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" SYNTHETIC APPROACHES TO THROMBOXANE B_2 "

A THESIS PRESENTED IN PART-FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

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BY

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Dedication

To my Wife Susan,

who finished this work

by giving me a reason to.

Acknowledgements.

Many thanks are due to the following people and organisations:-

The late Professor W.Parker, whose enthusiasm was a continual encouragement. Dr. J.S.Roberts for his advice and guidance during his supervision of this work.

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My Parents - who made it possible to start with.

Contents.

Abstract.

The first part of this thesis consists of a review concerning recent progress in the synthesis of thromboxane B_2. Mention is also made of the synthesis of related compounds and precursors, i.e. the endoperoxides, prostacyclin and thromboxane A_2 carbocyclic analogues. The biosynthesis and physiological properties of thromboxane B_2 and these related compounds are also discussed.

Key intermediates in a synthesis of thromboxane B_2, 6,8-dioxabycyclo[3.2.1]oct-2-ene(6) and the tricyclic lactone (5) were identified. The investigation of a synthesis leading to compound (6) in racemic form starting from the sodium salt of 3,4-dihydro-2H-pyran-2-carboxylic acid and the subsequent attempted elaboration of a γ-lactone ring on this compound by radical addition or dichloroketene addition to yield lactone (5) is described in Chapter 2. The isolation of a novel product of potassium tert-butoxide induced isomerisation is discussed. Work on a synthesis of compound (6) in optically active form starting from a sugar d-mannitol, by Grignard and Wittig reaction is also described. Chapter 2 concludes with a description of preliminary work done on two alternative approaches.

Chapter 3 contains experimental details of the reactions performed.

Chapter 1

INTRODUCTION

A discussion of the synthesis, biological and physiological properties of thromboxane B_2 and related metabolites.

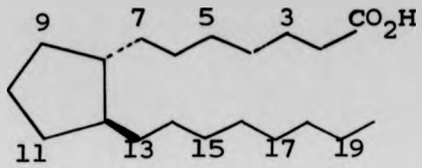
Historical Background

Prostaglandins (PG), a series of naturally occurring hydroxylated unsaturated fatty acids with a prostanoid 20-carbon skeleton, have been implicated as local hormones in a multitude of important physiological processes[1]. Since their discovery interest has rapidly expanded and future research may apply the acquired knowledge to such areas in medicine as thrombosis, asthma, gastric ulceration, blood pressure, inflammation and shock.

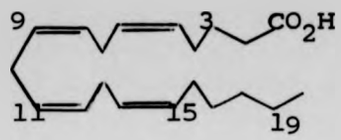
Early in the 1930's von Euler and Goldblatt[2,3] independently discovered a new factor in genital glands and human semen which displayed vasodepressor and smooth muscle stimulating activity. von Euler showed that the biological activity was due to a lipid soluble material with acidic properties which he termed "prostaglandin". However, because of interest in other natural products such as steroids and antibiotics, and of the difficulties in isolating prostaglandins, it was 1960 before Bergström and Sjövall isolated crystalline PGE_1 and $PGF_{1\alpha}$ from sheep seminal vesicles[4]. Within a few years Bergström *et al.*[5] isolated and elucidated the structure of thirteen different prostaglandins. Clinical interest in the prostaglandins was also increased by Vanes' report[6] of the involvement of prostaglandins in disease processes. In 1971 he demonstrated that aspirin-like drugs inhibited prostaglandin synthesis and Vane suggested that this was the biochemical mechanism of the anti-inflammatory activity of these drugs.

Prostaglandins are nominally described as oxidized derivatives of prostanoic acid (1) and are characterized by a five membered ring with two side chains containing, in total, 20 carbons. The semi - systematic nomenclature is

derived from the oxidation pattern[7].



(1)



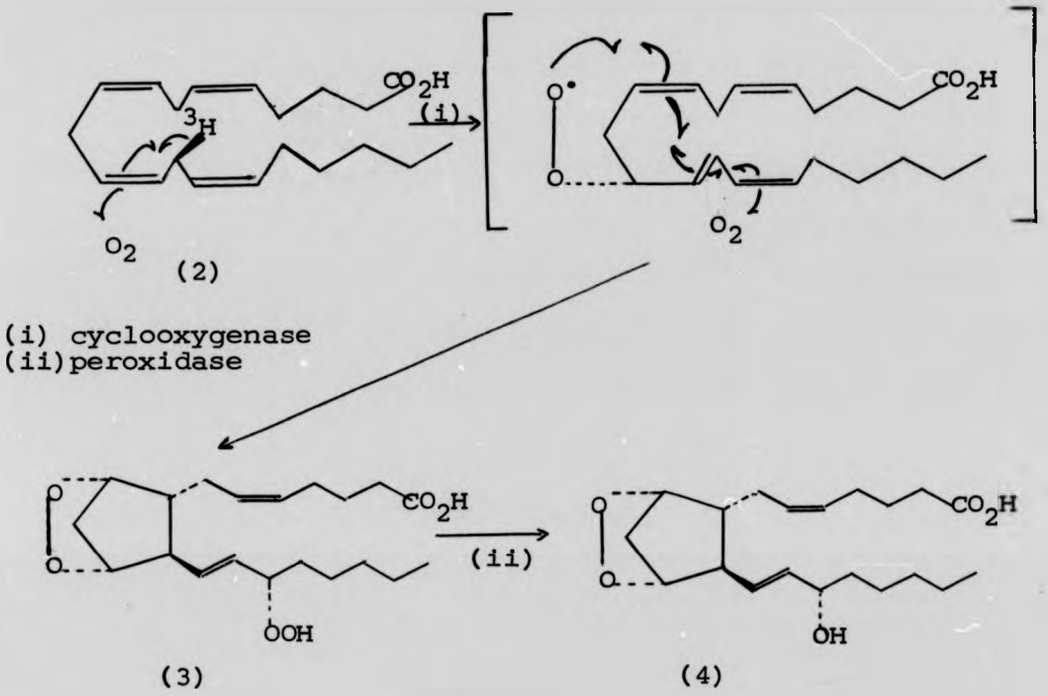
(2)

The Endoperoxides

That these compounds were biosynthesised from polyunsaturated fatty acids, e.g. arachidonic acid (2), was simultaneously demonstrated by Bergström et al.[8] and Van Dorp et al.[9] Further work by Samuelsson[10] led to the discovery that the oxygens attached to C-9 and C-11 originated from the same molecule of oxygen and that an endoperoxide was the most likely intermediate, but it was eight years before the endoperoxide intermediate PGH_2 (4) was isolated[11,12]. Subsequently, an additional endoperoxide with a hydroperoxy group at the C-15 position was isolated and named PGG_2(3)[12,13] (9α,11α-epidioxy-15(S)hydroperoxy-13-trans-prostenoic acid). The isolation of the endoperoxides was achieved by blocking the isomerase enzyme with mercury (II) p-hydroxybenzoate and rapid extraction to remove them from the aqueous environment. In contrast to the prostaglandins the endoperoxides have a short half-life of about five minutes in biological (aqueous) systems.

The formation[14] of PGG_2(3) from arachidonic acid (2) is catalysed by the endoperoxide synthetase complex in a two stage reaction, the first step being catalysed by a fatty acid cyclo-oxygenase (Scheme 1). This is a dioxygenase which introduces one molecule of oxygen at C-9 and a second

at C-15 of the fatty acid chain. The accompanying formation of a bond between carbon atoms 8 and 12 results in formation of the characteristic bicyclo [2.2.1] endoperoxide ring structure. PGH_2(4) is then formed by hydroperoxidase conversion of PGG_2(3).

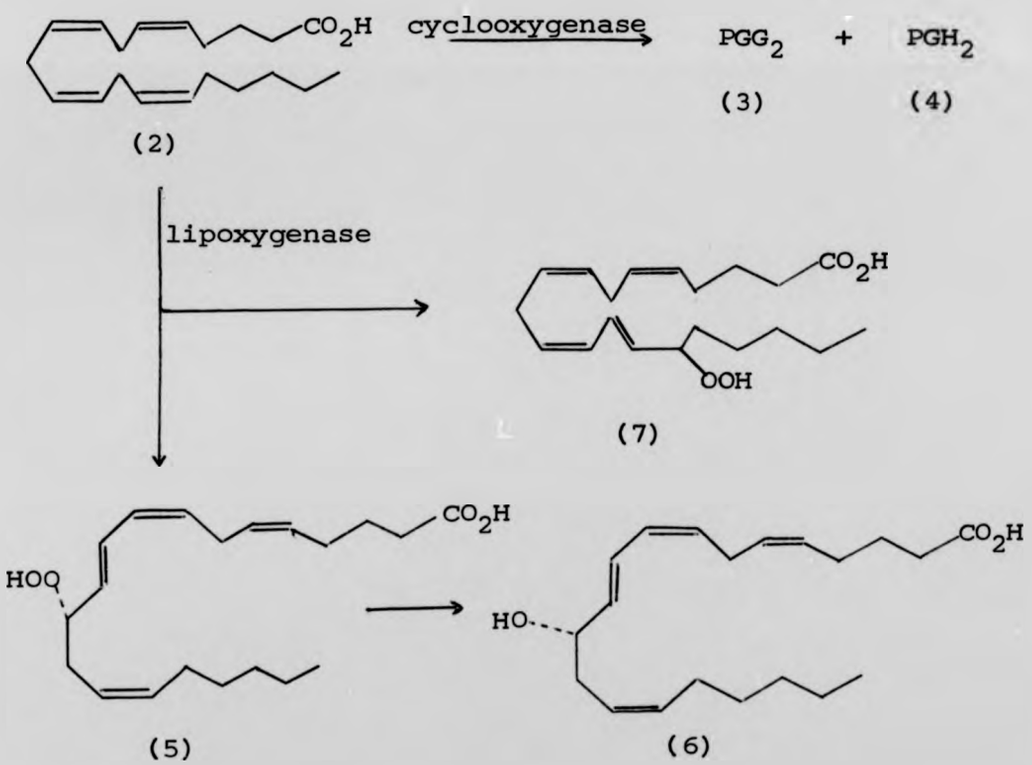


Scheme 1

Although these endoperoxide derivatives are themselves potent biological agents, their activity mainly depends upon their conversion into more active end-products. Further conversion of the endoperoxide is catalysed by various prostaglandin isomerase enzymes. The number of these isomerases, their mechanism of action, and the factors which determine the final conversion of the endoperoxide into the various "classical" prostaglandins are very incompletely understood.

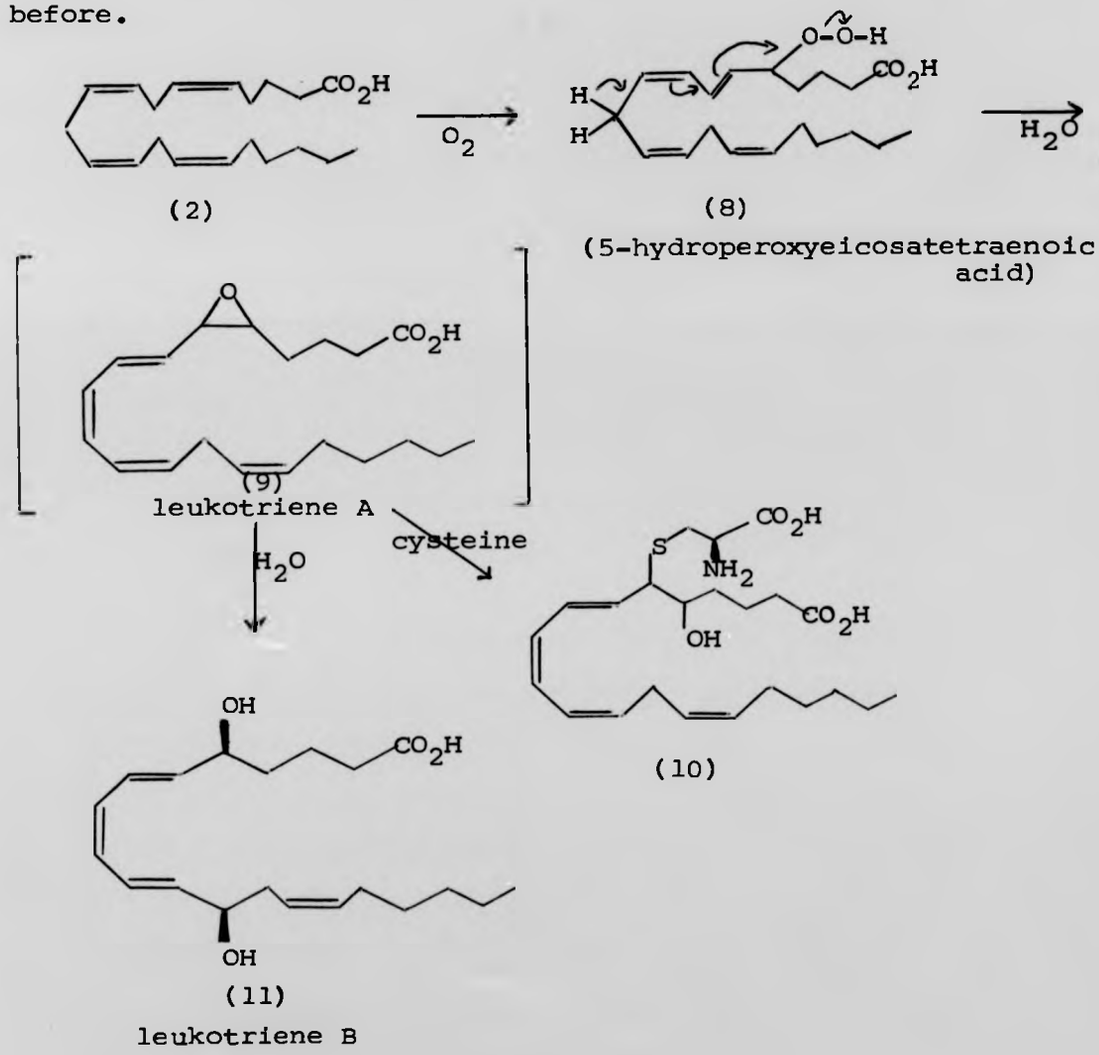
A very considerable body of work on the chemical synthesis of these primary prostaglandins has also been built up and a number of comprehensive reviews are in the literature[15,16].

When incubated with platelets it was found that arachidonic acid (2) is converted *via* two main pathways (Scheme 2). One proceeds *via* catalysis by a lipoxygenase enzyme[17] and results ultimately in the formation of the 20-carbon mono and polyhydroxy fatty acids *i.e.* 12L-hydroperoxy-5,8,10,14-eicosatetraenoic acid (HPETE) (5) and 12L-hydroxy-5,8,10,14-eicosatetraenoic acid (HETE) (6). Very little is known about the biological function of this pathway but the formation of 15-hydroperoxyarachidonic acid (7), a potent inhibitor of prostacyclin formation, may be of great importance to the vasclature[18,19]. The second pathway occurs *via* the cyclo-oxygenase enzyme route mentioned above and utilizes the cyclic endoperoxides PGG_2 (3) and PGH_2 (4).



Scheme 2

Recently a new addition to the series of compounds arising directly from arachidonic acid metabolism has been described. This new class, called the leukotrienes, was reported by Samuelsson *et al.*[20] and is not formed *via* the cyclooxygenase route (Scheme 3). Leukotriene C (10) exerts potent physiological actions, particularly in constricting bronchia during an asthma attack and it is also identical to the "slow reacting substance of anaphylaxis" (SRS-A), which had been recognised but not identified chemically before.



Scheme 3

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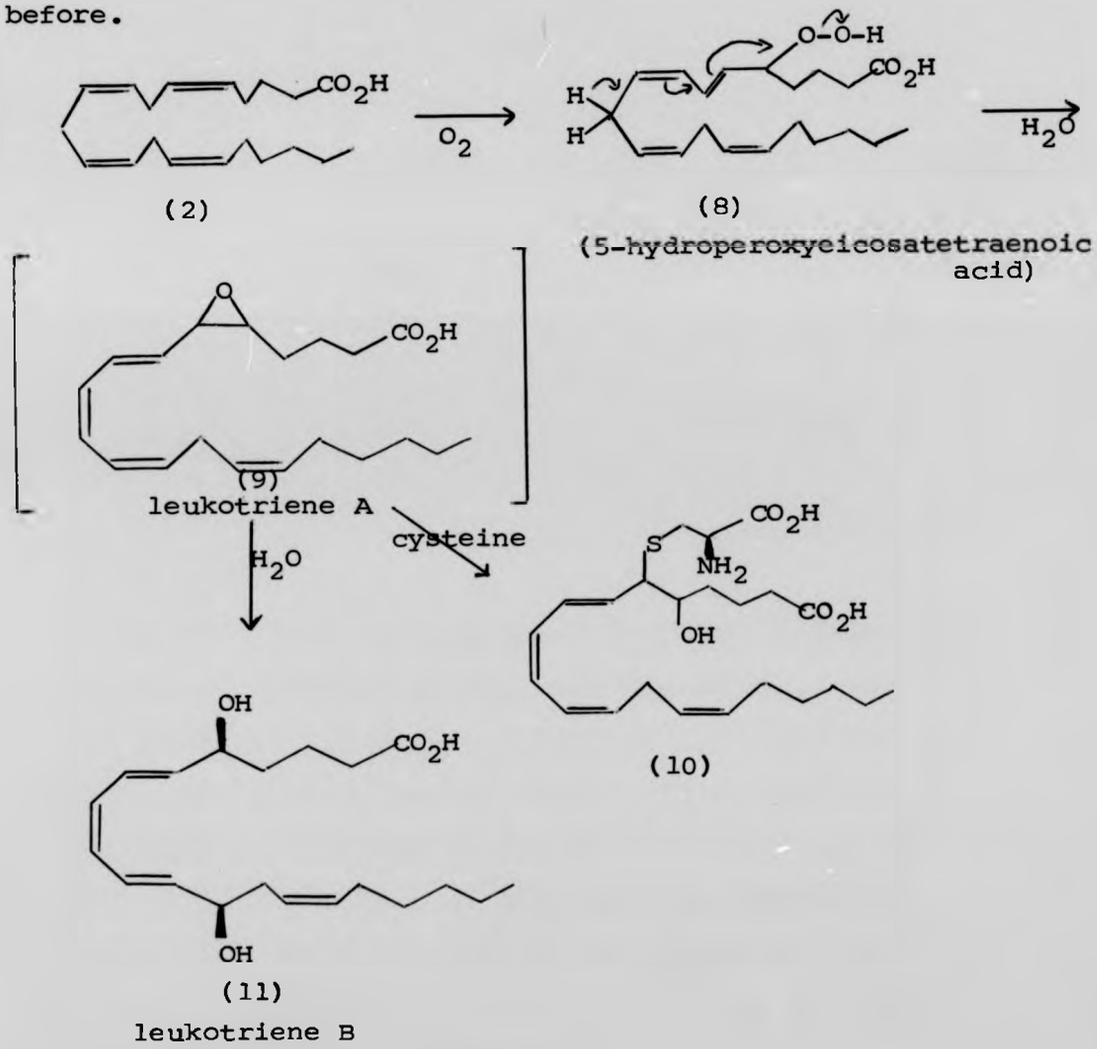
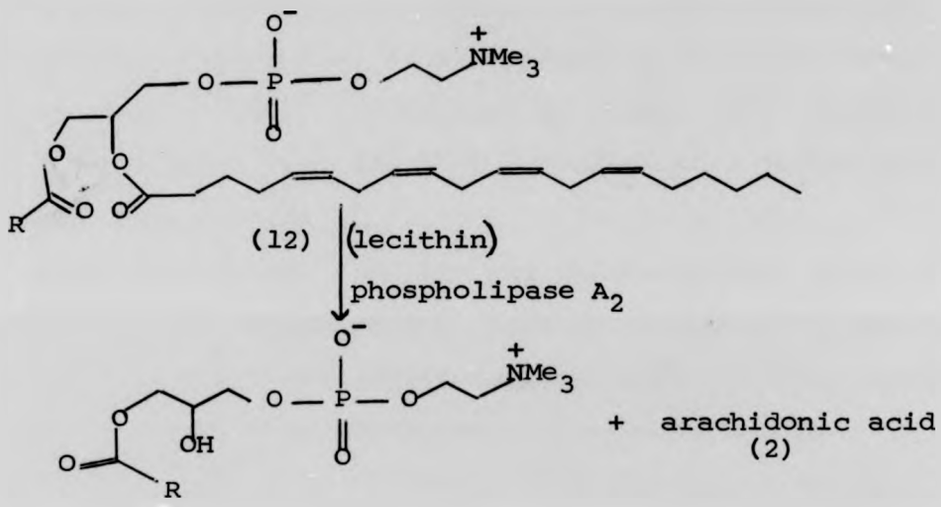


Scheme 3

The major source of arachidonic acid is the membrane phospholipid, principally lecithin (12). It is claimed that of the arachidonic acid released from platelets stimulated by thrombin 70% derives from phosphatidyl choline (lecithin), 25% from phosphatidyl inositol and 5% from phosphatidyl serine[21]. There does seem to be some possibility that in special cases some arachidonic acid may derive from triacyl glycerols (adipose tissue) or cholesterol esters (adrenal and ovarian tissue).



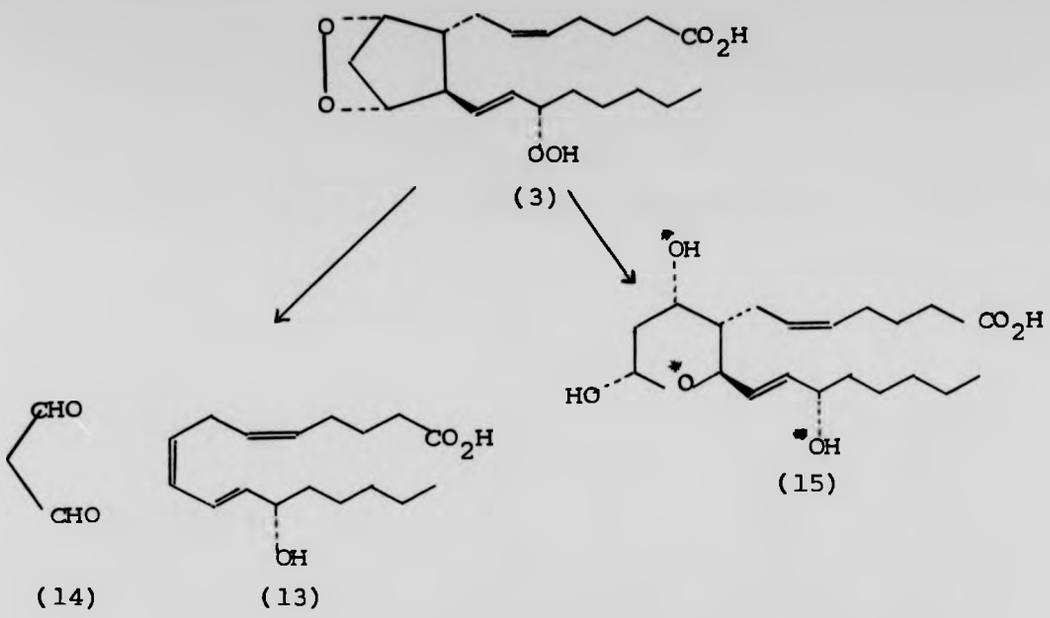
The Thromboxanes

A new concept concerning the role of the endoperoxides was recently introduced through the discovery of novel transformations of PGG_2(3) and PGH_2(4) which differ from the classical prostaglandin pathway. For example, the endoperoxides have a greater effect on airways and vascular smooth muscles than PGE_2 or $PGF_{2\alpha}$ and the endoperoxides were shown to possess the ability to induce rapid and irreversible aggregation of blood platelets, an activity not shown by their stable counterparts [11,13].

In 1969 Piper and Vane[22] described the release of a rabbit aorta contracting substance (RCS) from guinea pig lung but 6 years elapsed before Samuelsson *et al.*[23] finally identified this extremely unstable molecule. When PGG_2 (3) was incubated with human platelets[17,24] some HETE (6) and very small amounts of PGE_2 and $PGF_{2\alpha}$ were formed. The main metabolites isolated were hydroxyheptadecatrienoic acid (HHT) (13), which was formed by a retro Diels-Alder reaction on PGG_2 in which malondialdehyde (MDA) (14) was produced, and an equal amount of a novel metabolite [originally referred to as 12L-hydroxy-5,8,10-heptadecatrienoic acid (PHD)] thromboxane B_2 (TXB_2) (15)* in which the cyclopentane ring has been converted to a tetrahydropyranyl ring (Scheme 4).

When arachidonic acid (2) was incubated with platelets under $^{18}O_2$ the thromboxane B_2 (15) was found to be labelled with ^{18}O in only three positions as illustrated in Scheme 4. It was reasoned that thromboxane B_2 was derived by rearrangement of PGG_2 (or PGH_2) with subsequent addition of a molecule of water. In accord with this hypothesis an extremely unstable intermediate (thromboxane A_2 (TXA_2) (18), $t_{\frac{1}{2}}$ in aqueous medium @ 37°C = 30 secs.) was detected by trapping experiments (Scheme 5). Thus methanol, ethanol

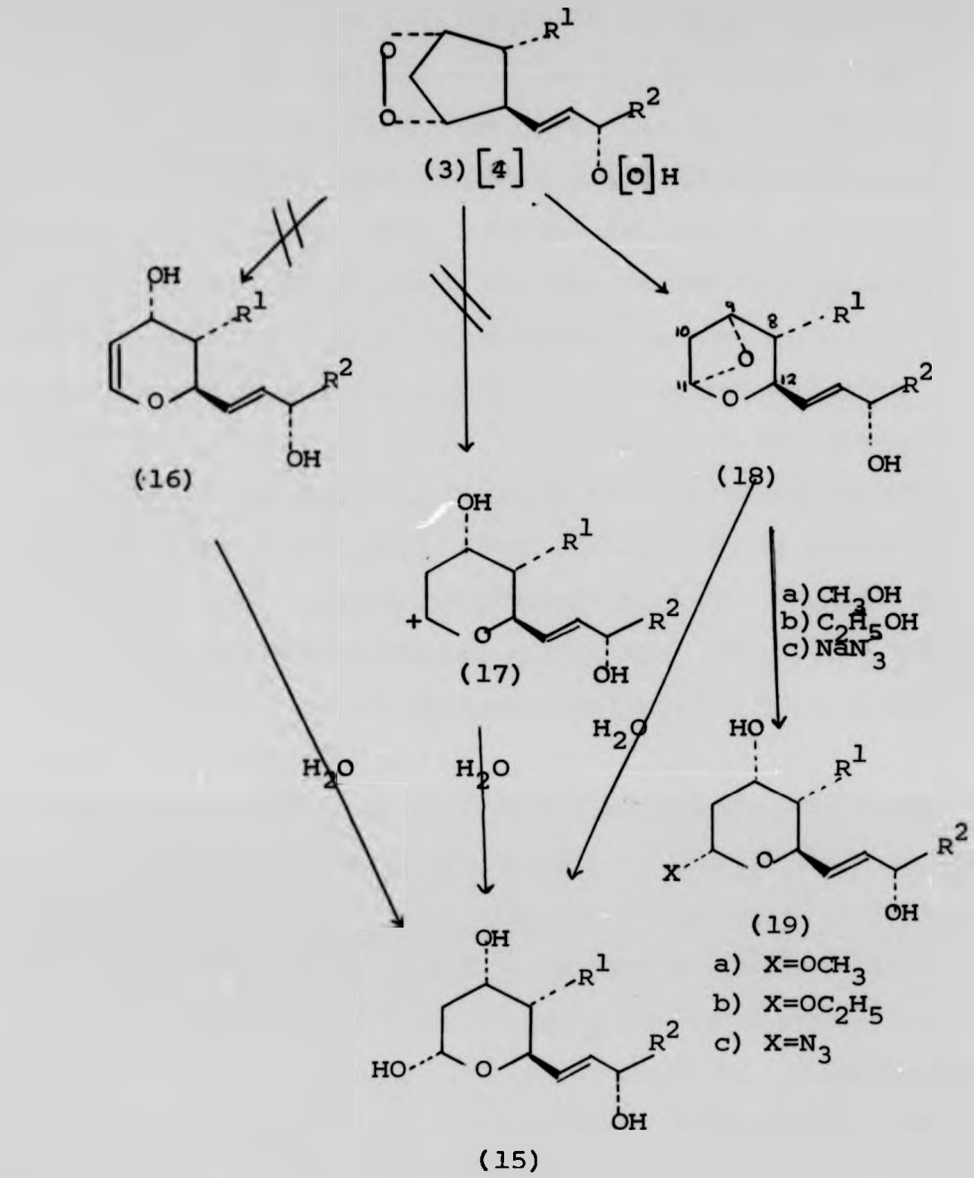
*Samuelsson and Hamberg[25] have proposed a nomenclature for thromboxanes in which the parent unsubstituted compound is thrombane and the corresponding carboxylic acid is thrombanic acid. Thus TXB_2 is called 9α,11,15(S)-trihydroxythromba-5Z,13E-dienoic acid.



Scheme 4

or sodium azide competed with water to afford the thromboxane B_2 derivatives (19) with the hemiacetal hydroxyl group substituted by methoxy, ethoxy and azido groups respectively. This intermediate displayed properties similar to Vanes' RCS mentioned previously and it has since been shown[1] that RCS is infact a mixture of thromboxane A_2 (18) together with some endoperoxides but the thromboxane is responsible for the majority of the biological activity.

These results are in agreement with the strained bicyclic structure proposed for thromboxane A_2 (18) since such a structure would be expected to be susceptible to nucleophilic attack at the acetal carbon (C-11). This structure is also compatible with the observation that the protons on carbons 5,6,8,9,11,12,14 and 15 of arachidonic acid (2) and PGG_2 (3) are retained in the conversion to thromboxane B_2 (19). The two other possible structures, the dihydropyran (16) and the carbonium ion (17) were shown



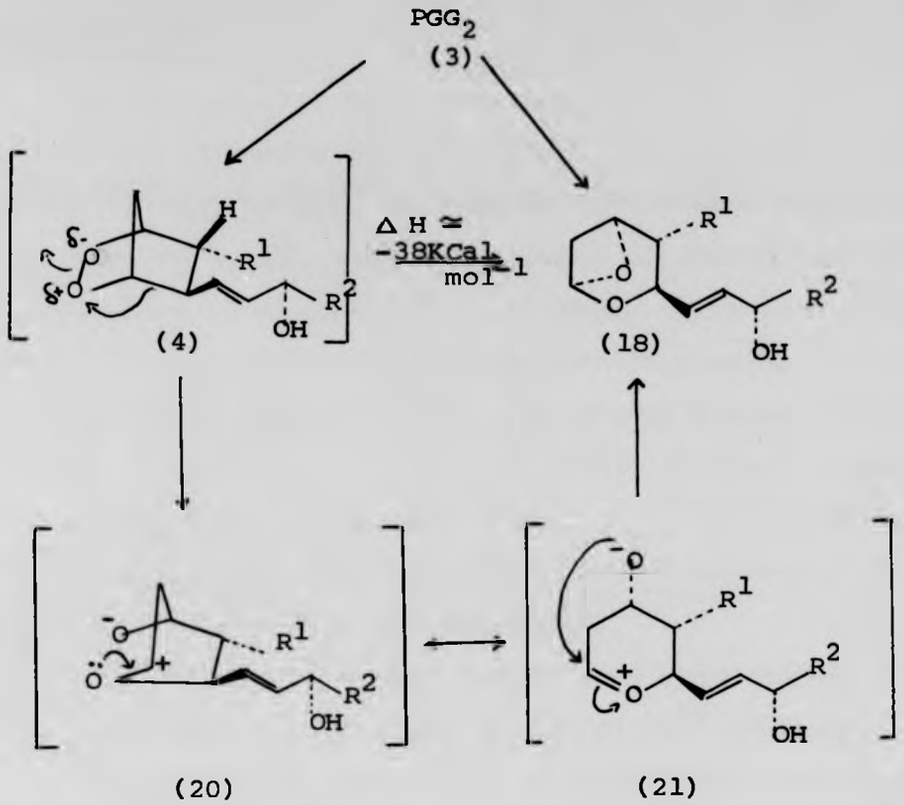
R^1 = CH_2 CO_2H R^2 = CH_2 CH_3

Scheme 5

to be unlikely because : 1) addition of CH_3OD to platelets incubated with arachidonic acid led to derivative (19a) with no carbon bound deuterium atom thus eliminating (16), and 2) the carbonium ion (17) was excluded because of its expectedly extremely short lifetime in aqueous solution.

The proposed mechanism[26] for the conversion of PGG_2 (3) to thromboxane A_2 (18) is illustrated in Scheme 6. It can be considered as a polarisation of the peroxide bridge leading to a carbon to oxygen migration with the formation of a secondary carbonium ion which is stabilized as the canonical form (21). This then collapses by formation of the oxetane ring to give thromboxane A_2 (18). Due to the relatively weak oxygen-oxygen single bond the transformation is seen to be energetically quite favourable from a simple summation of bond energies.

Thromboxane A_2 (18) is highly labile and hydrolyses with a half-life of about 30 seconds in saline solution or 3 minutes in blood to the stable thromboxane B_2 (19) which appears to be essentially physiologically inert. This instability probably ensures a transient and limited response at the immediate site of production. Thromboxanes have now been found in most organs and tissues of the body, viz platelets, lungs, leucocytes, umbilical artery, spleen, brain, kidney and seminal vesicles; indeed in some of these tissues this is the major route of arachidonic acid metabolism[27] and this widespread occurrence has caused much speculation regarding their physiological importance. Certain non-steroid anti-inflammatory drugs such as aspirin and indomethacin which inhibit the cyclo-oxygenase reaction can block the synthesis of thromboxanes and thus inhibit



R^1 = CH_2 ⟋⟍⟋⟍⟋⟍ CO_2H R^2 = CH_2⟋⟍⟋⟍ CH_3

Scheme 6

the platelet aggregation reaction both <u>in vitro</u> and <u>in vivo</u>. It has been possible experimentally to induce heart attacks[28] in male rabbits by administering thromboxane A_2 (18) produced from PGH_2 (4) by treatment with microsomal fractions of rabbit platelets. However, the question arises as to which physiological effects are caused by thromboxanes and which by endoperoxides.

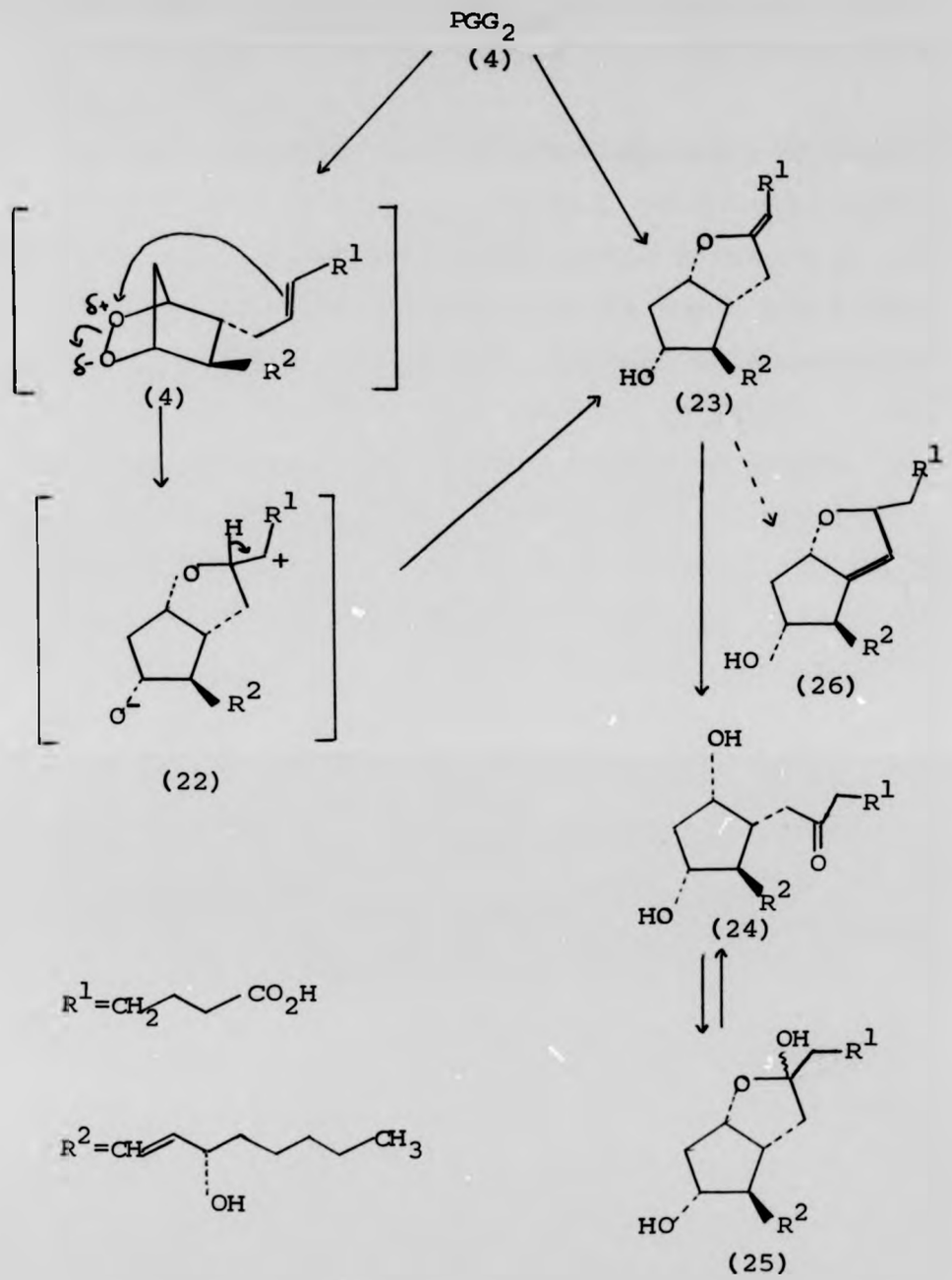
Prostacyclin

The metabolites of the endoperoxides are not restricted to the thromboxanes or "classical" prostaglandins, however. Recently Vane et al.[29] discovered that a microsomal fraction from pig or rabbit aorta transforms endoperoxides into an unstable, hitherto unknown substance, provisionally named PGX. It was shown that, unlike thromboxane A_2, PGX does not contract rabbit aorta; also, unlike thromboxane A_2, it relaxes rabbit mesenteric and coeliac artery. However, the most remarkable property of PGX is its potent ability to inhibit platelet aggregation[30] and to even bring about the reversal of platelet aggregation[18].

The structure of this arachidonic acid metabolite was postulated by Pace-Asciak and Wolfe[31] as being Δ^7-6(9)-oxy-$PGF_{1\alpha}$ (26) and it was five years before the structure was revised by Johnson et al.[32] and Corey et al.[33] as being that of compound (23). Since this structure contains a second ring system the name "prostacyclin" and the semi-systematic nomenclature PGI_2 was adopted.

The proposed mechanism for the conversion of PGG_2 (3) to PGI_2 (23) is complementary to that proposed for the formation of thromboxane A_2. In this case the endoperoxide bond is polarized in the opposite sense which causes participation of the 5,6-double bond leading to a secondary carbonium ion (22) which, by loss of the proton from C-6 gives PGI_2[26]. (Scheme 7). PGI_2 is the intermediate to Δ^7-6(9)-oxy-$PGF_{1\alpha}$ (26), Pace-Asciaks' compound. This isomerisation is unexplained, both from the mechanistic viewpoint and the biological reasons for such an isomerisation.

Prostacyclin is rather unstable in aqueous acidic or neutral media because of its enolether structure and is



Scheme 7

quite readily hydrolysed to 6-keto-$PGF_{1\alpha}$ (24) which is in rapid equilibrium with its lactol form (25). (Scheme 7).

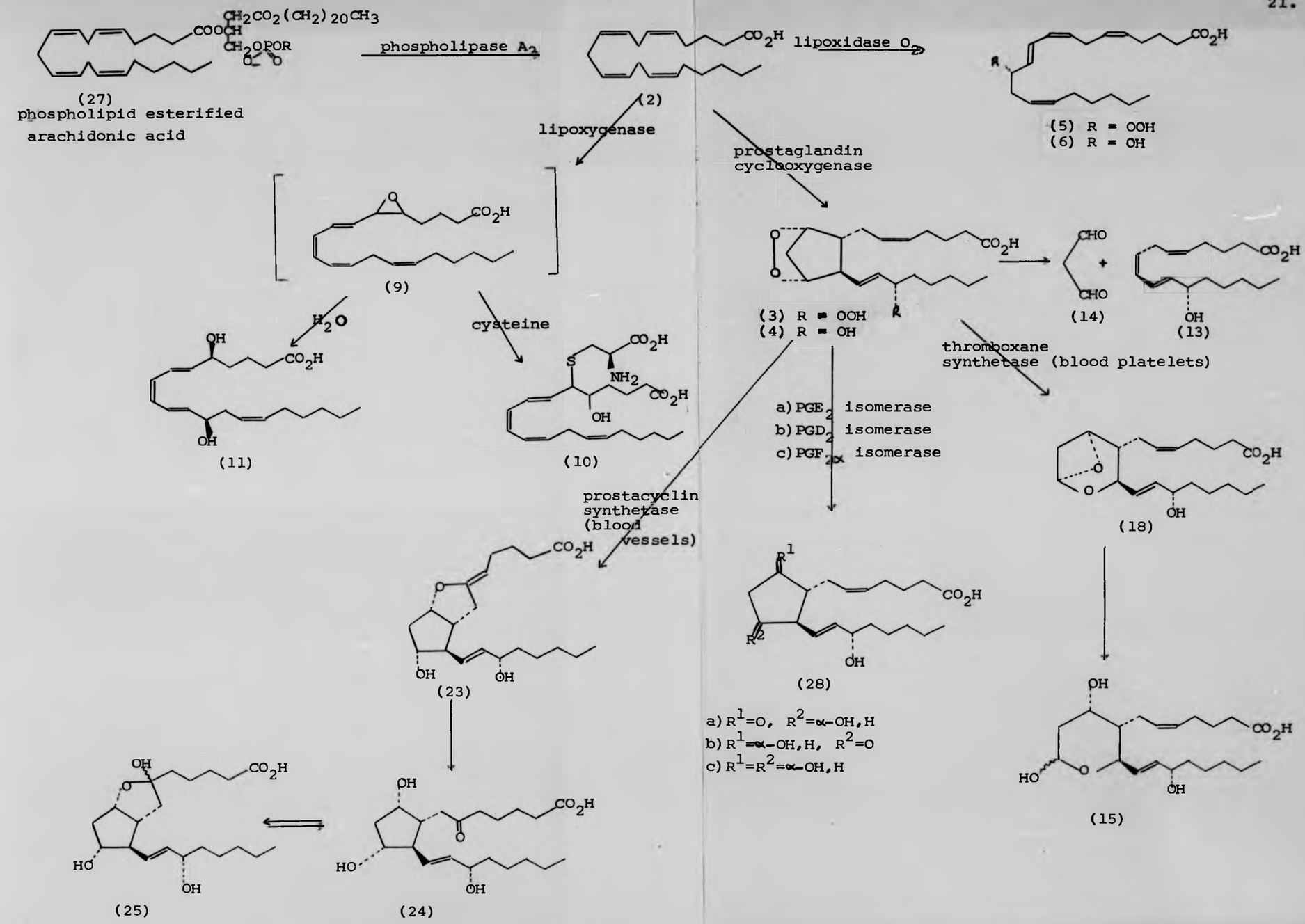
It thus seems likely that previously when 6-keto-$PGF_{1\alpha}$ was identified in various tissues the true active principle may have been PGI_2.

In most respects the biological activity of PGI_2 is the opposite of thromboxane A_2, inducing potent inhibition of platelet aggregation and smooth muscle relaxation. (PGI_2 is the most powerful anti-aggregatory agent known and as little as 1 ng/ml will inhibit collagen or arachidonic acid induced aggregation of platelets in vitro.) One important site in which the PGI_2 producing enzyme, prostacyclin synthetase, predominates is in vascular tissue[18]. Its formation by cultured endothelium is inhibited by several fatty acid hydroperoxides (e.g. 15- and 12-hydroperoxyarachidonic acids) derived from platlets[34] at very low concentrations.

Thus attention in research has shifted from the relatively stable prostaglandins to these unstable arachidonic acid pathway intermediates. The full range of currently known metabolites of the endoperoxides and arachidonic acid is illustrated in Scheme 8.

Mechanism of Action of Thromboxanes and Prostacyclin

The target tissues for thromboxane and prostacyclin appear to be primarily platelets and vascular smooth muscle cells. Their physiological activities are probably largely expressed through regulation of cyclic adenosine monophosphate (AMP) levels by interaction with the cellular adenylate cyclase systems[14,35], in common with the prostaglandin family in general. Since, in platelets, prostacyclin acts to raise c-AMP levels which inhibit aggregation and thromboxanes lower c-AMP and thus initiate aggregation, it means that regulation of aggregation in a



(27) phospholipid esterified arachidonic acid

(2)

(5) R = OOH
(6) R = OH

(9)

(11)

(10)

(3) R = OOH
(4) R = OH

(14)

(13)

(18)

(23)

(25)

(24)

(28)

a) R^1=O, R^2=α-OH,H
b) R^1=α-OH,H, R^2=O
c) R^1=R^2=α-OH,H

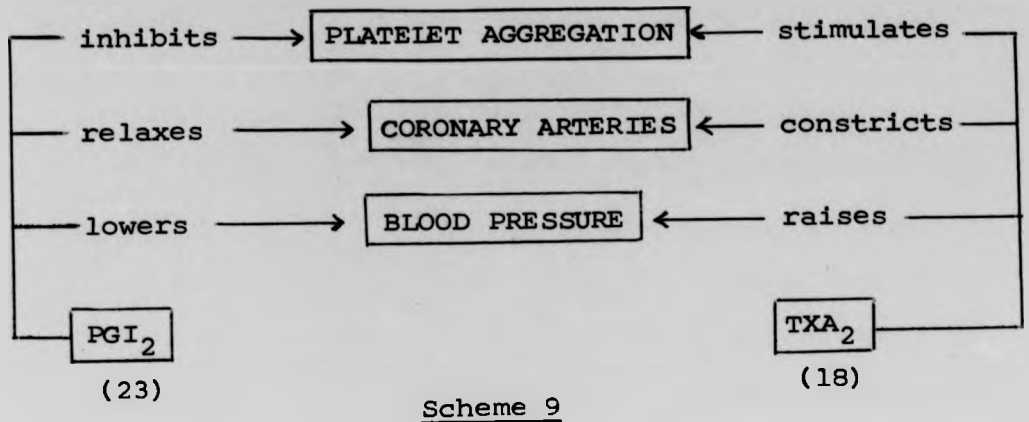
(15)

Scheme 8

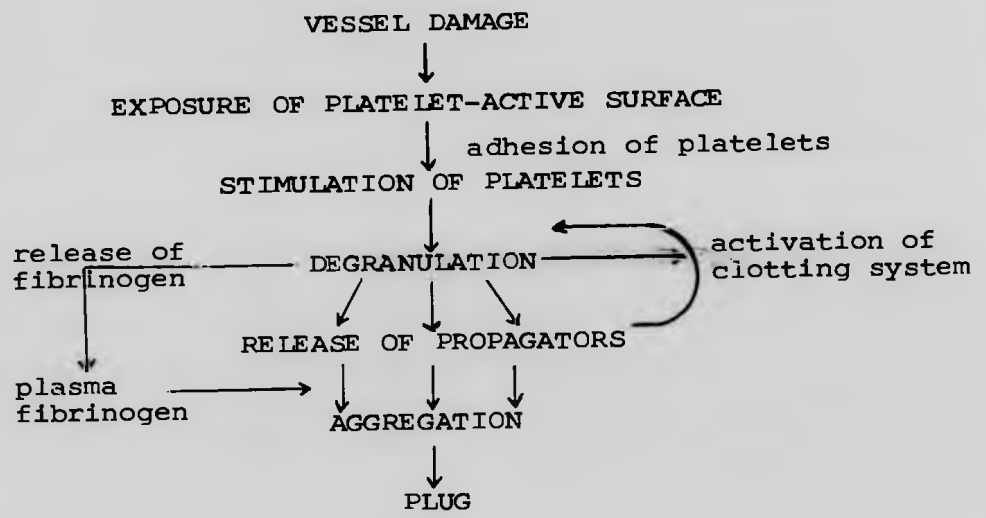
positive or negative manner should be possible. There are, however, a number of unknown effects of c-AMP interfering with platelet function[36].

Vane and Moncada[37], who have reported that prostacyclin is generated by human arterial and veinous tissue from arachidonic acid via PGG_2 or PGH_2, have elaborated on this concept. They proposed that some form of "dynamic equilibrium" exists between the aggregation promoted by platelet generated thromboxane A_2 and the inhibition of aggregation initiated by prostacyclin produced by the vascular endothelium. As a consequence of this they proposed that the normal integrity of the vessel walls is maintained by the vascular endothelium production of prostacyclin inhibiting the adherence of platelets and that prostacyclin may normally limit thrombus formation. However, they propose that when a vessel wall is damaged the formation of a normal haemostatic plug may be assisted by diminished prostacyclin production. This "dynamic equilibrium" is illustrated in Scheme 9. (Further information on the role of PGG_2/PGH_2 and thromboxane B_2 in platelet aggregation is presented by Holmsen[38] and Scheme 10 illustrates the participation of platelets in haemostasis and thrombosis.)

Platelets are essential for normal haemostasis and perform three distinct functions in response to vascular damage[36]. First there is occlusion of the injury site by adhesion and aggregation followed by promotion of blood coagulation by platelet constituents and thirdly release of substances affecting vascular smooth muscle and propagating aggregation referred to as the platelet release reaction.



Scheme 9



Scheme 10

Platelet aggregation and release can be triggered, both *in vivo* and *in vitro*, by a number of agents including ADP, thrombin, collagen and arachidonic acid. Aggregation can be followed photometrically and has been shown to take place in two stages[35]. First-phase aggregation occurs because of a change in the shape of the platelets leading to increased adhesion. If the initial stimulation is at

a low level then the first phase is reversible, but if the stimulus is of sufficient intensity then a membrane phospholipase A_2 is activated which leads to arachidonate release [c.f. lecithin (12)] and synthesis of thromboxane A_2 via the cyclooxygenase pathway. With the rise in thromboxane A_2, c-AMP levels decrease and the platelet release reaction is initiated. In this process ADP is liberated from the platelet granules thus initiating the second, essentially irreversible, phase of aggregation (Scheme 10).

Prostacyclin inhibits this clotting process, or even reverses it, by acting at the first-phase aggregation level. By interacting with receptors on the platelet membrane an increase in intraplatelet levels of c-AMP results[39,40]. This elevation of c-AMP inhibits hydrolysis of arachidonic acid by phospholipase A_2 and thus prevents the production of endoperoxides[41]. Whether inhibition of aggregation by blocking the platelet change of shape is also due to c-AMP still remains to be determined. Pre-incubation of platelets with as little as 30 pmol (~1 ng) of prostacyclin per ml. causes complete inhibition of aggregation.

However, the entire process of thrombus formation is a complex story and involves a number of areas separate from the arachidonic pathway. Thus, although the TXA_2/PGI_2 input is important it has been shown[1] that the release of ADP from platelet granules and the effect of plasma protein fibrinogen are equally important. Consequently prostacyclin, which does not interfere with the classical fibrinogen coagulation reaction, does not cause uncontrolled bleeding as does the administration of heparin.

It also appears that this opponent action of thromboxane A_2

and prostacyclin may be important in several other physiological processes. For example, prostacyclin may prevent gastric ulceration by inhibiting secretion, regulate blood pressure by controlling vascular tone, and control of inflammation by inhibiting protease secretion of polymorphonuclear leucocytes. There is also evidence that thromboxane A_2 is the natural ligand for the benzodiazepine receptors in brain tissue[42]. Thromboxane A_2 may also play an important role in the regulation of intracellular calcium movements in neurons and consequently should have important actions on both impulse conduction and synaptic transmission.

Areas of Current Research Interest

Since, by the nature of the compounds, isolation of greater than microgram quantities of these arachidonic acid metabolites, many of which are too unstable for any realistic period of study, has proven very difficult the synthetic preparation of these natural compounds, or stable analogues, has been an invaluable aid in providing materials for biological study. By utilizing these synthetic products great strides have been made in understanding the various metabolic pathways involved and medicinal chemistry has progressed some way towards applying these materials in a clinical environment.

Before considering the synthetic work on thromboxane B_2 in detail a brief review of the other main areas of current research interest is relevant.

A) Prostaglandin Structure / Property Relationship

Naturally occurring prostaglandins have a wide variety of pharmacological actions capable of affecting in one way

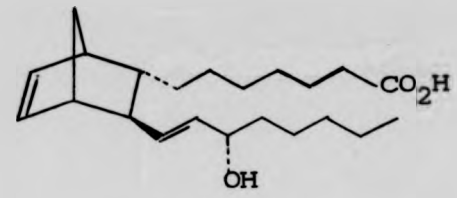
or another almost every organ of the body; the synthesis and biological activity of these naturally occurring prostaglandins has been the subject of numerous reviews[16,43]. The problems encountered in a medical application for a "natural prostaglandin" for a given function are that, although the function will be acted upon in the desired way, other functions in the receptor areas can be affected giving undesired side effects. However, since little is known about the nature or requirements of these receptor sites and only speculative information exists concerning the mode of action of the prostaglandins it is difficult to design selective prostaglandin analogues.

Virtually the only rationale which offers itself as a guide to designing analogues is to block the known pathways of prostaglandin metabolism in the hope that this might produce compounds with an enhanced duration of activity. For example, synthesis of prostaglandins substituted with a methyl group at C-15, thus blocking the deactivation by the primary inactivating enzyme, prostaglandin 15-hydroxydehydrogenase, showed enhanced activity compared with the corresponding naturally occurring prostaglandins.

The most common approaches to preparing analogues are grouped as follows : a) replacement of the ring; b) modifications at C-9 to C-11; c) α -chain analogues and d) ω -chain analogues. Many of the compounds prepared incorporate a combination of more than one of these features. These analogues are then generally screened for leuteolytic potency, abortifacient, hypolipidaemic and hypotensive properties, as inhibitors of platelet aggregation and for efficacy as bronchodilator, anti-secretory and anti-ulcer activity. This area has been covered in a number of reviews[16,44].

B) Prostaglandin Endoperoxide Analogues

Two years prior to the isolation of the prostaglandin endoperoxides the first endoperoxide analogue was synthesised[45]. This bicyclo [2.2.1] heptane derivative (29) resembled PGH_1 but it only displayed minor biological activity and further development of endoperoxide analogues was postponed until the physiological role of the endoperoxides was more fully understood.



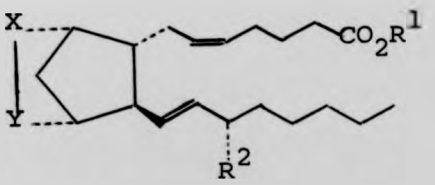
(29)

When the high potency of the endoperoxides in contracting smooth muscle and aggregating platelets was discovered[13] interest grew again in the properties of the prostaglandin endoperoxides. However, studies of the chemical reactions of these key biomolecules were hampered by the instability [e.g. PGH_2 (4) has a half life of 2.7 hours at 20°C in light petroleum ether and 30 minutes at 20°C in aqueous media] and uncertain purity of the small samples available by biosynthesis. Furthermore, the complexity of the molecular structures of the natural endoperoxides and their transformation products complicated identification, which was generally indirect and hence only tentative. The mechanistic details of prostaglandin endoperoxide chemistry and biochemistry, therefore, remain largely unknown.

Initially, the only method for preparing the endoperoxides

was via an enzyme-catalysed synthesis. Two methods have been reported describing these techniques[46,47] which required incubation of arachidonic acid with cyclooxygenase (extracted from various organs) then low temperature extraction into an aqueous free organic medium. This avoids the problems of thermolability and hydrolysis and allowed milligram quantities of PGH_2 and PGG_2 to be isolated.

Because of these difficulties an intensive synthetic effort was directed towards preparing analogues of the two endoperoxides. Although there was no assurance that these analogues would behave as mimics rather than antagonists of PGH_2 a large number have been prepared and some of these are outlined in Scheme 11[48].



