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The Synthesis of Prostaglandins From Cyclopentane Derivatives

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The advances in the synthesis of prostaglandin derivatives are examined.
The bibliography includes 129 references.

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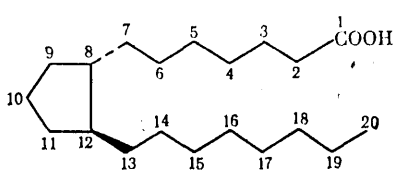
I. INTRODUCTION

Prostaglandins (PG) are biologically active substances with an extremely broad spectrum of action. The influence of PG on the smooth musculature of various organs, their hormone-like and antihormonal activity[1,2], etc. are being investigated at the present time. The therapeutic effect of these compounds is achieved when they are administered in extremely low amounts, of the order of nanograms. This justifies the use of PG as promising medicinal preparations in medicine (cardiology, gastroenterology, midwifery, gynaecology, etc.) and animal husbandry (regulation of the reproductive function of animals). PG and their principal precursors—polyunsaturated aliphatic acids (eicosatetraenoic and eicosatrienoic acids)—are contained in all mammalian tissues but as a rule in extremely small amounts. The highest content of PG is present in the seminal fluids of mammals and man. Thus the overall content of PG in human seminal fluid is on average 213–240 μg ml^{-1} and varies with age and state of health. The seminal fluid of the ram contains approximately 50 μg ml^{-1} of PG. PG has been found also in prostate glands, ovaries, brain tissue, the mucous membranes of the stomach and the intestine, spleen, kidneys, liver, pancreas, and the iris of the eye[3] but at a concentration many times smaller than in the seminal fluid of the ram and man, so that such tissues cannot serve as sources of large amounts of pure PG preparations.

The main natural sources of PG are their close precursors present in the gorgonia *Plexaura homomalla* at an unusually high concentration—2.6 wt.% relative to the dry weight[4].

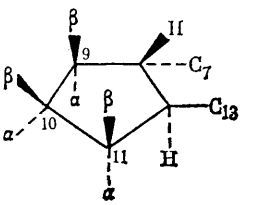
The need for large amounts of PG, which are essential for experimental and clinical studies, combined with the high cost of the preparations (up to 3000 dollars per gram) promoted a vigorous development of methods for the isolation and purification of PG and also stimulated the search for methods of synthesis of PG or their analogues.

PG are derivatives of the hypothetical prostanoic acid (I), the C(8)–C(12) atoms of which are incorporated in the cyclopentane ring (CPR):

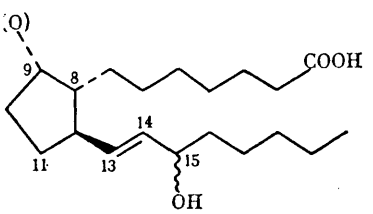


(I)

The CPR substituents are designated by the letter α when they are located on the same side of the plane of the ring as the carbon atom in the 7-position and by the letter β when they are on the other side:

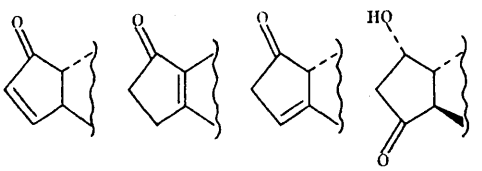


The C(1)–C(7) chain, terminating in a carboxy-group, is designated by convention as the α-chain (or the upper chain) and is located behind the CPR plane. All the PG are characterised by the presence of an oxygen-containing functional group (OH or C=O) at C(9), a hydroxy-group at C(15), and a *trans*-double bond between C(13) and C(14):

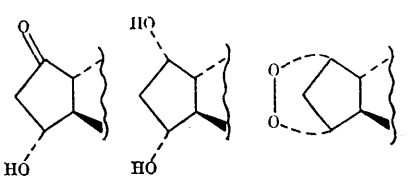


(II)

Depending on the number and type of the oxygen-containing functional groups, the degree of unsaturation of the CPR, and the position of the double bond in the latter, PG are divided into groups designated by the Latin letters, A, B, C, D, E, F, G, and H:



A B C D



E F_α G, H

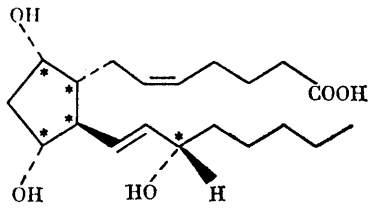
The degree of unsaturation, i.e. the number of double bonds in the PG molecule (in the side chains), is designated by the corresponding numerals: for example PGE_1 has only one C(13)–C(14) *trans*-double bond, PGE_2 has an additional

cis-double bond in the C(5)–C(6) position, and PGE_3 is characterised by the presence of a third *cis*-double bond in the C(17)–C(18) position. Analogous double bonds are also encountered in PG of other groups. As a consequence of the asymmetry of their molecules, PG exist in several isomeric forms. In natural PG the hydroxy-groups in the C(9), C(11), and C(15) positions always have the α-configuration (the PG in group F can exist in two isomeric forms relative to the hydroxy-group at the C(9) atom, namely α and β, which are always indicated after the numeral). Only the isomeric α-forms $PGE_{1,2,3\alpha}$ are encountered in nature. The PG in groups G and F are usually referred to as "basic" or "primary". In a pure form, PG are colourless crystalline powders readily soluble in organic solvents.

When the basic PG molecule is modified chemically by a particular group which is accompanied by a shortening of the alkyl chain, the prefix "nor" is added to the name of the PG; nor implies the shortening of the chain by one methyl group, dinor the shortening by two methyl groups, trinor the shortening by three methyl groups, etc. The number of the missing methyl group is also indicated. When the alkyl chain is lengthened, the prefix "homo" is added to the name of the PG with the simultaneous indication of the number of the new methyl groups (homo- dihomo-, trihomo-, etc.) and the number of the carbon atom to which the methyl group has been attached.

II. THE SYNTHESIS OF PROSTAGLANDINS

After the structure of the PG had been established[5], the synthesis of hormones of this class aroused much interest among synthetic chemists. The total synthesis of natural PG presents considerable difficulties not so much because of the lability of the compounds as due to the complexity of their chemical structure. PG can contain in their molecules up to five asymmetric centres, four of which are in the prostanoid ring and one in the side chain at the C(15) atom, so that the main problem in the total synthesis of PG is the stereospecific construction of these asymmetric centres. Thus the stereocontrolled syntheses of natural PG are in the main multistage processes and the yields of the final products are comparatively low:



($PGF_{2\alpha}$)

Analysis of the literature data makes it possible to divide the methods of synthesis of PG into three main groups:

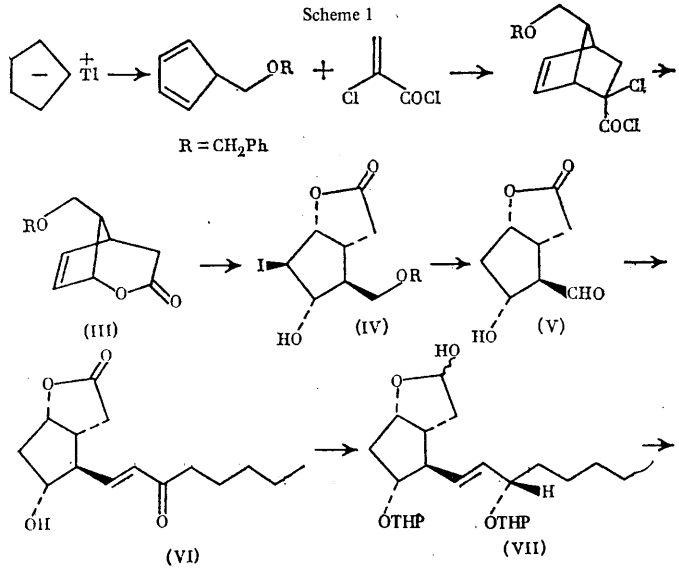
1. The synthesis of acyclic long-chain compounds in which the CPR is closed in one of the last stages.
2. The syntheses of PG from cyclopentane derivatives.
3. The enzymic synthesis from polyenoic acids (biosynthesis).

The growing interest in the second group of methods can be accounted for, on the one hand, by the relative availability of the initial cyclopentane derivatives and, on the other, by the comparative simplicity of the subsequent building up of the PG molecule. However, numerous studies in this field have been scarcely treated systematically and have not been surveyed. Mitra's monograph[6] is devoted to the synthesis of PG or their analogues without referring to the employment of cyclopentanes with functional-group substituents†; the review of Levkoeva and Yakhontov[7] is concerned with the synthesis of heterocyclic analogues of PG. Only a small amount of attention is devoted to PG in Azhgikhin's book[3]. A review dealing with the steric control in the synthesis of PG from bicyclic and tricyclic intermediates was published in 1980.[8] We therefore thought it useful to examine the most important studies on the synthesis of PG from cyclopentane derivatives.

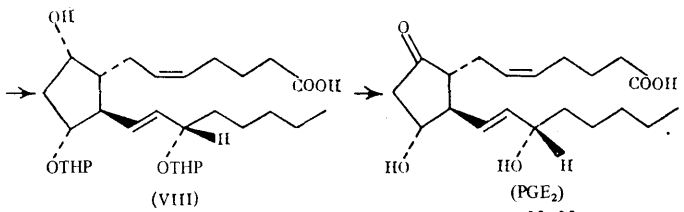
1. Synthesis From Bicyclic Compounds

One of the most significant achievements in the synthesis of PG is the practical application of bicyclic compounds which subsequently make it possible to proceed readily to the total synthesis of PG or their analogues. The key compound in these syntheses is the aldehydolactone (V) which is known in the literature as "Corey's aldehyde". One of the methods of synthesis of this compound[9–12], from cyclopentadienylthallium, is indicated in Scheme 1. The product of the interaction of the thallium derivative with benzyl chloromethyl ether is condensed with the dienophile, namely the chloride of 2-chloroacrylic acid, and the corresponding bicyclic compound is obtained, which is then converted by a series of reactions into 2-oxabicyclo[3.2.1]nonane (III). After the hydrolysis of compound (III) and subsequent treatment with potassium tri-iodide, the iodolactone (IV) is formed. This compound has the necessary configurations of all the nuclear centres. Its acylation, deiodination, and the conversion of the hydroxybenzyl group into an aldehyde group lead to the aldehydolactone (V), which then undergoes the Wittig condensation with the corresponding phosphorane to form compound (VI). The C(15)-keto-group is stereospecifically reduced and, after the conversion of the lactone into the lactol (VII), the α-chain is introduced by the Wittig reaction. Mild hydrolysis of the ester group leads to the intermediate (VIII). After the oxidation of the hydroxy-group at C(9) in compound (VIII) and the removal of the tetrahydropyranyl (THP) protecting group, PGE_2 is isolated. The conversion of compound (VIII) into PGE_1 is achieved by hydrogenating the former over a palladium catalyst.

Scheme 1



† See also J.S.Bindra and R.Bindra, "Prostaglandin Synthesis", Acad.Press, New York–San Francisco–London, 1977.

