Progress in Organic Chemistry

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8

Joint Editors

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FOREWORD

EIGHT THEMES covering a range of topics of current interest to organic chemists are discussed in the present volume, following the pattern laid down by the original editor of the series, Professor J. W. Cook, and successfully followed in earlier volumes. Four of the chapters are concerned directly with aspects of the chemistry of natural products and a fifth discusses the synthesis of a group of natural products by routes which simulate the supposed biosynthetic pathways. A sixth chapter reviews a fascinating series of chemiluminescent reactions, while the seventh and eighth chapters discuss practical and mechanistic aspects of two important reactions in organic chemistry. As in earlier volumes of the series all the authors are · specialists who have themselves contributed to the fields of work which they have reviewed.

In the first chapter, Dr. Clarkson reviews recent work on the synthesis of compounds of the prostaglandin series. The chemical structures of these compounds only became generally known about ten years ago, but since then they have aroused a great deal of interest on account of their powerful physiological action and potential therapeutic usefulness. Because of the difficulties encountered in obtaining sufficient material from natural sources attention has turned to the chemical synthesis of the compounds, and Dr. Clarkson gives an illuminating account of the ingenious methods which have been used to overcome the formidable difficulties involved.

The variety of complex structures found among the terpenoid class of natural products has provided a constant challenge to the synthetic organic chemist, as well as to those interested in biosynthesis. With a view to providing experimental evidence in support of biosynthetic proposals and speculations, and also, possibly, of developing more direct synthetic routes to the compounds concerned, increasing attention has been paid in recent years to the synthesis of natural products by routes which simulate the supposed biosynthetic pathway. In Chapter 2 Dr. Money's stimulating article provides a valuable survey of recent work in this direction in the terpenoid field, and draws attention to the remarkable successes which have already been achieved.

Two other classes of natural products of great current interest are the cannabinoids, which include the active components of *Cannabis* preparations, and the penicillins. The latter have recently acquired added interest through the discovery of the antibacterial activity of the related cephalosporins, and this work has given rise to ideas about structure—activity relationships in the series which are leading to attempts at chemical synthesis of analogues of the natural products. Among the cannabinoids, considerable progress has been made in elucidating the structures of many of the naturally

occurring compounds and in synthesising some of them. The fascinating chemistry involved in both these general fields is ably reviewed in Chapters 3 and 4 by Dr. Razdan and by Dr. Stoodley.

In Chapter 5 Dr. Hardy and Dr. Ridge give a clear and systematic account of recent work on the chemistry of cyclic peptides, an important group of compounds which includes a number of naturally occurring substances with powerful biological activity. The activity of many of the latter is dependent not only on their structure but also on their conformation, and the chemical factors which control this and the methods used for determining the conformations are among the topics discussed in this article.

One of the most intriguing natural phenomena is bioluminescence, the emission of visible light by living organisms. It is now known that this light emission is due to chemical reaction, but it is only in the last ten years that some insight has been gained into the mechanism of the phenomenon. The different types of chemical reaction which can give rise to chemiluminescence, the mechanism of light emission and the relation of the naturally occurring processes to the laboratory reactions are considered by Dr. McCapra in his most interesting and lucid account in Chapter 6.

The penultimate chapter of the book is concerned with nitration. Although this reaction has been used by organic chemists for a very long time and has been much studied it still holds some secrets. In a stimulating article Dr. Hartshorn and Dr. Schofield discuss some recent work on nitrating systems and some results which have been obtained from nitration which bear on the problem of aromatic reactivity.

Finally, Dr. McQuillin reviews catalytic hydrogenation under homogenous conditions with soluble transition metal catalysts. Because of the greatly increased selectivity which can often be obtained, these reactions have been receiving increased attention in recent years, and Dr. McQuillin gives a valuable survey of the scope of these reactions and discusses present knowledge about the reaction mechanisms.

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CONTENTS

THE SYNTHESIS OF PROSTAGLANDINS

R. Clarkson

INTRODUCTION

THE NAME prostaglandin was given by von Euler in 1935[1] to that part of the lipid fraction of human seminal plasma which showed powerful smooth muscle stimulatory properties. It was some 28 years later, however, before the chemical structures of the compounds responsible became generally known[2]. Since this initial phase, the growth of prostaglandin research has been almost logarithmic and the compounds have been shown to be involved in a wide range of physiological processes and to have potential therapeutic utility in several areas[3].

