the α,β-unsaturated aldehyde (181) and was the method of choice.

The synthetic route from the aldehyde (179) to the thromboxane analogue (192) proceeded without event and is summarised in scheme 19 overleaf.



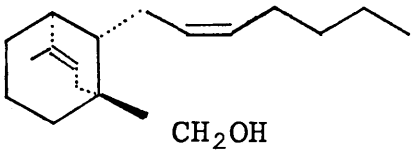
192

An interesting result to note was that the protons of the methylene adjacent to the alcohol in compound (190) appear as a singlet in the proton n.m.r. spectrum.

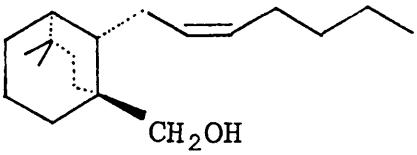


190

This is in contrast to the other alcohol analogues (152) and (175) where the signal appears as two doublets due to prochiral geminal anischronicity.



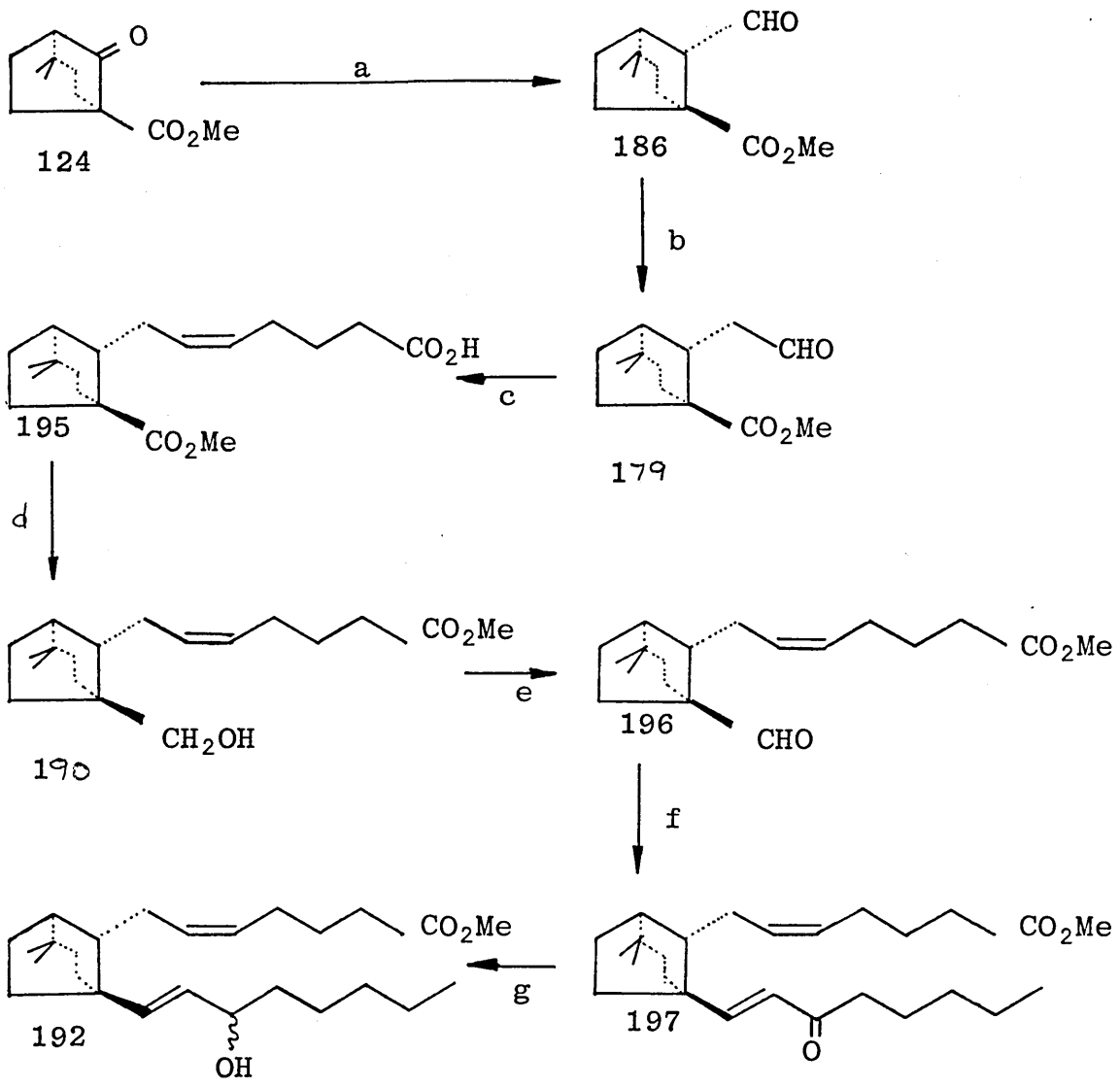
152



175

This result highlights the dependency of this phenomenon on the chiral environment.

SCHEME 19



Reagents : (a) $Ph_2P(O)\bar{C}HOCH_3$ then NaH followed by H_3O^+, (69%), (b) $Ph_3P{=}CHOCH_3$ then $Hg(OAc)_2$ followed by KI, (77%), (c) $Ph_3P\ CH(CH_2)_3CO_2^-K^+$, (87%) (d) Dibal then CH_2N_2, 90%, (e) P. C. C., (100%), (f) $(MeO)_2P(O)\bar{C}HC(O)C_5H_{11}\ Na^+$, (82%), (g) $NaBH_4$, (98%)

CHAPTER 7

EXPERIMENTAL

7.1 EXPERIMENTAL PROCEDURES

Nuclear magnetic resonance (N.m.r.) data were obtained on one or more of the following instruments : Jeol-C-60 (60 MHz) : Hitachi-Perkin Elmer R-600 Ft (60 MHz) : Varian EM390 (90 MHz) : Perkin Elmer R34 (220 MHz) : Bruker Spectrospin WM 250 (250 MHz) : Bruker Spectrospin WM 400 (400 MHz) : Bruker Spectrospin WP80 (80 MHz). Chemical shifts are quoted in parts per million (ppm). Tetramethylsilane was added as an internal standard, its resonance being assigned a value of zero ppm on the δ scale. The multiplicities are reported using the following abbreviations : s, singlet : d, doublet : t, triplet : q, quartet : m, multiplet : b, broad and J, apparent coupling constant in Hz.

Infrared (I.r.) spectra were obtained on a Pye-Unican SP 200 grating infrared spectrometer. Samples were in the form of thin liquid films or a 1% dispersion in potassium bromide (KBr). The i.r. figures quoted are frequency maxima (ν max) in reciprocal wavenumbers (cm^{-1}). The i.r. spectra are reported using the following convention : w, weak : m, medium : s, strong and b, broad. Only the strongest and/or structurally most important bands are reported.

Mass spectral (m.s.) data were obtained on a AEI M59 or MS 30 instruments. Samples were introduced by direct insertion probe and ionized by electron impact at 24 or 70 electron volts (eV). Some spectra have been obtained by

using chemical ionization with ammonia. Only the strongest and/or structurally most important peaks are quoted.

The microanalyses were carried out by Elemental Microanalysis Limited, Amberley, Beauworthy, Devon. Gas-liquid chromatograms (G.l.c.) were obtained on a Pye-Unican model GCV fitted with a flame ionization detector. Retention times are uncorrected and quoted in minutes.

Thin layer chromatograms (T.l.c.) were obtained using Merck "5734" plastic backed chromatography plates with incorporated fluorescent indicator. Compounds were visualised by quenching of fluorescence upon irradiation with ultra-violet light (254 nm), iodine vapour absorption and the use of one or more of the following spray reagents: molybdophosphoric acid (MPA), iodoplatinic acid (IPA), basic potassium permanganate ($KMnO_4$), ceric sulphate ($Ce_2(SO_4)_3$), 2,4-dinitrophenylhydrazine (DNP).

Short column chromatography was performed using either Merck "7736" (15-50 μm) or "7734" (70-230 mesh) silica gel. Solvents for chromatography were distilled prior to use. The petrol used for column chromatography was the fraction of petroleum spirit boiling between 40-60°.

Melting points are uncorrected.

Anhydrous reactions were run using magnetic stirring under a positive pressure dry nitrogen, dry glassware being obtained by flame drying and then cooling under a stream of nitrogen. All reaction temperatures were measured externally. All solvents for anhydrous reactions were distilled as follows: ether from lithium aluminium hydride;

tetrahydrofuran from potassium; dichloromethane, t-butanol, dimethylformamide, dimethyl sulphoxide and triethylamine from calcium hydride; diisopropylamine was dried over and distilled from calcium hydride and then stored under nitrogen over 3Å molecular sieves, n-Butyl lithium was used as a solution in hexane, stored under argon, and standardized prior to use against diphenylacetic acid.

Preparation of methyl 1-(3'-bromopropyl)-2-oxocyclopentane-carboxylate (53)

To a stirred suspension of sodium hydride (1.27 g, 42.5 mM, 80% dispersion in oil) in dimethylformamide (40 cm^3) in a three-necked flask (100 cm^3) fitted with a nitrogen inlet was added methyl 2-oxocyclopentanecarboxylate (52), (6 g, 4.2 mm). After 15 minutes, 1,3-dibromopropane (9 cm^3, 8.8 mm) was added. The resulting mixture was heated at 60°C for 4 hours during which time a white water soluble solid was deposited. The mixture was partitioned between ether (50 cm^3) and water (25 cm^3). The aqueous layer was extracted with ether (2 x 50 cm^3) and the combined ether extracts washed with water (3 x 50 cm^3), dried over magnesium sulphate and then evaporated.

The product was isolated by short-path column chromatography using 5% ethyl acetate in petrol as the eluting solvent.

Yield 4.45 g (40%)

I.r. (liquid film) : ν max 1725s (ester carbonyl), 1750 s (ketone carbonyl), 1450 m, 1240 s, 1165 cm^{-1}.

N.m.r. : δ_H (60 MHz; $CDCl_3$) 3.8 (s, 3H, $-CO_2\ C\underline{H}_3$), 3.4 (M, 2H $-C\underline{H}_2Br$), 2.7-1.5 (complex, 10H, $-C\underline{H}_2-C\underline{H}_2-$)

Mass spectrum : m/z 264 and 262 (M^+).

Preparation of 1-bromo-5-methyl-4,6-dioxaoctane (198)

3-Bromopropan-1-ol (5 g, 36 mM) and ethyl vinylether (7 cm^3, 70 mM) were placed in a flask with two drops of dilute hydrochloric acid (2M) in dichloromethane (20 cm^3). After 24 hours the mixture was washed with saturated aqueous sodium hydrogencarbonate (2 x 25 cm^3), dried over magnesium sulphate and evaporated.

Yield 7.37 g (97%)

G.l.c. 1 peak using P.E.G.A. at 160°C.

I.r. (liquid film) : ν max 1500 w, 1460 w, 1400 m, 1355 w, 1120 s, 1100 s, 1070 s cm^{-1}.

N.m.r. δ_H (60 MHz; $CDCl_3$) 4.8 (q, 1H, J = 6 Hz, -OC<u>H</u>(Me)O-) 4.0-3.3 (m, 6H, -C<u>H</u>$_2$Br and -C<u>H</u>$_2$O-) 2.2 (quintet, 2H, J = 7 Hz, $BrCH_2C\underline{H}_2CH_2O$-) 1.6-1.0 (m, 6H, 2 x C<u>H</u>$_3$)

Preparation of methyl 1-(5'-methyl-4',6'-dioxaoctyl)-2-oxocyclopentanecarboxylate (199)

Methyl 2-oxocyclopentanecarboxylate (52), (0.5 g, 3.5 mM) was added to a stirred solution of sodium hydride (0.1 g, 3.5 mM, 80% dispersion in oil) in dimethylformamide in a three-necked flask fitted with a nitrogen inlet. After 30 minutes (198), (1.36 g, 6.1 mM) was added. The resulting mixture was stirred and heated at 70°C for four hours. The mixture was partitioned between ether (25 cm^3) and water (100 cm^3). The aqueous layer was extracted into ether (2 x 25 cm^3) and the combined ether extracts washed with water (3 x 25 cm^3), dried over magnesium sulphate and then evaporated.

The crude product was chromatographed and two products were isolated. The major product was (199).

Yield 0.4 g (41%)

I.r. (liquid film) : ν max 1755 s (ketone carbonyl) 1725 s (ester carbonyl), 1460 s, 1390 m, 1120 s, 960 w, 925 w, cm^{-1}.

N.m.r. δ_H (60 MHz, $CDCl_3$) 4.6 (q, 1H, J = 6 Hz, -OC<u>H</u>(Me)O-), 4.2 (q, 2H, J = 7 Hz, -O<u>C</u>H_2CH_3), 3.7 (s, 3H, -$CO_2C\underline{H}_3$), 3.5 (m, 2H, -OC<u>H</u>$_2CH_2$-) 2.5-1.0 (complex, 16H)

Minor product, methyl 2-(6'-methyl-1',5',7'-trioxanonyl)-cyclopent-1-enecarboxylate. (200)

Yield 0.18 g (18%)

I.r. (liquid film) : ν max 1700 s (ester carbonyl), 1635 s (c=c of enol ether), 1455 m, 1390 m, 1240 s, 1140 s, 1065 s, cm^{-1}.

N.m.r. δ_H (60 MHz, $CDCl_3$) 4.6 (q, 1H, J = 6 Hz, -OC<u>H</u>(Me)O-) 4.2-3.0 (complex, 7H, -$CO_2C\underline{H}_3$ and -C<u>H</u>$_2$O-) 2.5-1.0 (complex, 16H).

<u>Preparation of methyl 1-(3'-hydroxypropyl)-2-oxocyclopentane -carboxylate (55)</u>

Methyl 1-(5'methyl-4,6'-dioxaoctyl)-2-oxocyclopentane-carboxylate (195), (0.39 g, 1.4 mM) was stirred for a few minutes with two drops of dilute hydrochloric acid in methanol (5 cm^3). The methanol was evaporated away and the residue taken up in ether (15 cm^3), washed with aqueous sodium hydrogencarbonate (2 x 5 cm^3), dried over magnesium sulphate and evaporated to give the product.

Yield 0.29 g (100%)

I.r. (liquid film) : ν max 3450 br (OH), 1730 s (CO), 1265 s, 1090 m, 1070 m, cm^{-1}

N.m.r. δ_H (60 MHz), $CDCl_3$) 3.8 (s, 3H, $-CO_2C\underline{H}_3$)
3.4 (m, 2H, $HOC\underline{H}_2-$) 3.3 (s, 1H, $-O\underline{H}$) 2.5-1.1 (complex, 10H, $-C\underline{H}_2C\underline{H}_2-$).
Mass spectrum : m/z 200 (M^+), 183 ($M^+ - OH$), 169 ($M^+ - OCH_3$) 142 ($M^+ - CO_2CH_3$).

Preparation of methyl 1-(3'-methanesulphonylpropyl)-2-oxocyclopentanecarboxylate (56)

Methyl 1-(3'-hydroxypropyl)-2-oxocyclopentanecarboxylate (55), (0.2 g, 1 mM) was dissolved in chloroform (2 cm^3) with three drops of pyridine. The mixture was cooled to 0^oC before mesyl chloride (0.2 cm^3, 2.6 mM) was added. Immediately the solution darkened to an orange colour and needle-like crystals were formed. The reaction mixture was left in the fridge overnight.

Water (6 cm^3) was then added to the mixture and the layers were separated. The aqueous layer was extracted with chloroform (2 x 5 cm^3). The combined chloroform extracts were washed with 2M hydrochloric acid (2 x 5 cm^3), dried magnesium sulphate and evaporated.

Yield 0.25 g (90%)
I.r. (liquid film) : ν max 1755 s (ketone carbonyl, 1730 s (ester carbonyl), 1465 m, 1420 m, 1410 s, 1180 s, 980 s, 940 s, cm^{-1}.
N.m.r. δ_H (60 MHz, $CDCl_3$), 4.35 (m, 2H, $-O_2SOC\underline{H}_2$), 3.8 (s, 3H, $-CO_2C\underline{H}_3$), 3.1 (s, 3H, $-OSO_2C\underline{H}_3$) 2.7-1.3 (complex), 10H, $-C\underline{H}_2C\underline{H}_2-$).

Attempted preparation of methyl 8-oxobicyclo[3.2.1]octane-carboxylate (51)

1. Using sodium hydride in dimethylformamide.

Sodium hydride (0.068 g, 1.4 mM, 50% dispersion in oil) was suspended in dimethylformamide (10 cm^3) and methyl 1-(3'-bromopropyl)-2-oxocyclopentanecarboxylate (53), (0.32 g, 1.3 mM) was then added. The resulting mixture was heated at 40°C for three hours and then poured into water (30 cm^3) and extracted with ether (3 x 10 cm^3). The combined ether extracts were dried over magnesium sulphate and chromatographed on a short path silica column using 20% ethyl acetate in petrol as the eluting solvent.

The major product was methyl 5-oxabicyclo[4.3.0]non-6-enecarboxylate (54).

I.r. (liquid film) : ν max 1725 s (ester carbonyl), 1670 (c=c of enol ether).

N.m.r. : δ_H (60 MHz, $CDCl_3$) 5.15 (br s, 1H, -C<u>H</u>=C-), 4.0 (m, 2H, -C<u>H</u>$_2$O-), 3.75 (s, 3H, -$CO_2C\underline{H}_3$), 2.85-1.2 (complex, 8H, -CH_2CH_2-).

Mass spectrum : m/z 182 (M^+)

G.l.c. 1 peak, retention time 28 minutes.

Conditions : Column 10% Apeizon L

N_2 flow rate 40 cm^3 min^{-1}

O_2 flow rate 40 cm^3 min^{-1}

Temperature 200°C

Retention times : methyl 1-(3'-bromopropyl)-2-oxocyclopentane-carboxylate (53) - 17 minutes

: methyl 1-(3'-mesylpropyl)-2-oxocyclopentane-carboxylate (56) - 16 minutes

: methyl 5-oxabicyclo[4.3.0]non-6-enecarboxylate (54) - 28 minutes

: polymeric species - 36, 39, 42, 47 and 64 minutes.

2. Using sodium hydride in tetrahydrofuran

Sodium hydride (0.082 g, 1.7 mM, 50% dispersion in oil) was suspended in tetrahydrofuran (12 cm^3) and methyl (1-(3'-bromopropyl)-2-oxocyclopentanecarboxylate (53), (0.44 g, 1.65 mM) was then added. The resulting solution was refluxed for three days. The reaction mixture was never homogenous. Gas liquid chromatography indicated that no reaction was apparent.

3. Using potassium tert-butoxide in tetrahydrofuran

Methyl 1-(3'-bromopropyl)-2-oxocyclopentanecarboxylate (53), (0.42 g, 1.6 mM) was dissolved in tetrahydrofuran (10 cm^3) and then potassium tert-butoxide (0.17 g, 1.6 mM) was added. The resulting solution was refluxed for 2 days. Gas liquid chromatography indicated that the major products were the O-alkylated product (54) and starting material (53).

4. Using lithium diisopropylamide in tetrahydrofuran

To a stirred solution of diisopropylamine (0.15 cm^3, 1.1 mM) in tetrahydrofuran (7 cm^3) at 0^oC was added n-butyl lithium (0.66 cm^3, 1 mM, 1.58 M in hexane). The solution was stirred for 20 minutes and cooled to -78^oC before methyl 1-(3'-bromopropyl)-2-oxocyclopentanecarboxylate (53), (0.25 g, 0.95 mM) was added. The solution was initially a very pale yellow colour which became darker on heating to 0^oC. The resulting solution was stirred at room temperature for

48 hours. Gas liquid chromatography indicated that the reaction mixture contained starting material (53), O-alkylated product (54) and polymeric material.

5. Using the lithium enolate of methyl 1-(3'bromopropyl)-2-oxocyclopentanecarboxylate (53) in toluene

To a stirred solution of diisopropylamine (0.27 cm^3, 1.9 mM) in tetrahydrofuran (5 cm^3) maintained at 0^oC was added n-butyl lithium (1.27 cm^3, 1.9 mM, 1.50 M in hexane). The solution was stirred for 15 minutes and cooled to -78^oC before methyl 1-(3'bromopropyl)-2-oxocyclopentanecarboxylate (53) was added. The mixture was stirred at -78^oC for 20 minutes. The tetrahydrofuran was then quickly evaporated away to give the lithium enolate of methyl 1-(3'-bromo-propyl)-2-oxocyclopentanecarboxylate. Dry toluene was added to this and the resulting mixture stirred and refluxed.

Gas liquid chromatography indicated a mixture of starting material (53), O-alkylated product (54) and polymer.

When methyl 1-(3'mesylpropyl)-2-oxocyclopentanecarboxylate (56) was substituted for methyl 1-(3'-bromopropyl)-2-oxocyclopentanecarboxylate (53) similar results were obtained.

6. Using potassium tert-butoxide in benzene

Potassium tert-butoxide (0.14 g, 1.26 mM), methyl 1-(3'bromopropyl-2-oxocyclopentanecarboxylate (53), (0.3 g, 1.4 mM) and benzene (10 cm^3) were placed in a dry two-necked flash (25 cm^3) fitted with a nitrogen inlet and a reflux condenser. The resulting reaction mixture was refluxed for three days under a positive pressure of nitrogen.

Gas liquid chromatography indicated a mixture of starting material (53), O-alkylated product (54) and polymer.

Similar products were obtained when toluene was used instead of benzene and again when methyl 1-(3'-mesylpropyl)-2-oxocyclopentanecarboxylate (56) was substituted for methyl 1-(3'bromopropyl)-2-oxocyclopentanecarboxylate (53) in both benzene and toluene.

Preparation of methyl 2-oxo-1-(3'-oxobutyl)cyclopentane-carboxylate (72)

A solution of methyl 2-oxocyclopentanecarboxylate (52), (5 g, 35 mM), methyl vinyl ketone (3 cm^3, 35.4 mM), triethylamine (1.2 cm^3, 8.6 mM) and dry benzene was allowed to stand at room temperature for seven days. The volatile components were removed under reduced pressure and the product distilled under vacuum.

B.pt 124-126° at 0.5 mm Hg

Yield 4.8 g (64%)

Elemental analysis : (Found C, 62.46; H, 7.78. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.60)

I.r. (liquid film) : ν max 1750 s (ketone carbonyl), 1720 s, (ester carbonyl), cm^{-1}

N.m.r. : δ_H (60 MHz, $CDCl_3$), 3.8 (s, 3H, $-CO_2C\underline{H}_3$), 2.9-1.5 (complex, 13H)

Preparation of methyl 5-methyl-6-oxa-7-oxobicyclo[3.2.2]-nonanecarboxylate (77)

While cooling in an ice-bath, concentrated sulphuric acid (1 cm^3) was added with swirling to methyl 2-oxo-1-(3'-oxobutyl)cyclopentanecarboxylate (72), (0.5 g, 2.4 mM).

The mixture was allowed to stand at room temperature overnight and was then poured on to ice and water (10 cm^3). The aqueous solution was neutralised with aqueous saturated sodium hydrogen-carbonate, and the solid product was filtered and washed with water. The solid was recrystallised from methanol and water.

