

PATENT SPECIFICATION

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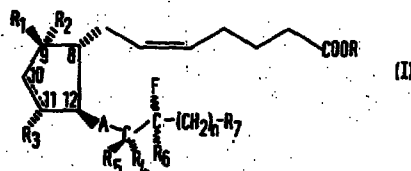
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(54) FLUORO-PROSTAGLANDINS AND PROCESS FOR THEIR PREPARATION

(71) We, CARLO ERBA SPA, 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:—

The present invention relates to a fluoroprostaglandins, a process for their preparation, pharmaceutical and veterinary compositions containing them, and treatments using them.

The invention provides optically active compounds of the formula (I)



or racemates thereof, wherein
 R is hydrogen or a C₁—C₁₂ alkyl group, and the symbol

represents a single or a double bond, and wherein, when the symbol

is a double bond, R₃ is a hydrogen atom and R₁ and R₂ together form an oxo group, and when the symbol

is a single bond, R₃ is hydroxy, and one of R₁ and R₂ is hydrogen and the other is hydroxy or carboxylic acyloxy or R₁ and R₂ together form an oxo group; and wherein

A is *trans*-CH=CH— or —C≡C—;
 one of R₅ and R₆ is hydroxy and the other is hydrogen;
 R₅ is a hydrogen, methyl or fluorine;
 n is zero, or an integer from 1 to 6; and

R₇ is methyl, C₂—C₇, cycloalkyl, or phenyl unsubstituted or optionally substituted by one or more substituents selected from halogen, C₁—C₆ alkoxy and trihalomethyl, with the proviso that when A is *trans*-CH=CH—, then R₇ is a C₂—C₇ cycloalkyl group; and pharmaceutically acceptable salts thereof when R is hydrogen.

In the formulae of this specification, the broken lines

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indicate that the substituents are in the α -configuration, i.e. are below the plane of the ring or of the chain, while the heavy solid lines

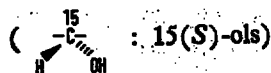
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indicate that the substituents are in the β -configuration, i.e. above the plane of the ring or of the chain; and the wavy line attachment

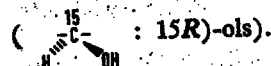
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indicates that the groups may be either in the α -configuration or in the β -configuration.

As is evident from formula (I), the double bond in the 5(6)-position is a *cis*-double bond, and the hydroxy group linked to the carbon atom in the 15-position may be either in the α -configuration



or in the β -configuration



When there is only one fluorine atom on the carbon atom in the 16-position it may be either a 16(S)-fluoro (α -configuration) or a 16(R)-fluoro (β -configuration) or a 16(S,R)-fluoro, i.e. the mixture of the 16S- and 16R- diastereoisomers. Analogously, when there is a methyl group on the carbon atom in 16-position, it may be either a 16(S)-methyl or a 16(R)-methyl or a 16(S,R)-methyl.

The alkyl and alkoxy groups may be branched or straight chain groups, and when R is a C₁—C₁₂ alkyl group, it is preferably a methyl, ethyl, propyl or heptyl group.

Preferably, one of R₁ and R₂ is hydrogen and the other is hydroxy, or R₁ and R₂, taken together, form an oxo group, but when one of R₁ and R₂ is carboxylic acyloxy, it is preferably an alkanoyloxy group containing up to 6 carbon atoms, a benzyloxy group or a *p*-phenylbenzyloxy group.

When R₃ is methyl, n is preferably 3 or 4; when R₃ is cycloalkyl or phenyl, n is preferably 1, the cycloalkyl group preferably being cyclopentyl, cyclohexyl or cycloheptyl; and when R₃ is a trihalomethyl-substituted phenyl group, the trihalomethyl group is preferably trifluoromethyl or trichloromethyl.

Examples of pharmaceutically and veterinarily acceptable salts are these with pharmaceutically or veterinarily acceptable metal cations, such as sodium, potassium, calcium and aluminium ions, or with organic amine cations, such as these derived from trialkylamines.

Specific examples of compounds of the invention are the following:

18,19,20-trinor-17-cyclohexyl-16(S,R)-fluoro-PGF₂₀,

18,19,20-trinor-17-cyclohexyl-16(S,R)-fluoro-PGE₂,

18,19,20-trinor-17-cyclohexyl-16S-fluoro-PGF₂₀,

18,19,20-trinor-17-cyclohexyl-16R-fluoro-PGF₂₀,

16 ϵ -fluoro-18,19,20-trinor-17-cyclopentyl-PGF₂₀,

16 ϵ -fluoro-18,19,20-trinor-17-cyclopentyl-PGE₂,

18,19,20-trinor-17-cyclohexyl-16,16-difluoro-PGF₂₀,

18,19,20-trinor-17-cyclopentyl-16,16-difluoro-PGF₂₀,

16 ϵ -fluoro-13,14-didehydro-PGF₂₀,

16 ϵ -fluoro-13,14-didehydro-PGE₂,

16 ϵ -fluoro-13,14-didehydro-PGA₂,

16 ϵ -fluoro-13,14-didehydro-PGF₂₀,

16(S)-methyl-16(R)-fluoro-13,14-didehydro-PGE₂,

16(R)-methyl-16(S)-fluoro-13,14-didehydro-PGE₂,

16(S),20-dimethyl-16(R)-fluoro-13,14-didehydro-PGE₂,

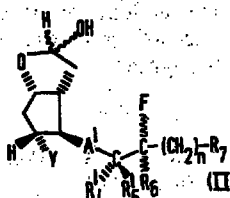
16(R),20-dimethyl-16(S)-fluoro-13,14-didehydro-PGE₂,

16 ϵ -methyl-16 ϵ -fluoro-13,14-didehydro-PGF₂₀,

16 ϵ -methyl-16 ϵ -fluoro-13,14-didehydro-PGF₂₀,

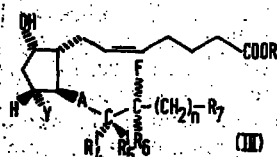
16 ξ -methyl-16 ξ -fluoro-13,14-didehydro-PGA₂,
 16,16-difluoro-13,14-didehydro-PGE₂,
 16,16-difluoro-13,14-didehydro-PGF_{2 α} ,
 16,16-difluoro-13,14-didehydro-PGA₂,
 18,19,20-trinor-17-cyclohexyl-16(R,S)-fluoro-13,14-didehydro-PGF_{2 α} ,
 18,19,20-trinor-17-cyclohexyl-16R-fluoro-13,14-didehydro-PGF_{2 α} ,
 18,19,20-trinor-17-cyclohexyl-16S-fluoro-13,14-didehydro-PGF_{2 α} ,
 18,19,20-trinor-17-cyclohexyl-16,16-difluoro-13,14-didehydro-PGF_{2 α} ,
 16 ξ -fluoro-18,19,20-trinor-17-cyclopentyl-13,14-didehydro-PGF_{2 α} ,
 16 ξ -fluoro-18,19,20-trinor-17-phenyl-13,14-didehydro-PGF_{2 α} ,
 16 ξ -fluoro-18,19,20-trinor-17-cyclopentyl-13,14-didehydro-PGE₂,
 16 ξ -fluoro-18,19,20-trinor-17-cyclohexyl-13,14-didehydro-PGE₂,
 16 ξ -fluoro-18,19,20-trinor-17-phenyl-13,14-didehydro-PGE₂,
 18,19,20-trinor-17-phenyl-16,16-difluoro-13,14-didehydro-PGF_{2 α} ,
 18,19,20-trinor-17-cyclopentyl-16,16-difluoro-13,14-didehydro-PGF_{2 α} ,
 18,19,20-trinor-17-phenyl-16,16-difluoro-13,14-didehydro-PGE₂,
 18,19,20-trinor-17-cyclopentyl-16,16-difluoro-13,14-didehydro-PGE₂, and
 18,19,20-trinor-17-cyclohexyl-16,16-difluoro-13,14-didehydro-PGE₂.

The compounds of formula (I) may be prepared by a process comprising reacting an optically active compound, or a racemate thereof, of formula (II)



wherein

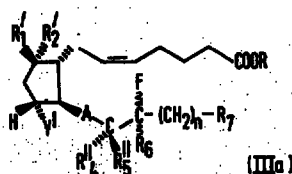
n, R₄, and R₅ are as defined above, A' is —C≡C— or —CH=CH—, wherein X is hydrogen or halogen, Y is hydroxy or a known protecting group bound to the ring by an ethereal oxygen atom, and one of R₄ and R₅ is hydroxy or a known protecting group bound to the chain by an ethereal oxygen atom, and the other is a hydrogen atom, with a Wittig reagent comprising the group of formula —(CH₂)₄—COOR, wherein R is a hydrogen atom or a C₁—C₁₂ alkyl group, to give a compound of formula (III)



wherein

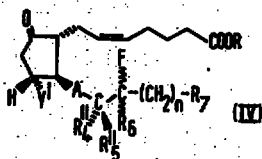
R, Y, A, R₄, R₅, R₆, R₇, and n are as defined above, which when Y is a known protecting group as above defined, and one of R₄ and R₅ is a known protecting group as above defined and the other is hydrogen, may be optionally esterified by methods known *per se* to give the 9 α - or 9 β -acyloxy derivative, and then, deesterifying by methods known *per se* the compound of formula (III) or its 9 α - or 9 β -carboxylic acyloxy derivative wherein Y is a known protecting group as defined above and/or one of R₄ and R₅ is a known protecting group as defined above and the other is hydrogen, so obtaining a compound of formula (I), wherein R₆ is a hydroxy group, the symbol

is a single bond, one of R₄ and R₅ is hydrogen, and the other is hydroxy carboxylic acyloxy, and one of R₄ and R₅ is a hydroxy group and the other is hydrogen, or, if desired, oxidizing the 9 α - or 9 β -hydroxy group in a compound of formula (IIIa)



wherein

R, A, R₃, R₇, and n are as defined above, one of R₁ and R₂ is hydrogen and the other is hydroxy, Y' is a known protecting group as defined above and one of R₄ and R₅ is a known protecting group as defined above and the other is hydrogen, to give a compound of formula (IV)



wherein

R, Y', A, R₄, R₅, R₆, R₇, and n are as defined above, which in turn is deetherified in the 11- and 15-positions to give, according to the reaction conditions used, either a compound of formula (I) wherein the symbol



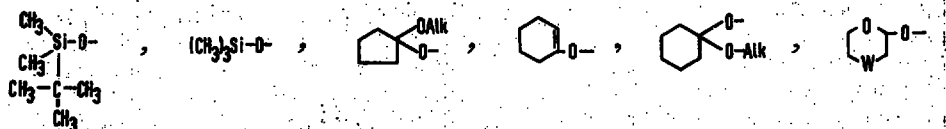
is a single bond, R₃ is hydroxy, and R₁ and R₂, taken together, form an oxo group, or a compound of formula (I) wherein the symbol



is a double bond, R₃ is hydrogen, and R₁ and R₂ together form an oxo group, and/or, if desired, reacting a compound of formula (I) wherein R is a hydrogen atom and the hydroxy group in the 11- and/or 15-position is optionally protected as described above, with a base, followed, if required, by deetherification, to give a salt of a compound of formula (I) wherein A is hydrogen, or esterifying a compound of formula (I) wherein R is a hydrogen atom and the hydroxy group in the 11- and/or 15-position is optionally protected as described above, followed, if required, by deetherification, to give a compound of formula (I) wherein R is C₁-C₁₂ alkyl, or hydrolyzing a compound of formula (I) wherein R is C₁-C₁₂ alkyl and the hydroxy group in the 11- and/or 15-position is optionally protected as described above, followed, if required, by deetherification to give a compound of formula (I) wherein R is a hydrogen atom.

