

PATENT SPECIFICATION

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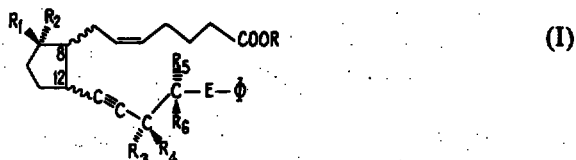
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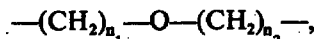
(54) 13,14-DEHYDRO-11-DEOXY-PROSTAGLANDINS AND
 PROCESS FOR THEIR PREPARATION

(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:—

The present invention relates to optically active 13,14-dehydro-11-deoxy-prostaglandins, to a process for their preparation and to pharmaceutical and veterinary compositions containing such compounds. The optically active compounds of the present invention have the formula:

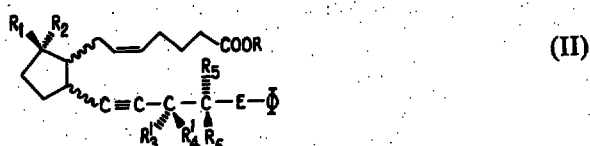


in which R is hydrogen, C₁—C₁₂ alkyl or a cation of a pharmaceutically or veterinarily acceptable base; one of R₁ and R₂ is hydrogen and the other is hydroxy or carboxylic acyloxy, or R₁ and R₂ together form an oxo group; one of R₃ and R₄ is hydrogen and the other is hydroxy; R₅ and R₆ each denote hydrogen, or one of R₅ and R₆ is either fluorine or hydrogen and the other is C₁—C₄ alkyl, E is —(CH₂)_n—, in which n is an integer of from 1 to 6, or



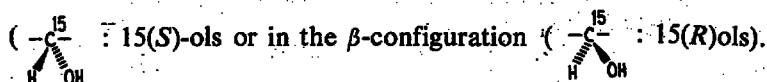
in which n₁ and n₂, which may be the same or different, each is zero, 1, 2 or 3; Φ is methyl; cycloalkyl or from 3 to 7 ring carbon atoms which optionally contains one or more ring oxygen or sulphur atoms; phenyl or phenyl substituted by halogen, C₁—C₄ alkoxy, phenyl, or trihalomethyl; the chains bound to the carbon atoms in the 8- and 12- positions having a *trans*-configuration with respect to each other.

The present invention also provides compounds of formula:



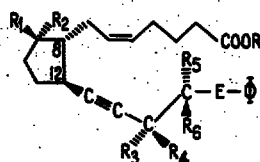
in which R, R₁, R₂, R₃, R₆, E and Φ are as hereinbefore defined, one of R₃' and R₄' represents a known protecting group bound to the chain by an ethereal oxygen

atom and the other is hydrogen, and the chains bound to the carbon atoms in the 8- and 12-positions have a *trans*-configuration with respect to each other. The double bond in the 5(6)-position is a *cis* double bond. In the formulae of this 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 heavy solid lines (—) indicate that the substituents in the β -configuration, i.e. above the plane of the ring or of the chain. 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- and 12-positions, must have a *trans*-configuration with respect to each other, 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 formula (I), the hydroxy group linked to the carbon atoms in the 15-position may be either in the α -configuration

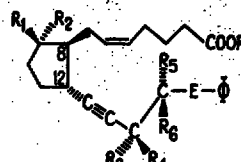


As stated above only one alkyl group may be linked to the carbon atoms in the 16-position. This may be either a 16(*S*)-alkyl (α -configuration) or a 16(*R*)-alkyl (β -configuration). Analogous when a fluorine atom is attached to the carbon atom in the 16-position, this substituent may be either a 16(*S*)-fluorine (α -configuration) or a 16(*R*)-fluorine (β -configuration).

The new compounds of the invention are therefore optically active compounds having the formulae:



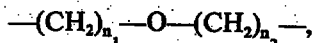
(Ia: nat-compounds)



[Ib: ent (or 8,12-diiso)-compounds]

where R_1 , R_2 , R , R_3 , R_4 , R_5 , R_6 , E and Φ are as defined above.

Alkyl and alkoxy groups may be branched or straight chain groups. When R is C_1 — C_{12} alkyl, it is preferably methyl, ethyl, propyl or heptyl. Preferably, one of R_1 and R_2 is hydrogen and the other is hydroxy, or R_1 and R_2 together form an oxo group. However, when one of R_1 and R_2 is carboxylic acyloxy, it is preferably alkanoyloxy containing up to 6 carbon atoms, benzoyloxy or *p*-phenyl-benzoyloxy. When one of R_3 and R_4 is C_1 — C_4 alkyl, it is preferably methyl. When E is $-(CH_2)_n$ — and Φ is methyl, n is preferably 4, 5 or 6; but when E is $-(CH_2)_n$ — and Φ is cycloalkyl or phenyl, n is preferably 2. When E is



it is preferably, when Φ is methyl, $-CH_2-O-CH_2-CH_2-$, while, when Φ is cycloalkyl or phenyl, E is preferably $-CH_2-O-$. Φ is preferably methyl, cyclopentyl, cyclohexyl or phenyl. However, if Φ is a trihalomethyl-substituted phenyl, the trihalomethyl group is preferably trifluoromethyl or trichloromethyl. Examples of cations of pharmaceutically or veterinarily acceptable bases are metallic cations, such as sodium, potassium, calcium and aluminium and organic amines, such as trialkylamines.

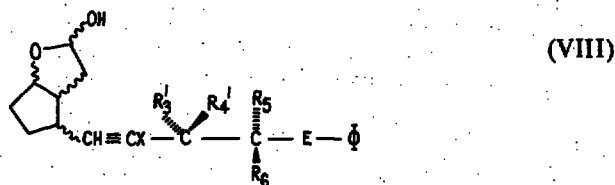
Particularly preferred compounds of the present invention are

- 9-oxo-15(*S*)-hydroxy-16(*S*)-methyl-*cis*-5-prosten-13-ynoic acid
- 9-oxo-15(*S*)-hydroxy-16(*S*)-methyl-3,12-diiso-*cis*-5-prosten-13-ynoic acid
- 9-oxo-15(*S*)-hydroxy-16(*R*)-methyl-*cis*-5-prosten-13-ynoic acid
- 9-oxo-15(*S*)-hydroxy-16(*R*)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid
- 9-oxo-15(*S*)-hydroxy-16(*S*),20-dimethyl-*cis*-5-prosten-13-ynoic acid
- 9-oxo-15(*S*)-hydroxy-16(*R*),20-dimethyl-*cis*-5-prosten-13-ynoic acid.
- 9-oxo-15(*S*)-hydroxy-16(*S*)-methyl-16(*R*)-fluoro-*cis*-5-prosten-13-ynoic acid.
- 9-oxo-15(*S*)-hydroxy-16(*S*)-fluoro-16(*R*)-methyl-*cis*-5-prosten-13-ynoic acid.
- 9-oxo-15(*R*)-hydroxy-16(*S*)-methyl-*cis*-5-prosten-13-ynoic acid.

9-oxo-15(R)-hydroxy-16(S)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
 9-oxo-15(R)-hydroxy-16(R)-methyl-*cis*-5-prosten-13-ynoic acid.
 9-oxo-15(R)-hydroxy-16(R)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid.
 9-oxo-15(R)-hydroxy-16(S),20-dimethyl-*cis*-5-prosten-13-ynoic acid.
 9-oxo-15(R)-hydroxy-16(R),20-dimethyl-*cis*-5-prosten-13-ynoic acid.
 9-oxo-15(R)-hydroxy-16(S)-methyl-16(R)-fluoro-*cis*-5-prosten-13-ynoic acid.
 9-oxo-15(R)-hydroxy-16(S)-fluoro-16(R)-methyl-*cis*-5-prosten-13-ynoic acid.

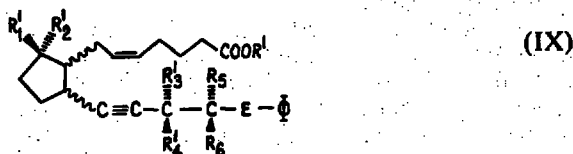
The compounds of formula (I) are prepared by

(i) reacting an optically active lactol of formula (VIII):



in which R_5 , R_6 , E and Φ are as hereinbefore defined,

X represents chlorine, bromine or iodine, one of R'_1 and R'_2 represents hydrogen and the other represents a known protecting group bound to the chain through an etheral oxygen atom, and the lactol ring is in the *trans*-configuration with respect to the side-chain bound to the 12-carbon atom (prostaglandin numbering) and the bond linking the lactol ring to the cyclopentane ring being in the *cis*-configuration with respect to each other; with a Wittig reagent comprising a group of formula $-(CH_2)_n-COOR'$ in which R' represents hydrogen or C_1-C_{12} alkyl to give an optically active compound of formula (IX):



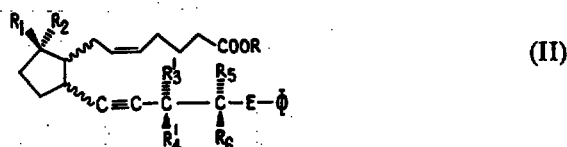
in which R'_1 , R'_2 , R'_3 , R'_4 , R_5 , R_6 , E and Φ are as hereinbefore defined, the chains bound to the carbon atoms in the 8- and 12-positions are in the *trans*-configuration with each other; and when the chain bound to the carbon atom in the 8-position is in the α -configuration R'_1 represents hydrogen and R'_2 represents hydroxy or when said chain is in the β -configuration R'_1 represents hydroxy and R'_2 represents hydrogen; and if desired,

(ii) either (a) esterifying a compound of formula (IX) in which R' represents C_1-C_{12} alkyl with a carboxylic acid in the presence of a compound of formula M^*Y_3 , in which M^* represents a metalloid of group VB of the Periodic Table and Y represents alkyl, dialkylamino or aryl, and a hydrogen acceptor to form a 9 α - or 9 β -acyloxy derivative with inversion of configuration of the substituents at the 9-position, or

(b) esterifying a compound of the formula (IX) in which R' represents C_1-C_{12} alkyl in a manner known *per se* to form 9 α - or 9 β -acyloxy derivative without inversion of configuration of the substituents at the 9-position.

(iii) subsequently saponifying the products of steps (a) and (b) above if desired, to yield the corresponding 9 α - or 9 β -hydroxy derivative, optionally also saponifying derivatives in which R' represents C_1-C_{12} alkyl to form compounds in which R' represents hydrogen; and then, if desired

(iv) reacting the compound thus formed in which R' represents hydrogen with a base to form a compound of formula (II):



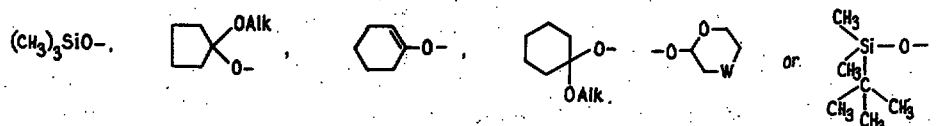
in which one of R_1 and R_2 represents hydrogen and the other represents hydroxy or carboxylic acyloxy; R'_3 , R'_4 , R_5 , R_6 , E and Φ are as hereinbefore defined and R .

represents a cation of a pharmaceutically or veterinarily acceptable base; and, if desired,

(v) oxidising the product of steps (i), (iii) or (iv) in which one of R_1 and R_2 represents hydrogen and the other represents hydroxy, to form an optically active compound of formula II in which R_1 and R_2 together form an oxo group;

(vi) de-etherifying the product of any one of steps (i) to (v) under mild, acidic conditions to form an optically active compound of formula I, and (vii) if desired, converting the compounds thus obtained into other compounds of formula (I) by known methods (as hereinafter defined).

The known protecting groups (i.e. ether groups) employed in the process of the present invention should be convertible to hydroxy groups by mild acidic hydrolysis. Examples are 1-alkoxycycloalkyloxy, 2-oxacycloalkyloxy whose cycloalkyl group optionally contains a further ring oxygen atoms, 1-alkoxyalkoxy, enol ether and silyl ether groups. The preferred groups are:

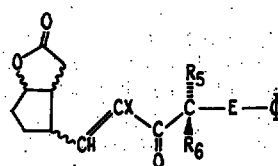


in which W is $-O-$ or $-CH_2-$, and Alk is a lower alkyl group.

The mild acidic hydrolysis step (vi) is performed with, for example, 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, a 0.1N to 0.25N poly-carboxylic acid (e.g. oxalic or citric acid) solution 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.

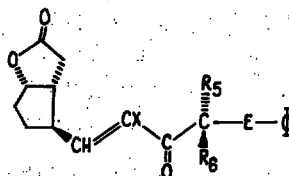
A compound of formula (I) thus formed may subsequently be converted into another compound of formula (I) by known methods, such methods being as heretofore used or as described in the chemical literature, for example, a compound of formula (I), in which R is C_1-C_{12} alkyl, may be hydrolysed, in an acidic or basic medium, to give a compound of formula (I) in which R is hydrogen. A compound of formula (I) in which R is hydrogen may be reacted with a base to give a compound of general formula (I) in which R is a cation, or a compound of general formula (I) in which R is hydrogen may be esterified to give the corresponding compound in which R is C_1-C_{12} alkyl.

The compound of formula (VIII) may be prepared by a multi-step process, starting from a lactone of formula:

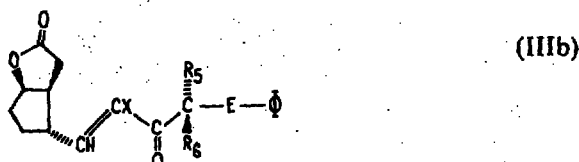


in which R_5 , R_6 , E and Φ are as defined above, and X is chlorine, bromine, or iodine; the lactone ring being in the *trans*-configuration with respect to the side chain, and the bonds linking the lactone ring to the cyclopentane ring bring in the *cis*-configuration with respect to each other, and the hydrogen atom linked to the carbon atom in the 13-position (prostaglandin numbering) and the halogen atom linked to the carbon atom in the 14-position (prostaglandin numbering) preferably being in the *trans*-configuration (geometric *trans*-isomers) with respect to each other.

The halo lactone of formula (III) is therefore either a compound of formula:

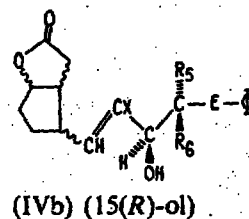
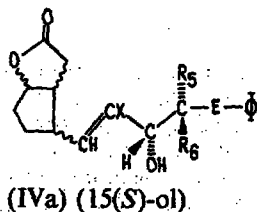


or a compound of formula:



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

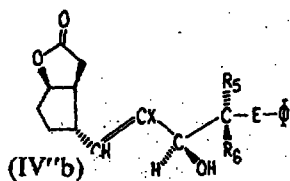
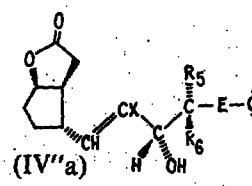
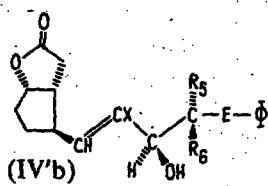
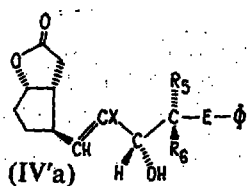
(a) Reduction of the 15-oxo-group (prostaglandin numbering) of the halo lactone of formula (III) to yield a mixture of the 15(*S*) and 15(*R*)-ols having the formulae (IVa) and (IVb):



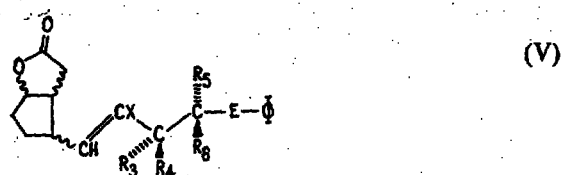
wherein X, R₃, R₄, E and Φ are as defined above.

The reduction of the 15-oxo-group may be suitably performed in an organic solvent, such as methanol, diethyl ether, 1,2-dimethoxyethane, dioxan, tetrahydrofuran, benzene, and mixtures thereof, by using e.g. metal borohydrides, in particular sodium borohydride, lithium borohydride, zinc borohydride, lithium triisobutylborohydride and potassium triisobutylborohydride.

