

PATENT SPECIFICATION

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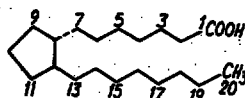


(54) PROSTANOIC ACID DERIVATIVES

(71) We, CARLO ERBA S.P.A., an Italian body corporate, of Via Carlo Imbonati 24, 20159 Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to prostanoid acid derivatives, to processes for making them and to pharmaceutical compositions containing them.

The natural prostaglandins are C—20 unsaturated, aliphatic hydroxy carboxylic acids in which the carbon atoms in the 8- and 12-positions are linked to form a five-membered ring. The basic carbon skeleton of prostanoid acid has the following structure:

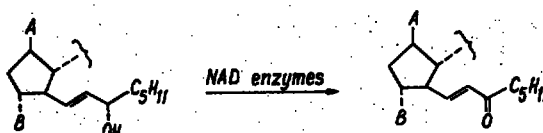


In the body, prostaglandins are synthesized from C—20 essential fatty acids by a microsomal enzymatic system.

The natural prostaglandins are known to have various physiological properties, i.e. hypertensive, hypotensive and smooth muscle stimulating activity. They also inhibit and reverse blood platelet adhesiveness and aggregation, which is the initial stage of thrombosis.

In general, the effects of prostaglandins are based on regulating the activity of smooth muscle, blood flow and secretion (including some endocrine gland secretions). Through these actions, they are able to affect many aspects of human physiology: in particular, they can be useful in the prevention of peptic ulcers, asthmatic access, hypertension, nasal congestion, as agents for abortion, as agents for inducing menstruation and the impeding the implantation of a fertilized ovum, and furthermore prostaglandins have been used in parturition to facilitate childbearing labour. Natural prostaglandins are, however, rapidly converted in the body to pharmacologically inactive metabolites; their short half life (about 10 minutes) is a hindrance to the use of natural prostaglandins as therapeutic agents.

Dehydrogenation of the allylic hydroxy function at C—15 which is present in all the naturally occurring prostaglandins, by 15-hydroxy-prostaglandin dehydrogenases (NAD-dependent enzymes), is the first and more important metabolic step:

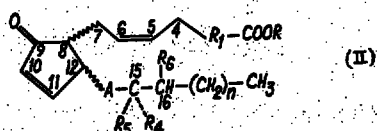
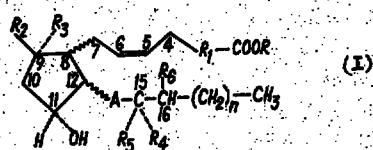


This first degradation step, involving the conversion into $\Delta^{13(14)}$ -15-oxo prostaglandins, transforms the prostaglandins into pharmacologically inactive metabolites [Anggard E., Acta Physiol. Scand., 66, 509 (1966); Kloeze J., Biochim. Biophys. Acta, 187, 285 (1969)].

The present invention provides new prostaglandin type compounds, wherein some molecular modification has occurred in order to obtain a favourable effect on biological parameters while maintaining a prostaglandin-like activity. More particularly, the invention provides pure optically active or racemic prostanic acid derivatives having a reduced metabolic degradation rate compared with natural prostaglandins, thus allowing an efficient therapeutic action at lower dosages.

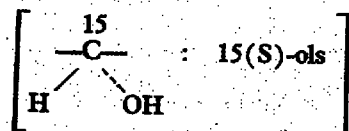
The prostanic acid derivatives of this invention can be used in the same applications as the natural prostaglandins discussed hereinbefore.

The compounds of the invention are those of general formulae (I) and (II)

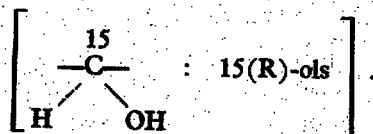


wherein R is a hydrogen atom, a pharmaceutically acceptable cation or a C_{1-18} alkyl or haloalkyl group; R_1 is $-\text{CH}_2\text{CH}_2-$, $-\text{OCH}_2-$, $-\text{SCH}_2-$, $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$; one of R_2 and R_3 is a hydrogen atom and the other is a hydroxy group or R_2 and R_3 together form an oxo group; A is $\text{trans-CH}=\text{CCl}-$ or $-\text{C}\equiv\text{C}-$, one of R_4 and R_5 is a hydrogen atom and the other is a hydroxy group; R_6 is a hydrogen atom or a C_{1-4} alkyl group; and n is 3 or 4; the chains bound to the carbon atoms in the 8-and 12-positions having the *trans*-configuration. The double bond in the 5(6)-position is a *cis*-double bond. When R_1 is $-\text{CH}=\text{CH}-$, it may be either *cis*- or *trans*-double bond. In the formulae of the Specification, the broken lines indicate that the substituents are in the α -configuration, i.e. are below the plane of the ring or of the chain, while the wavy line attachment () indicates that the groups may be either in the α -configuration, i.e. below the plane of the ring, or in the β -configuration, i.e. above the plane of the ring.

As stated above, the chains bound to the carbon atoms in the 8-position and in the 12-position must have the *trans*-configuration, i.e. these chains cannot be both in the α -configuration or both in the β -configuration; when one of them is in the α -configuration, the other is in the β -configuration and *vice versa*. As is evident from formulae (I) and (II), the hydroxy group linked to the carbon atom in the 15-position may be either in the α -configuration

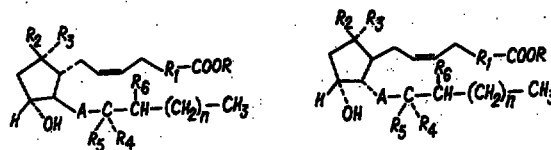


or in the β -configuration

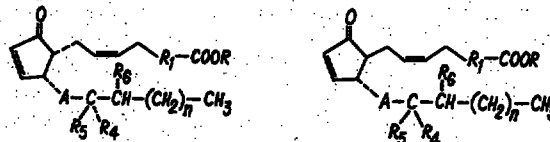


As stated above, the compounds of the invention can be in the form of optically active compounds or a racemic mixture.

The compounds of the invention are therefore either optically active compounds having the general formulae



and their racemates,
or optically active compounds having the general formulae



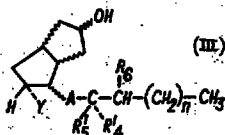
and their racemates.

The preferred compounds of the invention are those of general formula (I) wherein R_1 is $-\text{CH}_2\text{CH}_2-$ or $-\text{OCH}_2-$.

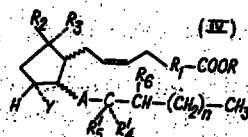
Examples of specific compounds of the invention are:

- 14-chloro-9 α ,11 α ,15(S)-trihydroxy-*cis*-5,*trans*-13-prostadienoic acid;
- 14-chloro-9 α ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5,*trans*-13-prostadienoic acid;
- 14-chloro-9 β ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5,*trans*-13-prostadienoic acid;
- 14-chloro-11 α ,15(S)-dihydroxy-9-oxo-*cis*-5,*trans*-13-prostadienoic acid;
- 14-chloro-15(S)-hydroxy-9-oxo-*cis*-5,10,*trans*-13-prostatrienoic acid;
- 14-chloro-11 α ,15(S)-dihydroxy-9-oxo-8,12-diiso-*cis*-5,*trans*-13-prostadienoic acid;
- 14-chloro-15(S)-hydroxy-9-oxo-8,12-diiso-*cis*-5,10,*trans*-13-prostatrienoic acid;
- 9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid;
- 16-methyl-9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid;
- 20-methyl-9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid;
- 9 α ,11 α ,15(S)-trihydroxy-3-oxa-*cis*-5-prosten-13-ynoic acid;
- 9 α ,11 α ,15(R)-trihydroxy-*cis*-5-prosten-13-ynoic acid;
- 9 α ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 16-methyl-9 α ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 20-methyl-9 α ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 9 α ,11 α ,15(S)-trihydroxy-3-oxa-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 9 β ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 11 α ,15(S)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid;
- 5 α -11 α ,15(R)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid;
- 16-methyl-11 α ,15(S)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid;
- 16-methyl-11 α ,15(R)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid;
- 11 α ,15(S)-dihydroxy-20-methyl-9-oxo-*cis*-5-prosten-13-ynoic acid;
- 11 α ,15(R)-dihydroxy-20-methyl-9-oxo-*cis*-5-prosten-13-ynoic acid;
- 11 α ,15(S)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid;
- 11 α ,15(R)-dihydroxy-9-oxo-3-oxa-*cis*-5-prosten-13-ynoic acid;
- 11 α ,15(S)-dihydroxy-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 11 α ,15(R)-dihydroxy-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 16-methyl-11 α ,15(S)-dihydroxy-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 16-methyl-11 α ,15(R)-dihydroxy-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 11 α ,15(S)-dihydroxy-20-methyl-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 11 α ,15(R)-dihydroxy-20-methyl-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 11 α ,15(S)-dihydroxy-9-oxo-3-oxa-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 11 α ,15(R)-dihydroxy-9-oxo-3-oxa-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
- 15S-hydroxy-9-oxo-*cis*-5,10-prostadien-13-ynoic acid;
- 16-methyl-15(S)-hydroxy-9-oxo-*cis*-5,10-prostadien-13-ynoic acid;
- 15(S)-hydroxy-20-methyl-9-oxo-*cis*-5,10-prostadien-13-ynoic acid;
- 15(S)-hydroxy-3-oxa-9-oxo-*cis*-5,10-prostadien-13-ynoic acid;
- 15(S)-hydroxy-9-oxo-8,12-diiso-*cis*-5,10-prostadien-13-ynoic acid;
- 16-methyl-15(S)-hydroxy-9-oxo-8,12-diiso-*cis*-5,10-prostadien-13-ynoic acid;
- 15(S)-hydroxy-20-methyl-9-oxo-8,12-diiso-*cis*-5,10-prostadien-13-ynoic acid; and
- 15(S)-hydroxy-9-oxo-3-oxa-8,12-diiso-*cis*-5,10-prostadien-13-ynoic acid;

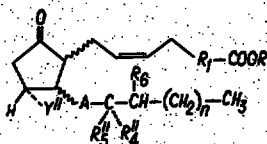
The 20-methyl compounds are those wherein n is 4. The compounds of general formulae (I) and (II) may be prepared by a process comprising reacting in known manner an optically active compound, or a racemic mixture of compounds of general formula (III)



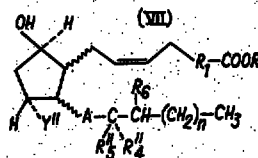
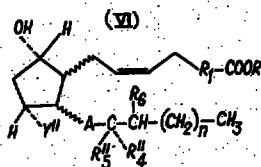
wherein R_6 , n and A are as defined above, one of R'_4 and R'_5 is a hydroxy or a known protecting group bound to the chain by an ethereal oxygen atom, and the other is a hydrogen atom, Y is a hydroxy or a known protecting group bound to the ring by an ethereal oxygen atom, the lactol ring being in the *trans*-configuration with respect to the hydroxy-aliphatic side chain, with a Wittig reagent comprising a group of formula $-\text{CH}_2\text{CH}_2-\text{R}_1-\text{COOR}$, wherein R_1 is as defined above, and R is a hydrogen atom or a C_{1-18} alkyl or haloalkyl group, to give a compound of general formula (IV)



wherein R , R_1 , Y , A , R'_4 , R'_5 , R_6 and n are as defined above, and wherein one of R_2 and R_3 is a hydroxy group and the other is a hydrogen atom, and then deetherifying in known manner the resulting compound of general formula (IV), wherein Y is a known protecting group as defined above and/or one of R'_4 and R'_5 is a known protecting group as defined above and the other is a hydrogen atom, or if desired oxidising the 9-hydroxy group in the compound of general formula (IV) wherein Y is a known protecting group as defined above and one of R'_4 and R'_5 is a known protecting group as defined above and the other is a hydrogen atom, to give a compound of general formula (V)



wherein R , R_1 , R''_4 , R''_5 , A , R_6 and n are as defined above, Y'' is a known protecting group as defined above, and one of R''_4 and R''_5 is a known protecting group as defined above, and the other is a hydrogen atom, which, in turn, may if desired be deetherified in known manner in the 11- and 15-positions, to give, according to the reaction conditions used, either a compound of general formula (I), wherein R_2 and R_3 together form an oxo group, or a compound of general formula (II), or alternatively the 9-oxo group in a compound of general formula (I) is reduced to give a mixture of the 9 α - and 9 β -ols of general formulae (VI) and (VII)



wherein R , R_1 , R''_4 , R''_5 , A , R_6 , Y'' and n are as defined above which mixture is then in either order, separated and deetherified in known manner to give a compound of general formula (I), wherein one of R_2 and R_3 is a hydroxy group and the other is a hydrogen atom, and then if desired reacting the compound of general formula (I) or (II) wherein R is a hydrogen atom, with a base to give a compound of general formula (I) or (II) wherein R is a cation, or esterifying a compound of general formula (I) or (II) wherein R is a hydrogen atom to give a compound of general formula (I) or (II) wherein R is a C_{1-18} alkyl or haloalkyl group, or hydrolysing a compound of general formula (I) or (II) wherein R is a C_{1-18} alkyl or haloalkyl group to give a compound of general formula (I) or (II) wherein R is a hydrogen atom.

The term "in known manner", as used herein, means that the method in question is in actual use or described in the literature on the subject.

Compounds of formula (IV) wherein A is $-\text{C}=\text{CCl}-$ can be converted in known manner into compounds of formula (IV) wherein A is $-\text{C}\equiv\text{C}-$. The conversion may be performed, for example, by using an excess of tert-BuOK (e.g. 2.1 to 3 moles) in a suitable organic solvent, for example dimethyl sulphoxide. Compounds wherein R is a hydrogen atom can be esterified or reacted with a pharmaceutical acceptable base, according to the usual methods of organic chemistry, to give compounds wherein R is a C_{1-18} alkyl or haloalkyl group or a pharmaceutically acceptable cation.

Examples of pharmaceutical acceptable cations are metallic cations, such as sodium, potassium, calcium and aluminium, or organic amine cations such as tri-alkylamines.

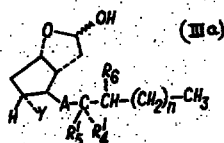
Compounds of formula (I) wherein one of R_2 and R_3 is a hydrogen atom and the other is a hydroxy group, and wherein R is a C_{1-18} alkyl or haloalkyl group, can be hydrolysed to give compounds of formula (I) wherein R_2 and R_3 have the same meanings and R is a hydrogen atom. The reaction can be performed according to the usual methods of organic chemistry, as is known to those skilled in the art.

Compounds of formula (I), wherein R_2 and R_3 together form an oxo group and wherein R is a C_{1-18} alkyl group, and compounds of formula (II), wherein R is a C_{1-18} alkyl group, can be enzymatically hydrolysed to give compounds of formula (I) wherein R_2 and R_3 together form an oxo group and wherein R is a hydrogen atom or, respectively, to give compounds of formula (II) wherein R is a hydrogen atom, for example by using a yeast esterase.

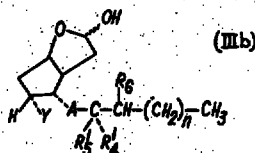
In the compounds of formulae (IV) to (VII), which may be either optically active or racemic compounds, the chains attached to the carbon atoms in the 8-position and in the 12-position, respectively, are always in the *trans*-configuration. As stated above, the starting material of formula (III) may be used either an optically active lactol or a racemic mixture thereof.

In the lactol of formula (III), the two bonds of the lactol ring indicated by the wavy line attachment (—) are in the *cis*-configuration, i.e. they are both below the plane of the cyclopentane ring or both above the plane of the cyclopentane ring, while, as stated above, the side chain is in the *trans*-configuration with respect to the lactol ring, i.e. it is below the plane of the cyclopentane ring when the lactol ring is above the plane of the cyclopentane ring, and *vice versa*. The lactol hydroxy group may be either in the α -configuration, i.e. below the plane of the lactol ring, or in the β -configuration, i.e. above the plane of the lactol ring.

The starting material may therefore be either a compound of formula



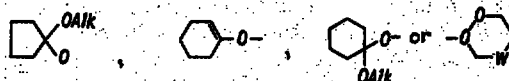
or a compound of formula



or a racemate mixture thereof.

When the compound (IIIa) is used as starting material, a compound (IV) wherein R_2 is a hydrogen atom and R_3 is a hydroxy group is obtained. When the compound (IIIb) is used as starting material, a compound (IV) wherein R_2 is a hydroxy group and R_3 is a hydrogen atom is obtained.

The known protecting groups (i.e. ether groups) should be convertible to hydroxy groups under mild reaction conditions, e.g. acid hydrolysis. Examples are 1-alkoxy-cycloalkyloxy groups, 2-oxa-cycloalkyl groups whose cycloalkyl moiety optionally contains a further ring oxygen atom, 1-alkoxy-alkyloxy groups, enol ether groups and silyl ether groups. The preferred groups are $(\text{CH}_3)_3\text{SiO}-$,



wherein W is —O— or —CH₂—, and Alk is a lower alkyl group. The Wittig reaction is suitably carried out using at least one mole, preferably 2—10 moles, of the Wittig reagent per mole of lactol.

The reaction is generally performed in an organic solvent, for example diethyl ether, hexane, dimethyl sulphoxide, tetrahydrofuran, dimethylformamide or hexamethylphosphoramide, in presence of a base, preferably sodium hydride and potassium tert-butoxide at 0°C to the reflux temperature of the reaction mixture, preferably at room temperature or below. The reaction can take a few minutes to several days depending on the temperature and concentration of the reaction mixture and the specific Wittig reagent used.

The term "Wittig reagent" includes compounds of general formula



wherein R₂ is aryl or alkyl, Hal is bromine or chlorine and R and R₁ are as defined above. When R₂ is alkyl it is suitably ethyl. The preparation of these reagents is discussed in detail by Tripett, Quart. Rev., 1963, XVII, No. 4, 406.

According to the reaction conditions used, it is possible to obtain, starting from a compound of general formula (III) wherein A is —C=CCl—, either a compound of formula (IV) wherein A is —C≡C—, or a compound of formula (IV) wherein A is —C=CCl—. The compound of formula (IV) wherein A is —C=CCl— may be, in fact, obtained as the only product by using, for example, 1.5 to 2.5 moles of Wittig reagent per mole of the compound of formula (III) and by using a reaction time of 10 to 30 minutes.

The compound of formula (IV) wherein A is —C≡C— may, on the other hand, be obtained as the only product, by using for example, 1.5 to 2.5 moles of Wittig reagent per mole of compound (III) and by using a reaction time of 2 to 10 hours. Alternatively, the compound of formula (IV) wherein A is —C≡C— may be obtained by using a reaction time of about 30 minutes and at least 5 moles of Wittig reagent per mole of compound (III).