The hydrolysis of a compound of formula (I) wherein R₁ and R₂ together form an oxo group and R is C₁-C₁₂ alkyl group, to give a compound of formula (I) wherein R₁ and R₂ together form an oxo group and R is hydrogen may be also carried out enzymatically, e.g. by using a yeast esterase.

The known protecting groups (i.e. ether groups) should be convertible to hydroxy groups under mild reaction conditions, e.g. acid hydrolysis. Examples are the groups



wherein W is —O— or —CH₂—, and Alk is a lower alkyl group.

When in the lactol of formula (II) A' is —CH=CH—, it is a *trans*-CH=CH—. When in the lactol of formula (II) A' is —CH=CX—, wherein X is halogen, preferably chlorine, bromine or iodine, the hydrogen atom linked to the carbon atom in the 13- position and the hydrogen atom linked to the carbon atom in the 14- position, may be either in the *trans*-position (geometric *trans*-isomers) or in the *cis*-position (geometric *cis*-isomers). Preferably, they are in the *trans*-position. When in the lactol of formula (II) A' is *trans*-CH=CH—, compounds of formula (III) wherein A is *trans*-CH=CH— are obtained; in this case, the Wittig reaction may be performed

by using about 2—3 moles of Wittig reagent per mole of lactol and the reaction lasts about one hour.

When in the lactol of formula (II) A' is $-\text{C}\equiv\text{C}-$ or $-\text{CH}=\text{CX}-$ where X is halogen compounds of formula (III) wherein A is $-\text{C}\equiv\text{C}-$ are obtained, and when A' is $-\text{C}\equiv\text{C}-$ or $-\text{CH}=\text{CX}-$ wherein X is bromine or iodine, the Wittig reaction may be performed using about two moles of Wittig reagent per mole of lactol and it is sufficient that the reaction lasts 10—20 minutes. When A' is $-\text{CH}=\text{CX}-$ wherein X is chlorine, it is necessary when using for example 1.5 to 2.5 moles of Wittig reagent per mole of lactol, to prolong the reaction time up to 10 hours. If it is desired to use shorter reaction times, it is necessary to employ a great excess of Wittig reagent (at least 5 moles of Wittig reagent per mole of lactol for reaction time of about 30 minutes).

The Wittig reaction is performed by using the conditions generally followed for this kind of reaction, i.e. in an organic solvent, for example diethyl ether, hexane, dimethyl sulphoxide, tetrahydrofuran, dimethylformamide or hexamethylphosphoramide, in the presence of a base, preferably sodium hydride or potassium *tert.* butoxide, at 0° C. to the reflux temperature of the reaction mixture, preferably at room temperature or below. The term "Wittig reagent" includes compounds of formula



wherein R_a is aryl or alkyl, Hal is bromine or chlorine and R is hydrogen or alkyl. When R_a is alkyl, it is preferably ethyl. The preparation of the Wittig reagent is discussed in detail by Tripett, *Quart. Rev.*, 1963, XVII, No. 4, 406. When, in the lactol of formula (II), A' is $-\text{CH}=\text{CX}-$, wherein X is bromine, chlorine or iodine, the dehydrohalogenation takes place during the reaction with the Wittig reagent as easily when the 13-hydrogen atom and the 14-halogen atom are in the *trans*-position as when they are in the *cis*-position.

The optional acylation of the 9 α -hydroxy group in the compound of formula (III) may be performed in a conventional manner, for example by treatment with an anhydride or a chloride of a carboxylic acid in presence of a base. In this case, a 9 α -acyloxy derivative is obtained. When the acylation is carried out with a carboxylic acid in presence of (A) a compound of formula $\text{M}'\text{Y}_3$, wherein M' is a metalloid of the V group and Y is an alkyl, dialkylamino or aryl group, and of (B) a hydrogen-acceptor, a 9 β -acyloxy derivative is obtained, due to the complete inversion of configuration of the hydroxy group in the 9-position. This reaction is preferably carried out at room temperature in an inert anhydrous solvent, preferably selected from aromatic hydrocarbons, such as benzene and toluene, and linear or cyclic ethers, for example diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran and dioxan. All the reagents, i.e. the compounds of formula $\text{M}'\text{Y}_3$, the esterifying carboxylic acid and the hydrogen-acceptor, are employed in the proportion of at least 1.5 mole per mole of alcohol, 2 to 4 moles of the reagents per mole of alcohol being preferred.

In the compound of formula $\text{M}'\text{Y}_3$, M' is preferably P, As or Sb, especially P, and Y, when alkyl, is preferably methyl, when aryl, preferably phenyl, and when dialkylamino, preferably dimethylamino. The compound of formula $\text{M}'\text{Y}_3$ is preferably triphenylphosphine, triphenylarsine, triphenylstibine, or hexamethyltriaminophosphine of formula $[(\text{CH}_3)_2\text{N}]_3\text{P}$.

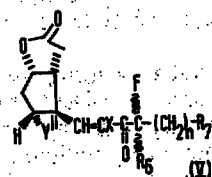
The hydrogen-acceptor used is preferably an ester or an amide of the azodicarboxylic acid, preferably ethyl azodicarboxylate, but also other hydrogen-acceptors may be used, for instance 2,3,5,6-tetrachloro-1,4-benzoquinone, 2,3-dicyano-5,6-dichloro-1,4-benzoquinone or azobisformamide.

The deetherification reaction of the compound of formula (III)—or of the 9 α - or 9 β -acyloxy derivative of this compound—wherein Y and/or one of R'_1 and R'_2 are a known protecting group as above defined, may be performed under conditions of mild acid hydrolysis, for example with mono- or poly-carboxylic 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, 0.1 to 0.25 N poly-carboxylic acid (e.g. oxalic or citric acid) is used in 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 α - or 9 β -hydroxy group to yield an oxo group may be carried out with, for example, Jones reagent or Moffatt reagent, and as stated above, the deetherification of the resulting compound of formula (IV) may give, according to the reaction conditions used, either a compound of formula (I) wherein the symbol

--- is a single bond, R_3 is hydroxy and R_1 and R_2 , taken together, form an oxo group, or a compound of formula (I) wherein the symbol --- is a double bond, R_3 is hydrogen and R_2 and R_3 , taken together, form an oxo group. The former compound may be obtained as the only product by operating at temperatures ranging between 25° C. and 35—38° C., while by operating at higher temperatures, for example, at the reflux temperature for about three hours, the latter compound may be obtained as the only product.

The lactol of formula (II) may be prepared, in turn, by means of a multi-step process using as starting material an optically active or racemic lactone of formula (V)

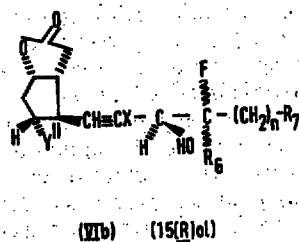
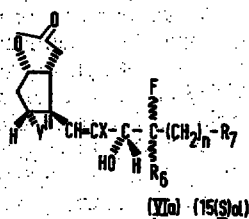


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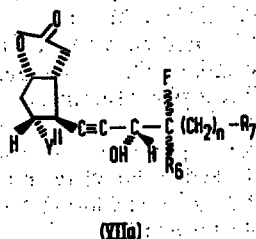
Y'' is hydroxy, carboxylic acyloxy or a known protecting group bound to the ring through an ethereal oxygen atom, X , R_3 , R_7 , and n are as defined above; and wherein the hydrogen atom linked to the carbon atom in the 13-position and the halogen atom linked to the carbon atom in the 14-position (prostaglandin numbering) may be either in the *trans*-position or in the *cis*-position.

The multi-step process to prepare the compound of general formula (II) starting from the lactone of formula (V) involves the following steps:

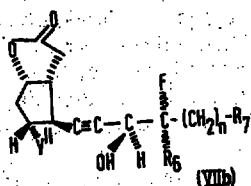
a) reduction of the 15-oxo group (prostaglandin numbering) of the lactone of formula (V) to yield a mixture of 15(*S*)- and 15(*R*)-ols having the formulae (VIa) and (VIb)



wherein Y'' , X , R_3 , R_7 , and n are as above defined, followed by the separation of the 15(*S*)-ol from the 15(*R*)-ol and, if desired, by the dehydrohalogenation of the separated alcohols wherein X is halogen to give a compound of formula (VIIa)

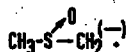


or a compound of formula (VIIb)

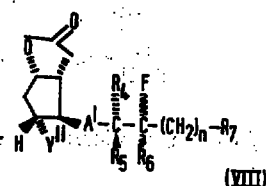


wherein Y'' , R_3 , R_7 , and n are as above defined. If desired, the reduction may follow the dehydrohalogenation. The reduction of the 15-oxo group may be suitably performed

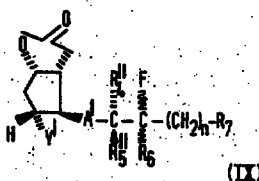
in an organic solvent, such as acetone, diethyl ether, 1,2-dimethoxyethane, dioxan, or benzene or their mixtures, by using e.g. metal borohydrides, in particular sodium borohydride, lithium borohydride, zinc borohydride, sodium trimethoxyborohydride. The separation of the 15(*S*)-ol from the 15(*R*)-ol may be performed by chromatography, e.g. silica gel chromatography or by fractionated crystallization. The dehydrohalogenation may be performed in a solvent, preferably dimethyl sulphoxide, dimethylformamide or hexamethylphosphoramide in presence of a base which may be for example an alkaline metal amide, potassium *tert.* butoxide or the anion



b) Conversion of a compound of formula (VIII)



wherein Y', R₄, R₅, A', and n are as defined above and one of R₄ and R₅ is a hydrogen atom and the other is a hydroxy group into a compound of formula (IX)

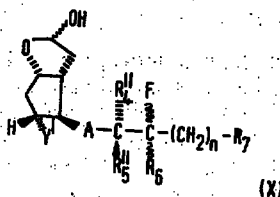


wherein A', R₄, R₅, and n are as defined above, Y' is a known protecting group bound to the ring through an ethereal oxygen atom, and one of R₄' and R₅' is a known protecting group bound to the chain by an ethereal oxygen atom and the other is a hydrogen atom. When, in the compound of formula (VIII), Y' is a carboxylic acyloxy group, the etherification of the compound of formula (VIII) to give a compound of formula (IX) is preceded by saponification, for example by mild treatment with an alkali, to give a compound of formula (VIII) wherein Y' is a hydroxy group. The etherification is preferably carried out by reacting the alcohol with a vinyl ether of formula



wherein W is —O— or —CH₂—, in presence of catalytic amounts of, for example, phosphorus oxychloride; *p*-toluenesulphonic acid or benzenesulphonic acid, or with a tri-substituted chlorosilane in presence of an acceptor base (for example a trialkylamine) for the hydrogen halide formed, or with a 1,1-dialkoxy-cyclopent(or hex)ane in the presence of an acid catalyst at the reflux temperature in an inert solvent and distilling the alcohol formed to obtain mixed dialkoxy ethers or enol ethers, according to the quantity of catalyst used or the heating time.

c) Reduction of the compound of formula (IX) to yield a lactol derivative of formula (X)



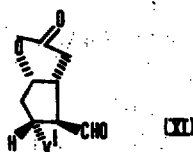
wherein Y', A', R₄', R₅', R₆, R₇, and n are as above defined. The reduction may be

performed by treatment with diisobutyl-aluminium hydride or sodium bis-(2-methoxyethoxy)-aluminium hydride in an inert solvent, for example, toluene, n-heptane, n-hexane or benzene or their mixtures, at below 30°C.