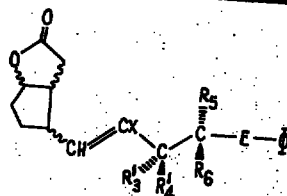
(b) Separation of the 15(*S*)-ol from the 15(*R*)-ol. This separation may be performed by column chromatography, e.g. silica gel chromatography, or by thin-layer chromatography, using, in both cases, as eluents, mixtures of methylene chloride diethyl ether or of cyclohexane diethyl ether as well as by fractional crystallization, for example from diethyl ether or diisopropyl ether, so as to obtain pure optically active isomers having the following formulae:



(c) Conversion of an optically active compound of formula (V)



in which one of X, R₃, R₄, E and Φ are as defined above, and one of R₃ and R₄ is hydrogen and the other is hydroxy, into an optically active compound of formula (VI)



(VI)

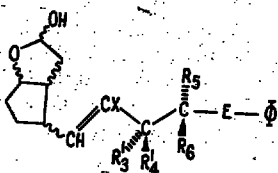
in which X, R₃, R₄, E and Φ are as defined above, and one of R'₃ and R'₄ is hydrogen and the other is a known protecting group bound to the chain through an ethereal oxygen atom. The etherification of the compound of formula (V) is preferably carried out with a vinylic ether of formula



(VII)

in which W is $-\text{O}-$ or $-\text{CH}_2-$, in the presence of catalytic amounts of, for example, *p*-toluenesulphonic acid of benzenesulphonic acid; or by reacting the compound of the formula (V) with a trisubstituted chlorosilane in the presence of a base (for example imidazole or a trialkylamine) as acceptor of the hydrochloric acid formed. Other vinylic ethers which may be used are 3-methoxy-5,6-dihydro-2*H*-pyran and 4-methoxy-5,6-dihydro-2*H*-pyran. The etherification can also preferably be effected by reacting the compound of formula (V), with a cyclopentanone or cyclohexanone diacetal in the presence of an acid catalyst at the reflux temperature in an inert solvent, and distilling off the alcohol formed to obtain mixed acetals or enol ethers, according to the amount of catalyst used and/or the heating time.

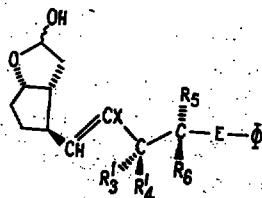
(d) Reduction of the compound of formula (VI) to give an optically active lactol of formula:



(VIII)

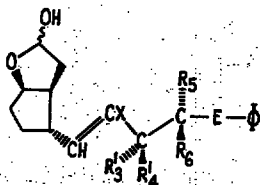
in which X, R'₃, R'₄, R₅, R₆, E and Φ are as defined above. The reduction may be performed by treatment with diisobutylaluminium hydride or sodium bis-(2-methoxyethoxy)-aluminium hydride in an inert solvent, such as toluene, *n*-heptane, *n*-hexane, benzene, or mixtures thereof, at below -30°C .

In the process of the present invention, when the lactol used for the Wittig reaction (step (i)) is of formula



(VIIIa)

a nat derivative of formula (IX) is obtained, in which R'₁ is hydrogen and R'₂ is hydroxy, while when the lactol used as starting material has the formula

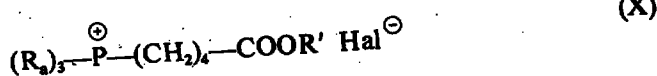


(VIIIb)

an ent derivative of formula (IX) is obtained, in which R'₁ is hydroxy and R'₂ is

hydrogen. The hydrogen atom linked to the carbon atom in the 13-position (prostaglandin numbering) and the hydrogen atom linked to the carbon atom in the 14-position (prostaglandin numbering) in the lactol of formula (VIII) may be either in the *trans*-configuration (geometric *trans*-isomers) or in the *cis*-configuration (geometric *cis*-isomers) with respect to each other. Preferably they are in the *trans*-configuration, since in the above method for the preparation of the lactol of formula (VIII) the geometric *trans*-isomers are obtained in a far higher percentage (92—95%) than the corresponding *cis*-isomers (5—8%). The Wittig reaction (step (i)) is performed employing the usual conditions 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 a temperature of from 0°C to the reflux temperature of the reaction mixture, preferably however at room temperature or below. When in the lactol of formula (VIII) 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 for the reaction to last from 10 to 20 minutes. However, when X is chlorine, it is necessary, when using for example from 1.5 to 2.5 moles of Wittig reagent per mole of lactol, to prolong the reaction time up to ten hours or, 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 times of about 30 minutes. Preferably, in the lactol of formula (VIII) X is bromine or iodine, since in this case both the triple bond formation and the Wittig reaction take place simultaneously by employing small amounts of the Wittig reagent and short reaction times.

The term "Wittig reagent" includes compounds of general formula



wherein R_2 is aryl or alkyl, Hal is bromine or chlorine and R' is hydrogen or C_1-C_{12} alkyl. When R_2 is alkyl, it is preferably ethyl. The preparation of the Wittig reagents is discussed in detail by Tripett, *Quart. Rev.*, 1963, XVII, No. 4, 406.

The optional esterification step (ii) of the process of the present invention to form a 9 α - or 9 β -acyloxy derivative may be performed by conventional methods, for example by reaction with an acid halide or anhydride, in the presence of a base. In this case, starting from a nat derivative of formula (IX), in which R'_1 is hydrogen and R'_2 is hydroxy, a 9 α -acyloxy nat-derivative is obtained; while starting from an ent-derivative of formula (IX), in which R'_1 is hydroxy and R'_2 is hydrogen, a 9 β -acyloxy ent-derivative is obtained.

However when the esterification is carried out with a carboxylic acid in the presence of a compound of formula M^*Y_3 , where M^* is a metalloid of group VB of the Periodic Table and Y is an alkyl, a dialkylamino or an aryl group, and a hydrogen acceptor inversion of configuration of the substituents in the 9-position occurs. Thus, starting from a nat-derivative of formula (IX) in which R'_1 is hydrogen and R'_2 is hydroxy, a 9 β -acyloxy nat-derivative is obtained, while starting from an ent-derivative of formula (IX) in which R'_1 is hydroxy and R'_2 is hydrogen, a 9 α -acyloxy ent-derivative is obtained. In other words, the esterification reaction involves the complete inversion of configuration of the hydroxy group in the 9-position. The reaction is preferably carried out at room temperature in an inert anhydrous solvent, which is preferably an aromatic hydrocarbon, such as benzene or toluene, a linear or cyclic ether, for example diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran or dioxan, or a halogenated hydrocarbon such as dichloromethane or dichloroethane. All the reagents used, i.e. the compounds of formula M^*Y_3 , the esterifying carboxylic acid and the hydrogen-acceptor, are employed in the proportion of at least 1.5 mole per each mole of alcohol. Preferably 2 to 4 moles of the each reagent is employed per mole of alcohol.

In the compound of formula M^*Y_3 , M^* is preferably P, As or Sb; especially P. When Y is alkyl, it is preferably methyl; when aryl, it is preferably phenyl; and when dialkylamino, it is preferably dimethylamino. The compound of formula M^*Y_3 is preferably triphenylphosphine, triphenylarsine, triphenylstibine or hexamethyltriaminophosphine of formula $[(CH_3)_2N]_3P$.

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

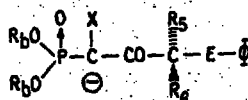
dicyano-5,6-dichloro-1,4-benzoquinone or azobisformamide. The saponification step (iii) is carried out by the usual methods, for example by using inorganic bases. The optional conversion of the products of step (iii) in which R represents hydrogen, into compounds of formula (II), in which R' represents a cation of a pharmaceutically or veterinarily acceptable base, is also carried out by conventional methods, for examples by salification with a base at room temperature in water or in a solvent miscible with water, followed by the removal of the solvent by evaporation.

By carrying out the appropriate combination of steps (i) to (iv), there is obtained an optically active compound of formula (II), in which one of R₁ and R₂ is hydrogen and the other is hydroxy or carboxylic acyloxy, R is hydrogen, C₁—C₁₂ alkyl or the cation of a pharmaceutically or veterinarily acceptable base and R', R', R', R', R', R', E and Φ are as defined above. The compound of formula (II) in which one of R₁ and R₂ is hydrogen and the other is hydroxy may then be oxidized in the 9-position to give an optically active compound of formula (II), in which R₁ and R₂ together form an oxo group. This oxidation may be carried out with, for example, Jones reagent or Moffatt's reagent. The product of any one of steps (i) to (v) of the process of the present invention may then be de-etherified to form an optically active compound of formula (I). The halo lactone of formula (III), which as described above is the starting point for a synthesis of the compound of formula (VIII), may be in turn prepared in one step by reacting an optically active aldehyde or racemic mixture of aldehydes of formula:



(XI)

in which the lactone ring is in the *trans*-configuration with respect to the aldehyde group and the bond linking the lactone ring to ring A are in a *cis*-configuration with an optically active phosphonate of formula:



(XII)

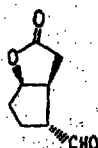
in which R₆ represents alkyl, and X, R₅, R₆, E and Φ are as defined above.

The reaction is suitably performed in a dry solvent, which preferably is benzene, 1,2-dimethoxyethane, tetrahydrofuran, dimethylformamide or mixtures thereof, in an inert gas atmosphere, and using a suspension of 1.5—2.5 molar equivalents of the compound of formula (XII) per mole of aldehyde. The starting material for this one-step process is therefore an aldehyde of formula:



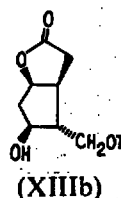
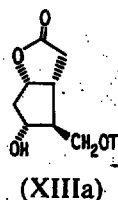
(XIa)

or an aldehyde of formula:

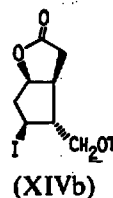
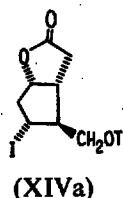


(XIb)

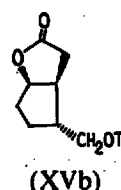
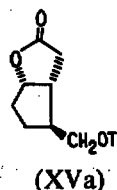
The aldehydes of formulae (XIa) and (XIb) may be prepared from the compounds of formulae (XIIIa) and (XIIIb) respectively:



in which T represents lower alkyl, benzyl, 2-tetrahydropyranyl, 1,4-dioxan-2-yl, or dimethyl-*tert*.butylsilyl. These are reacted with a mixture of N-iodosuccinimide and triphenylphosphine or a mixture of triphenyl phosphite and methyl iodide, forming compounds of formulae (XIVa) and (XIVb), depending upon the starting material chosen:



in which T is as defined above, which are then reduced, by using, e.g. sodium cyanoborohydride or sodium borohydride in dimethyl sulfoxide to give compounds of formulae (XVa) and (XVb) respectively:

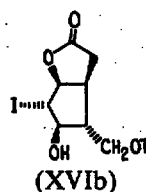
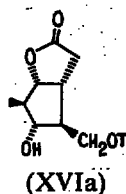


in which T is as defined above. These lactones are then converted into the corresponding compounds having a free hydroxy group in place of the —OT group, and are finally oxidized to give the aldehydes of formulae (XIa) and (XIb).

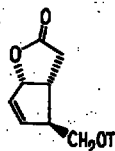
The conversion of the compounds of formulae (XVa) and (XVb) into compounds having a free hydroxy group may be performed by treatment with, e.g. BBr_3 , in a suitable solvent such as methylene chloride or ethyl acetate when T is lower alkyl or benzyl. Otherwise the conversion may be performed for example, by mild acidic hydrolysis. The oxidation to give the aldehydes of formulae (XIa) and (XIb) may be performed, for example, with Moffatt's reagent or with Collins reagent.

The compound of formula (XIIIa) (optically active or racemic derivative) may be prepared substantially as described by E. J. Corey, New York Acad. Sciences 180, 24 (1971), while the compound of formula (XIIIb) may be prepared as described in British Patent Specification No. 1,420,338.

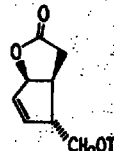
The compounds of formulae (XIIIa) and (XIIIb) may alternatively be prepared from iodo-hydroxy-lactones of formulae (XVIa) and (XVIb), respectively:



in which T is as defined above, by reaction with a compound of formula M^*Y , wherein M^* and Y are as defined above, and a carboxylic acid in an inert anhydrous solvent, such as benzene, toluene, dioxan, dichloromethane in the presence of a hydrogen-acceptor, for example an ester or an amide of azocarboxylic acid, so obtaining compounds of formula (XVIIa) and (XVIIb) respectively:



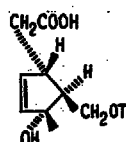
(XVIIa)



(XVIIb)

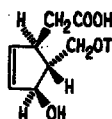
in which T is as defined above, which after saponification with a base, such as NaOH, in aqueous methanol are hydrogenated, e.g. with Pt O₂, to give, after acidification, e.g. with hydrochloric acid, the compounds of formulae (XIIIa) and (XIIIb), respectively.

A racemic mixture of, or an optically active, iodohydroxy-lactone of formula (XIVa) may be prepared by treating a compound of formula:



(XVIIIa)

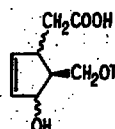
in which T is as defined above, which is in the form of a salt, e.g. with an alkali metal, with an aqueous solution of potassium triiodide at room temperature. The iodohydroxy-lactone of formula (XIVb) may be prepared by the same method, starting from the laevorotatory isomer of formula:



(XVIIIb)

in which T is as defined above, as described in British Patent Specification No. 1,420,338.

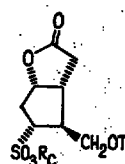
The optically active compound of formula (XVIIIa), i.e. the dextrorotatory isomer, may be prepared by resolution with optically active bases, e.g. dehydroabiethylamine, of a mixture of both optical isomers of a compound of formula:



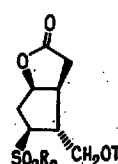
(XIX)

where T is defined above. The preparation of this compound is described by Corey *et al.*, J. Am. Chem. Soc. 1969, 91, 5675; *ibid.* 1971 93, 1489; *ibid.* 1971, 93, 4326.

Alternatively the aldehydes of formulae (XIa) and (XIb) may be prepared by reacting compounds of formulae (XIIIa) and (XIIIb), respectively, with a sulphonyl halide, to give compounds of formulae (XXa) and (XXb) respectively:



(XXa)



(XXb)

in which T is as defined above, and Rc represents the organic radical bound to the sulphur atom in the sulphonyl halide molecule and, for example, is methyl, phenyl or p-tolyl; which by treatment with MgI₂ in diethyl ether yield compounds of formulae (XIVa) and (XIVb) respectively. As described above, these are subsequently reduced, converted into the corresponding compounds having a free hydroxy group and finally oxidized to give the aldehydes of formulae (XIa) and (XIb), respectively.

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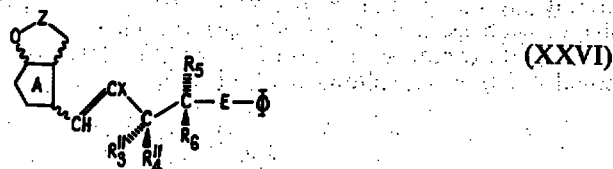
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in which R₁, R₂, R₃, E and Φ are as defined above, with, as a halogenating agent, Br₂, pyrrolidone hydrotribromide (PHTB), dioxane dibromide, N-chloroacetamide, N-chlorosuccinimide, N-bromosuccinimide, N-bromoacetamide, N-bromocaprolactame, or N-iodosuccinimide. By using an imide as the halogenating agent, the carbanion of the halo-phosphonate of formula (XII) is obtained directly by using only one equivalent of base; otherwise, it should be necessary to use another equivalent of a base to obtain the carbanion. If this alternative route is employed the phosphonate carbanion of formula (XXV) may be obtained by treatment of the phosphonate of formula (XXII) with an equivalent of a base, e.g. sodium, lithium or calcium hydride. Of the intermediates formed in the

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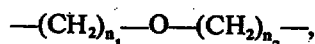
production of the compounds of the present invention, those of formula:



in which Z is >C=O or



one of R^3 and R^4 is hydrogen and the other is hydroxy or a known protecting group bound to the chain by an ethereal oxygen atom, or, when Z is >C=O , R^3 and R^4 , taken together, may also be an oxo group, R_5 and R_6 each denote hydrogen, or one of R_5 and R_6 is either fluorine or hydrogen and the other is C_1-C_4 alkyl; E is $-(CH_2)_n-$, in which n is an integer of from 1 to 6 or



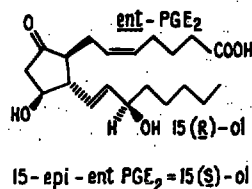
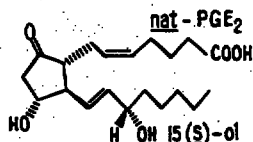
in which n_1 and n_2 , which may be the same or different, each is 0, 1, 2 or 3, Φ is methyl, cycloalkyl of from 3 to 7 ring carbon atoms which optionally contains one or more ring oxygen or sulphur atoms, phenyl, or phenyl substituted by halogen, C_1-C_4 alkoxy, phenyl or trihalomethyl; and X is chlorine, bromine or iodine, the lactol or lactol ring being in a *trans*-configuration with respect to the side-chain attached in the 12-position (prostaglandin numbering) and the bonds linking the lactol or lactol ring to ring A being in a *cis*-configuration with respect to each other; and a process for their manufacture, are described and claimed in Co-pending Application No. 52339/77 (Serial Number 1531568) which has been divided out of this Specification.