Chemistry

Over 20 different natural prostaglandins have now been isolated and the structures of the more important compounds are given in *Figure 1.1*. All are derived from the C-20 cyclopentane acid, prostanoic acid, which has the absolute stereochemistry shown. In prostaglandin-E_1 (PGE_1) the cyclopentane ring carries a β-ketol function and the alkyl chain contains a *trans*-allylic alcohol system. Prostaglandins of the second series (e.g. PGE_2) have in addition a *cis* double bond in the 5,6-position, while those of the third series (e.g. PGE_3) have a further *cis*-double bond at the 17,18-position. Replacement of the 9-keto group of either prostaglandin E_1, E_2 or E_3 by an α-hydroxyl group affords prostaglandin $F_{1\alpha}$, $F_{2\alpha}$ and $F_{3\alpha}$ respectively. Prostaglandins of the A-series (A_1, A_2, A_3) have the 9-keto-Δ^{10} system and are readily prepared by mild acid-catalysed dehydration of the corresponding prostaglandin E. Treatment of either a prostaglandin A or E with strong base leads to the
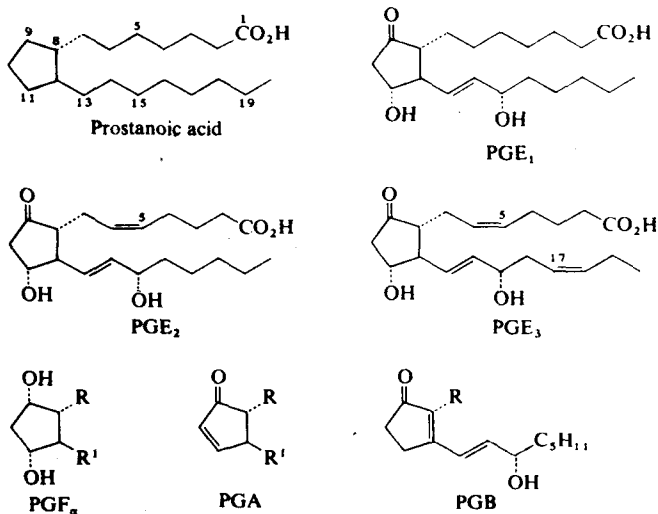
Figure 1.1

B-series which shows the dienone chromophore (λ_{max} 278 nm). This is frequently used as a means of estimating prostaglandins A or E. The six compounds (E, F_a, of the 1st, 2nd and 3rd series) are the primary prostaglandins[4] whose synthesis will be considered below. For details of their isolation, structure elucidation, biosynthesis and basic chemistry the reader is referred to the several excellent reviews which are now available, and in particular to those of Bergström[4] and of Samuelsson[5,6].

These primary compounds together with those of the A and B series are not the only naturally occurring prostaglandins. 19-Hydroxylated compounds are fairly common[7]; 8-iso-PGE$_1$ has been isolated[8]; a range of metabolites of primary prostaglandins have now been identified[9]; modified biosyntheses have produced homologues[10] and some rather unusual cyclic ethers[11]; and derivatives of 15-epi-A$_2$ have been isolated from a species of gorgonia[12]. The last finding is particularly interesting in that it could provide a supply of raw material for synthetic work (*see* below). However, these compounds are not themselves synthetic targets and the list is included merely to maintain perspective.

Biological Activity

This is a somewhat strange heading in a review concerned with synthesis but it is important that the main driving force behind the synthetic effort should be mentioned, however briefly.

The prostaglandins are fascinating not only on account of the wide range of biological response they produce but also because of their sheer potency. Concentrations as low as 1 part in 10^9 can readily be detected by biological assays. However, it is the demonstration, in the past few years, that prostaglandins have clear and important therapeutic utilities which has intensified

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the volume of research and has attracted almost all the large drug companies into the field.

Among the clinical studies recently carried out, the effects of prostaglandins on reproduction have been most widely studied and have shown the effectiveness of E_2 or $F_{2\alpha}$ as agents for inducing normal labour at term and for inducing therapeutic abortions. Their possible utility as contraceptives has also been demonstrated. Limited clinical investigation has been carried out into the use of prostaglandins for the relief of asthmatic bronchospasm and as agents to control blood pressure. Other potential clinical uses are in the treatment of thrombosis, of obesity and of certain types of stomach ulcers.

Of the many detailed reviews on the physiological actions of prostaglandins, those of Horton[13] and of Speroff and Ramwell[14] are particularly recommended. Shorter, more general accounts and speculations on the clinical future of prostaglandins are also available[15].

The prostaglandins have now been isolated from a wide variety of body tissues and fluids. They probably act as local regulatory hormones, being synthesised on demand at the site of action and then rapidly deactivated to limit their sphere of influence. This rapid metabolic deactivation of prostaglandins ($c.$ 95% of a dose of E_1 is deactivated by one pass through the circulation[16]) is one of the problems which must be overcome before they can be generally used in therapy. Another serious drawback is that prostaglandins have too wide a range of activity and ways must be found of selecting the particular type of action required if undesirable side effects are to be avoided. This latter problem becomes more acute in the case of metabolically stable prostaglandins.

Synthetic Aims

The main target of the synthetic chemists has been to make the primary prostaglandins available for detailed evaluation in both the laboratory and the clinic.