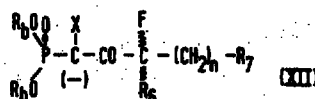
d) Optional deetherification of the compound of formula (X) to give a compound having the free 11- and 15- hydroxy groups. The deetherification may be carried out by mild acid hydrolysis, in a solvent miscible with water, with a solution of a mono- or poly- carboxylic acid.

All the compounds mentioned under items a) to d) may be either optically active compounds or racemic mixtures thereof.

The lactone of formula (V) may be in turn prepared by reaction of an optically active or racemic aldehyde of formula (XI)

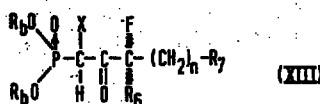


wherein Y'' is as defined above, with an optically active or racemic phosphonate carbanion of formula (XII)



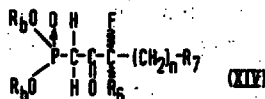
wherein R6 is lower alkyl, X, R6, R7, and n are as defined above. The reaction is suitably performed in a solvent which is preferably dry benzene, 1,2-dimethoxyethane, tetrahydrofuran, dimethylformamide or their mixtures, and using a suspension of 1.1—1.2 molar equivalent of the halo-phosphonate carbanion. When in the aldehyde of formula (XI) Y'' is an acyloxy group, it may be for example, acetoxy, propionyloxy, benzoyloxy and p-phenylbenzyloxy. When Y'' is a known protecting group bound to the ring through an ethereal oxygen atom, it may be for example one of the ethereal protecting groups reported here-above.

The aldehyde of formula (XI) may be prepared substantially as described by E. J. Corey et al., Ann. of New York Acad. of Sciences, 180, 24 (1971), and the phosphonate carbanion of formula (XII) may in turn be prepared by reacting a phosphonate of formula (XIII)



wherein R6, X, R6, R7, and n are as defined above, with an equivalent of a base, preferably sodium hydride, lithium hydride, calcium hydride, an alkyl lithium derivative or the anion CH3—SO2—CH2(-).

The phosphonate of formula (XIII), wherein X is halogen, may be obtained by halogenation of a phosphonate of formula (XIV)



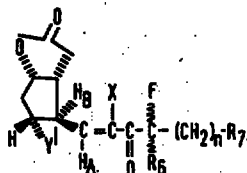
wherein R6, R6, R7, and n are as defined above, which halogenation may be carried out in a conventional manner, operating substantially as in the halogenation of β-ketoesters. The phosphonate of formula (XIV) may be prepared by known methods, e.g. according to E. J. Corey et al., J. Am. Chem. Soc. 90, 3247 (1968) and E. J. Corey and G. K. Kwiatkowski, J. Am. Chem. Soc., 88, 5654 (1966). Preferably, the phosphonate of formula (XIV) is prepared by reaction of lithium methylphosphonate with a lower alkyl ester of the optionally substituted aliphatic acid. When the aliphatic acid contains asym-

metric carbon atoms, it is possible to use either the racemic acid or one of its optical antipodes. The lower alkyl ester of the optionally substituted aliphatic acid may be prepared by conventional methods.

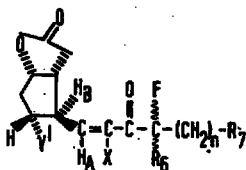
Alternatively, the phosphonate carbanion of formula (XII) wherein X is halogen may be prepared *in situ* by reacting a phosphonate carbanion of formula (XII), wherein X is hydrogen, and R_1 , R_2 , R_3 , and n are as defined above, with an equivalent of a halogenating agent selected from *N*-chloroacetamide, *N*-chlorosuccinimide, *N*-bromosuccinimide, *N*-bromocaprolactame and *N*-iodosuccinimide.

In the preparation of the halo-lactone of formula (V), wherein A' is $-\text{CH}=\text{CX}-$, according to the above methods, both compounds wherein the hydrogen atom linked to the carbon atom in the 13-position and the halogen atom linked to the carbon atom in the 14-position (prostaglandin numbering) are in the *trans*-position (geometric *trans*-isomers) and compounds wherein said atoms are in the *cis*-position (geometric *cis*-isomers) are obtained. The geometric *trans*-isomers are obtained in a far higher percentage (92–95%), while the geometric *cis*-isomers are obtained in a far lower percentage (5–8%).

The geometric *trans*-isomers of formula



can be easily distinguished from the geometric *cis*-isomers of formula



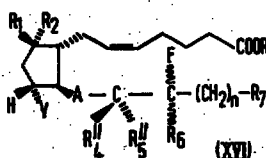
in that the H_A vinylic protons of the two isomers resonate at different positions and the coupling constants of the H_A vinylic proton with the H_B proton are very different (respectively 9 Hz for the *trans*-isomer and 10.2 Hz for the *cis*-isomer). Both the *trans*-isomers and the *cis*-isomers are intermediates for the synthesis of the 13,14-dehydroprostaglandins of the invention.

The lactol of formula (II) wherein A' is $-\text{C}\equiv\text{C}-$ may be also prepared by dehydrohalogenation of the lactol of formula (II) wherein A' is



wherein X is bromine, chlorine or iodine. The dehydrohalogenation may be carried out in an aprotic solvent preferably selected from dimethyl sulphoxide, dimethylformamide and hexamethylphosphoramide by treatment with a base preferably selected from potassium *tert*-butoxide, an alkali metal amide and the anion $\text{CH}_3-\text{SO}-\text{CH}_2^-$.

The invention includes compounds of formula (XVI)



wherein Y is hydroxy or a known protecting group bound to the ring by an ethereal oxygen atom, one of R_4'' and R_5'' is a known protecting group bound to the chain by an ethereal oxygen atom and the other is hydrogen, one of R_1 and R_2 is hydrogen and the other is hydroxy or carboxylic acyloxy or R_1 and R_2 , taken together, form an oxo group, and R_1 , R_2 , R_3 , A , n are as defined above.

The compounds of formula (I) may be used for the same therapeutical indications as natural prostaglandins, with respect to which, however, they offer the advantages of not being degradable by the enzyme 15-prostaglandin dehydrogenase, which, as is known, quickly inactivates natural prostaglandins, and of having a more selective therapeutical action. The compounds of formula (I), furthermore, competitively inhibit the degradation of natural prostaglandins by the same enzyme. In particular, the compounds of formula (I), wherein R_1 and R_2 are hydroxy, are provided with an outstanding luteolytic activity, i.e. they are useful as abortive agents, as shown by Table I, from which it results that the presence in C_{16} of a fluorine atom maintains the luteolytic activity unchanged, and, at the same time, reduces the contracturing activity in the uterine muscles, so allowing a dissociation between the two activities, while the compounds of formula (I), wherein R_1 and R_2 , together, form an oxo group, and R_3 is hydroxy, are in particular endowed with remarkable luteolytic and anti-ulcer activities, as shown by Table II, from which it results that the presence in C_{16} of a fluorine atom improves the anti-ulcer activity and causes a good luteolytic activity, while it reduces the capacity to stimulate smooth muscles, such as the ileum of guinea-pigs and the uterus of rats.

TABLE I

Compounds	Potency Ratio Rat Uterus	Abortion in Rats (*) (number of abortions/number of rats)
PGF _{2α}	1	0/10
18,19,20-trinor-17-cyclohexyl-PGF _{2α}	3.22	7/10
18,19,20-trinor-17-cyclohexyl-16(S,R)-fluoro-PGF _{2α}	0.33	6/12
18,19,20-trinor-17-cyclohexyl-13,14-di-dehydro-PGF _{2α}	10.59	10/10
18,19,20-trinor-17-cyclohexyl-13,14-di-dehydro-16(S,R)-fluoro-PGF _{2α}	3.29	10/10

(*) In this and the subsequent antifertility experiments, all the compounds are administered subcutaneously at a dose of 2 mg/kg b.w. (0.2 ml/100 g b.w.) to female rats on the 10th day of pregnancy after inspection of the uterus, and implanted fetuses are counted on the same day. Animals are killed on the 21st day of pregnancy and the presence of any fetal debris is counted as no abortion.

TABLE II

Compounds	Potency Ratio Ileum Uterus of Rats		Anti-ulcer activity	Number of abortions / Number of Rats
PGE ₂	1	1	1	0/10
18,19,20-trinor-17-cyclohexyl-PGE ₂	0.27	0.75	0.40	0/10
18,19,20-trinor-17-cyclohexyl-16(S,R)-fluoro-PGE ₂	0.11	0.55	1.20	10/12

The compounds of formula (I) can be administered orally, parenterally, or by intravenous or intrauterine (extra-amniotic or intra-aminotic) injection, 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, $\mu\text{g/kg}$ of mammal body weight per minute.

The invention also provides a pharmaceutical or veterinary composition comprising a compound of formula (I), or a veterinarily or pharmaceutically acceptable salt thereof, and a pharmaceutically or veterinarily acceptable carrier or diluent therefor. 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 further provides a method for the treatment of a warm-blooded non-human animal which comprises administering thereto a compound of the formula I or a pharmaceutically or veterinarily acceptable salt thereof.

The invention is illustrated by the following examples, where the abbreviations THP, DIOX, DMSO, THF, DMF, DIBA, HMPA, Et₂O, DME, respectively, refer to tetrahydropyran-2-yl, 1,4-dioxan-2-yl, dimethyl sulphoxide, tetrahydrofuran, dimethylformamide, diisobutylaluminum hydride, hexamethylenephosphoramidate, diethyl ether and 1,2-dimethoxyethane. Unless otherwise specified all optical rotations were determined at 20°C on 1% by weight solutions of the relevant compound.

Example 1.

A suspension of 1.220 g of NaH (80% dispersion in mineral oil) in 30 ml of dry DMSO, under nitrogen and with exclusion of moisture is heated at 58—65°C, until no more hydrogen evolves. After cooling to 4—8°C, 8.92 g of triphenyl-(4-carboxybutyl)-phosphonium bromide is added and the mixture is stirred until it is all dissolved, with formation of a dark red solution of the ylide, maintaining the temperature at 10—12°C by means of outside cooling. To this is added a solution in 5 ml of anhydrous DMSO of 1.2 g of 2 - {5 α - hydroxy - 3 α - (THP - oxy) - 2 β - [(3S) - 3 - (THP - oxy) - 4(R,S) - fluoro - 5 - cyclohexyl - trans - pentenyl] - 1 α - cyclopentyl} - ethanal γ -hemiacetal. The mixture is stirred for 4 hours, then diluted with 30 ml of water and extracted repeatedly (16 times with 5 ml each) with diethyl ether, to remove the triphenylphosphine oxide formed. The combined ethereal extracts are re-extracted with 0.5N NaOH (5 times with 5 ml) and then discarded. The combined aqueous alkaline extracts are acidified to pH 4.5 with 2N sulphuric acid and extracted with diethyl ether-pentane 1:1 v/v. These organic extracts are combined, washed until neutral, dried over Na₂SO₄, and evaporated to dryness, yielding 1.3 g of 7 - {5 α - hydroxy - 3 α - (THP) - oxy - 2 β - [(3S) - 3 - (THP - oxy) - 4(R,S) - fluoro - 5 - cyclohexyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - 5 - cis - heptenoic acid [18,19,20 - trinor - 17 - cyclohexyl - 16(R,S) - fluoro - PGF_{2a} 11,15 - bis - THP - ether].

