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The Synthesis of Prostacyclin and Its Analogues

V.A.Dombrovskii, E.V.Gracheva, and P.M.Kochergin

The advances in the synthesis of prostacyclin and its analogues are examined. The bibliography includes 114 references.

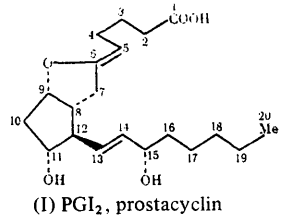
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I. INTRODUCTION

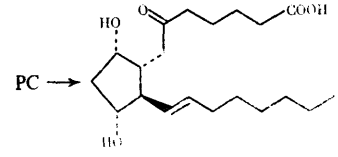
Much attention is being devoted at present to prostacyclin (PC)—a substance which is tens of times more active than any of the prostaglandins (PG). PC is formed from arachidonic acid in minute amounts in the heart and in the walls of the blood vessels. Investigators have assigned a special place to PC because, in contrast to PG, it does not decompose in the lungs and, circulating in the blood, it tends to reduce the arterial pressure. PC has yet another exceptional property—the ability to prevent the development of atherosclerosis and especially its severe consequence—the formation of clots in the blood vessels.[1]

By incubating the endoperoxides PGG_2 and PGH_2 with the enzyme system of the microsomal fraction of the arterial vessels, Vane and co-workers[2,3] observed in 1976 the formation of an unstable substance which proved to be a powerful inhibitor of the aggregation of platelets. This substance, initially designated by PGX, was subsequently characterised as (5Z)-9-deoxy-6,9α-oxido-Δ^5-$PGF_{1\alpha}$ [4,5] and now bears the trivial name prostacyclin or the abbreviation PGI_2 or (I). PC is at the present time the most powerful inhibitor of the aggregation of platelets[6] and possesses strong vasodilating properties.[2,7-9]



(I) PGI_2, prostacyclin

The chemistry of PC is determined by characteristic groups, one of which is the vinyl ether group incorporating the C(5)–C(6) atoms and the oxygen atom attached to C(9) in this molecule.[4,5,10] The potential value of PC as a therapeutic agent, particularly when its prolonged action is required, is appreciably reduced owing to the fact that its vinyl ether group is very readily and rapidly hydrolysed (the half-decomposition time is 10 min at pH 7.6 at 25 °C) which leads to the formation of 6-oxo-$PGF_{1\alpha}$.[11,12] The problem therefore arose of the synthesis of chemically stable analogues of PC possessing a high selective activity while retaining, in principle, the structure of PG, since PC, which is ultimately transformed into the usual $PGF_{1\alpha}$ metabolites, reduces the adhesion and sticking together of blood platelets 1000 times more effectively than the stable 6-oxo-$PGF_{1\alpha}$ and 30 times more effectively than PGE_1.[2,3] The tactics and strategy used in the synthesis of PG and their analogues, developed between 1960 and 1980,[13-15] helped to solve the problem of the synthesis of PC and its analogues.



6-oxo-PGF_1

The growing interest in PC analogues led to the publication of numerous studies on the synthesis and pharmacological properties of these compounds. However, the data on their synthesis have been scarcely treated systematically or surveyed. A monograph[16] and a review[17] are mainly devoted to the pharmacological properties of PC and its analogues and in another review[18] the methods of synthesis of PC and thromoboxanes are examined extremely concisely. We therefore thought it useful to review the most important studies on the synthesis of PC and its analogues.

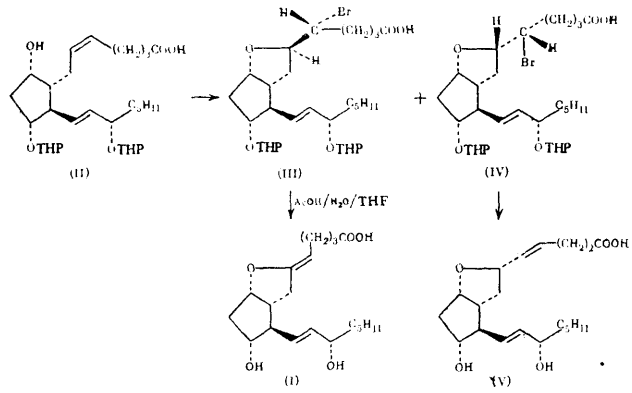
II. THE SYNTHESIS OF PROSTACYCLIN AND ITS ANALOGUES

1. Synthesis from Natural Prostaglandins and Their Analogues

The simplest and most general method of synthesis of PC and its analogues involves the modification of natural PG or their analogues, including the following series of reactions: (1) intermolecular nucleophilic addition of bromine or iodine to the C(5)–C(6) double bond of PG with the simultaneous formation of the ring; (2) elimination of HBr or HI with alkali or reductive elimination of iodine.

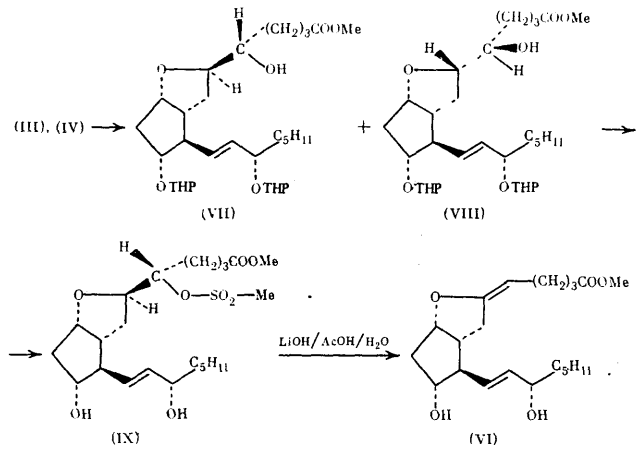
The required stereochemistry of the C(5) atom is retained in all the transformations, since the main processes are the *trans*-addition of the halogen to the double bond and the *trans*-elimination of HBr or HI. For example, the bromination of $PGF_{2\alpha}$ (II) with *N*-bromosuccinimide (NBS) yields a mixture of diastereoisomers of the 5-bromo-substituted PGI_1 (III) and (IV) (3 : 1). After the removal of the tetrahydropyranyl (THP) protecting group from the diastereoisomer (III) and the elimination of HBr by treatment with *t*-BuOK/BuOH, PC [compound (I)] is formed. The diastereoisomer (IV), formed as a minor product in the cyclisation stage, gives rise to Δ^4-6α-PGI_1 (V) after the same treatment as that described for compound (III) [19,20] (Scheme 1).

Scheme 1

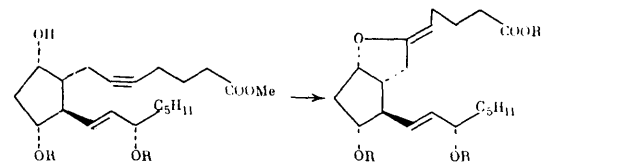


Corey and co-workers described the synthesis of (5*E*)-PGI_2 (VI) from the intermediates (III) and (IV),[21] whose treatment with K_2O and 18-crown-6 ether in dimethyl sulphoxide (DMSO) leads to the corresponding mixture of alcohols with inversion at the C(5) atom (85%). The mixture of alcohols is esterfied with diazomethane to compounds (VII) and (VIII), which are then converted into the methanesulphonate (IX) (84%) by reaction with methanesulphonyl chloride and triethylamine. The THP groups in compound (IX) are removed in the usual way and the product is hydrolysed to the corresponding acid, which is then treated with an excess of t-BuOK/BuOH to form compound (VI) (Scheme 2).

Scheme 2



Suzuki[22] proposed a simple stereospecific synthesis of PC, with a small number of stages, starting from the derivative 5,6-dihydro-$PGF_{2\alpha}$. The chiral acetylenic alcohol (X) is converted into the cyclic product (XI). The removal of the protecting groups in compound (XI) by treatment with tetra-n-butyl ammonium fluoride (TBAF) in tetrahydrofuran (THF) affords the methyl ester of PGI_2 (XII) (74%), the alkaline hydrolysis of which leads to PGI_2 (I).



(X): R = Si(Me)$_2$-t-Bu

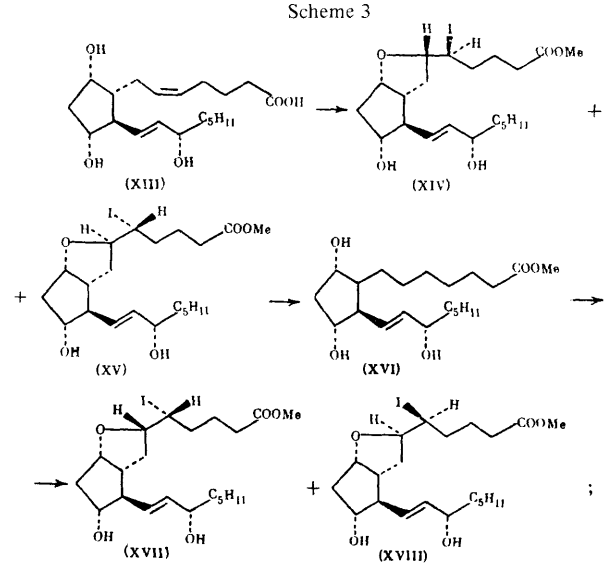
(XI): R = Si(Me)$_2$-t Bu, R^1 = Me

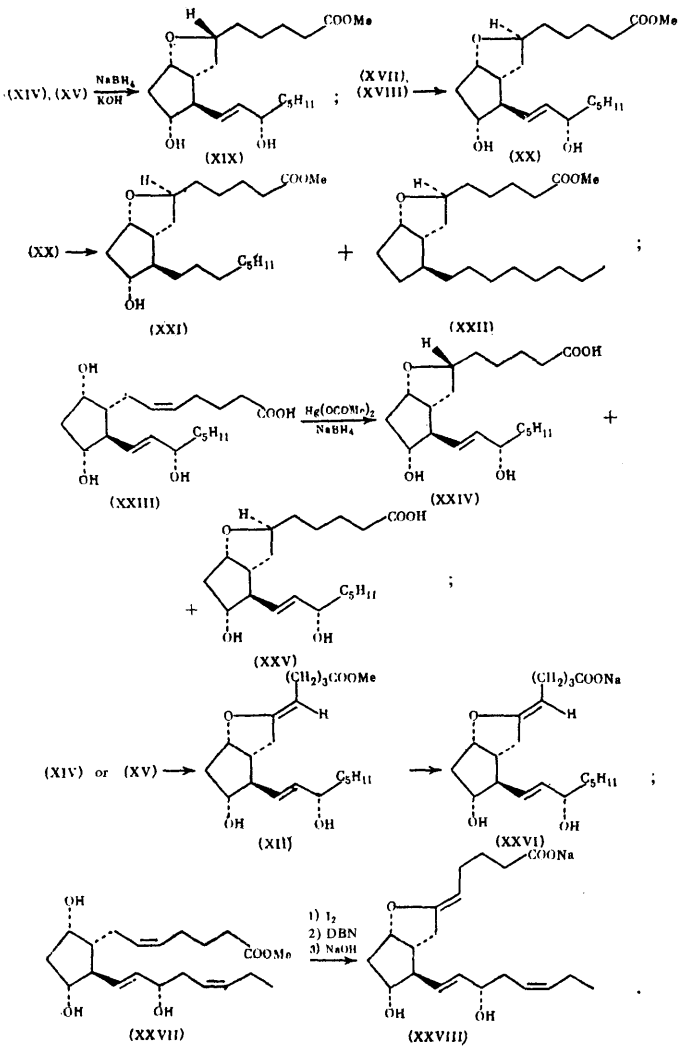
(XII): R = H, R^1 = Me

(XIII): R = H, R^1 = H

The sodium salts of PC and other compounds with a similar structure, which can be regarded as precursors of PC and its chemically stable analogues, have been synthesised. PGI_3 and Δ^6-PGI_1 with a double bond in the 6-*endo*-position, have been obtained.[10] The key compounds, the methyl esters of (5*S*, 6*S*)-5-iodo-PGI_1 (XIV) and (5*R*, 6*R*)-5-iodo-PGI_1 (XV), have been obtained by the reaction of the methyl ester of $PGF_{2\alpha}$ (XIII) with iodine in the presence of sodium carbonate. The diastereoisomeric methyl esters of (5*R*, 6*S*)-5-iodo-PGI_1 (XVII) and (5*S*, 6*R*)-5-iodo-PGI_1 (XVIII) are formed analogously from the methyl ester of 5-*trans*-$PGF_{2\alpha}$ (XVI). The reductive removal of iodine by treatment with $NaBH_4$ from the esters (XIV) and (XV) or (XVII) and (XVIII) leads to the methyl esters of (6*R*)-PGI_1 (XIX) and (6*S*)-PGI_1 (XX) respectively. Compounds (XIX) and (XX) can also be obtained by the reaction of compound (XIII) with mercury acetate and subsequent reduction with $NaBH_4$ or from the methyl ester of 6-oxo-$PGF_{2\alpha}$ by treatment with an excess of sodium cyanohydroborate. Catalytic reduction of compound (XX) gives rise to the methyl ester of (6*R*)-13,14-dihydro-PGI_1 (XXI) and the methyl ester of (6*S*)-13,14-dihydro-15-deoxy-PGI_1 (XXII). The compounds (6*R*)-PGI_1 (XXIV) and (6*S*)-PGI_1 (XXV), which have structures related to that of PGI_1, are obtained by the reaction of $PGF_{2\alpha}$ (XXIII) with mercury acetate and subsequent reduction with $NaBH_4$ or by the hydrolysis of the methyl esters (XIX) and (XX) respectively. The sodium salt of PC (XXVI) can be obtained from the iodo-esters (XIV) and (XV) by reaction with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) or with K_2O to form the methyl ester of PGI_2 (XII), which gives rise to the sodium salt of PGI_2 (XXVI) on treatment with NaOH. Treatment of PGF_3 (XXVII) in the same sequence gives rise to the sodium salt of PGI_3 (XXVIII) (Scheme 3).

Scheme 3





The racemic 11-deoxy-PC can be obtained analogously from the methyl ester of 11-deoxy-$PGF_{2\alpha}$.[23]

13-Oxa-13,14-dihydro-PGI_2 (XXXIII) and 13-thiadihydro-PGI_2 have been synthesised from the corresponding $PGF_{2\alpha}$ analogues via the stage involving the formation of the iodoester and subsequent deiodination.[24] The sodium salt (XXXIII) is obtained from the optically active epoxyalcohol (XXIX) whose interaction with the monosodium salt of the diol (XXX) gives rise to 13-oxa-13,14-dihydro-$PGF_{2\alpha}$ (XXXIa). The ester (XXXIb), formed after the esterification of compound (XXXIa), is converted into the iodoester (XXXII). The dehydrohalogenation of compound (XXXII) leads to the methyl ester (XXXIIIa) (90%), whose hydrolysis gives rise to the sodium salt (XXXIIIb).

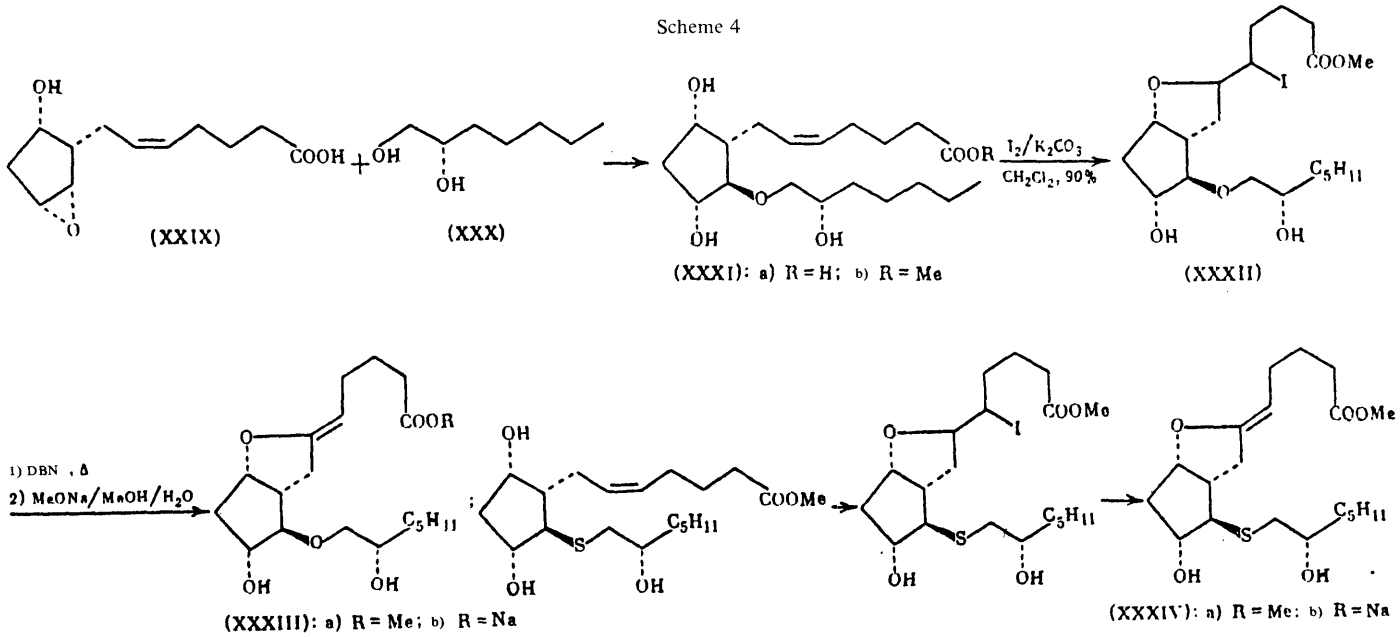
The same procedure was used to obtained the 13-thia-analogue (Scheme 4).