The compound (XXVI) where Z is



and one of R^3 and R^4 is hydrogen and the other is hydroxy, may be prepared by deetherifying, under reaction conditions described above, a compound of formula (VIII).

The compounds of formula (I) may be used for the same therapeutical purposes as natural prostaglandins. However, the compounds of the present invention possess the advantage over natural prostaglandins in that they are not substrates for the enzyme 15-prostaglandin dehydrogenase. As is well known, this enzyme quickly inactivates natural prostaglandins. Additionally, the compounds of the present invention are more selective in their therapeutical action than natural prostaglandins. In particular, the compounds of the invention are able to inhibit in humans gastric secretion as well as preventing formation of ulcerogenic lesions in the gastroduodenal tract at low dosages which possess a very favourable therapeutic index of from 1:6 to 1:20 (the ratio of the effective therapeutical dose: lowest dose inducing side effects (i.e. emesis and diarrhoea)). The compounds of the present invention, for example, 11-deoxy-16(S)-methyl-13,14-dehydro-PGE₂ (i.e. 9-oxo-15(S)-hydroxy-16(S)-methyl-*cis*-5-prosten-13-ynoic acid), and its 15-*epi* derivative (i.e. 9-oxo-15(R)-hydroxy-16(S)-methyl-*cis*-5-prosten-13-ynoic acid), 11-deoxy-16(S)-methyl-13,14-dehydro-15-*epi-ent*-PGE₂ (i.e. 16(S)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid) and 11-deoxy-16(R)-methyl-13,14-dehydro-15-*epi-ent*-PGE₂ (i.e. 9-oxo-15(S)-hydroxy-16(R)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid), unlike PGE₂, which is taken as the standard compound in the table that follows, are completely unable to stimulate smooth muscle, such as the ileum of guinea-pigs, the colon of gerbils and the uterus of rats. When administered, for instance subcutaneously, the compounds of the present invention are able to prevent stress-induced ulcerogenic lesions and to reduce gastric secretion (pyloric ligature test according to Shay) (H. Shay et al., Gastroenter., 26, 906 (1954)), as shown by the following Table:



TABLE

Compound	<i>In vitro</i> test: gerbil colon, guinea-pig ileum, rat uterus	Stress induced ulcera	Antisecretory activity
PGE ₂	1	1	1
11-deoxy-16(S)-methyl- 13,14-dehydro-PGE ₂	<0.01	7.25	4.2
11-deoxy-16(S)-methyl- 13,14-dehydro-15- <i>epi</i> -PGE ₂	<0.01	0.5	0.46
11-deoxy-16(R)-methyl- 13,14-dehydro-15- <i>epi</i> -ent-PGE ₂	<0.01	2.3	2.8
11-deoxy-16(S)-methyl- 13,14-dehydro-15- <i>epi</i> -ent-PGE ₂	<0.01	1.8	2.7

As can clearly be seen from this table, the ability of the specified compounds of the present invention to stimulate smooth muscle is less than one-hundredth of that of PGE₂. However, apart from 11-deoxy-16(S)-methyl-13,14-dehydro-15-*epi*-PGE₂, the ability of the specified compounds of the present invention to prevent stress-induced ulcerogenic lesions is from about 2 to 7 times that of PGE₂. Their activity in reducing gastric secretion is similarly increased compared with PGE₂. Although 11-deoxy-16(S)-methyl-13,14-dehydro-15-*epi*-PGE₂ is only about half as effective as PGE₂ in preventing ulcerogenic lesions and in reducing gastric secretion as indicated above, treatment with this compound as opposed to with PGE₂ is advantageous as the undesired side effect of smooth muscle stimulation is less evident when employing the compound of the invention.

The same compounds are also suitable as oestrum-inducing and ovulation-regulating agents as well as for hypertension, and circulatory and respiratory disorders.

The compounds of formula (I) can be administered orally, parenterally, or by intravenous or intrauterine (extra-amniotic or intra-amniotic) methods, 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 from 0.01 to 10, preferably from 0.05 to 1, $\mu\text{g/kg}$ of mammal body weight per minute.

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

The invention further provides a method of treating warm-blood, non-human animals which comprise administering to such animals an effective amount of a compound of the present invention. The composition 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.

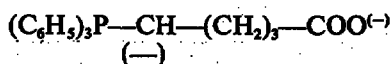
Examples of substances which can serve as carriers or diluents are water, gelatin, lactones, starches, magnesium stearate, talc, vegetable oil, benzyl alcohol and cholesterol.

The invention is illustrated by Examples 1 to 24, 43 and 45 to 49 below, Examples 25 to 42 and 44 illustrate the preparation of intermediates employed in the process of the invention, and Examples 3 to 5 illustrate alternative esterification.

techniques which may be employed to form compounds of formula (II). The abbreviations THP, DIOX, DMSO, THF, DMF, DIBA, HMPA, Et₂O, DME, respectively, refer to tetrahydropyranyl, 1,4-dioxan-2-yl, dimethyl sulphoxide, tetrahydrofuran, dimethylformamide, diisobutyl aluminium hydride, hexamethylphosphoramide, diethyl ether and 1,2-dimethoxyethane. Temperatures are measured in °C. Optical rotations are measured at a temperature of 20°C and a concentration of 1% by weight.

Example 1.

A suspension of 0.45 g of NaH (80% dispersion in mineral oil) in 13 ml of DMSO is heated at 58–65° in a nitrogen atmosphere with the exclusion of moisture until no more hydrogen evolves. After cooling to 4–8°, 3.3 g of triphenyl-(4-carboxybutyl)-phosphonium bromide is added and the mixture stirred until it is all dissolved, with formation of a dark red solution of the carbanion of



which is maintained by external cooling at temperature of from 10–12°C.

To this is added a solution of 0.58 g of 2-[2α-hydroxy-5β-(2'-bromo-3'(S)-hydroxy-4'(R)-methyloct-*trans*-1'-enyl)-cyclopent-1α-yl]ethanal *p*-hemiacetal 3'-(4"-methoxy-4"-THP)ether in 4 ml of anhydrous DMSO and the mixture stirred for 4 hours, then diluted with 20 ml of water and extracted with diethyl ether (16 × 3 ml) to remove the triphenylphosphoxide formed. The combined ethereal extracts are re-extracted with 0.5N NaOH (4 × 3 ml) and discarded. The combined aqueous alkaline extracts are acidified to pH 4.5 with 2N sulfuric acid and extracted with 1:1 v/v diethyl ether:pentane. The combined organic extracts are washed until neutral and dried over sodium sulfate, yielding 0.64 g of 9α,15(S)-dihydroxy-16(R)-methyl-*cis*-5-prosten-13-ynoic acid 15-(4"-methoxy-4"-THP)ether. By the same procedure, starting from the 3'-DIOX ethers, 3'-(2"-THP) ethers, 3'-(4"-methoxy-4"-THP) ethers, and 3'-(3"-methoxy-3"-THP) ethers of the following 2-(2α-hydroxy-cyclopent-1α-yl) ethanal *p* hemiacetals substituted in the 5β position by

(2'-bromo-3'(S)-hydroxyoct-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxynon-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxy-4'(S)-methyloct-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxy-4'(R)-methylnon-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxy-4'(R)-methyl-5'-cyclohexylpent-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxydec-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxy-5'-oxaoct-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxy-5'-oxanon-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxy-4'(R)-methyl-5'-oxaoct-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxy-4'(S)-methyl-5'-oxanon-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxy-5'-cyclopentylpent-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxy-5'-cyclohexylpent-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxy-5'-*p*-chlorophenylpent-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxy-5'-phenylpent-*trans*-1'-enyl)-;
 (2'-bromo-3'(S)-hydroxy-4'-cyclohexyloxy-but-*trans*-1'-enyl)-; and
 (2'-bromo-3'(S)-hydroxy-4'-phenoxybut-*trans*-1'-enyl)-;

the 15-DIOX ethers, (2"-THP)ethers, (4"-methoxy-4"-THP)ethers, and (3"-methoxy-3"-THP)ethers of the following compounds were obtained:

9α,15(S)-dihydroxy-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-20-methyl-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-16(S)-methyl-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-16(R)-20-dimethyl-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-16(R)-methyl-18,19,20-trinor-17-cyclohexyl-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-20-ethyl-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-17-oxa-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-17-oxa-20-methyl-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-17-oxa-16(R)-methyl-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-16(S)-20-dimethyl-17-oxa-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-18,19,20-trinor-17-cyclopentyl-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-18,19,20-trinor-17-cyclohexyl-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-18,19,20-trinor-17-*p*-chlorophenyl-*cis*-5-prosten-13-ynoic acid;
 9α,15(S)-dihydroxy-18,19,20-trinor-17-phenyl-*cis*-5-prosten-13-ynoic acid;

9 α ,15(*S*) - dihydroxy - 17,18,19,20 - tetranor - 16 - cyclohexyloxy - *cis* - 5 - prosten-13-ynoic acid; and

9 α ,15(*S*) - dihydroxy - 17,18,19,20 - tetranor - 16 - phenoxy - *cis* - 5 - prosten - 13 - ynoic acid.

Example 2.

A solution of the ylide obtained by the procedure described in Example 1, starting with 0.612 g of NaH, (80% dispersion in mineral oil) and 5.32 g of triphenyl-(4-carboxybutyl)-phosphonium bromide in 27 ml of DMSO is treated with a solution of 1.52 g of 2-[2 β -hydroxy-5 α -(2'-bromo-3'(*S*)-hydroxy-4'(*R*)-methylnon-*trans*-1'-enyl)-cyclopent-1 β -yl] ethanal γ -hemiacetal 3'-DIOX ether in 6 ml of anhydrous DMSO. After 10 hours at room temperature, it is diluted with 35 ml of water, acidified to pH 4.8 and extracted with diethyl ether: pentane 1:1v/v. The aqueous phase is discarded and the organic extracts are re-extracted with 0.2N KOH. The combined alkaline extracts are re-extracted with benzene:diethyl ether 70:30 v/v (3 $\times$ 5 ml). The aqueous alkaline phases are then acidified to pH 4.8 and extracted with diethyl ether: pentane 1:1. These organic extracts are combined, washed until neutral with saturated ammonium sulfate solution, dried and evaporated to give 1.38 g of 9 β ,15(*S*)-dihydroxy-16(*R*),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid 15-DIOX ether.

Using the same procedure but starting from the 3'-(2"-THP) ethers and 3'-DIOX ethers of the following 2-[2 β -hydroxycyclopent-1 β -yl] ethanal γ -hemiacetals substituted in the 5 α -position by (2'-bromo-3'(*R*)-hydroxy-4'(*R*)-methyl-non-*trans*-1'-enyl); (2'-bromo-3'(*S*)-hydroxyoct-*trans*-1'-enyl); (2'-bromo-3'(*S*)-hydroxy-5'-oxanon-*trans*-1'-enyl); (2'-bromo-3'(*S*)-hydroxy-4'(*S*)-methyloct-*trans*-1'-enyl) and (2'-bromo-3'(*S*)-hydroxy-4'(*S*)-methylnon-*trans*-1'-enyl); the 15-(2"-THP) ethers and 15-DIOX ethers of the following acids were obtained:

9 β ,15(*R*)-dihydroxy-16(*R*),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;

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

9 β ,15(*S*)-dihydroxy-17-oxa-20-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;

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

9 β ,15(*S*)-dihydroxy-16(*S*),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid.

Example 3.

A solution of 0.3 g of 9 α ,15(*S*)-dihydroxy-*cis*-5-prosten-13-ynoic acid 15-DIOX ether in 15 ml of diethyl ether is treated with an excess of an ethereal solution of diazomethane. This is kept for one hour at room temperature and then evaporated under vacuum to yield 0.3 g of methyl 9 α ,15(*S*)-dihydroxy-*cis*-5-prosten-13-ynoate 15-DIOX ether.

Example 4.

0.42 g of n-heptyl 9 β ,15(*S*)-dihydroxy-17-oxa-20-methyl-8,12-diiso-*cis*-5-prosten-13-ynoate 15-(2"-THP) ether is obtained by reacting 0.4 g of the free acid in 28 ml of CH₂Cl₂ and 0.8 ml of pyridine with 0.85 g of n-heptanol and 0.5 g of dicyclohexylcarbodiimide. After three hours the mixture is chromatographed on silica gel and eluted with cyclohexane:diethyl ether 70:30 v/v to give the ester.

Example 5.

Using one of the procedures described in Examples 3 or 4, by reacting one of the *cis*-5-prosten-13-ynoic acids prepared as described in Examples 1 and 2, with a diazoalkane (Example 3) or with an alcohol in the presence of dicyclohexylcarbodiimide (Example 4), the corresponding C₁—C₁₂ alkyl esters are prepared.

Example 6.

400 mg of *p*-phenylbenzoic acid are suspended in a solution of 450 mg of ethyl 9 α ,15(*S*)-dihydroxy-16(*R*)-methyl-*cis*-5-prosten-13-ynoate 15-(2"-THP) ether and 530 mg of triphenylphosphine in 25 ml of benzene. A solution of 348 mg of ethylazobiscarboxylate in 10 ml of benzene is added dropwise over 15 minutes with stirring and external cooling to maintain the temperature at about 10°C. When the acid is completely dissolved the mixture is washed with 0.1N sulfuric acid, water, 5% v/v sodium bicarbonate and water again, then evaporated to dryness. The residue is chromatographed by thin layer chromatography and eluted with methylenechloride:diethyl ether 90:10 v/v to give 0.59 g of ethyl

9 β ,15(S)-dihydroxy-16(R)-methyl-*cis*-5-prosten-13-ynoate 15-(2"-THP) ether 9-*p*-phenylbenzoate.

Example 7.

148 mg of propionic acid are added to a solution of 430 mg of methyl 9 β ,15(S)-dihydroxy-16(S),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoate 15-(2"-THP) ether and 530 mg of triphenylphosphine in anhydrous THF. It is cooled to 0° and a THF solution containing 348 mg of ethyl azobiscarboxylate is added. This is stirred for 15 minutes then evaporated to dryness. The residue is partitioned between diethyl ether:pentane 1:1 v/v and water and the organic phase washed with dilute acid, water, sodium bicarbonate and water again. It is dried and evaporated to dryness. The residue is chromatographed on 20 g of silica gel, eluted with cyclohexane:diethyl ether 75:25 v/v to give 452 mg of methyl 9 α ,15(S)-dihydroxy-16(S), 20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoate 15-(2"-THP) ether 9-propionate.

Example 8.

Using the procedures described in Examples 6 and 7, the carboxylic esters prepared as described in Examples 3 to 5, are reacted with triphenylphosphine in benzene and/or tetrahydrofuran and with one of the following carboxylic acids: formic, acetic, propionic, butyric, benzoic, phenylacetic, and *p*-phenylbenzoic and with ethyl azobiscarboxylate, to give the inverted 9-carboxylic acyloxy derivatives(9-formate, 9-acetate, 9-propionate, 9-benzoate, 9-phenyl-acetate, 9-*p*-phenylbenzoate) of the C₁—C₁₂ alkyl esters, preferably the methyl and ethyl esters, of the following compounds, as the 15-(2"-THP), 15-DIOX, 15-(4"-methoxy-4"-THP) and 15-(3'-methoxy-3"-THP) ethers:

9 β ,15(S)-dihydroxy-16(R)-methyl-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-20-methyl-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-20-ethyl-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-16(S)-methyl-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-16(R),20 dimethyl-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S) - dihydroxy - 17 - cyclohexyl - 16(R) - methyl - 18,19,20 - trinor - *cis* - 5 - prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-17-oxa-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-17-oxa-20-methyl-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-17-oxa-16(R)-methyl-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-17-oxa-16(S)-methyl-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-17-cyclopentyl-18,19,20-trinor-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-17-cyclohexyl-18,19,20-trinor-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-17-*p*-chlorophenyl-18,19,20-trinor-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S)-dihydroxy-17-phenyl-18,19,20-trinor-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(S) - dihydroxy - 16 - cyclohexyloxy - 17,18,19,20 - tetranor - *cis* - 5 - prosten - 13-ynoic acid;
 9 β ,15(S) - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - prosten - 13-ynoic acid;
 9 α ,15(S)-dihydroxy-16(R),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(S)-dihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(S)-dihydroxy-17-oxa-20-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(S)-dihydroxy-16(S),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(S)-dihydroxy-16(S)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(S) - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinor - 8,12 - diiso - *cis* - 5 - prosten-13-ynoic acid;
 All of these compounds are oils whose IR spectra indicate the absence of any bands attributable to free hydroxyl.