By the same procedure, if one starts with the individual 16S-fluoro and 16R-fluoro isomers as well as with one of the following aldehydes:

2 - {5 α - hydroxy - 3 α - (THP - oxy) - 2 β - [(3S) - 3 - (THP - oxy) - 4(R,S) - fluoro - 5 - cyclopentyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanol γ -hemiacetal;

2 - {5 α - hydroxy - 3 α - (THP - oxy) - 2 β - [(3S) - 3 - (THP - oxy) - 4,4 - difluoro - 5 - cyclopentyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanol γ -hemiacetal;

or
2 - {5 α - hydroxy - 3 α - (THP - oxy) - 2 β - [(3S) - 3 - (THP - oxy) - 4,4 - difluoro - 5 - cyclohexyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanol γ -hemiacetal;

one obtains the following compounds:

18,19,20 - trinor - 17 - cyclohexyl - 16(S) - fluoro - PGF_{2a} 11,15 - bis - THP - ether;

18,19,20 - trinor - 17 - cyclohexyl - 16(R) - fluoro - PGF_{2a} 11,15 - bis - THP - ether;

18,19,20 - trinor - 17 - cyclopentyl - 16(R,S) - fluoro - PGF_{2a} 11,15 - bis - THP - ether;

18,19,20 - trinor - 17 - cyclopentyl - 16,16 - difluoro - PGF_{2a} 11,15 - bis - THP - ether;

18,19,20 - trinor - 17 - cyclohexyl - 16,16 - difluoro - PGF_{2a} 11,15 - bis - THP - ether.

Example 2.

To a solution of the ylide prepared as described in Example 1, starting with 612 mg of NaH (80% dispersion in mineral oil) and 4.52 g of triphenyl-(4-carboxy-

butyl)-phosphonium bromide, in 25 ml of anhydrous DMSO is added a solution of 934 mg of 2 - (5 α - hydroxy - (3 - THP - oxy) - 2 β - [2 - bromo - (3S) - 3 - (THP - oxy) - 4(R,S) - fluoro - *trans* - 1 - nonenyl] - 1 α - cyclopentyl] - ethanal γ -hemiacetal in 8 ml of DMSO. The mixture is kept at room temperature for 10 hours, then diluted with 30 ml of water and extracted with diethyl ether to remove the triphenylphosphine oxide. The combined ethereal phases are re-extracted with 0.5N NaOH and then discarded. The combined aqueous alkaline phases are acidified to pH 4.5 and extracted with diethyl ether:pentane 1:1 v/v. These organic extracts are combined, washed until neutral with saturated aqueous ammonium sulphate solution, dried over sodium sulphate and evaporated to dryness. The yield is 860 mg of 13,14 - didehydro - 16(R,S) - fluoro - 20 - methyl - PGF_{2a} 11,15 - bis - THP - ether.

Example 3.

To a solution of 0.5 g of 18,19,20 - trinor - 17 - cyclohexyl - 16(R,S) - fluoro - PGF_{2a} 11,15 - bis - THP - ether in 8 ml of acetone is added 10 ml of a 0.25N aqueous solution of oxalic acid and the mixture is refluxed for 2 hours. The excess acetone is evaporated under vacuum, and the aqueous phase is extracted with diethyl ether. The organic extracts are combined, washed until neutral with a saturated ammonium sulphate solution, dried and evaporated to dryness. The residue is chromatographed on acid-washed silica gel, elution being effected with methylene chloride-ethyl acetate 8:2 v/v, to yield 320 mg of pure 18,19,20 - trinor - 17 - cyclohexyl - 16(R,S) -

fluoro - PGF_{2a}; $[\alpha]_D^{25} = +15.1^\circ$; $[\alpha]_{365}^{25} = +46.8^\circ$.

The diöxanyl ether may be deetherified by the same procedure.

Example 4.

A solution in anhydrous DMSO of 1.75 g of freshly sublimed potassium *tert*-butoxide is added to a solution of 3.46 g of triphenyl - (4 - carboxybutyl) - phosphonium bromide in 25 ml of DMSO, maintained at about 15°C, with constant stirring under an inert atmosphere. To the dark red solution of the ylide which is formed a solution of 770 mg of 2 - (5 α - hydroxy - 3 α - (DIOX - oxy) - 2 β - [2 - bromo - (3S) - (DIOX - oxy) - 4,4 - difluoro - 5 - phenyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl] - ethanal γ -hemiacetal in 10 ml of a 1:1 v/v mixture of DMSO:THF.

The mixture is stirred for 10 hours, then diluted with 30 ml of water and the aqueous phase is extracted with diethyl ether to remove the triphenylphosphine oxide. The ethereal extracts are re-extracted with 0.5N NaOH and then discarded. The aqueous alkaline phases are combined, acidified to pH 4.5 with 2N H₂SO₄ and extracted with diethyl ether:pentane 1:1 v/v. These organic extracts are washed until neutral with saturated ammonium sulfate solution and evaporated to dryness to give 700 mg of 18,19,20 - trinor - 17 - phenyl - 16,16 - difluoro - 13,14 - didehydro - PGF_{2a} 11,15 - bis - DIOX - ether.

Following the procedure of Example 2 or Example 4, starting from the following aldehydes either as the 3,5-bis-THP-oxy or the 3,5-bis-DIOX-oxy derivatives:—

- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - *trans* - 1 - octenyl] - 1 α - cyclopentyl] - ethanal γ -hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R) - fluoro - 4(S) - methyl - *trans* - 1 - octenyl] - 1 α - cyclopentyl] - ethanal γ -hemiacetal, and its 4(R) - methyl - 4(S) - fluoro - isomer;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4,4 - difluoro - *trans* - 1 - octenyl] - 1 α - cyclopentyl] - ethanal γ -hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - *trans* - 1 - nonenyl] - 1 α - cyclopentyl] - ethanal γ -hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(S) - fluoro - 4(R) - methyl - *trans* - 1 - nonenyl] - 1 α - cyclopentyl] - ethanal γ -hemiacetal and its 4(S) - methyl - 4(R) - fluoro - isomer;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4,4 - difluoro - *trans* - 1 - nonenyl] - 1 α - cyclopentyl] - ethanal γ -hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - *trans* - 1 - decenyl] - 1 α - cyclopentyl] - ethanal γ -hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4,4 - difluoro - *trans* - 1 - decenyl] - 1 α - cyclopentyl] - ethanal γ -hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(S) - fluoro - 5 - cyclopentyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl] - ethanal γ -hemiacetal;

- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4,4 - difluoro - 5 - cyclopentyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal and the individual 4(S)-fluoro and 4(R)-fluoro isomers;
 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4,4 - difluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - 5 - phenyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4,4 - difluoro - 5 - phenyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - (3S) - 3 - hydroxy - 4(R,S) - fluoro - 4 - (4' - fluorophenyl) - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - 4 - (3' - chlorophenyl) - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - 4 - (3' - trifluoromethylphenyl) - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
 the following compounds are obtained, either as the 11,15 - bis - THP - ethers or as the 11,15 - bis - DIOX - ethers:
 13,14 - didehydro - 16(R,S) - fluoro - PGF_{2a};
 13,14 - didehydro - 16(S) - methyl - 16(R) - fluoro - PGF_{2a} and its 16(S) - fluoro - 16(R) - methyl isomer;
 13,14 - didehydro - 16,16 - difluoro - PGF_{2a};
 13,14 - didehydro - 16,16 - difluoro - 20 - methyl - PGF_{2a};
 13,14 - didehydro - 16(S) - fluoro - 16(R), 20 - dimethyl - PGF_{2a} and its 16(R) - fluoro - 16(S) - methyl isomer;
 13,14 - didehydro - 16(R,S) - fluoro - 20 - methyl - PGF_{2a};
 13,14 - didehydro - 16(R,S) - fluoro - 20 - ethyl - PGF_{2a};
 13,14 - didehydro - 16,16 - difluoro - 20 - ethyl - PGF_{2a};
 18,19,20 - trinor - 17 - cyclopentyl - 16(S) - fluoro - 13,14 - didehydro - PGF_{2a};
 18,19,20 - trinor - 17 - cyclopentyl - 16,16 - difluoro - 13,14 - didehydro - PGF_{2a};
 18,19,20 - trinor - 17 - cyclohexyl - 16(R,S) - fluoro - 13,14 - didehydro - PGF_{2a} and the individual 16(S) - fluoro and 16(R) - fluoro isomers;
 18,19,20 - trinor - 17 - cyclohexyl - 16,16 - difluoro - 13,14 - didehydro - PGF_{2a};
 18,19,20 - trinor - 17 - phenyl - 16(R,S) - fluoro - 13,14 - didehydro - PGF_{2a};
 18,19,20 - trinor - 17 - phenyl - 16,16 - difluoro - 13,14 - didehydro - PGF_{2a};
 18,19,20 - trinor - 16(R,S) - fluoro - 17 - (4 - fluorophenyl) - 13,14 - didehydro - PGF_{2a};
 18,19,20 - trinor - 16(R,S) - fluoro - 17 - (3' - chlorophenyl) - 13,14 - didehydro - PGF_{2a};
 18,19,20 - trinor - 16(R,S) - fluoro - 16 - (3' - trifluoromethylphenyl) - di - 13,14 - didehydro - PGF_{2a};
 which are then deetherified by the procedure described in Example 3 to give the following free hydroxy acids:
 13,14 - didehydro - 16(R,S) - fluoro - PGF_{2a};
 13,14 - didehydro - 16(S) - methyl - 16(R) - fluoro - PGF_{2a} and its 16(S) - fluoro - 16(R) - methyl isomer;
 13,14 - didehydro - 16,16 - difluoro - PGF_{2a};
 13,14 - didehydro - 16,16 - difluoro - 20 - methyl - PGF_{2a};
 13,14 - didehydro - 16(S) - fluoro - 16(R), 20 - dimethyl - PGF_{2a} and its 16(R) - fluoro - 16(S) - methyl isomer;
 13,14 - didehydro - 16(R,S) - fluoro - 20 - methyl - PGF_{2a};
 13,14 - didehydro - 16(R,S) - fluoro - 20 - ethyl - PGF_{2a};
 13,14 - didehydro - 16,16 - difluoro - 20 - ethyl - PGF_{2a};
 18,19,20 - trinor - 17 - cyclopentyl - 16(S) - fluoro - 13,14 - didehydro - PGF_{2a};
 18,19,20 - trinor - 17 - cyclopentyl - 16,16 - difluoro - 13,14 - didehydro - PGF_{2a};
 18,19,20 - trinor - 17 - cyclohexyl - 16(R,S) - fluoro - 13,14 - didehydro - PGF_{2a} and the individual 16(S) - fluoro and 16(R) - fluoro isomers;
 18,19,20 - trinor - 17 - cyclohexyl - 16,16 - difluoro - 13,14 - didehydro - PGF_{2a};
 18,19,20 - trinor - 17 - phenyl - 16(R,S) - fluoro - 13,14 - didehydro - PGF_{2a};

18,19,20 - trinor - 17 - phenyl - 16,16 - difluoro - 13,14 - didehydro - PGF_{2a};
 18,19,20 - trinor - 16(R,S) - fluoro - 17 - (4' - fluorophenyl) - 13,14 - didehydro-
 PGF_{2a};
 18,19,20 - trinor - 16(R,S) - fluoro - 17 - (3' - chlorophenyl) - 13,14 - didehydro-
 PGF_{2a};
 18,19,20 - trinor - 16(R,S) - fluoro - 16 - (3' - trifluoromethylphenyl) - 13,14 - dide-
 hydro - PGF_{2a}.