In order to investigate the relation between the reactivity and structure, the sodium salts of native 13-thia-13,14-dihydro-PC and its 15-epi-, 15-methyl-, etc. analogues have been synthesised by a standard method from the corresponding methyl esters of native 13-thia-13,14-dihydro-$PGF_{2\alpha}$ and tested.[25]

A series of sulphur-containing PC have been synthesised stereoselectively by means of the new organoselenium methodology.[26]

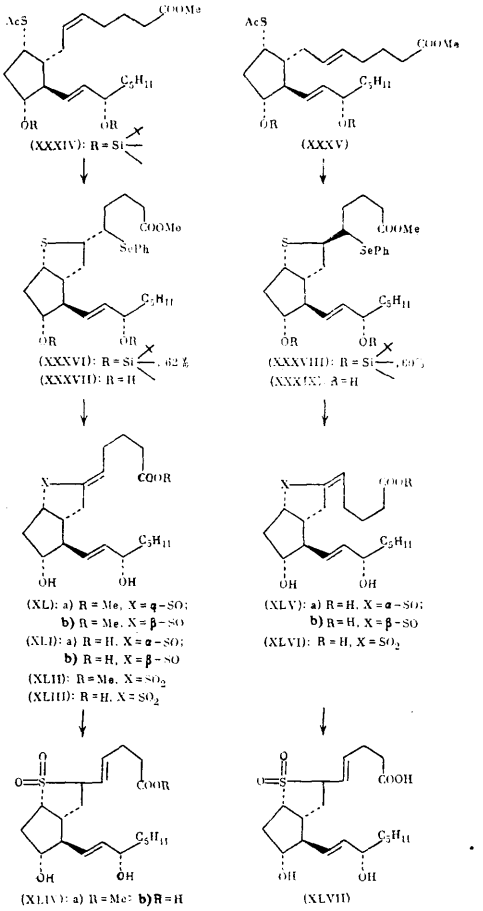
It has been observed that the methyl esters of (5*Z*)- and (5*E*)-$PGF_{2\alpha}$, (XXXIV) or (XXXV), cyclise on treatment with organoselenium compounds without the preliminary removal of the substituent protecting the thiol group. Thus compound (XXXIV) or (XXXV) reacts with phenylselenyl chloride at −78 °C to form the individual selenides (XXXVI) or (XXXVIII), which give rise to compounds (XXXVII) and (XXXIX) after the removal of selenium by treatment with TBAF. It is of interest that, when compound (XXXVII) is treated with the first equivalent of *m*-chloroperbenzoic acid (*m*-CPBA) (at −78 °C), only the sulphur atom is oxidised selectively, while after the addition of the second equivalent of *m*-CPBA at −78 °C and then heating to −20 °C, the selenium atom is oxidised effectively. Further heating to 20 °C leads to the formation of the isomeric (5*Z*)-sulphoxides (XLa) (18%) and (XLb) (53%). On the other hand, when a

Scheme 4



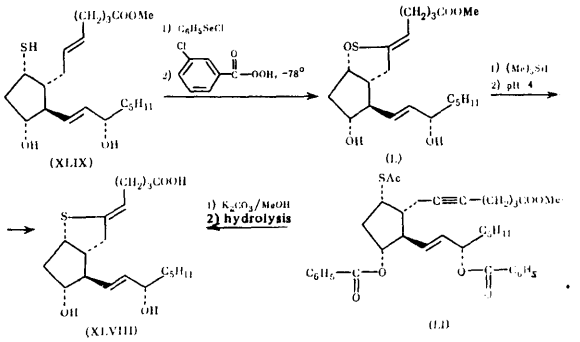
third equivalent of *m*-CPBA is added to the mixture of compounds (XLa, b), the sulphur atom is oxidised further with the exclusive formation of the (5Z)-sulphone (XLII) (86%). This sulphone can be obtained by adding four equivalents of H_2O_2 to the reaction mixture of compounds (XLa, b). Finally, the oxidation of the thioselenide (XXXVII) with H_2O_2 (8 equivalents, 20 °C) immediately affords the sulphone (XLII) as the main product (75%) together with a small amount of the non-conjugated (4*E*)-sulphone (XLII) (22%). The base hydrolysis of the methyl esters (XLa, b), (XLII), and (XLIVa) leads to the corresponding acids (XLIa, b), (XLIII), and (XLIVb) in satisfactory yields. The acids (XLVa, b), (XLVI), and (XLVII) have been obtained analogously, also in satisfactory yields, from the isomer of the thioselenide (XXXIX) using the oxidation methods described above (Scheme 5).

Scheme 5



The thia-PC (XLVIII) is obtained, like the previous compounds, by the organoselenium method using the methyl ester of 9-thia-5,6-$PGF_{2\alpha}$ (XLIX) as the initial compound. The sulphoxide (L) formed is reduced with iodotrimethylsilane to the corresponding thioether, whose hydrolysis leads to compound (XLVIII).[26-28] The thia-PC (XLVIII) can be obtained in two stages from the prostanoid (LI)[29] (Scheme 6).

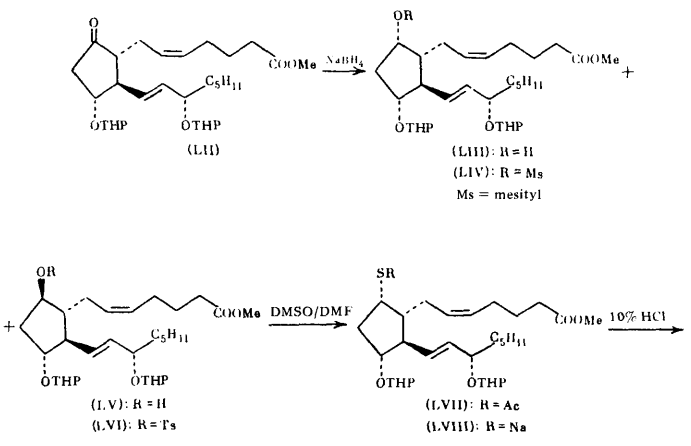
Scheme 6

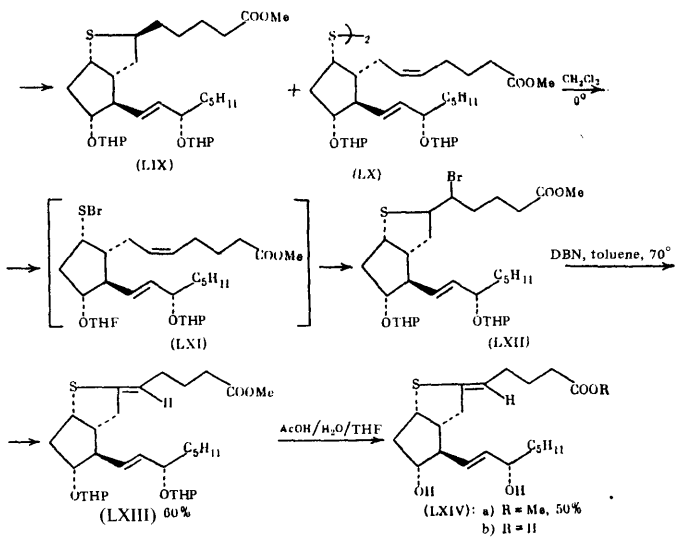


Δ^4-PGL_1 has been synthesised from $PGF_{2\alpha}$ by the method described above using organoselenium compounds.[19,20,30,31]

The starting compound in the synthesis of 9(0)-thia-PGI_2 is the methyl ester of PGE_2 (LII).[32] The reduction of compound (LII) leads to a 1 : 1 mixture of the alcohols (LIII) and (LV). In order to invert the configuration of the 9α-hydroxy-group in compound (LIII), the latter is converted into the methanesulphonate (LIV), the reaction of which with K_2O/18-crown-6 ether in DMSO and subsequent esterification with diazomethane afford the 9β-alcohol (LV) (60%). Treatment of the toluene-*p*-sulphonate (LIV) with sodium thioacetate makes it possible to introduce a sulphur atom with simultaneous inversion of the 9β-OH configuration to give the corresponding 9α-derivative (LVII) (55%). Mild hydrolysis of compound (LVII) leads to the cyclic sulphide (LIX) (60%) with a small admixture of the disulphide (LX), formed as a result of oxidation with atmospheric oxygen. The disulphide (LX) is obtained in 80% yield when the mercaptide (LVIII) reaction mixture is kept in atmospheric oxygen. Treatment of compound (LX) with bromine gives rise to the bromosulphide (LVII) and the reaction proceeds via intramolecular cyclisation with the initial formation of the bromosulphide (LXI). Compound (LXII) is then converted into the vinyl sulphide (LXIII) with the required (*syn*, *cis*) geometry). The removal of the protecting group in compound (LXIII) leads to the methyl ester of 9(O)-thia-PC (LXIVa). It is noteworthy that the relatively low yield in the hydrolysis stage indicates the partial decomposition of the final compound (LXIVa). Compound (LXIVa) is converted into compound (LXIVb) by alkaline hydrolysis (Scheme 7).

Scheme 7



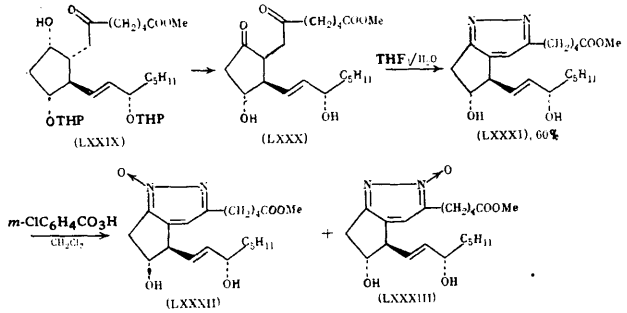


(5Z)- and (5E)-6,9-dithia-PC can be obtained via an analogous scheme from the methyl ester of PGE_2.[33]

The synthesis of 9-deoxy-9α,6-nitrilo-$PGF_{1\alpha}$ (LXXII) and of the corresponding cyclic imine in which the oxygen atom has been replaced by nitrogen have been described.[34] The first stage includes the conversion of the methyl ester of $PGF_{2\alpha}$ (LXV) into the 9β-epimer (LXVII) by reaction of compound (LXV) with triphenylphosphine, benzoic acid, and the diethyl ester of azodicarboxylic acid (DEADA) followed by treatment of the resulting 9β-benzoate (LXVI) with MeONa/MeOH. Toluene-*p*-sulphonation of the 9β-hydroxy-group and the removal of the THP protecting groups leads to the derivative monotoluene-*p*-sulphonated at the C(9) atom. Treatment of the 9β-toluene-*p*-sulphonate (LXVIII) with NaN_3 affords the 9α-azide (LXIX) which is converted on heating into the cyclic imine (LXXI) (80%). The acid (LXXII) has been obtained by the hydrolysis of the ester (LXXI) or, which is preferable, by the hydrolysis of the ester azide (LXIX) to the acid (LXX) with subsequent cyclisation to the iminoacid (LXXII)—a substance which contains 30% of the zwitter-ionic form. The acid (LXXII) readily gives rise to the hygroscopic hydrochloride (LXXIII), both imines, (LXXI) and (LXXIV), being stable in 1 M HCl solution at 25 °C. The reduction of the iminoester (LXXI) leads to the esters (LXXIVa, b). Both isomers are hydrolysed to the corresponding crystalline iminoacids (LXXVa, b), which exist fully in the zwitter-ionic form. Using the analogous sequence of reactions, the methyl ester of *cis*-Δ^4-$PGF_{1\alpha}$ (LXXVI) was converted in six stages into the 9α,5-nitrilo-analogues (LXXVII) and (LXXVIII) (Scheme 8).

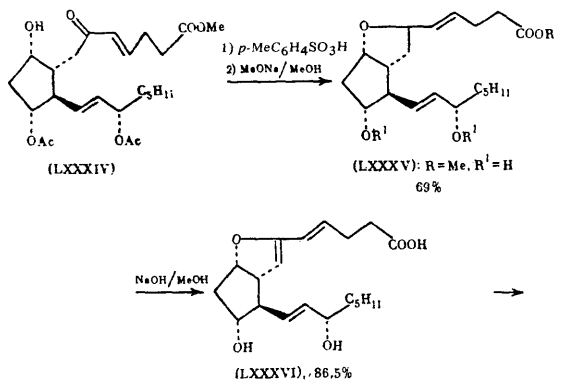
The synthesis of 6,9-pyridazo-PC (LXXXI) and its *N*-oxides (LXXXI), (LXXXII), and (LXXXIII) from the methyl ester of 6-oxo-$PGF_{1\alpha}$ (LXXIX) have been described.[35] Oxidation of compound (LXXIX) with pyridinium chlorochromate of Jones' reagent (CrO_3, acetone, −20 °C) and the removal of the THP protecting groups lead to the methyl ester of 6-oxo-PGE_1 (LXXX). Treatment of compound (LXXX) with hydrazine and oxidation over PtO_2 gives rise to the methyl ester (LXXXI), from which a mixture of the methyl esters (LXXXII) and (LXXXIII) is obtained (Scheme 9).

Scheme 9

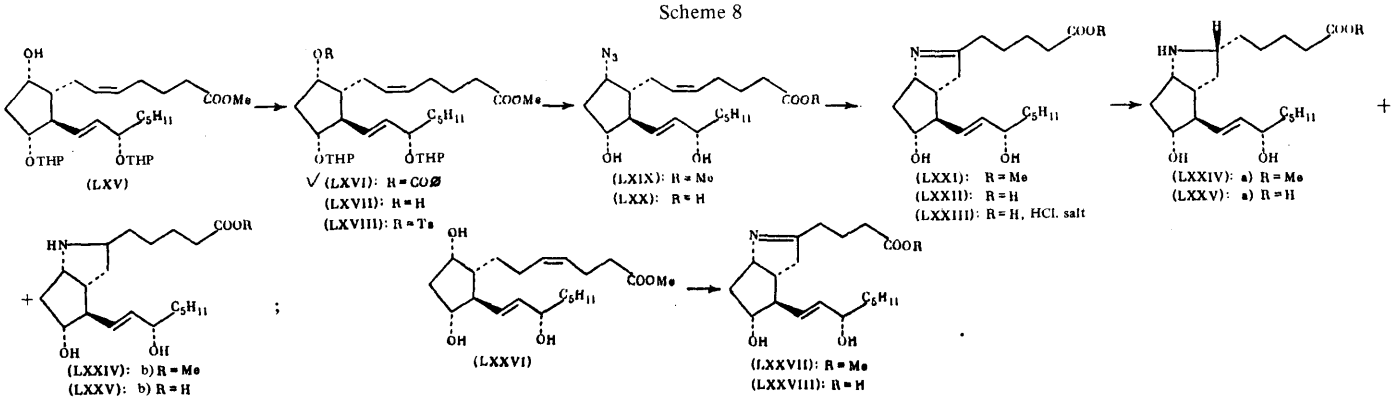


The pyrrole analogue of PC has been obtained from the protected 6-oxo-PGE_1 derivative by standard methods.[36]

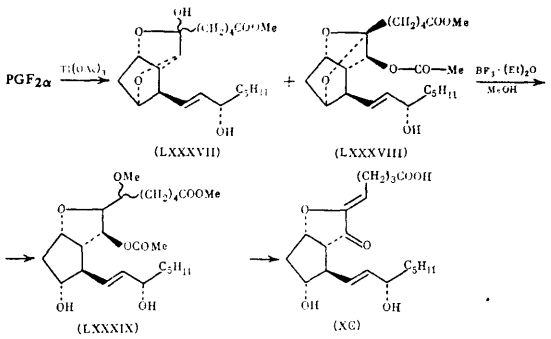
An analogue of PGI_2 has been synthesised in two stages from the readily available enone (LXXXIV).[37] After treating the methyl ester of 11(*O*),15(*O*)-diacetyl-4,5-dihydro-6-oxo-$PGF_{1\alpha}$ (LXXXIV) with toluene-*p*-sulphonic acid and subsequent methanolysis, the diene (LXXXV) is obtained whose hydrolysis leads to the isolation of the acid 4,5,6,7-tetrahydro-PGI_1 (LXXXVI):



Scheme 8



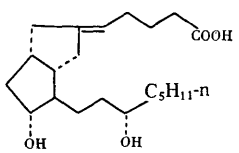
The conversion of the methyl ester of $PGF_{2\alpha}$ into the PC analogue (XC) by the reaction with thallium triacetate, leading to the formation of the hemiacetal (LXXXVII) and the acetate (LXXXVIII), has been described. Transacetylation of compound (LXXXVIII) affords the methyl acetal (LXXXIX), which can be readily converted into 7-oxo-PGI_2 (XC) in five stages: [38]



(LXXXVII) (LXXXVIII) (LXXXIX) (XC)

2. Synthesis of Carbacyclin

Among the PC analogues, carbacyclin (CC) (XCI) merits special attention. It was reported in 1981 [39] that, when this compound is administered to man intravenously, it causes an appreciable inhibition of platelet aggregation and does not have the side effects observed in the case of PC itself.[16] Carbacyclin can be regarded as a PC derivative in which the ethyl unit in the cyclic enol ether has been replaced by a methylene group:

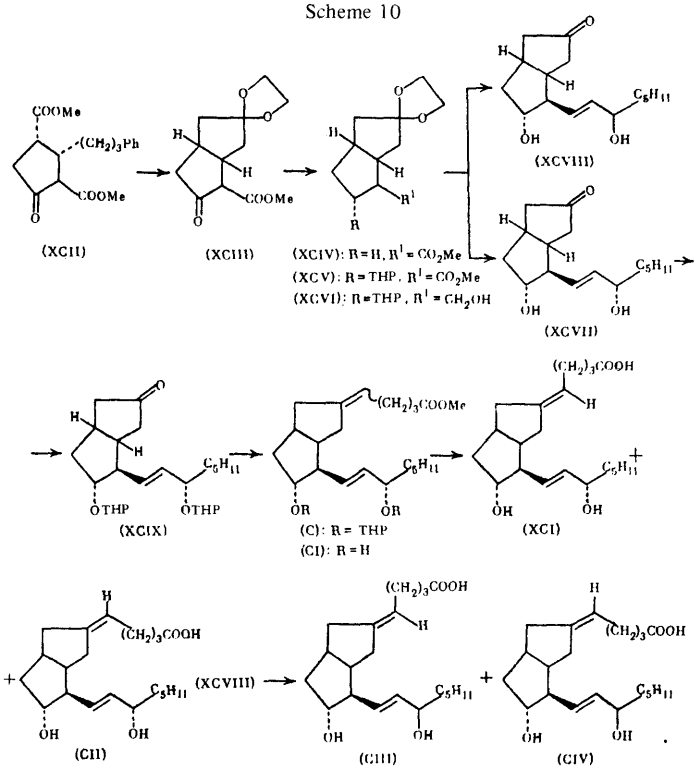


(XCI). CC

Several syntheses of CC were described almost simultaneously,[40–43] representing to some extent a repetition of the classical scheme for the synthesis of PG.