Example 9.

To a solution of an ether selected from those listed in Example 8, for example methyl 9 β ,15(S)-dihydroxy-16(R)-methyl-*cis*-5-prosten-13-ynoate 15-(tetrahydropyran-2"-yl) ether 9-*p*-phenylbenzoate (0.4 g) in 20 ml of acetone is added 15 ml of 0.15N oxalic acid and the mixture is refluxed for 45 minutes. The solvent is evaporated off under vacuum and the aqueous solution is extracted with diethyl ether, which is washed with saturated ammonium sulfate solution, dried and evaporated to dryness. The residue is purified by silica gel chromatography (eluted with cyclohexane-ethyl ether) to give 0.32 g of methyl 9 β ,15(S)-dihydroxy-16(R)-methyl-*cis*-5-prosten-13-ynoate 9-*p*-phenylbenzoate. The alkyl *cis*-5-prosten-13-

ynoate described in Example 8 can also be treated similarly.

Example 10.

A solution of a diester produced in Example 9, for instance, methyl 9 β ,15(S)-dihydroxy-16(R)-methyl-*cis*-5-prosten-13-ynoate 9-*p*-phenylbenzoate (0.32 g) in an anhydrous alcohol corresponding to the carboxyl ester, for example methanol, is treated at room temperature with 1.2 equivalents of anhydrous potassium carbonate (98 mg.) After two hours the reaction is complete and the mixture is neutralized with 15% v/v acetic acid in methanol and evaporated to dryness. The residue is taken up in diethyl ether, which is then washed until neutral, dried and evaporated to dryness. The residue is purified by silica gel chromatography, eluted with methylene chloride diethyl ether, to give 0.195 g of methyl 9 β ,15(S)-dihydroxy-16(R)-methyl-*cis*-5-prosten-13-ynoate. A solution of 0.1 g of this compound in 3 ml of methanol has added to it 0.5 ml of 10% w/v aqueous K₂CO₃, and is refluxed for 30 minutes. The solvent is evaporated off under vacuum and the residue diluted with water, then extracted with diethyl ether and the ethereal extracts discarded. The aqueous solution is acidified to pH 4.8, extracted with diethyl ether and the organic phase washed until neutral, dried and evaporated to dryness to yield 0.09 g of 9 β ,15(S)-dihydroxy-16(R)-methyl-*cis*-5-prosten-13-ynoic acid.

Example 11.

15 ml of 0.15N oxalic acid is added to a solution of 0.45 g of methyl 9 α ,15(S)-dihydroxy-16(S),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoate 15-(2"-THP) ether 9-propionate in 20 ml of acetone. After 5 hours at 40°C the acetone is evaporated and the residue extracted with ether to give 0.36 g of methyl 9 α ,15(S)-dihydroxy-16(S),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoate 9-propionate.

A solution of this compound in 20 ml of MeOH is refluxed for one hour with 5 ml of 10% w/v aqueous K₂CO₃. The methanol is evaporated off, the residue extracted with diethyl ether and these extracts discarded. The aqueous solution is acidified to pH 4.8 and saturated with ammonium sulfate, then extracted with diethyl ether. The combined ethereal extracts are dried and evaporated to dryness to give 0.27 g of pure 9 α ,15(S)-dihydroxy-16(S),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid.

Example 12.

Proceeding as described in Example 11, and starting from the compounds prepared in Examples 6, 7 and 8, the following free acids and their C₁—C₁₂ alkyl esters, preferably methyl and ethyl are obtained:

9 β ,15(S)-dihydroxy-16(R)-methyl-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-20-methyl-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-20-ethyl-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-16(S)-methyl-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-16(R),20-dimethyl-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-17-cyclohexyl-16(R)-methyl-18,19,20-trinor-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-17-oxa-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-7-oxa-20-methyl-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-17-oxa-16(R)-methyl-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-7-oxa-16(S)-methyl-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-17-cyclopentyl-18,19,20-trinor-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-17-cyclohexyl-18,19,20-trinor-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-17-*p*-chlorophenyl-18,19,20-trinor-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-7-phenyl-18,19,20-trinor-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-16-cyclohexyloxy-17,18,19,20-tetranor-*cis*-5-prosten-13-ynoic acid;
9 β ,15(S)-dihydroxy-16-phenoxy-17,18,19,20-tetranor-*cis*-5-prosten-13-ynoic acid;
9 α ,15(S)-dihydroxy-16(R),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
9 α ,15(S)-dihydroxy-16(R),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
9 α ,15(S)-dihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
9 α ,15(S)-dihydroxy-17-oxa-20-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
9 α ,15(S)-dihydroxy-16(S),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
9 α ,15(S)-dihydroxy-16(S)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
9 α ,15(S)-dihydroxy-17-cyclohexyl-18,19,20-trinor-8,12-diiso-*cis*-5-prosten-13-ynoic acid.

Example 13.

An ether such as is obtained in Example 8, for instance methyl 9 β ,15(S)-dihydroxy-17-oxa-*cis*-5-prosten-13-ynoate 15-(2"-THP) ether 9-benzoate (0.45 g) is refluxed for 2 hours in 25 ml of 5% w/v K₂CO₃ in MeOH:H₂O 80:20 v/v. The reaction mixture is evaporated under vacuum, the residue taken up in water, extracted with diethyl ether, and the organic phase discarded. The aqueous solution is acidified to pH 4.8 and extracted with diethyl ether (3 x 10 ml). The organic phases are combined, washed until neutral with saturated ammonium sulfate solution, dried and evaporated to dryness to yield 0.32 g of 9 β ,15(S)-dihydroxy-17-oxa-*cis*-5-prosten-13-ynoic acid 15-(2"-THP) ether.

Example 14.

Starting with 0.32 g of methyl 9 α ,15(S)-dihydroxy-16(S),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoate 15-(2"-THP) ether 9-propionate after treatment with 1.2 equivalents of anhydrous K₂CO₃ in anhydrous methanol for two hours at room temperature, neutralization with saturated NaH₂PO₄, evaporation of the solvent and extraction with diethyl ether one obtains 0.29 g of methyl 9 α ,15S-dihydroxy-16(S),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoate 15-(2"-THP) ether.

Example 15.

Using the procedure described in Examples 13 and 14 and starting from compounds prepared in Example 8, the corresponding 15-ethers of the 9,15-dihydroxy-*cis*-5-prosten-13-ynoic acids or the alkyl esters thereof are obtained. By deetherification, the corresponding 9,15-dihydroxy derivatives are obtained.

Example 16.

0.9 g of methyl 9 α ,15(S)-dihydroxy-16(S),20-dimethyl-*cis*-5-prosten-13-ynoate 15-(2"-THP) ether in 10 ml of benzene:DMSO 75:25 v/v are treated with 1.25 g of dicyclohexylcarbodiimide and 1.95 ml of a solution of pyridine trifluoroacetate (made by diluting 1 ml of trifluoroacetic acid and 2 ml of pyridine to 25 ml with benzene:DMSO 75:25 v/v). The mixture is stirred for 3 hours and then a solution of 0.55 g of oxalic acid dihydrate in MeOH is added and the reaction mixture diluted with 10 ml of water. The precipitate is filtered off and the organic phase is separated, evaporated to dryness then treated with 15 ml of acetone and 10 ml of 0.15N oxalic acid for 6 hours at 30°C. The acetone is distilled off under vacuum and the residue extracted with diethyl ether. The diethyl ether is evaporated off and the residue chromatographed on silica gel, eluted with CH₂Cl₂-diethyl ether, yielding 0.71 g of methyl 9-oxo-15(S)-hydroxy-16(S),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoate.

Example 17.

0.25 g of 9 β ,15(S)-dihydroxy-17-oxa-*cis*-5-prosten-13-ynoic acid 15-(2"-THP) ether in 10 ml of acetone is cooled to -15°C and 0.5 ml of Jones reagent is added. The reaction mixture is maintained at -10—12°C for 30 minutes. It is then diluted with 40 ml of benzene, washed repeatedly with saturated ammonium sulfate solution until neutral and evaporated to dryness. The crude reaction product is dissolved in 20 ml of acetone and 20 ml of 0.2N oxalic acid is added, and the mixture left at 40°C for 6 hours. The acetone is evaporated off under vacuum and the aqueous phase extracted with diethyl ether. The combined ethereal extracts are washed until neutral and then evaporated. The residue is chromatographed on silica gel, eluted with methylene chloride-diethyl ether, yielding 0.12 g of 9-oxo-15(S)-hydroxy-17-oxa-*cis*-5-prosten-13-ynoic acid.

Example 18.

Using the procedures of Examples 16 and 17 and starting from the ethers of the 9 α ,15(S); 9 β ,15(S); 9 α ,15(R) and 9 β ,15(R)-*cis*-5-prosten-13-ynoic acids obtained in Examples 1 to 5 and 10 to 15, either in free acid form or esters, oxidation with Jones reagent in acetone or with dicyclohexylcarbodiimide in benzene-DMSO and deetherification yielded the free acids or the C₁—C₁₂ alkyl esters of the following 9-oxo-derivatives:

- 9-oxo-15(S)-hydroxy-16(R)-methyl-*cis*-5-prosten-13-ynoic acid;
- 9-oxo-15(S)-hydroxy-20-methyl-*cis*-5-prosten-13-ynoic acid;
- 9-oxo-15(S)-hydroxy-16(S)-methyl-*cis*-5-prosten-13-ynoic acid;
- 9-oxo-15(S)-hydroxy-16(R),20-dimethyl-*cis*-5-prosten-13-ynoic acid;

- 9 - oxo - 15(S) - hydroxy - 16(R) - methyl - 18,19,20 - trinor - 17 - cyclohexyl - *cis*-5-prosten-13-ynoic acid;
 9-oxo-15(S)-hydroxy-20-ethyl-*cis*-5-prosten-13-ynoic acid;
 5 9-oxo-15(S)-hydroxy-17-oxa-*cis*-5-prosten-13-ynoic acid;
 9-oxo-15(S)-hydroxy-17-oxa-20-methyl-*cis*-5-prosten-13-ynoic acid;
 9-oxo-15(S)-hydroxy-17-oxa-16(R)-methyl-*cis*-5-prosten-13-ynoic acid;
 9-oxo-15(S)-hydroxy-17-oxa-16(S)-methyl-*cis*-5-prosten-13-ynoic acid;
 10 9 - oxo - 15(S) - hydroxy - 18,19,20 - trinor - 17 - cyclopentyl - *cis* - 5 - prosten -
 13-ynoic acid;
 9 - oxo - 15(S) - hydroxy - 18,19,20 - trinor - 17 - cyclohexyl - *cis* - 5 - prosten -
 13-ynoic acid;
 9 - oxo - 15(S) - hydroxy - 18,19,20 - trinor - 17 - *p* - chlorophenyl - *cis* - 5 -
 prosten-13-ynoic acid;
 15 9-oxo-15(S)-hydroxy-18,19,20-trinor-17-phenyl-*cis*-5-prosten-13-ynoic acid;
 9 - oxo - 15(S) - hydroxy - 17,18,19,20 - tetranor - 16 - cyclohexyloxy - *cis* - 5 -
 prosten-13-ynoic acid;
 9 - oxo - 15(S) - hydroxy - 17,18,19,20 - tetranor - 16 - phenoxy - *cis* - 5 -
 prosten-13-ynoic acid.

Example 19.

- 20 0.23 g of methyl 9 α ,15(S)-dihydroxy-16(S),20-dimethyl-8,12-diiso-*cis*-5-
 prosten-13-ynoate 15-(2"-THP) ether is dissolved in 2.5 ml of benzene:DMSO
 (75:25 v/v) and stirred at room temperature while 0.32 g of
 dicyclohexylcarbodiimide and then 0.48 ml of a solution of pyridine
 25 trifluoroacetate in benzene:DMSO (75:25 v/v) are added. Stirring is continued for 3
 hours and then a solution of 130 mg of oxalic acid dihydrate in 0.75 ml of methanol
 is added, followed by 3 ml of water and 10 ml of benzene. The mixture is filtered,
 the organic layer separated and the aqueous phase extracted with benzene. The
 organic phases are combined and washed until neutral and then evaporated to
 dryness. The yield is 0.22 g of methyl 9-oxo-15(S)-hydroxy-16(S),20-dimethyl-8,12-
 30 diiso-*cis*-5-prosten-13-ynoate 15-(2"-THP) ether. This compound is dissolved in 10
 ml of acetone and added to 8 ml of 0.25N citric acid. This is maintained for 6 hours
 at 40°C, concentrated under vacuum and extracted with diethyl ether. The organic
 phase is evaporated and the residue chromatographed on 1.2 g of silica gel, eluted
 35 with methylene chloride-diethyl ether, to give 0.14 g of methyl 9-oxo-15(S)-
 hydroxy-16(S),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoate.

Example 20.

- A solution of 0.49 g of 9 β ,15(S)-dihydroxy-16(R)-methyl-17-cyclohexyl-
 18,19,20-trinor-8,12-diiso-*cis*-5-prosten-13-ynoic acid 15-(2"-THP) ether in 20 ml of
 40 acetone is cooled to -20°C. To this is added 0.82 ml of Jones reagent. After one
 hour at -12° to -10°C, this is diluted with 80 ml of benzene and washed until
 neutral with saturated ammonium sulfate solution. The organic phase is dried and
 evaporated to dryness, the residue dissolved in 20 ml of acetone and 15 ml of 0.09N
 45 oxalic acid is added. This is left overnight at +40°C, then the solvent is evaporated
 off under vacuum and the residue extracted with diethyl ether. The combined
 organic extracts are evaporated to dryness and the residue purified by silica gel
 chromatography, to give 0.31 g of 9-oxo-15(S)-hydroxy-16(R)-methyl-17-
 cyclohexyl-18,19,20-trinor-8,12-diiso-*cis*-5-prosten-13-ynoic acid.

Example 21.

- Using the procedure described in Examples 19 and 20, some of the compounds
 50 prepared in Examples 2, 4, 8 and 15 are oxidised and deetherified to give the
 following 9-oxo-8,12-diiso-*cis*-5-prosten-13-ynoic acids or the C₁-C₁₂ alkyl esters
 thereof:
 9 - oxo - 15(S) - hydroxy - 16(R),20 - dimethyl - 8,12 - diiso - *cis* - 5 - prosten 13-
 ynoic acid;
 55 9 - oxo - 15(R) - hydroxy - 16(R),20 - dimethyl - 8,12 diiso - *cis* - 5 - prosten 13-ynoic
 acid;
 9-oxo-15(S)-hydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 9 - oxo - 15(S) - hydroxy - 17 - oxa - 20 - methyl - 8,12 - diiso - *cis* - 5 - prosten 13-
 ynoic acid;
 60 9 - oxo - 15(S) - hydroxy - 16(S) - methyl - 8,12 - diiso - *cis* - 5 - prosten - 13 ynoic
 acid;

9-oxo-15(*S*)-hydroxy-16(*S*),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;

Example 22.

A solution of 0.32 g of 9 α ,15(*S*)-dihydroxy-16(*R*)-methyl-*cis*-5-prosten-13-ynoic acid 15-(4"-methoxy-4"-THP) ether in 20 ml of acetone is treated at 38°C for 4½ hours with 15 ml of 0.15N oxalic acid. The solvent is distilled off under vacuum, the aqueous phase extracted with methylene chloride and the organic phases combined and washed until neutral and then concentrated to a small volume for chromatography on 1.8 g of silica gel, eluted with methylene chloride-ethyl acetate, to give 0.22 g of 9 α ,15(*S*)-dihydroxy-16(*R*)-methyl-*cis*-5-prosten-13-ynoic acid.

Example 23.

0.22 g of *n*-pentyl 9 β ,15(*S*)-dihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoate 15-DIOX ether in 10 ml of acetone is treated at 40°C with 6 ml of 0.1N oxalic acid. The solvent is evaporated off and the aqueous phase extracted with diethyl ether. The ethereal extracts are evaporated to dryness and purified by chromatography on silica gel (1.2 g) eluting with CH₂Cl₂-diethyl ether to give 0.14 g of *n*-pentyl 9 β ,15(*S*)-dihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoate.

Example 24.

