The synthesis of prostaglandin analogues

Thesis

THE SYNTHESIS OF PROSTAGLANDIN ANALOGUES

A Thesis presented for the degree of
Doctor of Philosophy
in the
Department of Chemistry
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by

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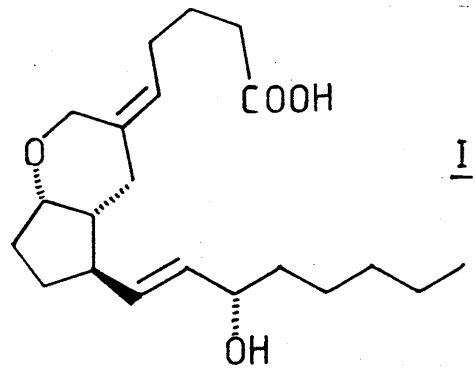
SUMMARY

A route was devised which led to the synthesis of 11-deoxyhomoprostacyclin(I), an analogue of prostacyclin (or PGI_2)(III). A novel synthetic route to 11-deoxyprostaglandins of the E and F series was also developed.

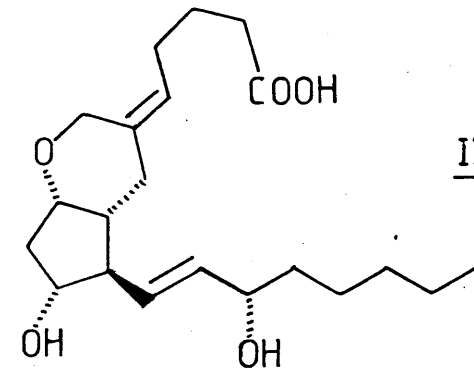
Natural PGI_2 (III) is unstable due to the lability of the enol ether moiety to hydrolysis, but has desirable biological properties, with potential therapeutic applications in the treatment or control of thrombosis. It was hoped that the analogue (I), in which the enol ether moiety has been split up by an extra methylene group, would exhibit similar biological properties. The 11-deoxy analogue(I) was chosen as the initial target since these molecules are easier to synthesise than their 11-hydroxylated counter parts and still exhibit interesting biological properties. The route was devised, however, to be sufficiently flexible so as to allow subsequent synthesis of the 11-hydroxylated analogue(II).

The key step was an organocuprate conjugate addition - enolate alkylation reaction. Using various alkylating agents such as allyl bromide or 2-methoxyallyl bromide, gave intermediates which were further functionalised to give the key bicyclic pyran type system. This was then converted by known procedures to the target(I).

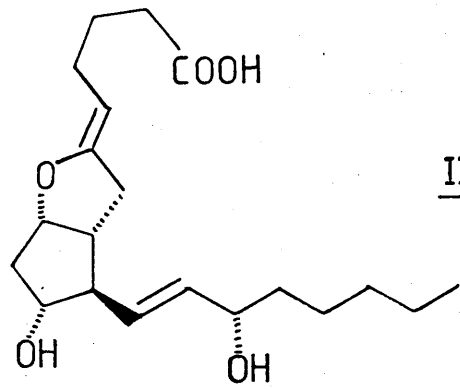
An interesting degradative oxidation of one of the intermediates on activated manganese dioxide led to the lactone (IV). This was converted by known procedures to the 'Corey Lactone an intermediate in the synthesis of 11-deoxy E and F prostaglandins thus constituting a new formal synthesis of these compounds.



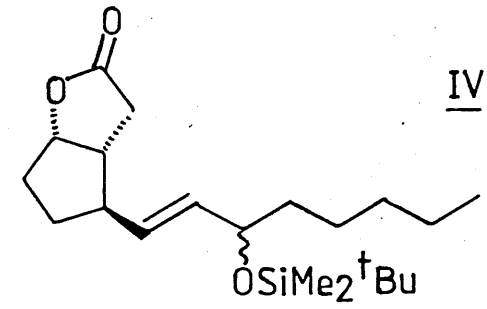
I



II



III



IV

ACKNOWLEDGEMENTS

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Chapter 1 INTRODUCTION

1.1 Background and Nomenclature of Prostaglandins

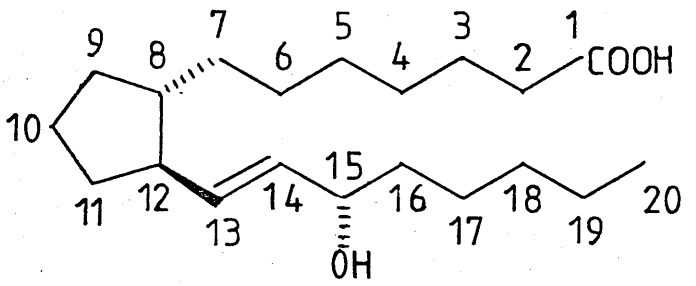
In the mid 1930's, Goldblatt[1] in England and Von Euler[2] in Sweden independently found that extracts of human seminal fluid and sheep vesicular glands had a profound stimulatory effect on smooth muscle preparations and also lowered blood pressure in various experimental animals. Von Euler showed that these effects were associated with a previously unknown factor which was differentiable from substances with a similar biological activity such as adrenaline, histamine or acetylcholine[3]. Except for the human source, the richest vertebrate supply was found in the prostate glands of sheep, and believing that the new factor was produced in this gland, Von Euler named it prostaglandin (PG). However it has since been found that prostaglandins are ubiquitous in all types of tissue, suggesting they may play a fundamental role in cellular activity.

Von Euler discovered[4] that prostaglandin contained no nitrogen, was lipid soluble, and had properties consistent with an unsaturated, hydroxylated, fatty acid. An oily residue from chloroform and ether extracts was converted to a water soluble barium salt, allowing a separation of the fatty acids from other impurities giving a stable, amorphous, highly active powder. Von Euler processed huge numbers of vesicular glands in this way, obtaining partly purified material, which when desiccated, was stable for many years.

It was not until 1957 that Bergström and Sjövall[5] succeeded in isolating a crystalline prostaglandin from freeze dried sheep prostate glands. This substance was named PGF due to its solubility in phosphate (Fosfate in Swedish) buffer solution. After extensive purification PGF was found only to have a stimulatory effect on rabbit smooth muscle and not also a vasodepressor effect as earlier crude extracts had done. This led to a search for a second active substance in the biological extract. Soon Bergström and Sjövall[6] reported the isolation of a second crystalline compound, which showed activity both on rabbit smooth muscle and on blood pressure. This compound, named PGE due to its solubility in Ether, appeared to be responsible for most of the biological activity in the extracts of sheep vesicular glands[6].

Within a few years, Bergström and his coworkers had isolated and elucidated the structures of a whole family of closely related prostaglandins[7]. The basic prostaglandin structure was shown to be a 20-carbon unsaturated carboxylic acid, bearing at least one hydroxyl function[8].

All prostaglandins are based on structure 1 and they differ in the substitution pattern of the five membered ring and in the number of additional double bonds in the 7 carbon(α) and 8 carbon(ω) side chains.



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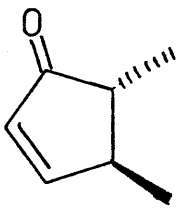
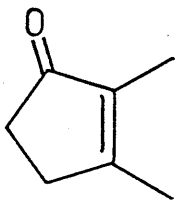
There are several basic families of prostaglandins differing in the nature of the substitution on the five membered ring. These are designated PGA, PGB, PGC, PGD, PGE and PGFα (Fig. 1).

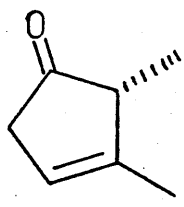
FIGURE 1



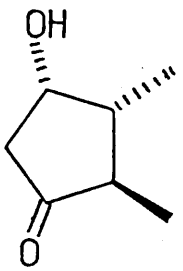
PGA



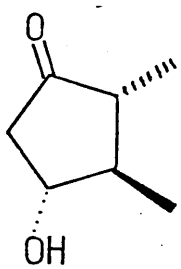
PGB



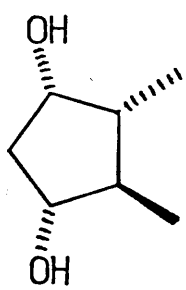
PGC



PGD



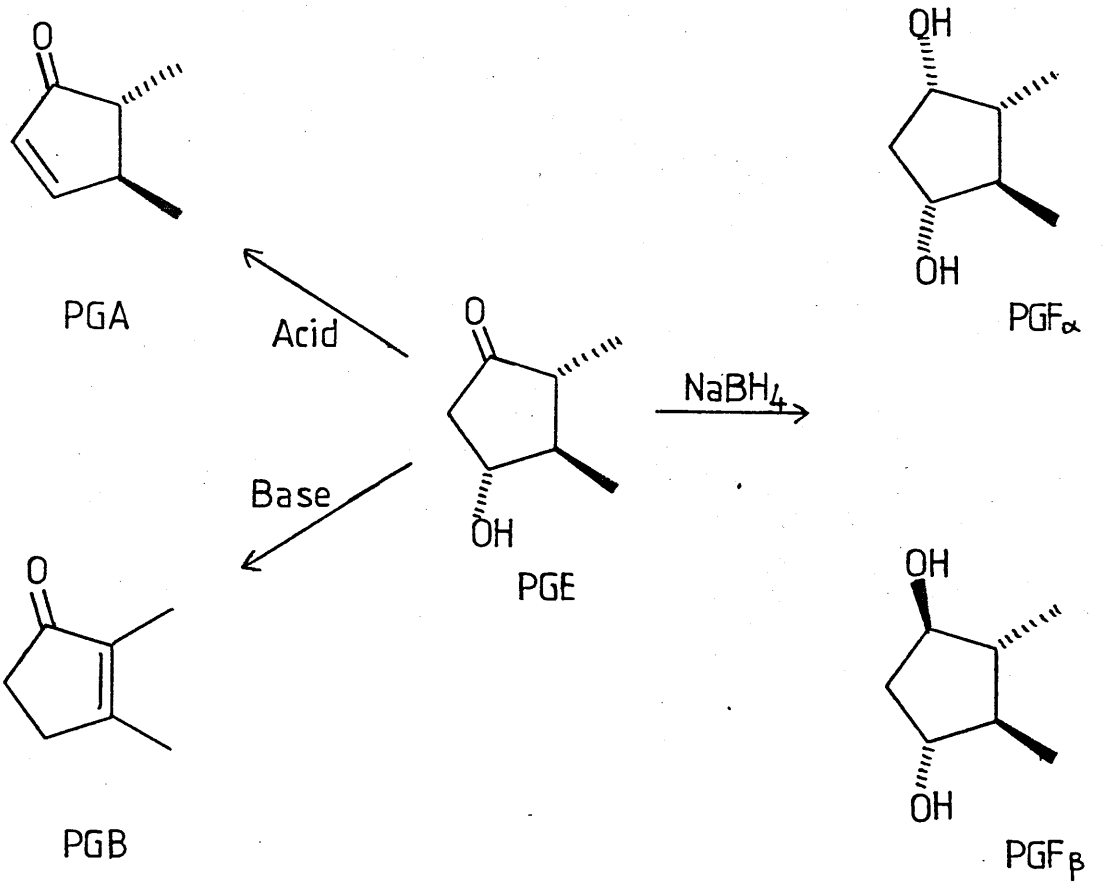
PGE



PGFα

The prostaglandins were found to be chemically interrelated as shown in Figure 2. Treatment of PGE prostaglandins with Acid gives PGA prostaglandins and treatment with Base gives PGB prostaglandins. Reduction of PGE gives two isomeric PGF prostaglandins. The naturally occurring isomer has a cis relationship between the 9-OH group and the 7 carbon α side chain, and is called PGFα. C and D prostaglandins were so named to complete the alphabetical sequence.

FIGURE 2



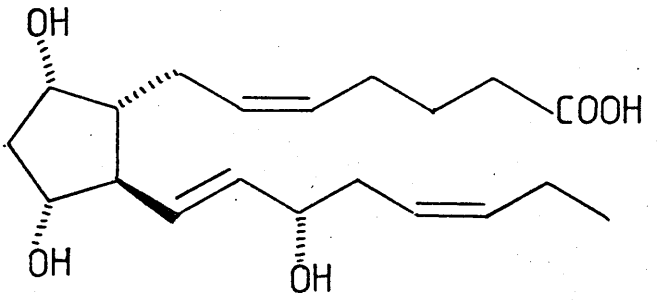
All prostaglandins have a trans-13,14 double bond but some have 1 or 2 additional double bonds in defined positions. To take this into account a subscript is used to denote the number of double bonds e.g.

PGE_1 has a trans-13,14 double bond

PGE_2 has a trans-13,14 double bond
and a cis-5,6 double bond

PGE_3 has a trans-13,14 double bond
a cis-5,6 double bond
and a cis-17,18 double bond

Based on the nomenclature, structure 2 would be called $PGF_{3\alpha}$



2

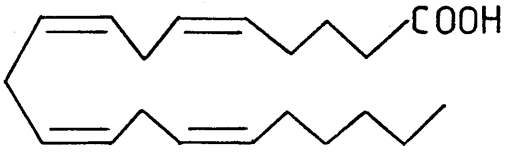
Prostaglandin structures as written correspond to absolute configurations of prostanoids from mammalian tissues. Structures are presented in a consistent format with the carboxy side chain to the upper right hand side (α configuration at ring junction) and the omega alkyl side chain extended to the lower right hand side (β configuration at the ring junction). Wedge shaped lines indicate β configuration (above ring plane) and broken lines, α

configuration (below ring plane). Wavy or straight lines indicate unknown, unspecified or a mixture of two configurations.

1.2 Biosynthesis

Prostaglandins act in a hormone-like way and are not stored in tissues but are produced in response to various stimuli and virtually every mammalian tissue examined has been shown to have some capacity to synthesise prostaglandin like materials.

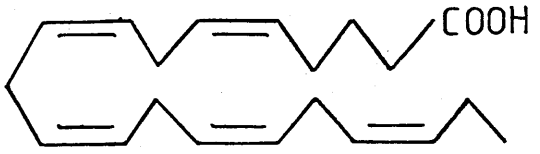
The structure of prostaglandins prompted speculation that they were derived from the naturally occurring poly-unsaturated fatty acids with twenty carbon atoms. This was confirmed and arachidonic acid (3) was shown to be the biosynthetic precursor of the '2' series prostaglandins[9].



3

Prostaglandins of the '1' and '3' series are biosynthesised from 8, 11, 14-eicosatrienoic acid (4) and 5, 8, 11, 14, 17-eicosapentaenoic acid (5) respectively.

4



5

The biosynthetic scheme shown in Figure 3 was proposed by Samuelsson for prostaglandins of the '2' series[10]. The key biosynthetic intermediate, the prostaglandin endoperoxide (PGH_2 6) was eventually isolated in 1973[11,12], and shown to be extremely unstable with a biological half life of a few minutes. Subsequently a second endoperoxide (PGG_2 7) was isolated[12,13].

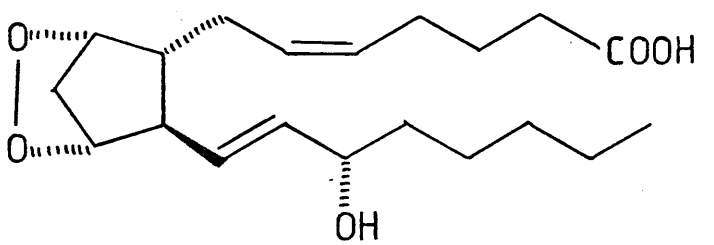


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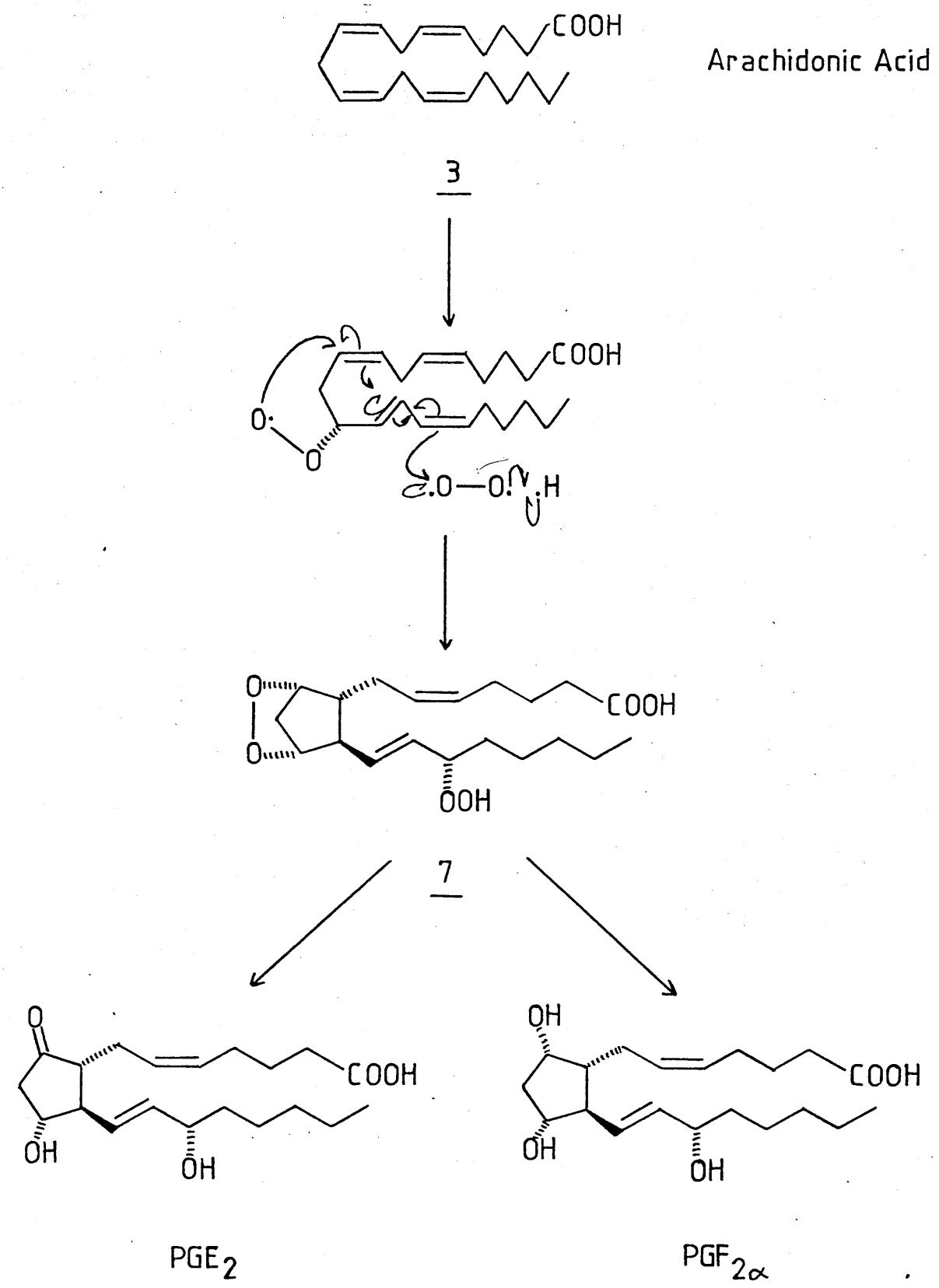
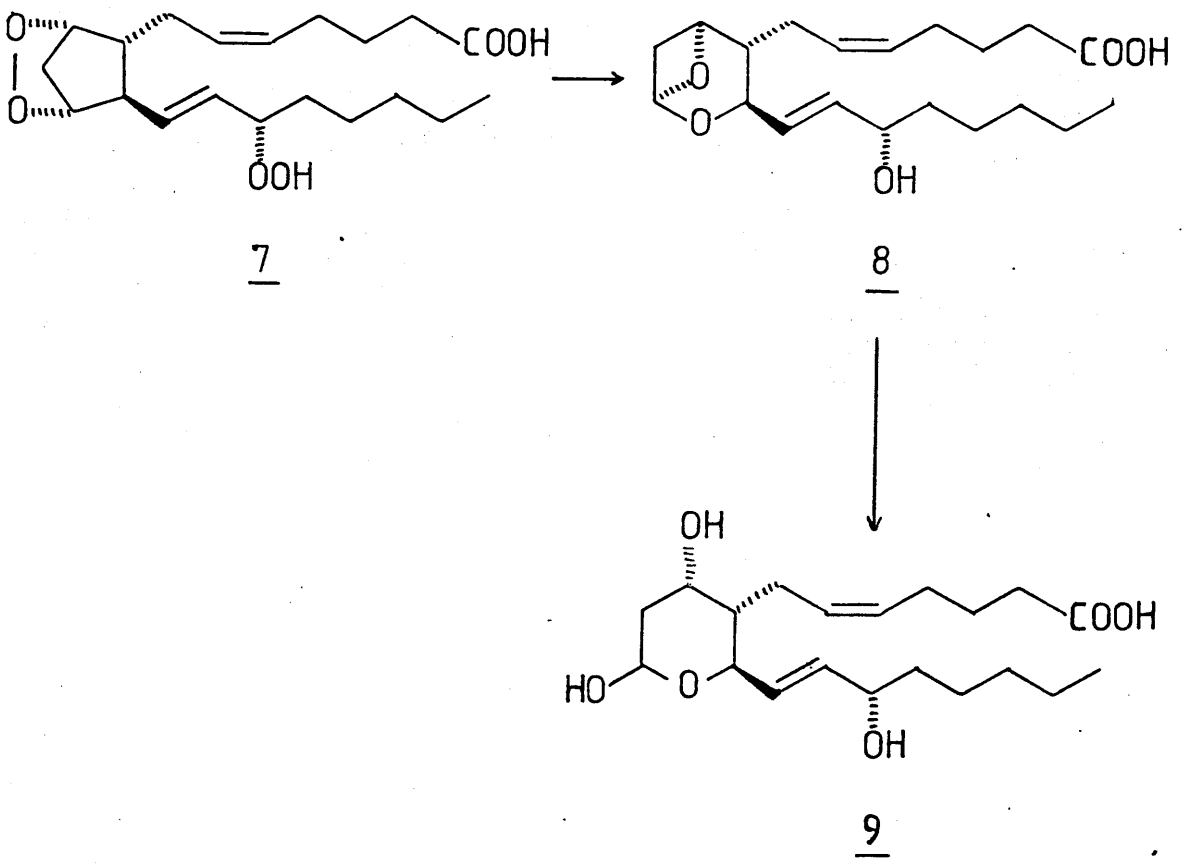
FIGURE 3


COOH
Arachidonic Acid
3
COOH
O
O
O—O
H
O
O
COOH
OOH
7
O
COOH
OH
OH
OH
COOH
OH
PGE2
PGF2α

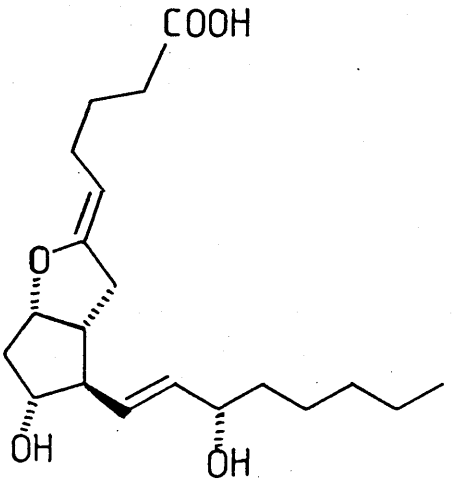
Incubation of PGG_2 (7) with human blood platelets was found to give the compound thromboxane B_2 (TXB_2) (9 Figure 4) as one of the major metabolites[14], but it was biologically inactive. Investigation of this process showed that the formation of TXB_2 9 proceeded via an exceedingly unstable and biologically potent molecule with a half life of only 32 seconds at physiological pH. This molecule called thromboxane A_2 (TXA_2), was assigned structure 8, which contained a strained bicyclic acetal, on the basis of trapping experiments[15] (Figure 4)

FIGURE 4



7 8 9

Then in 1976 yet another endoperoxide metabolite was isolated. Vane and coworkers[16] described an unstable, unidentified substance which they called PGX, formed by incubating PGG_2 with microsomes from rabbit or pig aorta. PGX unlike TXA_2 relaxes vascular smooth muscle. Its most remarkable property, however, is its potent ability to inhibit platelet aggregation[17] and even to bring about the reversal of platelet aggregation[18]. Collaboration between Vane's group and Upjohn's workers[19] resulted in the determination of the structure of PGX (10). It was renamed prostacyclin because of the additional ring it contained and given the alphabetical name of PGI_2. The properties of PGI_2 (10) will be discussed in more detail in Sections 1.4 and 1.5.



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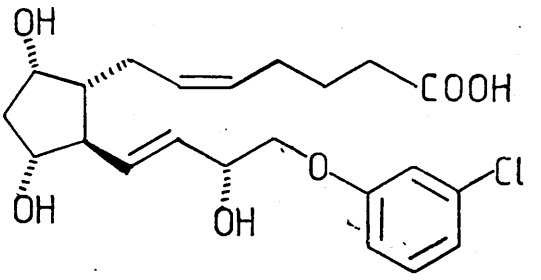
1.3 Biological Properties and Therapeutic Applications of Prostaglandins

The wide variety of physiological activities associated with prostaglandins offers potential therapeutic uses in many areas. These are summarised in Figure 5.

FIGURE 5 Potential Clinical utility of prostaglandins

System	Mode of action	Application
Reproductive	Stimulation of uterine muscle, luteolysis.	Induction of labour and termination of pregnancy. Menstrual regulation and control of oestrus cycle.
Respiratory	Relaxation of bronchial smooth muscle, bronchodilation.	Treatment of asthma and broncho-constriction.
Gastrointestinal	Inhibition of gastric acid secretion.	Treatment of peptic ulcers.
Cardiovascular Renal	Vasodilation, increased cardiac output, regulation of renal flow and sodium excretion.	Treatment of hypertension, shock, congestive heart failure and impaired renal function.
Platelets	Inhibition of platelet aggregation.	Treatment and prevention of thrombosis.

There are, however, drawbacks to the use of natural prostaglandins clinically. They lack selectivity due to their wide range of actions and so are prone to producing undesirable side effects. They also suffer from metabolic instability which makes their effective administration difficult. The only medical application to date is the use of PGE_2 (marketed by the Upjohn Company) for inducing labour and abortion. Hopes that synthetic analogues might be more selective have not been fulfilled. Synthetic prostaglandins have only been useful in veterinary medicine. I.C.I. for example produce chloroprostanol (11) as a luteolytic agent for farm animals.



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However there have been disappointingly few successful prostaglandin-based drugs despite an enormous amount of chemical, biological and pharmaceutical endeavour.

1.4 Potential Therapeutic Applications of Prostacyclin

The so called unstable arachidonic acid metabolites, the prostacyclins, thromboxanes and endoperoxides have similar but more potent biological activities than the prostaglandins themselves. In certain aspects, they are far more selective, notable examples being the cardiovascular effects of PGI_2 and TXA_2.

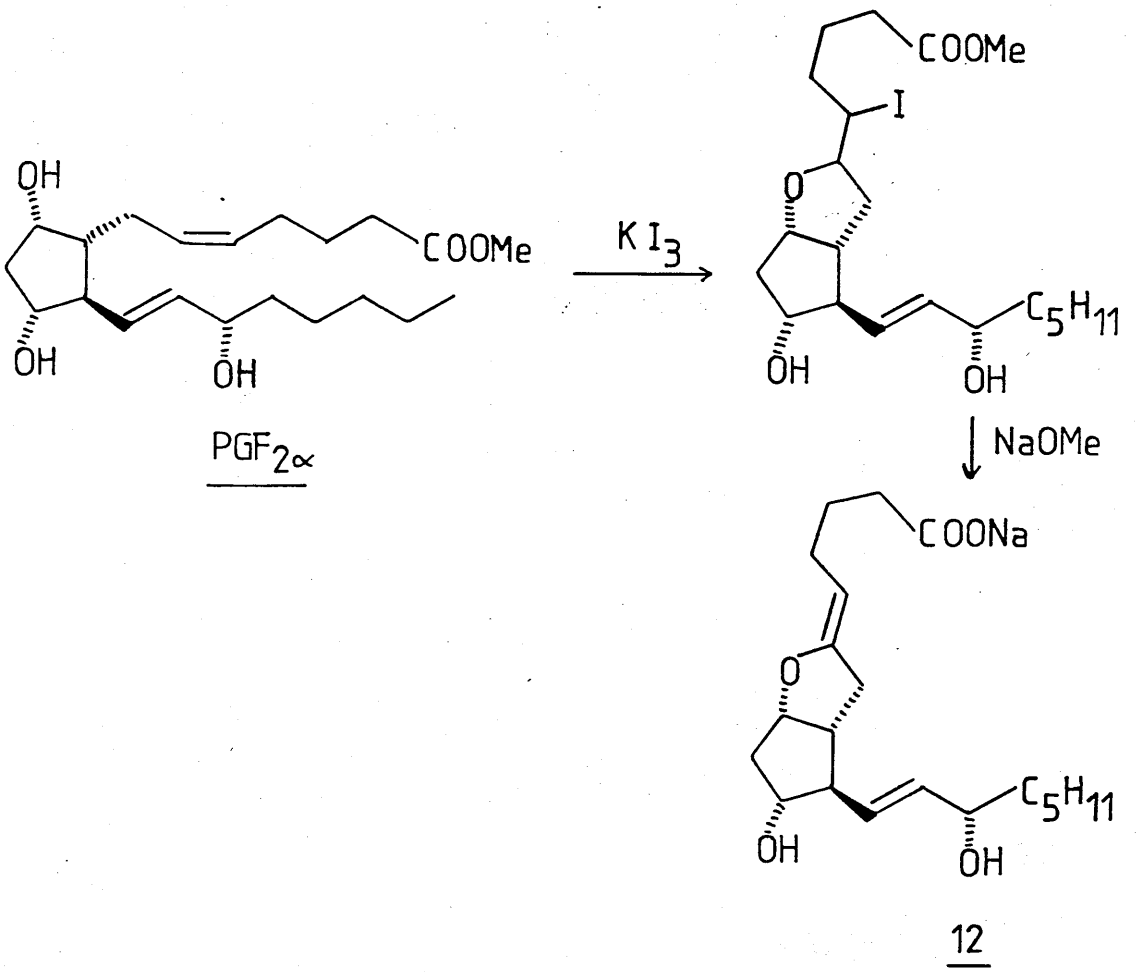
The biological role of PGI_2 and TXA_2, especially with respect to the blood clotting process, has been the subject of much speculation[20,21]. It is a possibility, that the intermediate endoperoxides, are converted by the platelets into potent vasoconstricting, platelet-aggregating TXA_2, whereas vessel walls convert the endoperoxides into potent vasodilating PGI_2 which inhibits platelet aggregation. The dynamic balance of these two substances may maintain blood vessel tone and platelet functionality and thereby be critical for thrombi formation.

The therapeutic potential for prostacyclin in the treatment of cardiovascular diseases is enormous. Thrombosis for example is the largest killer of young and middle-aged men in the Western World, and any agent which would prevent or reverse blood clot formation would be of great use.

Although prostacyclin can only be obtained in minute quantities by biological procedures, it can be prepared in large amounts (as its sodium salt 12) from $PGF_{2\alpha}$[22,26].

Figure 6 shows the shortest procedure, which was developed by Nicolaou[25] and Whittaker[26].

FIGURE 6



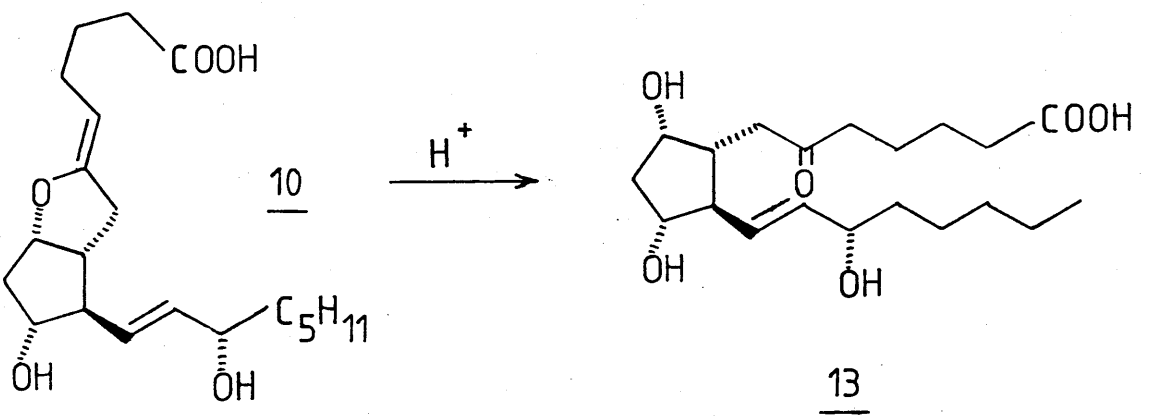
PGF2α

12

Unfortunately the very short half life of PGI_2 is almost certain to limit it's clinical uses. What is required is a stable synthetic analogue of PGI_2 having similar biological properties.

1.5 Prostacyclin Analogues

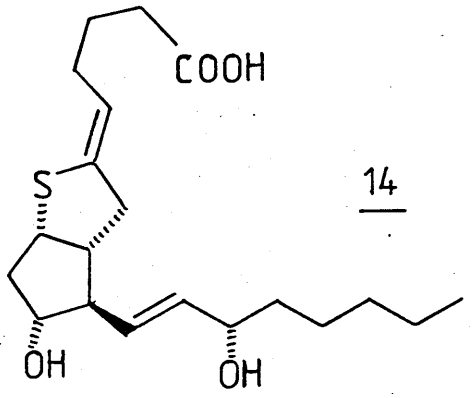
Prostacyclin (10) is rapidly converted to 6-keto $PGF_{2\alpha}$ (13) by hydrolysis of the enol ether grouping[27].



A large number of synthetic analogues have now been prepared and in general the strategy has been to confer stability by replacing the enol ether grouping in some way. The synthesis and biological activity of such analogues up to 1977 has been reviewed[21]. Notable synthetic analogues are 9-(O)-thiaprostacyclin (14) prepared from $PGF_{2\alpha}$,[28,29] 9-(O)-methanoprostacyclin (15) prepared by several groups using total syntheses[30], PGI_1 (16)[31] and the Δ^4 analogue (17)[32].

An alternative approach involved the formation of ring expanded analogues such as (18) in which ring strain was reduced[33].

Several of these analogues mimick the activity of PGI_2[21].



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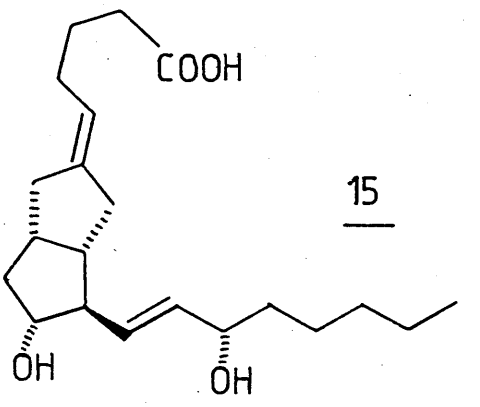

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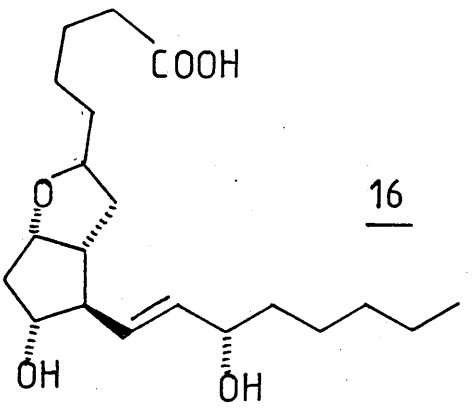

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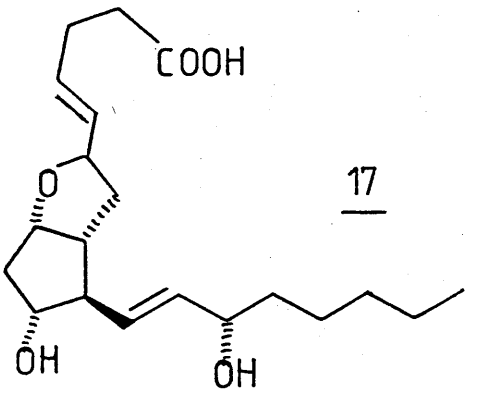

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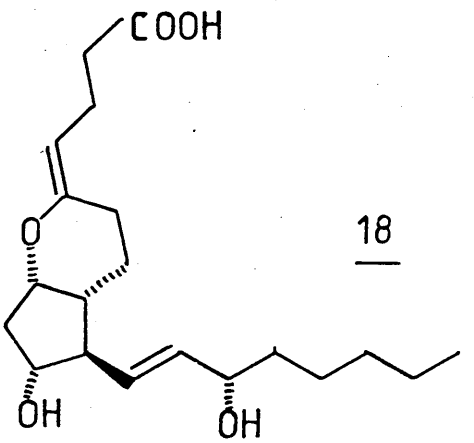

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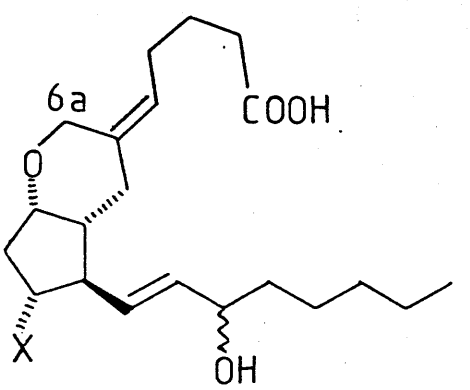
Chapter 2 SYNTHETIC AIMS AND STRATEGY

2.1 The Target Molecule

As discussed in Chapter 1, a variety of stable PGI_2 analogues have been prepared. The aim of this project was to synthesise the homoprostacyclin analogues 1.



1 — a X = H
b X = OH

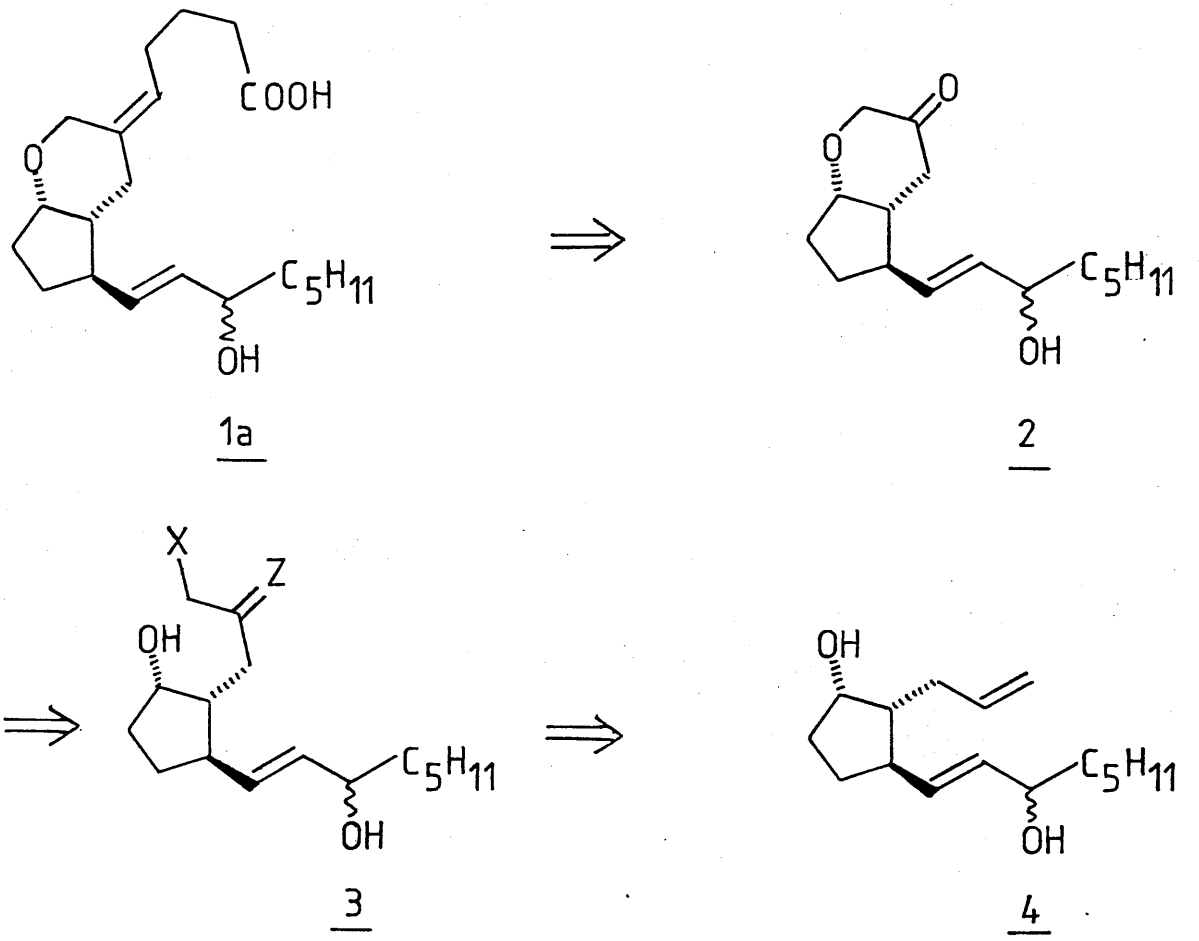
The enol ether grouping which is responsible for the hydrolytic instability of PGI_2 is not present in 1 by virtue of the additional methylene group (labelled 6a above).

11-Deoxyprostaglandins possess many of the biological properties of the natural compounds and they are usually more synthetically accessible. In view of this 11-deoxyhomoprostacyclin (1a) was adopted as the primary synthetic target. Any synthetic route developed for the synthesis of 1a should also be suitable for the synthesis of 1b.

2.2 The Synthetic Approach

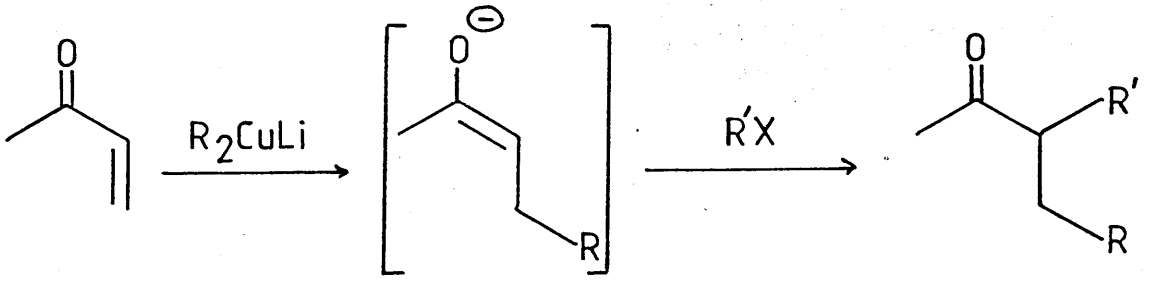
A wide variety of synthetic approaches have been used for the preparation of natural and synthetic prostaglandins[34]. A retro-synthetic analysis of 1a produced several possible synthetic approaches, but the most appealing was the one shown in Figure 1

FIGURE 1



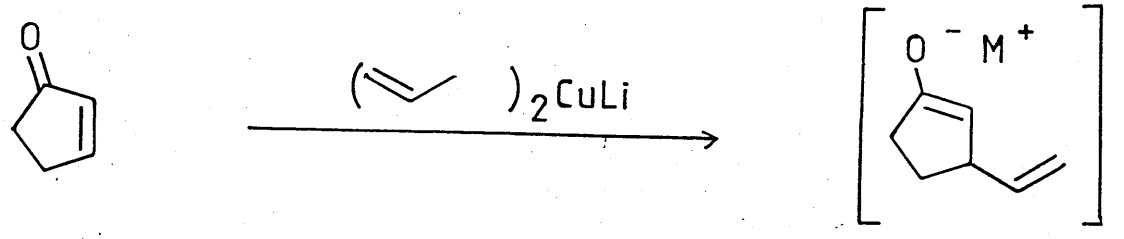
The use of the Wittig reaction to introduce the carboxybutyl portion of the α side chain has ample precedent[34]. A variety of approaches are possible for the synthesis of 2, but the cyclisation of a precursor such as 3 would seem likely to succeed. A variety of compounds with general structure 3 should be available from alkene 4 which in turn should be easily formed from ketone 5.

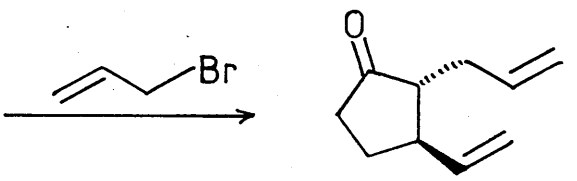
This synthetic approach has two major advantages. Compound 5 could also serve as a precursor to a variety of other 11-deoxyhomoprostaglandin analogues, and in addition a convergent synthesis of 5 should be available. A good deal of research has been carried out to devise conditions for converting α,β-unsaturated ketones to 2,3-disubstituted ketones. The most versatile approach uses the conjugate addition of organocuprates followed by alkylation of the intermediate enolate[35,38].



This approach has been used to elaborate cyclohexenone [36,37] and although the yields are often less satisfactory it can be applied to cyclopentenones if sufficiently reactive alkylating agents are employed[37,38]. For example

Posner and his coworkers prepared the 2,3-disubstituted cyclopentanone 6 in this manner[37].

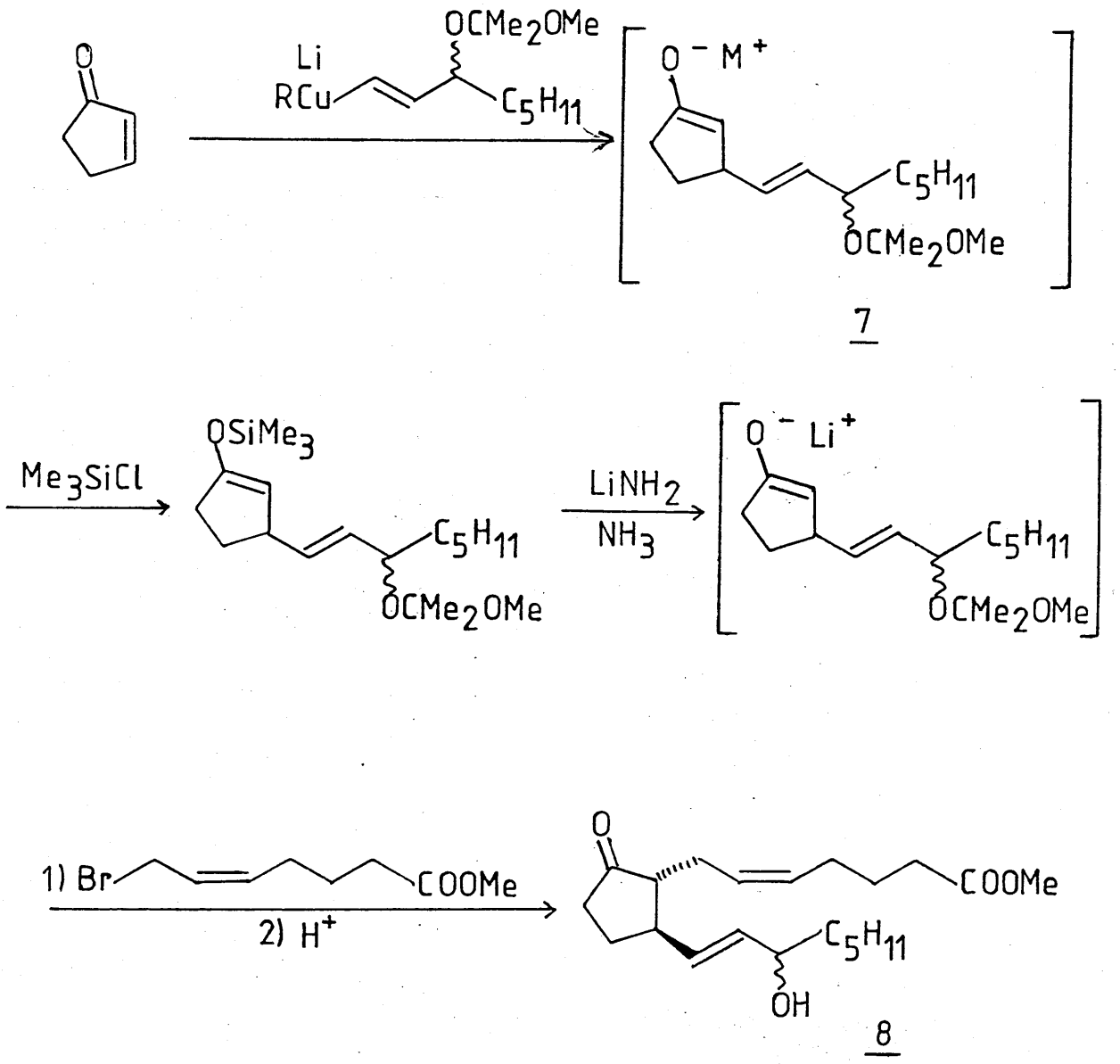




6

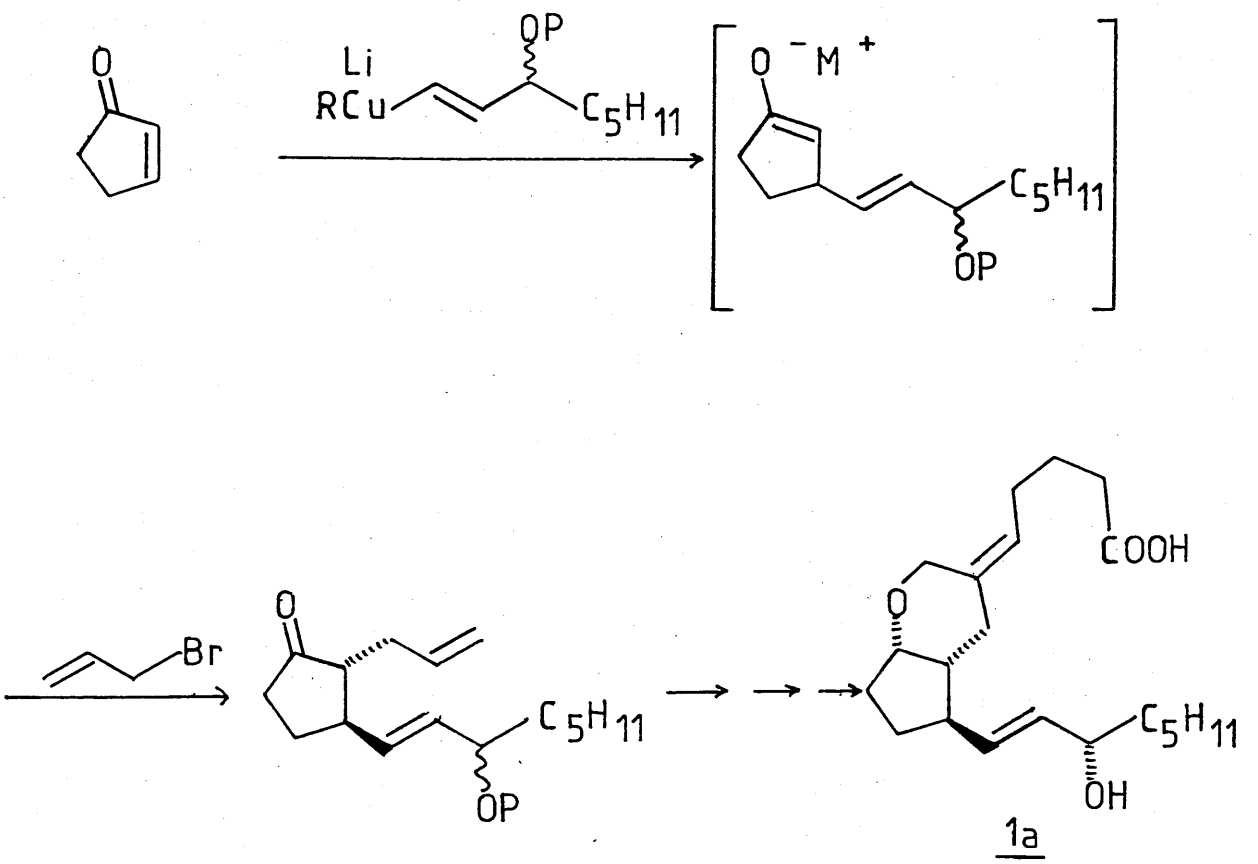
An elegant two step procedure for carrying out this type of reaction was developed by Patterson and Fried for the synthesis of 11-deoxy prostaglandins[39] 8 (Figure 2). This procedure was introduced when the direct alkylation of enolate 7 failed to give 8. Alkylation of silyl enol ethers derived from cyclohexenones has also been described[40].

