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SYNTHETIC APPROACHES TO THROMBOXANES

THESIS

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by

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ABSTRACT

The more recent developments in the fields of prostaglandin and thromboxane chemistry, and biochemistry, are briefly discussed. The existing syntheses of thromboxane-B_2 and analogues of thromboxane-A_2 are comprehensively reviewed.

Various synthetic approaches to, and the successful synthesis of, a key thromboxane-B_2 synthon from a sugar precursor are presented. Some synthetic approaches to a novel thromboxane-A_2 analogue are also discussed.

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A BRIEF SURVEY OF THE HISTORY AND DEVELOPMENT OF PROSTAGLANDINS

The biological activity of what were to become known as prostaglandins was first reported in the 1930's,[1,2] but it was not until thirty years later that Bergstrom,[3,4] at the Karolinski Institute succeeded in isolating and characterising several of the primary prostaglandins. Synthetic and biological investigations rapidly followed on. In 1964 Bergstrom[5] and van Dorp[6] demonstrated that the prostaglandins were derived from arachidonic acid, and soon after, Samuelsson provided experimental evidence for the intermediacy of the endoperoxides[7] and proposed a radical mechanism for their formation.[8] Meanwhile several total syntheses of the primary prostaglandins had been published. Numerous reviews of this area exist.[9]

The endoperoxides, being unstable compounds with half-lives of about 5 minutes in aqueous solution at room temperature were somewhat difficult to work with, and it was not until 1973 that Samuelsson succeeded in isolating PGH_2 (3), and shortly afterwards PGG_2[10-12] (4). The structures he proposed were eventually confirmed with the total synthesis of the compounds. PGH_2 methyl ester was prepared in 1977 by Johnson *et al.*[13] and Porter *et al.*,[14] and the less stable parent acid by Porter[15] the following year. The common intermediate in these syntheses was the dibromide (1) derived from the disulphonate ester of $PGF_{2\alpha}$ by reaction with lithium bromide (Scheme 1). Treatment of this by commercial lipase enzyme produced the free acid in good yield, which on reaction with a large excess of silver trifluoroacetate and hydrogen peroxide gave PGH_2 (3).

Porter[16] succeeded in synthesising PGG_2 shortly afterwards. PGG_2 can be formed from the tri-halide (4), in one step, by reaction with an excess of silver trifluoroacetate and hydrogen peroxide (Scheme 2).

The endoperoxides were found to be much more biologically active than the primary prostaglandins and soon became the focus of a considerable biological research effort.

In 1975, Samuelsson[17] isolated a new prostanoid, thromboxane-B_2 (TXB_2), from the incubation of human platelets with arachidonic acid. Accompanying its formation were 12-hydroxy-5,8,10-heptadecatrienoic acid (HHT) and malondialdehyde. Performing the incubation under labelled oxygen led to formation of TXB_2 labelled in the three positions shown (Scheme 3). An unstable intermediate in the formation of TXB_2 was detected by trapping experiments using several nucleophiles. Methanol, ethanol and sodium azide led to derivatives of TXB_2 with the hemiacetal hydroxyl group substituted by methoxy, ethoxy or azide. This indicated the strained oxetane structure (6) (Figure 4), which should be very susceptible to nucleophilic attack. Addition of deutero-methanol to the incubated platelets did not lead to incorporation of deuterium attached to carbon in the TXB_2 formed, thus ruling out the dihydropyran structure (7). The carbonium ion structure (8) could be excluded because of its extreme instability in aqueous medium.

TXB_2 has been synthesised by several different routes, the first total syntheses utilising non-prostanoid precursors coming from Corey et al.[94] and Hanessian et al.[95] TXA_2 is a very unstable molecule with a half-life of only 37 seconds in aqueous medium, and to date has not been synthesised, so its

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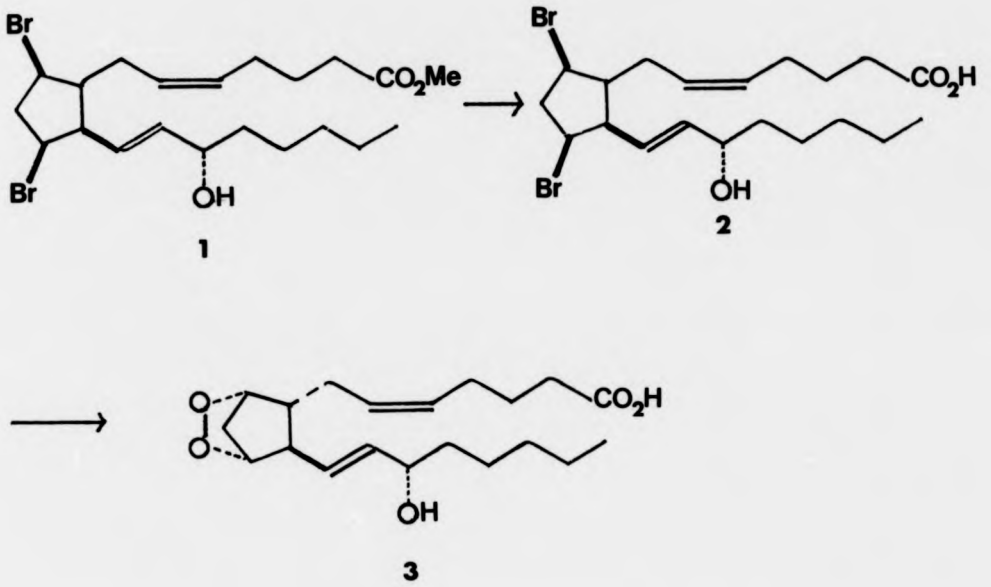
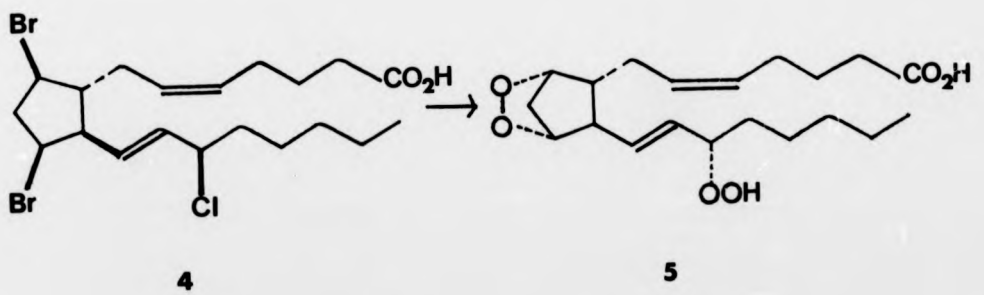
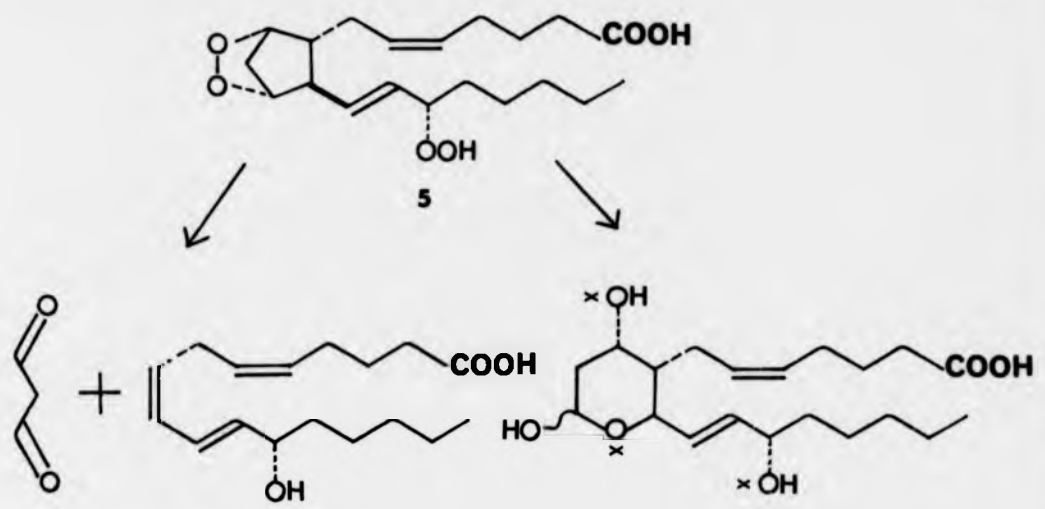


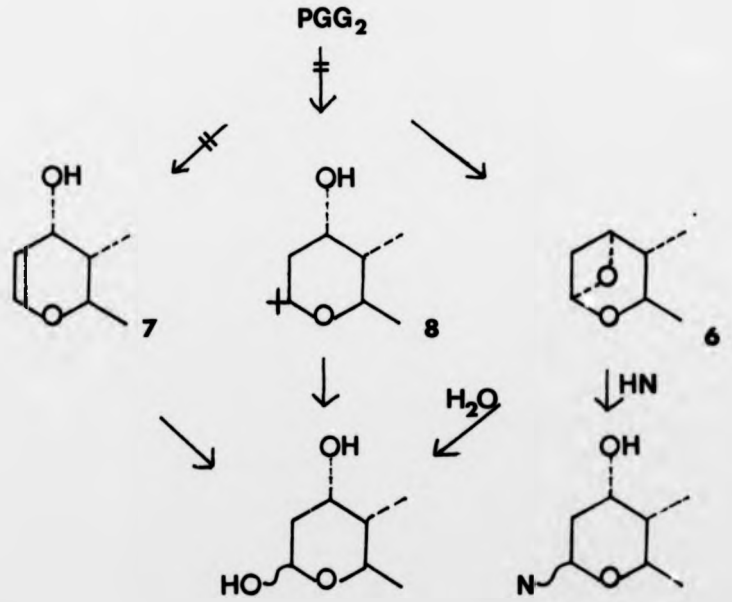
Scheme 1



Scheme 2



Scheme 3



Scheme 4

structure has not yet been finally confirmed. Several analogues have however been made,[20] with activities which suggest the proposed structure is correct.

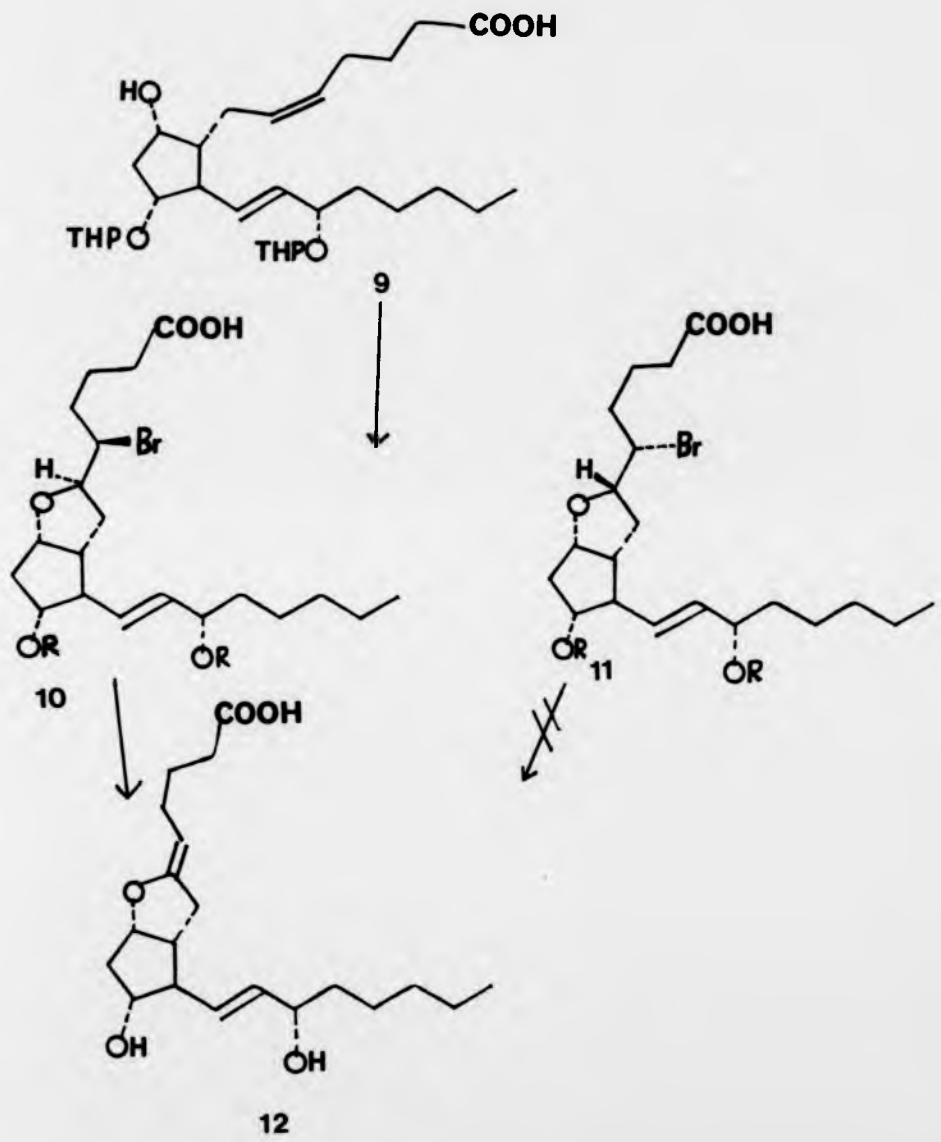
TXB_2 is not very active physiologically, but its precursor, TXA_2 is one of the most potent plateletaggregating and muscle constricting agents known.

Another unstable metabolite of the endoperoxides was isolated in 1976[21] and characterised soon after by Vane et al.[22] A synthesis by Corey[23] soon followed and confirmed the proposed structure. The starting material was the 11,15-bis-(tetrahydropyranyl)ether of $PGF_{2\alpha}$ (9) (Scheme 5). Bromo-etherification with N-bromosuccinimide in tetrahydrofuran produced a mixture of bromo-ethers (10) and (11). Removal of the tetrahydropyranyl protecting group followed by dehydro-bromination with potassium tert-butoxide gave PGI_2 (12), prostacyclin.

This compound is formed in the cell walls and has an almost opposite activity profile to that of TXA_2, being a potent anti-aggregating agent and a vasco-dilator.

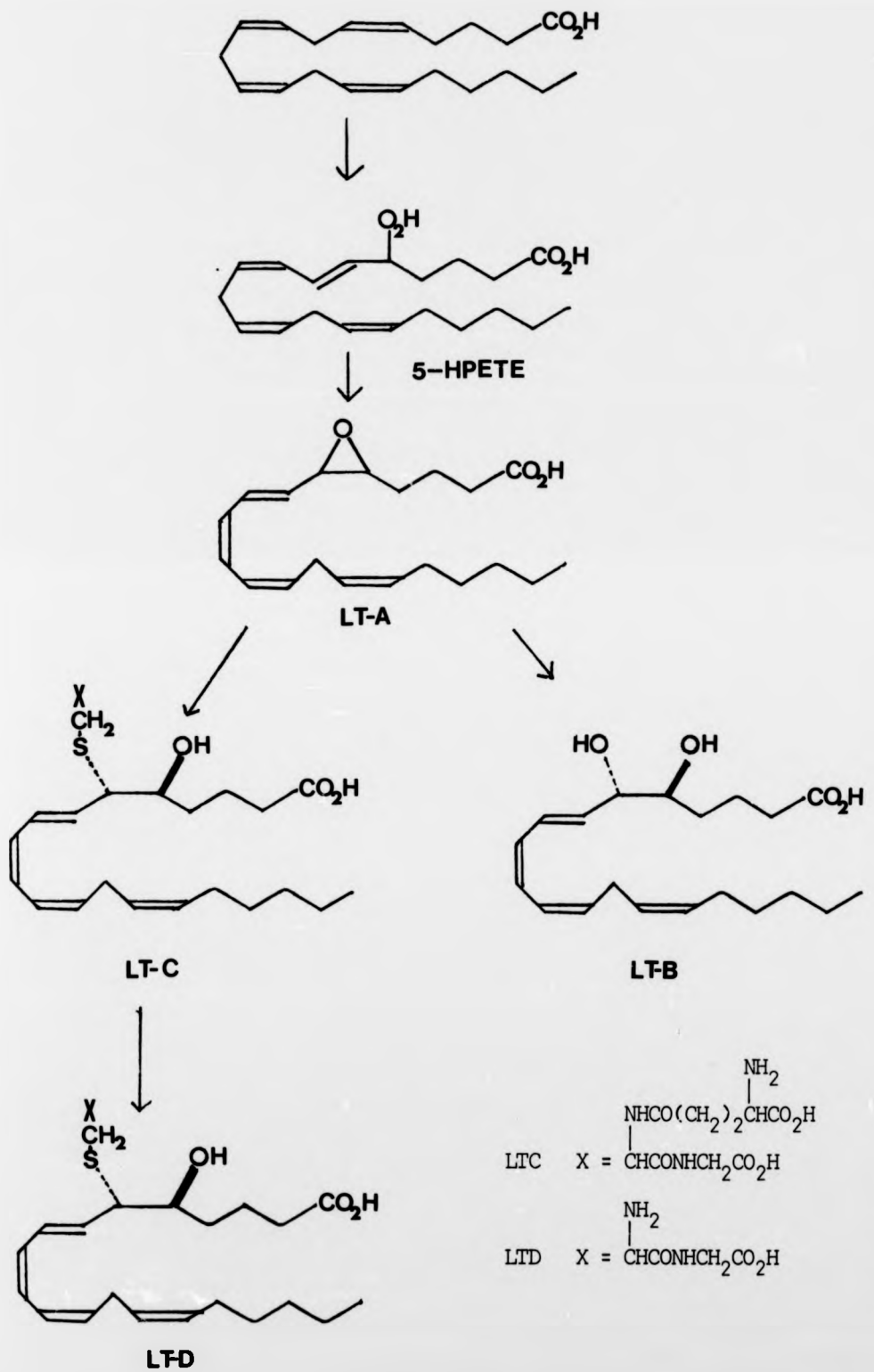
The balance of TXA_2 and PGI_2 may control many biological systems e.g. the maintenance of the vascular tone.

Recently yet another biologically active family of compounds derived from arachidonic acid has been identified. These have been named the leukotrienes (LT), Figure 6. The active member has been known since 1940, when the so-called slow reacting substance (SRS) was isolated from lung tissue.[25] However only in the past year has the structure been determined by Samuelsson et al.,[26] who identified three members of the family i.e. leukotrienes 'A', 'B', and 'C'. Leukotriene-C (LTC)


COOH
HO
THPO
THPO
9
COOH
Br
H
OR
OR
10
COOH
Br
H
OR
11
OR
COOH
OH
OH
12

Scheme 5

appears to be 5-hydroxy, 6-glutathionyl arachidonic acid, and has recently been synthesised by Corey et al.[27] Different tissues appear to produce leukotrienes with different amino-acid residues i.e. Piper[28] and Samuelsson[29] have isolated and identified a fourth member, named leukotriene-D, which contains a glycyl-cysteinyl residue. The leukotrienes are mediators of anaphylaxis and appear to be the major cause of the bronchospasm occurring during asthma attacks.


CO2H
O2H
CO2H
5-HPETE
O
CO2H
LT-A
X
CH2
S
OH
CO2H
LT-C
HO
OH
CO2H
LT-B
X
CH2
S
OH
CO2H
LT-D
NH2
NHCO(CH2)2CHCO2H
LTC X = CHCONHCH2CO2H
NH2
LTD X = CHCONHCH2CO2H

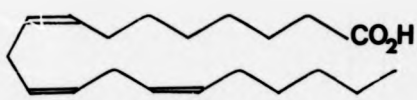
Scheme 6

BIOCHEMISTRY OF PROSTAGLANDINS

(i) Biosynthesis of Prostaglandins

The majority of prostaglandins are local hormones which do not exist as preformed stores, but are formed *in situ* as needed.[30] Almost every type of mammalian tissue examined has the capacity to synthesise prostaglandins, although the amount and type vary considerably between different tissues.

They are formed from the essential fatty acids,[31] the '1' series from dihomo-γ-linolenic acid (13), the '2' series from arachidonic acid (14), and the '3' series from 5,8,11,14,17 eicosapentaenoic acid (15).



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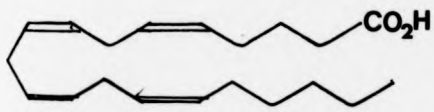

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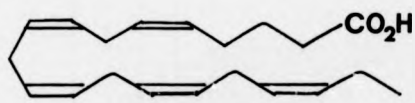

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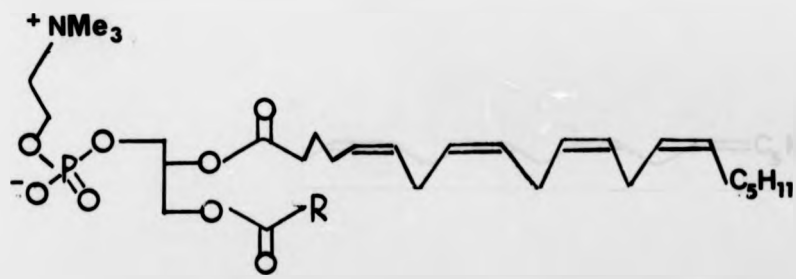
The '2' series is the most important biologically.

The major source of arachidonic acid is membrane phospholipid, principally lecithin (16).



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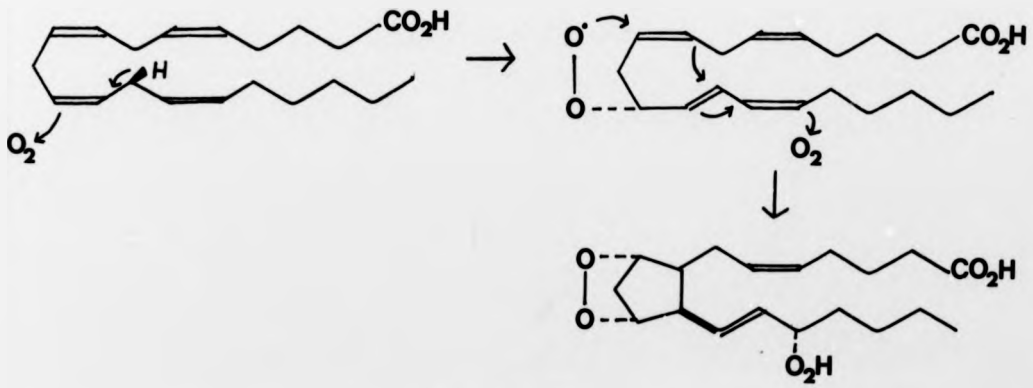
The enzyme responsible for cleaving the arachidonic acid from the 2-position of lecithin is phospholipase A_2. To liberate arachidonic acid from the membrane, various co-factors are needed by the phospholipase A_2. This dependence provides for a complicated biolcgical control mechanism on the availability of arachidonic acid.[32]

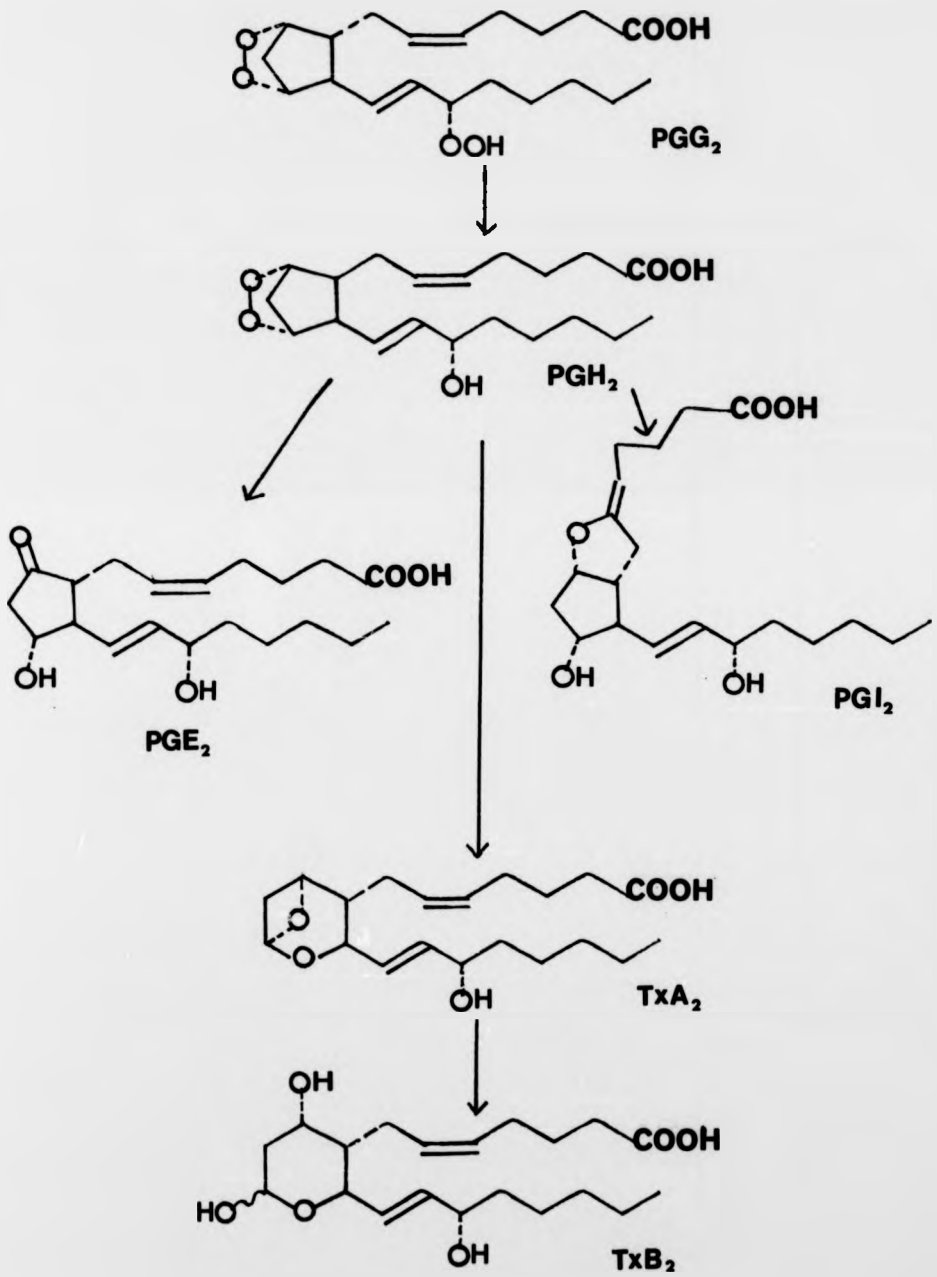
The released arachidonic acid is then acted upon by a microsomal enzyme called prostaglandin endoperoxide synthetase, or cyclo-oxygenase which, in the presence of heme, converts it into the endoperoxide PGG_2 (Figure 7). If tryptophan (a hydrogen donor) is also present, the PGG_2 is converted into PGH_2.

The enzyme has been isolated from sheep and bovine vesicular glands,[33] and appears to consist of two subunits each of 70,000 daltons weight. One mole of hemin per sub-unit is needed for full activity.[34]

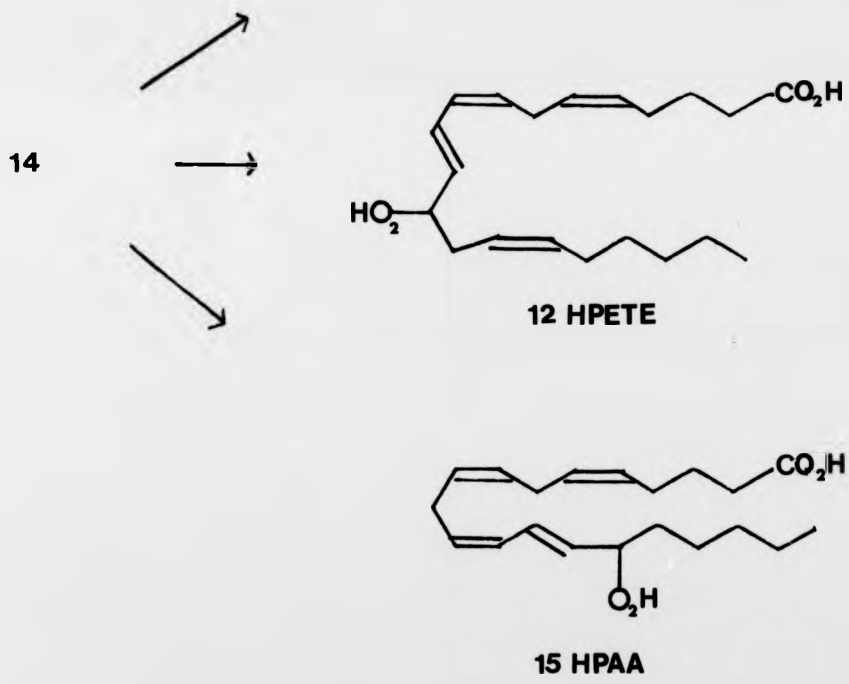
Studies have shown that the oxygen functions at C-9 and C-11 arise from one molecule of oxygen[35] possibly via a radical mechanism [36] (Scheme 8).



Scheme


COOH
OOH
PGG2
COOH
OH
PGH2
COOH
COOH
OH
OH
PGE2
OH
OH
PGI2
COOH
OH
TxA2
OH
COOH
HO
OH
TxB2

Scheme 7



Scheme 9

However recent evidence[37,38] suggests that singlet oxygen (as a metal complex) may be the initiator of the synthetase i.e. bilirubin, a singlet oxygen scavenger inhibits synthetase activity, and chemiluminescence characteristic of singlet oxygen has been observed.

Conversion to PGG_2 is not the only metabolic pathway which can be followed by arachidonic acid. In blood platelets a large proportion is converted, by lipoxygenase enzymes into 12-hydroperoxyeicosatetraenoic acid (12-HPETE), 15-hydroperoxy-arachidonic acid (15-HPAA), and 5-hydroperoxyeicosatetraenoic acid (5-HPETE) (Scheme 9).

The conversion into 15-HPAA, which is a potent inhibitor of the formation of prostacyclin may be of great importance in the vasculature.

5-HPETE is the precursor of the recently elucidated leuc o triene (LT) family of compounds.[26,28]

From PGG_2 to the primary prostaglandins i.e. PGE_2, $PGF_{2\alpha}$ and PGD_2, there are two necessary transformations, namely conversion of the endoperoxide bridge, by the endoperoxide isomerase enzyme, to a β-hydroxyketone etc., and reduction of the 15-hydroperoxy function to a hydroxyl function. There are therefore two possible pathways. Samuelsson[39] has examined the supernatent liquid from sheep seminal vesicles and identified the major prostaglandin metabolites (in the absence of excess glutathione) as 15-hydroperoxy-PGE_2 and 15-keto-PGE_2 (a metabolite of PGE_2). From this he inferred that the action of isomerase, followed by peroxidase, was the major pathway. However conflicting evidence comes from Ogino[40] who has partially

purified prostaglandin endoperoxide E isomerase, the enzyme which converts PGH_2 to PGE_2. He found that in the presence of glutathione PGG_2 was converted to 15-hydroperoxy-PGE_2. This compound was not converted to PGE_2 by prostaglandin endoperoxidase synthase, which converts PGG_2 to PGH_2. This indicated that the order of transformation is AA → PGG_2 → PGH_2 → PGE_2.

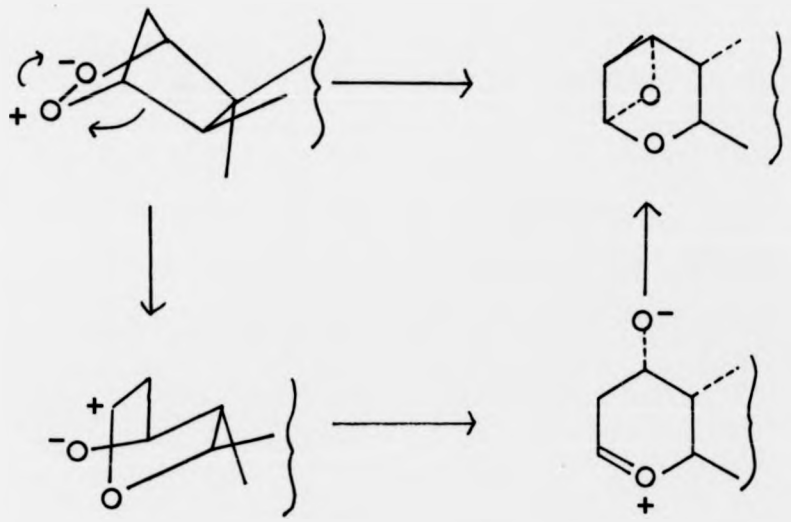
Thromboxane A_2 is obtained from arachidonic acid via the endoperoxides. It can be made by platelet, lung, leucocytes, umbilical artery, spleen, brain, kidney, and seminal vesicles, and in some of these tissues is the major pathway of arachidonic metabolism.[41] The enzyme which converts PGH_2 to TXA_2 has been detected in platelet from several species.[42-44]

The mechanism for the conversion of PGH_2 to TXA_2 could involve an initial polarisation of the endoperoxide bridge (Scheme 10). On the basis of a summation of bond energies, the transformation is energetically favourable $\Delta H = -38$ kcal mol^{-1}, but ring strain in TXA_2 will tend to destabilise the molecule.

Investigations in the '1' and '3' series, have shown that PGH_3 but not PGH_1 is converted into thromboxane.[45] Conflicting evidence has been reported for the conversion of PGH_1 to TXA_1 in platelets.[46]

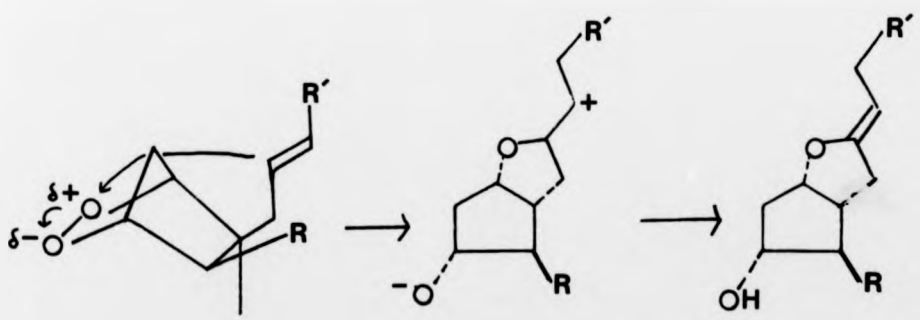
Incubation of endoperoxide with aortic microsomes produces prostacyclin.[47,48] Most arterial tissues, and also stomach, lung, uterus, seminal vesicles and inflammatory granuloma can produce PGI_2, although platelets cannot.

The conversion of PGG_2 to PGI_2 is brought about by the enzyme prostacyclin synthetase, which has so far not been



Scheme 10

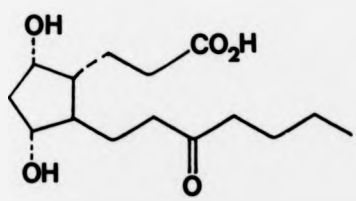
investigated. Mechanistically, one can see that polarisation of the endoperoxide bridge in the opposite direction to that occurring with TXA_2 could lead to PGI_2 (Scheme 11).



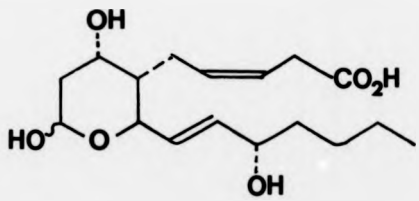
Scheme 11

Prostaglandin Metabolism

PGE_2 can be enzymatically converted to PGB_2 and PGC_2, which can also be obtained from PGA_2. Deactivation of prostaglandins in the body is rapid and involves a sequence of several degradative steps. The main one is oxidation of the 15-hydroxyl function to a ketone. This occurs rapidly in the lungs e.g. 95% of $PGF_{2\alpha}$ present in the blood stream is deactivated by one passage through the lungs.[51] Reduction of the Δ^{13} double bond, two sequences of β-oxidation to the acid side chain, and ω-oxidation to the lower side chain are the other degradative steps. This produces (17) which is the major human urinary metabolite of $PGF_{2\alpha}$.



17



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TXB_2 appears to be resistant to the 15-keto oxidase enzyme. The major metabolite in monkeys is reported to be the result of one sequence of β-oxidation[52,53] i.e. (18). This surprising result may be due to the rather unusual conformation which TXB_2 adopts. In the primary prostaglandin series, a 'hairpin' conformation is normal, whereas with TXA_2 a 'scorpion'

conformation seems to exist (see Figure 12). Presumably this makes TXB_2 a poorer substrate for the 15-hydroxy dehydrogenase enzyme than the other prostaglandins.

(ii) Biological Properties of Natural Prostaglandins

Since the early observations that prostaglandins were biologically very active, a large number of diverse effects have been discovered,[54,55] for instance - stimulation of the pregnant uterus, and termination of the lifespan of the corpus luteum

- control of gastric acid secretion in the stomach
- dilation and contraction of arteries
- control of the excretion of water and sodium ions from the kidneys
- dilation and contraction of the smooth muscle of the bronchial tract
- control of the aggregation of platelets and formation of thrombii
- involvement in various types of inflammation with effects on pain receptors, immune response and temperature control.

Many other diverse physiological effects are known or suspected, including those associated with defects in prostaglandin metabolism e.g. schizophrenia is thought to be due to a deficiency of PGE_1.[56]

These effects have been discovered for the primary prostaglandins over the past 15 years or so, and up until a few years ago, these compounds were considered to be the main cause of the effects. However the discovery of the 'unstable' prostanoids, i.e. the endoperoxides, thromboxanes, and prostacyclins, which have much greater potency and specificity than the primary prostaglandins has led to a different interpretation of the situation. It now seems that the 'unstable'

prostanoids may be the biologically important ones, and that the primary prostaglandins may simply be the end products of degradative endoperoxidase metabolism. Perhaps this is why, pharmacologically speaking, the primary prostaglandins with their poor specificity, have proven disappointing.

The mode of action of the prostaglandins seems, in many cases, to be based upon their effect on the cyclic nucleotides, 3',5'-adenosine monophosphate (c-AMP), and 3',5'-guanosine monophosphate (c-GMP). These are known as 'second messengers' i.e. epinephrine induces lipolysis in adipose tissue, not by direct activation of lipase, but by acting on the enzyme adenyl cyclase which catalyses the formation of c-AMP, which in turn activates lipase. c-AMP has been shown to have this rôle in a wide variety of stimulus-response systems. c-GMP has in many cases, an opposite effect to that of c-AMP.

PGE_1 and $PGF_{2\alpha}$, which often have opposite effects, have been proposed as two arms of a bidirectional intracellular control system.[57] PGE_1 stimulates c-AMP production whereas $PGF_{2\alpha}$ stimulates c-GMP. However this is almost certainly a simplification, as the other prostaglandins have strong effects on c-AMP e.g. PGD_2 and PGI_2[58,59] increase c-AMP levels whereas PGG_2 and TXA_2[60] reduce them. The effect on c-AMP levels fits with the other properties of prostaglandins e.g. smooth muscle contraction or platelet aggregation.

The interaction of prostaglandins with c-AMP seems to be at the cellular level. Special receptors have been found, localised in the cellular membrane. This is also where control

of c-AMP resides. Receptor binding data and structure activity relationships have led to the proposal of a hairpin conformation for primary prostaglandins. In this form, both side chains are parallel and separated by a van der Waals contact distance for their full length. Molecular models indicate that the structure of TXB_2 should be a good approximation to that of TXA_2. An x-ray diffraction study of TXB_2,[61] has shown that it does not have this conformation, but exists as two distinct 'scorpion' conformers with the upper carboxylic acid side chain either α or β to the ring (Figure 12). The hairpin conformation of TXB_2 seems to be unfavourable because of steric crowding of the side chains. This scorpion conformation may be necessary for receptor binding as TXA_1 which does not possess the Δ^5 double bond and cannot therefore take up the scorpion conformation is biologically inactive.

In some cases the 'unstable' prostanoids are hundreds of times more active than the primary prostaglandins, and as previously suggested, may be the active members of the prostaglandin family.

Observations that non-steroidal anti-inflammatory agents (aspirin, indomethacin) are potent inhibitors of prostaglandin synthetase[62-64] led to the suggestion that the primary prostaglandins were the mediators of the inflammatory process. However recent results from the use of other anti-inflammatory agents has shown that they can inhibit or stimulate primary prostaglandin production.[65] The common factor has been traced back to PGG_2. PGG_2 may not itself trigger the inflammation process, but may be the precursor of the unstable triggering agent, which could be TXA_2, 15-hydroperoxy-TXA_2 or the hydroxy radical postulated in the metabolism of PGG_2. TXB_2 is reported

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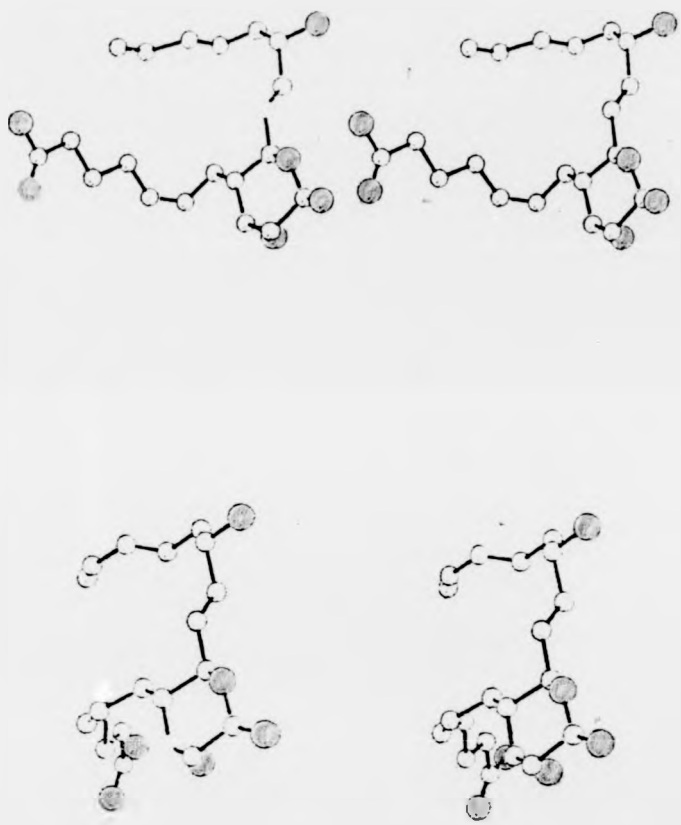


Figure 12a

Stereograms of the β-tail (top) and α-tail (bottom) conformers of the β-anomer of TXB_2

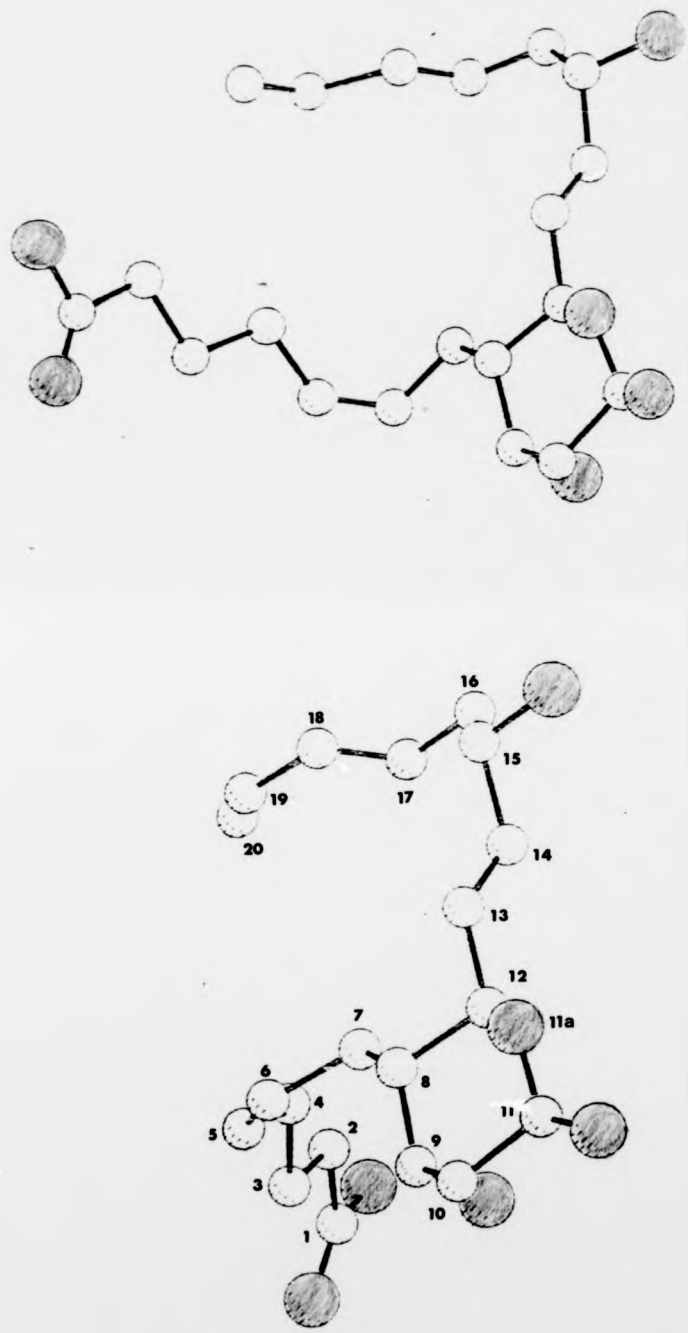


Figure 12b

Computor plots of the β-tail (top) and α-tail (bottom) conformers of the β-anomer of TXB_2

to promote chemotoxis of polymorphonuclear leucocytes,[66,67] important mediators of inflammation.

TXA_2 and PGI_2, the unstable metabolic products of the endoperoxides have profound and opposite effects on smooth muscle and platelet aggregation. PGI_2 is a vasco-dilator and inhibitor of platelet aggregation, and can in fact disperse preformed clumps of platelets whereas TXA_2 is a vasco-constrictor and potent aggregating agent.

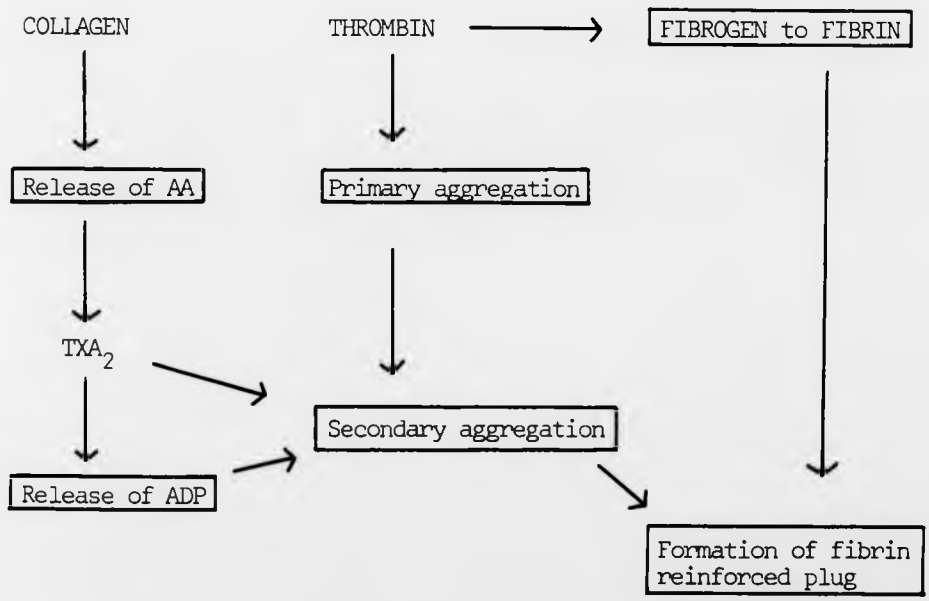
In blood vessels, there is a careful balance between TXA_2 and PGI_2. The vessel walls can rather inefficiently convert arachidonic acid to the endoperoxides, but can then convert these almost quantitatively to PGI_2. This prostacyclin synthetase activity is localised in the inner 5% of the vessel wall, the endothelium,[68] but also exists in the sub-endothelial layers. Blood platelets however can efficiently convert arachidonate ester to endoperoxide and on to TXA_2.

When a vessel wall is damaged, repair is effected by first forming a plug of aggregated platelets followed by a more substantial plug of fibrogen (Figure 13). Normally, platelets circulate in the blood quite freely, aggregation only taking place at the site of an injury.

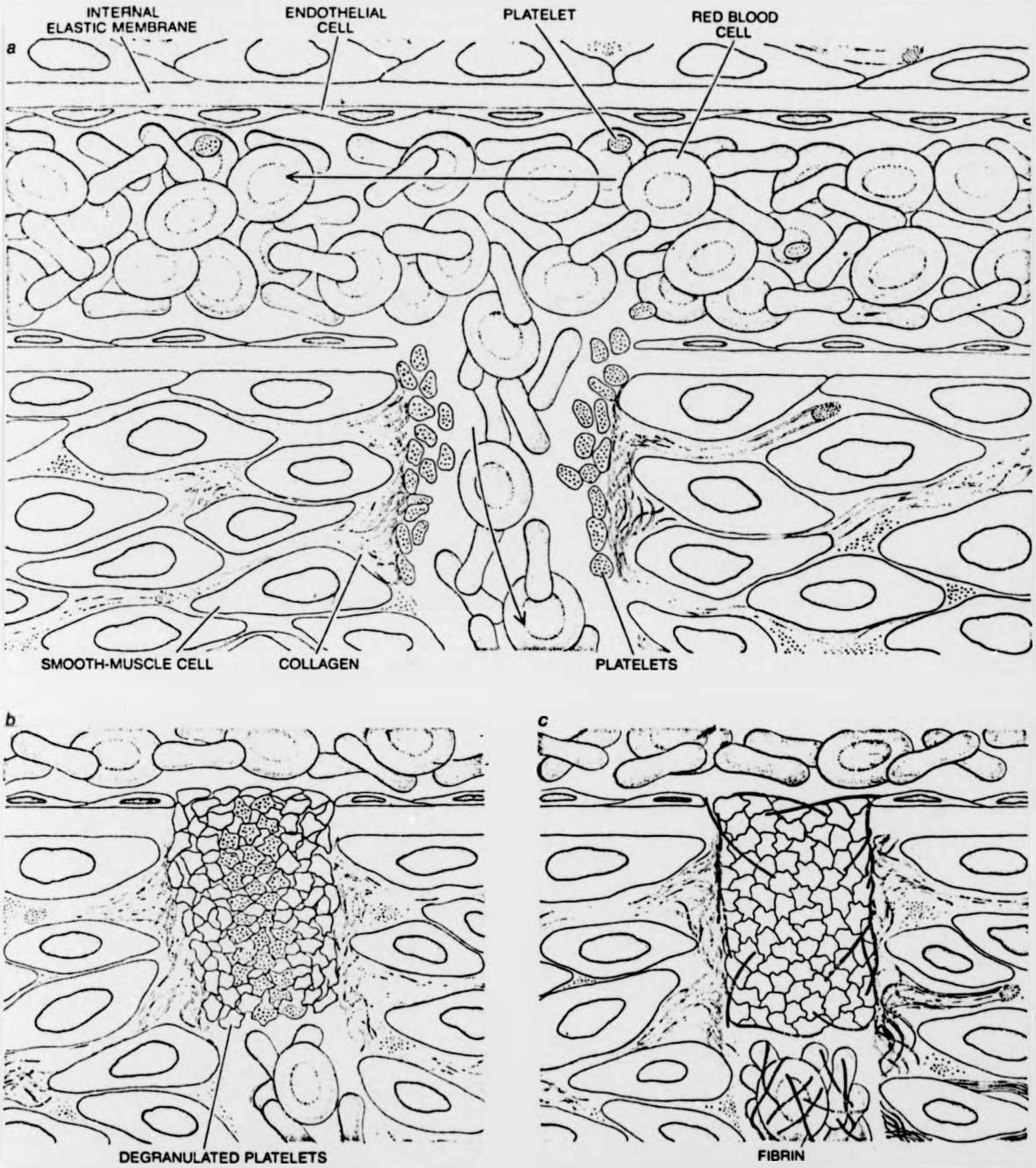
The mechanism of aggregation is quite complicated and only partially understood. Several parallel events occur, the relative importance of which have not yet been determined. It is known that when blood contacts a damaged vessel wall, two main events occur. (1) The release of thrombin from the platelets is stimulated. This causes conversion of fibrogen into fibrin, and also causes a slow initial aggregation of platelets. (2) Thrombin, and collagen present in the wall, then

cause the release of arachidonic acid from the platelet membrane. The arachidonic acid is metabolised to TXA_2 which induces a rapid secretion of adenosine diphosphate (ADP) and serotonin. Simultaneously a second vigorous phase of aggregation occurs. The uncertainty lies in whether TXA_2 or ADP are essential for, or are the main cause of this secondary aggregation (Scheme 14).

One view is that the rôle of TXA_2 is simply that of a stimulus for ADP release.[69] However it now seems likely that TXA_2 is a potent aggregatory agent in its own right, i.e. arachidonic acid caused aggregation of platelets deficient in cyclic nucleotides (including ADP).[70] It thus seems that TXA_2 may play the dominant rôle in secondary aggregation.



Scheme 14



ROLE OF PLATELETS IN HEMOSTASIS, or the stoppage of bleeding, is diagrammed. As blood begins to flow out through a cut in the vessel wall, platelets adhere to collagen in the wall (*a*). The platelets are thereby stimulated to secrete the contents of their granules, including ADP, and other passing platelets adhere to the first layer, building up a loose plug in the wound channel (*b*). Changes in the platelets and contact of blood with damaged cells convert the plasma protein prothrombin into the enzyme thrombin. The thrombin in turn converts fibrinogen into fibrin strands, which reinforce the platelet plug, and it also causes platelets to pack together more closely (*c*).

PGI_2 is a very potent inhibitor of platelet[68] and fibrogen aggregation. It has been suggested that the balance of TXA_2 and PGI_2 could be responsible for maintaining vascular tone.[71] PGI_2 formed by the endothelium would normally stop platelets adhering to its surface. Only where the endothelium had been damaged, with a resultant local decrease in PGI_2 production would TXA_2 synthesis begin and cause platelet aggregation. Thus the interaction of these compounds would maintain the integrity of the vessel walls.

The attractive idea that endoperoxides formed by the platelets, could be the substrate for both PGI_2 production in the endothelium, and TXA_2 production in the platelets themselves, has now been shown not to be the case.[72,73] No exchange of endoperoxides occurs.

Defects in the PGI_2-TXA_2 balance can have serious consequences. The bleeding defect in Greenland eskimos seems to be due to this cause.[74] It originates from the predominantly fish diet, which contains large amounts of eicosapentaenoic acid, the precursor of the '3' series of prostaglandins. Vane has suggested that synthesis of TXA_3 and PGI_3 is responsible. TXA_3, in contrast to TXA_2, has only a weak aggregatory effect whereas PGI_3 is as potent as PGI_2. Needleman has suggested another explanation based on the fact that eicosopentaenoic acid behaves analogously to arachidonic acid apart from not cyclising well when bound to cyclo-oxygenase. Thus high levels of eicosopentaenoic acid would tie up the cyclo-oxygenase, preventing arachidonic acid being metabolised through to TXA_2.

TXA_2 has been implicated in the progressive dermal ischemia occurring around the immediate area of a burn, i.e. the

gradual death of cells over a 24 hour period following a burn injury, mainly caused by coagulation of platelets. Jonsson[75] has shown that TXB_2 levels in the lymph of burn injured areas are much higher than in uninjured areas, reaching a maximum value after 2-4 hours. Delbeccaro,[76] using thromboxane synthetase inhibitors, found that damage around the burn was considerably decreased, and healing accelerated. Previously, inhibitors which took effect further back along the arachidonic acid metabolic chain had been used to achieve the same effects. Use of a specific TXA_2 synthetase inhibitor has now fixed on TXA_2 as the agent responsible.

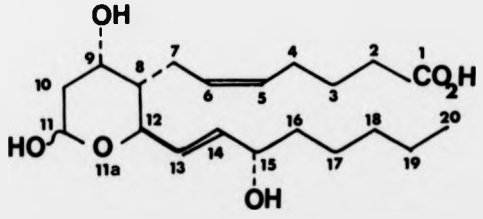
The logical connection between TXA_2 and diseases due to thrombotic disorders e.g. heart disease, has been further elaborated. Apparently cholesterol[77] rich platelets are exceptionally efficient at releasing arachidonic acid (an increase of 30% over normal) and converting this to TXA_2 (an increase of 60%), when stimulated by thrombin. Patients who have suffered heart attacks have been found to require less arachidonic acid to cause platelet aggregation[78] and also to have an augmented rate of conversion of arachidonic acid to TXA_2. This data suggests that body fat levels and TXA_2 are closely connected with heart disease.

The thromboxane field is rapidly developing at the present time, and we may soon be seeing a lot of useful new drugs for treatment of vascular disorders, inflammation, gastric conditions, burn injuries etc., appearing, the action of which will be based on their effect on TXA_2. To be suitable in this respect, the compound must either selectively inhibit TXA_2 synthetase i.e. stop the metabolic chain after formation of

the endoperoxides, so that the other prostaglandins are formed as normal, or, antagonise the TXA_2 receptor site. Excluding analogues of TXA_2 for the moment, the many selective inhibitors of TXA_2 synthetase known encompass a wide variety of chemical types e.g. imidazole,[79,80] dipyridamole and methimazole,[81] sodium p-benzyl-4[1-oxo-2-(3-chlorobenzyl)-3-phenylpropyl]-phenylphosphonate,[82,83] nordihydroguaioretic acid[84] and 2-isopropyl-3-nicotinyl indole.[85] Active prostaglandin analogues are 9,11-azaprosta-3,13-enoic acid,[69] 9,11-epoxymethanoprostanoic acid and 9,11-epoxymethano-15-hydroxyprosta-5,13-dienoic acid.[86] 9,11-Epoxyiminoprosta-5,13-dienoic acid[87] appears to be a receptor site antagonist as it suppresses TXA_2 induced aggregation of platelets without inhibiting the formation of TXA_2.