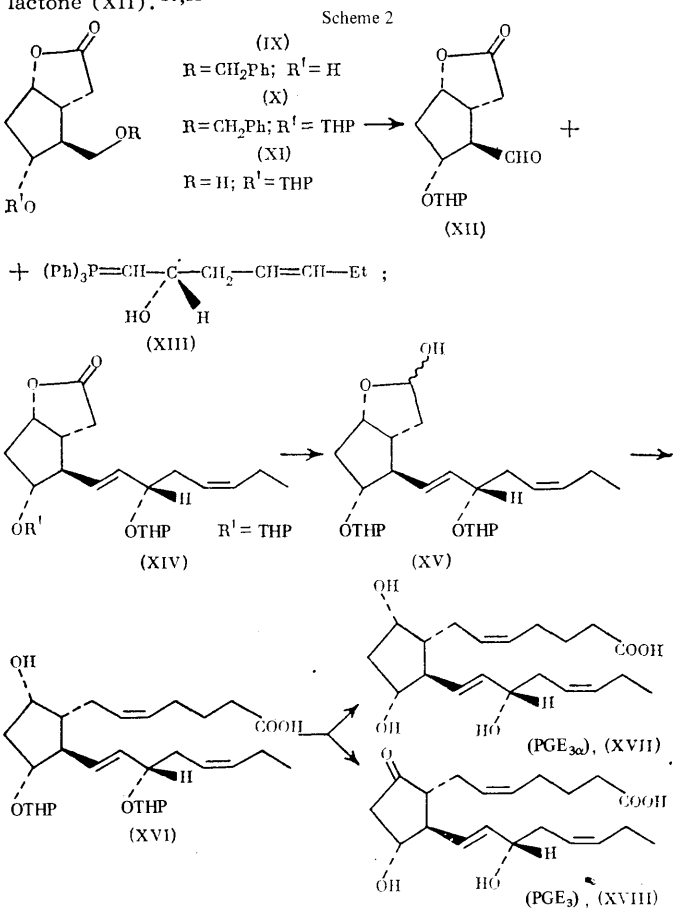


(VIII) (PGE$_2$)

Corey's aldehyde and its various modifications[13-18] have become key compounds in the various syntheses of PG. Thus the optically active PGE_3 and $PGF_{3\alpha}$ were synthesised for the first time from the optically active hydroxylactone (IX) (Scheme 2). The lactone (IX) was converted into the aldehyde (XII) after the protection of the hydroxy-group with THP, hydrogenation over Pd/C, and Collins oxidation ($2C_5H_5N.CrO_3$ in CH_2Cl_2) of the resulting alcohol. By condensation with the (*S*)-(+)-phosphonium salt (XIII), the aldehyde (XII) was converted stereospecifically into the unsaturated alcohol (XIV). After conversion into the bis-THP derivative, the allyl alcohol (XIV) was reduced with di-isobutylaluminium hydride (DIBAH) to the lactol (XV). The upper chain in compound (XVI) was built up stereospecifically by the Wittig reaction between the lactol (XV) and 5-triphenylphosphonovaleric acid. The removal of the THP protecting group on acid hydrolysis gives rise to $PGF_{3\alpha}$ (XVII) with $[\alpha]_{D^{26}} = +29.6°$. The oxidation of compound (XVI) with the Jones reagent (chromic acid–acetone) and subsequent removal of the THP protecting group and chromatographic separation lead to PGE_3 (XVIII) with $[\alpha]_{D^{24}} = -48.9°$.

PGE_1 and $PGF_{1\alpha}$ have been obtained analogously from the lactone (XII).[20,21]

Scheme 2

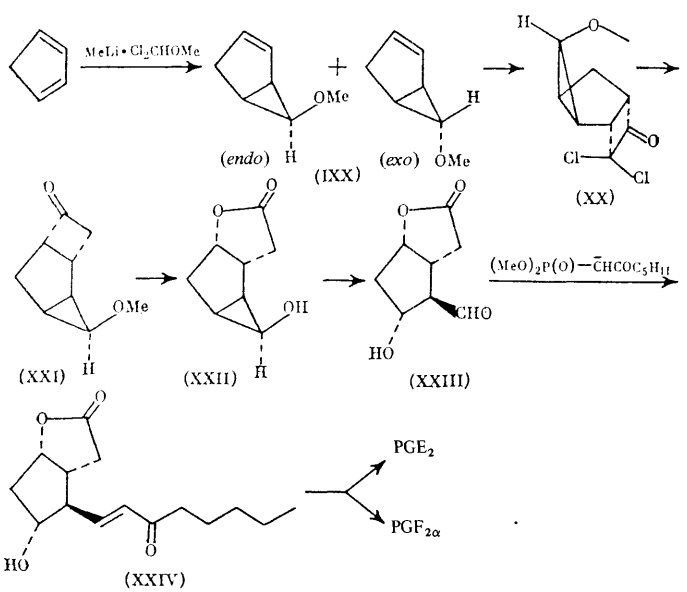


After the successful synthesis of PG using Corey's aldehyde, new methods of synthesis of key compounds from readily available reagents permitting an easy transition to the total synthesis of PG were sought. Thus Corey et al.[22] used 6-methoxybicyclo[3.1.0]hex-2-ene (XIX) as the key compound in the synthesis of PGE_2 and $PGF_{2\alpha}$ (*dl*), which were obtained by the condensation of dichloromethyl ethyl ether with cyclopentadiene as a 4:1 mixture of the *endo*- and *exo*-forms (Scheme 3). Refluxing of the 4:1 mixture with dichloroacetyl chloride in an excess of triethylamine leads to the tricyclic ketone (XX) whose dechlorination with zinc dust in glacial acetic acid followed by treatment of compound (XXI) with boron tribromide in CH_2Cl_2 results in the formation of the *endo*-cyclopropanol (XXII). The oxidation of compound (XXII) with a solution of H_2CrO_4 and $Ce(NH_4)_2(NO_3)_6$ in aqueous acetic acid leads to a mixture of three products, one of which is the required hydroxyaldehyde (XXVI). The aldehyde (XXIII) is fairly unstable and for this reason it is immediately condensed with the sodium derivative of 2-oxo-heptylphosphonate whereupon a mixture of products is obtained, from which the lactone (XXIV) is isolated chromatographically. Next the lactone (XXIV) is converted into the acetate derivative and then into PGE_2 and $PGF_{2\alpha}$ by standard methods.

11-Deoxy-PGE was synthesised in accordance with an analogous scheme by the reaction of 2-(6'-methoxycarbonylhexyl)cyclopent-2-en-1-one with dimethylsulphuranylidene acetate[23,24].

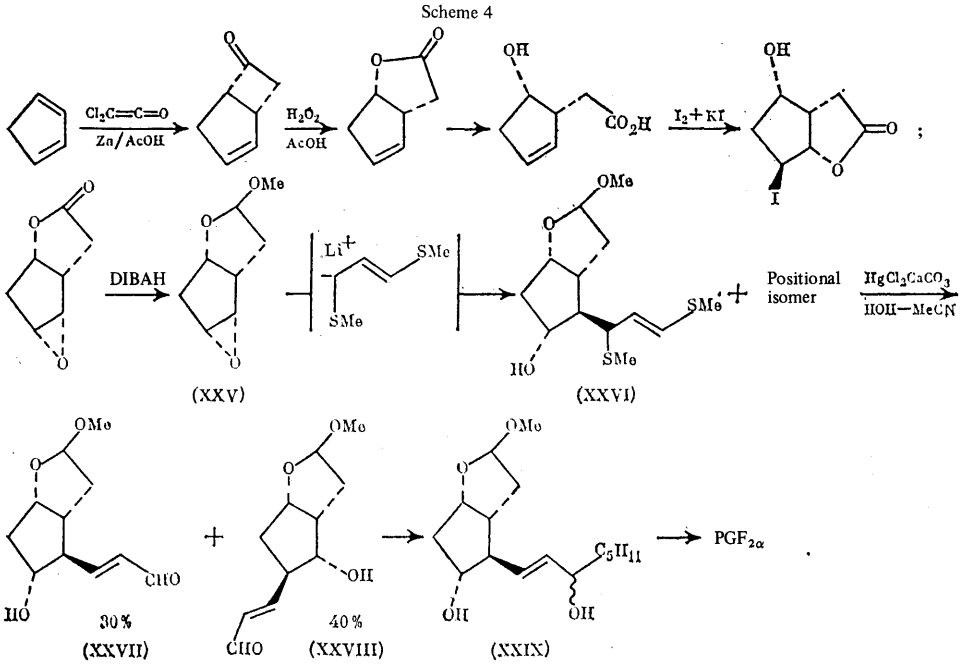
However, the oxidative opening of the cyclopropanol (XXII) ring to give the aldehyde (XXIII) proceeds with a low yield and for this reason Corey and Hayozi[25] developed a new approach to the synthesis of $PGF_{2\alpha}$ via the epoxidation of unsaturated bicyclic derivatives of cyclopentanone with subsequent regioselective opening of the oxide ring by the lithio-derivative of the vinyl sulphide MeS–CH_2–CH=CH–SMe (the β-nucleophilic equivalent of –CH=CH–CHO) which contains the potential C(13)–C(14) *trans*-double bond (Scheme 4).

Scheme 3



Condensation of the epoxyacetal (XXV) with 1,3-di(methylthio)allyl-lithium gives a mixture of the required product (XXVI) and its postional isomer. Hydrolysis of the mixture leads to a mixture of two unsaturated aldehydes, (XXVII) and (XXVIII), which were separated on a preparative scale.

Scheme 4

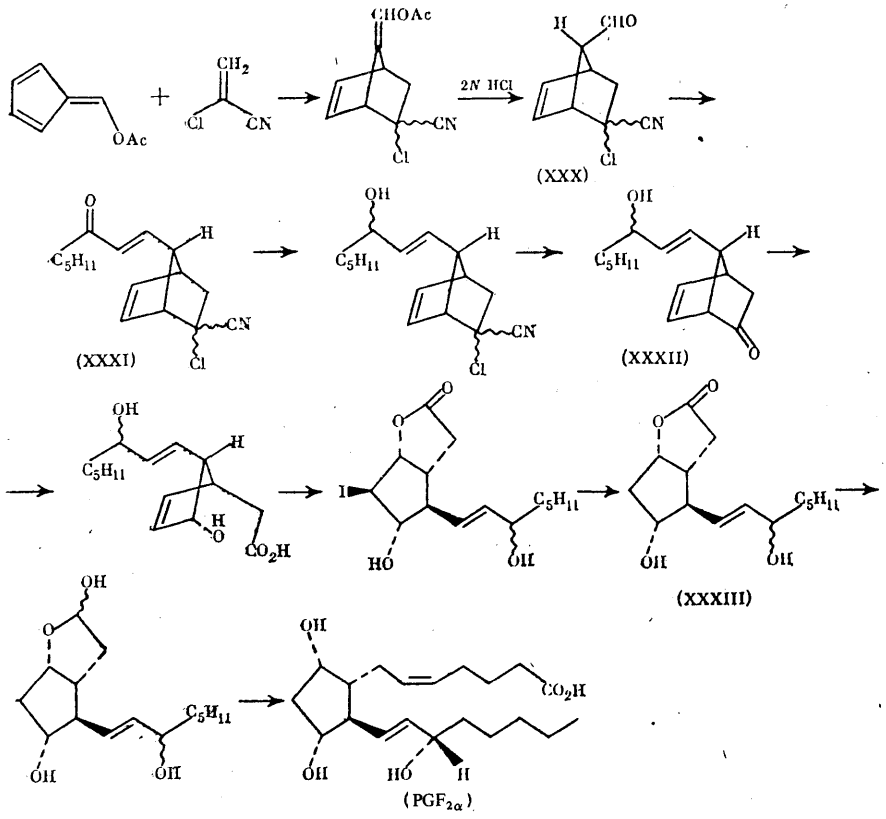


The condensation of the more polar aldehyde (XXVII) with n-butyl-lithium leads to a mixture of approximately equal amounts of the epimeric secondary alcohols. The acid hydrolysis of the more polar compound (XXIX) with subsequent isolation of the lactol and its condensation with the sodium derivative of 5-triphenylphosphonopentanoic acid yields $PGF_{2\alpha}$. The less polar epimer (XXIX) was converted in two stages into *dl*-15-epi-$PGF_{2\alpha}$ in the same way.

