A synthesis of prostaglandins.

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A SYNTHESIS OF PROSTAGLANDINS

By

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Declaration

I declare that the research presented herein is original work carried out by the author and has not been submitted for any other degree.

Signed: Date

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Contents.

Page no.

Acknowledgements.

Abstract.

Conventions.

1. Introduction to Prostaglandins and their synthesis. 5

2. The Diketone Fragment. 37

3. Cyclization Reactions and the Cyclopentenone Synthon. 51

4. Conjugate Addition Reactions of the Cyclopentenone Intermediates. 68

5. Completion of the Synthetic Sequence. Preparation of PGD_1 Methyl ester. 89

6. Ancillary Studies and Some Suggestions for Future Work. 110

7. Experimental Section. 129

References. 170

Study Programme. 178

Publications.

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Abstract

As an introduction current general approaches to the chemical synthesis of prostaglandins are reviewed latterly concentrating upon the synthesis of the 'D' series.

A total synthesis of the prostaglandin, PGD_1 methyl ester and epimers is presented this being developed using the following synthetic pathway.

Alkylation of alkyl dialkoxyacetates proved successful, results being in good agreement with those published en route by Huet. The resulting intermediates (including one bearing an α -prostanoid side chain) were converted in high yield over two steps to the desired α -diketodithianes thus improving a dangerous non-flexible literature procedure.

These compounds underwent a cyclization reaction with appropriate vinyl phosphonium salts (developed in our laboratories) to afford highly substituted cyclopentenones in greater than 70% yield.

The appropriate prostanoid cyclopentenones were transformed over three steps in 55% yield to a 2-alkylcyclopentenone substrate which was reacted with an organocuprate reagent as a means of introducing the ω-prostanoid side chain. Conjugate addition proceeded with asymmetric induction at the C-12 centre a 3.5:1 diastereomeric preference in favour of the desired stereochemistry was observed.

Reduction at the C-9 centre proceeded to give the undesired β -stereochemical outcome (this product was transformed into the C-9 epimer of PGD$_1$). Inversion of the stereochemistry at C-9 was achieved by an S_N2 displacement reaction to give the 9α-alcohol in 52% yield from its epimer. The resultant product was deprotected to afford PGD$_1$ methyl ester accompanied by its ent-15-epimer.

A total synthesis of (±) dihydrojasmololone is outlined incorporating a similar synthetic strategy and some suggestions for extension of the project are proposed.

Full experimental details are given.

Conventions.

A broken line: ---- denotes an α -configuration.

A solid tapered line: ◀ denotes a β -configuration.

A wavy line: ∼ denotes either an unknown or unspecified configuration.

CHAPTER 1

An Introduction to Prostaglandins and Their Synthesis

1.1 Historical background. 7

1.2 Prostaglandin nomenclature. 8

1.3 Biosynthesis, metabolism and biological significance of prostaglandins. 11

1.4 Chemical syntheses of prostaglandins. 16

  1.4.1 Objectives and problems of chemical synthesis. 16

  1.4.2 Major synthetic approaches to prostaglandins. 16

  1.4.3 Synthesis of 'D' series prostaglandins. 29

1.5 Proposed synthetic route to PGD_1 methyl ester. 33

1.1 Historical background

A major area of interest in synthetic organic chemistry over the past 20 years has been the production of prostaglandins and their analogues.

Goldblatt[1] (1933) and Von Euler[2] (1936) independently noted that extracts of seminal vesicles possessed the properties of lowering blood pressure in mammals and stimulating smooth muscle preparations; Von Euler named the active component 'prostaglandin' believing it to originate from the prostate gland. The post-war studies on these extracts were pioneered by Bergström and Von Euler and these culminated in the isolation of two active crystalline compounds which they labelled PGF_1[3] and PGE_1[4,5]. The structures of these compounds were elucidated[6,7] and, soon after, two groups independently discovered that incubation of unsaturated fatty acids with preparations of seminal vesicles afforded mixtures of prostaglandins[8,9].

Improvements in biosynthetic methods (as a result of elucidation of the biosynthetic pathway) and the discovery of a rich natural source[10] led to an exponential growth in prostaglandin research. The major pharmaceutical companies took an increasing interest once the wide spectrum of prostaglandin activities became apparent and several chemical syntheses were soon developed.

One of the last series of prostaglandins to be discovered was the 'D series'[11]; this group exhibits a potent inhibition of blood platelet aggregation amongst other effects but at the commencement of this project very few chemical syntheses were available due to susceptibility of the 'D-series' to dehydration. Our interest in the synthetic challenge of these compounds and Glaxo's pharmacological interest has led to the work contained herein.

1.2 Prostaglandin nomenclature.

The nomenclature of prostaglandins has developed in a semi-systematic way analogous to that of the steroids. The basic carbon skeleton is that of prostanoic acid (Fig. 1.2.1).

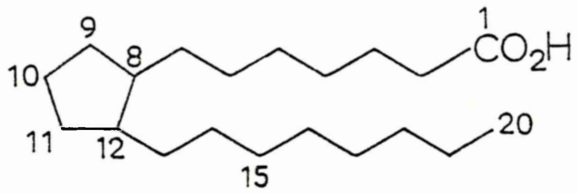
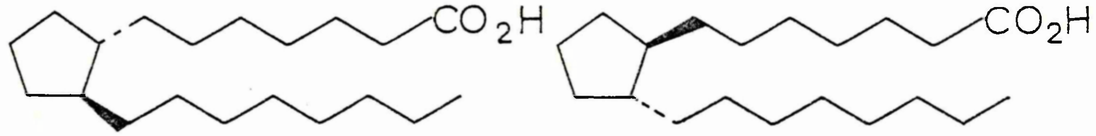


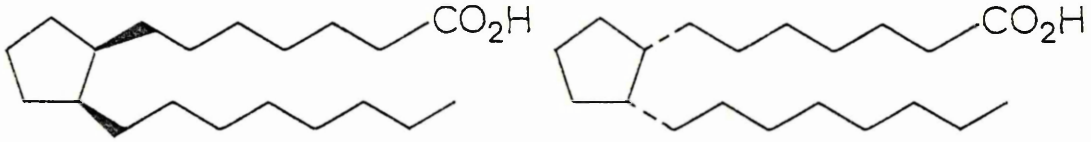
Fig. 1.2.1 Prostanoic acid

There are four stereochemical arrangements possible for the side chains (two diastereomeric pairs) (Fig. 1.2.2).



prostane

ent-prostane

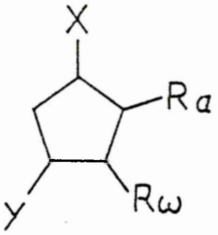


isoprostane

ent-isoprostane

Fig. 1.2.2 Stereochemical arrangement of prostanoic acid side chains

There are a number of prostaglandin families designated by a letter, which indicates a difference in the substitution pattern of the cyclopentane ring (Fig. 1.2.3).



Family	X	Y	Other elaboration
A	=O	H	10/11 double bond
B	=O	H_2	8/12 " "
C	=O	H_2	11/12 " "
D	~OH	=O	
E	=O	~OH	
F	~OH	~OH	
G	O--------O		

Fig. 1.2.3 Ring elaboration of different prostaglandin families

A member of series 'A' would be referred to as PGA, for example. The stereochemistry of the ring substituents is designated as being β or α depending on whether they are above or below the plane of the cyclopentane ring. In natural PGs the top C-8 side chain is directed α and the bottom C-12 side chain is directed β. Where ring hydroxyl group(s) are present they are directed α in the natural series.

Elaboration of the side chains with substituents and double bonds is denoted by the addition of a number as a subscript to the family letter in the following manner:

1 : indicates a 13,14-trans double bond and a 15α-hydroxyl substituent;

2 : indicates all the elaboration in 1 plus a 5,6-cis double bond;

3 : indicates all the elaboration in 1 and 2 plus a 17,18-cis double bond.

Some prostaglandins have an opposite stereochemistry at either the C-9, 11 or 15 positions (β rather than α). This is denoted by the addition of β as a suffix after the chain number for the C-9 position and as a numbered 'epi' prefix for C-11 and C-15. For example: 15-epi $PGF_{2\alpha}$ denotes a β configuration at C-15 and an α configuration at C-9.

Prostaglandin $PGF_{1\alpha}$ has the structure shown (Fig. 1.2.4).

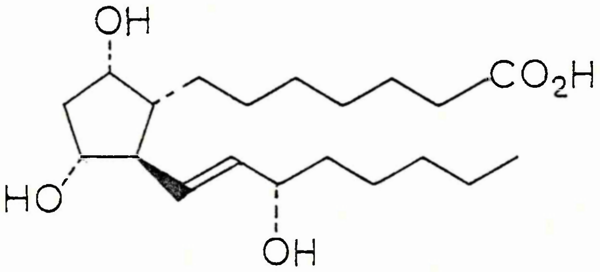


Fig. 1.2.4. $PGF_{1\alpha}$

As well as the primary prostaglandins there also exists a series of cyclic analogues known as prostacyclins (Fig. 1.2.5) abbreviated PGIs; their nomenclature is similar to that of the open chain forms.

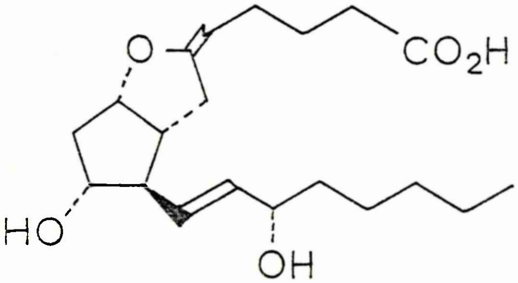


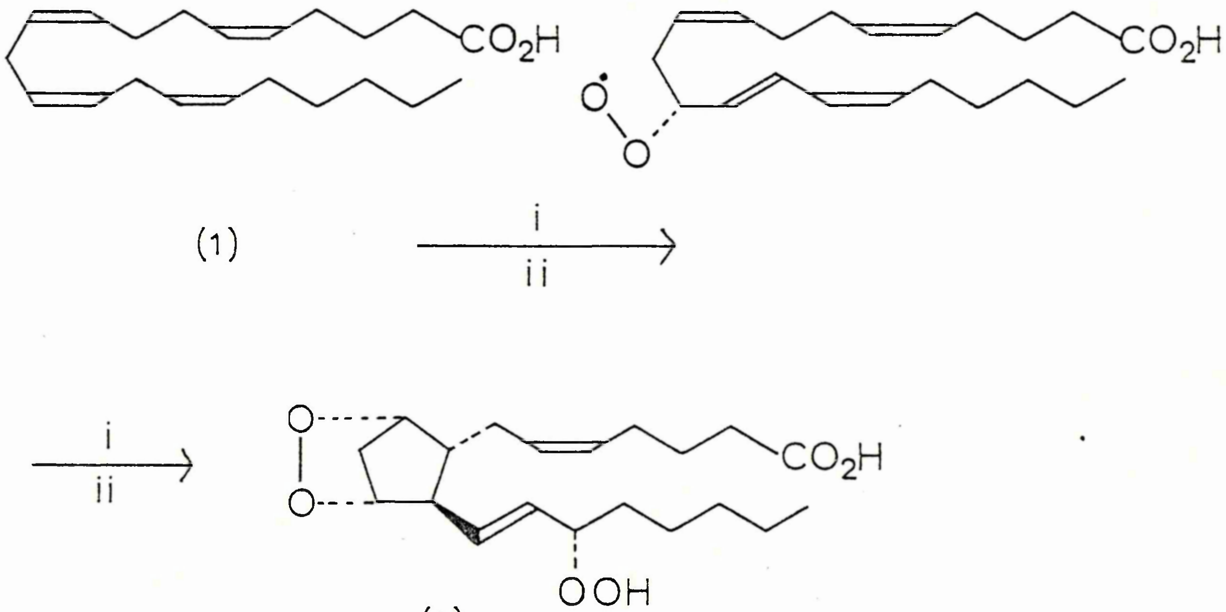
Fig. 1.2.5 Prostacyclin (PGI_2)

Several reviews of prostaglandin nomenclature have been published, the most comprehensive being that of Nelson[12]. The brief summary given above should be adequate to follow the text.

1.3 Biosynthesis, metabolism and biological significance of prostaglandins

The major prostaglandin families are biologically derived from certain C-20 polyunsaturated fatty acids[8,9]. The 2 series, for example has been shown to originate from aracadonic acid (5,8,11,14-eicosatetraenoic acid) (1).

The biosynthetic pathway has been elucidated by the use of radioactively labelled fatty acid substrates and it has been shown that three key steps are involved. Two short lived endoperoxide intermediates are formed by the sequential addition of two molecules of oxygen at C-11 and C-15 in the presence of the enzyme prostaglandin synthetase[13].



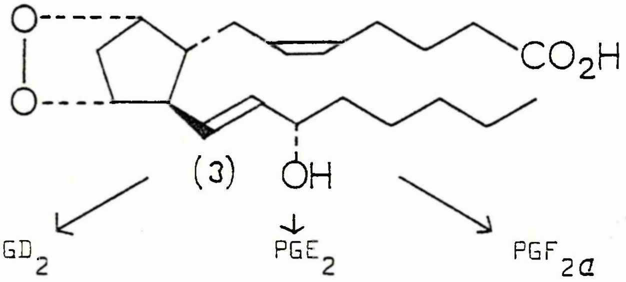
(1)

(2)

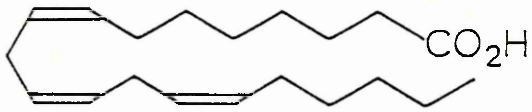
i O_2

ii Prostaglandin Synthetase

The endoperoxide (2), known trivially as PGG_2, is then enzymatically deoxygenated at C-15 to yield the endoperoxide PGH_2(3)[14] which isomerase enzymes convert into the appropriate prostaglandins.



Prostacyclin (Fig. 1.2.5) is also thought to be derived from PGH_2. The 1 series prostaglandins are biosynthesised by an identical pathway from bishomo- γ -linoleic acid (4).

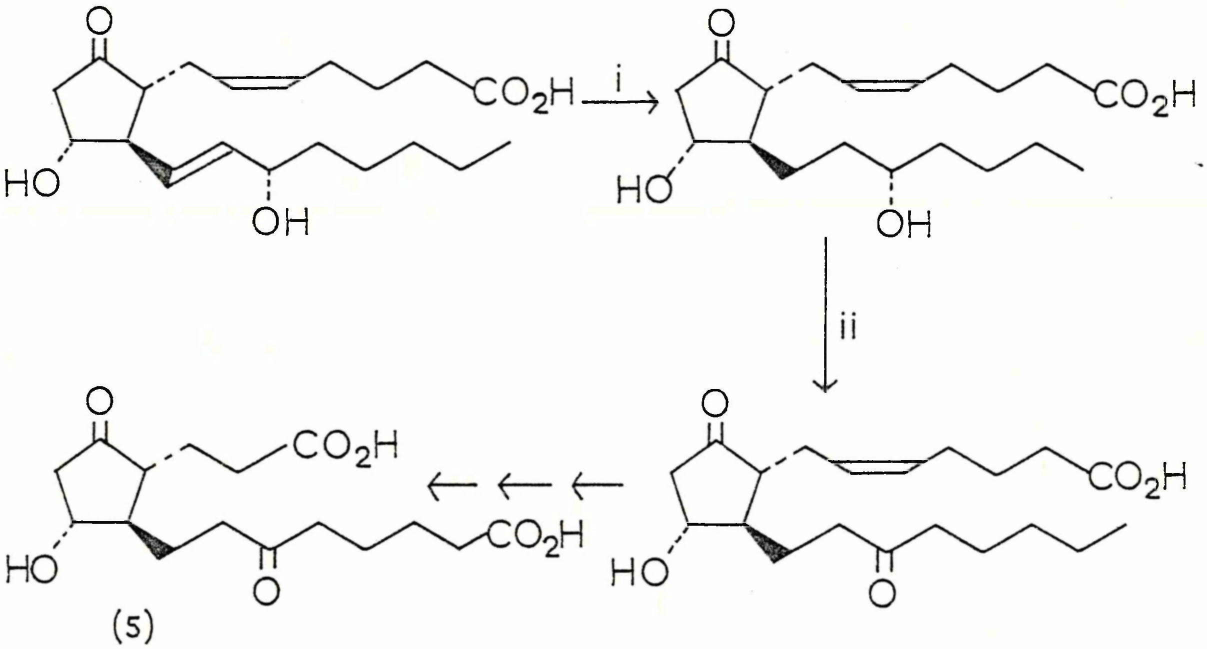


(4)

The endoperoxides PGG_2 and PGH_2 themselves have been shown to possess biological activity being potent blood platelet aggregators. They are, however, too short lived to be of any pharmaceutical use.

Prostaglandins are, through necessity, metabolised rapidly in mammals. The initial degradation occurs through enzymatic attack upon the functionalities of the lower side chain[15,16] (Fig. 1.3.1).

This is followed by oxidation to give the urinary metabolite (5)[17].



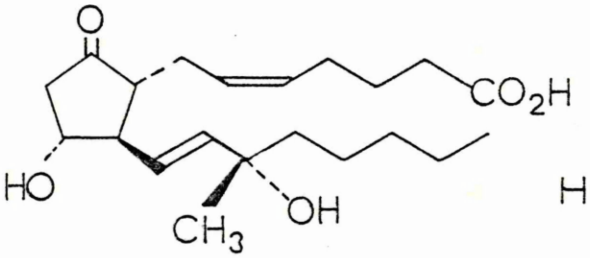
i Δ^{13}-reductase

ii 15-oxidase

Fig. 1.3.1 Metabolism of PGE_2

Tracer experiments have shown that 60% of a dose of tritium labelled PGE_2 was excreated within 20 hours of administration[18]. Primary metabolism appears to occur near the site of action; homogenates of various organs and tissues possess the ability to metabolise prostaglandins but subsequent metabolism is carried out by the liver.

It has been shown that the biological half lives of prostaglandins can be increased significantly by sterically or chemically blocking the sites of primary enzymatic attack. The analogues (6) and (7) possess similar or greater activities compared with PGE_2 but show a greater resistance to enzymatic attack[14a,17a].



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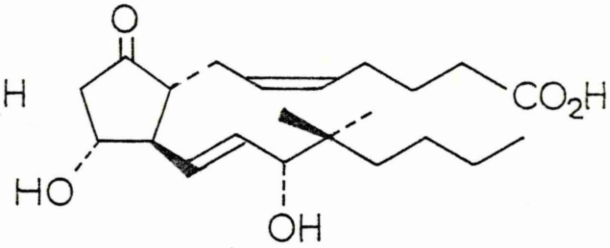
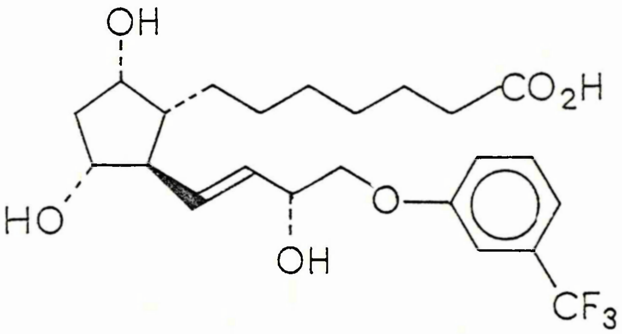


(7)

The prostaglandins exhibit a wide range of biological activities at very low concentrations; effects have been observed at levels as low as 10^{-9}g ml^{-1}. They act as regulators for many of the body's systems, being generated at the site of action and then rapidly metabolised to limit their sphere of influence. Some of the biological effects of prostaglandins are listed in Table 1.3.1.

It should be noted that one natural prostaglandin can affect many different systems thus limiting their use as pharmaceutical agents (at present only PGE_2 is used clinically). This lack of selectivity of action has encouraged the synthesis of prostaglandin analogues with the hope of isolating or enhancing specific effects. For commercial reasons information on the structure and activity of analogues is scarce, although 'Fluoprostenol' (8) is now used in the control of fertility of cattle and horses.



(8)

TABLE 1.3.1 BIOLOGICAL EFFECTS AND CLINICAL POTENTIAL OF PROSTAGLANDINS

Biological System	Observed response	Prostaglandin Eliciting response	Potential
Cardiovascular	Lowering of blood pressure	E_1, E_2	Treatment of hypertension/
	Increase in cardiac output	F_2 , C_2	Shock
Circulatory	Aggregation of blood platelets	E_2, G_2	Prevention of thrombosis
	Inhibition of Aggregation of blood platelets	I_2, E_1, D_2	
Bronchial	Contraction of bronchial smooth muscle	E_1, F_2	Treatment of Asthma
	Relaxation of bronchial smooth muscle	E_2	
Gastric	Inhibition of gastric secretion	E_1 A_1	Treatment of peptic ulcer
Reproductive	Luteolysis	F_2 , D_2	Control of Fertility
	Contraction of Uterus	E, F	Induction of labour
Nervous	Release of enkefalins	?	Alleviation of pain

1.4 Chemical Syntheses of Prostaglandins

1.4.1 Objectives and Problems of Chemical Synthesis

The objective of any chemical synthesis is to obtain the target molecule in high yield over as few steps as possible. In the case of a potential drug the synthesis should be adaptable to large scale, as economic as possible and incorporate a flexibility allowing the preparation of analogues.

The prostaglandins present several synthetic problems: firstly some possess labile functional groups such as the β-ketol system prone to dehydration; secondly they are stereochemically complex, $PGF_{2\alpha}$ having five asymmetric centres (*) and two double bonds (one cis, one trans). (Fig. 1.4.1.1)

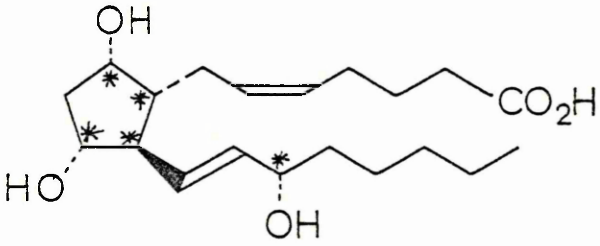


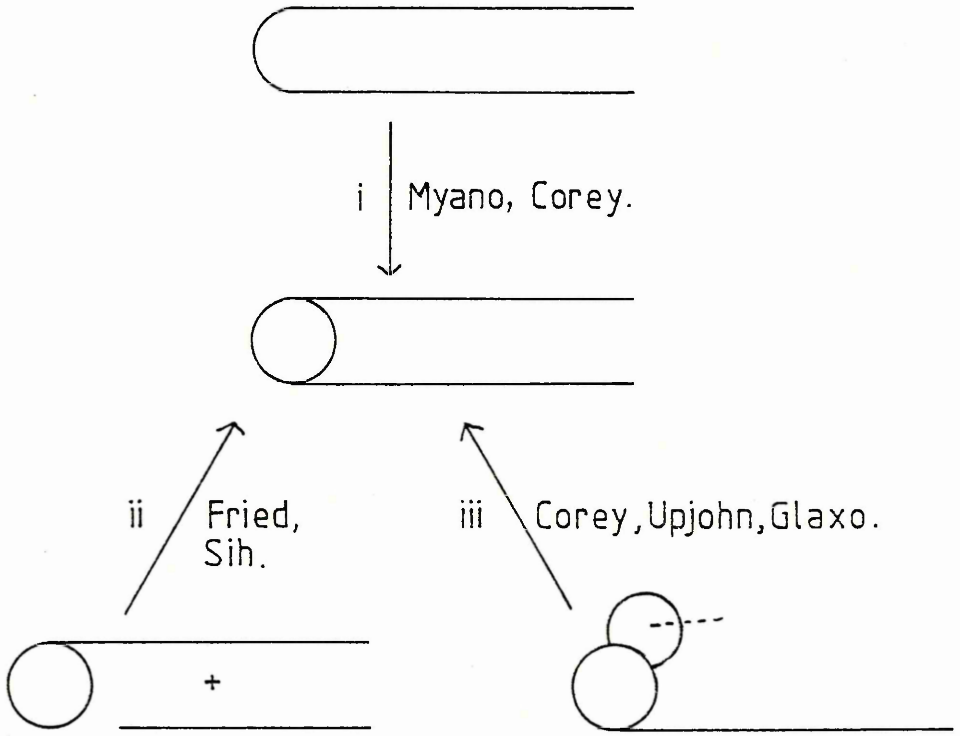
Fig. 1.4.1.1 Stereochemical complexity of $PGF_{2\alpha}$

The reactions involved should therefore possess a high degree of stereoselectivity to avoid lengthy separation and resolution sequences but be mild enough so as not to degrade the products.

1.4.2 Major Synthetic Approaches to Prostaglandins

Most of the current prostaglandin syntheses are covered in the books of Bindra[17] and Mitra[19] and also by several reviews[14,20,21,22].

The first chemical synthesis of a prostaglandin was published in 1967[23] and since then three major synthetic approaches have developed (Fig. 1.4.2.1):



i cyclization of acyclic precursors.

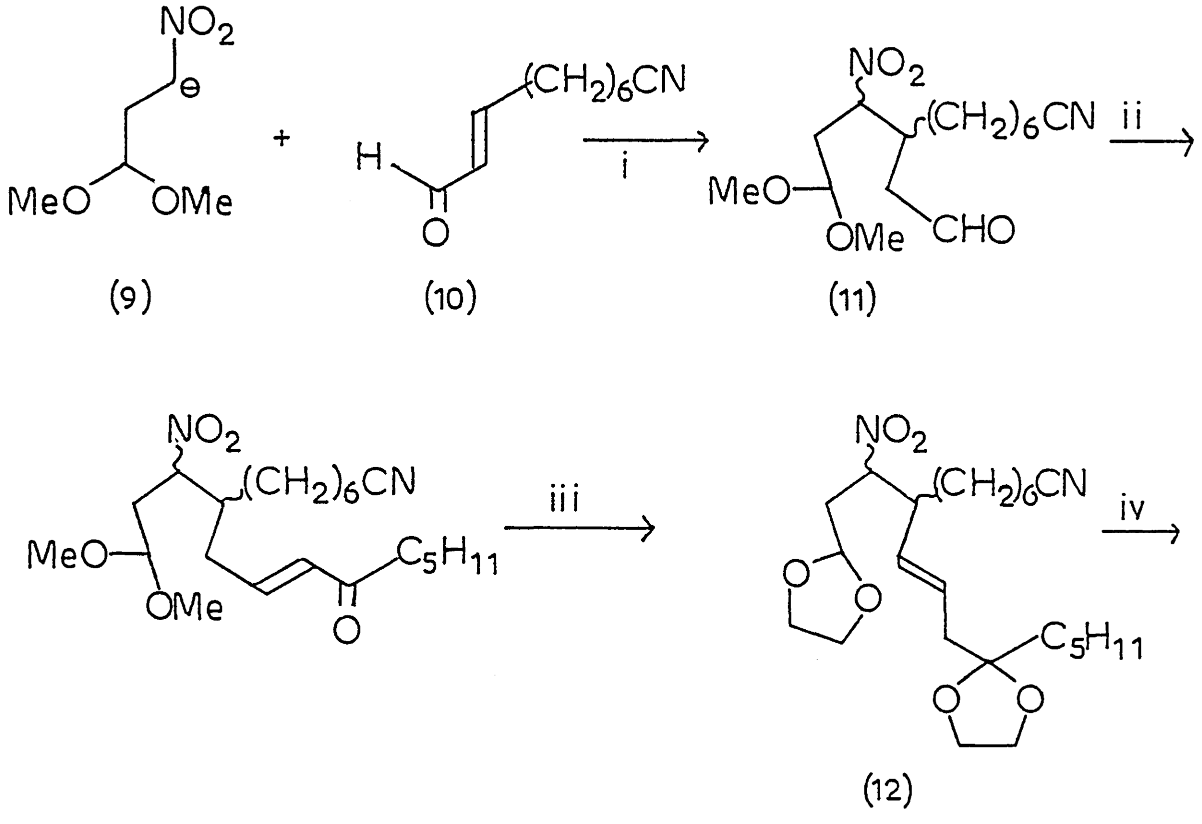
ii 1,4-conjugate addition to cyclopentenones.

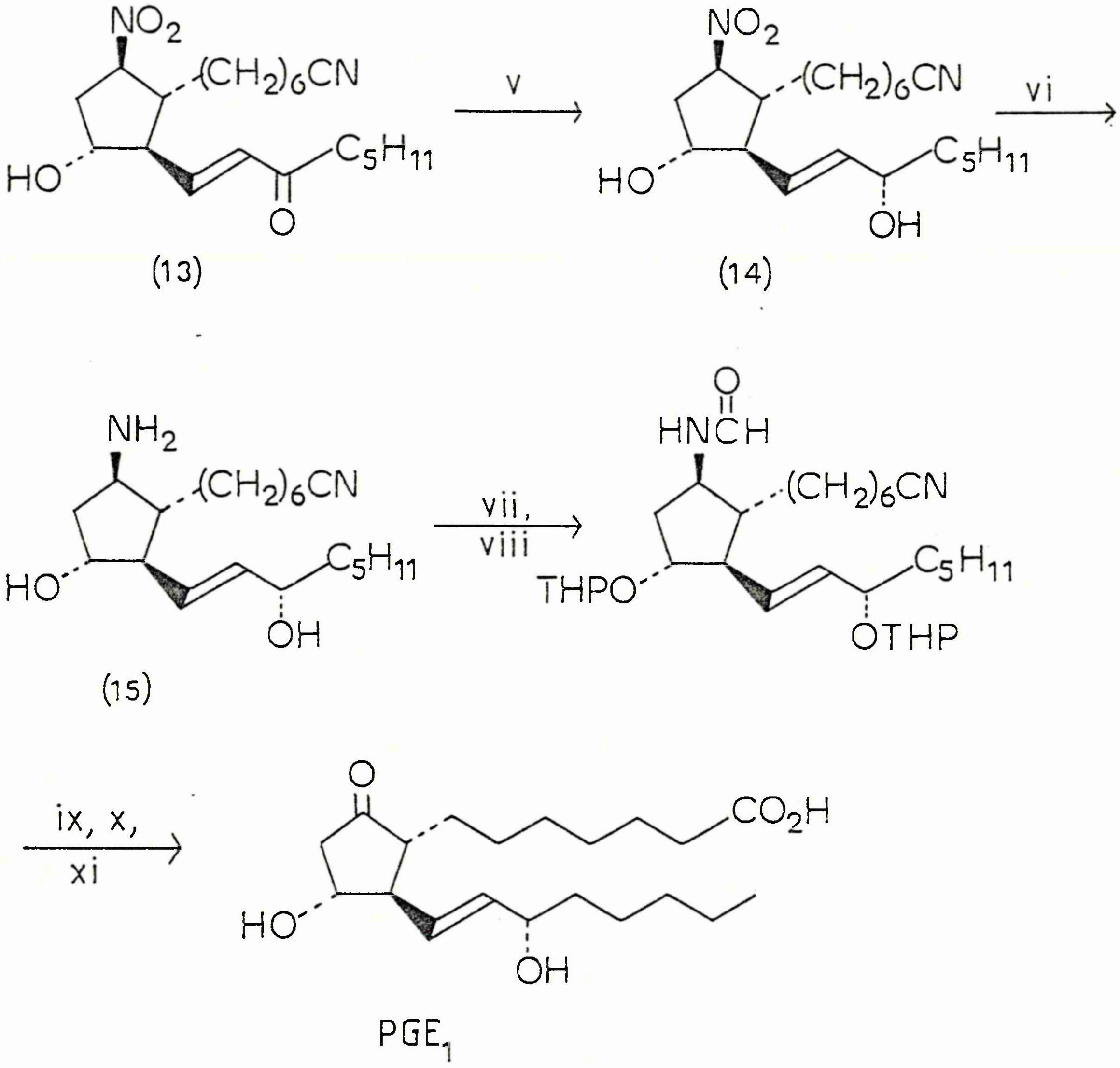
iii cleavage of bi or tricyclic intermediates.

Fig. 1.4.2.1 Major approaches to prostaglandin synthesis

The initial prostaglandin syntheses developed in the late 1960's and early 1970's were of type (i). Suitably substituted acyclic precursors were prepared and cyclized, usually via intramolecular aldol or Claisen condensation reactions. The resultant cyclopentanone was then elaborated and deprotected.

To illustrate this approach scheme(1.4.2.1.) shows Corey's second synthesis of PGE_1[24]. Michael addition of the nitronate anion (9) to the enone system (10) afforded the aldehyde (11) and the lower side chain was then elaborated by use of the phosphonate modification of the Wittig reaction[25]. Protection yielded the nitro-bis-dioxolane (12) which was cyclized by treatment with stannic chloride. Equilibration and hydrolysis afforded the nitroenone (13) which was reduced to yield an equimolar mixture of C-15 epimers. Reduction of the desired epimer (14) at C-9 generated the amine (15) (which could be resolved) and bromination followed by dehydrobromination and hydrolysis of the bis-protected amide afforded PGE_1.



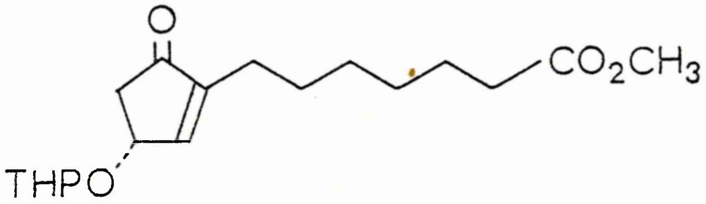


i	Base
ii	Sodium dimethyl-2-oxoheptylphosphonate (80%).
iii	Ethylene Glycol, TsOH, PhH (80%).
iv	$SnCl_4$, EtOAc.
v	$NaBH_4$.
vi	Al(Hg), Et_2O, MeOH(aq).
vii	$HCOOCOCH_3$.
viii	DHP, TsOH, dioxane.
ix	KOH, MeOH(aq).
x	NBS then DBN.
xi	CH_3CO_2H aq.

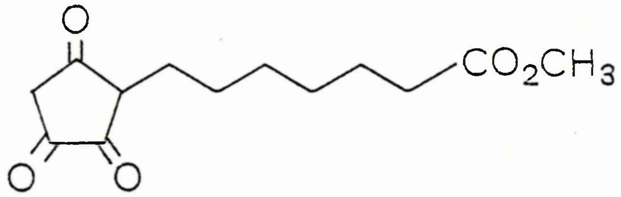
Scheme 1.4.2.1.

The start of the last decade saw the birth and development of the conjugate addition approach to prostaglandins. These convergent syntheses pioneered by Fried and Sih required two precursors : a cyclopentenone fragment and an organocuprate reagent.

To illustrate the approach one of the best examples is Sih's synthesis of PGE_1[26,27]. The cyclopentenone fragment (16) was derived from the 2-alkylcyclopenta-1,3,4-trione (17) (Scheme 1.4.2.2) to which there are several practical synthetic routes[28,29].

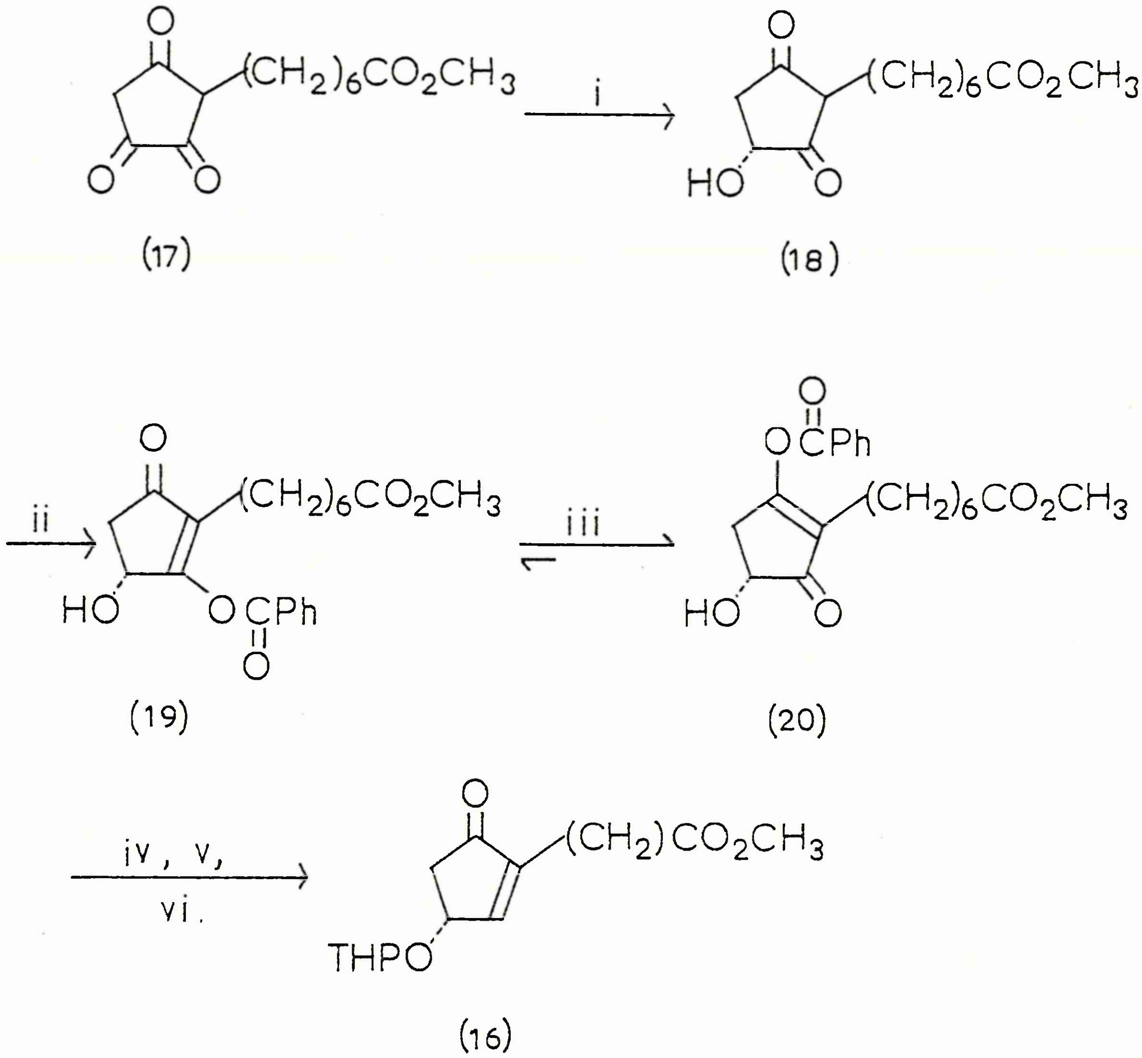


(16)



(17)

Reduction of the more labile carbonyl funtionality at C-11 was achieved by catalytic hydrogenation or asymmetrically with microorganisms.

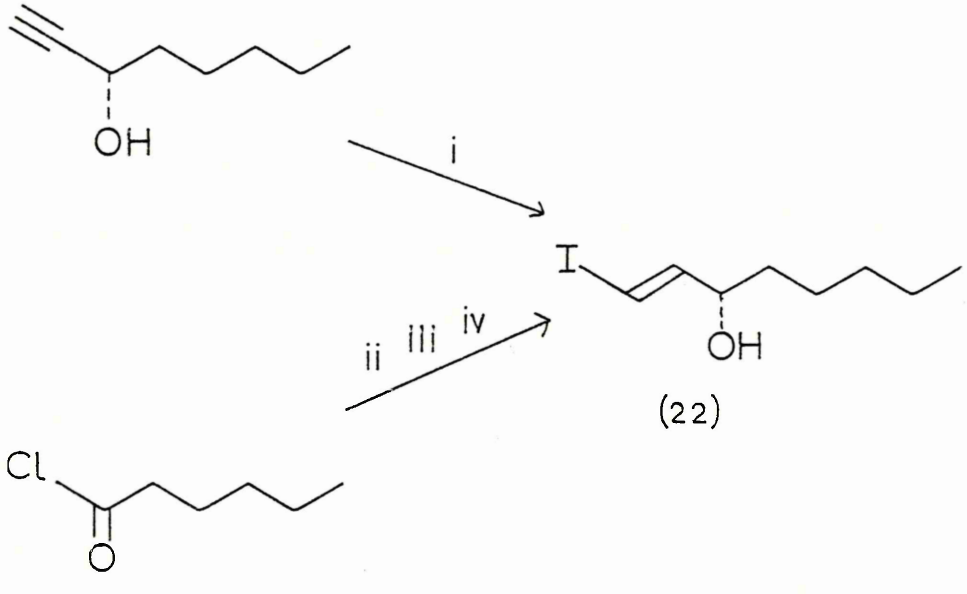


i. H_2/Pd
ii. Et_3N/PhCOCl
iii. H^+anhy.
iv. $NaBH_4$
v. H_3O^+
vi. DHP/TsOH/PhH

<u>Scheme 1.4.2.2</u>

Treatment of the product alcohol (18) with triethylamine/benzoyl chloride afforded a mixture of enol-benzoates (19) and (20) the latter predominating upon equilibration. Reduction of the free carbonyl functionality, acid catalysed rearrangement and protection of the alcohol afforded the enone (16).