Yield 0.3 g (60%)

M.pt. 100-102° (from MeOH and H_2O)

Elemental analysis : (Found C, 62.43; H, 7.75 $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.60)

I.r. (KBr disc) : ν max 3400 br (H_2O of crystallisation), 1740 s (lactone carbonyl), 1720 s (ester carbonyl), cm^{-1}

N.m.r. : δ_H (250 MHz, $CDCl_3$) 3.8 (s, 3H, $-CO_2C\underline{H}_3$), 2.6 (m, 1H, C(2)H), 2.2-1.7 (complex, 9H), 1.42 (s, 3H, $-OC\underline{H}_3$)

δ_C (250 MHz, $CDCl_3$) 172.9 (ester carbonyl), 171.9 (C7), 82.9 (C5), 52.6 (CH_3 of ester), 51.9 (C1), 38.0, 30.9, 30.0, 29.6 (C(5)Me), 24.7, 20.6.

Mass spectrum : m/z 212 (M^+)

Preparation of methyl 4-methyl-8-oxobicyclo[3.3.1]oct-3-enecarboxylate (78)

While cooling in an ice-bath, concentrated sulphuric acid (4 cm^3) was added with swirling to methyl 2-oxo-1-(3'-oxobutylcyclopentanecarboxylate (72), (4.6 g, 0.02 M). The mixture was allowed to stand in the ice-bath for 30 minutes, and then was poured on to iced water (25 cm^3). The aqueous solution was extracted with ether (3 x 25 cm^3). The combined ether extracts were washed with saturated aqueous sodium hydrogencarbonate (2 x 20 cm^3), dried over magnesium sulphate and evaporated.

The crude product was subjected to short path column chromatography on silica gel using 10% ethyl acetate in petrol to yield three products.

Methyl 4-methyl-8-oxobicyclo[3.3.1]oct-3-enecarboxylate (78), 1.32 g (31.5%)
Methyl 5-methyl-6-oxa-7-oxobicyclo[3.2.2]nonanecarboxylate (77), 0.85 g (19%)
Methyl 2-oxo-1-(3'-oxobutyl)cyclopentanecarboxylate (72), 1.1 g (24%)

Yield (78) 1.32 g (31.5%)
Elemental analysis : (Found C, 67.85, H, 7.20 $C_{11}H_{14}O_3$ requires C, 68.02, H, 7.26%)
I.r. (liquid film) : νmax 1755 (ketone carbonyl), 1725 (ester carbonyl), 1440 s, 1280 s, 1235 s, 1215 m, 1080 m, 1020 m, cm^{-1}
N.m.r. δ_H (250 MHz, $CDCl_3$) 5.3 (br s, 1H, =C<u>H</u>-), 3.77 (s, 3H, $-CO_2C\underline{H}_3$), 3.2 (dq. 1H, endo C(2)H), 2.8-2.6 (m, 2H exo C(2)H and endo C(6)H), 2.45 (m, 1H, C(5)H), 2.2-2 (complex, 3H) 1.73 (s, 3H, C(4)Me)

<u>Preparation of ethyl 2-oxo-1-(3'-oxobutyl)cyclopentane-carboxylate (66)</u>

A solution of ethyl 2-oxocyclopentanecarboxylate (5 g, 0.032 M), anhydrous methyl vinyl ketone (3 cm^3, 0.035 M), triethylamine (1.2 cm^3) and benzene (20 cm^3) was allowed to stand at room temperature for 7 days. The volatile components were removed and the product distilled under vacuum.

Yield 5.5 g (76%)

B.pt. 118-120°C at 0.5 mm Hg (lit., [61]140-142°C at 2.4 mm Hg).
I.r. (liquid film) : ν max 1750 s (ketone carbonyl), 1720 (ester carbonyl) 1370 m, 1260 m, 1165 s, 1030 m, cm^{-1}.
N.m.r. : δ_H (90 MHz, $CDCl_3$) 4.25 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2-$), 2.9-1.6 (complex, 13H), 1.2 (t, 3H, J = 7Hz, $-CO_2CH_2C\underline{H}_3$).

Preparation of ethyl 5-methyl-6-oxa-7-oxobicyclo[3.2.2]-nonanecarboxylate (79)

While cooling in an ice-bath, concentrated sulphuric acid (1 cm^3) was added dropwise with swirling to ethyl 2-oxo-(1-3'-oxobutyl)cyclopentanecarboxylate (66), (1.1 g, 4.8 mM). The resulting solution was allowed to stand at room temperature overnight and then was poured into ice and water (10 cm^3). The solid product was filtered and washed thoroughly with water.

Yield 0.8 g (73%)
M.pt. 57-58°C (from water methanol) (lit., [61]61-62°C)
M.pt. 58.5-59°C (from column using 10% ethyl acetate in hexane).
I.r. (Nujol mull) : ν max 1740 s (lactone carbonyl), 1715 s (ester carbonyl), 1450 m, 1200 s, 1050 s, cm^{-1}.
N.m.r. : δ_H (250 MHz, $CDCl_3$) 4.25 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2-$), 2.6 (m, 1H, C(2)H), 2.2-1.7 (complex, 9H), 1.4 (s, 3H, $-OC\underline{H}_3$), 1.3 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$)
δ_C (250 MHz, $CDCl_3$) 172.8 (ester carbonyl), 171.3 (lactone carbonyl), 82.8 (C5), 61.5 ($-CO_2\underline{C}H_2$), 51.8 (C1) 38.05, 30.9, 30.0, 29.6 (C(5)Me), 24.6, 20.6, 13.8 ($-CO_2CH_2\underline{C}H_3$).

Preparation of ethyl 2-oxo-1-(3'-oxobutyl)cyclohexane-carboxylate (73)

To a mixture of ethyl 2-oxocyclohexanecarboxylate (6.3 g, 0.037 M) and methyl vinyl ketone (10 cm^3, 0.12 M) was added triethylamine (5.6 cm^3, 0.039 M) with swirling and cooling. The reaction mixture was cooled in an ice-bath for one hour and then allowed to stand at room temperature for one week. The unreacted methyl vinyl ketone and triethylamine were removed by distillation under reduced pressure. The residue was dissolved in ether (40 cm^3). The ethereal extract was washed successively with 2M hydrochloric acid (20 cm^3), 2M aqueous sodium hydroxide (20 cm^3) and water (20 cm^3) and then dried over magnesium sulphate. Evaporation of the solvent gave the required Michael addition product.

Yield 8.6 g (97%)

B.pt. 70°C at 0.4 mm Hg

I.r. (liquid film) : ν max 1720 s (ester carbonyl), 1710 s (ketone carbonyl), 1445 m, 1365 m, 1130 m, 1095 m, cm^{-1}.

N.m.r. : δ_H (90 MHz, $CDCl_3$) 4.25 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2-$), 2.7 - 1.4 (complex, 15H), 1.2 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$)

Preparation of ethyl 4-methyl-9-oxobicyclo[3.3.1]non-3-enecarboxylate (83)

While cooling in an ice-bath, concentrated sulphuric acid (10 cm^3) was added dropwise with stirring to ethyl 1-(3'-oxobutyl)-2-oxocyclohexanecarboxylate (73), (10 g, 0.042 M). The resulting solution was left for one hour at 0°C and a further 45 minutes at room temperature. The mixture was then poured into a slurry of ice and water. The product was extracted with ether (3 x 25 cm^3) and the combined ether

extracts were washed successively with saturated aqueous sodium hydrogencarbonate (2 x 15 cm^3) and water (1 x 20 cm^3) and dried over magnesium sulphate.

The crude product was purified with flash column chromatography using 10% ether in hexane as the eluent.

Yield 5.5 g (59.5%)

I.r. (liquid film) : ν max 1730 s (ester carbonyl), 1710 s (ketone carbonyl), 1450 m, 1280 m, 1255 m, 1230 m, cm^{-1} (lit. [61] 1730 and 1720 cm^{-1})

N.m.r. : δ_H (250 MHz, $CDCl_3$) 5.65 (t, 1H = C<u>H</u>-), 4.23 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2$), 3.34 (br d, endo C(2)H) 2.73 (br t, endo C(8)H), 2.05-1.85 (complex, 4H), 1.69 (s, 3H, C(2)Me), 1.65 (m, 1H, exo C(7)H), 1.3 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$).

<u>Attempted preparation of ethyl 4-hydroxy-4-methyl-9-oxo-bicyclo[3.3.1]nonanecarboxylate</u>

1. Using concentrated sulphuric acid

With cooling in an ice-bath, concentrated sulphuric acid (98%, 0.4 cm^3) was added dropwise with swirling to ethyl 2-oxo-1-(3'-oxo-butyl)cyclohexanecarboxylate (1 g, 6 mM). The resulting solution was allowed to stand at 0^oC for one hour and room temperature for a further 45 minutes. Multiple elution TLC using 10% ethyl acetate in hexane indicated starting material (73) and the dehydrated product (83), ethyl 4-methyl-9-oxobicyclo[3.3.1]non-3-enecarboxylate.

The above was repeated using 0.2 cm^3 of concentrated sulphuric acid and exactly the same conditions. The product was substantially starting material (73) with some dehydrated product (83), ethyl 4-methyl-9-oxobicyclo[3.3.1]-

non-3-enecarboxylate.

2. Using concentrated hydrochloric acid with glacial acetic acid.

Ethyl 2-oxo-1-(3'-oxo-butyl)cyclohexanecarboxylate (1 g, 6 mM) was treated with acetic acid (4 cm^3), water (2 cm^3) and concentrated hydrochloric acid (1 cm^3). The mixture was warmed for a few minutes and allowed to stand at room temperature for 18 hours. TLC of the reaction mixture showed only starting material after this time.

The reaction mixture was then heated at 75°C for 96 hours. One major product was obtained after this time. The product was isolated by column chromatography. Spectral data indicated the Robinson annulation product, ethyl 4-oxobicyclo-[4.4.0]dec-5-enecarboxylate (87).

Rf 0.33 SiO_2 (30% ethyl acetate in hexane)
I.r. (liquid film) : ν max 1725 s (ester carbonyl), 1680 s and 1635 s (enone) 1465 (m), 1265 (m), 1240 (m), 1220 (m), cm^{-1},
N.m.r. : δ_H (60 MHz, $CDCl_3$) 5.85 (s, 1H, =C$\underline{H}$), 4.25 (q, 2H, J = 7 Hz, -OCOC$\underline{H}_2$-) 2.7-1.5 (complex, 12H), 1.2 (t, 3H, J = 7 Hz, -$COCH_2C\underline{H}_3$).

3. Using stannic chloride in benzene

A mixture of ethyl 1-(3'oxobutyl)-2-oxocyclohexanecarboxylate (0.5 g, 2.1 mM) and stannic chloride (0.25 cm^3, 2.2 mM) in benzene (6 cm^3) was heated at reflux for 45 minutes. Thin layer chromatography indicated that there were two products namely ethyl 4-oxobicyclo[4.4.0]dec-5-enecarboxylate (87) and ethyl 4-methyl-9-oxobicyclo[3.3.1]non-3-enecarboxylate (83).

4. Using boron trifluoride etherate in dichloromethane

Boron trifluoride etherate (0.3 cm^3, 2.4 mM) was added to a cold solution of ethyl 1-(3'oxobutyl)-2-oxocyclohexane-carboxylate (0.5 g, 2.1 mM) in dichloromethane (10 cm^3). The reaction flask was stoppered tightly and allowed to stand for 16 hours at 25°C. After this time, thin layer chromatography indicated that there were approximately equal amounts of two products, namely ether 4-oxobicyclo-[4.4.0]dec-5-enecarboxylate (87) and ethyl 4-methyl-9-oxo-bicyclo[3.3.1]non-3-enecarboxylate (83).

5. Using formic acid and concentrated sulphuric acid in an attempt to prepare ethyl 4-formoxy-4-methyl9-oxobicyclo-[3.3.1]nonanecarboxylate (88)

Concentrated sulphuric acid (0.2 cm^3) was slowly added to a solution of ethyl 1-(3'-oxobutyl)-2-oxocyclohexanecarboxylate (0.5 g, 3 mM) in formic acid (1 cm^3). The resulting mixture was left at room temperature overnight and then heated at 40°C for 4 hours. Thin layer chromatography of the reaction mixture at various intervals indicated starting material (73) and ethyl 4-methyl-9-oxobicyclo[3.3.1]-non-3-enecarboxylate (83) as the only product.

6. Using formic acid and ethyl 4-methyl-9-oxobicyclo[3.3.1]-non-3-enecarboxylate (83) in an attempt to prepare ethyl 4-formoxy-4-methyl-9-oxobicyclo[3.3.1]nonanecarboxylate (88).

Ethyl 4-methyl-9-oxobicyclo[3.3.1]non-3-enecarboxylate (0.5 g, 2.25 mM) was heated in formic acid (2 cm^3) at 60°C for 96 hours. Thin layer chromatography indicated that there was no apparent reaction.

Preparation of methyl 3-(methoxycarbonylmethylthio)-propionate (91)

To a stirred solution of methylthioglycolate (53 g, 0.58 M) and piperidine (0.5 cm^3), was added methyl acrylate (45 g, 0.52 M) over 45 minutes, while maintaining the reaction mixture at 40-50°C by external cooling. During the reaction, more piperidine (total 1 cm^3) was added in portions. After the methyl acrylate had been added, the reaction mixture was warmed to 50°C for a few minutes; washed with water, and dried over sodium sulphate. The dried oil on being distilled yielded a viscous colourless oil.

Yield 50 g (54%)

B.pt. 112°C at 0.5 mm Hg (lit., [65]111-112 at 2 mm Hg).

I.r. (liquid film) : ν max 1740 s (ester carbonyl), 1475 m, 1380 m, 1295 s, 1025 m, 955 m cm^{-1}

N.m.r. : δ_H (60 MHz $CDCl_3$) 3.7 (2s, 6H, $-CO_2C\underline{H}_3$), 3.2 (s, 2H, $-OCC\underline{H}_2S-$) 2.7 (complex, 4H, $-C\underline{H}_2CH_2-$)

Preparation of methyl 4-oxo-3-tetrahydrothiophenecarboxylate (90)

Methyl 3-(methoxycarbonylmethylthio)-propionate (91), (50 g, 0.28 M) was added dropwise over 30 minutes to refluxing sodium methoxide (0.78 M) in methanol, (18 g of sodium in 125 cm^3 of methanol). The resulting mixture was left until it reached room temperature.

The mixture was then poured on to crushed ice (125 cm^3)

with concentrated hydrochloric acid (75 cm^3). The oily layer was extracted into dichloromethane (2 x 75 cm^3). The combined extracts were washed with saturated aqueous sodium hydrogencarbonate (2 x 75 cm^3) and dried over sodium sulphate. The excess dichloromethane was removed and using a Vigreux column for vacuum distillation, the product was obtained near 84-86°C at 1 mm Hg. This was a pale yellow liquid and it crystallised into a fully crystalline pale yellow solid in the receiver.

Yield 18 g (40%)

M.pt. 36-38°C (lit., [65] 37.8°C

I.r. (KBr) : ν max 1760 s (ketone carbonyl), 1730 s (ester carbonyl), 1670 m (chelated conjugated ester carbonyl), 1630 m (conjugated alkene), 1460 s, 1245 s, 1050 m, cm^{-1}.

N.m.r. : δ_H (250 MHz, $CDCl_3$) 4.0-3.2 (complex) ≈ 11.5 (br, s enolic O<u>H</u>). δ_C (90 MHz, $CDCl_3$) 206.5 (-<u>C</u>O_2Me of keto form), 172.5 (-<u>C</u>O_2Me of enol form), 169.5 (-<u>C</u>O), 168.1 (C(3) of enol form), 99.1 (C(4) of enol form), 55.3 (-O<u>C</u>H_3 of enol form), 52.6 (C(3) of keto form), 51.5 (-O<u>C</u>H_3 of keto form) 37.4, 36.0, 31.3, 29.0

Mass spectrum : m/z 160 (M^+), 128 (M^+-MeOH).

<u>Preparation of Methyl 3-oxo-2-tetrahydrothiophenecarboxylate (89)</u>

1. Using lithium diisopropylamide

To a stirred solution of diisopropylamine (1.23 g, 12 mM) in tetrahydrofuran (15 cm^3) maintained at 0°C was added n-butyl lithium (7.6 cm^3, 12 mM, 1.58 M in hexane). The

solution was stirred for 15 minutes and cooled to -78°C before methyl 3-(methoxycarbonylmethylthio)propionate (91) (1.8 g, 0.95 mM) was added. The resulting solution was stirred at -78°C for 30 minutes and was gradually allowed to reach room temperature.

A mixture of products was obtained, one of which was the required product.

2. Using sodium methoxide

Methyl 3-(methoxycarbonylmethylthio)propionate (91), (3 g, 16.6 mM) was added over 15 minutes to a stirred suspension of sodium methoxide (1.3 g, 24 mM) in ether (6.5 cm^3). The mixture was slowly refluxed during the addition and set into a white paste before total addition of the diester was complete. The pasty reaction mixture was stirred for a further 30 minutes and then 2M hydrochloric acid was added until the solution was acid. The ether layer was separated and the aqueous layer extracted with ether (2 x 20 cm^3). The total ether extracts were washed with water (2 x 10 cm^3), dried over magnesium sulphate and evaporated.

The product was a mixture of two isomers, methyl 4-oxo-3-tetrahydrothiophenecarboxylate (90) and methyl 3-oxo-2-tetrahydrothiophenecarboxylate (89). The latter, the major product, was isolated using a short path silica column using 10% ethyl acetate in petroleum ether as the eluting solvent.

Yield 1.45 g (58%)

I.r. (liquid film) : ν max 1740 s (CO), 1660 w (chelated conjugated ester carbonyl), 1610 w (conjugated alkene), 1450 m, 1160 m, 1020 m, 1000 m, cm^{-1}

N.m.r. : δ_H (60 MHz, $CDCl_3$) 3.8 (s, 3H $-CO_2C\underline{H}_3$) 3.4-2.6 (complex, 4H, $-C\underline{H}_2C\underline{H}_2-$). δ_C (90 MHz, $CDCl_3$) 206.96 ($-\underline{C}O_2Me$), 169.0 (CO), 52.47 (C(2)), 51.89 ($-O\underline{C}H_3$), 38.71 (C(4)), 25.40 (C(5)).

Mass spectrum : m/z 160 (M^+)

Preparation of methyl 4-oxo-3(3'-oxobutyl)-3-tetrahydrothiophenecarboxylate (75)

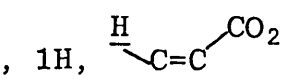
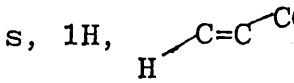
A solution of methyl 4-oxo-3-tetrahydrothiophenecarboxylate (90), (5 g, 0.032 M), methyl vinyl ketone (3 cm^3, 0.035 M), triethylamine (1.2 cm^3, 9 mM) and dry benzene (20 cm^3) was allowed to stand at room temperature for 4 days. The volatile components were then removed on the rotary evaporator and the resulting crude product was chromatographed on short path silica using 5% ethyl acetate in petrol to start with and then increasing to 20% ethyl acetate in petrol.

Three products were isolated, methyl 2-ethylidene-5-oxohexanoate (97), methyl 4-oxo-3-(3'-oxobutyl)-3-tetrahydrothiophenecarboxylate (75) and an inseparable mixture of unknowns (0.7 g).

Methyl 2-ethylidene-5-oxohexanoate:

Yield 0.6 g (12%)

I.r. (liquid film) : ν max 1720 s (CO), 1635 m (conjugated alkene), 1450 m, 1200 m, 1040 m, 820 m, cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$) 6.2 (s, 1H, ) 5.6 (s, 1H, ), 3.25 (s, 3H, $-CO_2C\underline{H}_3$) 2.6 (m, 4H, $-C\underline{H}_2C\underline{H}_2-$), 2.1 (s, 3H, $-COC\underline{H}_3$).

Methyl 4-oxo-3-(3'-oxobutyl)-3-tetrahydrothiophenecarboxylate:

Yield 3.4 g (47%)

Elemental analysis : (Found C, 52.28; H, 6.16. $C_{10}H_{14}O_4S$ requires C, 52.15; H, 6.13%).

I.r. (liquid film) : ν max 1730 s (CO), 1450 m, 1390 m, 1050 m, cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$) 3.75 (s, 3H, $-CO_2C\underline{H}_3$), 3.4 (d, 2H, J = 5 Hz, $-SC\underline{H}_2CO-$), 3.0-2.0 (complex, 9H)

Mass spectrum : m/z 230 (M^+)

Preparation of methyl 4-hydroxy-4-methyl-6-thia-8-oxo-bicyclo[3.2.1]octanecarboxylate (99)

While cooling in an ice-bath, concentrated sulphuric acid (1 cm^3) was added dropwise with swirling to methyl 4-oxo-3-(3'-oxobutyl)-3-tetrahydrothiophenecarboxylate (75), (0.5 g, 2.2 mM). The resulting solution was allowed to stand at 0^oC for one hour and for a further 45 minutes at room temperature. The mixture was then poured on to iced water (10 cm^3) and extracted with ether (3 x 15 cm^3). The combined ether extracts were washed with saturated sodium hydrogencarbonate (20 cm^3), dried over magnesium sulphate and evaporated.

The crude product was chromatographed on a short path silica column.

Yield 200 mgs (40%)

M.pt. 85.5-88°C

Elemental analysis: (Found C, 51.97; H 6.11. $C_{10}H_{14}O_4$ requires C, 52.15, H, 6.13%).

I.r. (KBr) : ν max 3,400 (OH), 1760 s (ketone carbonyl), 1735 s (ester carbonyl), 1305 m, 1240 m, 1135 m, 905 m cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$) 3.9 (s, 1H, C(5)H), 3.8 (s, 3H, $-CO_2C\underline{H}_3$), 3.6 (d, 1H, J = 11 Hz, endo C(7)H), 3.1 (s, 1H, $-O\underline{H}$), 2.7 (d, 1H, J = 11 Hz, exo C(7)H), 2.55-1.5 (complex 3H) 1.4 (s, 3H, C(4) $C\underline{H}_3$), 1.25 (s, 1H, exo C(3)H).

Mass spectrum : m/z 230 (M^+), 213 ($M^+-O\underline{H}$), 199 (M^+-OCH_3), 171 ($M^+-CO_2CH_3$).

Preparation of methyl 4-acetoxy-4-methyl-6-thia-8-oxo-bicyclo[3.2.1]octanecarboxylate (100)

Acetic anhydride (3 cm^3) was added to a mixture of methyl 4-hydroxy-4-methyl-6-thia-8-oxobicyclo[3.2.1]octanecarboxylate (99), (60 mgs, 0.25 mM) and 4-dimethylaminopyridine (64 mgs, 0.52 mM). Heat was immediately evolved and the solution changed to an orange colour. After leaving overnight, a brown solution was formed. Water (5 cm^3) and ether (5 cm^3) were added. The aqueous layer was extracted with ether (2 x 5 cm^3). The combined ether extracts were washed with sodium hydrogencarbonate (3 x 5 cm^3), dried over magnesium sulphate and evaporated.

The crude product was chromatographed on a short path silica column using 20% ethyl acetate in petrol as the eluting solvent.

Yield 52 mgs (76%)

M.pt. 74-75.5°C

I.r. (KBr) ν max 1750 s (CO), 1380 m, 1250 m, 1230 m, 1130 cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$) 3.95 (s, 1H, C(5)H), 3.9 (s, 3H, $-CO_2C\underline{H}_3$), 3.6 (d, 1H, J = 11 Hz, endo C(7)H), 2.7 (d, 1H, J = 11 Hz, exo C(7)H), 2.5-1.8 (complex, 3H), 2.0 (s, 3H, $OCOC\underline{H}_3$), 1.35 (s, 1H, exo C(3)H)

Mass spectrum : m/z 272 (M^+), 240 (M^+-CH_3OH), 229 (M^+-COCH_3) 213 ($M^+-OCOCH_3$)

Preparation of methyl 3-oxo-2-(3'-oxobutyl)-2-tetrahydrothiophenecarboxylate (74)

A solution of methyl-3-oxo-2-tetrahydrothiophenecarboxylate (89), (1.5 g, 9.4 mM), methyl vinyl ketone (1 cm^3, 12 mM), triethylamine (0.5 cm^3, 3.6 mM) and dry benzene were allowed to stand at room temperature for 7 days. The volatile components were removed on the rotary evaporator and a white crystalline solid crystallised out from the residue.