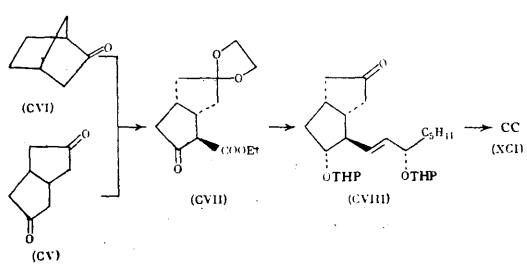
The synthesis of 9(*O*)-methano-PC (XCI) and of its three isomers (CII), (CIII), and (CIV), in which the *trans,cis*-diester (XCII), used in the total synthesis of $PGF_{2\alpha}$, serves as the starting material, has been described.[44] The diester (XCII) is converted in eleven stages into the *cis*-bicyclic ketone (XCIII), whose reduction leads to the basic *trans*-alcohol (XCIV). After protecting the OH group in compound (XCIV) to give a compound (XCV) and after reducing the ester group in the latter with $LiAlH_4$, the alcohol (XCVI) is obtained. The introduction of the allyl alcohol side chain into compound (XCVI) is achieved by standard methods using the diols (XCVII) and (XCVIII): (1) Collins oxidation (CrO_3. .Py/CH_2Cl_2); (2) condensation with tri-n-butyl-2-oxoheptylidenephosphorane; (3) reduction with $NaBH_4$; (4) the removal of THP protecting groups. After protecting the OH groups in compound (XCVII), the resulting ether (XCIX) is treated with the Wittig reagent obtained from 5-triphenylphosphonopentanoic acid and is then esterified with CH_2N_2 to form the ester (C) in the form of a mixture of regioisomers with respect to the C(5) atom. The removal of the protecting groups in compound (C) yields the diol (CI), whose hydrolysis leads to the formation of 9(*O*)-methano-PC (XCI) as the main product and 11α,15α-dihydroxy-6,9α-methyleneprosta-5(*Z*),13(*E*)-dienoic acid (CII); the 5(*E*)-isomer (CIII) and the 5(*Z*)-isomer (CIV) can also be obtained from the diol (XCVIII) by the same sequence of reactions (Scheme 10).

Scheme 10



(XCII) (XCIII) (XCIV): R = H, R¹ = CO_2Me (XCV): R = THP, R¹ = CO_2Me (XCVI): R = THP, R¹ = CH_2OH (XCVII) (XCVIII) (XCIX) (C): R = THP (CI): R = H (XCI) (CII) (CIII) (CIV)

The total synthesis of CC from the readily available *cis*-bicyclo[3.3.0]octane-3,7-dione (CV) in accordance with a similar scheme has been described.[42,44] The most important intermediate in all three syntheses is the monoketal (CVII). In order to prevent the partial hydrolysis of compound (CV) in its conversion to compound (CVII), a method of synthesis of compound (CVII) from 5-norborn-2-enone (CVI) was proposed in 1980.[45] The ester group in compound (CVII) can be converted into an aldehyde whose condensation with the Wittig reagent affords the key ketone (CVIII). It is converted into CC by standard methods:

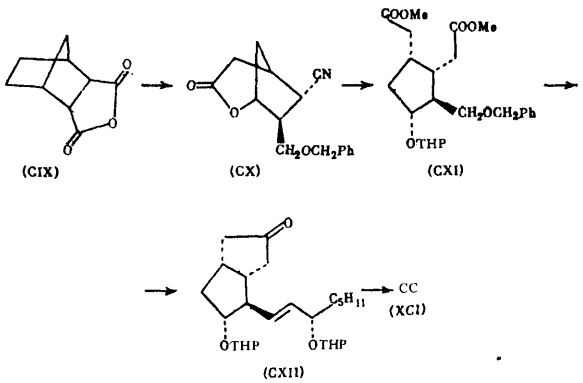


(CVI) (CVII) (CVIII) (CV) CC (XCI)

Three other total syntheses of CC [44,46,47] are based on cyclo-octa-1,3-diene and differ only by the stage in which it is converted into a derivative of *cis*-bicyclo[2.3.0]octan-3-one (CVIII).

A stereocontrolled multistage synthesis of CC from the anhydride of norborn-5-ene-2,3-dicarboxylic acid (CIX) using the methods employed in the synthesis of PG has been proposed.[48] The anhydride (CIX) is converted into the lactone (CX), whose alkaline hydrolysis and the subsequent

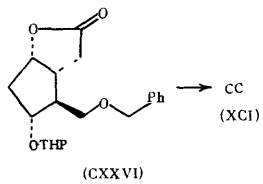
transesterification of the resulting dicarboxylic acid with CH_2N_2 lead to the diester (CXI) whose Dieckmann condensation and decarboxylation together with the addition of a side chain at the C(12) atom result in the formation of the CC precursor (CVIII), whose conversion into the CC presents no difficulty. The conversion of compound (CIX) into compound (CVIII) includes 24 stages:



A convenient synthesis of the optically active CC from the hydroxyacid (CXII),[49] which is converted into the cyclic ketone (CXIII), has been described. After protecting the OH group in compound (CXIII), the benzylethyl group in compound (CXIV) is subjected to hydrogenolysis, giving rise to the hydroxyketone (CXV), which is converted into the ester-alcohol (CXVI) (overall yield 77%): protection of the OH group by treatment with 2-methoxypropane, condensation with 4-carboxybutylenetriphenylphosphorane (4-CBTP), selective removal of the 2-methoxypropyl unit, and esterification with CH_2N_2. The alcohol (CXVI) is oxidised to the aldehyde (CXVII) using the complex SO_3.Py or DMSO-$(COCl)_2$, whose condensation with the phosphonate by the Emmons–Horner method results in the formation of the enone (CXVIII) (99%). After the removal of the THP group in compound (CXVIII), a mixture of the more polar compound (CXIX) and the less polar compound (CXX) is formed (1 : 1, 98%). The selective reduction of the oxo-group at the C(15) atom in compound (CXIX) with diisobutylaluminium 2,6-di-t-butyl-4-methylphenoxide leads to the (15*S*)-alcohol (CXXI) (83%) and the (15*R*)-alcohol (CXXII) (12%). Alkaline hydrolysis of compound (CXXI) gives rise to CC.

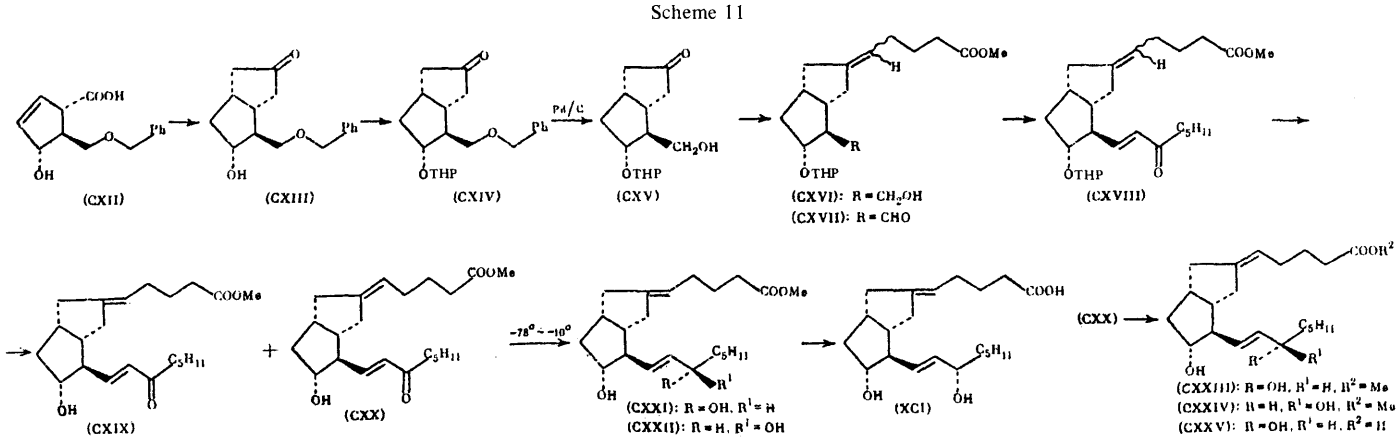
The (5*Z*,15*S*)-isomer (CXXII), the (5*Z*,15*R*)-isomer (CXXIV), and the acid (CXXV) are obtained from the enone (CXX) in the same way (Scheme 11).

CC can also be obtained from the lactone (CXXVI), which is used in the synthesis of natural PG:[49]

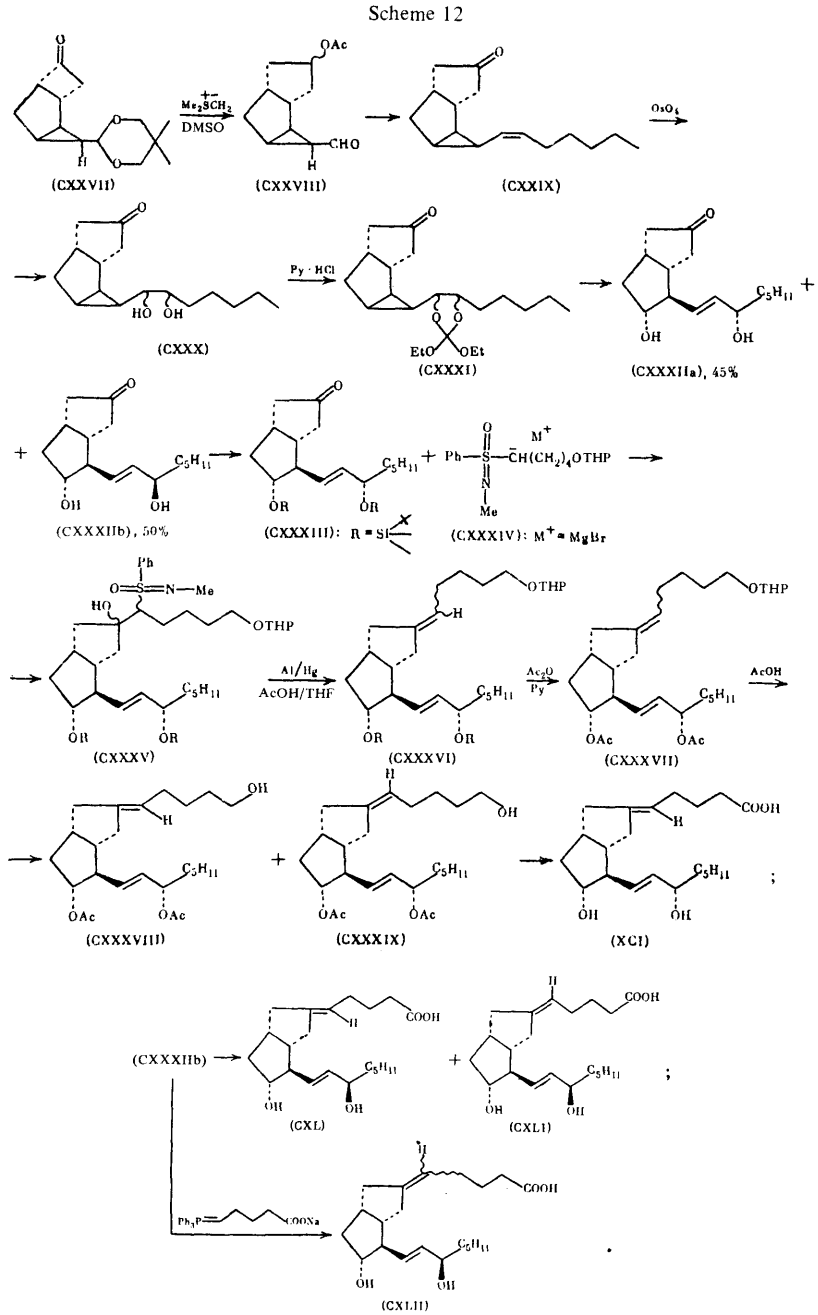


One of the ways of synthesising optically active CC involves the use of the familiar intermediate optically pure ketone (CXXVII),[40] which is converted into the *endo*-aldehyde (CXXVIII) when the latter is successively condensed with n-hexylidenetriphenylphosphorane, hydrolysed, and oxidised by Jones' reagent with formation of the tricyclic intermediate (CXXIX). The ketone (CXXIX) is converted into the isomeric *cis*-glycols (CXXX). The reaction of compound (CXXX) with triethyl orthopropionate affords the isomeric orthoesters (CXXXI), which are converted into the (15*S*)-ketonediol (CXXXIIa) and the (15*R*)-ketonediol (CXXXIIb) after solvolysis in 100% formic acid and alkaline hydrolysis. The condensation of the ketone (CXXXIII) with the anion of the sulphoxyimine (CXXXIV) leads to a mixture of adducts (CXXXV), which give rise to the isomeric [with respect to the C(5) atom] olefins (CXXXVI) on reductive elimination. The silyl groups are removed with TBAF and the diols formed are converted into the isomeric diacetates (CXXXVII). After removing the protecting group at the C(1) atom in compound (CXXXVII), a mixture of the unsaturated alcohols (CXXXVIII) is oxidised by Jones' reagent and hydrolysed with aqueous alkali to CC. Using the same methods, the corresponding (15*R*)-dihydroxy acids (CXL) and (CXLI) were obtained from the (15*R*)-ketonediol (CXXXIIb). Condensation of the ketonediol (CXXXIIb) with the Wittig reagent gives rise to a mixture of the C(5)-isomers and the dihydroxyacids (CXII) (Scheme 12).

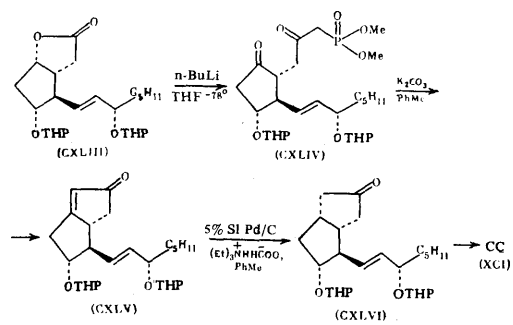
Scheme 11



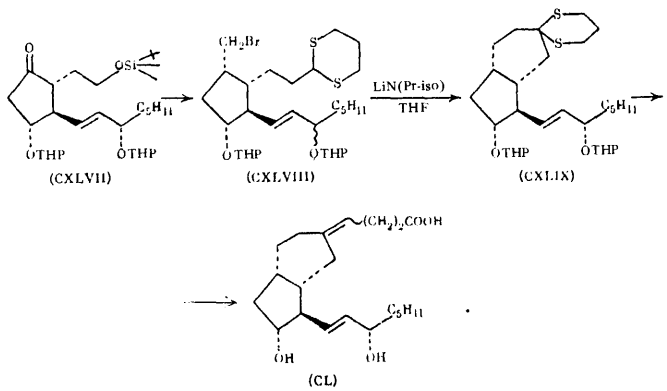
Scheme 12



The synthesis of CC via the key intermediate (CXLIII) has been described.[50,51] The reaction of compound (CXLIII) with the lithio-derivative of dimethyl methylphosphonate leads to a bicyclic alcohol, whose Collins oxidation produces the ketone (CXLIV). A suspension of the latter in 18-crown-6 ether is heated, the enone (CXLV) is obtained and its reduction affords compound (CXLVI). The condensation of the latter with 4-CBTP and subsequent removal of the THP protecting group leads to CC:

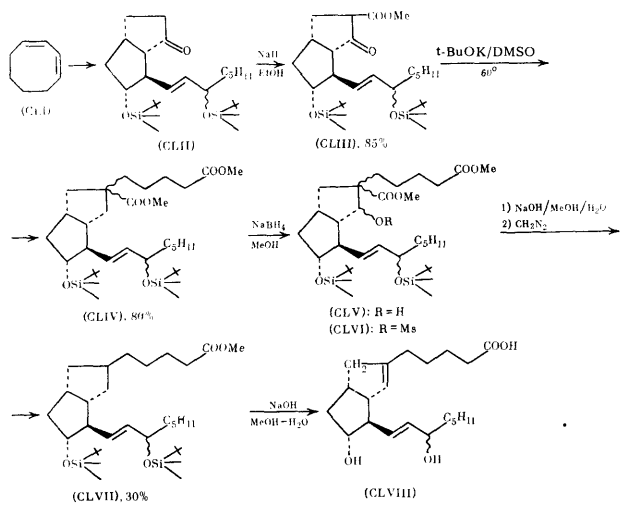


The 11-stage synthesis of 6α-carba-PGI_2 (CL) from the ketone (CXLVII) has been achieved.[52] The intermolecular alkylation of the dithiane (CXLVIII), obtained from compound (CXLVII) by the usual methods in 7 stages, is the key stage in the formation of the bicyclic compound (CXLIX), which is converted into compound (CL) in three stages:



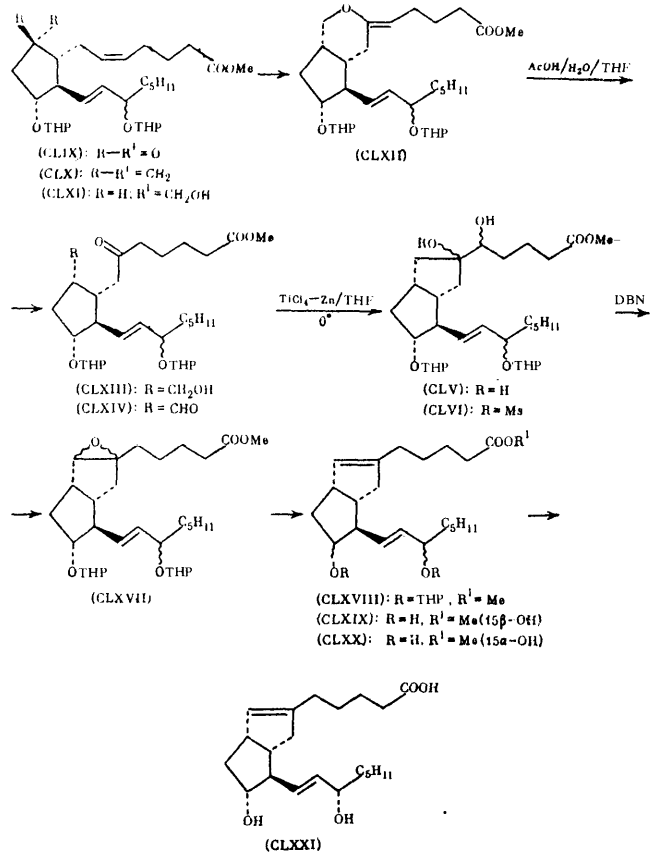
A method of synthesis of the carbon analogue Δ^6-PGI (CLVIII), using cyclo-octa-1,3-diene (CLI) as the starting compound, has been described.[53] The regioselective methoxycarbonylation of the ketone (CLII), obtained in 7 stages from compound (CLI), with dimethyl carbonate leads to the ketoester (CLIII). The reaction of compound (CLIII) with methyl 5-iodoheptanoate yields the alkylated product (CLIV) in the form of a mixture of stereoisomers with respect to the C(6) atom. The reduction of the ketone (CLIV) leads to a mixture of the diastereoisomeric alcohols (CLV) (90%), the methanesulphonation of which affords compound (CLVI). The decarboxylation and subsequent esterification of compound (CLVI) lead to the ester (CLIII). Despite the low yields of compound (CLIII), this synthesis has the advantage that the methoxycarbonyl functional group at the C(6) atom not only makes it possible to carry out successfully the alkylation at the C(6) atom but also promotes the introduction of a double bond between the C(5) and C(6) atoms. After the removal of the protecting groups in compound (CLVII) and hydrolysis, 9(*O*)-methano-Δ^6-PGI_1 (CLVIII) is isolated in the form of a mixture of diastereoisomers with respect to the C(15) atom (the 15α- and 15β-isomers) (Scheme 13).

Scheme 13



Using an intermolecular pinacol addition reaction as the key stage, 9(*O*)-methane-$\Delta^{6(9\alpha)}$-PGI_1 (CLXXI) was obtained.[54-57] The methylene group in the PGE_2 (CLIX) molecule is introduced by treatment with $Zn-CH_2Br_2-TiCl_4$, which results in the formation of compound (CLX) (80%). Cautious hydroboration of compound (CLX) with 9-borabicyclo[3.3.1]nonane (9-BBN) (THF, 0°) followed by treatment with an H_2O_2 solution leads to the primary alcohol (CLXI) (64.5%). The iodoesterification of the latter and treatment with DBN yield the enol ether (CLXII) (the main product), which is converted into the ketoalcohol (CLXIII). The oxidation of compound (CLXIII) with the complex SO_3.Py leads to the aldehyde (CLXIV), which is immediately introduced into the intermolecular pinacol addition reaction with formation of a mixture of the diastereoisomeric bicyclic diols (CLXV). The crude compound (CLXV) is converted into the methanesulphonate (CLXVI), which is in turn converted into the epoxy-derivative (CLXVII) and then into the *endo*-olefin (CLXVIII). After the removal of the THP protecting groups, a readily separable mixture of alcohols is obtained [the less polar 15β-isomer (CLXIX) and the more polar 15α-isomer (CLXX)]. Alkaline hydrolysis of compound (CLXX) leads to compound (CLXXI) (Scheme 14).

Scheme 14

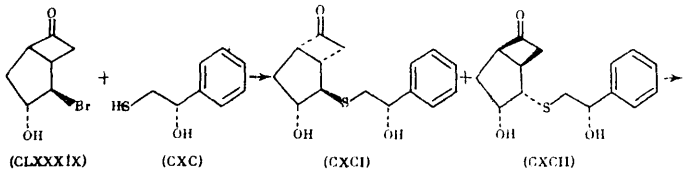


Using the intramolecular thermal ene reaction, (+)-9(*O*)-methano-$\Delta^{6(9\alpha)}$-PGI_1 (CLXXXVIII) was synthesised from the Corey lactone.[58] The aldehyde (CLXXVIII), necessary for the ene reaction, is obtained by converting the lactone (CLXXII) into the hydroxyester (CLXXIII) in the usual way: (1) reduction with diisobutylaluminium hydride (DIBAH); (2) condensation with 4-CBTP; 3) esterification with CH_2N_2 (overall yield 98%). The subsequent oxidation of compound

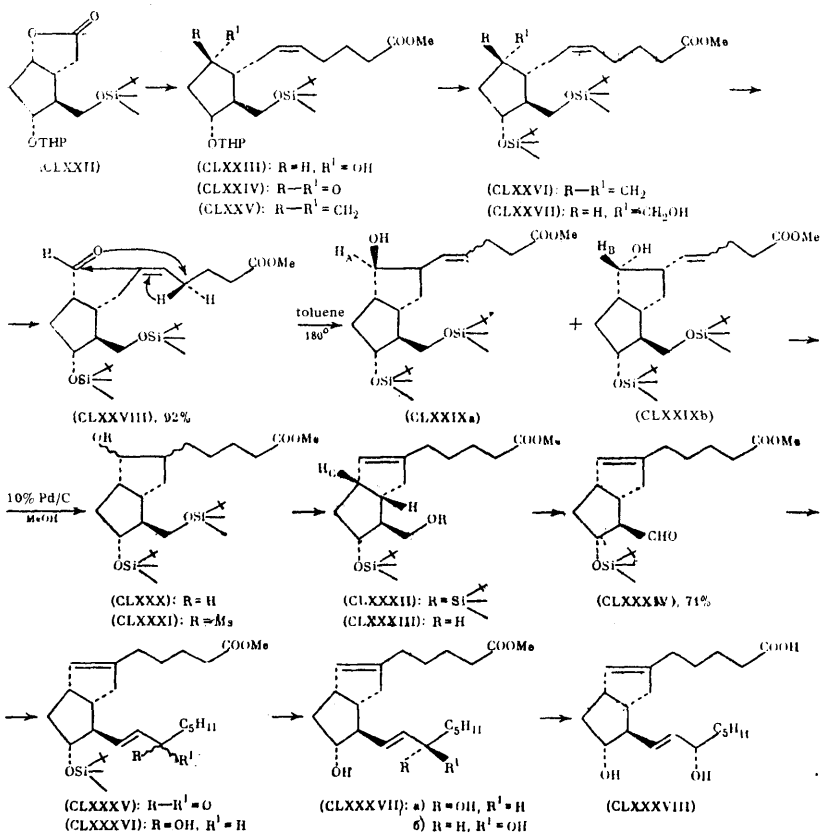
(CLXXIII) with pyridinium chlorochromate gives rise to the ketoester (CLXXIV) (92%). Substitution of the methylene group in the latter by treatment with $Zn-CH_2Br_2-TiCl_4$ leads to the diene (CLXXV) (81%). The thermally unstable THP-ether (CLXXV) is converted in two stages into the disilyl ether (CLXXVI), the hydroboration of which with 9-BBN and subsequent treatment with a solution of H_2O_2 produces the primary alcohol (CLXXVII), which is converted by the Collins oxidation into the aldehydes (CLXXVIII). The thermal ene reaction at 180 °C leads to two ene products: (CLXXIXa) (the main more polar isomer) and (CLXXIXb) (the minor less polar isomer). The mixture of these compounds is hydrogenated, which affords compound (CLXXX). On heating with diazabicycloundecene (DBU), the methanesulphonate (CLXXXI) gives rise to compound (CLXXXII). On treatment of the latter with a catalytic amount of pyridinium toluene-*p*-sulphonate, one obtains the key intermediate (CLXXXIII), whose oxidation produces the aldehyde (CLXXXIV), which condenses, without being isolated, with dimethyl 2-oxoheptylphosphonate to form the enone (CLXXXV) (71%). The reduction of compound (CLXXXV) with $NaBH_4$ gives rise to the C(15)-epimeric alcohols (CLXXXVI) and the removal of the protecting group leads to the more polar diol (CLXXXVIIa) (55%) and the less polar diol (CLXXXVIIb) (22%). Alkaline hydrolysis of compound (CLXXXVIIa) results in the formation of compound (CLXXXVIII) (Scheme 15).

An 8-stage synthesis of a CC analogue, namely the benzamidophenyl ester of (CC), has been achieved in 5% yield.[59] The key compounds for the synthesis of this analogue are the bromohydrin (CLXXXIX) and the thiol (CXC), which are in their turn obtained from cyclopentadiene and L-(+)-mandelic acid respectively. The addition of compound (CXC) to the bromohydrin (CLXXXIX) leads to a mixture of the isomers (CXCI) and (CXCII) which is difficult to separate. Treatment of the mixture with CH_2N_2 makes it possible to carry out a ring expansion reaction. The resulting mixture of compounds (CXCIII), (CXCIV), (CXCV), and (CXCVI) is readily separated by chromatography on silica gel. The Wittig condensation of compound (CXCIII) with the phosphorane obtained from phosphonium salts (CXCVII) results in the formation of a mixture of the *E*- and *Z*-isomers (CXCVIII) and (CXCIX), which is esterified with *p*-benzamidophenol and compound (CC) is isolated (Scheme 16).

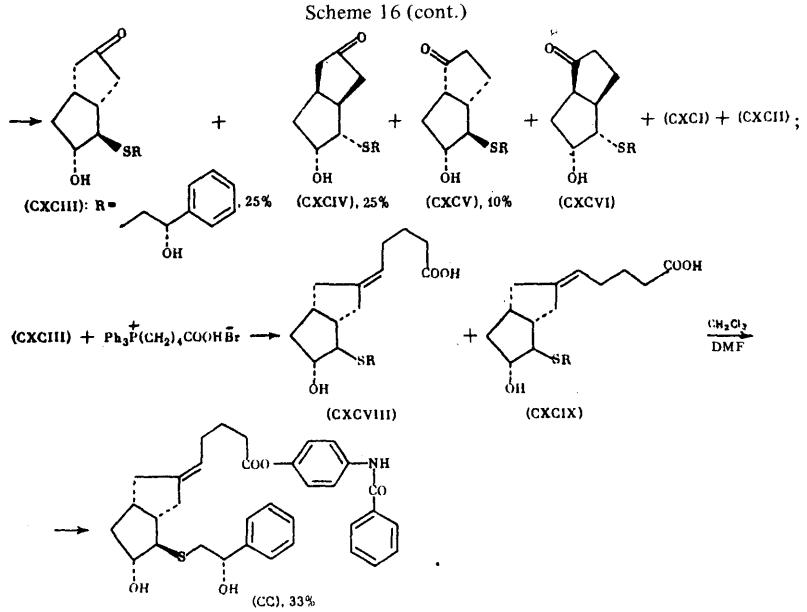
Scheme 16



Scheme 15

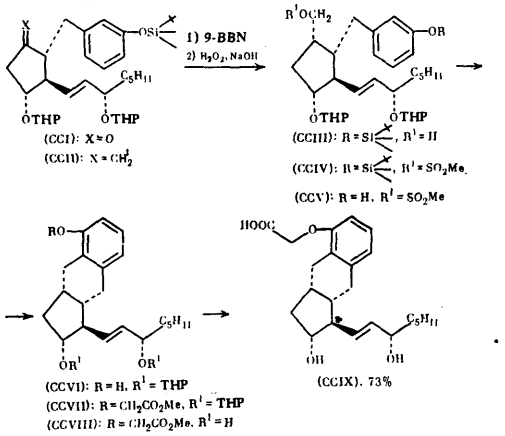


Scheme 16 (cont.)



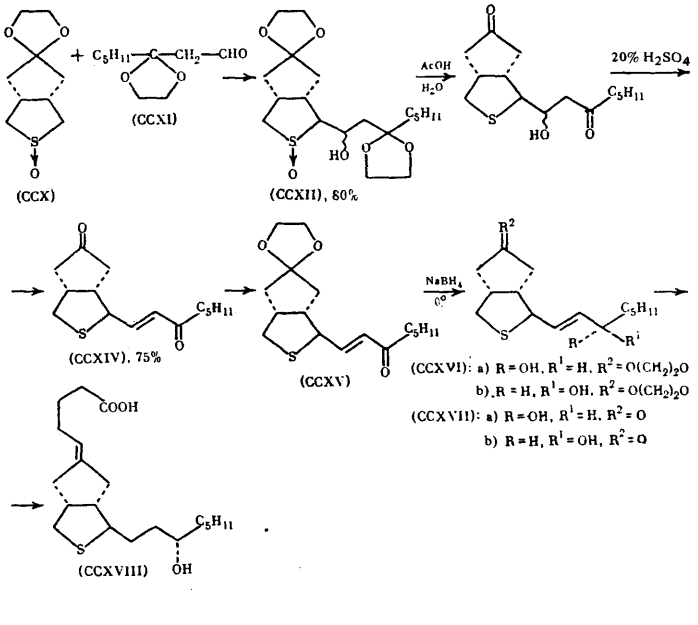
In order to discover PC analogues which are resistant to hydrolysis, benzoindene derivatives have been synthesised.[60,61] The starting material for the synthesis of such derivatives was compound (CCI), which is used in the synthesis of PG analogues.[62] The methylene group is introduced in two stages: the ketone reacts with the anion of methylphenyl-*N*-methylsulphoxyimine and this is followed by treatment of the adduct with aluminium amalgam (H_2O–AcOH–THF) with formation of compound (CCII) (72%), whose hydroboration and subsequent oxidation produce the alcohol (CCIII) (92%). The alcohol (CCIII) is converted into the methanesulphonate (CCIV) (88%), the silyl group in the latter is removed by treatment with TBAF, and compound (CCV) is refluxed with NaH in glyme until the formation of compound (CCVI), which is converted into the ester (CCVII) by treatment with NaH and methyl bromoacetate. After the removal of the THP protecting group, the ester (CCVIII) is formed and its alkaline hydrolysis affords the crystalline acid (CCIX) (Scheme 17).

Scheme 17

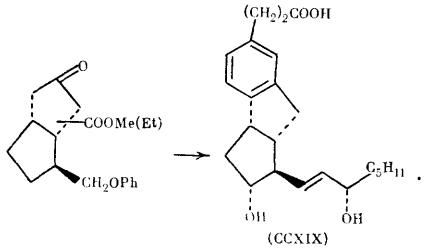


The synthesis of the ethylene ketal of tetrahydrobiscyclopentano[c]thiophen-5-one (CCX) and its conversion into the analogue 11-thia-CC have been described.[63] The synthone (CCX) has two functional groups, which makes it possible to introduce the necessary side chain fairly readily and also has a hydrogen atom activated by the sulphoxide group. The introduction of the ω-chain into the molecule is achieved by the reaction of the carbanion generated from compound (CCX) with the protected aldehyde (CCXI) to form a mixture of the aldols (CCXII), which is not separated. Treatment of the mixture with diborane with subsequent deketalisation leads to the formation of the β-hydroxyketone (CCXIII), whose dehydration affords the αβ-*trans*-enone (CCXIV). The ring carbonyl group is protected by treatment with 2-ethyl-2-methyl-1,3-dioxolan and compound (CCXV) formed is reduced to a mixture of the epimeric alcohols (CCXVIa, b). After the removal of the ketal protecting group, the mixture of compounds (CCXVIIa, b) is separated chromatographically. The condensation of the more polar C(15)-epimer (CCXVIIa) with 4-CBTP leads to compound (CCXVIII) and its (15*R*)-epimer in the form of a mixture of the *cis*,*trans*-isomers (Scheme 18).