FIGURE 2



Using this methodology a convenient one step procedure for the preparation of the 11-deoxyhomoprostacyclin precursor 5 from commercially available cyclopent-2-enone would be as shown in Figure 3

FIGURE 3



1a

An additional advantage of this convergent approach is that other alkylating agents could be employed in the enolate trapping step if the approach shown in Figure 1 proved unsuccessful.

2.3 The Synthetic Aims

The prime aim of this project is to devise a synthetic route for the preparation of 11-deoxyhomoprostacyclin (1a). The immediate synthetic objective can be summarised as follows;

1) To investigate the use of the organocuprate conjugate addition-enolate alkylation reaction for the synthesis of 5 and related compounds (Figure 3)

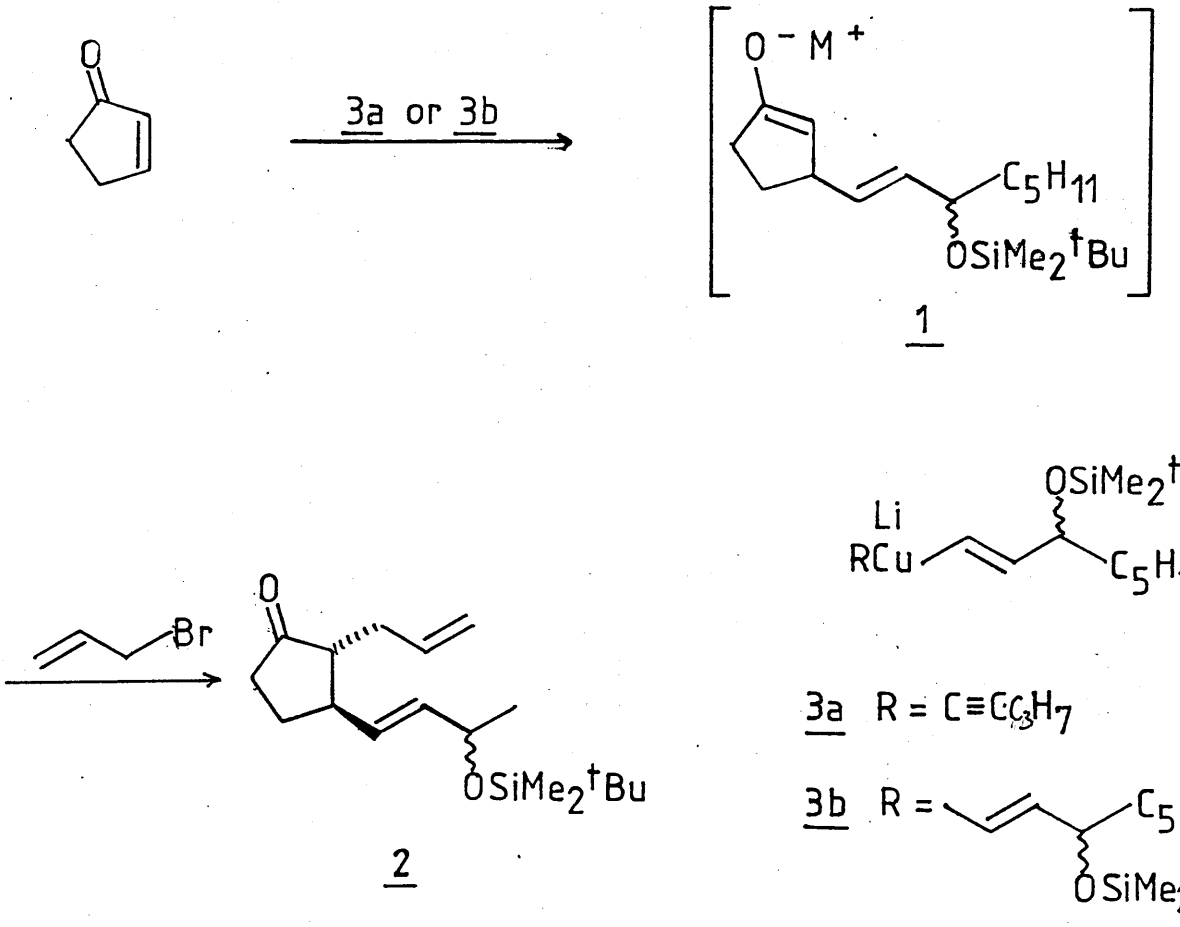
2) To examine methods for transforming 5 into 11-deoxyhomoprostacyclin.

Chapter 3 Results and Discussion

3.1 Conjugate addition-allyl bromide alkylation approach

The initial synthetic objective was to prepare the allyl cyclopentanone 2. The 'one-pot' organocuprate conjugate addition-alkylation procedure shown in figure 1 was investigated first.

FIGURE 1

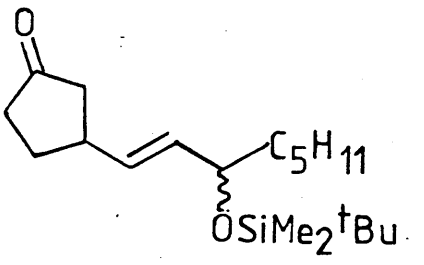


This highly convergent approach to the synthesis of 2 had the added advantage of readily available starting materials: cyclopent-2-enone is commercially available and cuprates 3a and 3b can be prepared by

literature procedures[41]

The basic dilemma of the 'one-pot' reaction is that the organocuprate conjugate additions proceed best in non-polar solvents such as diethyl ether[42,43], whereas the alkylation step usually requires more polar solvents such as THF or DME containing DMF, TMEDA or HMPA[35].

These generalisations were confirmed by initial studies using ether or THF as sole reaction solvent and following the reaction by t.l.c. Cyclopent-2-enone was clearly transformed to the corresponding enolate 1 (as evidenced by the t.l.c. identification of the corresponding ketone 4), but little or no alkylation of the enolate 1 was observed at a variety of temperatures on addition of allyl bromide, the major product being the unalkylated ketone 4. When the reaction was carried out in THF the conjugate addition step proceeded less well, but addition of allyl bromide did lead to a small amount of alkylated product.



4

In view of these initial results, the method of approach adopted was to carry out the conjugate addition reaction in diethyl ether and to subsequently modify the solvent system by the addition of one or more polar cosolvents just prior to alkylation. The results of these studies are summarised in table 1

TABLE 1

	conjugate addition solvent	alkylation solvent mixture	conjugate addition	alkylation
1	THF	THF	poor	poor
2	Ether	Ether	v.good	none
3[a]	THF	THF/HMPA/TMED	poor	poor
4[a,b]	Ether	Ether/HMPA/THF	v.good	fair
5	Ether	Ether/DME	v.good	none
6[a]	Ether	Ether/DME/HMPA	"	none
7[a,b]	Ether	Ether/HMPA	"	poor
8	Ether	Ether/DMF	"	poor

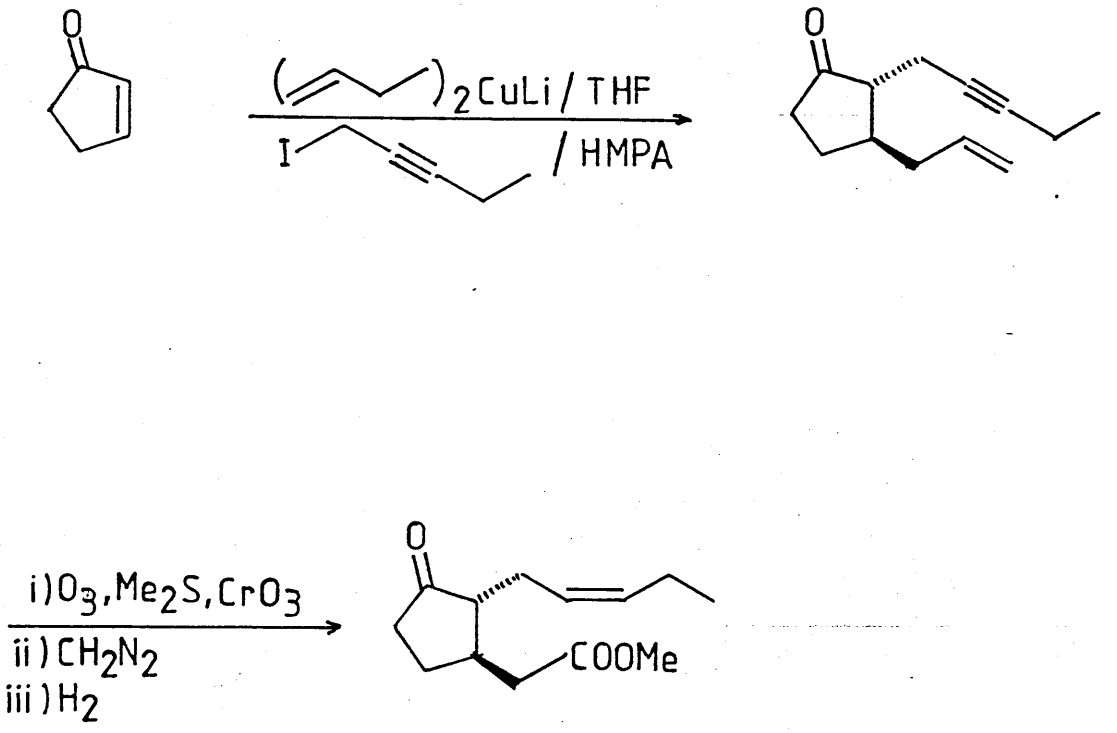
a) HMPA invariably froze at the reaction temperature to give a slush

b) several alkylated and polyalkylated products were observed

None of these results were very promising and although in some cases the desired product was present, the yields were invariably very low.

Homocuprates such as 3b, are inherently more reactive than mixed cuprates and have been used successfully in conjugate addition-alkylation reactions. For example methyl jasmonate has recently been prepared using this approach[3,8] as shown in figure 2.

FIGURE 2



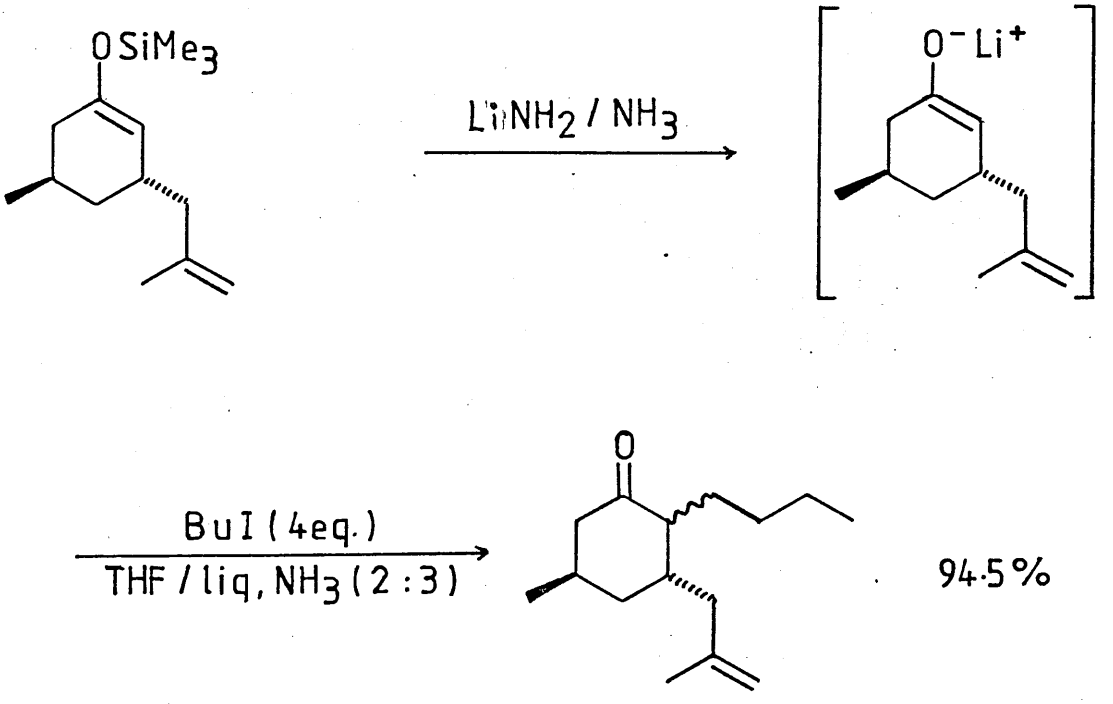
One drawback in the use of homocuprates (R_2CuLi) is that only one of the R groups is transferred and this is particularly wasteful if the group needs to be synthesised. In spite of this the reaction in figure 1 was carried out using the homocuprate 3b in THF and HMPA/TMED were added

with the alkylating agent. Unfortunately none of the desired product 2 was observed in this reaction and subsequent work utilised only the mixed cuprate 3a.

Having used all the solvent systems recommended for organocuprate-generated enolate alkylation,[35,37,39,43] new combinations were investigated.

Cyclohexanone lithium enolates, generated from the corresponding silyl enol ethers, are reported to be alkylated in fair to good yields in liquid ammonia-THF solvent systems[40] as shown in figure 3.

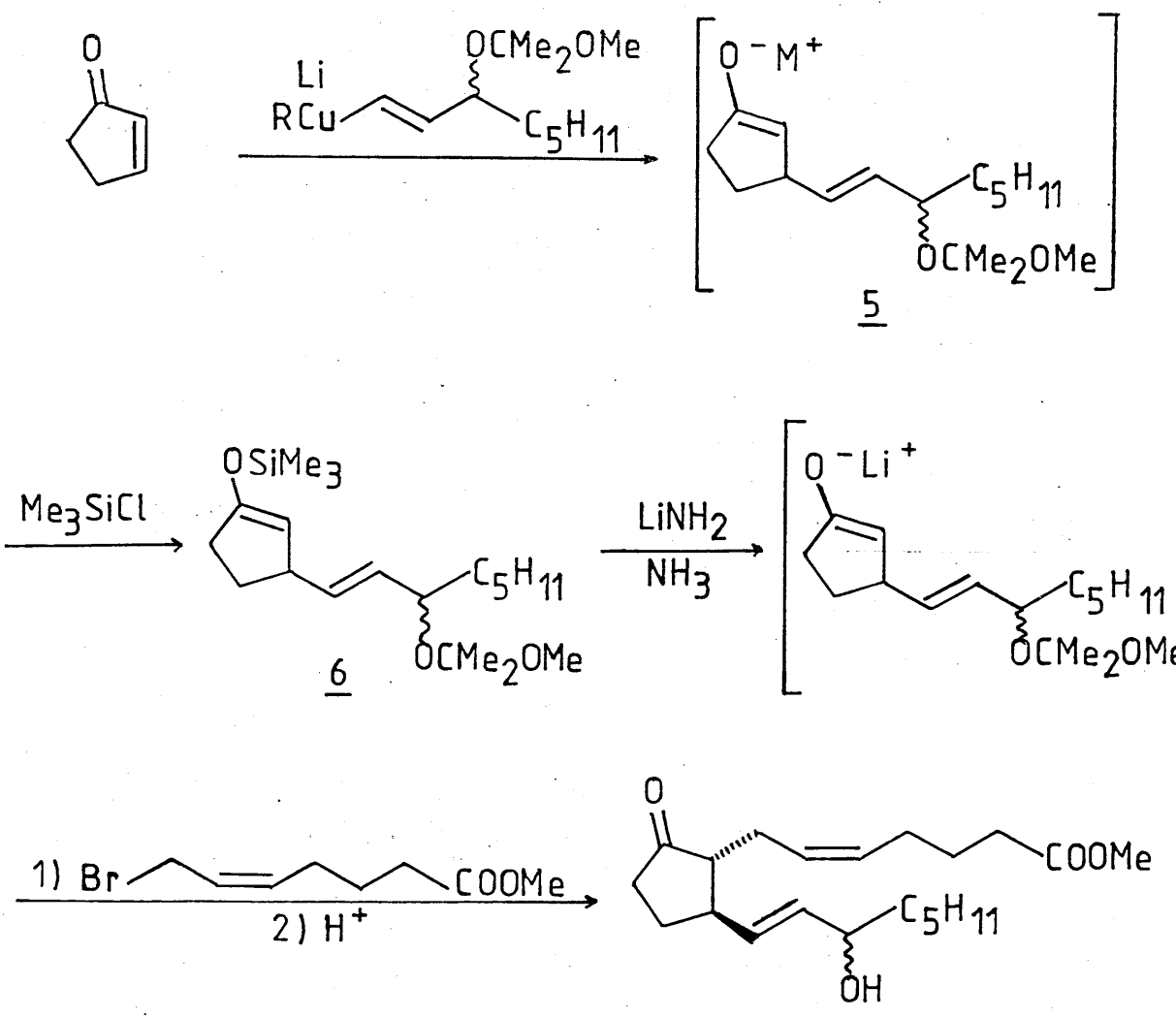
FIGURE 3



This observation led us to try liquid ammonia as an alkylation cosolvent in the 'one-pot' reaction. Thus the conjugate addition, using the mixed organocuprate 3a, was carried out in diethyl ether and then dry liquid ammonia was added just prior to addition of the allyl bromide. This system gave the allyl ketone 2 in far better yield than the procedures in table 1. However, extensive investigation resulted in a maximum yield of only 24% after chromatography, based on cuprate 3a.

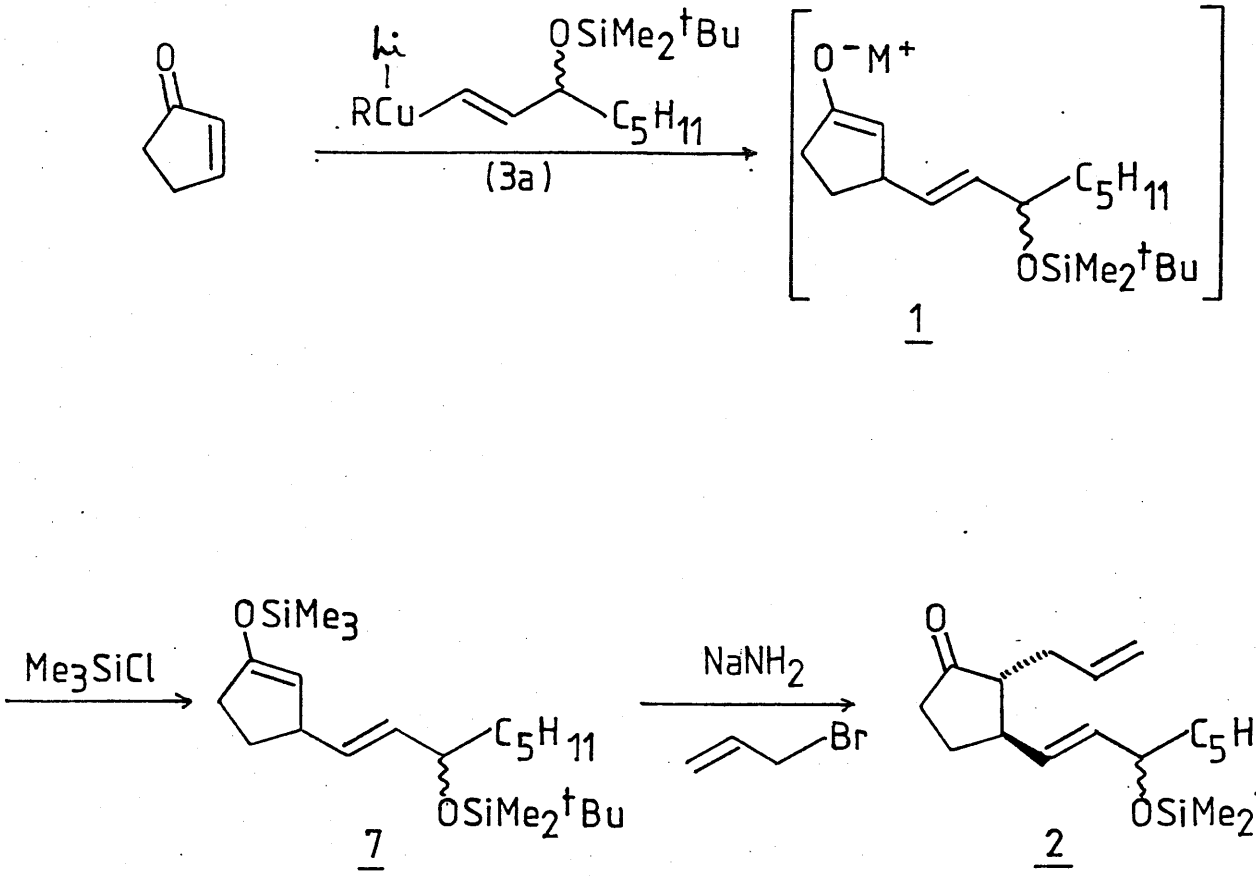
Difficulties have been encountered in alkylating cyclopentanone enolates during prostaglandin syntheses before[39,44]. Patterson and Fried overcame this problem during a synthesis of 11-deoxyprostaglandins by trapping the organocuprate-generated enolate(5) as its trimethylsilyl ether(6) and then regenerating and alkylating as shown in figure 4.

FIGURE 4



This procedure was applied to the synthesis of the allyl cyclopentanone 2 (figure 5). The silyl enol ether 7 could be purified by distillation although it was normally used directly.

FIGURE 5

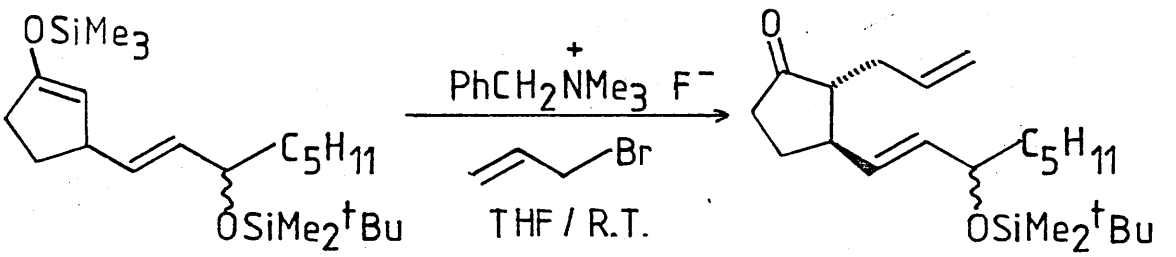


The silyl-trapping procedure gave the disubstituted cyclopentanone 2 in approximately 25% yield after chromatography. The 'one-pot' procedure was judged to be the preferred method of preparing 2 since the yields of both methods are similar but the silyl-trapping procedure is more expensive and time consuming.

However an improved procedure for preparing 2 was still required and several alternatives were investigated. Kuwajima has shown that quaternary ammonium enolates are more reactive than the corresponding lithium enolates

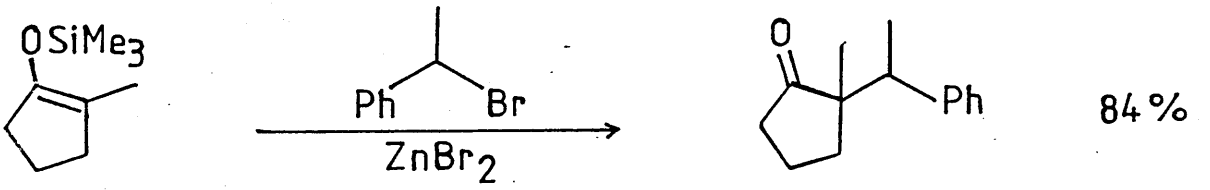
and they are easily prepared by treating silyl enol ethers with ammonium fluorides[45]. Since silyl enol ether 7 was readily available, we carried out the reaction shown in figure 6.

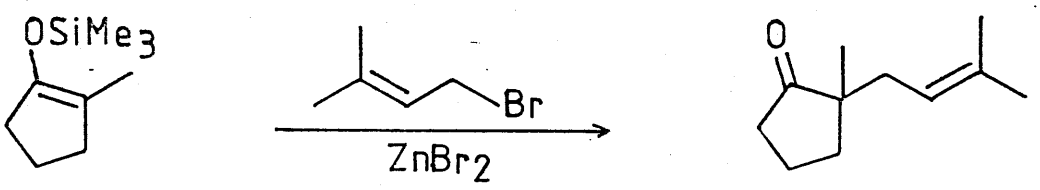
FIGURE 6



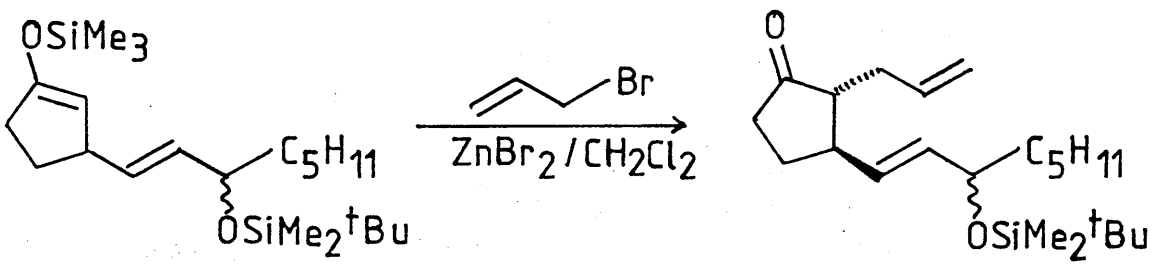
This reaction did not produce allylic ketone 2. The enolate 1 was apparently formed but alkylation did not occur under the reaction conditions employed, the only product being the unalkylated ketone 4.

Patterson and Fleming have shown that silyl enol ethers can be directly alkylated with reactive halides in the presence of a Lewis acid catalyst[46,47], eg,



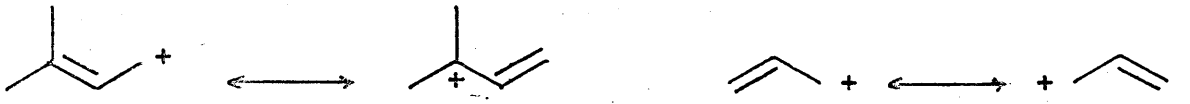


This procedure was applied to the preparation of allyl ketone 2:

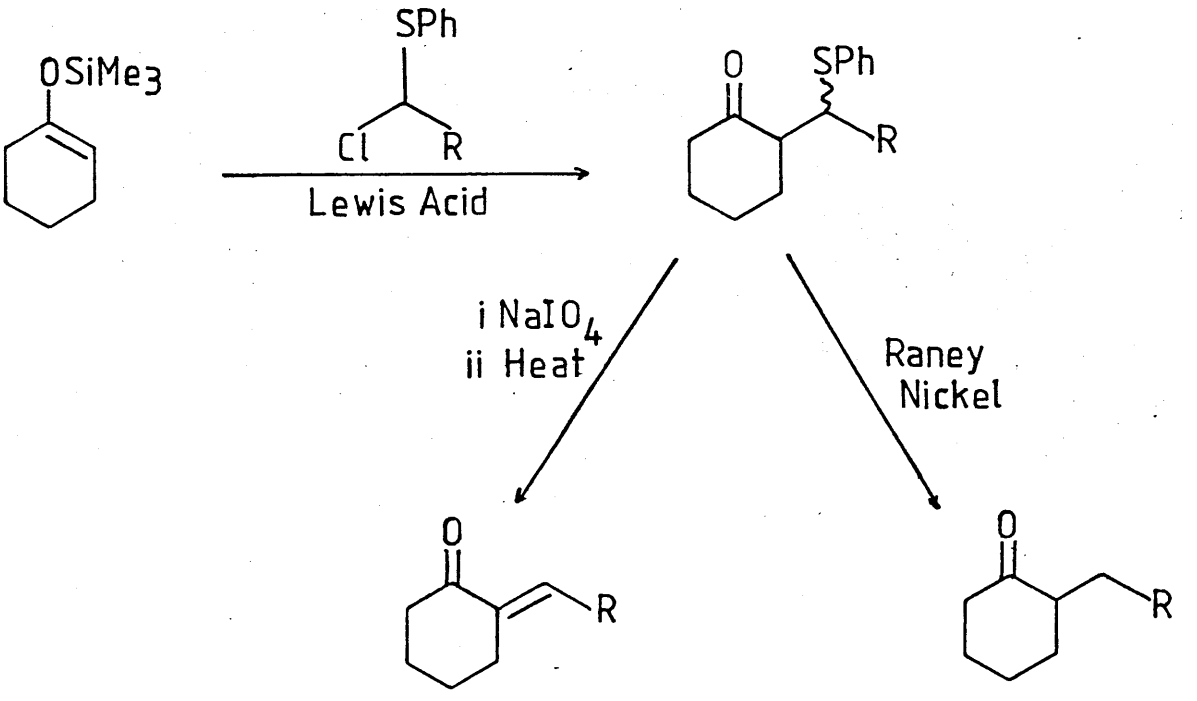


2

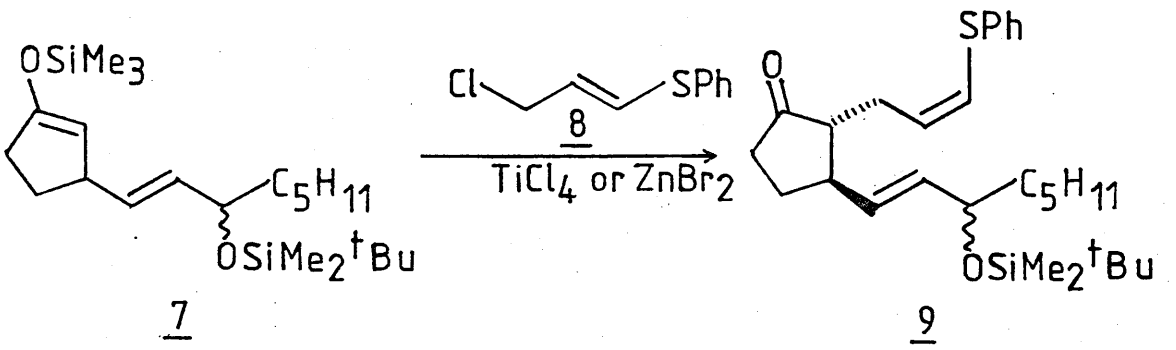
This reaction was not successful, only the unalkylated ketone 4 being recovered. Presumably allyl bromide, in contrast to dimethylallyl bromide for example, does not form a sufficiently stable carbonium ion in the presence of the Lewis acid to promote the alkylation reaction.



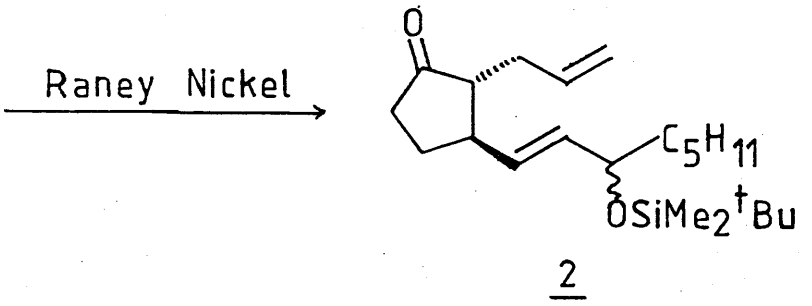
Later work by Patterson and Fleming[47] involved the Lewis acid catalysed alkylation of silyl enol ethers using phenylthio-stabilised alkylating agents. The alkylated products were converted to alkenes by oxidative elimination or alternatively the phenylthio-group was removed using Raney Nickel:



This procedure seemed suitable for application to our system as shown in the scheme outlined below:



7 9



2

The alkylating reagent 8 was prepared in two steps from allyl bromide using literature procedures[48]. Initial experiments, however, were not promising and this investigation was abandoned. Further work at the University of East Anglia[49] showed that the alkylation reaction proceeded in fair yield but the Raney-Nickel desulphurisation gave low yields for the conversion of 9 to 2.

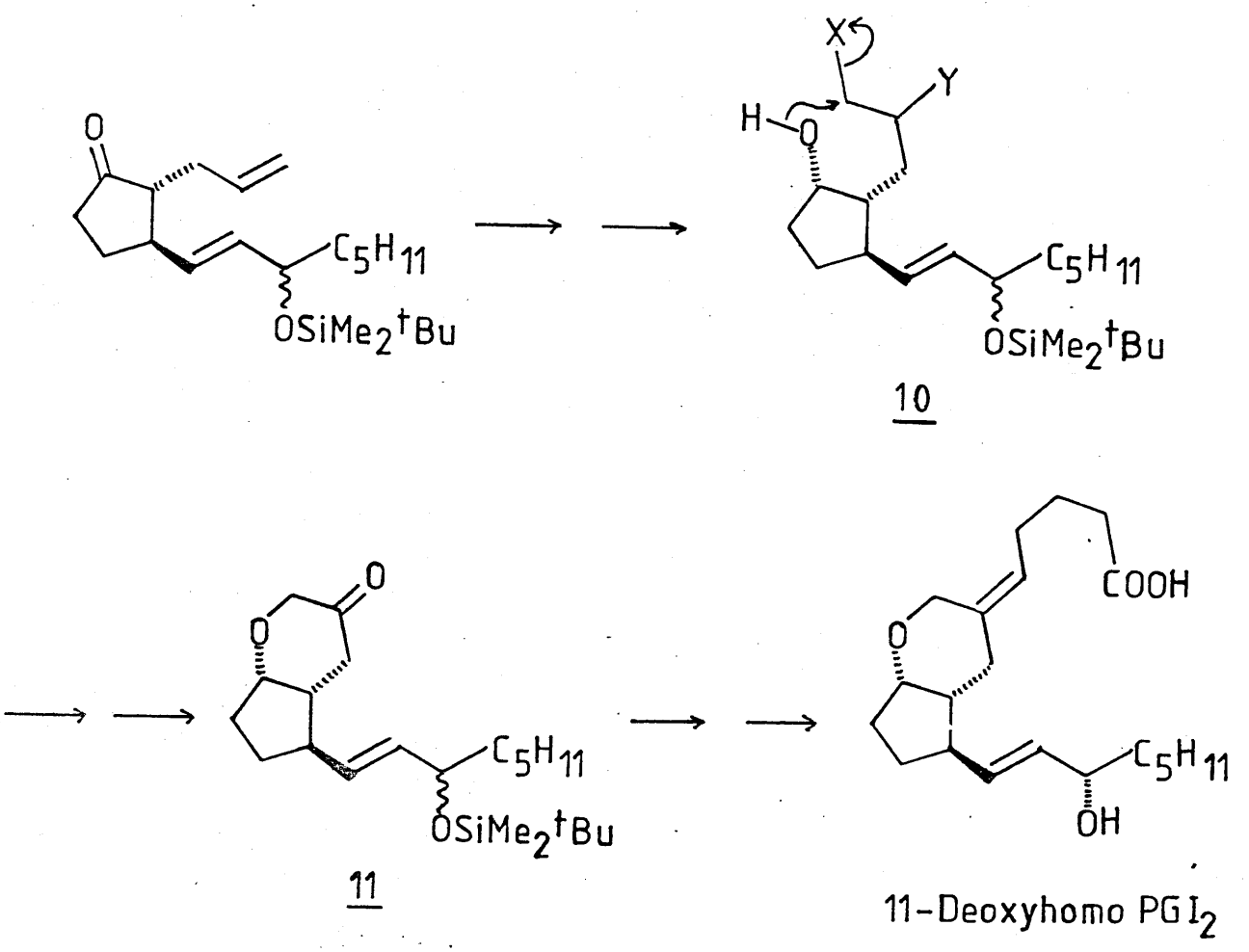
Alternative syntheses of the allyl ketone 2 (see Chapter 4) were not explored and the 'one-pot' procedure

was used throughout this investigation.

The *trans*-relationship between the substituents in 2 was assumed on the basis of related studies[37-39,50] and this assumption was borne out by subsequent transformations.

Having succeeded in our initial aim we next had to selectively functionalise the α side-chain double bond with a view to further elaboration towards preparing 11-deoxyhomoprostacyclin (figure 7)

FIGURE 7

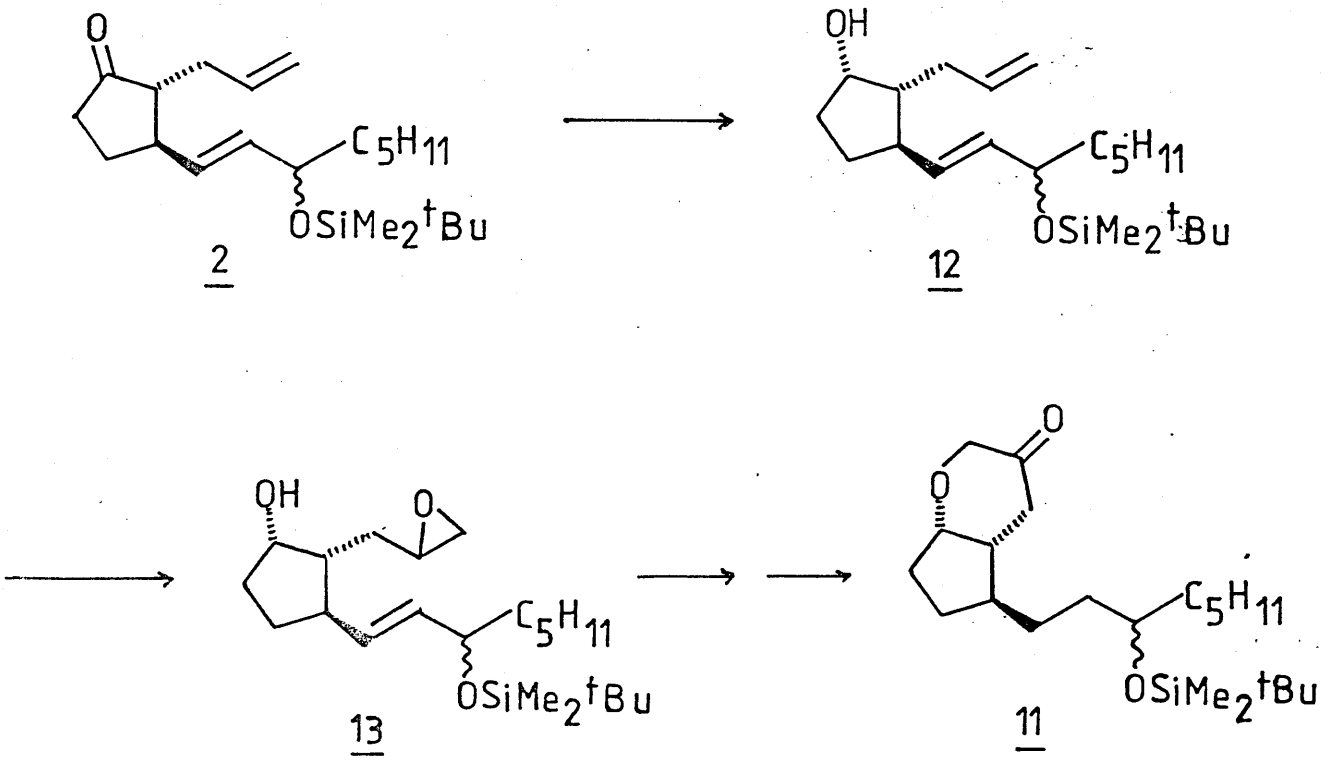


It was considered that a molecule of the type 10 (figure 7) with a leaving group (x) and an oxygen function or precursor to an oxygen-function (y) was needed to synthesise the key bicyclic intermediate 11. However, the first attempts at devising such a procedure led to a novel synthesis of 11-deoxyprostaglandins, as described in the next section.

3.1.1 Elaboration by Epoxidation; 11-deoxyprostaglandins

The first strategy employed for the conversion of the allyl ketone 2 to 11-deoxyhomoprostacyclin is outlined in figure 8. Regioselective epoxidation of the α side-chain double bond was required and it seemed likely that a 9-hydroxy group (prostaglandin numbering) might facilitate this reaction.

FIGURE 8

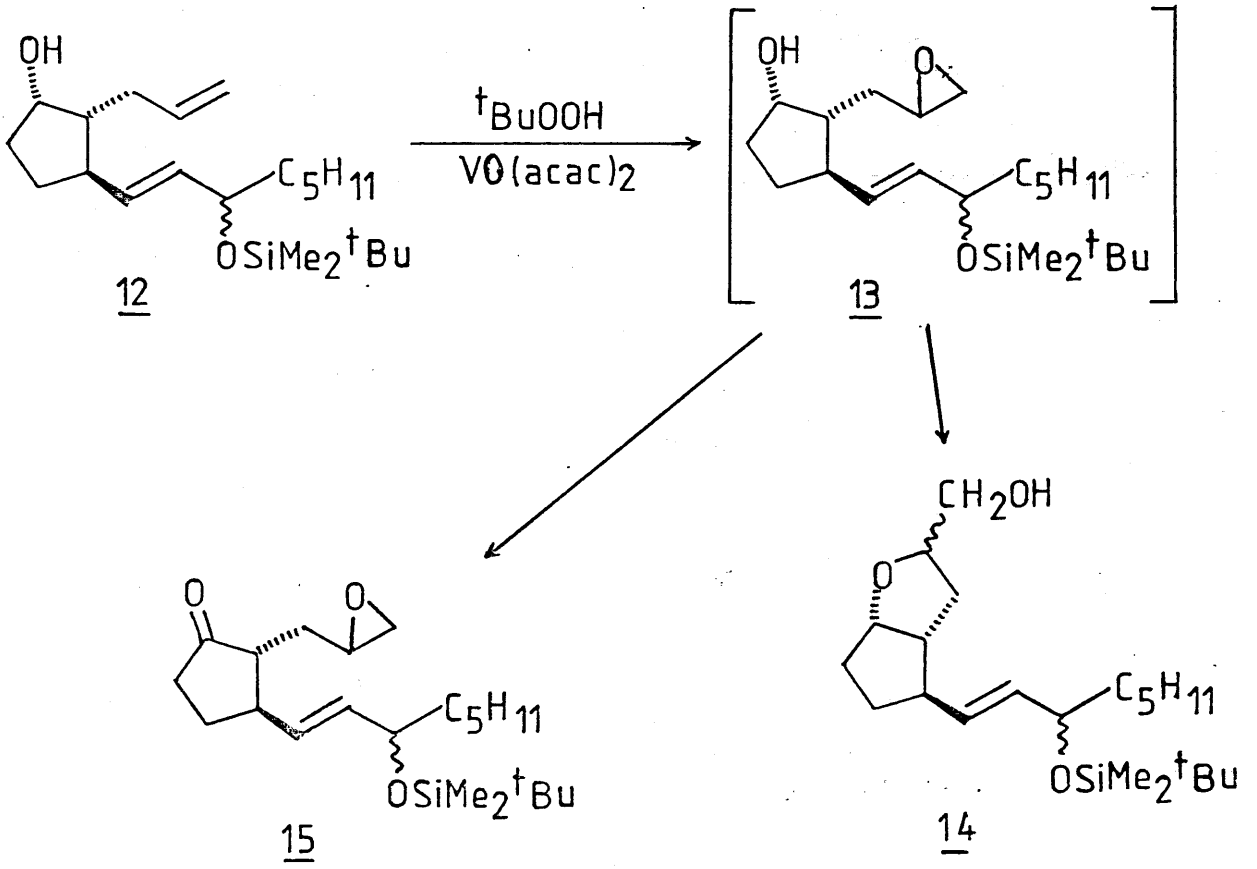


The ketone 2 was stereoselectively reduced in 92% yield to give the α-alcohol 12 using potassium tri(sec-butyl)borohydride. Reduction with sodium borohydride led to a mixture of two epimeric alcohols, thus confirming the stereospecificity of the bulky hydride reducing agent. There is ample precedent for this stereospecificity; hindered borohydride reducing agents have been employed for the stereoselective reduction of PGE_2 to $PGF_{2\alpha}$[51]. The principle involved is that the approach of the bulky reagent and hence the direction of attack by the hydride ion is constrained to the least hindered (β) face of the molecule.

Regioselective epoxidation of the α side-chain double bond was first attempted using m-chloroperbenzoic acid, but surprisingly, under a variety of conditions including: -78^{o} through to reflux in dichloromethane, (a radical inhibitor was required when reflux conditions were employed[52]), and dichloromethane-aqueous sodium bicarbonate biphasic systems,[53] this reagent did not display the necessary regioselectivity, with reaction also occurring at the β side-chain double bond. Although m-chloroperbenzoic acid has been used successfully to selectively epoxidise the α side-chain double bond in prostaglandins[54], the α side-chain double bond in alcohol 12 is only monosubstituted and therefore less nucleophilic.

An alternative epoxidation method developed by Sharpless and Michaelson is reported to proceed readily with allylic and homoallylic alcohols[55-57]. After a good deal of experimentation, this procedure using t-butylhydroperoxide was successfully used. Initially, the conditions for this reaction were a two-fold excess of t-butylhydroperoxide in refluxing toluene with vanadyl acetylacetonate as catalyst. These conditions gave complete conversion of starting materials to a relatively stable intermediate in less than 1h, This intermediate then slowly converted to more polar products. N.m.r. data on these products showed reaction had occured at the correct double bond, but was not consistent with an epoxide and the products were eventually identified as bicyclic alcohols 14 (Figure 9).

FIGURE 9

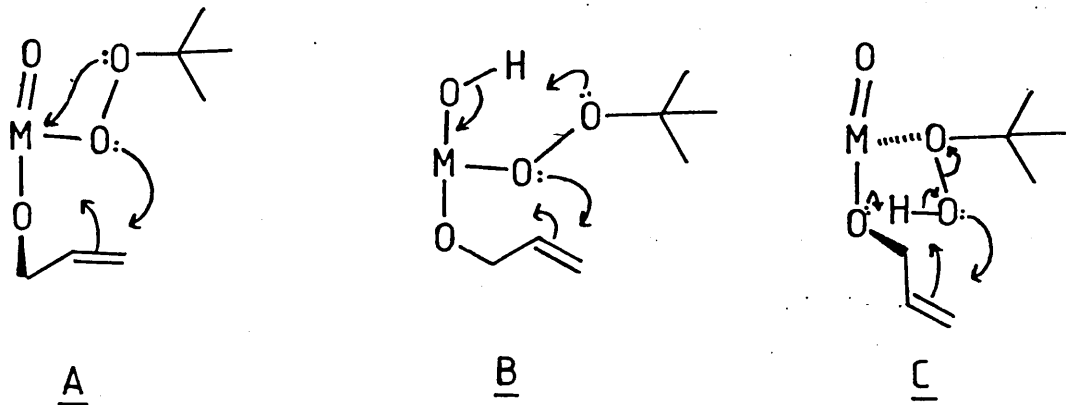


This would suggest that the relatively stable intermediate was the hydroxyepoxide 13. Evidence for this was obtained by the isolation from the reaction mixture of the ketoepoxide 15 formed from 13 presumably by over-oxidation. Addition of acid to a reaction mixture containing this intermediate appeared to catalysethe conversion of 13 to the products 14. In order to minimise the over-oxidation of 13 to the ketoepoxide 15, the conditions of the reaction were changed to stirring at ambient temperature, with one crystal of toluene-4-sulphonic acid present. The reaction under these new conditions, although much cleaner, was very slow (approx. 7 days).

