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SOME ASPECTS OF NOVEL PROSTANOID ACID SYNTHESIS

A Thesis Submitted to

Loughborough University of Technology

by

S. M. F. LAI

In Partial Fulfilment of the Requirements

for the Degree of

Doctor of Philosophy

Supervisor: Dr. B. A. MARPLES



December 1978. S.M.F. LAI

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Finally, I gratefully acknowledge the financial support provided by Beecham Pharmaceuticals Ltd. which made it possible for me to carry out this work.

SUMMARY

The synthesis of prostaglandins is reviewed and the strategy of the more important and interesting approaches is discussed.

The synthesis of a model prostanoid via a novel three-stage approach is described. This involved a Claisen type condensation of diethyl azelate to methyl nonyl ketone to form a C_{20} 1,3-diketo -ester. Dimethylation of the active methylene at the C-10 position of the 1,3-diketo-ester, followed by cyclisation across the C-8, C-12 positions, afforded the novel ethyl 10,10-dimethyl prost-8(12)-en-9,11-dionoate. This synthetic approach was subsequently applied to the preparation of the novel ethyl 10,10-dimethyl prost-8(12), 15-dien-9,11-dionoate and ethyl 10,10-dimethyl-15-benzyloxy-prost-8(12)-en-9,11-dionoate.

Other methods of effecting the C-8, C-12 cyclisation of 8,12-dibromo -10,10-dimethyl eicos-9,11-dionoic esters were investigated. Finally, the cyclisation of simpler 1,3-diketone models, 3,7-dibromo-5,5-dimethyl nona-4,6-dione and 5,9-dibromo-7,7-dimethyl trideca-6,8-dione was investigated.

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1. PROSTAGLANDINS

1.1 Introduction to Prostaglandins

Prostaglandins are a class of C_{20} -hydroxylated unsaturated fatty acids of mammalian origin. They are usually present in minute quantities in almost all animal organs. All investigations carried out so far would suggest that they are synthesized by an enzyme complex, prostaglandin synthetase¹ and very rapidly deactivated by other specific enzymes². It seems likely that in most instances, prostaglandins are not stored as such, but are readily formed from precursor unsaturated fatty acids, in response to a variety of stimuli^{3, 4}.

Biologically, these substances are unusual because of their ubiquity in the human organs, their broad spectrum of physiological activity and their very high potency. The problem of their physiological role is a complex one and there are indications that these substances may play a different role not only in each organ, but possibly in each tissue and cell⁵. Generally, they are regarded to be local modulators of cell function or tissue hormones. They seem to be involved in the regulation of the endocrine, reproductive, nervous, digestive, hemostatic, respiratory, cardiovascular and renal systems^{6,7}. Of considerable importance is the action of prostaglandins on smooth muscle beds. This has led to the first clinical use of a prostaglandin to induce human parturition⁸.

The presence of active factors in the seminal fluid of man was first reported by R. Kurzok and C. C. Lieb⁹ in 1930. This was followed by reports of similar findings by U. S. Von Euler¹⁰ and M. W. Goldblatt¹¹. However, due to difficulties in purification, the structure of these active substances remained unknown for a number of years. Eventually in 1957, S. Bergström and B. Samuelsson^{12,13} purified and isolated the first

pure crystalline PGF. This was followed by a series of elegant chemical elucidation work¹⁴⁻¹⁸ which culminated in the final proof of the structures of PGF₁ and the related PGE₁. Since then, the crystal structures^{19,20,21} and absolute configurations²² of these compounds and other members of the family of prostaglandins have been reported.

The nomenclature of prostaglandins is based on the C₂₀ prostanoid acid shown in figure 1.1. The prostaglandins are grouped into six basic families which differ from each other in the nature of the cyclopentane functionalities. The primary prostaglandins²³ are PGF and PGE; the other families which may be derived from them are PGA, PGB, PGC and PGD. Within each family of prostaglandin are members with different numbers of double bonds, such as PGE₁, PGE₂ and PGE₃.

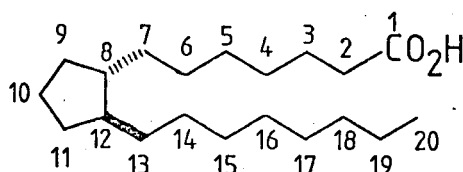
In addition to the six basic families of prostaglandins, more new families have been discovered. These are the prostaglandin endoperoxides^{25,26} (PGG and PGH), the prostacyclin²⁴ (PGX or PGI) and the related thromboxanes²⁴.

A major difficulty in the biological evaluation and practical application of prostaglandin was due to the short supply of the primary prostaglandins from natural sources. Early supplies of prostaglandins were obtained from extracts of ram seminal vesicles after lengthy purification procedures. However, the problem was partly overcome when biosynthetic studies^{27,28,29} showed that relatively larger quantities of prostaglandins could be prepared by the incubation of certain essential polyunsaturated fatty acids with enzyme extracts from sheep seminal vesicles.

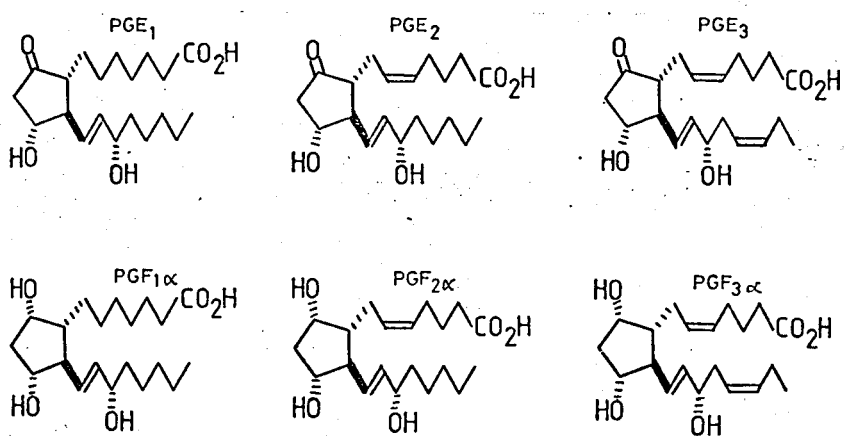
For many years, a laboratory scale-up of this biosynthetic route was used to obtain gram-quantities of prostaglandins for biological evaluation³⁰. More recently, the accidental discovery of a prostaglandin

FIGURE 1.1

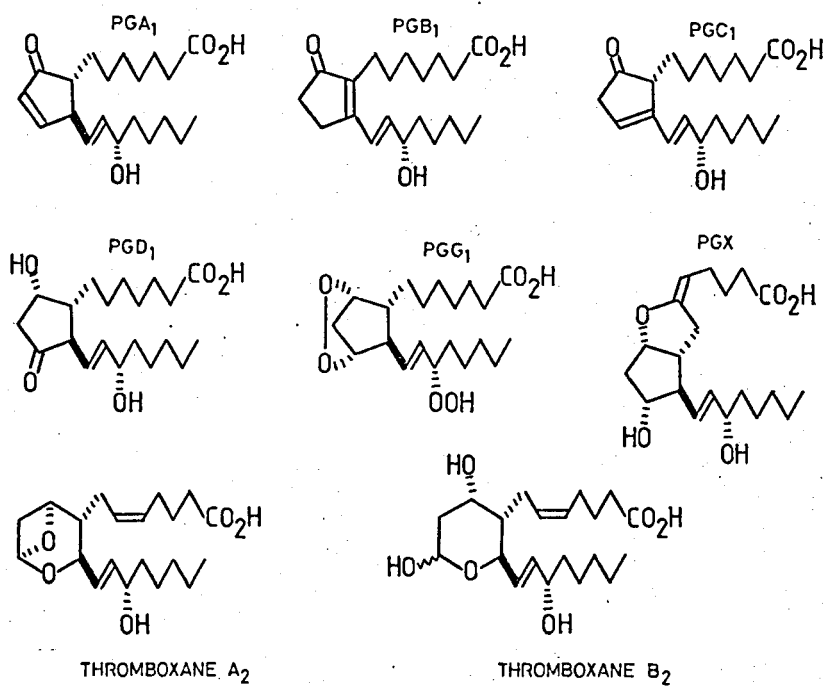
PROSTANOIC ACID



PRIMARY PROSTAGLANDINS



OTHER PROSTAGLANDINS AND RELATED THROMBOXANES



of the A family (15-epi-PGA₂) in the Carribean coral, Flexaura Homomalla³¹, has provided an unexpectedly large quantity of material (1.3% dry weight of PGA). This is presently being used for the synthesis of other primary prostaglandins, as well as for the preparation of modified entities^{32,33}.

With the anticipation that prostaglandins would become medically useful agents, it was necessary to devise efficient methods for their synthesis on a large scale. The scale-up of the biosynthetic route was not thought to offer the potential for large scale operation, nor the flexibility necessary to produce a wide range of different prostaglandins and their modified congeners. From the time that the first prostaglandin structures were known, chemical total synthesis has been investigated as a viable alternative. Only shortly after the final proof of the structure of the primary prostaglandins, the first total synthesis of (±)-PGE₁ and (±)-PGF₁ was reported by Just and Simonovitch³⁴ of McGill University. This was followed by a more definitive series of papers on the synthesis of (±)-PGE₁ and (±)-PGF_{1α} by E. J. Corey and his co-workers at Harvard University^{35,36}. Subsequently, they demonstrated the first total synthesis of PGE₁ in its natural enantiomeric form³⁷.

Since then, numerous total and partial syntheses of natural prostaglandins have been reported. This challenge in organic synthesis has consequently stimulated new ideas and led to the introduction of many novel synthetic methodologies. In the following section, the more general strategies of prostaglandin synthesis will be discussed.

As a result of the intensive research in the prostaglandin field, the volume of published literature has increased almost exponentially. Several reviews and books with varying emphasis on different aspects of prostaglandins are available. To cover some of the more vital literature,

a selected bibliography is included in a separate section at the end.

1.2 Prostaglandin synthesis and the choice of a synthetic target.

In the ideal total synthesis of prostaglandins, it is desirable to prepare all the primary prostaglandins and analogues in their optically active forms from a single precursor (synthon). Such a synthon could be prepared from chiral starting materials or by chemical resolution or stereospecific microbial transformation of achiral precursors at an early stage in the synthesis. In practice, the synthon generally bears the cyclopentane nucleus in a protected form and provides a degree of flexibility for the introduction of a variety of side-chains.

Generally, the primary synthetic target of most total syntheses is a member of the PGE or PGF family. This is due in part to the fact that prostaglandins of the A, B, C and D families can be prepared by further conversion of PGE or PGF. The latter pair are also interconvertible (see fig. 1.2).

The 1, 2 and 3 series within each prostaglandin family can generally be prepared by the introduction of side chains with different degrees of unsaturation. Alternatively, selective hydrogenation of the double bonds is possible in limited instances, fig. 1.3.

The major problems encountered in the total synthesis of prostaglandins are those of stereochemical control, lability of the prostaglandin molecule (as in the synthesis of PGE) and selective manipulation of the functional groups. In PGE₁ for instance, there are four asymmetric centres, three of these centres are contiguous on the cyclopentane nucleus and mutually trans. This is the more stable arrangement and, therefore, relatively easy to establish. The same is true of the trans C-13 double bond. However, stereochemical control of the fourth asymmetric centre at C-15 is difficult because of its remote position.

Furthermore, the general instability of PGE₁ is characterised by

FIGURE 1,2

INTERCONVERSION OF THE PG FAMILIES

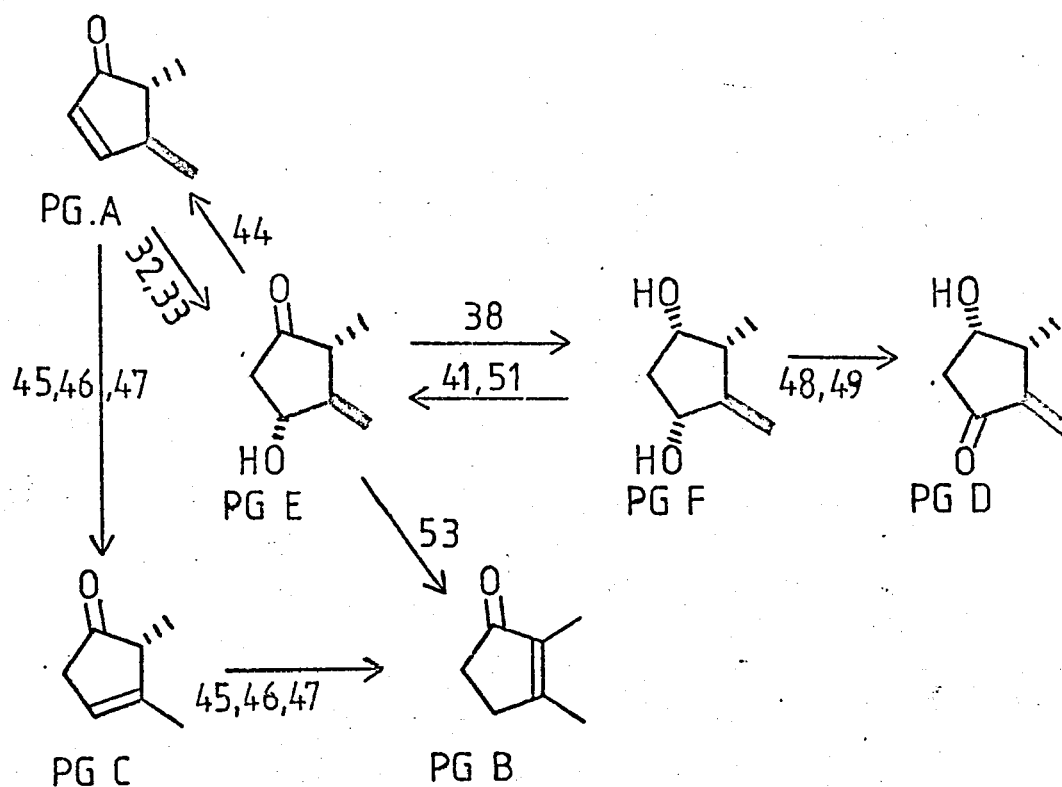
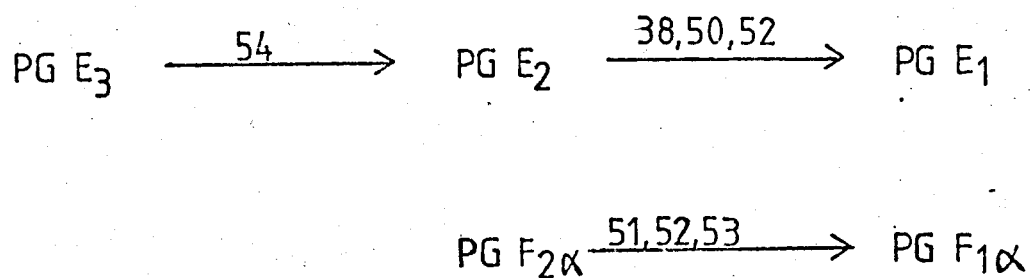


FIGURE 1,3

SELECTIVE HYDROGENATION OF PG E AND F SERIES



the significant dehydration of its 1,3-ketol system^{44,53} at pH values outside the 3-9 range. On the other hand, PGF_{1 α} possesses an extra asymmetric centre at the C-9 position which complicates the problem of synthesis. However, this is more than compensated for by the marked increase in the stability of the PGF_{1 α} molecule.

It is evident that the synthesis of PGE and PGF each presents its own particular set of problems. It is interesting, therefore, to examine in the following section, the various strategies and methodologies employed to solve these problems.

1.3 Strategies in prostaglandin synthesis

Prostaglandin synthesis can generally be classified into three main classes as shown in fig. 1.4.

- i) synthesis from acyclic precursors.
- ii) synthesis from cyclopentane or monocyclic precursors.
- iii) synthesis from polycyclic precursors.

In general, the syntheses of classes (i) and (ii) are beset by problems of stereochemical control and the selective protection and elaboration of functional groups are often difficult. Syntheses of class (iii) generally possess a degree of stereochemical control. Latent functionalities held within the rigid framework of these polycyclic systems can be used to bring about relative stereochemical control at several carbon centres. In addition, the further elaboration of these polycyclic precursors can often be achieved in a stereoselective manner by the use of bulky reagents.

(i) Synthesis of prostaglandin from acyclic precursors

The construction of the cyclopentane nucleus of the prostaglandin skeleton from acyclic precursors may be accomplished in a variety of ways. The various possible bond formations shown in fig. 1.5 generally rely on acid- or base-catalysed aldol type condensations. Of the five approaches shown, only the C-8, C-9 bond formation has not been reported.

In general the conversion of simple acyclic precursors to alicyclic products lack stereochemical control. However, in the synthesis of prostaglandins, this problem is reduced by the fact that the required relative configuration of the substituents at C-8, C-11 and C-12 of the cyclopentane nucleus is the more stable all-trans arrangement.

FIGURE 1,4

CLASSIFICATION OF PG SYNTHESIS

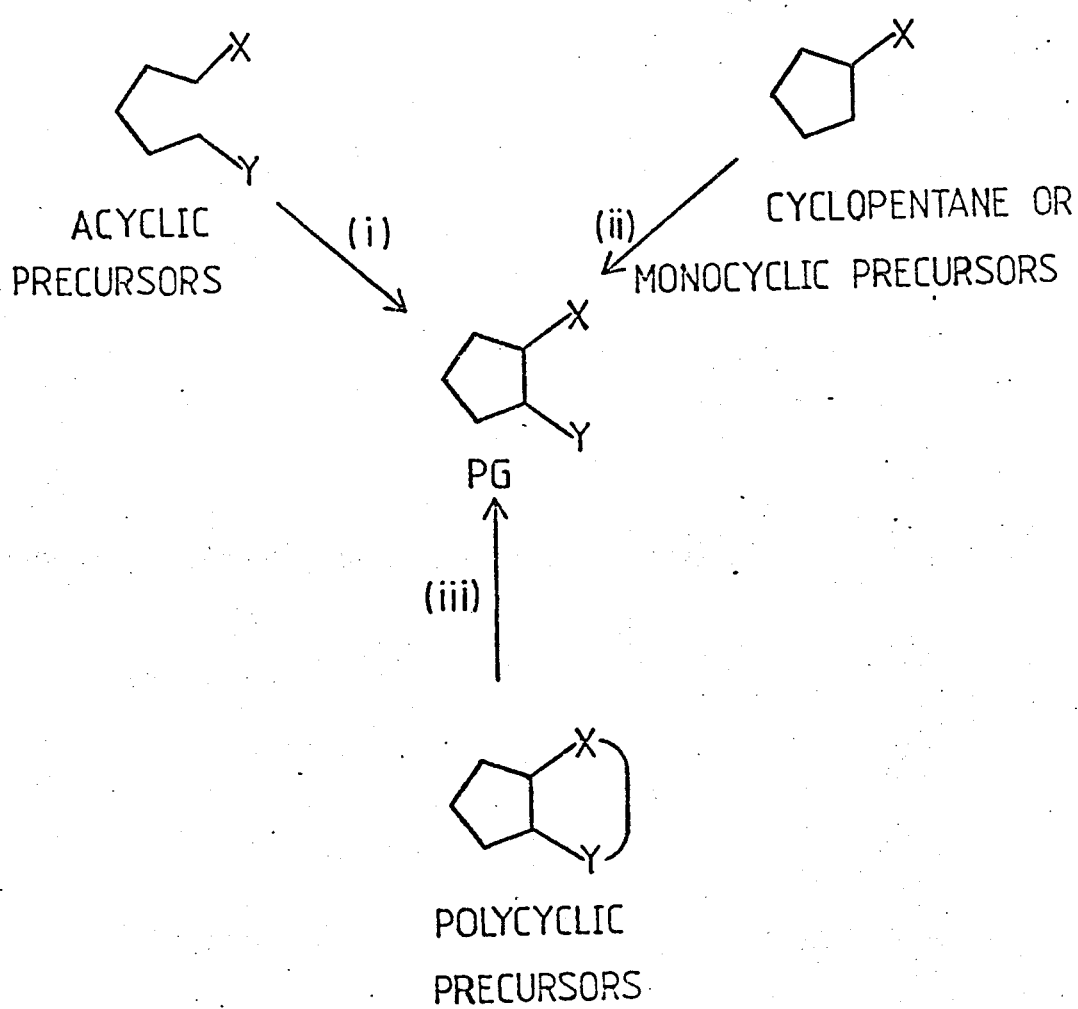
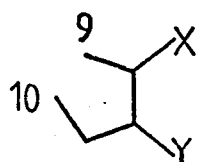


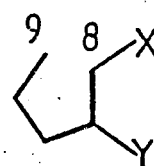
FIGURE 1,5

PG SYNTHESIS FROM ACYCLIC PRECURSORS

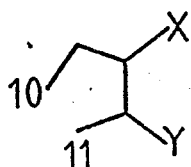
9,10 BOND FORMATION⁶⁵



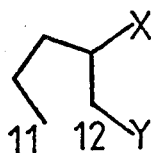
8,9 BOND FORMATION



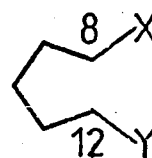
10,11 BOND FORMATION^{55b,64}



11,12 BOND FORMATION^{35-37,55a}



8,12 BOND FORMATION⁵⁶⁻⁶³



Historically, the approach via the C-11, C-12 bond formation by E. J. Corey et al^{35-37,55a} is of interest, as it led to the first total synthesis of PGE₁ in its natural enantiomeric form. A later improved version of this synthesis is outlined in fig. 1.6.

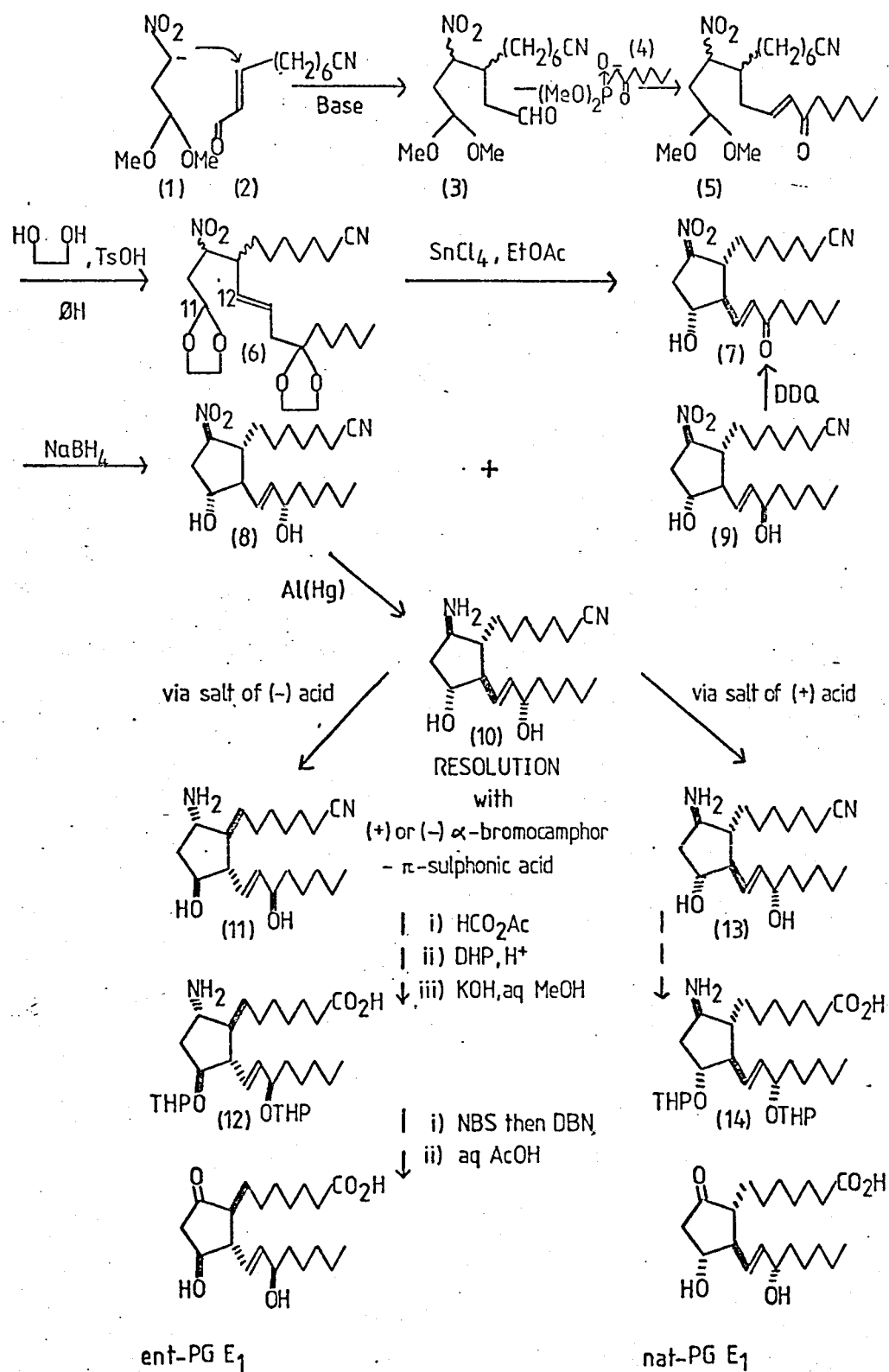
The reaction of 3-nitropropanoldimethylacetal¹⁰³ (1) with 9-cyano-2-nonanal^{104,105} (2) in the presence of base gave the Michael adduct (3) which was converted to the conjugate enone (5) using the Horner-Emmons^{127,128} modification of the Wittig reaction.

Protection of the C-15 carbonyl function gave the bis-dioxolan (6). Cyclisation of (6) in the presence of anhydrous stannic chloride³⁷ almost completely and stereoselectively gave the vinylogous aldol product (7), with only minor contamination by its 11 β -epimer. Reduction of the C-15 carbonyl group gave a mixture of epimeric diols (8) and (9) which were separated by chromatography. The desired nitro-cyclopentane diol (8) was subsequently reduced to the amino-derivative (10). Resolution at this stage with (-)- α -bromcamphor- π -sulphonic acid afforded the required enantiomer (13). Sequential N-formylation and protection of the hydroxyl groups of (13), followed by base hydrolysis, gave the protected amino-carboxylic acid (14). Bromination and dehydrobromination of the amino¹⁰⁶⁻¹⁰⁸ function, followed by carefully controlled acid hydrolysis, afforded optically active natural PGE₁.

As was expected, the stereochemical control of the remote C-15 centre was difficult. This was exemplified by the sodium borohydride reduction of (7) which afforded a mixture of the C-15 epimers (8) and (9). However, the undesired 15 β -epimer (9) could be reconverted to the precursor (7) by selective oxidation with DDQ. This recycling procedure allowed stereoselective channelling of the synthesis to the desired 15 α -epimer (8).

FIGURE 1,6

TOTAL SYNTHESIS OF NATURAL (-) PG E₁ ^{36,37}



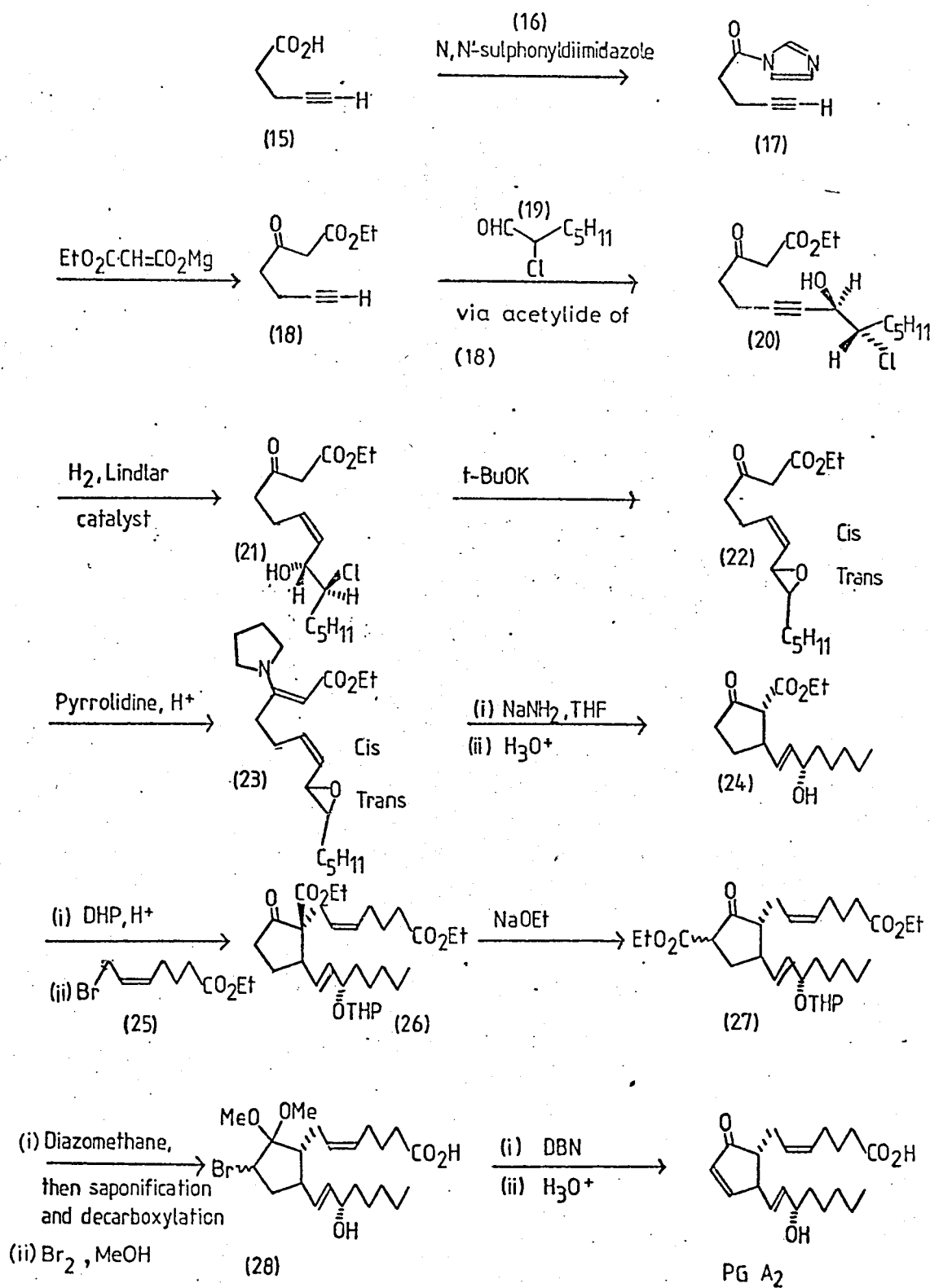
Although this approach by E. J. Corey succeeds in the total synthesis of nat-PGE₁, several difficulties still remain unresolved. For instance, complete stereospecific control of the C-11 centre has not been achieved. In addition, the generation of the 1,3-ketol system from the 1,3-hydroxylamine precursor (12) or (14) via the procedure described (Ruschig's method)¹⁰⁶⁻¹⁰⁸ is experimentally difficult.

More recently, two biomimetic routes^{58,63} have been reported. Of these, the Roussel-Uclaf approach⁶³ is conceptually one of the most interesting. This approach forges the C-8, C-12 bond and incorporates steric control at the C-12, C-13, C-14 and C-15 centres. This is achieved by a biogenetic type cyclisation of a conjugated epoxide. The synthesis is outlined in fig. 1.7.

The acetylenic acid (15) was converted to its acyl imidazole derivative (17). Reaction of (17) with the magnesium enolate of the hemiester of malonic acid, followed by decarboxylation, afforded the 1,3-diketo-ester (18). Transformation of (18) to its enol ether and subsequent alkylation with 2-chloro-heptanal produced the erythro-chlorohydrin (20) after acid hydrolysis. Partial hydrogenation of (20), followed by mild base treatment, afforded the key epoxide (22) which was to act as the electrophilic site in the biogenetic type cyclisation. Treatment of the pyrrolidine enamine (23) with sodamide in THF, followed by acid hydrolysis, provided the cyclopentanone (24) with the correct configuration at C-12, C-13, C-14 and C-15. The α -side chain at C-8 was introduced by alkylation with the bromo-olefin (25). Isomerization of the carbethoxy group from C-8 to C-10 was effected by a retro-Dieckmann cyclisation. Sequential methylation, saponification and decarboxylation of (27) afforded an intermediate methyl enol ether which on treatment with bromine

FIGURE 1,7

THE ROUSSEL-UCLAF APPROACH⁶³



in methanol gave the bromo-ketal (28). Dehydrobromination of (28), followed by cleavage of the protecting groups afforded PGA_2 .

The Roussel-Uclaf approach is of considerable theoretical interest because of the biogenetic type cyclisation of the cis-trans allylic epoxide (23) which in a single step introduces the requisite trans double bond at C-13, together with relative stereochemical control of the C-8, C-12 and C-15 centres. However, in practice, there are difficulties due to competing alternate modes of ring-closure.

(ii) Synthesis of prostaglandin from cyclopentane or monocyclic precursors

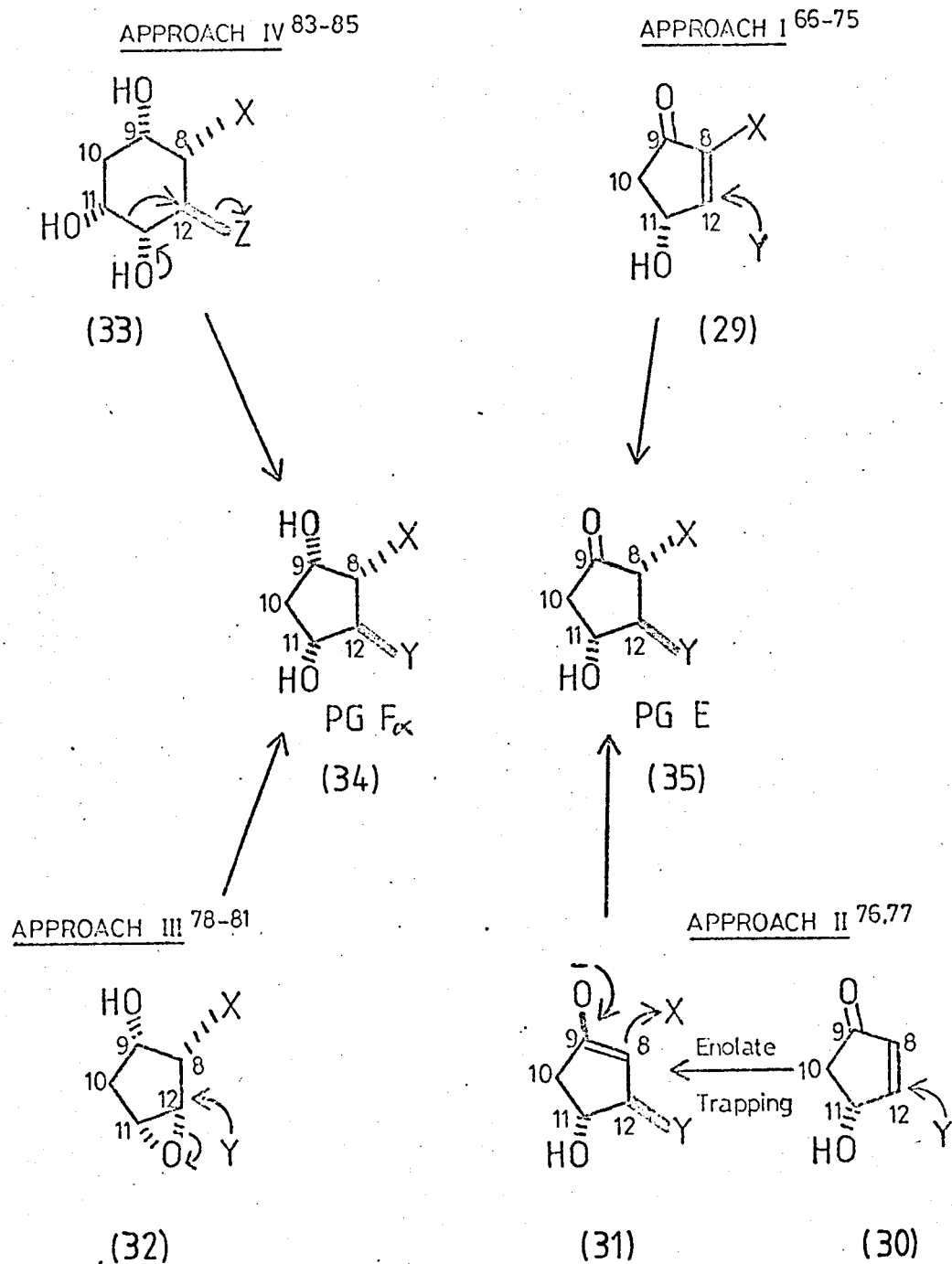
Several interesting variants of this general approach to prostaglandin synthesis have been developed. The strategy of the more important syntheses is outlined in fig. 1.8.

Generally, the synthesis commences with a preformed cyclopentane nucleus bearing the requisite functionality for the attachment of one or both the pendant side-chains. This is exemplified by synthetic approaches I, II and III. Alternatively, stereospecific ring contraction of a suitably functionalised cyclohexane precursor provides an entry to the cyclopentane template which is subsequently elaborated.

In the first three approaches, the relative configuration of the C-8, C-11 and C-12 centres is predetermined by the regiospecific approach of the nucleophilic component Y. For steric reason, the attack by the nucleophile Y is generally from the β -face, this establishes the desired mutually all -trans configuration at the C-8, C-11 and C-12 centres of the cyclopentane ring. Approach IV, however, employs the cyclohexane precursor (33) bearing the correctly disposed substituents and relies on stereospecific ring contraction for the formation of the mutually all-trans

FIGURE 1,8

PG SYNTHESIS FROM CYCLOPENTANE
OR MONOCYCLIC PRECURSORS

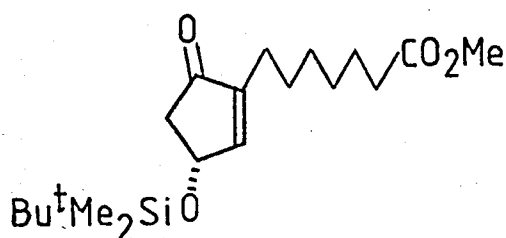


configuration in the product type (34).

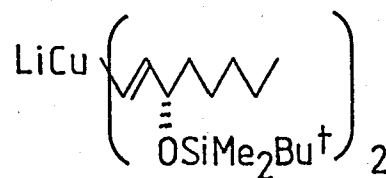
One of the simplest and shortest route to PGE is by synthetic approach I. This was elegantly demonstrated by C. J. Sih et al^{68,69} of Wisconsin University. This synthesis is shown in fig. 1.9.

Condensation of (36) with diethyl oxalate, followed by acid hydrolysis and esterification, afforded the trione (37). Stereospecific enzymatic reduction by Dipodascus Uninucleatus gave the 11(R)-alcohol (38). Reaction of (38) with mesityl sulphonyl chloride and triethylamine gave two isomeric enol sulphonates, (39) and (40). The major isomer (39) was reduced with excess sodium bis-(2-methoxyethoxy)-aluminium hydride, followed by acid-catalysed rearrangement and elimination to give the desired optically active cyclopentanone (41). Protection of the hydroxyl function of (41), followed by 1,4-addition of trans-divinyl cuprate (43), afforded the protected PGE₂ (44). Deprotection by acid hydrolysis and enzymatic de-esterification gave PGE₂.

The key conjugate addition step was extensively studied by C. J. Sih⁶⁶⁻⁶⁹ and other groups^{71,72,76}. The highest yield of approximately 65% was reported by Sih⁶⁷ for the stereospecific conjugate addition of the trans-divinyl cuprate (43) to the protected cyclopentanone (45).



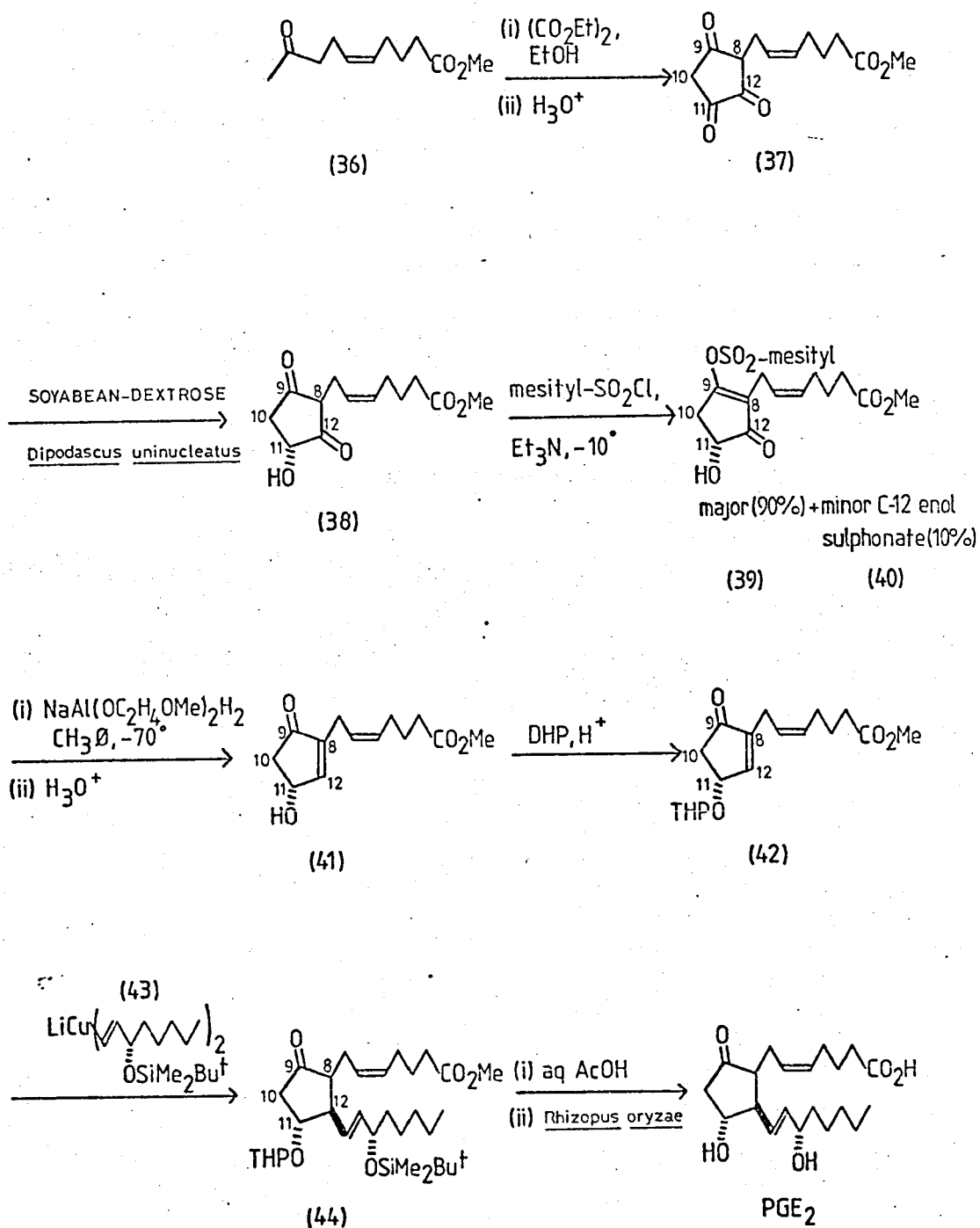
(45)



(43)

FIGURE 1,9

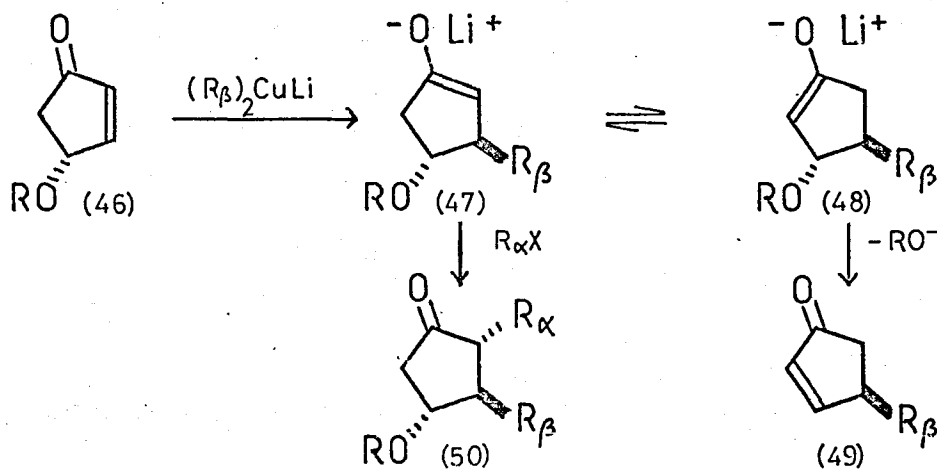
SIH'S SYNTHESIS OF PGE₂ VIA 1,4 ADDITION^{68,69}



An important drawback of this conjugate addition is that only half of the precursor divinyl cuprate (43) is consumed in the reaction. The use of alternative nucleophiles such as $(X_3P)_n(R_\beta)CuLi$ ⁶⁶⁻⁶⁹, $LiAl(Me)_3R_\beta$ ^{71,72} and $[ICuP(n-Bu)_3]_4/R_\beta MgBr$ complex⁷² has been reported. These alternative methods are less wasteful but unfortunately the yields of the conjugate addition are very much lower.

A logical extension of the 1,4-conjugate addition method is approach II. In theory both the α and β side-chains can be stereospecifically introduced to the cyclopentanone (46) by a sequence of 1,4-addition of R_β , followed by trapping of the resultant enolate (47) and attachment of the R_α chain. This sequence of reactions is shown in scheme 1.1.

Scheme 1.1

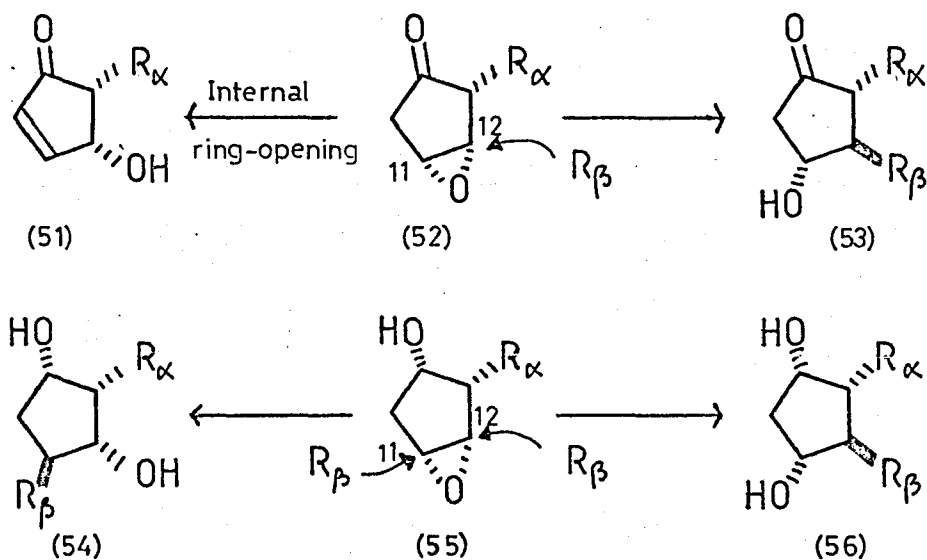


A major problem in this approach lies in the trapping of the kinetic-enolate (47) by a suitable electrophile. The intermediate enolate (47), formed by conjugate addition of the R_β side-chain, is in rapid equilibrium with the isomeric enolate (48). The latter eliminates RO^- to form the cyclopentanone (49). For instance in the synthesis of PGE type, it was found that the alkylation of (47) with reactive allylic halides was still sufficiently slow to allow equilibration to the isomeric

enolate (48).

By far the most successful solution to this problem has been described by G. Stork et al⁷⁷ of Columbia University. Trapping of the enolate type (47) was achieved with monomeric formaldehyde, which subsequently provided the necessary functionality for the further elaboration of the R_α side-chain. In the synthesis of 11-deoxy PGE_2 , where the elimination RO^- does not occur, successful enolate trapping and alkylation with a bromo-allyl side-chain has been reported.⁷⁶ Approach III relies on the nucleophilic displacement of a cyclopentane-epoxy species (52) or (55), by a nucleophilic R_β group. As shown in scheme 1.2, the strategy poses its own problems.

Scheme 1.2



Competitive internal ring-opening of the epoxide precursor (52) to the hydroxy-cyclopentenone (51) makes this approach inapplicable to

the direct synthesis of PGE type. As a result, approach III is limited to the synthesis of PGF type. However, a more important requirement of approach III is the regiospecific β -face attack at C-12 by the nucleophile $R\beta$. This is probably less likely from steric considerations. This problem is well illustrated by the early synthetic work of J. Fried et al⁸⁰ and E. J. Corey et al⁷⁸. Both these groups reported the C-11 alkylation by the nucleophile $R\beta$ as the major pathway.

The problem of the lack of regioselectivity in the ring-opening of the epoxide precursor (55) was subsequently overcome by J. Fried and C. J. Sih⁸¹. In the total synthesis of PGE and PGF, shown in fig. 1.10, they demonstrated that the presence of a suitably located carbinol function elsewhere in the epoxy-precursor (61), capable of forming a covalent aluminium-oxygen bond with the nucleophilic alane reagent (65), could direct intra-molecular alkynylation at C-12. The observed regioselectivity in the opening of the epoxide (61) is believed to be due to the preferred transition state complex (66) formed between (61) and two molecules of the alane reagent (65), scheme 1.3.