Yield 1.7 g (78.6%)

M.pt. 52.5-54.5°C

Elemental analysis : (Found C, 52.63; H, 6.34, requires C, 52.15; H, 6.13%)

I.r. (KBr) : ν max 1740 s (ring ketone), 1730 s (ester carbonyl), 1710 s (chain ketone), 1245 m, 1070 w, 900 w cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$) 3.75 (s, 3H, $-CO_2C\underline{H}_3$), 3.4-2.2 (complex, 8H) 2.1 (s, 3H, $-OCC\underline{H}_3$)

Mass spectrum : m/z 230 (M^+)

Attempted preparation of methyl 4-hydroxy-4-methyl-7-thia-8-oxobicyclo[3.2.1]octanecarboxylate

1. Using concentrated sulphuric acid

While cooling in an ice-bath, concentrated sulphuric acid (0.5 cm^3) was added dropwise with stirring to methyl 3-oxo-2-(3'-oxobutyl)-2-tetrahydrothiophenecarboxylate (74), (0.2 g, 0.87 mM). The resulting solution was left at 0^oC for one hour and then for a further 45 minutes at room temperature. After this time, the mixture was poured on to iced water (10 cm^3) and extracted into ether (3 x 10 cm^3). The majority of product was a black intractable tar. The combined ether extracts were washed with sodium hydrogencarbonate (15 cm^3), dried over magnesium sulphate and evaporated.

The crude product was chromatographed and the major product isolated.

Yield 48 mgs.

N.m.r. showed that there was no ester functionality.

2. Using stannic chloride in benzene

A mixture of methyl 3-oxo-2-(3'-oxo-butyl)-2-tetrahydro-thiophenecarboxylate (74), (0.5 g, 2.2 mM) and stannic chloride (0.25 cm^3, 2.2 mM) in benzene (7 cm^3) was heated at reflux for 45 minutes. The benzene layer was washed with water (5 cm^3) and dried over magnesium sulphate.

The majority of product was black insoluble tars, but the benzene extract showed one major product. This product

was isolated using a short path silica column using 10% ethyl acetate in petrol as the eluent.

The spectral data of the major product were consistent with methyl 4-oxo-9-thiabicyclo[4.3.0]non-5-enecarboxylate (101).

Yield 32 mgs

I.r. (liquid film) : ν max 1740 s (ester carbonyl), 1690 m and sh 1650 (enone), 1220 m, 1065 m, 1070 m cm^{-1}

N.m.r. : δ_H (60 MHz, $CDCl_3$) 5.8 (s, 1H, C<u>H</u>=), 3.7 (s, 3H, $-CO_2C\underline{H}_3$), 3.2-2 (complex, 8H).

<u>Preparation of ethyl 1-(3'-methyl-but-2'-enyl)-2-oxocyclohexanecarboxylate (106)</u>

Sodium hydride (0.28 g, 5.9 mM, 50% dispersion in oil) was placed on a three-necked flask and was washed three times with analar hexane. The system was then alternately evacuated and filled with nitrogen which removed the last traces of hexane. Dimethylformamide (10 cm^3) was added and to this suspension ethyl 2-oxocyclohexanecarboxylate (82) (1 g, 5.9 mM) was then slowly added by cannula over 15 minutes. The resulting pale yellow solution was stirred for a further 20 minutes before 1-bromo-3-methyl-but-2-ene (1 cm^3, 8.9 mM) was added. A white solid appeared after one hour and the reaction was complete in two hours.

The mixture was partitioned between dilute hydrochloric acid (50 cm^3) and ether (20 cm^3). The aqueous layer was extracted with ether (2 x 25 cm^3) and the combined ether

extracts washed with water (2 x 25 cm^3), dried over magnesium sulphate and then evaporated to give a yellow oil.

The crude product was subjected to bulb to bulb distillation to afford pure product.

Yield 1.3 g (92.6%)

B.pt. 104-106 at 0.5 mm Hg

Elemental analysis : (Found C, 70.16; H, 9.83. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.30%)

I.r. (liquid film) : ν max 1735 (ester carbonyl), 1712 (ketone carbonyl) cm^{-1}.

N.m.r. : δ_H (250 MHz, $CDCl_3$) 5.08 (t, 1H, J = 4.5 Hz, -C<u>H</u>=), 4.17 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2-$), 2.63-2.24 (complex, 5H), 2.1-1.36 (complex, 11H), 1.25 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$)

<u>Preparation of ethyl 2-acetoxy-1-(3!methylbut-2'-enyl)-cyclohex-2-enecarboxylate (107)</u>

Ethyl 1-(3'-methylbut-2'-enyl)-2-oxocyclohexanecarboxylate (106), (1 g, 4.2 mM) was heated with isoprop,enylacetate (15 cm^3) and toluene-p-sulphonic acid monohydrate (10 mgs) for 24 hours with slow removal of the generated acetone by distillation. Very little reaction was apparent. More toluene-p-sulphonic acid monohydrate (100 mgs) was added and the mixture heated for a further 24 hours with slow removal of the generated acetone by distillation.

The mixture was cooled and diluted with hexane (30 cm^3), and the organic layer was washed with aqueous sodium hydrogen-carbonate (15 cm^3) and dried over magnesium sulphate. The hexane and the isproprenylacetate were removed on the rotary

evaporator.

The evaporated product was chromatographed on a short path silica column (100 g) using 5% ethyl acetate in hexane as the eluting solvent.

Yield 0.8 g (75.4%) (based on recovered starting material of 0.1 g)

Elemental analysis : (Found C, 68.61; H, 8.68. $C_{16}H_{24}O_4$ requires C, 68.54; H, 8.63%).

I.r. (liquid film) : ν max 1763 s (acetate carbonyl), 1728 s (ester carbonyl), 1670 s (C=C) cm^{-1}

N.m.r. : δ_H (90 MHz, CCl_4), 5.57 (t, 1H, J = 3.5 Hz, AcOC=C<u>H</u>-), 5.1 (t, 1H, J = 5 Hz, C<u>H</u>=CMe_2), 4.1 (q, 2H, J = 7 Hz, -$CO_2C\underline{H}_2$), 2.45 (d, 2H, J = 7 Hz, -$C\underline{H}_2$CH=CMe_2) 2.15 (s, 3H, -OCOC<u>H</u>$_3$), 1.65 (2s, 6H, -C<u>H</u>$_3$) 2.15-1.65 (complex, 6H) 1.2 (t, 3H, J = 7 Hz).

<u>Preparation of ethyl 4,4-dimethyl-9oxobicyclo[3.3.1]nonane-carboxylate (105)</u>

While cooling in an ice-bath, ethyl 2-acetoxy-1-(3'-methyl-but-2'-enyl)cyclohex-2-enecarboxylate (107) (227 mgs, 0.81 mM) was added to a solution of stannic chloride (0.15 cm^3, 1.3 mM) in dichloromethane (50 cm^3). The reaction mixture was allowed to reach room temperature and was stirred for a further 3 hours with two drops of water.

Water (25 cm^3) was added to the reaction mixture and the aqueous layer was extracted with ether (2 x 30 cm^3). The

combined organic extracts were dried over magnesium sulphate and evaporated.

The crude product was chromatographed on a short path silica column using 5% ethyl acetate in hexane as the eluting solvent.

Yield 188 mgs (98%)

Accurate mass : 238.1596 (M^+). $C_{14}H_{22}O_3$ requires 238.1569

I.r. (liquid film) : ν max 1730 s (ester carbonyl) 1710 s (ketone carbonyl), 1460 m, 1370 m, 1160 m, 1060 m cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$). 4.2 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2-$), 3.0-1.45 (complex, 11H), 1.3 (t, 3H, J = 7 Hz, $-CO_2CH_2\underline{C}H_3$), 1.05 (s, 3H, $-C\underline{H}_3$), 0.95 (s, 3H, $-C\underline{H}_3$).

Preparation of ethyl 4-methylbicyclo[4.4.0]-dec-4,6-dienecarboxylate (111)

1. Using trimethylsilyltrifluoromethanesulphonate

To a stirred solution of ethyl 1-(3'methylbut-2'-enyl)-2-oxocyclohexanecarboxylate (106), (100 mg, 0.42 mM) in dichloromethane (10 cm^3) under a nitrogen atmosphere at 0^oC was added two drops of trimethylsilyltrifluoromethane-sulphonate. The mixture was slowly equilibrated to room temperature. After 3 hours the reaction mixture showed one major product. T.l.c. at various intervals during the three hours showed there to be numerous intermediates which finally disappeared to this one product.

Water (10 cm^3) was added and the layers separated. The aqueous layer was extracted with ether (2 x 7 cm^3) and

the combined organic extracts were dried over magnesium sulphate and evaporated.

The crude product was chromatographed on a short path silica column using 5% ethyl acetate in hexane as the eluting solvent. The major product was isolated and was shown to be ethyl 4-methylbicyclo[4.4.0]-dec-4,6-diene-carboxylate (111).

Yield 60 mgs (64%)

Accurate mass : 220.1458 (M^+). $C_{14}H_{20}O_2$ requires 220.1464.

U.v. absorptions : λ_{max} (EtOH) 231 (ε 18,000 $dm^3 mol^{-1} cm^{-1}$), 239 (18,000), 247 sh nm (12,400).

I.r. (liquid film) : ν max 1720 s (CO), 1445 m, 1230 m, 1195 m, 1150 m, 1090 m, 1025 m cm^{-1}

N.m.r. : δ_H (250 MHz, $CDCl_3$) 5.85 (s, 1H, CH=, C(5)H) 5.55 (br s, 1H, C(7)H), 4.15 (t, 2H, J = 7 Hz, $-CO_2C\underline{H}_2-$) 2.3-1.85 (complex, 6H) 1.7 (s, 3H, $\underline{Me}C=$), 1.65-1.25 (complex, 4H) 1.2 (t, 3H, $-CO_2CH_2C\underline{H}_3$) δ_C (250 MHz, $CDCl_3$) 175.6 (s, $-\underline{C}O_2Me$), 135.3 (s, C(6)), 134.2 (s, C(4)), 124.8 (d, C(7)), 123.6 (d, C(5)), 60.45 (t, $-CO_2\underline{C}H_2-$), 46.02 (s, C(1)), 34.5 (t, C(10), 34.0 (t, C(2)), 28.5 (t, C(3)), 25.4 (t, C(8)), 23.4 (q, C(4)$\underline{C}H_3$), 19.5 (t, C(9)), 14.3 (q, $-CO_2CH_2\underline{C}H_3$)

2. Using stannic chloride

While cooling in an ice-bath, ethyl 1-(3'-methylbut-2'-enyl)-2-oxocyclohexanecarboxylate (106) (0.1 g, 0.42 mM) was added to a solution of stannic chloride (0.02 cm^3, 0.17 mM) in dichloromethane (25 cm^3). The reaction mixture

was allowed to reach room temperature and was stirred for a further 16 hours with two drops of water. A very dark coloured solution was obtained which disappeared when water (25 cm^3) was added. The aqueous layer was extracted with ether (2 x 15 cm^3) and the combined extracts were dried over magnesium sulphate and evaporated.

The crude product was chromatographed on a short path silica column using 5% ethyl acetate in hexane as the eluting solvent.

Yield 63 mgs (68%) of (111)

3. Using trifluoromethanesulphonic acid

To a stirred solution of ethyl 1-(3'-methylbut-2'-enyl)-2-oxocyclohexanecarboxylate (106) (0.1 g, 0.42 mM) in dichloromethane (10 cm^3) under a nitrogen atmosphere at 0^oC was added trifluoromethanesulphonic acid (0.035 cm^3, 0.4 mM). The mixture was slowly equilibriated to room temperature and then stirred for a further 3 hours. T.l.c. indicated that ethyl 4-methylbicyclo[4.4.0]dec-4,6-diene-carboxylate (111) was the major product.

<u>Preparation of ethyl 4-methylbicyclo[4.4.0]dec-4,6-diene-carboxylate (111) from ethyl 1-(3'-methylbut-2'-enyl)-2-trimethylsilyloxycyclohex-2-ene-carboxylate (112)</u>

To a stirred solution of (112), (0.1 g, 0.32 mM) in dichloromethane (10 cm^3) under a nitrogen atmosphere at 0^oC was added trifluoromethanesulphonic acid (0.035 cm^3, 0.4 mM). The mixture was slowly equilibrated to room temperature and

then stirred for a further 3 hours.

The crude product was chromatographed on a short path silica column using 10% ethyl acetate in hexane as the eluting solvent. The major product (111) was isolated but the yield was not recorded.

Preparation of ethyl 1-(3'-chloro-3'-methylbutyl)-2-oxocyclohexanecarboxylate (108)

A stream of hydrogen chloride was bubbled through a stirred solution of ethyl 1-(3'-methylbut-2'-enyl)-2-oxocyclohexane-carboxylate (106), (2 g, 8.4 mM) in anhydrous ether (10 cm^3) for 2 minutes at -78°C. The mixture was then slowly heated up to room temperature whilst being gently aspirated with nitrogen. The last traces of hydrochloric acid were removed by stirring an ethereal solution of the product with sodium hydrogencarbonate until the ether layer was neutral. The sodium hydrogencarbonate was removed by filtration and the ether by evaporation. The tertiary chloride (108) was not further purified.

Yield 2.2 g (95.4%)

I.r. (liquid film) : ν max 1735 sh (ester carbonyl), 1710 (ketone carbonyl), 1450 m, 1370 m, 1020 m cm^{-1}.

N.m.r. : δ_H (250 MHz, $CDCl_3$) 3.23 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2-$), 2.6 - 2.4 (m, 2H, $-C\underline{H}_2CO$) 2.1 - 1.4 (complex 10H), 1.58 (s, 3H, $(C\underline{H}_3)_2C-$), 1.28 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$)

Preparation of ethyl (1-(3'chloro-3'-methylbutyl)-2-trimethylsilyloxycyclohex-2-enecarboxylate (109)

Ethyl 1-(3'-chloro-3'-methylbutyl-2-oxocyclohexane-carboxylate (108), (1 g, 3.64 mM) and ethyl trimethylsilyl-acetate (0.7 cm^3, 3.8 mM) were added to a solution of tetra-n-butylammonium fluoride (0.2 cm^3, 20 mM, 1 M in tetrahydrofuran) kept under nitrogen at 0^oC. A reaction took place immediately, accompanied by slight evolution of heat, and the colour changed to brown. The resulting mixture was stirred for a further two hours and then diluted with hexane, filtered and concentrated. The crude product was subjected to bulb to bulb distillation to yield pure product.

Yield 950 mgs (76%)

B.pt. $\simeq 220^oC$ at 0.5 mm Hg

I.r. (liquid film) : 1725 s (ester carbonyl)

1660 s (C=C) 1250 m, 930 m, 845 m cm^{-1}

N.m.r. : δ_H (250 MHz, $CDCl_3$) 4.85 (t, 1H, J = 4 Hz, C$\underline{H}$=), 4.15 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2$) 2.1 - 1.6 (complex, 10H), 1.55 (s, 6H, $(C\underline{H}_3)_2$ C-), 1.25 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$), 0.2 (s, 9H, $-Si(C\underline{H}_3)_3$)

Preparation of ethyl 1-(3'-methylbut-2-enyl)-2-trimethyl-silyloxycyclohexanecarboxylate (112) [98]

Chlorotrimethylsilane (0.8 cm^3, 6.3 mM) was added to a stirred mixture of ethyl 1-(3'methylbut-2'enyl)-2-oxocyclo-hexanecarboxylate (106), (1 g, 4.2 mM) and 1,8diazabicyclo-[5.4.0]undec-7-ene (0.95 cm^3, 6.4 mM) in dichloromethane (5 cm^3) at 40^oC. The mixture was heated at reflux under

nitrogen for 5 hours. The resulting mixture was diluted with hexane (15 cm^3) and washed with water (10 cm^3), saturated aqueous sodium hydrogencarbonate (5 cm^3), dried over magnesium sulphate and evaporated.

The crude product was subjected to bulb to bulb distillation to afford pure product.

Yield 1.15 g (88%)

I.r. (liquid film) : 1730 s (ester carbonyl), 1665 m and 1620 m (C=C), 1445 m, 1250 m, 845 s, 755 m cm^{-1}

N.m.r. : δ_H (60 MHz, $CDCl_3$) 4.85 (t, 1H, J = 7 Hz, -C<u>H</u>=CO-) 4.55 (t, 1H, J = 4 Hz, -C<u>H</u>=CMe_2), 3.88 (q, 2H, J = 7 Hz, -$CO_2C\underline{H}_2$-) 2.15 (d, 2H, J = 7 Hz, -$C\underline{H}_2$-CH=) 1.75 (m, 2H, $C\underline{H}_2$-CH=CMe_2), 1.5 (2s, 6H, =$C(C\underline{H}_3)_2$) 1.6 - 1.2 (complex, 4H), 1.3 (t, 3H, J = 7 Hz, -$CO_2CH_2C\underline{H}_3$) 0.2 (s, 9H, -$Si(C\underline{H}_3)_3$)

<u>Attempted preparation of 4,4-dimethyl-9-oxo-bicyclo[3.3.1]-nonanecarboxylate (105) from ethyl 1-(3'-chloro-3'-methyl-butyl)-2-trimethylsilyloxycyclohex-2-enecarboxylate (109)</u>

1. Using 1 equivalent of $TiCl_4$

To a stirred solution of titanium tetrachloride (0.063 cm^3, 0.57 mM) in dry dichloromethane (7 cm^3) at -78°C, under nitrogen, was added dropwise a solution of ethyl 1-(3'-chloro-3'-methylbutyl)-2-trimethylsilyloxycyclohex-2-enecarboxylate (108), (0.2 g, 0.58 mM) in dichloromethane (5 cm^3). The solution was allowed to heat to -23°C. The major product after two hours at this temperature was ethyl 1-(3'-chloro-3'-methylbutyl)-2-oxocyclohexanecarboxylate.

2. Using 1.5 equivalents of $TiCl_4$ and 0.5 equivalents of collidine.

To a stirred solution of titanium tetrachloride (0.094 cm^3, 0.86 mM) in dry dichloromethane (7 cm^3) at -78°C, under nitrogen, was added collidine (0.038 cm^3, 0.29 mM) and then a solution of ethyl 1-(3'-chloro-3'-methylbutyl)-2-trimethylsilyloxycyclohex-2-enecarboxylate (10ϙ), (0.2 g, 0.58 mM) in dichloromethane (5 cm^3). The solution was slowly equilibrated to 0°C. The major reaction product was again ethyl 1-(3'-chloro-3'-methylbutyl)-2-oxocyclohexanecarboxylate.

3. Using one equivalent of silver tetrafluoroborate

To a stirred solution of silver tetrafluoroborate (0.14 g, 0.71 mM) in dry dichloromethane (7 cm^3) at -78°C, under nitrogen, was added a solution of ethyl 1-(3'-chloro-3'-methylbutyl)-2-trimethylsilyloxycyclohex-2-enecarboxylate (10ϙ) (0.24 g, 0.68 cm^3) in dry dichloromethane (5 cm^3). The solution was slowly allowed to heat to 0°C. A flocculent precipitate was formed which became darker on exposure to light. After four hours, the precipitate was filtered and the filtrate concentrated.

N.m.r. and t.l.c. of this crude product suggested that the major constituent was ethyl 1-(3'-methylbut-2'-enyl)-2-oxocyclohexanecarboxylate (106).

Attempted cyclisation of ethyl 1-(3'-methylbut-2-enyl)-2-oxocyclohexanecarboxylate (106) with concentrated sulphuric acid to give 4,4-dimethyl-9-oxobicyclo[3.3.1]nonane-carboxylate (105)

While cooling in an ice-bath, concentrated sulphuric acid (0.2 cm^3) was added with swirling to ethyl 1-(3'-methylbut-2-enyl)-2-oxocyclohexanecarboxylate (106), (0.2 g, 0.84 mM). The mixture was allowed to stand at 0^oC for one hour and for a further one hour at room temperature. The resulting mixture was poured on to ice and water (10 cm^3) and ether (3 x 6 cm^3) extracts were washed with sodium hydrogen carbonate (10 cm^3), dried over magnesium sulphate and evaporated.

The crude product was chromatographed on a short path column using 5% ethyl acetate in hexane as the eluting solvent. Four products were isolated. None of the four products showed spectral data consistent with the cyclised product, ethyl 4,4-dimethyl-9-oxo-bicyclo[3.3.1]nonane-carboxylate. This method was not pursued any further and the products were not characterised.

Attempted rearrangement of ethyl 1-(3'-methylbut-2'-enyl)-2-trimethylsilyloxycyclohex-2-enecarboxylate (112) to give ethyl 2-trimethylsilyloxy-3-(2'methylbut-3'-en-2-yl)cyclo-hex-2-enecarboxylate (113)

1. Ethyl 1-(3'-methylbut-2'-enyl)-2-trimethylsilyloxy-cyclohex-2-enecarboxylate (112) (100 mgs) was heated at reflux in cyclohexane (2 cm^3) under nitrogen for 24 hours. No reaction was apparent.

2. Ethyl 1-(3'-methylbut-2'-enyl)-2-trimethylsilyloxy-cyclohex-2-enecarboxylate (112) (100 mgs) was placed in a 10 cm^3 autoclave with toluene (5 cm^3) and the mixture was heated at 200°C for 16 hours. No reaction was apparent.

3. Ethyl 1-(3'-methylbut-2'-enyl)-2-trimethylsilyoxy-cyclohex-2-enecarboxylate (112) (100 mgs) was placed in a 10 cm^3 autoclave with toluene (5 cm^3) and the mixture was heated at 300°C for 3 hours. No reaction was apparent.

4. Ethyl 1-(3'-methylbut-2'-enyl)-2-trimethylsilyloxy-cyclohex-2-enecarboxylate (112) (300 mgs) was heated at ≈ 300°C under nitrogen using a Wood's metal bath. After one hour t.l.c. suggested two products, the disilylated starting material (106) and the decarboxylated ketone (116). After three hours, there was one major product whose I.r. and N.m.r. were consistent with 2-(3'-methylbut-2'-enyl)cyclohexanone (116).

   I.r. (liquid film) ν max 1710 (CO), 1450 m, 1185 s, 1130 cm^{-1}

   N.m.r. : δ_H (60 MHz, $CDCl_3$) 5.13 (t, 1H, J = 4 Hz, C$\underline{H}$ $=CMe_2$) 2.65 - 1.5 (complex, 10H) 1.55 (2 s, 6H, $=C(C\underline{H}_3)_2$)

Attempted rearrangement of the potassium enolate of ethyl 1-(3'-methylbut-2'-enyl)-2-oxocyclohexanecarboxylate (117) to give ethyl 3(2'-methylbut-3'-en-2-yl)-2-oxocyclohexanecarboxylate (118)

A small amount of potassium hydride (20% dispersion in oil) was placed in a three-necked round-bottomed flask with tetrahydrofuran (10 cm^3) fitted with a magnetic stirrer, nitrogen inlet and bubbler. The flask was cooled to 0^oC before ethyl 1-(3'-methylbut-2'-enyl)-2-oxocyclohexanecarboxylate (117, 204 mgs) was added. The latter was added until the potassium hydride stopped effervescing. A dark yellow solution was formed. The mixture was refluxed for 24 hours. T.l.c. indicated that there was no apparent reaction.