The increase in rate and regioselectivity of epoxidation noted in allylic and homoallylic alcohols compared with normal olefins[55] would suggest a mechanism where the alcohol is coordinated to the metal-peroxide complex, with delivery of the reagent to the specific site. Several possible transition states have been suggested by Sharpless et al[56] (Figure 10).

FIGURE 10

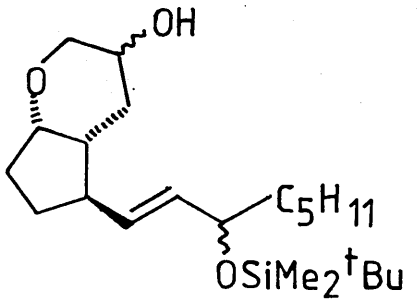
Proposed mechanisms for transition metal catalysed epoxidation of allylic alcohols[56]



A B C

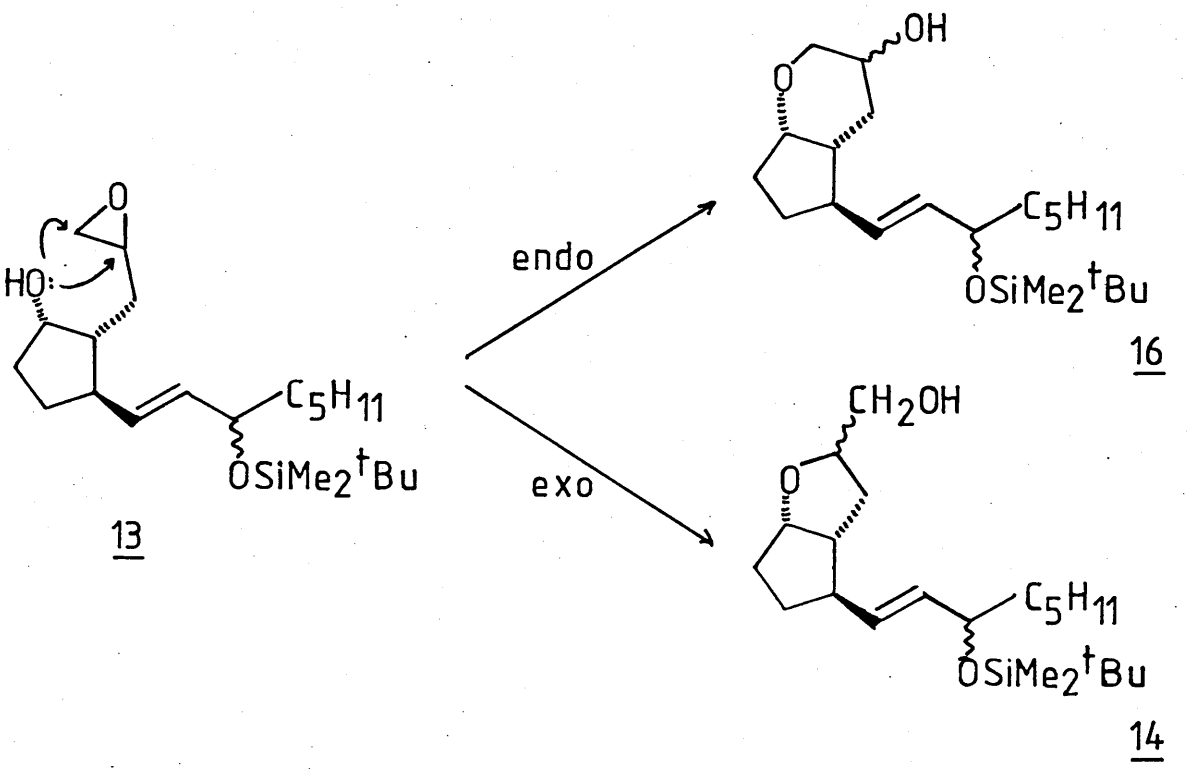
Although the required epoxidation site in 12 is bishomoallylic to an alcohol group it has been reported that even these systems with a relatively remote hydroxy-group are epoxidised ten times faster than purely hydrocarbon systems[55], and is probably the reason for the regioselectivity observed in the conversion of 12 to 14.

The exclusive cyclisation of hydroxyepoxide 13 to the tetrahydrofuranyl alcohols 14 rather than the tetrahydropyranyl alcohols 16 is in accord with the guidelines presented by Baldwin[58], and also some precedent in the literature[59].



16

Baldwin states that "The rules for opening three membered rings to form cyclic structures, seem to lie between those for tetrahedral(tet) and trigonal(trig) systems, generally preferring *exo* modes". The cyclisation of hydroxyepoxide 13 to alcohols 14 follows this generalisation as it proceeds by *exo* ring opening;



13

16

14

More specifically Baldwins Rules state that; 5-*Exo*-*Tet* and 5-*Exo*-*Trig* are favoured, 6-*Exo*-*Tet* is disfavoured, 6-*Endo*-*Tet* is favoured.

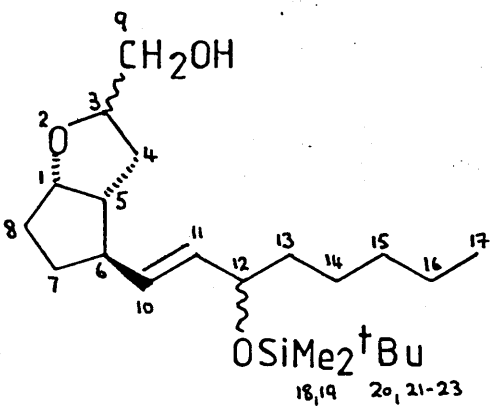
As the rules for epoxides are claimed to lie between those for tetrahedral and trigonal systems it is not surprising that cyclisation to give a five-membered ring is observed.

An n.m.r. analysis[60] confirmed that the cyclisation products were the tetrahydrofuranyl alcohols 14. Comparison of ^1H and ^{13}C n.m.r. spectra of 14a and 14b with model compounds 17a and 17b showed marked

similarities (Table 2).

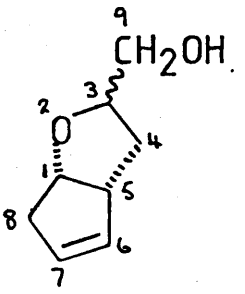
TABLE 2

Critical ^{1}H and ^{13}C chemical shifts (ppm from Me_4Si) for 14a,b and 17a,b



14 a) α-CH_2OH b) β-CH_2OH

17



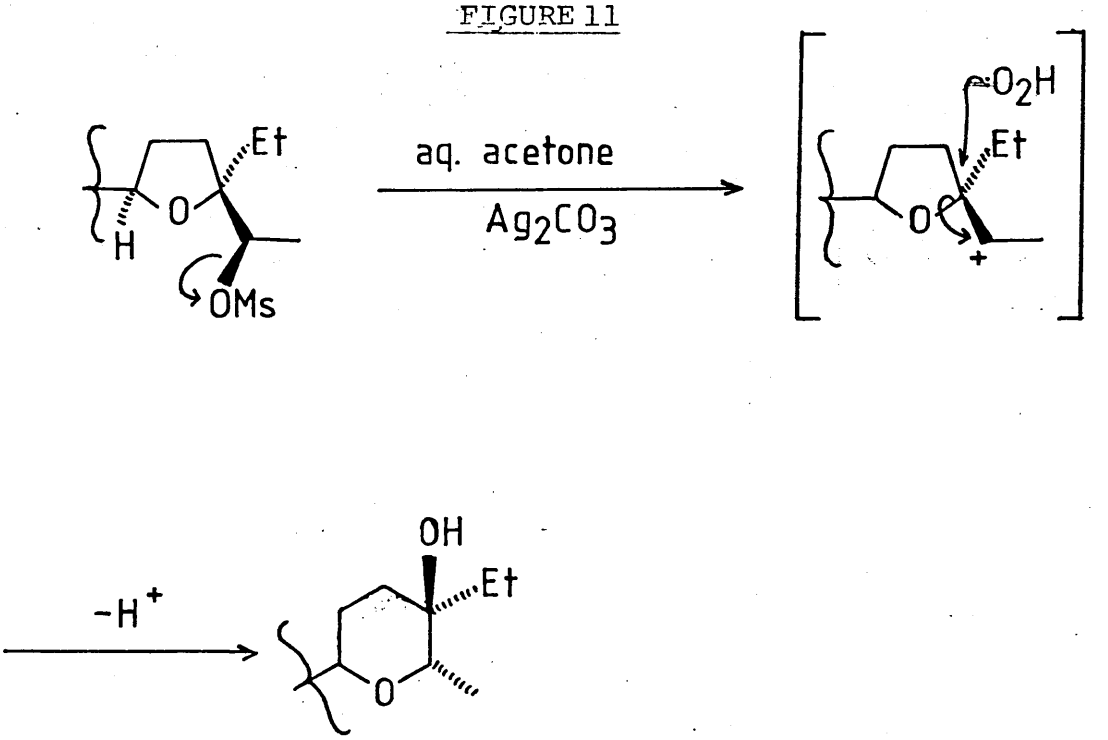
	C-1	C-3	C-9	H-1	H-3
14a	85.4	81.4	64.3	4.45	3.95
14b	84.6	78.9	64.2	4.57	4.15
17a	82.3	80.3	64.3	4.58	-
17b	81.3	78.7	63.6	4.75	-

The hydroxymethylene carbons (C-9) in 14a and 14b have very similar ^{13}C chemical shifts to the hydroxymethylene carbons in 17a and 17b and these values are typical of hydroxymethylene carbons in related carbohydrates (eg β-D-ribofuranose 62.9 ppm[61]). The signal for the methylene carbon next to oxygen in tetrahydropyranols (16) would be expected to be at significantly lower field; the α-carbon in tetrahydropyran is at 69.5 ppm[62] and a β-hydroxy group normally causes a downfield shift of 5-12 ppm[63].

The assignment of α and β stereochemistry to the diastereomeric alcohols 14 was also possible from the n.m.r. data in table 2. In related 2-oxabicyclo-octanes the chemical shifts of C-1 to C-3 have been found to occur at a higher field for the 3β-substituted isomer and the chemical shifts for H-1 and H-3 occur at higher field for the 3α-substituted isomer[64]. This relationship holds for 14a and 14b and 17a and 17b and leads to the structural assignments shown.

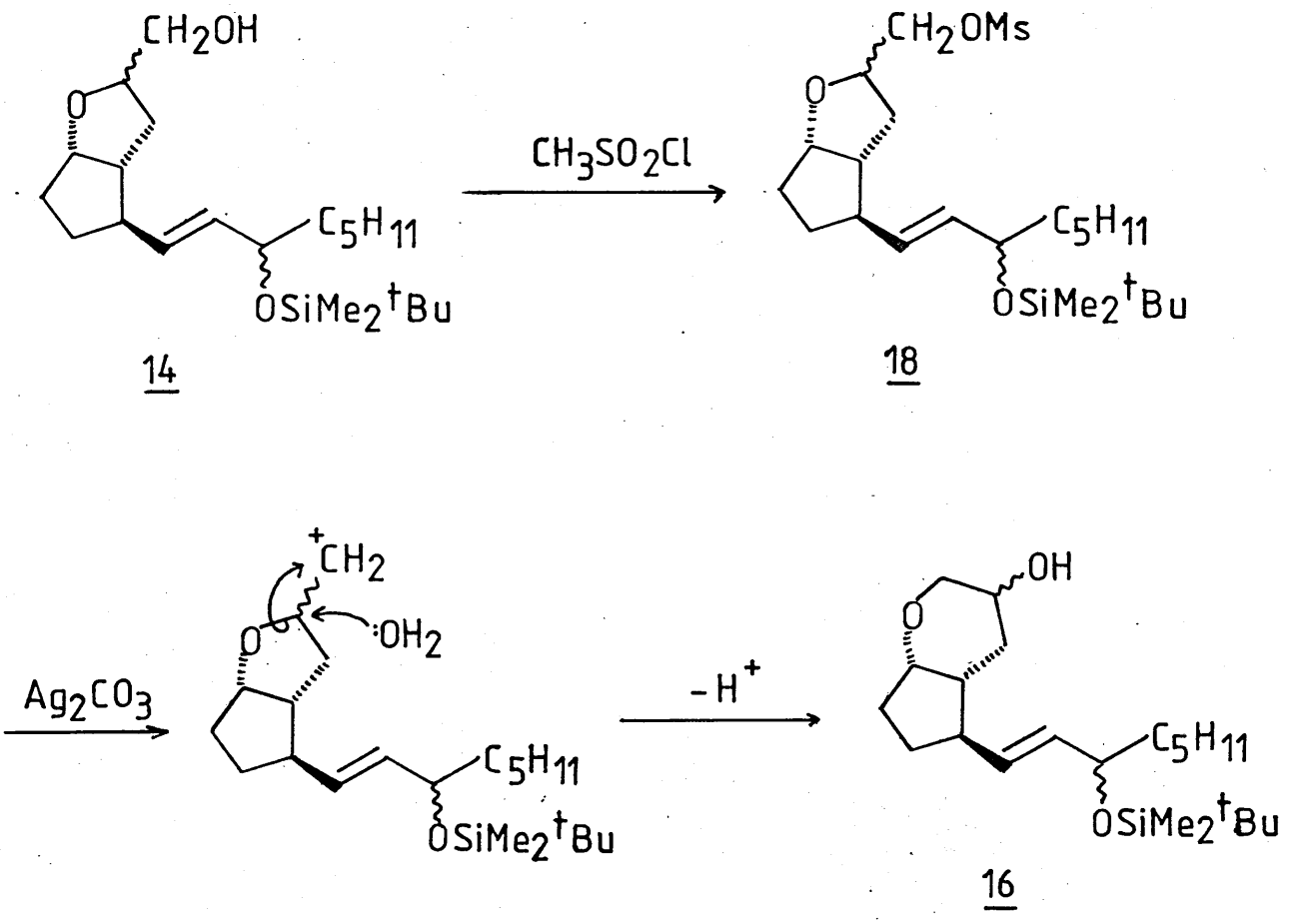
Alcohols 14 were not directly useful in the 11-deoxyhomoprostacyclin synthesis, but an attempt was made to carry out a ring expansion to give more useful intermediates. Such an approach was used by Kishi in his synthesis of lasolactoid A[57b] (Figure 11).

FIGURE 11



We decided to carry out the related process shown in Figure 12.

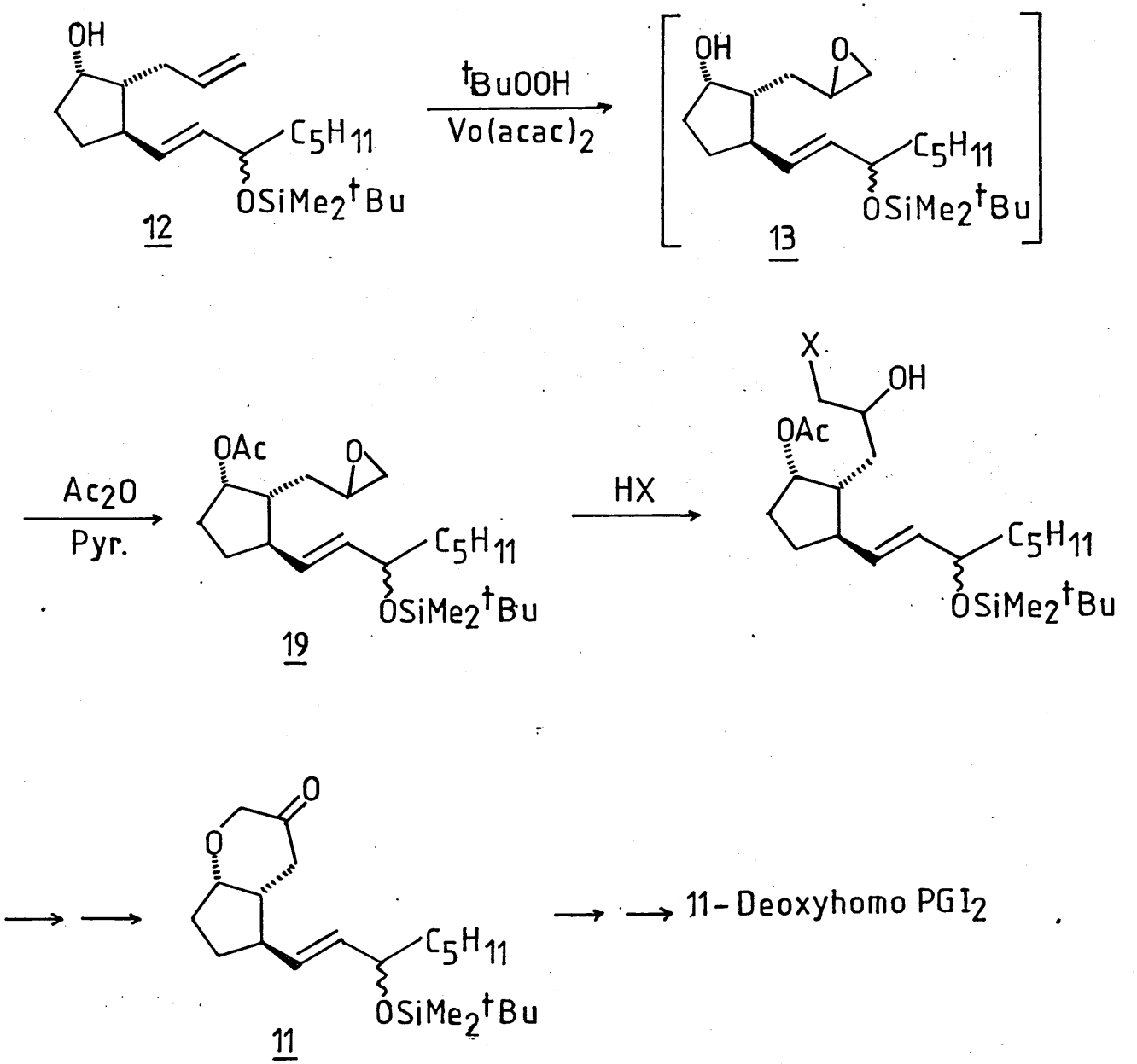
FIGURE 12



The alcohols 14 were mesylated to give 18 which were treated with silver carbonate in refluxing acetone-water mixtures. There were no identifyable products from this reaction with only starting material being recovered. The failure of this rearrangement is presumably due to the high energy of the primary carbonium ion compound compared to the secondary carbonium ion generated by Kishi (Figure 11).

One final effort was made to utilise this epoxidation approach for the synthesis of 11-deoxy-homoprostacyclin. An attempt was made to trap the intermediate hydroxyepoxide 13 before cyclisation, as the epoxyacetate 19. This epoxyacetate could then be opened by a hydrogen halide to afford a halohydrin, thus allowing controlled unambiguous cyclisation to give the key bicyclic precursor 11, to 11-deoxyhomo-prostacyclin, as shown in Figure 13.

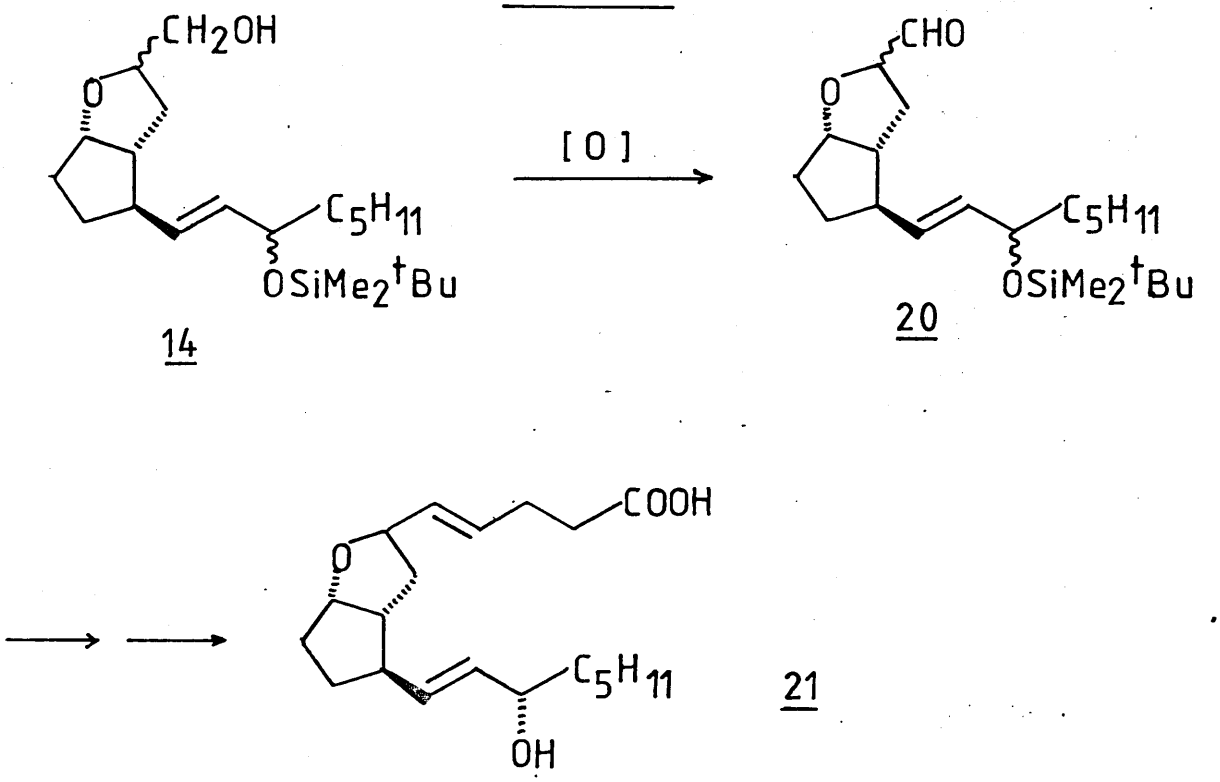
FIGURE 13



The hydroxyepoxide 13 was generated using the original reaction conditions of refluxing toluene, and when the concentration of 13 in the reaction mixture was judged to be at a maximum, acetic anhydride and pyridine were added. This acetylation reaction did not prove to be competitive with the previously noted cyclisation, indeed the acetylating reagents seemed to catalyse the ring closure, and no acetate 19 was detected. It is possible that an alternative trapping reagent could prove successful, but this approach was not investigated further.

The primary alcohols 14 were considered to be useful intermediates for the synthesis of 11-deoxy-Δ^4-prostacyclin analogues 21 and the synthesis shown in figure 14 was investigated. The corresponding 11-hydroxylated analogues have previously been prepared[22,65].

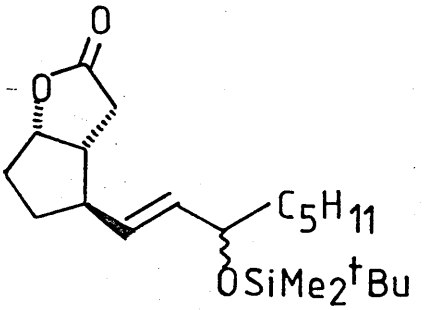
FIGURE 14



Oxidation of alcohols 14 to give the aldehydes 20, either together or separately could not be achieved with a wide variety of reagents and reactions eg, pyridinium chlorochromate, chromium trioxide-pyridine complex, Oppenauer, Moffatt, Jones, *etc*. Similar problems were reported during the oxidation of tetrahydrofurfuryl alcohol itself[66]. Oxidation was eventually achieved using activated manganese dioxide[67]. However the product of this reaction was not consistent with the aldehydes 20. The significant data were as follows:

Data obtained	Expected data
ν_{max}(C=O)-1765 cm^{-1}	ν_{max}(C=O)-1710-1730 cm^{-1}
n.m.r. - no aldehyde proton	n.m.r. - aldehyde proton
m/e - 351(M^+-CH_3)	m/e - 365(M^+-CH_3)

As can be seen from the above data a carbonyl frequency was seen in the infrared but was at higher wavenumber than expected. There was no aldehyde proton in the n.m.r. spectrum and finally the mass spectrum indicated that the molecular weight was 14 a.m.u.'s lower than expected. These data were consistent with the lactone 22 resulting from oxidative degradation.



22

The yield of this novel reaction was found to vary according to the experimental conditions and a full investigation was carried out in order to optimise the yield. The results of this study are summarised in table 3. Optimum conditions were found to be refluxing in dry toluene with 50 equivalents of activated manganese dioxide.

TABLE 3

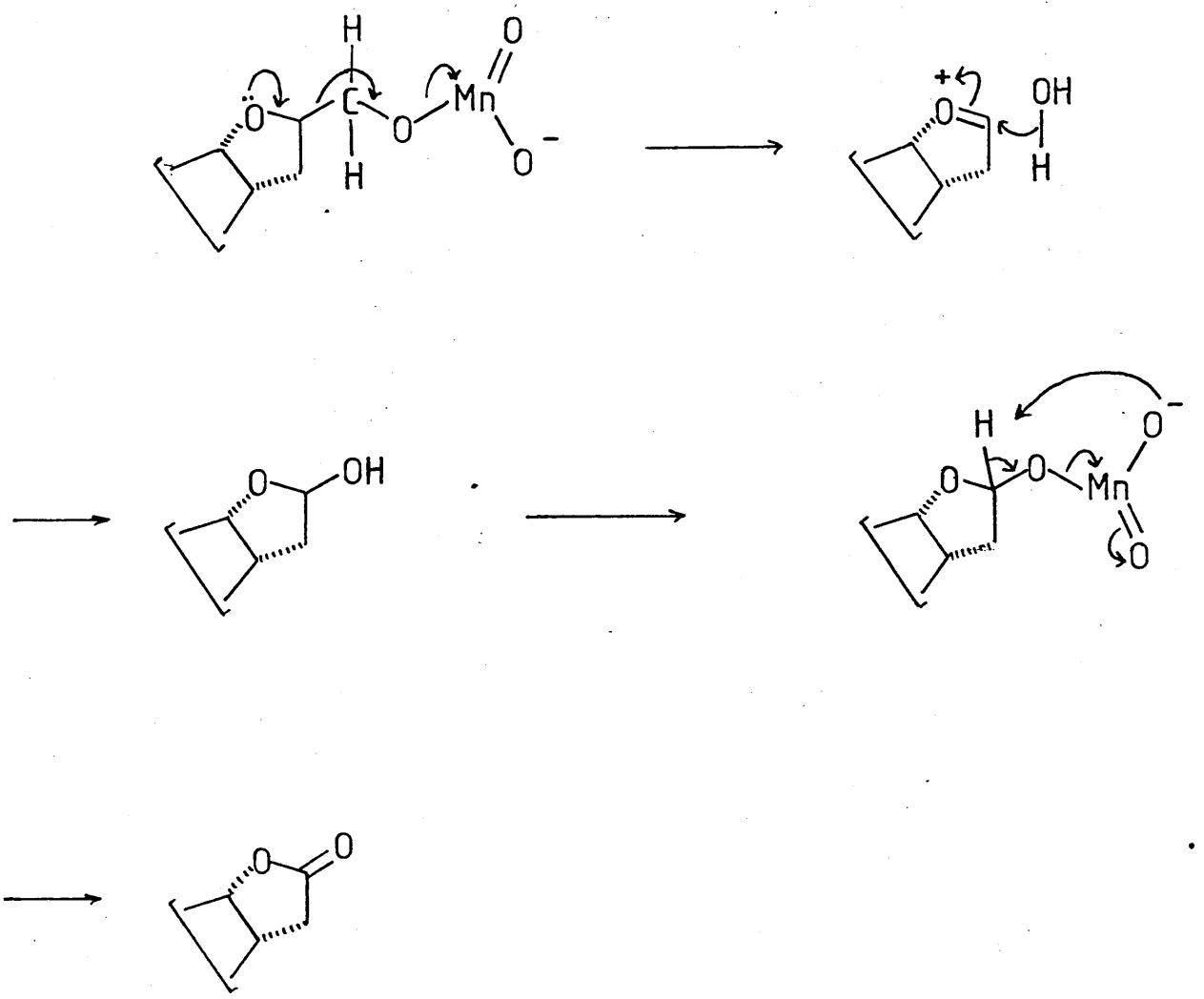
Preparation of lactone 22 by oxidative degradation

Substrate	Reagent (molar equivalents)[a]	Conditions[b] Refluxing solvent (time)	Yield
14a	MnO_2 (50)	60-80 petrol (8h)	34%
14b	MnO_2 (50)	60-80 petrol (15h)	34%
14a + 14b	MnO_2 (40)	60-80 petrol (20h)	38%
14a + 14b	MnO_2 (50)	acetone (20h)	30%
14a	MnO_2 (50)	toluene (2h)	44%
14b	MnO_2 (50)	toluene (8h)	46%

a) Either commercial (Alfa), or Attenburrow[67], active Manganese dioxide could be employed.

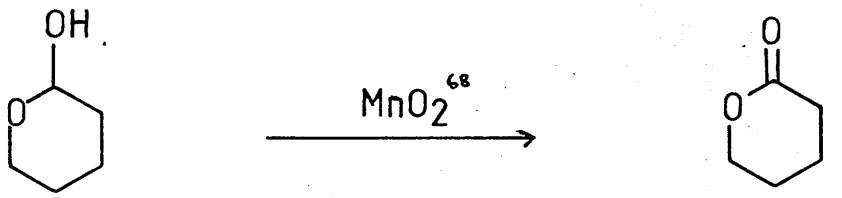
b) No appreciable reaction was observed at ambient temperature; the use of refluxing xylene led to considerable decomposition.

To our knowledge, manganese dioxide has not previously been used for the conversion of 3-hydroxy ethers to lactones[68] although it can be used to cleave vicinal diols[68] and the two processes are presumably related mechanistically. A possible mechanism is proposed below:



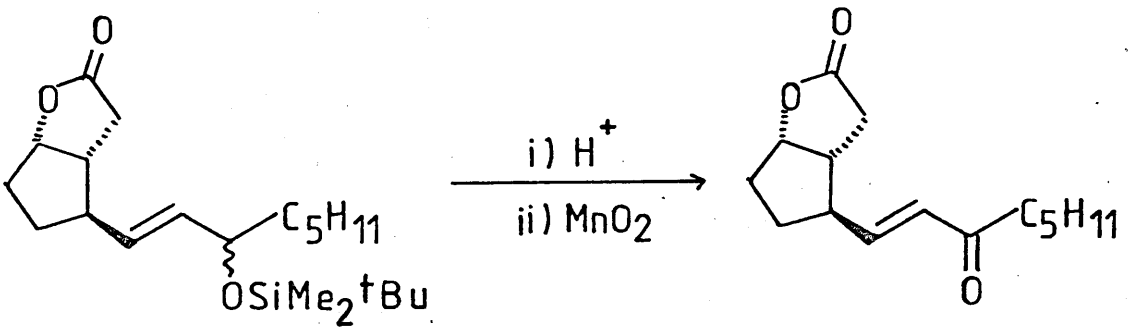
Manganese dioxide has been used to oxidise tetrahydropyran-2-ol to δ-valerolactone[68] and so the second part of the mechanism shown above has precedent.

Silver carbonate on celite has been used for the conversion of tetrahydrofurfuryl alcohol to γ-butyrolactone[69]. This reagent can be used to convert alcohols 14 to lactone 22, giving similar yields in refluxing benzene using from 10-50 equivalents.



The structure of lactone 22 was proved beyond any doubt by converting it to the known[70] α,β-unsaturated ketone 23 (Figure 15)

FIGURE 15



22 23

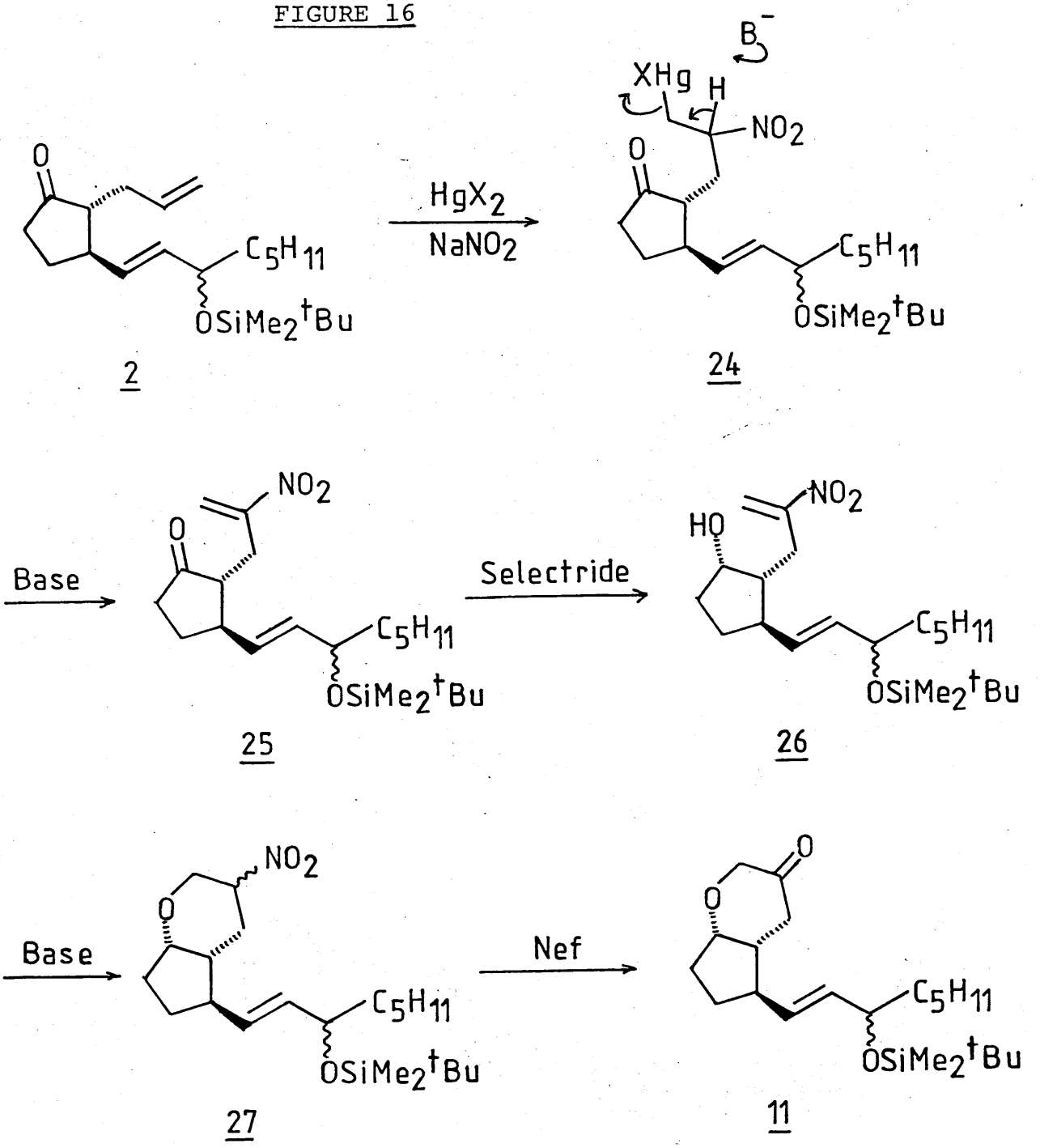
The spectral data (n.m.r., u.v. and i.r.) for 23 were consistent with the literature values[70]. Compound 23 has been converted to 11-deoxy $PGF_{2\alpha}$ and 11-deoxy PGE_2[70] and so this route constitutes a novel synthesis of these compounds.

3.1.2 Mercuration Approaches

At this stage, it was decided to try other procedures that would lead to selective functionalisation of the α side-chain and to this end, a variety of mercuration approaches were instigated. Regioselectivity in the mercuration of the allylic ketone 2 seemed likely since it has been reported that the reactivity of an olefin towards mercuration depends on the substitution of the olefin[71], and the series in decreasing reactivity is: $R_2C = CH_2 > RCH = CH_2 > cis - RCH = CHR > trans - RCH = CHR > R_2C = CHR > R_2C = CR_2$.

The first approach to be investigated is outlined in figure 16. This synthetic route uses nitromercuration as a means of preparing the α,β-unsaturated nitrocompound 25. Such compounds have recently been suggested as versatile synthetic intermediates by Corey[72].

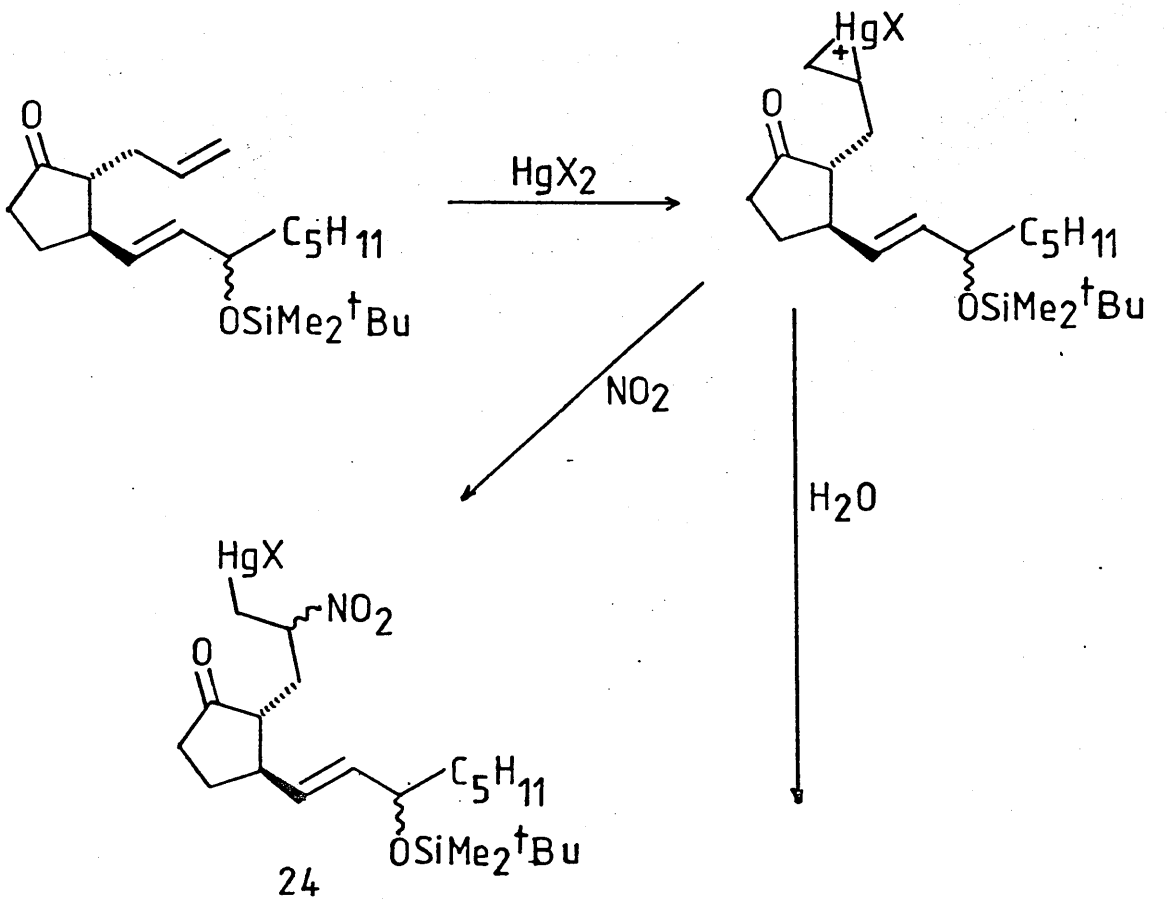
FIGURE 16



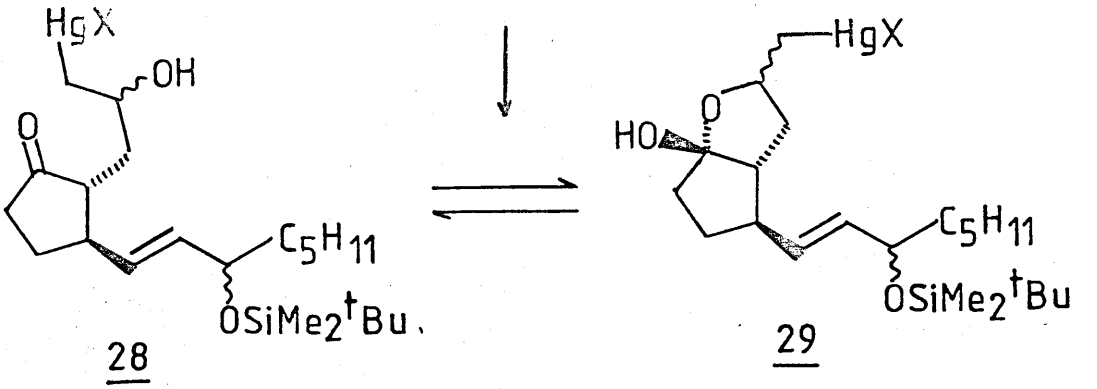
The nitromercuration methods developed by Bachman and Whitehouse[73] should effect the transformation of 2 to 24. Subsequent reductive elimination of the mercury as in Corey's method[72] should give the nitroolefin 25. Alcohol 26 formed by reduction of 25 should cyclise under basic conditions by conjugate addition to the

α,β-unsaturated nitro part of the molecule[74] to give the bicyclic nitro-compound 27. The Nef reaction[75] should then lead to the key intermediate 11.

However the initial mercuration step posed problems. The nitromercuration was attempted on ketone 2 using sodium nitrite and mercuric trifluoro-acetate, mercuric perchlorate or mercuric chloride in a variety of solvents, (water, phosphate buffer, aqueous THF and ethyl acetate-water). In addition, tetrabutylammonium perchlorate or dicyclohexyl 18-crown-6 ether was used as a phase transfer catalyst in the aqueous and biphasic systems. In every case nitromercuration (to give 24) was accompanied by oxymercuration giving 28 and 29 with oxymercuration predominating.

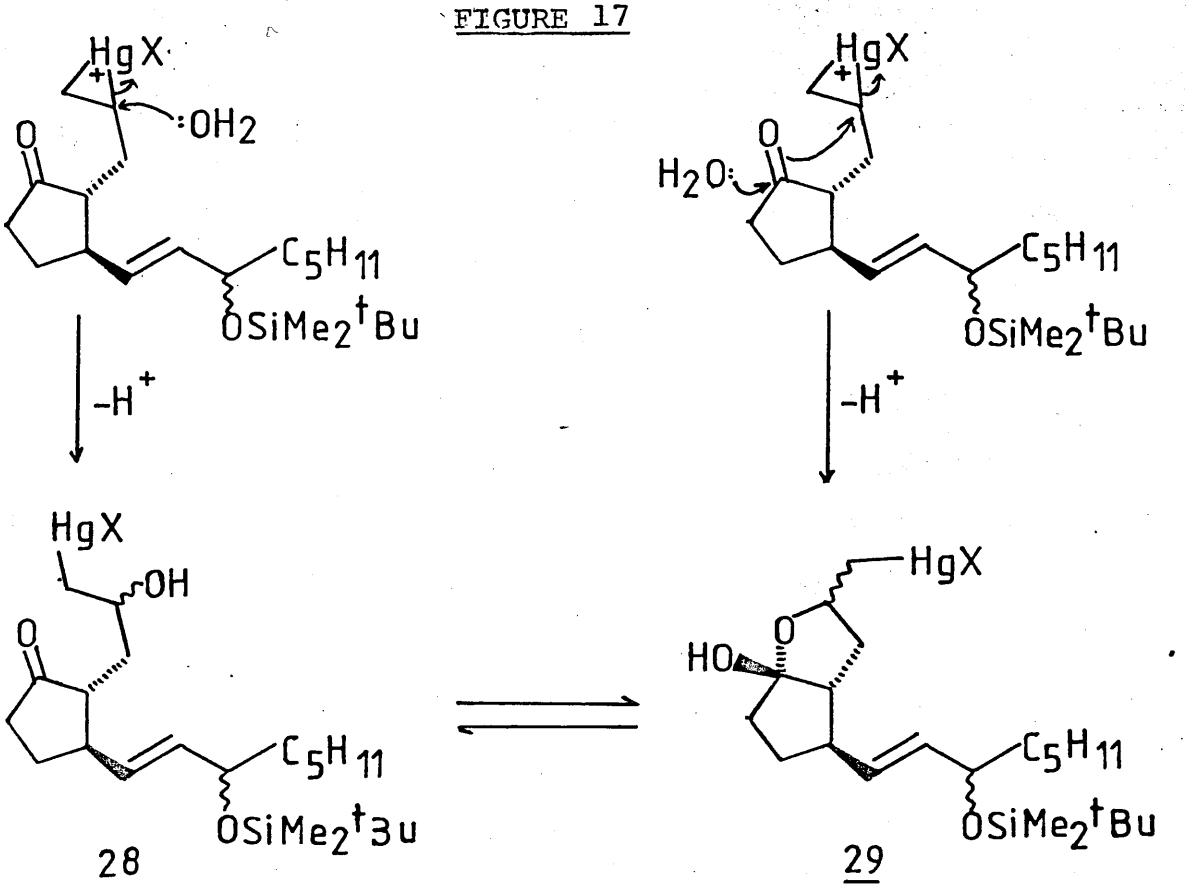


24



Although spectral data were consistent with the mixture of oxymercurated products 28 and 29, it is unclear whether normal oxymercuration occurs first with subsequent internal ketalisation of the product (Figure 17). The alternative formation of a mercurinium ion as first stage of mercuration followed by opening of this mercurinium ion by the keto-oxygen and subsequent nucleophilic attack by water (Figure 17) would also give the ring closed hemi-ketal 29. It will be observed that in the light of subsequent work the latter course of events gains more credibility.

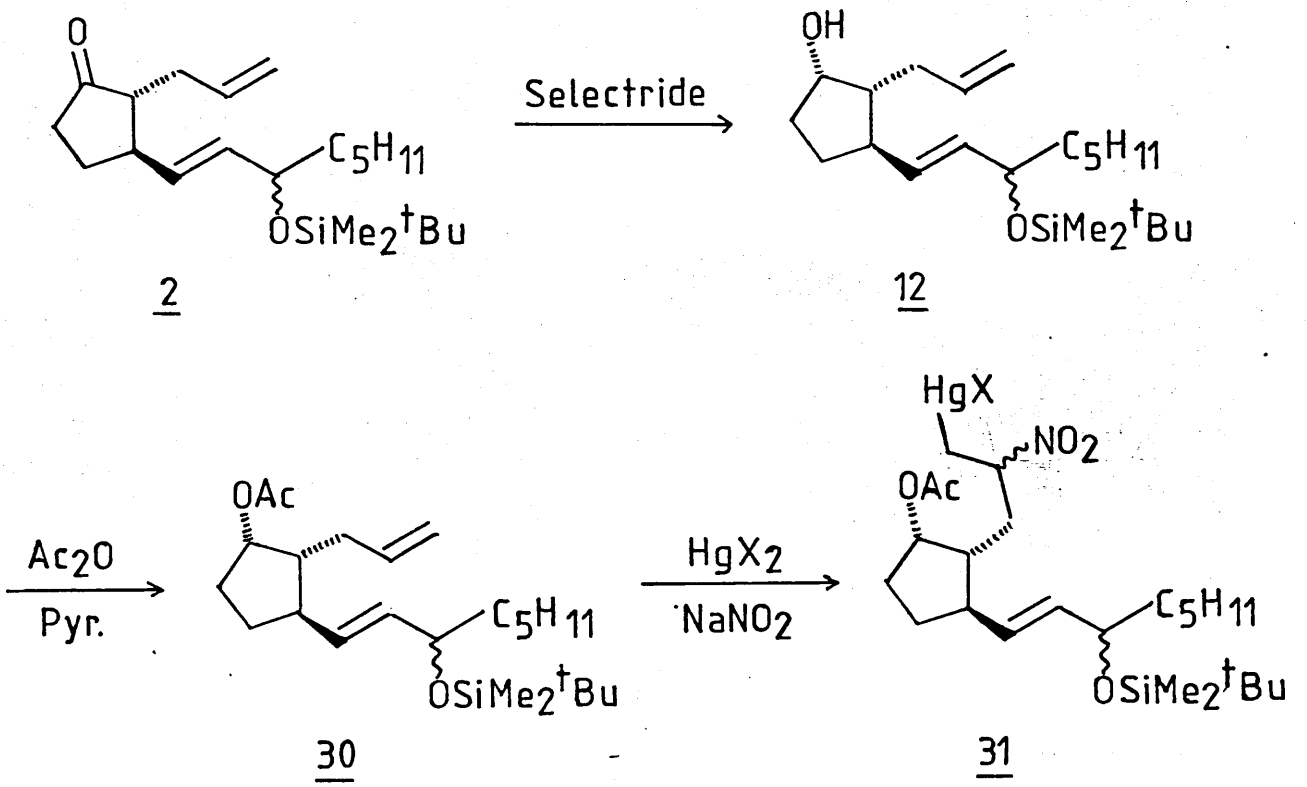
FIGURE 17



These reactions also commonly gave many other by-products and in all cases failed to go to completion.

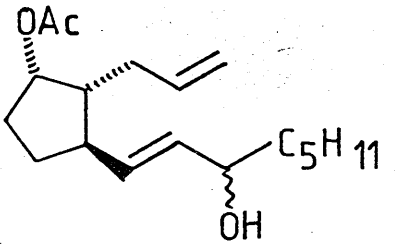
To eliminate the possibility of participation by the ketone oxygen during mercuration reactions, 2 was reduced with 'K-selectride' to give α-alcohol 12 and then acetylated with acetic anhydride in pyridine to give the α-acetate 30 (Figure 18). The nitro mercuration of 30 was then investigated.

FIGURE 18



Unfortunately only small amounts of the nitromercurated product 31 were obtained from this reaction.

Since aqueous systems had given the most promising nitromercuration results, those reactions were also tried on the acetate 32 in which the lipophilic silyl group had been removed.