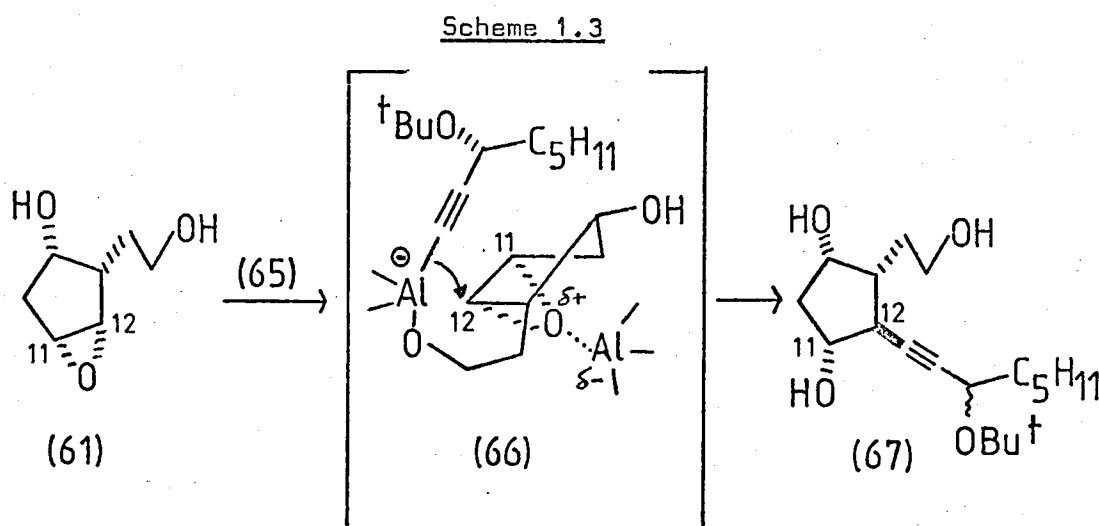
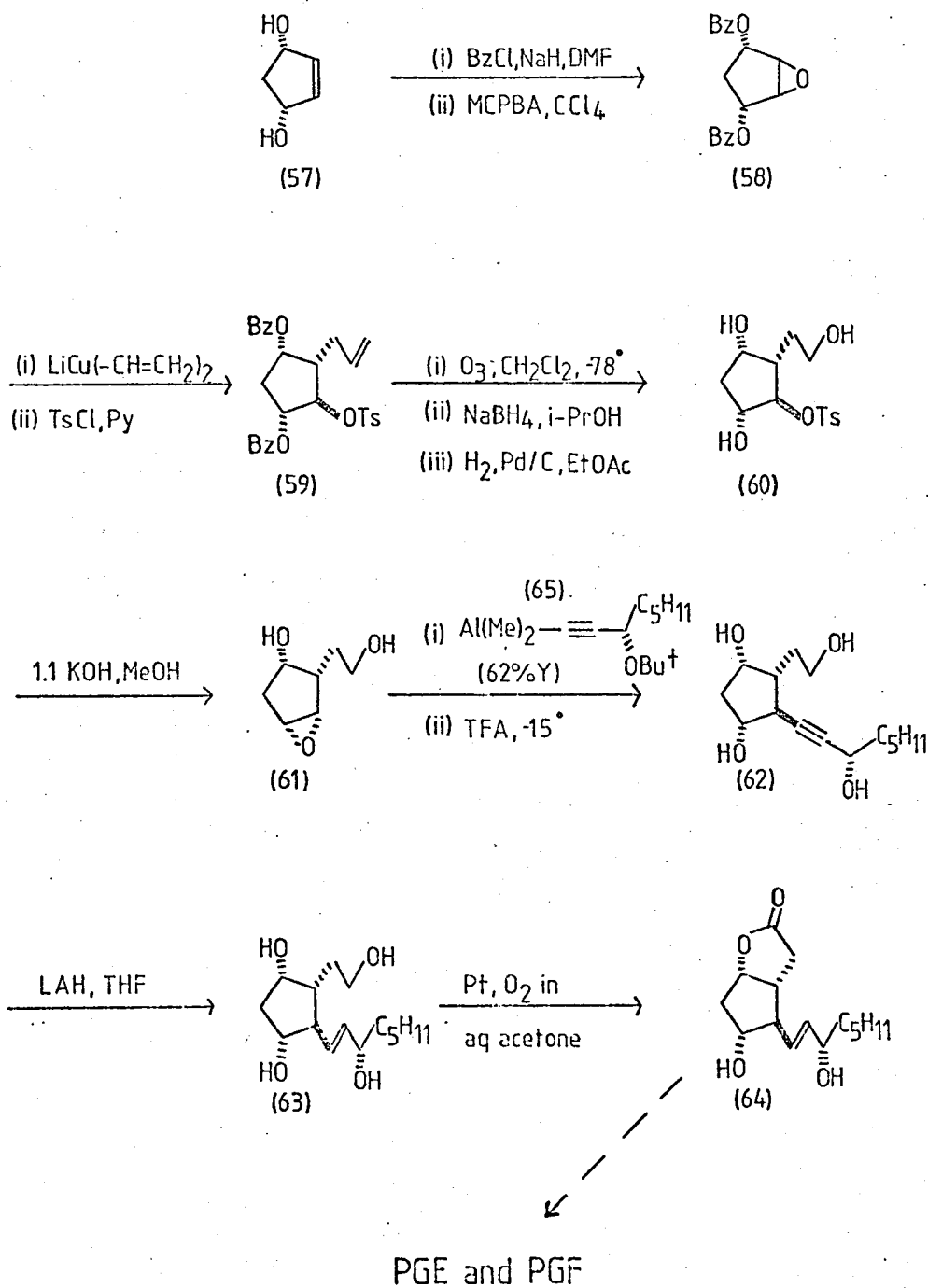


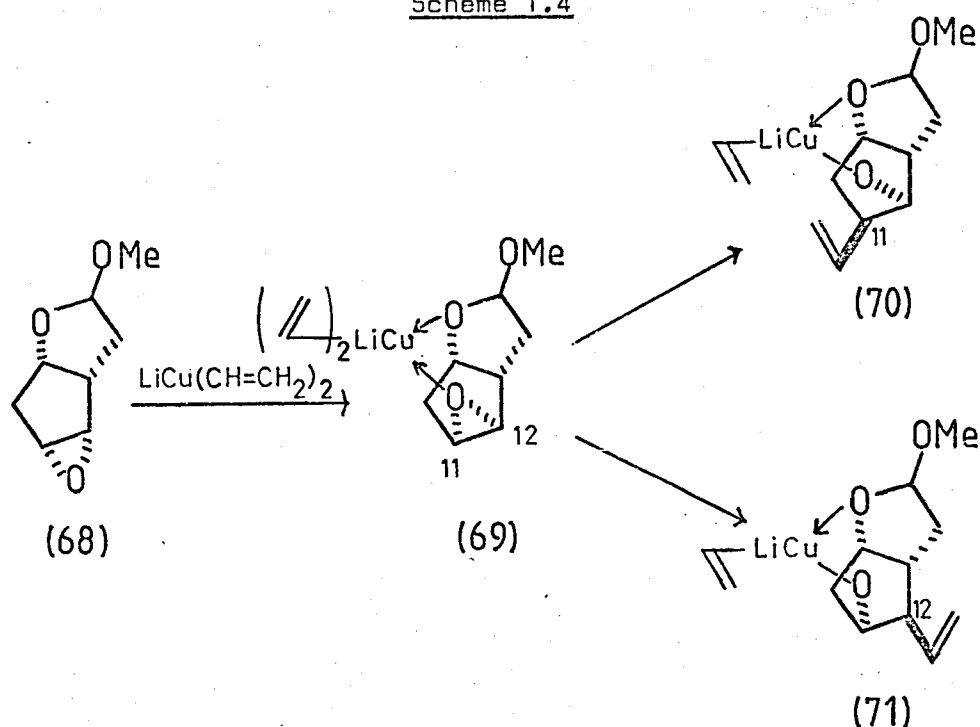
FIGURE 1,10

FRIED'S APPROACH TO REGIOSPECIFIC
RING-OPENING OF EPOXIDE⁸¹



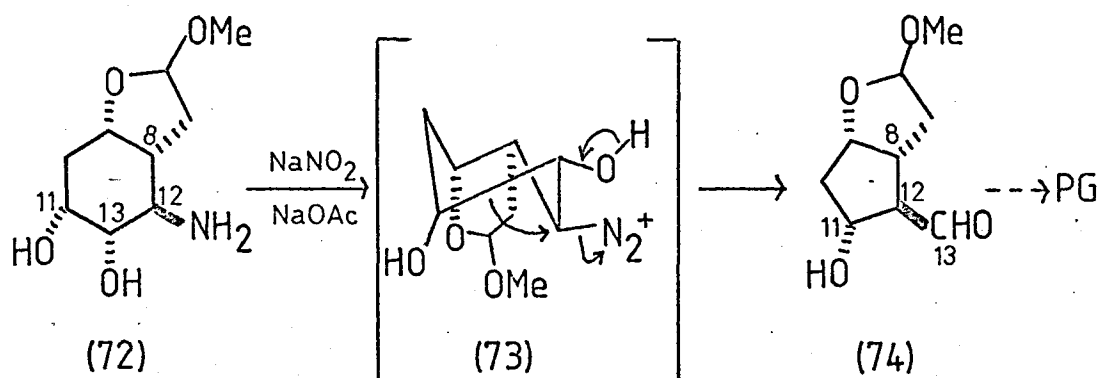
Similarly, E. J. Corey et al⁷⁹ found that the use of divinyl¹⁸⁷ copper lithium which permitted better complexation of the epoxide intermediate (71) (reduced steric interaction), compared with the alternative complex (70), directed the alkenylation to the C-12 position, scheme 1.4.

Scheme 1.4



Approach IV via the ring contraction of a cyclohexane nucleus has been effectively employed by both R. B. Woodward et al⁸³ and E. J. Corey et al⁸⁴ in the synthesis of primary prostaglandins. The key strategy in both the reported syntheses was based on a regiospecific pinacolic deamination sequence of a dihydroxy-amino-cyclohexane precursor (72) as shown in scheme 1.5. The resulting synthon (74) bears the requisite functionalities in the correct configuration and permits flexibility in the introduction of the α and β side-chains.

Scheme 1.5



The simpler and more attractive strategy based on the thallium(III) catalysed ring contraction of cyclohexene⁸² has been successfully applied to the synthesis of 11-deoxyprostaglandin⁸⁵ but not to primary prostaglandins.

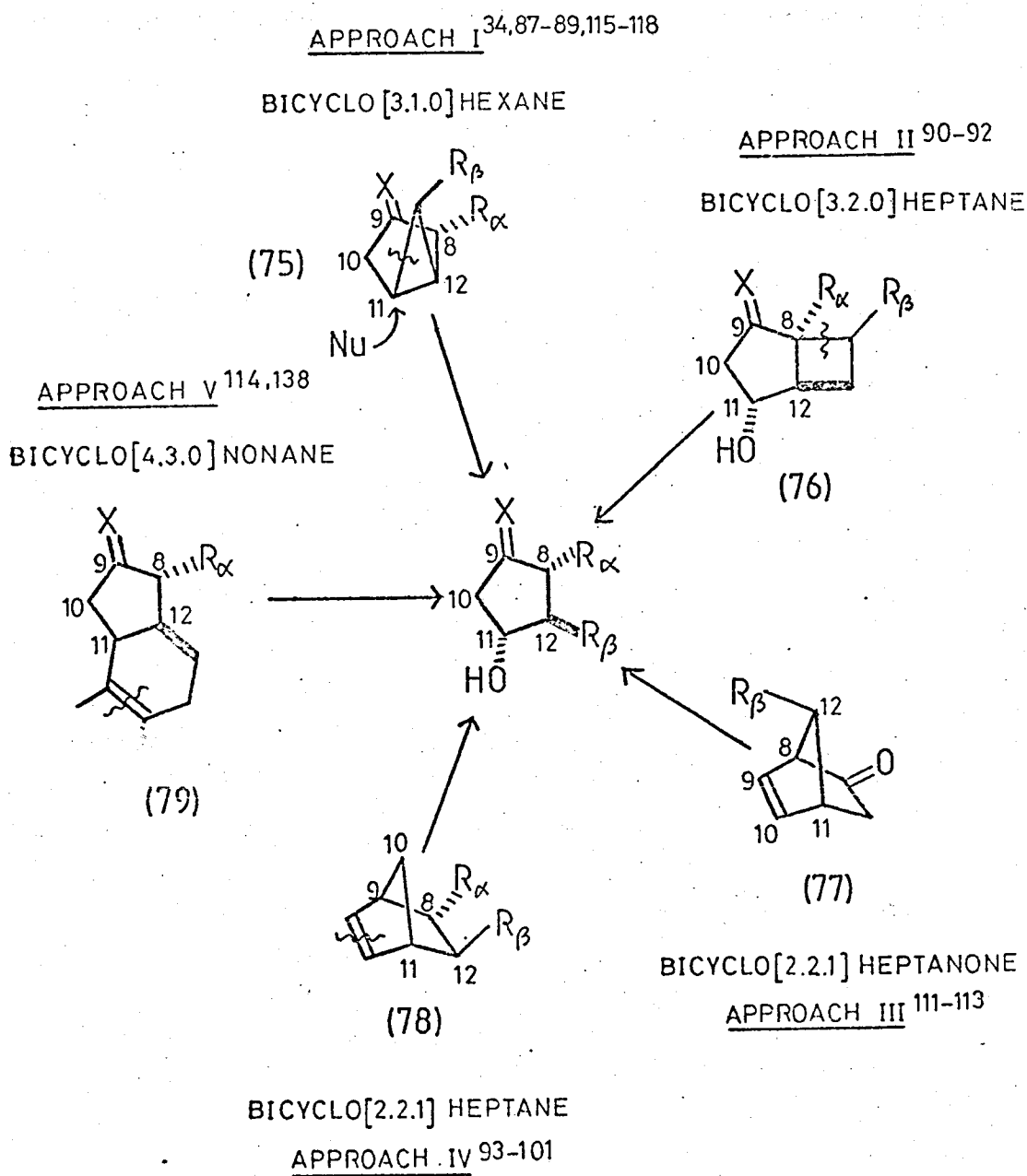
(iii) Synthesis of prostaglandin from polycyclic precursors

Prostaglandin synthesis via polycyclic systems is by far the most thoroughly investigated approach. It relies generally on the relatively easier proposition of controlling stereochemistry via rigid cage-like structures. Bulky reagents are then effectively employed to attack from predetermined directions. The subsequent cleavage of one or more rings releases internally protected functionalities which may be further elaborated. In theory at least, this strategy potentially allows total control over the stereochemical outcome of the cyclopentane substituents and even the remote C-15 chiral centre.

The main polycyclic precursors employed in prostaglandin synthesis are shown in fig. 1.11.

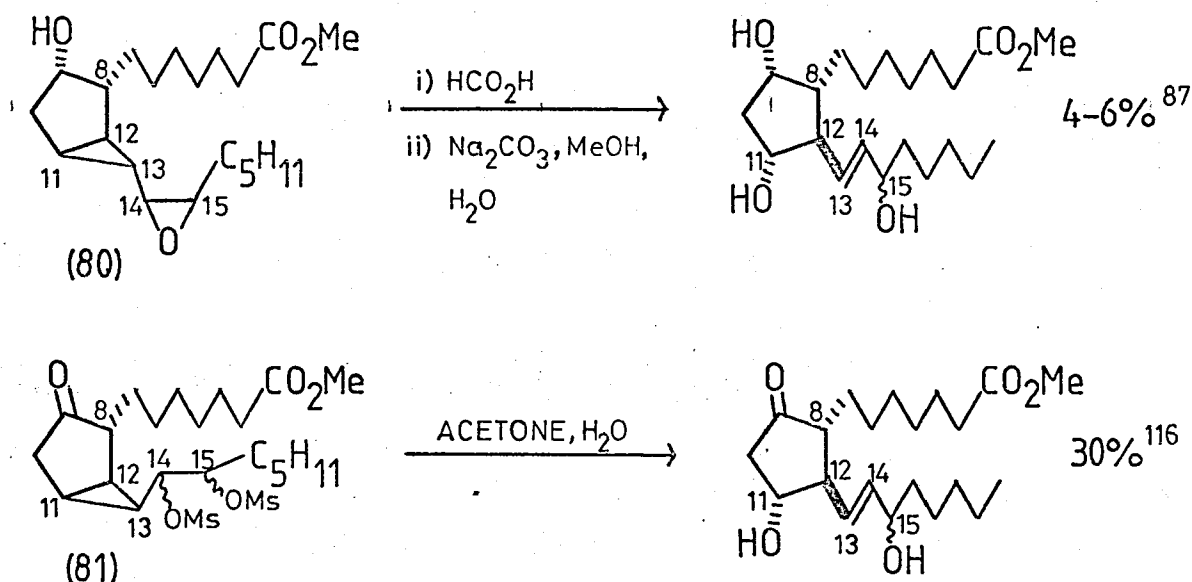
FIGURE 1,11

PG SYNTHESIS FROM POLYCYCLIC PRECURSORS



The strategy of approach I is based on the stereospecific solvolysis of an appropriately substituted bicyclo[3.1.0] hexane precursor. This results in the formation of an allylic homoallylic system at C-11 to C-15 as shown in scheme 1.6.

Scheme 1.6



This approach was first reported by Just and Simonovitch³⁴ of McGill University and later developed by other research groups^{87,115-118}.

It has been reasonably effective in the synthesis of prostaglandin of the E series¹¹⁶⁻¹¹⁸. Unfortunately, however, in spite of the massive effort that has gone into approach I, it does not appear to compete favourably with Corey's bicyclo[2.2.1] heptane route. (vide infra)

Approach II via a bicyclo[3.2.0] heptane has not been directly employed in the synthesis of natural prostaglandin⁹². However, a number of prostaglandin analogues^{90,91} have been prepared by this approach.

By far the most widely acclaimed and versatile prostaglandin synthesis is based on approach III, via a bicyclo [2.2.1] heptanone precursor. This route was devised by E. J. Corey et al^{111a} and has proved to be extremely effective in the synthesis of the entire natural prostaglandin family in their optically active forms. Although the synthetic route is lengthy, the overall yields for racemic PGF_{2α} (27%) and PGE₂ (23%) are reasonably good. It competes favourably with the biosynthetic route and in addition it offers much greater flexibility in analogue synthesis. Since the early work on this route was reported^{111a,b,c}, the synthetic has been varied, extended and developed by other research groups and presently adapted for pilot plant production in several industrial laboratories¹²¹.

The original synthetic route to PGF_{2α} and PGE₂ via the bicyclo [2.2.1] heptane intermediate is shown in fig. 1.12.

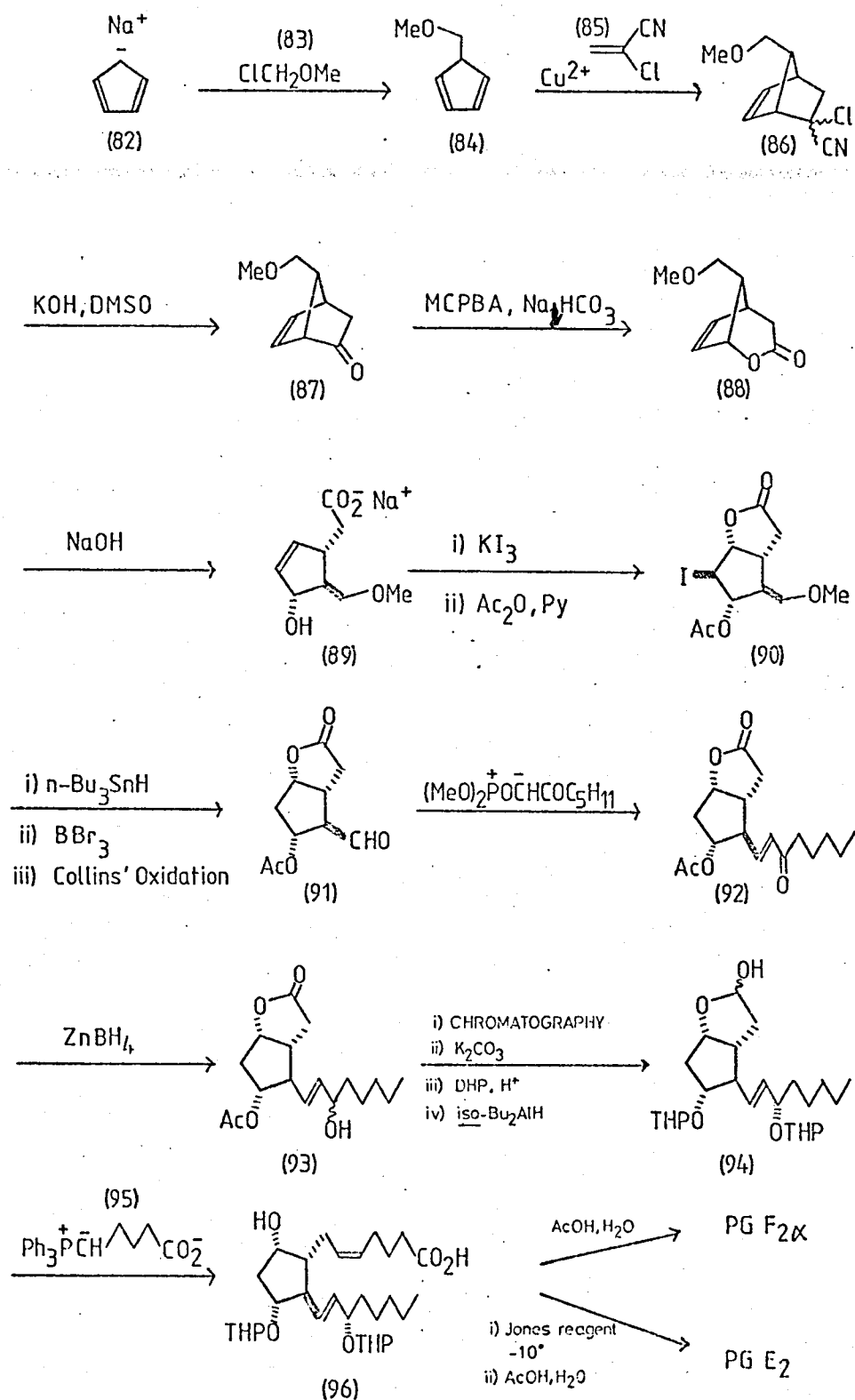
The sodium salt of cyclopentadiene (82) was alkylated with chloromethyl methyl ether (83), to give the intermediate (84), then immediately submitted to a Diels-Alder reaction with 2-chloroacrylonitrile. The bicyclic derivative (86) was hydrolysed with base to provide the unsaturated ketone (87) in high yield. Baeyer-Villiger oxidation of the ketone (87) with *m*-chloroperoxybenzoic acid in the presence of sodium bicarbonate gave the lactone (88) in almost quantitative yield. Base hydrolysis of the lactone group furnished the acid (89). Subsequent iodolactonization of (89), followed by acetylation, produced the key intermediate (90) which possessed the correct stereochemistry, as well as functionalities necessary to complete the synthesis.

Deiodination of (90) with tributyltin hydride, followed by cleavage

FIGURE 1.12

PG SYNTHESIS VIA THE BICYCLO [2.2.1] HEPTANE

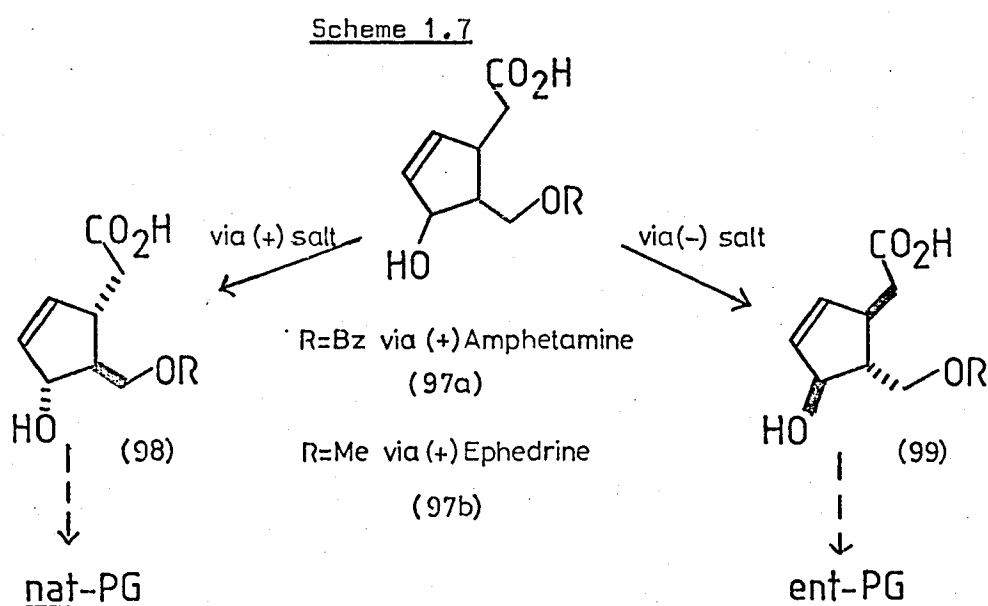
APPROACH BY E.J.COREY^{111a}



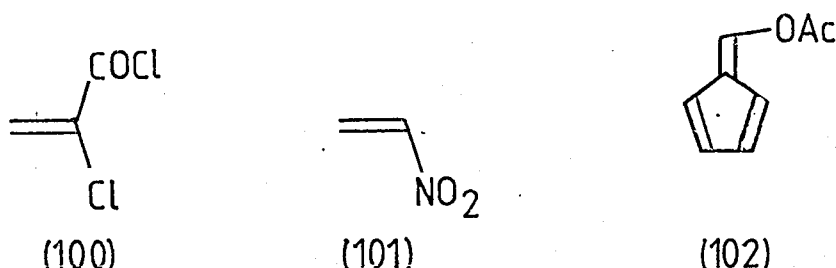
of the methyl ether group and subsequent Collins oxidation⁴³, afforded the corresponding acetoxy-aldehyde (91). A Horner-Emmons reaction of the aldehyde (91) completed the side-chain at C-12 position. Reduction of the keto-group of (92) with zinc borohydride, afforded a mixture of 15(R)- and 15(S)-isomers (93) which were separated by chromatography. Deprotection of the C-11 acetoxy-group of (93), followed by tetrahydropyranylation and reduction of the lactone group, furnished the intermediate hemiacetal (94).

The Wittig reaction of (94) with the ylid (95) provided $\text{PGF}_{2\alpha}$ in the protected form (96). Acid hydrolysis of the ether groups afforded $\text{PGF}_{2\alpha}$. Alternatively, Jones oxidation of (96), followed by acid treatment furnished PGE_2 .

To prepare optically pure $\text{PGF}_{2\alpha}$ and PGE_2 , it was necessary to resolve the methoxy-hydroxy acid (89) using (+)-ephedrine¹³¹. However, for the convenience of deprotection by hydrogenolysis, a benzyloxy-derivative (97a) was later to become the choice precursor in the synthesis. This was resolved using (+)-amphetamine¹³² (see scheme 1.7).

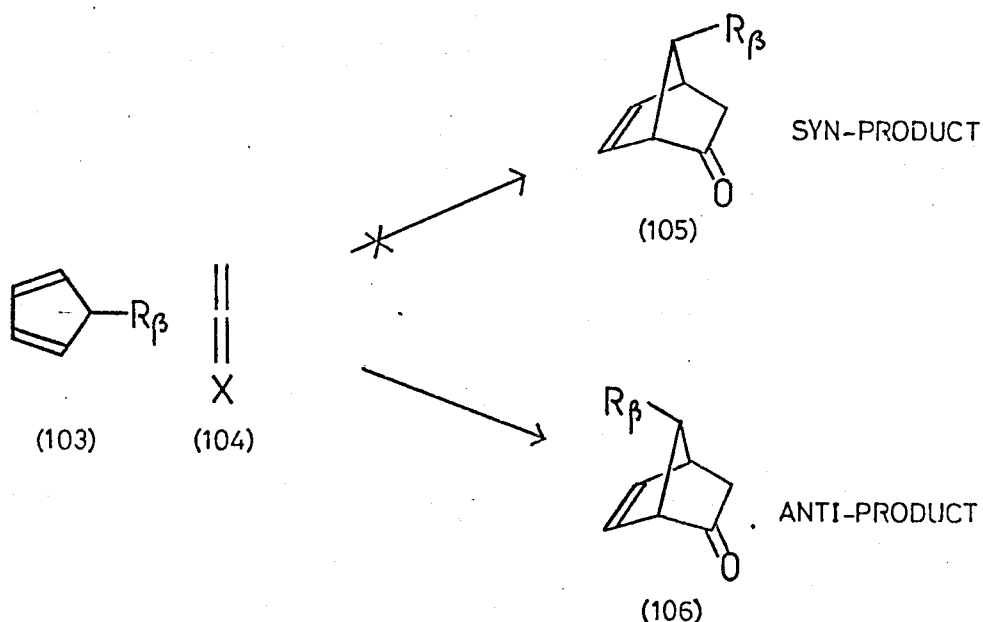


In the early synthetic work, it was found that the 5-substituted cyclopentadiene (84) underwent rapid [1,5] sigmatropic shift¹²² during the subsequent Diels-Alder reaction. To avoid this problem, other research groups employed highly reactive dienophiles such as α -chloroacrylyl chloride¹²³ (100) and nitroethylene¹²⁴ (101). The use of a 6-acetoxifulvene precursor^{113,125} (102) instead of the 5-substituted cyclopentadiene provided an alternate solution to the problem.



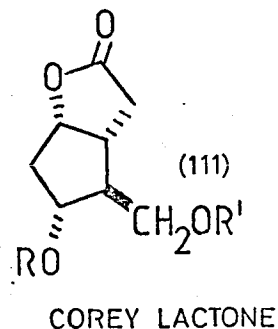
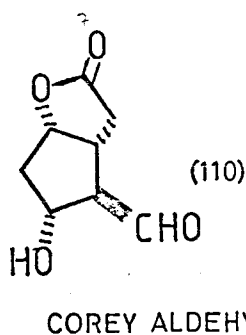
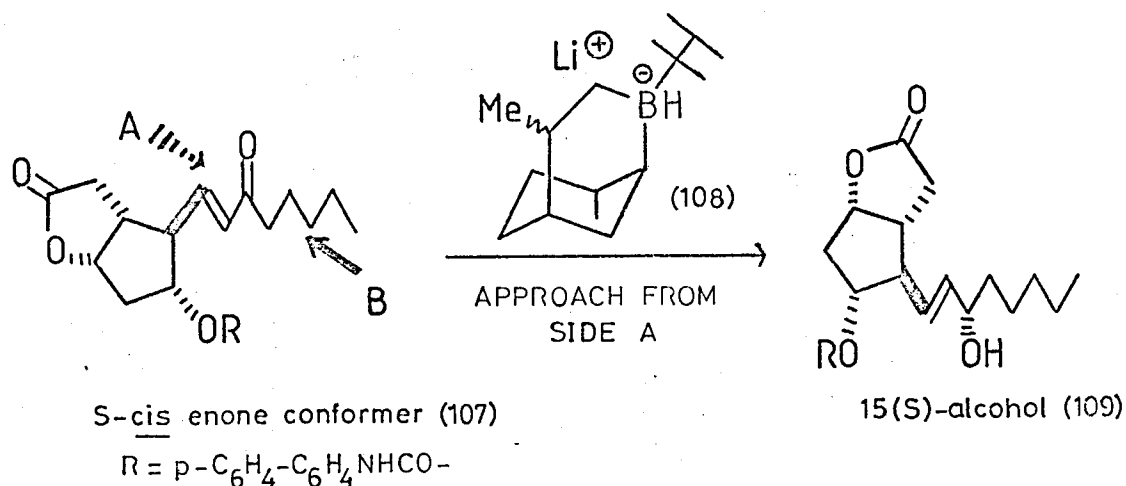
The key strategy of the approach by Corey lies in the use of the bicyclo[2.2.1]heptanone (106) to provide the relative configuration at junctions C-8, C-11 and C-12 of the PG cyclopentane nucleus. The crucial Diels-Alder addition of the 5-substituted cyclopentadiene (103) to the masked ketene (104) provides predominantly the anti-adduct¹²⁶ (106) as the key intermediate (see scheme 1.8). This step is vital to the strategy of the synthesis, as it effectively lodges the potential R_β side-chain at C-8 trans to the potential R_α side-chain at C-12. By a sequence of chemical manipulation, the keto function of (106) is ingeniously transformed to provide the two α -face hydroxyl groups at C-9 and C-11 in the form of the iodo-lactone (90). The latter possesses all the essential cyclopentane functionalities in the correct configuration.

Scheme 1.8



At a later stage in the development of this synthetic route, it was found that stereoselective reduction of the C-15 keto group could be achieved through the combined effect of a large protective group at C-11 and the use of certain bulky asymmetric borohydride reducing agents. Hence, it was shown that the protection of the C-11 hydroxyl group as the *p*-phenyl phenyl carbamate effectively stabilized the *S*-cis enone conformer (107) by good π - π contact with the R_β side-chain enone moiety. In addition, it directed the formation of the desired 15(S) alcohol (109) by severely shielding the approach of the reducing agent from side B (producing the 15(R) alcohol, see scheme 1.9). Using thexyl limonyl borohydride (108) as the reducing agent, Corey et al^{129,130} obtained quantitative yield of the desired allylic alcohol in the ratio of 92:8 (15(S) : 15(R)).

Scheme 1.9

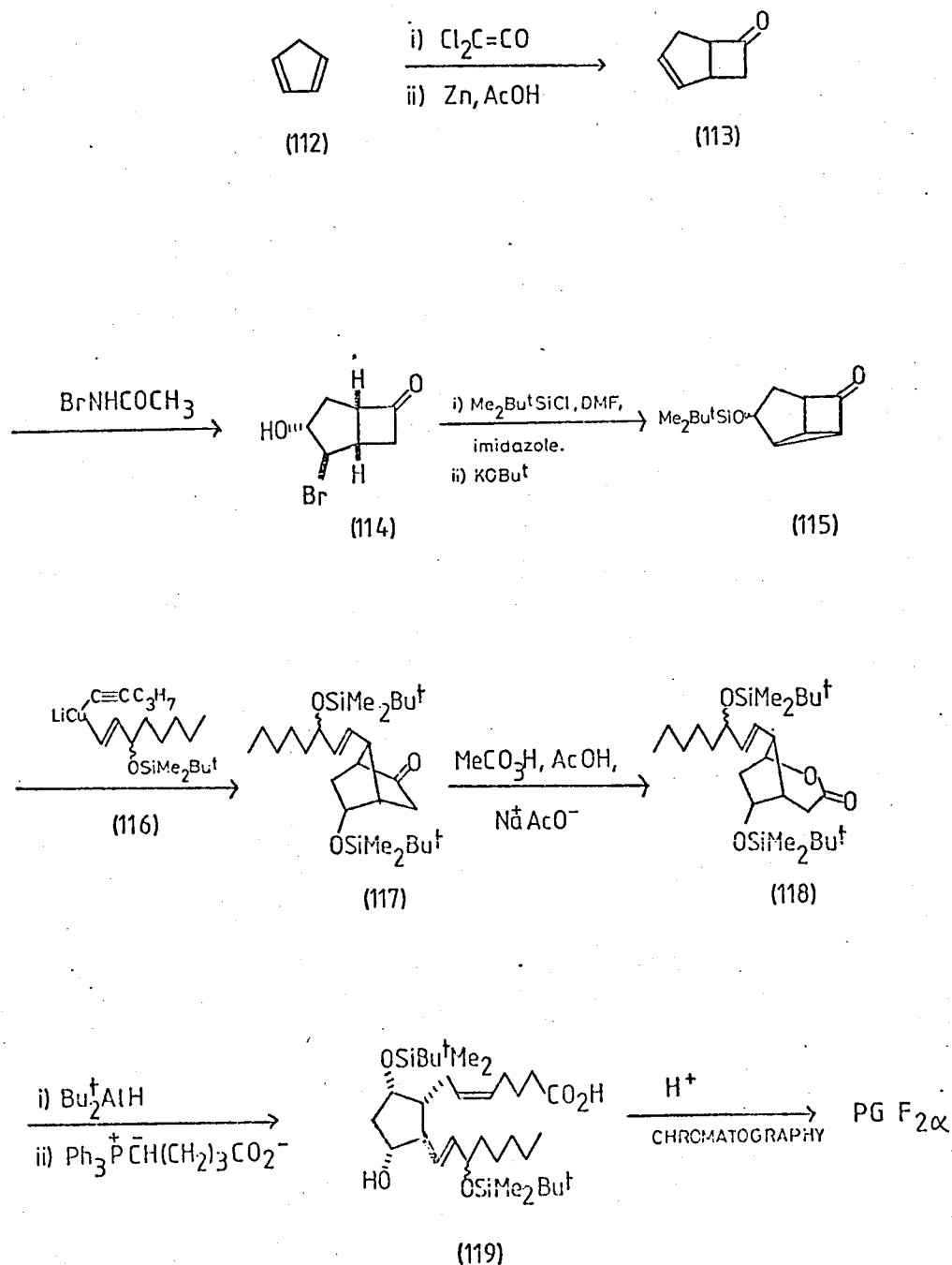


Currently, the Corey aldehyde (110) or lactone (111) is probably the most versatile synthon in the synthesis of natural prostaglandin and related analogues. Indeed, the synthesis of either (110) or (111) by any novel method constitutes a formal synthesis of prostaglandin.

An interesting and versatile variant of the bicyclo[2.2.1]heptanone approach has been reported by S. M. Roberts *et al.*^{192,193} of Salford University. The key bicyclo[2.2.1]heptanone intermediate (117) was derived from the homoconjugate addition of the dialkyl lithium cuprate (116) (bearing the R_β side chain) to the tricyclic ketone (115), as shown in fig. 1.13. Subsequent Baeyer-Villiger oxidation of (117), followed by reduction of the resultant lactone (118), afforded an intermediate

FIGURE 1.13

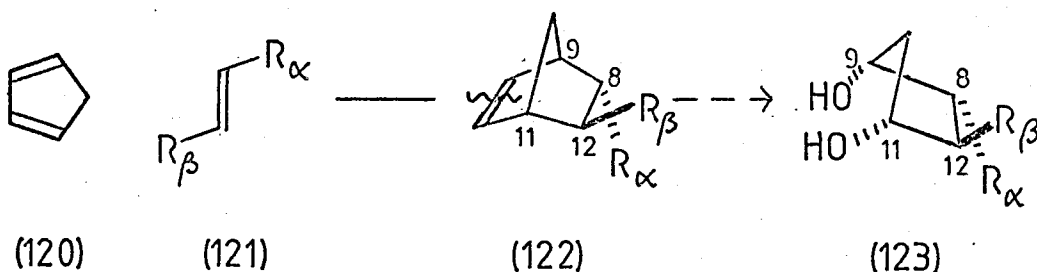
PG SYNTHESIS VIA THE BICYCLO[2.2.1]HEPTANE
APPROACH BY S.M.ROBERTS^{192,193}



cyclic hemiacetal which was converted to the protected $\text{PGF}_{2\alpha}$ by a Wittig reaction. Acid hydrolysis of (119) followed by chromatography furnished $\text{PGF}_{2\alpha}$.

Approach IV is also based on the bicyclo[2.2.1]heptane skeleton. However, as shown in scheme 1.10, a more simplified strategy is employed.

Scheme 1.10



A Diels-Alder cycloaddition of the cyclopentadiene (120) to the *trans* dienophile (121) affords the bicyclo[2.2.1]heptene adduct (122) which possesses the requisite stereochemistry for transformation into the prostaglandin cyclopentane nucleus (123). The key strategy lies in the use of the *trans* dienophile (121) to secure the *trans* geometry at junctions C-8 and C-12. In addition, the double bond formed from the cycloaddition serves as a latent pair of α -face carbonyl functions which are transformed by a C-O inversion sequence to the C-9 and C-11 hydroxyl groups. This bicyclo[2.2.1]heptene approach has been effectively employed by the I.C.I group^{94, 133} in the synthesis of primary prostaglandins.

Approach V is based on the cleavage of the six-membered ring of a bicyclo[4.3.0]nonane skeleton. This approach has been employed by the Merck group¹³⁸ in the synthesis of PGE_1 . However, the route appears too lengthy

and lacks flexibility. Other report on this approach has been limited to the synthesis of a PG analogue¹³⁶

2. PROSTANOIDS

2.1 Introduction to prostanoid

The term prostanoids was introduced by E. J. Corey¹¹² to designate the family of natural prostaglandins and synthetic prostaglandin-like compounds. The latter group of substances, better known as prostaglandin analogues or prostaglandin congeners, has in recent years gained considerable importance over their natural counterparts.

Due to the vast array of biological activity of the natural prostaglandins, it is difficult to use them in a therapeutic manner without the occurrence of side-effects. This problem is borne out by the fact that in spite of the intensive worldwide efforts of the pharmaceutical industry, there is only a single example of the marketing of a natural prostaglandin¹³⁹. This is PGF_{2α}, sold as an abortifacient under the trade name of Dinoprost by Upjohn & Co.. The second problem associated with the use of natural prostaglandins is their relatively short in vivo half lives. This rapid metabolic deactivation of prostaglandin by specific enzyme systems considerably reduces their therapeutic efficacy.

As a result of these difficulties, the present prostaglandin research trend has shifted largely to the synthesis and study of modified prostaglandins. Already, the initial structure - activity relationship studies have brought forth very encouraging results. In addition, they have also provided clear-cut evidence that it may be possible to design analogues that possess better metabolic stability and higher tissue selectivity.

The prostaglandin (PG) analogues are generally grouped into five classes:-

- (i) PGs with modified asymmetric centres.
- (ii) PGs with modified R_{α} side-chain.
- (iii) PGs with modified R_{β} side-chain.
- (iv) Ring-modified PGs.
- (v) Hybrid analogues.

Types (i) to (iv) are natural PGs with modifications at specified carbon centres or parts of the PG molecule. Type (v), however, incorporates simultaneous changes at different parts of the molecule and generally combines changes of the type (i) to (iv).

Generally, the syntheses of these analogues lack flexibility. This is due in part to the fact that most of the synthetic routes are designed solely to prepare a specific type of analogue. This is a serious drawback especially when one considers the few therapeutically useful drugs that have been discovered from the thousands that are screened. It is, therefore, the object of this project to develop a more general and flexible strategy in the construction of novel prostanoids.

2.2 A general approach to the synthesis of novel prostanoids

The general concept of the proposed novel synthetic route to a prostanoid is schematised in fig. 2.1.

The first stage of the synthesis involves a C-C bond formation of a general type, where the X group activates the carbon on both the side-chains in a complementary manner. The second stage requires the protection of the active methylene carbon at C-10. This is followed by a second C-C bond formation across the C-8 and C-12 positions. These reacting centres are again activated by the X-group. Finally, the removal of the protective Y group affords a prostanoid.

The synthetic scheme is attractively simple and offers a great deal of flexibility. In theory at least, a wide range of prostanoids may be prepared by varying the choice of the α - and/or β -side chains. Within limits, ring modified congeners, such as those derived by replacement of a ring carbon unit by a heteroatom (heteroprostanoids), may be synthesized by this approach.

Following the initial work carried out by Beecham Pharmaceuticals¹⁴⁰ which was later extended by C. B. Chapman¹⁴¹ in these laboratories, the general concept of the prostanoid synthetic plan took the form of a Claisen type condensation between diethyl azelate (C_9 carbon unit component) and methyl nonyl ketone (C_{11} carbon unit component) as its first step. This was followed by dimethylation of the active methylene at the C-10 position. The final stage cyclisation across the C-8 and C-12 positions provided an entry to a novel prostanoid. The reaction sequence is shown in figure 2.2.

Having obtained the first prostanoid (23) by this route,

FIGURE 2.1

GENERAL CONCEPT FOR THE SYNTHESIS OF PROSTANOID

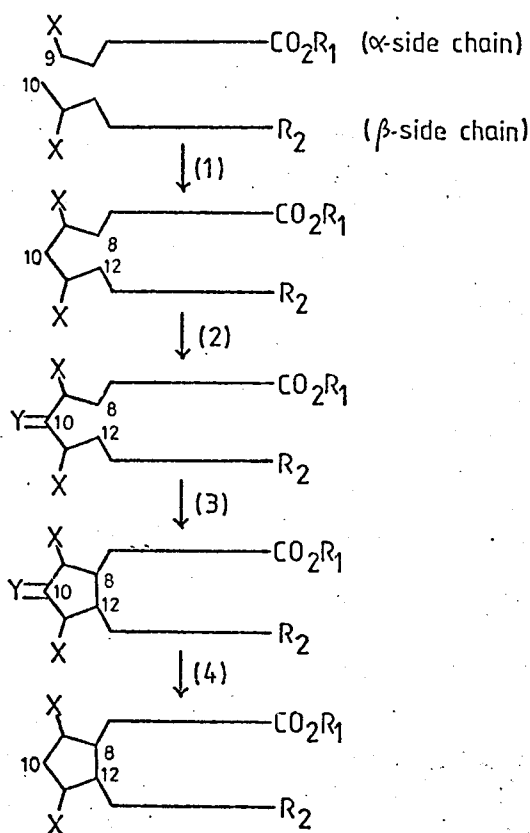
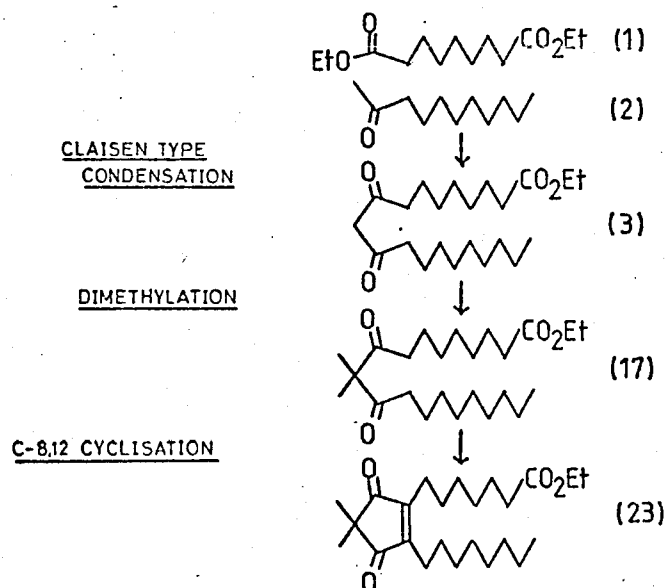


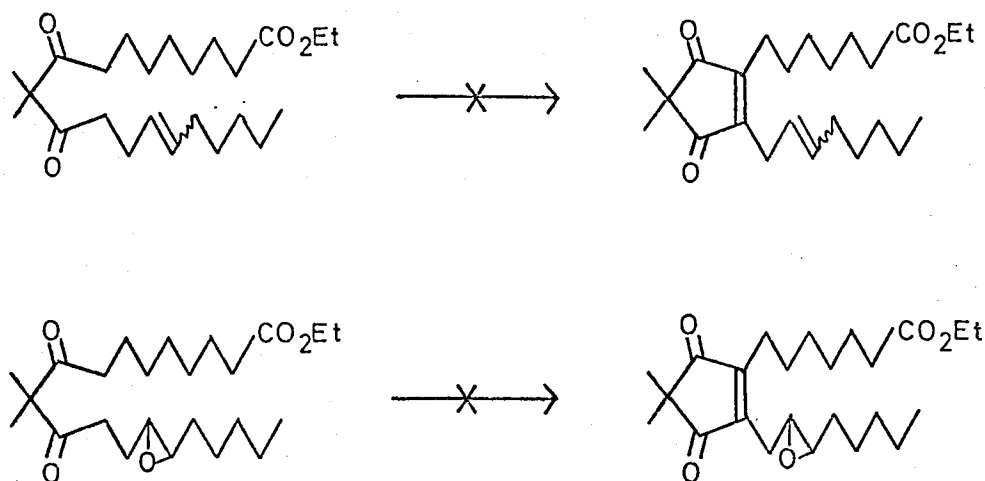
FIGURE 2.2

SYNTHESIS OF A MODEL PROSTANOID



C. B. Chapman¹⁴¹ prepared the C-14 functionalised precursors. However, his attempts to cyclise these precursors in a similar fashion failed to produce the anticipated prostanoids (see scheme 2.1).

Scheme 2.1

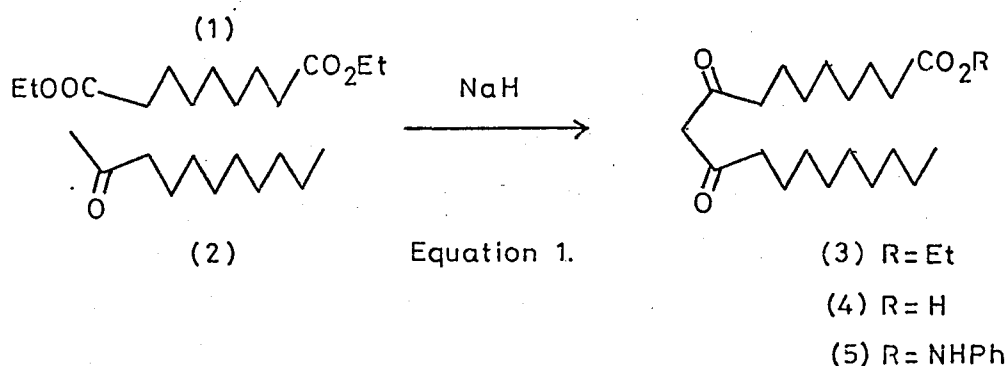


The present project reinvestigates the synthesis of the model prostanoid (23), applies the synthetic route to prepare C-15 functionalised prostanoids and studies the final cyclisation step in more detail.

3. SYNTHESIS OF THE MODEL PROSTANOID (23)

3.1 Formation of ethyl eicos-9,11-dionoate and related products

The first stage of the synthesis utilizes a Claisen type condensation to form a C₂₀ 1,3-diketo-ester. Hence, the acylation of methyl nonyl ketone (2) with diethyl azelate (DEA) gave ethyl eicos-9,11-dionoate (3) as the model precursor in the proposed synthetic scheme, equation 1.



Initial exploratory work on this step was carried out by Beecham Pharmaceuticals¹⁴⁰ and later used by C. B. Chapman¹⁴¹ in these laboratories. A 47% yield was reported for the 1,3-diketo-ester (3). However, subsequent work carried out in this project indicated that in practice, the yield was much lower and varied from batch to batch. This was suspected to be the result of variation in the induction period before the commencement of the reaction and the general lack of control over the reaction. It was also noted that on work-up in concentrated HCl, the ester (3) was partially hydrolysed to the corresponding acid (4).