Until recently PGE_1 and PGE_2 were biosynthesised (*see Figure 1.2*) from the essential fatty acids bishomo-γ-linolenic (Ia) and arachidonic (Ib) acids, respectively, using an enzyme preparation obtained from ram seminal
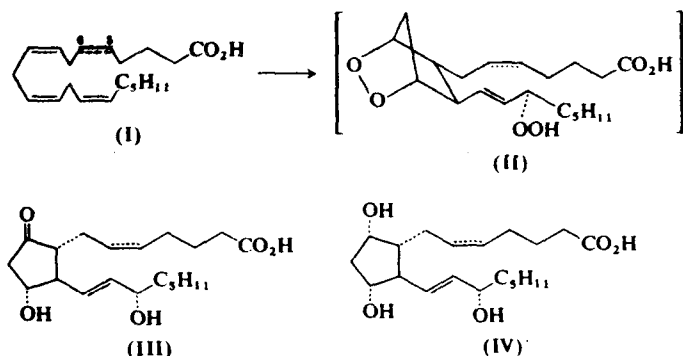

Figure 1.2. (a) 5,6-saturated; (b) 5,6-cis double bond

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vesicles[17,18]. It is generally assumed that a peroxide such as (II) is an intermediate which on rearrangement and/or reduction affords either E (III) or F_a (IV) prostaglandins. This particular preparation produces mainly PGE which, on borohydride reduction, affords both PGF_a and its 9-epimer (PGF_β) in roughly equal amounts[19]. The limitations of such a biosynthesis are apparent when one considers that an enzyme preparation from 1 kg of seminal vesicle tissue is needed to transform one gramme of essential fatty acid to give, at best 250–300 mg of PGE. The seminal vesicles from one ram weight approximately 20 g.

The first criterion then is that a chemical synthesis should compete effectively with biosynthesis. The second is that the synthesis should be easily modified in order to prepare analogues with improved selectivity and stability to metabolic degradation. Metabolism appears to be confined to the side-chains—β-oxidation of the acid side-chain to produce the essentially inactive *bis* and *tetra*-nor-acids[20], and oxidation of the 15-hydroxyl group to give the inactive a,β-unsaturated ketone[21]. An effective synthesis should therefore allow variation of the substitution around these areas of the molecule.

Choice of Synthetic Target

The motivation for, and aims of, the intensive effort on prostaglandin synthesis have now been established, but before turning to the synthetic problem itself, the first consideration must be which of the prostaglandins is the most useful and practical synthetic target.

It is important to be able to prepare compounds of the E-, F_a- and A-series since each shows a different range of biological activity. (Prostaglandins of the B-series are virtually inactive.) Since F_a- and A-prostaglandins can be readily prepared from the corresponding E, the latter would seem to be the most useful primary synthetic target. Prostaglandins of the 1, 2 and 3-series in general differ only quantitatively in their pharmacological properties. Thus it is not surprising that most of the syntheses which will be discussed are aimed at PGE_1.

There are, however, two difficulties. Firstly, prostaglandins of the E-series are the most labile (*see* below), and secondly, the reduction of PGE_1 to give PGF_{1a}, for example, is not stereospecific and produces an equal amount of the comparatively uninteresting epimer $PGF_{1\beta}$. Thus the synthesis of the much more stable PGF_a is an attractive alternative primary target, especially if selective protection of the 11- and 15-hydroxyl groups can be arranged to permit oxidation to the corresponding E.

Even though A-prostaglandins show potentially useful biological properties, their direct total synthesis appears to have received little attention, probably because they were regarded as less satisfactory intermediates to the primary prostaglandins. However, the discovery of a non-mammalian source of a PGA_2 derivative[12] has stimulated research into methods for converting this into PGF_{2a} and PGE_2 and this is discussed later.

Of the other prostanoic acid derivatives that have attracted synthetic effort, only 13,14-dihydro- and 11-desoxy-prostaglandins are discussed in this review. This somewhat arbitrary choice is dictated partly by considerations of space, partly by reasons of chemical interest and partly by the

biological activity of the compounds themselves. For details of the other syntheses such as those of PGB-compounds and oxa-prostaglandins, the reader is referred to earlier reviews[22].

SYNTHESES OF E AND F_α PROSTAGLANDINS

There are two main problems to be overcome during the synthesis of PGE_1. Firstly, since the molecule has four asymmetric centres and a *trans*-double bond, effective control of the relative stereochemistry is important. Three of the four asymmetric centres (8, 11 and 12) are contiguous on the five-membered ring and are mutually *trans*. This is the more stable arrangement and therefore relatively easy to establish. The same is true for the *trans*-double bond. However, stereochemical control of the fourth asymmetric centre at C-15 is unlikely because of its remote position. Secondly, prostaglandins of the E-series are labile due to the β-ketol system which dehydrates at a reasonable rate at values of pH outside the range 3–9.

In the synthesis of an F_α-prostaglandin the extra asymmetric centre complicates the stereochemical problem but this is perhaps more than compensated for by the marked increase in the molecule's stability (PGFs are moderately labile at very low values of pH presumably due to the ene–diol system at C-11 to C-15 which is both allylic and homo-allylic).

It is interesting to compare the various strategies used to meet these problems, and for this purpose it is convenient to divide the types of syntheses into two classes: those in which the cyclopentane ring is closed in the synthesis and the stereochemical problems tackled subsequently, and those in which a bicyclic system is used to effect some degree of stereochemical control.

Syntheses Incorporating Cyclopentane Ring Formation

Of the three routes included in this section, only one has been successfully taken through to a primary prostaglandin. They clearly illustrate the limitations of this general approach; viz. the difficulties in controlling stereochemistry and the problem of selective protection of functional groups.