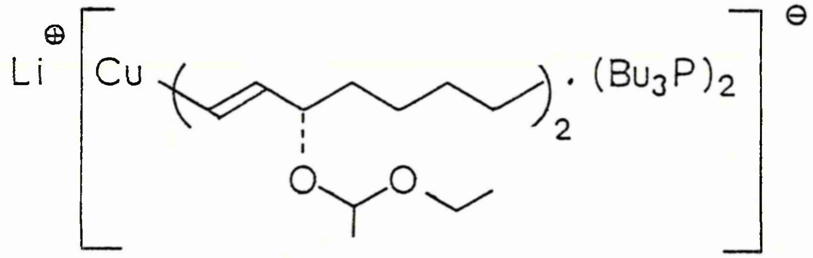
The organocuprate reagent (21) is derived from the iodo-allylic alcohol (22) which in turn may be prepared from 1-octyn-3-ol[30,31] or hexanoyl chloride[32] (Scheme 1.4.2.3). Resolution may be achieved at the final product or octynol stage through the (-)phenylethylamine salt



i $^{i}Bu_2AlH$, $^{i}Bu_3Al, I_2$
ii Acetylene/$AlCl_3$
iii $NaI/(CH_3)_2CO$
iv $LiAlH_4$

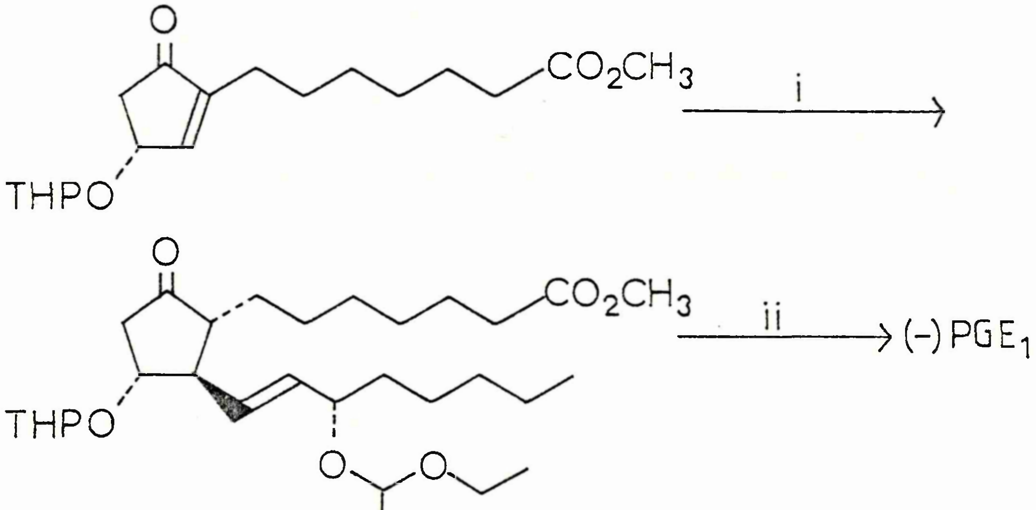
Scheme 1.4.2.3

of the hemiphthalate. Treatment of the protected alcohol with n-butyl lithium followed by bis(tri^{n}butyl phosphine) copper(I) iodide generated the cuprate reagent (21).



(21)

Conjugate addition of the reagent (21) to the enone (16) occurred exclusively to the sterically less hindered β-face of the molecule affording an enolate anion. Quenching of this anion afforded the bis-protected (-)PGE$_1$ (23) which was hydrolysed to the prostaglandin the yield being 65% from the enone (16) (Scheme 1.4.2.4).



(23)

i (21). ii H_3O^+.

Scheme 1.4.2.4

The stereochemical outcome at C-8 and C-12 is dictated by the configuration of the enone (16) and a highly stereospecific synthetic route to prostaglandins results. Although the synthesis is flexible allowing variation in both side chains the low thermal stability of the cuprate reagent causes problems upon scale up.

Running concurrently with this approach was one developed by Corey and the Harvard group involving the use of bicycloheptane intermediates. The route was conceived retrosynthetically[33] along the following lines (Fig. 1.4.2.2):

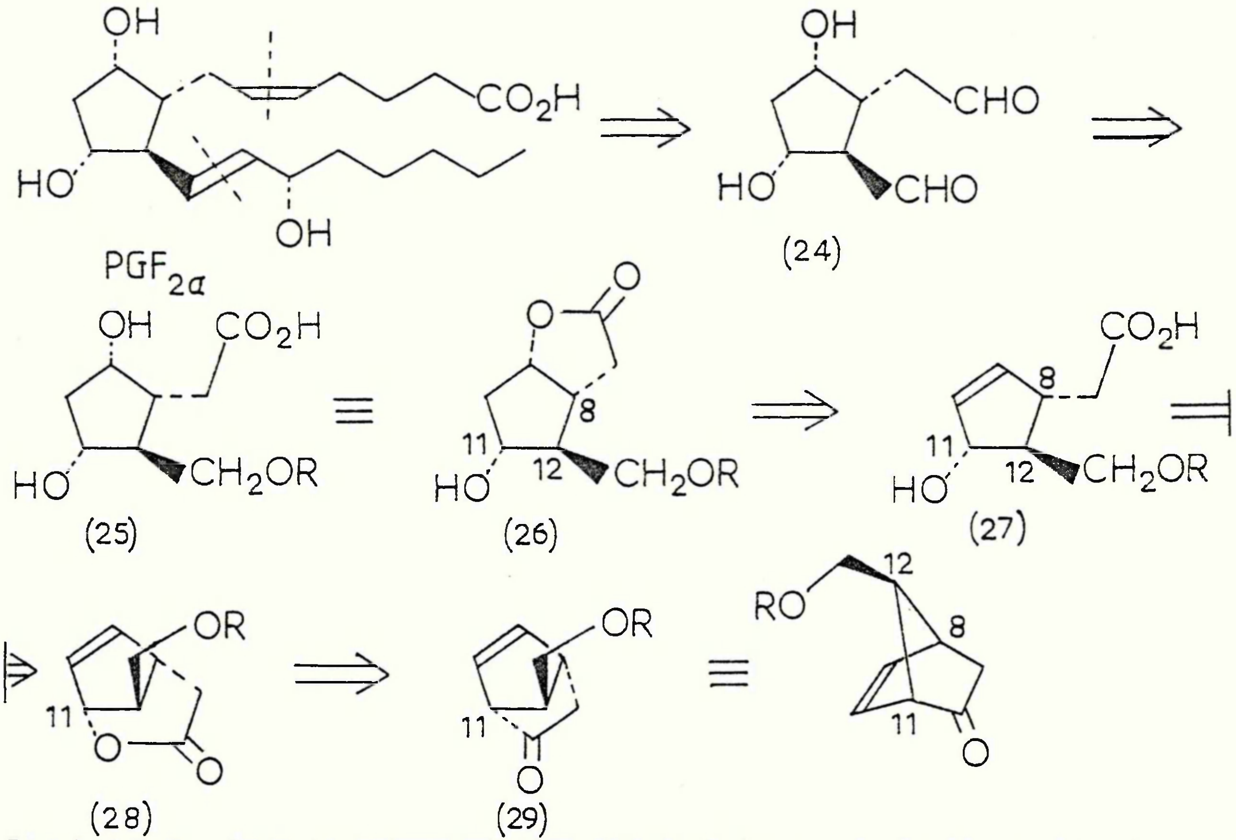
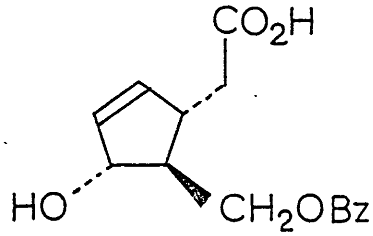


Fig 1.4.2.2 Corey's retrosynthetic approach to prostaglandin synthesis

Corey reasoned that both side chains of PGF$_{2\alpha}$ could be elaborated with Wittig reactions upon the dialdehyde (24). Differentiating the aldehyde groups, one as an acid, one as an alcohol, led him to consider the acid (25) which is equivalent to the lactone (26). The allylic alcohol (27) would provide a suitable precursor to this lactone. Retrolactionisation afforded the lactone (28) which he reasoned might be prepared by Baeyer-Villiger oxidation of the bicycloheptenone (29). In this approach the stereochemistry of the ring substituents is 'locked in' by the use of cyclic intermediates.

The synthesis was developed practically to the scheme (1.4.2.5)[34]. The hydroxy acid (30) was resolved via its amphetamine salt and carried through to optically active $PGF_{2\alpha}$.

Improvements upon Corey's initial sequence followed, most concerned with the preparation of the 'Corey lactone' (31) which in turn has been used to synthesize D, E and F series prostaglandins.



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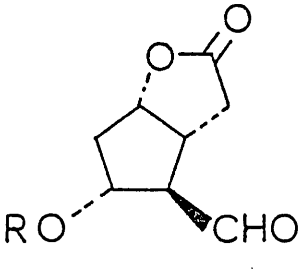

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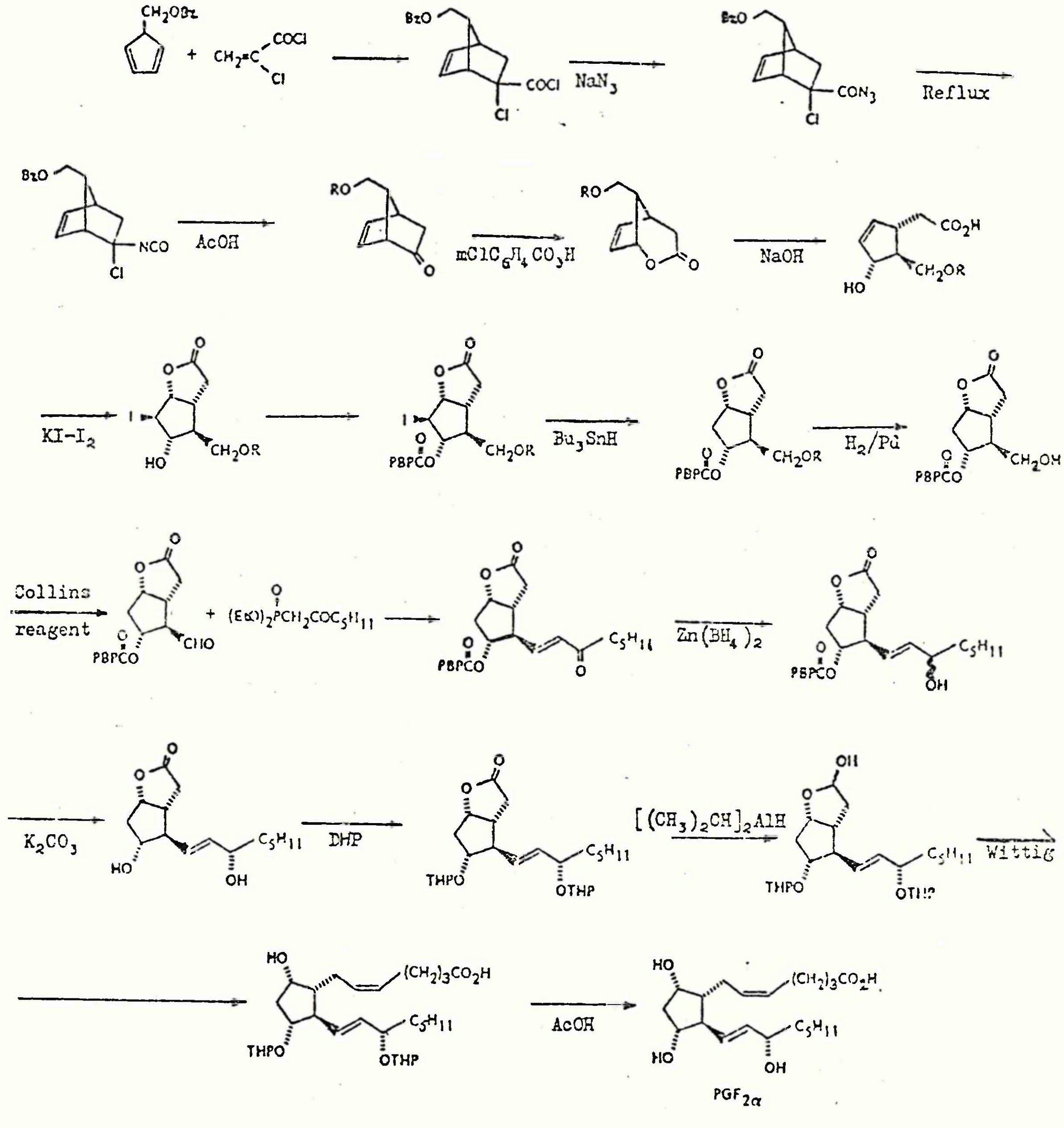
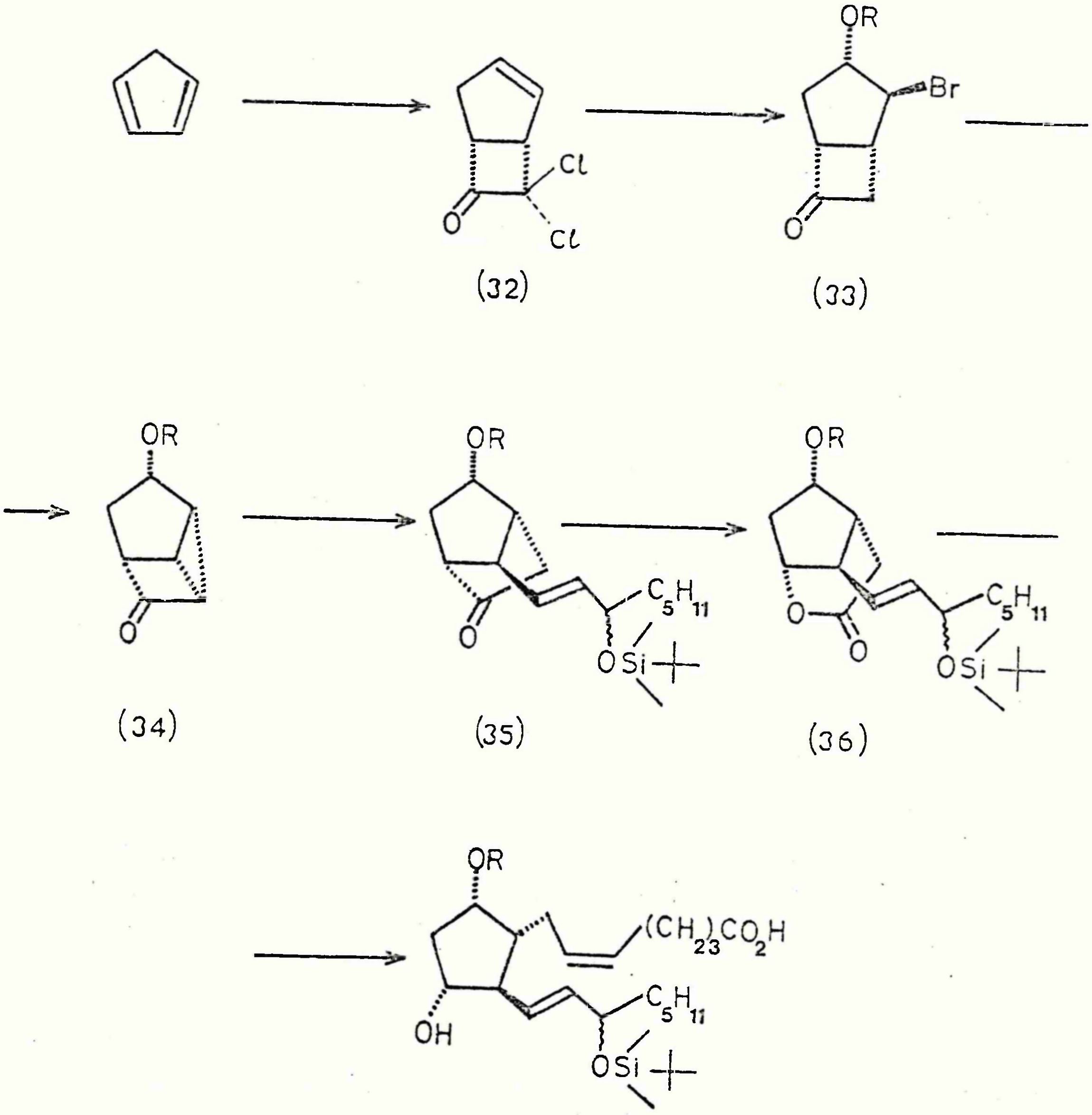


PBP = $-C_6H_4-C_6H_5-p$

Scheme 1.4.2.5 Corey Synthesis of PGF$_{2\alpha}$

The most elegant recent synthesis of a prostaglandin is that of the Glaxo-Salford group of Newton and Roberts first published in 1978. Use of the cyclic intermediates again plays a crucial role in setting up the stereochemistry of the ring substituents.

The reaction scheme (1.4.2.6) represents one of the shortest sequences to $PGF_{2\alpha}$ devised[35]. Starting from cyclopentadiene a (2 + 2) cycloaddition reaction with dichloroketene afforded the dichlorobicyclo [3.2.0] heptenone (32) which was dechlorinated. The bromohydrin (33) was the sole product upon treatment of the bicycloheptenone with N-bromoacetamide. Intramolecular nucleophilic displacement afforded the stable tricycle (34) which in turn was susceptible to nucleophilic cleavage specifically at the 7- position. Thus treatment with an organocuprate reagent afforded the bicyclo [3.2.1] heptanone (35). Baeyer-Villiger oxidation gave both of the twc possible lactones but the desired one (36) predominated at low temperatures. Reduction to the lactol and treatment with the appropriate Wittig reagent introduced the upper side chain. Deprotection afforded $PGF_{2\alpha}$.


Cl
Cl
(32)
OR
Br
(33)
OR
(34)
OR
C5H11
OSi
(35)
OR
C5H11
OSi
(36)
OR
(CH2)3CO2H
C5H11
OH
OSi

Scheme 1.4.2.6

In this approach the stereochemistry at all four ring positions is locked in the tricycle (34); use of optically active cuprate reagent dictates the stereochemistry at C-15. A review[36] of this approach to prostanoids has recently been published describing modifications to the above synthesis allowing preparation of all the primary prostaglandins (A ⟶ F).

1.4.3. Synthesis of 'D' series prostaglandins.

The 'D' series prostaglandins (Fig. 1.4.3.1) were one of the last natural prostanoid families to be isolated. Their discovery, reported in 1968[11], aroused great interest because as well as stimulating smooth muscle preparations[37] and possessing moderate anti-inflammatory properties they exhibited a potent ability to inhibit the aggregation of blood platelets[38].

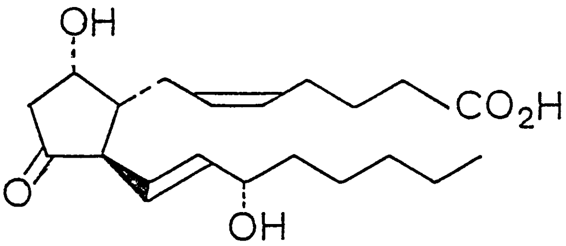
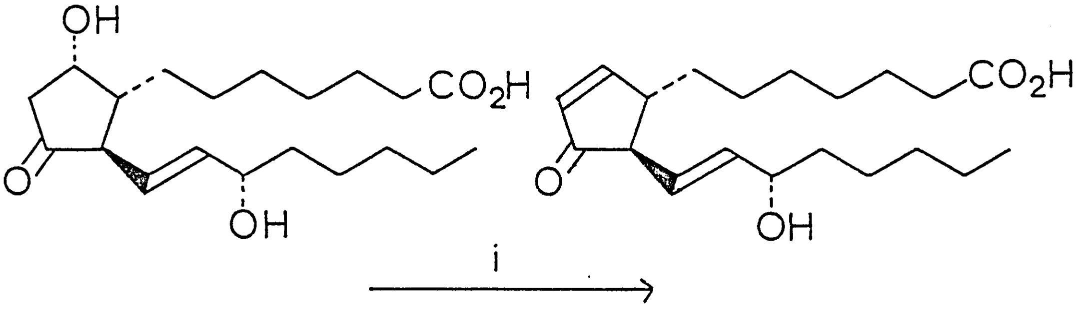


Fig. 1.4.3.1 PGD_2 an example of a 'D' series prostaglandin

The biosynthesis of PGD_1 was reported by Sih[39] in 1972 and was soon followed by the first chemical synthesis[40]. With one exception all the synthetic routes to PGD_1 or D_2 have involved the use of protection-oxidation-deprotection sequences upon an 'F' series prostaglandin. The major problem associated with this approach is concomitant dehydration of the β-ketol system in the product to afford an isoPGA derivative, (Fig. 1.4.3.2.).

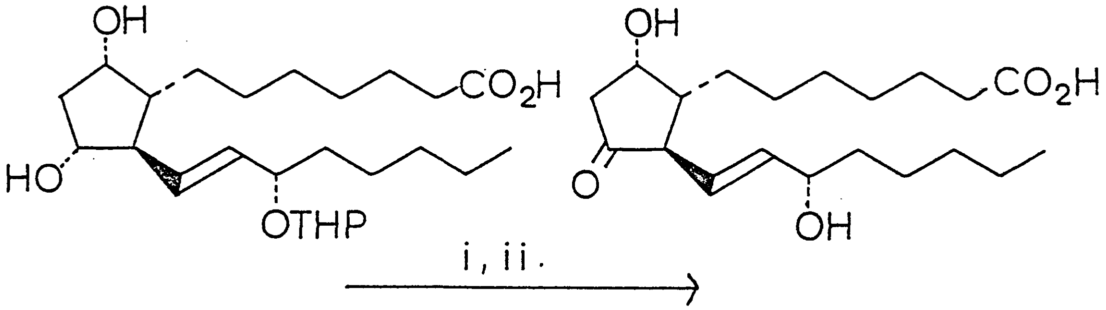


i $H_3O^{\oplus}$. or $\ddot{B}$

Fig. 1.4.3.2 Facile dehydration of PGD_1 to isoPGA_1

Other synthetic problems include protecting group 'scrambling' to afford PGE derivatives and isomerization of the 13,14-double bond into conjugation.

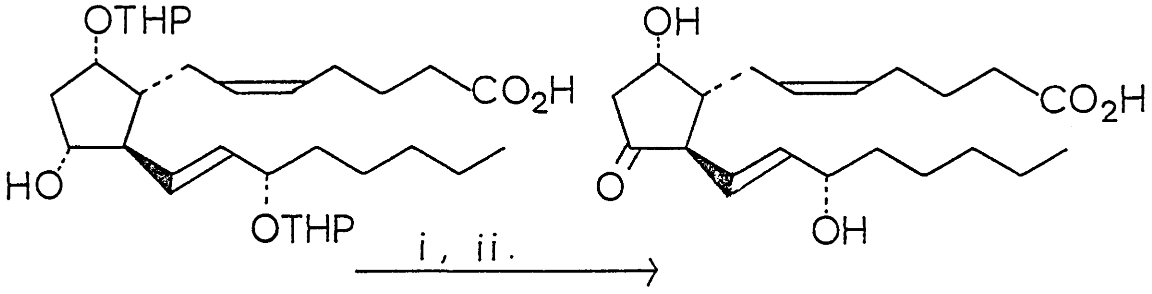
Hayashi[41] has oxidized 15-tetrahydrapyranyl $PGF_{2\alpha}$ with chromium trioxide to yield, after hydrolysis, a mixture containing PGD_2 (Fig. 1.4.3.3).



i. CrO_3. ii. $H_3O^{\oplus}$.

Fig. 1.4.3.3. Hayashi's synthesis of PGD_2.

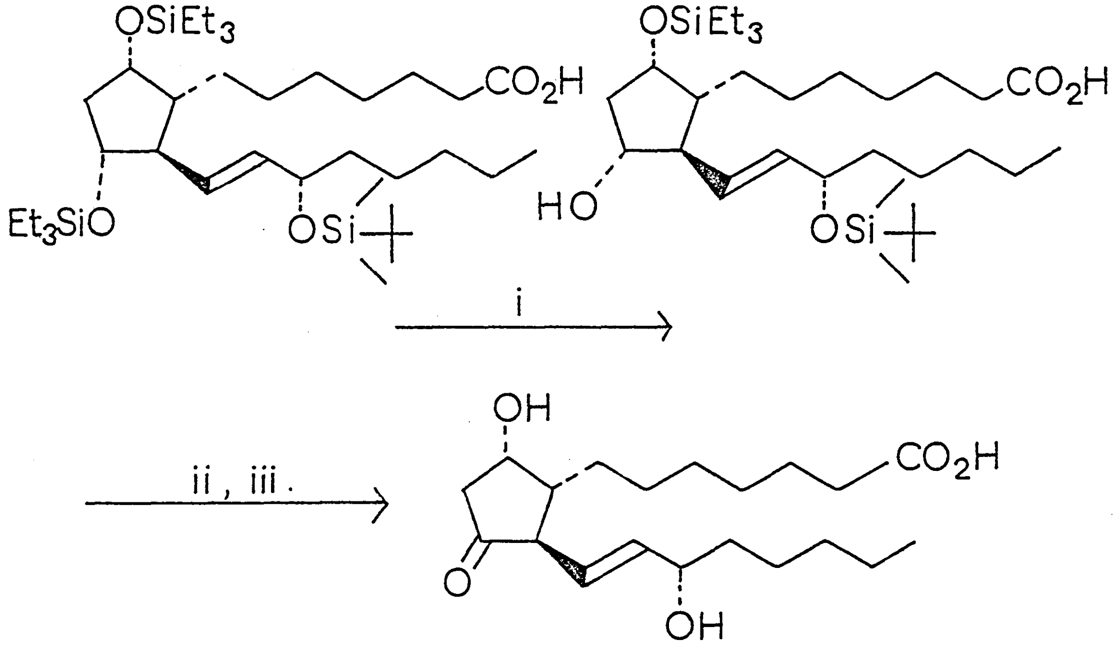
Jenny[42] has prepared PGD_2 in a similar manner oxidising the 9,15-bistetrahydropyranyl $PGF_{2\alpha}$. Deprotection affords a mixture of PGD_2 and PGE_2 (Fig. 1.4.3.4).



i. CrO_3. ii. H_2O, CH_3CO_2H, THF.

Fig. 1.4.3.4 Jenny's synthesis of PGD_2.

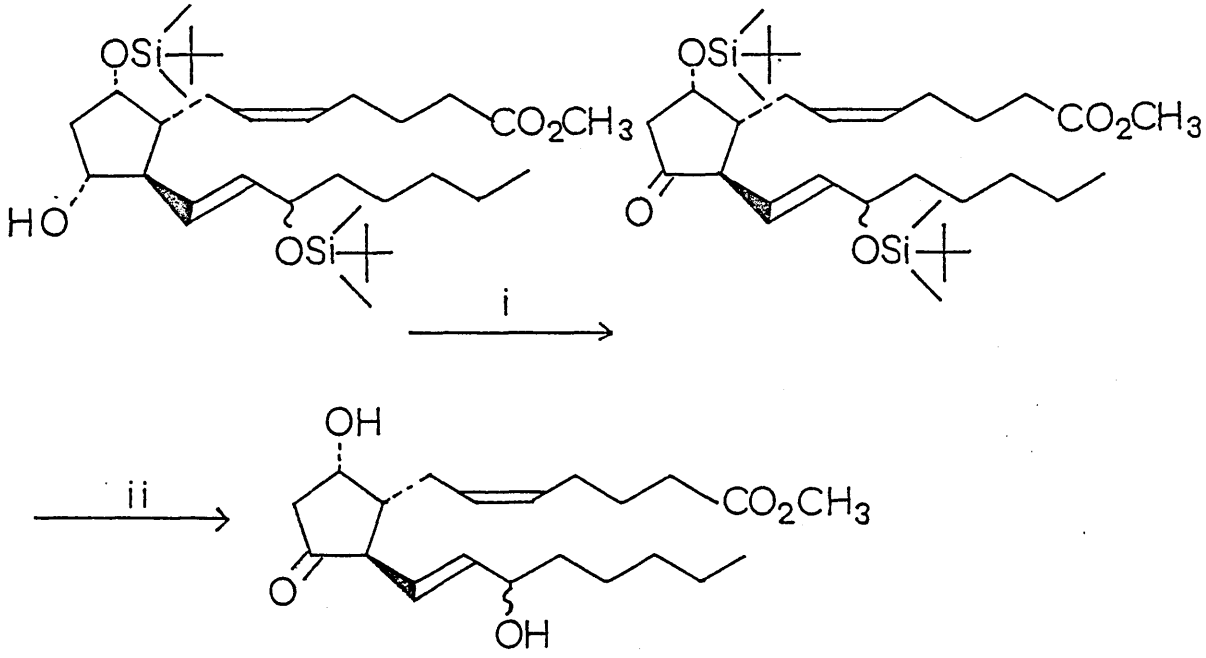
Probably the best of these protection-oxidation methods is that published by Scheinmann[43] in 1979. Selective hydrolysis of the 9,11-triethylsilyloxy-15-^{t}butyldimethylsilyloxy $PGF_{1\alpha}$ methyl ester yielded the 11-deprotected $PGF_{1\alpha}$ which was oxidized with Jones' reagent or pyridinium chlorochromate. Mild acid catalysed hydrolysis of the silyl protecting groups afforded PGD_1 methyl ester (Fig. 1.4.3.5).



i CH$_3$CO$_2$H,THF,H$_2$O, 1 hr.
ii py-CrO$_3$.
iii CH$_3$CO$_2$H,THF,H$_2$O.

Fig. 1.4.3.5 Scheinmann's selective hydrolysis/oxidation synthesis of PGD_1 Methyl Ester.

The Glaxo group have recently published the best synthesis of PGD_2 to date[44,45] (Fig. 1.4.3.6). Modification of their $PGF_{2\alpha}$ synthesis[35] afforded a bis silyl $PGF_{2\alpha}$ which was oxidized with pyridinium dichromate to yield the protected PGD_2. Deprotection was achieved by the use of aqueous hydrofluoric acid in acetonitrile to give a 70% yield of PGD_2 methyl ester and its C-15 epimer. The use of the latter reagent is essential to the success of the synthesis. Unlike previous systems mentioned it possesses both low acidity and high silicophilicity thus effecting smooth deprotection without dehydration.

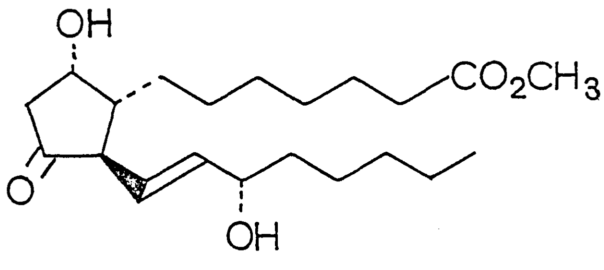


i py-$Cr_2O_7^{2-}$. ii HF,H_2O,CH_3CN.

Fig. 1.4.3.6 Glaxo synthesis of PGD_2 Methyl ester.

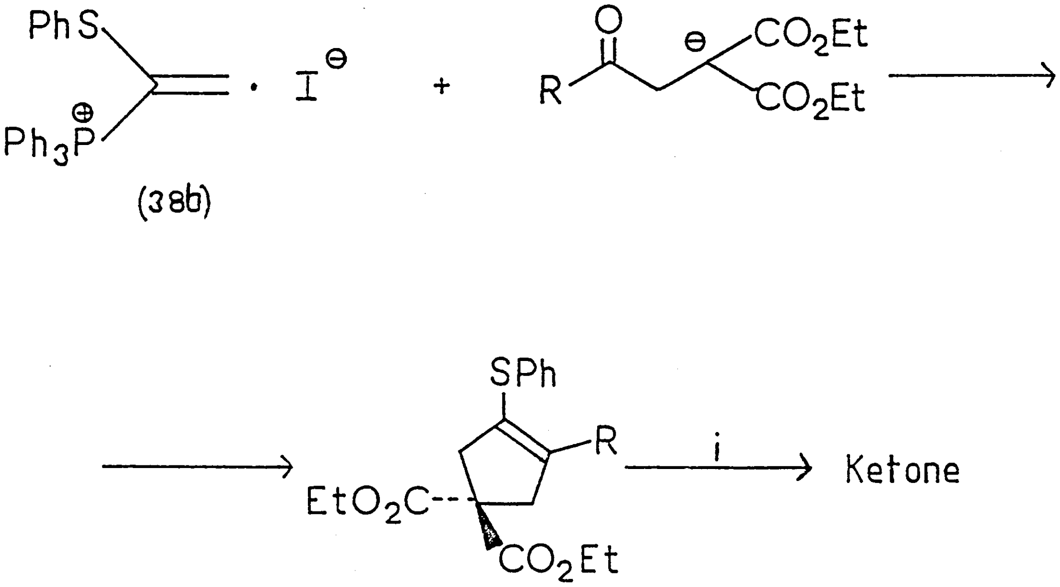
1.5 Proposed Synthetic route to PGD_1 Methyl Ester.

At the commencement of this project no good direct synthesis was available for 'D' series prostaglandins. This reasons prompted us to utilise some of our earlier work as a basis for a novel direct synthesis of PGD_1 methyl ester (37).



(37)

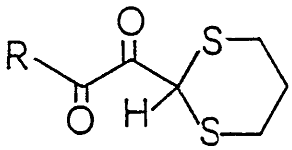
A high yielding synthesis of the novel substituted vinylphosphonium salt (38a) had recently been developed in our laboratories and its use in the synthesis of cyclopentanones demonstrated[46] (Fig. 1.5.1).



i. CF_3CO_2H.

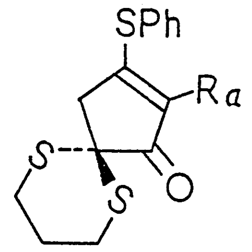
Fig. 1.5.1 Use of the vinylphosphonium salt in cyclopentanone synthesis

It was known that a synthesis of the diketodithiane (39) was available[47] and furthermore that it afforded cyclopentenones upon treatment with simple unsubstituted vinylphosphonium salts.



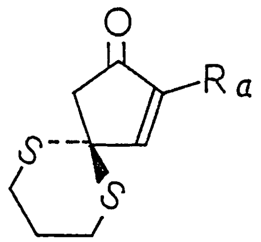
(39)

It occurred to us that the combination of the diketone (39) with our vinylphosphonium salt would afford the highly functionalized cyclopentenone (40).



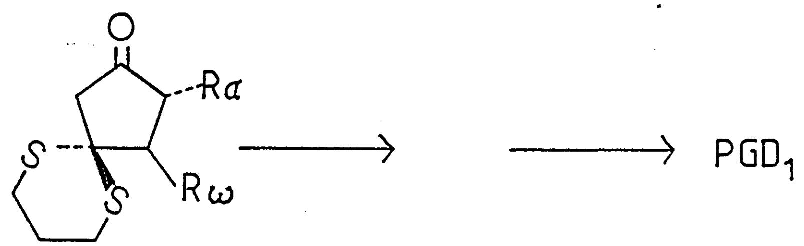
(40)

This cyclopentenone is a sulphur analogue of an intermediate used by Vanderwalle[48] in his synthesis of $PGF_{1\alpha}$. From this work and that of Sih[26,27] it was thought that the enone (41) could be prepared via the intermediate β-hydroxyvinylthioether.



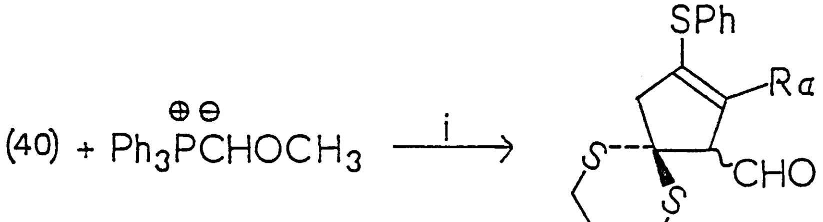
(41)

The cyclopentenone (41) would be a substrate for the cuprate reagents of Sih and Fried, thus the lower prostaglandin side chain could be introduced. Reduction and deprotection of the conjugate addition product (42) would yield the target molecule.



(42)

A less attractive alternative to the above scheme was also considered. This involved treatment of the ketone (40) with the Wittig reagent[49] (43), mild hydrolysis of the product would afford the aldehyde (44) from which the lower side chain could be elaborated via Corey's Wittig reagent[25]. Selective deprotection of the vinylthioether, reduction and hydrolysis of the dithiaketal would afford PGD_1.



(43)

(44)

i. H_3O^+.

2.1 Origin and proposed synthetic route. 39

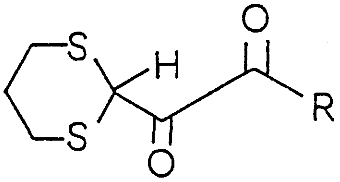
2.2 Preparation and alkylation of alkyl dialkoxyacetates. 42

2.3 Dithanylation of α , α -dialkoxyesters. 46

2.4 Ketal hydrolysis affording the diketone fragment. 48

2.1 Origin and proposed synthetic route

The diketone (39) represents a major part of the target molecule; it not only provides C-8, 11 and 12 of the cyclopentanone nucleus but also bears the complete α-side chain and the C-11 carbonyl functionality masked as its dithiane (Fig. 2.1.1).



(39)

a. R = CH_3
b. R = C_2H_5
c. R = C_5H_{11}
d. R = $(CH_2)_6CO_2H$

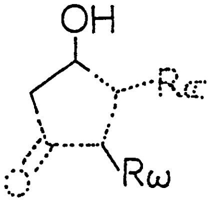
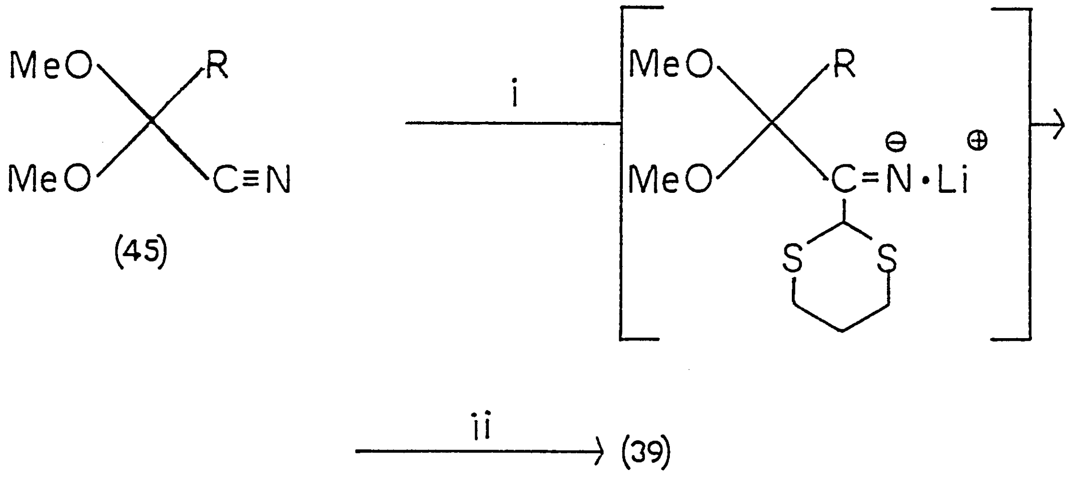


Fig. 2.1.1 Components of the target molecule provided by the diketone fragment (dashed lines)

The only reference to compounds of this type originate from the Sankyo group[47,50] in connection with their work on jasmone and rethrolone synthesis. In their communications the diketones (39a to c) were prepared by treating the appropriate α, α-dialkoxynitrile (45) with dithiane anion. Hydrolysis of the resultant imide afforded the desired diketone (39) in good yield (Fig. 2.1.2).

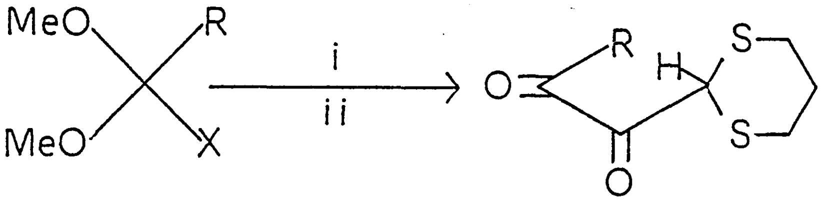


i. 2-lithio-1,3-dithiane. ii. HCl(aq)

Fig. 2.1.2 Kawamoto's synthysis of diketodithianes

The nitriles (45) were prepared according to the method of Erickson[51]. This involved treatment of an ortho ester with hydrogen cyanide gas. We were not attracted to this route, primarily because of the toxicity and handling problems of the latter but also the lack of flexibility imposed by the former. A new method for preparation of α, α-dialkoxynitriles has recently appeared in the literature[52] but is not amenable to large scale (for economic reasons). We therefore set out to design a safer, more flexible synthesis of the diketodithianes (39).

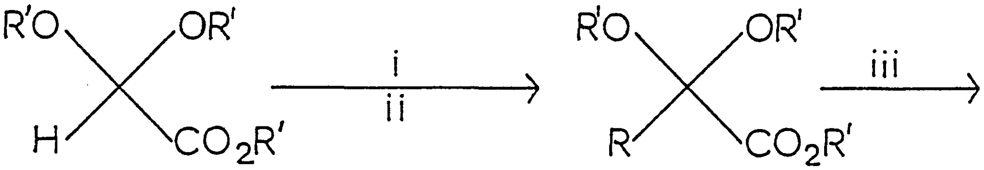
Examination of the above preparation suggested that we need only replace the nitrile functionality with some group X that upon treatment with dithiane anion affords a carbonyl functionality (Fig. 2.1.3). A literature search showed that the ester group (X = CO_2R') would fulfil this purpose[53,54].



i. 2-lithio-1,3-dithane . ii. $H_3O^{\oplus}$

Fig. 2.1.3 Alternative strategy to compounds (39)

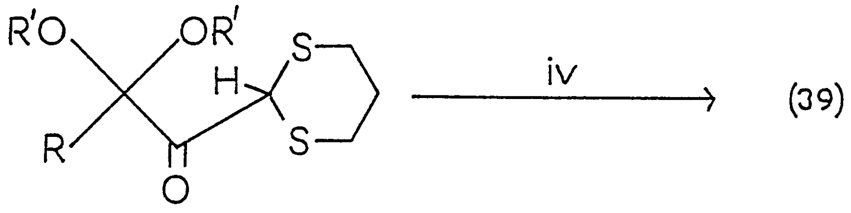
Accepting this proposition a synthesis of substituted α , α -dialkoxyesters was required and the recent work of Schlessinger[55] came to mind. In his isoavenaciolide synthesis he utilized the anion of ethyl 2,2-diethoxyacetate (46b). A further search revealed that the anion of methyl 2,2-dimethoxyacetate (46a) would react at the carbonyl group of aldehydes and ketones without appreciable self-condensation[56]. Although no examples of reactions involving alkylation of these anions could be found it was deemed a feasible synthetic route to substituted α,α-dialkoxyesters (47). The following sequence was thus devised (Fig. 2.1.4).