Example 5.

A solution of 0.37 g of 18,19,20 - trinor - 17 - cyclohexyl - 16(R,S) - fluoro-
 PGF_{2a} 11,15 - bis - THP - ether in 10 ml of acetone is cooled to -15°C and
 0.9 ml of Jones reagent is added. This is maintained at -10 to -12°C for 30 minutes,
 then diluted with 70 ml of benzene, washed repeatedly with saturated aqueous ammo-
 nium sulfate until neutral (10 x 5 ml). The organic layer is then dried over sodium sul-
 phate and evaporated to dryness. The crude reaction product is dissolved in 60 ml of
 acetone and combined with 80 ml of an aqueous 0.1N sodium oxalate solution. The mix-
 ture is maintained at 40°C for 10 hours. The acetone is evaporated under vacuum and
 the aqueous phase extracted with diethyl ether. The combined organic extracts are
 washed until neutral, dried and evaporated to dryness. The residue is chromatographed
 on acid-washed silica gel and eluted with methylene chloride-ethyl acetate to give 0.2 g
 of 18,19,20 - trinor - 17 - cyclohexyl - 16(R,S) - fluoro - PGE₂, $[\alpha]_D = -47.8^\circ$
 $[\alpha]_{25} = -291^\circ$ (EtOH).

Using the above procedure and starting with compounds prepared as described in
 Examples 1, 2, 3 and 4 in the form of the 11,15-bis-ethers, after oxidation with Jones
 reagent and subsequent deetherification the following PGE₂ derivatives are obtained:

18,19,20 - trinor - 17 - cyclopentyl - 16(R,S) - fluoro - PGE₂;
 18,19,20 - trinor - 17 - cyclopentyl - 16,16 - difluoro - PGE₂;
 18,19,20 - trinor - 17 - cyclohexyl - 16(R,S) - fluoro - PGE₂ and the individual
 16(S) and 16(R) isomers;
 18,19,20 - trinor - 17 - cyclohexyl - 16,16 - difluoro - PGE₂;
 13,14 - didehydro - 16(R,S) - fluoro - PGE₂; $[\alpha]_D = -3.6^\circ$ (EtOH);
 13,14 - didehydro - 16(S) - methyl - 16(R) - fluoro - PGE₂ and its 16(R) - methyl-
 16(S) - fluoro - isomer;
 13,14 - didehydro - 16,16 - difluoro - PGE₂;
 13,14 - didehydro - 16(R,S) - fluoro - 20 - methyl - PGE₂;
 13,14 - didehydro - 16(S) - fluoro - 16(R), 20 - dimethyl - PGE₂ and its 16(S) -
 methyl - 16(R) - fluoro isomer;
 13,14 - didehydro - 16,16 - difluoro - 20 - methyl - PGE₂;
 13,14 - didehydro - 16(R,S) - fluoro - 20 - ethyl - PGE₂;
 13,14 - didehydro - 16,16 - difluoro - 20 - ethyl - PGE₂;
 18,19,20 - trinor - 17 - cyclopentyl - 16(R,S) - fluoro - 13,14 - didehydro - PGE₂;
 18,19,20 - trinor - 17 - cyclopentyl - 16,16 - difluoro - 13,14 - didehydro - PGE₂;
 18,19,20 - trinor - 17 - cyclohexyl - 16(R,S) - fluoro - 13,14 - didehydro - PGE₂ and
 the individual 6(S) - fluoro and 16(R) - fluoro isomers;
 18,19,20 - trinor - 17 - cyclohexyl - 16,16 - difluoro - 13,14 - didehydro - PGE₂;
 18,19,20 - trinor - 17 - phenyl - 16(R,S) - fluoro - 13,14 - didehydro - PGE₂;
 18,19,20 - trinor - 17 - phenyl - 16,16 - difluoro - 13,14 - didehydro - PGE₂;
 18,19,20 - trinor - 16(R,S) - fluoro - 17 - (4' - fluorophenyl) - 13,14 - didehydro-
 PGE₂;
 18,19,20 - trinor - 16(R,S) - fluoro - 16 - (3' - chlorophenyl) - 13,14 - didehydro-
 PGE₂.

Example 6.

A solution of 0.59 g of 18,19,20 - trinor - 17 - cyclohexyl - 16(R,S) - fluoro-
 PGE₂ 11,15 - bis - THP - ether in 80 ml of acetone is refluxed with 50 ml of
 an aqueous 0.25N solution of oxalic acid for 6 hours. The acetone is evaporated under
 vacuum and the residue extracted repeatedly with diethyl ether. The combined ethereal
 extracts are washed with saturated aqueous ammonium sulphate, dried and evaporated
 to dryness. The residue is chromatographed on acid-washed silica gel, eluted with cyclo-
 hexane - ethyl acetate 80:20 v/v, yielding 300 mg of 18,19,20 - trinor - 17 - cyclo-
 hexyl - 16(R,S) - fluoro - PGA₂.

Using the above procedure and starting with compounds prepared as outlined in
 Example 5, in the form either of the free alcohols or of the 11,15-bis-THP-ethers or
 11,15-bis-DIOX-ethers, one prepares the following compounds:

18,19,20 - trinor - 17 - cyclopentyl - 16(R,S) - fluoro - PGA₂;
 18,19,20 - trinor - 17 - cyclohexyl - 16(R,S) - fluoro - PGA₂;

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13,14 - dehydro - 16(*R,S*) - fluoro - PGA_2 ;
13,14 - dehydro - 16(*S*) - methyl - 16(*R*) - fluoro - PGA_2 ;
13,14 - didehydro - 16,16 - difluoro - PGA_2 ;
13,14 - didehydro - 16(*R,S*) - fluoro - 20 - methyl - PGA_2 ;
13,14 - didehydro - 16(*S*) - fluoro - 16(*R*), 20 - dimethyl - PGA_2 ;
13,14 - didehydro - 16,16 - difluoro - 20 - methyl - PGA_2 ;
13,14 - didehydro - 16(*R,S*) - fluoro - 20 - ethyl - PGA_2 ;
13,14 - didehydro - 16,16 - difluoro - 20 - ethyl - PGA_2 ;
18,19,20 - trinor - 17 - cyclopentyl - 16(*R,S*) - fluoro - 13,14 - didehydro - PGA_2 ;
18,19,20 - trinor - 17 - cyclopentyl - 16,16 - difluoro - 13,14 - didehydro - PGA_2 ;
18,19,20 - trinor - 17 - cyclohexyl - 16(*S*) - fluoro - 13,14 - didehydro - PGA_2 and
is 16(*R*) isomer;
18,19,20 - trinor - 17 - cyclohexyl - 16,16 - difluoro - 13,14 - didehydro - PGA_2 ;
18,19,20 - trinor - 17 - phenyl - 16(*R,S*) - fluoro - 13,14 - didehydro - PGA_2 ;
18,19,20 - trinor - 17 - phenyl - 16,16 - difluoro - 13,14 - didehydro - PGA_2 .

Example 7.

To a solution of 0.58 g of 18,19,20 - trinor - 17 - cyclohexyl - 16(*R,S*) - fluoro - PGF_{2a} 11,15 - bis - THP - ether in 12 ml of HMPA are added 44 mg of NaOH dissolved in 1 ml of water. This is stirred for 1 hour. Then 150 mg of 1-bromopropane is added and the mixture stirred for a further 12 hours. 25 ml of water and are added and the mixture is extracted with diethyl ether. The combined organic phases are washed with saturated aqueous ammonium sulphate, dried and evaporated to dryness to give 600 mg of 18,19,20 - trinor - 17 - cyclohexyl - 16(*R,S*) - fluoro - PGF_{2a} 11,15 - bis - THP - ether *n* - propyl ester.

By this procedure, starting with the 11,15-bis-ethers described in Examples 1, 2 and 3 and using instead of the 1-bromopropane another haloalkyl compound (for instance methyl iodide, ethyl iodide, 4-bromobutane, 8-bromooctane, 10-bromodecane) one can prepare the methyl, ethyl, butyl, octyl or decyl esters of the corresponding 11,15-bis-ethers, that can then be deetherified by the procedure of Example 3 to give the free hydroxy esters.

Example 8.

To a solution of 0.6 g of 18,19,20 - trinor - 17 - cyclohexyl - 16(*R,S*) - fluoro - PGF_{2a} 11,15 - bis - THP - ether *n* - propyl ester in 15 ml of anhydrous THF are added 1.05 g of triphenylphosphine and 0.79 g of *p*-phenylbenzoic acid. The reaction mixture is maintained at 20–22°C and stirred while a solution of 0.7 g of ethyl azodicarboxylate in 6 ml of THF is added drop by drop over a five minute period. After an additional 10 minutes, the mixture is evaporated to dryness and the residue taken up in 75 ml of diethyl ether, washed with a saturated aqueous solution of sodium bicarbonate, then water and evaporated to dryness. The residue is dissolved in 25 ml of acetone and 18 ml of 0.2N aqueous oxalic acid solution are added. The mixture is refluxed for 30 minutes, concentrated under vacuum to remove the acetone, extracted with ethyl acetate and the organic phase is evaporated to dryness. The residue is chromatographed on silica gel, eluted first with cyclohexane-ethyl ether 6:4 v/v and then with diethyl ether to give 0.5 g of 18,19,20 - trinor - 17 - cyclohexyl - 16(*R,S*) - fluoro - $\text{PGF}_{2\beta}$ 9 - *p* - phenylbenzoate *n* - propyl ester. A solution of this compound in 10 ml of anhydrous propanol is treated with 140 mg of anhydrous potassium carbonate and the mixture is refluxed for an hour and 30 minutes. It is then neutralized, the solvent is evaporated off and the residue partitioned between methylene chloride and water. The organic phase is dried and evaporated to dryness and the residue is chromatographed on silica gel, first eluted with diethyl ether and then with diethyl ether-ethyl acetate 1:1 v/v. The yield is 340 mg of 18,19,20 - trinor - 17 - cyclohexyl - 16(*R,S*) - fluoro - $\text{PGF}_{2\beta}$ *n* - propyl ester. This compound is dissolved in a 8:2 v/v mixture of methanol-water and 215 mg of potassium carbonate are added. The mixture is refluxed for one hour. After evaporation of the solvent, the residue is taken up in water, acidified to pH 4.5 and extracted with ethyl acetate. After evaporation of the organic phase, 280 mg of 18,19,20 - trinor - 17 - cyclohexyl - 16(*R,S*) - fluoro - $\text{PGF}_{2\beta}$ are obtained.

