

PATENT SPECIFICATION

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- (21) Application No. 32897/75 (22) Filed 6 Aug. 1975
 (31) Convention Application No. 27654
 (32) Filed 25 Sept. 1974 in
 (33) Italy (IT)
 (44) Complete Specification published 24 Aug. 1977
 (51) INT CL³ C07C 177/00; A61K 31/00; C07D 307/12, 309/12, 319/12 333/16//307/93; C07F 9/40
 (52) Index at acceptance

C2C 1173 1175 1176 1177 1200 1210 1230 1472 147X 1511
 1672 1692 200 202 213 215 220 221 225 226 227 22X
 22Y 246 247 248 253 254 258 25Y 28X 295 302 304
 30Y 313 314 31Y 339 350 351 352 353 355 360 362
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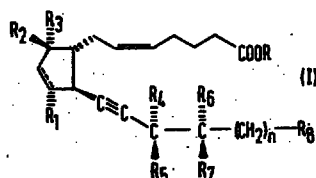


(54) PROSTAGLANDINS

(71) We, CARLO ERBA S.P.A., an Italian body corporate of Via Carlo Imbimati 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 ω -nor-cycloalkyl-13,14-didehydro-prostaglandins, to a method for their preparation and to pharmaceutical compositions containing them.

The compounds of the invention are optically active or racemic prostaglandins of formula (I)



wherein

R is a hydrogen atom, a C₁—C₁₂ alkyl group or a cation of a pharmaceutically acceptable base;

the symbol $\text{---}=\text{---}$ represents a single or a double bond, wherein, when the symbol $\text{---}=\text{---}$ is a double bond, R₁ is a hydrogen atom,

and R₂ and R₃ together form an oxo group, while, when the symbol $\text{---}=\text{---}$ is a single bond, R₁ is hydroxy,

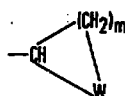
R₂ is hydrogen and R₃ is hydroxy or a carboxylic acyloxy or R₂ and R₃, taken together, form an oxo group;

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

R₆ and R₇ are independently hydrogen or C₁—C₄ alkyl;

n is zero, 1, 2 or 3;

R₈ is a radical



wherein m is 1, 2, 3, 4 or 5, and W is $-\text{CH}_2-$, an oxygen atom, a sulphur atom or a radical $>\text{NR}_6$, wherein R_6 is hydrogen or C_1-C_4 alkyl, or R_6 is 1-adamantyl, 2-norbornyl, 2-bicyclo[2,2,2]-octyl or 4-*t*-butylcyclohexyl.

The double bond in the 5(6)-position is a *cis*-double bond.

In the formulae of this specification, the broken lines

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

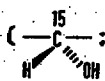
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indicate that the substituents are in the β -configuration, i.e. above the plane of the ring or of the chain; the wavy line attachment

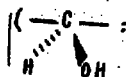
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indicates that the groups may be either in the α -configuration, i.e. below the plane of the ring, or in the β -configuration, i.e. above the plane of the ring.

As is evident from formula (I), the hydroxy group linked to the carbon atom in the 15- position may be either in the α -configuration



15(*S*)-ols) or in the β -configuration



15(*R*)-ols).

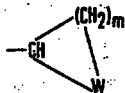
When on the carbon atom in the 16- position there is only one C_1-C_4 alkyl group, said substituent may be either a 16(*S*)-alkyl (α -configuration) or a 16(*R*)-alkyl (β -configuration) or a 16(*S,R*)-alkyl, i.e. the mixture of the two 16(*S*)- and 16(*R*)-diastereoisomers.

The alkyl groups may be branched or straight chain groups.

When R is a C_1-C_{12} alkyl group, it is preferably a methyl, ethyl or heptyl group;

When R_6 and/or R_7 are C_1-C_4 alkyl, the alkyl group is preferably methyl.

When in the radical



W is $-\text{CH}_2-$, said radical is preferably cyclopentyl, cyclohexyl or cycloheptyl; when W is an oxygen or a sulphur atom or a $>\text{NR}_6$ radical, m is preferably 3.

When R_6 is a 4-*t*-butylcyclohexyl radical, said radical may be in either the endo or exo configuration.

When R_6 is a carboxylic acyloxy group, it is preferably acetoxy, propionyloxy, benzoyloxy.

Examples of cations of pharmaceutically acceptable bases are either metallic cations, such as sodium, potassium, calcium, and aluminium or cations derived from organic amine, such as trialkylamines.

The nor-compounds are those wherein n is 3; the dinor-compounds are those wherein n is 2; the trinor-compounds are those wherein n is 1, and the tetranor-compounds are those wherein n is zero.

Examples of preferred compounds of the invention are the following:

9 α ,11 α ,15(S) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - *cis* - 5 - en - 13 - ynoic acid;

9 α ,11 α ,15(S) - trihydroxy - 18,19,20 - trinor - 17 - cycloheptylprost - *cis* - 5 - en - 13 - ynoic acid;

9 α ,11 α ,15(S) - trihydroxy - 18,19,20 - trinor - 17 - cyclopentylprost - *cis* - 5 - en - 13 - ynoic acid;

9 α ,11 α ,15(S) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - *cis* - 5 - en - 13 - ynoic acid 9 α - propionate;

9 α ,11 α ,15(S) - trihydroxy - 19,20 - dinor - 18 - cyclohexylprost - *cis* - 5 - en - 13 - ynoic acid;

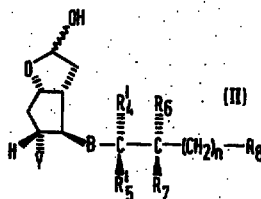
9 α ,11 α ,15(S) - trihydroxy - 17,18,19,20 - tetranor - 16 - cyclohexylprost - *cis* - 5 - en - 13 - ynoic acid;

9 - oxo - 11 α ,15(S) - dihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - *cis* - 5 - en - 13 - ynoic acid;

9 - oxo - 11 α ,15(S) - dihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(S) - methylprost - *cis* - 5 - en - 13 - ynoic acid;

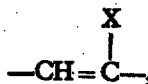
9 - oxo - 11 α ,15(S) - dihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(R) - methylprost - *cis* - 5 - en - 13 - ynoic acid.

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

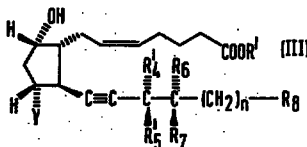


wherein

B is $\text{—C}\equiv\text{C—}$ or

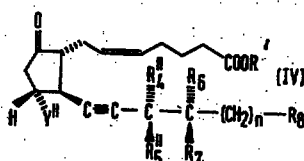


wherein X is bromine, chlorine or iodine, and wherein R₆, R₇, R₈ and n are as defined above, one of R₄ and R₅ is a hydroxy or a known protecting group bound to the chain by an ethereal oxygen atom, and the other is a hydrogen atom, Y is a hydroxy or a known protecting group bound to the ring by an ethereal oxygen atom, with a Wittig reagent comprising a group of formula $\text{—(CH}_2)_n\text{—COOR'}$, wherein R' is a hydrogen atom or a C₁—C₁₂ alkyl group, to give a compound of general formula (III)



wherein

R', Y, R₄, R₅, R₆, R₇, R₈ and n are as defined above, which, when Y is a known protecting group as above defined, and one of R₄ and R₅ is a known protecting group as above defined and the other is hydrogen, may be optionally esterified to give the 9 α -acyloxy derivative, and then, deetherifying the compound of formula (III) wherein Y is a known protecting group as above defined and/or one of R₄ and R₅ is a known protecting group as above defined and the other is hydrogen, or deetherifying the 9 α -acyloxy derivative of the compound of formula (III), so obtaining a compound of formula (I), wherein R₁ is a hydroxy group, the symbol $\text{—C}\equiv\text{C—}$ is a single bond, R₂ is hydrogen and R₃ is hydroxy or a carboxylic acyloxy, and one of R₄ and R₅ is a hydroxy group and the other is hydrogen, or, if desired, oxidizing the 9 α -hydroxy group in the compound of formula (III) wherein Y is a known protecting group as above defined, and one of R₄ and R₅ is a known protecting group as above defined and the other is hydrogen, to give a compound of general formula (IV)

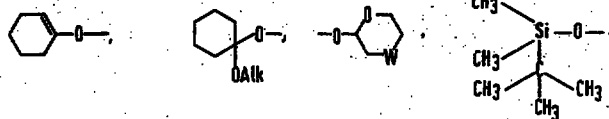


wherein

R' , R_6 , R_7 , R_8 and n are as above defined, Y'' is a known protecting group as defined above, and one of R''_4 and R''_5 is a known protecting group as defined above and the other is hydrogen, which, in turn, is deetherified to give, according to the reaction conditions used, either a compound of general formula (I) wherein the symbol $-----$ is a single bond, R_1 is hydroxy, and R_2 and R_3 taken together form an oxo group, or a compound of general formula (I) wherein the symbol $-----$ is a double bond, R_1 is hydrogen and R_2 and R_3 together form an oxo group, and then, if desired, reacting a compound of general formula (I) wherein R is a hydrogen atom with a base to give a compound of general formula (I) wherein R is a cation, or esterifying a compound of general formula (I) wherein R is a hydrogen atom, to give a compound of general formula (I) wherein R is C_1-C_{12} alkyl, or hydrolysing a compound of general formula (I) wherein R is C_1-C_{12} alkyl, to give a compound of general formula (I) wherein R is a hydrogen atom.

The hydrolysis of a compound of formula (I) wherein R_2 and R_3 together form an oxo group, and wherein R is C_1-C_{12} alkyl, to give a compound of formula (I) wherein R_1 and R_2 together form an oxo group and R is hydrogen, may be also carried out by enzymatic way, e.g. by using a yeast esterase.

The known protecting groups (i.e. ether groups) are convertible to hydroxy groups under mild reaction conditions, e.g. acid hydrolysis. Examples are 1-alkoxy-cycloalkoxy groups, 2-oxacycloalkoxy groups whose cycloalkyl group optionally has a further ring oxygen atom, and ether groups, 1-alkoxyalkoxy groups and silyl ether groups. The preferred groups are



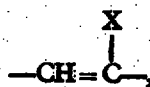
wherein W is $-O-$ or $-CH_2-$, and Alk is a lower alkyl group.

When in the lactol of formula (II) B is $-C\equiv C-$ or



wherein X is bromine or iodine, the Wittig reaction may be performed using about two moles of Wittig reagent per mole of lactol with a reaction time of 10-20 minutes.

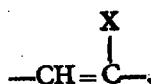
When in the lactol of formula (II) B is



wherein X is chlorine, it is necessary, by using for example 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).

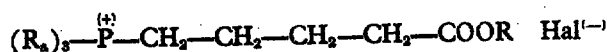
When in the lactol of formula (II) B is



wherein X is bromine, chlorine or iodine, the hydrogen atom linked to the carbon atom in the 13- position and the halogen atom linked to the carbon atom in the 14- position may be either in the *trans*-position (geometric *trans*-isomers) or in the *cis*-position (geometric *cis*-isomers). Preferably they are in the *trans*-position.

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

The term "Wittig reagent" includes compounds of general formula



wherein R_a is aryl or alkyl, Hal is bromine or chlorine and R is hydrogen or alkyl. When R_a is alkyl, it is preferably ethyl.

The preparation of the Wittig reagent is discussed in detail by Tripett, Quart. Rev., 1963, XVII, No. 4, 406.

It is preferable for economic reasons that B in the lactol of formula (II) is a



group, wherein X is bromine, chlorine or iodine, since the dehydrohalogenation then takes place during the reaction with the Wittig reagent in a single step and proceeds easily regardless of whether the hydrogen atom linked to the carbon atom in the 13- position and the halogen atom linked to the carbon atom in the 14- position are in the *trans*-position or the *cis*-position.

The optional acylation of the 9 α -hydroxy group in the compound of formula (III) with a carboxylic acid may be performed e.g. by treatment with a carboxylic acid anhydride or chloride in presence of a base, i.e. according to the usual methods of organic chemistry.

The deetherification reaction is performed by mild acid hydrolysis, for example with mono- or poly-carboxylic acid, e.g. formic, acetic, oxalic, citric and tartaric acid, and in a solvent, for example water, acetone, tetrahydrofuran, 1,2-dimethoxyethane and lower aliphatic alcohols.

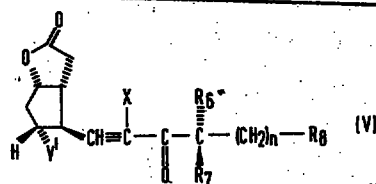
Preferably, 0.1 N to 0.25 N poly-carboxylic acid (e.g. oxalic or citric acid) is used in presence of a convenient low boiling cosolvent which is miscible with water and which can be easily removed *in vacuo* at the end of the reaction.

The oxidation of the 9 α -hydroxy group to yield an oxo group may be carried out with, for example, Jones reagent.

As above stated, the deetherification of the compound of general formula (IV) may give, according to the reaction conditions used, either a compound of general formula (I) wherein the symbol $-\text{---}-$ is a single bond, R_1 is hydroxy and R_2 and R_3 taken together form an oxo group, or a compound of general formula (I) wherein the symbol $=\text{---}=\text{---}=\text{---}$ is a double bond, R_1 is hydrogen and R_2 and R_3 taken together form an oxo group.

The former compound may be obtained as the only product, by operating at temperatures ranging between 25°C and 35—38°C, while by operating at higher temperatures, for example at the reflux temperature for about three hours, the latter compound is obtained as the only product.

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

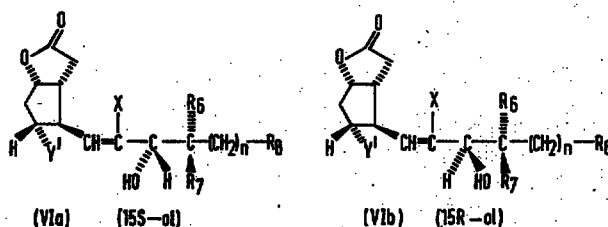


wherein

Y' is hydroxy, acyloxy or a known protecting group bound to the ring through an etheral oxygen atom, X, R₆, R₇, R₈ and n are as defined above; and wherein the hydrogen atom linked to the carbon atom in the 13- position and the halogen atom linked to the carbon atom in the 14- position (prostaglandin numbering) may be either in the *trans*-position or in the *cis*-position.

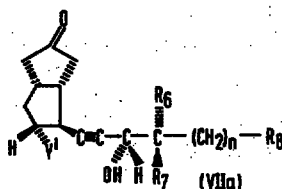
The multi-step process to prepare the compound of general formula (II) starting from the lactone of formula (V) involves the following steps:

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

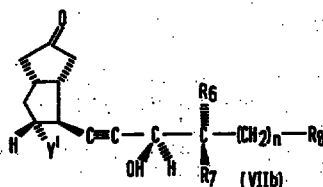


wherein

Y', X, R₆, R₇, R₈ and n are as above defined, followed by the separation of the 15(*S*)-ol from the 15(*R*)-ol and, if desired, by the dehydrohalogenation of the separated alcohols to give a compound of formula (VIIa)



or a compound of formula (VIIb)



wherein

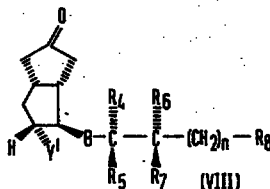
Y', R₆, R₇, R₈ and n are as above defined.

If desired, the reduction may follow the dehydrohalogenation.

The reduction of the 15-oxo group may be suitably performed in an organic solvent, such as acetone, diethyl ether, 1,2-dimethoxyethane, dioxan, or benzene or their mixtures, by using e.g. metal borohydrides, in particular sodium borohydride, lithium borohydride, zinc borohydride, sodium trimethoxyborohydride.

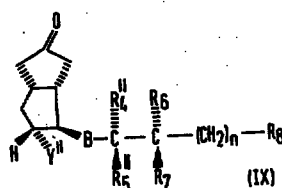
The separation of the 15(*S*)-ol from the 15(*R*)-ol may be performed by chromatography, e.g. silica gel chromatography or by fractionated crystallization. The dehydrohalogenation may be performed in a solvent, preferably selected from dimethyl sulphoxide, dimethylformamide, hexamethylphosphoramide in presence of a base which may be for example an alkaline metal amide, potassium *tert*.butoxide or an alkali metal methylsulphinyll methide.

b) Conversion of a compound of formula (VIII)



wherein

Y', R₆, R₇, R₈, B and n are as defined above and one of R₄ and R₅ is a hydrogen atom and the other is a hydroxy group into a compound of formula (IX)



wherein

B, R₆, R₇, R₈ and n are as defined above, Y'' is a known protecting group bound to the ring through an ethereal oxygen atom, and one of R''₄ and R''₅ is a known protecting group bound to the chain by an ethereal oxygen atom and the other is a hydrogen atom.