Scheme 18



In order to establish the relation between structure and activity for a series of PGI_2 analogues, a new aromatic CC analogue (CCXIX), which has no biological PC activity, was obtained by total synthesis (20 stages):[64]



(CCXIX)

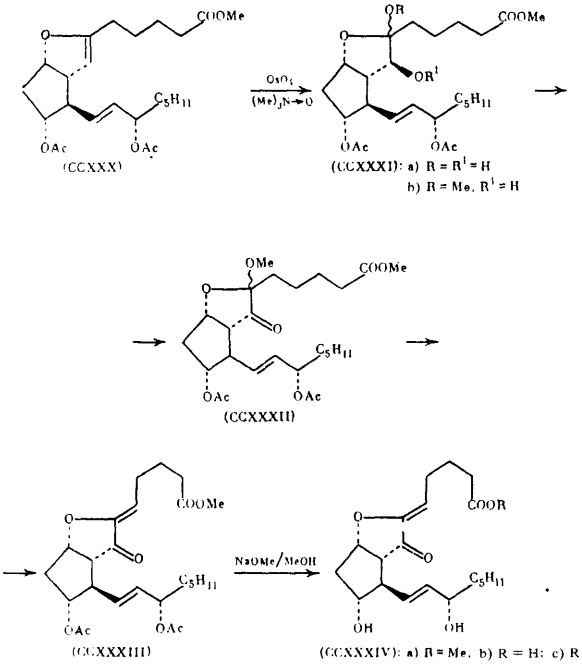
3. The Synthesis of Prostacyclin Analogues with an Enol Ether Double Bond Resistant to Hydrolysis

One of the effective ways of stabilising PC involves the introduction of electron-donating and electron-accepting substituents next to the enol ether group sensitive to hydrolysis or its replacement by another ether system.

Thus halogenation of the protected ethyl ester of PGI_2 (CCXX) proceeds stereoselectively with formation of the methyl ester of (5*R*)-5-Cl-Δ^6-PGI_1 (CCXXIIa) (60%) or the methyl ester of (5*R*)-5-Br-Δ^6-PGI_1 (CCXXIIb) (57%) with an admixture of the succinimido-adduct (CCXXIVa) (20%) or compound (CCXXIVb) (20%).[65] On the other hand, the halogenation of the acetyl-substituted methyl ester of PGI_2 (CCXXI) under the same conditions gives rise to a mixture of the diastereoisomers of the methyl ester of 5-Cl-Δ^6-PGI_2 (CCXIIIa) (58%, 5*R* : 5*S* = 5 : 3) or the methyl ester of 5-Br-Δ^6-PGI_1 (CCXXIIIb) (60%, 5*R* : 5*S* = 7 : 3) with the corresponding succinimido-adduct (CCXXIVc) (20%) or (CCXXIVd) (13%). The subsequent chlorination of the (5*R*)-allyl chloride (CCXXIIa) with *N*-chlorosuccinimide NCS leads to a mixture of the methyl esters of (5*E*,7*S*)- and (5*Z*,7*S*)-5,7-dichloro-PGI_2 (CCXXV) and (CCXXVI) (15 and 20% respectively). Treatment of the allyl chloride (CCXXIIa) with Py.TsOH leads to the hemiacetal (CCXXVII), whose dehydration with an excess of $MgSO_4$ in benzene results in the formation of the (5*E*)-vinyl chloride (CCXXVIIIa) (20%) and the (5*Z*)-vinyl chloride (CCXXIXa) (28%). The removal of the protecting groups in compounds (CCXXVIIIa) and (CCXXIXa) with TBAF leads to the methyl esters of (5*E*)-5-Cl-PGI_2 (CCXXVIIIb) (95%) and (5*Z*)-5-Cl-PGI_2 (CCXXIXb) (80%), whose alkaline hydrolysis resulted in the formation of the sodium salts (CCXXVIIIc) and (CCXXIXc) (Scheme 19).

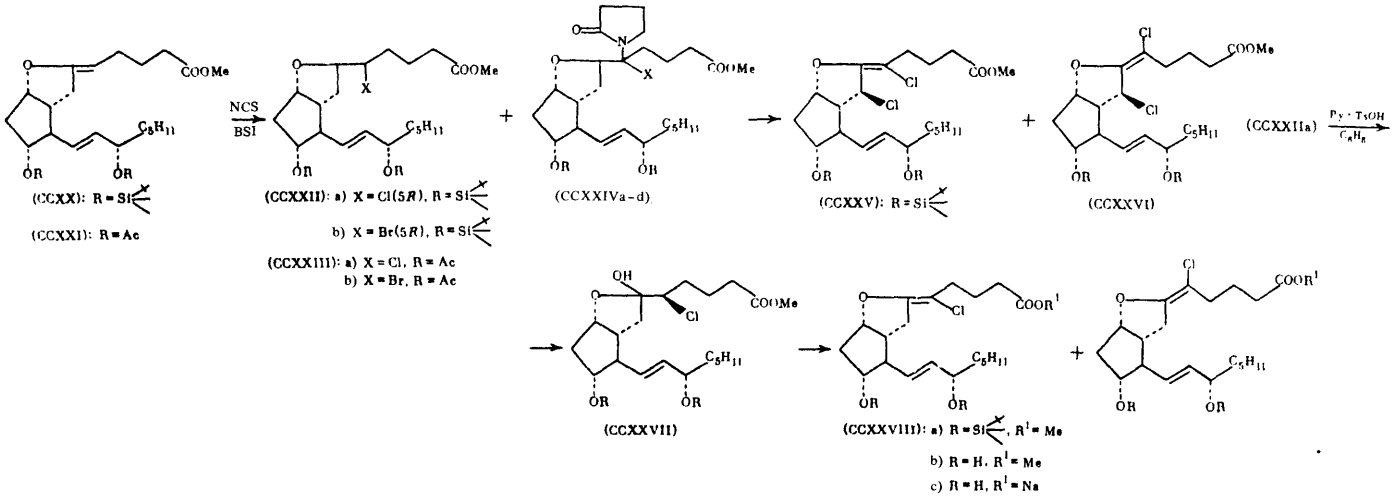
A five-stage synthesis of 7-oxo-PGI_2 (CCXXXIV) via the selective hydroxylation of the methyl ester of 11,15-diacetyl-Δ^6-PGI_1 (CCXXX) has been described. The stereochemistry of the intermediates has been determined and their conformational analysis has been carried out.[66] Selective hydroxylation of the enol ether double bond in compound (CCXXX) proceeds smoothly with formation of compound (CCXXXIa) (80%), which is converted into the isomeric methyl ketals by appropriate successive treatments (MeOH, $Et_2O.BF_3$); after chromatographic separation one obtains the pure *endo*-isomer (27%) and exo-isomer (51%) of compound (CCXXXIb). Oxidation of both isomers (pyridinium dichromate/DMF or pyridinium chlorochromate/NaOAc/CH_2Cl_2) leads to the *endo*- and *exo*-isomers of compound (CCXXXII) respectively, whose thermolysis at 160–170 °C affords compound (CCXXXIII) and deacetylation of the latter results in the formation of compound (CCXXXIV) (Scheme 20).

Scheme 20



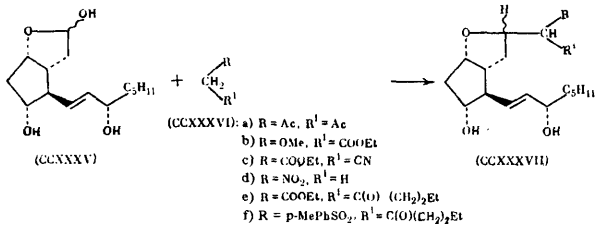
(CCXXX) (CCXXXI): a) R = R¹ = H; b) R = Me, R¹ = H (CCXXXII) (CCXXXIII) (CCXXXIV): a) R = Me, b) R = H; c) R = Na

Scheme 19

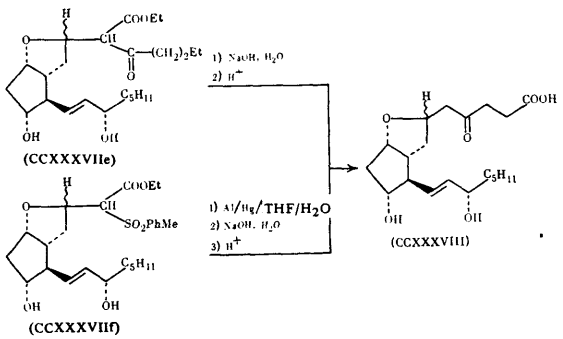


(CCXX): R = Si (CCXXI): R = Ac (CCXXII): a) X = Cl(5*R*), R = Si; b) X = Br(5*R*), R = Si (CCXXIII): a) X = Cl, R = Ac; b) X = Br, R = Ac (CCXXIVa–d) (CCXXV): R = Si (CCXXVI) (CCXXVII) (CCXXVIII): a) R = Si, R¹ = Me; b) R = H, R¹ = Me; c) R = H, R¹ = Na

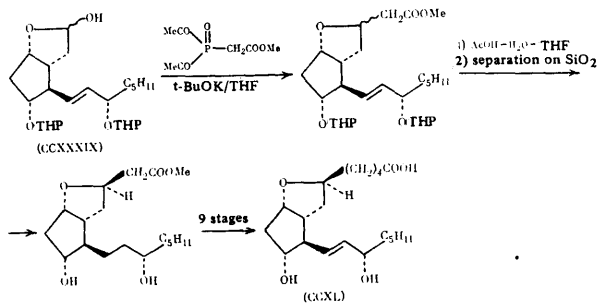
A simple method of synthesising the PC analogues (CCXXXVII) using the hemiacetal (CCXXXV) and a compound with an active methylene group [compounds (CCXXXVIa–f)] under the conditions of the Knoevenagel condensation has been proposed:[67,68]



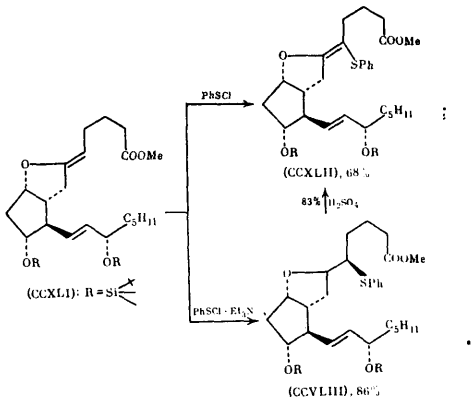
This method is extremely promising, since many compounds with an active methylene group can be condensed. The reaction can be carried out both with malonic and acetoacetic acid derivatives and with β-oxosulphones and aliphatic nitro-compounds. An advantage of this method is its simplicity, which makes it possible to apply it on an industrial scale. Despite the fact that the reaction results in the formation of all four possible isomers of compound (CCXXXVII), the Knoevenagel condensation has been used successfully as the key stage in the synthesis of the familiar 4-oxo-PGI_1 (CCXXXVIII):



An analogous strategy has been used to convert the lactone (CCXXXIX) into 6β-PGI_1 (CCXI), the Wittig condensation being used in the first stage instead of the Knoevenagel condensation:[69]

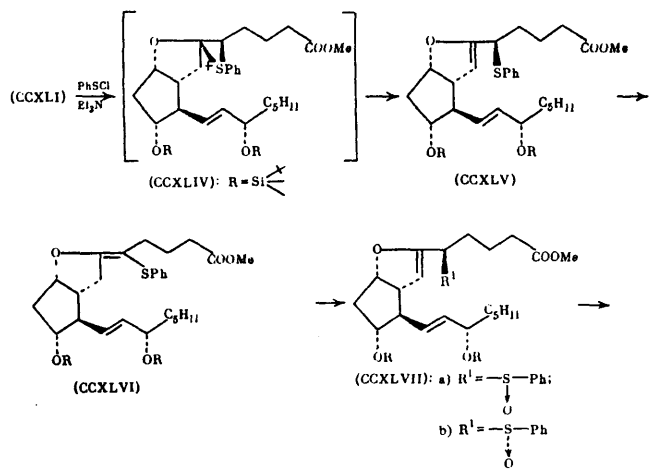


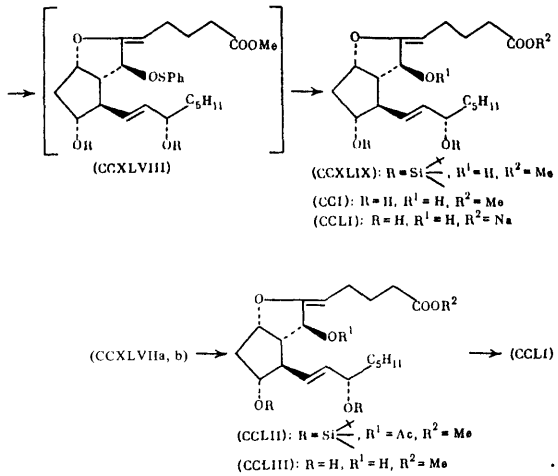
Several stable PGI_2 analogues containing electron-accepting substituents at the C(5) or C(7) atoms have been synthesised.[70] The methyl ester of PGI_2 (CCXLI) reacts with benzenesulphenyl chloride to form (5*E*)-5-phenylthio-PGI_2 (CCXLII) or (5*R*)-5-phenylthio-Δ^6-PGI_1 (CCXLIII) depending on the condensation conditions.



The synthesis of the stable analogues 7-hydroxy- and 7-acetoxy-PGI_2, the methyl ester of PGI_2, using the stereocontrolled sulphoxide–sulphenate rearrangement has been described.[71] The methyl ester (CCXLI) is converted into the allyl sulphide (CCXLV) (86%), the phenylthio-group attacking the less hindered β-side of the Δ^5-double bond with formation of the intermediate episulphonium ion (CCXLIV), in which the proton at the C(7) atom is abstracted with conversion into compound (CCXLV). It is of interest that, when a solution of compound (CCXLV) in $CHCl_3$ is treated with a catalytic amount of H_2SO_4, the Δ^6-double bond isomerises rapidly and readily to the (5*E*)-sulphide (CCXLVI) (83%) without the formation of the (5*Z*)-isomer. The oxidation of compound (CCXLVI) with *m*-chloroperbenzoic acid gives rise to an isomeric mixture of the sulphoxides (CCXLVIIa, b) (53%), which is not resolved into the isomers in view of the rapid epimerisation of allyl sulphoxides via the sulphenate ester (CCXLVIII) stage [(CCXLVIIa) ⇌ (CCXLVIII) ⇌ (CCXLVIIb)]. When a mixture of compounds (CCXLVIIa, b) is treated with diethylamine, the rearranged alcohol (CCXLIX) is obtained (68%). The silyl protecting groups in the latter are removed with TBAF to form the methyl ester of (7*S*)-hydroxy-PGI_2 (CCL) (87%), the alkaline hydrolysis of which affords the sodium salt of (7*S*)-hydroxy-PGI_2 (CCLI). Treatment of compounds (CCXLVIIa, b) with the acetic acid–pyridine mixture yields the acetate (CCLII) (62%). The removal of the protecting groups with TBAF leads to the methyl ester of (7*S*)-acetoxy-PGI_2 (CCLIII), whose hydrolysis results in the formation of compound (CCLI) (Scheme 21).

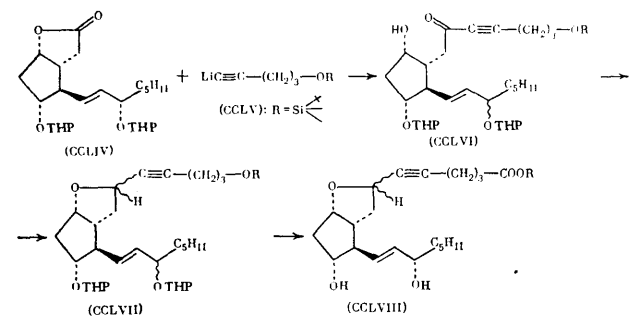
Scheme 21





An interesting synthesis, involving only a few stages, of the 4,4,5,5-tetrahydro-PC analogue (CCLVIII) has been developed.[72] The initial compound employed was the lactone (CCLIV), whose reaction with alkynyl-lithium (CCLV) results in its conversion into the ketone (CCLVI). The reduction of the keto-group with $NaBH_4$ and subsequent cyclisation in the presence of toluene-*p*-sulphonyl chloride in pyridine lead to the bicyclic compound (CCLVII). After the removal of the THP group in the usual way and alkaline hydrolysis, the latter is converted into compound (CCLVIII) (Scheme 22).

