1 413 831

PATENT SPECIFICATION (11) 1 413 831

(21) Application No. 55713/73 (22) Filed 1 Dec. 1972
(31) Convention Application No. 204 769
(32) Filed 3 Dec. 1971
(31) Convention Application No. 306 414
(32) Filed 14 Nov. 1972 in
(33) United States of America (US)
(44) Complete Specification published 12 Nov. 1975
(51) INT CL² C07C 177/00; A61K 31/19, 31/215; C07D 309/12//307/93
(52) Index at acceptance
C2C 1175 1176 147X 1672 200 201 202 204 20Y 213 215 220 225 226 227 22X 22Y 231 233 237 239 240 247 248 24X 253 258 25Y 26X 28X 292 294 295 29X 29Y 302 304 305 306 30Y 315 31Y 322 32Y 346 350 351 352 353 355 35Y 360 361 362 363 364 366 367 368 36Y 37X 386 387 388 389 38Y 401 402 409 40Y 431 435 43X 46Y 47X 490 491 500 502 504 509 50Y 620 623 624 625 628 633 634 635 638 643 648 652 655 658 65X 662 668 66X 672 679 67X 699 711 719 761 767 770 771 774 779 790 79Y BJ BU BW MV NC TA TU UF UL UN WD WJ
C3S 3B 3D 5 6 7B 7C 7D

(19)



(54) PROSTATRIENOIC ACID DERIVATIVES AND PROCESS

(71) We, SYNTEX CORPORATION, a Panamanian Corporation of Apartado Postal 7386, Panama, Panama, 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 certain novel prostaglandin derivatives, to a process for the production thereof and to certain novel intermediates obtained by this process.

More particularly, the present invention relates to prosta-4,5,13-*trans*-trienoic acid derivatives having oxygenated functions at C—9 and C—15 or at C—9, C—11 and C—15 positions of the molecule, and which may be further substituted at C—4, C—6 and/or C—15 by a methyl, ethyl or propyl group, as well as to the corresponding pharmaceutically acceptable, non-toxic esters, ethers and salts.

Prostaglandins are members of a new hormonal system with a remarkable range of biological and pharmaceutical properties. These compounds belong to a group of chemically related 20-carbon chain hydroxy fatty acids containing a five membered ring in the structure and different degrees of unsaturation, a number of which have been reported in the literature. For a review on prostaglandins and the definition of primary prostaglandins, see for example S. Bergström, *Recent Progress in Hormone Research*, 22, pp. 153—175 (1966) and *Science*, 157, page 382 (1967) by the same author.

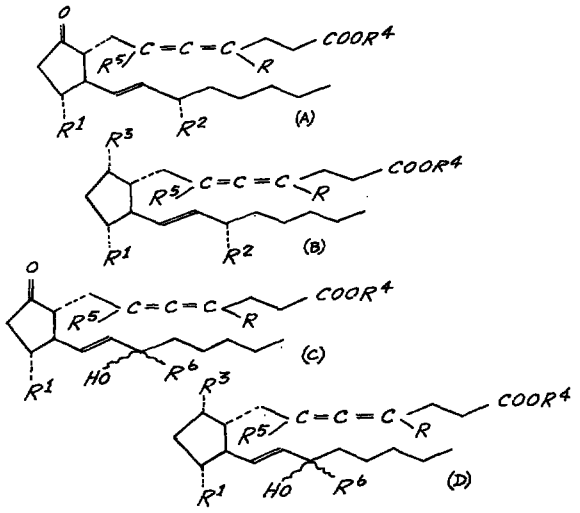
Prostaglandins are widely distributed in mammalian tissues and have been isolated from natural sources in very small amounts. In addition, a number of the naturally occurring prostaglandins have been prepared by chemical synthesis; note for example, *J. Am. Chem. Soc.*, 91, page 5675 (1969); *J. Am. Chem. Soc.*, 92, page 2586 (1970) and *J. Am. Chem. Soc.*, 93, pages 1489—1493 (1971) and references cited therein, W. P. Schneider et al., *J. Am. Chem. Soc.*, 90, page 5895 (1968); U. Axen et al., *Chem Commun.*, page 303 (1969) and W. P. Schneider, *Chem. Commun.*, page 304 (1969).

Because of the remarkable range of biological and pharmacological properties exhibited by this family of compounds, a great deal of interest has focused upon such compounds, and the preparation of analogs of such compounds; accordingly, we have discovered processes and intermediates for preparing modified prostaglandins and derivatives thereof.

[*Price 33p*]

SPECIFICATION AMENDED - SEE ATTACHED SLIP

The novel prostaglandin derivatives of the present invention can be represented by the following formulas:



wherein each of R and R^5 represents hydrogen, methyl, ethyl or propyl;

R^1 represents hydrogen, hydroxy or esterified or etherified hydroxy; each of R^2 and R^3 represents hydroxy or esterified or etherified hydroxy;

R^6 represents methyl, ethyl or propyl, and

R^4 represents hydrogen, a C_{1-4} alkyl group or the pharmaceutically acceptable, non-toxic salts of compounds in which R^4 is hydrogen; provided that if R^1 is not hydrogen it is the same as R^2 and R^3.

The dotted lines shown in the above formulas and in the formulas below indicate that the substituents are in α configuration, i.e., below the plane of the cyclopentane ring, and thus for convenience and simplicity depict one of the optically isomeric forms.

The wavy lines (§) indicate the α and β configuration, or mixtures thereof.

The double bond at C—13 in the compounds of the present invention has the same configuration as in natural prostaglandins of the PGE_1, PGE_2, $PGF_{1\alpha}$ or $PGF_{2\alpha}$ series, that is, the *trans* configuration.

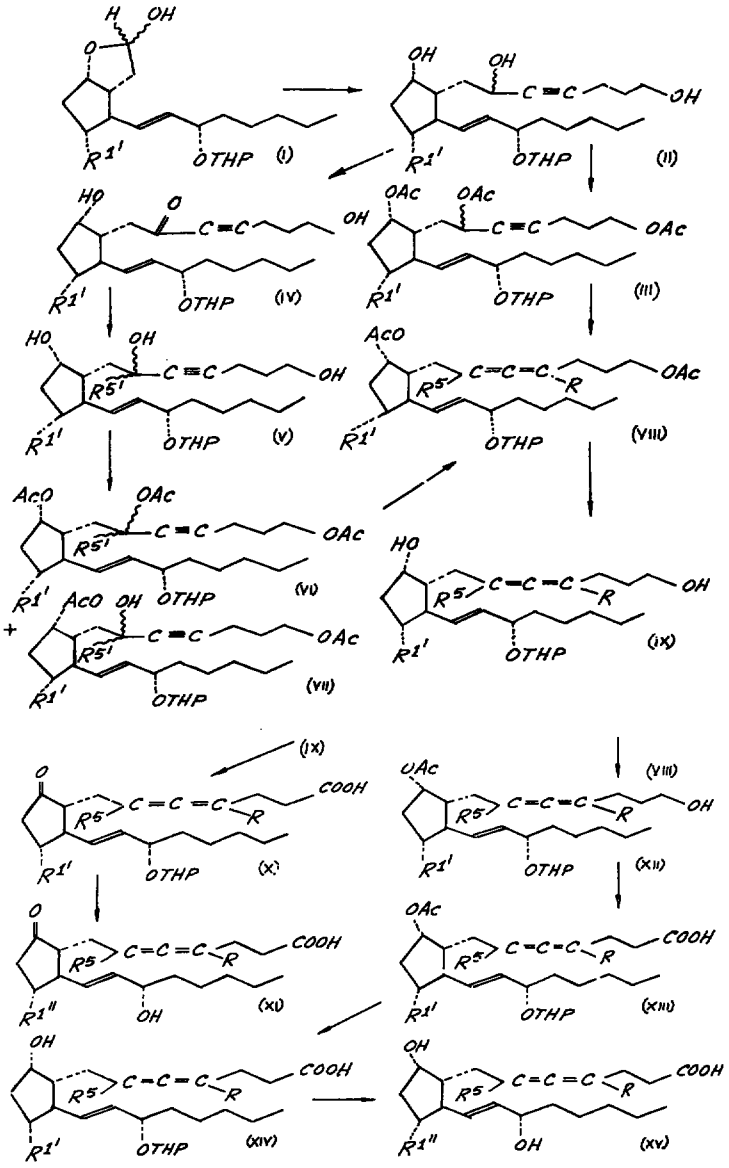
These novel compounds possess asymmetric centers and thus are produced as racemic mixtures. Notwithstanding the fact that one of the individual optical isomers, for convenience and simplicity, is depicted by formula herein, the present invention as claimed herein is directed to mixtures of the optical isomers.

The esterified or etherified hydroxy groups used herein are those physiologically acceptable hydrolyzable ester and ether groups employed in the pharmaceutical art which do not significantly adversely affect the pharmaceutical properties of the parent compound. The conventionally hydrolyzable esters are derived from hydrocarbon carboxylic acids. The term "hydrocarbon carboxylic acid" defines both substituted and unsubstituted hydrocarbon carboxylic acids. These acids can be completely saturated or possess varying degrees of unsaturation (including aromatic), can be of straight chain, branched chain, or cyclic structure, and preferably contain from one to 12 carbon atoms. In addition, they can be substituted by functional groups, for example, hydroxy, alkoxy containing up to 12 carbon atoms, nitro, amino and halogeno, attached to the hydrocarbon backbone chain. Typical conventional hydrolyzable esters thus included within the scope of the term and the present invention are acetate, propionate, butyrate, valerate, caproate, enanthate, caprylate, pelargonate, acrylate, undecenoate, phenoxyacetate, benzoate, phenylacetate, diphenylacetate, diethylacetate, trimethylacetate t-butylacetate, trimethylhexanoate, methylneopentylacetate, cyclohexylacetate, 3-cyclopentylpropionate, adamantoate, glycolate, methoxyacetate, hemisuccinate, hemiadipate, hemi-β-β-dimethylglutarate, acetoxyacetate, 2-chloro-4-nitro-benzoate, aminoacetate, diethylaminoacetate, piperidinoacetate, β-chloropropionate, trichloroacetate, β-chlorobutyrate, bicyclo-[2.2.2]-octane-1-carboxylate, and 4-methyl-bicyclo-[2.2.2]-oct-2-ene-1-carboxylate. The preferred conventional hydrolyzable ester is acetate.

Typical conventional hydrolyzable ethers include the tetrahydrofuran-2-yl, tetrahydropyran-2-yl and 4-methoxy-tetrahydropyran-4-yl ethers.

The salts are derived from pharmaceutically acceptable bases, and include metal salts such as sodium potassium, calcium, magnesium and aluminium, as well as organic amine salts such as ammonium, triethylamine, 2-dimethylamino ethanol, 2-(diethylamino)ethanol, lysine, arginine, caffeine, procaine, N-ethyl-piperidine and hydrabamine. The term "pharmaceutically acceptable" refers to salts which do not significantly adversely affect the properties of the parent compound.

The novel prostaglandin derivatives of the present invention except those which are further substituted at C—15 by a methyl, ethyl or propyl group can be obtained by a process illustrated by the following sequence of reactions:



wherein R and R^5 have the above-indicated meaning;

$R^{1'}$ is hydrogen or tetrahydropyran-2-yloxy;

$R^{1''}$ is hydrogen or hydroxy;

$R^{5'}$ is methyl, ethyl or propyl;

Ac is an acyl group containing from 1 to 4 carbon atoms, particularly acetyl and THP is tetrahydropyran-2-yl.

In practicing the above illustrated process the starting material [2′α-hydroxy-4′α-tetrahydropyran-2‴-yloxy-5′β-(3″α-tetrahydropyran-2‴-yloxyoct-1″-*trans*-enyl)cyclopent-1′α-yl]acetaldehyde-γ-hemiacetal or [2′-hydroxy-5′β-(3″α-tetrahydropyran-2‴-yloxyoct-1″-trans-enyl) cyclopent-1′α-yl]acetaldehyde-1,2′-hemiacetal (I) is treated with an excess of the dilithium salt of pent-4-yl-1-ol, in a suitable inert organic solvent to produce the corresponding trihydroxyacetylenic compound of formula II.

The dilithium salt of pent-4-yn-1-ol reagent is used in amounts comprised between about 5 to about 15 molar equivalents per molar equivalent of starting hemiacetal, using preferably about 10 molar equivalents. This reagent is prepared by reaction of pent-4-yn-1-ol and methyl lithium in diethyl ether solution, at a temperature of about −78°C to −50°C., under an inert atmosphere, such as provided by nitrogen or argon, for a period of between 15 to 24 hours, preferably for about 18 hours. The reagent thus prepared is combined with a solution of the hemiacetal of formula I in an ethereal solvent, maintaining the reaction mixture at a temperature comprised between 10°C to 30°C for about 4 to 10 hours, the reaction time depending upon the temperature used. In the preferred embodiments the reaction is conducted at room temperature (about 25°C.) for approximately 6 hours under substantially anhydrous conditions and under an inert atmosphere.

Suitable solvents for this reaction are dimethyl ether, diethyl ether, dipropyl ether and 1,2-dimethoxyethane, particularly diethyl ether.

The product is isolated by dilution with water, extraction with an organic solvent immiscible with water and evaporation of the solvent under reduced pressure, taking care that the temperature does not exceed 20°C. The trihydroxylated compound is purified by column chromatography to separate it from the undesired non-polar by-products. There is obtained a mixture of the 6α and 6β-hydroxy isomers, which can be separated into the individual isomers by thin layer chromatographic techniques, if desired.