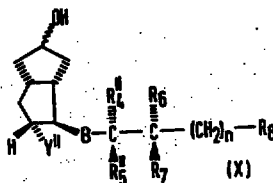
The etherification of the compound of formula (VIII) to give a compound of formula (IX) is preceded when, in the compound of formula (VIII), Y' is an acyloxy group, by saponification for example by mild treatment with an alkali, to give a compound of formula (VIII) wherein Y' is a hydroxy group.

The etherification is preferably carried out with a cyclic ether of formula



wherein W is —O— or —CH₂—, in presence of catalytic amounts of, for example, phosphorus oxychloride, *p*-toluenesulphonic acid or benzenesulphonic acid, or with a halosilane, for instance by reacting a trisubstituted chlorosilane in presence of an acid acceptor (for example a trialkylamine) for the hydrogen halide formed, or with a 1,1-dialkoxycycloalkane, for instance by reaction, in presence of an acid catalyst with a 1,1-dialkoxy-cyclopentane or cyclohexane, at the reflux temperature in an inert solvent and distilling off the alcohol as it is formed.

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



wherein

Y'', B, R''₄, R''₅, R₆, R₇, R₈ and n are as above defined.

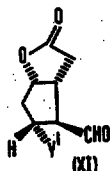
The reduction may be performed by treatment with diisobutylaluminium hydride or sodium bis-(2-methoxyethoxy)-aluminium hydride in an inert solvent, for example, toluene, n-heptane, n-hexane or benzene or their mixtures, at below 30°C.

d) Optional deetherification of the compound of formula (X) to give a compound having the free 11- and 15- hydroxy groups.

The deetherification may be carried out by mild acid hydrolysis, in a solvent miscible with water, with a solution of a mono- or poly- carboxylic acid.

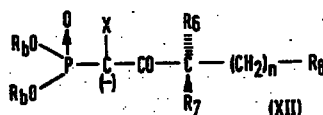
All the compounds mentioned under items a) to d) may be either optically active compounds or racemic mixtures thereof.

The lactone of formula (V) may be in turn prepared in an only one step by reaction of an aldehyde of formula (XI)



wherein

Y' is as defined above, with a halo-phosphonate carbanion of formula (XII)



wherein

R₆ is lower alkyl,

X R₆, R₇, R₈ and n are as defined above.

The reaction is suitably performed in a solvent which is preferably dry benzene, 1,2-dimethoxyethane, tetrahydrofuran, dimethylformamide or their mixtures, and using a suspension of 1.1—1.2 molar equivalent of the halo-phosphonate carbanion.

When in the aldehyde of formula (XI) Y' is an acyloxy group, it may be for example, acetoxy, propionyloxy, benzyloxy and *p*-phenylbenzyloxy. When Y' is a known protecting group bound to the ring through an ethereal oxygen atom, it may be for example one of the ethereal protecting groups described hereinbefore.

The aldehyde of formula (XI) may be prepared substantially as described by E. J. Corey et al., Ann. of New York Acad. of Sciences, 180, 24 (1971).

The halo-phosphonate carbanion of formula (XII) may be in turn prepared by reacting a halo-phosphonate of formula (XIII)

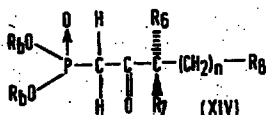


wherein

R₆, X, R₆, R₇, R₈ and n are as defined above,

with an equivalent of a base preferably selected from sodium hydride, lithium hydride, calcium hydride, an alkyl lithium derivative and an alkali metal-methylsulphonyl methide.

The halo-phosphonate of formula (XIII) may be obtained by halogenation of a phosphonate of formula (XIV)



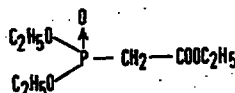
wherein

R₆, R₆, R₇, R₈ and n are as defined above.

The halogenation may be carried out in a conventional manner, operating substantially as in the halogenation of β -keto esters. The phosphonate of formula (XIV) may be prepared by known methods, e.g. according to E. J. Corey et al., J. Am. Chem. Soc. 90, 3247 (1968) and E.J. Corey and G.K. Kwiatkowski, J. Am. Chem. Soc., 88, 5654 (1966). Preferably, the phosphonate of formula (XIV) is prepared by reaction of lithium methylphosphonate with a lower alkyl ester of the optionally substituted ali-

phatic acid. When the aliphatic acid contains asymmetric carbon atoms, it is possible to use either the racemic acid or one of its optical antipodes.

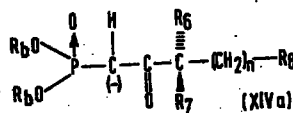
The lower alkyl ester of the suitable aliphatic acid may be prepared by known methods. For example, the ethyl β -cyclobutylpropionate may be prepared by condensing cyclobutanecarbaldehyde with a compound of formula



and then reducing, e.g. with Pd/C, the resulting ethyl β -cyclobutylacrylate. The ethyl esters of the γ -cyclopropylbutyric, γ -cyclobutylbutyric and δ -cyclopropylvaleric acids may be prepared, e.g. from the corresponding esters of cyclopropylacetic, cyclobutylacetic and cyclopropylpropionic acids, after reduction to the alcohols and conversion into the halides, by malonic acid synthesis, as is known in organic chemistry, followed by esterification of the obtained acids.

The esters, e.g. ethyl esters, of the substituted propionic acids, [e.g. cyclopropane-, cyclobutane-, cyclopentane-, cyclohexane-, cycloheptane-, 2-tetrahydrofuran-, 1-adamantane-, 2-norbornane-, 2-bicyclo[2,2,2]-octane- or 4-*t*-butylcyclohexane-propionic acids], may be prepared starting from the corresponding substituted acetic acids by known methods, e.g. by reduction of the substituted acetic acids to primary alcohols, conversion of the alcohols into the mesylates and then into the halides, and finally by reaction with a cyanide, e.g. an alkali metal cyanide, to give the nitriles of the substituted propionic acids which are subsequently converted into the substituted propionic esters by the usual method of organic chemistry. The α -methylation of the enolates of the above-described esters, which can be obtained by reaction of the esters with lithium diisopropylamide in tetrahydrofuran (according to the method described in Org. Synthesis, 50, 58 and in Tetrahedron Letters, 2425 (1973)) gives the α -methyl-substituted esters of the above acids, i.e. for example, α -methyl- β -cyclobutylpropionic, α -methyl- β -cyclopropylpropionic, α -methyl- β -cyclopentylpropionic, α -methyl- β -cyclohexylpropionic, α -methyl- γ -cyclopropylbutyric, α -methyl- γ -cyclobutylbutyric, α -methyl- δ -cyclopropylvaleric as well as the α -methyl-substituted esters of the other above-cited acids, which may be optionally resolved into the optical antipodes to give the 2(*S*)-methyl and the 2(*R*)-methyl derivative. The further methylation of the above-cited esters gives the α,α -dimethyl substituted esters of the above acids, i.e., for example, α,α -dimethyl- β -cyclobutylpropionic, α,α -dimethyl- β -cyclopropylpropionic, α,α -dimethyl- β -cyclopentylpropionic, α,α -dimethyl- β -cyclohexylpropionic, α,α -dimethyl- γ -cyclopropylbutyric, α,α -dimethyl- γ -cyclobutylbutyric, α,α -dimethyl- δ -cyclopropylvaleric as well as the α,α -dimethyl-substituted esters of the other above-cited acids.

Alternatively, the halo-phosphonate carbanion of formula (XII) may be prepared by reacting a phosphonate carbanion of formula (XIVa)



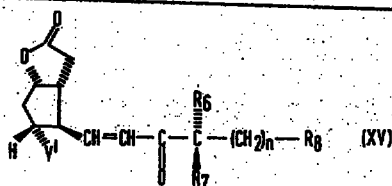
wherein

R_6 , R_8 , R_7 , R_8 and n are as defined above, with a halogenating agent selected from Br_2 , 2-pyrrolidone hydrotribromide (PHTB), dioxane dibromide, *N*-chloroacetamide, *N*-chlorosuccinimide, *N*-bromosuccinimide, *N*-bromoacetamide, *N*-bromocaprolactam, *N*-iodosuccinimide.

By using the imides as halogenating agents, the carbanion of the halo-phosphonate of formula (XII) is obtained directly with the use of only one equivalent of base; otherwise, it is necessary to use another equivalent of a base to obtain the carbanion of the halo-phosphonate.

The phosphonate carbanion of formula (XIVa) may be in turn obtained by the treatment of the phosphonate of formula (XIV) with an equivalent of a base, e.g. sodium, lithium or calcium hydride.

The halo-lactone of formula (V) wherein X is bromine may also be obtained by a multi-step process starting from lactone of formula (XV)

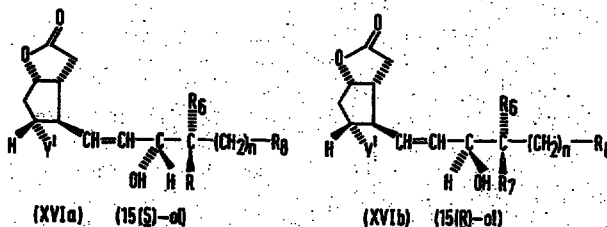


wherein

Y' , R_6 , R_7 , R_8 and n are as defined above, which may be prepared substantially as described by E. J. Corey et al., *Annals of New York Acad. of Sciences*, 180, 24 (1971).

This multi-step process involves the following steps:

a') reduction of the lactone of formula (XV) to give a mixture of the 15(S)- and 15(R)-ols of formulae (XVIa) and (XVIb).

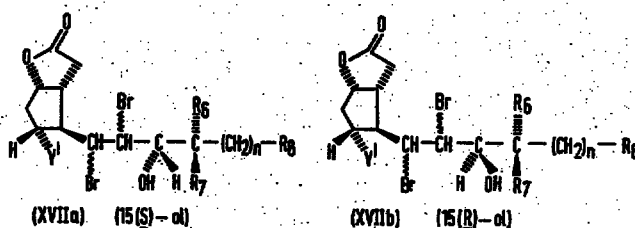


wherein

Y' , R_6 , R_7 , R_8 and n are as defined above.

The reduction may be performed in an organic solvent, such as acetone, diethyl ether and 1,2-dimethoxyethane, by using, for example, sodium borohydride, zinc borohydride, and lithium borohydride.

b') halogenation of the mixture of the two 15(R)- and 15(S)-ols to give a mixture of 13,14-dibromoalcohols of formulae (XVIIa) and (XVIIb)

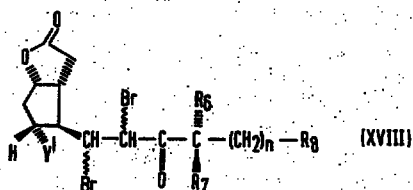


wherein

Y' , R_6 , R_7 , R_8 and n are as defined above.

The halogenation is carried out in a inert solvent, preferably selected from a halogenated solvent, e.g. dichloromethane, dichloroethane, CCl_4 and a linear or cyclic ether, e.g. tetrahydrofuran, dioxane, 1,2-dimethoxyethane or their mixtures, using the molar equivalent of halogenating agent or an excess of the same agent, which may be, e.g. Br_2 , dioxane dibromide, 2-pyrrolidone hydrotribromide.

c') oxidation of the mixture of the 13,14-dibromoalcohols to give a 13,14-dibromo-15-oxo-derivative of formula (XVIII)



wherein

Y' , R_6 , R_7 , R_8 and n are as defined above.

The oxidation is carried out at a temperature ranging between -25° and the room temperature, by using a dichloromethane solution of the pyridine-chromic anhydride complex or a sulphuric solution of chromic anhydride in acetone (Jones reagent), or a carbodiimide, working in dimethyl sulphoxide in presence of a suitable acid.

d') dehydrohalogenation of the 13,14-dibromo-15-oxo-derivative to give the halo-lactone of formula (V) wherein X is bromine.

The dehydrohalogenation may be performed by using an organic base, for example a *tert.*amine in an inert solvent, or alternatively by using an inorganic base, for example potassium acetate in a solvent such as methanol or ethanol.

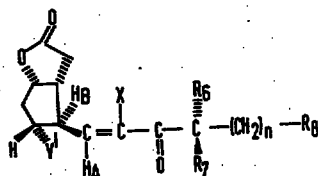
A further alternative process for the preparation of the halo lactone of formula (V) wherein X is bromine is the reaction of the lactone of formula (XV), in an ethereal anhydrous solvent such as tetrahydrofuran and 1,2-dimethoxyethane with a halogenating agent such as phenyltrimethylammonium tribromide and in particular 2-pyrrolidone-hydrotribromide (1.1—1.3 molar equivalents) to give directly the 13,14-dibromo-15-oxo-derivative of formula (XVIII) which is then dehydrohalogenated as above described, to give the halo-lactone of formula (V), wherein X is bromine.

Also in the alternative methods for the preparation of the halo-lactone of formula (V), all the compounds may be either optically active compounds or racemic mixtures thereof.

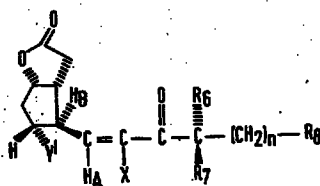
In the preparation of the halo-lactone of formula (V) according to the here-above described methods, both compounds wherein the hydrogen atom linked to the carbon atom in the 13-position and the halogen atom linked to the carbon atom in the 14-position (prostaglandin numbering) are in the *trans*-position (geometric *trans*-isomers) and compounds wherein said atoms are in the *cis*-position (geometric *cis*-isomers) are obtained.

The geometric *trans*-isomers are obtained in a far higher percentage (92—95%), while the geometric *cis*-isomers are obtained in a far lower percentage (5—8%).

The geometric *trans*-isomers of formula



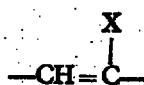
can be easily distinguished from the geometric *cis*-isomers of formula



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

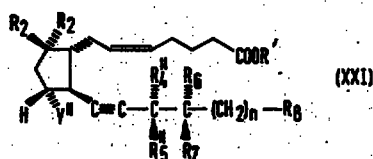
Anyway, both the *trans*-isomers and the *cis*-isomers are intermediates for the synthesis of the 13,14-didehydroprostaglandins of the invention.

The lactol of formula (II) wherein B is $-O\equiv C-$ may be also prepared by dehydrohalogenation of the lactol of formula (II) wherein B is



wherein X is bromine, chlorine or iodine. The dehydrohalogenation may be carried out in an aprotic solvent preferably selected from dimethyl sulphoxide, dimethylformamide and hexamethylphosphoramide by treatment with a base preferably selected from potassium *tert.*butoxide, an alkali metal amide and an alkali metal methylsulphinylmethide.

Optically active or racemic compounds of formula (XXI)



wherein

R' is hydrogen or C₁—C₁₂ alkyl, Y'', R'', R'', R₆, R₇, R₈ and n are as defined above, R₂ is hydrogen and R₃ is hydroxy or a carboxylic acyloxy or R₂ and R₃ together form an oxo group, are also compounds of the invention.

The compounds of formula (I) may be used for the same therapeutical indications as natural prostaglandins, and have the advantages of superior resistance to degradation by the enzyme 15-prostaglandin dehydrogenase, which quickly inactivates natural prostaglandins, and, of a more selective therapeutical action, as indicated below.

The compounds of formula (I) furthermore inhibit the degradation of natural prostaglandins by the aforesaid enzyme.

Using the 15-hydroxyprostaglandin dehydrogenase drawn from human placenta, *in vitro* tests carried out with for example 13,14-didehydro-17-cyclohexyl-18,19,20-trinor-PGF_{2a} (9 α ,11 α ,15(S)-trihydroxy-18,19,20-trinor-17-cyclohexylprost-*cis*-5-en-13-ynoic acid), showed that, while the inhibition with respect to PGE₂ is of a non-competitive kind (K_i=468 μ M), the inhibition becomes partially competitive with respect to PGF_{2a} (K_i=152 μ M).

The same compound (13,14-didehydro-17-cyclohexyl-18,19,20-trinor-PGF_{2a}) was compared with PGF_{2a} and with the olefinic analogue 9 α ,11 α ,15(S)-trihydroxy-18,19,20-trinor-17-cyclohexylprosta-*cis*-5,*trans*-13-dienoic acid (17-cyclohexyl-18,19,20-trinor-PGF_{2a}) in the following *in vitro* tests: guinea pig ileum test, rat uterus test, rat stomach fundus. The results are reported in the following Table, wherein to the activity of PGF_{2a} the conventional value of 1 was given in all the tests. The three tests relate to the determination of the spasmogenic activity.