Preferably, in the starting material of formula (III), A is —C=CCl—.

The deetherification of the compound of formula (IV) is performed under conditions of mild acid hydrolysis, for example with mono- or poly-carboxy acids e.g. formic, acetic, oxalic, citric and tartaric acid, and in a solvent, for example water, acetone, tetrahydrofuran, 1,2-dimethoxyethane and lower aliphatic alcohols. Preferably, 0.1N to 0.25N polycarboxylic acid (e.g. oxalic or citric acid) is used in the presence of a convenient low boiling co-solvent which is miscible with water and which can be easily removed *in vacuo* at the end of the reaction.

The oxidation of the 9-hydroxy group to yield an oxo group may be carried out with, for example, Jones reagent. As stated above, the deetherification of the compound of general formula (V) may give, according to the reaction conditions used, either a compound of general formula (I) wherein R₂ and R₃ together form an oxo group or a compound of general formula (II).

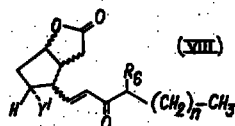
The compound of formula (I), wherein R₂ and R₃ together form an oxo group, may be obtained, as the only product, by operating at 25° to 40°C, while operating at higher temperatures, for example at the reflux temperature for about 3 hours, gives the compound of formula (II) as the only product. The reduction of the oxo group in the 9-position of the compound of formula (V) to give a mixture of the 9α-hydroxy and 9β-hydroxy-11-ethers may be performed for example by using sodium, lithium or zinc borohydride. This reduction is performed in order to obtain a compound of formula (I) wherein R₂ is a hydrogen atom and R₃ is a hydroxy group when the starting material is a lactol of formula (IIIb) and in order to obtain a compound of formula (I) wherein R₂ is a hydroxy group and R₃ is a hydrogen atom when the starting material is a lactol of formula (IIIa).

The separation of the 9α-hydroxy and 9β-hydroxy-11,15-bis-ethers from each other and from the free 11,15-diols may be carried out for example by chromatographic techniques, preferably column chromatography.

The subsequent deetherification may be performed as described above under conditions of mild acid hydrolysis, for example with oxalic acid in acetone.

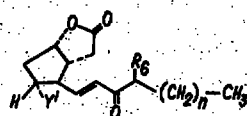
The compounds of general formula (III) may be prepared by means of a multi-

step process using as starting material an optically active lactone or racemic mixture thereof, of general formula (VIII)

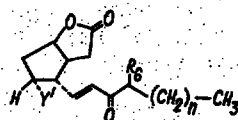


wherein R_6 and n are as defined above and Y' is a hydroxy group or an aliphatic, aromatic or cycloaliphatic carboxylic acyloxy group or a known protecting group bound to the cyclopentane ring by an ethereal oxygen atom and wherein the lactone ring is in the *trans*-configuration in respect of the oxo-aliphatic side chain.

The lactone used as starting material may therefore be either a compound of formula (VIIIa)



or a compound of formula (VIIIb)



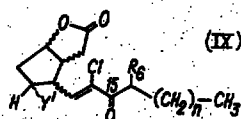
or a racemate thereof.

The compound of formula (VIIIa) may be prepared substantially as described by E. J. Corey *et al.*, *Annals of N.Y. Ac. of Sciences*, 180, 24 (1971). The compound of formula (VIIIb) may be prepared substantially as described in our Belgian Patent Specification No. 792.803.

The racemates may be prepared according to substantially the same methods.

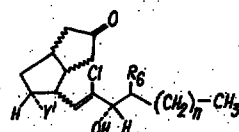
The multi-step process to obtain the compound of general formula (III) involves the following steps:

- (1) reaction of a compound of formula (VIII) with a halogenating agent to give a compound of formula (IX)

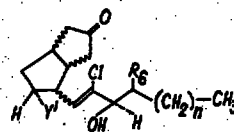


wherein Y' , R_6 and n are as defined above. A suitable halogenating agent is, for example, a sulphonyl chloride, preferably SO_2Cl_2 ; the reaction may be performed in a solvent which is preferably pyridine, acetone, acetic acid, toluene, diethyl ether, benzene, water and their mixtures;

- (2) reduction of the 15-oxo-group (prostaglandin numbering) of the compound of formula (IX) to yield a mixture of the 15(S) and 15(R) ols having the formulae



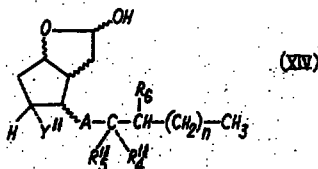
(Xa) [15(S)-ol]



(Xb) [15(R)-ol]

wherein Y' , R_6 and n are as defined above, followed by separation of the 15(S)-ol from the 15(R)-ol and subsequently, if desired, by dehydrohalogenation of the separated compounds to give a compound of formula (XIa)

- (4) reduction of the compound of general formula (XIII) to yield a lactol derivative of general formula (XIV)



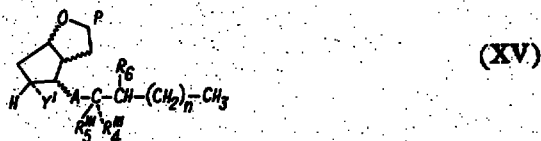
wherein A, Y'', n, R₆, R''₄ and R''₅ are as defined above. The reduction may be performed by treatment with diisobutylaluminum hydride or sodium bis-(2-methoxyethoxy) aluminum hydride in an inert solvent, for example toluene, n-heptane, n-hexane or benzene or their mixtures, at below -30°C;

- (5) optional deetherification of the compound of general formula (XIV) to give a compound having the free 11- and 15-hydroxy groups; the deetherification may be accomplished by mild acid hydrolysis, in a solvent miscible with water, with a solution of a mono- or polycarboxylic acid.

In all the compounds mentioned under (1) to (5) above which can be either optically active compounds or racemic mixtures thereof, the lactol ring or lactone ring is in the *trans*-configuration in respect of the side chain.

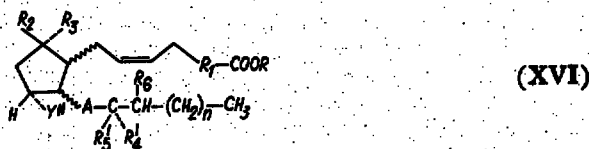
Of the above intermediates, the following are novel compounds:

- (a) the compounds of general formula (XV)

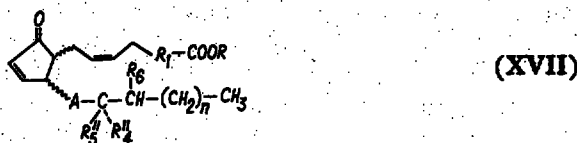


and the racemates thereof, wherein A, R₆ and n are as defined above, P is an oxo group or hydrogen atom and hydroxy group, Y' is a hydroxy group or an aliphatic, aromatic, or cycloaliphaticcarboxylicacyloxy group or a protecting group bound to the ring by an ethereal oxygen atom, said protecting group being a 1-alkoxycycloalkyloxy group, a 2-oxa-cycloalkyl group whose cycloalkyl moiety optionally contains a further ring oxygen atom, a 1-alkoxy-alkyloxy group, a silyl ether group or an enol-ether group, and one of R''₄ and R''₅ is a hydroxy group or a protecting group as defined for Y' bound to the chain by an ethereal oxygen atom and the other is a hydrogen atom or R''₄ and R''₅ together form an oxo group; these compounds are the subject of Patent Application No. 27313/75 (Serial No. 1,425,962)

- (b) the compounds of general formulae (XVI)



and (XVII)



and the racemates thereof, wherein R, R₁, R₂, R₃, A, R₆, R''₄ and R''₅ are as defined above and Y'' is a protecting group as defined for Y' bound to the ring by an ethereal oxygen atom.

In the compounds of general formula (XV) the steric configuration of the lactol or lactone ring, and of the side chain is as defined above. Analogously, in the compounds of general formulae (XVI) and (XVII), the side chains are in the *trans*-configuration, as defined above.

As indicated above, prostanic acid derivatives of formula (I) and (II) can be used in the same applications as natural prostaglandins, in comparison to which they offer however the advantage of a reduced metabolic degradation rate and furthermore of a more selective therapeutic action.

Pharmacological tests have proved, for example, that 9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid has a good spasmogenic activity *in vitro* on the uterus of rat, while tests *in vivo* in guinea-pigs have shown that 14-chloro-11 α ,15(S)-dihydroxy-9-oxo-*cis*-5,*trans*-13-prostadienoic acid and 14-chloro-11 α ,15(R)-dihydroxy-9-oxo-*cis*-5,*trans*-13-prostadienoic acid derivatives possess good anti-bronchospastic activity and are therefore useful in the treatment of asthma.

Furthermore, the compounds 9 α ,11 α ,15(R)-trihydroxy-*cis*-5-prosten-13-ynoic acid, 14-chloro-9 α ,11 α ,15(S)-trihydroxy-*cis*-5,*trans*-13-prostadienoic acid and 14-chloro-9 α ,11 α ,15R-trihydroxy-*cis*-5,*trans*-13-prostadienoic acid, for example, possess good anti-ulcer activity, as proved by tests performed *in vivo* in rats, while 11 α ,15S-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid has good hypotensive activity in rats.

The compounds of general formula (I) and (II) can be administered orally, parenterally or intravenously, by rectal suppositories or by inhalation. For example, they can be administered by intravenous infusion of a sterile isotonic saline solution at the rate of 0.01 to 10, preferably 0.05 to 1, μ g/kg of mammal body weight per minute.

The invention therefore also provides a pharmaceutical composition comprising a compound of general formula (I) and (II) and a pharmaceutically acceptable carrier or diluent.

The compositions may be prepared by conventional methods and can be, for example, in the form of tablets, capsules, pills, suppositories or bougies, or in liquid form e.g. solutions, suspensions or emulsions.

Examples of substances which can serve as carriers or diluents are water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oil, benzyl alcohol, and cholesterol.

The invention is illustrated by the following Examples, wherein the abbreviations "THP", "DIOX", "DMSO" and "DIBA" refer to 2-tetrahydropyranyl, 1,4-dioxan-2-yl, dimethyl sulphoxide and diisobutylaluminium hydride, respectively. Unless otherwise specified, the optical rotation determinations are performed at 20°C on 1% by weight solutions. Examples 1 to 23 and 25—32 illustrate the preparation of starting materials for the process of the invention.

EXAMPLE 1.

At room temperature, a solution of 0.02 mol of a 4-ester (acetate, propionate, *p*-phenylbenzoate) as well as of a 4-ether [tetrahydropyranyl ether (THP-ether), dioxanyl ether (DIOX-ether)] of 5 β -hydroxymethyl-2 α ,4 α -dihydroxycyclopentane-1 α -acetic acid γ -lactone, in either the optically active or racemic form, in 25% dimethyl sulfoxide (DMSO) in benzene (100 ml) [for example, a solution of dl-5 β -hydroxymethyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-propionate (4.56 g)] is treated with N,N'-dicyclohexylcarbodiimide (12.5 g) and pyridine trifluoroacetate (19.25 ml) in 25% DMSO in benzene [from pyridine (2 ml) and trifluoroacetic acid (1 ml) in 25 ml of 25% DMSO in benzene].

The mixture is stirred for 4 hours at room temperature and then treated with oxalic acid (5.46 g) in methanol (30 ml) to destroy the excess carbodiimide. After additional stirring for 45 minutes, the mixture is diluted with water (100 ml) and benzene (150 ml). The precipitate is filtered off and the organic layer is separated, washed with 5% sodium bicarbonate and saturated ammonium sulphate solution to neutrality, dried and evaporated to 20 ml to afford a solution (about 0.02 mol) of a 4-acyloxy (acetate, propionate, *p*-phenylbenzoate, formate) or of a 4-ether (THP-ether, DIOX-ether) of the 5 β -formyl-2 α ,4 α -dihydroxy-1 α -cyclopentane-acetic acid γ -lactone in either the optically active or the racemic form [for example a solution of about 0.02 mol of the dl-5 β -formyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-propionate].

EXAMPLE 2.

A stirred solution of dry pyridine (3.6 ml) in dry methylene chloride (90 ml), cooled at 5°, is treated with chromic anhydride (3.6 g); the stirring is continued for 15 minutes at 18—20°C to obtain a deep red solution.

A solution of 0.06 mol of a 4-ester (acetate, propionate, *p*-phenylbenzoate, formate) or of a 4-ether (THP-ether, DIOX-ether) of the 5 β -hydroxymethyl-2 α ,4 α -dihydroxycyclopentane-1 α -acetic acid γ -lactone, in either the optically active or racemic form [e.g. a solution of 2.11 g of 5 β -hydroxymethyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-*p*-phenylbenzoate; m.p. 129.5—131°, $[\alpha]_D = -87.5^\circ$ (CHCl₃)] in

dry methylene chloride is added thereto in a single portion, followed by vigorous stirring for 15 minutes. The organic layer is decanted and the inorganic materials are washed with methylene chloride and combined with the originally obtained organic layer.

After concentration of the solvent to 5—8 ml *in vacuo*, the residue is diluted with benzene (40—50 ml), treated with decolorant charcoal (1.5 g), filtered to afford, after concentration to 20 ml *in vacuo*, a benzene solution of about 0.06 mol of a 4-ester (acetate, propionate, *p*-phenylbenzoate, formate) or of a 4-ether (THP-ether, DIOX-ether) of the 5 β -formyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone, in either the optically active or the racemic form [e.g. 5 β -formyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-*p*-phenylbenzoate]. Alternatively, the benzene solution may be evaporated to dryness *in vacuo*, and the crude 5 β -formyl derivative is then dissolved in dimethoxyethane (20 ml).

EXAMPLE 3.

By utilizing one of procedures described in Examples 1 and 2, a 4-ester or a 4-ether of the 5 β -hydroxymethyl-2 α ,4 α -dihydroxy-cyclopentane-1 α -acetic acid γ -lactone (dl- or optically active compounds) are oxidized to yield the following 5 β -formyl derivatives (dl- or optically active compounds):

5 β -formyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-formate;
5 β -formyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-acetate;
5 β -formyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-DIOX-ether;
5 β -formyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-THP-ether.

EXAMPLE 4.

A stirred suspension of a 80% sodium hydride (NaH) dispersion in mineral oil (0.58 g) in dry benzene (70 ml) is slowly treated with dimethyl (2-oxoheptyl)-phosphonate (4.5 ml) in absolute benzene (15 ml).

When the evolution of hydrogen has ceased (1 hour), a solution of 0.02 mol of a 4-ester or of a 4-ether of the 5 β -formyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone [e.g. 4-propionate] in benzene, described above (see Examples 1, 2 and 3) is added with vigorous stirring to the suspension in benzene of the sodium salt of the phosphonate. After 20 minutes, 10% sodium dihydrogen phosphate solution is added, the organic layer is separated and washed twice with 10% sodium dihydrogen phosphate. Each aqueous wash solution is re-extracted with benzene and combined with the originally obtained layer. The organic phase is washed to neutrality with water, dried and evaporated to dryness to afford a 4-ester formate, acetate, propionate, *p*-phenylbenzoate or a 4-ether (DIOX-ether or THP-ether) of the 5 β -(3-oxooct-*trans*-1'-enyl)-2 α ,4 α -dihydroxy-1 α -cyclopentane-acetic acid γ -lactone, for example 5.15 g of the corresponding dl-4-propionate derivative.

EXAMPLE 5.

A stirred suspension of 80% NaH dispersion in mineral oil (198 mg) in dry 1,2-dimethoxyethane (30 ml) is slowly treated with dimethyl (2-oxooctyl)-phosphonate (1.32 ml) in dry 1,2-dimethoxyethane to obtain a finely suspension of the sodium salt of the phosphonate (1 hour). A solution of 0.006 mol of a 4-ester or 4-ether of the 5 β -formyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone [e.g. 4-*p*-phenylbenzoate] in 1,2-dimethoxyethane is then added.

After 1 hour, the reaction mixture is diluted with benzene (2 vol.), the organic layer is washed with a saturated sodium dihydrogen phosphate solution and with saturated ammonium sulphate solution until the washings are neutral and dried on sodium sulphate.

Removal of the organic solvents *in vacuo* affords a 4-ester or a 4-ether of the 5 β -(3'-oxonon-*trans*-1'-enyl)-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone [e.g. 4-*p*-phenylbenzoate].

Starting from the 4 acetate or propionate of the 5 β -formyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone, using the procedure above described, we prepared the corresponding 4-acetate or propionate of the following 5 β -(3'-oxonon-*trans*-1'-enyl)-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone (optically active or racemic).

EXAMPLE 6.

By reaction of a 4-acetate, propionate or *p*-phenylbenzoate of the 5 β -formyl-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone in benzene (Example 4) or 1,2-dimethoxy ethane (Example 5) with the sodium salt of (3-methyl-2-oxoheptyl) di-

methoxy phosphonate, we prepared the corresponding ester of the 5 β -(4'-methyl-3'-oxooct-*trans*-1'-enyl)-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone, optically active or racemic.

EXAMPLE 7.

Sulphuryl chloride (13.5 ml) is added dropwise with stirring to a solution of dl-5 β -(3'-oxooct-*trans*-1'-enyl)-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-*p*-phenylbenzoate (m.p. 120—122°; 4.8 g) in dry pyridine (95 ml), cooled at 0—5°C, the stirring is continued for 16 hours at 0—2°C.

The reaction mixture is then poured in cold 2N-H₂SO₄ (500 ml) and extracted several times with ethyl acetate (300 ml). The combined organic layers are washed with 4N-H₂SO₄, water, 5% NaHCO₃ and water again to neutrality, dried on sodium sulphate and evaporated to dryness *in vacuo*.

The crude residue (4.6 g) is then purified by filtration through a short silica gel column (40 g); elution with methylene chloride gives pure dl-5 β -(2'-chloro-3'-oxooct-*trans*-1'-enyl)-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid-4-*p*-phenylbenzoate (m.p. 149—150°; 3.2 g) also named as dl-14-chloro-9 α ,11 α -dihydroxy-15-oxo-3,4,5,6,7-pentanor-*trans*-13-prostenoic acid γ -lactone 11 α -*p*-phenylbenzoate.

EXAMPLE 8.

A mixture of isocyanuric chloride (0.9 g), acetic acid (9 ml), 5 β -(3'-oxonon-*trans*-1'-enyl)-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-acetate and acetone (90 ml) is refluxed for 2 hours, concentrated in vacuum to a small volume (25 ml) and then poured into cold 10% sodium carbonate solution. The aqueous phase is extracted repeatedly with ether and the combined organic layers are washed with water, dried on sodium sulphate and evaporated *in vacuo* to afford a crude chloro derivative, which is adsorbed on a silica gel column.

Elution with methylene chloride affords 5 β -(2'-chloro-3'-oxonon-*trans*-1-enyl)-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-acetate (1.06 g).