PGH_2(4): X-Y = O-O, R^1 = H, R^2 = OH

PGG_2(3): X-Y = O-O, R^1 = H, R^2 = OOH

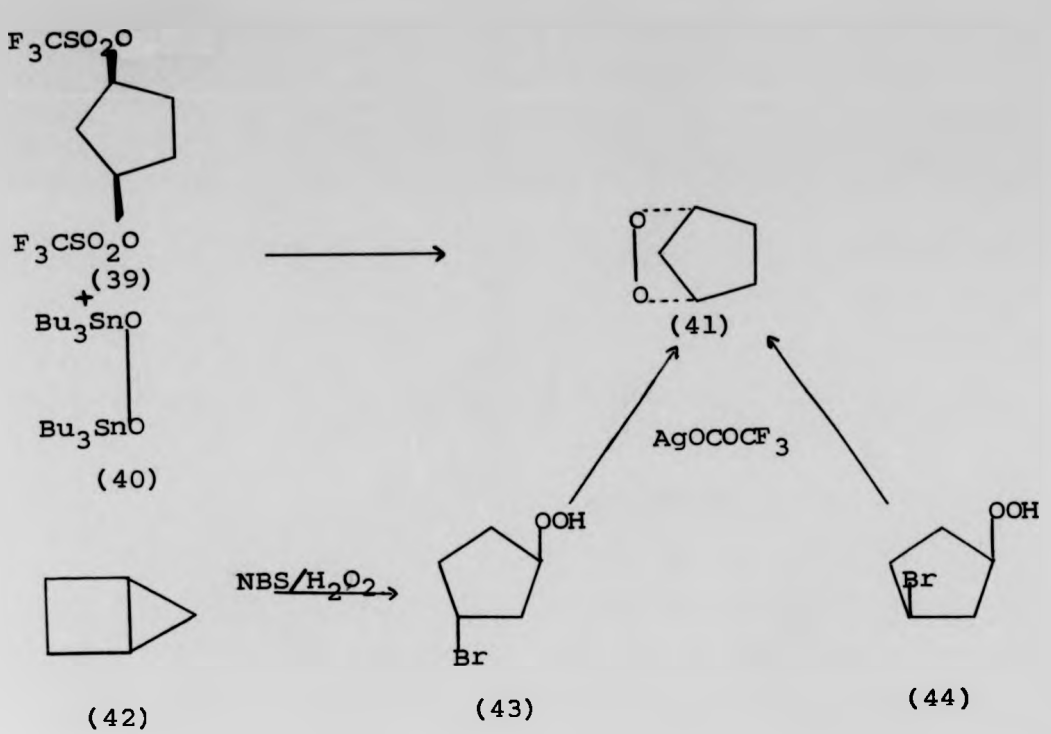
	X-Y	R^1	R^2
(30)	N=N	H	OH
(31)	O-CH_2	H	OH
(32)	CH_2-O	H	OH
(29)	CH=CH	H	OH
(33)	EtO_2C-C=C-C-CO_2Et	H	OH
(34)	$OCH(CH_3)O$	H	OH
(35)	S-S	CH_3	OH
(36)	S_2-S_2	H	OH
(37)	N=N	H	H
(38)	O-CH_2	H	H

Scheme 11

Perhaps the most studied analogues have been the two cyclic ethers (31) and (32)[49] and the aza analogue (30)[50]. These analogues possess very nearly the same molecular geometry as PGH_2(4) but are much more stable at 37°C, pH 7. The aza analogue (30) was about 7 fold more potent than PGG_2 in stimulating isolated rabbit aorta strips and mimicked PGG_2 and PGH_2 in their ability to induce platelet aggregation and release serotonin when added to human platelet-rich plasma. The biological properties of all three analogues have been compared in the same tests[51] and the ether (32) was found to be the most potent.

With the development of milder synthetic methodology for the construction of endoperoxides considerable work has been published on the preparation of the endoperoxide ring system 2,3-dioxabicyclo [2.2.1] heptane (41) and various derivatives thereof. For example, Salomon and Salomon[52] have developed a synthesis of (41) in 13% yield by reacting bis(tri-n-butyltin)peroxide (40) with the bis(triflate) (39) under vacuum and trapping the volatile product (41) at -78°C. Porter and Gilmore[53] exposed bicyclopentane (42) to N-bromosuccinimide and 98% hydrogen peroxide to afford the bromohydroperoxides (43) and (44) (1:1) which on treatment with silver trifluoroacetate gave (41). The trans compound (43) reacted quantitatively while this cis compound (44) reacted at a much slower rate and in lower yield. (Scheme 12)

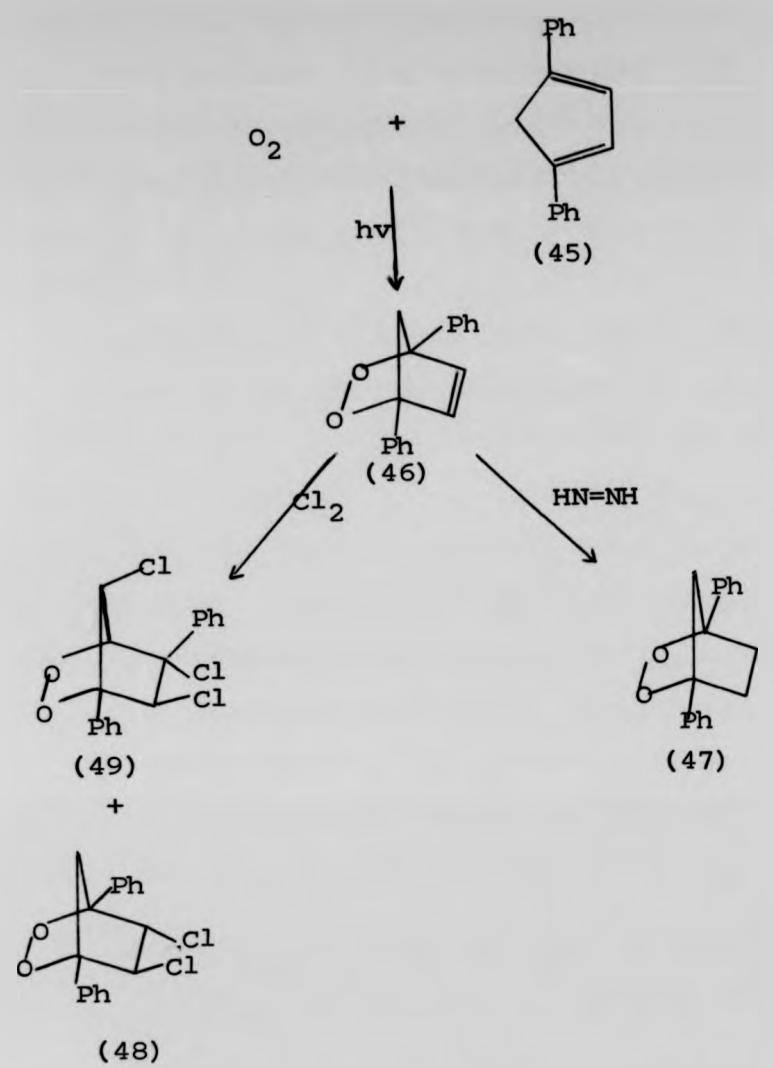
Coughlin et al.[54] have reported the syntheses of a series of saturated bicyclo [n.2.2] peroxides (n = 1 to 4) which, along with a homologous series of monocyclic peroxides, will be valuable for determining the effects of geometric constraints on the properties of dialkyl peroxides. The same group also reported the syntheses of a series of



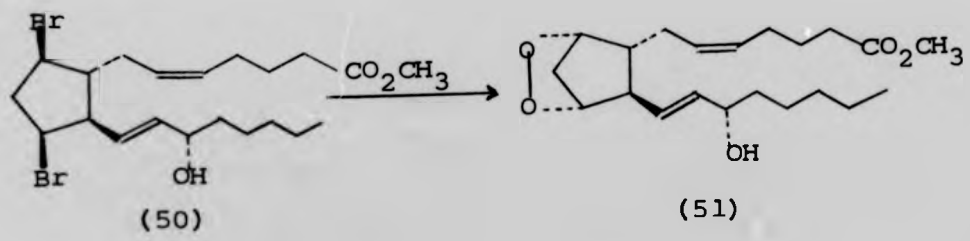
Scheme 12

derivatives of 2,3-dioxabicyclo [2.2.1] heptane by the route illustrated in Scheme 13. Diimide selectively reduces the carbon-carbon π bond of 1,4-diphenyl-2,3-dioxabicyclo [2.2.1] hept-5-ene (46) without reducing the sensitive O-O bond. Studies on the thermal reactivities of 2,3-dioxabicyclo [2.2.1] heptane, and derivatives, have also been published[55].

These approaches have been extended and Johnson *et al.*[56] reported the chemical synthesis of PGH_2 methyl ester (51). The dibromide precursor (50) was obtained from $PGF_{2\alpha}$ by a multistep sequence and, on reaction in an S_N2 manner with potassium hyperoxide in dimethyl sulfoxide[57] in the presence of 18-crown-6 ether, the PGH_2 deivative (51) was obtained in 3% yield. Porter *et al.*[58] have restudied this synthesis and report that conversion of (50) to (51) is possible using silver salts and hydrogen peroxide, as reported [53] for the


O2
hv
Ph
Ph
(45)
Ph
O
O
Ph
(46)
Cl2
HN=NH
Cl
Ph
Cl
Cl
O
O
Ph
(49)
+
Ph
O
O
Ph
(47)
Ph
Cl
Cl
O
O
Ph
(48)

Scheme 13


Br
Br
OH
(50)
CO2CH3
CO2CH3
OH
(51)

preparation of (41), and the PGH_2 derivative (51) was obtained in 20-25% yield. They also reported high performance liquid chromatography conditions for purifying the endoperoxide with minimum degradation compared with the large losses normally associated with a thin-layer chromatographic purification.

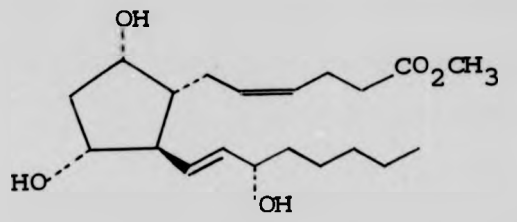
This synthetic method coupled with a facile purification technique opens the way for the synthesis of a variety of endoperoxide analogues and makes the parent free acid, PGH_2, potentially available by chemical synthesis. However, even the analogues prepared to date have had an impact on biological research, facilitating the study of the physiological role of the prostaglandin endoperoxides in the endoperoxide-induced platelet aggregation reaction, cardiovascular regulation by endoperoxides, the endoperoxide induced release of renin and thyroid hormone and the role of endoperoxides in the inflammatory process.

C) Medicinal Applications of Thromboxane A_2 and Prostacyclin

Interest has been aroused by the discovery of thromboxane A_2 and prostacyclin and the knowledge that a number of physiological processes may be governed by the opponent actions of these two compounds. However, little if any investigative work has been done on the physiological role of thromboxane B_2 (15) and the lack of isolated thromboxane A_2 coupled with the scarcity of stable analogues, has hampered progress in definitively establishing the role of thromboxane A_2.

Research on prostacyclin has currently overshadowed all other research in this field with several groups having synthesised this compound. The synthesis of prostacyclin will not be covered in detail but a large

number of syntheses have been reported [33,59] and a review has been written[48]. The basic rationale behind most of the synthetic approaches is an electrophilically-induced ring closure on $PGF_{2\alpha}$ methyl ester (52), using reagents such as phenylselenenyl chloride or a halogen, to generate the 5 membered ether ring in prostacyclin (23). A number of reviews have also been published on the various physiological applications of prostacyclin[60,61]. This availability of prostacyclin has stimulated research into its involvement in blood pressure regulation, shock, lysozomal stabilization and various types of inflammation.



(52)

A multitude of analogues and reports on their biological properties are also described in the literature and a survey of this field is beyond the scope of this review. Also, the diversity of the research into medicinal applications means that only an indication of some of the vital areas under study is possible here.

At present it is possible to influence the metabolic pathways of arachidonic acid at two stages ; 1) by inhibiting the cyclooxygenase enzyme or 2) by inhibiting the thromboxane synthetase reaction. It was known that aspirin, and other members of this class of drugs such as indomethacin and phenylbutazone, acted as a potent inhibitor of prostaglandin synthesis[6]. However, it was not until Samuelsson et al.[13,17] showed that aspirin inhibited the formation of the

endoperoxides PGG_2 and PGH_2 that it was demonstrated that the inhibition takes place at the cyclooxygenase stage of the system. A good correlation between the anti-inflammatory analgesic effects of these drugs in vivo and their ability to inhibit prostaglandin synthesis was observed. Also, since these drugs inhibited the cyclooxygenase enzyme and thus thromboxane A_2 synthesis, platelet aggregation is also inhibited. The mechanism of this inhibition is complex but it has been shown that aspirin brings about an acetylation of the cyclooxygenase leading to its permanent inactivation[62] and also abolishes the change of shape of the platelets. Consequently, in platelets which are incapable of resynthesizing the enzyme, a single exposure to aspirin serves to inactivate the platelet for the remainder of its 7-day circulating lifetime. This inhibition of cyclooxygenase will obviously block both prostacyclin and thromboxane production.

It is also possible to selectively block either thromboxane or prostacyclin production. Gorman et al.[63] reported that platelet aggregation induced by arachidonate or PGH_2 was inhibited by 9,11-azo-prosta-5,13-dienoic acid (37). Concomitantly production of thromboxane B_2 was prevented and an enhanced production of PGE_2 occurred. This indicated that ; a) the aza analogue was a specific inhibitor of thromboxane synthetase and b) the platelet aggregating activity of the endoperoxides is entirely due to their prior conversion to thromboxane A_2. Gryglewski et al.[30] have reported that tranylcypromine is a specific inhibitor of prostacyclin production. Thus synthetic compounds are available which can either block thromboxane/ prostacyclin production totally [and hence promote the

formation of HPETE (7)] or allow the production of either thromboxane or prostacyclin to be selectively blocked. This control could prove very important in managing various disease states which involve vasoconstriction and platelet aggregation.

In addition to their role in precipitating blood clotting, platelets are involved in the formation of atherosclerotic plaque. In the overall sequence of events leading to the development of atherosclerotic plaques, and ultimately a heart attack, products of the endoperoxide synthetase reaction are involved at various critical points. Endothelial injury appears to be a prerequisite for thrombus formation and since prostacyclin generation has been shown to centre in the endothelium[37] it appears that interruption of the prostacyclin production can initiate platelet aggregation over the damaged area. Also, these atherosclerotic plaques have been found to contain lipid hydroperoxides (such as 15-hydroperoxyarachidonic acid) which have been shown to inhibit prostacyclin synthetase[64]. This might explain the increased incidences of thrombosis observed in atherosclerotic patients.

The terminal event which initiates platelet aggregation and thrombus formation involves thromboxane production. However, in addition to enhancing platelet aggregation thromboxane A_2 also induces localized blood vessel contractions which accentuates the problem for an artery already partially blocked by atherosclerotic plaques. Blocking thromboxane A_2 synthesis at this stage, or interfering with the prostaglandin synthesis associated with the inflammatory response in the blood vessel wall, should have a beneficial effect.

Several non-steroidal anti-inflammatory drugs which inhibit the cyclooxygenase reaction have been found to retard the development of atherosclerotic plaques when administered to animals fed cholesterol and several clinical studies are being done on the effect of drugs, such as aspirin, on humans. (Initial results suggest up to 50% decrease in the death rate after a myocardial infarction has been achieved.) A second approach is to look for stable analogues of prostacyclin which display therapeutic effects on platelet functions at levels which do not significantly reduce blood pressure.

The importance of this work is illustrated by the fact that 1 million Americans experience a first myocardial infarction each year.

One new area of interest arises from the observation[61] that the <u>in vivo</u> anti-platelet deaggregatory activity of exogenous prostacyclin is enhanced after its passage through the pulmonary circulation of anaesthetized cats, probably because of a concomitant generation of endogenous prostacyclin by the lungs. It was postulated that the continuous biosynthesis of prostacyclin by pulmonary endothelium is a general physiological phenomenon, while the generation of thromboxane A_2 by lungs occurs in response to pathological stimuli. This "hormonal" circulating prostacyclin, as well as supplementing, may actually potentiate the anti-aggregatory and vasodilator activities of that prostacyclin which is generated locally by arterial walls. This may also be a rationale for "deep-breathing" exercises during stress situations since hyperventilation has been shown to be followed by release of a "prostacyclin-

like" substance from the lungs which is deaggregatory. Also, tobacco smoking, air pollution and lung disease may diminish the prostacyclin generating capacity of the lungs and thus disturb the homeostasis in coronary and cerebral circulation.

Other areas of interest include ; a) the control of blood clotting with prostacyclin while performing some external mechanical treatment, e.g. dialysis, b) the study of the effects of diet on the body's ability to produce thromboxane or prostacyclin, and c) the control of circulatory disorders.

These compounds obviously have great medical potential and any improvement in the understanding of their physiological functions, or the utilization of more function-specific analogues, will be of great importance.

D) Synthesis of Thromboxane B_2

The extremely labile thromboxane A_2 (18) has not yet been synthesised but a considerable effort has been devoted to the synthesis of its stable metabolite thromboxane B_2 (15). The obtention of sufficient quantities of this should allow detailed biological testing as well as the generation of antibodies for use in sensitive radioimmuno assay studies.

It is possible to consider all the reported synthesis of thromboxane B_2 in one of four classes :-

I) modification of an appropriate prostaglandin

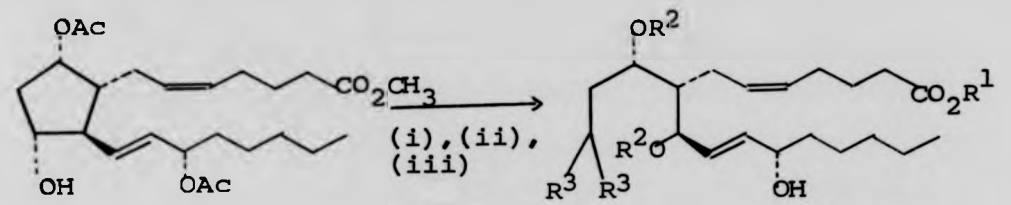
II) modification of a known prostaglandin precursor

III) total synthesis from non-chiral precursors

IV) total synthesis from chiral precursors

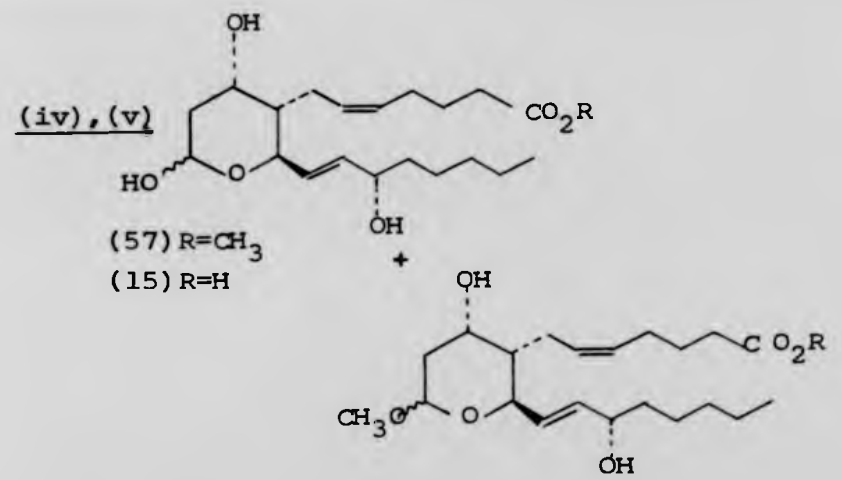
I) Prostaglandin Modification

It was perhaps not unexpected that the first synthesis of thromboxane B_2 should use as its starting material a prostaglandin or prostaglandin derivative. Schneider and Morge[65] reported quite a short route to thromboxane B_2 using 9,15-diacetoxy-$PGF_{2\alpha}$ methyl ester (53) as a starting point as shown in Scheme 14. The crucial step in this



(53)

(54) $R^1=CH_3$; R^2=Ac; $R^3=OCH_3$
(55) $R^1=CH_3$; R^2=H; $R^3=OCH_3$
(56) $R^1=R^2$=H; $R^3=OCH_3$



(i) $Pb(OAc)_4$, benzene; (ii) $HC(OMe)_3$, py, HCl, MeOH; (iii) MeOH, $^-$OMe; (iv) AcOH, H_2O, THF (4:2:1); (v) THF, 83% H_3PO_4, H_2O (12:1:10).

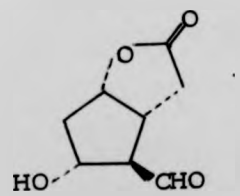
Scheme 14

synthesis consisted of a ring opening reaction initiated by

the action of lead tetraacetate on the homoallylic 11α-hydroxyl group to yield an unstable aldehyde which was protected as the dimethyl acetal (54) by reaction with trimethyl orthoformate and pyridine hydrochloride in methanol. Removal of the acetate groups with methanolic sodium methoxide gave (55), while aqueous basic hydrolysis gave the trihydroxy acid (56). Treatment of this dimethyl acetal (55) with a mixture of acetic acid, water and tetrahydrofuran gave a mixture of thromboxane B_2 methyl ester (57) and its cyclic methyl acetal (58). However, treatment of (55) with a tetrahydrofuran, water,85% phosphoric acid mixture gave largely thromboxane B_2 (15), which was purified and crystallised, and a small amount of its methyl acetal (59). The overall yield of thromboxane B_2 from (53) was approximately 25%.

II) Prostaglandin Precursor Modification

Perhaps the most utilized precursor in prostaglandin chemistry is the "Corey Aldehyde" (60). This precursor



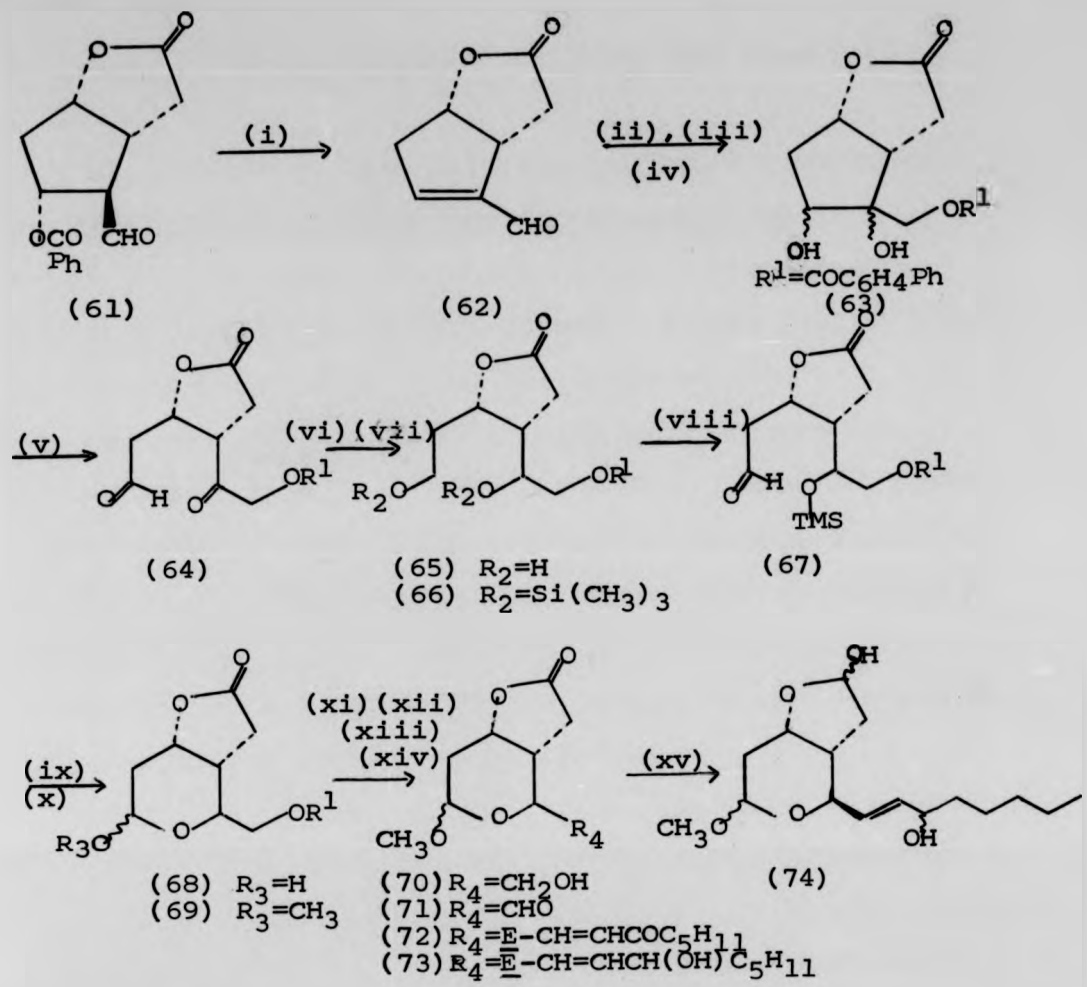
(60)

has functionality such that it can be used to generate a large proportion of the prostaglandin series. An analogous precursor for thromboxane synthesis would enable the facile preparation of the natural thromboxanes or various analogues. Two synthesis of thromboxane B_2 have been reported using such a precursor generated from an analogue of the

Corey-aldehyde. Both these syntheses give thromboxane B_2 in an optically-active form since the precursors prepared are optically active.

Starting from the prostanoid precursor (61) Nelson and Jackson[66] have developed a synthesis of the thromboxane precursor (71), using the key steps of a periodic cleavage of a diol followed by acetalization of the resulting aldehyde, and then elaborated this to thromboxane B_2 (15). (Scheme 15)

Treatment of (61) with florisil resulted in the formation of (62) which, after reduction with sodium borohydride in methanol and conversion to the p-phenylbenzoate derivative, was hydroxylated with osmium tetroxide, N-methylmorpholine N-oxide to give a mixture of cis-glycols (63). Cleavage of these diols with periodic acid led to the rather unstable aldehyde-ketone (64) which was reduced directly with sodium borohydride to afford (65). Differentiation of the two hydroxyl groups of (65) was achieved by first preparing the bis(trimethylsilyl ether) (66) and subjecting this to a Collins' oxidation to yield the aldehyde (67). Treatment of aldehyde (67) with methanolic acetic acid afforded (68) while treatment of (67) or (68) with methanolic hydrochloric acid yielded a mixture of methyl acetals (69) which were readily separated chromatographically. Treatment of each isomeric acetal ester (69) with methanolic sodium methoxide yielded the corresponding alcohol (70). Collins' oxidation of (70) (α-OCH_3) proceeded with difficulty and the intermediate (71) was treated directly with the ylide prepared from 2-oxoheptylphosphonate to afford (72) (α-OCH_3). Pfitzner-Moffat oxidation of (70) (β-OCH_3)



(61) (62) (63) $R^1=COC_6H_4Ph$

(64) (65) $R_2=H$ (66) $R_2=Si(CH_3)_3$ (67)

(68) $R_3=H$ (69) $R_3=CH_3$ (70) $R_4=CH_2OH$ (71) $R_4=CHO$ (72) $R_4=\underline{E}$-$CH=CHCOC_5H_{11}$ (73) $R_4=\underline{E}$-$CH=CHCH(OH)C_5H_{11}$ (74)

(59) a) α-OCH_3, 15$\underline{R}$; b) α-OCH_3, 15$\underline{S}$; c) β-OCH_3, 15$\underline{R}$; d) β-OCH_3, 15$\underline{S}$

(i) Florisil, EtOAc, 25°C; (ii) $NaBH_4$, MeOH; (iii) PhC_6H_4COCl; (iv) OsO_4,  ; (v) HIO_4, py, aq.-MeOH, 0°C; (vi) $NaBH_4$, ROH; (vii) silylation; (viii) CrO_3.py; (ix) AcOH, MeOH; (x) HCl, MeOH; (xi) NaOMe, MeOH; (xii) CrO_3.py; (xiii) KO$\underline{t}$-Bu, $(MeO)_2$-$P(O)CH_2COC_5H_{11}$, THF; (xiv) $Zn(BH_4)_2$, DME; (xv) $\underline{i}$-Bu_2AlH; (xvi) $Ph_3P{=}CH{-}(CH_2)_3CO_2Na$; (xvii) H_3PO_4-aq.THF.

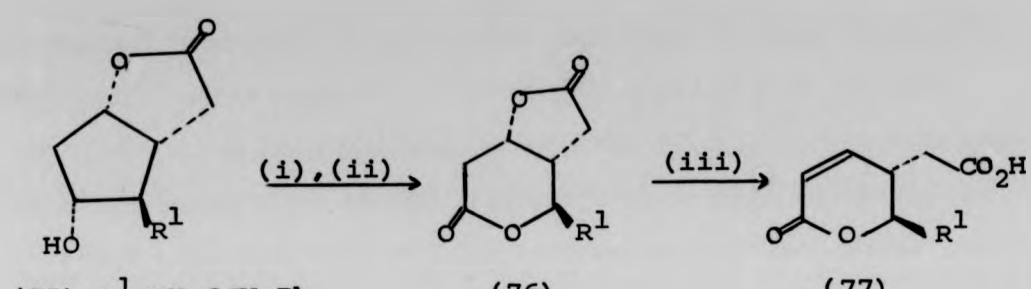
Scheme 15

proceeded normally to give (71) which was converted to (72) (β-OCH_3).

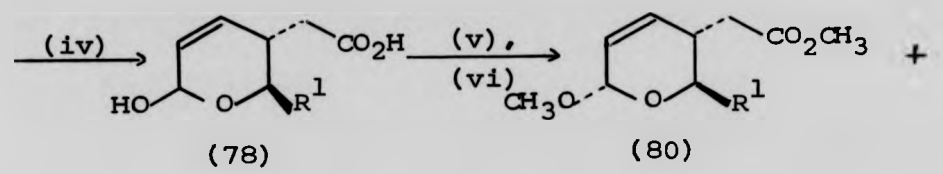
The remaining steps followed published procedures[67] and involved reducing the ketone function in (72) with zinc borohydride to give (73) which was then treated with diisobutylaluminium hydride (DIBAL) to give (74). Treatment of (74) (α-OCH_3) with the ylide prepared from 4-carboxybutyltriphenylphosphonium bromide gave the hemi-acetals (59a) and (59b) which were separated chromatographically. Likewise (59c) and (59d) were prepared and separated chromatographically. Subsequent hydrolysis of (59b) or (59d) yielded thromboxane B_2 in approximately 3% yield from (61), the intermediate alcohol (70) having been prepared in approximately 14% yield.

Similarily Kelly et al.[68] have reported a synthesis of the same thromboxane precursor (70) starting from the prostanoid intermediate (75) (Scheme 16). In this synthesis the hemiacetal function was introduced by a Baeyer-Villiger oxidation and subsequent reduction.

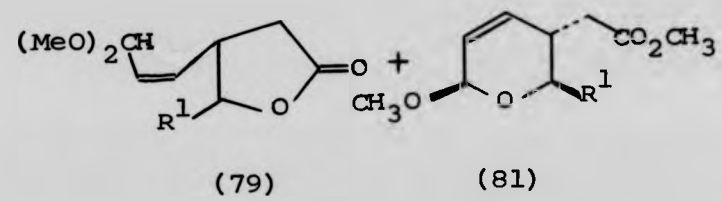
A Jones oxidation on (75) produced an unstable keto-lactone which then underwent a Baeyer-Villiger oxidation with m-chloroperoxybenzoic acid to give the crystalline derivative (76), which on treatment with a tertiary amine base (e.g. DBU), gave the elimination product (77). Reduction of lactone (77) with diisobutylaluminium hydride gave a lactol (78) which was treated directly with diazomethane then dry hydrogen chloride gas in methanol and trimethyl orthoformate to afford (80) as the major product, [compounds (79) and (81) were also isolated]. Conversion of (80) to the iodolactone (82) was achieved by saponification followed by iodolactonization with iodine and potassium



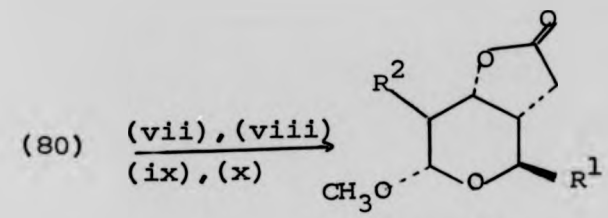
(75) $R^1=CH_2OCH_2Ph$ (76) (77)



(78) (80)



(79) (81)



(80) (82) $R^2=I$ (83) $R^2=H$ (70)

(i)Jones oxidation; (ii)m-CPBA; (iii)base; (iv)i-Bu_2AlH; (v)CH_2N_2; (vi)$HC(OCH_3)_3$,MeOH,HCl; (vii)NaOH; (viii)CO_2; (ix)KI,I_2; (x)Bu_3SnCl,$NaBH_4$,hv; (xi)H_2,Pd/C.

Scheme 16

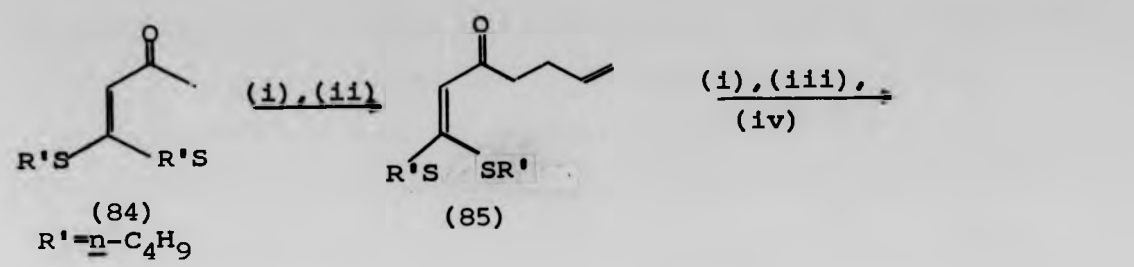
iodide. This iodolactone (82) was then de-iodinated with tri-n-butyltin hydride to give the crystalline lactone (83) which, after hydrogenation over 5% palladium/charcoal gave the debenzylated derivative (70). This alcohol, a single epimer at each chiral centre, was transformed into thromboxane B_2 (15) in an identical manner to that described in the previous synthesis. The yield for the preparation of the precursor (70) by this route is not known.

III) Racemic Synthesis

Only one synthesis of racemic thromboxane B_2 has been reported to date. This synthesis by Corey et al.[69] not only utilizes non-optically active starting materials but also, unlike the previous synthesis, does not involve the intermediacy of a prostanoid precursor. The synthesis is detailed in Scheme 17.

The readily available enone (84) was alkylated with lithium diisopropylamide (LDA) and allyl bromide to give (85), which then underwent similar lithiation (LDA) and subsequent reaction with aldehyde (94) to give the 1,2-adduct (86) as a non-separable mixture of diastereoisomers. Depyranylation of (86) gave the diol (87) which was cyclised directly to (88) by stirring in methylene chloride solution with a catalytic amount of insoluble acid. The tetrahydropyranyl (THP) derivative (89) was then formed.

The mixture of isomeric ketones (89) was then reduced with sodium borohydride to afford an easily separable mixture of diastereomeric alcohols from which the hydroxy lactone (90) could be isolated after chromatography and silver-induced removal of the thioketal function. On treating (90) with diisobutylaluminium hydride then



(84) R'=n-C_4H_9

(85)

(86) R=THP
(87) R=H

(88) R=H
(89) R=THP

(90)

(91)

(92)

(93)

(i)LDA; (ii)$BrCH_2CH{=}CH_2$;(iii)  (94);(iv)H_3O^+;
(v)CH_2Cl_2,TsOH; (vi)DHP,H^+; (vii)$NaBH_4$; (viii)$AgNO_3$,aq.MeCN,Ag_2O;
(ix)i-Bu_2AlH; (x)$BF_3.Et_2O$,CH_3OH; (xi)OsO_4; (xii)$NaIO_4$;
(xiii)$Ph_3P{=}CH(CH_2)_3CO_2Na$; (xiv)H_3PO_4,aq.THF.

Scheme 17

methanolic boron trifluoride etherate the hydroxy acetal (91) was obtained. Cleavage of the terminal methylene group by sequential exposure to osmium tetroxide/pyridine (to generate a diol) and sodium periodate led directly to the lactol-acetal (92). Reaction of (92) with the ylide prepared from 4-carboxybutyltriphenyl phosphonium bromide[67] followed by hydrolysis with 85% phosphoric acid, water, tetrahydrofuran (1:10:10) gave a mixture of (±) thromboxane B_2 (15) and the C-15 epimer (93) which could be separated chromatographically.

The C-15 epimer (93) was also converted to (15) using the superoxide displacement method[57]. Treatment of (93) with diazomethane then boron trifluoride etherate yielded the corresponding methyl ester-methyl acetal which was selectively transformed to the 15-mesylate with methanesulphonyl chloride/triethylamine. The unstable mesylate was subjected to displacement using potassium hyperoxide/18-crown-6 ether (potassium superoxide) in dimethyl sulphoxide/dimethylformamide/dimethoxyethane to give the methyl-acetal of thromboxane B_2 which yielded thromboxane B_2 (15) on hydrolysis.

This synthesis produces thromboxane B_2 in yields of *ca*. 5% without the conversion of the 15-epimer as described.

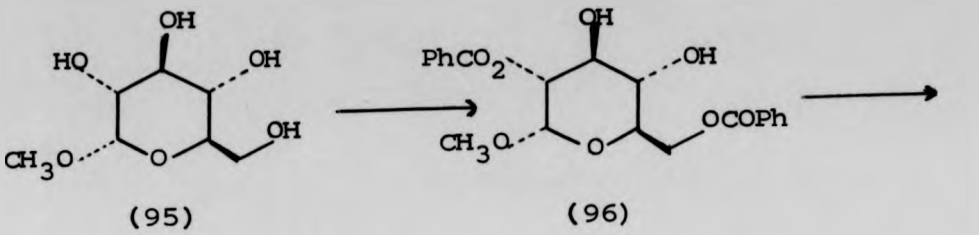
IV) Optically Active Synthesis

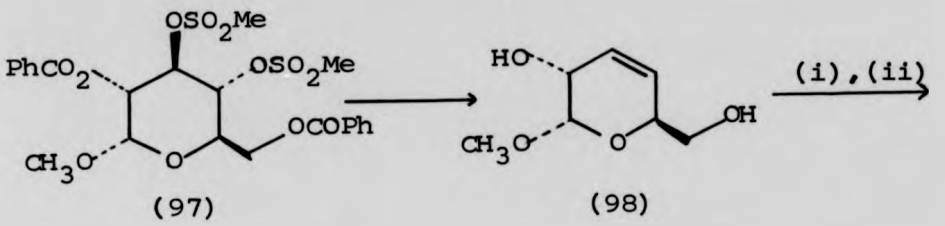
Currently, considerable synthetic effort is being devoted to the synthesis of complex, optically active, natural products. In order to simplify the synthetic procedures it is advantageous if some appropriately functionalized optically active precursors can be used and the use of sugars as starting materials have increased dramatically as a result of this. Sugars provide a highly

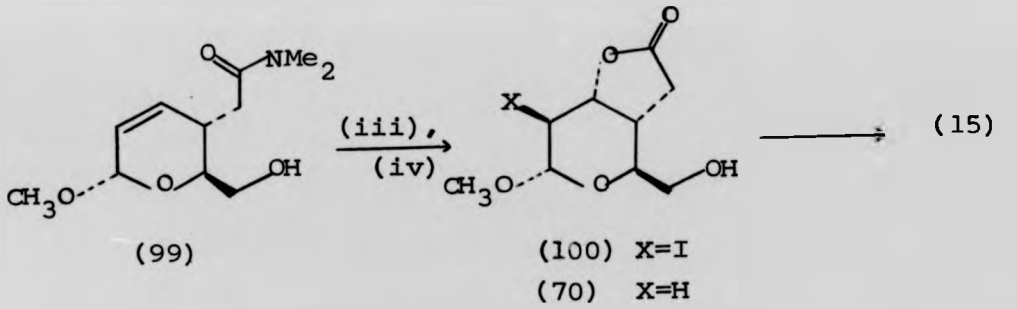
functionalized starting material with the chirality defined at up to five centres[70] which greatly simplifies the elaboration of optically active sites. All the syntheses described here have taken as their starting material D-glucose, or a close derivative.

Corey's group[71] have developed a simple, stereocontrolled route from α-methyl-D-glucoside (95) (Scheme 18). Using a known[72] and efficient sequence of reactions (95) was converted to the 4,5-unsaturated sugar (98) via intermediates (96) and (97). Claisen rearrangement of (98) by heating with excess N,N-dimethylacetamide dimethylaminal in diglyme, resulted in the stereospecific formation of the dimethylamide (99). This compound readily cyclised on treatment with iodine to form the iodolactone (100) which was deiodinated with tributyltin hydride to afford the hydroxylactone (70). This lactone was identical with material prepared by other routes[66,68] and was converted to thromboxane B_2 and the C-15 epimer using the same methodology. The C-15 epimer was then converted to thromboxane B_2 using the superoxide method described above.

Hanessian and Lavallee[73] were the first group to describe a stereospecific total synthesis of thromboxane B_2 starting from a sugar. They considered thromboxane to be a 2,4,6-trideoxy-D-ribo-hexose in which positions 4 and 6 are the sites of C-branching and chain extension respectively. Their synthesis was thus based on the stereospecific introduction of the acid side chain at C-4 and appropriate chain extension at C-6 in a suitable carbohydrate derivative. This is outlined in Scheme 19.

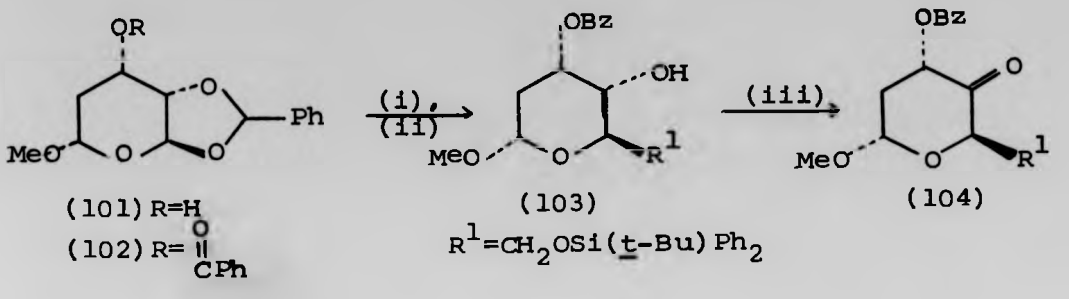






(i) $Me_2NC(Me)(OMe)_2$; (ii) K_2CO_3, MeOH; (iii) I_2, aq.THF; (iv) n-Bu_3SnH

Scheme 18



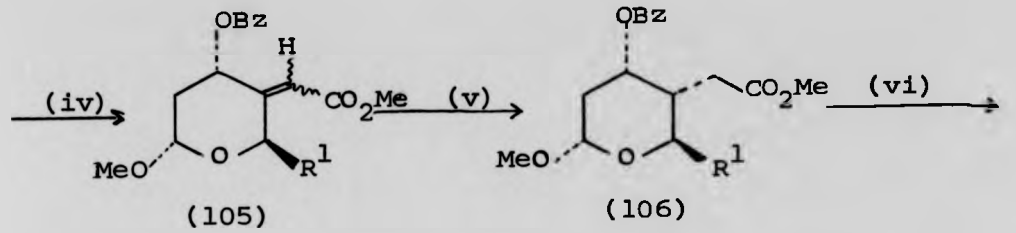
(101) R=H

(102) R= O ‖ CPh

(103)

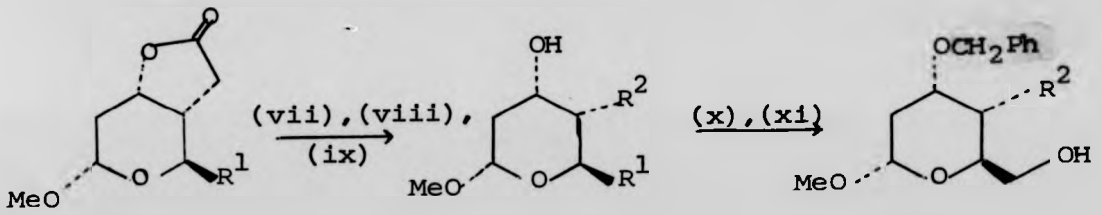
R^1=$CH_2OSi(\underline{t}\text{-Bu})Ph_2$

(104)



(105)

(106)

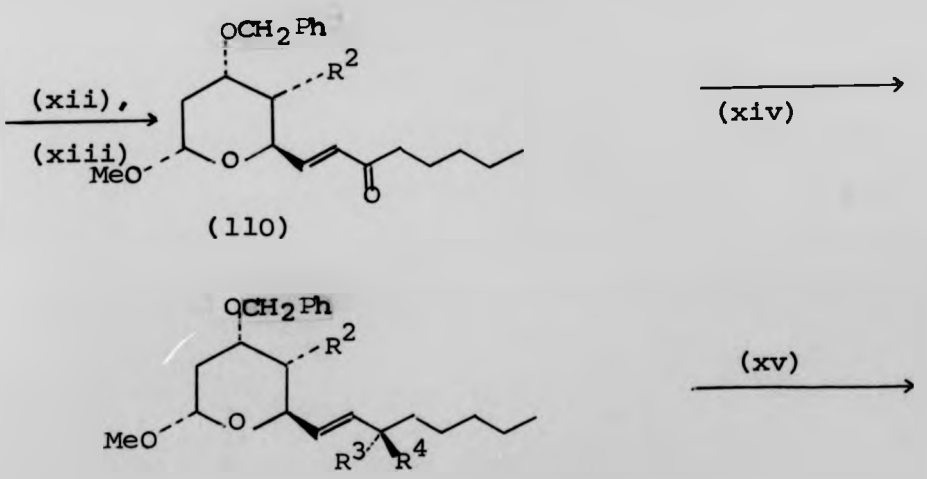


(107)

(108)

(109)

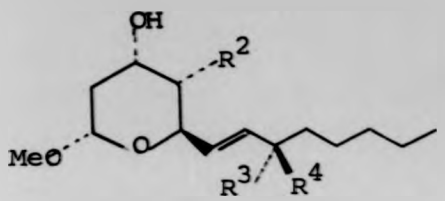
R^2= $CH_2CH{=}CH(CH_2)_3CO_2Me$



(110)

(111) R^4=H; R^3=OH

(112) R^4=OH; R^3=H



(113) R^4=H;R^3=OH
(114) R^4=OH;R^3=H

(xvi),(xvii) (15) + 15-epimer (93)

(i) $Pd(OH)_2$,H_2; (ii) t-$BuPh_2SiCl$; (iii) oxidation; (iv) $(MeO)_2$-$P(O)CH_2CO_2Me$, t-BuOK; (v) $Pd(OH)_2/C$,H_2; (vi) K_2CO_3,MeOH; (vii) i-Bu_2AlH; (viii) $Ph_3PCH(CH_2)_3CO_2Li$; (ix) CH_2N_2; (x) benzyl chloride; (xi) Bu_4NF,THF; (xii) CrO_3.py; (xiii) $Bu_3P{=}CHCO(CH_2)_4CH_3$; (xiv) $Zn(BH_4)_2$; (xv) K_2CO_3,MeOH; (xvi) aq.NaOH; (xvii) Dowex 50,H^+.

Scheme 19

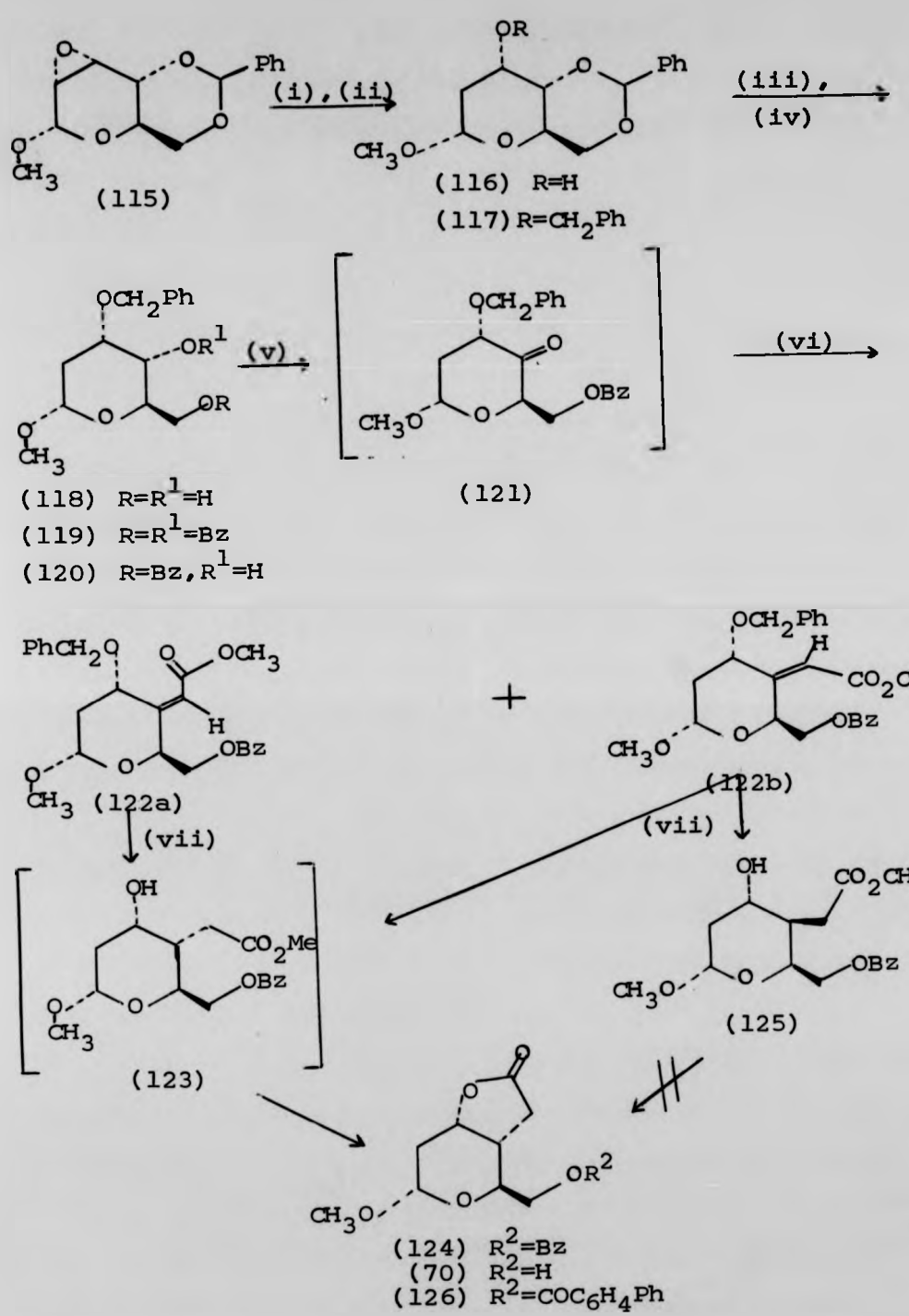
The derivative (101), which is readily accessible from D-glucose[74], was transformed to the benzoate derivative (102) which, on hydrogenolysis and selective silylation of the primary alcohol with tert-butyldiphenylsilyl chloride gave (103). Oxidation of the secondary alcohol in (103) with dimethylsulphoxide and 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride in the presence of pyridinium trifluoroacetate gave highly crystalline (104) with no detectable epimerisation at C-3. Condensation of (104) with the anion derived from trimethylphosphonoacetate and potassium tert-butoxide gave the olefin (105) as a mixture of geometrical isomers in high overall yield. Hydrogenation of the double bond and removal of the benzoyl groups with

methanolic potassium carbonate led to the ɣ-lactone (107) via compound (106). This lactone (107) is effectively identical to the intermediate (70) described previously.

The remaining pathway followed the well known methodology for the attachment of side chains described above. That is, the lactone (107) underwent reaction with DIBAL followed by treatment with 4-carboxybutyltriphenylphosphonium bromide in hexamethylphosphoric triamide (HMPT), in the presence of lithium bis(trimethylsilyl)amide, to give, after esterification, the branched chain derivative (108). Benzylation of (108) followed by treatment with tetra n-butylammonium fluoride gave (109)which, after Collins' oxidation and Wittig reaction afforded (110). Reduction with zinc borohydride gave a mixture of the epimeric products (111) and (112) which, after chromatographic separation underwent debenzoylation with methanolic potassium carbonate to give (113) and (114). Finally epimer (113) was converted to thromboxane B_2 by sequential de-esterification with aqueous sodium hydroxide followed by acid treatment on Dowex 50 (H^+).

This synthesis is practical and versatile, yielding thromboxane B_2 in ca. 17% yield from (101) and intermediate (107) in ca. 53% yield, assuming the wrong 15-epimer (114) is recycled to give the correct configuration.

Ohrui and Emoto[75] reported a synthesis of optically active key intermediates, analogous to these already described (70), for the synthesis of optically active thromboxanes which also takes as its starting material D-glucose. This synthesis closely paralleled that of Hanessian and Lavallee[73] with some minor changes in the protecting groups. However, at two or three stages some differences were observed in the



(i) LAH, THF; (ii) $PhCH_2Cl$, KOH; (iii) 85% AcOH; (iv) PhCOCl, py, CH_2Cl_2; (v) RuO_2, $NaIO_4$, CCl_4, H_2O [O]; (vi) $(CH_3)_2POCH_2CO_2CH_3$, n-BuLi, THF; (vii) 10% Pd/C, EtOH; (viii) silicic acid; (ix) NaOMe, MeOH; (x) p-PhC_6H_4COCl, py.

Scheme 20

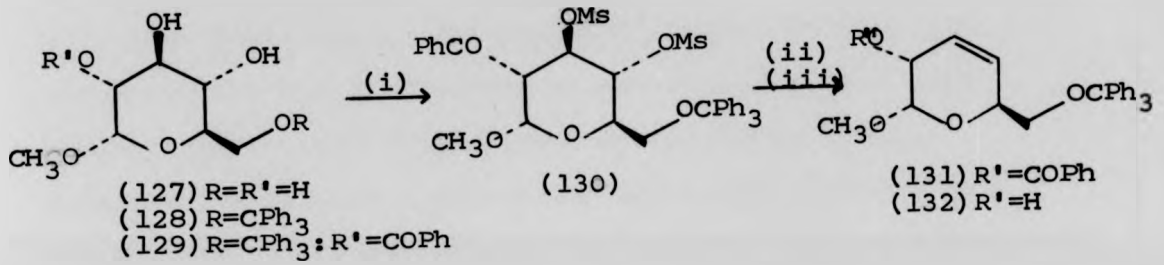
stability of compounds, or the products obtained, from those reported previously. The route followed by Ohrui and Emoto is detailed in Scheme 20.