Compound	Guinea Pig Ileum	Rat Uterus	Rat Stomach Fundus
PGF _{2a}	1	1	1
17-cyclohexyl-18,19,20-trinor-PGF _{2a}	0.60	3.23	1.86
13,14-didehydro-17-cyclohexyl-18,19,20-trinor-PGF _{2a}	0.17	15.7	1.96

The guinea pig ileum test consisted of a 10 ml thermostatic bath held at 35°C, containing the ileum of a male guinea pig, under 0.5 g traction, gassed with a mixture of O₂ and CO₂ in a Tyrode solution; this was left for 30 minutes to stabilize before the compounds were tested. The response was recorded using a isotonic frontal lever, long enough to amplify the response 4.5 times.

The rat uterus test consisted of a 10 ml thermostatic bath held at 29°C, in which oestrogenized rat uteri under 0.5 g traction were gassed with a mixture of O₂ and CO₂ in a Dejalon saline solution. The preparation was left to stabilize for 30 minutes before the compounds were tested. Response was measured using a isotonic frontal lever, long enough to amplify the response 4.5 times.

The rat stomach fundus test was performed in the following manner: male albino rats of the Sprague-Dawley strain weighing 200—250 g were utilized. The stomach fundus strip was prepared according to Vane (J. R. Vane, Brit. J. Pharmacol, 12, 344, (1957)). The strip was suspended in a 10 ml organ bath containing Tyrode solution gassed with a mixture of O₂ and CO₂ (95:5% v/v). The contractions of the strip were recorded using an isotonic frontal lever as in the preceding tests.

From the comparison of the activities in the three *in vitro* tests, it is evident that, independently from the species of animals used, a remarkable increase in activity was obtained selectively on the miometrium (the muscular part of the uterus), together with reduced activity on the muscle of the gastroenteric apparatus, indicating a reduction of the gastrointestinal side-effects which are always present when natural prostaglandins are administered. A comparison of the ratio of these test results on the uterus/ileum and uterus/stomach fundus shows that the reduction in side effects at a given therapeutic level is greater when the 13,14-didehydro analogues are employed:

Compound	Uterus/Ileum	Uterus/Stomach Fundus
PGF _{2α}	1	1
17-cyclohexyl-18,19,20-trinor-PGF _{2α}	5.4	1.7
13,14-didehydro-17-cyclohexyl-18,19,20-trinor-PGF _{2α}	91	8

The outstanding action of the 13,14-didehydro compounds on the miometrium and on the reproductive apparatus is also proven by measurement of the remarkable increase in luteolytic activity in the pregnant rat at the 9th—10th day of pregnancy. In fact, if the conventional value of 1 is given to the luteolytic activity of PGF_{2α}, the value of 30 would apply to the luteolytic activity of 17-cyclohexyl-18,19,20-trinor-PGF_{2α}, and the value of 200 to the luteolytic activity of 13,14-didehydro-17-cyclohexyl-18,19,20-trinor-PGF_{2α}.

Besides, the compounds of formula (I), e.g. 13,14-didehydro-17-cyclohexyl-18,19,20-trinor-PGF_{2α}, when tested against PGF_{2α} on the rat uterus, are able to antagonize PGF_{2α} specifically and selectively.

The 9-oxo-derivatives (PGE analogues) of formula (I), when compared with PGE₂ according to the method described by H. Shay et al., Gastroenter., 26, 906 (1954) are 2 to 4 times more active as gastric antisecretory agents than PGE₂, and the antisecretory activity is doubled when a single 16-alkyl group, particularly a methyl, is present in the 16(S) configuration, and quadrupled when it is in the 16(R) configuration.

The compounds of formula (I) can be administered orally, parenterally, or by intravenous or intrauterine (extra-amniotic or intra-amniotic), by rectal suppositories or by inhalation. For example, they can be administered by intravenous infusion of a sterile isotonic saline solution at the rate of 0.01 to 10, preferably 0.05 to 1, μg/kg of mammal body weight per minute.

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

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

The invention also provides a method of treating a non-human warm-blooded animal by administering a compound of general formula (I).

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

The invention is illustrated by the following Examples 1 to 21, wherein the abbreviations "THP", "DIOX", "DMSO", "THF", "DMF", "DIBA", and "Et₂O" refer to tetrahydropyranyl, dioxanyl, dimethylsulphoxide, tetrahydrofuran, dimethylformamide, diisobutylaluminium hydride and diethyl ether, respectively. Examples 22 to 50 illustrate for reference purposes the preparation of intermediates for use in making compounds according to the invention. All temperatures are expressed in degrees Centigrade, and optical rotations are measured at 20°C on 1% by weight solutions of the specified compounds in the specified solvents.

Example 1.

Under a nitrogen atmosphere, a suspension of 80% NaH (dispersion in mineral oil) (0.48 g) in dry DMSO (12 ml) was heated with stirring at 60° until no more hydrogen evolved (about 3 hours). The stirred mixture of sodium methylsulphinylmethide, $\text{CH}_3\text{SOCH}_2^{(-)}\text{Na}^{(+)}$, was cooled at 5—8° (and treated with crystalline triphenyl-(4-carboxybutyl)-phosphonium bromide (3.42 g) and the stirring was continued until this compound was completely dissolved. The deep orange-red solution of the ylide:



was then treated with a solution of 2 - [5 β - (2' - bromo - 3' - (S) - hydroxy - 5' - cyclohexylpent - trans - 1' - enyl) - 2 $\alpha,4\alpha$ - dihydroxycyclopent - 1 α - yl]acetaldehyde γ - hemiacetal - 3',4' - bis - THP ether (0.6 g) in dry DMSO (8 ml). After stirring overnight, under nitrogen atmosphere at room temperature, the reaction mixture was diluted with water (20 ml) and the alkaline phase was repeatedly extracted with diethyl ether to remove the triphenylphosphoxide; the ethereal extracts were combined, back-washed with 0.5N NaOH and then discarded. The alkaline washes were combined with the original alkaline phase, acidified to pH 4.8 and extracted several times with ethyl ether-pentane 1:1 by volume. The combined organic extracts were washed with saturated $(\text{NH}_4)_2\text{SO}_4$ solution, dried on Na_2SO_4 and evaporated to dryness, yielding 0.55 g of 9 $\alpha,11\alpha,15$ (S) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - cis - 5 - en - 13 - ynoic acid 11,15 - bis - THP ether (18,19,20 - trinor - 17 - cyclohexyl - 13,14 - didehydro - PGF $_{2a}$ 11,15 - bis - THP ether), an oil with $[\alpha]_D = -7.8^\circ$. Under the same conditions, starting with the 15-epimeric lactol: 2 - [5 β - (2' - bromo - 3(R) - hydroxy - 5' - cyclohexylpent - trans - 1' - enyl) - 2 $\alpha,4\alpha$ - dihydroxycyclopent - 1 α - yl]acetaldehyde - γ - hemiacetal - 3',4' - bis - THP ether, the product obtained was 9 $\alpha,11\alpha,15$ (R) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - cis - 5 - en - 13 - ynoic acid 11,15 - bis - THP ether (18,19,20 - trinor - 17 - cyclohexyl - 13,14 - didehydro - 15 - epi - PGF $_{2a}$ bis - THP - ether).

Individually, 250 mg of each of the two compounds was dissolved in 12 ml of acetone and refluxed with 0.2N oxalic acid (10 ml) three hours.

The acetone was evaporated off and the aqueous phases were extracted with ethyl acetate. The organic extracts for each product were combined, dried on Na_2SO_4 and the ethyl acetate removed under vacuum.

The resulting crude products were chromatographed on acid-washed silica gel (12 g) eluted with methylene chloride containing 15% by volume ethyl acetate and then 20% by volume ethyl acetate, to yield respectively 151 mg of 9 $\alpha,11\alpha,15$ (S) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - cis - 5 - en - 13 - ynoic acid (18,19,20 - trinor - 17 - cyclohexyl - 13,14 - didehydro - PGF $_{2a}$), $[\alpha]_D = +24^\circ$, $[\alpha]_{589} = +78^\circ$ (EtOH), and 142 mg of 9 $\alpha,11\alpha,15$ (R) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - cis - 5 - en - 13 - ynoic acid (18,19,20 - trinor - 17 - cyclohexyl - 13,14 - didehydro - 15 - epi - PGF $_{2a}$), $[\alpha]_D = +17.8^\circ$ (EtOH).

Example 2.

Working in a dry box and under nitrogen atmosphere, at 5—10°, a solution of triphenyl-(4-carboxybutyl)-phosphonium bromide (2.66 g) in 5 ml of dry DMSO, was added with stirring to a suspension in DMSO of the sodium methylsulphinylmethide $\text{CH}_3\text{SOCH}_2^{(-)}\text{Na}^{(+)}$, obtained by heating at 60° for 3 hours a suspension of 0.365 g of 80% NaH in 10 ml of dry DMSO. To the dark red solution of the ylide was then added 5 ml of a DMSO solution of 425 mg of 2 - [5 β - (2' - chloro - 3'(S) - hydroxy - 4'(S,R) - methyl - 5' - cyclohexylpent - trans - 1' - enyl) - 2 $\alpha,4\alpha$ - dihydroxycyclopent - 1 α - yl]acetaldehyde γ 1 hemiacetal 3',4' - bis - DIOX ether. The reaction mixture was stirred for 12 hours at room temperature. After dilution with water it was extracted with diethyl ether to remove the triphenylphosphoxide. The ethereal extracts were back-washed with dilute alkali (0.5N NaOH) and then discarded. The combined aqueous alkaline fractions were acidified to pH 4.8 with 2N sulfuric acid and extracted with a 1:1 by volume mixture of pentane:diethyl ether.

These extracts were washed until neutral and the solvent evaporated to yield 0.428 g of 9 $\alpha,11\alpha,15$ (S) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(S,R) - methylprost - cis - 5 - en - 13 - ynoic acid 11,15 - bis - DIOX ether. 0.128 g of this product were deetherified by the method described in Example 1, yielding, after chromatography on acid-washed silica gel eluted with CH_2Cl_2 -ethyl acetate 70:30 v/v, 62 mg of 9 $\alpha,11\alpha,15$ (S) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(S,R) -

methylprost - *cis* - 5 - en - 13 - ynoic acid, or 18,19,20 - trinor - 17 - cyclohexyl-16(*S,R*) - methyl - 13,14 - didehydro - PGF_{2α}, $[\alpha]_D = +13^\circ$ (EtOH).

Example 3.

Under inert gas atmosphere, to a solution of cooled (about 12–14°C) triphenyl-(4-carboxybutyl)-phosphonium bromide (3.1 g) in DMSO was added a solution of potassium *tert.*-butoxide (1.58 g). The stirring was continued until a strongly colored solution of the ylide was obtained, then 0.573 g of 2 - [5β - (2' - bromo - 3'(*S*)-hydroxy - 4'(*S*) - methyl - 5' - cyclohexylpent - *trans* - 1' - enyl) - 2α,4α - dihydroxycyclopent - 1α - yl]acetaldehyde γ - hemiacetal 3'(*S*), 4 - bis - THP ether, dissolved in a minimum quantity of dry DMSO, was added. The reaction mixture was stirred for 3 hours at room temperature, then placed in an ice bath and diluted with an equal volume of water. The alkaline aqueous phase was extracted with diethyl ether to remove the (C₆H₅)₃P=O. The ethereal extracts were back-washed with N NaOH and then discarded.

The aqueous alkaline phases were combined, acidified to pH 5 and extracted with diethyl ether-pentane 1:1 by vol, to give 0.52 g of 9α,11α,15(*S*) - trihydroxy - 18,19,20-trinor - 17 - cyclohexyl - 16(*S*) - methylprost - *cis* - 5 - en - 13 - ynoic acid 11,15-bis-THP ether.

A solution of 0.25 g of this compound in 6 ml of tetrahydrofuran was refluxed for 3 hours with 5 ml of 0.2N oxalic acid. The THF was removed under vacuum and the residue extracted with ethyl acetate. The combined ethyl acetate extracts were washed until neutral with a saturated (NH₄)₂SO₄ solution, dried and the solvent removed by evaporation. The residue was chromatographed on silicic acid gel (9 g) eluted with CH₂Cl₂ and with CH₂Cl₂-ethyl acetate 75:25 v/v, giving 120 mg of 9α,11α,15S-trihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16S - methylprost - *cis* - 5 - en - 13-ynoic acid [18,19,20 - trinor - 1(*S*) - methyl - 17 - cyclohexyl - 13,14 - didehydro-PGF_{2α}], $[\alpha]_D = +14^\circ$ (EtOH).

Example 4.

Using one of the procedures described in Examples 2 and 3, by reacting a DMSO solution of the ylide of triphenyl-(4-carboxybutyl)-phosphonium bromide (6 moles) with one mole of a 3',4-bis-DIOX or THP ethers of a γ-hemiacetal chosen from

2 - [5β - (2' - bromo - 3'(*S*) - hydroxy - 3'(*R*) - methyl - 5' - cyclohexylpent-*trans* - 1' - enyl) -

2 - [5β - (2' - bromo - 3'(*R*) - hydroxy - 4'(*S*) - methyl - 5' - cyclohexylpent-*trans* - 1' - enyl) - and

2 - [5β - (2' - bromo - 3'(*R*) - hydroxy - 4'(*R*) - methyl - 5' - cyclohexylpent-*trans* - 1' - enyl) - 2α,4α-dihydroxycyclopent - 1α - yl]acetaldehyde γ-hemiacetal, the 11,15-bis-DIOX ethers and 11,15-bis-THP ethers) of the corresponding prost-*cis*-5-en-13-ynoic acids are obtained, which are then deetherified to give, respectively:

9α,11α,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(*R*) - methylprost - *cis* - 5 - en - 13 - ynoic acid, $[\alpha]_D = +16^\circ$ (CHCl₃);

9α,11α,15(*R*) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(*S*) - methylprost - *cis* - 5 - en - 13 - ynoic acid, $[\alpha]_D = +12^\circ$ (CHCl₃);

9α,11α,15(*R*) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(*R*) - methylprost - *cis* - 5 - en - 13 - ynoic acid, $[\alpha]_D = +11^\circ$ (CHCl₃).

Example 5.

To a stirred solution of the ylide obtained by treatment of a solution of triphenyl-(4-carboxybutyl)-phosphonium bromide (2.4 g) in dry DMSO (8 ml) with 1.23 g of potassium *tert.*-butoxide, cooled to 5–8°, under inert gas, 0.42 g of 2 - [5β - (2' - bromo - 3'(*S*) - hydroxy - 5' - (2'' - norbornyl) - pent - *trans* - 1' - enyl) - 2α,4α-dihydroxycyclopent - 1α - yl]acetaldehyde γ - hemiacetal - 3',4 - bis - DIOX ether were added.

After stirring for 8 hours at room temperature, the mixture was diluted with water (13 ml) and after extraction of the alkaline solution with diethyl ether to remove the triphenylphosphoxide, back-washing of the ethereal extracts with 0.5N NaOH, and discarding of the ethereal phase, the combined aqueous phases were acidified to pH 4.6. The following extraction with diethyl ether-pentane 1:1 v/v yielded 0.39 g of 9α,11α,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - (2' - norbornyl) - prost - *cis* - 5-en - 13 - ynoic acid 11,15(*S*) - bis - DIOX ether. One hundred mg of this compound were deetherified in acetone-0.2N oxalic acid, to give 48 mg of 18,19,20 - trinor - 17 - (2' - norbornyl) - 13,14 - didehydro - PGF_{2α}.

Example 6.

In dry conditions under inert atmosphere a suspension of 0.48 g of 80% sodium hydride in 12 ml of DMSO was heated for 3 hours at 60°C, until all the hydrogen had evolved, giving a solution of $\text{CH}_3\text{SOCH}_2\text{Na}^{(+)}$ in DMSO. This was cooled to 0–5° and 3.5 g of triphenyl-(4-carboxybutyl)-phosphonium bromide were added and stirred until a deep red solution of the ylide was obtained. To this was then added 0.37 g of 2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-(2''-tetrahydrofuryl)-pent-trans-1'-enyl)-2 α ,4 α -dihydroxycyclopent-1 α -yl]acetaldehyde γ -hemiacetal dissolved in 4 ml of dry DMSO. This was stirred for 4 hours at room temperature, then diluted with water. It was extracted repeatedly with diethyl ether to remove the triphenylphosphoxide. The combined ethereal extracts were back-washed with alkali and then discarded. The aqueous alkaline phases were combined, acidified to pH 4.6 with sulfuric acid and extracted with ethyl acetate-pentane 1:1 v/v. These organic extracts were combined, washed until neutral with ammonium sulfate, dried and evaporated to dryness.

The residue was chromatographed on silicic acid gel (15 g), eluted with methylene chloride-ethyl acetate, to give 0.26 g of 9 α ,11 α ,15(S)-trihydroxy-18,19,20-trinor-17-(2'-tetrahydrofuryl)-prost-cis-5-en-13-ynoic acid 18,19,20-trinor-17-(2'-tetrahydrofuryl)-13,14-didehydro-PGF_{2a}.