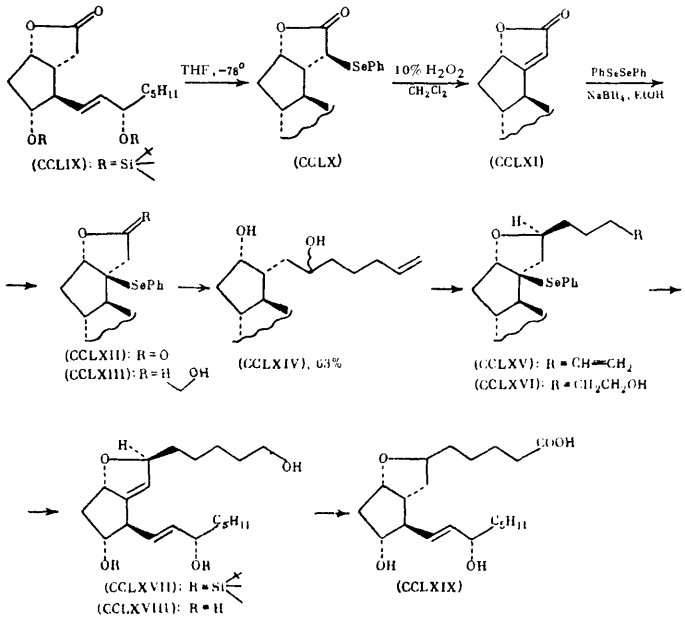
Scheme 22



A similar strategy, based on the use of the lactone (CCLIV), was used in the synthesis of 6β-Δ^7-PGI_1.[73]

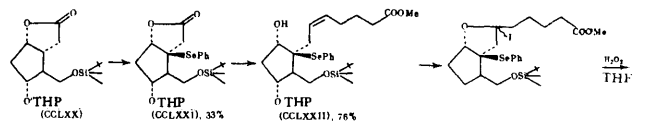
The synthesis of (6*R*)- and (6*S*)-Δ^7-PGI_1 (CCLXIX) [74] from the lactone (CCLIX) has been described. The reaction of the lactone with lithium diisopropylamide and treatment of the resulting enolate with PhSeCl yield the 7-phenylselenyl-lactone (CCLX) (90%), which is converted into the αβ-unsaturated lactone (CCLXI) via the phenylselenium oxide elimination stage. The lactone (CCLXI) is converted into the 8-phenylselenolactone (CCLXII), whose reduction with DIBAH gives rise to the lactone (CCLXIII). The alkylation of compound (CCLXIII) with 4-pentylmagnesium bromide leads to the olefin (CCLXIV). The formation of the 6,9-epoxy-unit in compound (CCLXIV) takes place on treatment with toluene-*p*-sulphonyl chloride (pyridine, 40 °C) or methanesulphonyl chloride (Et_3N, CH_2Cl_2, -78 °C). The conversion of compound (CCLXV) into (6*S*)-Δ^7-PGI_1 (CCLXIX) is carried out in four stages: (1) hydroboration of compound (CCLXV) and 9-BBN and subsequent oxidation afford the primary alcohol (CCLXVI); (2) treatment of compound (CCLXVI) with 10% H_2O_2 results in the formation of the unsaturated compound (CCLXVII); (3) mild acid hydrolysis of compound (CCLXVII) leads to the C(1) alcohol (CCLXVIII); (4) selective oxidation of compound (CCLXVIII) over Pt/O_2 produces compound (CCLXIX) (Scheme 23).

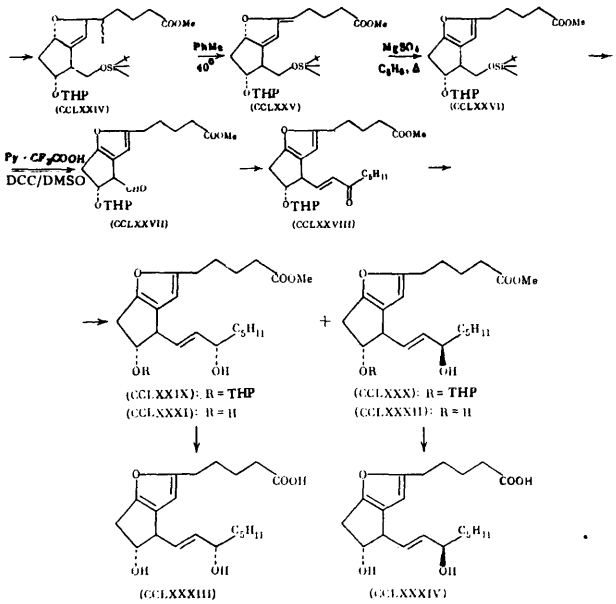
Scheme 23



Stable PC analogues having a furan ring instead of the enolic ether group have been synthesised.[75] The introduction of the phenylseleno-group in the α-position in the lactone (CCLXX) followed by treatment with $(MeSi)_2NLi$ and PhSeCl (THF), -70 °C, the elimination of the phenylseleno-group under oxidation conditions (H_2O_2), and the reintroduction of the phenylseleno-group ($NaHB_4$, PhSeSePh, EtOH) result in the formation of the β-phenylselenolactone (CCLXXI). The reduction of the latter with DIBAH (-70 °C), condensation with the lithium salt of 4-CBTP, and treatment of the resulting carboxylic acid with CH_2N_2 lead to the ester (CCLXII). The bicyclic iodoester (CCLXXIII) is obtained by treating compound (CCLXXII) with I_2 and $NaHCO_3$ with subsequent elimination of the phenylseleno-group and the formation of the dihydrofuran (CCLXXIV). The dehydroiodination of compound (CCLXXIV) with DBU gives rise to the very labile dienol ether (CCLXXV), which immediately isomerises to the furan derivative (CCLXXVI). The protecting group in compound (CCLXXVI) is removed with TBAF and the resulting alcohol is oxidised to the unstable aldehyde (CCLXXVII), which is condensed with dimethyl 2-oxoheptylphosphonate to form the enone (CCLXXVIII). The latter is reduced to $NaBH_4$ in the 15α- and 15β-alcohols (CCLXXIX) and (CCLXXX) (53% and 39% respectively). After removal of the THP protecting group in the usual way, the methyl esters (CCLXXXI) and (CCLXXXII) are obtained and then hydrolysed to the free acids (CCLXXXIII) and (CCLXXXIV) (Scheme 24).

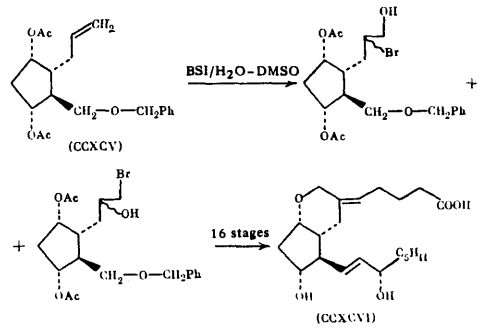
Scheme 24





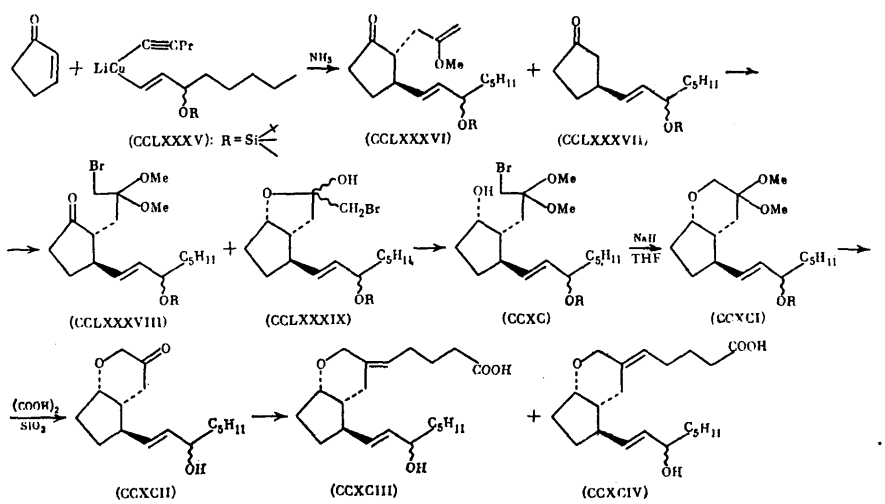
A synthesis of 11-deoxyhomo-PC analogues with a small number of stages has been proposed. The key stage in the synthesis is the reaction involving the coupled addition of organocuprate and alkylation of the resulting enolate.[76,77] Treatment of cyclopent-2-enone with the mixed cuprate (CCLXXXV) and alkylation of the intermediate enolate with 2-methoxyallyl bromide lead to a mixture of the alkylated product (CCLXXXVI) and the non-alkylated ketone (CCLXXXVII). Bromination of compound (CCLXXXVI) yields the α-bromoketal (CCLXXXVIII) together with the bicyclic acetal (CCLXXXIX). The stereospecific reduction of the keto-group in compound (CCLXXXVIII) with potassium *t*(*s*)-butylhydroborate leads to the α-alcohol (CCXC), which is cyclised to the ketal (CCXCI) with the simultaneous elimination of HBr. The hydrolysis and desilylation of compound (CCXCI) lead to the ketone (CCXCII), whose condensation with 4-CBTP gives rise to a mixture of compounds (CCXCIII) and (CCXCIV), which can be separated chromatographically (Scheme 25).

A similar approach to the synthesis of homo-PC (CCXCVI) is based on the use of the alkene (CCXCV). However, in the stage involving the addition of HOBr to the double bond, which precedes cyclisation, a low selectivity is observed:[78]

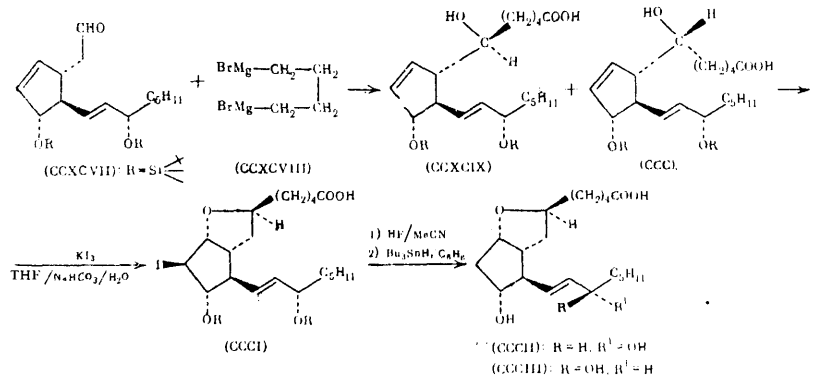


The stereoselective synthesis of the racemic 6β-PGI_1, which is a biologically active stable PC analogue, has been achieved.[79,80] The aldehyde (CCXCVII) reacts with an excess of the bis-Grignard reagent (CCXCVIII) and subsequent carboxylation with gaseous CO_2 affords a mixture of the acids (CCXCIX) (6α-OH) and (CCC) (6β-OH). When this mixture is treated with KI_3, the esters of 10β-iodo-derivative (CCCI) (34%) and the 6α-hydroxy-derivative (CCXCIX) (40%) are obtained. Compound (CCXCIX) is separated chromatographically, subjected to Collins oxidation, and then reduced with $NaBH_4$ to a mixture of compounds (CCXCIX) and (CCC), which is reused. When compound (CCCI) is treated with HF, (±)-6β-PGI_1 (CCCII) and (±)-6β-epi-PGI_1 (CCCIII) are obtained and are separated chromatographically (Scheme 26).

Scheme 25



Scheme 26

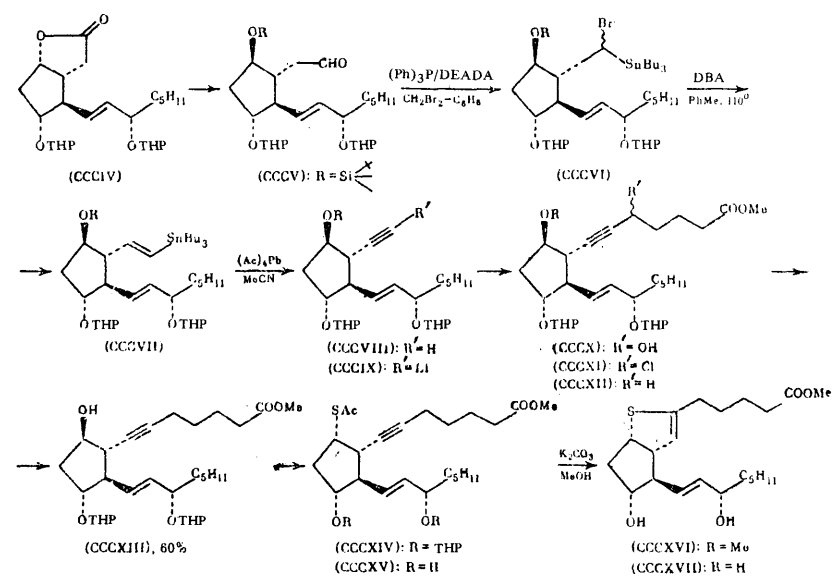


4. Prostacyclin Analogues From Which the O Atom in the 9-Position Has Been Replaced by Other Heteroatoms. Prostacyclin Analogues Containing Additional Heteroatoms

In order to elucidate the influence of the replacement of the O(9) atom by other heteroatoms, for example S and N, on the biological properties of PC, a series of syntheses were carried out, as a result of which it was possible to establish that the PC heteroanalogues exhibit a weaker biological activity than PC itself.[21,43]

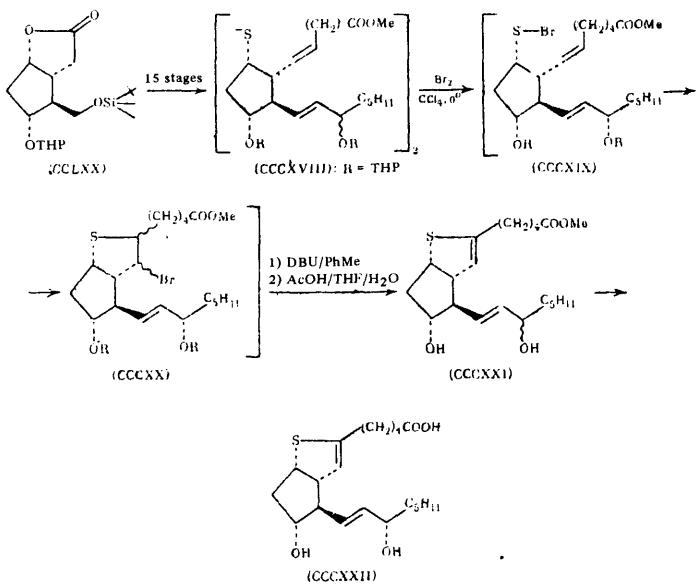
A new method for the conversion of the aldehyde into the acetylenic derivative via 1-alkenyltin was used in the synthesis of 9(*O*)-thia-Δ^6-PGI_1 (CCCXVII).[81] The initial aldehyde (CCCV) was obtained from the well known lactone (CCCIV) in six stages (overall yield 57%). The aldehyde is converted in two stages into the α-bromoalkyltin derivative (CCCVI) (54%). The elimination of HBr from compound (CCCVI) gives rise to the vinyltin derivative (CCCVII) in a satisfactory yield. Further treatment of compound (CCCVII) leads to the terminal acetylene (CCCVIII) (63%). The condensation of the lithio-derivative (CCCIX) with methyl 4-formylbutanoate results in the formation of the propargyl alcohol (CCCX). The replacement of the OH group in compound (CCCX) by chlorine leads to compound (CCCXI), whose subsequent treatment with tri-n-butyltin hydride affords the propargyl chloride (CCCXII). After the removal of the protecting group in compound (CCCXII), the 9β-alcohol (CCCXIII) is formed and is then converted into the 9α-thia-acetate (CCCXIV) by Volante's method [$(C_6H_5)_3P$/di-isopropyl azodicarboxylate in the presence of thioloacetic acid]. The removal of the THP group in compound (CCCXIV) yields compound (CCCXV) (83%), the subsequent hydrolysis of which gives rise to the dihydrothiophen derivative (CCCXVI) (endoenol, 66%). Alkaline hydrolysis of compound (CCCXVI) with LiOH in a THF–H_2O mixture followed by the adjustment of the pH to 4.01 with the aid of a buffer solution leads to compound (CCCXVII) (Scheme 27).

Scheme 27



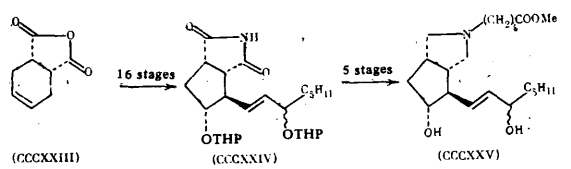
The synthesis of the chemically stable 9(*O*)-thia-Δ^6-PC (CCCXXII) from Corey's lactone (CCLXX), which is converted in the usual way into the disulphide (CCCXVIII), has been described. The bromination of compound (CCCXVIII), treatment with DBA, and the removal of protecting groups lead to different amounts of the methyl esters of compound (CCCXXI) and its 15-epimer. The conversion of the disulphide (CCCXVIII) into the sulphenyl bromide (CCCXIX) initiates a new intermolecular rearrangement with formation of the halogenotetrahydrothiophen derivative (CCCXX). Alkaline hydrolysis of compound (CCCXXI) affords compound (CCCXXII), which exhibits a high activity in the inhibition of the aggregation of platelets, comparable to the activity of 9(*O*)-thia-PC [82] (Scheme 28).

Scheme 28



(CCLXX) (CCCXVIII): R = THP (CCCXIX) (CCCXX) (CCCXXI) (CCCXXII)

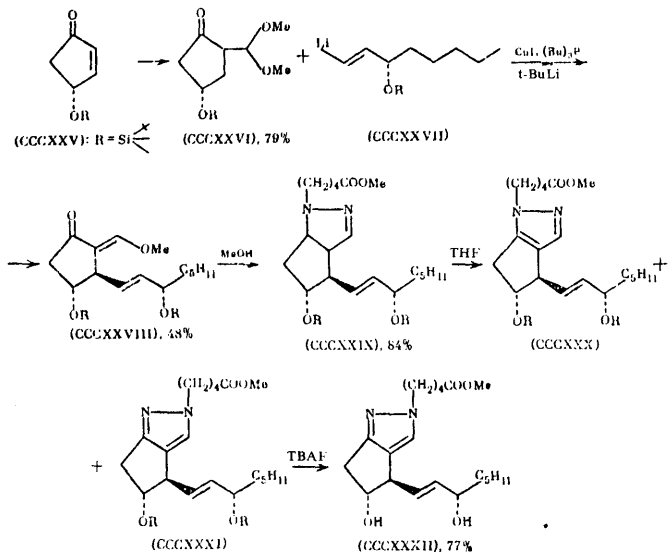
A multistage synthesis of racemic 6-aza-6,9-methano-PGI_2 (CCCXXV), which inhibits the aggregation of platelets, has been achieved. The anhydride (CCCXXIII) served as the starting material. It is converted into the imide (CCCXXIV) in 16 stages and the 6-aza-PC analogue (CCCXXV) was obtained from the latter in 5 stages: [83]



(CCCXXIII) (CCCXXIV) (CCCXXV)

A convergent approach to the chiral analogue of the heteroaromatic PC has been proposed. [84] The enone (CCCXXV) is initially converted into the dimethoxymethyl derivative (CCCXXVI): treatment with (1) phenylselenotrimethylsilane and trimethylsilyltrifluoromethanesulphonate, (2) trimethyl orthoformate, (3) pyridine, and (4) 30% H_2O_2. The reaction of compound (CCCXXVI) with the organocuprate reagent obtained from copper(I) iodide and the lithium derivative (CCCXXVII) gives rise to the product (CCCXXVIII). Its condensation with hydrazine hydrate affords the pyrazole derivative (CCCXXIX), whose potassium salt is treated with methyl 5-iodopentanoate, which leads to a 1 : 1 mixture of the products (CCCXXX) and (CCCXXXI) (67%). After the removal of the protecting groups in compound (CCCXXXI), compound (CCCXXXII) is obtained (Scheme 29).