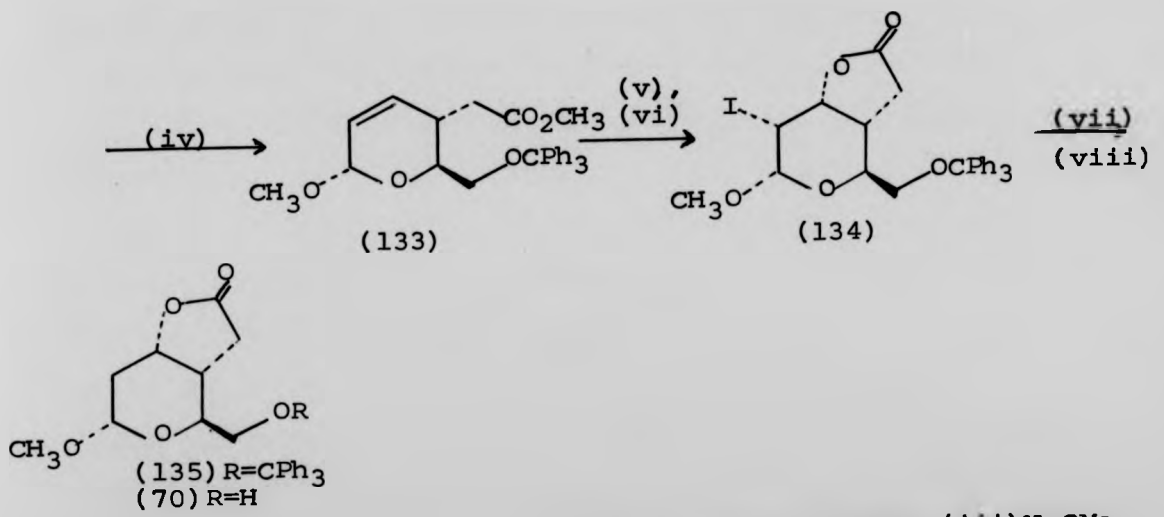
D-glucose was converted to derivative (115) using known methods[76]. Following lithium aluminium hydride reduction to (116) and formation of the benzyl ether (117) treatment with 85% acetic acid cleaved the acetal protecting group to give the diol (118). Attempted monobenzoylation with benzoyl chloride in pyridine gave predominately (120) wherein the primary alcohol has been protected, however, a little of the bisbenzoylation product (119) was separated chromatographically. Oxidation of (120) with ruthenium dioxide and sodium metaperiodate gave the ketone (121) which appeared unstable [c.f. analogous crystalline stable ketone (104)] and was treated directly with the ylide prepared from trimethylphosphonoacetate and n-butyl lithium to give a 1:1 mixture of α,β-unsaturated esters (122a) and (122b). After a chromatographic purification (122a) was hydrogenated over 10% palladium/charcoal to (123) which changed slowly to the γ-lactone (124) on standing. Consequently, crude (123) was treated directly with silicic acid to give crystalline (124).

However, the catalytic reduction of (122b) under similar conditions gave a 1:1 mixture of (123) and (125) rather than solely (123) as would be expected from Hanessian and Lavallee's results[73]. That the hydroxy ester (125) could not be lactonized under similar conditions which caused (123) to be lactonized indicated that the ester and hydroxyl groups were in a trans relation on the pyranose ring. Treatment of (124) with methanolic sodium methoxide

afforded (70) in ca. 17% yield from (115) while treatment of (70) with p-phenylbenzoylchloride gave the corresponding p-phenylbenzoate (126). Both (70) and (126) have been reported[66,71] as intermediates in the synthesis of thromboxane B_2.

The synthetic approach to thromboxane B_2 reported by Hernandez[77] also concentrates on the preparation of a versatile precursor and takes as its starting point a commercially available derivative of glucose, methyl-α-D-glucopyranose (127) (Scheme 21).





(i) $MeSO_3Cl$, $(Et)_3N$, CH_2Cl_2; (ii) Zn/Cu couple, KI, DMF; (iii) NaOMe, MeOH, CH_2Cl_2; (iv) trimethylorthoacetate, propionic acid, reflux xylene; (v) NaOH, aq.THF; (vi) KI, I_2, 0.5M $NaHCO_3$; (vii) nBu_3SnCl, $NaBH_4$, 50%EtOH-THF; (viii) HCl, CH_2Cl_2.

Scheme 21

afforded (70) in ca. 17% yield from (115) while treatment of (70) with p-phenylbenzoylchloride gave the corresponding p-phenylbenzoate (126). Both (70) and (126) have been reported[66,71] as intermediates in the synthesis of thromboxane B_2.

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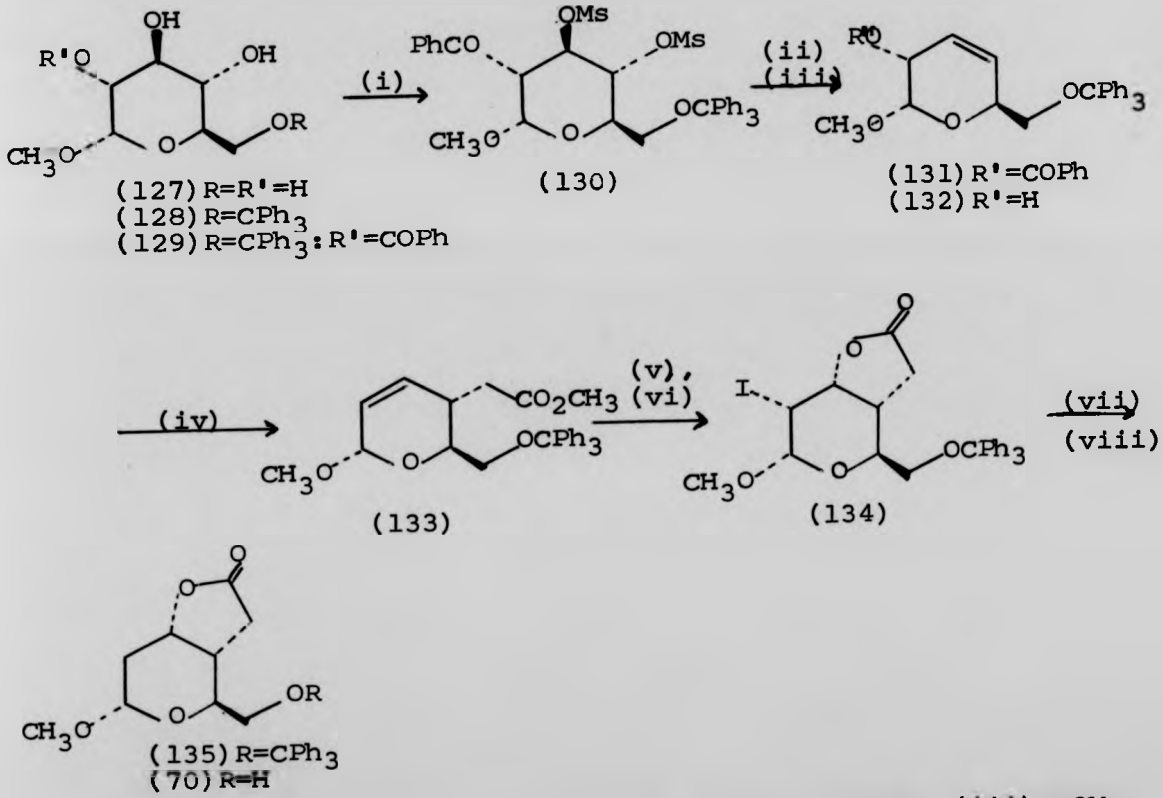


(127) R=R'=H
(128) R=CPh_3
(129) R=CPh_3; R'=COPh

(130)

(131) R'=COPh
(132) R'=H

(133)

(134)

(135) R=CPh_3
(70) R=H

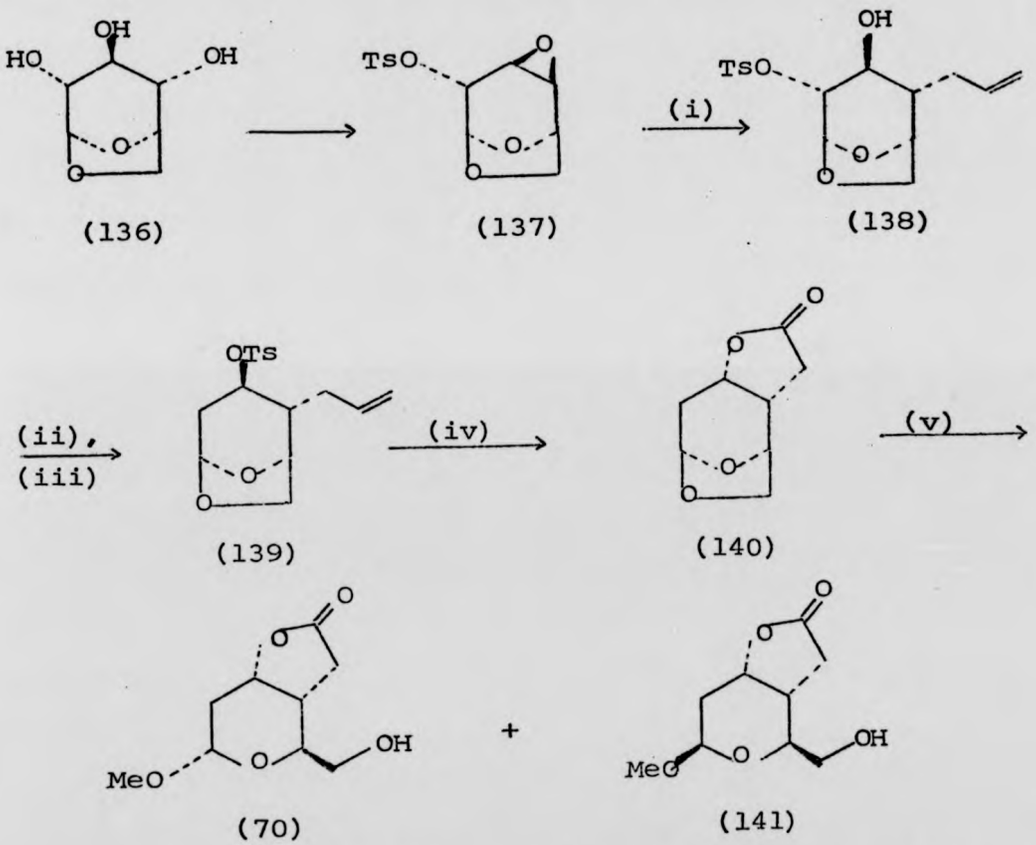
(i) $MeSO_3Cl$, $(Et)_3N$, CH_2Cl_2; (ii) Zn/Cu couple, KI, DMF; (iii) NaOMe, MeOH, CH_2Cl_2; (iv) trimethylorthoacetate, propionic acid, reflux xylene; (v) NaOH, aq.THF; (vi) KI, I_2, 0.5M $NaHCO_3$; (vii) nBu_3SnCl, $NaBH_4$, 50%EtOH-THF; (viii) HCl, CH_2Cl_2.

Scheme 21

Reaction of the glucose derivative (127) with triphenylmethyl chloride (triethylamine, dimethylformamide and catalytic 4-dimethylaminopyridine) gave the trityl ether (128). Selective activation of the hydroxyl group at C-2 was then achieved by formation of the di-*n*-butylstannylene derivative which was subsequently transformed with benzoyl chloride and triethylamine to (129). Reaction of (129) with methanesulphonyl chloride afforded the dimesylate (130) which produced a mixture of (131) and (132) on treatment with a zinc-copper couple but subsequent *trans*-esterification with sodium methoxide afforded pure (132). The allylic alcohol (132), when subjected to the conditions of the orthoester Claisen rearrangement, was transformed to the ester (133). Alkaline hydrolysis followed by iodolactonization led to the iodolactone (134) which, on treatment by tri-*n*-butyltin hydride, afforded the highly crystalline lactone (135). Removal of the trityl group with hydrogen chloride gave the intermediate hydroxy lactone (70) in *ca*. 21% yield from (127).

Kelly and Roberts[78] have reported a simple, stereo-controlled synthesis of the thromboxane B_2 synthon (70) starting from the readily available starting material laevoglucosan (1,6-anhydro-β-*D*-glucopyranose) (136). (Scheme 22). Laevoglucosan was first converted into the epoxy-tosylate (137) and subsequently into the allyl derivative (138). Reduction of this epoxide (138) followed by tosylation produced the tosylate (139) which, on oxidation, gave directly the tricyclic lactone (140). Cleavage of the 1,6-anhydro bridge produced the two bicyclic lactones (70) and (141) in *ca*. 29% yield from (136) in

the ratio of 1.55:1. These two isomers were readily separated by chromatographic methods. Conversion to thromboxane B_2 would be by standard "prostaglandin" methodology. This synthesis offers the potential of permitting stereospecific introduction of other C-4 side chains by organometallic-induced opening of the epoxide (137) and subsequent inversion of the C-3 configuration.



(i) allylmagnesium chloride/cuprous iodide; (ii) lithium triethylborohydride/THF; (iii) p-toluenesulphonyl chloride; (iv) RuO_2, excess $NaIO_4$, aq. acetone; (v) Amberlyst 15.H^+, methanol.

Scheme 22

All the syntheses, or partial syntheses, of thromboxane B_2 described have a number of features in common. In almost all cases the same key precursor, or slightly modified precursor, was the target compound, i.e. the thromboxane analogue of "Corey's aldehyde", compound (70). The various synthetic strategies, particularly with the synthesis of optically active material, were all quite similar with the overall yields between 10 and 20%. The synthetic methodology and reactions used were very similar to those developed for the synthesis of prostaglandins and this explains the publication of such a large number of syntheses of a complex molecule in a short period.

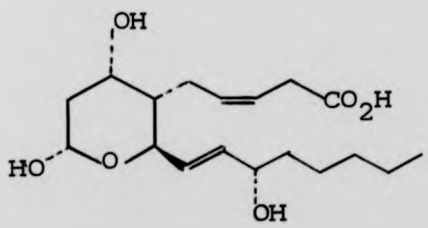
E) Metabolism of Thromboxane B_2

Although studies continue, thromboxane B_2 has not yet been shown to display any significant biological activity. Because of the significance of thromboxane A_2, quantification of its synthesis under various conditions has potentially important biological applications, however, owing to its lability measurement of the metabolite thromboxane B_2 is necessary to reflect the quantity of thromboxane A_2 formed[22,24].

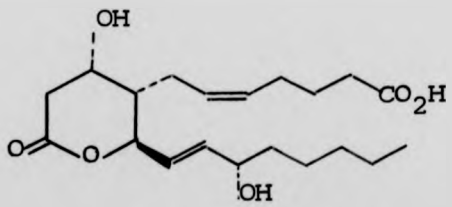
As well as standard physical analytical techniques such as thin layer chromatography several important biological assay methods for thromboxane B_2 have been developed. Fitzpatrick et al.[79,80] have reported both electron capture gas chromatographic detection of thromboxane B_2 and oxime derivatives of thromboxane B_2 as well as HPLC detection of the oxime derivatives. Morita et al.[81] report the characterization of thromboxane B_2 by combined gas chromatography and chemical-ionization mass spectrometry.

Examples of typical biological methods reported are based on radioimmuno assays of the derived mono-O-methyl-thromboxane B_2[82] or thromboxane B_2-^{125}I-tyramide[83]. Another common biological assay for the thromboxanes is to use isolated rabbit aorta and observe the induced contraction/relaxations on administering the assay material.

However, this approach of monitoring a primary, apparently stable, metabolite proved unreliable when applied to a study of primary prostaglandins. Instead a more reliable index proved to be the measurement of the circulating and urinary prostaglandin metabolites. It seemed likely that a similar approach would be required for the monitoring of thromboxane B_2 levels and Roberts et al.[84] proceeded on this basis to identify several urinary metabolites of thromboxane B_2 in the monkey. The major metabolic pathway was shown to be through β-oxidation to dinor thromboxane B_2 (142). The second most abundant metabolite being obtained by dehydrogenation of the alcohol group at C-11 to yield the δ-lactone 11-dehydro-thromboxane B_2 (143).



(142)



(143)

Considerable work remains to be done but once the complete picture of thromboxane B_2 metabolites has been formed it will be possible to assess accurately the

thromboxane A_2 levels induced by various stimuli by monitoring and quantifying these metabolites.

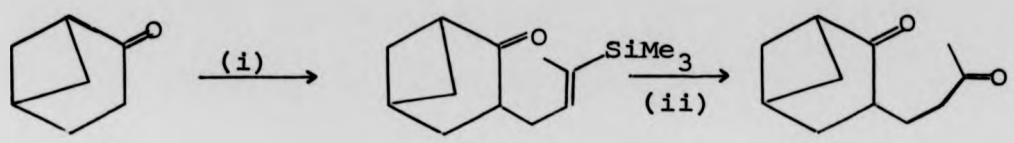
F) Thromboxane A_2 Analogues

The instability of thromboxane A_2 has inhibited its clinical investigation, the structure having been assigned on the indirect evidence of trapping experiments, the use of labelled precursors and the knowledge of its breakdown to the stable thromboxane B_2. Because of these difficulties the study of the synthesis and biological action of stable structural relatives is desirable.

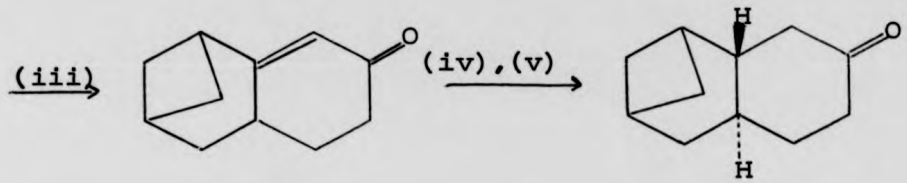
The most realistic analogues are those which are closest structurally but also stable, i.e., those in which one or both of the oxygens in the bicyclic structure is replaced by another atom. Reports of the preparation of analogues have been slow to appear largely because the structures involved are unusual and difficult to synthesise. A number have now been reported and in every case an oxygen atom has been replaced by a carbon grouping to give the carbocyclic thromboxane A_2 (CTA_2) analogue increased stability.

The first analogues reported had both the oxygen atoms in the bicyclic structure replaced by methylene groups. Ohuchida et al.[85] reported the preparation of dl-(9,11), (11,12)-dideoxa-(9,11),(11,12)-dimethylene thromboxane A_2 (144) from the bicyclic ketone (145). (Scheme 23).

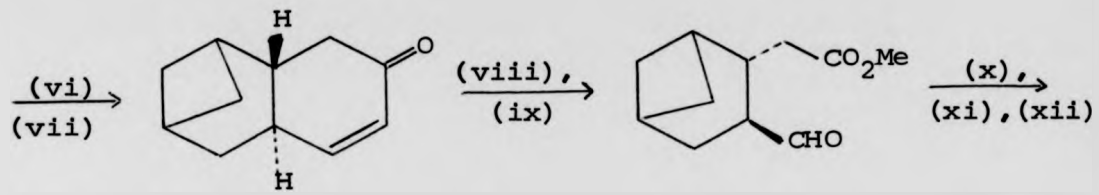
The bicyclic ketone (145), obtained in ca. 28% yield from ethyl p-hydroxybenzoate in seven steps by a literature method, underwent alkylation, epoxidation and acid treatment to yield the diketone (147) in ca. 42% yield. Cyclisation, reduction and oxidation gave the trans-fused ring system (149)



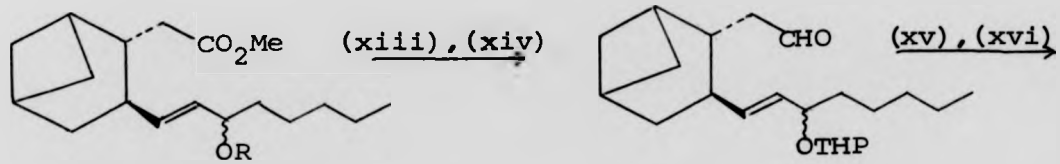
(145) (146) (147)



(148) (149)

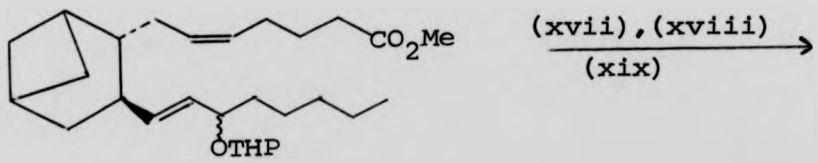


(150) (151)

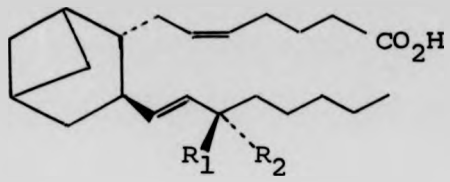


(152) R=H
(153) R=THP

(154)



(155)



(156) R_1=OH, R_2=H
(144) R_1=H, R_2=OH

(i) lithium diisopropylamide(2eq.), (E)-trimethyl-(3-iodo-1-propenyl)-silane, HMPA(1.leq.); (ii) m-CPBA, CH_2Cl_2; formic acid CH_2Cl_2; (iii) 10% aq.KOH, MeOH; (iv) Li, liq NH_3, t-butanol; (v) Jones oxidation; (vi) 2-carboxyethyltriphenyl phosphonium perbromide, THF; (vii) LiBr, Li_2CO_3, DMF; (viii) OsO_4, py, aq.$NaHSO_3$; (ix) $Pb(OAc)_4$, MeOH, benzene; (x) n-Bu_3P=CHC(O)$(CH_2)_4CH_3$, Et_2O; (xi) $NaBH_4$, MeOH; (xii) THP; (xiii) DIBAL; (xiv) SO_3, py, $(CH_3CH_2)_3N$, DMSO; (xv) $Ph_3P(CH_2)_4CO_2H$, $CH_3SOCH_2^-$ Na^+, DMSO; (xvi) CH_2N_2; (xvii) acid; (xviii) chromatography; (xix) 5%aq.KOH, MeOH.

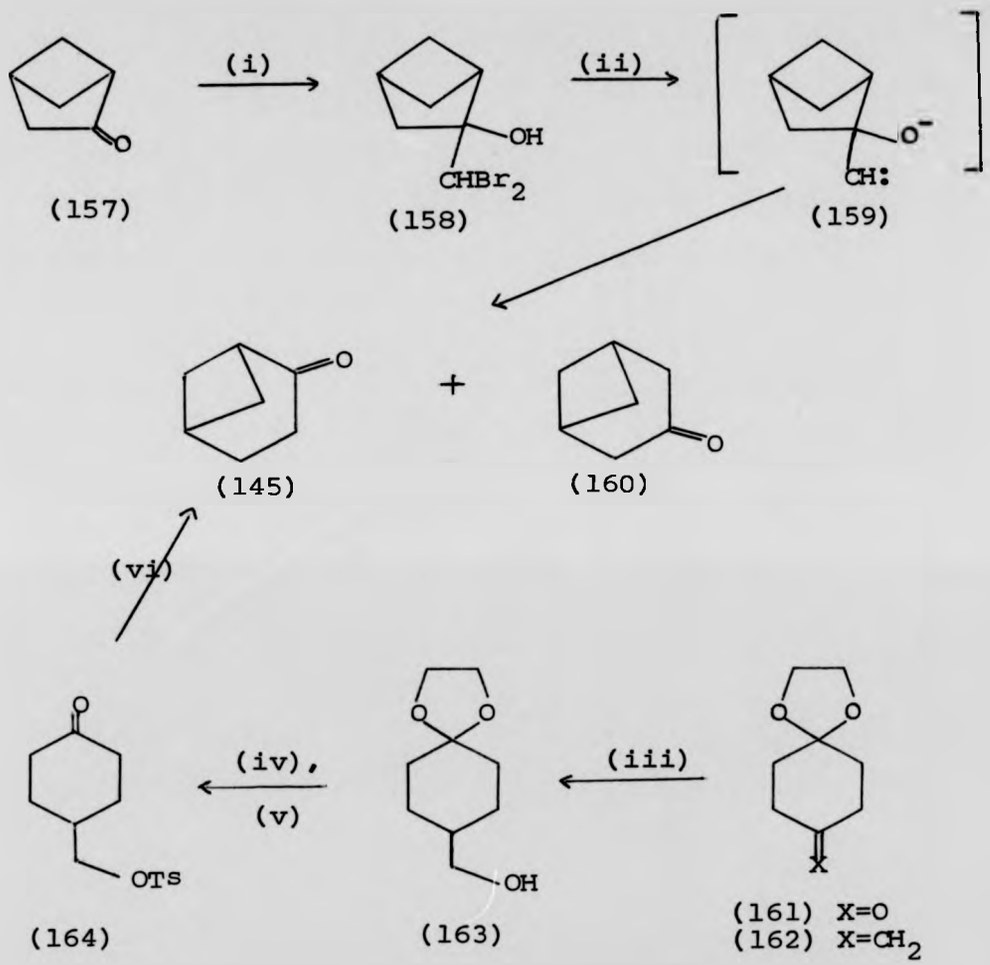
Scheme 23

which was converted to the enone system (150) by bromination/dehydrobromination [ca. 10% from (145)]. Oxidation of the olefin with osmium tetroxide followed by oxidative cleavage yielded the key ester aldehyde (151) system which only required the addition of the α- and ω-chains. This was done in a standard manner and, after removal of the various protecting groups and a chromatographic separation of the C-15 epimers, the desired acid (144) and the C-15 epimer (156) were both obtained in ca. 1% yield from ketone (145).

The main problem in this synthesis was the very low yield of starting ketone (145) obtained using the literature method. The other main drawback may well be the length of the synthesis.

Nicolaou et al.[86] also selected bicyclo[3.1.1]heptan-2-one, (145) as their starting material. They decided

that the literature preparations of this material were unsatisfactory and thus developed two alternative routes, both short and relatively high yielding. (Scheme 24.)



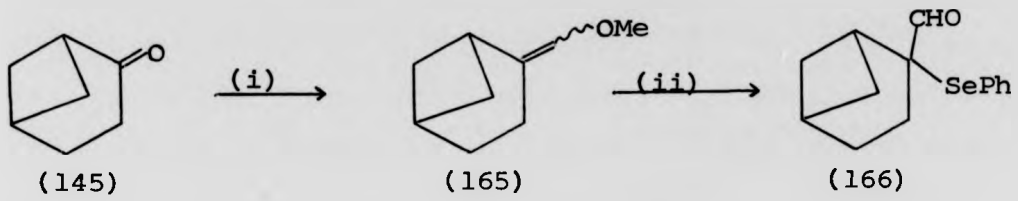
(i) LDA, CH_2Br_2, THF; (ii) n-BuLi, Et_2O; (iii) diisoamylborane, NaOH, H_2O_2; (iv) TsCl, py; (v) AcOH, THF, H_2O (2:1:1); (vi) KH, Me_2SO.

Scheme 24

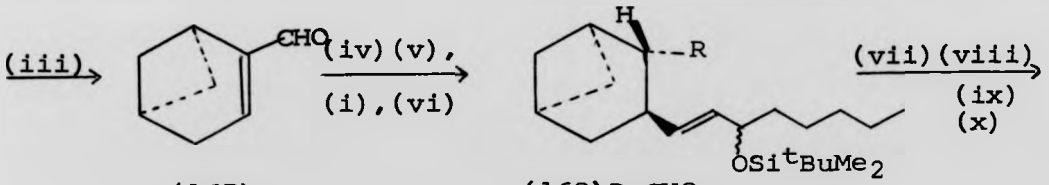
In the first approach bicyclo [2.1.1] hexan-2-one (157) was ring-expanded *via* intermediate (158). Treatment of the dibromoalcohol (158) with n-butyllithium generated the

β-oxidocarbenoid (159) which underwent rearrangement to the ketone (145) and its regioisomer (160) [75% total yield with (145) predominating ca.6:1], which were separable chromatographically. A slightly longer but more selective route was developed starting with 1,4-cyclohexanedione and proceeding via intermediates (161)-(164) to yield only the ketone (145) in ca. 47% yield.

This ketone (145) was then converted to the carbocyclic thromboxane A_2 (144) as shown in Scheme 25.

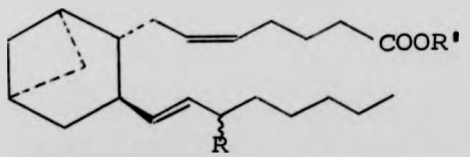


(145) (165) (166)



(167)

(168) R=CHO
(169) R=CH=CHOMe
(170) R=CH_2CHO



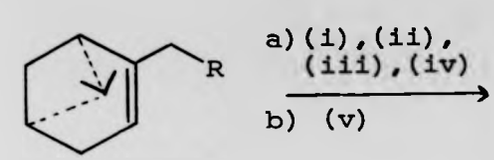
(171) R=OSi^{t}BuMe$_2$; R'=CH_3
(172) R=α-OH; R'=CH_3
(173) R=β-OH; R'=CH_3
(144) R=α-OH; R'=H
(156) R=β-OH; R'=H

(i) PPh_3=CHOMe, THF, toluene; (ii) PhSeCl, CH_2Cl_2, toluene; (iii) m-CPBA, CH_2Cl_2, diisopropylamine; (iv) (±)-trans-1-lithio-1-octen-3-ol tert-butyldimethylsilyl ether, 1-pentynylcopper hexamethylphosphoric triamide; (v) K_2CO_3; (vi) $Hg(OAc)_2$, KI, THF(aq); (vii) K salt of 4-carboxybutylidenetriphenylphosphorane, Me_2SO; (viii) CH_2N_2; (ix) AcOH, THF, H_2O (3:2:2); (x) THF, LiOH, H_2O.

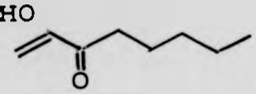
Scheme 25

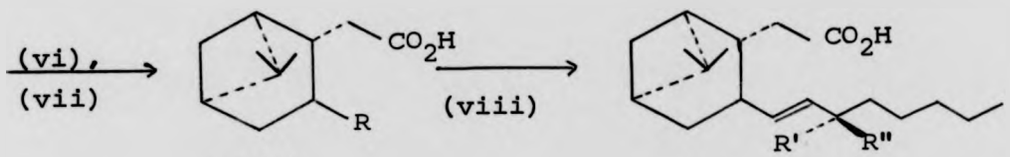
Treatment of (145) with methoxymethylenetriphenylphosphorane afforded the enol ether (165) which was converted to the α,β-unsaturated aldehyde (167) in 56% yield from (145). The lower side chain was then introduced by 1,4-addition of a cuprate reagent to give the trans-aldehyde (168) as the major product of this reaction and was obtained exclusively as the thermodynamically more stable isomer (mixture of C-15 epimers) after exposure to potassium carbonate [31% from (145)]. The upper side chain was completed by inserting a methylene group between the aldehyde group and the ring then reacting this aldehyde with the appropriate Wittig reagent. After diazomethane treatment this yielded the methyl ester (171) as a mixture of diastereoisomers at C-15 in ca. 19% yield from (145). After removal of the silyl ether the two diastereoisomers (172) and (173) were separated chromatographically then the esters cleaved to yield the acid (144) and the C-15 epimer (150) in ca. 17% yield. Optically active (+)-CTA_2 and (-)-CTA_2 were prepared by using an optically active cuprate reagent when elaborating the lower chain.

Ansell et al[87] have reported the synthesis of the stable analogue (174), and the C-15 epimer (175), starting from the commercially available pinene derivative 2-[(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl] ethanol (176). (Scheme 26). Hydroboration with 9-BBN of the THP ether (177) followed by carbonylation, reduction and treatment with hydrogen peroxide afforded aldehyde (178) as the only isolable product. Wittig-Horner reaction of (178) gave the enone (179) which on hydrolysis and oxidation afforded the carboxylic acid (180). Reduction of (180) gave the diastereoisomeric alcohols (181) and (182) which



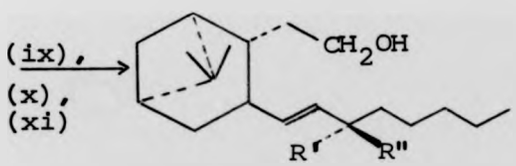
(176) R=CH_2OH
(177) R=CH_2OTHP

(178) R=CHO
(179) R= 



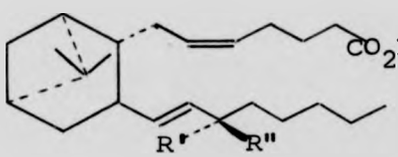
(180)

(181) R'=OH, R" =H
(182) R'=H, R"=OH



(183) R'=OTHP, R' =H
(184) R'=H, R" =OTHP

(xii)
(xiii)
(xiv)



(174) R'=OH, R" =H
(175) R'=H, R" =OH

(i) 9-BBN; (ii) CO; (iii) lithium aluminium tri-t-butoxyhydride; (iv) H_2O_2; (v) dimethyl(2-oxoheptyl)phosphonate; (vi) AcOH, H_2O, THF (6:4:1); (vii) chromium trioxide, conc. sulphuric acid, DMF; (viii) lithium tri-s-butylborohydride, THF; (ix) CH_2N_2; (x) THP ether formation; (xi) $LiAlH_4$; (xii) pyridinium chlorochromate; (xiii) (4-carboxybutyl) triphenylphosphonium bromide, KOt-Bu, THF; (xiv) AcOH, H_2O, THF.

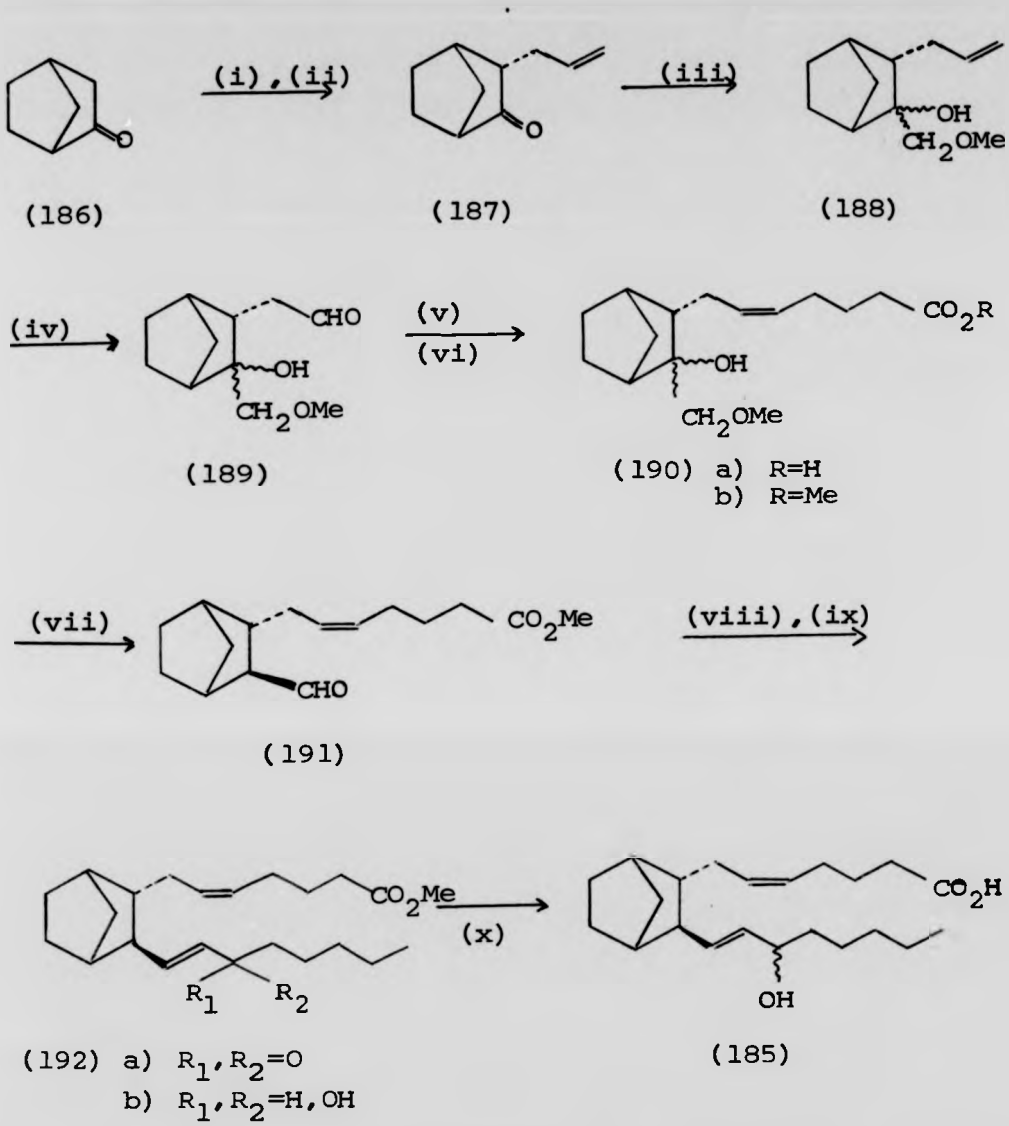
Scheme 26

were separated by chromatography on silica gel.

Each of the diastereoisomers (181) and (182) were converted into the primary alcohols (183) and (184) and subsequently oxidised to the corresponding aldehydes which, on the reaction with the appropriate phosphorane and cleavage of the THP ether, gave the thromboxane analogues (174) and (175).

A fourth approach to an analogue in which both oxygen atoms in the bicyclic system are replaced by carbon was reported by Barraclough[88]. Analogue (±)-(185) was prepared by a simple route starting with the alkylation of (±)-norcamphor (186) to yield exo-3-allylnorcamphor (187). (Scheme 27). Reaction of ketone (187) with a Grignard reagent gave the mixed epimeric alcohols (188) which, after oxidative cleavage, afforded the aldehydes (189). Subsequent reaction with the appropriate Wittig reagent yielded the acid (190a) which was esterified, purified by column chromatography and the masked aldehyde deprotected to yield the endo-aldehyde (191) in ca. 22% yield from ketone (186). Aldehyde (191) underwent a Wittig-Horner reaction with the sodio derivative of diethyl 2-oxoheptylphosphonate and the resulting enone (192a), on reduction with sodium borohydride, afforded a mixture of epimeric alcohols (192b) which were distinguishable by thin layer chromatography. Hydrolysis of the ester yielded the target analogue (185) and the C-15 epimer which were separable by preparative HPLC. This method has been applied successfully to the elaboration of other bicyclic ketones to give stable thromboxane A_2 analogues.

In order to make an analogue as structurally close as possible but also stable it would be desirable to replace only one of the oxygen atoms in the bicyclic system. This



(186) (187) (188)

(189)

(190) a) R=H
b) R=Me

(191)

(192) a) R_1, R_2=O
b) R_1, R_2=H,OH

(185)

(i) LDA, THF; (ii) $BrCH_2CH=CH_2$; (iii) $MeOCH_2MgBr$; (iv) OsO_4, $NaIO_4$; (v) $Ph_3P=CH(CH_2)_3CO_2$ Na, DMSO; (vi) CH_2N_2; (vii) formic acid; (viii) sodium 2-oxoheptylphosphonate; (ix) $NaBH_4$; (x) KOH, H_2O, MeOH.

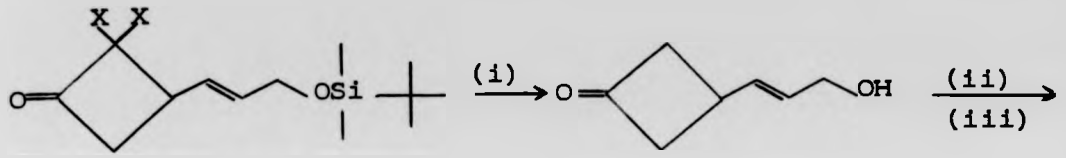
Scheme 27

gives rise to two possible compounds, the synthesis of which have been described in separate papers.

The synthesis of the thromboxane A_2 analogue (193) has been described by Corey *et al.*[89]. (Scheme 28.) *trans*-2,4-

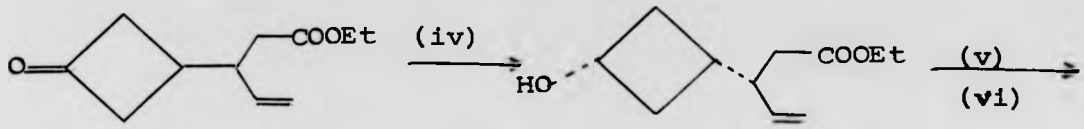
Pentadien-1-ol was converted to the t-butyldimethylsilyl ether which, on subsequent reaction with dichloroketene, yielded the cyclobutanone (194) which was dechlorinated to the cyclobutanone (195). Following desilylation, heating of (196) with triethylorthoacetate and propionic acid gave the Claisen rearrangement product (197) and subsequently the cis-alcohol (198) stereospecifically. Cyclisation of (199) to the oxabicyclo [3.1.1] heptane system was difficult but was achieved using benzene as solvent and mercuric trifluoroacetate followed by treatment with iodine to yield compound (199). Reaction of this iodide (199) with sodium azide afforded the azido ester (200) in ca. 10% yield from ketone (194). It was possible to convert the azide (200) to aldehyde (201) in one step, the latter immediately being submitted to a Wittig reaction to yield the enone ester (202). Standard elaboration of this compound (202) finally produced a mixture of C-15 diastereomeric acids (193 and 204) which were readily separated by chromatography to leave the desired thromboxane A_2 analogue (193).

The preparation of the other analogue (195) where only one oxygen atom has been replaced was reported by Maxey and Bundy[90] starting from the PGA_2 methyl ester 15-t-butyldimethylsilyl ether (206) (Scheme 29). This was converted to the TMS-cyanohydrin (207), reduced to the diol (208), and subsequently ring expanded to yield the β,γ-unsaturated ketone (209). Conversion of (209) into the conjugated isomer (210) followed by oxidation and esterification provided key intermediate (210) in ca. 6% yield from (206). Epoxidation of enone (210) afforded a mixture of α,β-epoxyketones (211) which, after careful chromatographic separation, were reduced to the corresponding β-hydroxyketone



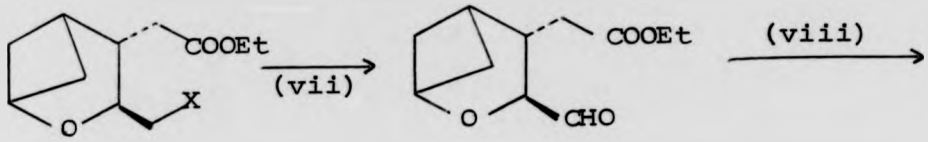
(194) X=Cl
(195) X=H

(196)



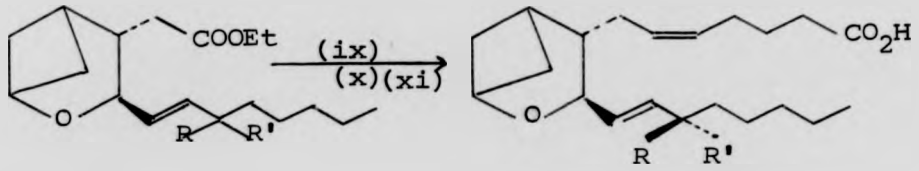
(197)

(198)



(199) X=I
(200) X=N_3

(201)

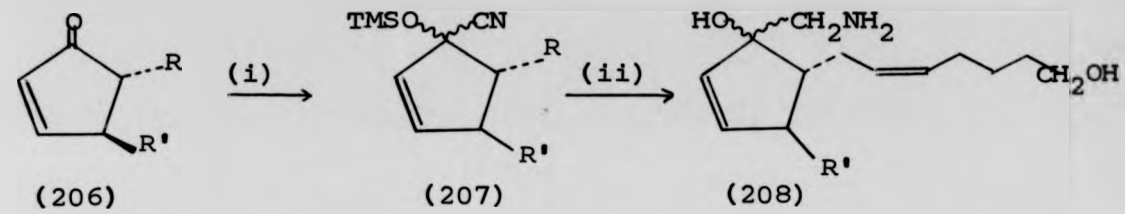


(202) R,R'=O
(203) R,R'=H,OH

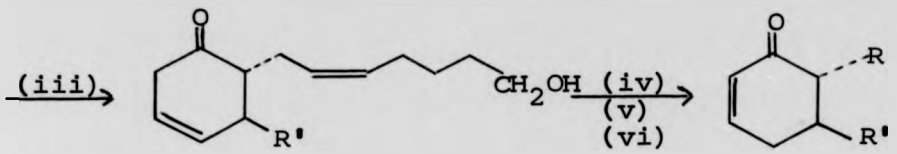
(193) R=H, R'=OH
(204) R=OH, R'=H

(i)MeOH,Dowex 50W-X8; (ii)heat,triethylorthoacetate, propionic acid; (iii)H_3O^+; (iv)$NaBH_4$,EtOH; (v)benzene, mercuric trifluoroacetate,I_2; (vi)sodium azide,THF; (vii)methyl fluorosulphonate; (viii)Na^+.dimethyl 2-oxoheptyl-phosphonate; (ix)$ZnBH_4$,dimethoxyethane; (x) DIBAL; (xi)ylide from 5-triphenylphosphoniopentanoic acid,DMSO.

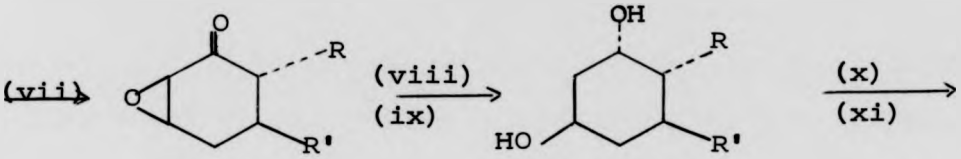
Scheme 28



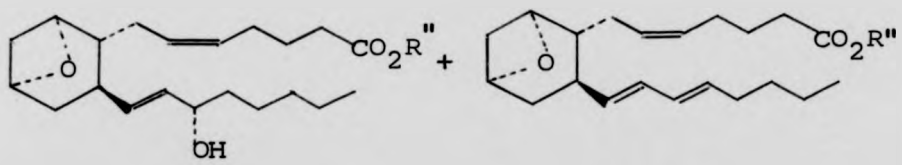
(206) (207) (208)



(209) (210)

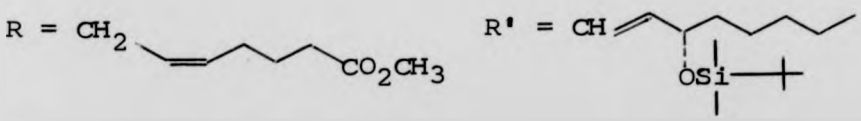


(211) (212)



(213) R"=CH_3
(205) R"=H

(214) R"=CH_3
(215) R"=H



(i) trimethylsilyl cyanide, $CHCl_3$, neopentyl alcohol, KCN, 18-crown-6 ether; (ii) $LiAlH_4$; (iii) nitrous acid; (iv) THF, basic alumina; (v) Jones oxidation; (vi) CH_2N_2; (vii) alkaline H_2O_2; (viii) aluminium amalgam; (ix) L-selectride; (x) trifluoromethanesulphonic anhydride, CH_2Cl_2; (xi) LiOH, THF, H_2O.

Scheme 29

and subsequent reduction of either β-hydroxyketone with L-selectride produced the diol (212). [Use of $AlBH_4$ in the

reduction gave a 1:1 mixture of diols (epimeric at C-9) .]

Numerous attempts to form the desired 9α,11α-oxetane by converting the more accessible C-11 hydroxyl of diol (212) to a leaving group, followed by internal displacement were unsuccessful. However, addition of trifluoromethane sulphonic anhydride afforded, after careful work-up, the desired oxetane (213) (25%) accompanied by 20-30% of the 13,15-diene (214). Hydrolysis afforded the desired oxetane acid (205), 11a-carbathromboxane A_2.

Biological evaluation of all these analogues is still at an early stage but initial results demonstrated activity as thromboxane A_2 antagonists, inhibition of the biosynthesis of thromboxanes without compromising PGI_2 production, irreversible platelet aggregation and biological activity "which could not have been predicted".

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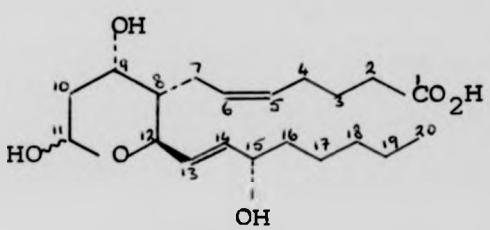
Chapter 2

DISCUSSION

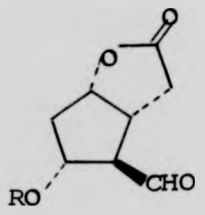
SECTION A

When designing the synthesis of thromboxane B_2 (1) two important points were recognised. First, for any synthesis of thromboxane B_2 to be of general utility it is essential that it should also be adaptable for the preparation of analogues. The preparation of such analogues is essential to facilitate the detailed study of the physiological activity of thromboxane B_2 *in vivo* and to aid the development of any potential pharmacological applications that may be identified. In common with prostaglandin chemistry the best way to achieve this is to identify a versatile precursor which is suitably functionalized such that, not only can thromboxane B_2 be readily prepared, but a wide range of analogues can also be elaborated, principally incorporating modifications to the two chains.

Secondly, thromboxane B_2 possesses three chiral centres, the stereochemistry of which must be controlled in any potentially useful synthesis. The stereochemical features of the two side chains, *i.e.* the α-hydroxyl group at C-15 and the two olefinic bonds, have been ignored since standard techniques have been developed for elaborating these side chains in previous prostaglandin synthesis[1].



(1)

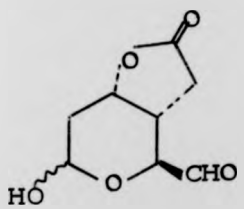


(2)

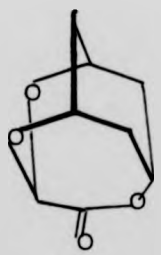
(R=Ac, $CO_2C_6H_4Ph$, THP, COPh.)

Because of the similarities between thromboxane B_2 and the prostaglandins in general the simplest method of preparing thromboxane B_2 appeared to be to adopt the techniques developed for prostaglandin synthesis. Perhaps the most widely used prostaglandin precursor is the "Corey Aldehyde" (2) which has been used in numerous syntheses and enables the preparation of most of the natural prostaglandins. Because of the proven success of this intermediate it was decided to aim for an analogous precursor when preparing thromboxane B_2, *viz* the bicyclic aldehyde (3).

This compound possesses the central pyran ring and the chiral centres which will become C-8, C-9, and C-12 in thromboxane B_2 are all in the correct configuration. Further elaboration of this intermediate should be possible using the standard conditions developed for prostaglandin syntheses. [Since this work was instigated a number of syntheses of thromboxane B_2 have been published and the majority of these also use compound (3), or a close analogue, as the key precursor to thromboxane B_2; see Introduction.]



(3)

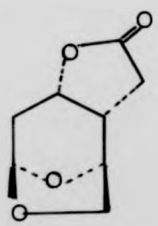


(4)

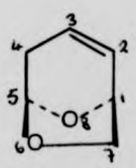
Recently a new approach has come to be adopted for designing the synthesis of complex natural products. This is the use of a "retro-synthetic" analysis as described by

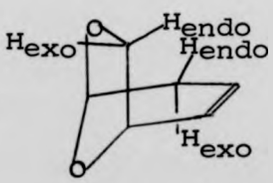
Corey et al.[2], where the effect of cleaving, or forming, various bonds in the target molecule is assessed in an attempt to extrapolate back to a feasible starting material. This approach has featured in all the various synthetic routes considered in this work.

One factor borne in mind when considering these retrosynthetic approaches was the success achieved when polycyclic intermediates have been used to "lock" a molecule in a certain conformation hence giving greater control of the stereochemistry at the various chiral centres. For example Woodward et al.[3] utilized the tricyclic lactone (4) in a stereospecific synthesis of the Corey Aldehyde in its lactol form. When this approach was applied to considering a possible precursor to the aldehyde (3) the most promising compound was the tricyclic lactone (5A), which should undergo facile cleavage of the acetal grouping to regenerate the primary alcohol function which could then be oxidised to the aldehyde (3). Preparation of compound (5A) in optically active form would satisfy both the criteria set down initially, viz facile preparation of analogues and all the chiral centres 'locked' in the required configuration.



(5A)





(6)

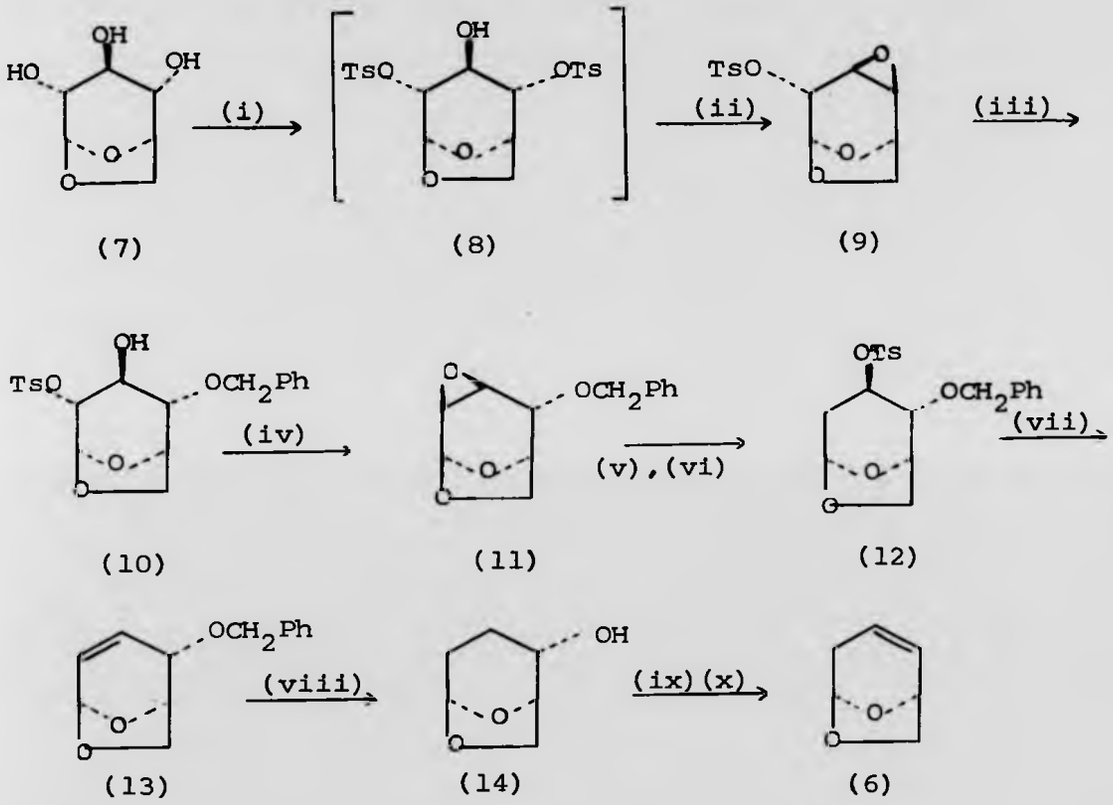
Retrosynthetically, the next step was considered to be 'loss' of the γ-lactone ring in compound (5A) giving 6,8-dioxabicyclo [3.2.1] oct-2-ene (6). It was envisaged that the lactone ring might be elaborated onto (6) by either

dichloroketene addition and subsequent modifications or else directly by radical addition of acetic acid. A study of models suggested that if compound (6) were to be isolated with the configuration shown then stereochemical interactions between the 2-membered bridge and any incoming reagent would affect the stereochemistry of the lactone formation. It was predicted that the lactone ring would form trans to the two membered bridge, i.e. in the required α-configuration, thus generating the chiral centres to become C-8 and C-9 in thromboxane in the correct configurations. Consequently 6,8-dioxabicyclo [3.2.1] oct-2-ene (6) was identified as the primary synthetic target.

The olefin (6) can also be regarded as an anhydrosugar*, a class of compounds about which an abundant literature exists[4]. There is currently a growing interest in using sugars as starting materials for the synthesis of optically active natural products, e.g. the previously described synthesis of thromboxane B_2 (see Introduction), because: a) they contain a number of chiral centres in suitably functionalized forms, b) they are generally cheap and readily obtainable, and c) there is a considerable background literature on the various transformations that are possible.

*It is worth noting that authors in sugar chemistry do not refer to olefin (6) by the IUPAC nomenclature or numbering system used here. Instead it is called 1,6-anhydro-2,3,4-trideoxy-β-D-glycero-hex-2-enopyranose and the numbering system is as shown below.

When compound (6) was considered in this manner it was possible to devise a paper synthesis based on reactions reported by Černý *et al.*[5-8] and this is illustrated in Scheme 1 where 1,6-anhydro-β-D-glucopyranose (laevoglucosan) (7) is used as the chiral source.



(i) TsCl, py; (ii) NaOMe; (iii) $PhCH_2OH, H^+$; (iv) NaOMe; (v) $LiAlH_4$; (vi) TsCl, py; (vii) KO*t*-Bu; (viii) H_2, HOAc, Pd/C ; (ix) TsCl, py; (x) KO*t*-Bu.

Scheme 1

Even if reproducible exactly as reported this method would be too long and would produce olefin (6) in too low a yield to be practicable. Consequently, initial work was based on a reported short synthesis of the olefin (6)[9,10] in racemic form to provide preliminary samples rapidly for

study. This work is discussed in Section B.