Using the same procedure, but replacing the hemiacetal derivative with 2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-(2''-tetrahydrothienyl)-pent-trans-1'-enyl)-2 α ,4 α -dihydroxycyclopent-1 α -yl]acetaldehyde γ -hemiacetal, gave the 18,19,20-trinor-17-(2'-tetrahydrothienyl)-13,14-didehydro-PGF_{2a}.

Example 7.

Using the procedure described in Example 1, 0.3 g of NaH (80% dispersion in mineral oil) in 9 ml of DMSO was reacted to give sodium methylsulphinyldimethylphosphine oxide $\text{CH}_3\text{SOCH}_2\text{Na}^{(+)}$, and then treated with 2.2 g of triphenyl-(4-carboxybutyl)-phosphonium bromide to give the ylide.

The solution of the ylide was cooled to 10–12°, and under argon, 520 mg of 2-[5 β -(2'-bromo-3'(S)-hydroxy-5-(2'-bicyclo[2,2,2]octyl)-pent-trans-1'-enyl)-2 α ,4 α -dihydroxycyclopent-1 α -yl]acetaldehyde γ -hemiacetal 3',4-bis-DIOX ether were added. This was stirred for 2 hours and then diluted with 15 ml of water. It was extracted with benzene-diethyl ether 7:3 (by vol) to remove the triphenylphosphoxide. The organic extracts were back-washed with 0.6N NaOH and discarded. The alkaline aqueous phases were combined and acidified to pH 4.6 and then extracted with diether:pentane 1:1 (by vol). The combined organic extracts were washed until neutral with a saturated solution of ammonium sulfate, dried and evaporated to dryness. 0.48 g of 9 α ,11 α ,15(S)-trihydroxy-18,19,20-trinor-17-(2'-bicyclo[2,2,2]octyl)-prost-cis-5-en-13-ynoic acid 11,15-bis-DIOX ether was obtained.

0.25 g of this compound were refluxed with 10 ml of acetone and 8 ml of 0.2N citric acid. The acetone was removed *in vacuo* and the residue extracted with ethyl acetate. The combined ethyl acetate extracts were washed until neutral, dried on Na_2SO_4 and evaporated to dryness. The residue was chromatographed on silicic acid gel and eluted with cyclohexane-ethyl acetate to give 0.11 g of 18,19,20-trinor-17-(2'-bicyclo[2,2,2]octyl)-13,14-didehydro-PGF_{2a}.

In a similar way, starting with one of the 3',4-bis-DIOX or THP ethers of the γ -hemiacetals listed below:

2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-cycloheptylpent-trans-1'-enyl)-2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-(1'-adamantyl)-pent-trans-1'-enyl)-

2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-(4''-tert-butylcyclohexyl)-pent-trans-1'-enyl)-

2-[5 β -(2'-bromo-3'(S)-hydroxy-6'-cyclohexylhex-trans-1'-enyl)-

2-[5 β -(2'-bromo-3'(S)-hydroxy-4'-cyclohexylbut-trans-1'-enyl)-

2-[5 β -(2'-bromo-3'(S)-hydroxy-4'-cyclopentylbut-trans-1'-enyl)-

2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-cyclopropylpent-trans-1'-enyl)-

2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-cyclopentylpent-trans-1'-enyl)-

2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(R)-methyl-5'-cyclopentylpent-trans-1'-enyl)- and

2-[5 β -(2'-bromo-3'(S)-hydroxy-4'-(1''-adamantyl)-but-trans-1'-enyl)-2 α ,4 α -dihydroxycyclopent-1 α -yl]acetaldehyde γ -hemiacetal,

the 11,15-bis-DIOX ethers and 11,15-bis-THP ethers) of the corresponding prost-13-ynoic acids were obtained, which were then deetherified to give the following free acids:

- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - cycloheptylprost - *cis* - 5-en - 13 - ynoic acid, $[\alpha]_D = +22^\circ$ (EtOH);
- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - (1' - adamantyl) - prost-*cis* - 5 - en - 13 - ynoic acid;
- 5 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - [(4' - *tert* - butyl) - cyclohexyl] - prost - *cis* - 5 - en - 13 - ynoic acid;
- 9 α ,11 α ,15(*S*) - trihydroxy - 19,20 - dinor - 18 - cyclohexylprost - 5 - *cis* - en - 13 - ynoic acid, $[\alpha]_D = +18^\circ$; $[\alpha]_{30,0^\circ} = +44^\circ$ (EtOH);
- 10 9 α ,11 α ,15(*S*) - trihydroxy - 17,18,19,20 - tetranor - 16 - cyclohexylprost - *cis* - 5 - en - 13 - ynoic acid $[\alpha]_D = +18^\circ$; $[\alpha]_{30,0^\circ} = +88^\circ$ (EtOH);
- 9 α ,11 α ,15(*S*) - trihydroxy - 17,18,19,20 - tetranor - 16 - cyclopentylprost - *cis* - 5 - en - 13 - ynoic acid $[\alpha]_D = +19^\circ$ (EtOH);
- 15 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - cyclopropylprost - *cis* - 5 - en - 13 - ynoic acid, $[\alpha]_D = +21^\circ$ (EtOH);
- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - cyclopentylprost - *cis* - 5 - en - 13 - ynoic acid, $[\alpha]_D = +20^\circ$ (EtOH);
- 15 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - cyclopentyl - 16(*R*) - methylprost - *cis* - 5 - en - 13 - ynoic acid;
- 20 9 α ,11 α ,15(*S*) - trihydroxy - 17,18,19,20 - tetranor - 16 - (1' - adamantyl) - prost-*cis* - en - 13 - ynoic acid.

Example 8.

A solution of 0.395 g of 2 - [5 β - (2' - chloro - 3'(*S*) - hydroxy - 4'(*S*) - methyl - 5' - cyclopentylpent - *trans* - 1' - enyl) - 2 α ,4 α - dihydroxycyclopent - 1 α - yl]acetaldehyde γ - hemiacetal 3',4 - bis - THP ether in 4 ml of DMSO was reacted with a solution of the ylide obtained by the procedure outlined in Example 1, starting with 0.34 g of NaH (80% dispersion in mineral oil), 9 ml of DMSO and 2.4 g of triphenyl-(4-carboxybutyl)-phosphonium bromide. The reaction mixture was allowed to stand for 8 hours at room temperature and for 2 hours at 38°C.

It was then cooled and diluted with 13 ml of water, and extracted with benzene-diethyl ether 70:30 (by vol) to remove the triphenylphosphoxide. The organic extract was back-washed with 0.8N NaOH and discarded. The aqueous alkaline fractions were combined, acidified to pH 4.6 and extracted with diethyl ether-pentane to give 0.34 g of 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - cyclopentyl - 16(*S*) - methylprost - *cis* - 5 - en - 13 - ynoic acid 11,15 - bis - THP ether.

When 0.17 g of this compound were deacetalated in THF-0.2N oxalic acid, 98 mg of 18,19,20 - trinor - 17 - cyclopentyl - 16(*S*) - methyl - 13,14 - didehydro-PGF_{2 α} , $[\alpha]_D = +16^\circ$ (EtOH), were obtained.

Example 9.

A solution of 0.34 g of 2 - [5 β - (2' - bromo - 3'(*S*) - hydroxy - 5' - cyclohexylpent - *trans* - 1' - enyl) - 2 α ,4 α - dihydroxycyclopent - 1 α - yl]acetaldehyde γ - hemiacetal in 5 ml of trimethyl orthoformate and 25 ml of benzene was heated with 1.9 g of *p*-toluenesulfonic acid for 2 hours at 40°C. Then 30 mg of anhydrous potassium carbonate were added and stirred for 10 minutes, after which the material was transferred to a separating funnel, washed with 8% by wt. NaHCO₃ and with water until neutral, dried and evaporated to dryness.

The residue of 4 β - (2' - bromo - 3'(*S*) - hydroxy - 5' - cyclohexylpent - *trans* - 1' - enyl) - 5 α - hydroxy - 2 ξ - methoxy - 3,3 ϵ ,4,5,6,6 ϵ - hexahydro - 2H - cyclopenta[b]furan was thoroughly dried and dissolved in 3 ml of DMSO. This solution was added to a solution of 150 mg of potassium *tert*-butoxide in DMSO. After 3 hours at room temperature, it was diluted with water and extracted with diethyl ether to obtain 0.24 g of 4 β - (3'(*S*) - hydroxy - 5 - cyclohexylpent - 1' - ynyl) - 5 α - hydroxy - 2 ξ - methoxy - 3,3 ϵ ,4,5,6,6 ϵ - hexahydro - 2H - cyclopenta - [b]furan which was deetherified with acetone and 0.2N oxalic acid (10 ml—8 ml for 2 hours, reflux) to give 0.24 g of 2 - [5 β - (3'(*S*) - hydroxy - 5 - cyclohexylpent - 1' - ynyl) - 2 α ,4 α - dihydroxy - cyclopent - 1 α - yl]acetaldehyde γ - hemiacetal.

A solution of this compound in DMSO was combined with a solution of the ylide of triphenyl-(4-carboxybutyl)-phosphonium bromide prepared from NaH (80% dispersion in mineral oil, 150 mg), 5 ml of DMSO and 1.1 g of triphenyl-(4-carboxybutyl)-phosphonium bromide.

The reaction mixture was stirred for 45 minutes, then diluted with water. The triphenylphosphoxide was extracted with diethyl ether which was back-washed with 0.8N NaOH. The combined alkaline phases were acidified with 2N sulfuric acid to pH 4.8 and extracted with ethyl acetate-pentane 1:1 by vol.

After percolation through an acid silica gel column, 0.21 g were obtained of 18,19,20 - trinor - 17 - cyclohexyl - 13,14 - didehydro - PGF_{2a}, $[\alpha]_D = +23.9^\circ$, $[\alpha]_{365} = +78.1^\circ$ (EtOH).

Example 10.

0.53 g of 2 - [5 β - (2' - chloro - 3'(S) - hydroxy - 5' - cyclopentylpent - trans - 1' - enyl) - 2 α ,4 α - dihydroxycyclopent - 1 α - yl]acetaldehyde γ - hemiacetal 3',4-bis - DIOX ether in 8 ml of acetone and 8 ml of 0.2N oxalic acid was refluxed for 1 hour and 30 minutes. After evaporation of the acetone *in vacuo* and extraction with ethyl acetate, 0.36 g were obtained of 2 - [5 β - (2' - chloro - 3'(S) - hydroxy - 5' - cyclopentylpent - trans - 1' - enyl) - 2 α ,4 α - dihydroxycyclopent - 1 α - yl] - acetaldehyde γ - hemiacetal.

By treatment with 3 mg of *p*-toluenesulfonic acid in benzene 3 ml of methyl orthoformate, under the conditions outlined in Example 10, 0.34 g of the hexahydrocyclopenta[b]furan-2-ol methyl ether were obtained.

Under nitrogen, a solution of 90 mg of 80% NaH in mineral oil in 4 ml of DMSO was heated at 60°C for 3 hours, until all the hydrogen had evolved. To the cooled solution of the sodium methylsulphiny methylide CH₃-SO-CH₂⁻Na⁺ obtained in this way was added a solution of the lactol-methyl ether in 1.5 ml of DMSO. This was left for 12 hours at room temperature then heated for 2 hours to 40°C, cooled and diluted with water. It was then extracted with ethyl ether.

The organic phases were washed until neutral, dried, and the solvent removed by evaporation, to give 0.29 g of 4 β - (3'(S) - hydroxy - 5' - cyclopentylpent - 1'-ynyl) - 5 α - hydroxy - 2 ξ - methoxy - 3,3c,8,4,5,6,6c β - hexahydro - 2H - cyclopenta[b]furan.

This compound was deetherified with THF 0.2N oxalic acid under reflux, yielding 0.24 g of the hexahydrocyclopenta[b]furan-2-ol which was then reacted with 2.5 molar equivalent of the ylide of triphenyl-(4-carboxybutyl)-phosphonium bromide in DMSO, to give, after chromatography on silicic acid gel, 0.21 g of 18,19,20-trinor-17-cyclopentyl-13,14-didehydro-PGF_{2a}, $[\alpha]_D = +20^\circ$ (EtOH).

Example 11.

1-bromopropane (125 mg) was added to a solution of 0.52 g of 18,19,20-trinor-17-cyclohexyl-13,14-didehydro-PGF_{2a} 11,15-bis-THP ether in 1.5 ml of hexamethylphosphorotriamide which previously had been stirred for 1 hour with 0.09 ml of 50% NaOH (w/v).

After additional stirring for 6 hours at room temperature the mixture was diluted with water (4 vol.), extracted with diethyl ether, which was washed with water until neutral and evaporated to yield 0.51 g of 18,19,20-trinorcyclohexyl-13,14-didehydro-PGF_{2a} 11,15-bis-THP ether propyl ester, $[\alpha]_D = -6^\circ$ (CHCl₃). By the same procedure, starting with one of the bis-ethers such as those in Examples 1-10, reaction with the appropriate alkyl halide or dialkyl sulfate, the corresponding esters were prepared.

Example 12.

A solution of an ester of a 9 α ,11 α ,15 ξ -trihydroxy-18,19,20-norprost-cis-5-en-13-ynoic acid 11,15-bis-ether obtained by the method of Example 11 [for example a solution of 18,19,20-trinor-17-cyclohexyl-13,14-didehydro-PGF_{2a} 11,15-bis-THP ether propyl ester (0.15 g) in acetone (10 ml)] was refluxed with 0.2N aqueous oxalic acid (8 ml) for 1 hour and 30 minutes. The acetone was removed *in vacuum* and the aqueous phase was repeatedly extracted with diethyl ether.

The combined organic layers were washed until neutral dried and evaporated to dryness affording the corresponding 9 α ,11 α ,15-trihydroxy-18,19,20-norprost-cis-5-en-13-ynoic acid alkyl esters, after chromatographic purification on silica gel, using methyl-ene chloride:ethyl acetate 80:20 (by vol.) as eluent.

In this way, for example, 18,19,20-trinor-17-cyclohexyl-13,14-didehydro-PGF_{2a} propyl ester ($[\alpha]_D = +19^\circ$ (CHCl₃), 95 mg) was prepared.

Example 13.

A solution of a 9 α ,11 α ,15 ξ - trihydroxy - 18,19,20 - norprost - cis - 5 - en - 13-ynoic acid 11,15-bis-ether (as, for example, 0.28 g of 18,19,20 - trinor - 17 - cyclohexyl - 13,14 - didehydro - PGF_{2a} 11,15 - bis - THP ether) in dry pyridine (1.8 ml) was treated with 145 mg of propionic anhydride overnight at room temperature. The reaction mixture was partitioned between ethyl ether and a 30% w/v aqueous solution of citric acid. The organic phases were combined, washed until neutral and

evaporated to dryness. The resulting 9-*o*-acyl 9 α ,11 α ,15 ξ -trihydroxy-18,19,20-norprost-*cis*-5-en-13-ynoic acid-11,15-bis-ether (for example 18,19,20-trinor-17-cyclohexyl 9-*o*-propionyl 13,14-didehydro-PGF_{2 α} 11,15-bis-THP ether) was then deetherified in acetone-0.2N oxalic acid, extracted with ethyl acetate and the reaction product chromatographed on silicic acid gel (10 g:g of acid) eluted with cyclohexane-diethyl ether, yielding the 9-*o*-acyl 9 α ,11 α ,15 ξ -trihydroxy-18,19,20-norprost-*cis*-5-en-13-ynoic acid [in the example, 185 mg of 18,19,20-trinor-17-cyclohexyl-9-*o*-propionyl-13,14-didehydro-PGF_{2 α} [α]_D = +1° (CHCl₃)].

Example 14.

A solution of 0.36 g of propyl 9 α ,11 α ,15(S)-trihydroxy-18,19,20-trinor-17-cyclohexylprost-*cis*-5-en-13-ynoate 11,15-bis-THP ether in 18 ml of acetone was cooled to -15° and then treated with 0.8 ml of Jones' reagent, added over 4 minutes. The reaction mixture was allowed to warm up to -10 to -8°C and kept for 20 minutes at that temperature. After dilution with benzene (108 ml) the organic phase was repeatedly washed with saturated (NH₄)₂SO₄ until neutral, dried and evaporated to dryness, yielding 0.35 g of propyl 9-oxo-11 α ,15(S)-dihydroxy-18,19,20-trinor-17-cyclohexylprost-*cis*-5-en-13-ynoate 11,15-bis-THP ether.

A solution of this crude product in acetone (15 ml) was deacetalated by treatment for 8 hours at 38-40°C, with an aqueous 0.2N solution of oxalic acid (16 ml).