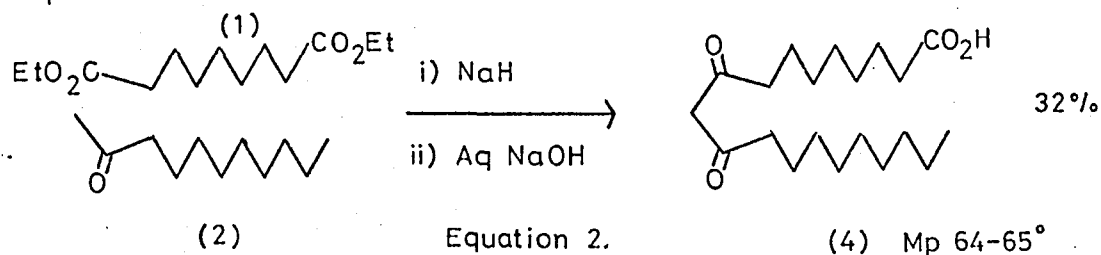
In an effort to improve the yield and to introduce more control over the reaction, a series of modified Claisen condensation conditions were applied. The results of these experiments are given in table 3.1.

Table 3.1

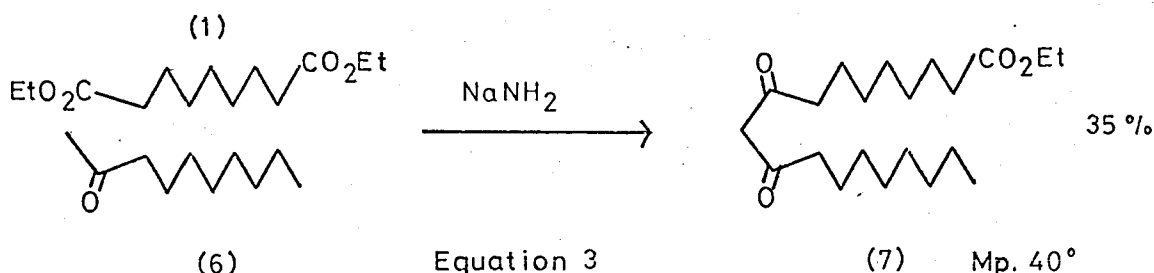
Method	Base	Solvent	Products %		Overall %Y
			Ester (3)	Acid (4)	
1	NaH	DEA	22	16	38
2	NaH	DEA in large excess.	18	17	35
3	NaH	DEA and DME	20	25	45
4	NaOEt	EtOH	0	0	0
5	NaH	THF, trace EtOH	28	19	47
6	NaH	DMF	35	9	44

The best result for the Claisen condensation was obtained when a solution of methyl nonyl ketone in THF, with a catalytic trace of anhydrous ethanol¹⁴² was added slowly to a stirred slurry of sodium hydride in DEA and THF. Scale-up experiments and subsequent trials showed that the reaction was more manageable and more reproducible than the early method 1.

In order to avoid the difficulty of having to deal with an end-product mixture of ester and acid, the partially purified crude product from the Claisen condensation was directly hydrolysed in aqueous base and purified as the crystalline eicos-9,11-dionoic acid (4), mp 64-65°. An overall yield of about 30% of pure acid (4) was generally recorded, equation 2.



The overall yield of 32% of (4) is comparable with the result of a similar Claisen type condensation reported by Brooke and Smith¹⁴³. They condensed methyl octyl ketone with DEA in sodamide. The resultant crude product was purified via a copper (II) chelate to give 35% of crystalline ethyl nonadec-9,11-dionoate (7), equation 3.

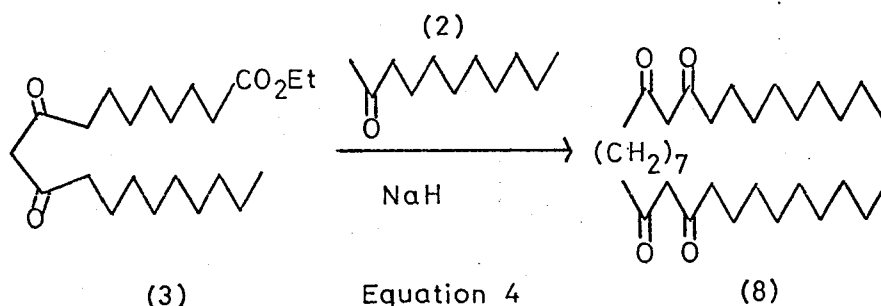


Our attempts to purify the semi-solid ethyl eicos-9,11-dionoate (3) via its copper (II) chelate were unsuccessful. The latter precipitated out of an aqueous methanolic solution of copper (II) acetate as a gelatinous bluish-grey waxy semi-solid.

The spectral data of ethyl eicos-9,11-dionoate (3) were consistent with the proposed structure and identical to the data obtained by C. Chapman¹⁴¹. The corresponding crystalline eicos-9,11-dionoic acid (4) showed spectral data typical of a 1,3-diketo-acid. The IR spectrum of (4) showed bands for the carboxylic acid (3330-3040 and 1688 cm⁻¹) and the enolizable 1,3-diketo-system (1640(s) cm⁻¹). The ¹H-NMR showed characteristic peaks at δ 0.87(t, terminal Me), 1.16-1.93 (m, methylene envelope), 3.57 (s, <1H), 5.49 (s, 1H) and 9.38 - 10.60 (broad s, 1H, D₂O exchangeable). The relative intensities of signals at δ 3.57 (-CO-CH₂-CO-) and 5.49 (-(HO)C=CH-CO-) indicated that the equilibrium mixture of (4) consisted mainly of the enol-form (ca 70-80%). Satisfactory accurate

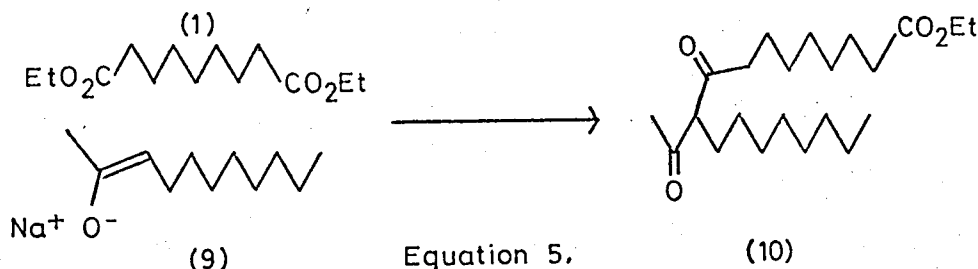
mass measurement, ~~elemental analysis~~ and ^{13}C -NMR (see Appendix) data were obtained for the acid (4)

An important side-reaction of the Claisen condensation was the further condensation of ethyl eicos-9,11-dionoate with a second mole of methyl nonyl ketone. This afforded a white crystalline C_{31} - tetrone (8), equation 4, which was previously characterised by C. B. Chapman¹⁴¹.



The formation of the tetrone (8) accounted for a loss of about 10-15% Y of ethyl eicos-9,11-dionoate. In addition, the side-reaction consumed an equal molar amount of the substrate (2), therefore, resulting in a overall loss of 20-30%Y of ethyl eicos-9,11-dionoate. One possible solution to this problem would be to use the sodium salt of the mono-ester of azelaic acid^{144,145}.

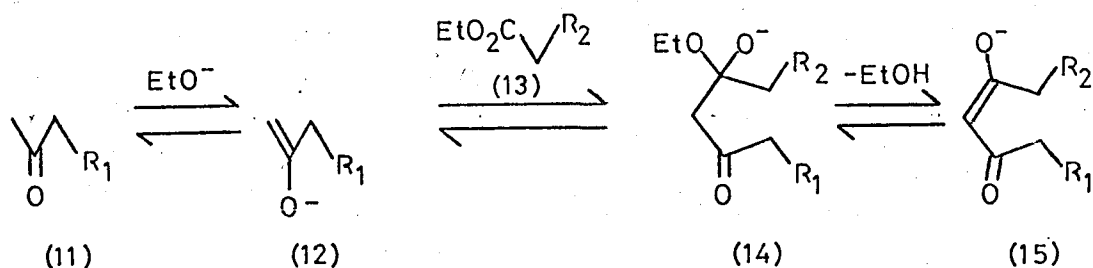
An interesting point arose from the investigation of the Claisen condensation. This was the absence of any significant quantity of the product (10), derived from the condensation of the thermodynamic enolate¹⁰⁹ (9) as represented by equation 5.



This was inferred from the ^1H -NMR spectra of all batches of crude ethyl eicos-9,11-dionoate. None of the crude products showed any significant signal due to the acetyl function of (10). Other reports¹⁴⁶ confirmed this general observation that higher methyl alkyl ketones form nearly exclusively the methyl derivative and that the ease of acylation of a particular ester and base decreased in the order $\text{CH}_3\text{CO} > \text{RCH}_2\text{CO} > \text{R}_2\text{CHCO}$.

A second point of interest was the lack of 1,3-diketo-products in the condensation of DEA with methyl nonyl ketone using sodium ethoxide in ethanol. Other reports¹⁴⁶ on the use of this base in the acylation of methyl ketones with long chain esters have been quoted as being unsatisfactory. The failure of the ethoxide/ethanol system to produce 1,3-diketones in these cases is thought to be due to two factors. Firstly, the ethoxide base is too weak to generate an adequate concentration of the enolate (12) to effect condensation, see scheme 3.1.

Scheme 3.1



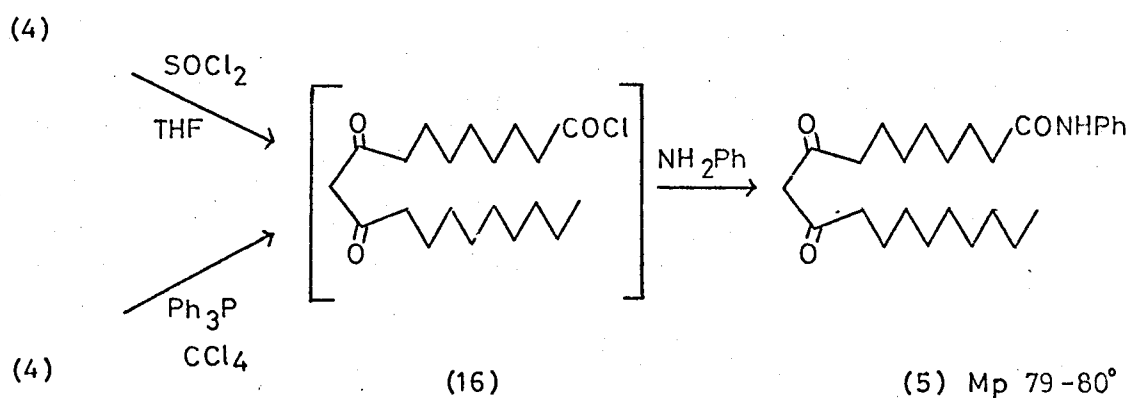
Secondly, the ease of nucleophilic attack of the enolate (12) on the ester (13) is influenced by the structure of the latter. This behaviour is related directly to the relative rates of alkaline hydrolysis of esters in the presence of a particular base. ($\text{HCO}_2\text{Et} > \text{CH}_3\text{CO}_2\text{Et} > \text{higher straight-chain aliphatic esters}$). Hence, more forcing conditions are required

for the acylation of methyl nonyl ketone by long chain esters such as DEA.

In the course of this work, it was found that neither the second stage ester nor the target prostanoid were crystalline. As a result, an attempt was made to prepare other derivatives of eicos-9,11-dionoic acid (4) that would confer crystallinity to the final prostanoid. Moreover, a highly crystalline product at an early stage and at subsequent stages of the synthetic route would considerably reduce the difficulties of purification. A crystalline prostanoid derivative amenable to X-ray structural examination was also hoped for.

Attention was focussed on the preparation of an amide derivative of eicos-9,11-dionoic acid (4). Preliminary trials were carried out to prepare the corresponding acid chloride (16) in situ, followed by reaction with excess aniline, scheme 3.2.

Scheme 3.2



Two methods for the formation of the acid chloride (16) were

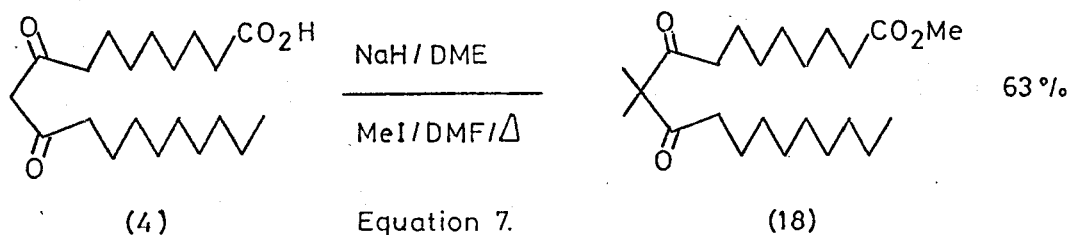
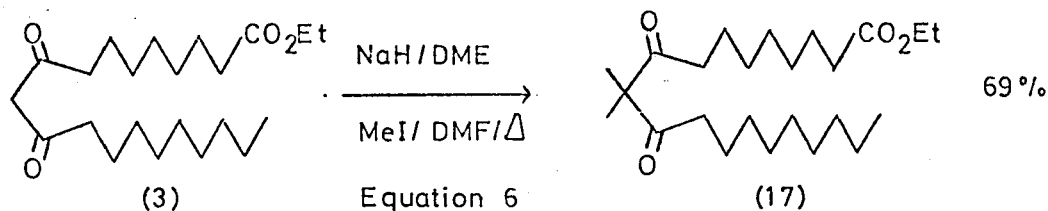
attempted. The first of these was the reaction of thionyl chloride with eicos-9,11-dionoic acid in THF. The reaction was monitored by ^1H -NMR and found to be complete after a 60-80 minutes reflux period. Subsequent reaction with aniline afforded the purified anilide (5) in 23%. The second method employed triphenylphosphine/carbon tetrachloride¹⁴⁷ under reflux. This was a much milder procedure and became the preferred method. Addition of aniline to the acid chloride (16) formed under these conditions, followed by recrystallisation, afforded the anilide (5) as pure crystalline needles in 44%.

The anilide (5) was characterised by its IR spectrum which showed a distinct N-H (3340 cm^{-1}) and strong carbonyl (1658 and 1637 cm^{-1}) bands. The ^1H -NMR indicated peaks at δ 0.88 (t, terminal Me), 1.14-1.94 (m, methylene envelope), 2.17-2.63 ($-\text{CH}_2-$, C-8 and C-12), 3.57 (s, $<1\text{H}$), 5.48 (s, 1H) and 6.96-7.68 (m, 6H, one D_2O exchangeable proton). Accurate mass measurement of the molecular ion and elemental analysis were consistent with the proposed structure (5).

3.2 Dimethylation of ethyl eicos-9,11-dionoate (3)

In order to carry out the C-8 to C-12 ring-closure to form the cyclopentane nucleus of the prostane structure, it was essential to block the active methylene at the C-10 position, so as to avoid complications due to reaction at this centre. The ideal blocking group would be one that was easy to introduce and subsequently deprotected under neutral conditions; such as a 1,3-dithiolan moiety introduced via the 1,3-dithiotosylate¹⁴⁸.

However, early work by Beecham Pharmaceuticals¹⁴⁰ and C. B. Chapman¹⁴¹ indicated that dimethylation of the C-10 position could be conveniently carried out to potentially generate a novel class of 10,10-dimethyl prostanoids¹⁴⁹⁻¹⁵³. These unusual prostanoids would be of interest from a biological point of view, since dimethylation of the C-10 position was likely to result in enhanced chemical stability of the molecule. Deviations in the conformation of these 10,10-dimethyl prostanoids from the natural prostaglandins were likely to contribute to altered tissue selectivity and/or metabolic stability and consequently provide a better insight into the structure-activity relationships of prostaglandins. Hence, the dimethylation of ethyl eicos-9,11-dionoate (3) using two moles equivalent of sodium hydride in a solution of excess iodomethane in DMF/DME, afforded purified ethyl 10,10-dimethyl eicos-9,11-dionoate (17), equation 6, in about 70%. Similarly, the dimethylation of eicos-9,11-dionoic acid(4) using three moles equivalent of sodium hydride, under the same conditions, afforded purified methyl 10,10-dimethyl eicos-9,11-dionoate (18), equation 7, in 63%.

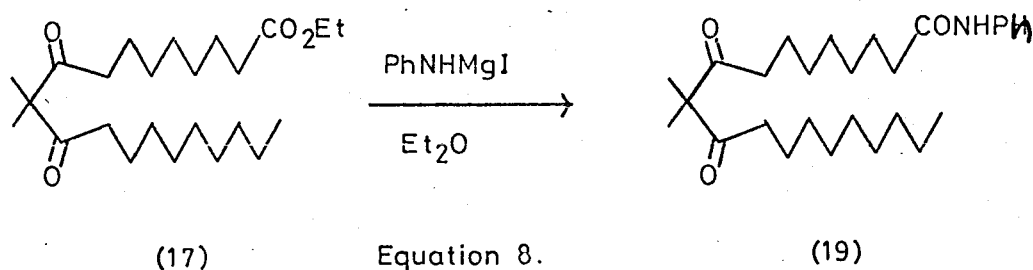


The IR spectra of the 10,10-dimethyl esters (17) and (18) showed characteristic bands at 1742 (ester carbonyl), 1720 and 1698 (keto-carbonyls) cm^{-1} . The ^1H -NMR spectra of these esters showed common peaks at δ 0.89 (t, terminal Me), 1.10–1.87 (m, methylene envelope), 1.32 (s, C-10 gem-dimethyl) and 2.18–2.56 (m, $-\text{CH}_2-$ at C-2, C-8 and C-12). In addition, the ethyl ester (17) showed the characteristic triplet (1.25 δ)/quartet (4.13 δ) pattern, while the methyl ester (18) showed the typical singlet (3.67 δ). The mass spectra gave only weak molecular ions for both the esters, however, each showed four strong fragment ions derived from the two modes of α -cleavage of the 1,3-diketo moiety. Further structural evidence was obtained from the ^{13}C -NMR spectrum of the ethyl ester (17) (see Appendix).

The crude products of the dimethyl esters (17) and (18) showed a distinct lack of O-alkylation products, although the use of DMF in such reactions have been reported^{154,155} to favour O- versus C-alkylation. However, there was evidence of ester exchange. This was apparent in the ^1H -NMR spectrum of the crude ethyl ester (17) which showed a low intensity

singlet at 3.67 δ , comparable to the carbomethoxy signal of the methyl ester (18). In addition, some batches of purified dimethyl esters showed trace contamination of over-methylated products. The ^1H -NMR spectra of these batches showed a characteristic doublet at 1.10 δ ($J = 7\text{Hz}$) assigned to ($\text{CH}_3\text{-CH(COR)-CH}_2\text{-}$).

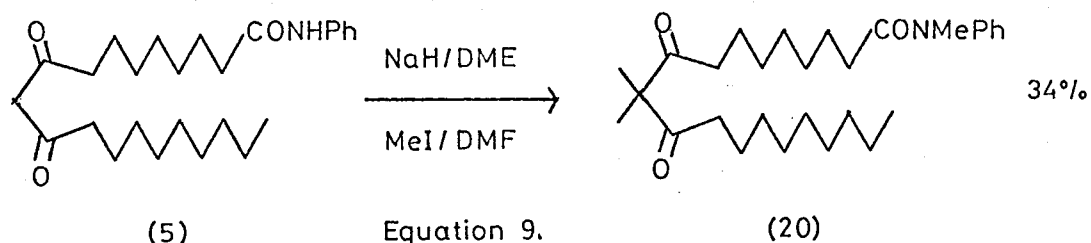
An early attempt was made to prepare the dimethyl anilide (19) by direct amidation of the corresponding dimethyl ethyl ester (17), using N-phenylaminomagnesium iodide (prepared in situ)^{137,156} equation 8. However, this approach was found to be unsatisfactory and the crude



product from equation 8 was found to contain mainly half-chain components derived from the cleavage of the 1,3-diketo moiety of (17). One of these cleavage products was identified by spectral analysis to be the anilide of decanoic acid.

An alternative approach to the anilide (19) was to dimethylate N-phenyl eicos-9,11-dionamide (5), using the procedure developed for the corresponding esters (17) and (18). An initial trial methylation indicated complication due to the formation of an N-methylated product. In order to avoid having to deal with a mixture of products, sufficient base was used to carry the reaction through to the N-methyl anilide (20).

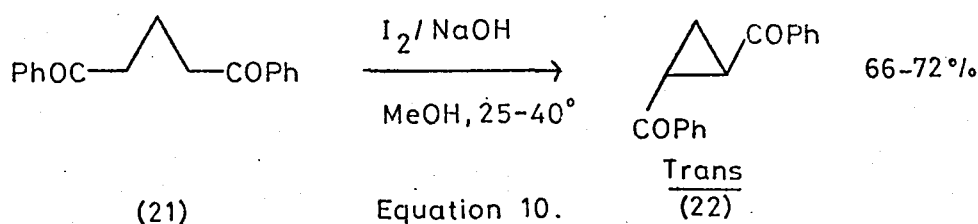
Hence, the trimethylation of the anilide (5) afforded the purified N-methyl anilide (20) in 34%, equation 9.



Unfortunately, the N-methyl anilide (20) was a viscous yellow liquid at room temperature and showed no tendency to crystallise. In view of this, further work on (20) was abandoned and it was hoped that an anilide could be formed at a later stage in the synthetic scheme. This appeared promising as it was found that the final stage prostanoid ethyl ester (23) (*vide infra*), could be conveniently hydrolysed to the corresponding prostanoid acid (24). Furthermore, it was felt that the carboxylic acid to acid chloride transformation by the triphenylphosphine/carbon tetrachloride method was sufficiently mild as to be applicable to the conversion of prostanoid acid (24) to its acid chloride. The latter could then be converted to the corresponding anilide (47).

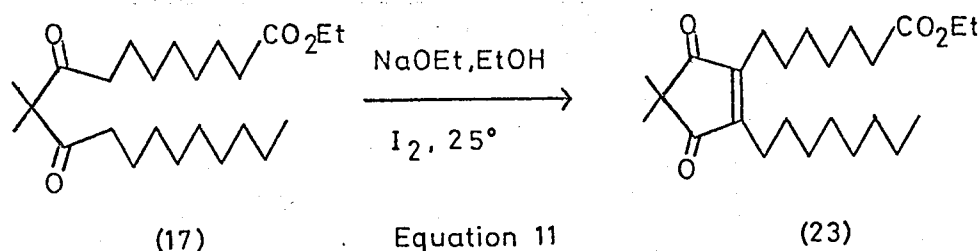
3.3 Formation of ethyl 10,10-dimethyl prost-8(12)-en-9,11-dionoate and related derivatives

The final stage of the synthetic scheme involves an intramolecular ring-closure across the C-8 and C-12 positions of ethyl 10,10-dimethyl eicos-9,11-dionoate (17). Cyclisation of this type should theoretically be feasible, as the reaction centres are mutually activated by the adjacent carbonyl groups. In practice, a number of methods for effecting ring-closures of this type has been reported¹⁷⁷⁻¹⁸¹ (vide infra). However, a simple and attractive method used in the synthesis of 1,2-diaroyl cyclopropanes^{157,158} appeared to be suitable for our purpose. The synthesis involved an oxidative intramolecular cyclisation of a 1,3-diaroyl propane in iodine and methanolic sodium hydroxide, equation 10.



Direct application of this reaction to the cyclisation of ethyl 10,10-dimethyl eicos-9,11-dionoate (17) was carried out by C. B. Chapman¹⁴¹. It was found to be unsatisfactory and led to ester-exchange and hydrolysis of the starting material (17). However, the use of anhydrous sodium ethoxide in ethanol gave satisfactory results and a 40% yield of ethyl 10,10-dimethyl prost-8(12)-en-9,11-dionoate (23) was reported¹⁴¹, equation 11. A more thorough study of the reaction in this project

indicated a much lower and more variable yield (14-41%)



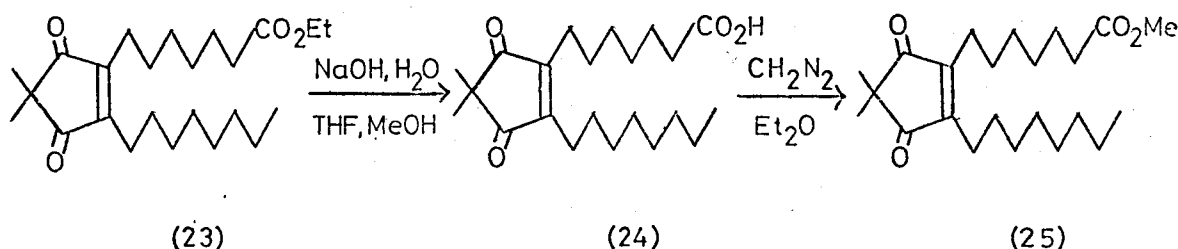
Purified ethyl 10,10-dimethyl prost-8(12)-en-9,11-dionoate (23) was isolated as a pale yellow liquid. Its IR spectrum showed characteristic bands at 1743 (ester carbonyl), 1698 (keto-carbonyl), 1625 (double bond) cm^{-1} and a conspicuous 'doublet' at 1382 and 1360 cm^{-1} (gem-dimethyl at C-10). The ^1H -NMR spectrum of (23) showed peaks at δ 0.89 (t, terminal Me), 1.05-1.88 (m, methyl, methylene envelope), 1.12 (s, gem-dimethyl at C-10), 2.16-2.53 (m, $-\text{CH}_2-$ at C-2, C-7 and C-13) and 4.15 (q, 2H). The integral of the multiplet at 2.16-2.53 δ was first reported by C. B. Chapman¹⁴¹ as representative of 4 protons. The explanation forwarded was that only two of the four methylenic protons at C-7 and C-13 were within the deshielding cone of the carbonyl groups of the cyclopentene-1,3-dione system. As a result, the signal due to these two protons was moved downfield to overlap with the signal due to the two C-2 methylenic protons. However, the prostanoid (23) and other simple 4,5-dialkyl cyclopent-4-en-1,3-diones synthesized in this project, and similar cyclopentene-1,3-diones reported in literature¹⁵⁹⁻¹⁶¹, did not appear to show this special magnetic anisotropic effect due to the conformational preference of the pendent chains. It was concluded,

therefore, that the prostanoid (23) obtained by C. B. Chapman was probably impure.

The mass spectra of the ethyl ester (23) and the corresponding methyl ester (25), both showed strong molecular ions at m/e 392 (62%) and m/e 378 (9%) respectively. This was in contrast to the esters of the precursor 10,10-dimethyl eicos-9,11-dionoic acid, where extensive α -cleavage of the 1,3-diketo moiety was observed.

The UV spectrum of (23) indicated a strong absorption band at λ_{\max} 250nm ($\epsilon=9,620$). Aqueous base hydrolysis of (23), followed by preparative TLC, afforded the corresponding 10,10-dimethyl prost-8(12)-en-9,11-dionoic acid (24). This showed an improved absorption coefficient of $\epsilon=11,470$ at λ_{\max} 250nm. Subsequent esterification of (24) in ethereal diazomethane, followed by preparative TLC, afforded the prostanoid methyl ester (25) as the purest sample obtained so far, with λ_{\max} at 250nm ($\epsilon = 12,350$), scheme 3.3.

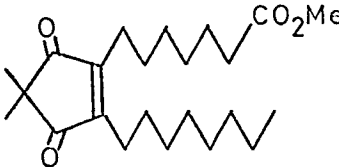
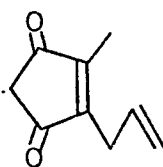
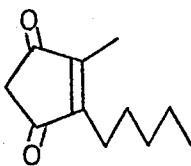
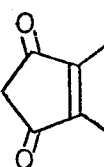
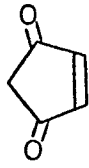
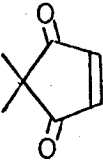
Scheme 3.3



The UV absorption obtained for these prostanoids compared favourably with UV data reported for similar cyclopentene-1,3-diones (see table 3.2).

† This is the best ϵ value obtained for (23)

Table 3.2

Cyclopent-4-en-1,3-dione	λ_{\max}	Extinction coefficient, ϵ	Reference
 <p>(25)</p>	250nm (EtOH)	12,350	
 <p>(26)</p>	242nm (EtOH)	12,600	162,163
 <p>(27)</p>	246nm (MeOH)	11,400	162
 <p>(28)</p>	246nm (MeOH)	14,900	161
 <p>(29)</p>	222nm (EtOH)	14,450	188
 <p>(30)</p>	219nm	6,030	175

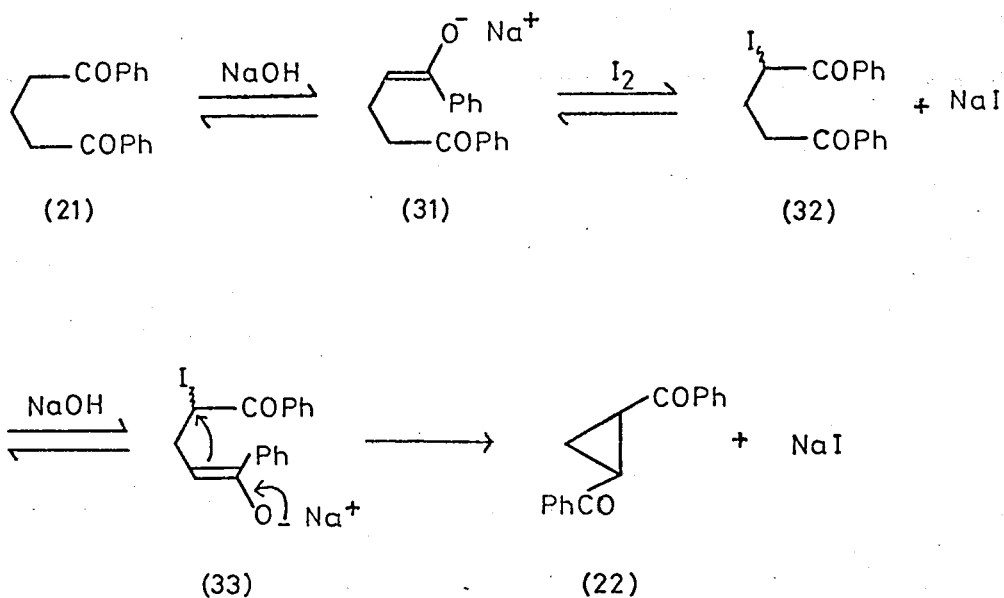
The 4,5-dialkyl-cyclopent-4-en-1,3-dione moiety of examples (26), (27) and (28) showed absorption values close to the 250nm absorption maximum of the prostanoid ester (25). The extinction coefficients of these examples were also comparable in relation to the high intensity absorption of $\epsilon = 12,350$ exhibited by (25). In contrast to (25), the mentioned examples all possessed a C-2 methylene group in the cyclopent-4-en-1,3-dione moiety. However, a comparison of examples (29) and (30) showed that dimethylation of the C-2 position resulted in only a small hypsochromic shift. Similarly, the absorption maxima of the corresponding 2,2-dimethyl cyclopent-4-en-1,3-dione chromophores of examples (26), (27) and (28) would not be expected to show significant deviation from the quoted values. This is consistent with reports that 2-unsubstituted cyclopent-4-en-1,3-dione exists wholly in the diketo-form^{190,191} and that the C-2 methylenic protons are essentially non-acidic. Further support for the UV data of (25) was later obtained from 4,5-dialkyl-2,2-dimethyl-cyclopent-4-en-1,3-diones prepared via a different cyclisation procedure (see section V and VI).

A mechanism for the cyclisation of 1,3-dibenzoyl propane to the corresponding 1,2-trans-dibenzoyl cyclopropane was proposed by I. Colon, G. W. Griffin and E.J. O'Connell¹⁵⁸, scheme 3.4.

The initial step involves a base-promoted iodination of the diketone (21) to form the intermediate α -iododiketone derivative (32). This is followed by a second deprotonation by the base to form the enolate (33). Intramolecular cyclisation by an SN_2 displacement of iodide affords the trans-dibenzoyl cyclopropane (22).

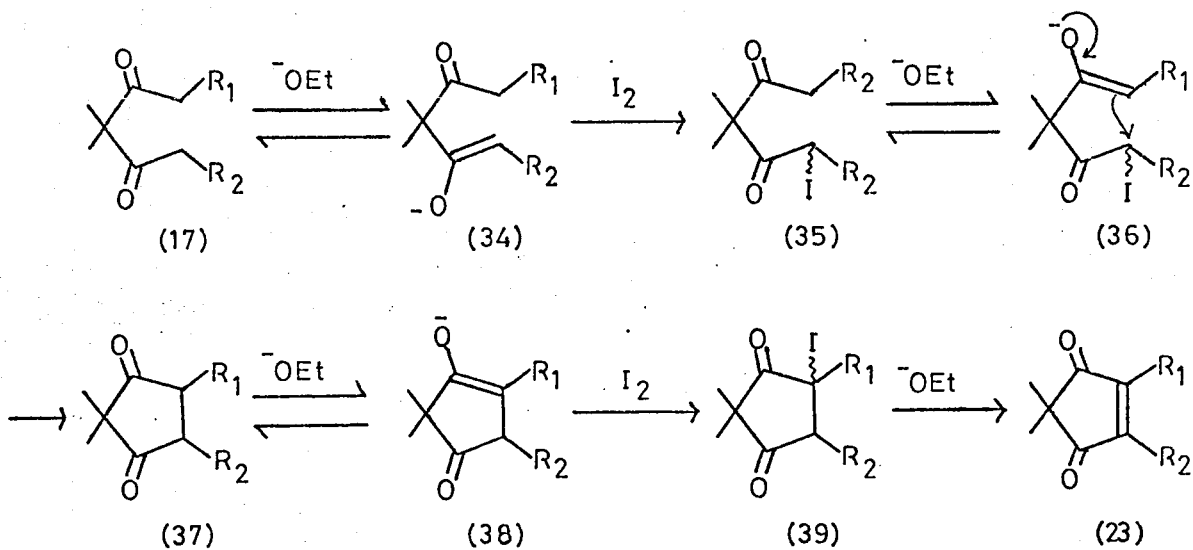
A similar mechanistic pathway for the cyclisation of ethyl 10,10-

Scheme 3.4



dimethyl eicos-9,11-dienoate (17) in sodium ethoxide/iodine was proposed by C. B. Chapman¹⁴¹. The proposed mechanism is shown in scheme 3.5.

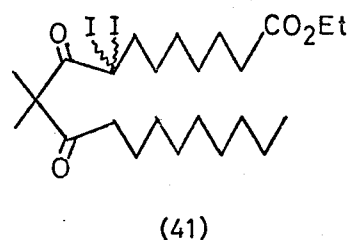
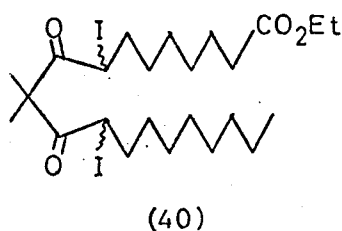
Scheme 3.5



where $R_1 = (CH_2)_6CO_2Et$
 $R_2 = (CH_2)_7CH_3$

The complete reaction sequence shown on scheme 3.5 consumed four moles of base and two moles of iodine. Experiments showed that low yields were obtained when only two moles of base was used. The intermediate 10,10-dimethyl prost-9,11-dionoic ester (37) was never detected and it was suggested, therefore, that the reaction proceeded through a slow initial cyclisation, followed by a rapid iodination and dehydrohalogenation to yield the prostanoid (23).

The fact that the elusive intermediate (37) was never detected also suggested that an alternative pathway may be operative. This could involve the initial formation of diiodo-derivatives (40) and (41), followed by cyclisation and dehydroiodination. For the present, either one or both of these diiodo-species may serve as intermediates in the cyclisation process. Further discussion and speculation on this possible pathway will be presented at a later stage.



Due to the low and varying yield of the cyclisation reaction, equation 11, it was thought that the prostanoid (23) was undergoing decomposition on silica gel during preparative TLC. This appeared to be supported by the apparent discrepancy between the estimated yield (25-50%, determined from UV data of crude product) and the isolated yield (14-41%) of the prostanoid (23). The stability of the prostanoid (23) was accordingly checked and found to be unchanged after 24 hours in a slurry of silica gel in chloroform. The apparent loss (approximately 10%)

was therefore attributed to separable UV active (absorbing at 250nm region) by-products present in the crude product.

Attention was also focussed on the cyclisation reaction conditions. In an attempt to optimise the yield of (23), the following variables were altered accordingly.

(a) Reagent mole ratios

For optimum yield, it was found that 4 - 5 moles equivalent of base was required. The use of 2 moles equivalent of sodium ethoxide resulted in a significantly lower yield of the prostanoid (23). Two moles equivalent of iodine was required for the cyclisation reaction. However, it was found that excess iodine did not appear to have any adverse effect on the yield of the prostanoid (23). Under the optimum condition of 4-5 moles equivalent of sodium ethoxide and 2 moles equivalent of iodine, it was often found that the yield still varied. This suggested that other equally important factors were influencing the course of the cyclisation reaction.

(b) Conditions of reaction

It became clear from the experiments above that the base contact time was an important factor in the cyclisation reaction. The normal procedure of the reaction was to add the ethyl 10,10-dimethyl eicos-9,11-dienoate (17) to a stirred solution of sodium ethoxide in dry ethanol, under an atmosphere of nitrogen. Before the addition of an ethanolic solution of iodine, a period of about ten minutes was allowed for the formation of an equilibrium mixture of (17) and its corresponding enolate. It was suspected, and later confirmed that retro-Claisen

cleavage of (17) occurred when the latter was left too long in the sodium ethoxide solution. Subsequently, it was found that the base contact time could be reduced to 45 seconds, without significant loss in yield of the prostanoid (23).

A final point for consideration was the purity of the starting material, ethyl 10,10-dimethyl eicos-9,11-dienoate (17). Some earlier cyclisation experiments in this project and those of C. B. Chapman¹⁴¹ made use of precursor (17) whose purity was based on spectral evidence and homogeneity on TLC. However, a GLC analytical system was later developed to further check the purity of (17). A re-examination of these earlier batches of (17) was made and they were found to be reasonably pure (>90% purity, by normalisation).

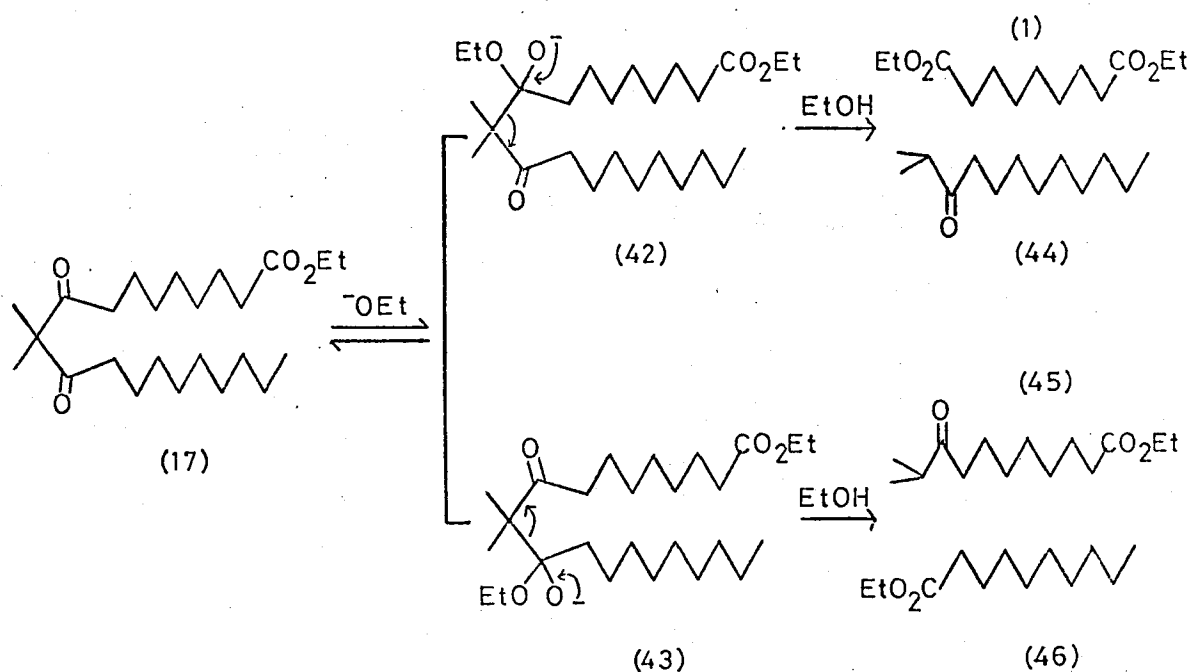
From the preceding investigations of the NaOEt/iodine cyclisation, the following conditions were found to afford optimum yield of the prostanoid (23).

- (i) The optimum mole ratio of base : iodine : diketo-ester (17) was found to be 4-5 : 2 : 1.
- (ii) The time allowed for the equilibration of the diketo-ester (17) in ethanolic sodium ethoxide was about 45 seconds and should not exceed 10 minutes.
- (iii) In the absence of experimental data on the effect of the rate of addition of iodine on the cyclisation reaction, the addition of iodine should be carried out as recommended by Colon, Griffin and O'Connell¹⁵⁸; that is the iodine solution should be added "at such a rate that the colour was immediately discharged".

This normally took between 2-5 minutes.

A more fruitful endeavour was the examination of the side-products of the cyclisation reaction. It provided some important clues to the major side-reaction that was occurring concurrently with the cyclisation process. A GLC analysis of the crude product of the cyclisation of (17) indicated the presence of 'paired' peaks derived from the retro-Claisen cleavage of (17). The cleavage of the 1,3-diketo-ester (17) is depicted in scheme 3.6.

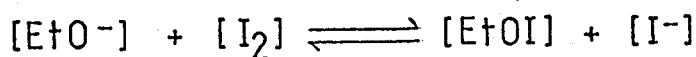
Scheme 3.6



A total of eight peaks were normally recorded. Four of these were accounted for by the retro-Claisen cleavage of (17), while the remaining four were thought to be derived from the cleavage of the

corresponding α -iododerivatives of (17). One of the by-products was positively identified as diethyl azelate and was shown to be present in 10-15% w/w of the crude product. This figure was translated into a 17-25% loss of ethyl eicos-9,11-dionoate (17). However, in the retro-Claisen cleavage of (17), nucleophilic attack at the C-9 and C-11 carbonyls of the 1,3-diketo moiety was probably non-selective. Working on this premise, nucleophilic attack at C-11 was equally likely and should produce an equivalent amount of ethyl decanoate (46). Hence, the overall loss of starting material (17), via the two modes of retro-Claisen cleavage was estimated at 34-50%. Taking the upper limit of this loss, it was apparent that the maximum yield of the prostanoid (23) in the cyclisation reaction could not exceed 50%. This estimation did not include losses due to the cleavage of α -iodo derivatives of (17), in which case, the yield of the prostanoid (23) would be even lower. Having established that a considerable quantity of the ethyl 10,10-dimethyl eicos-9,11-dionoate (17) was lost through retro-Claisen cleavage, attempts were made to curb this side-reaction.

In the course of this work, it became evident that iodine was also consumed rapidly by sodium ethoxide. The latter was thought to be converted to ethyl hypoiodite according to equation 12. This observation was supported by similar reports¹⁶⁴⁻¹⁶⁷ of the conversion of a methanolic solution of iodine and sodium methoxide into methyl hypoiodite.



Equation 12.

In this solution, the concentration of molecular iodine is known to be very low^{164,165}. By analogy, the ethanolic solution of iodine in sodium ethoxide was presumed to contain only a low concentration of ethoxide base and iodine. Theoretically, this appeared to be the ideal solution to carry out the cyclisation reaction. It was thought that the low concentration of ethoxide would reduce the extent of the retro-Claisen cleavage and still provide an adequate concentration of the enolate of (17) for iodination and cyclisation to proceed. The cyclisation reaction under this condition could be envisaged to proceed in a manner similar to that shown earlier on scheme 3.5, except that ethyl hypoiodite would replace iodine as the iodinating species.

This approach was investigated and the results of the experiments are shown in table 3.3.

Table 3.3

Method	Mole ratio of reactants	Reaction time	Result
1	4 ⁻ OEt : 2I ₂ : 1 (17)	15 mins.	Mainly retro-Claisen cleavage products with trace amounts of (17) and (23).
2	4 ⁻ OEt : 4I ₂ : 1 (17)	15 mins.	Unreacted (17)
3	4.5 ⁻ OEt : 4I ₂ : 1 (17)	2 hrs. 14 hrs.	Retro-Claisen cleavage products detected. Mainly retro-Claisen cleavage products with trace amounts of (17) and (23)

Method 1 was carried out using the theoretical molar ratio of reagents required for the complete cyclisation of ethyl 10,10-dimethyl eicos-9,11-dionoate (17) to the prostanoid (23). However, within 15 minutes at room temperature, extensive cleavage of (17) occurred. In order to prevent this, method (2) was carried out using equimolar quantities of sodium ethoxide and iodine. This ethanolic solution, containing mainly ethyl hypoiodite and sodium iodide, failed to react with (17). In the final method 3, a slight excess of base was introduced and the progress of the reaction was monitored by GLC. In the initial two hours, the rate of the retro-Claisen cleavage was noticeably slower than that found for method 1. However, on standing at room temperature after 14 hours, the crude product consisted mainly of retro-Claisen cleavage products.

The salient results of the investigation were the lack of any significant quantity of prostanoid (23) in all the crude products and the apparent stability of (17) under the conditions of method 2. From the result of the method 2 experiment, it was inferred that the concentration of base was probably too low to allow cyclisation to proceed at a reasonable rate. However, in method 1 and 3, the presence of excess base did not result in the cyclisation of (17), but instead led to extensive retro-Claisen cleavage. It was evident, therefore, that ethyl hypoiodite was ineffective as an iodinating species and that the competition between cyclisation and retro-Claisen cleavage was, at least in part, governed by the rate of iodination.

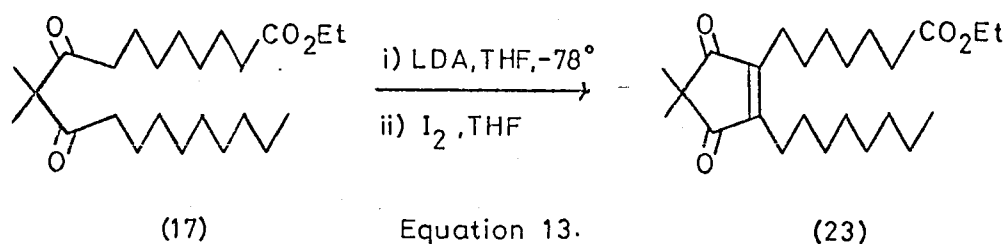
It became apparent from this investigation that molecular iodine played a vital role in the original sodium ethoxide/iodine cyclisation of (17) and that the ethyl hypoiodite formed as a side-reaction was

essentially unreactive.

It was clear from the sodium ethoxide/iodine cyclisation and the ethyl hypoiodite experiments that the use of nucleophilic base such as ethoxide suffered from a number of disadvantages. Firstly, ester - exchange occurred at the ester side-chain. Secondly, nucleophilic attack by the ethoxide at the C-9 and C-11 carbonyls led to extensive retro-Claisen cleavage of the starting material (17). Finally, α -halo derivatives of (17) which were suspected to be intermediates in the cyclisation were prone to SN_2 substitution by nucleophilic bases. A rational solution to these problems was the use of sterically hindered bases.

The first of these bases employed was sodium tert-butoxide. Under the same reaction conditions as the original sodium ethoxide/iodine method, the reaction of (17) in sodium tert-butoxide/tert-butanol gave no UV active products. The GLC analysis of the crude mixture showed the presence of volatile cleavage products which were partially obscured by the tailing effect of acidic products. On subsequent methylation in ethereal diazomethane and GLC analysis, the crude mixture distinctly showed four characteristic retro-Claisen cleavage products and no C_{20} esters. Further experiment with sodium tert-butoxide was abandoned as it was evident that the major course of the reaction was the cleavage of (17).

The use of the sterically hindered lithium diisopropylamide base was marginally more successful. The use of 3.5 moles equivalent of the base in a solution of (17) in THF at -78° , followed by the dropwise addition of iodine in THF, afforded a crude mixture containing the prostanoid (23), equation 13.



Although the loss of (17) through retro-Claisen cleavage was noticeably lower than that found for the original sodium ethoxide/iodine cyclisation of (17), there appeared to be no improvement in the yield of the prostanoid (23) (estimated at 10-15%). The GLC analysis of a purified sample of the crude mixture showed the presence of the prostanoid (23), along with inseparable starting material (17) and an unknown C₂₀ component.

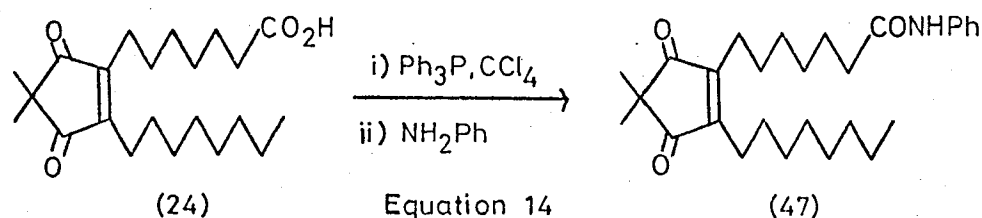
The unknown C₂₀ component was initially suspected to be an intermediate in the reaction, possibly the elusive ethyl 10,10-dimethyl prost-9,11-dionoate (37), (see earlier scheme 3.5). However, when a solution of the partially purified product mixture was subjected to reflux in DDQ/benzene, the relative proportion of the C₂₀ unknown to the inseparable prostanoid (23) and starting material (17) remained unchanged. Retreatment of the partially purified product mixture with LDA/THF at -78°, followed by addition of iodine/THF, resulted in the loss of starting material (17) while the relative proportion of the C₂₀ unknown to the prostanoid (23) remained unaltered. It was evident from these experiments that the C₂₀ unknown was not the intermediate (37), nor was it an intermediate in the cyclisation reaction.

The ¹H-NMR spectrum of the partially purified product mixture of the LDA/iodine reaction showed a cluster of peaks at 4.00-4.40 δ which appeared to be a combination of two sets of carboethoxy quartets and a triplet. However, these peaks overlapped too closely to each other to

allow the coupling pattern to be unambiguously defined. The group of peaks in the 2.15-2.50 δ region consisted of the characteristic triplet at 2.45 δ (methylenic protons at C-7 and C-13) and an unusually weak triplet at 2.27 δ (methylenic protons at C-2). The relative integral of these peaks indicated four instead of the six expected protons. This inconsistency in the proton count suggested that the unknown C₂₀ component could be derived from the reaction of the C-2 methylene group of (17) and/or (23).