The subsequent elaboration of this olefin (6) to the tricyclic lactone system (5) by either reaction with dichloroketene and subsequent elaboration or else by radical addition of acetic acid is discussed in Section C. Having obtained the tricyclic lactone the internal acetal would be equilibrated in acidic methanol solution[11] to open the [3.2.1] system. Subsequent oxidation of the primary alcohol would yield the bicyclic aldehydic lactone system (3), where the alcohol grouping has been substituted for a methoxy group, which has recently been shown[12] to be a precursor to thromboxane B_2.

An alternative approach which would result in the preparation of optically active olefin (6) was arrived at by continuing the retro-synthetic analysis on compound (6). This suggested that the sugar d-mannitol (15) was a suitable source of optically active material and the subsequent reaction scheme using this compound and acrolein is discussed in Section D.

Initial work has also been started on a number of other potential routes and these are briefly described in Section E to give some indication of possible future extensions of this work.

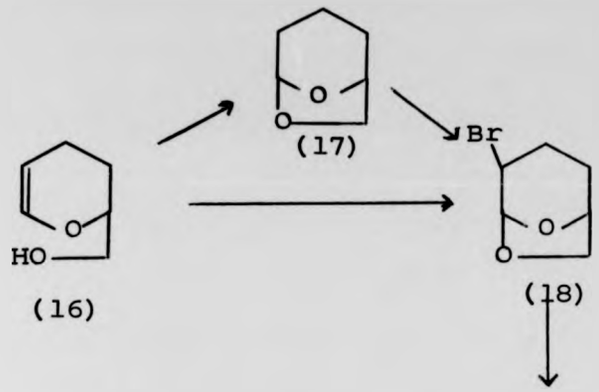
SECTION B

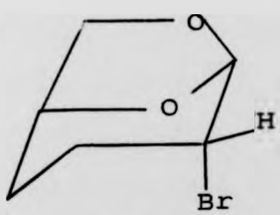
Synthesis of Racemic 6,8-dioxabicyclo [3.2.1] oct-2-ene (6)

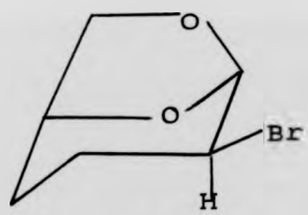
A short, direct synthesis of olefin (6) has been reported by Murray, Williams, and Brown[9] and Sweet, and Brown[10]. Since full experimental details had apparently been reported it was intended to use this method to prepare sufficient amounts of the racemic olefin, simply and rapidly, to facilitate study of the lactone elaboration step. In the event the reported conditions proved virtually impossible to reproduce and a large number of modifications were attempted.

The reported sequence of reactions was quite brief and is illustrated in Scheme 2. Initially, it was intended to prepare 2-(hydroxymethyl)-3,4-dihydro-2H-pyran (16) by the dimerisation of acrolein followed by sodium borohydride reduction of the product[13]. The Diels-Alder dimerisation was attempted but no discrete product was obtained due to extensive polymerisation, this being caused mainly by the faulty design of the high pressure reaction vessel used.

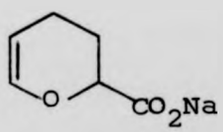
Instead, an alternative starting material was found, the commercially available sodium salt of 3,4-dihydro-2H-pyran-2-carboxylic acid (20). Initially, attempts to reduce this salt directly to the required alcohol (16) using lithium aluminium hydride proved unsuccessful due to the insolubility of this salt in a variety of organic solvents; even continuous extraction techniques using a soxlet extractor did not give the desired result. Consequently the salt was first acidified with dilute sulphuric acid in a biphasic aqueous/diethyl ether system[14]

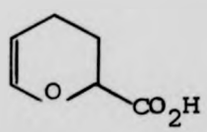


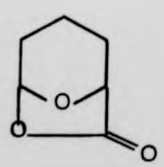




Scheme 2







to produce the unstable carboxylic acid (21). A polymer, which was retained in the aqueous layer, was also produced from this unstable acid. According to the literature

report[14] this polymer undergoes decomposition on thermolysis to produce 7-oxo-6,8-dioxabicyclo [3.2.1] octane (22), a novel lactone system[15]. Because of the tendency of the free acid (21) to polymerise on standing it was immediately reduced to the alcohol (16) using lithium aluminium hydride in diethyl ether. The alcohol, which was produced in good yield, [approximately 65% based on the sodium salt (20)] was stable for storage under refrigerated conditions.

A reexamination of the direct reduction of the sodium salt (20) to the alcohol (16) by-passing the unstable free acid (21) resulted in a simpler method and an improved yield of the alcohol. By treating a suspension of the sodium salt (20) with lithium aluminium hydride and diethyl ether at reflux temperature for ca. 16 hours the yield was improved to over 90%. This provided a simple, high-yield route to the starting alcohol (16) and avoided the troublesome, and dangerous, acrolein dimerisation.

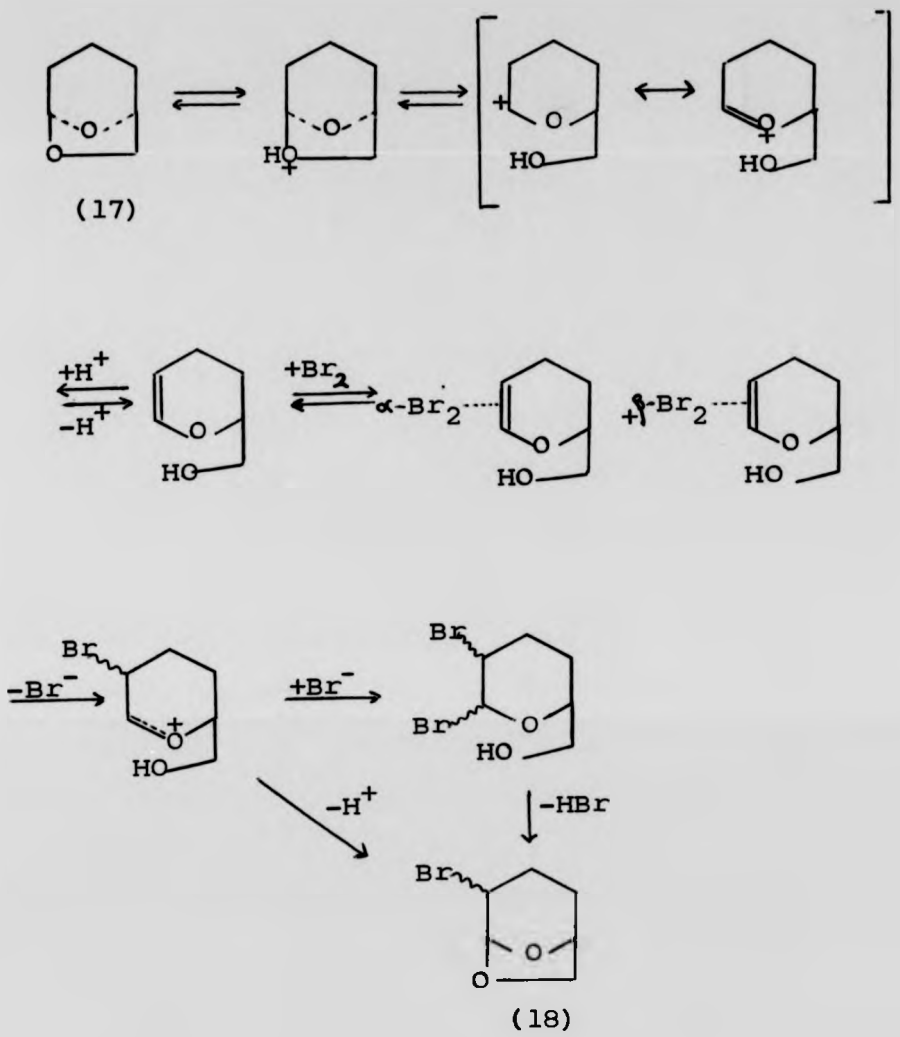
Sweet and Brown[10] prepared the olefin 6,8-dioxabicyclo-[3.2.1] oct-3-ene (19) as an intermediate for the synthesis of 1,6-anhydro-4-deoxy-β-DL-xylo-hexopyranose. First of all they heated the alcohol (16) in refluxing benzene containing a catalytic amount of p-toluenesulphonic acid to obtain the previously reported[16,17] 6,8-dioxabicyclo [3.2.1] octane (17) in a variable yield of 40 - 65%. This material was then brominated using a bromination method reported for the bromination of acyclic acetals[18] (bromine in carbon tetrachloride) to obtain apparently one product, bromide (18b), with the bromine cis with respect to the anhydro-ring.

Dehydrohalogenation of (18) with hot alcoholic potassium hydroxide was sluggish and gave in 24 hours only a 30% conversion to the olefin (19), along with much (50%)

unchanged bromide (18). A glc analysis of the starting bromide indicated only one symmetrical peak, which the authors took to be indicative of one compound. The resulting olefin was then modified further to prepare the target sugar.

This work had a number of flaws and a subsequent paper by Murray, Williams, and Brown[9] corrected a number of these. First, a minor modification to the acid-catalysed cyclisation of the alcohol (16) resulted in consistent yields of 88-94%. Secondly, they suspected that the low yield in the dehydrobromination reaction resulted from the bromine atom in the preferred chair conformation of (18) not being in a trans diaxial relationship with a vicinal hydrogen atom. Also, if the finely divided sodium carbonate buffer was not included in the bromination reaction the yields rose and infact addition of hydrogen bromide caused an increase in the reaction rate initially. When this bromide was studied on a freshly prepared glc column (20% butanediol succinate on chromosorb W) two overlapping peaks in the area ratio of 3:2 were observed and assigned as trans and cis-4-bromo-6,8-dioxabicyclo [3.2.1] octane, (18a) and (18b), respectively. These two products could not be separated by glc.

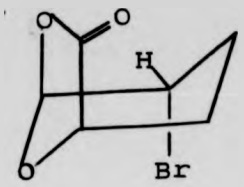
Murray, Williams, and Brown[9] also presented two mechanistic schemes which took this experimental evidence into account. The relative effectiveness of the two paths is not known but path B is reproduced in Scheme 3 since it is directly relevant to this work. Treatment of alcohol (16) under these bromination conditions was reported to yield a 1:1 mixture of (18a) and (18b) in 65% yield. As illustrated, the lack of stereochemical control in this bromocyclisation



Scheme 3

was explained by invoking the intervention of the lone pair of electrons on the oxygen of the pyran ring. These participated in opening the bromonium ion non-stereopecifically to form an intermediate oxonium ion which then underwent nucleophilic attack by the alcohol group to yield the bromide (18).

Interestingly, when the sodium salt (20) was reacted as a suspension under these bromination conditions the



(23)

bromide (23) was isolated as a white crystalline solid. This bromide was shown to have purely the axial configuration shown. (This is discussed in more detail in Section E.)

Treatment of the bromide (18) with refluxing ethanolic potassium hydroxide[9] yielded olefin (19) and some unreacted bromide which was identified by a 100 mHz nmr study to be the equatorial isomer (18b). In this stable conformation with the bromine atom equatorial there is no proton suitably orientated to aid the elimination step of loss of HBr. Also, even at the elevated temperatures used the activation energy for a ring flip to occur, thereby moving the bromine into a pseudo-axial configuration and hence lining it up for elimination, must be too great, consequently the equatorial isomer is left unreacted.

Although it was intended to cyclise the alcohol (16) directly to the bromide (18) a sample of 6,8-dioxabicyclo-[3.2.1] octane (17) was also prepared as a standard for glc study. This was necessary because experience showed this compound to be a common contaminant in the alcohol (16). This most likely occurred because of cyclisation catalysed by acidic sites on the glass walls of a flask. The cyclisation method used was as described by Murray et al.[9] A small scale reaction yielded a product with a retention time on glc (5% butanediol succinate) of 3.1

minutes which corresponded with the minor impurity peak seen in the glc trace of the alcohol (16). The alcohol had a retention time of 3.75 minutes.

The bromocyclisation of alcohol (16) was then attempted using the method of Murray et al.[9] This required dissolving the alcohol (16) in dry carbon tetrachloride and then adding a bromine/carbon tetrachloride solution dropwise with stirring. This caused the temperature to rise up to 35 or 40°C and hydrogen bromide was evolved profusely. A dark brown tarry by-product was also formed which tlc study suggested was polymeric in nature, perhaps due to some alcohol (16) which polymerised under the acidic conditions. When the solvent was removed a viscous reddish/yellow fuming oil resulted, which on distillation (ca. 65°C at 0.5mm Hg) yielded a pale yellow oil which still emitted acid fumes. This distillation caused numerous difficulties because of regular product decomposition and emission of hydrogen bromide. The purified, distilled material also appeared to decompose very rapidly. The maximum yield obtained was 49% compared with a reported yield of 65%. A glc study using an almost new 5% butanediol succinate column (153°C) showed two peaks with retention times of 17.5 and 18.5 minutes in approximately 1:1 ratio corresponding to the axial and equatorial isomers of bromide (18) respectively. The nmr spectrum of this mixture was very similar to that published[10] and showed the characteristic bridgehead protons H-1 and H-5 at approximately δ 4.5 and δ 5.5 ppm respectively.

When the reaction conditions were modified by chilling the reaction flask to 0 - 10°C during addition of the bromine solution the final yield was found to increase to

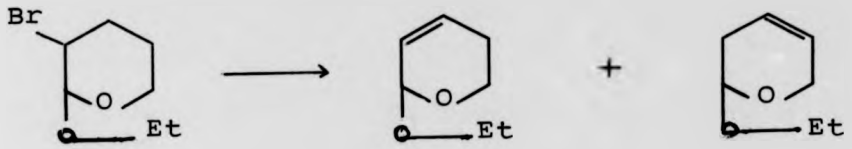
ca. 65 - 70% but no change in the axial : equatorial ratio was obtained. Since only the axial isomer appeared to undergo elimination of hydrogen bromide to yield an olefin the effective yield was only half this figure. Also, as will be discussed later, it became important to remove the unreactive bromide from the system, or to prevent or limit its formation initially.

Sweet and Brown[10] originally reported that the product from the ethanolic potassium hydroxide induced dehydrobromination of bromide (18) was 6,8-dioxabicyclo [3.2.1] - oct-3-ene (19). Detailed examination[9] on a freshly prepared glc column (5% butanediol succinate) subsequently showed two well separated peaks in the ratio of 1:9. After preparative glc, nmr analysis indicated the main product was olefin (19) and the minor product was 6,8-dioxabicyclo [3.2.1] oct-2-ene (6). The mixture of these two olefins gave an nmr spectrum identical with that previously reported[10] to be due to pure olefin (19). The proportion of the two olefins depended on the proportion of base to bromide (18) used during the dehydrohalogenation.

An isomerisation reaction of a similar type had previously been observed[19] when the base-induced dehydrohalogenation of 3-bromo-2-ethoxytetrahydropyran (24) with ethanolic potassium hydroxide was carried out at high temperature. As well as the expected[20] formation of 2-ethoxy-5,6-dihydro-2H-pyran (25), 6-ethoxy-5,6-dihydro-2H-pyran (26) was also isolated. Pure samples of (25) could also be partly converted to (26) by prolonged high temperature treatment with base.

The elimination of hydrogen bromide from the mixture of axial and equatorial bromides (18) was tried using the

reported literature conditions[9] of refluxing in ethanolic potassium hydroxide for 24 hours, followed by cooling, filtration, then removal of the bulk of the solvent by fractional distillation at room temperature. Water was then added to the residual dark mass and the mixture continuously extracted with diethyl ether. After drying, the ether extract was freed from solvent by fractional distillation and the residual black oil was distilled under reduced pressure to give the olefin (19).



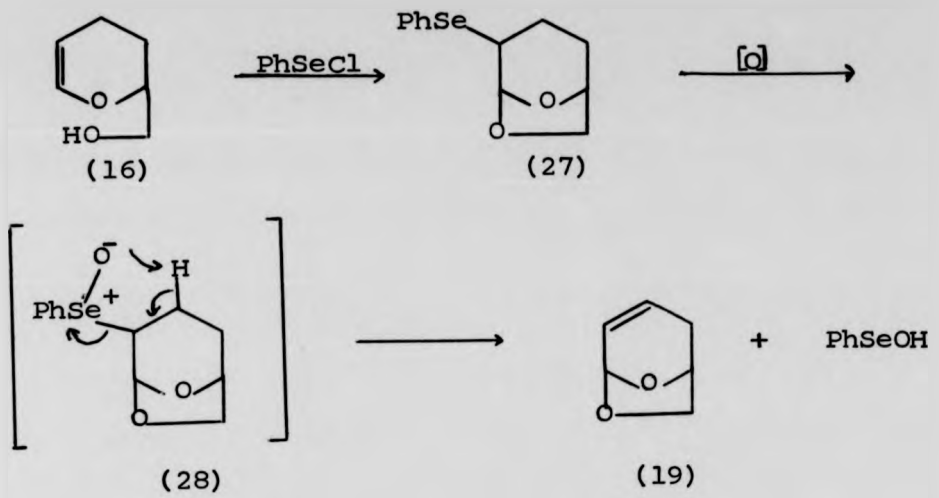
(24) (25) (26)

It proved virtually impossible to repeat these literature conditions for a number of reasons. First, during the diethyl ether continuous extraction some of the remaining ethanol was also extracted which in turn transferred considerable quantities of water to the diethyl ether extract resulting in an ethanol/water/diethyl ether mixture. Secondly, bicyclic systems such as olefin (19) are commonly quite strained and compounds, while stable at room temperature, tend to be very volatile, (c.f. bicyclo-[3.3.1] nonane, sublimes at 169-170°C; bicyclo [2.2.1] heptane, sublimes). Consequently, when the ethanol was removed from the product by fractional distillation, glc study indicated that a considerable portion of the product was also removed. Thirdly, a report by Pecka and Černý[8] confirmed the suspected water solubility of this olefin (19), and olefin (6),

by describing a steam distillation of the olefins and subsequently measuring their optical rotations in aqueous solutions. This water solubility added further to the problems of the product being partitioned between aqueous and organic phases during the reaction work-up.

Because of the experimental difficulties the samples of olefin (19) isolated were small (yields between 0-40%) and almost always contaminated with solvents, predominantly ethanol. Sufficient material was isolated, however, to allow a spectral analysis and glc study to be made. The 100 mHz nmr specturm of both the olefins (19) and (6) have been kindly supplied by Prof. M. Černý and the 60 mHz nmr spectrum of the product from the dehydrobromination reaction is in excellent agreement with that supplied by Černý of olefin (19), although a few minor resonances due to impurities were also present. The most significant features were H-1, δ=4.64(m);H-5, δ=5.48(d);H-3, δ=5.72(m);H-4, δ=5.91(m) ppm. A glc study (5% butanediol succinate) showed a single symmetrical peak with two minor impurities. One of these was suspected to be the other olefinic isomer (6) which is formed by isomerisation of olefin (19). The other impurity peak had a retention time identical with that of 6,8-dioxa-bicyclo [3.2.1] octane (17).

In an attempt to prepare a pure sample of olefin (19) an alternative method was considered. Nicolaou and Lysenko[21] described the use of phenylselenenyl chloride in the synthesis of cyclic ethers. This reagent has also been used in the successful synthesis of sensitive compounds, e.g. prostacyclin (PGI_2)[22] (see Introduction). It was decided to adopt a similar approach for this problem and the anticipated route is illustrated in Scheme 4.



Scheme 4

4-Phenylselenenyl-6,8-dioxabicyclo[3.2.1]octane (27) was formed by reacting the alcohol (16) with phenylselenenyl chloride in dichloromethane at -76°C under nitrogen. The product was purified by column chromatography on silica and was isolated as a pale yellow oil in ca.64% yield, with the last traces of unreacted phenylselenenyl chloride being very difficult to remove. The nmr spectrum showed characteristic resonances for phenyl protons, the H-1 and H-5 bridgehead protons and H-4 as a multiplet at δ=3.2ppm. It was not determined from the nmr spectrumwhether the addition of phenylselenenyl chloride proceeded stereospecifically or not.

The subsequent oxidative cleavage of the phenylselenenyl group in (27) proved more troublesome, however. One advantage of using the phenylselenenyl grouping was that the elimination of the selenoxide formed from this group to yield the olefin occurs by syn elimination. Thus,

although both possible isomers may be formed, both should also eliminate to give only 6,8-dioxabicyclo [3.2.1] oct-3-ene (19). Nicolaou et al.[22] and Sharpless et al.[23] described the use of hydrogen peroxide in tetrahydrofuran to form the selenoxide and subsequent warming to room temperature promoted the elimination reaction. However, when this method was applied to compound (27) the product was shown by chromatographic and nmr study to be a complex range of products with none predominating, although nmr and glc study indicated some of the olefin (19) was formed.

Reich[24] has described a variety of conditions for this oxidation/elimination reaction and a number of these were studied in an attempt to increase the yield of the olefin (19) and minimise the by-products. The water solubility of this olefin was also borne in mind since it was suspected this caused difficulties in the work-up of the hydrogen peroxide reaction. Both m-chloroperoxybenzoic acid in dichloromethane and a buffered biphasic hydrogen peroxide mixture (CH_2Cl_2, pyridine, water) were tried as oxidising systems but in both cases a range of products was observed as well as the required olefin.

An alternative method[24] was to use ozone as the oxidant. This was studied using standardised, ozone-saturated dichloromethane solution at -76°C to prepare the selenoxide. Monitoring the reaction by tlc indicated that the selenenyl group was wholly converted to the selenoxide form. However, when the elimination was attempted by gradually warming the flask to room temperature the main product was recovered starting material (27) with a little olefin (19) and some minor impurities.

The reaction was repeated using the same conditions to

form the selenoxide but diisopropylamine was added at -76°C after completion of the selenoxide formation. The reaction mixture was then added to refluxing carbon tetrachloride, also containing a little diisopropylamine. This amine was present to remove the phenylseleninic acid formed in the reaction since this acid catalyses the decomposition of the selenoxide to the starting phenylselenenyl compound[24]. Although this reaction gave a few by-products column chromatography (Kieselgel HF_{254}, CH_2Cl_2) and microdistillation (15mm Hg, oil bath 90°C) gave a pale yellow oil in about 70% yield. The nmr spectrum of this material corresponded very closely to that published by Černý[9] for the olefin (19).

The availability of this pure sample of olefin (19) proved by tlc and glc comparisons that the olefin (19) had been the major product in all the previous dehydrobromination reactions.

An alternative method for forming the selenoxide has also been considered. This was based on a method described by Drabowicz et al.[25] for the preparation of sulphoxides using an aqueous potassium hydrogen carbonate solution and bromine. The selenoxide (28) was prepared and isolated but proved unstable for storage. Immediate cleavage using refluxing carbon tetrachloride and diisopropylamine resulted in isolation of the olefin (19) in a yield similar to that obtained with ozone. This method is thus equally successful but much simpler to perform and may provide a method of general applicability for selenoxide formation. Unfortunately the economics of using selenium, and possible hazards if large quantities were used, ruled out its regular use as a synthetic intermediate on the scale required.

The olefin (19) formed in the dehydrobromination of the bromide (18) was 'contaminated' with small quantities of the other olefinic isomer (6) and residual equatorial bromide (18b). Since this latter olefin, 6,8-dioxa-bicyclo [3.2.1] oct-2-ene (6), is the olefin required for this synthetic sequence, conditions were sought to move the isomerisation equilibrium towards this compound. Murray, Williams, and Brown[9] reported that using proportions of sodium hydride in 1,2-dimethoxyethane to bromide (18) greater than 3:1 gave increased amounts of (6) relative to (19). Also, refluxing a 19:1 mixture of (19):(6) in potassium hydroxide/95% ethanol for 24 hours resulted in a 60% recovery of a 2:3 mixture of (19) and (6). [This experiment required a base to olefin ratio of *ca*. 7:2 to influence the position of the equilibrium in a favourable direction.]

This reaction was studied further by refluxing a sample of olefin (19) in a potassium hydroxide/ethanol mixture for several days and gradually increasing the molar ratio of base from 4:1 to 12:1. The reaction was monitored by removing aliquots and studying these by glc. [This work assumed that the minor peak in the glc attributed to olefin (6) by Murray *et al*.[9] was the correct assignment. However, once pure samples of olefin (6) were obtained this was confirmed.] No isomerisation of pure 6,8-dioxabicyclo [3.2.1] oct-3-ene (19) was observed until after 84 hours reflux with a base : olefin ratio of 8:1 when a new product, with a retention time identical with that of the minor component from the dehydrobromination reaction, was obtained. After *ca*. 156 hours the isomerisation had progressed to give a 4:1 ratio of the required olefin

(6):starting olefin (19). This dramatic change in the relative proportions of the two olefins occurred quite suddenly once sufficient potassium hydroxide had been added. This achievement of a 1:4 ratio was a considerable improvement on the reported ratio of 2:3 [olefins (19):(6)] but, unfortunately, a number of by-products were produced during this prolonged reflux. Visually, this was observed as the formation of a deep brown colour ; analytically, some unexplained peaks were observed in the glc traces.

This reaction was repeated by refluxing the olefin (19) (~0.3g) in a potassium hydroxide (9g)/95% ethanol,water mixture for 48 hours. Glc study then indicated that the isomerisation was almost complete so saturated brine was added and the mixture extracted with diethyl ether. Removal of the solvent by careful distillation left a brown oil contaminated with ethanol. Two distillations (~15mm Hg, oven temperature 100°C) gave a colourless liquid (0.16g, 53% yield) which glc study showed to be predominately the isomerised olefin (6) contaminated with a little olefin (19), 6,8-dioxabicyclo [3.2.1] octane (17) and solvent. The nmr spectrum of the main olefinic product was in good agreement with that supplied by Černý[8] for olefin (6).

This appeared to provide a potentially useful method for preparing olefin (6) in reasonable yields, however, this reaction proved to be very inconsistent. On some occasions the olefin was obtained in low yields quite highly contaminated with impurities while on other occasions no olefin was isolated, 6,8-dioxabicyclo [3.2.1] octane (17) being the only isolable product. In the latter cases the olefin (6) was shown by glc to be present during the isomerisation but no trace was found after the reaction

work-up. This may have been due to a combination of the volatility and water solubility of the olefin.

In an attempt to abbreviate the route from bromide (18), once the dehydrobromination was complete more sodium hydroxide was added to the mixture and the isomerisation attempted. Although isomerisation was seen to be occurring from glc study, unlike the above experiments where pure olefin (19) was used as starting material, the purification of the product olefin (6) was made even more difficult by the presence of the equatorial bromide isomer which survived the elimination step. Also, more unidentified by-products were produced and it proved virtually impossible to isolate the olefin (6) from the product mixture.

In an attempt to increase the activity of the potassium hydroxide some 18-crown-6 ether was added[26]. It was hoped this would cut down any ion-pair formation and decrease the isomerisation time and consequently decrease the level of by-products. In the dehydrobromination reaction a slightly higher than normal amount of olefin (6) was formed but little difference was observed in the levels of impurities formed during the isomerisation stage, although the reaction did proceed more rapidly.

Although this method could produce the required olefin (6) the yields were very variable and low and the purification of the product time consuming and inefficient. Since the original aim was to develop a simple, high yield, low cost synthesis an alternative series of reactions was sought for the dehydrobromination/isomerisation stage.

Murray *et al.*[9] also reported the use of potassium *tert*-butoxide in *tert*-butanol to carry out the dehydrobromination

of bromide (18). This base system appeared to have the advantage that isomerisation of olefin (19) to olefin (6) was also promoted using the same conditions and very little of the unisomerised olefin (19) was isolated, the olefin (6) being the main product. [36% yield of a 4:96 mixture of (19):(6).] The method required[9] reacting the bromide (18) with a 3 molar equivalent of potassium tert-butoxide in tert-butanol at 80°C for 24 hours. Half the solvent was then removed by fractional distillation, the residue diluted with water then continuously extracted with diethyl ether. This ether extract yielded a crude product which, on distillation, gave the two olefins in the ratio above. This reaction has also been utilized by Černý et al.[8] in a general preparation of the olefin (6) for synthetic studies. Unfortunately this reaction proved considerably more difficult than the literature reports suggested and presented a number of problems.

Initial studies followed the method of Murray et al.[9] where glc monitoring of reaction aliquots showed quite clearly that the axial bromide (18a) reacted quite rapidly,with the olefin (19) being formed. The reported reaction time of 24 hours appeared insufficient for the isomerisation to proceed significantly, however, and refluxing for 48 hours was required before glc study of aliquots indicated a predominance of olefin (6). Removal of the tert-butanol by distillation proved inefficient since glc study showed quantities of the olefins were lost in the distillate. It also proved very difficult to remove all the solvent from the product since some tert-butanol was carried into the diethyl ether extract of the quenched reaction mixture. This reaction also produced

a large number of by-products. Thus the yields were much lower than anticipated due to losses in the various distillates and the product olefin was contaminated, even after distillation, with solvent, 6,8-dioxabicyclo [3.2.1] oct-3-ene (19), 6,8-dioxabicyclo [3.2.1] octane (17), the unreacted equatorial bromide isomer (18b) and various unidentified by-products. The ratio of olefin (6) : olefin (19) by glc was *ca.* 4:1, the unisomerised olefin (19) being identified by coinjection with an authentic sample. The retention time of olefin (6) corresponded exactly with the material prepared *via* the potassium hydroxide/ethanol isomerisation.

The dehydrobromination reaction and isomerisation reaction both appeared to be proceeding as reported, the main problems appeared to be connected with the isolation of the pure olefin. It was decided to incorporate the work-up described by Pecka and Černý[68] where the reaction mixture was quenched with water, the *tert*-butanol removed by distillation using a Vigreux column, then the product was removed from the residue by steam distillation and subsequently extracted from the aqueous layer with dichloromethane.

This modification appeared to have some success in that careful glc monitoring of both the *tert*-butanol and dichloromethane removed by distillation indicated only small quantities of the olefins were lost in these distillates. The steam distillate was cloudy, had a characteristic odour, and yellow oil droplets were present. It was possible to extract the product quite efficiently from the aqueous layer when there was no competing solvent

such as tert-butanol. Unfortunately, although this modification led to a cleaner and simpler reaction work-up the final product was still contaminated with equatorial bromide (18b), olefin (19), and the bicyclic saturated compound (17). Also, loss of product was caused by charring in the distillation flask.

By carefully controlling the isomerisation reaction it was possible to minimise the levels of olefin (19) in the product but the equatorial bromide was always present in approximately equimolar amounts with the product olefin. Yields of olefin (6) of up to 50-60% were obtained in this manner. Thus, while the yields from this reaction are not high they would be adequate if a method for separating the olefin (6) from this mixture was found.

When a sample of a mixture of the two olefins and the residual bromide was subjected to preparative tlc it was possible to separate most of the bromide from the olefins. A subsequent study of these olefins using silver nitrate impregnated analytical tlc plates indicated a separation was possible and, consequently, a column of silver nitrate impregnated silica gel was tried. This enabled a small sample of the olefin (6) to be isolated contaminated with only trace levels of the isomeric olefin (19). The nmr spectrum of this olefin was effectively identical to that reported by Černý and Pecka[8]. The glc retention time also corresponded exactly with that of the material produced from the dehydrobromination/isomerisation reaction. Unfortunately, while silver nitrate impregnated columns allow the purification of small samples of pure

olefin (6) they are economically impracticable on a larger scale.

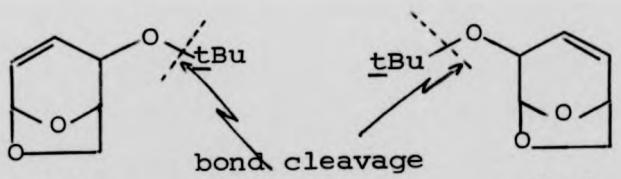
On one occasion, while performing the steam distillation, a number of fractions were collected and monitored by glc to see if any separation occurred during distillation. No significant separation was observed, the olefins and the bromide appearing to co-distill.

During one reaction a small quantity of a pale yellow oil was obtained with a boiling point much higher than that expected. Initial nmr studies suggested that tert-butanol was still present in the sample but repeated distillations failed to remove this resonance from the spectrum and it was impossible to detect any tert-butanol by glc study. After purification on a silica gel column the product crystallised. Recrystallisation from petrol ether (40-60^{o}C) yielded a white crystalline solid. (Melting point 57-59^{o}C). The glc retention time of this compound, which gave rise to one symmetrical peak, was very similar to that of the olefin (6) but the nmr spectrum had more features in common with the nmr spectrum of the olefin (19).

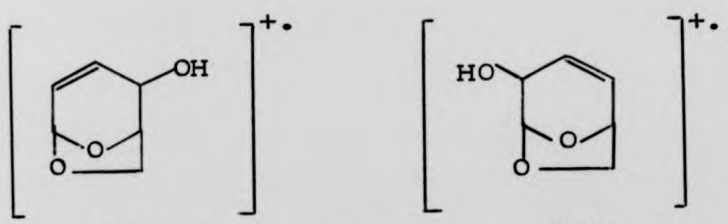
This material was then studied by mass spectroscopy and the base peak was found to be 128 m/e, with the second most intense peak being at 57 m/e (87.4%). The expected olefin (6) has a molecular weight of 112 so a discrepancy of 16 m/e existed, equivalent to one oxygen atom. Since m/e 57 is the molecular weight of a $(CH_3)_3C^+$ grouping it was concluded that the tert-butoxy grouping observed in the nmr spectrum was indeed part of the molecule and not residual solvent. Two possible structures were compatible with this spectral information, structures (29) and (30), which

could give rise to fragments (31), (32), and (33). Compounds (29) and (30) would have a molecular weight of m/e 184 and in the mass spectrum a peak of intensity 1.2% was observed at this m/e value.

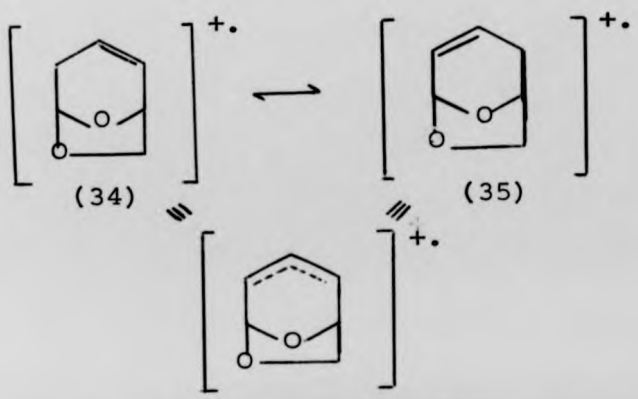
This type of cleavage of an ether linkage is quite common in mass spectrometry[27], as is the picking up of a hydrogen atom during the passage through the mass spectrometer. Peaks were also observed at the m/e values of 112 (1.0%) and 73 (2.5%) for the alternative splitting to yield fragments (34) or (35), and (36) respectively. This splitting only contributes to a minor extent because of the added stability of the tertiary carbonium ion formed by the first type of cleavage.



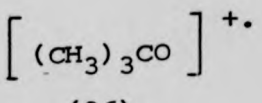
(29) (30)



(31) m/e=128 (32) (33) m/e=57



(34) (35)



(36)

A high resolution mass spectrum study of these two fragments [(31) or (32) and (33)] from compound (29) or (30) confirmed the molecular formulae of these ions.

	m/e (found)	C	H	O	m/e (calc.)
(31) or (32)	128.0473	6	8	3	128.0472
(33)	57.0705	4	9	0	57.0711

The infra-red spectrum provided little information, other than that an alcohol group was absent in the product, consequently the apparent existence of an alcohol group in ion (31) or (32) is attributable to an ionised fragment picking up a proton in the mass spectrometer.

In an attempt to distinguish whether isomer (29) or (30) was formed, and to assign the stereochemistry, spin decoupling nmr studies were carried out and the results correlated with data published by Černý et al.[8] on the two olefins (6) and (19). The anticipated variations in the spectra of compounds (6) and (19) if a tert-butoxy group were included in each compound are detailed in Table 1. (For this exercise it was assumed that a bulky group such as this would adopt a pseudo equatorial configuration.) The results obtained from the decoupling experiments are outlined in Table 2.

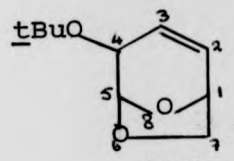
This nmr spectrum is extremely complex and it was impossible to assign all the coupling constants. However, a comparison of the general outline and chemical shift values with those of the two olefins (6) and (19) demonstrated a much greater similarity with olefin (19) which suggested the product was compound (29). The various differences between the two spectra were very similar to those predicted

Expected Changes in the Couplings Observed for Olefins (6) and (19)

(Assuming the tert-butoxy group adopts a pseudo equatorial configuration.)

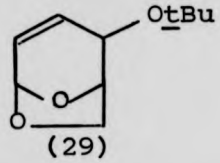
[Lost ≡ a coupling which was present in olefin (6) or (19) but is expected to be changed in olefin (30) or (29).]

A



(30)

B



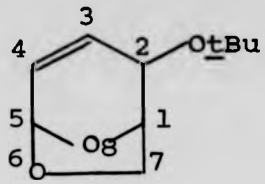
(29)

Proton	δ ppm	Couplings Hz		Proton	δ ppm	Couplings Hz	
H_2	6.03	$J_{2,4e}$=1.9	lost	H_4	5.91	$J_{4,2e}$=1.2	lost
H_5	5.66	$J_{5,4e}$=0.8	lost	H_3	5.72	$J_{3,2e}$=4.0	lost
H_3	5.65	$J_{3,4e}$=3.8	lost	H_5	5.48	No Change	
H_1	4.59	No Change		H_1	4.64	$J_{1,2e}$=1.0	lost
H_{7endo}	3.99	No Change		H_{7exo}	3.97	No Change	
H_{7exo}	3.74	$J_{7exo,4e}$=0.85	lost	H_{endo}	3.70	No Change	
H_{4ax}	2.53	$J_{4ax,4e}$=17.7	lost	H_{2ax}	2.78	$J_{2ax,2eq}$=17.7	lost
				H_{2e}	1.87		lost

[Chemical shifts are those reported by Černý[8] for olefins (6),(19).]

Table 1

in Table 1 (B) and a careful comparison of the couplings and coupling constants indicated the compound had structure (29) with the tert-butoxy group in a pseudo equatorial position, as would be expected for a bulky grouping such as this. (In Černý's original paper[8] a number of coupling



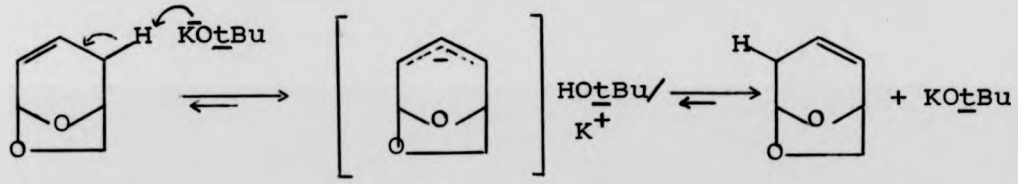
(29)

Proton	Chemical Shift (δ, ppm)	Couplings (Hz)	Proton Irradiated
H-4	5.91 (multiplet)	$J_{4,3}$=9 $J_{4,5}$=3.5 $J_{4,2ax}$=1 $J_{4,2e}$ -	H_{7endo}
H-3	5.55 (multiplet)	$J_{3,4}$=8 $J_{3,2ax}$=4.5 $J_{3,2}$= -	H_1 H_{7endo}
H-5	5.4 (doublet)	$J_{5,4}$=3.5	
H-1	4.5 (multiplet)	$J_{1,2ax}$=1 $J_{1,2e}$= - $J_{1,7endo}$=2 $J_{1,7exo}$=8	H_{7endo} H_{7exo} H_{7endo}
$H\text{-}7_{exo}$	3.9 (d of d)	$J_{7exo,7endo}$=8.5 $J_{7exo,1}$=8 $J_{7exo,2ax}$= -	H_1 H_{7endo}
$H\text{-}7_{endo}$	3.45 (d of d)	$J_{7endo,7exo}$=9 $J_{7endo,1}$=2 $J_{7endo,2ax}$= -	
H_{2e}	-		
H_{2ax}	3.5 (multiplet)	$J_{2ax,2e}$= - $J_{2ax,5}$= ? $J_{2ax,3}$= ?	H_1 , H_5 peak sharpened up

Table 2

constants are omitted, presumably because of the complex nature of the spectrum.)

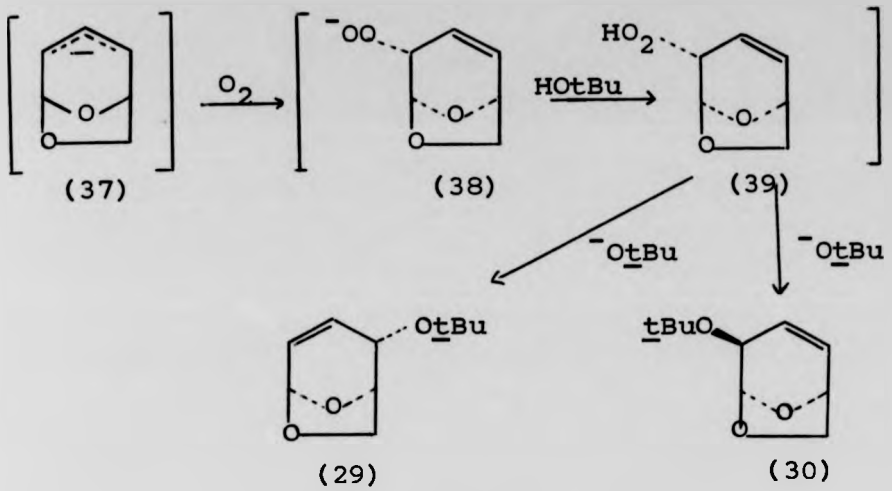
A possible explanation of this result was that while the dehydrobromination/isomerisation was proceeding some oxygen was accidentally admitted to the nitrogen filled reaction vessel. While under nitrogen, it was suspected that the reactive intermediate present was probably the delocalised anionic system (37) which removes a proton from the solvent to yield an olefin. [Pecka and Černý[8] have studied the equilibrium, Scheme 5, which is established when isomerising olefin (19) to olefin (6).]



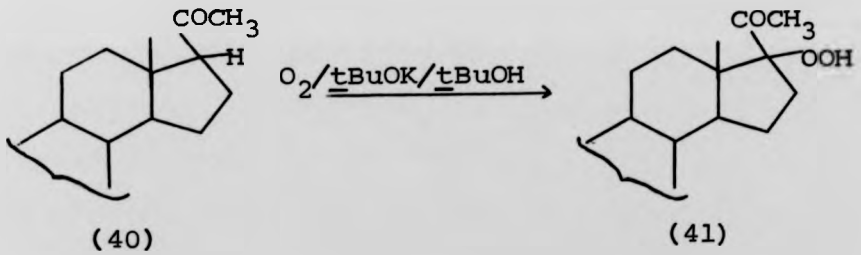
(19) (37) (6)

Scheme 5

However, if oxygen was admitted it was possible that anion (37) reacted with it to generate a peroxide species (38), presumably trans to the 2-membered bridge, which would equilibrate with the solvent to give the hydroperoxide (39). (Scheme 6) [A precedent exists for this type of reaction between oxygen and carbanions in potassium tert-butoxide reactions[28,29]. For example, a hydroperoxide can be formed on the D-ring of a steroid. (Scheme 7)] Two hydroperoxides could be formed but it was thought that compound (39) was the more likely since the parent olefin (6) was the predominant product in the normal isomerisation.



Scheme 6



Scheme 7

This hydroperoxide could then undergo a S_N2 or S_N2' substitution with butoxide anion. If the hydroperoxide was formed at C-4 and in a trans orientation to the 2-membered bridge then S_N2 substitution would be unlikely because steric interaction between the bulky tert-butyl group and the 2-membered bridge would interfere. However, S_N2' substitution, which proceeds with a syn relationship of the displacing and leaving group, on the hydroperoxide (39) would avoid the largest of the possible steric interactions. The compound would then presumably undergo a ring twist

to bring the axial tert-butoxide group into a sterically more favourable pseudo equatorial position, thus yielding compound (29). This would provide a feasible explanation for the observed product.

Although the samples of 6,8-dioxabicyclo [3.2.1] oct-2-ene (6) prepared by the above methods were adequate to make a preliminary study of subsequent steps the reactions gave extremely low yields and involved chromatographic purifications thus making this method unsuitable for the preparation of any larger quantities of the olefin (6). Consequently, each step was re-examined.

Bromocyclisation of Alcohol (16) to Bromide (18)

There are a number of problems associated with this reaction. Although the bromocyclisation occurred quite readily to give a reasonable yield of crude material this yield dropped on distillation due to product decomposition. (This was not referred to in the literature but may be due to either thermal decomposition or else induced by residual hydrogen bromide in the sample.) Also, although the base conditions used favoured the formation of the required olefin (6) the product was still obtained as an approximately 1:1 mixture with the unreacted equatorial bromide isomer (18b) which was difficult to separate.

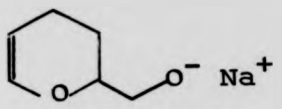
A number of attempts were made to remove this unreactive equatorial bromide. Preferential crystallisation of one of the bromide isomers from the mixture of (18a) and (18b) was studied. The bromides were very soluble in diethyl ether but chilling and the addition of a few drops of petroleum ether (40-60) resulted in the formation of a precipitate which, after isolation, melted on warming. A

study by glc showed this precipitate to be identical to the starting mixture and no enhancement of either isomer was achieved. Silica gel chromatography (silica:substrate =100:1 using a low polarity solvent) was studied using both the mixture of bromides and the mixture of olefin and unreacted bromide but no useful separation was achieved. It was also not possible to separate the residual bromide from the olefin by distillation without resorting to sophisticated spinning band methods.

Chemical methods were then sought to distinguish between these compounds. It was hoped that preparation of either the phosphonium or phosphonate salt would cause the unreacted bromide (18b) to precipitate from the reaction mixture as a salt. However, it was not possible to form the phosphonium salt on a pure sample of the bromide isomers. An alternative approach attempted to invert the stereochemistry of the unreacted bromide using a group which could then undergo an elimination reaction. It was hoped to convert a mixture of the bromide isomers to the iodo-equivalents using sodium iodide in methyl ethyl ketone[30]. However, glc and nmr monitoring gave no indication of either loss of bromide or formation of the iodide.

Since removal of the equatorial bromide seemed to be impractical, methods were sought to avoid its formation in the initial bromocyclisation. Two aspects were considered: a) the effect of carrying out the bromocyclisation under kinetic control and b) the influence of alternative brominating agents. The former was attempted by working at lower temperatures (-20 to 10^{o}C) but glc study indicated no enhancement of either isomer occurred. An alternative approach was to first generate the alkoxide (42) using a

sodium hydride/THF suspension with subsequent addition of bromine to effect the cyclisation. It was hoped this would mimic the bromocyclisation of the sodium salt (20) which produced only the axial bromocyclic lactone (23). In this way attack by the hydroxyl group on the bromonium ion intermediate might be favoured relative to the participation of the oxygen atom in the pyran ring. In practice the yield was quite low (35%) and, although fewer by-products were produced a glc study indicated no enhancement of either isomer had occurred.



(42)

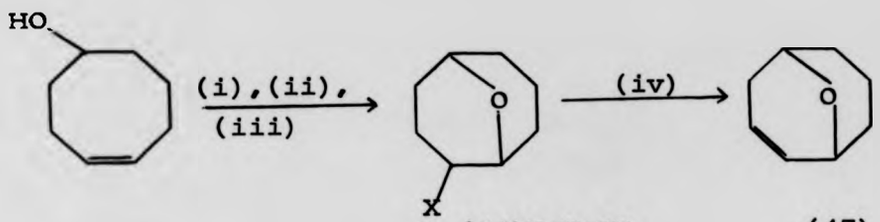
In an attempt to increase the stereoselectivity of the reaction pyridinium hydrogenbromide perbromide ($C_5H_5\overset{+}{N}HBr_3^-$) was used as a brominating agent [31]. The alcohol (16) was added to a vigorously stirred slurry of the perbromide, the mixture filtered and solvent removed to leave a pale brown oil (67% yield). Again, this reaction produced fewer by-products but no significant enhancement of either isomer.

Alternative Methods for the Cyclisation of Alcohol (16)

The use of phenylselenenyl chloride to effect the cyclisation of alcohol (16) has already been described. However, this was discarded from further use for a number of reasons. A variety of alternatives to this reagent exist and a number of these have been examined.

Paquette and Storm[32] and Bordwell and Douglass[33] have

reported the oxymercuration of 4-cycloocten-1-ol (43) using mercuric nitrate in aqueous potassium nitrate solution to yield endo-2,6-epoxycyclooctyl-mercuric nitrate (44). (Scheme 8). Conversion of (44) to the mercuric iodide (45) then iodination of (45) gave the bicyclic iodide (46) which on treatment with base yielded the bicyclic olefin (47). A similar sequence was reported using mercuric acetate to perform the oxymercuration step.

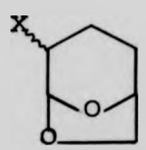


(43) (44)X=$HgNO_3$ (45)X=HgI (46)X=I (47)

(i)$Hg(NO_3)_2$, $KNO_{3(aq)}$; (ii)KI, $NaOH_{(aq)}$; (iii)I_2, CCl_4; (iv)KO<u>t</u>Bu, THF.

Scheme 8

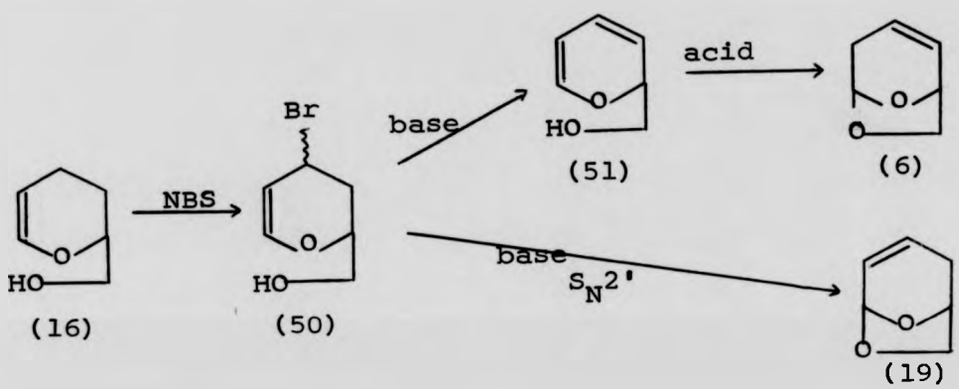
When this approach was applied to the alcohol (16) the required intermediate was compound (48) or (49). Using the reaction methods described in the literature neither of these compounds were isolated.



(48) X=$HgNO_3$
(49) X=HgOAc

Another cyclisation utilizing N-bromosuccinimide (NBS) was examined. In an attempt to prepare 3-bromo-2-(hydroxy-

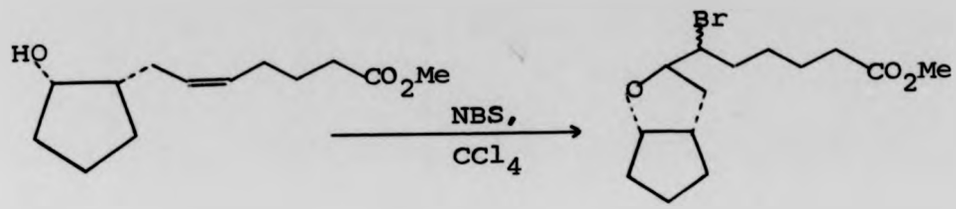
methyl)-3,4-dihydro-2H-pyran (50) alcohol (16) was reacted with NBS to effect allylic bromination. Compound (50) would then be utilized as shown in Scheme 9. The intention was that elimination of hydrogen bromide from a monocyclic compound would enable both possible isomers of the bromide to eliminate, hence leading to 2-(hydroxymethyl)-pyran (51). The subsequent cyclisation to olefin (6) would then be acid catalysed.



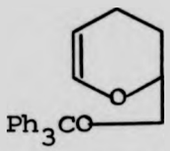
Scheme 9

The main product isolated from the reaction of NBS with alcohol (16) was not compound (50) but 4-bromo-6,8-dioxabicyclo [3.2.1] octane (18) in *ca.* 50% yield. This reaction had fewer by-products than the standard bromocyclisation route but again glc study indicated that both the bromide isomers were present with the equatorial one in slight excess.

In this reaction NBS acted as a source of positive bromine rather than as a source of bromine radicals. There are reported examples of NBS being applied to reactions like this, *e.g.* the bromocyclisation of (52) to (53)[34]. In an attempt to favour a radical allylic bromination reaction



(52) (53)

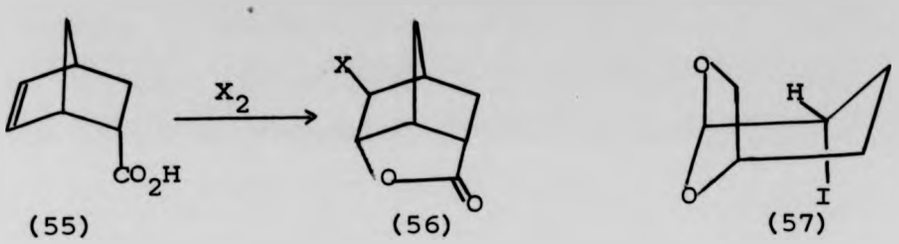


(54)

the internal hydroxyl nucleophile was protected as the trityl derivative (54)[35]. Reaction of NBS with this compound in dry carbon tetrachloride appeared to result in cleavage of the trityl group, however, and no identifiable products were isolated.

Because of the difficulties associated with controlling the stereochemistry during the bromocyclisation reaction it was decided to study the effect of substituting iodine for bromine in this sequence. The rationale for this was found in literature reports that iodolactonisation gave more steric control of the products than bromolactonisation[36]. For example if, in Scheme 10, X=I then the product of the reaction of acid (55) with the halogen would be as shown but if X=Br then Wagner-Meerwein rearrangement products were detected. It was reasoned that if an analogous control was displayed during the iodocyclisation of alcohol (16) then the axial iodide (57) might predominate.

Two literature references to iodocyclisation reactions[37,38] were found which employed similar conditions to those described for the iodolactonisation reactions[36]. Consequently,



Scheme 10

these conditions [addition of an iodine/potassium iodide solution to an aqueous solution of the alcohol (16) in the presence of a potassium carbonate buffer] were the first studied. The reaction proceeded as described in the literature but, unlike the reported examples where the product often crystallised out of solution, great difficulty was encountered in extracting the product from aqueous solution. Although inefficient, extracting the solution with dichloromethane yielded sufficient iodide for study. Continuous extraction methods were tried but these appeared to lead to decomposition of the product in the refluxing organic solvent.

The nmr spectrum of this iodide (57) was very similar to that of the analogous bromide (18) and using glc conditions which differentiated between the axial and equatorial bromide isomers only one symmetrical peak was observed for the iodide. This was a good indication that only one isomer had formed but gave no clue as to which one. Later success with the dehydroiodination reaction confirmed this was the axial isomer. Although the iodide was rather unstable in the mass spectrometer it was possible to obtain an accurate mass on the molecular ion which confirmed the molecular formula.

A variety of iodocyclisation conditions which avoided the use of water were studied. In all cases the iodide (57) was formed in varying yields with varying levels of by-products, especially of a polymeric nature. Two different types of system used were:

a) Alcohol (16) was dissolved in dichloromethane or carbon tetrachloride with potassium carbonate as a buffer then iodine, dissolved in the same solvent, was added.

b) Alcohol (16) was dissolved in tetrahydrofuran or diethyl ether under nitrogen then sodium hydride was added followed by iodine crystals or iodine dissolved in diethyl ether.