(a) In Corey's first synthesis of PGE_1,[23] his main concern was to generate the β-ketol system under the mildest possible conditions and as late as possible in the scheme. The plan was to synthesise the 9-amine and convert this into the 9-ketone via the corresponding imine. Ingenious new methods were developed for oxidising model primary amines[24] though in the actual synthesis the known Ruschig method (illustrated below) was the only successful one.
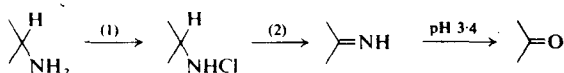
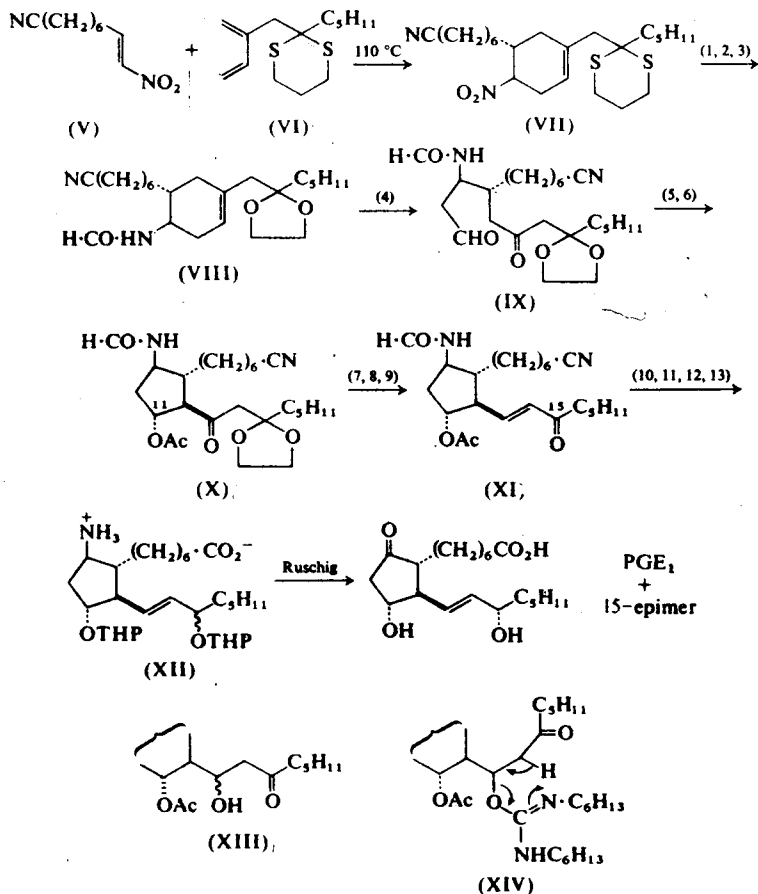Reagents: (1) *N*-chlorosuccinimide; (2) MeO⁻

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Figure 1.3. (1) Al/Hg; (2) HCO·OAc; (3) (HOCH₂)₂/HgCl₂; (4) OsO₄/pyr then Pb(OAc)₄; (5) diazabicyclononene; (6) Ac₂O/pyr; (7) NaBH₄; (8) H⁺; (9) dicyclohexylcarbodiimide/CuCl₂; (10) Zn(BH₄)₂; (11) OH⁻; (12) dihydropyran/H⁺; (13) OH⁻

The full route is given in *Figure 1.3*.

A Diels–Alder reaction between the diene (VI) (from bromomethyl-butadiene and the lithium dithiane) and the nitro-olefin (V) gave the cyclohexene (VII) as the predominant product. It was converted by standard reactions into the formamido-ketal (VIII), the olefinic group of which was cleaved in two steps to the keto-aldehyde (IX). The cyclopentane ring was formed by an aldol condensation using 1,5-diazabicyclo[4,3,0]non-5-ene as base (this minimises dehydration of the aldol), and the hydroxy ketone was isolated as its acetate (X). As expected the alkyl chains were fixed in the *trans* position and the major product had the C-11 acetate in the 'natural' relative configuration (*a*). The configuration of the formamido group is of course of little consequence.

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The sequence employed to convert (X) into the enone (XI) is particularly noteworthy. Reduction of the ketone with borohydride and cleavage of the ketal affords a β-hydroxy-δ-acetoxyketone (*see* partial structure XIII) which has to be dehydrated without concomitant elimination of the 11-acetoxy group to give the unwanted dienone. This was achieved using dicyclohexylcarbodiimide in the presence of cuprous ion. The iso-urea formed is assumed to eliminate by the cyclic mechanism shown in (XIV).