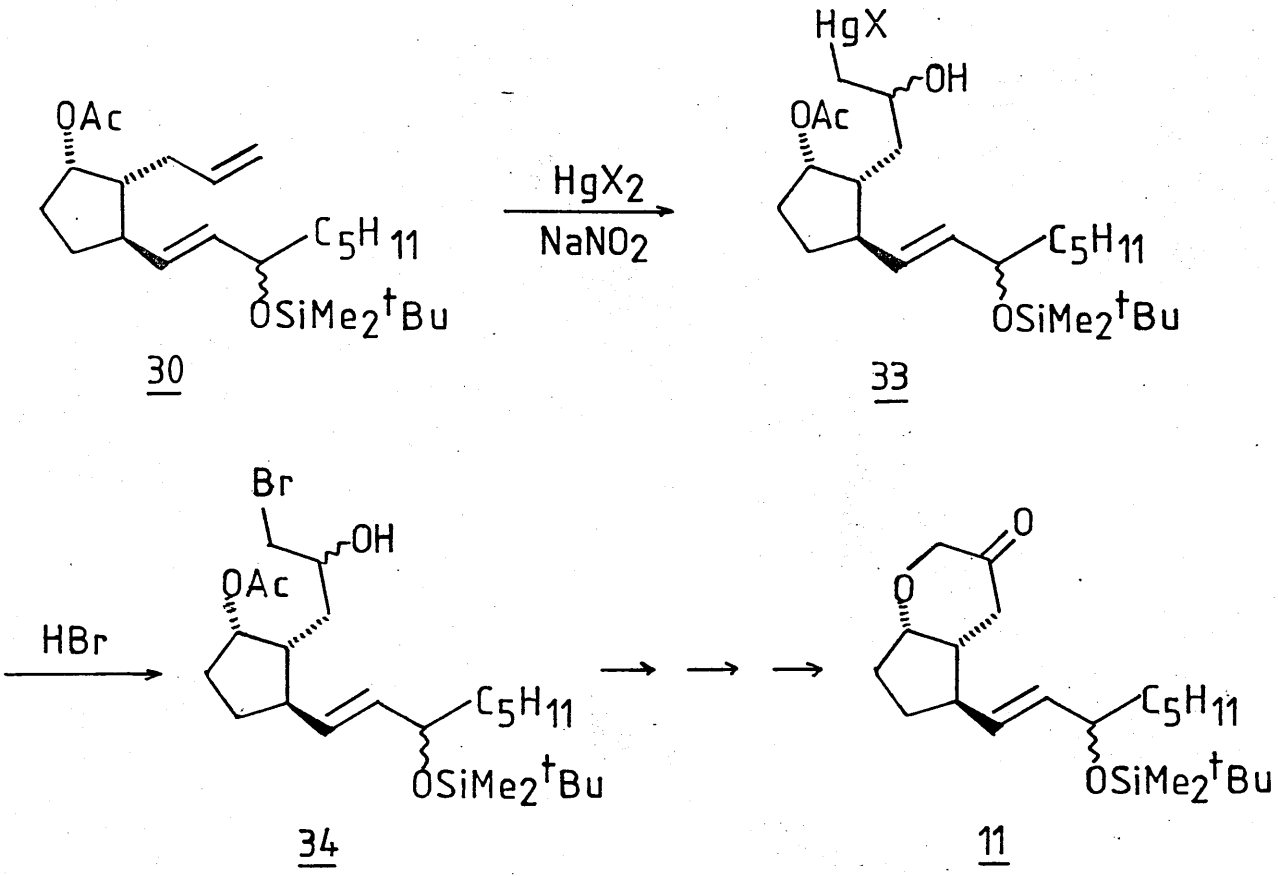


32

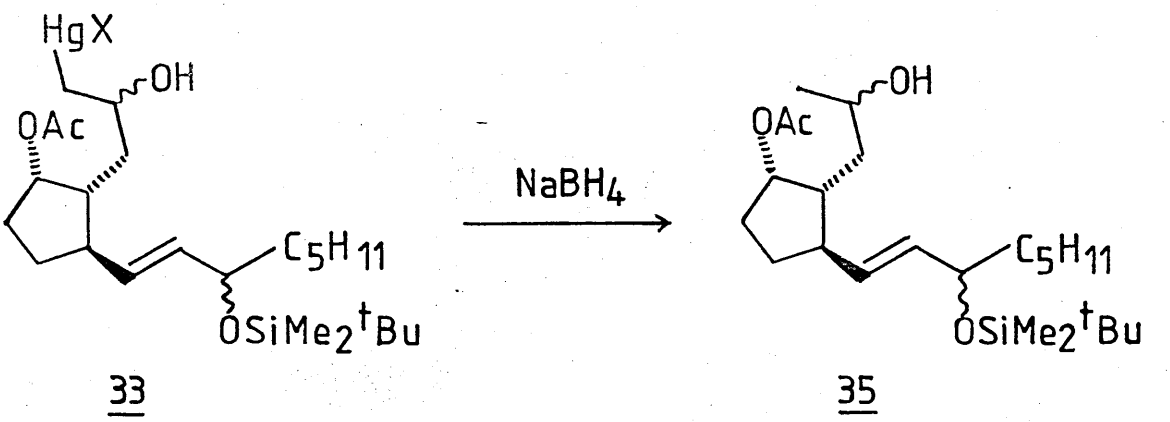
However, once again, low yields of nitromercuration were observed.

Since these mercuration reactions had shown regioselectivity with a predominant amount of oxy-mercuration, an attempt was made to optimise the yield of the oxy-mercuration reaction. This hydroxy mercurated product could be a precursor to bromohydrin type molecules which could be valuable intermediates in a synthesis of the key bicyclic intermediate 11. The whole proposed scheme is shown in figure 19.

FIGURE 19



Mercuric trifluoroacetate is reported to be a good reagent for the oxymercuration of dienes[71] and we found this reagent to be superior to the more often used mercuric acetate. A study of solvent systems for oxymercuration indicated that THF-water (4:1) was the best[76], and the first stage of the reaction to form bromohydrin 34 (Figure 19) was carried out to give the oxymercurated product 33. The success of the process was shown by reducing 33 with sodium borohydride according to the method of Brown[77] to give alcohols 35 in 57% yield.



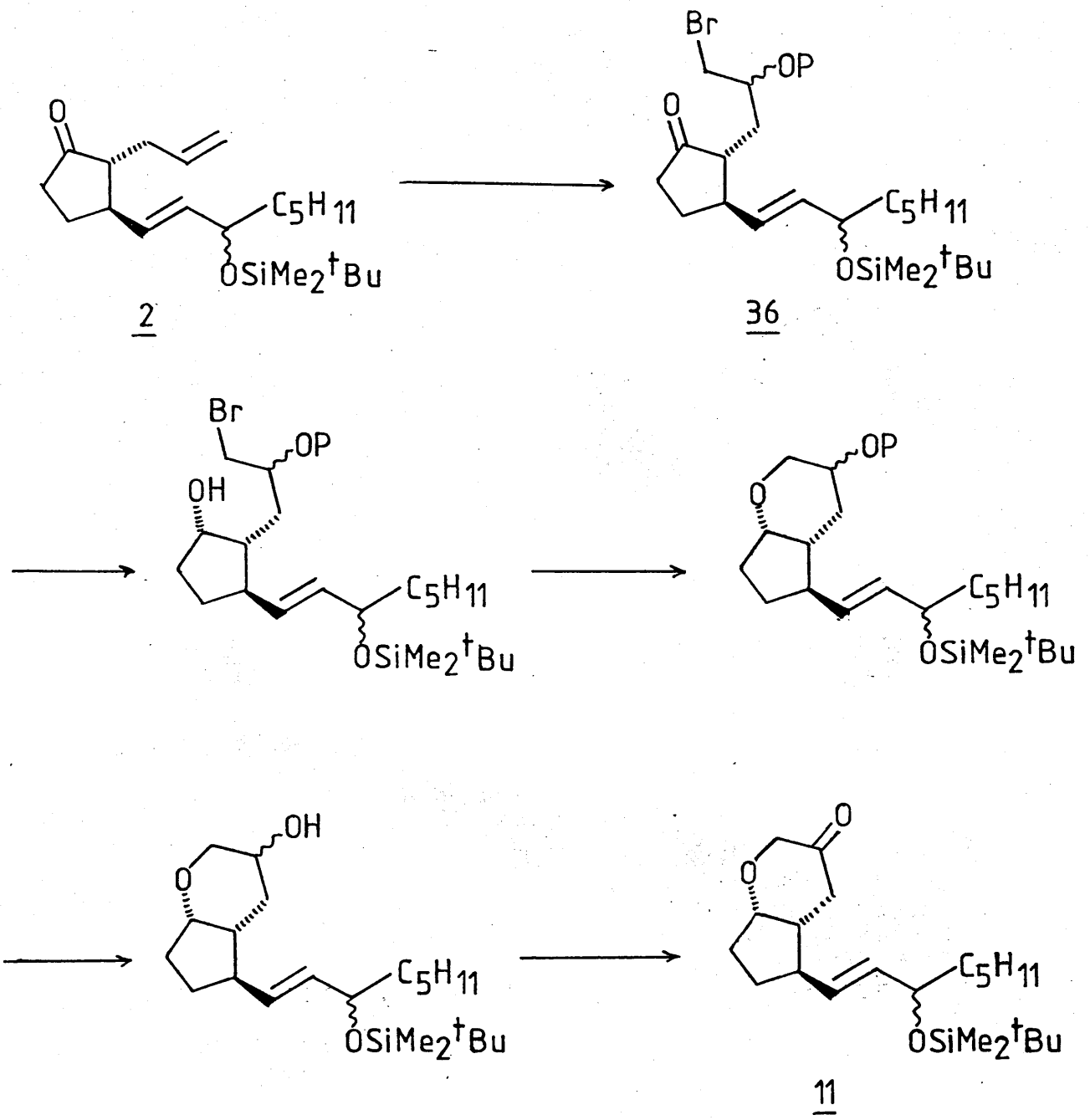
33 35

There are ample precedents for the displacement of organomercuryhalides with halogens ie. $RHgX + X_2 \rightarrow RX + HgX_2$[71,78]. However the attempted displacement of mercury with bromine was not successful leading to non-specific bromination and the production of a large number of products. At this point parallel investigations were showing promise and these mercuration approaches were abandoned.

3.1.3 Bromohydrin and Related Approaches

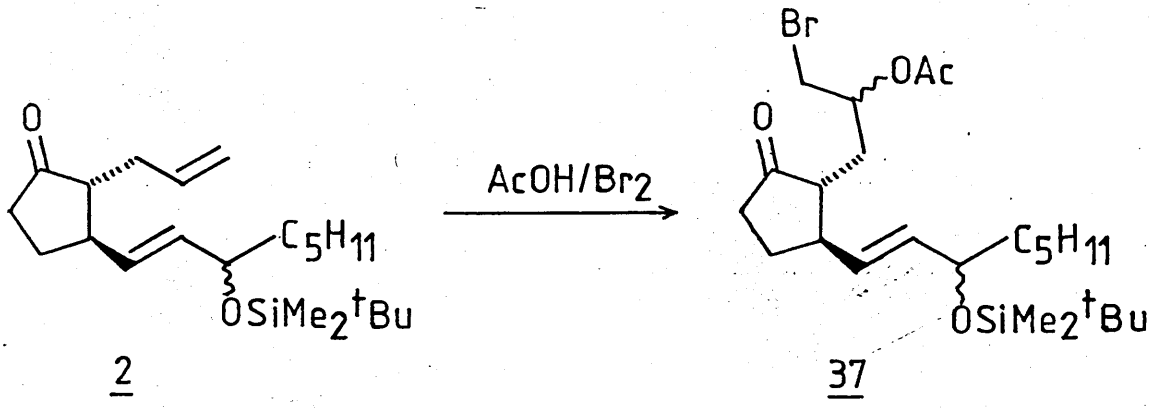
The possibility that ketone 2 could be converted to bromohydrin 34, as discussed in the last section was appealing. Direct conversion to a protected bromohydrin 36 would provide a very short route to 11-deoxyhomoprostacyclin (Figure 20).

FIGURE 20



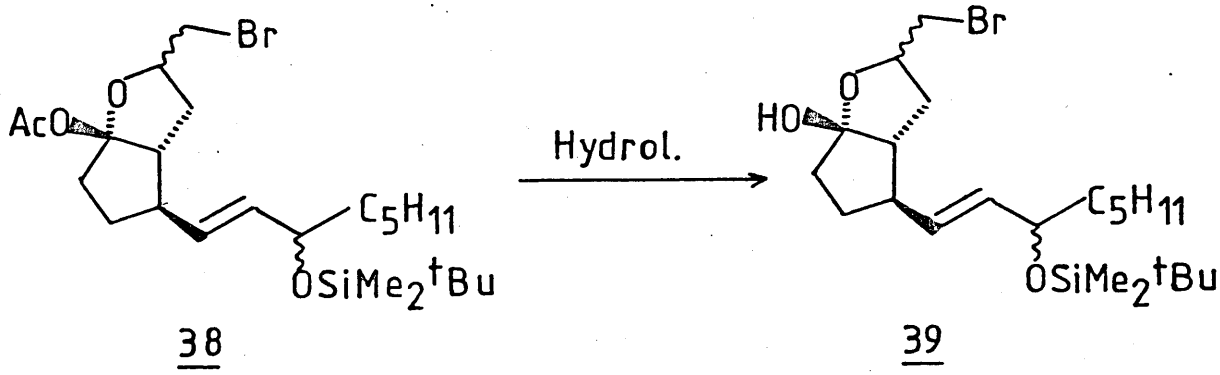
The first approach to synthesise a bromohydrin of type 36 is outlined in figure 21.

FIGURE 21



2 37

The attempted conversion of ketone 2 to the acetoxy-bromohydrin 37 was carried out using bromine in dry glacial acetic acid. The reaction proceeded smoothly, but on analysis of the product, it became clear that cyclisation had occurred to give 38. This was apparent from the fact that there was only one carbonyl absorption in the infrared at 1740 cm^{-1}, and although n.m.r. showed the acetate CH_3 at δ 2.0 there was no signal corresponding to the CH-OAc proton, usually seen at δ 5.3-5.1. The product also seemed labile to hydrolysis and when chromatographed on silica, gave a more polar product, thought to be the hemiacetal 39, formed by acetate hydrolysis.

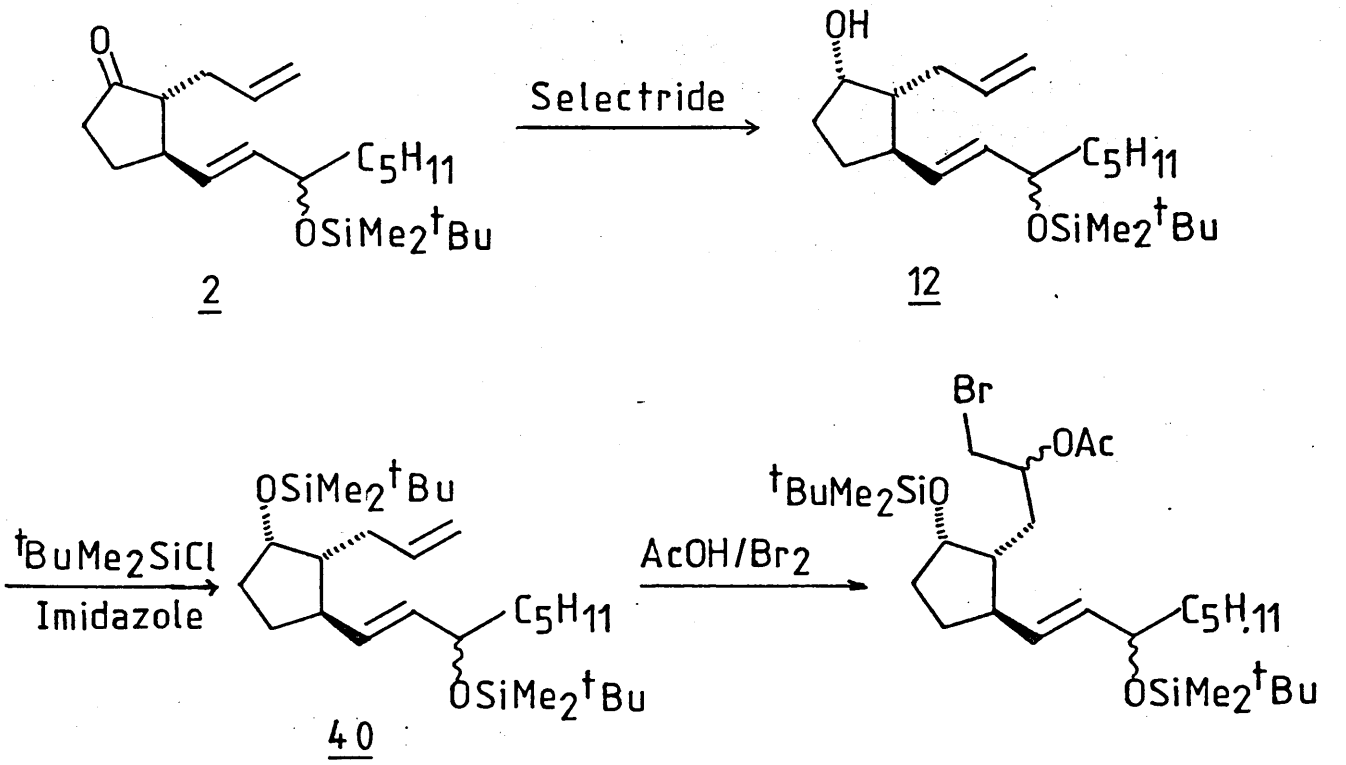


38 39

It appears that an oxygen containing functional group at the 9-position (prostaglandin numbering) will readily cyclise to produce oxabicyclo-[3.3.0] systems. This was first observed in the epoxidation work when hydroxyepoxide 13 spontaneously closed to give alcohols 14, and later there was evidence for the same kind of participation during the mercuration work, when the mercurinium ion was intramolecularly opened by the ketone oxygen to give the hemi-acetal 29.

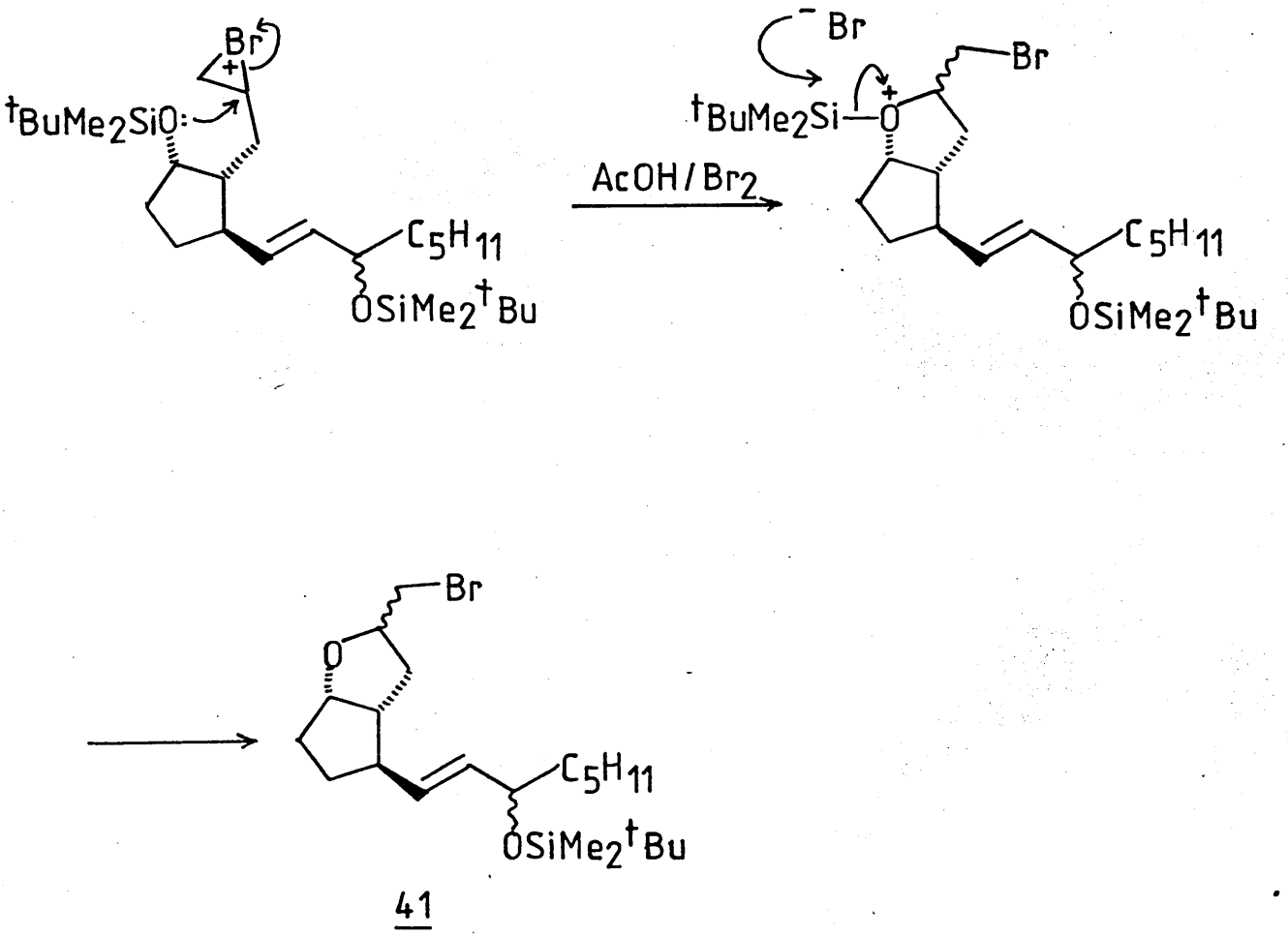
In an attempt to overcome this interference by the carbonyl group, it was decided to follow the route shown in figure 22 and try to form the acetoxybromide from silyl ether 40.

FIGURE 22



The ketone 2 was reduced with 'K-selectride' to give α-alcohol 12, which was silylated with *tert*-butyldimethylsilyl chloride to give the di-silylated compound 40. Again a smooth reaction of this compound occurred with bromine in glacial acetic acid but from an analysis of the product it was apparent that no acetate group was present and the product was identified to be the bromomethyl bicyclic ether 41. Again the mechanism involved was presumably an initial formation of the bromonium ion followed by intramolecular attack by oxygen with subsequent desilylation (Figure 23).

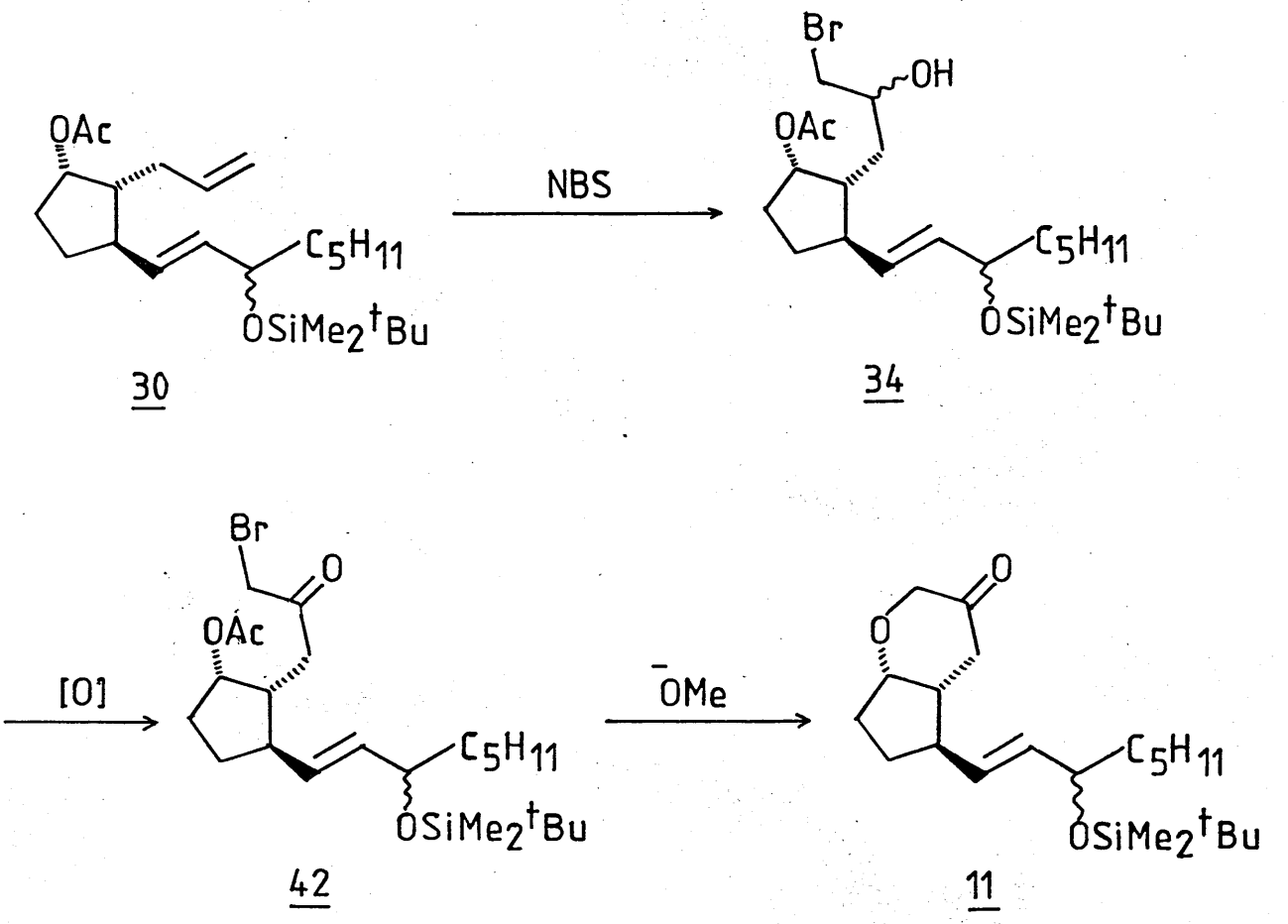
FIGURE 23



41

In view of these problems it was decided to try direct bromohydrin formation using N-bromosuccinimide on the acetate 30. This would lead to the synthesis of the key bicyclic intermediate 11 shown in Figure 24.

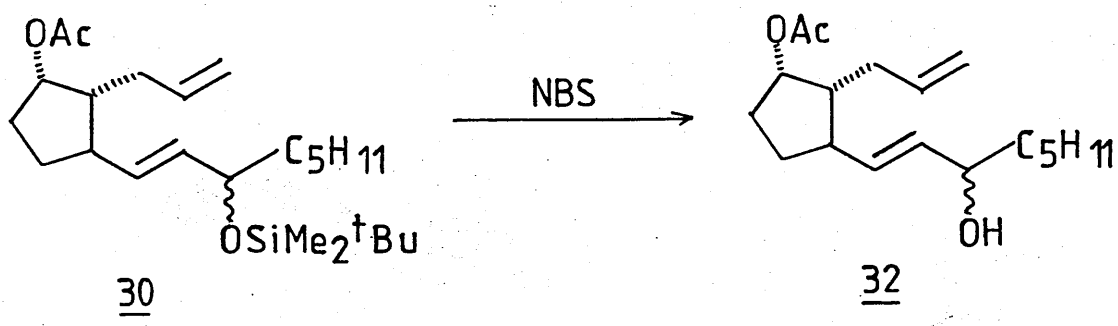
FIGURE 24



Direct formation of the bromohydrin 34 from 30 would be followed by oxidation to give the α-bromoketone 42. This compound could then be cyclised to the bicyclic ketone 11 in one step using sodium methoxide.

Reaction of the acetate 30 with N-bromosuccinimide gave a very clean reaction, but analysis of the products showed that there had been no reaction at the alkene sites and the product was in fact the desilylated

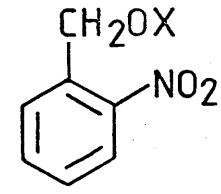
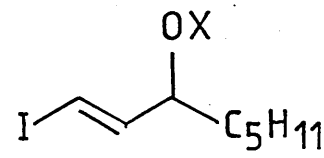
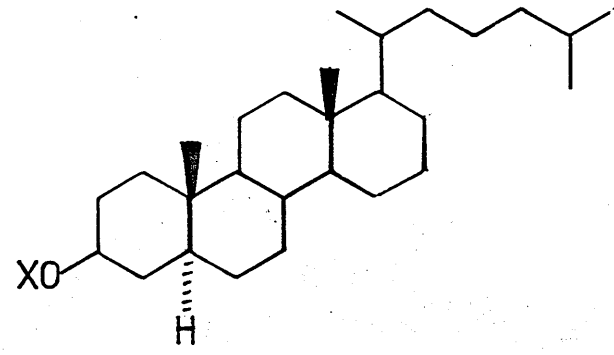
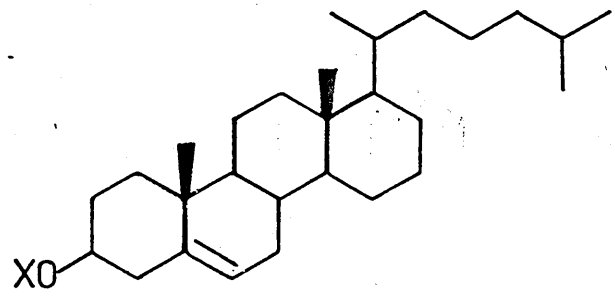
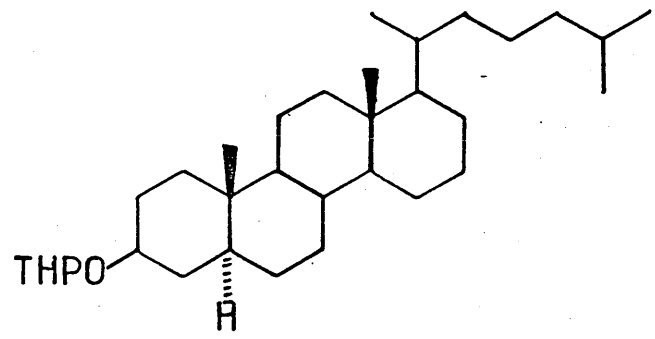
acetate 32.



30 32

The desilylation was confirmed by resilylating with *tert*-butyldimethylsilyl chloride to give back the starting acetate 30. An investigation into the synthetic utility of this reaction as a selective method for the removal of the *tert*-butyldimethylsilyl group was carried out in these laboratories[79] and would seem to offer a useful alternative to the standard conditions ie. H^+ or F^- [80]. The results of this work are summarised in table 4. As can be seen from entry 6 N-bromosuccinimide can be used as a desilylating agent in the presence of acid sensitive groups such as THP.

TABLE 9[a]

Substrate/Product	yield[b]
	74%
$CH_2(CH_2)_3C{\equiv}CCH_2OX$	85%
	86%
	88%
	88%
	No reaction after 17h.

Substrate X = $SiMe_2{}^tBu$

Product X = OH

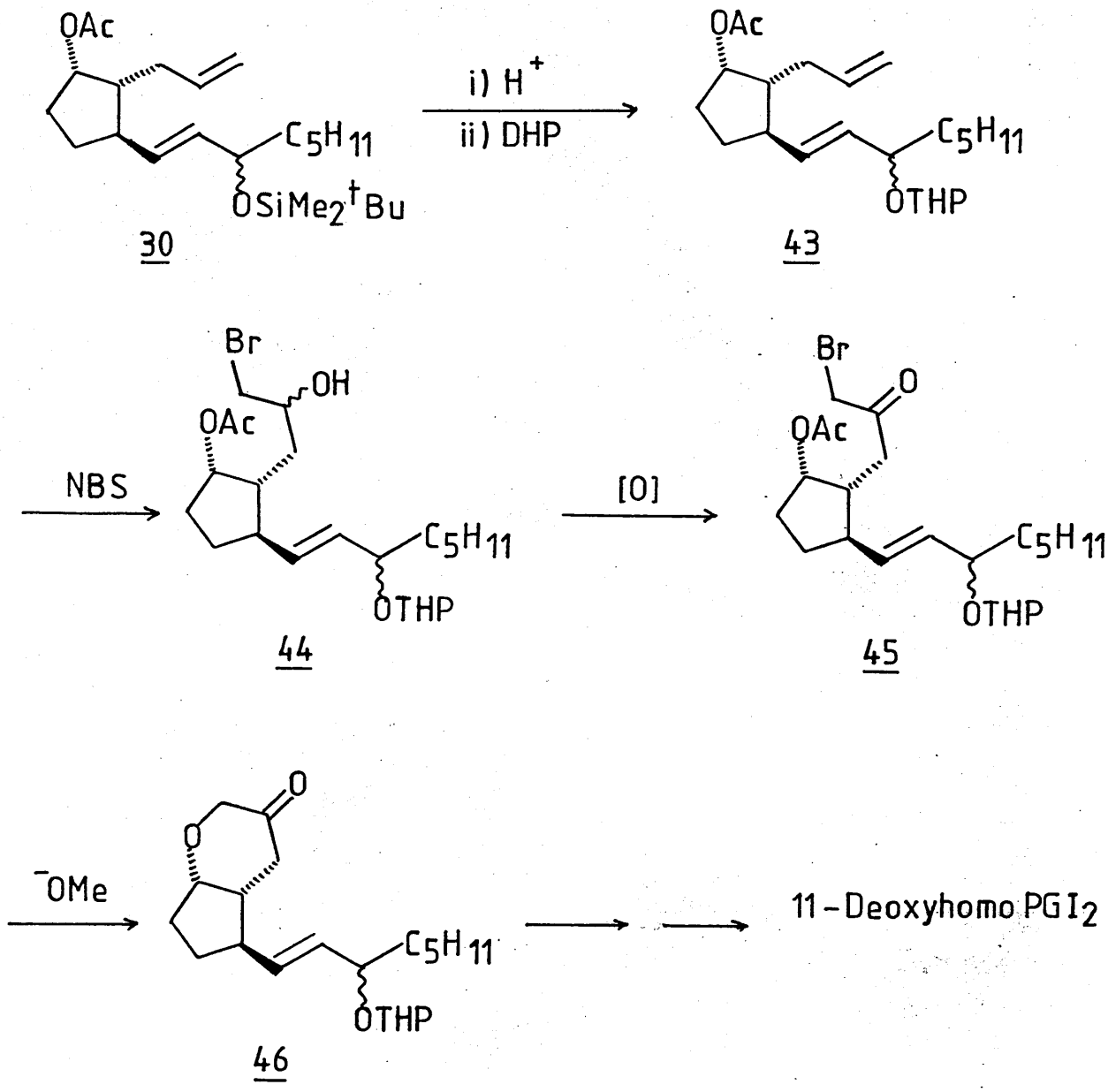
a the substrates were treated with 1;1 equivalents of NBS in aqueous DMSO or aqueous DMSO-THF for up to 17 hours.

b based on actual yield of products after recrystallisation distillation or chromatography.

The reaction appears to proceed by way of an ionic, rather than radical mechanism. Deprotection occurs efficiently in the absence of light and in the presence of excess triethylamine. In view of the stability of the THP group and the known ability of NBS as an efficient scavenger of hydrobromic acid, it does not seem likely that the active reagent is H^+. It may well be the slow release of bromine that is responsible for the reaction.

Since the silyl protecting group was sensitive to the reaction conditions necessary for bromohydrin formation, it was proposed that the silyl protecting group be removed and replaced with a group insensitive to NBS such as THP (Figure 25).

FIGURE 25

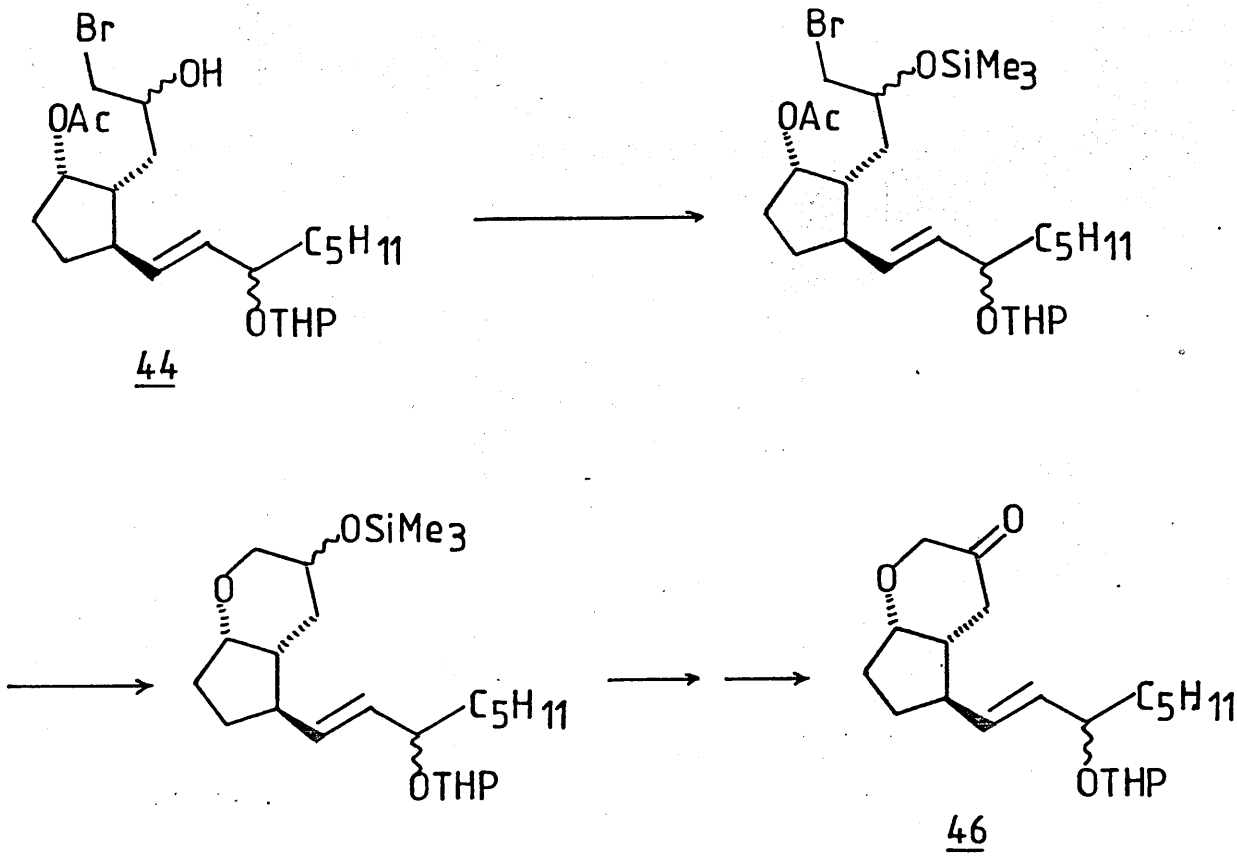


The acetate 30 was desilylated with acid and reprotected as the THP ether 43, under standard conditions. The THP derivative 43 was successfully converted to the bromohydrin 44. With 44 in hand it was decided to try the oxidation/cyclisation route

shown in figure 25. The oxidation of bromohydrin 44 to the α-bromoketone 45 proved to be very difficult with a variety of oxidising agents such as NBS, potassium permanganate-copper sulphate, pyridinium dichromate, Jones reagent and Moffatt. The oxidation was eventually effected using pyridinium chlorochromate but gave the bromoketone 45 in only 22% yield, and this was not considered to be synthetically viable at this stage of the synthesis.

The alternative route shown in figure 26 was to protect the bromohydrin OH in 44 as a silyl ether, deacetylate, then cyclise, remove the silyl group and finally oxidise (deprotection of the silyl ether with anhydrous fluoride or NBS would leave the acid sensitive THP group intact).

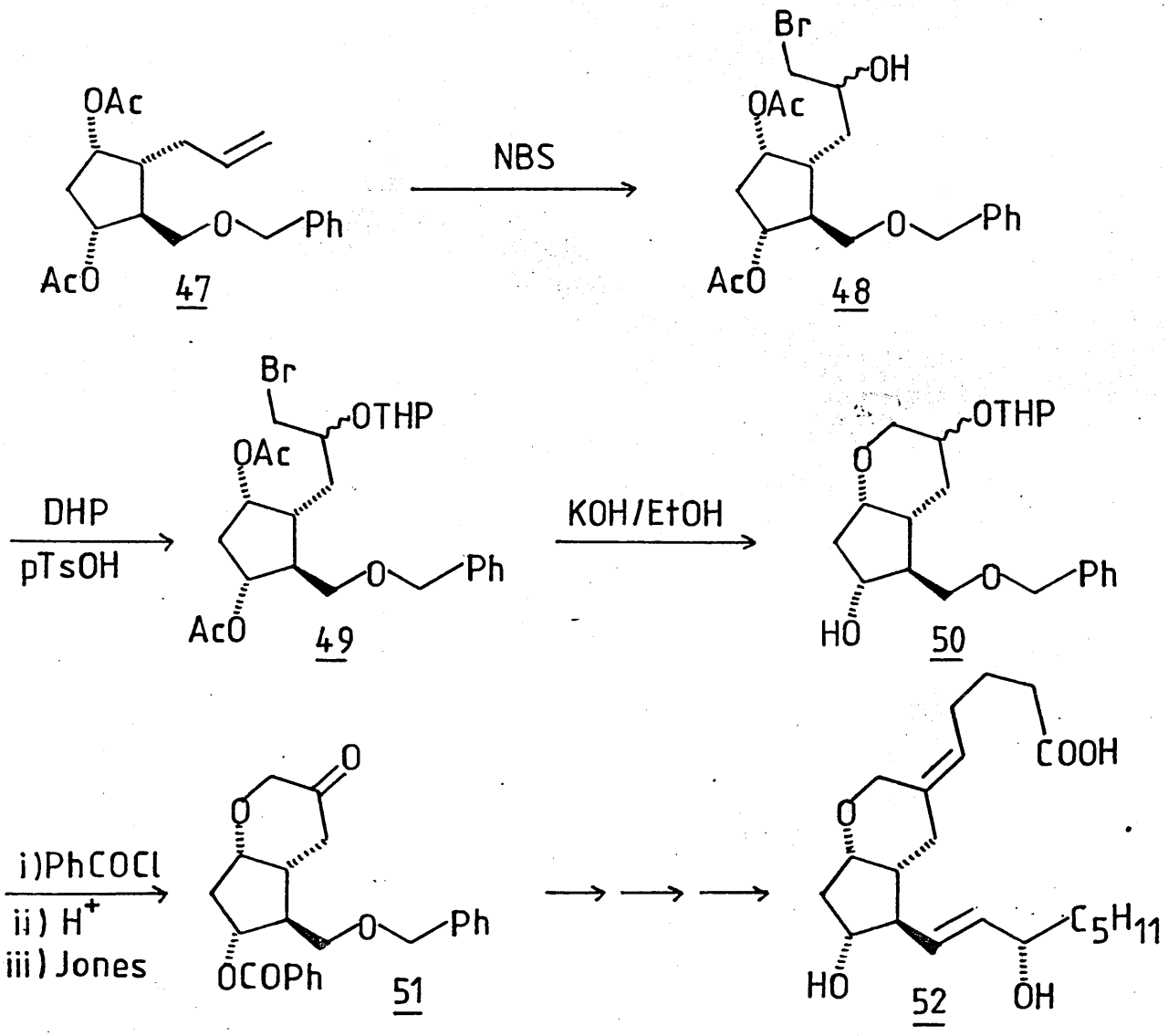
FIGURE 26



Silylation of 44 on a pilot scale using hexamethyldisilizane in DMF and sodium sulphate as catalyst looked very promising with clean conversion of bromohydrin 44 to a less polar material. However, due to the length of the synthetic approach, involving several protections and deprotections a different and more direct route was explored.

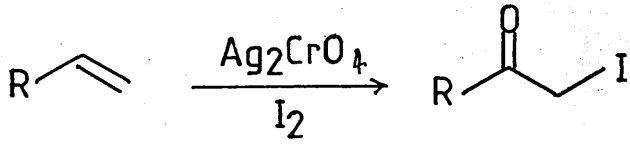
Since the completion of this work, a synthetic route to homoprostacyclin 52 has been published[81], in which a similar strategy to that shown in figure 26 has been employed. This synthesis is shown in figure 27.

FIGURE 27



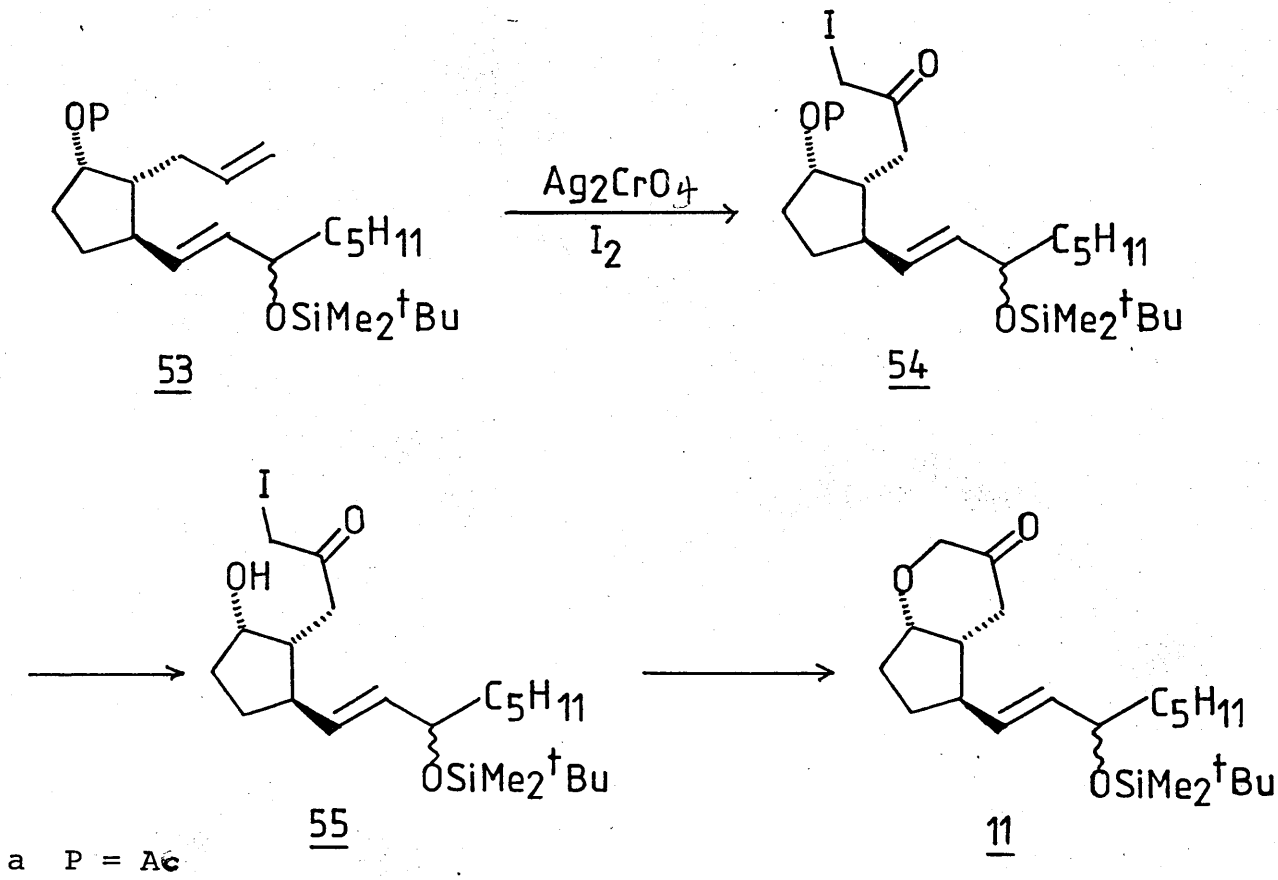
Compound 47 was prepared from a Corey lactone derivative and then converted to bromohydrin 48. Protection of bromohydrin as 49 was followed by cyclisation to give 50. Subsequent deprotection of 50 and oxidation gave the bicyclic ketone 51. The synthesis of homoprostacyclin 52 was then completed using standard prostaglandin methodology.

Cardillo and Shimitzu have reported the direct conversion of alkenes to α-iodoketones by the use of iodine and silver chromate[82].



This reagent has only been used on simple substrates but it appeared to offer a viable synthetic alternative to bromohydrin formation. A revised synthetic procedure based on this conversion is shown in figure 28.

FIGURE 28



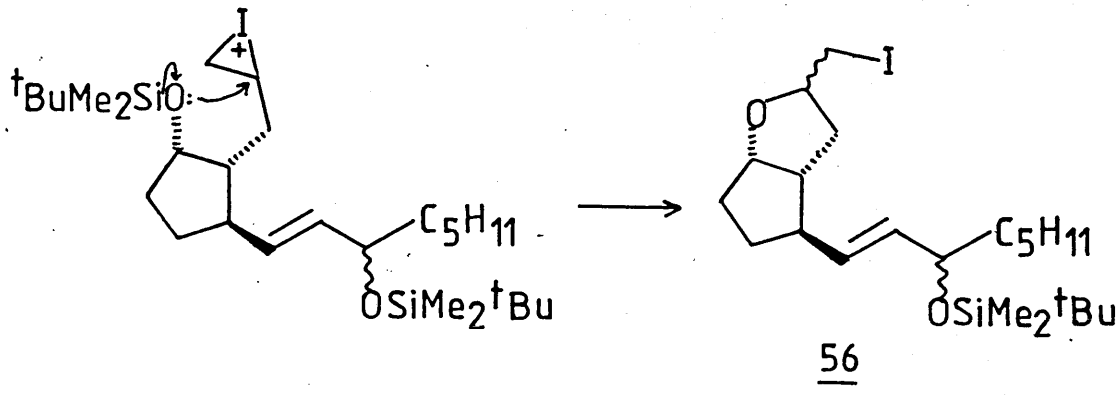
a P = Ac
b P = $SiMe_2{}^tBu$
c P = THP

As the scheme in figure 28 shows, this represents a very direct route to the key bicyclic ketone 11 and hence 11-deoxyprostaglandin. The reaction of 53a with silver chromate/iodine proceeded smoothly to give 54a in 46% after chromatography. However in order to cyclise to give the bicyclic ketone 11 we first need to remove the acetate to give 55, and this proved impossible in the presence of the fairly sensitive α-haloketone functionality, using NaOMe,

potassium carbonate /DMF, sodium hydroxide /DMSO or toluene-4-sulphonic acid/methanol. An unsuccessful attempt was also made to protect the carbonyl group as its dimethyl ketal using boron trifluoride /methanol to reduce the lability of this α-haloketone grouping.