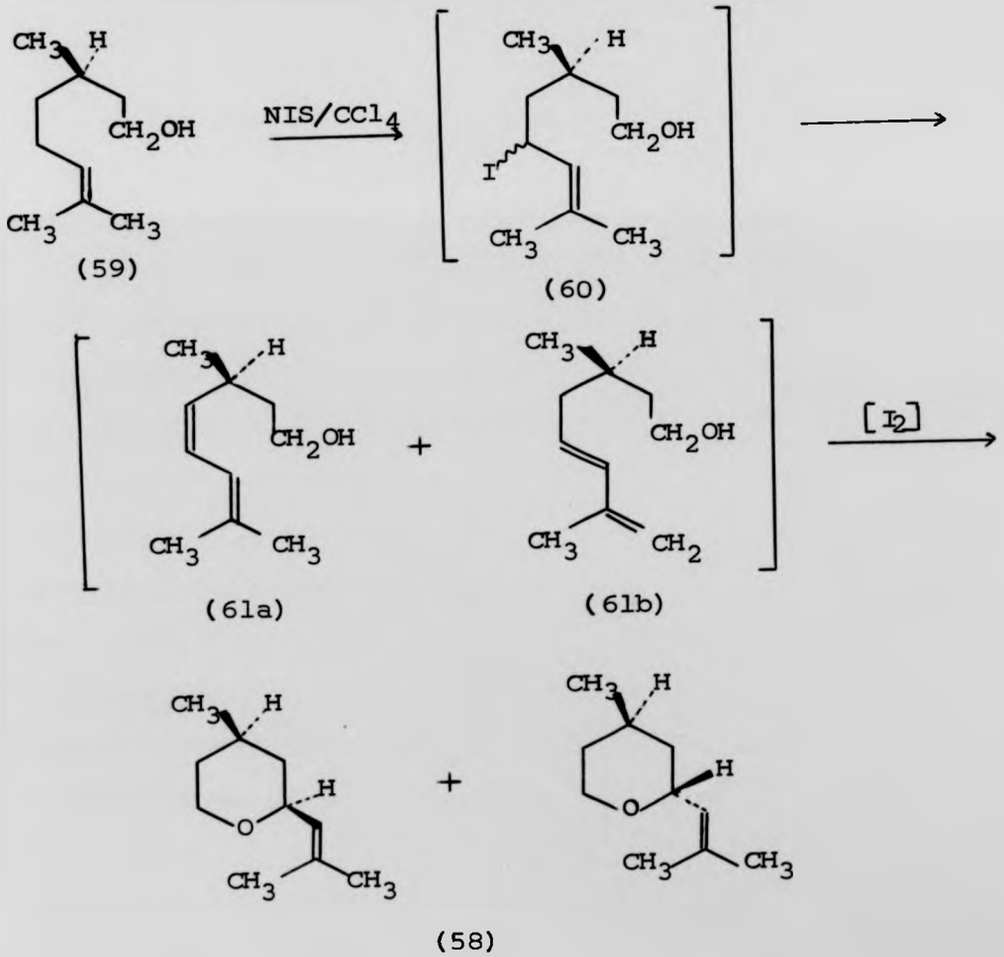
(All these reactions were performed at room temperature in the dark.)

Tlc monitoring of these reactions indicated that in several cases the majority of the by-products were formed during the work-up of the reaction and in all cases the levels of by-products relative to the iodide (57) were greatly increased. This may have been due to either instability of the iodide or acid-catalysed decomposition. A pure sample of the iodide distilled with decomposition (0.2-0.5mm Hg, oven temperature 100°C).

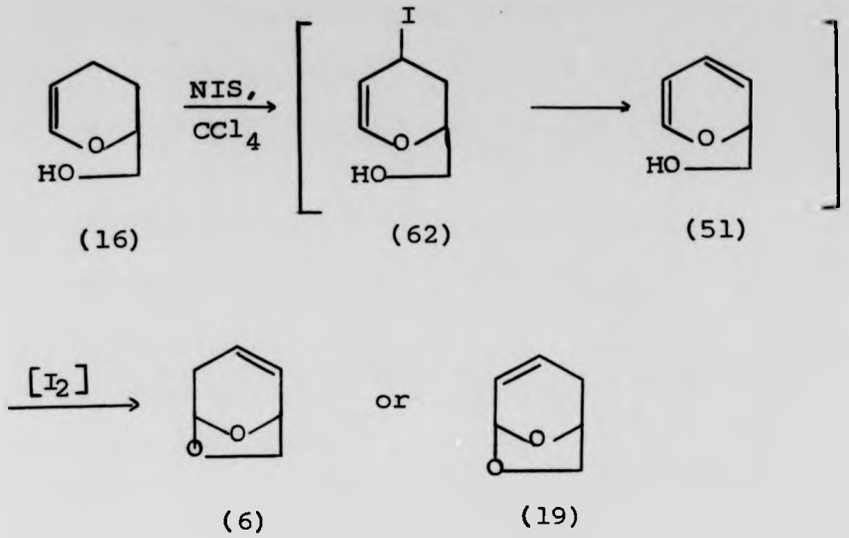
As with the bromocyclisation reactions, glc study indicated one of the most predominant impurities was 6,8-dioxabicyclo [3.2.1] octane (17), which, although present in the starting material, in many cases also appeared to be formed in the cyclisation reaction. When the reaction of the alcohol (16) in carbon tetrachloride was repeated with no buffer present the main product was 6,8-dioxabicyclo [3.2.1] octane (17) formed by acid-catalysed cyclisation (c.f. the bromocyclisation reaction[9,10] where the presence of acid is reported to facilitate the formation of the bromide). However, on one occasion the saturated compound

(17) was still the main product when potassium hydroxide was used as a buffer in dry dichloromethane at 5°C in the dark.

A communication by Taneja et al.[39] reported the synthesis of rose oxide (58) from citronellol (59) utilizing an iodocyclisation step. This is illustrated in Scheme 11. If a similar type of reaction were to occur between alcohol (16) and N-iodosuccinimide (NIS) then the envisaged sequence is illustrated in Scheme 12. This was identical to the method proposed using NBS. (Scheme 9).



Scheme 11



Scheme 12

This reaction was studied by dissolving alcohol (16) in dry carbon tetrachloride and studying the addition of NIS under a variety of temperature conditions. In each case the only products isolated were the bicyclic iodide (57) and 6,8-dioxabicyclo [3.2.1] octane (17). No trace of olefin (6) or either compounds (62) or (51) were detected. This reaction appeared similar to the NBS example discussed previously, that is, rather than effect allylic iodination the NIS appears to be acting as a source of positive iodine. Reports exist of NIS reacting in this manner[34].

Considered as an iodocyclisation this reaction was quite facile and, after a chromatographic purification to remove the mainly polymeric impurities, the iodide (57) was obtained in ca. 40% yield. Unfortunately, the preparation of NIS was quite expensive, requiring the formation of N-silver succinimide from silver oxide and succinimide

then its subsequent reaction with iodine. Consequently a compound was required which embodied the relevant features of NIS, i.e. a source of positive iodine and a suitable functionality to act as a buffer in the reaction, but was cheap to prepare.

The compound chosen was pyridine periodide, $C_5H_5NI_2$. The dark green periodide crystals were prepared by the reaction of pyridine with iodine in carbon tetrachloride[40]. (No references were found to the use, or preparation, of pyridine periodide but a few were found to pyridine perbromide as a convenient source of bromide[40].) Reaction of pyridine periodide with the alcohol (16) was studied under a variety of solvent and temperature conditions but while the bicyclic iodide (57) was produced in all the examples, in most cases several by-products were also obtained and none of these reactions were as successful as those using NIS.

Pyridine perbromide was also prepared[40] and the reaction of this compound with alcohol (16) studied in a variety of solvents. It was apparent that, while the yields of the bicyclic bromide (18) were unimpressive and the two isomers were formed in approximately equal amounts, lower levels of by-products were achieved. This was compatible with the previous observation that any bromocyclisation or iodocyclisation reactions that incorporated a buffer had fewer by-products and when the buffering efficency dropped the levels of by-products rose. This was contrary to the literature reference[9] where it was suggested that the absence of a buffer was beneficial.

On the basis of these observations the bromocyclisation of alcohol (16) in carbon tetrachloride was restudied over a range of temperatures but with different levels of anhydrous potassium carbonate being added as a buffering agent. (This required vigorous stirring since the potassium carbonate tended to agglomerate during the reaction.) After studying a large permutation of conditions it was found that if the reaction was performed at 15 $\pm$ 2^{o}C with the potassium carbonate in a one molar equivalent to the alcohol, not only were lower levels of by-products produced but a glc study showed that the axial bromide (18a) was formed exclusively in ca. 30% yield. If any other temperature or ratio of potassium carbonate was used varying amounts of the equatorial bromide were obtained. No explanation for this observation has been found but it is possible that the potassium ion is being coordinated by the pyran oxygen and the alcohol group thus effectively 'tying-up' the lone pair of electrons and also holding the molecule in a fixed stereochemistry. This restriction of the rotational mobility may have affected the stereochemical control of the bromocyclisation.

Consequently, the problem of removing the residual equatorial bromide (18b) from the dehydrobromination reaction product was eventually avoided by selectively preparing the axial bromide, albeit in lowish yield.

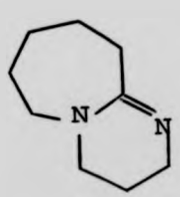
Dehydrobromination Reaction

Concurrently with the study of the cyclisation reaction a variety of elimination/isomerisation reactions were also under study. It was hoped that a modification in the reaction conditions used would : a) increase the yield of olefin (6),

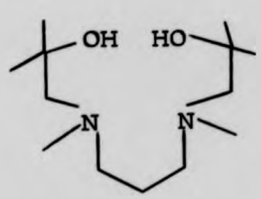
and b) simplify the work-up procedure. These conditions restricted the choice of reaction conditions to a strong non-nucleophilic base in a readily removable solvent.

In view of the complexity of the reaction when potassium tert-butoxide in tert-butanol was used the initial approach adopted was to prepare the olefin (19) and study its subsequent isomerisation to the olefin (6). The preparation of olefin (19) has already been described using ethanolic potassium hydroxide as the base but while this yielded the olefin (19) the yields were variable and it was difficult to remove all the solvent from the product.

As an alternative method for the preparation of olefin (19) 1,5-diazabicyclo [5.4.0] undec-5-ene (DBU)[41] (63) was first used with carbon tetrachloride or dimethylsulphoxide as solvent. This had only a limited success and better results were obtained when it was used with no solvent. After reacting DBU (2 molar equivalents) and the mixture of bromides (18) at 110°C for 24 hours it was possible to distil 6,8-dioxabicyclo [3.2.1] oct-3-ene (19) directly from the reaction mixture in up to 40% yield. Glc study indicated no isomerisation product was formed and because of this, and the cost, no further work was done with DBU.



(63)

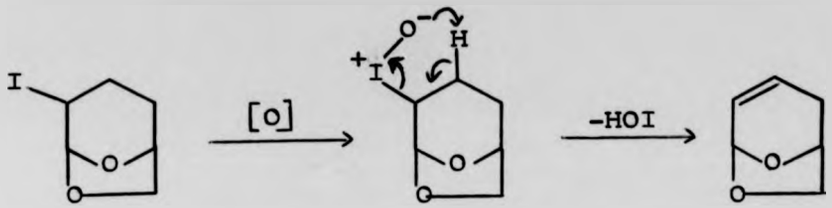


(64)

Other bases studied were a) sodium hydride in dimethoxyethane, b) lithium diisopropylamide in tetrahydrofuran, c) the alkoxide of amine (64) in benzene, and d) N,N'-di-*o*-tolylguanidine. In all cases olefin (19) was formed from the mixture of bromide isomers (18) with no sign of any isomerisation to olefin (6). However, none of these reagents showed any advantage over ethanolic potassium hydroxide in yield, purity or ease of the reaction and, in some cases, the range of by-products was increased.

A small quantity of 4-iodo-6,8-dioxabicyclo [3.2.1] octane (57) was prepared and a similar study was carried out. Glc monitoring indicated that when this halide underwent a dehydrohalogenation reaction all the starting material was utilized, in sharp contrast to the analogous bromide where the equatorial isomer remained unreacted. This acted as corroborative evidence for the previous deduction that only one isomer of the iodide was formed. Glc study also showed a major by-product of some reactions was 6,8-dioxabicyclo [3.2.1] octane (17). As mentioned previously this compound was formed in the iodocyclisation reactions but some of the base conditions studied appeared to produce it.

Prompted by work by Beeley and Sutherland[42] an elimination utilizing an iodoso intermediate was attempted. (Scheme 13). Although tlc study of the reaction of the iodide with *meta*-chloroperoxybenzoic acid in dichloromethane with disodium hydrogen orthophosphate as buffer indicated loss of the starting iodide the attempted elimination of HOI resulted in 6,8-dioxabicyclo [3.2.1] octane (17) being the only detectable product. When ozone in dichloromethane



(57) (65) (19)

Scheme 13

was used tlc study gave no indication of the formation of an iodoso intermediate (65) and after work-up only the starting iodide and compound (17) were detected.

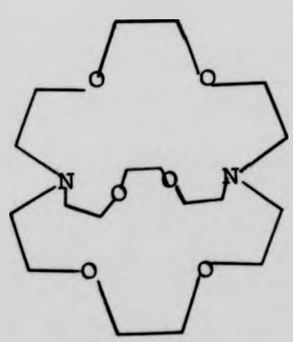
Of all the methods examined, the use of ethanolic potassium hydroxide appeared to be the most successful for preparing olefin (19). Indeed, when this reaction was restudied using the pure axial bromide (18a), olefin (19) was prepared relatively simply in up to 50 - 60% yield.

The isomerisation of olefin (19) to olefin (6), and the associated problems, have already been described when using a high concentration of potassium hydroxide in ethanolic solution or potassium tert-butoxide in tert-butanol. A number of other base systems which were studied using the olefin (19), prepared above, as starting material proved unsuccessful. For example, a) lithium diisopropylamide in tetrahydrofuran was restudied but very little isomerisation occurred and numerous by-products were produced, b) neither potassium 3-aminopropylamide[43], a strong catalytic base reported to isomerise β-pinene to α-pinene, nor n-butyllithium/tetramethylethylene diamine[44] appeared to effect any significant levels of isomerisation, c) none

of the high boiling bases mentioned previously which would have allowed direct distillation of the product, (guanidine, DBU) caused any isomerisation.

The main difficulty with the tert-butoxide/tert-butanol reaction was the isolation and purification of the product, the ratio of olefin (6) to the unwanted isomer (19) being acceptable. In an attempt to alleviate the problems in the work-up solid potassium tert-butoxide was tried as a base, from which it was hoped to distill olefin (6) directly. Glc monitoring, however, indicated little isomerisation occurred, the main isolated product being unreacted olefin (19).

The use of potassium tert-butoxide was studied under a variety of conditions and the use of dimethylsulphoxide as solvent with a kryptate (kryptofix-4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo [8.8.8] -hexacosan) (66) appeared promising. Dimethylsulphoxide is a better solvent than tert-butanol for ions, readily forming solvent separated ion pairs, i.e. at low concentrations potassium tert-butoxide is present as solvent separated ion pairs. At high



(66)

concentrations of base, aggregation becomes important to the point that each added molecule of base merely adds to the total of aggregated species. Thus, no matter how high the concentration of potassium tert-butoxide, the resulting activity of the solution is that of a small concentration of monomeric base in equilibrium with a larger concentration of aggregated species. Maskornick[45] has shown that for the potassium tert-butoxide/dimethylsulphoxide catalysed isomerisation of 2-methylbicyclo-[2.2.1]hepta-2,5-diene to 5-methylenebicyclo[2.2.1]hept-2-ene addition of 18-crown-6 ether resulted in at least a power of ten increase in the concentration of non-aggregated base compared to the same reaction without 18-crown-6 ether. This occurred because 18-crown-6 ether has the ability to completely satisfy the coordination sites of a potassium ion by encompassing it in a ring of ether oxygens. This causes a breakdown of the potassium tert-butoxide aggregate in solution, hence increasing the activity of the potassium salt.

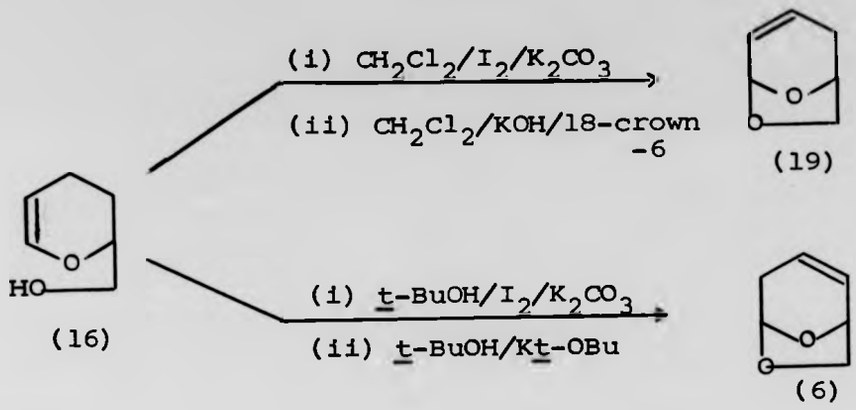
Kryptate (66) has a greater affinity for potassium than does 18-crown-6 ether and when this material was used the results were dramatic. A reaction was studied using an olefin (19) : potassium tert-butoxide : kryptate ratio of 1:2:1. Standing at room temperature overnight gave 50% isomerisation and on standing at room temperature for a week the isomerisation had improved to 88%. When the reaction was repeated using 18-crown-6 the reaction required heating to 100°C for 2 hours to achieve a 90% isomerisation.

Unfortunately, although these conditions were mild and gave a good ratio of the required isomer, the problems of

removing the solvent and purifying the product were not reduced.

When the dehydroiodination of 4-iodo-6,8-dioxabicyclo-[3.2.1] octane (57) with potassium tert-butoxide in tert-butanol was studied the reaction was found to produce low levels of by-products. After the aqueous/steam distillation work-up described previously the two olefins (6) and (19) were isolated in variable yields of up to 20 - 25% based on the starting alcohol (16), the only significant impurity on occassions being 6,8-dioxabicyclo [3.2.1] octane (17). The ratio of (6) to (19) depended, as with the dehydrobromination, on the period of refluxing and the concentration of the base. As previously, no unreacted iodide was detected in the reaction products.

Since the bicyclic iodide (57) proved very difficult to isolate but the subsequent dehydroiodination seemed to be a fairly facile reaction allowing isolation of pure 6,8-dioxbicyclo [3.2.1] oct-2-ene (6), or the isomer (19), relatively easily, conditions were sought which would not require isolation of the iodide, i.e. a 'one-pot' reaction. Two such sets of conditions were developed and these are illustrated in Scheme 14. To obtain olefin (19) the iodocyclisation of alcohol (16) was carried out in dichloromethane using anhydrous potassium carbonate as buffer. Excess iodine was removed by reaction with sodium metabisulphite then, after filtration, powdered potassium hydroxide and 18-crown-6 ether were added and the mixture refluxed. Although this yielded the olefin (19), the main product was frequently 6,8-dioxabicyclo [3.2.1] octane (17) which detracted from the utility of this reaction sequence.



Scheme 14

To produce 6,8-dioxabicyclo [3.2.1] oct-2-ene (6) the iodocyclisation of alcohol (16) was carried out in tert-butanol, again with anhydrous potassium carbonate present as a buffer. This was quite a slow reaction but glc studies showed no 6,8-dioxabicyclo [3.2.1] octane (17) was produced. Excess iodine was removed by reaction with sodium metabisulphite and, after filtration, the mixture was added to a prepared solution of potassium tert- butoxide in tert-butanol under nitrogen. After refluxing for 24 hours the reaction was worked-up as for the analogous dehydrobromination reaction. This gave mixtures of the two olefins in about 7% yield.

Conclusion

A variety of cyclisation and elimination/isomerisation reaction conditions have been studied with varying degrees of success. Of all these, the best route to date was based on the original literature references[9,10] but with a significant number of modifications incorporated.

a) The axial bromide (18a), prepared stereoselectively by careful control of temperature and buffer levels, was converted to 6,8-dioxabicyclo [3.2.1] oct-3-ene (19) in *ca.* 50% yield using ethanolic potassium hydroxide. When this olefin was refluxed in a concentrated ethanolic potassium hydroxide solution for 2 days, quenched with brine and extracted with diethyl ether, 6,8-dioxabicyclo-[3.2.1] oct-2-ene (6) was obtained in maximum *ca.* 35% yield contaminated with isomer (19) and 6,8-dioxabicyclo [3.2.1]-octane (17).

b) The mixture of bromides (18) was treated with potassium *tert*-butoxide/*tert*-butanol at reflux for 24 hours. After removal of *tert*-butanol by distillation a dichloromethane extraction of the subsequent steam distillate gave the olefin (6) in a maximum yield of *ca.* 55%, contaminated with unreacted bromide, the isomeric olefin (19) and compound (17). The yield based on the starting alcohol was lower when the axial bromide was used but the product was purer.

Both these reactions were very variable, the yields quoted being the maximum observed but, on many occasions, no product at all was isolated. This severely restricted the quantities of the olefin (6) which were available to investigate the subsequent stages.

SECTION C

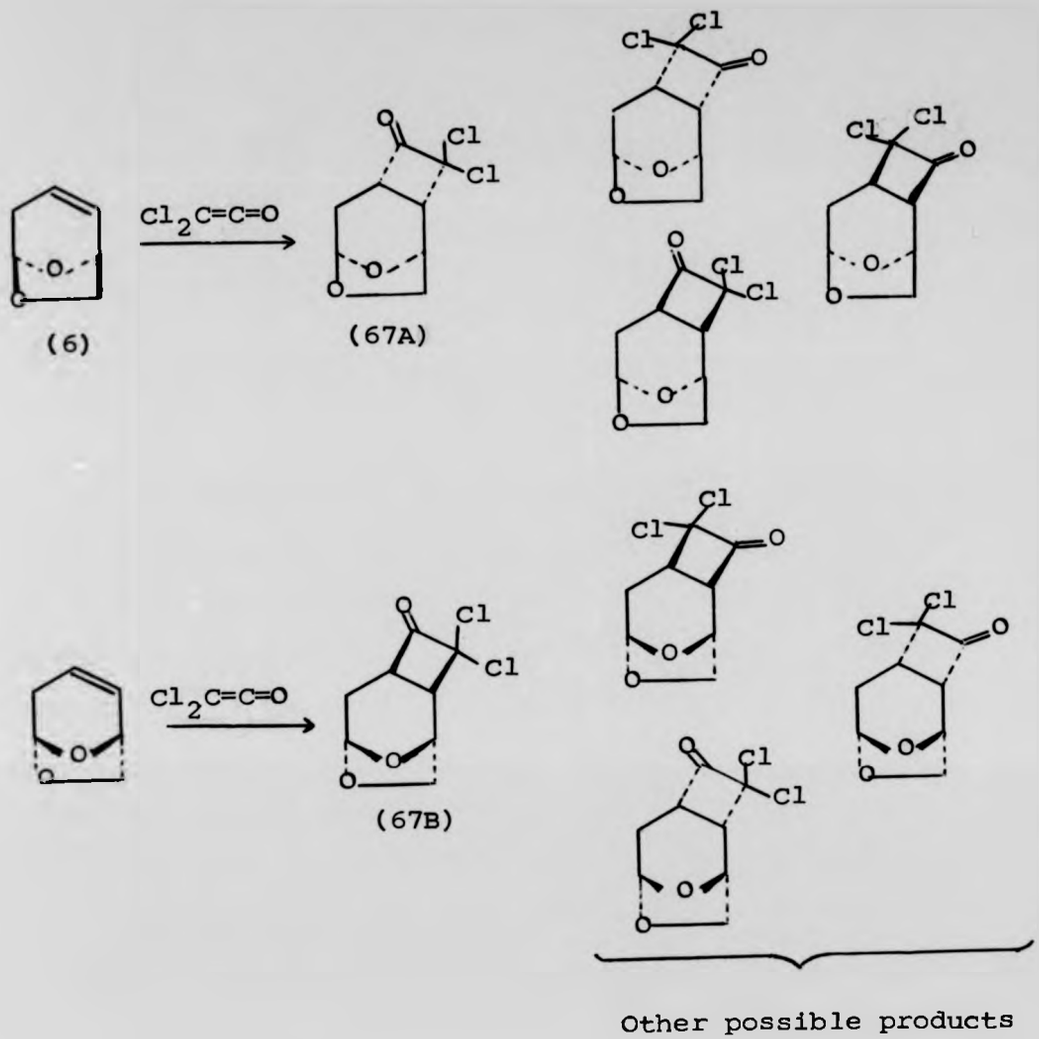
Elaboration Of The Lactone Ring On 6,8-dioxabicyclo [3.2.1] oct-2-ene (6).

Having prepared the olefin (6) the next step of the synthesis required the generation of a γ-lactone ring on carbons 2 and 3 to produce the tricyclic system (5) as a mixture of enantiomers. It was envisaged that there were two possible routes to achieve this.

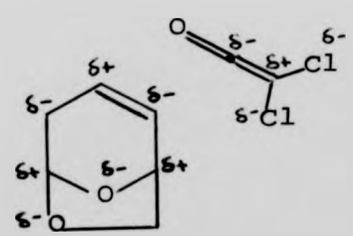
One method utilized addition of dichloroketene across the double bond[46,47]. If olefin (6) was used in racemic form there are 8 possible products from this reaction, (Scheme 15), only one of which could eventually be elaborated to thromboxane B_2 in the correct optically active form, i.e. the tricyclic ketone (67A).

While it is possible that the other compounds may be formed it is unlikely that significant amounts will be produced for one or both of two reasons. The olefin and dichloroketene are most likely to be polarised by the inductive effect of oxygen or chlorine as illustrated in Scheme 16, thus leading to the preferential orientation of the dichloroketene during reaction. Also, it is more likely, on grounds of steric interactions, that the dichloroketene will approach the olefin in an orientation trans with respect to the anhydro bridge. Subsequent de-chlorination and Baeyer-Villiger oxidation should leave the stereochemistry unaltered and produce the tricyclic lactone (5A) and its enantiomer (5B).

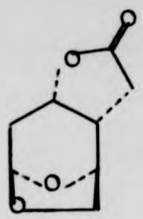
The second method involved the formation of a radical from acetic acid[48] and the addition of this radical to the



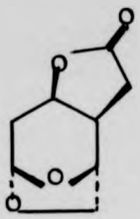
Scheme 15



Scheme 16

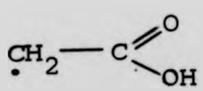


(5A)



(5B)

olefin (6) to yield the tricyclic lactone (5). This reaction depended on the selective formation and selective oxidation of an organic free radical by a metal oxidant. Potentially, 8 products could again be expected when using the racemic mixture of olefins but the same steric considerations as described above suggested that all approaches would be trans to the anhydro bridge. Also, the proposed mechanism for the radical formation and reaction suggested that the radical formed is (68) which would imply initial attack by the relatively electron rich carbon-2 and thus lead to the required orientation of the lactone.



(68)

Dichloroketene Addition

A number of different reaction conditions are known for carrying out dichloroketene additions[46,47], particularily with reactive olefins. Since dichloroketen is unstable and polymerises readily, it was generated in situ in the presence of the olefin by : 1) the dehydrohalogenation

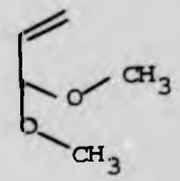
of a dichloroacetyl halide with an amine like triethylamine, or 2) the dehalogenation of a trichloroacetyl halide (usually trichloroacetyl bromide) with activated zinc. Both methods have disadvantages, however. For example, a) tertiary amines and/or ammonium salts catalyse the decomposition of dichloroketen, b) zinc salts catalyse the polymerisation of certain olefins, and c) generally a large excess of olefin must be used.

The first conditions used were described by Krepski and Hassner[46]. This utilized the dehalogenation of trichloroacetyl chloride by activated zinc in the presence of the olefin (6) and phosphorous oxychloride. A small excess of acid chloride (ca. 5%) was reported to be generally sufficient and it was assumed that the phosphorous oxychloride functioned by complexing the zinc chloride produced in the reaction. When these reaction conditions were applied to the olefin (6), however, an ir study of the crude products showed no absorption between 1800 and 1810 cm^{-1} (this is the characteristic position for a dichlorocyclobutanone stretching absorption[46,47]) indicating that no tricyclic ketone (67) was formed.

It was suspected that the phosphorous oxychloride might be coordinating with the two oxygen atoms in the olefin and thus changing the reaction in some manner. When phosphorous oxychloride was omitted from the reaction a crude product mixture was obtained which exhibited two carbonyl stretching frequencies at 1805 and 1770 cm^{-1}. However, it proved impossible to isolate the compound which gave rise to the absorption at 1805 cm^{-1} since the material appeared to decompose during the chromatographic separation.

More recently Bak and Brady[47] reported the use of high dilution reaction conditions to perform similar reactions. The reagents used, barring phosphorous oxychloride, were identical but the solutions were much more dilute and the addition times and refluxing periods were considerably longer. Again, an ir study of the crude reaction product indicated an absorption at 1800 cm^{-1} but it proved impossible to isolate one compound which gave rise to this absorption. Some purification was achieved by preparative tlc and a nmr study of this semi-purified material indicated that the two bridgehead protons on C-1 and C-5 were present but any further purification and analysis was impossible.

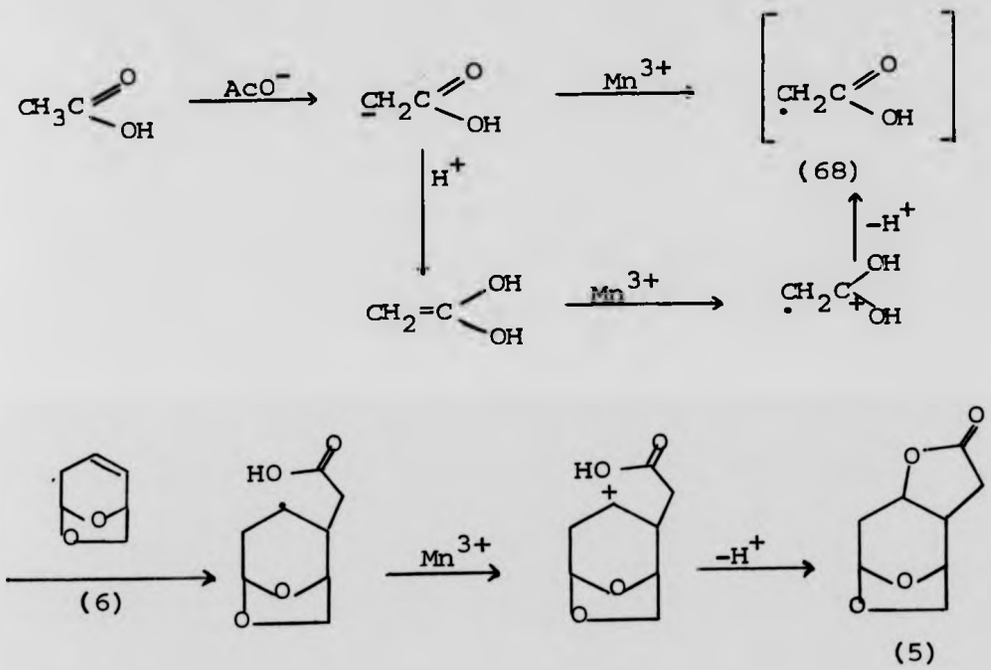
Bak and Brady reported[47] a number of olefins which gave unsuccessful cycloadditions due to deactivating electronic effects in the molecule. One example was the dimethylacetal of acrolein (69) which is related to the two olefins (6) and (19) in an electronic sense, i.e. there are two deactivating oxygen atoms in close proximity to the olefin. This reported failure of an analogous compound provided corroborative evidence which suggested that because of the deactivating groups in the molecule it will not be possible to construct the γ-lactone ring on the olefin (6) using this approach.



(69)

Radical Addition

The alternative method required adding 'acetic acid' across the double bond in the olefin (6) in the presence of a stoichiometric amount (2 equivalents/ mole of lactone) of a metal oxidant. This method was reported by Heiba et al.[48] and the proposed mechanism is illustrated in Scheme 17.

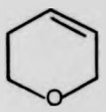


Scheme 17

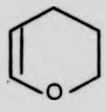
This lactone synthesis depended on five basic mechanistic requirements : 1) the selective direct generation of carboxyalkyl radicals; 2) the difficult oxidation of the initially formed carboxyalkyl radical; 3) the rapid and selective addition of this radical to the olefin; 4) the fast oxidation of the resulting adduct radical to the carbonium ion; and 5) the rapid cyclisation of the carbonium ion to the lactone.

When the reaction was attempted no identifiable product was isolated and no trace of a lactone carbonyl absorption was observed in the crude product mixture.

To study this reaction further 2,3-2H-dihydropyran (70) and 4,5-2H-dihydropyran (71) were used as analogues but in neither case was any identifiable product isolated.



(70)



(71)

It was suspected that these failures could be explained by again considering the deactivating effect of the oxygen atoms on the electronic environment of the double bond in the olefin (6). (Heiba et al.[48] reported that diethylmaleate and methyl acrylate were both effectively unreactive due to the deactivating effect of the carbonyl groups.)

Conclusion

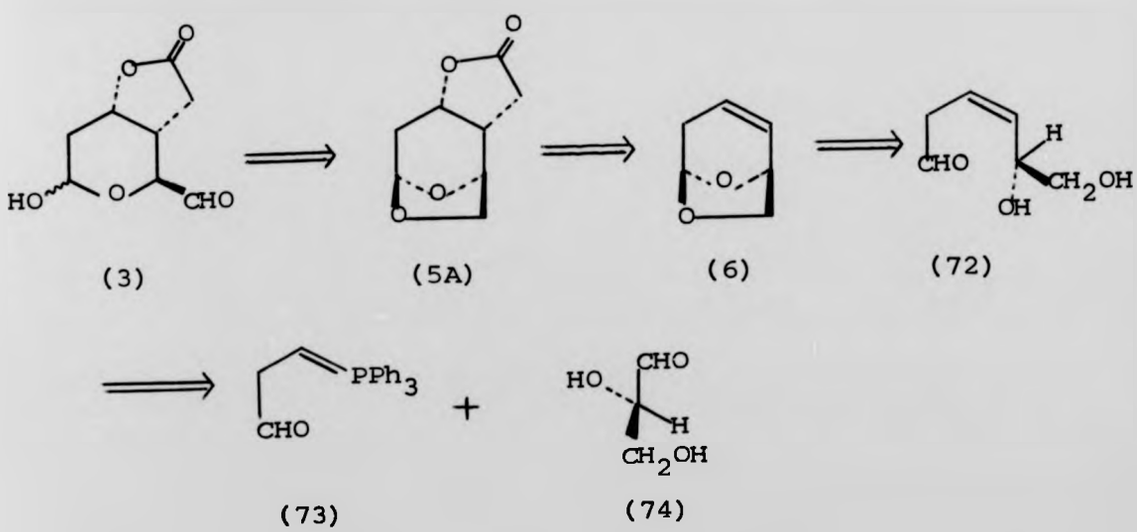
In view of these problems it appeared unlikely that either of these approaches would lead to the required tricyclic lactone. Consequently, either an alternative method to elaborate the lactone function or else a substantially altered approach was required to enable thromboxane B_2 to be prepared via this route utilizing 6,8-dioxabicyclo-[3.2.1] oct -2-ene (6).

SECTION D

Synthesis Of Optically Active 6,8-dioxabicyclo [3.2.1] oct-2-ene (6).

It was initially intended that the synthesis described in Section B would rapidly provide quantities of olefin (6) in racemic form to allow an early evaluation of the proposed lactone synthesis described in Section C. If this route proved successful it was then intended to prepare olefin (6) in an optically active form and carry it through to prepare the naturally occurring diastereoisomer of thromboxane B_2.

The route to prepare the optically active olefin (6) was more speculative than the synthesis of racemic material but, because of the difficulties encountered in the synthesis of the racemic compound, increasing effort was expended on this route. The original approach was developed by continuing the retrosynthetic analysis started in Section A and is illustrated in Scheme 18.

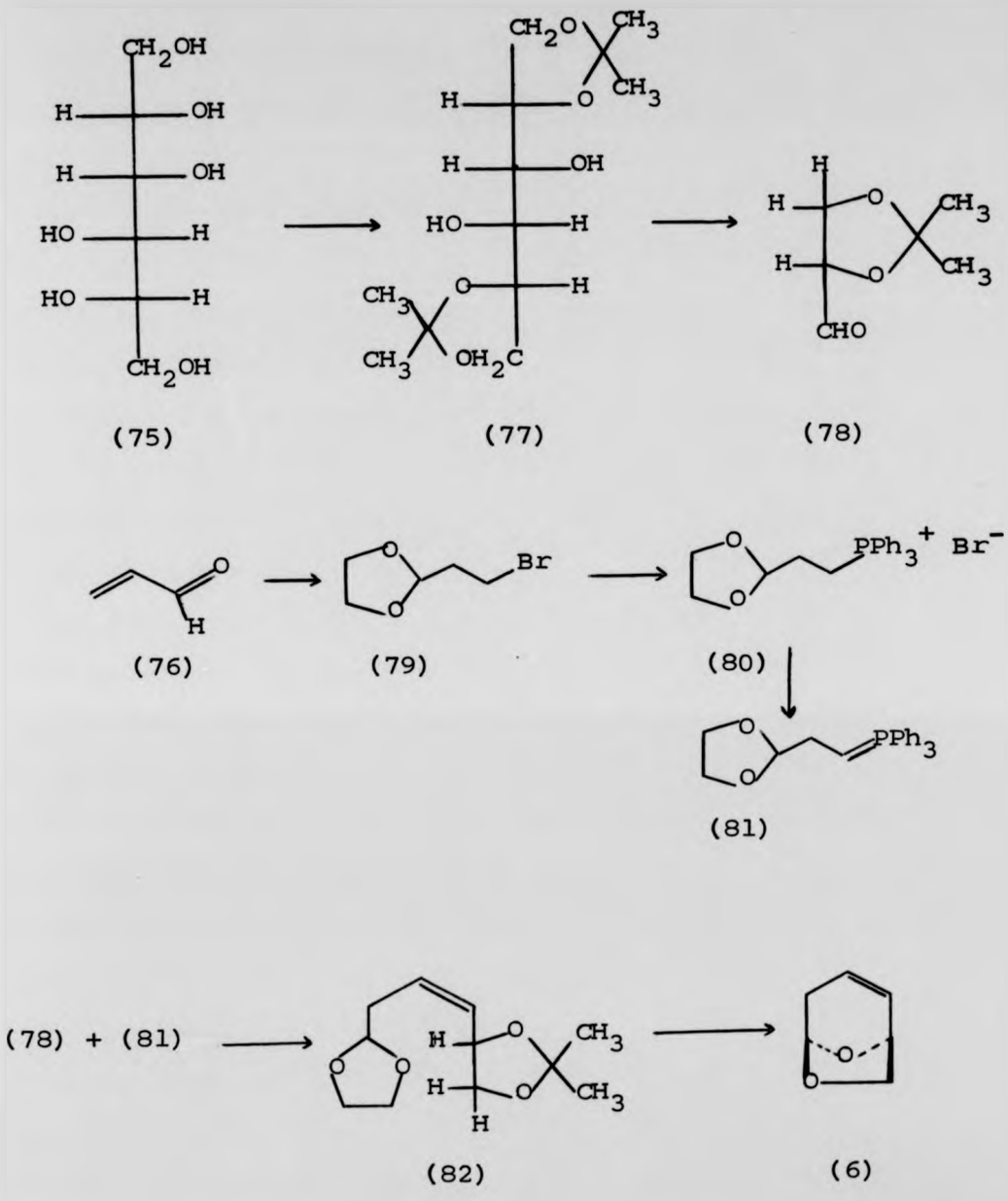


Scheme 18

In olefin (6) both bridgehead carbon atoms (C-1 and C-5) are chiral centres and it follows that stereochemical control at one of these centres will dictate the chirality of the other centre. In a retrosynthetic sense the open form of (6) is the aldehydic diol (72) which contains only one chiral centre at what will be C-1 in compound (6) and thus control of this centre will define the stereochemistry at C-5 on cyclisation.

The olefinic linkage in compound (72) suggested that this compound could be formed from two 'halves' using a Wittig reaction, namely the phosphorane (73) and R-glyceraldehyde (74), both in a suitably protected form. R-Glyceraldehyde (74), which would introduce the chiral centre at C-1 in the required configuration, can be readily generated from the sugar d-mannitol (75). The phosphorane (73) was envisaged as being derived from acrolein (76). On the basis of this analysis a synthetic scheme was devised and is illustrated in Scheme 19. Thus, introduction of this one preformed chiral centre early in the synthesis potentially results in control of all the chiral centres formed subsequently and would effect a stereospecific synthesis of thromboxane B_2.

R-Glyceraldehyde (74) was quite readily prepared as the suitably protected isopropylidene derivative (78) using reported methods. d-Mannitol (75) was first reacted with a zinc chloride/acetone solution to produce 1,2,5,6-di-O-isopropylidene-d-mannitol[49,50] (77) as a white crystalline material in approximately 70% yield. Several recrystallisation methods exist for purification of this material, e.g. water, or chloroform solution with hexane being added to initiate precipitation. This



Scheme 19

compound is quite stable for storage over prolonged periods.

Di-O-isopropylidene-d-mannitol subsequently underwent oxidative cleavage of the diol with lead tetraacetate in benzene[51] to yield isopropylidene R-glyceraldehyde (78)

(acetone d-glyceraldehyde). This literature method worked well and gave an acceptable yield of approximately 80%. A few exploratory experiments were tried to substitute sodium meta-periodate for lead tetraacetate but this presented no advantages and the initial yields were no better than those obtained with lead tetraacetate[52]. Unfortunately, isopropylidene R-glyceraldehyde (78) was unstable for extended storage[51], polymerising overnight even with chilling, and thus must be freshly generated from di-O-isopropylidene d-mannitol immediately prior to use. This lack of stability also thwarted attempts to substitute toluene for benzene in the reaction. While it was possible to rapidly distill isopropylidene R-glyceraldehyde (boiling point ca. 65°C, o.2 mmHg) with little degradation the temperature required to remove toluene as opposed to benzene proved totally impractical in terms of decreased yields. These two reactions provide isopropylidene R-glyceraldehyde (78) in ca. 56% yield with the optically active diol suitably protected as a labile ketal from which the alcohol functionality can be regenerated under mild conditions.

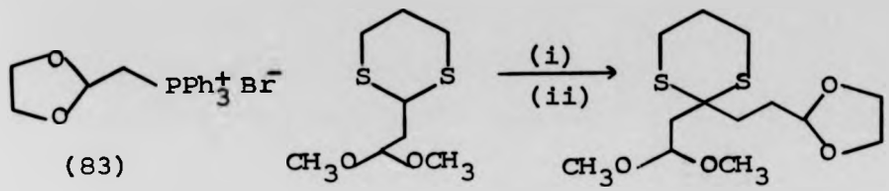
This compound (78) also has two characteristic resonances in the nmr spectrum which make it simple to monitor the fate of this compound in subsequent reactions. Namely, two singlets at δ=1.3 and δ=1.5 ppm, indicated the presence of the isopropylidene protecting group and the doublet at δ=9.7 ppm indicated the presence of the aldehyde group.

The retrosynthetic analysis suggested that acrolein was a suitable starting material for the synthesis of the other 'half' of compound (72). However, the aldehydic function must first be protected and the olefin suitably

elaborated. Büchi and Wüest[53] have described the synthesis of 1,3-dioxan-2-(2-bromoethane)(79)*. Use of this compound meant the aldehyde function was protected as an acetal and should thus be regenerated under the same conditions as those used for deprotection of the diol in isopropylidene R-glyceraldehyde (78). Acrolein was added to a solution of hydrogen bromide and ethylene glycol and both acetal formation (utilizing the ethylene glycol) and anti-Markovnikoff addition of hydrogen bromide across the olefin occurred to give 1,3-dioxan-2-(2-bromoethane) (79) in ca. 53% yield in one step. This material was quite stable for storage but, as tends to be general with halides, coloured a little on standing and was always distilled prior to use. There are also some useful characteristic resonances in the nmr spectrum of this compound, namely the triplet at δ=4.9ppm due to the methine proton, the continued presence of which shows that the acetal grouping is still intact, and the triplet at δ=3.5 ppm due to the bromoethyl group.

The next stage required the conversion of bromide (79) into the phosphonium bromide salt (80). No literature references to this material were found but the lower homologue 1,3-dioxan-2-ylmethyltriphenylphosphonium bromide (83) has been reported[54] as a stable, crystalline material. There is also a precedent for nucleophilic displacement of bromide from 1,3-dioxan-2-(2-bromoethane) (79) by the dithiane derivative[55] (84). On this basis the preparation of 1,3-dioxan-2-(2-ylethyltriphenylphosphonium bromide) (80) was expected to be quite straightforward using the standard reaction of triphenylphosphine with an alkyl halide.

* See page 170



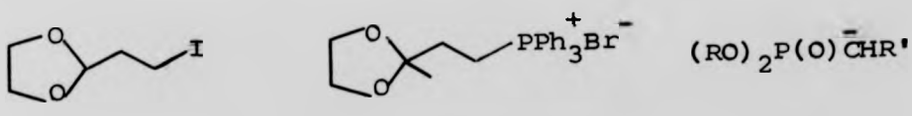
(83) (84) (85)

(i) n-BuLi
(ii) (79)

In the event it proved impossible to prepare this salt. Reaction between a halide and triphenylphosphine normally occurs quite readily, only requiring mixing of the two reagents and, generally, heating and sometimes a solvent. A variety of solvents and temperatures were studied as shown in Table 3, but on no occasion was any trace of product observed. (The product was expected to be an ionic salt and hence crystalline with a characteristic coupling of ca. 20 - 25 Hz appearing in the nmr spectrum due to phosphorus-proton coupling.)

The bromide (79) was also converted to the iodide (86) using sodium iodide in methyl ethyl ketone[30] but it also proved impossible to form the phosphonium salt of this halide.

Since these reactions were attempted it has been reported[56] that the methyl analogue 1,3-dioxan-2-methyl-2-(2-ylethylphosphonium bromide) (87) cannot be prepared either, a brown oil being the main product.



(86) (87) (88)

A modification of the Wittig reaction was developed by Horner *et al.*[57] and by Wadsworth and Emmons[58]. This made use of resonance-stabilized phosphonate carbanions (88), where R' is a group capable of stabilizing the adjacent anion, *e.g.* a carbonyl group. While this stabilization could not occur in the phosphonate salt of compound (79) the reaction conditions used to form these phosphonates were studied to see if any phosphorous compound could be made to react with the carbon-halogen bond in compound (79). A number of approaches were tried as indicated in Table 3, but again no evidence of any reaction could be detected. For example, diethylphosphite $[P(O)(OEt)_2H]$ was reacted with n-butyl lithium to generate the lithium derivative $[LiP(O)(OEt)_2]$ which was then mixed with the bromide (79) and the mixture transferred to a nmr tube. Continuous monitoring indicated loss of the bromide but no identifiable products were formed. Similarily, reaction of the sodium derivative $[NaP(O)(OEt)_2]$ with bromide (79) produced no identifiable material except unreacted bromide.

SOLVENT	REAGENT	CONDITIONS
Benzene	Triphenylphosphine	Room temperature, stirring
Xylene	"	Reflux overnight
Acetonitrile	"	Reflux overnight, stir 1 week
Cyclohexane	"	Reflux 24 hours
No solvent	"	"
No solvent	$(EtO)_3P$	70°C with nmr monitoring[58]
Hexane	$P(O)(OEt)_2H$, nBuLi	Room temperature[59]
THF	$P(O)(OEt)_2H$, Na	Room temperature[59]

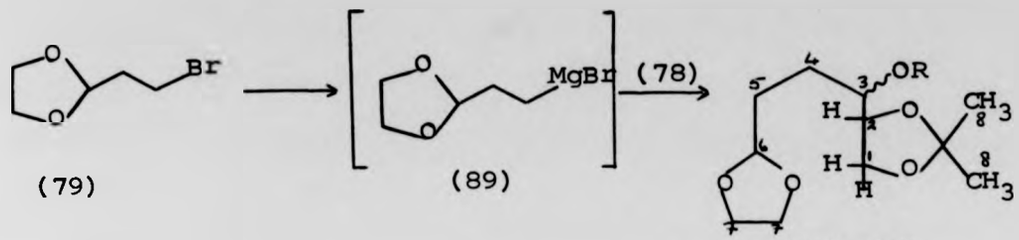
Table 3

No explanation has been found for this failure, although, as will be seen in later work, it appears as if the dioxan ring may be exerting some influence on the overall molecule.

Since it proved impossible to introduce the olefin functionality in (82) by combining compounds (78) and (79) in a Wittig reaction an alternative was sought. Büchi and Wüest[53] have reported the preparation of the Grignard reagent (89) from compound (79). Reaction of this Grignard with aldehyde (78) would result in the formation of an alcohol (90) which could then undergo an elimination reaction to afford olefin (82). However, unlike the Wittig reaction where it is possible to influence the ratio of *cis* to *trans* olefin formed by a careful choice of solvent and base, an elimination reaction such as that envisaged would yield a predominance of the thermodynamically more stable olefin - the *trans* olefin - rather than the required *cis* isomer. Consequently the synthetic strategy was modified to that outlined in Scheme 20.

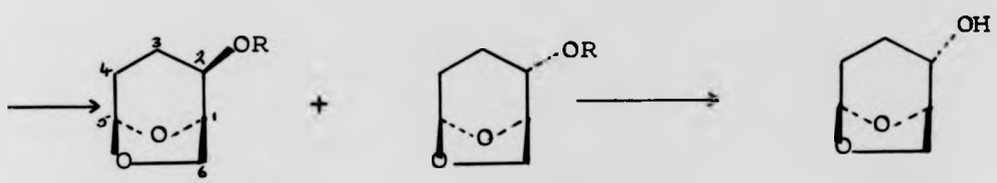
The conversion of 2α-hydroxy-6,8-dioxabicyclo [3.2.1] octane (14) to 6,8-dioxabicyclo [3.2.1] oct-2-ene (6) has been described by Pecka and Černý[8] in two steps *via* the tosylate and subsequent elimination with potassium *tert*-butoxide [Scheme 1, compound (14) ⟶ compound (6)]. These changes result in a much lengthened route.

This modified route involved a Grignard reaction on isopropylidene *R*-glyceraldehyde (78) to generate an alcohol (90). Since the aldehyde (78) contains an asymmetric centre adjacent to the carbonyl group it is to be expected that this may have some effect on the approach of a nucleophile.



(79) (89) (78)

(90) R=H
(91) R=$COCH_3$
(92) R=CH_2Ph
(93) R=$CH_2CH=CH_2$
(94) R=MEM



(95) R=$COCH_3$
(96) R=CH_2Ph
(97) R=$CH_2CH=CH_2$
(98) R=MEM

(99) R=$COCH_3$
(100) R=CH_2Ph
(101) R=$CH_2CH=CH_2$
(102) R=MEM

(14)

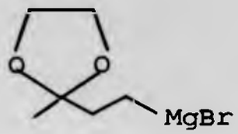
Scheme 20

Cram's rule[60] of 'steric control of asymmetric induction' states that '..the diastereoisomer will predominate which would be formed by the approach of the entering group from the least hindered side of the double bond when the rotational conformation of the C-C bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent asymmetric centre.' Thus, in this Grignard reaction if a predominance of either diastereoisomeric alcohol is seen, then according to Cram's rule it should be the one in which the R-alcohol group has been formed. However, at some stage there must be a separation

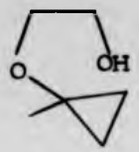
of the two diastereoisomers since after cyclisation only the axial alcohol will undergo elimination readily. The alcohol would be subsequently protected (91-94), the two acetal protecting groups cleaved to permit cyclisation and finally deprotection to yield alcohol (14).

It was anticipated that the main yield losses would be due to a) losses in the separation of diastereoisomers and b) the use of the Grignard reagent (89). There are several literature references to the use of this reagent[61,62] and the method of preparation by Büchi and Wüest[53] proceeded exactly as reported. Marfat and Helquist[63] have reported an apparently more facile synthesis of this Grignard reagent utilizing THF and magnesium powder but this method was never investigated. However, Eaton _et al._[62] have reported that the Grignard reagent is unstable and tends to polymerise and rearrange, expecially at temperatures above 35°C. Although this may be causing a reduction in the yield, it has never stopped the reaction occurring to some degree - as has been reported by Eaton _et al._[62] Ponaras[64] has reported that 3,3-ethylene-dioxybutyl-magnesium bromide (103) may form 1-methylcyclopropyl-(2-hydroxyethyl)ether (104) if the temperature exceeds 25°C. Presumably compound (89) may rearrange by a similar mechanism and undergo polymerisation _via_ a _trans_-ketalisation reaction utilizing the liberated hydroxyl groups. [It may be reactions such as these involving the dioxan ring that cause difficulties in forming the Wittig reagent (81).]

Thus, although stability problems were anticipated with this reagent careful control of the reaction conditions kept these to a minimum.



(103)



(104)

Addition of freshly prepared isopropylidene R-glyceraldehyde (78) to the Grignard reagent (89) afforded the alcohol (90). A tlc study of the product mixture indicated two main compounds and two minor ones. Distillation proved to be an unsatisfactory method of purification but 'flash-chromatography'[65] resulted in a rapid and efficient separation. Glc also enabled a separation of the components and this technique was used to monitor the reaction. The alcohol (90) was isolated as a stable oil in ca. 33% yield based on the 1,3-dioxan-2-(2-bromoethane) (79) used and was characterised spectroscopically.

It was not clear from the nmr spectrum or tlc studies whether both diastereoisomers of this alcohol were formed or not. However, the glc trace (5% Apiezon L, 102°C) showed two peaks in the ratio ca. 1:2 which may be due to the two diastereoisomeric forms of the alcohol. If both diastereoisomers were formed it was impractical to isolate either at this stage.

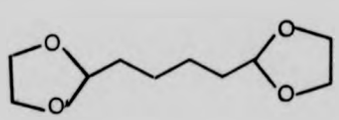
Alternatives to this Grignard reagent have been recognised, such as a lithio derivative[62], but in the present study this was not investigated.

The next step required protection of this newly formed alcohol group with an acid stable, readily removable, protecting group since the cyclisation conditions required

to generate the bicyclic system from the protected derivative of alcohol (90) involved acid catalysis. Few acid stable hydroxyl protecting groups are reported in the literature but a variety of the more commonly used ones were studied. Table 4 presents a summary of those investigated.

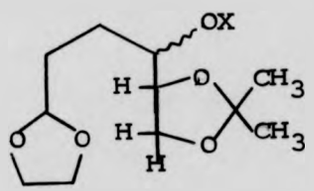
The first attempt was to simply prepare the acetate of the alcohol (90) using the classical reagents, pyridine and acetic anhydride[66]. This required heating overnight at ca.70°C after which time a tlc study indicated several products were obtained but the main product was identified as the acetate (91). This was isolated in ca.60% yield by preparative tlc and the structure confirmed spectroscopically. The various by-products were unidentified, although one had properties which would be compatible with compound (105). A tlc study of the pure acetate showed two overlapping peaks, presumably due to the two possible diastereoisomers, but again these were inseparable. The nmr spectrum also showed some evidence of the presence of diastereoisomers, the acetate methyl group at δ=2.0 ppm appearing as a pair of singlets in a ratio of 2:1. The use of sodium acetate and acetic anhydride as an alternative reagent was investigated but this showed no improvement.

This appeared to be quite a sterically hindered acetate to form and prolonged heating was eventually required. An alternative method for forming sterically hindered acetates was described by Beaucage and Ogilvie[67] but this was decided to be unnecessary at this stage.



(105)

The formation of the benzyl ether (92) was initially attempted by the method of Czernecki *et al.*[68] which required sodium hydride to form an alkoxide followed by the addition of benzyl chloride. While this method produced some benzyl ether the yield was low, *ca.* 20%, and the reaction produced numerous by-products which were separated chromatographically.