SYNTHESES OF THROMBOXANE-B_2

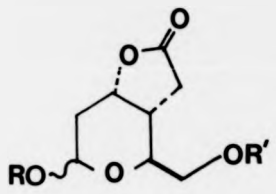
TXB_2 is structurally very similar to the primary prostaglandins, containing the several functionalities and chiral centres which have made these compounds troublesome synthetic targets. The primary prostaglandins have four asymmetric centres in a cyclopentyl ring, but in TXB_2 the C-11 hydroxyl group is part of a hemi-acetal and can readily isomerise in aqueous acid or neutral medium. Thus, control of this centre is not necessary in a synthesis. The equilibrium mixture of C-11 isomers contains a preponderance of the axial (α) isomer, due to the stabilising influence of the anomeric effect, in common with the majority of sugars having a polar substituent at this position. The relative stereochemistry of the other substituents on the ring is analogous to that in the primary prostaglandins with the C-8 and C-12 substituents trans and the C-8 and C-9 cis. This numbering refers to the thromboxane molecule numbered as shown with the ring oxygen considered as 11a.[88]



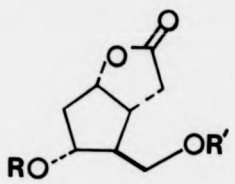
The C-15 asymmetric centre on the lower side chain has the S configuration as in the primary prostaglandins.

As the side chains are identical to those in the primary prostaglandins, one approach to a synthesis would be that already used for these compounds[89] i.e. development of a ring system with the necessary stereochemistry and functionality

to allow addition of the side chains by Wittig type reactions. This would involve the synthesis of a compound of type (19) analogous to the Corey lactone (20)[90].



19



20

In fact six of the eight published syntheses use this compound as an intermediate. It was made from a derivative of the lactone (20) in two of the earlier works, whilst the remaining four syntheses have used carbohydrate precursors. The resemblance of (19) to a pyranoid sugar is obvious, the pyranoid ring should be available intact by choosing a sugar of suitable stereochemistry.

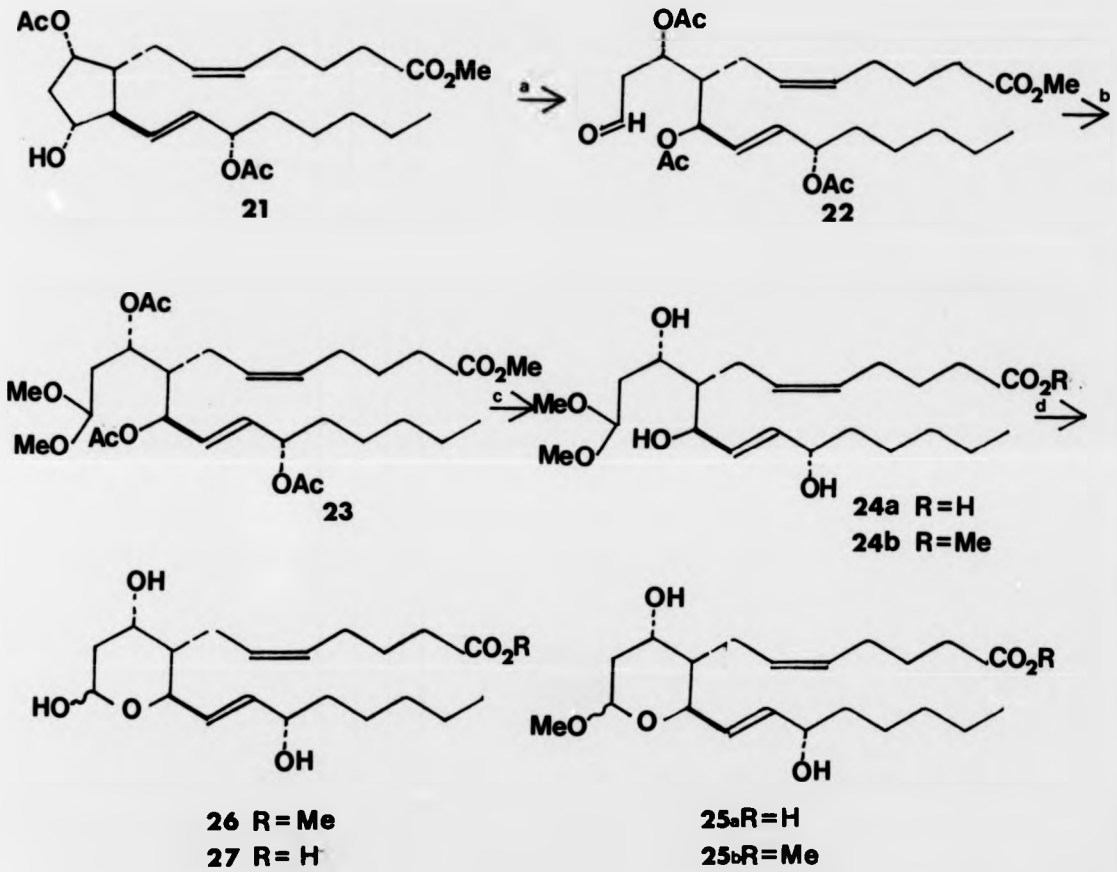
Two alternative strategies have been used in the remaining two syntheses. The Upjohn group have used a derivative of $PGF_{2\alpha}$ as a starting material in a short efficient route of TXB_2, whilst Corey et al. has reduced the problem down to basics and has developed a total synthesis building up the molecule through a series of alkylations, from simple starting materials. As carbohydrates have played such an important rôle in this area, the reported syntheses, in the following discussion have been divided up into non-carbohydrate and carbohydrate based.

(i) Non-Carbohydrate based Syntheses

Schneider and Morge[91] have developed the shortest route of the three published by the Upjohn Company, using 9,15-diacetoxy-$PGF_{2\alpha}$ methyl ester as the starting point. The key step was the cleavage of the 11-12 bond of the cyclopentane ring, utilising the homo-allylic alcohol moiety for the necessary activation. Cleavages of this type, induced by lead tetra-acetate are known in the steroid field.

The reaction of (21) (Scheme 15) with lead tetra-acetate thus led to the rather unstable acetoxy-aldehyde (22) which was converted directly to its dimethyl acetal (23). Removal of the acetoxy groups with methanolic sodium methoxide gave the ester (24b) whilst use of aqueous base yielded the acid (24a). Transacetalisation was then carried out using aqueous acetic acid, for the ester (24b). This resulted in the production of a mixture of TXB_2 methyl ester (26) with the corresponding methyl acetal (25b), itself a mixture of the α and β isomers in the ratio 1:2. The acid (24a) on treatment with tetrahydrofuran, water, 85% phosphoric acid gave largely TXB_2 (27) with a small amount of its methyl acetal (25a).

The remaining two syntheses from the Upjohn Company utilise Corey's bicyclic lactone, as a starting material, and involve different methods for cleaving the C_{11}-C_{12} bond of this compound. Nelson and Jackson[92] developed a diol at C_{11}-C_{12} by treatment of (28) with florisil to give the α,β-unsaturated aldehyde (29), which, after reduction of the aldehyde moiety and protection of the resultant primary alcohol as the p-phenylbenzoate, was hydroxylated to the required compound (30) using osmium



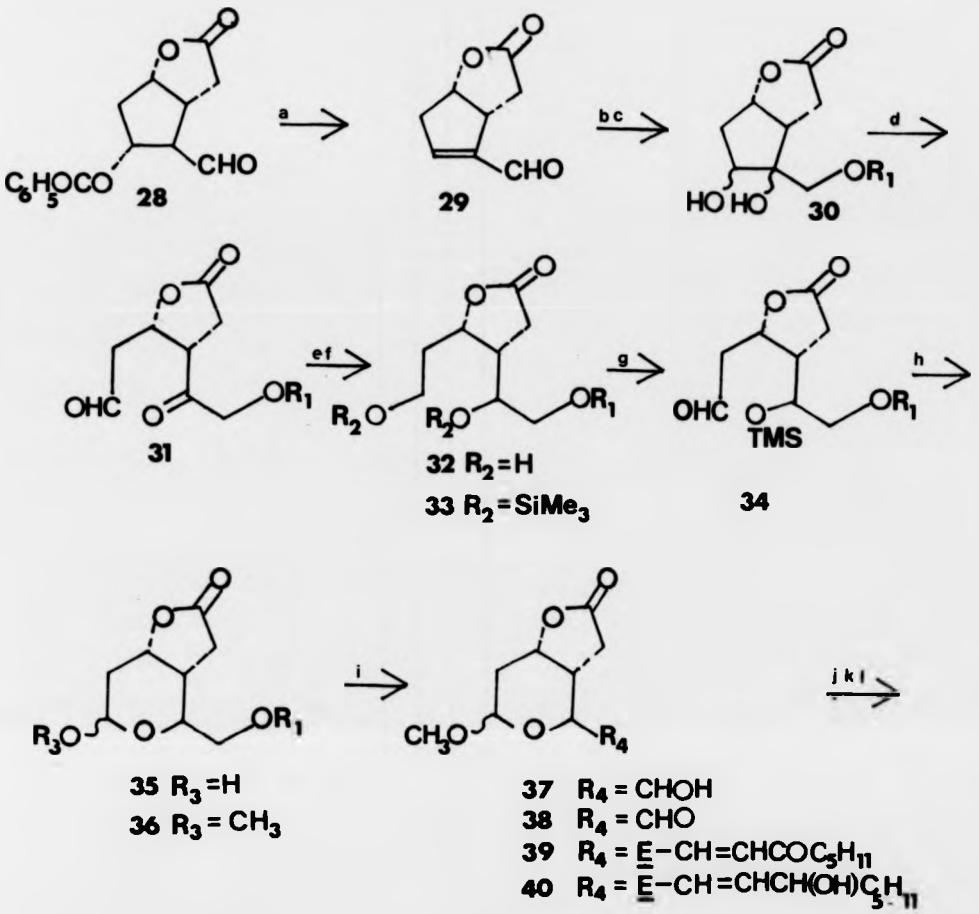
(a) $Pb(OAc)_4$, C_6H_6, RT, (b) $HC(OMe)_3$, HCl, MeOH,

(c) aq.-base, (d) aq.H_3PO_4, THF, R.T.

Scheme 15

tetroxide. Cleavage of the C_{11}-C_{12} bond was then possible with paraperiodic acid to the rather unstable aldehyde-ketone (31) which was directly reduced to the diol (32). Selective oxidation of the primary alcohol of (32) was achieved indirectly by first preparing the bis-(trimethylsilyl ether) derivative (33) then subjecting this to Collins oxidation. The aldehyde (34) thus obtained, on treatment with methanolic acetic acid, cyclised to the hemi-acetal (35). Use of methanolic HCl caused the conversion of (34) or (35) into the methyl acetal (36), isolated as a mixture of the α and β isomers. This compound is the thromboxane equivalent of Corey's cyclopentyl bicyclic lactone intermediate, and by its synthesis the main chemical problem of formation of the ring acetal group had been solved, therefore allowing the completion of the synthesis of TXB_2 to be performed using well-known methodology.

Thus Nelson and Jackson continued the synthesis by cleaving the ester protecting group of the α isomer with base, and oxidising the resultant primary alcohol to the aldehyde (38). Alkylation of this with the ylide derived from dimethyl-2-oxo-heptylphosphonate and potassium tert-butoxide afforded (39) with the desired trans-Δ^{13} double bond. Reduction of the enone carbonyl function resulted in the epimeric C-15 alcohols (40). Reduction to the lactol (41) with di-isobutyl aluminium hydride allowed addition of the upper side chain using the ylide prepared from 4-carboxybutyltriphenylphosphonium bromide and dimsyl sodium, to produce (25a) and (25b), with the required cis-Δ^5 double bond. The β isomer of (36) was similarly treated to produce a mixture of (25c) and (25d). Hydrolysis of (25b) and (25d) with aqueous acid yielded TXB_2 (27a) as a crystalline solid.



(a) Florisil, (b) $NaBH_4$, CH_3OH,

(c) OsO_4, N-methylmorpholine N-oxide,

(d) paraperiodic acid, pyridine aq.MeOH,

(e) $NaBH_4$, (f) Silylation, (g) Collins[O],

(h) HCl, MeOH, (i) NaOMe, MeOH, (j) Collins[O],

(k) $(MeO)_2P(O)CH_2C(O)C_5H_{11}$, t-BuOK, THF, (l) Dibal,

(m) $Ph_3P{=}CH(CH_2)_3CO_2Na$, (n) Sepn.,

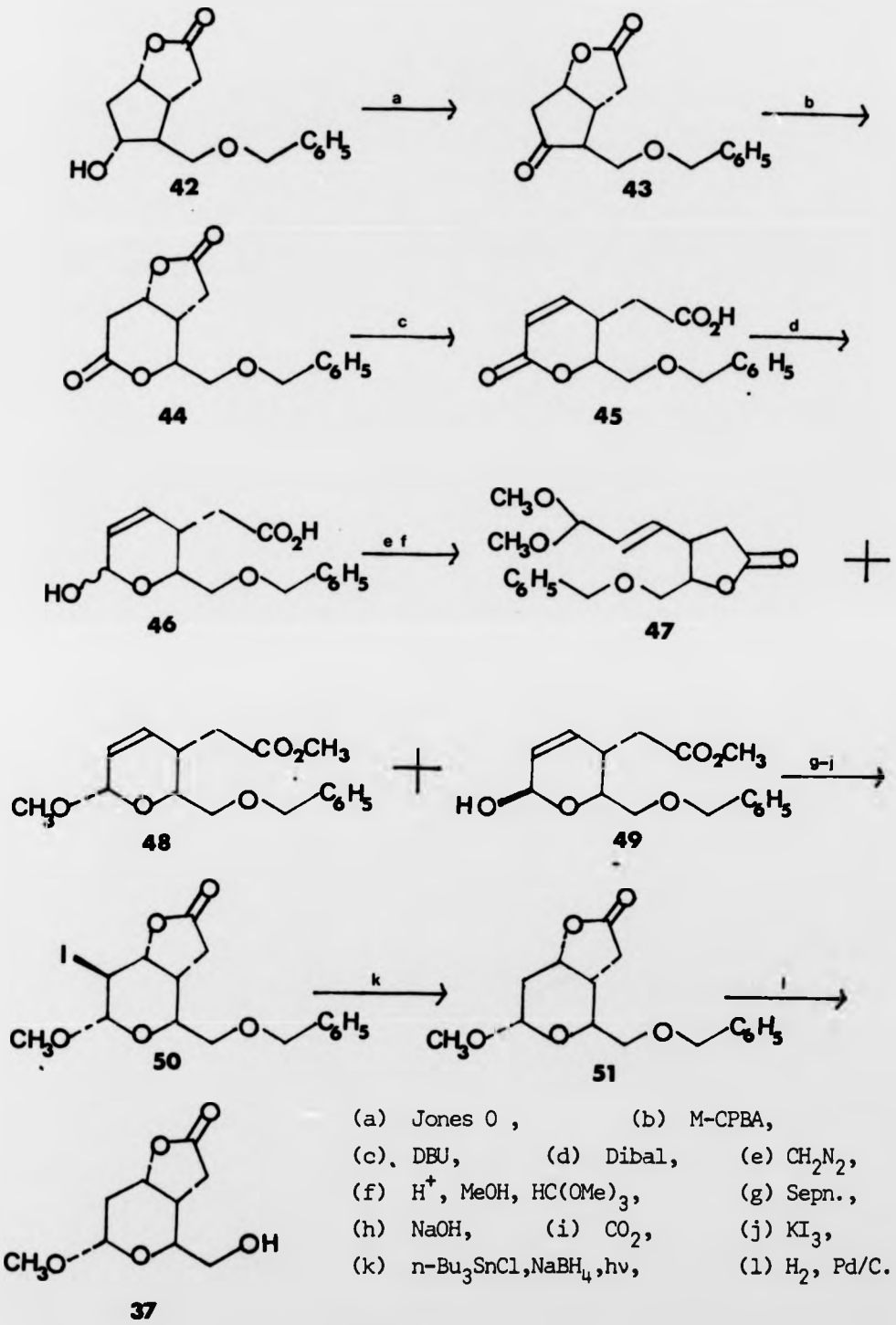
Scheme 16

Kelly, Schletter and Stein[93] developed another synthesis from the bicyclic lactone derivative (42) (Scheme 17). Jones oxidation to the ketone (43) allowed introduction of the 11a ring oxygen by a Baeyer-Villiger reaction with m-chloro-peroxybenzoic acid, to give the crystalline dilactone (44). A rather involved scheme was then necessary to reduce the C-11 carbonyl group to an alcohol. Thus treatment of (44) with 1,5-diazabicyclo[5,4,0]undec-5-ene resulted in the elimination product (45).

Reduction to the hemi-acetal with DiBAL was then possible giving (46), which after esterification with diazo-methane was converted to the isomeric methyl acetals (48) and (49). Protection of the hemi-acetal was necessary as the α, β-cis-unsaturated aldehyde (46) was liable to isomerisation to the trans form, and indeed some material resulting from this (47), was isolated along with (48) and (49).

The α isomer (48), was subjected to iodo-cyclisation to yield (50), which after de-iodination and removal of the benzyl protecting group gave the desired product (37).

The total synthesis by Corey et al.,[94] does not involve a prostanoid precursor, the molecule being built up by a series of alkylation reactions. The enone (53) (Scheme 18) was the starting material. Alkylation with allyl bromide gave (54), the lithio derivative of which underwent an aldol reaction with the aldehyde (55) to produce an inseparable mixture of ethyro and threo isomers (56) the desired isomer, which would have the side chains in the trans configuration after cyclisation, predominating. Thus after depyranylation to (57), the pyran ring


a
b
c
d
e f
g-i
k
l
42
43
44
45
46
47
48
49
50
51
37
(a) Jones O , (b) M-CPBA,
(c) DBU, (d) Dibal, (e) CH_2N_2,
(f) H^+, MeOH, $HC(OMe)_3$, (g) Sepn.,
(h) NaOH, (i) CO_2, (j) KI_3,
(k) n-Bu_3SnCl,$NaBH_4$,hν, (l) H_2, Pd/C.

Scheme 17

was formed by an acid-catalysed intramolecular Michael reaction to yield (58) as a mixture of the C-8, C-12 cis and trans isomers, each of which was also a mixture of the C-15 diastereomers. No cis to trans isomerisation was observed during this reaction. Reduction of the ketone function to the alcohol with sodium borohydride yielded an easily separable mixture of diastereomers. (60) having the correct stereochemistry was elaborated into TXB_2 by removal of the dithioacetal protecting group to give the hydroxy lactone (61), which was reduced with DiBAL and converted to the methyl acetal (62) by transacetalisation with methanol and boron trifluoride etherate. The remaining steps were straightforward and involved hydroxylation of (62) with osmium tetroxide, followed by cleavage of the resultant diol using sodium meta-periodate, to yield the lactol (41). Addition of the upper side chain was accomplished with the ylide derived from 4-carboxybutylphosphonium bromide and dimsyl sodium, leaving acid hydrolysis to produce TXB_2 (27a) and its C-15 epimer (27b).

The C-15 epimer thus produced was convertible to TXB_2 by superoxide displacement of the protected mesyl derivative, followed by deprotection.

(ii) Carbohydrate based Syntheses

The preceding syntheses produced racemic products and it was obviously desirable to perfect a chiral synthesis. Carbohydrates have in the past few years received increasing attention as sources of chirality useful in the synthesis of optically-active materials. Their many advantages include:- low cost, ease of structure determination by ^1H and ^{13}C NMR, regio- and stereo-selectivity in their reactions and the

(a) LDA, THF, HMPA, -25^{o}, 5h

(b) CH_2CHCH_2Br

(c) LDA, THF, -25^{o}

(d) H_3O^{+}

(e) CH_2Cl_2, TsOH

(f) DHP, H^{+}

(g) $NaBH_4$, EtOH

(h) Sepn.

(i) $AgNO_3$, Ag_2O, aq.CH_3CN

(j) Dibal

(k) CH_3OH, $BF_3.Et_2O$

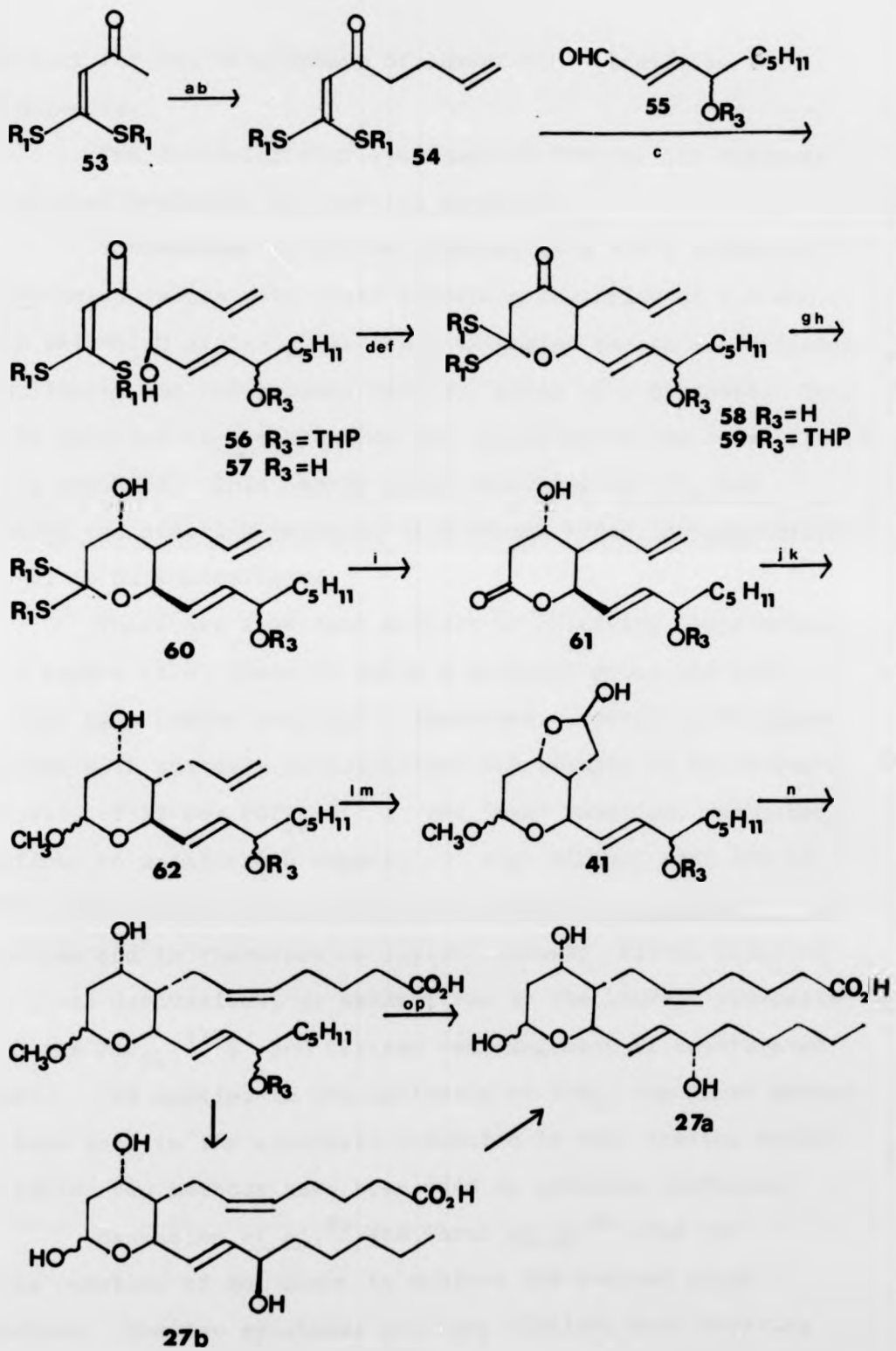
(l) OsO_4, Pyridine

(m) $NaIO_4$

(n) $Ph_3P{=}CH(CH_2)_3CO_2Na$

(o) H_3PO_4, aq.THF

(p) Sepn.


ab
53
54
OHC
55
C5H11
OR3
c
def
56 R3 = THP
57 R3 = H
gh
58 R3 = H
59 R3 = THP
i
60
jk
61
lm
62
n
41
op
27a
27b

Scheme 18

potential for the development of latent functionalities in the molecule.

The following four syntheses of TXB_2 or its synthons all utilise D-glucose as starting material.

Thromboxane B_2 can be regarded as a 2,4,6 trideoxy-D-ribo-hexopyranose with chain branching occurring at C-4 and chain extension at C-6. The chain extension can be accomplished by utilising the C-6 primary hydroxyl group of a pyranose. This can be oxidised to the aldehyde and subjected to the conventional Wittig sequence. This leaves chain branching at C-4, and assuming the starting material is a normal sugar, deoxygenation at C-2, to be accomplished.

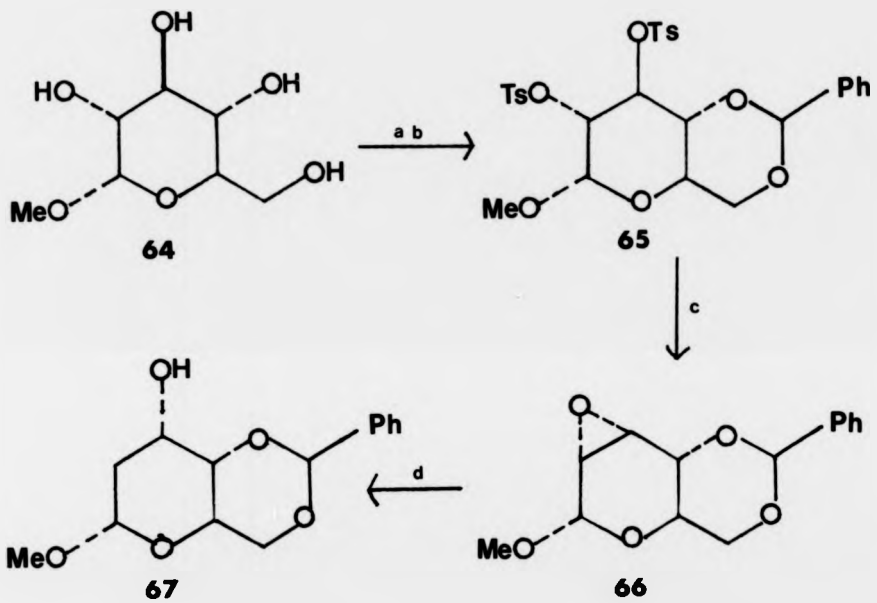
There are four main methods of obtaining chain-branched deoxy sugars (i.e. those in which a hydroxyl group has been replaced by a carbon residue). These are:- reaction of sugar epoxides with suitable nucleophiles, for example in Hanession's synthesis of 11-oxa $PGF_{2\beta}$ [116]; the 'oxo' reaction, and other additions to unsaturated sugars, e.g. Michael addition to enones (the oxo reaction tends to be non-regio or stereo-selective and is therefore of limited value); Wittig reaction with ulose derivatives, as exemplified by the Lourens synthesis of 11-oxa $PGF_{2\alpha}$ [117]; and Claisen rearrangement of unsaturated sugars. As applied to the synthesis of TXB_2, the first method has been used in the synthesis presented in this thesis, whilst the latter two methods have been used in previous syntheses.

Hanession *et al.*[95] and Ohrui *et al.*[96] used the Wittig reaction of an ulose to achieve the desired chain branching. The two syntheses are very similar, both starting

with the 2-deoxy ribo sugar (67), available from D-glucose by regio-selective reduction of the oxirane (66) (Scheme 19). Scheme 20 shows the route to the key bicyclic lactone (76) shared by both syntheses.

Hanession achieved cleavage of the benzylidene group of the 3-benzoate derivative (68) by hydrogenolysis. Selective protection of the primary hydroxyl group of (69) was performed with tert-butyldiphenylsilyl chloride, a reagent developed for this purpose in Hanession's laboratory. Oxidation of the free 4-hydroxyl group gave the crystalline 4-ulose (71) which was alkylated with trimethylphosphonoacetate in the presence of potassium tert-butoxide. This resulted in a mixture of the two isomeric unsaturated esters (72) and (73). Hydrogenation of this mixture with palladium hydroxide on charcoal gave only the more stable 4-equatorial product (74), which on treatment with base, cyclised to the crystalline lactone (76a).

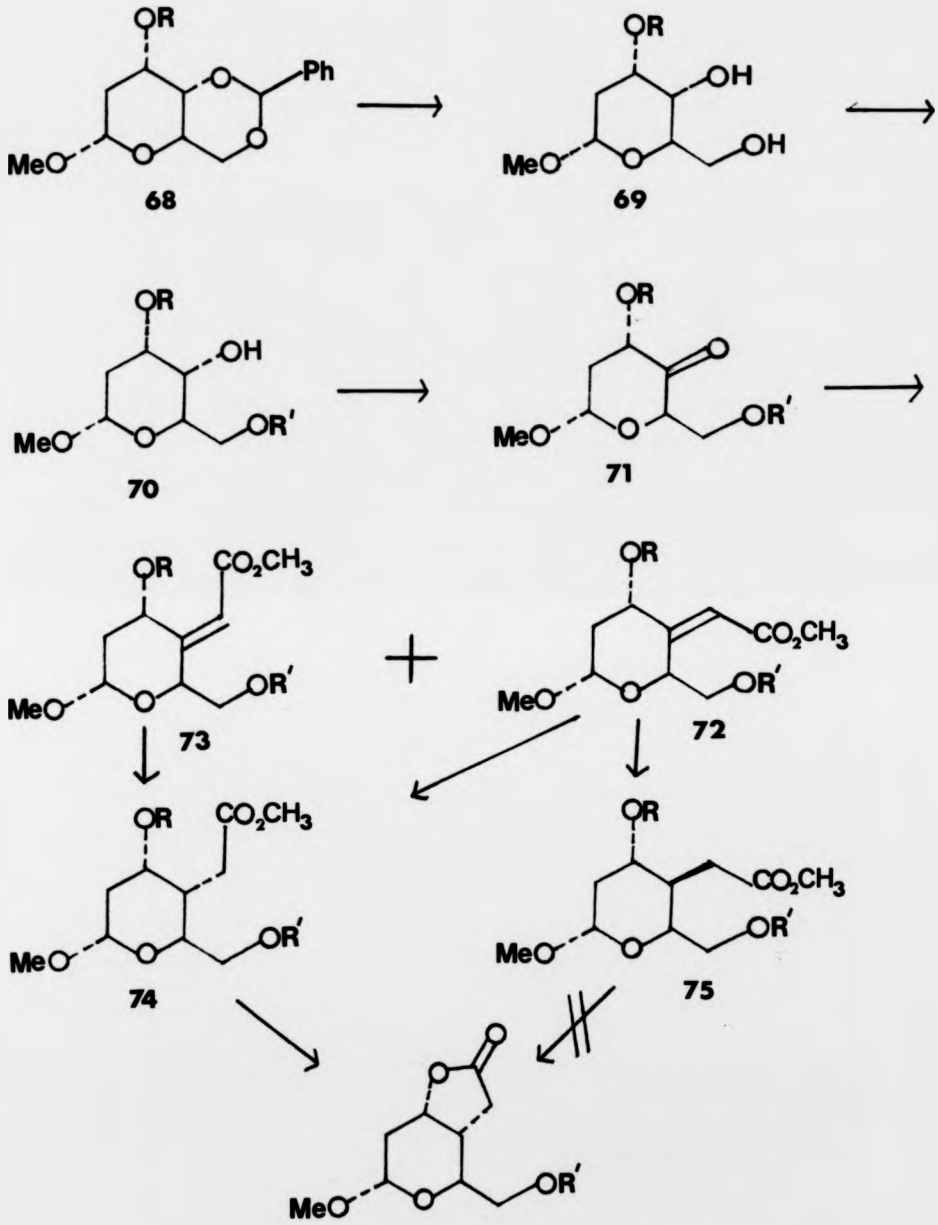
Ohrui et al. protected the 3-hydroxy group as a benzyl ether. The benzylidene group was removed using aqueous acetic acid, and the resulting free primary hydroxyl group protected as the benzoate ester. This reaction with benzoyl chloride was not quite as selective as Hanession's use of t-butyldiphenylsilyl chloride, with 12% of the 5-O-benzoate being formed also. Oxidation and alkylation as above gave the unsaturated esters (72) and (73). Ohrui found that hydrogenolysis of the E isomer (73) using palladium on charcoal gave the expected equatorial isomer (74). However the Z isomer (72) produced a 1:1 mixture of this equatorial isomer with the less stable axial D-xylo isomer (75). This 3,4-trans compound would not cyclise on subsequent treatment with silica in refluxing toluene, whereas



(a) PhCHO, H^+, (b) TsCl, pyridine,

(c) NaOMe, MeOH, (d) $LiAlH_4$, THF

Scheme 19



76a $R' = Si^tBuPh_2$
76b $R' = Bz$

Scheme 20

the 3,4 cis isomer did, affording the desired lactone (76b), isolated as a syrup.

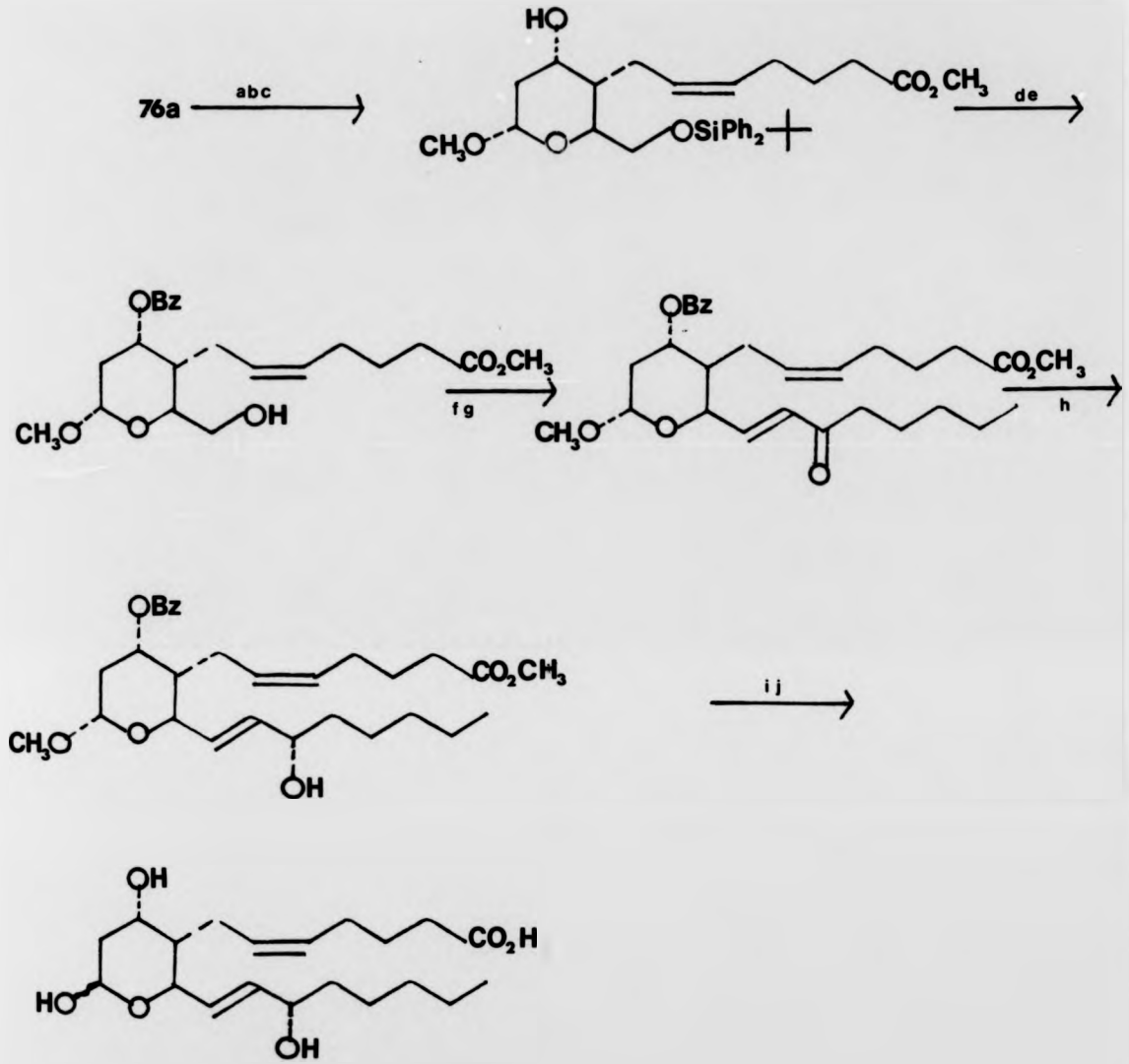
Hanession used this lactone to complete the synthesis of chiral TXB_2 by standard prostaglandin methodology as outlined in Scheme 21.

A Claisen rearrangement was utilised by Corey et al.[97] and Hernandez[98] as the key step in the synthesis of the bicyclic lactone. This type of reaction was first applied to the carbohydrate field by Ferrier and Vethaviyasor[99] who demonstrated that it was possible to transfer stereochemistry across the ring

Somewhat milder versions of this reaction were used by Corey and Hernandez.

The key intermediate was the unsaturated sugar (77). Corey synthesised this by the route developed by Holder and Fraser-Reid,[100] as shown in Scheme 23. The crucial step was the dibenzoylation of (78) to produce (79) which went in moderate yield. This succeeds because the primary and C-2 hydroxyl groups are more acidic than the others. Subsequent mesylation to (80) followed by reductive elimination by the method of Tipson and Cohen,[101] and deesterification gave the desired allylic alcohol (77a).

A slight variation on this route was developed by Hernandez who began by protecting the primary hydroxyl group of (78) as the trityl ether. The selectivity in the benzoylation of (81) was increased by first forming the di-n-butylstannylene derivative which was subsequently transformed into the benzoate (82) in 85% yield. Mesylation and reductive elimination as above,



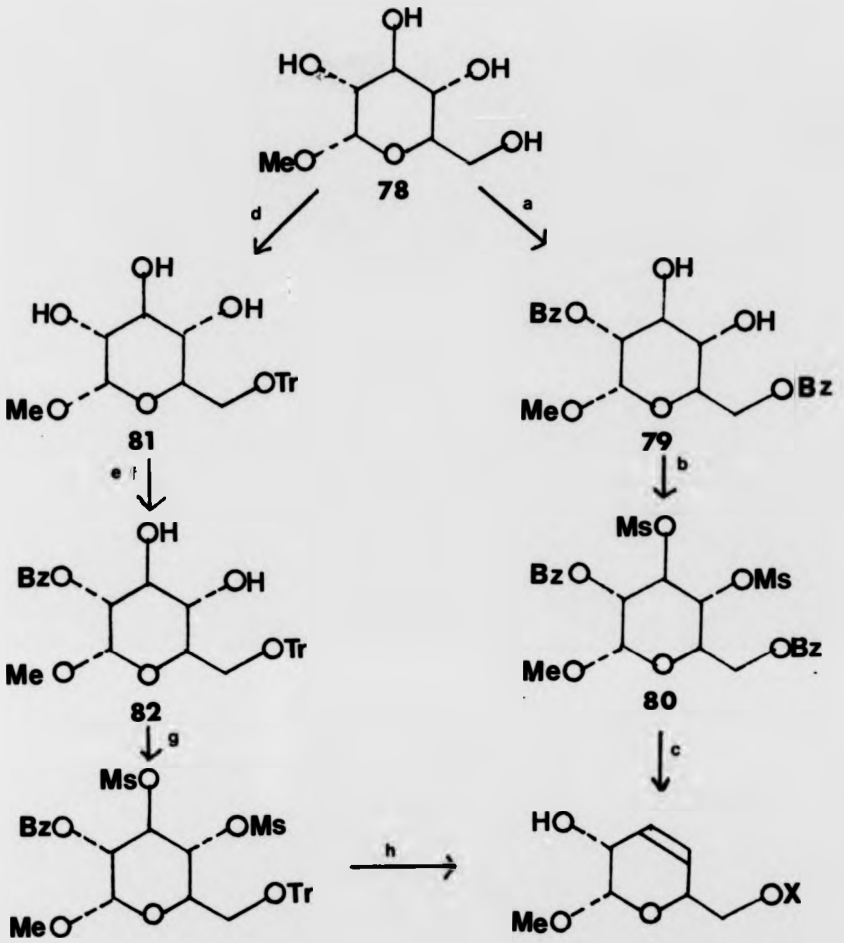
(a) Dibal, (b) $Ph_3P{=}CH(CH_2)_3CO_2Li$,

(c) CH_2N_2, (d) BzCl, (e) Bu_4NF, THF,

(f) Collins[O], (g) $Bu_3PCHC(O)C_5H_{11}$, (h) $Zn(BH_4)_2$,

(i) K_2CO_3, MeOH, (j) H^+

Scheme 21



(a) BzCl, pyridine, (b) MsCl, pyridine,

(c) Zn, NaI, DMF, (d) TrCl, DMF, (e) n-Bu_2SnO, MeOH,

(f) BzCl, triethylamine, THF, (g) MsCl, triethylamine,

(h) Zn/Cu, KI, DMF

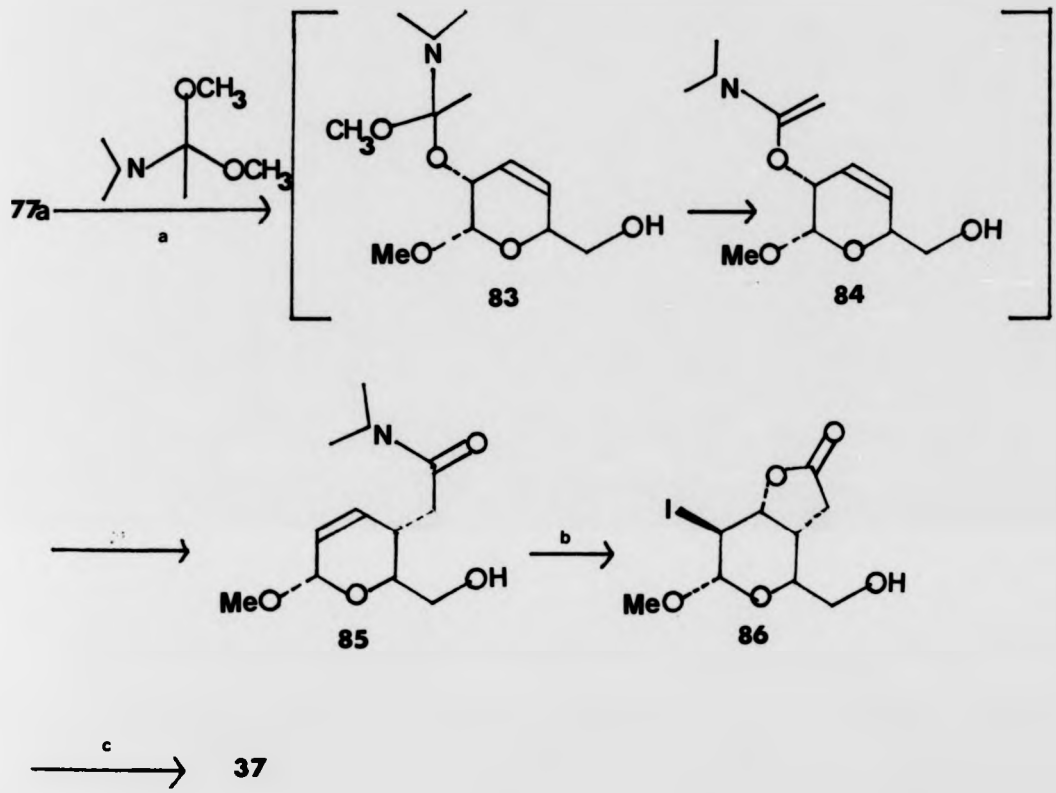
Scheme 23

then gave (77b).

The allylic alcohol moiety of the sugar (77) was now available for conversion into a suitable precursor for a Claisen rearrangement which would attach a two-carbon unit equatorially at C-4.

To accomplish this Corey used the Eschenmoser variation[102] on the basic reaction which involved heating the alcohol in diglyme with 1-dimethylamino-1,1-dimethoxyethane. Apparently the mechanism of this reaction involves trans-acetalisation to give (83) (Scheme 24), which loses methanol to give the 1,5 diene (84) the rearrangement of which occurs in a stereoselective manner furnishing the desired product (85) in good yield. Iodo-cyclisation of (85) afforded the bicyclic lactone (86) which was de-iodinated using tributyltin hydride to the nicely crystalline lactone (37).

The conditions used by Hernandez where those developed by Johnson et al.,[103] and involved the use of trimethylortho-acetate with a catalytic amount of propionic acid in refluxing xylene. This method leads to lower yields of rearranged ester (87) due to the sensitivity of hex-2-enopyranosides such as (87) to acid conditions. The mechanism of the reaction is similar to that of the Eschenmoser reaction, involving formation of a mixed orthoester which loses methanol forming a 1,5 diene capable of rearrangement. De-esterification of (87) yielded the free acid (88) which was subjected to iodo-cyclisation and de-iodination as above to yield the trityl derivative of (37). Thus detritylation yielded free (37) identical to the material obtained by Corey.

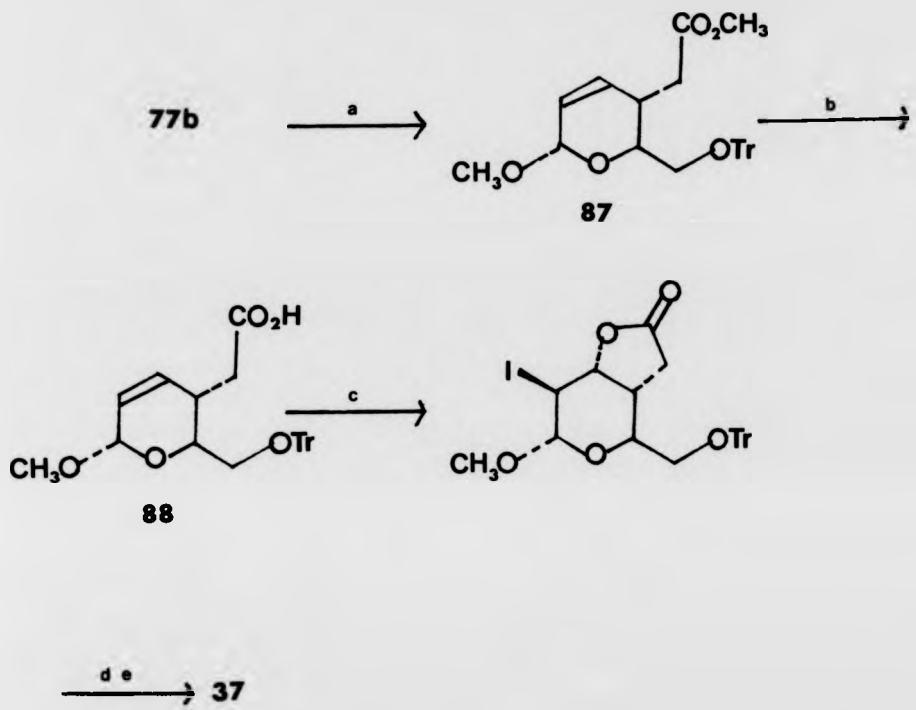


(a) Diglyme, 160°

(b) I_2, THF

(c) n-Bu_3SnH

Scheme 24



(a) $CH_3C(OMe)_3$, H^+, xylene

(b) NaOH, H_2O, THF

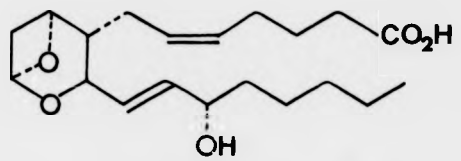
(c) KI/I_2, K_2CO_3

(d) n-Bu_3SnH

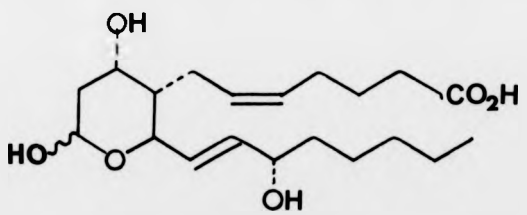
(e) HCl, CH_2Cl_2

Scheme 25

SYNTHESIS OF ANALOGUES OF THROMBOXANE A_2



Tx-A_2 **6**

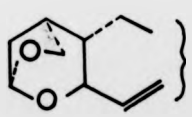


Tx-B_2

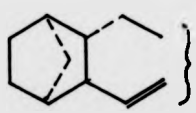
Thromboxane A_2 contains the very unusual 2,7-dioxa-bicyclo[3,1,1] heptane skeleton, previously unknown in biological systems. This system is naturally very labile, due to high ring strain and to the electrophilicity of the acetal carbon. In fact its half life is only 32 seconds in neutral aqueous solution at 37°C. TXA_2 is thus a very difficult synthetic target, and has not, in fact, been synthesised at the present time. Several stable analogues have however been made.

Different strategies are apparent for producing stable, closely related analogues of TXA_2. One could replace one, or both oxygen atoms by less electronegative atoms which would have a stabilising effect by reducing the electrophilicity of C5 of the bicyclic system. This is the method adopted by most of the syntheses to date, with replacement of one or both oxygens by carbon. A closer analogue would require the use of an electronegative element such as sulphur or nitrogen, and in fact the di-thia or di-aza analogues should be appreciably more stable than TXA_2, but no syntheses involving these heteroatoms has been reported.

An alternative strategy involves expansion of the oxetane ring to decrease the ring strain in the system. This was the strategy of a synthetic investigation reported in this thesis whose object was the synthesis of the 2,8-dioxabicyclo-[3,2,1]octane system (87), which contains approximately the same spacial arrangement of the two ring oxygens as that found in TXA_2.



87

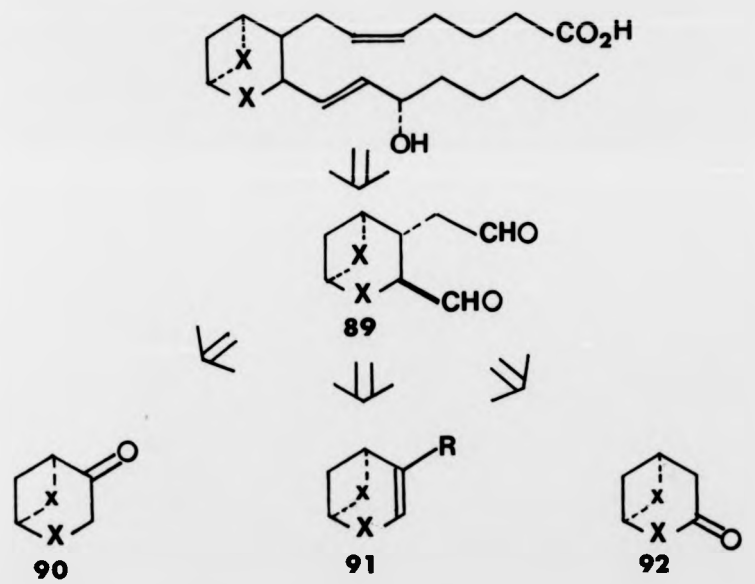


88

The bicyclo[2,2,1]carbocyclic skeleton (88) was the object of a recent synthesis of a TXA_2 analogue by Barraclough.

The remaining stereochemistry of the molecule is identical to that in TXB_2 and the primary prostaglandins and

its formation is therefore susceptible to the same techniques. Therefore the major problem in producing a TXA_2 analogue is that of creating the bicyclicsystem. This problem has been approached in two ways. The more commonly used sequence is the development of a bicyclicsystem as the initial phase of the synthesis, then functionalisation of the system to enable addition of the prostanoid side chains, commonly by Wittig type reactions.



Thus a molecule of type (89) is the key compound, whose elaboration into a TXA_2 analogue would be relatively straightforward. The precursor of this would be a functionalised bicyclic system such as (90), (91) and (92).

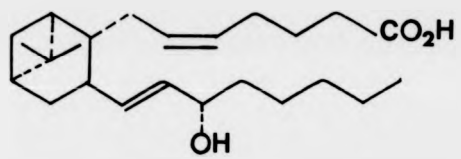
Another way of approaching the problem is to utilise an existing prostanoid, which, as it will contain the side-chains already, will require only elaboration of the ring into a suitable bicyclicsystem. This is the approach used in the Upjohn

synthesis of 11a-carbathromboxane A_2 from a derivative of PGA_2.

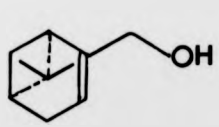
For convenience in the following discussion, the syntheses have been divided up into those in which both oxygen atoms have been replaced by carbon, and those in which only one oxygen atom has been replaced by carbon.

1. Carbocyclic Analogues of TXA_2

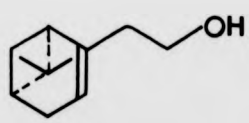
(i) Pinane-TXA_2 (PTA_2)



Once the structure of TXA_2 became known, several groups were quick to realise the potential of the pinene family of compounds to provide a readily available source of the optically active bicyclo[3,1,1]heptane skeleton. Three syntheses exist utilising (-)-myrtenol (93), the alcohol (94), and (-)-pinene (95).



93

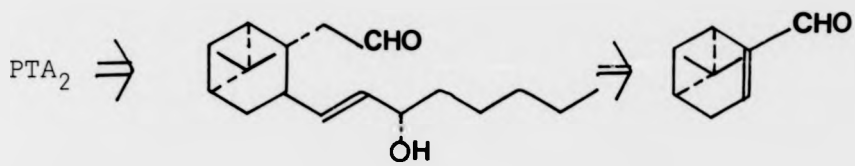


94

95

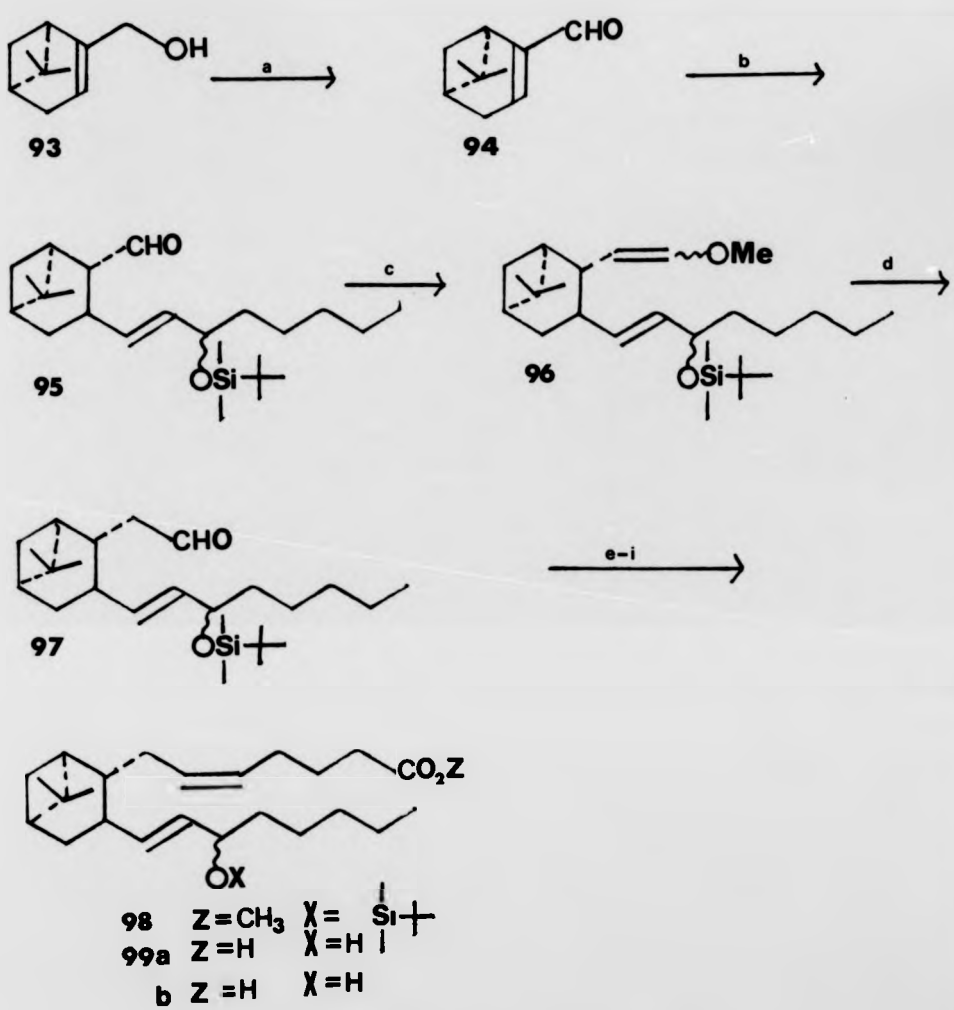
These precursors of PTA_2 contain sufficient functionality to enable the side chains of the prostanoid nucleus to be elaborated with relative ease.

Nicolaou *et al.*[104] developed a rather compact route utilising a conjugate addition to place the lower chain and a Wittig reaction to place the upper one.



(-)-Myrtenol (93) (Scheme 26) was oxidised to the α,β-unsaturated aldehyde (94) which, on treatment with the mixed cuprate derived from (±)-*trans*-lithio-1-octen-3-ol *tert*-butyldimethylsilyl ether and 1-pentynylcopper hexamethylphosphorous triamide complex, afforded the 2,3 *trans* adduct (95) in high yield. Attack, as expected, occurs from the less hindered *exo* side. One carbon homologation of the aldehyde (95) was then accomplished by a Wittig reaction with methoxymethylenetriphenylphosphorane to give the enol ether (96) followed by mild hydrolysis with mercuric acetate and potassium iodide in aqueous tetrahydrofuran. The liberated aldehyde (97) was then exposed to the usual Wittig reaction to place the upper side chain, and after esterification, gave a mixture of the 15*R* and 15*S* PTA_2 silyl ether methyl esters (98). A sequence of acid hydrolysis, separation of the C-15 epimers, and base hydrolysis of the ester group then produced pure (+)-PTA_2 (99a).

The sequence developed by Ansell *et al.*[105] aims for



(a) MnO_2, CH_2Cl_2, (b) Li(1-octen-3-ol t-butyldimethyl silyl ether) and 1-pentynylcopper HMPA complex,

(c) $Ph_3PCHOMe$, (d) $Hg(OAc)_2$, KI, aq.THF,

(e) $Ph_3PCH(CH_2)_3CO_2Na$,

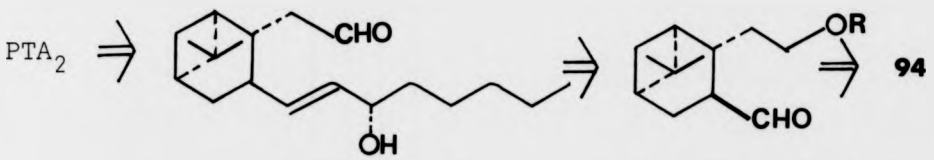
(f) CH_2N_2,

(g) AcOH, aq. THF,

(h) Sepn., (i) LiOH, H_2O, THF

Scheme 26

the classic prostanoid synthon which will enable both side chains to be placed by Wittig reactions. The formyl precursor of the lower side chain is elaborated by a hydroboration process.