(46) (47)

a. $R' = CH_3$
b. $R' = C_2H_5$

a. $R = CH_3, R' = CH_3$
b. $R = C_2H_5, R' = CH_3$
c. $R = (CH_2)_6CO_2H,$
$R' = CH_3$



(48)

a. R = CH_3, R' = CH_3

b. R = $(CH_2)_6CO_2H$,
R' = CH_3

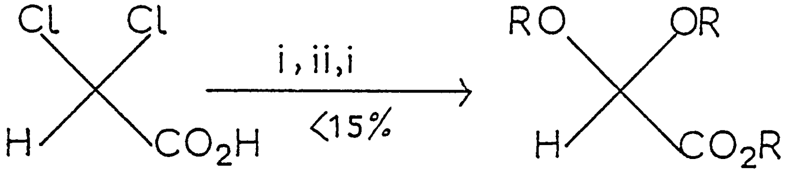
i. Lithium diisopropylamide.
ii. RX.
iii. 2-lithio-1,3-dithiane.
iv. Aqueous acid.

Fig. 2.1.4 Proposed alternative synthetic scheme to the diketones (39)

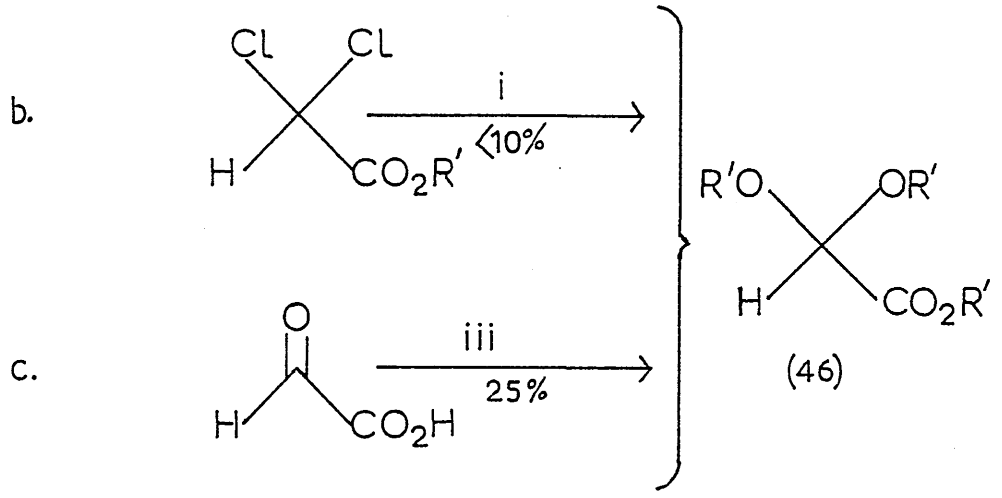
2.2 Preparation and alkylation of alkyl dialkoxyacetates.

The esters (46) were found to be commercially available but their price was prohibitive for use as a starting material in a total synthesis; we therefore decided to prepare our own supply. This proved exceedingly more difficult than first anticipated. Several references describing the preparation of the ester (46) were discovered[57,59] but in our hands none of the routes outlined below could be realized, in even moderate yield (Fig. 2.2.1).

a.



(46)

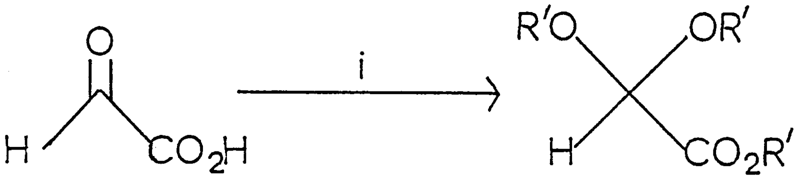


i. OR'.   ii. $SOCl_2$.   iii. $R'OH/HCl(g)$.

Fig. 2.2.1 Various unsuccessful syntheses of the esters (46).

The failure of the latter route (Fig. 2.2.1c) can be attributed to the formation of an equilibrium mixture.

It was known that orthoesters could be used as reagents in the preparation of both esters and ketals[59]. Furthermore it was known that the dimethylketal of methyl pyruvate could be prepared by the use of trimethyl orthoformate and an anhydrous acid catalyst[60]. Practical application of this information allowed us to prepare the esters (46) in ca. 80% yield from glyoxylic acid (49) and the appropriate trialkyl orthoformate (Fig. 2.2.2).

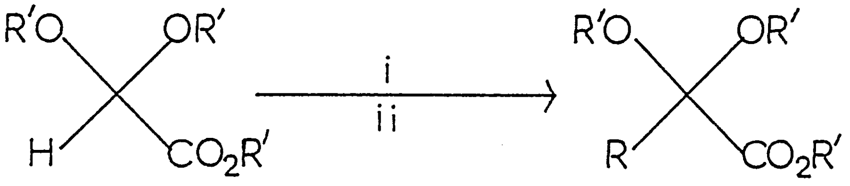


(49)

i. $(R'O)_3CH$, pTsOH

Fig. 2.2.2 Preparation of the esters (46) from glyoxylic acid.

The anions of the esters (46) (generated by lithium diisopropylamide) reacted smoothly with simple alkyl halides to give high yields of the alkylated products (47). We were gratified to receive confirmation of these results with the publication of almost identical work by Huet et al[61]. These results are summarised in Table 2.2.1.



(46) (47)

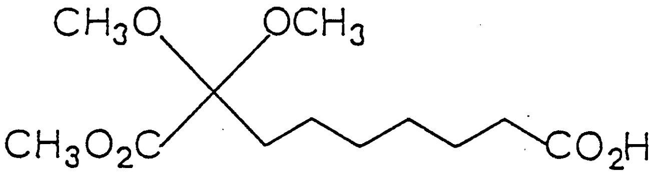
i. Lithium diisopropylamide. ii. RX.

(46) R'.	Alkyl halide (R).	Yield/%.	Lit.[61] yield/%.
CH_3	CH_3I	70.6(a)	50(b)
C_2H_5	"	72.6(b)	-
CH_3	C_2H_5I	71.4(a)	50
C_2H_5	"	70.0(a)	-
C_2H_5	C_4H_9Br	10.0(a)	-
CH_3	C_4H_9Br	-	55(b)
CH_3	$C_6H_5CH_2Br$		70(b)
CH_3	$H_2C = CHCH_2Br$	57(b)	50(b)

a. GLC yield on reaction mixture.
b. Yield after column or distillation.

Table 2.2.1 Comparison of yields for the alkylation of alkyldialkoxyacetates with literature values.

Efforts were immediately directed towards optimizing the alkylation affording the half-acid (47c). Very little reaction was observed when



(47c)

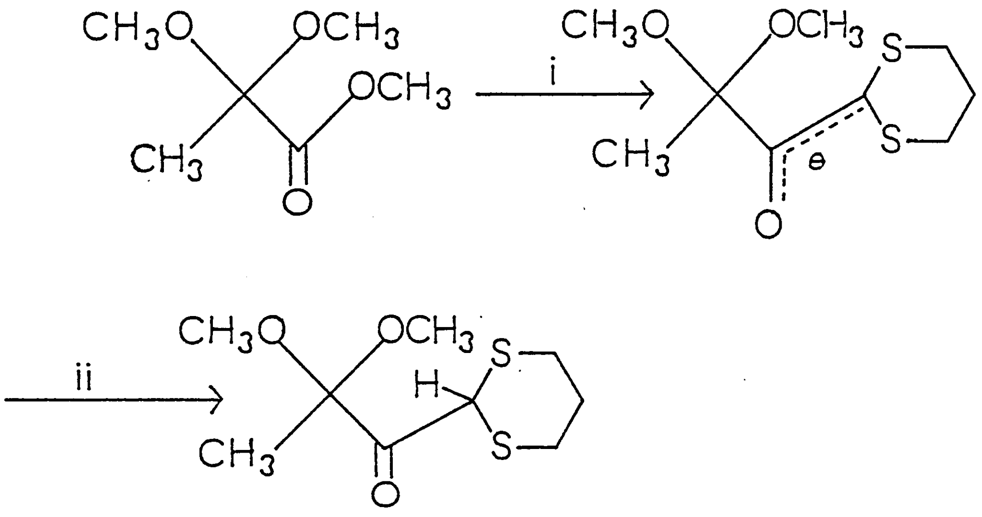
7-bromoheptanoic acid was used as alkylating agent, but, with the iodo-derivative moderate yields of alkylated product were obtained accompanied by a large amount of unreacted starting material. Upon further investigation the poor yields were attributed to two factors, the low solubility of lithium 7-iodoheptanoate in the reaction medium and decomposition/self-condensation of the anion of the ester (46a) even at 0°C. Both were improved by increasing the amount of tetrahydrafuran solvent in the reaction mixture. The anion stability was increased because of dilution, solvation and the use of an intermediate temperature for the reaction (-30°C). The yield of the half-acid (47c) from 7-iodoheptanoic acid was optimised to 73%, the product requiring no further purification. The scale of the reaction was limited to ca. 20g of starting acid because of the large volume of solvent and the temperatures required, the use of hexamethylphosphoramide (HMPA) as solubilizing agent was not investigated.

2.3 Dithanylation of the α, α-dialkoxyesters

Reaction of the ester (47a) with dithiane anion in the presence of one equivalent of lithium diisopropylamide proceeded rapidly at -78°C to give the ketone (48a) in near quantitative yield. The extra equivalent of base was added to ensure that the product was rapidly converted to its enolate anion, thus preventing further reaction[62] (Fig. 2.3.1).

It was shown that the anion of bis(phenylthio)methane[63] would undergo an analogous reaction, nmr studies indicating that the product (50) existed as a 2:1 mixture of keto-enol tautomers. This information was to prove useful when the reactions of the half-acid (47c) with dithiane anion were studied.

This reaction proceeded to afford roughly equal amounts of two compounds. The desired acid (48b) was obtained in ca. 55% yield, the majority of the remainder being an unknown chromatographically more polar compound with almost identical spectral characteristics to

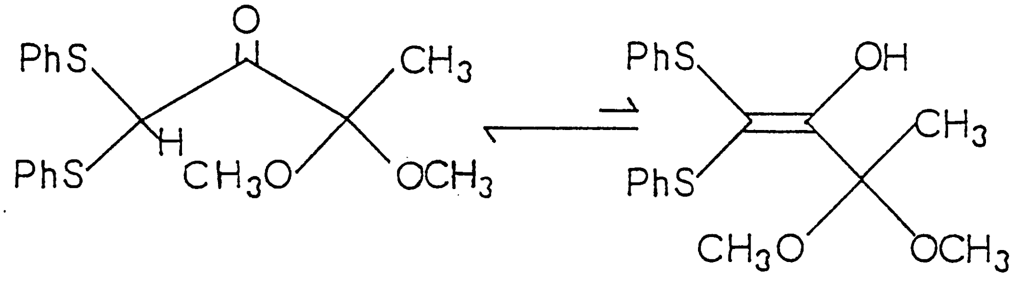


(48a)

i. 2-lithio-1,3-dithiane, lithium diisopropylamide. ii. H_2O.

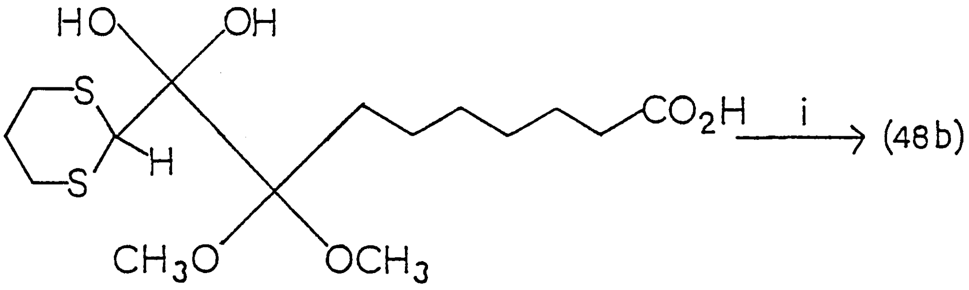
Fig. 2.3.1 Preparation of the ketone (48a).

those possessed by the acid (48b). There was no evidence in the nmr spectrum for the enol tautomer as observed in the bis(phenylthio) case (50), but an enhanced hydroxyl peak in the infrared spectrum gave a clue as to the product's identity.



(50)

It was noted that this byproduct slowly decomposed to the acid (48b) the process being accelerated by high vacuum or azeotroping with benzene. A possible explanation of the experimental observations is that the by product is the unstable hydrate (51) of the desired product which slowly dehydrates under appropriate conditions (Fig. 2.3.2).



(51)

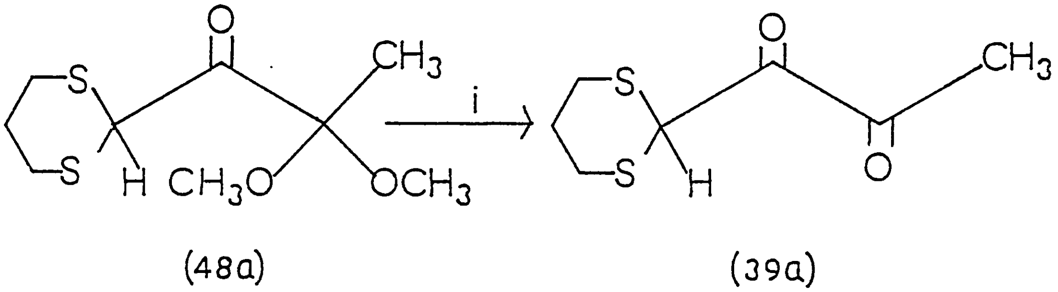
i. $-H_2O$.

Fig. 2.3.2 Dehydration of hydrate (51).

Such hydrates are known to exist when the carbonyl functionality is flanked by electron withdrawing substituents; glyoxylic acid (49) for example, exists in hydrate form. The supposition of a hydrate (51) seems to be valid since the yield for this dithianylation step was optimized to 90% from the half acid (47c), the product requiring no further purification.

2.4 Ketal Hydrolysis Affording the Diketone Fragment.

This final hydrolysis step is analogous to that of Kawamoto[47] (Fig. 2.4.1) but it was noted that his reagent (4% hydrochloric acid) only effected the conversion slowly and in low yield primarily because the reaction mixture was not homogeneous. 9% hydrochloric acid/ tetrahydrafuran, however, provided a 69% distilled yield of the diketone (39a) from its ketal (48a) (Fig. 2.4.1). This reagent was, however, less effective for the system bearing the prostanoid chain, a large amount of polymeric material being isolated.



i. 9% HCl/THF

Fig. 2.4.1 Preparation of model diketone fragment.

Ketal hydrolysis proceeds via a carbonium ion intermediate in accordance with the mechanism outlined (Fig. 2.4.2). Reactions involving the generation of carbonium ion intermediates were being studied for a subsequent step in the synthetic sequence and one of the reagents employed was moist trifluoroacetic acid (TFA). This reagent proved an excellent agent for the hydrolysis of ketals, the diketones (39) being obtained in near quantitative yield.

The highly dissociated nature of TFA means it is a readily available source of protons required to generate the carbonium ion intermediate.

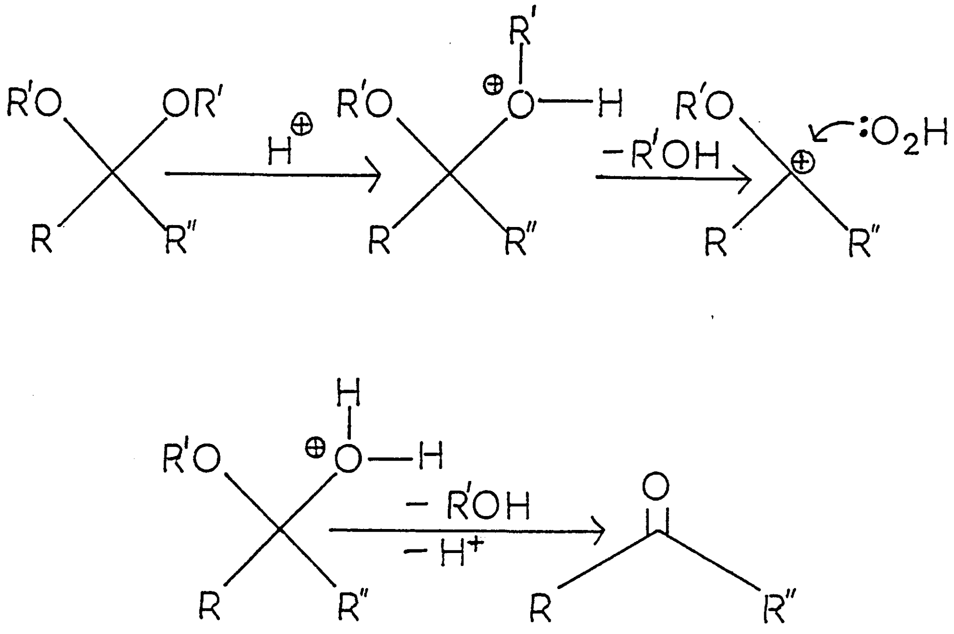


Fig. 2.4.2 Accepted mechanism of ketal hydrolysis

Commercial TFA contains ca. 2% water, but, it was found that 5% aqueous TFA afforded the best yields of hydrolysis products.

CHAPTER 3

Cyclization Reactions and the Cyclopentenone Synthon.

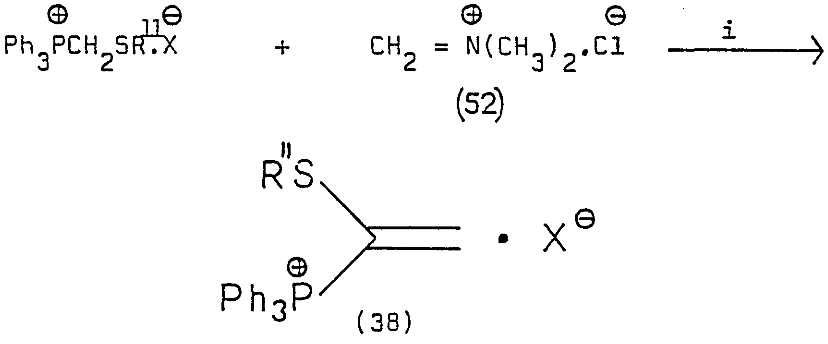
3.1 Substituted vinyl phosphonium salts. 53

3.2 Cyclization reactions. 54

3.3 The cyclopentenone synthon. 58

3.1 Substituted vinyl phosphonium salts

Vinyl phosphonium salts have been successfully employed in a variety of reactions affording both carbo and heterocyclic compounds[64]. We have recently demonstrated the preparation of the substituted vinyl phosphonium salts (38) (Fig. 3.1.1) and shown their synthetic utility[46].



$$Ph_3\overset{\oplus}{P}CH_2SR^{11}.\overset{\ominus}{X} \quad + \quad CH_2 = \overset{\oplus}{N}(CH_3)_2.\overset{\ominus}{Cl} \xrightarrow{i}$$

(52)

(38)

a $R^{11} = CH_3$, $X = Cl^{\ominus}$

b $R^{11} = ph$, $X = I^{\ominus}$

i CH_3CN, Δ .

Fig. 3.1.1 Preparation of substituted vinyl phosphonium salts.

The mechanism of this reaction is thought to involve base catalysis (Fig. 3.1.2) by dimethylamine originating from thermal decomposition or hydrolysis of the iminium salts (52) (paraformaldehyde the other product of decomposition crystallizes in the condenser during a successful reaction). Addition of anhydrous acid results in no reaction.

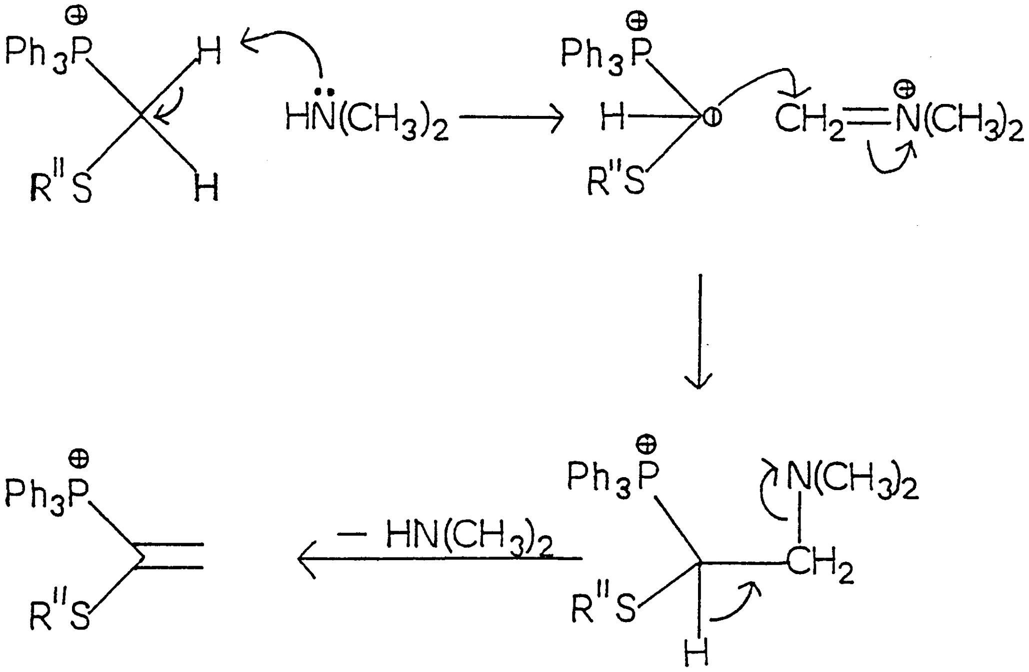


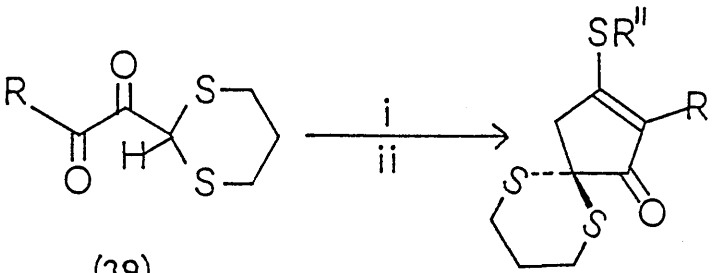
Fig. 3.1.2 Proposed mechanism for base catalysed formation of the vinyl phosphonium salts (38).

Yields from these preparations are in excess of 90% and are unaltered by a different counter ion or sulphur substituent. The latter, however, does affect the rate of reaction. Nmr studies have shown that reaction is complete within 15hours reflux for the phenylthio derivative (38a) whereas the methylthio derivative (38b) requires at least 60hours reflux.

3.2 Cyclization reactions

Having developed a viable synthetic route to the diketone fragment (39) its reaction with our substituted vinyl phosphonium salts was studied.

Reaction of the diketones (39) with sodium hydride afforded anions to which the appropriate vinyl phosphonium salt was added. The desired cyclopentenones (53) were isolated in high yield after chromatography (Fig. 3.2.1), (Table 3.2.1).



(39)

(53)

a. $R = CH_3$, $R'' = CH_3$
b. $R = CH_3$, $R'' = Ph$
c. $R = (CH_2)_6CO_2H$, $R'' = CH_3$
d. $R = (CH_2)_6CO_2H$, $R'' = Ph$
e. $R = (CH_2)_6CO_2CH_3$, $R'' = CH_3$
f. $R = (CH_2)_6CO_2CH_3$, $R'' = Ph$

i. NaH/THF.
ii. (38).

Fig. 3.2.1. Preparation of cyclopentenone intermediates.

(39)R	(38)R''	Yield/%	Product
CH_3	CH_3	74.5	53a
CH_3	Ph	75	53b
$-(CH_2)_6CO_2H$	CH_3	78.5	53c
$-(CH_2)_6CO_2H$	Ph	76.2	53d

Table 3.2.1

An added advantage obtained in the prostanoid derivatives (63c and d) was that the unwanted triphenylphosphine oxide could be removed by base extraction of the product from the reaction mixture.

The mechanism of the above cyclization reaction is at first glance slightly obscure; a Michael type addition of the anion of the diketones (39) to the vinyl phosphonium salt affords an ylid which undergoes an intramolecular Wittig reaction involving the β-carbonyl functionality to afford the cyclopentenone (Fig. 3.2.2). The five membered ring is favoured over the four for thermodynamic reasons.

Comparison of the yields obtained with those quoted by Kawamoto[47] confirms previous observations that the sulphur substituent enhances the reactivity of the vinyl phosphonium salt probably by promoting formation of the intermediate ylid and stabilizing it once formed. Comparison of methyl vinyltriphenylphosphonium bromide with (methylthio) methylvinyl phosphonium chloride shows a difference of 25% in the yield obtained upon reaction with the anion of the diketone (39a).

Once again a difference in reaction rates was noted between the methylthio and phenylthio substituted salts, reaction times differing by a factor of two.

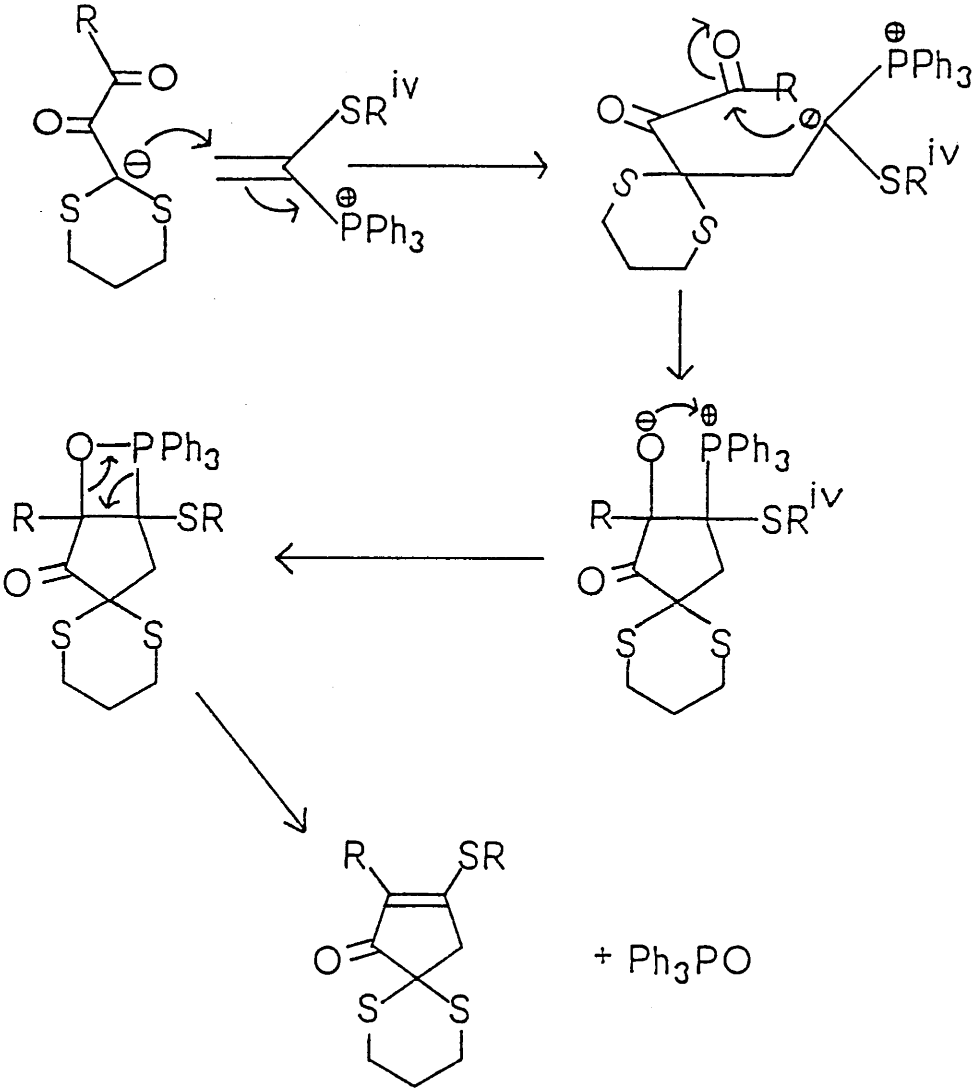
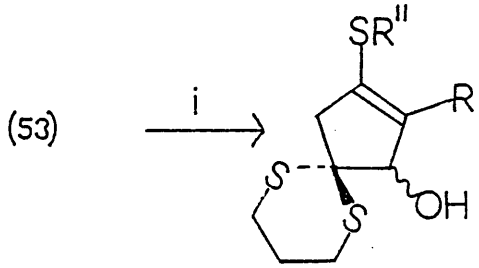


Fig. 3.2.2 Mechanism of cyclization reaction.

3.3 The cyclopentenone synthon.

Reduction of the free carbonyl functionality of the cyclopentenones (53) was first studied upon the model phenylthio system (53b).

This reduction was effected by sodium borohydride in near quantitative yield; the unstable allylic alcohol (54b) could be isolated with care. Reduction of the analogous prostanoid system (53f) was equally facile, no reduction of the terminal ester group being observed. (Fig. 3.3.1).



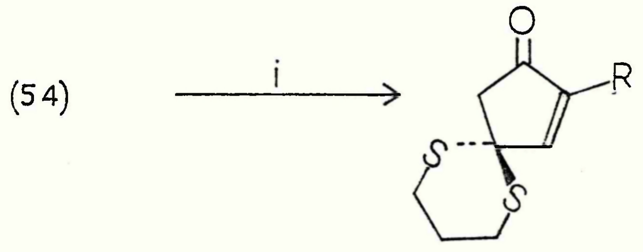
(54)

a. R = CH_3, R" = CH_3.
b. R = CH_3, R" = Ph.
c. R = $(CH_2)_6CO_2H$, R" = CH_3.
d. R = $(CH_2)_6CO_2H$, R" = Ph.
e. R = $(CH_2)_6CO_2CH_3$, R" = CH_3.
f. R = $(CH_2)_6CO_2CH_3$, R" = Ph.

i. [R]

Fig. 3.3.1 Intermediate allylic alcohols (54).

All attempts to induce rearrangement of these allylic alcohols (54b and f) into the corresponding enones in adequate yield proved unsuccessful. Numerous acidic systems were studied but all afforded unstable multicomponent mixtures containing no more than 20% of the desired enones (55) (Fig. 3.3.2).

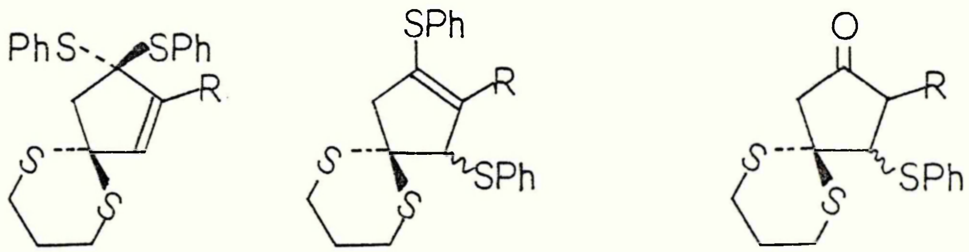


i. H_3O^+.

55 a. $R = CH_3$.
b. $R = (CH_2)_6CO_2CH_3$.

Fig. 3.3.2. Cyclopentenone synthons (55).

Nmr analysis of these by products indicated incorporation of thiophenol in the molecules and it was postulated that one or both of two side reactions were taking place : either the intermediate carbonium ion in the reaction was being trapped by thiophenol liberated from another molecule or this liberated thiophenol was reacting with the product enone to give the 1,4-adduct (56) (Fig. 3.3.3).



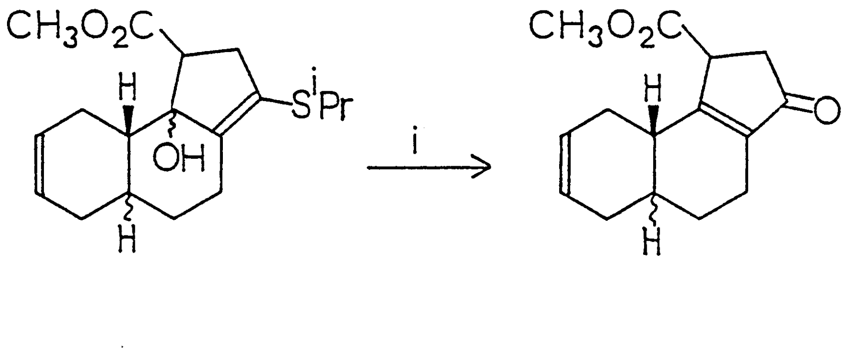
Trapped carbonium ion by products (56)

Fig. 3.3.3 Postulated by products from rearrangement reactions.

Both of these hypotheses were partially discounted when addition of thiophenol trapping agents such as methyl vinyl ketone, benzhydrol, or 3-methylbut-3-en-2-one to the reaction mixtures failed to produce a significant improvement in the yields of the enones (55).

During these studies the first of a series of papers on the reactions of β-hydroxy-vinyl thioethers was published by Omote[65]. This paper discussed the general synthetic utility of the compounds and demonstrated the scope and limitations of the reactions. Several important features were noted : firstly, rearrangements were effected by the use of a concentrated hydrochloric acid/ methanol system; secondly, alkylthio analogues afforded higher yields of the product enone than the corresponding arylthio compounds; finally, incomplete reduction of the precursor β-thioenone was sometimes observed.

Nakagawa[66] in his communication concentrated upon the use of ^{t}butylthio derivatives in the preparation of highly substituted aldehydes. Concluding this wealth of timely information Marino demonstrated the use of an isopropylthio derivative in his decalone



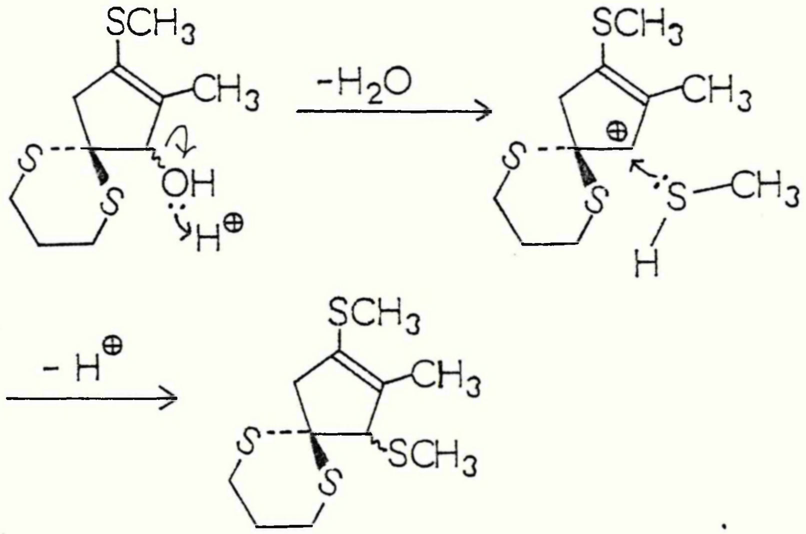
i. HCl(dil)

Fig. 3.3.4 Relevant step in Marino's decalone synthesis.

synthesis[67] (Fig. 3.3.4).

Rearrangement of our phenylthio derivatives (54) using Omote's system led to no significant improvement in enone yields of the prostanoid system (54f) though the yield of model enone (55a) was increased to 44% from the corresponding ketone (54b).

On the basis of the acquired information the methylthio cyclopentenones (53a and e) were prepared. Reduction of the free carbonyl functionality with sodium borohydride now proved extremely difficult. The model system (53a) required elevated temperatures for several hours with this reagent but reduction with lithium aluminium hydride proved facile. Rearrangement of the resulting allylic alcohol (54b) afforded a two component mixture comprising 68% of the desired enone (55a) and 20% of a by product whose spectral data wereconsistant with the structure (57).



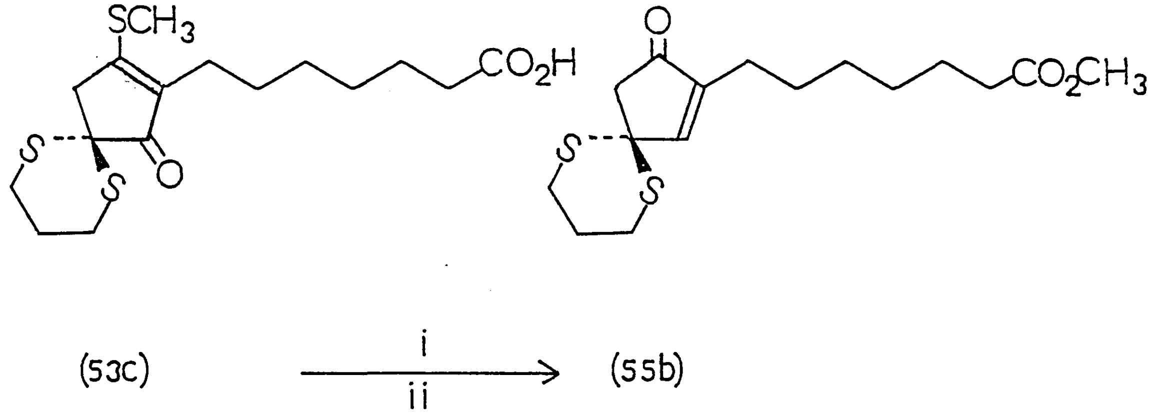
(57)

Fig. 3.3.5 Mechanism of formation of the by product (57).

The latter, formed by trapping of the intermediate carbonium ion by methane thiol (Fig. 3.3.5) is analogous to a previously proposed structure (Fig. 3.3.3).

The increased difficulty of reduction observed in the methylthio model was to prove a problem in the prostanoid system (53e). Sodium borohydride would only effect reduction under conditions that also led to reduction of the terminal ester group. These conditions also proved too fierce for the terminal acid group of the compound (53c). A study was therefore undertaken to find a reducing agent of sufficient strength to reduce the free carbonyl functionality of the acid (53c) without also reducing the terminal carboxyl function. A review[68] by Walker proved useful in these studies. Of the reagents listed Red-Al(lithium-2-methoxyethoxy-aluminium hydride) proved a too powerful reductant whereas lithium tri^{t}butoxyaluminium hydride proved too weak a reducing agent. Borane-type reducing agents were discounted for reasons to be outlined later and initial studies with lithium borohydride proved fruitless. It was noted, however, that addition of methanol to the reaction mixtures containing the latter reducing agent produced a vigorous effervescence (due to partial decomposition of the reagent). Examination of the resulting reaction mixture indicated to our surprise that complete reduction of the substrate, in the desired manner, had taken place. The resulting allylic alcohol (54c) was very unstable and could not be isolated. Immediate rearrangement of this intermediate alcohol proceeded smoothly with partial esterification of the carboxylic acid group.

The esterification was driven to completion by addition of concentrated sulphuric acid. Chromatography afforded a 59% yield of the desired cyclopentenone synthon (55b) over the three steps from the acid (53c) (Fig. 3.3.6).

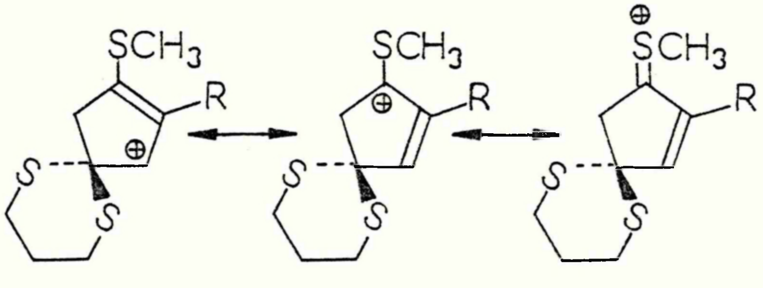


i. $LiBH_4$, CH_3OH.
ii. conc HCl/CH_3OH 1:2, then conc H_2SO_4.

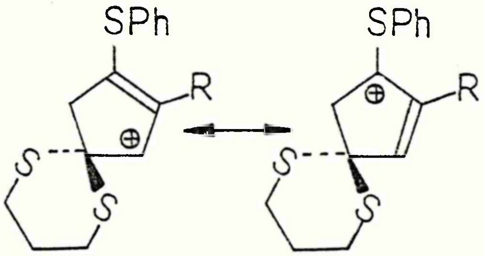
Fig. 3.3.6 Preparation of the cyclopentenone synthon (55b).

The "catch 22" situation encountered in this sequence can be explained in terms of the nature of the sulphur substituent attached to the cyclopentenone ring and the fact that the free carbonyl functionality is that of a vinylogous thioester rather than a normal ketone.

If one assumes the rearrangement of the allylic alcohols (54) to proceed via a carbonium ion intermediate[65], as suggested earlier, then examination of the contributing canonical structures is enlightening (Fig. 3.3.7).



(58a) (58b) (58c)



(59a) (59b)

Fig. 3.3.7 Major contributing canonical structures of intermediate carbonium ions derived from the alcohols (54).

Because the lone pairs on the sulphur are to some extent associated with the π-system of the aromatic ring in intermediate (59) a structure analogous to (58c) is much less favourable. It's contribution to the resonance hybrid is therefore small whereas the contribution of (58c) will enhance the positive charge at the adjacent carbon thus encouraging hydrolysis at the required position (Fig. 3.3.8).