In a later study ring opening in the tricyclic epoxide (XXV) in the total synthesis $PGF_{2\alpha}$ was achieved with a higher regioselectivity on treatment with divinyl cuprate[26].

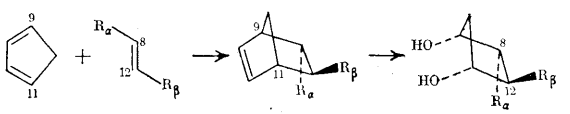
An alternative synthesis of $PGF_{2\alpha}$ is based on the employment of acetoxyfulvene as the starting compound[27-31] in the synthesis of the key compound (XXX) via Scheme 5:

Scheme 5



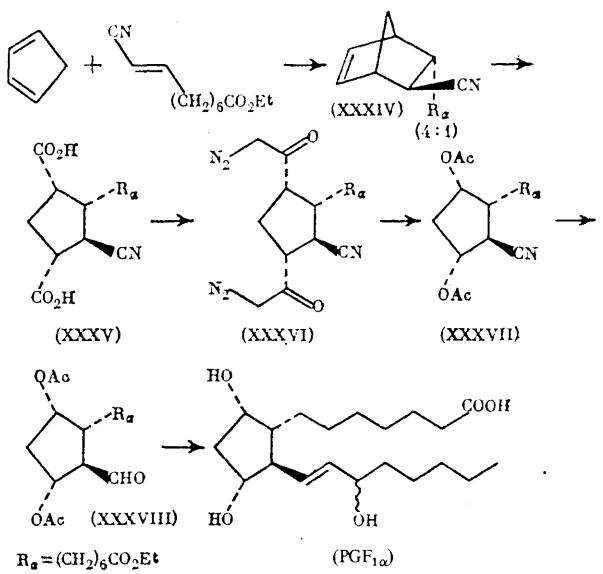
The bicycloheptenal (XXX) reacted with the lithio-derivative of dimethyl 2-oxoheptylphosphonate with formation of the *trans*-enone (XXXI) whose reduction with DIBAH and subsequent alkaline hydrolysis of the chloronitrile group lead to the ketone (XXXII). Baeyer–Villiger oxidation (H_2O_2, KOH) of compound (XXXII) and the iodolactonisation of the hydroxyacid salt formed *in situ* lead to the iododiol whose deiodination with tri-n-butyltin hydride affords the diol (XXXIII). After the reduction of compound (XXXIII) by DIBAH to the *gem*-acetal (XXXIV) and its condensation with the sodium salt of (4-carboxybutyl)triphenylphosphorane, $PGF_{2\alpha}$ was obtained together with the C(15)-epimer. Chromatographic separation of this mixture makes it possible to obtain the racemic $PGF_{2\alpha}$. The conversion into PGE_1 of the A and B series was achieved by standard methods[9].

5,6-Disubstituted bicyclo[2.2.1]hept-2-enes can serve as convenient precursors for the construction of PG. This strategy in the synthesis was first developed and modified by Katsube and co-workers[32–36]. The disubstituted bicyclo[2.2.1]-heptene is obtained by the Diels–Alder reaction between cyclopentadiene and the corresponding substituted *trans*-olefine, the dienophile giving rise to the C(8) and C(12) atoms incorporated in the cyclopentane ring:



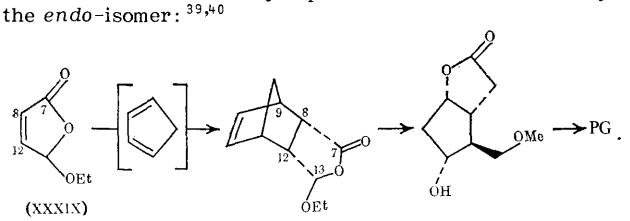
One of the examples of this approach is the synthesis of $PGE_{1\alpha}$ [32] (Scheme 6).

Scheme 6

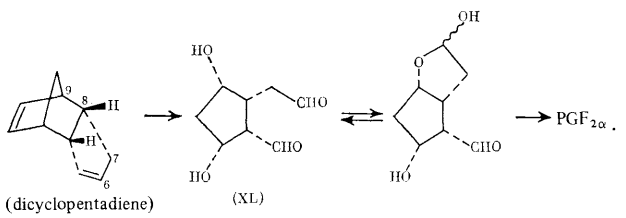


The Diels–Alder reaction between 2-cyano-9-ethoxycarbonyl-*trans*-non-2-ene, obtained by a standard method in four stages from diethyl suberate and cyclopentadiene at 150 °C in an autoclave, leads to a mixture of *exo*-2-cyano-3-(6′-ethoxycarbonylhexyl)bicyclo[2.2.1]hept-5-ene (XXXIV) and the corresponding *endo*-derivatives in proportions of 4:1, which were separated by chromatography on silica gel (SG). The ozonolysis of the *exo*-derivative of compound (XXXIV) and subsequent oxidative decomposition of the ozonide with an aqueous solution of performic acid yielded 3,5-dicarboxy-1α-cyano-2-β-(6′-ethoxycarbonylhexyl)cyclopentane (XXXV). Treatment of the latter with phosgene in a DMF–benzene mixture led to an acid dichloride, which gave rise, after treatment with a solution of diazomethane in ether, to the corresponding bisdiazoketone (XXXVI), which was converted into 3,5-diacetyl-1α-cyano-2β-(6′-ethoxycarbonylhexyl)cyclopentane (XXXVII). The oxidation of compound (XXXVII) with *m*-$ClC_6H_4CO_3H$ in $CHCl_3$ gave rise to 3,5-diacetoxy-2β-(6′-ethoxycarbonylhexyl)-1α-formylcyclopentane (XXXVIII), which was subsequently made to react with $Bu_3P{=}CH{-}CO{-}(CH_2)_4Me$, the condensation product was separated chromatographically, the C=O group at C(15) was reduced with sodium tetrahydroborate, the acetate protecting group was removed by hydrolysis, and $PGF_{1\alpha}$ was obtained.

It is noteworthy that this approach[32–38] to the synthesis of PG suffers from a significant disadvantage, since the reaction between cyclopentadiene and the corresponding substituted *trans*-olefin produces a mixture of the *exo*- and *endo*-adducts whose separation creates additional difficulties. However, the use of compound (XXXIX) (the β-formylacrylic acid pseudoester) as the dienophile in the Diels–Alder reaction with cyclopentadiene leads exclusively to the *endo*-isomer:[39,40]



An interesting 13-stage stereoselective synthesis of $PGF_{2\alpha}$, where the key compound is Turner's intermediate (XL), obtained from the readily available *endo*-dicyclopentadiene by successive oxidation, has been achieved[41,42]:



However, in this case the Diels–Alder reaction with symmetrically substituted dienophiles should not be carried out. The cyclopentene ring in dicyclopentadiene serves as a source of one or two aldehyde groups which are essential for the subsequent construction of the α- and β-chains of PG respectively.

It is also possible to use 3-alkylcyclopentane-1,2,4-triones but only to a limited extent, since in this case the synthesis consists of many stages[43–48]. Thus the synthesis of *dl*-$PGF_{1\alpha}$ has been achieved (Scheme 7). 5-Ethoxycarbonyl-3-(3-methylbut-2-enyl)cyclopentane-1,2,4-trione (XLI) has been obtained by the cyclisation of two molecules of 6-methylhept-5-en-2-one and four molecules of $(COOC_2H_5)_2$. Subsequent treatment with alkali and then acid yields compound (XLII) and conversion into the acetal following treatment with orthoformic ester and subsequent condensation with 1-heptyl-7-methoxymagnesium bromide lead to the dione (XLIII). The latter was reduced initially with Zn/HOAc and then with Li/NH_3 to form a mixture of diols, whose catalytic hydrogenolysis gave rise to the corresponding cyclopentanediols (XLIV). Treatment