Alternative protecting groups were tried in order to facilitate the subsequent deprotection. The first to be tried was the *tert*-butyldimethylsilyl group (Figure 28, 53b) which can be removed under fairly mild acidic conditions, with anhydrous fluoride or with NBS. Although the formation of silyl ether 53b, from the corresponding alcohol 12, proceeded smoothly, the oxidation with silver chromate-iodine did not give the desired iodoketone 54b, but instead gave the bicyclic iodomethyl ether 56, presumably due to the recurring problem of intramolecular oxygen participation to open the initially formed iodonium ion (Figure 29).

FIGURE 29

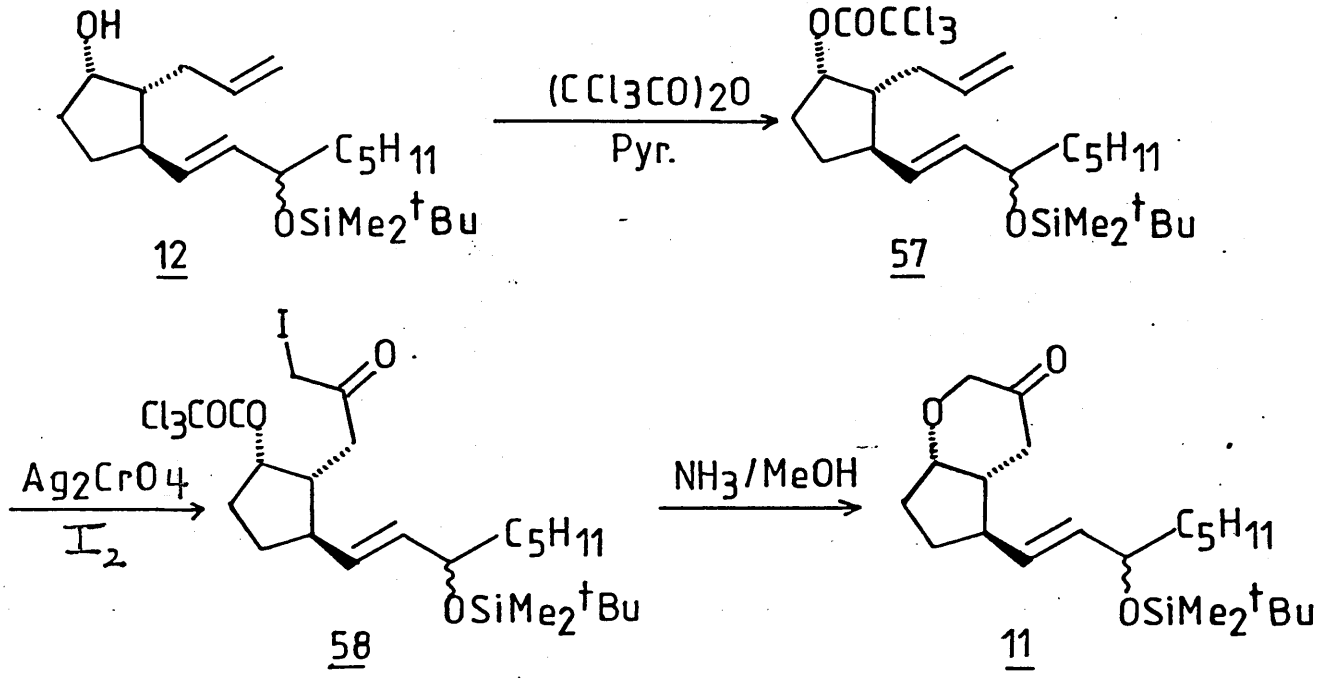


56

The tetrahydropyranyl derivative 53c (Figure 28) was prepared next, and since it is more electron withdrawing than the silyl group, it was hoped that it would deactivate the interfering oxygen by rendering it less nucleophilic. Unfortunately this failed to stop the ring closure and the major product was again the iodomethyl bicyclic ether 56 which presumably arises by a similar mechanism to that shown in figure 29.

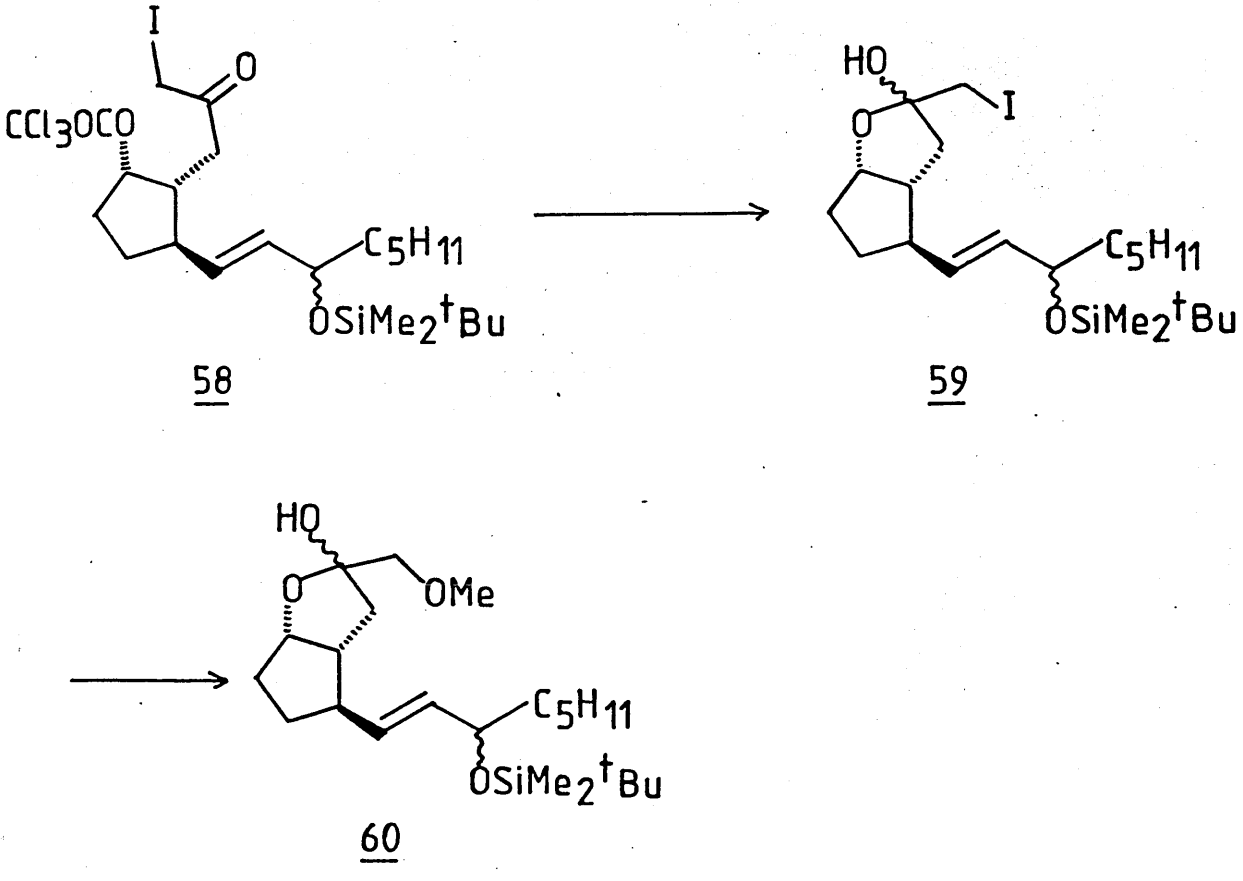
What was required was an easily removed protecting group with similar electronic properties to acetate. The chloroacetate group has been reported to be much more susceptible to hydrolysis than acetate[83] and the trend could be expected to extend to the trichloroacetate group which should be more labile than the chloroacetate. It is also reported that the chloroacetate group can be removed under conditions as mild as anhydrous methanol 50% saturated with dry ammonia gas[83]. The procedure shown in figure 30 was therefore followed.

FIGURE 30



Alcohol 12 was protected using trichloroacetic anhydride/pyridine giving the trichloroacetate 57 (Figure 30). This reaction was extremely fast and took only two minutes at ambient temperature, compared with corresponding acetylation which often took more than 24h. Compound 57 then underwent the same reaction with silver chromate iodine as the acetate 53a to give the iodoketone 58 in 44% yield after chromatography. When the removal of the trichloroacetate group was tried with solutions of dry ammonia gas in methanol compound 60 was isolated in 84% yield. Presumably the trichloroacetate group was removed and ring closure occurred to give the hemiketal 59, with subsequent nucleophilic substitution of methoxide for iodine to give 60 (Figure 31)

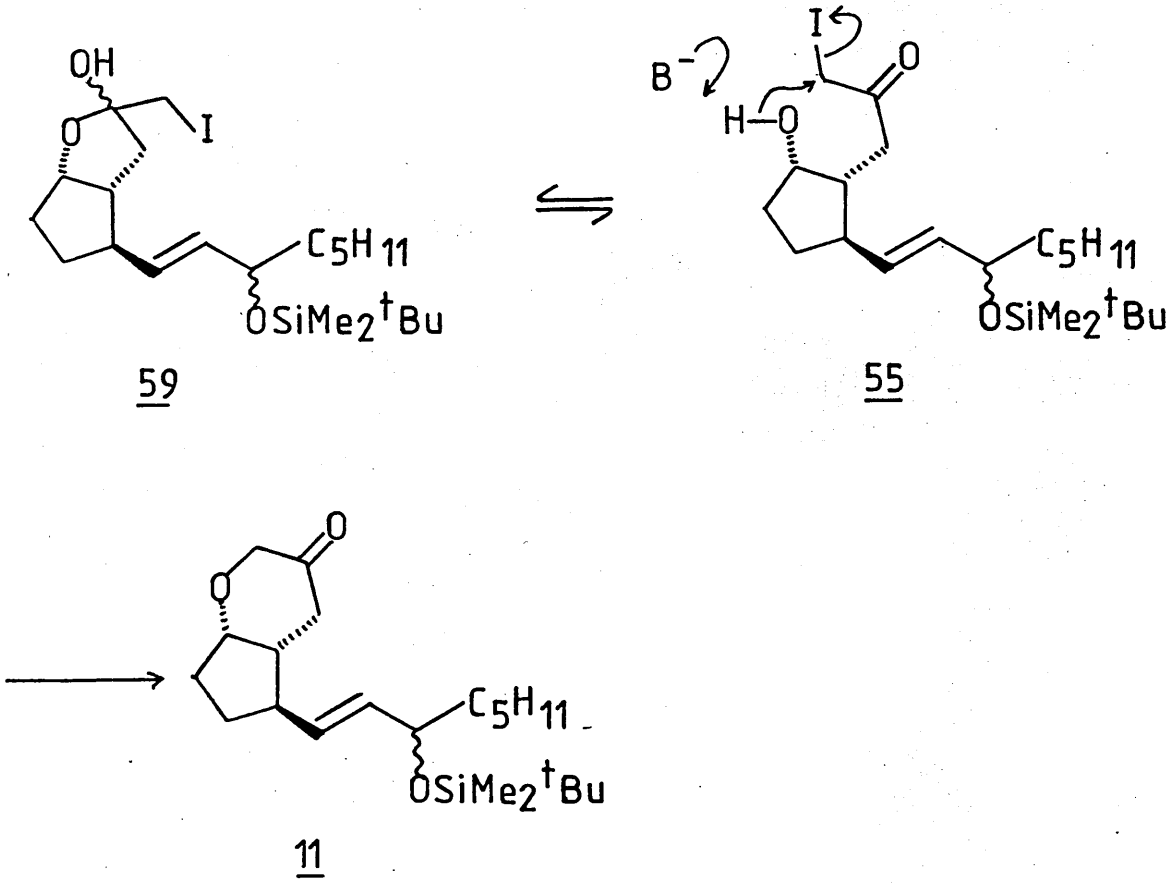
FIGURE 31



Optimum conditions for the removal of the trichloroacetate group, without concomitant displacement of iodine to give 60 were found to be a 10% solution of methanol in diethyl ether, saturated with dry ammonia gas at 0 °C which gave 59 in 45% yield.

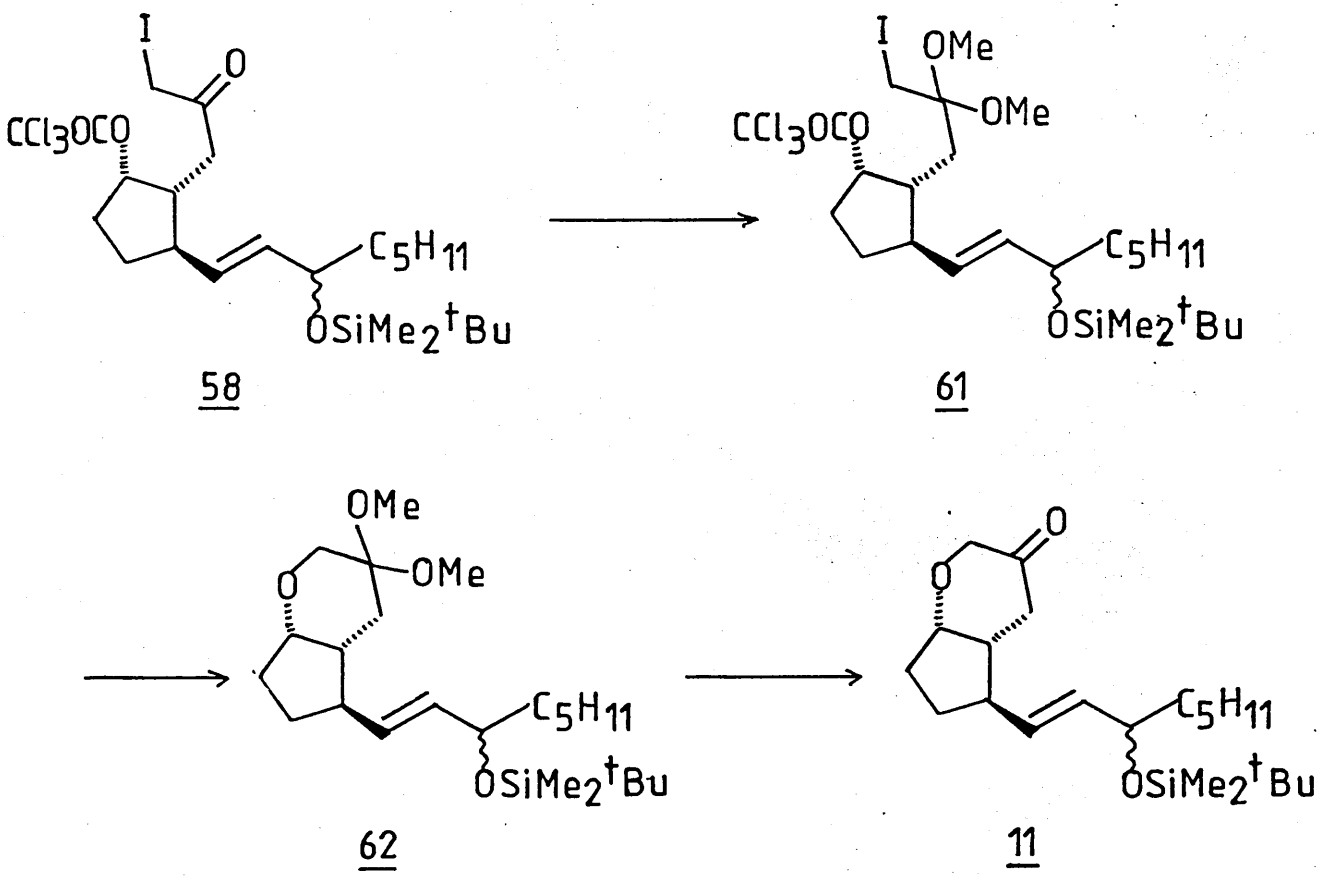
With 59 in hand the cyclisation to give 11 was attempted. The hydroxyketone form,(55) of hemiacetal 59 should cyclise on treatment with base to give the desired ketone 11 (Figure 32)

FIGURE 32



This was attempted by heating 59 with the following base/solvent combinations: DBU/ether, NaH/refluxing ether, NaH/refluxing THF, and NaH/refluxing DME, but none gave cyclisation. The alternative course of action was to mask the carbonyl group in compound 58 as a ketal to preclude internal hemiketal formation, which occurs on removal of the trichloroacetate group. Subsequent cyclisation to 62 and acetal hydrolysis would be expected to give 11 (Figure 33)

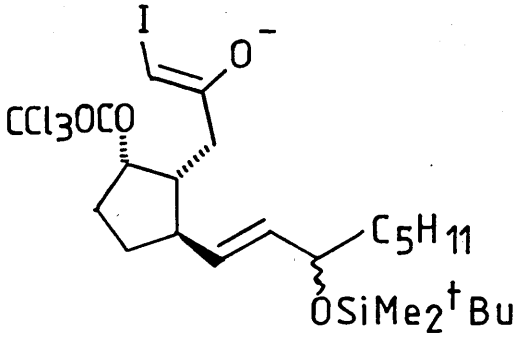
FIGURE 33



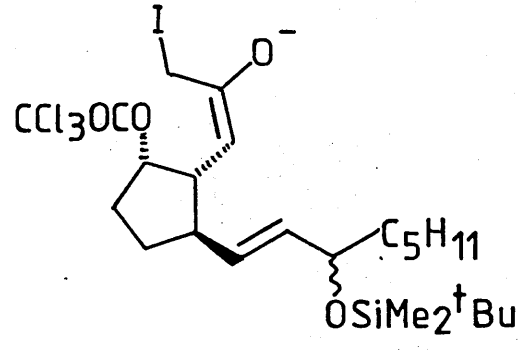
The ketalisation of 58 to give 61 was attempted under a wide variety of conditions, such as: trimethyl formate/ammonium chloride/methanol, boron trifluoride/ methanol, toluene-4-sulphonic acid/methanol, pyridinium tosylate/ ethylene glycol/benzene[84] and methoxytrimethyl silane/trimethylsilyl trifluoromethane sulphonate[85], but only starting material was recovered.

One final interesting observation was made concerning the reactivity of 58. It was decided to investigate the reaction between 58 and a non nucleophilic base. Treatment of 58 with DBU gave a smooth reaction to give one main product. Micro analytical and mass spectroscopy data indicated a loss of HI.

Since DBU is a fairly strong base it is reasonable to assume the initial formation of an enolate which could be one of the two shown below would be the first step.

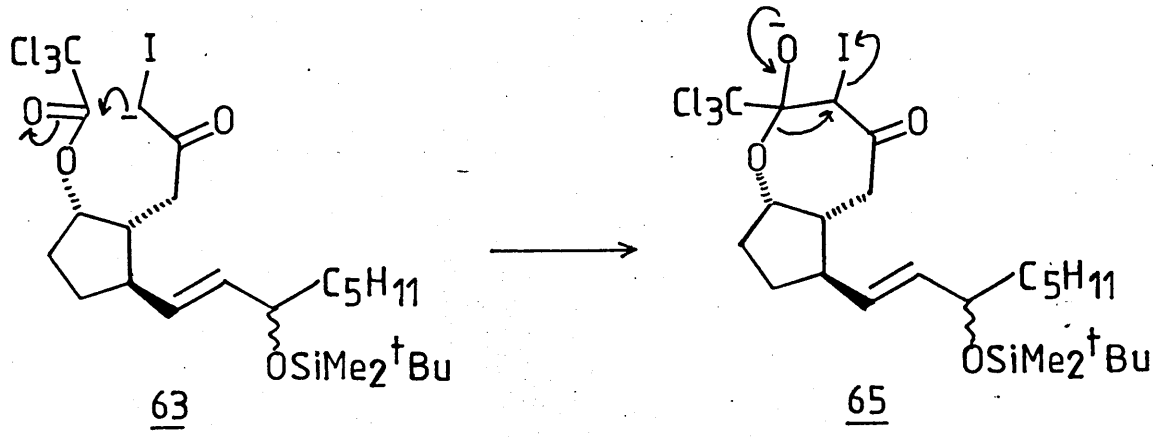


63

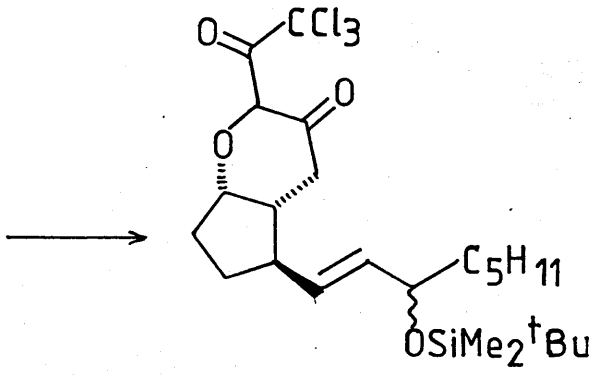


64

If the fates of these enolates are considered separately, it is possible to draw a scheme in which enolate 63 gives the bicyclic ketone 66 via the seven membered hemi-ketal 65.

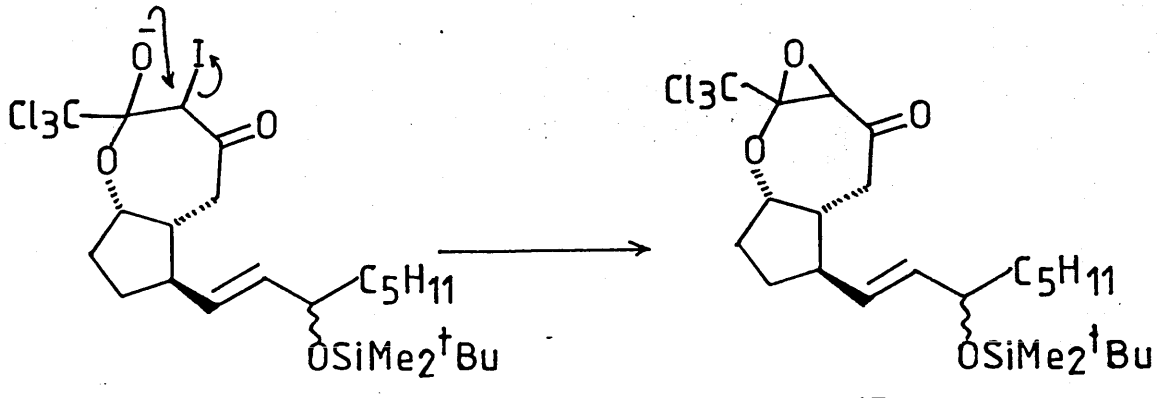


63 65



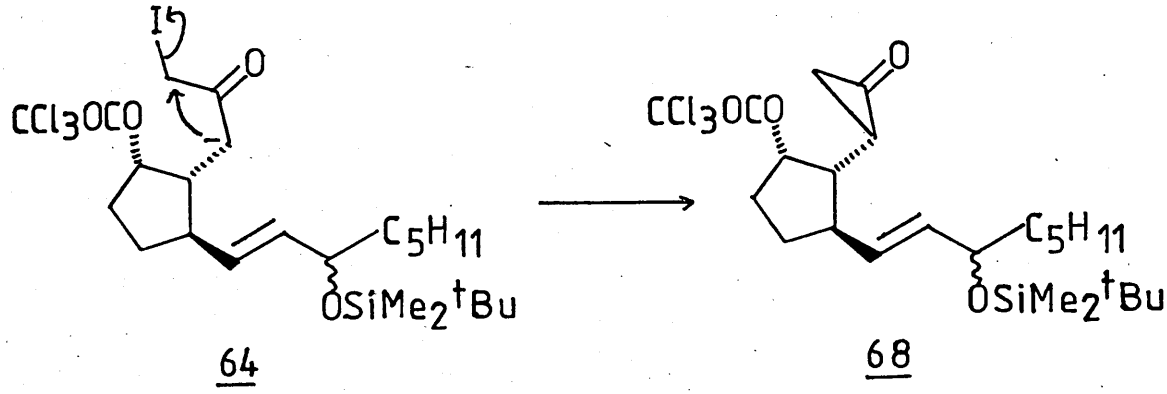
66

An alternative structure derived from the same intermediate hemi-ketal 65, is the epoxy-ketone 67.



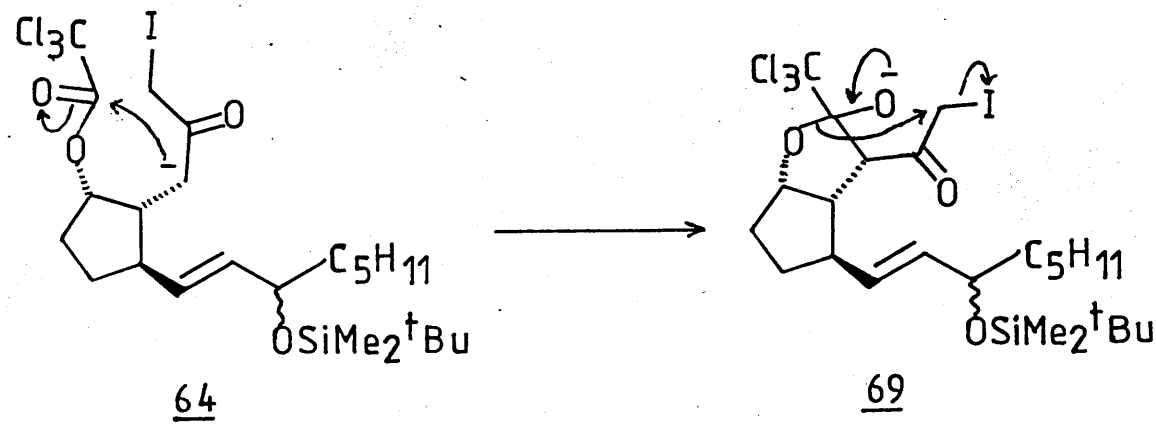
65 67

One fate of the alternative enolate 64 could be to give the unlikely, strained, cyclopropanone 68.

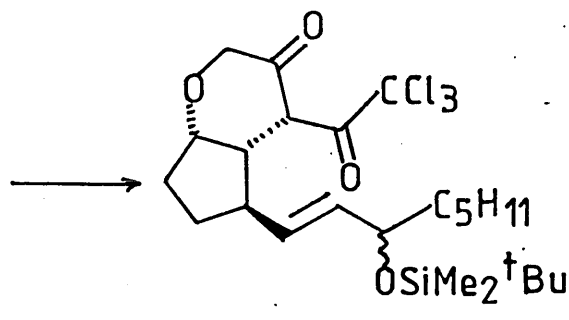


64 68

However it is more likely that the enolate 64 would again give rise to compounds such as the bicyclic ketone 70 via a hemi-ketal 69.

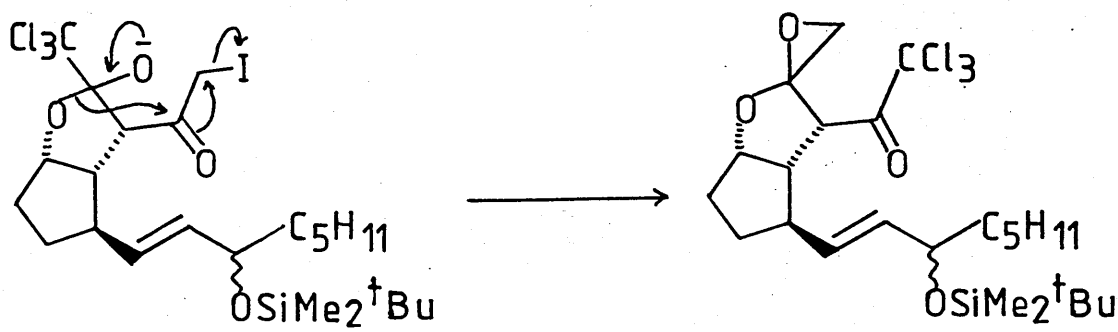


64 69

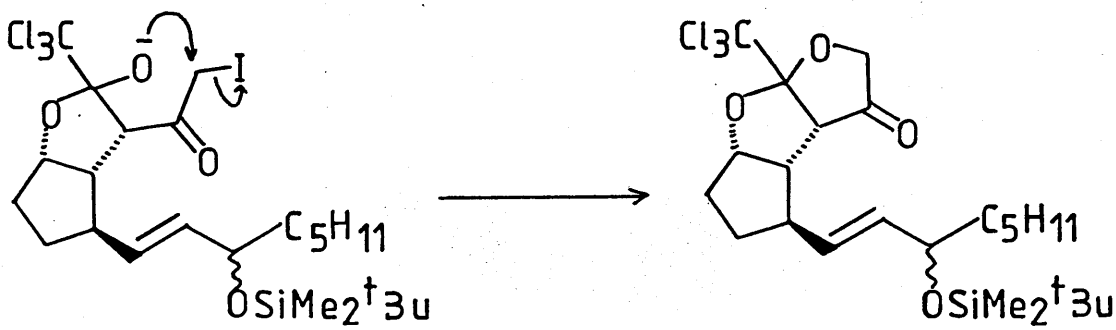


70

From the same intermediate 69 the epoxy-ketone 71 and the tricyclic ketal 72 could possibly occur as indicated in the following schemes.



69 71



69 72

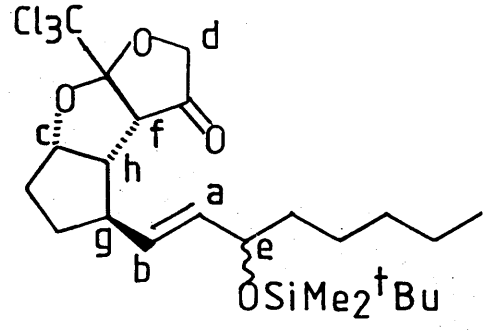
The infrared spectrum, determined as a solution in bromoform, showed the carbonyl stretching frequency to be at 1760 cm^{-1}. This rules out the cyclopropanone 68 which would be expected to have a carbonyl stretching frequency in excess of 1780 cm^{-1} due to ring strain. Also ruled out is the seven membered epoxy-ketone 67 in which the carbonyl stretching frequency would be expected to be at 1725-1705 cm^{-1}. Since there is only one carbonyl frequency at 1760 cm^{-1} this also tends to rule out the bicyclic diketones 66 and 70.

This leaves just compounds 71 and 72 which could both possibly have carbonyl stretching frequencies this high (71 has α-chloro groups and 72 is a five membered ring ketone).

Proton n.m.r. spectra[86] were run in both C_6D_6 and $CDCl_3$ at 90 MHz and also at 200 MHz in $CDCl_3$. ^{13}C nmr were recorded at 62.9 MHz in $CDCl_3$. On the basis of these data the structure of this compound is thought to correspond to the tricyclic ketone 72, possibly formed by the mechanism shown in the above scheme. The salient features of the proton n.m.r. spectra are shown below:

Chem Shift (δ) $CDCl_3$	Chem Shift (δ) C_6D_6	Couplings (Hz)	Assignments (see below)
5.65	5.62	15, 5.5	a
5.45	5.40	15, 6	b
4.91	4.32	6, 6, 2	c
4.47	4.0[1]	16.5	d
4.10	4.11	6, 6	e
2.20	3.20	2	f[2]
2.75	2.60	-	g
2.38	1.92	9.5, 6, 2	h

Coupling Constants (approximately)[3]
J_{ab} = 15 Hz
$J_{ae,bg}$ = 5 - 6 Hz
J_{ch} = 6 Hz
J_{gh} = 9.5 Hz
J_{fh} = 2 Hz
J_d(gem) = 16.5 Hz

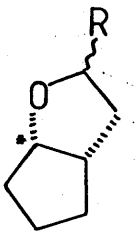


1 Centre of AB system (singlet in $CDCl_3$)

2 Two doublets (for the two epimers ?)

3 Confirmed by spin decoupling experiments

The methine proton (c) at δ 4.91 in $CDCl_3$ from its position and splitting pattern is characteristic of the system shown below.



The large geminal coupling constant of protons (d) and their chemical shift strongly suggests that it is a methylene group between carbonyl and ether oxygen. This large geminal coupling constant also conclusively rules out the alternative structure 71, since the geminal coupling constant for oxiranes is very small (4-6 Hz).

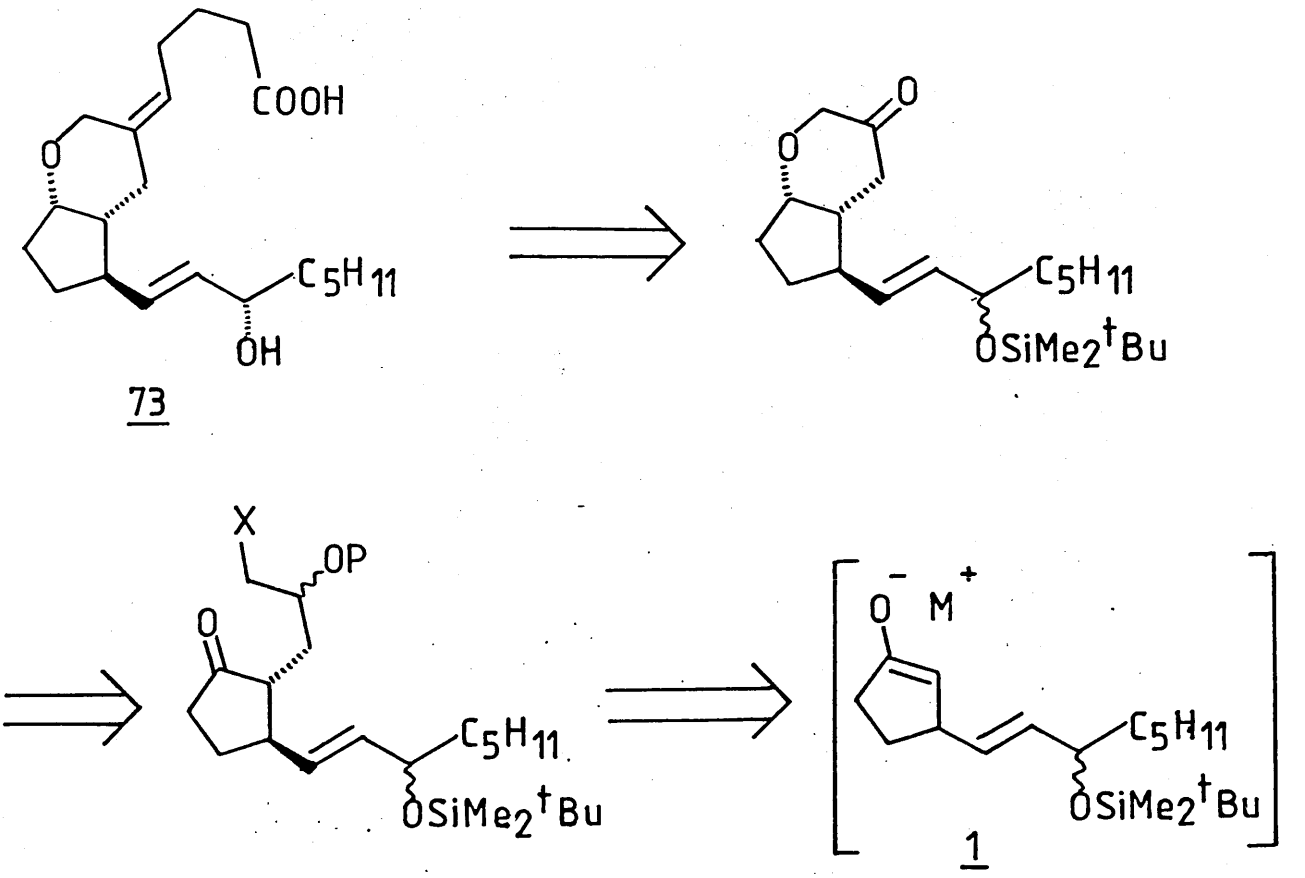
The structure 71 is also unlikely on chemical shift grounds: from consideration of shielding of the oxirane methylene protons, a large difference in their chemical shifts would be expected, whereas the

methylene protons in these spectra are isochronous in $CDCl_3$ and nearly so in C_6D_6. The other chemical shifts and coupling constants shown are not inconsistent with proposed structure 72. ^{13}C n.m.r. data is also consistent with structure 72 and is given in the experimental section.

3.2 Conjugate addition-alternative alkylating agents

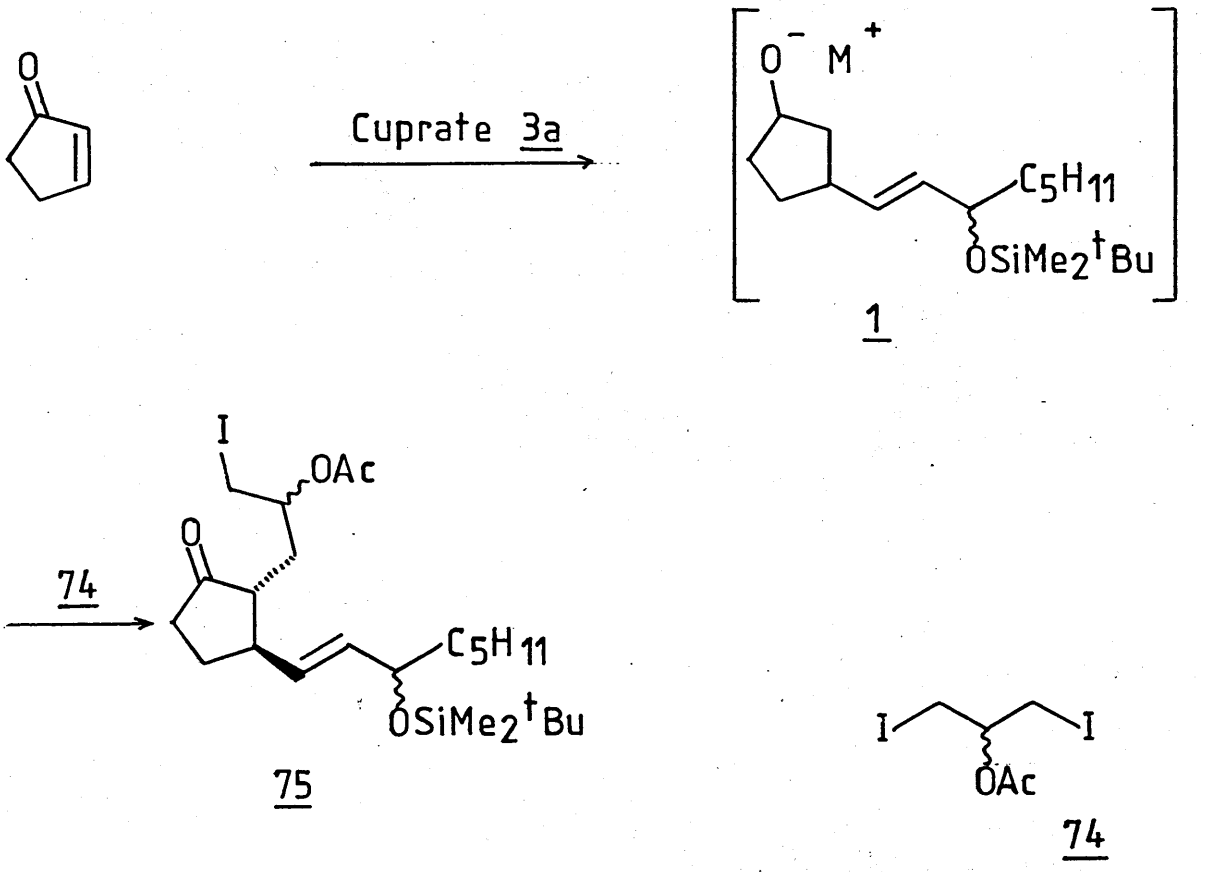
A retro-synthetic analysis of the target 11-deoxy-homoprostacyclin 73 (Figure 34) indicates that the use of an alkylating agent already functionalised with the elements of a halohydrin or a masked halohydrin would be of great synthetic utility.

FIGURE 34



Initial attempts to introduce this type of functionalised α side-chain were made using 2-acetoxy-1,3-diiodopropane 74 (Figure 35) to give the protected halohydrin 75.

FIGURE 35

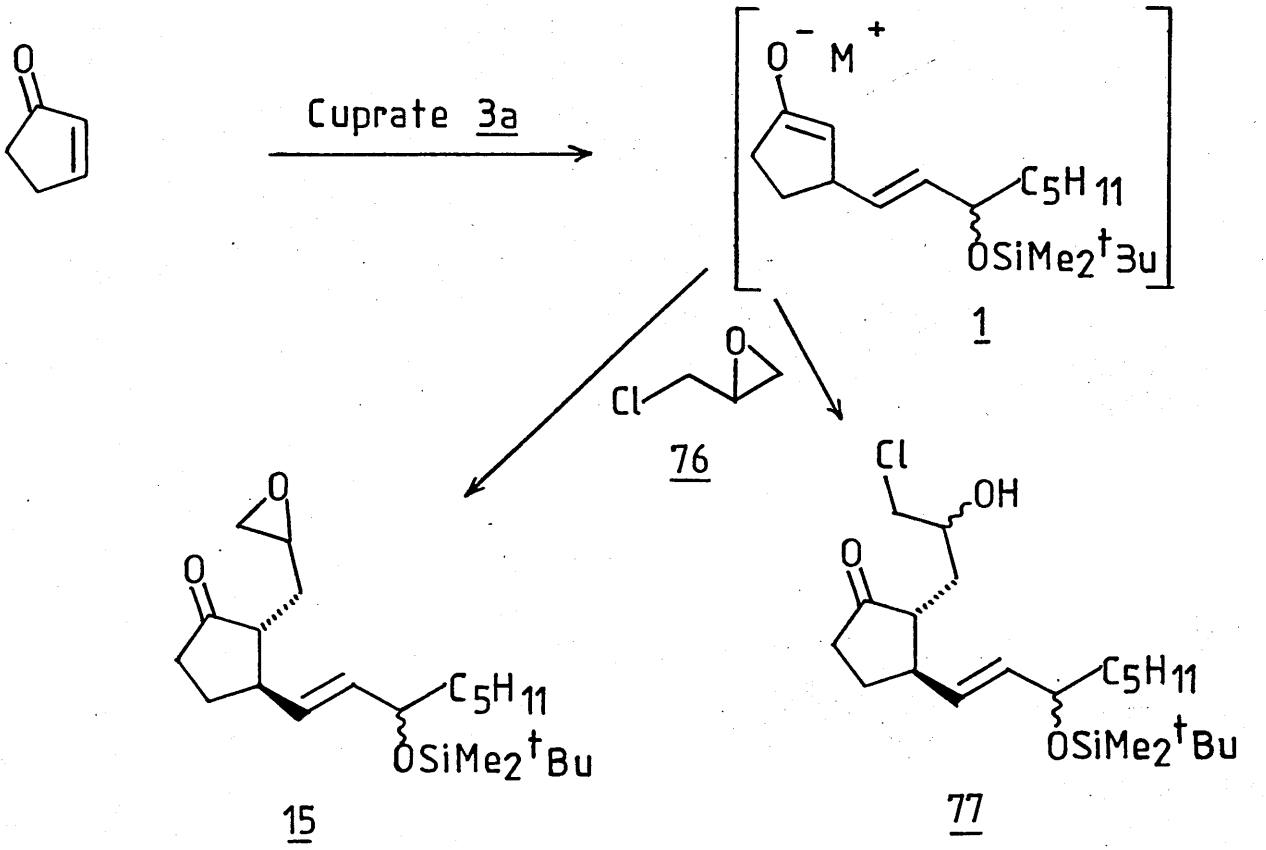


A variety of conditions were employed for the alkylation reaction and either unalkylated ketone 4 or a mixture of products were obtained.

The second alkylating agent tried was epichlorohydrin 76, which was expected to give either

ketoepoxide 15 or halohydrin 77 (Figure 36). Epichlorohydrin has been reported to react with Grignard reagents to produce chlorohydrins[87].

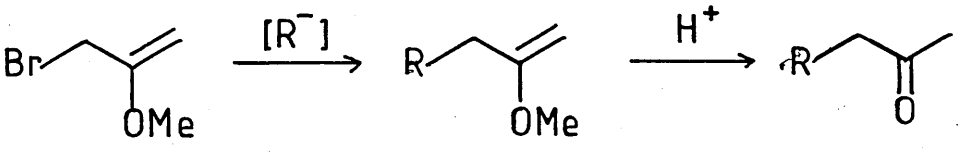
FIGURE 36



Once again the alkylation reaction was unsatisfactory. It is believed that these alkylating agents 74 and 75 are insufficiently electrophilic to react with enolate 1.

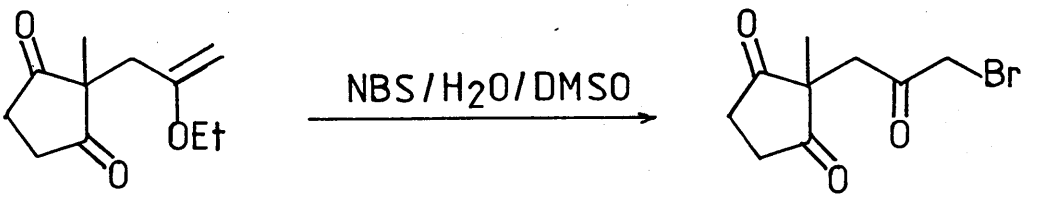
3.2.1 Methoxyallyl bromide

Methoxyallyl bromide 78 has been reported to be a useful alkylating agent for the introduction of a masked acetonyl side-chain[88] eg:



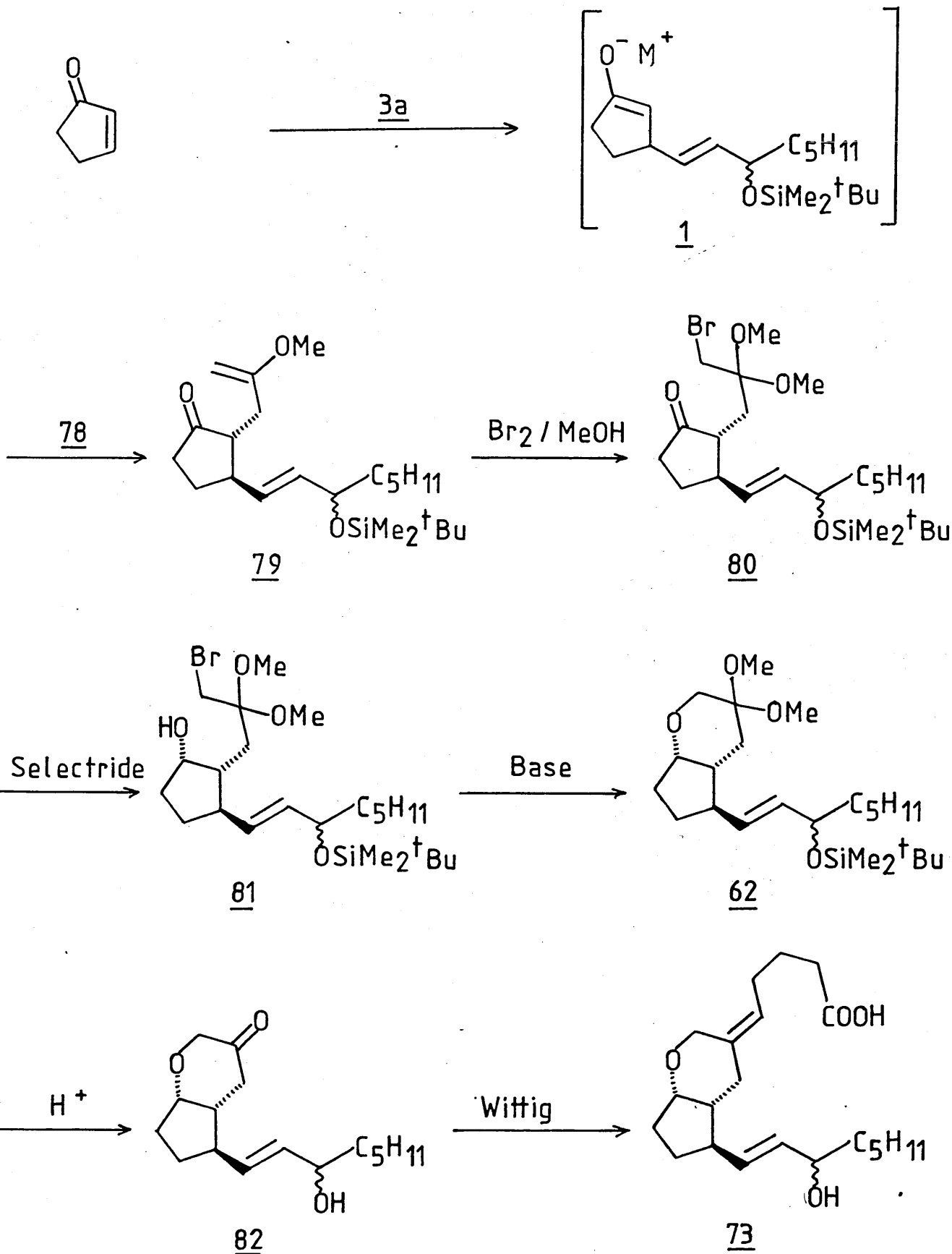
78

A modification of this procedure has recently been used by Trost to prepare α-bromoketones[89].