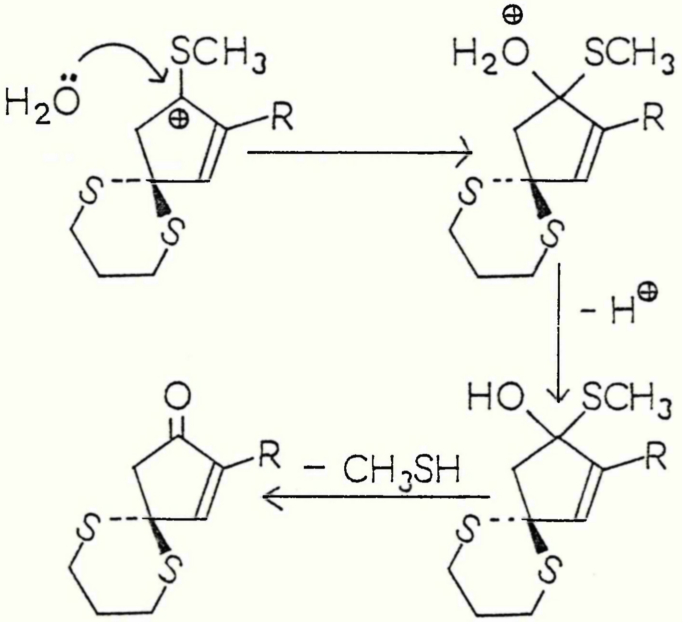


Fig. 3.3.8 Hydrolysis of intermediate (58c) to products

The volatility of the methane thiol leaving group also contributes to the success of the rearrangement being quickly dissipated to air rather than remaining in solution to trap another intermediate carbonium ion as thiophenol does.

Unfortunately the stereoelectronic effects that favour the rearrangement tend to deactivate the carbonyl functionality towards reduction. The electron withdrawing nature of the phenylthio substituent tends to enhance the slight positive charge on the carbonyl carbon thus rendering it more susceptible to hydride attack. The methylthio substituent decreases the net positive charge through resonance (Fig. 3.3.9).

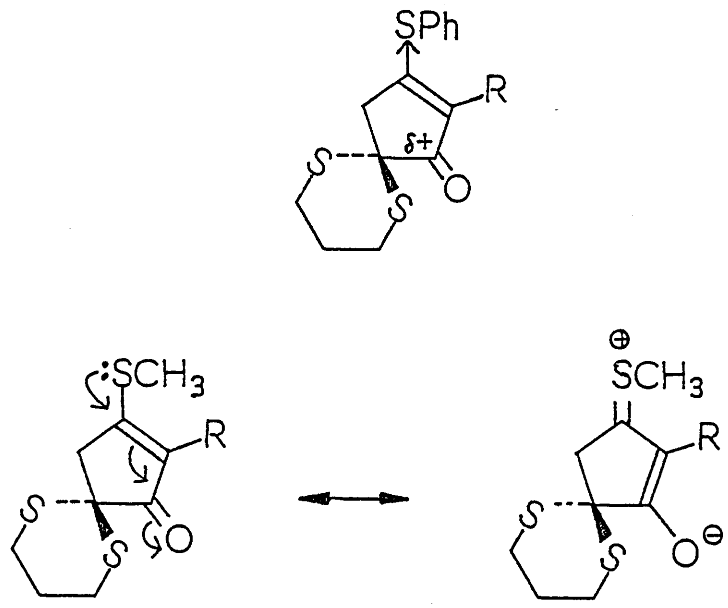


Fig. 3.3.9. Stabilizing and destabilizing effects of sulphur substituents on carbonyl carbon

The reducing agent of choice must redress the charge balance probably by co-ordination of the lithium ion to the carbonyl oxygen (Fig. 3.3.10). The reducing species is postulated to be some form of methoxylborohydride (Fig. 3.3.11) but time has not allowed further investigation of this reduction by say the preparation and study of stoichiometric lithium methoxylborohydrides (m = 1 → 3).

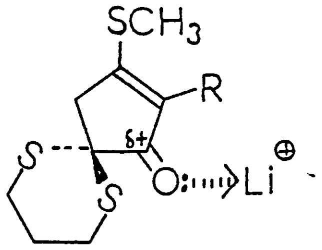


Fig. 3.3.10 Enhancement of positive charge at carbonyl carbon by lithium co-ordination.

$$Li^{\oplus}\left[BH_n(OCH_3)_m\right]^{\ominus}$$

where $n + m = 4$ and $n \nless 1$.

Fig. 3.3.11 Postulated methoxyborohydride species.

CHAPTER 4

Conjugate addition reactions of the cyclopentenone intermediates.

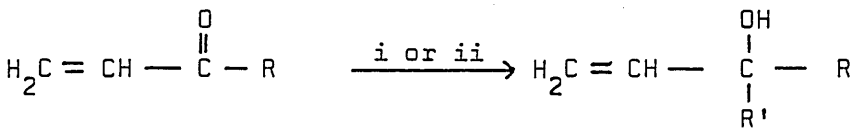
4.1 Historical and background information. 70

4.2 Choice of cuprate reagent and model addition reactions. 73

4.3 Preparation of prostanoid intermediates and mechanistic discussion of reaction. 78

4.1 Historical and background information

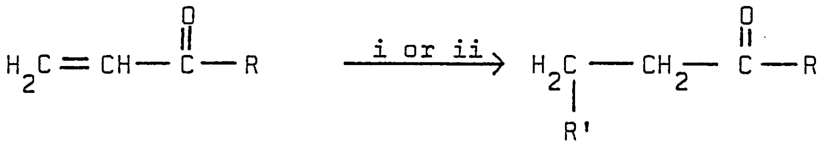
Organolithium and organomagnesium (Grignard) reagents react with α, β-unsaturated carbonyl compounds to afford predominantly the 1,2-adduct (Fig. 4.1.1.). In 1941[69] it was discovered that catalytic amounts of copper(I) salts[70], when added to Grignard solutions promoted the 1,4-addition mode (Fig. 4.1.2) sometimes to the exclusion of the 1,2-process.



$$H_2C{=}CH{-}C({=}O){-}R \xrightarrow{\text{i or ii}} H_2C{=}CH{-}C(OH)(R'){-}R$$

i. R'Li.
ii. R'MgX.

Fig. 4.1.1. 1,2- Addition mode.



$$H_2C{=}CH{-}C({=}O){-}R \xrightarrow{\text{i or ii}} H_2C(R'){-}CH_2{-}C({=}O){-}R$$

i. R'_2CuLi.
ii. $R'MgX/CuCl$.

Fig. 4.1.2. 1,4- Addition mode.

Later studies were to show that organocopper reagents such as lithium dimethylcopper[71] would also afford the 1,4-adducts.

The use of organocopper reagents in organic synthesis was developed by Posner and Corey through the mid 1960s and the scope and utility has been described in several reviews[72,73,74,75].

The stoichiometric organocopper reagents currently favoured in organic synthesis are the homo- and heterocuprate complexes.

The homocuprate reagent has an empirical formula (60) only one of the R-substituents is transferred to the substrate while the other remains bound to the copper. The ligands L, when present, are trisubstituted phosphines and although not essential to the reaction they do have an effect on the stability and reactivity of the organocopper reagent. Prepared from two equivalents of an organolithium compound and a copper(I) complex, most homocuprate reagents have a limited stability at temperatures above $-20^{\circ}C$, the usual mode of decomposition being via coupling reactions.

$$Li^{+} \ [Cu\ R_2\ L_2]^{-}$$

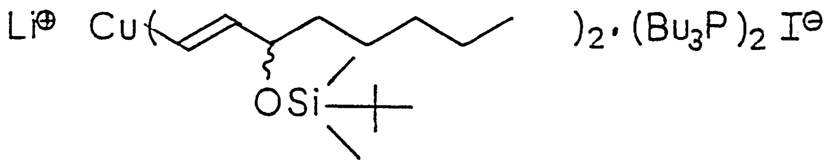
(60)

The less reactive heterocuprate reagents, empirical formula (61), can be prepared either from an organocopper compound-complex and organolithium reagent or by sequential addition of the latter to a copper(I) complex. Transfer of the R or R' substituent depends on the strength of the carbon-copper bond formed and this decreases in the order $-C \equiv C-$, $-C = C-$, $-C - C-$. Most common heterocuprate reagents employ an acetylenic R' group thus ensuring transfer of the R-substituent. The two main advantages of the heterocuprates over the homocuprates are their greater temperature stability and the fact that they consume only one equivalent of a possibly expensive precursor so are more economical.

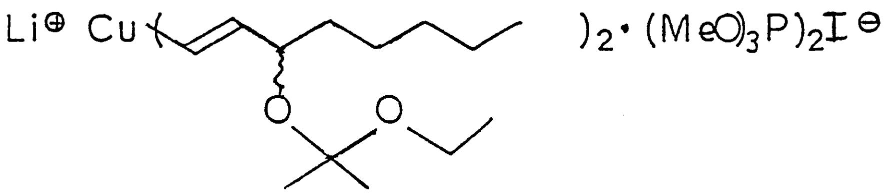
$$Li^+[Cu\ R\ R'L_2]^-$$

(61)

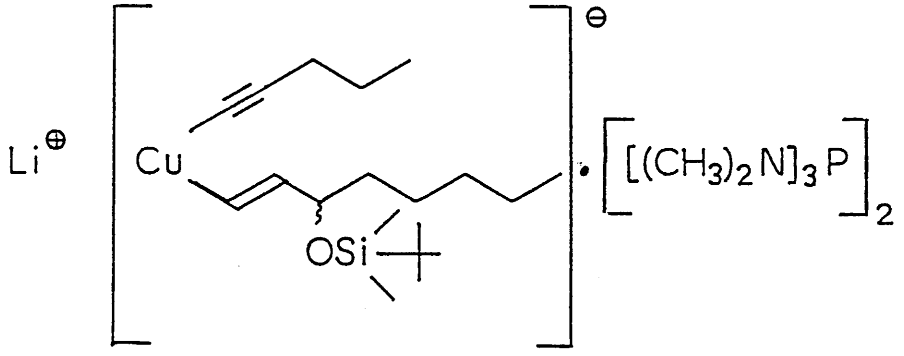
The organocopper reagents favoured by the prostanoid chemists for the introduction of the lower ω-side chain are the homocuprates of Sih[26,27] (62) and Fried[32] (63) (the preparation of which has already been outlined) and the heterocuprate reagent (64) developed by Corey[77] and employed both by the Glaxo group to open their tricyclic intermediate[35]; by Scheinmann in his PGD$_1$ synthesis[43] and by Fried[76].



(62)



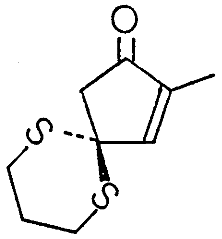
(63)



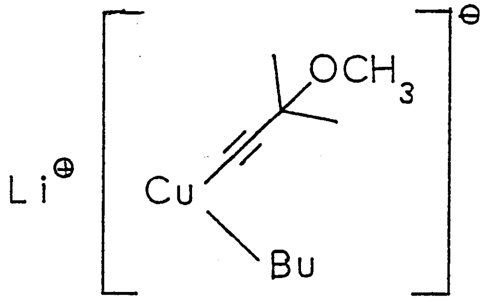
(64)

4.2 Choice of cuprate reagent and model addition reactions.

The model enone (55a) showed a distinct lack of reactivity towards a wide range of heterocuprate reagents bearing either a simple alkyl substituent or the full ω-prostanoid side chain. Amongst reagents investigated were the heterocuprate (64) and the methoxybutyne cuprate (65) of Corey[78]. In all cases active cuprate reagent was shown to be present by addition of cyclohexenone to the reaction mixture and analysis for the 3-substituted cyclohexanone.

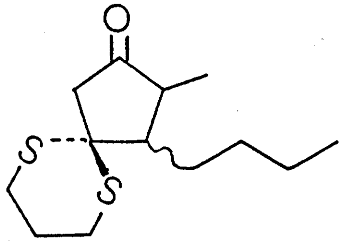


(55a)



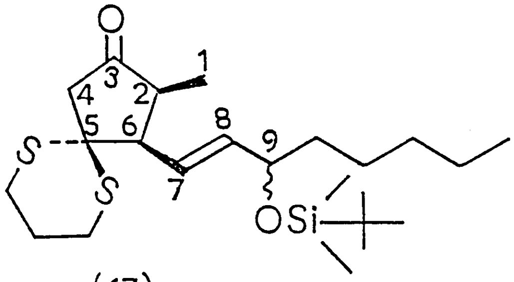
(65)

Investigations with the homocuprate reagents proved to be more successful. Addition of an ^{n}butyl cuprate with tri-^{n}butylphosphine ligands, to the model enone, proceeded rapidly at -78°C affording an 85% yield of the desired 1,4-adduct (66) after chromatography. The stereochemical outcome of this reaction was not determined.

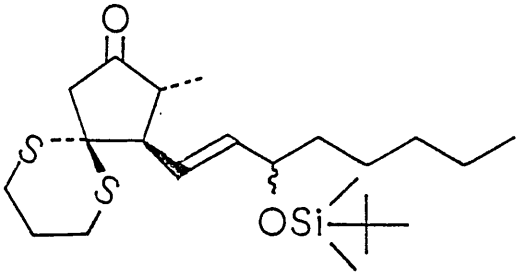


(66)

Rapid conjugate addition to this enone was also observed when Sih's reagent (62) was employed. However, a small amount (10-15%) of unreacted enone was invariably recovered along with the products. Two chromatographically separable products were isolated in the ratio 1.48 : 1; these had identical infrared and mass spectral characteristics but differed in their proton n.m.r spectra. Since it was known that the C - 15 epimers of prostanoid systems are not chromatographically separable when bearing the t-bdms protecting group[79] it was thought that the two products were the cyclopentanones with the ω-side chain either cis (67)



(67)

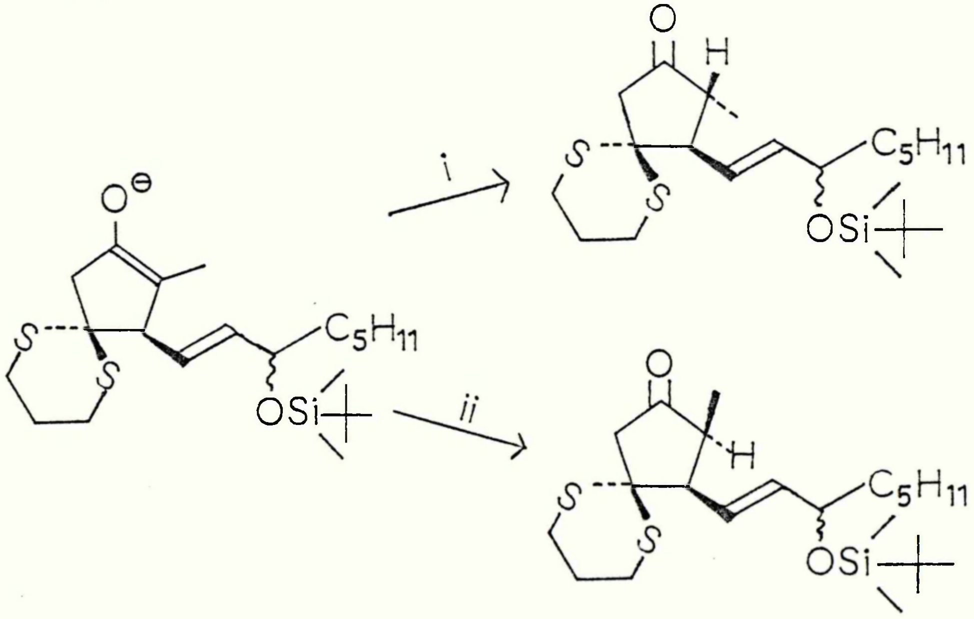


(68)

or trans (68) to the methyl substituent.

Although the initial trials and optimization studies were carried out using racemic cuprate reagent, for simplicity the ensuing discussion will be based upon reactions of the resolved 15 S - reagent.

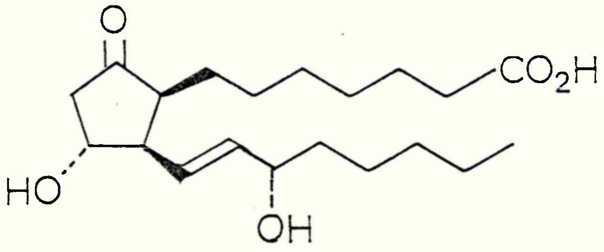
This situation has rarely been reported by previous workers using this approach to prostaglandins and is most likely due to the fact that the substrate enones either bore a substituent at the potential C - 11 position (usually a protected alcohol functionality) or the complete ω-prostanoid side chain. The thermodynamic requirement for the side chains to be trans is much greater in these systems. The production of cis and trans isomers occurs when the intermediate enolate (generated during the addition reaction) is protonated (Fig. 4.2.1).



i. H$^{\oplus}$ above
ii. H$^{\oplus}$ below

Fig. 4.2.1. Products resulting from enolate protonation.

In the case shown the enolate is produced when the cuprate reagent attacks from above the plane of the cyclopentanone ring. Protonation can then occur from above or below the ring plane to give the trans or cis isomers respectively. Some natural prostaglandins do contain small amounts of the cis isomer; the Upjohn group have shown that PGE_1 exists in an equilibrium mixture containing as much as 10% of the 8-iso derivative (69)[80,81].

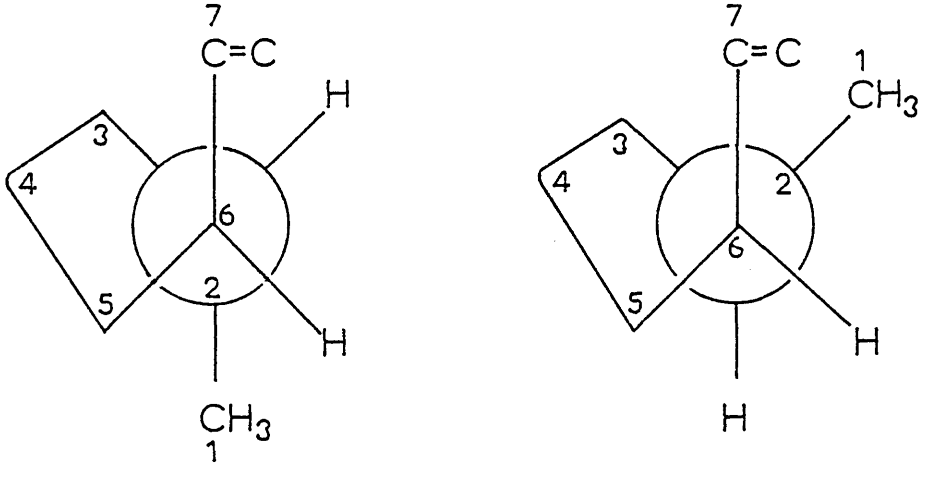


(69)

Although it was suspected that the predominating product possessed the trans arrangement (68) on thermodynamic grounds, it was carbon - 13 nmr that provided proof of the stereochemistry of the two products.

Carbons three bonds distant from a substituent have been shown to exhibit upfield shifts due to sterically induced polarization of the carbon hydrogen bonds[82]. In rigid cyclic systems such as ours this effect is at a maximum when the substituent and the γ-carbon are in a gauche conformation. This is known as the γ-gauche effect.

If one examines the Newman projections of the adducts (67) and (68) (Fig. 4.2.2) it can be seen that in the cis case the C-2 methyl is gauche to the C-7 carbon whereas in the trans case it is anticlinal. Therefore, in the trans isomer these resonances should be observed down field (higher δ-value) of the corresponding resonances for the cis isomer. [The numbering system employed for the adducts (67) and (68) is not strictly correct since they are in fact di-substituted-dithiaspirodecanone systems. The use of a prostanoid style of numbering makes referal to the carbons in the lower side chain easier, thus simplifying the discussion.]



trans(68) cis(67)

Fig. 4.2.2 Newman projections along the C-6, C-2 bonds of the cyclopentanones (67) and (68).

On the basis of the data obtained (Table 4.2.1) the predominating chromatographically more polar isomer was assigned the trans stereochemistry.

	CH_3/ppm	C-7/ppm
cis	10.7	123.4
trans	12.9	125.1

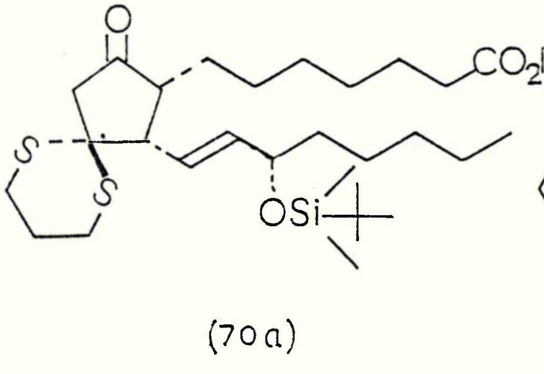
Table 4.2.1 ^{13}C nmr data for the model 1,4-adducts (67) and (68).

In the carbon nmr spectra some resonances appeared as doublets due to the presence of diastereoisomers. The adducts (67) and (68) are derived by attack of the cuprate reagent from above the plane of the cyclopentanone ring (Fig. 4.2.1). Their diastereoisomers originate from attack of the reagent below the ring plane. As the enone is symmetrical one would expect attack from above or below to be roughly equally likely, this being reflected by a 1 : 1 intensity ratio for the distereomeric resonances, however, the spectral data obtained suggests a ratio between 2 and 3 to 1.

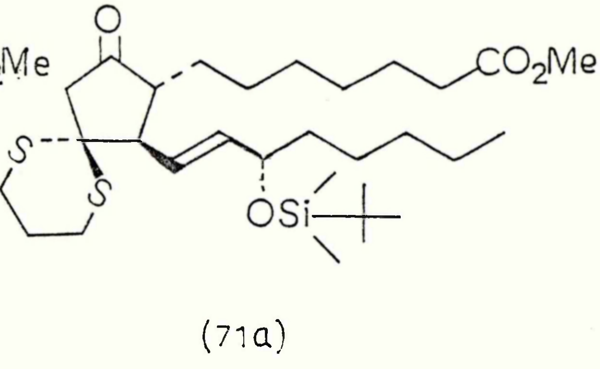
The above result was confirmed by deprotection at C-9 which allowed separation of the diastereomeric alcohols the chromatographically more polar diastereomers predominating by a factor of 2.4 : 1 for both cis and trans isomers.

4.3 Preparation of the prostanoid intermediates and mechanistic discussion of reaction.

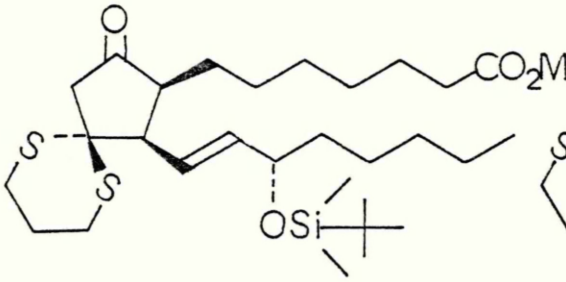
With the information obtained from the model compounds attention was now turned to the prostanoid systems. Conjugate addition of the cuprate reagent (62) proceeded in a similar manner to the model system; the cis (70) and trans (71) pairs of diastereoisomers were isolated in 63% combined yield.



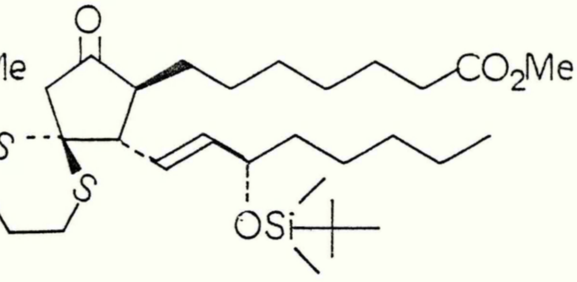
(70a)



(71a)



(70 b)



(71 b)

The more polar pair of diasteromers (71) predominated to the extent of 2.3 : 1 and were assigned the trans stereochemistry on the basis of their carbon-13 nmr data (Table 4.3.1). The increase in trans to cis ratio was expected because of the greater thermodynamic requirement involved with the full α-prostanoid side chain as compared to a methyl group.

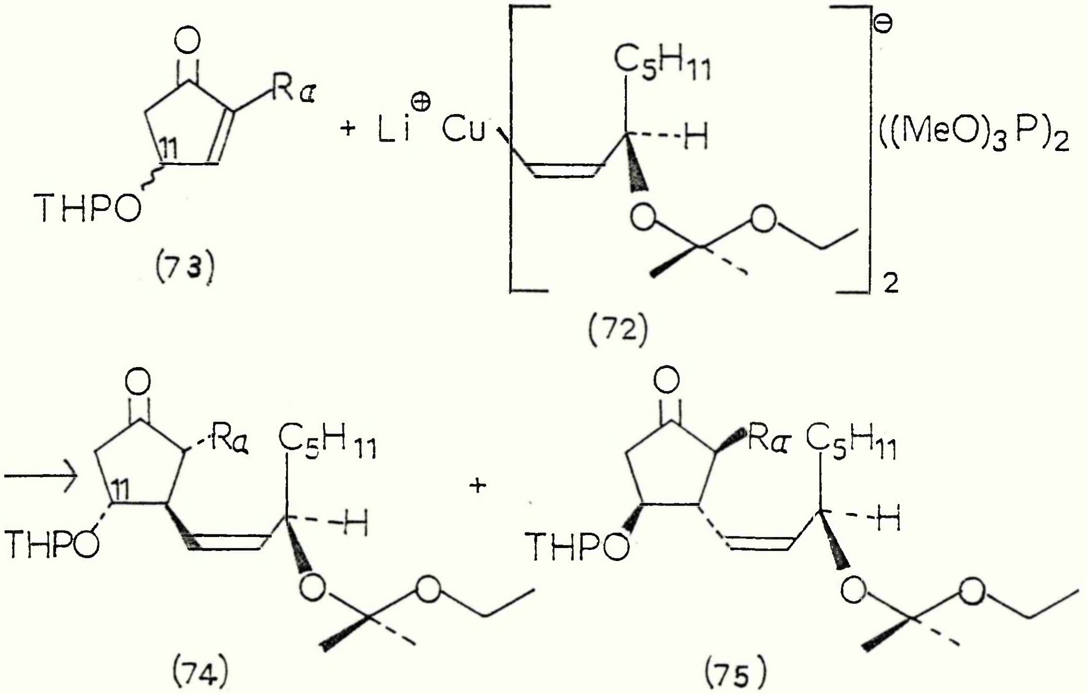
	C-7/ppm	C-13/ppm (prostaglandin numbering).
cis	25.4	123.14
trans	26.3	125.7

Table 4.3.1. Carbon-13 n m r data for prostanoid adducts.

Deprotection at C-15 confirmed the carbon-13 data that both cis and trans isomers were a ca. 3.5 : 1 mixture of diasteromers. The more polar was initially assigned the structure (71a) on the basis of published chromatographic data for analogous PGE_1 systems. Confirmation of this assignment is given later.

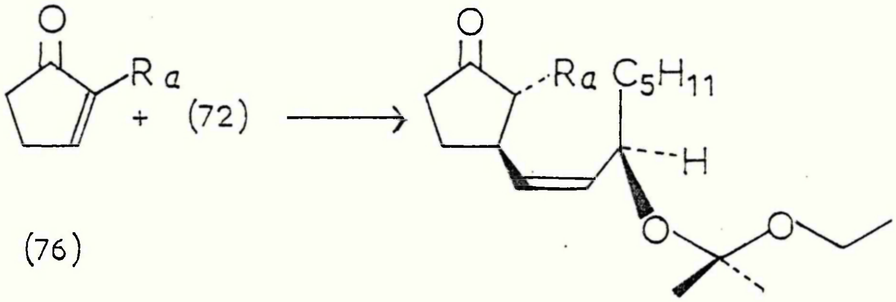
In the prostanoid system the cuprate addition initially only proceeded with a 50-80% conversion of substrate enone. The reaction was accompanied by the deposition of a white precipitate which was found to be rich in substrate and unreacted side chain. The liquors were found to contain very little enone but were rich in the addition products. Addition of excess phosphine ligand or solvent failed to dissolve this precipitate or prevent its formation. However, it was found that when the ratio of cuprate reagent to substrate was raised from 2 : 1 to 3.4 : 1 the precipitate dissolved within the hour at -78°C and this was accompanied by complete consumption of the enone substrate.

The excess of the desired diastereomer (71a) over the ent-15-epi isomer (71b) has only been observed by one other group and represents an asymmetric induction of the stereochemistry at the C-12 centre by the substituent at C-15 (3 carbons distant). Fried[83] has shown that the 13,14- cis cuprate reagent (72) reacted with the racemic enone (73) to afford a 6.2 : 1 mixture of the 1,4-adducts (74) and (75). When the reaction was carried out using racemic reagent in 3-fold excess over the resolved enone only one isomer was isolated[84,19a].



(73) (72) (74) (75)

In these reactions there is a preferred side of attack for the cuprate reagent (the face opposite to that in which the C-11 substituent lies). There is no such steric restraint for the 11-deoxy enone (76) but again it was shown that not only was there a preferred face of addition but also that α or β - attack was governed by the stereochemistry of the C-15 substituent.



When Fried used the trans reagent (63) he only observed a slight deviation from the expected 1 : 1 diastereomeric ratio. This latter case is similar to our experimentally encountered situation where the enone (55b) is 11,11-disubstituted and possesses the same plane of symmetry as the 11-deoxy derivative (76). However, we have observed asymmetric induction with a trans reagent and found the preferred side of attack to be from the β -face for the 15 S-cuprate, the same face as Fried's cis-15R- reagent. Whether these reagents have the same spatial orientation about the chiral carbon in solution is debatable.

In his paper Fried suggests that the diastereomeric transition state (12 β ,15R) is formed more rapidly because it is of lower energy than the corresponding (12 α ,15R) state and therefore a kinetic resolution occurs in which the substrate enone is consumed by β-attack more rapidly than by α-attack. Under kinetic conditions the (12β,15R) product predominates and unreacted enone is recovered. In the case of the racemic cyclopentenone (73) the recovered substrate is optically active possessing the 11S - configuration (all the 11R substrate is consumed). Fried also proposed the formation of a planar cuprate reagent by coordination of the C-15 oxygen with the copper and suggests such a reagent would favour regio-specific attack on the enone through a coordinated intermediate.

We agree that in our example there must be a difference in formation energy between the two diastereomeric transition states (the (12β,15S) state appearing to be of lower energy) but do not totally accept the proposition of a copper-C-15 oxygen co-ordinated cuprate reagent. We have several reasons for this: firstly models suggest our trans reagent is unable to form a planar species; secondly co-ordination would be disfavoured in the presence of excess ligand but the stereochemical outcome of the reaction is not affected by the presence of extra phosphine; thirdly we utilized the bulky ^{t}butyl dimethylsilyl protecting group for the C-15 alcohol whereas Fried used the smaller 1-ethoxyethyl ether group. The size of our protecting group would make formation of an oxygen-copper complex unlikely on steric grounds (in fact the oxygen present in the ethoxyethyl ether protecting group would seem better placed to co-ordinate).

We feel that the preference for face of attack is a purely steric one based upon the orientation of the bulky C-15 protecting group. Rotation about the carbon-15-oxygen bond is restricted because of conformational effects in the cuprate reagent and also the rotational energy available to the system is limited because of the low reaction temperature used and may even be less than that required to flip from one conformation to, or through, an energetically less favourable one. On this hypothesis the conformation of lowest energy must be such that the C-15 group sterically hinders attack from the unfavoured face of the cyclopentenone increasing the activation energy of the transition state relative to the activation energy required to form the diastereomer.

In trying to justify this hypothesis we have examined molecular models but to little avail, primarily because the detailed structure of the cuprate reagent in solution is not known. A dimeric arrangement is thought to exist for the simplest example lithium dimethyl copper(I) (Fig. 4.3.1.1) but this is far removed from the complex reagent (62).

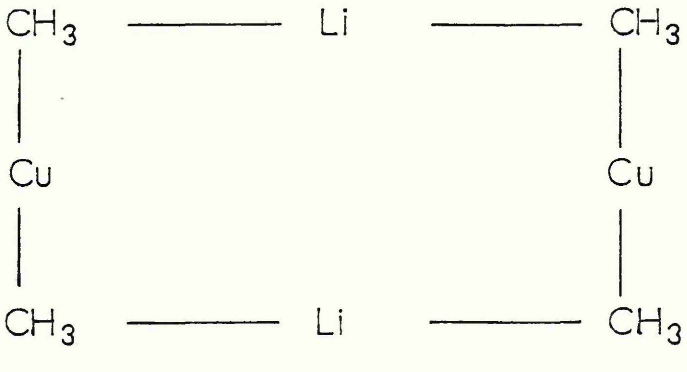


Fig. 4.3.1. · Proposed structure of lithium dimethylcopper.

Another major problem is the exact nature of the transition state and what it comprises. This led us to examine the mechanistics of organocuprate addition.

Although there is no accepted detailed mechanism for the copper promoted 1,4-conjugate addition process there does exist a consensus of opinion as to the main features. Initial proposals invoked a radical process in which an electron is donated from the copper to the enone system to form a copper(II) charge transfer complex. Transfer of an alkyl radical regenerates the copper(I) species and the complex breaks down to give the enolate anion (Fig. 4.3.2).

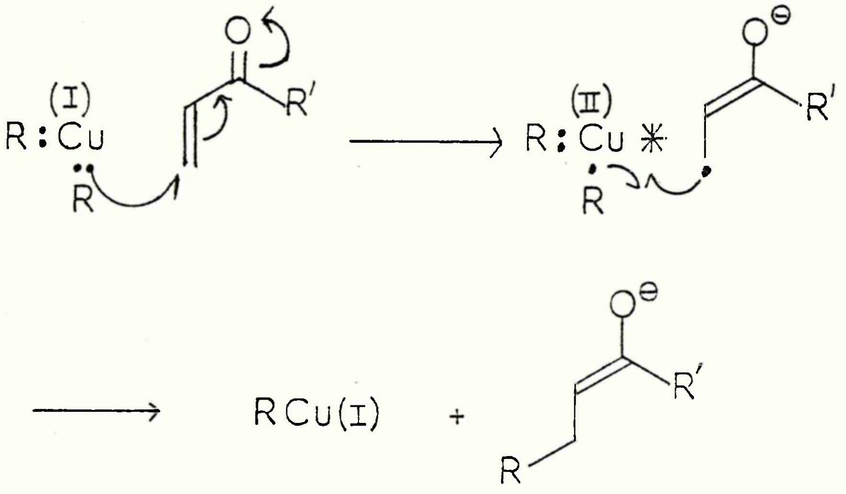


Fig. 4.3.2. Radical mechanism for cuprate addition

In his latest mechanistic proposals[74] Posner has postulated the intermediacy of copper(III) species formed by oxidative nucleophilic attack of the copper dimer complex. Reductive elimination of the R-group generates the enolate (Fig. 4.3.3).

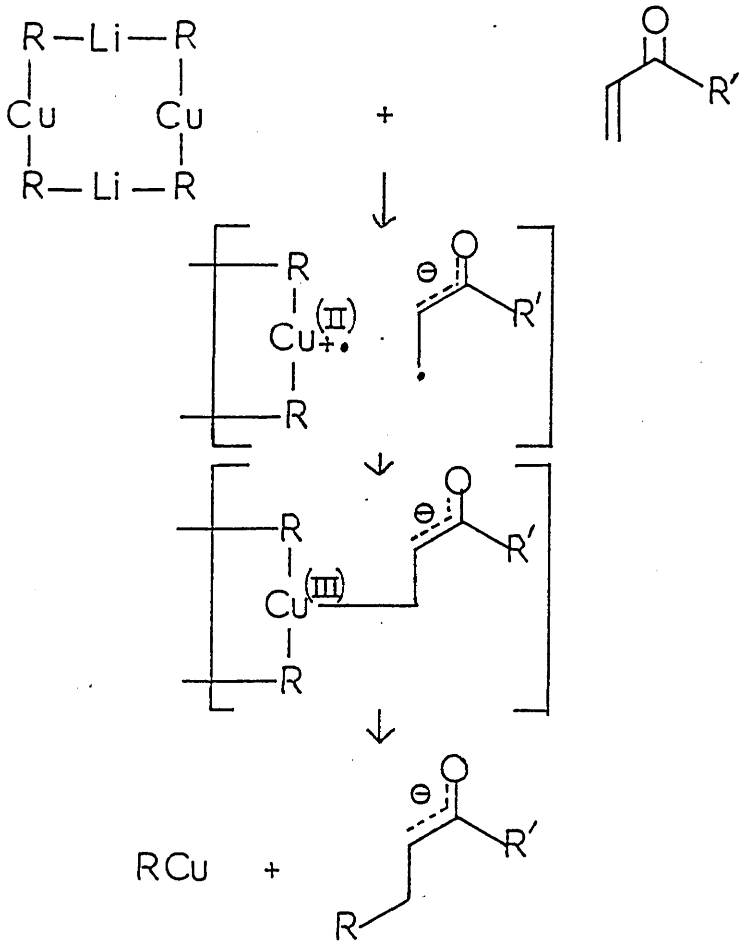


Fig. 4.3.3 One of Posners latest mechanistic proposals.

The latter mechanism may account for the experimental observation that most organocuprate addition reactions normally require at least a 2-3 fold excess of the copper reagent to go to completion. The extra copper species would be tied up with the reacting one in the dimer.

Berlan[85] has recently proposed that the addition reaction proceeds via a π -complex between the double bond of the enone and the copper in a two electron transfer process, the lithium co-ordinating to the oxygen (Fig. 4.3.4).

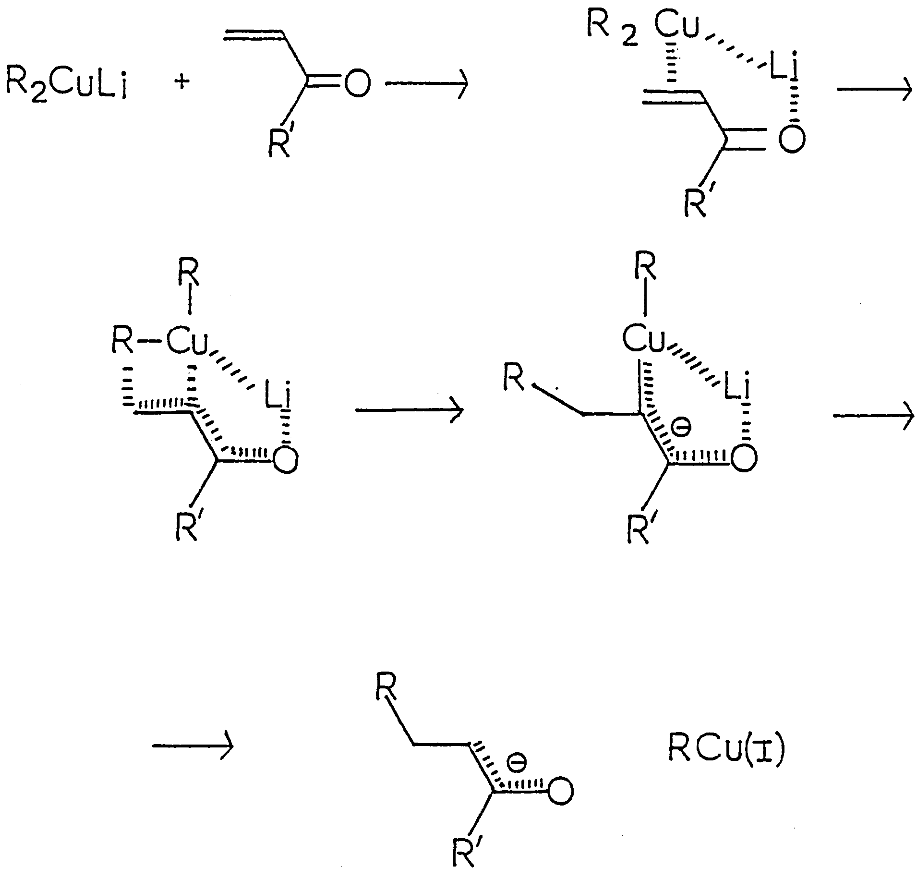


Fig. 4.3.4 Berlans mechanistic proposals for organocuprate addition

The transfer of an R substituent from the copper to the substrate is accompanied by formation of the enolate.

Our experimental results certainly tend to suggest that some form of enone- cuprate is being formed. The fact that the 'complex' only proceeds to products in the presence of a vast excess of cuprate reagent would tend to invoke a mechanism involving two molecules of reagent. As hydrolysis of the complex regenerates enone and quenched cuprate, and not adducts, this indicates that the second molecule of reagent is required to attack the enone-cuprate complex to give the adducts. In our case co-ordination via the sulphurs of the dithiane ring might deliver the cuprate species to the desired position of attack but this is unlikely in the presence of excess phosphine ligand. One proposition might be that a copper radical enolate is formed by one electron transfer between oxygen and copper followed by subsequent rearrangement. The second copper species then attacks at the radical terminus

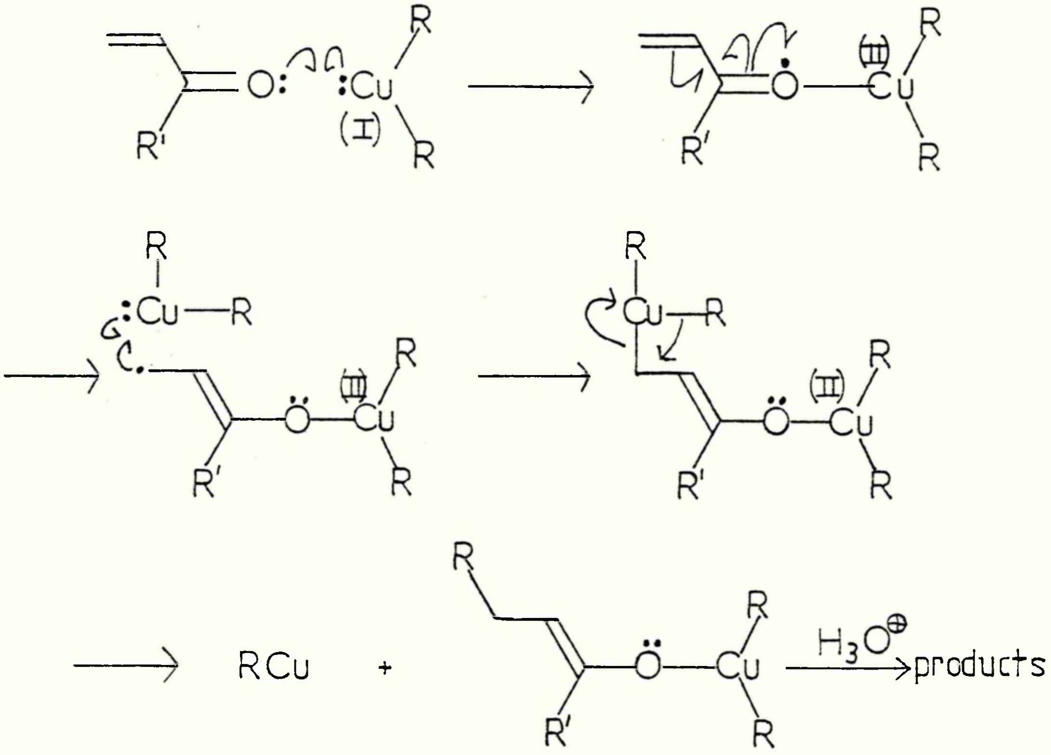


Fig. 4.3.5 A mechanistic proposal involving two molecules of copper reagent

forming another copper(II) species which re-arranges via a 1,2-alkyl shift. Quenching of the enolate affords the adducts.