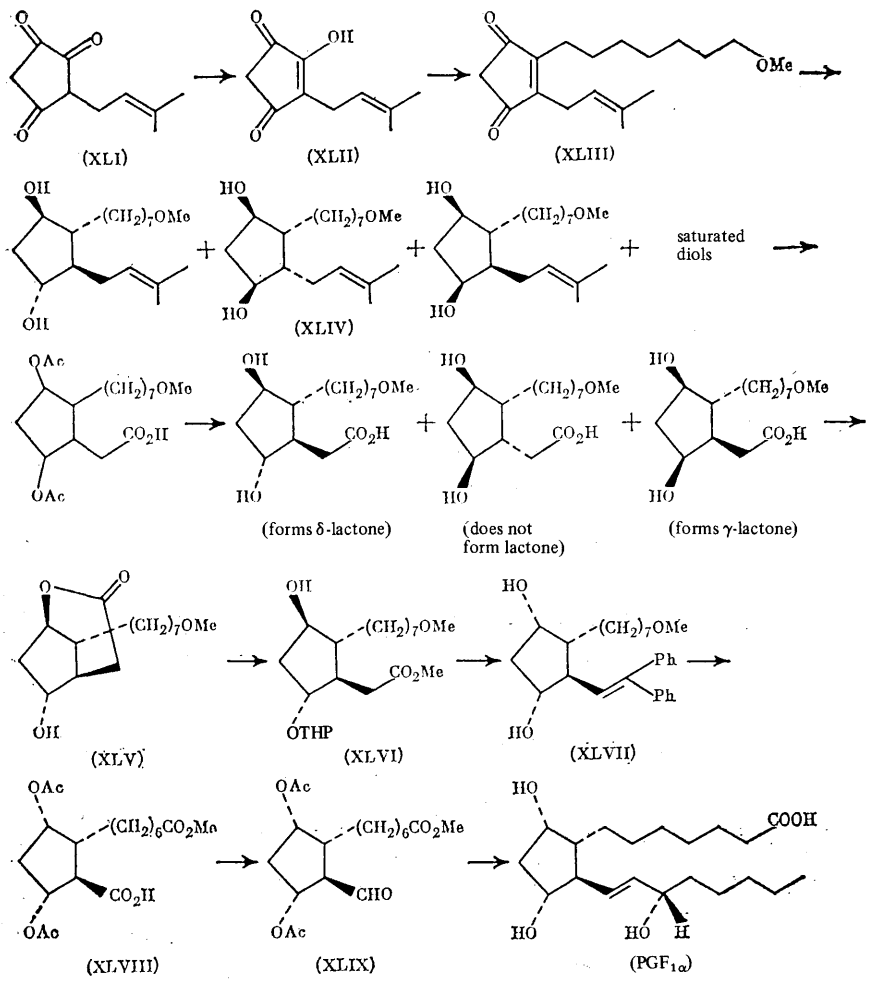
of the diols (XLIV) with acetic anhydride and oxidation with a mixture of $KMnO_4$ and $NaIO_4$ produced the corresponding diacetates of the acids, whose hydrolysis afforded the diols. The latter were converted into the δ-lactone (XLV) on treatment with TsOH. The OH group at C(11) in the δ-lactone (XLV) was protected with THP, after which the product was subjected to alkaline hydrolysis and was treated with an ethereal solution of diazomethane. The OH groups at C(9) in the resulting ester (XLVI) were protected and the latter was condensed in the form of the acetate with phenylmagnesium bromide. The diol (XLVII) was obtained on acidification. After the protection of the hydroxy-groups in compound (XLVII) with acetic anhydride, the methoxy-group was cleaved with boron tribromide to give the hydroxy-group and the subsequent oxidation of this group with the RuO_4–$NaIO_4$ mixture and esterification with diazomethane led to the ester-acid (XLVIII). The reduction of the carboxy-group with diborane and its subsequent Collins oxidation afforded the required aldehyde (XLIX), whose condensation with the corresponding phosphonate, the reduction of the C=O group at C(15) with $Zn(BH_4)_2$, and acid hydrolysis produced $PGF_{1\alpha}$.

2. Synthesis via the Coupled Addition of Organometallic Derivatives

The 1,4-addition of organometallic reagents to 4-alkoxy-2-alkylcyclopent-2-enones, which makes it possible to proceed readily to the total synthesis of PG, has been fairly widely used recently. The addition of divinyl cuprates to substituted cyclopentenones has been studied independently by two groups of investigators[49,50]. The method is used widely, employing various soluble complexes of copper iodides. This approach also permits the development of methods of synthesis of 4-alkoxycyclopentenones. (±)-PGE_1, (±)-11-deoxy-PGE_1, the corresponding $F_{1\alpha}$ and $F_{1\beta}$ derivatives, and (±)-9-oxo-13-*cis*-prostanoic acid[49] have been obtained by this procedure. The synthesis of PGE_1 is illustrated in Scheme 8.[49]

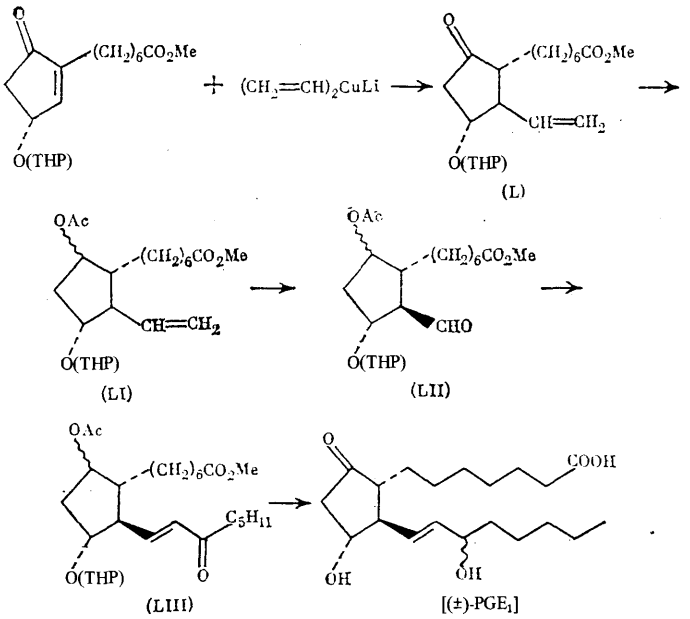
The main reaction is the coupled addition of $(CH_2{=}CH)_2CuLi$ {prepared from bis(trimethyl phosphite)copper cyanide $[(MeO)_3P]_2CuCN$ and vinyl-lithium in ethereal solution} to 4-O(THP)-2-(6'-methoxycarbonylhexyl)cyclopent-2-en-1-one with formation of (±)-vinylcyclopentanone (L) having the required steric configurations of all three asymmetric centres

Scheme 7

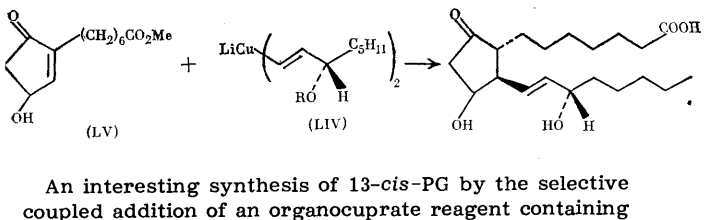


of the cyclopentane ring. The subsequent stages in the synthesis of the required PG were performed without the purification of the intermediate compounds. The reduction of the vinyl ketone (L) with sodium tetrahydroborate and subsequent acetylation with acetic anhydride yielded the C(9)-epimeric acetate (LI), whose ozonolysis led to the unstable aldehyde (LII). Its condensation with dimethyl 2-oxoheptylphosphonate yielded the α,β-unsaturated ketone (LIII). The subsequent reduction of the keto-group at C(15) with $Zn(BH_4)_2$, the alkaline hydrolysis of the ester groups at C(9) and C(1), and oxidation of the OH group at C(9) with the Jones reagent led to a mixture of (±)-PGE_1 and (±)-15-epi-PGE_1. The mixture was separated by preparative thin-layer chromatography (TLC), yielding (±)-PGE_1 (3.6%) and (±)-15-epi-PGE_1 (3.2%). (±)-11-Deoxy-PGE_1 and the corresponding $F_{1\alpha}$ and $F_{1\beta}$ derivatives were synthesised by the same procedure from other cyclopentenone derivatives.

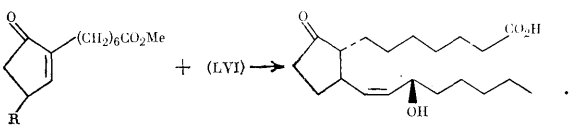
Scheme 8



Another approach[50-61] to the synthesis of PG consists in the coupled addition of the corresponding substituted organocuprate reagent (LIV) to the enone (LV):

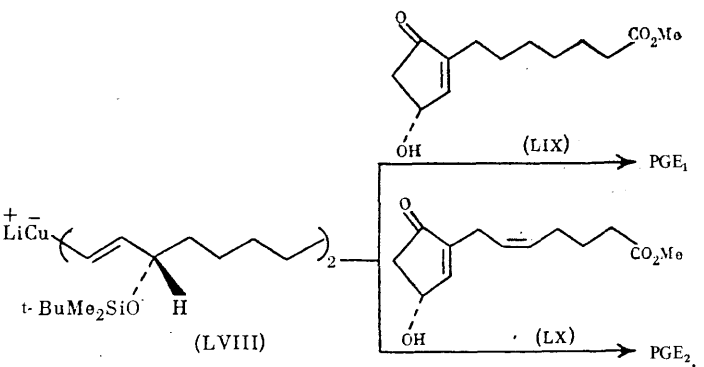


An interesting synthesis of 13-*cis*-PG by the selective coupled addition of an organocuprate reagent containing functional groups has been carried out[62]. It has been established that *cis*-LiCu[CH=CHCH(C_5H_{11})OC(Me)$_2$.OCH_2]$_2$ (LVI) gives rise to high yields of 1,4-adducts with a high degree of stereoselectivity, in contrast to the *trans*-isomer. Thus the interaction of compound (LVI) and 4-R-2-methoxycarbonyl-hexylcyclopent-2-enone (R=H) leads to the racemic 11-deoxy-13-*cis*-PGE_1 after mild hydrolysis (with 20% CH_3COOH). The interaction of compound (LVI) with compound [LVII, R=OC(Me)$_2$OMe] under the same conditions results in the formation of *dl*-11-hydroxy-13-*cis*-PGE_1:



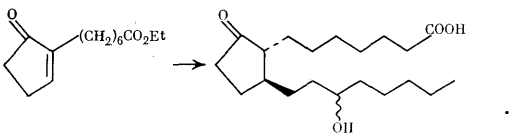
(LVII)

The bio-organic asymmetric synthesis of (−)-PGE_1 and (−)-PGE_2,[63-65] carried out by the coupled addition of organocuprate derivatives (LVII) [obtained from *trans*-3(*S*)-hydroxy-1-iodooct-1-ene] to the enones (LIX) and (LX) respectively may also be of interest:



It is noteworthy that the chiral centres in the key synthons (LIX) and (LX) were produced with the aid of microbiological enzymes. Different microbiological oxidation and reduction methods were used to convert the prochiral substances into optically active prostaglandin synthons. The microbiological reactions have been discussed and compared with the corresponding non-enzymic reactions used in the total synthesis of PGE_1 and PGE_2.[51]

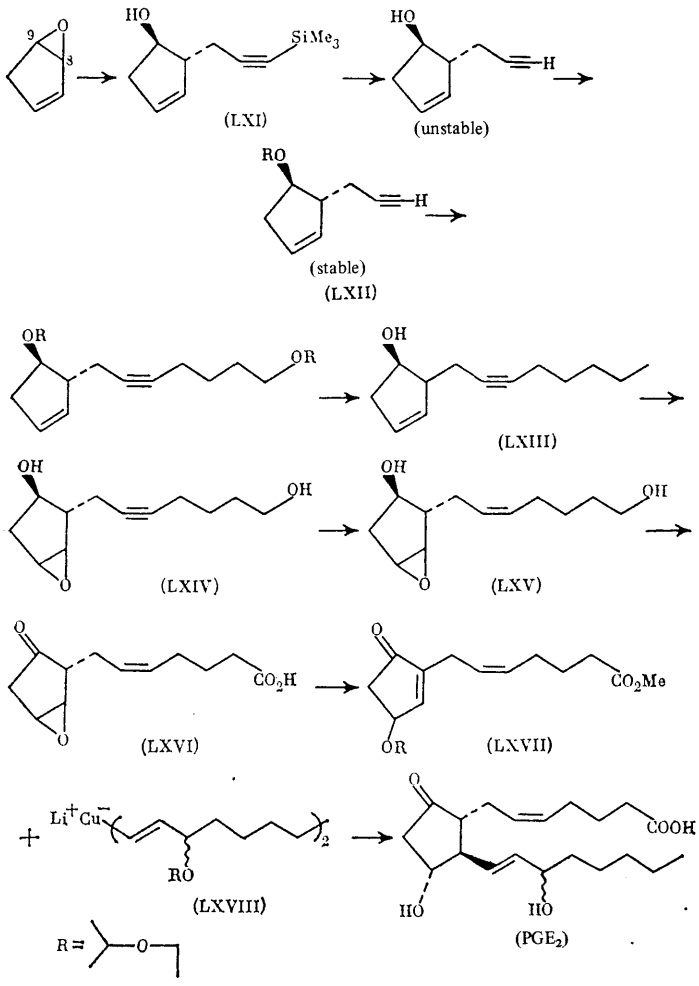
In connection with the synthesis of the racemic 11-deoxy-13-dihydro-PGE_1,[66-68] the coupled addition of t-butoxy-1-octylmagnesium bromide to 2-(6'-ethoxycarbonylhexyl)-cyclopent-2-en-1-one in the presence of Cu(I)I.PBu_3 has been described:



A general method of synthesis for 4-hydroxycyclopentenes—convenient key compounds for the direct synthesis of the PGE series—has been developed[69-71] (Scheme 9). The reaction of the epoxide derived from cyclopentadiene with the lithium salt of trimethylprop-1-ynylsilane leads to *trans*-2-(prop-2-ynyl)cyclopent-3-enol (LXI), whose interaction with ethyl vinyl ether results in the formation of the α-ethoxyethyl ether (LXII). The lithium salt of the latter is alkylated by the α-ethoxyethyl ether of 4-bromobutanol followed by the removal of the protecting groups and the formation of the diol (LXIII). The double bond of the diol (LXIII) is oxidised to the epoxy-group in (LXIV) and, after hydrogenation over 5% $Pd/BaSO_4$ in the presence of traces of quinoline, the *cis*-olefin (LXV) is obtained, its hydroxy-group being oxidised by the Jones reagent to give compound (LXVI). The epoxy-ring in compound (LXVI) is opened by successive treatment with triethylamine and trichloroacetaldehyde to

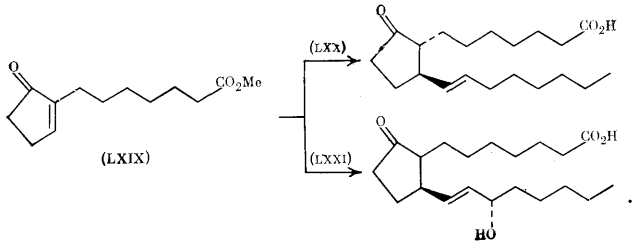
give compound (LXVII). The coupled addition of the lithium dialkylcuprate (LXVIII) (obtained from the ethyl ether of *trans*-1-iodo-oct-1-en-3-ol) to compound (LXVII) leads to a mixture of the C(15)-epimers of PGE_2.

Scheme 9



It is noteworthy that the conversion of epoxycyclopentanones (LXVI) into 4-hydroxycyclopentenones requires specific conditions for the opening of the epoxy-ring and for this reason their practical employment in the synthesis of PG is limited.

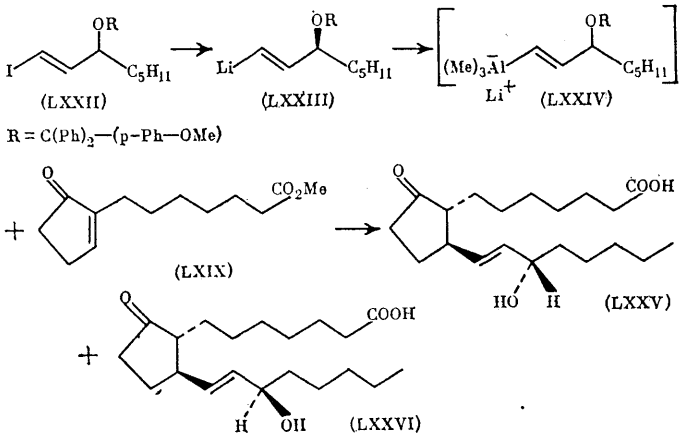
A preparatively significant synthesis of an important intermediate in the preparation of PG, namely 2-(ω-methoxycarbonylhexyl)cyclopent-2-enone (LXIX), and its single-stage conversion into the prostane skeleton have been described[72]. Octa-1,7-diene has been hydroborated by the Brown method (B_2H_6 in THF, I_2, NaOH, and HCl in aqueous THF) to form 8-iodo-oct-1-ene, from which a Grignard reagent was prepared. The latter reacts with 2-methoxycyclopent-2-enone, forming 2-(oct-7-enyl)cyclopent-2-enone. This ketone is oxidised in succession by *m*-$ClC_6H_4CO_3H$ and then H_5IO_6 to give the corresponding aldehyde, which is oxidised by the Jones reagent to the acid from which the ester (LXIX) is obtained. The reaction of compound (LXIX) with *trans*-$C_6H_{13}CH{=}CHLi$ (LXX) in the presence of n-Bu_3PBuI and subsequent hydrolysis led to the formation of *dl*-11,15-dideoxy-PGE_1 in 75% yield relative to compound (LXIX). When compound (LXIX) is treated with (3*S*)-*trans*-MeCH(OEt)OCH(C_6H_{11})CHCHLi (LXXI), equal amounts of 11-deoxy-PGE_1 and 11-deoxy-15-epi-PGE_1 are formed:



Like other organometallic reagents, alanates and alanes are capable of 1,4-addition to 4-alkoxycyclopentenones[73-76]. Lithium alanates are obtained from alanes by the reduction of 3-alkoxyacetylenes, the reaction usually proceeding with a 40% yield and leading to an olefin having the *cis*-configuration. However, when the alcoholic protective group at the C(15) atom is bulky, only the *trans*-olefin is formed. The simplest method of synthesising the alanate reagent involves the reaction of *trans*-vinyl-lithium with R_3Al.

A method of synthesis of 11,15-dideoxy-PGE_1, the corresponding E_2 and $F_{1\alpha}$ derivatives, 11-deoxy-PGE_1, and PGE_1 by the stereospecific coupled addition of lithium *trans*-1-alkenylalanate to the α-alkylated cyclopentene ring has been proposed[73] (Scheme 10):

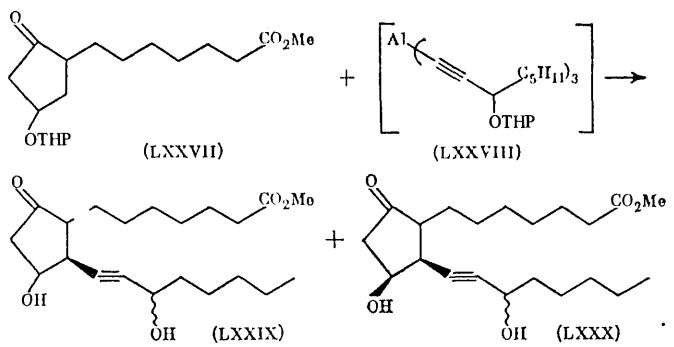
Scheme 10



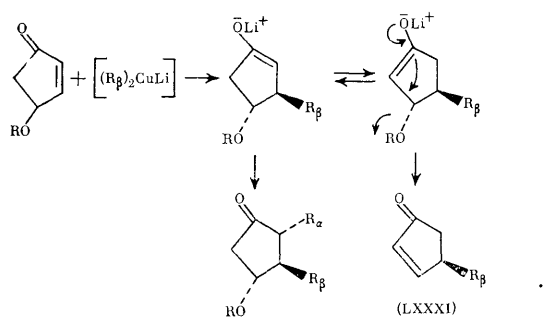
The protected 1-iodo-*E*-oct-2-en-3-ol (LXXII), obtained from the corresponding acetylenic derivative, is metallated by n-BuLi to compound (LXXIII), whose treatment with trimethylaluminium leads to the lithium alanate reagent (LXXIV). The coupled addition of the alanate (LXXIV) to the cyclopentenone (LXIX) leads, after chromatographic separation, the removal of the protective group, and hydrolysis, to *dl*-11-deoxy-PGE_1 and its C(15)-epimer (LXXVI) in proportions of 44:56 respectively.

Alanes also add to 4-alkoxycyclopentenones[77,78] with formation of PG. The reaction of the key compound (LXXVII) with tri(3-tetrahydropyranyloxyoct-1-ynyl)aluminium (LXXVIII) results in the formation, after hydrolysis and chromatography on silica gel, of the methyl ester of (±)-11β, 15(*RS*)-dihydroxy-9-oxoprost-3-ynoic acid (LXXIX) and the methyl ester of (±)-11β, 15(*RS*)-dihydroxy-9-oxo-8-isoprost-13-ynoic acid (LXXX) (Scheme 11):

Scheme 11



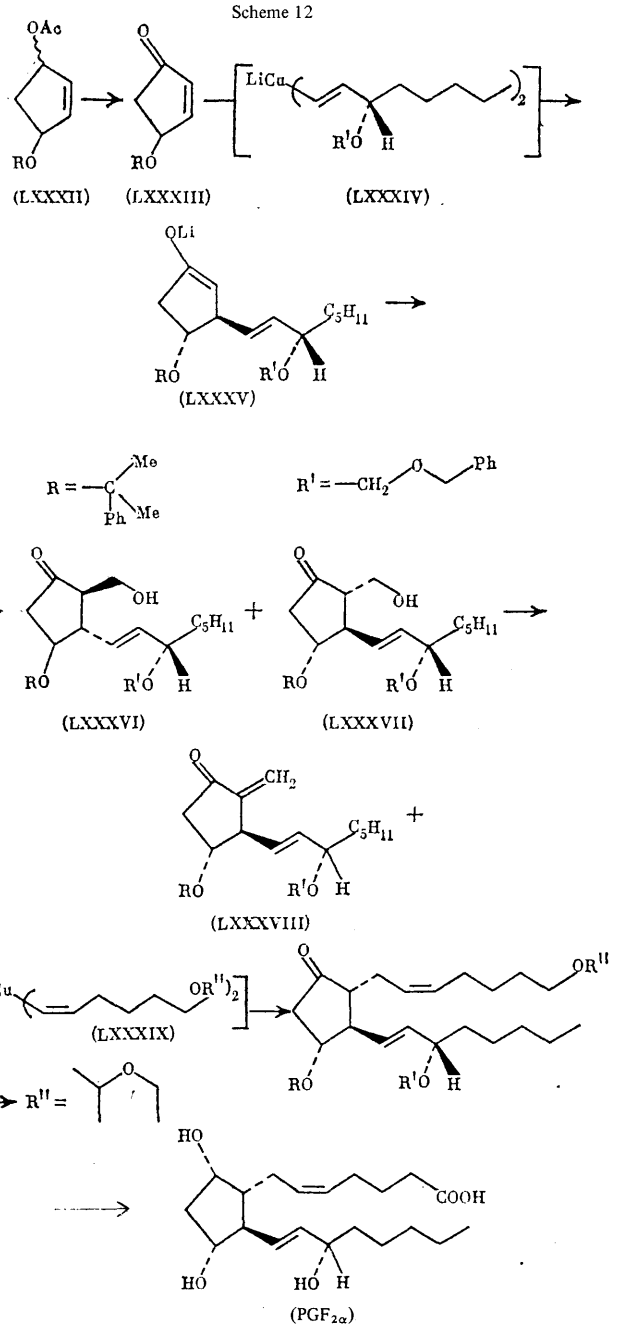
The 1,4-addition of the β-chain to 4-alkoxycyclopent-2-enone and the trapping of the resulting enolates with a finished α-chain or a potential α-chain may be regarded as one of the simplest approaches to the synthesis of PG and one involving a small number of stages. The β-chain is added in the *trans*-position of the C(11)-alkoxy-group by the Michael reaction and the subsequent trapping of the enolate leads to the complete *trans*-orientation of the three substituents in the cyclopentane ring. The main criterion of the successful application of this method of synthesis of PG is the selection of a suitable trapping agent. The low rate of trapping of the enolate of 4-alkoxycyclopent-2-enone leads to equilibrium between the enolates, which results in the elimination of the alkoxy-group with formation of the cyclopentenone (LXXXI). For example, alkylation even by reactive electrophiles, such as allyl halides, hinders only slightly the attainment of the state of equilibrium of the enolate:



An interesting solution of this problem involves the use of formaldehyde, which is an extremely reactive electrophile, in the synthesis of $PGF_{2\alpha}$ and 15-epi-$PGF_{2\alpha}$, where 4-cumenyloxycyclopenten-2-one (LXXXIII) was employed as the key compound[79–82]. The synthesis of $PGF_{2\alpha}$ was achieved in eight stages with an overall yield of 17% (Scheme 12).

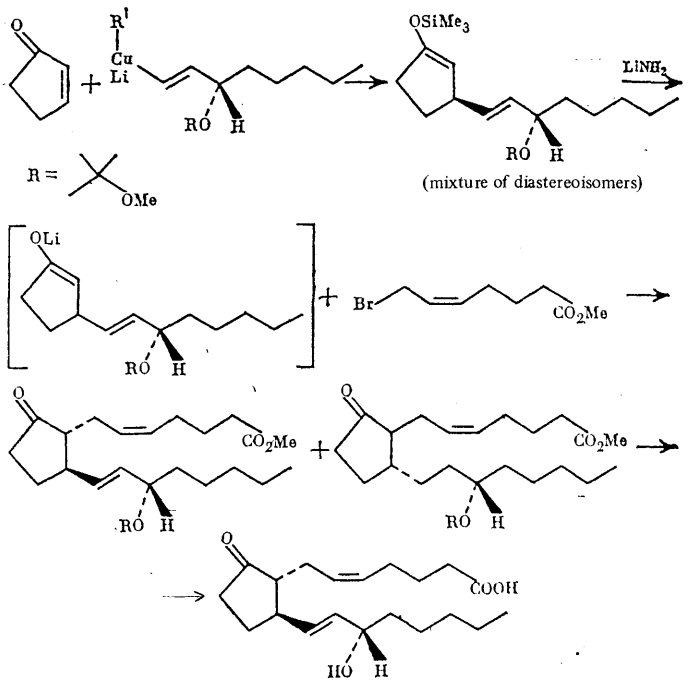
An aqueous solution of $Fe_2(SO_4)_3$ is added to cyclopentadiene, cumenyl peroxide, and $Cu(OAc)_2$ in acetic acid and 4-cumenyloxycyclopent-2-enyl acetate (LXXXII) is obtained, its alkaline hydrolysis and subsequent Jones oxidation resulting in its conversion into compound (LXXXIII). The addition of the cuprate reagent (LXXXIV) to compound (LXXXIII) in the presence of Bu_3P/CuI leads to the regiospecific enolate ion (LXXXV), whose interaction with an ethereal solution of formaldehyde produces a mixture of the alcohols (LXXXVI) and (LXXXVII) in proportions of 1 : 1.3. The dehydration of compound (LXXXVII) produces the exocyclic enone (LXXXVIII). The 1,4-addition of compound (LXXXIX) to the enone (LXXXVIII), the successive reduction of the C=O group at C(9), and the removal of the protective groups and hydrolysis lead to $PGF_{2\alpha}$, with $[\alpha]_D$ = +22.7°, and 15-epi-$PGF_{2\alpha}$.

Scheme 12



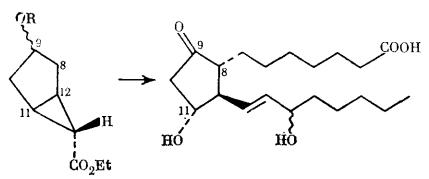
A three-stage synthesis of 11-deoxy-PGE_2 with an overall yield of 20–60%, where the β-chain was introduced by the coupled 1,4-addition of the mixed cuprate to Δ^2-cyclopentenone and the α-chain was introduced by the alkylation of a specifically oriented enolate ion, has been developed[83] (Scheme 13):

Scheme 13



3. Synthesis Based on Symmetrical Intermediate Compounds

Just and Simonovitch[84] were the first to show that a symmetrical intermediate can be used to construct the asymmetric PG molecule:

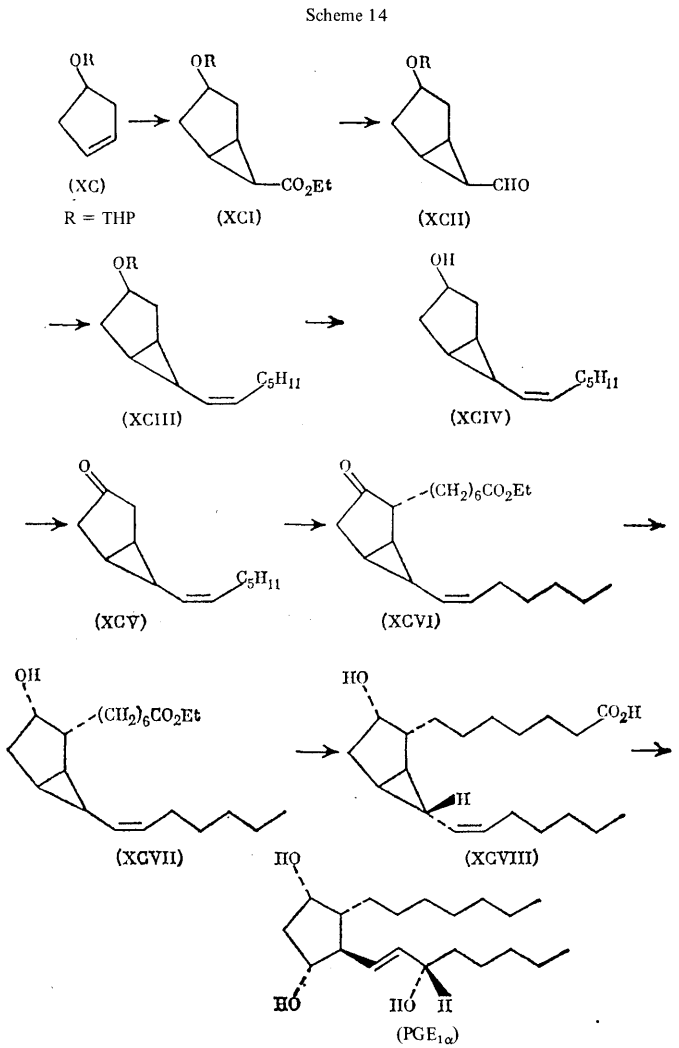


The main condition is the formation of the allyl alcohol system in the β-chain on solvolysis of the corresponding substituted cyclopropylmethanol derivative. This procedure was developed further and modified in other studies[85,86].

Scheme 14 illustrates the general method of synthesis of *dl*-$PGF_{1\alpha}$.[84] When cyclopentenol is treated with dihydropyran in the presence of $POCl_3$, the THP ether (XC) is formed quantitatively, its interaction with ethyl diazoacetate in the presence of copper powder leading to a mixture of the *syn-anti*- and *exo-endo*-isomers. When the mixture is refluxed with sodium methoxide in methanol, only the *exo*-isomer (XCI) (*syn–anti* mixture) is obtained. The ester group in the *exo*-isomer (XCI) is reduced with lithium tetrahydroaluminate to the alcoholic group (*syn–anti* mixture), which is oxidised with dilute Jones reagent to the aldehyde (XCII). The condensation of the latter with the phosphorane $(C_6H_5)_3P{=}CHC_5H_{11}$ leads to four isomers, which were separated by chromatography on Al_2O_3 with isolation of the required olefin (XCIII), whose acid hydrolysis yields the alcohol (XCIV) in the form of a mixture of four isomers, which can also be separated with the aid of TLC. The mixture (XCIV) is oxidised with a dilute Jones reagent and the resulting mixture of ketones (XCV) is also separated by TLC. The ketone (XCV) interacts with the methyl ester of 7-iodoheptanoic acid in demthylcellosolve in the presence of t-BuOK with formation of compound (XCVI), which, without being purified, is reduced with $NaBH_4$ to compound (XCVII). Alkaline hydrolysis of compound (XCVII) leads to the acid (XCVIII), a 1% solution of the latter (without purification) in 97–100% formic acid being treated with sodium carbonate, the mixture is then treated with 30% H_2O_2, the mixture of products is isolated and separated by TLC, and $PGF_{1\alpha}$ is obtained.

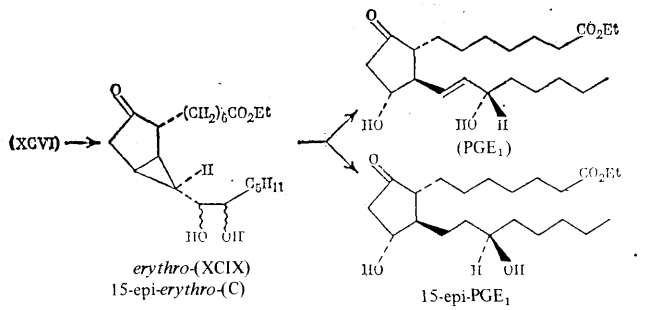
PGE_1 is obtained analogously by treating compound (XCVI) with a mixture of HCOOH and H_2O_2.