Using the procedures of Examples 7 and 8, starting with compounds prepared as described in Examples 1, 2, 3, or 4 the following compounds are prepared as free acids or as alkyl esters:

18,19,20 - trinor - 17 - cyclopentyl - 16(*R,S*) - fluoro - $\text{PGF}_{2\beta}$;
18,19,20 - trinor - 17 - cyclopentyl - 16,16 - difluoro - $\text{PGF}_{2\beta}$;
18,19,20 - trinor - 17 - cyclohexyl - 16(*R,S*) - fluoro - $\text{PGF}_{2\beta}$;

- 18,19,20 - trinor - 17 - cyclohexyl - 16,16 - difluoro - PGF_{2β};
 13,14 - didehydro - 16(R,S) - fluoro - PGF_{2β};
 13,14 - didehydro - 16(S) - methyl - 16(R) - fluoro - PGF_{2β} and its 16(R) - methyl-
 16(S) - fluoro isomer;
 5 13,14 - didehydro - 16,16 - difluoro - PGF_{2β};
 13,14 - didehydro - 16(R,S) - fluoro - 20 - methyl - PGF_{2β};
 13,14 - didehydro - 16(S) - fluoro - 16(R), 20 - dimethyl - PGF_{2β} and its 16(S) -
 methyl - 16(R) - fluoro isomer;
 10 13,14 - didehydro - 16,16 - difluoro - 20 - methyl - PGF_{2β};
 13,14 - didehydro - 16(R,S) - fluoro - 20 - ethyl - PGF_{2β};
 13,14 - didehydro - 16,16 - difluoro - 20 - ethyl - PGF_{2β};
 18,19,20 - trinor - 17 - cyclopentyl - 16(R,S) - fluoro - 13,14 - didehydro - PGF_{2β};
 18,19,20 - trinor - 17 - cyclopentyl - 16,16 - difluoro - 13,14 - didehydro - PGF_{2β};
 18,19,20 - trinor - 17 - cyclohexyl - 16(R,S) - fluoro - 13,14 - didehydro - PGF_{2β};
 15 18,19,20 - trinor - 17 - phenyl - 16(R,S) - fluoro - 13,14 - didehydro - PGF_{2β}.

Example 9.

- 0.78 g of 2 - {5α - hydroxy - 3α - (p - phenylbenzoyloxy) - 2β - [3(R) -
 hydroxy - 4(S) - fluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1α - cyclopentyl} -
 acetic acid γ-lactone in 25 ml of anhydrous methanol is reacted for two hours at room
 20 temperature with 150 mg of anhydrous K₂CO₃. It is then neutralized and treated with
 Amberlite (Registered Trade Mark) IR 120 resin (H⁺), filtered and the filtrate
 evaporated to dryness. The residue is taken up in 10 ml of dichloroethane and treated
 with 0.8 ml of 2,3-dihydropyran and 4 mg of *p*-toluenesulphonic acid. After 2 hours at
 room temperature, add 0.3 ml of pyridine and evaporate to dryness to give 0.9 g of
 25 2 - {5α - hydroxy - 3α - (THP - oxy) - 2β - [3(R) - (THP - oxy) - 4(S) fluoro - 5 -
 cyclohexyl - *trans* - 1 - pentenyl] - 1α - cyclopentyl} - acetic acid γ-lactone. This is
 dissolved in 10 ml of toluene, cooled to -60°C, and under an atmosphere of nitrogen
 is treated with 6.5 ml of DIBA (0.5M in toluene). After 30 minutes at -60°C, the
 excess reagent is destroyed with 7 ml of a 2M solution of isopropanol in toluene. 0.88 g
 30 of 2 - {5α - hydroxy - 3α - (THP - oxy) - 2β - [3(R) - (THP - oxy) - 4(S) - fluoro -
 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1α - cyclopentyl} - ethanal γ-hemiacetal. This
 compound is then reacted by the procedure outlined in Example 1 with the ylide gener-
 ated from 0.92 g of NaH and 6.7 g of triphenyl - (4 - carboxybutyl) - phosphonium
 bromide in 20 ml of DMSO, giving 0.96 g of 18,19,20 - trinor - 17 - cyclohexyl -
 35 16(S) - fluoro - 15 - *epi* - PGF_{2α} 11,15 - bis - THP - ether. This compound is de-
 etherified in acetone with aqueous oxalic acid, as described in Example 3, to give the
 18,19,20 - trinor - 17 - cyclohexyl - 16(S) - fluoro - 15 - *epi* - PGF_{2α} [α]_D = +4.8°
 (EtOH): In a parallel procedure, by oxidation of the 11,15 - bis - tetrahydropyranyl-
 ether derivative with Jones reagent, according to the procedure of Example 5, followed
 40 by deetherification, 18,19,20 - trinor - 17 - cyclohexyl - 16(S) - fluoro - 15 - *epi*-
 PGE₂, is obtained [α]_D = -63.2°, [α]₅₈₉ = -326° (EtOH).

Example 10.

- 8 ml of 0.2N oxalic acid are added to a solution of 380 mg of 18,19,20 - trinor -
 17 - cyclohexyl - 16(S,R) - fluoro - 13,14 - didehydro - PGF_{2α} 11,15 - bis - THP-
 45 ether, [α]_D = +9°, [α]₅₈₉ = +102° (acetone) in 10 ml of acetone. After 12 hours
 at 38°C the acetone is evaporated under vacuum and the residue is extracted with di-
 ethyl ether. The organic extracts are evaporated to dryness and the residue chromato-
 graphed on silica gel, eluted with 50:50 v/v methylene chloride:ethyl acetate, to give
 50 120 mg of 18,19,20 - trinor - 17 - cyclohexyl - 16(S,R) - fluoro - 13,14 - didehydro-
 PGF_{2α}, [α]_D = 38° (EtOH).

Example 11.

- 0.65 g of 18,19,20 - trinor - 17 - cyclohexyl - 16(S,R) - fluoro - 13,14 - dide-
 hydro - PGF_{2α} 11,15 - bis - THP - ether is dissolved in 20 ml of acetone. The
 solution is cooled to -15°C and 1.3 ml of Jones reagent are added. After 15 minutes,
 55 the mixture is diluted with 100 ml of benzene and washed until neutral with 20% w/v
 ammonium sulphate solution, dried over sodium sulphate and evaporated to dryness to
 give 0.52 g of 18,19,20 - trinor - 17 - cyclohexyl - 16(S,R) - fluoro - 13,14 - dide-
 hydro - PGE₂ 11,15 - bis - THP - ether, [α]_D = -23° (acetone). This compound
 is dissolved in 15 ml of acetone, 12 ml of 0.1N oxalic acid is added, and the mixture
 60 allowed to stand for 12 hours at 37°C. The acetone is distilled off under vacuum, the
 residue is extracted with ethyl acetate and the ethyl acetate extracts evaporated to dry-

ness. The residue (0.39 g) is chromatographed on 12 g of silica gel and eluted with methylene chloride-ethyl acetate (80:20 v/v) to give 0.2 g of 18,19,20-trinor-17-cyclohexyl-16(*S,R*)-fluoro-13,14-didehydro-PGE₂, $[\alpha]_D = -6.2^\circ$ (EtOH).

Intermediates for use in preparing the compounds of the invention can be prepared as follows:—

Preparation 1.

A suspension of 410 mg. of NaH (80% dispersion in mineral oil) in 100 ml of anhydrous benzene is added dropwise with constant stirring to a solution of 3.82 g of dimethyl- [2-oxo-3 ξ -fluoro-4-cyclohexylbutyl]phosphonate in 10 ml of anhydrous benzene in an inert atmosphere with exclusion of moisture. The mixture is stirred for one hour, then a solution of 2 g of 2-([2 β -formyl-5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)]-1 α -cyclopentyl)-acetic acid γ -lactone in anhydrous benzene is added all at once. The mixture is stirred for 15 minutes and then 100 ml of a saturated aqueous solution of monobasic sodium phosphate is added, and the organic phase is separated, washed until neutral, dried and evaporated to dryness. The residue is chromatographed on silica gel and eluted with cyclohexane-ethylacetate 8:2 to give 2.1 g of 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[3-oxo-4 ξ -fluoro-5-cyclohexyl-*trans*-1-pentenyl]-1 α -cyclopentyl)-acetic acid γ -lactone, m.p. 127–129°C.

Preparation 2.

To a suspension of 410 mg of NaH (80% dispersion in mineral oil) in 150 ml of anhydrous THF is added dropwise a solution of 3.82 g of dimethyl [2-oxo-3(*R,S*)-fluoro-4-cyclohexyl]-butylphosphonate in 10 ml of THF. The mixture is stirred for one hour until no more hydrogen is evolved, the 2.432 g of N-bromosuccinimide is added all at once and the mixture stirred for a further 15 minutes. A solution of 2 g of 2-([2 β -formyl-3 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)]-1 α -cyclopentyl)-acetic acid γ -lactone in THF is added, and the mixture is stirred for one hour and then diluted with 200 ml of a 6% w/v aqueous solution of monobasic sodium phosphate. The organic phase is separated, washed until neutral, dried and evaporated to dryness. After chromatography on a silica gel column, 1.9 g of 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-22 β -[2-bromo-3-oxo-4(*R,S*)-fluoro-5-cyclohexyl-*trans*-1-pentenyl]-1 α -cyclopentyl)-acetic acid γ -lactone are obtained.

Following the procedures of Preparations 1 and 2, the following γ -lactones are obtained:—

- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[3-oxo-4(*R,S*)-fluoro-5-cyclopentyl-*trans*-1-pentenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[3-oxo-4,4-difluoro-5-cyclopentyl-*trans*-1-pentenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[3-oxo-4(*R,S*)-fluoro-5-cyclohexyl-*trans*-1-pentenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[3-oxo-4,4-difluoro-5-cyclohexyl-*trans*-1-pentenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[2-bromo-3-oxo-4(*R,S*)-fluoro-*trans*-1-octenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[2-bromo-3-oxo-4,4-difluoro-*trans*-1-octenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[2-bromo-3-oxo-4(*S*)-fluoro-*trans*-1-octenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[2-bromo-3-oxo-4(*R*)-methyl-4(*R*)-fluoro-*trans*-1-octenyl]-1 α -cyclopentyl)-acetic acid γ -lactone and its 4(*R*)-methyl-4(*S*)-fluoro isomer;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[2-bromo-3-oxo-4(*R,S*)-fluoro-*trans*-1-nonenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[2-bromo-3-oxo-4(*S*)-fluoro-4(*R*)-methyl-*trans*-1-nonenyl]-1 α -cyclopentyl)-acetic acid γ -lactone and its 4(*S*)-methyl-4(*R*)-fluoro isomer;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[2-bromo-3-oxo-4,4-difluoro-*trans*-1-nonenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[2-bromo-3-oxo-4(*R,S*)-fluoro-*trans*-1-decenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[2-bromo-3-oxo-4,4-difluoro-*trans*-1-decenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[2-bromo-3-oxo-4(*R,S*)-fluoro-5-cyclopentyl-*trans*-1-pentenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;
- 2- (5 α -hydroxy-3 α -(*p*-phenylbenzoyloxy)-2 β -[2-bromo-3-oxo-4,4-difluoro-5-cyclopentyl-*trans*-1-pentenyl]-1 α -cyclopentyl)-acetic acid γ -lactone;

- fluoro - 5 - cyclopentyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone;
- 2 - {5 α - hydroxy - 3 α - (*p* - phenylbenzoyloxy) - 2 β - [2 - bromo - 3 - oxo - 4(*R,S*) - fluoro - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone and the individual 4(*R*) and 4(*S*) isomers;
- 2 - {5 α - hydroxy - 3 α - (*p* - phenylbenzoyloxy) - 2 β - [2 - bromo - 3 - oxo - 4,4 - difluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone;
- 2 - {5 α - hydroxy - 3 α - (*p* - phenylbenzoyloxy) - 2 β - [2 - bromo - 3 - oxo - 4(*R,S*) - fluoro - 5 - phenyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone;
- 2 - {5 α - hydroxy - 3 α - (*p* - phenylbenzoyloxy) - 2 β - [2 - bromo - 3 - oxo - 4,4 - difluoro - 5 - phenyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone;
- 2 - {5 α - hydroxy - 3 α - (*p* - phenylbenzoyloxy) - 2 β - [2 - bromo - 3 - oxo - 4(*R,S*) - fluoro - 5 - (4' - fluorophenyl) - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone;
- 2 - {5 α - hydroxy - 3 α - (*p* - phenylbenzoyloxy) - 2 β - [2 - bromo - 3 - oxo - 4(*R,S*) - fluoro - 5 - (3' - chlorophenyl) - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone;
- 2 - {5 α - hydroxy - 3 α - (*p* - phenylbenzoyloxy) - 2 β - [2 - bromo - 3 - oxo - 4(*R,S*) - fluoro - 5 - (3' - trifluoromethylphenyl) - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone.