Reduction of the 15-ketone (XI) with zinc borohydride (used to minimise conjugate addition and base-catalysed elimination) gave a mixture of C-15 epimeric alcohols, which were taken to the amino-acid mixture (XII) in which the 11- and 15-hydroxyl groups were protected as tetrahydropyranyl ethers. Application of the Ruschig procedure then gave a mixture of PGE$_1$ and its 15-epimer which were separated by chromatography.
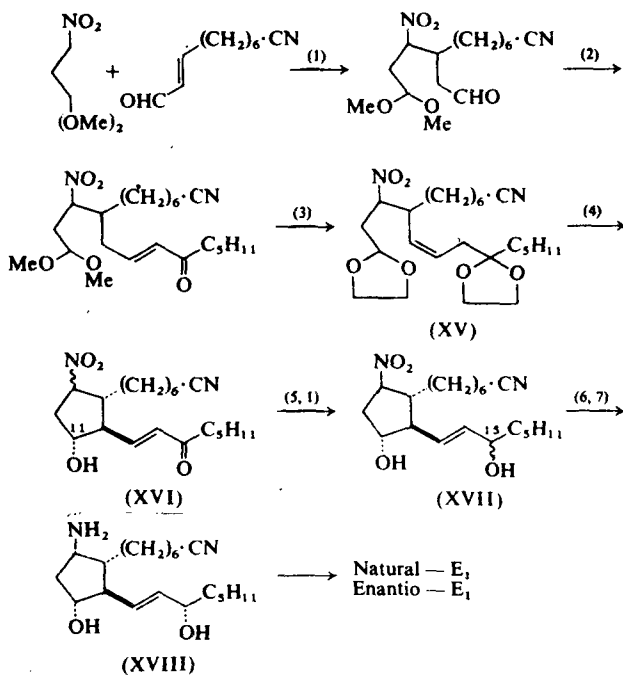

Figure 1.4. (1) base; (2) $(MeO)_2PO\ \bar{C}HCOC_5H_{11}$; (3) $(HOCH_2)_2/H^+$; (4) SnCl$_4$; (5) Zn(BH$_4$)$_2$; (6) chromatography; (7) Al/Hg

Improvements to the early steps of this route were described in subsequent papers[25,26] and are summarised in *Figure 1.4*. A fascinating reaction is the cyclisation of the bis-ketal (XV) (prepared as illustrated by a Michael reaction followed by ketalisation) which in the presence of anhydrous stannic chloride is almost completely stereospecific to give the nitrocyclopentane (XVI). If water was added to the reaction more of the 11β-hydroxy compound was obtained. The 11α-hydroxyketone was reduced to a mixture

of diols (XVII) from which the required α-isomer could be separated by chromatography and the unwanted β-isomer recycled by oxidation to the enone (XVI). Reduction of the nitro-group of diol (XVII, one pure isomer at C-15) gave the amino-nitrile (XVIII) which could be resolved as the bromocamphorsulphonate. By completing the sequence as in *Figure 1.3*, both natural and enantiomeric isomers of PGE₁ were obtained. The various 15- and 11-epimers were also obtained and some rather interesting structure–activity relationships were demonstrated[27].

Although several of the stereochemical problems have been resolved, the generation of the β-ketol system from the β-hydroxyamine is experimentally very difficult, and thus the route is not suitable for either large-scale production or for the synthesis of analogues.

(b) The second synthesis to be considered under this heading, that of Miyano and Dorn[28], has yet to produce a primary prostaglandin. Nevertheless, it is included here on account of its potential utility and its direct simplicity. The steps are shown in *Figure 1.5*.
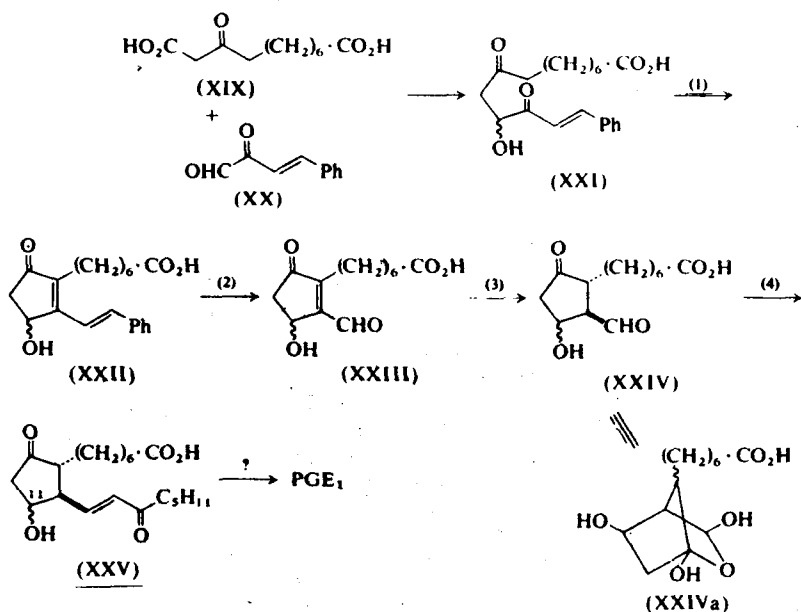

Figure 1.5. (1) base; (2) OsO₄/NaIO₄; (3) Zn/AcOH; (4) Ph₃P=CHCOC₅H₁₁

The cyclopentane system is formed by two aldol-type condensations which are induced to take place in the required direction by an ingenious choice of starting materials, namely the β-keto-acid (XIX) and styrylglyoxal (XX). The first condensation with concomitant decarboxylation gave the aldol (XXI) in quantitative yield which, with base, cyclised to the dienone (XXII). Selective cleavage of the styryl double bond in (XXII) afforded the aldehyde

(XXIII) which, because of its enedione system, could be reduced with zinc and acetic acid to give the crude saturated aldehyde (XXIV) which is assumed to exist as a mixture of cyclic hydrates, one of which is depicted by structure (XXIVa). Wittig condensation of this crude aldehyde gave a 20–25% yield of a mixture of 15-dehydro-PGE$_1$ and its 11-epimer, which were separated by chromatography.