Under the reaction conditions described above, a likely complication would be the formation of C-2 iodo-derivatives of (17) or (23). This would account for the low intensity of the 2.27 δ triplet (methylenic protons at C-2) and the appearance of a downfield triplet at 4.27 δ ($-\text{CH}_2 - \text{CHI} - \text{CO}_2\text{Et}$). Iodination of the C-2 position of (17) or (23) is not unusual, as it is known that ester enolates can be generated in LDA/THF at -78° , and subsequently elaborated at the α -position by the addition of suitable electrophiles^{168,169}.

A common feature of all the cyclisation reactions employed so far is the low yield of the prostanoic acid (23) and the contamination of the latter by inseparable side-products. As a part of our continued search for a pure crystalline derivative of the prostanoic acid (23), we turned our attention to the formation of an anilide derivative of 10,10-dimethyl prost-8(12)-en-9,11-dionoic acid (24). Hence, the sequential treatment of the acid (24) with triphenylphosphine/carbon tetrachloride and aniline, afforded the anilide (47) as a very viscous pale brown liquid, equation 14.



The IR spectrum of the anilide (47) showed typical peaks at 3340 (N - H band), 1734, 1694, 1667 (three carbonyl bands), 756 and 692 cm^{-1} (monosubstituted benzene bands). The ^1H - NMR spectrum showed characteristic peaks at δ 0.88 (t, terminal methyl), 1.13 (s, gem-dimethyl), 1.20-1.80 (m, methylene envelope) 2.25-2.60 (m, methylenes at C-2, C-7 and C-13) and 7.00-7.68 (m, aromatic and NH protons). The high resolution mass spectrum gave the correct mass measurement for the molecular ion of (47), m/e 439 (10%). Further structural evidence was obtained from the ^{13}C - NMR of (47) (see Appendix). The UV spectrum showed an absorption at λ_{max} 244nm ($\epsilon = 20,630$) due to the combined effect of the cyclopent-4-en-1,3-dione and anilide chromophores of (47). The UV spectrum of the anilide of eicos-9,11-dionic acid indicated the anilide chromophore absorption at λ_{max} 243nm ($\epsilon = 15,080$). In combination with the cyclopent-4-en-1,3-dione chromophore (λ_{max} 250nm, $\epsilon = 12,350$), the expected UV absorption of (47) is at λ_{max} 243-250nm ($\epsilon = 27,400$). Based on these UV figures, the partially purified anilide (47) (λ_{max} 244nm, $\epsilon = 20,630$) was estimated at a purity of 75%. This was later substantiated by reversed phase HPLC analysis of (47).

At this point, further work with the anilide derivatives was abandoned. Attention was directed at the preparation of C-15 functionalised prostanoids. It was thought that with the introduction of a C-15 functionality, the problems of separation encountered in the model prostanoid (23) could be considerably reduced.

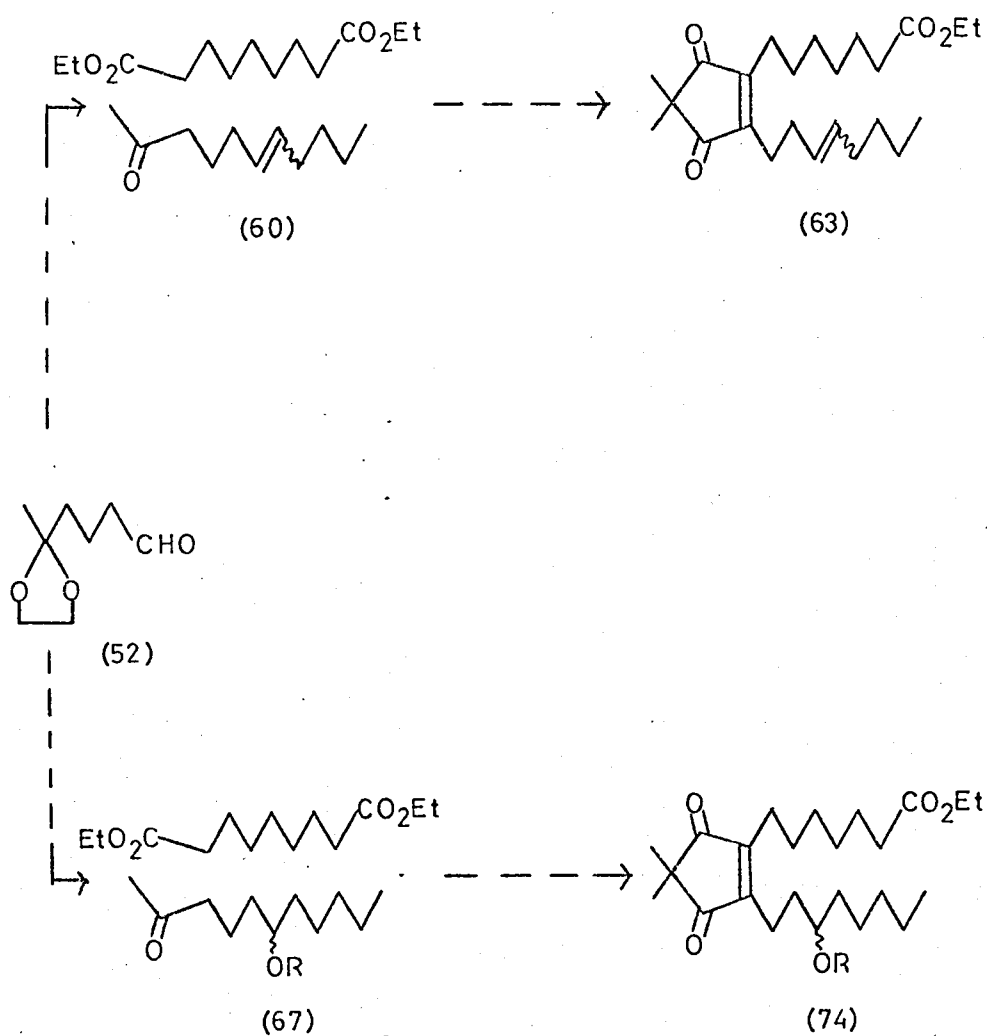
4. SYNTHESIS OF C-15 FUNCTIONALISED PROSTANOIDS

The synthesis of the model prostanoid (23) in the preceding work formed the basis for a more general synthesis of functionalised prostanoids. Although the model synthesis was beset by problems of purification and low yield, it was nevertheless a viable route to 10,10 dimethyl prost-8(12)-en-9,11-dionic acid and its derivatives. It was necessary, therefore, to define the generality of the synthetic route for the preparation of other related analogues. Suitable target species would be C-15 functionalised prostanoids which could be elaborated at a later stage to C-15 hydroxylated analogues. A C-15(S) hydroxyl group is of considerable importance as it is present in all biologically active natural prostaglandins and essential for substantial agonist activity¹⁷⁰.

In the synthesis of C-15 functionalised prostanoids, it is necessary to replace the substrate, methyl nonyl ketone (as in the model prostanoid route), with suitably functionalised methyl nonyl ketones. For this purpose, undec-6-en-2-one (60) and 6-benzyloxy-2-undecanone (67) were prepared from a common precursor, 5-(1,3-dioxalan)-hexanal (52). These functionalised methyl nonyl ketones were subsequently transformed into C-15 functionalised prostanoids by the application of the model synthetic route, scheme 4.1.

Scheme 4.1

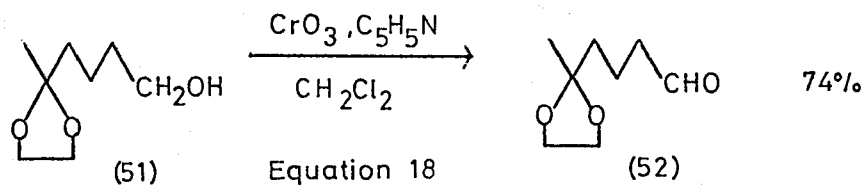
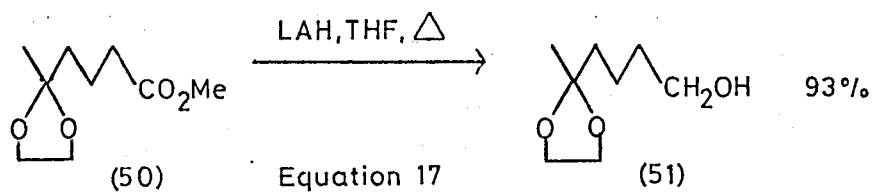
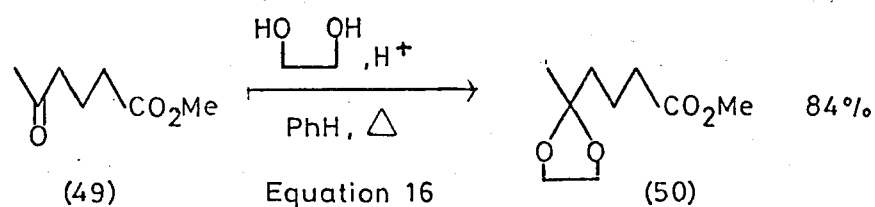
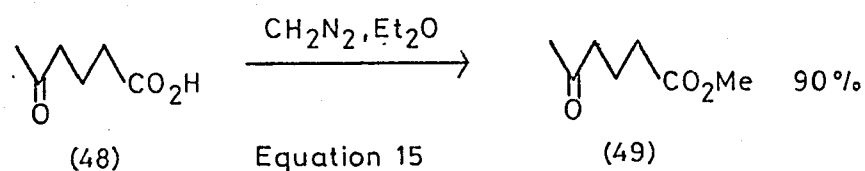
SYNTHESIS OF C-15 FUNCTIONALISED PROSTANOIDS



4.1 General route for the preparation of 5-(1,3-dioxolan)-hexanal

The synthetic route for the preparation of the required 5-(1,3-dioxolan)-hexanal is depicted in scheme 4.2.

Scheme 4.2



The above synthetic route was first established by C. B. Chapman¹⁴¹ in the preparation of the lower homologue, 4-(1,3-dioxolan)-pentanal. This was followed by successful attempts at preparing the 5-(1,3-dioxolan)-hexanal. The yields shown in scheme 4.2, have been fully optimised in this project.

Commercially available 4-acetylbutyric acid (48) was methylated using ethereal diazomethane (generated from Diazald) at room temperature. The purified methyl 4-acetylbutyrate (49) was obtained in nearly quantitative yield. Protection of the keto function as a 1,3-dioxolan was readily carried out by heating methyl 4-acetylbutyrate (49), ethane-1,2-diol and a trace amount of *p*-toluene sulphonic acid in benzene, with azeotropic removal of water. The purified methyl 5-(1,3-dioxolan)-hexanoate (50) was subsequently reduced to the corresponding alcohol (51) with lithium aluminium hydride in refluxing THF. Oxidation of the alcohol (51) in a solution of chromium trioxide/pyridine complex in dry dichloromethane at room temperature, afforded the key precursor 5-(1,3-dioxolan)-hexanal (52).

The overall yield of 5-(1,3-dioxolan)-hexanal (52) from 4-acetylbutyric acid was about 50%. With the exception of the final stage Collins' oxidation, the reactions were readily reproducible. The Collins' oxidation of the alcohol (51) was found to be very sensitive to moisture. Yields ranging from 40-74% were obtained. In addition, the purified 5-(1,3-dioxolan)-hexanal (52) was found to be unstable when left for long periods at room temperature. It was, therefore, used immediately in subsequent chain extension reactions.

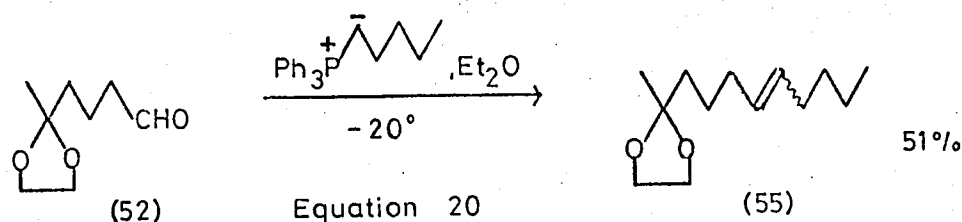
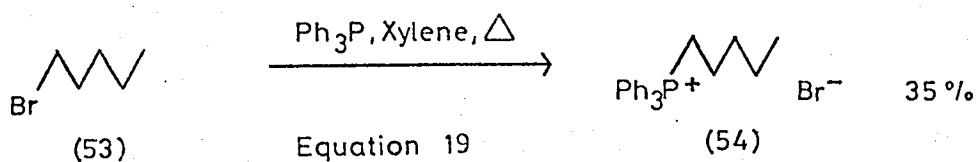
4.2 Route to undec-6-en-2-one and subsequent formation of ethyl
10,10-dimethyl prost-8(12), 15-dien-9,11-dionoate

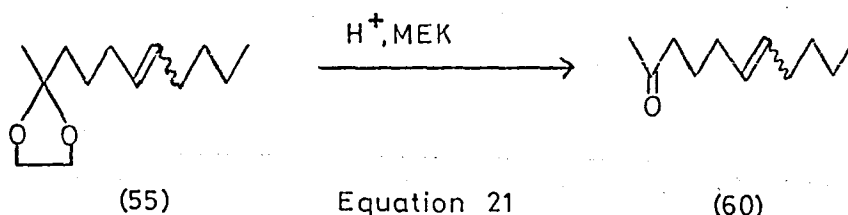
The prime objective was to prepare a C-15 functionalised prostanoid by the use of a suitably functionalised methyl nonyl ketone in the established model prostanoid synthetic route. Undec-6-en-2-one(60) was selected for this purpose. The application of this functionalised methyl nonyl ketone to the model prostanoid synthetic scheme, would by analogy, furnish ethyl 10,10-dimethyl prost-8(12),15-dien-9,11-dionoate (63).

The introduction of the C-15 double bond formed part of a plan that would permit further elaboration of the β -alkyl side-chain. Epoxidation of this double bond, followed by reductive epoxide ring-opening was envisaged to provide a C-15 or C-16 hydroxyl group. It was thought that steric crowding by the cyclopentene-1,3-dione nucleus at one end of the β -alkyl side-chain would lead to stereoselective epoxide ring-opening in favour of the desired C-15 hydroxyl prostanoid.

Undec-6-en-2-one (60) was prepared according to scheme 4.3

Scheme 4.3





n-pentyltriphenyl phosphonium bromide was prepared by heating *n*-pentylbromide with an equimolar amount of triphenyl phosphine in dry xylene¹⁷¹. Early attempts using this procedure invariably resulted in the formation of a brown viscous semi-solid product which was difficult to recrystallise. The problem was eventually resolved by heating a more dilute solution of triphenyl phosphine with *n*-pentyl bromide in dry xylene, under a gentle stream of nitrogen. On cooling to room temperature, pure white crystalline phosphonium salt (54) was obtained in 35%.

In the subsequent Wittig olefination, the *n*-pentyl triphenyl phosphonium ylid, formed *in situ* by the addition of *n*-BuLi at -20° , was allowed to react with freshly prepared 5-(1,3-dioxolan)-hexanal (52), to afford a crude mixture of olefins (55). Successive chromatographic purification of the crude, afforded a mixture of *cis/trans* isomers (55) in 51%.

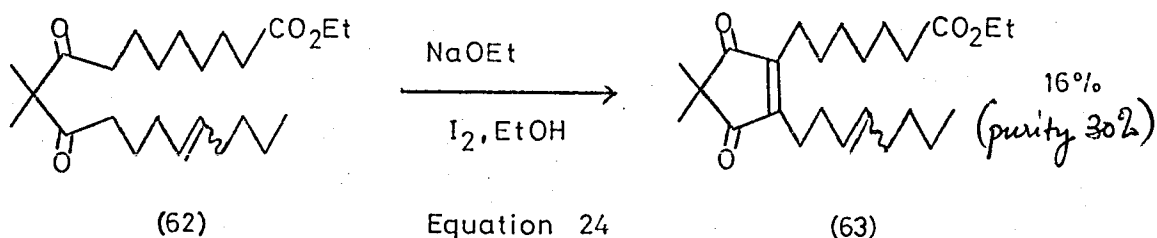
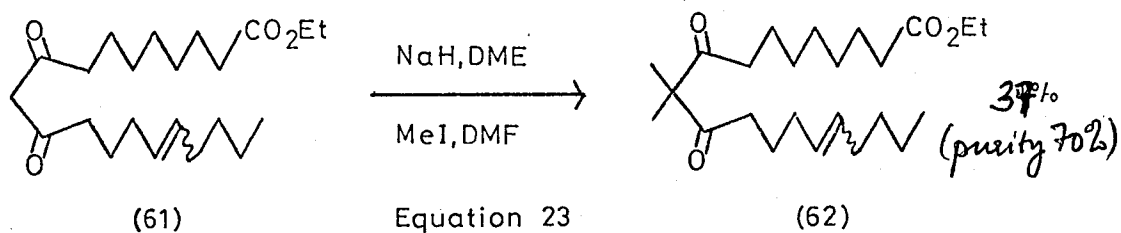
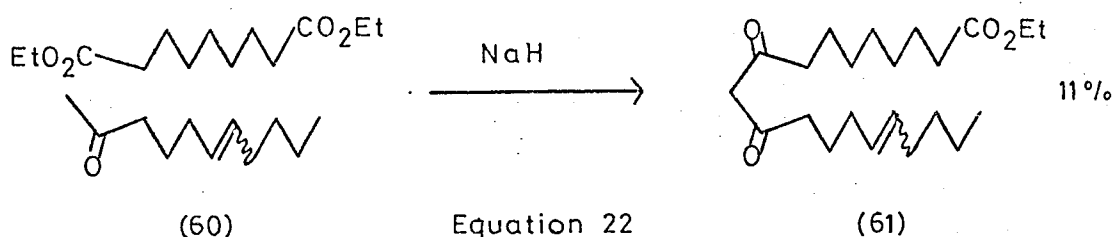
Acid hydrolysis of (55) afforded the crude isomeric undec-6-en-2-one (60) in quantitative yield (purity of 95% by GLC).

The IR spectrum of undec-6-en-2-one (60) showed typical bands at 3010 and 969 cm^{-1} for the disubstituted double bond and a strong carbonyl band at 1720 cm^{-1} . The ^1H -NMR spectrum of (60) showed characteristic signals at δ 0.89 (t, terminal methyl), 1.18-1.50 (m, $-\text{CH}_2-\text{CH}_2-$), 1.50-1.86 (m, $-\text{CH}_2-$), 1.86-2.20 (m, $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$), 2.13 (s, $\text{CH}_3-\text{CO}-$), 2.33 (t, $-\text{CH}_2-\text{CO}-$) and 5.13-5.58 (m, $-\text{CH}=\text{CH}-$). The accurate mass measurement gave the required

molecular ion of (60) at m/e 168 (14%, measured 168.1518, calculated 168.1514).

Undec-6-en-2-one was subsequently subjected to the three-stage prostanoid synthetic route shown in scheme 4.4.

Scheme 4.4.



The Claisen condensation of undec-2-en-6-one to diethyl azelate gave the crude 1,3-diketo-ester (61) as expected. Careful column chromatography and preparative TLC separation of the crude product, afforded

purified ethyl eicos-15-en-9,11-dionoate (61) as a viscous yellow oil in 11%.

The IR spectrum of (61) showed characteristic bands at 1610 and 1739cm^{-1} , assigned respectively to the enolizable 1,3-diketo and ester functions. The $^1\text{H-NMR}$ spectrum showed typical signals at δ 0.88 (t, terminal methyl), 1.10-1.87(m, methyl methylene envelope), 1.87-2.19 (m, $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$), 2.19-2.62 (m, methylenes at C-2, C-8 and C-12), 3.54 (s, $-\text{CO}-\text{CH}_2-\text{CO}-$), 4.14 (q, $-\text{O}-\text{CH}_2\text{CH}_3$), 5.29-5.46 (m, $-\text{CH}=\text{CH}-$) and 5.49 (s, $-\text{CO}-\text{CH}=\text{C}(\text{OH})-$). The low resolution mass spectrum of (61) showed the presence of the required molecular ion at m/e 366 (highest ion) and a fragment ion at m/e 321, $[\text{M} - \text{OEt}]^+$.

Dimethylation of the 1,3-diketo-ester (61), followed by preparative TLC, afforded ³⁷4% yield of purified ethyl 10,10-dimethyl eicos-15-en-9,11-dionoate (62) as a viscous yellowish oil. The GLC analysis of the purified sample indicated a purity of about 70% (by normalisation).

The IR spectrum of (62) showed characteristic carbonyl bands at 1738, 1720 and 1700cm^{-1} . The $^1\text{H-NMR}$ spectrum showed typical peaks at δ 0.88 (t, terminal methyl), 1.08-1.80 (m, methylene, methyl envelope), 1.33 (s, gem-dimethyl), 1.80-2.18 (m, $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$), 2.18-2.54 (m, methylenes at C-2, C-8 and C-12), 4.12 (q, $-\text{O}-\text{CH}_2\text{CH}_3$) and 5.22-5.51 (m, $-\text{CH}=\text{CH}-$).

The C-8, C-12 cyclisation of (62) was achieved using the sodium ethoxide/iodine procedure. Purification of the crude product by preparative TLC, afforded 16% of ethyl 10,10-dimethyl prost-8(12), 15-dien-9,11-dionoate (63) as a yellowish oil.

The IR spectrum of the prostanoid (63) showed strong carbonyl

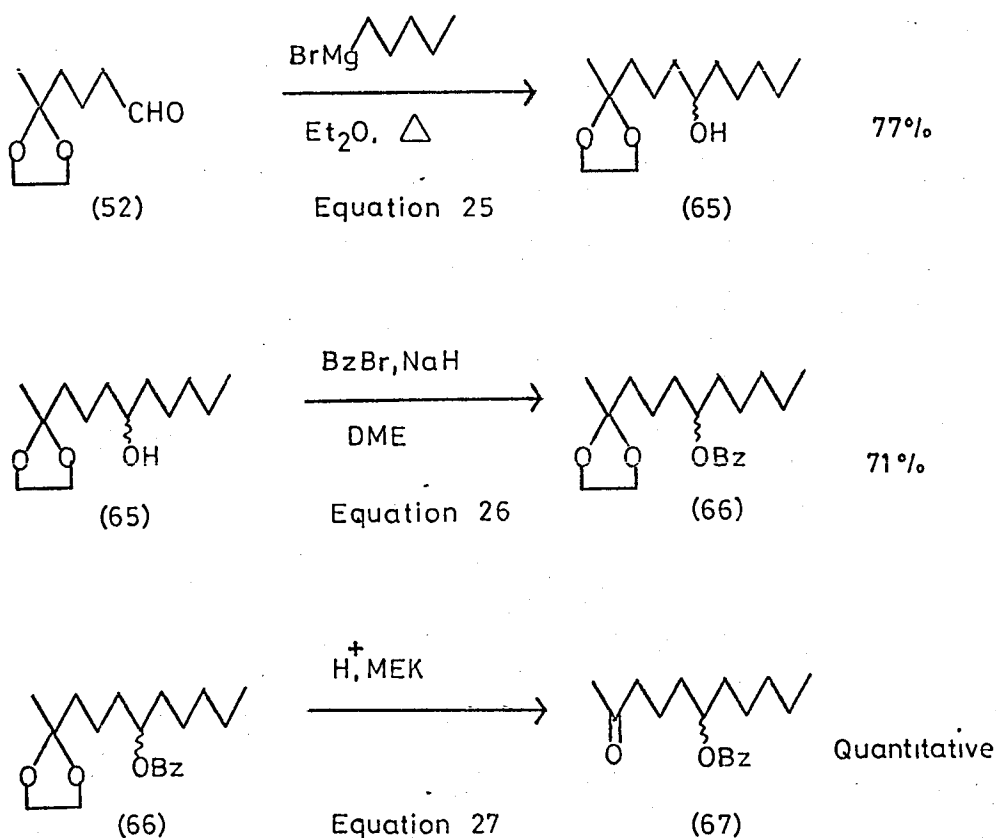
bands at 1737 and 1698 cm^{-1} . However, the expected conjugated double bond stretch of the dimethyl cyclopentene -1,3-dione moiety was too weak to be assigned with certainty. The same was true of the C-15 double bond stretch at 969 cm^{-1} . The ^1H -NMR spectrum of (63) showed characteristic signals at δ 0.90 (t, terminal methyl), 1.01-1.87 (m, methylene, methyl envelope), 1.87-2.16 (m, $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$), 2.16-2.65 (m, methylenes at C-2, C-7 and C-13), 4.15 (q, $-\text{O}-\text{CH}_2-\text{CH}_3$) and 5.25-5.56 (m, $-\text{CH}=\text{CH}-$). A sharp singlet at 1.13 δ in the methylene envelope provided strong evidence for the presence of the C-15 functionalised prostanoid (63). This characteristic signal was assigned to the magnetically equivalent C-10 gem-dimethyl of (63). The unusually intense carbethoxy triplet (1.26 δ) and quartet (4.15 δ) and an isopropyl doublet (1.07 δ , $\text{CH}_3-\underset{|}{\text{CH}}-\text{CH}_3$) suggested the presence of diethyl azelate and co-products of the retro-Claisen cleavage of the precursor (62). The GLC analysis of (63) indicated a mixture of diethyl azelate (20%), half-chain components (50%) and the prostanoid (63) (30%). The UV spectrum of (63) showed a broad absorption band at λ_{max} 242nm, $\epsilon = 3,640$. The low resolution mass spectrum of (63) showed the intense molecular ion $[\text{M}]^+$ at m/e 390 (30%) and the corresponding $[\text{M} - \text{OEt}]^+$ (15%) fragment ion.

The purity of prostanoid (63) sample as determined by GLC (30%), compared favourably with the figure estimated from the UV absorption (28%, based on the UV absorption of the model prostanoid, λ_{max} 250nm, $\epsilon = 12,350$). It was evident from these purity figures and the spectral data of (63) that the cyclisation of (62), using the sodium ethoxide/iodine procedure, produced only a low yield of the C-15 functionalised prostanoid (63), together with other inseparable retro-Claisen cleavage products.

4.3 Route to 6-benzyloxy-2-undecanone and subsequent formation of ethyl 10,10-dimethyl-15-benzyloxy - prost-8(12)-en-9,11-dionoate

The successful application of the three-stage prostanoid synthetic route to the preparation of the model prostanoid (23) and the Δ^{15} -prostanoid (63), encouraged us to concentrate our effort on the direct preparation of a C-15 hydroxyl prostanoid. This could be achieved by the use of an appropriately hydroxylated methyl nonyl ketone substrate in the prostanoid synthetic route. The required δ -hydroxyl methyl nonyl ketone was prepared from 5-(1,3-dioxolan) hexanal according to scheme 4.5.

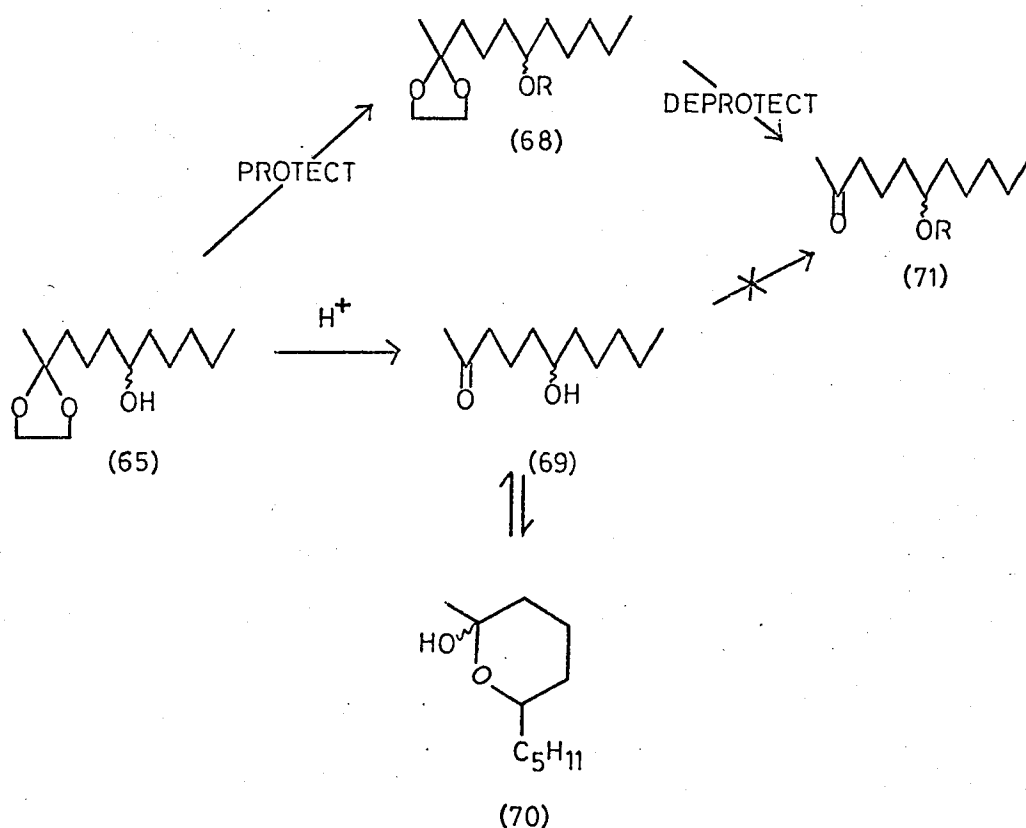
Scheme 4.5



The Grignard reaction of *n*-pentylmagnesium bromide with the protected aldehyde (52), followed by column chromatographic separation of the crude product, afforded 2-(1,3-dioxolan)-undecan-6-ol (65) as a thick colourless oil. The IR spectrum of (65) showed absorption bands due to hydroxyl (3450 cm^{-1}) and ketal (1064 cm^{-1}) groups. The $^1\text{H-NMR}$ spectrum showed typical signals at δ 0.84 (t, terminal methyl), 1.05-1.78 (m, methylene, methyl envelope), 1.91 (s, -OH, D_2O exchangeable), 3.60 (m, $-\text{CH}-\text{OH}$) and 3.92 (s, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$).

Earlier work by C. B. Chapman¹⁴¹ indicated that the protection of the hydroxyl group of the ketal alcohol (65) or the keto-alcohol (69) was difficult, scheme 4.6. For instance, the hydroxyl function of the keto-alcohol (69) could not be protected as the tetrahydropyranyl ether.

Scheme 4.6



This was presumed to be due to the favourable formation of the six-membered cyclic hemi-ketal (70). It was also found that the ketal alcohol (65) failed to form the benzyl ether under a variety of alkylation conditions; such as BzCl/KOH in toluene, BzBr/NaH in DMF and Ag₂O in methyl iodide.

In this project, some of the earlier methods of benzylation were reinvestigated and a number of different methods were attempted. The results are summarised in table 4.1.

Table 4.1

Reagents	Results of GLC analysis
i) NaH/DMF ¹⁷² BzBr/17h/R.T. N ₂ .	60% starting material (65), 20-40% benzylated product (66) and large amount of dibenzyl ether.
ii) NaH/DMSO ¹⁷³ BzBr/17h/R.T. N ₂ .	Mainly starting material (65), trace amount of benzylated product (66) and 20% dibenzyl ether.
iii) NaH/THF BzO-P ⁺ (NMe ₂) ₃ PF ₆ ⁻ 13h/Δ/N ₂	Mainly starting material (65) and less than 10% benzylated product (66).
iv) NaH/DME BzBr/46h/R.T. N ₂ .	Trace amount of starting material (65), 70% benzylated product (66) and small amount of dibenzyl ether.

The use of NaH/DMF/BzBr afforded a variable 20-40% of the ketal

benzyl ether (66), together with large amounts of starting material (65) and dibenzyl ether. The latter was separated from the product (66) with difficulty. The lack of reactivity of the ketal alcohol (65) was thought to be due to the low solubility of sodium hydride in DMF. This led to the use of sodium hydride in DMSO/BzBr. The soluble dimethyl base was initially formed¹⁷³ and to it was added the ketal alcohol (65), followed by benzyl bromide. However, on work-up, this produced mainly dibenzyl ether and only a trace amount of product (66).

The tris-(N,N-dimethyl)-benzyloxy phosphonium salt (reagents iii) , developed in these laboratories¹⁷⁴ as an alkylating agent, was employed in an attempt to effect benzylation without the inherent difficulties associated with the use of benzyl bromide. This was, however, equally unsuccessful.

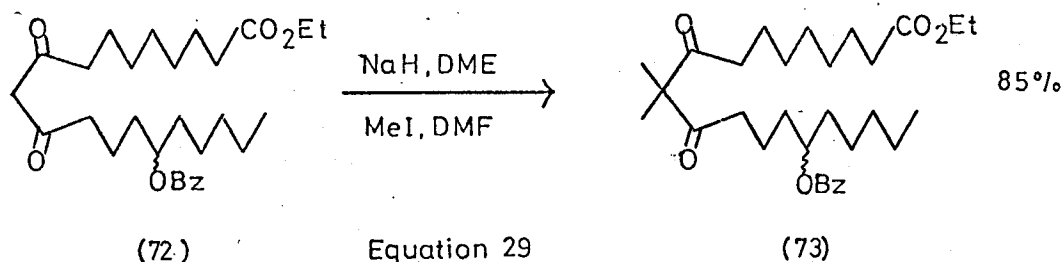
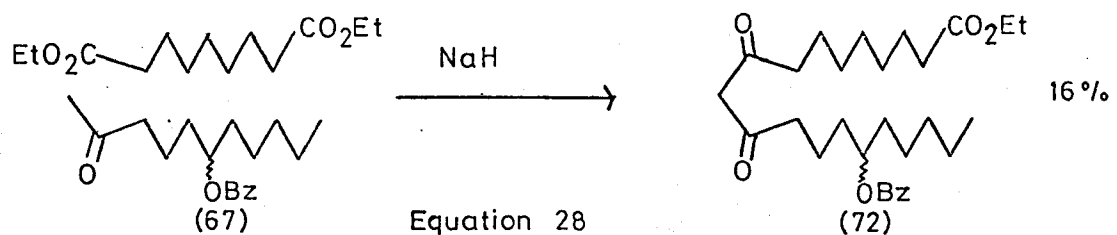
Eventually, an attempt was made using a mixture of NaH/DME/BzBr. DME was selected for its ability to partially solvate Na^+ . It was hoped that this would reduce the problem of heterogeneity. The initial experiment was monitored by GLC. The benzylated product (66) to starting material (65) ratio measured after 21 and 45 hours were (70:30) and (95:5) respectively. After numerous attempts, the benzylation was optimized to produce 71% of purified ketal benzyl ether (66) as a thick colourless oil.

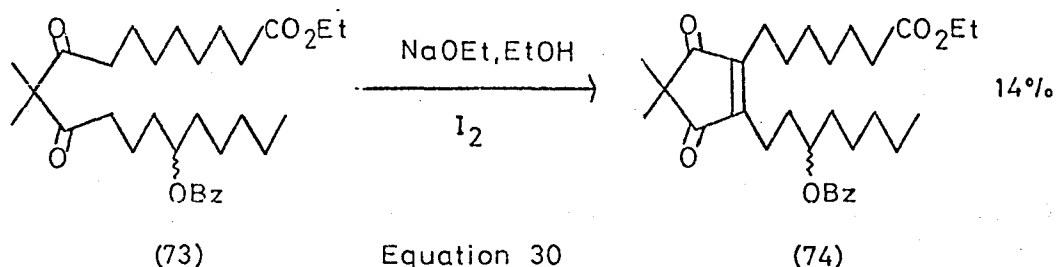
The selective deprotection of the ketal benzyl ether (66) by acid hydrolysis, afforded quantitative yield of the keto-benzyl ether (67). However, in subsequent work, it was found that the crude ketal benzyl ether (66) could be directly hydrolysed in acid and purified as the keto-benzyl ether (67) in an overall yield of 69%.

The IR spectrum of the 6-benzyloxy-2-undecanone (67) showed characteristic bands for the carbonyl (1715 cm^{-1}) and the benzyl groups (3030 , 733 and 696 cm^{-1}). The ^1H -NMR spectrum of (67) showed typical signals at δ 0.89 (t, terminal methyl) 1.16-1.90 (m, methylene envelope), 2.10 (s, $\text{CH}_3\text{CO-}$), 2.43 (t, $-\text{CH}_2-\text{CO-}$), 3.39 (broad m, $-\text{CH}-\text{OBz}$), 4.49 (s, $-\text{O}-\text{CH}_2-\text{Ph}$) and 7.16-7.48 (m, aromatic protons). The accurate mass measurement of the molecular ion $[\text{M}]^+$ (measured 276.2091, calculated 276.2089) established the correct formula of (67).

The next stage was to subject the 6-benzyloxy-2-undecanone (67) to the prostanoid synthetic route as shown in scheme 4.7.

Scheme 4.7





The first stage Claisen condensation of 6-benzyloxy-2-undecanone (67) with diethyl azelate, using sodium hydride, gave a crude mixture containing the 1,3-diketo-ester (72). The light-ends in the crude mixture was removed by passing the latter down a uniformly heated vigreux column (200-210°/0.5 torr). The partially purified heavy-ends was successively separated by column chromatography and preparative TLC, to afford 16% of ethyl 15-benzyloxy eicos-9,11-dionoate (72) as a viscous yellow oil.

The IR spectrum of (72) showed the typical ester (1739 cm^{-1}), enolizable 1,3-diketone (1607 cm^{-1}) and benzyl (3030, 732 and 696 cm^{-1}) bands. The $^1\text{H-NMR}$ spectrum showed characteristic signals at δ 0.89 (t, terminal methyl), 1.15-1.90 (m, methyl, methylene envelope), 2.15-2.70 (m, methylenes at C-2, C-8 and C-12), 3.40 (broad m, $-\text{CH}-\text{OBz}$), 3.50 (s, $-\text{CO}-\text{CH}_2-\text{CO}-$), 4.48 (s, $-\text{O}-\text{CH}_2\text{Ph}$), 5.45 (s, $-\text{CO}-\text{CH}=\text{COH}$) and 7.32 (m, aromatic protons).

Treatment of the 1,3-diketo-ester (72) with NaH/MeI in DME/DMF at reflux temperature, followed by preparative TLC, afforded purified ethyl 15-benzyloxy-10,10-dimethyl eicos-9,11-dionoate (73) in 85% yield.

The IR spectrum of the dimethyl 1,3-diketo-ester (73) showed characteristic bands for the ester (1736 cm^{-1}), the keto- (1719, 1696 cm^{-1}) and the benzyl (3045, 734 and 697 cm^{-1}) groups. The $^1\text{H-NMR}$ spectrum showed typical peaks at δ 0.88 (t, terminal methyl), 1.13-1.85 (m, methyl,

methylene envelope), 2.17-2.54 (m, methylenes at C-2, C-8 and C-12), 3.21-3.53 (broad m, $-\underline{\text{CH}}-\text{OBz}$), 4.13 (q, $-\text{O}-\underline{\text{CH}}_2\text{CH}_3$), 4.49 (s, $-\text{O}-\underline{\text{CH}}_2-\text{Ph}$) and 7.32 (m, aromatic protons). The presence of a weak singlet signal at 3.67 δ indicated contamination by a trace amount of the methyl ester of (73), formed by an ester-exchange side-reaction. The accurate mass measurement of (73) indicated no $[\text{M}]^+$ ion. Extensive fragmentation across the C-9, C-10 and the C-10, C-11 bonds of (73), however, characteristically produced the corresponding C_{12} and C_9 long chain ethyl esters ions at m/e 242 (7%) and m/e 199 (18%) respectively.

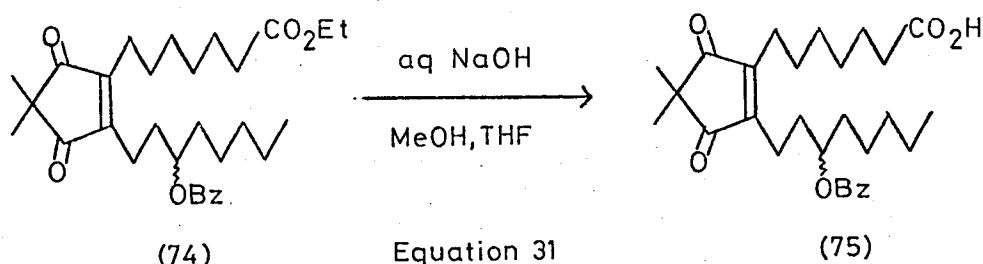
The final stage C-8, C-12 cyclisation of (73) was carried out by the sodium ethoxide/iodine method. The crude product was purified by preparative TLC to afford 14% ethyl 15-benzyloxy-10,10-dimethyl prost-8(12)-en-9,11-dionoate (74) as a viscous yellow oil.

The IR spectrum of the prostanoid (74) showed typical bands for the benzyl (3040, 735 and 697 cm^{-1}), the ester carbonyl (1739 cm^{-1}), and the cyclopentene-1,3-dione (1694 and 1629 cm^{-1}) groups. The ^1H -NMR spectrum showed characteristic signals at δ 0.88 (t, terminal methyl), 1.03-1.90 (m, methyl, methylene envelope), 1.12 (s, gem-dimethyl at C-10), 2.17-2.59 (m, methylenes at C-2, C-7 and C-13), 3.26-3.62 (broad m, $-\underline{\text{CH}}-\text{OBz}$), 4.14 (q, $-\text{O}-\underline{\text{CH}}_2\text{CH}_3$), 4.54 (s, $-\text{O}-\underline{\text{CH}}_2\text{Ph}$) and 7.25-7.53 (m, aromatic protons). The UV spectrum of the purified prostanoid (74) showed a typical absorption band at λ_{max} 248nm ($\epsilon = 5,790$) for the dimethyl cyclopentene-1,3-dione chromophore. The accurate mass measurement of the molecular ion $[\text{M}]^+$ (measured 498.3338, calculated 498.3345) established the correct formula of the prostanoid (74).

The UV measurement of (74) (λ_{max} 248nm, $\epsilon = 5,790$) indicated

an estimated purity of 45-50%. In addition, the $^1\text{H-NMR}$ of (74) showed two singlet signals (at 4.54 and 4.50 δ) instead of a single peak for the $-\text{O}-\text{CH}_2\text{Ph}$ group. This indicated the presence of other benzyl ether contaminants in the sample. The mass spectrum of (74) also showed strong fragment ions at m/e 199 (40%) and m/e 242 (10%) which suggested that the dimethyl 1,3-keto-ester precursor (73) was present as a contaminant.

In an attempt to remove the contaminants, (74) was hydrolysed in aqueous sodium hydroxide to the corresponding crude prostanoic acid (75), equation 31. Separation of the crude product by preparative TLC, afforded purified 15-benzyloxy-10,10-dimethyl prost-8 (12)-en-9,11-dionoic acid (75).



The IR spectrum of the prostanoic acid (75) showed characteristic bands for the benzyl (3045, 736 and 697 cm^{-1}), the carboxylic acid (broad shoulder at 3000-3500, 1714 cm^{-1}) and the dimethyl cyclopentene-1,3-dione (1741, 1698 and 1629 cm^{-1}) groups. The $^1\text{H-NMR}$ spectrum showed typical signals at δ 0.90 (t, terminal methyl), 1.11 (s, gem-dimethyl at C-10), 1.18-1.89 (m, methylene envelope), 2.18-2.70 (m, methylenes at C-2, C-7 and C-13), 3.25-3.63 (m, $-\text{CH}-\text{OBz}$), 4.54 (s, $-\text{O}-\text{CH}_2\text{Ph}$) and

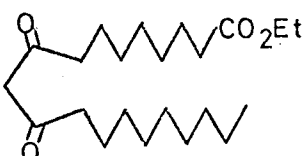
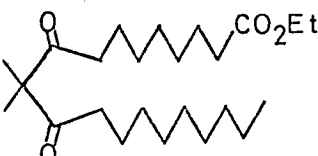
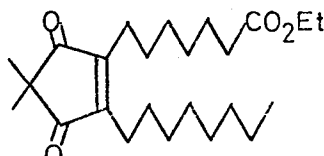
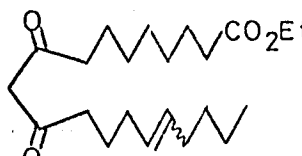
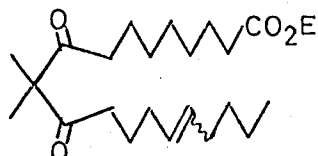
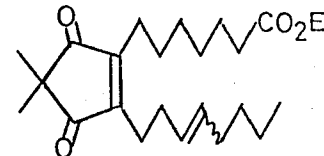
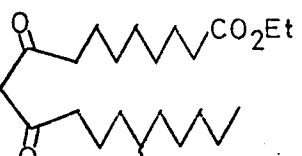
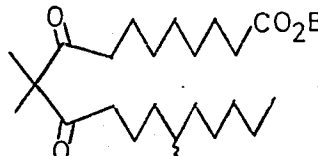
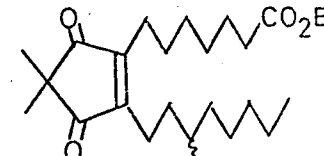
7.35 (m, aromatic protons). By comparison with the corresponding prostanoid ester (74), the prostanoic acid (75) showed a relatively weaker signal at 4.50 δ . This indication of a slight improvement in purity was reflected in the UV data of (75) (λ_{max} 250nm, $\epsilon = 5,820$). The accurate mass measurement of (75) gave a distinct molecular ion, $[M]^+$ at m/e 470 (measured 470.3037, calculated 470.3032).

5. DISCUSSION OF THE PROSTANOID SYNTHESSES

The success of the synthesis of the model prostanoid (23) and the two C-15 functionalised prostanoids (63) and (74), described in the preceding sections, established the generality of the prostanoid synthetic scheme.

The overall results of these individual syntheses are shown in table 5.1.

Table 5.1

Claisen condensation	Dimethylation at C-10	C-8,C-12 cyclisation
 (3) 38%	 (17) 69%	 (23) 14-41%
 (61) 11%	 (62) 21%	 (63) 16%
 (72) 20%	 (73) 85%	 (74) 14%

The first stage Claisen condensation of the δ -functionalised 2-undecanones with diethyl azelate appeared to be general. However, the yields of (61) and (72) were lower than that obtained for (3). This was

probably due to the much lower scale at which the Claisen condensations of the δ -functionalised 2-undecanones were carried out. The low yields were expected to improve on scale-up and optimisation and not thought to be a serious limitation to the overall synthetic route.

The second stage dimethylation reactions also appeared to be general and did not present difficulties. Again, the low yield of (62) was not thought to be typical and was likely to improve on scale-up and optimisation.

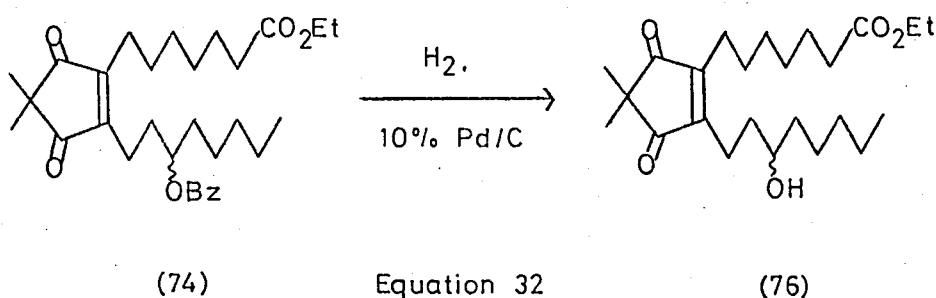
The final stage C-8, C-12 cyclisation was found to be general for the C-15 functionalised dimethyl-1,3-diketo-esters (62) and (73). However, as expected the yields of the corresponding C-15 functionalised prostanoids (63) and (74) were low. As a result of the large variation in the yield of the cyclisation leading to the model prostanoid (23), we were uncertain if the low yields of the prostanoids (63) and (74) were a direct effect of the added constraint of the C-15 functionality in the ~~is~~alkyl side-chain.

An additional problem occurred with the benzyloxy prostanoid series. Neither the dimethyl benzyloxy -1,3-diketo-ester (73), nor the corresponding benzyloxy prostanoid (74), could be analysed by GLC. As a result, the purity of this series was based solely on TLC homogeneity and the consistency of spectroscopic data. However, these were later augmented by HPLC analysis.

Early attempts at purifying the model prostanoid (23) by normal-phase HPLC (silica gel) provided evidence of decomposition. Consequently, this method of purification was abandoned. However, investigations into the use of reversed-phase HPLC was resumed when it was found that preparative TLC separation, although satisfactory for the model prostanoid

(23), was shown to be less effective for the benzyloxy prostanoid (74). It was found that (74) could be partially purified by reversed-phase HPLC (C_{18} bonded porasil A/ UV_{254} detection) with methanol as the mobile phase. For example, a single passage of the benzyloxy prostanoid (74) (λ_{max} 248nm, ϵ = 5,350) through a semi-preparative reversed-phase column, afforded a partially purified sample of the prostanoid (λ_{max} 248nm, ϵ = 5,940). Although the analysis on a finer grade analytical column indicated the purified sample to be still impure, the poorer resolution of the semi-preparative column limited improvement.

As mentioned in section 4, the base hydrolysis of the benzyloxy prostanoid (74), followed by preparative TLC of the benzyloxy prostanoid acid (75), resulted in a slight improvement in purity. Purification of the crude benzyloxy prostanoid acid (75) by reversed-phase HPLC showed some promise. An alternate approach via controlled hydrogenation of the benzyloxy prostanoid (74) to the C-15 hydroxyl prostanoid (76) was also briefly investigated, equation 32. However, for reasons discussed at the beginning of section 6, both these approaches have not been fully exploited.