EXAMPLE 9.

A solution of 5 β -(3'-oxooct-*trans*-1'-enyl)-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-*p*-phenylbenzoate (m.p. 80—82°C, $[\alpha]_D = -146^\circ$ (CHCl₃); 1.2 g) in acetone (80 ml) is treated with isocyanuric chloride (0.85 g) in the presence of 10% aqueous perchloric acid (8 ml) and refluxed for 2 hours.

The reaction mixture is concentrated *in vacuo* to small volume, diluted with water and extracted repeatedly with ether.

The combined organic layers are washed with 5% NaHCO₃ and water to neutrality, dried (Na₂SO₄) and evaporated to dryness to afford 5 β -(2'-chloro-3'-oxooct-*trans*-1-enyl)-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-*p*-phenbenzoate (0.85 g), m.p. 150—151°, $[\alpha]_D = -126.5^\circ$ (CHCl₃).

EXAMPLE 10.

Sulphuryl chloride (10.5 ml) is added dropwise to a stirred solution of 5 α -(3'-oxooct-*trans*-1-enyl)-2 β ,4 α -dihydroxy-1 β -cyclopentane acetic acid γ -lactone 4-*p*-phenylbenzoate (6.52 g) in dry pyridine (80 ml), cooled at 0—2° and the stirring is continued for 12 hours at this temperature.

The reaction mixture is then poured into ice-water, acidified and repeatedly extracted with ethyl acetate. The combined organic layers are washed to neutrality, dried (Na₂SO₄) and evaporated to dryness to afford, after crystallization from methanol-ether, the 5 α -(2'-chloro-3'-oxooct-*trans*-1'-enyl)-2 β ,4 α -dihydroxy-1 β -cyclopentaneacetic acid γ -lactone-4-*p*-phenylbenzoate (5.8 g) also named as 14-chloro-9 β ,11 α -dihydroxy-15-oxo-3,4,5,6,7-pentanor-8,12-diiso-*trans*-13-prostenoic-acid γ -lactone 11 α -*p*-phenylbenzoate.

EXAMPLE 11.

Using the 5 α -(4'-methyl-3'-oxooct-*trans*-1'-enyl)-2 β ,4 α -dihydroxy-1 β -cyclopentyl-acetic acid γ -lactone 4-*p*-phenylbenzoate (1.2 g) in the procedure of Example 9, the following is prepared:

5 α -(2'-chloro-4'-methyl-3'-oxooct-*trans*-1'-enyl)-2 β ,4 α -dihydroxy-1 β -cyclopentaneacetic acid γ -lactone 4-*p*-phenylbenzoate (0.93 g) also named as 14-chloro-16-methyl-9 β ,11 α -dihydroxy-15-oxo-3,4,5,6,7-pentanor-8,12-diiso-*trans*-13-prostenoic acid γ -lactone 11 α -*p*-phenylbenzoate.

EXAMPLE 12.

A stirred solution of 5 α -(3'-oxonon-*trans*-1'-enyl)-2 β ,4 α -dihydroxy-1 β -cyclopentaneacetic acid γ -lactone 4-*p*-phenylbenzoate (0.97 g) in dry pyridine (15 ml), cooled at 0°C, is treated with sulphuryl chloride (1.6 ml) and allowed to stand at 0° for 12 hours under stirring.

The reaction mixture is then poured into ice-water, acidified with 4N-H₂SO₄ and extracted with ethyl acetate. The organic extracts are washed till the washings are neutral, dried (Na₂SO₄) and evaporated to dryness to afford, after crystallization from methanol, the 5 α -(2'-chloro-3'-oxonon-*trans*-1'-enyl)-2 β ,4 α -dihydroxy-1 β -cyclopentane-acetic acid γ -lactone 4-*p*-phenylbenzoate (0.64 g), also named as 14-chloro - 9 β ,11 α - dihydroxy - 20 - methyl - 15 - oxo - 3,4,5,6,7 - pentanor - 8,12-diiso - *trans* - 13 prostanoic acid γ - lactone 11 - *p* - phenylbenzoate.

EXAMPLE 13.

To a stirred solution of dl-5 β -(4'-methyl-3'-oxooct-*trans*-1'-enyl)-2 α ,4 α -dihydroxy-1 α -cyclopentaneacetic acid γ -lactone 4-formate (2.3 g) in dry pyridine, sulphuryl chloride (2.5 mol equiv.) is added dropwise; the reaction mixture is allowed to stand at 0° for 10 hours under stirring. It is then diluted with ice-water, acidified to pH 3 with 4N H₂SO₄ and extracted with ether-methylene chloride (4:1). The combined organic extracts are washed till the washings are neutral, dried (Na₂SO₄) and evaporated to dryness *in vacuo* to afford, after crystallization the dl-5 β -(2'-chloro-4'-methyl - 3' - oxooct - *trans* - 1' - enyl) - 2 α ,4 α - dihydroxy - 1 α - cyclopentaneacetic acid γ - lactone 4 - formate (2.05 g) also named as dl - 13t - 14 - chloro - 16 - methyl - 9 α ,11 α - dihydroxy - 15 - oxo - 3,4,5,6,7 - pentanor - *trans* - 13 - prostenoic acid γ -lactone-11 α -formate.

EXAMPLE 14.

Using the *trans*-enone-lactones prepared in Example 4, 5 and 6, in the procedure of Examples 7 and 13 the 11-esters (acetate, *p*-phenylbenzoate, formate, propionate) and 11-THP-ether and 11-DIOX-ether of the following compounds:

- 14 - chloro - 9 α ,11 α - dihydroxy - 15 - oxo - 3,4,5,6,7 - pentanor - *trans* - 13 prostenoic acid γ - lactone;
- 14 - chloro - 9 α ,11 α - dihydroxy - 20 - methyl - 15 - oxo - 3,4,5,6,7 - pentanor - *trans* - 13 - prostenoic acid γ - lactone;
- 14 - chloro - 16 - methyl - 9 α ,11 α - dihydroxy - 15 - oxo - 3,4,5,6,7 - pentanor - *trans* - 13 - prostenoic acid γ - lactone,

are prepared.

EXAMPLE 15.

dl - 14 - chloro - 9 α ,11 α - dihydroxy - 15 - oxo - 3,4,5,6,7 - pentanor - *trans* - 13 - prostenoic acid γ -lactone 11-*p*-phenylbenzoate (2.55 g) in dry 1,2-dimethoxyethane (39.5 ml) is added to a 0.065M-zinc borohydride in diethyl ether (220 ml) under vigorous stirring. The stirring is continued for 2½ hours; the excess reagent is then destroyed by cautious addition of 2N-H₂SO₄ and the organic layer is separated and washed with 2N-H₂SO₄ and water to neutrality. Each of the aqueous wash solutions is re-extracted with diethyl ether and combined with the organic phase. After drying (Na₂SO₄) and removal of the solvents *in vacuo*, the residue, consisting of a mixture of the two epimeric alcohols, 15(S) and 15(R), is absorbed on a silica (0.45 kg) column. Elution with diethyl ether gives the dl-14-chloro-9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentanor-*trans*-13-prostenoic acid γ -lactone 11-*p*-phenylbenzoate (1.6 g) as an oil and the dl-14-chloro-9 α ,11 α ,15(R)-trihydroxy-3,4,5,6,7-pentanor-*trans*-13-prostenoic acid γ -lactone 11-*p*-phenylbenzoate (0.9 g; m.p. 126—128°C).

EXAMPLE 16.

To a stirred 0.05M-zinc borohydride in ether (500 ml), a solution of 14-chloro-9 α ,11 α -dihydroxy-15-oxo-3,4,5,6,7-pentanor-*trans*-13-prostanoic acid γ -lactone 11-*p*-phenylbenzoate (4.8 g) in dry 1,2-dimethoxyethane is added. After 15 minutes, the excess reagent is destroyed by cautious addition of saturated sodium chloride solution.

The zinc hydroxyde precipitate is dissolved by adding 2N-H₂SO₄, and the organic layer is separated and washed with 2N sulphuric acid and water until the washings are neutral. Each of the aqueous wash solutions is re-extracted with diethyl ether and combined with the organic phase.

After drying (Na₂SO₄) and removal of the solvents *in vacuo*, the residue is

absorbed on silica (0.9 kg) column. By elution with diethyl ether, 14-chloro-9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentano-*trans*-13 prostenoic acid γ -lactone 11-*p*-phenylbenzoate [2.7 g; $[\alpha]_D = -79.5^\circ$ (CHCl₃)] and 14-chloro-9 α ,11 α ,15(R)-trihydroxy-3,4,5,6,7-pentano-*trans*-13 prostenoic acid γ -lactone 11-*p*-phenylbenzoate [2.2 g; m.p. 83—85°C; $[\alpha]_D = -89^\circ$ (CHCl₃)], are obtained.

EXAMPLE 17.

Using the chloro-*trans*-enone-lactones prepared in Example 14, in the procedure of Examples 15, 16, the 11-acetate, formate, propionate and *p*-phenylbenzoate and the 11-THP-ether and 11-DIOX-ether of the following compounds:

- 10 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentano - *trans* - 13 - prostenoic acid γ -lactone;
 - 14 - chloro - 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentano - *trans*-13 - prostenoic acid γ -lactone;
 - 15 14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentano - *trans*-13 - prostenoic acid γ -lactone;
 - 14 - chloro - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentano - *trans* - 13 - prostenoic acid γ -lactone;
 - 14 - chloro - 20 - methyl - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentano - *trans*-13 - prostenoic acid γ -lactone;
 - 20 14 - chloro - 16 - methyl - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentano - *trans*-13 - prostenoic acid γ -lactone
- are obtained.

EXAMPLE 18.

Sodium borohydride (40 mg) is added to a stirred solution of 14 - chloro-9 α ,11 α - dihydroxy - 15 - oxo - 3,4,5,6,7 - pentano - 8,12 - diiso - *trans* - 13 prostenoic acid γ -lactone 4 - *p* - phenylbenzoate (0.4 g) in methanol (10 ml) and methylene chloride (5 ml), cooled to 0—5°C. The stirring is continued for 30 minutes, the excess reagent is destroyed by addition of saturated NaH₂PO₄ solution (1.5 ml) and the mixture is evaporated almost to dryness *in vacuo*. After dilution with ethyl acetate, the organic layer is washed with water till the washings are neutral, dried (Na₂SO₄) and evaporated to dryness to afford a crude product which is absorbed on silica (80 g) column.

Elution with diisopropyl ether-diethyl ether (75:25) gives 14-chloro-9 β ,11 α ,15(R)-trihydroxy-3,4,5,6,7-pentano-8,12-diiso-*trans*-13-prostanoic acid γ -lactone 11-*p*-phenylbenzoate (0.15 g) and 14-chloro-9 β ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentano-8,12-diiso-*trans*-13-prostenoic acid γ -lactone 11-*p*-phenylbenzoate, also named as 5 α -[2'-chloro - 3'(S) - hydroxy - oct - *trans* - 1' - enyl] - 2 β ,4 α - dihydroxy - 1 β - cyclopentane acetic acid γ -lactone 4 - *p* - phenylbenzoate.

EXAMPLE 19.

Using the chloro - *trans* - enone - lactones prepared in Examples 11 and 12, in the procedure of Examples 15 and 16 (reduction with zinc borohydride in 1,2-dimethoxyethane - diethyl ether) and Example 18 (reduction with sodium borohydride in methanol-methylene chloride), we prepared:

- 45 14 - chloro - 20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentano - 8,12-diiso - *trans* - 13 - prostenoic acid γ -lactone 11 - *p* - phenylbenzoate;
- 14 - chloro - 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentano - 8,12-diiso - *trans* - 13 - prostenoic acid γ -lactone 11 - *p* - phenylbenzoate;
- 14 - chloro - 20 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentano - 8,12-diiso - *trans* - 13 - prostenoic acid γ -lactone - 11 - *p* - phenylbenzoate;
- 50 14 - chloro - 16 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentano - 8,12-diiso - *trans* - 13 - prostenoic acid γ -lactone 11 - *p* - phenylbenzoate.

EXAMPLE 20.

A solution of 14-chloro-9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentano-*trans*-13-prostenoic acid γ -lactone 11-*p*-phenylbenzoate (1.6 g) in methanol is treated with 7.8 ml of 20% aqueous potassium carbonate, refluxed for 1 hour, cooled at room temperature and treated with 4N-H₂SO₄ (6 ml). The mixture is stirred for 3 hours at room temperature, the precipitate salts are filtered and the filtrate is concentrated *in vacuo* to remove the methanol. The residue is diluted with ethyl acetate and the organic phase is

separated. The aqueous layer is repeatedly extracted with ethyl acetate (5 x 25 ml) and then the organic layers are combined, washed first with saturated sodium bicarbonate to remove the *p*-phenylbenzoic acid and then with saturated sodium chloride solution till the washings are neutral, dried (Na₂SO₄) and evaporated to dryness *in vacuo* to afford the 14-chloro-9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentanor-*trans*-13 prostenoic acid γ -lactone, also named as 5 β - (3' - chloro - 3(S) - hydroxy - oct - *trans* - 1' - enyl) - 2 α ,4 α - dihydroxy - 1 α - cyclopentane acetic acid γ -lactone, as an oil: $[\alpha]_D = -17.8^\circ$ (CHCl₃); 0.93 g (yield 92%). This compound, in benzene (30 ml) is refluxed with the aqueous azeotrope being removed by a water trap, and the cooled solution is treated with 2,3-dihydropyran (1.2 ml) and *p*-toluenesulphonic acid (10 mg) in benzene (3 ml).

After 6 hours at room temperature, the benzene layer is washed with 5% sodium bicarbonate and then with water till the washings are neutral, and the solvent is evaporated *in vacuo* to afford a crude product which is absorbed on a silica (30 g) column. Elution with cyclohexane/ethylacetate (80:20) affords, as an oil, pure 14-chloro-9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentanor-*trans*-13-prostenoic acid γ -lactone 9 α ,15(S)-bis-THP-ether (1.41 g); $[\alpha]_D = -58.6^\circ$ (CHCl₃), also named as 5 β - (2' - chloro - 3'(S) - hydroxy - oct - *trans* - 1' - enyl) - 2 α ,4 α - dihydroxy - 1 α - cyclopentane acetic acid γ -lactone 4 α ,3'(S) - bis - THP - ether.

EXAMPLE 21.

14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso-*trans* - 13 - prostenoic acid γ -lactone 11 - *p* - phenylbenzoate (2.4 g) in dry methanol (30 ml) is treated with anhydrous potassium carbonate (0.77 g) under stirring for 40 minutes at 10°C. The reaction mixture is neutralized with 15% aqueous acetic acid, evaporated almost to dryness and diluted with ether.

The organic layer is repeatedly washed with 5% NaHCO₃ and then with water till the washings are neutral, dried (Na₂SO₄) and the solvent is evaporated *in vacuo* to afford 14-chloro-9 β ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentanor-8,12-diiso-*trans*-13-prostenoic acid γ -lactone (1.45 g).

This compound, in dry benzene (30 ml) is treated with 1,4-diox-2-ene-(2.2 ml) and *p*-toluenesulphonic acid (9.5 mg) in benzene (4 ml).

After 6 hours at room temperature, the organic phase is washed with 5% NaHCO₃ and then with water till the washings are neutral and the solvents are evaporated to dryness *in vacuo* to afford a crude product which is absorbed on a silica (60 g) column. Elution with cyclohexane-ethyl acetate (80:20) affords pure 14-chloro-9 β ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentanor-8,12-diiso-*trans*-13-prostenoic acid γ -lactone 11 α ,15(S)-bis-DIOX-ether (2.12 g) also named as 5 α -[2' - chloro - 3(S) - hydroxy - oct-*trans* - 1' - enyl) - 2 β ,4 α - dihydroxy - 1 β - cyclopentane acetic acid γ -lactone 4 α ,3'(S) - bis - 1,4 - dioxan - 2 - yl ether.

EXAMPLE 22.

Starting from an 11-acetate, propionate, formate or *p*-phenylbenzoate of 14-chloro-9,11,15-trihydroxy-3,4,5,6,7-pentanor - *trans* - 13 - prostenoic acid γ -lactone and following the procedures described in Examples 20 and 21, we prepare the free hydroxy derivatives, the 11 α ,15-bis-THP-ether and the 11 α ,15-bis-DIOX-ether of the following compounds:

14 - chloro - 9 α ,11 α -15(S) - trihydroxy - 3,4,5,6,7 - pentanor - *trans* - 13 - prostenoic acid γ -lactone;

14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - 20 - methyl - 3,4,5,6,7 - pentanor - *trans*-13 - prostenoic acid γ -lactone;

14 - chloro - 16 - methyl - 9 α ,11 α ,15(S)-trihydroxy - 3,4,5,6,7 - pentanor - *trans* - 13 - prostenoic acid γ -lactone;

14 - chloro - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - *trans* - 13 - prostenoic acid γ -lactone;

14 - chloro - 20 - methyl - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - *trans*-13 - prostenoic acid γ -lactone;

15 - chloro - 16 - methyl - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - *trans*-13 - prostenoic acid γ -lactone;

14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - *trans*-13 - prostenoic acid γ -lactone;

14 - chloro - 20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor-8,12-diiso - *trans* - 13 - prostenoic acid γ -lactone;

- 15 - chloro - 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12-diiso - *trans* - 13 - prostenoic acid γ - lactone;
 14 - chloro - 9 β ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - *trans* - 13 - prostenoic acid γ - lactone;
 5 14 - chloro - 20 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12-diiso - *trans* - 13 - prostenoic acid γ - lactone;
 14 - chloro - 16 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12-diiso - *trans* - 13 - prostenoic acid γ - lactone.

EXAMPLE 23.

- 10 Lithium borohydride (200 mg) is added, portion wise, to a stirred solution of an 11 α -THP ether or 11 α -DIOX-ether, of 14-chloro-9 α ,11 α - dihydroxy - 15 - oxo-3,4,5,6,7 - pentanor - *trans* - 13 - prostenoic acid γ - lactone (2.2 g) in methanol (40 ml); the stirring is continued for 30 minutes. The excess reagent is then destroyed by
 15 addition of a saturated sodium dihydrogen phosphate solution and the reaction mixture is concentrated to small volume *in vacuo*, diluted with ether and washed with water to until the washings are neutral. After drying (Na₂SO₄) and removal of solvents *in vacuo*, the residue is absorbed on a silica (400 g) column and eluted with diisopropyl ether:diethyl ether (50:50) to afford 1.05 and 0.95 g, respectively, of the two epimers,
 20 15S and 15R, of 14 - chloro - 9 α ,11 α ,15 - trihydroxy - 3,4,5,6,7 - pentanor - *trans* - 13 - prostenoic acid γ - lactone 11 α - THP - ether or -DIOX - ether, which are optionally reacted with 2,3 - dihydropyran and 1,4 - diox - 2 - ene to give the corresponding 11 α ,15 - bis - THP - ether and 11 α ,15 - bis-DIOX - ether.