The tetrahydrofuran was aspirated away and replaced with diglyme. The resulting mixture was heated at 120^oC for 24 hours. T.l.c. indicated starting material.

The reaction mixture was cooled and poured on to 2M hydrochloric acid (50 cm^3). The aqueous layer was extracted with ether (3 x 20 cm^3) and the combined ether extracts washed with saturated sodium hydrogencarbonate (20 cm^3) and dried over magnesium sulphate. The evaporated product was chromatographed on a short path silica column using 5% ethyl acetate in hexane as the eluting solvent.

N.m.r. confirmed that the isolated product was identical with starting material.

Investigation of the reaction of palladium II acetate with ethyl 1;(3'-methylbut-2'-ene)-2-trimethylsilyloxyhex-2'-enecarboxylate (112)

A solution of ethyl 1-(3'-methylbut-2enyl)-2-trimethylsilyloxyhex-2'-enecarboxylate (112) (0.092 g, 0.3 mM) in anhydrous dichloromethane (3 cm^3) and acetonitrile (3 cm^3) was added dropwise by cannula to a solution of palladium II acetate (0.067 g, 0.3 mM) in anhydrous acetonitrile (3 cm^3). The resulting solution was stirred overnight at room temperature. Two products were isolated by short column silica chromatography. They were identified as desilylated starting material (106) and the α,β-unsaturated ketone, ethyl 1-(3'-methylbut-2'-enyl)-2oxocyclohexanecarboxylate (122).

I.r. (liquid film) ν max 1730 s (ester carbonyl), 1690 (ketone carbonyl), 1630 m (conjugated C=C), 1450 m, 1395 cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) 6.9 (m, 1H, -C<u>H</u>=CHCO), 6.05 (d, 1H, J = 8 Hz, =C<u>H</u>CO), 5.1 (t, 1H, J = 4 Hz), 4.15 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2-$), 2.8 - 1.8 (complex), 6H, 1.75 (s, 3H, $=CC\underline{H}_3$), 1.7 (s, 3H, $=CC\underline{H}_3$), 1.2 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$)

Preparation of methyl 1-(3'-methylbut-2'-enyl)-2-oxocyclopentanecarboxylate (125)

To a stirred suspension of sodium hydride (0.56 g, 0.014 M, 60% dispersion in oil) in dimethylformamide (15 cm^3) was added methyl 2-oxocyclopentanecarboxylate (52), (2 g, 0.014 M) in dimethylformamide (5 cm^3) under nitrogen at 0°C.

After 30 minutes, a pale yellow solution was formed and 1-bromo-3-methylbut-2-ene (2 cm^3, 0.017 M) was added. The resulting solution was stirred at 40°C for 3 hours.

The mixture was partitioned between dilute hydrochloric acid (60 cm^3) and ether (25 cm^3). The aqueous layer was extracted with ether (2 x 30 cm^3). The combined ether extracts were dried and evaporated. The crude product was chromatographed on a short path silica column using 10% ethyl acetate in hexane as the eluent.

Yield 2.8 g (95%)

Elemental analysis : (Found C, 68.68; H, 8.61. $C_{12}H_{18}O_3$ requires C, 68.54; H, 8.63%).

I.r. (liquid film) ν max 1755 s (ketone carbonyl), 1730 s (ester carbonyl) 1460 m, 1445 m, 1415 w, 1385 w cm^{-1}.

N.m.r. : δ_H (8 MHz, $CDCl_3$) 5.05 (t, 1H, J = 5 Hz, $-C\underline{H}=CMe_2$), 3.7 (s, 3H, $-CO_2C\underline{H}_3$) 2.75 - 1.75 (complex, 8H), 1.7 (s, 3H, $=CC\underline{H}_3$) 1.6 (s, 3H, $=CC\underline{H}_3$).

Preparation of methyl 1-(3'methylbut-2-enyl)-2-acetoxy-cyclopent-2-enecarboxylate (126)

Methyl 1-(3'-methylbut-2'-enyl)-2-oxocyclopentane-carboxylate (125) (8.4 g, 0.04 M) was heated with isoprop enylacetate (70 cm^3) and toluene-p-sulphonic acid (3g) for 7 days with slow removal of the generated acetone by distillation. In order to ensure complete reaction, it was necessary to distil away some of the isoprop enyl-acetate (35 cm^3) with the acetone.

The mixture was cooled and diluted with ether (40 cm^3) and water (25 cm^3). The aqueous layer was extracted with ether (3 x 20 cm^3) and the combined ether extracts washed with aqueous sodium hydrogencarbonate (2 x 20 cm^3) and dried over magnesium sulphate.

The evaporated product was chromatographed on a short path silica column using 10% ethyl acetate in petrol as the eluent.

Yield 9 g (89%)

The elemental analysis on two occasions was unsuccessful since the product (126) decomposes to methyl 2-oxocyclopentanecarboxylate (52).

I.r. (liquid film) : ν max 1775 s (acetate carbonyl), 1745 s (ester carbonyl), 1670 (C=C) 1450 m, 1390 cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) 5.75 (t, 1H, J = 3.5 Hz, AcOC=C<u>H</u>-), 5.05 (t, 1H, J = 5 Hz, -C<u>H</u>=CMe_2), 3.75 (s, 3H, -$CO_2C\underline{H}_3$), 2.8 - 1.8 (complex, 6H), 1.7 (s, 3H, =$CC\underline{H}_3$), 1.6 (s, 3H, =$CC\underline{H}_3$).

<u>Preparation of 4,4-dimethyl-8-oxobicyclo[3.2.1]octane-carboxylate (124)</u>

While cooling in an ice-bath, methyl 1-(3'-methylbut-2'-enyl)-2-acetoxycyclopentanecarboxylate (126) (320 mgs, 1.27 mM) was added to a solution of stannic chloride (0.24 cm^3, 2 mM) in dichloromethane. The reaction mixture was allowed to reach room temperature and then stirred for a further three hours.

Water (20 cm^3) was added to the reaction mixture and the aqueous layer extracted with ether (2 x 40 cm^3). The combined organic extracts were dried over magnesium sulphate and evaporated.

The crude product was chromatographed on a short path silica column using 15% ethyl acetate in petrol as the eluting solvent.

Yield 235 mgs (88%)

M.pt. 63.5 - 65°C

Elemental analysis : (Found C, 68.23; H, 8.67. $C_{12}H_{18}O_3$ requires C, 68.54; H, 8.62%)

I.r. (KBr) : ν max 1750 s (ketone carbonyl), 1720 s (ester carbonyl), 1470 m, 1445 m, 1280 m, 1135 m, 1075 m cm^{-1}

N.m.r.: δ_H (80 MHz, $CDCl_3$) 3.75 (s, 3H, $-CO_2C\underline{H}_3$), 2.6 - 1.1 (complex, 9H), 1.0 (s, 6H $=C(C\underline{H}_3)_2$), (80 MHz, C_6D_6) 3.5 (s, 3H, $-CO_2C\underline{H}_3$), 2.7 - 1.9 (m, 2H), 1.8 - 0.9 (complex, 7H), 0.85 (s, 3H $=CC\underline{H}_3$), 0.55 (s, 3H, $=CC\underline{H}_3$).

Preparation of methyl 4-methylbicyclo[4.3.0]non-4,6-diene-carboxylate

To a stirred solution of methyl 1-(3'-methylbut-2'-enyl)-2-oxocyclopentanecarboxylate (125), (223 mgs, 1.06 mM) in dichloromethane (10 cm^3) under a nitrogen atmosphere at 0°C was added trimethylsilyltrifluoromethanesulphonate (0.5 cm^3). The mixture was slowly equilibrated to room temperature. After 4½ hours, the reaction mixture was poured on to water (10 cm^3). The layers were separated and the aqueous layer, extracted with ether (2 x 10 cm^3).

The combined organic extracts were dried over magnesium sulphate and evaporated.

The crude product was chromatographed on a short path silica column using 5% ethyl acetate in petrol as the eluting solvent.

Yield 133 mgs (65%)
Accurate mass : 192.1156 (M^+). $C_{12}H_{16}O_2$ requires 192.1150.
I.r. (liquid film) : 1725 s (ester carbonyl), 1450 m, 1440 m, 1260 m, 1190 m cm^{-1}.
N.m.r. : δ_H (80 MHz, $CDCl_3$) 6.05 (s, 1H, C(5)H), 5.5 (br s, 1H, C(7)H), 3.7 (s, 3H, $-CO_2C\underline{H}_3$), 2.7 - 1.3 (complex, 8H), 1.7 (s, 3H, C(4)$C\underline{H}_3$).

Preparation of methyl 1-(prop-2'-enyl)-2-oxocyclopentane-carboxylate

To a stirred suspension of sodium hydride (0.2 g, 6.8 mM, 80% dispersion in oil) in dimethylformamide (15 cm^3) under nitrogen was added methyl 2-oxocyclopentanecarboxylate (0.99 g, 7 mM) which was stirred for 30 minutes. After this time 1-chloroprop-2-ene (2 cm^3, 24 mM) was added. The resulting mixture was heated at 60°C for 3 hours when the reaction mixture became a white suspension.

The mixture was partitioned between dilute hydrochloric acid (50 cm^3) and ether (20 cm^3). The aqueous layer was extracted into ether (2 x 25 cm^3). The combined ethereal extracts were washed, dried over magnesium sulphate and evaporated. This crude product was chromatographed on a

short path silica column using ethyl acetate in petroleum ether as the eluting solvent.

Yield 0.55 g (44%)

I.r. (liquid film) : ν max 1760 s (ketone carbonyl), 1730 s (ester carbonyl) 1465 m, 1240 s, 1075 m, 1050 w, 940 m cm^{-1} (lit., [99] 1752 s, 1727 s, 1231, 926 cm^{-1}).

N.m.r. : δ_H (80 MHz, $CDCl_3$) 6 - 4.9 (complex, 3H, $-C\underline{H}=C\underline{H}_2$) 3.72 (s, 3H, $-CO_2C\underline{H}_3$) 2.9 - 1.8 (complex, 8H).

Mass spectrum : m/z 182 (M^+)

Preparation of methyl (1-(prop-2'-enyl)-2-acetoxycyclopent-2-enecarboxylate (127)

Methyl 1-(prop-2'-enyl)-2-oxocyclopentanecarboxylate (1 g, 5.5 mM) was heated with isoprop enylacetate (30 cm^3) and toluene-p-sulphonic acid (300 mgs) for 96 hours whilst the isoprop enylacetate (20 cm^3) and the generated acetone was slowly removed by distillation.

The mixture was then cooled and diluted with ether (30 cm^3). The ethereal extract was washed with sodium hydrogen carbonate (2 x 15 cm^3), dried over magnesium sulphate and evaporated.

The crude product was chromatographed on a short path silica column using 10% ethyl acetate in petroleum ether as the eluent.

Yield 0.98 (80%)

Elemental analysis : (Found C, 64.45; H, 7.41. $C_{12}H_{16}O_4$

requires C, 64.26; H, 7.48%).

I.r. (liquid film) : ν max 1760 s (acetate carbonyl), 1735 (ester carbonyl), 1650 (C=C) 1450 m, 1030 s, 1070 m, 935 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) 6 - 5.5 (complex, 2H, -C<u>H</u>=CH_2 and C<u>H</u>=COAc), 5.27 - 4.95 (complex, 2H, -CH=C<u>H_2</u>), 3.75 (s, 3H, -$CO_2C\underline{H}_3$), 2.8 - 1.8 complex, 6H), 2.2 (s, 3H, -OCOC<u>H_3</u>).

<u>Preparation of methyl 3-(3'-methylbut-2'-enyl)-4-oxo-3-tetrahydrothiophenecarboxylate (132) and methyl 3-(2'-methylbut-3'-en-2-yl)-4-oxo-3-tetrahydrothiophenecarboxylate (133)</u>

Sodium hydride (0.26 g, 6.5 mM, 60% dispersion in oil) was suspended in dimethylformamide (10 cm^3) under nitrogen and cooled to 0°C. Methyl 4-oxo-3-tetrahydrothiophene-carboxylate (90) (1 g, 6.25 mm) was added to this suspension over 15 minutes. The resulting solution was stirred at room temperature for 20 minutes to give a yellow coloured solution. 1-bromo-3-methylbut-2-ene (0.9 cm^3, 7.7 mM) was then added and after one hour the yellow colour disappeared and a white solid precipitated.;

The mixture was partitioned between dilute hydrochloric acid (50 cm^3) and ether (20 cm^3). The aqueous layer was extracted into ether (2 x 25 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated to give a yellow oil.

The crude product was chromatographed on a short path

silica column using 5% ethyl acetate in petroleum ether as the eluting solvent to give two products.

Yield (132), 0.75 g (52.6%)

Elemental analysis : (Found C, 57.74; H, 7.00. $C_{11}H_{16}O_3S$ requires C, 57.86; H, 7.06%)

I.r. (liquid film) : ν max 1730 (CO), 1440 m, 1230 m, 1100 w, 1035 w cm^{-1}

N.m.r. : δ_H (200 MHz, $CDCl_3$) 4.8 (m, 1H, C<u>H</u>=C) 3.75 (s, 3H, $-CO_2C\underline{H}_3$), 3.45 (d, 1H, J = 12 Hz), 3.4 (d, 1H, J = 20 Hz), 3.3 (d, 1H, J = 20 Hz), 2.9 (d, 1H, J = 12 Hz), 2.55 (m, 2H, $C\underline{H}_2CH=$), 1.7 (2 s, 6H, $-C=C(C\underline{H}_3)_2$)

Mass spectrum : m/z 228 (M^+) 160 ($M^+-CH_2CH=CMe_2$).

Yield (133), 0.36 g (25%)

Elemental analysis : (Found C, 57.97; H, 7.25. $C_{11}H_{16}O_3$ requires C, 57.86; H 7.06%)

I.r. (liquid film) : ν max 1725 (CO), 1440 m, 1215 m, 1030 w, 920 w cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$) 6.25 (dd, 1H, C<u>H</u>=CH_2) 5.15 (d, 1H, J = 3 Hz, $C\underline{H}_2$=CH-), 4.95 (d, 1H, J = 5 Hz, $C\underline{H}_2$=CH-), 3.75 (s, 3H, $-CO_2C\underline{H}_3$) 3.4 - 2.4 (complex, 4H), 1.3 (s, 6H $(C\underline{H}_3)_2$-).

Mass spectrum : m/z 228 (M^+) 160 ($M^+-CMe_2-CH=CH_2$)

<u>Preparation of methyl 1-(2'-methylbut-3'-en-2-yl)-3-oxo-2-tetrahydrothiophenecarboxylate (124)</u>

Sodium hydride (0.25 g, 6.25 mM, 60% dispersion in oil) was suspended in dimethylformamide (10 cm^3) under nitrogen and cooled to 0°C. Methyl 3-oxo-2-tetrahydrothiophene-

carboxylate (89), (1 g, 6.25 mM) was added to this suspension over 10 minutes. The resulting solution was stirred at room temperature for 20 minutes to give a pale yellow coloured solution. 1-bromo-3-methylbut-2-ene (1 cm^3, 8.6 mM) was then added and immediately a cloudiness appeared and the yellow colour diminished. After 10 minutes t.l.c. indicated that there was no starting material.

The mixture was partitioned between dilute hydrochloric acid (50 cm^3) and ether (20 cm^3). The aqueous layer was extracted into ether (2 x 25 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated to give a pale yellow oil.

The crude product was chromatographed on a short path silica column using 20% ethyl acetate in petroleum ether as the eluting solvent.

Yield 1.3 g (91%)

Elemental analysis : (Found C, 57.62; H, 7.17. $C_{11}H_{16}O_3S$ requires C, 57.85; H, 7.06%)

I.r. (liquid film) : ν max 1740 s (CO), 1440 m, 1265 m, 1225 m, 1195 m cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$) 6 - 6.5 (dd, 1H, $C\underline{H}=CH_2$) 5.15 (d, 1H, J = 3 Hz, $C\underline{H}_2=CH$) 4.95 (d, 1H, J = 5 Hz, $C\underline{H}_2=CH$) 3.75 (s, 3H, $-CO_2C\underline{H}_3$), 3.1 - 1.5 (complex 4H), 1.25 (s, 6H, $-C(C\underline{H}_3)_2$).

Attempted preparation of the enol-acetate of methyl 2-(2'-methylbut-3'-en-2-yl)-3-oxo-2-tetrahydrothiophenecarboxylate (134)

Methyl 2-(2'-methylbut-3'-en-2-yl)-3-oxo-2-tetrahydrothiophenecarboxylate (0.25 g, 1.1 mM) was heated with isopropenylacetate (10 cm^3) and toluene-p-sulphonic acid (100 mgs) for 24 hours whilst isoprop enylacetate (3 cm^3) and the generated acetone were slowly removed by distillation.

The mixture was then cooled and diluted with ether (15 cm^3). The ethereal extract was washed with aqueous saturated sodium hydrogencarbonate (2 x 7 cm^3) dried over magnesium sulphate and evaporated.

The crude product was chromatographed on a short path silica column using ethyl acetate in petrol as the eluent.

The major product was found to be methyl 3-acetoxy 4,5-dihydro-2-thiophenecarboxylate(138)

Yield 200 mgs (71%)

I.r. (liquid film) : ν max 1780 (acetate carbonyl), 1735 (ester carbonyl), 1640 (C=C), 1455 m, 1485 m, 1460 m, 1075 m, 1040 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) 3.75 (s, 3H, $-CO_2C\underline{H}_3$), 3.45 - 2.85 (m, 4H,) 2.2 (s, 3H, $-OCOC\underline{H}_3$).

Attempted preparation of ethyl 9-formyl-4-methylbicyclo-[3.3.1] non-3-enylcarboxylate (143)

Sodium hydride (41 mgs, 1.36 mM, 60% dispersion in oil) was placed in a three-necked flask under argon. The sodium hydride was washed three times with sodium dried petrol. The system was then alternately evacuated and filled with argon which removed the last traces of petrol. Dimethyl sulphoxide (1 cm^3) was introduced via a syringe and the mixture heated at 60-65^{o}C for approximately 1 hour when a clear green-grey solution was obtained.

Methoxymethyltriphenylphosphonium chloride (0.469 g, 1.36 mM) in warm dimethyl sulphoxide (2 cm^3) was added to the solution of methylsulphinyl-carbanion. The resulting red solution was stirred at 0^{o}C for 20 minutes before ethyl 4-methyl-9-oxocyclohexanecarboxylate (83) (308 mgs, 1.38 mM) in dimethyl sulphoxide (1 cm^3) was added. The resulting reaction mixture was left stirring at room temperature for two hours and at 60^{o}C for several hours.

T.l.c. indicated that the reaction mixture contained starting material (83), triphenylphosphine, triphenyl-phosphine oxide and methoxymethyldiphenylphosphine oxide.

Attempted preparation of ethyl 9-formyl-4-methylbicyclo-[3.3.1] non-3-enylcarboxylate (143)

To a stirred solution of diisopropylamine (0.14 cm^3, 1 mM) in tetrahydrofuran (5 cm^3) maintained at 0^{o}C was added n-butyl lithium (0.67 cm^3, 0.9 mM, 1.4 M in hexane). The solution was stirred for twenty minutes at this

temperature. Toluene (5 cm^3) was then added followed by methoxymethyldiphenylphosphium chloride (349 mgs, 1 mM). The bright red solution was stirred at 0°C for 15 minutes before the ketone (83), (119.4 mgs, 0.5 mM) in toluene was added dropwise at the same temperature. The resulting mixture was stirred at room temperature overnight and for 4 hours at 40°C. T.l.c. indicated that no reaction was apparent.

Preparation of ethyl 9-formyl-4-methylbicyclo[3.3.1]non-3-enylcarboxylate (143)

Methoxymethyldiphenylphosphine oxide (0.296, 1.05 mM) in dry tetrahydrofuran (6 cm^3) was added by cannula to a solution of lithium diisopropylamide [from di-isopropylamine (0.14 cm^3, 1 mM) and n-butyl lithium (0.7 cm^3, 1 mM; 1.44 M in hexane)] in tetrahydrofuran (6 cm^3) at 0°C for 10 minutes. The deep red mixture was cooled to -78°C and ethyl 4-methyl-9-oxobicyclo[3.3.1]non-3-enylcarboxylate (83) (0.219 g, 0.88 mM) in dry tetrahydrofuran (0.5 cm^3) was added by cannula dropwise. The solution was allowed to warm to room temperature and then stirred for a further 30 minutes. Saturated ammonium chloride solution (10 cm^3) and ether (10 cm^3) were then added. The aqueous layer was extracted with ether (3 x 10 cm^3), and the combined organic layers dried over magnesium sulphate and evaporated under reduced pressure to give a yellow oil. This diphenylphosphinoyl derivative was not further purified or characterised.

The yellow oil was dissolved in dry tetrahydrofuran (12 cm^3) and stirred with sodium hydride (0.06 g, 2.5 mM, 60% dispersion in oil) for two hours. The mixture was filtered through Hyflo to remove the gelatinous precipitate of sodium diphenylphosphinite. The residue was washed with ether (30 cm^3) and the combined organic fractions were evaporated under reduced pressure. The crude product was chromatographed on a short path silica column to give a geometric mixture of two enol ethers (142).
I.r. (liquid film) : ν max 1725 s (ester carbonyl), 1670 m and 1660 m (enol ether), 1460 m, 1450 m, 1160 m, 1120 m cm^{-1}.

The enol ethers (142) were dissolved in ethanol with three drops of dilute hydrochloric acid and stirred for 7 hours. The ethanol was then evaporated under reduced pressure and ether (10 cm^3) and water (5 cm^3) were added. The layers were separated and the aqueous layer extracted with ether (2 x 10 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated.

Yield = 0.213 g (91%)
The n.m.r indicated the presence of two epimeric aldehydes in the ratio of 2:1 of ethyl 4-methyl-9-[syn]-formylbicyclo[3.3.1]-non-3-enylcarboxylate (143) to ethyl 4-methyl-9-[anti]-formylbicyclo[3.3.1]non-3-enylcarboxylate.

Short path silica column chromatography using 3% ethyl acetate in hexane was used to separate the two epimeric aldehydes.

Ethyl 4-methyl-9-[anti]-formylbicyclo[3.3.1]non-3-enyl-carboxylate.

I.r. (liquid film) : 1720 s (CO), 1455 m, 1160 m, 1130 m, 1050 w cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) 9.45 (s, 1H, -C<u>H</u>O), 5.5 (s, 1H, C<u>H</u>=), 4.15 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2CH_3$), 3.0 - 1.4 (complex, 9H), 1.25 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$).

Ethyl 4-methyl-9-[syn]-formylbicyclo[3.3.1]non-3-enyl-carboxylate (143).

Elemental analysis : Found C, 71.06; H, 8.63. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.5%).

I.r. (liquid film) : ν max 1700 brs (CO), 1450 m, 1300 m, 1270 m, 1145 m, 1125 m, 1040 m, 940 m cm^{-1}.

N.m.r. : δ_H (200 MHz, $CDCl_3$) 9.7 (s, 1H, -C<u>H</u>O), 5.57 (brs, 1H, =C<u>H</u>), 4.25 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2-$), 2.64 - 1.4 (complex, 9H), 1.25 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$).

<u>Preparation of ethyl 9-[syn]-formyl-4-methylbicyclo[3.3.1]-non-3-enylcarboxylate (143)</u>

The two epimeric aldehydes (83 mgs, 0.35 mM) were dissolved in ethanol (5 cm^3) and a very small amount of sodium was added. The resulting solution was left standing at room temperature for 14 hours. Dilute hydrochloric acid was then added until the solution was neutral. The ethanol was removed on the rotary evaporator and ether (10 cm^3) and water (10 cm^3) were added. The layers were separated and the aqueous layer extracted with ether (2 x 10 cm^3).