Compound of formula II is then esterified under conventional conditions, i.e., using a carboxylic acid chloride or carboxylic acid anhydride in pyridine solution to produce the corresponding triester, the compounds of formula III. The preferred esterifying agent is acetyl chloride, conducting the reaction at room temperature for about 6 hours. In the case of using a carboxylic anhydride, e.g., acetic anhydride, the esterification is slower, requiring reaction times of the order of 12 to 18 hours or higher temperatures to obtain complete esterification.

Upon selective oxidation of the trihydroxyacetylenic compound of formula II, for example with manganese dioxide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in a suitable inert organic solvent, e.g., chloroform or tetrahydrofuran, there is produced the corresponding dihydroxy-keto-acetylenic compound of formula IV. This reaction is conducted at room temperature for a period of time of about 4 to 6 hours under vigorous stirring, using a large excess of the oxidizing agent. The oxidizing agent is then separated by filtration and the reaction product isolated by conventional techniques, such as evaporation of the solvent and purification of the residue by thin layer chromatography.

The compounds of formula IV are converted into the corresponding 6-alkylated derivatives of formula V by reaction with methyl, ethyl or propyl lithium or the corresponding alkyl magnesium halides. The reaction is typically effected at a temperature in the range of 10°C. to 30°C., preferably at room temperature using an excess of about 2 to 10 molar equivalents, of the alkylating agent per mole of starting material, and preferably about 4 molar equivalents, in a suitable inert organic solvent, using particularly ethereal solvents such as diethyl ether and tetrahydrofuran for a period of time of about 30 minutes to 2 hours depending upon the temperature used. The course of the reaction can be followed by t.l.c. The product is isolated from the reaction mixture by conventional means, such as dilution with water, extraction with an organic solvent immiscible with water and evaporation of the solvent under vacuo, at low temperature, followed by purification by thin layer chromatography, obtaining a mixture of 6α-hydroxy-6β-alkyl- and 6β-hydroxy-6α-alkyl compounds of formula V.

The compounds of formula V are then esterified *via* formation of the lithium salts, followed by reaction with a carboxylic acid chloride in pyridine solution, to produce the corresponding triester of formula VI, in mixture with the diesterified compound of formula VII, which are separated by chromatographic techniques. Thus, the compounds of formula V are allowed to react at room temperature with at least 3 molar equivalents of methyl lithium in diethyl ether solution, for a period

of time of the order of 1 to 5 hours, preferably for about 3 hours, after which time there is added an excess of the acyl chloride, using particularly acetyl chloride and pyridine, maintaining the reaction mixture at room temperature for several hours to effect esterification, preferably for about 12 to 18 hours. The esterified products are then isolated from the reaction mixture in a conventional manner, preferably by dilution with water, extraction with a solvent immiscible with water, evaporation and separation of the triesterified and diesterified compounds of formulas VI and VII respectively, by chromatography.

The allenic compounds of formula VIII, substituted or unsubstituted at C—4 and unsubstituted at C—6 (VIII, R=H, Me, Et or Pr and R^5 H) can be obtained by reaction of a triacyloxy acetylenic compound of formula III with a lithium dialkyl copper reagent. The reaction is conducted under an inert atmosphere, i.e., under argon or nitrogen atmosphere, in an ether solvent. The dialkyl copper reagents used are those wherein the dialkyl radicals are the same, each alkyl group containing from 1 to 3 carbon atoms, e.g., lithium dimethyl copper, lithium diethyl copper, and lithium dipropyl copper, particularly lithium dimethyl copper. These reagents can be prepared by reaction of cuprous iodide with an alkyl lithium in diethyl ether as solvent, as described for example by P. Rona et al. in *J. Am. Chem. Soc.* 91, 3289(1969).

In this transformation, the reaction conditions and the amount of the lithium dialkyl copper used determine the product obtained. Thus, when the reaction is conducted at very low temperatures, i.e., at temperatures of the order of −50°C to −78°C for typically about 3 to 7 hours, using about four molar equivalents of the dialkyl copper reagent, employing especially dimethyl copper as reagent, there is obtained the allenic compound unsubstituted at C—4 and C—6 (VIII, R and R^5=H). The reaction can be followed by t.l.c.; at temperatures of about 70°C the reaction is complete within about 5 hours. When the reaction is effected at about 0°C. for the same typical reaction time, but using only about one molar equivalent of the organocopper reagent there are obtained the 4-alkyl substituted allenes (VIII, R=Me, Et, Pr, R^5- H) in which the alkyl group corresponds to the alkyl group of the reagent.

In any case, the allenic compounds are isolated from the reaction mixture *via* conventional techniques, such as dilution with ammonium chloride solution, extraction, evaporation of the solvent and purification by chromatography, avoiding temperatures higher than room temperature.

When the above described reactions with a lithium dialkyl copper are effected upon the 6-alkyl-triesters of formula VL, there are obtained the corresponding 6-alkyl- or 4,6-dialkyl allenes of formula VIII (R- H, Me, Et, Pr; R^5 Me, Et, Pr), the 6-monoalkylated compounds being obtained when the reaction is conducted using about 4 molar equivalents of the lithium dialkyl copper as reagent, at about −70°C, and the dialkyl derivatives when there is used about 1 molar equivalent of the organocopper reagent, at about 0°C., as described hereinbefore for the 6 unsubstituted compounds.

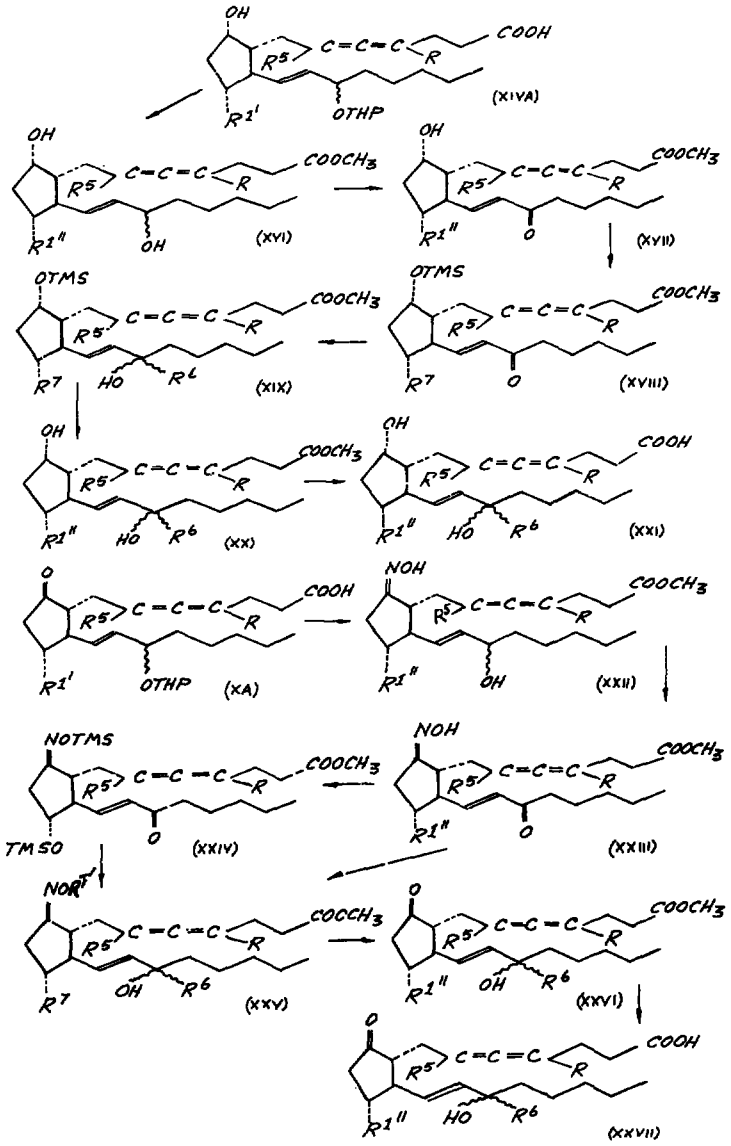
The acyloxy groups in any of the allenic compounds represented by formula VIII are then hydrolyzed under alkaline conditions, using a dilute solution of an alkali metal hydroxide or alkali metal carbonate in a lower aliphatic alcohol, at room temperature or below for a period of time sufficient to complete the reaction, ranging from about 12 to about 24 hours. The preferred reagent used is anhydrous (calcined) potassium carbonate using methanol as solvent, for a period of time of about 6 to 18 hours, thus obtaining the corresponding dihydroxy compound of formula IX.

Upon oxidation of a dihydroxy compound of formula IX with for example chromium trioxide, using particularly the stoichiometric amount of an 8N solution of chromic acid in acetone solution in the presence of sulfuric acid at about −10°C for about 2 hours (Jones' reagent) there is produced the corresponding keto acid derivative of formula X, whose tetrahydropyranyloxy groups are hydrolyzed, for example under mild acidic conditions, to yield the prostatrienoic acid compounds of formula XI, namely 9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, 9-oxo-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid, the 4 or 6-methyl, ethyl or propyl- and 4,6-dialkyl derivatives thereof, in which the alkyl groups can be alike or different. This hydrolysis is carried out using preferably an aqueous solution of a weak acid such as acetic acid, oxalic acid and tartaric acid. Conveniently, the crude compound of formula X is dissolved in an organic solvent miscible with water, e.g. tetrahydrofuran and dioxane, before addition of the acid reagent. The reaction is conducted at a temperature comprised between 20°C. to 50°C., for a

period of time of about 4 to 18 hours, depending upon the temperature used. The preferred reagent is aqueous acetic acid, at concentrations of 40 to 80% V/V. It is particularly convenient to use a 65:35 acetic acid-water mixture. However, other concentrations are also practical.

By reaction of the diacyloxy allenic compounds of formula VIII with 1.1 molar equivalents of anhydrous potassium carbonate in methanol solution, at about 0°C., there is selectively saponified the primary acyloxy group. This selective hydrolysis can be followed by t.l.c.; generally, it is complete in about 90 minutes to about 2 hours. The compounds of formula XII thus-obtained are oxidized with 8N chromic acid as described hereinabove for the dihydroxylated allenes, to produce the corresponding carboxylic acid, i.e., the compounds of formula XIII. The protecting groups are in turn hydrolyzed by the above-described methods, i.e., the acyloxy group is hydrolyzed under alkaline conditions, using preferably anhydrous potassium carbonate in methanol, at room temperature or below, to yield the compounds of formula XIV, in which the tetrahydropyranyloxy groups are cleaved by for example mild acid treatment, using particularly 65% aqueous acetic acid, thus obtaining the trihydroxy prostatrienoic acid derivatives of formula XV, namely 9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid, 9α15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid and the 4 or 6-methyl, ethyl or propyl and the 4,6-dialkyl derivatives thereof in which the alkyl group can be the same of different.

The novel prostaglandin derivatives of the present invention further substituted at C—15 by a methyl, ethyl or propyl group can be obtained by a process illustrated by the following sequence of reactions, in which for the sake of convenience and simplicity the formulas are depicted in one of the optically isomeric forms.



wherein R, $R^{1'}$, $R^{1'''}$, R^5 and R^6 have the above-indicated meanings; R^7 is hydrogen or trimethylsilyloxy; TMS is trimethylsilyl ($Si[CH_3]_3$); and $R^{7'}$ is hydrogen or trimethylsilyl.

In practicing the process illustrated above a compound of formula XIVA, in which the hydroxyl group at C—15 is in α or β-configuration, or mixtures thereof, the β-isomer being prepared by the above described process (I through VIII→XII→XIV) but starting from the corresponding 3''β tetrahydropyranyloxy isomer of compound of formula I, is converted into an alkyl ester, preferably into the methyl ester, by reaction with diazomethane in ether solution, and thereafter the tetrahydropyranyloxy groups present hydrolyzed with, for example 65% V/V aqueous acetic acid, as described hereinabove to yield the corresponding compound of formula XVI, which is selectively oxidized at C—15, for example with manganese dioxide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in a suitable inert organic solvent, e.g., chloroform and tetrahydrofuran, to produce the corresponding 15-oxo compound of formula XVII. This reaction is conducted at room temperature, for a period of time of about 18 to 40 hours, under vigorous stirring using a large excess of the oxidizing agent. The oxidizing agent is added portion-wise at 4—6 hours intervals, and the course of the reaction can be followed by thin layer chromatography or by periodic determination of the ultraviolet spectrum. When the reaction is complete the oxidizing agent is separated by

filtration and the reaction product isolated by conventional techniques such as evaporation of the solvent and purification of the residue by thin layer chromatography or chromatography on Florisil.

Compound XVII is then converted into the corresponding mono- or ditrimethylsilyl ether of formula XVIII by procedures known in the art, see for example Pierce, "Silylation of Organic Compounds", Pierce Chemical Co., Rockford, 111. (1968). Conveniently, this reaction can be done by using a mixture of hexamethyldisilazane and trimethylchlorosilane as etherifying agent.