Thus the alcohol (94) is pyranylated and the protected derivative (100) subjected to a sequence of 1) 9-borabicyclo[3,3,1]nonane, 2) carbon monoxide, 3) lithium tri-tert-butoxy-aluminium hydride and finally neutral hydrogen peroxide. This produced (101) as the only product. The stereospecificity of the hydroboration has a precedent in the reaction of (-)-α-pinene with 9-BBN, with the borane approaching from the less hindered exo side, and the subsequent carbonylation proceeding with retention of configuration. A Wittig-Horner reaction with dimethyl(-2-oxaheptyl)phosphate placed the lower side chain. The reduction of this enone (102) required a somewhat lengthy series of protection and deprotection steps. First (102) was depyranylated and the resultant alcohol oxidised to the acid (103). This was followed by reduction of the enone carbonyl with L-selectride to produce a mixture of the C-15 epimers (104a) and (104b) which were separated. Finally, esterification with diazomethane, pyranylation of the C-15 alcohol and reduction of the ester group with lithium aluminium hydride gave the pyranyl alcohol (105). A sequence of oxidation to the aldehyde (106), Wittig reaction, and

(a) DHP, H^+

(b) 9-BBN

(c) CO

(d) $LiAl(OBu^t)_3H$

(e) H_2O_2

(f) $(MeO)_2P(O)CH_2C(O)C_5H_{11}$

(g) AcOH, aq.THF

(h) CrO_3, H_2SO_4, DMF

(i) $LiB(sec\text{-}Bu)_3H$

(j) Sepn.

(k) CH_2N_2

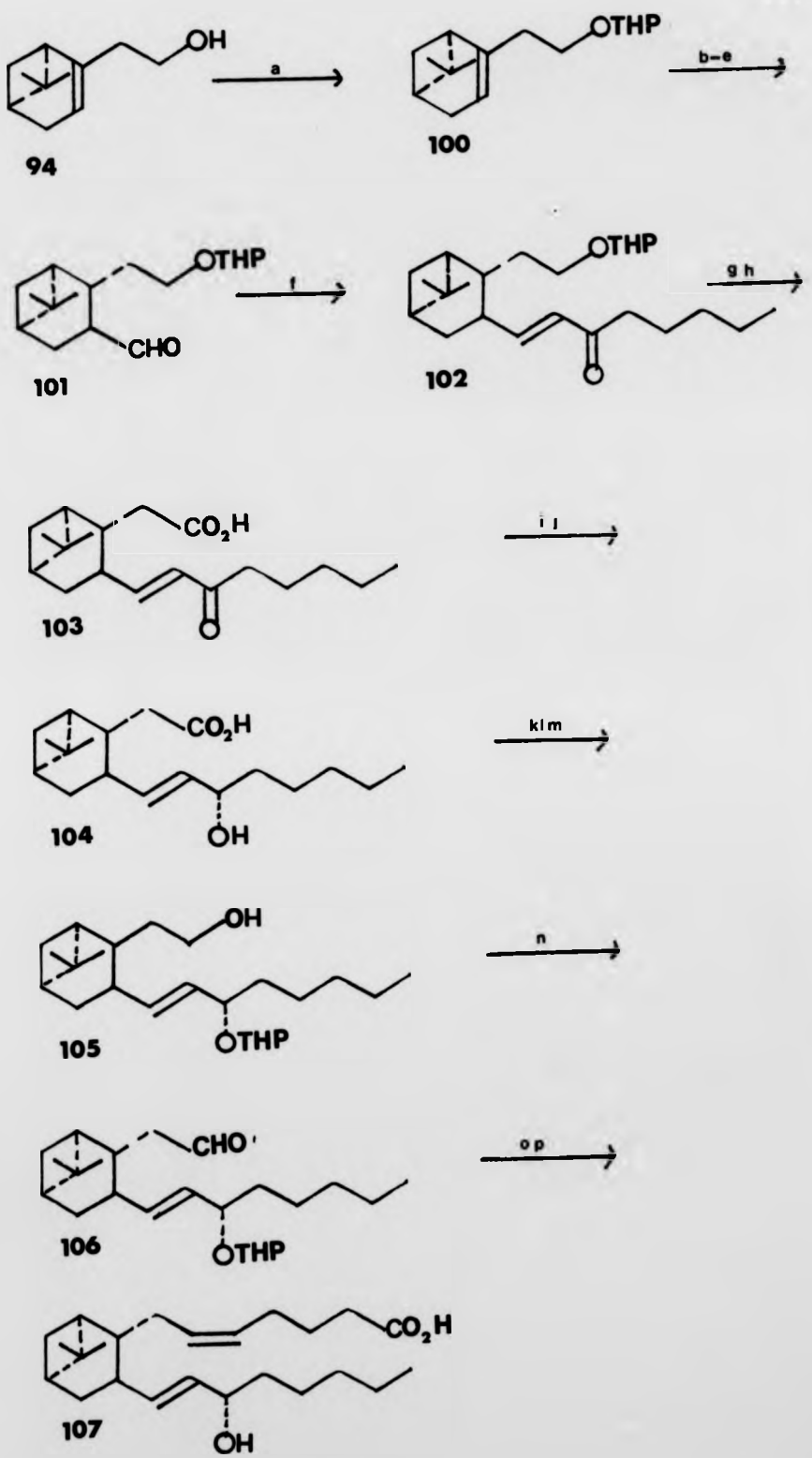
(l) DHP, H^+

(m) $LiAlH_4$

(n) pyridinium chlorochromate

(o) $PH_3PCH(CH_2)_3CO_2K$

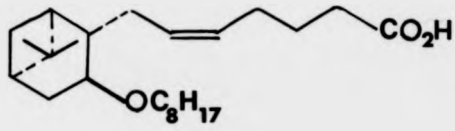
(p) H_3O^+


OH
a
OTHP
b–e
94
100
OTHP
f
CHO
OTHP
g h
101
102
CO2H
i l
103
CO2H
k l m
104
OH
OH
n
105
OTHP
CHO
o p
106
OTHP
CO2H
107
OH

Scheme 27

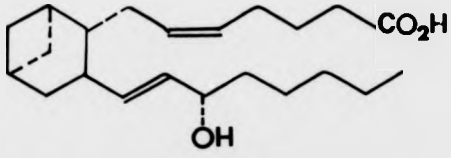
depyranylation then gave the desired PTA_2 (107).

A third synthesis of a pinane-type analogue of TXA_2 has been achieved by Fried et al.[106] Utilising (+) and (-)-pinene as starting materials, compounds of type (108) were produced.



108

(ii) Carbocyclic-TXA_2 (CTA_2)

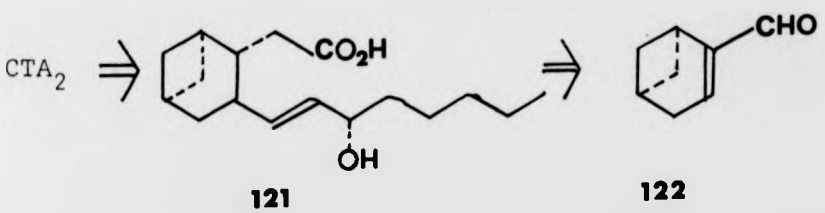


109

This somewhat closer analogue of TXA_2 has been the subject of two separate syntheses. No readily available bicyclo starting material existed commercially, so a suitable method of construction of the bicyclo[3,1,1] system was a major consideration. The ketone (115) was the common starting material for both syntheses. This compound had been made previously,[107,108]

but these syntheses were relatively long and inefficient. This situation led Nicolaou in his synthesis of carbocyclic TXA_2[109] to attempt to develop a better route to it. He produced two, the first of which is rather short and involves ring expansion of the available bicyclo[2,1,1]hexanone (111) (Scheme 28). This was achieved by reaction of (111) with lithio dibromomethane at -78°C to give the adduct (112) which on treatment with n-butyl lithium lost bromine to form the carbene intermediate (113). Rearrangement of this yielded the two-isomeric ketones (114) and (115) in the ratio 1:6. A somewhat longer but more selective route developed by Nicolaou starts with 1,4-cyclohexanedione (116) (Scheme 29). Mono-protection of the dione was achieved by formation of the di-acetal followed by carefully controlled acid hydrolysis to yield keto-acetal (117) in 65% yield. Reaction of (117) with methylenetriphenylphosphorane gave (118) which was hydroborated to the alcohol (119).

Tosylation and removal of the acetal protecting group produced the keto-tosylate (120), which, by intra-molecular displacement of tosylate by the enolate anion, produced by dimsyl potassium gave the desired ketone (115).



121 **122**

The strategy devised by Nicolaou involved transformation of ketone (115) into the α,β-unsaturated aldehyde (122) which by analogous reactions to those employed in the synthesis of PTA_2 could be elaborated into CTA_2. Thus ketone (115)

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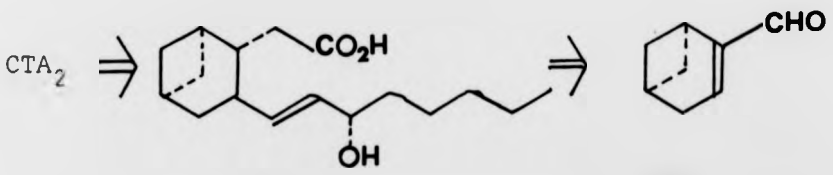
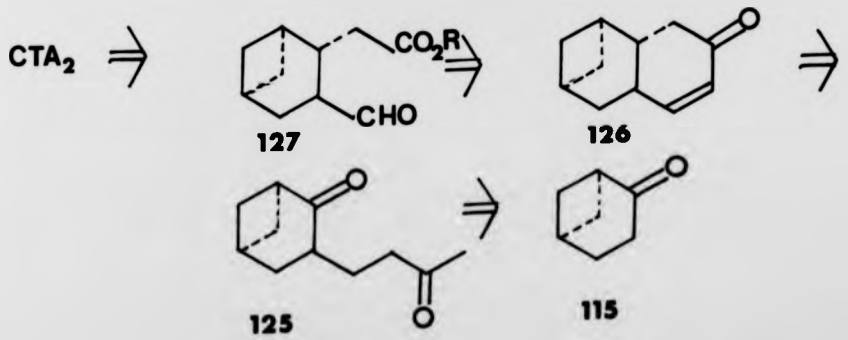


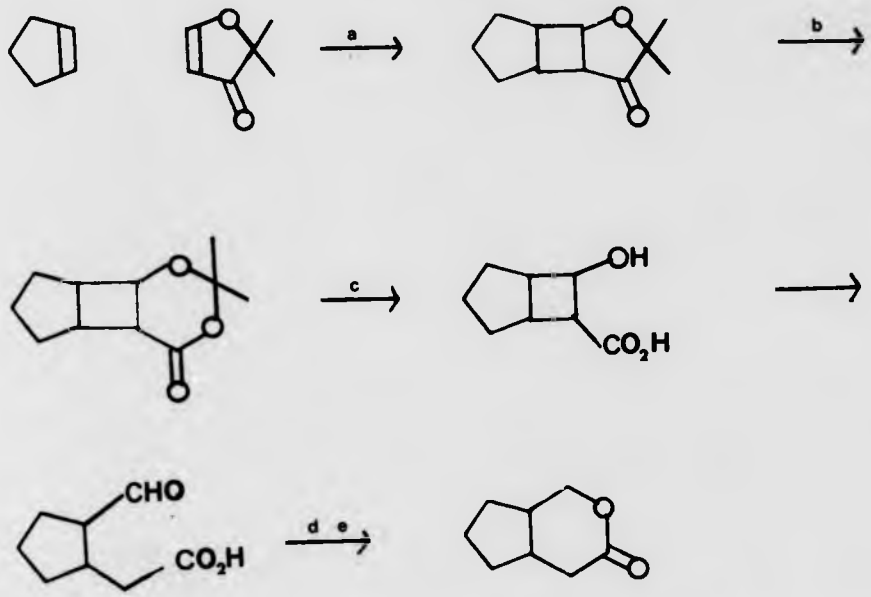
121 **122**

The strategy devised by Nicolaou involved transformation of ketone (115) into the α,β-unsaturated aldehyde (122) which by analogous reactions to those employed in the synthesis of PTA_2 could be elaborated into CTA_2. Thus ketone (115)

(Scheme 30) was homologated to the enol ether (123) using methoxymethylenetriphenylphosphorane. Utilisation of some recently developed selenium chemistry then led to the desired α,β-unsaturated aldehyde (122). Phenylselenyl chloride reacted with (123) to produce the selenide (124) which on oxidation to the selenoxide with m-chloroperoxybenzoic acid and treatment with di-isopropylamine underwent elimination to give (122). As expected, this reacted in an analogous manner to the intermediate (94) in the synthesis of PTA_2, and thus led by the same sequence of reactions to the epimeric C-15 alcohols of CTA_2 which were separable by chromatography. Preparation of optically active (+)-CTA_2 and (-)-CTA_2 was possible in the above sequence by using (+)-trans-1-iodo-1-octen-3-ol-tert-butyldimethylsilyl ether which served as a resolving agent as well as a carrier of the lower side chain.

The synthesis by Ouchida et al.[110] used the same starting material i.e. bicyclo[3,1,1]hexan-2-one, which they prepared from ethyl p-hydroxybenzoate by the method of Musso.[107] A somewhat different strategy to that of Nicolaou was used, with the two alkyl branches being introduced by an alkylation of ketone (115), and an internal aldol condensation of (125) giving the key intermediate (126) which after cleavage of the double bond could readily be elaborated to CTA_2.

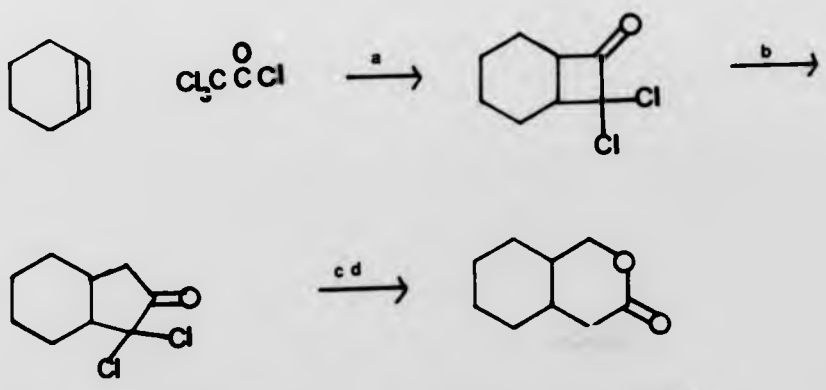




(a) hν, (b) m-CPBA, (c) aq.MeOH,

(d) $NaBH_4$, iso-PrOH, (e) H^+

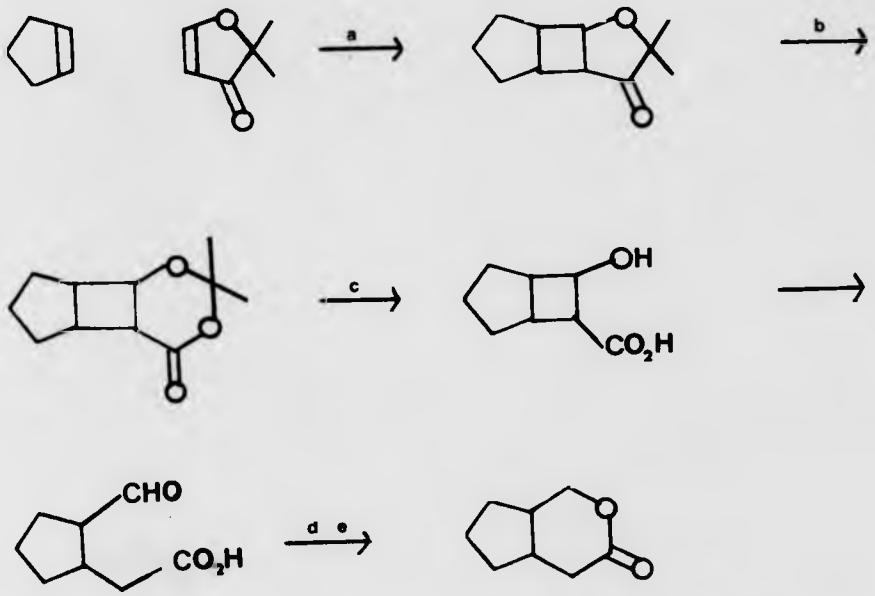
Scheme 28



(a) Zn-Cu/$POCl_3$, ether, (b) CH_2N_2, ether, MeOH,

(c) m-CPBA, (d) Zn, AcOH, 70°

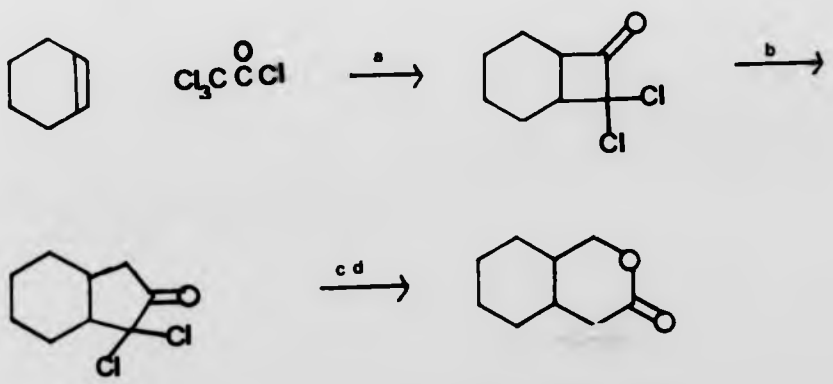
Scheme 29



(a) hν, (b) m-CPBA, (c) aq.MeOH,

(d) $NaBH_4$, iso-PrOH, (e) H^+

Scheme 28



(a) Zn-Cu/$POCl_3$, ether, (b) CH_2N_2, ether, MeOH,

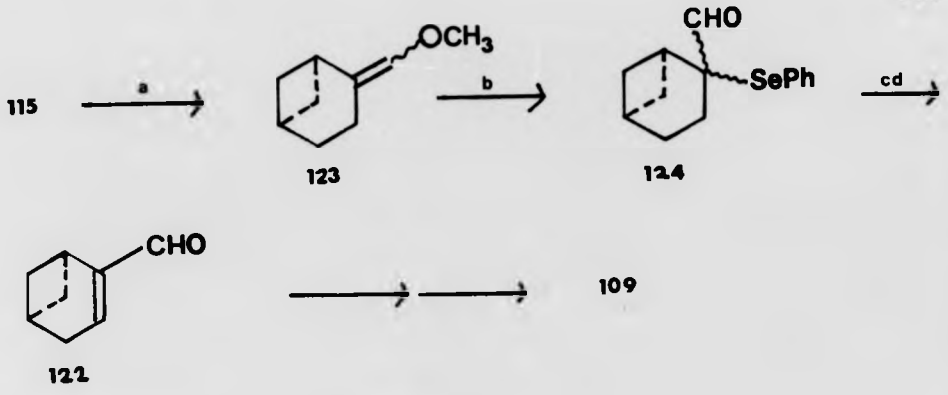
(c) m-CPBA, (d) Zn, AcOH, 70°

Scheme 29

Thus, treatment of ketone (115) (Scheme 31) with lithium di-isopropylamide followed by (E)-trimethyl-(3-iodo-1-propenyl)silane led to (128).

The vinyl silane moiety was then converted to a ketone by epoxidation followed by acid induced rearrangement to yield (125). This diketone, on treatment with aqueous base, underwent an internal aldol condensation to the enone (129). Reduction of this with lithium in liquid ammonia followed by Jones oxidation led to the more stable trans tricyclicketone (130). The target enone (126) was achieved by a selective bromination of (130) with 2-carboxyethyltriphenylphosphonium perbromide followed by dehydrobromination with LiBr and Li_2CO_3 in dimethylformamide. Presumably the selectivity in this bromination is due to steric effects. The methylene group at C3 of the bicyclicsystem would be hindered due to its cis relationship with the α methylene group of the cyclobutane ring. This group would also disfavour attack on the α face, thus the more accessible C5 position reacts preferentially.

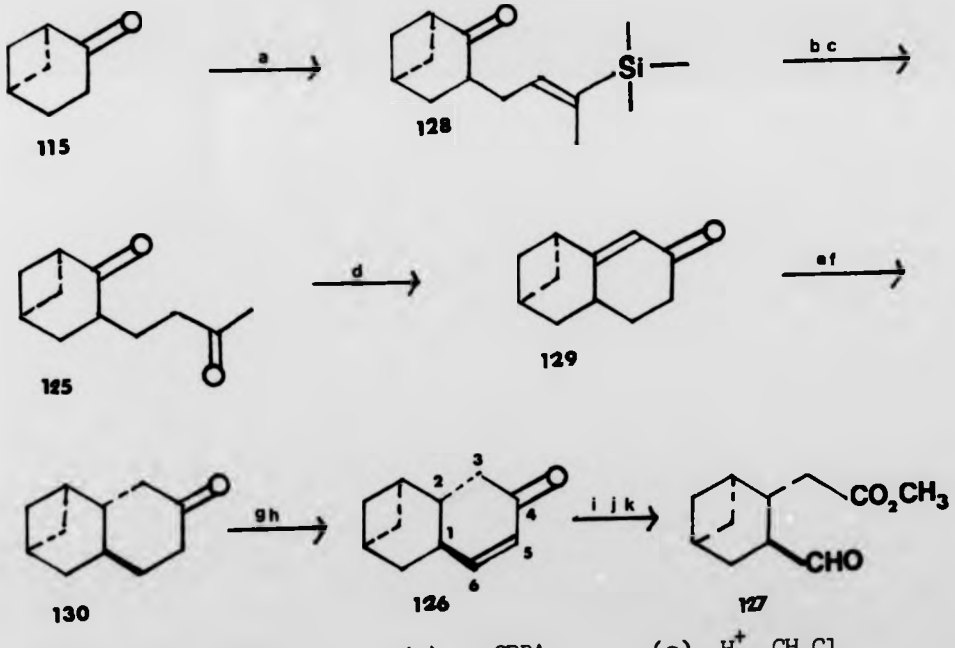
Cleavage of the double bond of (126) was accomplished with OsO_4 and $NaIO_4$ to yield the CTA_2 synthon (127). With the synthesis of this key compound, the remainder of the synthesis was straightforward, and yielded finally the separable C-15 epimers of CTA_2 (109a) and (109b) (Scheme 32).



(a) $Ph_3PCHOMe$, (b) PhSeCl,

(c) m-CPBA, (d) iso-Pr_2NH

Scheme 30



(a) E-$ICH_2CH{=}CCH_3(SiMe_3)$, (b) m-CPBA, (c) H^+, CH_2Cl_2

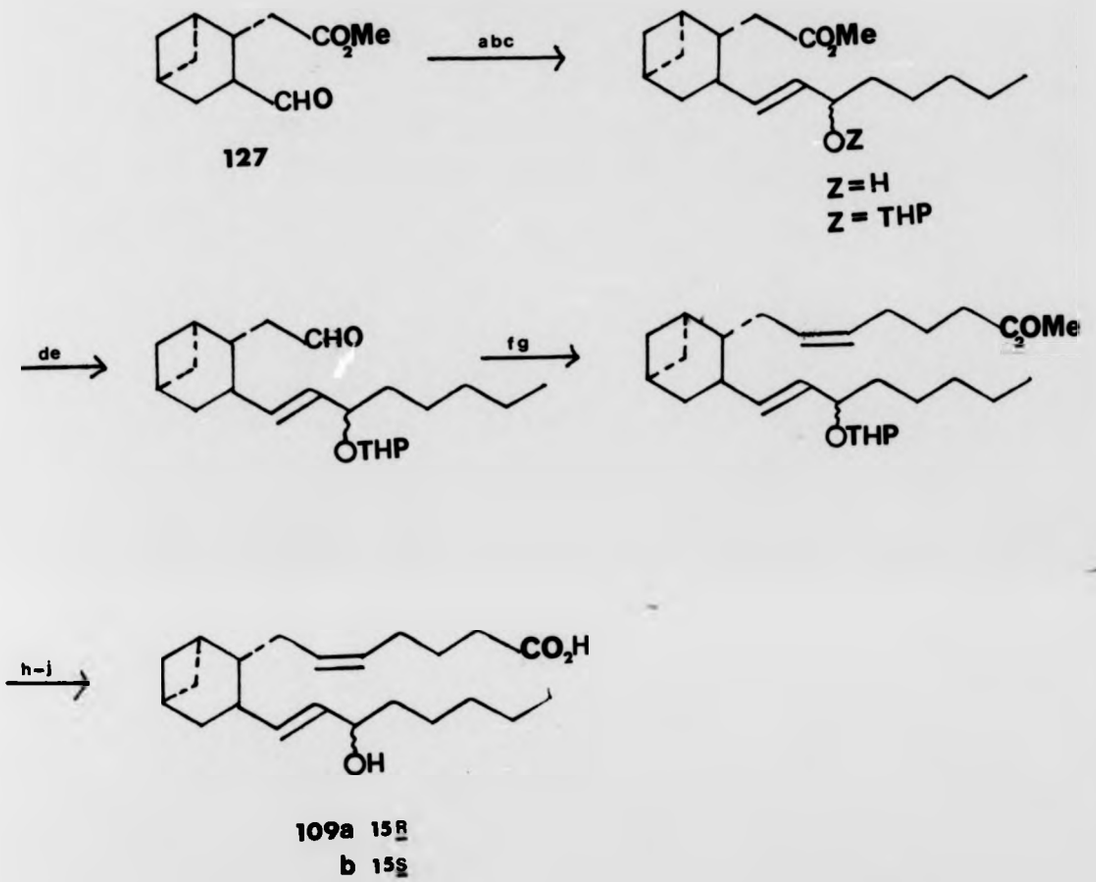
(d) OH^-, (e) Li, NH_3, t-BuOH, (f) Jones[O],

(g) 2-carboxyethyltriphenylphosphonium bromide,

(h) LiBr, Li_2CO_3,

(i) OsO_4, (j) $NaIO_4$ (k) CH_2N_2

Scheme 31



127

109a 15R
b 15S

(a) $n\text{-}Bu_3PCHC(O)C_5H_{11}$, (b) $NaBH_4$, (c) DHP, H^+,

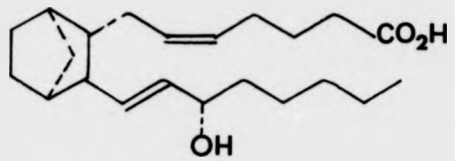
(d) Dibal, (e) SO_3, pyridine, Et_3N, DMSO,

(f) $Ph_3PCH(CH_2)_3CO_2Na$, (g) CH_2N_2, (h) H_3O^+,

(i) Sepn., (j) KOH, H_2O, MeOH

Scheme 32

(iii) Norbornane-TXA$_2$ (NTA$_2$)

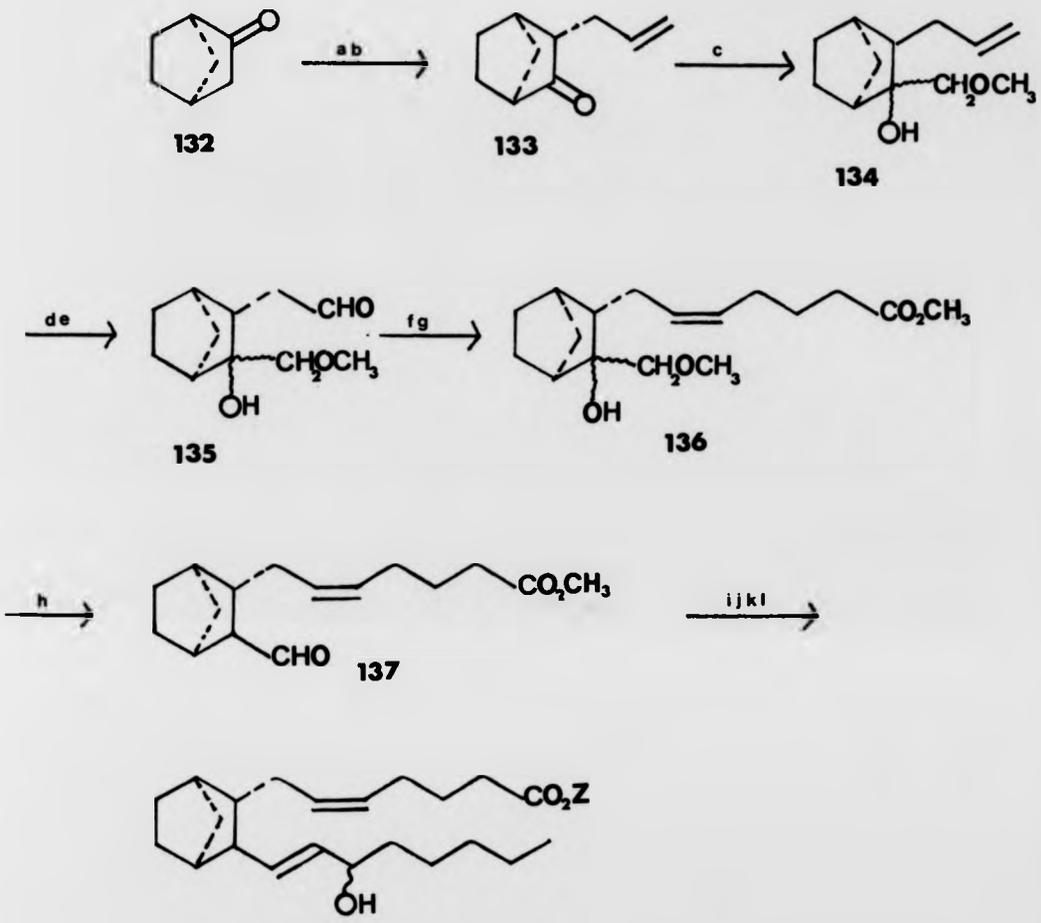


131

A somewhat distantly related analogue is this compound made by Barraclough[111] containing the norbornane skeleton. Here again, the synthesis has been built around the availability of a suitable bicyclic starting material, in this case norbornan-2-one. Barraclough has applied the methodology he has developed for this synthesis, to the synthesis of other analogues from various bicyclic ketones.

Norbornan-2-one (132) (Scheme 33) was alkylated with allyl bromide from the more accessible exo side to yield the exo substituted ketone (133). Homologation of the carbonyl carbon was achieved by reaction with methoxymethyl magnesium bromide to yield the adduct (134).

Osmium tetroxide/sodium metaperiodate cleavage of the double bond to an aldehyde (135) followed by the usual Wittig reaction with the ylide derived from $PH_3I^{\bullet}(CH_2)_4CO_2H$ and subsequent esterification produced (136). The masked aldehyde function was now liberated with formic acid to give the trans compound with an endo formyl group. This, on reaction with the sodio derivative of diethyl 2-oxoheptylphosphonate and reduction of the enone with N_aBH_4, yielded the C-15 epimeric alcohols (138a) and (138b). Finally ester hydrolysis and separation of the epimers produced NTA$_2$ (139b).



(a) $Li(i\text{-}Pr)_2N$, (b) $CH_2{=}CHCH_2Br$,

(c) $MeOCH_2MgBr$, (d) OsO_4, (e) $NaIO_4$,

(f) $Ph_3PCH(CH_2)_3CO_2Na$, (g) CH_2N_2, (h) HCO_2H,

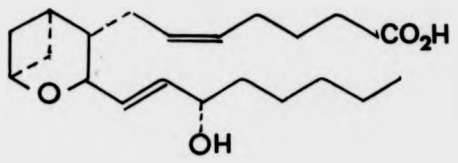
(i) $(EtO)_2P(ONa)CHC(O)C_5H_{11}$, (j) $NaBH_4$,

(k) KOH, aq.MeOH, (l) Sepn.

Scheme 33

2. Oxa-analogues of TXA_2

(i)



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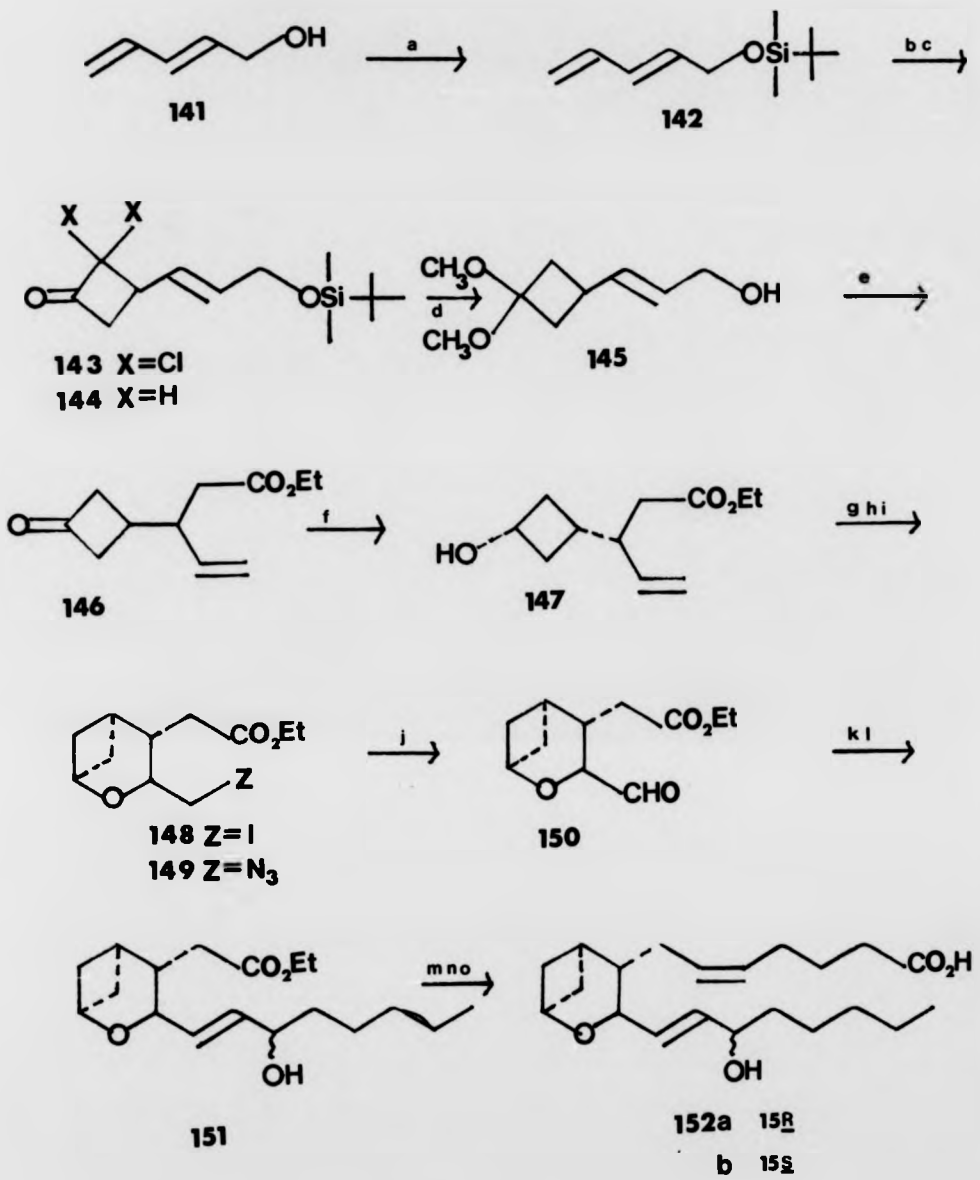
This synthesis by Corey et al.[112] is of a compound rather more closely related to TXA_2. It contains a 2-oxabicyclo[3,1,1]heptane skeleton, and as this system was previously unknown, its creation and elaboration into a TXA_2 analogue are correspondingly more involved than in the previous syntheses of carbocyclic analogues. In fact the strategy adopted by Corey is that of forming the bicyclicsystem with precursors of the side chains already in place, and this, not surprisingly, turns out to be quite difficult to achieve. The synthesis is outlined in Scheme 34. trans-2,4-Pentadien-1-ol (141) was protected as the t-butyldimethylsilyl ether (142) and then subjected to a [2 + 2] cycloaddition with dichloroketene derived from trichloroacetyl chloride and zinc. The addition occurred in a regio-selective manner to give (143), which on dechlorination produced (144).

Addition of the two carbon unit precursor of the upper side chain was achieved by removal of the silyl protecting group of (144) exposing the allylic alcohol moiety which then underwent a Claisen orthoester rearrangement using the method



(a) t-$BuMe_2SiCl$, (b) CCl_3COCl-Zn, (c) Zn/Cu,

(d) H^+, MeOH, (e) $CH_3C(OEt)_3$, H^+, (f) $NaBH_4$,

(g) benzene, $Hg(CF_3CO_2)_2$, (h) I_2, (i) NaN_3, DMF,

(j) CH_3SO_2F, (k) $(MeO)_2P(O)CH_2C(O)C_5H_{11}$,NaH,

(l) $NaBH_4$, (m) Dibal, (n) $Ph_3P{=}CH(CH_2)_3CO_2Na$,

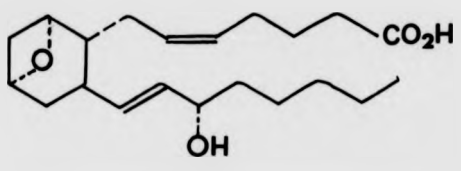
(o) Sepn.

Scheme 34

of Johnson[103] to yield the ester (146). Stereoselective reduction with sodium borohydride then gave the cis alcohol (147), needed for cyclisation to the oxa-bicyclo[3,1,1] system. This cyclisation however proved difficult to achieve, the normal methods for iodo-cyclisation and oxymercuration failing to work. Suitable conditions were eventually found to be treatment with mercuric trifluoroacetate in benzene followed by addition of excess iodine. This gave stereospecifically only the iodo ether (148) with the two carbon side chains trans to one another.

Attempts to form a δ-lactone from (148) by intramolecular displacement of iodide by the acid anion failed, so a rather roundabout method was used to convert the iodo-ether into the desired synthon (150). This involved displacement of iodide by azide, and the subsequent conversion of this directly to the aldehyde by the novel use of methyl fluorosulphonate. With the synthesis of this important intermediate, the main synthetic problems had been solved, and there remained only the relatively straightforward elaboration of (150) to a TXA_2 analogue by known methodology, as outlined in the scheme. After separation of the two C-15 epimers, the thromboxane analogue (152b) was isolated.

(ii) 11a-Carbathromboxane A_2



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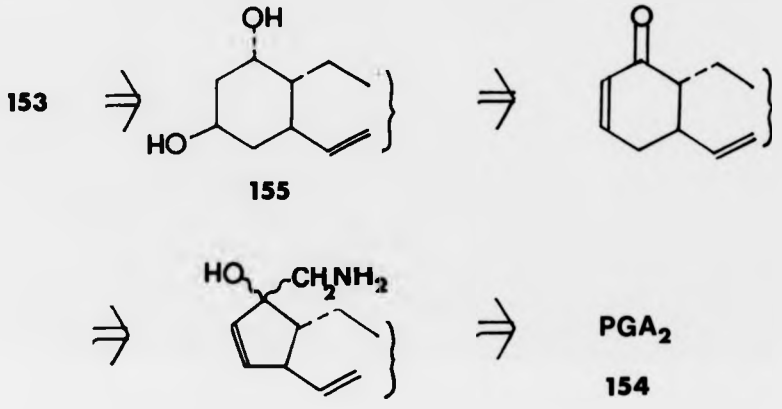
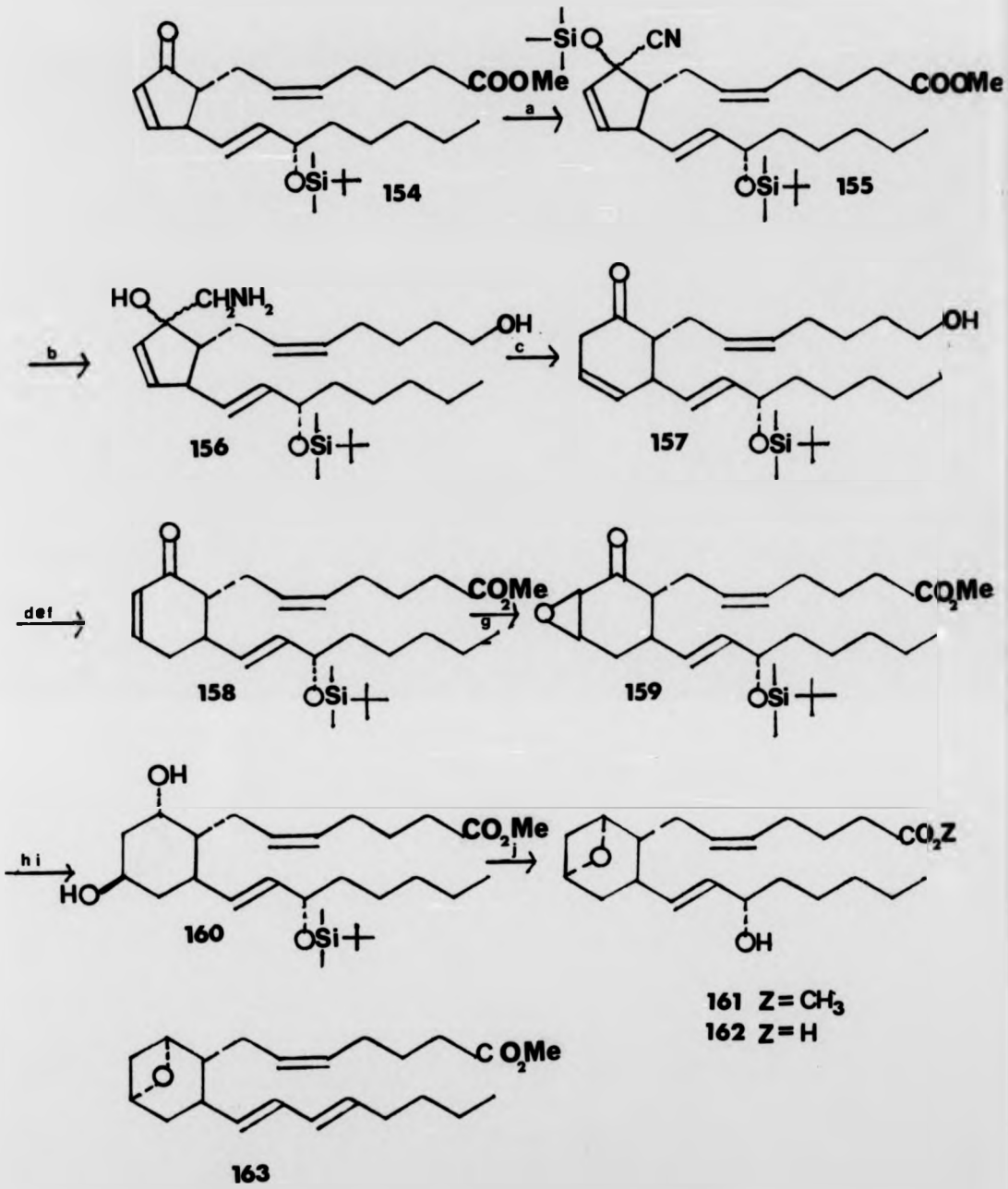
This complimentary analogue to that produced by Corey, is the result of work by Maxy and Bundy[113] of the Upjohn

Company. In contrast to all the previous syntheses, this work uses a prostanoid starting material i.e. PGA_2 methyl ester 15-t-butydimethylsilyl ether (154) which requires only the development of the cyclopentenone ring into the required bicyclic system. This was achieved by a rather short, if inefficient, route.



The oxetane system was to be formed by an intramolecular nucleophilic displacement which required the synthesis of the trans diol (155). This was carried out as shown in Scheme 35. Ring expansion of the PGA_2 derivative (154) was achieved by formation of the cyanohydrin (155) using the recently developed trimethylsilyl cyanide. This was reduced with lithium aluminium hydride to (156) which on diazotisation with nitrous acid, rearranged to the desired β,γ-unsaturated ketone (157). The alternative ring expansion regioisomer was not detected. Conversion of (157) to the conjugated ketone (158) was achieved by treatment with basic alumina, followed by Jones oxidation and esterification with diazomethane. Conversion of this to the desired diol (160) presented a few problems as epoxidation with

alkaline peroxide gave both isomers, the desired β-epoxyketone (159) being the minor component. However reduction of this with sodium amalgam gave the β orientated hydroxy ketone, which on reduction with L-Selectride yielded stereospecifically the desired trans diol. The planned cyclisation to the oxetane system was somewhat difficult to achieve. Attempts to convert the more accessible 11β alcohol group into a leaving group followed by internal displacement were unsuccessful under normal conditions, however it was found that treatment of the diol with trifluoromethylsulfonic anhydride at -78°C gave, on careful isolation, a 25% yield of the desired 9α, 11α oxetane (161) accompanied by 25% of the dehydration product, the diene (163). Ester hydrolysis under standard conditions then afforded the target thromboxane analogue (162).



(a) $(CH_3)_3SiCN$, (b) $LiAlH_4$, (c) HNO_2,

(d) Al_2O_3, (e) Jones [O], (f) CH_2N_2,

(g) H_2O_2, OH^-, (h) Na/Hg, (i) $LiB(sec\text{-}Bu)_3H$,

(j) $(CF_3SO_2)_2O$

Scheme 35

BIOLOGICAL PROPERTIES OF TXA_2 ANALOGUES

Most of the TXA_2 analogues so far synthesised appear to be primarily antagonists of coronary artery constriction, plateletaggregation, and thromboxane synthetase. Comprehensive biological data has been reported only by Nicolaou *et al.* for carbocyclic-TXA_2 (CTA_2)[114] and pinane-TXA_2 (PTA_2).[104] The following information is available on other analogues:- 11a-carba-TXA_2[113] is an inhibitor of PGH_2 induced aggregation of human platelets; norbornane-TXA_2 (NTA_2)[111] has a pronounced hypotensive effect, but is only a weak inhibitor of ADP-induced plateletaggregation and TXA_2 synthetase; (9α-11α)-carba-TXA_2[112] is reported as having "biological activity which could not have been predicted", but this activity is not specified.

PTA_2 has the properties listed in Table 1:-

TABLE 1 Properties of PTA_2

(1) Inhibits coronary artery contraction by prostaglandin endoperoxide analogs, ID_{50} 0.1 μM

(2) Stabilises lysosomes at 1 μM

(3) Inhibits aggregation by prostaglandin endoperoxide analogs, ID_{50} 2.0 μM

(4) Inhibits thromboxane synthetase, ID_{50} 50 μM

(5) Has no effect on PGI_2 synthetase at 100 μM

(6) Has no effect on the inhibition of platelet aggregation by PGD_2 or PGI_2.

The inhibition of coronary artery contraction and plateletaggregation at low concentrations must be a direct antagonistic effect and not inhibition of enzyme activity, as the endoperoxide analogs cannot be converted to TXA_2. PTA_2 did not inhibit primary aggregation induced by ADP of epinephrine, but did inhibit secondary aggregation, induced by these agents, or arachidonic acid. This indicates that at these low concentrations, PTA_2 can antagonise the effects of endogenously formed TXA_2. At higher concentrations PTA_2 did inhibit TXA_2 synthetase. A significant finding was that no effect on the synthesis or actions of prostacyclin was observed. These properties make PTA_2 attractive as a therapeutic agent for thrombotic and other disorders. A recent investigation has shown that PTA_2 is beneficial in cases of circulatory shock.[115]

CTA_2 has similar properties to PTA_2 with respect to inhibition of TXA_2 synthetase, inhibition of plateletaggregation by endoperoxide analogues and ADP and lack of effect on prostacyclin synthetase. However a very surprising difference exists in their effects on vascular smooth muscle. PTA_2 has no direct effect, whereas CTA_2 appears to be the most potent vasco-constrictor among the known prostanoids. It produced constriction at a concentration of only 29 pM, was four times more potent than 9,11-azo-PGH_2 and forty times more potent that PGH_2. $PTXA_2$ antagonised the effects of $CTXA_2$ on arterial muscle, indicating that $CTXA_2$ is a pure TXA_2 agonist for vasco-constriction. CTA_2 is also an agonist of TXA_2 in its effect on lysosomes, being a potent lysosomal labilising agent.

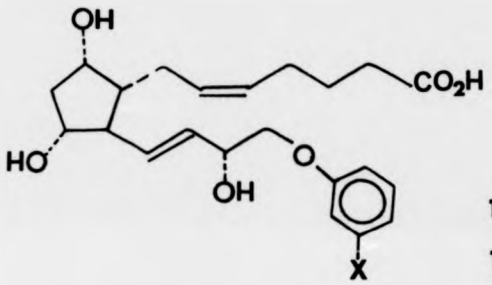
This dissociation of vasco-constrictor and platelet

aggregatory activities adds some weight to the proposal of Needleman [42] that the primary rôle of TXA_2 is as a vasoconstrictor and that any effects on platlets may be secondary to its effect on vascular tone. TXA_2 has been shown to have a primary but perhaps not essential rôle in secondary aggregation, and, in fact, no unequivocal evidence that TXA_2 is essential for induction of aggregation has been reported.

PHARMACOLOGICAL DEVELOPMENT

The development of medically therapeutic reagents from the prostaglandins has not been as rapid as was first envisaged. This is mainly because of their lability in biological systems and the many side effects associated with their use.

The first prostaglandins to be marketed commercially were Equimate (164) and Estrumate (165)



164 x=CF_3

165 x=Cl

These compounds are several hundred times more potent than $PGF_{2\alpha}$ as luteolytic agents, but do not produce the gastro-intestinal side effects associated with the use of the latter.

Adding an alkyl group at the 15 or 16 position renders the molecule less susceptible to the main prostaglandin metabolising enzyme, 15-dehydro-oxygenase. 15-Methyl-$PGF_{2\alpha}$ methyl ester has been used extensively for the induction of abortion in women. Some newer compounds which produce fewer gastro-intestinal side effects are 16-phenoxy-tetranor-PGE_2 methylsulphonylamide; 16:16-dimethyl <u>trans</u> Δ^2 PGE, methyl ester and 9-deoxo-16,16-dimethyl 9-methylene PGE_2. Apart from

from 15- and 16-alkylated prostaglandins, the primary prostaglandins have seen little useful application in man.

The discovery of the more recent unstable prostanoids has presented new opportunities for medical research. Selective inhibitors of thromboxanes, leukotrienes etc. could be very powerful, selective therapeutic agents in such fields as thrombosis inflammation, shock, gastric disorders, etc. TXA_2 analogues have been shown to be useful in shock treatment, whilst other thromboxane synthetase inhibitors have been used in treating thrombosis and scalds. Prostacyclin has been tested as a treatment for heart disease and has been used during haemoperfusion, haemodialysis and heart-valve replacement.

The prostaglandin field is almost twenty years old now and still seems to be expanding rapidly, as new inroads are made into the arachidonate metabolic pathway. The coming years should see a great advance on the biological side and also the practical application of this knowledge in the form of some valuable and exciting new drugs.

REFERENCES

1. U. S. von Euler, Arch.Exp.Pathol.Pharmakol.,(1934), 175 78.
2. M. Goldblatt, Chem.Ind.,(London), (1933), 52 208.
3. S. Bergström and J. Sjövoll, Acta Chem.Scand., 14,1693 (1960).
4. B. Samuelsson, J.Am.Chem.Soc., 85,1878 (1963).
5. S. Bergström, H. Danielsson and B. Samuelsson, Biochem.Biophy.Acta,90,207 (1964).
6. D. A. von Dorp, R. K. Beerthuis, D. H. Hugteren and H. Vonkeman, Biochem.Biophys.Acta,90,204 (1964).
7. B. Samuelsson, J.Am.Chem.Soc., 87,3011 (1965).
8. M. Hamberg and B. Samuelsson, J.Biol.Chem., 242,5336 (1967).
9. (a) A. Mitra: The Synthesis of Prostaglandins. John Wiley & Sons 1977;
   (b) W. Bartmann, Angew.Chem., 87,143 (1975);
   (c) P. H. Bently, Chem.Soc.Rev., 2,29 (1973).
10. M. Hamberg and B. Samuelsson, Proc.Nat.Acad.Sci.USA, 70,899 (1973).
11. D. H. Nugteren and E. Hazelhof, Biochem.Biophys.Acta, 326,448 (1973).
12. M. Hamberg, J. Svensson, T. Wakabayashi and B. Samuelsson, Proc.Nat.Acad.Sci.USA,71,345 (1974).
13. R. A. Johnson, E. G. Nidy, L. Baczynskyj and R. R. Gorman, J.Am.Chem.Soc., 100,660 (1978).
14. N. A. Porter, J. D. Byers, R. C. Mebane, D. W. Gilmore and J. R. Nixon, J.Org.Chem., 43,2088 (1978).
15. N. A. Porter, J. D. Byers, K. M. Holden and D. B. Menzel, J.Am.Chem.Soc., 101,4319 (1979).
16. N. A. Porter, J. D. Byers, A. E. Ali and T. E. Eling, J.Am.Chem.Soc., 102,1183 (1980).
17. M. Hamberg, J. Svensson and B. Samuelsson, Proc.Nat.Acad.Sci.USA,72,2994 (1975).

18. F. Shafizadeh and P.P.S. Chin, Carbohydr.Res., 46, 149 (1976).

19. P. Köll, T. Schultek and R. W. Rennecke, Chem.Ber., 109, 337 (1976).

20. See pages 49-71

21. S. Moncada, R. Gryglewski, S. Bunting and J. R. Vane, Nature, 263, 663 (1976).

22. R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Sun, N. Wittaker, S. Bunting, J. Salmon, S. Moncada and J. R. Vane, Prostaglandins, 12, 915 (1976).

23. E. J. Corey, G. E. Keck and I. Székely, J.AmerChem.Soc., 99, 2006 (1977).

24. S. Moncada, E. A. Higgs and J. R. Vane, Lancet I., 18, (1977).

25. C. H. Kellaway and E.R.Q. Trethewie, J.Exp.Physiol., 30, 121 (1940).

26. S. Hammarstrom, R. C. Murphy, B. Samuelsson, D. A. Clark, C. Mioskowski and E. J. Corey, Biochem.Biophys.Res.Commun., 91, 1266 (1979).

27. E. J. Corey, D. A. Clark, G. Goto, A. Morfat and C. Mioskowski, J.Amer.Chem.Soc., 102, 1436 (1980).

28. H. R. Morris, G. W. Taylor, P. J. Piper and J. R. Pippins, Nature, 285, 104 (1980).

29. L. Örning, S. Hammarström and B. Samuelsson, Proc.Nat.Acad.Sci.USA, 77, 2014 (1980)

30. K. H. Gibson, Chem.Soc.Rev., 6, 489 (1977).

31. S. Bergstrom, R. Ryhage, B. Samuelsson and J. Sjövall Acta Chem.Scand., 16, 501 (1962).

32. F. P. Nijkemp, R. J. Flower, S. Moncada and J. R. Vane, Nature, 263, 479 (1976).

33. T. Miyamoto, N. Ogino, S. Yamamoto and O. Hayashi, J.Biol.Chem., 251,2629 (1976).

34. M. Hemler, W.E.M. Lands and W. L. Smith, J.Biol.Chem., 251,5575 (1976).

35. B. Samuelsson, J.Amer.Chem.Soc., 87,3011 (1965).

36. M. Hamberg and B. Samuelsson, J.Biol.Chem., 242,5336 (1967).

37. A. Rahimtula and P. J. O'Brien, Biochem.Biophys.Res.Comm., 70,893 (1976).

38. L. J. Marnett, P. Wlodawer and B. Samuelsson, Biochem.Biophys.Res.Comm., 60,1286 (1974).

39. M. Hamberg, J. Svensson and B. Samuelsson in 'Advances in Prostaglandin and Thromboxane Research', eds. B. Samuelsson and R. Paoletti, Raven Press, New York, 1 19 (1976).

40. N. Ogino, T. Miyamoto, S. Yamamoto and S. Hayashi, J.Biol.Chem., 252, 890 (1977).

41. C. R. Pace-Asciak, Prostaglandins,13,811 (1977).

42. P. Needleman, S. Moncada, S. Bunting, J. R. Vane, M. Hamberg and B. Samuelsson, Nature,261,558 (1976).

43. S. Hammarström and P. Falardeau, Proc.Nat.Acad.Sci.USA, 74,3691 (1977).

44. F. F. Sun, Biochem.Biophys.Res.Comm., 74,1432 (1977).

45. P. Needleman, M. Minkes and A. Raz, Science,193,163 (1976).

46. P. Falardeau, M. Hamberg and B. Samuelsson, Biochem.Biophys.Acta,441,193 (1976).

47. S. Moncada, R. Gryglewski, S. Bunting and J. R. Vane, Nature,263,663 (1976).

48. R. Gryglewski, S. Bunting, S. Moncada, R. J. Flower and J. R. Vane, Prostaglandins, 12, 685 (1976).

49. H. Polet and L. Levine, Arch.Biochem.Biophys., 168, 96 (1975).

50. H. Polet and L. Levine, J.Biol.Chem., 250, 351 (1975).

51. B. Samuelsson, Federation Proc., 31, 1442 (1972).

52. L. J. Roberts II, B. J. Sweetman, J. L. Morgan, N. A. Payne and J. A. Oates, Prostaglandins, 13, 631 (1977).

53. H. Kindahl, Prostaglandins, 13, 619 (1977).

54. B. Samuelsson, M. Goldyne, E. Granström, M. Hamberg, S. Hammarström and C. Malmsten, Ann.Rev.Biochem., 997 (1978).

55. J. Svensson, Acta.Biol.Med.Germ., 37, 731 (1978).

56. D. Horrobin, New Scientist, 642 (1980).

57. N. D. Goldberg, R. F. O'Dean and M. K. Haddox, Adv.Cyclic Nucleotide Res., 3, 155 (1973).

58. R. R. Gorman, S. Bunting and O. V. Miller, Prostaglandins, 13, 377 (1977).

59. J. E. Tateson, S. Moncada and J. R. Vane, Prostaglandins, 13, 389 (1977).

60. O. V. Miller and R. R. Gorman, J.Cyclic Nucleotide Res., 2, 79 (1976).

61. D. A. Langs, S. Fortier, M. G. Erman and G. T. de Titta, Nature, 281, 237 (1979).

62. J. B. Smith and A. L. Willis, Nature New Biol., 231, 235 (1971).

63. J. R. Vane, Nature New Biol., 231, 232 (1971).

64. S. H. Ferreira, S. Moncada and J. R. Vane, Nature New Biol., 231, 237 (1971).

65. F. A. Kuehl Jr., J. L. Humes, R. W. Egan, E. A. Ham, G. C. Beveridge and C. G. Von Arman, Nature, 265, 171 (1977).

66. J. R. Boot, W. Dawson and D. J. Osbourne, Brit.J.Pharmacol., 58,471P (1976).

67. J. R. Boot, W. Dawson and E. A. Kitchen, J.Physiol.,(London), 257,47P (1976).

68. S. Moncada, E. A. Higgs and J. R. Vane, Lancet I,18 (1977).

69. M. B. Zucker, Scientific American, 242,(6) 70 (1980).

70. K. M. Meyers, C. L. Seachord, H. Holmsen, J. Bryan-Smith and D. J. Prieur, Nature, 282,331 (1979).

71. S. Moncada, R. J. Gryglewski, S. Bunting and J. R. Vane, Prostaglandins,12,715 (1976).

72. G. Hornstra, E. Haddeman and J. A. Don, Nature, 279,66 (1979).

73. P. Needleman, J.Clin.Invest., 63,345 (1979).

74. M. Foegh, Nature, 281,14 (1979).

75. C. E. Jonsson, Y. Shimizu, B. B. Fredholm, E. Granström and E. Oluo, Acta.Physiol.Scand., 107,377 (1979).

76. E. J. Delbaccaro, M. C. Robson, J. P. Heggars and R. Swaminathan, Surgery,137 (1980).

77. M. J. Stuart, J. M. Gerrard and J. G. White, New Eng.J.Med., 302,6 (1980).

78. A. Szczeklik, R. J. Gryglewski, J. Musial, L. Grodzinska, M. Serwońska, L. Wójcikświtek and E. Marcinkiewicz, Acta.Biol.Med.Germ., 37,741 (1978).