Scheme 14



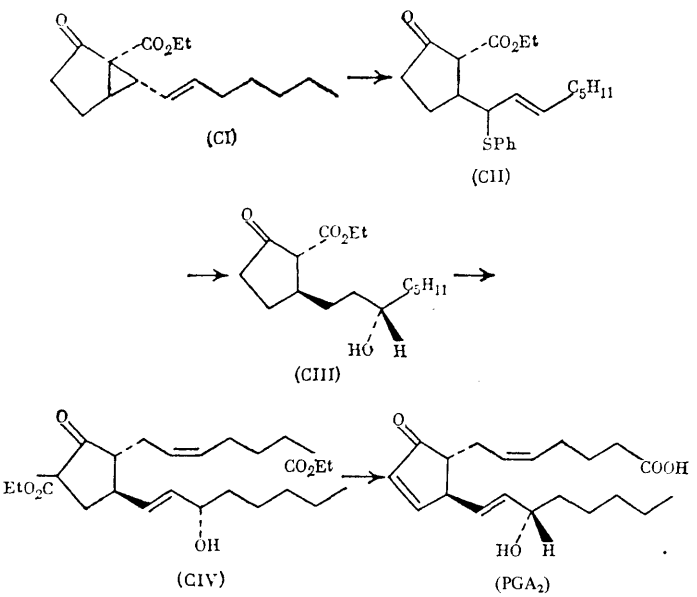
Subsequent studies showed[87–90] that, among all the approaches to the synthesis of PG via the bicyclo[3.1.0]hexane system, the best results have been obtained when the stage involving the transition from compound (XCVI) to PG was modified. Thus the hydroxylation of compound (XCVI) with OsO_4 leads to two glycols (XCIX) and (C) in approximately equal amounts[87]. The conversion of the less polar glycol (XCIX) into its bismethanesulphonate with subsequent solvolysis in a 2:1 acetone–water mixture leads to the ethyl ether of (±)-PGE_1 [17–18% relative to the glycol (XCIX)] and 19% of the ethyl ether of (±)-15-epi-PGE_1. The more polar glycol (C) produces a 19% yield of the ethyl ether of (±)-PGE_1 and a 16–17% yield of the ethyl ether of 15-epi-PGE_1.

PGE_3, (±)-PGE_2, $PGF_{2\alpha}$, and $PGF_{2\beta}$ have been obtained under the same conditions[88-90].



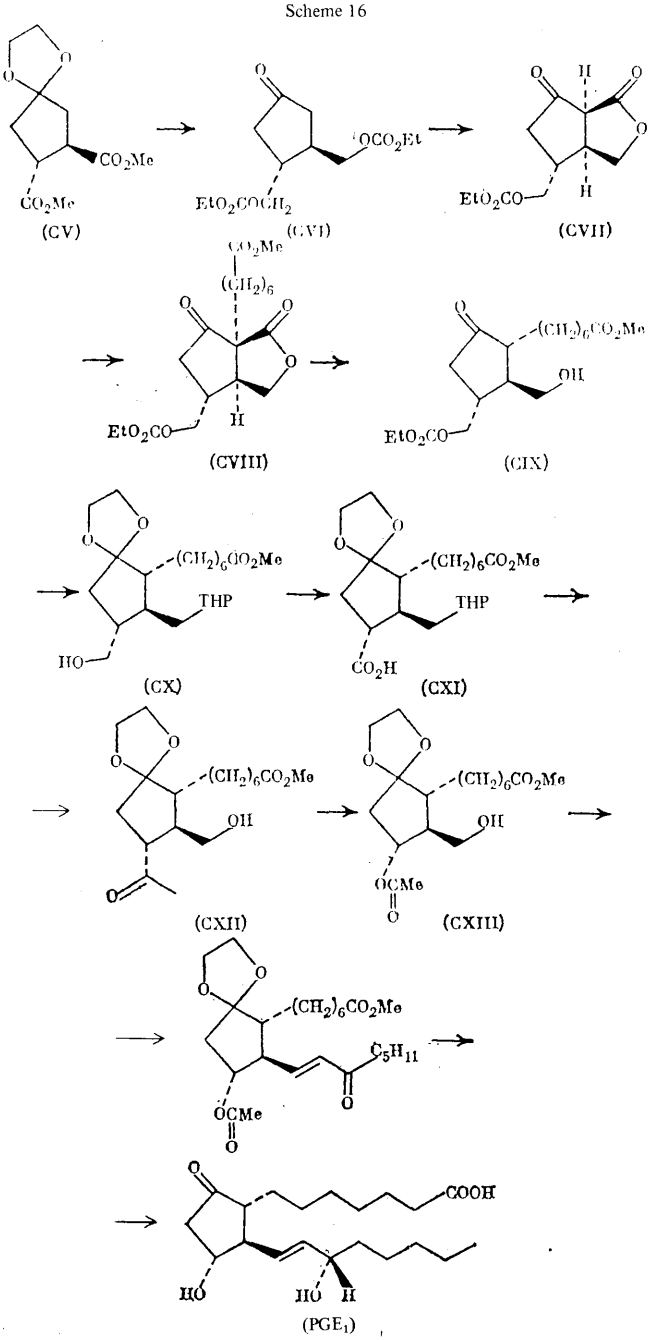
An interesting method for the opening of the cyclopropane ring has been proposed by a group of investigators[91-94]. In the stereoselective synthesis of PGA_2,[88] the cyclopropane ring in the key compound (CI) is readily opened by thiophenol in the presence of t-BuOK to give compound (CII). Subsequent oxidation with m-$ClC_6H_4CO_3H/CH_2Cl_2$ and reductive rearrangement of the sulphide (CII) by trimethyl phosphite in methanol lead to the hydroxyester (CIII). The alkylation of compound (CIII) with subsequent retro-Dieckman cyclisation give rise to the ketoester (CIV), which yields PGA_2 after hydrolysis and oxidation (Scheme 15).

Scheme 15



The syntheses of PGE_1, 11-deoxy-PGE_2, and 11α-hydroxymethyl-PGE_2 [95-97] from a symmetrical key compound, namely 3,4-dimethoxycarbonylcyclopentanone ethylene ketal (CV), obtained by the dimerisation of dimethyl maleate, has been proposed. The reduction of the ester groups in compound (CV) to alcoholic groups with $LiAlH_4$ and subsequent treatment with $ClCO_2C_2H_5$ in pyridine and then with aqueous toluene-p-sulphonic acid lead to the ketone (CVI), whose treatment with t-BuOK affords the lactone (CVII). Alkylation of the latter with methyl 7-iodoheptanoate in the presence of t-BuOK leads to the lactone (CVIII). Refluxing of compound (CVIII) in aqueous dioxan with Na_2HPO_4 and subsequent conversion into an acetal by the ethylene glycol/toluene-p-sulphonic acid mixture make it possible to obtain the corresponding hydroxyketal (CIX). Protection, alkaline hydrolysis, and transesterification with ethereal CH_2N_2 of compound (CIX) lead to the formation of the alcohol (CX), which is oxidised with CrO_3 in pyridine to the acid (CXI). On treatment with $(COCl)_2$ and condensation with Me_2CuLi, the potassium salt of the acid (CXI) is converted into the methyl ketone (CXII), whose oxidation with CF_3CO_3H/Na_2HPO_4 in CH_2Cl_2 leads to the acetate (CXIII). The latter is converted into dl-PGE_1 on oxidation of the hydroxymethyl group to the aldehyde group followed by its Wittig condensation with the corresponding phosphorane $(n\text{-}C_4H_9)_3P{=}CH{-}CO{-}C_5H_{11}$, the reduction of the oxo-group at the C(15) atom to the hydroxy-group, and the removal of the acetal protective group (Scheme 16).

Scheme 16



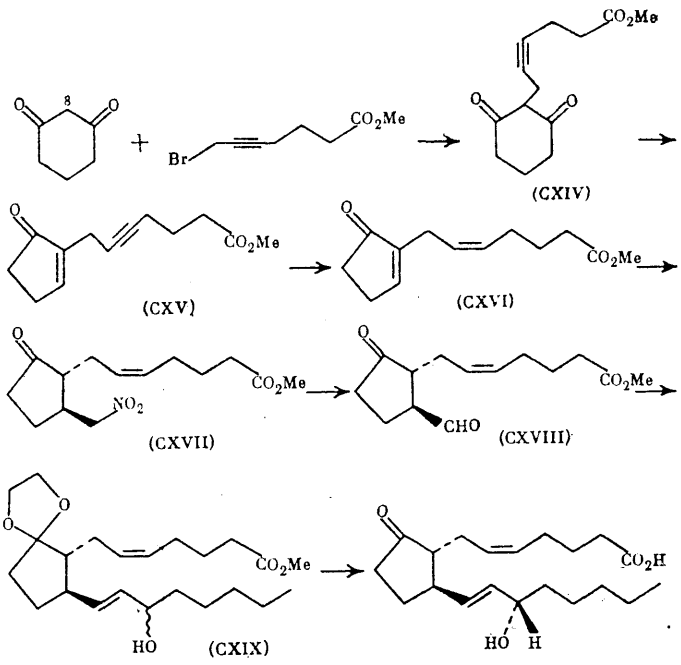
4. Synthesis Using Methods for Ring Contraction and Expansion

Bagli and Bogri[98] were the first to use the ring contraction method for the construction of the prostane ring in the synthesis of (±)-11-deoxy-PGE_1, PGE_2, and their C(15)-epimers in accordance with Scheme 17.

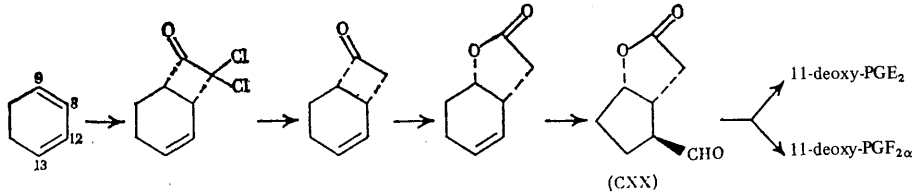
Cyclohexane-1,3-dione interacts with the methyl ester of 7-bromohept-5-ynoic acid in the presence of sodium hydride in DMF to form compound (CXIV). When the latter is treated with t-BuOCl and sodium carbonate, a rearrangement gives rise to compound (CXV), whose reduction with hydrogen (in the presence of the Lindlar catalyst) leads to the *cis*-olefin (CXVI) and the latter reacts with nitromethane in methanol in the presence of sodium methoxide to form the nitroketone (CXVII). Its treatment with sodium methoxide and subsequent hydrolysis with dilute H_2SO_4 (the Nef reaction) results in the formation of the aldehyde (CXVIII), whose condensation with the corresponding phosphonate and subsequent reduction of the C=O group at C(15) to the alcoholic group and the removal of the acetal protective group lead to 11-deoxy-PGE_2.

A similar ring contraction method was later employed to synthesise $PGF_{2\alpha}$.[99,100]

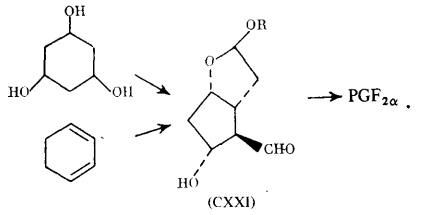
Scheme 17



Corey's approach[101] to the synthesis of 11-deoxy-PGE_2 and $PGF_{2\alpha}$ involves the contraction of the cyclohexa-1,3-diene ring and includes the following stages: (1) treatment with dichloroacetic acid in the presence of $(C_2H_5)_3N$; (2) reduction with Zn/AcOH; (3) oxidation with H_2O_2/H_2O–AcOH; (4) rearrangement under the influence of $Tl(NO_3)_3$ and oxidation with H_2O–$HClO_4$, $NaClO_4$ to the aldehyde (CXX), which is subsequently converted by standard methods into 11-deoxy-PGE_2 and 11-deoxy-$PGF_{2\alpha}$.