Preparation 3.

- 2.03 g of 2 - {5 α - hydroxy - 3 α - (*p* - phenylbenzoyloxy) - 2 β - [3 - oxo - 4(*R,S*) - fluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone are dissolved in 120 ml of a 5:1 v/v mixture of anhydrous diethyl ether; DME and 280 ml of a 0.07M solution of Zn(BH₄)₂ in diethyl ether are added dropwise with stirring at room temperature. Stirring is continued for 30 minutes and then 40 ml of a saturated aqueous sodium chloride solution and 55 ml of 2N H₂SO₄ are added. The organic phase is separated off and washed until neutral, then dried and evaporated to dryness. The residue is chromatographed on a silica gel column eluted with methylene chloride - diethyl ether 9:1 v/v. 1.18 g of 2 - {3 α - hydroxy - 3 α - (*p* - phenylbenzoyloxy) - 2 β - [3(*S*) - hydroxy - 4(*R,S*) - fluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone and 780 mg of 2 - {5 α - hydroxy - 3 α - (*p* - phenylbenzoyloxy) - 2 β - [3(*R*) - hydroxy - 4(*R,S*) - fluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone and obtained, m.p. 116—118°C, $[\alpha]_D = -105^\circ$ (CHCl₃).

Preparation 4.

- 1.18 g of 2 - {5 α - hydroxy - 3 α - (*p* - phenylbenzoyloxy) - 2 β - [3(*S*) - hydroxy - 4(*R,S*) - fluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone is dissolved in 60 ml of anhydrous methanol. 360 mg of anhydrous K₂CO₃ are added and the mixture is stirred for 4 hours. It is diluted with a saturated solution of monobasic sodium phosphate and filtered. The filtrate is concentrated to a small volume, taken up in water and extracted with ethyl acetate. The combined organic phases are washed until neutral, dried and evaporated to dryness. The residue is chromatographed on silica gel, eluted with a mixture of cyclohexane-ethyl acetate. 750 mg of 2 - {3 α ,5 α - dihydroxy - 2 β - [3(*S*) - hydroxy - 4(*R,S*) - fluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone is obtained.

Preparation 5.

- 370 mg of 2 - {3 α ,5 α - hydroxy - 2 β - [3(*S*) - hydroxy - 4(*R,S*) - fluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone is dissolved in 50 ml of anhydrous benzene, and 2 mg of *p*-toluenesulphonic acid and 0.3 ml of 1,2-dihydropyran are added. The mixture is allowed to stand at room temperature for 4 hours, then washed with 3% w/v aqueous potassium carbonate and with water until neutral, dried and evaporated. 560 mg of 2 - {5 α - hydroxy - 3 α - (THP - oxy) - 2 β - [3(*S*) - (THP - oxy) - 4(*R,S*) - fluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid γ -lactone is obtained.

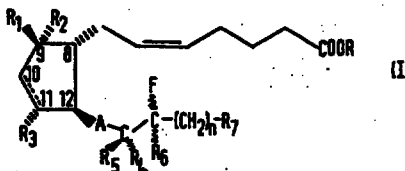
Preparation 6.

- 460 mg of 2 - {5 α - hydroxy - 3 α - (THP - oxy) - 2 β - [3(*S*) - (THP - oxy) - 4(*R,S*) - fluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - acetic acid

4(*R,S*) - fluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ -hemiacetal in 10 ml of acetone is treated with 5 ml of 0.25N aqueous oxalic acid and refluxed for 90 minutes. The solvent is evaporated off under vacuum and the aqueous phase is extracted with ethyl acetate. The combined organic extracts are washed with saturated aqueous ammonium sulfate, dried and evaporated to dryness. The residue is chromatographed on silica gel and eluted with ethyl acetate, to give 320 mg of 2-{3 α ,5 α - dihydroxy - 2 β - [3(*S*) - hydroxy - 4(*R,S*) - fluoro - 5 - cyclohexyl - *trans*-1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ -hemiacetal.

WHAT WE CLAIM IS:—

1. Optically active compounds of the formula (I)



or racemates thereof, wherein

R is hydrogen or a C₁—C₁₂ alkyl group; and the symbol

====

represents a single or a double bond; and wherein, when the symbol

====

is a double bond, R₃ is a hydrogen atom and R₁ and R₂ together form an oxo group, and when the symbol

====

is a single bond, R₃ is hydroxy, and one of R₁ and R₂ is hydrogen and the other is hydroxy or carboxylic acyloxy or R₁ and R₂ together form an oxo group; and wherein

A is *trans*-CH=CH— or —C≡C—;

one of R₄ and R₅ is hydroxy and the other is hydrogen;

R₆ is a hydrogen, methyl or fluorine;

n is zero, or an integer from 1 to 6; and

R₇ is methyl, C₂—C₆ cycloalkyl, or phenyl unsubstituted or optionally substituted by one or more substituents selected from halogen, C₁—C₆ alkoxy and trihalomethyl, with the proviso that when A is *trans*-CH=CH—, then R₇ is a C₂—C₆ cycloalkyl group; and pharmaceutically acceptable salts thereof when R is hydrogen.

2. 18,19,20-trinor-17-cyclohexyl-16(*S,R*)-fluoro-PGF_{2a}.

3. 18,19,20-trinor-17-cyclohexyl-16(*S,R*)-fluoro-PGE₂.

4. 18,19,20-trinor-17-cyclohexyl-16(*S*)-fluoro-PGF_{2a}.

5. 18,19,20-trinor-17-cyclohexyl-16(*R*)-fluoro-PGF_{2a}.

6. 16 ξ -fluoro-18,19,20-trinor-17-cyclopentyl-PGF_{2a}.

7. 16 ξ -fluoro-18,19,20-trinor-17-cyclopentyl-PGE₂.

8. 18,19,20-trinor-17-cyclohexyl-16,16-difluoro-PGF_{2a}.

9. 18,19,20-trinor-17-cyclopentyl-16,16-difluoro-PGF_{2a}.

10. 16 ξ -fluoro-13,14-didehydro-PGF_{2a}.

11. 16 ξ -fluoro-13,14-didehydro-PGE₂.

12. 16 ξ -fluoro-13,14-didehydro-PGA₂.

13. 16 ξ -fluoro-13,14-didehydro-PGF_{2 β} .

14. 16(*S*)-methyl-16(*R*)-fluoro-13,14-didehydro-PGE₂.

15. 16(*R*)-methyl-16(*S*)-fluoro-13,14-didehydro-PGE₂.

16. 16(*S*), 20-dimethyl-16(*R*)-fluoro-13,14-didehydro-PGE₂.

17. 16(*R*), 20-dimethyl-16(*R*)-fluoro-13,14-didehydro-PGE₂.

18. 16 ξ -methyl-16 ξ -fluoro-13,14-didehydro-PGF_{2a}.

19. 16 ξ -methyl-16 ξ -fluoro-13,14-didehydro-PGF_{2 β} .

20. 16 ξ -methyl-16 ξ -fluoro-13,14-didehydro-PGA₂.

21. 16,16-difluoro-13,14-didehydro-PGE₂.

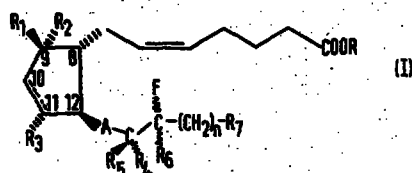
22. 16,16-difluoro-13,14-didehydro-PGF_{2a}.

23. 16,16-difluoro-13,14-didehydro-PGA₂.

4(*R,S*) - fluoro - 5 - cyclohexyl - *trans* - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ -hemiacetal in 10 ml of acetone is treated with 5 ml of 0.25N aqueous oxalic acid and refluxed for 90 minutes. The solvent is evaporated off under vacuum and the aqueous phase is extracted with ethyl acetate. The combined organic extracts are washed with saturated aqueous ammonium sulfate, dried and evaporated to dryness. The residue is chromatographed on silica gel and eluted with ethyl acetate, to give 320 mg of 2-{3 α ,5 α - dihydroxy - 2 β - [3(*S*) - hydroxy - 4(*R,S*) - fluoro - 5 - cyclohexyl - *trans*-1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal.

WHAT WE CLAIM IS:—

1. Optically active compounds of the formula (I)



or racemates thereof, wherein

R is hydrogen or a C₁—C₁₂ alkyl group; and the symbol

represents a single or a double bond; and wherein, when the symbol

is a double bond, R₃ is a hydrogen atom and R₁ and R₂ together form an oxo group, and when the symbol

is a single bond, R₃ is hydroxy, and one of R₁ and R₂ is hydrogen and the other is hydroxy or carboxylic acyloxy or R₁ and R₂ together form an oxo group; and wherein

A is *trans*—CH=CH— or —C≡C—;

one of R₄ and R₅ is hydroxy and the other is hydrogen;

R₆ is a hydrogen, methyl or fluorine;

n is zero, or an integer from 1 to 6; and

R₇ is methyl, C₂—C₆, cycloalkyl, or phenyl unsubstituted or optionally substituted by one or more substituents selected from halogen, C₁—C₆ alkoxy and trihalomethyl, with the proviso that when A is *trans*—CH=CH—, then R₇ is a C₂—C₆ cycloalkyl group; and pharmaceutically acceptable salts thereof when R is hydrogen.

2. 18,19,20-trinor-17-cyclohexyl-16(*S,R*)-fluoro-PGF_{2a}.

3. 18,19,20-trinor-17-cyclohexyl-16(*S,R*)-fluoro-PGE₂.

4. 18,19,20-trinor-17-cyclohexyl-16(*S*)-fluoro-PGF_{2a}.

5. 18,19,20-trinor-17-cyclohexyl-16(*R*)-fluoro-PGF_{2a}.

6. 16 ϵ -fluoro-18,19,20-trinor-17-cyclopentyl-PGF_{2a}.

7. 16 ϵ -fluoro-18,19,20-trinor-17-cyclopentyl-PGE₂.

8. 18,19,20-trinor-17-cyclohexyl-16,16-difluoro-PGF_{2a}.