Upon reaction of the trimethylsilyloxy compound with a slight molar excess of an alkyl lithium or an alkyl-magnesium halide in which the alkyl group is methyl, ethyl or propyl, using particularly methyl, ethyl or propyl-lithium or methyl-, ethyl- or propylmagnesium bromides as reagents there are obtained the corresponding 15ξ-alkyl-15ξ-hydroxy compounds of formula XIX. In the preferred embodiments, the reaction is carried out using 1.1 to 1.2 molar equivalents of the alkylating agent per molar equivalent of starting compound, using diethyl ether or tetrahydrofuran as solvents, at a temperature comprised between -78°C. to room temperature, for a period of time of the order of 2 to 10 hours and under an inert atmosphere, preferably under argon atmosphere. The silyloxy groups of the crude mixture of alkylated compounds are immediately hydrolyzed to afford the compounds of formula XX. The hydrolysis is effected by following known methods for transforming silyl ethers into alcohols, and preferably by dissolving the compound of formula XIX in a lower aliphatic alcohol-water mixture, e.g., 50—80% aqueous methanol or ethanol, maintaining the solution at a temperature of between 0°C. to room temperature for a period of time of about 18 hours to several days, the reaction time depending upon the temperature at which the hydrolysis takes place. This hydrolysis can be optionally done in the presence of a small amount of an organic or inorganic acid, or in the presence of carbon dioxide which will hasten the cleavage of the trimethylsilyloxy groups.

The mixture of 15α-hydroxy-15β-alkyl- and 15β-hydroxy-15α-alkyl compounds of formula XX is separated at this stage by thin-layer chromatographic techniques, and the methyl ester group in the individual isomers is in turn hydrolysed by chemical or enzymatic methods, to yield the corresponding 15α-hydroxy-15β-alkyl and 15β-hydroxy-15α-alkyl prostatrienoic acids of formula XXI.

When this hydrolysis is effected chemically, the alkyl ester compound of formula XX is dissolved in a lower aliphatic alcohol such as methanol or ethanol and treated with an aqueous solution of an alkali metal carbonate, e.g. sodium carbonate or potassium carbonate at a temperature above room temperature, of the order of about 30°C. to 50°C., preferably at about 40°C. for a period of time of about 12 to 20 hours, preferably for about 16 hours, thus yielding, after acidification, the corresponding prostatrienoic acid compound of formula XXI. This hydrolysis is preferably conducted under an inert atmosphere, i.e., under nitrogen or argon atmosphere.

Compound XX can be alternatively hydrolyzed by using enzymes in aqueous solutions. For this enzymatic hydrolysis, there is preferably used a crude pancreatic lipase commercially available (Sigma Steapsin), however, other enzyme systems which are known as useful for the hydrolysis of compounds unstable to alkaline or acid conditions can also be practical. Other lipases obtainable from bacterial sources, such as the partially purified lipase obtained from *Corynebacterium acnes* culture supernatant can also be used, or a lipase of those that are known to act on water insoluble esters of long chain fatty acids (L. Sarda et al, *Biochem. Biophys. Acta.* 23:264 (1957)), or baker's yeast (C. J. Sih et al, *J. C. S. Chem. Comm.* 240 (1972)).

The hydrolysis of compound XX with the crude pancreatic lipase can be conducted in a buffered aqueous solution containing sodium chloride and calcium chloride, at a neutral or almost neutral pH, at a temperature of between 22°C. to 30°C., preferably at about 25°C. to 27°C., adjusting the pH of the reaction mixture to 7.2 to 7.4 by addition of, for example dilute sodium hydroxide solution, at intervals. Compound of formula XX is dissolved in the previously prepared buffered lipase aqueous solution by sonication at about 37°C. using from about 0.5 ml. to about 1 ml. of the lipase solution per milligram of substrate. The methyl ester group is readily hydrolyzed within a short period of time, of the order of 5 minutes to 1 hour. The course of the reaction can be followed by thin layer chromatography; when the hydrolysis is complete, the free acid can be isolated from the reaction mixture by conventional techniques, such as acidification with a dilute acid solution, e.g., using dilute hydrochloric acid, extraction with a solvent

immiscible with water such as diethyl ether, ethyl acetate, chloroform and methylene chloride, evaporation of the solvent and purification of the residue by column chromatography, thin layer chromatography or liquid chromatography; good results in the separation of the acid XXI from the lipase have been obtained by column chromatography on Florisil (Registered Trade Mark).

By esterification of the carboxylic acid function of compounds of formula X or the 15β-tetrahydropyranyloxy epimers (both represented by formula XA), with an ethereal solution of diazomethane followed by hydrolysis of the tetrahydropyranyloxy functions present in the molecule with aqueous acetic acid, as described hereinbefore, and protection of the 9-oxo group as the oxime by known methods, i.e., by reaction with hydroxylamine hydrochloride in aqueous methanol and in the presence of sodium acetate, conducting the reaction at room temperature for about 16 to 24 hours, there is obtained the corresponding compound of formula XXII. This compound is then selectively oxidized, for example with manganese dioxide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone as described hereinabove in detail for the obtention of compound XVII, to produce the corresponding 15-oxo compound of formula XXIII.

By reaction of a compound of formula XXIII, ($R^{1'''}$=hydroxy) with a silylating agent, using particularly a mixture of hexamethyldisilazane and trimethylchlorosilane there is produced the corresponding trimethylsilyloxy derivative represented by formula XXIV.

Treatment of compound XXIII ($R^{1'''}$=H) or compound XXIV with a slight molar excess of an alkyl (methyl, ethyl or propyl) lithium or the corresponding alkyl magnesium halide, there is obtained the corresponding 15ξ-alkyl-15ξ-hydroxy compound of formula XXV [mixture of 15(R) and 15(S) isomers]. This reaction is preferably carried out in ether or tetrahydrofuran solution, using 1.1 to 1.2 molar equivalents of the alkylating agent per molar equivalent of starting compound, at a temperature of between −78°C. to room temperature, for a period of time of 2 to 10 hours, under an inert atmosphere.

The mixture of 15α-hydroxy-15β-alkyl and 15β-hydroxy-15α-alkyl compounds [15 (S) and 15 (R) prostatrienoic acid derivatives, respectively] is separated into the individual isomers by thin layer chromatography, (previous hydrolysis of the trimethylsilyloxy group when present with aqueous methanol) and thereafter the oxime is hydrolyzed to regenerate the 9-oxo function, thus producing the separated 15 (R) and 15 (S) prostatrienoic acid ester compounds of formula XXVI. The deoximation reaction is effected under mild conditions, for example by the methods described by E. J. Corey et al, in *J. Am. Chem. Soc.* 92, 5276 (1970) or A. McKillop et al, *J. Am. Chem. Soc.* 93, 4918 (1971) and references cited therein.

The first method involves the conversion of the oxime into the *O*-acetate derivative followed by reaction with an excess, using at least 2 molar equivalents, of chromous acetate in 90% aqueous tetrahydrofuran, at a temperature of the order of 25°C. to 65°C. for about 10 to 24 hours.

The second method comprises treatment of the oxime with thallium (III) nitrate, using about 1 to 1.1 molar equivalents of the reagent per mole of starting compound. The reaction is conducted at room temperature or below for a short period of time, of the order of 5 to 30 minutes, in an inert organic solvent, followed by filtration of the thallium (I) nitrate which precipitates, and brief treatment of the filtrate with dilute acid to decompose the intermediate nitroso compound. In accordance with our invention, this reaction is conducted in methanol solution, at about 20°C. using aqueous acetic acid to decompose the nitroso intermediate.

Hydrolysis of the oxime can also be effected using titanium trichloride as described by Timms and Wilsmith, *Tetrahedron Letters*, 195 (1971).

Alternatively the compounds of formula XXVI (wherein $R^{1'''}$ is hydrogen are obtained by oxidation of the compounds of Formula XX (wherein $R^{1'''}$ is hydrogen) with chromium trioxide-dipyridine complex (prepared as described by J. C. Collins et al, *Tetrahedron Letters*, 3363 (1968)].

Alternatively the compounds of formula XXVI (wherein $R^{1'''}$ is hydroxyl) are obtained by treating the compounds of formula XX (wherein $R^{1'''}$ is hydroxyl) according to the method disclosed by E. W. Yankee et al., *J. A. C. S.*, 94,3651 (1972)]; namely, selective silylation at the 11-position of XX (wherein $R^{1'''}$ is hydroxyl), followed by oxidation with Collins' reagent and subsequent hydrolysis with aqueous methanol containing a trace of acetic acid to yield the compounds of formula XXVI (wherein $R^{1'''}$ is hydroxyl).

Alternatively, the hydrolysis of the oxime can be effected on the mixture of

the 15 (R) and 15 (S) isomers, separating the individual isomers afterwards by thin layer chromatography.

The alkyl ester group in compounds of formula XXVI is hydrolyzed by chemical or enzymatic methods, e.g., by reaction with potassium carbonate in aqueous methanol or with a crude pancreatic lipase, respectively, as described hereinbefore in detail for the 9α-hydroxylated compounds, thus producing the free acids of formula XXVII.

The hydroxyl groups in compounds of formulas XI and XV and the secondary hydroxyl groups in compounds of formulas XXI and XXVII can be esterified or etherified in a conventional manner, to produce mono-, di-, or triesters, or mono, di or triethers, depending upon the particular prostaglandin derivatives. Esterification can be accomplished by reaction of the hydroxylated compound with a carboxylic acid anhydride or chloride of less than 12 carbon atoms in pyridine solution.

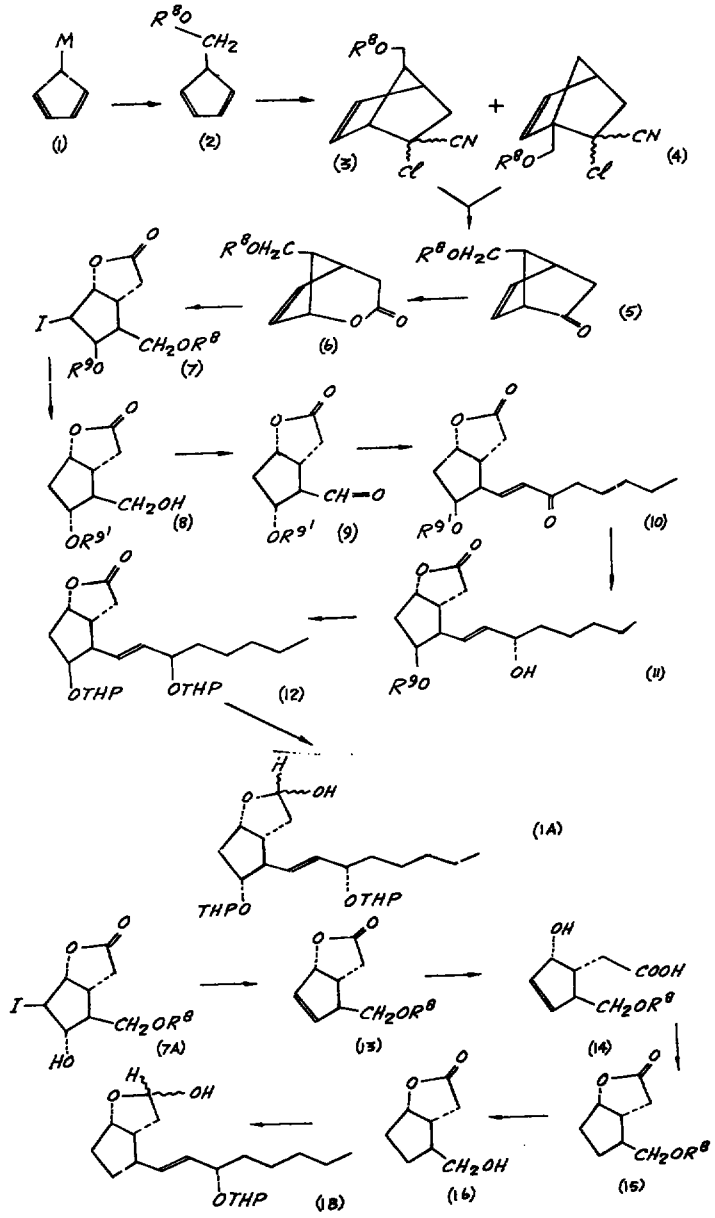
Etherification can also be carried out by conventional techniques. For example, reaction with dihydropyran, dihydrofuran or 4-methoxy-5,6-dihydro-2H-pyran in an inert solvent such as, for example, methylene chloride or benzene and in the presence of an acid catalyst (e.g. *p*-toluene-sulfonic acid, *p*-toluenesulfonyl chloride) produces the tetrahydropyran-2'-yloxy, tetrahydrofuran-2'-yloxy or 4'-methoxytetrahydropyran-4'-yloxy derivatives, respectively.

Although the esterification or etherification reactions are usually effected using an excess of the esterifying or etherifying agents, it is preferably to use at least one molar equivalent of said reagents per hydroxyl group present in the starting compound.

The alkyl esters of the carboxylic acid function can be prepared by treatment of the free acid with an excess of diazoalkane such as diazomethane, diazoethane or diazopropane in ether or methylene chloride solution, in a conventional manner, or by reaction with the desired lower alkyl iodide in the presence of lithium carbonate, at room temperature.

The salts of the prostanoic acids of the present invention can be prepared by treating the corresponding free acids with about one molar equivalent of a pharmaceutically acceptable base per molar equivalent of free acid. Suitable pharmaceutically acceptable bases include, for example, sodium hydroxide, trimethylamine, triethylamine, tripropylamine, β-(dimethylamino)ethanol, β-(diethylamino)ethanol, arginine, lysine, caffeine and procaine. Typically, the reaction is conducted in an aqueous solution, alone or in combination with an inert, water miscible organic solvent, at a temperature of about from 0° to 30°C, preferably at room temperature. Typical inert, water miscible organic solvents include methanol, ethanol, isopropanol, butanol and dioxane. When divalent metal salts are prepared such as the calcium salts or magnesium salts, the free acid starting material is treated with at least one half molar equivalent of the pharmaceutically acceptable base.