The combined ether extracts were dried over magnesium sulphate and evaporated.

Yield (143) 79 mgs (96%).

Attempted preparation of ethyl 9-[syn]-formylmethyl-4-methylbicyclo[3.3.1]non-3-enylcarboxylate (139)

To a stirred solution of diisopropylamine (0.21 cm^3, 1.5 mM) in tetrahydrofuran (12 cm^3) maintained at 0^oC was added n-butyl lithium (1.4 cm^3, 1.5 mM, 1.44 M in hexane). The solution was stirred for twenty minutes at this temperature. Methoxymethyldiphenylphosphine oxide (0.42 g, 1.5 mM) in tetrahydrofuran (10 cm^3) was then added by cannula and the mixture stirred for 10 minutes. The deep red solution was then cooled to -78^oC and the aldehyde (143), (0.303 g, 1.3 mM) in dry tetrahydrofuran (2 cm^3) added by cannula dropwise. The solution was allowed to warm to room temperature and then stirred for a further 30 minutes. Saturated ammonium chloride solution (20 cm^3) and ether (20 cm^3) were then added. The aqueous layer was extracted with ether (3 x 10 cm^3), and the combined organic layers dried over magnesium sulphate and evaporated under reduced pressure to give a yellow oil. T.l.c. indicated that all the aldehyde (143) had disappeared. The diphenyl phosphinoyl derivative (146) was not further purified or characterised.

The yellow oil was dissolved in dry tetrahydrofuran (20 cm^3) and stirred with sodium hydride (0.9 g, 22 mM, 60%

dispersion in oil) for 96 hours. T.l.c. indicated that no enol ether had been formed.

Preparation of ethyl 9-[syn]-formylmethyl-4-methyl-bicyclo[3.3.1]non-3-enylcarboxylate (139)

To a stirred solution of diisopropylamine (0.38 cm^3, 2.7 mM) in tetrahydrofuran (8 cm^3) maintained at 0^oC was added n-butyl lithium (1.88 cm^3, 1.7 mM, 1.44 M in hexane). The solution was stirred for twenty minutes at this temperature. Toluene (6 cm^3) was then added followed by methoxymethyltriphenylphosphonium chloride (0.93 g, 2.7 mM). The bright red solution was stirred at 0^oC for 15 minutes before the aldehyde (143), (0.303 g, 1.28 mM) in toluene (1 cm^3) was added dropwise at the same temperature. After 45 minutes, t.l.c. indicated that the reaction was complete and the mixture was quenched with ice-water (25 cm^3) and ether (70 cm^3). The organic layer was separated and the aqueous phase re-extracted with ether (2 x 25 cm^3). The combined organic solution was dried over magnesium sulphate and evaporated to afford an oily residue which was subjected to short path column chromatography using 25% ethyl acetate in petrol as the eluting solvent to give the enol ethers (147).

I.r. (liquid film) : ν max 1725 (CO) 1675 and 1660 (enol ether), 1460 m, 1450 m, 1060 m, 1020 m cm^{-1}.

N.m.r. : δ_H (60 MHz, $CDCl_3$) 5.5 (m, 3H, -C<u>H</u>=), 4.0 (q, 2H, J = 7 Hz $-CO_2C\underline{H}_2-$) 3.5 (s, 2.5 H, $-OC\underline{H}_3$) 3.3 (s, 0.5 H, $-OC\underline{H}_3$) 2.5 - 1 (m, 9H) 1.7 (3H, $=CC\underline{H}_3$) 1.2 (t, 3H, J = 7 Hz,

$-CO_2CH_2C\underline{H}_3$).

The enol ethers (147) were dissolved in tetrahydrofuran (13.6 cm^3) and water (1.5 cm^3) and stirred under argon and treated with mercuric acetate (0.721 g, 2.3 mM). After one hour at room temperature, the yellow mixture was poured on to a 7% aqueous potassium iodide solution (100 cm^3) and extracted with benzene (2 x 75 cm^3). The combined organic layers were washed with 7% aqueous potassium iodide (2 x 50 cm^3), dried over magnesium sulphate and evaporated under reduced pressure.

The crude product was subjected to short-path column chromatography using 40% ethyl acetate in petrol as the eluent.

Yield 0.24 g (75%) (from aldehyde (143))

I.r. (liquid film) : ν max 2075 w (aldehyde), 1725 s (CO), 1495 w, 1450 w, 1260 m, 1130 m, 1115 m, 1090 m, 1005 m cm^{-1}.

N.m.r. : δ_H (200 MHz, $CDCl_3$) 9.42 (s, 1H, -C$\underline{H}$O), 5.55 (s, 1H, =C$\underline{H}$-), 4.25 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2CH_3$), 2.9 - 2.55 (m, 2H, $-C\underline{H}_2CHO$), 2.2 - 1.4 (complex, 9H) 1.7 (s, 3H, $=CC\underline{H}_3$), 1.25 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$)

The dinitrophenylhydrazone of the aldehyde (148) was prepared.

M.pt. 156-158°C.

Preparation of 7-[-5-(ethoxycarbonyl)-2-methylbicyclo-[3.3.1]non-2-en-9-yl]-[syn]-(±)-5-(Z)-heptenoic acid (140)

Potassium tert-butoxide (2.46 g, 0.022 M) and (4-carboxybutyl)triphenylphosphonium bromide (4.86 g, 0.011 M) were quickly ground together and then placed in a dry two-necked flask under nitrogen. Tetrahydrofuran (125 cm^3) was distilled on to the solids to give a bright orange solution which was stirred for 30 minutes. A solution of the aldehyde (139) (1 g, 0.004 M) in dry tetrahydrofuran (15 cm^3) was added in a single portion with stirring and the resulting solution was stirred for a further one hour.

Saturated aqueous ammonium chloride (50 cm^3) was added, followed by dilute hydrochloric acid until the reaction mixture was acidic, and then ether (25 cm^3) was added. The layers were separated and the aqueous layer was extracted with ether (3 x 25 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated to yield a viscous oil.

The crude product was subjected to short-column chromatography on silica using 40% ethyl acetate in petrol as the eluting solvent.

Yield 1.6 g (87%)

Elemental analysis : (Found C, 69.24; H, 8.70. $C_{20}H_{30}O_4$ requires C, 69.74; H; 8.77%).

I.r. (liquid film) : ν max 2700-2500 br (OH), 1740 - 1710 s (CO), 1445 m, 1255 m, 1070 m, 1040 m, 870 w.

N.m.r. : δ_H (200 MHz, $CDCl_3$) 5.55 (br, s, C<u>H</u>=CMe), 5.35 (m, 2H, -C<u>H</u>=C<u>H</u>-) 4.15 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2-$) 2.6 (m, 1H) 2.34 (t, 2H, J = 7 Hz, $-C\underline{H}_2CO_2H$), 1.35 - 2.2 (complex, 18H), 1.25 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$).
Mass spectrum : m/z 334 (M^+), 319 (M^+-CH_3).

<u>Preparation of methyl 7-[-5-(hydroxymethyl)-2-methyl-bicyclo[3.3.1]non-2-en-9-yl]-[syn]-(±)-5-(Z)-heptenoate (152)</u>

The acid ester (140), (0.191 g, 0.57 mM) and toluene (5 cm^3) were placed in a flame-dried three-necked flask fitted with a nitrogen inlet and cooled to -78°C. Diisobutyl-aluminium hydride (1.1 cm^3, 1.7 mM, 25% w/w in toluene), was slowly added over 5 minutes. When t.l.c. indicated that the reaction was complete, water (5 cm^3) was added and the reaction mixture allowed to reach room temperature. Dilute hydrochloric acid (15 cm^3) and ether (10 cm^3) were added to the reaction mixture. The layers were separated and the aqueous layer extracted with ether (3 x 10 cm^3). An ethereal solution of diazomethane was added to the combined organic extracts which were then dried over magnesium sulphate and evaporated after the excess diazomethane had vapourised.

The crude product was chromatographed on a short path silica column using 30% ethyl acetate in petrol as the eluting solvent.
Yield 0.153 g (87%)
Elemental analysis : (Found C, 74.64; H, 9.96; O, 15.72.

$C_{19}H_{30}O_3$ requires C, 74.46; H, 9.87; O, 15.66%).

I.r. (liquid film) : ν max 3450 brm (OH), 1740 (CO), 1445 m, 1380 m, 1025 m, 1050 m cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$) 5.5 (complex, 3H, -C<u>H</u>=), 3.7 (s, 3H, $-CO_2C\underline{H}_3$), 3.5 (d, 1H, J = 11 Hz one of $-C\underline{H}_2OH$), 3.2 (s, 1H, J = 11 Hz, one of $-C\underline{H}_2OH$), 2.5 - 1.2 (complex, 21H), 2.1 (s, 1H -O<u>H</u>).

Mass spectrum : m/z 306 (M^+), 275 (M^+-OMe).

<u>Preparation of methyl 7-[-5-formyl-2-methylbicyclo[3.3.1] non-2-en-9-y-]-[syn]-(±)-5-(Z)-heptenoate (153)</u>

Pyridinium chlorochromate (0.2 g, 0.93 mM) was suspended in anhydrous dichloromethane (2 cm^3). The alcohol (152) (0.2182, 0.71 mM) in dichloromethane (1 cm^3) was then added in one portion to the magnetically stirred suspension. After 4 hours, dry diethyl ether (10 cm^3) was added and the supernatant liquid decanted from the black gum. The insoluble residue was washed with dry diethyl ether (3 x 5 cm^3) and then passed through a short silica gel column. The solvent was removed by evaporation.

Yield 0.199 g (92%)

I.r. (liquid film) : ν max 2875 w (CHO), 1740 s (aldehyde carbonyl), 1720 (ester carbonyl), 1445 m, 1240 w cm^{-1}.

N.m.r. : (80 MHz, $CDCl_3$) 9.4 (s, 1H, -C<u>H</u>O), 5.55 (br s, H, -C<u>H</u>=CMe), 5.35 (m, 2H, -C<u>H</u>=C<u>H</u>-), 3.65 (s, 3H, $-CO_2C\underline{H}_3$), 2.6 - 1.2 (complex, 21H).

Preparation of methyl 7-[-5-(3-oxo-1-(E)-octenyl)-2-methylbicyclo[3.3.1]non-2-en-9-yl]-[syn]-(±)-5-(Z)-heptenoate (155)

To a suspension of sodium hydride (0.0285 g, 0.72 mM, 80% dispersion in oil) in tetrahydrofuran (2 cm^3) under nitrogen was added dimethyl 2-oxoheptylphosphonate (0.152 g, 0.686 mM) in tetrahydrofuran (1 cm^3) by cannula. A yellow coloured solution was formed initially, after 5 minutes a white precipitate was deposited and after 10 minutes the reaction mixture had completely solidified. After 30 minutes, the aldehyde (153), (0.1986 g, 0.65 mM) in tetrahydrofuran (3 cm^3) was added by cannula. The resulting solution was stirred at room temperature for 48 hours.

Saturated ammonium chloride (10 cm^3) and ether (10 cm^3) were added and the layers separated. The aqueous layer was extracted with ether (2 x 10 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated.

The crude product was subjected to short path silica chromatography using 20% ethyl acetate in petrol as the eluting solvent.

Yield 0.2251 g (87%)

Elemental analysis : (Found C, 77.94; H, 10.04. $C_{26}H_{40}O_3$ requires C, 77.96; H, 10.06)

I.r. (liquid film) : ν max 1740 s (ester carbonyl), 1675 s and 1625 s (enone), 1380 m cm^{-1}

N.m.r. : δ_H (200 MHz, $CDCl_3$), 6.75 (d, 1H, J = 15.5 Hz, OC-C<u>H</u>=), 6.1 (d, 1H, J = 15.5 Hz, C<u>H</u>=CHCO), 5.57 (br s, 1H, -C<u>H</u>=CMe), 5.35 (m, 2H, -C<u>H</u>=C<u>H</u>-) 3.67 (s, 3H, $-CO_2C\underline{H}_3$), 2.55 (t, 2H, J = 7 Hz, $-C\underline{H}_2CO$) 2.4 - 1.15 (complex, 27H) 0.9 (m, 3H, $-C\underline{H}_3$).

Mass spectrum : m/z 400 (M^+)

<u>Preparation of 7-[-5-formyl-2-methylbicyclo[3.3.1]non-2-en-9-yl]-[syn]-(±)-5-(Z)-heptenoic acid (151)</u>

Pyridinium chlorochromate (0.13 g, 0.6 mM) was suspended in anhydrous dichloromethane (2 cm^3). The acid-alcohol (150), (0.119, 0.41 mM) in dichloromethane (1 cm^3) was then added in one portion to the magnetically stirred suspension. After 6 hours, dry diethyl ether (10 cm^3) was added and the supernatant liquid decanted from the black gum. The insoluble residue was washed with dry diethyl ether (3 x 5 cm^3) and then passed through a short silica gel column. The solvent was evaporated to give a yellow gum.

Yield 43 mgs (36%)

I.r. (liquid film) : ν max 2500 br (OH), 2775 w (CHO), 1720 s (CO), 1450 m, 1390 w, 1150 m, 1125 m, 1070 m, 1040 m cm^{-1}.

N.m.r. : (220 MHz, $CDCl_3$) 9.4 (s, 1H, -C<u>H</u>O), 5.7 - 5.3 (complex, 2H, C<u>H</u>=), 2.7 - 1.2 (complex, 17H).

<u>Preparation of 7-[-5-(3-oxo-1-(E)-octenyl)-2-methylbicyclo[3.3.1]non-2-en-9-yl]-[syn]-(±)-5-(Z)-heptenoic acid 157</u>

To a suspension of sodium hydride (7.2 mgs, 0.18 mM, 80%

dispersion in oil) in tetrahydrofuran (1 cm^3) under nitrogen was added dimethyl 2-oxoheptylphosphonate (40 mgs, 0.18 mM) in tetrahydrofuran (1 cm^3) by cannula. A yellow coloured solution was formed initially, after 5 minutes a white precipitate was deposited and after 10 minutes the reaction mixture had completely solidified.

The sodium salt of the aldehyde (156) was prepared by adding the aldehyde (151) (43 mgs, 0.15 mM) to a suspension of sodium hydride (16 mgs, 0.15 mM, 80% dispersion in oil) in tetrahydrofuran (1 cm^3). The sodium salt of the aldehyde (156) was then added by cannula to the reaction mixture. On stirring overnight, some of the solid had disappeared but the reaction had not gone to completion. The reaction mixture was then heated at 30°C for 12 hours when the solid disappeared and the reaction was complete.

Saturated ammonium chloride (10 cm^3) and ether (10 cm^3) were added and the layers separated. The aqueous layer was extracted with ether (2 x 10 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated.

The crude product was subjected to short path silica chromatography using 40% ethyl acetate in petrol as the eluting solvent.

Yield (not recorded)

I.r. (liquid film) : ν max 3200 br (OH), 1700 s (CO), 1670 m and 1620 m (enone) 1170 w, 990 w.

N.m.r. : δ_H (200 MHz, $CDCl_3$) 7.75 (br, 1H, $-CO_2\underline{H}$), 6.8 (d, 1H, J = 15.5 Hz, OC-C$\underline{H}$=), 6.1 (d, 1H, J = 15.5 Hz, -C$\underline{H}$=CHCO), 5.5 (br s, 1H, -C$\underline{H}$=CMe), 5.35 (m, 2H, -C$\underline{H}$=C$\underline{H}$-), 2.55 (t, 2H, J = 7 Hz, $-C\underline{H}_2CO$), 2.35 (t, 2H, J = 7 Hz, $-C\underline{H}_2CO_2H$), 2.25 - 1.2 (complex, 27H), 0.9 (t, 3H, J = 7 Hz, $-CH_2C\underline{H}_3$).

Preparation of methyl 7-[-5-(3-hydroxy-1-(E)-octenyl)-2-methylbicyclo[3.3.1]non-2-en-9-yl]-[syn]-(±)-5-(Z)-heptenoate (159)

The enone (155), (0.0537 g, 0.134 mM) was dissolved in methanol (2 cm^3) and cooled to 0^oC. Sodium borohydride (20 mgs, 0.53 mM) was then added and the reaction carefully monitored by t.l.c. When the reaction was complete, water (2 cm^3) was added and the methanol was removed under reduced pressure. Ether (3 cm^3) was added to the residue and the layers separated. The aqueous layer was extracted with ether (2 x 5 cm^3). The combined ethereal extracts were dried over magnesium sulphate and evaporated.

The crude product was subjected to short path silica chromatography using 30% ethyl acetate in petrol as the eluent.

Yield 0.0515 g (96%)

Accurate mass : 402.3130 (M^+) $C_{26}H_{42}O_3$ requires 402.3134

I.r. (liquid film) : ν max 3450 br (OH), 1745 s (CO), 1450 m, 1160 w, 980 m cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$) 5.5 (complex, 3H, C<u>H</u>=C-), 4.1 (m, 1H, C<u>H</u>-OH), 3.65 (s, 3H, $-CO_2C\underline{H}_3$) 2.4 - 1.0 (complex, 32H) 0.9 (t, 3H, $-CH_2C\underline{H}_3$)

Mass spectrum : 402 (M^+) 384 (M^+-H_2O).

<u>Preparation of diethyl 2,2-diethoxyethylphosphonate</u>

Into a three-necked round-bottomed flask (2 litres) fitted with a magnetic stirrer, dropping funnel, and nitrogen inlet was placed bromoacetaldehyde diethylacetal (410 g, 2.08 M) and a gentle stream of nitrogen was then passed continuously through the system. To the stirred solution, was added dropwise triethylphosphite (316 g, 1.9 M) over a period of 30 minutes at 110-120°C. The mixture was then stirred for 3 hours at 160°C. The bromoethane evolved was trapped by a condenser and a receiver cooled in an ice-bath. The low boiling material (below 100°C) was distilled at 10 mm Hg. The residual oil was fractionally distilled under low vacuum.

Yield 328 g (68%)

B.pt 96-98 (0.6 mm Hg) (lit., [92]b.pt 101-3°C at 0.8 mM Hg)

I.r. (liquid film) : ν max 1485 m, 1450 m, 1396 m, 1375 m, 1350 m, 960 s, 860 s.

N.m.r. : δ_H (250 MHz, $CDCl_3$), 4.9 (dt, 1H, J = 6 Hz, $-CH_2C\underline{H}$), 4.1 (2q, 4H, J = 7 Hz, $(CH_3C\underline{H}_2O)_2P(O)-$) 3.75 - 3.5 (m, 4H - $CH(OC\underline{H}_2CH_3)$, 2.2 (dd, 2H, J = 19 and 6 Hz, $-CHC\underline{H}_2P(O)$), 1.35 (t, 6H, J = 7 Hz, $(C\underline{H}_3CH_2O)_2P(O)$), 1.2 (t, 6H, J = 7 Hz, $-CH(OCH_2C\underline{H}_3)$.

Preparation of diethyl formylethylphosphonate

A mixture of diethyl 2,2-diethoxyethylphosphonate (320 g, 1.28 M), water (600 cm^3) and dowex 50W-X8, a polymer supported sulphonic acid (6g), was vigorously stirred on a steam bath for 2 hours. During this period, ethanol was allowed to distil from the reaction vessel. The mixture was filtered and the filtrate concentrated to give the aldehyde as a pale yellow oil. Toluene was used to azeotrope the last traces of water.

Yield 233 g (97.7%)

Rf 0.3 SiO_2 (EtAc)

I.r. (liquid film) : ν max 2750 w (CHO) 1730 s (CO) 1440 m, 1385 m, 1370 m, 1250 s, 1170 m

N.m.r. : δ_H (250 MHz, $CDCl_3$), 9.7 (m, 1H, -C<u>H</u>O), 4.1 (2q, 4H, J = 7 Hz, $CH_3C\underline{H}_2O$-), 3.1 (dd, 2H, J = 22 and 3.5 Hz, $P(O)C\underline{H}_2CH$), 1.35 (t, 6H, J = 7 Hz, 2 x $C\underline{H}_3$-).

Preparation of diethyl 2-(cyclohexylamino)vinylphosphonate

Into a 250 cm^3 three-necked round-bottomed flask fitted with a magnetic stirrer, dropping funnel and nitrogen inlet were placed diethyl formylmethylphosphonate (33 g, 0.18 g) and analar methanol (125 cm^3). Under a nitrogen atmosphere, cyclohexylamine (19.5 cm^3, 0.17 M) was added in portions to the stirred solution, over a period of 5 minutes. During the addition, the temperature was maintained at 0-5°C by cooling with an ice-bath. The mixture was stirred for an additional 10 minutes at room temperature, and then the methanol was removed on the

rotary evaporator using low vacuum without heating. The residue was dissolved in dry ether (100 cm^3) and dried over potassium carbonate. The ether was removed and the residual oil was distilled using a heating mantle under reduced pressure. The product was collected at 120°C-150°C at 0.2 mM Hg and crystallised when left for a few weeks in the refrigerator with a few authentic seeds.

Yield 34 g (69%)

M.pt 46-49°C (lit., [92] m.pt 58-61°)

I.r. (liquid film) : ν max 1620 (C=C), 1455 m, 1395 m, 1370 m, 1220 s, 1060 s, 960 s cm^{-1}

N.m.r. : δ_H (250 MHz, CCl_4) 7.7 - 5.9 (m, 2H, C<u>H</u>=C<u>H</u>), 5.0 - 4.3 (br, 1H, N<u>H</u>), 4.0 (m, 4H, $CH_3C\underline{H_2}O$-), 2.1 - 1.0 (complex, 10H), 1.3 (t, 6H, J = 7 Hz, $C\underline{H_3}CH_2O$-).

<u>Preparation of ethyl 4-methyl-9-(2'-oxoethylidene)-bicyclo[3.3.1]non-3-enecarboxylate (165)</u>

Into a three-necked round-bottomed flask (25 cm^3), fitted with a dropping funnel, magnetic stirrer and nitrogen inlet were placed sodium hydride (0.1 g, 2.1 mM, 50% dispersion in oil) and anhydrous tetrahydrofuran (1 cm^3). A solution of diethyl 2-(cyclohexylamino)vinyl phosphonate (0.6 g; 2.3 mM) in tetrahydrofuran (2 cm^3) was added dropwise to the stirred mixture over a period of 15 minutes. During the addition, the temperature was maintained at 0-5°C with an ice-bath. The mixture was further stirred for 15 minutes at 0-5°C before a solution of ethyl 4-methyl-9-oxobicyclo[3.3.1]non-3-enecarboxylate (83), (0.5 g, 2.3 mM)

in tetrahydrofuran (1.5 cm^3) was added dropwise over a period of 10 minutes at 0^oC. The resulting mixture was stirred at room temperature overnight.

The mixture was then poured into cold water (20 cm^3) and extracted with ether (3 x 10 cm^3). The combined ether extracts were washed with saturated sodium chloride (2 x 5 cm^3), dried over sodium sulphate, and the ether evaporated under reduced pressure.

The residue was dissolved in benzene (6 cm^3) and water (18 cm^3) with oxalic acid dihydrate (0.36 g) were then added. The resulting solution was stirred under reflux for 2 hours.

The aqueous layer was extracted with ether (2 x 10 cm^3) and the combined organic extracts were washed with water (6 cm^3), saturated sodium chloride (6 cm^3), dried over magnesium sulphate and evaporated.

The crude product was chromatographed on a short path silica column using 5% ethyl acetate in hexane as the eluting solvent.

Two products were isolated.