β-Hydroxy-aldehydes such as (XXIV) are intermediates in several of the prostaglandin syntheses. They dehydrate readily and are usually reacted without attempted purification and under the mildest possible conditions. Thus it is a little surprising that Miyano and Dorn chose to use the feebly reactive triphenyl phosphorane (reagent 4) when much more reactive Wittig-type reagents are available (cf. the following synthesis and the one by Corey described in the next section). The low yield from this Wittig reaction could, however, reflect the purity of the starting aldehyde, suggesting poor steric control in the previous reduction.

The authors did not describe a method for selective reduction of the 15-keto group. However, prostaglandin 15-dehydrogenase is relatively easy to isolate[20] although the equilibrium set up by this enzyme is on the side of the 15-ketone. If a means could be found to shift this equilibrium position in favour of the 15-alcohol, this route could become the basis of a very attractive and direct synthesis.
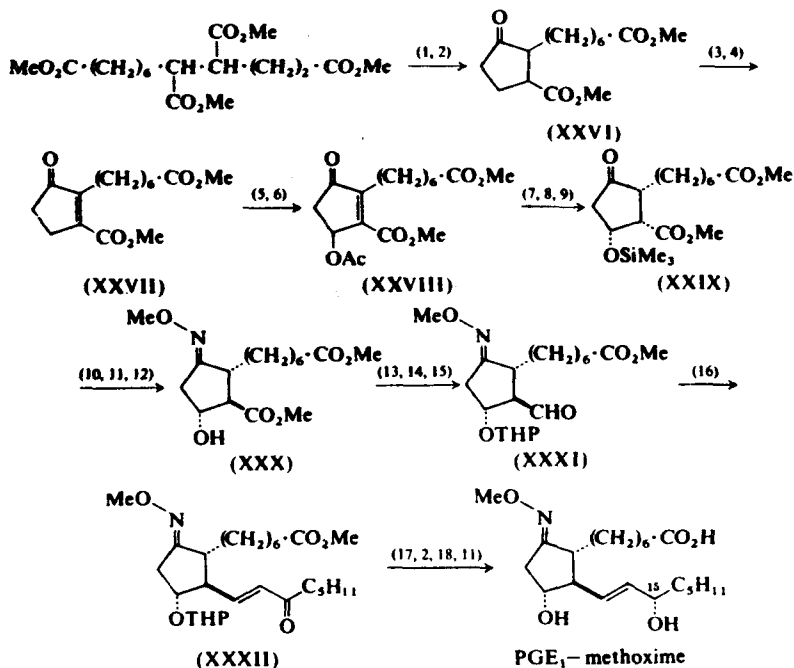

Figure 1.6. (1) NaH; (2) H$^+$; (3) Br$_2$; (4) Et$_3$N; (5) NBS; (6) AgOAc; (7) MeOH/H$^+$; (8) silylation; (9) H$_2$/Raney Ni; (10) MeONH$_2$·HCl/pyr; (11) K$_2$CO$_3$/MeOH; (12) esterification; (13) dihydropyran/H$^+$; (14) NaBH$_4$; (15) modified Moffat oxidation; (16) Bu$_3$P=CHCOC$_5$H$_{11}$; (17) NaBH$_4$; (18) p.l.c.

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(c) Finch and Fitt's route[29] is the final one to be considered in this section (*see Figure 1.6*). Using the cyclopentenone (XXVII) they were able to introduce the 11-oxygen and elaborate the C_8 side-chain with excellent control of stereochemistry but, as in previous routes, effective protection of the β-ketol system turned out to be the main difficulty.

The enone (XXVII) (prepared as shown) was allylically acetoxylated then hydrogenated to the saturated ketone (XXIX). Note that the allylic oxygen function was protected from hydrogenolysis as the trimethylsilyl ether. The bulky silyloxy group also controls the direction of hydrogenation and leads to the all *cis*-configuration shown. The carbonyl of the β-ketol system was protected as the methoxime, and the secondary methoxycarbonyl group was epimerised with potassium carbonate in methanol to give, after re-esterification, compound (XXX) in which the required stereochemistry has now been established. It is somewhat surprising that since the hydroxyl group is in the β-position with respect to the ester function it does not eliminate under these conditions, to give the α,β-unsaturated ester.

The remainder of the synthesis is relatively straightforward. The aldehyde (XXXI) was very labile (it dehydrated to give the α,β-unsaturated aldehyde) and the reactive tributylphosphorane (reagent 16) was used in the subsequent Wittig reaction (cf. previous synthesis). It will be noted that again no control of C-15 stereochemistry is possible and the two isomers have to be separated.