The compounds of formula I used as starting materials in the above described processes can be obtained by the following sequence of reactions:



wherein R^8 represents methyl or benzyl;

R^9 represents hydrogen or *p*-phenylbenzoyl;

$R^{9'}$ represents *p*-phenylbenzoyl and

M represents sodium or thallium.

Briefly, this method comprises the reaction of cyclopentadienylsodium or cyclopentadienyl thallium (*1*), obtained by reaction of cyclopentadiene with sodium hydride or aqueous thallous sulfate in the presence of potassium hydroxide (E. J. Corey et al, *J. Am. Chem. Soc.* 93, 1489 (1971)), with a slight excess of chloromethyl methyl ether or chloromethyl benzyl ether in tetrahydrofuran at approximately −55°C., to yield respectively the 5-methoxymethyl-1,3-cyclopentadiene *2*, (R^8=methyl) or 5-benzyloxymethyl-1,3-cyclopentadiene *2*, (R^8=benzyl) which are subjected to the Diels Alder reaction with an excess (about 5 molar equivalents) of 2-chloroacrylonitrile in the presence of cupric fluoroborate as catalyst to yield a mixture of the *endo-exo* cyano nitriles of formulas (*3*) and (*4*) (R^8=methyl or benzyl, respectively). This mixture of stereoisomeric nitriles is treated with potassium hydroxide in dimethyl sulfoxide to yield the *anti*-bicyclic ketones of formula (*5*), i.e. 7-*syn*-methoxymethyl-2-norbornen-5-one (R^8 methyl)

or 7-*syn*-benzyloxymethyl-2-norbornen-5-one (R^8 benzyl) respectively, which upon reaction with a slight molar excess of *m*-chloroperbenzoic acid in methylene chloride in the presence of sodium bicarbonate results in selective Baeyer-Villiger oxidation to form the corresponding lactone (*6*), namely 2-oxa-8-*syn*-methoxymethylbicyclo (3.2.1)oct-6-en-3-one, (R^8 methyl) and 2-oxa-8-*syn*-benzyloxymethylbicyclo (3.2.1) oct-6-en-3-one (R^8 benzyl). Saponification of the foregoing lactones of formula (*6*) with 2.5 equivalents of sodium hydroxide in aqueous methanol, followed by neutralization with carbon dioxide and treatment with 2.5 equivalents of aqueous potassium triiodide solution at 0—5°C. produce the respective hydroxy-iodolactones of formula (*7*), namely (2'α,4'α-dihydroxy-3'β-iodo-5'β-methoxy-methylcyclopent-1'α-yl) acetic acid, γ-lactone (R^8=methyl, R^9=H) and (2'α,4'α-dihydroxy-3'β-iodo-5'β-benzyl-oxymethylcyclopent-1'α-yl) acetic acid, γ-lactone (R^8=benzyl, R^9=H), which are esterified with *p*-biphenylcarboxylic acid chloride in pyridine, under conventional conditions to yield the corresponding *p*-phenylbenzoates (*7*, R^9= *p*-phenylbenzoyl).

These compounds are then submitted to deiodination using tri-n-butyl tin hydride in the presence of catalytic amounts of azobisisobutyronitrile in benzene solution, and thence to cleavage of the 5'β-benzyloxymethyl or 5'β-methoxymethyl group to produce the hydroxymethyl compound (*8*).

The benzyloxymethyl group is cleaved by hydrogenolysis in the presence of palladium-charcoal and perchloric acid as catalysts, in a suitable organic solvent; the methoxymethyl group is hydrolyzed by reaction with boron tribromide in methylene chloride, at a temperature comprised between about 78°C. to 0°C.

Oxidation of a hydroxymethyl compound (*8*) with chromium trioxide-dipyridine complex (prepared as described by J. C. Collins et al in *Tetrahedron Letters* 3363 (1969)) in methylene chloride, at about 0°C. affords the aldehyde (9), which without purification is transformed stereo-specifically into the *trans*-enone lactone of formula (*10*) by treatment with the sodium anion of dimethyl 2-oxoheptylphosphonate in dimethoxyethane, at room temperature for about 2 hours. Treatment of the enone with an excess of zinc borohydride in dimethoxyethane, at room temperature for about 1 hour produces a mixture of α and β-hydroxy compounds, which is separated by thin layer chromatography on silica gel to obtain the desired α-hydroxylated compound in pure form (*11*, R^9 *p*-phenylbenzoyl). The *p*-phenylbenzoyloxy group is then hydrolyzed under alkaline conditions, using preferably anhydrous potassium carbonate in methanol, and the diol is etherified with dihydropyran in methylene chloride solution and in the presence of *p*-toluenesulfonic acid, to give the bistetrahydropyranyloxy compound (*12*), which by reduction with diisobutylaluminum hydride in toluene, at about −60°C produces the lactol, namely [2'α-hydroxy-4'α-tetrahydropyran-2'''-yloxy-5'-β-(3''α-tetrahydropyran-2'''-yloxyoct-1''-*trans*-enyl) cyclopent-1'α-yl] acetaldehyde-γ-hemiacetal, (I A).

By reaction of a hydroxy iodolactone of formula (*7A*) with freshly distilled phosphorus oxychloride in pyridine solution, first at 0°C. and thereafter at room temperature there is obtained the dehydrolactone compound of formula (13). In order to prevent hydrogenolysis of the allylic hydroxyl during the reduction of the double bond, the lactone group is opened by treatment with 2N methanolic sodium hydroxide followed by careful neutralization with 3N hydrochloric acid in ethyl acetate to pH—6, to produce the hydroxyacid (*14*). Catalytic reduction of this hydroxyacid with Raney nickel in methanol solution followed by brief exposure to acid produces the lactone (*15*), which is hydrolyzed to the hydroxymethyl compound (*16*) by the abovementioned methods, i.e., by hydrogenolysis in the case of the benzyloxymethyl compound (15, R^8 benzyl) or by reaction with boron tribromide for the methoxymethyl derivative (*15*, R^8 methyl).

The hydroxymethyl compound of formula (*16*) is then converted into the desired [2'α-hydroxy-5'β-(3''α-tetrahydropyran-2'''-yloxyoct-1''-*trans*-enyl) cyclopent-1'α-yl acetaldehyde γ-hemiacetal, the compound of formula (*IB*) by oxidation with chromium trioxide-dipyridine complex to the aldehyde, condensation of the aldehyde with the sodium anion of dimethyl 2-oxoheptylphosphonate to produce the *trans* enone lactone, selective reduction of the oxo group with zinc borohydride to yield [2'α-hydroxy-5'β-(3''αhydroxyoct-1''-*trans*-enyl) cyclopent-1'α-yl] acetic acid γ-lactone, in mixture with the 3''β-hydroxy isomer, separation of the isomers by thin layer chromatography, etherification of the 3''α-hydroxy compound with dihydropyran and reduction of lactone ring with diisobutyllaluminum hydride, as described in detail hereinbefore with regard to the transformation of compund (*9*) into compound (*IA*).

The compounds, esters and salts of the invention exhibit prostaglandin-like biological activities and thus are useful in the treatment of mammals where the use of prostaglandins are indicated. The compounds, esters and salts of the invention are bronchodilators and thus are useful in treating mammals for bronchial spasm or wherever strong bronchodilators are indicated. These compounds are also useful in controlling or palliating hypertension in mammals and further exhibit central nervous system depressant activity in mammals, and are useful as sedatives. In addition, the compounds are useful for inducing labor, in pregnancy, and for inducing menses to correct or reduce menstrual abnormalities.

The compounds and/or salts, of the invention, can be administered in a wide variety of dosage forms, either alone or in combination with other pharmaceutically compatible medicaments, in the form of pharmaceutical compositions suited for oral or parenteral administration or inhalation in the case of bronchodilators. The compounds are typically administered as pharmaceutical compositions consisting essentially of the compounds and/or salts, of the invention, and a pharmaceutical carrier. The pharmaceutical carrier can be either a solid material, liquid or aerosol, in which the compound and/or salt is dissolved, dispersed or suspended, and can optionally contain small amounts of preservatives and/or pH-buffering agents. Suitable perservatives which can be used include, for example, benzyl alcohol. Suitable buffering agents include, for example, sodium acetate and pharmaceutical phosphate salts.

The liquid compositions can, for example, be in the form of solutions, emulsions, suspensions, syrups, or elixirs. The solid compositions can take the form of tablets, powders, capsules or pills, preferably in unit dosage forms for simple administration or precise dosages. Suitable solid carriers include, for example, pharmaceutical grades of starch, lactose, sodium saccharin, talcum and sodium bisulfite.

For inhalation administration, the compounds and/or salts can, for example, be administered as an aerosol comprising the compounds or salts in an inert propellant together with a co-solvent (e.g. ethanol) together with optional preservatives and buffering agents. Additional general information concerning the inhalation administration of aerosols can be had by reference to U.S. Patents 2,868,691 and 3,095,355.

The compounds of this invention are typically administered in dosages of about from 0.1 to 10 mg. per kg. of body weight. The precise effective dosage will, of course, vary depending upon the mode of administration, condition being treated and host.

The following Preparations and Examples illustrate the invention, but are not intended to limit its scope. Also unless expressly stated to the contrary, racemic mixtures are used as starting materials, and correspondingly, racemic mixtures are obtained as products. The abbreviation t.l.c. refers to thin-layer chromatography and all mixture ratios used with regard to liquids refer to volume ratios. Also, where necessary, preparations and examples are repeated to provide sufficient starting material for subsequent Examples. Examples 1 to 4, 7, 10 to 13, 15, 21, 26 and 27 describe the preparation of intermediates and starting materials.

PREPARATION 1.

A. To a stirred solution of 125 g. of thallium sulfate and 50 g. of potassium hydroxide in 750 ml. of water are added, under an atmosphere of argon, 43 ml. of freshly distilled cyclopentadiene and the mixture is vigorously stirred for 10 minutes; the yellow precipitate formed is filtered off, washed with ice water, methanol and ether, to yield 132 g. of cyclopentadienylthallium.

B. A mixture of 216.28 g. of benzyl alcohol, 61.44 g. of paraformaldehyde, 481.6 g. of anhydrous magnesium sulfate and 1,200 ml. of methylene chloride is cooled to a temperature of between −50°C. to −55°C. in a dry ice-acetonitrile bath, and the stirred cold solution is saturated with anhydrous hydrogen chloride gas. The reaction mixture is kept at −50°C. to −55°C. for 10 minutes further, and then the excess of hydrogen chloride is eliminated by passing a stream of nitrogen during 30 minutes. The reaction mixture is filtered and the solid material washed well with pentane, and the combined filtrates are evaporated to dryness at a temperature below 30°C., to produce an oil which is distilled under reduced pressure to yield chloromethyl benzyl ether.

C. A suspension of 132 g. of cyclopentadienylthallium in 200 ml. of anhydrous ether is cooled to −20°C. in a dry ice-carbon tetrachloride bath. To the cooled mixture are added under stirring and under an argon atmosphere, in a 15-minute

period, 90 g. of chloromethyl benzyl ether. The reaction mixture is stirred for 3—1/2 hours at −20°C., it is then filtered in a filtration flask previously cooled to −78°C. and the solid precipitate washed with cold pentane (78°C.).

The filtered solution is immediately added to a mixture of 216 g. of anhydrous α-chloroacrylonitrile and 30 g. of anhydrous cupric fluorborate, previously cooled to −78°C. The reaction mixture is evaporated to half its original volume at a temperature not higher than 0°C., and the concentrate is stirred at 0°C. for 48 hours. The reaction mixture is then poured into 200 ml. of saturated sodium chloride solution, and extracted three times with ether. The combined extracts are washed with saturated sodium bicarbonate solution (2 × 200 ml.) and saturated sodium chloride solution (2 × 200 ml.), dried over magnesium sulfate and evaporated to dryness under reduced pressure. The resulting residue is purified by filtration through 100 g. of silica gel using benzene as eluant, thus obtaining the pure 5-chloro-5-cyano-7-*syn*-benzyloxymethylbicyclo-(2.2.1)-hept-2-ene.

PREPARATION 2.

To a well-stirred slurry of 74.1 g. of cyclopentadienylthallium in 100 ml. of anhydrous diethyl ether cooled to −20°C. to −22°C. (internal temperature) in a dry ice-carbon tetrachloride bath under an argon atmosphere, are added dropwise, in a 15-minute period, 20.13 g. of chloromethyl methyl ether and the slurry is stirred at −20°C. to −22°C. for 7 hours. The reaction mixture is then filtered into a precooled (−70°C., dry ice-acetone) flask and the residue of thallium chloride washed with three 100 ml. portions of cold (−70°C.) diethyl ether. The combined filtrate is added dropwise from a dropping funnel with a dry ice jacket to a suspension of 29.65 g. of cupric tetrafluoroborate in 87.5 g. of anhydrous α-chloroacrylonitrile maintained at 0°C. When the addition is complete, the mixture is stirred at 0°C. in the dark for 18 hours. One hundred milliliters of saturated sodium chloride solution are then added and the reaction mixture extracted with diethyl ether. The ether extracts are successively washed with saturated sodium bicarbonate (2 × 100 ml.) and sodium chloride (2 × 100 ml.), and dried over magnesium sulfate. Evaporation under reduced pressure at room temperature gives 5-chloro-5-cyano-7-*syn*-methoxymethylbicyclo-(2.2.1) hept-2-ene as a clear pale yellow oil.