Even considering all the above there is still no satisfactory mechanistic explanation of our experimental results.

The mechanistics of copper promoted 1,4-conjugate addition will no doubt receive a great deal more attention. Unfortunately our experimental work does little to clarify the situation.

CHAPTER 5

Completion of the Synthetic Sequence. Preparation of PGD_1 methyl ester.

5.1 Reduction of the C-9 carbonyl functionality. 91

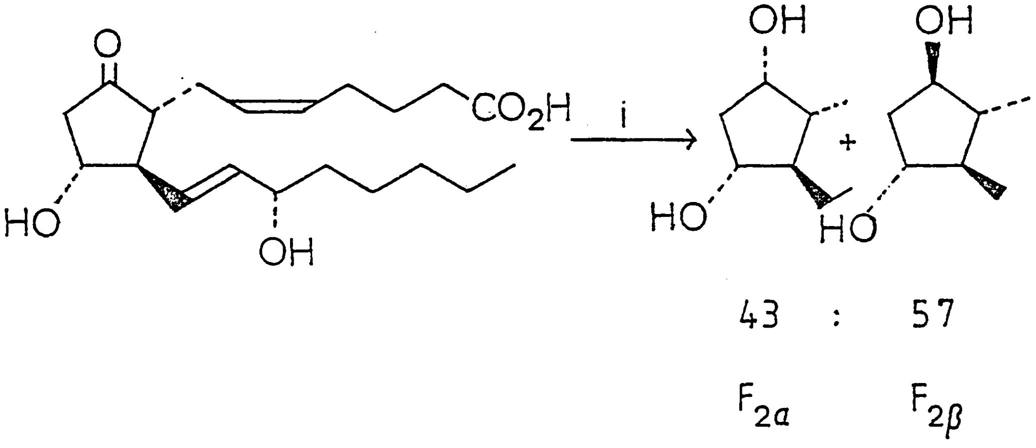
5.2 Inversion of stereochemistry at the C-9 centre. 97

5.3 Deprotection of the C-11 carbonyl functionality. 102

5.4 Desilylation affording PGD_1 methyl ester. 105

5.1 Reduction of the C-9 carbonyl functionality.

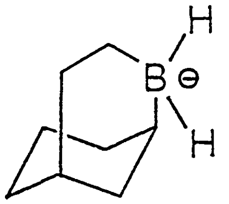
Reduction of the C-9 carbonyl functionality of E-series PG's to the corresponding PGF was one of the initial chemical investigations carried out on prostaglandins (Fig. 5.1.1). It was shown that sodium borohydride reduction proceeded non-stereoselectively affording mixtures of the corresponding 9α and 9β - alcohols, the latter undesired isomer slightly predominating[86,87].



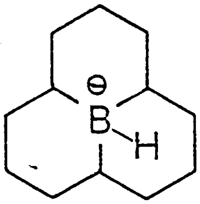
i. $NaBH_4/EtOH/H_2O$.

Fig. 5.1.1 Sodium borohydride reduction of natural PGE_2.

In 1971 Corey demonstrated that this type of reduction could be achieved totally stereoselectively[88,17a] by the use of the bulky trialkylborohydride reagents (77)[89] and (78)[90] derived from limonyl borane and thexyl borane respectively, yields of the 9α -alcohols being virtually quantitative.

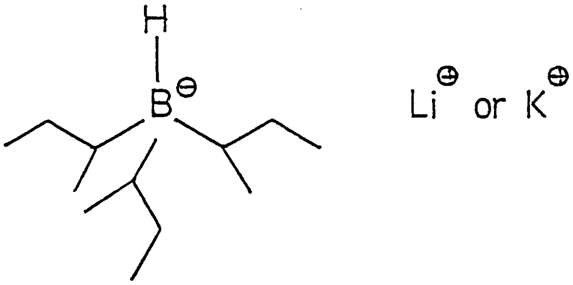


(77)



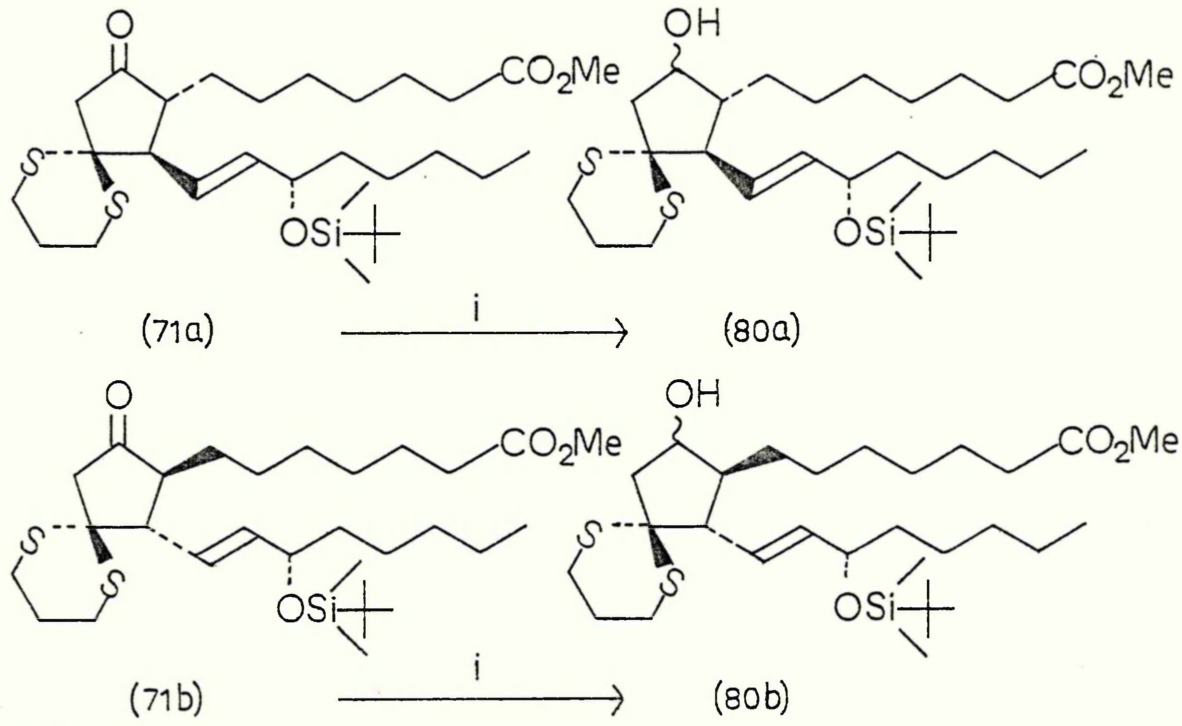
(78)

Other reagents possessing similar stereoselectivity are potassium and lithium[91] tri-^{s}butylborohydrides (K and L- selectrides (79)). Of these two reagents it has been claimed that the potassium salt[92] provides the greater stereoselectivity.



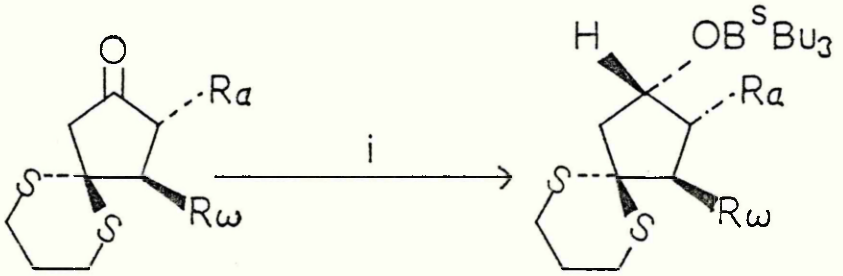
(79)

Reduction of the diastereomeric ketones (71) with K-selectride at -30°C proceeded with total consumption of the starting material within the hour, but not more than a 30% yield of the product alcohols (80) could be isolated on work up.



i.[R].

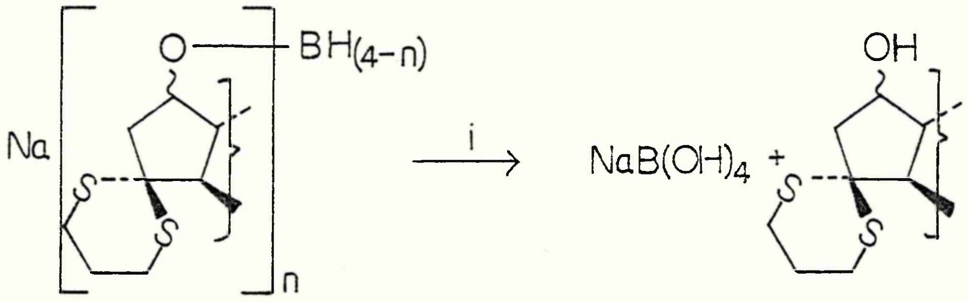
The residue of the reaction mixture was isolated and a by-product separated though it could not be identified. As the ketone precursor had been totally consumed it was assumed that addition of the hydride reagent had taken place and that the problem lay in the work up procedure.



i. KBH^{s}Bu$_3$.

The standard oxidative work up procedure[90] could not be employed for this reduction as oxidation of the sulphur protecting group would also occur. This might lead to uncontrolled deprotection, as the dithiane monosulphoxide is considerably easier to hydrolyse[53].

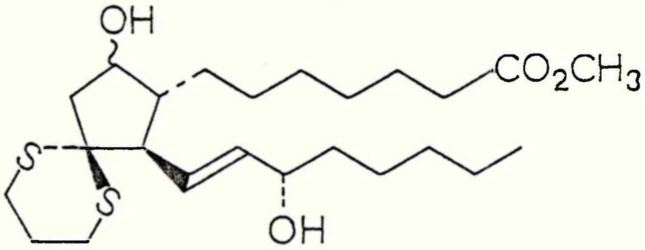
The acidic work up used liberates tri-^{s}butyl boric acid and it is believed that this forms some type of intractable complex with the sulphur atoms in the molecule. Some similar results were being observed in model systems employing diborane and catechol-borane. However, it was demonstrated that sodium borohydride reduction proceeded smoothly. When employed in the reduction of the ketone (71) this reagent provided a near quantitative yield of the product alcohol. None of the proposed complex was observed, most likely because the boron species is completely hydrolysed during the work up (Fig. 5.1.2).



i. $4H_2O$.

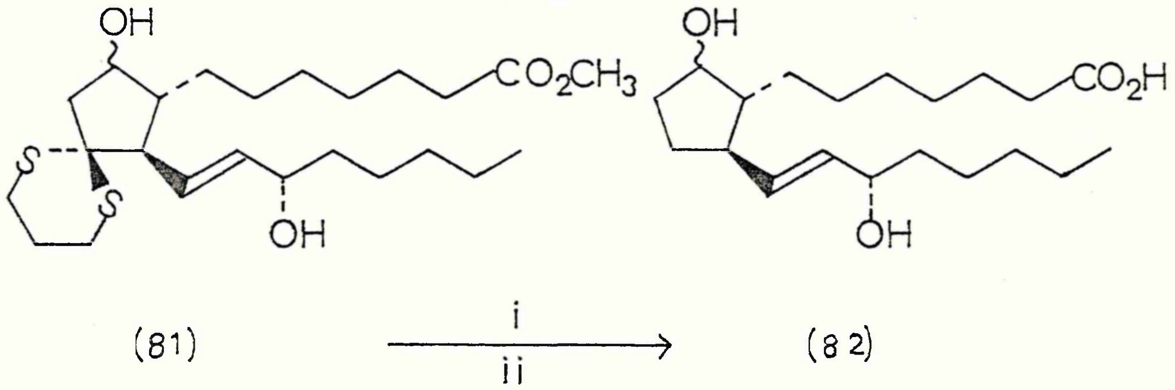
Fig. 5.1.2 Hydrolysis of the borate adduct derived from sodium borohydride reduction.

In an attempt to introduce some stereoselectivity into this reduction the reactions were carried out at -40°C, but the product alcohol was identical with that obtained at room temperature. It was also chromatographically homogeneous and had identical Tlc and hplc data to the K-selectride product. This was an interesting result since, as it was known that the C-9 epimers of $PGF_{1\alpha}$ [87] and its 11-deoxy derivatives[93] could be chromatographically separated, a two component mixture was expected. Therefore, either the C-9 epimers were not separable in this system or only one of them was being produced. We favoured the latter and this was confirmed upon examination of the proton nmr of the alcohols (80). At 220 MHz the resonance due to the C-9 methine proton was observed as a broad singlet occurring at 3.92 ppm. Further studies at 400 MHz failed to resolve this resonance in the diastereomeric mixture. However, when a deuterium exchange experiment was performed on the diol (81) (obtained by desilylation of the alcohols (80)) the corresponding resonance resolved into an eight line signal. The Upjohn group[93] have shown that a methine resonance occurring around 3.9 ppm is indicative of a 9 β - configuration for the hydroxyl substituent. The corresponding 9 α -alcohol methine resonance is quoted as occurring around 4.2 ppm.



(81)

Rapid confirmation of the stereochemistry at C-9 was achieved by treatment of the diol (81) with Raney nickel (W 2)[94]. The resulting product was saponified to give the 11-deoxy PGF_1 derivative (82) (Fig. 5.1.3)



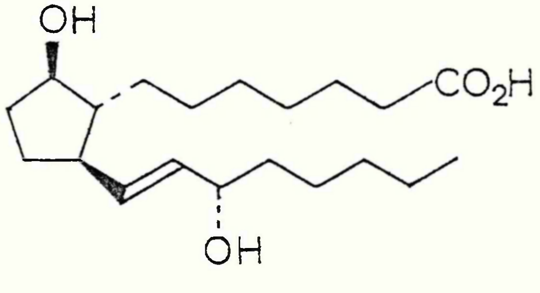
(81) $\xrightarrow[ii]{i}$ (82)

i. RaNi(W 2)

ii. K_2CO_3/MeOH

Fig. 5.1.3 Preparation of 11-deoxy PGF derivative (82)

This acid co-chromatographed with an authentic sample of 11-deoxy PGF_1 (83) (Glaxo group research ref. no. AH19365)



(83)

confirming that sodium borohydride reduction of the ketones (71) had proceeded with total stereoselectivity to yield the undesired 9 β-alcohols. This comparison also confirmed the stereochemistry at C-15 (previously assigned upon a chromatographic precedent from the literature) since 9,15-epi-11-deoxy PGF$_1$ does not co-chromatograph with 9-epi-11-deoxy PGF$_1$[93].

Examination of molecular models of the ketone (71a) supplies little information as to why the α -face of the molecule is significantly less hindered than the β as it must be since none of the 9 β -alcohol is observed. The most likley conformation of the cyclopentanone ring is a puckered one in which the dithiane ring and the two side chains are all quasi-equitorial (Fig. 5.1.4) but

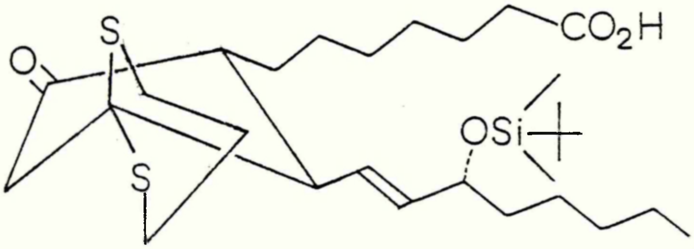
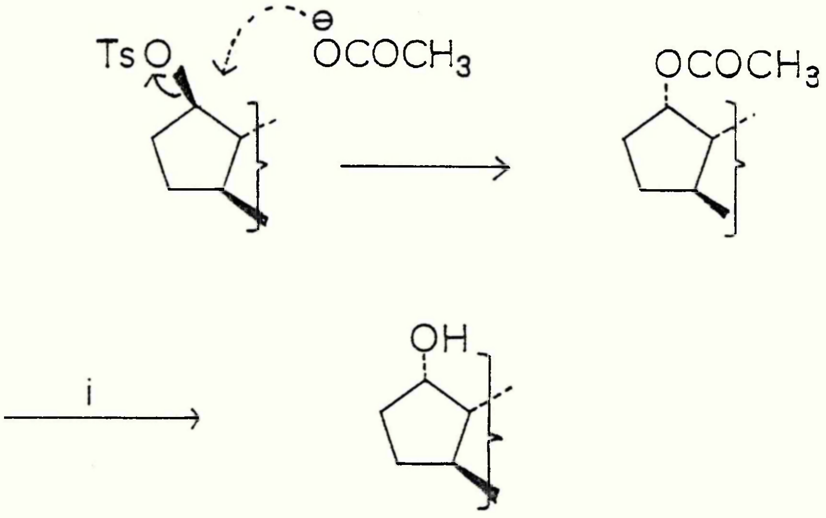


Fig. 5.1.4 A possible conformation of the cyclopentanone (71a).

free access is available to the hydride species from both sides of the molecule. One might invoke a mechanism whereby the hydride species is delivered stereoselectively to the α -face by the sulphur substituents. An X-ray crystallographic study upon the ketone (70a) may shed some light on the situation.

5.2 Inversion of stereochemistry at the C-9 centre.

Stereochemical inversions of this type have been achieved in prostanoid chemistry by conversion of the alcohol functionality to a good leaving group and performing an S_N2 displacement reaction with an oxygen nucleophile. Corey has inverted the stereochemistry of the C-9[95] and C-15[96] hydroxyl groups in this manner by displacement of the tosylates with the superoxide (O_2^-) nucleophile, while formate anion has been used in inversion sequences upon mesylates and tosylates[17c,97] of PGE and F_1 derivatives. Vandewalle[98] has demonstrated C-9 stereochemical inversion by displacement of a tosylate with acetate anion; hydrolysis of the ester affords the inverted alcohol (Fig. 5.2.1).

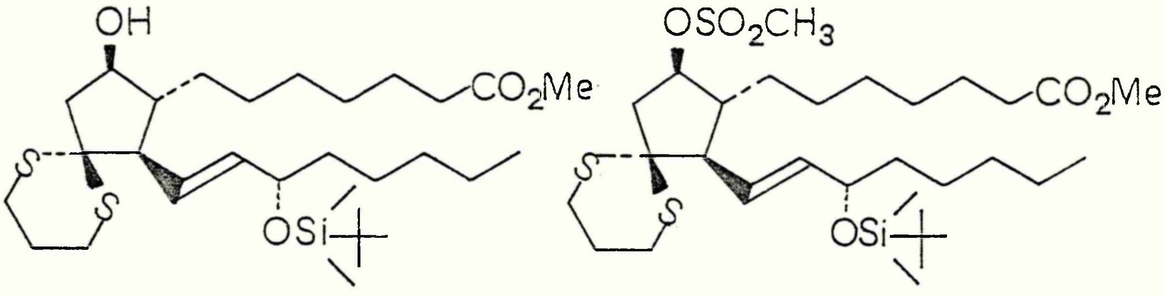


i. H_3O^+

Fig. 5.2.1 Vandewalle's inversion sequence at the C-9 centre.

For our inversion sequence we chose the acetate nucleophile as a source was readily available. The quantitative yield of the 9 β-epimer from the reduction step allowed the crude product to be carried through the inversion sequence reducing the number of separation steps to one.

The tosylate of the alcohols (80) could not be prepared by the standard methods but mesylation proceeded cleanly in near quantitative yield (Fig. 5.2.2).

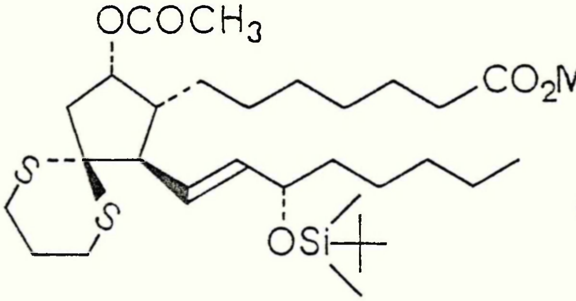


(80a) $\xrightarrow{i}$ (84a)

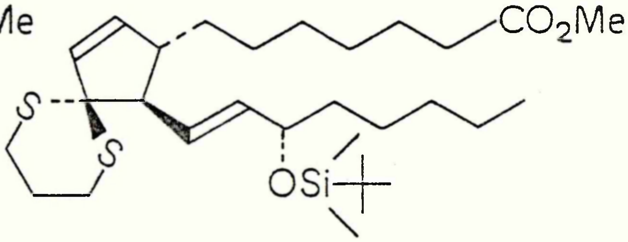
i. methane sulphonyl chloride/pyridine.

Fig. 5.2.2 Mesylation of the 9 β -alcohols (80).

Refluxing the crude mesylates (84) with anhydrous tetra ^{n}butylammonium acetate in dry acetone afforded a mixture comprising 65% the desired diastereomeric 9 α -acetates (85) and 13% of the elimination product (86).

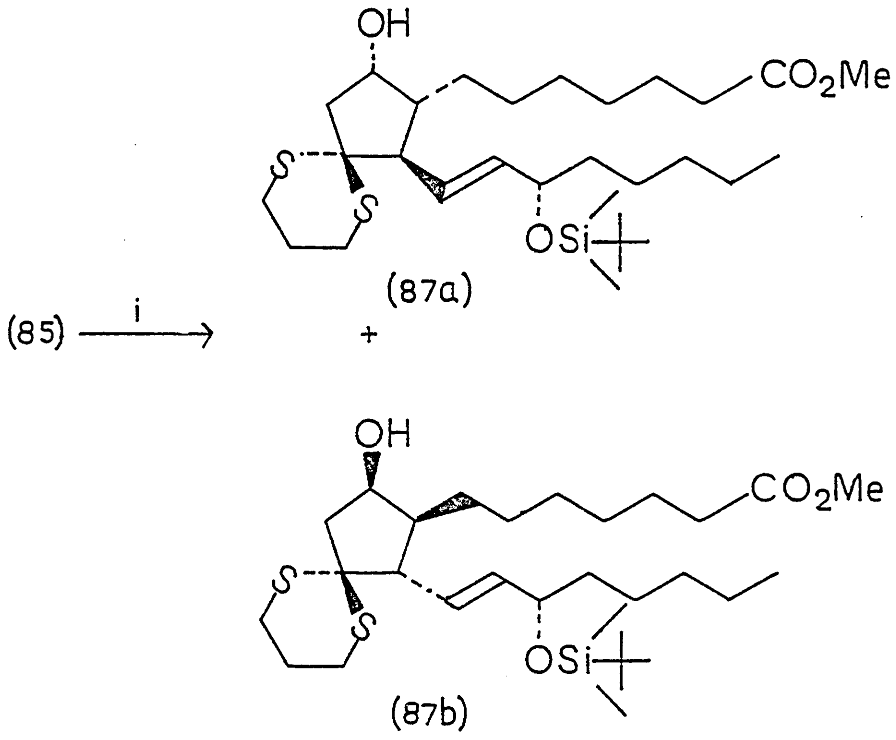


(85a)



(86a)

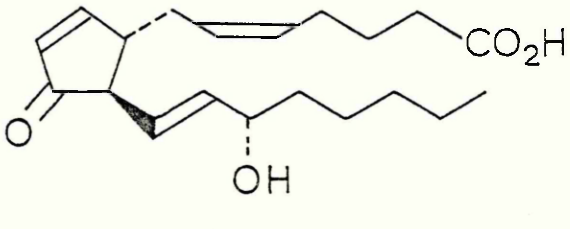
Treatment of the diastereomeric acetates (85) with sodium methoxide in methanol afforded the desired 9 α -alcohols (87) and allowed the terminal methyl ester group to be retained. The total yield for the inversion sequence ranged from 53% to 58% from the 9 β -alcohols (80).



i. NaOCH$_3$/CH$_3$OH.

Examination of the proton nmr spectra of the alcohols (87) revealed that the C-9 methine resonance had undergone a down field shift to ca. 4.18 ppm in accordance with the Upjohn findings. These alcohols (87) were also chromatographically separable from their 9 β -precursors being less polar, in common with most prostanoid systems.

The by-product (86) from the inversion sequence is itself an interesting molecule being the 11-dithiaketal of iso-PGA$_1$ methyl ester. The Glaxo group have recently published a synthesis of the 2 series analogue (88) and have shown that it is a potent inhibitor of gastric secretion[99].



(88)

Treatment of the 9β-mesylates (84) with a non-nucleophilic base such as diazabicycloundecene (DBU) in place of the acetate anion should promote the elimination option and lead to a short

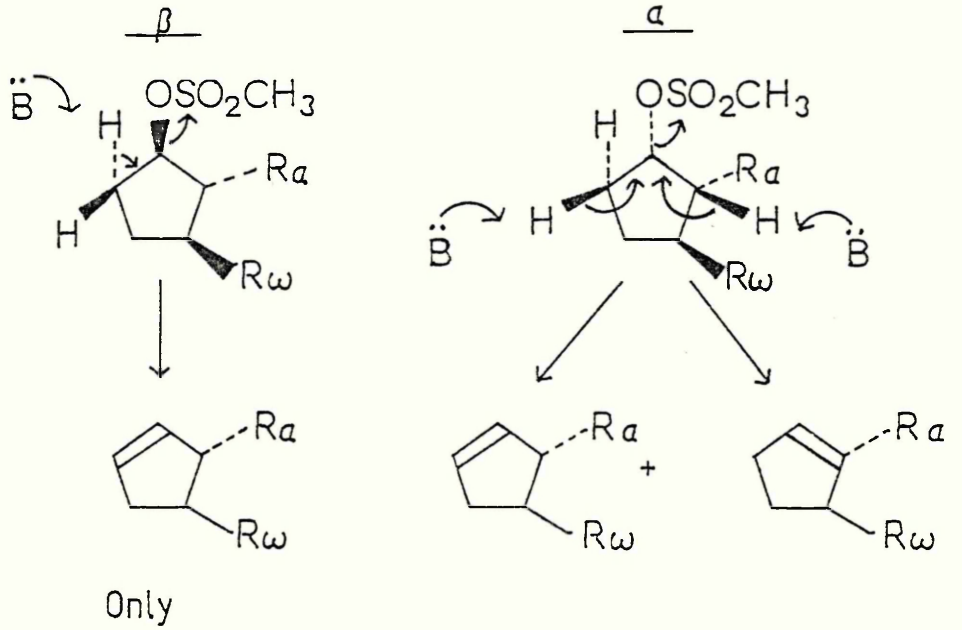


Fig. 5.2.3. Elimination products of 9α and 9β-mesylates.

flexible synthesis of iso PGA_1. The 9 β -epimer is required since it only possesses one proton in a suitable configuration for elimination whereas the 9 α has two (Fig. 5.2.3.)

5.3 Deprotection of the C-11 carbonyl functionality

In deciding upon which order to remove the protecting groups from the alcohols (87) the stability of the final product had to be considered. As it had been shown that the β -ketol system of PGD_2 was stable to conditions required to remove the ^{t}butyldimethylsilyl protecting group[100] it was concluded that hydrolysis of the dithiaketal should be investigated first (Fig. 5.3.1).

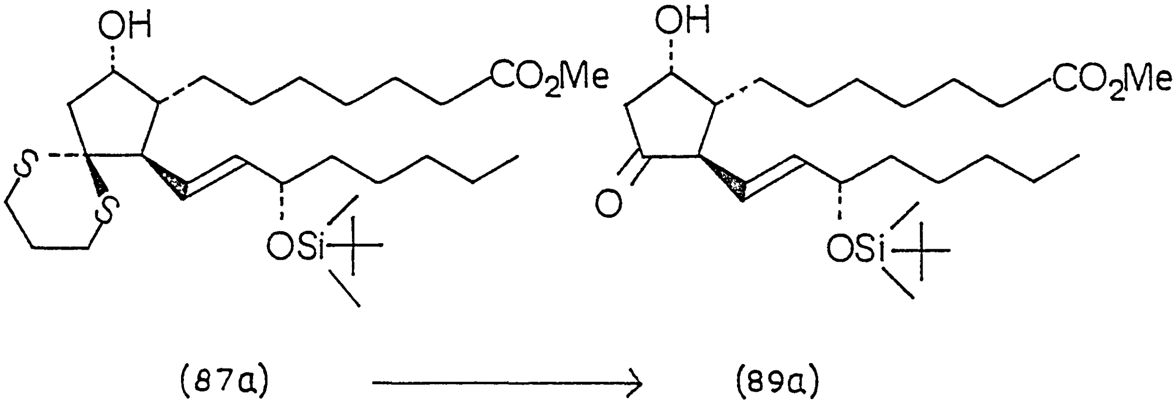


Fig. 5.3.1 Hydrolysis of C-11 -dithiaketal.

Since the introduction of the dithiane protecting group, numerous procedures have been developed for its hydrolysis to a carbonyl functionality, some vigorous, some mild. Several surveys of the uses of this group and deprotection methods have been published[53,54] but Corey[101] has recommended the use of a procedure involving silver catalysed oxidative hydrolysis with N-halosuccinimides to generate a β-ketol system, in particular N-chlorosuccinimide/ silver nitrate. This hydrolysis proceeds with formation of nitric acid which is neutralized by addition of 2,6-lutidine as buffer. The mechanism of hydrolysis is shown below (Fig. 5.3.2).

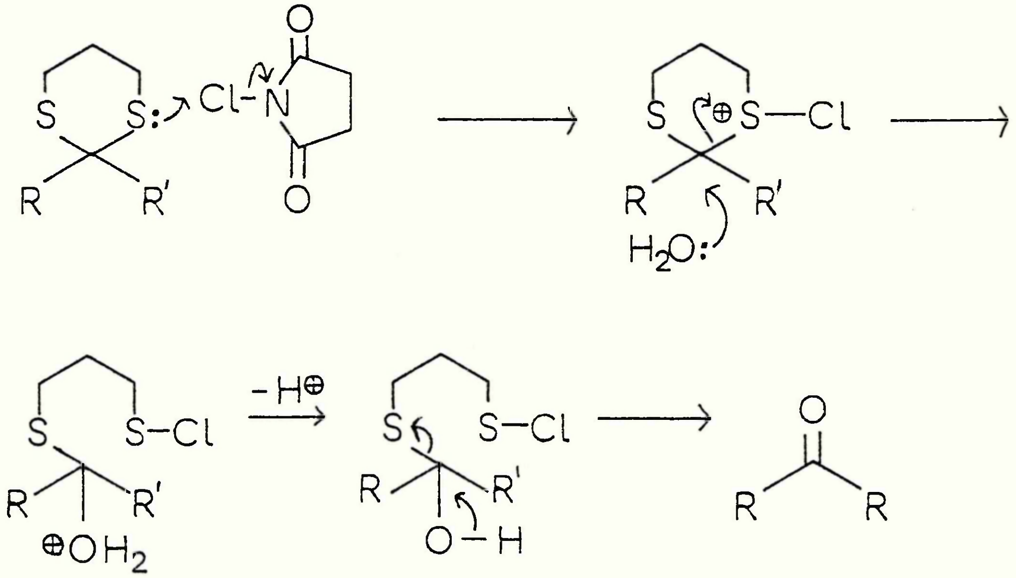
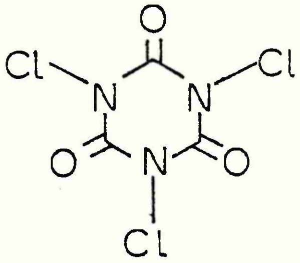
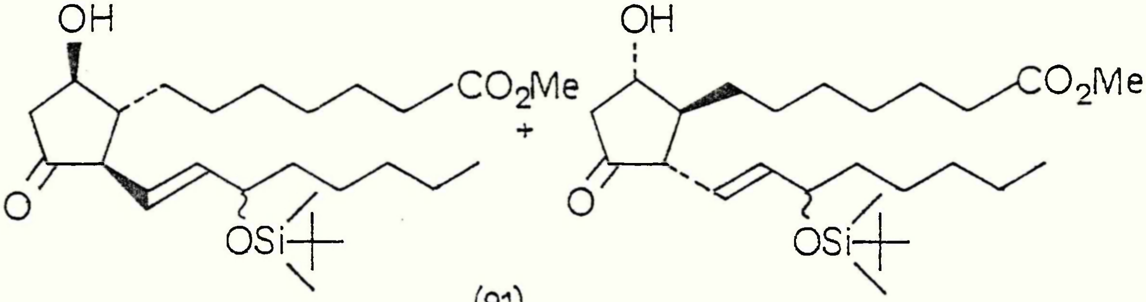


Fig. 5.3.2 Mechanism of oxidative hydrolysis of dithiaketals.

Treatment of the 9β-alcohols (80) with this reagent afforded no discernable product although all the substrate was consumed. Recently Olah[102] suggested trichlorisocyanuric acid (90) as a suitable alternative to N-chlorosuccinimide and it was found that very brief treatment (<1min) of the alcohols (80) with this reagent afforded a 52% yield of the β-ketols (91).



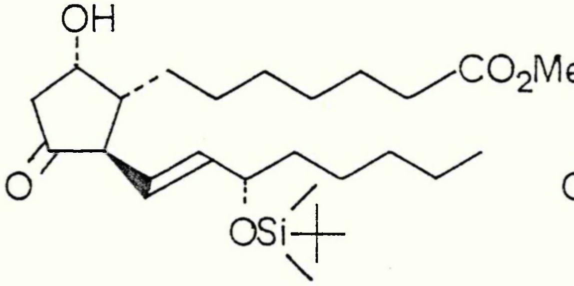
(90)



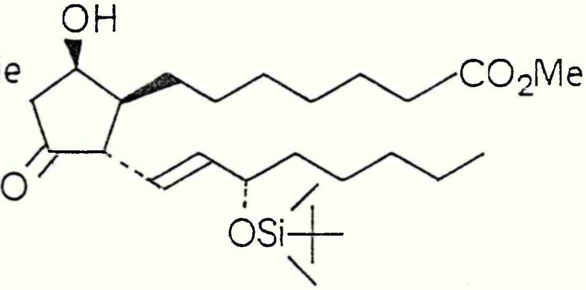
(91)

A similar conversion could not be reproduced for the 9α - alcohols (87) with this reagent for as yet unknown reasons. Further consideration of the deprotection methods available led us to investigate the boron trifluoride/mercuric oxide system of Vedejs[103]. It was thought that as the acidic species liberated during deprotection was hydrofluoric acid (HF) side reactions would be reduced, since it was known that the β -ketol system is stable in the presence of this acid[100]. At the same time the HF concentration should not rise to such a level as to induce unwanted desilylation at C-15. In practice small amounts of the desilylation products were observed but a 60% yield of the diastereomeric β-ketols (89) was obtained.

In both the 9 α and 9 β - products the diasteromers were not chromatographically separable; however C-9 epimeric mixtures were, the 9 β being of lower polarity than the 9 α in common with most prostanoid systems.



(89a)



(89b)

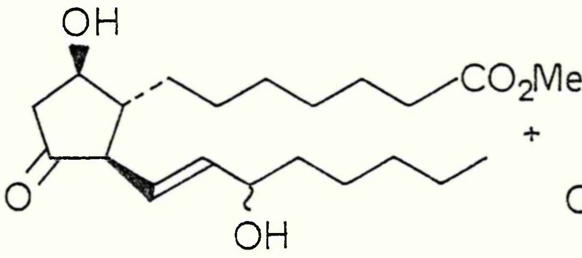
One attractive deprotection with a similar philosophy behind it was the use of an N-chloro succinimide reagent in conjunction with silver fluoride as silver ion source. The acidic species generated would then be HF and not nitric acid as with silver nitrate. Addition of HF to this reaction mixture would then achieve deprotection at C-15 to yield the desired PG. This strategy failed in practice probably because the reagent (AgF) that was available to us was in an advanced state of decomposition.

5.4 Desilylation affording PGD_1 methyl ester.

The final deprotection step was trivial in nature since it had been demonstrated that intermediates in the synthetic sequence such as the alcohols (80) and the ketones (70) could be desilylated by the use of the reagent developed by the Glaxo group[100].

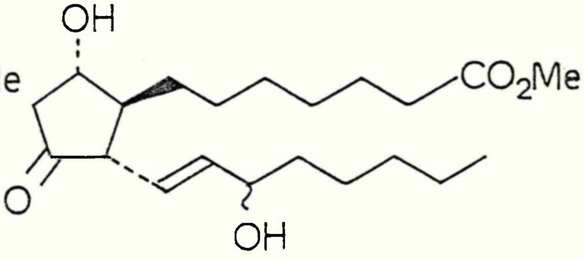
Treatment of the 9 β -ketols (91) with 5% hydrofluoric acid/

acetonitrile/THF afforded a 2.6:1 mixture of the diastereomers (92) in moderate yield, these being chromatographically separable.



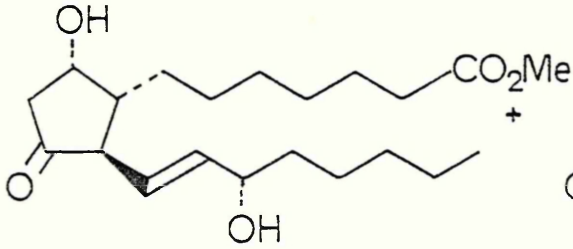
+

(92a)



(92b)

Desilylation of the 9α ketols (89) afforded a 68% yield of PGD$_1$ methyl ester (37) and its diastereomer ent-15-epi PGD$_1$, methyl ester (93) in the ratio 3.5:1.



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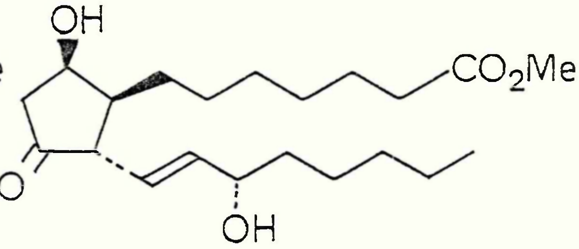
(37)



(93)

Mass spectral data for PGD$_1$ methyl ester has been published by Sih[39]. The fragmentation pattern observed for our compound is consistent with the literature data with the exception of a strong peak at m/e 250 which was totally absent in our spectrum. Accurate masses were determined for 3 characteristic fragments as well as the molecular ion and all were within experimental error of the calculated values.

The proton magnetic resonance spectrum of PGD_1 methyl ester (Fig. 5.4.1) was recorded but the sample did not benefit from the experience (acidic impurities in the nmr solvent initiated decomposition). The spectrum obtained bears a strong similarity to the data published for PGD_2 methyl ester by Jenny[42]. The chemical shift values for the lower side chain and ring protons being almost identical (Table 5.4.1) (Fig. 5.4.2). The only direct comparison spectrum obtainable (Upjohn) was not of sufficiently high field to be of use.

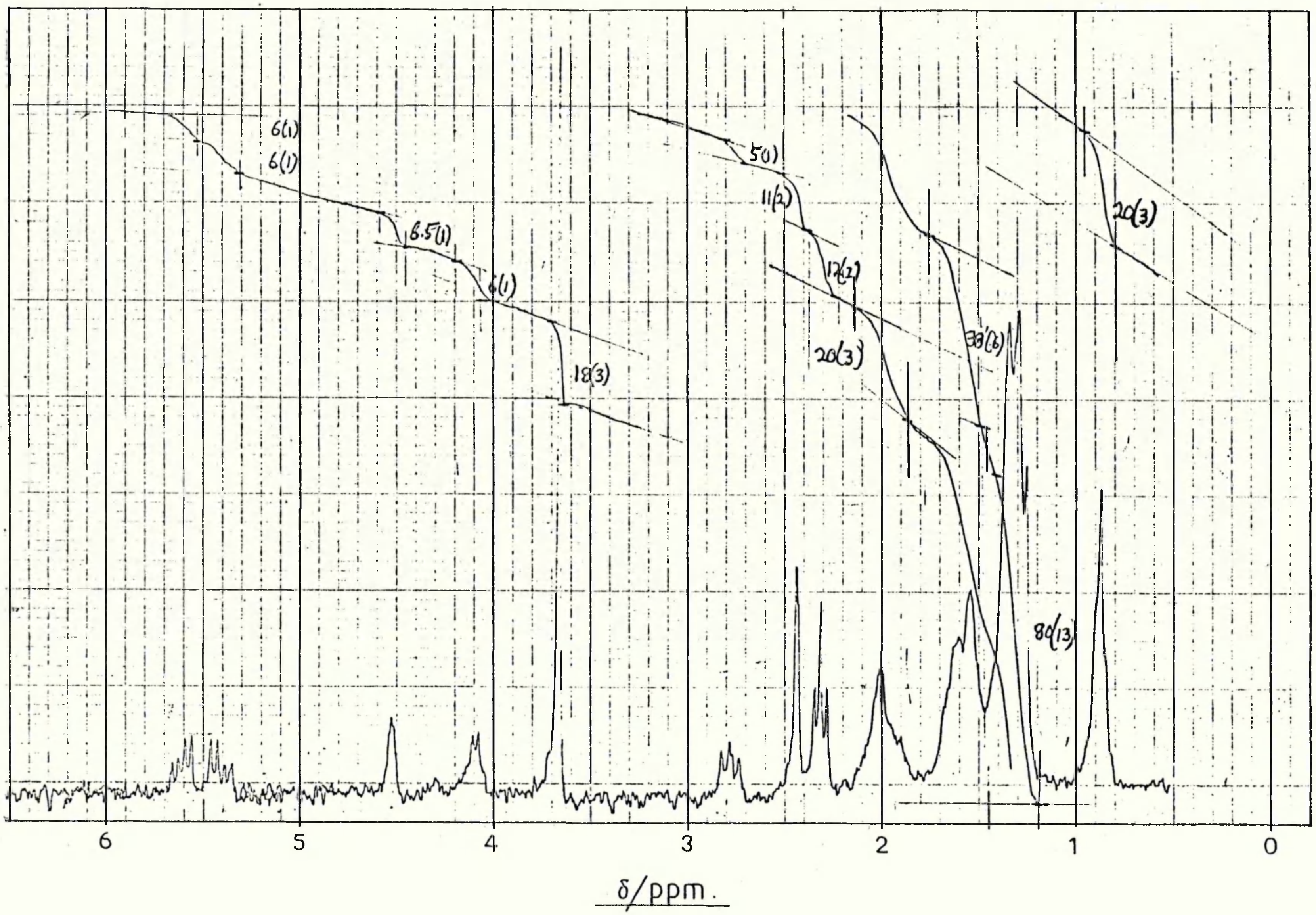


Fig. 5.4.1. 220 MHz proton magnetic resonance spectrum of PGD_1 Methylester.