EXAMPLE 24.

- 25 Under a nitrogen atmosphere, a stirred solution of 14 - chloro - 9 α ,11 α ,15(S)-trihydroxy - 3,4,5,6,7 - pentanor - *trans* - 13 - prostenoic acid γ - lactone 11 α ,15S-bis - THP - ether (1.41 g) in dry toluene (43 ml), cooled at -60°, is treated over 20 minutes with 0.5 M diisobutyl aluminium hydride solution (15.8 ml). The mixture is stirred for an additional 30 minutes at -60°C and then treated with 12 ml of a 2M-isopropanol solution in toluene. After 10 minutes the mixture is warmed up to 0-2°,
 30 treated with water, sodium sulphate (2.8 g) and Celite (1.2 g; "Celite" is a Registered Trade Mark) and is then filtered. The filtrate is evaporated to dryness *in vacuo* to afford, as an oil, 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - *trans* - 13 - prostenal γ - lactone 11 α ,15(S) - bis - THP - ether (1.38 g), [α]_D = -62° (CHCl₃), also named as 5 β - (2' - chloro - 3'(S) - hydroxyoct - *trans* - 1' - enyl) - 2 α ,4 α - dihydroxy - 1 α - cyclopentaneacetaldehyde γ - lactol 4' α ,3'(S) - bis - THP-ether.

- Under a nitrogen atmosphere, freshly sublimed potassium *tert*-butoxide (1.4 g) in dry (by distillation from calcium hydride, H₂O $\leq$ 0.02%) DMSO (20 ml) is added to a stirred solution of this lactol (1.18 g) and of triphenyl (4-carboxybutyl) phosphonium bromide (2.8 g) in dry DMSO (20 ml); the mixture is cooled in a ice-water
 40 bath so that the temperature of the reaction mixture does not exceed 20°C. The deep red solution is stirred for additional 30 minutes at room temperature, diluted with ice-water (70 ml). The aqueous phase is extracted repeatedly with ether until all the triphenyl phosphoxide has been removed, and the combined organic layers are re-extracted with 5% sodium bicarbonate. The pH of the combined aqueous phases is adjusted to 4.5-4.7 with 4N-sulphuric acid, followed by extraction with diethyl ether/pentane (1:1). The organic layers are combined, washed with saturated ammonium sulphate solution, dried (Na₂SO₄) and evaporated *in vacuo* to afford the
 45 14-chloro-9 α ,11 α ,15(S)-trihydroxy-cis-5,trans-13-prostadienoic acid 11 α ,15S-bis-THP-ether (1.41 g), [α]_D = -41.7° (CHCl₃), also named as 14-chloro-PGF_{2 α} 11 α ,15S-bis-THP-ether.

EXAMPLE 25.

- Under a nitrogen atmosphere a mixture of 70% solution of sodium bis-(2-methoxyethoxy)aluminium hydride in benzene (2.24 ml) and toluene (8 ml) is added dropwise to a stirred solution of 14-chloro-9 α ,11 α ,15(R)-trihydroxy-3,4,5,6,7-pentanor-*trans*-13-prostenoic acid γ -lactone 11 α ,15(R)-bis-THP-ether (2.6 g), [α]_D = +56° (CHCl₃) in dry toluene (60 ml), cooled at -50° to -55°C. The stirring is continued for three hours; the excess reagent is then destroyed by cautious addition of 5% acetone solution in toluene.

- 60 After ten minutes the mixture is warmed up to 0-2°C, treated with a saturated sodium dihydrogen phosphonate solution (3 ml) and the crystalline inorganic precipitate is filtered.

The filtrate is evaporated to dryness *in vacuo* to give 14-chloro-9 α ,11 α ,15(R)-trihydroxy-3,4,5,6,7-pentanor-*trans*-13-prostenal γ -lactol 11 α ,15(R)-bis-THP-ether (2.55 g) $[\alpha]_D^{25} = +32.4^\circ$ (CHCl₃), as an oil.

EXAMPLE 26.

Using the lactone 11,15-bis-ethers prepared in Example 22, in the procedure of Examples 24 (diisobutyl aluminium hydride reduction) and 25 [sodium bis-(2-methoxy ethoxy) aluminium hydride reduction], we prepared the 11,15 bis-THP-ether and bis-DIOX-ether of the following lactol compounds:

- | | | |
|----|---|----|
| 10 | 14-chloro-9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentanor- <i>trans</i> -13-prostenal γ -lactol; | |
| | 14 - chloro - 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - <i>trans</i> -13 - prostenal γ - lactol; | 10 |
| | 14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - <i>trans</i> -13 - prostenal γ - lactol; | |
| 15 | 14 - chloro - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - <i>trans</i> - 13 - prostenal γ - lactol; | 15 |
| | 14 - chloro - 20 - methyl - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - <i>trans</i> -13-prostenal γ - lactol; | |
| | 14 - chloro - 16 - methyl - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - <i>trans</i> -13 - prostenal γ - lactol; | |
| 20 | 14 - chloro - 9 β ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - <i>trans</i> -13 - prostenal γ - lactol; | 20 |
| | 14 - chloro - 20 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12-diiso - <i>trans</i> - 13 - prostenal γ - lactol; | |
| 25 | 14 - chloro - 16 - methyl - 9 β ,11 α ,15R - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - <i>trans</i> - 13 - prostenal γ - lactol; | 25 |
| | 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - <i>trans</i> -13 - prostenal γ - lactol; | |
| | 14 - chloro - 20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12-diiso - <i>trans</i> - 13 - prostenal γ - lactol; | |
| 30 | 14 - chloro - 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12-diiso - <i>trans</i> - 13 - prostenal γ - lactol. | 30 |

EXAMPLE 27.

7.2% diisobutyl aluminium hydride solution in toluene (16 ml) is added over 15 minutes to a stirred solution of 14-chloro-9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentanor-*trans*-13-prostenoic acid γ -lactone 11-*p*-phenylbenzoate (1.15 g) in dry toluene, cooled at -60° and the stirring is continued for 30 minutes. The reaction mixture is then treated with 2N-isopropanol solution in toluene and after 10 minutes is warmed up to $0-2^\circ$, treated with water (1 ml), anhydrous sodium sulphate (2 g) and Celite (2.5 g) and is then filtered.

The filtrate is evaporated to dryness *in vacuo* to afford a crude product which is absorbed on silica (30 g) column. Elution with cyclohexane-ethyl acetate 4:6 gives the 14-chloro-9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentanor-*trans*-13 prostenal γ -lactol.

Starting from an 11-ester of a 14-chloro-9 α ,11 α ,15-trihydroxy-3,4,5,6,7-pentanor-*trans*-13-prostenoic acid γ -lactone, in similar way by reduction with diisobutylaluminium hydride we prepared the following compounds:

- | | | |
|----|---|----|
| | 14-chloro-9 α ,11 α ,15(R)-trihydroxy-3,4,5,6,7-pentanor- <i>trans</i> -13-prostenal γ -lactol; | |
| | 14-chloro-16-methyl-9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentanor- <i>trans</i> -13-prostenal γ -lactol; | |
| 50 | 14 - chloro - 16 - methyl - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - <i>trans</i> -13 - prostenal γ - lactol; | 50 |
| | 14 - chloro - 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - <i>trans</i> -13 - prostenal γ - lactol; | |
| | 14 - chloro - 20 - methyl - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - <i>trans</i> -13 - prostenal γ - lactol; | |
| 55 | 14 - chloro - 9 β ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - <i>trans</i> -13 - prostenal γ - lactol; | 55 |
| | 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - <i>trans</i> -13 - prostenal γ - lactol; | |
| 60 | 14 - chloro - 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - 8,12-diiso - <i>trans</i> - 13 prostenal γ - lactol; | 60 |

- 14 - chloro - 16 - methyl - $9\beta,11\alpha,15(R)$ - trihydroxy - 3,4,5,6,7 - pentanor - 8,12-diiso - *trans* - 13 - prostenal γ - lactol;
 14 - chloro - 20 - methyl - $9\beta,11\alpha,15(S)$ - trihydroxy - 3,4,5,6,7 - pentanor - 8,12-diiso - *trans* - 13 - prostenal γ - lactol;
 5 14 - chloro - 20 - methyl - $9\beta,11\alpha,15(R)$ - trihydroxy - 3,4,5,6,7 - pentanor - 8,12-diiso - *trans* - 13 prostenal γ - lactol.

EXAMPLE 28.

10 Freshly sublimed potassium *tert*-butoxide (1.3 equiv., 0.27 g) is added to a stirred solution of *dl*-14-chloro- $9\alpha,11\alpha,15(R)$ -trihydroxy-3,4,5,6,7-pentanor-*trans*-13-prostenoic acid γ - lactone 11,15 - bis - THP - ether (0.85 g) in DMSO (5 ml). After 6 hours at room temperature, the reaction mixture is diluted with water, acidified to pH 4 and extracted with diethyl ether.

15 The organic layer is washed with water until the washings are neutral, dried (Na_2SO_4) and after removal of solvent *in vacuo* the residue is absorbed on silica gel column. Elution with cyclohexane-ether (1:1) affords pure *dl*- $9\alpha,11\alpha,15(R)$ -trihydroxy-3,4,5,6,7 - pentanor - 13 - prostynoic acid γ - lactone - 11,15 - bis - THP - ether (0.62 g).

20 Starting with the chloro - lactone 11,15 - bis - ethers prepared in Example 22, and following the same procedure, we prepared the 11,15 - bis - THP - ether or bis-DIOX - ether of the following compound, as the *dl* - mixture and as an optically active compound:

- 25 $9\alpha,11\alpha,15(S)$ - trihydroxy - 3,4,5,6,7 - pentanor - 13 - prostynoic acid γ - lactone;
 16 - methyl - $9\alpha,11\alpha,15(S)$ - trihydroxy - 3,4,5,6,7 - pentanor - 13 - prostynoic acid γ - lactone;
 25 $9\alpha,11\alpha,15(R)$ - trihydroxy - 3,4,5,6,7 - pentanor - 13 - prostynoic acid γ - lactone;
 20 - methyl - $9\alpha,11\alpha,15(R)$ - trihydroxy - 3,4,5,6,7 - pentanor - 13 prostynoic acid γ - lactone;
 16 - methyl - $9\alpha,11\alpha,15(R)$ - trihydroxy - 3,4,5,6,7 - pentanor - 13 - prostynoic acid γ - lactone;
 30 $9\beta,11\alpha,15(R)$ - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - 13 - prostynoic acid γ - lactone;
 20 - methyl - $9\beta,11\alpha,15(R)$ - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - 13-prostynoic acid γ - lactone;
 16 - methyl - $9\beta,11\alpha,15(R)$ - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - 13-prostynoic acid γ - lactone;
 35 $9\beta,11\alpha,15(S)$ - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - 13 - prostynoic acid γ - lactone;
 20 - methyl - $9\beta,11\alpha,15(S)$ - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - 13-prostynoic acid γ - lactone;
 40 16 - methyl - $9\beta,11\alpha,15(S)$ - trihydroxy - 3,4,5,6,7 - pentanor - 8,12 - diiso - 13-prostynoic acid γ - lactone.

EXAMPLE 29.

45 A mixture of 14 - chloro - $9\alpha,11\alpha,15(S)$ - trihydroxy - 3,4,5,6,7 - pentanor - *trans*-13 - prostenoic acid γ - lactone 11,15S - bis - DIOX - ether (3.2 g) and 1.5 - diazabicyclo - [4.3.0] - non - 5 - ene (1.3 equiv.) in benzene is heated at 50° for 6 hours and filtered. After concentration to small volume, the reaction mixture is absorbed on a neutral alumina (15 g) column and eluted with benzene to afford $9\alpha,11\alpha,15(S)$ - trihydroxy - 3,4,5,6,7 - pentanor - 13 - prostynoic acid γ - lactone - 11,15S - bis-DIOX - ether (1.6 g).

EXAMPLE 30.

50 The 14 - chloro - $9\alpha,11\alpha,15(R)$ - trihydroxy - 3,4,5,6,7 - pentanor - *trans* - 13 prostenoic acid γ - lactone 11 α - *p* - phenylbenzoate (2.1 g) is converted by reaction with 2,3-dihydropyran in benzene in the presence of *p*-toluenesulphonic acid into the 15R-THP-ether (2.48 g). This compound is reacted with 1.3 equiv. (0.6 g) of 1.5-diazabicyclo-[4.3.0]-non-5-ene in benzene for 16 hours at room temperature. The reaction mixture is then filtered, concentrated to small volume to afford after filtration of neutral aluminium oxide $9\alpha,11\alpha,15(R)$ -trihydroxy-3,4,5,6,7-pentanor-13-prostynoic acid γ -lactone 11 α -*p*-phenylbenzoate 15R-THP-ether (2.38 g).

60 A solution of this product in acetone is treated with 0.5N-oxalic acid solution (50 ml) at reflux temperature for 30 minutes, to afford after concentration, dilution

with water and filtration, the 9 α ,11 α ,15(R)-trihydroxy-3,4,5,6,7-pentano-13-prostynoic acid γ -lactone 11 α -*p*-phenylbenzoate (1.72 g).

A solution of this product in acetone (30 ml) is treated with Jones reagent (3.5 ml) at -10°C or 5 minutes, the reaction mixture is diluted with benzene (150 ml) and the organic layer is washed till neutral with a saturated ammonium sulphate solution. Evaporation of solvents gives 9 α ,11 α - dihydroxy - 15 - oxo - 3,4,5,6,7 - pentano - 13 - prostynoic acid γ - lactone 11 α - *p* - phenylbenzoate (1.25 g).

To a stirred solution of 0.065M zinc borohydride in ether (220 ml), a solution of the above compound (2.6 g) in dry 1,2-dimethoxyethane is added. After 2½ hours, the excess reagent is destroyed with 2N-H₂SO₄, the organic layer is separated, washed till the washings are neutral with saturated (NH₄)₂SO₄ solution, dried (Na₂SO₄) and evaporated to dryness to give a mixture of two 15(S) and 15(R)-epimeric alcohols, which mixture is absorbed on silica (130 g) column.

Following elution with isopropyl ether affords 9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentano-13-prost-13-yn-6-oi acid- γ -lactone 11 α -*p*-phenylbenzoate (1.02 g) and its 15(R)-epimer (0.82 g).

The 15(S)-epimer (1.43 g) is then treated in methanol (25 ml) with 20% aqueous potassium carbonate solution (6 ml) at reflux temperature for 1 hour. The reaction mixture is cooled, acidified and stored for 2 hours at room temperature.

The precipitate salts are filtered, the filtrate is concentrated *in vacuo* to small volume to afford after extraction with diethyl ether-methylene chloride (4:1) 9 α ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentano - 13 - prostynoic acid γ - lactone (0.81 g). Following reaction in benzene of this product with 2,3-dihydropyran in the presence of catalytical amounts of *p*-toluenesulphonic acid affords the 9 α ,11 α ,15(S)-trihydroxy - 3,4,5,6,7 - pentano - 13 - prostynoic acid γ - lactone 11 α ,15S - bis - THP-ether (1.32 g).

EXAMPLE 31.

A solution of 9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentano-13-prostynoic acid γ -lactone 11 α ,15(S)-bis-THP-ether (1.32 g) in toluene is reacted with a 0.5M solution of diisobutyl aluminium hydride in toluene (10 ml) at -60° for 30 minutes. The excess reagent is destroyed by addition of a 2M solution of isopropanol in toluene (6 ml). After 15 minutes, the reaction mixture is warmed to 0°, treated with water (1.2 g), sodium sulphate (2.8 g), Celite (2.8 g) and filtered.

The filtrate is evaporated to dryness *in vacuo* to give 9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7 - pentano - 13 - prostynal γ - lactol 11 α ,15S - bis - THP - ether (1.25 g).

EXAMPLE 32.

Using the 9,11,15-trihydroxy-3,4,5,6,7-pentano-13-prostynoic acid γ -lactone 11 α ,15-bis-ethers prepared in the Example 28 in the procedure of the Examples 24, 31 (reduction with diisobutylaluminium hydride) and 25 [reduction with sodium-bis-(2-methoxyethoxy) aluminium hydride], we prepared the 11 α ,15--THP-ether and 11 α ,15-bis-DIOX-ether of the following lactol derivatives:

- 9 α ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentano - 13 - prostynal γ - lactol;
- 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentano - 13 prostyn - 6 - al γ - lactol;
- 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentano - 13 - prostynal γ - lactol;
- 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentano - 13 - prostynal γ - lactol;
- 20 - methyl - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentano - 13 prostynal γ - lactol;
- 16 - methyl - 9 α ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentano - 13 - prostynal γ - lactol;
- 9 β ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentano - 8,12 - diiso - 13 - prostynal γ - lactol;
- 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentano - 8,12 - diiso - 13 - prostynal γ - lactol;
- 20 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentano - 8,12 - diiso - 13 - prostynal γ - lactol;
- 20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentano - 8,12 - diiso - 13 - prostynal γ - lactol;
- 16 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 3,4,5,6,7 - pentano - 8,12 - diiso - 13 - prostynal γ - lactol;
- 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentano - 8,12 - diiso - 13 - prostynal γ - lactol.

EXAMPLE 33.

Under a nitrogen atmosphere, a suspension of 80% sodium hydride (0.87 g) in dry dimethyl sulphoxide (23 ml) is heated with stirring at 60° until the evolution of hydrogen ceases (3 hours).

The stirred mixture of methyl sulphinylcarbanide cooled to 5–10° is treated with triphenyl(4-carboxybutyl)-phosphonium bromide (5.78 g) in dry DMSO (23 ml); the deep orange-red solution of the ylide is then treated with a solution of 14-chloro-9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentanor-*trans*-13-prosteneal γ -lactol 11,15-bis-THP-ether (1.35 g) in dry DMSO (10 ml). The mixture is stirred for an additional 45 minutes and then diluted with ice-water (50 ml) and extracted repeatedly with ether until all the triphenylphosphoxide has been removed and the combined organic layers are re-extracted with 5% sodium bicarbonate. The pH of the combined aqueous phases is adjusted to 4.5–4.7 with 4N-sulphuric acid, followed by extraction with diethyl ether-pentane (1:1).

The organic layers are combined, washed with saturated (NH₄)₂SO₄ solution, dried (Na₂SO₄) and evaporated to dryness to afford a mixture (80:20) of 14-chloro-9 α ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13 prostadienoic acid 11 α ,15S-bis-THP-ether, also named as 14-chloro-PGF_{2 α} 11,15-bis-THP-ether and of 9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prostene-13-ynoic acid 11,15-bis-THP-ether also named as 13,14-dehydro-PGF_{2 α} 11,15-bis-THP-ether.