PREPARATION 3.

To a stirred solution of 100 g. of 5-chloro-5-cyano-7-*syn*-benzyloxymethylbicyclo-(2.2.1) hept-2-ene in 368 ml. of dimethylsulfoxide is added dropwise, in a 15-minute period and under an argon atmosphere, a hot solution of 105.2 g. of potassium hydroxide in 52.6 ml. of water. The reaction mixture is stirred for 28 hours at room temperature, diluted to twice its volume with ice water and extracted several times with diethyl ether. The combined organic extract is washed twice with saturated sodium carbonate solution, dried over magnesium sulfate and evaporated to dryness. The residue is purified by distillation under high vacuum (0.6 mm.) to yield 7-*syn*-benzyloxymethyl-2-norbornen-5-one, homogeneous on t.l.c.

By the same procedure but using 5-chloro-5-cyano-7-*syn*-methoxymethylbicyclo-(2.2.1) hept-2-ene in lieu of 5-chloro-5-cyano-7-*syn*-benzyloxymethylbicyclo-(2.2.1) hept-2-ene there is obtained 7-*syn*-methoxymethyl-2-norbornen-5-one.

PREPARATION 4.

To a suspension of 55 g. of *m*-chloroperbenzoic acid and 43.5 g. of sodium bicarbonate in 570 ml. of anhydrous methylene chloride are added 57 g. of 7-*syn*-benzyloxymethyl-2-norbornen-5-one, in a 15-minute period and under stirring, maintaining the temperature at about 25°C. The reaction mixture is stirred for three hours further and diluted with methylene chloride. The resulting mixture is vigorously stirred with 470 ml. of saturated aqueous sodium sulfite solution, the organic layer is separated and washed with saturated sodium sulfite solution. The aqueous phase is extracted with methylene chloride and the combined organic methylene chloride extracts are dried over magnesium sulfate and evaporated to dryness under reduced pressure, thus yielding 2-oxa-8-*syn*-benzyloxymethylbicyclo-(3.2.1) oct-6-en-3-one as an homogenous oil.

By the same procedure but using 7-*syn*-methoxymethyl-2-norbornen-5-one in place of 7-*syn*-benzyloxymethyl-2-norbornen-5-one there is obtained 2-oxa-8-*syn*-methoxymethylbicyclo-(3.2.1) oct-6-en-3-one.

PREPARATION 5.

To a solution of 60 g. of 2-oxa-8-*syn*-benzyl-oxymethylbicyclo-(3.2.1) oct-6-en-3-one in 70 ml. of methanol is added, at 0°C., a solution of 30 g. of sodium hydroxide in 247 ml. of water, and the resulting mixture is stirred at room temperature for three hours. The methanol is then evaporated under *vacuo* at a temperature below 30°C., cooled to 0°C. and extracted with diethyl ether to eliminate the unsapoinifiable products. The aqueous phase is neutralized with carbon dioxide and immediately treated with a solution of 188.1 g. of iodine and 369 g. of potassium iodide in 275 ml. of water. The reaction mixture is stirred for 48 hours at 0°C. and diluted with sodium sulfate solution until complete decoloration. It is then saturated with sodium potassium tartrate and extracted with methylene chloride. The organic extracts are dried over magnesium sulfate and evaporated to dryness under reduced pressure. The oily residue is crystallized from diethyl ether-methylene chloride, to yield the pure (2'α,4'α-dihydroxy-3'β-iodo-5'β-benzyloxymethylcyclopent-1'α-yl) acetic acid γ-lactone.

PREPARATION 6.

To a solution of 39.45 g. of (2'α,4'α-dihydroxy-3'β-iodo-5'β-benzyloxymethylcyclopent-1'α-yl) acetic acid γ-lactone in 152 ml. of anhydrous pyridine is added 32.8 g. of *p*-biphenylcarboxylic acid chloride. The resulting solution is stirred at room temperature for one hour; 9 ml. of water are then added, and the mixture stirred for one hour to destroy the excess reagent. The solvents are eliminated under reduced pressure and the residue is dissolved in methylene chloride-cyclohexane (3:2). The organic solution is washed successively with 10% hydrochloric acid solution, saturated sodium bicarbonate solution and saturated sodium chloride solution, dried over magnesium sulfate and concentrated, to yield (2'α-hydroxy-4'α-*p*-phenylbenzoyloxy-3'β-iodo-5'β-benzyloxymethylcyclopent-1'α-yl) acetic acid γ-lactone, which can be purified by crystallization.

By the same procedure, (2'α,4'α-dihydroxy-3'β-iodo-5'β-methoxymethylcyclopent-1'α-yl) acetic acid γ-lactone is converted into (2'α-hydroxy-4'α-*p*-phenylbenzoyloxy-3'β-iodo-5'β-methoxymethylcyclopent-1'α-yl) acetic acid 1,2'-lactone.

PREPARATION 7.

To a solution of 61 g. of (2'α-hydroxy-4'α-*p*-phenylbenzoyloxy-3'β-iodo-5'β-benzyloxymethylcyclopent-1'α-yl) acetic acid γ-lactone in 610 ml. of benzene (dried over molecular sieves) is added 45.25 g. of tri-*n*-butyl tin hydride, prepared according to the procedure of H. G. Kuivila and O. F. Beumel, Jr., *J. Am. Chem. Soc.*, *83*, 1246 (1961) and 211 mg. of azobisisobutyronitrile. The mixture is stirred at 50°C. for 30 minutes, then the benzene is removed by evaporation under reduced pressure, the oily residue is dissolved in 1.5.1 of diethyl ether and the ethereal solution is washed several times with 5% aqueous sodium hydroxide solution and then with saturated sodium chloride solution, dried over magnesium sulfate and evaporated under *vacuo*. The residue is chromatographed on 915 g. of silica gel using as first eluant diethyl ether-hexane (1:1) to remove non-polar tin by-products. The fractions eluted with ethyl acetate afford the desired (2'α-hydroxy-4'α-*p*-phenylbenzoyloxy-5'β-benzyloxymethylcyclopent-1'α-yl) acetic acid γ-lactone.

In a similar manner, (2'α-hydroxy-4'α-*p*-phenylbenzoyloxy-3'β-iodo-5'β-methoxymethylcyclopent-1'α-yl) acetic acid γ-lactone is converted into (2'α-hydroxy-4'α-*p*-phenylbenzoyloxy-5'β-methoxymethylcyclopent-1'α-yl) acetic acid γ-lactone.

PREPARATION 8.

A. To a prehydrogenated suspension of 1 g. of 10% palladium charcoal catalyst in 200 ml. of anhydrous 1,2-dimethoxyethane are added 10 g. of (2'α-hydroxy-4'α-*p*-phenylbenzoyloxy-5'β-benzyloxymethylcyclopent-1'α-yl) acetic acid γ-lactone and 1 ml. of perchloric acid, and the mixture is stirred under hydrogen atmosphere until the absorption of hydrogen ceases. The catalyst is then separated by filtration and washed with diethyl ether. The combined organic filtrates are washed with sodium bicarbonate solution, dried over magnesium sulfate and evaporated to dryness under reduced pressure. Crystallization of the residue from chloroform yields (2'α-hydroxy-4'α-*p*-phenylbenzoyloxy-5'β-hydroxymethylcyclopent-1'α-yl) acetic acid γ-lactone.

B. A stirred solution of 15 g. of (2'α-hydroxy-4'α-*p*-phenylbenzoyloxy-5'β-

methoxymethylcyclopent-1'α-yl) acetic acid γ-lactone in 190 ml. of anhydrous methylene chloride is cooled to −78°C. in a dry ice-acetone bath and treated with 25 ml. of boron tribromide. The stirred mixture is allowed to warm rapidly to 0°C. and kept at this temperature for 50 minutes. To the resultant solution is then added 270 ml. of diethyl ether to decompose excess boron tribromide, maintaining the reaction mixture at 0°C. It is then poured into a vigorously stirred slurry of 96 g. of sodium bicarbonate in 500 ml. of a saturated solution of sodium potassium tartrate; the organic layer is separated and the aqueous phase extracted with methylene chloride. The combined organic extracts are dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue is purified by crystallization from chloroform to afford (2'α-hydroxy-4'α-p-phenylbenzoyloxy-5'β-hydroxymethylcyclopent-1'α-yl) acetic acid γ-lactone, identical to the product obtained in Part A.

C. To a suspension of 300 g. of Celite (Registered Trade Mark) diatomaceous earth (dried for 24 hours at 105°C.) and 61.5 g. of chromium trioxide-dipyridine complex (prepared as described by J. C. Collins et al., *Tetrahedron Letters* 3363 (1968) in 610 ml. of anhydrous methylene chloride, cooled to 5°C. are added under stirring 10 g. of 2'α-hydroxy-4'α-p-phenylbenzoyloxy 5'β-hydroxymethylcyclopent-1'α-yl) acetic acid γ-lactone dissolved in 60 ml. of methylene chloride and the mixture is stirred for 10 minutes further, maintaining the temperature between −5°C. and 0°C.; 100 g. of sodium bisulfite mono-hydrate are then added and the mixture is stirred for an additional 10-minute period, filtered through magnesium sulfate and the solids washed with methylene chloride, receiving the filtrate in a flask cooled to −60°C. in a dry ice-acetone bath. The combined filtrates are evaporated to dryness under reduced pressure, at a temperature below 0°C., obtaining (2'α-hydroxy-4'α-p-phenylbenzoyloxy-5'β-formylcyclopent-1'α-yl) acetic acid γ-lactone as an homogeneous oil.

PREPARATION 9.

A solution of 22 g. of (2'α,4'α-dihydroxy-3'β-iodo-5'β-benzyloxymethylcyclopent-1'α-yl) acetic acid γ-lactone in 60 ml. of anhydrous pyridine is cooled to 0°C. and treated dropwise, under stirring, with a mixture of 8 ml. of phosphorus oxychloride and 20 ml. of pyridine. When the addition is complete, the reaction is stirred for 30 minutes at room temperature, and the solvent is eliminated under reduced pressure. The oily residue is dissolved in methylene chloride, and the organic solution washed with 10% hydrochloric acid solution, reextracting the aqueous phases with methylene chloride.

The combined organic extracts are then washed with saturated sodium sulfite solution until complete decoloration, dried over magnesium sulfate and evaporated to dryness under reduced pressure to yield (2'α-hydroxy-5'β-benzyloxymethylcyclopent-3'-en-1'α-yl) acetic acid γ-lactone as a colorless oil.

In a similar manner, starting from (2'α,4'α-dihydroxy-3'β-iodo-5'β-methoxymethylcyclopent-1'α-yl) acetic acid γ-lactone there is obtained (2'α-hydroxy-5'β-methoxymethylcyclopent-3'-en-1'α-yl) acetic acid γ-lactone.

PREPARATION 10.

A stirred solution of 13 g. of (2'α-hydroxy-5'β-benzyloxymethylcyclopent-3'-en-1'α-yl) acetic acid γ-lactone in 20 ml. of methanol is cooled to 0°C. and treated dropwise with a solution of 6.5 g. of sodium hydroxide in 65 ml. of water; when the addition is complete the reaction mixture is stirred for one hour at room temperature. The methanol is then eliminated under reduced pressure at a temperature below 30°C., and the resulting aqueous solution cooled to 0°C. and extracted with diethyl ether, to eliminate the unsaponifiable products. The aqueous phase is carefully acidified to pH 5—6 with 3N hydrochloric acid at 0°C., 100 ml. of ethyl acetate are then added and thereafter the reaction mixture is acidified to pH 2—3. The organic phase is separated and the aqueous phase is saturated with sodium chloride, extracting it with six 50 ml. portions of ethyl acetate. The combined extracts are washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under vacuo. Crystallization of the residue from hexane-methylene chloride gives the pure (2'α-hydroxy-5'β-benzyloxymethylcyclopent-3'-en-1'α-yl) acetic acid.

In a similar manner (2'α-hydroxy-5'β-methoxymethylcyclopent-3'-en-1'α-yl) acetic acid γ-lactone is converted into (2'α-hydroxy-5'β-methoxymethylcyclopent-3'-en-1'α-yl) acetic acid.

PREPARATION 11.

To a prehydrogenated suspension of 10 g. of Raney nickel in 200 ml. of methanol is added 13 g. of (2'α-hydroxy-5'β-benzyloxymethylcyclopent-3'-en-1'α-yl) acetic acid, and the mixture is stirred under hydrogen atmosphere until the uptake of hydrogen ceases; the catalyst is then separated by filtration and washed well with diethyl ether. The combined organic filtrates are evaporated to dryness under reduced pressure and the oily residue is dissolved in 200 ml. of ethyl acetate. The resultant solution is then treated with 3N hydrochloric acid until a pH of 2—3 is obtained, stirring the reaction mixture for 30 additional minutes. It is then neutralized with sodium bicarbonate, dried over magnesium sulfate and evaporated to dryness under *vacuo*, thus yielding (2'α-hydroxy-5'β-benzyloxymethylcyclopent-1'α-yl) acetic acid γ-lactone, homogeneous on t.l.c.