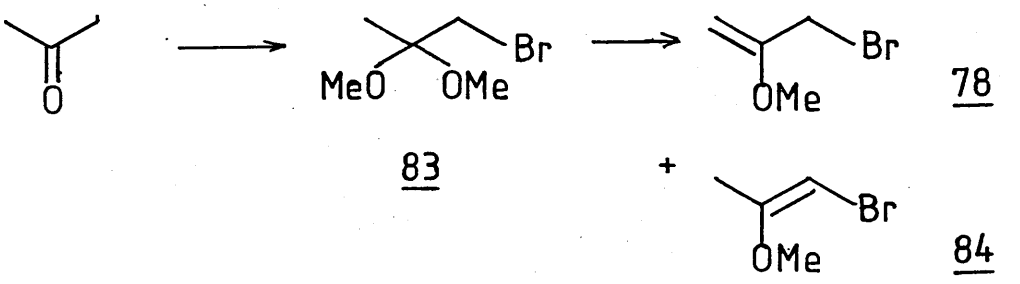
It seemed reasonable to exploit this methodology in the synthesis of 11-deoxy-homoprostacyclin by investigating the route shown in figure 37.

FIGURE 37

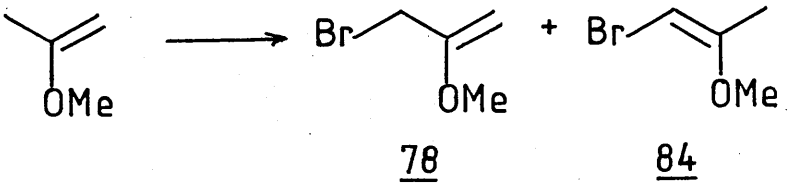


There are several ways of preparing methoxyallyl bromide 78 and two of these are outlined below.

Method 1[88]



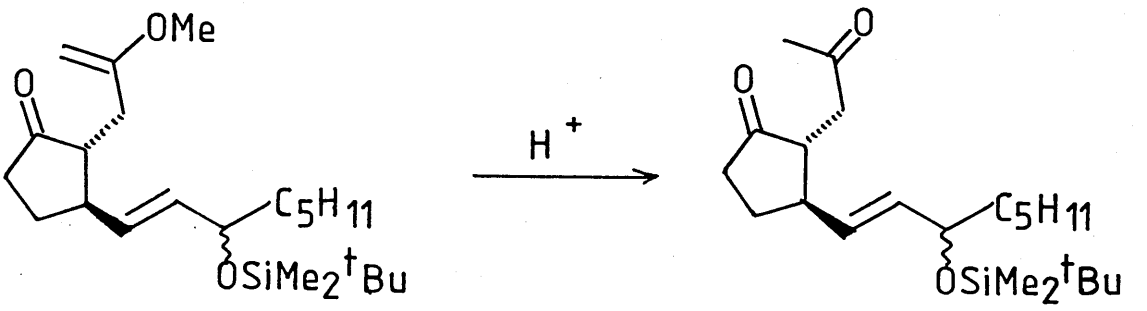
Method 2[90]



Method 1 was found to be preferable. 1-Bromo-2,2-dimethoxypropane 83 was prepared directly from acetone using the method of Garbisch[91]. 83 was then pyrolysed with diisopropylethylammonium-p-toluenesulphonate, (a cracking catalyst) giving methanol and a mixture of the desired 2-methoxyallyl bromide 78 and the isomeric 1-bromo-2-methoxy-prop-1-ene 84. The mixture of 2-methoxyallyl bromide 78 and 84 was used in the 'one-pot' conjugate addition-enolate alkylation reaction to give the desired methoxy enol ether 79 (Figure 37).

The alternative route to 79 via the silyl enol ether 7 (as in Figure 5) was again tried but gave generally lower yields (12% overall) than the 'one-pot' method (16% overall).

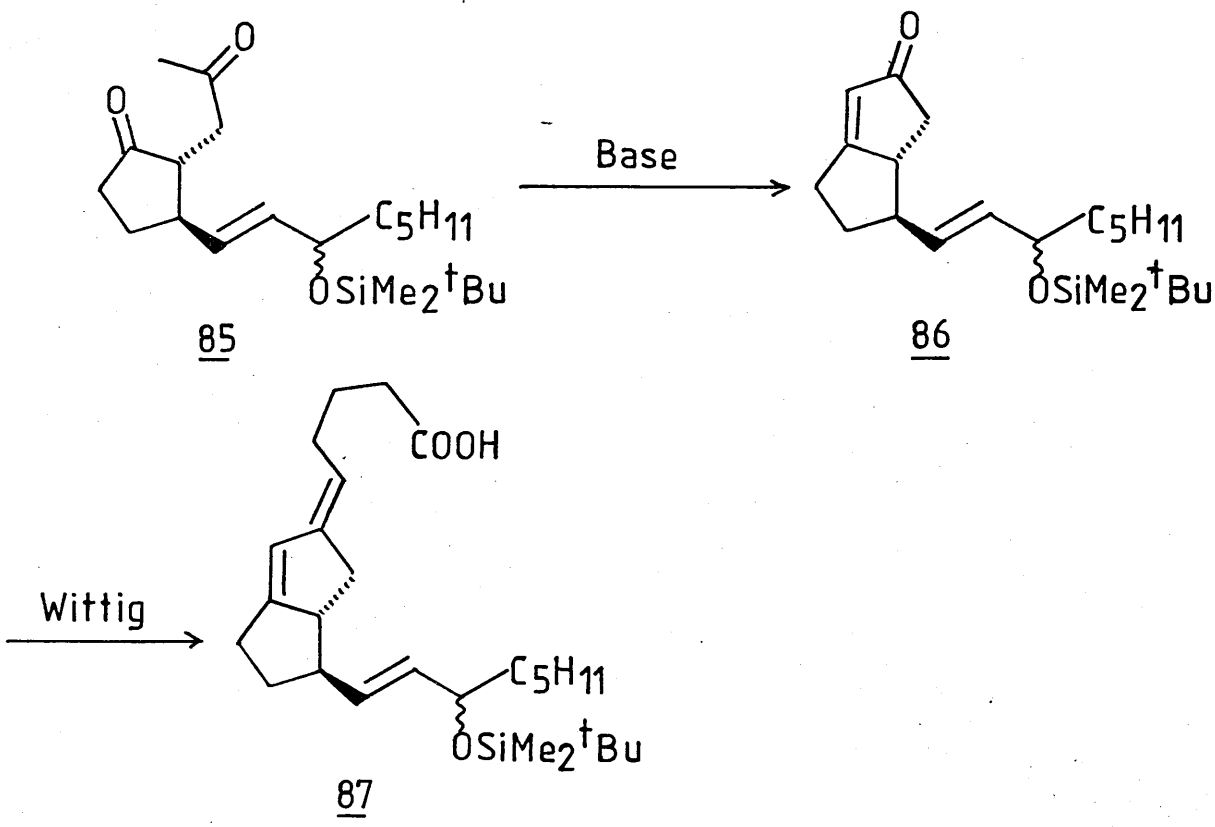
The methoxyenol ether 79 was found to be labile to hydrolysis giving the diketone 85.



79 85

Partial hydrolysis of 79 to 85 occurred during purification on silica, if the silica was not first pretreated with triethylamine (1% by weight on the silica), and hydrolysis of 79 to 85 could be achieved in quantitative yield in dilute solutions of aqueous oxalic acid in THF.

A preliminary investigation was carried out to see if the diketone 85 would undergo an intramolecular aldol reaction to give the bicyclic enone 86, a precursor to the novel prostaglandin I_2 analogue 87.

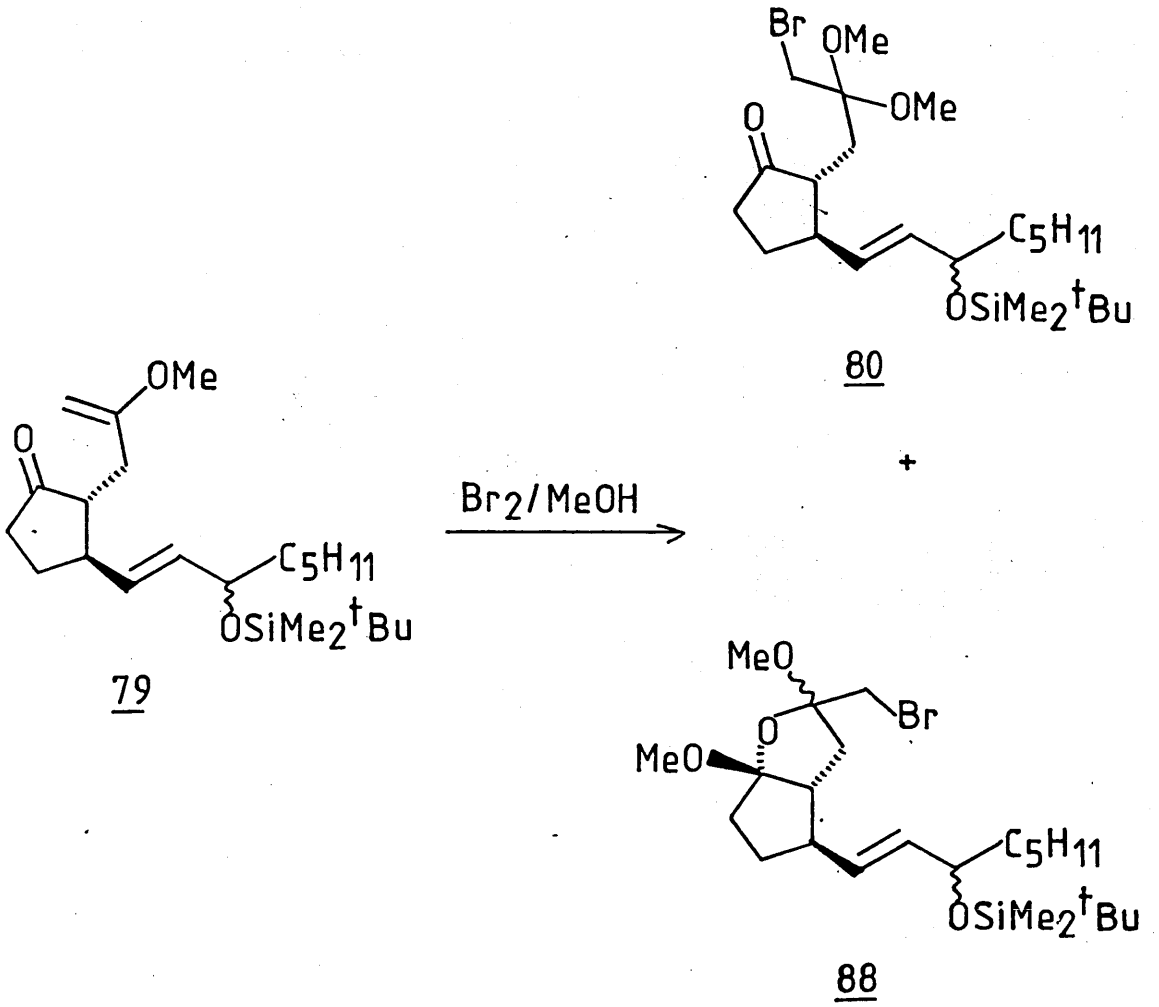


85 86 87

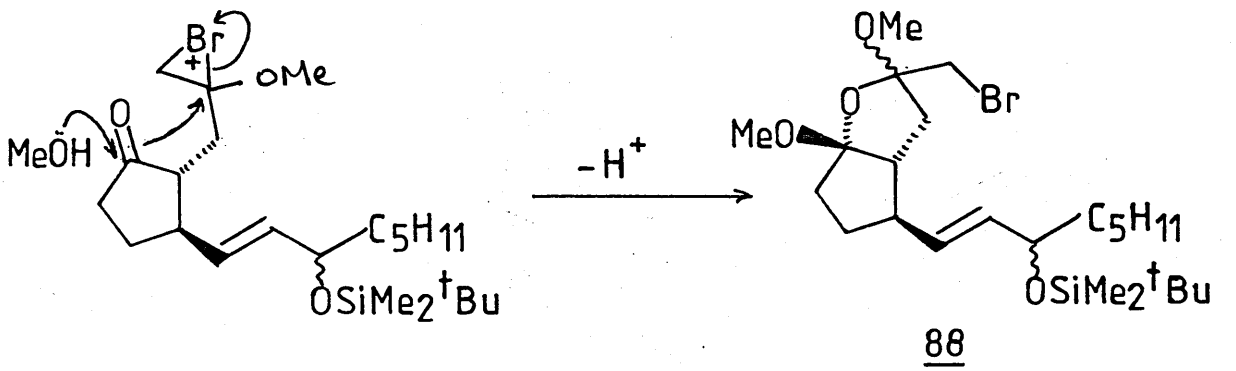
Although there are many literature precedents for the formation of these five membered cyclic enones by intramolecular aldol condensation[92,93] in these cases the substrates were invariably more highly substituted. Unfortunately, the aldol condensation did not take place under standard alkaline treatment (potassium hydroxide in refluxing aqueous ethanol). The difficulty in obtaining bicyclo-[3.3.0]-oct-1-enones by aldol reactions has previously been noted[88,89,93].

With methoxyenol ether 79 in hand the synthetic route outlined in figure 37 was followed. The first reaction was the bromination of the enol ether in

methanol to give the α-bromo dimethyl ketal 80. There is a precedent for this type of reaction occurring in the presence of a prostaglandin ω side-chain[94]. When this reaction was carried out on 79 the desired product 80 was obtained in 44% yield after chromatography and a less polar pair of products, whose spectral data were consistent with bicyclic acetals 88 were also obtained in 18% yield.



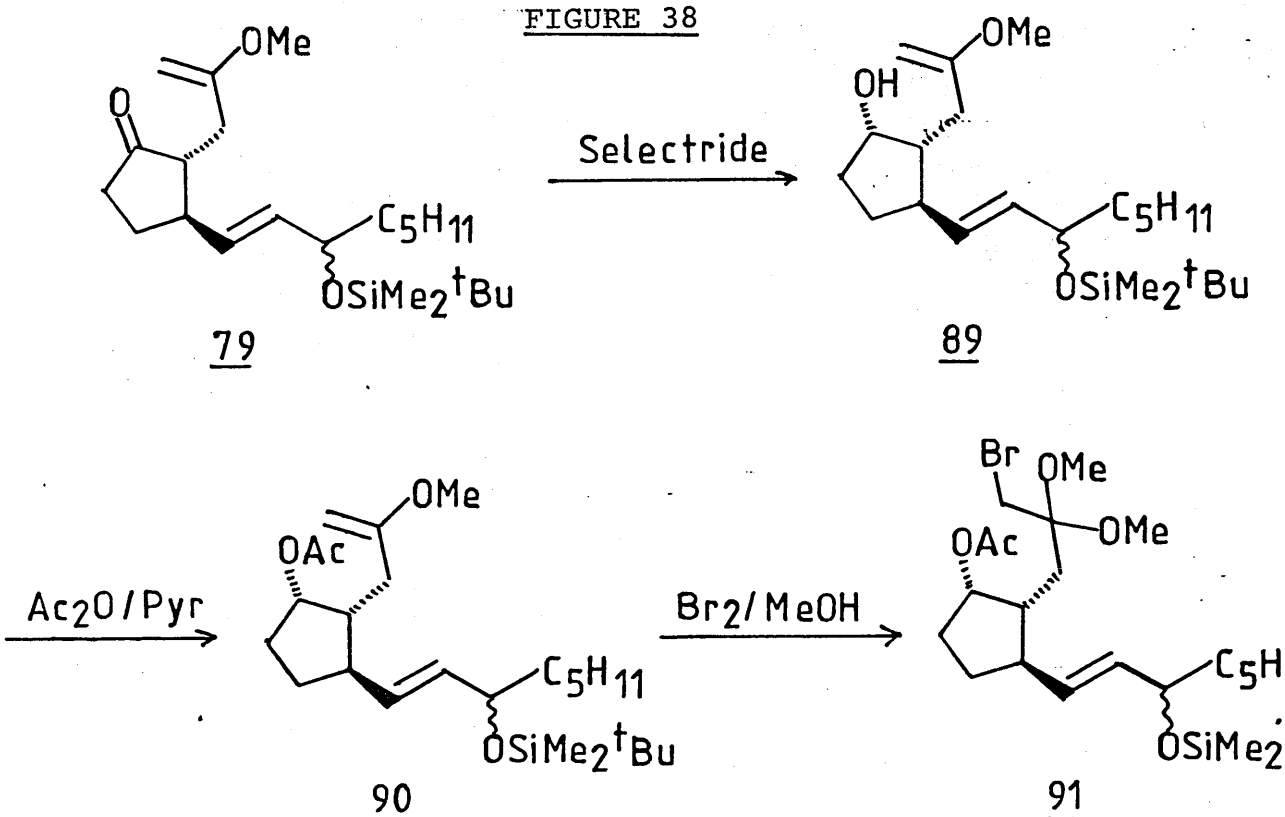
Again the interference by the oxygen at C-9 is occurring, probably giving rise to 88 by the mechanism outlined below.



88

An alternative route outlined in figure 38 shows an attempt to avoid the intramolecular attack by oxygen.

FIGURE 38

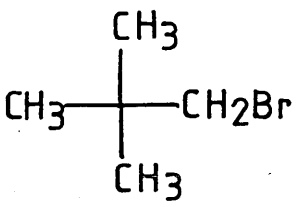


79 89 90 91

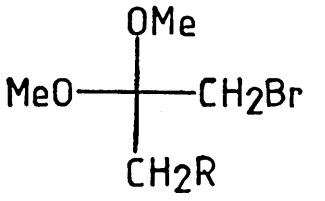
Reduction of the ketone 79 to the α-alcohol 89 proceeded smoothly with 'K-selectride' reducing agent. However attempts to acetylate 89 to give 90 were unsuccessful, resulting in recovery of starting material 89. In view of this failure, the synthetic route shown in figure 37 was readopted in spite of the low yields in the bromination step. The α-bromo dimethylketal 80 was reduced with 'K-selectride' to give the α-alcohol 81 in 95% yield.

Initial attempts to cyclise 81 were carried out with sodium hydride in DMSO, but problems were encountered in separating the products from DMSO. Sodium hydride in refluxing THF was the reagent of choice and gave the bicyclic ketal 62 in 58% yield. However, this reaction was very slow, taking two days at reflux in THF. This was presumably due to the fact that cyclisation was taking place onto a neopentyl-like centre (figure 39) and SN_2 reactions at neopentyl centres are known to be subject to extreme steric hindrance[95].

FIGURE 39



Neopentyl Bromide

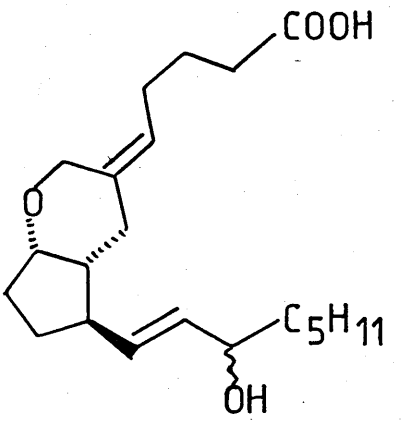


81

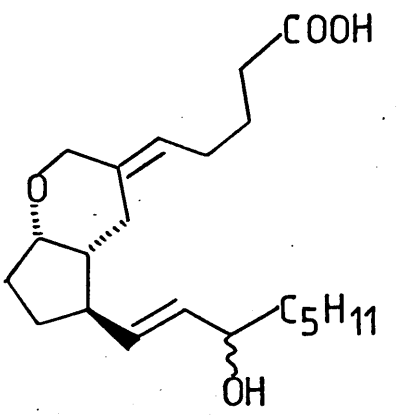
The bicyclic ketal 62 was de-ketalised and desilylated in one step using 10% by weight of a 10% aqueous oxalic acid solution on silica in dichloromethane[96]. This gave the key bicyclic ketone intermediate, 82 in 79% yield.

The synthesis was completed by carrying out a Wittig reaction with an excess of the ylid derived from 4-carboxybutyl-triphenylphosphoniumbromide and potassium *tert*-butoxide, directly on the ketoalcohol 82 in THF at ambient temperature, under nitrogen. The target molecules *Z*-and *E*- 11-deoxyhomoprostacyclin 73 were obtained as a mixture of 15-epimers. The two compounds were separated by chromatography. The more polar was assigned the *Z*- structure 73a because of the broad AB system seen in the nmr (J=12Hz) due to the 6a protons, (these protons sterically interact in the *Z*-configuration with the upper side chain)[81]. The less polar *E*-isomer 73b showed a broad singlet for the 6a protons. These data compare favourably with that obtained for the 11-hydroxylated compound recently prepared by Skebulla[81]. The H-5 olefinic protons were also fairly characteristic in chemical shift[81] at 5,22 in the *Z* isomer and 5.34 in the *E* isomer.

The 15-epimers were inseparable in several different solvent systems.



73a



73b

The biological properties of 73a and 73b are currently under investigation.

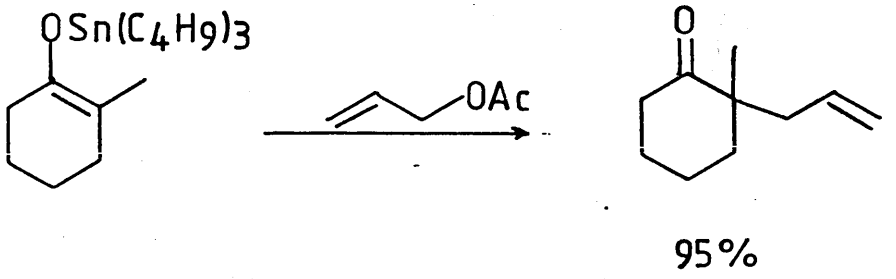
Chapter 4 Further Work

4.1 Elaboration of existing synthetic routes or intermediates

The target molecule produced by the synthetic route discussed in Chapter 3 will be screened for biological activity with platelet preparations in order to ascertain the compounds possible clinical utility as a therapeutic agent in the treatment or cure of thrombosis. In the event of these tests giving promising results, a more efficient route to these target compounds would be valuable and some possible schemes, to this end are presented here,

4.1.1 Conjugate addition-enolate alkylation, a more efficient alkylation step

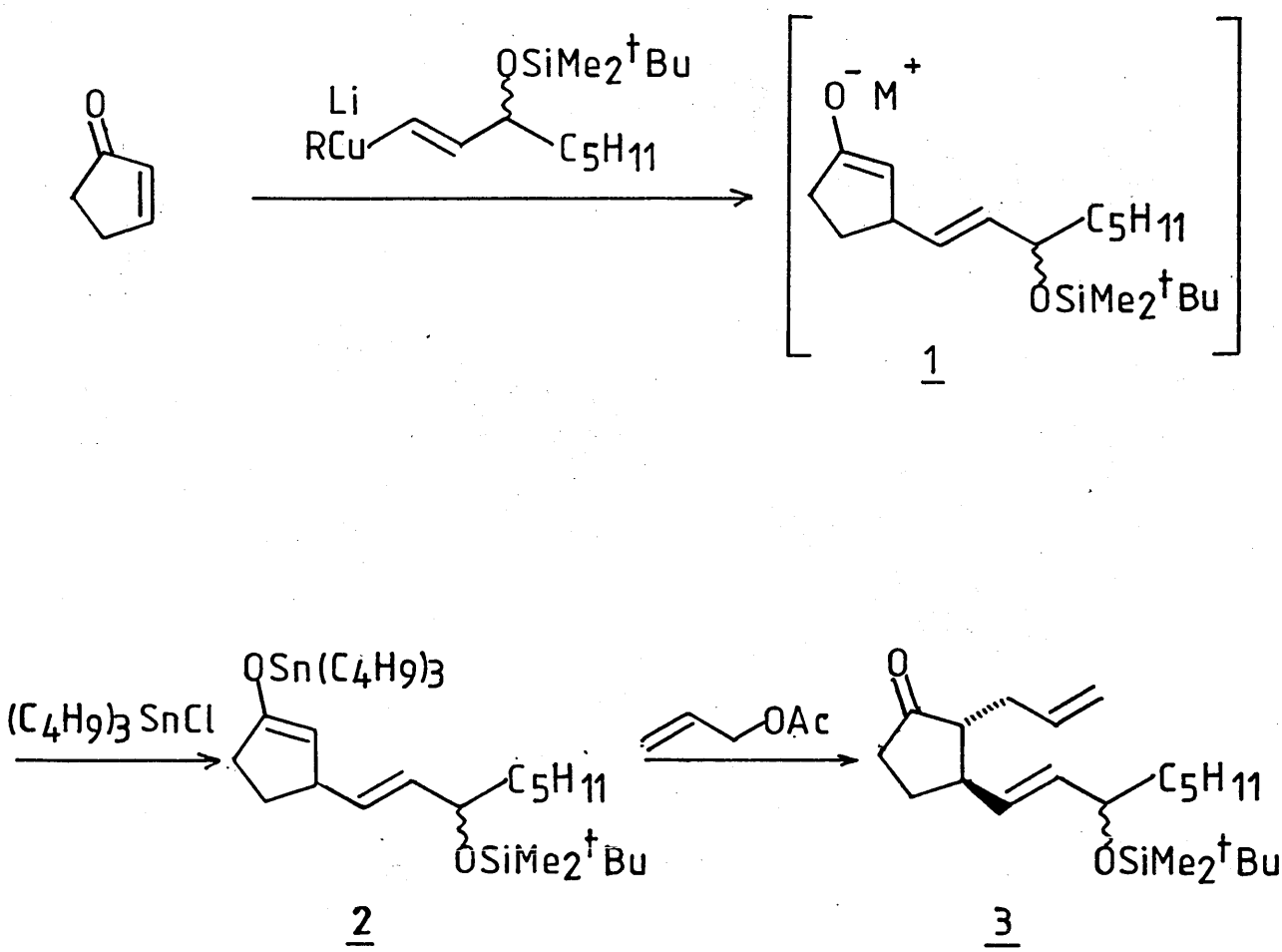
Tri-n-butyltin enol ethers are reported to be alkylated in high yield with allylic acetates[97].



95%

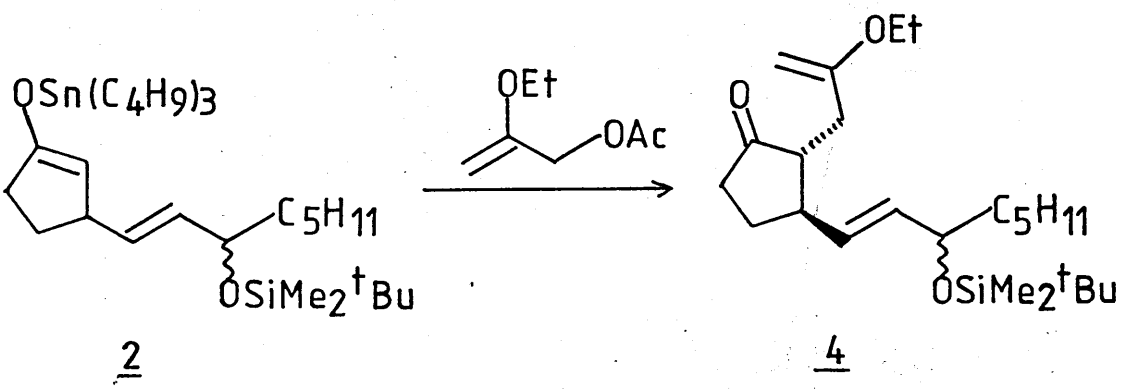
These enol stannanes can be prepared by treating the lithium enolate with tri-n-butyltin chloride[97]. This reaction could be applied to the initial conjugate addition-enolate alkylation reaction (figure 1) by trapping the intermediate lithium enolate 1 as the tri-n-butylstannyl enol ether 2, which could then be alkylated with allyl acetate to to give ketone 3.

FIGURE 1



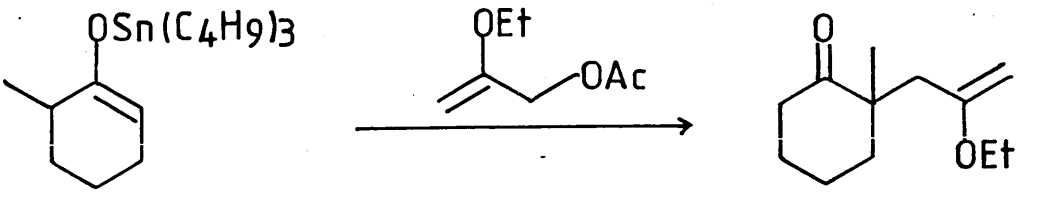
Perhaps more useful still, in view of the ultimate success of the synthetic route using an intermediate, with a 2-methoxyallyl side-chain in the molecule (compound 70 in Figure 37, Chapter 3), would be the use of 2-ethoxyallyl acetate in the alkylation of enol stannane 2 (Figure 2) to give ethoxy enol ether 4.

FIGURE 2



2 4

However, it would appear that 2-ethoxyallyl acetate is a much more sluggish alkylating agent and leads to equilibration of the enolate in six membered systems to give the product of the thermodynamic enolate[97]

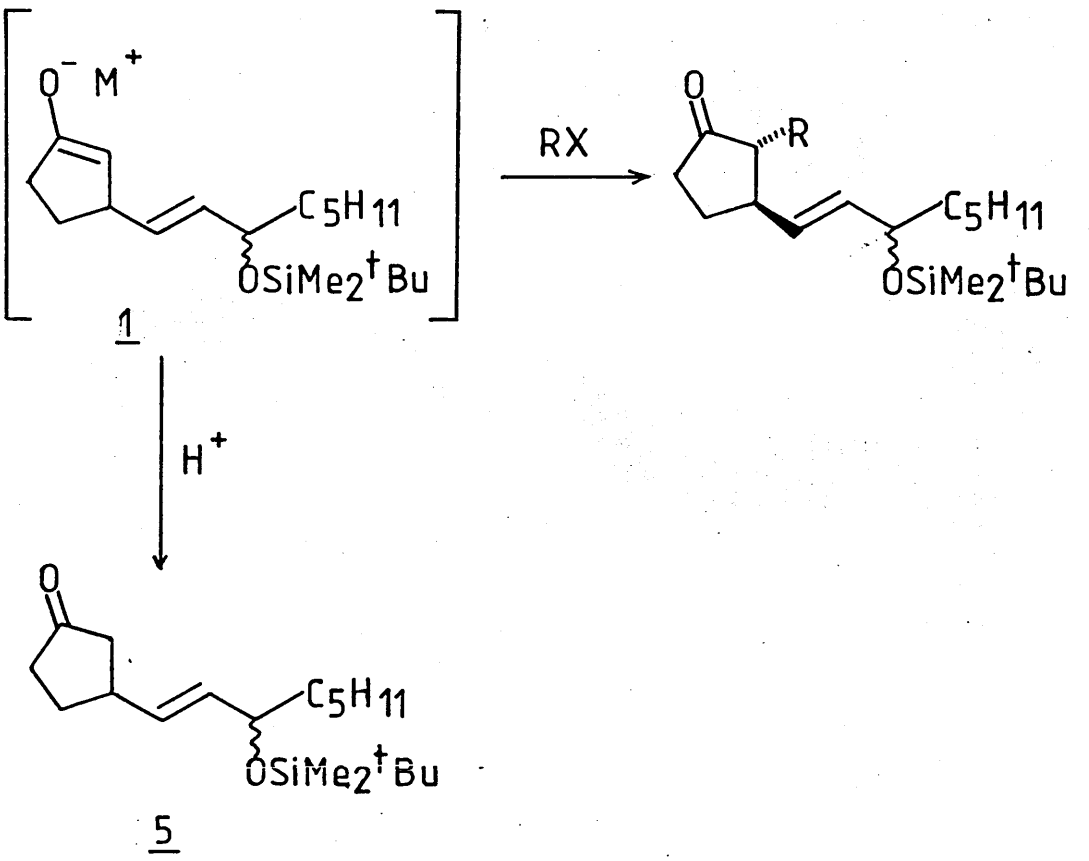


Equilibration of this type in our system would lead to a loss of regioselectivity and would therefore not be of use.

4.1.2 Recycling of potentially useful by products

During conjugate addition-enolate alkylation reactions a major by-product 5 (Figure 3) arises from quenching of unreacted enolate.

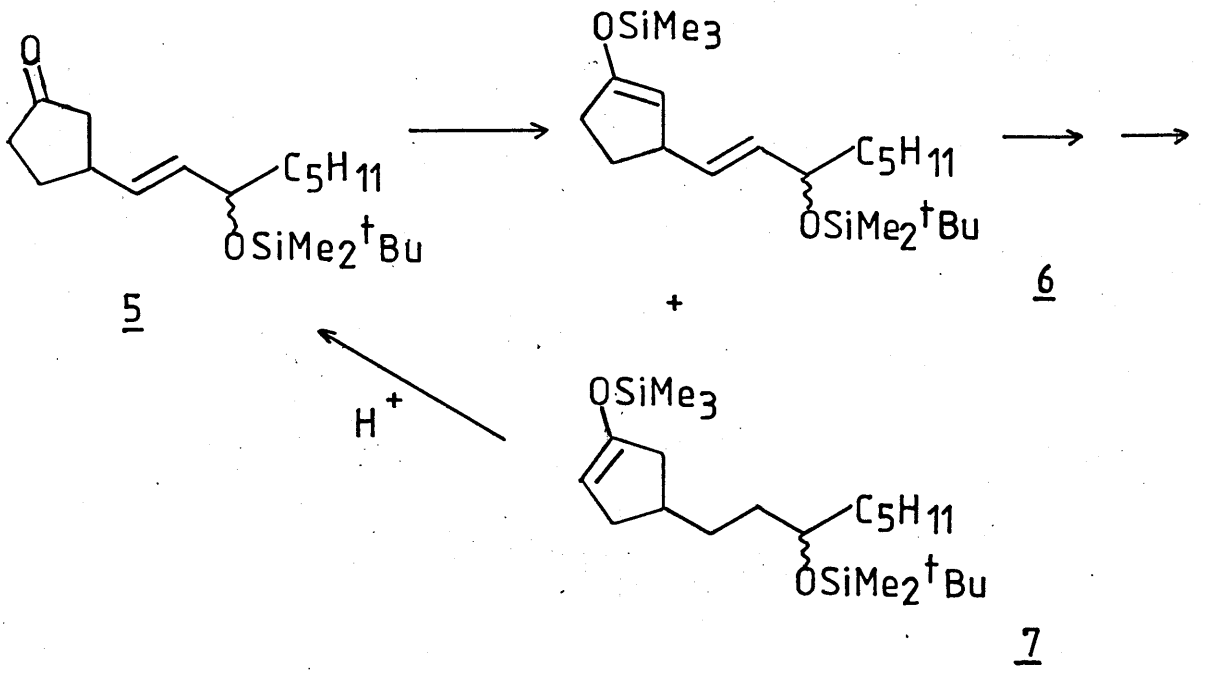
FIGURE 3



It may be possible to enolise this ketone under equilibrating conditions, trap the enolates as the

trimethylsilyl ethers 6 and 7 (Figure 4). Separation of these enol ethers at this stage would allow 6 to be saved and the other enol ether 7 to be recycled again.

FIGURE 4



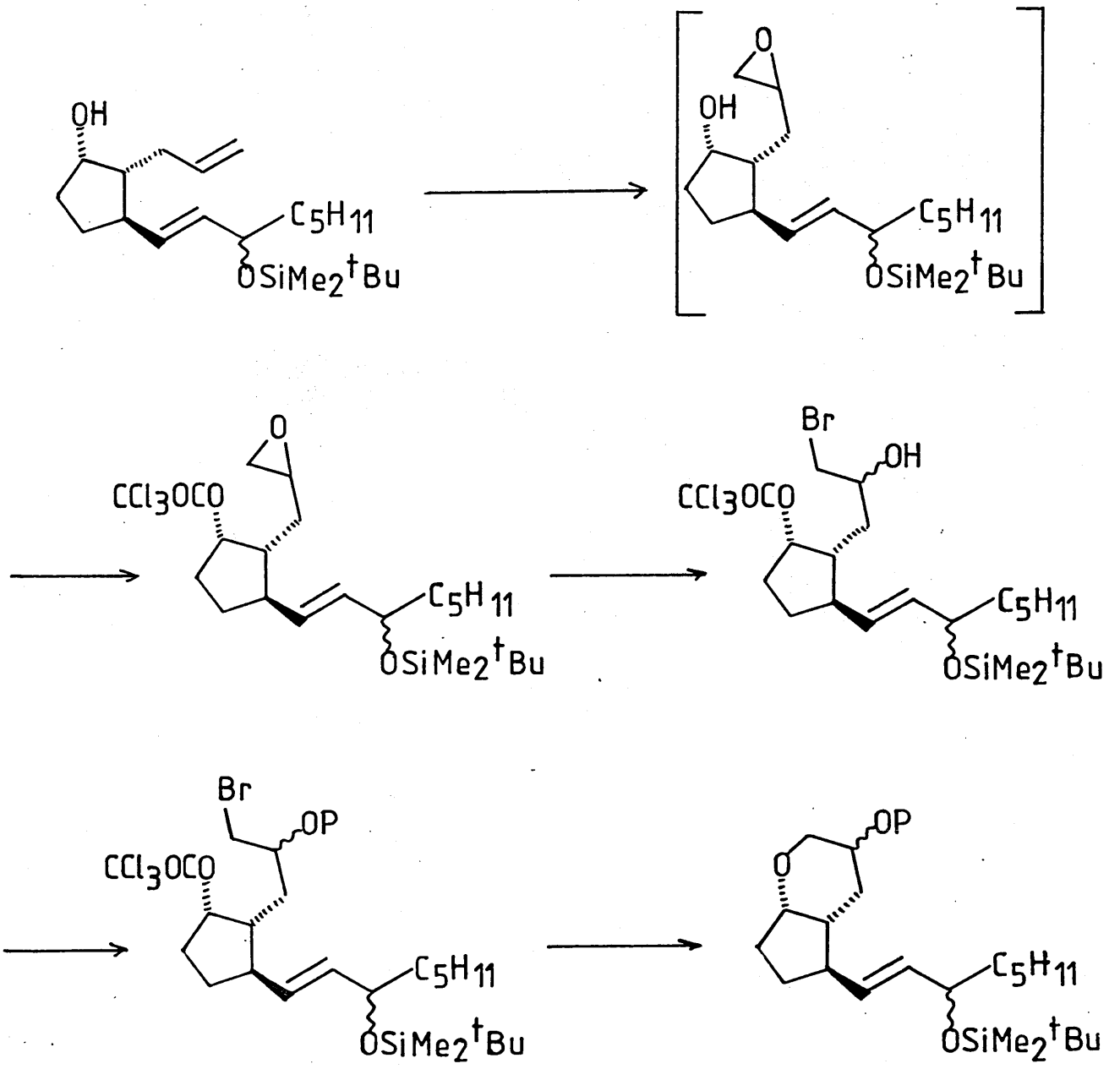
Enol ether 6 could then be used in alkylation reactions as described in Chapter 3.

4.1.3 Modification of epoxide route

The epoxide approach to the synthesis of the target 11-deoxyhomoprostacyclin was not successful due to the uncontrolled closure of the epoxidised alcohol, (Figure 8, Chapter 3) and an attempt was made to trap

out the hydroxyepoxide as its acetate (Figure 13, Chapter 3). This however was unsuccessful which was considered to be due to the relatively slow rate of acetylation. Subsequent work has shown trichloroacetic anhydride to be very much more reactive than acetic anhydride in acetylation reaction (2 min for trichloroacetylation compared with 24h for acetylation). A possible reaction scheme which combines these observations is shown in figure 5.

FIGURE 5



4.1.4 The Bromohydrin route to 11-deoxyhomoprostacyclin

The bromohydrin route to the target molecule, illustrated in figure 6 has been followed as far as the silylated bromohydrin 8. In view of the recent report of the synthesis of homoprostacyclin which used a very similar procedure (Figure 27, Chapter 3), it seems likely that the route in figure 6 would also lead to the target molecules 9.

FIGURE 6

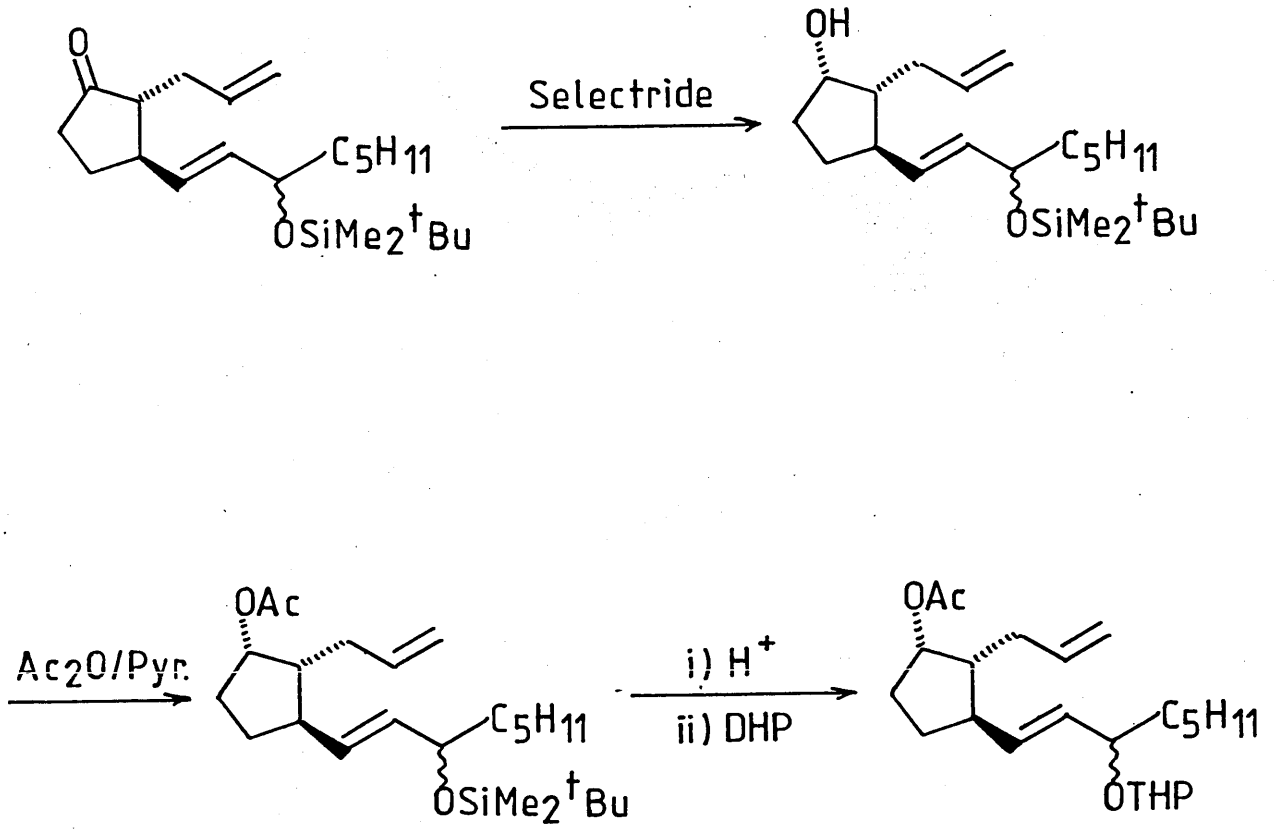
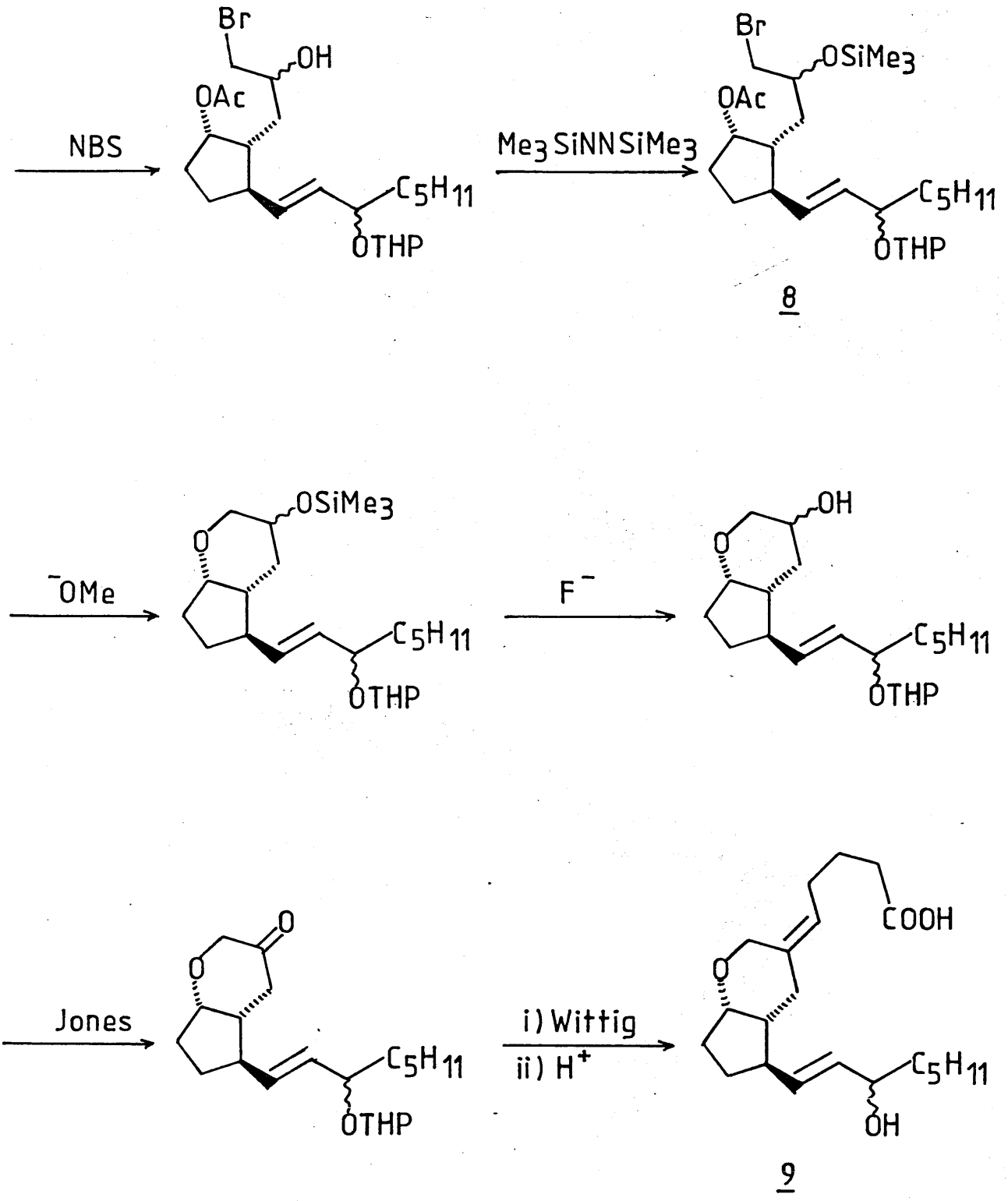


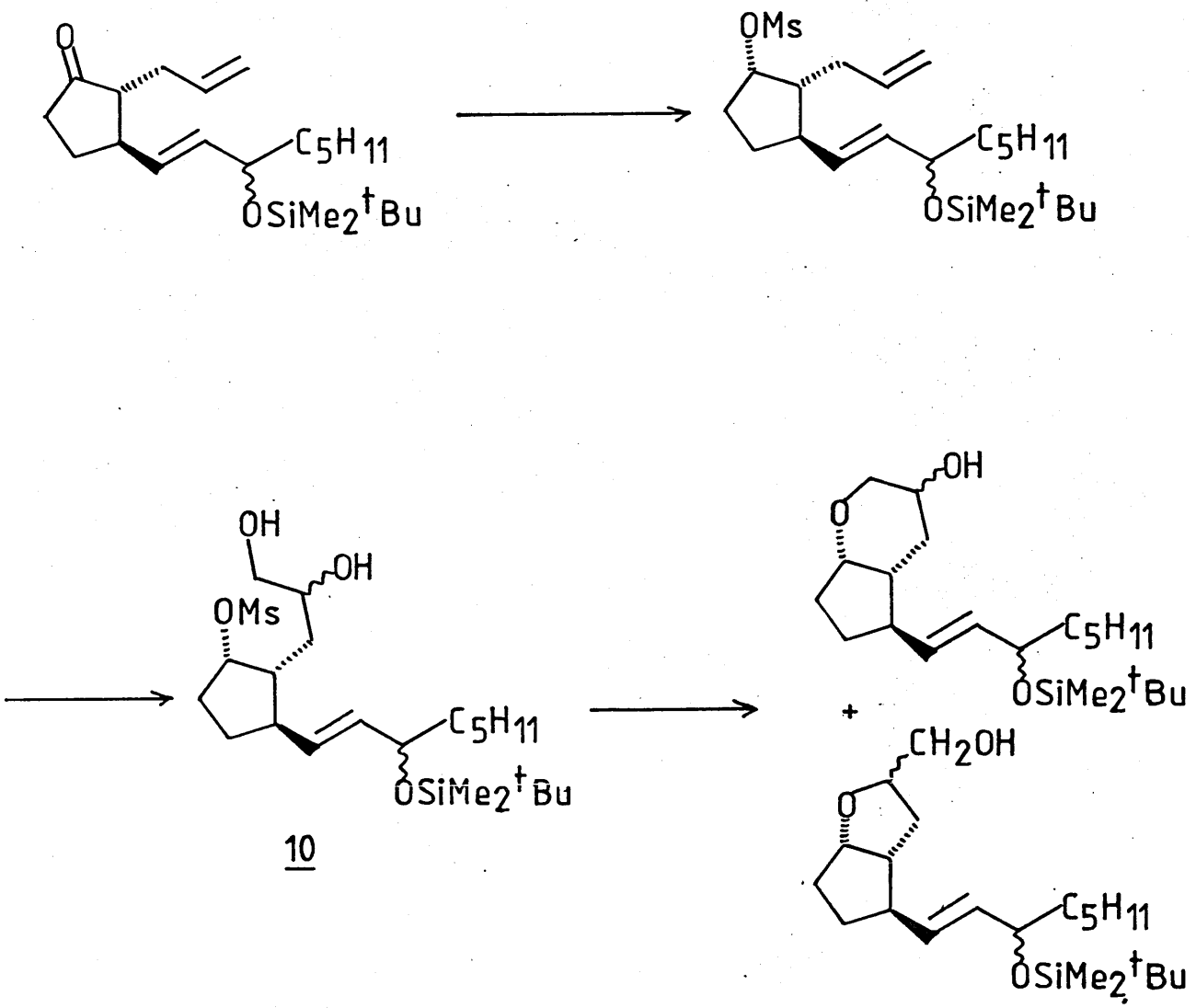
FIGURE 6 cont'd.