Ethyl 4-methyl-9-(E)-(2'-oxoethylidene)bicyclo[3.3.1]-
[illegible]non-3-enecarboxylate (165)

Yield 148 mgs (19%)

I.r. (liquid film) : ν max 1725 s (ester carbonyl), 1670 s and 1625 m (enone), 1440 m, 1235 m, 1150 m, 1070 m, 855 m cm^{-1}.

N.m.r. : δ_H (250 MHz, $CDCl_3$) 10.1 (d, 1H, J = 11 Hz, -C<u>H</u>O), 5.6 (m, 2H, C<u>H</u>=C), 4.25 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2CH_3$), 3.9 (br s, 1H, C(5)H), 3.1 (br d, 1H, J = 21 Hz, endo C(2)H), 2.35 - 2.1 (m, 2H, exo C(2)H and endo C(8)H). 2 - 1.55 (complex, 8H), 1.25 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$).

<u>Ethyl 4-methyl-9-(Z)-(2'-oxoethylidene)bicyclo[3.3.1]-nonan-3-enecarboxylate (166)</u>

Yield 55 mgs, n.m.r. showed it to be contaminated with 45% of starting material.

N.m.r. : δ_H (250 MHz, $CDCl_3$), 9.55 (d, 1H, J = 11 Hz, -C<u>H</u>O), 5.9 (d, 1H, =C<u>H</u>CHO) 5.55 (br s, 1H, C<u>H</u>=CCH_3) 4.2 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2CH_3$), 3.15 (br d, 1H, J = 21 Hz, C(2)H endo), 2.75 (br s, 1H, C(5)H) 2.5 - 1.5 (complex, 9H), 1.25 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$).

<u>Attempted preparation of 4,4-dimethyl-9-(2-oxoethylidene)-bicyclo[3.3.1]nonanecarboxylate (162)</u>

Into a three-necked round-bottomed flask (25 cm^3) fitted with a dropping funnel, magnetic stirrer, and nitrogen inlet were placed sodium hydride (0.0902g, 2.2 mM, 60% dispersion in oil) and anhydrous tetrahydrofuran (1 cm^3). A solution of diethyl 2-(cyclohexylamino)vinyl phosphonate (0.5669 g, 2.2 mM) in tetrahydrofuran (2 cm^3) was added dropwise to the stirred mixture over a period of 15 minutes. During the addition, the temperature was maintained at 0-5°C with an ice-bath. The mixture was further stirred for 15 minutes at 0-5°C before a solution of ethyl 4,4-dimethyl-9-oxobicyclo[3.3.1]nonanecarboxylate (105), (0.4007 g, 1.7 mM)

in tetrahydrofuran (2 cm^3) was added dropwise over a period of 10 minutes at 0°C. On addition of the ketone to the flask, there was an effervescence which indicated unreacted sodium hydride. The mixture was stirred overnight at room temperature and then heated at 60°C for 10 hours when a gummy precipitate in a dark orange solution. T.l.c. indicated the presence of only starting material.

Preparation of N-tert-butylacetaldimine

N-tert-butylamine (7.18 cm^3, 0.068 M) was added at 0°C to acetaldehyde (3.82 cm^3, 0.068 M) and stirred at this temperature for 30 minutes. Potassium hydroxide pellets were then added and the layers separated. The organic layer was dried overnight over potassium hydroxide and then distilled over calcium hydride.

Yield 5.8 g (86%)

B. pt. 80-82°C

I.r. (liquid film) : ν max 1675 s (C=C), 1470 m, 1360 s, 1210 s, 1115 m, 940 m cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$), 7.7 (q, 1H, J = 9 Hz, $=C\underline{H}CH_3$), 1.9 s (d, 3H, $CH_3CH=$), 1.15 (s, 9H, $-C(C\underline{H}_3)_3$).

Preparation of N-tert-butyl-2-(trimethylsilyl)acetaldimine (167)

To a stirred solution of diisopropylamine (2.84 cm^3, 0.02 m) in tetrahydrofuran (25 cm^3) at 0°C was added n-butyl lithium (13.2 cm^3, 0.02 M, 1.53 M in hexane) which was stirred for 30 minutes. N-tert-butylacetaldimine

(2 g, 0.02 M) was added to this lithium diisopropylamide solution at 0°C to give a bright yellow coloured solution and it became an orange colour on cooling to -78°C. After 15 minutes, the solution was cooled to -78°C and trimethylsilylchloride (2.56 cm^3, 0.02 M) in tetrahydrofuran (2 cm^3) was added dropwise. On the addition, the colour faded and a cloudy white solution was formed. The reaction mixture was slowly warmed to 0°C and stirred at this temperature for 3 hours. Then the solution was poured on to water (50 cm^3) and extracted with ether (3 x 25 cm^3). The combined organic extracts were dried overnight over potassium carbonate. The ether was removed and the residual liquid distilled from calcium hydride.

Yield 2.3 g (67%)

B.pt. 155-160°C

I.r. (liquid film) : ν max 1650 (C=C), 1450 m, 1350 s, 1240 s, 1160 m, 1130 m, 900 s cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$), 8.6 (t, 1H, J = 14 Hz, -N=C<u>H</u>CH_2-) 2.8 (d, 2H, J = 14 Hz, -N=CH$C\underline{H}_2$-) 2.1 (s, 9H, -$C(C\underline{H}_3)_3$) 1.0 (s, 9H, -$Si(C\underline{H}_3)_3$).

<u>Preparation of ethyl 4,4-dimethyl-9-(Z)-(2'oxoethylidene)-bicyclo[3.3.1]nonanecarboxylate (162)</u>

To a stirred solution of diisopropylamine (3.8 cm^3, 27 mM) in tetrahydrofuran (50 cm^3) at 0°C was added n-butyl lithium (17.75 cm^3, 27 mM, 1.53 M in hexane) which was stirred for 30 minutes before n-tert-butyl-2-(trimethyl-

silyl)-acetaldimine (167) (4.46 g, 26 mM) was added. The deep red reaction mixture was stirred for 15 minutes more, cooled to -78°C and treated with ethyl 4,4-dimethyl-9-oxobicyclo[3.3.1]nonanecarboxylate (105), (2.5 g, 10.5 mM). The resulting mixture was warmed to approximately -20°C over a 3 hour period and then quenched with water (20 cm^3). Solid oxalic acid was added to bring the pH to 4.5 and stirred for 30 minutes more. The reaction mixture was poured on to brine (40 cm^3) and extracted with ether (3 x 40 cm^3). The combined organic extracts were washed with saturated aqueous sodium bicarbonate, then dried over magnesium sulphate and evaporated.

The crude product was subjected to short path silica column chromatography using 15% ethyl acetate in petrol as the eluting solvent.

Yield 1.9 g (69%)

I.r. (liquid film) : ν max 1730 s (ester carbonyl), 1685 s and 1625 m (enone), 1400 w, 1375 m, 1240 s, 1160 m, 850 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) 9.5 (d, 1H, J = 9 Hz, -C<u>H</u>O), 5.8 (d, 1H, J = 9 Hz, -C<u>H</u>=), 4.1 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2CH_3$), 2.6 - 1.4 (complex, 11H), 1.25 (t, 3H, J = 7Hz, $-CO_2CH_2C\underline{H}_3$), 1.0 (s, 3H, $-CC\underline{H}_3$), 0.9 (s, 3H, $-CC\underline{H}_3$)

Attempted preparation of ethyl 4,4-dimethyl-9-(formyl-methyl)bicyclo[3.3.1]nonanecarboxylate (163)

Into a flame-dried three-necked flask under nitrogen was added dimethylformamide (20 cm^3) followed by a blue solution of 0.36 M chromium II sulphate (5.7 cm^3, 2 mM). The α,β-unsaturated aldehyde (168), (92.0 mgs, 0.36 mM) in dimethylformamide (2 cm^3) was then added by cannula.

After stirring overnight, the solution changed to a turquoise colour and t.l.c. showed there to be exclusively one product.

The solution was diluted with water (30 cm^3) and ammonium sulphate (5 g) was added. The mixture was extracted with ether (4 x 40 cm^3), and the combined ether extracts were dried over magnesium sulphate and evaporated. The crude product was subjected to short path column chromatography using 15% ethyl acetate in petrol.

The product was found to be ethyl 4,4-dimethyl-9-(E)-(2'-oxoethylidene)bicyclononanecarboxylate (169).

I.r. (liquid film) : ν max 1720 s (ester carbonyl), 1665 s and 1617 m (α,β-unsaturated aldehyde) 1450 m, 1260 m, 1160 m, 1055 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) : 10.0 (d, 1H, J = 9 Hz, -C<u>H</u>O), 5.75 (d, 1H, J = 9 Hz, =C<u>H</u>), 4.15 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2CH_3$), 2.6 - 1.4 (complex, 10H), 1.25 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$) 1.05 (s, 3H, $-CC\underline{H}_3$), 0.9 (s, 3H, $-CC\underline{H}_3$).

Preparation of ethyl 9-[syn]-(formylmethyl)4,4-dimethyl-bicyclo[3.3.1]nonanecarboxylate (163)

The α,β-unsaturated aldehyde (168), (141.8 mgs, 0.56 mM) was dissolved in ethyl acetate (5 cm^3) and petrol (5 cm^3) and a palladium on carbon catalyst (100 mgs) was then added. The reaction mixture was then subjected to standard hydrogenation conditions. 12.5 cm^3 of hydrogen had been taken up within one hour and t.l.c. indicated that the reaction had gone to completion.

The mixture was filtered through hyflo and the filtrate then evaporated.

Yield 139 mgs (98%)

I.r.(liquid film) : ν max 2720 (CHO), 1725 (CO), 1400 m, 1375 m, 1260 m, 1160 m, 1060 w, 1050 w cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$), 9.65 (t, 1H, J = 2.5 MHz, -CHO), 4.1 (m, 3H, $-CO_2\underline{CH_2}CH_3$), 2.6 (m, 2H, $-\underline{CH_2}CHO$), 2.2 - 1.3 (complex, 11H), 1.25 (t, 3H, J = 7 Hz, $-CO_2CH_2\underline{CH_3}$), 1.05 (s, 3H, $-C\underline{CH_3}$), 0.95 (s, 3H, $-C\underline{CH_3}$).

The aldehyde (168) rapidly oxidised to 2-[-5-(carboxymethyl)-2,2-dimethylbicyclo[3.3.1]non-9-yl]-[syn]-(±)-ethanoic acid (171) in deutrochloroform.

M.pt. 116°-118°C

Elemental analysis : (Found C, 68.17; H, 9.33. $C_{16}H_{26}O_4$ requires C, 68.05; H, 9.28).

I.r. (kBr) : ν max 3450 (br, OH), 1720 (ester carbonyl), 1705 (acid carbonyl), 1395 w, 1370 w, 1340 w, 1220 w, 1160 m cm^{-1}.

N.m.r. : δ_H (400 MHz, $CDCl_3$) : 4.1 (m, 3H, $-CO_2C\underline{H}_2CH_3$), 2.5 (m, 3H, $-C\underline{H}_2CO_2H$ and C(1')H), 2.1 - 1.3 (complex, 11H), 1.25 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$), 1.05 (s, 3H, $-CC\underline{H}_3$), 0.95 (s, 3H, $-CC\underline{H}_3$)

Attempted preparation of ethyl 9-[syn]formyl-4,4-dimethyl-bicyclo[3.3.1]nonylcarboxylate (160)

To a stirred solution of diisopropylamine (0.7 cm^3, 0.5 mM) in tetrahydrofuran (5 cm^3) maintained at 0^oC was added n-butyl lithium (0.33 cm^3, 0.49 mM, 1.48 M in hexane). The solution was stirred for twenty minutes at this temperature. Methoxymethyldiphenylphosphine oxide (115 mgs, 0.49 mM) in tetrahydrofuran (1 cm^3) was then added by cannula and the mixture stirred for 10 minutes. The deep red solution was then cooled to -78^oC and the ketone (105), (74.4 mgs, 0.325 mM) in dry tetrahydrofuran (0.5 cm^3) was added by cannula dropwise. The solution was allowed to warm to room temperature and then stirred for a further 3 hours. Saturated ammonium chloride solution (5 cm^3) and ether (5 cm^3) were then added. The aqueous phase was extracted with ether (3 x 5 cm^3), and the combined organic extracts dried over magnesium sulphate and evaporated under reduced pressure to give a yellow oil.

The yellow oil was dissolved in tetrahydrofuran (8 cm^3) and stirred with sodium hydride (64 mgs, 1.6 mM, 60% dispersion in oil) overnight. The mixture was filtered through Hyflo to remove the gelatinous precipitate of sodium diphenyl-phosphinite. The residue was washed with ether (50 cm^3) and the combined organic fractions were evaporated under reduced pressure.

The crude product was chromatographed on a short-path silica column to give a geometric mixture of enol ethers (173).

Yield 23.4 mgs (27%)

I.r. (liquid film) : ν max 5.7 (s, 1H, C<u>H</u>=), 4.1 (q, 2H, $-CO_2\underline{CH_2}CH_3$), 3.5 (s, 1H, $-OC\underline{H_3}$), 3.4 (s, 1H, $-OC\underline{H_3}$), 2.6 - 1.5 (complex, 10H), 1.25 (t, 3H, $-CO_2CH_2C\underline{H_3}$), 0.9 (2s, 6H, 2 x $C\underline{H_3}$).

The resulting enol-ethers (173) were dissolved in acetone (5 cm^3) with a few drops of dilute hydrochloric acid and stirred for 4 hours. The ethanol was evaporated under reduced pressure and then ether (5 cm^3) and water (5 cm^3) added. The layers were separated and the aqueous phase extracted with ether (2 x 5 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated.

I.r. (liquid film) : ν max 2730 w (CHO), 1725 s (CO), 1470 m.

N.m.r. : δ_H (80 MHz, $CDCl_3$), 9.65 (s, 1H, -C<u>H</u>O), 4.15 (q, 2H, J = 7 Hz, $-CO_2C\underline{H_2}CH_3$), 3.1 (br s, 1H, C(9)H), 2.2 - 1.4 (complex, 15H) 1.4 - 0.8 (complex, 9H).

<u>Preparation of 9-[anti]-formyl-4,4-dimethylbicyclo[3.2.1]-octylcarboxylate (161)</u>

The aldehyde (160), (20 mgs) was dissolved in ethanol (2 cm^3) and a very small amount of sodium was added. The resulting solution was left standing overnight at room temperature. Dilute hydrochloric acid was then added until the solution was neutral. The ethanol was evaporated under reduced pressure and ether (5 cm^3) and water (2 cm^3) added. The layers were separated and the aqueous phase re-extracted with ether (2 x 2 cm^3). The combined ether extracts were

dried over magnesium sulphate and evaporated. Only an impure sample was obtained.

I.r. (liquid film) : ν max 2730 (CHO), 1725 (CO).
N.m.r. : δ_H (80 MHz, $CDCl_3$) : 9.7 (s, 1H, -C<u>H</u>O), 4.1 (q, 2H, $-CO_2C\underline{H}_2CH_3$), 2.7 (br s, 1H, -C(9)H), 0.95 (s, 3H, $-CC\underline{H}_3$), 0.75 (s, 3H, $-CC\underline{H}_3$). A full assignment could not be made because of the impurity of the sample.

<u>Preparation of 7-[-5-(ethoxycarbonyl)-2,7-dimethyl-bicyclo[3.3.1]non-9-yl]-[syn]-(±)-5-(Z)-heptenoic acid (170)</u>

Potassium tert-butoxide (2 g, 18 mM) and (4-carboxybutyl)-triphenylphosphonium bromide (4 g, 9 mM) were quickly ground together and then placed in a dry two-necked flask under nitrogen. Tetrahydrofuran (75 cm^3) was distilled on to the solids to give a bright orange solution which was stirred for 30 minutes. A solution of the aldehyde (163), (880 mgs, 4.3 mM) in dry tetrahydrofuran (10 cm^3) was added in one portion with stirring and the resulting solution stirred for a further one hour. Saturated aqueous ammonium chloride (100 cm^3) was added, followed by dilute hydrochloric acid until the reaction mixture was acidic, and then ether (150 cm^3) was added. The layers were separated and the aqueous layer was extracted with ether (3 x 100 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated to give a yellow oil.

The crude product was subjected to short-column chromatography on silica using 40% ethyl acetate in petrol

as the eluent.

Yield = 1.03 g (74%)

Elemental analysis : (Found C, 70.80; H, 9.90. $C_{21}H_{24}O_4$ requires C, 70.97; H, 10.12%).

I.r. (liquid film) : ν max 3300 br (OH), 1720 (CO), 1440 w, 1380 w, 1240 m, 1160 m, 1045 m cm^{-1}.

N.m.r. : δ_H (400 MHz, $CDCl_3$) 9.3 - 8.5 (br s, -O<u>H</u>), 5.4 (m, 2H, -C<u>H</u>=C<u>H</u>-), 4.1 (m, 2H, $-CO_2C\underline{H}_2CH_3$), 2.4 (t, 3H, J = 7 Hz, $-C\underline{H}_2CO_2H$), 2.3 - 1.34 (complex, 20H), 1.25 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$), 1.05 (s, 3H, $-CC\underline{H}_3$), 0.95 (s, 3H, $-CC\underline{H}_3$).

δ_C (80 MHz, $CDCl_3$) 179.4 (<u>C</u>=O), 177.9 (<u>C</u>=O), 130.2 (<u>C</u>H=), 129.1 (<u>C</u>H=), 60.1 (<u>C</u>-CO_2Et), 46.6, 45.9, 40.4, 40.05, 35.8, 35.4, 33.46, 32.4, 31.6, 29.7, 29.1, 26.8, 25.5, 24.5, 21.1, 14.2.

<u>Preparation of methyl 7-[-5-(hydroxymethyl)-1,2-dimethyl-bicyclo[3.3.1]non-9-yl]-[syn]-(±)-5-(Z)-heptenoate (175)</u>

The acid ester (170) (1.2654 g, 3.9 mM) and toluene (20 cm^3) were placed in a flame-dried three-necked flask fitted with a nitrogen inlet and cooled to -78°C. Diisobutylaluminium hydride (8 cm^3, 12.2 mM, 25% w/w in toluene), was slowly added over 5 minutes. When t.l.c. indicated that the reaction had gone to completion, water (10 cm^3) was added and the reaction mixture allowed to reach room temperature. Dilute hydrochloric acid (25 cm^3) and ether (25 cm^3) were added to the reaction mixture. The layers were separated and the aqueous layer extracted with ether (3 x 25 cm^3).

An ethereal solution of diazomethane was added to the combined organic extracts. The excess diazomethane was volatised away and then the organic extract dried over magnesium sulphate and evaporated under reduced pressure.

The crude product was chromatographed on a short path silica column using 30% ethyl acetate in petrol as the eluting solvent.

Yield 0.8555 g (74%)
Accurate mass :

I.r. (liquid film) : ν max 3500 br (OH), 1720 s (CO), 1440 m, 1200 m, 1020 m.
N.m.r. : δ_H (80 MHz, $CDCl_3$) 5.5 (m, 2H, C<u>H</u>=), 3.75 (s, 3H, $-CO_2C\underline{H}_3$), 3.4 (d, 1H, J = 11 Hz, $-C\underline{H}_2OH$), 3.0 (d, 1H, J = 11 Hz, $-C\underline{H}_2OH$), 2.5 - 1.2 (complex, 18H), 1.5 (s, 1H, -O<u>H</u>), 1.1 (s, 3H, $-CC\underline{H}_3$) 0.95 (s, 3H, $-CC\underline{H}_3$) (J = 7 Hz, $-CO_2CH_2C\underline{H}_3$), 1.0 (s, 3H, $-CC\underline{H}_3$), 0.9 (s, 3H, $-CC\underline{H}_3$).

<u>Preparation of methyl 7-[-5-formyl-2,2-dimethylbicyclo-[3.3.1]non-9-yl]-(±)-5-(Z)-heptenoate (193)</u>

Pyridinium chlorochromate (0.756 g, 3.5 mM) was suspended in anhydrous dichloromethane (15 cm^3). The alcohol (175) (0.5374 g, 1.66 mM) in dichloromethane (5 cm^3) was then added in one portion to the magnetically stirred suspension. After 3 hours, dry diethylether (30 cm^3) was added and the supernatant liquid decanted from the black gum. The insoluble residue was washed with dry diethylether (3 x

15 cm^3) and the ether extracts passed through a short-path silica gel column. The solvent was removed by evaporation.

Yield 0.5332 g (100%)

I.r. (liquid film) : ν max 2730 w (CHO), 1740 (CO), 1475 m, 1380 m, 1175 m.

N.m.r. : δ_H (80 MHz, $CDCl_3$), 9.4 s (C<u>H</u>O), 5.4 (m, 2H, C<u>H</u>=C<u>H</u>), 3.7 (s, 3H, $-CO_2C\underline{H}_3$), 1.5 - 1.2 (complex, 18H), 1.02 (s, 3H, $-CC\underline{H}_3$) 0.95 (s, 3H, $-CC\underline{H}_3$).

<u>Preparation of methyl 7-[-5-(3-oxo-1-(E)-octenyl)-2,2-dimethylbicyclo[3.3.1]non-9-yl]-[syn]-(±)-5-(Z)-heptenoate (194)</u>

To a suspension of sodium hydride (79.3 mgs, 2 mM, 60% dispersion in oil) in tetrahydrofuran (15 cm^3) under nitrogen was added dimethyl 2-oxoheptylphosphonate (0.4521 g, 2 mM) in tetrahydrofuran (3 cm^3) by cannula. A yellow coloured solution was formed initially, after 5 minutes a white precipitate was deposited and after 10 minutes the reaction mixture had completely solidified. After 30 minutes, the aldehyde (193), (0.5332 g, 1.66 mM) in tetrahydrofuran (3 cm^3) was added by cannula. The resulting solution was stirred at room temperature for 48 hours.

Saturated ammonium chloride (20 cm^3) and ether (20 cm^3) were added and the layers separated. The aqueous layer was extracted with ether (3 x 20 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated

under reduced pressure.

The crude product was subjected to short-path silica chromatography using 25% ethyl acetate in petrol as the eluting solvent.

Yield 0.5442 g (79%)
Accurate mass : 416.3300 (M^+) $C_{27}H_{44}O_3$ requires 416.3290.
I.r. (liquid film) : ν max 1720 s (ester carbonyl), 1660 m and 1600 m (enone), 1440 m, 1345 m, 1145 cm^{-1}.
N.m.r. : δ_H (80 MHz, $CDCl_3$) 6.7 (d, 1H, J = 16 Hz, =C<u>H</u>CO), 5.95 (d, 1H, J = 16 Hz, C<u>H</u>=CHCO), 5.35 (m, 2H, $-CH_2C\underline{H}=CH-$), 3.7 (s, 3H, $-CO_2C\underline{H}_3$), 2.7 - 1.1 (complex, 31H), 0.95 (s, 3H, $-CC\underline{H}_3$), 1.05 (s, 3H, $-CC\underline{H}_3$)
Mass spectrum : m/z 416 (M^+, 58), 345 (78), 317 (100), 151 (60), 99 (62).

<u>Preparation of methyl 7-[-5-(3-hydroxy-1-(E)-octenyl)-2,2-dimethylbicyclo[3.3.1]nonyl]-[syn]-(±)-5-(Z)-heptenoate (176)</u>

The enone (194), (130 mgs, 0.3 mM) was dissolved in methanol (5 cm^3) and cooled to 0°C. Sodium borohydride (40 mgs, 1 mM) was then added and the reaction carefully monitored by t.l.c. When the reaction was complete, water (5 cm^3) was added and the methanol was removed under reduced pressure. Ether (8 cm^3) was then added and the layers separated. The aqueous layer was extracted with ether (2 x 10 cm^3). The combined ethereal extracts were dried over magnesium sulphate and evaporated.