In a similar manner, (2'α-hydroxy-5'β-methoxymethylcyclopent-3'-en-1'α-yl) acetic acid is converted into (2'α-hydroxy-5'β-methoxymethylcyclopent-1'α-yl) acetic acid γ-lactone.

PREPARATION 12.

By following the method of Preparation 8, Parts A and B, respectively, (2'α-hydroxy-5'β-benzyloxymethylcyclopent-1'α-yl) acetic acid γ-lactone and (2'α-hydroxy-5'β-methoxymethylcyclopent-1'α-yl) acetic acid γ-lactone are converted into (2'α-hydroxy-5'β-hydroxymethylcyclopent-1'α-yl) acetic acid 1,2'-lactone, which upon oxidation with chromium trioxide-dipyridine complex, in accordance with the method of Part C of Preparation 8, affords (2'α-hydroxy-5'β-formylcyclopent-1'α-yl) acetic acid γ-lactone.

PREPARATION 13.

A. A solution of 100 g. of dimethyl methylphosphonate in 670 ml. of anhydrous tetrahydrofuran is cooled to −78°C. under an argon atmosphere. To the cold solution are added dropwise under stirring and under argon atmosphere, 495 ml. of a 0.1M solution of n-butyllithium in tetrahydrofuran, maintaining the temperature at −70°C. When the addition is complete the reaction mixture is maintained under the same conditions for 10 additional minutes, a solution of 58 ml. of methyl caproate dissolved in 187 ml. of tetrahydrofuran is then carefully added, maintaining the temperature at −78°C. The reaction mixture is stirred at −78°C. for two hours followed by stirring for four hours at room temperature. The excess base is neutralized with acetic acid and the solvent is evaporated under high vacuo. The residue is dissolved in diethyl ether-water (1:1, 950 ml. each), the ethereal phase is separated, washed with water and dried over magnesium sulfate. The ether is evaporated and the residue is purified by vacuum distillation, thus obtaining the pure dimethyl 2-oxoheptylphosphonate.

B. To a suspension of 1.55 g. of sodium hydride (previously washed with pentane, under argon) in 355 ml. of 1,2-dimethoxyethane freshly distilled from lithium aluminium hydride is added, under stirring and under an atmosphere of argon, a solution of 7.1 g. of dimethyl 2-oxoheptylphosphonate in 150 ml. of 1,2-dimethoxyethane. The reaction mixture is stirred for 30 minutes at room temperature and 10 g. of (2'α-hydroxy-4'α-*p*-phenylbenzoyloxy-5'β-formylcyclopent-1'α-yl) acetic acid γ-lactone are added. The reaction mixture is stirred at room temperature for two hours further, it is then carefully neutralized with acetic acid (to pH 7) and evaporated to dryness under reduced pressure at a temperature below 30°C. The solid residue is purified by chromatography on Florisil, using methylene chloride as eluant, to obtain [2'α-hydroxy-4'α-*p*-phenylbenzoyloxy-5'β-(3''-oxooct-1''-*trans*-en-1''-yl)-cyclopent-1'α-yl] acetic acid γ-lactone and a small amount of dimethyl 2-oxoheptylphosphonate.

In a similar manner, (2'α-hydroxy-5'β-formylcyclopent-1'α-yl) acetic acid γ-lactone is converted into [2'αhydroxy-5'β-(3''-oxooct-1''-*trans*-en-1''-yl) cyclopent-1'-α-yl] acetic acid γ-lactone.

PREPARATION 14.

To a stirred solution of 5.34 g. of [2'α-hydroxy-4'α-*p*-phenylbenzoyloxy-5'β-(3'''-oxooct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid γ-lactone in 36 ml. of 1,2-dimethoxyethane fresly distilled from lithium aluminium hydride are added 9 ml. of zinc borohydride reagent in anhydrous dimethoxyethane. The reaction mixture is stirred for an additional hour at room temperature, and treated with a saturated solution of sodium bitartrate until the evolution of gas ceases. It is then diluted with methylene chloride, dried over magnesium sulfate and evaporated to

dryness under vacuo at a temperature below 30°C. to yield [2'α-hydroxy-4'α-p-phenylbenzoyloxy-5'β-(3''α-hydroxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid γ-lactone in mixture with the 3''β-hydroxy isomer.

The oily mixture is separated into the individual isomers by t.l.c. using a mixture of benzene-methylisobutyl ketone (2:1) as eluant.

By the same method, [2'α-hydroxy-5'β-(3''-oxooct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid, γ-lactone is converted into [2'α-hydroxy-5'β-(3''α-hydroxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid γ-lactone in mixture with the 3''β-hydroxy isomer, which are separated by thin layer chromatography.

The zinc borohydride reagent is prepared from 0.025 mol of fused zinc chloride, 0.050 mol of sodium borohydride and 50 ml. of 1,2-dimethoxyethane, stirring the mixture for 16 hours and filtering the insoluble material under argon atmosphere.

PREPARATION 15.

A solution of 3.7 g. of [2'α-hydroxy-4'α-p-phenylbenzoyloxy-5'β-(3''α-hydroxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid γ-lactone in 37 ml. of anhydrous methanol is treated with 1.14 g. of anhydrous potassium carbonate, and the reaction mixture stirred for two and one-half hours at room temperature. It is then cooled to 0°C. and adjusted with 1ON aqueous hydrochloric acid until a pH of 2—3 is obtained. Ethyl acetate is added and the organic solution washed with saturated sodium bicarbonate solution and saturated sodium potassium bitartrate solution, dried over magnesium sulfate and evaporated to dryness under vacuo. The residue is purified by filtration through a Florisil column (130 g.). The fractions eluted with methylene chloride-ethyl acetate give methyl *p*-biphenyl carboxylate and the fractions eluted with ethyl acetate yield [2'α,4'α-dihydroxy-5'β-(3''α-hydroxyoct-1''*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid γ-lactone.

PREPARATION 16.

To a solution of 2.3 g. of [2'α,4'α-dihydroxy-5'β-(3''α-hydroxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid γ-lactone in 23 ml. of methylene chloride are added 2.3 ml. of freshly distilled dihydropyran and 23 mg. of anhydrous *p*-toluenesulfonic acid. The reaction mixture is stirred for 15 minutes at room temperature, a few drops of pyridine are added and diluted with diethyl ether. The ethereal solution is washed with 100 ml. of 50% aqueous sodium chloride solution and then with saturated sodium chloride solution. The organic phase is separated, dried over magnesium sulfate and evaporated to dryness under reduced pressure, at approximately 0°C., thus yielding [2'α-hydroxy-4'α-tetrahydropyran-2'''-yloxy-5'β-(3''α-tetrahydropyran-2'''-yloxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid γ-lactone, as an oil.

In a similar manner, [2'α-hydroxy-5'β-(3''α-hydroxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid γ-lactone is converted into [2'α-hydroxy-5'β-(3''α-tetrahydropyran-2'''-yloxyoct-1''-*trans*-en-1''-yl cyclopent-1'α-yl] acetic acid γ-lactone.

PREPARATION 17.

One gram of [2'α-hydroxy-4'α-tetrahydropyran-2'''-yloxy-5'β-(3''α-tetrahydropyran-2'''-yloxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid γ-lactone is dissolved in 20 ml. of anhydrous toluene. The solution is cooled to –60°C. and to the cold sclution is added 3.43 ml. of a mixture of 1 ml. of diisobutyl aluminium hydride and 3 ml. of anhydrous toluene, stirring the reaction mixture for 15 minutes at –60°C. It is then diluted with methanol until the evolution of gas ceases, the mixture is stirred for 15 minutes further at room temperature and diluted with ether. The organic phase is then separated, washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness at about 0°C. to produce [2'α-hydroxy-4'α-tetrahydropyran-2'''-yloxy-5'β-(3''α-tetrahydropyran-2'''-yloxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetaldehyde γ-hemiacetal.

Likewise, [2'α-hydroxy-5'β-(3''α-tetrahydropyran-2'''-yloxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid γ-lactone is converted into [2'α-hydroxy-5'β-(3''α-tetrahydropyran-2'''-yloxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetaldehyde γ-hemiacetal.

PREPARATION 18.

In accordance with the methods described in Preparations 15, 16 and 17, 2 g. of [2'α-hydroxy-4'α-p-phenylbenzoyloxy-5'β-(3''β-hydroxyoct-1''-*trans*-en-1''-yl)

cyclopent-1'α-yl] acetic acid γ-lactone are converted successively into [2'α,4'α-dihydroxy-5β-(3''β-hydroxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid γ-lactone, [2'α-hydroxy-4'α-tetrahydropyran-2'''-yloxy-5'β-(3''β-tetrahydropyran-2'''-yloxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetic acid γ-lactone and [2'α-hydroxy-4'α-tetrahydropyran-2'''-yloxy-5'β-(3''β-tetrahydropyran-2'''-yloxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl) acetaldehyde γ-hemiacetal.

EXAMPLE 1.

A mixture of 2.14 g. of pent-4-yn-1-ol and 250 ml. of anhydrous ether is cooled under an argon atmosphere to −70°C. in a dry ice-acetone bath. To the stirred cold mixture is added dropwise 26.2 ml. of 2M methyl lithium in diethyl ether. After addition of this reagent, the reaction mixture is allowed to attain room temperature, stirring for 18 hours further. A solution of 380 mg. of [2'α-hydroxy-4'α-tetrahydro-pyran-2'''-yloxy-5'β-(3''α-tetrahydropyran-2'''-yloxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetaldehyde γ-hemiacetal in 5 ml. of anhydrous ether is added, and the mixture is stirred for six hours at room temperature. It is then poured into ice water and extracted several times with diethyl ether. The combined organic extracts are washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under reduced pressure, at a temperature not higher than 20°C. The residue is purified by chromatography on Florisil. The fractions eluted with ethyl acetate-methanol (90:10) give 11*a*, 15*a*-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol.

The 6α and 6β-hydroxy isomers can be separated by t.l.c. on silica gel, using a mixture of methylene chloride-ether (1:1) as eluant.

In a similar manner, [2'α-hydroxy-5'β-(3''α-tetrahydropyran-2'''-yloxyoct-1''-*trans*-en-1''-yl) cyclopent-1'α-yl] acetaldehyde γ-hemiacetal is converted into 15α-tetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol.

EXAMPLE 2.

A mixture of 300 mg. of 11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol, 2 ml. of pyridine and 0.2 ml. of acetyl chloride is stirred at room temperature for six hours. It is then poured into water and extracted with diethyl ether. The organic extract is washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under vacuo to yield 11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ9α-triol triacetate which can be purified by filtration through Florisil.

By the same method 15α-tetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,1,6ξ,9α-triol is converted into 15α-tetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate.

EXAMPLE 3.

A stirred suspension of 117.5 mg. of cuprous iodide in 2 ml. of anhydrous diethyl ether is cooled to about −10°C. under an atmosphere of argon, and treated with two molar equivalents of a 2M solution of methyl lithium in diethyl ether. The resultant colorless solution is cooled to −75°C. in a dry ice-acetone bath, a solution of 100 mg. of 11α,15α-bistetrahydropryan-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ9α-triol triacetate in 13 ml. of anhydrous diethyl ether is then added and the reaction mixture stirred at −75°C. for five hours. The temperature of the mixture is raised to −10°C., saturated ammonium chloride solution is added, and the mixture is stirred for one hour and extracted with diethyl ether. The organic extract is washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue is purified by chromatography on Florisil. The fraction eluted with methylene chloride-diethylether (80:20) afford the pure 11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate.

In a similar manner, but using 15α-tetrahydropyranyloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate as starting compound, there is obtained 15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate.

EXAMPLE 4.

A mixture of 110 mg. of 11α,15α-bis-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate, 50 mg. of anhydrous potassium carbonate and 2 ml. of anhydrous methanol is stirred at room temperature for 18 hours, under an argon atmosphere. The solvent is then eliminated under reduced pressure, water is added and the product extracted with diethyl ether. The ether extract is washed

with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under *vacuo*, thus yielding 11α,15α-bistetrahydropyranyloxyprosta-4,5,13-*trans*-triene-1,9α-diol.

In a similar manner, 15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate is converted into 15α-tetrahydropyranyloxyprosta-4,5,13-*trans*-triene-1,9α-diol.

EXAMPLE 5.

A solution of 300 mg. of 11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol in 10 ml. of acetone is cooled to −10°C. and treated under an atmosphere of nitrogen and with stirring, with 0.8 ml. of an 8N solution of chromic acid (prepared by mixing 26 g. of chromium trioxide with 23 ml. of concentrated sulfuric acid and diluting with water to 100 ml). The reaction mixture is stirred for 90 minutes further at −10°C., a few drops of isopropanol are then added to destroy the excess reagent, and the mixture diluted with ethyl acetate. The solution is immediately washed three times with sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under reduced pressure. To the oil residue is added 2.4 ml. of a mixture of acetic acid-water (65.35), and the reaction mixture is stirred at room temperature for 18 hours, it is then evaporated to dryness under *vacuo* and the residue purified by t.l.c. using ethyl acetate as eluant, to give the pure 9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid.

Likewise, 15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-19α-diol is converted into 9-oxo-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid.

EXAMPLE 6.