After the removal of the acetone *in vacuo*, the aqueous phase was extracted with diethyl ether; the combined ethereal extracts were washed until neutral, dried and evaporated to dryness. The residue (0.34 g) was chromatographed on silica gel eluted with methylene chloride and with methylene chloride-ethyl acetate 80:20 v/v affording 0.21 g of 9-oxo-11 α ,15(S)-dihydroxy-18,19,20-trinor-17-cyclohexylprost-*cis*-5-en-13-ynoic acid propyl ester [18,19,20-trinor-17-cyclohexyl-13,14-didehydro-PGE₂ propyl ester, [α]_D = -45° (CHCl₃)].

Example 15.

A solution of 0.3 g of 9 α ,11 α ,15(S)-trihydroxy-18,19,20-trinor-17-cyclohexyl-16(S,R)-methylprost-*cis*-5-en-13-ynoic acid 11,15-bis-DIOX ether in 12 ml of acetone was cooled to -15°C and 0.6 ml of Jones' reagent were added dropwise. It was allowed to warm up to -10 to -8°C and kept there for 20 minutes, then diluted with 50 ml of benzene. The benzene was washed repeatedly with 30% ammonium sulfate until neutral, dried on sodium sulfate and evaporated to dryness, yielding 0.3 g of 9-oxo-11 α ,15(S)-dihydroxy-18,19,20-trinor-17-cyclohexyl-16(S,R)-methylprost-*cis*-5-en-13-ynoic acid 11,15-bis-DIOX ether. A solution of 0.15 g of this compound in 10 ml of tetrahydrofuran were treated with 12 ml of 0.2N oxalic acid for 7 hours at 38°C. The THF was removed by vacuum (water bath temperature under 40°) and the aqueous phase extracted with ethyl acetate. The combined organic extracts were washed until neutral, dried and evaporated to dryness. The residue was chromatographed on silicic acid gel eluted with CH₂Cl₂-ethyl acetate 80:20 v/v, to give 85 mg of 9-oxo-11 α ,15(S)-dihydroxy-18,19,20-trinor-17-cyclohexyl-16(S,R)-methylprost-*cis*-5-en-13-ynoic acid [18,19,20-trinor-17-cyclohexyl-16(R,S)-methyl-13,14-didehydro-PGE₂, [α]_D = -48° (EtOH)].

Example 16.

To a solution of 0.15 g of 9 α ,11 α ,15(S)-trihydroxy-18,19,20-trinor-17-cyclopentylprost-*cis*-5-en-13-ynoic acid 11,15-bis-THP ether (Example 8) in 6 ml of acetone, cooled to -12° was added, with stirring, 0.3 ml of Jones' reagent. After 15 minutes at -10° it was diluted with 30 ml of benzene. The organic phase was washed with saturated ammonium sulfate until neutral, dried over MgSO₄ and evaporated to dryness.

A solution of the resulting 9-oxo-11 α ,15(S)-dihydroxy-18,19,20-trinor-17-cyclopentylprost-*cis*-5-en-13-ynoic acid 11,15-bis-THP ether in acetone (8 ml) was deetherified by reaction at 38° with 0.2N oxalic acid (9 ml). The acetone was removed in a rotating vacuum evaporator and the aqueous phase was extracted with diethyl ether. The combined ethereal extracts were washed until neutral, dried on MgSO₄ and evaporated to dryness.

The residue (0.13 g) was chromatographed on 1.5 g of acid-washed silica gel, eluted with methylene chloride-ethyl acetate 80:20 v/v to give 56 mg of 18,19,20-trinor-17-cyclopentyl-13,11-didehydro-PGE₂, [α]_D = -41° (EtOH).

Example 17.

0.25 g of 9 α ,11 α ,15(R) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexyl-16(S) - methylprost - *cis* - 5 - en - 13 - ynoic acid 11,15 - bis - THP ether was oxidized in acetone with Jones' reagent to give the corresponding 9-oxo-derivative. This was deetherified with acetone-0.2N oxalic acid at 38°C and after chromatography on silicic acid gel, 0.11 g of 18,19,20 - trinor - 17 - cyclohexyl - 16(S) - methyl-15 - *epi* - 13,14 - didehydro - PGE₂, [α]_D = -41° (EtOH) was obtained.

Example 18.

Starting from one of the 11,15 - bis - DIOX ether and 11,15 - bis - THP ether of a 9 α ,11 α ,15(S) or a 9 α ,11 α ,15(R) - trihydroxyprost - *cis* - 5 - en - 13 - ynoic acid, either as the free acid or as one of the esters described in Examples 1 to 8 and 11, oxidation in acetone with Jones' reagent, by the procedures described in Examples 14 to 17, afforded the corresponding (free or esterified), 9-oxoprost-*cis*-5-en-13-ynoic acid, 11,15-bis-DIOX ether or 11,15-bis-THP ether, which were then deetherified as described in the procedure of preceding Examples, to give:

18,19,20 - trinor - 17 - cyclohexyl - 13,14 - didehydro - PGE₂, [α]_D = -51° (EtOH);

18,19,20 - trinor - 17 - cyclohexyl - 13,14 - didehydro - 15 - *epi* - PGE₂, [α]_D = -47° (EtOH);

18,19,20 - trinor - 17 - cyclohexyl - 16(S,R) - methyl - 13,14 - didehydro - PGE₂;

18,19,20 - trinor - 17 - cyclohexyl - 16(S) - methyl - 13,14 - didehydro - PGE₂;

18,19,20 - trinor - 17 - cyclohexyl - 16(R) - methyl - 13,14 - didehydro - PGE₂;

18,19,20 - trinor - 17 - cyclohexyl - 16(S) - methyl - 13,14 - didehydro - 15 - *epi*-PGE₂, [α]_D = -41° (EtOH);

18,19,20 - trinor - 17 - cyclohexyl - 16(R) - methyl - 13,14 - didehydro - 15 - *epi* - PGE₂;

18,19,20 - trinor - 17 - (2' - norbornyl) - 13,14 - didehydro - PGE₂;

18,19,20 - trinor - 17 - (2' - tetrahydrofuryl) - 13,14 - didehydro - PGE₂;

18,19,20 - trinor - 17 - (1' - adamantyl) - 13,14 - didehydro - PGE₂;

18,19,20 - trinor - 17 - (2' - bicyclo[2,2,2]octyl) - 13,14 - didehydro - PGE₂;

18,19,20 - trinor - 17 - cycloheptyl - 13,14 - didehydro - PGE₂;

18,19,20 - trinor - 17 - [(4' - *tert* - butyl) - cyclohexyl] - 13,14 - didehydro-PGE₂;

18,19,20 - trinor - 17 - cyclopropyl - 13,14 - didehydro - PGE₂;

18,19,20 - trinor - 17 - cyclopentyl - 13,14 - didehydro - PGE₂;

18,19,20 - trinor - 17 - cyclopentyl - 16(S) - methyl - 13,14 - didehydro - PGE₂;

18,19,20 - trinor - 17 - cyclopentyl - 16(R) - methyl - 13,14 - didehydro - PGE₂;

17,18,19,20 - tetranor - 16 - cyclohexyl - 13,14 - didehydro - PGE₂;

17,18,19,20 - tetranor - 16 - cyclopentyl - 13,14 - didehydro - PGE₂;

17,18,19,20 - tetranor - 16 - (1' - adamantyl) - 13,14 - didehydro - PGE₂;

19,20 - dinor - 18 - cyclohexyl - 13,14 - didehydro - PGE₂.

Example 19.

A solution of 0.3 g of methyl 9 - oxo - 11 α ,15(S) - dihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - *cis* - 5 - en - 13 - ynoate 11,15 - bis - THP ether in 40 ml of acetone and 50 ml of 0.2N aqueous oxalic acid was refluxed for 6 hours. The acetone was removed under vacuum and the aqueous phase extracted with diethyl ether. The combined ethereal extracts were washed until neutral, dried and the ether evaporated *in vacuo* to afford, after thin-layer chromatography (cyclohexane-diethyl ether), 0.12 g of 15(S) - hydroxy - 9 - oxo - 18,19,20 - trinor - 17 - cyclohexylprosta - *cis* - 5,10 - dien - 13 - ynoic acid methyl ester (18,19,20 - trinor - 17 - cyclohexyl - 13,14 - didehydro - PGA₂).

Example 20.

A solution of 11 α ,15S - dihydroxy - 9 - oxo - 18,19,20 - trinor - 17 - cyclopentyl - 16(S) - methylprost - *cis* - 5 - en - 13 - ynoic acid 11,15 - bis - THP ether (0.4 g) in 40 ml of acetone was treated with 40 ml of 0.25N oxalic acid for 6 hours under reflux. The acetone was removed *in vacuo* and the aqueous phase extracted repeatedly with diethyl ether. The combined ethereal extracts were washed with saturated ammonium sulfate solution and dried, yielding, after preparative thin-layer chromatography of the residue on silica gel plates (using benzene-ethyl acetate-acetic acid 130:24:6 v/v/v as eluent), 15(S) - hydroxy - 9 - oxo - 18,19,20 - trinor - 17 - cyclopentyl - 16(S) - methylprosta - *cis* - 5,10 - dien - 13 - ynoic acid.

Example 21.

Using the procedures described in Examples 19 and 20, the 9-oxo-prost-*cis*-5-en-13-ynoic acid 11,15-bis-ethers (both free acids and esters) of Example 18 were deetherified at reflux temperatures (65—70°) with acetone-0.25N aqueous oxalic acid to give the esters and the free acids of the following compounds:

- 18,19,20-trinor-17-cyclohexyl-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-cyclohexyl-13,14-didehydro-15-*epi*-PGA₂;
- 18,19,20-trinor-17-cyclohexyl-16(*S,R*)-methyl-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-cyclohexyl-16(*S*)-methyl-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-cyclohexyl-16(*R*)-methyl-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-cyclohexyl-16(*S*)-methyl-13,14-didehydro-15-*epi*-PGA₂;
- 18,19,20-trinor-17-cyclohexyl-16(*R*)-methyl-13,14-didehydro-15-*epi*-PGA₂;
- 18,19,20-trinor-17-(2'-norbornyl)-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-(2'-tetrahydrofuryl)-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-(1'-adamantyl)-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-(2'-bicyclo[2,2,2]octyl)-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-cycloheptyl-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-[(4'-*tert*-butyl)-cyclohexyl]-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-cyclopropyl-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-cyclopentyl-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-cyclopentyl-16(*S*)-methyl-13,14-didehydro-PGA₂;
- 18,19,20-trinor-17-cyclopentyl-16(*S*)-methyl-13,14-didehydro-PGA₂;
- 17,18,19,20-tetranor-16-cyclohexyl-13,14-didehydro-PGA₂;
- 17,18,19,20-tetranor-16-cyclopentyl-13,14-didehydro-PGA₂;
- 17,18,19,20-tetranor-16-(1'-adamantyl)-13,14-didehydro-PGA₂;
- 19,20-dinor-18-cyclohexyl-13,14-didehydro-PGA₂.

Preparation of intermediates

Example 22.

To a solution of 13.1 g of dimethyl[(2-oxo-4-cyclohexyl)butyl]phosphonate in 200 ml of tetrahydrofuran were added 27.28 g of 2-pyrrolidone hydrotribromide (PHT). The reaction mixture was left overnight with stirring. The precipitate which separated out was filtered off, the THF was evaporated under vacuum (bath temperature below 30°) and the residue taken up in diethyl ether, which was washed until neutral.

After drying and evaporation of the diethyl ether, the residue was chromatographed on silica gel, eluted with cyclohexane-diethyl ether to obtain 9.32 g of dimethyl[(1-bromo-2-oxo-4-cyclohexyl)-butyl]phosphonate.

Bromine: found 23.18, calculated 23.42.

Example 23.

A solution of 18.34 g of dimethyl[(2-oxo-4-cyclohexyl)-butyl]phosphonate was added dropwise to a stirred suspension of 2.1 g of sodium hydride (80% dispersion in mineral oil) in 60 ml of dry benzene with exclusion of moisture.

Stirring was continued until the evolution of hydrogen had ceased. Then 9.65 g of N-chlorosuccinimide was added and the mixture stirred for 1 hour.

The reaction mixture was washed with a solution of 5% (w/v) NaH₂PO₄, a solution of 7% (w/v) KI and 7% (w/v) sodium thiosulfate, and then with water until neutral. After drying and evaporating the solvent, the residue was purified by distillation, giving 11.2 g of dimethyl[(1-chloro-2-oxo-4-cyclohexyl)-butyl]phosphonate, b.p. 120—126° (1.2 mm Hg).

Example 24.

A solution of 10 g of dimethyl[(2-oxo-4-cyclopentyl)butyl]phosphonate in 10 ml of acetic acid was cooled in an ice and water bath and, with stirring, 2 drops of a solution of HBr in acetic acid were added and then, dropwise, a solution of 6.5 g of bromine in 3 ml of acetic acid, was added until a faint color persisted. The mixture was then diluted with 2 vol. of water and extracted with dichloromethane, and the extract was washed with saturated ammonium sulfate solution until neutral, dried and evaporated to dryness. The residue was purified by chromatography on a silica gel column,

giving 7.4 g of dimethyl[(1-bromo-2-oxo-4-cyclopentyl)-butyl]phosphonate. Bromine: found 24.32, calculated 24.30.

Example 25.

To a suspension of 30 mg of 80% NaH in 4 ml of benzene was added dropwise a solution of 297 mg of dimethyl[(1-chloro-2-oxo-4-cyclohexyl)-butyl]phosphonate in 4 ml of benzene and stirring continued until the evolution of hydrogen ceased. Then 184 mg of 2-(4-acetoxy 5 β -formyl-2 α -dihydroxycyclopent-1 α -yl)acetic acid γ -lactone in benzene was added. After stirring for 15 minutes, it was filtered and the filtrate washed with a 5% (w/v) solution of NaH₂PO₄ and water until neutral, dried and evaporated to dryness. The residue was chromatographed on silica gel, eluted with CH₂Cl₂-diethyl ether 95:5, yielding 240 mg of 2-[4 α -acetoxy-5 β -(2'-chloro-3'-oxo-5'-cyclohexylpent-1'-trans-enyl)-2 α -hydroxycyclopent-1 α -yl]acetic acid γ -lactone (λ max 242 m μ , ϵ =9,900).

Example 26.

To a stirred solution of 68 mg of sodium ethoxide in 10 ml of 1,2-dimethoxyethane, were added 340 mg of dimethyl[(1-bromo-2-oxo-4-cyclohexyl)-butyl]phosphonate, and stirring was continued until all the reagent had dissolved. Then a solution of 2-[4 α -acetoxy-5 β -formyl-2 α -hydroxycyclopent-1 α -yl]acetic acid γ -lactone (185 mg) in benzene was added.

After stirring for 30 minutes, it is diluted with a 5% w/v solution of NaH₂PO₄ in water.

The organic phase was washed until neutral and evaporated to dryness. The residue after purification on silica gel (CH₂Cl₂-diethyl ether 95:5 v/v) gave 282 mg of [4 α -acetoxy-5 β -(2'-bromo-3'-oxo-5'-cyclohexylpent-1'-trans-enyl)-2 α -hydroxycyclopent-1 α -yl]acetic acid γ -lactone (λ max 251 m μ , ϵ =11,700).

Example 27.

A stirred suspension of 15 mg of NaH (80% dispersion in mineral oil) in 1.5 ml of DMSO was heated to 60° until no more hydrogen evolved. The solution of sodium methylsulphinyll methide obtained in this way was cooled to 10–12° and diluted with 4 ml of anhydrous benzene. To this was then added a solution of 165 mg of dimethyl[(1-bromo-2-oxo-4-cyclopentyl)-butyl]phosphonate in benzene and stirring was continued for 30 minutes. To this mixture was then added a benzene solution of 92 mg of 2-(4 α -acetoxy 5 β -formyl-2 α ,4 α -dihydroxycyclopent-1 α -yl)acetic acid γ -lactone and stirring continued for 20 minutes. The reaction mixture was diluted with 25 ml of benzene, washed with 5% (w/v) NaH₂PO₄ and water until neutral, dried and the solvent evaporated off.

After chromatography on silica gel (methylene chloride-diethyl ether 96:4 v/v) the residue yielded 120 mg of 2-[4 α -acetoxy-5 β -(2'-bromo-3'-oxo-5'-cyclopentylpent-1'-trans-enyl)-2 α -hydroxycyclopent-1 α -yl]acetic acid γ -lactone (λ max 252 m μ , ϵ =10,950).

Example 28.