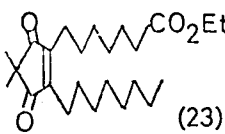
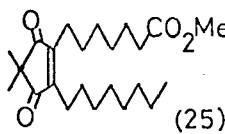
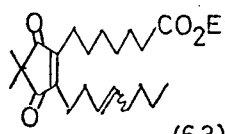
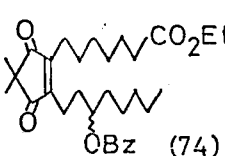
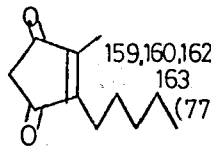
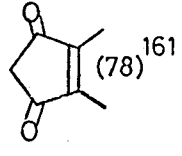
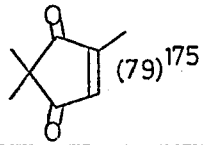
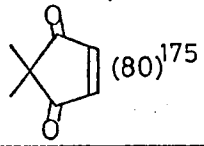
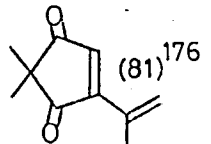
As it was extremely difficult to purify the C-15 functionalised prostanoids, we focussed our attention on the spectroscopic evidence for

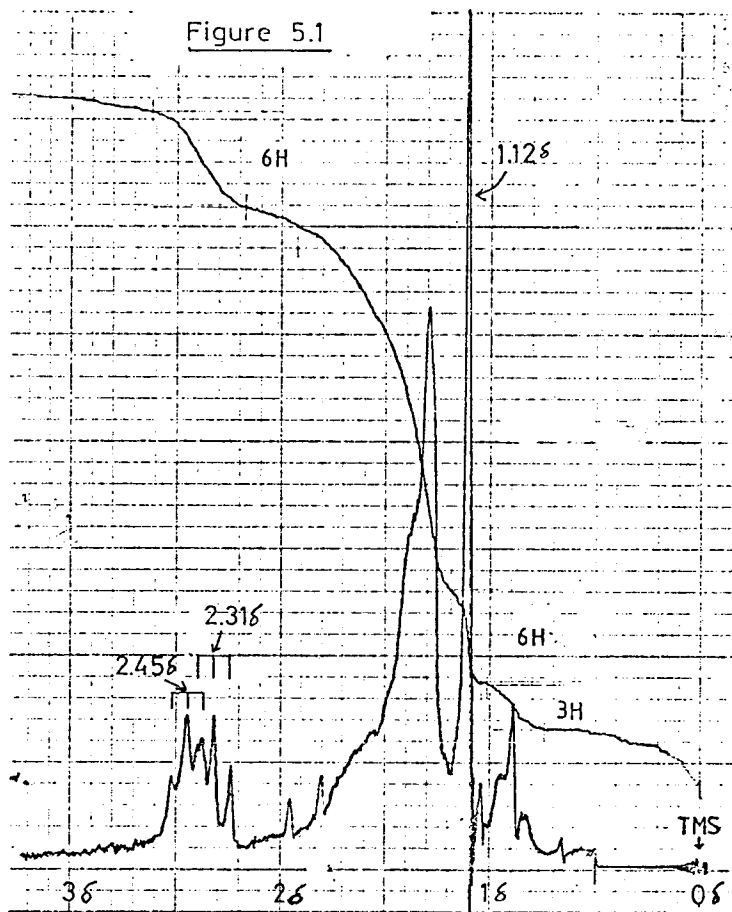
the presence of these species in their respective purified samples. Table 5.2 summarises the common and recognisable spectroscopic data related to the dimethyl cyclopentene-1,3-dione nucleus in each of the prostanoids prepared so far. Corresponding spectroscopic data reported for similar cyclopentene-1,3-dione systems are also included.

Typically, the prostanoids showed IR absorption bands for the ester carbonyl ($1730\text{--}1743\text{ cm}^{-1}$) and the cyclopentene-1,3-dione group ($1694\text{--}1698$ and $1625\text{--}1630\text{ cm}^{-1}$). In examples (77), (78) and (79), the corresponding cyclopentene-1,3-dione groups showed absorption bands at $1750(\text{w})$, $1710(\text{s})$ and $1620\text{--}1650(\text{w})\text{ cm}^{-1}$. In these examples, the cyclopentene-1,3-dione carbonyl bands appeared as two peaks at $1750(\text{w})$ and $1710(\text{s})$. In the case of the prostanoids, however, the weak band at 1750 cm^{-1} was presumably obscured by the strong ester carbonyl band at $1730\text{--}1743\text{ cm}^{-1}$. This supposition was later confirmed by the IR spectra of similar 4,5-dialkyl-2,2-dimethyl cyclopent-4-en-1,3-diones (143) and (147) (*vide infra*) which showed typical carbonyl bands at $1740(\text{w})$, $1693(\text{s})$ and $1625\text{--}1630(\text{w})\text{ cm}^{-1}$.

The ^1H -NMR spectra of the prostanoids were characterised by two important sets of peaks; the C-10 gem-dimethyl protons at $1.12\delta (\text{s}, 6\text{H})$ and the C-7 and C-13 methylenic protons (adjacent to the cyclopentene-1,3-dione nucleus) at $2.45\delta (\text{t}, 4\text{H})$. The triplet at 2.45δ generally overlapped with C-2 methylenic protons at $2.31\delta (\text{t}, 2\text{H})$ to form a characteristic pair of triplets, see figure 5.1.

Table 5.2

	IR (cm ⁻¹)	NMR (δ)	UV (nm)	MS
 (23)	1739, 1699 1631	1.12 (s, 6H) 2.30 (t, 2H) 2.46 (t, 4H)	λ_{\max} 250 $\epsilon = 9,620$ (EtOH)	[M] ⁺ (62%) [M-OEt] ⁺ (25%)
 (25)	1743, 1698 1625	1.12 (s, 6H) 2.32 (t, 2H) 2.45 (t, 4H)	λ_{\max} 250 $\epsilon = 12,350$ (EtOH)	[M] ⁺ (9%) [M-OMe] ⁺ (5%)
 (63)	1730, 1698 1630	1.13 (s, 6H) 2.31 (t, 2H) 2.45 (t, 4H)	λ_{\max} 242 $\epsilon = 3,640$ (EtOH)	[M] ⁺ (30%) [M-OEt] ⁺ (15%)
 (74)	1738, 1694 1629	1.12 (s, 6H) 2.30 (t, 2H) 2.46 (t, 4H)	λ_{\max} 249 $\epsilon = 5,950$ (EtOH)	[M] ⁺ (3%) [M-OEt] ⁺ (4%)
 (77)	1750, 1710 1650	2.40 (t, 2H)	λ_{\max} 246 $\epsilon = 11,400$ (MeOH)	
 (78)	1750, 1710 1640		λ_{\max} 246 $\epsilon = 14,900$ (MeOH)	
 (79)	1750, 1710 1620	1.10 (s, 6H)		
 (80)	1750, 1710	1.12 (s, 6H)	λ_{\max} 219 $\epsilon = 6,030$	
 (81)	1740, 1702 1610	1.20 (s, 6H)	λ_{\max} 284 $\epsilon = 10,470$	



Correspondingly similar gem-dimethyl signals, as seen in examples (79) and (80), appeared at comparable chemical shift values of 1.10–1.12 δ (s, 6H). While in example (77), the methylene adjacent to a similar cyclopentene-1,3-dione group also appeared at a comparable chemical shift value of 2.40 δ (t, 2H).

The UV data reported for examples (77) and (78) compared favourably with our best UV data for (25), λ_{max} 250nm, ϵ = 12,350, (also see table 3.2). This figure has been used as a reference standard (assuming 100% purity) to determine the purity of the other prostanoids.

In addition to these spectroscopic data, we obtained the ^{13}C -NMR spectra of the model prostanoid (25) and its corresponding anilide (47). These data further confirmed the presence of the 2,2-dimethyl cyclopent-4-en-1,3-dione moiety (see Appendix).

From the overall results of the application of the prostanoid

synthetic plan and the examination of the spectral data of the resultant prostanoids (23), (25), (63) and (74), we were able to establish that:-

- i) the prostanoid synthetic route was general, as shown by the synthesis of the three main prostanoids (23), (63) and (74).
- ii) the C-15 functionalised prostanoids (63) and (74) could only be partially purified by tedious and repetitive chromatographic separation procedures.
- iii) the yield of the final stage C-8, C-12 cyclisation was low and, therefore, seriously limiting the effectiveness of the overall synthetic route.

6. THE SYNTHESIS OF THE MODEL PROSTANOID VIA A DIBROMO PRECURSOR

An overall assessment of the results of the prostanoid synthesis in the last section left us with two options.

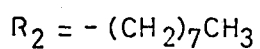
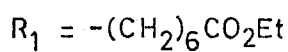
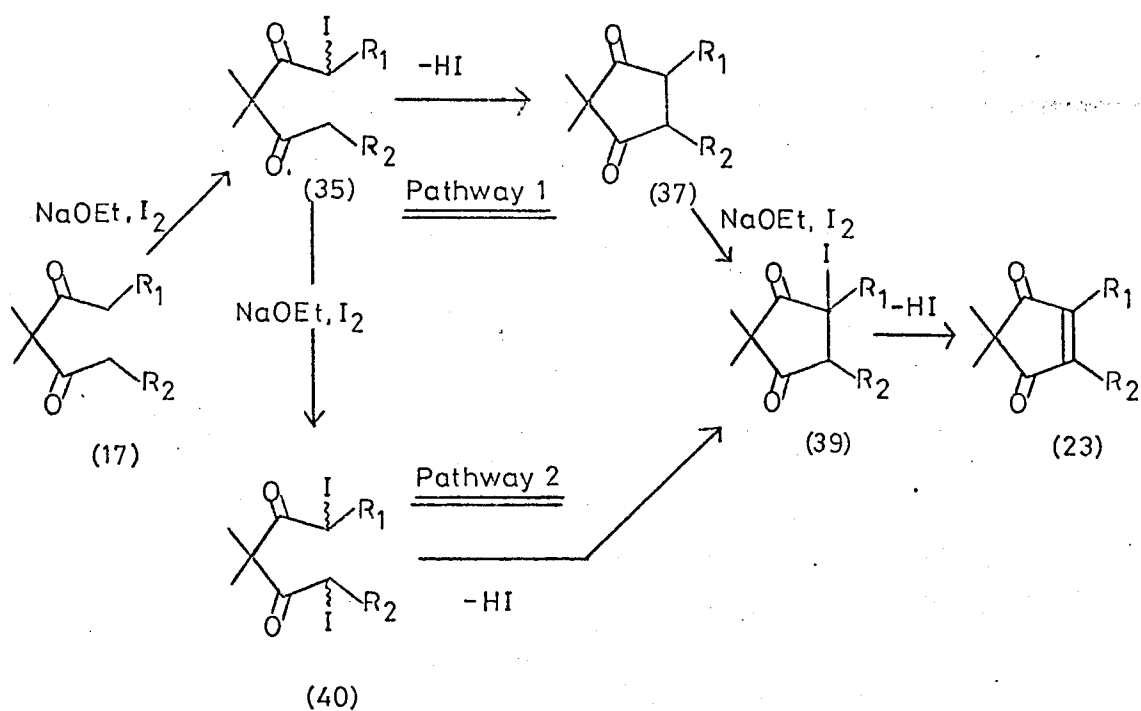
- i) To develop and extend the work on the C-15 functionalised prostanoids.
- ii) To examine alternative C-8, C-12 cyclisation procedures with the object of improving the yield of this crucial step.

We were satisfied that the prostanoid synthetic route was general and applicable to the synthesis of C-15 functionalised prostanoids. At that point in time, it was felt that development work on the C-15 functionalised prostanoids was not of immediate importance. We opted to investigate alternative methods of effecting the C-8, C-12 cyclisation of the 10,10-dimethyl eicos-9,11-dionoic ester. It was clear that the low yield of the cyclisation step was the key problem limiting the potential of the prostanoid synthetic plan. Furthermore, it was argued that if the yield of the cyclisation reaction could be significantly improved, the problems of purification may become less severe.

In essence, the sodium ethoxide/iodine cyclisation of 10,10-dimethyl eicos-9,11-dionoic ester can be envisaged as proceeding via an iodo-species (35) or a diiodo-species (40) as discussed in section 3. The postulated mechanistic pathway is shown in scheme 6.1.

It is interesting to note that pathway 2 offers an alternative approach to the C-8, C-12 cyclisation of (17). In a generalised form, this approach is envisaged as a two-stage synthetic process, scheme 6.2.

Scheme 6.1



Scheme 6.2

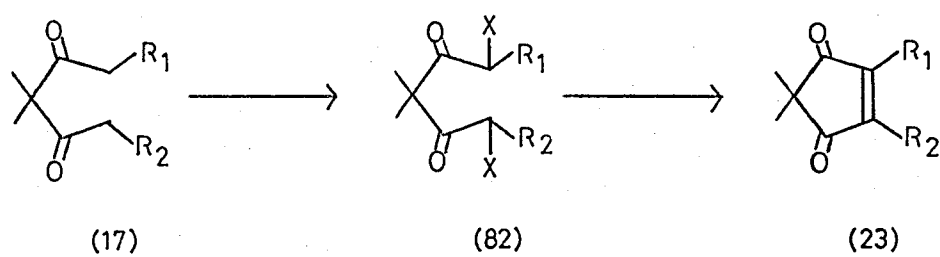
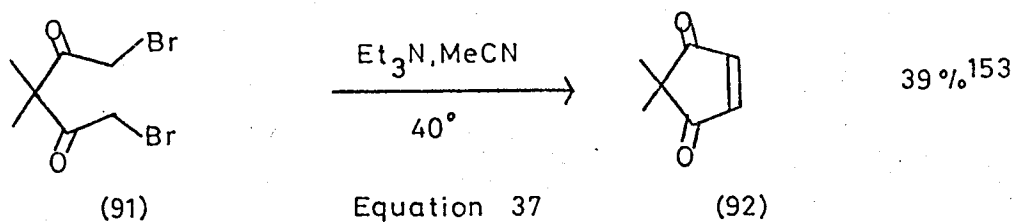
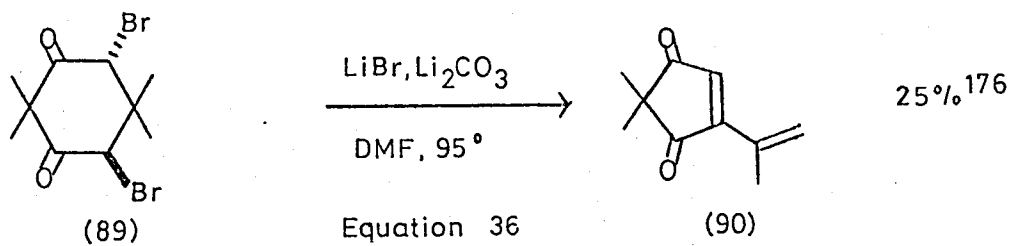
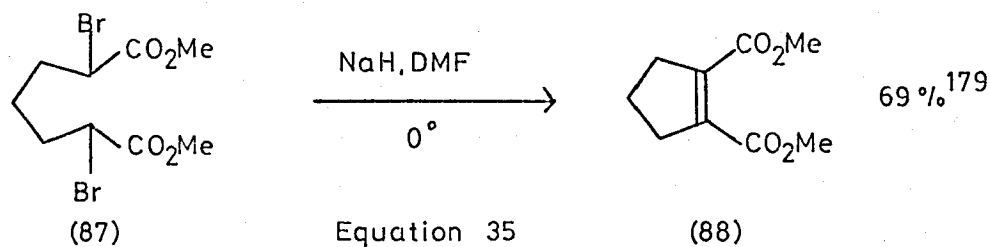
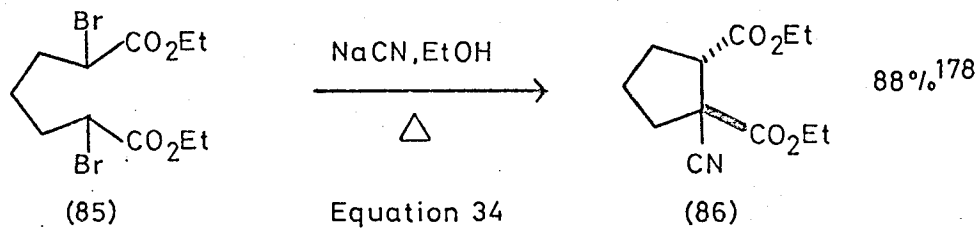
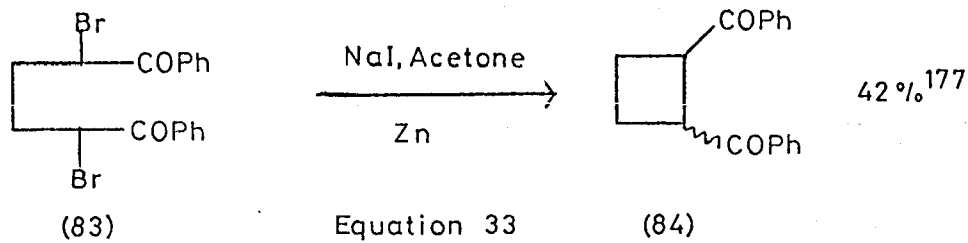
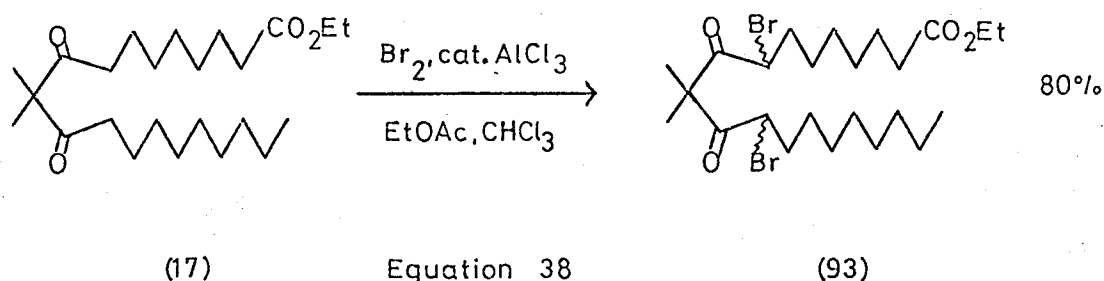


Figure 6.1

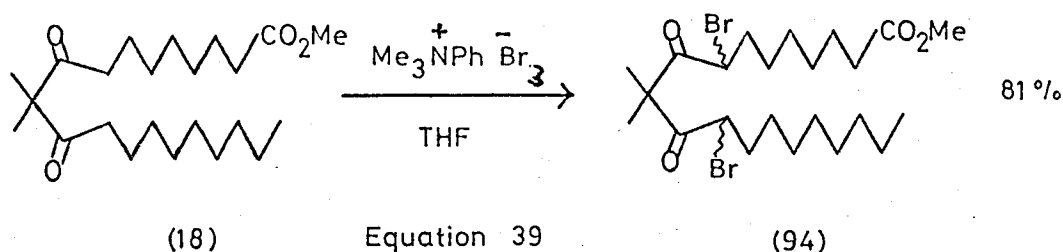


This step-wise synthetic approach to the prostanoïd (23) is potentially more versatile in that the cyclisation step can be carried out by a variety of methods. Precedents for similar intramolecular cyclisation of aliphatic dihalogeno-diketo derivatives have been established as indicated in figure 6.1. The example in equation (37) is particularly interesting in the context of our work.

We, therefore, were encouraged to embark on the proposed scheme 6.2 and prepared the required dihalogeno precursor (93) as indicated in equation 38.



Controlled bromination of (17) with two moles equivalent of bromine and a catalytic amount of aluminium trichloride,¹¹⁰ followed by chromatographic separation, afforded 80% of the dihalogeno derivative (93). However, it was found at a later stage that the bromination could be carried out more conveniently using the crystalline trimethylphenyl ammonium perbromide¹³⁴ in dry THF, equation 39.



The purified 8,12-dibromo-10,10-dimethyl eicos-9,11-dionoic esters (93) and (94) were obtained as lachrymatory and viscous colourless liquids. They appeared to be diastereomeric mixtures which were only partially separated after careful preparative TLC (see below).

The IR spectrum of (93) showed characteristic ester carbonyl (1740cm^{-1}) and keto-carbonyl ($1730(\text{s})$, $1700(\text{m})$) bands. The relative intensity of the two peaks in the latter band contrasted considerably with the keto-carbonyl band ($1720(\text{m})$, $1698(\text{s})$) of the precursor (17). The ^1H -NMR spectrum showed characteristic peaks at δ 0.88 (t, terminal methyl), 1.10-1.50 (m, methyl, methylene envelope), 1.50-1.75 (4 x s, gem-dimethyl at C-10), 1.75-2.15 (m, methylenes at C-7 and C-13), 2.29 (t, $-\text{CH}_2-\text{CO}_2\text{Et}$), 4.14 (q, $\text{CH}_3\text{CH}_2-\text{O}-$), 4.54 and 4.57 (2 x t, $-\text{CHBr}-\text{CH}_2-$). The low resolution mass spectra of both the methyl ester (94) and the ethyl ester (93) did not show their respective molecular ions. However, they both gave characteristic $[\text{M} - \text{Br}]^+ \text{ion}^{181}$ as a 'doublet' and $[\text{M} - \text{OR}]^+$ ion (where R = Et or Me) as a 'triplet'. The $[\text{M} - \text{OR}]^+$ 'triplet' appeared in the correct m/e region of 500-510, but unfortunately the actual m/e value could not be determined with accuracy.

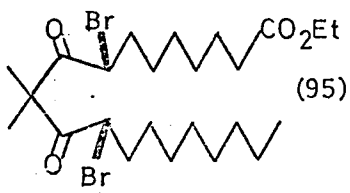
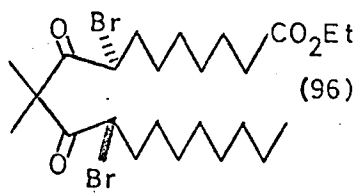
Careful preparative TLC of the diastereomeric mixture afforded two bands containing the partially purified diastereomers (95) and (96), table 6.1. From the ^1H -NMR spectra of these individual bands, we established that the signals at 1.59, 1.61 and 4.54 δ were associated with the low Rf band, while the corresponding signals at 1.56, 1.69 and 4.57 δ were related to the higher Rf band.

The TLC analysis of the crude diastereomeric product (93) showed the low Rf band to be in slight excess of the high Rf band. The relative intensity of the $-\text{CHBr}-$ triplets at 4.54 and 4.57 δ in the ^1H -NMR

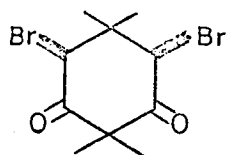
suggested that the ratio was ca. 60:40 (Low Rf : High Rf bands). Subsequent preparative TLC of this mixture, followed by isolation and analysis of the low Rf band material indicated an improved (70:30) diastereomeric composition. A second successive purification of this low Rf band material, however, did not result in any further improvement in purity. This suggested that the low Rf band material was undergoing isomerization at the second successive stage of purification and reverting to the limiting diastereomeric composition of (70:30). Further attempts at separating these diastereomers was therefore abandoned.

A tentative assignment of the ^1H -NMR spectra of the diastereomers of (93) was made on the basis of the molecular symmetry of these species, table 6.1.

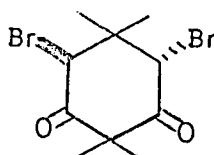
Table 6.1

Diastereomers	Gem-dimethyl at C-10	Bromomethine	TLC
 <p>(95) <u>meso</u>-isomer 40% of mixture</p>	δ 1.56 (s, 3H) δ 1.69 (s, 3H)	δ 4.57 (t, 2H)	High Rf band
 <p>(96) (+,-)-isomer 60% of mixture</p>	δ 1.59 (s, 3H) δ 1.61 (s, 3H)	δ 4.54 (t, 2H)	Low Rf band

The ^1H -NMR spectra of the pure crystalline cis and trans diastereomers (97) and (98) have recently been reported¹⁷⁶.



Cis-diastereomer
(97)



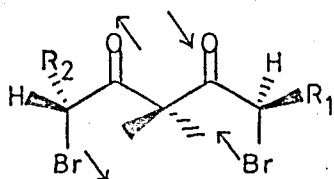
Trans-diastereomer
(98)

It was found that the more symmetric trans-diastereomer (98) showed only two singlets at 1.25 and 1.55 δ for the pair of gem-dimethyl groups. On the other hand, the more complex cis-diastereomer (97) showed a different chemical shift for each of the four methyl groups.

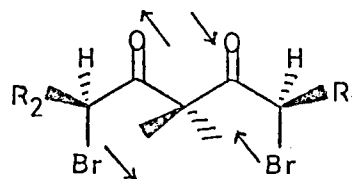
In the case of the alicyclic dibromo-diketo diastereomers (97) and (98), where the respective conformations are relatively well-defined, a more reliable ^1H -NMR assignment of these diastereomers can be made.

However, the same is not true of the acyclic dibromo-diketo diastereomers (95) and (96), where the respective conformational preference resulting from the overall effect of dipole-dipole and steric interactions is unknown. From the observation of molecular models, it is suggested that the preferred conformations of (95) and (96) are likely to resemble those shown in scheme 6.3.

Scheme 6.3



(99)
(+,-)-isomer

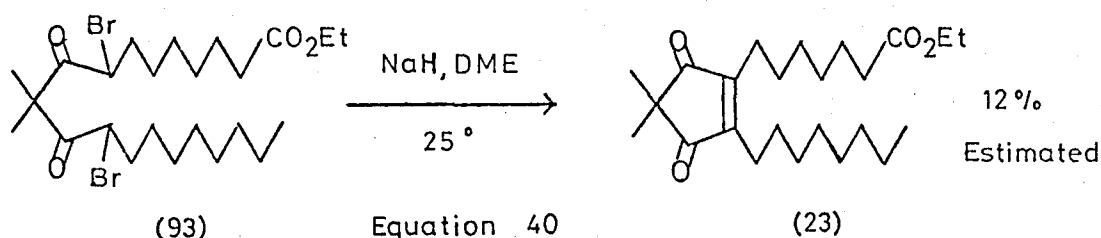


(100)
meso-isomer

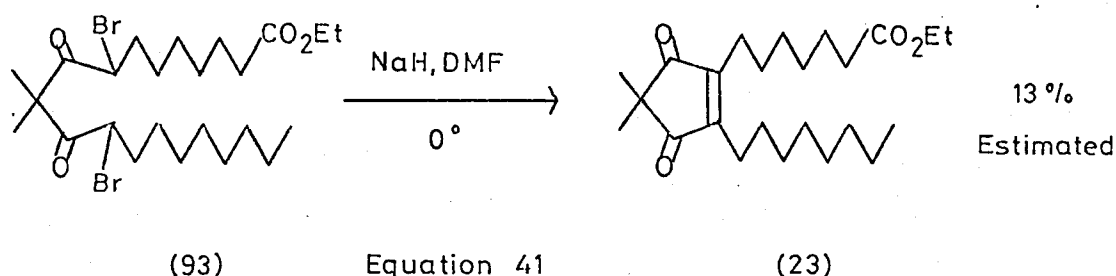
In both these conformations, the carbonyl group is thought to be anti-periplanar to the adjacent bromo-substituent by virtue of their mutual dipole-dipole interaction. In each case, further relief of the dipole-dipole interaction of the 1,3-dicarbonyl system can be brought about by the slight tilting of each carbonyl group away from each other. These resultant conformations, (99) and (100), also appear to suffer relatively less steric crowding as compared with other possible conformations. It must be stressed that these preferred conformations, (99) and (100), are only qualitative models, and therefore, the $^1\text{H-NMR}$ assignment of (95) and (96) based on these conformations must remain conjectural.

For our purpose, the diastereomeric mixtures of (93) and (94) were thought to be less important from the point of view of the proposed C-8, C-12 cyclisation. We, therefore, proceeded to investigate the cyclisation reactions of these compounds.

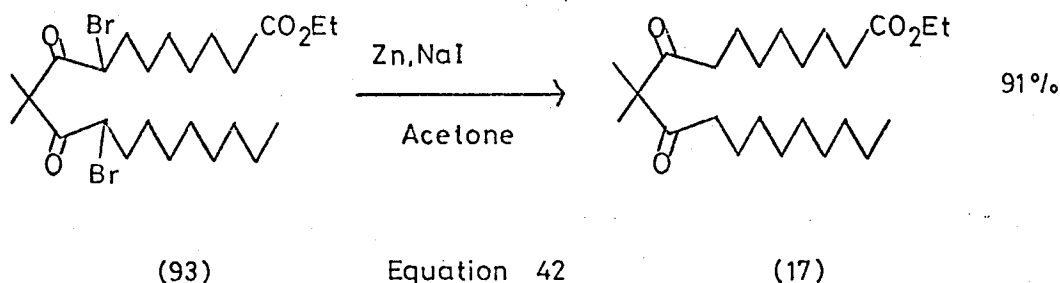
The treatment of the dibromo-ester (93) with sodium hydride in DMF at room temperature, afforded a trace amount of the model prostanoid (23). Several later attempts at optimising the yield of the reaction failed to bring about any significant improvement. The highest estimated yield of the model prostanoid (23) was found to be 12%, equation 40.



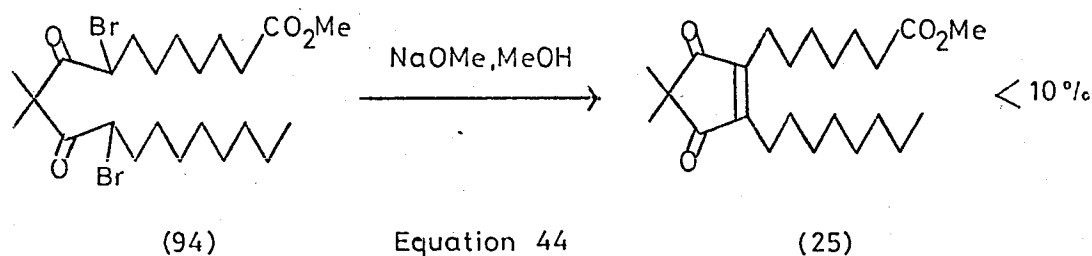
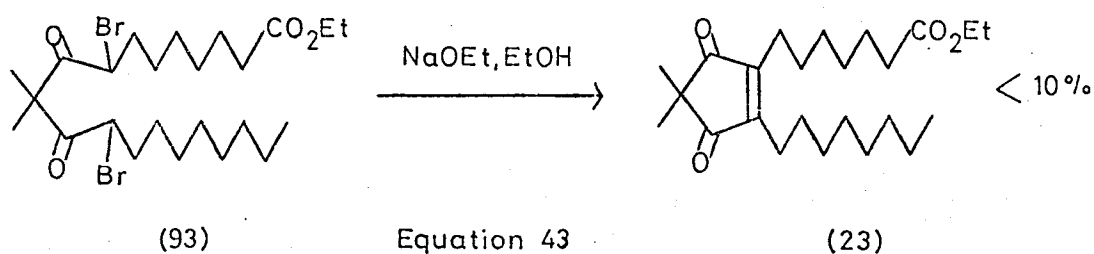
Following the conditions employed by R. N. McDonald et al ¹⁷⁹, equation 35, the dibromo-ester (93) was treated with sodium hydride in DMF at 0°, equation 41. This reaction afforded an estimated 13% yield of the model prostanoic acid (23). The same reaction carried out at room temperature for 18 hours gave a complex mixture of UV active products.



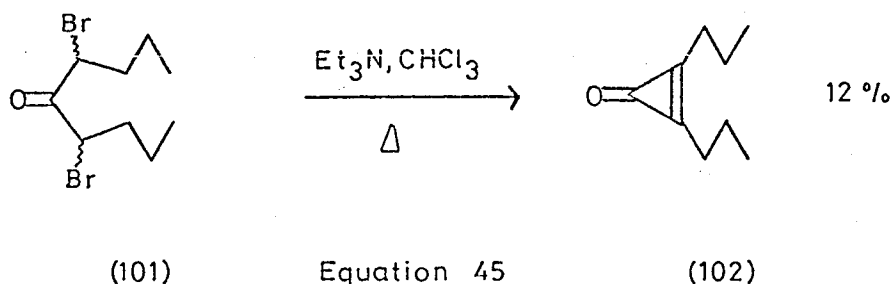
A reductive coupling reaction of the dibromo-ester (93) was carried out in a mixture of zinc dust and sodium iodide in acetone, according to the conditions reported by J. B. Conant et al ¹⁷⁷, equation 33. However, instead of the expected intramolecular C-8, C-12 coupling reaction, the dibromo-ester (93) was cleanly reduced to the dimethyl ester (17) in very high yield, equation 42.



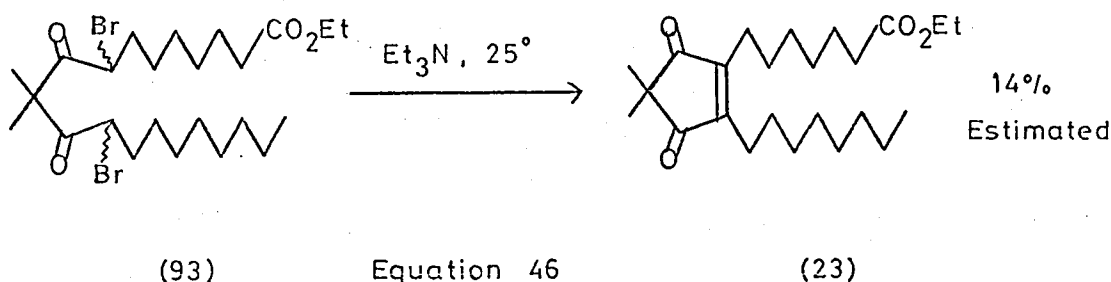
These less successful results led us to examine the prospect of effecting the C-8, C-12 cyclisation by the use of suitable alkoxide bases on the dibromo-esters (93) and (94). It was thought that the increased steric crowding by the α -bromo substituents on the 1,3-diketo moiety would reduce the extent of the competitive retro-Claisen cleavage which was predominant in the reaction of the diketo-ester (17) with sodium ethoxide/iodine. However, this was not the case and both the reactions according to equations 43 and 44 resulted in extensive retro-Claisen cleavage. Only a trace quantity of the respective prostanoids (23) and (25) was obtained in each case.



As before, we proceeded to solve the problem of the retro-Claisen cleavage in these reactions by replacing the alkoxide bases with a less nucleophilic nitrogenous base. Work by R. Breslow et al¹⁸² indicated that a modified Farvoskii type cyclisation could be brought about using a weaker base such as triethylamine, equation 45.

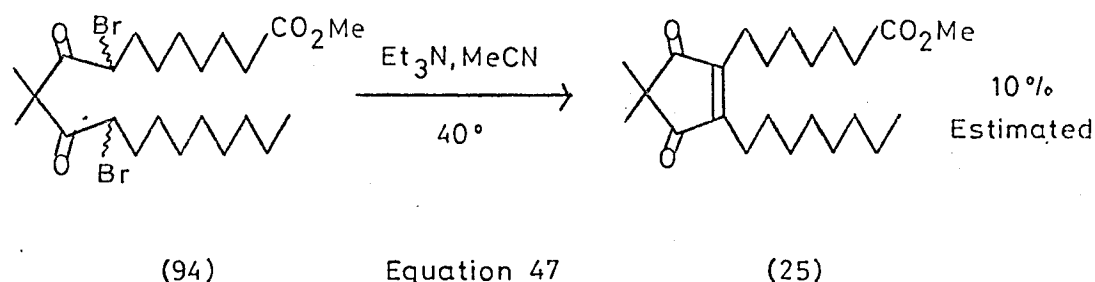


In an early attempt, the dibromo-ester (93) was treated with neat triethylamine at room temperature, equation 46. The resultant crude mixture indicated the presence of UV active products absorbing in the 240-250nm region. Subsequent GLC analysis of the crude indicated an estimated 14% yield of the model prostanooid (23).

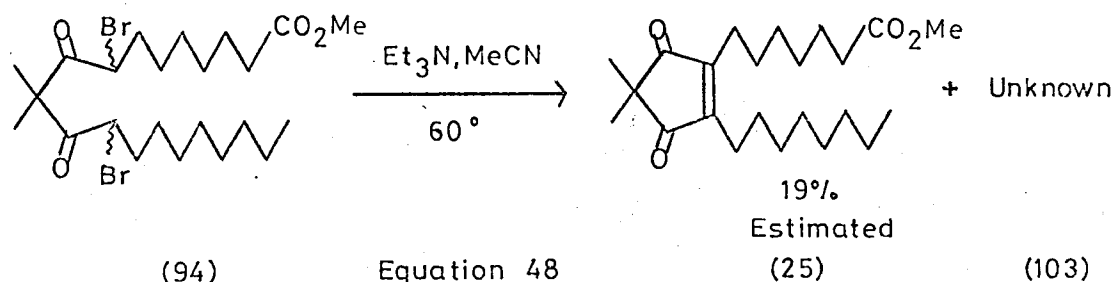


More recently, E. McDonald ¹⁵³ et al reported the cyclisation of 1,5-dibromo-3,3-dimethyl 2,4-pentanedione (91) in triethylamine /MeCN, equation 37. Encouraged by this report and by our earlier findings, we followed up this work and employed a triethylamine/MeCN solvent mixture. Hence, the treatment of the dibromo-ester (94) under the

reaction conditions reported by E. McDonald et al¹⁵³, afforded an estimated 10% yield of the model prostanoid (25), along with a considerable amount of unreacted starting material (94), equation 47.

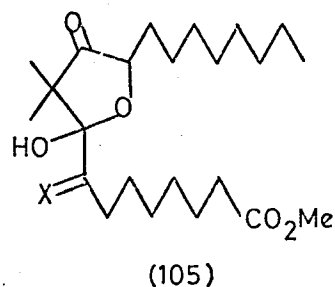
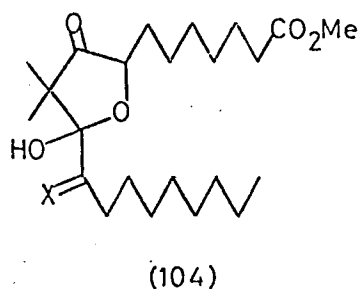


Subsequently, the reaction conditions were improved to afford an estimated 19% yield of the model prostanoid (25) and a major non-UV active product (103), equation 48.



The unknown product (103) was isolated from the crude product mixture as a viscous, colourless oil. The IR spectrum showed characteristic carbonyl bands (1723 , 1740 and 1765cm^{-1}) and a broad hydroxyl band (3440cm^{-1}). The ^1H -NMR spectrum of (103) showed signals at δ 0.89 (t, terminal methyl), 1.02, 1.04, 1.17, 1.18 (4x s, 6H),

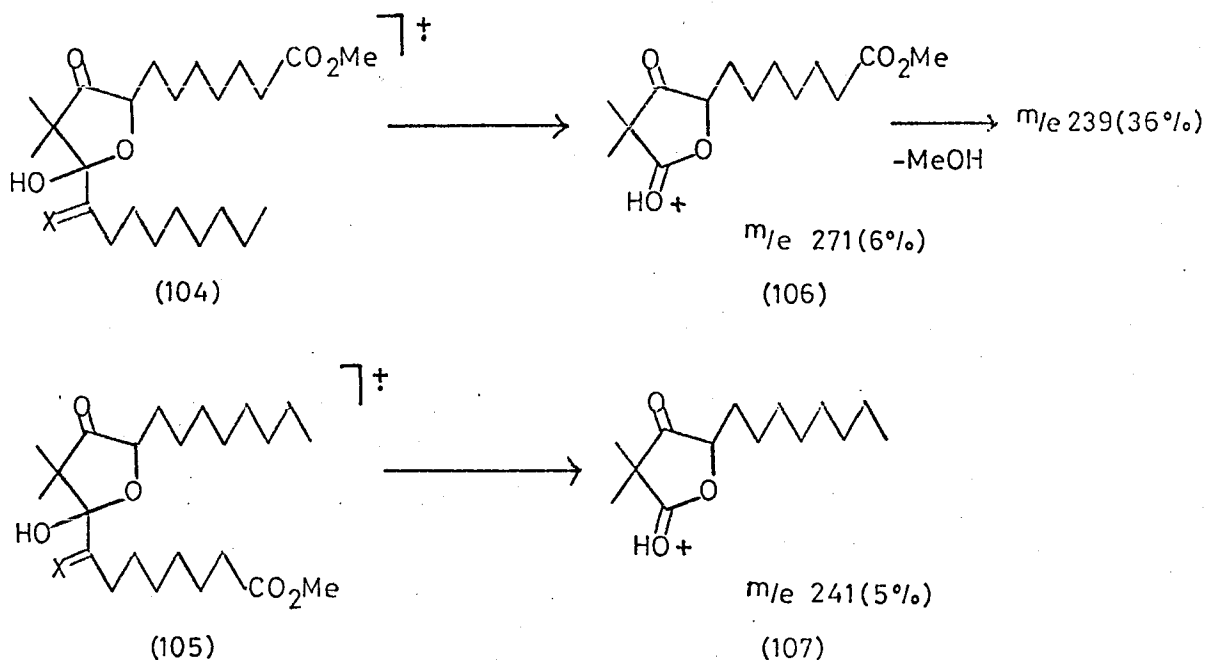
1.25-1.90 (m, methylene envelope), 2.32 (t, $-\text{CH}_2\text{CO}_2\text{Me}$), 2.60-2.93 (m, 2H), 3.67 (s, $\text{O}-\text{CH}_3$) and 4.10-4.39 (m, 1H). The presence of the hydroxyl proton was not obvious and could not be located by D_2O exchange. The accurate mass measurement showed important ions at m/e 271 (6%), 241 (36%), 239 (36%), 171 (35%), 153 (24%), 141 (52%) and 57 (100%). The GLC analysis of (103) was unsatisfactory and although it appeared to be homogeneous on TLC, the spectral data indicated it to be a complex mixture of isomeric cyclic hemi-ketals. These were tentatively assigned the general structures (104) and (105).



where $X = \text{=O}$ (a)
 $= -\text{H}, -\text{OH}$ (b)
 $= -\text{H}, -\text{Br}$ (c)

Although the mass spectrum of the unknown (103) did not show the molecular ion for (104) or (105), the fragment ions provided strong evidence in favour of these proposed structures. The accurate mass measurement of the highest ion at m/e 271 ($\text{C}_{14}\text{H}_{23}\text{O}_5$) and the next highest ion at m/e 241 ($\text{C}_{14}\text{H}_{25}\text{O}_3$) suggested the fragmentation (104) \longrightarrow (106) and (105) \longrightarrow (107) respectively, scheme 6.4

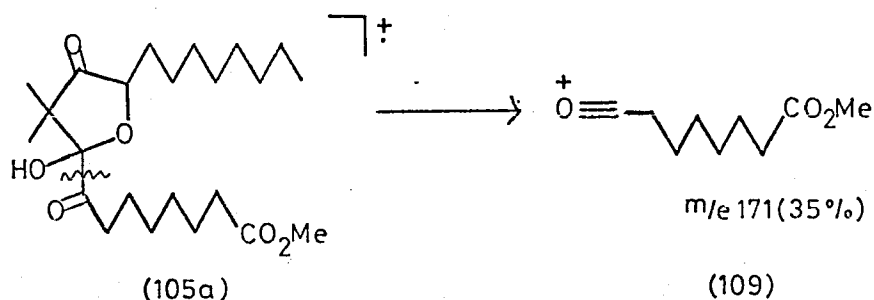
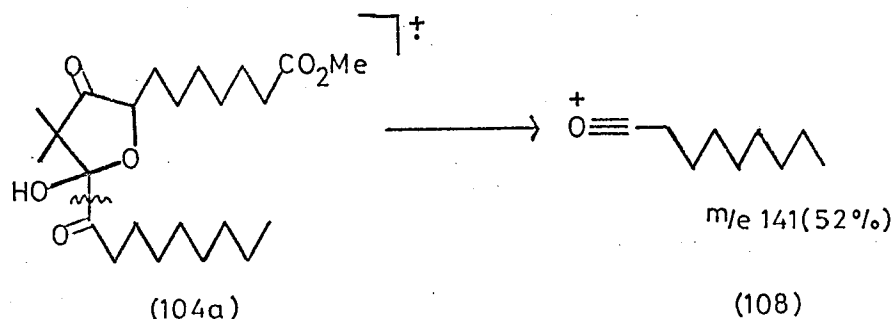
Scheme 6.4



More specifically, the weight of the spectral data of the unknown (103) was in favour of the cyclic hemi-ketal (104a) and (105a). The mass spectrum of the unknown (103) showed strong fragment ions at *m/e* 141 and 171 which suggested the α -cleavage of a ketonic side-chain component as shown in scheme 6.5. The carbonyl bands in the IR spectrum of (103) could now be assigned to the aliphatic α -hydroxyl keto-group (1723cm^{-1}), the ester group (1740cm^{-1}) and the substituted furan-2-one moiety^{184,185} (1765cm^{-1}). The previously unassigned signals in the ¹H-NMR spectrum of (103) could be accounted for by the cyclic hemi-ketals (104a) and (105a). The four singlet signals at δ 1.02, 1.04, 1.17 and 1.18 were assigned to the C-10-gem-dimethyl

protons of (104a) and (105a). The remaining multiplets at δ 2.60-2.92 (m, 2H) and 4.30-4.39 (m, 1H) were assigned respectively to the $-\text{CO}-\text{CH}_2-$ and $-\text{CO}-\text{CH}(\text{O})-\text{CH}_2-$ groups of (104a) and (105a).

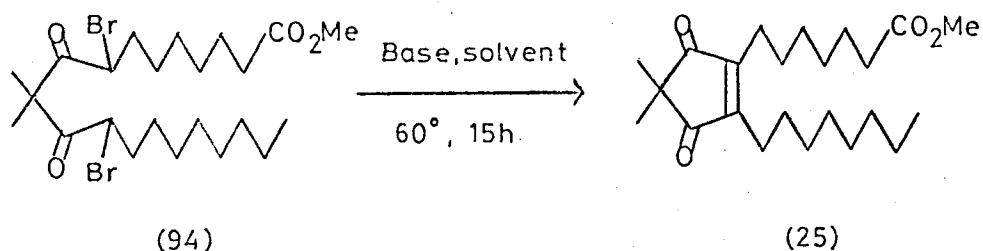
Scheme 6.5



Although the mass spectrum of (103) lacked convincing evidence for species (104b), (104c), (105b) and (105c), we could not on the basis of the spectral data accumulated so far, rule out the presence of these species in the unknown mixture. These species were proposed from a mechanistic consideration of the cyclisation reaction (see section 8).

The cyclisation of the dibromo-ester (94) was briefly investigated to determine other possible combinations of base and solvent. A number

Table 6.2



Base	Solvent	Result
Et_3N	MeCN	Model prostanoid (25) Control (100%)
Pyridine	MeCN	No GLC product.
2,6-lutidine	MeCN	Model prostanoid (25) absent Starting material present
Aniline	MeCN	Model prostanoid (25) absent Unknown (unidentified)
Piperidine	MeCN	Model prostanoid (25) present 60% relative.
Et_3N	DMF	Model prostanoid (25) present, 30% relative.
Et_3N	DMSO	Model prostanoid (25) present, 20% relative.
Et_3N	THF/HMPA	Model prostanoid (25) present, 10% relative.

of comparative experiments were carried out. The results are shown in table 6.2. These reactions were monitored by GLC and the yield of the model prostanoid (25) in each case was estimated against a control reaction.

As shown in table 6.2, all other combinations of base and solvent were found to be inferior to the triethylamine/MeCN mixture (the control). Only the use of piperidine/MeCN gave the model prostanoid (25) in relatively significant quantity. Combinations of MeCN with pyridine, 2,6-lutidine and aniline gave no trace of the model prostanoid (25). However, in the case of the aniline/MeCN combination, the reaction afforded a major unidentified product. In addition, it was also found that the use of triethylamine in different solvents appeared to offer no improvement over the triethylamine/MeCN combination.

7. INVESTIGATION OF THE CYCLISATION OF SIMPLE 1,5-DIALKYL-1,5-DIHALOGENO -3,3-DIMETHYL-PENTA-2,4-DIONES

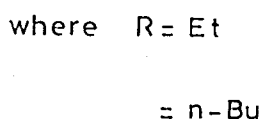
In the preceding section, it was shown that the C-8, C-12 cyclisation of methyl 8,12-dibromo-10,10-dimethyl eicos-9,11-dionoate (94) in triethylamine/MeCN, afforded the model prostanoid (25) and a co-product which was tentatively identified as a mixture of cyclic hemiketals (104a) and (105a). In a related study in this section, we extended this work and examined the triethylamine/MeCN cyclisation reaction in more detail. In order to simplify the investigation, two simple 1,5-dialkyl-1,5-dibromo penta-2,4-diones (131) and (132) were employed as models.

The object of the study was to

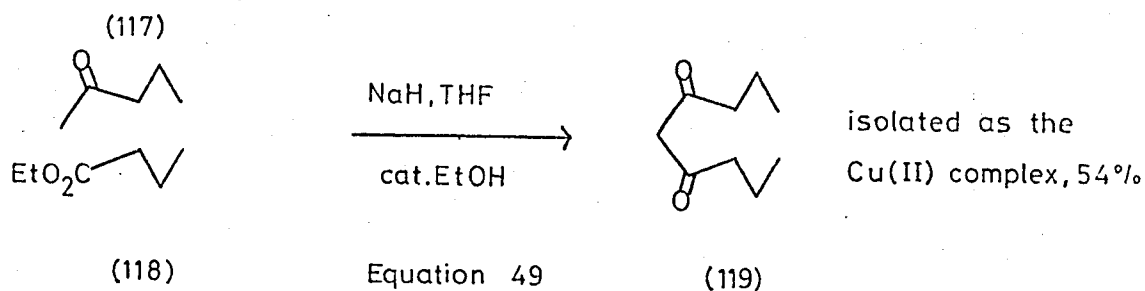
- i) investigate the effect of the side-chain length on the triethylamine/MeCN cyclisation of these dibromo-diketones.
- ii) positively identify the co-product formed in the triethylamine /MeCN cyclisation of these dibromo-diketones.
- iii) obtain UV data on the pure 4,5-dialkyl-2,2-dimethyl cyclopent-4-en-1,3-diones (143) and (147) for comparison with those of the prostanoids.
- iv) investigate the cyclisation of the corresponding diiodo-diketones (137) and (138) in sodium ethoxide/EtOH and triethylamine /MeCN.

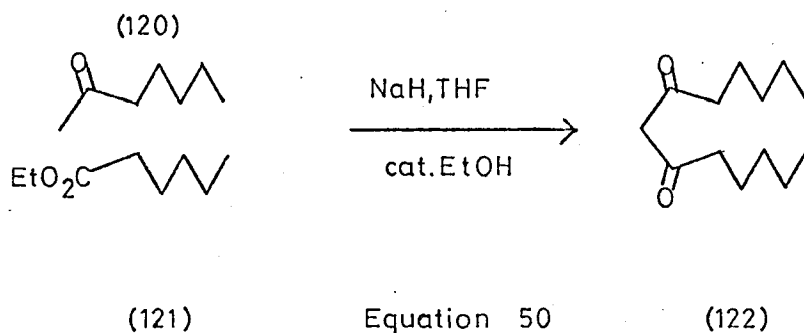
The proposed plan was carried out according to the general scheme 7.1.