The crude product was subjected to short-path silica chromatography using 20% ethyl acetate in petrol as the eluent.

Yield = 124 mgs (96%)

Accurate mass :

I.r. (liquid film) : ν max 3400 br (OH), 1720 (ester carbonyl), 1440 m, 1345 m, 1010 m, 960 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) : 5.4 (m, 4H, -C<u>H</u>=C<u>H</u>-), 4.0 (m, 2H, C<u>H</u>$_2$-OH), 3.7 (s, 5H, -$CO_2C\underline{H}_3$), 2.4 - 1.1 (complex, 30H) 1.05 (s, 3H, -CC<u>H</u>$_3$), 0.95 (s, CC<u>H</u>$_3$), 1.5 (s, 1H, -O<u>H</u>).

Mass spectrum :

<u>Attempted preparation of methyl 4,4-dimethyl-9-(2'-oxo-ethylidene)bicyclo[3.2.1] octanecarboxylate (178)</u>

To a stirred solution of diisopropylamine (0.1 cm^3, 0.71 mM) in tetrahydrofuran (20 cm^3) at 0^oC was added n-butyl lithium (0.43 cm^3, 0.63 mM, 1.48 M in hexane) which was stirred for 20 minutes. N-tert-butyl-2-(trimethylsilyl)-acetaldimine (167), (109.4 mgs, 6.3 mM) was then added to give a bright red solution. The reaction mixture was stirred for 15 minutes more, cooled to -78^oC and treated with methyl 4,4-dimethyl-8-oxobicyclo[3.2.1]carboxylate (124), (110.1 mgs, 0.52 mM). The resulting mixture was warmed to approximately -20^oC over a 3 hour period and then quenched with water (10 cm^3). Solid oxalic acid was added

to bring the pH to 4.5 and the mixture was stirred for 30 minutes more. The reaction mixture was poured on to brine (15 cm^3) and extracted with ether (3 x 20 cm^3). The combined organic extracts were washed with saturated aqueous sodium hydrogencarbonate (15 cm^3), then dried over magnesium sulphate and evaporated.

The crude product was subjected to short-path silica column chromatography using 10% ethyl acetate in petrol as the eluting solvent.

The isolated product was not the expected α,β-unsaturated aldehyde (178). It had the following spectral characteristics:

Yield 72 mgs

Appearance : waxy solid

Accurate mass : 349.2439 (M^+), $C_{14}H_{35}N_1O_2Si$ requires 349.2437.

I.r. (kBr) : ν max 1730 sh, 1675 s (amide carbonyl), 1645 sh, 1460 m, 1370 m, 1335m, 1245 m, 1115 m, 1080 m cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$) 6.35 (d, 1H, J = 12 Hz, =CH-N-), 4.9 (d, 1H, J = 12 Hz, =C<u>H</u>$SiMe_3$), 2.0 - 1.2 (complex, 9H), 1.5 (s, 9H, -NCC($C\underline{H}_3$)$_3$), 1.1 (s, 3H, -CC<u>H</u>$_3$), 0.85 (s, 3H, -CC<u>H</u>$_3$) 0.1 (s, 9H, -Si($C\underline{H}_3$)$_3$.

Mass spectrum : m/z 349 (M^+), 252, 222, 196, 75.

Preparation of methyl 4,4-dimethyl-8-(2'-oxoethylidene)-bicyclo[3.2.1]octanecarboxylate (178) and ethyl 4,4-dimethyl-8-(2'-oxoethylidene)bicyclo[3.2.1]octanecarboxylate (181)

Into a three-necked round-bottomed flask (25 cm^3) fitted with a nitrogen inlet, septum and magnetic stirrer were placed sodium hydride (42.3 mgs, 0.1 mM, 60% dispersion in oil) and anhydrous tetrahydrofuran (1 cm^3). A solution of diethyl 2-(cyclohexylamino)vinyl phosphonate (233.1 mgs, 0.9 mM) in tetrahydrofuran (1 cm^3) was added dropwise by cannula over a period of 10 minutes. During the addition the temperature was maintained at 0-5°C with an ice-bath. The mixture was further stirred for 15 minutes at 0-5°C before a solution of methyl 4,4-dimethyl-8-oxobicyclo-[3.2.1]octanecarboxylate (124) (158.9 mgs, 0.76 mM) in tetrahydrofuran (2 cm^3) was added dropwise by cannula over a period of 10 minutes at 0°C. The resulting mixture was heated and stirred at 40°C overnight.

The mixture was then poured into cold water (10 cm^3) and extracted with ether (3 x 10 cm^3). The combined ether extracts were washed with saturated sodium chloride (5 cm^3) and evaporated under reduced pressure.

The residue was dissolved in benzene (6 cm^3) and water (18 cm^3) with oxalic acid dihydrate (0.8 g) were then added. The resulting solution was stirred under reflux for 2 hours.

The aqueous layer was extracted with ether (2 x 10 cm^3) and

the combined organic extracts were dried over magnesium sulphate and evaporated under reduced pressure. The crude product was chromatographed on a short-path silica column using 5% ethyl acetate in petrol as the eluting solvent.

Two products were isolated.

Methyl 4,4-dimethyl-8-(2'-oxoethylidene)bicyclo[3.2.1]-octanecarboxylate (178)

Yield 27.2 mgs (15%)

I.r. (liquid film) : ν max 1735 s (CO), 1680 m and 1635 m (α,β-unsaturated aldehyde), 1400 m, 1380 m, 1200 m, 1165 m, 1130 m, 1095 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) 9.5 (d, 1H, J = 11 Hz, -C<u>H</u>O), 5.75 (d, 1H, J = 11 Hz, -C<u>H</u>=), 3.7 (s, 3H, $-CO_2C\underline{H}_3$), 2.5 - 1.2 (complex, 9H), 1.0 (s, 3H, $-CC\underline{H}_3$), 0.9 (s, 3H, $-C(C\underline{H}_3)$.

Ethyl 4,4-dimethyl-8-(2'-oxoethylidene)bicyclo[3.3.1]octane-carboxylate (181)

Yield 57.6 mgs (30%)

I.r. (liquid film) : ν max 2730 w (C<u>H</u>O), 1725 s (ester carbonyl), 1675 m and 1625 m (α,β-unsaturated aldehyde), 1395 m, 1375 m, 1160 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) 9.9 (d, 1H, J = 11 Hz, -C<u>H</u>O), 5.9 (d, 1H, J = 11 Hz, =C<u>H</u>), 4.7 (q, 2H, J = 7 Hz, $-CO_2C\underline{H}_2CH_3$), 3.1 (d, 1H, J = 5 Hz, C(5)H), 2.5 - 1.4 (complex, 8H), 1.2 (t, 3H, J = 7 Hz, $-CO_2CH_2C\underline{H}_3$), 1.0 (s, 3H, $-CC\underline{H}_3$), 0.95 (s, 3H, $-CC\underline{H}_3$).

Preparation of methyl 8-[syn]- formyl-4,4-dimethylbicyclo-[3.2.1]octylcarboxylate (186)

To a stirred solution of diisopropylamine (1.1 cm^3, 7.8 mM) in tetrahydrofuran (10 cm^3) maintained at 0^oC was added n-butyl lithium (5.2 cm^3, 7.7 mM, 1.48 in hexane). The solution was stirred for a further twenty minutes at this temperature. Methoxymethyldiphenylphospine oxide (1.84 g, 7.8 mM) in tetrahydrofuran (5 cm^3) was then added by cannula and the mixture stirred for 10 minutes. The deep red solution was then cooled to -78^oC and the ketone (124), (1.46 g, 7 mM) in dry tetrahydrofuran (5 cm^3) added by cannula dropwise. The solution was allowed to warm to room temperature and then stirred for a further 30 minutes. Saturated ammonium chloride solution (40 cm^3) and ether (30 cm^3) were then added and the layers separated. The aqueous phase was extracted with ether (3 x 20 cm^3), and the combined organic extracts dried over magnesium sulphate and evaporated under reduced pressure to give a yellow oil. This diphenylphosphinoyl derivative was not further purified or characterised.

The yellow oil was dissolved in dry tetrahydrofuran (20 cm^3) and stirred with sodium hydride (1 g, 25 mM, 60% dispersion in oil) for two hours. The mixture was then filtered through Hyflo to remove the gelatinous precipitate of sodium diphenylphosphinite. The residue was washed with ether (50 cm^3) and the combined organic fractions were evaporated under reduced pressure.

The crude product was chromatographed on a short-path silica column to give a geometric mixture of two enol ethers (185).

I.r. (liquid film) : ν max 1735 s (CO), 1705 m (C=C), 1275 m, 1165 m, 1130 m, 1080 m.
N.m.r. : δ_H (80 MHz, $CDCl_3$) 5.85 (s, 0.2H, $\underline{H}C=$), 5.65 (s, 0.8H, $\underline{H}C=$) 3.75 (s, 0.6H, $-CO_2C\underline{H}_3$), 3.7 (s, 2.4H, $-CO_2C\underline{H}_3$), 3.55 (s, 0.6H, $-OC\underline{H}_3$), 3.45 (s, 2.4H, $-OC\underline{H}_3$), 2.7 - 1.1 (complex, 9H), 0.75 (s, 6H, $-C(C\underline{H}_3)_2$).

The enol ethers (185) were dissolved in acetone (30 cm^3) with a few drops of dilute hydrochloric acid and stirred for 5 hours. The ethanol was evaporated under reduced pressure and then ether (40 cm^3) and water (25 cm^3) added. The layers were separated and the aqueous phase extracted with ether (2 x 25 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated.

Yield = 1.07 g (69%) from ketone (124)
I.r. (liquid film) : ν max 1730 s (CO), 1400 w, 1380 w, 1280 m, 1235 w, 1200 w, 1170 m, 1080 m cm^{-1}.
N.m.r. : δ_H (80 MHz, $CDCl_3$) 10.0 ($C\underline{H}O$), 3.7 (s, 3H, $-CO_2C\underline{H}_3$), 2.9 (d, 1H, J = 5 Hz, C(5)H), 2.4 (br, s, 1H, C(8)H), 2.2 - 1.0 (complex, 8H), 0.9 (s, 3H, $-CC\underline{H}_3$), 0.8 (s, 3H, $-CC\underline{H}_3$).

The aldehyde (186) was oxidised in $CDCl_3$ to give the acid (188).

Elemental analysis : (Found, C, 64.63; H, 8.31, $C_{13}H_{20}O_4$ requires C, 64.98; H, 8.39%).

I.r. (liquid film) : ν max 3300 br (OH), 1735 (ester carbonyl), 1700 (acid carbonyl), 1280 m, 1230 m, 1195 m, 1175 m, 1075 m cm^{-1}.

N.m.r. : δ_H (400 MHz, $CDCl_3$) 3.69 (s, 3H, $-CO_2C\underline{H}_3$), 3.09 (dd, C(8)H, J = 2 Hz and 6 Hz), 2.3 (m, 3H), 2.4 (dt, 1H, H_3 endo) 1.2 - 1.3 (m, 5H) 0.95 (s, 3H, $-CC\underline{H}_3$), 0.87 (s, 3H, $-CC\underline{H}_3$).

Preparation of methyl 8-[anti]-formyl-4,4-dimethylbicyclo-[3.3.1]octylcarboxylate (187)

The aldehyde (186) (303 mgs, 1.3 mM) was dissolved in methanol (5 cm^3) and a very small amount of sodium was added. The resulting solution was left standing at room temperature for 14 hours. Dilute hydrochloric acid was then added until the solution was neutral. The methanol was removed on the rotary evaporator and ether (10 cm^3) and water (5 cm^3) added. The layers were separated and the aqueous phase extracted with ether (2 x 5 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated.

Yield 298 mgs (98%)

I.r. (liquid film) : ν max 2730 w (CHO), 1730 s (CO), 1280 m, 1235 m, 1200 m, 1170 m cm^{-1}

N.m.r. : δ_H (80 MHz, $CDCl_3$) 9.5 ($-C\underline{H}O$), 3.7 (s, 3H, $-CO_2C\underline{H}_3$), 3.0 (s, 1H, C(8)H), 2.2 - 1.1 (complex, 9H), 1.05 (s, 3H, $-CC\underline{H}_3$), 0.95 (s, 3H, $-CC\underline{H}_3$).

The aldehyde (187) oxidised in $CDCl_3$ to give the acid (189).

Elemental analysis : (Found C, 65.17; H, 8.31. $C_{13}H_{20}O_4$ requires C, 64.98; H, 8.39%)

M.pt. 127-130°C

I.r. (kBr) : ν max 3430 br (OH), 1730 (ester carbonyl), 1705 (acid carbonyl), 1285 s, 1245 m, 1170 m, 1080 m cm^{-1}.

N.m.r. : δ_H (250 MHz, $CDCl_3$) - text.

Preparation of methyl 8-[anti]-formylmethyl-4,4-dimethyl-bicyclo[3.2.1]octylcarboxylate (191)

To a stirred solution of diisopropylamine (0.23 cm^3, 1.64 mM) in tetrahydrofuran (6 cm^3) maintained at 0°C was added n-butyl lithium (1.11 cm^3, 1.64 mM, 1.48 M in hexane) and stirred for a further twenty minutes. Toluene (5 cm^3) was then added followed by methoxymethyltriphenylphosphonium chloride (0.5834 g, 1.7 mM). The bright red solution was stirred at 0°C for 15 minutes before the aldehyde (187) (0.1542 g, 0.69 mM) in toluene (1 cm^3) was added dropwise at the same temperature. After 35 minutes, t.l.c. indicated that the reaction was complete and the reaction had become a bright yellow colour. Ice-water (25 cm^3) and ether (50 cm^3) were added to the reaction mixture and the layers were separated. The aqueous phase was re-extracted with ether (2 x 25 cm^3) and the combined organic extracts dried over magnesium sulphate and evaporated to afford an oily residue which was subjected to short-path column chromatography.

The resulting isolated enol ethers were dissolved in tetrahydrofuran (13.5 cm^3) and water (1.5 cm^3) and treated

with mercuric acetate (0.525 g, 1.64 mM). After one hour at room temperature the yellow mixture was poured on to a 7% potassium iodide solution (100 cm^3) and extracted with benzene (2 x 75 cm^3). The combined organic extracts were washed with 7% aqueous potassium iodide (2 x 50 cm^3), dried over magnesium sulphate and evaporated under reduced pressure.

The crude product was subjected to short-path silica column chromatography using 25% ethyl acetate in petrol as the eluting solvent.

Yield 0.1364 g (84%)

I.r. (liquid film) : ν max 2700 (CHO), 1725 (CO), 1465 m, 1280 m, 1165 m, 1070 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) 9.7 (br s, 1H, -C<u>H</u>O), 3.65 (s, 3H, $-CO_2C\underline{H}_3$), 2.85 - 1.15 (complex, 11H), 1.05 (s, 3H, $-CC\underline{H}_3$), 0.87 (s, 3H, $-CC\underline{H}_3$).

<u>Preparation of methyl 8-[syn]-(formylmethyl)-4,4-dimethyl-bicyclo[3.2.1]octylcarboxylate (179)</u>

To a stirred solution of diisopropylamine (1.98 cm^3, 1.4 mM) in tetrahydrofuran (25 cm^3) maintained at 0^oC was added n-butyl lithium (9.45 cm^3, 14 mM, 1.48 M in hexane) and stirred for a further twenty minutes. Toluene (20 cm^3) was then added followed by methoxymethyltriphenylphosphonium chloride (4.79 g, 1.4 mM). The bright red solution was stirred at 0^oC for 20 minutes before the aldehyde (186) (1.1072 g, 4.94 mM) in toluene (5 cm^3) was added dropwise

by cannula at the same temperature. After 40 minutes t.l.c. indicated that the reaction was complete and the reaction mixture was poured on to iced-water (100 cm^3). Ether (100 cm^3) was then added and the layers separated. The aqueous phase was re-extracted with ether (3 x 50 cm^3) and the combined organic extracts dried over magnesium sulphate and evaporated to afford an oily residue which was subjected to short-path column chromatography.

The resulting isolated enol ethers were dissolved in tetrahydrofuran (40 cm^3) and water (5 cm^3) and treated with mercuric acetate (3 g, 9.4 mM). After one hour at room temperature the yellow mixture was poured on to 7% potassium iodide solution (250 cm^3) and extracted with benzene (3 x 150 cm^3). The combined organic extracts were washed with 7% aqueous potassium iodide (2 x 100 cm^3), dried over magnesium sulphate and evaporated under reduced pressure.

The crude product was subjected to short-path silica column chromatograhy using 15% ethyl acetate in petrol as the eluting solvent.

Yield 0.898 g (77%)

I.r. (liquid film) : ν max 2700 (CHO), 1720 (CO), 1440 m, 1270 m, 1160 m, 1070 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) 9.7 (br s, 1H, -C<u>H</u>O), 3.65 (s, 3H, $-CO_2C\underline{H}_3$), 2.75 (m, 2H, $-C\underline{H}_2CHO$), 2.1 - 1.1 (complex, 9H), 1.0 (s, 3H, $-CC\underline{H}_3$), 0.9 (s, 3H, $-CC\underline{H}_3$).

Preparation of 7-[-5-(methoxycarbonyl)-2,2-dimethyl-bicyclo[3.2.1]oct-8-yl]-[syn]-(±)-5-(Z)-heptenoic acid (195)

Potassium tert-butoxide (2.5 g, 0.022 M) and (4-carboxybutyl)triphenylphosphonium bromide (5 g, 0.11 M) were quickly ground together and then placed in a dry two-necked flask under nitrogen. Tetrahydrofuran (125 cm^3) was distilled on to the solids to give a bright orange solution which was stirred for 30 minutes. A solution of aldehyde (179), (1.3 g, 0.0055 M) in dry tetrahydrofuran (15 cm^3) was added in one portion with stirring. The resulting solution was stirred for a further one hour. Saturated aqueous ammonium chloride (50 cm^3) was added followed by dilute hydrochloric acid until the reaction mixture was acidic, and then ether (25 cm^3) was added. The layers were separated and the aqueous layer was extracted with ether (3 x 30 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated to give a yellow oil.

The crude product was subjected to short-column chromatography on silica using 35% ethyl acetate in petrol as the eluting solvent.

Yield 1.51 g (85%)

I.r. (liquid film) : ν max 3300 br (OH), 1735 (ester carbonyl), 1720 (acid carbonyl), 1470 m, 1450 m, 1250 m, 1170 m, 1080 m, 1050 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$), 10.45 (br s, $-CO_2\underline{H}$), 5.4 (m, 2H, $-C\underline{H}=C\underline{H}-$), 3.65 (s, 3H, $-CO_2C\underline{H}_3$), 2.5 - 1.15 (complex, 16H) 1.0 (s, 3H, $-CC\underline{H}_3$), 0.85 (s, 3H, $-CC\underline{H}_3$).

Mass spectrum :

Preparation of methyl 7-[-5-(hydroxymethyl)-2,2-dimethyl-bicyclo[3.2.1]oct-8-yl]-[syn]-($\pm$)-5-(Z)-heptenoate (190)

The acid ester (195), (0.9817 g, 3.0 mM) and toluene (25 cm^3) were placed in a flame-dried three-necked flask fitted with a nitrogen inlet and cooled to -78°C. Diisobutylaluminium hydride (6.2 cm^3, 9.4 mM, 25% w/w in toluene), was slowly added over 5 minutes. When t.l.c. indicated that the reaction was complete, water (25 cm^3) was added and the reaction mixture allowed to reach room temperature. Dilute hydrochloric acid (50 cm^3) and ether (40 cm^3) were added to the reaction mixture. The layers were separated and the aqueous layer extracted with ether (3 x 40 cm^3). An ethereal solution of diazomethane was added to the combined organic extracts. The excess diazomethane was allowed to volatilise away and then the organic extracts were dried and evaporated.

The crude product was chromatographed on a short path silica column using 20% ethyl acetate in petrol as the

eluting solvent.

Yield 0.8406 g (90%)

Accurate mass :

I.r. (liquid film) : ν mas 3400 br (OH), 2900 s, 2830 s, 1720 s (CO), 1420 m, 1345 m, 1080 m, 1020 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$) 5.5 (m, 2H, -C<u>H</u>=C<u>H</u>) 3.7 (s, 3H, -$CO_2C\underline{H}_3$), 3.4 (s, 2H, -$C\underline{H}_2CH$), 2.5 - 1.2 (complex, 9H), 1.0 (s, 3H, -$CC\underline{H}_3$), 0.85 (s, 3H, -$CC\underline{H}_3$).

Mass spectrum :

<u>Preparation of methyl 7-[-5-formyl-2,2-dimethylbicyclo-[3.2.1]oct-8-yl]-[syn]-(±)-5-(Z)-heptenoate (196)</u>

Pyridinium chlorochromate (0.7 g, 3.2 mM) was suspended in anhydrous dichloromethane (15 cm^3). The alcohol (190) (687.3 mgs, 2.2 mM) in dichloromethane (5 cm^3) was then added in one portion to the magnetically stirred suspension. After 3 hours, dry diethylether (25 cm^3) was added and the supernatant liquid decanted from the black gum. The insoluble residue was washed with dry diethylether (3 x 25 cm^3) and the combined ether extracts then passed through a short silica gel column. The solvent was evaporated to give a pale yellow oil.

Yield 680 mgs (100%)

I.r. (liquid film) : ν max 2750 (CHO), 1740 (CO), 1470 m, 1380 m, 1170 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$), 9.4 (s, 1H, -C<u>H</u>O), 5.35 (m, 2H, -C<u>H</u>=C<u>H</u>-), 3.7 (s, 3H, $-CO_2C\underline{H}_3$), 2.5 - 1.1 (complex, 18H), 1.02 (s, 3H, $-CC\underline{H}_3$), 0.9 (s, 3H, $-CC\underline{H}_3$).

<u>Preparation of methyl 7-[-5-(3-oxo-1-(E)-octenyl)-2,2-dimethylbicyclo[3.3.1]oct-8-yl]-[syn]-(±)-5-(Z)-heptenoate (197)</u>

To a suspension of sodium hydride (13.7 mgs, 0.34 mM, 60% dispersion in oil) in tetrahydrofuran (12 cm^3) under nitrogen was added dimethyl 2-oxo-heptylphosphonate (73 mgs, 0.38 mM) in tetrahydrofuran (2 cm^3) by cannula. A yellow coloured solution was formed which was stirred for 30 minutes. The aldehyde (196), (100.6 mgs, 0.33 mM) was then added in tetrahydrofuran (2 cm^3) by cannula to the reaction mixture. The resulting mixture was stirred at 40°C overnight.

Saturated ammonium chloride (10 cm^3) and ether (10 cm^3) were then added and the layers separated. The aqueous layer was extracted with ether (3 x 10 cm^3). The combined ether extracts were dried over magnesium sulphate and evaporated.

The crude product was subjected to short-path silica chromatography using 15% ethyl acetate in petrol as the eluent.

Yield 108.6 mgs (82%)

Accurate mass :

I.r. (liquid film) : ν max 1730 (CO), 1670 m and 1630 m (enone), 1450 m, 1365 m, 1280 m, 1025 m cm^{-1}.

N.m.r. : δ_H (80 MHz, $CDCl_3$), 6.75 (d, 1H, J = 17 Hz, =CHCO), 6.0 (d, 1H, J = 17 Hz, -CH=CHCO), 5.35 (m, 2H, CH=CH), 3.65 (s, 3H, $-CO_2CH_3$), 2.7 - 0.8 (complex, 35H).