79. P. Needleman, A. Raz, J. A. Ferrendelli and M. Minkes, Proc.Nat.Acad.Sci.USA,74,1716 (1977).

80. S. Moncada, S. Bunting, K. Mullane, P. Thorogood, J. R. Vane, A. Raz and P. Needleman, Prostaglandins,13, 611 (1976).

81. A. L. Allyl, M. S. Manku, D. P. Harrobin, R. O. Morgan, M. Karmazin and R. D. Karmoli, Prostaglandins, 14, 607 (1977).

82. P. S. Kulkarni and K. E. Eakins, Prostaglandins, 12, 465 (1976).

83. P. S. Kulkarni and K. E. Eakins, Brit.J.Pharmacol., 60, 135 (1977).

84. S. Hammarström and P. Falardeau, Proc.Nat.Acad.Sci.USA, 74, 3691 (1977).

85. R. J. Gryglewski, A. Zmuda and R. Korbut, Nature, 267, 627 (1977).

86. F. F. Sun, Biochem.Biophys.Res.Comm., 74, 1432 (1977).

87. F. A. Fitzpatrick, G. L. Bundy, R. R. Gorman and T. Honohan, Nature, 275, 764 (1978).

88. B. Samuelyson, M. Hamberg, L. J. Roberts II, and J. A. Oates, Prostaglandins, 16, 857 (1978).

89. E. J. Corey and J. W. Suggs, J.Org.Chem., 40, 2554 (1975).

90. E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker and N. M. Weinshenker, J.Amer.Chem.Soc., 92, 397 (1970).

91. W. P. Schneider and R. A. Morge, Tetrahedron Letters, 3283 (1976).

92. N. A. Nelson and R. W. Jackson, Tetrahedron Letters, 3275 (1976).

93. R. C. Kelly, I. Schletter and S. J. Stern, Tetrahedron Letters, 3279 (1976).

94. E. J. Corey, M. Shibasaki, J. Knolle and T. Sugara, Tetrahedron Letters, 785 (1977).

95. S. Hanession and P. Lavellee, Can.J.Chem., 55, 562 (1977).

96. H. Ohrui and S. Emoto, Agric.Biol.Chem., 41 1773 (1977).

97. E. J. Corey, M. Shibasaki and J. Knolle, Tetrahedron Letters, 1625 (1977).

98. O. Hernandez, Tetrahedron Letters, 219 (1978).

99. R. J. Ferrier and N. Vethaviyasar, J.Chem.Soc.Perk.I., 1791 (1973).

100. N. L. Holder and B. Fraser-Reid, Can.J.Chem., 51, 3357 (1973).

101. R. S. Tipson and A. Cohen, Carbohydr.Res., 1, 338 (1965).

102. A. E. Wick, D. Felix, K. Steen and A. Eschenmoser, Helv.Chim.Acta, 47, 2425 (1964) and 52, 1030 (1969).

103. W. S. Johnson, L. Wertheman, W. R. Bartlett, T. J. Brockson, T. Li, D. J. Faulkner and M. R. Petersen, J.Amer.Chem.Soc., 92, 741 (1970).

104. K. Nicolaou, R. L. Magolda, J. Bryan-Smith, D. Aharony, E. F. Smith and A. M. Lefer, Proc.Nat.Acad.Sci.USA, 76, 2566 (1979).

105. M. F. Ansell, M.P.L. Caton, M. N. Palfreyman and K.A.J. Stuttle, Tetrahedron Letters, 4497 (1979).

106. J. Fried, J. Barton, S. Kittisopikul, P. Needleman and A. Wyche Abstracts, 4th Int.Prostaglandin Conference, Washington D.C., May 1979, p.37.

107. H. Musso, K. Naumann and K. Grychtol, Chem.Ber., 100, 3614 (1967)

108. T. Gibson, J.Org.Chem., 37, 700 (1972).

109. K. C. Nicolaou, R. L. Magolda and D. A. Claremon, J.Amer.Chem.Soc., 102, 1404 (1980).

110. S. Ouchida, N. Hamanaka and M. Hayashi, Tetrahedron Letters, 3661 (1979).

111. P. Barraclough, Tetrahedron Letters, 1897 (1980).

112. E. J. Corey, J. W. Ponder and P. Ulrick, Tetrahedron Letters, 137 (1980).

113. K. M. Maxey and G. L. Bundy, Tetrahedron Letters, 445 (1980).

114. A. L. Lefer, E. F. Smith III, H. Araki, J. Bryan-Smith, D. Aharony, D. A. Claremon, R. L. Magolda and K. C. Nicolaou, Proc.Nat.Acad.Sci.USA, 77, 1706 (1980).

115. A. L. Lefer, H. Araki, J. Bryan-Smith, K. C. Nicolaou and R. L. Magolda, Prostaglandins and Medicine, 3, 139 (1979)

116. S. Hanessian, P. Dextrase, A. Fougerousse and Y. Guidon, Tetrahedron Letters, 3983 (1974)

117. G. J. Lourens and J. M. Koekeomer, Tetrahedron Letters, 3719 (1975)

1. INTRODUCTION

The aim of this research project was to develop a total synthesis of chiral thromboxane B_2 utilising a carbohydrate precursor to provide both the basic tetrahydropyranyl ring, and the appropriate asymmetric centres. At the inception of the work no carbohydrate-based syntheses of TXB_2 or suitable synthons had been published. In the following year however, four such routes were revealed, by the groups of Hanessian,[1] Corey,[2] Hernandez,[3] and Ohrui,[4] all using D-glucose as starting material.

Sugars had, of course, been previously exploited in[8] the synthesis of other optically-active compounds, and indeed, their involvement in the prostaglandin field dates back to 1974 when D-glucose was used as a precursor of the 11-oxa series of primary prostaglandins. Much of the subsequent work on carbohydrate-based prostaglandin syntheses was carried out by the groups of Stork and Hanessian. Two general strategies are available for using carbohydrates. In the first, the sugar moiety acts as a template to build stereochemical features into the product, with the sugar eventually being destroyed so it does not serve as a discrete entity in the final product. In the second, the sugar furanoid or pyranoid ring is transferred to the product intact.

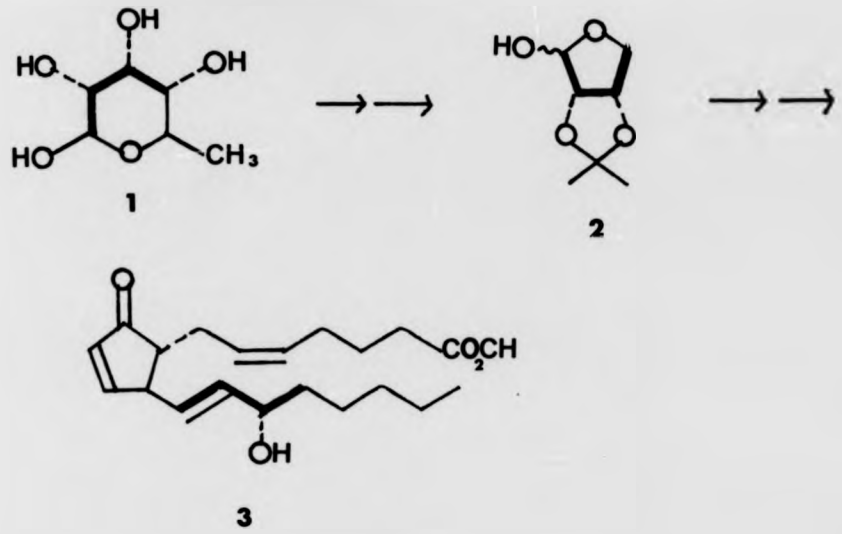
In prostaglandin work, one of the first examples of the template method was the synthesis of chiral PGA_2 (3) from rhamnose (1), by Stork,[5] Scheme 1. The chirality of C-15 is transferred from the sugar directly, and that at C-12 by a Claisen rearrangement involving C-14. Stork subsequently

developed a synthesis of PGE_1, utilising D-glyceraldehyde for control of the configuration at C-11, Scheme 2.[6] A crucial intermediate was the chiral enone (5), the stereochemistry of conjugate addition to which was kinetically controlled by the asymmetry at C-11, to give the correct configurations at C-8 and C-12.

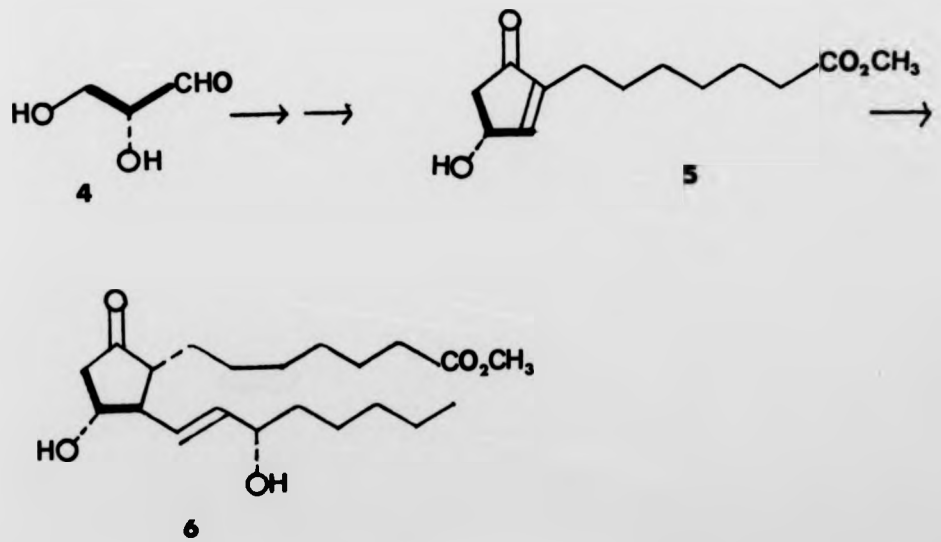
A recent synthesis by Stork[7] of PGE_2 and $PGF_{2\alpha}$ involved transferring two of the chiral centres from a sugar into the prostaglandin molecule, i.e. those at C-11 and C-15, Scheme 3. The configuration at C-12 was transferred from C-14 via a Claisen rearrangement. Subsequent alkylation of the ketone was controlled by C-12 to give the required trans configuration. In this, and the previous syntheses, one can see how the asymmetric sugar fragments have been cleverly used to control most of the stereochemistry of the molecule.

The furanoid ring of sugars has been used to build 11-oxa prostaglandin analogues by Hanessian, and by Lourens and Koekemoer. Hanessian et al[9] used the 1,4-anhydride (7) obtainable from glucose by reduction and acid-induced cyclisation, Scheme 4. This led to the 2,3-epoxide (8) which was used to introduce the required chain-branching by reaction with sodio diethyl malonate. Standard prostaglandin methodology then converted this to 11-oxa $PGF_{2\beta}$ (9).

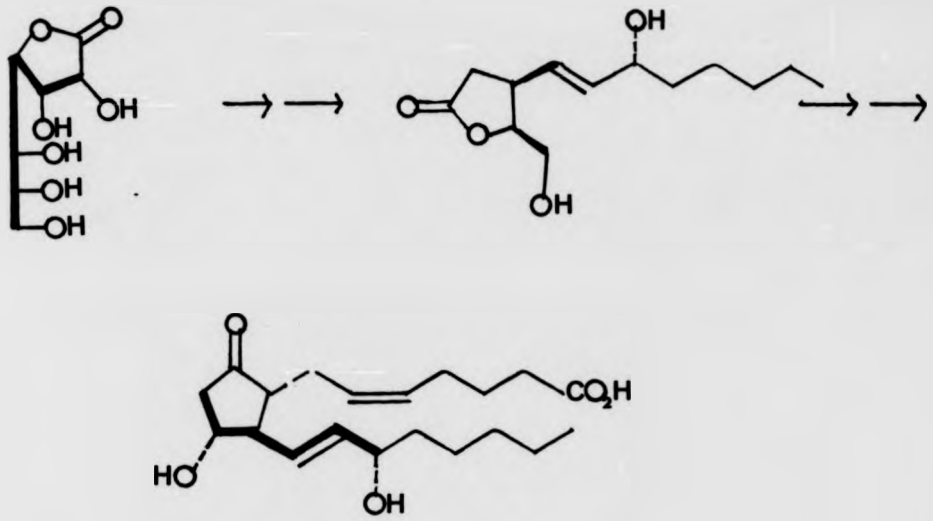
Lourens and Koekemoer[10] adopted a slightly different approach. Utilising glucose again, the 3-ulose (10) was synthesised, Scheme 5. This was then used to introduce chain branching via a Wittig reaction. Deoxygenation at the 1 position was accomplished by formation of a thio-glycoside (11) and subsequent reduction. A 10-substituted 11-oxa $PGF_{2\alpha}$ has also been made by analogous methods.[11]



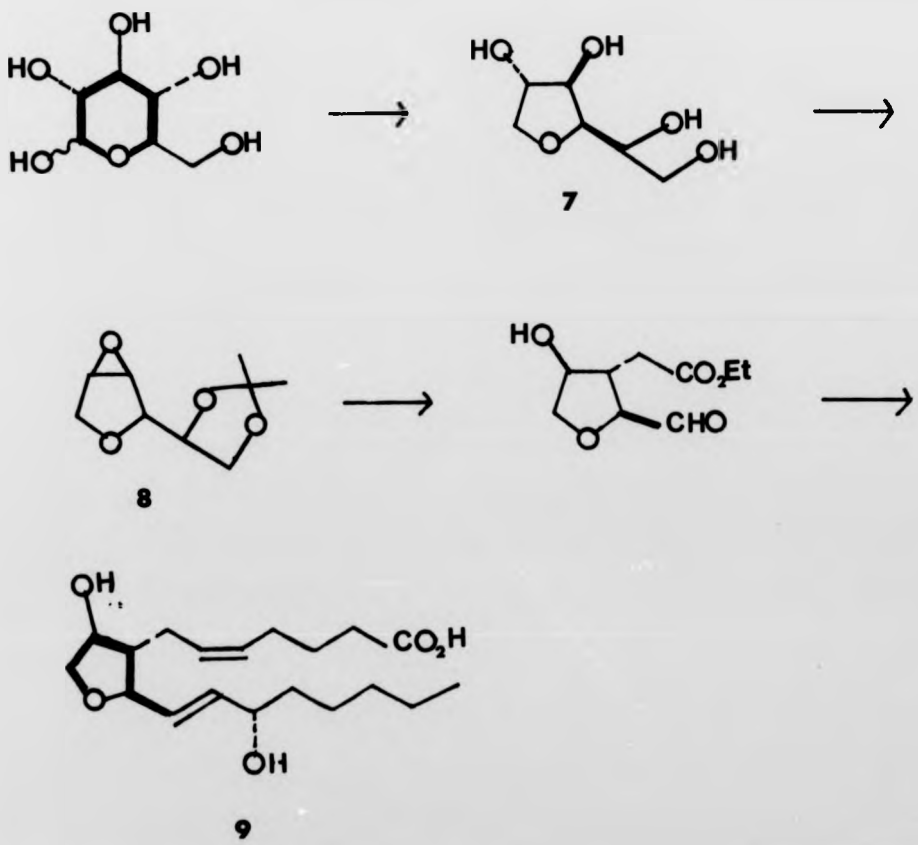
Scheme 1



Scheme 2



Scheme 3



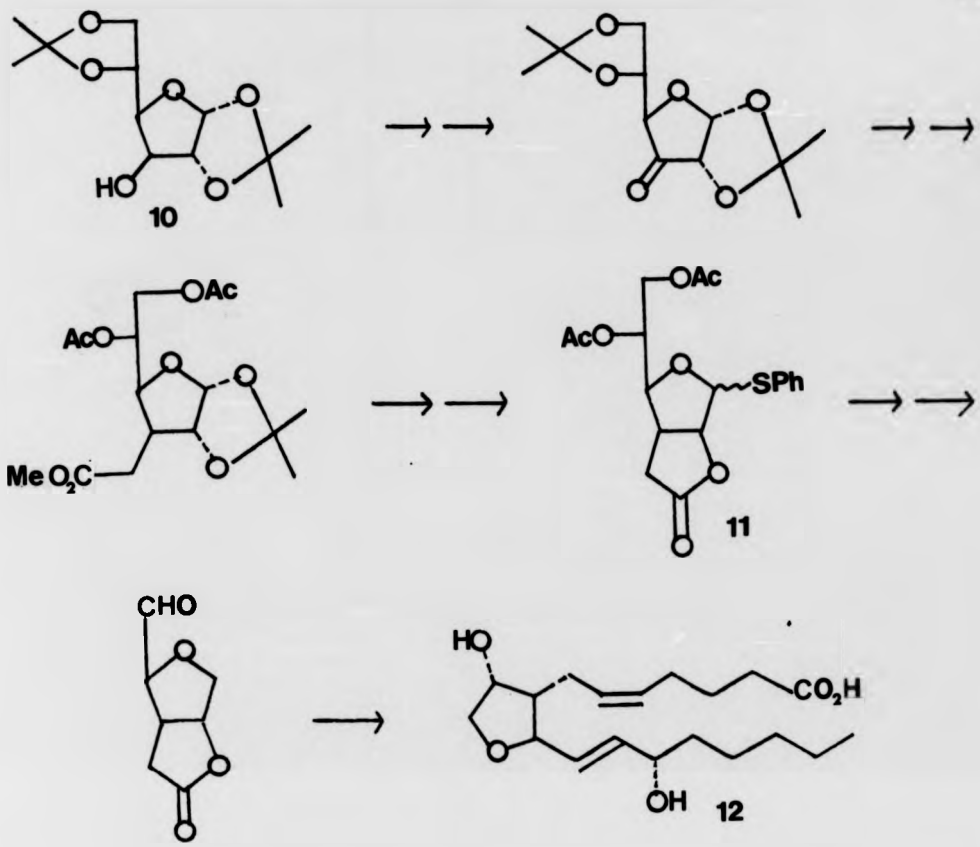
Scheme 4

TXB_2 is an obvious candidate for cyclic transfer from a suitable pyranose sugar. This type of strategy has not been widely applied, although several syntheses of natural products do exist where transfer of a pyranoid ring has occurred. The antibiotic asperlin (16) was recently synthesised from D-galactose.[12] Reaction of the tetraacetate derived from (14) with hydrobromic acid resulted in the key 1-bromo sugar (15) which was subsequently converted to the glycal and thus to asperlin, Scheme 6.

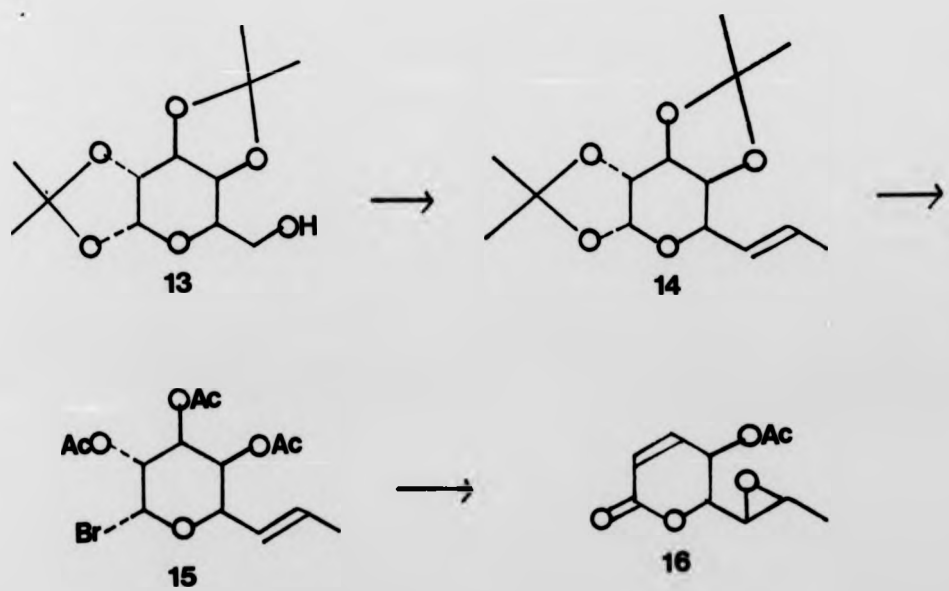
α-Multistriatin (19), an insect pheromone has been prepared from D-glucose via the enone[13] (17), Scheme 7. Conjugate addition of dimethylcopperlithium followed by a Wittig reaction gave the doubly branched sugar (18). Further branching, at C-5, was introduced via a Grignard reaction at the aldehydic moiety of (18).

Pyranoid ring transfer was also used in a recent synthesis of (-)-cis-rose oxide[14], Scheme 8. The epoxide (20), readily available from D-glucose, was opened in a regiospecific manner with lithium dimethylcuprate to give the trans product (21). Conversion of this to the thio-glycoside and reduction with Raney nickel produced the glucitol (22). The unsaturated side chain was then introduced by a Wittig process to give pure (-)-cis-rose oxide (23). The approach adopted by us has in fact, many similarities to the synthesis of cis-rose oxide outlined above.

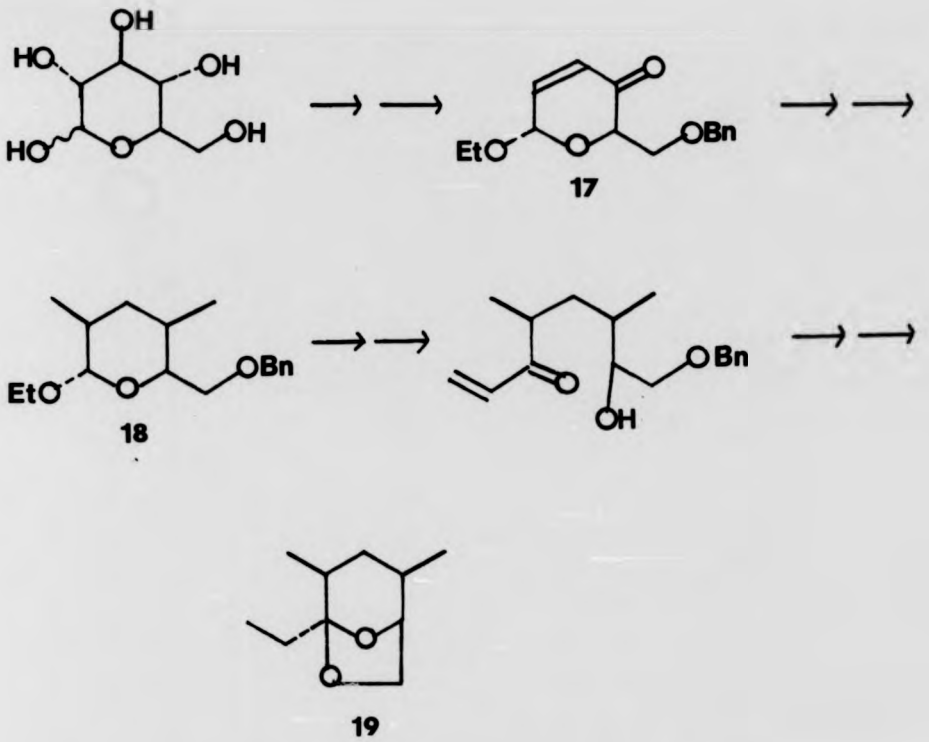
As was pointed out in the discussion of existing syntheses of TXB_2, the bicyclic lactone (24) is an ideal synthon, and thus was our initial target compound. In contrast



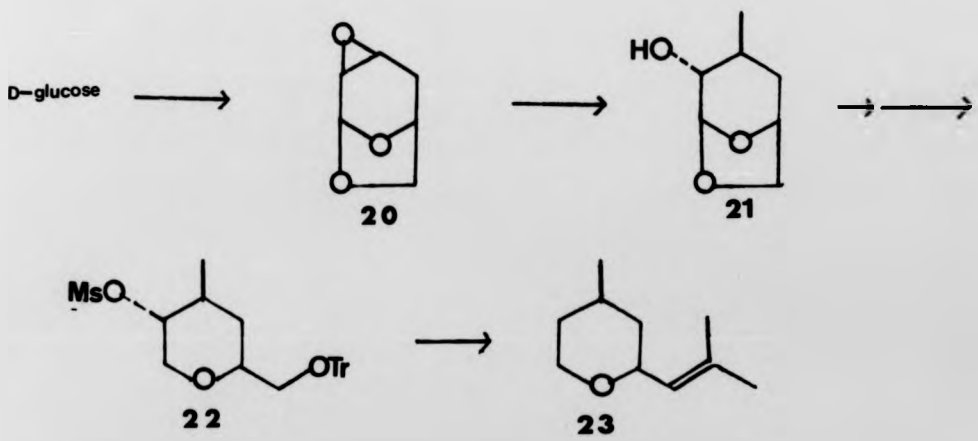
Scheme 5



Scheme 6

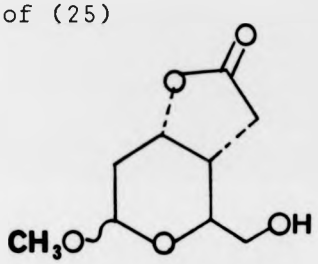


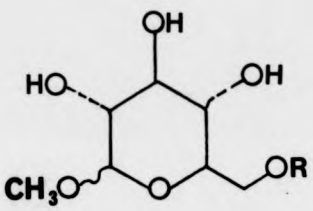
Scheme 7

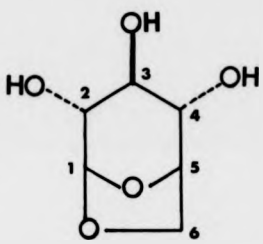


Scheme 8

to the other carbohydrate-based syntheses of TXB_2, we did not use D-glucose methyl pyranoside (25) but the 1,6-anhydro-pyranoside form, (26). The reasons were that sugar (25) exists primarily in the $^4C_1$ conformation with the three secondary hydroxyl groups equatorially orientated. This produces both a lack of differentiation in the reactivities of these groups, and a lack of conformational rigidity as twisting and ring-flip can readily occur. These factors mean that relatively little regio or stereoselectivity will be observed in the reactions of (25)





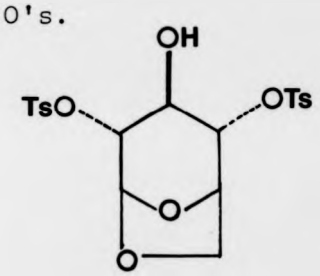


(24) (25) (26)

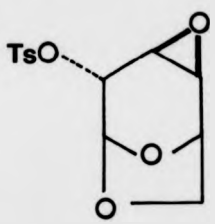
The anhydro form (26) on the other hand is conformationally rigid, locked in a $^1C_4$ conformation with all the hydroxyl groups axially orientated. Extensive investigations by Černý *et al.*[15] have revealed that considerable selectivity is a property of this system, caused by the *trans*-axial arrangement of the hydroxyl groups, and the steric and electrostatic effects of the 1,6-anhydro bridge. The results obtained by Černý indicated that (26) could be a very suitable starting material for the synthesis of chiral compounds in general, and TXB_2 in particular.

The epoxide (20) derived from (26) was the key compound in the previously described synthesis of cis-rose oxide by Ogawa et al.[14] A further advantage of using this derivative, is that the 1,6-anhydro function is effectively acting as a protecting group for both the C-1 and C-6 hydroxyl functions. Its removal can be accomplished at a suitable point in the synthesis, simply by acid-catalysed cleavage with methanol.

The functionalised derivatives of (26) used by us, (27) and (28), were the result of the initial basic research on this bicyclo system carried out by Černý et al. in the 1960's.



(27)

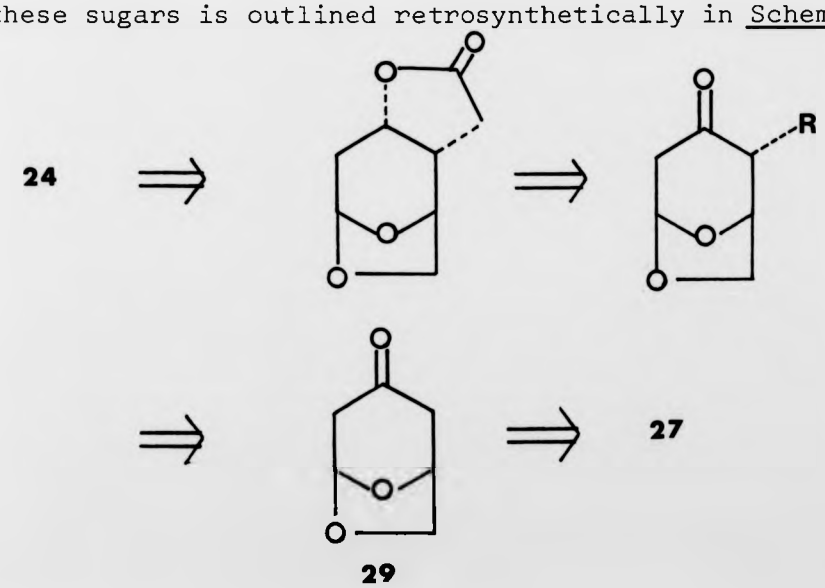


(28)

Differentiation between the hydroxyl groups was possible as (26) undergoes selective di-esterification to produce (27). This well known reaction is thought to be possible because of unfavourable steric interaction between the 3-axial hydroxyl group and the anhydro bridge, slowing its rate of reaction with bulky reagents. p-Toluenesulphonyl chloride and anhydride, benzyloxycarbonyl chloride, benzoyl chloride and anhydride all yield the 2,4-diesters as the major products. Smaller reagents, however, such as acetyl chloride react unselectively to give mixtures of the three possible diesters.[15] A contributory factor seems to be the strong hydrogen bonding present between

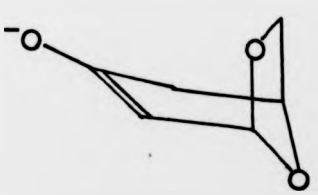
the two hydroxyl groups at C-2 and C-4, even when one is esterified, causing an increase in their acidity.[16] Further functionalisation is possible by treating (27) with base whereupon a remarkably selective internal displacement of tosylate anion occurs yielding (28). The relative reactivity of the 2 and 4-O-tosyl groups in this reaction has been estimated to be 1:24,[15] so only about 5% of the isomeric 2,3-epoxy tosylate is formed. These values have been confirmed by us (see page 105). The rate difference is thought to be due to an unfavourable electrostatic interaction between the alkoxide anion on C-3 and the oxygen of the anhydro bridge, preventing movement towards C-2.

The first approach to the TXB_2 synthon (24) based on these sugars is outlined retrosynthetically in Scheme 9



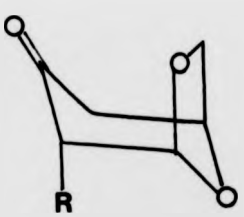
Scheme 9

We envisaged alkylation of the ketone (29) proceeding in a stereoselective, but perhaps not regioselective manner. If one considers the enolates (30) and (31), attack of an alkylating agent from the endo side will be considerably hindered by the 1,6-anhydro bridge, so alkylation should give those products resulting from exo attack i.e. (32) and (33). The position of attack is more difficult to predict as the asymmetry in the molecule is quite small. The initial aim therefore was to try and find conditions which would lead to the enolate (31) as the major product. The complications associated with attempting to alkylate these enolates were initially avoided by trapping them as their silyl enol ether derivatives. This was also advantageous in simplifying the identification of the products.

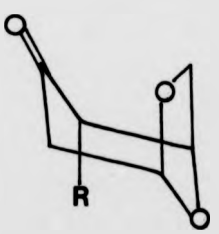


(30)

(31)



(32)

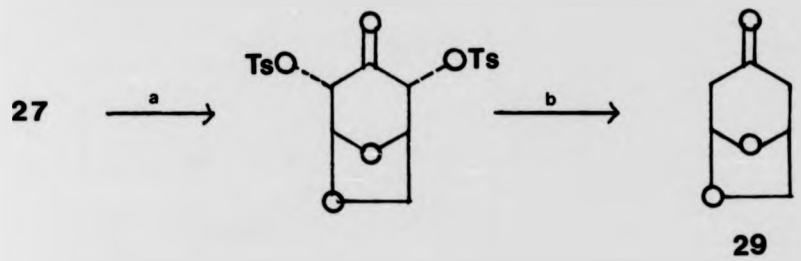


(33)

2. SYNTHESIS AND REACTIONS OF 1,6-ANHYDRO-2,4-DIDEOXY-β-D-GLYCERO-HEXOPYRANOS-3-ULOSE (29)

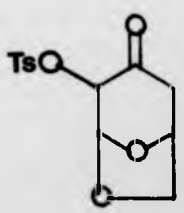
2(i) Synthesis of (29)

The ketone of (29) has been synthesised by Černý by the route shown in Scheme 10.[17] The key step is hydrogenolysis of the tosyl groups. This usually results in cleavage of the sulphur-oxygen bond to produce the parent alcohol. When the tosyl group is adjacent to a ketone however, it is activated for carbon-oxygen bond cleavage. The type of Raney nickel used by Černý as catalyst for this hydrogenolysis is designated 'T1',[18] and is especially active at ambient temperature and pressure. Raney nickel normally requires a high partial pressure of hydrogen, and indeed the original paper describing the T1 catalyst specifies an atmosphere of hydrogen for its use. The conditions described by Černý however, do not mention the addition of hydrogen. When these conditions were used, no reaction occurred. Using one atmosphere of hydrogen, reduction did occur to produce several products. These included starting material, partially reduced mono-tosyl compounds (34) and (35) in the ratio 6:1, the desired ketone (29), and a small amount of the alcohol (36). Prolonged reaction with excess catalyst did not significantly change this product distribution, so it appears that the Raney nickel is being de-activated possibly by poisoning with the tosylate anion produced during the reduction, or because of a decrease in the pH of the mixture caused by p-toluenesulphonic acid. No products resulting from removal of only the 2-O-tosyl group were detected, so presumably removal of the 4-O-tosyl group must be the first step in the reaction. This selectivity may be a result of the orientation which the molecule adopts when

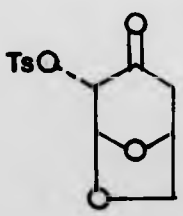


(a) Jones[O], (b) Raney nickel

Scheme 10



34



35

36

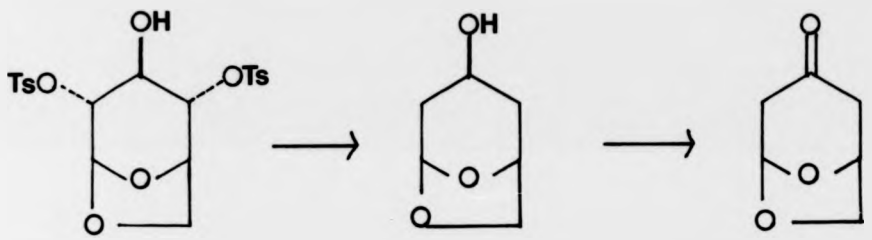
coordinated to the catalyst surface allowing more facile approach of hydrogen to C-4 than to C-2. The mechanism of Raney nickel reduction depends on several factors e.g. the solvent, pH of the solution, the leaving group involved, etc., and can proceed with either inversion or retention of configuration. Inversion tends to occur with good leaving groups e.g. tosylate. If an SN_2 type process is operating in this case, then another explanation of the observed selectivity suggests itself.

The 2-O-tosyl group isomerises to the equatorial position more rapidly than the 4-O-tosyl group. If an SN_2 process is operating, then one might expect axial groups to react faster than equatorial ones, as the approach of hydrogen would be less sterically crowded. Therefore, if isomerisation is faster than reduction of the axial tosyl groups, one would expect the D-threo compound (34) to be preferentially formed, and its reduction to be the rate determining step.

To try and prevent isomerisation occurring, the reduction was performed with a buffer present, but this had little effect. With added base, triethylamine or sodium hydroxide, complete reaction of (38) did occur, but produced very polar products, from which the ketone (29) could not be isolated.

The best yield of the ketone (29) obtained in this reduction was only 29%. As this was not very satisfactory alternative methods were investigated i.e. using an electron transfer process. Černý had reduced (35) using zinc and acetic anhydride, but had obtained only a very poor yield of (29).[19] It was found that both a Birch reduction with calcium in liquid ammonia, and reduction using dimethylcopperlithium,[20] caused

removal of the tosyl groups, but produced complicated mixtures with no ketone (29) detectable. As none of these methods were very successful an alternative approach was investigated. An obvious method of producing (29) from available compounds was direct reduction of the ditosyl alcohol (27) with hydride to produce the alcohol (36) which could then be oxidised.



(36)

Tosylates on reaction with hydride usually undergo one of three types of reaction:-

(i) C-O bond fission

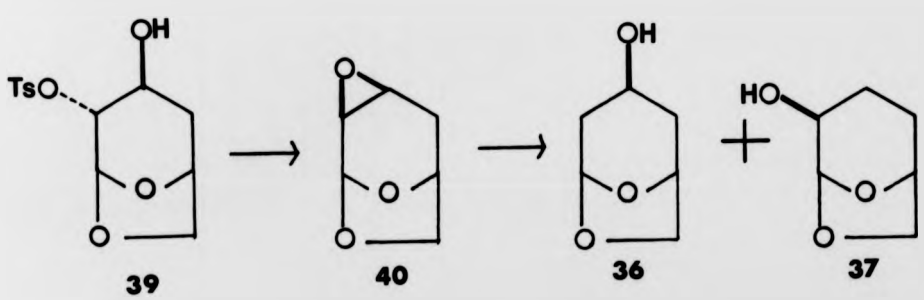
(ii) S-O bond fission

(iii) elimination of p-toluenesulphonic acid.

Which reaction occurs depends mainly on the structure of the tosylate and on the source of hydride. Primary tosylates tend to undergo C-O bond fission to produce hydrocarbons, whereas secondary and hindered tosylates undergo S-O bond fission and

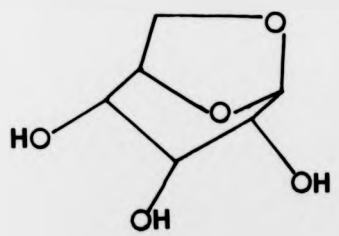
elimination reactions. The reaction of secondary tosylates is greatly affected by their steric environment as lithium aluminium hydride is a bulky reagent. The orientation of sugar tosylate groups therefore influences their reactions. Considering nucleophilic substitution in general, equatorial tosylates tend to be unreactive as the nucleophile has a sterically crowded axial approach path e.g. in the rigid 1,6-anhydropyranose skeleton, the only equatorial group displaceable is the 4-O-tosyl group. The most easily displaceable is the axial 3-O-tosyl group, but if axial substituents are present at the 2 and/or 4 positions, the approach path of the nucleophile becomes so hindered that no reaction occurs. Inductive effects also influence reactivity, the main effect being that of the '-I' acetal group on C-2. This so reduces electron density at this position that nucleophilic substitution becomes almost impossible.

The reaction of secondary sugar tosylates with hydride has been found to give normally the alcohol. For instance, Černý has found that reduction of (39) with $LiAlH_4$ produces the two alcohols (36) and (37) in high yield in the ratio 4:1, Scheme 11.[21]



Scheme 11

The 3,4-dideoxy threo alcohol (37) is formed via the epoxide (40). This tendency for 1,2-hydroxy-tosylate derivatives of levoglucosan to undergo internal displacement of tosylate is well known, and results from the conformationally rigid skeleton maintaining the neighbouring groups in a suitable trans-diaxial arrangement. The levoglucosan molecule reacts in most cases in the $^{1}C_{4}$ conformation (26). The alternative $B_{O,3}$ conformation (41) is less favourable by about 3-6 kJ mol^{-1},[15] even though it does allow reorientation of the axial hydroxyl groups to an equatorial configuration.



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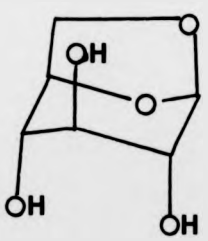
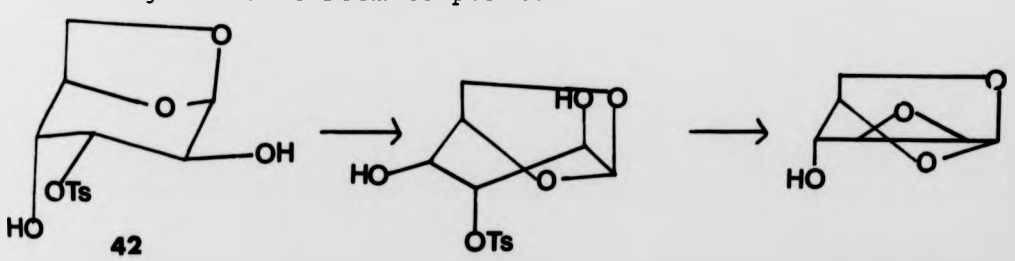


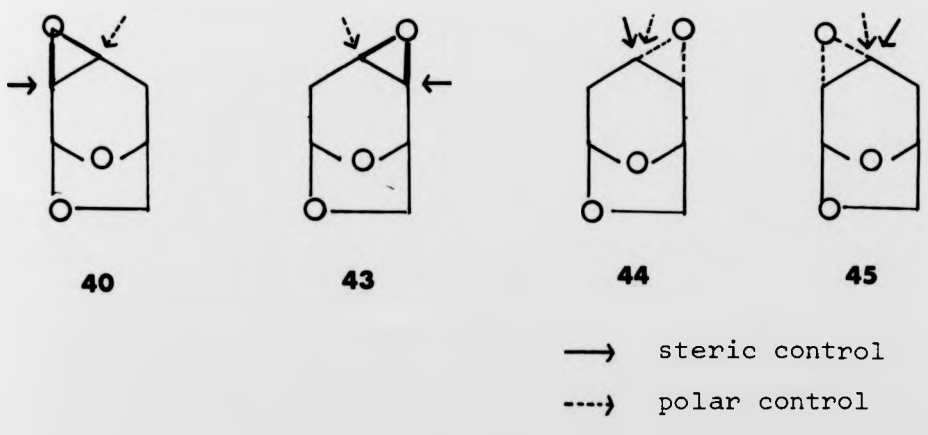
(26)

If one considers a 1,6-anhydropyranose having equatorially-orientated groups e.g. (42), then it must assume an unstable skew form S_{O}^{5} to enable displacement of tosylate to occur, Scheme 12. In fact this compound requires prolonged reflux for reaction to occur, whilst levoglucosan derivatives readily react at room temperature.



Scheme 12

This is fortuitous in allowing the indirect removal of tosyl groups as found by Černý in the reduction of (39). With this as the major reaction pathway, the products obtained for a given epoxide will depend on the direction of epoxide ring opening. In the steroid field the Fürst-Plattner rule has been formulated to predict this. It considers the transition state of the ring opening and predicts that in the absence of other major steric or inductive effects, trans diaxial products are favoured. In the tetrahydropyranyl ring of sugars, polar effects due to the ring oxygens affect this reaction. Černý[22] has investigated the four epoxides (43-45) and (40) and found that hard bases cause normal diaxial ring opening, but soft bases being more influenced by polar effects give more of the abnormal diequatorial product, Scheme 13.



Scheme 13

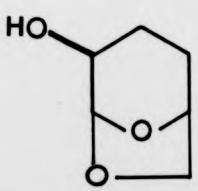
Lithium aluminium hydride is a bulky reagent and tends to produce the normal diaxial products. Thus epoxide (40) is reduced to give the alcohols (36) and (37) in the ratio 1.7:1.0.[22] On comparison of this result with that for the reduction of (39)

i.e. the two alcohols are obtained in a ratio of 4:1, it is apparent that some direct displacement of tosylate anion by hydride must be occurring in the latter case. This is somewhat surprising as the 2-O-tosyl group is known to be particularly unreactive towards nucleophiles.

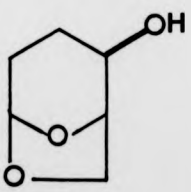
On the basis of the above evidence, the reduction of the readily available (27) and (28) seem to offer a good opportunity of obtaining reasonable yields of the alcohol (36). These reactions were therefore investigated.

On reduction of the ditosylate (27) with lithium aluminium hydride at room temperature, the monotosylate (39) was obtained as the predominant product. On reduction in refluxing tetrahydrofuran, the reduction went to completion and a mixture of isomeric dideoxy alcohols were isolated in 70% yield. Analysis by NMR and GC demonstrated that these were the alcohols (36), (37) and (46) in the percentage ratio 68.5:30:1.5.

36



37

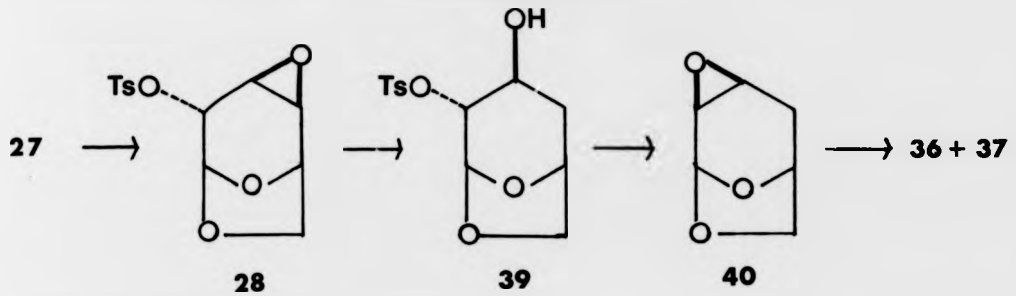


46

Mono-deoxy sugars resulting from S-O bond cleavage were isolated in a yield of about 20%.

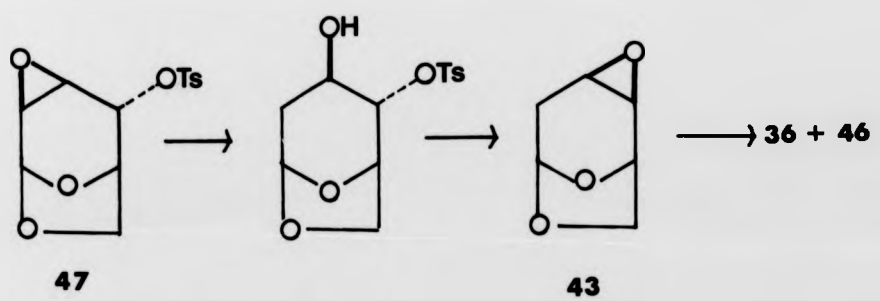
On stopping the reduction after partial completion and isolating the intermediates present, the compounds (28), (39), (40), (36) were obtained. It is thus obvious that this reduction

follows the path shown in Scheme 14.



Scheme 14

Formation of (28) from (27) occurs readily on treatment with most bases. The cleavage of the tosyl epoxide (28) is completely regiospecific as the axial tosyl group at C-2 serves to hinder nucleophilic attack at C-3. Formation of the epoxide (40) is much less facile than that of (28) as shown by the selectivity in the formation of (28), and the fact that reduction of (27) at room temperature stops at (39). There does however seem to be some of the isomeric tosyl-epoxide (47) formed, leading as shown in Scheme 15 to the small amount of the 4-threo alcohol (46) found in the product mixture.

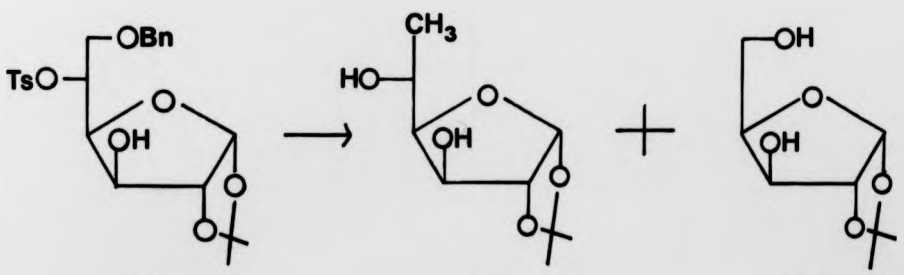


Scheme 15

Only about 5% of the reaction should go through (47), and as reduction of (43) has been found to give (36) and (46) in the ratio of 3:1,[15] then only about 1.5% of alcohol (46) should be produced, which is in fact what was found.

In order to confirm that this alcohol was indeed being formed from (27), some of the pure epoxide (28) was subjected to direct reduction. As no (47) should be present, no (46) should form, and indeed on analysis of the product mixture the alcohols (36) and (37) were present in the percentage ratio 65:35 with no trace of (46) detectable.

The question of whether direct displacement of tosylate anion by hydride is occurring in these reductions is again raised by the variation in the ratio of (36) and (37) obtained above, i.e. 2.2:1.0 and that obtained by Cerny for reduction of (40) i.e. 1.7:1.0. If this direct displacement is occurring then it can only be due to the formation of an alumino-complex between the 3-alcohol and lithium aluminium hydride which is assisting attack of hydride at the C-2 and C-4 positions of (27) and (39).



48 49 50

Scheme 16

This type of neighbouring group participation has been

invoked before in sugar chemistry. The furanose (48) on reduction with lithium aluminium hydride gives (49) and (50). In the case of (49) a 5,6-epoxide is implicated in its formation, whereas (50) is thought to result from direct hydride displacement of the tosyl group by a 3-O-alumino complex, Scheme 16.[23]

To examine these ideas further, a derivative of (27) was made with the 3-hydroxy group protected as the methoxy-ethoxymethyl ether (51). Reduction of this under the usual conditions gave as the only product, the diol (52), which was fully characterised as its di-acetate (53). Thus in the absence of a free 3-hydroxyl group hydride displacement of tosylate does not occur and the usual reaction of secondary tosylates, i.e. by S-O bond fission, predominates. These findings demonstrate that the 'epoxide route' is the major pathway for tosylate removal, and are strong evidence for the existence of a 3-O-alumino-complex causing the direct displacement of tosylate by hydride which the various ratios of (36) and (37) obtained in the above reductions suggest is occurring.

The limiting factor in achieving high yields of the 3-alcohol (36) from reduction of (27) is the poor regioselectivity in the reduction of the epoxide (40). Theoretically, one could increase the amount of diaxial opening by the use of a more sterically demanding reagent. The trialkylborohydrides are a recently introduced class of hydride reducing agents,[24] which have shown considerable selectivity in epoxide reductions and reduction of carbonyl compounds. By the variation of the alkyl substituents present, some very hindered reducing agents have been produced. An additional advantage which may result

from their use is a decreased amount of S-O bond fission. In contrast to lithium aluminium hydride it has been found that for the reaction of lithium triethylborohydride with cyclic secondary tosylates, S-O bond fission does not normally occur. As this class of reagent had not previously been applied to the carbohydrate field, an investigation into the reduction of sugar tosylates would provide general as well as specific information on its usefulness.

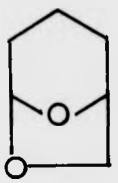
Reduction of 2,4-di-O-tosyl-levoglucosan (27) with lithium triethylborohydride went readily at room temperature. A high yield of the dideoxy alcohols (36), (37) and (46) was obtained, with no appreciable amounts of mono-deoxy products resulting from S-O bond fission being apparent. The percentage ratio of the three alcohols was 91.5:7.5:1.0, so the expected increase in regioselectivity of reduction of (40) is occurring. This encouraging result suggested that the larger reagent, lithium tri-sec-butylborohydride, might be even more selective. On reducing (27) with this reagent no significant change in the alcohol ratio was produced i.e. observed percentage ratio of (36), (37) and (46) was 85:14:1.

One complicating factor associated with the use of these reagents is the formation of the olefins (54) and (55) and the saturated compound (56). These were detected by GC analysis, and their identities confirmed by co-injections with authentic samples.[25] The amount of these compounds formed varies from about 5% for lithium triethylborohydride to about 15-20% for lithium tri-sec-butylborohydride, and depends on the length of the reaction period, prolonged reactions producing large amounts. Their most likely precursor is the 3-alcohol (36).

This would exist in the reaction mixture as a weak trialkyborane complex of the corresponding lithium alkoxide and might well be susceptible to elimination of $HOBEt_3$ by excess hydride

(54)

(55)



(56)

The reduction of cyclohexyl tosylates by various trialkylborohydrides, has been examined by Brown and Krishnamurthy who found that elimination was an important side reaction. Typically, a 15-20% yield of the olefin resulting from elimination was obtained with lithium triethylborohydride, but this rose to 48% with lithium tri-sec-butylborohydride. These findings demonstrate that trialkylborohydrides are relatively basic and confirm the tendency for elimination shown by lithium tri-sec-butylborohydride in the reduction of (27).

Cerny has treated the 2,4-dideoxy-3-O-tosylate derivative of (36) with potassium tert-butoxide and obtained (54) and (55) in the ratio 2:1, apparently determined by kinetically controlled proton abstraction. The equilibrium mixture of the two olefins could be obtained by prolonged reflux with tert-butoxide and consisted of (54) and (55) in the ratio 1:5.5. The Δ^3 olefin (55) is the thermodynamically more stable. The ratio of (54) and (55) obtained in reactions using lithium triethylborohydride was 2:1 indicating that kinetic control is operating. With lithium tri-sec-butylborohydride this ratio

changed to 5:1. It seems unlikely that the controlling factor in proton abstraction from (36) is steric in nature as the molecule is almost symmetrical. Control must be due to the enhanced acidity of the C-2 protons, caused by the inductive effect of the adjacent acetal group. The small amount of (56) formed must be due to direct displacement of oxytrialkylborane anion by excess hydride. As these side-reactions are obviously undesirable, the conditions for reduction with lithium triethylborohydride were adjusted to minimise them. Use of just over one equivalent of hydride, at $0^{o}C$, led to repeatable yields of 90%.

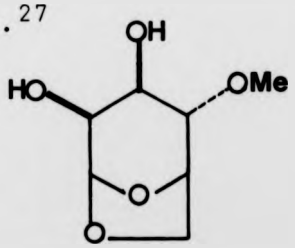
An interesting aspect of these reductions is whether the extremely powerful nucleophilic borohydrides are capable of directly displacing the tosyl groups of 2,4-di-O-tosyl levoglucosan (27). The known facility of reactions of cyclohexyl tosylates suggested that they might be. Accordingly the MEM derivative (51) was subjected to the usual reduction conditions, but no reaction occurred and (51) was recovered unchanged. This demonstrated that in the conversion (27) to (39) no direct displacement was occurring although it was still possible in the conversion of (39) to (36). To test this point, the epoxide (40) was synthesised by an alternative method[26] and directly reduced with Super-Hydride. The ratio of alcohols (36) and (37) obtained was 4.56:1.0 which is little different from that obtained by reduction of (39) i.e. 5.2:1.0. This indicates that little or no direct displacement of tosylate by hydride occurs at any stage in the reaction. This result complements the evidence

obtained for anchimeric assistance in reductions using lithium aluminium hydride. The 3-O-borane complex once formed cannot further react having no available hydride, whereas the 3-O-alumino complex has three hydride atoms capable of delivery.

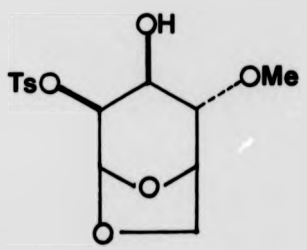
2(ii) Selectivity in the reactions of 1,6-anhydro-2,4-dideoxy-β-D-threo hexopyranose (36) and 1,6-anhydro-3,4-dideoxy-β-D-threo-hexopyranose (37)

Having obtained a good yield of the mixture of alcohols (36) and (37), a method was required to separate them. Chromatographic separation was tried using silica gel, but without success. Although preparative GC or HPLC would probably have worked, a more convenient chemical method was sought first of all. The idea was to exploit the steric differences between (36) and (37) to allow selective reaction of one. The alcohol (36) has an axial hydroxyl group hindered by the 1,6-anhydro bridge, whereas (37) possesses a relatively unhindered equatorial hydroxyl group.

The initial approach was to derivatise (37) by reaction with a bulky reagent, and then chromatographically separate (36). Toluene-p-sulphonyl chloride would have given some selectivity, but not sufficient for our needs e.g. the 1,6-anhydropyranose (57) could be selectively sulphonylated to (58), but only in 65% yield.[27]



(57)



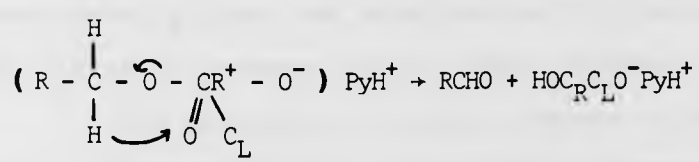
(58)

Weiz et al.[28] had shown that in the steroid field, N,N-diethyltrimethylsilylamine is capable of selectively silylating equatorial cyclohexyl alcohols in the presence of axial ones. Application of this reagent to the mixture of (36) and (37) showed that at room temperature, reaction was very rapid but not very selective. At 0°C, however, reaction of the mixture for 45 minutes allowed quantitative reaction of (37) with minimal reaction of (36). Chromatographic separation of (36) and the trimethylsilyl ether of (37) was not possible as rapid hydrolysis of the silyl ether occurred on silica gel, but a simpler method of separation based on relative solubilities was developed. This involved quenching the reaction mixture with water, and extracting the silyl ether with a small portion of dichloromethane. Any of the 3-alcohol (36) co-extracted in this process was recovered by extracting the dichloromethane with several portions of water. The combined aqueous extracts were then continuously extracted with dichloromethane for one day, to give the 3-alcohol, in about 80% yield contaminated with only 2-3% of (37).

Having now available a high-yielding method for the production of (36), all that remained was its oxidation to the target ketone (29). The reagent chosen for this transformation was pyridinium chlorochromate, a mild and convenient oxidising agent developed by Corey and Suggs.[29] This reagent had not been previously applied to sugars. In the course of oxidising (36), a considerable rate difference was discovered for the oxidation of (36) and its isomer (37). Investigation revealed this to be of the order of 30:1 with (36) reacting faster.