Scheme 7.1



The Claisen condensation of 2-pentanone (117) and 2-heptanone (120) with the respective esters (118) and (121), with sodium hydride/THF, in each case afforded the 1,3-diketones (119) and (122), equations 49 and 50. These 1,3-diketones were isolated and purified as their greyish blue crystalline Cu(II) complexes. The acidification of these complexes, followed by extraction into ether and distillation under reduced pressure, in each case, afforded the free 1,3-diketones (119) and (122) as viscous colourless liquids.





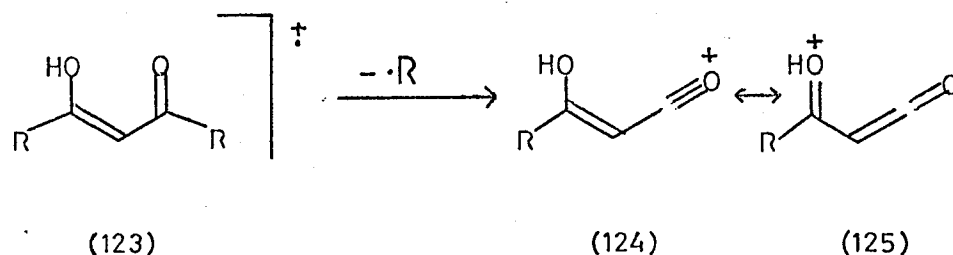
Isolated as the
Cu(II) complex, 72%.

The IR spectra of the enolizable 1,3-diketones (119) and (122) showed the typically broad and strong carbonyl bands at 1610cm^{-1} . The $^1\text{H-NMR}$ spectrum of the 1,3-diketone (119) showed typical signals at δ 0.98 (t, terminal methyls), 1.43-1.94 (sextet, 4H), 2.30, 2.53 (2 x t, methylenes at C-3 and C-7), 3.58 (s, $-\text{CO}-\text{CH}_2-\text{CO}-$) and 5.51 (s, $\text{CO}-\text{CH}=\text{C}(\text{OH})-$). The $^1\text{H-NMR}$ spectrum of (122) displayed a pattern similar to that of (119) with typical signals at δ 0.89 (t, terminal methyls), 1.13-1.84 (m, methylene envelope), 2.28, 2.51 (2 x t, methylenes at C-5 and C-9), 3.56 (s, $-\text{CO}-\text{CH}_2-\text{CO}-$) and 5.48 (s, $\text{CO}-\text{CH}=\text{C}(\text{OH})-$). In each case, the ratio of the enol-to keto-tautomers as determined from the relative intensity of the peaks at about δ 5.50 and 3.60 was found to be (8:1) for (119) and (6:1) for (122); thereby indicating a slightly higher enolic content for the short side-chain 1,3-diketone (119).

The low resolution mass spectra of (119) and (122) showed the respective molecular ions at m/e 156 (21%) and m/e 212 (13%). In each case, extensive α -cleavage of the 1,3-diketone, with loss of an alkyl radical ($\cdot\text{R}$), gave a resonance stabilized fragment ion of the

type (124) as the base peak, scheme 7.2.

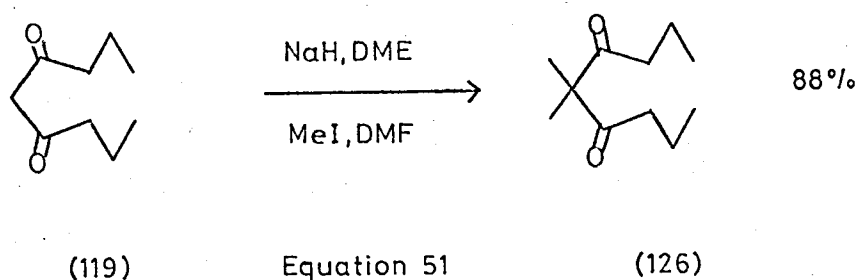
Scheme 7.2

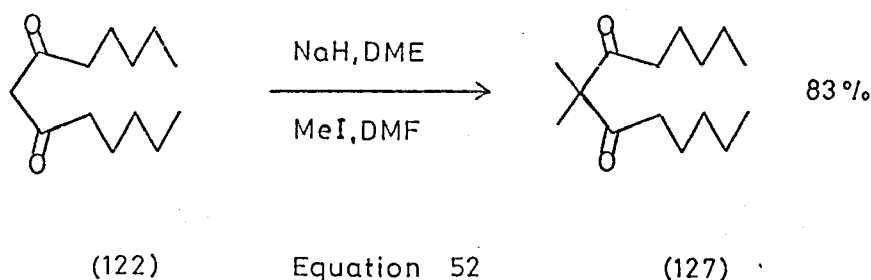


where R = n-propyl
= n-pentyl

This fragmentation pattern has been found to be typical of tautomeric 1,3-diketones with high enolic content¹⁸³. Further structural evidence for (119) and (122) was obtained from their ¹³C-NMR spectra (see Appendix).

In each case, the dimethylation of the 1,3-diketones (119) and (122) afforded good yields of the respective crude dimethyl 1,3-diketones (126) and (127), equations 50 and 51. Further purification of the respective crude products by distillation under reduced pressure afforded > 80% of pure dimethyl 1,3-diketones (126) and (127).



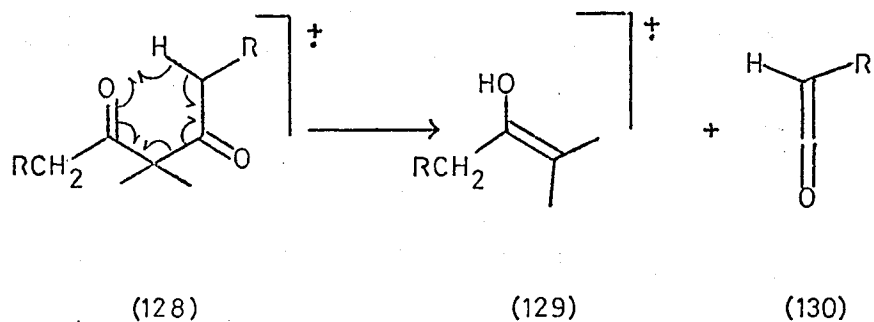


The IR spectra of these dimethyl 1,3-diketones (126) and (127) showed distinct carbonyl bands at 1698(s) and 1718(m) cm^{-1} . The $^1\text{H-NMR}$ spectrum of (126) showed characteristic peaks at δ 0.90 (t, terminal methyls), 1.35 (s, gem-dimethyl at C-5), 1.40-1.85 (sextet, methylenes at C-2 and C-8) and 2.41 (t, methylenes at C-3 and C-7). The $^1\text{H-NMR}$ spectrum of (127) showed signals at δ 0.90 (t, terminal methyls), 1.03-1.80 (m, methylene envelope), 1.35 (s, gem-dimethyl at C-7) and 2.41 (t, methylenes at C-5 and C-9). The high resolution mass spectra of the dimethyl 1,3-diketones (126) and (127) did not show their respective molecular ions. However, a major fragment ion of the type (129), derived in each case from the McLafferty rearrangement of the molecular ion with the expulsion of a neutral ketene species (130) was observed, scheme 7.3. This mode of fragmentation of (126) and (127) produced the respective daughter ions at m/e 114 (90%) and m/e 142 (100%).

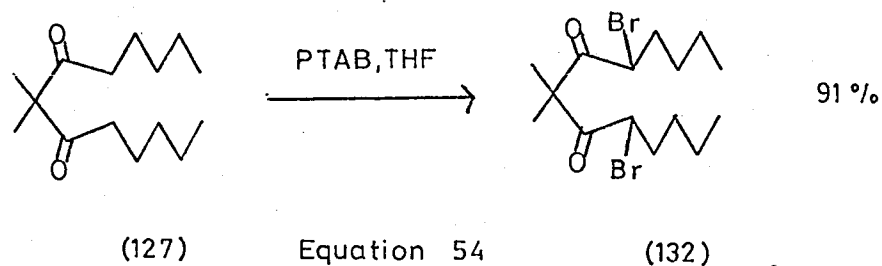
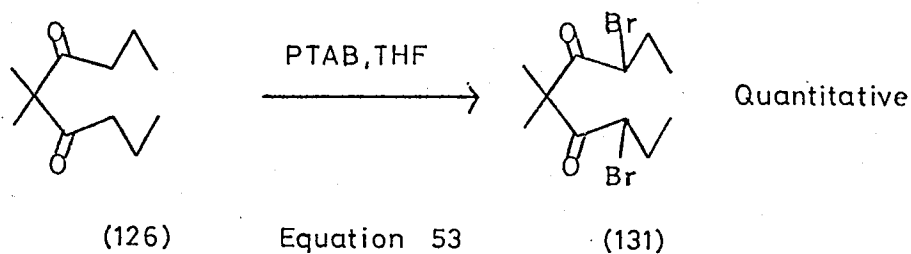
In each case, the bromination of the dimethyl 1,3-diketones (126) and (127) with phenyltrimethylammonium perbromide in THF, afforded the respective crude dibromo-1,3-diketones (131) and (132), equations 53 and 54. Purification of the crude products by column chromatography gave high yield of (131) and (132) as viscous

lachrymatory pale yellow oils.

Scheme 7.3



where $\text{R} = \text{Et}$
 $= \text{n-Bu}$

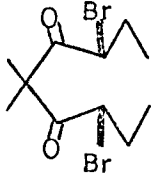
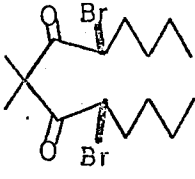
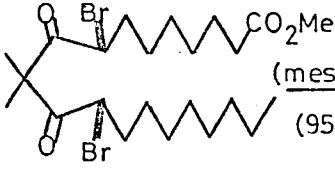
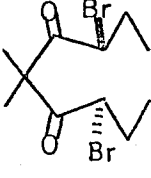
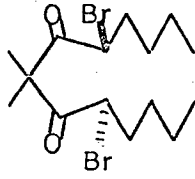
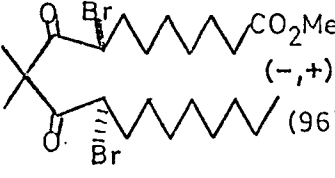


The IR spectra of (131) and (132) showed characteristic carbonyl bands at $1728(\text{s})$ and $1699(\text{s}) \text{ cm}^{-1}$. Examination of the ^1H -NMR spectra of (131) and (132) revealed, in each case, the presence of diastereomers.

The ^1H -NMR spectrum of (131) showed distinct signals at δ 1.00, 1.03 (2xt, terminal methyls), 1.56, 1.61 and 1.69 (3xs, gem-dimethyls at C-5), 2.02 (quintet, methylenes at C-2 and C-8), 4.50 and 4.54 (2xt, $-\text{CH}_2-\text{CHBr}-\text{CO}-$). The ^1H -NMR spectrum of (132) was less distinct and showed peaks at δ 0.92 (t, terminal methyls), 1.06-1.52 (m, methylene envelope), 1.56, 1.61, 1.69 (3xs, gem-dimethyl at C-7), 1.79-2.25 (m, methylenes at C-4 and C-10), 4.55 and 4.58 (2xt, $-\text{CH}_2-\text{CHBr}-\text{CO}-$). A tentative assignment of the ^1H -NMR spectra, with respect to the diastereomers, was made on the basis of the relative intensity of the 'paired' peaks and on molecular symmetry argument referred to in section 6. Table 7.1 shows the ^1H -NMR assignment of the diastereomers of (131) and (132) in comparison with those of ethyl 8,12-dibromo-10,10-dimethyl eicos-9,11-dienoate (93).

As shown on table 7.1, the gem-dimethyl signal for the (+, -) diastereomers (135) and (136) appeared as a sharp singlet at 1.61 δ . However, the corresponding gem-dimethyl signal of the (+, -) diastereomer (96) appeared as two equal intensity singlets at 1.59 and 1.61 δ . This slight separation of the C-10 gem-dimethyl signal was attributed to the unsymmetric nature of the side-chains attached to the C-8 and C-12 positions of (96). In the case of the meso-diastereomers (133), (134), and (95), all the gem-dimethyl signals appeared as two equal intensity singlets at identical chemical shift values of 1.56 and 1.69 δ . The bromo-methine signals of the (+, -) diastereomers (136) and (96) appeared at 4.54 δ (triplet), however, the shorter side-chain congener (135) showed an upfield shift of this signal to 4.50 δ (triplet). In addition, the two terminal methyl groups

Table 7.1 ^1H -NMR assignment of Pertinent Signals (δ)

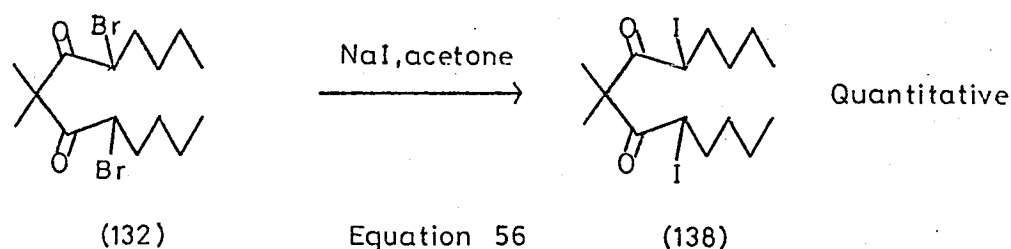
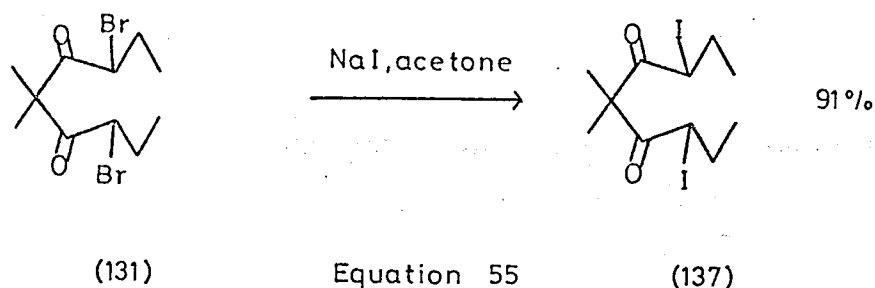
DIASTEREOMERS	Terminal Me	$(\text{CH}_3)_2\text{C}$	$\text{CHBr}-\text{CH}_2$	$-\text{CHBr}$
 (meso) (133)	1.03(t)	1.56(s) 1.69(s)	2.03(quin)	4.54(t)
 (meso) (134)	0.92(t)	1.56(s) 1.69(s)	1.79-2.25(m)	4.57(t)
 (meso) (95)	0.88(t)	1.56(s) 1.69(s)	1.80-2.15(m)	4.57(t)
 $(-,+)$ (135)	1.00(t)	1.61(s)	2.30(quin.)	4.50(t)
 $(-,+)$ (136)	0.92(t)	1.61(s)	1.79-2.25(m)	4.54(t)
 $(-,+)$ (96)	0.88(t)	1.59(s) 1.61(s)	1.80-2.15(m)	4.54(t)

of the short side-chain dibromo-diketone (131) appeared as two triplets at 1.00 and 1.03 δ , these were assigned respectively to the (+, -) and meso-diastereomers (135) and (133).

In addition, the relative intensities of the diastereomeric pairs of triplets assigned to the bromo-methine and terminal methyl groups of (131) indicated a (50:50) mixture of the (+, -) and meso-diastereomers. However, in the case of (132), the relative intensities of the diastereomeric pair of triplets assigned to the bromo-methine groups suggested a (60:40) mixture of the (+, -) and meso-diastereomers. This diastereomeric composition compared more favourably with the diastereomeric ratio (60:40, (+, -): meso) found for ethyl 8,12-dibromo-10,10-dimethyl eicos-9,11-dienoate (93).

As expected, the low resolution mass spectra of (131) and (132) did not show the respective molecular ions. However, in each case, the highest fragment ion was characterised by an equal intensity doublet due to the isotopic $[M-Br]^+$ (16-18%) species.

Treatment of the dibromo-1,3-diketones (131) and (132) with sodium iodide in dry acetone, in each case, afforded the respective diiodo-1,3-diketones (137) and (138), equations 55 and 56. These diiodo-1,3-diketones were thermally unstable and darkened from a pale yellow to a reddish brown viscous liquid when left at room temperature for extended periods. In view of this, (137) and (138) were only prepared from the more stable dibromo-diketone precursors when required and used immediately in subsequent reactions.

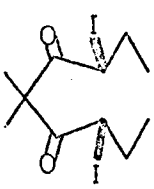
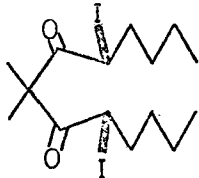
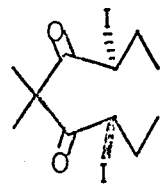
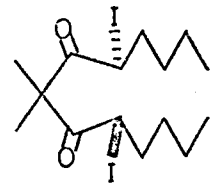


The IR spectra of (137) and (138) showed characteristic carbonyl bands at 1688 and 1719 cm^{-1} . In the case of (138), an additional weak band at 1620 cm^{-1} indicated the presence of dehydroiodination contaminants. The ^1H -NMR spectrum of (137) showed typical peaks at δ 0.98, 1.01 (2xt, terminal methyls), 1.67, 1.73, 1.80 (3xs, gem-dimethyl at C-5), 1.73-2.30 (quintet, methylenes at C-2 and C-8), 4.65 and 4.70 (2xt, $-\text{CH}_2-\text{CHI}-\text{CO}-$). The ^1H -NMR spectrum of (138) showed comparable signals at δ 0.93 (t, terminal methyls), 1.09-1.60 (m, methylene envelope), 1.67, 1.72, 1.80 (3xs, gem-dimethyl at C-7), 1.74-2.14 (m, methylenes at C-4 and C-10), 4.71 and 4.76 (2xt, $-\text{CH}_2-\text{CHI}-\text{CO}-$).

Table 7.2 shows the tentative assignment of the ^1H -NMR spectra of the diastereomeric mixtures (137) and (138).

Table 7.2

$^1\text{H-NMR}(\delta)$ assignment of (meso) and (+,-) diastereomers of (137) and (138)

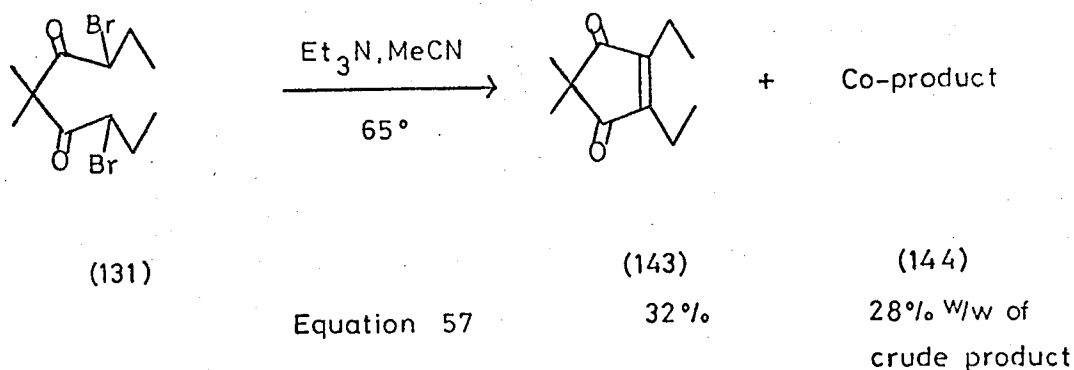
Diastereomer	Terminal methyls	$(\text{CH}_3)_2\text{C}$	$-\text{CH}_2\text{-CHI-}$ $-\text{CHI-CH}_2-$
 (meso) (139)	1.01	1.67 1.80	1.73-2.20 4.70
 (meso) (140)	0.93	1.67 1.80	1.74-2.14 , 4.76
 (-,+) (141)	0.98	1.73	1.73-2.20 4.65
 (-,+) (142)	0.93	1.72	1.74-2.14 , 4.71

In comparison with their respective dibromo-1,3-diketone precursors (131) and (132), the diiodo-1,3-diketones (137) and (138) showed a relative downfield shift of the CHI (ca. 0.15-0.17ppm) and the gem-dimethyl (ca. 0.11-0.21ppm) signals, while the rest of the signals showed a slight upfield shift (0.02-0.04ppm). In both cases, the (+,-)/(meso) diastereomeric ratio of (137) and (138) as determined from the relative intensities of the two ($-\text{CHI}-\text{CO}-$) triplets was found to be (70:30).

As with the dibromo-1,3-diketones, (137) and (138) lacked the respective molecular ions. The highest fragment ion detected in each was the $[\text{M}-\text{I}]^+$ species.

With the dibromo-diketones (131), (132) and the diiodo-derivatives (137), (138) in hand, we proceeded with the planned investigation of the cyclisation of these compounds in triethylamine/MeCN.

Hence the cyclisation of the diastereomeric mixture of (131) in triethylamine/MeCN at 65° , followed by preparative TLC, afforded the expected 4,5-diethyl-2,2-dimethyl cyclopent-4-en-1,3-dione (143) and the corresponding unknown co-product (144), equation 57.



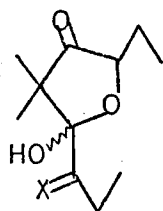
The IR spectrum of (143) showed characteristic carbonyl bands

(1741(m), 1693(s), 1630(m) cm^{-1}) attributed to the cyclopentene-1,3-dione moiety. The ^1H -NMR spectrum of (143) showed typical peaks at δ 1.14, 1.14 (s and t, 12H) and 2.52 (t, 4H). The overlapping singlet and triplet at 1.14 δ were assigned to the gem-dimethyl (singlet at 1.14 δ) and the terminal methyl (triplet at 1.14 δ) protons. The UV spectrum of (143) indicated an absorption band at λ_{max} 245nm, ϵ = 8,670 and accurate mass measurement gave the molecular ion $[\text{M}]^+$ (4%) (measured 180.1141, calculated 180.1132). Further confirmation of the structure of (143) was obtained from its simple ^{13}C -NMR spectrum which showed six peaks; two of which were in the lowfield sp^2 carbon region while the remaining four were in the highfield sp^3 carbon region (see Appendix).

The co-product (144) was isolated as a viscous colourless oil. It was homogeneous on TLC and GLC, and appeared to be non-UV active on silica gel, HF_{254} . The IR spectrum of (144) showed typical hydroxyl band (3450cm^{-1}), carbonyl bands (1764 and 1726cm^{-1}) and C-O bands (1098 and 1045cm^{-1}). The ^1H -NMR spectrum of (144) showed complex sets of multiplet at δ 0.93-1.28 (m, terminal methyls and gem-dimethyl), 1.58-2.12 (m, 4H), 2.62-3.07 (m, 2H) and 3.90-4.52 (m, 2H, one D_2O exchangeable proton). The accurate mass spectrum of (144) indicated the absence of bromine and important fragment ions appeared at m/e 157, $\text{C}_8\text{H}_{13}\text{O}_3$ (51%), 115, $\text{C}_5\text{H}_7\text{O}_3$ (46%), 112, $\text{C}_7\text{H}_{12}\text{O}$ (25%), 87, $\text{C}_4\text{H}_7\text{O}_2$ (69%), 71, $\text{C}_4\text{H}_7\text{O}$ (24%), 70, $\text{C}_4\text{H}_6\text{O}$ (62%), 69, $\text{C}_4\text{H}_5\text{O}$ (100%), and 57, $\text{C}_3\text{H}_5\text{O}$ (38%).

These spectral data seemed to support the earlier supposition that the unknown was a complex isomeric mixture of the cyclic hemiketal (145). However, in this instance, the bromo species (145c) was ruled

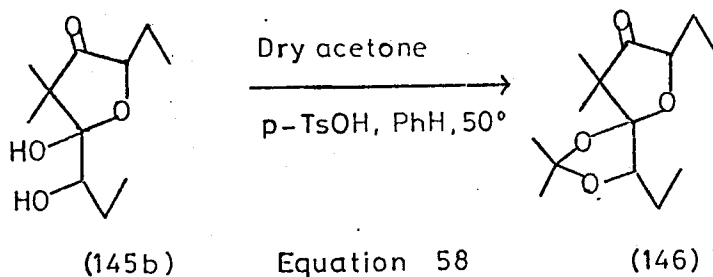
out by the mass spectral evidence (no Br^+ or HBr^+ species detected).



(145)

where $\text{X} = \text{C}=\text{O}$ (a)
 $= -\text{H}, -\text{OH}$ (b)
 $= -\text{H}, -\text{Br}$ (c)

In a separate experiment, an attempt was made to prepare the cyclic isopropylidene derivative of (145b), by treatment of the co-product (145) with dry acetone and a catalytic amount of p-TsOH¹⁸⁰, equation 58. This was unsuccessful. Although all of the co-product (144) was consumed in the reaction, it was evident from the TLC, ^1H -NMR and IR spectra that the crude product was a complex mixture of α,β -unsaturated ketones, hydroxy-ketones and contained only an insignificant amount of the anticipated cyclic isopropylidene derivative (146).



(145b)

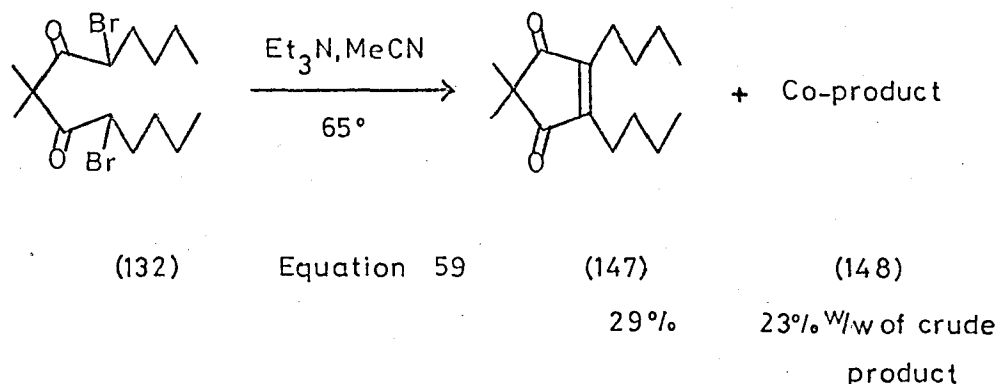
Equation 58

(146)

Due to the complex nature of the ^1H -NMR spectrum of the co-product (144), a more detail structure elucidation was left to a later stage when the homologous co-product (148) from the triethylamine/MeCN cyclisation of (132) was obtained.

The cyclisation of the dibromo-1,3-diketone (132) in triethylamine/

Me/CN at 65^o, followed by preparative TLC, afforded 4,5-dibutyl-2,2-dimethyl cyclopent-2-en-1,3-dione (147) and the co-product (148), equation 59.

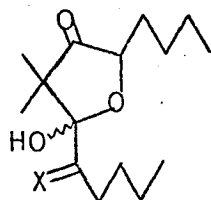


The IR spectrum of (147) showed characteristic carbonyl bands (1741(w), 1697(s) and 1627(w) cm⁻¹) attributed to the cyclopentene-1,3-dione moiety. The ¹H-NMR spectrum of (147) showed typical peaks at δ 0.94 (t, terminal methyls), 1.12 (s, gem-dimethyl), 1.21-1.72 (m, methylene envelope) and 2.47 (t, 4H). An extensively purified sample of (147) indicated an intense UV absorption band at λ_{max} 249nm, ϵ =11,260. The high resolution mass spectrum of (147) indicated the presence of the molecular ion [M]⁺ (9%) (measured 236.1776, calculated 236.1776). Further confirmation of the structure of (147) was obtained from the ¹³C-NMR spectrum which showed eight peaks; two of which were in the lowfield sp² carbon region while the remaining six were in the highfield sp³ carbon region (see Appendix).

The IR spectrum of the co-product (148) showed characteristic hydroxyl band (3430 cm⁻¹), carbonyl bands (1762 and 1720 cm⁻¹) and C-O bands (1101 and 1045 cm⁻¹). The ¹H-NMR spectrum of (148) showed typical peaks at δ 0.94 (t, terminal methyls), 1.01, 1.18 (2xs, gem-

dimethyl), 1.26-2.00 (m, methylene envelope), 2.61-2.94 (m, 2H), 3.49-4.05 (broad s, D₂O exchangeable proton) and 4.10-4.45 (m, 1H). At higher resolution, the multiplet at 2.61-2.94 and 4.10-4.45 δ appeared, in each case, as a pair of overlapping triplets ($J = 8\text{Hz}$). These triplets were broad and their coupling pattern was not well-defined. The high resolution mass spectrum of (148) showed the presence of isotopic bromo-species $[(149c)-OH]^+$ at m/e 320 ($C_{14}^{13}C, H_{26}O_2^{81}Br$), 319 ($C_{15}H_{26}O_2^{81}Br$), 318 ($C_{14}^{13}C, H_{26}O_2^{79}Br$) and 317 ($C_{15}H_{26}O_2^{79}Br$) in low relative abundance. High intensity fragment ions appeared at m/e 185(97%), 167(39%), 115(63%), 97(100%), 87(76%), and 85(58%).

The spectral data for (148) appeared to be consistent with the proposed general structure (149). However, in this case, the co-product (148) appeared to be diastereomeric mixture of (149a) contaminated with (149c).

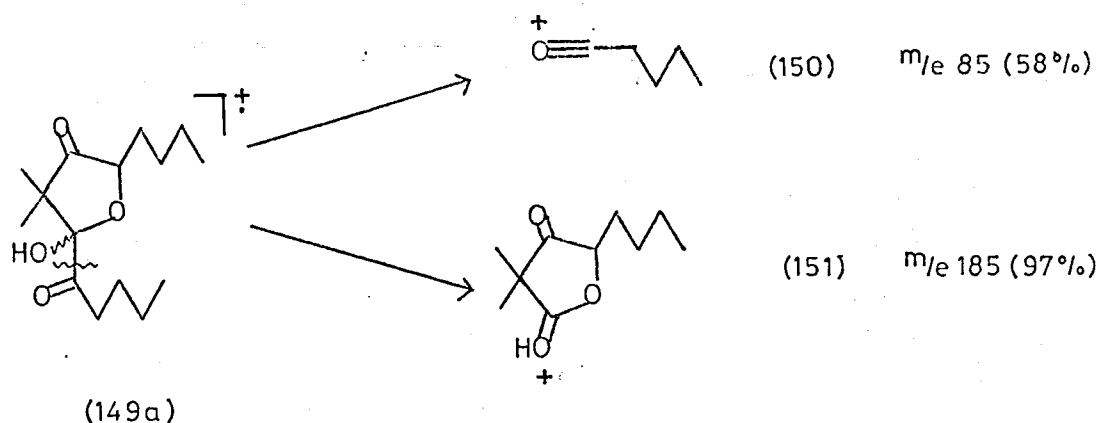


(149)

- where X = $\equiv O$ (a)
 = $-OH, -H$ (b)
 = $-Br, -H$ (c)

The presence of (149c) was inferred from the accurate mass measurement of the four isotopic ions from the $[(149c)-OH]^+$ species and the fragment ion $[(149c)-HBr]^+$ at m/e 254 (11%). Although the molecular ion for the proposed species (147a) was not detected, the appearance of strong daughter ions at m/e 185(97%) and 85(58%) was consistent with the anticipated breakdown of (149a), scheme 7.4.

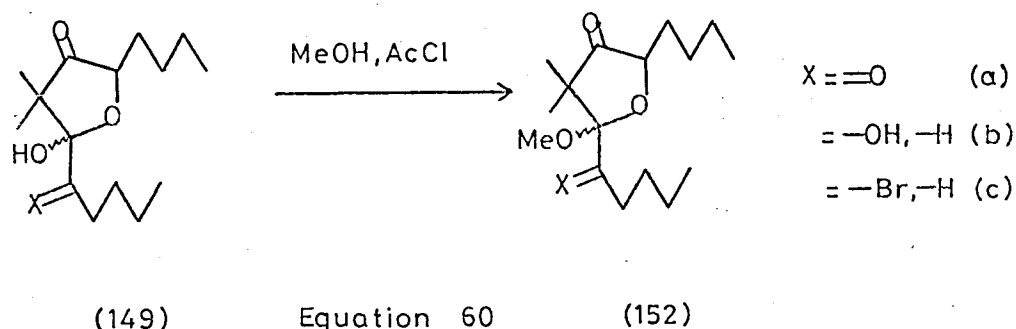
Scheme 7.4



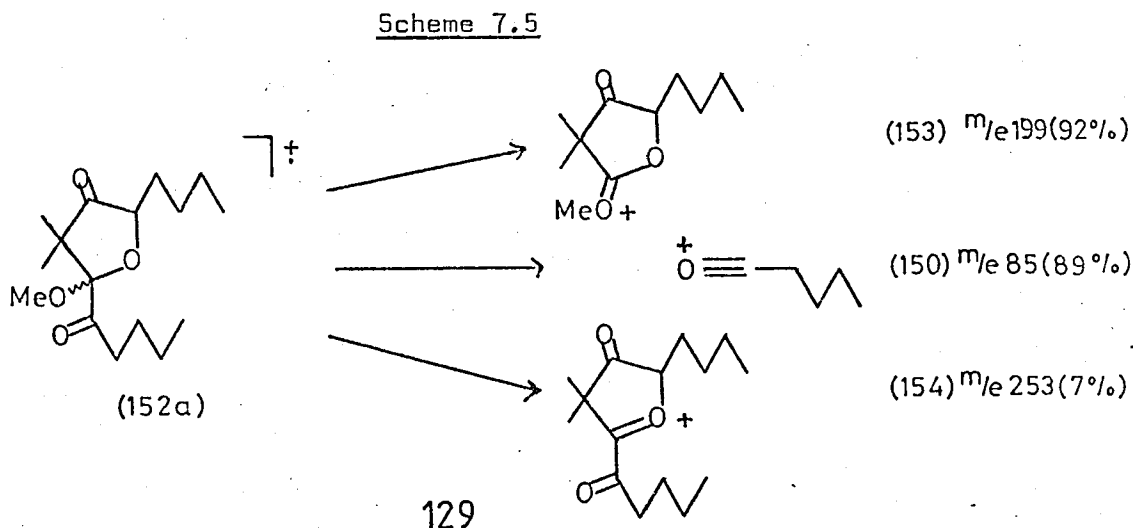
The α -cleavage of (149a) results in two daughter ions (150) and (151), with charge retention predominantly on the latter resonance stabilized species.

The ¹H-NMR spectrum of (148) supported the supposition that the co-product consisted mainly of (149a) and the multiplets at δ 2.61-2.94 (2xt,2H) and 4.10-4.45 (2xt,1H) were tentatively assigned to (-CH₂-CH₂-CO-C(O)-O-) and (-CH₂-CH(CO)-O-) respectively. The minor contamination by the bromo-species (149c) would not be apparent as the (-CH₂-CH(Br)-C-) triplet would be obscured within the multiplet at δ 4.10-4.45. The IR spectrum of (148) was also consistent with the proposed structure (147a); with the aliphatic and furan-2-one^{184,185} type carbonyl bands at 1720 and 1764cm⁻¹ respectively.

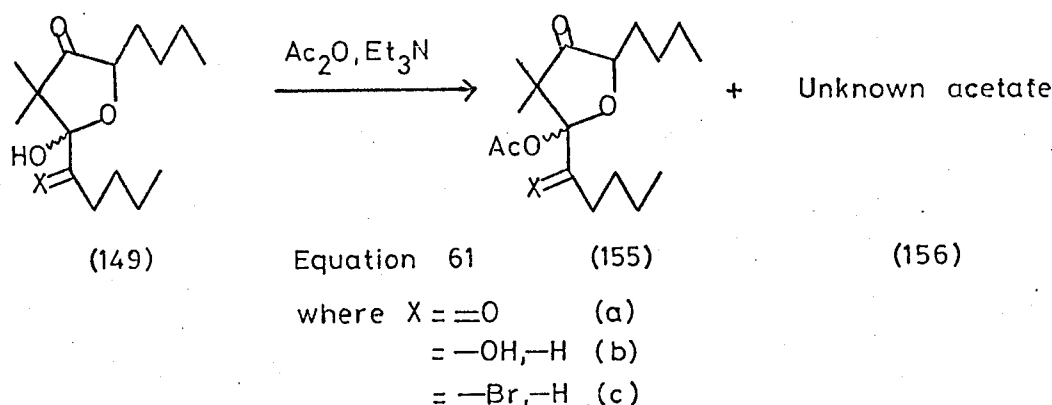
Further proof of the proposed cyclic hemiketal structure (149a) came from the formation of the cyclic methyl ketal (152a) when the co-product (148) was treated with anhydrous MeOH and a catalytic amount of HCl, equation 60.



The IR spectrum of (152a) showed the disappearance of the precursor hydroxyl band and the presence of sharp bands due to the carbonyl (1766 and 1725 cm^{-1}) and C-O (1116 , 1074 and 1032 cm^{-1}) groups. The $^1\text{H-NMR}$ spectrum of (152a) showed characteristic peaks at δ 0.94, 0.94 (s and t, 9H), 1.19 (s, 3H), 1.10–2.05 (m, methylene envelope), 2.67 (t, $-\text{CH}_2-\text{CO}-$), 3.22 (s, $\text{CH}_3-\text{O}-$), 3.95 (broad t, 1H) and 4.10–4.45 (broad m, <1H). The broad multiplet at δ 4.10–4.45 was suspected to be due to the presence of the bromo-cyclic methyl ketal contaminant. (152c). The low resolution mass spectrum of (152) showed important fragment ions at m/e 279, $[(152c)-\text{Br}]^+$ (9%), 253 $[(152a)-\text{OMe}]^+$ (7%), 199 (92%), 97 (82%) and 85 (89%). The strong fragment ions at m/e 199 and 85 were presumably derived from the α -cleavage of (152a), scheme 7.5.



Acetylation of (149) in acetic anhydride/triethylamine and a catalytic amount of 4-(diethylamino)-pyridine,¹⁸⁹ equation 61, afforded a crude mixture of acetates. By careful repetitive preparative TLC, the mixture was separated into two components. A lower R_f band acetate was isolated as a viscous colourless liquid and identified as the acetate (155a). A marginally higher R_f band afforded a similar quantity of a semi-crystalline unidentified acetate (156).



As expected, the IR spectrum of (155a) in the 1700-1800 cm⁻¹ region remained virtually unchanged. The carbonyl bands appeared at 1760 and 1729 cm⁻¹ and other strong C-O bands (1239, 1109, 1028 and 999 cm⁻¹) were apparent. The ¹H-NMR spectrum of (155a) showed characteristic peaks at δ 0.94 (t, terminal methyls), 1.00, 1.23 (2xs, gem-dimethyl), 1.30-1.40 (m, methylene envelope), 2.04 (s, CH₃CO-), 2.39, 2.60 (d of t, 1H, J_{gem} = 19Hz, J_{vic} = 7.5Hz), 3.13, 3.33 (d of t, 1H, J_{gem} = 19Hz, J_{vic} = 7.5Hz), and 4.12 (t, -CH₂-CH(CO)-O-). The two sets of doublet of triplets were assigned to α-methylene protons (-CH₂-CH₂-CO-). The large chemical shift difference (0.74 ppm) between these geminal protons was attributed to the anisotropy of the neighbouring acetoxy-

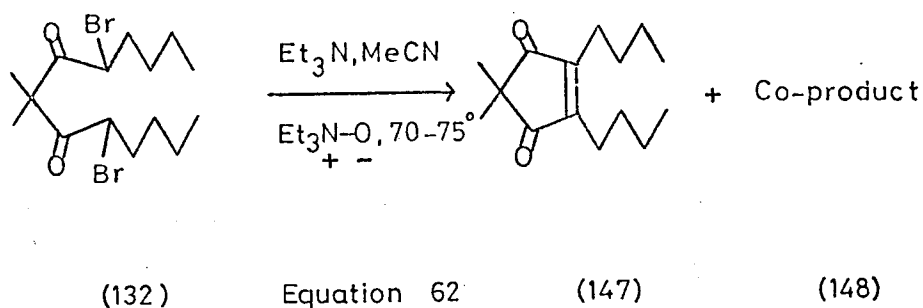
substituent. Each of these methylenic protons showed a very large geminal coupling constant, $J_{\text{gem}} = 19\text{Hz}$ which was further splitted into triplets by a typical vicinal coupling constant, $J_{\text{vic}} = 7.5\text{Hz}$. The high resolution mass spectrum of (155a) did not give the required molecular ion but showed relevant fragment ions at m/e 269, $[\text{M}-\text{CH}_3\text{CO}]^+$ (5%), 253 $[\text{M}-\text{CH}_3\text{CO}_2]^+$ (7%), 227, $[\text{M}-85]^+$ (10%), 185 (98%) and 85 (85%) which were rationalised in terms of the proposed structure (155a). It is noteworthy that the mass spectra of (152a) and (155a) provide strong evidence of the ketonic side-chain in the form of the common fragment ion m/e 253 (also see scheme 7.5).

The unknown acetate (156) was shown by spectral evidence (see experimental) to be a mono-acetate with the alkyl side-chains intact. The ^1H -NMR spectrum displayed two unusual overlapping doublets at δ 4.14 ($J=8\text{Hz}$) and 4.23 ($J=8\text{Hz}$). Decoupling experiment showed that the two doublets were ~~not coupled to each other, but~~ individually coupled to signals at δ 1.60 and 1.75, within the methylene envelope. This could not be rationalised in terms of possible structures related to the ketal acetate (155). Furthermore, its semi-crystalline nature led us to suspect that it was probably still impure.

The presence of the cyclic hemiketal (149a) in the triethylamine/MeCN cyclisation of the dibromo-1,3-diketone (132) was unusual in that one of the carbon bearing the bromo-substituents was over-oxidised in the reaction. Accordingly, the presence of an oxidant or oxidants in the reaction mixture was suspected.

A possible candidate was triethylamine N-oxide which could be a contaminant in triethylamine. The former was prepared by the oxidation of triethylamine with m-chloroperbenzoic acid ¹⁸⁶. A molar

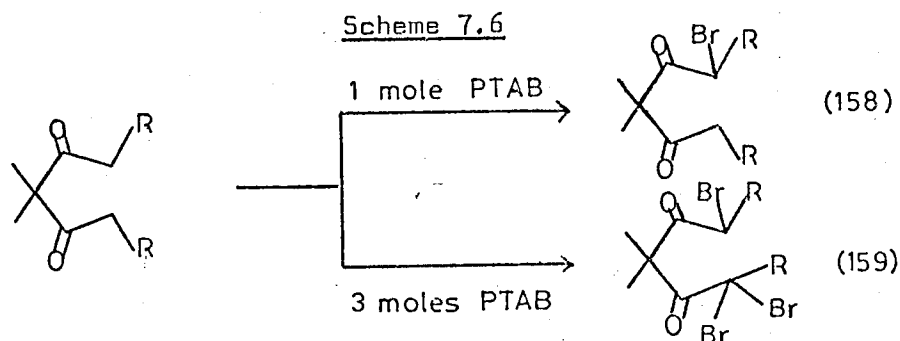
equivalent of triethylamine N-oxide was added to the (132) and the triethylamine/MeCN cyclisation reaction was carried out under the usual conditions, equation 62.



35% estimated

A GLC comparison of the crude product of equation 62 with the crude product of the normal triethylamine/MeCN cyclisation of (132), indicated no significant change in the ratio of the co-product (148) to the dimethyl cyclopentene-1,3-dione product (147).

Another possible explanation for the presence of the over-oxidised product (149a) was the contamination of the dibromo-1,3-diketone precursor (132) by a tribromo-1,3-diketone species of the type (159), scheme 7.6.

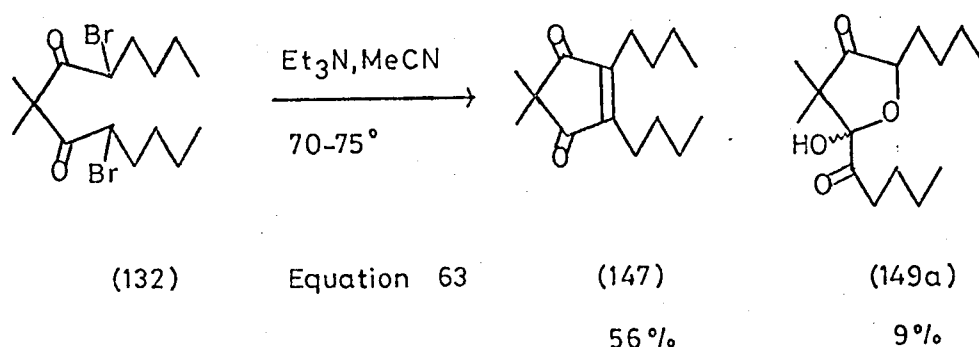


In some early work on the bromination of methyl 10,10-dimethyl eicos

-9,11-dionoate (17) with phenyltrimethylammonium perbromide, we succeeded in preparing the monobromo-species type (158). However, several attempts to prepare the tribromo-species type (159) by using three moles equivalent of phenyltrimethylammonium perbromide consistently failed. This observation, along with correct $^1\text{H-NMR}$ integration obtained for the dibromo-1,3-diketone (132) were incompatible with the significant amount of the cyclic hemiketal (149a) being derived from the tribromo-species (159).

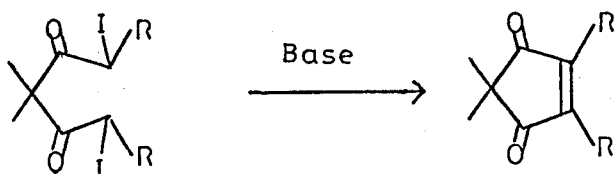
The presence of other oxidants such as oxygen, bromine, or an active source of bromonium species were also anticipated. The latter two oxidants could plausibly be derived from the disproportionation of the dibromo-1,3-diketone (132).

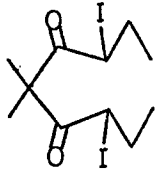
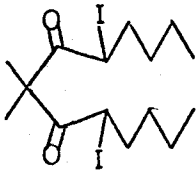
Although the oxidant responsible for the production of the cyclic hemiketal (149a) was not determined, it was subsequently found that the relative amount of (149a) could be reduced considerably by carrying out the reaction under nitrogen, using freshly prepared dibromo-1,3-diketone (132) and anhydrous freshly distilled triethylamine and MeCN. Under these conditions, the cyclisation was eventually optimised and vastly improved, to produce the dimethyl cyclopentene-1,3-dione (147) in 56% and the cyclic hemiketal (149a) in about 9% yield, equation 63.



To complete this series of investigation, we studied the triethylamine/MeCN and sodium ethoxide/EtOH cyclisations of the diiodo-derivatives (137) and (138). The results of this investigation are shown in table 7.3.

Table 7.3



diiodo ketone	Base	%Y	Result
 (137)	Et ₃ N/MeCN	15	Four other products, with large amount of α, β unsaturated ketones.
	2EtO ⁻ /EtOH	16	Retro-Claisen products present
 (138)	Et ₃ N/MeCN	30	Co-product present, suspected to be the cyclic hemiketal (149a)
	2EtO ⁻ /EtOH	24	Two retro-Claisen products present.

As evident from the investigation, the use of the diiodo-1,3-diketones (137) and (138) in the triethylamine/MeCN cyclisation did not result in any vast improvement in the yield of the 4,5-dialkyl 2,2-dimethyl cyclopent-4-en-1,3-dione. It was found that the short

side-chain diiodo-1,3-diketone (137) underwent dehydroiodination to form α,β -unsaturated ketones. This was evident from the $^1\text{H-NMR}$ spectrum of the crude product which showed strong doublets at about $\delta 1.85$ ($J=8\text{Hz}$) assigned to ($\text{CH}_3\text{-CH=C-}$) and multiplets in the $\delta 5.90\text{-}7.40$ region (vinylic protons of α,β -unsaturated ketone). In contrast, the crude product of the triethylamine/MeCN cyclisation of the longer side-chain diiodo-1,3-diketone (138) showed a distinct lack of α,β -unsaturated ketones and the presence of a co-product (17% w/w of crude product) suspected to be the cyclic hemiketal (149a).

The sodium ethoxide/EtOH cyclisation of the diiodo-1,3-diketones (137) and (138) afforded a comparatively lower yield of the respective 4,5-dialkyl-2,2-dimethyl cyclopent-4-en-1,3-dione. The cyclisation of (137) was a poor reaction. Six by-products were detected by GLC and four of these were presumed to be retro-Claisen cleavage products. It was also apparent from the $^1\text{H-NMR}$ spectrum of the crude product mixture that α -ethoxy ketones/esters were present. However, no α,β -unsaturated ketones/esters were detected. The cyclisation of (138) was a much cleaner reaction. Two major retro-Claisen cleavage products and two minor by-products were evident from the GLC analysis of the crude product mixture. The $^1\text{H-NMR}$ spectrum of the crude product mixture also showed the presence of ethyl ester and α -ethoxy ketones/esters but lacked evidence of α,β -unsaturated ketones/esters.

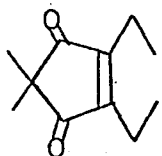
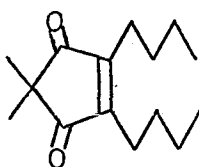
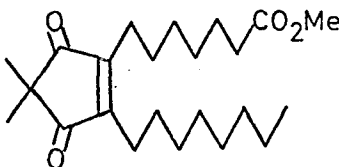
8 GENERAL DISCUSSION

The general concept of the proposed prostanoid synthetic scheme was shown to be viable through the synthesis of the model prostanoid. In the subsequent stages, the scheme was applied to C-15 functionalised prostanoids with partial success. At that point, it became evident that the overall effectiveness of the three-stage synthesis was seriously reduced by the poor yield of the C-8, C-12 cyclisation and difficulties encountered in the purification of the prostanoids. As a result, efforts were directed at investigating other methods of effecting the same ring-closure.

In the course of this extended investigation, it was found that the Claisen condensation of 2-heptanone with ethyl hexanoate afforded 72% yield (isolated as the Cu(II) complex) of the trideca-6,8-dione (122). This supported earlier speculation that the Claisen condensation of methyl nonyl ketone with DEA (32% yield at best) could be vastly improved and that the loss of the product, ethyl eicos-9,11-dionoate (3), via further condensation of the latter with a second molecule of methyl nonyl ketone was the reason for the low yield.