This mixture is absorbed on acid-washed silica (180 g) column and eluted with cyclohexane-ethyl acetate, to obtain in the following order: 13,14-dehydro-PGF_{2 α} bis-THP-ether (0.21 g), [α]_D = –18° (CHCl₃) and 14-chloro-PGF_{2 α} bis-THP-ether (0.98 g), [α]_D = –41.7° (CHCl₃).

EXAMPLE 34.

Under a nitrogen atmosphere, to a stirred solution of 14-chloro-9 α ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13-prostadienoic acid 11,15-bis-THP-ether in dry DMSO (3 ml) is added a solution of potassium *tert*-butoxide (0.075 g) in dry DMSO (6 ml) and the stirring is continued for 2 hours.

The reaction mixture is then diluted with water (10 ml), acidified to pH 4.5 and extracted repeatedly with diethyl ether. The combined organic layers are washed with saturated ammonium sulphate solution till the washings are neutral, dried and evaporated to dryness *in vacuo* to afford 9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prostene-13-ynoic acid 11,15-bis-THP-ether (0.118 g), [α]_D = –18° (CHCl₃).

EXAMPLE 35.

At 5–10°C, a solution of triphenyl(4-carboxybutyl)-phosphonium bromide (2.56 g) in dry DMSO (10 ml) is added to a suspension of methyl sulphinylcarbanide obtained starting from 80% NaH (0.35 g) and dry DMSO (10 ml) using the procedure described in Example 33. The deep orange-red solution of the ylid is then treated with 14-chloro-9 β ,11 α ,15(R)-trihydroxy-3,4,5,6,7-pentanor-8,12-diiso-*trans*-13-prosteneal γ -lactol 11,15-bis-DIOX-ether (0.6 g) dissolved in dry DMSO (13 ml). The mixture is stirred for 12 minutes and then rapidly diluted with water (33 ml).

After extraction with diethyl ether until all the triphenyl phosphoxide has been removed, the combined organic layers are re-extracted with 5% sodium bicarbonate. The pH of the combined aqueous phases is adjusted to pH 4.5–4.7 with 2N-H₂SO₄, followed by extraction with diethyl ether-pentane (1:1).

These organic layers are combined, washed until neutral, dried (Na₂SO₄) and evaporated to dryness to give 14-chloro-9 β ,11 α ,15(R)-trihydroxy-8,12-diiso-*cis*-5, *trans*-13 prosta, dienoic acid 11 α ,15(R)-bis-DIOX-ether (0.55 g), also named as 14-chloro-15-epi-8,12-diiso-PGF_{2 β} 11,15R-bis-DIOX-ether.

EXAMPLE 36.

Under a nitrogen atmosphere, a stirred suspension of 80% sodium hydride dispersion in mineral oil (1.08 g) in dry DMSO is heated at 60° to give a solution of methyl sulphinylcarbanide in DMSO (about 3 hours).

This stirred mixture, cooled to 5–10°, is treated with triphenyl(4-carboxybutyl)-phosphonium bromide (7.98 g) in DMSO (24 ml); the deep orange-red solution of the ylid is then treated with 14-chloro-9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7-pentanor-*trans*-13 prosteneal γ -lactol (0.45 g) in DMSO (20 ml).

After 8 minutes, 26 ml of the red solution are withdrawn from the reaction mixture, diluted with ice-water (26 ml) and extracted repeatedly with diethyl ether until all the triphenyl phosphoxide has been removed. The combined organic layers are

re-extracted with 5% NaHCO₃; then the pH of the combined aqueous phases is adjusted to pH 4.5—4.7 with 2N-H₂SO₄, followed by extraction with diethyl ether.

These combined organic layers are washed with 10% ammonium sulphate, dried (Na₂SO₄) and evaporated to dryness *in vacuo* to afford a crude product (0.15 g) which is absorbed on an acid-washed silica (15 g) column.

Elution with cyclohexane-ethyl acetate (1:1) and with ethyl acetate gives pure 14-chloro-9 α ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13 prostadienoic acid (0.131 g), [α]_D = -6.9°C (ethanol) also named as 14-chloro-PGF_{2a}. After 12 hours, the remaining portion of the reaction mixture (two-thirds of the initial mixture) is diluted with water (50 ml).

The aqueous phase is extracted with ether to remove the triphenyl phosphoxide and after re-extraction with 0.5N-NaOH, the organic layer is discarded.

The combined alkaline extracts are acidified with 2N-H₂SO₄ to pH 4, and extracted with diethyl ether, the combined organic layers are washed until neutral, dried and evaporated to dryness *in vacuo*.

Absorption of the residue (310 ml) on acid washed-silica (30 g) column, followed by elution with ethyl acetate affords 9 α ,11 α ,15(S)-trihydroxy-*cis*-5 prosten-13-ynoic acid (0.22 g), [α]_D = +28° (ethanol), also named as 13,14-dehydro-PGF_{2a}.

Using the same procedure, the 14-chloro-lactol derivatives of Example 25 are reacted with the Wittig reagent derived from (4-carboxybutyl)-triphenylphosphonium bromide to afford the following compounds:

15 - chloro - 9 α ,11 α ,15(R) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic acid;

14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5, *trans* - 13 prostadienoic acid;

14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - 20 - methyl - *cis* - 5, *trans* - 13 - prostadienoic acid;

14 - chloro - 20 - methyl - 9 α ,11 α ,15(R) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic acid;

14 - chloro - 16 - methyl - 9 α ,11 α ,15(R) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic acid;

14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;

14 - chloro - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;

14 - chloro - 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;

14 - chloro - 16 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;

14 - chloro - 20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;

14 - chloro - 20 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;

9 α ,11 α ,15(R) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid;

9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5 - prosten - 13 - ynoic acid;

16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid;

16 - methyl - 9 α ,11 α ,15(R) - trihydroxy - *cis* - 5 - prost - 5 - en - 13 - ynoic acid;

20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid;

20 - methyl - 9 α ,11 α ,15(R) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid;

9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - *cis* - 5 - prosten - 13 - ynoic acid;

16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5 - prosten - 13 - ynoic acid;

16 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - *cis* - 5 - prosten - 13 - ynoic acid;

20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5 - prosten - 13 - ynoic acid;

20 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - *cis* - 5 - prosten - 13 - ynoic acid.

EXAMPLE 37.

At -60°C reduction of 9 α ,11 α ,15(R)-trihydroxy-3,4,5,6,7-pentanor-13-prostyn- α -lactone 11 α -p-phenylbenzoate (0.82 g) with sodium-bis-(2-methoxyethoxy)-aluminum hydride (3.5 equiv.) affords, after chromatographic purification on silica gel column, the 9 α ,11 α ,15R - trihydroxy - 3,4,5,6,7 - pentanor - 13 - prost - yn - 6 - α - lactol (0.31 g).

Following the procedure described in Example 36, a solution of this compound in DMSO (10 ml), is treated with the ylid solution obtained starting from 5.32 g of (4-carboxybutyl)-triphenylphosphonium bromide to obtain after chromatographic purification on acid-washed silica (34 g) gel (cyclohexane-ethyl acetate 30:70), the 9 α ,11 α ,15(R) - trihydroxy - *cis* - 5 - prosten - 13 - yn - oic acid, [α]_D = +31.5° (ethanol), as a colourless oil (0.27 g).

EXAMPLE 38.

Under a nitrogen atmosphere, to a stirred mixture of [β - (carboxymethoxy)ethyl]-triphenylphosphonium bromide (6.15 g) and 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - 3,4,5,6,7 - pentanor - *trans* - 13 - prosten - 6 - al - γ - lactol 11 α ,15S - bis - DIOX-ether (2.6 g) in dry DMSO (32 ml) cooled at 12–15°, is added a solution of freshly sublimed potassium *tert*-butoxide (3.05 g) in dry DMSO (42 ml). After an additional stirring for 10 minutes, the reaction mixture is cooled and diluted with water (75 ml). The aqueous phase is extracted repeatedly with diethyl ether to remove the triphenylphosphoxide.

The combined organic layers, after re-extraction with 5% NaHCO₃ solution, are discarded; then the pH of the combined aqueous phases is adjusted to pH 4.5–4.7 with an acid followed by extraction with pentane-diethyl ether (1:1). The combined organic extracts are washed with saturated ammonium sulphate solution until the washings are neutral, dried (Na₂SO₄) and evaporated to dryness *in vacuo* to afford the 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - 3 - oxa - *cis* - 5, *trans* - 13 - prostadienoic acid 11 α ,15(S) - bis - DIOX - ether also named as 14 - chloro - 3 - oxa - PGF_{2a} 11 α ,15(S) - bis - DIOX - ether.

Using this procedure, the 11,15-bis-DIOX-ethers and the 11,15-bis-THP-ethers of the 14-chloro lactols of Example 25, are reacted with the following triphenylphosphonium bromide derivatives:

- [β - (carboxymethoxy)ethyl]triphenylphosphonium bromide;
- [β - (carboxymethylthio)ethyl]triphenylphosphonium bromide;
- (4 - carboxybut - *trans* - 3 - enyl)triphenylphosphonium bromide;
- (4 - carboxybut - *cis* - 3 - enyl)triphenylphosphonium bromide;
- (4 - carboxybut - 3 - ynyl)triphenylphosphonium bromide;

to afford the following 11 α ,15-DIOX or 11 α ,15-THP-prostadienoic acids, as well as the optically active compounds and the *dl*-mixtures:

- 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - 3 - oxa - *cis* - 5, *trans* - 13 - prostadienoic acid;
- 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - 3 - thia - *cis* - 5, *trans* - 13 - prostadienoic acid;
- 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 2, *cis* - 5, *trans* - 13 - prostatrienoic acid;
- 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - *trans* - 2, *cis* - 5, *trans* - 13 - prostatrienoic acid;
- 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5, *trans* - 13 - prostadien - 2 - ynoic acid;
- 14 - chloro - 9 α ,11 α ,15(R) - trihydroxy - 3 - oxa - *cis* - 5, *trans* - 13 - prostadienoic acid;
- 14 - chloro - 9 α ,11 α ,15(R) - trihydroxy - 3 - thia - *cis* - 5, *trans* - 13 - prostadienoic acid;
- 14 - chloro - 9 α ,11 α ,15(R) - trihydroxy - *cis* - 2, *cis* - 5, *trans* - 13 - prostatrienoic acid;
- 14 - chloro - 9 α ,11 α ,15(R) - trihydroxy - *cis* - 2, *cis* - 5, *trans* - 13 prostatrienoic acid;
- 14 - chloro - 9 α ,11 α ,15(R) - trihydroxy - *cis* - 5, *trans* - 13 prostadien - 2 - ynoic acid;
- 14 - chloro - 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - 3 - oxa - *cis* - 5, *trans* - 13 - prostadienoic acid;
- 14 - chloro - 20 - methyl - 9 α ,11 α ,15(R) - trihydroxy - 3 - oxa - *cis* - 5 - *trans* - 13 - prostadienoic acid;
- 14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - 3 - oxa - *cis* - 5, *trans* - 13 - prostadienoic acid;
- 14 - chloro - 16 - methyl - 9 α ,11 α ,15(R) - trihydroxy - 3 - oxa - *cis* - 5, *trans* - 13 - prostadienoic acid;
- 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 3 - oxa - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;

- 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 3 - thia - 8,12 - diiso - cis - 5, trans - 13 - prostadienoic acid;
 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - cis - 2, cis - 5, trans - 13 - prostatrienoic acid;
 5 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - cis - 2, cis - 5, trans - 13 - prostatrienoic acid;
 14 - chloro - 9 β ,11 α ,15(R) - trihydroxy - 3 - oxa - 8,12 - diiso - cis - 5, trans - 13 - prostadienoic acid;
 10 14 - chloro - 9 β ,11 α ,15(R) - trihydroxy - 3 - thia - 8,12 - diiso - cis - 5, trans - 13 - prostadienoic acid;
 14 - chloro - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - cis - 2, cis - 5, trans - 13 - prostatrienoic acid;
 14 - chloro - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - trans - 2, cis - 5, trans - 13 - prostatrienoic acid;
 15 14 - chloro - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - cis - 2, cis - 5, trans - 13 - prost-2-yn-oic acid;
 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - cis - 2, trans - 13 prostadien-2-yn-oic acid;
 20 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 20 - methyl - 3 - oxa - 8,12 - diiso - cis - 5, trans - 13 prostadienoic acid;
 14 - chloro - 20 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 3 - oxa - 8,12 - diiso - prostadienoic acid;
 14 - chloro - 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 3 - oxa - 8,12 - diiso - cis - 5, trans - 13 - prostadienoic acid;
 25 14 - chloro - 16 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 3 - oxa - 8,12 - diiso - cis - 5, trans - 13 prostadienoic acid;
 which are optionally converted into their methyl esters and/or then deetherified.

EXAMPLE 39.

Under a nitrogen atmosphere, to a stirred mixture of 9 α ,11 α ,15(S)-trihydroxy-3,4,5,6,7 - pentanor - 13 - prostynal γ - lactol 11 α ,15(S) - bis - THP - ether (1.3 g) and of (4 - carboxybutyl)triphenylphosphonium bromide (3.08 g) in dry DMSO (16.5 ml), cooled at 15—18°C, is added potassium *tert*-butoxide (1.54 g, freshly sublimed) in dry DMSO (20 ml). After an additional stirring for 12 hours at room temperature, the reaction mixture is diluted with water (40 ml), repeatedly extracted with diethyl ether to remove the triphenyl phosphoxide.

The combined organic layers are re-extracted with 0.5N sodium hydroxide solution and discarded.

The combined aqueous phases are acidified to pH 4.5—4.7 and re-extracted with a pentane-diethyl ether mixture (1:1). These combined organic extracts are washed with a saturated ammonium sulphate solution until the washings are neutral, dried (Na₂SO₄) and evaporated to dryness *in vacuo* to give 9 α ,11 α ,15(S)-trihydroxy-cis-5-prosten - 13 - ynoic acid 11 α ,15(S) - bis - THP - ether [α]_D = -18° (1.43 g as a colourless oil) also named as 13,14 - dehydro - PGF_{2a} 11 α - 15(S) - bis - THP - ether. Following this procedure, the 11,15 - bis - THP - ethers and the 11,15 - bis - DIOX - ethers of the 13,14 - yn lactols of Examples 31 and 32 are reacted with the (4 carboxybutyl)-triphenylphosphonium bromide to afford the following bis ethers (11 α ,15-THP or 11 α ,15-DIOX)-cis-5-prosten-13-ynoic acids, as well as optically active or dl-compounds;

- 9 α ,11 α ,15(S) - trihydroxy - cis - 5 prosten - 13 - ynoic acid;
 50 9 α ,11 α ,15(R) - trihydroxy - cis - 5 - prosten - 13 - ynoic acid;
 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - cis - 5 prosten - 13 - ynoic acid;
 20 - methyl - 9 α ,11 α ,15(R) - trihydroxy - cis - 5 - prosten - 13 - ynoic acid;
 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - cis - 5 - prosten - 13 - ynoic acid;
 16 - methyl - 9 α ,11 α ,15(R) - trihydroxy - cis - 5 - prosten - 13 - ynoic acid;
 55 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - cis - 5 - prosten - 13 - ynoic acid;
 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - cis - 5 - prosten - 13 - ynoic acid;
 20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - cis - 5 - prosten - 13 - ynoic acid;
 20 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - cis - 5 - prosten - 13 - ynoic acid;
 60 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - prost - 5 - ene - 13 - ynoic acid;

16 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - *cis* - 5 - prosten - 13 - ynoic acid;

which are optionally deetherified or optionally converted into their methyl esters and then deetherified.

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EXAMPLE 40.

Using the following triphenylphosphonium bromide derivatives:

- [β -(carboxymethoxy)ethyl]-triphenylphosphonium bromide,
 [β -(carboxymethylthio)ethyl]-triphenylphosphonium bromide,
 (4-carboxybut-*trans*-3-enyl)-triphenylphosphonium bromide,
 (4-carboxybut-*cis*-3-enyl)-triphenylphosphonium bromide,
 (4-carboxybut-3-ynyl)-triphenylphosphonium bromide;

in the procedure of Example 39, gives the following bis ethers (11 α ,15-THP or 11 α ,15-DIOX)-*cis*-5-prosten-13-ynoic acids, as the optically active compounds or *dl*-mixture:

- 9 α ,11 α ,15(S) - trihydroxy - 3 - oxa - *cis* - 5 - prost - 5 - en - 13 - ynoic acid;
 9 α ,11 α ,15(S) - trihydroxy - 3 - thia - *cis* - 5 - prosten - 13 - ynoic acid;
 9 α ,11 α ,15(S) - trihydroxy - *cis* - 2, *cis* - 5 - prostadien - 13 ynoic acid;
 9 α ,11 α ,15(S) - trihydroxy - *trans* - 2, *cis* - 5 prostadien - 13 - ynoic acid;
 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 2,13 - diynoic acid;
 9 α ,11 α ,15(R) - trihydroxy - 3 - oxa - *cis* - 5 - prosten - 13 - ynoic acid;
 9 β ,11 α ,15(S) - trihydroxy - 3 - oxa - 8,12 - diiso - *cis* - 5 - prosten - 13 - ynoic acid;
 9 β ,11 α ,15(R) - trihydroxy - 3 - oxa - 8,12 - diiso - *cis* - 5 - prosten - 13 - ynoic acid;
 9 β ,11 α ,15(S) - trihydroxy - 3 - thia - 8,12 - diiso - *cis* - 5 - prosten - 13 - ynoic acid;
 which are optionally deetherified or optionally converted into their methyl esters and then deetherified.

EXAMPLE 41.

Under a nitrogen atmosphere, a mixture of 14-chloro-9 β ,11 α ,15(S)-trihydroxy-8,12-diiso-*trans*-13-prostenal γ -lactol-11,15 bis-DIOX-ether (2.6 g) and of (4-carboxybutyl)-triphenylphosphonium bromide (6.1 g) in dry DMSO (32 ml), externally cooled at 15-18°C, was treated with a solution of freshly sublimed potassium *tert*-butoxide (3.05 g) in dry DMSO (42 ml) over five minutes.

After an additional stirring for 15 minutes, the reaction mixture is diluted with water (75 ml) and worked up in usual manner (removal of triphenylphosphoxide with diethyl ether, acidification of the alkaline aqueous phases, and re-extraction with a 1:1 mixture of pentane-ether) to afford the 14-chloro-9 β ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5, *trans*-13-prostadienoic acid 11 α ,15(S) - bis - DIOX - ether (2.7 g), also named as 14 - chloro - 8,12 - diiso - PGF_{2 β} 11 α ,15(S) - bis - DIOX - ether.