Shift, δ /ppm	Integral and type.	Coupling constant.	Assignment.	Ref. values[42]
0.88	3 t	-	a	-
2.01	3 m	-	bcd	-
2.31	2 t	7	e	-
2.44	2 d	2.8	f,g	2.45, 4
2.78	1 dd	hm 7.8	h	2.87, 7.8
		hb 12.2		12
3.68	3 s	-	j	3.68 -
4.09	1 q	6.7	k	4.09, 7
4.55	1 q	2.8	l	4.47, 4
5.41	1 dd	mn 16.7	m	5.43, 16
		mh 6.7	-	8.7
5.61	1 dd	nm 16.7	n	5.63, 16
		nk 6.7	-	7
1.2 1.75	18 m	-	rest	

Table 5.4.1 Proton assignments in nmr spectrum of PGD_1 methyl ester at 220 MHz.

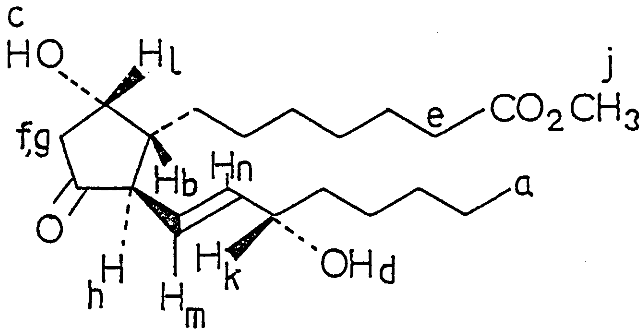


Fig. 5.4.2. Proton assignments from table 5.4.1.

CHAPTER 6

Ancillary Studies and Some Suggestion for Future Work.

6.1 Introduction. 112

6.2 A total synthesis of the rethrolone (±) dihydrojasmololone. 112

6.3 Towards a synthesis of dihydrojasmone and "2" series prostanoids. 117

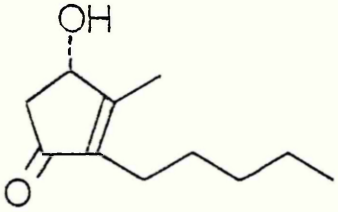
6.4 Investigations into a synthesis of 11-deoxy-9,10-diketoprostanoids. 124

6.1 Introduction

During the development of the prostaglandin synthesis several interesting model intermediates have been prepared. In order to obtain a clearer picture of the synthetic utility of these intermediates ancillary projects have been undertaken and while some are, as yet, uncompleted the reactions do give an indication as to the versatility of the synthesis. These reactions also form the basis of some suggestions for further studies.

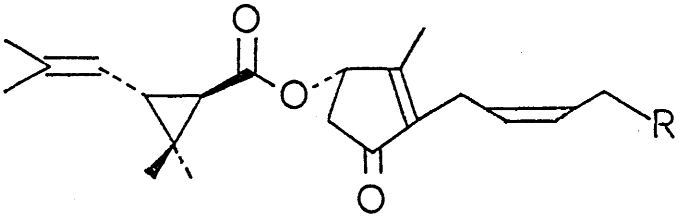
6.2.1 A total synthesis of the rethrolone (∓) dihydrojasmololone

Dihydrojasmololone (94) has a structural similarity to PGD_1 although the β-ketol system is to some extent stabilized by the presence of a double bond in the ring. The rethrolones are the cyclopentanoid alcohol fragment of the naturally occurring pyrethroid insecticides[104] possessing the general structure (95).



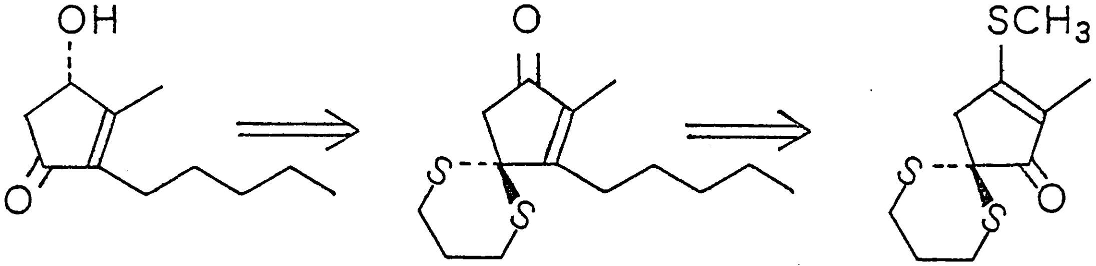
(94)

Several synthetic routes to this group of compounds have been developed[105] including one using a similar strategy to the one employed below[50].



(95)

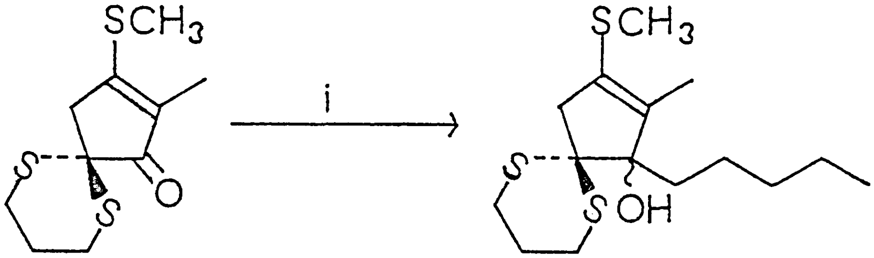
On examining structure (94) we thought that it might be derived from the model intermediate (53a) in a similar manner to the model enone (55a) (Fig. 6.2.1.1.).



(53a)

Fig. 6.2.1.1. Retrosynthetic derivation of rethrolone synthesis

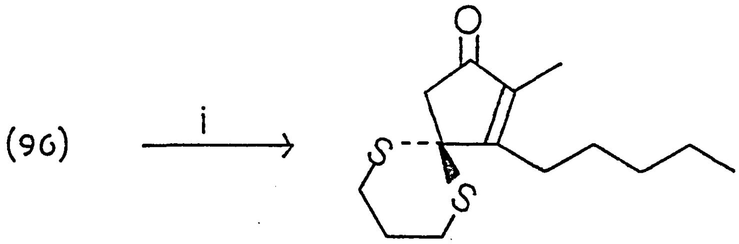
The vinylogous thioester (53a) was found to be unreactive to ^{n}pentyl magnesium bromide but treatment with ^{n}pentyl lithium afforded the intermediate allylic alcohol (96) quantitatively.



(96)

i. $^nC_5H_{11}Li$.

This was rearranged to the enone (97) without isolation in 80% yield (Fig. 6.2.1.2)

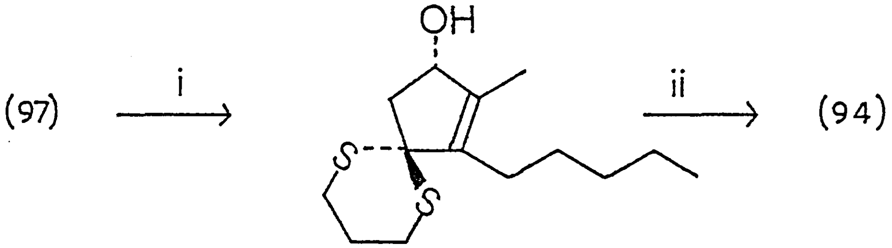


(97)

i. cHCl/MeOH.

Fig. 6.2.1.2 Preparation of the enone intermediate (97).

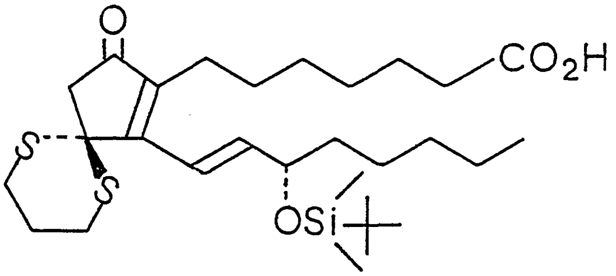
Reduction of the free carbonyl functionality with sodium borohydride proceeded smoothly in high yield and oxidative hydrolysis of the resulting allylic alcohol with N-chlorosuccinimide afforded racemic dihydrojasmololone in moderate yield. The yield in the final deprotection step was not optimized but it is felt a shorter reaction time at lower temperatures would be beneficial.



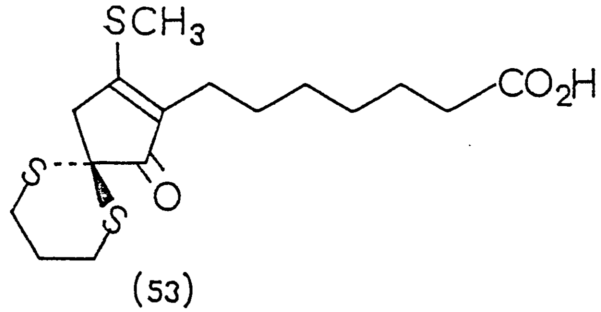
i $NaBH_4$/MeOH/THF.
ii NCS/$AgNO_3$.

6.2.2. 8,12-Didehydraprostaglandins.

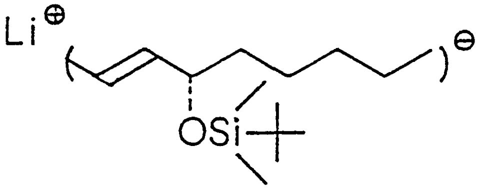
With the success of the above scheme attempts were made to apply a similar approach in the preparation of 8,12-didehydraprostaglandins[106] through the intermediate (98). Treatment of the lithium salt of the acid (53c) with the vinyl lithium reagent (99) and quenching afforded the allylic alcohol (100) which was of very low stability and could not be isolated. All attempts to induce rearrangement to the desired



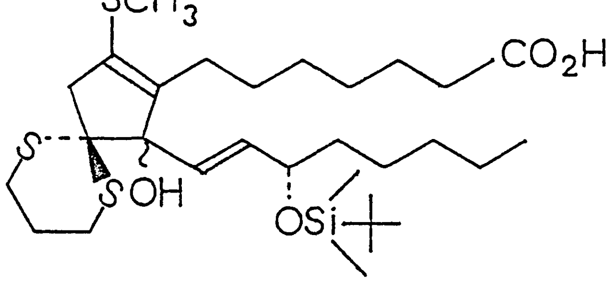
(98)



(53)



(99)



(100)

enone (98) were unsuccessful, multicomponent mixtures being isolated from the acidic systems used.

Generation of a carbocation at this C-12 centre may lead to migration of either double bond into conjugation (Fig. 6.2.2.1) and decomposition of the resulting dienes could then occur via polymerization; the desired dienone (98) may itself be of limited stability.

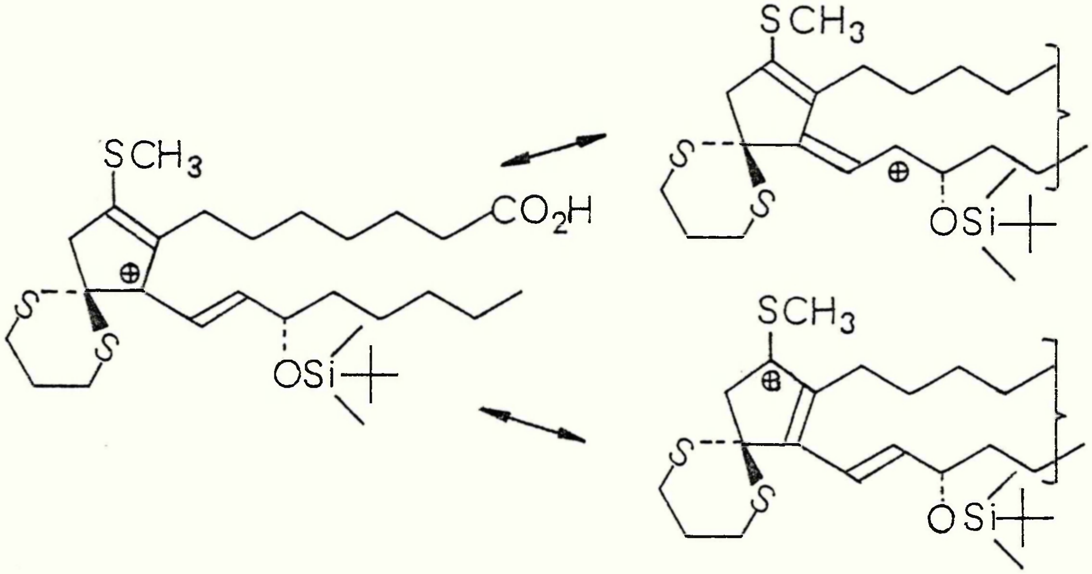
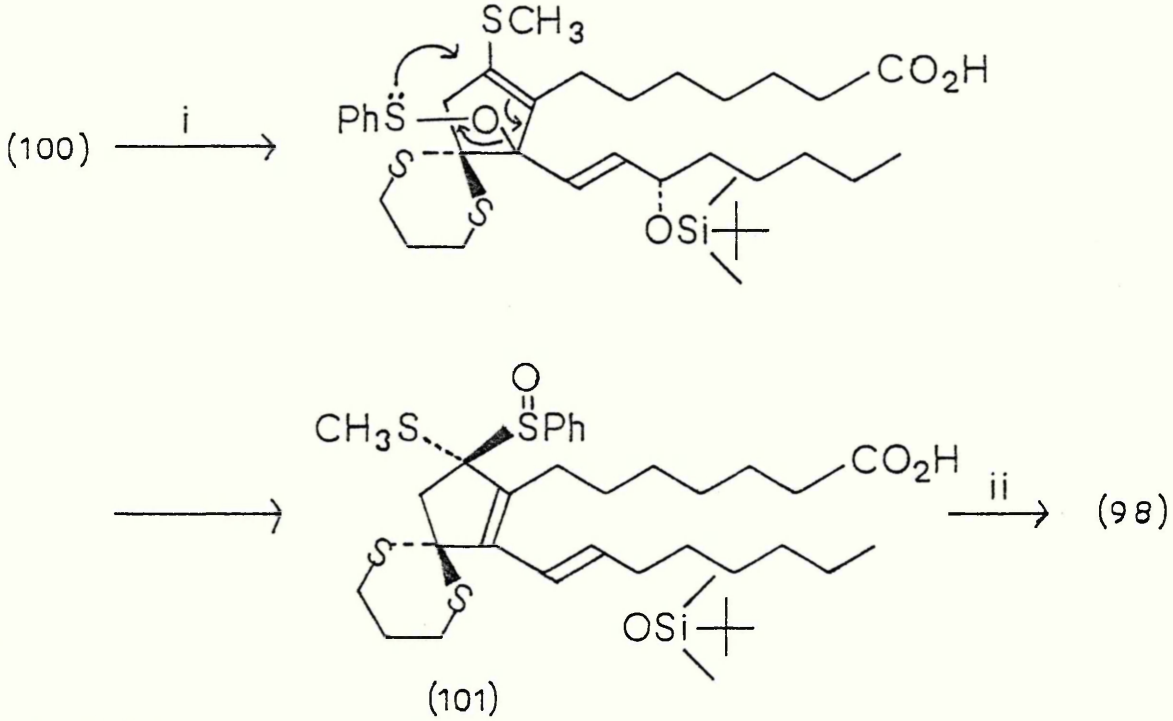


Fig. 6.2.2.1 Alternative rearrangement products of the carbocation derived from the acid (100).

Although investigations have been suspended at this point in time one possible solution to the problem is outlined below (Fig. 6.2.22). Were one to prepare the sulphenate ester of the alcohol (100) this might then undergo a [3.3] sigmatropic rearrangement[107] to give the sulphoxide[84] (101) which would only require very mild hydrolysis conditions to generate the enone (98).



i. PhSCl.
ii. mild $H_3O^{\oplus}$.

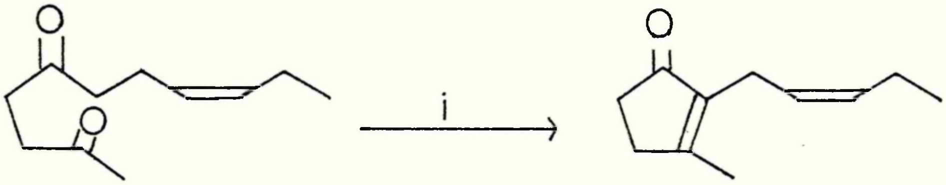
Fig. 6.2.2.2 Possible sulphenate ester rearrangement to afford the enone (98).

The desired sulphenate ester could be prepared by trapping the intermediate vinyl lithium adduct with phenyl sulphenyl chloride but there may be some steric resistance to entry of the electrophile at the crowded 12-position (PG numbering).

6.3 Towards a synthesis of dihydrojasmone and "2" series prostanoids

The jasmones (102) are a series of cyclopentanoid compounds found in bergamot oil. They are of great importance in the perfumery industry and we felt they served as useful models for prostaglandins.

There is no shortage of viable synthetic routes to the jasmones . This is amplified by the reviews of Ho[108] abd Ellison[105] the main approach being the synthesis of the 1,4-diketone precursor (102) which is cyclized by means of an intramolecular aldol condensation (Fig. 6.3.1)

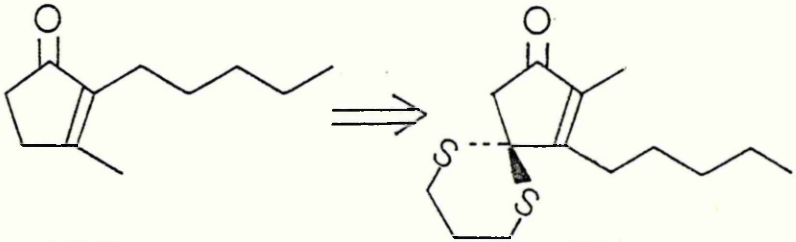


(102) (103)

i. $\ddot{B}$

Fig. 6.3.1 A key step in many jasmone syntheses.

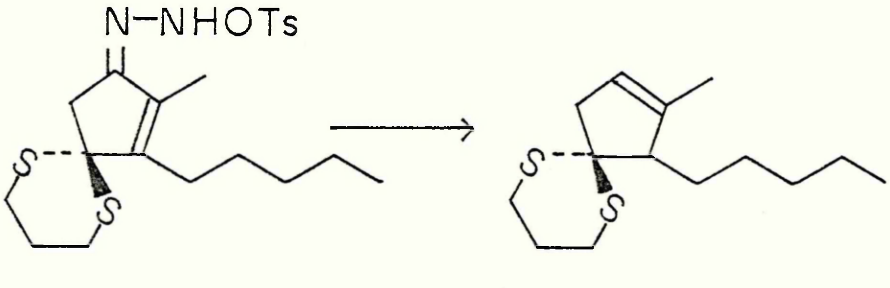
Dihydrojasmone (104) lacks one of the oxygen functionalities of of the rethrolones and although the relative positions of the substituents are transposed we felt that the anone (97) would provide a suitable precursor.



(104) (97)

Two operations are required to achieve the conversion, complete reduction of the free carbonyl group and hydrolysis of the dithiaketal group.

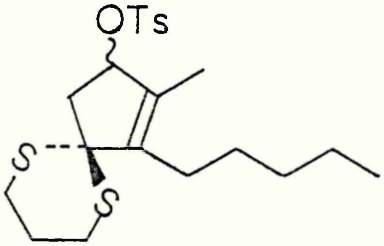
To date the former operation has proved the main stumbling block. Wolf-Kishner reduction of (97) only afforded polar by-products as did Clemmensen's procedure. A more recent method involving reduction of the tosylhydrazone (105) with catecholborane[109] afforded only a form of the boron-sulphur complex and when sodium cyanoborohydride[110] was employed as reducing agent yields were very low (Fig. 6.3.2).



(105)

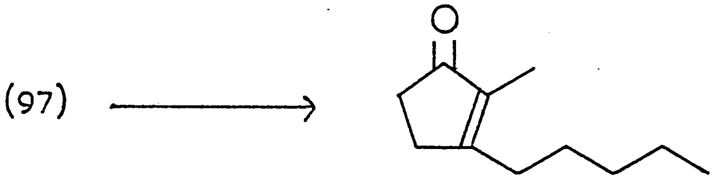
Fig. 6.3.2. Desired reduction of tosylhydrazone (105)

Reduction of the allylic tosylate (106) with various hydride reducing agents have not sc far proved successful although this option has not been fully investigated. It has been shown, however, that the



(106)

enone (97) may be desulphurized with Raney nickel in a similar manner to the 11-deoxy prostanoid preparations previously outlined,(Fig. 6.3.3) some over reduction of the product iso-dihydrojasmone (107) also occurs.

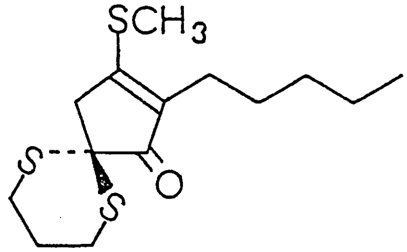


(107)

i. RaNi W2/Et_2O

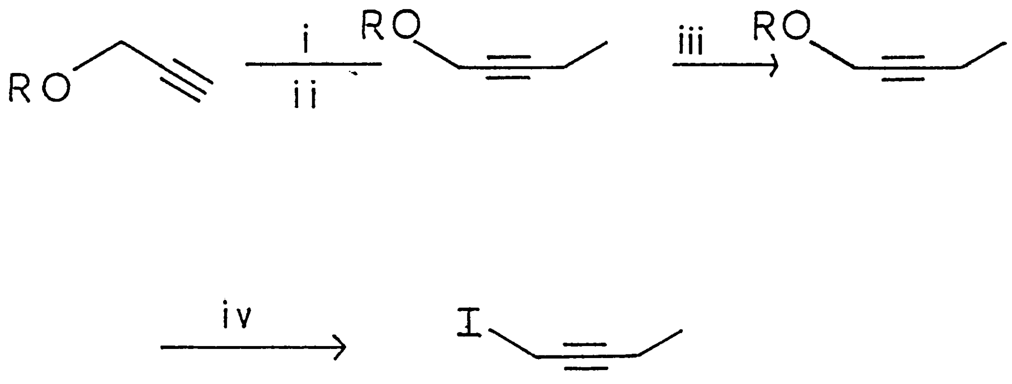
Fig. 6.3.3 Desulphurization of the enone (97)

In the present situation the most expedient route to dihydrojasmone involves a square one synthesis of the ^{n}pentyl substituted ketone (108). Treatment with methyl lithium, rearrangement and desulphurization should afford the target molecule. We would however, prefer to obtain both jasmones and rethrolones from a common intermediate namely the ketone (53a).



(108)

A synthesis of the intermediate (109) for the preparation of the unsaturated Jasmone side chain is in the development stage following the scheme outlined (Fig. 6.3.4).



(109)

i. ^{n}Buli.
ii. EtI.
iii. $H_3O^{\ominus}$.
iv. Ph_3PI_2.

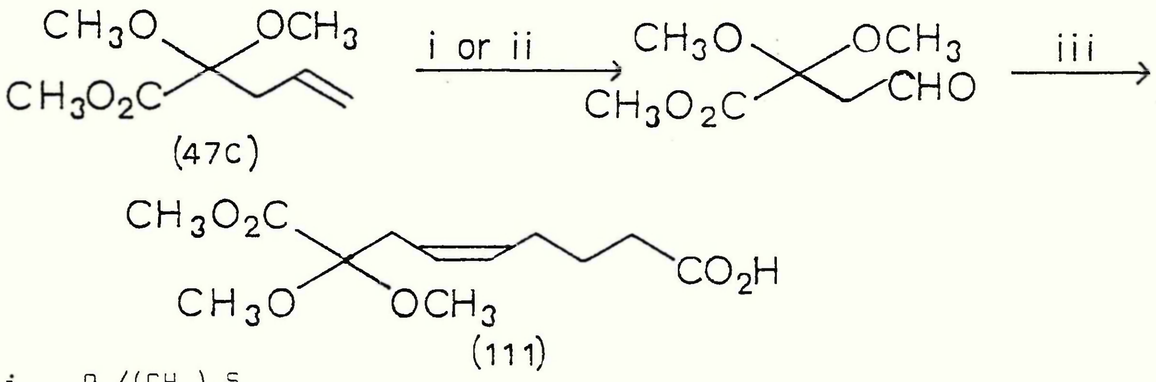
Fig. 6.3.4 A synthetic route to the intermediate (109).

Alkylation of the protected propargyl alcohol with ethyl iodide proceeded in 54% distilled yield and hydrolysis afforded the alcohol which only iodinated in low yield for as yet unknown reasons.

One of the principle reasons for investigating this route was to use it as a model for the preparation of the "2" series prostanoid intermediate (110). The ester has been prepared before and Roussel

(110)

hold a patent on a similar synthetic route[111]. We are also developing an alternative strategy to the "2" series prostanoids employing the ester (43c) which is readily available (Fig. 6.3.5).



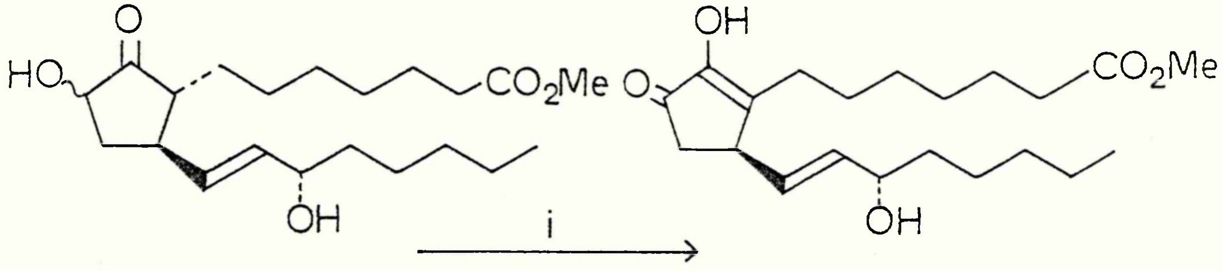
i. $O_3/(CH_3)_2S$
ii. $OsO_4/NaIO_4$
iii. $Ph_3\overset{\oplus}{P}—\bar{C}H(CH_2)_3CO_2^-$

Fig. 6.3.5 Alternative strategy avoiding the intermediate (110)

The Wittig reagent used is common in prostanoid chemistry. However, at present, the aldehyde can only be prepared in very low yield. The desired acid (111) would then be carried through the main synthetic sequence to afford "2" series compounds.

6.4.1 Investigations into a synthesis of 11-deoxy -9,10-diketoprostanoids

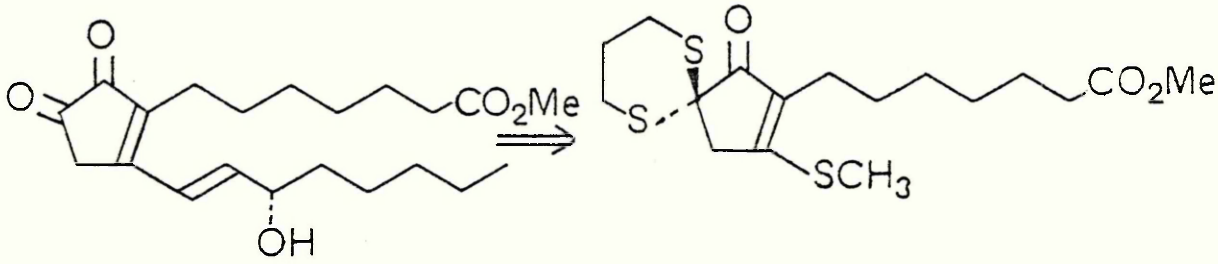
These prostanoid analogues are a chellenging synthetic target by nature of the α -diketone functionality required on the cyclopentanone nucleus. Caton[112] has recently shown that these derivatives may be prepared by base catalysed auto-oxidation of the 10-hydroxy-9-oxo compounds the product existing as the 8,9-enol tautomer (Fig. 6.4.1.1).



i. O_2/NaOH/MeOH.

Fig. 6.4.1.1 Caton's preparation of 9,10-diketoprostaglandins.

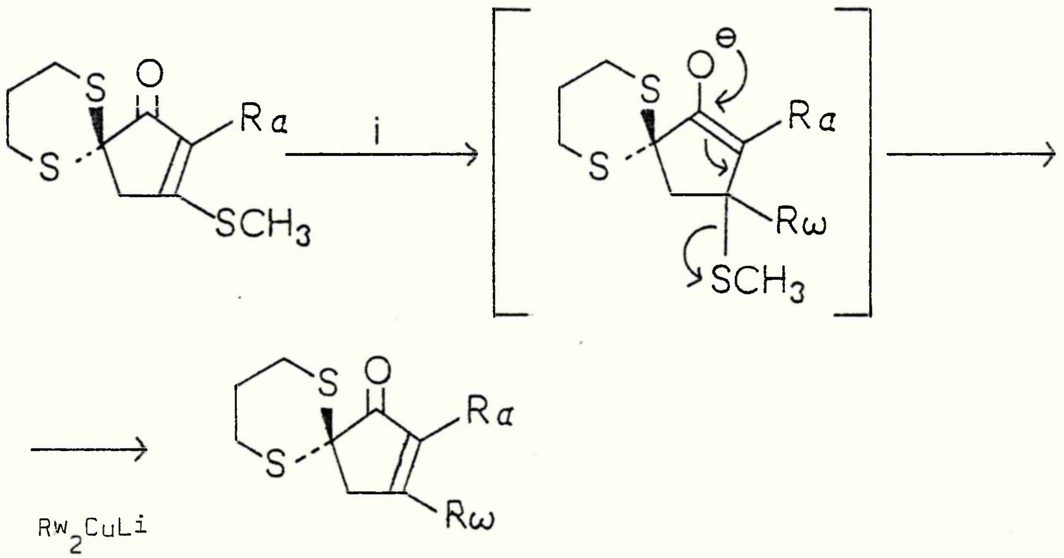
The ester (53e) bears all the requisite functionalities to generate the above system for a PGB analogue (112) the two operations required being the replacement of the methylthio ether with the lower prostanoid side chain and hydrolysis of the dithiaketal (Fig. 6.4.1.2).



(112) (53e)

Fig. 6.4.1.2 Synthetic approach to 9,10-diketo PGB derivatives

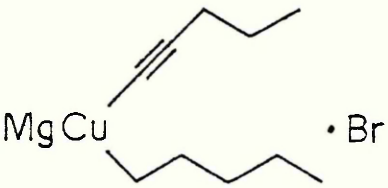
One possibility that immediately came to mind was to perform a conjugate addition reaction upon the enone system present in the ester (53e). It was reasoned that the intermediate enolate would collapse spontaneously with the expulsion of the thiomethoxide anion to generate the new enone system (Fig. 6.4.1.3.).



i. $\mathrm{Rw_2CuLi}$

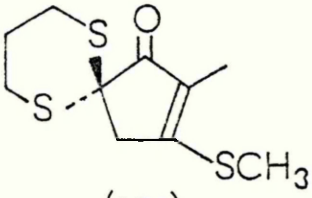
Fig. 6.4.1.3 Required mode of conjugate addition to the ester (53e)

Investigations were initially carried out on the model system (53a). Low yields were obtained when a magnesio-hetrocuprate developed by Posner[113] was employed but the cuprate reagent (113) afforded the desired enone (114) in 48% isolated yield (Fig. 6.4.1.4).

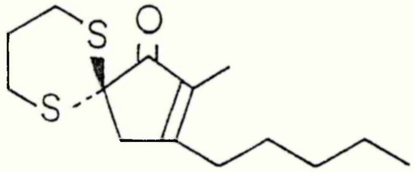


$\mathrm{Li\ Cu(C_5H_{11})_2(PBu_3)_2}$

(113)



(53a)



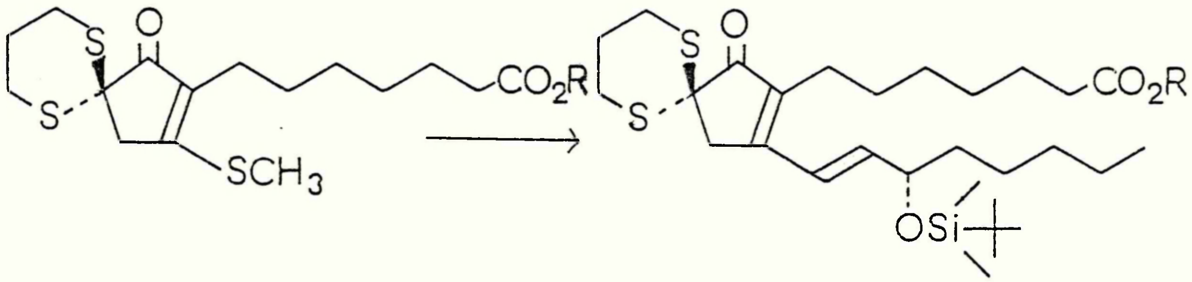
(114)

i. $\mathrm{(113)/Et_2O/CH_2Cl_2}$.

Fig. 6.4.1.4 Preparation of model cuprate adduct (114)

It was noted that the orange coloured intermediate enolate collapsed within 10 minutes at -78°C.

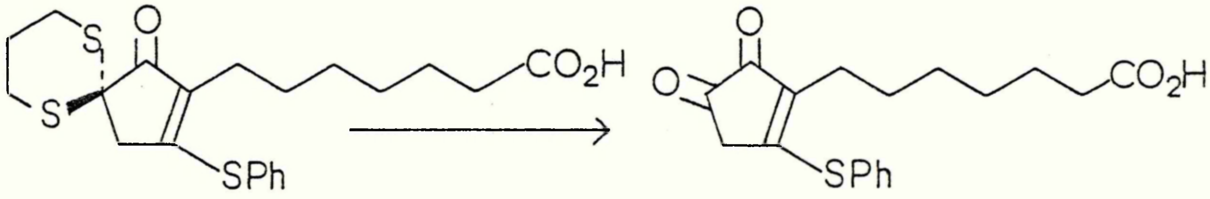
Attempts to achieve a similar reaction using the prostanoid cuprate (62) upon the ester (53e) have met with little success but from the experience gained in the mainstream project it is hoped to reinvestigate this approach (Fig. 6.4.1.5).



i (62)/Et_2O

<u>Fig. 6.4.1.5</u> <u>So far unsuccessful conjugate addition reaction</u>.

One encouraging observation is that hydrolysis of the dithiaketal system of the enone (53d) has been achieved using N-bromosuccinimide (NBS). In common with other systems encountered the α -dione (115) is a characteristic lemon yellow colour.

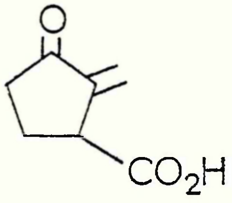


(53d)

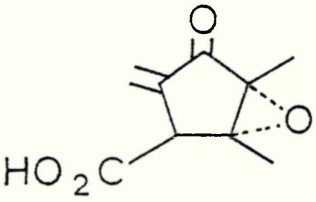
(115)

6.4.2 Preliminary investigations and propositions for synthesis of some cyclopentanoid antibiotics

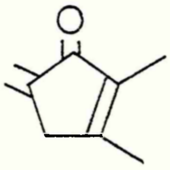
Recently some simple cyclopentanoid derivatives have been demonstrated to possess anti-bacterial activity, Sarkomycin (116) and methylenomycin A (117) and B (118) being two examples. A few total syntheses of these compounds are now available[114].



(116)

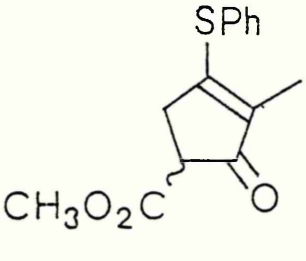


(117)



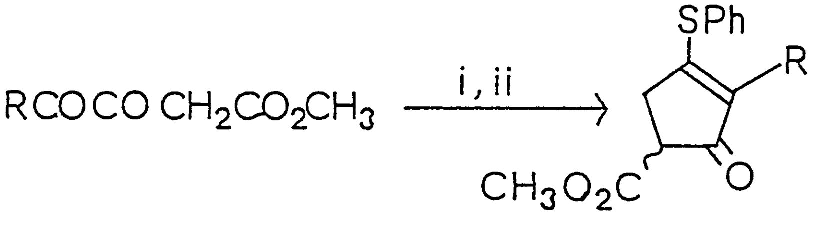
(118)

A more recent synthesis of methylenomycin A has employed the use of the cyclopentenone (119) as a key intermediate which bears structural similarities to several of the compounds available to us[115].



(119)

The intermediate (119) might also be prepared by a cyclization reaction involving one of our vinyl phosphonium salts (38) with the anion of a 3,4-diketoester (120) (Fig. 6.4.2.1).

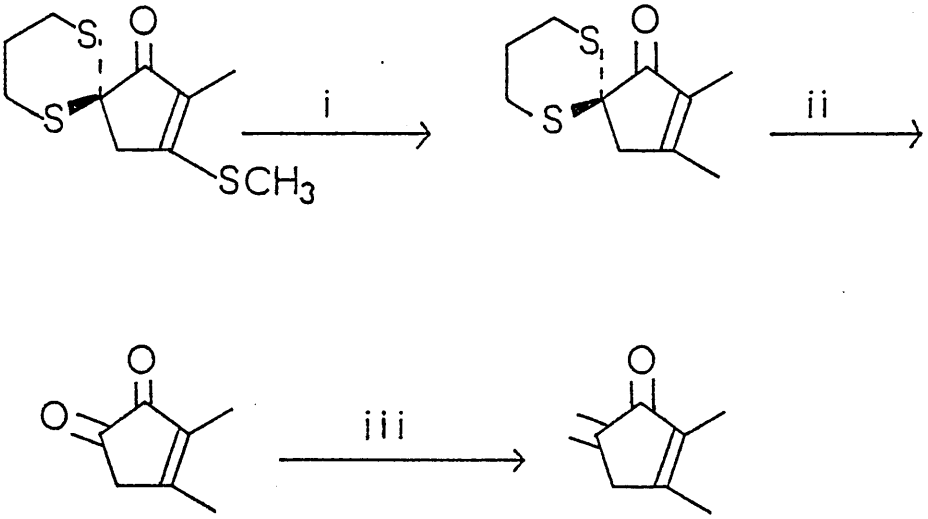


(120)

i. NaH.
ii. (38a).

Fig. 6.4.2.1

With the intermediates immediately to hand the most attractive synthetic target is the antibiotic methylenomycin B (118) which we would



i. Me_2CuLi.
ii. $NB_3(AC)NO_3$.
iii. $Ph_3P^+CH_2^-$.

Fig. 6.4.2.2 Proposed synthetic route to Methylenomycin B.

envisage preparing in a three step sequence from the cyclopentenone (53a) (Fig. 6.4.2.2) to afford the enone (103).

We have already established a precedent for the cuprate addition step and demonstrated a deprotection to afford an α-dione. It is hoped that the Wittig reagent will show a preference for the non-conjugated carbonyl functionality.

7.1 General notes

Proton magnetic resonance (Pmr) data were obtained upon one or more of the following instruments: Joel - C60 (60 MH_3); Hatachi-Perkin elmer R-600 FT (60 MHz); Varian EM390 (90 MHz); Perkin-Elmer R34 (220 MHz) and Bruker Spectrospin WM250 (250MHz) and WM400 (400 MHz) spectrometers.

Carbon-13 magnetic resonance (Cmr) data were obtained upon a Jeol CFT 160A spectrometer (24.3 MHz).

Chemical shifts are quoted in parts per million (ppm). Tetramethylsilane was added as internal standard, its resonance being assigned a value of zero ppm on the delta (δ) scale. Abbreviations: doublet (d), double doublet (dd), multiplet (m), singlet (s) and triplet (t).

Infrared spectral (Ir) data were obtained upon a Pye-Unicam SP200 grating infrared spectrometer samples being in the form of thin liquid films (smear), potassium bromide dispersions (KBr), or bromoform solutions ($CHCBr_3$). Frequencies (ν) were measured in reciprical wavenumbers (cm^{-1}).

Mass spectral (ms) data were obtained upon AEI MS9 or MS 30 instruments. Samples were introduced by direct insertion probe and ionized by electron impact at 24 or 70 electron volts (eV).

Microanalyses were performed by the analytical department of Glaxo Group Research (Ware) Ltd., Ware, Herts.

Gas-liquid chromatograms (Glc) were obtained upon a Pye-Unicam model GCV fitted with a flame ionization detector. Retention times (Tr') are uncorrected and quoted in minutes (mins).

Thin layer chromatograms (Tlc) were obtained using Merck '5734' plastic backed chromatography plates with incorporated fluorescent indicator. Compounds were visualised by quenching of fluorescence upon irradiation with ultra-violet light (254nm); Iodine vapour adsorption and the use of one or more of the following spray reagents : molybdophosphoric acid (MDA), iodoplatinic acid (IPA), basic potassium permanganate ($KMnO_4$) and 2,4-dinitrophenylhydrazine (DNP).