4.1.5 Reverse direction ring closure

All routes explored so far have attempted to form the pyran ring using a leaving group at the end of the α side-chain and a nucleophilic alkoxide on the cyclopentane ring. Ring closure in the reverse direction with the leaving group on the cyclopentane ring and the oxygen nucleophile on the end of the α side-chain is feasible and a scheme is shown in figure 7.

FIGURE 7



Both possible closures of 10 are allowed according to Baldwins Rules[58] (5-*exo*-tet and 6-*exo*-tet) and a mixture of the 5,6 bicyclic pyran system and the 5,5 bicyclic furan system would probably be formed. A separation at this stage and further elaboration of the pyran bicycle could give the target 11-deoxyhomoprostacyclin 9.

4.2 Molecular Roulette

The relatively flexible synthetic route described in Chapter 3 can be easily modified at many stages to give slightly different 11-deoxyhomoprostacyclin derivatives. By changing the cuprate and the Wittig reagent, α and ω side-chain modified analogues can be prepared and tested for biological activity.

4.3 Alternative target molecules

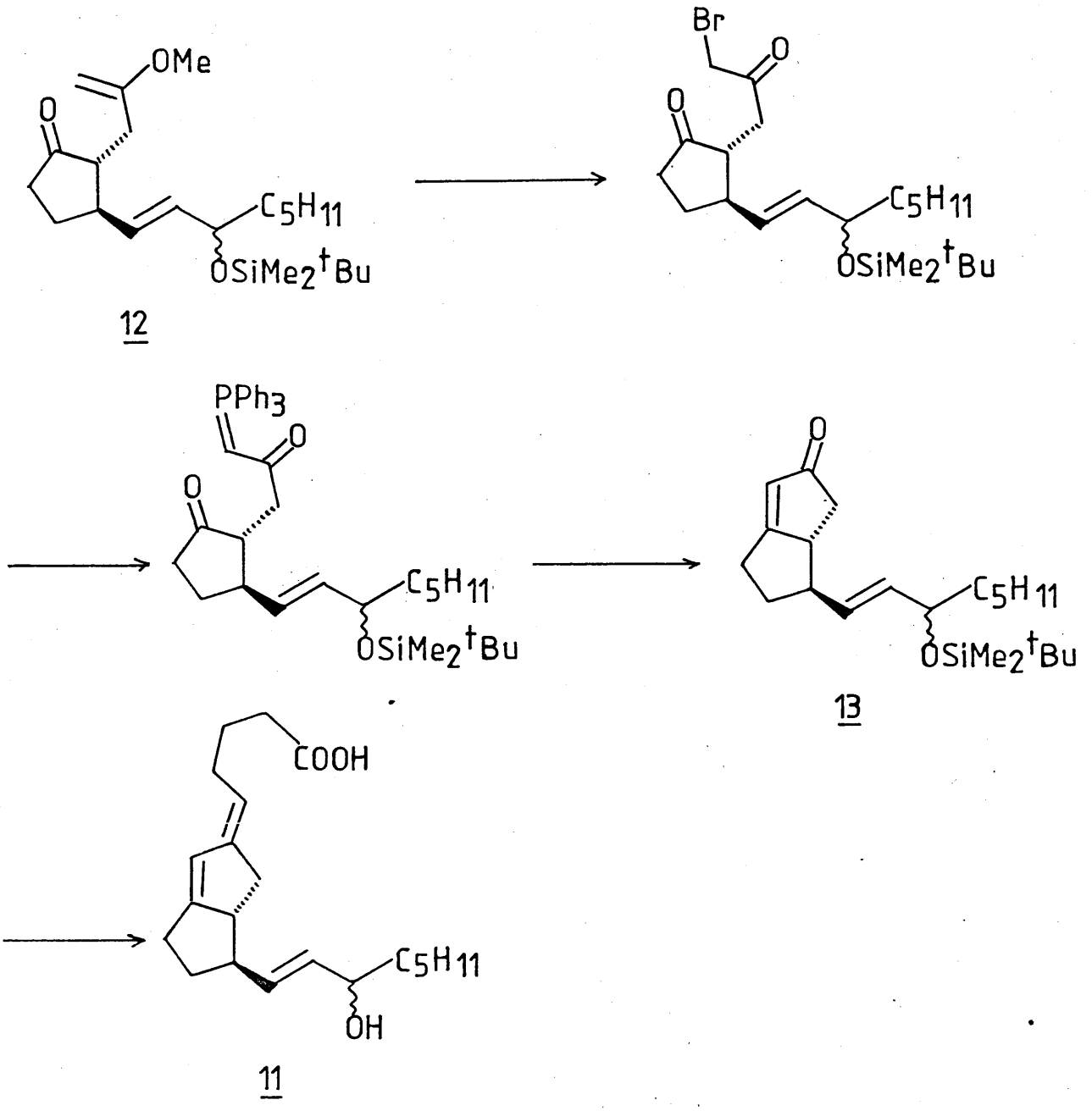
4.3.1 11-Deoxycarboprostacyclin analogues

There has been a great deal of interest in carbocyclic prostaglandins[98]. Modifications to the work in this thesis may lead to a synthesis of the novel 11-deoxycarboprostacyclin analogue 11 (Figure 8).

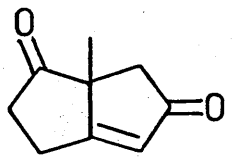
An attempted synthesis using the aldol reaction was described in Chapter 3 (compound numbers 85 to 86).

It may well be that the Wittig reaction could be used to form enone 13 and hence prostacyclin analogue 11 from the available enol ether 12 by the route shown in figure 8.

FIGURE 8

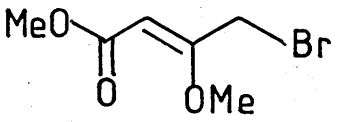


A similar method was used by Trost to prepare 14[89]



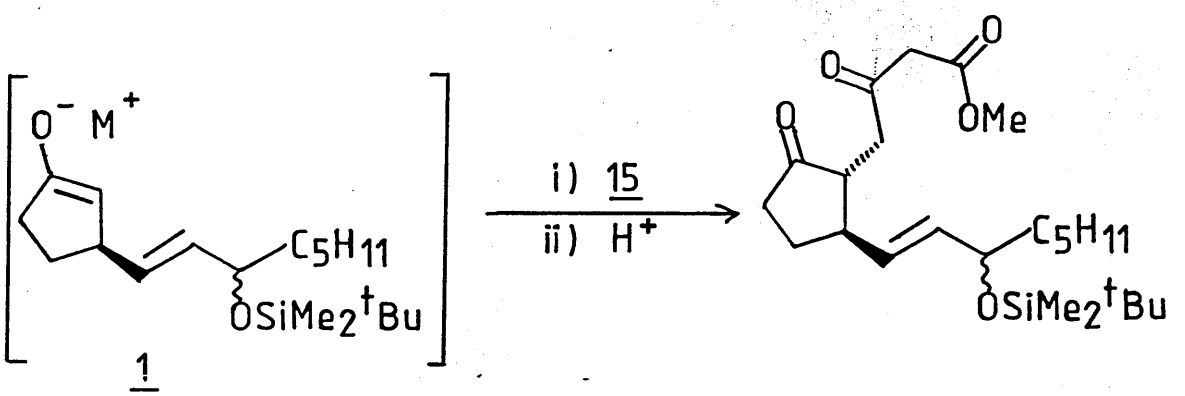
14

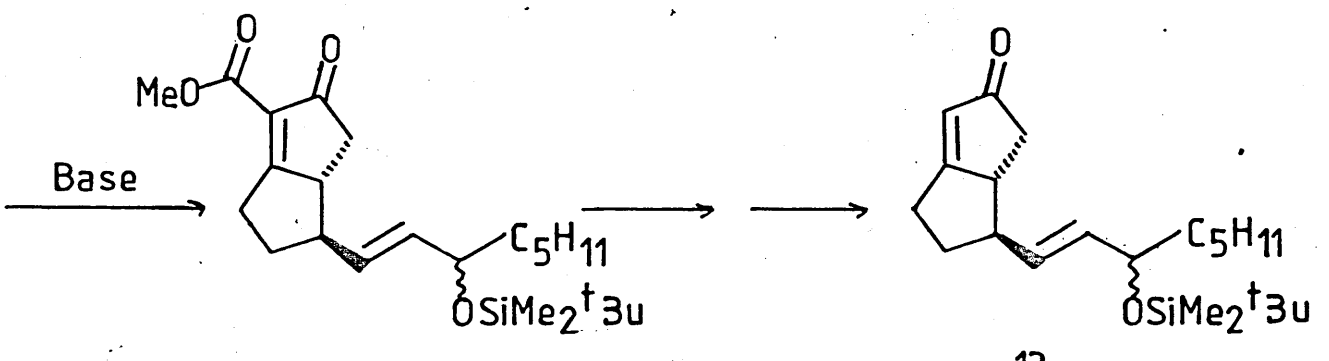
An alternative procedure for the preparation of enone 13 would be by employing an alkylating agent such as 15[99] in the conjugate addition-alkylation reaction as shown in figure 9.



15

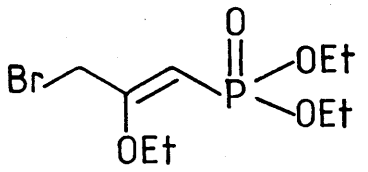
FIGURE 9





13

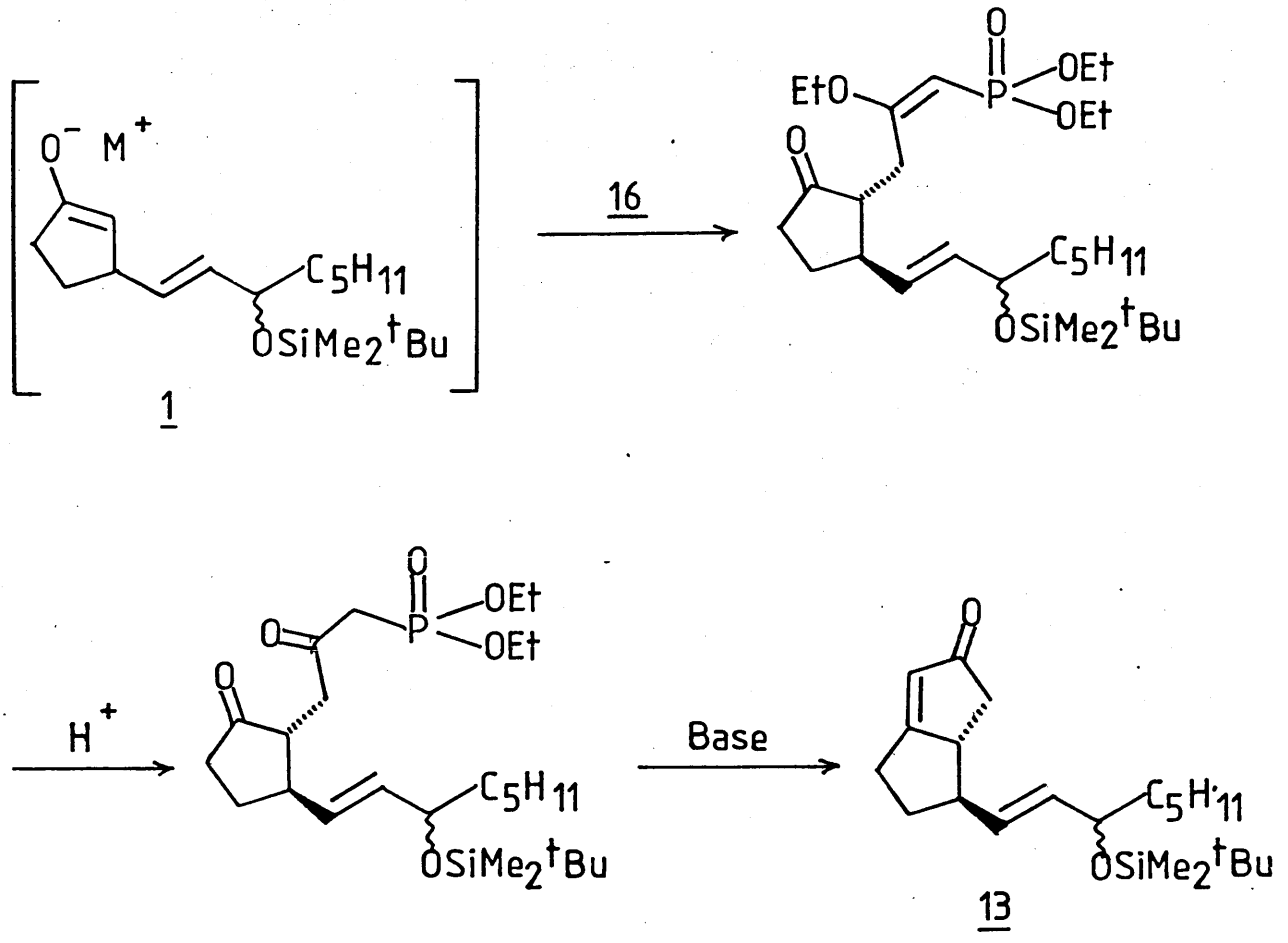
A third method also employs a modified alkylating agent 16[100] in the initial conjugate addition enolate alkylation step.



16

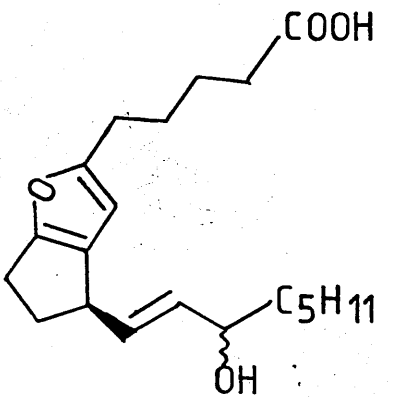
Alkylation with phosphonate 16 would allow a subsequent internal Wittig reaction to give the α,β-unsaturated bicyclic ketone 13 (Figure 10).

FIGURE 10



4.3.2 Fused furan prostacyclin analogues

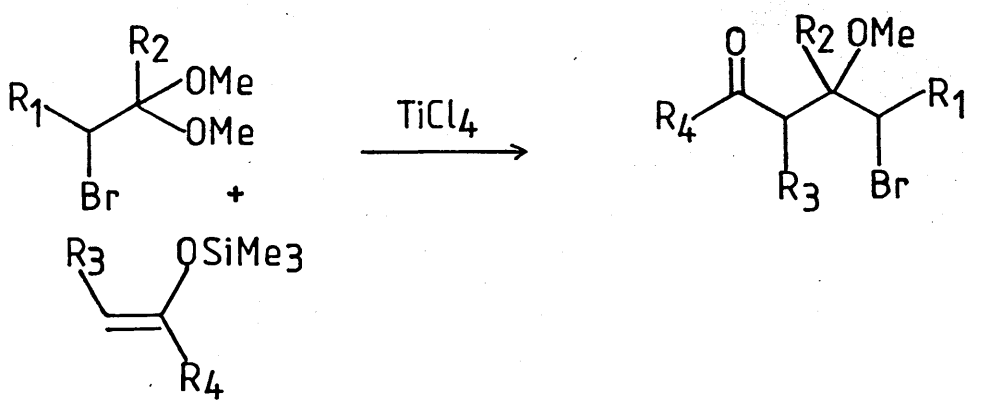
The fused furan analogues 16 would be of considerable interest

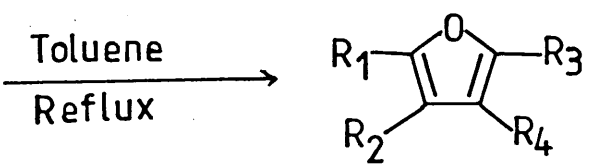


16

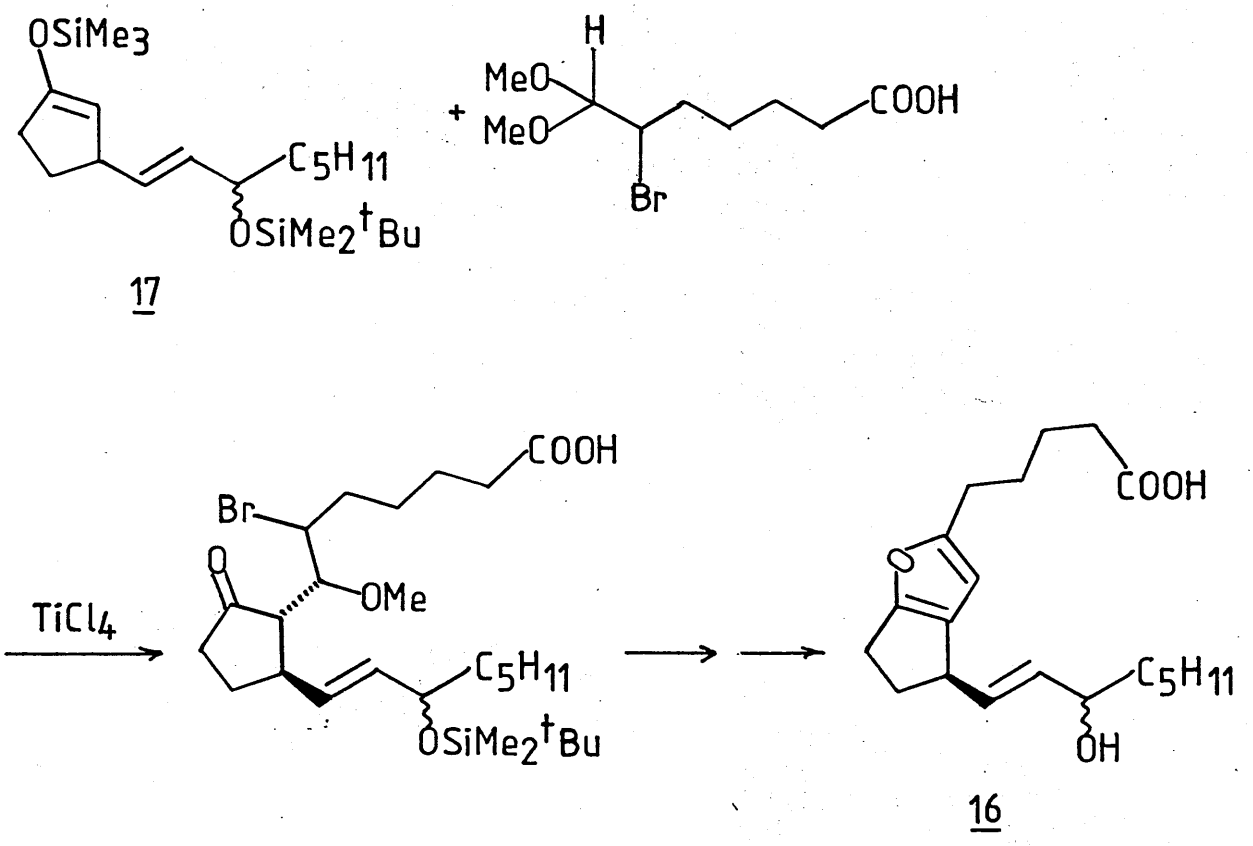
One way of preparing this compound would be to utilise Mukayama's procedure for forming furans from silyl enol ethers[101] (Figure 11)

FIGURE 11





A scheme is shown below which outlines the use of this kind of reaction in the synthesis of the analogues 16.



Chapter 5 EXPERIMENTAL

5.1 General Directions

Nuclear magnetic resonance (n.m.r.) spectra were recorded with either a Bruker WP60 or Perkin Elmer R12B instrument unless otherwise stated. The solvent used was deuterochloroform unless otherwise stated and chemical shifts are given in δ (ppm) downfield from tetramethylsilane. Infrared spectra were obtained with either a Pye Unicam SP1000 or SP1050 instrument and were normally run as thin films. Ultra violet spectra were recorded with a Perkin Elmer Coleman 275 instrument and mass spectra with a Kratos-AEI MS30/74 or MS50 instrument.

Qualitative thin layer chromatography (t.l.c.) was carried out using Camlab Polygram 5 x 20cm plates. Plates were developed by spraying with a five per cent solution of ammonium molybdate in five per cent sulphuric acid, (ammonium molybdate must first be dissolved in the concentrated acid and then this solution added very carefully to water) or a five per cent solution of dodecamolybdophosphoric acid in n-propanol, and then heated until the material appeared as dark blue/green spots against a white or yellow background. Plates used for the separation of olefinic materials were immersed in a 10% aqueous solution of silver nitrate and then dried in an oven for 5h at 120 ^{o}C then used in the normal way. Preparative thin layer chromatography was performed using Merck 2mm preparative plates. The compounds were extracted from the silica using a suction column and

diethyl ether as eluent. Column chromatography was performed using a "medium pressure short bed" technique. Merck t.l.c. grade silica gel H, type 60 (Merck 7736) was used, and was packed as a slurry in 60-80 petrol or hexane. A column depth of approximately five to eight centimetres, when fully compressed, was used. A variety of column sizes were used to give the requisite bed depth with varying quantities of silca gel (table 1). Pressure was provided by means of a Gallenkamp hand bellows. Mixtures to be separated were dissolved in petrol or hexane and loaded carefully onto the silica by running the solution down the sides of the column. Mixtures that were not soluble in petrol or hexane were dissolved in diethyl ether or ethyl acetate, and silica gel (five per cent of the original weight of column packing), was added. The solvent was subsequently removed to leave the mixture adsorbed onto the silica gel. This silica gel was then loaded gently onto the top of the column. This method facilitates loading of the mixture in a very narrow band at the column top. The elution solvent was normally a mixture of diethyl ether or ethyl acetate in 60-80 petrol or hexane and the ratios chosen for column elution were those which gave an Rf of approximately 0.15 on t.l.c. of the desired component. If the eluent contained greater than five per cent ether, gradient elution up to the final ratio was used to prevent damage to the column. Fractions were collected either in 15ml tubes or 100ml Ehrlenmeyer flasks depending on column size, and the separation followed by t.l.c. until all the desired component had been eluted (usually 15 min - 2h)

TABLE 1

Column dia. (mm)	wt. of silca (g)	bed depth (cm)	crude mixture (g)
90	100-200	4.0-8.0	5.00-10.00
60	50-90	4.0-8.0	2.50- 4.50
45	25-45	4.0-7.0	1.25- 2.25
30	10-20	3.5-7.0	0.50- 1.00
20	3.8	2.5-6.0	0.15- 0.40

In the text of the experimental section, ether refers to diethyl ether and petrol to the fraction boiling between 60 and 80 ^{o}. A "normal ether work-up" implies three extractions with ether, a wash with saturated brine, drying with anhydrous magnesium sulphate and removal of the solvent under reduced pressure.

5.2 Purification of Solvents

Acetic Acid, Acetone and Methanol

These liquids were all dried by standing over 4A molecular sieves for a minimum period of 48h.

Ammonia (liquid)

Ammonia was collected as a liquid and transferred to a three necked flask. Lithium metal was added until the deep blue colour persisted indicating that the ammonia was dry. The ammonia was then distilled from the lithium

solution, under nitrogen, through a flexible p.v.c. tube into a collecting vessel cooled in an acetone-solid CO_2 bath.

Benzene and Toluene

These solvents were dried by standing over sodium wire for a minimum period of 48h.

Diethyl Ether, Dimethoxy Ethane, Dimethyl Formamide, Dimethyl Sulphoxide, Hexamethylphosphoramide, Tetrahydrofuran and Tetramethylethylenediamine

These solvents were all dried and purified by standing over crushed calcium hydride for 24h, refluxing for 1h and then distilling from the calcium hydride under nitrogen.

Ethyl Acetate and 60^{o}-80^{o} Petrol

These solvents were purified for chromatography by distillation. Petrol required dry for reactions was dried over sodium wire for a minimum period of 48h before distillation.

Tetrachloromethane and Dichloromethane

These solvents were dried and purified by stirring with phosphorus pentoxide at ambient temperature for 24h, boiled under reflux for 1h and finally distilled from the phosphorus pentoxide under nitrogen.

5.3 Preparation and Purification of Reagents

2-Acetoxy-1,3-diiodopropane (74)

1,3-dichloropropan-2-ol (5g, 38.8 mmol) was dissolved in analar acetone (30 ml) containing sodium iodide (17.5g, 0.465 m). The reaction mixture was refluxed and stirred for 36h. The solution was cooled and filtered and the residue washed well with acetone. The combined filtrates were then concentrated under reduced pressure and poured into distilled water. This mixture was then extracted three times with ether, and the combined ether extracts washed with 10% sodium thiosulphate solution, followed by saturated brine, dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to yield *1,3-diiodopropan-2-ol* (10g, 83%) as an oil.

1,3-Diiodopropan-2-ol (10g, 28.3 mmol) was dissolved in dry toluene (50 ml) and pyridine (24.6g, 0.28 m). Acetic anhydride (32.7g, 0.28 m) was then added and the reaction mixture stirred at ambient temperature overnight. The reaction mixture was poured into distilled water and extracted 3 times with ether. The combined ether extracts were washed with 2% hydrochloric acid, followed by saturated brine, dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to yield the product (74) (10.9g, 96%). Spectral data was consistent with the assigned structure.

Benzyltrimethylammonium fluoride (BTAF)

This reagent was prepared according to the method of Kuwajima and Nakamura,[45] by carefully mixing equimolar amounts of benzyltrimethylammonium hydroxide and 47% hydrofluoric acid and drying the product at 100° @ 1mm Hg for 24h, finely pulverising, and drying again for 24h. This material was highly hygroscopic and was stored under dry nitrogen in a sealed container.

3-Bromoprop-1-ene (allyl bromide)

This reagent was stirred with crushed calcium hydride for 24h at ambient temperature, refluxed for 1h then distilled from the calcium hydride under nitrogen.

3-Bromo-2-methoxyprop-1-ene (78)

Method a[88]

1-Bromopropan-2-one was prepared according to the method of Levene[88]. A 1 litre 3-necked flask with mechanical stirrer was equipped with a reflux condenser, thermometer and 100 ml dropping funnel (the stem of which must reach nearly to the bottom of the flask). Water (400 ml), analar acetone (125 ml) and glacial acetic acid (93 ml) were put in the flask and the temperature of the contents raised to 65° on a water bath. Then bromine (87 ml) was carefully added via the separating funnel avoiding any accumulation of unreacted bromine. When all the bromine had been added and the solution fully decolourised, water (200 ml) was added

and the reaction mixture cooled to 10°C. The solution was made neutral to congored indicator with solid anhydrous sodium carbonate. The oil that separated was collected, dried over anhydrous calcium chloride and vacuum distilled. The fraction boiling between 38-48° at 13 mm was collected, giving *1-bromopropan-2-one* (yield 111g) (literature[88] 117-120g). Caution! the product is a severe lachrymator.

1-Bromo-propan-2-one (110g, 0.803 mol), trimethyl formate (96 ml, 0.88 mol), methanol (40 ml) and concentrated sulphuric acid (16 drops) were mixed and stirred at ambient temperature for 2h. The reaction mixture was made basic with triethylamine (3.2 ml) and concentrated in vacuo to remove trimethyl formate. The resulting mixture was added to methanol (300 ml) at 0° containing sodium hydroxide (30g). The reaction mixture was then given a normal ether work-up and dried over anhydrous potassium carbonate. The solvent was removed under reduced pressure and the resulting liquid was distilled to give *1-bromo-2,2-dimethoxypropane* (78.56g, 54% yield) (literature[88] 80% yield).

1-Bromo-2,2-dimethoxypropane (25g) and diisopropyl-ethylamine toluene-4-sulphonic acid (see separate entry) (0.4g), were heated at 150°-190° (bath temperature) while distilling off the methanol through a 12" Vigreaux fractionating column. The temperature of the bath was never

allowed to exceed 200° and methanol distillation kept at about 1 drop per second so as to give complete reaction in approximately 1.5h. After methanol removal was complete (as indicated by a rise in distillation head temperature to higher than 130°), the column was removed and the product mixture rapidly distilled through a short path distillation head resulting in the collection of 13.9g of a mixture of the *1-bromo-2,2-dimethoxypropane* starting material (14%), the desired *3-bromo-2-methoxyprop-1-ene (78)*, (67%), and the isomeric *1-bromo-2-methoxyprop-1-ene (84)*, (19%), (product ratios were determined by nmr integration ratios). This mixture was used without further purification.

Method b (the procedure of choice)

1-Bromo-2,2-dimethoxypropane (83) was prepared directly from acetone by the method of Garbisch[91]. Analar acetone (58g, 1) was dissolved in anhydrous methanol (1 litre) and a small portion of bromine was added. The mixture was stirred at ambient temperature until the colour discharged (if bromine persisted the reaction mixture was warmed until the bromine reacted). The remainder of the bromine (160g, 1) was added slowly so as to just maintain a slight colouration in the solution (it was necessary to cool the reaction mixture in ice to keep the temperature below 25°). The mixture was poured into a slurry of anhydrous potassium carbonate (330g) in petrol (1 litre) and stirred until the hydrogen bromide in the reaction mixture was neutralised. Water (1 litre)

was then added and the mixture partitioned. The aqueous portion was extracted with a further 500 ml of petrol. The combined petrol extracts were dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to give a liquid. This was distilled to give pure *1-bromo-2,2-dimethoxypropane* (83) (92.4g, 50%). This material was then cracked to give the *3-bromo-2-methoxy-prop-1-ene* (78) as in method a.

Method c[44]

A slurry of N-bromosuccinimide (50g, 0.28 mol) in tetrachloromethane (150 ml) was prepared and heated to 55° on a water bath. The water bath was then removed and 2-methoxyprop-1-ene (20 ml, 0.278 m) was added slowly (30 min) to the stirring suspension. The heat of reaction should maintain the reaction temperature between 55° and 65°. After a total reaction time of 45 min the reaction mixture was cooled to between 10° and 20° in an ice bath and quickly filtered through celite to remove the precipitated succinimide and any excess N-bromosuccinimide. The mixture was then concentrated, washed with 2M sodium hydroxide solution (2 x 300 ml) followed by ice cold water (2 x 100 ml). The solution was then dried over anhydrous calcium chloride and stored as an approximately 50% solution in tetrachloromethane over anhydrous sodium carbonate. 12g of material was recovered (literature 30g). The material was a mixture of the desired *3-bromo-2-methoxyprop-1-ene* (78) (70%) and the isomeric *1-bromo-2-methoxyprop-1-ene* (84) (30%) (isomer ratios determined by

nmr). Method b was the procedure of choice for the preparation of this reagent.

Trans-3-(t-butyldimethylsilyloxy)oct-1-enyl iodide

This reagent was prepared according to preparative detail sheets supplied by Glaxo Research, Ware. A 1 litre 3-necked flask fitted with a mechanical stirrer, gas inlet tube and a gas outlet tube was surrounded by an ice/water bath. Acetylene was purified by passing it through water, sulphuric acid, sodium hydroxide pellets and finally self indicating silica gel. The system was slowly flushed with acetylene for 3 min. Carbon tetrachloride (450g) was poured into the flask and acetylene bubbled through for 5 minutes. Powdered aluminium chloride (73.5g) was added and acetylene was bubbled through the mixture with stirring for 5 min. The gas inlet tube was replaced by a dropping funnel and hexanoyl chloride (Aldritch 63.6g) was added to the reaction mixture with stirring over a period of 20 min. The dropping funnel was replaced by a gas inlet tube and acetylene bubbled through for approximately 2.5h. The reaction mixture was poured into a mixture of crushed ice (800g) and saturated sodium chloride (300 ml) with vigorous stirring. The organic layer was separated and the aqueous layer extracted with ether (3 x 100 ml). Hydroquinone (2g) was added to the combined organic layers and the mixture dried over calcium chloride overnight. The dark brown liquid was decanted from the solid and the solid washed with carbon tetrachloride. These washings were added to the main solution and hydroquinone (2g) was added. The

solvent was removed under reduced pressure and the remaining dark red liquid was distilled to give trans *1-chloro-3-oxooctene* (64.6g, 85%) as a pale yellow oil (57°, 0.5mm).

Trans-1-chloro-3-oxooctene (25.4g) was refluxed and stirred for 3h in acetone (150ml) in the presence of sodium iodide (34.6g). The solution was cooled and filtered, the solid washed thoroughly with acetone, then the filtrate concentrated to Ca. 50ml. The concentrate was diluted with water (200 ml) and extracted with ether (300 ml). The yellow extract was washed with water (2 x 100 ml), 10% sodium thiosulphate (100 ml) and dried over anhydrous magnesium sulphate. The solvent was then removed under reduced pressure to give a brown oil which solidified on standing to give trans *1-iodo-3-oxooctene* (39.7g, 98%) as a red solid.

Trans-1-iodo-3-oxooctene (39.5g) was dissolved in ethanol (150 ml) and was treated at room temperature with excess sodium borohydride until no carbonyl absorption was visible by IR. The solution was then diluted with water and acidified with 2M hydrochloric acid to destroy excess borohydride and extracted with ether (3 x 150 ml). The combined ether extracts were washed with 10% sodium thiosulphate (250 ml) then saturated sodium chloride solution (400 ml). The extract was dried over anhydrous magnesium sulphate and the solvent evaporated to give *trans-iodo-3-hydroxy-octene* (35.6g, 89%) as a brown oil.

Trans-1-iodo-3-hydroxyoctene (34.5g), imidazole (23.6g) and t-butyldimethylsilylchloride (24.4g) were stirred together for 23h in dry DMF (75 ml). The solution was diluted with water and extracted with petrol (3 x 100 ml). The combined extracts were washed once with water and dried over anhydrous magnesium sulphate. The solvent was evaporated to give a yellow oil which was chromatographed eluting with petrol to give the product (41.5g, 83%) as a pale pink oil. The product was stored in the dark under nitrogen.

n-Butyllithium

The concentration of active n-butyllithium in hexane solutions, (as supplied commercially by Aldrich Chemical Co.), was determined using the double titration method of Gilman[1,2]. A 5 or 10 ml aliquot was withdrawn by syringe and hydrolysed by adding to water (10 ml). This was titrated with standard acid to determine total alkali using phenolphthalein indicator. A second 5 or 10 ml aliquot was withdrawn and added to a solution of benzyl chloride (1 ml) in anhydrous ether (10 ml). The mixture was allowed to stand for 1 min then hydrolysed with water (10 ml) and titrated with standard acid (vigorous shaking of this latter biphasic mixture is necessary to obtain an accurate end-point). This second titration determined the alkali present in forms other than butyllithium. Thus the difference between the two titrations represents the concentration of n-butyllithium.

t-Butyl hydroperoxide

This reagent was purified according to the method of Bartlett and McBride[103]. t-Butyl hydroperoxide was extracted into cold 15% aqueous potassium hydroxide and the free hydroperoxide regenerated by neutralising with solid ammonium chloride. The mixture was distilled under reduced pressure and the centre fraction, boiling at 35°-36° at 8.5mm was collected.

3-Chloro-1-thiophenoxyprop-1-ene (8)

This reagent was prepared according to the method of Mura, Bennett and Cohen.[48] A suspension of N-chlorosuccinimide (6 mmol) in tetrachloromethane (15 ml) containing 1-thiophenoxyprop-1-ene (6 mmol) was stirred under nitrogen at 5°C for 24h. The product mixture was then filtered and the solvent evaporated at ambient temperature in vacuo to yield the *product* (8).

Diisopropyl ethyl ammonium toluene-4-sulphonate

Diisopropyl ethyl ammonium toluene-4-sulphonate was prepared according to the method of Jacobson[88]. Toluene-4-sulphonic acid monohydrate (3.80g, 22 mmol) was dissolved in anhydrous methanol (10 ml) and diisopropyl ethylamine (2.80g, 22 mmol) was added. The resulting solution was concentrated in vacuo yielding an oil which on standing crystallised. The solid was crushed and the last traces of

solvent removed under high vacuum to give diisopropyl ethyl ammonium sulphonate (quantitative yield).

3-Iodoprop-1-ene

This reagent was washed with 10% sodium thiosulphate solution, dried over anhydrous magnesium sulphate in the dark. The material was then stirred over crushed calcium hydride at ambient temperature for 24h, refluxed for 1h, and distilled from the calcium hydride under nitrogen and with the exclusion of light.

Jones reagent (8N chromic acid)

Concentrated sulphuric acid (23 ml) was added carefully to a solution of chromium trioxide (26.72g) in water (20 ml) and the resulting solution was diluted to 100 ml with water.

Manganese dioxide (activated)

This reagent was prepared according to the method of Attenburrow et al[67]. Manganese sulphate tetrahydrate (111g) in water (150 ml) was added simultaneously with a 40% aqueous solution of sodium hydroxide (117 ml) to a hot stirred solution of potassium permanganate (96g) in water (600 ml) over a period of Ca 1h. The precipitated manganese dioxide was filtered and washed with water until the washings were colourless and neutral. The manganese dioxide was

dried at between 100° and 120° then ground to a fine powder to yield 89.9g (lit.[67] 90g).

Mercuric Perchlorate

Perchloric acid (16.4 ml, 0.2m) was added carefully to a stirred suspension of mercuric oxide (21.6g, 0.1m) in water (50 ml). The solution was stirred for 2h at ambient temperature and the neutral solution of mercuric perchlorate was filtered to remove any excess mercuric oxide and diluted to 100 ml with water to give a 1M solution. Caution! This substance can be detonated by shock, heat, or chemical reaction when dry.

Pent-1-ynyl copper

This reagent was prepared according to the method of Castro Gaughan and Owsley[104]. To a suspension of copper sulphate pentahydrate (108.6.g) in water (126 ml) under nitrogen, was added concentrated ammonia solution (315 ml). The suspension was stirred under nitrogen for Ca 15 min. A solution of hydroxylamine hydrochloride (160g) in water (1680 ml) was added. The reaction mixture was stirred for a further 30 min under nitrogen. 1-Pentyne (30g, 44 ml) in ethanol (400 ml) was added followed by a further 500 ml of ethanol to give a dense yellow precipitate. This suspension was stirred for approximately 15 min and then filtered under nitrogen. The residue was washed thoroughly with first water then ethanol and finally ether. The yellow solid was dried at 40° under vacuum and bottled under nitrogen to yield *pent-1-ynylcopper* (53g, 91%).

Pyridine

This reagent was distilled and stored over solid sodium hydroxide pellets and 4A molecular sieves.

Pyridinium dichromate

This reagent was prepared according to the method of Corey and Schmidt[105]. Chromium trioxide was dissolved in the minimum amount of water and an equimolar amount of redistilled pyridine was added. The precipitated product was collected by filtration and dried at 100°.

Pyridinium toluene-4-sulphonate

This was prepared according to the method of Miyashita, Yoshikoshi and Grieco[106]. Toluene-4-sulphonic acid (5.70g, 30 mmol) was added to redistilled pyridine (12.1 ml, 50 m mol) with stirring at ambient temperature. After stirring for 20 min the excess of pyridine was removed under reduced pressure to afford a quantitative yield of pyridinium toluene-4-sulphonate as slightly hygroscopic colourless crystals. Recrystallisation from acetone gave the pure salt (6.8g, 90%).

Silver carbonate on celite

This reagent was prepared according to the method of Fetizon[69]. Celite was first purified by washing repeatedly

with a 10% solution of concentrated hydrochloric acid in methanol then washing with distilled water until the washings were neutral, and finally drying in an oven at 120° for 24h. A solution of silver nitrate (17g 0.1 mol) in distilled water (100 ml) was prepared, and purified celite (15g) was added to it. This slurry was stirred at ambient temperature and a solution of anhydrous sodium carbonate (5.56g, 52.5 mmol) in water (150 ml) slowly added. The mixture was stirred for a further 10 min. The yellow/green suspension was filtered off and dried on a rotary evaporator, azeotroping the last traces of water off with benzene. Effective molecular weight of reagent = 570.

Silver chromate

This was prepared according to the method of Cardillo and Shimitzu[82]. A solution of silver nitrate (17g, 0.1 mol) in water (200 ml) was added to a stirred solution of potassium chromate (9.7g, 50 mmol) in water (200 ml). Reddish brown silver chromate was quantitatively precipitated. The precipitate was filtered, washed successively with water, dried in vacuo, finely pulverised, and dried again in vacuo at 96° for 5h.

Tetra-n-butylammonium fluoride

This reagent was prepared by careful neutralisation of a 40% solution of tetra-n-butylammonium hydroxide (Aldrich) with a stoichiometric quantity of 47% aqueous hydrofluoric acid

(test by litmus). The water was removed on a rotary evaporator, the last traces being azeotroped off with benzene. This material was highly hygroscopic and was stored in a sealed container under nitrogen.

Tetra-n-butylammonium perchlorate

This reagent was prepared by the same method as the previous reagent substituting 70% perchloric acid for 47% hydrofluoric acid.

Triethylamine

This reagent was stirred at ambient temperature with crushed calcium hydride for 24h, refluxed for 1h, and distilled from the calcium hydride under nitrogen.

Trimethylchorosilane

This reagent was purified by stirring at ambient temperature over crushed calcium hydride for 24h, refluxing for 1h and finally distilling from the calcium hydride under nitrogen.

5.4 Experimental Procedures

2α-Allyl-3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] cyclopentanone (2)

a) "One pot" procedure

n-Butyllithium (55 mmol) was added to a stirred solution of 3-(t-butyldimethylsilyloxy)oct-1-enyl iodide (18.4g, 50 m mol) in dry ether (40 ml) under nitrogen at -78 °. After 1h a freshly prepared solution of pent-1-ynylcopper (7.2g, 55 mmol) in dry ether (50 ml) and hexamethylphosphoroustriamide

(21 ml, 110 mmol) was added slowly and the mixture stirred for a further 1h at -78 °C to ensure complete formation of the *cuprate* (3a). Cyclopent-2-enone (6.15g, 75 mmol) in dry ether (100 ml) was added to the solution of (3a) very slowly over 30 min and the mixture stirred for a further 1h at -78 °C. Dry liquid ammonia (distilled from sodium, 150 ml) was then added followed by allyl bromide (28g, 0.23 mol). The cooling bath was removed and the ammonia allowed to evaporate overnight. The mixture was poured into distilled water, and a normal ether work-up gave an oil which was chromographed on silica. Elution with 3% ether-hexane gave the *ketone* (2) (4.38g, 24%) as an oil (R_f 0.29 in ether-hexane 1:9); ν_{max} 1750 (C=O), 970 (C=C), 1255, 1075 br, 835 ($OSiMe_2$ ^tBu) cm^{-1}; δ 5.86-5.58 (1H, m, $-C\underline{H}=CH_2$), 5.60-5.46 (2H, m, $-C\underline{H}=C\underline{H}-$), 5.12-4.94 (2H, m, $-CH=C\underline{H}_2$), 4.12-4.00 (1H, m, $C\underline{H}-OSi$), 0.90 (12H, s and m, $Si-C(C\underline{H}_3)_3$ and $-CH_2-C\underline{H}_3$), 0.06 and 0.02 (6H, s and m, $Si(C\underline{H}_3)_2$), 2.65-1.15 (16H, m, remainder); m/e 349 (M^+-CH_3), 307 ($M^+-C(CH_3)_3$), 293 ($M^+-C_5H_{11}$) (Found M^+-CH_3, 349.2561. $C_{21}H_{37}O_2Si$ requires 349.2564); (Found: C, 72.5; H, 10.8. $C_{22}H_{40}O_2Si$ requires C, 72.5; H, 11.1%).

b) Silyl trapping procedure

The above procedure was followed as far as the slow addition of the cyclopent-2-enone solution and the stirring for 1h at -78°C. THF (100ml) was then added, followed by a mixture of trimethylsilyl chloride (30ml) and triethylamine (40ml). The reaction was left to warm to ambient temperature

(Ca. 1h), ice was added to quench the excess trimethylsilyl chloride, and the mixture extracted with hexane (3 x 200 ml). The combined extracts were washed with ice cold 2% sulphuric acid (4 x 150 ml) to precipitate the copper/HMPA complex, followed by 8% sodium hydrogen carbonate solution (200 ml). Drying with anhydrous magnesium sulphate and evaporation of the solvent *in vacuo* gave the silyl enol ether (7) as an oil (this could be purified by distillation at 115 °, 0.1 mm see p. 40 .) The crude silyl enol ether (7) was dissolved in THF (100 ml) and added to a mixture of lithium amide (50 mmol) in liquid ammonia (150 ml) at -78 °. The reaction was warmed to -40 ° for 30 min to ensure complete formation of the enolate, and allyl bromide (28g, 0.23 mol) in THF (50 ml) was added rapidly, the cooling bath removed and the ammonia allowed to boil off overnight. The mixture was poured into distilled water, given a normal ether work-up, and purified by column chromatography as before giving *ketone* (2) (4.56g, 25%) as an oil identical with the previously prepared compound.