Using the procedures in Examples 22 and 23 for deetherification of the ethers listed in Examples 1 to 5, as either free acids of their carboxylic acid esters, the following acids or the C₁-C₁₂ alkyl esters thereof are obtained:

9 α ,15(*S*)-dihydroxy-16(*R*)-methyl-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-20-methyl-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-16(*S*)-methyl-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-16(*R*),20-dimethyl-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-16(*R*)-methyl-18,19,20-trinor-17-cyclohexyl-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-18,19,20-trinor-17-cyclopentyl-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-18,19,20-trinor-17-cyclohexyl-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-18,19,20-trinor-17-*p*-chlorophenyl-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-18,19,20-trinor-17-phenyl-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-17,18,19,20-tetranor-16-cyclohexyloxy-*cis*-15-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-17,18,19,20-tetranor-16-phenoxy-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-20-ethyl-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-17-oxa-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-7-oxa-20-methyl-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-17-oxa-16(*R*)-methyl-*cis*-5-prosten-13-ynoic acid;
 9 α ,15(*S*)-dihydroxy-17-oxa-16(*S*)-methyl-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(*S*)-dihydroxy-16(*R*),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(*R*)-dihydroxy-16(*R*),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(*S*)-dihydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(*S*)-dihydroxy-17-oxa-20-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid;
 9 β ,15(*S*)-dihydroxy-16(*S*)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid; and
 9 β ,15(*S*)-dihydroxy-16(*S*),20-dimethyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid.

Example 25.

A stirred solution of 5 g of 2-[2 β ,4 α -dihydroxy-5 α (3"-methoxy-tetrahydropyran-3"-ylloxymethyl)cyclopent-1 β -yl]acetic acid *p*-lactone in 15 ml of pyridine is treated with 4.2 g of *p*-toluenesulphonyl chloride. This is maintained for 12 hours at room temperature, then diluted with water and ice and extracted with ethyl ether. The organic extracts are washed with a 30% aqueous solution of citric acid, 10%

sodium bicarbonate and water until neutral, dried and evaporated to dryness, to give 6.9 g of 2-[2 β -hydroxy-5 α -(3"-methoxy-tetrahydropyran-3"-yloxymethyl)-4 α -*p*-toluenesulphonyloxycyclopent-1 β -yl]acetic acid *p*-lactone. A solution of this compound in anhydrous diethyl ether is combined with a solution of MgI₂ in anhydrous diethyl ether (prepared by gradually adding 24.5 g of iodine to a suspension of 2.46 g of magnesium, in 200 ml of anhydrous diethyl ether, until it is all in solution). After this has been added to the tosylate, the mixture is stirred for 1½ hours and then decomposed by careful addition of water and ice with forceful mixing. The organic phase is separated off and the aqueous phase re-extracted. The combined organic extracts are evaporated to dryness to give a mixture of 2-[2 β -hydroxy-4 α -iodo-5 α -(3"-methoxytetrahydropyran-3"-yloxymethyl)cyclopent-1 β -yl]acetic acid *p*-lactone and 2-[2 β -hydroxy-5 α -hydroxymethyl-4 α -iodo-cyclopent-1 β -yl]acetic acid *p*-lactone. The two compounds can be separated by silica gel chromatography, with elution by cyclohexane-methylene chloride 20:80 v/v. The mixture is dissolved in benzene and 0.8 molar equivalents of 3-methoxy-2,3-dihydro-4*H*-pyran and 0.08 molar equivalents of *p*-toluenesulphonic acid are added. This is maintained for 3 hours at room temperature, then washed with 10% sodium bicarbonate, and water until neutral, then evaporated to dryness to give 5.3 g of 2-[2 β -hydroxy-4 α -iodo-5 α -(3"-methoxytetrahydropyran-3"-yloxymethyl)-cyclopent-1 β -yl]acetic acid *p*-lactone. This product is dissolved in benzene and treated at 50° with 1.6 molar equivalents of tributyltin in hydride, under nitrogen. After 12 hours, the benzene phase is washed repeatedly with a 10% solution of sodium and potassium tartrate, the organic phase is evaporated to dryness and the residue of crude 2-[2 β -hydroxy-5 α -(3"-methoxy-tetrahydropyran-3"-yloxymethyl)-cyclopent-1 β -yl]acetic acid *p*-lactone is dissolved in 50 ml of acetone and treated overnight at room temperature with 15 ml of 1*N* H₂SO₄. The acetone is evaporated off under vacuum, the aqueous phase is saturated with ammonium sulphate and extracted with ethyl ether. The organic phases are washed to neutrality, evaporated to dryness and purified by silica gel chromatography, with methylene chloride as eluent, giving 1.93 g of 2-(2 β -hydroxy-5 α -hydroxymethylcyclopent-1 β -yl)acetic acid *p*-lactone, m.p. 50—52°.

Example 26.

A solution of 7.95 g of 2-(5 α -methoxymethyl-2 β -hydroxy-cyclopent-3-en-1 β -yl)acetic acid *p*-lactone in 290 ml of methanol is refluxed with a solution of 26.25 g of potassium carbonate in 33 ml of water until the *p*-lactone group is completely saponified. After cooling, 1 g of PtO₂ is added and hydrogenation at normal pressure is continued until 1 molar equivalent of hydrogen has been taken up. The catalyst is filtered out, the reaction mixture is acidified to pH 3 and allowed to stand for 3 hours at room temperature. The solvent is evaporated off, the residue extracted with diethyl ether, the ethereal layer is then washed until neutral and evaporated to dryness, to yield 7.5 g of 2-(5 α -methoxymethyl-2 β -hydroxy-cyclopent-1 β -yl)acetic acid *p*-lactone, $[\alpha]_D^{25} = +14.8^\circ$; $[\alpha]_{365}^{25} = +66.4^\circ$ (CHCl₃).

Similarly starting from 2-(5 α -benzyloxymethyl-2 β -hydroxycyclopent-3-en-1 β -yl)acetic acid *p*-lactone and from 2-[5 β -methoxymethyl(or 5 β -benzyloxymethyl)-2 α -hydroxy-cyclopent-3-en-1 α -yl]acetic acid *p*-lactone; 2-[5 α -benzyloxymethyl-2 β -hydroxy-cyclopent-1 β -yl]acetic acid *p*-lactone, 2-[5 β -benzyloxymethyl-2 α -hydroxy-cyclopent-1 α -yl]acetic acid *p*-lactone, and 2-[5 β -methoxymethyl-2 α -hydroxy-cyclopent-1 α -yl]acetic acid *p*-lactone are obtained.

Example 27.

7.5 g of 2-[5 α -methoxymethyl-2 β -hydroxy-cyclopent-1 β -yl]acetic acid *p*-lactone are dissolved in 300 ml of methylene chloride. Under a nitrogen atmosphere and at -70° over a period of 10 minutes, 10.4 ml of a solution of boron tribromide in methylene chloride is added. After standing for 20 minutes at -70°, the temperature is allowed to rise to 0°, where it is maintained for one hour, and then to room temperature, at which temperature the reaction mixture is allowed to stand for 3 hours. The excess reagent is decomposed with water and ice, the organic phase is separated off and the aqueous phase re-extracted with chloroform. The combined organic phases are washed repeatedly with saturated sodium bicarbonate solution, then with water, dried over Na₂SO₄ and evaporated to dryness to give 6.18 g of 2-[5 α -hydroxymethyl-2 β -hydroxy-cyclopent-1 β -yl]-acetic acid *p*-lactone, m.p. 52—53°; $[\alpha]_D^{25} = +27.3^\circ$, $[\alpha]_{365}^{25} = +110^\circ$ (CHCl₃).

Using the same procedure and starting from the compounds listed in Example

26, one prepares the 2-[5 β -hydroxymethyl-2 α -hydroxy-1 α -cyclopentyl]acetic acid γ -lactone, m.p. 50—51°; $[\alpha]_D = -26^\circ$; $[\alpha]_{365} = -110^\circ$ (CHCl₃).

Example 28.

13.2 g of 2-[2 α ,4 α -dihydroxy-5 β -(1,4-dioxan-2-yl-oxymethyl)-cyclopent-1 α -yl]acetic acid γ -lactone are reacted in 26 ml of pyridine with 1.15 molar equivalents of *p*-toluenesulphonyl chloride, to give the 2-[2 α -hydroxy-5 β -(1,4-dioxan-2-yl-oxymethyl)-4 α -*p*-toluenesulphonyloxy-1 α -cyclopentyl]acetic acid γ -lactone. A solution of this product in anhydrous diethyl ether is cooled to 0—2° and 10 molar equivalents of MgI₂ in anhydrous diethyl ether are added. The mixture is stirred for one hour and then hydrolyzed with water and ice to obtain a mixture of the 2-[2 α -hydroxy-4 β -iodo-5 β -hydroxymethyl-cyclopent-1 α -yl]acetic acid γ -lactone and the dioxanyl ether thereof which is then dissolved in 30 ml of acetone. 8 ml of 1N H₂SO₄ are added. The solvent is evaporated off and the aqueous layer extracted with ethyl acetate to give 12.8 g of 2-[2 α -hydroxy-5 β -hydroxymethyl-4 β -iodo-cyclopent-1 α -yl]acetic acid γ -lactone. This compound is dissolved in anhydrous benzene and 1.6 molar equivalents of tributyl-tin hydride and 0.2 g of azobisisobutyronitrile added, and then the reaction is allowed to proceed at 55° for 18 hours. The reaction mixture is evaporated to dryness and chromatographed on silica gel, to yield 6.8 g of 2-[2 α -hydroxy-5 β -hydroxymethyl-cyclopent-1 α -yl]acetic acid γ -lactone.

Example 29.

4.7 g of 2-[5 β -hydroxymethyl-2 α -hydroxy-cyclopent-1 α -yl]acetic acid γ -lactone in 112 ml of benzene and 37 ml of anhydrous DMSO is combined with 18.75 g of dicyclohexylcarbodiimide and 28.9 ml of a solution of pyridine trifluoroacetate in DMSO. After stirring for 3 hours, add drop by drop 8.2 g of oxalic acid dihydrate in 45 ml of methanol, then dilute with 100 ml of water and 200 ml of benzene. The precipitate of dicyclohexylurea is filtered off, the organic phase is separated and the water phase is repeatedly washed with benzene. The combined organic phases are washed to neutrality and evaporated to dryness, to yield 4.62 g of 2-[5 β -formyl-2 α -hydroxy-cyclopent-1 α -yl]acetic acid γ -lactone.

In the same way, starting from 2-[5 α -hydroxy-methyl-2 β -hydroxy-cyclopent-1 β -yl]acetic acid γ -lactone, the 2-[5 α -formyl-2 β -hydroxy-cyclopent-1 β -yl]acetic acid γ -lactone is prepared. Both of these aldehydes are used without further purification.

Example 30.

A solution of 7.76 g of dimethyl (2-oxo-3(*R*)-methylheptyl)phosphonate in 120 ml of 1,2-dimethoxyethane is added dropwise with stirring, under an inert gas atmosphere, to a suspension of 0.96 g of an 80% dispersion of NaH in mineral oil in 120 ml of anhydrous 1,2-dimethoxyethane. Stirring is continued until no more hydrogen is evolved. After one hour, 5.91 g of N-bromosuccinimide is added and the mixture stirred for a further 15 minutes. A solution of 3.12 g of 2-[5 β -formyl-2 α -hydroxy-cyclopent-1 α -yl]acetic acid γ -lactone, is added all at once and the mixture stirred for one hour. The reaction mixture is neutralised by adding a saturated solution of NaH₂PO₄, then diluted with benzene, the aqueous phase separated and re-extracted with more benzene. The combined organic phases are dried and evaporated to dryness. The residue is chromatographed on silica gel with cyclohexane-methylene chloride 80—20 v-v, to give 6.76 g of 2-[2 α -hydroxy-5 β -(2'-bromo-3'-oxo-4'(*R*)-methyloct-*trans*-1'-enyl)cyclopent-1 α -yl]acetic acid γ -lactone.

Example 31.

In the procedure of Example 30, when N-bromoacetamide is used instead of the N-bromosuccinimide and dimethyl (2-oxo-3(*S*,*R*)-methyl-4-oxaoctyl)phosphonate replaces the specified phosphonate, the carbanion of dimethyl (1-bromo-2-oxo-3(*S*,*R*)-methyl-4-oxaoctyl)phosphonate is obtained, and then by reacting it with the 5 β -formyl derivative, 2-[2 α -hydroxy-5 β -(2'-bromo-3'-oxo-3'(*S*,*R*)-methyl-5'-oxanon-1'-*trans*-1'-enyl)-cyclopent-1 α -yl]acetic acid γ -lactone is formed.

Example 32.

In the procedure of Example 30 if N-bromocaprolactam is used instead of N-bromosuccinimide and the phosphonate used is dimethyl (2-oxooctyl)phosphonate, the carbanion obtained is that of dimethyl (1-bromo-2-oxooctyl)phos-

phonate, which reacts with 2-(2 β -hydroxy-5 α -formyl-cyclopent-1 β -yl)acetic acid γ -lactone to give 2-[2 β -hydroxy-5 α -(2'-bromo-3'-oxonon-1'-*trans*-1'-enyl)-cyclopent-1 β -yl]acetic acid γ -lactone.

Example 33.

Using in the procedures described in Examples 30 and 32 a haloimide chosen from N-bromosuccinimide, N-bromoacetamide and N-bromocaprolactam and reacting this with the carbanion of the corresponding non-halogenated phosphonate, one obtains *in situ* the carbanion of the following phosphonates:

dimethyl (1-bromo-2-oxo-3(*R*)-methylheptyl)phosphonate;
 dimethyl (1-bromo-2-oxoheptyl)phosphonate;
 dimethyl (1-bromo-2-oxooctyl)phosphonate;
 dimethyl (1-bromo-2-oxo-3(*S*)-methylheptyl)phosphonate;
 dimethyl (1-bromo-2-oxo-3(*R*)-methyloctyl)phosphonate;
 dimethyl (1-bromo-2-oxo-3(*R*)-methyl-4-cyclohexylbutyl)phosphonate;
 dimethyl (1-bromo-2-oxononyl)phosphonate;
 dimethyl (1-bromo-2-oxo-4-oxaheptyl)phosphonate;
 dimethyl (1-bromo-2-oxo-4-oxaactyl)phosphonate;
 dimethyl (1-bromo-2-oxo-3(*R*)-methyl-4-oxaheptyl)phosphonate;
 dimethyl (1-bromo-2-oxo-3(*S*)-methyl-4-oxaactyl)phosphonate;
 dimethyl (1-bromo-2-oxo-4-cyclopentylbutyl)phosphonate;
 dimethyl (1-bromo-2-oxo-4-cyclohexylbutyl)phosphonate;
 dimethyl (1-bromo-2-oxo-4-*p*-chlorophenylbutyl)phosphonate;
 dimethyl (1-bromo-2-oxo-4-phenylbutyl)phosphonate;
 dimethyl (1-bromo-2-oxo-4-cyclohexyloxybutyl)phosphonate; and
 dimethyl (1-bromo-2-oxo-4-phenoxybutyl)phosphonate;

which, when reacted with either of the two aldehydes 2-(2 α -hydroxy-5 β -formyl-cyclopent-1 α -yl)acetic acid γ -lactone or 2-(2 β -hydroxy-5 α -formyl-cyclopent-1 β -yl)acetic acid γ -lactone, prepared as described in Example 29, gives the following:

2-[2 α -hydroxy-5 β -(2'-bromo-3'-oxooct-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxonon-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxodec-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxo-4'(*R*)-methyloct-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxo-4'(*S*)-methyloct-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxo-4'(*R*)-methylnon-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxo-5'-oxaact-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxo-5'-oxanon-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxo-4'(*R*)-methyl-5'-oxaact-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxo-5'-cyclopentylpent-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxo-5'-cyclohexylpent-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxo-5'-phenylpent-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxo-5'-*p*-chlorophenylpent-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxo-5'-cyclohexyloxy-pent-*trans*-1'-enyl);
 5 β -(2'-bromo-3'-oxo-5'-phenoxy-pent-*trans*-1'-enyl); and
 5 β -(2'-bromo-3'-oxo-4'(*R*)-methyl-5'-cyclohexylpent-*trans*-1'-enyl); -cyclopent-1 α -yl]acetic acid γ -lactones; and
 2-[2 β -hydroxy-5 α -(2'-bromo-3'-oxo-4'(*R*)-methylnon-*trans*-1'-enyl);
 5 α -(2'-bromo-3'-oxooct-*trans*-1'-enyl);
 5 α -(2'-bromo-3'-oxo-5'-oxanon-*trans*-1'-enyl);
 5 α -(2'-bromo-3'-oxo-4'(*S*)-methyloct-*trans*-1'-enyl);
 5 α -(2'-bromo-3'-oxo-4'(*S*)-methylnon-*trans*-1'-enyl) - cyclopent-1 β -yl]acetic acid γ -lactones.

Example 34.