DERIVATIVE	REAGENT	REFERENCES
$X=COCH_3$ (91)	a) acetic anhydride/ sodium acetate b) pyridine/ acetic anhydride	private correspondence (66)
$X=CH_2Ph$ (92)	a) THF/NaH/t-butyl-ammonium iodide/$PhCH_2Cl$ b) benzene/KOH/ benzyl chloride	(68) (69)
$X=CH_2CH=CH_2$ (93)	a) THF/NaH/t-butyl-ammonium iodide/ allyl chloride b) benzene/KOH/ allyl chloride	(68) (69)
$X=CH_2OCH_2CH_2OCH_3$	a) THF/NaH/MEM chloride	(70)

Table 4

Instead, greater success was achieved using the method of Lythgoe *et al.*[69] In this case a benzene/potassium hydroxide system was used with the water that was produced being removed by the use of a Dean and Stark apparatus. Although this reaction required a two day reflux, probably due to steric hindrance, it proved to be a much cleaner

reaction and, although distillation proved to be unsatisfactory, column chromatography rapidly removed the one major impurity (thought to be residual benzyl chloride) to give the benzyl derivative (92) in up to 64% yield. This material was fully characterized spectroscopically, the nmr spectrum still showing the characteristic methine proton triplet, the isopropylidene methyl groups and the phenyl group resonances. There was no indication from the nmr spectra whether there was one or two diastereoisomers present but tlc indicated two compounds with very similar R_f values. (The glc conditions studied, 5% Apiezon L, 138°C, gave no indication of two compounds.) Again a separation at this stage appeared impractical. The benzyl ether should be much more acid stable than the acetate and is normally quite readily cleaved by hydrogenolysis over Pd/C catalyst.

Another acid stable protecting group is the allyl ether which can also be readily cleaved by the use of Pd/C in acidic methanol solution. The preparation of the allyl ether derivative (93) was first attempted by the method of Czernecki *et al.*[68] but this gave no identifiable product. Instead the method of Lythgoe *et al.*[69] was adopted using allyl bromide and this was more successful with yields of up to 60% being obtained. This material was characterized spectroscopically and the nmr spectrum quite clearly showed the presence of the allyl group and the two acetal protecting groups. No evidence of the presence of two diastereoisomers was found. Difficulty was experienced in purifying sufficient quantities of this product chromatographically.

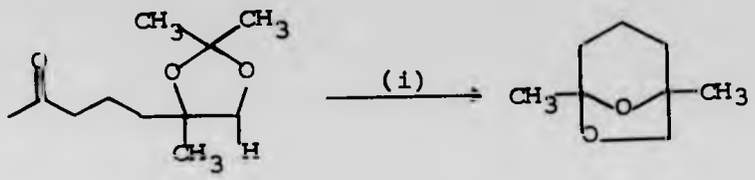
The final derivative considered was the methoxyethoxymethyl ether (MEM) (94). This is a general method for protecting

hydroxyl groups introduced by Corey *et al.*[70] The MEM group was attached by first forming the alkoxide in THF with sodium hydride then adding MEM chloride. After stirring at 0°C, a brief reflux and then work-up, the MEM derivative (94) was isolated by distillation in 41% yield as a colourless oil. This material was fully characterized and the nmr spectrum again showed clearly the various protecting groups. No indication of the presence of more than one diastereoisomer was seen in the nmr spectrum, or by the tlc or glc (5% Apiezon L) studies. The MEM ether is cleaved by reaction with powdered anhydrous zinc bromide in dichloromethane solution.

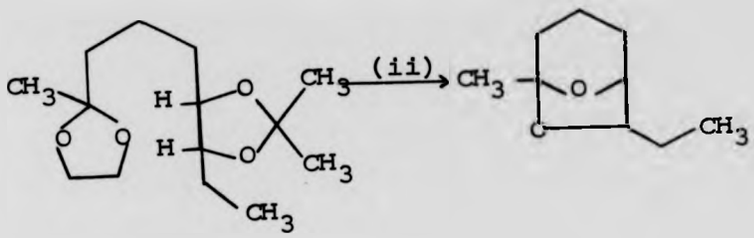
The main features all these protecting groups have are that: a) no new complicating stereochemical features were introduced, b) they are stable in the presence of mild acids, and c) they can normally be readily removed in conditions that will not affect the intramolecular acetal system that is to be formed.

Having prepared the protected alcohol derivative conditions were required which would cleave the acetal and ketal groupings and promote intramolecular acetal formation. Fortunately the target compound (14) was very similar to a number of natural compounds, *e.g.* frontalin (106) and *exo*-brevicomin (107).

Ohrui and Emoto[71] reported the synthesis of (*s*)-(-)-frontalin (106) from *D*-glucose. This was a multistep synthesis but only the last step, which required acid-catalysed formation of an intramolecular ketal from the acyclic compound (108), is of relevance here. This is quite closely related to the system under study and the reported



(108) (106)



(109) (107)

(i) Et_2O, H_2O, p-TSA, reflux; (ii) 70% MeOH, H_2O, p-TSA, R.T.

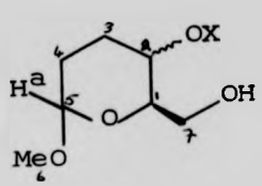
yield of 85.7% appeared encouraging. An even closer analogy was found in the synthesis of (-)-(1S,7S)-exo-brevicomin (107) by Meyer[72]. Here the crucial step involved the acid-catalysed cyclisation of the acyclic compound (109) to the bicyclic system (107). Again the reported yield of 86% was very encouraging. Although these two reagents appeared quite similar both were studied and quite different results were obtained.

The use of the acetate grouping as a protecting group was discontinued because of its instability in the acidic conditions employed. When acetate (91) was subjected to either of the cyclisation conditions described above a wide range of products was observed, presumably formed by cleavage of the acetate group . There was some suggestion from nmr studies that the reaction was producing some bicyclic acetate (95) and (99) but it was impossible to

isolate any material with the required spectral characteristics from the mass of chromatographically similar by-products.

When forming a bicyclic system such as (99) there are two characteristic resonances in the nmr spectra which should appear due to the protons on C-1 and C-5. The resonances of these protons almost invariably appear as broadened singlets at approximately δ=4.5 and δ=5.5 ppm respectively[4]. Consequently, if any nmr study of a crude reaction mixture should show these two resonances it is an excellent indication that a cyclisation to the bicyclic system has occurred.

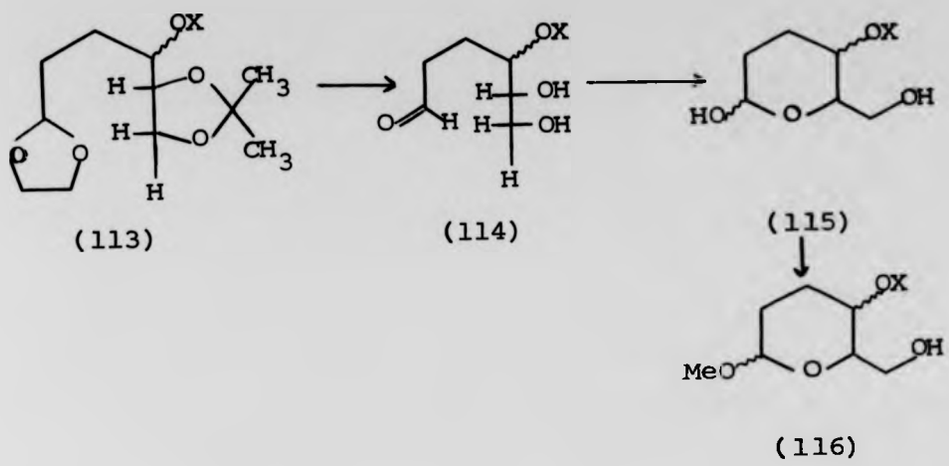
The benzyl derivative (92), the allyl derivative (93) and the MEM derivative (94) were stirred at room temperature with wet methanol and a catalytic amount of para-toluene-sulphonic acid[72] then subjected to an aqueous work-up. Tlc study showed that a variety of products was obtained in all three cases, but in all cases a new product predominated which had a lower R_f value than did the starting material. The nmr spectra of these three crude reaction products looked similar, except for the resonances of the different protecting groups, and showed no sign of any resonance at δ=4.5 or 5.5 ppm indicating no bicyclic material had formed. Because of the low R_f value it was relatively straight forward in each case to isolate these new products in ca. 60% yield by preparative tlc and a careful study of the spectral data indicated the most likely structures to be (110) - (112) respectively.



(110) X=CH_2Ph
(111) X=$CH_2CH{=}CH_2$
(112) X=MEM

The ir spectrum indicated a weak OH stretching band. A broad singlet at about δ=2.2ppm in the nmr spectra, which integrated for one proton, disappeared on shaking with D_2O apparently confirming the presence of a hydroxyl group. This would also explain the low tlc R_f value this compound displayed. A singlet at δ=3.2 ppm integrating for three protons confirmed the presence of a methoxy grouping and a multiplet at δ=4.7ppm was assigned to proton H^a. A study of similar compounds reported in the literature[73] indicated that δ=4.7 ppm was a characteristic chemical shift for protons in this environment.

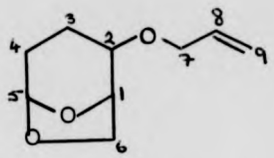
A possible explanation for this finding is illustrated in Scheme 21. Initially, the acetal protecting groups would be cleaved to regenerate the aldehydic and diol functions. This was followed by protonation of the aldehyde then nucleophilic attack by the secondary alcohol to form the monocyclic hemi-acetal system shown. The hemi-acetal alcohol would then be protonated. However, rather than intramolecular attack by the primary alcohol this protonated species undergoes nucleophilic attack by methanol to yield the methoxy derivative (116). It is also possible that a dimethoxy acetal derivative of the aldehyde was formed which then underwent protonation and intramolecular displacement, or that the bicyclic system was formed but was immediately opened by protonation and nucleophilic attack by methanol. It seems likely, however, that intramolecular attack will be the preferred process with the mechanism illustrated being the most probable. No mention was made in the literature of any of this type of reaction by-product being observed.



Scheme 21

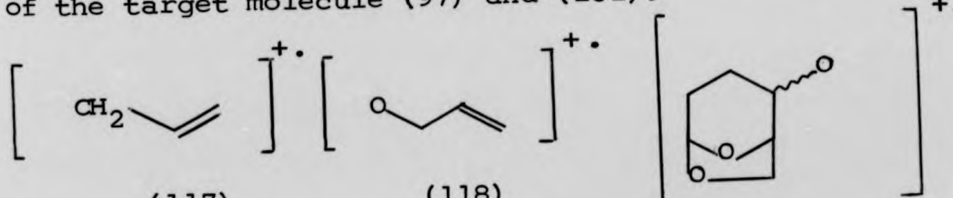
It was decided that if this monocyclic system was placed in a damp, non-participating organic solvent the equilibrium would be re-established in favour of the derivatives (96)-(102). When the benzyl derivative (110) was dissolved in wet diethyl ether and refluxed[71] for 4 days material was isolated in good yield (ca. 50%) which, by spectral analysis, appeared to have the bicyclic skeleton of compounds (96) and (100). The tlc study indicated two very similar compounds were present but no attempt was made to separate them. The main spectral features were that in the nmr spectrum the resonance due to the methoxy protons had vanished and resonances at δ=4.5 and 5.5 ppm due to H-1 and H-5 had appeared. Also the R_f value found by tlc was significantly higher than that of (110) or (92) thus indicating a much less polar compound had formed. Similar studies were carried out with both the allyl and MEM derivatives and , after allowing for differences in the protecting groups, identical results were observed. This results in the required bicyclic material.

Since the use of wet, acidic diethyl ether avoids the problem of competing nucleophilic reagents the open chain alkyl derivative (93) was then subjected directly to reaction in wet acidic diethyl ether and refluxed. Work-up and column chromatography resulted in isolation of (97) and (101) in approximately 35% yield from the one step process. The structure of this product was confirmed by spin decoupling studies, various characteristic resonances in the nmr spectrum and mass spectrometry.



(97), (101)

Protons H-1,δ=4.5; H-5,δ=5.5; H-8,δ=5.8; H-9,δ=5.2; H-3,and H-4 δ=1.7 ppm were all quite readily assignable. Spin decoupling on H-8 caused a doublet at δ=4 ppm to collapse to a singlet while a doublet at δ=3.7 ppm remained practically unaltered. Decoupling on H-1 caused the doublet at δ=3.7 ppm to collapse to a singlet while the doublet at δ=4.0 ppm was effectively unaltered. In the mass spectrum high intensity peaks were found at m/e values consistent with structures (117)-(119), all these fragments being consistent with the likely fragmentation of the target molecule (97) and (101).



(117) (118) (119)

When the benzyl ether (92) was subjected to these cyclisation conditions very little sign of reaction was observed, only trace amounts of the bicyclic product (96) and (100) being observed. Since the use of wet acidic methanol involved a two step reaction and wet acidic diethyl ether had limitations in its application an alternative cyclisation system was sought.

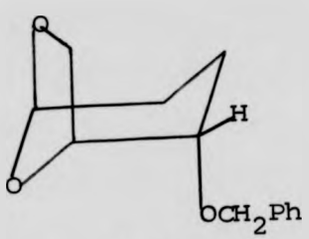
Work by Cooper and Dolby[74] on the synthesis of 4-hydroxycyclopentanones involved the cleavage of acetals using 50% aqueous perchloric acid and dioxane in a 1:1 mixture at 0°C, viz compound (120) gave (121). When the allyl ether derivative (93) was subjected to these conditions a similar result to that obtained with wet acidic diethyl ether was observed. However, when the open chain benzyl ether derivative (92) was subjected to these conditions two new products with higher tlc R_f values than the starting material were obtained in a clean reaction. These two benzyl ether derivatives (96) and (100) had very similar R_f values which were also very similar to the material obtained from the reaction of the monocyclic benzyl ether (110) in wet acidic diethyl ether.

(120) (121)

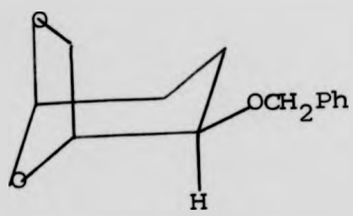
R= n-butyl, $(CH_2)_6CHO$, $(CH_2)_6CH(OCH_3)_2$

A chromatographic separation was attempted on this mixture of benzyl ethers using preparative tlc and this was most effective. The two compounds were isolated in 16.4% (higher R_f) and 18.0% yield respectively; this is

ca. 4% overall yield based on 1,3-dioxan-2-(2-bromoethane) (79) used. These compounds were then analysed spectroscopically; the nmr spectra of both were very similar, showing only minor differences, with the salient features being H-5 and H-1 protons and the benzyl ether protecting group. No attempt was made to assign the stereochemistry at C-2 in either compound from the nmr spectra. Both compounds were distilled on a kugelrohr, (0.25 mm Hg, oven 130-150°C) with the higher R_f material forming white crystals while the lower R_f material remained as an oil. Recrystallisation from hexane produced white needle crystals, melting point 47-48°C, which gave an α_D of -63.9° (c=0.0054,$CHCl_3$). Literature values have been reported[8] for compound (100) of melting point 47°C and optical rotation -66°. [The other diastereoisomer (96) had an optical rotation of -37.2° (c=0.0215,$CHCl_3$).]



(100)



(96)

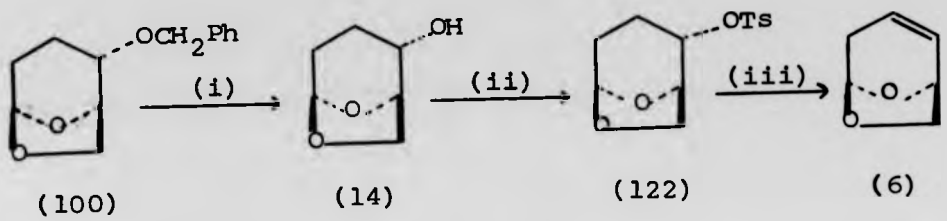
This chromatographic separation gave the two diastereoisomers in approximately a 1:1 ratio. It would appear from this that the chiral centre in isopropylidene R-glyceraldehyde (78) caused no appreciable selectivity on which face of the aldehyde the Grignard reagent attacked when forming the carbon skeleton of the alcohol (90).

As well as being stable to acid conditions it was

essential that these protecting groups should be readily cleaved. Boss and Scheffold[75] reported the cleavage of allyl ethers using acidic aqueous methanol with a Pd/C catalyst. Because of the relative success in preparing the cyclised allyl derivatives(97) and (101) in aqueous acidic diethyl ether it was hoped to substitute this solvent for methanol in the cleavage step and combine the cyclisation and protecting group cleavage into a 'one-pot' reaction. Unfortunately, under these conditions no cleavage of the allyl group was observed. When the literature conditions were applied still no cleavage of the allyl group was observed but, as expected, the monocyclic allyl ether (111) was isolated. Consequently the use of the allyl ether protecting group was studied no further.

The cleavage of the MEM group in compounds (98) and (102), which were prepared by treatment of (94) with acidic aqueous diethyl ether, was attempted using zinc bromide in dichloromethane as reported[70]. Tlc monitoring indicated a new lower R_f material was being formed but insufficient material was isolated for characterisation and owing to other priorities the work was suspended at this stage.

The cleavage of the benzyl ether in compound (100) may be achieved by hydrogenolysis over palladium/charcoal catalyst and work on the benzyl derivative (100) has been reported by Pecka and Černý[8]. They reported the conversion of the benzyl ether (100) to the olefin (6) in three steps (38% yield) *via* hydrogenolysis to the alcohol (14), formation of tosylate (122) and subsequently potassium *tert*-butoxide induced elimination to afford the olefin (6). (Scheme 22).



(100) (14) (122) (6)

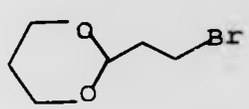
(i) hydrogenolysis Pd/C; (ii) p-TSA chloride; (iii) KOtBu

Scheme 22

However, even if this route were to be reproduced exactly as reported it would result in the synthesis of optically active olefin (6) in only ca. 1.5% overall yield from 1,3-dioxan-2-(2-bromoethane) (79). Since this is only an intermediate with several subsequent steps being required to obtain thromboxane B_2 it was decided that this route was too long with too low a yield to be practical.

Stowell and Keith[76] reported the preparation of 2-(2-bromoethyl)-1,3-dioxan (123) from acrolein, hydrogen bromide and propan-1,3-diol. They also described the subsequent preparation of the phosphonium salt (124) by reaction of the bromide (123) with triphenyl phosphine in cyclohexane. This work was repeated and 2-(1,3-dioxan-2-yl)-ethyltriphenylphosphonium bromide (124) was isolated as a crystalline solid in excellent yield (75%). The reaction of 1,3-dioxan-2-(2-bromoethane) (79) with triphenyl phosphine was then repeated using these reaction conditions however, a negligible amount of solid was precipitated. Thus, quite a surprising difference in reactivity has been demonstrated between the bromides (79) and (123).

The authors described[76] the preparation of the Wittig reagent (125) from the phosphonium salt (124) using n-butyllithium, which generally led to a mixture of cis and trans-olefins, or potassium tert-butoxide in tetrahydrofuran, which generally gave only cis olefins.



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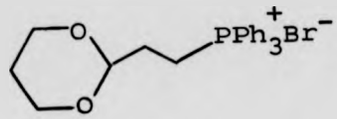

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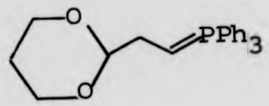
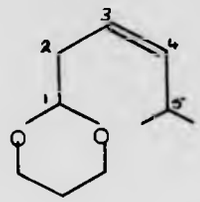


(125)

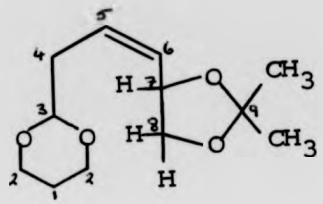


(126)

An initial trial reaction was done using n-butyllithium to generate the Wittig reagent (125) which was subsequently reacted with 2-methylpropanal. This afforded the olefin (126) in good yield and a study of the olefinic coupling constants in the nmr spectrum ($J_{3,4}$=7Hz) indicated the stereochemistry of the olefin was likely to be cis. Other spectral evidence was compatible with the structure indicated. This proved to be a good model for the subsequent reactions with isopropylidene glyceraldehyde (78).

Reaction of the Wittig reagent (125) with the aldehyde (78) proved to be quite straightforward. The Wittig reagent was generated by the reaction of n-butyllithium with the phosphonium salt (124) in THF solution at -23°C as a characteristically red/brown solution. Subsequent addition of freshly generated aldehyde (78), work-up and a flash chromatographic purification of the fairly clean

reaction product mixture yielded the required olefin (127) in ca. 45% yield. This olefin was fully characterised spectroscopically and the molecular formula confirmed by microanalysis. Optical rotation studies showed it to be optically active with an α_D = -7.78° (c=0.0221, $CHCl_3$). Scale expansion and spin decoupling enabled the various resonances in the nmr spectrum to be assigned thus confirming the structure.

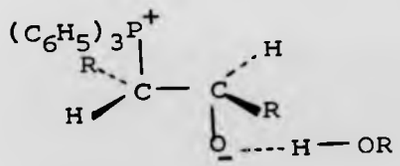


(127)

By spin decoupling on the proton H-7, the ABX_2 system of protons H-4, H-5, and H-6 was clearly seen from which it was possible to measure the olefinic coupling $J_{5,6}$= 11 ± 0.4 Hz. This tended to suggest that the compound had a cis stereochemistry about the olefin but it is not totally conclusive. (Cis couplings are typically about 10 Hz while trans couplings are about 16 Hz; each coupling, however, can extend over a considerable range and there is a large overlapping section where a coupling could indicate cis or trans stereochemistry.) The nmr spectrum does show clearly, however, that contrary to the literature report[76] the use of n-butyllithium has led to only one geometric isomer being formed.

In general[77], the percentage of cis-isomer in the product mixture of a Wittig reaction increases with:

a) increasing reactivity of the carbonyl function, b) a reaction medium consisting of a lithium salt in solution, and c) the use of a protonic solvent. Both the catalysis of the reaction and the increased proportion of cis-isomer are believed to be attributable to coordination of the carbonyl oxygen with the protonic solvent or lithium cation. This causes delocalisation of the negative charge which may increase the proportion of cis-isomer by both retarding the reversal of the initial addition step and by favouring the formation of a solvated betain (128), the precursor of a cis-olefin, rather than the betain (129), the precursor of a trans-olefin.



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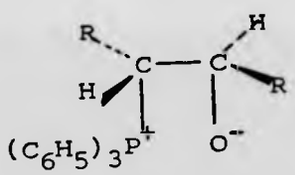
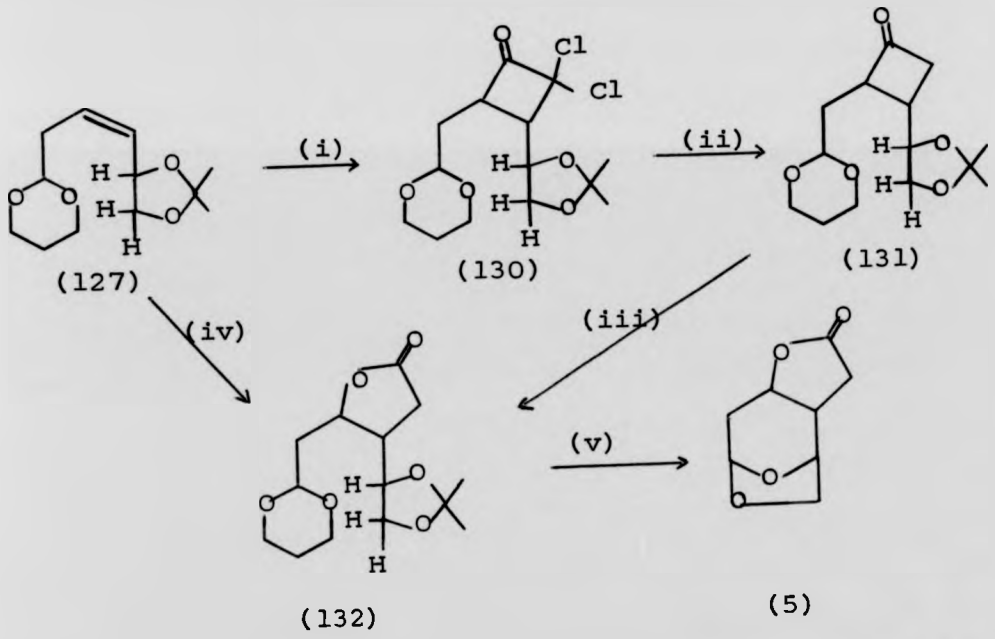


(129)

The reaction was also studied using potassium tert-butoxide and THF but this method produced more by-products and was not studied further.

It was intended to form the olefin (6) directly from olefin (127) by cleavage of the protecting groups and subsequent cyclisation of the product. Because of the success achieved with an aqueous dioxan/perchloric acid system[74] in cyclising compound (92) the same approach was adopted. However, both glc and tlc monitoring of the reaction products failed to detect any of the bicyclic material (6).

The bicyclic olefin is quite a strained system and it may be that the energy required to overcome this strain in performing the cyclisation is too great. An alternative approach was to reduce this strain by converting the two olefinic carbons from sp^2 hybrids to sp^3 hybrids, i.e. removal of the olefin by elaborating it to a δ-lactone prior to cyclisation rather than elaborating a δ-lactone on the cyclised olefin. The two methods considered for forming a δ-lactone, and the problems involved, were covered in greater detail in Section C and their application to this system is illustrated in Scheme 23.



(i) $Cl_2C{=}C{=}O$; (ii) Zn, HOAc; (iii) $C_6H_5CO_3H$; (iv) $Mn(OAc)_2.4H_2O$, CH_3CO_2H, $KMnO_4$, $(CH_3CO)_2O$, NaOAc; (v) $HClO_4$, dioxan.

Scheme 23

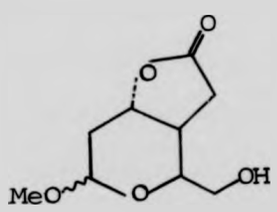
As a model for the radical addition of acetic acid as described by Heiba et al.[48] the reaction was first tried

on olefin (126). The expected decolourisation of the potassium permanganate was observed and, while it proved difficult to remove all the residual acetic acid, the ir spectrum of the crude product indicated a lactone might be present by a carbonyl stretching frequency at 1760 cm^{-1}. The nmr spectrum was very indistinct and no conclusive features were evident.

Identical reaction conditions were applied to the diacetal olefin (127). Again the colour changes indicative of the reaction proceeding were observed and tlc monitoring indicated a range of compounds was being formed. The apparently main product was isolated with difficulty by column chromatography and an ir study showed a carbonyl stretching frequency at 1772 cm^{-1} which was compatible with reported literature values for γ-lactones[78]. The reaction was then repeated a number of times to enable sufficient material to be prepared for further study. A number of similarities in the nmr spectra of this product and the starting olefin (127) were apparent, i.e. there still appeared to be an isopropylidene group and an acetal function protecting the aldehyde. However, there were changes in the olefinic region and a methylene group α to a carbonyl was apparent. A comprehensive series of decoupling experiments on most of the major multiplets was carried out but it was still not possible to assign all the resonances unequivocally. Subsequent tlc study under slightly less polar conditions indicated that two compounds with almost identical R_f values were present. This made an accurate analysis of the nmr spectrum impractical.

A sample of the tricyclic lactone (5) has been prepared by an alternative method in these laboratories[79] and was available for use as a tlc standard. Since the spectral information available was quite compatible with the proposed structure (132), but a more detailed purification and analysis was not feasible, it was decided to proceed on the assumption that this material was compound (132). Subjecting this material to conditions known to cause cyclisation to the 6,8-dioxabicyclo [3.2.1] octane skeleton, while carefully monitoring the reaction mixture by tlc for any trace of the tricyclic lactone (5), appeared to be the most appropriate approach in the time available.

Again, the reaction conditions of choice were the use of aqueous dioxan/perchloric acid as used previously[74]. The reaction was carried out exactly as in previous cases and tlc monitoring indicated a new product was formed with an R_f very similar to that of the authentic tricyclic lactone (5). Attempts to isolate this material using preparative tlc were made but the minute quantities obtained showed no conclusive results on spectral analysis. The cyclisation was also studied using damp acidic methanol in an attempt to form the bicyclic system (133) but after 12 days of stirring at room temperature there was no sign of any reaction.



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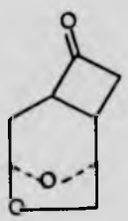


(134)

The alternative approach was to react the olefin (127) with dichloroketene. The method used was that described by Bak and Brady[47] where trichloroacetyl chloride was reacted with activated zinc in the presence of the olefin (127) under high dilution conditions. Tlc study indicated that one main product was produced with a variety of by-products. An ir spectrum of this crude material contained a strong carbonyl stretching band at 1800 cm^{-1} which is indicative of the presence of a dichloro-substituted cyclobutanone ring[46,47]. However, the dimer of dichloroketene also absorbs at around 1800 cm^{-1} and caution must be exercised when assigning these stretching frequencies. The nmr spectrum indicated that some unreacted olefin remained plus some unidentified material.

Purification was attempted by distillation, and by 'flash' column chromatography, but it was not possible to isolate a pure sample of the major product so no fuller characterisation was possible. Consequently it was purely conjecture that this product had the structure (130).

In view of this difficulty the reaction product mixture was subjected to conditions which cause the dechlorination of dichloroketene derivatives. It was hoped that if the main product was compound (130) removal of the chlorine atoms would simplify the purification by changing the R_f of the main product relative to the rest of the products. This method was developed by Corey and Ravindranathan[80] and utilized zinc and acetic acid.

Again a range of products was formed with the ir spectrum of the crude product showing a carbonyl stretching frequency at 1780 cm^{-1}, which is consistent with the

presence of an unsubstituted cyclobutanone[46,47]. It was possible to isolate the main product which displayed this carbonyl adsorption in a fairly pure state. However, an nmr study did not support the structure as being that expected, viz compound (131). Rather, the resonances seen at δ=5.5ppm and δ=4.7 ppm indicated the structure to be tricyclic in nature, these resonances being in positions characteristic of the C-5 and C-1 protons respectively in a bicyclo [3.2.1] system such as this. The resonances due to the two protecting groups have also disappeared.

This being the case it appears that these acidic conditions have induced cleavage of the protecting groups and cyclisation of the resultant diol/aldehyde system to the tricyclic compound (134). Again, because of pressure of time, it was attempted to carry this material through to a known product, and a Baeyer-Villiger reaction was attempted using conditions described by Lee et al.[81] using authentic tricyclic lactone (5) as a tlc standard. This was done on too small a scale to allow any product to be isolated but the tlc monitoring indicated a new product was formed with an R_f almost identical to that of the authentic sample of the tricyclic lactone.

Conclusion

The original synthetic approach proved unsuccessful, although later attempts to cyclise the olefin (127) indicated that had the olefin (82) been prepared it was unlikely that it would have been possible to cause this compound to cyclise to the olefin (6). Instead, the alternative approach using a Grignard reaction resulted

in the preparation of the optically active benzyl ether (100) in low yield. The conversion of this derivative to optically active (6) has been reported[8].

Recently reported work led to the successful synthesis of the olefin (127). Although the reactions describing the attempted elaboration of a lactone on this olefin (127) were cursory in nature the addition of dichloroketene appeared to give a very encouraging result which shows potential for future study.

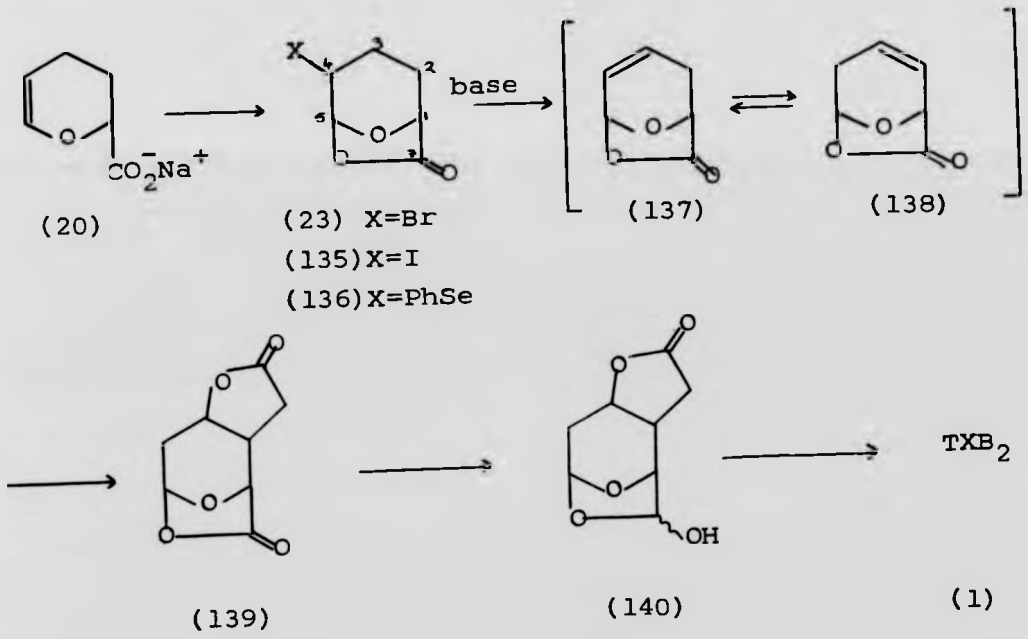
Corrigendum

Compound (79) has been wrongly named as 1,3-dioxan-2-(2-bromoethane) and should be named 2-(2-bromoethyl)-1,3-dioxolane (79).

SECTION E

Alternative Approaches

While work progressed on the two main approaches a number of alternative routes were considered and preliminary experimental work was initiated on two of them. The first approach, using the bicyclic lactone (23),(135), or (136) is illustrated in Scheme 24. This approach was developed from the previously mentioned observation that bromocyclisation of a suspension of the sodium salt (20) appeared to yield only the axial isomer of bromide (23).



(20) (23) X=Br (135) X=I (136) X=PhSe (137) (138) (139) (140) (1)

Scheme 24

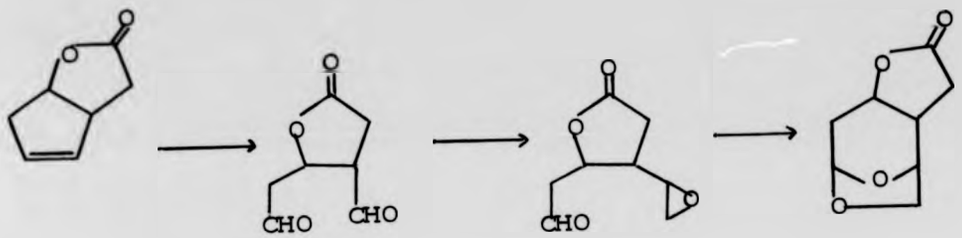
Kato et al.[82] have reported the preparation of olefin (137) from iodide (135) in 61-71% yield via a dehydrohalogenation reaction. However, the assumption was made that it would be possible to isomerise olefin (137) to olefin

(138) in a manner similar to that used for 6,8-dioxabicyclo-[3.2.1]oct-3-ene (19). The potential advantages of an approach like this were : a) the stereospecificity of the cyclisation step, b) the lower side chain of thromboxane B_2 could be attached by a Wittig reaction on lactol (140), a standard technique used to attach the upper chain, and c) the presence of a lactone function might influence the reactivity of the olefin with, for example, dichloroketene.

The initial lactonisation reaction proved to be very facile, e.g. stirring the sodium salt in carbontetrachloride overnight with bromine yielded the bromide (23) as white needle crystals in 48% yield. (This reaction has also been attempted using iodine and phenylselenenylchloride.) Compound (23) showed one peak on glc (5% butanediol succinate) and an accurate mass was obtained on the two molecular ions. Scale expansions and spin decoupling studies on the 90 mHz nmr spectrum showed couplings $J_{4eq,3ax}$=4 Hz and $J_{4eq,3eq}$=1 Hz. Because of the size of these couplings it appears that the bromide must be in the axial position with none of the other isomer present, otherwise much larger couplings would be observed.

Alternative reagents for inducing the cyclisation and the use of a variety of bases for the dehydrohalogenation reaction were under study when the project finished.

A second approach utilized 2-oxabicyclo [3.3.0] oct-6-en-3-one (141). (Scheme 25). It was intended that the double bond in (141) should be cleaved to the dialdehyde (142) then, either directly, or by first protecting the primary aldehyde, this compound would be reacted with the Corey ylide[83] (144). If this led directly to the epoxide (143)

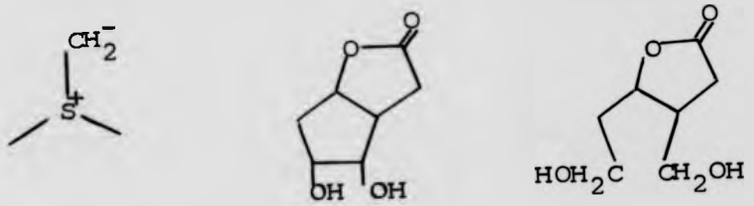


(141) (142) (143) (5)

Scheme 25

this epoxide would be cyclised[74] in acid conditions to yield the tricyclic intermediate (5).

The first step of this reaction was attempted using osmium tetroxide and sodium metaperiodate or ozone with a variety of reductive work-up procedures. All the olefin (141) reacted under these conditions but the only product appeared to be polymeric.



(144) (145) (146)

Instead, the reaction was attempted in two stages. First, the preparation of the diol (145) using a method described by Sharpless et al.[84] was attempted. The cleavage of this diol to the dialdehyde (142) would then be attempted using lead tetraacetate. The preparation of diol (146) was also under study using ozonolysis followed by reduction in an aqueous ethanolic solution of sodium borohydride when the project ran out of time.

These two approaches may provide a new direction for any future work.

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Chapter 3

EXPERIMENTAL DETAILS

GENERAL

Melting points were determined on a Kofler block and are uncorrected.

Ultra violet spectra were recorded on a Perkin Elmer 402 ultraviolet and visible spectrophotometer. Infra red spectra were determined on a Perkin Elmer 577 grating infra red spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Perkin Elmer R10 (60 mHz) or R32 (90mHz) machine and were determined in deuterochloroform. Signal positions are given as δ values using trimethylsilane as an internal standard.

Mass spectra and accurate masses were obtained on a Jeol JMS-D100 machine and were kindly run by Mr. D.F.Dance.

Thin layer chromatography (tlc) was performed on Merck silica gel F_{254} plates, the plates being visualised by a combination of ultraviolet light, iodine vapour and ceric ammonium sulphate spray. Preparative tlc and column chromatography were also conducted using Merck silica gel F_{254}.

Elemental analyses were performed by Dr. F.B.Strauss, Microanalytical Laboratory, Oxford.

Analytical gas chromatography (gc) was performed on Perkin Elmer F11, Perkin Elmer F17, and Perkin Elmer F30 machines. Columns used were support coated open tubular, 2m x 1/8".

Distillations were accomplished using Büchi Kugelröhr bulb-to-bulb systems and the temperatures reported are oven temperatures at distillation.

Thanks are due to Glaxo Group Research, Ware, for a gift of 2-oxabicyclo [3.3.0] oct-6-en-3-one (139).

SECTION A

1. Attempted dimerisation of acrolein[1].

Acrolein (100 ml), benzene (30 ml), and hydroquinone (1 g) were stirred in a high pressure reaction vessel under nitrogen and heated to 170°C for 5 hours. This resulted in the formation of a brown polymer which completely coated the interior of the vessel and was highly resistant to solvents.

2. Formation of 3,4-dihydro-2H-pyran-2-carboxylic acid (21) from the sodium salt (20)[2,3].

A solution of the sodium salt (30 g, 0.2 mole) in water (90 ml) and diethyl ether (90 ml) was chilled and slowly acidified with sulphuric acid solution (7.7 ml in 30 ml of water). The aqueous layer was removed, extracted with diethyl ether and the combined organic layers were dried ($MgSO_4$). This material was then normally used directly because of a tendency for it to polymerise but the unstable acid could be isolated by evaporation of the solvent. ν_{max} 3500-2800, 1730, 1650, 1440, 1240, 1080, 1040, 915, and 735 cm^{-1}; δ:7.6(1H,s,CO_2H), 6.35(1H,d,H5), 4.75(1H,m,H4), 4.5(1H,m,H1), and 2.1(4H,m,H2,3) ppm; tlc (ethyl acetate) R_f = 0.12.

3. Reduction of acid (21) to the alcohol (16).

The dry ethereal solution from Experiment 2 was added dropwise, with stirring, to lithium aluminium hydride (5.32 g, 1 mole equivalent) in diethyl ether (150 ml) at 5°C. After the addition was complete the mixture was stirred at room temperature for 2 hours then held at reflux for 2 hours. After chilling, any residual lithium

aluminium hydride was destroyed by adding ethyl acetate then water (200 ml). The aqueous layer was thoroughly extracted with diethyl ether (5x50 ml) and the combined organic layers dried ($MgSO_4$) and evaporated to leave a viscous oil (16.7 g, 67%).

ν_{max} 3350, 1635, 1235, 1060, 990, 960, 895, 885, 810, and 720 cm^{-1}; δ:6.3(1H,d), 4.6(1H,m), 4.0(2H,m), 3.6(2H,d), and 1.8(4H,m) ppm; tlc (ethyl acetate) R_f = 0.24; glc [5% butanediolsuccinate (BDS), 150°C] R_t = 3.9 min. plus a small peak R_t=3.1 min.

4. Direct reduction of 3,4-dihydro-2H-pyran-2-carboxylic acid, sodium salt (20).

Method A: The sodium salt (0.5 g, 3.3m.mole) was placed in a soxlet extractor. Warm THF from a refluxing solution of lithium aluminium hydride (0.125 g, 1 mole equivalent) and THF (100 ml) was continuously passed through the extractor. After several days no detectable levels of the sodium salt had reacted.

Method B: Lithium aluminium hydride (3.0 g, 1.2 mole equivalent) was added to a stirred suspension of the sodium salt (10 g, 0.067 mole) in dry diethyl ether (100 ml). This gave a gentle reaction which continued for 2-3 hours after which the mixture was then refluxed overnight. After cooling, residual lithium aluminium hydride was destroyed with a few drops of ethyl acetate then water (100 ml). The aqueous layer was extracted with diethyl ether (5x30 ml) and the combined organic layers dried ($MgSO_4$) and evaporated to leave the alcohol (16) (5.8 g, 76%).

5. Preparation of 6,8-dioxabicyclo [3.2.1] octane (17)[4,5].

A solution of alcohol (16) (0.5 g, 3 m. mole) and

p-toluenesulphonic acid (20 mg) in dry benzene (10 ml) was heated to reflux for 2 hours. After cooling a slight excess of sodium methoxide (80 mg) was added to neutralise the acid and the mixture stirred for 30 minutes. The solvent was removed by fractional distillation to leave a black tarry liquid. The product was distilled from this mixture (15mm Hg, oven 50°C, an acetone/solid CO_2 bath was applied to the collecting flask) (0.12 g, 24%) and collected as a white solid, m.pt. 45-48°C.

ν_{max} 1425, 1330, 1205, 1165, 1115, 1075, 1035, 1010, and 985 cm^{-1}; δ :5.5(1H,bs,H-5), 4.5(1H,vbs,H-1), 3.9(2H,m,H-7), and 1.2-2.9(6H,m,H-2,H-3,H-4) ppm; tlc (benzene/acetone 10:1) R_f = 0.49; glc (5%BDS, 150°C) R_t = 3.1 mins.

6. Preparation of 4-bromo-6,8-dioxabicyclo[3.2.1]octane (18)[4,5].

To a stirred solution of the alcohol (16) (20.0 g, 0.17 mole) in carbon tetrachloride (264 ml, freshly distilled from P_2O_5) at room temperature was added dropwise, over a period of 2 hours, a solution of bromine (28.06 g, 0.17 mole). This caused a slight temperature rise and hydrogen bromide was released which was trapped using potassium hydroxide pellets. After addition was complete the mixture was stirred at room temperature for a further hour then the deep red organic layer was decanted from the oily precipitate and the solvent removed to leave a brown oil. (Temperature was always maintained below 30°C.) After distillation (0.5mm Hg, 70°C) a pale yellow oil resulted (16.2 g, 49%). (This material turned deep red/brown on storage, even at low temperatures in the dark.)

ν_{max} 1430, 1330, 1220, 1170, 1110, 1070, 1040, 1010, 985, 960, 910, 890, 790, 765, and 725 cm^{-1}; δ :5.6(1H,bs,H-5),

4.7(1H,vbs,H-1), 4.3-3.9(3H,m,H-7,H-4), and 3.0-1.3(4H,m,H-2, H-3) ppm; tlc (benzene/acetone 1:1) R_f = 0.52; glc (5% BDS, 150°C) endo isomer (18b) R_t = 16.7 mins. : exo isomer (18a) R_t = 15.7 mins. = 1:1 ; Mass spectrum M^+= 192 and 194 (1:1).

7. Dehydrobromination of bromide (18) using ethanolic potassium hydroxide.

General method[5]

To a stirred solution of powdered potassium hydroxide (5.8 g, 0.1 mole) in 95% ethanol (100 ml) was added the bromide (10 g, 52 m.mole). This resulted in the formation of a white precipitate. After stirring at room temperature for 1 hour the mixture was refluxed for 24 hours during which time it rapidly turned a very dark brown. After cooling the mixture was worked up in one of two ways:

A) The mixture was filtered and then 3/4 of the ethanol removed by fractional distillation. (Glc study of the distillate indicated low levels of the product were co-distilled.) The resulting solution was diluted with water (30 ml) and continuously extracted with diethyl ether. The organic phase was then dried and the solvent removed by fractional distillation to leave an oil which was purified by distillation (15 mm Hg, oven 80-100°C).

B) Water (200 ml) was added then the ethanol was removed by fractional distillation. The product was then obtained by steam distillation from the dark brown residue and subsequent dichloromethane extraction of this distillate. After drying ($MgSO_4$) the solvent was removed to leave an oil which was purified by distillation (15 mm Hg, oven 80-100°C).

Using an exo/endo bromide mixture.

1) Bromide (18) (4.5g, 22.5m.mole) reacted with potassium

hydroxide (2.52 g, 45 m.mole) in 95% ethanol (40 ml) and worked up using method A gave a colourless liquid after distillation (1.3 g, 50%).
Glc (5% BDS, 150°C) olefin (19) R_t = 3.4 mins also significant levels of the unreacted endo-bromide (18b) were observed; the nmr spectrum was a composite of a mixture of compounds.

2) Bromide (1.0 g, 5.2 m.mole) reacted with potassium hydroxide (0.58 g, 10 m.mole) in 95% ethanol (10 ml) and worked up by method B gave a colourless liquid after distillation (80 mg).
Glc (5% BDS, 150°C) olefin (19) R_t = 3.4 mins., compound (17) R_t = 2.2 mins. and the endo-bromide (18b) were observed, but in lower levels than when method A was used.

Using exo bromide (18a).

The bromide (0.7 g, 3.6 m.mole) reacted with potassium hydroxide (0.58 g, 10 m.mole) in 95% ethanol (10 ml) and worked up by method A yielded a colourless oil after distillation (0.24 g, 58%).
Glc (5% BDS, 150°C) olefin (19) R_t = 3.4 mins., there was no evidence of the isomeric olefin (6) or bromide (18b) and only very small levels of compound (17) R_t = 2.2 mins.; the nmr and ir were identical to those described in Experiment 9 method D for the olefin (19).

8. Phenylselenenyl chloride induced cyclisation of alcohol (16)[6].

A solution of phenylselenenyl chloride (1.84 g, 9.6 m.mole) in dry dichloromethane (60 ml) under nitrogen was chilled to -78°C. (This reddy/brown solution became deep yellow on cooling.) To this was added dropwise, with stirring,

over a 30 minute period the alcohol (16) (1.0 g, 8.8 m.mole) in dry dichloromethane. [During addition, the solution turned red then pale yellow and finally pale green. Monitoring by tlc (CH_2Cl_2) indicated that when the pale green colour appeared all the alcohol had reacted and a new, strongly uv active compound had formed.] After warming to room temperature the solvent was removed to yield a yellow oil (3.08 g). This was purified by column chromatography (60% dichloromethane/ 40% petrol ether, till all the excess phenylselenenyl chloride was eluted then 100% dichloromethane) to yield a pale yellow oil (1.51 g, 64.0%). ν_{max} 3015, 2940, 2880, 1570, 1470, 1430, 1330, 1310, 1280, 1150, 1115, 1070, 1020, 990, 960, 935, 900, 885, 850, 790, 740, and 690 cm^{-1}; δ :7.4(2H,m,Ph), 7.2(3H,m,Ph), 5.5(1H,d,H-5), 4.35(1H,m,H-1), 3.7(2H,m,H-7 *exo*,*endo*), 3.2(1H,m,H-4), and 2.4-1.2(4H,m,H-2, H-3) ppm; tlc (dichloromethane) R_f = 0.42.

9.Attempted oxidative cleavage of the phenylselenenyl derivative (27).

Method A:- Hydrogen peroxide in THF[6,7].

To a stirred solution of the phenylselenenyl derivative (0.5 g, 1.9 m.mole) in tetrahydrofuran (30 ml) at 0°C was added dropwise hydrogen peroxide (3 molar equivalents). Stirring was continued for 3 hours then the mixture was washed with saturated sodium carbonate solution (3x10 ml). The sodium carbonate was extracted with diethyl ether and the combined organic layers were dried ($MgSO_4$) and studied. Glc (5% BDS, 150°C) olefin (19) R_t = 3.5 mins. plus several by-products; tlc (dichloromethane) indicated a range of products had formed, all of very similar R_f values.

Method B:- Buffered biphasic hydrogen peroxide[8].

To a solution of the phenylselenenyl derivative (27) (0.3 g, 1.2 m.mole) in dichloromethane (20 ml) was added pyridine (0.23 g, 3 m.mole). This solution was chilled (5°C) and hydrogen peroxide solution (3 molar equivalents) was added dropwise and a slightly exothermic reaction occurred. After a further 1 hour stirring the mixture was poured onto dichloromethane (30 ml) and 7% sodium bicarbonate solution (30 ml). The aqueous phase was extracted with dichloromethane (3x15 ml) and the combined organic phases were then washed with 10% hydrochloric acid solution (10 ml). This acid was then extracted with dichloromethane (2x10 ml) and the combined organic phases washed with saturated brine solution (20 ml) and dried ($MgSO_4$). The volume was reduced by fractional distillation. Tlc and glc study of this concentrated solution showed the same results as reported in Method A.

Method C:- Oxidative cleavage using m-chloroperoxybenzoic acid[8].

To a stirred solution of the phenylselenenyl derivative (27) (0.4 g, 1.5 m.mole) in dichloromethane (25 ml) was added m-chloroperoxybenzoic acid (2.2 mole equivalents) in small portions while holding the temperature at 0-5°C. The addition of the per-acid took 3 hours and the solution was then allowed to warm to room temperature. After 2 hours stirring the almost colourless solution turned deep brown and a precipitate appeared. Tlc study (CH_2Cl_2) indicated that all the starting material had now reacted and a range of products formed. The reaction mixture was then added to dichloromethane (25 ml) and 10% sodium carbonate solution (10 ml). The aqueous phase was carefully extracted

with dichloromethane (3x10 ml) and the combined organic phases washed with saturated brine solution (10 ml) and dried ($MgSO_4$). The solution was then concentrated by fractional distillation to leave a brown solution. Tlc and glc study both indicated that some of the olefin (19) had formed but there were too many by-products to make a purification feasible.

Method D:- Oxidative cleavage using ozone[8,9,10].

A standard saturated solution of ozone was prepared by bubbling ozone enriched oxygen into dry dichloromethane (30 ml) at -76°C. This resulted in a royal blue dichloromethane solution of ozone (0.04 molar).

A) The phenyl selenenyl derivative (27) (0.30 g, 1.1 m.mole) was dissolved in dry dichloromethane (20 ml) and chilled to -76°C. To this was slowly added, with stirring, the standard ozone solution (30 ml, 1.2 m.mole). This resulted in a clear colourless solution. Tlc study (CH_2Cl_2) indicated no starting material remained, only the selenoxide (28), R_f = 0.05. The mixture was then allowed to warm to room temperature and left for 12 hours. Solvent was then removed by fractional distillation and the resulting concentrated solution purified by preparative tlc (50% Et_2O, 50% petrol ether).

The main product isolated was recovered starting material (27) (0.17 g, 57%). The remaining material isolated was unidentified except for one fraction (0.015 g) which had glc, tlc, and nmr properties consistent with those of the olefin (19) described in Method D (B) below.

B) To a stirred solution of the phenyl selenenyl derivative (27) (0.5 g, 1.9 m.mole) in dry dichloromethane was added at -76°C

the standard ozone solution (60 ml, 2.4 m.mole). After stirring for 1 hour diisopropylamine (0.9 ml) was added and this solution was then added in 10 ml portions to a refluxing solution of carbon tetrachloride (30 ml) and diisopropylamine (0.5 ml). The solvent was then removed by fractional distillation to leave an orange/yellow oil and precipitate. This material was partially purified by column chromatography (CH_2Cl_2) to give a yellow oil which was subsequently purified by distillation (15 mm Hg, oven 90°C) to give a pale yellow oil (0.15 g, 71%).
ν_{max} 3040, 2960, 2890, 1635, 1475, 1425, 1380, 1330, 1305, 1170, 1100, 1030, 1015, 985, 975, 920, 900, 860, and 700 cm^{-1}; δ: 5.8(2H,m,H-3,H-4), 5.45(1H,d,H-5), 4.6(1H,m,H-1), 3.9(1H,m,H-7_{exo}), 3.75(1H,m, H-7_{endo}), 2.75(1H,m,H_{2ax}, $J_{2ax,2eq}$=17.7 Hz), and 1.85(1H,m,H-2_{eq}) ppm; tlc (CH_2Cl_2) R_f = 0.28; glc (5% BDS, 150°C) R_t=3.35 mins.

Method E:- Formation of the selenoxide (28) using aqueous potassium bicarbonate and bromine[9].

To a vigorously stirred solution of the selenenyl derivative (27) (0.2 g, 0.75 m.mole) in dichloromethane (2 ml) and 10% aqueous potassium hydrogen carbonate solution (2 ml) at 5°C was added dropwise a dilute solution of bromine (0.12 g in dichloromethane, 3ml). After 10 minutes only a very pale colour remained and tlc study (CH_2Cl_2) indicated that all the starting material had reacted to produce a material with R_f = 0.05. The aqueous layer was removed, saturated with salt and extracted with dichloromethane (2x5 ml). The combined organic phases were dried and evaporated to leave a pale brown oil (0.49 g).

This oil was dissolved in dry dichloromethane (10 ml) and diisopropylamine (0.5 ml) and slowly added to a refluxing solution of dry carbontetrachloride (20 ml) and diisopropylamine (0.3 ml). After 10 minutes the mixture was cooled, filtered and the solvent volume reduced by fractional distillation. The product was initially purified by column chromatography (CH_2Cl_2) and subsequently by distillation (15 mm Hg, oven 90°C) to give a pale yellow oil (40 mg, 47%). Spectroscopic and physical study indicated this compound was identical to that described in Method D (B) above, Experiment 9.

10. Isomerisation of the olefin (19) to olefin (6) using ethanolic potassium hydroxide.

Powdered potassium hydroxide (9 g) was added to 95% ethanol/water (20 ml) to give a colourless homogeneous solution. The olefin (19) (0.3 g, 2.7 m.mole) was then added and the solution heated to reflux for 48 hours. Then ethanol (15 ml) was removed by fractional distillation and the residue quenched with saturated brine solution (50 ml). This mixture was extracted with diethyl ether which was then dried and the volume reduced by fractional distillation. The resultant dark brown oil was purified by two distillations (15 mm Hg, oven 90°C) to yield a colourless oil (160 mg, 53.5%).
ν_{max} 3040, 2965, 2890, 1635, 1480, 1420, 1380, 1310, 1170, 1040, 1020, 985, 975, and 925 cm^{-1}; δ: 6.0(1H,m,H-4), 5.6(2H,m,H-1,H-3), 4.6(1H,t,H-5), 4.0(1H,d,H-6_{endo}), 3.75(1H,m,H-6_{exo}), 2.5(1H,m,H-2_{ax}), and 2.0(1H,m,H-2_{eq}) ppm; tlc (CH_2Cl_2) R_f = 0.28; glc (5% BDS) R_t = 2.6 mins., minor impurities were olefin (19) R_t = 3.4 mins., and compound (17) R_t = 2.2 mins.