Scheme 29

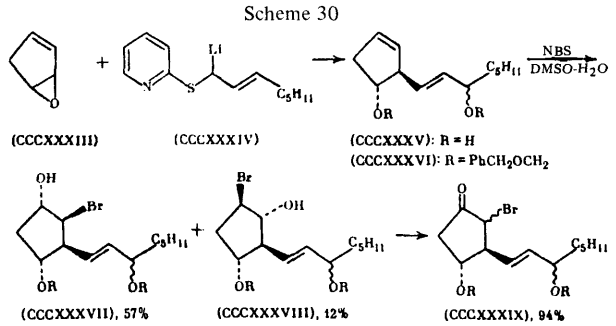


(CCCXXV): R = Si (CCCXXVI), 79% (CCCXXVII) (CCCXXVIII), 48% (CCCXXIX), 84% (CCCXXX) (CCCXXXI) (CCCXXXII), 77%

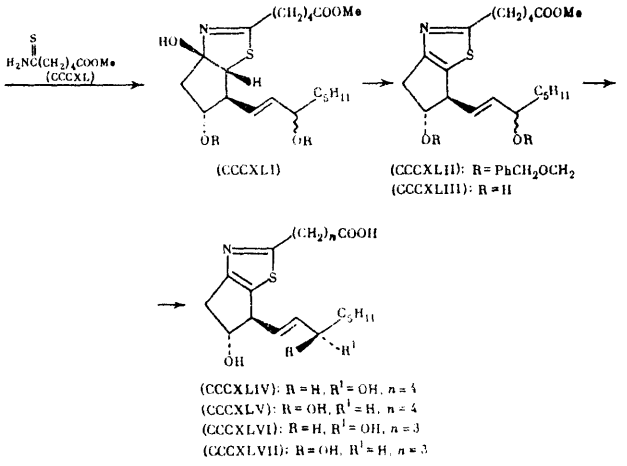
Thiazole analogues of PC are obtained from compound (CCCXXV), synthesised in several stages by the opening of the epoxy-ring in the 3,4-epoxycyclopentene (CCCXXXIII) by treatment with the lithio-derivative (CCCXXXIV). [85] The hydroxy-groups in the diol (CCCXXXV) are protected in the form of the bisbenzyloxymethyl ethers (CCCXXXVI), which give rise to an appreciable steric hindrance to electrophilic attack on the double bond in the side chain.

Treatment of compound (CCCXXXVI) with NBS gives rise to a mixture of two readily separated bromohydrins (CCCXXXVII) and (CCCXXXVIII). Oxidation of the main bromohydrin (CCCXXXVII) with pyridinium chlorochromate yields the bromoketone (CCCXXXIX) in the form of a mixture of epimers at C(8). The reaction of compound (CCCXXXIX) with the thioamide (CCCXL) leads to the hydroxythiazoline (CCCXLI), which is treated, without being isolated, with the complex of $(C_6H_5)_3P$ and DEADA, to give the thiazole (CCCXLII). After the removal of the protecting groups in compound (CCCXLII) and alkaline hydrolysis of the diol (CCCXLIII), the PC analogue (CCCXLIV) and its 15-epimer (CCCXLV) are obtained and are separated chromatographically. The nor-PC analogue (CCCXLVI) and its 15-epimer (CCCXLVII) are obtained analogously from the bromoketone (CCCXXXIX) and a thiazole derivative obtained from the methyl ester of glutaric acid monoamide (Scheme 30).

Scheme 30



(CCCXXXIII) (CCCXXXIV) (CCCXXXV): R = H (CCCXXXVI): R = $PhCH_2OCH_2$ (CCCXXXVII), 57% (CCCXXXVIII), 12% (CCCXXXIX), 94%

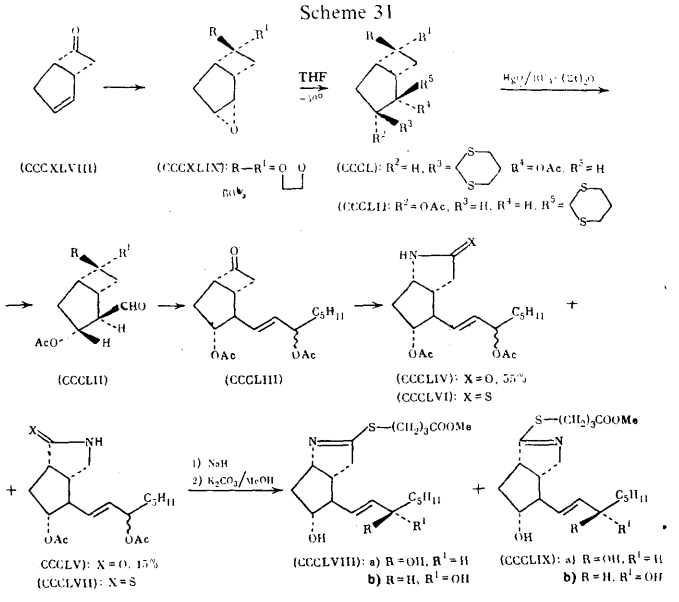


(CCCXLII): R = $PhCH_2OCH_2$
(CCCXLIII): R = H

(CCCXLIV): R = H, R^1 = OH, n = 4
(CCCXLV): R = OH, R^1 = H, n = 4
(CCCXLVI): R = H, R^1 = OH, n = 3
(CCCXLVII): R = OH, R^1 = H, n = 3

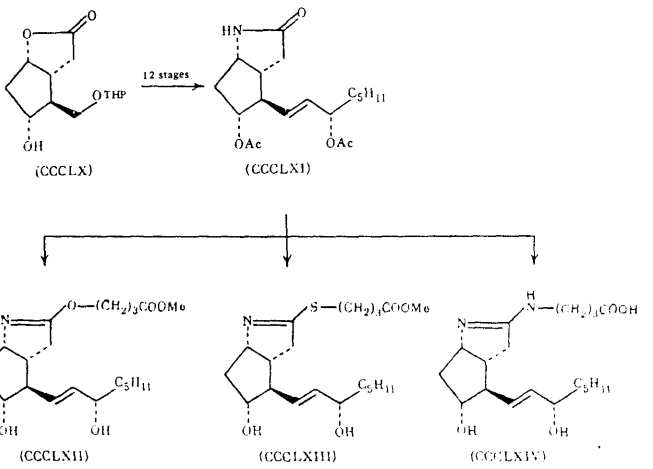
The synthesis of β-thiaimino-PC using bicyclo[3.2.0]hept-2-en-6-one (CCCXLVIII), the intermediate in the synthesis of natural PG, as the starting material has been described.[86] The ketone (CCCXLVIII) is converted by a standard method into the ketal (CCCXLIX) whose treatment with 2-lithiodithiane followed by acylation gives rise to the crystalline acetates (CCCL) and (CCCLI) (2 : 8, 61%), which are readily separated by crystallisation. Selective hydrolysis of the dithiane unit in the acetate (CCCLI) results in the formation of the aldehyde (CCCLII), whose condensation with the corresponding phosphonate, the reduction of the enone produced ($ZnBH_4$, diglyme), acylation, and the removal of the ketal protecting group lead to the ketone (CCCLIII). Treatment of compound (CCCLIII) with *o*-mesitylenesulphonylhydroxylamine yields the crystalline lactam (CCCLIV) and the isomeric lactam (CCCLV). On heating the mixture of lactams (P_4S_{10}.Py, toluene), the mixture of the thiolactams (CCCLVI) and (CCCLVII) is obtained (80%), whose alkylation with ethyl γ-bromobutyrate followed by the hydrolysis of the acetate groups affords a mixture of compounds (CCCLVIIIa, b) and (CCCLIXa, b) in an overall yield of 64%, which can be readily separated chromatographically (Scheme 31).

Scheme 31



(CCCXLVIII) (CCCXLIX): R—R^1 = O, O, 60% (CCCL): R^2 = H, R^3 = S, S, R^4 = OAc, R^5 = H (CCCLI): R^2 = OAc, R^3 = H, R^4 = H, R^5 = S, S (CCCLII) (CCCLIII) (CCCLIV): X = O, 55% (CCCLVI): X = S (CCCLV): X = O, 15% (CCCLVII): X = S (CCCLVIII): a) R = OH, R^1 = H b) R = H, R^1 = OH (CCCLIX): a) R = OH, R^1 = H b) R = H, R^1 = OH

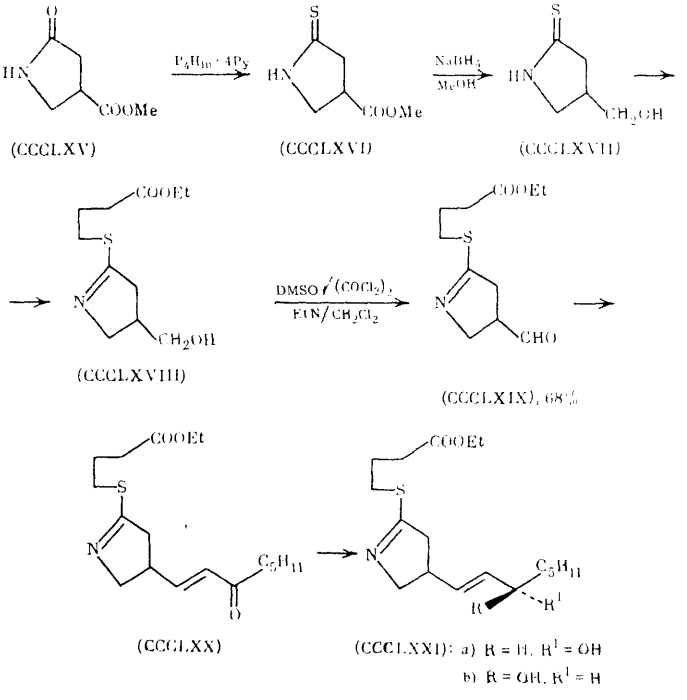
The lactone (CCCLX) can be converted into the lactam (CCCLXI), which is the key synthone in the synthesis of 4-oxa-9-aza-PGI_1 (CCCLXII), 4-thia-9-aza-PGI_1 (CCCLXIII), and 4,9-diaza-PGI_1 (CCCLXIV).[87]



(CCCLX) (CCCLXI) (CCCLXII) (CCCLXIII) (CCCLXIV)

The racemic thiolactam esters (CCCLXXIa, b) are obtained from 4-methoxypyrrolidin-2-one (CCCLXV) via compound (CCCLXVI) and *S*-alkylation of the thiolactam alcohol (CCCLXVII) with ethyl ω-bromobutyrate to the thiaimino-alcohol (CCCLXVIII). After the oxidation of the OH group in compound (CCCLXVIII), the aldehyde (CCCLXIX) is obtained and its condensation with dimethyl 2-oxoheptylphosphonate leads to the enone (CCCLXX). The reduction of the last compound with diisobornyloxyaluminium isopropoxide yields a 1 : 1 mixture of the epimers (CCCLXXIa, b) which can be separated chromatographically (Scheme 32).[88]

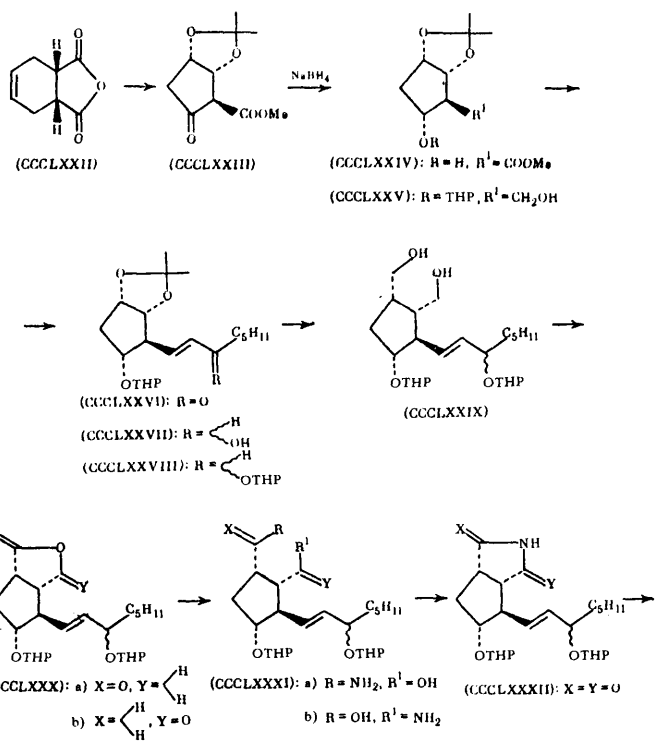
Scheme 32

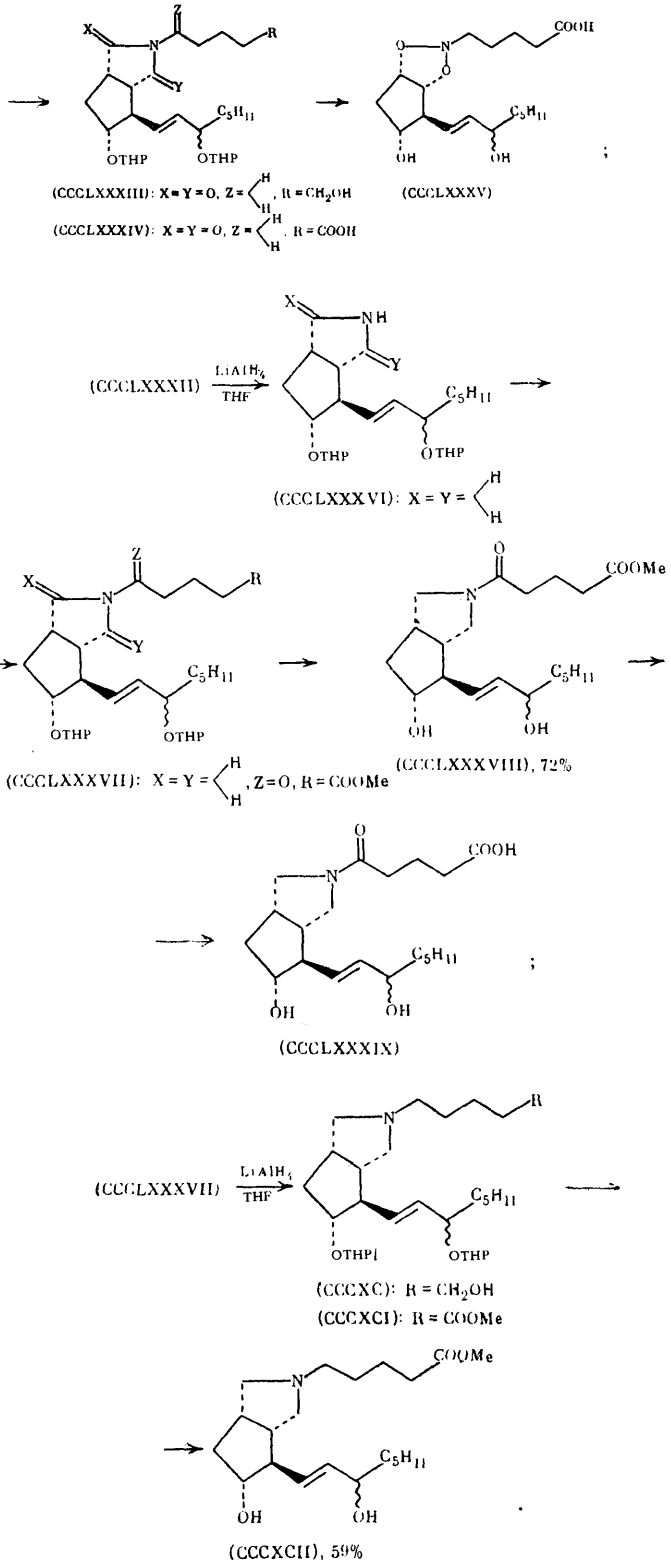


(CCCLXV) (CCCLXVI) (CCCLXVII) (CCCLXVIII) (CCCLXIX), 68% (CCCLXX) (CCCLXXI): a) R = H, R^1 = OH b) R = OH, R^1 = H

The synthesis of analogues of *dl*-6-aza-6,9-methano-PGI_1 (CCCLXXXV), (CCCLXXXVIII), (CCCLXXXIX), and (CCCXCII) from the anhydride (CCCLXXII), which is converted in 5 stages into the β-ketoester (CCCLXXIII), has been achieved.[89] Reduction of the keto-group makes it possible to obtain compound (CCCLXXIV). By protecting the OH group in compound (CCCLXXIV) and reducing the ester group with DIBAH, one can obtain the alcohol (CCCLXXV), whose oxidation to the aldehyde and subsequent condensation with dimethyl 2-oxoheptylphosphonate give rise to the enone (CCCLXXVI). The reduction of the keto-group in compound (CCCLXXVI) with $NaBH_4$ leads to a mixture of the C(15)-epimers (CCCLXXVII), which is converted, without being isolated, into compound (CCCLXXVIII) and the latter is converted into the diol (CCCLXXIX) by reaction with pyridinium toluene-*p*-sulphonate. The Sarett oxidation of compound (CCCLXXIX) leads to a mixture of two isomeric γ-lactones (CCCLXXXa, b), b) (94%) and their treatment with hydrazine results in the formation of a mixture of the amidoalcohols (CCCLXXXIa, b), whose oxidation gives rise to the imide (CCCLXXXII). The reaction of the imide with 5-aminopentanol leads to the imidoalcohol (CCCLXXXIII), the Sarett oxidation of which affords the imidoacid (CCCLXXXIV). After the removal of the protecting groups in compound (CCCLXXXIV), compound (CCCLXXXV) is obtained. The reduction of compound (CCCLXXXII) leads to the formation of the cyclic amine (CCCLXXXVI), which is converted into the amidoester (CCCLXXXVII) after treatment with glutaric anhydride and esterification with CH_2N_2. The removal of the protecting groups in compound (CCCLXXXVII) affords compound (CCCLXXXVIII), whose alkaline hydrolysis leads to compound (CCCLXXXIX). The reduction of compound (CCCLXXXVII) leads to the formation of the aminoalcohol (CCCXC). It is successively oxidised by the Jones' method and esterified with CH_2N_2 to the aminoester (CCCXCI) and, after the removal of the protecting groups in the latter, compound (CCCXCII) is obtained (Scheme 33).