Mass spectrum :

Preparation of methyl 7-[-5-(3-hydroxy-1-(E)-octenyl)-2,2-dimethylbicyclo[3.3.1]oct-8-yl]-[syn]-(±)-5-(Z)-heptenoate (192)

The enone (197), (303 mgs, 0.75 mM) was dissolved in methanol (5 cm^3) and cooled to 0^oC. Sodium borohydride (92 mgs, 2.5 mM) was then added and the reaction carefully monitored by t.l.c. When the reaction was judged to be complete, water (5 cm^3) was added and the methanol removed under reduced pressure. Ether (10 cm^3) was then added and the layers separated. The aqueous phase was extracted with ether (3 x 5 cm^3). The combined ethereal extracts were dried over magnesium sulphate and evaporated.

The crude product was subjected to short-path silica chromatography using 25% ethyl acetate in petrol as the eluting solvent.

Yield 298 mgs (98%)

Accurate mass :

I.r. (liquid film) : ν max 3400 br (OH), 1720 (ester carbonyl), 1440 m, 1345 m, 1010 m, 955 m cm^{-1}.

N.m.r. δ_H (80 MHz, $CDCl_3$), 5.7 - 5 (complex, 4H, -C<u>H</u>=C<u>H</u>-), 4.05 (m, 2H, -C<u>H</u>$_2$OH), 3.65 (s, 3H, -$CO_2C\underline{H}_3$), 2.5 - 1.1 (complex, 28H) 0.95 (s, 3H, -C<u>H</u>$_3$), 0.85 (s, 3H, -C<u>H</u>$_3$) 1.7 (1H, -O<u>H</u>)

Mass spectrum :

<u>X-ray Analysis</u>

Methyl 5-methyl-6-oxa-7oxobicyclo[3.2.2]nonanecarboxylate (77)

Crystal data : Crystals are triclinic, with <u>a</u> = 7.177, <u>b</u> = 6.669, <u>c</u> = 12.898 Å, α = 119.0, β = 91.8, γ = 88.5°, space group $P\bar{1}$, Z = 2, R = 0.047 for 1317 independent reflections having $\underline{I}/\underline{\sigma}(\underline{I})$ 3.0^+.

2,4-Dinitrophenyl hydrazone of 9-[syn]-(formylmethyl)-4,4-dimethylbicyclo[3.3.1]non-3-enecarboxylate (148)

Crystal data : Crystals are triclinic, with <u>a</u> = 16.456, <u>b</u> = 9.266, <u>c</u> = 7.220 Å, α = 94.76, β = 89.78, γ = 79.93°, space group $P\bar{1}$, R = 0.059 for 1469 independent reflections.

REFERENCES

1. E. J. Corey, Y. Arai and C. Mioskowski, J. Amer. Chem. Soc., 1979, 101, 6749.

2. S. Bergström, H. Danielson and B. Samuelsson, Biochim. Biophys. Acta, 1964, 90, 204.
   D. A. Van Dorp, R. K. Beerthius, D. H. Nutgerm and H. Von Keman, Biochim. Biophys. Acta., 1964, 90, 207.

3. K. C. Nicolaou, G. P. Gasic and W. E. Barnette, Angew. Chem. Internat. Ed., 1978, 17, 293.
   K. H. Gibson, Chem. Soc. Rev., 1977, 6, 489.

4. U. S. von Euler, Arch. Exp. Pathol. Pharmakol., 1934, 175, 78.
   M. Goldblatt, Chem. Ind. (London), 1933, 52, 208.

5. S. Bergström and J. Sjövall, Acta Chem. Scand., 1960, 14, 1693.
   S. Bergström, R. Ryhage, B. Samuelsson and J. Sjövall, J. Biol. Chem. 1963, 238, 355.
   B. Samuelsson, J. Amer. Chem. Soc., 1963, 85, 1878.

6. (a) P. J. Piper and J. R. Vane, Nature, 1969, 223, 29.
   (b) M. Hamberg, J. Svensson and B. Samuelsson, Proc. Natl. Acad. Sci. U.S.A., 1975, 72, 2994.

7. S. Moncada, R. Gryglewski, S. Bunting and J. R. Vane, Nature, 1976, 263, 663.
   C. Pace-Asiak and L. S. Wolfe, Biochemistry, 1971, 70, 3657.
   R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Sun, N. Wittaker, S. Bunting,

J. Salmon, S. Moncada and J. R. Vane, Prostaglandins, 1976, 12, 915.

E. J. Corey, G. E. Keck, I. Szekély, J. Amer. Chem. Soc., 1977, 99, 2006.

8. P. Borgeat and B. Samuelsson, Proc. Natl. Acad. Sci. U.S.A., 1979, 76, 3213.

P. Borgeat and B. Samuelsson, J. Biol. Chem., 1979, 254, 2643.

P. Borgeat, M. Hamberg and B. Samuelsson, Proc. Natl. Acad. Sci. U.S.A., 1979, 76, 2148.

R. C. Murphy, S. R. Hammarstrom and B. Samuelsson, Proc. Natl. Acad. Sci. U.S.A., 1979, 76, 4275.

9. T. K. Bills, J. B. Smith and M. J. Silver, Biochim. Biophys. Acta., 1976, 424, 303.

10. B. Samuelsson, J. Amer. Chem. Soc., 1965, 87, 3011.

11. D. H. Nugteren and E. Hazelhof, Biochim. Biophys. Acta., 1973, 326, 448.

12. M. Hamberg, J. Svensson, T. Wakabayashi and B. Samuelsson, Proc. Natl. Acad. Sci. U.S.A., 1974, 71, 345.

13. M. Hamberg and B. Samuelsson, Proc. Natl. Acad. Sci. U.S.A., 1973, 70, 899.

14. S. Bergström, L. A. Carlson and J. R. Weeks, Pharmacological Reviews, 1968, 20, 1.

15. R. Gryglewski, B. Panczeko, R. Korbut and L. Ocetkiewicz, Prostaglandins, 1975, 10, 343.

S.C.L. Hong and L. Levine, Proc. Natl. Acad. Sci. U.S.A., 1976, 73, 1730.

29. W. Bartman and G. Beck, Angew. Chem. Int. Edt., 1982, 21, 751.
R. J. K. Taylor in "New Synthetic Routes to Prostaglandins and Thromboxanes" Ed. S. M. Roberts and F. Scheinmann, Academic Press, London, 1982, p.191.

30. J. C. Sih and D. R. Graber, J. Org. Chem., 1978, 43, 3798.

31. K. Shimoji, Y. Konishi, Y. Arai, M. Hayashi and H. Yamanto, J. Amer. Chem. Soc., 1978, 100, 2547.

32. K. C. Nicolaou, W. E. Barnette, G. P. Gasic and R. L. Magolda, J. Amer. Chem. Soc., 1977, 99, 7736.
K. C. Nicolaou, W. E. Barnette, G. P. Gasic and R. L. Magolda, J. Amer. Chem. Soc., 1981, 103, 3472.
M. Shibasaki and S. Ikegami, Tetrahedron Lett., 1977, 4037.
M. Shibasaki and S. Ikegami, Tetrahedron Lett., 1978, 559.

33. K. C. Nicolaou, W. J. Sipio, R. L. Magolda, S. Seitz, and W. E. Barnette, J. C. S. Chem. Commun., 1978, 1067.
I. Kojima and K. Sakai, Tetrahedron Lett., 1978, 3743.
M. Shibasaki, J. Ueda and S. Ikegami, Tetrahedron Lett., 1979, 433.

34. M. Hamberg and B. Samuelsson, Proc. Natl. Acad. Sci. U.S.A., 1974, 71, 3400.
M. Hamberg, B. Samuelsson and J. Svensson, Proc. Natl. Acad. Sci. U.S.A., 1974, 71, 3824.

35. M. Hamberg, B. Samuelsson, and J. Svensson, Proc. Natl. Acad. Sci. U.S.A., 1975, 72, 2994.

36. S. Hammarström, J. A. Lindgren and P. Roos in "Advances in Prostaglandin and Thromboxane Research", Vol 6, Raven Press, New York, 1980, p.221.

37. E. J. Corey, J. W. Ponder and P. Ulrich, Tetrahedron Lett., 1980, 137.

38. K. M. Maxey and G. L. Bundy, Tetrahedron Lett., 1980, 445.

39. S. Ohuchida, N. Hamanaka and M. Hayashi, Tetrahedron Lett., 1979, 3661.
S. Ohuchida, N. Hamanaka and M. Hayashi, Tetrahedron, 1983, 39, 4257.

40. K. C. Nicolaou, R. L. Magolda and D. A. Clameron, J. Amer. Chem. Soc., 1980, 102, 1404.
A. M. Lefer, E. F. Smith III, H. Araki, J. B. Smith, D. Aharony, D. A. Clameron, R. L. Magolda and K. C. Nicolaou, Proc. Natl. Acad. Sci. U.S.A., 1980, 77, 1706.

41. M. F. Ansell, M. P. L. Caton and K. A. J. Shuttle, Tetrahedron Lett., 1982, 1955.

42. S. Kosuge, N. Hamanaka and M. Hayashi, Tetrahedron Lett., 1981, 1345.

43. S. Ohuchida, N. Hamanaka and M. Hayashi, Tetrahedron Lett., 1981, 1349.

S. Ohuchida, N. Hamanaka and M. Hayashi, Tetrahedron, 1983, 39, 4263.
S. Ohuchida, N. Hamanaka and M. Hayashi, Tetrahedron, 1983, 39, 4269.

44. S. Ohuchida, N. Hamanaka and M. Hayashi, J. Amer. Chem. Soc., 1981, 103, 4597.
S. Ohuchida, N. Hamanaka and M. Hayashi, Tetrahedron, 1983, 39, 4273.

45. S. Ohuchida, N. Hamanaka, S. Hashimoto and M. Hayashi, Tetrahedron Lett., 1982, 2883.

46. S. Kosuge, M. Hayashi and N. Hamanaka, Tetrahedron Lett., 1982, 4057.

47. T. K. Schaaf, D. L. Bussolotti and M. J. Parry, J. Amer. Chem. Soc., 1981, 103, 6502.

48. K.C. Nicolaou, R. L. Magolda, B. Smith, D. Aharony, E. F. Smith and A. M. Lefer, Proc. Natl. Acad. Sci. U.S.A., 1979, 76, 2566.

49. M. F. Ansell, M. P. L. Caton, M. N. Palfreyman and K. A. J. Shuttle, Tetrahedron Lett., 1979, 4492.
M. F. Ansell, M. P. L. Caton and K. A. J. Shuttle, J. Chem. Soc. Perkin I, 1984, 1069.

50. P. Barraclough, Tetrahedron Lett., 1980, 1897.

51. P. Needleman, A. Raz, J. A. Ferrendelli and M. Minks, Proc. Natl. Acad. Sci. U.S.A., 1977, 74, 1716.
T. Miyamoto, K. Taniguchi, T. Tanouchi and F. Hirata, Adv. Prostaglandin Thromboxane Res., 1980, 6, 443.

52. H. M. Tyler, C. A. P. D. Saxton and M. J. Parry, Lancet, 1981, i, 629.
P.E. Cross, Ann. Reports Med. Chem., 1982, 17, 79.

53. E. J. Corey, S. G. Pyne and A. I. Schafer, Tetrahedron Lett., 1983, 3291.

54. D. Aharony, J. B. Smith, E. F. Smith, A. M. Lefer, R. L. Magolda and K. C. Nicolaou, Adv. Prostaglandin Thromboxane Res., 1980, 6, 489.

55. R. Mayer in "Newer Methods of Preparative Organic Chemistry", Vol. 2, Academic Press, New York, 1963, p. 101.
R. Mayer, Chem. Ber., 1958, 91, 1616

56. H. O. House in "Modern synthetic reactions", W. A. Benjamin. Inc., California 1972, p. 492.

57. S. J. Etheredge, J. Org. Chem., 1966, 31, 1990.

58. C. F. Wilcox and C. J. Whitney, J. Amer. Chem. Soc., 1967, 89, 2933.

59. (a) J. A. Marshall and D. A. Schaeffer, J. Org. Chem., 1965, 30, 3642.

59. (b) A. C. Cope and M. E. Synerholm, J. Amer. Chem. Soc., 1950, 72, 5228.

60. A. B. Smith III, B. A. Wexler and J. Slade, Tetrahedron Lett., 1982, 1631.

61. W. G. Dauben and J. W. McFarland, J. Amer. Chem. Soc., 1960, 82, 4245.

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

63. K. C. Nicolaou and Z. Lysenko, J. Amer. Chem. Soc., 1977, 99, 3185.
K. C. Nicolaou and Z. Lysenko, J. Chem. Soc. Chem. Commun., 1977, 293.

64. W. S. Johnson, J. J. Krost, R. A. Clement and J. Dutta, J. Amer. Chem. Soc., 1960, 82, 614.

65. R. B. Woodward and R. H. Eastman, J. Amer. Chem. Soc., 1946, 68, 2229.

66. O. Hromatka, D. Binder and K. Eichinger, Montash. Chem., 1973, 104, 1520.

67. F. Duus, Tetrahedron, 1981, 37, 2633.

68. S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler and M. J. Urbigkit, Tetrahedron, 1963, 19, 1625.
S. J. Rhoads, J. Org. Chem., 1966, 31, 171.

69. P. G. Baraldi, A. Barco, S. Benetti, F. Moroder, G. P. Pollino, D. Simoni and V. Zanirato, J. Chem. Soc. Chem. Commun., 1982, 1265.

70. W. Steglich and G. Holfe, Angew. Chem. Int. Edt., 1969, 8, 981.

71. J. C. Farlie, G. L. Hodgson and T. Money, J. Chem. Soc. Perkin I, 1973, 2109.

72. M. T. Reetz, Angew. Chem., Int. Ed. Engl., 1982, 21, 96.

73. T. H. Chan, I. Paterson and J. Pinsonnault, Tetrahedron Lett., 1977, 4183.

74. E. Nakamura, T. Murofushi, M. Shimizu and I. Kuwajima, J. Amer. Chem. Soc., 1976, 98, 233.

75. H. M. R. Hoffman, Angew. Chem. Int. Edt., 1969, 8, 556.
W. Oppolzer and V. Smeckus, Angew. Chem. Int. Edt., 1977, 17, 476.

76. T. R. Hoye, S. J. Martin and D. R. Peck, J. Org. Chem., 1982, 47, 331.

77. L. F. Fieser and M. Fieser, in "Steroids", Reinhold, New York, 1959.
R. B. Woodward, J. Amer. Chem. Soc., 1941, 63, 1123.
R. B. Woodward, J. Amer. Chem. Soc., 1942, 64, 72 and 76.

78. W. P. Jackson, S. V. Ley and J. A. Martin, Tetrahedron Lett., 1981, 22, 2601.

79. Y. Ito, T. Hirao and T. Saegusa, J. Org. Chem., 1978, 43, 1011.

80. A. S. Kende, B. Roth and P. J. Sanfilippo, J. Amer. Chem. Soc., 1982, 104, 1784.

81. S. J. Rhoads and N. R. Raulins, Org. React., 1974, 22, 1.

82. C. Earnshaw, C. J. Wallis and S. Warren, J. Chem. Soc. Perkin I, 1979, 3099.

83. E. J. Corey and S. Nozoe, J. Amer. Chem. Soc., 1965, 87, 5728.

84. K. C. Nicolaou, R. L. Magolda and D. A. Clameron, J. Amer. Chem. Soc., 1980, 102, 1404.

85. R. F. Newton and A. H. Wadsworth, J. Chem. Soc. Perkin I, 1982, 823.

86. E. R. H. Walker, Chem. Soc. Rev., 1976, 5, 23.
C. Szantay, L. Toke, P. Kohontis, J. Org. Chem., 1966, 31, 1447.

87. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 1975, 2647.
G. Piancatelli, A. Scettri and M. D'Auria, Synthesis, 1982, 245.

88. W. S. Wadsworth and W. D. Emmons, J. Amer. Chem. Soc., 1961, 83, 1773.
L. Horner, H. Hoffman, W. Klink, H. Ertel and V. G. Toscano, Ber., 1962, 95, 581.

89. J. S. Bindra and R. Bindra in "Prostaglandin Synthesis", Academic Press, New York, 1977, p.201.

90. E. J. Corey, I. Vlattas, N. H. Andersen and K. Harding, J. Amer. Chem. Soc., 1968, 90, 3247.

91. W. A. C Brown, J. Martin and G. A. Sim, J. Chem. Soc. (C), 1844, 1965.
G. Eglinton, J. Martin and W. Parker, J. Chem. Soc. (C), 1243, 1965.

92. W. Nagata, T. Wakabayashi and Y. Hayase, Org. Synth., 53, 44.
P. North, personal communication.

93. E. J. Corey, D. Enders and M. G. Bock, Tetrahedron Lett., 1976, 7.

94. A. Zurqiyah and C. E. Castro, Org. Synth., 49, 98.

95. M. F. Ansell, M. P. L. Caton and P. C. North, Tetrahedron Lett., 1981, 1723.

96. D. H. Williams and I. Fleming in "Spectroscopic methods in organic chemistry", McGraw-Hill, England, 2973, p.101.

97. J. H. Noggle and R. E. Schirmer in "The Nuclear Overhauser effect, chemical applications", Academic Press, New York, 1971.

98. Y, Taniguchi, J. Inanaga and M. Yamaguchi, Bull. Chem. Soc. Jpn., 1981, 54, 3229.

99. C. S. Marvell and W. W. Moyer, Jr., J. Amer. Chem. Soc., 1957, 79, 4990.

RESEARCH STUDY PROGRAMME

As part of the research programme, the author has attended the following lecture courses at Sheffield City Polytechnic and Sheffield University :

Medicinal Chemistry
Protecting Groups
Organometallic Chemistry

Has undertaken the following directed learning programme :

"Organic Synthesis" : B M Trost and T Vedejs

The author has presented a research colloquium on this work at the sponsoring establishment and has attended colloquia at Sheffield City Polytechnic and Sheffield University presented by internal and external speakers.

The author has attended symposia on :

Natural Product Synthesis (Leeds 1981)
Medicinal Chemistry (Canterbury 1983)
Stereochemistry (Sheffield 1980, 1981 and 1982)

The author has also undertaken a three months training period at the collaborating body's laboratory during which time she presented monthly progress reports.

The Acid-catalysed Cyclisation of Methyl 1-(3-Oxobutyl)-2-oxocyclopentanecarboxylate: *X*-Ray Analysis of the Product

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An *X*-ray analysis confirms that the acid-catalysed cyclisation of methyl 1-(3-oxobutyl)-2-oxocyclopentanecarboxylate leads to the formation of methyl 5-methyl-7-oxo-6-oxabicyclo[3.2.2]nonane-1-carboxylate *via* a rearrangement reaction.

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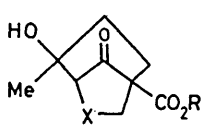
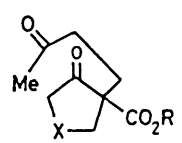
In the course of a synthetic project we have attempted to synthesise the hydroxy-ester (**1**). Since the corresponding ethyl ester (**2**) has been reported[1] to be the major product from acid catalysed cyclisation of the diketoester (**5**) we submitted (**4**) to the same reaction conditions (95% H_2SO_4, room temp., 16 h) in an attempt to prepare (**1**). However, we found that the properties of the product obtained (60%; m.p. 100—102 °C) were not consistent with the structure (**1**); rather the spectral data were consistent with the lactonic structure (**10**) [M^+, m/z 212; i.r., ν 1745 and 1718 cm^{-1}; ^1H n.m.r., δ 3.8 (3H, s), 1.42 (3H, s), 2.6 (1H, m), and 1.75—2.2 (9H, m); ^{13}C n.m.r., δ 172.7, 171.9, 82.9, 52.6, 51.9, 38.0, 30.9, 30.0, 29.6, 24.7, and 20.6 p.p.m.]. In order to confirm this result an *X*-ray analysis was undertaken.

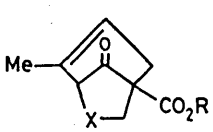
Crystal data: triclinic, $a = 7.177(2)$, $b = 6.669(2)$, $c = 12.898(4)$ Å, $\alpha = 119.0(1)$, $\beta = 91.8(1)$, $\gamma = 88.5(1)°$, space group $P\bar{1}$, $Z = 2$, $R = 0.047$ for 1317 independent reflections having $I/\sigma(I) > 3.0$.†



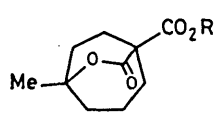
(**1**) R = Me, X = CH_2
(**2**) R = Et, X = CH_2
(**3**) R = Me, X = S



(**4**) R = Me, X = CH_2
(**5**) R = Et, X = CH_2
(**6**) R = Et, X = CH_2CH_2
(**7**) R = Me, X = S



(**8**) R = Me, X = CH_2
(**9**) R = Et, X = CH_2CH_2



(**10**) R = Me
(**11**) R = Et

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

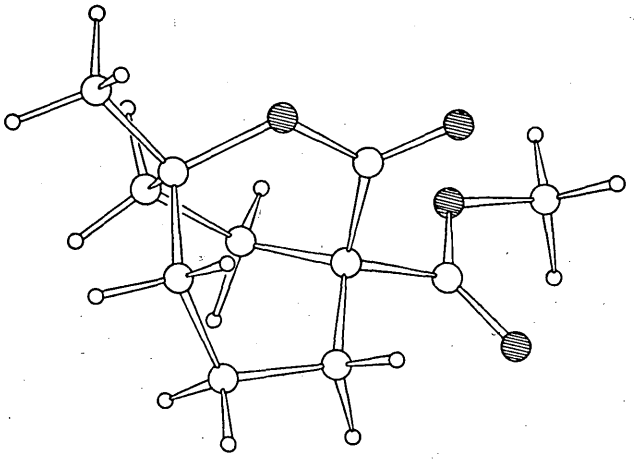


Figure 1. *X*-Ray structure of the lactone (**10**).

The *X*-ray structure is shown in Figure 1, and it confirms the product as the lactone (**10**). Rearrangements leading to similar cycloheptane systems have been observed previously[2] although lactones obtained in those systems were γ-lactones whereas (**10**) is a δ-lactone. Using short reaction times the alkene (**8**) was isolated along with (**10**) but further treatment of (**8**) with H_2SO_4 led to its conversion into (**10**). Reaction of the related diketoesters (**6**) and (**7**) with H_2SO_4 did not lead to lactone formation but instead gave (**9**) and (**3**) respectively. This behaviour is attributed to the lower strain present in (**9**) and (**3**) compared to (**8**).

In the light of these results we have repeated the literature reaction with (**5**) and find the ^1H and ^{13}C n.m.r. spectra of the product (75%; m.p. 58—59 °C, lit.[1] 61—62 °C) to be almost identical with those of (**10**) apart from differences associated with the change from a methyl to an ethyl ester. Thus the compound described in the literature is not in fact (**2**) but is (**11**).

This ring system has also been obtained by phenylselenyl or phenylsulphenyl lactonisation of a cycloheptene-carboxylic acid.[3]

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References

1 W. G. Dauben and J. W. McFarland, *J. Am. Chem. Soc.*, 1960, **82**, 4245.
2 G. L. Buchanan, A. C. W. Curran, J. M. McCrae, and G. W. McLay, *Tetrahedron*, 1967, **23**, 4729.
3 K. C. Nicolaou and Z. Lysenko, *J. Am. Chem. Soc.*, 1977, **99**, 3185; K. C. Nicolaou and Z. Lysenko, *J. Chem. Soc., Chem. Commun.*, 1977, 293.