A. A mixture of 100 mg. of 11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate, 27.5 mg. (1.1 molar equivalents) of anhydrous potassium carbonate and 2 ml. of anhydrous methanol is stirred at 0°C. for two hours, under an argon atmosphere. The solvent is then eliminated under reduced pressure, water is added and the product extracted with diethyl ether. The diethyl ether extract is washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under vacuo. The residue is purified by t.l.c., to produce the pure 9α-acetoxy-11α,15α,bistetrahydropyranyloxyprosta-4,5,13-*trans*-trien-1-ol.

Upon oxidation of the foregoing compound with 8N chromic acid, in accordance with the method of Example 5, there is produced 9α-acetoxy-11α,15α-bistetrahydropyran-2-yloxyprosta-4,5,13-*trans*-trienoic acid. The latter compound is then treated with anhydrous potassium carbonate (25 mg.) in methanol, in accordance with the method of Example 4, followed by acidification with oxalic acid to afford 9α-hydroxy-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid.

B. A solution of 50 mg. of 9α-hydroxy-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid in 0.15 ml. of tetrahydrofuran is treated with 1.3 ml. of 65% aqueous acetic acid. The reaction mixture is stirred at 45°C. for four hours, cooled to 0°C. and evaporated to dryness under reduced pressure; the oily residue is purified by t.l.c. using chloroform:methanol (9:1) as eluant, thus yielding the pure 9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid.

In a similar manner but using 15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate as starting compound there are successively obtained 9α-acetoxy-15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trien-1-ol, 9α-acetoxy-15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid, 9α-hydroxy-15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid and 9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid.

EXAMPLE 7.

A. To a vigorously stirred suspension of 10.4 g. of cuprous iodide in 200 ml. of diethyl ether, cooled to 0°C., is added dropwise a 2M solution of methyl lithium in diethyl ether, under argon atmosphere, until a colorless solution of lithium dimethyl copper reagent is obtained.

In a similar manner but using ethyl lithium and propyl lithium instead of methyl lithium, the lithium diethyl copper and lithium di-*n*-propyl copper reagents are prepared.

B. A solution of 100 mg. of 11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6⅛,9α-triol triacetate in 3 ml. of anhydrous diethyl ether is cooled to 0°C. and treated, under argon atmosphere, with one molar equivalent of lithium

dimethyl copper (prepared as described in Part A). The reaction mixture is stirred for five hours at 0°C., saturated ammonium chloride solution is added, and the mixture is stirred for one hour and extracted with diethyl ether. The organic extract is washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue is purified by chromatography on Florisil. The fractions eluted with methylene chloride-diethyl ether (80:20) afford the pure 11α,15α-bistetrahydropyran-2'-yloxy-4-methylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate.

Similarly, but using one molar equivalent of lithium diethyl copper and lithium dipropyl copper *in lieu* of lithium dimethyl copper there are respectively obtained 11α,15α-bistetrahydropyran-2'-yloxy-4-ethylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate and 11α,15α-bistetrahydropyran-2'-yloxy-4-propylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate.

Likewise, but using 15α-tetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate in lieu of 11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate there are obtained respectively 15α-tetrahydropyran-2'-yloxy-4-methylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate, 15α-tetrahydropyran-2'-yloxy-4-ethylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate and 15α-tetrahydropyran-2'-yloxy-4-propylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate

EXAMPLE 8.

Examples 4 and 5 are repeated using 11α,15α-bistetrahydropyran-2'-yloxy-4-methylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate as starting material, to produce successively 11α,15α-bistetrahydropyran-2'-yloxy-4-methylprosta-4,5,13-*trans*-triene-1,9α-diol, 4-methyl-9-oxo-11α, 15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid and 4-methyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid.

In a similar manner, starting from 11α,15α-bistetrahydropyran-2'-yloxy-4-ethylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate, 11α,15α-bistetrahydropyran-2'-yloxy-4-propylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate, 15α-tetrahydropyran-2'-yloxy-4-methylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate and 15α-tetrahydropyran-2'-yloxy-4-ethylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate there are obtained as final products 4-ethyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, 4-propyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, 4-methyl-9-oxo-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid and 4-ethyl-9-oxo-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid, respectively.

EXAMPLE 9.

By following the method of Example 6, 11α,15α-bistetrahydropyran-2'-yloxy-4-methylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate is converted successively into 9α-acetoxy-11α,15α-bistetrahydropyran-2'-yloxy-4-methylprosta-4,5,13-*trans*-trien-1-ol, 4-methyl-9α-acetoxy-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid, 4-methyl-9α-hydroxy-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid, and 4-methyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid.

In a similar manner 11α,15α-bistetrahydropyran-2'-yloxy-4-ethylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate, 11α,15α-bistetrahydropyran-2'-yloxy-4-propylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate and 15α-tetrahydropyran-2'-yloxy-4-methylprosta-4,5,13-*trans*-triene-1,9α-diol diacetate are converted respectively into 4-ethyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid, 4-propyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid and 4-methyl-9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid.

EXAMPLE 10.

To a solution of 2 g. of 11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol in 60 ml. of anhydrous tetrahydrofuran is added 4.6 g. of activated manganese dioxide, and the reaction mixture is stirred for 90 minutes at room temperature; the manganese dioxide is filtered off and washed with acetone and combined filtrates are evaporated to dryness unver *vacuo*. The residue is redissolved in 60 ml. of anhydrous tetrahydrofuran, 4.6 g. of manganese dioxide are then added and the mixture stirred under the same conditions for 90 minutes further. The manganese dioxide is separated by filtration and washed with hot acetone. The combined organic filtrates are evaporated to dryness under reduced pressure, and the residue is purified by thin layer chromatography, using a 1:1 methylene chloride-diethyl ether mixture containing 0.4% of methanol as eluant to

obtain 6-oxo-11α,15α,bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,9α-diol in pure form.

Similarly, 15α-tetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol is converted into 6-oxo-15α-tetrahydropyranyloxyprost-13-*trans*-en-4-yne-1,9α-diol.

The same results are obtained when using 2,3-dichloro-5,6-dicyano-1,4-benzoquinoline in place of manganese dioxide.

EXAMPLE 11.

To a stirred solution of 275 mg. of 6-oxo-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,9α-diol in 69 ml. of anhydrous diethyl ether, there is added dropwise, at room temperature and under argon atmosphere, 0.96 ml. of a 2.2M solution of methyl-lithium in diethyl ether (4 molar equivalents). The reaction mixture is maintained at room temperature for 1 hour and then poured into a saturated aqueous ammonium chloride solution. The organic phase is separated and the aqueous phase extracted with diethyl ether. The combined organic extracts are washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue is purified twice by thin layer chromatography, using a (49:49:2) methylene chloride-diethyl ether-methanol mixture as eluant for the first run, and then a (60:39:1) mixture of the same solvents for the second chromatography, to obtain 6ξ-methyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol in pure form.

Likewise, starting from 6-oxo-15α-tetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,9α-diol there is obtained 6ξ-methyl-15α-tetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol.

By the same method but using equivalent amounts of ethyl lithium and propyl lithium in place of methyl lithium, 6-oxo-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,9α-diol is converted respectively into 6ξ-ethyl-11α, 15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne,1,6ξ,9α-triol and 6ξ-propyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne,1,6ξ,9α-triol.

EXAMPLE 12.

To a solution of 200 mg. of 6ξ-methyl-11α-bistetrahydropyran-2'-yloxyprost-*trans*-en-4-yne-1,6ξ,9α-triol in 20 ml. of anhydrous diethyl ether there is added 1 ml. of a 2.2 M solution of methyl lithium in diethyl ether, and the reaction mixture is stirred at room temperature for 3 1/2 hours. The reaction mixture is then cooled to 0°C. in an ice bath and treated dropwise under stirring with 0.62 ml. of acetyl chloride and thereafter 1.22 ml. of pyridine are added. The resultant mixture is then stirred at room temperature for 18 hours, water is then added and the product extracted with diethyl ether. The organic extracts are washed 3 times with saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under *vacuo*. The residue is purified by t.l.c. using methylene chloride-diethyl ether (80:20), thus obtaining 6ξ-methyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate and 6ξ-methyl - 11α,15α, - bistetrahydropyranyloxyprost - 13 - *trans*-en-4-yne-1,6ξ,9α-triol 1,9α-diacetate.

In a similar manner starting from 6ξ-methyl-15α-tetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol, 6ξ-ethyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol and 6ξ-propyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol there are obtained respectively:
6ξ-methyl-15α-tetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate and 6ξ-methyl-15α-tetrahydropyranyloxyprost-13-*trans*-en-4-yne-1,6ξ,9α, triol 1,9α-diacetate;
6ξ - ethyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate and 6ξ-ethyl-11α-15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol 1,9α-diacetate; and 6ξ-propyl-11α,15α-bistetrahydropyranyloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate and
6ξ - propyl - 11α,15α-bistetrahydropyranyloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol 1,9α-diacetate.

EXAMPLE 13.

A stirred suspension of 117.5 mg. of cuprous iodide in 2 ml. of anhydrous diethyl ether is cooled to about −10°C. under an atmosphere of argon, and treated with 2 molar equivalents of a 2M solution of methyl lithium in diethyl ether. The

resultant colorless solution is cooled to −70°C. in a dry ice-acetone bath, a solution of 100 mg. of 6ξ-methyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate in 3 ml. of anhydrous ether is then added and the reaction mixture stirred at −70°C. for 5 hours. The temperature of the mixture is raised to −10°C., saturated ammonium chloride is added, and the mixture is stirred for 1 hour and extracted with diethyl ether. The organic extract is washed with saturated sodium chloride solution, dried over magnexium sulfate and evaporated to dryness under reduced pressure, to afford 6-methyl-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trien-1,9α-diol diacetate.

In a similar manner, but using 6ξ-methyl-15α-tetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate, 6ξ-ethyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate and 6ξ-propyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate, in place of 6ξ-methyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate there are obtained 6-methyl-15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trien-1,9α-diol diacetate, 6-ethyl-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trien-1,9α-diol diacetate and 6-propyl-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate, respectively.

EXAMPLE 14.

A mixture of 110 mg. of 6-methyl-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate 50 mg. of anhydrous potassium carbonate and 2 ml. of anhydrous methanol is stirred at room temperature for 18 hours, under an argon atmosphere. The solvent is then eliminated under reduced pressure, water is added and the product extracted with diethyl ether. The diethyl ether extract is washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under reduced pressure to afford 6-methyl-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol.

Upon oxidation of the latter compound with 8N chromic acid followed by hydrolysis of the tetrahydropyranyloxy functions with aqueous 65% acetic acid, in accordance with the methods of Example 5, there is produced 6-methyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid.

Likewise, starting from 6-methyl-15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate, 6-ethyl-11α-15α-bis-tetra-hydro-pyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate and 6-propyl-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9-diol diacetate there are produced as final products 6-methyl-9-oxo-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid, 6-ethyl-9-oxo-11α-15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid and 6-propyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, respectively.

EXAMPLE 15.

A solution of 100 mg. of 6ξ-methyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-ene-4-yne-1,6ξ,9α-triol triacetate in 3 ml. of anhydrous diethyl ether is cooled to 0°C. and treated, under argon atmosphere, with one molar equivalent of lithium dimethyl copper, (prepared as described in part A of Example 7). The reaction mixture is stirred for 5 hours at 0°C., saturated ammonium chloride solution is added, and the mixture is stirred for 1 hour and extracted with diethyl ether. The organic extract is washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue is purified by chromatography on Florisil. The fractions eluted with methylene chloride-diethyl ether (80:20) afford the pure 4.6-dimethyl-11α,15α-bistetrahydropyranyloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate.

In a similar manner but using 6ξ-methyl-15α-tetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate, 6ξ-ethyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate and 6ξ-propyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triacetate as starting materials there are obtained respectively 4,6-dimethyl-15α-tetrahydropyranyloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate, 4-methyl-6-ethyl-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate, and 4-methyl-6-propyl-11α,15α-bistetrahydropyranyloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate.

Similarly, but using 1 molar equivalent of lithium diethyl copper and lithium dipropyl copper *in lieu* of lithium dimethyl copper, 6ξ-methyl-11α,15α-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6ξ,9α-triol triacetate is converted respectively into 4-ethyl-6-methyl-11α,15α-bistetrahydropyran-2'yloxyprosta-

4,5,13-*trans*-triene-1,9α-diol diacetate and 4-propyl-6-methyl-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate.

EXAMPLE 16.

Examples 4 and 5 are repeated using 4,6-dimethyl-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate as starting material, to produce successively 4,6-dimethyl-11α-15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol, 4,6-dimethyl-9-oxo-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid and 4,6-dimethyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid.

In a similar manner, starting from 4,6-dimethyl-15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol-diacetate.

4-methyl-6-ethyl-11α,15α-bistetrahydropyran-2'-yloxy-prosta-4,5,13-*trans*-triene-1,9α-diol diacetate,

4-methyl-6-propyl-11α,15α-bistetrahydropyran-2'-yloxy-prosta-4,5,13-*trans*-triene-1,9α-diol diacetate,

4-ethyl-6-methyl-11α,15α-bistetrahydropyran-2'-yloxy-prosta-4,5,13-*trans*-triene-1,9α-diol diacetate and

4-propyl-6-methyl-11α,15α-bistetrahydropyran-2'-yloxy-prosta-4,5,13-*trans*-triene,1,9α-diol diacetate, there are produced, as final products:

4,6-dimethyl-9-oxo-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid,

4-methyl-6-ethyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid,

4-methyl-6-propyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid,

4-ethyl-6-methyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, and

4-propyl-6-methyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, respectively.