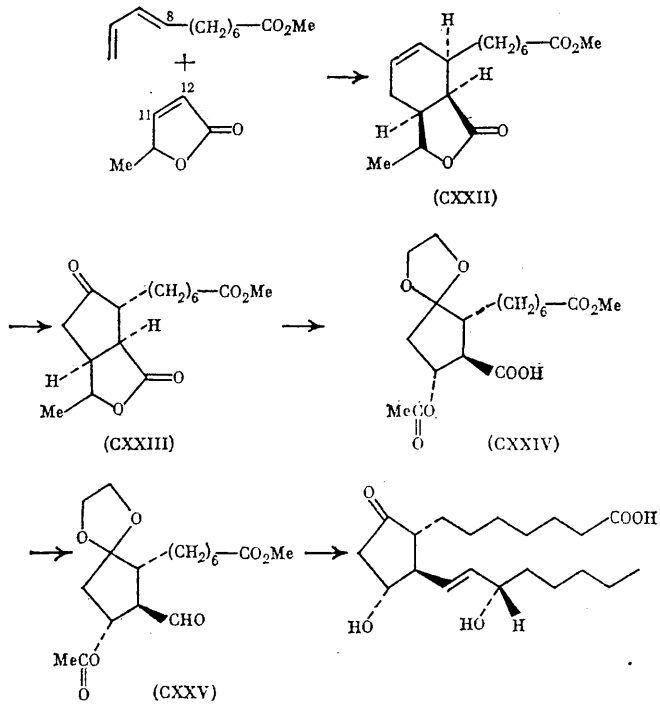


Syntheses have been described where *cis*-cyclohexane-1,3,5-triol[102] and cyclohexa-1,3-diene[103] are used as the starting materials for the synthesis of the key aldehyde (CXXI), which is readily converted into $PGF_{2\alpha}$:



An unusual solution of the problem of the synthesis of PGE_1 [104] consists in the Diels–Alder reaction between the methyl ester of undeca-8,10-dienoic acid and β-angelica lactone, leading to the *cis*-lactone (CXXII), which is oxidised with O_3 in CH_2Cl_2 and then with H_2O_2 in acetic acid to the lactone derived from the cyclopentanone (CXXIII), whose conversion into the acetal and alkaline hydrolysis lead to a lactonoacid, whose lactone ring is opened by a series of reactions to give the acid (CXXIV). It was found that the conversion of the carboxy-group into the aldehyde group without involving the methoxycarbonyl group at C(1) (Scheme 18) is impossible and the acid (CXXIV) was therefore reduced in the form of the acylimidazole derivative with $AlH(OBu\text{-}t)_3$ to the aldehyde (CXXV), which was subsequently converted by standard methods into PGE_1 in a yield higher than 50%.

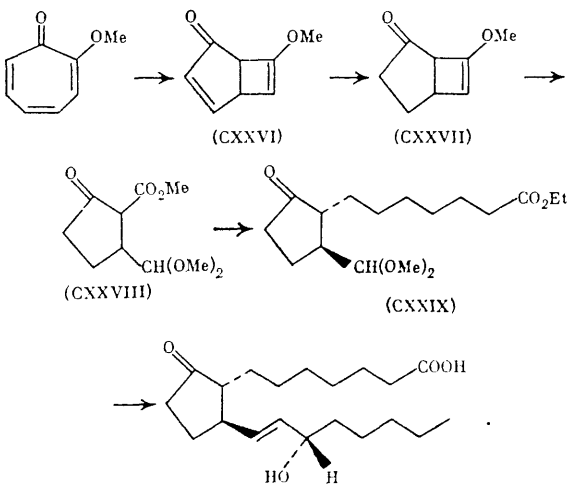
Scheme 18



The capacity of the methyl ether of α-tropolone for ring contraction on photochemical valence tautomerisation has been used successfully in the synthesis of *dl*-11-deoxy-PGE_1.[105]

The methyl ether of α-tropolone is irradiated with the light of a high-pressure mercury lamp to form 7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (CXXVI), which is hydrogenated over platinum to compound (CXXVII). The latter is subjected to ozonolysis in a mixture of CH_2Cl_2 and methanol, the product is treated with liquid SO_2, and cyclopentanone acetal (CXXVIII) is obtained. The latter is alkylated with ethyl 7-iodoheptanoate in the presence of KH/DMSO with subsequent decarboxylation to the *trans*-cyclopentanone (CXXIX). The acetal group is removed and compound (CXXIX) is condensed with the corresponding phosphonate. After a series of simple operations, *dl*-11-deoxy-PGE_1 is isolated (Scheme 19).

Scheme 19

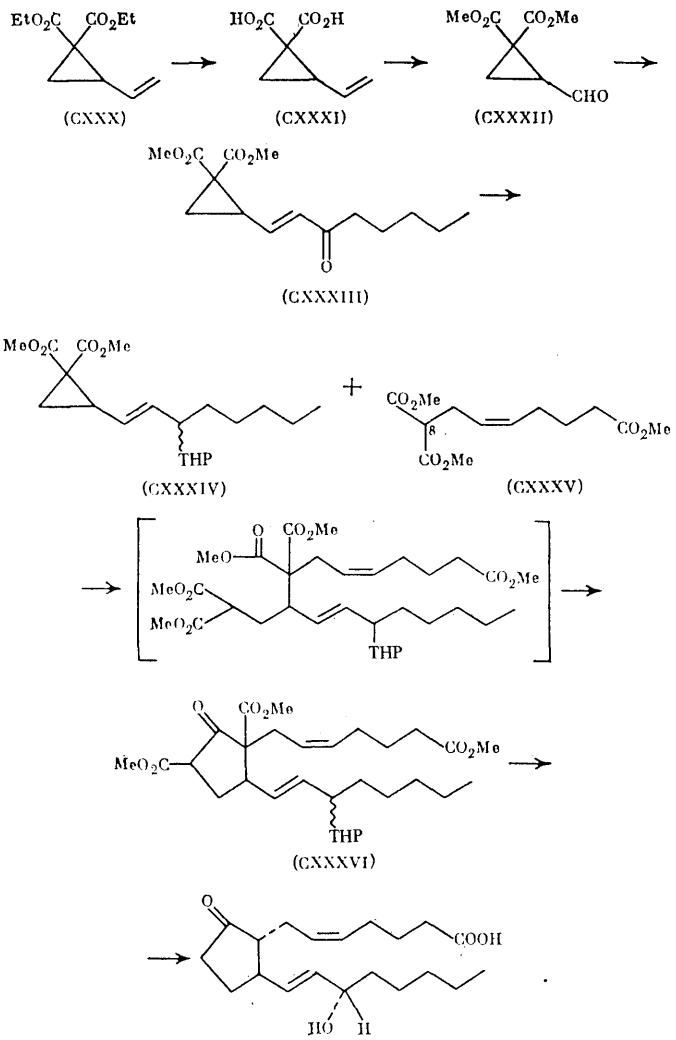


A number of syntheses of PG involve as the key stage the ring expansion reaction of cyclopropane derivatives. Thus an effective synthesis of *dl*-11-deoxy-PGE_2 and its C(15)-epimer is based on the familiar reaction in which the diethyl ester of 1-vinylcyclopropane-2,2-dicarboxylic acid (CXXX) is converted into 2,3-diethoxy-carbonyl-3-vinyl-1-cyclopentanone on treatment with sodiomalonic ester[106,107].

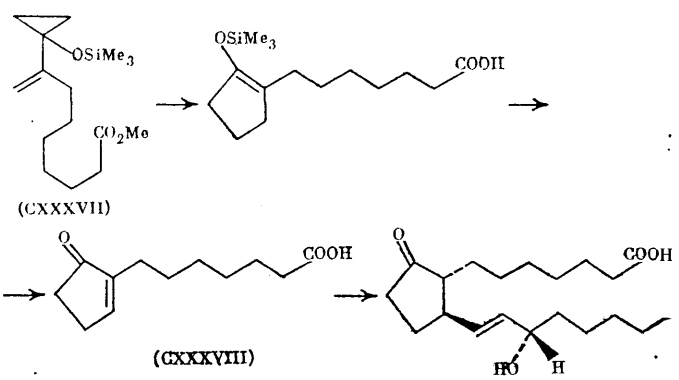
(±)-2-Vinylcyclopropane-1,1-dicarboxylic acid (CXXXI), obtained by alkaline hydrolysis from compound (CXXX), is resolved into its optical isomers with the aid of brucine; (−)-(CXXXI) is esterified with CH_2N_2 to the dimethyl ester, which is converted by ozonolysis and subsequent decomposition of the resulting ozonide with Me_2S into the aldehyde (CXXXII).

The condensation of the latter with $(MeO)_2P(O)CH_2CO.C_5H_{11}$-n leads to compound (CXXXIII), which is reduced with $NaBH_4$ to a mixture of the epimeric alcohols, whose THP ethers (CXXXIV) are allowed to react with the methyl ester of *cis*-hept-3-ene-1,1,7-tricarboxylic acid (CXXXV) in the presence of sodium methoxide with formation of compound (CXXXVI). The subsequent removal of the protective group, hydrolysis with alkali, and chromatographic separation of the epimers lead to 11-deoxy-PGE_2 in a yield up to 68% (Scheme 20):

Scheme 20



The rearrangement of the trimethylsilyl derivative of the cyclopropanol (CXXXVII) to the cyclopentanone (CXXXVIII), which is a key product in the synthesis of 11-deoxy-PGE_1, has been described[108]:



A series of new approaches to the synthesis of PG, for example, on the basis of a photochemical method, have been described in recent years[109–112]. (±)-$PGF_{2\alpha}$ has been synthesised in this way using the photolysis of a bicyclic cyclobutanone to give a γ-lactol as the key stage[109].

A synthesis of $PGF_{2\alpha}$ via carbopalladisation involving a small number of stages has been achieved[113]. The key reaction is that between cyclopentenyldimethylamine, obtained by the addition of HCl to cyclopentadiene followed by treatment with dimethylamine, and lithium tetrachloropalladate and sodiomalonic ester.

A new direct method for the conversion of castor oil into PGH_1 has also been developed[114].

However, the above approaches to the synthesis of PG have not found extensive applications.

Studies designed to obtain PG analogues, which are synthetically more readily available than natural PG and which have the same and in certain cases a higher or comparable biological activity, have been developing vigorously in recent years.

The search for synthetic analogues of PG is also dictated by other causes. In the study of the action of PG on the human organism, undesirable side effects are frequently observed (a deficiency of natural PG as therapeutic agents is the short time of their action, which necessitates frequent repeated administration of the preparations). Preparations whose structure if close to that of natural PG but which act more selectively on individual systems and functions of the organisms and are more stable, less toxic, and better tolerated by man are therefore being sought.

After the preparation of the review for publication, a number of communications on the same subject were published[115–129].

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