To a 0.02 M solution of zinc borohydride in diethyl ether (70 ml) is added a solution of 0.85 g of 2-[2 α -hydroxy-5 β -(2'-bromo-3'-oxo-4'(*S*)-methyloct-*trans*-1'-enyl)-cyclopent-1 α -yl]acetic acid γ -lactone in 25 ml of diethyl ether. This is stirred for 30 minutes, the excess reagent is destroyed by careful addition of 0.5N sulphuric acid. The ethereal phase is separated off and washed until neutral, dried and evaporated to dryness. The residue is chromatographed on silica gel, eluted with cyclohexane-methylene chloride, to give 0.62 g of 2-[5 β -(2'-bromo-3'(*S*)-hydroxy-

4'(*S*)-methyloct-*trans*-1'-enyl)-2 α -hydroxy-cyclopent-1 α -yllacetic acid γ -lactone and 0.22 g of the 3'(*R*) isomer.

Example 35.

At a temperature maintained between -7° and -5° , a solution of 29 mg of NaBH₄ in 3 ml of methanol is added dropwise into 0.43 g of 2-[2 β -hydroxy-5 α -(2'-bromo-3'-oxo-4'(*R*)-methyloct-*trans*-1'-enyl)-cyclopent-1 β -yllacetic acid γ -lactone in 8 ml of methanol. This is stirred for 30 minutes and then 70 ml of saturated aqueous NaH₂PO₄ is added and the mixture extracted with ethyl acetate. From the organic phase, after evaporation of the solvent and chromatography on silica gel, eluted with cyclohexanemethylene chloride 2:8, one obtains 0.3 g of 2-[2 β -hydroxy-5 α -(2'-bromo-3'(*S*)-hydroxy-4'(*R*)-methyloct-*trans*-1'-enyl)-cyclopent-1 β -yllacetic acid γ -lactone and 0.092 g of the (*R*)-isomer.

Example 36.

To 4.2 ml of a 0.25 M solution of lithium tri-*sec*-butyl-borohydride is added (at -30°) a solution of 357 mg of 2-[5 β -(2'-bromo-3'-oxo-4'(*S*)-methyl-non-1'-*trans*-1'-enyl)-2 α -hydroxy-cyclopent-1 α -yllacetic acid γ -lactone. After stirring for 45 minutes the excess reagent is destroyed by addition of 2 ml of acetone. The reaction mixture is neutralized with monosodium phosphate and evaporated under vacuum. The residue is taken up in methylene chloride and after evaporation of the solvent from the organic phase the residue is chromatographed on silica gel, eluted with methylene chloride, yielding 0.28 g of 2-[5 β -(2'-bromo-3'(*S*)-hydroxy-4'(*S*)-methyl-non-*trans*-1'-enyl)-2 α -hydroxy-cyclopent-1 α -yllacetic acid γ -lactone.

Example 37.

Using one of the procedures described in Examples 34 and 36 by reduction of the *trans*-enone prepared as described in Examples 30 to 33 with NaBH₄, Zn(BH₄)₂ or lithium tri-*sec*-butylborohydride, the following alcohols are obtained:

2-[2 α -hydroxy-
5 β -(2'-bromo-3'(*S*)-hydroxyoct-*trans*-1'-enyl);
5 β -(2'-bromo-3'(*S*)-hydroxynon-*trans*-1'-enyl);
30 5 β -(2'-bromo-3'(*S*)-hydroxydec-*trans*-1'-enyl);
5 β -(2'-bromo-3'(*S*)-hydroxy-4'(*R*)-methyloct-*trans*-1'-enyl);
5 β -(2'-bromo-3'(*S*)-hydroxy-4'(*R*)-methylnon-*trans*-1'-enyl);
5 β -(2'-bromo-3'(*S*)-hydroxy-5'-oxaoct-*trans*-1'-enyl);
5 β -(2'-bromo-3'(*S*)-hydroxy-5'-oxanon-*trans*-1'-enyl);
35 5 β -(2'-bromo-3'(*S*)-hydroxy-4'(*R*)-methyl-5'-oxaoct-*trans*-1'-enyl);
5 β -(2'-bromo-3'(*S*)-hydroxy-4'(*S*)-methyl-5'-oxaoct-*trans*-1'-enyl);
5 β -(2'-bromo-3'(*S*)-hydroxy-5'-cyclopentylpent-*trans*-1'-enyl);
5 β -(2'-bromo-3'(*S*)-hydroxy-5'-cyclohexylpent-*trans*-1'-enyl);
40 5 β -(2'-bromo-3'(*S*)-hydroxy-5'-phenylpent-*trans*-1'-enyl);
5 β -(2'-bromo-3'(*S*)-hydroxy-5'-*p*-phenylpent-*trans*-1'-enyl);
5 β -(2'-bromo-3'(*S*)-hydroxy-5'-cyclohexyloxypent-*trans*-1'-enyl);
5 β -(2'-bromo-3'(*S*)-hydroxy-5'-phenoxy-pent-*trans*-1'-enyl); and
5 β - (2' - bromo - 3'(*S*) - hydroxy - 4'(*R*) - methyl - 5' - cyclohexylpent -
45 *trans*-1'-enyl); -cyclopent-1 α -yllacetic acid γ -lactones, and
2-[2 β -hydroxy-
5 α -(2'-bromo-3'(*S*)-hydroxy-4'(*R*)-methylnon-*trans*-1'-enyl);
5 α -(2'-bromo-3'(*S*)-hydroxyoct-*trans*-1'-enyl);
5 α -(2'-bromo-3'(*S*)-hydroxy-5'-oxanon-*trans*-1'-enyl);
5 α -(2'-bromo-3'(*S*)-hydroxynon-*trans*-1'-enyl);
50 5 α -(2'-bromo-3'(*S*)-hydroxy-4'(*S*)-methyloct-*trans*-1'-enyl);
5 α - (2' - bromo - 3'(*S*) - hydroxy - 4'(*S*) - methylnon - *trans* - 1' - enyl); -
cyclopent-1 β -yllacetic acid γ -lactones,
and their 3'(*R*)-hydroxy isomers.

Example 38.

A solution of 0.69 g of 2-[2 α -hydroxy-5 β -(2'-bromo-3'(*S*)-hydroxy-4'(*R*)-methyloct-*trans*-1'-enyl)-cyclopent-1 α -yllacetic acid γ -lactone in anhydrous benzene is reacted with 0.26 g of 4-methoxy-5,6-dihydro-2*H*-pyran and a benzene solution containing 3.5 mg of *p*-toluenesulphonic acid. The reaction mixture is left overnight at room temperature, then the organic phase is washed with 5% w/v sodium bicarbonate and water until neutral and evaporated to dryness, to give 0.91 g of 2-[2 α -hydroxy-5 β -(2'-bromo-3'(*S*)-hydroxy-4'(*R*)-methyloct-*trans*-1'-enyl)-cyclopent-1 α -yllacetic acid γ -lactone 3'-(4"-methoxytetrahydropyran-4"-yl)ether.

Example 39.

If, in the procedures outlined in Example 38 the 4-methoxy-5,6-dihydro-2H-pyran is replaced with 1,4-dioxane, starting from 2-[2 β -hydroxy-5 α -(2'-bromo-3'(S)-hydroxy-4'(R)-methylnon-*trans*-1'-enyl)cyclopent-1 β -yl]acetic acid γ -lactone (3.5.10⁻³ moles) in benzene and reacting with 3.72.10⁻³ moles of 1,4-dioxane in the presence of 3.5.10⁻⁵ moles of *p*-toluenesulphonic acid, one obtains 3.5.10⁻³ moles of 2-[2 β -hydroxy-5 α -(2'-bromo-3'(S)-hydroxy-4'(R)-methylnon-*trans*-1'-enyl)-cyclopent-1 β -yl]acetic acid γ -lactone 3'-DIOX ether.

Example 40.

Proceeding as in Examples 38 and 39 and starting with alcohols prepared as described in Examples 34, 35, 36 and 37, reaction with 4-methoxy-5,6-dihydro-2H-pyran, 3-methoxy-5,6-dihydro-2H-pyran, 2,3-dihydro-pyran or 1,4-dioxane, the corresponding 3'-(4"-methoxytetrahydropyran-4"-yl), 3'-(3"-methoxytetrahydropyran-3"-yl) and 3'-(tetrahydropyran-2"-yl) and 3'-(1,4-dioxan-2-yl)ethers are obtained.

Example 41.

A solution of 0.9 g of 2-[2 α -hydroxy-5 β -(2'-bromo-3'(S)-hydroxy-4'(R)-methyloct-*trans*-1'-enyl)-cyclopent-1 α -yl]acetic acid γ -lactone 3'-(4"-methoxytetrahydropyran-4"-yl) ether in 40 ml of anhydrous toluene is cooled to -60° and, under an atmosphere of inert gas, 7.6 ml of a 0.5M solution of diisobutylaluminium hydride in toluene is added. The mixture is allowed to stand for 30 minutes at -60°, then 7 ml of 2M isopropanol in toluene are added and the mixture allowed to return to room temperature. 0.8 ml of water, 2 g of anhydrous sodium sulphate and 2 g of filter earth are added with constant stirring. The mixture is filtered and evaporated to dryness to obtain 0.9 g of pure 2-[2 α -hydroxy-5 β -(2'-bromo-3'(S)-hydroxy-4'(R)-methyloct-*trans*-1'-enyl)-cyclopent-1 α -yl]ethanal γ -hemiacetal 3'-(4"-methoxytetrahydropyran-4"-yl)ether.

Example 42.

Using the procedure of Example 41 for reduction of γ -lactones such as those of Example 16, with DIBA, the 2"-THP, DIOX, 4"-methoxy-4"-THP and 3"-methoxy-3"-THP ethers of the following γ -hemiacetals are obtained:

2-[2 α -hydroxy-5 β -(2'-bromo-3'(S)-hydroxyoct-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxynon-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxydec-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxy-4'(R)-methyloct-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxy-4'(R)-methylnon-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxy-5'-oxaoct-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxy-5'-oxanon-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxy-4'(R)-methyl-5'-oxaoct-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxy-4'(S)-methyl-5'-oxaoct-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxy-5'-cyclopentylpent-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxy-5'-cyclohexylpent-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxy-5'-phenylpent-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxy-5'-*p*-chlorophenylpent-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxy-5'-cyclohexyloxy-*trans*-1'-enyl);
5 β -(2'-bromo-3'(S)-hydroxy-5'-phenoxy-*trans*-1'-enyl); and
5 β -(2'-bromo-3'(S)-hydroxy-4'(R)-methyl-5'-cyclohexylpent-*trans*-1'-enyl); cyclopent-1 α -yl]ethanal γ -hemiacetals; and
2-[2 β -hydroxy-5 α -(2'-bromo-3'(S)-hydroxy-4'(R)-methylnon-*trans*-1'-enyl);
5 α -(2'-bromo-3'(S)-hydroxyoct-*trans*-1'-enyl);
5 α -(2'-bromo-3'(S)-hydroxy-5'-oxanon-*trans*-1'-enyl);
5 α -(2'-bromo-3'(S)-hydroxynon-*trans*-1'-enyl);
5 α -(2'-bromo-3'(S)-hydroxy-4'(S)-methyloct-*trans*-1'-enyl);
5 α -(2'-bromo-3'(S)-hydroxy-4'(S)-methylnon-*trans*-1'-enyl);
cyclopent-1 β -yl]ethanal γ -hemiacetals and their 3'(R)-isomers.

Example 43.

A solution of 0.32 g of 9-oxo-15(S)-hydroxy-16(S)-methyl-*cis*-5-prosten-13-ynoic acid in anhydrous diethyl ether is saturated by bubbling a stream of ammonia.

gas through it. The ammonium precipitate is filtered out and dried under vacuum at 40°, then stored at -10°.

Example 44.

A solution of 3.1 g of 2-(2 β ,4 β -dihydroxy-3 α -iodo-5 α -methoxymethyl-cyclopent-1 β -yl)acetic acid γ -lactone, 5.24 g of triphenylphosphine and 1.21 g of acetic acid in 30 ml of THF is combined with a solution of 3.48 g of ethyl azobiscarboxylate. This mixture is stirred for 2 hours then evaporated to dryness. The residue is chromatographed on silica gel with cyclohexane-diethyl ether, yielding 1.49 g of 2-(2 β -hydroxy-5 α -methoxymethyl-cyclopent-3-en-1 β -yl)acetic acid γ -lactone, m.p. 47-48°, $[\alpha]_D = -256^\circ$.

By the same method, employing as starting material the corresponding 5 α -benzyloxy-methyl and the 2-[2 α ,4 α -dihydroxy-3 β -iodo-5 β -methoxymethyl (or 5 β -benzyloxymethyl)cyclopent-1 α -yl]acetic acid γ -lactone, the following compounds are prepared:

2-(2 β -hydroxy-5 α -benzyloxymethyl-cyclopent-3-en-1 β -yl)-acetic acid γ -lactone; 2-(2 α -hydroxy-5 β -benzyloxymethyl-cyclopent-3-en-1 α -yl)-acetic acid γ -lactone; and 2-(2 α -hydroxy-5 β -methoxymethyl-cyclopent-3-en-1 α -yl)-acetic acid γ -lactone.

Example 45.

A suspension of 0.31 g of sodium hydride (80% dispersion in mineral oil) in 35 ml of 1,2-dimethoxyethane is stirred and a solution of 2.5 g of dimethyl (2-oxo-3(S)-methylheptyl)phosphonate in 15 ml of 1,2-dimethoxyethane is added dropwise. When the evolution of hydrogen has ceased, 1.9 g of N-bromosuccinimide is added and the mixture stirred for 30 minutes. The sodium derivative of dimethyl (1-bromo-2-oxo-3(S)-methylheptyl)phosphonate is thus formed. A solution of 1 g of dl-2(5 β -formyl-2 α -hydroxy-cyclopent-1 α -yl)acetic acid γ -lactone in 10 ml of 1,2-dimethoxyethane is added. The mixture is stirred for one hour then diluted with 6 volumes of benzene, and washed with aqueous 5% w/v sodium chloride solution until neutral. The organic layer is dried over Na₂SO₄ and evaporated to dryness. The residue is chromatographed on silica gel, eluted with methylene chloride-diethyl ether (97:3 v/v), to give 1.85 g of dl-2-[5 β -(2'-bromo-3'-oxo-4'(S)-methyloct-*trans*-1'-enyl)-2 α -hydroxycyclopent-1 α -yl]acetic acid γ -lactone, λ_{max} 250 m μ (E = 9,800).

A solution of 2.5 g of this product in anhydrous diethyl ether is added drop by drop to a 0.11 M solution of zinc borohydride in 100 ml of diethyl ether. After stirring for 30 minutes, the excess reagent is decomposed with 4N H₂SO₄. The mixture is washed with water until neutral and evaporated to dryness, giving a mixture of 4-epimeric alcohols that can be separated by column chromatography. When this residue is chromatographed on a 350 g silica gel column, eluted with methylene chloride, the following are obtained: *nat*-2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(S)-methyloct-*trans*-1'-enyl)-2 α -hydroxycyclopent-1 α -yl]acetic acid γ -lactone, $[\alpha]_D = -13^\circ$; $[\alpha]_{365} = -41^\circ$ (chloroform), 0.9 g;

ent-2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(S)-methyloct-*trans*-1'-enyl)-2 α -hydroxycyclopent-1-yl]acetic acid γ -lactone (also called 2-[5 α -(2'-bromo-3'(R)-hydroxy-4'(S)-methyloct-1'-*trans*-1'-enyl)-2 β -hydroxycyclopent-1 β -yl]acetic acid γ -lactone); $[\alpha]_D = +2.6^\circ$; $[\alpha]_{365} = +12^\circ$ (chloroform); 0.34 g;

ent-2-[5 β -(2'-bromo-3'(R)-hydroxy-4'(S)-methyloct-*trans*-1'-enyl)-2 α -hydroxycyclopent-1 α -yl]acetic acid γ -lactone (also called 2-[5 α -(2'-bromo-3'(S)-hydroxy-4'(S)-methyloct-*trans*-1'-enyl)-2 β -hydroxycyclopent-1 α -yl]acetic acid γ -lactone); $[\alpha]_D = +19.6^\circ$; $[\alpha]_{365} = +80^\circ$ (chloroform); 0.62 g; and finally

nat-2-[5 β -(2'-bromo-3'(R)-hydroxy-4'(S)-methyloct-*trans*-1'-enyl)-2 α -hydroxycyclopent-1 α -yl]acetic acid γ -lactone, $[\alpha]_D = -28^\circ$, $[\alpha]_{365} = -105^\circ$; 0.38 g.