Treatment of a mixture (36) and (37) with excess pyridinium chlorochromate resulted in quantitative oxidation of (36) within one hour whereas (37) required 24 hours for complete reaction. This in fact formed the basis for another method for separating (36) and (37). The crude mixtures of the alcohols were oxidised for one hour, and the resultant ketone (29) could be readily separated by chromatography. This procedure made the selective silylation method redundant.

The rate difference is understandable when one considers the known reactions of chromic acid with secondary alcohols. With unhindered alcohols the initial equilibrium to form a chromate ester is fast, and the subsequent decomposition of the ester is the rate-limiting step. However if the formation of the chromate ester results in severe steric interaction, then its decomposition rate is accelerated, as steric strain is being relieved. Thus, in the absence of competing side reactions, the most hindered alcohol is oxidised fastest. Banerji[30] has found the mechanism of reaction of pyridinium chlorochromate to be very similar to that of chromic acid, with the rate limiting step involving a hydride transfer from the chromate ester



In the case of the alcohols (36) and (37), the rate of reaction of (36) will be accelerated as it is hindered by the 1,6-anhydro bridge. In the carbohydrate field, few

selective oxidising agents are known. Platinum/oxygen is known to preferentially oxidise axial hydroxyl groups in the order 3a > 4a > 2a > 4e > 2e > 3e.[31] Bromine will also selectively oxidise axial groups at C-3. Chromic acid reagents, when applied to sugars usually result in maximum yields of only about 10%. Pyridinium chlorochromate is therefore potentially a very useful reagent for selective oxidations in this field.

2(iii) Formation of the silyl enol ether derivatives of 1,6-anhydro-2,4-dideoxy-β-D-*glycero*-hexopyranos-3-ulose (29)

The aim of this investigation was to discover the relative amounts of the two possible regioisomeric enol ethers formed under various conditions and attempt to optimise production of the Δ^3 isomer. A useful discussion on the formation of the enolate ions of unsymmetrical ketones is given by House.[32]

For an unsymmetrical ketone, the regioisomeric enolate predominating under any given conditions will depend on the nature of the asymmetry, i.e. presence of adjacent alkyl, or unsaturated groups, and also whether the conditions allow equilibration between the two regio-isomers to occur.

The presence of a proton source of pK near or below 20 e.g. unreacted ketone, or a protic solvent like *tert*-butanol will allow equilibration, as will the use of potassium or sodium as the counter-ion. These counter-ions produce an enolate ion pair which is sufficiently covalent to undergo equilibration. Thus addition of a base like potassium *tert*-butoxide to a

solution of the ketone in tert-butanol should produce the enolates under equilibrating conditions, with the thermodynamically more stable one predominating. This is usually the more conjugated or the more substituted one. Use of non-equilibrating conditions allows control to be exercised in the initial hydrogen abstraction step, so using a hindered base like lithium di-isopropylamide will produce the kinetically favoured enolate, this usually being the less substituted one. To avoid equilibration occurring, a lithium counter-ion must be used with a non-protic, non-polar solvent, and the presence of unreacted ketone must be avoided. Trapping of the enolates as their enol ethers does not appear to alter the distribution of the regioisomers. The enolates can be regenerated by the addition of one equivalent of methyl lithium. A major synthetic advantage of this method is that it avoids the use of excess base and the resultant problems of dialkylation.

Formation of the kinetically favoured enolate of (29) was attempted using lithium di-isopropylamide (LDA) in diethyl ether at -70°C. Quenching with chlorotrimethylsilane solution resulted in a product mixture which GC analysis showed to consist of two main components, with some ketone (29) in percentage ratio 64:20:5. The assignment of the structure of the major component was based on NMR, by analogy with the two isomeric olefins (54)[33] and (55)[33] and the enol acetate (59).[21] These examples showed that for a double bond in the Δ^2 position $J_{1,2} \sim 3\text{-}6$ Hz and in the Δ^3 position $J_{4,5} \sim 4.5$ Hz. The product of the above reaction was shown to have $J_{1,2} \sim 6.1$ Hz by decoupling experiments and must therefore be the Δ^2 isomer (60).

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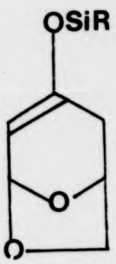
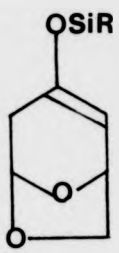




(60) R = Me_3

(63) R = $^tBuMe_2$ (64)

NMR did not reveal the identity of the minor component.

Attempted purification of (60) on silica gel led to hydrolysis of the enol ether to the parent ketone. In fact, it was found that the enol ether reverted to the ketone even in a dry solution of dichloromethane at 0°C.

(59)

Further evidence confirming the identity of (60) was obtained by GC-mass spectrometric analysis of the product mixture. On an Apiezon column the ketone (29) was eluted first (M^+ 128) followed by the silyl enol ether (M^+ 200, with characteristic fragment ions at 73, $^+Si(CH_3)_3$, and 75, $H\overset{+}{O}Si(CH_3)_3$.)

As these trimethylsilyl derivatives seem very labile, a more stable protecting group was sought. Corey et al. have

shown the tert-butyldimethylsilyl group to be about 10^3 [34] times more stable than the trimethylsilyl group, so this was used in the form of an imidazole-silane complex formed by addition of two equivalents of imidazole to a solution of tert-butyldimethylsilyl chloride, followed by removal of the precipitated imidazolinium hydrochloride by filtration. This avoided the possibility of this salt acting as a proton donor and allowing equilibration to occur.

Formation of the enolates as above, followed by quenching led to the isolation of one major product identified by NMR as the regio-isomer (63). No trace of the other isomer was detected. The enol ether (63) was quite stable and could be purified by chromatography, and distilled.

The above experiments indicate that the Δ^2 isomer is the predominant product of kinetically controlled enolisation. There should be little steric differentiation between the 2 and 4 positions, so the observed selectivity must result from the inductive effect of the acetal group on C-2 increasing the acidity of protons attached to this position. This same effect should destabilise a double bond in the Δ^2 position and indeed Černý has found that at equilibrium induced by base, the relative amounts of the unsaturated compounds (54) and (55) are 15.5% and 84.5% respectively, demonstrating that the Δ^3 isomer is thermodynamically favoured. One would expect a mixture of equilibrated enolates to mirror this distribution.

Three sets of conditions were used in an attempt to form equilibrated mixtures of (63) and (64). The first involved using potassium tert-butoxide in tert-butanol but this was unsuccessful due to the difficulty of isolating the products

from the tert-butanol solution. Potassium hydride in tetrahydrofuran was tried next. This base was developed by Brown[35] and is very reactive, metallating most ketones in quantitative yield, to give the equilibrium mixture of isomers directly. As potassium hydride is insoluble in non-reactive organic solvents, reaction proceeds at the crystal surface and is therefore susceptible to surface effects. This may explain why, in initial attempts to enolise (29) with potassium hydride the base seemed to be inactive. Reaction of the ketone with excess potassium hydride for two hours at room temperature caused only about 20% of it to enolise. When the reaction was allowed to proceed after the addition of the silylating agent, enolisation continued and the ketone was gradually, over 3 days, converted to the silyl enol ether. This was identified once again as the Δ^2 isomer with none of the Δ^3 isomer detectable.

Chlorotrimethylsilane has been found to substantially slow down the rate of reaction of KH to the extent that even in THF at reflux KH will not enolise cyclohexanone.[36] This poisoning effect may be due to formation of a surface coating of potassium chloride, derived by breakage of the Si-Cl bond. In the above reactions this effect was not apparent, perhaps because the use of an imidazole-silane complex means that very few chloride ions will be present. The same paper shows that this mixture of potassium hydride and trimethylchlorosilane when used in dioxane, does not give a truly equilibrated mixture of regioisomers, but one partway between the two extremes. This may mean that silylation of the enolate once formed, is more rapid than equilibration processes. If this is so, the formation of the Δ^2 regio-isomer in the above

experiment is not a valid indication that this is the more thermodynamically stable.

A third attempt at forming the thermodynamically more stable isomer used the classic method of House[37] with chlorotrimethylsilane and triethylamine in dimethylformamide. The triethylamine hydrochloride formed in this reaction is sufficiently acidic to cause equilibration of the silyl enol ethers. On performing the reaction, only a complex tarry mixture of products was produced, none of which could be identified.

A different approach was to use the available Δ^2 isomer (63) and attempt to isomerise it directly. Accordingly (63) was subjected to p-toluenesulphonic acid in refluxing carbon tetrachloride, conditions which Stork[38] has found sufficient to isomerise trimethylsilyl enol ethers. However, no reaction occurred. More vigorous conditions were applied in the form of an NMR scale experiment using boron trifluoride-acetic acid complex. This simply polymerised the material to a black tar, without revealing if isomerisation had occurred.

These experiments have definitely established that the Δ^2 isomer (30) is the predominant product of kinetically controlled enolisation, but have failed to find conditions which would produce the Δ^3 isomers. By analogy with the olefins (54) and (55), it seems that the Δ^3 enol ether isomer should be thermodynamically more stable. The above experiments have not confirmed this. Reaction with potassium hydride should have produced a mixture containing at least perhaps 20-30% (64) as should the attempted isomerisation of (63) with acid, but their failure to do so although casting doubt on the idea that

the Δ^3 isomer is thermodynamically more stable do not disprove it. From the synthetic viewpoint, alkylation of (29) does not seem a suitable method for introduction of an alkyl unit at C-4.

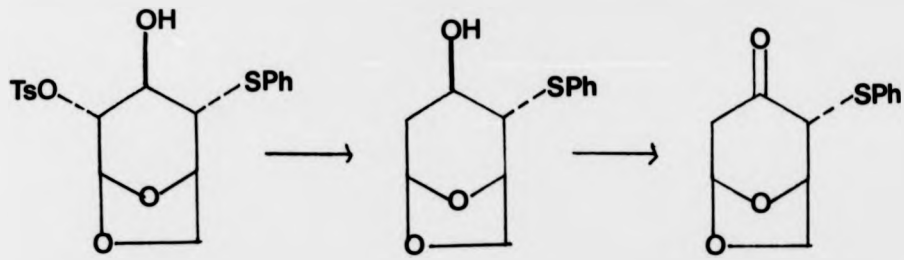
The application of the above work to the synthesis of 1,6-anhydro-2,4-dideoxy-β-D-threo-hexopyranose has been reported.[39]

3. SYNTHESIS AND REACTIONS OF 1,6-ANHYDRO-2-DEOXY-4-S-PHENYL-4-THIO-β-D-ERYTHRO-PYRANOS-3-ULOSE AND 1,6-ANHYDRO-2-DEOXY-4-S-PHENYL-4-THIO-β-D-THREO-PYRANOS-3-ULOSE

In the previous chapter, enolisation of the 2,4-dideoxy ketone (29) was found to give the Δ^2 regio-isomer under all conditions examined. To permit alkylation at the 4 position, it is necessary to direct enolisation to the Δ^3 isomer. This could be done by blocking the 2 position or by placing a carbanion stabilising substituent in the 4 position. The latter strategy promises a greater chance of success, and so was adopted. Introduction of such a substituent at C-4 of the ketone (29) is just as difficult as alkylating at this position, so the substituent must be introduced at an earlier stage. Nucleophilic opening of the epoxide (28) has been shown to be stereo- and regio-specific, giving a 4-substituted gluco sugar as the product. Substituents such as H, OH, OMe, PhO, $PhCH_2S$, NH_2, N_3, F and I have been introduced in this manner.[15] There are no reports of carbon nucleophiles being used.

Of the above mentioned nucleophiles, sulphur would serve as a useful directing substituent. The presence of a phenylthio group alpha to a ketone enhances the thermodynamic acidity of the adjacent proton by about 10^3 [40]. As the thiophenoxide anion is also the most powerful sulphur nucleophile, its introduction via the epoxide (28) should be straightforward. The subsequent steps to the desired α-thio-ketone then involve simply removal of the tosyl group using the previously developed trialkylborohydride methodology, and oxidation to the

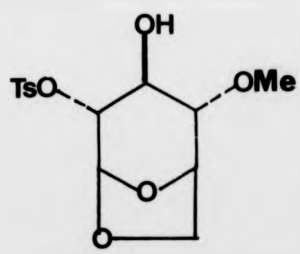
ketone with pyridinium chlorochromate as shown in Scheme 17.



(65) (66) (67)

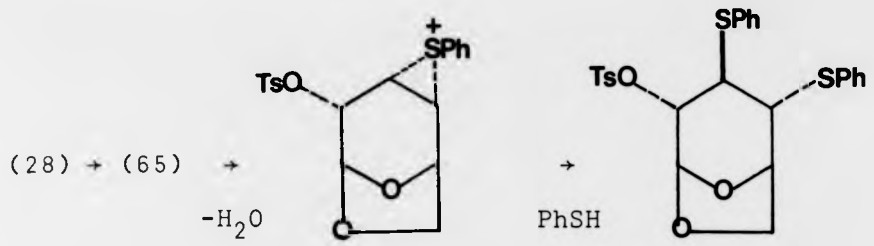
Scheme 17

The formation of (65) from (28) can be performed under acid or base catalysis. The reaction using acid catalysis was investigated first, as literature examples suggested it may give a cleaner product. For example, Bochov and Yoznyi[41] had found that sulphuric acid catalysed reaction of (28) with methanol led to a high yield of (68).



(68)

Accordingly, these conditions were used for the reaction of (28) with thiophenol. Two products were formed concurrently, these being identified as the expected product (65) and the di-thio-compound (69) in the ratio 2:1 in 50% yield.

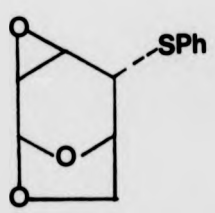


The configuration of (69) was confirmed by NMR decoupling experiments ($J_{3,4}$ = 1½ Hz, $J_{4,5}$ = 1½ Hz). At this point it is perhaps worth pointing out the considerable value of proton NMR for structure elucidation in this system. Owing to the rigid $^1C_4$ conformation, the couplings shown by the ring protons are very characteristic of their relative configuration. The antiperiplanar axial-axial orientation of hydrogen atoms results in $J_{2a,3a}$ or $J_{3a,4a}$ in the range 9.0 to 9.9 Hz. The synclinal arrangements of axial-equatorial and equatorial-equatorial hydrogens atoms are readily assignable, with axial-equatorial couplings typically 3.5-5.0 Hz and equatorial-equatorial less than 2.5 Hz. For $J_{1,2}$ the -I effect lowers both $J_{1,2a}$ and $J_{1,2e}$ to the range 1.5 - 2.5 Hz. The assignment of the proton signals is usually possible as they tend to be spread over several ppm. The H-1 resonance is always obvious as it resonates at lowest field due to the -I effect of the neighbouring acetal group. In compound (69) the couplings $J_{3,4}$ and $J_{4,5}$ are typical of an equatorial-equatorial arrangement of hydrogen atoms indicating the D-gluco conformation shown. As the 3-S-phenylthio group is axially orientated it has not been introduced by a simple S_N2 mechanism. A carbonium ion intermediate is unlikely, as this would probably suffer exo attack to yield an equatorial 3-S-phenylthio group.

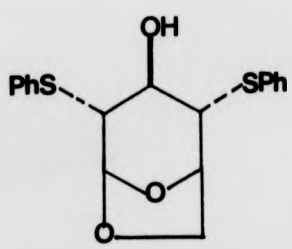
The intermediacy of the episulfonium ion (70) seems more likely.

In an attempt to minimise the extent of formation of (69), a variety of other acid catalysts were examined. Amberlite IR 120 acid ion exchange resin in refluxing benzene led to a very slow reaction with concomitant cleavage of the 1,6-anhydro bridge. Several carboxylic acids were examined. Acetic and trichloro-acetic acids caused darkening of the solution and a low yield of (65), but trifluoroacetic acid was found to work well, giving a good yield of (65) accompanied by about 10% of the di-thio compound (69). Attempts were made to optimise this trifluoroacetic acid-catalysed reaction by varying the solvent, time, and temperature of reaction, but conditions could not be found which precluded formation of (69).

Recently a convenient method for cleavage of epoxides using the Lewis acid, alumina, has been developed by Posner and Rodgers.[42] This involves treating the epoxide with neutral alumina which has been doped with about 4% of the nucleophilic reagent, and normally results in stereospecific ring-opening. Cyclohexene oxide has been successfully cleaved by thiophenol using this method. Application to the epoxide (28) led to isolation of three products, namely (65), (72) and (73) in yields of 20%, 5%, and 20% respectively.



(72)

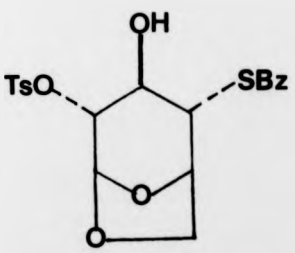


(73)

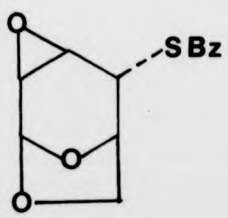
The configuration of these compounds was conclusively proven by NMR decoupling experiments.

The products obtained are in fact those expected from a base-catalysed reaction, in which the alkoxide ion of (65) can lead to (72) by internal displacement of tosylate. Posner has postulated that adsorption of compounds of the type R-X-H onto alumina will cause heterolytic cleavage of the heteroatom-hydrogen bond ($RX^- + H^+$), thus enhancing the nucleophilicity and basicity of the heteroatom. This idea seems to be confirmed by the products obtained from (28) detailed above.

Under base-catalysed nucleophilic attack the epoxide (28) normally reacts by the previously mentioned sequence to eventually produce the 2,4-disubstituted gluco pyranose. This holds true for sulphur nucleophiles, as Vegh and Hardeggar[43] have isolated compounds (74) to (76) from reaction of the epoxide (28) with the sodio derivative of benzyl mercaptan.



(74)



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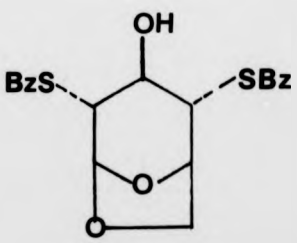
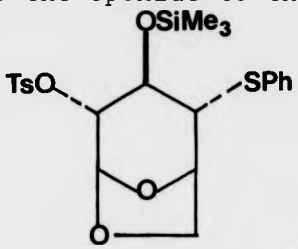


(76)

On reaction of (28) with sodium thiophenoxide, the expected analogous products (65), (72) and (73) were obtained. The formation of the epoxide (72) appeared to be the rate limiting step, but attempts to utilise this fact, and halt the reaction at this point proved unsuccessful.

If one could trap the alkoxide anion of (65) on its formation, then reaction should halt here. The recent success of trimethylsilane-based reagents e.g. iodotrimethylsilane and cyanotrimethylsilane suggested the possible use of phenylthiotrimethylsilane to cleave the epoxide to the β-O-trimethylsilyl-hydroxy sulphide (77).



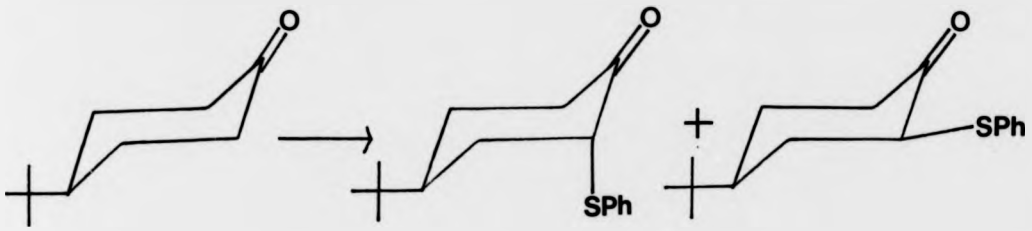
(77)

Phenylthiotrimethylsilane is known,[44] and by analogy with other silicon-sulphur compounds should be an active silylating agent for alcohols.[45] It was found possible to form phenylthiotrimethylsilane in situ by mixing chlorotrimethylsilane and sodium thiophenoxide in tetrahydrofuran. A white precipitate, presumably of sodium chloride, formed, leaving a clear solution of the thio-silane. Unfortunately this was found to be an insufficiently strong nucleophile to effect cleavage of the epoxide (28). However, if excess thiophenoxide anion was present, this did cleave the epoxide whilst the phenylthiotrimethylsilane acted as the silylating agent. In this way a 95% yield of (65) was realised, the product being uncontaminated with (72) or (73). Although in this case, with the hindered epoxide (28), reaction with phenylthiotrimethylsilane is very slow, the reagent may prove useful for the cleavage of unhindered epoxides to β-hydroxy sulphides under mild neutral conditions.

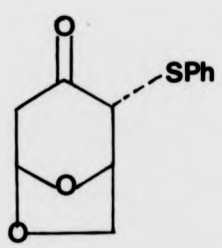
Reduction of the 4-thio compound (65) with lithium triethylborohydride was straightforward and proceeded to give a good yield of (66), isolated as a crystalline solid. TLC indicated that this reduction went via the 2,3-epoxide (72) as expected. The identity of this compound was confirmed by isolation and characterisation, from a partially completed reaction. In contrast to the unsubstituted 2,3-epoxide (204), the reduction of (72) is completely regiospecific. Presumably this is due to steric hindrance to attack at the 3-position by the axial 4-substituent.

Sulphides are readily oxidised, so before attempting conversion of (66) to (67), a model experiment was done to determine if thioanisole was oxidisable by pyridinium chlorochromate. It was found that over three hours, 25% of the thioanisole was oxidised as shown by NMR analysis of the product. As oxidation of (66) should require only about 45 minutes, secondary oxidation of the sulfide should occur to a minor extent only. In fact, oxidation of (66) proceeded to give a good yield of the ketone. It was found that the slightly acidic nature of the oxidation conditions caused isomerisation of the thiophenyl group to the equatorial orientation, so that the isomeric ketones (67) and (78) were isolated in the ratio 0.8 : 1.0. Attempts to isomerise the remaining axially substituted ketone (67) in the mixture with both acid and base proved unsuccessful, so presumably this is the equilibrium distribution. It is unusual that such a large amount of the apparently thermodynamically less stable isomer (67) should be present at equilibrium. Trost and Bridges have found that in the absence of severe steric interactions, a phenylthio group

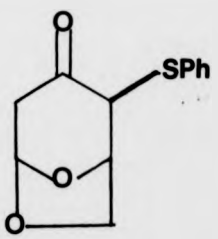
situated alpha to a ketone in a cyclohexane ring prefers to be axial.[46] On sulfenylating ketone enolates this phenomenon was also apparent,[47] e.g. both 4-tert-butyl cyclohexanone and 2-methyl cyclohexanone produced equilibrium mixture containing the compounds having an axially or equatorially orientated thiophenyl group in the ratio 2:1 respectively.



The phenomenon is probably related to the α-halo effect known for α-halo ketones.[48] In these compounds the halo substituent prefers to be axially orientated, as this relieves an unfavourable electrostatic interaction between the carbonyl and C-X dipoles.



(67)

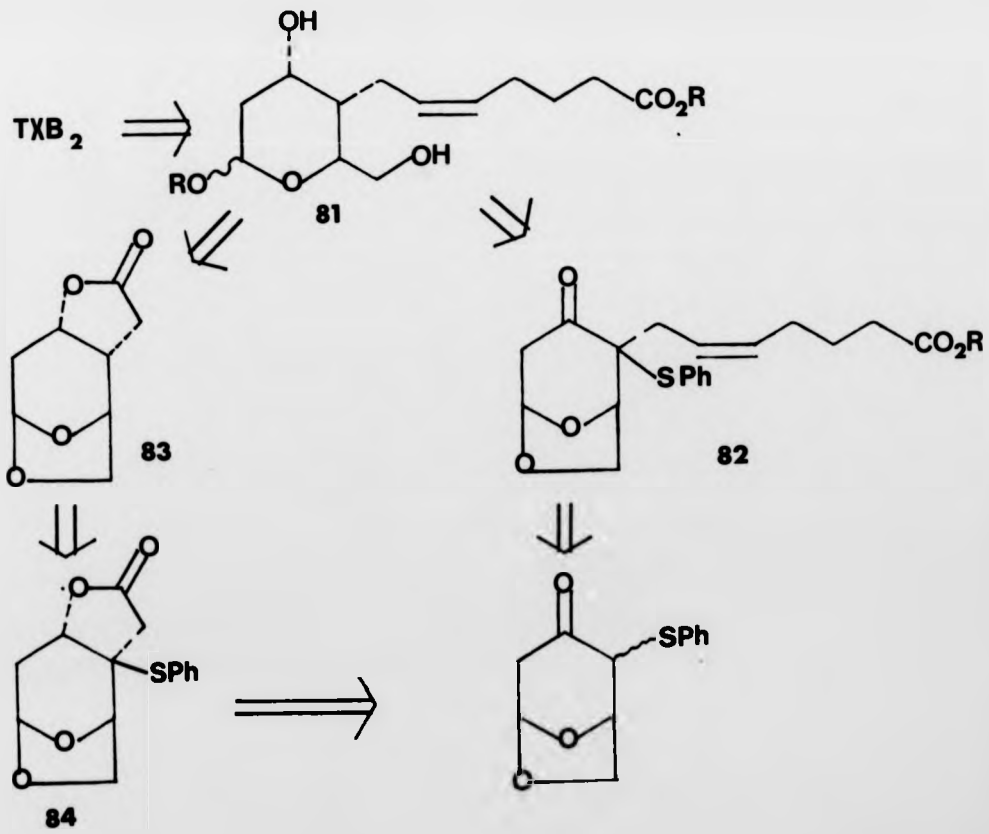


(78)

Separation of the two ketone isomers was not strictly necessary as the asymmetry of C-4 is lost on enolisation, however it was possible to effect a separation by multiple crystallisation. The threo isomer (78) remained in the mother liquors.

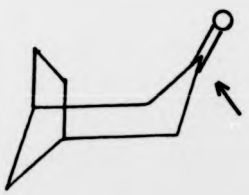
The isomerisation of (67) could be prevented by buffering the pyridinium chlorochromate with sodium acetate, and avoiding its exposure to silica or alumina during purification.

Alkylation of either ketone isomer should result in exo attack to yield the compound with an axially orientated alkyl substituent, required for elaboration into TXB_2. Two approaches to TXB_2 utilising these ketones are possible. Alkylation can be used to introduce either, a convenient carbon unit suitable for elaboration into the full carboxylic acid side-chain, or the intact side chain itself, Scheme 18.

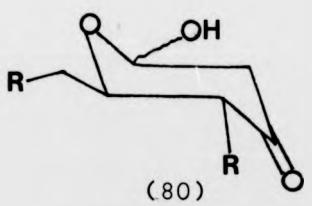


Scheme 18

Both approaches present the problem of controlling the stereochemistry at C-3, on reduction of the ketone function. Reduction of the analogous ketone group at C-9 of the primary prostaglandins with hindered trialkylborohydrides, has shown that the major directing influence comes from the adjacent alkyl substituent on C-8.[49] This directs attack from above to give the α-orientated alcohol. In the bicyclic system the analogous substituent on C-4 will again direct attack from above to give the α-alcohol. In this case, however, the 1,6-anhydro bridge may exert an equal or greater influence in the opposite direction causing <u>exo</u> attack and giving the β-alcohol, e.g. in bicyclo[3,2,1]octan-3-one (79), it is known that attack on the ketone group by large reagents is exclusively <u>exo</u>.[50]



(79)



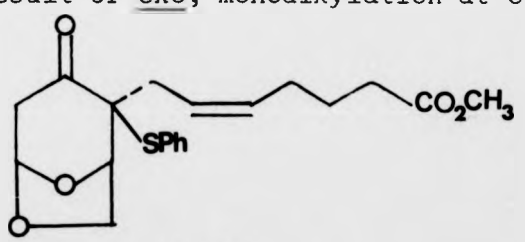
(80)

If one cleaves the anhydro bridge, the tetrahydropyranyl ring immediately flips into the $^4C_1$ conformation with the side chains equatorial (80). This compound has a conformation analogous to that of the primary prostaglandins and will probably be reduced stereoselectively in the same manner. In the synthetic scheme it therefore becomes necessary to open the bicyclic system before reduction of the ketone. This means the development of two hydroxy groups, at C-9 and C-13 (thromboxane numbering), with the resultant necessity for several extra protection and de-protection steps.

Alkylation of (67) with the intact carboxylic acid side chain offered a short route to (81) so this route was investigated. The alkylating agent chosen was methyl 7-bromo-cis-5-heptenoate. This was synthesised from propargyl alcohol in an overall yield of 28% as shown in Scheme 19. This route was based on a synthesis of methyl 7-iodo-5-heptynoate by Corey et al.[51]

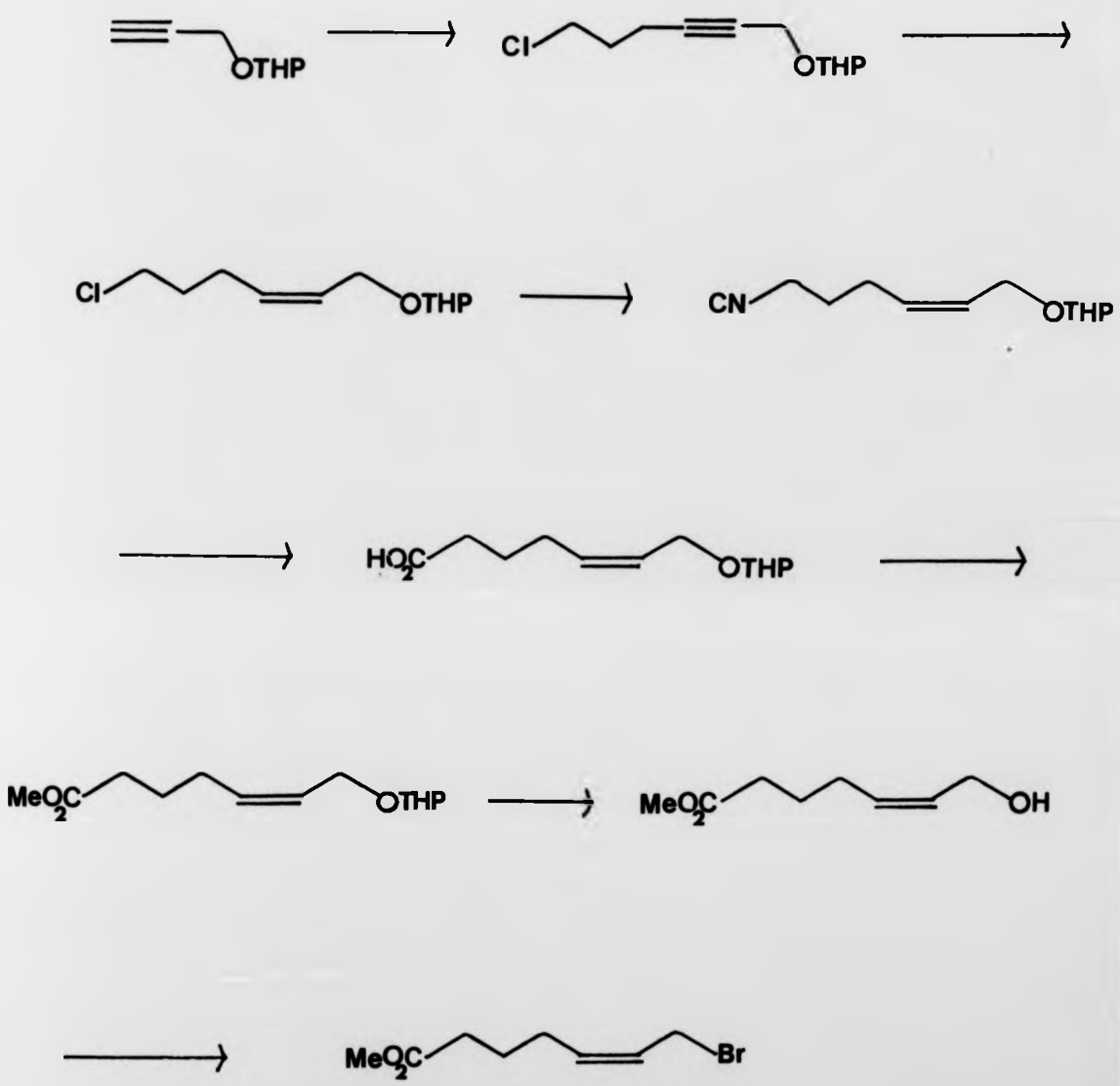
Complications arising from the presence of an ester moiety were not anticipated, as the enhanced acidity of the α-thio-ketone should lead to its reaction preferentially over proton abstraction from the ester moiety.

On reaction of the bromide with the enolate derived from (67) by treatment with sodium hydride, for twenty hours at room temperature (82) was obtained in 42% yield. Only this compound, the result of exo, monoalkylation at C-4 was present.

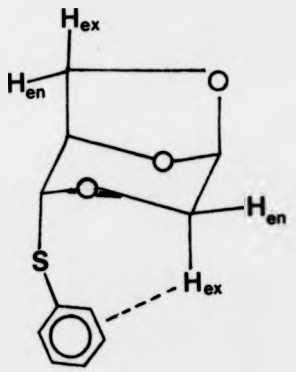


(82)

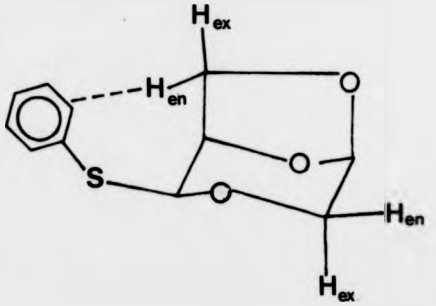
The configuration at C-4 could not be established by NMR decoupling experiments as it is a quaternary centre. The configuration assigned was indicated by analogy with the isomeric ketones (67) and (78). These show chemical shifts in their proton NMR spectrum, arising from deshielding of the C-2 and C-6 methylene protons by the thiophenyl group. This deshielding effect has been noted in analogous α-thio cyclohexanones.[46]


OTHP
Cl
OTHP
Cl
OTHP
CN
OTHP
HO2C
OTHP
MeO2C
OTHP
MeO2C
OH
MeO2C
Br

Scheme 19



(67)



(78)

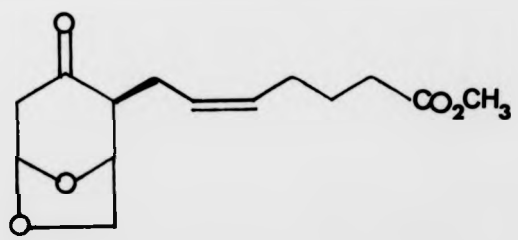
	(67)		(78)		(82)	
	δ	Δδ	δ	Δδ	δ	Δδ
H-2 ENDO	2.49		2.70		2.60	
		0.6		0.0		0.0
$H\text{-}2_{EXO}$	3.10		2.70		2.60	
$H\text{-}6_{ENDO}$	3.86		4.26		4.15	
		0.0		0.5		0.5
$H\text{-}6_{EXO}$	3.86		3.75		3.65	

In compound (67), with the thiophenyl group axial, $H\text{-}2_{EXO}$ experiences deshielding and moves downfield, whilst $H\text{-}6_{ENDO}$ is unaffected.

In compound (78) with the thiophenyl group equatorially orientated, $H\text{-}6_{ENDO}$ suffers deshielding whilst the C-2 protons remain undisturbed. In the alkylation product (82), the difference in chemical shift of the C-2 protons is under 0.1 ppm whereas that of the C-6 protons is about 0.4 ppm. These figures

are similar to those for the ketone (78), indicating an equatorial orientation for the thiophenyl group. The alkylation was also performed using potassium hydride as base. This resulted in a cleaner reaction to produce (82) in an isolated yield of 63%.

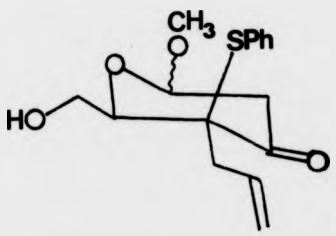
At this point methods for removal of the thiophenyl group were investigated, these being aluminium-mercury amalgam,[52] sodium-mercury amalgam[53] and Raney nickel. Reduction did not occur with aluminium-mercury amalgam. Sodium-mercury amalgam was used in a solution buffered with disodium hydrogen phosphate and caused complete reduction even at 0°C, to yield several products from which the desulphenylated ketone could be isolated in only low yield. This material appeared to have the structure (85) confirmed by proton NMR decoupling, i.e. $J_{4,5} \sim 4$ Hz, indicating an axial proton on C-4. The side chain has isomerised



(85)

to the equatorial orientation. Deactivated 'W2' Raney nickel was the most successful method, again giving (85), this time in 80% yield. The isomerisation by Raney nickel was predictable as the mechanism of the reduction is thought to involve free radicals and can allow racemisation to take place at the centre to which carbon is attached. The large alkyl side chain will thus be able to epimerise to the thermodynamically more stable

equatorial form. Isomerisation could be avoided by converting the compound to the $^4C_1$ conformation by cleaving the anhydro bridge (86). With the alkyl side-chains now equatorial and the thiophenyl group axial, reduction with Raney nickel should have no effect on the C-4 substituent.



(86)

To test this idea, cleavage of the 1,6-anhydro bridge of (82) was attempted using p-toluenesulphonic acid in methanol. This was unsuccessful as the prolonged reaction period necessary caused the mixture to blacken and led to no identifiable products. Investigation into this route was terminated at this point.

The second approach utilising the α-thio-ketones involved the synthesis of the tricyclic lactone (83), as outlined in Scheme 18. Of the various possible routes to this lactone, the alkylation of (67) with potassium iodo-acetate and methyl bromoacetate were investigated in the first instance. Potassium iodo-acetate had been used by Brownridge and Warren[54] who found it gave better yields than did halo-esters. On mixing this reagent with the enolate derived from (67), no reaction occurred even after prolonged reflux. The ketone (67) is

sterically hindered and requires a long reaction time with most alkylating reagents. It is probable that the iodo-acetate reagent is insufficiently reactive for reaction with (67) to occur, this being due to an electrostatic repulsion between the enolate and the acetate anion. Methyl bromoacetate did react as expected to give a good yield of the C-4 mono-alkylated product. This was again shown to consist of only one isomer by TLC and ^{1}H NMR spectroscopy. The establishment of the configuration at C-4 was not straightforward as both the C-2 and C-6 methylene groups were non-equivalent with $\Delta\delta$ H-2 $\sim$ 0.26 ppm and $\Delta\delta$ H-6 $\sim$ 0.34 ppm. It appeared likely that as in the previous alkylation, reaction has occurred from the exo side to produce (87). The splitting of the C-6 protons would therefore be due to an equatorially orientated thiophenyl group as in (78) and (82), whilst that of the C-2 protons must be due to deshielding by the ester group.

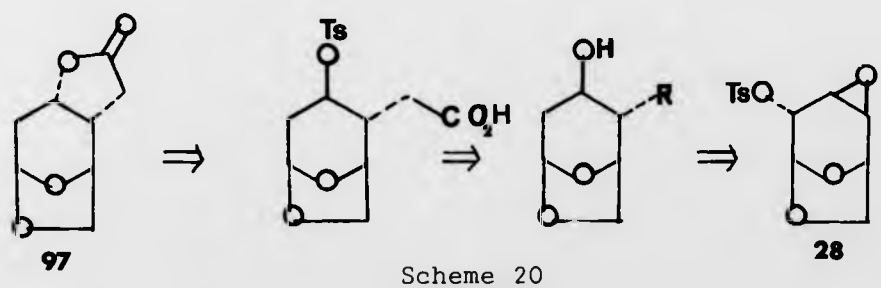
Conversion of (87) into the lactone (84) should be possible either by reduction of the ketone group to the β-orientated alcohol, tosylation, and subsequent displacement by carboxylate anion,[55] or by a sequence involving treatment of the keto-acid derivative of (87) with sodium acetate and acetic anhydride to produce an enol acetate, which could be reduced to the lactone.[56] As the first step in the latter sequence, the ester (87) was subjected to aqueous sodium hydroxide, in an attempt at de-esterification. However, these conditions proved too vigorous and resulted in the formation of several products some lacking the thiophenyl group. A small amount

of material was tentatively identified as the desired keto-acid, mainly based on infra-red evidence [ν 1725 and 1625 cm^{-1}]. The strong absorption at 1625 cm^{-1} was interpreted as resulting from the chelated enol tautomer of the keto-acid.

Investigation into this route was terminated here. Hopefully, with further work the above routes would have proven successful. The strategy for elaboration of (82) into (81) seems reasonably certain, whilst conversion of (81) into TXB_2 simply involves standard methodology. The route is unsatisfactory however in that the asymmetry of C-3 of the carbohydrate precursor is destroyed during the synthesis and must subsequently be re-established. A more elegant route would utilise the asymmetry at C-3 of the sugar to develop the required α-orientated alcohol. This aim has been achieved in the synthesis of the TXB_2 synthon described in the following chapter.

4. SYNTHESIS OF THE TXB_2 SYNTHON, METHYL 2,4-DIDEOXY-4-C-CARBOXYMETHYLENE-β-D-XYLO-HEXOPYRANOSIDE-γ-LACTONE (24)

The epoxide (28) reacts with most heteroatomic nucleophiles in the 'normal' manner to produce diaxial products with the D-gluco configuration. It follows that reaction with a suitable carbon nucleophile should lead to the introduction of an axially orientated alkyl chain at C-4, suitable for elaboration into TXB_2. As was the case for the ketone (67), the alkyl substituent can be either the complete protected side chain, or can be a two carbon synthon suitable for formation of the lactone. The latter strategy is more suitable in this case, as the presence of an axially orientated hydroxyl group at C-3 lends itself to formation of a lactone by an intramolecular displacement of a suitable derivative, by carboxylate anion, as shown in Scheme 20.



Scheme 20

This approach allows stereochemical control of the asymmetric centres at C-3 and C-4 of the sugar molecule, to produce the TXB_2 synthon (24) in a completely stereocontrolled manner.

The key step in the scheme is the alkylation of the

tosyl-epoxide (28). This is required to proceed normally (i.e. to give a di-axial product), and without involvement of the tosyl substituent present on C-2. No reports of this type of alkylation of epoxy derivatives of levoglucosan exist in the literature, although this approach has been used to introduce alkyl chain branching in other sugars, e.g. the previously described syntheses of 11-oxa prostaglandins.[9,10] Regio-selective ring opening of cyclopentane epoxides has been used to introduce precursors of the prostaglandin side chains.[57] Allylic cyclopentene epoxides have also been utilised.[58]

Several organo-metallic reagents were examined for suitability in this reaction including derivatives of sodium, lithium, magnesium, and copper. The widely used sodio-dimethyl-malonate was found to require vigorous conditions for reaction with the epoxide. These resulted in cleavage of the tosyl group to the alcohol, as well as reaction of the epoxide, to yield apparently a di-hydroxy acid [(ν 3600 (OH), 3480 (OH) and 1722 cm^{-1} (CO_2H)]. This material was difficult to purify, and was not fully characterised.

A more nucleophilic reagent was obviously required, and thus the lithio and copper lithio derivatives of ethyl acetate were examined. Using the procedure of Ratkhe,[59] lithio-ethyl acetate was generated from bromo-ethyl acetate at -78°C. It was found that this material did not react with the epoxide over the temperature range -78°C to 0°C, the upper temperature being the stability limit for the reagent. Copper-lithium dialkyls are known to possess enhanced reactivity

over lithium alkyls, and may be capable of overcoming the steric constraints which appear to be the most likely cause of the unreactivity of the epoxide (28). Accordingly, the preparation of the copper-lithium derivative of ethyl acetate, $\{Li[Cu(CH_2CO_2Et)_2]\}$ was attempted. As no previous syntheses of this compound could be found in the literature, the method used was an adaptation of that for di-allyl copper lithium.[49a] The material thus obtained failed to react with the epoxide over the temperature range -78°C to 0°C, the epoxide being recovered unchanged. The most likely cause for the failure of these reactions is the decomposition of the organo-metallic reagents, either by ccupling, or by condensation reactions. To minimise this problem, an alternative strategy was adopted, namely, the introduction of an allyl group. Metallo allyl compounds are also prone to coupling reactions, but their extent is much less than with the ester reagents e.g. the allyl Grignard reagent is quite stable up to 0°C. The formation of π-bonded complexes is possible with the allyl ligand, these often being relatively stable. The epoxide (28) was initially treated with allyl magnesium chloride, prepared according to the method in Organic Syntheses,[60] but this failed to cause any reaction. Mukaiyama[61] has reported that the addition of one equivalent of titanium tetrachloride causes normally unreactive aliphatic α,β-unsaturated acetals to react with Grignard reactions, producing allylic ethers. The titanium tetrachloride was thought to be functioning as a Lewis acid, complexing with the acetal oxygens and thus aiding the removal of one. One could envisage a Lewis acid increasing the

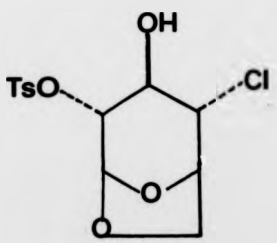
reactivity of an epoxide in the same manner, by complexing with the oxygen atom of the epoxide ring. This idea was tested by repeating the reaction of (28) with allyl Grignard, this time in the presence of one equivalent of aluminium trichloride. After addition of the chloride, the Gilman test[62] proved negative, so presumably the Grignard reagent had been removed from the solution either by an exchange reaction with the aluminium, i.e.

$$RMgBr + AlCl_3 \rightarrow RAlCl_2 + MgBrCl$$

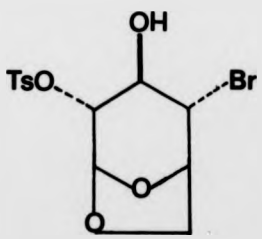
which seems unlikely, on the basis of known organoaluminium chemistry,[63] or a coupling reaction has occurred, i.e.

$$2RMgBr \rightarrow R\text{-}R + MgBr_2 + Mg \ .$$

The material produced did, in fact, react with the epoxide over two days at room temperature to give a 71% yield of an inseparable mixture of (90) and (91).



(90)

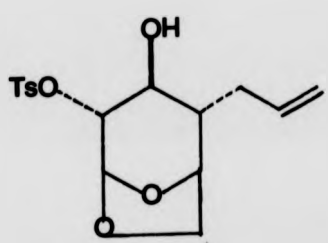


(91)

The presence of two compounds in the product was revealed by proton NMR spectroscopy. The presence of an axial substituent at C-4 in both compounds was demonstrated by the low value of $J_{4,5}$ (1-2 Hz). The confirmation that these substituents were halide atoms was obtained by MS analysis.

The spectrum of the mixture showed two peaks of equal intensity at m/e 225 and 223 corresponding to loss of a tosyl group from (91) and two peaks at m/e 179 and 181 in the ratio 3:1, corresponding to loss of a tosyl group from (90). No trace of the desired C-alkylated compound could be found. Aluminium alkyls are known to be relatively nucleophilic, so the absence of any C-alkylated product argues against their formation.

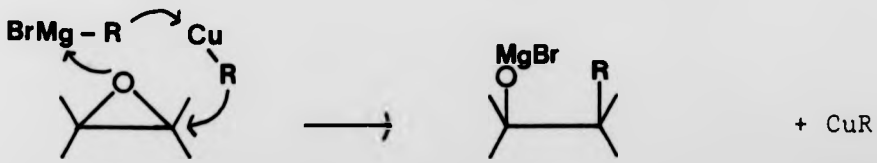
A recent report by Linstrumelle[64] et al., described the catalytic effect of the presence of a small amount of copper(I) iodide on the reaction of Grignard reagents with epoxides. Salts of copper and other transition metals have long been known to influence Grignard reactions. Early work concentrated on their effect on the position of addition to enones,[65] however their general utility was soon recognised and extended to coupling reactions of Grignard reagents,[66] and to the reactions of lithium alkyls.[67] The effect of adding about 10 mole % of copper(I) iodide to the reaction of (28) with allyl magnesium chloride was dramatic. At 0°C, complete reaction occurred over twenty-four hours to produce the desired product (92) in about 90% yield. TLC indicated the presence of a small amount of two more polar products, both lacking tosyl groups. To date their structures have not been elucidated.



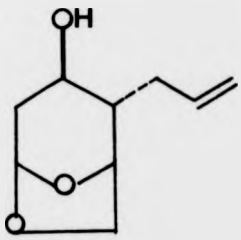
(92)

The catalytic effect of copper(I) salts on Grignard reactions has been known for a long time and much effort has been devoted to elucidation of the nature of the catalyst and the mechanism of the reaction. It is known that alkyl lithium or Grignard reagents, on addition to one equivalent of copper(I) iodide below 0°C, produce alkyl copper e.g. methyl copper has been isolated as an unstable polymeric material,[68] whilst phenyl copper separates from the solution as a grey powder.[69] Most alkyl copper compounds are stable below 0°C, and are known to be appreciably more stable in tetrahydrofuran than in ether.[66b] In the presence of excess methyl lithium, a lithium dialkyl cuprate species, solvated by solvent molecules, is known to form[67] i.e. $Li[CuR_2].(EtO)_n$, whilst the phenyl compound forms a complex of type $[Ph_4Cu]PhLi.Et_2O_{3.5}$.[69] The identity of the reactive species formed from excess Grignard reagent and copper(I) iodide is much less certain. It does not appear to be of the form $MgBr[CuR_2]$,[67] but appears to contain mono-alkyl copper(I) species. These however do appear to form some type of complex with the excess Grignard reagent, this complex being solvated by the solvent present.[66a] In the absence of oxygen this complex seems to be indefinitely stable.

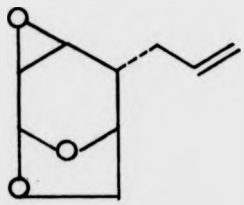
The mechanism of this reaction can be represented, in a greatly simplified form, as involving nucleophilic attack on the epoxide by the copper alkyl, with regeneration of the copper alkyl by one mole of Grignard reagent, i.e.



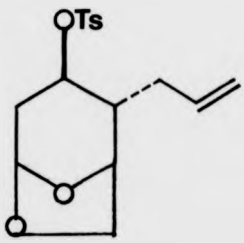
The reduction of (92) with lithium triethylborohydride was straightforward, and resulted in an 85% yield of (93). As expected, this reaction went via the epoxide (94), which reacted regiospecifically, in an analogous manner to the reaction of the thio-epoxide (72). This demonstrates that steric hindrance by an axial substituent at C-4, to <u>exo</u> attack at C-3 is a general phenomenon.



(93)



(94)

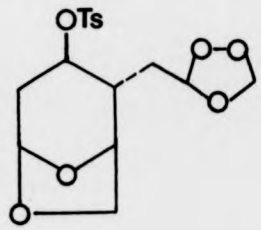


(95)

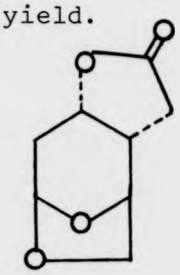
Tosylation of the alcohol (93) proceeded normally to yield the highly crystalline tosylate (95). The planned synthetic sequence required oxidative cleavage of the double bond to a carboxylic acid moiety, and in order to accomplish this, several methods were tried, with varying success.

The classic Lemieux method using potassium permanganate and sodium metaperiodate in aqueous tert-butanol produced no isolable products. Ozonolysis[70] was an attractive alternative due to the ease of work-up involved. This was first attempted in dichloromethane, which should allow formation of the ozonide, and indeed the tosylate (95) reacted rapidly to give one product, presumed to be the ozonide (96). The method chosen for decomposition of the ozonide was an oxidative one, involving treatment with alkaline hydrogen peroxide. This should have produced the carboxylic acid, but in fact, had no effect on (96).

On heating the solution to 80°C, the ozonide did decompose, probably by thermal breakdown, to give several products, of which the only isolable one was identified as the tricyclic lactone (97), obtained in 20% yield.



(96)

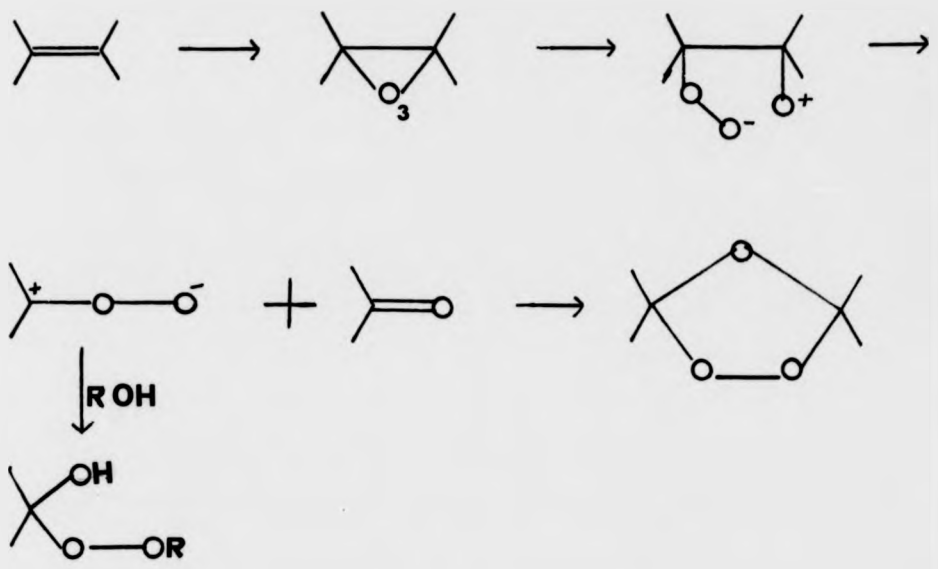


(97)

This material had a characteristic infra-red absorption at 1760 cm^{-1}, and proton coupling constants (determined by decoupling experiments) of $J_{2\alpha-3} \sim 8$ Hz, $J_{2\beta-3} \sim 8$ Hz, $J_{3,4} \sim 3$ Hz and $J_{4,5} \sim 1.5$ Hz. These indicate that the substituents at C-3 and C-4 are equatorial and axial respectively. The identical a-a and e-a values of the $J_{2,3}$ coupling constants indicate that the chair conformation of the 6-membered ring is slightly flattened.

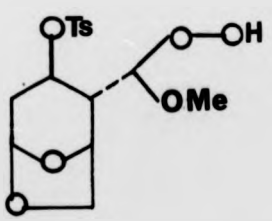
As the ozonide (96) appears to be exceptionally stable, the reaction was repeated under conditions which would prevent its formation. This involved using a reactive solvent (methanol) to trap the zwitterion (98) and produce an alkoxy hydroperoxide, Scheme 21.

Alkoxy hydroperoxides are susceptible to hydrolysis to the aldehyde, although their decomposition can sometimes require more vigorous oxidising or reducing conditions. Ozonolysis of (95) in methanol produced a relatively polar

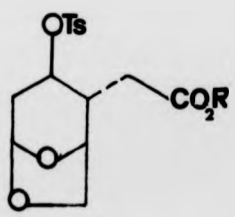


Scheme 21

product which was not isolated, but presumed to be (99). Decomposition was accomplished with the reducing agent, sodium sulphite. This resulted in two new products being formed, which were directly oxidised with alkaline hydrogen peroxide. This produced a mixture of products, three of which were separated and identified as the lactone (97), the ester (100), and the hydroperoxide (99) in respective yields of



(99)

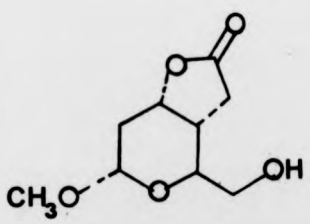


(100) R = Me
(101) R = H

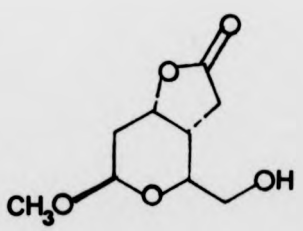
5%, 5%, and 20%. The main evidence for the proposed structure (100) was a carbonyl absorption of 1727 cm^{-1} in the infra-red spectrum, a methoxy singlet at δ 3.68 in the ^1H NMR spectrum and a high resolution mass determination of the molecular ion of (100), which confirmed the molecular formula. The compound assigned as the methoxy hydroperoxide, oxidised potassium iodide solution, exhibited a strong infra-red absorption centred on 3,400 cm^{-1} (characteristic of hydroperoxides), and had a methoxy singlet at δ 3.49 in the ^1H NMR spectrum. It has previously been found that reduction of alkoxy hydroperoxides by redox processes can result in a mixture of products, including esters, aldehydes and alkanes.[71] It therefore seems likely that the ester (100) results from the reduction of (95) by sulphite. There would presumably also be some aldehyde formed, which would be converted to the acid (101) by the subsequent peroxide oxidation, and could spontaneously lactonise to give (97). In view of the difficulties encountered in the decomposition of these peroxy-compounds, it was decided to investigate some other reagents. The two others commonly used for oxidative cleavage of double bonds are based on osmium tetroxide and ruthenium tetroxide in combination with sodium metaperiodate. Only a catalytic amount of the transition metal oxide is needed, as the metaperiodate can continuously reoxidise it from the +4 to the active +8 oxidation level. Use of the somewhat less toxic ruthenium dioxide in aqueous acetone was surprisingly and gratifyingly successful, causing complete reaction of (95) in 1½ hours to give the desired lactone (97) in 90% yield, as the only product. The presumed intermediate in this reaction is

the carboxy-tosylate (101), although neither this nor any other intermediate was detected by t.l.c. As the reaction mixture becomes quite acidic, the acid moiety will presumably react to form the lactone. It is unlikely that protonation of the tosyl group is necessary for its displacement, as performing the reaction with a buffer present (which maintained the pH above 6), did not hinder the lactonisation step.

In achieving the synthesis of the tricyclic lactone (97), the main stereochemical problems involved in producing TXB_2 had been overcome. The substituents at C-3, C-4, and C-5 of the ring were now correctly orientated for elaboration into TXB_2 by standard methodology. To reach the known synthon (24), all that remained was deprotection of the C-6 primary hydroxyl group by cleavage of the 1,6-anhydro bridge. Literature examples[72] had indicated that Amberlite IR 120 acid ion-exchange resin, was a suitable catalyst for this transformation. However, on performing the reaction with (97) the expected product was obtained (as a mixture of the α and β anomers), in a yield of only 45%.



(24)



(102)

In an attempt to improve the yield, several milder acid catalysts were examined.

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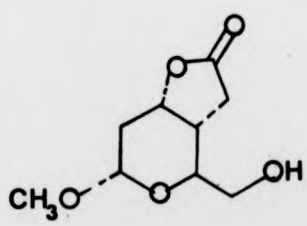
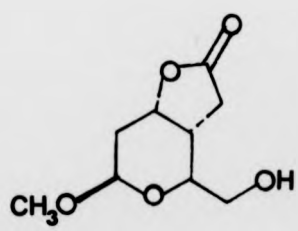


(24)

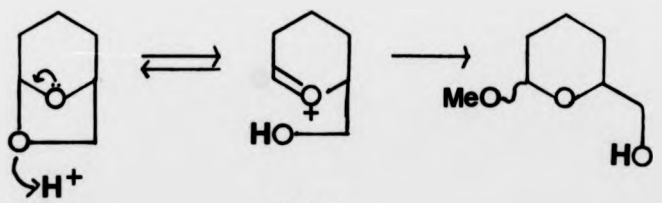


(102)

In an attempt to improve the yield, several milder acid catalysts were examined.