Following the procedure of Example 22, 16.5 g of dimethyl[(2-oxo-4-(2'-norbornyl)-butyl]phosphonate in 250 ml of anhydrous tetrahydrofuran were treated with 32.8 g of 2-pyrrolidone hydrotribromide to give 17.2 g of dimethyl[(1-bromo-2-oxo-4-(2'-norbornyl)-butyl]phosphonate. Under nitrogen, to a solution of 354 mg of this phosphonate in toluene cooled to -15°C was added, dropwise, with stirring 1 molar equivalent of a solution of butyl lithium in heptane, which is stirred until gas evolution ceases.

The mixture is warmed to 0–5° and a solution of 180 mg of 2-(4 α -acetoxy-5 β -formyl-2 α -hydroxycyclopent-1 α -yl)-acetic acid γ -lactone in benzene is added. Stirring is continued for another 20 minutes, then the mixture is diluted with 5% (w/v) aqueous NaH₂PO₄, the organic phase is separated, washed until neutral, dried and the solvent removed by evaporation.

After purification on silica gel, 210 mg of 2-[5 β -(2'-bromo-3'-oxo-5'-(2'-norbornyl)-pent-1'-trans-enyl)-2 α ,4 α -dihydroxycyclopent-1 α -yl]acetic acid γ -lactone (λ max 251 m μ , ϵ =11,000) were obtained.

Example 29.

Under inert gas, 72 mg of NaH (80% dispersion in mineral oil) in 3 ml of DMSO were heated with stirring to 60° until no more hydrogen evolved.

The solution was cooled to 10–12° and diluted with 20 ml of benzene. Over a 15 minutes period, a solution of 0.75 g of dimethyl[(2-bromo-2-oxo-4-cyclohexyl)]-

phosphonate was added dropwise. After stirring for 30 minutes more, a solution of 0.7 g of 2 - (5 β - formyl - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl)acetic acid γ -lactone in 15 ml of benzene was added. After 30 minutes, it was diluted with 30 ml of benzene and 30 ml of a 5% w/v aqueous solution of NaH₂PO₄. The organic layer was separated off, washed until neutral, dried and the solvent evaporated off. After chromatographic purification on silica gel (eluent CH₂Cl₂-ether 90:10) and crystallization from ethyl ether, 0.82 g were obtained of 2 - [5 β - (2' - bromo - 3' - oxo - 5' - cyclohexylpent - 1' - *trans* - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl)acetic acid γ -lactone m.p. 155—157°C.

Example 30.

To a suspension of 104 mg of NaH (80% dispersion in mineral oil) in 30 ml of benzene, a solution of 904 mg of dimethyl[(2-oxo-4-cyclohexyl)-butyl]phosphonate in 10 ml of benzene was added dropwise and stirred for an hour. A gelatinous suspension was formed to which was added, all at once, 614 mg of finely divided N-bromosuccinimide. After 15 minutes of stirring, a solution of 1.05 g of (5 β - formyl - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxy) - cyclopent - 1 α - yl)acetic acid γ -lactone in 20 ml of benzene was added.

The mixture was stirred for 20 minutes and then diluted with 20 ml of 6% (w/v) aqueous NaH₂PO₄. The organic phase was separated, washed until neutral, dried and the solvent removed by evaporation.

After purification on a silica gel column, 1.17 g of 2 - [5 β - (2' - bromo - 3' - oxo - 5' - cyclohexylpent - 1' - *trans* - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ -lactone m.p. 154—156°C, were obtained.

A solution of 2 g of this compound in 20 ml of 1,2-dimethoxyethane and 80 ml of diethyl ether was dropped into a 0.14M Zn(BH₄)₂ ethereal solution (150 ml).

After 30 minutes the *trans*-enone lactone was completely reduced. A saturated aqueous sodium chloride solution was added to decompose the excess reagent, then 2N H₂SO₄ to adjust the mixture to pH 3.5.

The organic phase was washed until neutral and evaporated to dryness. The residue was chromatographed on 100 g of silica gel to give by elution with cyclohexane-ethyl acetate 80:20 v/v and then 60:40 v/v, respectively 1.245 g of 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - cyclohexylpent - 1' - *trans* - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ -lactone m.p. 124—126°C and 0.485 g of the 3'R-hydroxy epimer, m.p. 177—179°C.

Example 31.

When dimethyl[(2' - oxo - 3'(S) - methyl - 4' - cyclohexyl) - butyl]phosphonate (950 mg) was substituted for the phosphonate used in Example 30 and the halogenating reagent was N-bromoacetamide (480 mg), reaction with the aldehyde gave rise to 2 - [5 β - (2' - bromo - 3' - oxo - 4'(S) - methyl - 5' - cyclohexylpent - 1' - *trans* - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ -lactone m.p. 144—146°C.

Example 32.

Following the procedure outlined in Example 30, with dimethyl[(2-oxo-3'(R)-methylcyclohexyl) - butyl]phosphonate (0.95 g) and N-bromocaprolactam as halogenating reagent, 2 - [5 β - (2' - bromo - 3' - oxo - 4'(R) - methyl - 5' - cyclohexylpent - 1' - *trans* - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ -lactone m.p. 139—141°C was obtained.

Example 33.

To a suspension of 72 mg of 80% NaH in benzene was added dropwise a solution of 680 mg of dimethyl[(2-oxo-4-cyclopentyl) - butyl]phosphonate in 10 ml of benzene. After stirring for 90 minutes, 370 mg of N-chlorosuccinimide were added and stirring continued for 30 minutes.

To the carbanion of the chloro-phosphonate so obtained was added a solution of 0.875 g of 2 - (5 β - formyl - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl)acetic acid γ -lactone in 20 ml of benzene.

Stirring was continued for 20 minutes, then 5% (w/v) aqueous NaH₂PO₄ was added and the organic phase was separated, washed until neutral, dried with MgSO₄ and evaporated to dryness. The resulting crude product (1.4 g) was chromatographed on silica gel (eluted with CH₂Cl₂), yielding 0.98 g of 2 - [5 β - (2' - chloro - 3' - oxo - 5' - cyclopentyl - pent - 1' - *trans* - enyl) - 2 α - dihydroxy - 4 α - *p* - phenylbenzoyloxy - cyclopent - 1 α - yl]acetic acid γ -lactone.

This compound was characterized by NMR spectra, where the proton of H₁, appeared as a doublet centered at 6.75 δ , with a coupling constant with the 5_aH proton of J_{AB} = 9 Hz. These values were clearly different from those for the epimer *cis*-chloro-enone in which the H₁ proton appeared as a doublet at 6.00 δ , with a coupling constant J_{AB} = 10.2 Hz with the 5_aH proton.

Example 34.

In the procedure outlined in Example 33, when the phosphonate was replaced by the analogue dimethyl[(2-oxo-3-methyl-4-cyclopentyl)-butyl]phosphonate and the N-chlorosuccinimide by N-chloroacetamide, the product obtained was 2-[5 β -(2'-hydroxy-4 α -p-phenylbenzoyloxycyclopent-1 α -yl)acetic acid γ -lactone.

Example 35.

Starting with the following phosphonates:

dimethyl(2-oxo-4-cyclohexylbutyl)-phosphonate;
 dimethyl(2-oxo-3(*S,R*)-methyl-4-cyclohexylbutyl)-phosphonate;
 dimethyl(2-oxo-3(*S*)-methyl-4-cyclohexylbutyl)-phosphonate;
 dimethyl(2-oxo-3(*R*)-methyl-4-cyclohexylbutyl)-phosphonate;
 dimethyl[2-oxo-4-(2'-nor-bornyl)-butyl]phosphonate;
 dimethyl[2-oxo-4-(2'-tetrahydrofuryl)-butyl]phosphonate;
 dimethyl[2-oxo-4-(2'-tetrahydrothienyl)-butyl]phosphonate;
 dimethyl[2-oxo-4-(1'-adamantyl)-butyl]phosphonate;
 dimethyl[2-oxo-4-(2-bicyclo[2,2,2]octyl)-butyl]phosphonate;
 dimethyl(2-oxo-4-cycloheptylbutyl)-phosphonate;
 dimethyl[1-oxo-4-(4'-tert-butylcyclohexyl)-butyl]phosphonate;
 dimethyl(2-oxo-4-cyclopropylbutyl)-phosphonate;
 dimethyl(2-oxo-4-cyclopentylbutyl)-phosphonate;
 dimethyl(2-oxo-3(*S*)-methyl-4-cyclopentylbutyl)-phosphonate;
 dimethyl(2-oxo-3(*R*)-methyl-4-cyclopentylbutyl)-phosphonate;
 dimethyl(2-oxo-3-cyclohexylpropyl)-phosphonate;
 dimethyl(2-oxo-3-cyclopentylpropyl)-phosphonate;
 dimethyl[2-oxo-3-(1'-adamantyl)-propyl]phosphonate;
 dimethyl(2-oxo-5-cyclohexylpentyl)-phosphonate;
 and proceeding as described for Examples 22, 23, 24 and 28, the corresponding 1-halogen (1-chloro and 1-bromo)-phosphonates were prepared.

Example 36.

By the method described in Examples 25 to 34, a 4-ester, in particular 2-[5 β -formyl-2 α -hydroxy-4-p-phenylbenzoyloxycyclopent-1 α -yl]acetic acid γ -lactone, is reacted with a bromo phosphonate, either using one of the halo phosphonates described in Example 35, or generating the halo phosphonate *in situ* by reaction with a convenient N-bromoimide, to prepare the following γ -lactones:

2-[5 β -(2'-bromo-3'-oxo-5'-cyclohexylpent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-4'(*S,R*)-methyl-5'-cyclohexylpent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-4'(*S*)-methyl-5'-cyclohexylpent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-4'(*R*)-methyl-5'-cyclohexylpent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-5'-(2'-norbornyl)-pent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-5'-(2'-tetrahydrofuryl)-pent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-5'-(2'-tetrahydrothienyl)-pent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-5'-(1'-adamantyl)-pent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-5'-(α' -bicyclo[2,2,2]octyl)-pent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-5'-cyclopentylpent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-5'-cyclopropylpent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-5'-(4'-tert-butylcyclohexyl)pent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-5'-cyclopentylpent-1'-trans-enyl)-;
 2-[5 β -(2'-bromo-3'-oxo-4(*S*)-methyl-5'-cyclopentylpent-1'-trans-enyl)-;

2 - [5 β - (2' - bromo - 3' - oxo - 4'(R) - methyl - 5' - cyclopentylpent - 1' - trans-enyl)-;

2 - [5 β - (2' - bromo - 3' - oxo - 4' - cyclohexylbut - 1' - trans - enyl)-, m.p. 184—185°C;

2 - [5 β - (2' - bromo - 3' - oxo - 4' - cyclopentylbut - 1' - trans - enyl)-;

2 - [5 β - (2' - bromo - 3' - oxo - 4' - (1 - adamantyl) - but - 1' - trans - enyl)-;

2 - [5 β - (2' - bromo - 3' - oxo - 6' - cyclohexylhex - 1' - trans - enyl)- 2 α -hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl] acetic acid γ - lactones, m.p. 148—149°C.

All these compounds were characterized by their NMR spectra, in which the olefinic proton appeared as a doublet centered around 6.94 δ , with a coupling constant J_{AB} = 9 Hz with the 5 α proton of the cyclopentane ring. In the geometric bromo-*cis*-enone isomers the same olefinic proton showed itself as a doublet centered at 6.18 δ , with a coupling constant J_{AB} = 10.2 Hz.

Example 37.

To a stirred solution of 0.05 M zinc borohydride in diethyl ether (250 ml), were added a solution of 2.4 g of 2 - [5 β - (2' - chloro - 3' - oxo - 4'(S) - methyl - 5' - cyclopentylpent - 1' - trans - enyl) - 2 α - hydroxy - 4 β - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone dissolved in 30 ml of 1,2 - dimethoxyethane. 30 minutes after the last portion of reagent was added, the excess reagent was destroyed by careful addition of a saturated NaCl solution. The precipitate of Zn(OH)₂ was dissolved by acidification with 2N sulfuric acid and the organic phase was separated off, washed until neutral, dried and the solvent removed under vacuum. The residue was chromatographed on 450 g of silica gel eluted with methylene chloride-diethyl ether to give 1.24 g of 2 - [5 β - (2' - chloro - 3'(S) - hydroxy - 4'(S) - methyl - 5' - cyclopentylpent - 1' - trans - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone and 0.61 g of the 3'(R) epimeric alcohol.

Example 38.

Sodium borohydride (80 mg) was added under stirring to a solution of 2 - [5 β - (2' - chloro - 3' - oxo - 5' - cyclopentylpent - 1' - trans - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone (0.4 g) in 10 ml of methanol and 5 ml of methylene chloride cooled to -5 to -10°C. After stirring for 30 minutes at that temperature, the excess reagent was destroyed by addition of 15% (w/v) aqueous acetic acid and the mixture evaporated *in vacuo*. The residue was taken up in water-methylene chloride and the organic layer washed until neutral and evaporated to dryness. The crude product, a mixture of the two 3'(S) and 3'(R) epimeric alcohols, was chromatographed on 80 g of silica gel. Elution with diethyl ether-diisopropyl ether 75:25 v/v gave 0.15 g of 2 - [5 β - (2' - chloro - 3'(S) - hydroxy - 5' - cyclopentylpent - 1' - trans - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone and 0.1 g of the 3'(R) alcohols.

Example 39.

When, in the procedure outlined in Example 38, the *trans* enone derivative was replaced with 2 - [5 β - (2' - bromo - 3' - oxo - 5' - (2' - tetrahydrofuryl) - pent - 1' - trans - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone, both of the epimeric alcohols were obtained, which after elution from a silica gel column with methylene chloride-diethyl ether 90:10 v/v yields 0.10 g of [5 β - (2' - bromo - 3'(R) - hydroxy - 5' - (2' - tetrahydrofuryl) - pent - 1' - trans - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone and 0.21 g of the epimeric 3'(S) alcohol. A stirred solution of 0.7 g of this compound in 30 ml of anhydrous methanol was treated with 210 mg of K₂CO₃ at room temperature, for 4 hours and then neutralized by addition of 15% w/v aqueous acetic acid. The methanol was removed under vacuum and the residue partitioned between ethyl acetate and 10% w/v aqueous sodium chloride. The organic layer was separated, washed until neutral, dried and the solvent evaporated off to give the free dihydroxy-lactone:

2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - (2' - tetrahydrofuryl) - pent - 1' - trans - enyl) - 2 α ,4 α - dihydroxycyclopent - 1 α - yl]acetic acid γ - lactone (0.49 g).

To a solution of this compound in 20 ml of anhydrous benzene was added 0.35 g of 2,3-dihydropyran and a solution in benzene of 2.5 mg of *p*-toluenesulfonic acid. The mixture was maintained at room temperature for 3 hours, then washed with 3% w/v aqueous potassium carbonate and then with water until neutral. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel and eluted with

cyclohexane-ethyl acetate-pyridine 80:20:0.1 to give 0.675 g of pure 2-[5 β -(2'-bromo-3'(S)-hydroxy-5-(2'-tetrahydrofuryl)-pent-1'-trans-enyl)-2 α ,4 α -dihydroxycyclopent-1 α -yl]acetic acid γ -lactone 3'S,4 α -bis-THP-ether.

Example 40.

A stirred solution of 1.3 g of 2-[5 β -(2'-bromo-3'-oxo-4'(S)-methyl-5'-cyclohexylpent-1'-trans-enyl)-2 α -hydroxy-4 α -p-phenylbenzoyloxycyclopent-1 α -yl]acetic acid γ -lactone in 20 ml CH₂Cl₂ and 25 ml of methanol, cooled to -10°, was treated with 120 mg of NaBH₄ and left for 30 minutes at 0-2°C to obtain complete reduction of the oxo group. After neutralization with 15% w/v aqueous acetic acid and solvent evaporation under vacuum, the residue was transferred to a silica gel column (250 g) with methylene chloride and eluted with methylene chloride containing increasing amounts of an ethyl ether. The first product to be eluted was 0.72 g of 2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(S)-methyl-5'-cyclohexylpent-1'-trans-enyl)-2 α -hydroxy-4 α -p-phenylbenzoyloxycyclopent-1 α -yl]acetic acid γ -lactone and the second was 0.36 g of the epimeric 3'(S)-alcohol.

The 3'S-alcohol was then treated in methanol (25 ml) with 6 ml of an aqueous 20% w/v solution of K₂CO₃ for one hour under reflux. The reaction mixture was cooled, acidified to pH 1 and left for 2 hours at room temperature. The salts, which precipitated out, were removed by filtration and the filtrate, concentrated *in vacuo* to a small volume which was extracted with methylene chloride-ethyl acetate to give 0.46 g of 2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(S)-methyl-5'-cyclohexylpent-1'-trans-enyl)-2 α ,4 α -dihydroxycyclopentane-1 α -yl]acetic acid γ -lactone.