2α-Allyl-3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] cyclopentan-1α-ol (12)

A solution of potassium tri-(sec-butyl)borohydride in THF (Aldrich k-selectride, 2.67 mmol) was slowly added to a stirred solution of ketone (2) (650 mg, 1.78 mmol) in THF (30 ml) under nitrogen at -40 °. The temperature was allowed to rise to 0 ° over 1h and the excess reagent was hydrolysed by the careful addition of water. 3M sodium

hydroxide solution (0.98 ml, 2.94 mmol) was then added followed by 30% hydrogen peroxide (1.1 ml, 9.6 mmol) to oxidise the borane. The mixture was stirred at 0 °C for 1h. A normal ether work-up gave an oil which was chromatographed. Elution with ether-hexane 1:9 gave *alcohol* (12) (600 mg, 92%) as an oil (R_f 0.31 in ether-hexane 1:4); ν_{max} 3380 (br, OH), 965 (C=C), 1250, 1070 (br), 830, 770 ($OSiMe_2^tBu$) cm^{-1}; δ 6.00-5.73 (1H, m, $\underline{CH}=CH_2$), 5.50-5.34 (2H, m, $\underline{CH}=\underline{CH}$), 5.16-4.95 (2H, m, $CH=CH_2$), 4.32-4.17 (1H, m, $\underline{CH}$-OH), 4.10-3.96 (1H, m, $\underline{CH}$-OSi), 0.91 (12H, s and m, $SiC(\underline{CH_3})_3$ and $CH_2-\underline{CH_3}$), 0.08 and 0.04 (6H, s and s, $Si(\underline{CH_3})_2$), 2.46-1.16 (17H, m, remainder); m/e 366 (M^+), 351 (M^+-CH_3), 309 ($M^+-C(CH_3)_3$), 295 ($M^+-C_5H_{11}$), (Found M^+ 366.2950. $C_{22}H_{42}O_2Si$ requires 366.2954); (Found: C, 72.2; H, 11.6 $C_{22}H_{42}O_2Si$ requires C, 72.1; H, 11.6%)

6β-[Trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-3α and 3β-hydroxymethyl-cis α-2-oxabicyclo [3.3.0] octane (14)

Alcohol (12) (2.92g, 7.96 mmol) was dissolved in dry toluene (250 ml) containing vanadyl acetylacetonate (80 mg, 0.29 mmol) and toluene-4-sulphonic acid (one crystal). The mixture was stirred and t-butylhydroperoxide (2.16g, 24 mmol) was added over 30 min. The reaction was then stirred at ambient temperature for 7 days and then poured into 10% sodium metabisulphite solution. A normal ether work-up afforded an oil which was chromatographed. Elution with ether-petrol 1:3 gave first the α-*hydroxymethylene diastereomer (14d)* (300 mg, 10%) as an oil (R_f 0.20 in

ether-petrol, 1:1); ν_{max} 3430 (OH), 970 (C=C), 1250, 1075 (br), 835, 775 (OSiMe$_2^t$Bu) cm^{-1}; δ 5.45-5.30 (2H, m, CH=CH), 4.45 (1H, m, O-CH), 4.02 (1H, m, CH-OSi), 3.95 (1H, m, CH-CH_2OH), 3.78 and 3.58 (2H, AB part of ABX, J_{AB} 12Hz, J_{AX} 4Hz, J_{BX} 7Hz, CH_2OH), 2.45-2.30 (2H, m, CH-CH= and OH), 0.88 (12H, s and m, SiC(CH_3)$_3$ and CH_2-CH_3), 0.04 and 0.00 (6H, s and s, Si(CH_3)$_2$, 2.20-1.20 (17H, m, remainder); ^{13}C nmr ($CDCl_3$-25.2 MHz) δ 132.7 and 132.2 C=C, 81.4 O-CH-CH_2OH, 73.5 C-OSi, 64.3 CH_2OH, -4.1 and -4.6 Si(CH_3)$_2$; m/e 369 (M^+-CH_3), 351 (M^+-CH_2OH), 325 (M^+-C(CH_3)$_3$), 311 (M^+-C_5H_{11}), (Found M^+-CH_2OH, 351.2724. $C_{21}H_{39}O_2Si$ requires 351.2719). This was followed by a mixture of (14a) and (14b) (1.26g, 41%) as an oil and finally by the β-*hydroxymethylene diastereomer* (14b) (327 mg, 11%) as an oil (R_f 0.17 in ether-petrol, 1:1); ν_{max} 3440 (OH), 970 (C=C), 1250, 1075(br), 835, 775 (OSiMe$_2^t$Bu) cm^{-1}; δ 5.55-5.30 (2H, m, CH=CH), 4.57 (1H, m, OCH), 4.15 (1H, m, CH-CH_2OH), 4.02 (1H, m, CH-OSi), 3.69 (br) and 3.52 (br) (2H, AB part of ABX, CH_2OH), 0.88 (12H, s and m, SiC(CH_3)$_3$ and CH_2-CH_3), 0.04 and 0.00 (6H, s and s, Si(CH_3)$_2$), 2.4-1.2 (17H, m, remainder); ^{13}C nmr ($CDCl_3$-25.2 MH) δ 133.1 and 132.3 C=C, 78.9 O-CH-CH_2OH, 73.5 CH-OSi, 64.2 CH_2OH, -4.1and -4.7 Si(CH_3)$_2$; m/e 369 (M^+-CH_3), 351 (M^+-CH_2OH), 325 M^+-C(CH_3)$_3$), 311 (M^+-C_5H_{11})

6β-[Trans-3-t-butyldimethylsilyloxy)oct-1-enyl] cis α-2-oxabicyclo [3.3.0] octan-3-one (22)

Bicyclic alcohol (14a) (40 mg, 0.104 mmol) was dissolved in dry toluene (10 ml), active manganese dioxide[67] (440 mg, 5 mmol) was added and the mixture was boiled under reflux,

After 8h the mixture was cooled and filtered through a bed of celite. The celite was washed well with ether, the filtrates were combined, dried with anhydrous magnesium sulphate and the solvent removed *in vacuo* to give an oil. Purification by preparative t.l.c. eluting with ether-petrol (1:1) and extraction of the material R_f 0.17 gave recovered (14a)(4 mg) and extraction of the band at R_f 0.50 gave *lactone* (22) (16 mg, 44% based on reacted 14a) as an oil; ν_{max} 1765 (C=O), 980 (C=C), 1260, 1090 (br), 845 ($OSiMe_2^tBu$) cm^{-1}; δ 5.52-5.44 (2H, m, CH=CH), 5.02-4.92 (1H, m, O-CH), 4.15-4.03 (1H, m, CH-OSi), 0.96 (12H, s and m, $OSiC(CH_3)_3$ and CH_2-CH_3), 0.09 and 0.07 (6H, s and s, $O-Si(CH_3)_2$) 2.88-1.18 (16H, m, remainder); m/e 351 (M^+-CH_3), 309 ($M^+-C(CH_3)_3$), 295 ($M^+-C_5H_{11}$); (Found C, 68.9; H, 10.5. $C_{21}H_{38}O_3Si$ requires C, 68.8; H, 10.5%)

6β-(Trans-3-oxo-oct-1-enyl)-cis α-2-oxabicyclo [3.3.0] octan-3-one (23)

Lactone (22) (164 mg, 0.447 mmol) was stirred in THF containing 10% of 10% aqueous hydrochloric acid for 4 days at ambient temperature. A normal ether work-up was followed by preparative t.l.c.. Using ether as eluent extraction of the material R_f 0.15 gave the desilylated alcohols which were dissolved in dichloromethane (10 ml). Active manganese dioxide[67] (440 mg, 5 mmol) was added and the mixture stirred at ambient temperature for 5 days. Filtration through a bed of celite, removal of the solvent *in vacuo*

gave an oil. Purification by preparative t.l.c. using ether as eluent and extraction of the material with R_f 0.5 gave the *enone* (23) (75 mg, 67%) as an oil; ν_{max} 1780 (O-C=O), 1675, 1630, 970 (C=C) cm^{-1}; λ_{max} (CH_3OH) 224 nm (log ε 4.15); δ 6.64 and 6.11 (2H, dd, J_1 6Hz, J_2 16Hz CH=CH), 5.02-4.92 (1H, m, CH-O), 0.90 (3H, s, CH_2-CH_3), 2.86-1.14 (16H, m, remainder); m/e 250(M^+), 194(M^+-56) 179(M^+-C_5H_{11}), (Found M^+, 250.1591. $C_{15}H_{22}O_3$ requires 250.1569)

1α-Acetoxy-2α-allyl-3β-[trans-3-(t-butyldimethylsilyloxy) oct-1-enyl]cyclopentane (30)

Alcohol (12) (536 mg, 1.46 mmol) was dissolved in dry toluene (30 ml) containing pyridine (2.313g, 29.20 m mol) and acetic anhydride (2.985g, 29.20 mmol). The reaction mixture was stirred at ambient temperature for two days. A normal ether work-up, with an extra dilute hydrochloric acid wash to remove pyridine, afforded *acetate* (30) (580 mg, 97%) as an oil, pure by t.l.c. (R_f 0.26 in ether-hexane, 1:9); ν_{max} 1740 (C=O), 970 (C=C), 910 and 1005 ($CH=CH_2$), 1250, 835, 1080 (br), 775 ($OSiMe_2^tBu$) cm^{-1}; δ 6.00-4.80 (6H, m, CH=CH, $CH=CH_2$ and CH-OAC), 4.02 (1H, m, CH-OSi), 2.00 (3H, S, $COCH_3$) 0.85 (12H, m and s, CH_2-CH_3 and OSi $C(CH_3)_3$, 0.00 (6H, s and s $OSi(CH_3)_2$, 2.60-1.10 (16H, m, remainder); m/e 393 (M^+-CH_3), 351 (M^+-$C(CH_3)_3$), 337 (M^+-C_5H_{11}); (Found: C, 70.7; H, 10.9. $C_{24}H_{44}O_3Si$ requires C, 70.5; H, 11.0).

1α-Acetoxy-3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-2α-(2-hydroxypropyl)cyclopentane (35)

Acetate (30) (200 mg, 0.49 mmol) was dissolved in THF-water 4:1 (10 ml) and cooled to 0°. Solid mercuric (bis)trifluoroacetate (250 mg, 0.59 mmol) was added in one portion and the reaction mixture stirred for 10 min. 10% sodium bicarbonate (10 ml) was then added to neutralise the trifluoroacetic acid followed by sodium borohydride (10 mg 0.025 mmol) and the mixture stirred for a further 30 min. The mixture was filtered through a bed of celite to remove precipitated mercury and then given a normal ether work-up to yield an oil which was purified by preparative t.l.c. Elution with ether-hexane (3:2) and extraction of materials with R_f 0.36 and Rf 0.28 gave the *epimeric alcohols* (35a) (58 mg, 28%) and (35b) (61 mg, 29%) respectively, as oils. δ, 5.50-5.02 (3H, m, CH=CH and CH-OAc), 4.20-3.48 (3H, m, CH-OH and CH-OSi), 2.00 (3H, s, CH_3C=O), 0.84 (12H, m and s CH_2-CH_3 and $SiC(CH_3)_3$, 0.00 (6H, s, $Si(CH_3)_2$), 2.68-1.00 (19H, m, remainder).

Attempted nitromercuration of 2α-allyl-3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] cyclopentanone (2)

Method (a) ketone (2) (500 mg, 1.37 mmol) was dissolved in THF-water 4:1 (50 ml) and solid sodium nitrite (284 mg, 4.11 mmol) followed by mercuric (bis)trifluoroacetate (643 mg, 1.51 mmol) in water (2 ml) were added and the reaction mixture stirred at ambient temperature for 40h. Saturated brine (30 mls) was added and the mixture stirred

vigorously for 2.5h in order to displace trifluoroacetate attached to mercury with chloride. The reaction mixture was then diluted with water (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined extracts were dried over magnesium sulphate and the solvent removed under reduced pressure to give an oil. The mixture was chromatographed eluting with ethyl acetate-petrol (3:7) which gave *3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-2α-(3-chloromercuro-2-hydroxypropyl)cyclopentanone* (28) in equilibrium with the hemiacetal form (29) (353 mg, 42%) as a viscous gum which later solidified (Rf 0.20 in ethyl acetate-petrol, 3:7); ν_{max} (solution, 0.5% in $CHBr_3$ 1.0 mm cell) 3360(br)(OH), 1725 (C=O), 1250, 1060 (br), 835, 775 ($OSiMe_2^tBu$) cm^{-1}; δ 5.7-5.2 (2H, m, CH=CH), 4.8 (br) and 4.3-3.8 (2H, s and m, -O-CH) (hemiacetal form) CH-OH and CH-OSi), 0.90 (12H, s and m, $SiC(CH_3)_3$ and CH_2CH_3) 0.05-0.00 (6H, s and s, $Si(CH_3)_2$, 2.5-1.0 (18H, m, remainder).

Method (b) A solution of sodium nitrite (38 mg, 0.55 m mol) in water (2 ml) was added to ketone (2) (100 mg, 0.275 m mol) followed by mercuric perchlorate solution (0.275 ml of 1M solution, 0.275 mmol) and the mixture stirred vigorously to mix the two phases at ambient temperature overnight. The reaction mixture was given the same work-up as in method a to yield an oil. This was chromotagraphed, eluting with ethylacetate-petrol (3:17) to give first *3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-2α-(3-chloromercuro-2-nitropropyl)cyclopentanone* (24) (20 mg, 11%) as a gum (Rf 0.50 in ethyl acetate-petrol, 3:7); ν_{max} 1730 (C=O), 1540 and 1360 (NO_2), 1250, 1060 (br) 835, 775 ($OSiMe_2^tBu$) cm^{-1};

δ 5.8-5.0 (3H, m, CH=CH and CH-NO_2), 4.1 (1H, m, CH-OSi), 0.89 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$) 0.02 (6H, s and s, $Si(CH_3)_2$, 2.7-1.0 (18H, m, remainder). Further elution gave the *oxymercurated product (28)* as an oil identical with the product of method (a).

Attempted nitromercuration of 1α-acetoxy-2α-allyl-3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] cyclopentane (30)

Method (a) Details are identical to those in method (a) for the attempted nitromercuration of ketone (2) the reaction gave an oil which was chromatographed to yield *1α-acetoxy-3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-2α-(3-chloromercuro-2-hydroxypropyl)cyclopentane (33)* (80 mg, 49%) as a gum (Rf 0.22 in ethyl acetate-petrol, 3:7); ν_{max} 3500 (br) (OH), 1730 (C=O), 1255, 1075 (br), 835, 775 ($OSiMe_2^tBu$) cm^{-1}.

Method (b) Acetate (30) (140 mg, 0.34 mmol) was dissolved in ethyl acetate (1 ml) and solid sodium nitrite (80 mg, 0.58 mmol) was added followed by mercuric perchlorate (0.51 ml of 1M solution, 0.51 mmol). Water (2 ml) was then added with a catalytic quantity of tetrabutylammonium perchlorate as phase transfer catalyst, and the reaction mixture was stirred vigorously at ambient temperature for 2h. Work-up was as in method (a) of the attempted nitro mercuration of ketone (2) giving an oil. Chromatography eluting with ethyl acetate-petrol (1:9) gave first *1α-acetoxy-3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-2α*

-(3-chloromercuro-2-nitropropyl)cyclopentane (31) (70 mg, 29%) as a gum (Rf 0.54 in ethyl acetate-petrol, 3:7); ν_{max} 1740 (C=O), 1550 and 1360 (NO_2), 1255, 1075 (br), 835 775 ($OSiMe_2^tBu$) cm^{-1}; δ 5.5-4.9 (4H, m, CH=CH, CH-NO_2 and CH-OAc), 4.0 (1H, m, CH-OSi), 2.0 (3H, s, $OCOCH_3$), 0.9 (12H, s and m, $SiC(CH_3)_3$ and CH_2CH_3), 0.0 (6H, s, $Si(CH_3)_2$), 2.4-1.1 (18H, m, remainder). This was followed by *oxymercurated product (33)* identical with that from method (a).

Attempted preparation of 2α-(2-Acetoxy-3-bromopropyl) -3β- [trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] cyclopentanone (37)

Ketone (2) (1.00g, 2.74 mmol) was dissolved in dry glacial acetic acid (25 ml) containing anhydrous sodium acetate (1.21g, 38.70 mmol). A freshly prepared solution of bromine (480 mg, 3.01 mmol) in glacial acetic acid (10 ml) was added very slowly (30 min) under nitrogen. After a further 30 min the reaction mixture was poured into ether containing anhydrous potassium carbonate (85g) to neutralise the acetic acid and given a normal ether work-up. Separation by column chromatography eluting with ether-petrol 1:19 afforded pure ketal *1β-acetoxy-3-bromomethyl-6β- [trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-cis α-2-oxabicyclo [3.3.0] octane (38)* (200 mg, 15%) as an oil (Rf 0.25 in ether-hexane, 1:9); ν_{max}, 1740 (C=O), 980 (C=C), 1260, 1085(br) 845 ($OSiMe_2^tBu$) cm^{-1}; δ 5.60-5.30 (2H, m, CH=CH), 5.2-4.4 (1H, m, OCH-CH_2Br), 4.05 (1H, m, CH OSi), 3.60-3.40 (2H,

d, $\underline{CH_2}Br$), 2.0 (3H, s, $COCH_3$) 0.88 (12H, s and m, $SiC(CH_3)_3$ and CH_2CH_3), 0.03 (6H, s, $Si(CH_3)_2$, 3.00-1.10 (16H, m, remainder); m/e, 444 and 442 (M^+-AcOH), 431 and 429 (M^+-C_5H_{11}), 387 and 385 (M^+-$C(CH_3)_3$ and AcOH), (Found: M^+-58, 444.1902 and 442.1898. $C_{22}H_{39}O_2BrSi$ requires 444.1883 and 442.1903).

2α-Allyl-1α-(t-butyldimethylsilyloxy)-3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] cyclopentane (40)

Alcohol (12) (200 mg, 0.55 mmol) was dissolved in dry DMF (10 ml) and imidazole (93 mg, 1.38 mmol) and then t-butylchlorodimethylsilane (99 mg, 0.66 mmol) were added. The reaction mixture was stirred at ambient temperature for 2 days. Reaction was not complete after this time and so the mixture was heated to 50 ^{o} in a water bath for 3h. The reaction mixture was poured into saturated brine and extracted once with ether. The ether extract was washed once with water to remove DMF and then the solvent was removed in vacuo to yield 250 mg of an oil. This was chromatographed, eluting with ether-hexane (1:49) to give the pure *product* (40) (167 mg, 64%) as an oil (Rf 0.60 in ether-hexane, 1:19); ν_{max}, 975 (C=C), 1260, 1065(br), 845, 780 ($OSiMe_2^tBu$) cm^{-1}; δ 6.10-4.67 (5H, m, CH=CH and $CH=CH_2$), 4.22-3.75 (2H, m, CH-OSi x 2), 0.85(21H, s and m, $Si(CH_3)_3$ x 2 and CH_2CH_3) 0.00 (12H, s, $Si(CH_3)_2$ x 2); m/e 465 (M^+-CH_3), 423 (M^+ - $C(CH_3)_3$), 409 (M^+ - C_5H_{11}), (Found M^+ - CH_3, 465.3567. $C_{27}H_{53}Si_2O_2$ requires 465.3584).

Attempted preparation of 2α-(2-acetoxy-3-bromopropyl)-1α-(t-butyldimethylsilyloxy)-3β-[trans-3-(t-butyldimethylsilyloxy) oct-1-enyl] cyclopentane

Olefin (40) (50 mg, 0.10 mmol) was dissolved in dry glacial acetic acid (5 ml) containing anhydrous sodium acetate (40 mg, 0.50 mmol) and NBS (20 mg, 0.11 mmol). The reaction mixture was stirred at ambient temperature under nitrogen for 3h. Anhydrous potassium carbonate (12g) was added to neutralise the acetic acid and the mixture given a normal ether work-up to give an oil (56 mg). This was chromatographed eluting with ether-petrol (1:19) to yield pure *3-bromomethyl-6β-[trans-3-(t-butyldimethylsilyloxy) oct-1-enyl]-cis α-2-oxabicyclo [3.3.0] octane* (41) (20 mg, 45%) as an oil (Rf 0.44 in ether-hexane, 1:9); δ 5.65-5.35 (2H, m, CH=CH), 4.85-3.80 (3H, m, CHOSi and CHO-CH), 3.55-3.30 (2H, q, $CH\ CH_2Br$), 0.88 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$), 0.04 (6H, s, $Si(CH_3)_2$), 2.70-1.10 (16H, m, remainder).

Attempted preparation of 1α-acetoxy-3β-[trans-3-(t-butyl dimethylsilyloxy) oct-1-enyl] -2α-(2-hydroxy-3-bromopropyl) cyclopentane (34)

Acetate (30) (250 mg, 0.612 mmol) was dissolved in DMSO-water (18:1, 19 ml) and N-bromosuccinimide (109 mg 0.612 mmol) was added in one portion and the reaction mixture stirred at ambient temperature for 16h. A normal ether work-up was followed by column chromatography. Elution with ether-petrol (1:4) gave *1α-acetoxy-2α-allyl-3β-*

(trans-3-hydroxyoct-1-enyl) cyclopentane (32) (143 mg, 79%) as an oil. (Rf 0.22 in ether-petrol, 1:1 ν_{max} 3415 (OH), 1740 (C=O), 970 (C=C) cm^{-1}; δ 6.25-4.80 (6H, m, CH=CH, $CH=CH_2$ and CH OAc), 4.15 (1H, m, CHOH), 2.00 (3H, s, $COCH_3$), 0.85 (3H, m, CH_2CH_3), 2.80-0.90 (17H, m, remainder); m/e, 276 (M^+-H_2O), 223 ($M^+ - C_5H_{11}$) (Found M^+-H_2O 276.2092. $C_{18}H_{28}O_2$ requires 276.2089).

1α-Acetoxy-2α-allyl-3β-[trans-3-(tetrahydropyran-2-yloxy) oct-1-enyl] cyclopentane (43)

Alcohol (32) (330 mg, 1.12 mmol) was dissolved in dry benzene (40 ml) and dihydropyran (283 mg, 3.36 mmol) plus phosphorylchloride (one drop) were added and the reaction mixture stirred at ambient temperature overnight. The reaction mixture was given a normal ether work-up plus a sodium bicarbonate wash to remove any acid. The mixture was chromatographed, eluting with ether-hexane 1:19 to give the *product* (43) (424 mg, 93%) as an oil (Rf 0.14 in ether-hexane, 1:9); ν_{max}, 1775 (C=O), 975 (C=C) cm^{-1}; δ 6.10-4.50 (7H, m, $CH=CH_2$, CH=CH, CH-OAc and O-CH-O), 1.97 (3H, s, $COCH_3$); m/e 307 ($M^+ - C_5H_{11}$); (Found: C, 72.7; H, 10.0. $C_{23}H_{38}O_4$ requires C, 73.0; H, 10.1%)

1α-Acetoxy-2α-(2-hydroxy-3-bromopropyl)-3β-[trans-3-(tetrahydropyran-2-yloxy) oct-1-enyl] cylcopentane (44)

Olefin (43) (370 mg, 0.98 mmol) was dissolved in DMSO-water (18:1, 57 ml), N-bromosuccinimide (191 mg, 1.1 eq) was added and the mixture stirred at ambient temperature for 3h. The reaction was then given a normal ether work-up but with a water wash in place of saturated brine to remove DMSO. The mixture was chromatographed and eluting with ether-petrol (3:17) gave the *bromohydrin* (44) (344 mg, 74%) as an oil (Rf 0.15 in ether-petrol, 1:1); ν_{max} 3450 (OH), 1735 (C=O) cm^{-1} δ, 5.65-5.05 (3H, m, CH=CH and CHOAc), 4.65 (1H, brs, O-CH-O), 4.40-3.1 (6H, m, O-CH_2, CH_2 Br, CH-OH, CH-OTHP), 2.00 (3H, s, $COCH_3$) 3.15-0.55 (24H, m, remainder); m/e 372 (M^+-THP-2-ol) 314 (M^+-102-AcOH), 301 (M^+-102-C_5H_{11}), 243 (M^+-THP-2-ol - AcOH - C_5H_{11}). (Found M^+-THP-2-ol, 372.1313 $C_{18}H_{29}O_3Br$ requires 372.1301).

1α-Acetoxy-2α(2-oxo-3-bromopropyl)-3β-[trans-3-(tetrahydropyran-2-yloxy)oct-1-enyl] cyclopentane (45)

Bromohydrin (44) (168 mg, 6.35 mmol) was dissolved in dichloromethane (10 ml) and anhydrous sodium acetate (29 mg, 6.35 mmol) followed by pyridinium chlorochromate (380 mg, 6.35 mmol) was added and the suspension stirred at ambient temperature overnight. The suspension was filtered through celite and given a normal ether work-up. The mixture was then chromatographed, eluting with ether-petrol 1:9 to give the *α-bromoketone (45)* (37 mg, 22%) as an oil (Rf 0.60 in ether-petrol, 1:4); ν_{max} 1740 (C=O) cm^{-1}, δ, 5.60-4.85 (3H, m, CH=CH and CH-OAc), 4.50 (1H, brs, OCHO), 4.15-3.15 (5H, m, CH_2Br, CH-OH and OCH_2); 2.77-2.50 (2H, m, CH_2C=O), 1.95

(3H, s, $OCOCH_3$), 2.50-0.60 (23H, m, remainder);

1α-Acetoxy-3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-2α-(3-iodo-2-oxopropyl)cyclopentanone (54a)

Silver chromate (394 mg, 1.25 mmol) and powdered 4A molecular sieves (400 mg) were suspended in dry dichloromethane (5 ml) under nitrogen and cooled to 0°. Iodine (380 mg, 1.50 mmol) was added followed by pyridine (54 mg, 0.50 mmol) and the suspension stirred at 0° under nitrogen for 5 min. Acetate (30) (408 mg, 1.00 mmol) was added in dichloromethane (2 ml) and the suspension stirred for 30 min at 0° then for a further 2h at ambient temperature. The reaction mixture was filtered through a pad of celite and the celite washed well with ether. The organic phase was washed first with 10% sodium thiosulphate solution and then saturated brine. After removal of the solvent under reduced pressure the crude mixture was chromatographed, eluting with ether-hexane (1:9) to yield first unreacted *acetate* (30) (46 mg, 11%) as an oil followed by pure *iodoketone* (54a) (222 mg, 46% based on converted starting material) as an oil (Rf 0.52 in ether-hexane, 2:3); ν_{max}, 1740 and 1715 (C=O), 1255, 1080 (br), 840, 780 ($OSiMe_2{}^tBu$) cm^{-1}; δ, 5.52-5.03 (3H, m, CH=CH and CH-OAc), 4.13-3.87 (1H, m, CH-OSi), 3.71 (2H, s, CH_2I), 2.87-2.62 (2H, m, $CH_2C=O$) 1.99 (3H, s, $OCOCH_3$), 0.85 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$) 0.00 (6H, s, $Si(CH_3)_2$; m/e 493 ($M^+ - C(CH_3)_3$), 479 ($M^+ - C_5H_{11}$), (Found $M^+ - C(CH_3)_3$, 493.1293 $C_{20}H_{34}O_4SiI$ requires 493.1273); (Found: C, 52.15; H, 7.89; I, 23.28. $C_{24}H_{43}O_4SiI$ requires C, 52.35; H, 7.87; I, 23.05%).

Attempted preparation of 1α-(t-butyldimethylsilyloxy) -3β- [trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] -2α- (3-iodo-2-oxopropyl)cyclopentane (54b)

Silver chromate (244 mg, 0.78 mmol) and powdered 4A molecular sieves (250 mg) were suspended in dry dichloromethane (3 ml) under nitrogen and cooled to 0°. Iodine (236 mg, 0.93 mmol) was added followed by pyridine (33 mg, 0.31 mmol) and the suspension stirred at 0° under nitrogen for 5 min. Olefin (40) (298 mg, 0.62 mmol) was added in dichloromethane (1.5 ml) and the mixture stirred for 30 min at 0°. The mixture was filtered through celite, rinsing with ether, washed with 10% sodium thiosulphate followed by saturated brine and the solvent removed under reduced pressure. The crude mixture was chromatographed eluting with ether-hexane (1:24) to yield *6β- [trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] -3-iodomethyl -cisα-2-oxabicyclo [3.3.0] octane* (56) (250 mg, 82%) as an oil (Rf 0.38 in ether-hexane, 1:9); ν_{max} 1255, 1080 (br), 835, 775, ($OSiMe_2{}^tBu$) cm^{-1}; δ 5.55-5.33 (2H, m, CH=CH), 4.81-3.56 (3H, m, CHOSi, CHO and OCH CH_2I), 3.46-3.12 (2H d and d, (diastereomers) CH_2I), 0.86 (12, m and s, CH_2CH_3 and $SiC(CH_3)_3$) 0.00 (6H, s, $Si(CH_3)_2$). 3.00-1.05 (16H, m, remainder); m/e 477 (M^+-CH_3), 435 ($M^+-C(CH_3)_3$), 421 ($M^+-C_5H_{11}$), (Found $M^+-C(CH_3)_3$, 435.1240 $C_{18}H_{32}O_2ISi$ requires 435.1218); (Found: C, 53.83; H, 8.60. $C_{22}H_{41}O_2SiI$ requires C, 53.64; H, 8.39%).

2α-Allyl-3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] -1α-tetrahydropyran-2-yloxy cyclopentane (53c)

Alcohol (12) (1.0g, 2.73 mmol) was dissolved in benzene (50 ml), dihydropyran (688 mg, 8.19 mmol) plus phosphoryl chloride (one drop) were added and the reaction mixture was stirred at ambient temperature for 43h. The reaction was given a normal ether work-up with a saturated sodium bicarbonate wash included to remove any acidic material. The crude mixture was purified by chromatography, eluting with ether-petrol (1:99) to yield the *product* (53c) (1.124 g, 92%) as an oil (Rf 0.25 in ether petrol, 1:19); δ 4.30-3.08 (10H, m, CH=CH_2, CH=CH, CHOSi, CH-OTHP, OCHO and OCH_2), 0.84 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$) 0.00 (6H, s, $Si(CH_3)_2$, 2.80-1.05 (22H, m, remainder).

Attempted preparation of 3β-[trans-3-(t-butyldimethylsilyloxy) oct-1-enyl]-2α-(3-iodo-2-oxopropyl)-1α-tetrahydropyran-2-yloxy cyclopentane (54c)

Silver chromate (394 mg, 1.25 m mol) and powdered 4A molecular sieves (400 mg) were suspended in dry dichloromethane (5 ml) under nitrogen and cooled to 0°. Iodine (380 mg, 1.50 mmol) was added followed by pyridine (54 mg, 0.50 mmol) and the suspension stirred at 0° under nitrogen for 5 min. Olefin (53c) (450 mg, 1.00 mmol) was added in dichloromethane (2 ml) and the mixture stirred for 30 minutes at 0°. The mixture was filtered through celite and the celite washed well with ether. The organic phase was then washed successively with 10% sodium thiosulphate, and saturated brine. The solvent was

removed in vacuo and the crude mixture chromatographed, eluting with ether-hexane (1:24) to yield *6β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-3-iodomethyl-cis α-2-oxabicyclo [3.3.0] octane* (56) details as before.

2α-Allyl-3β- [trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] 1α-trichloroacetoxy cyclopentane (57)

A solution of trichloroacetic anhydride (476 mg, 20 m mol) and pyridine (320 mg, 4.0 mmol) in toluene (25 ml) was prepared and alcohol (12) (366 mg, 1.0 mmol) in toluene (5 ml) was added. After 5 min the reaction mixture was given a normal ether work-up with an extra hydrochloric acid wash to remove pyridine. The crude material was chromatographed and eluted with ether-hexane (1:99) to give the *product* (57) (430 mg, 84%) as an oil Rf 0.52 in ether-hexane, 1:19); ν_{max}, 1765 (C=O), 975 (C=C), 1255, 1085(br), 835, 777 ($OSiMe_2^tBu$) cm^{-1}; δ 6.15-4.70 (6H, m, CH=CH, CH=CH_2 and CHOCO) 4.10-3.80 (1H, m, CHOSi), 0.83 (12H, m and , CH_2CH_3 and $SiC(CH_3)_3$), 0.00(6H, s, $Si(CH_3)_2$), 2.65-1.00 (16H, m, remainder)

3β-[Trans-3-(t-butyldimethylsilyloxy)oct-1-eny]-2α-(3-iodo-2-oxopropyl)-1α-trichloroacetoxycyclopentane (58)

Silver chromate (394 mg, 1.25 mmol) and powdered 4A molecular sieves (400 mg) were suspended in dry dichloromethane (5 ml) under nitrogen and cooled to 0^o. Iodine (380 mg, 1.50 mmol) was added followed by pyridine (54 mg, 0.50 m mol) and the mixture stirred at 0^o under nitrogen for 5 min.

Trichloroacetate (57) (512 mg, 1 mmol) in dichloromethane (2 ml) was added and the mixture stirred for 30 min at 0° then for a further 2h at ambient temperature. The suspension was filtered through a pad of celite and the celite washed well with ether. The organic phase was washed successively with 10% sodium thiosulphate solution then saturated brine and the solvent removed *in vacuo* to give a crude mixture. This mixture was chromatographed eluting with ether-hexane (1:99) to yield the *product* (58) (288 mg, 44%) as an oil (Rf 0.44 in ether-hexane, 1:9); ν_{max}, 1765 and 1715 (C=O), 1255, 1080(br) 835, 780 (OSiMe$_2^t$Bu) cm^{-1}; δ 5.55-5.20 (3H, m, CH=CH) and CH-OCO), 4.15-3.80 (1H, m, CH-OSi), 3.70 (2H, s, CH_2I), 2.97-2.72 (2H, m, CH_2CO), 0.82 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$) 0.02 and 0.00 (6H, s and s, $Si(CH_3)_2$) 2.60-1.00 (14H, m, remainder)

6β-[Trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-3-hydroxy-3-iodomethyl-cisα-2-oxabicyclo [3.3.0] octane (59)

A solution of dry methanol (2 ml) in ether (18 ml) was saturated with dry ammonia gas and iodoketone (58) (200 mg, 0.31 mmol) was added and the reaction mixture was kept at 4° overnight. Purification by chromatography, eluting with ether-hexane (1:9) gave pure *product* (59) (70 mg, 45%) as an oil (Rf 0.41 in ether-hexane, 3:7); ν_{max}, 3400 (OH), 1260, 1070(br), 840, 780 (OSiMe$_2^t$Bu) cm^{-1}; δ 5.45-5.25 (2H, m, CH=CH), 4.80-4.50 (1H, m, CH-O), 4.07-3.75 (1H, m, CH-OSi), 3.50-3.35 (2H, d, CH_2I) 0.80 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$) 0.00 (6H, s, $Si(CH_3)_2$), 2.87-1.00 (17H, m,

remainder); $\frac{m}{e}$, 508 M^+, 490 (M^+-H_2O), 451 ($M^+-C(CH_3)_3$), 437 ($M^+-C_5H_{11}$), (Found M^+, 508.1845. $C_{22}H_{41}SiO_3I$ requires 508.1872)

6β-[Trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-3-hydroxy-3-methoxy-cisα-2-oxabicyclo [3,3,0] octane (60)

Iodoketone (58) (150 mg, 0.23 mmol) was dissolved in dry methanol (10 ml) which had been saturated with dry ammonia gas. After 5 min the reaction mixture was given a normal ether work-up and purified by column chromatography, eluting with ether-hexane (1:4), gave the product (66) (80 mg, 84%) as an oil (Rf 0.09 in ether-hexane, 3:7); ν_{max}, 3480 (OH), 1735 (weak) (C=O), 1260, 1070(br), 840, 780 ($OSiMe_2^tBu$) cm^{-1}, δ, 5.50-5.30 (2H, m, CH=CH), 4.76-4.43 (1H, m, CHO), 4.14-3.80 (1H, m, CH-OSi), 3.73-3.47 (3H, m, CH_2OMe and OH), 3.04 and 3.00 (3H, d, OCH_3), 0.83 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$), 0.00 (6H, m, $Si(CH_3)_2$), 2.80-1.00 (16H, m, remainder); $\frac{m}{e}$ 381 (M^+-OCH_3), 355 ($M^+-C(CH_3)_3$),341 ($M-C_5H_{11}$), Found M^+, 381.2807. $C_{22}H_{41}O_3Si$ requires 381.2825)

Reaction of 3β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] 2α-(3-iodo-2-oxopropyl)-1α-trichloroacetoxy cyclopentane (58) with DBU

Iodoketone (58), (327 mg, 0.50 mmol) was dissolved in dry ether and DBU (88 mg, 0.55 mmol) was added and the

reaction stirred at ambient temperature for 3h. The white precipitate formed during reaction was filtered off on celite and the celite was washed well with ether. The filtrate was evaporated under reduced pressure and purified by chromatography, eluting with ether-hexane (5:195) to yield *9β-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-3-trichloromethyl-2,4-dioxatricyclo-[3.6.0.0^{3,7}]-undecan-6-one* (cis anti cis configuration) (72) (61 mg, 23%) as an oil. (Rf 0.25 in ether-hexane, 3:17); ν_{max} 1770 (C=O), 1265 1080(br), 825, 780 (OSiMe$_2$^{t}Bu) cm^{-1}; δ, 5.65-5.45 (2H, m, CH=CH), 4.91 (1H, m, CHO), 4.47 (2H, , CH$_2$O), 4.10 (1H, m, CHOSi), 3.20 (1H, m, CHC=O), 2.75 (1H, m, CH-CH=CH), 2.38 (1H, m, CH-CH-C=O), 0.85 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$), 0.00 (6H, s, $Si(CH_3)_2$, 2.2-1.0 (12H, m, remainder); ^{13}C nmr ($CDCl_3$-25.2 MHz) δ 210.5 (C=O) 135.6 and 129.7 (C=C,) 120.1 (O-C-O,) 100.3 (CCl_3,) 75.5 (O-C-C=O), 73.4 (CH-OSi), -4.08 -4.6 ($OSi(CH_3)_2$) m/e, 509 (M^+-CH_3), 467 ($M^+-C(CH_3)_3$), 453 ($M^+-C_5H_{11}$); (Found C, 54.66; H, 7.32. $C_{24}H_{39}Cl_3O_4Si$ requires C, 54.80; H, 7.53%).

3-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-1-trimethylsilyloxy cyclopent-1-ene (7)

n-Butyllithium (55 mmol) was added to a stirred solution of 3-(t-butyldimethylsilyloxy)oct-1-enyl iodide (18.4g, 50 mmol) in dry ether (40 ml) under nitrogen at -78°. After 1h a freshly prepared solution of pent-1-ynylcopper (7.2g, 55 mmol) in dry ether (50 ml) and

hexamethylphosphoroustriamide (21 ml, 110 mmol) was added slowly and the mixture stirred for a further 1h at -78° to ensure complete formation of the *cuprate* (3a). Cyclopent-2-enone (6.15g, 75 mmol) in dry ether (100 ml) was added to the solution of (3a) very slowly over 30 min and the mixture stirred for a further 1h at -78°. THF (100 ml) was then added, followed by a mixture of trimethylsilyl chloride (30 ml) and triethylamine (40 ml). The reaction was left to warm to ambient temperature (Ca. 1h), ice was added to quench the excess trimethylsilylchloride, and the mixture extracted with hexane (3 x 200 ml). The combined extracts were washed with ice cold 2% sulphuric acid (4 x 150 ml) to precipitate the copper/HMPA complex, followed by 8% sodium hydrogen carbonate solution (200 ml). Drying with anhydrous magnesium sulphate and evaporation of the solvent in vacuo gave crude *silyl enol ether* (7) (26.1g) as an oil. The crude reaction mixture was vacuum distilled at 0.1 mm Hg and the fraction boiling between 100-125° yielded *silyl enol ether* (7) (13.194g, 66%) as an oil. (Rf 0.55 in hexane); ν_{max}, 1255, 1060 (br), 840 ($OSiMe_2{}^tBu$), 928 (=C-$OSiMe_3$), 970 (C=C) cm^{-1}; δ, 5.7-5.1 (2H, m, CH=CH), 4.52 (1H, m, C=CH) 4.00 (1H, m, CHOSi), 3.20 (1H, m, CH), 0.88 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$, 0.09 (9H, s, $Si(CH_3)_3$) 0.00 (6H, s, $Si(CH_3)_2$), 2.3-1.0 (12H, m, remainder)

3β-[Trans-3-(t-butyldimethylsilyloxy)oct-1-enyl]-2α-(2-methoxyprop-2-enyl)cyclopentanone (79)

Method (a) Silyl enol ether (7) (3.96 g, 10 mmol) was dissolved in THF (30 ml) and added to a mixture of lithium amide (11 mmol) in distilled liquid ammonia (50 ml) at -78°. The reaction mixture was warmed to -40° for 30 min to ensure complete formation of the enolate, and 3-bromo-2-methoxyprop-1-ene (22 mmol) in THF (15 ml) was added rapidly, the cooling bath removed and the ammonia allowed to boil off overnight. The mixture was poured into distilled water. The reaction mixture was given a normal ether work-up, the solvent removed *in vacuo* and the crude mixture chromatographed on silica containing 2% by weight of triethylamine, eluting with ether-hexane 3:97 to yield a mixture of the *product* (79) and *3β-[trans-3-(t-butyldimethyl silyloxy)oct-1-enyl] cyclopentanone* (4) (1.487 g). Both compounds were coincident on t.l.c. (Rf 0.23 in ether-hexane, 1:9). Silver nitrate impregnated plates separated the two compounds showing a ratio of approximately 4:6 of (79) to (4). A slurry of silica gel (25 g) and 10% silver nitrate solution (50 ml) was prepared and dried in an oven overnight at 130°, crushed back into a powder, and packed into a column in the usual way. The mixture was then chromatographed on this column, eluting with ether-hexane (1:19) to yield pure *product* (79) 390 mg, 10%) as an oil, δ 5.50-5.38 (2H, m, CH=CH), 4.07-3.93 (1H, m, CHOSi), 3.30 (2H, s, MeOC=CH_2), 3.45 (3H, s, OCH_3), 0.79 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$ 0.03 and 0.00 (6H, s and s, $Si(CH_3)_2$); m/e, 394 M^+, 337 (M^+-$C(CH_3)_3$), 323 (M^+-C_5H_{11}) (Found M^+ 394.2926. $C_{23}H_{42}O_3Si$ requires 394.2903).

Method (b) - "One pot" n-Butyllithium (27.5 mmol) was added to a stirred solution of 3-(t-butyldimethylsilyloxy) oct-1-enyl iodide (9.2 g, 25 mmol) in dry ether (20 ml) under nitrogen at -78°. After 1h a freshly prepared solution of pent-1-ynylcopper (3.43 g, 26.25 mmol) in dry ether (20 ml) and hexamethylphosphoroustriamide (9.8 ml, 52.5 mmol) was added slowly and the mixture stirred for a further 1h at -78° to ensure complete formation of cuprate (3a). Cyclopent-2-enone (3.07 g, 32.5 mmol) in dry ether (50 ml) was added to the solution of (3a) very slowly over 30 min and the mixture stirred for a further 1h at -78°. Dry liquid ammonia (distilled from sodium 200 ml) was then added followed by 3-bromo-2-methoxyprop-1-ene (125 mmol). The cooling bath was removed and the ammonia allowed to evaporate overnight. The mixture was poured into distilled water, and given a normal ether work-up. The crude mixture was separated as in method a to give the *methoxy enol ether* (79) (1.58 g, 16%) as an oil identical with the compound prepared by method a .

3β [trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] -2α-(2-oxopropyl)cyclopentanone (85)

A mixture of methoxyenol ether (79) and quenched enolate (4) from a conjugate addition enolate alkylation reaction (these materials are chromatographically coincident) (150 mg) was dissolved in THF (5 ml) and 10% aqueous oxalic acid (0.25 ml) was added and the mixture stirred at ambient

temperature. After 2h the oxalic acid was neutralised by the addition of saturated sodium hydrogen carbonate solution (1 ml) and given a normal ether work-up, to afford an oil. Purification by preparative t.l.c., eluting with ether-petrol 1:4, and extraction of the material with Rf 0.20 gave the *product* (85) (55 mg) as an oil, ν_{max} 1725 and 1745 (C=O cyclic and exocyclic) 1260, 1070 (br), 835 and 775 ($OSiMe_2^tBu$) cm^{-1}; δ 5.60-5.40 (2H, m, CH=CH), 4.15-4.00 (1H, m, CH-OSi), 2.18 (3H, s, $CH_3C=O$), 0.92 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$) 0.04 and 0.06 (6H, s and s, $Si(CH_3)_2$) 2.80-1.15 (16H, m, remainder); m/e 365 (M^+ $-CH_3$), 323 ($M^+-C(CH_3)_3$), 309 ($M^+ -C_5H_{11}$) (Found M^+ - $C(CH_3)_3$, 323.2060. $C_{18}H_{31}O_3Si$ requires 323.2043).

2α-(3-Bromo-2,2-dimethoxypropyl)-3β-[trans-3-(t-butyl dimethylsilyloxy)oct-1-enyl] cyclopentanone (80)

Methoxy enol ether (79) (110 mg, 0.28 mmol), was dissolved in methanol (5 ml). Anhydrous sodium acetate (90 mg, 1.12 mmol) was added and the reaction mixture cooled to -78°. Bromine (48 mg, 0.31 mmol) in methanol (3 ml) was added slowly to the stirred reaction mixture. After 10 min the reaction mixture was poured into sodium hydrogen carbonate solution then given a normal ether work-up. Chromatography, eluting with ethyl acetate-petrol 1:19 afforded first *3-bromomethyl-6β-[trans-3-(t-butyl dimethylsilyloxy)oct-1-enyl]-1,3-dimethoxy-cisα-2-oxabicyclo [3.3.0] octane (88)* (25 mg, 18%) as an oil (Rf

0.57 in ethyl acetate-petrol, 1:9); ν_{max} 1740 (w) (ketal), 1260, 1080, 840, 780 (OSiMe$_2^t$Bu) cm^{-1}; δ, 5.38 (2H, m, CH=CH), 4.1-3.0 (9H, m, 4 x s, m, CH-OSi, OCH_3, CH_2Br) 0.80 (12H, m and s, CH_2CH_3, and $SiC(CH_3)_3$) 0.00 (6H, s, $Si(CH_3)_2$, 2.40-1.00 (16H, m, remainder). This was followed by the *product (80)* (62 mg, 44%) as an oil, (Rf 0.27 in ethyl acetate-petrol, 1:9); ν_{max} 1740 (C=O), 1250, 1075, 835, 775 (OSiMe$_2^t$Bu), 1052 (OMe) cm^{-1}; δ, 5.8-5.3 (2H, m, CH=CH), 4.07 (1H, m, CHOSi), 3.7-3.3 (2H, m, CH_2Br), 3.2 and 3.15 (6H, s and s, OCH_3), 0.85 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$) 0.00 (6H, s, $Si(CH_3)_2$), 2.7-1.1 (16H, m, remainder); m/e, 474 (M^+-OCH_3), 448 (M^+-57) (Found (M^+-31) 473.2073 and 475.2076. $C_{23}H_{40}O_3SiBr$ requires 473.2086 and 475.2032).

2α-(3-Bromo-2,2-dimethoxypropyl)-3β-[trans-3-(t-butyldimethyl silyloxy)oct-1-enyl] cyclopent-1α-ol (81)

A solution of potassium tri-(sec-butyl)borohydride in THF (Alditch K-Selectride, 1.07 mmol) was slowly added to a stirred solution of ketone (80) (270 mg, 0.534 mmol) in THF (30 ml) under nitrogen at -40°. The temperature was allowed to rise to 0° over 1h and the excess reagent hydrolyised by the careful addition of water. 3M Sodium hydroxide solution (0.3 ml, 0.587 mmol) was then added followed by 30% hydrogen peroxide (0.35 ml, 2.88 mmol) to oxidise the borane. The mixture was stirred at 0° for 1h. A normal ether work-up gave an oil. Chromatography, eluting with ether-hexane (1:4) afforded *product (81)* (250 mg, 93%) as an oil (Rf 0.32 in ether-hexane, 1:1); δ 5.4-5.2 (2H,

m, C<u>H</u>=C<u>H</u>), 4.3-3.75 (2H, m, <u>CH</u>-OH and C<u>H</u>OSi), 3.75-3.10 (8H, m, CH_2Br and OCH_3) 0.83 (12H, m and s, CH_2CH_3 and $SiC(CH_3)_3$) 0.00 (6H, s, $Si(CH_3)_2$), 2.40-1.03 (17H, m, remainder).

7β- [Trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] -4,4-dimethoxy-cis α-2-oxabicyclo [3.4.0] nonane (62)

Alcohol (<u>81</u>) (190 mg 0.38 mmol) was dissolved in THF (50 ml) and 50% sodium hydride in oil (36 mg 0.76 m mol) was added. The reaction mixture was boiled under reflux for two days, and then poured into distilled water and given a normal ether work-up. Chromatography, eluting with ether-hexane (1:9) gave the *product* (<u>62</u>) (92 mg, 58%) as an oil (Rf 0.35 in ether-hexane, 1:4); ν_{max} 1745 (w) (ketal), 1260, 1065, 845, 785 ($OSiMe_2{}^tBu$); δ 5.6-5.1 (2H, m, C<u>H</u>=C<u>H</u>) 4.2-3.7 (2H, m, C<u>H</u>OSi and C<u>H</u>O), 3.35-2.9 (8H, m, $OC\underline{H}_2$ and $OC\underline{H}_3$). 0.80 (12H, m and s, $CH_2C\underline{H}_3$ and $SiC(CH_3)_3$), 0.00 (6H, s, $Si(\underline{CH_3})_2$), 2.9-1.1 (16H, m, remainder); m/<u>e</u> 395 (M^+-OCH_3), (Found (M^+-OCH_3), 395.2955 $C_{23}H_{43}O_3Si$ requires 395.2929). (Found C,67.62; H, 10.94 $C_{24}H_{46}O_4Si$ requires C, 67.55; H, 10.87%).

7β-(Trans-3-hydroxyoct-1-enyl)-cis α-2-oxabicyclo [3.4.0] nonan-4-one (82)

A slurry of 230-400 mesh silica gel (1g) in dichloromethane (3ml) was prepared and 10% aqueous oxalic

acid (0.1 ml) was added and the slurry stirred until the aqueous oxalic acid had been adsorbed onto the silica gel (30 min). Ketal (62) (100 mg, 0.23 mmol) in dichloromethane (0.5 ml) was added and the reaction mixture stirred for 2 days at ambient temperature. Solid anhydrous sodium carbonate was added to neutralise the oxalic acid and after stirring for 5 min the reaction mixture was filtered and the silic gel washed well with ether. Evaporation of the solvent in vacuo and preparative t.l.c., eluting with ether, gave at RF 0.37 the *product* (82) 48 mg, 79%) as a white crystalline solid. ν_{max} 1737 (C=O), 3470 (OH) cm^{-1}; δ 5.7-5.3 (2H, m CH=CH), 4.1 and 3.75, 4.2-3.9 (4H, AB 18 Hz and m, OCH_2-C, CH-OH and CH-O), 0.88 (3H, m, CH_2-CH_3) 2.8-1.1 (17H, m, remainder); ^{13}C nmr ($CDCl_3$-25.2MHz) δ 210.7 (C=O) 133.7 and 132.0 (C=C), 72.8 (O-C-C=O), 72.6 and 72.4 (epimers) (C-OH); m/e 266 M^+, 248 (M^+-H_2O), 195 ($M^+-C_5H_{11}$) (Found M^+, 266.1906 $C_{16}H_{26}O_3$ requires 266.1881); (Found C,72.46; H,9.84 $C_{16}H_{26}O_3$ requires C, 72.14; H, 9.84%).

4-(4-carboxybutenyl)-7β- (trans-*3-hydroxyoct-1-enyl*)-cis α-*2-oxabicyclononane* (73)

4-carboxybutyl-triphenylphosphonium bromide (330 mg, 0.75 mmol) and potassium tert-butoxide (170 mg, 1.5 mmol) were weighed into a flask which was then flushed with nitrogen and maintained under a nitrogen atmosphere. THF (5 ml) was added and the deep red ylid solution stirred for 30 min at ambient temperature. Bicyclic ketone (82) (50 mg, 0.19 mmol) in THF (1 ml) was added rapidly in one portion

and the reaction mixture stirred at ambient temperature, under nitrogen for 2h. The reaction mix was poured into saturated ammonium chloride, and aqueous sodium hydroxide solution added. The mixture was extracted once with ether and the extract containing triphenylphosphine oxide discarded. The solution was then made acid to litmus by the addition of dilute HCl and extracted three times with ether. The ether extracts were combined, dried over anhydrous sodium sulphate, and the solvent removed under reduced pressure to yield a semi-crystalline product. Chromatography, eluting with acetic acid : ether : hexane 1:89:210, afforded first the least polar of the two tlc components, *(E)-4-(4-carboxybutenyl)-7β-(trans-3-hydroxyoct-1-enyl)cisα-2-oxabicyclo-[3.4.0]-nonane.* (73b) (21mg, 32%) as an off white crystalline solid (Rf 0.45 in acetic acid: ether 1:99), ν_{max} 3430 (OH), 1720 (C=O), 1060 (C-O) cm^{-1}; δ 6.15 (2H, s, O<u>H</u> and COO<u>H</u>), 5.44-5.10 (3H, m, C<u>H</u>=C<u>H</u> and -C<u>H</u>=), 4.15-3.80 (3H, m, C<u>H</u>$_2$O and C<u>H</u>OH); <u>m</u>/<u>e</u> 350 M^+, 332 (M^+-H_2O), 279 (M^+-C_5H_{11}), (Found M^+ 350.2435. $C_{21}H_{34}O_4$ requires 350.2457). This was followed by *(Z)-4-(4-carboxybutenyl)-7β-(trans-3-hydroxyoct-1-enyl)-cisα-2-oxabicyclo-[3.4.0]-nonane* (73a) (32mg, 49%) as an off white crystalline solid (Rf 0.41 in acetic acid : ether 1:99), ν_{max} 3410 (OH), 1715 (C=O), 1065 (C-O) cm^{-1}; δ 6.69 (2H, s, O<u>H</u> and COO<u>H</u>), 5.60-5.00 (3H, m, C<u>H</u>=C<u>H</u> and -CH=), 4.70-3.62 (3H, ABq J=12H$_z$, OC<u>H</u>$_2$ and m, C<u>H</u>OH); <u>m</u>/<u>e</u> 350 M^+, 332 (M^+-H_2O), 279 (M^+ - C_5H_{11}) (Found M^+ 350.2541. $C_{21}H_{34}O_4$ requires 350.2457).

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