Using the (4 - carboxybutyl) - triphenylphosphonium bromide to form the ylid by reaction with potassium *tert*-butoxide (Example 41) or with methyl sulphiny-carbanide (Example 35), the 11,15-bis-DIOX-ethers and the 11,15-bis-THP-ethers of the 14-chloro lactols of Example 25 are reacted to afford the following bis-11 α ,15-DIOX or 11 α ,15-THP-prostadienoic acid, as optically active or *dl*-compounds:

- 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic acid;
 14 - chloro - 9 α ,11 α ,15(R) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic acid;
 14 - chloro - 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis*-5, *trans* - 13 - prostadienoic acid;
 14 - chloro - 20 - methyl - 9 α ,11 α ,15(R) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic acid;
 14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5, *trans* 13 - prostadienoic acid;
 14 - chloro - 16 - methyl - 9 α ,11 α ,15(R) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic acid;
 14 - chloro - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;
 14 - chloro - 20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans*-13 - prostadienoic acid;
 14 - chloro - 20 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;

14 - chloro - 16 - methyl - 9 β ,11 α ,15(R) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans*-
13 - prostadienoic acid;
14 - chloro - 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans*-
13 - prostadienoic acid,
which are optionally deetherified or optically converted in their methyl esters and then
deetherified.

EXAMPLE 42.

Under nitrogen atmosphere, to a stirred mixture of *dl*-14-chloro-9 α ,11 α ,15(S)-
trihydroxy - 3,4,5,6,7 - pentanor - *trans* - 13 - prost enal γ - lactol 11 α ,15(S) - bis-
THP - ether (8.28 g) and of (4 - carboxybutyl) - triphenylphosphonium bromide
(27.6 g) in dry DMSO (120 ml) cooled at 17–20°C, is added a solution of potas-
sium *tert*-butoxide (15.68 g) in dry DMSO (180 ml).

The reaction mixture is stirred for 14 hours at room temperature, then diluted
with water (300 ml) and worked up in the usual manner to give *dl*-9 α ,11 α ,15(S)-
trihydroxy-*cis*-5-prosten-13-ynoic acid 11 α ,15-bis-THP-ether (7.95 g). This product
(1.95 g) in benzene is treated with an ethereal solution of diazomethane (1.25 equiv.)
and after 15 minutes the reaction mixture is evaporated to dryness *in vacuo* to afford
the crude methyl ester (2 g), which is dissolved in acetone (115 ml) and heated with
0.1N aqueous oxalic acid (80 ml) for 12 hours at 40°C.

After removal of the acetone *in vacuo* the aqueous phase is extracted repeatedly
with ether, the combined organic layers are washed with saturated ammonium sulphate
solution, dried (Na₂SO₄) and evaporated *in vacuo* to dryness to give crude *dl*-
9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid methyl ester (1.6 g).
This product is absorbed on a silica (30 g/g) column and subsequent elution with
cyclohexane-ethylacetate (65:35) gives pure *dl*-13,14-dehydro-PGF_{2a} methyl ester
(1.22 g, m.p. 74.5–75.5°C).

A solution of this compound (0.6 g) in methanol (76 ml)-water (8 ml) is
treated with potassium hydroxide (0.4 g) for 2 hours at room temperature, then with
saturated sodium dihydrogen phosphate solution to pH 6.4–6.8 and after removal
of methanol *in vacuo*, the reaction mixture is diluted with 0.1N aqueous oxalic acid.

Following extraction with diethyl ether and washing to neutrality with saturated
ammonium sulphate solution afford, after drying on Na₂SO₄ and removal of solvent
in vacuo, pure *dl*-9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid (0.52 g, m.p.
80–82°C).

EXAMPLE 43.

Using an excess of the ylid derived from (4-carboxybutyl)-triphenylphosphonium
bromide by reaction with freshly sublimed potassium *tert*-butoxide or with methyl
sulphinylcarbanide, the 11 α ,15-bis (11,15-THP and 11,15-DIOX) of 14-chloro-lactols
of Example 25 and before, are reacted to give the following 11 α ,15-THP or 11 α ,15-
DIOX-*cis*-5-prosten-13-ynoic acids, as well as the optically active compounds or *dl*-
mixture:

9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid;
9 α ,11 α ,15(R)-trihydroxy-*cis*-5-prosten-13-ynoic acid;
20-methyl-9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid;
20-methyl-9 α ,11 α ,15(R)-trihydroxy-*cis*-5-prosten-13-ynoic acid;
16-methyl-9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid;
16-methyl-9 α ,11 α ,15(R)-trihydroxy-*cis*-5-prosten-13-ynoic acid;
9 β ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
9 β ,11 α ,15(R)-trihydroxy-8,12-diiso-*cis*-5-prostene-13-ynoic acid;
20-methyl-9 β ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
20-methyl-9 β ,11 α ,15(R)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
16-methyl-9 β ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
16-methyl-9 β ,11 α ,15(R)-trihydroxy-8,12-diiso-prost-5-ene-13-ynoic acid;

which are optionally deetherified or optionally converted in their methyl esters and
then deetherified.

EXAMPLE 44.

Using [β -(carboxymethoxy)ethyl]triphenylphosphonium bromide in the pro-
cedure of Example 43 gives 11 α ,15-bis ethers of the following compounds:

9 α ,11 α ,15(S)-trihydroxy-3-oxa-*cis*-5-prosten-13-ynoic acid and its 15(R)-epimer;
20-methyl-9 α ,11 α ,15(S)-trihydroxy-3-oxa-*cis*-5-prosten-13-ynoic acid and its 15(R)-epimer;
9 β ,11 α ,15(S)-trihydroxy-3-oxa-8,12-diiso-*cis*-5-prosten-13-ynoic acid and its 15(R)-epimer.

Using [β -(carboxymethylthio)ethyl] triphenylphosphonium bromide in the procedure of the Example 43 gives:

9 α ,11 α ,15(S)-trihydroxy-3-thia-*cis*-5-prosten-13-ynoic acid and its 15(R)-epimer;
20-methyl-9 α ,11 α ,15(S)-trihydroxy-3-thia-*cis*-5-prosten-13-ynoic acid and its 15(R)-epimer;
9 β ,11 α ,15(S)-trihydroxy-3-thia-8,12-diiso-*cis*-5-prosten-13-ynoic acid and its 15(R)-epimer.

Using (4-carboxybut-*cis*-3-enyl)triphenylphosphonium bromide in the procedure of the Example 43 gives:

9 α ,11 α ,15(S)-trihydroxy-*cis*-2, *cis*-5-prostadien-13-ynoic acid and its 15(R)-epimer;
9 β ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-2, *cis*-5-prostadien-13-ynoic acid and its 15(R)-epimer.

Using (4-carboxybut-*trans*-3-enyl)triphenylphosphonium bromide in the procedure of the Example 43 gives:

9 α ,11 α ,15(S)-trihydroxy-*trans*-2, -*cis*-5-prostadien-13-ynoic acid and its 15(R)-epimer;
9 β ,11 α ,15(R)-trihydroxy-*trans*-2, *cis*-5-prostadien-13-ynoic acid and its 15(R)-epimer.

Using (4-carboxy-but-3-ynyl)triphenylphosphonium bromide in the procedure of Example 43 gives:

9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-2,13-diynoic acid and its 15(R)-epimer;
9 β ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-2,13-diynoic acid and its 15(R)-epimer.

All these compounds are optionally deetherified or are optionally converted into their methyl esters and then deetherified.

EXAMPLE 45:

A stirred solution of 14-chloro-9 α ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13-prostadienoic acid 11 α ,15(S)-bis-THP-ether (1.4 g) in acetone (28 ml), cooled at -18° , is treated with Jones reagent [2.8 ml; prepared by adding concentrated sulphuric acid (61 ml) to chromic anhydride (70 g) in water (500 ml)]. The mixture is stirred at -10° to -12°C for an additional 20 minutes, diluted with benzene (80 ml), washed with saturated ammonium sulphate solution until the washings are neutral, dried (Na_2SO_4) and then evaporated to dryness *in vacuo* to yield, as an oil, 14-chloro-11 α ,15(S)-dihydroxy-9-oxo-*cis*-5, *trans*-13-prostadienoic acid 11,15-bis-THP-ether [$\alpha]_D = -82^{\circ}$ (CHCl_3), which is then deetherified in acetone with 0.1N aqueous oxalic acid.

EXAMPLE 46.

Using the 9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid 11,15-bis-THP-ether in the procedure of Example 45 gives 11 α ,15(S)-dihydroxy-9-oxo-prost-*cis*-5-en-13-ynoic acid 11,15-bis-THP-ether, [$\alpha]_D = -82.6^{\circ}$ (CHCl_3).

A solution of this compound (1.4 g) in acetone (200 ml) is treated with 0.1N aqueous oxalic acid (270 ml) at 33° to 37°C for 6 hours; then, after removal of acetone *in vacuo*, the aqueous phase is repeatedly extracted with ether. The combined organic extracts (250 ml) are washed with saturated ammonium sulphate solution until the washings are neutral, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue (1.1 g) is adsorbed on an acid washed silica (75 g) column [the acid washed silica gel is prepared by treatment of SiO_2 (1 kg) with 2.2 litres of 7N-HCl, under stirring for 2 hours, followed by filtration, washing until there are no of Cl^- ions in the eluate and activation at 120°C under vacuum for two days] and eluted with cyclohexane-ethyl acetate mixtures. The eluates from 150—50 cyclohexane-ethyl acetate give, after removal of the solvents *in vacuo*, the oil 11 α ,15(S)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid [13,14-dehydro-PGE $_2$] (0.75 g), [$\alpha]_D = -15.1^{\circ}$ (ethanol). Using the

15(R)-epimer in this procedure gives the oic 5c-11 α ,15(R)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid [13,14-dehydro-15-epi-PGE₂], [α]_D = +31.6° (ethanol).

EXAMPLE 47.

Starting from the corresponding 9,11,15-trihydroxy-prostanoic acid 11,15-bis-DIOX-ether or THP-ether or their methyl esters, oxidation with Jones reagent, followed by deetherification give the following (optically active or *dl*-compounds):

- | | | |
|----|---|----|
| 5 | 14 - chloro - 11 α ,15(S) - dihydroxy - 9 - oxo - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| | 14 - chloro - 11 α ,15(R) - dihydroxy - 9 - oxo - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| 10 | 14 - chloro - 16 - methyl - 11 α ,15(S) - dihydroxy - 9 - oxo - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | 10 |
| | 14 - chloro - 16 - methyl - 11 α ,15(R) - dihydroxy - 9 - oxo - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| | 14 - chloro - 16 - methyl - 11 α ,15(S) - dihydroxy - 9 - oxo - 3 - oxa - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| 15 | 14 - chloro - 16 - methyl - 11 α ,15(R) - dihydroxy - 9 - oxo - 3 - oxa - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | 15 |
| | 14 - chloro - 11 α ,15(S) - dihydroxy - 20 - methyl - 9 - oxo - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| 20 | 14 - chloro - 11 α ,15(R) - dihydroxy - 20 - methyl - 9 - oxo - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | 20 |
| | 14 - chloro - 16 - methyl - 11 α ,15(S) - dihydroxy - 9 - oxo - 8,12 - diiso - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| | 14 - chloro - 11 α ,15(S) - dihydroxy - 9 - oxo - 8,12 - diiso - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| 25 | 14 - chloro - 11 α ,15(S) - dihydroxy - 20 - methyl - 9 - oxo - 8,12 - diiso - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | 25 |
| | 14 - chloro - 11 α ,15(S) - dihydroxy - 20 - methyl - 9 - oxo - 3 - oxa - 8,12 - diiso - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| 30 | 14 - chloro - 16 - methyl - 11 α ,15(R) - dihydroxy - 9 - oxo - 8,12 - diiso - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | 30 |
| | 14 - chloro - 11 α ,15(R) - dihydroxy - 9 - oxo - 8,12 - diiso - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| | 14 - chloro - 11 α ,15(R) - dihydroxy - 20 - methyl - 9 - oxo - 8,12 - diiso - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| 35 | 14 - chloro - 11 α ,15(R) - dihydroxy - 20 - methyl - 9 - oxo - 3 - oxa - 8,12 - diiso - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | 35 |
| | 14 - chloro - 11 α ,15(S) - dihydroxy - 9 - oxo - 3 - oxa - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| 40 | 14 - chloro - 11 α ,15(R) - dihydroxy - 9 - oxo - 3 - oxa - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | 40 |
| | 14 - chloro - 11 α ,15(S) - dihydroxy - 9 - oxo - 3 - oxa - 8,12 - diiso - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| | 14 - chloro - 11 α ,15(R) - dihydroxy - 9 - oxo - 3 - oxa - 8,12 - diiso - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid; | |
| 45 | 11 α ,15(S) - dihydroxy - 9 - oxo - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | 45 |
| | 11 α ,15(R) - dihydroxy - 9 - oxo - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| | 11 α ,15(S) - dihydroxy - 9 - oxo - <i>cis</i> - 5 - prosten - 13 - ynoic acid | |
| | 16-methyl-11 α ,15(S) - dihydroxy - 9 - oxo - 3 - oxa - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| 50 | 11 α ,15(S) - dihydroxy - 9 - oxo - 3 - oxa - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | 50 |
| | 11 α ,15(S) - dihydroxy - 20 - methyl - 9 - oxo - 3 - oxa - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| | 16-methyl-11 α ,15(R) - dihydroxy - 9 - oxo - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| | 11 α ,15(R) - dihydroxy - 20 - methyl - 9 - oxo - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| | 11 α ,15(R) - dihydroxy - 20 - methyl - 9 - oxo - 3 - oxa - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| 55 | 16-methyl-11 α ,15(R) - dihydroxy - 9 - oxo - 3 - oxa - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | 55 |
| | 11 α ,15(R) - dihydroxy - 9 - oxo - 3 - oxa - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| | 11 α ,15(S) - dihydroxy - 9 - oxo - 8,12 - diiso - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| | 16-methyl-11 α ,15(S) - dihydroxy - 9 - oxo - 8,12 - diiso - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| | 11 α ,15(S) - dihydroxy - 20 - methyl - 9 - oxo - 8,12 - diiso - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| 60 | 11 α ,15(S) - dihydroxy - 9 - oxo - 3 - oxa - 8,12 - diiso - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | 60 |
| | 16-methyl-11 α ,15(S) - dihydroxy - 20 - methyl - 9 - oxo - 3 - oxa - 8,12 - diiso - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| | 11 α ,15(S) - dihydroxy - 20 - methyl - 9 - oxo - 3 - oxa - 8,12 - diiso - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| | 11 α ,15(R) - dihydroxy - 9 - oxo - 8,12 - diiso - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |
| | 16-methyl-11 α ,15(R) - dihydroxy - 9 - oxo - 8,12 - diiso - <i>cis</i> - 5 - prosten - 13 - ynoic acid; | |

11 α ,15(R)-dihydroxy-20-methyl-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 11 α ,15(R)-dihydroxy-9-oxo-3-oxa-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 11 α ,15(R)-dihydroxy-20-methyl-9-oxo-3-oxa-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 16-methyl-11 α ,15(R)-dihydroxy-9-oxo-3-oxa-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 16-methyl-11 α ,15(R)-dihydroxy-9-oxo-3-oxa-8,12-diiso-*cis*-5-prosten-13-ynoic acid;

EXAMPLE 48.

A solution of *dl*-14-chloro-9 α ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13 prostadienoic acid 11 α ,15S-bis-THP (0.228 g) in pyridine (0.6 ml) is treated with acetic anhydride (0.2 ml) at room temperature. After 12 hours, the mixture is poured in 20% aqueous citric acid (10 ml) and extracted repeatedly with ether (80 ml). The combined organic phases are washed with 2N citric acid, water and a saturated ammonium sulphate solution until the washings are neutral, dried (Na₂SO₄) and evaporated to dryness *in vacuo* to afford *dl*-14-chloro-9 α ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13-prostadienoic acid 11 α ,15(S)-bis-THP-ether 9-acetate (0.22 g). A solution of this compound in acetone (24 ml) is treated with 0.2N aqueous citric acid and heated for 20 hours at 38–40°C; after removal of acetone *in vacuo*, the reaction mixture is extracted with ether.

The combined organic extracts are washed until the washings are neutral, dried and evaporated to dryness *in vacuo* to afford a crude product (0.18 g), which is adsorbed on an acid washed silica (1.4 g) column and eluted with cyclohexane-ethyl acetate mixtures.

The eluates from 150/50 cyclohexane-ethylacetate give, after removal of the solvents *in vacuo*, the oil *dl*-14-chloro-9 α ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13-prostadienoic acid 9-acetate.

Starting from the corresponding 9,11 α ,15-trihydroxy-11 α ,15-bis-ethers, treatment in pyridine with a convenient anhydride or with a convenient chloride of a carboxylic acid, followed by deetherification, gives the following:

14-chloro-9 α ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13-prostadienoic acid 9 propionate;
 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic acid 9-*p* - phenylbenzoate;
 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic acid 9-benzoate;
 9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid 9-acetate;
 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid 9 - *p* - phenyl benzoate;
 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid 9 - propionate;
 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid 9 - benzoate;
 14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic acid 9 - acetate;
 14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic acid 9 - *p* - phenylbenzoate;
 14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic acid 9 - benzoate;
 14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5, *trans* - 13 prostadienoic acid 9 - propionate;
 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid 9 - acetate;
 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid 9 - *p* - phenylbenzoate;
 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid 9 - benzoate;
 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid 9 - propionate.

EXAMPLE 49.

A stirred solution of 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid 11 α ,15S - bis - DIOX - ether (2.4 g) in acetone (48 ml), cooled at -20°C, is treated with Jones reagent (4.8 ml).

The mixture is stirred at -20° to -10°C for an additional 25 minutes, diluted with benzene (160 ml) and washed repeatedly with saturated ammonium sulphate solution (10 x 15 ml) until the washings are neutral; the aqueous washings are re-extracted with benzene and the combined organic layers are dried (Na₂SO₄), evaporated to dryness *in vacuo* to give 14 - chloro - 11 α ,15(S) - dihydroxy - 9 - oxo - 8,12 - diiso-*cis* - 5, *trans* - 13 - prostadienoic acid 11 α ,15(S) - bis - DIOX - ether (2.4 g).

A solution of this product in acetone (100 ml) is treated with 0.1N - aqueous oxalic acid for 5 hours at 38°C, and then, after removal of acetone *in vacuo*, the aqueous phase is extracted with ether (5 x 20 ml).

The combined organic layer is washed with a saturated ammonium sulphate solution until the washings are neutral, dried and evaporated to dryness to give a crude product, which is adsorbed on acid washed-silica (150 g) column.