To a solution of 0.89 g of the first alcohol 2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(S)-methyloct-*trans*-1'-enyl)-2 α -hydroxycyclopent-1 α -yl]acetic acid γ -lactone in 10 ml of methylene chloride, add 0.26 g of 2,3-dihydropyran and 6 mg of *p*-toluenesulphonic acid. Let stand for two hours at room temperature, add 0.2 ml of pyridine and evaporate to dryness, to give 1.01 g of 2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(S)-methyloct-*trans*-1'-enyl)-2 α -hydroxycyclopent-1 α -yl]acetic acid γ -lactone THP ether $[\alpha]_D = -19.8^\circ$, $[\alpha]_{365} = -58^\circ$ (CHCl₃).

This compound is dried with benzene, dissolved in anhydrous toluene and cooled to -60°C. Over a 15 minutes period, 10.4 ml of a 0.5 M solution of diisobutylaluminium hydride in toluene is added. After stirring for 40 minutes at

–60°, the excess reagent is decomposed by adding dropwise a 2M solution of isopropanol, and maintaining the reaction mixture at –60°. It is then warmed to room temperature and 0.9 ml of water, 1.2 g of filter earth and 3 g of sodium sulphate are added. The mixture is filtered and evaporated to dryness. A solution of 1.01 g of the lactol obtained above in 1.1 ml of dimethyl sulphoxide is added under a nitrogen atmosphere to a solution of the ylide prepared by adding under nitrogen 1.14 g of potassium tert-butoxide to a solution of 2.21 g of triphenyl-(4-carboxybutyl)-phosphonium bromide in 8 ml of dimethyl sulphoxide. The mixture is stirred for 3 hours, diluted with 3 ml of 1N KOH and 10 ml of water, then extracted with diethyl ether to remove the triphenyl-phosphoxide. The ethereal extracts are re-extracted with 3 × 5 ml of 0.5N KOH and then discarded. The combined alkaline phases are acidified to pH 4.8 and extracted with diethyl ether-pentane 50:50 v/v. The organic extracts are washed twice with 5 ml of saturated ammonium sulphate solution, dried and evaporated to dryness, yielding 1.1 g of 16(S)-methyl-9 α ,15(S)-dihydroxy-*cis*-5-prosten-13-ynoic acid 15-tetrahydropyran-2''-yl ether, m/e (M^+ 434) ($M^+ - H_2O$ 412), ($M^+ - 84$ 350). This compound is dissolved in 30 ml of acetone and cooled to –15° to –20°, then 1 ml of Jones reagent is added, and the reaction mixture allowed to stand at this temperature for 2 hours. It is then diluted with 80 ml of benzene, the organic phase is washed with saturated ammonium sulphate solution and evaporated to dryness, to give 1.06 g of 16(S)-methyl-9-oxo-15(S)-hydroxy-*cis*-5-prosten-13-ynoic acid 15-tetrahydropyran-2''-yl ether. This is dissolved in 60 ml of acetone and warmed to 36° after addition of 50 ml of 0.1N aqueous oxalic acid. After 8 hours at 36°, the acetone is removed under vacuum. The aqueous phase is extracted with ethyl acetate. The organic phase is washed until neutral with saturated ammonium sulphate solution and evaporated to dryness.

The residue is chromatographed on silica gel eluted with methylene chloride-cyclohexane 80:20 v/v and 90:10 v/v and finally with methylene chloride alone, giving 0.68 g of 16(S)-methyl-9-oxo-15(S)-hydroxy-*cis*-5-prosten-13-ynoic acid, an oil, $[\alpha]_D = +4.2^\circ$, $[\alpha]_{365} = +38^\circ$ (EtOH) (also called 11-deoxy-16(S)-methyl-13,14-dehydro-PGE₂).

Proceeding as described above and starting with the other alcohols, the following compounds are obtained:

16(S)-methyl-9-oxo-15(R)-hydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid, $[\alpha]_D = -5.4^\circ$, $[\alpha]_{365} = +57^\circ$ (EtOH) (also called *ent*-11-deoxy-16(S)-methyl-13,14-dehydro-PGE₂);

16(S)-methyl-9-oxo-15(S)-hydroxy-8,12-diiso-*cis*-5-prosten-13-ynoic acid (also called *ent*-11-deoxy-16(S)-methyl-15-*epi*-13,14-dehydro-PGE₂) $[\alpha]_D = -10^\circ$, $[\alpha]_{365} = +63^\circ$ (EtOH);

16(S)-methyl-9-oxo-15(R)-hydroxy-*cis*-5-prosten-13-ynoic acid, (also called 11-deoxy-16(S)-methyl-15-*epi*-13,14-dehydro-PGE₂), $[\alpha]_D = +9.3^\circ$, $[\alpha]_{365} = -54^\circ$ (EtOH).

Example 46.

A suspension of 676 mg of 80% sodium hydride in 90 ml of 1,2-dimethoxyethane is added dropwise over a 30 minutes period to a solution of dimethyl (2-oxo-3(R)-methylheptyl)phosphonate in 10 ml of 1,2-dimethoxyethane. The mixture is stirred for a further 30 minutes and then 4.15 g of N-bromosuccinimide are added and the mixture stirred for another 30 minutes. 2.5 g of 2-(5 α -formyl-2 β -hydroxycyclopent-1 β -yl)acetic acid γ -lactone, $[\alpha]_D = +25.3^\circ$ (CHCl₃), in 10 ml of benzene are added and the mixture stirred for one hour. 30 ml of saturated solution of monobasic sodium phosphate and 90 ml of benzene are added to the mixture. The organic phase is separated, dried over Na₂SO₄ and evaporated to dryness. The residue is chromatographed on silica gel, eluted with dichloromethane-cyclohexane 70:30 v/v to give 2.98 g of 2-[5 α -(2'-bromo-3'-oxo-4'(R)-methyloct-*trans*-1'-enyl)-2 β -hydroxycyclopent-1 β -yl]acetic acid γ -lactone, λ_{max} 252 m μ , E = 8,900.

This compound is dissolved in 100 ml of anhydrous diethyl ether and added dropwise to 180 ml of a 0.07 M solution of zinc borohydride in diethyl ether. After 30 minutes this is treated with 4N sulphuric acid and 25 ml of saturated sodium chloride solution. The organic phase is washed to neutral, evaporated to dryness and chromatographed on 150 g of silica gel, eluted with cyclohexane-methylene chloride (30:70 v/v, 20:80 v/v and finally 10:90 v/v), yielding 1.86 g of 2-[5 α -(2'-bromo-3'(R)-hydroxy-4'(R)-methyloct-*trans*-1'-enyl)-2 β -hydroxycyclopent-1 β -yl]acetic acid γ -lactone, $[\alpha]_D = +17^\circ$, $[\alpha]_{365} = +49.5^\circ$, and 0.38 g of 2-[5 α -(2'-

bromo-3'(S)-hydroxy-4'(R)-methyloct-*trans*-1'-enyl)-2 β -hydroxycyclopent-1 β -yl]acetic acid γ -lactone, $[\alpha]_D^{25} = +34^\circ$, $[\alpha]_{365}^{25} = +129^\circ$. Reaction of the first of these two epimeric alcohols with 2,3-dihydropyran (0.8 ml) in 15 ml of dichloromethane, in the presence of *p*-toluenesulphonic acid, gives the corresponding 3'(R)-tetrahydropyranyl ether, which is then reacted at -60° with 2 molar equivalents of diisobutylaluminium hydride to give the corresponding lactol 2-[5 α -(2'-bromo-3'(R)-hydroxy-4'(R)-methyloct-*trans*-1'-enyl)-2 β -hydroxycyclopent-1 β -yl]ethanal γ -lactol 3'-THP (2'') ether, $[\alpha]_D^{25} = +12^\circ$ (chloroform).

To a solution of 1.65 g of this compound in 5 ml of dimethyl sulphoxide, was added the ylide prepared from 16.6 g of triphenyl (4-carboxybutyl)-phosphonium bromide and 1.4 g of sodium hydride in 45 ml of dimethyl sulphoxide. The mixture was allowed to stand for 30 minutes at 20° , then diluted with 20 ml of 1N NaOH and 20 ml of water. The triphenylphosphoxide is removed by extraction with diethyl ether. The aqueous phase is acidified to pH 4.8 and extracted with diethyl ether: pentane 1:1 v/v. After evaporation of the solvent, 1.2 g of 9 β ,15(R)-dihydroxy-16(R)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid 15-tetrahydropyran-2''-yl ether is obtained, which is dissolved in 40 ml of acetone, cooled to -10° to -12° C and oxidized by addition of 3 ml of Jones reagent. After 40 minutes at -10° , the mixture is diluted with saturated ammonium sulphate solution, dried over sodium sulphate and evaporated to dryness. The residue (1.08 g) is dissolved in 100 ml of acetone and combined with 110 ml of 0.1N oxalic acid and warmed for 60 hours at 40° .

The acetone is evaporated off under vacuum, the residue is extracted with ethyl acetate and organic phase evaporated to dryness. The residue is chromatographed on silica gel, eluted with methylene chloride, to give 0.6 g of 9-oxo-15(R)-hydroxy-16(R)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid or *ent*-16-(R)-methyl-11-deoxy-13,14-dehydro-PGE₂, an oil, $[\alpha]_D^{25} = -2.3^\circ$, $[\alpha]_{365}^{25} = +131^\circ$ (EtOH).

In the same way, beginning with the other epimeric alcohol, 9-oxo-15(S)-hydroxy-16(R)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid is prepared, $[\alpha]_D^{25} = -11^\circ$, $[\alpha]_{365}^{25} = +159^\circ$ (EtOH).

Example 47.

A solution of 8.64 g of dimethyl (2-oxo-3(S)-methyl-3(R)-fluoroheptyl)-phosphonate is added, dropwise, to a stirred suspension of sodium hydride (80% dispersion in mineral oil, 1.02 g). When no more hydrogen is evolved, the mixture is treated with N-bromosuccinimide (6.14 g) and stirred for 30 minutes so obtaining the sodium salt of dimethyl (1-bromo-2-oxo-3(S)-methyl-3-fluoroheptyl)-phosphonate. Then a solution of 2-(5 β -formyl-2 α -hydroxycyclopent-1 α -yl)acetic acid γ -lactone (4.6 g) in benzene (30 ml) is added to the phosphonate solution. The reaction mixture is stirred for one hour at room temperature, washed with aqueous 10% v/v NaH₂PO₄ solution, dried over Na₂SO₄ and evaporated to dryness. The residue is chromatographed on silica gel (250 g) and eluted with benzene-methylene chloride (60:40), to give 8.21 g of 2-[5 β -(2'-bromo-3'-oxo-4'(S)-methyl-4'(R)-fluorooct-*trans*-1'-enyl)-2 α -hydroxy-cyclopent-1 α -yl]acetic acid γ -lactone ($\lambda_{\max} = 251 \text{ m}\mu$; E = 9,250). By reduction of this compound with sodium borohydride (1.1 g) in methylene chloride:ethanol (1:1 v/v) (120 ml) at -10° , and usual work up, a mixture of the epimeric alcohols is obtained (8.1 g) which is chromatographed on 0.9 kg of silica gel to afford 3.6 g of 2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(S)-methyl-4'(R)-fluorooct-*trans*-1'-enyl)-2 α -hydroxycyclopent-1 α -yl]acetic acid γ -lactone and 2.9 g of the 3'(R)-hydroxy epimer. A solution of the 3'(S)-alcohol in methylene chloride is treated at room temperature with 2,3-dihydropyran (1.68 g) and *p*-toluenesulphonic acid (25 mg) and then after three hours with pyridine (0.12 ml). After removal of the solvents *in vacuo*, the crude residue 2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(S)-methyl-4'(R)-fluorooct-*trans*-1'-enyl)-2 α -hydroxy-cyclopent-1 α -yl]acetic acid γ -lactone 3'-(2''-THP) ether is dissolved in dry toluene. Under a nitrogen atmosphere this stirred solution, cooled at -60° , is treated over 20 minutes with a 0.5M diisobutylaluminium hydride solution (40 ml). The mixture is stirred for 30 minutes at -60° and then treated with 20 ml of a 2M isopropanol solution in toluene. The mixture is heated to room temperature, treated with water, sodium sulphate and Celite (Registered Trade Mark), filtered. The filtrate is evaporated to dryness in vacuum to afford 4.3 g of crude 2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(S)-methyl-4'(R)-fluorooct-*trans*-1'-enyl)-2 α -hydroxy-cyclopent-1 α -yl]ethanal γ -hemiacetal 3'-(2''-THP) ether, which is reacted with the ylide prepared from 16.6 g of triphenyl (4-carboxybutyl)-phosphonium bromide and 1.44 g of sodium hydride in 45 ml of dimethyl sulphoxide. The mixture is

allowed to stand for one hour at 20° and then after dilution with 1N NaOH (20 ml) and water (20 ml) the triphenylphosphoxide removed by extraction with diethyl ether. Acidification of aqueous alkaline phases to pH 4.5, extraction with pentane:diethyl ether (1:1 v/v), and evaporation of the solvents *in vacuo* afforded 3.48 g of 9 α ,15(*S*)-dihydroxy-16(*S*)-methyl-16(*R*)-fluoro-*cis*-5-prosten-13-ynoic acid 15-(2"-THP) ether. A solution of 1.2 g of this compound in acetone (40 ml) is treated with 25 ml of 0.2N aqueous oxalic acid for 2 hours at reflux temperature. After removal of the acetone *in vacuo* the aqueous phase is extracted repeatedly with diethyl ether, the combined organic layers are washed with saturated ammonium sulphate solution, dried and evaporated *in vacuo* to dryness. The crude product is adsorbed on acid-washed silica gel (20 g/g) and subsequent elution with cyclohexane-methylene chloride yielded 0.68 g of pure 9 α ,15(*S*)-dihydroxy-16(*S*)-methyl-16(*R*)-fluoro-*cis*-5-prosten-13-ynoic acid.

Using a similar procedure and starting from the epimeric 3'(*R*)-hydroxy derivative, 9 α ,15(*R*)-dihydroxy-16(*S*)-methyl-16(*R*)-fluoro-*cis*-5-prosten-13-ynoic acid and its 15-THP ether derivative are obtained.

Example 48.

A stirred solution of 9 α ,15(*S*)-dihydroxy-16(*S*)-methyl-16(*R*)-fluoro-*cis*-5-prosten-13-ynoic acid 15-(2"-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° for 20 minutes, diluted with benzene (80 ml), washed with saturated ammonium sulphate solution until neutral, dried (Na₂SO₄) and then evaporated to dryness *in vacuo* to yield as an oil, 9-oxo-15(*S*)-hydroxy-16(*S*)-methyl-16(*R*)-fluoro-*cis*-5-prosten-13-ynoic acid 15-(2"-THP) ether, which is dissolved in acetone (80 ml). This solution is treated for 4 hours with 0.2N aqueous oxalic acid (50 ml) at 45°; then, after removal of acetone *in vacuo*, the aqueous phase is repeatedly extracted with diethyl ether. The combined ethereal extracts are washed with saturated ammonium sulphate solution, dried over Na₂SO₄ and evaporated to dryness in vacuum. The residue (1.1 g) is absorbed on an acid washed silica gel and then by elution with cyclohexane-methylene chloride (70:30 v/v)-9-oxo-15(*S*)-hydroxy-16(*S*)-methyl-16(*R*)-fluoro-*cis*-5-prosten-13-ynoic acid (0.72 g) is obtained.

Using the 15(*R*)-epimer in this procedure, the 9-oxo-15(*R*)-hydroxy-16(*S*)-methyl-16(*R*)-fluoro-*cis*-5-prosten-13-ynoic acid is obtained.

Example 49.

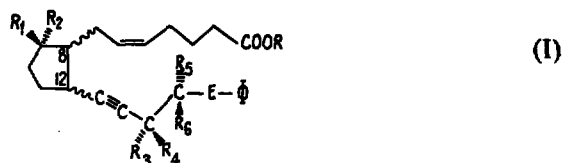
Using dimethyl (2-oxo-3(*R*)-methyl-3(*S*)-fluoroheptyl)phosphonate in the procedure of the Examples 47 to 48, the following compounds are obtained: 9 α ,15(*S*)-dihydroxy-16(*R*)-methyl-16(*S*)-fluoro-*cis*-5-prosten-13-ynoic acid 15-(2"-THP)-ether;

9-oxo-15(*S*)-hydroxy-16(*R*)-methyl-16(*S*)-fluoro-*cis*-5-prosten-13-ynoic acid 15-(2"-THP) ether and their 15(*R*)-epimers, which are deetherified with acetone-0.2N aqueous oxalic acid to afford after chromatographic purification the following: 9 α ,15(*S*)-dihydroxy-16(*R*)-methyl-16(*S*)-fluoro-*cis*-5-prosten-13-ynoic acid;

9-oxo-15(*S*)-hydroxy-16(*R*)-methyl-16(*S*)-fluoro-*cis*-5-prosten-13-ynoic acid and their 15(*R*)-epimers.