11. Dehydrobromination and isomerisation of the bromide (18) using potassium hydroxide.

The bromide mixture (18) (7.5 g, 39 m.mole) was added to a solution of potassium hydroxide (4.37 g, 78 m.mole) in 95% ethanol (70 ml) under nitrogen at room temperature. The mixture was then refluxed for 24 hours during which time the solution rapidly turned dark brown and a precipitate formed. The reaction was then cooled and powdered potassium hydroxide (9.4 g) added. This mixture was refluxed for 48 hours then ethanol (40 ml) was removed by fractional distillation. The residue was diluted with saturated brine solution (100 ml) and extracted with diethyl ether. After drying ($MgSO_4$) the solvent was removed by fractional distillation to leave a yellow oil. This was partially purified by fractional distillation to yield a pale yellow oil (3.8 g). Glc (5% BDS, 150°C) olefin (6) [R_t = 2.6 mins.] : endo-bromide (18b) [R_t = 16.7 mins] ≃ 1:1, minor products were the olefin (19) R_t = 3.4 mins, and the compound (17) R_t = 2.2 mins.

12. Dehydrohalogenation of the bromide (18).

Method A[3,4]:- Potassium (4.15 g, 0.11 mole) was reacted with deoxygenated t-butanol (110 ml) under nitrogen to produce a homogeneous solution. To this was added, dropwise with stirring, the bromide (18) (7 g, 0.035 mole) causing a vigorous exothermic reaction. The mixture was then held at reflux for 24 hours whence it turned dark brown. Half the t-butanol was then removed by fractional distillation and the resulting dark brown residue was diluted with water

and continuously extracted with diethyl ether for 12 hours. After drying the organic phase ($MgSO_4$), the solvent was removed by fractional distillation to leave a brown residue which was distilled (10 mm Hg, oven 90°C) to give a pale yellow oil (1.48 g). The ir and nmr spectra were identical with those reported in Experiment 6; glc (5% BDS, 153°C) R_t = 16.7 min [endo-bromide (18b)], plus a number of minor impurities.

Glc examination of the t-butanol removed by distillation indicated the desired product had co-distilled. Glc (5% BDS, 153°C) olefin (6) [R_t = 2.6 mins], and olefin (19) [R_t = 3.4 mins] in ca. 2:1 ratio.

On repeating the reaction on a smaller scale the reaction mixture was diluted with water prior to the distillation and the entire mixture was continuously solvent extracted with diethyl ether. After drying, ($MgSO_4$) the solvent was removed by fractional distillation to leave a brown residue. Glc study indicated this contained the products but in a low level and with numerous by-products.

Method B :- The reaction conditions were identical to those described in Method A until immediately after the 24 hour reflux when an alternative work-up procedure described by Pecka and Černý[11] was incorporated.

Bromide (18) (30 g, 0.16 mole) was refluxed for 36 hours in a solution of potassium t-butoxide [potassium (20g, 0.5 mole) in deoxygenated t-butanol (450 ml)] under nitrogen. Water (300 ml) was then added and the t-butanol removed by fractional distillation using a very long vigreux column packed with glass beads. The t-butanol distilled at 78-79°C then the water came over bringing the product as a steam

distillate. The initial fractions came off cloudy with a pale yellow oil and after 150 ml the water became clear. Extra water was added and 400ml was removed in total. (This distillation took over 12 hours.) The aqueous layers were then thoroughly extracted with dichloromethane, which was dried ($MgSO_4$) then removed by fractional distillation. (Glc study detected no product in the distillate.) This left a pale brown oil (12.4 g).

Glc (5% BDS, 150°C) olefin (6) [R_t = 2.6 mins.]: olefin (19) [R_t = 3.4 mins.] ≃ 3:1, bromide (18b) R_t = 16.7 mins.

13. Isolation of t-butoxide derivative (29) from a dehydrobromination reaction of bromide (18).

The reaction was carried out exactly as described previously using bromide (18) (5.0 g, 26 m.mole) in potassium t-butoxide. On this occasion air was inadvertently admitted during the 24 hour reflux. After 24 hours glc monitoring indicated that all the axial bromide had reacted and a range of products obtained. The reaction was quenched with water (45 ml) and worked up as previously. The aqueous distillate was collected, extracted and the extract dried ($MgSO_4$) and solvent removed in the normal manner to leave a yellow oil (0.77 g). This was distilled (15 mm Hg, oven 190°C) to give a very pale yellow oil (0.33 g). Nmr studies on the crude product indicated a t-butyl group was present [tlc (benzene/acetone 10:1) indicated a number of impurities were still present]. This material was then purified further by column chromatography (Et_2O) followed by preparative tlc (benzene/acetone 10:1) to give a chromatographically pure sample (0.08 g).

ν_{max} 1380, 1360, 1250, 1185, 1120, 1095, 1060, 1020, 985, 960, 940, 895, 870, 790, 760, and 710 cm^{-1}; δ :5.91(1H,m,H-4), 5.55(1H,m,H-3), 5.4(1H,d,H-5), 4.5(1H,m,H-1), 3.90(1H,m,H-7_{exo}), 3.45(1H,m,H-7_{endo}), 3.5(1H,m,H-2_{ax}), and 1.3(9H,s) ppm; tlc (CH_2Cl_2) R_f = 0.31 ; glc (5% BDS, 150°C) R_t = 2.7 mins. ; mass spectrum M^+ = 184, $(CH_3)_3C^{+\cdot}$ = 57; Found :C,64.99; H,8.82%. $C_{10}H_{16}O_3$ requires C,65.19; H,8.75%.

14. Attempted preferential crystallisation of the exo or endo bromide (18).

The mixture of bromides was dissolved in the minimum volume of diethyl ether and chilled in an acetone/CO_2 bath. After a few minutes two drops of petrol ether (40-60) were added and precipitation occurred. The flask was warmed and the precipitate redissolved. After very slow cooling the supernatant was removed from the precipitated crystals and both were studied by glc (5% BDS, 150°C). (The crystals melted as they warmed-up to 0°C.) The glc study of the precipitate and the mother liquor showed identical ratios of the exo and endo bromides and both were identical to the starting bromide, i.e. endo [R_t = 16.7 mins] : exo [R_t = 15.7 mins] ≃ 1:1.

15. Attempted preparation of the phosphonium salt of the bromide (18).

The bromide (0.10 g) was reacted with recrystallised triphenylphosphine (0.15 g) in both dry benzene and dry dichloromethane at room temperature and at reflux. In all four experiments tlc monitoring (benzene/acetone 10:1) indicated that no new products, other than decomposition products of the bromide, were formed. In both cases

refluxing the mixture caused a precipitate to form but tlc analysis indicated this was triphenylphosphine.

An equimolar amount of the bromide (18) and triethylphosphite were reacted at room temperature for several days but no trace of a reaction could be detected by tlc or nmr studies.

16. Attempted chromatographic separation of the bromide (18b) from the olefins (6) and (19).

A column of silica gel (100 g) (30-120 mesh) was packed in 50% diethyl ether and 50% petrol ether. A bromide (18b) / olefin mixture [(6) and (19)] (1 g) was loaded and eluted with the same solvent. Fractions were collected (7 ml) and studied by glc (5% BDS, 150°C). Each fraction showed the same ratio of olefin : bromide as was seen in the original sample, i.e. olefin (6) [R_t = 2.6 mins.] : olefin (19) [R_t = 3.4 mins.] : bromide (18b) [R_t = 16.7 mins.] ≃ 9:1:10 .

17. Attempted conversion of the bromide (18) to the iodo-derivative (57)[12].

To a pale yellow solution of sodium iodide (0.32 g, 2.1 m.mole) in methyl ethyl ketone (5 ml) was added the exo and endo-bromide mixture (18) (0.2 g, 1.04 m.mole). Addition caused immediate formation of a brown colour and within ½ hour a white precipitate could be seen. Glc study (5% BDS, 150°C) indicated no reduction in the level of bromide had occurred so reflux was started. After 8 hours glc study still indicated that no bromide had reacted and no product was formed. After isolation, the nmr spectrum of the crude product was identical with that of the starting bromide mixture.

18. Bromocyclisation of alcohol (16) using pyridinium salts.

Pyridinium hydrogen bromide perbromide ($C_5H_5N^+HBr_3^-$) was recrystallised from glacial acetic acid to form red needle crystals which were dried under vacuum.

To a vigorously stirred slurry of the perbromide (0.63 g, 2.0 m.mole) in dry carbon tetrachloride (10 ml) held at 5-10°C the alcohol (16) (0.25 g, 2.2 m.mole) in dry carbon tetrachloride was added slowly over ½ hour. During this period the crystals appeared to become a little paler in colour and on prolonged stirring a clear colourless solution resulted with residual orange crystals coagulated on the bottom of the flask. The organic phase was decanted and the solvent removed to leave a pale brown oil (0.29 g, 67%).
Glc (5%, BDS, 150°C) endo- bromide [R_t = 16.7 mins.] : exo- bromide [R_t = 15.7 mins.] = 1:1 ; spectral and physical characteristics were identical to those reported previously for the mixture of bromides. See Experiment 6.

19. Formation of the alkoxide of alcohol (16) and its subsequent bromocyclisation.

The alcohol (16) (0.5 g, 4.4 m.mole) was dissolved in dry THF (10 ml) and an excess of sodium hydride added under an inert atmosphere. Once the initial effervescence had subsided the mixture was refluxed for 4 hours. After cooling the reddy brown liquid was removed from the residual sodium hydride, chilled to ca. 0°C and bromine (0.77 g, 1.1 mole equivalents) in carbon tetrachloride was added dropwise causing a white precipitate to form. After a further 2 hours stirring the precipitate was removed by filtration and the solvent evaporated to leave a dark brown viscous

oil (0.98 g). This material was distilled (0.5 mm Hg, oven 90°C) to give a pale yellow oil (0.30 g, 35%). Glc (5% BDS, 150°C) endo-bromide [(18b) R_t = 16.7 mins.] : exo-bromide [(18a) R_t = 15.6 mins.] ≃ 3 : 5, compound (17) R_t = 2.2 mins. was also observed. Spectral characteristics for this mixture were identical with those reported previously. See Experiment 6.

20. Preparation pyridine perbromide[13].

To a vigorously stirred solution of bromine (10 g, 0.125 mole) in petrol ether (30 ml) at ca. 5°C was added pyridine (5 g, 0.06 mole) in petrol ether (10 ml). Initially this caused an extremely vigorous reaction which gradually subsided and, after a slow addition over 1 hour, orange crystals had formed and the petrol solution was practically colourless. The crystals were then separated, washed thoroughly with petrol, and dried (12.62 g, 88%).

21. Bromocyclisation of alcohol (16) using pyridine perbromide.

To a stirred solution of the alcohol (16) (0.1 g, 0.9 m.mole) in diethyl ether (10 ml) at room temperature was added pyridine perbromide ($C_5H_5NBr_2$) (0.21 g, 1 mole equivalent). After 12 hours stirring tlc study (80% diethyl ether/petrol ether) indicated that all the starting material had reacted to give two main products with R_f values compatible with those of the exo and endo-bromides. The solvent was decanted from the coagulated solid in the flask and evaporated to leave a pale yellow oil (0.07 g, 41.5%). Glc (5% BDS, 150°C) exo-bromide [(18a) R_t = 15.6 mins.] : endo-bromide [(18b) R_t = 16.7 mins.] ≃ 1 : 1, compound (17) R_t = 2.2 mins. was also detected. Spectral properties of

this mixture were identical to those reported previously. See Experiment 6.

22. Attempted cyclisation of alcohol (16) using mercuric nitrate[14,15].

The alcohol (2 g, 18 m.mole) was added dropwise over a period of 10 minutes to a stirred suspension of mercuric nitrate monohydrate (5.8 g, 17 m.mole) and potassium nitrate (1.7 g, 17 m.mole) in water (17 ml). Stirring was continued at room temperature for 1 week whence a black precipitate was observed. Tlc study (Et_2O) indicated that all the starting material had reacted and a new low R_f material had formed. The mixture was then extracted with diethyl ether (3x30 ml) (litmus paper indicated both aqueous and organic layers were acidic due to nitric acid released during the reaction). Addition of saturated brine solution to the aqueous layer caused immediate precipitation of a milky coloured material. The aqueous layer was then neutralised with saturated potassium bicarbonate and the precipitate removed. This material was soluble only in 10% potassium hydroxide to give a black solution and showed no reaction on addition of potassium iodide. This precipitate remained unidentified. No identifiable material was isolated from the diethyl ether extract after drying ($MgSO_4$) and evaporation.

23. Attempted cyclisation of alcohol (16) using mercuric acetate[14,15].

The alcohol (16) (0.5 g, 4.5 m.mole) was added dropwise over 5 minutes to a stirred solution of mercuric acetate (1.28 g, 4 m.mole) and sodium acetate trihydrate (0.55 g,

4 m.mole) in water (5 ml). After 10 minutes a white precipitate was observed but a sample of the reaction mixture tested with 10% sodium hydroxide solution gave a yellow mercuric oxide precipitate indicating the reaction was incomplete. Stirring was continued for 1 week at which time a black precipitate was seen in the flask. Addition of brine to the separated solution caused a white precipitate to form which was isolated. (This precipitate was insoluble in EtOH, Et_2O, EtOAc, or $CHCl_3$.) This dissolved in 10% sodium hydroxide solution to give a black solution which gave no reaction when potassium iodide was added. Material remained unidentified.

24. Cyclisation of alcohol (16) using N-bromosuccinimide.

N-Bromosuccinimide (1.16 g, 6.5 m.mole) was added to a vigorously stirred solution of the alcohol (16) (0.5 g, 4.4 m.mole) in dry carbon tetrachloride (6 ml). Stirring was continued for 6 hours at room temperature during which time a sticky orange precipitate formed. The mixture was then filtered and the solvent evaporated to yield a yellow oil (0.69 g). This material was purified by preparative tlc (60% diethyl ether/petrol ether) to yield a pale yellow oil (0.41 g, 48%).

Ir and nmr spectra were identical to those previously reported for bromide (18), see Experiment 6 ; glc (5% BDS, 150°C) endo-bromide [(18b) R_t = 16.7 mins.] : exo-bromide [(18a) R_t = 15.7 mins.] ≃ 3 : 2 ; tlc (80%diethyl ether/petrol ether) R_f = 0.59 and 0.52.

When the reaction was repeated at -20°C and 0°C the ratio of exo : endo-bromides obtained was unchanged.

25. Reaction of N-bromosuccinimide with the trityl derivative (54).

The trityl derivative (54) (0.3 g, 0.84 m.mole) was dissolved in carbon tetrachloride (5 ml) and N-bromosuccinimide (0.18 g, 1.2 mole equivalents) added. After stirring for ½ hour at room temperature the mixture was refluxed for 12 hours. Tlc study indicated that all the starting material had reacted. After cooling, the mixture was filtered and the solvent evaporated to yield a yellow gum (0.4 g). This was purified by preparative tlc (40% diethyl ether/petrol ether) and a number of components separated but no material identifiable by spectroscopic or physical studies was isolated. (Trityl derivative kindly supplied by A. Kelly).

26. Preparation of the iodide (57).

Method A:- Potassium iodide/iodine in sodium bicarbonate solution[16,17].

The alcohol (16) (2.0 g, 18 m.mole) was dissolved in water (100 ml) containing sodium bicarbonate (4.42 g, 53 m.mole) to give a homogeneous solution. To this was slowly added iodine (6.7 g, 53 m.mole) and potassium iodide (17.5 g, 0.11 mole) in water (50 ml). This resulted in instantaneous decolourisation of the iodine solution and a vigorous evolution of gas. At the completion of the addition the homogeneous reaction mixture, now dark brown, was stirred at room temperature for 3 hours in the dark. Excess iodine was destroyed by adding sodium metabisulphite solution and the aqueous mixture was carefully extracted with dichloromethane (5x50 ml), the extracts dried ($MgSO_4$) and evaporated to leave a yellow, partially crystalline, oil (0.56 g). Re-extraction of the aqueous phase yielded

more product (0.14 g). (Continuous extraction was considered but glc study indicated severe decomposition of the product occurred in the hot organic solvent.) This material was purified by preparative tlc (90% benzene/acetone) and column chromatography (50% diethyl ether/petrol ether) to yield a pale brown oil (120 mg, 3%). The product decomposed on distillation and some decomposition occurred on the tlc plate and column.

ν_{max} 2960, 2900, 2860, 1485, 1445, 1360, 1340, 1315, 1290, 1190, 1125, 1060, 1020, 990, 935, 910, 885, 790, and 735 cm^{-1}; δ: 5.4(1H,bs,H-5), 4.4(1H,m,H-1), 4.0(1H,m,H-4), 3.8(2H,m,H-7), and 2.5 - 1.5(4H,m,H-2, H-3) ppm; tlc (80% diethyl ether/ petrol ether) R_f = 0.54 ; glc (5% BDS, 150°C) R_t = 18.5 mins., and a little of compound (17) R_t = 2.2 mins. ; mass spectrum M^+ = 239.9650 (calc. M^+ = 239.9674), fragments $C_6H_9O_2$ = 113, and I^+ = 127 (a lot of decomposition occurred on the probe in the mass spectrometer).

Method B:- Iodocyclisation of alcohol (16) in organic solvent with and without a buffer.

General method:- The alcohol (1.0 g, 8.8 m.mole) was dissolved in dichloromethane or carbon tetrachloride (15 ml) in the presence of potassium carbonate or powdered potassium hydroxide (2 mole equivalents) if required. To this was added iodine (1.23 g, 1.1 equivalents) either in the same organic solvent (15 ml) or as crystals. The reaction mixture was stirred at room temperature for 3 hours then sodium metabisulphite was added to destroy excess iodine. After filtering, the solvent was evaporated. Purification was carried out by either preparative tlc or column chromatography and the final products were compared

by spectroscopic and chromatographic methods with pure samples. Full physical and spectral characteristics of the iodide (57) are described in Experiment 26, Method A.

Comments: In each case the yields were low and very variable with varying levels of by-products, some inseparable, however, each reaction had two points in common: a) tlc monitoring (80% diethyl ether/petrol) immediately prior to the reaction work-up compared with the isolated crude product indicated substantial decomposition occurred during work-up, and b) 6,8-dioxabicyclo [3.2.1] octane (17) was always present, and in the absence of buffer became the main product.

Method C:- Formation of alkoxide of alcohol (16) and subsequent iodocyclisation.

A stirred solution of the alcohol (16) (0.5 g, 4.4 m.mole) in dry THF (10 ml) under N_2 was treated with sodium hydride (0.16 g, 1.5 mole equivalent). The solution of the alkoxide was then separated from the residual sodium hydride and iodine (0.62 g, 1.1 mole equivalent) was added to the solution resulting in an exothermic reaction. After 4 hours this solution was filtered through celite and the solvent evaporated to leave an oil with a precipitate. The material was redissolved in THF and the solid removed by filtration. The solvent was then removed to leave a viscous brown oil (0.75 g). This was purified by preparative tlc (80% diethyl ether/petrol ether) to yield a pale brown oil (0.19 g, 18%). Nmr and ir spectra were identical to those reported previously, see Experiment 26, Method A ; glc (5% BDS, 150°C) R_t = 18.5 mins. and a little of compound (17) R_t = 2.2 mins.

If diethyl ether was used then exactly the same results were achieved.

27. Preparation of N-silver succinimide[18].

A solution of sodium hydroxide (10.7 g, 0.27 mole) in water (50 ml) was added dropwise rapidly to a stirred solution of silver nitrate (41.5 g, 0.245 mole) in water (112 ml) at room temperature. The precipitated silver oxide was collected and washed with water, sucked dry briefly, and added in one portion to a boiling solution of succinimide (22.16 g, 0.223 mole) in water (667 ml) in the dark. After boiling for 25 minutes the suspension was suction filtered through a preheated Buchner in the dark and the filtrate allowed to stand at room temperature while the N-silver succinimide crystallised. The pale silvery precipitate was collected and dried in a vacuum oven at 60°C (20.9 g, 45.5% based on the succinimide used).

28. Preparation of N-iodosuccinimide[18].

N-Silver succinimide (18 g, 87 m.mole) was shaken vigorously with iodine (20 g, 79 m.mole) and dry dioxan (90 ml) in a wide mouthed brown bottle for a few minutes then periodically for an hour. The mixture was then warmed to 60°C for 5 minutes and filtered through a prewarmed Buchner filter in the dark. Dry carbon tetrachloride (200 ml) was then added to the brown solution and chilled for 12 hours (-8 to -20°C). The crystals were then collected, washed with dry carbon tetrachloride (25 ml), and dried in a desiccator to leave white needle crystals (12.5 g, 70.4%). M.Pt. = 190 - 198°C (literature value = 193 - 199°C).

29. Reaction of N-iodosuccinimide with alcohol (16)[19].

N-Iodosuccinimide (2.95 g, 13 m.mole) was added with stirring to the alcohol (16) (1 g, 8.7 m.mole) in dry

carbon tetrachloride (11 ml). This resulted in an exothermic reaction and gradual evolution of a pink iodine colour. After 10 minutes at room temperature the flask was placed in a hot water bath and the temperature gradually raised over 15 minutes until the mixture was refluxing. After gentle reflux for 60 minutes the flask was cooled and powdered sodium thiosulphate (2 g) added. In a short time the deep brown colour was removed then the mixture was filtered and the solvent evaporated to leave a pale orangey oil (1.96 g). Glc and tlc study showed this to be mainly the iodide (57) with only small levels of impurities. This material was purified by preparative tlc (60% diethyl ether/petrol ether) to yield a pale yellow oil (1.02 g, 48%). This material decomposed on distillation (0.2 mm Hg, oven 150°C) to give a yellow distillate.
Nmr and ir spectra were identical to those described previously for iodide (57), see Experiment 26 Method A ; tlc (80% diethyl ether/petrol ether) R_f = 0.54 ; glc (5% BDS, 150°C) R_t = 18.5 mins.

Comments:- Other experiments varied the use of reflux by: a) addition of N-iodosuccinimide to a refluxing solution of the alcohol, b) addition of N- iodosuccinimide at room temperature with rapid elevation to reflux. In both cases the sole significant product was the iodide (57), no olefin (6) or (19) or compound (17) were detected.

30. Preparation of pyridine periodide.

Pyridine (10 g, 0.127 mole) was added to a stirred solution of iodine (32.15 g, 0.127 mole) in dry carbon tetrachloride (200 ml) at 0°C. After standing for 12 hours the dark green precipitate was removed, washed with carbon tetrachloride and sucked dry (32.3 g, 76%); m.pt. = 65 - 72°C.

The purity of this product was determined by titration with thiosulphate[20].

$$2S_2O_3^{2-} + I_2 \longrightarrow S_4O_6^{2-} + 2I^-$$

A standard solution of pyridine periodide was prepared [1.8397 g in acetone (100 ml) = 0.0553 molar if product is 100% pure)] and titrated against standard 0.1 N thiosulphate solution. The acetone solution (25 ml) was placed in a flask and water (80 ml) was added. This caused a brown precipitate to form. Then the sodium thiosulphate solution was added from a burrette. Once the solution turned a clear pale brown colour, fresh starch solution (2 ml) was added. The deep blue solution was then titrated till the colour just disappeared. 23.25 ml of 0.1 N sodium thiosulphate solution was required, thus indicating the periodide solution was 0.0465 molar.
The purity of the pyridine periodide was thus 82.6%.

31. Iodocyclisation of alcohol (16) using pyridine periodide.

General Method:- The alcohol (1 g, 8.7 m.mole) was dissolved in the solvent (20 ml) and the temperature adjusted. Pyridine periodide (3.5 g, 8.8 m.mole) was then added with stirring. The reaction was monitored by tlc (80% diethyl ether/ petrol ether) and stirring was continued until all the starting material had reacted. The organic phase was then separated from the precipitated oil or solid and evaporated. The crude product was studied by glc and tlc and shown to contain the iodide (57).

Combinations of reaction conditions used:
diethyl ether:- -76°C, 0°C, room temperature, and room temperature warmed slowly to reflux.

carbon tetrachloride:- room temperature.

petrol ether:- 0°C.

In all cases, glc study (5% BDS, 150°C) indicated that some iodide had formed in each reaction but tlc always showed the same wide range of by-products were also present. Diethyl ether tended to have lower levels of these by-products but not significantly so.

32. Bromocyclisation of alcohol (16) yielding the exo-bromide (18a).

To a vigorously stirred solution of the alcohol (5.0 g, 44 m.mole) in dry carbon tetrachloride (75 ml) with powdered, anhydrous potassium carbonate (6.0 g, 44 m.mole) at 15°C ± 2°C was added slowly dropwise, over a 3 hour period, bromine (7.25 g, 46 m.mole) in dry carbon tetrachloride (40 ml). Initial additions of bromine were rapidly decolourised but as the addition progressed a brown colour developed and the potassium carbonate tended to coagulate. After stirring for a further 2 hours the mixture was filtered and the solvent evaporated to leave a very viscous, pale yellow oil (7.26 g). This material was purified by column chromatography (60% diethyl ether/ petrol ether) to give a pale yellow oil (2.03 g, 24%). (Yields between 10 and 45% were observed.) Purification could also be effected by distillation (0.2 mm Hg, oven 120°C) but this was not as effecient in removing the by-products. Spectral and physical properties were effectively unchanged relative to those of the exo/endo mixture reported previously, see Experiment 6; tlc (60% diethyl ether/petrol ether) R_f = 0.48 ; glc (5% BDS, 150°C) exo-bromide (18a) R_t = 15.7 mins. with a trace of the endo-bromide (18b) R_t = 16.7 mins and compound (17) R_t = 2.3 mins.

If the reaction was terminated immediately following the addition of bromine then significantly greater levels of 6,8-dioxabicyclo [3.2.1] octane (17) were observed.

33. Dehydrobromination of exo-4-bromo-6,8-dioxabicyclo-[3.2.1]octane (18a) to the olefin (6).

The reaction and work-up conditions used were identical to those described in Experiment 12, Method B.

The bromide (18a) (1.84 g, 9.5 m.mole) was reacted with potassium t-butoxide [potassium (0.85 g, 23 m.mole) in deoxygenated t-butanol (20 ml)] . After 24 hours reflux a glc study indicated that no bromide remained. Then water (40 ml) was added and the t-butanol removed by fractional distillation. Glc study indicated trace quantities of product were lost in this distillate. The aqueous fraction was then distilled and extracted with dichloromethane. After drying ($MgSO_4$) and fractional distillation to remove the solvent a pale yellow oil remained which was distilled (15 mm Hg, oven 100°C) to give an almost colourless oil (0.33 g, 30.6%).

The nmr and ir spectra were identical to those reported previously, see Experiment 10; glc (5% BDS, 150°C) R_t = 2.6 mins., two minor impurities were olefin (19) R_t = 3.4 mins. and compound (17) R_t = 2.2 mins.

34. Dehydrobromination of the bromide (18) using 1,5-diazabicyclo [5.4.0] undec-5-ene.

The freshly prepared bromide mixture (18) (0.5 g, 2.6 m.mole) and 1,5-diazabicyclo [5.4.0] undec-5-ene (0.58 g, 3.9 m.mole) were mixed together with stirring. This caused a mildly exothermic reaction and rapid generation of a deep brown colour. This mixture was stirred at 80°C

overnight, during which time a colourless liquid condensed at the neck of the flask. After cooling, the equipment was rearranged and the product was distilled directly from the reaction mixture (10 mm Hg, oven 100°C) giving a colourless liquid (130 mg).
Glc (5% BDS, 150°C) olefin (19) R_t = 3.4 mins., and the endo-bromide (18b) R_t = 16.7 mins.

Freshly prepared exo-bromide (18a) (0.56 g, 2.9 m.mole) reacted with 1,5-diazabicyclo [5.4.0] undec-5-ene (0.7 g, 4.7 m.mole) as described above produced a pale yellow oil (0.09 g, 27%).
The nmr and ir spectra were identical to those reported previously, see Experiment 9 Method D(b); glc (5% BDS, 150°C) olefin (19) R_t = 3.4 mins.

35. Dehydrobromination of the bromide (18) using sodium hydride[22].

To a vigorously stirred solution of the bromide mixture (2.5 g, 0.013 mole) in dry 1,2-dimethoxyethane (19 ml) was added sodium hydride (0.063 g) and then 1 minute later dry ethanol (0.063 ml). This caused the mixture to turn from a pale yellow colour to pale brown with a slight precipitate. This procedure was repeated until all the sodium hydride (0.32 g, 13 m.mole) and all the ethanol (0.126 ml) had been added. Stirring was continued for a further hour during which time more precipitate formed, then the mixture was refluxed for 1½ hours. Approximately 17 ml of solvent was then removed by fractional distillation. Dry diethyl ether (12.5 ml) was then added to the residue and the precipitate removed by filtration. The solvent was then removed by fractional distillation to leave a

overnight, during which time a colourless liquid condensed at the neck of the flask. After cooling, the equipment was rearranged and the product was distilled directly from the reaction mixture (10 mm Hg, oven 100°C) giving a colourless liquid (130 mg).
Glc (5% BDS, 150°C) olefin (19) R_t = 3.4 mins., and the endo-bromide (18b) R_t = 16.7 mins.

Freshly prepared exo-bromide (18a) (0.56 g, 2.9 m.mole) reacted with 1,5-diazabicyclo [5.4.0] undec-5-ene (0.7 g, 4.7 m.mole) as described above produced a pale yellow oil (0.09 g, 27%).
The nmr and ir spectra were identical to those reported previously, see Experiment 9 Method D(b); glc (5% BDS, 150°C) olefin (19) R_t = 3.4 mins.

35. Dehydrobromination of the bromide (18) using sodium hydride[22].

To a vigorously stirred solution of the bromide mixture (2.5 g, 0.013 mole) in dry 1,2-dimethoxyethane (19 ml) was added sodium hydride (0.063 g) and then 1 minute later dry ethanol (0.063 ml). This caused the mixture to turn from a pale yellow colour to pale brown with a slight precipitate. This procedure was repeated until all the sodium hydride (0.32 g, 13 m.mole) and all the ethanol (0.126 ml) had been added. Stirring was continued for a further hour during which time more precipitate formed, then the mixture was refluxed for 1½ hours. Approximately 17 ml of solvent was then removed by fractional distillation. Dry diethyl ether (12.5 ml) was then added to the residue and the precipitate removed by filtration. The solvent was then removed by fractional distillation to leave a

pale brown oil which was purified by distillation (15 mm Hg, oven 80 - 100°C) (63 mg).
Glc (5% BDS, 150°C) olefin (19) R_t = 3.4 mins., endo-bromide (18b) R_t = 16.7 mins., and compound (17) R_t = 2.2 mins.

36. Dehydrobromination of exo-bromide (18a) using a guanidine base.

The exo-bromide (18a) (0.9 g, 4.7 m.mole) was added to N,N' -di-O-tolylguanidine (sym) (3 g) and the solid mixture was heated to 100°C for 24 hours during which time a brown colour spread through the mixture. The product was then distilled directly from the reaction mixture (15 mm Hg, oven up to 140°C) to yield a colourless liquid (50 mg). (At 120°C the reaction mixture melted).
Glc (5% BDS, 150°C) low level of olefin (19) R_t = 3.4 mins., and predominately unreacted exo-bromide (18a).

37. Dehydrobromination of the exo-bromide (18a) using base (64)

This base was kindly supplied by Dr. F.G.Riddell.

A solution of the base (0.64 g, 2.6 m.mole) in dry benzene (25 ml) was refluxed overnight in a Dean and Stark apparatus. After cooling, the Dean and Stark was removed. Sodium hydride (0.07 g, 1.1 mole equivalents) was then added to give a pale yellow solution. Bromide (18a) (0.5 g, 2.6 m.mole) in dry benzene (5 ml) was added and heat applied. As the temperature rose the colour darkened to a deep brown and the mixture was refluxed for 12 hours.

After cooling, solid ammonium chloride was added. The mixture was then filtered through silica gel (15 g, 60-120 mesh) and the silica washed with diethyl ether. The

deep brown colour all stuck to the top of the silica. The solvent was then removed by fractional distillation to leave an orange oil which was further purified by distillation (15 mm Hg, oven 100°C) to yield a colourless oil (140 mg, 47%).

The nmr and ir spectra were identical to those reported previously for the olefin (19), see Experiment 9 Method D(b); glc (5% BDS, 150°C) olefin (19) R_t = 3.4 mins., and a little of compound (17) R_t = 2.2 mins.

This olefin (140 mg) in benzene (2 ml) was added to another sample of the base (64) prepared as above. The mixture was heated to reflux for 30 hours then the reaction was worked-up as above. Glc study of the product indicated that no isomerisation of the olefin (19) to the olefin (6) had occurred.

38. Dehydrobromination of bromide (18) using potassium t-butoxide in dimethyl sulphoxide.

To a deoxygenated solution of potassium t-butoxide (9.2 g, 82 m.mole) in freshly distilled dimethyl sulphoxide (200 ml) under nitrogen was added the bromide (3.1 g, 16 m.mole) in dimethyl sulphoxide (20 ml). This caused rapid formation of a deep brown colour. After stirring for 3 hours at room temperature the reaction mixture was held at 80°C for 24 hours. (Glc study prior to heating indicated that all the axial-bromide had reacted and only the olefin (19) and the equatorial bromide (18b) were detectable.)

After cooling, water (200 ml) was added and the product removed by steam distillation via a vigreux column. The aqueous layer, which was cloudy and had an obnoxious odour, was extracted with dichloromethane. The combined

organic fractions were dried ($MgSO_4$) and the solvent removed by fractional distillation to leave a brown oil. This was partially purified by distillation (15 mm Hg, oven 100°C) to yield a pale yellow oil (260 mg).
Glc (5% BDS, 150°C) olefin (6) [R_t = 2.6 mins.] : olefin (19) [R_t = 3.4 mins.] = 1 : 1 ; Olefin mixture : endo-bromide (18b) [R_t = 16.7 mins.] = 2 : 3.

39. Dehydrobromination of bromide (18) using lithium diisopropylamine

To redistilled diisopropylamine (0.78 g, 7.7 m.mole) in dry tetrahydrofuran (10 ml) at -20°C under nitrogen, n-butyllithium (3.9 ml of ca. 1.95 molar, i.e. 2.6 m.mole) was added with stirring. After 30 minutes the bromide (0.5 g, 2.6 m.mole) in THF (4 ml) was added to this clear, colourless solution. This caused the rapid generation of a deep brown colour. At the completion of addition the mixture was warmed to room temperature and stirred for 12 hours. The reaction was then quenched with saturated potassium sodium tartrate solution and the mixture extracted with chloroform. After drying ($MgSO_4$) the solvent was removed by fractional distillation to leave a pale brown oil. This was partially purified by distillation (15 mm Hg, oven 100°C) to yield a colourless oil (130 mg).
Glc (5% BDS, 150°C) olefin (19) R_t = 3.4 mins., bromide (18b) R_t = 16.7 mins., and compound (17) R_t = 2.2 mins.

40. Dehydroiodination via an iodoso-intermediate (65)[23].

The preparation of the iodoso-intermediate (65) was attempted in two ways:
A) To a stirred mixture of the iodide (57) (0.10 g, 0.4 m.mole) and disodium hydrogen phosphate (Na_2HPO_4) in dichloromethane

(5 ml) was added m-chloroperoxybenzoic acid (0.1 g) at room temperature. Stirring was continued for 1 hour, after which time tlc study (80% diethyl ether /petrol ether) indicated that all starting material had reacted and a lower R_f compound formed.

B) A saturated dichloromethane solution of ozone (10 ml) at -76°C was added to a stirred solution of the iodide (57) (0.1 g) in dichloromethane (5 ml).

In both cases the resultant solution was added to refluxing dichloromethane resulting in a pale brown solution. Glc (5% BDS, 150°C) in both cases neither olefin (19) or olefin (6) was detected. The main product from method A was compound (17) while method B produced unreacted iodide (57).

41. Dehydroidination of iodide (57) using 1,5-diazabicyclo-[5.4.0] undec-5-ene.

1,5-diazabicyclo [5.4.0] undec-5-ene (0.2 g) was added to a solution of the iodide (57) (0.1 g, 0.4 m.mole) in dry dichloromethane (5 ml) at room temperature and held for 3 days. The solvent was then removed by fractional distillation and the resulting oil distilled (15 mm Hg, oven 100°C) to yield colourless oil (19 mg, 40%). The nmr and ir spectra of this material were identical to those previously reported for the olefin (19), see Experiment 9, Method D(b); glc (5% BDS, 150°C) olefin (19) R_t = 3.4 mins., a little of compound (17) R_t = 2.2 mins. was also detected.

42. Dehydroiodination of iodide (57) using powdered potassium hydroxide.

A solution of the iodide (57) (0.2 g, 0.83 m.mole) and

18-crown-6 ether (0.2 g) in dry dichloromethane (20 ml) was treated with powdered potassium hydroxide (0.4 g, 7.1 m.mole) at reflux for 24 hours. After cooling, the reaction mixture was poured directly onto a silica column (10 g) packed in dichloromethane. The product was then eluted with dichloromethane and the solvent removed by fractional distillation to leave an oil (43 mg, 45%). The nmr and ir spectra were identical to those reported previously for the olefin (19), see Experiment 9, Method D(b); glc (5% BDS, 150°C) olefin (19) R_t = 3.4 mins., low concentrations of compound (17) R_t = 2.2 mins. were observed.

43. Preparation of 18-crown-6 ether[24].

Triethylene glycol (112.5 g, 0.75 mole) and 60% potassium hydroxide solution (109 g of 85% potassium hydroxide in 70 ml of water) in THF (600 ml) reacted with 3,6-dioxa-1,8-dichlorooctane (140.3 g, 0.75 mole) in THF (100 ml) to produce a deep brown oil. After distillation (0.4 mm Hg, oven 100-160°C) and precipitation as the acetonitrile complex this yielded the 18-crown-6 ether (40 g) as white crystals.

44. Isomerisation of olefin (19) to olefin (6).

Method A :- (Potassium t-butoxide in t-butanol)

To a solution of potassium t-butoxide [potassium (0.32 g) in t-butanol (8.19 ml)] under nitrogen at room temperature was added the olefin (19) (0.5 g, 3.6 m.mole). This rapidly generated a dark brown colour. After being held at 80°C for 24 hours the mixture was cooled then some of the solvent (4 ml) was removed by fractional distillation. Water (25 ml) was then added and the mixture continuously

extracted with diethyl ether for 12 hours. After drying ($MgSO_4$) the solvent was removed by fractional distillation to yield a pale brown oil (0.31 g, 62%).
Glc (5% BDS, 150°C) olefin (6) [R_t = 2.6 mins.] : olefin (19) [R_t = 3.4 mins.] = 2 : 1 , no other product was detected.

Method B :- (Potassium t-butoxide in dimethyl sulphoxide with 18-crown-6 ether)

To a stirred solution of potassium t-butoxide (0.20 g, 2 mole equivalents) and 18-crown-6 ether (0.47 g) in dry dimethyl sulphoxide (15 ml) under nitrogen was added the olefin (19) (0.10 g, 0.89 m.mole). This caused a brown colour to develop rapidly. After stirring at room temperature for 12 hours glc study indicated a considerable level of isomerisation had occurred to give a 1:1 mixture of olefin (19) and olefin (6). The mixture was heated to reflux for 2 hours then cooled. Saturated sodium chloride solution was then added (30 ml) and the mixture extracted with diethyl ether. The combined organic layers were washed once with saturated sodium chloride solution (15 ml) then dried ($MgSO_4$) and the solvent removed by fractional distillation to leave a pale brown oil contaminated with a little dimethyl sulphoxide.
Glc (5% BDS, 150°C) olefin (6) [R_t = 2.6 mins.] : olefin (19) [R_t = 3.4 mins.] = 9 : 1 , various by-products were also detected and the product was contaminated with dimethyl sulphoxide.

Method C :- (Lithium diisopropyl amide in THF)

To a stirred solution of diisopropylamine (0.57 g, 3 mole equivalents) in tetrahydrofuran (10 ml) at -20°C under nitrogen was added n-butyllithium (0.36 g). After

½ hour the olefin (19) (0.1 g, 0.89 m.mole) was added dropwise. The mixture was then allowed to warm to room temperature during which time it developed a dark brown colour. The mixture was then heated to 50°C for 24 hours and, after cooling, a sample was quenched with water and extracted into diethyl ether.

Glc (5% BDS, 150°C) olefin (6) [R_t = 2.6 mins.] : olefin (19) [R_t = 3.4 mins.] = 1 : 1, significant levels of by-products were also detected.

Method D :- (Potassium hydroxide in ethanol with 18-crown-6 ether)[25]

The olefin (19) (0.2 g, 1.8 m.mole) was added to a mixture of potassium hydroxide (0.29 g, 5.2 m.mole) and 18-crown-6 ether (1.37 g, 5.2 m.mole) in ethanol (10 ml) and refluxed for 48 hours. The reaction was worked up as previously, see Experiment 7, and a pale yellow oil was isolated (75 mg).

Glc (5% BDS, 150°C) olefin (6) [R_t = 2.6 mins.] : olefin (19) [R_t = 3.4 mins.] = 2 : 1 , a few minor impurities were also observed.

Method E :- (n-Butyllithium and trimethylethylenediamine)[26]

To a stirred solution of n-butyllithium in hexane (0.67 m.mole, 0.43 ml of 1.42 molar hexane solution) under a static nitrogen atmosphere was added dropwise trimethylethylenediamine (0.08 g, 0.7 m.mole). To the resulting pale solution was added the olefin (19) (0.07 g, 0.6 m.mole). This resulted in the rapid formation of a deep brown colour and an exothermic reaction. The mixture was then held at room temperature for 3 days. The reaction was quenched with saturated sodium chloride solution (2 ml) and extracted with diethyl ether. The organic phase was then

dried ($MgSO_4$) and solvent removed by fractional distillation to leave an oil (40 mg).

Glc (5% BDS, 150°C) olefin (6) [R_t = 2.6 mins.] : olefin (19) [R_t = 3.4 mins.] = 1 : 2 , a very low level of by-products was also detected.

Method F :- (Potassium-3-aminopropylamide in 3-amino-propylamine)[27,28]

Potassium-3-aminopropylamide in 3-aminopropylamine was prepared exactly as described[27]. The base mixture (0.2 ml) was added to a stirred solution of the olefin (19) (0.1 g, 0.89 m.mole) in dry diethyl ether (1 ml) at 0°C under nitrogen. This caused the generation of a dark brown colouration. Stirring was continued at 0°C for 1 hour then at room temperature for 24 hours. The reaction was then quenched with saturated salt solution (3 ml) and extracted with diethyl ether (4x5 ml). After drying ($MgSO_4$), the solvent was removed by fractional distillation to leave an oil (65 mg).

Glc (5% BDS, 150°C) olefin (6) [R_t = 2.6 mins.] : olefin (19) [R_t = 3.4 mins.] = 1 : 1 , a very low level of by-products was also detected.

Method G :- (Solid potassium t-butoxide)

The olefin (19) (200 mg, 1.8 m.mole) was added to sublimed potassium t-butoxide (200 mg) resulting in the immediate appearance of a brown colouration. The mixture was held at 80°C for 24 hours then quenched with saturated salt and extracted with diethyl ether. After drying ($MgSO_4$) and removal of the solvent by distillation an oil was isolated (120 mg).

Glc (5% BDS, 150°C) this indicated no isomerisation had occurred.

dried ($MgSO_4$) and solvent removed by fractional distillation to leave an oil (40 mg).

Glc (5% BDS, 150°C) olefin (6) [R_t = 2.6 mins.] : olefin (19) [R_t = 3.4 mins.] = 1 : 2 , a very low level of by-products was also detected.

Method F :- (Potassium-3-aminopropylamide in 3-amino-propylamine)[27,28]

Potassium-3-aminopropylamide in 3-aminopropylamine was prepared exactly as described[27]. The base mixture (0.2 ml) was added to a stirred solution of the olefin (19) (0.1 g, 0.89 m.mole) in dry diethyl ether (1 ml) at 0°C under nitrogen. This caused the generation of a dark brown colouration. Stirring was continued at 0°C for 1 hour then at room temperature for 24 hours. The reaction was then quenched with saturated salt solution (3 ml) and extracted with diethyl ether (4x5 ml). After drying ($MgSO_4$), the solvent was removed by fractional distillation to leave an oil (65 mg).

Glc (5% BDS, 150°C) olefin (6) [R_t = 2.6 mins.] : olefin (19) [R_t = 3.4 mins.] = 1 : 1 , a very low level of by-products was also detected.

Method G :- (Solid potassium t-butoxide)

The olefin (19) (200 mg, 1.8 m.mole) was added to sublimed potassium t-butoxide (200 mg) resulting in the immediate appearance of a brown colouration. The mixture was held at 80°C for 24 hours then quenched with saturated salt and extracted with diethyl ether. After drying ($MgSO_4$) and removal of the solvent by distillation an oil was isolated (120 mg).

Glc (5% BDS, 150°C) this indicated no isomerisation had occurred.

Method H :- (Potassium t-butoxide in THF)

To a stirred solution of potassium t-butoxide (200 mg) in dry THF (3 ml) at room temperature under nitrogen was added the olefin (19) (200 mg, 1.8 m.mole) and the mixture refluxed for 24 hours. After cooling, the mixture was quenched with a saturated salt solution and extracted with diethyl ether. After drying ($MgSO_4$) the solvent was removed by fractional distillation to leave an oil (110 mg).

Glc (5% BDS, 150°C) olefin (6) [R_t = 2.6 mins.] : olefin (19) [R_t = 3.4 mins.] = 3 : 2.

45. 'One-pot' iodocyclisation/dehydroiodination.

Method A :- (Potassium t-butoxide in t-butanol)

To a vigorously stirred mixture of the alcohol (16) (10.0 g, 88 m.mole) in dry t-butanol (100 ml) with anhydrous potassium carbonate (24.3 g, 2 mole equivalents) in the dark was added, dropwise over 4 hours, iodine (24.6 g, 1.1 mole equivalents) in the minimum amount of dry t-butanol (260 ml). Glc study (5% BDS, 150°C) and tlc (80% diethyl ether/petrol ether) indicated that at this stage the iodide (57) had formed, contaminated with some polymeric material. After a further 2 hours stirring sodium metabisulphite was added to remove excess iodine. This left a deep red/brown solution.

The base was prepared by reacting potassium (10.3 g, 3 mole equivalents of 100% yield of the iodide) with t-butanol (250 ml) under nitrogen.

The solution of the iodide was added to the solution of the base via a Buchner filter and as soon as the two

solutions came into contact the iodide solution was decoloured and a white milky precipitate formed. On completion of the addition the reaction mixture was refluxed for 36 hours. Glc and tlc study at this stage indicated that all the iodide (57) had reacted and two olefins, (6) and (19), had been formed in the ratio 2 : 1, as well as a small amount of compound (17).

After cooling, water (400 ml) was added and the t-butanol removed by fractional distillation. Distillation was continued and the water fraction (300 ml) was collected and then continuously extracted with dichloromethane for 10 hours. The organic phase was dried ($MgSO_4$) and the solvent removed by fractional distillation to leave a yellow oil (1.4 g). This material was distilled (15 mm Hg, oven 80°C) to yield a pale yellow oil (0.5 g, 5%). Nmr spectrum was identical to that reported for the 1:1 mixture of olefins (6) and (19)[4,5] ; glc (5% BDS, 150°C) olefin (6) [R_t = 2.7 mins.] : olefin (19) [R_t = 3.5 mins.] = 3 : 2, a little of compound (17) R_t = 2.3 mins. was also present.

Method B :- (Potassium hydroxide in dichloromethane with 18-crown-6 ether)

To a vigorously stirred mixture of the alcohol (16) (1.0 g, 9 m.mole) in dry dichloromethane (16 ml) with finely powdered potassium carbonate (2.4 g, 24 m.mole) at 5°C in the dark was slowly added over 2 hours iodine (2.6 g, 10 m.mole) in dry dichloromethane (60 ml). Glc study indicated that all the starting alcohol had been converted to the iodide with only a small level of the compound (17).

The mixture was then filtered via a Buchner funnel into a flask containing 18-crown-6 ether (2.6 g).

Powdered potassium hydroxide pellets (3.0 g, 54 m.mole) were added and the mixture refluxed for 48 hours. The reaction mixture was then cooled, filtered and the solvent removed by fractional distillation to leave a deep brown oil (0.54 g). This product was purified by distillation (15 mm Hg, oven 80°C) to give a colourless oil (59 mg, 6%). The nmr spectrum was very similar to that previously described for the olefin (19), see Experiment 9; glc (5% BDS, 150°C) olefin (19) R_t = 3.3 mins. with trace levels of olefin (6) R_t = 2.6 mins., and compound (17) R_t = 2.2 mins.

Note:- The buffer efficency is very important. It is necessary to use 3 mole equivalents and ensure it is finely ground and vigorously stirred. If the conditions varied from this the main product isolated was compound (17).

SECTION B

46. Preparation of activated zinc[29].

A stirred suspension of zinc dust (10.0 g, 0.15 mole) in water (40 ml) was degassed by bubbling nitrogen for 15 minutes. Hydrated copper sulphate (1.18 g, 4.7 m.mole) was then added and the black suspension stirred for 45 minutes, still with nitrogen addition. The zinc-copper couple was collected using a sintered funnel under a stream of nitrogen, washed successively with degassed water (100 ml) and degassed acetone (100 ml) then dried at reduced pressure. After storing under nitrogen the couple should be used within 1 week of activation.

47. Preparation of trichloroacetyl chloride[29].

Thionyl chloride (51 ml, 84.5 g, 0.71 mole) was added dropwise over ½ hour to a stirred solution of trichloroacetic acid (97.0 g, 0.59 mole) and dimethylformamide (3 ml) at 85°C. Heating was maintained for 2 hours after which time the reflux had subsided. The product was then distilled (15 mm Hg, oven 30°C) and redistilled to yield a colourless liquid (66.5 g, 62.6%).

48. Addition of dichloroketene to indene[29].

This was carried out exactly as described in the literature. Distillation of the crude product (0.4 mm Hg, oven 170°C) gave white crystals (52%).
ν_{max} 1805 cm^{-1}; δ: 7.3(4H,m,Ph), 4.5(2H,m), and 3.3(2H,m) ppm; tlc (80% diethyl ether/petrol ether) R_f = 0.64 (indene R_f = 0.71).

49. Reaction of dichloroketene with the olefin (6).

Method A[29]:-

A solution of freshly distilled trichloracetyl chloride (0.33 g, 1.84 m.mole) and freshly distilled phosphoryl chloride (0.28 g, 1.84 m.mole) in dry diethyl ether (2 ml) was added dropwise over a 20 minute period to a stirred suspension of activated zinc (0.126 g, 1.92 m.mole) and the olefin (6) (200 mg, 1.76 m.mole) in dry diethyl ether (4 ml) under nitrogen. When the addition was complete the mixture was held at reflux for 2 hours. After cooling, the mixture was filtered through celite and the solution concentrated under vacuum. An equal volume of pentane was then added and after a few minutes stirring the solution was decanted from the precipitated sticky zinc salts. After washing with cold water, cold saturated sodium bicarbonate, and cold saturated brine the solution was dried ($MgSO_4$). The solvent was then removed under vacuum to leave a brownish oil and a little solid. ν_{max} 1770 cm^{-1}; tlc (80% diethyl ether/petrol ether) showed a range of products.

Method B :-

This was performed exactly as in Method A except phosphorous oxychloride was omitted. Other starting materials and method were identical to that described above. Removal of solvent left a crude oil (80 mg). ν_{max} 1805, 1770 cm^{-1}; tlc (80% diethyl ether/petrol ether) showed a range of products.
Purification was performed using preparative tlc (60% diethyl ether/petrol ether) but no material was isolated which displayed the ν_{max} 1805 cm^{-1}.

Method C[30] :-

A solution of freshly distilled trichloroacetyl chloride (1.1 g, 6 m.mole) in dry diethyl ether (63 ml) was added over a 2½ hour period to a stirred,refluxing mixture of the olefin (6) (0.7 g, 6 m.mole) in dry diethyl ether (63 ml) with activated zinc (1.25 g) under nitrogen. After stirring at reflux for 16 hours the mixture was cooled and filtered through celite. The solvent was then removed under vacuum until 15 ml remained. Pentane (25 ml) was added to this yellow/brown solution causing an initial cloudiness. Continued stirring caused precipitation of zinc salts. The organic solution was then decanted and the solvent evaporated to yield a pale brown oil.
ν_{max} 1800, 1745 cm^{-1}.

This material was purified by preparative tlc (80% diethyl ether/petrol ether) and column chromatography (40% diethyl ether/petrol ether). The relevant fraction was then distilled (0.1 mm Hg, oven 70°C) to yield a colourless oil.
ν_{max} 2970, 2930, 1800, 1755, 1700, 1595, 1450, 1370, 1310, 1260, 1205, 1165, 1125, 1025, 990, 870, 850, and 810 cm^{-1}; δ: 5.4(1H,bs, H-5), 4.5(1H,m, H-1), 3.9(2H,m, H-7), and 3.1(1H,m,H-4)ppm;tlc (80% diethyl ether/petrol ether) R_f = 0.65 plus impurities.

50.Reaction of a radical of acetic acid with the olefin (6)[31].

Manganous acetate tetrahydrate (0.64 g, 2.5 m.mole) was dissolved in glacial acetic acid (3.6 ml) by heating to 90°C. Potassium permanganate (0.096 g, 0.6 m.mole), acetic anhydride (0.9 ml) and sodium acetate (1.5 g) were then added. This resulted in a very viscous deep brown/purple colour. The olefin (6) (0.2 g, 1.8 m.mole) was

added and the mixture warmed to 110°C and held for 2 hours. After cooling, water (10 ml) was added and the separated aqueous layer was extracted with diethyl ether (4x10 ml). After washing the combined organic extracts with concentrated potassium carbonate solution and re-extracting the aqueous washings with diethyl ether the combined organic layers were dried ($MgSO_4$) and solvent evaporated to leave a crude brown oil (106 mg). Ir study indicated no lactone carbonyl resonance was present.

51. Reaction of a radical of acetic acid with 2,3-dihydropyran.

This was performed exactly as described in Experiment 50. Reagents used were manganous acetate tetrahydrate (12.72 g, 0.05 mole); glacial acetic (72 ml); potassium permanganate (1.92 g, 0.012 mole); acetic anhydride (18 ml); sodium acetate (30 g); and 2,3-dihydropyran (3.0 g, 0.0358 mole). No identifiable product was isolated and ir study of the crude product indicated no lactone carbonyl resonance was present.

SECTION C

52. Preparation of 1,2,5,6-di-O-isopropylidene-d-mannitol (77).

Method A[32] :-

Zinc chloride in stick form (71.0 g, 0.52 mole) was dissolved in dry acetone (352 ml). After chilling, the slightly turbid zinc chloride solution was decanted, filtered and added to d-mannitol (75) (36.4 g, 0.2 mole) with vigorous mechanical stirring. After stirring for 2 hours at room temperature the solution was rapidly filtered and the filtrate immediately added to a solution of anhydrous potassium carbonate (112 g, 0.81 mole) in water (112 ml). This mixture was stirred as long as possible then left overnight.

After filtration, the solid cake was washed with chloroform (5x200 ml), and the aqueous layer was extracted with chloroform (3x200 ml). The combined organic layers were dried and evaporated to yield a crude white crystalline product (45.1 g). This material was purified by dissolving in chloroform (1 ml per gram) and adding heptane (10 ml per gram). The mixture was then boiled and, after hot filtration, was diluted with heptane (10 ml per gram) and stored overnight in the cold. The white fluffy needle crystals of (77) were then collected (27.3 g, 53%), m.pt. 120-122°C.

ν_{max} 3500, 2990, 1385, 1375, 1240, 1155, 1070, and 850 cm^{-1}; δ:4.2 - 3.6(8H,m), 2.45(2H,bs, OH), 1.3(3H,s), and 1.4 (3H,s)ppm.

Method B[33] :-

Zinc chloride (27.0 g, 0.20 mole) was dissolved in dry acetone (135 ml). After cooling, the slightly turbid zinc

chloride solution was decanted from the precipitated insoluble materials and added to finely powdered d-mannitol (17.0 g, 0.093 mole) with vigorous stirring. After stirring for 2 hours at room temperature the solution was filtered and the filtrate processed immediately.