Short column chromatography was performed using either Merck '7736' (15 - 50μm) or '7734 (70 - 230 mesh) silica gel. Solvents for chromatography were distilled prior to use.

Melting points are uncorrected.

Dry etrahydrafuran (THF) was obtained by distillation from potassium.

Dry diethyl ether was obtained by distillation from lithium aluminium hydride.

'Petrol' refers to that fraction of petroleum spirit boiling between 40 and 60°C.

Diisopropylamine was dried over and distilled from calcium hydride. This reagent was stored under nitrogen, over 3Å molecular sieves.

Cuprous iodide was purified by exaustive extraction with dry THF.

^{n}Butyl lithium was used as a solution in hexane stored under argon and standardized prior to use against diphenylacetic acid.

Glyoxylic acid hydrate was obtained commercially (Aldrich).

7-Bromoheptanoic acid and racemic E-1-Iodo-3-(^{t}butyldimethylsilyloxy)oct-1-ene were supplied by Glaxo. E(3S)-1-iodooct-1-en-3-ol was prepared by the method of Fried[32] from Hexanoyl chloride[116]. The product possessed a specific rotation (α^{20}_{D}) of +8.28° and an optical purity of 92%.

7.2 Experimental Methods.

Methyl 2,2-dimethoxyacetate (46a).

To a solution of glyoxylic acid hydrate (50g, 0.544 mol) in trimethyl orthoformate (543g, 2.72 mol) contained in a spinning band round bottomed distillation flask (1000ml) was added toluene-p-sulphonic acid (10g). The flask was sealed with a drying tube and left to stand for three hours. Anhydrous potassium carbonate (2.8g) was added and the flask attached to a spinning band column. Distillation under a continually increasing vacuum afforded a colourless liquid b_{20} 64 - 7°C, 57.4g (78.6%). Lit.[58] b_{18} 60 - 61°C.

Glc. 10% polyethylene glycol adipate (PEGA) on chromasorb, N_2 40 ml/min, 150°C 1 μl neat. Tr' 4.13 (1%), 5.72 (99%).

Ir. (smear) ν : 2860 (OCH_3), 1760 (CO ester).

Pmr. ($CDCl_3$), δ : 3.54 (s, 6H) (OCH_3 ketal), 3.93 (s, 3H) (OCH_3 ester), 4.97 (s 1H) (CH).

Ethyl 2,2-diethoxyacetate (46b).

As (46a) a colourless liquid b_2 58-63°C (80%). Lit.[58] b_{15} 83-5°C.

Glc. As methyl derivative. Tr' 6.38 (100%).

Ir. (smear) ν : 2800 (OEt), 1760 (CO ester).

Pmr. ($CDCl_3$), δ : 1.25, 1.31 (2 x t, 9H)(CH_3), 3.68 (q,4H) (ketal CH_2), 4.25 (q,2H)(ester CH_2), 4.88 (s, 1H)(CH).

Ethyl 2,2-diethoxypropanoate

A solution of diisopropylamine (12.04g, 120 mmol) in THF (600 ml) under nitrogen was cooled to -78°C (CO_2 acetone) and a solution of ^{n}butyl lithium (75 ml, 120 mmol) added dropwise with stirring over ten minutes. Following ten minutes stirring a solution of ethyl diethoxyacetate (46b) (17.6g, 100 mmol) in THF (20 ml) was added over fifteen minutes whereupon a solution of methyl iodide (28.4 g, 200 mmol) in THF (20 ml) was added over five minutes. The reaction mixture was allowed to warm up over one hour and the solvent removed. The residue was partitioned between water (100 ml) and ether (100 ml), the aqueous layer run off and extracted with a further portion of ether (50 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$) and the solvent evaporated. The residue was distilled under vacuo to afford a colourless oil $b_{0.5}$ 48-52°C (14.66 g 77%)
Lit.[61] b_1 60 - 62°C.

Glc. as (47b). Tr' 5.3 (100%).

Ir. (smear), ν : 1750 (CO ester).

Pmr. ($CDCl_3$), δ: 1.25 (2xt, 9H) ($C\underline{H}_3CH_2$), 1.35 (s, 3H) (CH_3), 3.55 (q, 4H) (ketal CH_2), 4.15 (q, 2H) (ester CH_2).

Methyl 2,2-dimethoxybutanoate.

As (47b), quenched with iodomethane. A pale yellow oil (71.4%).

Glc. As (46b) Tr'. 0.95 (3.8%) 4.5 (87%), 12.1 (9.2%).

Ir. (smear), ν : 1750 (CO ester).

Pmr. ($CDCl_3$), δ : 0.71 (t, 3H) ($C\underline{H}_3CH_2-$), 1.93 (q, 2H) ($CH_3C\underline{H}_2$), 3.28 (s, 6H) (OCH_3 ketal), 3.84 (s, 3H) (OCH_3 ester).

Methyl 2,2-dimethoxypent-4-enoate.

As (47b), quenched with allyl bromide. A colourless oil $b_{0.1}$ 47 - 52°C (57%). Lit.[61] b_{13} 102°C.

Ir. (smear), ν : 1750 (CO ester), 1660 (C = C).

Pmr. ($CDCl_3$), δ : 2.55 (d, J=7Hz, 2H) (CH_2), 3.26 (s, 6H) (OCH_3 ketal), 3.7 (s, 3H) (OCH_3 ester), 5.05 (2xm, 2H) ($C\underline{H}_2$ = CH), 5.66 (m, 1H) (CH_2 = $C\underline{H}$).

Methyl-2,2-dimethoxypropanoate (47a).

As (47b), quenched with ethyl iodide. A colourless oil (70.6%). Also prepared from ethyl pyruvate in a similar manner to (46a).

$b_{0.6}$ 60-4°C 57%.

Glc. As (46a) Tr' 3.55 min.

Ir. (smear), ν : 1750 (CO ester).

Pmr. ($CDCl_3$), δ : 1.48 (s, 3H) (CH_3), 3.28 (s, 6H) (ketal OCH_3), 3.79 (s, 3H) (ester OCH_3).

8,8-Dimethyoxy-8-carbomethoxyoctanoic acid (47c)

To a dry, 3-necked flask (1000 ml) equipped with magnetic stirrer, N_2 balloon and pressure equalizing dropping funnel was added dry THF (500 ml) and diisopropylamine (15.9 g, 0.1125 mol). After cooling to -78°C ^{n}butyl lithium (73.5 ml of 1.53M) was added dropwise over ten minutes with stirring. Following a further twenty minutes stirring a solution of methyl-2,2-dimethoxyacetate (47a) (9.225 ml, 75 mmol) in dry THF (20 ml) was added dropwise with stirring over 20 minutes. The resulting solution was stirred at -78°C for thirty minutes whereupon 7-iodoheptanoic acid (9.3g, 36.6 mmol) in THF (20 ml) was added dropwise with stirring over fifteen minutes. The flask was then stoppered and shaken at -30°C for sixteen hours (overnight).

The reaction mixture was quenched with water (300 ml) and transferred to a separating funnel where the aqueous layer was run off. The organic layer was extracted with water (2 x 100 ml) and discarded. The combined aqueous extracts were washed with ether (3 x 100 ml) and carefully acidified to pH5 (dilute hydrochloric acid) as indicated by a pH meter. After extraction with ether (3 x 100 ml) the aqueous layers were re-acidified (pH5) and re-extracted with ether (100 ml). The combined organic layers were washed with water (2 x 100 ml) and brine (100 ml). Drying ($MgSO_4$) and removal of the solvent yielded a pale yellow oil (9.96g, 81%).

Tlc. Rf 0.35 (DNP) (40% ethyl acetate : 59% petrol : 1% acetic acid.).

Ir. (smear), ν : 3500 - 2500 (OH acid), 1740 (CO ester), 1705 (CO acid).

Pmr. ($CDCl_3$), δ : 1-2 (m, 10H) (alkyl $C\underline{H}_2$'s), 2.36 (t, 2H) ($C\underline{H}_2CO_2H$), 3.27 (s, 6H) ($-OC\underline{H}_3$ ketal), 3.8 (s, 3H) ($OC\underline{H}_3$ ester), 10.58 (broad s, 1H) ($CO_2\underline{H}$).

Ms. M/e 231.1235 ($M-OCH_3$, $C_{11}H_{19}O_5$ requires 231.1238), 217.1414 ($M-CO_2H$, $C_{11}H_{21}O_4$ requires 217.1440), 203 ($M-CO_2Me$), 133 $(CH_3O)_2CO_2Me$).

Microanalysis. $C_{12}H_{22}O_6$ requires C 54.9%, H 8.4%. Found C54.1%, H 8.17%. (Best Obtained)

8,8-Diethoxy-8-carboethoxyoctanoic acid.

As (47c). A viscous yellow oil 59.6% after chromatography.

Tlc. Rf 0.41 (DNP) (40% ethyl acetate : 59% petrol : 1% acetic acid.)

Ir. (smear), ν : 3500 - 2500 (OH acid), 1745 (CO ester), 1710 (CO acid).

Pmr. ($CDCl_3$), δ : 1-21 (m, 10H), 2.4 (t, J=7.2Hz 2H) ($C\underline{H}_2CO_2H$), 3.54 (q, J=7.2Hz 4H) ($OC\underline{H}_2CH_3$ ketal), 4.3 (q, 2H) ($OC\underline{H}_2CH_3$ ester), 9.8 (br s, 1H) ($CO_2\underline{H}$).

1-(1,3-Dithian-2-yl)-2,2-dimethoxypropan-1-one (48a).

To a dry, 3 necked flask (3000 ml) equipped with magnetic stirrer, nitrogen balloon and pressure equalizing dropping funnel (250ml) with septum inlet was added: THF (1210 ml), 1,3-dithiane (14.95 g, 0.125 mol) and diisopropylamine (17.44 ml, 0.125 mol). This mixture was cooled to $-78^{\circ}C$ and ^{n}butyl lithium solution (242 ml, 0.249 mol) added dropwise with stirring over twenty minutes. Following a further twenty minutes stirring at $-78^{\circ}C$ a solution of methyl 2,2-dimethoxypropanoate (47a) (18.53g, 0.125 mol) in dry THF (150 ml) was added dropwise with stirring over thirty minutes. The resulting solution was stirred for a further twenty minutes, quenched with water, and transferred to a separating funnel (2000 ml). The aqueous layer run off and extracted with ether (2 x 100 ml). The combined organic layers were washed with brine (200 ml), dried ($MgSO_4$) and the solvent removed to yield a brown oil which crystallized. Recrystallization (light petroleum) yielded a white crystalline solid (26.8g, 91%) Mpt. 46-8$^{\circ}C$.

Tlc. Rf 0.5 (DNP, MPA , UV) (20% ethyl acetate : 80% petrol).

Ir. (melt), ν : 2850 (OCH_3), 1715 (CO ketone).

Pmr. ($CDCl_3$), δ : 1.55 (s, 3H) (alkyl CH_3), 2-2.5 (m, 4H) (dithiane "4" and "6" CH_2's), 2.5-2.8 (m, 2H) (dithiane "5" CH_2), 3.325 (s, 6H) (ketal OCH_3), 4.875 (s, 1H) (dithiane "2" CH).

Ms. m/e, 225 (M^+-OCH_3), 119 (dithiane$^+$), 89 ($CH_3C^+(OCH_3)_2$).

Microanalysis. $C_9H_{16}O_3S_2$ requires C, 45.8%; H, 6.8%.

Found: C, 45.68%; H, 6.72%.

8,8-Dimethoxy-9-oxo-(1,3-dithan-2-yl)nonanoic acid (48b).

To a dry, 3-necked flask (100 ml) equipped with magnetic stirrer, N_2 balloon and pressure equalizing dropping funnel was added dry THF (50 ml), 1,3-dithiane (0.48 g, 4 mmol) and diisopropylamine (1.13 ml, 8 mmol). The mixture was cooled to -78°C and ^{n}butyl lithium solution (7.48 ml of 1.53 M) added over five minutes with stirring. Following a further period of stirring (thirty minutes at -78°C) a solution of the half acid (47c) (0.83 g, 3.2 mmol) in THF (10 ml) was added dropwise over ten minutes with stirring. The flask was stoppered and shaken at -30°C for five hours.

The resulting solution was quenched with water (50 ml) and partitioned with ether (50 ml). The aqueous layer was separated off and the organic layer extracted with water (2 x 10 ml). The combined aqueous layers were washed with ether (50 ml), acidified to pH 5 (as indicated by a pH meter) and quickly extracted with ether (2 x 50 ml). The aqueous layer was re-acidified to pH 5, re-extracted with ether

(25 ml) and the combined organic layers washed with water (25 ml). Drying ($MgSO_4$) and removal of the solvent yielded a pale yellow oil (1.23 g) which was chromatographed on silica gel (50 g of 7736) (eluted with 20% ethyl acetate : 79% petrol 1% acetic acid). This yielded a colourless oil (48b) (0.56g, 55%).

Tlc. Rf. 0.32 (DNP, MPA, UV) (40% ethyl acetate : 59% petrol : 1% acetic acid).

Ir. (smear), ν : 3650 - 2300 (OH acid), 1740 (CO acid), 1710 (CO ketone).

Pmr. ($CDCl_3$), δ : 1-2 (m, 10H), (alkyl CH_2's + dithiane "5" $C\underline{H}_2$), 2-3.6 (m, 6H) (dithiane "4 and 6" equitorial $C\underline{H}$'s, $C\underline{H}_2CO_2H$, $C(OCH_3)_2C\underline{H}_2$), 3.22 (s, 6H) ($OC\underline{H}_3$), 3.3-3.6 (m, 2H) (dithiane "4 and 6" axial CH's), 4.68 (s, 1H) (dithiane "2" $C\underline{H}$), 10.0 (s, 1H) ($CH_2CO_2\underline{H}$).

Microanalysis. $C_{15}H_{26}O_5S_2$ requires C, 51.4%; H, 7.48%.
Found : C, 50.27%, H, 7.5%. (best obtained)

8,9-Dioxo-9-(1,3-dithiane-2-yl)nonanoic acid (39d).

The acid (48b) (5.85 g, 16.7 mmol) was dissolved in 5% aqueous trifluoroacetic acid (25ml) and stirred at room temperature for ten minutes. The mixture was diluted with ether (175 ml) poured into water (100 ml) and the aqueous layer separated. The bright yellow organic phase was washed with water (5 x 50 ml) and 1% sodium bicarbonate solution (2 x 5 ml). The organic phase was dried ($MgSO_4$), diluted with petrol (50 ml) and the solvent volume reduced to ca. 40 ml. The resulting bright yellow solid was filtered off, washed with small portions of petrol and air dried to afford 3.28 g (74%) of the dione (39d) M.pt 96 - 98°C.

Tlc. Rf. 0.32 (DNP, MPA, UV) (40% ethyl acetate : 59% petrol : 1% acetic acid).

Ir. ($CHCBr_3$), ν : 1740 (CO acid), 1710 (CO dione).

Pmr. ($CDCl_3$), δ : 1.2 - 2.2 (m, 10H), 2.33 (t, 2H) ($COC\underline{H}_2$), 2.5 (d of t, 2H) (dithiane "4" and "6" equatorial), 2.82 (t, 2H) ($C\underline{H}_2CO_2H$), 9.79 (s, 1H) ($-CO_2\underline{H}$).

Microanalysis $C_{13}H_{20}O_4S_2$ requires C, 51.28%, H, 6.62%.

Found C, 51.2%, H, 6.81%.

1-(1,3-Dithian-2-yl)propan-1,2-dione (39a)

As (39d) from (48a). A bright yellow crystalline solid (98.2%) M.pt. 43-45°C, $b_{0.05}$ 90 - 95°C. Lit.[47] $b_{0.2}$ 102-4°C.

Tlc. Rf 0.5 (DNP, MPA, UV) (20% ethyl acetate : 80% petrol).

Ir. (smear), ν : 1710 (CO ketone).

Pmr. ($CDCl_3$), δ : 1.75 - 2.8 (m, 4H) (dithane "4 and 6" axial and "5" $C\underline{H}_2$'s), 2.48 (s, 3H) ($C\underline{H}_3$), 2.95 - 3.55 (m, 6H) (dithiane "4 and 6" equatorial $C\underline{H}_2$'s), 5.1 (s, 1H) (dithiane "2" $C\underline{H}$).

Microanalysis . $C_7H_{10}O_2S_2$ requires C, 44.18%, H, 5.3%.

Found : C, 44.14%, H, 5.13%.

Methylthiomethyltriphenylphosphonium Chloride

A solution of triphenylphosphine (262 g, 1 mol) and methylthiochloromethane (96.6 g, 1 mol) in acetonitrile (1L) was refluxed for five hours at which time it was allowed to cool to room temperature slowly and the resulting white crystalline solid filtered off and washed with ether. The liquors were reduced in volume by 50% and a second crop obtained upon cooling to 0°C. Total yield 293 g (86.7 %).

Ir. (KBr), ν : 3050, 2850, 2750.

Pmr. ($CDCl_3$), δ:2.15(s, 3H) ($SC\underline{H}_3$), 5.3 (d, 2H) ($C\underline{H}_2$), 7.8 (m, 15H) ($\underline{Ph}_3P$).

Phenylthiomethyltriphenylphosphonium iodide.

As the methylthio derivative from iodomethyl phenyl sulphide[117]. A yellow amorphous solid (91%).

Pmr. ($CDCl_3$), δ : 5.38 (d, 2H) ($C\underline{H}_2$), 7.4 (m, 5H) ($SP\underline{h}$), 7.85 (m, 15H) ($\underline{Ph}_3P$).

1-Methylthiovinyltriphenylphosphonium chloride (38a).

To a solution of the methylthiomethyltriphenylphosphonium chloride (50 g, 0.14 mol) in dry acetonitrile (250 ml) was rapidly added N,N-dimethyliminium chloride[118] (28.1g, 0.3 mol). The mixture was refluxed under nitrogen to completion of reaction as indicated by the disappearance of the doublet resonance at δ : 5.3 ppm (ca. 60 Hrs.). The solvent was removed, the residue taken up in chloroform (250 ml) and washed with water : brine 1 : 1 (3 x 50 ml). Drying ($MgSO_4$) and removal of the solvent afforded a pale yellow oil which crystallized upon trituration with dry ether. The solid was dried and ground to a fine powder 43.5 g (84%). M.pt 134-8°C.

Pmr. ($CDCl_3$), δ : 2.7 (s, 3H) (SCH_3), 6.1, 6.45, 7.2 (m, 2H) (vinylic $C\underline{H}_2$), 7.8 (m, 15H) ($\underline{Ph}_3P$).

Microanalysis . $C_{21}ClH_{20}SP$ requires C, 68.0%, H, 5.44%.

Found C, 65.09%, H 5.79%. Analysis consistant with one molecule of water of crystallization. $C_{21}ClH_{22}OSP$ requires C, 64.86% H, 5.70%.

1-Phenylthiovinyltriphenylphosphonium iodide[46] (38b).

As (38a). Reaction required ca. fifteen hours reflux. A yellowish amorphous solid 89%.

Pmr. ($CDCl_3$), δ : 6.35, 6.7, 7.01 (3 x M, 2H) (vinylic CH_2), 7.55 (m, 5H) (-SPh), 7.95 (m, 15H) (Ph_3P).

2-Methyl-3-phenylthio-6,10-dithiaspiro [4.5] -dec-2-en-1-one (53b).

To a dry three necked flask (100 ml) was added the dione (39a) (1.19 g, 6.26 mmol) and dry THF (25 ml) under a nitrogen atmosphere. After cooling to 0°C sodium hydride (0.34 g, 7 mmol) (washed prior to use with dry petrol) was added in two portions with vigorous stirring. The resulting suspension was stirred for thirty minutes at 0°C after which time the phosphonium salt (38b) (3.1 g, 6.89 mmol) was added. A reaction took place over thirty minutes during which time the lemon colour of the solution was discharged. The resulting mixture was poured into water (100 ml) and extracted with chloroform (3 x 25 ml). The combined organics were dried ($MgSO_4$), filtered and silica gel (70 - 230 mesh, 3g) added to the filtrate. Removal of the solvent afforded a yellow powder which was placed upon a silica gel column (70, 230 mesh, 90g) and eluted with 10% ethyl acetate : 90% petrol. This afforded a white highly crystalline solid 1.447 g (75%) M.pt 159 - 162°C.

A recrystallized sample (petrol) melted 162.5 - 163°C.

Tlc. Rf. 0.32 (DNP, UV, $KMno_4$) (20% ethyl acetate : 80% petrol).

Ir. ($CHBr_3$), ν : 1680 (CO ketone), 753, 690 (-SPh)

Pmr. ($CDCl_3$), δ : 1.6 (m, 2H) ("8" $C\underline{H}_2$), 1.78 (t, 3H), (CH_3), 2.1 (d of t 2H) ("7" and "9" equatorial CH_2's), 2.52 (q, 2H) (cyclopentenone CH_2), 3.99 (m, 2H) '"7" and "9" axial CH's), 6.8 - 7.1 (m, 5H) (SPh).

Microanalysis. $C_{15}H_{16}OS_3$ requires C, 58.2%; H, 5.2%.

Found C, 58.2%; H, 5.6%.

2-Methyl-3-methylthio-6,10-dithiaspiro [4.5] dec-2-en-1-one.(53a).

As (53b) from (39a) and (38a). A white crystalline solid. M.pt 163 - 6°C (74.5%).

Tlc. Rf. 0.33 (DNP, UV, $KMNO_4$) (20% ethyl acetate : 80% petrol).

Ir. (KBr), ν : 1690 (CO ketone), 1600 (C = C-SMe)

Pmr. ($CDCl_3$), δ : 1.7 (t, J=2Hz, 3H) (CH_3), 1.5-3 (m, 4H) (dithiane "7" and "9" equatorial + "8"), 2.34 (s, 3H) ($S\underline{C}H_3$), 2.79 (q, J = 2Hz, 2H) (ring $C\underline{H}_2$), 3.97 (t of d, 2H) ("7" and "9" axial $C\underline{H}_2$s).

Microanalysis. $C_{10}H_{14}OS_3$ requires C, 48.74%, H, 5.73%

Found C, 48.96%, H, 5.71%.

2-(6-Carboxyhexyl)-3-methylthio-6,10-dithiaspiro[4.5] dec-2-en-1-one (53c).

To the diketone (39c) (3.04 g, 10 mmol) in THF (75 ml) was added sodium hydride (0.6 g of an 80% oil dispersion, 20 mmol). Following fifteen minutes stirring at room temperature the vinyl phosphonium salt(38a) (3.75g, 10 mmol) was added in one portion with stirring.

After forty minutes the reaction mixture was diluted with water (150 ml) and transferred to a separating funnel (500 ml) where the aqueous layer was run off. The organic phase was extracted with water (2 x 50 ml) and the combined aqueous layers washed with ether (4 x 50 ml). After acidification with dilute hydrochloric acid the aqueous phase was extracted with ether (4 x 50 ml) and discarded. The combined ether layers were washed with water (50 ml), brine (50 ml) and dried ($MgSO_4$).

Removal of the solvent yielded a brown oil which was chromatographed on silica gel (150 g) (eluted with 10% ethyl acetate : 89% light petroleum : 1% acetic acid). This yielded (39c) (0.16 g) and pure (53c) (2.677 g, 78.5% based on recovered diketone), as a white crystalline solid M.pt. 88 - 90°C.

<u>Tlc</u>. Rf. 0.2 (DNP, UV, $KMnO_4$) (30% ethyl acetate : 69% petrol : 1% acetic acid).

<u>Ir</u>. (KBr), ν : 3700 - 2400 (OH, acid), 1710 (CO acid), 1680 (CO ketone), 1610 (C=C-SMe).

<u>Pmr</u>. ($CDCl_3$). δ:1.48, (m,8H)(alkyl CH_2's), 2-2.8 (2 x m, 8H) ("7" and "9" CH equatorial, "8" CH_2, $C\underline{H}_2$, $C\underline{H}_2CO_2H$), 2.4 (s, 3H) ($SC\underline{H}_3$), 2.8 (s, 2H) (ring $C\underline{H}_2$), 3.93 (t of d, 2H) ("7 and 9" $C\underline{H}$ axial), 9.75 (s, 1H) ($CO_2\underline{H}$).

<u>Microanalysis</u>. $C_{16}H_{24}O_3S_3$ requires C, 53.3%; H, 6.71%.

Found: C, 53.2% H, 6.61%.

2-(6-Carboxyhexyl)-3-phenylthio-6,10-dithiaspiro[4.5] dec-2-en-1-one (53d).

As (53c). A white crystalline solid M.pt 99.5-101.5°C (76.2%).

Tlc. Rf. 0.14 (DNP, IPA, UV, $KMNO_4$) (30% ethyl acetate : 69% petrol : 1% acetic acid).

Ir. ($CHBr_3$), ν : 3490 - 2350 (OH acid), 1738, 1700 (CO acid), 1680 (CO ketone).

Pmr. (C_6D_6), δ :1-18 (m, 10H), 2-2.3 (m, 4H) (chain "7"$C\underline{H}_2$ + dithiane "7" and "9" equatorial), 2.41 (t, 2H) ($C\underline{H}_2CO_2H$), 2.57 (s, 2H) (ring $C\underline{H}_2$), 4.0 (m, 2H) (dithiane "7" + "9" axial), 6.7-7.2 (m, 5H) (-S$\underline{Ph}$), 10.1 (s, 1H) ($CO_2\underline{H}$).

Microanalysis $C_{21}H_{26}O_3S_3$ requires C, 59.68%, H, 6.2%.

Found: C, 59.69%, H, 6.26%.

2-(6-Carbomethoxy)-3-phenylthio-6,10-dithiaspiro[4.5] dec-2-en-1-one (53f).

To a solution of the acid (53d) (1.202 g) in ether (10 ml) was added an ethereal solution of diazomethane until a yellow colour persisted. The solvent was evaporated using a nitrogen gas stream and the residue taken up in 20% ethyl acetate : 80% petrol (10 ml) and filtered through a short column of silica gel (70 - 230 mesh) (20 g) eluted with the same solvent. Removal of the solvent afforded a pinkish waxy solid, 1.185 g (91%) M.pt 42-3°C.

Tlc. Rf. 0.16 (IPA , UV, $KMnO_4$) (10% ethyl acetate : 90% petrol).

Ir. ($CHBr_3$), ν : 1730 (CO ester), 1680 (CO ketone).

Pmr. Identical to acid (53d) except 3.79 (s, 3H) (OCH_3).

Microanalysis. $C_{22}H_{28}O_3S_3$ requires C, 60.5%, H, 6.46%

Found: C, 60.46%, H, 6.57%.

2-(6-Carbomethoxy)-3-methylthio-6,10-dithiaspiro [4.5] dec-2-en-1-one (53e).

As (53f). A colourless oil (94%).

Tlc. Rf. 0.21 (IPA, UV, $KMnO_4$) (10% ethyl acetate : 90% petrol).

Ir. ($CHBr_3$), ν : 1740 (CO ester), 1690 (CO ketone).

Pmr. ($CHCl_3$). As (53c) except 3.7 (s, 3H) (OCH_3).

2-(6-Carbomethoxy)-3-phenylthio-6,10-dithiaspiro [4.5] dec-2-en-1-ol (54f).

To a cooled (0°C) solution of the ester (53f) (99mg, 0.23 mmol) in THF/methanol 1 : 1 (5 ml) was added sodium borohydride (17.5 mg, 0.46 mmol). The reaction mixture was stirred at 0°C until reduction was complete (Tlc, ca. 40 mins.) whereupon it was diluted with water (20 ml) and extracted with ether (3 x 10 ml). The combined organics were washed with dilute hydrochloric acid (5 ml), saturated brine (5 ml) and dried ($MgSO_4$). Removal of the solvent afforded a whiteish cloudy oil 100 mg (100%) which was filtered through a short column of silica (70 - 230 mesh, 5 g) eluted with 30% ethyl acetate : 70% petrol. This yielded a white waxy solid. M.pt. 42 - 5°C 91mg (90.3%) which was unstable at room temperature.

Tlc. Rf. 0.2 (DNP, UV, MPA, $KMnO_4$) (30% ethyl acetate : 70% petrol).

Ir. (smear); ν : 3440 (OH), 1740 (CO ester).

Pmr. ($CDCl_3$) similar to precursor. δ : 3.68 (s, 3H) (OCH_3), 4.73 (br d, 1H) (C<u>H</u>OH).

Microanalysis. $C_{22}H_{30}O_3S_3$ requires C, 60.2%, H 6.9%.

Found: C, 59.74%, H, 7.2%.

2-Methyl-6,10-dithiaspiro[4.5] dec-1-en-3-one.(55a).

To the ketone (53a) (1g, 4.05 mmol) dissolved in dry THF (25 ml) was added lithium aluminium hydride (150 mg). The flask was sealed with a drying tube and the contents stirred magnetically for thirty minutes whereupon methanol was added slowly. The resulting solution was poured into a stirred mixture of methanol : concentrated hydrochloric acid 2 : 1. Following fifteen minutes stirring the mixture was diluted with water (200 ml) and extracted with ether (3 x 20 ml). The combined organic extracts were washed with 5% sodium bicarbonate solution (2 x 25 ml) and dried ($MgSO_4$). Filtration and removal of the solvent afforded a pale yellow oil (864 mg) which was pre adsorbed on silica gel (70 - 230 mesh) and chromatographed ("7736", 30 g) eluted with 10% ethyl acetate : 89% petrol : 1% triethylamine. This afforded the desired enone 536 mg (66%) M.pt. 51 - 3°C and a by-product (57) as a pale yellow oil (240 mg).

Enone.

Tlc. Rf. 0.1 (DNP, MPA, UV, $KMnO_4$) (5% ethyl acetate : 95% petrol)

Ir. (smear), ν : 3080 (C=C), 1715 (CO enone), 1640 (C=C).

Pmr. ($CDCl_3$), δ : 1.84 (d, 3H) (CH_3), 2.1 (m, 2H) (dithiane "8" CH_2), 2.92 (s, 2H) ("4" CH_2), 3.02 (m, 4H) (dithiane "7" and "9" CH_2s), 7.52 (m, 1H) (alkene C<u>H</u>).

Microanalysis. $C_9H_{12}OS_2$ requires C, 53.9%, H, 6.04.

Found: C, 54.03%, H 6.05%.

Byproduct.(57).

Tlc. Rf. 0.55 (UV, MPA, $KMnO_4$) (15% ethyl acetate : 85% petrol).

Ir. (smear), ν : 1720, 1640 (vinyl thioether) 1440.

Pmr. (CDCl$_3$), δ : 1.72, (s, 2H)(C$\underline{H}_2$), 1.85 (S, 3H) (satd SC$\underline{H}_3$), 2.21 (S, 3H) vinylic (SC$\underline{H}_3$), 2.9 (m, 6H) (dithiane), 3.72 (S, 1H) (methine-C$\underline{H}$SCH$_3$).

Ms. M/e 278 ($m^{+}_{\cdot}$), 231 (m - SCH$_3$), 216, 183.

Microanalysis. $C_{11}H_{18}S_4$ requires C, 47.44%, H, 6.51%

Found: C, 47.47%, H 6.47%.

2-(6-Carbomethoxyhexyl)-6,10-diathiaspiro[4.5]-dec-1-en-3-one (55b).

To a dry three necked flask (500 ml) equipped with magnetic stirrer was added the acid (53c) (490 mg, 1.36 mmol), THF (30 ml) and lithium borohydride (300 mg). To the cloudy suspension produced was added methanol (2 ml) dropwise over twenty minutes. The resulting reaction mixture was poured carefully into a stirred solution of methanol concentrated hydrochloric acid 2:1 (50 ml) and the pale green solution which resulted was stirred for ten minutes whereupon concentrated sulphuric acid (5 ml) was added dropwise. Following ten minutes stirring the reaction mixture was diluted with water (200 ml) and extracted with ether (3 x 50 ml). The combined organic extracts were washed with water (2 x 25 ml), brine (25 ml) and dried (MgSO$_4$). Removal of the solvent afforded a pale yellow oil which was chromatographed upon silica gel ("7736", 30 g) eluted with 15% ethyl acetate : 85% petrol to afford the desired enone as a pale yellow oil. M.pt 13^{o}C. 250 mg (56%).

Tlc. Rf. 0.29 (UV, KMnO$_4$, MPA) (25% ethyl acetate : 75% petrol).

Ir. (smear), ν : 1745 (CO ester), 1708 (CO ketone), 1630 (C=C)

Pmr. ($CDCl_3$), (400 MH_3), δ : 1.28 (m, 4H), 1.49 (m, 2H), 1.57 (m, 2H), 2.02 (m, 2H), 2.15 (d of t, $J=7.5$ & $1.5 H_3$ 2H) (vinylic CH_2), 2.26 (t, $J=7.5 H_3$ 2H) ($C\underline{H}_2CO_2CH_3$), 2.84 (S, 2H) (ring $C\underline{H}_2$), 2.9 (m, 2H), 3.02 (m, 2H), (ring $C\underline{H}_2$), 2.9 (m, 2H), 3.02 (m, 2H), 3.60 (s, 3H) (ester $C\underline{H}_3$) 7.38 (s, 1H) (vinylic proton).

Microanalysis. $C_{16}H_{24}O_3S_2$ requires C, 58.5%, H, 7.36%.

Found: C, 58.47%, H, 7.34%.

1-^{n}Butyl-2-methyl-6,10-dithiaspiro[4.5]decan-3-one.(66).

To a suspension of copper (I) iodide (190 mg, 1 mmol) in dry ether (10 ml) under nitrogen was added tri^{n}butylphosphine (0.51 ml, 2 mmol). The mixture was stirred at room temperature until all the solid had dissolved whereupon the solution was cooled to -78°C and a solution of ^{n}butyl lithium (1.35 ml, 2 mmol) added dropwise over three minutes. A yellow solution was generated, the colour fading as a white precipitate appeared. The resulting suspension was stirred for thirty minutes at -78°C when a solution of the enone (55a) (120 mg, 0.6 mmol) in dry ether (5 ml) was added via canula over two minutes. The reaction mixture turned a bright yellow then a deep orange in colour and analysis (Tlc) indicated consumption of the substrate within five minutes. After stirring at -78°C for thirty minutes the reaction mixture was poured into a vigorously stirred solution of ammonium chloride. The resulting mixture was transferred to a separating funnel and the aqueous layer run off and extracted with ether (2 x 25 ml). The combined organics were washed with portions of 10% ammonium sulphate (adjusted to pH9 with ammonia (.880)) until the

the aqueous layer was no longer blue. After a brine wash (5 ml) the organics were dried ($MgSO_4$) and the solvent removed. The resultant oil was chromatographed upon silica gel ("7736", 50 g) eluted with petrol (200 ml) then 5% ethyl acetate : 95% petrol collecting 20 ml fractions. This afforded a white waxy solid. M.pt. 48 - 52°C 131 mg (85%).

Tlc. Rf. 0.25 (MPA, DNP, UV) (10% ethyl acetate : 90% petrol).

Ir. (smear), ν : 1750 (CO ketone).

Pmr. ($CDCl_3$), δ: 0.95 (t, 3H) ($C_3H_6C\underline{H}_3$), 1.2, 1.25 (2 x d, 3H) ($C\underline{H}_3$), 1.3 (s, 2H) (ring CH_2), 1.55 - 2.4 (m, 10H), 2.9 (AB, 2H) (dithiane eq), 3.55 (AB, 2H) (dithiane ax).

Ms. M/e 258.1079 ($M^{+\cdot}$, $C_{13}H_{22}OS_2$ requires 258.1047), 257.1024 (m-1, $C_{13}H_{21}OS_2$ requires 257.1016).

1-(E-3-(^{t}Butyldimethylsilyloxy)oct-1-enyl)-2-methyl-6,10-dithiaspiro[4.5]decan-3-one.(67) and (68).

To a solution of E-1-iodo-3-(t-butyldimethylsilyloxy)oct-1-ene (3.5 ml, 10.72 mmol) in dry ether (50 ml) contained in a three necked flask (100 ml) equipped with nitrogen balloon and septum inlet was added a solution of ^{n}butyl lithium in hexane (6.7 ml, 10.72 mmol) at -78°C. The resulting solution was stirred at -78°C for one hour when a solution of bis(tri ^{n}butylphosphine) copper(I) iodide (5.38 mmol) in dry ether (40 ml) was added dropwise over five minutes via cannula. The resulting pale yellow solution was stirred for thirty minutes at -78°C whereupon a solution of the enone (55a) (536 mg, 2.68 mmol) in ether (10 ml) was added via cannula over five minutes. The mixture was stirred at -78°C for one hour and poured into a vigorously stirred saturated ammonium chloride solution (250 ml). After 10 minutes stirring the layers were separated and the aqueous phase extracted with ether (2 x 50 ml). The combined organics were washed with 10% ammmonium sulphate sclution (adjusted to pH9 with ammonium hydroxide) until the aqueous layer was no longer blue and dried ($MgSO_4$). Removal of the solvent afforded a pale yellow oil which was filter-chromatographed upon silica gel (70-230 mesh, 250g) eluted with 0 to 20% ethyl acetate : petrol over 2 litres. This yielded three fractions recovered starting material 183 mg, cis isomer + ^{n}butyl phosphine and a mixture of cis and trans isomers. The latter two fractions were combined and rechromatographed upon silica gel (7736, 30g) eluted with 5% ethyl acetate : 95% petrol to afford pure cis isomer 242 mg and pure trans isomer 357 mg, total 599 mg (72% upon recovered starting material) ratio 1:1.48.

<u>Cis isomer</u>. A colourless oil.

<u>Tlc</u>. Rf. 0.115 (DNP, MPA, UV) (5% ethyl acetate : 95% petrol) x 4.

<u>Ir</u>. (smear), ν : 1750 (CO ketone), 1258 (O-Si$\overset{/}{\underset{\backslash}{+}}$).

<u>Pmr</u>. ($CDCl_3$), δ : 0.03, 0.05, 0.1 (3 x s, 6H) (epimeric Si-C$\underline{H}_3$), 0.8 - 1 (s+M, 15H) (Si-$^t\underline{Bu}$, CH_3 and terminal CH_3), 2.03 (m, 2H) (dithiane "5"), 2.6, 2.93 (AB) and 2.5 - 3.3 (m, 8H) (CH_2 cyclopentane ring, dithiane "4" and "6", CH C2 & C6), 4.12 (q, 1H) (C$\underline{H}$ $OSiMe_2{}^tBu$), 5.2 (dd, 1H) (C$\underline{H}$=CH C8), 5.68 (dd x 2, 1H) (alkene C7 epimers). (Numbering system CH4).

Cmr. ($CDCl_3$), δ :-4.7 (q), -4.3 (q) ($SiMe_2$), 10.7 (q)(C1) 14 (q) (C14), 18.2(S) (S $\underline{C}Me_3$), 22.6(t)(C13), 24.8(t)(dithiane "5"), 24.9 (t)(C11), 25.8 (q)($SiC\underline{Me}_3$), 27.4, 28.1 (2 x t) (dithiane "4" and "6"), 31.8 (t) (C12), 38.5 (t) (C10), 46.4 (d) (C2), 50.5 minor diastereomer, 50.7 major diastereomer (t) (C4), 52.7(S) (C5) 54 major, 54.3 minor (d) (C6), 72.8 major, 72.9 minor (d)(C9) 123.4 minor, 123.6 major (d) (C7), 138.2 major, 138.6 minor (d)(C8), 214.6(S)(C3). Diastereomer ratio ca. 2.5:1.

Ms. M/e 422 ($M^{\ddagger}$), 385, 371 ($M-C_5H_{11}$), 311, 132.

Microanalysis. $C_{23}H_{42}O_2S_2S_1$ requires C, 62.39%, H, 9.56%.

Found: C, 62.0; H, 9.45%.

Trans isomer A waxy solid. M.pt 28 - 30°C.

Tlc. Rf. 0.091 (DNP, MPA, UV) (5% ethyl acetate : 95% petrol) x 4.

Ir. (smear) , ν : 1750 cm^{-1} (CO ketone).

Pmr. ($CDCl_3$), δ : 0.1 (s,6H) ($s_1(C\underline{H}_3)_2$), 0.92 (s+m, 12H) (^{t}bu + C14$C\underline{H}_3$)), 1.1 (m, 3H) (C1$C\underline{H}_3$) , 1.2-1.8 (m, 8H) (C10-13 CH_2s), 1.8 - 2.3 (m, 2H) (dithiane "5"), 2.4 - 2.7 (m), 2.7 -3.2 (m), 2.7; 3.4 (2 x AB) (C4CH_2), 4.18 (q,1H)(C9 methine), 5.5-6 (m,2H) (alkene C$\underline{H}$s).

Cmr. ($CDCl_3$), δ :-4.7, -4.1 (q)($SiCH_3$), 12.9(q)(C1), 14.0(q) (C14), 18.3(s)($\underline{C}(CH_3)_3$), 22.7 (t) (C13), 25(t)(C11), 25.5(t)(dithiane C5), 25.9 (q)($(\underline{C}H_3)_3$), 27.1, 28.3 (2 x t) (dithiane C4 & C6), 31.8 (t) (C12), 38.3 (t)(C10), 46.3 major, 46.6 minor (d) (C2), 54.5 (s) (C5), 54.8 (t) (C4), 59.1 major, 59.4 minor (d) (C6), 73.1 (d)(C9), 125.1 minor, 125.4 major (d) (C7), 138.1 major, 138.8 minor (d) (C8), 214.5 (s) (C3).

Diastereomer ratio 4:1.

Ms. M/e 442 ($M^{+\cdot}$).

Microanalysis . Requirement as cis isomer.

Found: C, 61.8%, H, 9.26%.

1 β-(E(3S)-3-^{t}Butyldimethylsilyloxy)oct-1-en-1-yl)-2 α-(6-carbomethoxyhexyl)-6,10-dithiaspiro[4.5]decan-3-one.(70) and (71).