Although no method for removing the methoxime protecting group was disclosed, the Ciba workers claim to have developed a new satisfactory procedure and their publication is awaited with interest. Although marred by its length, this route successfully overcomes many of the key problems in prostaglandin synthesis. It has a good deal in common with the immediately previous route and one is tempted to try to hybridise the two in order to incorporate the directness of the former scheme.

Syntheses Using Bicyclic Intermediates

In general, the more rigid a molecule is, the easier it becomes to control stereochemistry during its synthesis. Thus it is a common practice to use, in a synthetic scheme, intermediates with one or more additional rings which are cleaved in the later stages. This principle has been successfully applied in routes to the prostaglandin molecule and is illustrated by the three syntheses described below. At present the more generally useful approaches fall into this category.

The Bicyclo[3,1,0]hexane Route—The basic idea behind this route, devised by Just, was that the allylic–homoallylic system (C-11 to C-15) of correct stereo-chemistry could be generated by solvolysis of the appropriately

(XXXIII)　　　　　　　　　　(XXXIV)

10
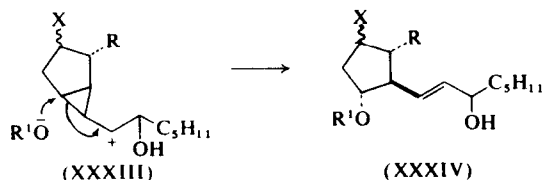
substituted cyclopropyl carbonium ion (derivable from the epoxide, for example) as shown on p. 10 (XXXIII → XXXIV).

An encouraging precedent was available from the work of Wiberg and Ashe[30], who had shown that solvolysis of the simple bicyclic tosylate (XXXV) gave mainly ring-opened products (XXXVI; R = Ts and Ac).

(XXXV)   →   (XXXVI)   80%
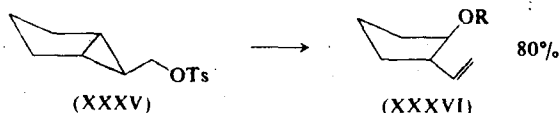
Details of their route were first published by Just and Simonovitch[31] in 1967 but they had neither resolved the fairly formidable stereochemical problems nor found solvolytic conditions which favoured cyclopropane ring opening, and it is unlikely that they isolated any natural prostaglandin although their
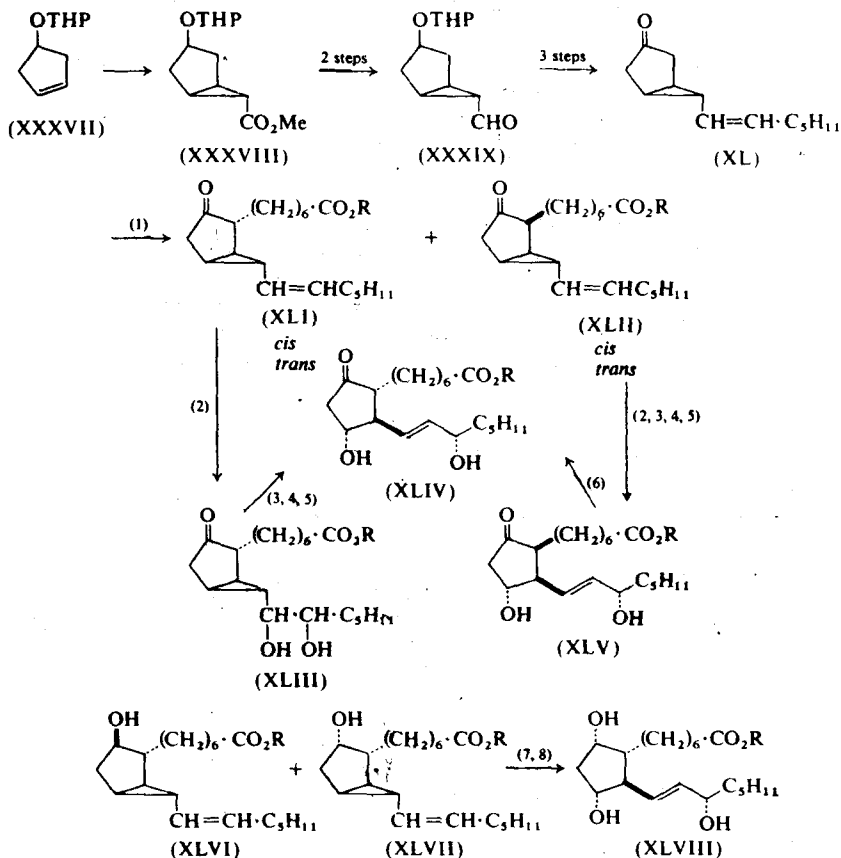

OTHP

(XXXVII)

OTHP
CO_2Me
(XXXVIII)

2 steps

OTHP
CHO
(XXXIX)

3 steps

O
$CH=CH\cdot C_5H_{11}$
(XL)

(1)