The filtrate was added to a solution of anhydrous potassium carbonate (34.0 g) in water (34 ml) and diethyl ether (135 ml) with vigorous stirring. After 40 minutes the organic layer was decanted and the residual precipitate washed with a 1:1 diethyl ether/acetone mixture (300 ml). The combined organic layers were dried and evaporated to yield (77) (18.17 g, 74.6%). The product was then purified by recrystallisation from an ethyl acetate/petrol ether mixture.

53. Preparation of isopropylidene R-glyceraldehyde (78).

Method A :-

The d-mannitol derivative (77) (0.1 g, 0.38 m.mole) in freshly distilled methanol (8 ml) was added to sodium periodate (0.8 g, 3.7 m.mole) in water (9 ml) with stirring. If the solution turned cloudy initially more methanol was added (ca. 5 ml) until the solution cleared. After a few minutes a white solid was precipitated ($NaIO_3$). After stirring for 2 hours the aqueous methanolic solution was thoroughly extracted with diethyl ether (4x20 ml). The organic layers were combined, dried and evaporated to yield a viscous oil (70 mg). No identifiable material was isolated from this crude product.

Method B[33(b)]:-

To a stirred suspension of the d-mannitol derivative (77) (0.197 g, 0.75 m.mole) in dry, thiophene free benzene (6 ml) at room temperature was rapidly added lead tetraacetate.

The addition was monitored by testing the reaction mixture with starch/iodide paper. If a slight excess of lead tetraacetate was observed extra d-mannitol derivative (77) was added to remove this excess. After stirring for 1 hour the tacky plumbous salts had been triturated to a fine powder. The mixture was then filtered and the benzene removed by either careful distillation or by evaporation. The resulting clear colourless oil was then purified by distillation (15 mm Hg, 85°C) to give isopropylidene R-glyceraldehyde (78) as a colourless oil with a characteristic smell (0.23 g, ca. 100%).

ν_{max} 1710, 1370, 1250, 1215, 1070, 845, and 785 cm^{-1};
δ:9.7(1H,d,CHO J=2Hz), 4.3(1H,dt,J=2Hz and 6Hz), 4.1(2H,dd, J=3Hz and 6Hz), 1.45(3H,s), and 1.4(3H,s) ppm.

54. Preparation of 1,3-dioxan-2(2-bromoethane) (79)[34].

Hydrogen bromide was slowly bubbled through freshly distilled ethylene glycol (40.0 g, 0.65 mole) at 5-10°C. Bubbling continued until sufficient hydrogen bromide had been dissolved, ca. 6 hours (20.95 g, 0.23 mole). To this viscous, almost colourless solution at 0°C freshly distilled acrolein (11.2 g, 0.20 mole) was added dropwise. This caused the mixture to change to a deep brown colour. After warming to room temperature and stirring for 1 hour the mixture was extracted with pentane (3x75 ml). The combined extracts were washed with 5% sodium bicarbonate solution (2x50 ml), dried and evaporated. This left a pale yellow oil (ca. 25 ml) which was purified by distillation (15 mm Hg, oven 125°C) to yield the bromide (79) as a clear colourless oil (19.14 g, 52.9%).

ν_{max} 2960, 2880, 1475, 1405, 1210, 1130, 1070, 1020, 890, and

640 cm^{-1}; δ :4.9(1H,t,J=5Hz), 3.85(4H,m), 3.45(2H,t,J=7Hz), and 2.15(2H,dt,J=5.0Hz and 7Hz) ppm; tlc (80% diethyl ether/petrol ether) R_f = 0.54.

55.Preparation of the phosphonium salt (80) from bromide (79).

Method A :-

To a stirred solution of the bromide (79) (1.0 g, 5.5 m.mole) in dry benzene (2.5 ml), triphenyl phosphine (1.74 g, 6.6 m.mole) in dry benzene (10 ml) was added dropwise. After 1 hour the benzene was evaporated to leave a cloudy liquid which nmr study indicated to be starting material and triphenyl phosphine.

Overnight reflux of the same reaction mixture yielded droplets of a chloroform soluble brown oil. This material would not crystallise and spectral studies gave no indication of a phosphonium salt being formed.

If xylene was substituted for benzene, refluxing the mixture caused a black crystalline solid to form. Nmr study of this compound indicated the phosphonium salt had not formed. Product was unidentified.

If acetonitrile was substituted for benzene and the mixture was refluxed no change in the final product was observed.

Method B[35] :-

To the bromide (79) (0.20 g, 1.1 m.mole) in cyclohexane (2.5 ml) was added triphenyl phosphine (0.55 g, 2.1 m.mole). This mixture was refluxed for 24 hours with stirring. After this time a very small amount of solid had appeared. The nmr spectrum of this material appeared very similar to the starting bromide and continued reflux for 3 days did not alter the yield of product. There was no indication of a phosphonium salt being formed.

Method C[36] :-

The bromide (79) (0.33 g, 1.82 m.mole) and triphenyl phosphine (0.5 g, 1.9 m.mole) were heated in an oil bath for several hours at 100°C. After a short while a dark brown bottom layer began to form and after continued heating (30 hours) this was found to be solid. This material was soluble in chloroform but an nmr study revealed the spectrum of this material to be very similar to the starting material with no evidence of a phosphonium salt having been formed. It was not possible to purify this material by column chromatography or recrystallisation.

56. Preparation of 1,3-dioxan-2(2-iodoethane) (86)[37].

Sodium iodide (0.55 g, 3.7 m.mole) was dissolved in butan-2-one (10 ml) to give a pale yellow solution. The bromide (79) (0.33 g, 1.82 m.mole) was added and after standing for 30 minutes, during which time a white precipitate of sodium bromide formed, was refluxed for 6 hours then left overnight at room temperature. The mixture was then filtered, evaporated and the brown oil dissolved in carbon tetrachloride and washed with aqueous thiosulphate solution. After drying ($MgSO_4$) and evaporation the iodide (86) was isolated as a colourless oil (0.33 g, 78.6%). ν_{max} 2960, 2880, 1480, 1400, 1210, 1135, 1070, 1025, 885, and 640 cm^{-1}; δ :4.9(1H,t), 3.9(4H,m), 3.2(2H,t),and 2.2(2H,dt) ppm; tlc (80% diethyl ether/petrol ether) R_f = 0.56.

57. Preparation of the phosphonium salt from iodide (86).

The iodide (86) (0.33 g, 1.45 m.mole) and triphenyl phosphine (0.35 g, 1.34 m.mole) were heated at reflux in dry xylene (6 ml) for 6 hours. A brown oil appeared which

solidified on cooling. The nmr spectrum of this material was incompatible with the formation of a phosphonium salt and the material remained unidentified.

58. Preparation of the phosphonate (88) and its subsequent reactions.

Method A[38] :-

The bromide (79) (0.33 g, 1.82 m.mole) was added to freshly distilled triethyl phosphite (0.30 g, 1.81 m.mole) under nitrogen. The mixture was heated to initiate the reaction which was monitored by tlc (50% diethyl ether/petrol ether). This indicated that a new, very polar material was forming, although some starting material remained. The mixture was then heated to 160°C for 4 hours. The nmr spectrum of the crude product was incompatible with the formation of a phosphonate salt.

The reaction was repeated in an nmr tube and monitored regularly. After 3 days at 100°C and addition of a little more triethylphosphite (0.10 g) a product was obtained by distillation (15 mm Hg, oven 170°C).

δ: 4.8(1H,t), 3.9(4H,q), 3.8(4H,m), 3.5(2H,dt,J=12Hz), 1.9(2H,m,J=24Hz), and 1.3(6H,m) ppm ; tlc (50% diethyl ether/petrol ether) R_f = 0.1 .

An anion was then generated on this phosphonate by reacting with a large excess of sodium hydride in dry benzene under nitrogen. This caused an evolution of gas. After stirring for 1 hour the excess sodium hydride was allowed to settle and the slightly cloudy solution containing the anion was transferred to a reaction vessel containing one of two carbonyl compounds:

a) Addition of butan-2-one to this solution caused

effervescence and after 15 minutes at room temperature the solution had adopted a pale yellow colour. Tlc study (80% diethyl ether/petrol ether) showed nothing except very low R_f material. The reaction was then quenched with water, all the colour transferring to the aqueous layer at pH12. The aqueous layer was extracted with diethyl ether (3x50 ml) and the combined organic layers dried and evaporated. The pale yellow oil recovered in high yield proved to be the starting phosphonate unreacted.

b) Cyclopentanone, added to the anion solution, caused a little effervescence and, after stirring for 2 hours, the solvent was removed. Tlc study (80% diethyl ether/petrol ether) indicated a new uv active material was present. The nmr spectrum showed no indication of any olefinic product and most of the starting phosphonate was recovered.

Method B :-

a) n-Butyllithium (0.9 ml of a 1.6 molar solution) was added with stirring to diethylphosphite (200 mg, 1.4 m.mole) at -76°C under nitrogen. After stirring for 1 hour the bromide (79) (200 mg, 1.1 m.mole) was added and the mixture warmed to room temperature. A sample was then transferred to an nmr tube to monitor the reaction. Little change was observed but deuterochloroform was added to dissolve a viscous liquid which formed. After evaporation of the solvent, crystals appeared. The nmr spectrum of this material indicated that no phosphonate was forming.

b)[39] Sodium (0.1 g, 4.3 m.mole) was added to diethylphosphite (0.5 g, 3.6 m.mole) in dry THF to form a colourless solution and liberate hydrogen. When the solution was homogeneous

the bromide (79) (0.25 g, 1.38 m.mole) was added. After 20 minutes a cloudiness was seen and after stirring overnight a white water soluble precipitate was isolated. The organic layer was then eluted through a short column of silica gel and evaporated to give a crude oil (0.48 g). This was purified by distillation (15 mm Hg, oven 200-250°C) to yield an oil (0.15 g, 42%).

ν_{max} 2990, 1480, 1445, 1395, 1255, 1165, 1040, 980, and 690 cm^{-1} ; the nmr spectrum and tlc were identical to those described previously in Method A above.

This material was then reacted as described above with butan-2-one or cyclopentanone. In both cases the bromide (79) was isolated.

59. Preparation of the alcohol (90)[34].

The Grignard reagent was prepared by adding the bromide (79) (7.5 g, 41.4 m.mole) in dry THF (130 ml) to magnesium turnings (2.98 g, 124 m.mole) under nitrogen with stirring over a 2½ hour period. The reaction was initiated with 1,2-dibromoethane and the temperature was held between 10 and 20°C. Stirring was continued for 1 hour after the addition was complete to give a clear, olive brown solution with a small excess of magnesium present.

To this mixture was added dropwise, with stirring, at 10-20°C a solution of freshly prepared aldehyde (78) (5.24 g, 40 m.mole) in dry diethyl ether (150 ml). This addition took 2 hours and the resultant solution was a clear, grey colour which was stirred for 12 hours.

Ice cold 10% ammonium chloride solution (100 ml) was then added, the aqueous layer extracted with diethyl ether (3x100 ml) and the combined organic extracts washed with

saturated brine solution, dried and evaporated to give the crude product as a yellow oil (5.56 g). A tlc study (diethyl ether) indicated several products had formed. The main one, R_f = 0.36, was isolated by 'flash' column chromatography using diethyl ether as eluent [3.67 g, 39.5% based on the aldehyde (78) used]. The oil was distilled (0.4 mm Hg, oven 110-140°C). (Yields varied considerably with up to 60.6% being obtained on one occassion.) ν_{max} 3420, 2980, 2880, 1635, 1380, 1370, 1210, 1150, 1070, and 850 cm^{-1} ; δ :4.9(1H,t,H-6), 4.0-3.5(8H,m,H-1, H-2, H-3, H-7), 3.2(1H,bs,OH), 1.8(4H,m,H-4, H-5), 1.42(3H,s), and 1.35(3H,s) ppm ; glc (5% apiezon L, 193°C) R_t = 10.8 mins. and 11.1 mins., in the ratio 1 : 2 ; tlc(diethyl ether) R_f = 0.36; Found C,56.62; H,8.73%. $C_{11}H_{20}O_5$ requires C,56.88; H,8.68%.

60.Preparation of the acetate (91).

The alcohol (90) (1.5 g, 6.5 m.mole) in dry pyridine (5 ml) and acetic anhydride (6 ml) was held at room temperature for 1 hour then at 90°C for 5 hours and 70°C overnight. After cooling,the reaction mixture was diluted with diethyl ether (50 ml) and washed in turn with saturated copper sulphate solution (3x20 ml), dilute sodium hydroxide solution (2x20 ml) and saturated brine solution (2x20 ml). The organic phase was then dried and evaporated to leave the crude product as a yellow oil (1.36 g). This was then purified using preparative tlc (40% ethyl acetate/petrol ether) (1.08 g, 60.7%).
ν_{max} 2920, 2860, 1720, 1360, 1220, 1130, 1035, 950, 845, and 750 cm^{-1} ; δ :4.8(2H,m,H-6, H-3), 3.9(7H,m,H-7, H-1, H-2), 2.0 and 2.1(3H,s, diastereoisomers), 1.7(4H,m,H-4, H-5), 1.4(3H,s), and 1.3(3H,s) ppm ; tlc (40% ethyl acetate/

petrol ether) R_f = 0.28 ; glc (5% apiezon L, 193°C) R_t = 5.3 mins. and 5.4 mins. in the ratio 1 : 2.

61. Preparation of the benzyl ether (92).

Method A[40] :-

Sodium hydride (0.06 g, 2.5 m.mole) was slowly added to a cooled, stirred, solution of the alcohol (90) (0.50 g, 2.16 m.mole) in dry THF (10 ml) under nitrogen. A few crystals of tetrabutyl ammonium iodide (ca. 0.009 g) were added then benzyl chloride (0.32 g, 2.5 m.mole) was added dropwise with stirring. The reaction was followed by the tlc study of aliquots quenched in a water/diethyl ether mixture using 66% diethyl ether/petrol ether as tlc solvent.

After standing overnight, diethyl ether (10 ml) and florisil (60-100 mesh) (2.0 g) were added and the solvent evaporated. The florisil was then eluted with dry petrol ether which, after evaporation, yielded a pale yellow oil (0.4 g) in which tlc study indicated 3 components. This material was purified by preparative tlc (66% diethyl ether/petrol ether) and the main compound was isolated (R_f = 0.51). This was the benzyl ether (92) (0.11 g, 15.8%) and distillation gave an analytical sample (0.1 mm Hg, oven 150-160°C).

ν_{max} 3020, 2930, 2880, 1450, 1370, 1075, 945, 855, 800, 740, and 700 cm^{-1} ; δ : 7.25(5H,s,Ph), 4.8(1H,t), 4.55(2H, s), 3.8(4H,m), 3.5-4.1(4H,m,H-1, H-2, H-3), 1.7(4H,m, H-4, H-5), 1.35(3H,s), and 1.3(3H,s) ppm ; uv (ethanol) 209.5 nm with minor absorbances at 247, 251.5, 257, 263, and 266.5 nm ; glc (5% apiezon L 193°C) R_t = 10.3 mins. and 14.4 mins. ; Found C,67.18; H,8.22%. $C_{18}H_{26}O_5$ requires C,67.06; H,8.13%.

Method B[41] :-

Powdered potassium hydroxide pellets (3.0 g) were added to the alcohol (90) (1.0 g, 4.3 m.mole) in dry benzene (100 ml). Benzyl chloride (5.0 g, 39.5 m.mole) was then added and the mixture refluxed in a Dean and Stark apparatus for 48 hours. After this time water (0.1 ml) had been collected and tlc study (diethyl ether) indicated a new uv active, higher R_f compound had formed (R_f = 0.46). After cooling, the reaction mixture was poured onto water (100 ml) and the aqueous layer extracted with diethyl ether (3x100 ml). The combined organic extracts were dried and evaporated to leave a yellow oil. This was purified first by distillation then by 'flash' column chromatography (50% diethyl ether/petrol ether) to give the benzyl ether (92) as a pale yellow oil (0.93 g, 66.9%). The spectral and physical properties were identical to those reported in Method A.

62. Preparation of the allyl ether (93).

Method A[40]:-

Sodium hydride (0.08 g, 3.3 m.mole) was added to the alcohol (90) (0.50 g, 2.16 m.mol) in dry tetrahydrofuran under nitrogen with stirring. After 1 hour allyl chloride (0.19 g, 2.5 m.mole) was slowly introduced and the reaction then stirred for 5 days. The reaction was monitored by tlc study (90% diethyl ether/acetone) of aliquots quenched in an ether/water mixture. The brown solution was then filtered through celite and evaporated to leave a brown/yellow oil (0.41 g). This was purified first by 'flash' column chromatography (90% diethyl ether/acetone), then by distillation (0.05 mm Hg, oven 150-160^{o}C). The allyl

ether derivative (93) was obtained as an oil (90 mg, 15.3%). ν_{max} 3000, 2940, 2890, 1650, 1455, 1382, 1373, 1260, 1215, 1145, 1080, 925, 850, and 735 cm^{-1} ; δ: 5.85(1H,m), 5.2(2H,m), 4.9(1H,t), 3.9(8H,m,H-1, H-2, H-3, H-7), 3.5(2H,m,H-9), 1.7(4H,m,H-5, H-4), 1.4(3H,s), and 1.35(3H,s) ppm ; glc (5% apiezon L, 193°C) R_t = 14.4 mins. ; tlc (diethyl ether) R_f = 0.59 ; Found C,61.94; H,8.89%. $C_{14}H_{24}O_5$ requires C,61.74; H,8.82% .

Method B[41] :-

Powdered potassium hydroxide pellets (1.0 g) were added to the alcohol (90) (0.30 g, 1.29 m.mole) in dry benzene (35 ml). Allyl bromide (1.5 g, 12.4 m.mole) was then added and the mixture refluxed in a Dean and Stark apparatus for 14 hours. After cooling, the reaction mixture was poured onto water (50 ml) and the aqueous layer extracted with diethyl ether (3x50 ml). The combined organic extracts were dried and evaporated to leave a pale yellow oil (0.85 g). This material was purified by distillation and the ally ether derivative was obtained as an oil (180 mg, 51.4%). (Yields of up to 76% were obtained on occasion.) The spectral and physical properties were identical to those reported in Method A.

63. Preparation of the methoxyethoxymethyl ether (94)[42].

To freshly purified alcohol (90) (0.5 g, 2.16 m.mole) in dry THF under nitrogen was added sodium hydride (0.06 g, 2.5 m.mole). Once the effervescence ceased the mixture was stirred for 1 hour at room temperature then methoxyethoxy-methyl chloride (0.32 g, 1.2 mole equivalents) was added at 0°C. The reaction mixture was stirred overnight then the white precipitate of sodium chloride was removed by

filtration and the solvent removed to leave a crude yellow oil (0.58 g). This material was distilled (0.1 mm Hg, oven 160°C) to yield a colourless viscous oil (0.28 g, 41%). A further distillation gave an analytical sample. ν_{max} 1450, 1370, 1260, 1220, 1140, 1050, and 860 cm^{-1}; δ :4.85(4H,m,H-3, H-6, H-9), 3.95 and 3.65 (11H,m,H-1, H-2, H-7, H-10), 3.4(3H,s,H-11), 1.75(4H,m,H-4, H-5), 1.35 and 1.45(6H,s,H-8) ppm ; glc (5% apiezon L, 193°C) R_t = 10.3 and 14.4 mins. ; Found C,56.34; H,8.81%. $C_{15}H_{28}O_7$ requires C,56.23; H,8.81%.

64. Cyclisation of the acetate (91).

Method A[43]:-

A mixture of the acetate (91) (0.2 g, 0.7 m.mole), p-toluenesulphonic acid (0.05 g), water (0.1 ml), and diethyl ether (10 ml) were refluxed overnight. After the reaction mixture was cooled to room temperature diethyl ether (10 ml) was added. The organic layer was then washed successively with saturated sodium bicarbonate solution and saturated sodium chloride solution and dried over magnesium sulphate. The solvent was then evaporated to leave a viscous oil (0.06 g). The various components were separated as much as possible by preparative tlc (40% ethyl acetate/petrol ether). An nmr study of the lowest R_f band gave a very weak spectrum which indicated a resonance at δ = 5.4 ppm. Further purification or analysis was not feasible.

Method B[44] :-

The acetate (91) (0.29 g, 1.1 m.mole) was dissolved in 70% methanol /water (10 ml) with p-toluenesulphonic acid (20 mg) and stirred at room temperature for 48 hours.

Diethyl ether (50 ml) was added, then the ether layer was washed with water (3x10 ml). The aqueous layer was re-extracted with diethyl ether (50 ml) and the combined ether extracts dried ($MgSO_4$) and the solvent evaporated to leave a viscous oil (0.14 g). Tlc study showed this consisted of a number of compounds and purification using preparative tlc was insufficient to allow any meaningful spectroscopic study of the products.

65. Cyclisation of the ether derivative (94).

Method A:-

This was attempted in an identical manner to that described in Experiment 64, Method A.

A mixture of the ether (94) (0.1 g, 0.3 m.mole), p-toluenesulphonic acid (0.03 g), water (0.1 ml), and diethyl ether (10 ml) was used. This yielded a pale yellow oil (0.09 g) as a crude product. This material was partially purified by preparative tlc (80% diethyl ether/petrol ether). δ:5.5(1H,m), 4.8(2H,s), 4.5(1H,m), 3.6(7H,m), 3.3(3H,s), and 1.7(4H,m) ppm. No further analysis was done because of the low purity of the sample.

Method B :-

This was attempted in an identical manner to that described in Experiment 64, Method B.

A mixture of the ether (94) (0.2 g, 0.63 m.mole), 70% methanol/water (10 ml), and p-toluenesulphonic acid (20 mg) was stirred at room temperature for 4 days. After work-up and removal of the solvent a viscous oil remained (0.13 g) The main product was isolated by preparative tlc (50% diethyl ether/petrol ether).

ν_{max} 3460, 1450, 1370, 1260, 1100, 1040, and 800 cm^{-1}; δ: 4.7(3H,m,H-6, H-8), 3.6(9H,m,OH, H-1, H-2, H-3, H-9, H-10), 3.4(6H,s,H-7, H-11), and 1.5(4H,m,H-4, H-5) ppm; tlc(65% diethyl ether/petrol ether) R_f = 0.12 .

66. Cyclisation of allyl ether (93).

Method A :-

This was carried out in an identical manner to that described in Experiment 64, Method A.

A mixture of the allyl ether (93) (0.5 g, 1.8 m.mole), p-toluenesulphonic acid (0.02 g), diethyl ether (80 ml) and water (16 ml) was stirred at room temperature for 3 days. The aqueous layer was removed and extracted with diethyl ether (3x50 ml). The combined organic layers were then washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and the solvent evaporated to leave a yellow oil (0.44 g). This was purified by column chromatography (50% diethyl ether/petrol ether) to yield the cyclised material (97) and (101) (0.11 g, 36%). An analytical sample was prepared by distillation (0.1 mm Hg, oven 65°C). ν_{max} 1330, 1255, 1130, 1090, 1025, 900, 870, 790, and 730 cm^{-1}; δ: 5.8(1H,m,H-8), 5.45(1H,bs,H-5), 5.2(2H,m,H-9), 4.5(1H,m, H-1), 4.0(2H,m,H-7), 3.7(2H,d,H-6), 3.3(1H,m,H-2), and 1.75(4H,m,H-3, H-4) ppm , irradiation at δ=5.8 ppm caused the signal at δ= 4.0 to collapse to a singlet, irradiation at δ= 4.5 caused the signal at δ= 3.7 to collapse to a singlet ; tlc (70% diethyl ether/petrol ether) R_f = 0.36 ; glc (5% apiezon L, 193°C) R_t = 3.35 mins. ; Found C,63.48; H,8.26% . $C_9H_{14}O_3$ requires C,63.51; H,8.29%.

Method B :-

This was carried out in an identical manner to that described in Experiment 64, Method B.

A mixture of the allyl ether (93) (0.08 g, 0.3 m.mole), 70% methanol/water (5 ml), and p-toluenesulphonic acid (20 mg) was stirred at room temperature for 3 days. Standard work-up conditions gave a yellow oil (70 mg). This material was partially purified by preparative tlc (80% diethyl ether/petrol ether).
ν_{max} 3450, 1400, and 1100 cm^{-1}; δ :5.7(1H,m,H-9), 5.2(2H, m,H-10), 4.6(1H,m,H-5), 4.0(2H,m,H-1, H-2), 3.7(2H,bs,H-7), 3.5(1H,bs,OH), 3.4(2H,d,H-8), 3.3(3H,s,H-6), and 1.9(4H, m,H-3, H-4) ppm ; tlc (diethyl ether) R_f = 0.12 ; glc (5% apiezon L, 193°C) R_t = 4.7 mins.

67. Cyclisation of benzyl ether (92)

Method A :-

This was carried out in an identical manner to that described in Experiment 64, Method A.

After refluxing for 24 hours the starting material was recovered in 100 % yield.

Method B :-

This was carried out in an identical manner to that described in Experiment 64, Method B.

A mixture of the benzyl ether (92) (0.3 g, 9.3 m.mole), 70% methanol/water (100 ml) and p-toluenesulphonic acid (20 mg) was stirred at room temperature for 30 hours after which time tlc study (40% ethyl acetate/petrol ether) indicated that the reaction had gone to completion. After the standard work-up a brown oil was obtained (0.31 g).

This was partially purified by preparative tlc (30% ethyl acetate/petrol ether) (0.06 g, 27%) and a sample prepared for microanalysis by distillation (0.2 mm Hg, oven 170°C). ν_{max} 3450, 3030, 1450, 1370, 1215, 1130, 1075, 950, 910, 735, and 700 cm^{-1} ; δ : 7.4(5H,s), 4.6(3H,m,H-5, H-8), 3.8(2H,m,H-1, H-2), 3.5(2H,d,H-7), 3.4(3H,s,H-6), 2.3(1H,bs, OH), and 2.0(4H,m,H-3,H-4) ppm ; tlc (40% ethyl acetate/petrol ether) R_f = 0.22 ; glc (5% apiezon L, 103°C) R_t = 6.4 mins. ; Found C,66.74; H,8.01% . $C_{14}H_{20}O_4$ requires C,66.65; H,7.99% .

68. Conversion of the monocyclic ether (112) to the bicyclic system (98) and (102).

The monocyclic ether (112) (130 mg) was stirred in 70% benzene/water (10 ml) with p-toluenesulphonic acid for 48 hours at room temperature. Tlc study (diethyl ether) indicated that the reaction went to completion and a higher R_f product formed. The aqueous layer was extracted with diethyl ether (3x10 ml) and the combined organic phases dried ($MgSO_4$) and the solvent removed. No identifiable material was isolated.

69. Conversion of the monocyclic benzyl ether (110) to the bicyclic system (96) and (100).

The monocyclic benzyl ether (110) (30 mg) was stirred in diethyl ether (10 ml) and water (4 ml) with p-toluene-sulphonic acid (10 mg) for 4 days at room temperature then refluxed for 3 days. Tlc study (40% ethyl acetate/ petrol ether) showed that the reaction proceeded to completion with the formation of two products with higher R_f values. After cooling, the aqueous layer was removed,

extracted with diethyl ether and the combined organic phases dried ($MgSO_4$) and evaporated to leave an oil (20 mg). This material was shown to have identical spectral and physical properties to those reported, see Experiment 70.

70. Cyclisation of the benzyl ether (91)[45].

The benzyl ether (200 mg, 0.6 m.mole) was added to a chilled solution of hydroperchloric acid (4.2 ml of 60% acid made up to 5 ml with water and then 5 ml of dioxan added) and held at 0°C for 6 hours. The mixture was then extracted with diethyl ether (4x20 ml) and the combined ether layers washed with saturated sodium bicarbonate solution (3x15 ml) and saturated sodium chloride solution (2x15 ml). The combined aqueous washings were re-extracted with diethyl ether (1x10 ml) and the combined organic phases dried ($MgSO_4$) and the solvent evaporated to leave a pale yellow oil (110 mg). Tlc study indicated two new products (40% ethyl acetate/petrol ether) R_f = 0.34 and 0.47 (starting material R_f = 0.40). These were separated by preparative tlc then distilled.

a) Higher R_f material (96) R_f = 0.47.

Distillation (0.25 mm Hg, 140°C) gave an oil (23 mg, 16.4%).

ν_{max} 3060, 3030, 1740, 1700, 1600, 1490, 1455, 1375, 1355, 1330, 1270, 1205, 1130, 1095, 1030, 1000, 985, 930, 910, 880, 850, 830, 740, and 700 cm^{-1} ; δ :7.2(5H,s), 5.3(1H,s, H-5), 4.45(2H,s,H-9), 4.35(1H,m,H-1), 4.1(1H,m,H-2), 3.6(2H, m,H-7), and 1.55(4H,m,H-3, H-4) ppm ; M^+ = 220 m/e ; $[\alpha]_D^{20°C}$ = -37.2° (c = 0.0215, $CHCl_3$) ; Found C,71.02; H,7.27% . $C_{13}H_{16}O_3$ requires C,70.89; H,7.34%.

b) Lower R_f material (100) R_f = 0.34.

Distillation (0.25 mm Hg, oven 140°C) gave white crystals, m.pt. = 47 - 48°C (literature value[11] = 47°C) after recrystallisation from hexane, (25.2 mg, 18.0%). ν_{max} 3060, 3030, 1740, 1600, 1495, 1455, 1365, 1335, 1330, 1255, 1210, 1185, 1130, 1100, 1065, 1030, 1000, 975, 900, 870, 785, 735, and 700 cm^{-1} ; δ :7.25(5H,m,Ph), 5.45(1H,s,H-5), 4.5(2H,s,H-9), 4.4(1H,m,H-1), 3.7(2H,m,H-7), 3.25(1H,m,H-2), and 1.75(4H,m,H-3, H-4) ppm ; M^+ = 220 m/e ; $[\alpha]_D^{20°C}$ = -63.9° (c = 0.0054, $CHCl_3$) (literature value[11] $[\alpha]_D^{20°C}$ = -66°); Found C,70.98; H,7.42% . $C_{13}H_{16}O_3$ requires C,70.89; H,7.34%.

71. Attempted cleavage of the ether group in (98) and (102)[42].

The ether (98) and (102) (17 mg) in dry dichloromethane (5 ml) was stirred vigorously with dry zinc bromide (0.3 g). Tlc study (diethyl ether) indicated the reaction proceeded to completion rapidly. After the addition of saturated sodium bicarbonate solution the organic phase was washed with saturated brine solution, dried ($MgSO_4$) and the solvent evaporated to leave a viscous oil. Insufficient material was isolated for an analytical study.

72. Attempted cleavage of the allyl ether grouping in (97) and (101)[46].

Method A :-

A solution of the bicyclic ether (97) and (101) (0.1 g) in methanol (5 ml) and water (1 ml) was treated with 10% Pd/C (50 mg) and p-toluenesulphonic acid at reflux with stirring for 18 hours. After cooling, the reaction mixture was filtered and extracted with diethyl ether.

The organic phase was dried ($MgSO_4$) and evaporated to leave a colourless viscous oil (60 mg). Spectral and physical analysis indicated this product was identical to compound (111), see Experiment 66 Method B.

Method B :-

A solution of the bicyclic allyl ether (97) and (101) (50 mg) in diethyl ether (20 ml) and water (3 ml) was treated with 10% Pd/C (10 mg) and p-toluenesulphonic acid at reflux for 30 hours. After filtering through celite the aqueous layer was separated and extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$) and the solvent evaporated to leave a colourless oil (15 mg).

ν_{max} 1410, 1260, 1180, 1110, 1050, and 820 cm^{-1} ; the sample was too small for an nmr study ; tlc (90% diethyl ether/petrol ether) R_f = 0.19 (starting material R_f = 0.65).

73. Preparation of the bromide (123)[35].

Acrolein (36.5 g, 0.65 mole) in dry dichloromethane (200 ml) was reacted with hydrogen bromide gas for 8 hours at room temperature. After flushing with nitrogen, propane-1,3-diol (49.5 g, 0.65 mole) and p-toluenesulphonic acid hydrate (1 g) were added. After 15 minutes the initial evolution of heat ceased and stirring under nitrogen at room temperature was continued overnight. The pale yellow/brown solution was neutralised using saturated sodium bicarbonate solution, washed with water and dried. The solvent was removed to leave a viscous brown oil (106 g) which was distilled (3 mm Hg, oven 110°C), b.pt. 70-75°C, to yield a very pale yellow oil (95.5 g, 75.5%).

ν_{max} 2930, 2840, 1715, 1420, 1375, 1260, 1235, 1120, 1005, 910, 880, 845, and 730 cm^{-1} ; δ :4.6(1H,t), 3.9(4H,m), 3.4(2H,t), and 2.1(4H,m) ppm.

74. Preparation of the phosphonium salt (124)[35].

A solution of the bromide (123) (9.41 g, 48 m.mole) and triphenyl phosphine (20.0 g, 76 m.mole) were stirred together in cyclohexane (25 ml) at reflux for one day. The mixture was then cooled and the liquid decanted to leave a brown, hard precipitate. This was broken up and then finely ground. The pale yellow crystals were washed with diethyl ether (200 ml) and petrol ether (200 ml) and stored overnight in a vacuum. These phosphonium salt crystals were now a pale creamy colour (16.5 g, 74.7%), m.pt. = 202 - 206°C.

75. Reaction of the phosphonium salt (124) with iso-butyraldehyde.

A suspension of the phosphonium salt (124) (1.0 g, 2.2 m.mole) in dry THF (12 ml) under nitrogen was treated with n-butyllithium (2.8 ml of a 1.6 molar solution, 2.2 m.mole) at -23°C with stirring. This deep red/brown mixture was stirred for 1.5 hours then freshly distilled iso-butyraldehyde (0.16 g, 2.2 m.mole) in dry THF (3 ml) was added. The mixture was held at -23°C for 2 hours then warmed to room temperature and stirred under nitrogen for 8 hours. The reaction mixture was then poured onto water (70 ml) and carefully extracted with diethyl ether (4x50 ml). The combined extracts were dried and evaporated to leave a viscous brown oil (1.01 g). The product was purified first by distillation (0.4 mm Hg, oven 110-130°C) then by

ν_{max} 2930, 2840, 1715, 1420, 1375, 1260, 1235, 1120, 1005, 910, 880, 845, and 730 cm^{-1} ; δ: 4.6(1H,t), 3.9(4H,m), 3.4(2H,t), and 2.1(4H,m) ppm.

74. Preparation of the phosphonium salt (124)[35].

A solution of the bromide (123) (9.41 g, 48 m.mole) and triphenyl phosphine (20.0 g, 76 m.mole) were stirred together in cyclohexane (25 ml) at reflux for one day. The mixture was then cooled and the liquid decanted to leave a brown, hard precipitate. This was broken up and then finely ground. The pale yellow crystals were washed with diethyl ether (200 ml) and petrol ether (200 ml) and stored overnight in a vacuum. These phosphonium salt crystals were now a pale creamy colour (16.5 g, 74.7%), m.pt. = 202 - 206°C.

75. Reaction of the phosphonium salt (124) with iso-butyraldehyde.

A suspension of the phosphonium salt (124) (1.0 g, 2.2 m.mole) in dry THF (12 ml) under nitrogen was treated with n-butyllithium (2.8 ml of a 1.6 molar solution, 2.2 m.mole) at -23°C with stirring. This deep red/brown mixture was stirred for 1.5 hours then freshly distilled iso-butyraldehyde (0.16 g, 2.2 m.mole) in dry THF (3 ml) was added. The mixture was held at -23°C for 2 hours then warmed to room temperature and stirred under nitrogen for 8 hours. The reaction mixture was then poured onto water (70 ml) and carefully extracted with diethyl ether (4x50 ml). The combined extracts were dried and evaporated to leave a viscous brown oil (1.01 g). The product was purified first by distillation (0.4 mm Hg, oven 110-130°C) then by

ν_{max} 2930, 2840, 1715, 1420, 1375, 1260, 1235, 1120, 1005, 910, 880, 845, and 730 cm^{-1} ; δ:4.6(1H,t), 3.9(4H,m), 3.4(2H,t), and 2.1(4H,m) ppm.

74. Preparation of the phosphonium salt (124)[35].

A solution of the bromide (123) (9.41 g, 48 m.mole) and triphenyl phosphine (20.0 g, 76 m.mole) were stirred together in cyclohexane (25 ml) at reflux for one day. The mixture was then cooled and the liquid decanted to leave a brown, hard precipitate. This was broken up and then finely ground. The pale yellow crystals were washed with diethyl ether (200 ml) and petrol ether (200 ml) and stored overnight in a vacuum. These phosphonium salt crystals were now a pale creamy colour (16.5 g, 74.7%), m.pt. = 202 - 206°C.

75. Reaction of the phosphonium salt (124) with iso-butyraldehyde.

A suspension of the phosphonium salt (124) (1.0 g, 2.2 m.mole) in dry THF (12 ml) under nitrogen was treated with n-butyllithium (2.8 ml of a 1.6 molar solution, 2.2 m.mole) at -23°C with stirring. This deep red/brown mixture was stirred for 1.5 hours then freshly distilled iso-butyraldehyde (0.16 g, 2.2 m.mole) in dry THF (3 ml) was added. The mixture was held at -23°C for 2 hours then warmed to room temperature and stirred under nitrogen for 8 hours. The reaction mixture was then poured onto water (70 ml) and carefully extracted with diethyl ether (4x50 ml). The combined extracts were dried and evaporated to leave a viscous brown oil (1.01 g). The product was purified first by distillation (0.4 mm Hg, oven 110-130°C) then by

preparative tlc (40% diethyl ether/petrol ether) (0.28 g, 75%).

ν_{max} 1630, 1510, 1340, 1205, 1150, 1060, 1005, 915, and 880 cm^{-1} ; δ :5.25(2H, $J_{3,4}$ = 7Hz), 4.5(1H,t), 4.2-3.3 (4H,m), 2.4(2H,m), 2.0(1H,m), 1.2(2H,m), 1.0(3H,s), and 0.9(3H,s) ppm.

76. Preparation of the olefin (127)[35].

Method A :-

To the phosphonium salt (124) (1.14 g, 2.5 m.mole) suspended in dry THF (2.5 ml) under nitrogen was added a 0.5 molar solution of freshly resublimed potassium t-butoxide (0.28 g, 2.5 m.mole) in dry THF (5 ml) with stirring. This caused the suspension to disappear and a deep red/brown colour was generated. Stirring was continued for 1 hour at room temperature.

The aldehyde (78), freshly prepared, (0.5 g, 3.8 m.mole) in dry THF (2 ml) was added slowly to the reaction mixture causing a discharge of the intense reddy colour and forming a pale brown solution with a precipitate. This was stirred at room temperature for 2 hours then poured onto water (50 ml) and extracted with diethyl ether (3x70 ml). The combined pale yellow organic extracts were dried ($MgSO_4$) and evaporated to leave an orange oil (1.06 g).

'Flash' column chromatography (40% diethyl ether/petrol ether) enabled the separation of various fractions, none of which possessed the necessary spectral characteristics of an olefin.

Method B :-

This was carried out in the same manner as was described previously, see Experiment 75.

To the phosphonium salt (124) (24.0 g, 52.8 m.mole) in dry THF (300 ml) under nitrogen at - 23°C was added n-butyllithium (67.2 ml of a 1.6 molar solution, 52.8 m.mole) with stirring. After 1 hour the freshly prepared aldehyde (78) (7.2 g, 55 m.mole) in dry THF (60 ml) was added dropwise. After standing for 1 hour the reaction was warmed to room temperature and held for 6 hours. The mixture was then poured onto water (1½ l) and extracted with diethyl ether (4x150 ml). After drying ($MgSO_4$), and removal of solvent, a brown oil remained (22.24 g). Tlc study (80% diethyl ether/petrol ether) indicated a wide range of products, the main one having an R_f = 0.39. 'Flash' column chromatography (40% diethyl ether/petrol ether) gave a good separation and the product olefin was isolated as a pale yellow oil (5.38 g, 44.9%), b.pt = 160°C at 0.15 mm Hg. ν_{max} 1640, 1500, 1370, 1240, 1210, 1140, 1060, 1010, 915, 860, and 730 cm^{-1}; δ :5.5(2H,m,H-5, H-6, $J_{5,6}$ = 11 ± 0.4Hz), 4.75(1H, dt,H-7), 4.45(1H,t,H-3), 4.0(2H,m,H-8, H-9), 3.4 - 3.8(6H,m,H-1, H-2), 2.35(2H,dd,H-4), 1.25 and 1.35 (6H,2s,H-10) ppm ; tlc (80% diethyl ether/petrol ether) R_f = 0.39 ; $[\alpha]_D^{20°C}$ = -7.78° (c = 0.0221, $CHCl_3$) ; Found C,63.20; H,8.88% . $C_{12}H_{20}O_4$ requires C,63.14; H8.83%.

77. Cyclisation of the olefin (127)[45].

Perchloric acid solution (6 ml) (12.6 ml,6% perchloric acid made up to 15 ml with water and then 15 ml dioxan added) was chilled to 0°C. The olefin (127) (100 mg) was then added in dioxan (1 ml). The mixture was stirred at 0°C for 5 hours. Then diethyl ether (10 ml) was added and

the solution neutralised with solid sodium bicarbonate. The aqueous layer was carefully extracted with diethyl ether (4x20 ml) and the combined organic layers dried ($MgSO_4$) and evaporated. The aqueous layer was also extracted with dichloromethane and the extracts dried and evaporated. Tlc study (80% diethyl ether/petrol ether) indicated that no starting material remained ; the nmr spectrum showed no olefinic or bridgehead protons ; glc (5% BDS, 100°C) showed that no olefin (6) was present.

78.Attempted addition of dichloroketene to the olefin (127)[30].

Activated zinc (2.0 g, 34 m.mole) was suspended in a solution of the olefin (127) (2.0 g, 8.8 m.mole) in dry diethyl ether (160 ml) under nitrogen. This was refluxed and stirred vigorously. To this was added very slowly over a 1½ hour period a solution of trichloroacetyl chloride (1.60 g, 8.8 m.mole) in dry diethyl ether (133 ml). Once the addition was complete the reaction was stirred and refluxed for an additional 16 hours.

The zinc was then removed by filtration through celite and most of the solvent evaporated. Pentane, a volume equivalent to three times that of the remaining diethyl ether, was then added and the mixture stirred to precipitate zinc salts. These were removed by filtration and the solvent was then evaporated to leave a pale yellow oil (2.78 g). This crude material was partially purified using preparative tlc (30% diethyl ether/petrol ether) and one band isolated (200 mg). Tlc study (80% diethyl ether/petrol ether) later showed this product still contained at least three compounds but further purification was not

possible.

ν_{max} 1805, 1760, 1380, 1240, 1140, 1060, 1005, 920, and 815 cm^{-1} ; δ :7.0(1H,m), 4.5(1H,t), 3.3-4.1(9H,m), 2.3(3H,m), 1.3(3H,s), and 1.2(3H,s) ppm ; tlc (80% diethyl ether/petrol ether) R_f = 0.32, 0.34, and 0.35 .

79.Attempted formation of a lactone on the olefin (126)[31].

Manganous acetate tetrahydrate (0.15 g, 0.5 m.mole) was dissolved in glacial acetic acid (1 ml) by warming to 90°C under nitrogen using an oil bath. At that temperature potassium permanganate (0.02 g, 0.1 m.mole) was added by stirring. Acetic anhydride (0.2 ml) was then added followed by sodium acetate (fused) (0.3 g, 3.7 m.mole). The olefin (126) (50 mg, 0.30 m.mole) was then added in a diethyl ether solution (1 ml).

The mixture was warmed up to reflux (160°C) and held for 1 hour. After that time the deep purple manganous colour had faded to a pale brown colour and the reaction was cooled.

The mixture was quenched with water, extracted with diethyl ether, and the organic extracts dried ($MgSO_4$) and evaporated. The remainder of the acetic acid was then removed by distillation to leave a pale brown oil (15 mg). ν_{max} 1760, 1725, 1465, 1375, 1260, 1140, 1100, 1010, 915, 800, 720, and 650 cm^{-1} ; tlc (80% diethyl ether/petrol ether) this indicated a range of products had formed.

80.Attempted formation of a lactone on the olefin (127)[31].

Manganous acetate tetrahydrate (4.66 g, 18.4 m.mole) was dissolved in glacial acetic acid (26.4 ml) under nitrogen

by raising the temperature to 85°C. Potassium permanganate (0.7 g, 4.4 m.mole) was then added followed by acetic anhydride (6.6 ml) and sodium acetate (11.0 g, 134 m.mole). The olefin (127) (3.0 g, 13.2 m.mole) was then added in glacial acetic acid solution (10 ml) and the reaction mixture refluxed for 16 hours. Although the dark brown manganic colour still remained the reaction was worked up as previously described, see Experiment 79, to leave a viscous brown oil (3.30 g). This was partially purified by column chromatography (70% diethyl ether/petrol ether) to leave an oil (0.51 g).

ν_{max} 1775, 1370, 1240, 1140, 1075, 1040, 1020, and 730 cm^{-1} ; δ : 4.6(2H,m,H-7, H-3), 4.0(m,H-8, H-9), 2.0(3H,m,H-4, H-11), 1.4(3H,s,H-10), and 1.3(3H,s,H-10) ppm , this is not a comprehensive analysis of the nmr spectrum ; tlc (80% diethyl ether/petrol ether) R_f = 0.4 and 0.45 plus numerous minor impurities.

81. Attempted formation of compound (5).

Method A[45] :-

The conditions used were as described previously, see Experiment 70. The product from Experiment 80, the lactone (132), was used (50 mg). The reaction was monitored by tlc (90% dichloromethane/ethyl acetate) using an authentic sample of lactone (5) as a standard.

The reaction was worked-up as previously to yield an oil (ca. 10 mg); tlc (90% dichloromethane/ethyl acetate) R_f = 0.23 (authentic sample R_f = 0.26) ; insufficient material was available for a spectral analysis.

Method B[44] :-

The conditions used were as described previously, see Experiment 64. After 12 days of study no sign of a reaction occurring was observed.

82. Attempted dechlorination of compound (130)[47].

The compound (130) (200 mg, 0.59 m.mole) was stirred with activated zinc (200 mg, 3.1 m.mole) and glacial acetic acid (1.0 ml) at 45-50°C for 1½ hours after which time zinc (40 mg, 0.6 m.mole) was added and the temperature raised to 70-75°C for 10 minutes. After cooling, petrol ether (30 ml) and water (20 ml) were added and the organic layer discarded. The aqueous phase was extracted with dichloromethane (30 ml) to yield, after drying ($MgSO_4$) and evaporation of the solvent, a colourless oil (50 mg) which tlc study (60% diethyl ether/petrol ether) showed to consist of a range of products. Preparative tlc (60% diethyl ether/petrol ether) gave some purification and an oil was obtained (15 mg).

ν_{max} 1780, 1580, 1450, 1380, 1290, 1120, 930, and 840 cm^{-1} ; δ : 5.5(1H,m), 4.7(1H,m), 3.7(2H,m), 3.3(m), 1.8(m), and 1.2(m) ppm, this is not a comprehensive analysis of the nmr spectrum ; tlc (60% diethyl ether/petrol ether) R_f = 0.11 .

83. Attempted Baeyer-Villiger oxidation of the product from Experiment 82[48].

Hydrogen peroxide (30%) (0.58 ml) and fused sodium acetate (0.09 g) were added to a stirred solution of the product from Experiment 82, the ketone (131) (50 mg) in glacial acetic acid (4.1 ml). The solution was stirred at room

temperature for 6 hours and then water (1.7 ml), sodium sulphite (0.33 g) and dichloromethane (3 ml) were added cautiously and the mixture stirred for ½ hour. The organic layer was then separated, neutralised with saturated sodium bicarbonate and washed with water (3 ml). After drying ($MgSO_4$) the solvent was evaporated to give an oil.
Tlc (95% diethyl ether/methanol) $R_f = 0.22$ [lactone (5) $R_f = 0.29$] ; insufficient material was available for a spectral analysis.

SECTION D

84. Bromolactonisation of the sodium salt (20).

Bromine (8.0 g, 50 m.mole) in dry carbon tetrachloride (80 ml) was added very slowly at room temperature to a vigorously stirred suspension of the sodium salt of 2-carboxy-3,4-dihydropyran (20) (8.0 g, 53 m.mole) in dry carbon tetrachloride (100 ml). After stirring for 12 hours the mixture was filtered, the collected precipitate washed with chloroform and the solvent evaporated. Tlc study (50% ethyl acetate/diethyl ether) indicated that some unreacted free acid was present so the product was re-dissolved in diethyl ether and washed with saturated sodium bicarbonate. After re-extracting the aqueous washings the combined organic layers were dried ($MgSO_4$) and the solvent evaporated to leave white crystals. These were recrystallised from diethyl ether to give colourless crystals (5.22 g, 48.2%). These were further purified by sublimation (0.5 mm Hg, 45°C) , m.pt. = 101.5 - 103°C. ν_{max} 1790, 1450, 1440, 1360, 1320, 1295, 1275, 1200, 1170, 1105, 1045, 1025, 1010, 1000, 920, 865, 785, 760, 715, 660, and 620 cm^{-1} ; δ :5.88(1H,m,H-5), 4.45(1H,m,H-1), 4.15(1H,m,H-4, $J_{4eq,3ax}$ = 4Hz, $J_{4eq,3eq}$ = 1Hz), and 1.6-2.8(4H,m,H-2, H-3) ppm ; M^+ = 207.9560 (calculated 207.9568), 205.9580 (calculated 205.9580) , main fragments were 44 m/e ($CO_2^{+\cdot}$) and 83 m/e ($C_5H_7O^{+\cdot}$) ; tlc (50% ethyl acetate/diethyl ether) R_f = 0.48 ; glc (5% BDS, 150°C) R_t = 38.5 mins.

85. Iodolactonisation of the sodium salt (20).

The sodium salt (20) (1.0 g, 6.7 m.mole) was rapidly

added to a vigorously stirred solution of iodine (2.6 g, 10.2 m.mole) in dry carbon tetrachloride (50 ml). After stirring for 12 hours in the dark the mixture was filtered and the solvent evaporated to leave pale brown crystals (0.9 g, 53%). These were purified by recrystallisation from diethyl ether or sublimation (0.3 mm Hg, 100°C), m.pt. 93 - 95°C.

ν_{max} 1790, 1205, 1170, 1100, 1035, 1020, and 915 cm^{-1} ; δ: 5.85(1H,m,H-5), 4.35(1H,m,H-1), 4.2(1H,m,H-4, $J_{4eq,3ax}$ = 5Hz, $J_{4eq,3eq}$ = 1Hz), and 1.8 - 2.8(4H,m,H-2, H-3) ppm ; M^+ = 253.9442 (calculated 253.9428) ; tlc (50% ethyl acetate/diethyl ether) R_f = 0.50 ; glc (5% BDS, 150°C) R_t = 42.2 mins.

86. Phenylselenenyl chloride induced cyclisation of the sodium salt (20).

The sodium salt (20) (0.3 g, 2.0 m.mole) was added to a vigorously stirred solution of phenylselenenyl chloride (0.42 g, 2.0 m.mole) in dry dichloromethane (30 ml) at -78°C under nitrogen. After 3 hours the mixture was warmed to room temperature and stirred for 12 hours. The solvent was then removed and the product purified by column chromatography (dichloromethane) to yield a pale yellow oil (0.12 g, 21%).

ν_{max} 1770, 1160, 1090, 1050, 1040, 1010, 900, and 720 cm^{-1} ; δ: 7.8(5H,m,Ph), 5.8(1H,m,H-5), 4.3(1H,m,H-1), 3.3(1H,m,H-4), and 1.5 - 2.5(4H,m,H-2, H-3) ppm ; tlc (dichloromethane) R_f = 0.42.

87. Dehydrobromination and dehydroiodination of the halolactones (23) and (135).

A number of bases were under evaluation. In each case

the conditions used were similar to those developed for the dehydrohalogenation of bromide (18).

Method A :- The use of 1,5-diazabicyclo [5.4.0] undec-5-ene , see Experiment 34.

Method B :- The use of potassium t-butoxide, see Experiment 12.

Method C :- The use of sodium hydride, see Experiment 35.

No conclusive results had been obtained with any of these bases when the work was concluded.

88. Reductive cleavage of compound (141).

Method A[49] :-

Osmium tetroxide solution (1.27 ml, 0.0254 g) was added to a solution of the olefinic lactone (141) (0.25 g) in diethyl ether (10 ml) and water (10 ml). After 5 minutes a black precipitate of osmate ester was observed. The temperature was then stabilised between 24 and 26°C and sodium metaperiodate (0.856 g) added over 30 minutes. Initial addition caused discharge of the black colour. Stirring was continued for 12 hours.

Diethyl ether (10) and water (10 ml) was added to dissolve the white precipitate. The separated aqueous phase was then extracted with diethyl ether and the combined ether layers were dried ($MgSO_4$). Sodium metaperiodate was then added resulting in the discharge of the black colour which had appeared in the ether solution. The solvent was evaporated and a pale green oil resulted.

An nmr study showed no aldehydic protons ; tlc (70% diethyl ether/petrol ether) showed only low R_f material which caused streaks on the plate.

The reaction was repeated using THF as the solvent with similar results.

Method B :-

The generation of the ozone solution and its use was as described in Experiment 9, Method D. The resulting ozonide from reaction of ozone with the olefin (141) was subjected to a variety of work-up conditions:

a) Triphenyl phosphine[50] was added to the reaction mixture at -60°C (1 mole equivalent). After 2 hours the mixture was warmed to room temperature and the solvent evaporated to yield a clear, colourless oil.
Tlc (70% diethyl ether/petrol ether) showed low R_f material which caused streaks on the tlc plates.

b) A solution of sodium sulphite[51] in water (1 mole equivalent) was added to the ozonide solution at -70°C. A slightly exothermic reaction occurred. After warming to room temperature the separated aqueous phase was saturated with sodium chloride and carefully extracted with diethyl ether.
The combined organic layers were dried ($MgSO_4$) and evaporated to leave a pale yellow oil.
Tlc (70% diethyl ether/petrol ether) showed low R_f material which caused streaks on the tlc plates.

89. Preparation of the diol (145)[52].

To a solution of tetraethylammonium acetate, prepared *in situ* from tetraethylammonium chloride and sodium acetate, in acetone (8 ml) was added the olefinic lactone (141) (0.5 g, 4.0 m.mole) and 70% t-butylhydroperoxide (0.79 g, 6.0 m.mole). After chilling to 0°C osmium tetroxide solution (0.1 m.mole) was added and after 1 hour the mixture was warmed to room temperature and held for 12 hours.

Diethyl ether (20 ml) and 10% sodium metabisulphite solution (3 ml) were added then, after 2 hours, solid sodium chloride was added to saturate the aqueous phase. The separated aqueous phase was continuously extracted with dichloromethane for 1 day then the combined organic phases were dried ($MgSO_4$) and the solvent evaporated to leave a viscous oil (0.43 g) which crystallised on standing, m.pt. = 94 - 97°C.

ν_{max} 3400, 2920, 1750, 1350, 1175, 1095, 1005, 905, 805, and 620 cm^{-1} ; δ :4.9(1H,m,H-5), 4.0(2H,m,H-2, H-3), 3.4(2H,bs,OH), 2.7(3H,m,H-6, H-1), and 2.0(2H,m,H-4) ppm ; M^+ = 158.0585 (calculated 158.0585) ; tlc (80% dichloromethane/methanol) R_f = 0.38 .

90. Ozonolysis of the olefin (141)[53].

Ozone rich oxygen was bubbled through a solution of the olefin (141) (0.5 g, 4.0 m.mole) in chloroform (15 ml) at -23°C. When a blue colour formed the mixture was flushed with oxygen and warmed to room temperature to yield a viscous solution containing a white solid.

A solution of sodium borohydride (1.2 g, 6 - 7 mole equivalents) in 50% aqueous ethanol (10 ml) was then chilled and added dropwise to the solution of ozonide. After the addition was complete the mixture was left at room temperature for 12 hours. After acidification (10% sulphuric acid) the aqueous layer was separated and continuously extracted with chloroform. The combined organic layers were dried ($MgSO_4$) to yield a viscous oil after removing the solvent.

ν_{max} 3450, 2970, 2910, 1770, 1485, 1420, 1375, 1330, 1280, 1230, 1170, 1100, 1045, 1015, 910, 860, 785, 730, and 665 cm^{-1}.

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