WHAT WE CLAIM IS:—

1. An optically active compound of the formula:



in which R is hydrogen, C₁₋₁₂ alkyl, or a cation of a pharmaceutically or veterinarily acceptable base; one of R₁ and R₂ is hydrogen and the other is hydroxy or carboxylic acyloxy, or R₁ and R₂ together form an oxo group; one of R₃ and R₄ is hydrogen and the other is hydroxy; R₅ and R₆ each denote hydrogen, or one of R₅ and R₆ is either fluorine or hydrogen and the other is C₁-C₄ alkyl; E is -(CH₂)_n-, in which n is an integer of from 1 to 6, or



allowed to stand for one hour at 20° and then after dilution with 1N NaOH (20 ml) and water (20 ml) the triphenylphosphoxide removed by extraction with diethyl ether. Acidification of aqueous alkaline phases to pH 4.5, extraction with pentane:diethyl ether (1:1 v/v), and evaporation of the solvents *in vacuo* afforded 3.48 g of 9 α ,15(S)-dihydroxy-16(S)-methyl-16(R)-fluoro-*cis*-5-prosten-13-ynoic acid 15-(2"-THP) ether. A solution of 1.2 g of this compound in acetone (40 ml) is treated with 25 ml of 0.2N aqueous oxalic acid for 2 hours at reflux temperature. After removal of the acetone *in vacuo* the aqueous phase is extracted repeatedly with diethyl ether, the combined organic layers are washed with saturated ammonium sulphate solution, dried and evaporated *in vacuo* to dryness. The crude product is adsorbed on acid-washed silica gel (20 g/g) and subsequent elution with cyclohexane-methylene chloride yielded 0.68 g of pure 9 α ,15(S)-dihydroxy-16(S)-methyl-16(R)-fluoro-*cis*-5-prosten-13-ynoic acid.

Using a similar procedure and starting from the epimeric 3'(R)-hydroxy derivative, 9 α ,15(R)-dihydroxy-16(S)-methyl-16(R)-fluoro-*cis*-5-prosten-13-ynoic acid and its 15-THP ether derivative are obtained.

Example 48.

A stirred solution of 9 α ,15(S)-dihydroxy-16(S)-methyl-16(R)-fluoro-*cis*-5-prosten-13-ynoic acid 15-(2"-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° for 20 minutes, diluted with benzene (80 ml), washed with saturated ammonium sulphate solution until neutral, dried (Na₂SO₄) and then evaporated to dryness *in vacuo* to yield as an oil, 9-oxo-15(S)-hydroxy-16(S)-methyl-16(R)-fluoro-*cis*-5-prosten-13-ynoic acid 15-(2"-THP) ether, which is dissolved in acetone (80 ml). This solution is treated for 4 hours with 0.2N aqueous oxalic acid (50 ml) at 45°; then, after removal of acetone *in vacuo*, the aqueous phase is repeatedly extracted with diethyl ether. The combined ethereal extracts are washed with saturated ammonium sulphate solution, dried over Na₂SO₄ and evaporated to dryness in vacuum. The residue (1.1 g) is absorbed on an acid washed silica gel and then by elution with cyclohexane-methylene chloride (70:30 v/v)-9-oxo-15(S)-hydroxy-16(S)-methyl-16(R)-fluoro-*cis*-5-prosten-13-ynoic acid (0.72 g) is obtained.

Using the 15(R)-epimer in this procedure, the 9-oxo-15(R)-hydroxy-16(S)-methyl-16(R)-fluoro-*cis*-5-prosten-13-ynoic acid is obtained.

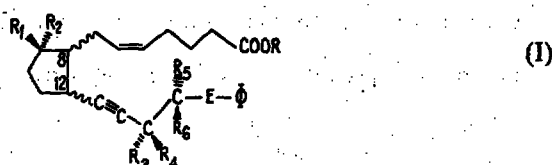
Example 49.

Using dimethyl (2-oxo-3(R)-methyl-3(S)-fluoroheptyl)phosphonate in the procedure of the Examples 47 to 48, the following compounds are obtained: 9 α -15(S)-dihydroxy-16(R)-methyl-16(S)-fluoro-*cis*-5-prosten-13-ynoic acid 15-(2"-THP)-ether;

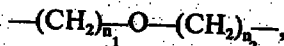
9-oxo-15(S)-hydroxy-16(R)-methyl-16(S)-fluoro-*cis*-5-prosten-13-ynoic acid 15-(2"-THP) ether and their 15(R)-epimers, which are deetherified with acetone-0.2N aqueous oxalic acid to afford after chromatographic purification the following: 9 α ,15(S)-dihydroxy-16(R)-methyl-16(S)-fluoro-*cis*-5-prosten-13-ynoic acid; 9-oxo-15(S)-hydroxy-16(R)-methyl-16(S)-fluoro-*cis*-5-prosten-13-ynoic acid and their 15(R)-epimers.

WHAT WE CLAIM IS:—

1. An optically active compound of the formula:



in which R is hydrogen, C₁₋₁₂ alkyl, or a cation of a pharmaceutically or veterinarily acceptable base; one of R₁ and R₂ is hydrogen and the other is hydroxy or carboxylic acyloxy, or R₁ and R₂ together form an oxo group; one of R₃ and R₄ is hydrogen and the other is hydroxy; R₅ and R₆ each denote hydrogen, or one of R₅ and R₆ is either fluorine or hydrogen and the other is C₁-C₄ alkyl; E is -(CH₂)_n-, in which n is an integer of from 1 to 6, or



in which n_1 and n_2 , which may be the same or different, each is zero, 1, 2 or 3; Φ is methyl; cycloalkyl of from 3 to 7 ring carbon atoms which optionally contains one or more ring oxygen or sulphur atoms; phenyl or phenyl substituted by halogen, C_1-C_4 alkoxy, phenyl, or trihalomethyl; the chains bound to the carbon atoms in the 8- and 12-positions having a *trans*-configuration with respect to each other.

2. Compound according to claim 1, in which R represents methyl, ethyl, propyl or heptyl.

3. Compound according to claim 1, in which R represents a sodium, potassium, calcium or aluminium cation or a trialkylamine.

4. Compound according to any one of the preceding claims, in which one of R_1 and R_2 is hydrogen and the other is hydroxy, or R_1 and R_2 together form an oxo group.

5. Compound according to any one of claims 1 to 3, in which one of R_1 and R_2 is hydrogen and the other is alkanoyloxy containing up to 6 carbon atoms, benzoyloxy or *p*-phenylbenzoyloxy.

6. Compound according to any one of the preceding claims, in which one of R_3 and R_6 is either fluorine or hydrogen, and the other is methyl.

7. Compound according to any one of claims 1 to 6, in which Φ is cycloalkyl or phenyl and E is $-(CH_2)_2-$.

8. Compound according to any one of claims 1 to 6, in which Φ is cycloalkyl or phenyl and E is $-CH_2-O-$.

9. Compound according to any one of claims 1 to 8, in which Φ is cyclopentyl, cyclohexyl or phenyl.

10. Compound according to any one of claims 1 to 6, in which Φ is methyl.

11. Compound according to claim 10, in which E is $-(CH_2)_n-$, wherein n is 4, 5 or 6.

12. Compound according to claim 10, in which E is $-CH_2-O-CH_2-CH_2-$.

13. Compound according to any one of claims 1 to 6, in which Φ is trifluoromethylphenyl or trichloromethylphenyl.

14. 9-oxo-15(*S*)-hydroxy-16(*S*)-methyl-*cis*-5-prosten-13-ynoic acid.

15. 9-oxo-15(*S*)-hydroxy-16(*S*)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid.

16. 9-oxo-15(*S*)-hydroxy-16(*R*)-methyl-*cis*-5-prosten-13-ynoic acid.

17. 9-oxo-15(*S*)-hydroxy-16(*R*)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid.

18. 9-oxo-15(*S*)-hydroxy-16(*S*),20-dimethyl-*cis*-5-prosten-13-ynoic acid.

19. 9-oxo-15(*S*)-hydroxy-16(*R*),20-dimethyl-*cis*-5-prosten-13-ynoic acid.

20. 9-oxo-15(*S*)-hydroxy-16(*S*)-methyl-16(*R*)-fluoro-*cis*-5-prosten-13-ynoic acid.

21. 9-oxo-15(*S*)-hydroxy-16(*S*)-fluoro-16(*R*)-methyl-*cis*-5-prosten-13-ynoic acid.

22. 9-oxo-15(*R*)-hydroxy-16(*S*)-methyl-*cis*-5-prosten-13-ynoic acid.

23. 9-oxo-15(*R*)-hydroxy-16(*S*)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid.

24. 9-oxo-15(*R*)-hydroxy-16(*R*)-methyl-*cis*-5-prosten-13-ynoic acid.

25. 9-oxo-15(*R*)-hydroxy-16(*R*)-methyl-8,12-diiso-*cis*-5-prosten-13-ynoic acid.

26. 9-oxo-15(*R*)-hydroxy-16(*S*),20-dimethyl-*cis*-5-prosten-13-ynoic acid.

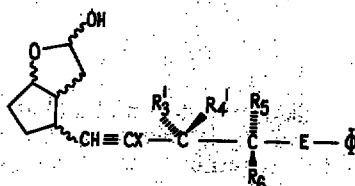
27. 9-oxo-15(*R*)-hydroxy-16(*R*),20-dimethyl-*cis*-5-prosten-13-ynoic acid.

28. 9-oxo-15(*R*)-hydroxy-16(*S*)-methyl-16(*R*)-fluoro-*cis*-5-prosten-13-ynoic acid.

29. 9-oxo-15(*R*)-hydroxy-16(*S*)-fluoro-16(*R*)-methyl-*cis*-5-prosten-13-ynoic acid.

30. A process for the preparation of a compound as defined in claim 1, which comprises

(i) reacting an optically active lactol of formula (VIII):



(VIII)

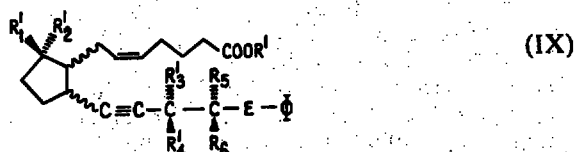
in which R_3 , R_6 , E and Φ are as defined in claim 1, X represents chlorine, bromine or iodine, one of R_3 and R_4 represents hydrogen and the other represents a known



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protecting group bound to the chain through an ethereal oxygen atom, and the lactol ring is in the *trans*-configuration with respect to the side-chain bound to the 12-carbon atom (prostaglandin numbering) and the bonds linking the lactol ring to the cyclopentane ring being in the *cis*-configuration with respect to each other; with a Wittig reagent comprising a group of formula $-(CH_2)_4-COOR'$ in which R' represents hydrogen or C_1-C_{12} alkyl, to give an optically active compound of formula (IX):



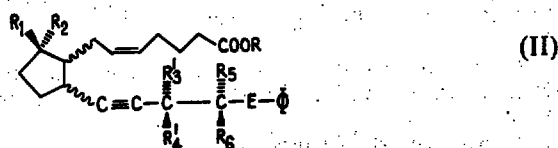
in which R' , R'_3 , R'_4 , R_5 , R_6 , E and Φ are as hereinbefore defined, the chains bound to the carbon atoms in the 8- and 12-positions are in the *trans*-configuration with each other; and when the chain bound to the carbon atom in the 8-position is in the α -configuration R'_1 represents hydrogen and R'_2 represents hydroxy or when said chain is in the β -configuration R'_1 represents hydroxy and R'_2 represents hydrogen; and if desired,

(ii) either (a) esterifying a compound of formula (IX) in which R' represents C_1-C_{12} alkyl with a carboxylic acid in the presence of a compound of formula M^vY_3 , in which M^v represents a metalloid of group VB of the Periodic Table, and Y represents alkyl, dialkylamino or aryl, and a hydrogen acceptor to form a 9α - or 9β -acyloxy derivative with inversion of configuration of the substituents at the 9-position, or

(b) esterifying a compound of the formula (IX) in which R' represents C_1-C_{12} alkyl in a manner known *per se* to form a 9α - or 9β -acyloxy derivative without inversion of configuration of the substituents at the 9-position;

(iii) subsequently saponifying the products of steps (a) and (b) above if desired, to yield the corresponding 9α - or 9β -hydroxy derivative, optionally also saponifying derivatives in which R' represents C_1-C_{12} alkyl to form compounds in which R' represents hydrogen; and then if desired

(iv) reacting the compound thus formed in which R' represents hydrogen with a base to form a compound of formula (II):



in which one of R_1 and R_2 represents hydrogen and the other represents hydroxy or acyloxy; R'_3 , R'_4 , R_5 , R_6 , E and Φ are as hereinbefore defined and R represents a cation of a pharmaceutically or veterinarily acceptable base; and, if desired,

(v) oxidising the product of steps (i), (iii) or (iv), in which one of R_1 and R_2 represents hydrogen and the other represents hydroxy, to form an optically active compound of formula II in which R_1 and R_2 together form an oxo group;

(vi) de-etherifying the product of any one of steps (i) to (v) under mild acidic conditions to form an optically active compound of formula I as defined in claim 1, and (vii) if desired, converting the compounds thus obtained into other compounds of formula (I) by known methods (as hereinbefore defined).

31. Process according to claim 30, in which, in step (i), X denotes bromine or iodine in the compound of formula (VIII) and the Wittig reaction is carried out employing about two moles of Wittig reagent per mole of lactol over a period of from 10 to 20 minutes.

32. Process according to claim 30, in which, in step (i), X denotes chlorine in the compound of formula (VIII) and the Wittig reaction is carried out employing from 1.5 to 2.5 moles of Wittig reagent per mole of lactol over a period of up to 10 hours.

33. Process according to claim 30, in which, in step (i), X denotes chlorine in the compound of formula (VIII) and the Wittig reaction is carried out employing at least 5 moles of Wittig reagent per mole of lactol for a period of about 30 minutes.



34. Process according to any one of claims 30 to 33, in which, in step (i), the Wittig reagent employed is of formula:



in which R_2 represents aryl or alkyl, Hal represents bromine or chlorine and R' represents hydrogen or C_1-C_{12} alkyl.

35. Process according to claim 34, in which R' represents methyl.

36. Process according to any one of claims 30 to 35, in which, in step (ii) (a), a compound of formula M^vY_3 is employed, wherein M^v denotes P, As or Sb and Y denotes methyl, phenyl or dimethylamino.

37. Process according to claim 36, in which triphenylphosphine, triphenylarsine, triphenylstibine or hexamethyltri-aminophosphine of formula $[(CH_3)_6N]_3P$ is employed as the compound of formula M^vY_3 .

38. Process according to claim 30, substantially as hereinbefore described in any one of Examples 1, 2, 7 to 19, 21, 22, 24 or 43.

39. Process according to claim 30, substantially as hereinbefore described in any one of Examples 6 or 20.

40. Process according to claim 30, substantially as hereinbefore described in Example 23.

41. Process according to claim 30, substantially as hereinbefore described in any one of Examples 45 to 49.

42. Prostaglandin derivatives as defined in claim 1 whenever prepared by the process of any one of claims 30 to 38.

43. Prostaglandin derivatives as defined in claim 1 whenever prepared by the process of any one of claims 30 and 39.

44. Prostaglandin derivatives as defined in claim 1 whenever prepared by the process of any one of claims 30 and 40.

45. Prostaglandin derivatives as defined in claim 1 whenever prepared by the process of any one of claims 30 and 41.

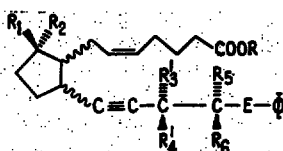
46. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of claims 1 to 29 or 42 and a pharmaceutically or veterinarily acceptable carrier or diluent.

47. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 43 and a pharmaceutically or veterinarily acceptable carrier or diluent.

48. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 44 and a pharmaceutically or veterinarily acceptable carrier or diluent.

49. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 45 and a pharmaceutically or veterinarily acceptable carrier or diluent.

50. A compound of formula:



in which R , R_1 , R_2 , R_3 , R_6 , E and Φ are as defined in claim 1, one of R'_1 and R'_2 represents a known protecting group bound to the chain by an ethereal oxygen atom and the other is hydrogen, and the chains bound to the carbon atoms in the 8- and 12-positions have a *trans*-configuration with respect to each other.

51. A process for the preparation of a compound as defined in claim 50, comprising steps (i) to (v) of the process defined in claim 30.

52. A compound of formula (II) whenever prepared by the process of claim 51.

53. A method for the treatment of a warm-blooded, non-human animal which comprises administering thereto an effective amount of a compound as claimed in any one of claims 1 to 29 or 42 to 45.

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