The eventual synthesis of the symmetrical 4,5-dialkyl-2,2-dimethyl cyclopent-4-en-1,3-diones (143) and (147) provided similar models with which the prostanoids could be compared. A comparison of the pertinent spectral data of these compounds is given in table 8.1. This comparison as a whole provides more substantial evidence in support of the proposed prostanoid structure.

Table 8.1

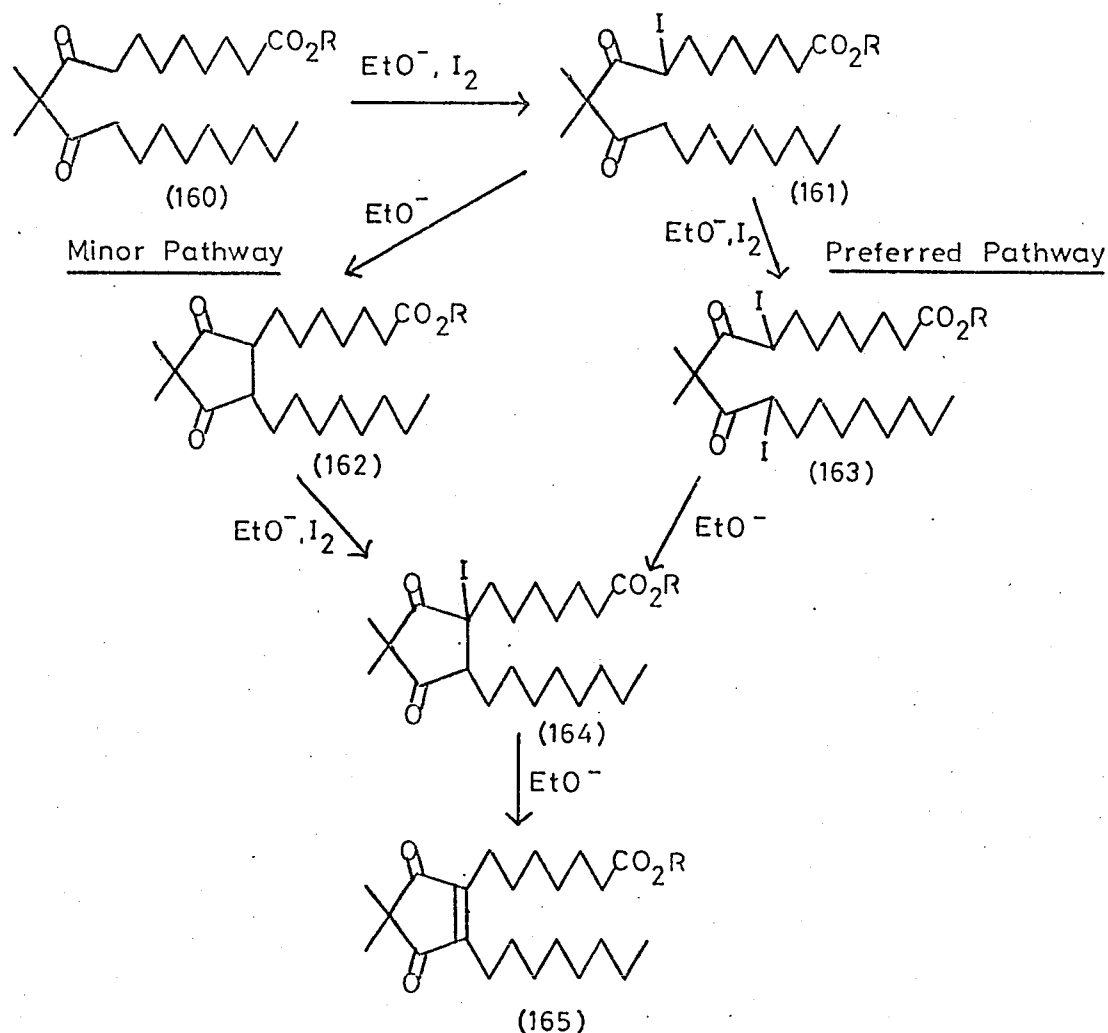
Cyclopentene-1,3-diones	UV(EtOH)nm	IR(film)cm ⁻¹	¹ H-NMR(CDCl ₃) δ
 (143)	245 $\epsilon = 8,670$	1630(m), 1693(s) 1741(w)	1.12(s, 6H) 2.52(q, 4H)
 (147)	249 $\epsilon = 11,260$	1627(w), 1697(s) 1741(w)	1.12(s, 6H) 2.47(t, 4H)
 (25)	250 $\epsilon = 12,350$	1625(w), 1698(s) 1743(s)	1.12(s, 6H) 2.45(t, 4H)

The sodium ethoxide/EtOH cyclisation of the diiodo-1,3-diketones (137) and (138) provided insight into the mechanism of the sodium ethoxide/iodine cyclisation of the esters of 10,10-dimethyl eicos-9,11-dionoate. The relatively high yields of the dimethyl cyclopentene-1,3-diones (143) and (147) obtained from the sodium ethoxide/EtOH reaction of the respective diiodo-1,3-diketones (137) and (138) strongly suggest that the analogous 8,12-diiodo-10,10-dimethyl eicos-9,11-dionoic ester (163) could be an important intermediate in the sodium ethoxide/iodine cyclisation reaction. Hence, the stepwise cyclisation of ethyl 10,10-dimethyl eicos-9,11-dionoate (via an intermediate dimethyl cyclopent-1,3-dione) proposed by C. B. Chapman¹⁴¹ is probably a minor mechanistic

pathway. A more plausible mechanistic pathway is included in scheme 8.1.

Scheme 8.1

Mechanistic pathways of the sodium ethoxide/iodine cyclisation

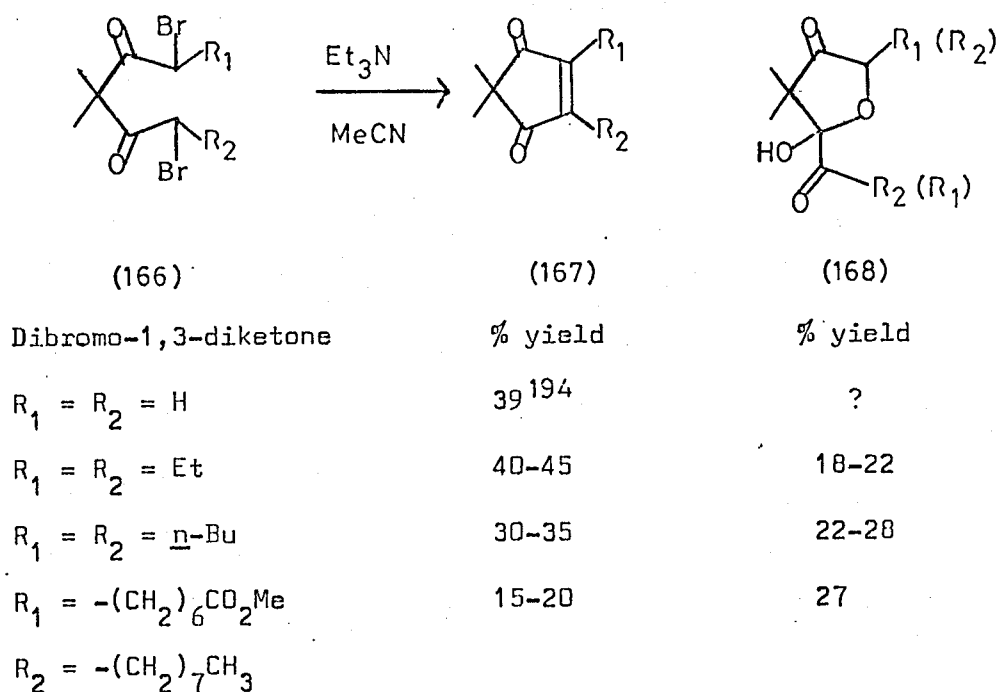


It is significant that the sodium ethoxide/EtOH cyclisation of the esters of 8,12-dibromo-10,10-dimethyl eicos-9,11-dienoic acid gave 10% or less of the expected model prostanooids (23) and (25). This low yield of dimethyl cyclopentene-1,3-dione product is in contrast with the

relatively high yield obtained from the cyclisation of the diiodo-1,3-diketones (137) and (138). This discrepancy in the results may be rationalised in terms of the poorer leaving group ability of the bromide versus the iodide ion. However, this rationale and the proposed 'preferred pathway' must remain tentative in view of the lack of information on the sodium ethoxide/EtOH cyclisation of the esters of 8,12-diiodo-10,10-dimethyl eicos-9,11-dionoic acid.

Our investigation into other methods of cyclisation led us to the general triethylamine/MeCN cyclisation of 1,5-dibromo-2,4-diketones of the type (166), scheme 8.2.

Scheme 8.2



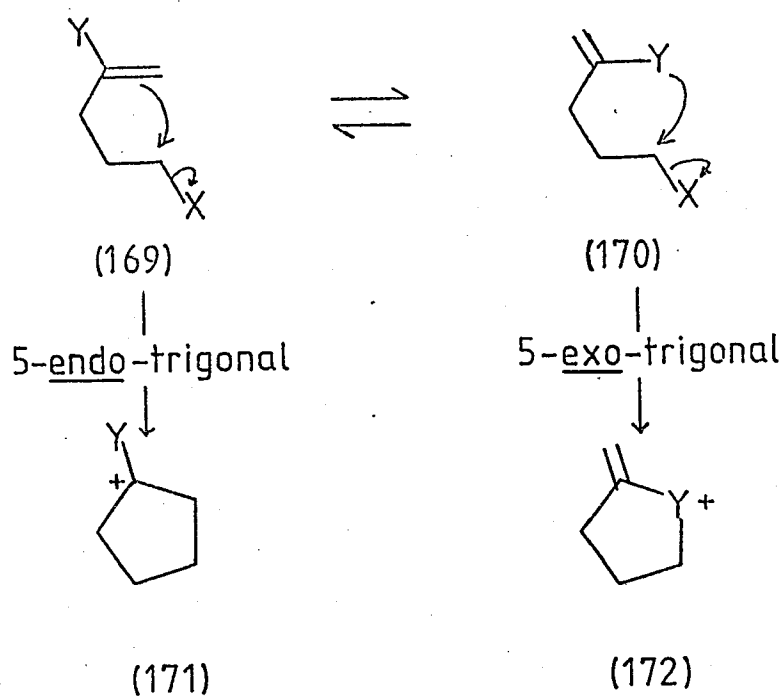
Scheme 8.2 indicates conservative estimated yields of the various dimethyl cyclopentene-1,3-dione derivatives under similar reaction

conditions. The figures suggest a progressive reduction in yield of (167) with the increase in the length of the side-chains. This trend is compatible with the simple steric and entropy argument that the formation of the prostanoid (23) would be relatively more demanding than the formation of the short side-chain cyclopentene-1,3-dione (143). On the other hand, the yields of the cyclic hemiketal (168) show a reverse trend. However, the reason for this trend is still unclear.

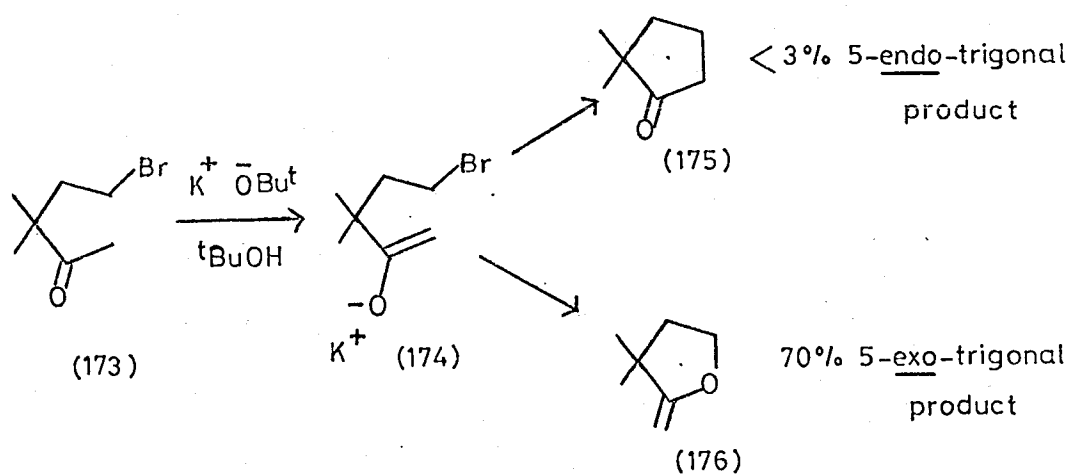
It must be emphasized that the estimated yields of the dimethyl cyclopentene-1,3-dione derivatives (167) and the cyclic hemiketal (168) were unoptimised. Furthermore, the cyclisation reaction behaved somewhat unpredictably¹⁹⁴. In fact more recently, it was found that the most consistent and favourable reaction conditions afforded 56% of dimethyl cyclopentene-1,3-dione (147) and very little of the cyclic hemiketal (149a).

An interesting and unusual feature of the triethylamine/MeCN ring-closure of the dibromo-1,3-diketone (132) is the high yield of the dimethyl cyclopentene-1,3-dione derivative (147) (56%Y). In contrast to this, J. E. Baldwin *et al*¹⁹⁶⁻¹⁹⁸ and more recently H. O. House *et al*¹⁹⁹ have shown that five-membered ring-closure of the general type shown in scheme 8.3, classified as a 5-endo-trigonal process is disfavoured. The preferred pathway is via the 5-exo-trigonal process. This general rule was exemplified by the ring-closure of the α -bromoketone (173), scheme 8.4

Scheme 8.3



Scheme 8.4

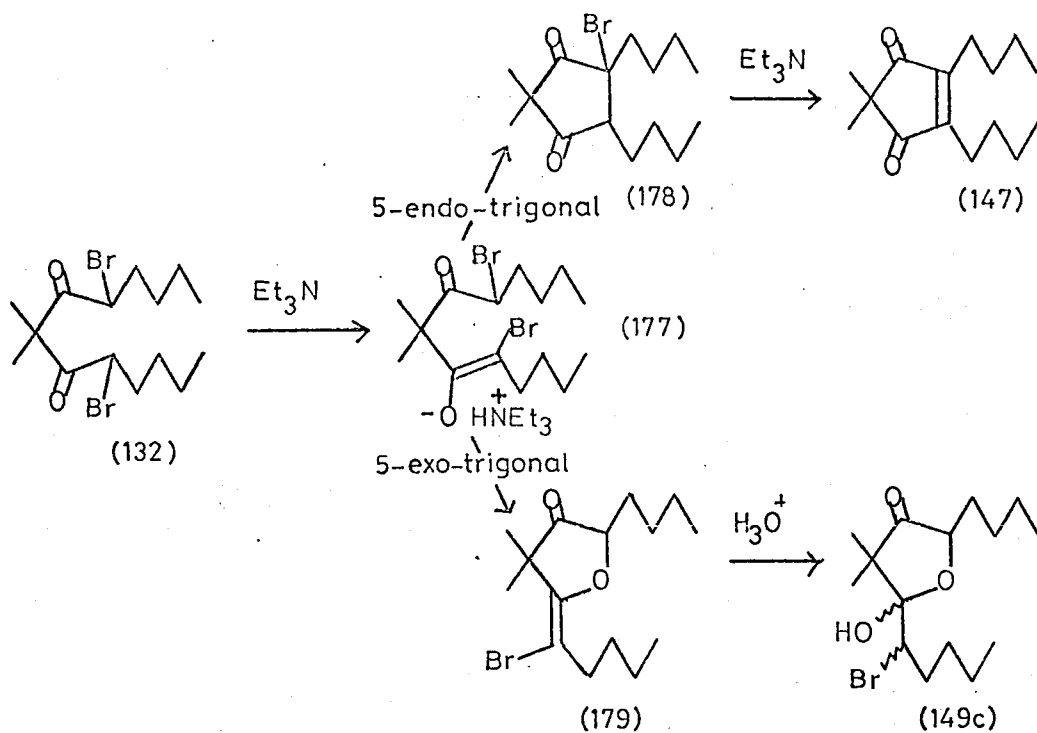


The remarkable difference between these two cyclisations is thought to result from the stereochemical control of the alkylation of the ambident nucleophilic anion. The C-alkylation requires the electrophile to approach perpendicular to the plane of the enolate anion and with the C-Br orbital colinear to the α -carbon of the enolate in an internal SN_2 type geometry. Study of molecular models indicates that this transition state can only be attained with substantial distortion of normal carbon bond angle. The alternative O-alkylation requires approach of the non-bonded electron pair on the oxygen atom in-plane with the C-Br bond. This is sterically less strained and favours the formation of the enol ether product (176).

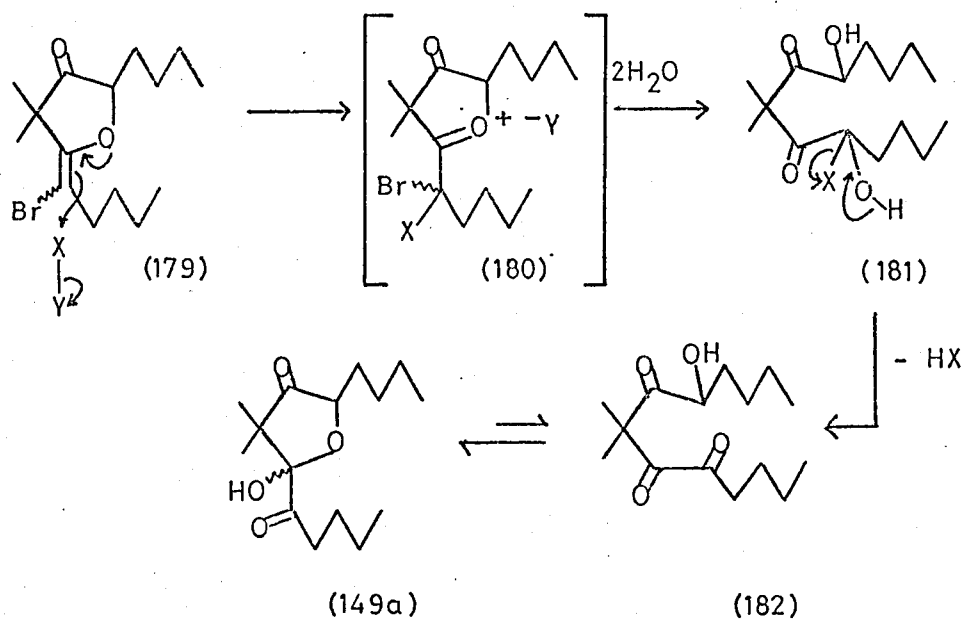
The same stereoelectronic argument when applied to the 5-membered ring-closure of the dibromo-1,3-diketone (132) should predominantly afford the 5-exo-trigonal product (179). On subsequent acid work-up, (179) would hydrolyse to afford the cyclic hemiketal (149c), scheme 8.5. However, in contradication of this argument the ring-closure of (177) afforded the 5-endo-trigonal product (147) (56%) as the major pathway. The alternate 5-exo-trigonal ring-closure was thought to result in the formation of the co-products (149a), (149b) and (149c) and deemed to be a minor pathway.

The formation of the cyclic hemiketal (149a) (9%) is thought to be derived by further oxidation of the 5-exo-trigonal intermediate (179) by an unknown species, scheme 8.6.

Scheme 8.5



Scheme 8.6

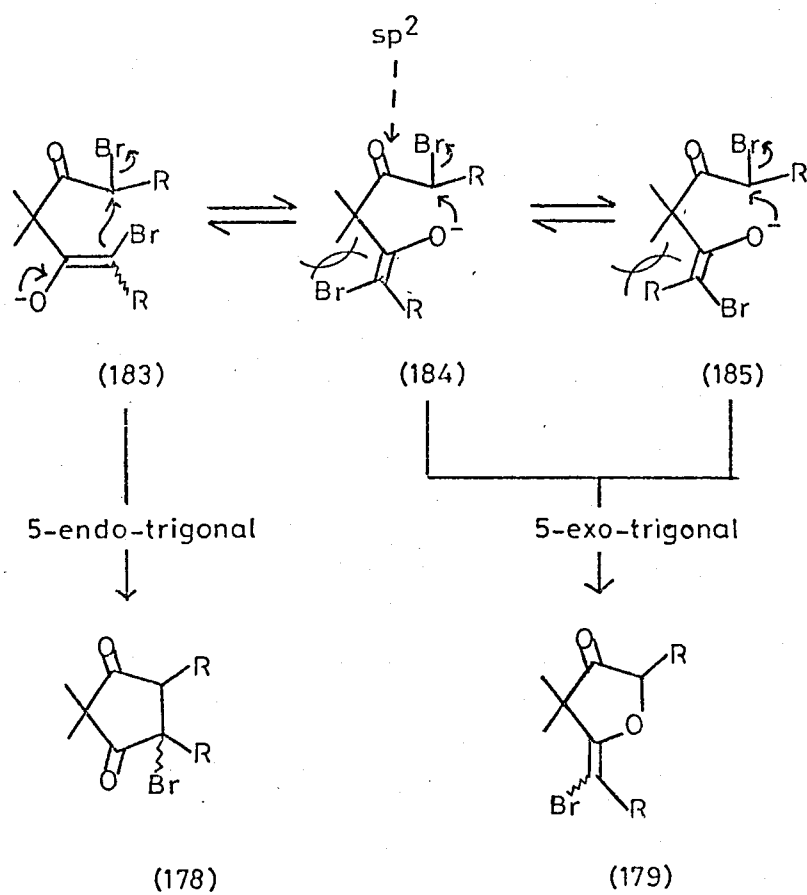
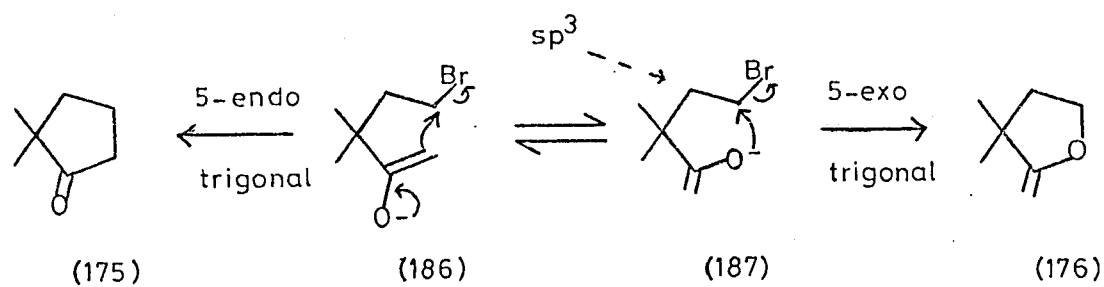


The abnormal 5-endo-trigonal ring-closure observed in this case may be due to structural differences between J. E. Baldwin's model (173) and our model (132). The first of these differences is the change in the state of hybridization of the carbon adjacent to the leaving group (-Br). In (132) the carbon in question is sp^2 whereas the analogous carbon in (173) is sp^3 . Study of molecular models indicates that the change in bond angle of ca. 110° (sp^3) to 120° (sp^2 carbonyl) does not appear to facilitate the requisite steric alignment of the reaction centres of (177) so as to favour the endo-trigonal approach. In order to examine this molecular model prediction, it was necessary to transform one of the carbonyls of (132) into an sp^3 centre. Unfortunately, attempts to prepare either the mono-dioxolan or the mono-dithiolan derivative of methyl 8,12-dibromo-10,10-dimethyl eicos-9,11-dienoate (94) failed and we were unable to test our supposition.

Another important difference between (132) and (173) is the presence of the extra bulky bromine atom and the long side-chains in the former. Molecular models indicate that the transition states (184) and (185) leading to the 5-exo-trigonal product (179) suffer serious steric compression arising from the interaction between the geminal dimethyl group and the bulky bromo-substituent or alternately the alkyl side-chain of the enolate. This steric congestion is virtually absent in the bromoketone enolate (187), scheme 8.7.

A comparison of the transition states (183) and (186) leading to the respective endo-trigonal products (178) and (175) did not reveal a large difference in steric demand. It is, therefore, likely that unfavourable steric interaction leading to transition states (184) and (185) has resulted in a change in the predicted ratio of the exo:endo-

Scheme 8.7



trigonal products.

A further consideration may be made regarding the enolate ion-pair in each case. In the case of the bromoketone (173), scheme 8.4, the deprotonation by potassium tert-butoxide results in the K^+ enolate intermediate. On the other hand, the deprotonation of the dibromo-1,3-diketone (132), scheme 8.5, by triethylamine leads to the

Et_3NH^+ enolate intermediate. It is known the O- versus C-alkylation of these ambident enolate anions is often very sensitive to the choice of solvent and counter-ions amongst other factors¹⁵⁵. This apparent difference between the triethylamine/MeCN and the potassium tert-butoxide/ t BuOH cyclisations has not been investigated and, therefore, a direct comparison of their results must be viewed with caution. This is further emphasized by the fact that cyclisation of the dibromo-1,3-diketone (132) in triethylamine/DME and triethylamine/benzene do not produce any significant quantity of the dimethyl cyclopentene-1,3-dione product (147), therefore, indicating that solvent effects are also of paramount importance.

" We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time "
" Little Gidding ", (1942)
T.S. Eliot (1888-1965).

9. EXPERIMENTAL

All solvents were routinely distilled before use and aprotic solvents were stored over sodium wire. Dimethyl sulphoxide, N,N-dimethylformamide and triethylamine were dried using calcium hydride. Tetrahydrofuran was distilled from lithium aluminium hydride as required and tertiary butanol was dried by distillation from potassium tertiary butoxide. Acetonitrile, chloroform and dichloromethane were distilled over phosphorus pentoxide. Unless otherwise stated, all solutions of product in organic solvents were evaporated on a rotary evaporator, under water-pump pressure.

Analytical thin layer chromatography (T.L.C.) was carried out on silica gel (Merck HF₂₅₄) with 0.8mm thickness. Preparative T.L.C. was carried out in a similar manner but with larger plates. Analytical gas-liquid chromatography was run using Pye 104 series with a hydrogen flame ionisation detector (FID) and temperature programme facility. The five foot columns used were:-

- (i) 3% OV 17 on 80-100 Gas chromosorb Q
- (ii) 3% SE 30 on 80-100 Gas chromosorb Q

¹H-NMR spectra were recorded from 20% w/v solutions in deuteriochloroform, using tetramethylsilane as internal standard, at 90 MHz using Perkin Elmer R32 spectrometer. Infra-red (IR) spectra were determined for thin films (for liquids) and potassium bromide (KBr) disc (for solids) using a Perkin Elmer 177. Ultra-violet (UV) spectra were recorded using a Pye Unicam SP800 spectrophotometer. Mass spectra (MS) were recorded on an A.E.I. MS12 spectrometer. High resolution mass spectrometry was carried out on a A.E.I. MS9 at P.C.M.U.

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

1. Preparation of eicos-9,11-dionoic acid (4)

A solution of 2-undecanone (8.5g, 0.05 mole) in dry distilled THF (25ml/EtOH(0.5ml)) was added dropwise (over a period 0.5h) to a stirred suspension of diethyl azelate (24.4g, 0.1 mole) in sodium hydride (5g of a 60% dispersion in oil; washed with dry benzene) and THF (50ml), under nitrogen blanket. After the complete addition of the ketone, the resultant yellowish brown slurry was stirred for an hour at room temperature and a further one hour at 60°. The reaction mixture was finally left stirring at room temperature for 15 hours.

The resultant mixture was acidified with glacial acetic acid (20 ml) and evaporated under reduced pressure. The yellowish white precipitate was taken up in ether (300ml) and washed with water (4 x 50ml). The organic phase was separated, dried with anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford a crude product.

The crude product was taken up in dry xylene (25 ml) and passed down a vigreux column at 220°/0.5 torr to afford crude ethyl eicos-9,11-dionoate (18.97g) as the heavy-end. The crude ester was taken up in pet. ether 60-80 and recrystallised to remove the C₃₁ tetrone as a white crystalline solid. The mother liquor was spun down to afford partially purified ethyl eicos-9,11-dionoate (3) (16.52g, 89%).

A portion of the partially purified ester (10g, 0.027 mole) was magnetically stirred in an aqueous solution of sodium hydroxide (10g) in MeOH: THF : H₂O (350ml:150ml:100ml) for 4 hours at room temperature.

The resultant mixture was evaporated under reduced pressure, taken up in ether (250ml), cooled in an ice-bath and cautiously acidified with concentrated HCl (30ml). The organic phase was separated, washed with

water (4 x 40ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure, to afford crude eicos-9,11-dionoic acid (9.31g).

Purification of the crude acid by column chromatography (silica gel 400g, CHCl_3 : Pet. ether 60-80°, 1:1) afforded purified acid (5.17g). Two successive recrystallisation of the purified acid furnished pure eicos-9,11-dionoic acid (4) (3.94g, 43%; estimated yield based on the total amount of partially purified ester is 32%), mp 64-65°

IR(KBr disc) cm^{-1} : 3440, 3140, 1719, 1689, 1641, 1463, 1441, 1423, 1238, 905, 785 and 725.

$^1\text{H-NMR}$ (CDCl_3) δ : 0.88 (t, 3H), 1.12-1.85 (m, methylene envelope 24H), 2.17-2.62 (m, 6H), 3.57 (s, <1H), 5.48 (s, 1H) and 9.80 (s broad, 2H, D_2O exchangeable protons).

MS : $[\text{M}]^+$ measured 340.2618, calculated 340.2614, $\text{C}_{20}\text{H}_{36}\text{O}_4$
Others $[\text{M}-\text{H}_2\text{O}]^+$, m/e 171 (82%), 155 (60%) and 100 (100%).

Elemental analysis : Found C=69.8 H=10.5
Theory C=70.54 H=10.66

2.Preparation of the anilide of eicos-9,11-dionoic acid

A solution of dry triphenylphosphine (589mg, 2.25 m moles) and eicos-9,11-dionoic acid (170mg, 0.5m moles) in dry carbon tetrachloride/benzene (10ml:5ml) was magnetically stirred and refluxed in an oil bath (ca. 85°) for 4 hours, with the exclusion of moisture.

A white suspension of the phosphine oxide was formed. The resultant suspension was allowed to cool to room temperature. A solution of dry aniline (280mg, 3m moles) in carbon tetrachloride (1 ml) was added and the suspension was left stirring overnight.

The resultant mixture was evaporated under reduced pressure and taken up in ether (150ml). It was thoroughly washed with 2N HCl (3x25ml), water (4x25ml) and dried over anhydrous magnesium sulphate. On evaporation of the solvent, the crude anilide (0.703g, 100%Y) was obtained as a gluey solid containing excess triphenylphosphine.

The crude product was purified by preparative TLC (Silica gel, Pet. ether 60-80/CHCl₃ ,3:5) and recrystallised from Pet-ether 60-80°/EtOH to afford pure N-phenyl eicos-9,11-dionamide (5) (91mg,44%) as a white crystalline solid.

m.p. 78.5-79.5°, white micro-crystalline solid.

Elemental analysis: Found C = 75.5 H = 10.1 N = 3.5
Theory C = 75.13 H = 9.94 N = 3.37

IR(KBr)cm⁻¹: 3340, 1658, 1637, 1601, 1549, 1443, 901, 781, 761 and 731.

¹H-NMR(CDCl₃) δ 0.88 (t,3H), 1.04-1.98 (m, methylene envelope), 2.16-2.64 (m,6H), 3.56 (s,<1H), 5.48 (s,1H), 6.92-7.66 (m,6H, one D₂O exchangeable proton).

MS : [M]⁺ measured 415.3090 (25%),calculated 415.3086 C₂₆H₄₁N₁O₃

Others m/e 246 (59%), 204 (100%), 135 (93%) and 94 (73%)

3. Dimethylation of ethyl eicos-9,11-dienoate (3)

A solution of ethyl eicos-9,11-dienoate (4.56g, 12.5m moles) in dry DME (40ml) was added dropwise to prewashed sodium hydride (0.76g, 32m moles), under a gentle stream of nitrogen. The resultant slurry was stirred for 0.5h, followed by the addition of a solution of iodomethane (5.72g, 40m moles) in dry DMF (100ml). The resultant suspension was stirred for a further 0.5h and then maintained at reflux temperature for 6h.

The resultant mixture was evaporated under reduced pressure and water (50ml) was cautiously added. The mixture was extracted with ether (2x100ml). The ethereal layer was separated, washed with more water (4x20ml) and dried over anhydrous magnesium sulphate. Evaporation of the ether, afforded crude ethyl 10,10-dimethyl eicos-9,11-dienoate (4.77g, 96%Y) as a viscous pale brown oil.

Purification of the crude product by column chromatography (silica gel. Pet. ether 60-80°/ether, 9 : 1) afforded pure ethyl 10,10-dimethyl eicos-9,11-dienoate (17) (3.43g, 69%Y) as a pale yellow oil.

IR(film)cm⁻¹ : 1740, 1720, 1700, 1471, 1369, 1180, 1033 and 722.

¹H-NMR (CDCl₃) δ : 0.87 (t, 3H), 1.10-1.87(m, methyl, methylene envelope-33H),
2.31 (t, -CH₂-CO₂Et), 2.38 (t, C-8, C-12 methylenes-4H),
4.13 (q, -OCH₂-CH₃)

MS : [M-OEt]⁺ 351 (44%)

Others m/e 198 (100%) and 155 (100%).

4. Preparation of methyl 10,10-dimethyl eicos-9,11-dienoate (18)

A solution of eicos-9,11-dienoic (0.68g, 2m moles) in dry DME (14ml) was added dropwise to prewashed sodium hydride (336mg/60% dispersion in oil, 8.4m moles), under a gentle stream of nitrogen. Brisk effervescence followed and the suspension was magnetically stirred at room temperature for 20 minutes. A solution of iodomethane (1.136g, 8m moles) in dry DMF (33ml) was then added and the reaction mixture stirred for a further 30 minutes. The temperature was gradually raised to reflux point (ca.120-130^o), maintained for 6 hours and left stirring overnight at room temperature.

The resultant mixture was evaporated under reduced pressure and taken up in ether (150ml) and water (25ml). The organic phase was separated, thoroughly washed with water (3x20ml) and dried over anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure afforded the crude product (740mg, 97%Y).

Purification of the crude product by preparative TLC (silica gel, Pet. ether 60-80°/ether, 3:2) afforded methyl 10,10-dimethyl eicos-9,11-dienoate (18) (478mg, 63%Y) as a colourless viscous oil.

IR(film)cm⁻¹ : 1742, 1720, 1698, 1367, 1199, 1172, 1165 and 722

¹H-NMR(CDCl₃) δ : 0.89 (t,3H), 1.18-1.82 (m, methylene envelope),
1.34 (s,6H), 2.31, 2.39 (2t,6H) and 3.67(s,3H).

MS : [M]⁺ measured 382.3088 (0.5%), calculated 382.3083 C₂₃H₄₂O₄
Others m/e 351 (1%), 228 (69%), 198 (86%), 185 (38%)
155 (62%), 82 (100%) and 71 (58%).

5. Bromination of ethyl 10,10-dimethyl eicos-9,11-dienoate (17) using bromine

A solution of bromine (480mg, 3m moles) in chloroform/ethyl acetate (2.5ml:2.5ml) was added in one portion to a magnetically stirred solution of ethyl 10,10-dimethyl eicos-9,11-dienoate (396mg, 1m mole) in the same solvent mixture (15ml). A catalytic amount of anhydrous aluminium trichloride was added and the solution was stirred at room temperature for 18 hours.

The resultant mixture was evaporated under reduced pressure and taken up in ether (100ml). The solution was washed with saturated aqueous sodium bicarbonate (10ml), water (3x20ml) and dried over anhydrous magnesium sulphate. Evaporation of the solvent gave the crude dibromo-ester (93) (583mg)

Purification of the crude product by preparative TLC (silica gel, Pet. ether/ether, 19:1) afforded ethyl 8,12-dibromo-10,10-dimethyl eicos-9,11-dienoate (93) as two close bands containing the different isomers; a high R_f band (198mg, 36%Y) and a low R_f band (243mg, 44%).

IR(film)cm⁻¹ : 1740, 1730, 1700, 1465, 1371, 1180 and 1035

MS : [M-OEt]⁺ 507, 509, 510, triplet 1:2:1, (ca. 5%)
Others m/e, [M-Br]⁺ 227 (15%) and 279 (15%)

High R_f band

¹H-NMR(CDCl₃) δ : 0.90 (t,3H), 1.10-1.50 (m, methyl,methylene envelope),
1.57, 1.70 (2s,6H), 1.85-2.19 (m,4H), 2.30 (t,2H),
4.15 (q,2H) and 4.59 (t,2H)

Low R_f band

¹H-NMR(CDCl₃) δ : 0.90 (t,3H), 1.10-1.50 (m, methyl,methylene envelope),
1.60, 1.62 (2s,6H), 1.85-2.19 (m,4H), 2.30 (t,2H),
4.15 (q,2H) and 4.56 (t,2H).

6. Dibromination of methyl 10,10-dimethyl eicos-9,11-dienoate (18)

A solution of methyl 10,10-dimethyl eicos-9,11-dienoate (227mg, 0.6m mole) in dry THF (3ml) was added in one portion to a magnetically stirred solution of trimethylphenylammonium perbromide (459mg, 1.22m moles) in the same solvent (2ml). The resultant clear orange solution developed into a clear white suspension after 6 hours at room temperature.

The resultant mixture was evaporated under reduced pressure and taken up in ether (150ml) and water (20ml). The organic phase was separated, thoroughly washed with water (3x20ml) and dried over anhydrous magnesium sulphate. Evaporation of the solvent afforded the crude product (407mg)

Purification of the crude product by preparative TLC (silica gel, Pet. ether 60-80/ether, 9:1, 3 passes) afforded two bands of partially separated isomeric methyl 8,12-dibromo-10,10-dimethyl eicos-9,11-dienoate (94) as viscous lachrymatory oils. (High Rf band 93mg, 29%Y and low Rf band 128mg, 40%Y : total 69%Y). If the separation of the diastereomers is not required, the dibromo-ester can be isolated as a single band by preparative TLC (silica gel, Pet. ether 60-80/ether, 7:1) in 81%Y.

Methyl 8,12-dibromo-10,10-dimethyl eicos-9,11-dienoate (94) epimers

IR(film) cm^{-1} : 1735, 1723, 1700, 1370, 1255, 1200 and 1120
 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.88 (t,3H), 1.10-1.50 (m, methylene envelope),
1.56,1.59, 1.62, 1.69 (4s,6H), 1.85-2.15 (m,4H),
2.32 (t,2H), 3.67 (s,3H), 4.55 and 4.58 (2t,2H).
MS : $[\text{M-MeOH}]^+$ 506, 508, 510 (1:2:1), (ca. 5%)
Others m/e $[\text{M-Br}]^+$ 461 (25%), 459 (25%) and 265 (6%),
263 (6%).

7. Preparation of ethyl 10,10-dimethyl prost-8(12)-en-9,11-dionoate (23)
via the sodium ethoxide/iodine cyclisation procedure

A solution of ethyl eicos-9,11-dionoate (99mg, 0.25m moles) in dry EtOH (10ml) was added in one portion to a magnetically stirred solution of sodium ethoxide (from 29mg, 1.25m moles of sodium) in EtOH (10ml), under a nitrogen blanket. The yellow solution was stirred for 45 seconds and a solution of iodine (443mg, 1.25m moles) in EtOH (15ml) was added dropwise over a period of 18 minutes. During the addition, the colour of iodine was continuously and instantly discharged. The final reaction mixture was stirred for a further 2 minutes at room temperature and evaporated under reduced pressure to afford a beige solid. The latter was taken up in ether (70ml) and water (20ml). Excess iodine was removed by shaking the mixture with sodium metabisulphite. The organic layer was separated, washed with water (2x20ml), dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford the crude prostanoid (115mg, UV: λ_{\max} 250nm, ϵ = 4,110).

Purification of the crude product by preparative TLC, afforded ethyl 10,10-dimethyl prost-8(12)-en-9,11-dionoate (23) (45mg, 46%, λ_{\max} 250nm ϵ = 7,150) as a pale yellow oil.

IR(film)cm⁻¹ : 1739, 1699 and 1631

¹H-NMR(CDCl₃) δ : 0.88 (t, 3H), 1.12(s, 6H), 1.10-1.85(m, methylene, methyl envelope), 2.15-2.60 (m, 6H) and 4.13 (q, 2H).

MS : [M]⁺ m/e 392 (62%) and [M-OEt]⁺ m/e 347 (25%)

8. Hydrolysis of ethyl 10,10-dimethyl prost-8(12)-en-9,11-dionoate (23)
and re-esterification of the prostanoid acid (24)

A solution of ethyl 10,10-dimethyl prost-8(12)-en-9,11-dionoate (230mg, 0.59m mole) in THF/MeOH/H₂O (10ml:1.5ml:10ml) and sodium hydroxide (400mg) was magnetically stirred at room temperature for 16 hours.

The resultant solution was cooled in an ice-bath and acidified with conc. HCl to pH1. The solution was saturated with sodium chloride and extracted with ether (2x25ml). The organic layer was separated, washed with water (2x25ml) and dried over anhydrous magnesium sulphate. Evaporation of the ether under reduced pressure, afforded the crude acid (250mg).

Purification of the crude acid by preparative TLC (silica gel, ether), afforded ethyl 10,10-dimethyl prost-8(12)-en-9,11-dionoic acid (24) (60mg, 28%) as a pale yellow liquid.

IR(film)cm⁻¹ : 3500-3000, 1742, 1713, 1705 and 1629
¹H-NMR(CDCl₃)δ : 0.89 (t,3H), 1.12(s,6H), 1.18-1.87(m, methylene envelope), 2.25-2.63 (m,6H) and 8.61-9.69 (broad s 1H,D₂O exchangeable).
UV(EtOH) : λ_{max} 250nm, ε =11,470.

The prostanoid acid (24) (45mg, 0.12m mole) was re-methylated with ethereal diazomethane at room temperature to afford the crude methyl ester (25) (41mg). Purification of the crude ester by preparative TLC (silica gel, Pet. ether 60-80°/ether,5:3), afforded methyl 10,10-dimethyl prost-8(12)-en-9,11-dionoate (25) (21mg, 45%).

IR(film) cm^{-1} : 1743, 1698, 1625, 1382 and 1360.
 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.89 (t,3H), 1.12 (s,6H), 1.20-1.85 (m, methylene envelope), 2.32, 2.45 (2t,6H) and 3.67(s,3H)
 MS : $[\text{M}]^+$ (9%) measured 378.2774, calculated 378.2770
 $[\text{M-OMe}]^+$ (5%) and $[\text{M-MeOH}]$ (6%)
 UV(EtOH) : λ_{max} 250nm, $\epsilon=12,350$.

9.Preparation of methyl 10,10-dimethyl prost-8(12)-en-9,11-dionoate (25)
via the cyclisation of methyl 8,12-dibromo-10,10-dimethyl eicos-9,11-
dionoate (94) in triethylamine/MeCN

A solution of the dibromo-ester (94) (222mg, 0.4m mole) in triethylamine/MeCN (2ml:3ml) was magnetically stirred and maintained at 60° for 14 hours (with exclusion of moisture).

The resultant brown suspension was evaporated under reduced pressure and taken up in ether (150ml) and water (25ml). The suspension was washed with dilute HCl (5ml). The organic phase was separated, washed with water (3x25ml) and dried over anhydrous magnesium sulphate. Evaporation of the ether, afforded the prostanoid ester (25) (100mg, 65%, UV : λ_{max} 250nm, ϵ =3660).

Purification of the crude product by preparative TLC (silica gel, Pet. ether 60-80°/ether, 9:1, 3 passes), afforded methyl 10,10-dimethyl prost-8(12)-en-9,11-dionoate (25) (22mg, 14%, UV : λ_{max} 250nm, ϵ =8,440). The prostanoid methyl ester (25) prepared via the sodium ethoxide/iodine cyclisation of methyl 10,10-dimethyl eicos-9,11-dionoate (17) was identical to the prostanoid methyl ester (25) prepared here.

10. Methylation of 4-acetyl-butyric acid (48)

An ethereal solution of diazomethane generated from N-methyl-N-nitroso-p-toluene sulphonamide ²⁰⁰ was added dropwise to a magnetically stirred solution of 4-acetyl-butyric acid (25.6g, 197m moles) in ether (50ml). Methylation was presumed to be completed when a persistent yellow coloration appeared and no further efferverscence was apparent on the addition of more diazomethane solution.

The resultant solution was stirred at room temperature for 30 minutes and then evaporated under reduced pressure to afford crude methyl ester (26.08g, 92%Y) as a yellow oil.

Purification by column chromatography (silica gel, Pet. ether 60-80^o/ether, 2:3) afforded pure methyl 4-acetyl-butyrate (49) (25.48g, 90%Y) as a pale yellow oil.

IR(film)cm⁻¹ : 1739, 1715, 1438, 1366, 1158 and 1071.

¹H-NMR(CDCl₃) δ : 1.75-2.06 (m, 2H), 2.14 (s, 3H), 2.39(t, 2H), 2.55 (t, 2H) and 3.69 (s, 3H)

11. Preparation of methyl 5-(1,3-dioxolan)-hexanoate (50)

A solution of dry ethane-1,2-diol (14.10g, 0.23m mole), methyl 4-acetyl butyrate (21.87g, 0.15 mole) and a few crystals of p-toluene-sulphonic acid in dry benzene (250ml) was magnetically stirred and refluxed in a Dean and Stark trap for 24 hours.

The resultant solution was cooled to room temperature, washed with water and dried over anhydrous magnesium sulphate. Removal of benzene under reduced pressure afforded the crude ketal ester (26.52g, 93%Y).

Purification of the crude product by column chromatography (silica gel, Pet. ether 60-80°/ether, 2:3) afforded pure methyl 5-(1,3-dioxolan)-hexanoate (50) (24.84g, 87%Y) as a colourless thick oil.

IR(film) cm^{-1} : 1739, 1436, 1377, 1257, 1198, 1172, 1063, 947 and 844.
 $^1\text{H-NMR}(\text{CDCl}_3) \delta$: 1.32 (s, 3H), 1.62-1.88 (m, 4H), 2.25-2.50 (m, 2H), 3.69 (s, 3H) and 3.96 (s, 4H).

12. Preparation of 5-(1,3-dioxolan) hexanol (51)

A solution of methyl 2-(1,3-dioxolan)-hexanoate (11.2g, 0.06 mole) in dry THF (125ml) was added dropwise to a magnetically stirred slurry of lithium aluminium hydride (4g, 0.105 mole) in dry THF (125ml), under a gentle stream of nitrogen. A mild exothermic reaction ensued. After this initial reaction had subsided, the suspension was kept under reflux for 12 hours.

The resultant mixture was cooled in an ice-bath to below 5°. Water (5ml) was added cautiously in small portions, followed by 15% aqueous sodium hydroxide (12ml) and more water (5ml). The resulting white suspension was stirred for 15 minutes and filtered off. The filtrate was dried over anhydrous magnesium sulphate. Subsequent removal of THF, afforded the crude ketal alcohol (8.9g, 93%Y).

Purification by column chromatography (silica gel, ether) afforded pure 5-(1,3-dioxolan)-hexanol (51) (15.14g, 86%Y) as a colourless thick oil.

IR(film)cm⁻¹ : 3430, 1461, 1377, 1222, 1069, 948 and 855

¹H-NMR(CDCl₃) δ : 1.31 (s, 3H), 1.41-1.81 (m, 6H), 2.72 (s, 1H, D₂O exchangeable) 3.63 (t, 2H) and 3.96 (s, 4H).

13. Preparation of 5-(1,3-dioxolan)-hexanal (52)

Dry chromium trioxide ²⁰¹ (24g, 240m moles) was added in portions to an ice-cooled, magnetically stirred solution of dry pyridine (38g, 480m mole) in dry dichloromethane (600ml), under a slow stream of nitrogen. The dark red solution was allowed to warm up to room temperature gradually (approximately 1.5 hours). A solution of 5-(1,3-dioxolan)hexanol (6.4g, 40m moles) in dry dichloromethane (40ml) was added in one portion to the oxidant. The reaction mixture was stirred thoroughly for 20 minutes and then filtered through Hi-flo Supercel. The gluey residue left over was washed with dichloromethane (4x100ml). All washings and filtrate were combined and evaporated under reduced pressure. Excess pyridine was removed by azeotropic distillation with dry benzene, under reduced pressure. The partially purified crude product was then taken up in ether (3x100ml), filtered through glass wool and evaporated under reduced pressure to afford reasonably pure aldehyde (6.26g, 99%Y).

Further purification by column chromatography (silica gel, chloroform) afforded pure 5-(1,3-dioxolan) hexanal (52) (5.56g, 88%Y).

IR(film)cm⁻¹ : 2730, 1725, 1378, 1253, 1223, 1148, 1072, 948, 855 and 757.

¹H-NMR(CDC1₃) δ : 1.34 (s, 3H), 1.59-1.91 (m, 4H), 2.30-2.64 (m, 2H) 3.96 (s, 4H) and 9.70-9.85 (m, 1H).

14. Preparation of 2-(1,3-dioxolan)-undec-6-ene (55)

A solution of n-butyl lithium (10.2ml, 3.7M, 38m moles) was added dropwise to a magnetically stirred suspension of n-pentyl phosphonium bromide (15.7g, 38m moles) in dry ether (220ml) at -20° , under a gentle stream of nitrogen. The suspension was stirred for an hour and then allowed to reach 0° . 5-(1,3-dioxolan) hexanal (4g, 25m moles) in dry ether (50 ml) was added to the orangey brown suspension of the phosphonium ylid in a dropwise manner. A thick yellow precipitate was thrown out of solution. More ether (100ml) was added to keep the slurry thin. The reaction mixture was allowed to warm to room temperature and stirred for a further 10 minutes.

The resultant suspension was quenched with water (10ml). The organic phase was separated, washed with more water (3x50ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure to afford the crude product (7.87g)

The crude product was purified by column chromatography (TLC silica gel, chloroform/benzene, 3:17, under pressure, 10psi) to afford 2-(1,3-dioxolan)-undec-6-ene (55) (2.73g, 51%Y) as a pale yellow oil.

IR(film) cm^{-1} : 3010, 1462, 1378, 1252, 1217, 1118, 1064, 968, 945 and 870.

$^1\text{H-NMR}(\text{COCl}_2)$ δ : 0.90 (t, 3H), 1.27-1.84 (m, methylene envelope), 1.32 (s, 3H), 1.90-2.23 (m, 4H), 3.94 (s, 4H), 5.28-5.52 (m, 2H).