9. 18,19,20-trinor-17-cyclopentyl-16,16-difluoro-PGF_{2a}.

10. 16 ϵ -fluoro-13,14-didehydro-PGF_{2a}.

11. 16 ϵ -fluoro-13,14-didehydro-PGE₂.

12. 16 ϵ -fluoro-13,14-didehydro-PGA₂.

13. 16 ϵ -fluoro-13,14-didehydro-PGF_{2 β} .

14. 16(*S*)-methyl-16(*R*)-fluoro-13,14-didehydro-PGE₂.

15. 16(*R*)-methyl-16(*S*)-fluoro-13,14-didehydro-PGE₂.

16. 16(*S*), 20-dimethyl-16(*R*)-fluoro-13,14-didehydro-PGE₂.

17. 16(*R*), 20-dimethyl-16(*R*)-fluoro-13,14-didehydro-PGE₂.

18. 16 ϵ -methyl-16 ϵ -fluoro-13,14-didehydro-PGF_{2a}.

19. 16 ϵ -methyl-16 ϵ -fluoro-13,14-didehydro-PGF_{2 β} .

20. 16 ϵ -methyl-16 ϵ -fluoro-13,14-didehydro-PGA₂.

21. 16,16-difluoro-13,14-didehydro-PGE₂.

22. 16,16-difluoro-13,14-didehydro-PGF_{2a}.

23. 16,16-difluoro-13,14-didehydro-PGA₂.





γ -lactone is dissolved in 20 ml of anhydrous toluene. This solution is cooled to -70°C and maintained at temperatures not higher than -60°C while adding dropwise a solution of 7.21% w/v DIBA in toluene. After it has all been added, the mixture is stirred for an additional 30 minutes. Then 3.2 ml of 2M isopropanol in anhydrous toluene are added, the temperature is allowed to rise to 0°C and 2 ml of water added. Stirring is continued for about 20 minutes and then 500 mg of Celite (Registered Trade Mark) and 1.0 g of anhydrous sodium sulphate are added. The mixture is filtered and the filtrate evaporated to give 400 mg of 2 - {5 α -hydroxy - 3 - (THP - oxy) - 2 β - [3(S) - (THP - oxy) - 4(R,S) - fluoro - 5 - cyclohexyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanol γ - hemiacetal.

Following the procedures of Preparations 3 to 5 and starting from compounds prepared according to the procedures of Preparations 1 and 2, the following compounds are obtained (either as the 3,5-bis-THP-oxy or 3,5-bis-DIOX-oxy derivatives):—

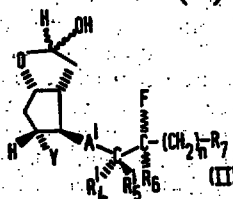
- 2 - {3 α ,5 α - dihydroxy - 2 β - [3(S) - hydroxy - 4(R,S) - fluoro - 5 - cyclopentyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [3(S) - hydroxy - 4,4 - difluoro - 5 - cyclopentyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [3(S) - hydroxy - 4(R,S) - fluoro - 5 - cyclohexyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal and the individual 4(S) and 4(R) isomers;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [3(S) - hydroxy - 4,4 - difluoro - 5 - cyclohexyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - trans - 1 - octenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(S) - methyl - 4(R) - fluoro - trans - 1 - octenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal and the 4(S) - fluoro - 4(R) - methyl isomer;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4,4 - difluoro - trans - 1 - octenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - trans - 1 - nonenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(S) - fluoro - 4(R) - methyl - trans - 1 - nonenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal and the 4(S) - methyl - 4(R) - fluoro isomer;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4,4 - difluoro - trans - 1 - nonenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - trans - 1 - decenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4,4 - difluoro - trans - 1 - decenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - 5 - cyclopentyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4,4 - difluoro - 5 - cyclopentyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - 5 - cyclohexyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal and the individual 4(S) and 4(R) isomers;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4,4 - difluoro - 5 - cyclohexyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - 5 - phenyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4,4 - difluoro - 5 - phenyl - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - 5 - (4'-fluorophenyl) - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - 5 - (3'-chlorophenyl) - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal;
- 2 - {3 α ,5 α - dihydroxy - 2 β - [2 - bromo - 3(S) - hydroxy - 4(R,S) - fluoro - 5 - (3'-trifluoromethylphenyl) - trans - 1 - pentenyl] - 1 α - cyclopentyl} - ethanal γ - hemiacetal.

These compounds can be deetherified as shown in the following Example (whether they are 3,5-bis-THP-oxy or 3,5-bis-DIOX-oxy derivatives).

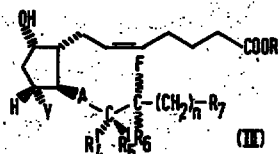
Preparation 7.

0.5 g of 2 - {5 α - hydroxy - 3 α - (THP - oxy) - 2 β - [3(S) - (THP - oxy) -

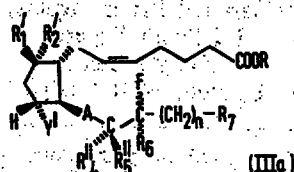
24. 18,19,20-trinor-17-cyclohexyl-16(*R,S*)-fluoro-13,14-didehydro-PGF_{2α}.
 25. 18,19,20-trinor-17-cyclohexyl-16(*R*)-fluoro-13,14-didehydro-PGF_{2α}.
 26. 18,19,20-trinor-17-cyclohexyl-16(*S*)-fluoro-13,14-didehydro-PGF_{2α}.
 27. 18,19,20-trinor-17-cyclohexyl-16,16-difluoro-13,14-didehydro-PGF_{2α}.
 28. 16 ϵ -fluoro-18,19,20-trinor-17-cyclopentyl-13,14-didehydro-PGF_{2α}.
 29. 16 ϵ -fluoro-18,19,20-trinor-17-phenyl-13,14-didehydro-PGF_{2α}.
 30. 16 ϵ -fluoro-18,19,20-trinor-17-cyclopentyl-13,14-didehydro-PGE₂.
 31. 16 ϵ -fluoro-18,19,20-trinor-17-cyclohexyl-13,14-didehydro-PGE₂.
 32. 16 ϵ -fluoro-18,19,20-trinor-17-phenyl-13,14-didehydro-PGE₂.
 33. 18,19,20-trinor-17-phenyl-16,16-difluoro-13,14-didehydro-PGF_{2α}.
 34. 18,19,20-trinor-17-cyclopentyl-16,16-difluoro-13,14-didehydro-PGF_{2α}.
 35. 8,19,20-trinor-17-phenyl-16,16-difluoro-13,14-didehydro-PGE₂.
 36. 18,19,20-trinor-17-cyclopentyl-16,16-difluoro-13,14-didehydro-PGE₂.
 37. 18,19,20-trinor-17-cyclohexyl-16,16-difluoro-13,14-didehydro-PGE₂.
 38. Any one of the compounds according to Claim 1 hereinbefore specifically named except those according to Claims 2 to 37.
 39. A process for the preparation of compounds according to Claim 1, comprising reacting an optically active compound of formula (II)



- or racemate thereof, wherein *n*, *R*₄ and *R*₇ are as defined in claim 1, *A'* is $\text{—C}\equiv\text{C—}$ or —CH=CX— , wherein *X* is hydrogen or halogen, *Y* is hydroxy or a known protecting group bound to the ring by an ethereal oxygen atom, and one of *R*₄ and *R*₅ is hydroxy or a known protecting group bound to the chain by an ethereal oxygen atom, and the other is a hydrogen atom, with a Wittig reagent comprising the group of formula $\text{—(CH}_2\text{)}_n\text{—COOR}$, wherein *R* is a hydrogen atom or a *C*₁–*C*₁₂ alkyl group, to give a compound of formula (III)



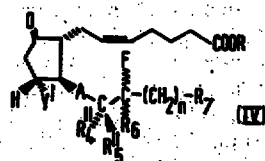
- wherein *A* is as defined in claim 1, and *R*₄, *Y*, *R*₄, *R*₅, *R*₆, *R*₇ and *n* are as defined above, which compound (III) when *Y* is a known protecting group as above defined, and one of *R*₄ and *R*₅ is a known protecting group as above defined and the other is hydrogen, may be optionally esterified by methods known *per se* to give the 9 α - or 9 β -acyloxy derivative, and then deetherifying by methods known *per se* the compound of formula (III) or its 9 α - or 9 β -carboxylic acyloxy derivative 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 hydrogen, so obtaining a compound of formula (I), wherein *R*₄ is a hydroxy group, the symbol — is a single bond, one of *R*₄ and *R*₅ is hydrogen, and the other is hydroxy or carboxylic acyloxy, and one of *R*₄ and *R*₅ is a hydroxy group and the other is hydrogen, or, if desired, oxidizing the 9 α - or 9 β -hydroxy group in a compound of formula (IIIa)



- wherein *R*₄, *A*, *R*₄, *R*₅ and *n* are as defined above, one of *R*₄ and *R*₅ is hydrogen and the other is hydroxy, *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 hydrogen, to give a compound of formula (IV)



31



wherein R, Y, A, R', R'', R₃, R₇, and n are as defined above, which in turn is deetherified in the 11- and 15-positions to give, according to the reaction conditions used, either a compound of formula (I) wherein the symbol

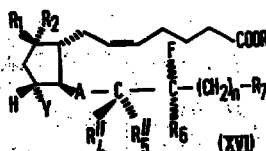
is a single bond, R₃ is hydroxy, and R₁ and R₂, taken together, form an oxo group, or a compound of formula (I) wherein the symbol

is a double bond, R₃ is hydrogen, and R₁ and R₂ together form an oxo group, and/or, if desired, reacting a compound of formula (I) wherein R is a hydrogen atom and the hydroxy group in the 11- and/or 15-position is optionally protected as described above, with a base, followed, if required, by deetherification, to give a salt of a compound of formula (I) wherein R is hydrogen, or esterifying a compound of formula (I) wherein R is a hydrogen atom and the hydroxy group in the 11- and/or 15-position is optionally protected as described above, followed, if required, by deetherification, to give a compound of formula (I) wherein R is C—C₁₂ alkyl, or hydrolyzing a compound of formula (I) wherein R is C—C₁₂ alkyl and the hydroxy group in the 11- and/or 15-position is optionally protected as described above, followed, if required, by deetherification to give a compound of formula (I) wherein R is a hydrogen atom.

40. A process according to Claim 39 substantially as described in any one of the foregoing Examples 1 to 11.

41. A compound of formula (I) as defined in Claim 1 produced by a method according to Claim 39 or 40.

42. A compound of formula



wherein Y is hydroxy or a known protecting group bound to the ring by an ethereal oxygen atom, one of R₁' and R₂' is a known protecting group bound to the chain by an ethereal oxygen atom and the other is hydrogen, one of R₁ and R₂ is hydrogen and the other is hydroxy or carboxylic acyloxy or R₁ and R₂, taken together, form an oxo group, and R₃, R₄, R₇, A, n are as defined in claim 1.

43. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of claims 1 to 38, or a pharmaceutically or veterinarily acceptable salt thereof, and a pharmaceutically or veterinarily acceptable carrier or diluent therefor.

44. A method for the treatment of a warm-blooded non-human animal which comprises administering thereto a compound as claimed in any one of claims 1 to 38, or a pharmaceutically or veterinarily acceptable salt thereof.

J. A. KEMP & CO.,
Chartered Patent Agents,
14, South Square,
Gray's Inn,
London, WC1R 5EU.