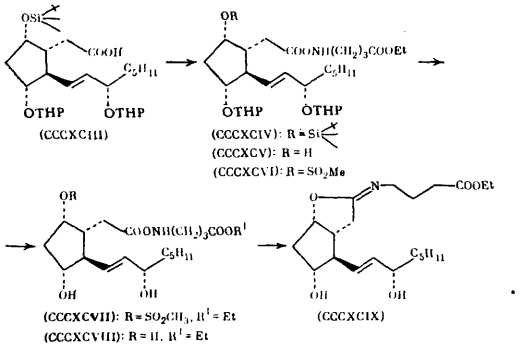
Scheme 33





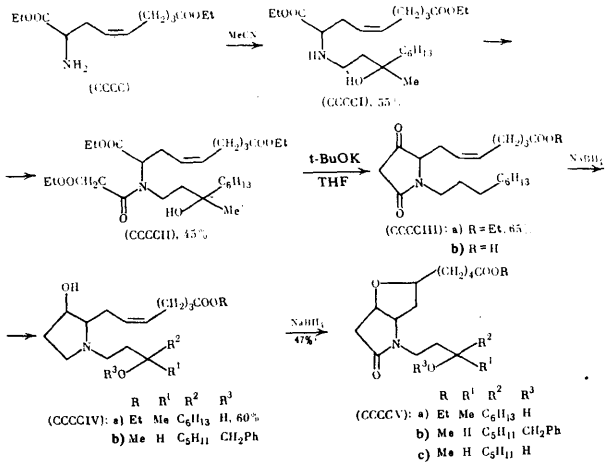
The synthesis of the optically active 5-aza-PC derivative (CCCXCIX) in which the enol ether unit has been replaced by the iminoether system has been described.[90-92] The acid (CCCXCIII) is first converted into a mixture of anhydrides

and the latter are converted by reaction with ethyl 4-aminobutanoate into the amine (CCCXCIV), whose reaction with TBAF produces the alcohol (CCCXCV). Subsequent removal of the protecting groups in the latter leads to the crystalline compound (CCCXCVII) (81%). The interaction of this compound with LiBr ($NaHCO_3$, DMF) leads to a mixture of compounds (CCCXCIX) and (CCCXCVIII), whose separation is the most important stage. Compound (CCCXCVIII) (30%) is isolated from the organic layer by partition between 0.1 *N* citrate buffer (pH 4) and the 4 : 1 ether-dichloroethane mixture. The crystalline compound (CCCXCIX) (51%) is isolated from the aqueous layer by treatment with Na_2CO_3 (pH 8) and extraction with CH_2Cl_2:



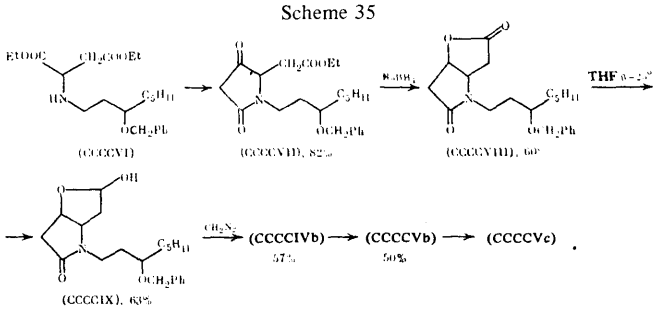
Analogues of 12-aza-PC can be obtained in two ways.[93] The first approach (Scheme 34) is based on the use of the amine (CCCC), whose treatment with 3-methyl-1-(toluene-*p*-sulphonyloxy)nonan-3-ol leads to compound (CCCCI), whose acylation with monoethyl malonate yields compound (CCCCII). The cyclisation of the latter to (CCCCIIIa) and treatment with anhydrous $MgSO_4$ afford compound (CCCCIIIb). Its reduction and treatment of compound (CCCCIVa) with mercury trifluoroacetate followed by reduction make it possible to obtain the 12-aza-PC analogue (CCCCVa).

Scheme 34



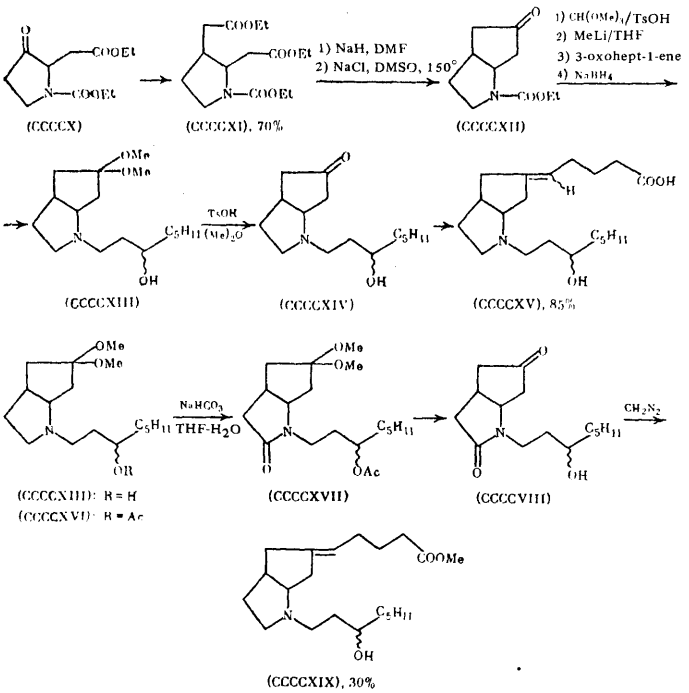
The second approach (Scheme 35) involves the application of the amine (CCCCVI), which is cyclised by the method described above. The potassium salt (CCCCVII) is reduced *in situ* to the bicyclic lactone (CCCCVIII). Its treatment with lithium tri-t-butoxyhydroaluminate leads to the lactol (CCCCIX), whose condensation with 4-CBTP and esterification give rise to compound (CCCIVb). The cyclisation of the latter to compound (CCCCVb) and hydrogenolysis over Pd/C result in the formation of the 12-aza-PC analogue (CCCCVc).

Scheme 35



In the search for anticlotting agents, the 12-azacarba-PC analogues (CCCCXV) and (CCCCXIX) have been synthesised from the common intermediate (CCCCXIII) (Scheme 36).[94] By reaction with $(MeO)_2OPCHNaCOOMe$ and subsequent hydrogenation, compound (CCCCX) is converted into the triester (CCCCXI), which is subjected to Dieckmann cyclisation and decarboxylation to give compound (CCCCXII). The ketone (CCCCXII) is converted into the dimethyl ketal (CCCCXIII) in four stages (overall yield 57%). After the removal of the protecting group in compound (CCCCXIII), the ketone (CCCCXIV) is obtained and condensed with 4-CBTP to form compound (CCCCXV). The intermediates in the synthesis of compound (CCCCXV), necessary for the conversion of the pyrrolidinone ring into a five-membered lactam, are used to synthesise the analogue (CCCCXIX). By protecting the OH group in compound (CCCCXIII) and by oxidising compound (CCCCXVI) with NBS, we obtain the 3-oxo-derivative (CCCCXVII). After the removal of the protecting groups, the hydroxy-ketone (CCCCXVIII) is condensed with the phosphorane to obtain an acid, whose subsequent esterification leads to compound (CCCCXIX).

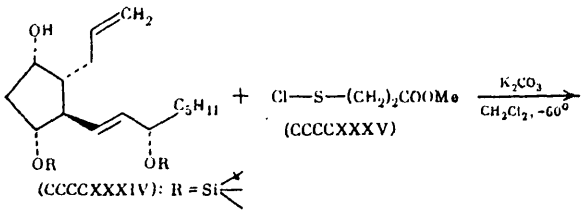
Scheme 36



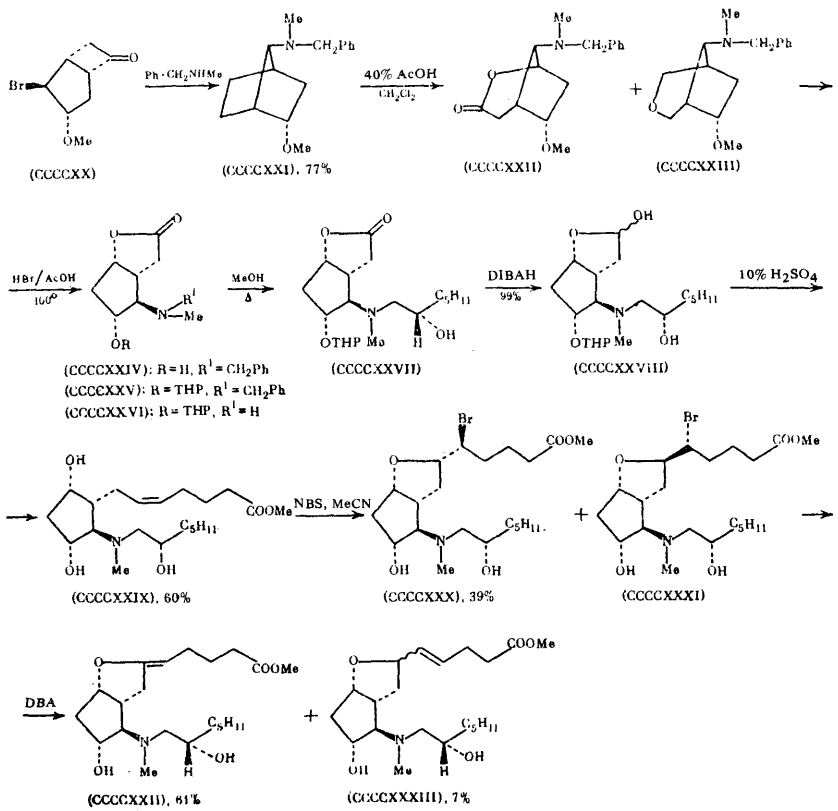
The stereoselective synthesis of the methyl ester of 13-aza-PC in 10 stages from the readily available 2-*exo*-bromo-3-*endo*-methoxybicyclo[3.2.0]heptan-6-one (CCCCXX) has been described.[95] The heptanone is converted into compound (CCCCXXI) and subjected to Baeyer–Villiger oxidation to give a mixture of the isomeric lactones (CCCCXXII) and (CCCCXXIII). The lactone (CCCCXXII) is kept in a mixture of acids, whereupon the methyl ester is cleaved with the simultaneous rearrangement of the δ-lactone to the γ-lactone (CCCCXXIV) (69%). Compound (CCCCXXIV) is converted via its hydroxy-group into the protected lactone (CCCCXXV). It is then hydrogenated over a Pd catalyst to the secondary amine (CCCCXXVI). The introduction of a ω-chain into this amine is achieved by reaction with (*S*)-pentyl oxide. The reduction of the lactone (CCCCXXVII) to the lactol (CCCCXXVIII), its subsequent condensation with 4-CBTP, and the removal of the protecting groups gives rise to the triol (CCCCXXIX). The hydrochloride of the latter is converted into the bromoesters (CCCCXXX) and (CCCCXXXI) (*endo* : *exo* = 3 : 1, 39%). Dehydrohalogenation of the two isomers after chromatographic separation leads to the methyl ester (CCCCXXXII) and its (4*E*)-isomer (CCCCXXXIII) (Scheme 37).

The addition of the alkanesulphonyl chloride (CCCCXXXV) to the alcohol (CCCCXXXIV) at −60 °C produces the bicyclic thiaesters (CCCCXXXVI) and (CCCCXXXVII). These diaesteroisomers are separated chromatographically and are converted, after the removal of the protecting groups and hydrolysis, into the 4-thia-PCI_1 analogues (CCCCXXXVIII) and (CCCCXXXIX) (Scheme 38).[96]

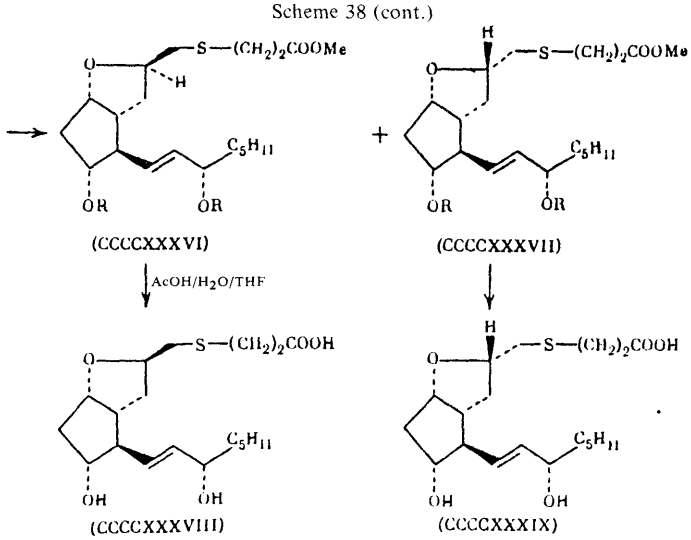
Scheme 38



Scheme 37



Scheme 38 (cont.)



After the review had been prepared for publication, a number of communications on the subject were published. Thus a new method for the construction of the ω-chain, with a stereospecific introduction of the 15α-hydroxy-group, was used in the synthesis of (±)-6,9α-methano-PGI_3.[97,98] Corey obtained a satisfactory yield of CC by an intramolecular thermal ene reaction.[99] The synthesis of CC from the key compound 2-(formylmethyl)-1-methylcyclopentane using a rhodium(I) complex has been achieved.[100] A new version of the synthesis of (+)-isocarbacyclin from a chiral substituted Corey's lactone has been developed.[101] In order to investigate biological activity, 6α-carba-PGI_3 has been synthesised from (1*S*,2*R*,3*R*,5*R*)-7,7-ethylenedioxy-2-formyl-3-tetrahydropyranyloxybicyclo[3.3.0]octane.[102] A method has been proposed for the synthesis of 13-thia-CC.[103] Cyanocarbacyclins have been synthesised using the stereospecific 1,4-hydrogenation of the corresponding conjugated dienes catalysed by the $ArCr(CO)_3$ complex as the key stage.[104] In the search for new stable and active PC analogues, (5*E*)- and (5*Z*)-(±)-CC were synthesised from cyclopent-2-en-1-one.[105] A synthesis of native (+)-9(*O*)-methano-PC from racemic (1*S**,5*R**)-7,7-ethylenedioxy-3-oxobicyclo[3.3.0]octane has been developed.[106] A simple synthesis of 13,14-didehydro-6,9α-methano-PC via the ethylene ketal of 3-oxotricyclo[4.3.0.$0^{2,4}$]nonan-8-one has been described.[107] A new CC analogue, namely 4,4,5,5-tetradehydro-9(*O*)-methane-$\Delta^{6(9\alpha)}$-PGI_1, has been synthesised using the regiocontrolled opening of the β-propyl-lactone ring by reaction with dialkylaluminium acetimide as the key stage.[108] A new synthesis of (+)-6α-CC from *cis*-bicyclo[3.3.0]octane-3,7-dione has been proposed.[109] The methyl ester of (±)-PGI_2 and its 15-epimer have been synthesised from 2-(cyclopent-2-enyl)-1-(2-oxocyclopentyl)ethanol.[110] In view of the interest in the antineoplastic properties of PC, the methyl ester of 12,13-didehydro-PC has been synthesised from 7-chloronorbornadiene.[111] A new synthesis of racemic 4-oxo-PC from 7-*endo*-t-butyldimethoxy-6-*exo*[3′(*S**)-butyldimethoxyoct-1′(*E*)-enyl]-3-oxo-2-oxabicyclo[3.3.0]octane† has been described.[112] Synthetic schemes have been devised for imidazoline, furan, thiophen, and pyrrole PC analogues.[113,114]

† The amended name of this compound is tentative since the original authors do not give it a name. The Russian text reads ...7-*endo*-*t*-butyldimethyloxy(BDMS)-6-*exo*-[3′(*S**).(BDMS-oxy)oct-1′(*E*)-enyl]-3-oxo-2-oxabicyclo[3.3.0]-octane [112] [Ed.of Translation].

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