A solution of this product in anhydrous benzene was reacted with 0.4 g of 1,4-diox-2-ene and 4 mg of anhydrous *p*-toluenesulfonic acid, for 3 hours at room temperature. The organic phase was washed with 5% w/v potassium carbonate and with water until neutral, dried and evaporated to dryness to yield 0.68 g of 2-[5 β -(2'-bromo-3'S-hydroxy-4'(S)-methyl-5'-cyclohexylpent-1'-trans-enyl)-2 α ,4 α -dihydroxycyclopentane-1 α -acetic acid γ -lactone 3',4-bis-DIOX ether.

Example 41.

Starting with the 1'-trans-2-halo-3'-oxoketones such as in Example 36 and earlier ones, working according to the procedures described in Examples 30, 37, 38, 39 and 40, the reduction of the α -halo enone group, either with a solution of zinc borohydride in diethyl ether or with sodium borohydride in methanol, gave rise to the epimeric 2'-halo-3'(S)-hydroxy and 2'-halo-3'(R)-hydroxy alcohols that were separated on column to give the individual epimeric derivatives, which were then saponified to give the corresponding bicyclic lactone-3',4-dihydroxy derivatives, then reacted with 2,3-dihydropyran or 1,4-diox-2-ene to give the following (2 α ,4 α -dihydroxycyclopent-1 α -yl)acetic acid γ -lactones:

- 2-[5 β -(2'-chloro-3'(S)-hydroxy-4'(S,R)-methyl-5'-cyclopentylpent-1'-trans-enyl)-;
- 2-[5 β -(2'-chloro-3'(S)-hydroxy-5'-cyclopentylpent-1'-trans-enyl)-;
- 2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-cyclohexylpent-1'-trans-enyl)-;
- 2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(S,R)-methyl-5'-cyclohexylpent-1'-trans-enyl)-;
- 2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(S)-methyl-5'-cyclohexylpent-1'-trans-enyl)-;
- 2-[5 β -(2'-bromo-3'(S)-hydroxy-4'(R)-methyl-5'-cyclohexylpent-1'-trans-enyl)-;
- 2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-(2''-norbornyl)-pent-1'-trans-enyl)-;
- 2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-(2''-tetrahydrofuryl)-pent-1'-trans-enyl)-;
- 2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-(2''-tetrahydrothienyl)-pent-1'-trans-enyl)-;
- 2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-(1''-adamantyl)-pent-1'-trans-enyl)-;
- 2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-(2''-bicyclo[2,2,2]octyl)-pent-1'-trans-enyl)-;
- 2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-cycloheptylpent-1'-trans-enyl)-;
- 2-[5 β -(2'-bromo-3'(S)-hydroxy-5'-cyclopropylpent-1'-trans-enyl)-;

- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - (4 - tert - butylcyclohexyl) - pent-1' - trans - enyl)-;
 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - cyclopentylpent - 1' - trans - enyl)-;
 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4'(S) - methyl - 5' - cyclopentylpent-1' - trans - enyl)-;
 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4'(R) - methyl - 5' - cyclopentylpent-1' - trans - enyl)-;
 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4' - cyclohexylbut - 1' - trans - enyl)-;
 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4' - cyclopentylbut - 1' - trans - enyl)-;
 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4' - (1'' - adamantyl) - but - 1' - trans-enyl)-; and
 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 6' - cyclohexylhex - 1' - trans - enyl)-
 2 α ,4 α - dihydroxycyclopent - 1 α - yl]acetic acid γ - lactones,
 and their 3'(R) epimeric alcohols, either as the 4-esters (particularly the 4-p-phenylbenzoate) or as the free 3',4-diols and their 3',4-bis-THP ethers and 3',5-bis-DIOX ethers.

Example 42.

- A solution of 7.2% DIBA in toluene (16 ml) was added over a 15 minute period to a stirred solution of 2 - [5 β - (2' - chloro - 3'(S) - hydroxy - 4'(S,R) - methyl-5' - cyclopentylpent - 1' - trans - enyl) - 2 α ,4 α - dihydroxycyclopent - 1 α - yl]acetic acid γ -lactone 3',4-bis-DIOX ether (1.1 g) in dry toluene, cooled to -60°.
 Stirring was continued for 30 minutes, then the reaction mixture was treated with 2N-isopropanol in toluene, and after 10 minutes warmed to 0-2°C and treated with 1 ml of water, 2 g of anhydrous sodium sulfate and 2.5 g of celite, then filtered. The filtrate was evaporated to dryness under vacuum to give 1.05 g of 2 - [5 β - (2' - chloro-3'(S) - hydroxy - 4'(S,R) - methyl - 5' - cyclopentylpent - 1' - trans - enyl) - 2 α ,4 α -dihydroxycyclopent - 1 α - yl]acetaldehyde γ - hemiacetal 3',4 - bis - DIOX ether.

Example 43.

- Following the procedure described in Example 42, 0.57 g of 2 - [5 β - (2' - bromo-3'(S) - hydroxy - 5' - cyclohexylpent - 1' - trans - enyl) - 2 α ,4 α - dihydroxycyclopent-1 α - yl]acetic acid γ - lactone 3'S,4 - bis - THP ether was reacted with 4.4 ml of 0.5M DIBA solution to give 0.57 g of 2 - [5 β - (2' - bromo - 3'(S) - hydroxy-5' - cyclohexylpent - 1' - trans - enyl) - 2 α ,4 α - dihydroxycyclopent - 1 α - yl]acetaldehyde γ - hemiacetal 3'S,4 - bis - THP ether.

Example 44.

- Under nitrogen, a mixture of a 70% solution of sodium bis-(2-methoxyethoxy)-aluminium hydride in benzene (0.58 ml) and toluene (4 ml) was added dropwise to a stirred solution of 0.68 g of 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - (2'' - tetrahydrofuryl) - pent - 1' - trans - enyl) - 2 α ,4 α - dihydroxycyclopent - 1 α - yl]acetic acid γ -lactone 3',4-bis-THP ether in 25 ml of anhydrous toluene, cooled to -60 to -65°C.

- Stirring was continued for 3 hours, then the excess reagent was destroyed by careful addition of 5% acetone in toluene. After 10 minutes, the mixture was warmed to 0-2°C, treated with a saturated solution of NaH₂PO₄ (3 ml) and the crystalline precipitate filtered out.

- The filtrate was evaporated to dryness *in vacuo* to give 0.66 g of 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - (2'' - tetrahydrofuryl) - pent - 1' - trans - enyl) - 2 α ,4 α - dihydroxycyclopent - 1 α - yl]acetaldehyde γ - hemiacetal 3'S,4 - bis - THP ether. 0.4 g of this compound was treated in acetone (8 ml) with 4 ml of 0.2N oxalic acid and refluxed for 90 minutes; the solvent was removed under vacuum and the aqueous phase extracted with ethyl acetate. The combined organic extracts were washed with saturated ammonium sulfate until neutral, dried and evaporated to dryness.

- The residue was chromatographed on silica gel, eluted with cyclohexane-diethyl acetate 70:30 to yield 0.25 g of pure 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - (2'' - tetrahydrofuryl) - pent - 1' - trans - enyl) - 2 α ,4 α - dihydroxycyclopent - 1 α - yl]acetaldehyde γ -lactol.

Example 45.

- Starting from one of the 2-(cyclopent-1 α -yl)acetic acid γ -lactone 3',4-bis-THP ethers and 3',4-bis-DIOX ethers) listed in Example 41, by reduction of the γ -lactone group with DIBA, according to the procedure given in Examples 42 and 43 or with sodium bis-(2-methoxyethoxy)-aluminium hydride, as described in Example 41, the 3',4-bis-ethers of the following γ -hemiacetals were obtained:

- 2 - [5 β - (2' - chloro - 3'(S) - hydroxy - 4'(S,R) - methyl - 5' - cyclopentyl) - pent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - chloro - 3'(S) - hydroxy - 5' - cyclopentylpent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - cyclohexylpent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4'(S,R) - methyl - 5' - cyclohexylpent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4'(S) - methyl - 5' - cyclohexylpent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4'(R) - methyl - 5' - cyclohexylpent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - (2'' - norbornyl) - pent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - (2'' - tetrahydrofuryl) - pent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'S - hydroxy - 5' - (2'' - tetrahydrothienyl) - pent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'S - hydroxy - 5' - (1'' - adamantyl) - pent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - (2'' - bicyclo[2,2,2]octyl) - pent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - cycloheptyl - pent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - cyclopropylpent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - (4'' - tert - butylcyclohexyl) - pent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 5' - cyclopentylpent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4'(S) - methyl - 5' - cyclopentylpent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4'(R) - methyl - 5' - cyclopentylpent - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4' - cyclohexylbut - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4' - cyclopentylbut - 1' - trans - enyl)-;
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 4' - (1'' - adamantyl) - but - 1' - trans - enyl)-; and
- 2 - [5 β - (2' - bromo - 3'(S) - hydroxy - 6' - cyclohexylhex - 1' - trans - enyl) - 2 α ,4 α - dihydroxycyclopent - 1 α - yl]acetaldehyde γ - hemiacetal, and their 3'(R)-epimeric alcohols, as the 3',4-bis-THP ethers and the 3',4-bis-DIOX ethers that, when desired, were deetherified in acetone-0.2N oxalic acid to give the 3',4-free diols.

Example 46.

A solution of 2.6 g of 2 - [5 β - hydroxymethyl - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone in 38 ml of benzene-DMSO (75:25) was reacted with 4.6 g of dicyclohexylcarbodiimide and 7.5 ml of a solution of in pyridine-trifluoroacetate (2 ml of pyridine- 1 ml of trifluoroacetic acid in 25 ml of benzene:DMSO 75:25 v/v).

After 3 hours, the excess reagent was destroyed by reaction with 2.8 g of oxalic acid in 6 ml of methanol, then diluted with 80 ml of water and 80 ml of benzene. After filtration, the filtrate was washed until neutral, dried and concentrated under vacuum to 15 ml (solution of the aldehyde).

To a suspension of 334 mg of 80% sodium hydride in 80 ml of benzene was added dropwise a solution of 3.92 g of dimethyl(2-oxo-4-cyclohexylbutyl)phosphonate in 15 ml of benzene. This was stirred for 2 hours; then the solution of aldehyde was added. After an additional 20 minutes of stirring, the mixture was filtered and the filtrate washed with 5% (w/v) NaH₂PO₄ and sodium chloride until neutral, then evaporated to dryness. After crystallization from hexane, 2.38 g were obtained of 2 - [5 β - (3' - oxo - 5' - cyclohexylpent - 1' - trans - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone m.p. 104-106°C.

Two g of this compound were dissolved in 20 ml of 1,2-dimethoxyethane and 40 ml of diethyl ether and added dropwise to 250 ml of 0.05M zinc borohydride in diethyl ether. After 30 minutes, the excess reagent was destroyed with 2N sulfuric acid. The organic phase was separated, washed until neutral and evaporated to dryness to give 2.1 g of crude 2 - [5 β - (3'(S,R) - hydroxy - 5' - cyclohexylpent - 1' - trans - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ -lactone.

This compound was dissolved in 30 ml of anhydrous THF and reacted with

4.78 g of 2-pyrrolidone hydrotribromide, overnight at room temperature, with constant stirring. It was diluted with 120 ml of diethyl ether, filtered and the filtrate washed with saturated ammonium sulfate until neutral. After drying over MgSO_4 , it was evaporated *in vacuo* on a water bath less than 40°C . The crude 2 - [5β - (1',2') - dibromo - 3'(S,R) - hydroxy - 5' - cyclohexylpentyl) - 2α - hydroxy - 4α - *p* - phenylbenzoyloxycyclopent - 1α - yl]acetic acid γ - lactone (about 3 g) was dissolved in 150 ml of acetone, cooled to 0° and oxidized by addition of 8.2 ml of Jones' reagent. After 5 minutes, it was diluted with 7 volumes of benzene and washed until neutral with a saturated ammonium sulfate solution, dried on MgSO_4 and concentrated under vacuum to $\frac{1}{2}$ volume. Then 2.5 ml of triethylamine were added and it was left overnight at room temperature. The mixture was washed with 40% (w/v) citric acid solution (3 times 8 ml), then with ammonium sulfate until neutral, then dried and evaporated to give 2.6 g of crude product which was crystallized from diethyl ether to give 1.2 g of 2 - [5β - (2' - bromo - 3' - oxo - 5' - cyclohexylpent - 1' - *trans* - enyl) - 2α - hydroxy - 4α - *p* - phenylbenzoyloxycyclopent - 1α - yl]acetic acid γ - lactone m.p. $154-156^\circ\text{C}$.

Example 47.

Sulfonyl chloride (13.5 ml) was added dropwise, with constant stirring to a solution of 4.8 g of 2 - [5β - (3' - oxo - 5' - cyclohexylpent - 1' - *trans* - enyl) - 2α - hydroxy - 4α - *p* - phenylbenzoyloxycyclopent - 1α - yl]acetic acid γ - lactone in 95 ml of anhydrous pyridine, cooled to $0-5^\circ\text{C}$ and the stirring continued at $0-2^\circ$ for 16 hours.

The reaction mixture was then poured into cold 2N H_2SO_4 (500 ml) and extracted many times with ethyl acetate.

The combined organic extracts were washed with 4N H_2SO_4 , water, 5% NaHCO_3 and water until neutral, dried over MgSO_4 and evaporated to dryness under vacuum. The crude residue (4.82 g) was purified by chromatography through a short silica gel column (40 g). Elution with CH_2Cl_2 gave pure 2 - [5β - (2' - chloro - 3' - oxo - 5' - cyclohexylpent - 1' - *trans* - enyl) - 2α - hydroxy - 4α - *p* - phenylbenzoyloxy - 1α - yl] - acetic acid γ - lactone (2.96 g).

Example 48.

Using the procedure described in Example 46, by reaction of 2 - [5β - formyl - 2α - hydroxy - 4α - *p* - phenylbenzoyloxycyclopent - 1α - yl]acetic acid γ - lactone with the sodium salts of the following phosphonates:

dimethyl(2 - oxo - 3 - cyclohexylpropyl)phosphonate and dimethyl(2 - oxo - 5 - cyclohexylpentyl)phosphonate, there were prepared respectively:

2 - [5β - (3' - oxo - 4' - cyclohexylbut - 1' - *trans* - enyl) - 2α - hydroxy - 4α - *p* - phenylbenzoyloxycyclopent - 1α - yl]acetic acid γ - lactone m.p. $140-142^\circ$, $[\alpha]_D = -128^\circ$ (CHCl_3) and

2 - [5β - (3' - oxo - 6' - cyclohexylhex - 1' - *trans* - enyl) - 2α - hydroxy - 4α - *p* - phenylbenzoyloxycyclopent - 1α - yl]acetic acid γ - lactone m.p. $92-93^\circ\text{C}$, $[\alpha]_D = -118^\circ$ (CHCl_3).

Example 49.

A solution of 300 mg of 2 - [5β - (3' - oxo - 6' - cyclohexylhex - 1' - *trans* - enyl) - 2α - dihydroxy - 4α - *p* - phenylbenzoyloxycyclopent - 1α - yl]acetic acid γ - lactone in 6 ml of anhydrous tetrahydrofuran was mixed with 360 mg of 2-pyrrolidone hydrotribromide and maintained for 3 hours with constant stirring, then diluted with 20 ml of benzene. After filtration, the filtrate had 0.25 ml of triethylamine added and it was maintained at $25-28^\circ\text{C}$ for 2 hours, after which it was washed with 1N H_2SO_4 and water until neutral.

It was dried and evaporated to dryness to give 0.35 g of crude product. After crystallization from $\text{MeOH}/\text{CH}_2\text{Cl}_2$, 280 mg were obtained of 2 - [5β - (2' - bromo - 3' - oxo - 6' - cyclohexylhex - 1' - *trans* - enyl) - 2α - hydroxy - 4α - *p* - phenylbenzoyloxycyclopent - 1α - yl]acetic acid γ - lactone m.p. $148-149^\circ\text{C}$, $[\alpha]_D = -96^\circ$ (CHCl_3).

The same compound was also obtained by a completely independent procedure as described below:

To a suspension of 60 mg of 80% NaH in 8 ml of benzene, a solution of 0.553 g of dimethyl(2 - oxo - 5 - cyclohexylpentyl)phosphonate in 5 ml of benzene was added dropwise. When all the hydrogen had evolved, to the suspension of the carbanion of the phosphonate prepared in this way was added all at once 0.365 g of N-bromo-succinimide. This was stirred for 20 minutes and then a solution of 0.35 g of 2 - [5β -

formyl - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ -lactone in 10 ml of benzene was added and stirring continued for 30 minutes.

The organic phase was washed until neutral with water, dried and the solvent evaporated off. After crystallization from methanol, 0.36 g were obtained of 2 - [5 β - (2' - bromo - 3' - oxo - 6' - cyclohexylhex - 1' - *trans* - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ -lactone m.p. 148—149°C.