To a cooled (-78°C) solution of (3S)-1-iodo-3-(^{t}butyldimethylsilyloxy) oct-1-ene (8.54 ml, 26 mmol) in dry ether (125 ml) under a nitrogen atmosphere was added a solution of ^{n}butyl lithium (16.25 ml, 26 mmol) dropwise over five minutes. After stirring for a further twenty-five minutes a solution of bis(tri-^{n}butylphosphine)copper(I) iodide (13 mmol) in ether (20 ml) was added dropwise, via cannula, over a period of ten minutes. The resulting pale yellow solution was stirred at -78°C for a period of thirty minutes whereupon the enone (55b) (1.25g, 3.8 mmol) dissolved in ether (10 ml) was added dropwise over five minutes. During stirring for one hour at -78°C the observed precipitate dissolved to yield a pale green solution which was allowed to warm to -30°C over one hour and then slowly poured into a vigorously stirred mixture of ice cold saturated ammonium chloride (200 ml) and dilute hydrochloric acid (10 ml). After five minutes stirring the layers were separated and the aqueous fraction extracted with ether (2 x 50 ml). The combined organic layers were washed with 10% ammonium sulphate solution (adjusted to pH9 with ammonium hydroxide)(25 ml portions) until the aqueous layer was no longer blue. After washing with saturated brine (25 ml) and drying (MgSO$_4$) removal of the solvent afforded a colourless oil which was filter chromatographed upon silica gel (70 - 230 mesh, 500g) eluted with 0 to 20% ethyl acetate over 5 litres collecting 100 ml fractions. Fractions (5 to 25 were combined and re-chromatographed upon silica gel ("7734", 100 g) eluted with 5% ethyl acetate : 95% petrol to afford cis isomer 437 mg and trans isomer 760 mg. Total 1.197 g (55.1%) ratio 1:1.175. (Ratios have been in the range 1.9 to 2.5:1, however, in this case some trans isomer could not be separated from a by product of similar Rf and so was lost.

Cis isomer : a colourless gum.

Tlc. Rf 0.445 (DNP,MPA, UV) (15% ethyl acetate : 85% petrol).

Ir. (smear), ν : 1745 (CO ketone), 1260 (O-Si), 850, 785 (^{t}bu).

Pmr. (CDCl$_3$), Similar to cis methyl analogue, δ : 0.04, 0.06 (s,6H) (SiMe$_2$), 0.9 (s+m, 12H) (SiCMe$_3$ + terminal CH$_3$), 1.1 - 1.9 (M, 18H) (alkyl envelope), 2.07 (m, 2H) (dithiane "5" CH$_2$), 2.33 (t, 2H) (C$\underline{H}_2$CO$_2$CH$_3$), 2.7, 3.0 (AB, 2H) (C10 CH$_2$) 2.5 - 3.2 (m, 5H) (dithiane 4 and 6 C$\underline{H}_2$s, C8 methine), 3.35 (dd, J=7.5 and 10.5H$_3$, 1H) (C12 methine), 3.69 (s, 3H) (CO$_2$C$\underline{H}_3$) 4.16 (br q, 1H) (C15 methine), 5.2 (dd, J= 10.5 and 16H$_3$, 1H) (C13 C$\underline{H}$), 5.72 (2 x dd, 1H) (C14 C$\underline{H}$ diasteriomers).

Cmr. (CDCl$_3$), δ : -4.8 (q), -4.4 (q) (Si-$\underline{C}$H$_3$), 14(t) (C20), 18.2 (s) (Si$\underline{C}$(CH$_3$)$_3$), 22.7 (t) (C19), 24.8, 24.9 x 2 (C3, C17 and dithiane C5), 25.4 (t) (C7), 25.8 (q)(SiC($\underline{C}$H$_3$)$_3$), 27 (t) (C6), 27.4 (t), 28.1 (t) (C4 and 6 dithiane), 29 (t) (C4), 29.2 (t) (C5), 31.9 (t) (C18), 34.0 (t) (C2), 38.6 (t) (C16), 50.7 major diastereomer, 50.6 minor (t) (C10) 51.3 (q) ($CO_2\underline{C}H_3$), 51.8 (s + d) (C8 and C11) 52.9 major, 52.6 minor (d) (C12), 72.8 (d) (C15), 123.1 (d) (C13), 138.4 major, 138.1 minor (d) (C14), 173.9 (s) (C1), 214 (s) (C9).

Ms. M/e 570 ($M^{+\cdot}$), 537, 511 (M - CO_2CH_3).

Microanalysis. $C_{30}H_{54}O_4S_2Si$ requires C,63.11%, H,9.53%.
Found: C,62.91%, H 9.31%.

Trans isomer. A white waxy gum.

Tlc. Rf. 0.371 (DNP, MPA, UV) (15% ethyl acetate : 85% petrol).

Ir. (smear), ν : 1750 (CO ketone), 1260 (OSi) 850, 785 (^{t}bu).

Pmr. ($CDCl_3$), δ: 0.08 (S, 6H) ($Si(C\underline{H}_3)_2$), 0.9 (s + m, 12H) (^{t}buSi, C20 $C\underline{H}_3$), 1.1 - 1.7 (M, 18H) (alkyl envelope), 2.02 (m, 2H) (dithiane "5" $C\underline{H}_2$), 2.29 (t, 2H) ($C\underline{H}_2CO_2CH_3$), 2.4 - 3.1 (m, 5H) (dithiane "4 and 6" $C\underline{H}_2$s, C12 methine), 2.65, 3.37 (2d, 2H) (C10 $C\underline{H}_2$), 3.66 (s, 3H) ($CO_2C\underline{H}_3$), 4.19 (q, 1H) (C15 methine), 5.5 - 6 (m, 2H) ($C\underline{H}=C\underline{H}$).

Cmr. ($CDCl_3$), δ: -4.7, -4.1 (q) ($SiMe_2$), 14 (q) (C20), 18.3 (s) ($Si\underline{C}Me_3$), 22.6 (t) (C19), 24.8 (2xt) (C3 and C17), 25.4 (t) (dithiane C5), 25.9 (q) ($SiC(\underline{C}H_3)_3$), 26.4 (t) (C6), 27.0 (t), 28.3 (2 xt) (C7, dithiane C4 and 6), 28.9 (t)(C5), 29.4 (t) (C4), 31.8 (t) (C18), 33.9 (t) (C2), 38.2 (t) (C16), 50.9 (d) (C8), 51.3 (q) ($CO_2\underline{C}H_3$), 54.7 (s) (C12), 55.1 (t) (C10), 56.5 (d) (C12), 73.0 (d) (C15), 125.8 major, 125.6 minor (d) (C13), 138.7 major, 138.0 minor (d) (C14), 173.8 (s) (C1), 214.2 (s) (C9).

Ms. M/e 570 ($M^{+\cdot}$), 511 ($M-CO_2CH_3$).

Microanalysis. Requirement as other isomer.

Found: C, 63.01%, H 9.78%.

1 β -(E-3-(^{t}Butyldimethylsilyloxy)oct-1-en-1-yl)-2-methyl-6,10-dithiaspiro[4.5]decan-3β -ol).

To a stirred solution of the ketone (68) (99 mg, 0.21 mmol) in methanol : THF 1:1 (10 ml) at -50°C was added sodium borohydride (50 mg, 1.3 mmol). The reaction mixture was maintained between -30 and -40°C for three hours whereupon it was poured into water (50 ml) and extracted with ether (3 x 20 ml). The combined organics were washed with 0.1M hydrochloric acid (10 ml), water (10 ml), brine (10 ml) and dried ($MgSO_4$). Removal of the solvent afforded a colourless gum 99 mg (99.5%).

Tlc. Rf. 0.25 (MPA, UV, $KMnO_4$) (10% ethyl acetate : 90% petrol x 2).

Ir. (smear). ν : 3480 (OH), 1260 (OSi), 845, 780 (^{t}bu).

Pmr. ($CDCl_3$), δ : 0.1 (s, 6H) ($SiMe_2$), 0.92 (s + m, 12H) (^{t}bu + terminal CH_3), 1.08 (2 x 3H) (diastereomeric methyl), 1.15 (m, 6H) (alkyl envelope), 1.42 (m, 2H) ($C\underline{H}_2C_4H_9$), 1.91 (m, 1H) (C6 $C\underline{H}$), 2.02 (m, 2H) (dithiane 5 CH_2), 2.18 (m, 1H), ($CH_3C\underline{H}$), 2.48 (dd, 1H) (C4 H_α), 2.68 (m, 1H) (C4 H_β), 2.92 (m, 4H) (dithiane "4 and 6" CH_2's), 3.86 (brs, 1H) (C3 methine), 4.16 (m, 1H) (C9 methine), 5.54 (m, 1H), 5.72 (m, 1H) (diastereomeric alkenes).

Cmr. ($CDCl_3$), δ : -4.8, -4.13 (2 x q) ($Si\underline{Me}_2$), 14 (q) (C14), 17.1 (S) (C1), 18.3 (s) ($Si\underline{C}(CH_3)_3$), 22.7 (t) (C13), 25.1, 25.5 (2 x t) (dithiane 5 + C11), 25.9 (q) (^{t}buCH_3s), 27.2, 28.3

(2 x t) (dithiane C4 and C6), 31.8 (t) (C12), 38.4 (t) (C10), 48.1 major, 48.5 minor (d) (C2), 50.6 (S) (C5), 57.8 major 58.1 minor (d) (C6), 62.1 (t) (C4), 73.4 (d) (C9), 78.8(d) (C3), 126.9 (d) C7, 137.3 major, 137.9 minor (d) (C8).

Microanalysis. $C_{23}H_{44}O_2S_2Si$ requires 58.3%, H,9.35% .

Found: C,57.9%, H,9.54%.

1β-(E(3S)-3-(^{t}Butyldimethylsilyloxy)oct-1-en-1-yl)-2α(6-carbomethoxyhexyl)-6.10-dithiaspiro[4.5]decan-3-ol (80)

As Methyl model. A colourless oil 100%.

Tlc. Rf. 0.4 (MPA, UV, $KMnO_4$) (30% ethyl acetate : 70% petrol) x 2.

Ir. (smear), ν : 3480 (OH), 1740 (CO ester), 1255 (OSi), 845, 780 (^{t}bu).

Pmr. ($CDCl_3$), δ: 0.1 (t, 6H) ($SiMe_2$), 0.91 (s + t, 12H) (^{t}bu + C20 CH_3), 1.3 (m, 12H) (alkyl envelope), 1.49, 1.64 (2 x m, 6H) C16, C3, C6 CH_2s), 1.88 (m, 1H), 2.1 (m, 2H) (dithiane5 CH_2), 2.16 (m, 1H), 2.2 (m, 1H), 2.32 (t + AB, 3H),(C2 CH_2, C10 CH_2), 2.82, 3.04 (2 x m, 4H) (dithiane 4 and 6 CH_2s), 3.68 (s, 3H) ($CO_2\underline{CH_3}$), 3.92 (brm, 1H) (C9 methine), 4.12 (q, 1H) (C15 methine), 5.53, 5.71 (2 x AB, 2H) (diastereomeric alkenes).

Microanalysis. $C_{30}H_{56}O_4S_2Si$ requires C, 62.88%, H, 9.85% .

Found: C, 62.78%, H, 9.45%.

1 β -(E(3S)-Oct-1-en-3-ol-1-yl)-2 α -(6-Carbomethoxyhexyl)-6,10-dithiaspiro[4.5]decan-3 β -ol). (81).

The ester (80) (100 mg, 0.21 mmol) was dissolved in a mixture of THF : acetonitrile 1:1 containing 5% $^{v}/v$ 40% aqueous hydrofluoric acid (5ml). The solution was stirred for thirty minutes at room temperature whereupon it was poured into 5% sodium bicarbonate solution (20 ml) and extracted with chloroform (3 x 10 ml). The combined organics were washed with water (10 ml), brine (10 ml) and dried ($MgSO_4$). Removal of the solvent afforded a colourless oil which was chromatographed upon silica gel ("7736", 10g) eluted with ethyl acetate 35% : petrol 65% to afford the ent-15-epimer (14 mg) and the title compound (51.6 mg) Total 65.6 mg (78 %), ratio 1:3.75.

Tlc. Rf. 0.42 and 0.49 (MPA, UV, $KMnO_4$) (20% ethyl acetate : 80% petrol) x 3.

Major isomer.

Ir. (smear), ν :3480 (OH), 1745 (CO ester).

Pmr. ($CDCl_3$), δ : 0.9 (t, 3H)(C20 CH_3), 1.32 (m,12H) (alkyl envelope), 1.5, 1.62 (2 x m) (C3,C6,C16,CH_2s), 1.99 (m,2H) (dithiane 5 C H eq+ C10β ?), 2.14 (m, 1H) (dithiane 5 CH ax 2.17 (brt, J=10Hz, 1H) (C8 methine), 2.3 (t, 3H) ($C\underline{H}_2CO_2CH_3$), 2.32 (AB, 1H) (C10 α ?), 2.78 (q of t, 2H) (dithiane 4 & 6 2.84 (2 x d, J=2 & 8.5Hz, 1H) (C12 methine), 3.07 (t x AB, 2H) (dithiane 4 & 6 ax), 3.68 (s, 3H) ($CO_2C\underline{H}_3$), 3.92 (3 x AB, J=2, 2 & 7.5 Hz, 1H) (C9 methine), 4.15 (q, 1H) (C15 methine), 5.58 (dd, J=7 & 14.8 Hz, 1H) (C14 alkene), 5.78 (dd, J=8.5 & 14.8 Hz, 1H) (C13 alkene).

Cmr ($CDCl_3$), δ : 14 (q) (C20), 22.7 (t) (C19), 24.9, 25.1 (2 x t)

C3 & C17), 25.5 (t) (dithiane C5), 26.9 (t), 27.4, 28.2 (2 x t) (C6, dithiane C4 & 6), 29 (t) (C5), 29.4 (t) (C4), 31.7 (t) (C18), 33.1 (t) (C7), 34 (t) (C2), 37 (t) (C16), 50.1 (d) (C8), 51.5 (q) ($CO_2\underline{C}H_3$), 53.6 (s) (C11), 58.6 (t) (C10), 60.5 (d) (C12), 72.7 (d) (C15), 76.8 (d) (C9), 128.4 (d) (C13), 137.3 (d) (C14), 174.2 (s) (C1).

Ms. M/e 458.2472 ($M^{+\cdot}$, $C_{24}H_{42}O_4S_2$ requires 458.2465).

1 β-(E)-oct-1-en-3-ol-1-yl)-2 α-(6-carbomethoxyhexyl)-6,10-dithiaspiro[4.5]decan-3-one.

As (81) from the ester (71). Chromatography (silica gel "7736", eluted 25% ethyl acetate :75% petrol) afforded 2 components as colourless oils: ent-15-epimer (21.3%) and little compound (75%).

Total 96%, ratio 3.5 :1.

Tlc. Rf. 0.224 & 0.345 (DNP, MPA, UV) (30% ethyl acetate : 70% petrol) x 2.

Major isomer.

Ir. (smear), ν: 3500 (OH), 1745 (CO ester), 1730 sh (CO ketone).

Pmr. ($CDCl_3$), δ : 0.9 (t, 3H) (C20 CH_3), 1.1 - 1.9 (m, 19H) (Alkyl envelope), 1.8-2.2 (m, 3H) (C12 methine, dithiane 5 CH_2), 2.3 (t, 2H)(C2 CH_2), 6.9-7.4, 7.3 & 7.5 (m, 6H) (C8 methine + dithiane 4 & 6 CH_2s), 3.42 (AB, 1H)(C10 CH_2), 3.67 (s,3H) ($-CO_2C\underline{H}_3$), 4.2 (m, 1H) (C15 methine), 5.71, 5.87 (2dd, 2H) (alkene C$\underline{H}$s).

Ms. M/e 456.2371 ($M^{+\cdot}$, $C_{24}H_{40}O_4S_2$ requires 456.2366), 438.2240 (m-H_2O, $C_{24}H_{38}O_3S_2$ requires 438.2220).

Methyl (13E,15S)-9 β -hydroxy-15-^{t}butyldimethylsilyloxy-11-oxo-prost-13-enoate.(91).

To a stirred solution of the alcohols (81) (220.5 mg, 0.385 mmol) dissolved in acetonitrile: acetone: water (45:45:10, 15 ml) was added silver nitrate (131 mg, 0.77 mmol). Upon dissolution the mixture was cooled to -5^{o}C and a solution of trichloroisocyanuric acid (89.5 mg, 0.385 mmol) in acetonitrile:water (85:10, 1ml) added in one portion. After stirring for one minute (during which time a white precipitate was deposited) the mixture was rapidly poured into 1% sodium bicarbonate solution, extracted with ether (3 x 20 ml) and washed with water (1 x 10 ml), brine (1 x 10 ml). Drying ($MgSO_4$) and removal of the solvent afforded a pale green oil which was rapidly chromatographed upon silica gel ("7736", 20g) eluted with ethyl acetate 40% : petrol 60% to afford the title compounds 112 mg (60.4%).

Tlc. Rf. 0.14 (DNP, UV, MPA, $KMnO_4$) (25% ethyl acetate : 75% petrol).

Ir. (smear), ν : 3500 (OH), 1750 (CO ester), 1730 sh(CO ketone), 1260 (OSi), 850, 785 (^{t}bu).

Pmr. ($CDCl_3$), δ : 0.1 (s, 6H) ($SiMe_2$), 0.95 (s,9H) (^{t}buSi), 1.3-1.9 (m, 21H) (alkyl envelope), 1.95 (m, 2H), 2.31 (t, 2H) ($C\underline{H}_2CO_2Me$), 3.69 (s, 3H) ($CO_2C\underline{H}_3$), 4.05, 4.19 (2 x m, 2H) (C9 & C15 methines), 5.6 (m, 2H) (alkene C$\underline{H}$ s).

Ms. M/e 425 (m-^{t}bu), 411 (m-C_5H_{11}), 407 (m-H_2O-^{t}bu) 325.

Microanalysis. $C_{27}H_{50}O_5S_1$ requires C, 67.1%, H,10.5%

Found: C,66.71%, H,10.37.

Methyl (13E,15S), 9β,15α -dihydroxy-11-oxoprost-13-enoate.(92a)+(92b).

The silyl ethers (91) (35 mg, 72 mmol) were dissolved in a mixture of 40% hydrofluoric acid : THF : acetonitrile (5% : 45% : 45%) (5 ml) and stirred at room temperature for one hour whereupon the mixture was poured into dilute sodium bicarbonate solution and rapidly extracted with chloroform (3 x 10 ml). The combined organics were washed with water (5 ml), saturated brine (5 ml), dried ($MgSO_4$). Removal of the solvent (ice cold water bath, high vacuum) afforded a brown oil which was chromatographed upon silica gel ("7736", 10 g) eluted with ethyl acetate 60% petrol 40% to afford the title compounds 13.8 mg (92) + ent -15-epimer diastereomers (92b) 5.2mg, total 19 mg (71%), ratio 2.66 : 1.

Tlc. Rf. 0.194 & 0.247 (DNP, $KMnO_4$, MPA) (75% ethyl acetate : 25% petrol).

Ir. (smear), ν : 3450 (OH), 1740 (CO ester) ketone).

Pmr. ($CDCl_3$), δ : 0.9 (m, 3H)(C20 CH_3), 1.36 (m, 19H) (alkyl envelope), 2.34 (m, 8H)(C2 CH_2 + remainder except) 3.69 (m,3H) ($CO_2\underline{CH}_3$), 4.15 (2 x m, 2H) (C9 & C15 methine) 5.6 (m, 2H) (alkene).

Ms. M/e 350 (m-H_2O), 297 (m-C_5H_{11}), 279 (297-H_2O), 247 (279-MeOH).

1β-(E(3s)-(3-^{t}Butyldimethylsilyloxy)oct-1-en-1-yl)-2α-(6-carbomethoxyhexyl)-6,10-dithiaspiro[4.5]decan-3α-ol (87).

Mesylation.

To a stirred solution of the crude alcohols (81) (373 mg, 0.65 mmol) in dry pyridine (10 ml) was added methane sulphonyl chloride (110.5 mg, 0.97 mmol). The mixture was stood at room temperature for thirty minutes during which time it warmed and a precipitate was deposited. At this point in time the mixture was poured into 0.5M hydrochloric acid (50 ml) and extracted with ether (3 x 20 ml). The combined organics were washed with 0.5M hydrochloric acid (3 x 10 ml) brine (10 ml) and dried ($MgSO_4$). Evaporation of the solvent afforded a pale brown oil which was placed under high vacuum overnight to remove the excess methane sulphonyl chloride.

Tlc. Rf. 0.39 (UV, MPA)(20% ethyl acetate : 80% petrol).

Ir. (smear), ν : 1740 (C=0 ester), 1260 (0-Si).

Pmr. ($CDCl_3$), δ : 3.01 (s, 3H) ($-OSO_2C\underline{H}_3$), 4.88 (m,1H) (C9 methine).

3 α-acetate (85).

The crude mesylate from above was dissolved in dry acetone (20 ml) and tetra-^{n}butylammonium acetate (500 mg) added rapidly. The whole was refluxed under nitrogen overnight and poured into water (50 ml). The resulting solution was extracted with ether (3 x 20 ml) and the combined organics washed with water (20 ml), brine (20 ml) and dried ($MgSO_4$). Removal of the solvent afforded a brown oil which was chromatographed upon silica gel ("7736", 30 g) eluted with ethyl acetate 7.5% : petrol 92.5% to afford the elimination product (86) (50 mg) and the 9 α -acetate (95) 248 mg (61.9%).

Acetate.

Tlc. Rf. 0.57 (UV, MPA)(20% ethyl acetate : 80% petrol).

Ir. (smear), ν : 1750 cm^{-1} (C=0 esters).

Pmr. ($CDCl_3$), δ:2.04 (s,3H) ($C\underline{H}_3CO_2-$), 5.22 (m,1H) (C-9 methine).

Elimination product (86).

Tlc. Rf. 0.65 (MPA, UV)(20% ethyl acetate : 80% petrol.).

Ir. (smear), ν : 1750 (CO ester), 1655 (C=C).

Pmr. ($CDCl_3$), δ : 0.09 (s,6H) (OSi $\underline{Me}_2$), 0.9 (s, 12H) (OSi^{t}bu, C20 CH_3), 1.1-1.7 (m, 16H) (alkyl envelope), 1.9 (m), 2.24 (t, 2H) ($C\underline{H}_2CO_2Me$), 2.6 (m, 2H), 2.85 (m, 6H), 3.65 (s, 3H) ($O\underline{CH}_3$), 4.15 (brq, 1H), (C15 methine), 5.6-5.95 (AB, 3H) (C13,14-alkene, + C9 alkene), 5.95 (d,1H) (C10 alkene).

Ms. M/e 554.3297 ($C_{30}H_{54}O_3S_2Si$ requires 554.3311), 422.233 (m-^{t}buMe$_2$SiOH).

3 α -alcohol (87).

The acetates (85) were dissolved in a solution of sodium methoxide in methanol (prepared from sodium(0.5 g)and absolute methanol (10 ml)) and stood at room temperature for two hours whereupon it was poured into dilute hydrochloric acid (50 ml) and extracted with ether (3 x 20 ml). The combined organics were washed with water (2 x 20 ml), brine (20 ml) and dried ($MgSO_4$). Removal of the solvent afforded a colourless gum 195 mg (84.4%) (52.3% for sequence).

Tlc. Rf. 0.2 (UV, MPA, $KMnO_4$) (20% ethyl acetate : 80% petrol).
(C-9 epimer Rf 0.16).

Ir. (smear), ν : 3450 (OH), 1750 (CO ester).

Pmr. Similar to epimer except 4.28 (m,1H) (C9 methine).

Ms. M/e 572.3402 ($M^{\dot{+}}$ $C_{30}H_{56}O_4S_2Si$ requires 572.3417), 541 (m-OCH_3), 515 (m-^{t}Bu), 501 (m-C_5H_{11}).

Methyl (13E,15S)-9α -hydroxy-15-^{t}butyldimethylsilyloxy-11-oxo-prost-13-enoate (89a) + ent-15-epimer (89b).

To a stirred suspension of red mercuric oxide (45 mg,1.8mmol) in 15% aqueous THF (8 ml) was added freshly distilled boron trifluoride diethyl etherate (25 ml, 0.88 mmol). The mixture was cooled to 0°C and the alcohols (87) (55mg, 1.8 mmol) added in THF solution (2 ml). The resulting solution was stirred until Tlc indicated complete hydrolysis (15-30 mins) whereupon it was diluted with ether (20 ml) and washed with 1% sodium bicarbonate solution (5 ml), water (5 ml), saturated brine (5 ml) and dried ($MgSO_4$). Removal of the solvent at low temperature afforded a yellow oil which was rapidly chromagraphed upon silica gel ("7736", 3 g) eluted with 30% ethyl acetate : 70% petrol. This afforded the title compounds (89a) + (89b) 23 mg (49.6%).

Tlc. Rf. 0.31 (DNP, $KMnO_4$, MPA)(50% ethyl acetate : 50% petrol.)

Ir. (smear), ν : 3500 (OH), 1750 (C=O ester), 1730 sh (C=O ketone), 1260 (O-Si), 850, 785 (^{t}bu).

Pmr. ($CDCl_3$), δ : 0.09 (s,6H) (Si-CH_3), 0.9 (s,9H) (Si-C$(CH_3)_3$), 1.34(m), 2.3 (t, 3H) ($C\underline{H}_2CO_2CH_3$), 2.85 (m), 3.68 (s, 3H) ($CO_2C\underline{H}_3$), 4.11 (m,1H) (C15 methine), 4.15 (m,1H) (C9 methine, 5.48 (m,2H) ($C\underline{H}=C\underline{H}$).

Ms. M/e 482 ($M^{+\cdot}$) 464 (m-H_2O), 425 (m-^{t}bu), 411 (m-C_5H_{11}, 351 (m-^{t}bu $(CH_3)_2SiO$).

Methyl (13E,15S)-9α,15-dihydroxy-11-oxoprost-13-enoate.(37). (PGD$_1$ methyl ester) + ent-15-epi PGD$_1$ methyl ester (93).

As (91) 21mg of ester (89) afforded after flash column chromatography afforded 11mg (68%). The mixture of epimers was rechromatographed upon silica gel ("7736", 10g) eluted with 55% ethyl acetate : 45% petrol collecting 2 ml fractions. This afforded PGD$_1$ methyl ester (7 mg) M.pt. 38-42°C and its ent-15-epimer (2mg). Ratio 3.5:1.

PGD$_1$ methyl ester.

Tlc. Rf. 0.25 (DNP, MPA,KMnO$_4$) (75% ethyl acetate : 25% petrol).

Ir. (smear), ν : 3500 cm^{-1} (OH), 1750 cm^{-1} (C=O ester), 1730 cm^{-1} (sh) (C=O ketone).

Pmr. (CDCl$_3$), δ : 0.88 (t, 3H)(C20 CH$_3$), 1.2-1.75 (m,18H), 2.01 (m,3H), 2.31 (t, 3H) (C$\underline{H}_2$CO$_2$CH$_3$) 2.44 (d,2H), 2.78 (dd,1H), 3.68 (s,3H) (OC$\underline{H}_3$), 4.09 (q, 1H)(C9 C$\underline{H}$OH), 4.55 (q,1H)(C15 C$\underline{H}$OH), 5.41 (dd,1H) (C13 C$\underline{H}$), 5.61 (dd,1H)(C13 C$\underline{H}$).

Ms. M/e 368.2542 ($M^{+\cdot}$,$C_{21}H_{36}O_5$ requires 368.2563), 297.1684 (M-C_5H_{11}, $C_{16}H_{23}O_4$ requires 297.1702), 279.1608 (297-H_2O,$C_{16}H_{23}O_4$ requires 279.1596), 247.1337 (279-CH_3OH,$C_{15}H_{19}O_3$ requires 247.1334).

ent-15-epi PGD$_1$ methyl ester

Tlc. Rf. 0.19 (DNP, MPA, KMnO$_4$) (75% ethyl acetate : 25% petrol).

Ir. Identical to above.

Pmr. Similar to PGD$_1$ methyl ester, except 4.28 (m,1H) (C-9-methine).

Ms. M/e 297,279.

1-Pentyl-2-methyl-6,10-dithiaspiro[4.5]dec-1-en-3-one.(97).

To a stirred, cooled (0 to 10^{o}C) solution of the ketone (53a) (496 mg, 2 mmol) in THF (10 ml) was added ^{n}pentyl lithium (2 ml of 1.05M solution in pentane, 2.1 mmol). Upon complete consumption of the substrate (Tlc) the reaction mixture was carefully poured into a stirred solution of cHydrochloric acid : methanol 1 : 2 (25 ml) (fume cupboard). The solution was stirred for ten minutes , diluted with water (100 ml) and extracted with ether (3 x 25 ml). The combined organics were washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Removal of the solvent afforded a pale brown oil which was chromographed upon silica gel ("7736", 30 g) eluted with 5% ethyl acetate : 94% petrol : 1% triethylamine to afford a colourless oil 436 mg (80%) which crystallized. M.pt 46-8^{o}C.

Tlc. Rf. 0.11 (DNP, MPA, UV), (5% ethyl acetate : 95% petrol)

Ir. (smear), ν : 1720 cm^{-1} (C=O enone), 1640 cm^{-1} (C=C).

Pmr. ($CDCl_3$), δ: 0.4 - 1.7 (m,9H), 1.78 (s,3H)(CH_3), 1.9-2.5 (m,8H),
2.2(s,2H) (ring CH_2).

Microanalysis. $C_{14}H_{22}OS_2$ requires C,62.17%,C, 8.2%.
Found: C,62.44%, H,8.14%.

1-Pentyl-2-methyl-6,10-dithiaspiro[4.5]dec-1-en-3-ol.

To a solution of the ketone (97) (436 mg, 1.61 mmol) in THF: methanol 1:1 (10 ml) was added sodium borohydride (62 mg). The mixture was stirred for thirty minutes, diluted with water (50 ml) and extracted with ether (3 x 25 ml). The combined organic layers were washed with water (10 ml), saturated brine (10 ml) and dried ($MgSO_4$). Removal of the solvent afforded a colourless oil 370 mg (84.5%).

Tlc. Rf. 0.15 (MPA, DNP, UV)(10% ethyl acetate : 90% petrol).

Ir. (smear), ν : 3300 cm^{-1} (OH), 1670 cm^{-1} (weak C=C).

Pmr. Similar to enone except 4.55, (m,1H) (methine).

Ms. M/e 272 ($M^{\dot{+}}$).

2-Pentyl-3-methyl-4-hydroxycyclopent-2-en-1-one (94).

To a solution of 1-^{n}Pentyl-2-methyl-6,10-dithiaspiro[4.5]dec-1-en-3-ol (355 mg, 1.36 mmol) in 20% aqueous acetonitrile (10 ml) was added a solution of N-chlorosuccinimide (726 mg, 5.44 mmol) and silver nitrate (1.04 g, 6.125 mmol) in 20% aqueous acetonitrile (25 ml). As a white precipitate was deposited saturated sodium bisulphite, sodium bicarbonate and sodium chloride (5 x 1 ml portions of each) were added over five minutes. The resulting solution was filtered through celite, extracted with dichloromethane (2 x 30 ml) and the combined organics washed with water (10 ml) and dried ($MgSO_4$). Removal of the solvent afforded a brown oil which was chromatographed upon silica gel ("7736" 10 g) eluted with 30% ethyl acetate : 70% petrol to yield the title compound 80 mg (33%).

Tlc. Rf. 0.2 (UV, MPA, $KMnO_4$) (20% ethyl acetate : 80% petrol).

Ir. (smear), ν : 3400 cm^{-1} (OH), 1700 cm^{-1} (C=O, enone), 1655 cm^{-1} (C=C).

Pmr. ($CDCl_3$); δ : 0.9 (t,3H) (chain CH_3), 1.3 (m,6H)(chain CH_2's).

2.12 (s,3H) (CH_3), 2.3 (m,2H) (CH_2-C=C), 2.3, 2.35 (2 x d, 1H) (C<u>H</u>-CHOH), 2.68, 2.9 (2 x d , 1H) (C<u>H</u>CHOH), 4.22 (brd,1H) (C<u>H</u>OH).

<u>Ms</u>. M/e 182.1299 (M^{+},$C_{11}H_{18}O_2$ requires 182.1307), 167 (m-15), 111 (m-71).

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As part of the research programme the author has attended the following lecture courses at Sheffield City Polytechnic and Sheffield University:

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'The Synthon Approach' : S.W. Warren.

The author has presented a research coloquium upon this work at the sponsering establishment and has attended colloquia at Sheffield University and Sheffield City Polytechnic presented by internal and external speakers.

The author has attended symposia upon:

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Natural Product Chemistry (London 1980).

Stereochemistry (Sheffield 1978, 1979, 1980).

The author has also undertaken a three months training period at the collaborating bodies laboratories during which time he presented monthly progress reports to the prostaglandin research group.

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TOTAL SYNTHESIS OF PROSTAGLANDIN D_1 METHYL ESTER AND 9-EPI-PROSTAGLANDIN D_1 METHYL ESTER

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and Alan H. Wadsworth
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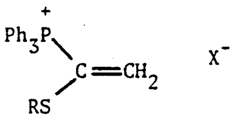
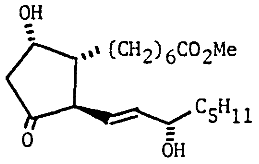
Summary: *Syntheses of the title compounds are described via the dithiane enone (VIII); cuprate addition to (VIII) proceeds with asymmetric induction.*

Although much effort has been devoted to prostaglandin synthesis there have been very few approaches[1] to the D series of compounds, which are of interest in view of their ability to inhibit platelet aggregation. We have previously described the synthesis of the vinyl phosphonium salt (I) and its use in the synthesis of cyclopentanones.[2] We now describe the use of the related salt (II)[3] in the synthesis of PGD_1 derivatives including PGD_1 methyl ester (III).



I, R = Ph, X = I
II, R = Me, X = Cl



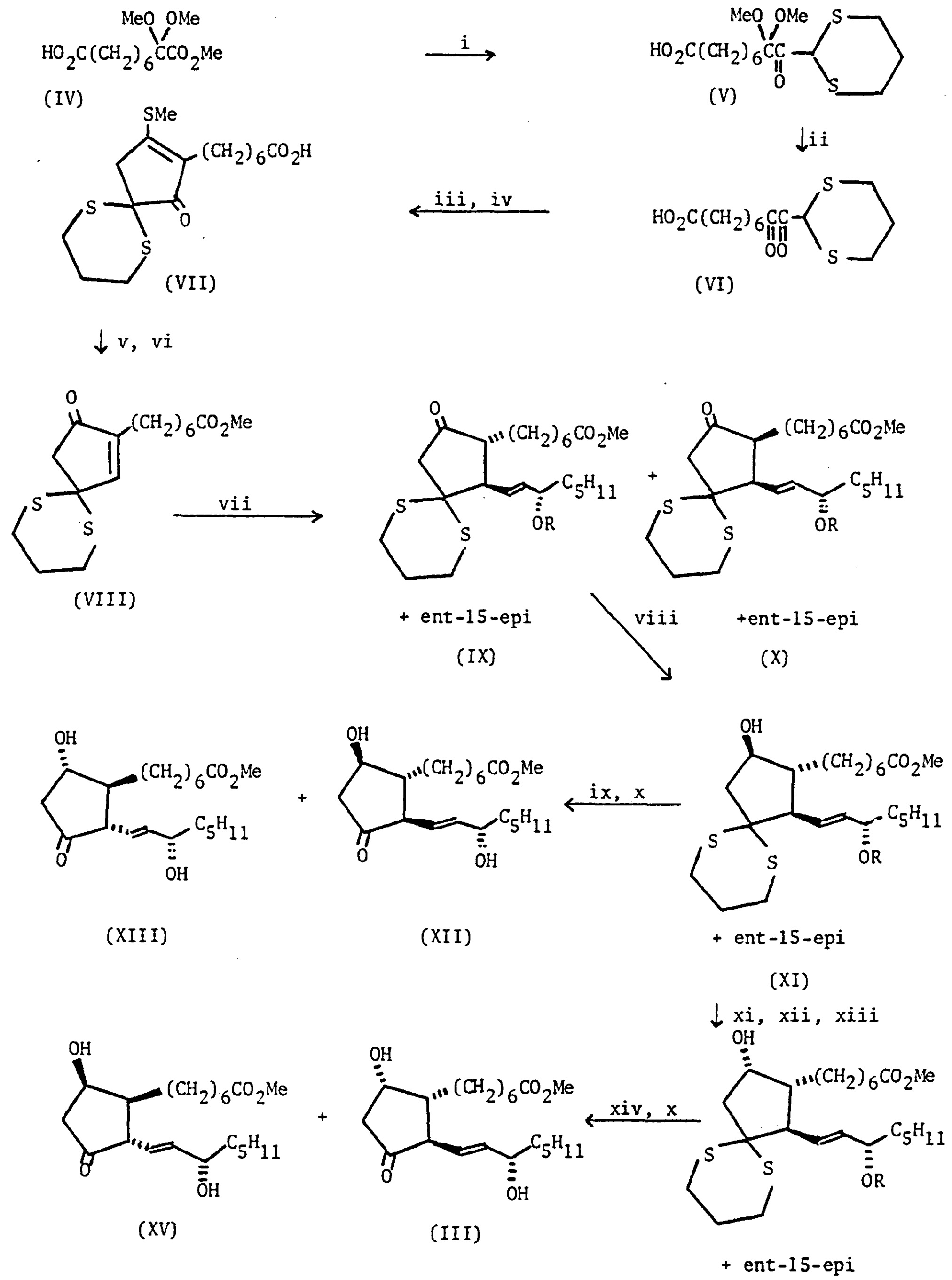
III

Alkylation of methyl dimethoxyacetate[4] with the lithium salt of 7-iodoheptanoic acid gave (IV) (73%) which was treated with the anion of dithiane to give (V)[5,6] (59%). Hydrolysis with aqueous TFA gave the diketodithiane (VI) (97%; m. 96-98°). Cyclisation was accomplished on treatment of (VI) with phosphonium salt (II) in the presence of sodium hydride, giving (VII) (79%; m. 88-90°). Reduction of the vinylogous thioester in (VII) followed by acid catalysed rearrangement and esterification gave (VIII) (59%; oil; IR (neat) 1745, 1708, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45, s, 1 H).

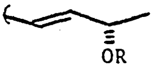
The enone (VIII) was unreactive towards heterocuprate reagents of the type often used in PG synthesis[1,7] but reacted with an excess of the homocuprate reagent to give a 2.2:1 mixture of (IX) (IR (neat) 1750 cm^{-1}) and (X) (IR (neat) 1750 cm^{-1}) (total 56%)[8].

If an excess of cuprate reagent was not used then considerable amounts of the enone (VIII) were recovered. The production of the *cis*-isomer (X) is unusual. It is presumed that the dithiane ring is affecting the conformation of the cyclopentane in such a way as to reduce the preference for protonation of the enolate from that side which leads to the *trans* arrangement of the C-8 and C-12 side chains. Attempts to isomerise (X) to (IX) using a mild base were unsuccessful.

Scheme



R = $SiMe_2{}^tBu$

Reagents (see scheme opposite) i, LDA, dithiane; ii, TFA/H_2O; iii, NaH; iv, (II); v, $LiBH_4$, THF, MeOH; vi, HCl, MeOH; vii, LiCu($C_5H_{11})_2$; viii, $NaBH_4$, MeOH; ix, trichloroisocyanuric acid, $AgNO_3$; x, HF, MeCN, H_2O; xi, $MeSO_2Cl$, pyridine; xii, $Bu_4N^+OAc^-$; xiii, NaOMe, MeOH; xiv, HgO, $BF_3.Et_2O$.

Reduction of (IX) with sodium borohydride proceeded stereospecifically to give, rather surprisingly, the 9β-alcohol (XI) (100%; IR (neat) 3460, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88, br s, 1 H). Careful analysis of the 400 MHz ^1H NMR spectrum showed the absence of the 9α-alcohol. H-9 in 9β-hydroxy PG's is known to occur at approx. 0.3 ppm upfield from the corresponding signal in 9α-hydroxy PG's[9]. Hydrolysis of the dithiane group followed by desilylation gave a separable mixture of (XII) (IR (neat) 3450, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) similar to that of (III) except the signal at δ 4.55 in the latter for H-9 is replaced by a signal at δ 4.1) and (XIII) (total 43%).

Inversion of stereochemistry at C-9 in (XI) was accomplished via an S_N2 displacement on the mesylate leading to (XIV) (58%; IR (neat) 3500, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.2, m, 2 H). Hydrolysis of the dithiane in (XIV) proceeded only in poor yield using trichloroisocyanuric acid/$AgNO_3$[10] but was readily achieved (50%) using HgO/$BF_3.Et_2O$[11]. Desilylation then afforded a 3.7:1 separable mixture of PGD_1 methyl ester (III) (IR (neat 3560, 1745, 1730 (sh) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.61, dd, 1 H; 5.41, dd, 1 H; 4.55, m, 1 H; 4.09, m, 1 H; 3.68, s, 3 H; 2.78, dd, 1 H; 2.44, d, 1 H; 2.31, t, 2 H; 2.01-0.88, m, 22 H) and (XV) (total 68%).

Further confirmation of the stereochemical assignments was obtained by the synthesis of 11-deoxy PGF derivatives. Thus the mixture (XI) was desilylated and then separated. The major isomer was treated with Raney Ni followed by NaOH to give a product which co-chromatographed with authentic 11-deoxy $PGF_{1\alpha}$. Similar treatment of (XIV) gave a product chromatographically identical to 11-deoxy $PGF_{1\beta}$.

The ratios of (XII):(XIII) and (III):(XV) indicate that the cuprate reaction shows considerable selectivity in producing the configuration found in the natural PG's[12]. Such a pronounced selectivity is not usually observed in cuprate reactions which add the intact C-12 PG side chain to enones either unsubstituted or with a single oxygen functionality at C-11. Again it is presumed to be the spiro dithiane system which is causing subtle differences in the transition states leading to the two diastereoisomers.

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12. Desilylation of (X) showed it was also a 3.7:1 mixture of diastereomers.

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