Pyridinium tosylate has been reported as being a catalyst for acetal exchange.[73] On its application to the reaction of (97) with methanol, however, only a small amount of (24) and (102) was formed after a substantial time period. Lanthanide metal chlorides are apparently very effective catalysts for acetal formation.[74] In the expectation that they might also be catalysts of acetal exchange, cerium(III) chloride heptahydrate was reacted with a solution of (97) in methanol, containing trimethyl orthoformate as a water scavenger, but after two days, no change had occurred.

It appears from the above results that a reasonably strong acid catalyst is necessary, in order to force the equilibrium over to (103), and lead to the methoxy-acetal



(103)

products. This final step should not be reversible as ring flip occurs on formation of (24) and (102), as will be discussed later. The resultant $^{4}C_{1}$ conformation does not permit formation of a 1,6-anhydro bridge. Amberlite IR 120 resin is based on sulphonic acid, but is not particularly suitable for this reaction, as it is meant to be used in aqueous solutions. It is a cross-linked polystyrene gel-type resin, and normally contains 49-55% water, necessary to maintain its pore structure. When this water is removed, as was done for use in the reaction of (97), considerable shrinkage occurs, with the result that

diffusion of solvent and substrate through the resin is considerably reduced, with concomitant loss of some catalytic activity. A comparable resin suitable for non-aqueous solutions is however available. Amberlyst 15 acidic ion-exchange resin is also based on sulphonic acid, but is a macro-reticular resin, with large pores which do not disappear when the swelling solvent, water, is removed. In fact the commercially available form contains only 1% water. Amberlyst 15 should therefore possess much greater catalytic activity than the dried form of Amberlite IR 120, and possibly lead to a faster, cleaner reaction. Indeed, the resin led to complete reaction in a quarter of the time, and resulted in a 81% isolated yield of (24) and (102).

The ratio of (24) and (102) thus obtained was 1.55:1.0. The preponderance of the α isomer is in accord with the anomeric effect which stabilises axially orientated polar groups at the anomeric position, but the anomeric effect does not normally manifest itself in polar solvents. In work reported by Brown et al.,[72] the epoxide (43) was treated with Amberlite IR 120 resin in refluxing methanol to produce the α and β methoxy anomers in the ratio of 2:1, the α anomer predominating as was the case with (97). The α-anomer thus obtained, on treatment with hot aqueous sulphuric acid in dioxane yielded a 1:1 mixture of the hemiacetals which on standing for 6 hours in D_2O muta-rotated to a mixture of the α and β anomers in the ratio of 1:2. The preponderance of the α anomer obtained from reaction of the bicyclic compounds (43) and (97) appears from the above results to possibly be due to steric effects. The intermediate oxonium ion (103) will, before ring flip occurs, be in the $^1C_4$

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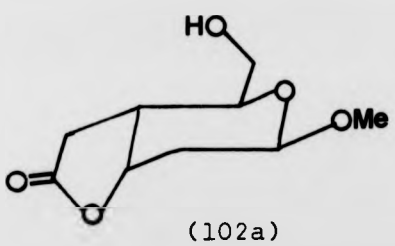
conformation with C-6 axially orientated. This group may well hinder nucleophilic attack from the β face of the molecule. In the methoxy acetals in a $^4C_1$ conformation, no steric hindrance to attack at C1 is present, so equal amounts of both anomers are formed.

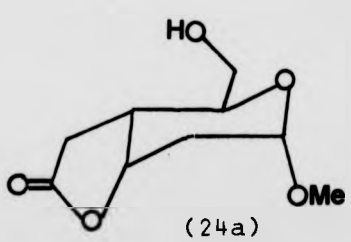
The two isomeric alcohols (24) and (102) were readily separated by the technique of flash chromatography.[75] The α-methoxy anomer was obtained as an oil (several reports of this being a crystalline compound exist[76]), and the β-methoxy anomer as a crystalline solid. These compounds possessed identical infra-red and proton NMR spectra to those reported in the literature.[77,78,2,3,4]

The α-methoxy anomer had identical TLC mobility to that of an authentic sample.[79] In addition, the α-anomer was converted quantitatively into the known p-phenylbenzoate derivative which had a slightly higher melting point and optical rotation than the values quoted.[80]

The proton NMR spectra of these alcohols were extensively investigated, both by resonance decoupling experiments and by the lanthanide shift technique. The coupling constants obtained are shown in Table 1. These make it apparent that ring inversion has occurred, from the $^1C_4$ of the 1,6-anhydropyranose to the thermodynamically more stable $^4C_1$ forms (24a) and (102a).



(102a)



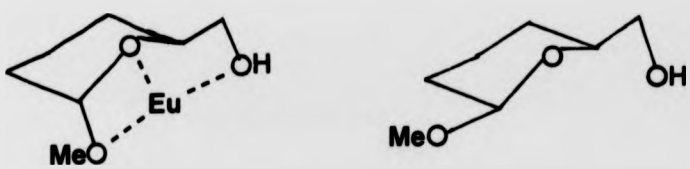
(24a)

The coupling constants demonstrate that H-1 is axial in the β anomer ($J_{1,2ax} \sim 10$ Hz), and equatorial in the α anomer ($J_{1,2} \sim 3$ Hz), that H-3 is equatorial ($J_{2,3} \sim 2.5$ Hz), and that H-4 and H-5 are both axial ($J_{4,5} \sim 10$ Hz).

The chemical shifts of the proton resonances in both anomers are identical, apart from those for H-1 and C-2 methylene protons. Table 2 lists these. The shift in the resonance of H-1 is a result of the orientation of the geminal methoxy group. It is known that equatorial protons on a carbon bearing a polar substituent in a cyclohexane ring usually resonate at lower field than their axial counterparts, the shift usually being 0.1 to 0.2 ppm. The chemical shift differences of the C-2 protons in the two anomers also find analogy in reported work.[81] It is known that a polar axial substituent causes the resonance of a vicinal equatorial proton to move upfield by 0.1 to 0.3 ppm, and that of an axial proton to move downfield by about 0.3 ppm. A polar equatorial substituent causes the resonance of both axial and equatorial vicinal protons to move upfield by up to 0.3 ppm. Thus for the axial H-2 proton the change in chemical shift caused by altering the orientation of the vicinal anomeric methoxy group from equatorial (β) to axial (α) cause a downfield shift of 0.34 ppm, whilst the equatorial H-2 proton experiences an upfield shift of 0.2 ppm, in agreement with reported values.

The lanthanide shift reagent $Eu(fod)_3$ was used to help identify the resonance position of poorly resolved signals and to obtain coupling constants. Europium shift reagents coordinate with electron rich sites in the molecule, and shift all resonances downfield, the degree of shifting of a proton

signal depending on its spatial orientation with respect to the shift reagent. Normally these complexes are unstable on the NMR time-scale, and the observed spectra are usually time averaged, resulting from the shift reagent coordinating to several different sites in the molecule. On addition of $Eu(fod)_3$ to the anomers (24) and (102), the largest shifts were observed as expected, for those protons nearest the primary hydroxyl group, as this will be the main coordination site of the $Eu(fod)_3$. Table 3 shows the shifts obtainable before line broadening began to occur. The behaviour of the α-anomer was anomalous in that H-1, H-5 and H-6 experienced much larger changes in chemical shift than the corresponding protons in the β-anomer. In addition the C-6 pair of protons in the α-anomer became non-equivalent, and exhibited a coupling constant of ∿ 11 Hz with $\Delta\delta$ ∿ 1000 Hz. This behaviour suggests that the $Eu(fod)_3$ is remaining static with respect to the α-anomer (24), and that the time-averaging process, which causes the C-6 methylene protons to be equivalent in the β-anomer is not occurring. Examination of molecular models shows that a type of cage is formed in the α-anomer by the acetal oxygen atoms and the primary hydroxyl group. This cage is not possible in the β-anomer.



Coordination of the europium to the three oxygen atoms in this cage could lead to formation of a stable complex (on the NMR time scale). This would explain the anomalously large shifts of the C-1, C-5 and C-6 protons, and the non-equivalence of the C-6 protons.

The remaining steps necessary for conversion of the synthon (24) into TXB_2 and its C-15 epimer, have been performed by several groups,[82] and involve standard 'prostaglandin' methodology.

With the isolation of (24) and (102), the aim of this research project has been realised.[83] The strategy of utilising the asymmetry of a carbohydrate precursor to yield a chiral product has proved successful. The synthesis has been relatively short, has used readily available starting materials, and has been stereospecific.

TABLE 1

J(Hertz) (observed)

Proton	β-anomer		α-anomer	
1	$J_{1,2\ AX}$	∿8.5	$J_{1,2}$	∿3.0
	$J_{1,2\ EQ}$	∿2		
2	$J_{2\ AX,3}$	∿2.5	$J_{2,3}$	∿3.5
	$J_{2\ EQ,3}$	∿2.5		
3	$J_{3,4}$	∿5.0	$J_{3,4}$	∿5.0
4	$J_{4,5}$	∿10.0	$J_{4,5}$	∿10.5
5	$J_{5,6}$	∿1	$J_{5,6}$	∿1

TABLE 2

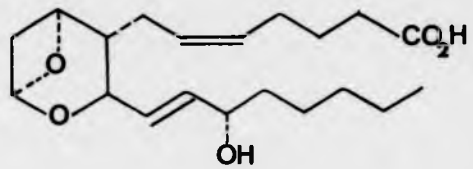
Proton	δ(ppm) β-anomer	δ(ppm) α-anomer	Δ(δ)
1	4.61	4.82	+ 0.21
$^2_{AX}$	1.77	2.11	+ 0.34
$^2_{EQ}$	2.31	2.11	- 0.20

TABLE 3

Proton	Δδ (ppm) for addition of 0.2 equivalent of $Eu(fod)_3$	
	α-anomer	β-anomer
1	2.9	1.6
$^2_{AX}$	1.1	1.0
$^2_{EQ}$	1.1	1.0
3	0.9	1.0
4	2.6	2.1
5	3.4	2.4
6	2.4	3.6
6	4.0	3.6
7	1.0	1.0
OCH_3	0.8	1.1

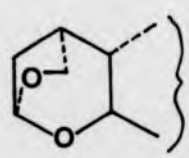
5. SYNTHETIC APPROACHES TO AN ANALOGUE OF THROMBOXANE A_2

Thromboxane A_2 is an unstable derivative of PGG_2 possessing structure (130). In aqueous solution at 37°C and pH 7.4, TXA_2 has a half-life of 32 seconds, being converted into its stable metabolite, TXB_2.



(130)

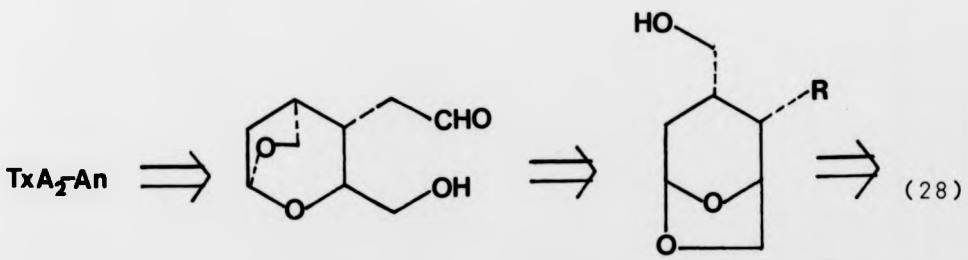
This high reactivity results from the presence of a highly electrophilic carbon (C-11), contained in a strained bicyclo[3,1,1]heptane system. Various analogues have been made, in which one or both oxygens have been substituted by carbon. This strategy has produced stable compounds by lowering the electrophilicity of C-11 (see pages 49 - 71). An alternative strategy for obtaining stable analogues while maintaining the two oxygen atoms is to lower the reactivity of the system by expanding the strained oxetane ring to form a 2,7-dioxabicyclo-[3,2,1]octane skeleton.



Comparison of molecular models of this system and the 2,7-dioxabicyclo[3,1,1]heptane system indicate that the relative positions of the oxygen atoms in the two bicyclo

systems should be similar, i.e. having a separation of ∿ 2.5Å. In the former system the oxetane oxygen will be displaced about 1Å further away from C-3 than in the latter system. Molecular models also indicate that the configuration of the two side chains does not vary greatly between the two structures. The similarities in this pair of bicyclic molecules suggest that the bicyclo[3,2,1]octane analogue may well possess interesting physiological properties.

The synthetic approach to this bicyclic system utilised, as a starting point, derivatives of the analogous 6,8-dioxa-bicyclo[3,2,1]octane system, i.e. derivatives of 1,6-anhydropyranose. Scheme 22 shows a retro-synthetic analysis of the proposed route.

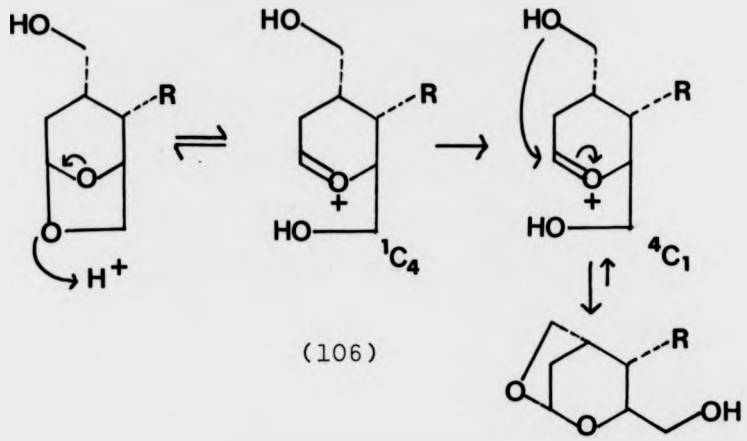


(104) (105)

Scheme 22

The key intermediate (104) possesses suitable functionality for elaboration of the two side chains by Wittig processes. The synthesis of (104) from a suitable precursor (105), was the most critical transformation in the whole synthesis, and was dependent on an internal trans-acetalisation

of (105) as outlined in Scheme 23.

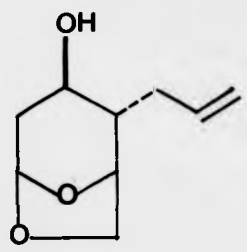


(106)

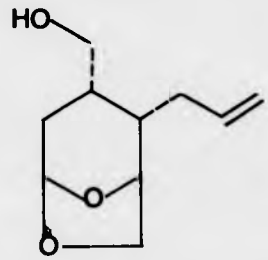
Scheme 23

On treatment of (105) with an acid catalyst in an aprotic medium, the 1,6-anhydro bridge should be cleaved to give the oxonium ion intermediate (106). This will rapidly and irreversibly invert from the $^{1}C_{4}$ conformation with C-6 and the group 'R' axially orientated, to the $^{4}C_{1}$ conformation with these groups equatorial, this being the thermodynamically more stable conformer. By way of analogy, the tricyclic lactone (97) is known to undergo rapid ring inversion on cleavage of the anhydro bridge with acid. Once in the $^{4}C_{1}$ conformation, the oxygen of the C-3 hydroxymethyl substituent is ideally situated to undergo reaction with C-1 and form (104). The group R was required to be readily convertible to the formyl moiety without interference with the acetal function. The methodology developed for synthesis of the tricyclic lactone (97) was applicable here. The proposed synthesis of a compound suitable for conversion into

(104) was in fact based on the alcohol (93).



(93)

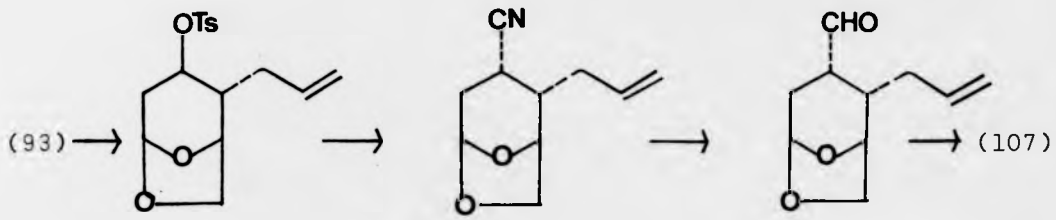


(107)

As the alkyl group has been previously shown to be readily oxidisable to a carbonyl function in the tosylate (95), it seems suitable for the present synthesis. Synthesis of a suitable intermediate (107) therefore required only a one carbon homologation of the alcohol at C-3, with inversion of the stereochemistry at this centre. In fact this relatively straightforward transformation has proved impossible to perform to date. The following discussion details the various attempts made. Some success was achieved with the unsubstituted ketone (29) in model investigations, but all efforts to prepare (107) were unsuccessful. The reasons for these failures seem to centre on the unusual nature of the bicyclic system itself. Some possible explanations will be presented in the following discussion.

The method of homologation initially investigated was introduction of a cyanide group by a displacement of tosylate from (95).

An S_N2 process should result in the cyanide being equatorially orientated. Reduction with di-iso butyl-aluminium hydride should result in the equatorially orientated aldehyde (109), reducible to the alcohol (107) with lithium aluminium hydride.



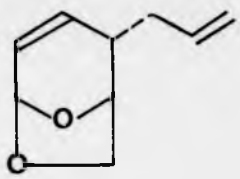
(95) (108) (109)

Scheme 24

The reaction was initially performed in dimethylsulfoxide and resulted in a 95% yield of the diene (110), a result of elimination of p-toluenesulphonic acid. The confirmation that (110) was the Δ^2 diene and not the Δ^3, was provided by decoupling experiments on the proton NMR spectrum, and its optical rotation. Decoupling showed that H-2 was an olefinic proton coupled to H-1 and $J_{1,2} \sim 4$ Hz. The optical rotation was large and positive in accord with that of other compounds containing a Δ^2 double bond, e.g. (54), (59) and (63). The presence of a Δ^3 double bond seems to cause the value of the optical rotation to be large and negative, e.g. (55).

As is the case with many anions, the reactivity of cyanide is greatly enhanced in dipolar aprotic media. This is due to preferential solvation of the cation, leaving a 'naked' cyanide anion. The basicity (hydrogen nucleophilicity) and (carbon) nucleophilicity both tend to be increased, but normally the basicity of the anion is dominant, and where an E2 process is possible, this tends to occur.

This type of process is especially facile in the case of (95) due to the rigid trans-di-axial arrangement of the tosyl

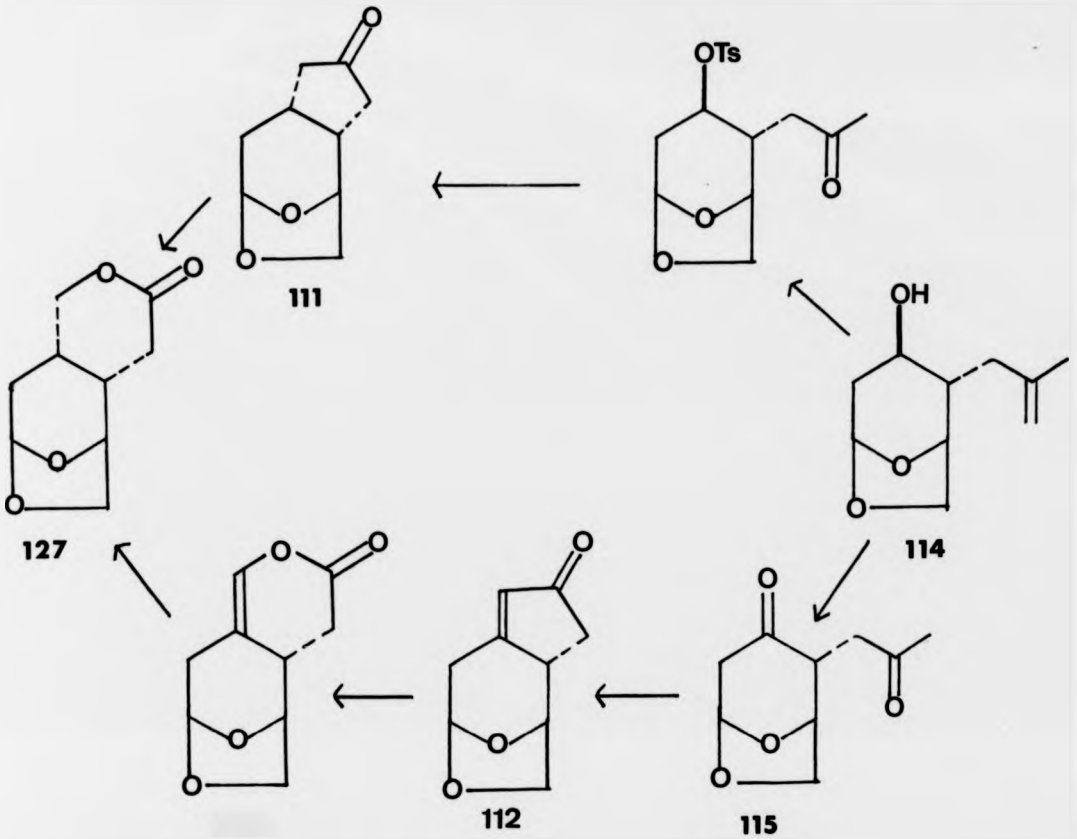


(110)

group and H-2_{EXO}, and also the slightly acidic nature of the C-2 protons (see Chapter 2.III). It is sometimes possible to alter the balance of S_N2 and E2 processes by changing the solvent e.g. in hydroxylic solvents, cyanide normally reacts by an S_N2 mechanism. On trying the above reaction in ethanol, the rate was found to be considerably reduced, and the diene again appeared to be the sole product. N-methyl pyrrolidine and hexamethylphosphoramide appear to favour substitution,[84] but their use again led to the diene.

As an intermolecular S_N2 reaction on the axial 3-O-tosyl groups seemed to be very elusive, an intramolecular reaction was considered as a means of forming the carbon-carbon bond. Delivery of a nucleophilic carbon by the alkyl chain attached at C-4 seemed likely to succeed. Two routes utilising this idea were considered, Scheme 25.

Introduction of an acetonyl group at C-4 could then lead via the enolate, to either, an aldol condensation with a carbonyl group at C-3 or displacement of a 3-O-tosyl group. The latter route would produce a symmetrical cyclopentanone (111) which would probably give isomeric δ-lactones on Baeyer-Villiger

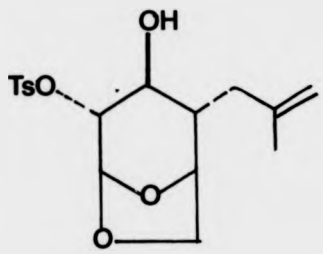


Scheme 25

oxidation. The enone (112) was a more suitable substrate as it is known that Baeyer-Villiger oxidation of enones often leads to the enol ester.[85] There were, however, some problems associated with this route as it seemed likely that the conditions of the aldol condensation might lead to epimerisation of the substituent at C-4.

The investigation was initiated by the introduction of an acetonyl synthon, the methallyl group, utilising the previously explored copper(I) catalysed Grignard reaction with

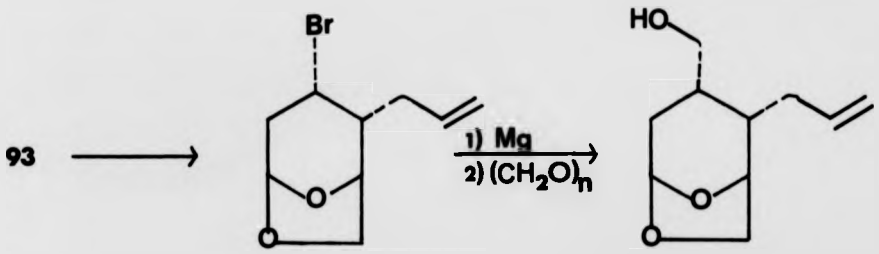
the epoxide (28). This led to the crystalline compound (113). Reduction of this with lithium triethylborohydride proceeded stereospecifically to yield the alcohol (114). This material was transformed into the diketone (115) in one step by reaction with ruthenium dioxide and sodium metaperiodate in a biphasic



(113)

system of dichloromethane and water. This erythro ketone was found to undergo epimerisation of the acetonyl side-chain during chromatography on silica, to yield a mixture of the two isomers. This mixture was treated with sodium hydride in benzene[86] in an attempt to effect an aldol condensation, but this resulted in a complex mixture which yielded no isolatable products. No further work was carried out on this route.

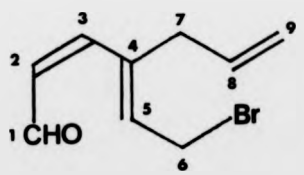
An alternative strategy for the synthesis of (107) is outlined below.



(116)

This quite short route involves synthesis of the exo 3-bromide, its conversion to a Grignard reagent, and reaction with formaldehyde. The exo 3-bromide is required as it is known that both the formation of a Grignard reagent from a halide, and its subsequent reaction occur with retention of configuration.[87] Racemisation of Grignard reagents does not normally occur below about 100°C.[88] Therefore the exo-bromide should lead to an exo hydroxymethyl group in (107).

The bromide (116) was synthesised using the reagents triphenylphosphine and carbon tetrabromide in acetonitrile. This reaction occurred with inversion of configuration to give the desired exo bromide ($J_{2AX-3} \sim 11$ Hz) in about 40% yield. A large amount of another product was also formed. This was rather unstable, and could not be purified for micro-analysis, nor did it provide a readily assignable mass spectrum. An assignment of the structure as (117) was made on IR, UV and NMR evidence.



(117)

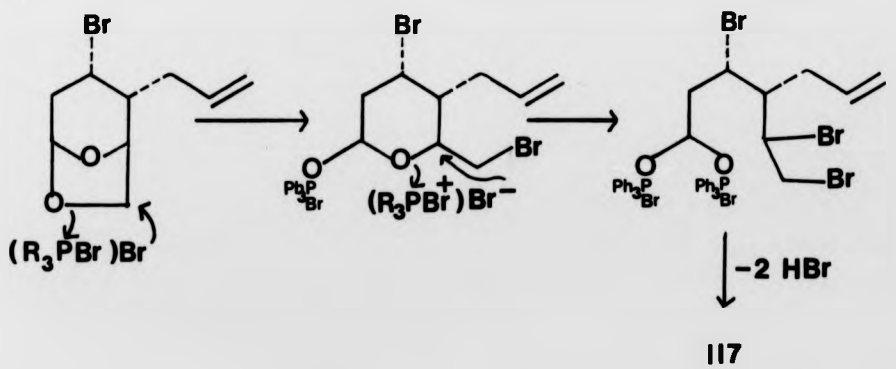
This consisted of a strong infra-red absorption at ν_{MAX} 1680 cm^{-1}, indicating a conjugated carbonyl group. A first order analysis of the proton NMR spectrum using decoupling techniques demonstrated the presence of the conjugated aldehyde moiety, i.e. δ 9.56 (d, 1H, H-1, $J_{1,2} \sim 7$ Hz), 5.70 (m, 1H, H-2, $J_{1,2} \sim 7$, $J_{2,3} \sim 20$ Hz),

7.02 (d, 1H, H-3, $J_{2,3} \sim 20$ Hz); attached to a quaternary carbon (C-4) to which was also attached the allyl group: δ 3.13 (d, 2H, (C-7) CH_2, $J_{7,8} \sim 5$ Hz), 5.70 (m, 1H, H-8, $J_{8,7} \sim 5$, $J_{8,9_{CIS}} \sim 11$, $J_{8,9_{TRANS}} \sim 17$ Hz), 4.9-5.2 (m, 2H, (C-9) CH_2). The presence of allylic bromide was also apparent: δ 6.27 (t, 1H, H-5, $J_{5,6} \sim 9$ Hz), 4.04 (d, 2H, (C-6) CH_2). The ultra-violet spectrum had maximum absorbance at ∿ 283 nm which is the correct position for this structure as calculated by the Woodward-Fieser rules. It seems likely that (117) is formed by cleavage of the acetal group and dehydrobromination by triphenyl-dibromophosphorane (Ph_3PBr_2). In the absence of a proton source this is the most basic and reactive intermediate formed by the reaction of triphenylphosphine and carbon tetrabromide,[89] i.e.

$$Ph_3P + CBr_4 \rightarrow [Ph_3P\text{-}CBr_3]^+ Br^-$$

$$[Ph_3P\text{-}CBr_3]^+ Br^- + Ph_3P \rightarrow Ph_3P{=}CBr_2 + Ph_3PBr_2$$

Cleavage of the acetal group may occur in an analogous fashion to that with iodotrimethylsilane.

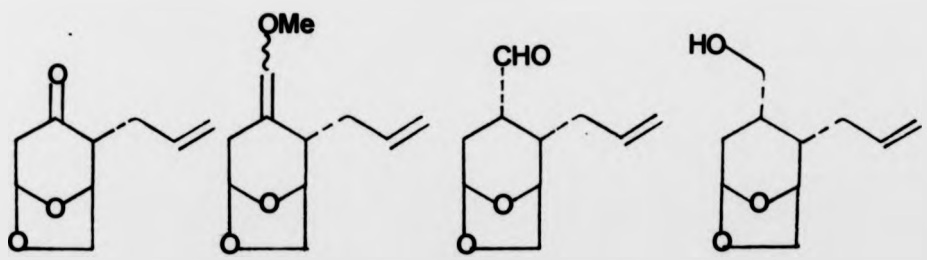


117

The basicity of these reagents is demonstrated by the facile dehydration of carboxamides to nitriles.

Attempts to prepare the Grignard derivative of (116) led to the disappearance of the bromide but not to the formation of the Grignard reagent. Formation of the lithio derivative of (116) was also attempted, but again led to the reaction of the bromide and no isolatable products.

Another approach to the aldehyde (109) involved introduction of the one carbon unit by a Wittig reaction with the ketone (118). Methylenetriphenylphosphorane would have resulted in an exocyclic double bond which would have proven difficult to hydroborate in the presence of the allyl group. Therefore methoxymethylenetriphenylphosphorane[90] was chosen. This should lead to an enol ether (119), which could be readily hydrolysed to the aldehyde, Scheme 26.



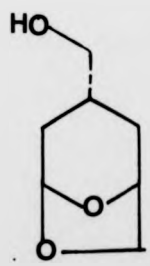
(118) (119) (109) (107)

An excellent review of homologation of carbonyl compounds exists.[91] To investigate the applicability of this approach, the unsubstituted 6,8-dioxabicyclo[3,2,1]octan-3-one (29) was used as a model substrate. In fact, this sequence of reactions worked well with (29). Reaction with the phosphorane

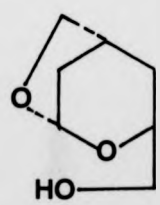
led to the isomeric enol ethers (120) and (121) in equal amounts as judged by GLC analysis. These were separable by column chromatography. The NMR spectra of this pair of compounds differed in the chemical shifts of the H-2, H-4 and H-6 protons, presumably due to the influence of the enol ether oxygens, however it was not possible to definitely assign a structure to each spectrum.

These enol ethers were hydrolysed under mild conditions which did not affect the acetal function ($HgOAc_2$-KI-H_2O-THF), to produce the aldehyde (122) as one epimer. This was proven by exposure to base equilibrating conditions. No change in GLC Rt, TLC Rf, or NMR spectrum was noted indicating that the aldehydic group is <u>exo</u> in (122).

The reduction of the aldehydic moiety was performed with lithium aluminium hydride and provided the desired alcohol (123) in reasonable yield. As this alcohol has no substituent at C-4, the driving force for the previously discussed rearrangement should be minimal, however it seemed likely that a 50:50 mixture of (123) and (124) might result.



(123)



(124)

On treating (123) with Amberlyst acidic ion exchange resin in dry benzene for a prolonged period, TLC and GC could detect no change. As (123) and (124) would be expected to possess very similar chromatographic properties, TLC and GC might be insensitive to a successful reaction, so this negative result was not considered to be damning evidence against the rearrangement.

With the successful transformation of the model ketone (29) to the hydroxymethyl substituted compound (123), the formation of the target compound (107), by the same route seemed certain of success. This sequence was initiated by synthesis of the allyl-ketone (118) from the alcohol (93) using pyridinium chlorochromate buffered with sodium acetate. These conditions did not result in epimerisation of the C-4 substituent, thus demonstrating once again the suitability of pyridinium chlorochromate for the synthesis of ketones with the thermdynamically less stable α-substituent.

Gas chromatography demonstrated that the reaction of this ketone with methoxymethylenetriphenylphosphorane was very slow at -70°C, but extremely rapid on warming to room temperature. The disappearance of the ketone was accompanied by the formation of very polar products, detectable only by TLC. The reaction was repeated, with a slow controlled stepwise increase in temperature from -75°C to -50°C to -40°C, at which point all the ketone had disappeared and a large number of new peaks, of shorter retention time had appeared on the gas chromatogram. No identifiable products could be isolated from this reaction.

The explanation of the totally different results obtained from the reactions of the two ketones (29) and (118) with methoxymethylenetriphenylphosphorane seems to lie in the influence of the axial 4-substituent on the steric environment of the ketone moiety. Bicyclo[3,2,1]octan-3-one is known to be so sterically hindered that with large reagents, only exo attack on the ketone moiety occurs, this being about 200 times slower than with cyclohexanone.[50] In (118) the 4-C-allyl group will substantially hinder exo attack on the ketone, so forcing the reaction along another pathway. It seems likely that this will involve enolisation of the ketone, probably to give initially the Δ^2 isomer which may then isomerise to the more stable Δ^3 isomer. As no ketone was recoverable from the reaction, this enolate must subsequently react to produce non-isolatable polar products. A tendency for alkoxymethylenetriphenylphosphoranes to give poor yields with enolisable substrates has been noted before.[92]

Recent work has demonstrated that phosphonate reagents are much superior to phosphoranes for the formation of the homologous enol ether from enolisable ketones.[93] Protected derivatives of diethylhydroxymethylphosphonate are particularly suitable and readily synthesised. The lithio metallated derivatives of these compounds form relatively stable 1,2-adducts with ketones. These can be decomposed to the olefinic product by heating or by treatment with potassium tert-butoxide. With enolisable ketones it was found necessary to perform the reaction below -100°C to obtain good yields.

An investigation into this reaction was initiated by the synthesis of the tetrahydropyranyl derivative of diethyl hydroxymethylphosphonate as outlined below:-

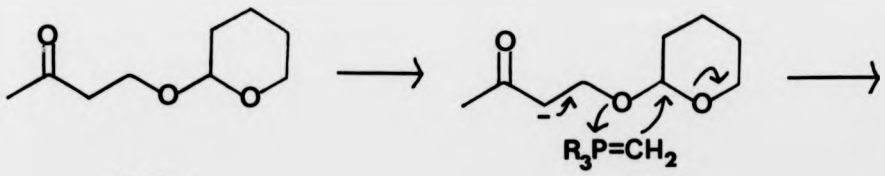
$$(EtO)_2PO + (CH_2O)_n \rightarrow (EtO)_2P(O)CH_2OH \rightarrow (EtO)_2P(O)CH_2OTHP$$

This derivative was particularly attractive due to the likely ease of hydrolysis of the enol ether product. On reaction of the lithio derivative of this phosphonate with the ketone (118), the ketone was recovered in about 40% yield as the only isolable product. The C-4 substituent had been isomerised into an equatorial orientation indicating that enolisation had taken place. It has been reported that the hindered ketone camphor gave only a 12% yield of the 1,2-adduct under these conditions,[93] so it seems probable that this reagent may be generally unreactive towards hindered ketones.

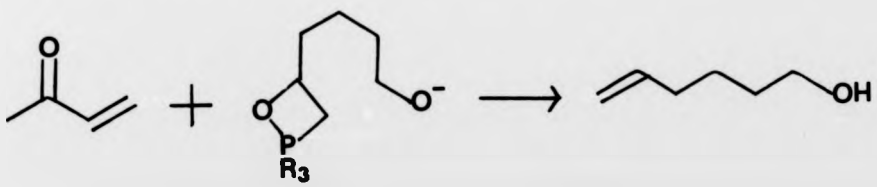
The failure of the Wittig and Horner-Eammons reactions prompted the investigation of another approach to (109). This involved conversion of the ketone (118) into a spiro-epoxide. These compounds are known to rearrange on treatment with a Lewis acid by a carbonium ion mechanism to yield the epimeric aldehydes,[94] which could presumably be isomerised to the desired exo epimer with base. The reagents commonly used for this transformation are dimethylsulphoxonium methylide,[95] dimethylsulphonium methylide[95] and diazomethane.[96] These were all examined. On reaction of the ketone (118) with the less reactive of the two sulphur ylids, dimethysulphoxonium methylide, the ketone rapidly disappeared to give a complex mixture of products. The more reactive ylid dimethylsulphonium methylide allows the

reaction to be performed at lower temperature, thus helping to prevent undesirable side reactions. On the application of this reagent to the ketone (118), the rapid reaction led once again to a complex, unidentifiable mixture of products.

It was noted that the spectral characteristics of the crude products from the above two reactions, and the Wittig reaction with methoxymethylenetriphenylphosphorane were all very similar. This suggested that all three reactions were involving the enolisation of the ketone and its subsequent decomposition by a common route. An unusual reaction of methylenetriphenyl-phosphorane with the keto-acetal (125) has been reported[97] and appears to be relevant to the above reactions of (118).



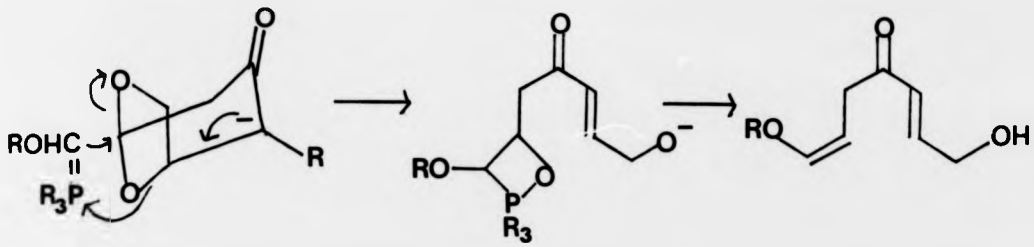
(125)



Enolisation of the ketone is followed by cleavage of the ethereal carbon-oxygen bond assisted by participation of the Wittig reagent to eventually produce the enone and the hydroxy olefin.

An analogous retro-Michael type reaction could be

envisaged for (118) i.e.



This reaction apparently requires the participation of an electrophilic hetero-atom containing strong base, i.e. phosphorous or sulphur ylids, as in their absence the enolates are quite stable. The recovery of the ketone from the reaction with the phosphonate reagent may be explained as resulting from the phosphorous being insufficiently electrophilic to coordinate to O-5, and polarise the C-5-O-5 bond. In the infra-red spectra of the product mixtures obtained from these unsuccessful reactions a strong absorption at 1675-1685 cm^{-1} indicated the possible presence of an enone function. The lack of a resonance assignable to H-1 of the bicyclic system in the NMR spectrum confirmed that the acetal moiety had been destroyed.

The third method of epoxidation of (118) involved the use of diazomethane. This compound should not be sufficiently basic to cause enolisation of (118), so the complications discussed above should not occur. An important side reaction of diazomethane with carbonyl compounds is the formation of a carbonyl compound with one more carbon than the starting material.

The ratio of the two possible products can be influenced by both steric and electronic effects. Lewis acids accelerate the reaction and suppress formation of the epoxide, whilst electron withdrawing groups α to the ketone tend to increase the amount of epoxide formed. With carbohydrates, bearing hydroxyl groups adjacent to the ketone, the epoxide is often the sole product.[98] With bicyclic systems, ring strain often leads to predominant formation of the ring-enlarged ketone, e.g. bicyclo[3,2,1]octan-3-one reacts slowly to give bicyclo-[4,2,1]octan-3-one.[99] As these literature examples did not definitely predict what would occur in the case of (118), the reaction was investigated. It was found that in ether, no reaction occurred. On the addition of methanol a very slow reaction commenced, but as after three days a substantial amount of ketone was still present, the reaction was abandoned. The identity of the small amount of product formed could not be established.

Methods for direct conversion of a ketone to a nitrile[100] exist, e.g. using p-toluenesulphonylmethyl isocyanide (TOSMIC). This has been extended to give good yields with both enolisable and hindered ketones.[101] Unfortunately, on application of this method to the ketone (118) the usual mixture of unidentifiable products resulted.

The above results do not augur well for the eventual success of the homologation of the allyl ketone. The abnormally large steric hindrance to approach to the carbonyl group, combined with facile enolisation, mean that most strongly basic reagents are liable to be unsuccessful. The presence of an

electrophilic heteroatom in the reagent seems to aid the proposed retro-Michael reaction, so it seems likely that the newer silicon based reagents, e.g. $MeOCH_2SiMe_3$,[102] $ClCH_2SiMe_3$[103] and $(CH_2)_3S_2CH_2SiMe_3$[104] would precipitate this side reaction.

At the conclusion of this work, there were several promising methods under consideration which, due to lack of time, could not be fully investigated. A potentially general method for the homologation of hindered enolisable ketones has been developed by Corey et al.[105] for the homologation of the intermediate (126), required in a synthesis of the diterpene aphidicolin.

The one carbon unit was actually introduced under neutral conditions via a cyano-hydrin, Scheme 27. Subsequent elaboration into the 1-trimethylsilyl-2-trimethylsilyloxy alkoxy moiety followed by a 1,2-silyl shift produced a β-alkoxy-silane susceptible to a Petersen olefination reaction to yield the silyl enol ether.

An alternative method which is at present under investigation in these laboratories is that of Orere and Reese[100] for conversion of a ketone directly into the homologous nitrile. This involves reaction of the 2,4,6-tri-isopropyl-benzene-sulphonylhydrazone of the ketone with potassium cyanide in methanol. Good yields have been obtained with the hindered ketone pinacolone. The mechanism of this reaction has not yet been elaborated, however from reported examples, it offers a good chance of success with (118).

A slightly different approach involves the synthesis

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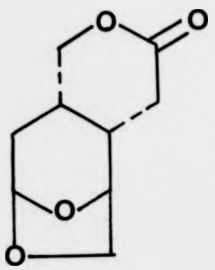
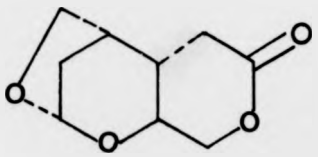
A slightly different approach involves the synthesis

of the tricyclic δ-lactone (127)

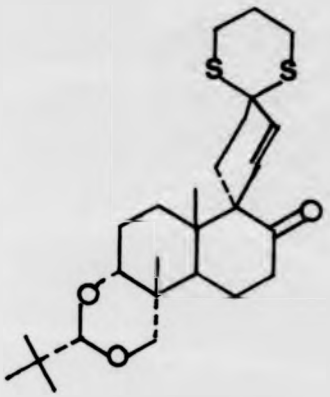




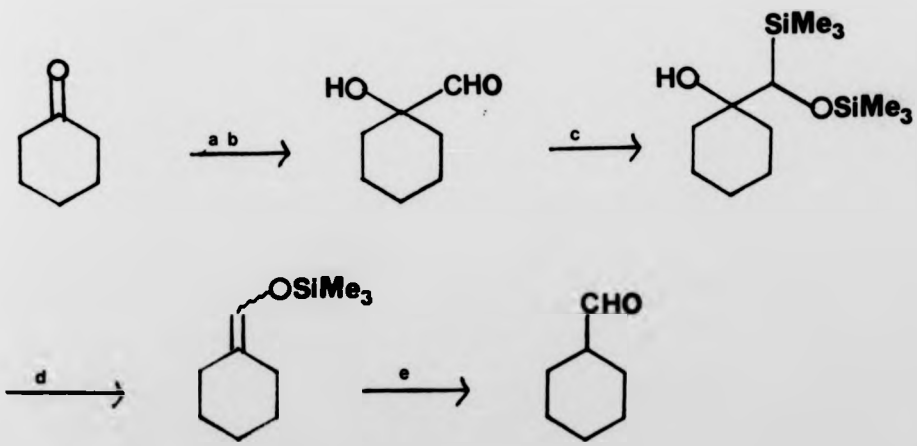
(127) (128)

Acid-catalysed rearrangement of this should result in the isomeric δ-lactone (128). The synthesis of this compound does however present considerable problems. A suitable precursor may be the Δ^3 olefin (55), readily available by isomerisation of the Δ^2 olefin (see page 116). Elaboration into a δ-lactone could be accomplished using the method of Baldwin and Crimmins,[106] Scheme 28. Alternatively a variation of the procedure of Greene and Depres,[107] with a Baeyer-Villiger oxidation of the intermediate α,α-dichlorocyclopentanone might lead to the desired δ-lactone, Scheme 29.

The above, or other procedures will, it is felt, eventually lead to the successful synthesis of a suitable synthon and enable the completion of the proposed novel route to a TXA_2 analogue.



126



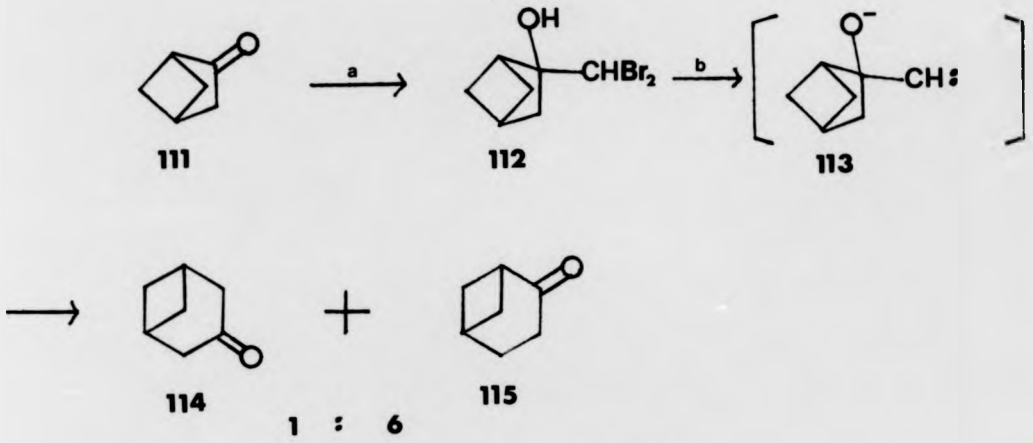
(a) Me_3SiCN, ZnI_2, $CHCl_3$, (b) Dibal,

(c) Me_3SiLi, HMPA, -35°, (d) LDA, THF, 23°

(e) H_3O^+

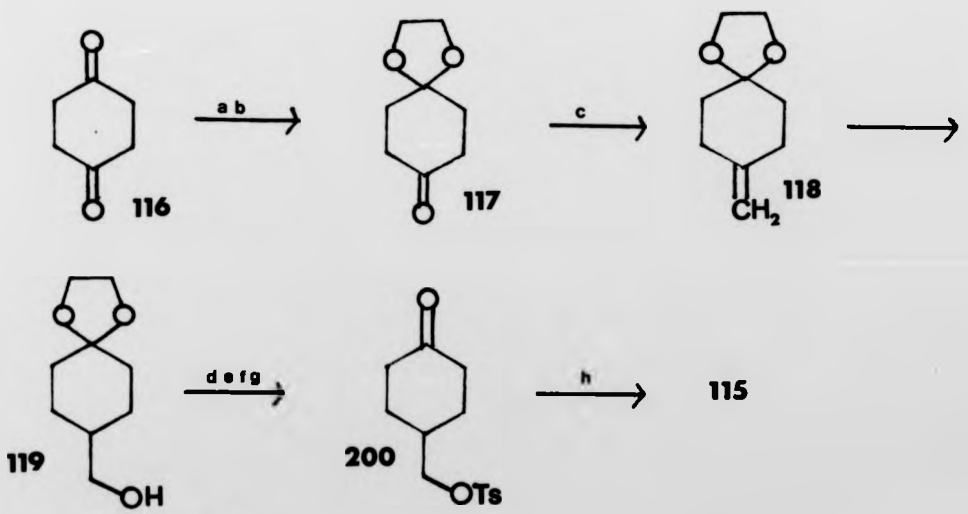
Scheme 27

For schemes 28 and 29 turn to page 60



(a) LDA, CH_2Br_2, -78°, (b) n-BuLi

Scheme 28



(a) $(CH_2OH)_2$, H^+, (b) AcOH, aq.THF, (c) Ph_3PCH_2,

(d) $(iso\text{-}amyl)_2BH$, (e) NaOH, H_2O_2, (f) TsCl, pyridine,

(g) AcOH, aq.THF, (h) $CH_3S(O)CH_3^-K^+$

Scheme 29

REFERENCES

1. S. Hanessian and P. Lavellee, Can.J.Chem., 55, 562 (1977)
2. E. J. Corey, M. Shibasaki and J. Knolle, Tetrahedron Letters, 1625 (1977)
3. O. Hernandez, Tetrahedron Letters, 219 (1978)
4. H. Ohrui and S. Emoto, Agric.Biol.Chem., 41, 1773 (1977)
5. G. Stork and S. Raucher, J.Amer.Chem.Soc., 98, 1583 (1976)
6. G. Stork, T. Takahashi, I. Kawamoto and T. Suzuki, J.Amer.Chem.Soc., 100, 8272 (1978)
7. G. Stork, T. Takahashi, T. Suzuki and I. Kawamoto, unpublished results, see reference 8a.
8. a) B. Fraser-Reid and R. C. Anderson, Fortschritte d.Chem. Org.Naturst., 39, 1 (1980)
   b) S. Hanessian, Accs.Chem.Res., 12, 159 (1979)
9. S. Hanessian, P. Dextrase, A. Fougerousse and Y. Gurdon, Tetrahedron Letters, 3983 (1974)
10. G. J. Lourens and J. M. Koekeomer, Tetrahedron Letters, 3719 (1975)
11. S. D. Gero, J. Cleophax, D. Mercier and A. Olesher, in 'Synthetic Methods for Carbohydrates', 4 (1977)
12. S. Lesage and A. S. Perlin, Can.J.Chem., 56, 2889 (1978)
13. D. E. Plaumann, M.Sc. Thesis, Univ. of Waterloo, 1977, see reference 8a.
14. T. Ogawa, M. Takasaka and M. Matsui, Carbohydr.Res., 60, C4 (1978)
15. M. Černý and J. Staněk, Jr., Adv.Carbohydr.Chem.Biochem., 34, 23 (1977)

16. J. M. Macleod, L. R. Schroeder and P. A. Seib, Carbohydr.Res., 30, 337 (1973)

17. M. Černý, J. Pacák and J. Staněk, Carbohydr.Res., 15, 379 (1970)

18. N. A. Dominguez, I. C. Lopez and R. Franco, J.Org.Chem., 26, 1625 (1961)

19. J. Pecka, J. Staněk Jr., and M. Černý, Coll.Czech.Chem.Comm., 26, 2542 (1961)

20. J. R. Bull and A. Tuinman, Tetrahedron Letters, 4349 (1973)

21. J. Pecka, J. Staněk Jr., and M. Černý, Coll.Czech.Chem.Comm., 39, 1192 (1974)

22. J. Halbych, T. Trnka and M. Černý, Coll.Czech.Chem.Comm., 38, 2151 (1973)

23. E. J. Hedgley, O. Mérész and W. G. Overend, J.Chem.Soc., (C), 888 (1967)

24. a) H. C. Brown and S. Krishnamurthy, Tetrahedron, 35, 567 (1979)

    b) H. C. Brown, S. C. Kim, and S. Krishnamurthy, J.Org.Chem., 45, 1 (1980)

    c) H. C. Brown and S. Krishnamurthy, J.Org.Chem., 41, 3064 (1976)

25. Kindly supplied by J. M. Hutchinson.

26. M. Černý and J. Pacák, Coll.Czech.Chem.Comm., 26, 94 (1961)

27. G. O. Aspinall and G. Zweifal, J.Chem.Soc., 2271 (1957)

28. I. Weiz, K. Felfoldi and K. Kovacs, Synthesis, 26 (1970)

29. E. J. Corey and J. W. Suggs, Tetrahedron Letters, 2647 (1975)

30. K. K. Banerji, Bull.Chem.Soc.Jap., 51, 2732 (1978)

31. K. Heyns, J. Weger and H. Paulsen, Chem.Ber., 100, 2317 (1967), and 98, 327 (1965)

32. 'Modern Synthetic Reactions', H. O. House, W. A. Benjamin, (1972).

33. a) F. Sweet and R. K. Brown, Can.J.Chem., 46, 2289 (1968)
b) T. P. Murray, C. S. Williams and R. K. Brown, J.Org.Chem., 36, 1311 (1971)

34. E. J. Corey and A. Venkateswarlu, J.Amer.Chem.Soc., 94, 6190 (1972)

35. C. A. Brown, J.Org.Chem., 39 (1974) 1324, 3913.

36. P. H. Hudrlik and J. M. Takacs, J.Org.Chem., 43, 3861 (1978)

37. H. O. House, L. J. Czuba, M. Gall and H. D. Olmstead, J.Org.Chem., 34, 2324 (1969)

38. G. Stork and P. F. Hudrlik, J.Amer.Chem.Soc., 90, 4462 (1968)

39. A. G. Kelly and J. S. Roberts, Carbohydr.Res., 77, 231 (1979)

40. B. M. Trost, Chem.Rev., 78, 363 (1978)

41. A. F. Bochov and Y. V. Yoznyi, Carbohydr.Res., 32, 1 (1974)

42. G. H. Posner and D. Z. Rodgers, J.Amer.Chem.Soc., 99, 8208 (1977)

43. L. Vegh and E. Hardegger, Helv.Chim.Acta, 56, 1792 (1973)

44. K. A. Hooton and A. L. Alfred, Inorg.Chem., 4, 671 (1965)

45. E. W. Abel and D. A. Armitage, Adv.Inorg.Chem., 5, 2 (1967)

46. B. M. Trost and A. J. Bridges, J.Amer.Chem.Soc., 98, 5017 (1976)

47. B. M. Trost, T. N. Salzmann and K. Hiroi, J.Amer.Chem.Soc., 98, 4887 (1976)

48. E. J. Corey, J.Amer.Chem.Soc., 75, 2301 (1953)

49. Inter alia a) J. Fried, C. H. Lin, J. C. Sih, P. Dalven and G. F. Cooper, Tetrahedron Letters, 311 (1970);
b) G. Stork, C. Kowalski and G. Garcia, J.Amer.Chem.Soc., 97, 3258 (1975);

c) E. J. Corey and R. K. Varma, J.Amer.Chem.Soc., 93, 7319 (1971)

50. E. Volpi, G. Biggi and F. Pietra, J.Chem.Soc., Perk.II, 571 (1973)

51. E. J. Corey and H. S. Sachdev, J.Amer.Chem.Soc., 95, 8483 (1973)

52. H. J. Monteiro, J.Org.Chem., 42, 2324 (1977)

53. B. M. Trost, H. C. Arndt, P. E. Stredge and T. R. Verhoeven, Tetrahedron Letters, 3477 (1976)

54. P. Brownridge and S. Warren, J.Chem.Soc., Chem.Comm., 465 (1977)

55. Inter alia a) J. J. Partridge, N. K. Chadha and M. R. Uskovic, J.Amer.Chem.Soc., 95, 7171 (1973);

b) M. Naruto, K. Ohno and N. Naruse, Chemistry Letters, 1419 (1978)

56. Inter alia a) P. A. Greico, Y. Ohfure and G. Majetich, J.Amer.Chem.Soc., 99, 7393 (1977);

b) J. A. Marshall and W. R. Synder, J.Org.Chem., 40, 1656 (1975);

c) P. de Clerq and M. Vandewalle, J.Org.Chem., 42, 3447 (1977)

57. Inter alia, references 49a and 49b and

a) G. Stork and M. Isobe, J.Amer.Chem.Soc., 97, 6260 (1975);

b) E. J. Corey and R. Noyori, Tetrahedron Letters, 311 (1970)

58. M.A.W. Finch, T. V. Lee, S. M. Roberts and R. F. Newton, J.Chem.Soc.,Chem.Comm., 677 (1979)

59. M. W. Ratkhe, J.Amer.Chem.Soc., 92, 3222 (1970)

60. Organic Syntheses, Coll.Vol. 4, 749.

61. H. Ishikawa and T. Mukaijama, Chemistry Letters, 305 (1975); 1077 (1974)

62. H. Gilman and F. Schulze, J.Amer.Chem.Soc., 47, 2002 (1925)

63. Organometallic Compounds 1 (1967), G. E. Coates and K. Wade, Methuen.

64. C. Huynh, F. Derguini-Boumechal and G. Linstrumelle, Tetrahedron Letters, 1503 (1979)

65. a) J. Munch-Peterson, C. Bretting, P. M. Jorgensen, S. Refn. V. K. Anderson, and A. Jart, Acta.Chem.Scand., 15, 277 (1961)

b) M. S. Kharasch and P. O. Tawney, J.Amer.Chem.Soc., 63, 2308 (1941)

66. a) V. D. Parker, L. H. Pietti, R. M. Salinger and C. R. Noller, J.Amer.Chem.Soc., 86 (1964) 1110

b) M. Tamura and J. Kochi, J.Amer.Chem.Soc., 93, 1486 (1971)

c) K. Onuma and H. Hashimoto, Bull.Chem.Soc.Jap., 45, 2582 (1972)

67. H. O. House, W. L. Respass and G. M. Whitesides, J.Org.Chem., 31, 3128 (1966)

68. H. Gilman and J. M. Straley, Rec.Trav.Chem., 55, 821 (1936)

69. G. Costa, A. Camus, L. Gatti and N. Marsich, J.Organomet.Chem., 5, 568 (1966)

70. P. S. Bailey, Ozonation in Organic Chemistry, Organic Chemistry, 39, Academic Press.

71. S. Murai, N. Sonoda and S. Tsutsumi, Bull.Soc.Chem.Jap., 37, 1187 (1964)

72. R. M. Srivastova and R. K. Brown, Can.J.Chem., 48, 830 (1970)

73. R. Sterzycki, Synthesis, 724 (1979)

74. J. Lucke and A. L. Gemal, J.Chem.Soc.Chem.Comm., 976 (1978)

75. W. Clark-Still, M. Kohn and A. Mitra, J.Org.Chem., 43, 2933 (1978)

76. Three references state that this compound is an oil (4,77,78), while two other references give a m.p. of 101-101.5 and 102-103°C respectively (2,3)

77. For syntheses of racemic compounds:
a) N. A. Nelson and R. W. Jackson, Tetrahedron Letters, 3275 (1976)

78. b) R. C. Kelly, I. Schletter and S. J. Stein, Tetrahedron Letters, 3279 (1976)

79. Kindly supplied by Drs. N. A. Nelson and R. C. Kelly of the Upjohn Company.

80. see ref. 4 .