The mother liquors from the two different synthesis were combined and evaporated to dryness for separation by thin layer chromatography (silica gel developed in methylene chloride-diethyl ether 96:4).

An additional 90 mg of the *trans* enone and 50 mg of the isomer 2 - [5 β - (2' - bromo - 3' - oxo - 6' - cyclohexylhex - 1' - *cis* - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ -lactone, m.p. 129—131°C, were obtained. The compounds were identified on the basis of NMR spectra.

Trans derivative: H_1 , 6.94 δ , J_{AB} = 9 Hz.

Cis derivative: H_1 , 6.18 δ , J_{AB} = 9 Hz.

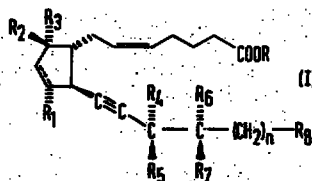
Example 50.

Using the procedure outlined in Example 49, starting from 2 - [5 β - (3' - oxo - 4' - cyclohexylbut - 1' - *trans* - enyl) - 2 α - dihydroxy - 4 α - *p* - phenylbenzoyloxy - cyclopent - 1 α - yl]acetic acid γ -lactone, by addition of bromine followed by dehydrohalogenation and by direct synthesis (that is alkylation), of the 2 - [5 β - formyl - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ -lactone with the carbanion of dimethyl(1-bromo-2-oxo-3-cyclohexylpropyl)-phosphonate generated *in situ*, we prepared 2 - [5 β - (2' - bromo - 3' - oxo - 4' - cyclohexylbut - 1' - *trans* - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ -lactone m.p. 181—182°C, $[\alpha]_D = -90.7^\circ$ ($CHCl_3$).

H_1 , 6.93 δ , J_{AB} = 9 Hz, and from the mother liquors the *cis*-isomer was isolated, m.p. 149—149.5°C, $[\alpha]_D = -192^\circ$ ($CHCl_3$), H_1 = 6.18 δ , J_{AB} = 10.2 Hz.

WHAT WE CLAIM IS:—

1. Optically active or racemic prostaglandins of the following general formula (I)



wherein

R is a hydrogen atom, a C_1 — C_{12} alkyl group or a cation of a pharmaceutically acceptable base;

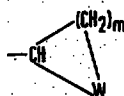
the symbol --- represents a single or a double bond, wherein, when the symbol --- is a double bond,

R_1 is a hydrogen atom,

and R_2 and R_3 together form an oxo group, while, when the symbol --- is a single bond, R_1 is hydroxy,

R_2 is hydrogen and R_3 is hydroxy or a carboxylic acyloxy or R_2 and R_3 , taken together, form an oxo group; one of R_4 and R_5 is hydroxy and the other is hydrogen; R_6 and R_7 are independently hydrogen or C_1 — C_4 alkyl; n is zero, 1, 2 or 3;

R_8 is a radical



wherein m is 1, 2, 3, 4 or 5 and W is $\text{---CH}_2\text{---}$, an oxygen atom, a sulphur atom or a radical $>NR_9$, wherein R_9 is hydrogen or C_1 — C_4 alkyl, or R_9 is 1-adamantyl, 2-norbornyl, 2-bicyclo[2,2,2]-octyl or 4-*t*-butylcyclohexyl.



formyl - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ -lactone in 10 ml of benzene was added and stirring continued for 30 minutes.

The organic phase was washed until neutral with water, dried and the solvent evaporated off. After crystallization from methanol, 0.36 g were obtained of 2 - [5 β - (2' - bromo - 3' - oxo - 6' - cyclohexylhex - 1' - *trans* - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone m.p. 148—149°C.

The mother liquors from the two different synthesis were combined and evaporated to dryness for separation by thin layer chromatography (silica gel developed in methylene chloride-diethyl ether 96.4).

An additional 90 mg of the *trans* enone and 50 mg of the isomer 2 - [5 β - (2' - bromo - 3' - oxo - 6' - cyclohexylhex - 1' - *cis* - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone, m.p. 129—131°C, were obtained. The compounds were identified on the basis of NMR spectra.

Trans derivative: H_1 , 6.94 δ , J_{AB} = 9 Hz.

Cis derivative: H_1 , 6.18 δ , J_{AB} = 9 Hz.

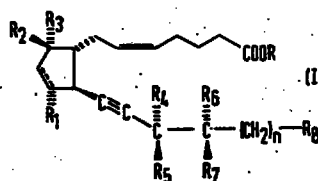
Example 50.

Using the procedure outlined in Example 49, starting from 2 - [5 β - (3' - oxo - 4' - cyclohexylbut - 1' - *trans* - enyl) - 2 α - dihydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone, by addition of bromine followed by dehydrohalogenation and by direct synthesis (that is alkylation), of the 2 - [5 β - formyl - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone with the carbanion of dimethyl(1 - bromo - 2 - oxo - 3 - cyclohexylpropyl)-phosphonate generated *in situ*, we prepared 2 - [5 β - (2' - bromo - 3' - oxo - 4' - cyclohexylbut - 1' - *trans* - enyl) - 2 α - hydroxy - 4 α - *p* - phenylbenzoyloxycyclopent - 1 α - yl]acetic acid γ - lactone m.p. 181—182°C, $[\alpha]_D$ = -90.7° ($CHCl_3$).

H_1 , 6.93 δ , J_{AB} = 9 Hz, and from the mother liquors the *cis*-isomer was isolated, m.p. 149—149.5°C, $[\alpha]_D$ = -192° ($CHCl_3$), H_1 = 6.18 δ , J_{AB} = 10.2 Hz.

WHAT WE CLAIM IS:—

1. Optically active or racemic prostaglandins of the following general formula (I)



wherein

R is a hydrogen atom, a C_1 — C_{12} alkyl group or a cation of a pharmaceutically acceptable base;

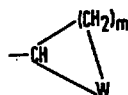
the symbol --- represents a single or a double bond, wherein, when the symbol --- is a double bond,

R_1 is a hydrogen atom,

and R_2 and R_3 together form an oxo group, while, when the symbol --- is a single bond, R_1 is hydroxy,

R_2 is hydrogen and R_3 is hydroxy or a carboxylic acyloxy or R_2 and R_3 , taken together, form an oxo group; one of R_4 and R_5 is hydroxy and the other is hydrogen; R_6 and R_7 are independently hydrogen or C_1 — C_4 alkyl; n is zero, 1, 2 or 3;

R_8 is a radical



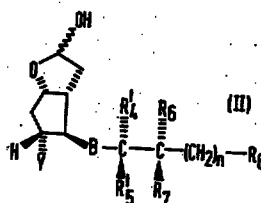
wherein m is 1, 2, 3, 4 or 5 and W is $\text{---CH}_2\text{---}$, an oxygen atom, a sulphur atom or a radical $>NR_9$, wherein R_9 is hydrogen or C_1 — C_4 alkyl, or R_9 is 1-adamantyl, 2-norbornyl, 2-bicyclo[2,2,2]-octyl or 4-*t*-butylcyclohexyl.



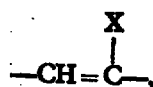
2. A compound selected from
- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - *cis* - 5 - en-13 - ynoic acid;
- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - cyclopentylprost - *cis* - 5 - en-13 - ynoic acid;
- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - (2' - norbornyl) - prost - *cis* - 5 - en - 13 - ynoic acid;
- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - (1' - adamantyl) - prost - *cis* - 5 - en - 13 - ynoic acid;
- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - (2' - bicyclo - [2,2,2] - octyl) - prost - *cis* - 5 - en - 13 - ynoic acid;
- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - cycloheptylprost - *cis* - 5 - en - 13 - ynoic acid;
- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(*S*) - methylprost - *cis* - 5 - en - 13 - ynoic acid;
- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(*R*) - methylprost - *cis* - 5 - en - 13 - ynoic acid;
- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(*S,R*) - methylprost - 5 - *cis* - en - 13 - ynoic acid;
- 9 α ,11 α ,15(*S*) - trihydroxy - 18,19,20 - trinor - 17 - [(4' - *tert*.butyl) - cyclohexyl] - prost - *cis* - 5 - en - 13 - ynoic acid;
- 9 - oxo - 11 α ,15(*S*) - dihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - *cis* - 5 - en - 13 - ynoic acid;
- 9 - oxo - 11 α ,15(*S*) - dihydroxy - 18,19,20 - trinor - 17 - (2' - norbornyl) - prost - *cis* - 5 - en - 13 - ynoic acid;
- 9 - oxo - 11 α ,15(*S*) - dihydroxy - 18,19,20 - trinor - 17 - (1' - adamantyl) - prost - *cis* - 5 - en - 13 - ynoic acid;
- 9 - oxo - 11 α ,15(*S*) - dihydroxy - 18,19,20 - trinor - 17 - (2' - bicyclo - [2,2,2] - octyl) - prost - *cis* - 5 - en - 13 - ynoic acid;
- 9 - oxo - 11 α ,15(*S*) - dihydroxy - 18,19,20 - trinor - 17 - cycloheptylprost - *cis* - 5 - en - 13 - ynoic acid;
- 9 - oxo - 11 α ,15(*S*) - dihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(*S*) - methyl - prost - *cis* - 5 - en - 13 - ynoic acid;
- 9 - oxo - 11 α ,15(*S*) - dihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(*R*) - methyl - prost - *cis* - 5 - en - 13 - ynoic acid;
- 9 - oxo - 11 α ,15(*S*) - dihydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(*S,R*) - methylprost - *cis* - 5 - en - 13 - ynoic acid;
- 9 - oxo - 11 α ,15(*S*) - dihydroxy - 18,19,20 - trinor - 17 - [(4' - *tert*.butyl) - cyclohexyl]prost - *cis* - 5 - en - 13 - ynoic acid;
- 9 - oxo - 15(*S*) - hydroxy - 18,19,20 - trinor - 17 - cyclohexylprosta - *cis* - 5,10 - dien - 13 - ynoic acid;
- 9 - oxo - 15(*S*) - hydroxy - 18,19,20 - trinor - 17 - cyclopentylprosta - *cis* - 5,10 - dien - 13 - ynoic acid;
- 9 - oxo - 15(*S*) - hydroxy - 18,19,20 - trinor - 17 - (2' - norbornyl) - prosta - *cis* - 5,10 - dien - 13 - ynoic acid;
- 9 - oxo - 15(*S*) - hydroxy - 18,19,20 - trinor - 17 - (1' - adamantyl) - prosta - *cis* - 5,10 - dien - 13 - ynoic acid;
- 9 - oxo - 15(*S*) - hydroxy - 18,19,20 - trinor - 17 - (2' - bicyclo - [2,2,2] - octyl) - prosta - *cis* - 5,10 - dien - 13 - ynoic acid;
- 9 - oxo - 15(*S*) - hydroxy - 18,19,20 - trinor - 17 - cycloheptylprosta - *cis* - 5,10 - dien - 13 - ynoic acid;
- 9 - oxo - 15(*S*) - hydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(*S*) - methylprosta - *cis* - 5,10 - dien - 13 - ynoic acid;
- 9 - oxo - 15(*S*) - hydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(*R*) - methylprosta - *cis* - 5,10 - dien - 13 - ynoic acid;
- 9 - oxo - 15(*S*) - hydroxy - 18,19,20 - trinor - 17 - cyclohexyl - 16(*S,R*) - methylprosta - *cis* - 5,10 - dien - 13 - ynoic acid;
- 9 - oxo - 15(*S*) - hydroxy - 18,19,20 - trinor - 17 - [(4' - *tert*.butyl) - cyclohexyl] - prosta - *cis* - 5,10 - dien - 13 - ynoic acid;
- 9 α ,11 α - 15(*S*) - trihydroxy - 19,20 - dinor - 18 - cyclohexylprost - *cis* - 5 - en - 13 - ynoic acid; and
- 9 α ,11 α - 15(*S*) - trihydroxy - 17,18,19,20 - tetranor - 16 - cyclohexylprost - *cis* - 5 - en - 13 - ynoic acid;
- or an alkyl ester or salt thereof, or a 4 α -o-acyl (the acyl radical being derived from a carboxylic acid) derivative of a PGF $_x$ analogue or an ester of such a derivative.



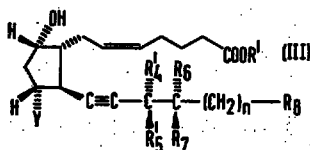
3. Process for the preparation of prostaglandins of formula (I) according to claim 1, comprising reacting an optically active compound, or a racemic mixture of compounds, of general formula (II)



5 wherein
B is $\text{---C}\equiv\text{C---}$ or

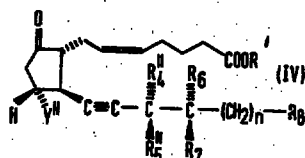


10 wherein X is bromine, chlorine or iodine, and wherein R_6 , R_7 , R_8 and n are as defined in claim 1, one of R'_4 and R'_5 is a hydroxy or a known protecting group bound to the chain by an ethereal oxygen atom, and the other is a hydrogen atom, Y is a hydroxy or a known protecting group bound to the ring by an ethereal oxygen atom, with a Wittig reagent comprising a group of formula $\text{---(CH}_2)_4\text{---COOR'}$, wherein R' is a hydrogen atom or a $C_1\text{---}C_{12}$ alkyl group, to give a compound of general formula (III)



15 wherein

R'_4 , Y, R'_5 , R_6 , R_7 , R_8 and n are as defined above, which, when Y is a known protecting group as above defined, and one of R'_4 and R'_5 is a known protecting group as above defined and the other is hydrogen, optionally esterifying the compound of formula III to give the 9 α -acyloxy derivative (as hereinbefore defined) and then de-
20 etherifying the compound of formula (III) wherein Y is a known protecting group as above defined and/or one of R'_4 and R'_5 is a known protecting group as above defined and the other is hydrogen, or deetherifying the 9 α -acyloxy derivative of the compound of formula (III), to obtain a compound of formula (I), wherein R_1 is a hydroxy group, the symbol $\text{---}=\text{---}$ is a single bond, R_2 is hydrogen and R_3 is hydroxy or a carboxylic
25 acyloxy, and one of R_4 and R_5 is a hydroxy group and the other is hydrogen, or, if desired, oxidizing the 9 α -hydroxy group in the compound of formula (III) wherein Y is a known protecting group as above defined, and one of R'_4 and R'_5 is a known pro-
30 tecting group as above defined and the other is hydrogen, to give a compound of general formula (IV)



35 wherein

R'_4 , R_6 , R_7 , R_8 and n are as above defined, Y'' is a known protecting group as defined above, and one of R''_4 and R''_5 is a known protecting group as defined above and the other is hydrogen, which, in turn, is deetherified to give, according to the reaction conditions used, either a compound of general formula (I) wherein the symbol $\text{---}=\text{---}$ is a single bond, R_1 is hydroxy, and R_2 and R_3 taken together form an oxo group, or a compound of general formula (I) wherein the symbol $\text{---}=\text{---}$ is a double bond, R_1



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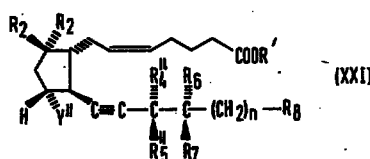
is hydrogen and R_2 and R_3 together form an oxo group, and then, if desired, reacting a compound of general formula (I) wherein R is a hydrogen atom with a base to give a compound of general formula (I) wherein R is a cation, or esterifying a compound of general formula (I) wherein R is a hydrogen atom, to give a compound of general formula (I) wherein R is C_1-C_{12} alkyl, or hydrolysing a compound of general formula (I) wherein R is C_1-C_{12} alkyl, to give a compound of general formula (I) wherein R is a hydrogen atom.

4. A process according to claim 3 substantially as described in any one of the foregoing Examples 1 to 21.

5. A compound according to claim 1 when prepared by a process according to claim 3 or 4.

6. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim 1, 2, or 5 and a pharmaceutically acceptable carrier or diluent.

7. An optically active or racemic compound of formula (XXI)



wherein

R_2 is hydrogen and R_3 is hydroxy or a carboxylic acyloxy, or R_2 and R_3 together form an oxo group, R' is hydrogen or a C_1-C_{12} alkyl, Y'' is a known protecting group bound to the ring through an ethereal oxygen atom, one of R''_4 and R''_5 is a known protecting group bound to the chain through an ethereal oxygen atom, and the other is hydrogen, R_6 , R_7 , R_8 and n are as defined in claim 1.

8. A process for preparing a compound of formula (XXI) as defined in claim 7 substantially as hereinbefore described.

9. A method for treating a non-human warm-blooded animal which comprises administering a compound as claimed in claim 1, 2, or 5.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1977.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.