Elution with ethyl acetate-cyclohexane (1:1), after removal of solvents *in vacuo*, gives pure 14 - chloro - 11 α ,15(S) - dihydroxy - 9 - oxo - 8,12 - diiso - *cis* - 5, *trans* - 13 prostadienoic acid also named as 14 - chloro - 8,12 - diiso - PGE₂ (0.92 g).

EXAMPLE 50.

An ethereal solution of 14-chloro-9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 prostadienoic acid 11,15 - bis - DIOX - ether is treated at room temperature, with a diazoalkane (e.g. diazomethane) solution (1.2 equiv.). After 30 minutes, the mixture is evaporated to dryness *in vacuo* to afford 14-chloro-9 β ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5, *trans*-13 prostadienoic acid 11,15-bis-DIOX-ether-methyl ester.

Using this procedure, the methyl esters and the ethyl esters of the 14-chloro-prostadienoic acid as well as of the prosten-13-ynoic acid are prepared.

EXAMPLE 51.

To a solution of 9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid 11 α ,15(S)-bis-DIOX-ether in pyridine (2.75 ml) and methylene chloride (27 ml) are added *n*-octanol (0.9 g) and N,N'-cyclohexylcarbodiimide (0.5 g). After 2½ hours, the reaction mixture is filtered, concentrated *in vacuo* to small volume and then adsorbed on a silica column. Subsequent elution with cyclohexane-ethylacetate-pyridine (800:200:5) affords pure 9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid octyl ester 11 α ,15S-bis-DIOX-ether (0.96 g).

A solution of this compound in acetone (50 ml), after addition of 0.1N aqueous oxalic acid (40 ml), is warmed for 12 hours at 35–40°. After removal of acetone *in vacuo* and extraction of aqueous phase with ether, the combined ethereal extracts are washed with saturated sodium chloride solution, dried (Na₂SO₄) and evaporated to dryness *in vacuo*, to give, after chromatographic purification on a silica column [elution with cyclohexane-ethyl acetate 7:3], pure 9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid *n*-octyl ester.

Starting from the corresponding 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5, *trans* - 13 - prostadienoic 11,15 - bis - ether in the same way as from the above corresponding trihydroxy-*cis*-5-prosten-13-ynoic acid 11,15-bis-ether and working up as described above, by esterification with a convenient alcohol optionally followed by deetherification, the 11,15-bis-DIOX-ether and -THP-ether and the 11,15-free alcohols of the following esters:

- 9 α ,11 α ,15(S)-trihydroxy-*cis*-5 prosten-13-ynoic acid 2,2,2-trichloroethyl ester;
- 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 prosten - 13 - ynoic acid *n* - decylester;
- 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 prosten - 13 - ynoic acid *n* - octadecyl ester;
- 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid *n* - dodecyl ester;
- 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid *n* - hexyl ester;
- 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid *n* - octyl ester;
- 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid *n* - decyl ester;
- 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid *n* - octadecyl ester;
- 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid 2,2,2 - trichloroethyl ester;
- 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid *n* - hexyl ester;
- 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid *n* - octyl ester;
- 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid *n* - decyl ester;
- 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid *n* - octadecyl ester;
- 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid *n* - hexyl ester;
- 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - *cis* - 5 - prosten - 13 - ynoic acid *n* - tri-chloroethyl ester;

	14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid 2,2,2-trichloroethyl ester;	
	14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 prostadienoic acid n - octyl ester;	
5	14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid n - hexyl ester;	5
	14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 prostadienoic acid n - decyl ester;	
10	14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid n - dodecyl ester;	10
	14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid n - octadecyl ester;	
	14 - chloro - 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid - 2,2,2 - trichloroethyl ester;	
15	14 - chloro - 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid n - hexyl ester;	15
	14 - chloro - 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid n - octyl ester;	
20	14 - chloro - 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid n - decyl ester;	20
	14 - chloro - 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid n - dodecyl ester;	
	14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid n - octadecyl ester;	
25	14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid - 2,2,2 - trichloroethyl ester;	25
	14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid - n - hexyl ester;	
30	14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid n - octyl ester;	30
	14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid n - decyl ester;	
	14 - chloro - 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - <i>cis</i> - 5, <i>trans</i> - 13 - prostadienoic acid n - octadecyl ester;	
35	9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid 2,2,2-trichloroethyl ester;	35
	9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid n - hexyl ester;	
40	9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid n - octyl ester;	40
	9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid n - decyl ester;	
	9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid n - octadecyl ester;	
45	20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid trichloroethyl ester;	45
	20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid n - hexyl ester;	
50	20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid n - octyl ester;	50
	20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid n - decyl ester;	
	20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid n - octadecyl ester;	
55	16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid - 2,2,2 - trichloroethyl ester;	55
	16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid n - hexyl ester;	
60	16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid n - octyl ester;	60
	16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid n - decyl ester;	
	16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - <i>cis</i> - prosten - 13 - ynoic acid - n - octadecyl ester;	

- 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - 5 - *cis*, *trans* - 13 - prostadienoic acid 2,2,2 - trichloroethyl ester;
- 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid n - hexyl ester;
- 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid n - octyl ester;
- 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid n - decyl ester;
- 14 - chloro - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid n - octadecyl ester;
- 14 - chloro - 20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid 2,2,2 - trichloroethyl ester;
- 14 - chloro - 20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid n - hexyl ester;
- 14 - chloro - 20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid n - octyl ester;
- 14 - chloro - 20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid n - decyl ester;
- 14 - chloro - 20 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid n - octadecyl ester;
- 14 - chloro - 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid 2,2,2 - trichloroethyl ester;
- 14 - chloro - 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid n - hexyl ester;
- 14 - chloro - 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid n - octyl ester;
- 14 - chloro - 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid n - decyl ester;
- 14 - chloro - 16 - methyl - 9 β ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid n - octadecyl ester.

EXAMPLE 52.

A stirred solution of 9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid octyl ester 11 α ,15(S)-bis-DIOX-ether (0.67 g) in acetone, cooled at -20°, is treated with Jones reagent (1.25 ml). The mixture is stirred at -20° to -10°C for 15 minutes, diluted with benzene and washed with a saturated ammonium sulphate solution until neutral, dried (Na₂SO₄) and evaporated to dryness *in vacuo* to afford the 11 α ,15(S)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid n-octyl ester 11 α ,15S-bis-DIOX-ether (0.62 g).

A solution of this compound in acetone—0.1N aqueous oxalic acid (1:1) is warmed for 6 hours at 33—38°; after removal of acetone *in vacuo*, the aqueous phase is extracted with ether. The combined organic layers are washed till the washings are neutral, dried (Na₂SO₄) and evaporated to dryness *in vacuo*. The residue is adsorbed on a silica gel column and eluted with cyclohexane-ethyl acetate (8:2) to afford, after removal of the solvents *in vacuo*, 11 α ,15(S)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid n-octyl ester.

Starting from the corresponding esters (methyl, ethyl, 2,2,2-trichloroethyl, n-hexyl, n-octyl, n-decyl, n-dodecyl) of the 11,15-bis-DIOX and THP ethers of the prostenoic acid, prepared as described in Examples 50 and 51, oxidation with Jones reagent affords the corresponding esters (methyl, ethyl, 2,2,2-trichloroethyl, n-hexyl, n-octyl, n-decyl, n-dodecyl) 11,15-bis-DIOX and THP ethers, which can be optionally deetherified, of the following 9-oxo-derivatives:

- 14-chloro-11 α ,15(S)-dihydroxy-9-oxo-*cis*-5, *trans*-13-prostadienoic acid;
- 14-chloro-11 α ,15(R)-dihydroxy-9-oxo-*cis*-5, *trans*-13-prostadienoic acid;
- 14 - chloro - 20 - methyl - 11 α ,15(S) - dihydroxy - 9 - oxo - *cis* - 5, *trans* - 13 - prostadienoic acid;
- 14 - chloro - 20 - methyl - 11 α ,15(R) - dihydroxy - 9 - oxo - *cis* - 5, *trans* - 13 - prostadienoic acid;
- 14 - chloro - 16 - methyl - 11 α ,15(S) - dihydroxy - 9 - oxo - *cis* - 5, *trans* - 13 - prostadienoic acid;
- 14 - chloro - 16 - methyl - 11 α ,15(R) - dihydroxy - 9 - oxo - *cis* - 5, *trans* - 13 - prostadienoic acid;
- 11 α ,15(S)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid;
- 11 α ,15(R)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid;

- 11 α ,15(S)-dihydroxy-20-methyl-9-oxo-*cis*-5-prosten-13-ynoic acid;
 11 α ,15(R)-dihydroxy-20-methyl-9-oxo-*cis*-5-prosten-13-ynoic acid;
 16-methyl-11 α ,15(S)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid;
 16-methyl-11 α ,15(R)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid;
 5 14 - chloro - 11 α ,15(S) - dihydroxy - 9 - oxo - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;
 14 - chloro - 11 α ,15(R) - dihydroxy - 9 - oxo - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;
 10 14 - chloro - 16 - methyl - 11 α ,15(S) - dihydroxy - 9 - oxo - 8,12 - *cis* - 5, *trans* - 13 - diiso - prostadienoic acid;
 14 - chloro - 16 - methyl - 11 α ,15(R) - dihydroxy - 9 - oxo - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;
 14 - chloro - 11 α ,15(S) - dihydroxy - 9 - oxo - 20 ω - homo - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;
 15 14 - chloro - 11 α ,15(R) - dihydroxy - 9 - oxo - 20 ω - homo - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;
 11 α ,15(S)-dihydroxy-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 11 α ,15(R)-dihydroxy-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 20 11 α ,15(S)-dihydroxy-20-methyl-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 11 α ,15(R)-dihydroxy-20-methyl-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 16 - methyl - 11 α ,15(S) - dihydroxy - 9 - oxo - 8,12 - diiso - *cis* - 5 - prosten - 13-ynoic acid;
 16 - methyl - 11 α ,15(R) - dihydroxy - 9 - oxo - 8,12 - diiso - *cis* - 5 - prosten - 13-ynoic acid.

EXAMPLE 53.

A stirred solution of 11 α ,15(S)-dihydroxy-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid methyl ester 11 α ,15S-bis-THP-ether (0.54 g) in methanol-methylene chloride (1:1) (20 ml), cooled at 0°C, is treated with sodium borohydride (50 mg) and the stirring is continued for an additional 30 minutes; the excess reagent is then destroyed by addition of few drops of acetone and the mixture is concentrated *in vacuo* to small volume. After dilution with diethyl ether, the organic layer is washed until the washings are neutral with 10% ammonium sulphate solution, dried (Na₂SO₄) and evaporated to dryness *in vacuo* to give 9 α ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid methyl ester 11,15-bis-THP-ether (0.5 g), which is deetherified by treatment with acetone (24 ml) and 0.2N-aqueous citric acid (30 ml) for 20 hours at 38–40°C.

After removal of acetone *in vacuo*, the aqueous phase is repeatedly extracted with ether, the combined organic layers are washed with 15% (NH₄)₂SO₄ solution until the washings are neutral, dried (Na₂SO₄) and evaporated to dryness *in vacuo* to give a crude product (0.46 g) which is purified by elution on a silica column with cyclohexane-ethyl acetate mixtures. The eluates (from cyclohexane-ethylacetate 1:1), after removal of solvents *in vacuo*, give pure 9 α ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid methyl ester (0.28 g).

A solution of this compound (0.12 g) in methanol is treated with 2N sodium hydroxide (2 equiv.), refluxed for 30 minutes, concentrated *in vacuo* to small volume, and diluted with water. The aqueous phase is extracted with diethyl ether, the combined organic layers after re-extraction with 0.5N sodium hydroxide are discarded. The pH of the combined alkaline layers is adjusted to pH 4.5–4.6, followed by extraction with diethyl ether. These combined organic phases are washed with saturated (NH₄)₂SO₄ solution until the washings are neutral, dried (Na₂SO₄) and evaporated to dryness to afford pure 9 α ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid (0.068) as a colourless oil.

EXAMPLE 54.

Using the procedure of Example 53, the 14-chloro-11,15-dihydroxy-9-oxo-8,12-diiso-prostadienoic ester 11,15-bis-ether derivatives and the 9-oxo-8,12-diiso-prosten-13-ynoic ester 11,15-bis-ether derivatives of Example 52, are reacted with sodium borohydride to afford, after deetherification the esters (methyl, ethyl, 2,2,2-trichloroethyl, octyl, n-hexyl, n-decyl, n-dodecyl) and after optional saponification, the free acids of the following compounds:

- 9 α ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 20-methyl-9 α ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 60 16 - methyl - 9 α ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5 - prosten - 13 - ynoic acid;

- 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;
16 - methyl - 14 - chloro - 9 α ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid;
14 - chloro - 20 - methyl - 9 α ,11 α ,15(S) - trihydroxy - 8,12 - diiso - *cis* - 5, *trans* - 13 - prostadienoic acid.

EXAMPLE 55.

A stirred solution of 14 - chloro - 11 α ,15(S) - dihydroxy - 9 - oxo - *cis* - 5, *trans* - 13 - prostadienoic acid methyl ester 11,15 - bis - THP (0.89) in 20 ml of methanol-methylene chloride (1:1) is reacted with sodium borohydride (100 mg). After additional stirring for 30 minutes, the excess reagent is destroyed by addition of few drops of acetone. The mixture is concentrated to small volume *in vacuo*, diluted with diethyl ether-methylene chloride (5:1) washed with 10% (NH₄)₂SO₄ solution until the washings are neutral and dried (Na₂SO₄). After removal of the solvents *in vacuo*, the residue is adsorbed on a silica (100 g) column and eluted with cyclohexane-ether mixtures to obtain in this order: 14-chloro-PGF_{2a} methyl ester 11,15-bis-THP-ether (0.2 g) and 14-chloro-9 β ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13-prostadienoic acid methyl ester 11,15-bis-THP-ether (0.39 g).

This product is deetherified by treatment with acetone (20 ml) and 0.2N citric acid (15 ml) for 12 hours at 38—40° to afford 14-chloro-9 β ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13-prostadienoic acid methyl ester (0.2 g).

Finally, this methyl ester is reacted in methanol with 0.1 potassium hydroxide (2 equiv.) at reflux temperature for 30 minutes to give 14-chloro-9 β ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13-prostadienoic acid (0.08 g) also named as 14-chloro-PGF_{2 β} .

EXAMPLE 56.

Using the procedure of Example 55, the 14-chloro-11,15-dihydroxy-9-oxo-prostadienoic acid ester 11,15-bis-ether derivatives and the 9-oxo-prosten-13-ynoic acid ester 11,15-bis-ether derivatives of Example 52, are reacted with sodium borohydride to afford after deetherification the esters (methyl, ethyl, 2,2,2-trichloroethyl, n-hexyl, n-octyl, n-decyl, n-dodecyl) and after optional saponification, the free acids of the following compounds:

- 14-chloro-9 β ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13-prostadienoic acid;
14-chloro-16-methyl-9 β ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13-prostadienoic acid;
14-chloro-20-methyl-9 β ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13-prostadienoic acid;
9 β ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid;
16-methyl-9 β ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid;
20-methyl-9 β ,11 α ,15S-trihydroxy-*cis*-5-prosten-13-ynoic acid.

EXAMPLE 57.

A solution of dl-14-chloro-11 α ,15(S)-dihydroxy-9-oxo-*cis*-5, *trans*-13-prostadienoic acid 11,15-bis-THP-ether (also named as dl-14-chloro-PGE₂ 11,15-bis-THP-ether) in acetone (40 ml) is treated with 0.2N-oxalic acid (54 ml) and warmed for 6 hours at 60—65°C. After removal of the acetone *in vacuo*, the aqueous phase is repeatedly extracted with ether; the combined organic layers are washed with saturated (NH₄)₂SO₄ solution until the washings are neutral, dried (Na₂SO₄). After removal of solvents, the residue is purified by preparative T.L.C. on silica platts using benzene-ethyl acetate-acetic acid (130:24:12) as eluent, to obtain dl-14-chloro-15(S)-hydroxy-9-oxo-*cis*-5, 10-*trans*-13-prostatrienoic acid (0.12 g) also named as dl-14-chloro-PGA₂.

EXAMPLE 58.

Using the procedure of Example 57, the 14-chloro-11,15-dihydroxy-9-oxo-prostadienoic acid 11,15-bis-ethers of Examples 45 and 47 and their esters of Example 52 are deetherified at 60—65° with acetone-0.2N aqueous oxalic acid to afford the esters (methyl, ethyl, 2,2,2-trichloroethyl, n-hexyl, n-octyl, n-decyl, n-dodecyl) and the free acids of the following optically active and dl-compounds:

- 14 - chloro - 15(S) - hydroxy - 9 - oxo - *cis* - 5,10, *trans* - 13 - prostatrienoic acid and its 15R-epimer;
14 - chloro - 15(S) - hydroxy - 20 - methyl - 9 - oxo - *cis* - 5,10, *trans* - 13 - prostatrienoic acid and its 15R-epimer;
14 - chloro - 16 - methyl - 15(S) - hydroxy - 9 - oxo - *cis* - 5,10, *trans* - 13 - prostatrienoic acid and its 15R-epimer;

- 14 - chloro - 15(S) - hydroxy - 9 - oxo - 3 - oxa - *cis* - 5,10, *trans* - 13 - prostatictri-
enoic acid and its 15(R)-epimer;
14 - chloro - 15(S) - hydroxy - 9 - oxo - *cis* - 2, *cis* - 5,10 - *trans* - 13 - prostatictetra-
enoic acid and its 15(R)-epimer;
5 14 - chloro - 15(S) - hydroxy - 9 - oxo - *trans* - 2, *cis* - 5,10, *trans* - 13 - prostatictetra-
enoic acid and its 15(R)-epimer;
14 - chloro - 15(S) - hydroxy - 9 - oxo - *cis* - 5,10, *trans* - 13 - prostaticdien - 2 - ynoic
acid and its 15(R)-epimer;
10 14 - chloro - 15(S) - hydroxy - 9 - oxo - 8,12 - diiso - *cis* - 5,10, *trans* - 13 - prosta-
tri-enoic acid and its 15(R)-epimer;
14 - chloro - 15(S) - hydroxy - 9 - oxo - 3 - oxa - 8,12 - diiso - *cis* - 5,10, *trans* - 13 -
prostatictri-enoic acid and its 15(R)-epimer;
14 - chloro - 16 - methyl - 15(S) - hydroxy - 9 - oxo - 8,12 - diiso - *cis* - 5,10, *trans* -
13 - prostatictri-enoic acid and its 15(R)-epimer;
15 14 - chloro - 15(S) - hydroxy - 20 - methyl - 9 - oxo - 8,12 - diiso - *cis* - 5,10, *trans* -
13 - prostatictri-enoic acid and its 15(R)-epimer.