81. a) G. Kotovych and G.H.M. Aarts, Can.J.Chem., 58, 1111 (1980)
b) N. S. Bhacca and D. H. Williams, Applica. of NMR Spectroscopy in Organic Chemistry, (1964), Holden-Day.

82. see refs. 77 and 78 .

83. A. G. Kelly and J. S. Roberts, J.Chem.Soc.Chem.Comm., 228 (1980)

84. A.L.J. Beckwith and G. Moad, J.Chem.Soc., Perk.II, 1726 (1975)

85. a) H. M. Walton, J.Org.Chem., 22, 1161 (1957)
b) G. B. Payne and P. H. Williams, J.Org.Chem., 24, 284 (1959)

86. E. Brown and M. Ragault, Tetrahedron Letters, 1927 (1973)

87. F. R. Jenson and K. L. Nakamaye, J.Amer.Chem.Soc., 88, 3437 (1966)

88. E. A. Hill, J.Org.Chem., 31, 20 (1966)

89. R. Appel, Angew.Chem.internat.Edit., 14, 801 (1975)

90. G. Wittig and E. Krauss, Angew.Chem., 71, 127 (1959)

91. S. F. Martin, Synthesis, 633 (1979)

92. a) S. G. Levine, J.Amer.Chem.Soc., 80, 6150 (1958)
b) A. Ferwanah, W. Pressler and C. Reichardt, Tetrahedron Letters, 3979 (1973)

93. a) C. Earnshaw, C. J. Wallis and S. Warren, J.Chem.Soc., Chem.Comm., 314 (1977)
b) A. F. Kludge and I. S. Cloudsdale, J.Org.Chem., 44, 4847 (1979)

94. B. N. Blackett, J. M. Coxon, M. P. Hartshorn, B.L.J. Jackson and C. N. Muir, Tetrahedron, 25, 1479 (1969)

95. E. J. Corey and M. Chaykovsky, J.Amer.Chem.Soc., 87, 1353 (1965)

96. C. D. Gutsche, Org.React., 8, 364 (1954)

97. B. Janiston and W. Hansel, Chem.Ber., 108, 1036 (1975)

98. Inter alia:
a) R. D. King, W. G. Overend, J. Wells and N. R. Williams, J.Chem.Soc., Chem.Comm., 726 (1967)
b) D. Horton and J. S. Jewell, Carbohyd.Res., 2, 251 (1966)

c) D. Horton and E. K. Just, Carbohyd.Res., 18, 81 (1971)

d) S. Hagen, T. Anthonson and L. Kilaas, Tetrahedron, 35, 2583 (1979)

99. G. Fachinetti, F. Pietra and A. Marsili, Tetrahedron Letters, 393 (1971)

100. a) D. Hoppe, Angew.Chem.internat.Edit., 13, 789 (1974)

b) D. M. Orere and C. B. Reese, J.Chem.Soc., Chem.Comm., 280 (1977)

101. O. H. Oldenziel, D. van Leusen and A. M. van Leusen, J.Org.Chem., 42, 3114 (1977)

102. P. Magnus and G. Roy, J.Chem.Soc., Chem.Comm., 822 (1979)

103. C. Burford, F. Cooke, E. Ehlinger and P. Magnus, J.Amer.Chem.Soc., 99, 4536 (1977)

104. P. F. Jones, M. F. Lappert and A. C. Szary, J.Chem.Soc., Perk.I, 2272 (1973)

105. E. J. Corey, M. A. Tius and J. Das, J.Amer.Chem.Soc., 101, 1742 (1980)

106. S. W. Baldwin and M. T. Crimmins, Tetrahedron Letters, 4197 (1978)

107. A. E. Greene and J-P. Deprés, J.Amer.Chem.Soc., 101, 4003 (1979)

108. Methods in Carbohyd.Chem., II, Eds., R. L. Whistler and M. L. Wolfram, Academic Press (1968)

109. M. Černý, L. Kalvoda and J. Pacák, Coll.Czech.Chem.Comm.,

GENERAL EXPERIMENTAL AND ABBREVIATIONS

Melting points are uncorrected and were determined on a Kofler hot stage apparatus. Optical rotations were determined on a Perkin-Elmer polarimeter, model 141, using a 1 cm cell. Infra-red spectra were recorded on a Perkin-Elmer 577 spectrophotometer in dilute chloroform solution. Ultraviolet spectra were recorded on a Perkin-Elmer 402 spectrophotometer in dilute chloroform solution.

Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R32 90 MHz spectrometer in deutero-chloroform solution using tetramethylsilane as internal standard. Chemical shifts are quoted in p.p.m. downfield from tetramethylsilane.

Gas-liquid chromatography was performed on a Perkin-Elmer F11 machine with a flame ionisation detector. Retention times are quoted in minutes. Peak areas were measured with a Supergrator computing integrator.

Mass spectra and high resolution mass determinations were obtained by Mr. D. F. Dance using a Jeol JMS-D100 mass spectrometer.

Microanalyses were obtained by Dr. F. B. Strauss of Oxford University.

Analytical t.l.c. plates were examined under ultra-violet illumination, and then stained with iodine vapour and/or ceric ammonium sulphate, followed by heating to $\sim 150^{\circ}$. Keiselgel G (Merck 7731) was used for preparative t.l.c. Keiselgel 60 (Merck 9385) was used for column chromatography, utilising the procedure of Clark-Still et al.[75]

Solvents were removed using a Büchi Rotavapour-R at a pressure of 20 mm and the lowest convenient temperature, generally 40-50°. Flask to flask distillations were performed using a Büchi GKR-50 apparatus. Reactions requiring anhydrous conditions were performed in flame dried flasks fitted with Suba-seal rubber septa, under an atmosphere of dry nitrogen. Transfer of solutions was accomplished using syringe technique. Solvents were generally distilled before use. Dry solvents were obtained by the normal methods.

t.l.c.	thin layer chromatography
i.r.	infra red
u.v.	ultra violet
n.m.r.	nuclear magnetic resonance
g.l.c.	gas liquid chromatography
m.s.	mass spectra
m/e	mass divided by charge
$[M^+]$	molecular ion
m.p.	melting point

s	singlet	
d	doublet	
t	triplet	(in n.m.r. spectra)
q	quartet	
m	multiplet	

Leavoglucosan by pyrolysis of starch

A one litre round-bottom flask was filled to one-third capacity with maize starch and connected via 2 cm glass tubing to a one litre conical flask immersed in a cooling bath (CCl_4/CO_2). The system was evacuated using a water pump, and the maize starch heated for approximately ½ hour with a yellow luminous bunsen flame. The distillate contained in the conical flask was then dissolved in acetone, filtered, and evaporated to a small volume. This procedure was repeated in methanol, treated with charcoal, filtered, evaporated to a thick liquid, triturated, and left in a fridge to crystallise. The brown crystals thus obtained were recrystallised from iso-propanol to give leavoglucosan (1,6-anhydro-β-D-glucopyranose) (∿ 10g) m.p. 172°C (lit.[108] 172°C)

Leavoglucosan from penta-O-acetyl-β-D-glucopyranose

(i) Tetraacetyl-β-phenyl-D-glucose

To a melt composed of phenol (213g, 2.27M) and p-toluenesulphonic acid (3g) was added penta-acetyl-β-D-glucose (220g, 0.563M). This was heated on a steam bath for 1¼ hours, under reduced pressure, with the acetic acid produced being distilled off during the heating. The resultant syrup was poured into hot water (1ℓ) and extracted with dichloromethane (1.25ℓ). The organic extract was washed with NaOH solution (8 x 500 ml), water (2 x 500 ml) and dried with calcium chloride. Removal of the solvent gave yellow crystals which were recrystallised from boiling ethanol (200 ml) to give tetraacetyl-β-phenyl-D-glucose, 150 gm, yield 65%, m.p. 119-120°C (lit.[108] m.p. 120-122°C).

(ii) 1,6-anhydro-β-D-glucopyranose triacetate

To a solution of sodium hydroxide (117 gm) water (1ℓ) was added tetra-acetyl-β-phenyl-D-glucose (150 gm). The solution was then maintained at a gentle reflux for 20 hours. After cooling the solution was neutralised with a solution consisting of conc. sulphuric acid (124g) and ice (124g). The solution was then concentrated to dryness on a steam bath under reduced pressure. The residue was extracted with ethanol (1ℓ). The ethanolic solution was concentrated to dryness under reduced pressure and the residue acetylated by cautious addition of acetic anhydride (0.41ℓ). After heating for 1 hour on a steam bath, the excess anhydride was decomposed by the addition of water (34 ml), and the acetic acid removed by distillation under reduced pressure. The residue was extracted with chloroform (0.55ℓ) and this extract washed with water (2 x 150 ml). After removal of the chloroform, the residue was crystallised from 95% ethanol (45 ml) to give 36.5 gm of 1,6-anhydro-β-D-glucopyranose triacetate m.p. 107-108°C, yield 37%, (lit.[108] m.p. 107-108°C).

(iii) 1,6-anhydro-β-D-glucopyranose

The triacetate (50g) was dissolved in methanol (500 ml) and 50 ml of a 1% solution of sodium in methanol was added. After 15 minutes, this was neutralised with Amberlite IR120 (H^+) resin, treated with charcoal, filtered, and evaporated to dryness. Recrystallisation from methanol yielded pure 1,6-anhydro-β-D-pyranose, yield nearly quantitative, m.p. 172°C, (lit.[108] m.p. 172°C).

2,4-di-O-tosyl-1,6-anhydro-β-D-glucopyranose (27)

To 1,6-anhydro-β-D-glucopyranose (9g) dissolved in dry pyridine (40 mls) was added a solution of p-toluene-sulphonyl chloride (33g) in dry dichloromethane (30 mls) over 30 minutes, with efficient stirring and the temperature maintained at 20°C. After 3 days the mixture was poured into iced water (500 ml), and extracted with dichloromethane (2 x 100 ml). This extract was washed with 5% sulphuric acid (5 x 25 mls), water (2 x 25 mls), and dried over magnesium sulphate. After removal of the solvent, the residue was recrystallised from ethanol to give 16g of 2,4-di-O-tosyl-1,6-anhydro-β-D-glucopyranose, m.p. 116-117°C, yield 61%, (lit.[19] m.p. 116-118°C).

2-O-tosyl-1,6-3,4-dianhydro-β-D-galactopyranose (28).

The pure ditosylate (27) or the crude material obtained before recrystallisation, were both suitable substrates for this reaction.

The crude ditosylate (61g) was dissolved in dry chloroform (400 ml), dry methanol (200 ml) and 100 ml of 25% sodium methoxide solution added dropwise, with cooling over ½ hour. After stirring for 36 hours at room temperature, water (100 ml) was added and the layers were separated. The chloroform solution was washed with water (3 x 30 ml) and dried ($MgSO_4$). After removal of the solvent, the residue was recrystallised from hot 5:1 methanol/chloroform to give 18g of needle-shaped crystals, m.p. 151-152°C, (lit.[19] m.p. 147-148°C).

1,6-anhydro-2,4-di-O-tosyl-β-D-ribo-hexopyranos-3-ulose

To a solution of 1,6-anhydro-2,4-di-O-tosyl-β-D-glucopyranose (7.5g) in acetic acid (70 ml) and sulphuric acid (1 ml) cooled to 20°C, was added a solution of chromium trioxide (4g) in water (5 ml) over 10 minutes. After 15 min. the mixture was poured into 100 ml of chloroform and 100 ml of water. After separation of the layers, the chloroform layer was washed with water (4 x 50 ml) and dried ($MgSO_4$). After removal of solvent, the residue was triturated with ether and left in the fridge. This resulted in 5.3g of the ulose, m.p. 106-107°C, yield 67% (lit.[109] m.p. 108-110°).

Catalytic reduction of the di-tosyl ketone

(i) In the absence of hydrogen 1,6-anhydro-2,4-di-O-tosyl-β-D-ribo-hexopyranos-3-ulose (6.5g) was dissolved in acetone (80 ml) and 80 ml of Raney nickel 'T1' suspension added. After stirring for 40 minutes, the solution was filtered, the solvent removed, and the residue extracted with hot ether. On cooling, the starting ketone crystallised out (0.51g, recovery 78%).

(ii) In the presence of hydrogen

To the ditosyl ketone (0.25g) in acetone (3 ml) was added Raney nickel 'T1' suspension (10 ml) and the mixture stirred for 40 minutes under 1 atmosphere of hydrogen. The mixture was filtered, the solvent removed, and the residue extracted with ether. From the ether solution, the ditosyl ketone (0.1g) crystallised out. After removal of ether, the residue was subjected to preparative T.L.C. This resulted in the isolation of the isomeric mono-tosyl ketones, 1,6-anhydro-

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2-O-tosyl-4-deoxy-β-D-threo-hexopyranos-3-ulose (34) and 1,6-anhydro-2-O-tosyl-4-deoxy-erythro—hexopyranos-3-ulose (35) as an inseparable mixture (0.07g). NMR indicated the ratio of these compounds to be 6:1. Also isolated was an oil which was distilled (140°C, 1 mm) to give 1,6-anhydro-2,4-dideoxy-β-D-glycero-hexopyranos-3-ulose (29) (0.04g), $[\alpha]_D^{25}$-99° (c 3, chloroform); lit.[17] $[\alpha]_D$-98°.

Birch reduction of 1,6-anhydro-2,4-di-O-tosyl-β-D-ribo-hexopyranos-3-ulose

A solution of 2g of the ketone in dry tetrahydrofuran (80 ml) and dry methanol (20 ml) was cooled to -78°C. To 200 mls of ammonia condensed into a flask was added enough metallic sodium to impart a permanent blue solution, and then a further 1g of sodium was added. To the ammonia solution was slowly added the ketone solution. After 10-15 minutes the solution decolourised, the ammonia was evaporated off, and the residue extracted with ether (100 ml). Preparative TLC of this material yielded no identifiable compounds.

Dimethyl copper lithium reduction of 1,6-anhydro-2,4-di-O-tosyl- -D-ribo-hexopyranos-3-ulose

Dimethyl copper lithium was synthesised as follows. To copper(I) iodide (0.2g) in dry tetrahydrofuran (3 ml) cooled to -10°C, was added dropwise methyl lithium in tetrahydrofuran/hexane (4 ml, 0.85M). A yellow colour developed immediately (due to CuMe) and this slowly disappeared to give a colourless solution of dimethyl copper lithium.

To this solution, was slowly added the ketone (0.1g) in tetrahydrofuran (2 ml). After 1 hour at -10°C, saturated

ammonium chloride solution (3 ml) was added. This solution was extracted with dichloromethane, the extract washed with sat. NaCl solution, and dried ($MgSO_4$). TLC indicated the presence of a multitude of products. Preparative TLC produced no identifiable compounds.

Reduction of 1,6-anhydro-2,4-di-O-tosyl-β-D-glucopyranose (27) with $LiAlH_4$

To a solution of the ditosylate (27, 1.0g) in dry tetrahydrofuran (50 ml) was added $LiAlH_4$ (0.75g). The solution was refluxed under nitrogen for 16 hours. To the cooled mixture was added wet ether to decompose the excess hydride. The mixture was then filtered, dried (Na_2SO_4) and evaporated to an oily residue (0.2g). Preparative TLC resulted in the isolation of some very polar material assumed to be isomeric mono-deoxy sugars (0.03g.
δ 5.05-5.45 (1H), 4.2-4.6 (1H), 3.7-4.2 (4H), and 1.3-2.7 (2H). Also isolated was an oil (0.17g), which by GC analysis (SCOT Carbowax 20M, 50', 165°C, flow rate 14 ml/min) consisted of 1,6-anhydro-2,4-dideoxy-β-D-threo-hexopyranose (36, Rt 3.2), 1,6-anhydro-3,4-dideoxy-β-D-threo-hexopyranose (37, Rt 4.54) and 1,6-anhydro-2,3-dideoxy-β-D-threo-hexopyranose (46, Rt 6.77) in the percentage ratio 68.5:31:1.5. The assignment of the peaks as these isomers was based on data obtained by Černý et al.[22]

Reduction of 2-O-tosyl-1,6-3,4-dianhydro-β-D-galactopyranose (28) with $LiAlH_4$

To the tosyl-epoxide (0.5g) in dry tetrahydrofuran (50 ml) was added $LiAlH_4$ (0.5g). After refluxing for 8 hours, the mixture was worked up in an analogous manner to the previous

reduction. This yielded 0.16g of an oil which g.l.c. analysis demonstrated was composed of the alcohols (36) and (37) in the percentage ratio 65:35.

1,6-anhydro-3-O-(2-methoxyethoxymethyl)-2,4-di-O-tosyl-β-D-glycopyranose (51)

To a solution of (27) (2.75g) in dry acetonitrile (50 ml) was added triethyl (2-methoxyethoxymethyl) ammonium chloride (2.64g). The solution was refluxed for 48 hours, and then cooled, poured into ice-water (300 ml), and extracted with dichloromethane (100 ml). The extract was washed with water, aqueous ammonium chloride, and water, dried ($MgSO_4$) and concentrated. The resulting oil was eluted from silica gel (300g) with light petroleum-ether-ethyl acetate (5:3.5:1.5). The early fractions contained 2-O-tosyl-4-chloro-1,6-anhydro-β-D-glucopyranose (90) (0.65g), m.p. 175-176.5°.

Anal. Calc. for $C_{13}H_{15}O_6SCl$: C, 46.6; H, 4.50; S, 9.60. Found: C, 46.8; H, 4.50; S, 9.57%.

The later fractions contained (51) (1.94g, 60%), m.p. 98.5-99.5, $[\alpha]_D^{25}$ -33° (c 1, chloroform).

Anal. Calc. for $C_{24}H_{30}O_{11}S_2$: C, 51.60; H, 5.41; S, 11.48. Found: C, 51.77; H, 5.43; S, 11.66%.

Attempted reduction of (51) with $LiAlH_4$

To a solution of (51) (1.0g) in dry tetrahydrofuran (50 ml) was added $LiAlH_4$ (0.5g) and the solution refluxed for 8 hours under nitrogen. The usual work-up afforded on oil (0.4g) which was purified by preparative t.l.c. The oil obtained showed one spot on t.l.c. (Rf. 0.08, benzene-acetone, 9:1) and appeared to be 1,6-anhydro-3-O-(2-methoxyethoxymethyl)-β-D-

glucopyranose (52) (0.3g).

δ 5.45 (s, 1H, H-1), 4.83 (s, 2H, MEM-CH_2), 4.56 (s, 1H, H-5), 4.04 (m, 1H, H-6_{ENDO}), 3.66 (m, 8H, H-6_{EXO}, MEM-CH_2, H-2, H-3, H-4), and 3.42 (s, 3H, MEM-CH_3).

Acetylation of (52)

To a solution of the diol (52) (0.045g) in dry pyridine (1 ml) was added acetic anhydride (0.5 ml). After standing for 15 hours at room temperature, the solution was poured into water (15 ml) and extracted with dichloromethane (3 x 15 ml). This extract was washed with copper sulphate solution, sodium bicarbonate solution and water. After drying ($MgSO_4$) and removal of solvent, the di-acetate, 1,6-anhydro-3-O-(2-methoxyethoxymethyl)-2,4-di-O-acetyl-β-D-glucopyranose (53) (0.049g) was obtained as a crystalline solid. Recrystallisation from methanol afforded pure material, m.p. 84-85°C, $[\alpha]_D^{25}$ - 35.4°, (c 3, chloroform).

δ 5.46 (s, 1H, H-1), 4.85 (s, 2H, MEM-CH_2), 4.56-4.8 (m, 3H, H-5, H-2, H-4), 4.20 (d, 1H, H-6_{ENDO}), 3.5-4.0 (m, 6H, MEM-CH_2, H-6_{EXO}, H-3), 3.39 (s, 3H, MEM-CH_3), and 2.18 (2 x s, 6H, OAc).

Reduction of (27) with lithium triethylborohydride

To a solution of (27) (3.5g) in dry tetrahydrofuran (50 ml) under nitrogen at 0°C was added dropwise with stirring, a solution of lithium triethylborohydride (45 mM) in tetrahydrofuran over 2 hours. After 18 hours, water (7 ml) was added dropwise at 0°C, followed by a mixture of 3M sodium hydroxide (25 ml) and 30% hydrogen peroxide (20 ml). After warming to room temperature and stirring for 1 hour, dichloromethane

(150 ml) was added and the aqueous layer saturated with potassium carbonate, separated, and then continuously extracted with dichloromethane for 10 hours. The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue extracted with hot ether. Concentration of the extract yielded an oil (0.86g) which was shown by g.l.c. to be 90% pure and to contain (36), (37) and (46) in ratio 91.5:7.5:1.0.

Reduction of (27) with lithium tri-sec-butylborohydride

To a solution of (27) (1.23g, 2.6 mM) in dry tetrahydrofuran at 0°C under nitrogen was added dropwise over 20 minutes, a solution of lithium tri-sec-butylborohydride (16 mM). After 8½ hours the excess hydride was decomposed by the addition of 5 ml of water. This was followed by the normal work-up to give an oil (0.27g). Analysis by g.l.c. (15' Apiezon L, 127°C, flow rate 20 ml/min) revealed the presence of the alcohols (36), (Rt 5.83, 60%), (37) (Rt 6.58, 10%), (46) (Rt 7.74, 0.7%), the olefins (54) (Rt 2.78, 13%), (55) (Rt 2.37, 2.5%), and the saturated compound (56) (Rt 2.1, 2.5%). The identities of the compounds (54) - (56) were confirmed by co-injections both on the above column and on a butanediol succinate column, (150°C, 10% BDS 15', flow rate 20 ml/min), (54), Rt 4.0; (55), Rt 3.0; (56), Rt 3.6.

1.6:2,3-dianhydro-4-deoxy-β-D-lyxo-hexopyranose (40)

To the hydroxy tosylate (39), (0.55g) in chloroform (10 ml) and methanol (4 ml) was added 25% sodium methoxide solution (1 ml). After standing at room temperature for 18 hours, water (6 ml) was added, the layers were separated and the aqueous

layer washed with chloroform (2 x 5 ml). The combined chloroform solutions were dried ($MgSO_4$) and the solvent removed. The residue was dissolved in ether and treated with charcoal. Filtration and removal of solvent gave an oil (0.195g). This was distilled (flask to flask, 80°C, 0.2 mm) to give a crystalline material (0.142g, 61%), m.p. 67-68°C (lit. m.p. 69-70°C), $[\alpha]_D^{25}$ -28° (c 1, chloroform), (lit.[26] $[\alpha]_D^{29}$ -35° (c 1, water)).

Reduction of (40) with lithium triethylborohydride

To the epoxide (40, 0.14g) in dry tetrahydrofuran (5 ml) at 0°C under nitrogen was added a solution of lithium triethylborohydride in tetrahydrofuran (2 ml) dropwise. After 8 hours the solution was worked up in the normal manner to yield an oil (0.126g). Analysis by g.l.c. showed this consisted of (36) and (37) in 90% yield in ratio 4.56:1.0.

Reaction of a mixture of (36) and (37) with diethyltrimethylsilylamine

To a solution of the mixture (0.78g) in dry acetone (10 ml) at 0° was added diethyltrimethylsilylamine (0.29g), and the solution was stirred for 45 minutes at 0°. G.l.c. (15', 5% Apiezon L, 127°C, 20 ml/min) then showed the removal of (37) with concomitant formation of its trimethylsilylether derivative (Rt 14.0), and a small amount of the trimethylsilylether derivative of (36) (Rt 10.8). Water (10 ml) was added, the acetone was evaporated, and the aqueous solution extracted with dichloromethane (10 ml), and then continuously with dichloromethane for 20 hours. The latter extract was dried ($MgSO_4$) and

concentrated to give the pure alcohol (36) (0.62g, 80%), $[\alpha]_D^{25}$ -80° (c 1, water); lit.[21] $[\alpha]_D^{25}$ -81°.

δ 5.65 (s, 1H, H-1, 4.52 (m, 1H, H-5), 4.33 (d, 1H, $H\text{-}6_{ENDO}$), 4.04 (m, 1H, H-3), 3.72 (m, 1H, $H\text{-}6_{EXO}$), and 1.6-2.4 (m, 4H, $H\text{-}2_{EXO,ENDO}$, $H\text{-}4_{EXO,ENDO}$).

Oxidation of a mixture of (36) and (37) with pyridinium chlorochromate

A solution of the mixture of alcohols (36) and (37) (0.13g) in dichloromethane (2 ml) at 25°C, was added dropwise to a stirred suspension of pyridinium chlorochromate (0.43g) in dichloromethane (5 ml). After 1 hour, the solvent was removed, and the residue was extracted with ether. The extract was concentrated and the residue was eluted from silica gel (10g) with benzene-ethanol (98:2) to give first, 1,6-anhydro 2,4-dideoxy-β-D-glycero-hexopyranos-3-ulose (29) (0.078g), $[\alpha]_D^{25}$ -99° (c 3, chloroform); lit.[17] $[\alpha]_D$ -98°. The later fractions contained the alcohol (37), (0.011g).

δ 5.27 (s, 1H, H-1), 4.47 (m, 1H, H-5), 3.7-3.9 (m, 2H, $H\text{-}2_{ENDO}$, $H\text{-}6_{ENDO}$), 3.55 (dd, 1H, $H\text{-}6_{EXO}$, $J_{6ENDO,6EXO} \sim 9$, $J_{6EXO,5} \sim 5$ Hz), and 2.5-1.3 (m, 4H, $H\text{-}3_{EXO,ENDO}$, $^{4}_{EXO,ENDO}$).

Formation of the tert-butyldimethylsilyl enol ethers of (29) using lithium di-isopropylamide

To a solution of lithium di-isopropylamide (2.7 mM) in dry tetrahydrofuran (15 ml), prepared by the addition of di-isopropylamine (0.272g, 2.9 mM) to methyl lithium (2.7 mM) in tetrahydrofuran at 0°C, followed by stirring for 10 minutes and cooling to -70°. was added dropwise with stirring under nitrogen, the ketone (29), (0.23g, 1.8 mM) dissolved in

tetrahydrofuran (10 ml). After stirring for 10 minutes, a solution of tert-butyldimethylsilyl chloride and imidazole in tetrahydrofuran was added all at once at -70°. This solution was prepared by the addition of tert-butyldimethylsilyl chloride (1g) to imidazole (0.95g) in dry tetrahydrofuran (20 ml) at room temperature followed by filtration under N_2 to give a clear solution.

The reaction mixture was then allowed to warm to room temperature and quenched with ice-water (20 ml). This solution was extracted with dichloromethane, and this extract was washed with aqueous sodium bicarbonate solution (3 x 20 ml), water (2 x 20 ml) and dried ($MgSO_4$). After removal of solvent, the remaining oil was shown by g.l.c. (SCOT Carbowax 20M, 141°, 10 ml/min) to consist of one main component (Rt 29.8, 85%). This was distilled (flask to flask, 100°C, 0.2 mm) to afford pure 3-O-tert-butyldimethylsilyl-1,6-anhydro-2,4-dideoxy-β-D-glycero-hex-2-enopyranose (0.15g, 50%).

δ 7.23 (d, 1H, H-2), 5.26 (d, 1H, H-1, $J_{1,2}$ = 6Hz), 4.35 (m, 1H, H-5, $J_{5,4EXO}$ = 13, $J_{5,4ENDO}$ = 4Hz), 3.7-3.8 (m, 2H, H-6_{EXO},6_{ENDO}), 2.62 (dd, 1H, H-4_{EXO}, $J_{4EXO,4ENDO}$ = 16, $J_{4EXO,5}$ = 13 Hz), 2.28 (dd, 1H, H-4_{ENDO}) and 0.8 (s, 9H, t-Bu).

$[\alpha]_D^{25}$ + 131.5° c 1.5 (chloroform).

Anal. Calc. for $C_{12}H_{22}O_3S$: C, 59.46, H, 9.15.

Found: C, 59.54, H, 9.15%.

Attempted formation of the trimethylsilyl enol ethers of (29) using potassium tert-butoxide

To a solution of potassium (0.1g) in dry t-butanol (10 ml) under N_2 at room temperature was added with stirring a solution of (29), (0.13g) in tetrahydrofuran (1 ml). After

25 minutes the reaction was quenched with a solution of chlorotrimethylsilane (3 mM) and triethylamine (1 mM) in tetrahydrofuran (5 ml). After pouring into water (10 ml), the solution was extracted with dichloromethane (2 x 25 ml). The extracts were washed with water (5 x 20 ml), dried ($MgSO_4$) and the solvent removed to leave a tert-butanol solution. The tert-butanol was removed by evaporation at low pressure (0.5 mm) to leave a residue which appeared to be entirely inorganic.

Formation of the tert-butyldimethylsilyl enol ethers of (29) using potassium hydride

Approximately 0.4 ml of KH suspension was placed in a 3-necked flask under nitrogen and washed with hexane (3 x 3 ml) to remove the mineral oil present. After addition of tetrahydrofuran (10 ml), a solution of (29) (0.14g) in tetrahydrofuran (1.5 ml) was introduced dropwise at room temperature. This caused minimal hydrogen evolution. After stirring for 0.5h, a solution of the tert-butyldimethyl silylating agent (3 equivs, prepared as previously described) was introduced. T.l.c. (benzene-acetone, 9:1) demonstrated that all the ketone had reacted after 3 days. After 4 days the mixture was poured in dichloromethane-water (50 ml), the layers separated, the organic layer washed with brine and dried (Na_2SO_4). Solvent removal yielded a brown oil (0.63g). This was purified by flash chromatography using as solvent, light petroleum ether-ether-ethyl acetate (6:3.5:0.5) to yield the silyl enol ether (63) (0.2g, 70% yield). G.l.c. and n.m.r. analysis did not reveal the presence of the isomeric Δ^3 enol ether.

Attempted formation of the trimethylsilyl enol ethers of (29) using triethylamine

To a solution of (29) (0.1g, 0.78 mM) in dry dimethylformamide (5 ml) were added chlorotrimethylsilane (0.184 ml, 1.5 equiv.) and triethylamine (0.33 ml, 3 equiv.). The solution was refluxed under N_2 for 16 hours, by which time it had turned black. After pouring into dichloromethane-water (70 ml) the layers were separated, the organic layer being washed with water and dried. After treatment with charcoal, the solvent was removed to produce an oil (0.04g). Examination by g.l.c. showed that this was composed of over 14 products. The two main peaks (comprising about 30% of the mixture) may have been the desired enol ethers, however the n.m.r. spectrum revealed no identifiable features.

Attempted isomerisation of (63) with an acid catalyst

To a solution of (63) (0.07g) in dry carbon tetrachloride was added dry p-toluenesulphonic acid. This solution was refluxed for 3 days, but t.l.c. indicated no reaction. The solution was then filtered, concentrated and examined by n.m.r. This confirmed the presence of (63) with no substantial impurities. To this solution was added one drop of boron trifluoride-acetic acid complex. The solution immediately turned dark brown. N.m.r. showed that all peaks due to (63) had disappeared, with the formation of no assignable new resonances.

Acid catalysed reaction of (28) with thiophenol

(1) With sulphuric acid

To a solution of the epoxide (28) (1g) in dry benzene (4 ml) and freshly distilled thiophenol (4 ml) was added, with stirring, conc. sulphuric acid (0.3 ml, 1.5 equiv). After

stirring for 7 hours, chloroform was added, and the solution washed with water, sodium bicarbonate solution and water. After drying, ($MgSO_4$), removal of solvent, yielded an oil, which was extracted with light petroleum ether to remove excess thiophenol. This resulted in a thick oil (0.9g) which was applied to silica (60g, eluting solvent, benzene-methanol, 97:3 to 94:6) to give in the early fractions, 1,6-anhydro-2,4-dideoxy-2,4-diphenythio-β-D-glucopyranose (69), (0.23g).

δ 7.67 (d, 2H, Ts), 7.24 (d, 2H, Ts), 7.13 (m, 5H, SPh), 7.02 (m, 5H, SPh), 5.34 (s, 1H, H-1), 4.4-4.65 (m, 2H, H-2, H-5), 4.39 (d, 1H, $H\text{-}6_{ENDO}$, $J_{6ENDO,6EXO}$ = 7.5 Hz), 3.63 (m, 1H, $H\text{-}6_{EXO}$), 3.34 (s, 1H, H-3), 3.22 (s, 1H, H-4, $J_{4,5}$ = 1.5, $J_{3,4}$ = 1.5 Hz) and 2.30 (s, 3H, CH_3).

Calc. m/e: 500.0787 (M^+). Found m/e: 500.0947 ($C_{25}H_{24}O_5S_3$)

The latter fractions produced 1,6-anhydro-4-deoxy-4-phenylthio-2-O-tosyl-β-D-glucopyranose (65), (0.42g) as an oil.

δ 7.31 (m, 5H, SPh), 7.55 (dd, 4H, Ts), 5.36 (s, 1H, H-1), 4.63 (d, 1H, H-5, $J_{5,6EXO}$ = 6 Hz), 4.31 (s, 1H, H-2, $J_{2,3}$ = 2 Hz), 4.07 (d, 1H, $H\text{-}6_{ENDO}$, $J_{6EXO,6ENDO}$ = 9 Hz), 3.92 (s, 1H, H-3, $J_{3,4}$ = 2 Hz), 3.70 (dd, 1H, $H\text{-}6_{EXO}$), 3.20 (s, 1H, H-4, $J_{4,5}$ = 2 Hz) and 2.35 (s, 3H, CH_3).

$[\alpha]_D^{25}$ -27^o c 1 (chloroform)

Calc. m/e: 408.0702. Found m/e: 408.

0730, ($C_{19}H_{20}O_6S_2$)

(2) With Amberlite IR 120 (H^+) resin

To a solution of (28), (1g) in dry benzene (2 ml) and thiophenol (0.5 ml) was added dry Amberlite IR 120 (H^+)

stirring for 7 hours, chloroform was added, and the solution washed with water, sodium bicarbonate solution and water. After drying, ($MgSO_4$), removal of solvent, yielded an oil, which was extracted with light petroleum ether to remove excess thiophenol. This resulted in a thick oil (0.9g) which was applied to silica (60g, eluting solvent, benzene-methanol, 97:3 to 94:6) to give in the early fractions, 1,6-anhydro-2,4-dideoxy-2,4-diphenythio-β-D-glucopyranose (69), (0.23g).

δ 7.67 (d, 2H, Ts), 7.24 (d, 2H, Ts), 7.13 (m, 5H, SPh), 7.02 (m, 5H, SPh), 5.34 (s, 1H, H-1), 4.4-4.65 (m, 2H, H-2, H-5), 4.39 (d, 1H, $H\text{-}6_{ENDO}$, $J_{6ENDO,6EXO}$ = 7.5 Hz), 3.63 (m, 1H, $H\text{-}6_{EXO}$), 3.34 (s, 1H, H-3), 3.22 (s, 1H, H-4, $J_{4,5}$ = 1.5, $J_{3,4}$ = 1.5 Hz) and 2.30 (s, 3H, CH_3).

Calc. m/e: 500.0787 (M^+). Found m/e: 500.0947 ($C_{25}H_{24}O_5S_3$)

The latter fractions produced 1,6-anhydro-4-deoxy-4-phenylthio-2-O-tosyl-β-D-glucopyranose (65), (0.42g) as an oil.

δ 7.31 (m, 5H, SPh), 7.55 (dd, 4H, Ts), 5.36 (s, 1H, H-1), 4.63 (d, 1H, H-5, $J_{5,6EXO}$ = 6 Hz), 4.31 (s, 1H, H-2, $J_{2,3}$ = 2 Hz), 4.07 (d, 1H, $H\text{-}6_{ENDO}$, $J_{6EXO,6ENDO}$ = 9 Hz), 3.92 (s, 1H, H-3, $J_{3,4}$ = 2 Hz), 3.70 (dd, 1H, $H\text{-}6_{EXO}$), 3.20 (s, 1H, H-4, $J_{4,5}$ = 2 Hz) and 2.35 (s, 3H, CH_3).

$[\alpha]_D^{25}$ -27° c 1 (chloroform)

Calc. m/e: 408.0702. Found m/e: 408.0730, ($C_{19}H_{20}O_6S_2$)

(2) With Amberlite IR 120 (H^+) resin

To a solution of (28), (1g) in dry benzene (2 ml) and thiophenol (0.5 ml) was added dry Amberlite IR 120 (H^+)

resin (2g). The solution was refluxed for 16 hours, during which time t.l.c. (benzene-acetone, 9:1) showed the formation of only a small amount of polar product. On normal work-up, the epoxide was recovered unchanged (0.8g).

(3) With trifluoroacetic acid

A solution of (28) (0.5g) in chloroform (2 ml), benzene (5 ml) and trifluoroacetic acid (0.25 ml) was refluxed for 24 hours, with thiophenol (1 ml). The normal work-up yielded an oil (1.04g) which was applied to silica gel (120g, eluting solvent benzene-acetone, 9.1). The latter fractions provided (65) as a semi-crystalline solid (0.5g, 80%).

(4) With trichloroacetic and acetic acids

Using an analogous procedure to '3' above, these catalysts resulted in minimal reaction, with formation of coloured impurities.

Alumina-catalysed reaction of (28) with thiophenol

Alumina (freshly opened WOELM N, Act.1; 8.8g), was placed in a dry flask under N_2 and dry tetrahydrofuran (10 ml) and dry thiophenol (0.33 ml) added. After stirring for 5 minutes, the epoxide (28) (0.35g) in tetrahydrofuran (10 ml) was added all at once. After stirring at room temperature (20 hours), the mixture was poured into methanol and left for 3 hours. After filtration through celite, and removal of solvent, the residual oil was washed with light petroleum ether, and applied to a silica gel column eluting solvent:light petroleum ether-ether-ethyl acetate (5:5:0.4) . The early fractions contained 1,6:2,3-dianhydro-4-deoxy-4-phenylthio-β-D-manno-hexopyranose (72), (0.02g).

δ 7.2-7.5 (m, 5H, SPh), 5.72 (d, 1H, H-1, $J_{1,2}$ = 3 Hz), 4.54 (m, 1H, H-5), 3.72-3.82 (m, 2H, H-6_{EXO}, H-6_{ENDO}),

3.4-3.53 (m, 2H, H-2, H-3), 3.24 (d, 1H, H-4, $J_{4,3}$ = 3.5 Hz).
$[\alpha]_D^{25}$ +46, (c 1; chloroform); m.p. 116-116.5°.
Calc. m/e: 236.0502 (M^+). Found m/e: 235.0507 ($C_{12}H_{12}O_3S$)
Anal. Calc. for $C_{12}H_{12}O_3S$: C, 61.0; H, 5.12; S, 13.57.
Found: C, 60.74; H, 5.36; S, 13.70%.

This was followed by 1,6-anhydro-2,4-dideoxy-2,4-phenylthio-β-D-glucopyranose (73) (0.07g).
δ 7.15-7.55 (m, 10H, 2 x SPh), 5.67 (s, 1H, H-1),
4.68 (d, 1H, H-5, $J_{5,6EXO} \sim 5$ Hz), 4.1-4.2 (m, 2H, H-3, $H\text{-}6_{ENDO}$),
3.75 (dd, 1H, $H\text{-}6_{EXO}$, $J_{6EXO,6ENDO}$ = 7 Hz), 3.30 (s, 2H, H-2,
H-4, W/2 ~ 9 Hz), 2.55 (s, 1H, OH)
$[\alpha]_D^{25}$ -54.4° (c 1; chloroform); m.p. 108-110°C.
Calc. m/e: 346.0698 (M^+). Found m/e: 346.0701 ($C_{18}H_{18}O_3S_2$)

The final fractions yielded (65) (0.09g).

Reaction of (28) with sodium thiophenoxide

(1) Using one equivalent of thiophenoxide

To a solution of (28) (1g) in methanol-chloroform was added a solution of sodium methoxide (10 equiv.) and thiophenol (1.2 equiv., 0.28 ml). This mixture was stirred at room temperature for 24 hours. T.l.c. (benzene-acetone, 9:1) indicated the presence of (28) (Rf 0.38), (72) (Rf 0.45), and several minor products. The solution was neutralised with dil. sulphuric acid and then extracted with dichloromethane. The normal work-up yielded a semi-crystalline oil from which the epoxide (28) could be partially recovered by recrystallisation.

(2) Using excess thiophenoxide

The reaction was performed as above, using 10 equivalents (2 ml) of thiophenol. T.l.c. indicated the formation of (72) with concomitant formation of (73) (Rf 0.28).

Sulphenylation of (28) in the presence of a silylating agent

To a solution of (28) (0.3g) and chlorotrimethylsilane (0.2 ml) in tetrahydrofuran (5 ml) at 0°C under N_2 was added sodium thiophenoxide (0.4g). This gradually dissolved, and a white precipitate formed. T.l.c. indicated reaction was complete after 10 hours at room temperature. Chloroform was added and the solution neutralised with dil. HCl. The layers were separated, the organic layer was washed with water, dried ($MgSO_4$), and the solvent removed. The residual oil was washed with light petroleum either to yield a thick gum (0.42g, 95% yield) which t.l.c. showed to be pure (65).

Reduction of (65) with lithium triethylborohydride

To a solution of (65) (0.5g) in dry tetrahydrofuran at 0°C under N_2 was added dropwise a solution of lithium triethylborohydride (2.5 equiv.) in tetrahydrofuran (2 ml). After stirring at 0°C for 0.5 hours, the mixture was warmed to room temperature. T.l.c. indicated reaction was complete after 8 hours. Water (2 ml) was added dropwise at 0°C, and then the solvent was removed. The residue was extracted with dichloromethane, dried ($MgSO_4$), filtered through celite, and the solvent removed to give an oil (0.3g) containing triethylborane. This impurity was evaporated off at low pressure, and the resultant oil crystallised from methanol to give 1,6-anhydro-2,4-dideoxy-4-phenylthio-β-D-arabino-hexopyranose (66) (0.23g). δ 7.1-7.5 (m, 5H, SPh), 5.65 (s, 1H, H-1, W/2 ∿ 5 Hz), 4.68 (d, 1H, H-5, $J_{5,6EXO}$ = 6 Hz), 4.55 (d, 1H, $H\text{-}6_{ENDO}$, $J_{6EXO,ENDO}$ = 8 Hz), 3.99 (s, 1H, H-3, W/2 ∿ 9 Hz), 3.78 (dd, 1H, $H\text{-}6_{EXO}$), 3.42 (s, 1H, H-4, W/2 ∿ 5 Hz), 2.36 (dd, 1H, $H\text{-}2_{EXO}$,

$J_{2EXO,2ENDO}$ = 15, $J_{2EXO,3}$ = 5.5, $J_{2EXO,1}$ = 1.5 Hz) and 1.84 (d, 1H, H-2_{ENDO}).

$[\alpha]_D^{25}$ -44.2 (c 1; chloroform); m.p. 74.5-76°C

Anal. Calc. for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; S, 13.46. Found: C, 60.58; H, 5.92; S. 13.57%.

Oxidation of (66) with pyridinium chlorochromate

To a suspension of pyridinium chlorochromate (6g) and anhydrous sodium acetate (0.4g) in dichloromethane at 0°C, was added dropwise with stirring, a solution of (66), (2.2g) in dichloromethane (5 ml). After stirring (2 hours) at room temperature the solution was diluted with 5 volumes of dry ether and filtered through celite. The solution was concentrated, and treated with activated charcoal. After filtration and removal of solvent, an oil (1.5g) was obtained which on crystallisation from methanol gave 1,6-anhydro-2,4-dideoxy-4-phenylthio-β-D-erythro-hexopyranos-3-ulose (67) (1.3g).

δ 7.35 (m, 5H, SPh), 5.78 (s, 1H, H-1, W/2 5 Hz), 4.92 (m, 1H, H-5, $J_{5,4}$ = 1.5 Hz), 3.86 (d, 2H, H-$6_{EXO,6ENDO}$), 3.56 (s, 1H, H-4), 3.10 (dd, 1H, H-2_{EXO}, $J_{2EXO,2ENDO}$ = 16, $J_{2EXO,1}$ = 2 Hz), 2.49 (d, 1H, H-2_{ENDO}).

$[\alpha]_D^{25}$ -52.3° (c 1.4; chloroform); m.p. 96-97°C.

Anal. Calc. for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12; S, 13.57. Found: C, 60.98; H, 5.10; S, 13.72%.

In the absence of sodium acetate, a mixture of (67) and (78) was produced. Repeated crystallisations from methanol yielded mother liquors enriched in (78):

δ 7.2-7.5 (m, 5H, SPh), 5.78 (t, 1H, H-1, $J_{1,2}$ = 2 Hz), 4.64 (t, 1H, H-5, $J_{5,4}$ = 8 Hz), 4.26 (d, 1H, $H\text{-}6_{ENDO}$), 4.18 (d, 1H, H-4), 3.75 (dd, 1H, $H\text{-}6_{EXO}$, $J_{6EXO,6ENDO}$ = 6, $J_{6EXO,5}$ = 5 Hz) and 2.71 (d, 2H, $H_{2EXO,2ENDO}$).

Syntheses of methyl 7-bromo-cis-5-heptenoate

(1) 3-tetrahydropyranyloxy-propyne

To a stirred solution of propargyl alcohol (12.6g) and dihydropyran (18.9g), cooled to 0°, was added phosphoryl chloride (0.15 ml). The mixture was stirred at room temperature (15 hours), then potassium hydroxide solution (50 ml) was added. The solution was extracted with ether, dried ($MgSO_4$) and the solvent removed. Distillation of the residue (60°C, 20 mm), gave, after a small forerun, 3-tetrahydropyranyloxy-propyne (17.5g, 60%).

δ 4.76 (s, 1H, W/2 ∿ 6 Hz), 4.21 (d, 2H, J = 2 Hz), 3.4-4.0 (m, 2H), 2.42 (t, 1H), 1.5-2.0 (m, 6H).

(2) 1-tetrahydropyranyloxy-6-chloro-2-hexyne

To a solution of 3-tetrahydropyranyloxy-propyne (34g, 0.254M) in dry tetrahydrofuran (200 ml) cooled to -70° under N_2, was added dropwise over 1 hour, a solution of butyl lithium (1.66 ml of 1.6M sol), in tetrahydrofuran. After further stirring (1 hour), the solution was warmed to room temperature and 1-bromo-3-chloropropane (41g) in tetrahydrofuran (25 ml) was added dropwise over 1 hour. After further stirring (1 hour), the solution was refluxed (24 hours), cooled, and the solvent removed. The residue was extracted with ether,

the extract washed with water (3 x 100 ml), dried ($MgSO_4$) and the solvent removed to yield an oil (42.8g, 77%). This was distilled (120°C, 0.2 mm).

δ 4.75 (s, 1H), 4.2 (t, 2H, J = 1.5 Hz), 3.2-4.0 (m, 4H), 2.1-2.6 (m, 2H), 1.8-2.1 (m, 2H) and 1.3-1.8 (m,6H).

(3) 1-tetrahydropyranyloxy-6-chloro-cis-2-hexene

A solution of 1-tetrahydropyranyl-6-chloro-hexyne (29.1g) in methanol (200 ml) containing Lindlar catalyst (0.5g) was stirred under hydrogen (52 hours). The solution was then filtered and the solvent removed to yield an oil (29.1g). N.m.r. indicated the absence of any unreacted acetylene (absence of resonances at δ 4.2).

δ 5.3-5.5 (m, 2H), 4.65 (s, 1H, W/2 ∿ 6 Hz), 3.4-3.9 (m, 2H), 3.25-3.5 (m, 4H), 2.0-2.3 (m, 2H), 1.7-1.8 (m, 2H) and 1.2-1.6 (m, 6H).

ν 3010 and 1660 cm^{-1}.

(4) 7-tetrahydropyranyloxy-cis-5-heptenyronitrile

To a solution of sodium cyanide (16.6g) in DMSO (400 ml) was added, at 50° with stirring, a solution of 1-tetrahydropyranyloxy-6-chloro-cis-2-hexene (28g) in DMSO (30 ml). After 8 hours, the solution was cooled, poured into brine (450 ml), and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and the solvent removed to yield an oil (30.8g), which appeared as one spot on t.l.c. (Rf 0.23, eluting solvent: light petroleum ether-ethyl acetate, 9:1)

ν 2200 cm^{-1}.

(5) 7-tetrahydropyranyloxy-cis-5-heptenoic acid

To a solution of sodium hydroxide (15g) in water (75 ml) and methanol (125 ml), the cyanide (29g) was added. The solution was refluxed (18.5 hours), cooled, acidified with dil. sulphuric acid to pH3 and extracted with ether (2 x 150 ml). This extract was dried ($MgSO_4$) and the solvent removed to yield an oil (32.9g).

δ 5.4-5.6 (m, 2H), 4.5 (m, 1H), 4.1 (m, 2H), 3.5-3.7 (m, 2H), 2.0-2.4 (m, 4H) and 1.3-2.0 (m, 8H).

ν_{MAX} 1720 cm^{-1}.

(6) Methyl 7-tetrahydropyranyloxy-cis-5-heptenoate

To a solution of the acid (20g) in dry ether, was added in small portions, an ethereal solution of diazomethane. After sitting for 1 hour at room temperature, t.l.c. indicated complete reaction. The ethereal solution was left overnight, and then concentrated, to yield an oil (21.5g), which was distilled (flask to flask, 100°C, 0.1 mm) to give methyl 7-tetrahydropyranyloxy-cis-5-heptenoate.

ν_{MAX} 1735 cm^{-1}.

(7) Methyl 7-hydroxy-cis-5-heptenoate

A solution of 7-tetrahydropyranyloxy-cis-5-heptenoate methyl ester (25.5g) in methanol (200 ml) with p-toluenesulphonic acid (0.4g) was stirred at room temperature (15 hours). Removal of the solvent afforded an oil which was dissolved in ether and washed with sodium bicarbonate solution (2 x 150 ml) and water (2 x 50 ml), dried ($MgSO_4$), and concentrated to yield an oil (14.0g).

δ 5.5 (s, 2H), 4.1 (d, 2H, $J \sim 6$ Hz), 3.6 (s, 3H), 1.3-2.5 (m, 6H).

(8) Methyl 7-bromo-cis-5-heptenoate

A solution of methyl 7-hydroxy-cis-5-heptenoate (13.4g) in ether (40 ml) and pyridine (1.8 ml) was cooled to -10°C. To this was added dropwise with stirring, a solution of phosphorous tribromide (4 ml) in ether (4 ml). The solution was then stirred at 0°C for ½ hour, and at room temperature for 2½ hours. After pouring into cold, dil. hydrochloric acid, the layers were separated and the ethereal layer washed with sodium bicarbonate solution and water, and dried ($MgSO_4$). Removal of the solvent yielded an oil (14.9g) which was distilled (flask to flask, 70°C 0.1 mm) to give pure methyl 7-bromo-cis-5-heptenoate.

δ 5.40 (m, 2H), 3.9 (d, 2H, J ~ 6 Hz), 3.6 (s, 3H), 1.3-2.5 (m, 6H)

ν_{MAX} 1735 cm^{-1}

m/e Found: 141 (M^+-Br).

Alkylation of 1,6-anhydro-2,4-dideoxy-4-phenylthio-β-D-erythro-hexopyranos-3-ulose with methyl 7-bromo cis-5-heptenoate

(1) Using sodium hydride

In a dry flask under N_2 was placed sodium hydride dispersion (0.033g, 1.05 equiv.) This was washed with dry pentane (3 x 2 ml) and the solvent evaporated off in a stream of nitrogen. Dry tetrahydrofuran (7 ml) was then added and the solution cooled to 0°. To this solution was added the ketone (67) (0.2g) in tetrahydrofuran (6 ml) over 10 minutes. Hydrogen evolution began on warming to room temperature. After stirring at room temperature (1 hour) a solution of the bromide (0.245g) in tetrahydrofuran (5 ml) was added. After 24 hours the solution was cooled, and saturated ammonium chloride solution (10 ml) added.

After removal of the tetrahydrofuran, the residue was extracted with ether (2 x 50 ml). This was washed with brine (2 x 5 ml), and dried ($MgSO_4$). Removal of solvent yielded an oil, (0.34g). This was purified by preparative t.l.c. (silica gel, eluting solvent:petroleum ether-ether-ethyl acetate, 5:5:1), to give pure (4S)-1,6-anhydro-2,4-dideoxy-4-phenylthio-4-(7-methyloxycarbonyl-cis-2-heptenyl)-β-D-glycero-hexopyranos-3-ulose (82):

δ 7.3 (s, 5H, SPh), 5.65 (s, 1H, H-1, $J_{1,2}$ = 1.5 Hz), 5.4-5.6 (m, 2H), 4.52 (d, 1H, H-5, $J_{5,6EXO}$ = 8 Hz), 4.16 (d, 1H, $H\text{-}6_{ENDO}$), 3.67 (dd, 1H, $H\text{-}6_{EXO}$, $J_{6EXO,6ENDO}$ = 7 Hz), 3.50 (s, 3H), 2.60 (s, 2H, $H\text{-}2_{EXO,2ENDO}$), 1.6-2.4 (m, 8H).

ν_{MAX} 1720, 1733 cm^{-1}.

Anal. Calc. for $C_{20}H_{24}O_5S$: C, 63.80, H, 6.43; S, 8.52. Found: C, 64.02; H, 6.54; S, 8.34%.

(2) Using potassium hydride

Approximately 1.25 equiv. of potassium hydride suspension (0.45g) was placed in a dry flask under nitrogen and washed with dry pentane (3 x 5 ml). Dry tetrahydrofuran (20 ml) was added followed by a solution of the ketone (0.63g, 2.7 mM) in tetrahydrofuran (10 ml), dropwise over 0.5 hours. Hydrogen evolution was rapid, and had ceased after a further 0.5 hours. A solution of the bromide (0.45g, 1.3 equiv.) in tetrahydrofuran (7 ml) was then added rapidly. After 17 hours at room temperature, the solution was diluted with ether (80 ml) and filtered. Removal of the solvent gave a brown oil (0.8g). Purification by preparative t.l.c. (eluting solvent:light petroleum ether-ether-ethyl acetate, 6:3:3), yielded pure (82), (0.37g, 65%).

After removal of the tetrahydrofuran, the residue was extracted with ether (2 x 50 ml). This was washed with brine (2 x 5 ml), and dried ($MgSO_4$). Removal of solvent yielded an oil, (0.34g). This was purified by preparative t.l.c. (silica gel, eluting solvent:petroleum ether-ether-ethyl acetate, 5:5:1), to give pure (4S)-1,6-anhydro-2,4-dideoxy-4-phenylthio-4-(7-methyloxycarbonyl-cis-2-heptenyl)-β-D-glycero-hexopyranos-3-ulose (82):

δ 7.3 (s, 5H, SPh), 5.65 (s, 1H, H-1, $J_{1,2}$ = 1.5 Hz), 5.4-5.6 (m, 2H), 4.52 (d, 1H, H-5, $J_{5,6EXO}$ = 8 Hz), 4.16 (d, 1H, $H\text{-}6_{ENDO}$), 3.67 (dd, 1H, $H\text{-}6_{EXO}$, $J_{6EXO,6ENDO}$ = 7 Hz), 3.50 (s, 3H), 2.60 (s, 2H, $H\text{-}2_{EXO,2ENDO}$), 1.6-2.4 (m, 8H).

ν_{MAX} 1720, 1733 cm^{-1}.

Anal. Calc. for $C_{20}H_{24}O_5S$: C, 63.80, H, 6.43; S, 8.52.
Found: C, 64.02; H, 6.54; S, 8.34%.

(2) Using potassium hydride

Approximately 1.25 equiv. of potassium hydride suspension (0.45g) was placed in a dry flask under nitrogen and washed with dry pentane (3 x 5 ml). Dry tetrahydrofuran (20 ml) was added followed by a solution of the ketone (0.63g, 2.7 mM) in tetrahydrofuran (10 ml), dropwise over 0.5 hours. Hydrogen evolution was rapid, and had ceased after a further 0.5 hours. A solution of the bromide (0.45g, 1.3 equiv.) in tetrahydrofuran (7 ml) was then added rapidly. After 17 hours at room temperature, the solution was diluted with ether (80 ml) and filtered. Removal of the solvent gave a brown oil (0.8g). Purification by preparative t.l.c. (eluting solvent:light petroleum ether-ether-ethyl acetate, 6:3:3), yielded pure (82), (0.37g, 65%).

Desulphurisation of (82)

(1) With aluminium-mercury amalgam

To a solution of (82) (0.3g) in 10% aqueous tetrahydrofuran was added aluminium foil, the surface of which had been amalgamated with mercury (0.24g). Hydrogen evolution occurred and the metal dissolved completely over 1 hour. Saturated ammonium chloride solution (10 ml) was added, the tetrahydrofuran removed, and the residue extracted with ether (2 x 50 ml). The extract was washed with brine (2 x 5 ml), dried (Na_2SO_4) and the solvent removed to yield an oil (0.27g). N.m.r. and t.l.c. indicated that this was mainly (82).

(2) With sodium-mercury amalgam

To a solution of (82) (0.025g) in dry methanol (2 ml) containing di-sodium hydrogen phosphate (0.04g) cooled to 0°, was added with stirring, 2% sodium-mercury amalgam (0.32g). T.l.c. indicated that polar materials rapidly formed. After 2 hours, water (2 ml) was added, the methanol removed, and the residue extracted with dichloromethane (3 x 30 ml). After drying ($MgSO_4$) and removal of solvent, the resultant oil was washed with light petroleum ether to yield a thick oil (0.01g). T.l.c. and n.m.r. indicated that one of several components present was the ketone (85).

(3) With Raney nickel

Raney nickel (W2) (2g) in ethanol was washed with acetone, and then refluxed in acetone for 2 hours. To this de-activated material was added a solution of (82) (0.1g) in acetone, and the solution refluxed (3 hours). After cooling, the solution was filtered through celite and the solvent

removed to yield an oil (0.1g). This was applied to a preparative t.l.c. plate (eluting solvent:benzene-ethyl acetate, 7:3) to give as a semi-crystalline oil (0.08g, 95%) 1,6-anhydro-2,4-dideoxy-4-(7-methyloxycarbonyl-cis-2-heptenyl)-β-D-threo-hexopyranos-3-ulose (85).

δ 5.66 (s, 1H, H-1), 5.36 (m, 2H), 4.61 (t, 1H, H-5, $J_{5,4}$ = 3.5, $J_{5,6EXO}$ = 5.5 Hz), 3.75 (d, 1H, H-6_{ENDO}), 3.66 (dd, 1H, H-6_{EXO}, $J_{6EXO,6ENDO}$ = 8 Hz), 3.56 (s, 3H), 2.65 (m, 1H, H-4), 2.51 (s, 2H, H-$2_{EXO,2ENDO}$, W/2 ∿ 1.5 Hz), 2.1-2.35 (m, 4H), 1.9-2.1 (m, 2H) and 1.64 (q, 2H).