MS : $[\text{M}]^+$ measured 212.1778 (weak), calculated 212.1776
Others m/e $[\text{M}-\text{CH}_3]^+$ 197 (8%) and 87 (100%).

15. Hydrolysis of 2-(1,3-dioxolan)-undec-6-ene (55)

A 60% aqueous perchloric acid solution (0.5ml) was added dropwise to a magnetically stirred solution of 2-(1,3-dioxolan)-undec-6-ene (144mg, 0.67m mole) in methyl ethyl ketone (10ml). The solution was stirred at room temperature for 2.5 hours.

Powdered sodium bicarbonate was added until brisk efferverscence ceased. The suspension was taken up in ether (50ml), washed thoroughly with water (2x10ml) and dried over anhydrous magnesium sulphate. Evaporation of the ether afforded the crude product (196mg)

Purification by preparative TLC (silica gel, benzene/chloroform 1:1) afforded undec-6-en-2-one (60) (87mg, 77%Y) as a pale yellow oil.

IR(film)cm ⁻¹	:	3010, 1720, 1455, 1367, 1159 and 969
¹ H-NMR(COCl ₃) δ	:	0.89 (t,3H) 1.18-1.50 (m,4H), 1.50-1.86(m,2H), 1.86-2.20(m,4H), 2.13(s,3H), 2.33(t,2H) and 5.13-5.58(m,2H).
MS	:	[M] ⁺ measured 168.1513 (14%), calculated 168.1514 Others m/e 125(14%) and 110(59%)

16. Preparation of 2-(1,3-dioxolan)-6-undecanol (65)

A solution of n-pentyl bromide (8.73g, 58m moles) in dry ether (20ml) was added dropwise to a magnetically stirred suspension of magnesium turnings (1.30g, 54m moles) and a few crystals of iodine in dry ether (100ml), under a gentle stream of nitrogen. When the exothermic reaction ceased, the suspension was refluxed for 15 minutes and then allowed to cool to room temperature.

A solution of 5-(1,3-dioxolan) hexanal (5.50g, 35m moles) in dry ether (30ml) was added dropwise to the Grignard reagent. When the initial exothermic reaction had ceased, the mixture was refluxed for 30 minutes and allowed to cool to room temperature.

The resultant mixture was taken up in ether (50ml), quenched with saturated ammonium chloride and filtered. The residue was washed with more ether (2x20ml). The filtrate and washings were combined and dried over anhydrous magnesium sulphate. Evaporation of the ether afforded the crude ketal alcohol (7.95g, 99%Y).

Purification by column chromatography (silica gel, ether) afforded pure 2-(1,3-dioxolan)-6-undecanol (65) (6.17g, 77%Y).

IR(film) cm^{-1} : 3450, 1460, 1378, 1223, 1146, 1064, 947 and 863.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.84 (t, 3H), 1.05-1.78(m, 17H), 1.91 (broad s, 1H, D_2O exchangeable), 3.60 (broad m, 1H) and 3.92 (s, 4H).

17. Preparation of 2-(1,3-dioxolan)-6-benzyloxy -undecane (66)

A solution of 2-(1,3-dioxolan)-6-undecanol (460mg, 2m moles) in dry DME (5ml) was added dropwise to a slurry of prewashed sodium hydride (300mg, 80% dispersion in oil, 10m moles) in dry DME (25ml). The suspension was magnetically stirred under a gentle stream of nitrogen for 2 hours. A dry solution of benzyl bromide (835mg, 5m moles) in DME, (5ml) was added dropwise to the reaction mixture and stirred at room temperature for 48 hours.

Methanol (10ml) was added to the resultant mixture, stirred for an hour and evaporated under reduced pressure. The semi-solid obtained was taken up in ether (100ml), washed with water (4x25ml) and dried over anhydrous magnesium sulphate. Removal of ether under reduced pressure afforded the crude ketal benzyloxy-ether (635mg, 99%Y).

Purification by column chromatography (silica gel, benzene/chloroform, 7:3) afforded pure 2-(1,3-dioxolan)-6-benzyloxy -undecane (66) (453mg, 71%Y) as a pale yellow oil.

IR(film) cm^{-1} : 3035, 1453, 1374, 1204, 1094, 1063, 946, 863, 732 and 696.

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 0.89 (t, 3H), 1.21 (s, 3H), 1.25-1.70 (m, methylene envelope, 14H), 3.32 (broad m, 1H), 3.84 (s, 4H), 4.45 (s, 2H) and 7.10-7.40 (m, 5H).

MS : $[\text{M}]^+$ measured 305.2116 (5%), calculated 305.2117.

18. Hydrolysis of 2-(1,3-dioxolan)-6-benzyloxy -undecane (66)

A 60% aqueous solution of perchloric acid (2.5ml) was added dropwise to a stirred solution of 2-(1,3-dioxolan)-6-benzyloxy -undecane (1.22g, 3.8m moles) in methyl ethyl ketone (50ml). The solution was stirred at room temperature for 2.5 hours.

Powdered sodium bicarbonate was added in portions until brisk efferverscence ceased. Ether (100ml) was added and the organic phase was separated, washed with water (4x25ml) and dried over anhydrous magnesium sulphate. Removal of ether under reduced pressure afforded the crude product in quantitative yield.

If necessary, the crude may be purified by column chromatography (silica gel, Pet. ether 60-80°/ether, 4:1). In most cases, the crude 2-(1,3-dioxolan)-6-benzyloxy -undecane obtained by benzylation of the precursor alcohol was directly hydrolysed without prior purification. The major impurity, dibenzyl ether, is easily removed by column chromatography (as above). The yield of the 6-benzyloxy -2-undecanone (67) based on the ketal alcohol is about 69%Y.

IR(film)cm ⁻¹	: 3030, 1715, 1495, 1453, 1356, 1160, 1090, 1065, 733 and 696.
¹ H-NMR(CDC1 ₃) δ	: 0.89 (t, 3H), 1.16-1.90 (m, methylene envelope), 2.10 (s, 3H), 2.43 (t, 2H), 3.39 (broad t, H), 4.49 (s, 2H) and 7.16-7.48 (m, 5H).
MS	: [M] ⁺ measured 276.2091 (weak), calculated 276.2089 Others m/e 170 (33%) and 91 (100%).

19. Preparation of ethyl eicos-15-en-9,11-dionoate (61)

A solution of undec-6-en-2-one (1.2g, 7m moles) in dry diethyl azelate (0.5g, 2m moles) was added to a magnetically stirred slurry of prewashed sodium hydride (0.92g, 50% dispersion in oil, 19m moles) in diethyl azelate, (2.9g, 12m moles), under a gentle stream of nitrogen. The temperature was then gradually brought to 60° and maintained for an hour. The reaction mixture was subsequently left to cool to room temperature and stirred overnight.

Dry ethanol (10ml) was added to the resultant mixture to destroy excess sodium hydride. It was then taken up in ether (100ml) and acidified with conc. HCl to pH 1. The organic phase was separated, thoroughly washed with water (3x20ml) and dried over anhydrous magnesium sulphate. Evaporation of the ether afforded the crude product (4.65g).

Purification by column chromatography (silica gel, Pet. ether 60-80°/ether, 90:1) afforded ethyl eicos-15-en-9,11-dionoate (61) (463mg, 13%Y) as a yellow viscous oil.

IR(film)cm⁻¹ : 1739, 1610, 1460, 1371, 1180, 1034, 969 and 774.
¹H-NMR(CDCl₃) δ : 0.88 (t, 3H), 1.10-1.87 (m, methyl methylene envelope),
1.87-2.19 (m, 4H), 2.30 (t, 6H), 3.54 (s, <1H),
4.14 (q, 2H), 5.29-5.46 (m, 2H) and 5.46 (s, 1H).
MS : [M]⁺ 366 (13%), [M-OEt]⁺ 321 (32%)
Others m/e 256 (53%), 199 (74%) and 153 (32%)

20. Preparation of ethyl 10,10-dimethyl eicos-15-en-9,11-dionoate (62)

A solution of ethyl eicos-15-en-9,11-dionoate (377mg, 1.03m moles) in dry DME (10ml) was added to prewashed sodium hydride (108mg, 60% dispersion in oil, 2.7m moles), under a gentle stream of nitrogen. Brisk efferverscence followed and the suspension was magnetically stirred at room temperature for 15 minutes. A solution of iodomethane (470mg, 3.3m moles) in dry DMF (15ml) was added and the reaction mixture stirred for a further 30 minutes. It was brought to reflux temperature (100° - 110°) and maintained for 6 hours. Finally, it was allowed to cool to room temperature and left stirring overnight.

The resultant mixture was evaporated under reduced pressure and taken up in ether (100ml) and water (50ml). The organic phase was separated, washed with more water (3x20ml) and dried over magnesium sulphate. Evaporation of the ether afforded the crude product (351mg, 86%Y).

Purification of the crude product by preparative TLC (silica gel, benzene/chloroform, 1:1) afforded ethyl 10,10-dimethyl eicos-15-en-9,11-dionoate (62) (150mg, 37%Y) as a viscous pale yellow oil.

IR(film) cm^{-1} : 1738, 1720, 1700, 1468, 1369, 1179, 1110 and 1032.
 $^1\text{H-NMR}(\text{CDCl}_3) \delta$: 0.88 (t, 3H), 1.08-1.80 (m, methyl, methylene envelope), 1.33 (s, 6H), 1.80-2.18 (m, 4H), 2.18-2.54 (m, 6H), 4.12 (q, 2H) and 5.22-5.51 (m, 2H).

21. Preparation of ethyl 10,10-dimethyl prost-8(12),15-dien-9,11-dionoate (63)

A solution of ethyl 10,10-dimethyl eicos-15-en-9,11-dionoate (100mg, 0.25m mole) in dry ethanol (5ml) was added to a solution of sodium ethoxide (prepared from Na, 35mg, 1.52m mole) in dry ethanol (5ml), under a slow stream of nitrogen. The yellowish solution so formed was magnetically stirred for 2 minutes. A solution of iodine (130mg, 0.51m mole) in dry ethanol (5ml) was added dropwise over a period of a minute. After the completion of iodine addition, the solution was stirred at room temperature for a further 45 minutes.

The resultant mixture was evaporated under reduced pressure to give a yellowish white residue. This was taken up in ether (50ml) and water (10ml). Sodium metabisulphite was added and the suspension was thoroughly shaken. The organic phase was separated, washed with water (4x10ml) and dried over anhydrous magnesium sulphate. Evaporation of the ether afforded the crude product (73mg, 74%Y).

Purification of the crude product by preparative TLC (silica gel, chloroform/benzene, 1:1) afforded ethyl 10,10-dimethyl prost-8(12), 15-dien-9,11-dionoate (63) (16mg, 16%Y) as a yellow oil.

IR(film)cm⁻¹ : 1738, 1698, 1630(w), 1466, 1373, 1178, 1108 and 1034
¹H-NMR(CDCl₃) δ : 0.90 (t, 3H), 1.01-1.87 (m, methyl, methylene envelope)
1.13 (s, <6H), 1.87-2.16 (m, <4H), 2.31, 2.45 (2t, >6H),
4.15 (q, 2H) and 5.25-5.56 (m broad, 1H).
MS : [M]⁺ 390 (30%) and [M-OEt]⁺ 345 (15%)
UV(EtOH) : λ_{max} 242, ε = 3,640
GC : Purity approximately 30% (by normalisation)

22. Preparation of ethyl 15-benzyloxy-eicos-9,11-dionoate (72)

A solution of 6-benzyloxy-2-undecanone (1.38g, 5m moles) in dry ether (5ml) was added dropwise (over a period of an hour) to a magnetically stirred slurry of diethyl azelate (2.44g, 10m moles) and prewashed sodium hydride (0.6g, 60% dispersion in oil, 15m mole) in ether (5ml), under a gentle stream of nitrogen. After the addition of ketone was completed, the suspension was gradually raised to 65° and maintained at that temperature for an hour. It was then allowed to cool to room temperature and left to stir overnight.

The resultant brown mixture was taken in benzene (50ml) and dry ethanol (4ml). More benzene (100ml) was added and the suspension was acidified with conc. HCl (4ml). The organic phase was separated, washed with saturated aqueous sodium bicarbonate, followed by water (2x20ml) and dried over anhydrous magnesium sulphate. Evaporation of benzene afforded the crude product (2.58g, 100%Y).

The crude product was passed down a heated vigreux column (200-210°/0.5torr) to remove DEA and other light-ends. The partially purified heavy-ends (1.78g, 75%Y) was further purified by column chromatography (silica gel, Pet. ether 60-80°/ether, 17:3). Final purification by preparative TLC (silica gel, Pet. ether 60-80°/ether, 7:3) afforded pure ethyl 15-benzyloxy-eicos-9,11-dionoate (72) (0.38g, 16%Y).

IR(film)cm⁻¹ : 1735, 1606, 732 and 696

¹H-NMR(CDCl₃) δ : 0.89 (t, 3H), 1.15-1.90 (m, 25H), 2.15-2.70 (m, 6H),
3.40 (m, broad, 1H), 3.50 (s, <1H), 4.12 (q, 2H),
4.48 (s, 2H), 5.45 (s, >1H) and 7.32 (s, 5H)

MS : no [M]⁺, measured 199.1334 (100%), C₁₁H₁₉O₃
Others m/e 178 (82%), 157 (83%), 153 (32%) and
152 (98%).

23. Preparation of ethyl 15-benzyloxy-10,10-dimethyl eicos-9,11-dionoate (73)

A solution of ethyl 15-benzyloxy-eicos-9,11-dionoate (808mg, 1.7m moles) in dry DME (21ml) was added dropwise to prewashed sodium hydride (164mg, 60% dispersion in oil, 4.3m moles), under a gentle stream of nitrogen. Brisk effervescence followed and the suspension was magnetically stirred at room temperature for 10 minutes. A solution of iodomethane (1.39g, 9.8m moles) in dry DMF (8ml) was added and stirred for a further 30 minutes. The reaction mixture was then gradually brought to reflux point (ca. 100-110°) and maintained for 6 hours. It was then left to cool to room temperature and stirred overnight.

The resultant mixture was evaporated under reduced pressure and taken up in ether (150ml) and water (20ml). The organic phase was separated, washed with more water (3x20ml) and dried over magnesium sulphate. Evaporation of the ether under reduced pressure, afforded the crude product (842mg, 99%Y).

Purification of the crude product by preparative TLC (silica gel, Pet. ether 60-80°/ether, 13:7) afforded ethyl 15-benzyloxy-10,10-dimethyl eicos-9,11-dionoate (73) (722mg, 85%).

IR(film)cm⁻¹ : 3080, 3045, 1736, 1719, 1696, 1462, 1369, 1176, 1091, 734 and 697.

¹H-NMR(CDCl₃) δ : 0.88 (t, 3H), 1.13-1.85 (m, methyl, methylene envelope), 2.17-2.54 (m, 6H), 3.21-3.53 (broad m, 1H), 4.13(q, 2H), 4.49 (s, 2H), 7.32 (m, 5H).

MS : No[M]⁺, measured 349.2742 (2%), C₂₂H₃₇O₃, [M-C₉H₁₃O₂]⁺ Others m/e 242 (7%), 199 (18%), 153 (10%), 125 (19%), 105 (74%) and 91 (100%)

24. Preparation of ethyl 15-benzyloxy-10,10-dimethyl prost-8(12)-en
-9,11-dionoate (74)

A solution of ethyl 15-benzyloxy-10,10-dimethyl eicos-9,11-dionoate (251mg, 0.5m mole) in dry ethanol (5ml) was added dropwise to a magnetically stirred solution of sodium ethoxide (prepared from Na, 58mg, 2.5m mole) in the same solvent (5ml), under a gentle stream of nitrogen. The resultant solution was stirred for 5 minutes at room temperature. A solution of iodine (254mg, 1m mole) in dry ethanol (6ml) was added dropwise (over a period of 2 minutes) and the reaction mixture was stirred at room temperature for a further 10 minutes.

The resultant mixture was evaporated under reduced pressure and taken up in ether (120ml) and water (35ml). The organic phase was separated, washed with sodium metabisulphate, water (2x20ml) and dried over anhydrous magnesium sulphate. Evaporation of the ether afforded the crude product (273mg)

Purification of the crude product by preparative TLC (silica gel, Pet. ether 60-80°/ether, 4:1, 3 passes) afforded ethyl 15-benzyloxy-10,10-dimethyl prost-8(12)-en-9,11-dionoate (74) (35mg, 14%Y) as a viscous yellow oil.

IR(film)cm⁻¹ : 1738, 1694, 1629, 1463, 1371, 1350, 1302, 1180, 1094, 735 and 697.

¹H-NMR(CDCl₃) δ : 0.89 (t, 3H), 1.03-1.90 (m, methyl, methylene envelope), 1.12 (s, 6H), 2.17-2.59 (m, 6H), 3.26-3.62 (m broad, 1H), 4.14 (q, 2H), 4.50(weak), 4.54 (2s, 2H) and 7.25-7.53 (m, 5H)

MS : $[M]^+$ measured 498.3338 (3%), calculated 498.3345
Others m/e $[M-OEt]^+$ (4%), 391 (25%) and 91 (100%)

UV(EtOH) : λ_{\max} 248nm, $\mathcal{E} = 5,790$

25. Preparation of nona-4,6-dione (119)

A solution of 2-pentanone (17.6g, 0.2 mole) in dry THF (40ml) and EtOH (0.5ml) was added dropwise (over a period of one hour) to a magnetically stirred slurry of prewashed sodium hydride (20.2g, 50% dispersion in oil, 0.42 mole) in ethyl butyrate (46.4g, 0.4 mole) and THF (40ml), under a gentle stream of nitrogen. An exothermic reaction commenced after 30 minutes. When the addition of ketone was complete, the reaction mixture was maintained at 60° for an hour. The thick brown suspension was then left to stir overnight at room temperature.

The crude product was evaporated under reduced pressure and taken up in ether (300ml) and water (100ml). The suspension was stirred in an ice-bath and acidified to pH1 by the dropwise addition of conc. HCl (50ml). The organic phase was separated, washed with water (4x50ml) and evaporated under reduced pressure to give the crude 1,3-diketone.

The copper complex^{202,203} of the 1,3-diketone was directly formed by the addition of a hot filtered aqueous solution of copper acetate (18.6g, 0.1 mole in 200ml of water) to a stirred solution of the 1,3-diketone in MeOH (100ml). The copper complex precipitated out of solution instantly. The suspension was allowed to cool to room temperature and the supernatant was decanted. The blue copper complex was redissolved in boiling MeOH (500ml) and on cooling to room temperature, greyish blue needles (20.26g, 54%Y) mp 159.5-160°, was obtained.

To obtain free nona-4,6-dione, the copper complex (7.47g, 0.02mole) was taken up in ether (150ml) and shaken with 2N HCl(75ml). The organic phase was separated, washed with water (4x20ml) and dried over anhydrous magnesium sulphate. On evaporation of the solvent, free nona-4,6-dione

(7.19g >100%Y) was obtained. Distillation at atmospheric pressure afforded pure nona-4,6-dione (119) (5.45g, 87%Y), bp 205-206^o, as a clear viscous strong smelling oil.

Copper (II) complex, mp 159.5-160^o (lit. 156^o 204)

Elemental analysis : Found C = 57.8 H = 8.0 Cu = 16.8

(C₉H₁₆O₂)₂Cu Theory C = 57.81 H = 8.09 Cu = 16.99

Nona-4,6-dione (119)

bp 205-206^o/1 atm. (lit bp 85-86^o/11 torr²⁰⁵)

IR(film)cm⁻¹ : 1707 (w), 1610 (s), and 945

¹H-NMR(CDC1₃) δ : 0.98 (t, 6H), 1.43-1.94 (m, 4H), 2.30, 2.52 (2t, 4H)
3.58 (s, < 1H) and 5.51 (s, 1H).

MS : [M]⁺ m_e 156 (21%) C₉H₁₆O₂
Others m/e 113 (100%), 71 (42%) and 43 (42%)

26. Preparation of trideca-6,8-dione (122)

A solution of 2-heptanone (22.8g, 0.2 mole) in dry THF (40ml) and EtOH (0.5ml) was added dropwise (over a period of an hour) to a magnetically stirred slurry of prewashed sodium hydride (20.2g, 50% dispersion in oil, 0.42 mole) in ethyl hexanoate (57.6g, 0.4 mole) and THF (80ml) under a gentle stream of nitrogen. An exothermic reaction commenced after 30 minutes. When the addition of the ketone was complete, the reaction mixture was warmed to 60° and maintained at that temperature for an hour. The thick brown suspension was stirred overnight at room temperature.

The resultant mixture was evaporated under reduced pressure and taken up in ether (300ml). The stirred suspension was cooled in an ice-bath and acidified to pH 1 by the dropwise addition of conc. HCl (50ml). The organic phase was separated, thoroughly washed with water (4x50ml) and evaporated under reduced pressure to afford the viscous 1,3-diketone.

The 1,3-diketone copper (II) complex was directly obtained by the addition of a hot filtered aqueous solution of copper acetate (18.6g, 0.1 mole in 150ml of water) to a solution of the diketone and allowed to cool to room temperature. The aqueous supernatant was decanted and the copper complex was redissolved in boiling MeOH (900ml). On standing to cool, greyish blue needles of the copper complex (34.6g, 72%Y), mp 120-121° was obtained.

To obtain free trideca-6,8-dione, its copper complex (14.32g, 0.03 mole) was taken up in ether (200ml) and shaken with 2N HCl (75ml). The organic phase was separated, washed with water (4x20ml) and dried over anhydrous magnesium sulphate. On evaporation of the ether, free trideca-6,8-dione (122) (12.58g, 99%Y) was obtained. Distillation of this product afforded pure trideca-6,8-dione (11.93g, 94%Y) as a viscous strong smelling

colourless oil.

Copper (II) complex, mp $120-121^{\circ}$, bluish grey needles, (lit. $119-120^{\circ}$ ²⁰⁶)

Elemental analysis : Found C = 64.7 H = 9.9 Cu = 13.2

$(C_{13}H_{24}O_2)_2Cu$ Theory C = 64.34 H = 9.54 Cu = 13.07

Trideca-6,8-dione (122)

bp. $124-126^{\circ}/2.5$ torr (lit. $162-164^{\circ}/20$ torr²⁰⁷)

IR(film) cm^{-1} : 0.89 (t, 6H), 1.13-1.84 (m, 12H), 2.28, 2.51 (2t, 4H),
3.56 (s, <1H) and 5.48 (s, 1H)

MS : $[M]^{\dagger} m/z$ 212 (13%), $C_{13}H_{24}O_2$
Others m/e 141 (100%), 99 (78%) and 71 (33%)

27. Dimethylation of nona-4,6-dione (119) and trideca-6,8-dione (122)

A solution of the 1,3-diketone (2m moles) in dry DME (10ml) was added dropwise to prewashed sodium hydride (192mg, 50% dispersion in oil, 4m moles), under a gentle stream of nitrogen. The suspension was magnetically stirred for a period of 15 minutes. A solution of iodomethane (710mg, 5m moles) in dry DMF (10ml) was added dropwise (over a period of 30 minutes) to the suspension and stirred for a further 30 minutes. The reaction mixture was then gradually brought to 100° in an oil bath and maintained at that temperature for 2 hours. The solution was left to cool to room temperature and left stirring overnight.

The resultant suspension was evaporated under reduced pressure and taken up in ether (150ml). The organic phase was washed with water (4x20ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure. The crude dimethyl 1,3-diketone was obtained as a pale yellow oil with peppermint odour. This was further purified by distillation under reduced pressure.

5,5-dimethyl nona-4,6-dione (126), 88%Y.

bp 105-110°/8 torr (lit. bp 129-130°/18 torr ²⁰⁸)

IR(film)cm⁻¹ : 1718, 1698, 1368, 1110 and 1009

¹H-NMR(CDCl₃) δ : 0.90 (t, 3H), 1.35 (s, 6H), 1.40-1.85 (m, 4H)
and 2.41 (t, 4H)

MS : m/e 114 (90%), 105 (5%), 99 (9%), 86 (31%)
and 71 (100%).

7,7-dimethyltrideca-6,8-dione (127) 83%Y

bp 115-120°/ 1 torr

IR(film)cm⁻¹ : 1721, 1699, 1385, 1368, 1119, 1045 and 999.

¹H-NMR(CDC1₃)δ : 0.89 (t, 6H), 1.03-1.80 (m, methylene envelope),
1.33 (s, 6H) and 2.33 (t, 4H).

MS : m/e 142 (49%), 99 (100%), 86 (67%), 71 (62%) and
71 (21%).

28. Preparation of the dibromo-diketones (131) and (132) from their
respective 1,3-diketones (126) and (131)

A solution of the dimethyl 1,3-diketone (3m moles) in dry THF (2.5ml) was added in one portion to a magnetically stirred solution of triphenylmethyllumonium perbromide, (2.26g, 6m moles) in dry THF (2.5ml). The orange solution was stirred overnight at room temperature. (Precipitation of the ammonium salt generally occurs after 15-60 minutes).

The resultant suspension was evaporated under reduced pressure and taken up in ether (150ml)/water (20ml). The organic phase was washed with more water (4x20ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure (do not overheat above 50°). The crude dibromo-diketone was obtained as a thick, pale yellow, lachrymatory oil. This was further purified by column chromatography (silica gel, Pet. ether 60-80°/ether, 3:1) to afford pure dibromo-diketone.

3,7-dibromo-5,5-dimethyl nona-4,6-dione (131)

IR(film)cm⁻¹ : 1728, 1699, 1383, 1320, 1110, 1030 and 900.
¹H-NMR(CDCl₃) δ : 1.00 (t, 3H), 1.03 (t, 3H), 1.56, 1.61, 1.69 (3s, 6H),
2.03 (m, 4H), 4.50 (t, 1H) and 4.54 (t, 1H).
MS : [M-HBr]⁺, 262 (16%), 260 (16%)
Others m/e 151 (31%), 149 (31%), 123 (30%), 121 (31%),
113 (49%), 95 (61%), 57 (59%) and 41 (100%)

5,9-dibromo-7,7-dimethyltrideca-6,8-dione (132)

IR(film) cm^{-1} : 1728, 1699, 1371, 1110 and 1047

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 0.92 (t, 6H), 1.06-1.52 (m, 8H), 1.56, 1.61, 1.69 (3s, 6H), 1.79-2.25 (m, 4H), 4.54(t, 1H) and 4.57 (t, 1H).

MS : $[\text{M-HBr}]^+$ 318 (18%), 316 (18%)
Others m/e 247 (6%), 249 (6%), 177 (7%), 179 (7%),
141 (51%), 123 (80%), 97 (52%), 85 (68%), 70 (43%)
and 69 (100%).

29. Preparation of diiodo-diketones (137) and (138) from their respective dibromo-diketones (129) and (130)

A solution of sodium iodide²¹⁰ (480mg, 3.2m mole) in dry acetone (6ml) was added in one portion to a magnetically stirred solution of the dibromo-diketone (1.5m mole) in the same solvent (6ml). Immediate precipitation of sodium bromide occurred and the reaction mixture was stirred at room temperature for 30 minutes.

The resultant mixture was evaporated under reduced pressure, taken up in ether (150ml) and washed with sodium metabisulphite, followed by water (4x20ml). The organic phase was separated, dried over anhydrous magnesium sulphate and evaporated under reduced pressure (do not heat) to afford the diiodo-diketone as a viscous yellow liquid.

3,7-diiodo-5,5-dimethylnona-4,6-dione (137) (91%Y)

IR(film)cm⁻¹ : 1719 and 1688
¹H-NMR(CDC1₃) δ : 0.98, 1.01 (2t, 6H), 1.67, 1.73, 1.80 (3s, 6H),
1.73-2.20 (quintet, 4H), 4.65 and 4.70 (2t, 2H)
MS : [M-I]⁺ m/e 309 (5%)

5,9-diiodo-7,7-dimethyltrideca-6,8-dione (138) (100%Y)

IR(film)cm⁻¹ : 1720 and 1690 (contaminant peak at 1620).
¹H-NMR(CDC1₃) : 0.93 (t, 6H), 1.09-1.60 (m, 8H), 1.67, 1.72, 1.80
(3s, 6H), 1.74-2.14 (m, 4H), 4.71 and 4.76 (2t, 2H).
MS : [M-I]⁺ m/e 365 (52%)
TLC : Silica gel, Pet. ether 60-80/ether (3:1)
In each case, the diiodo-diketone appeared as two bands which ran very close to one another. They were presumed to be the (+,-) and (meso) isomers.

30. Preparation of 4,5-diethyl-2,2-dimethyl-cyclopent-4-en-1,3-dione (143)

A magnetically stirred solution of 3,7-dibromo-5,5-dimethyl nona-4,6-dione (131) (684mg, 2m moles) in dry triethylamine (8ml) and acetonitrile (12ml) was maintained at near reflux temperature (oil bath at 65-70°) for 16 hours, with the exclusion of moisture.

The resultant dark brown suspension was evaporated under reduced pressure and taken up in ether (150ml). The suspension was washed with 2N HCl(2x10ml) and water (4x20ml). The organic phase was separated, dried over anhydrous magnesium sulphate and evaporated under reduced pressure to afford a crude dark brown oil (344mg, 96%Y).

The crude product was separated into two major components by preparative TLC (silica gel, Pet. ether 60-80°/ether, 4:1). The higher Rf band afforded the 4,5-diethyl-2,2-dimethyl-cyclopent-4-en-1,3-dione (143) as a yellow oil (114mg, 32%Y). The lower Rf band afforded an unknown cyclic hemiketal as a viscous colourless oil (97mg, 28% w/w of crude product).

4,5-diethyl-2,2-dimethyl-cyclopent-4-en-1,3-dione (143)

IR(film)cm⁻¹ : 1741, 1693, 1630, 1381, 1351, 1302, 1178 and 1078.
¹H-NMR(CDCl₃) δ : 1.14, 1.14 (s, t, 12H) and 2.52 (q, 4H).
MS : [M]⁺ measured 180.1141 (4%), calculated 180.1150, C₁₁H₁₆O₂
[M + H]⁺ measured 181.1223 (24%), calculated 181.1128, C₁₁H₁₇O₂
Others m/e 112 (24%), 85 (33%), 71 (27%), 70 (49%)
and 69 (100%)

Unknown cyclic hemiketal (144)

IR(film) cm^{-1} : 3450, 1764, 1726, 1383, 1098 and 1045

NMR(CDCl_3) δ : 0.93-1.28 (m, 12H), 1.58-2.12 (m, 4H), 2.62-3.07 (m, 2H), 3.90-4.52 (m, 2H, one exchangeable proton).

MS : Highest ion measured 198.1254 (3%), $\text{C}_{11}\text{H}_{18}\text{O}_3$ cal.198.1256 and strong ion at 157.0863 (51%), $\text{C}_8\text{H}_{13}\text{O}_3$ cal.157.0864 Others m/e 115 (46%), 112 (25%), 87 (69%), 71 (24%), 70 (62%), 69 (100%) and 57 (38%).

31. Preparation of 4,5-di-*n*-butyl-2,2-dimethyl-cyclopent-4-en-1,3-dione (147)

A magnetically stirred solution of 5,9-dibromo-7,7-dimethyl trideca-6,8-dione (690mg, 1.73m moles) in dry triethylamine (8ml) and acetonitrile (12ml) was maintained at 70-75^o, under a gentle stream of nitrogen, for a period of 19 hours.

The resultant dark brown suspension was evaporated under reduced pressure and taken up in ether (150ml). The suspension was washed with 2N HCl (2x10ml), followed by a thorough wash with water (4x20ml). The organic phase was separated, dried over anhydrous magnesium sulphate and evaporated under reduced pressure to afford the crude product (456mg, >100%Y) as a dark brown oil.

The crude product was purified into two major components by preparative TLC (silica gel, Pet. ether 60-80^o/ether, 3:1). The higher R_f band afforded 4,5-di-*n*-butyl-2,2-dimethyl-cyclopent-4-en-1,3-dione (147) (228mg, 56%Y) as a clear yellow oil. The lower R_f band afforded an unknown cyclic hemiketal (148) as a colourless viscous oil (44mg, 10% w/w of crude).

4,5-di-*n*-butyl-2,2-dimethyl-cyclopent-4-en-1,3-dione (147)

IR(film)cm⁻¹ : 1740, 1693, 1625, 1380, 1352, 1302, 1172, 1089 and 1010.

¹H-NMR(CDCl₃)δ : 0.94 (t, 6H), 1.12 (s, 6H), 1.21-1.72 (m, 8H) and 2.47 (t, 4H).

MS : [M]⁺ measured 236.1776 (9%), calculated 236.1776, C₁₅H₂₄O₂

Lower Rf unknown (148)

IR(film) cm^{-1} : 3430, 1763, 1722, 1384, 1259, 1138, 1113 and 1054.

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 0.94, 1.01 (t + s, 9H), 1.18 (s, 3H), 1.26-2.00 (m, methylene envelope), 2.62-2.94 (m, 2H), 3.49-4.05 (broad s, 1H, D_2O exchangeable) and 4.05-4.45 (m, 1H)

MS : Ions measured at

320.1145(2%), calculated 320.1130 ($\text{C}_{14}^{13}\text{H}_{26}\text{O}_2^{81}\text{Br}_1$)

319.1116(9%), calculated 319.1095 ($\text{C}_{15}\text{H}_{26}\text{O}_2^{81}\text{Br}_1$)

318.1111(3%), calculated 318.1149 ($\text{C}_{14}^{13}\text{H}_{26}\text{O}_2^{79}\text{Br}_1$)

317.1139(10%), calculated 317.1114 ($\text{C}_{15}\text{H}_{26}\text{O}_2^{79}\text{Br}_1$)

Others m/e 254(11%), 237(16%), 185(97%), 97(77%), 85(100%)
and 71(41%)

32 Formation of methyl ketal (152a) from the unknown cyclic hemiketal (148)

A solution of the unknown cyclic hemiketal (148) (50mg) in anhydrous MeOH (2ml) and acetyl chloride (2 drops) was magnetically stirred at room temperature, under a gentle stream of nitrogen, for a period of 16 hours and subsequently maintained at 40° for 8 hours.

The resultant solution was evaporated under reduced pressure and dried by azeotropic removal of added dry benzene (2x5ml), to afford the crude product (52mg, 100%Y) as a viscous colourless oil.

The crude product was purified by preparative TLC (silica gel, Pet. ether 60-80°/ether, 3:1) to afford the methyl cyclic ketal (152a) (27mg, 53%Y) and unreacted cyclic hemiketal (148) (13mg) (Yield of methyl ketal (152a) based on reacted cyclic hemiketal is 69%).

IR(film)cm⁻¹ : 1766, 1725, 1383, 1365, 1116 and 937.

NMR(CDCl₃) δ : 0.76-1.10 (m, 9H), 1.19 (s, 3H), 1.10-2.10 (m, methylene envelope), 2.67 (t, 2H), 3.21 (s, 3H) and 3.66-4.43 (m, 1H).

MS : m/e 253 (7%), 199 (92%), 97 (82%), 85 (98%), 70 (98%) and 57 (100%).

33. Acetylation of the unknown cyclic hemiketal (148)

A solution of the unknown hemiketal (149mg) in dry acetic anhydride (224mg), triethylamine (10ml) and a few crystals of 4-dimethylamino-pyridine¹⁸⁹ was magnetically stirred at room temperature for 88 hours, under a nitrogen blanket.

The resultant solution was evaporated under reduced pressure and taken up in ether (150ml). The organic phase was washed with 2N HCl (2ml), water (4x20ml) and dried over anhydrous magnesium sulphate. Removal of the ether under reduced pressure, afforded the crude cyclic ketal acetate (180mg) as a pale yellow oil.

The crude product was purified by preparative TLC (silica gel, Pet. ether 60-80°/ether 4:1) to give a mixture of acetates (115mg). On TLC these acetates appeared as two very close bands. This partially purified mixture of acetates was further separated by careful preparative TLC (silica gel, Pet. ether 60-80°, 2 passes followed by Pet. ether 60-80°/ether 4:1, single pass) to afford a high R_f band as a semi-crystalline solid (45mg) and a low R_f band as a viscous colourless oil (53mg).

Higher R_f. acetate (156)

IR(film)cm ⁻¹	: 1740, 1720, 1382, 1373, 1255, 1182 and 926
¹ H-NMR(CDCl ₃) δ	: 0.93 (t, 6H), 1.35, 1.37 (2s, 6H), 1.20-1.95 (m, methylene envelope), 2.06 (s, 3H), 4.16 and 4.20 (2d, 1H).
MS	: m/e 253 (8%), 242 (32%), 158 (21%), 140 (100%), 125 (15%), 96 (26%), 85 (53%) and 70 /100%

Lower Rf acetate (155a)

IR(film) cm^{-1} : 1760, 1729, 1384, 1371, 1239, 1109 and 932

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 0.94 (t, 6H), 1.00 (s, 3H), 1.23 (s, 3H), 1.30-1.90 (m, methylene envelope), 2.04 (s, 3H), 2.39, 2.60 (2t, 1H), 3.13, 3.33 (2t, 1H) and 4.12 (t, 1H)

MS : m/e 269 (5%), 253 (7%), 227 (10%), 185 (98%), 167 (11%), 115 (14%), 97 (29%), 87 (12%), 85 (85%), 70 (22%), 57 (33%) and 43 (100%)

34. Cyclisation of the diiodo-diketones (137) and (138) in triethylamine/
acetonitrile

A magnetically stirred solution of the diiodo-diketone (0.5m mole) in dry triethylamine (4ml) and acetonitrile (6ml) was maintained at 65° for a period of 16 hours, with the exclusion of moisture.

The resultant suspension was evaporated under reduced pressure and taken up in ether (150ml)/water (20ml). The organic phase was separated, washed with 2N HCl(5ml), followed by water (3x20ml) and dried over anhydrous magnesium sulphate. On evaporation of the solvent, a dark brown crude product was obtained.

The amount of the dimethyl cyclopentene-1,3-dione (144) and (147) in their respective crude products was estimated by GLC and UV determinations.

Purification of the crude product in each case, afforded a higher Rf. band containing the dimethyl cyclopentene-1,3-dione and a lower Rf. band containing an unknown cyclic hemiketal.

35. Cyclisation of the diiodo-diketones (137) and (138) in sodium ethoxide/
ethanol.

A solution of the diiodo-diketone (0.5m mole) in anhydrous ethanol (5ml) was added dropwise (addition period of about a minute) to a magnetically stirred solution of sodium ethoxide (1m.mole) in ethanol (5ml) at room temperature, under a gentle stream of nitrogen. The yellowish solution was stirred for a further 45 minutes.

The resultant solution was evaporated under reduced pressure and taken up in ether (150ml)/water (10ml). The organic phase was separated, washed with more water (3x20ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded the crude product.

The amount of the dimethylcyclopentene-1,3-dione (144) and (147) in their respective crude products was estimated by GLC and UV determinations.

APPENDIX

The ^{13}C -NMR spectra of a selected number of compounds prepared in this project are presented here. A correlation diagram of ^{13}C -NMR chemical shifts relative to tetramethylsilane (TMS) of these compounds are shown in figure 1. Details of the ^{13}C -NMR spectra of these compounds are entered below.

^{13}C -NMR data (CDCl_3 , in ppm relative to TMS)

Assignments are based on the numbering system shown in figure 1.

- (i) 4,5-diethyl-2,2-dimethyl cyclopent-4-en-1,3-dione (143)
207.25 (C-4, C-6), 156.90 (C-3, C-7), 45.38 (C-5), 19.94 (C-10, C-11),
17.19 (C-2, C-8) and 12.69 (C-1, C-9).
- (ii) 4,5-di-n-butyl-2,2-dimethyl cyclopent-4-en-1,3-dione (147)
207.51 (C-6, C-8), 156.20 (C-5, C-9), 45.46 (C-7), 30.30 (C-4, C-10),
23.80 (C-3, C-11), 22.96 (C-2, C-12), 20.03 (C-14, C-15) and
13.79 (C-1, C-13).
- (iii) Methyl 10,10-dimethyl prost-8(12)-en-9,11-dionoate (25)
207.34 (C-9, C-11), 156.27 (C-8, C-12), 51.39 (C-23), 45.54 (C-10),
34.00 (C-2), 31.81 (C-18), 29.79 (C-7, C-13), 29.48 (C-4),
29.17 (a), 27.99 (a), 24.80 (C-3), 24.02 (a), 22.61 (C-19),
20.04 (C-21, C-22) and 14.04 (C-20).
- N.B.: ^1H -NMR spectrum of the same sample confirmed the presence of the carbomethoxy group. However, the ^{13}C -NMR spectrum only showed the $-\text{COOCH}_3$ carbon (51.39 ppm), the acyl carbon ($-\text{C}(=\text{O})\text{OCH}_3$, expected at ca. 174.1) was not detected.

(iv) N-phenyl 10,10-dimethyl prost-8(12)-en-9,11-dionamide (47)

207.71, 207.38 (C-9, C-11), 171.16 (C-1), 156.46, 155.94 (C-12, C-8),
138.00, 129.02, 124.27, 119.85 (aromatic ring carbons), 45.52 (C-10),
37.65 (C-2), 31.87 (C-18), 30.11 (a), 29.72 (a), 29.46 (a),
29.26 (a), 29.13 (a), 28.81 (a), 28.22 (a), 27.96 (a),
25.49 (a), 25.36 (a), 23.93 (a), 22.70 (a), 20.03 (C-21, C-22)
and 14.11 (C-20).

N.B.: More peaks appeared in the spectrum than can be accounted for by
the number of carbons possessed by (47). The presence of impurities is
expected as the UV data of (47) showed it to be impure.

(v) 5,5-dimethyl nona-4,6-dione (126)

209.52 (C-4, C-6), 62.31 (C-5), 40.30 (C-3, C-7), 21.31 (C-10, C-11),
17.27 (a) and 13.65 (a)

(vi) 7,7-dimethyl trideca-6,8-dione (127)

209.42 (C-6, C-8), 62.48 (C-7), 38.34 (C-5, C-9), 31.51 (C-3, C-11),
23.61 (C-4, C-10), 22.61 (C-2, C-12), 21.35 (C-14, C-15) and
13.92 (C-1, C-13)

(vii) Ethyl 10,10-dimethyl eicos-9,11-dionoate (17)

209.53 (C-9, C-11), 173.45 (C-1), 62.40 (C-10), 60.06 (C-23),
38.30 (C-8, C-12), 34.27 (C-2), 31.93 (C-18), 29.47 (a),
29.30 (a), 29.12 (a), 29.01 (a), 24.91 (C-3), 23.74 (C-7),
22.69 (C-19), 21.29 (C-21, C-22), 14.27 (C-24), and 14.09 (C-20)

(viii) Ethyl 10,10-dimethyl-15-benzyloxy eicos-9,11-dionoate (74)

209.53 (C-9, C-11), 173.56 (C-1), 138.94, 128.24, 127.66, 127.31
(aromatic ring carbons), 78.65 (C-15), 70.70 (O-CH₂Ph),
62.22 (C-10), 60.00 (C-23), 38.30 (C-8, C-12), 34.20 (C-2),

33.62 (a), 33.10 (a), 32.05 (C-18), 28.95 (a),
24.91 (C-3), 23.68 (C-7), 22.63 (C-19), 21.29 (C-21, C-22),
19.65 (a), 14.21 (C-24) and 14.09 (C-20).

(ix) Nona-4,6-dione (119)

(204.06), 194.33 (C-4, C-6), 99.28 (C-5)²¹⁴, (57.18), (45.74),
40.45 (C-3, C-7), 19.29 (C-2, C-8), (19.02), (17.05),
13.78 (C-1, C-9).

(x) Trideca-6,8-dione (122)

(203.96), 194.44 (C-6, C-8), 99.04 (C-7), (57.19), (43.77),
38.49 (C-5, C-9), (31.46), 25.57 (C-4, C-10), (23.30),
22.60 (C-2, C-12) and 13.95 (C-1, C-13).

(xi) Ethyl eicos-9,11-dionoate (3)

194.32 (C-9, C-11), 173.45 (C-1), 99.00 (C-10), 60.06 (C-23),
38.42 (C-8, C-12), 34.33 (C-2), 31.99 (C-18), 29.36 (a),
29.12 (a), 25.79 (a), 24.97 (C-3), 22.75 (C-19), 14.33(C-24)
and 14.15 (C-20)

(xii) Eicos-9,11-dionoic acid (4)

(204.50), 194.44 (C-9, C-11), 179.82 (C-1), 99.00 (C-10), (57.02),
(43.74), 38.36 (C-8, C-12), 34.03 (C-2), 31.93 (C-18), 29.36 (a),
29.01 (a), 25.67 (a), 24.62 (C-3), (23.39), (23.27), 22.69
(C-19) and 14.09 (C-20)

(xiii) Ethyl 15-benzyloxy-eicos-9,11-dionoate (74)

194.38, 194.03 (C-9, C-11), 173.68 (C-1), 139.00, 128.24, 127.66,
127.37 (aromatic ring carbons), 99.00 (C-10), 78.59 (C-15),
70.76 (O-CH₂Ph), 60.12 (O-CH₂CH₃), (55.20), (43.74),

38.36 (C-8, C-12), 34.27 (C-2), 33.68 (a), 33.33 (a),
31.99 (C-18), 28.95 (a), 25.61 (a), 24.91 (a), (23.27),
22.63 (C-19), 21.52 (a), 14.21 (O-CH₂-CH₃) and 14.03 (C-20)

(xiv) 6-benzyloxy-undeca-2-one (67)

208.53 (C-2), 139.06, 128.24, 127.72, 127.37 (aromatic ring carbons)
78.65 (C-6), 70.76 (O-CH₂Ph), 43.62 (C-3), 33.68 (a), 33.22 (a)
32.05 (C-9), 29.71 (a), 24.97 (a), 22.63 (C-10), 19.71 (a)
and 14.03 (C-11)

(xv) Diethyl azelate (1)

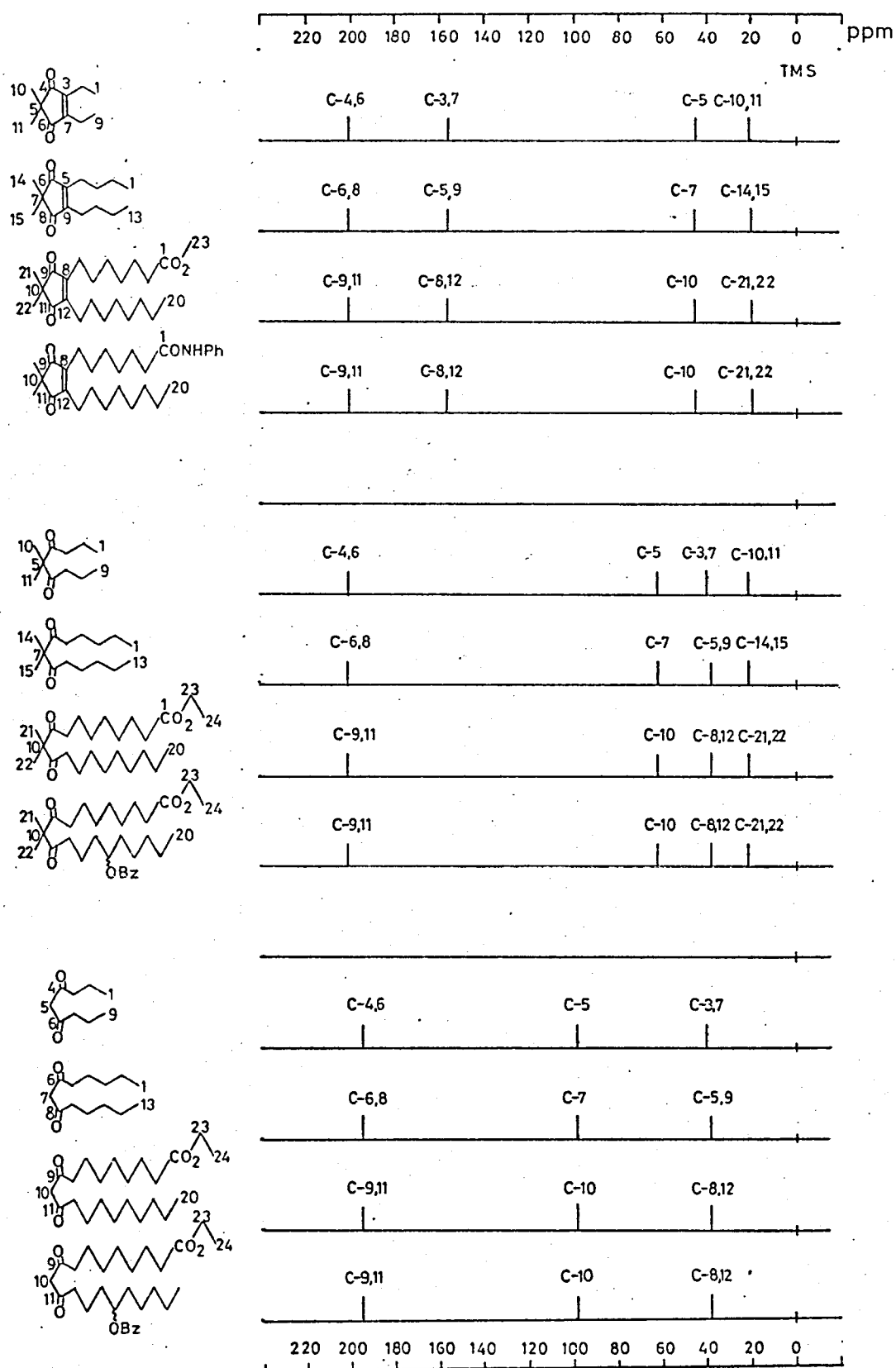
173.68 (C-1), 60.12 (O-CH₂CH₃), 34.33 (C-2, C-8), 28.95 (C-4,5,
and 6), 24.91 (C-3, C-7) and 14.27 (O-CH₂-CH₃)

N.B.: (a), assignment ambiguous or undetermined. Weak signals are shown
in brackets.

The ¹³C-NMR assignments made above were based on a careful comparison
between known ¹³C-NMR data of natural PG^{39, 40}, PG analogues⁴² and
other relevant model compounds, ^{86, 119, 120, 135}.

APPENDIX FIGURE 1.

CORRELATION DIAGRAM OF ^{13}C NMR CHEMICAL SHIFTS RELATIVE TO
TMS OF SOME PROSTANOIDS AND RELATED COMPOUNDS.



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