O
$(CH_2)_6\cdot CO_2R$
$CH=CHC_5H_{11}$
(XLI)
cis
trans

+

O
$(CH_2)_6\cdot CO_2R$
$CH=CHC_5H_{11}$
(XLII)
cis
trans

(2)

O
$(CH_2)_6\cdot CO_2R$
C_5H_{11}
OH   OH
(XLIV)

(2, 3, 4, 5)

(3, 4, 5)

(6)

O
$(CH_2)_6\cdot CO_2R$
$CH\cdot CH\cdot C_5H_{11}$
OH OH
(XLIII)

O
$(CH_2)_6\cdot CO_2R$
C_5H_{11}
OH   OH
(XLV)

OH
$(CH_2)_6\cdot CO_2R$
$CH=CH\cdot C_5H_{11}$
(XLVI)

+

OH
$(CH_2)_6\cdot CO_2R$
$CH=CH\cdot C_5H_{11}$
(XLVII)

(7, 8)

OH
$(CH_2)_6\cdot CO_2R$
C_5H_{11}
OH   OH
(XLVIII)

Figure 1.7. (1) KOBuᵗ/I(CH₂)₆CO₂R; (2) OsO₄; (3) MeSO₂Cl/pyr; (4) aq. acetone; (5) chromatography; (6) KOAc; (7) *m*-chloroperbenzoic acid; (8) HCO₃H

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products did show biological activity. Nevertheless, the basic concept independently attracted two industrial research groups to explore its potential.

In a detailed account[32] the Smith, Kline and French group concluded that the published method was not a practical route but by suitable modification PGB_1 as well as biologically active PGF_1 isomers could be obtained.

The Upjohn group, in collaboration with Just, although confirming the impracticality of the first route, nevertheless developed a workable synthesis and have been able to prepare PGE_1, E_2 and E_3 as well as several analogues[33]. Limited space does not permit of a detailed account of the early work, and only the successful syntheses are discussed below (*see Figure 1.7*).

The aldehyde (XXXIX), as a mixture of isomers about the protected carbinol group, was obtained by a conventional sequence from the cyclopentene (XXXVII) via the ester (XXXVIII). It gave a mixture of *cis*- and *trans*-olefinic ketones (XL) which were separately alkylated to give the isomeric esters (XLI) and (XLII). The α-epimer (XLI), of required stereochemistry, was the minor product (35%). Reaction of the *cis*-isomer of (XLI) with osmium tetroxide gave, as expected, two *erythro*-glycols while the *trans*-isomer gave the corresponding *threo*-pairs (XLIII). It is interesting to note that hydroxylation using buffered performic acid (the conditions originally used by Just) was not stereospecific and gave all four glycols from each olefin.

Generation of the cyclopropyl carbonium ion by solvolysis, in aqueous acetone, of the *bis*-mesylate of glycols (XLIII) gave a mixture of products from which PGE_1 methyl ester (XLIV; R = Me) could be isolated in 5–10% yield. Since it is not possible to hydrolyse the methyl ester without dehydrating the β-ketol, PGE_1 was prepared via the 1,1,1-trichloroethyl ester which was cleaved by reduction with zinc in acetic acid.
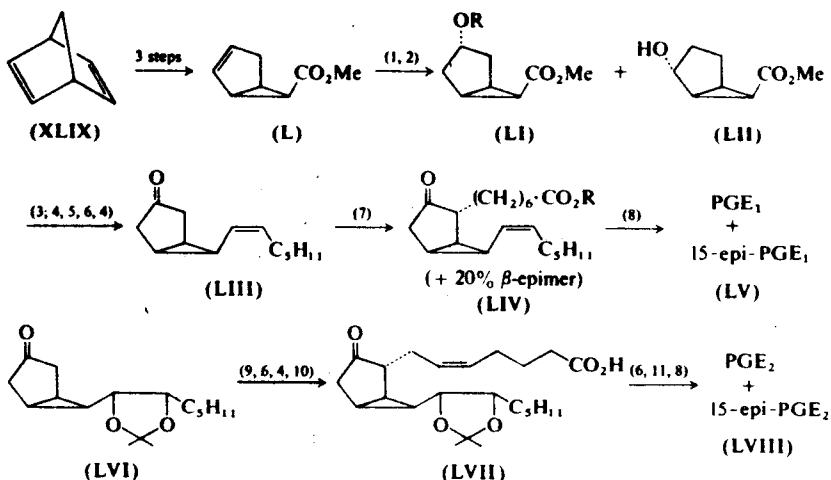

Figure 1.8. (1) $B_2H_6/H_2O_2/^-OH$; (2) dihydropyran/H^+; (3) $LiAlH_4$; (4) Jones oxidation; (5) $Ph_3P=CHC_5H_{11}$; (6) H^+; (7) $I(CH_2)_6CO_2R$/base; (8) solvolysis of glycol *bis*-mesylates; (9) $BrCH_2 \cdot C\equiv C \cdot (CH_2)_3 CH_3 \cdot O \cdot THP/KOBu^t$; (10) $H_2/Pd/BaSO_4/pyr.$; (11) esterification

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