ν_{MAX} 1717-1735 cm^{-1}

Calc. m/e: 268.1311 (M^+). Found: 268.1310, ($C_{14}H_{20}O_5$).

Attempted cleavage of the anhydro bridge of (82)

A solution of (82) (0.067g) in dry methanol (5 ml) with p-toluenesulphonic acid (0.035g) was refluxed. T.l.c. indicated a slow reaction with formation of several products. After 24 hours the methanol was removed and the residue extracted with chloroform. On removal of the chloroform, the residual oil, on examination by n.m.r. showed no assignable signals.

Alkylation of (67) with methyl bromoacetate

An analogous procedure to that used in the alkylation of (67) with methyl 7-bromo-cis-5-heptenoate was adopted. A solution of (67) (0.35g) was added to a magnetically stirred suspension of potassium hydride in tetrahydrofuran. On the cessation of hydrogen evolution, a solution of methyl bromoacetate (3 equiv.) in tetrahydrofuran (10 ml) was rapidly introduced. After 24 hours at room temperature, the normal method of work-up afforded an oil (0.4g). This was purified by preparative t.l.c. (eluting solvent:light petroleum ether-

ether-ethyl acetate, 4:3:3) to give as an oil (Rf 0.5, 0.27g, 63%), (4S)-1,6-anhydro-2,4-dideoxy-4-phenylthio-4-(methyloxycarbonyl-methyl)-β-D-glycero-hexopyranos-3-ulose (87):

δ 7.18-7.58 (m, 5H, SPh), 5.72 (s, 1H, H-1), 4.56 (d, 1H, H-5, $J_{5,6EXO}$ = 7 Hz), 4.18 (d, 1H, H-6_{ENDO}), 3.82 (dd, 1H, H-6_{EXO}, $J_{6EXO,6ENDO}$ = 9 Hz), 3.67 (s, 3H, CO_2Me), 3.33 (d, 1H, $CHCO_2Me$), 2.70 (d, 1H, $CHCO_2Me$, J = 15 Hz), 3.00 (dd, 1H, H-2_{EXO}, $J_{2EXO,1}$ = 2, $J_{2EXO,2ENDO}$ = 15 Hz), 2.66 (d, 1H, H-2_{ENDO}).

ν_{MAX} 1720, 1733 cm^{-1}.

Attempted de-esterification of (87)

A solution of (87) (0.110g) and sodium hydroxide (2 equiv.) in methanol (5 ml) was stirred at room temperature. T.l.c. indicated a rapid reaction with the formation of several products. After 1 hour, the solution was acidified to pH 4.5 and brine added. This solution was then extracted with dichloromethane (3 x 20 ml), the extract dried ($MgSO_4$) and the solvent removed to yield an oil (0.065g) which was washed with light petroleum ether to leave 0.035g of material. This was applied to a silica column (eluting solvent benzene-ethyl acetate (7:3) to methanol-ethyl acetate (2:8)) from which was obtained two materials (Rf methanol-ethyl acetate (3:7), 0.7 and 0.3). The more polar product appeared to have suffered cleavage of the anhydro bridge. The less polar material was the main component of the mixture

δ 7.2-7.4 (m, 5H, SPh), 5.63 (s, 1H, W/2 ~ 6 Hz), 4.4 (d, 1H, J ~ 6 Hz), 3.5-4.1 (m) and 2.2-2.6 (m).

ν_{MAX} 1725, 1627 cm^{-1}.

Reaction of the epoxide (28) with sodio-dimethylmalonate

The epoxide (28) (0.3g 1mM) was dissolved in a solution of sodium (0.45g) in methanol (20 ml)/dichloromethane (10 ml). Dimethylmalonate (0.17 ml, 1.5 equiv.) was added over 2 min with efficient magnetic stirring. As t.l.c. showed no reaction at room temperature, the solution was refluxed under N_2. After 12 hours, the solution was acidified with 2M sulphuric acid, the methanol removed, and the residue extracted with dichloromethane (6 x 20 ml) to yield after removal of solvent, an oil (0.2g). This was applied to a preparative t.l.c. plate (eluting solvent, ethylacetate/methanol (6:4)). One main band was taken off (0.08g). This material appeared to be 1,6-anhydro-4-deoxy-4-(carboxymethyl)-β-D-glucopyranose:

δ 5.49 (s, 1H, H-1), 4.50 (m, 1H, H-5), 4.1 (s, 1H, H-2), 3.95 (dd, 1H, H-6_{EXO}, $J_{6EXO,6ENDO}$ = 8, $J_{6EXO,5}$ = 2.5 Hz), 3.55-3.8 (m, 3H, H-6_{ENDO}, H-2, H-3), 2.95 (s, 2H, CH_2CO_2H, W/2 ∿ 4 Hz)

ν 3600, 3480, 1722, 1600 cm^{-1}

Reaction of the epoxide (28) with lithio-ethylacetate

To solution of butyl lithium (10.24 mM) in hexane (7 ml) under N_2 was added a solution of hexamethyldilazane (1.2 ml) in tetrahydrofuran (5 ml) dropwise with stirring over 5 minutes. The solution was then refluxed (½ hour) and the solvent distilled off under N_2. The residue was dissolved in dry tetrahydrofuran (20 ml) and cooled to -78°. To this solution was added a solution of dry ethylacetate (0.64 ml) in

tetrahydrofuran (6 ml) with stirring over 3 min. After a further 0.5 hours, a solution of the epoxide (28) (0.5g, 1.68 mM) in tetrahydrofuran was added. After 1 hour, t.l.c. showed no reaction so the temperature was gradually raised in 10° steps to reach 0°C after a further 2 hours. After 10 hours at 0°C, no reaction had occurred. Work-up yielded the unreacted epoxide (0.43g, 86% recovery).

Attempted reaction of (28) with copper lithium-ethylacetate

To a solution of lithio-ethylacetate (13 ml) prepared as above, was added copper(I) iodide (0.64g, 3.34 mM) in small portions at -78°C. This resulted in a red coloured solution which was stirred at -78°C for a further 0.25h. To this solution was added a solution of the epoxide (0.5g, 1.68 mM) in tetrahydrofuran. The reaction conditions were adjusted as in the reaction with lithio ethylacetate, and resulted in no reaction occurring. Work-up yielded the epoxide (28) (0.42g, 85% recovery).

Reaction of (28) with allyl magnesium halide

(1) In the absence of a catalyst

Dry, petrol ether washed magnesium turnings (20g) (0.81M), were placed in a dry flask under N_2 and dry tetrahydrofuran (250 ml) and some crystals of iodine and ethylene dibromide (0.2 ml) added. This mixture was stirred mechanically until the brown iodine colour had gone, and then cooled to -15° (carbon tetrachloride-dry ice bath). To this solution was added dropwise over 3 hours, a solution of allyl halide (0.1M) in dry tetrahydrofuran (20 ml) at -15°C. After addition, the solution was stirred at -10°C for a further 0.5h.

To this solution was added the epoxide (28) (5g, 16.8 mM) in tetrahydrofuran, and the mixture was then mechanically stirred at 0° under N_2 for 24 hours. The solution was then poured into saturated ammonium chloride solution (50 ml), and the tetrahydrofuran removed. The residue was extracted with dichloromethane, washed with water and dried ($MgSO_4$). Removal of the solvent yielded 3.75g of crystalline material identical to the epoxide (28).

(2) In the presence of aluminium trichloride

To a solution of allyl magnesium bromide prepared as described above was added the epoxide (28) (5g) in tetrahydrofuran and the solution stirred for 1 hour. Aluminium trichloride (0.23g) was then added all at once. The initially yellow coloured solution rapidly developed a precipitate. The solution was then stirred for 2 days at room temperature. The reaction was quenched with saturated ammonium chloride, dichloromethane added, the layers separated, the organic layer dried ($MgSO_4$) and the solvent removed to yield an oil (8g), which t.l.c. (benzene-acetone (9:1)), showed to consist of one main spot (Rf 0.2). The oil was applied to a preparative t.l.c. plate (eluting solvent benzene-acetone, 9:1), and one band removed (4.5g). This material appeared to be a mixture of 1,6-anhydro-2-O-tosyl-4-deoxy-4-bromo-β-D-glucopyranose (91), and 1,6-anhydro-2-O-tosyl-4-deoxy-4-chloro-β-D-glucopyranose (90):

δ 7.81 (d, 2H, Ts), 7.32 (d, 2H, Ts), 5.36 (s, 1H, H-1, W/2 ∿ 5 Hz), 4.71 (d, 1H, H-5, $J_{5,6EXO}$ = 5 Hz), 4.56 (d, 1H, H-5, $J_{5,6EXO}$ = 5 Hz), 3.8-4.3 (m, 2H, $H\text{-}6_{ENDO}$, H-3), 3.66 (dd, 1H, $H\text{-}6_{EXO}$, $J_{6EXO,6ENDO}$ = 8 Hz), 3.2-3.55 (m, 2H, H-2, H-4) and 2.42 (s, 3H, CH_3)

m/e found: 225,223 (M^+(91)-Ts) and 179,181 (M^+(90)-Ts).

This mixture could not be separated, on any t.l.c. system investigated.

(3) In the presence of copper(I) iodide

A solution of allyl magnesium chloride prepared as above was added over 15 minutes under N_2 to a suspension of the epoxide (5g, 16.8 mM) and copper(I) iodide (1g, 5 mM) in dry tetrahydrofuran (50 ml) cooled to 0^o and mechanically stirred. The suspension turned black on addition of the Grignard reaction. This mixture was mechanically stirred at 0^oC (24 hours) at which time t.l.c. (chloroform-ethyl acetate 9:1) showed complete reaction of (28) with formation of one main product (Rf 0.25).

To the cold stirred solution was added dropwise with stirring hydrochloric acid (12 ml, 2M) until the solution was acidic. The resultant clear supernatant liquid was then decanted from the black granular precipitate, the precipitate washed with dichloromethane, the combined organic extracts concentrated, and the residue extracted with dichloromethane (3 x 50 ml). This extract was washed with brine (3 x 20 ml), dried ($MgSO_4$), and concentrated to an oil (6.5g). This material was applied to a silica gel column (300g, eluting solvent chloroform-ethyl acetate (19:1) increasing to (88:12)). The later fractions yielded pure 1,6-anhydro-2-O-tosyl-4-deoxy-4-(2-propenyl)-β-D-glucopyranose (92) (5g, 89%):

δ 7.57 (dd, 4H, Ts), 5.5-6.0 (m, 1H, -CH=C), 5.24 (s, 1H, H-1), 5.5-5.25 (m, 2H, $=CH_2$), 4.39 (d, 1H, H-5, $J_{5,6EXO}$ = 5 Hz),

4.23 (s, 1H, H-2, W/2 ∿ 5 Hz), 4.07 (d, 1H, H-6_{ENDO}, $J_{6ENDO,6EXO}$ = 6 Hz), 3.80 (dd, 1H, H-6_{EXO}), 3.7 (s, 1H, H-3, W/2 ∿ 5 Hz), 2.43 (s, 3H), 2.34 (m, 2H (CH_2-C=)) and 1.72 (m, 1H, H-4).

ν 1640, 1600 cm^{-1}

$[\alpha]_D^{25}$ -58° (c 1, chloroform); m.p. 65-67°

m/e found: 185 (M^+-Ts)

Anal. Calc. for $C_{16}H_{20}O_6S$: C, 56.5; H, 5.9; S, 9.4.
Found: C, 56.3; H, 6.03; S, 9.22%.

Reduction of (92) with lithium triethylborohydride

To a solution of (92) (2.2g) in dry tetrahydrofuran (100 ml) cooled to 0° under N_2, was added with stirring a solution of lithium triethylborohydride (20 ml of 1M sol) in tetrahydrofuran dropwise over 5 min. After stirring at room temperature (8 hours), water (2 ml) was cautiously added at 0°, followed by 2M sodium hydroxide solution (12 ml) and 30% hydrogen peroxide (12 ml). The solution was stirred at 0°C for a further hour, and then allowed to warm to room temperature. By this time, a precipitate of sodium borate had formed. The tetrahydrofuran was removed, and the residue extracted with dichloromethane (3 x 50 ml). This extract was washed with brine (2 x 20 ml), dried ($MgSO_4$) and concentrated to a semi-crystalline oil (1.1g). T.l.c. (benzene-acetone, 9:1) showed one main step (Rf 0.08). Preparative t.l.c. using the above solvent system yielded pure 1,6-anhydro-2,4-dideoxy-4(2-propenyl)-β-D-arabino-hexopyranose (93), (0.9g, 82%). Distillation (flask to flask, 80°, 0.2 mm) yielded analytically pure material.

G.l.c. analysis (SCOT Carbowax 20M, 180°C, 15 ml/min) showed one peak, Rt 9.6:

δ 5.6-6.05 (m, 1H, CH=C), 5.57 (s, 1H, H-1, W/2 ∿ 5 Hz), 5.0-5.2 (m, 2H $C=CH_2$), 4.38 (d, 1H, H-5, $J_{5,6EXO}$ = 5 Hz), 4.30 (d, 1H, $H\text{-}6_{ENDO}$, $J_{6EXO,6ENDO}$ = 7 Hz), 3.72 (dd, 1H, $H\text{-}6_{EXO}$), 3.69 (m, 1H, H-3, W/2 ∿ 7 Hz), 2.85 (s, 1H, OH), 2.1-2.3 (m, 2H, CH_2-C=C), and 1.7-2.0 (m, 3H, $H\text{-}2_{EXO}$, $^2_{ENDO}$, H-4).

$[\alpha]_D^{25}$ -66.5° (c 0.9, chloroform)

Anal. Calc. for $C_9H_{14}O_3$: C, 63.51; H, 8.30.

Found: C, 63.28; H, 8.22%.

Tosylation of the alcohol (93)

To a solution of (93) (1.2g) in dry pyridine (30 ml) and dry chloroform (10 ml) was added with stirring, a solution of p-toluenesulphonyl chloride (2g) in pyridine (10 ml) over 5 min. with stirring at room temperature. After 48 hours, water (25 ml) was added, and the layers separated. The chloroform layer was washed with water (2 x 15 ml), copper sulphate solution (4 x 15 ml) and water (2 x 15 ml), dried ($MgSO_4$) and concentrated to a semi-crystalline oil (1.7g). Crystallisation from hot ethanol yielded pure 1,6-anhydro-2,4-dideoxy-3-O-tosyl-4(2-propenyl)-β-D-arabino-hexopyranose (95) (1.6g, 70%):

δ 7.73 (d, 2H, Ts), 7.27 (d, 2H, Ts), 5.5-5.8 (m, 1H, -CH=C), 5.40 (s, 1H, H-1, W/2 ∿ 5 Hz), 4.9-5.1 (m, 2H, $=CH_2$), 4.49 (s, 1H, H-3, W/2 ∿ 8 Hz), 4.39 (d, 1H, H-5, $J_{5,6EXO}$ = 6 Hz), 4.29 (d, 1H, $H\text{-}6_{ENDO}$, $J_{6EXO,6ENDO}$ = 7 Hz), 3.71 (dd, 1H, $H\text{-}6_{EXO}$), 2.41 (s, 3H, CH_3) and 1.8-2.3 (5H, H-4, $H\text{-}2_{EXO}$, $^2_{ENDO}$, CH_2-C=C)

ν 1640, 1600 cm^{-1}

$[\alpha]_D^{25}$ -70° (c 0.9, chloroform); m.p. 100-100.5°

Anal. Calc. for $C_{16}H_{20}O_5S$: C, 59.24; H, 6.21; S, 9.88.

Found: C, 59.40; H, 6.30; S, 10.17%.

Attempted Lemieux oxidation of (95)

The tosylate (0.5g, 1.5 mM) was added to a suspension of potassium carbonate (2.8g, 20 mM) sodium metaperiodate (2.6g, 12 mM) and potassium permanganate (0.04g, 0.25 mM) in 56% tert-butanol (160 ml). This suspension was stirred at room temperature (24 hours), and then worked-up by saturating the solution with potassium carbonate, acidifying to pH.5 with dil. hydrochloric acid, and extracted with chloroform. This extract was dried ($MgSO_4$) and concentrated to an oil containing tert-butanol. T.l.c. indicated the main product had an Rf 0.2 (chloroform-ethyl acetate-acetone (9:0.5:0.5), cf. the tosylate (95) (Rf 0.6). The oil was further concentrated by pumping at low pressure (0.5 mm), and the residue (0.05g) applied to a preparative t.l.c. plate. The main band of the plate yielded only 0.01g of material which could not be identified.

Ozonolysis of (95) in dichloromethane solution

The tosylate (0.5g) was dissolved in dry dichloromethane and the solution cooled to -65°. Air containing 5-10% ozone was bubbled through the solution, until the potassium iodide trap began turning yellow (0.5h), at which time the dichloromethane solution was blue. Air was then bubbled through the solution until it had decolourised. T.l.c. (benzene-acetone, 9:1) indicated the transformation of the tosylate (Rf 0.6) into one main product (Rf 0.55). To this dichloromethane solution at 0°C, was added a solution of sodium bicarbonate (0.5g) and 30% hydrogen peroxide (0.5 ml) in water (5 ml). After 2 hours at room temperature no reaction had occurred. The solution was then heated at 37° for 1 hour, followed by heating at 78° for 1 hour.

T.l.c. indicated partial decomposition of the ozonide with the formation of several new products. (Rf, 0.41, 0.27, 0.22). The solution was extracted with dichloromethane, washed with brine, and concentrated to yield an oil (0.2g). This was applied to a preparative t.l.c. plate, the main band of which yielded as a crystalline solid (0.05g) 1,6-anhydro-2,4-dideoxy-4-carboxymethylene-β-D-xylo-hexopyranose-γ-lactone (97):

δ 5.50 (s, 1H, H-1, $J_{1,2EXO}$ = 2.5, $J_{1,2ENDO}$ = 1.5 Hz), 4.82 (m, 1H, H-3, $J_{3,2EXO}$ = 8, $J_{3,2ENDO}$ = 8, $J_{3,4}$ = 3 Hz), 4.52 (s, 1H, H-5, $J_{5,4}$ = 1, $J_{5,6EXO}$ = 1, $J_{5,1}$ = 1 Hz), 3.82 (m, 2H, H-6_{EXO},6_{ENDO}), 2.55-2.75 (m, 2H, H-4, (CH_2CO_2)), 2.38 (m, H-2_{EXO}, $J_{2EXO,2ENDO}$ = 14 Hz), and 1.59 (m, 1H, H-2_{ENDO}).

ν 1777 cm^{-1}

$[\alpha]_D^{25}$ -6.4° (c 0.3, CH_2Cl_2); m.p. 151-151.5°.

Anal. Calc. for $C_8H_{10}O_4$: C, 56.47; H, 5.92.

Found: C, 56.62; H, 6.05%.

Ozonolysis of (95) in methanol solution

The tosylate (95) (0.96g, 3 mM) was dissolved in dichloromethane (20 ml) and methanol (20 ml) and the solution cooled to -70°. Ozone was bubbled through until the potassium iodide trap colourised, and the solution turned blue. Excess ozone was removed by bubbling air through the solution. At this point t.l.c. (chloroform-ethyl acetate 9:1) showed formation of one main product (Rf 0.13, cf (95) Rf 0.56). The solution was then warmed to 0°C and excess sodium sulphite solution added. After 0.5h t.l.c. showed the disappearance of the hydroperoxide (Rf 0.13) and the formation of two new products (Rf 0.32, 0.40). To this solution was added sodium bicarbonate (0.7g, 2 equiv.)

and 30% hydrogen peroxide (0.7 ml) in water (5 ml). This was stirred at 0°C (0.75h) and room temperature (18h). T.l.c. showed the presence of several compounds (Rf 0.1, 0.22, 0.33, 0.43, 0.5). The solution was diluted with dichloromethane, acidified to pH 6 and the layers separated. The aqueous layer was extracted with dichloromethane, the combined organic layers dried ($MgSO_4$) and concentrated to an oil (0.76g). This was applied to a preparative t.l.c. plate (eluting solvent:chloroform-ethyl acetate, 8:2), to give three distinct bands, of which the least polar proved to be (100) (0.06g), 1,6-anhydro-2,4-dideoxy-3-O-tosyl-4-(methoxycarbonylmethyl)-β-D-arabino-hexopyranose: δ 7.76 (d, 2H, Ts), 7.31 (d, 2H, Ts), 5.42 (s, 1H, H-1, W/2 ∿ 6 Hz), 4.57 (s, 1H, H-3, W/2 ∿ 10 Hz), 4.37 (d, 1H, H-5, $J_{5,6EXO}$ = 5 Hz), 4.25 (d, 1H, H-6_{ENDO}, $J_{6ENDO,6EXO}$ = 8 Hz), 3.75 (dd, 1H, H-6_{EXO}), 3.69 (s, 3H, CO_2Me), 2.3-2.7 (m, 2H, CH_2CO_2Me), 2.43 (s, 3H, CH_3), 1.96 (d, 1H, H-4, J_{4,CH_2} = 10 hz), and 1.87 (s, 2H, H-2_{EXO},2_{ENDO}, W/2 ∿ 9 Hz).

ν_{MAX} 1727 cm^{-1}

m/e Calc. 356.0930 ($C_{16}H_{20}O_7S$).

Found: 356.0860 (M^+).

The central band (Rf 0.4) proved to be the tricyclic lactone (97) (0.02g).

The most polar material (Rf 0.1) appeared to be (99) (0.2g), 1,6-anhydro-2,4-dideoxy-2-O-tosyl-4-(2-methoxy-2-hydroperoxy-ethyl)-β-D-arabino-hexopyranose: δ 7.76 (d, 2H, Ts), 7.32 (d, 2H, Ts), 5.42 (s, 1H, H-1, W/2 ∿ 5 Hz), 4.84 (m, 1H, CHOO), 4.67 (s, 1H, H-3, W/2 ∿ 7 Hz), 4.34 (d, 1H, H-5, $J_{5,6EXO}$ = 6 Hz), 4.24 (d, 1H, H-6_{ENDO}, $J_{6EXO,6ENDO}$ = 8 Hz), 3.73 (dd, 1H, H-6_{EXO}), 3.49 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3),

2.3-2.0 (m, 2H, CH_2COO), 1.98 (d, 1H, H-4, J_{4,CH_2} = 7 Hz) and 1.9-1.6 (m, 2H, H-2_{EXO},2_{ENDO}).

ν 3400 cm^{-1}.

Oxidation of (95) with ruthenium dioxide and sodium metaperiodate

To a suspension of ruthenium dioxide (0.02g) and sodium metaperiodate (0.5g) in 30% aqueous acetone (15 ml) was added with magnetic stirring, a solution of the tosylate (95) (0.11g) in acetone (2 ml). The solution immediately changed from a yellow to a black colour. After stirring at room temperature (1.5h), the solution had assumed a greenish-yellow tinge. T.l.c. (chloroform-ethyl acetate 9:1) indicated reaction was complete, with the product having the same Rf as the lactone (97). Iso-propanol (4 ml) in acetone (15 ml) was added dropwise, and the solution stirred (1 hour). The solution was then filtered through celite, the residue washed with acetone, and the combined fractions concentrated. The residue was extracted with dichloromethane (3 x 15 ml), dried ($MgSO_4$) and concentrated to yield a crystalline solid (0.7g). Recrystallisation from ethanol yielded pure (97) (0.53g, 90%).

Attempted cleavage of the anhydro bridge of (97)

(1) With Amberlite IR 120 (H^+) resin

The lactone (97) (0.27g) was dissolved in dry methanol (20 ml) and dry Amberlite IR 120 (H^+) resin (1g) was added. The solution was refluxed for 20 hours, at which time t.l.c. (ether-methanol, 19:1) indicated complete reaction of (97) with formation of two main products (Rf 0.26 and 0.14). The solution was cooled, filtered, and the solvent removed to yield an oil (0.3g). This

was applied to a silica gel column (17 x 3.5 cm), (eluting solvent; ether-methanol 9:1). The early fractions gave unreacted (97) (0.05g) followed by (102) (0.06g) as a crystalline solid, which was recrystallised from chloroform to afford pure methyl 2,4-dideoxy-4-carboxymethylene-β-D-xylo-hexopyranoside-γ-lactone[78a,78b] :

δ 4.79 (q, 1H, H-3, $J_{3,2\beta}$ = 2.5, $J_{3,2\alpha}$ = 2.5, $J_{3,4}$ = 5 Hz), δ 4.61 (dd, 1H, H-1, $J_{1,2\beta}$ = 8.5, $J_{1,2\alpha}$ = 2 Hz), 3.6-3.9 (m, 2H, H-6_α, H-6_β), 3.49 (s, 3H, OCH_3), 3.45 (m, 1H, H-5, $J_{5,4}$ = 10 Hz), 2.8-2.5 (m, 2H, H-4, $CH_\beta COO$, $J_{4,5}$ = 10, $J_{3,4}$ = 5 Hz), 2.31 (m, 1H, H-2_α, $J_{2,2}$ = 15, $J_{2\alpha,1}$ = 2, $J_{2\alpha,3}$ = 2.5 Hz), 2.25 (d, 1H, $CH_\alpha COO$, J_{CH_α,CH_β} = 15.5 Hz) and 1.77 (m, 1H, H-2_β, $J_{2\beta,1}$ = 8.5, $J_{2\beta,3}$ = 2.5, $J_{2\beta,2\alpha}$ = 15 Hz).

$[\alpha]_D^{25}$ -99° (c 0.4, chloroform); m.p. 125-126°C

ν 1774 cm^{-1}

Anal. Calc. for $C_9H_{14}O_5$: C, 53.47; H, 6.98.
Found: C, 53.52; H, 6.88%.

The later fractions afforded as an oil (24) (0.09g), methyl 2,4-dideoxy-4-carboxymethylene-α-D-xylo-hexopyranoside-γ-lactone :

δ 4.82 (t, 1H, H-1, $J_{1,2}$ = 3 Hz), 4.66 (q, 1H, H-3, $J_{3,2}$ = 3.5, $J_{3,4}$ = 5 Hz), 3.5-3.8 (3H, m, H-6_α, H-6_β, H-5, $J_{5,4}$ = 10.5, $J_{5,6}$ ~ 2 Hz), 3.32 (s, 3H, OCH_3), 2.4-2.8 (m, 2H, $CH_\beta CO_2$, H-4, $J_{3,4}$ = 5, $J_{4,5}$ = 10.5 Hz), 2.27 (d, 1H, $CH_\alpha CO_2$, $J_{H\alpha,H\beta}$ = 15.5 Hz) and 2.2-2.05 (m, 2H, H-2_α, H-2_β, $J_{1,2}$ = 3, $J_{2,3}$ = 3.5 Hz)

ν 1775 cm^{-1}

$[\alpha]_D^{25}$ +92.7° (c 1.5, chloroform). (lit. +86.6,[77a] +100°[77b], +85°[77c])

Anal. Calc. for $C_9H_{14}O_5$: C, 53.47; H, 6.98.
Found: C, 51.95; H, 6.93%.

(2) With pyridinium tosylate

To a solution of (97) (0.1g) in dry methanol (5 ml) was added pyridinium tosylate (0.15g) and the solution refluxed. After 48 hours, t.l.c. indicated only partial reaction of the tricyclic lactone (97). This reaction was not further investigated.

(3) With cerium(III) chloride

Cerium(III) chloride heptahydrate (0.022g) and trimethyl orthoformate (0.05g) were mixed in dry methanol (1 ml) and stirred for 10 min. Then the lactone (97) (0.01g) was added and the stirring continued. After 48 hours, t.l.c. indicated no reaction. Work-up yielded unchanged starting material.

(4) With Amberlyst 15 (H^+) resin

To a solution of (97) (0.2g) in dry methanol (50 ml) was added Amberlyst 15 (H^+) resin (0.2g) and the mixture refluxed for 8 hours. The solution was worked up as in the reaction with Amberlite IR 120 (H^+) resin to yield after chromatography, (24) (0.1g), and (102), (0.07g).

Methyl 6-O-(p-phenylbenzoyl)-2,4-dideoxy-4-carboxymethylene-α-D-xylo-hexopyranoside-γ-lactone

To a solution of p-phenylbenzoyl chloride (0.068g, 0.3 mM) in dry pyridine (1 ml) was added (24) (0.052g, 0.26 mM), and the mixture stirred at room temperature for 24 hours. Water (1 ml) was added, and stirring continued for (0.75h). Dichloromethane (20 ml) was added, the layers separated, the aqueous layer extracted with dichloromethane (10 ml), and the combined organic extracts washed with copper sulphate solution (5 ml),

brine (5 ml) and dried (Na_2SO_4). Removal of solvent yielded a crystalline solid (0.11g). This was recrystallised twice from hot methanol to give (0.075g, 70%) of pure methyl 6-O(p-phenylbenzoyl)-2,4-dideoxy-4-carboxymethylene-α-D-xylo-hexopyranoside-γ-lactone.

δ 8.2-7.1 (m, 9H, Ph-Ph), 4.83 (t, 1H, H-1), 4.64 (q, 1H, H-3), 4.5-4.4 (m, 2H, H-6_α, H-6_β), 4.0 (m, 1H, 4.0), 2.8-2.3 (m, 3H, H-4, CH_2COO), 2.13 (t, 2H, H-2_α, H-2_β) and 3.33 (s, 3H, OMe)

ν 1782, 1716, 1609, 1600 cm^{-1}

$[\alpha]_D^{25}$ +50.3° (c 0.5, chloroform), (lit.[77b] +48.6)

m.p. 154-155° (lit.[77b] 149-150°)

Anal. Calc. for $C_{22}H_{22}O_6$: C, 69.1; H, 5.8.

Found: C, 68.9; H, 5.68%.

1,6-anhydro-2,4-dideoxy-4-(2-propenyl)-β-D-erythro-hexopyranos-3-ulose (118)

The alcohol (93) (0.47g, 2.8 mM) was dissolved in dry dichloromethane (10 ml) and this solution added dropwise over 10 min. to a stirred suspension of anhydrous sodium acetate (0.1g) and pyridinium chlorochromate (0.9g, 4.2 mM), in dichloromethane (10 ml). The mixture was stirred at room temperature (8 hours) and then diluted with 5 volumes of dry ether. This solution was filtered, the gummy residue washed with ether, the combined ether extracts treated with activated charcoal, filtered and the solvent removed to yield an oil (0.5g). This was purified by column chromatography (silica gel (Merck 9385, 17 cm x 3.5 cm), eluting solvent:light petroleum ether-ether-ethyl acetate, 7.5:2.5:0.5 rising to 6.5:3.0:0.5) to yield pure (119) as a semi-crystalline oil (0.35g, 70%). An analytical sample was prepared by distillation flask to flask (80° 0.2 mm):

δ 5.72 (t, 1H, H-1, $J_{1,2}$ = 1 Hz), 6.0-5.5 (m, 1H, CH=C), 5.0-5.2 (m, 2H, $C=CH_2$), 4.64 (m, 1H, H-5, $J_{5,6}$ = 3 Hz), 3.82 (m, 2H, $H\text{-}6_{ENDO}$,6_{EXO}), 2.53 (d, 2H, CH_2-C=C, $J_{CH_2,4}$ = 1.5 Hz), 2.2-2.5 (m, H-4, $H\text{-}2_{EXO}$,2_{ENDO}).

$[\alpha]_D^{25}$ -225° (c 0.2, chloroform)

Anal. Calc. for $C_9H_{12}O_3$: C, 64.27; H, 7.19.

Found: C, 64.70; H, 7.41%.

Reaction of (95) with sodium cyanide

(1) In dimethylsulphoxide

The tosylate (95) (0.5g, 1.54 mM) was dissolved in dry dimethylsulphoxide (10 ml) and dry sodium cyanide (3 mM) added. The solution was stirred at 80°C for 28 hours. Dichloromethane (100 ml) was added, and the mixture washed with water (3 x 10 ml), dried ($MgSO_4$) and concentrated to an oil (0.24g). T.l.c. showed this consisted of one non-polar compound. Purification was effected by column chromatography (silica gel, 15 cm x 2.5 cm, eluting solvent:light petroleum ether_dichloromethane:ethyl acetate, 3:6:2) to give as a semi-crystalline oil 1,6-anhydro-2,3,4-trideoxy-4-(2-propenyl)-erythro-hex-2-enopyranose (110) (0.23g, 90%). An analytical sample was prepared by distillation, (flask to flask, 80°, 1 mm):

δ 5.5-6.0 (m, 1H, CH=C), 5.83 (d, 1H, H-2, $J_{1,2}$ = 4 Hz), 5.66 (s, 1H, H-3, W/2 9 Hz), 5.42 (d, 1H, H-1, $J_{1,2}$ = 4 Hz), 5.2-4.9 (m, 2H, $C=CH_2$), 4.48 (d, 1H, H-5, $J_{5,4}$ = 1.5, $J_{5,6EXO}$ = 7.5, $J_{5,6ENDO}$ = 2 Hz), 3.94 (t, 1H, $H\text{-}6_{EXO}$, $J_{6EXO,6ENDO}$ =8, $J_{5,6EXO}$ = 7.5 Hz), 3.61 (dd, 1H, $H\text{-}6_{ENDO}$, $J_{5,6ENDO}$ = 2 Hz),

2.45-2.2 (m, 2H, CH_2-C=C) and 1.93 (m, 1H, H-4, $J_{4,5}$ = 1.5, $J_{3,4}$ = 1 Hz)

$[\alpha]_D^{25}$ +224.6° (c 0.1, chloroform)

Anal. Calc. for $C_9H_{11}O_2$: C, 71.13; H, 7.82.

Found: C, 70.89; H, 8.01.

(2) In ethanol, or N-methyl pyrrolidine or hexamethyl-phosphoramide

The tosylate (95) (0.05g) was dissolved in the dry solvent (2 ml) and dry sodium cyanide (0.05g) added. The solutions were stirred at 55°C for 24 hours. T.l.c. showed that the reactions in ethanol and N-methylpyrrolidine had gone to a small extent with formation of (110). The reaction in ethanol was maintained at reflux for 4 days, after which time t.l.c. showed approximately 50% of the tosylate had reacted to form (110).

The reactions were not further investigated.

1,6-anhydro-2-O-tosyl-4-deoxy-4-(2-methyl-2-propenyl)-β-D-glucopyranose (113)

Petrol washed and dried magnesium turnings (7g, 0.29M) were placed in a dry flask under N_2 and dry tetrahydrofuran added (100 ml). A small amount of a solution of methallyl chloride (3.26g, 36 mM) in tetrahydrofuran (15 ml) was added, along with some crystals of iodine. The solution was heated to reflux, at which time it decolourised. The solution was then cooled to -15° (CCl_4/CO_2 bath) and the chloride solution added dropwise over 2 hours. Stirring was continued for a further 0.5h, and then the solution of methallyl magnesium chloride was added over 15 min. to a mechanically stirred suspension of the epoxide (28) (1.8g, 6 mM) and copper(I) iodide (0.2g, 1mM) in

tetrahydrofuran (20 ml) at 0°C under N_2. Stirring was continued at 0°C (24 hours).

The cold solution was acidified to pH 6.0 with dil. hydrochloric acid, dichloromethane added, the layers separated, and the aqueous layer washed with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated to an oil (3.14g). This was applied to a column (silica gel Merck 9385, eluting solvent:chloroform, ethyl acetate, 9:1 to 17:3) to give in the later fractions (113) (1.9g, 90%) as a crystalline solid.

δ 7.7 (d, 2H, Ts), 7.3 (d, 2H, Ts), 5.30 (s, 1H, H-1), 4.7-5.0 (m, 2H, $C=CH_2$), 4.41 (d, 1H, H-5, $J_{5,6EXO}$ = 4.5 Hz), 4.32 (s, 1H, H-2, W/2 ∿ 7 Hz), 4.08 (d, 1H, $H\text{-}6_{ENDO}$, $J_{6EXO,6ENDO}$ = 6.5 Hz), 3.72 (dd, 1H, $H\text{-}6_{EXO}$, $J_{5,6EXO}$ = 4.5, $J_{6EXO,6ENDO}$ = 6.5 Hz), 3.73 (s, 1H, H-3, W/2 ∿ 9 Hz), 2.6 (s, 1H, OH), 2.49 (s, 3H, CH_3), 2.36 (d, 2H, CH_2-C=C), 1.85 (m, 1H, H-4) and 1.75 (s, 3H, CH_3)

$[\alpha]_D^{25}$ -66° (c 0.1 chloroform); m.p. 103-105°

Anal. Calc. for $C_{17}H_{22}O_6S$: C, 57.61; H, 6.26; S, 9.05.
Found: C, 57.93; H, 6.53; S, 8.95.

1,6-anhydro-2,4-dideoxy-4-(2-methyl-2-propenyl)-β-D-arabino-hexopyranose (114)

To a solution of (113) (1.8g) in dry tetrahydrofuran, stirred at 0°C under N_2 was added dropwise over 15 min, a solution of lithium triethylborohydride (15 mM) in tetrahydrofuran (15 ml). Stirring was continued at room temperature (9 hours). The solution was then cooled to 0°, and water (2 ml) cautiously added, followed by 2M sodium hydroxide (12 ml) and

30% hydrogen peroxide (12 ml). After stirring at 0°C for a further 1h, then the tetrahydrofuran was removed, and the residue extracted with dichloromethane. This extract was washed with brine, dried ($MgSO_4$) and concentrated to an oil (0.67g), which failed to crystallise. T.l.c. and n.m.r. indicated that this material was pure (114):

δ 5.60 (s, 1H, H-1, W/2 ∿ 7 Hz), 4.84 (d, 2H, $C=CH_2$), 4.5-4.2 (m, 2H, H-5, $H\text{-}6_{ENDO}$), 3.9-3.7 (m, 2H, H-3, $H\text{-}6_{EXO}$), 3.06 (s, 1H, OH), 2.4-1.8 (m, 5H, H-4, $H\text{-}2_{EXO}$,$^2_{ENDO}$, CH_2-C=C) and 1.79 (s, 3H, CH_3).

1,6-anhydro-2,4-dideoxy-4-(2-methyl-2-propenyl)-β-D-erythro-hexopyranos-3-ulose

A solution of the alcohol (114) (0.6g, 3.3 mM) in dichloromethane was added to a stirred suspension of anhydrous sodium acetate (0.2g) and pyridinium chlorochromate (1.8g, 8mM) over 15 mins. After stirring at room temperature (18 hours), the reaction was worked up in the normal manner to afford an oil (0.5g). This was purified on a column (eluting solvent;light petroleum-ether-ethyl acetate, 6.0:3.5:0.5) to yield as a semi-crystalline oil (0.4g 65%), 1,6-anhydro-2,4-dideoxy-4-(2-methyl-2-propenyl)-β-D-erthyro-hexopyranos-3-ulose:

δ 5.74 (t, 1H, H-1, $J_{1,2}$ = 1.5 Hz), 5.0-4.8 (m, 2H, $C=CH_2$), 4.63 (t, 1H, H-5, $J_{5,6}$ = 3 Hz), 3.86 (d, 2H, $H\text{-}6_{EXO}$,$^6_{ENDO}$), 2.2-2.7 (m, 5H, $H\text{-}2_{EXO}$,$^2_{ENDO}$, H-4, CH_2-C=C) and 1.78 (s, 3H, CH_3)

ν 1723 cm^{-1}

1,6-anhydro-2,4-dideoxy-4-(2-oxopropyl)-β-D-erthyro-hexopyranos-3-ulose (115)

To a suspension of sodium metaperiodate (2g) and ruthenium dioxide (0.02g) in water (10 ml) was added a solution

of the alcohol (114) (0.07g) in dichloromethane. This mixture was very vigorously magnetically stirred, for 4 hours. The layers were separated, the aqueous layer was extracted with dichloromethane, and the combined organic extracts were treated with isopropanol (1 ml). After standing 30 min, the extract was washed with brine (2 x 5 ml), dried (Na_2SO_4) and concentrated to an oil (0.062g). This material appeared to be the pure erthyro isomer (115), however after purification by preparative t.l.c. (eluting solvent:benzene-acetone, 9:1), n.m.r. revealed the presence of the threo isomer to the extent of ∿ 30%, apparent from new H-1, H-5 and CH_3CO signals: δ 5.74 (t, 1H, H-1, $J_{1,2}$ ∿ 1.5 Hz), 4.67 (t, 1H, H-5, $J_{5,6}$ = 3 Hz), 3.92 (d, 2H, H-6_{EXO},6_{ENDO}), 3.0-2.5 (H-4, H-2_{EXO},2_{ENDO}, CH_2CO) and 2.21 (s, 3H, CH_3CO).

[Selected data for threo isomer:

δ 5.80 (t, H-1), 4.74 (m, H-5), 2.25 (s, CH_3CO)]

ν 1720 cm^{-1}.

Attempted aldol condensation of (115)

To a suspension of sodium hydride suspension (0.04g) in dry benzene (5 ml) containing a trace of tert-amyl alcohol under N_2 was added the diketone (115) (0.04g). The solution was stirred at room temperature for 18 hours, after which time t.l.c. showed the disappearance of the diketone, with no apparent product spots. Some methanol was added, the solution was diluted with ether and washed with brine (2 x 5 ml). After drying (Na_2SO_4) and removal of solvent, a residual solid (0.01g) was obtained which could not be identified.

1,6-anhydro-2,3,4-trideoxy-3-bromo-4-(2-propenyl)-β-D-ribo-hexopyranose (116)

The alcohol (93) (0.46g) was added to a solution of carbon tetrabromide (2.9 mM, 1g) in dry acetonitrile (20 ml) and the mixture cooled to 0°. Then triphenylphosphine (0.79g, 3.0 mM) was added. The solution initially turned yellow, then became colourless, and after 15 min. a white precipitate appeared. The reaction mixture was stirred at 0°C for 8 hours, at which time t.l.c. (benzene-acetone, 9:1) indicated complete reaction of (93) with formation of two products (Rf 0.53 and 0.58).

Ether (50 ml) was added, the mixture was filtered, and the filtrate concentrated to an oil. This oil was applied to a silica gel column (eluting solvent:benzene) and provided in the early fractions the bromide (116) (0.23g 40%) as an oil. G.l.c. analysis (SCOT Carbowax 20M, 153°, 10 ml/min) showed only one compound was present (Rt 6.37):

δ 6.1-5.5 (m, 1H, CH=C), 5.39 (s, 1H, H-1, W/2 ∿ 6 Hz), 5.3-5.0 (m, 2H, $C=CH_2$), 4.71 (m, 1H, H-3, $J_{3,2EXO}$ = 10, $J_{3,2ENDO}$ = 5, $J_{3,4}$ = 5 Hz), 4.53 (d, 1H, H-5, $J_{5,6EXO}$ = 5 Hz), 3.95-3.7 (m, 2H, $H\text{-}6_{EXO},{}^{6}_{ENDO}$), 2.8-2.2 (m, 3H, H-4, CH_2-C=C), 2.12 (dd, 1H, $H\text{-}2_{ENDO}$, $J_{2ENDO,3}$ = 5, $J_{2ENDO,2EXO}$ = 10 Hz) and 1.9 (m, 1H, $H\text{-}2_{EXO}$, J_{2EXO} = 1.5, $J_{2EXO,2ENDO}$ = 10, $J_{2EXO,3}$ = 10 Hz).

m/e Found: 153 (M^{+}-Br).

The later fractions provided as an oil (117) (0.16g) 4-(2-propenyl)-6-bromo-cis-2, trans-4-hexadienal:

δ 9.56 (d, 1H, H-1, $J_{1,2}$ = 7 Hz), 7.02 (d, 1H, H-3, $J_{2,3}$ = 20 Hz), 6.27 (t, 1H, H-5, $J_{5,6}$ = 9 Hz), 6.22 (dd, 1H, H-2, $J_{1,2}$ = 7, $J_{2,3}$ = 20 Hz), 5.70 (m, 1H, H-8, $J_{8,9CIS}$ = 11, $J_{8,9TRANS}$ = 17 Hz), 5.2-4.9 (m, 2H, H-9_{CIS}, H-9_{TRANS}), 4.04 (d, 2H, 2 x H-6, $J_{5,6}$ = 9 Hz) and 3.13 (d, 2H, 2 x H-7, $J_{7,8}$ = 5 Hz)

ν_{MAX} 1680 cm^{-1}

λ_{MAX} 283 nm

Reaction of (29) with methoxymethylene triphenylphosphorane

Methoxymethylene triphenylphosphonium chloride (1.2g, 3.5 mM) was added to dry tetrahydrofuran (10 ml) under N_2 and to this stirred suspension was added dropwise over 5 mins, n-butyl lithium (2.3 mM) in hexane. The solution rapidly turned dark red. After 2 hours at room temperature all solid material had dissolved. The solution was cooled to -78° and a solution of the ketone (0.15g, 1.17 mM) was added dropwise over 5 mins. G.l.c. monitoring (SCOT Carbowax 20M, 172°C, 14 ml/min) showed that on warming to room temperature a rapid reaction occurred, with the ketone (Rt 6.3) being converted into the two isomeric enol ethers in ratio 1:1 (Rt 5.3 and 6.3). The reaction was stirred at 0°C for 1h, and then quenched with methanol (0.5 ml). The solution was diluted with ether, filtered, dried ($MgSO_4$), and treated with charcoal. Filtration through celite gave a colourless solution which was concentrated to an oil (0.54g). This was applied to a chromatographic column (60g silica, eluting solvent:light petroleum

ether-ethyl acetate-ether, 6.0:1.0:3.0) to give in the early fractions, one enol ether isomer (0.03g, Rt 5.95):

δ 5.87 (s, 1H, C=CH, W/2 ~ 7 Hz), 5.51 (s, 1H, H-1, W/2 ~ 4Hz), 4.54 (s, 1H, H-5, W/2 ~10 Hz), 3.76 (m, 2H, H-6_{EXO},6_{ENDO}), 3.52 (s, 3H, OMe), 2.59 (d, 1H, H-2_{ENDO}, $J_{2ENDO,2EXO}$ = 14 Hz), 2.4-2.2 (m, 2H, H-4_{EXO},4_{ENDO}), 2.04 (d, 1H, H-2_{EXO}, $J_{2ENDO,2EXO}$ = 14 Hz)

ν_{MAX} 1687 cm^{-1}

The later fractions provided the isomeric enol ether (0.03g, Rt 6.9):

δ 5.87 (s, 1H, C=CH, W/2 ~ 7 Hz), 5.52 (s, 1H, H-1, W/2 ~ 4 Hz), 4.55 (m, 1H, H-5, W/2 ~ 11 Hz), 3.85 (d, 1H, H-6_{ENDO}, $J_{6ENDO,6EXO}$ = 6 Hz), 3.73 (d, 1H, H-6_{EXO}), 3.53 (s, 3H, OMe), 2.71 (d, 1H, H-2_{ENDO}, $J_{2ENDO,2EXO}$ = 14 Hz), 2.58 (d, 1H, H-4_{EXO}, $J_{4EXO,4ENDO}$ = 12 Hz), 2.06 (d, 1H, H-4_{ENDO}), 1.92 (d, 1H, H-2_{EXO}, $J_{2EXO,2ENDO}$ = 14 Hz)

ν_{MAX} 1687 cm^{-1}

1,6-anhydro-2,3,4-trideoxy-3-formyl-β-D-erythro-hexopyranose (109)

A mixture of the two isomeric enol ethers (119) (0.0125g) was dissolved in 10% aqueous tetrahydrofuran (2.2 ml) and to this solution was added with stirring mercuric acetate (0.08g). G.l.c. monitoring showed the slow disappearance of the enol ether peaks and the formation of a new peak (Rt 7.9). The reaction was complete in 3 hours, after which time an aqueous solution of potassium iodide (2.5 mM) was added. The tetrahydrofuran was removed, and the residue was extracted with dichloro-

methane (4 x 5 ml). This was dried (Na_2SO_4), and concentrated to an oil (0.0095g). This material appeared to be the aldehyde (109):

δ 9.66 (s, 1H, CHO), 5.54 (s, 1H, H-1, W/2 ∿ 5 Hz), 4.38 (m, 1H, H-5, W/2 ∿ 10 Hz), 3.75 (d, 1H, $H\text{-}6_{ENDO}$, $J_{6EXO,6ENDO}$ = 6 Hz), 3.51 (dd, 1H, $H\text{-}6_{EXO}$, $J_{6ENDO,6EXO}$ = 6, $J_{6EXO,5}$ = 4.5 Hz), 3.45 (m, 1H, H-3), 2.6-1.9 (m, 4H, $H\text{-}2_{EXO}$,$^{2}_{ENDO}$, $H\text{-}4_{EXO}$,$^{4}_{ENDO}$)

ν_{MAX} 1723 cm^{-1}

One prolonged exposure of this material to triethylamine in dichloromethane (20 hours, 20°) g.l.c., t.l.c., and n.m.r., showed no change occurring.

1,6-anhydro-2,3,4-trideoxy-3-(-hydroxymethyl)-β-D-erythro-hexopyranose (107)

To the aldehyde (109) (0.008g) in dry tetrahydrofuran (2 ml), was added, at 0° with stirring under N_2, a solution of lithium aluminium hydride in tetrahydrofuran (2 ml). G.l.c. showed a rapid reaction occurring, with the formation of a new peak (Rf 6.4). T.l.c. demonstrated reaction was complete in 2 hours (petrol ether-ether-ethyl acetate: 4.5:1) with conversion of the aldehyde (Rf 0.41) to the alcohol (Rf 0.08). Wet ether (1 ml) was added, followed by dichloromethane (10 ml). The solution was dried (Na_2SO_4) and concentrated to an oil (0.006g). N.m.r. indicated that this was the alcohol (107):

δ 5.53 (s, 1H, H-1, W/2 ∿ 6 Hz), 4.47 (m, 1H, H-5, W/2 ∿ 10 Hz), 3.9-3.6 (4H, m, $H\text{-}6_{ENDO}$, $H\text{-}6_{EXO}$, CH_2OH), 2.3-1.5 (5H, m, H-3, $H\text{-}2_{EXO}$,$^{2}_{ENDO}$, $H\text{-}4_{EXO}$,$^{4}_{ENDO}$)

ν 3600 cm^{-1}

Attempted rearrangement of (107)

The alcohol (107) (0.006g) was dissolved in dry benzene (1 ml) and Amberlyst 15 (H^+) resin (0.01g) added. This solution was stirred at room temperature (6 days), and then refluxed (2 days). G.l.c. and t.l.c. showed no change over this period.

Reaction of (118) with methoxymethylenetriphenylphosphorane

Methoxymethylenetriphenylphosphoniumchloride (2.45g) suspended in tetrahydrofuran (25 ml) under nitrogen and butyl lithium (5 mM) in hexane (3 ml) added dropwise over 5 min. The solution was stirred at room temperature for 2 hours and then cooled to -78°C. A solution of the ketone (118) (0.2g, 1.19 mM) in tetrahydrofuran (2 ml) was then added dropwise. The reaction was monitored by g.l.c. (SCOT Carbowax 20M, 171°C, 14 ml/min) and slowly warmed. After 2 hours at -70°, a new peak had appeared (Rt 0.31 ∿ 20%). On warming to -50°C and stirring for 3 hours, four additional peaks had appeared (Rt 1.6, 5%; 2.0, 5%; 3.1, 25%; 3.4, 20%; 4.1, 10%) whilst the ketone peak (Rt 7.8) now constituted about 15% of the chromatogram. The ketone peak had declined to ∿ 5% after 0.5h at -40°. The reaction was quenched at this point by the addition of water (0.5 ml). The mixture was extracted with dichloromethane, dried (Na_2SO_4) and concentrated. T.l.c. showed the presence of several polar products. An infra-red spectrum of the crude mixture possessed absorbances at ∿ 1680 and 1720 cm^{-1}. The material was applied to a preparative t.l.c. plate (eluting solvent:light petroleum ether:ether-ethyl acetate, 6:3.2:0.8), but no identifiable products were recovered.

Attempted rearrangement of (107)

The alcohol (107) (0.006g) was dissolved in dry benzene (1 ml) and Amberlyst 15 (H^+) resin (0.01g) added. This solution was stirred at room temperature (6 days), and then refluxed (2 days). G.l.c. and t.l.c. showed no change over this period.

Reaction of (118) with methoxymethylenetriphenylphosphorane

Methoxymethylenetriphenylphosphoniumchloride (2.45g) suspended in tetrahydrofuran (25 ml) under nitrogen and butyl lithium (5 mM) in hexane (3 ml) added dropwise over 5 min. The solution was stirred at room temperature for 2 hours and then cooled to -78°C. A solution of the ketone (118) (0.2g, 1.19 mM) in tetrahydrofuran (2 ml) was then added dropwise. The reaction was monitored by g.l.c. (SCOT Carbowax 20M, 171°C, 14 ml/min) and slowly warmed. After 2 hours at -70°, a new peak had appeared (Rt 0.31 ∿ 20%). On warming to -50°C and stirring for 3 hours, four additional peaks had appeared (Rt 1.6, 5%; 2.0, 5%; 3.1, 25%; 3.4, 20%; 4.1, 10%) whilst the ketone peak (Rt 7.8) now constituted about 15% of the chromatogram. The ketone peak had declined to ∿ 5% after 0.5h at -40°. The reaction was quenched at this point by the addition of water (0.5 ml). The mixture was extracted with dichloromethane, dried (Na_2SO_4) and concentrated. T.l.c. showed the presence of several polar products. An infra-red spectrum of the crude mixture possessed absorbances at ∿ 1680 and 1720 cm^{-1}. The material was applied to a preparative t.l.c. plate (eluting solvent:light petroleum ether:ether-ethyl acetate, 6:3.2:0.8), but no identifiable products were recovered.

Reaction of (118) with lithio-diethyl-(2-tetrahydropyranyloxymethyl) phosphonate

Di-isopropylamine (0.102g) was dissolved in tetrahydrofuran (5 ml) and cooled to -70° under N_2. To this stirred solution was added dropwise n-butyl lithium (1 mM) in hexane (0.64 ml). This was followed by a solution of diethyl-(2-tetrahydropyranyloxymethyl) phosphonate (0.241g, 0.96 mM) in tetrahydrofuran (2 ml) added dropwise over 10 min. The solution was then cooled to -100° and a solution of the ketone (118) (0.15g, 0.9 mM) in tetrahydrofuran (2 ml) added dropwise over 20 min. This solution was stirred at -100° (1h) slowly warmed to room temperature, and then refluxed for 6 hours. The solution was then poured into ether, and washed with 20% citric acid, water, and 5% sodium bicarbonate solution. Drying (Na_2SO_4) and removal of solvent yielded an oil (0.143g). This was applied to a column (silica gel, eluting solvent:petrol ether:ether:ethyl-acetate, 8:1.5:0.5). The early fractions provided the unreacted ketone (118) (0.04g) and what appeared to be its C-4 epimer (0.03g). Rf of the two epimers 0.42 and 0.39. The latter fractions provided diethyl-(2-tetrahydropyranyloxymethyl) phosphonate (0.11g).

Reaction of (118) with dimethylsulphoxonium methylide

Sodium hydride dispersion (0.31g) was placed in a 3-necked flask under nitrogen and washed with pentane (2 x 5 ml). Residual solvent was removed in a nitrogen stream. Dimethyl-sulfoxide (5 ml) was added followed by trimethylsulphoxonium iodide (0.2g, 0.9 mM). Vigorous evolution of hydrogen occurred. After stirring for 45 mins, a solution of the ketone (118) (0.13g, 0.8 mM) in dry dimethylsulfoxide (1.5 ml) was added

dropwise at room temperature. The solution was stirred at room temperature for 2 hours, and then at 50° for 1.5h. T.l.c. indicated complete reaction of the ketone with formation of polar products.

The reaction mixture was poured into cold water (50 ml) and extracted with dichloromethane (3 x 25 ml). The extract was washed with brine (15 ml), dried (Na_2SO_4), and the solvent removed to yield an oil (0.09g). The infra-red spectrum of this material showed absorbances at 1690 and 3600 cm^{-1}. Purification was attempted by preparative t.l.c. (chloroform-ethyl acetate-methanol, 8:2:0.3). This resulted in the isolation of no identifiable materials.

Reaction of (118) with dimethylsulphonium methylide

Trimethylsulphonium iodide (0.45g, 2 mM) was added to dry tetrahydrofuran (15 ml) and the suspension cooled to 0° under N_2. A solution of n-butyl lithium (1.8 mM) in hexane (1.1 ml) was added dropwise with stirring over 5 min. The solution was stirred at 0° for 15 min and then cooled to -20°. A solution of the ketone (118) (0.2g, 1.2 mM) in tetrahydrofuran (5 ml) was then added dropwise over 10 min. T.l.c. indicated a rapid reaction to produce polar products. After 2 hours the mixture was poured into iced water and extracted with dichloromethane (3 x 20 ml). The extract was washed with brine (10 ml), dried (Na_2SO_4) and the solvent removed to yield an oil (0.04g). Infra-red examination of this material showed absorbances at 1720 and 1685 cm^{-1}. As t.l.c. indicated a complex mixture, similar to that obtained above, the reaction was not further investigated.

Reaction of (118) with diazomethane

Diazomethane, free of alcohol, was generated by addition of an ethereal solution of Diazald to solution of potassium hydroxide in aqueous ethoxyethanol at 70°C, with removal of the diazomethane by co-distillation with the ether.

The ketone (118) (0.01g) was dissolved in ether (3 ml) and cooled to 0°. Then a portion of the ethereal diazomethane solution (3 ml) was added. The mixture was then stirred at room temperature. As the diazomethane rapidly polymerised at this temperature, regular additions of diazomethane were made to maintain a reasonable concentration. After 2.5 days t.l.c. indicated that no reaction had occurred. Methanol (2 ml) was added, and reaction continued for 3 days. After this time t.l.c. indicated only minimal reaction.

The reaction mixture was then worked up, but the product isolated contained Diazald and ethoxyethanol. These impurities effectively prevented positive identification of the product as unreacted (118).

Reaction of (118) with p-toluenesulphonylmethyl isocyanide

To a solution of p-toluenesulphonylmethyl isocyanide (0.71g, 3.6 mM) in dry dimethylsulphoxide (10 ml) cooled to 0° under N_2 was added potassium tert-butoxide (0.67g, 3.6 mM) followed by methanol (0.1 ml). To this solution was added the ketone (118) (0.2g, 1.2 mM) in tetrahydrofuran (1 ml). The mixture was stirred at room temperature (2 hours) and then heated to 50° for 10 hours. T.l.c. indicated that a complex mixture of products had resulted. After cooling, the reaction mixture was

neutralised with aqueous ammonium chloride solution and extracted with petrol ether. The residue was then extracted with dichloromethane. This extract was washed with water, dried (Na_2SO_4) and concentrated to an oil (0.04g). N.m.r. showed no identifiable signals. The reaction was not further investigated.

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