EXAMPLE 59.

A solution of 16 - methyl - 11 α ,15(S) - dihydroxy - 9 - oxo - *cis* - 5 - prosten-
13 - ynoic acid n - octyl ester 11,15 - bis - DIOX - ether (0.6 g) in acetone (45 ml)
20 and 0.25 N aqueous oxalic acid (54 ml) is warmed at 60—65° for 6 hours and after
removal of acetone *in vacuo*, the aqueous phase is repeatedly extracted with ether-
methylene chloride (5:1). The combined organic layers are washed with a saturated
(NH₄)₂SO₄ solution until neutral, dried on Na₂SO₄ and evaporated to dryness. The
25 residue is purified by preparative TLC chromatography (eluent cyclohexane-diethyl
ether) to give the 16-methyl-15(S)-hydroxy-9-oxo-*cis*-5,10-prostadien-13-ynoic acid
n-octyl ester (0.25 g).

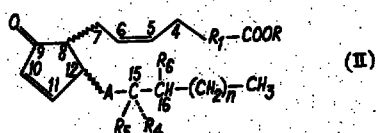
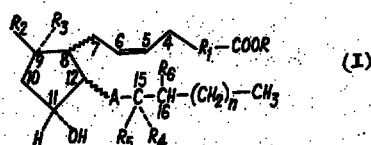
EXAMPLE 60.

Using the procedure of Example 59, the 11,15-dihydroxy-9-oxo-prosten-13-ynoic
acid 11,15-bis-ethers of Examples 46 and 47 and their esters of Example 52 are de-
30 etherified at 60—65° with acetone-0.25N aqueous oxalic acid to afford the esters
(methyl, ethyl, 2,2,2-trichloroethyl, n-hexyl, n-octyl, n-decyl, n-dodecyl) and the free
acids of the following optically active and *dl*-compounds:

- 15(S) - hydroxy - 9 - oxo - *cis* - 5,10 - prostadien - 13 - ynoic acid and its 15R-epimer;
15(S) - hydroxy - 20 - methyl - 9 - oxo - *cis* - 5,10 - prostadien - 13 - ynoic acid
35 and its 15(R)-epimer;
16-methyl-15(S)-hydroxy-9-oxo-*cis*-5,10-prostadien-13-ynoic acid and its 15R-epimer;
15(S)-hydroxy-9-oxo-8,12-diiso-*cis*-5,10-prostadien-13-ynoic acid and its 15(R)-
epimer;
15(S)-hydroxy-20-methyl-9-oxo-8,12-diiso-*cis*-5,10-prostadien-13-ynoic acid and its
40 15(R)-epimer;
16-methyl-15(S)-hydroxy-9-oxo-8,12-diiso-*cis*-5,10-prostadien-13-ynoic acid and its
15(R)-epimer;
15(S) - hydroxy - 9 - oxo - 3 - oxa - 8,12 - diiso - *cis* - 5,10 - prostadien - 13 - ynoic
acid and its 15(R)-epimer;
45 15(S)-hydroxy-9-oxo-3-oxa-*cis*-5,10-prostadien-13-ynoic acid and its 15(R)-epimer.

WHAT WE CLAIM IS:—

1. A compound of general formula (I) or (II)



- 14 - chloro - 15(S) - hydroxy - 9 - oxo - 3 - oxa - *cis* - 5,10, *trans* - 13 - prostatictri-
enoic acid and its 15(R)-epimer;
14 - chloro - 15(S) - hydroxy - 9 - oxo - *cis* - 2, *cis* - 5,10 - *trans* - 13 - prostatictetra-
enoic acid and its 15(R)-epimer;
5 14 - chloro - 15(S) - hydroxy - 9 - oxo - *trans* - 2, *cis* - 5,10, *trans* - 13 - prostatictetra-
enoic acid and its 15(R)-epimer;
14 - chloro - 15(S) - hydroxy - 9 - oxo - *cis* - 5,10, *trans* - 13 - prostatictri- 2 - ynoic
acid and its 15(R)-epimer;
10 14 - chloro - 15(S) - hydroxy - 9 - oxo - 8,12 - diiso - *cis* - 5,10, *trans* - 13 - prosta-
tri-enoic acid and its 15(R)-epimer;
14 - chloro - 15(S) - hydroxy - 9 - oxo - 3 - oxa - 8,12 - diiso - *cis* - 5,10, *trans* - 13 -
prostatictri-enoic acid and its 15(R)-epimer;
14 - chloro - 16 - methyl - 15(S) - hydroxy - 9 - oxo - 8,12 - diiso - *cis* - 5,10, *trans* -
13 - prostatictri-enoic acid and its 15R - epimer;
15 14 - chloro - 15(S) - hydroxy - 20 - methyl - 9 - oxo - 8,12 - diiso - *cis* - 5,10, *trans* -
13 - prostatictri-enoic acid and its 15(R)-epimer.

EXAMPLE 59.

A solution of 16 - methyl - 11 α ,15(S) - dihydroxy - 9 - oxo - *cis* - 5 - prosten-
13 - ynoic acid n - octyl ester 11,15 - bis - DIOX - ether (0.6 g) in acetone (45 ml)
20 and 0.25 N aqueous oxalic acid (54 ml) is warmed at 60—65° for 6 hours and after
removal of acetone *in vacuo*, the aqueous phase is repeatedly extracted with ether-
methylene chloride (5:1). The combined organic layers are washed with a saturated
(NH₄)₂SO₄ solution until neutral, dried on Na₂SO₄ and evaporated to dryness. The
25 residue is purified by preparative TLC chromatography (eluent cyclohexane-diethyl
ether) to give the 16-methyl-15(S)-hydroxy-9-oxo-*cis*-5,10-prostadien-13-ynoic acid
n-octyl ester (0.25 g).

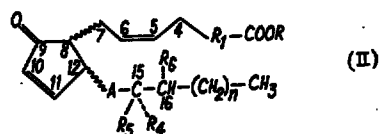
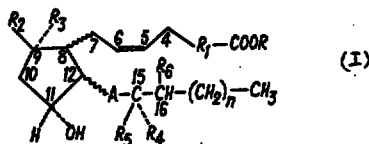
EXAMPLE 60.

Using the procedure of Example 59, the 11,15-dihydroxy-9-oxo-prosten-13-ynoic
acid 11,15-bis-ethers of Examples 46 and 47 and their esters of Example 52 are de-
30 etherified at 60—65° with acetone-0.25N aqueous oxalic acid to afford the esters
(methyl, ethyl, 2,2,2-trichloroethyl, n-hexyl, n-octyl, n-decyl, n-dodecyl) and the free
acids of the following optically active and *dl*-compounds:

- 15(S) - hydroxy - 9 - oxo - *cis* - 5,10 - prostadien - 13 - ynoic acid and its 15R-epimer;
15(S) - hydroxy - 20 - methyl - 9 - oxo - *cis* - 5,10 - prostadien - 13 - ynoic acid
35 and its 15(R)-epimer;
16-methyl-15(S)-hydroxy-9-oxo-*cis*-5,10-prostadien-13-ynoic acid and its 15R-epimer;
15(S)-hydroxy-9-oxo-8,12-diiso-*cis*-5,10-prostadien-13-ynoic acid and its 15(R)-
epimer;
15(S)-hydroxy-20-methyl-9-oxo-8,12-diiso-*cis*-5,10-prostadien-13-ynoic acid and its
40 15(R)-epimer;
16-methyl-15(S)-hydroxy-9-oxo-8,12-diiso-*cis*-5,10-prostadien-13-ynoic acid and its
15(R)-epimer;
15(S) - hydroxy - 9 - oxo - 3 - oxa - 8,12 - diiso - *cis* - 5,10 - prostadien - 13 - ynoic
acid and its 15(R)-epimer;
45 15(S)-hydroxy-9-oxo-3-oxa-*cis*-5,10-prostadien-13-ynoic acid and its 15(R)-epimer.

WHAT WE CLAIM IS:—

1. A compound of general formula (I) or (II)





* C L M S *

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wherein R is a hydrogen atom, a pharmaceutically acceptable cation or a C₁₋₁₈ alkyl or haloalkyl group; R₁ is —CH₂CH₂—, —OCH₂—, —SCH₂—, —CH=CH— or —C≡C—; one of R₂ and R₃ is a hydrogen atom and the other is a hydroxy group or —C≡C—; one of R₂ and R₃ together form an oxo group; A is *trans*-CH=CCl— or —C≡C—; one of R₄ and R₅ is a hydrogen atom and the other is a hydroxy group; R₆ is a hydrogen atom or a C₁₋₄ alkyl group; and n is 3 or 4; the chains bound to the carbon atoms in the 8- and 12-positions having the *trans*-configuration.

2. A compound according to claim 1 in racemic form.
3. A compound according to claim 1 or 2 wherein A is *trans*-CH=CCl—.
4. A compound according to claim 1 or 2 wherein A is —C≡C—.
5. 14-Chloro-9 α ,11 α ,15(S)-trihydroxy-*cis*-5, *trans*-13-prostadienoic acid.
6. 14-Chloro-9 α ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5, *trans*-13-prostadienoic acid.
7. 14-Chloro-9 β ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5, *trans*-13-prostadienoic acid.
8. 14-Chloro-11 α ,15(S)-dihydroxy-9-oxo-*cis*-5, *trans*-13-prostadienoic acid.
9. 14-Chloro-15(S)-hydroxy-9-oxo-*cis*-5,10, *trans*-13-prostatrienoic acid.
10. 14-Chloro-11 α ,15(S)-dihydroxy-9-oxo-8,12-diiso-*cis*-5, *trans*-13-prostadienoic acid.
11. 14-Chloro-15(S)-hydroxy-9-oxo-8,12-diiso-*cis*-5,10, *trans*-13-prostatrienoic acid.
12. 9 α ,11 α ,15(S)-Trihydroxy-*cis*-5-prosten-13-ynoic acid.
13. 16-Methyl-9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid.
14. 20-Methyl-9 α ,11 α ,15(S)-trihydroxy-*cis*-5-prosten-13-ynoic acid.
15. 9 α ,11 α ,15(S)-Trihydroxy-3-oxa-*cis*-5-prosten-13-ynoic acid.
16. 9 α ,11 α ,15(R)-Trihydroxy-*cis*-5-prosten-13-ynoic acid.
17. 9 α ,11 α ,15(S)-Trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
18. 16-Methyl-9 α ,11 α ,15(S)-trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
19. 20-Methyl-9 α ,11 α ,15(S)-Trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
20. 9 α ,11 α ,15(S)-Trihydroxy-3-oxa-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
21. 9 β ,11 α ,15(S)-Trihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
22. 11 α ,15(S)-Dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid.
23. 11 α ,15(R)-Dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid.
24. 16-Methyl-11 α ,15(S)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid.
25. 16-Methyl-11 α ,15(R)-dihydroxy-9-oxo-*cis*-5-prosten-13-ynoic acid.
26. 11 α ,15(S)-Dihydroxy-20-methyl-9-oxo-*cis*-5-prosten-13-ynoic acid.
27. 11 α ,15(R)-Dihydroxy-20-methyl-9-oxo-*cis*-5-prosten-13-ynoic acid.
28. 11 α ,15(S)-Dihydroxy-9-oxo-3-oxa-*cis*-5-prosten-13-ynoic acid.
29. 11 α ,15(R)-Dihydroxy-9-oxo-3-oxa-*cis*-5-prosten-13-ynoic acid.
30. 11 α ,15(S)-Dihydroxy-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
31. 11 α ,15(R)-Dihydroxy-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
32. 16-Methyl-11 α ,15(S)-dihydroxy-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
33. 16-Methyl-11 α ,15(R)-dihydroxy-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
34. 11 α ,15(S)-Dihydroxy-20-methyl-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
35. 11 α ,15(R)-Dihydroxy-20-methyl-9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
36. 11 α ,15(S)-Dihydroxy-9-oxo-3-oxa-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
37. 11 α ,15(R)-Dihydroxy-9-oxo-3-oxa-8,12-diiso-*cis*-5-prosten-13-ynoic acid.



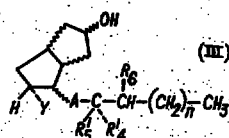
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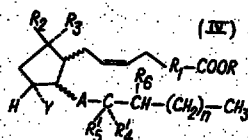
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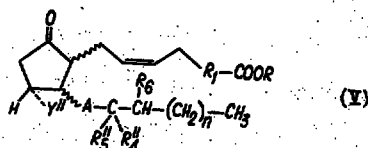
38. 15(S)-Hydroxy-9-oxo-*cis*-5,10-prostadien-13-ynoic acid.
 39. 16-Methyl-15(S)-hydroxy-9-oxo-*cis*-5,10-prostadien-13-ynoic acid.
 40. 15(S) - Hydroxy - 20 - methyl - 9 - oxo - *cis* - 5,10 - prostadien - 13 - ynoic acid.
 41. 15(S)-Hydroxy-3-oxa-9-oxo-*cis*-5,10-prostadien-13-ynoic acid.
 42. 15(S)-Hydroxy-9-oxo-8,12-diiso-*cis*-5,10-prostadien-13-ynoic acid.
 43. 16 - Methyl - 15(S) - hydroxy - 9 - oxo - 8,12 - diiso - *cis* - 5,10 - prostadien - 13 - ynoic acid.
 44. 15(S) - Hydroxy - 20 - methyl - 9 - oxo - 8,12 - diiso - *cis* - 5,10 - prostadien - 13 - ynoic acid.
 45. 15(S) - Hydroxy - 9 - oxo - 3 - oxa - 8,12 - diiso - *cis* - 5,10 - prostadien-13 - ynoic acid.
 46. A process for the preparation of a compound according to any one of the preceding claims, the process comprising reacting in known manner an optically active or racemic compound of general formula (III)



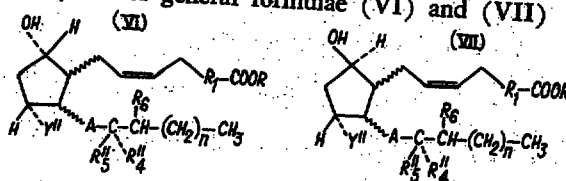
wherein R_6 , n and A are as defined in claim 1, one of R'_1 and R'_2 is a hydroxy or a known protecting group bound to the chain by an ethereal oxygen atom, and the other is a hydrogen atom, Y is a hydroxy or a known protecting group bound to the ring by an ethereal oxygen atom, the lactol ring being in the *trans*-configuration with respect to the hydroxy-aliphatic side chain, with a Wittig reagent comprising a group of formula $-\text{CH}_2\text{CH}_2-\text{R}_1-\text{COOR}$, wherein R_1 is as defined in claim 1, and R is a hydrogen atom or a C_{1-18} alkyl or haloalkyl group, to give a compound of general formula (IV)



wherein R , R_1 , Y , A , R'_1 , R'_2 , R_6 and n are as defined above, and wherein one of R_2 and R_3 is a hydroxy group and the other is a hydrogen atom, and then deetherifying in known manner the resulting compound of general formula (IV), wherein Y is a known protecting group as defined above and/or one of R'_1 and R'_2 is a known protecting group as defined above and the other is a hydrogen atom, or if desired oxidising the 9-hydroxy group in the compound of general formula (IV) wherein Y is a known protecting group as defined above and one of R'_1 and R'_2 is a known protecting group as defined above and the other is a hydrogen atom, to give a compound of general formula (V)



wherein R , R_1 , R''_1 , R''_2 , A , R_6 and n are as defined above, Y'' is a known protecting group as defined above, and one of R''_1 and R''_2 is a known protecting group as defined above, and the other is a hydrogen atom, which, in turn, may if desired be deetherified in known manner in the 11- and 15-positions, to give, according to the reaction conditions used, either a compound of general formula (I), wherein R_2 and R_3 together form an oxo group, or a compound of general formula (II), or alternatively the 9-oxo group in a compound of the general formula (I) is reduced to give a mixture of the 9 α - and 9 β -ols of general formulae (VI) and (VII)





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wherein R , R_1 , R'' , R''' , A , R_6 , Y'' and n are as defined above which mixture is then, in either order, separated and deetherified in known manner to give a compound of general formula (I), wherein one of R_2 and R_3 is a hydroxy group and the other is a hydrogen atom, and then if desired reacting the compound of general formula (I) or (II) wherein R is a hydrogen atom, with a base to give a compound of general formula (I) or (II) wherein R is a cation, or esterifying a compound of general formula (I) or (II) wherein R is a hydrogen atom to give a compound of general formula (I) or (II) wherein R is a C_{1-18} alkyl or haloalkyl group, or hydrolysing a compound of general formula (I) or (II) wherein R is a C_{1-18} alkyl or haloalkyl group to give a compound of general formula (I) or (II) wherein R is a hydrogen atom.

47. A process according to claim 46 wherein a compound of general formula (IV) wherein A is $-\text{C}=\text{CCl}-$ is converted in known manner into a compound of general formula (IV) wherein A is $-\text{C}\equiv\text{C}-$.

48. A process according to claim 46 substantially as described herein.

49. A compound of general formulae (I) or (II) prepared by a process according to any one of claims 46 to 48.

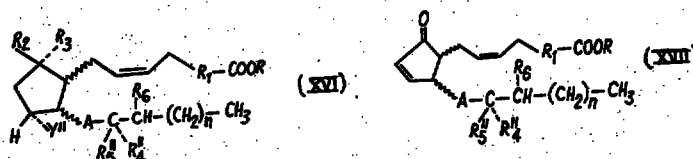
50. A pharmaceutical composition comprising a compound according to any one of claims 1, 2, 5 to 45 and 49 and a pharmaceutically acceptable carrier or diluent.

51. A pharmaceutical composition comprising a compound according to claim 3 and a pharmaceutically acceptable carrier or diluent.

52. A pharmaceutical composition comprising a compound according to claim 4 and a pharmaceutically acceptable carrier or diluent.

53. A composition according to claim 50 substantially as described herein.

54. A compound of general formula (XVI) or (XVII)



wherein R , R_1 , R_2 , R_3 , A , R_6 and n are as defined in claim 1, one of R'' , and R''' is a protecting group bound to the chain by an ethereal oxygen atom, said protecting group being a 1-alkoxycycloalkyloxy group, a 2-oxa-cycloalkyl group whose cycloalkyl moiety optionally contains a further ring oxygen atom, a 1-alkoxy-alkyloxy group, a silyl ether group or an enol-ether group, and the other is hydrogen atom, and Y'' is a protecting group as defined for R'' , and R''' , bound to the ring by an ethereal oxygen atom, the chains bound to the carbon atoms in the 8- and 12- positions having the trans-configuration, or a racemate thereof.

55. A process for the preparation of a compound according to claim 54, the process being as described in claim 46.

56. A compound of general formula (XVI) or (XVII) prepared by a process according to claim 55.

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