EXAMPLE 17.

A solution of 453 mg. of 6-methyl-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate in 5 ml. of methanol is cooled to −10°C. and treated, under argon atmosphere, with 1.1 molar equivalents of potassium carbonate. The reaction mixture is stirred for 6 hours at −10°C. and then evaporated to dryness under reduced pressure, water is added and the product extracted with diethyl ether. The diethyl ether extract is washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under *vacuo*. The residue is purified by t.l.c., to produce the pure 6-methyl-9α-acetoxy-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trien-1-ol.

Upon oxidation of the foregoing compound with 8N chromic acid, in accordance with the method of Example 5, there is produced 6-methyl-9α-acetoxy-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid.

A mixture of 300 mg. of 6-methyl-9α-acetoxy-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid, 5 ml. of anhydrous methanol and 150 mg. of anhydrous potassium carbonate is stirred at room temperature for 18 hours, under an argon atmosphere. The solvent is then eliminated under reduced pressure, water is added and then acidified with acetic acid. The product is extracted with diethyl ether and the organic extract washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under reduced pressure, to afford 6-methyl-9α-hydroxy-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid.

A solution of 50 mg. of 6-methyl-9α-hydroxy-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid in 0.15 ml. of tetrahydrofuran is treated with 1.3 ml. of 65% aqueous acetic acid. The reaction mixture is stirred at 45°C. for 4 hours, cooled to 0°C. and evaporated to dryness under reduced presure; the oily residue is purified by t.l.c. using chloroform:methanol (9:1) as eluant, thus yielding the pure 6-methyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid.

Likewise, starting from:

4,6-dimethyl-15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate,

4,6-dimethyl-11α,15α-bistetrahydropyran-2'-yloxy-prosta-4,5,13-*trans*-triene-1,9α-diol diacetate,

4-methyl-6-ethyl-11α,15α-bistetrahydropyran-2'-yloxy-prosta-4,5,13-*trans*-triene-1,9α-diol diacetate,
4-ethyl-6-propyl-11α,15α-bistetrahydropyran-2'-yloxy-prosta-4,5,13-*trans*-triene-1,9α-diol diacetate,
4-ethyl-6-methyl-11α,15α-bistetrahydropyran-2'-yloxy-prosta-4,5,13-*trans*-triene-1,9α-diol diacetate, and
4-propyl-6-methyl-11α,15α-bistetrahydropyran-2'-yloxy-prosta-4,5,13-*trans*-triene-1,9α-diol diacetate,

there are produced as final products:

4,6-dimethyl-9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid,
4,6-dimethyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid,
4-methyl-6-ethyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid,
4-ethyl-6-propyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid,
4-ethyl-6-methyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid and
4-propyl-6-methyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid, respectively.

EXAMPLE 18.

A mixture of 400 mg. of 9α-hydroxy-11α,15α-bistetrahydropyran-2'-yloxy-prosta-4,5,13-*trans*-trienoic acid and 60 ml. of etheral diazomethane is maintained at room temperature for 30 minutes. The solvent is then evaporated under *vacuo*, to yield 9α-hydroxy-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

In a similar manner, from the corresponding free acids there are produced the following compounds:

9α-hydroxy-15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
6-methyl-9α-hydroxy-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
4,6-dimethyl-9α-hydroxy-15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
4-methyl-6-ethyl-9α-hydroxy-11α,15α-bistetrahydropyran-2'-yloxy-prosta-4,5,13-*trans*-trienoic acid methyl ester,
4-propyl-6-methyl-9α-hydroxy-11α,15α-bistetrahydropyran-2'-yloxy-prosta-4,5,13-*trans*-trienoic acid methyl ester,
9-oxo-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
9-oxo-15α-tetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
4-methyl-9-oxo-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
6-methyl-9-oxo-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
4,6-dimethyl-9-oxo-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid methyl ester, and
4-propyl-6-methyl-9-oxo-11α,15α-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

EXAMPLE 19.

Examples 1, 2, 3, 6 (part A) and 18 are repeated but using [2'α-hydroxy-4'α-tetrahydropyran -2'''-yloxy-5'β-(3''β-tetrahydropyran-2'''-yloxyoct-1''-*trans*-en-1''-yl)cyclopent-1'α-yl] acetaldehyde γ-hemiacetal as starting material, thus obtaining successively 11α,15β-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6$\S$,9α-triol, 11α,15β-bistetrahydropyran-2'-yloxyprost-13-*trans*-en-4-yne-1,6$\S$,9α-triol triacetate, 11α,15β-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-triene-1,9α-diol diacetate, 9α-acetoxy-11α,15β-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trien-1-ol, 9α-acetoxy-11α,15β-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid, 9α-hydroxy-11α,15β-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-

trienoic acid and 9α-hydroxy-11α,15β-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

EXAMPLE 20.

A solution of 500 mg. of 9α-hydroxy-11α,15β-bistetrahydropyran-2'-yloxyprosta-4,5,13-*trans*-trienoic acid methyl ester in 10 ml. of 65% aqueous acetic acid is stirred at room temperature for 18 hours. It is then evaporated to dryness under reduced pressure, the residue is dissolved in ethyl acetate and the solvent is eliminated by distillation under *vacuo*. The residue is purified by chromatography on 50 g. of Florisil. The fractions eluted with diethyl ether-ethyl acetate (80:20) yield the pure 9α,11α,15β-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

In a similar manner, starting from the corresponding 11α,15α-bistetrahydropyran-2'-yloxy or 15α-tetrahydropyranyloxy compounds there are obtained the following products:

9α,11α,15α-dihydroxyprosta-4,5,13*trans*-trienoic acid methyl ester,
9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
6-methyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
4,6-dimethyl-9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
4-methyl-6-ethyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester and
4-propyl-6-methyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

EXAMPLE 21.

To a solution of 750 mg. of 9α,11α,15β-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester in 15 ml. of anhydrous tetrahydrofuran are added 3 g. of activated manganese dioxide, and the reaction mixture is stirred at room temperature for 6 hours, the manganese dioxide is filtered off and washed with acetone, the combined filtrates are evaporated to dryness under reduced pressure. The residue is redissolved in tetrahydrofuran and stirred with another 3 g. batch of manganese dioxide as above, repeating the operation twice. After final evaporation of the solvent and purification of the residue by chromatography on Florisil there is obtained the pure 9α,11α-dihydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester.

By repeating the above procedure but using 9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester as starting material there is also obtained 9α,11α-dihydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester.

In a similar manner, starting from 9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester, 6-methyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester, 4,6-dimethyl-9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,

4-methyl-6-ethyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester and
4-propyl-6-methyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester there are respectively obtained:
9α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,
6-methyl-9α,11α-dihydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,
4,6-dimethyl-9α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,
4-methyl-6-ethyl-9α,11α-dihydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester and
4-propyl-6-methyl-9α,11α-dihydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester.

EXAMPLE 22.

A. To a stirred mixture of 6 ml. of hexamethyldisilazane and 1.2 ml. of trimethylchlorosilane there is added a solution of 200 mg. of 9α,11α-dihydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester in 20 ml. of anhydrous tetrahydrofuran, under an argon atmosphere and the resulting mixture is stirred at room temperature, under anhydrous conditions for 16 hours. It is then evaporated

to dryness under reduced pressure.The residue is dissolved in 10 ml. of toluene and the solvent eliminated under *vacuo*, repeating the operation several times, thus obtaining the crude 9α,11α-bis(trimethylsilyloxy)-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester.

B. The foregoing crude product is dissolved in 20 ml. of anhydrous diethyl ether, and the resulting solution is cooled to −78°C. in a dry ice-acetone bath. To the stirred cold solution is added dropwise a diethyl ether solution of 1.1 molar equivalents of methyl lithium (2.8 ml. of 0.22 M methyl lithium in diethyl ether) under stirring and under an argon atmosphere. The resulting stirred mixture is allowed to attain room temperature, and stirred 2 additional hours at this temperature. It is then poured into saturated solution of ammonium chloride, the ethereal phase is separated, washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under *vacuo*, thus obtaining the crude 9α,11α-bis(trimethylsilyloxy)-15ξ-hydroxy-15ξ-methylprosta-4,5,13-*trans*-trienoic acid methyl ester. (Mixture of 15α-hydroxy-15β-methyl and 15β-hydroxy-15α-methyl compounds).

C. A solution of 250 mg. of the crude 9α,11α-bis(trimethylsilyloxy)-15ξ-hydroxy-15ξ-methylprosta-4,5,13-*trans*-trienoic acid methyl ester in 10 ml. of 70% aqueous methanol is kept at room temperature for 72 hours. The reaction mixture is then evaporated to dryness under reduced pressure and the residue containing a mixture of 9α,11α,15α-trihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid methyl ester and 9α,11α,15β-trihydroxy-15α-methylprosta-4,5,13-*trans*-trienoic acid methyl ester compounds, purified by thin layer chromatography using ethyl, acetate-diethyl ether (75:25) as eluant, thus obtaining the individual isomers, i.e., 9α,11α,15α-trihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid methyl ester and 9α,11α,15β-trihydroxy-15α-methylprosta-4,5,13-*trans*-trienoic acid methyl ester in pure form.

By repeating the procedures described in this Example but using as starting materials in part A the compounds listed below:

9α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,
6-methyl-9α,11α-dihydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,
4,6-dimethyl-9α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,
4-methyl-6-ethyl-9α,11α-dihydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester and
4-propyl-6-methyl-9α,11α-dihydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,

there are obtained as final products, respectively:

9α,15α-dihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid methyl ester and
9α,15β-dihydroxy-15α-methylprosta-4,5,13-*trans*-trienoic acid methyl ester;
6,15β-dimethyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester and 6,15α-dimethyl-9α,11α,15β-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester;
4,6,15β-trimethyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester and 4,6,15α-trimethyl-9α,11α,15β-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester;
4,15β-dimethyl-6-ethyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester; and 4-propyl-6,15β-dimethyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester and 4-propyl-6,15α-dimethyl-9α,11α,15β-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

EXAMPLE 23.

Twenty milligrams of 9α,11α,15α-trihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid methyl ester are dissolved in a mixture of 2ml. of methanol, 2 ml. of water and 90 mg. of potassium carbonate. The reaction mixture is maintained at 40°C. for 16 hours under nitrogen atmosphere, 10 ml. of water are then added, and the reaction mixture is then evaporated under reduced pressure to half volume. It is then acidified with 50% acetic acid and extracted several times with ethyl

acetate. The combined organic extracts are dried over sodium sulfate and evaporated to dryness under reduced pressure to yield 9α,11α,15α-trihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid.

In a similar manner 9α,15α-dihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid methyl ester and 6,15α-dimethyl-9α,11α,15β-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester are converted into the corresponding free acids.

EXAMPLE 24.

A. A suspension of 4 g. of crude pancreatic lipase (Sigma L—3126) in 40 ml. of an 0.1 M sodium chloride and 0.05 M calcium chloride solution in water is stirred at 25°C for one hour. The mixture is then centrifuged for one hour at 5000 rev./min. and at 25°C. to 30°C. The supernatant is neutralized with 1 N sodium hydroxide solution to pH 7.2 to 7.4 and used directly for the hydrolysis of the prostaglandin derivatives of the invention.

B. Forty-two milligrams of 9α,11α,15α-trihydroxy-15β-methylprosta-4,5-13-*trans*-trienoic acid methyl ester are dissolved by sonication at 37°C. for 20 minutes in 30 ml. of the lipase solution prepared as described in part A. The reaction mixture is magnetically stirred for 15 minutes at 25°C. to 26°C., adjusting constantly the pH at 7.2 to 7.4 during the reaction period with 1 N sodium hydroxide solution. The reaction mixture is then acidified to pH 2.5 using an 0.2 N hydrochloric acid solution and the product extracted several times from the solution with ethyl acetate and diethyl ether. The combined organic extracts are dried over magnesium sulfate and evaporated to dryness under *vacuo*. The residue is dissolved in methylene-chloride and chromatographed on 3 g. of Florisil. The column is eluted successively with methylene chloride-diethyl ether mixtures, diethyl ether, diethyl ether-ethyl acetate mixtures, pure ethyl acetate and ethyl acetate-methanol (80:20). The fractions eluted with the latter solvent mixture afford the pure 9α,11α,15α-trihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid, identical to the product obtained in Example 23.

In a similar manner by following the above procedure, the remaining alkyl ester compounds obtained in Example 22 as final products are converted into the corresponding free acids.

EXAMPLE 25.

To a solution of 500 mg. of 9-oxo-11α,15α-bistetrahydropyranyloxyprosta-4,5,13-*trans*-trienoic acid methyl ester in 10 ml. of 65% aqueous acetic acid is stirred at room temperature for 18 hours. It is then evaporated to dryness under reduced pressure, the residue is dissolved in ethyl acetate and the solvent is eliminated by distillation under *vacuo*. The residue is purified by chromatography on 50 g. of Florisil. The fractions eluted with diethyl ether-ethyl acetate (80:20) yield the pure 9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

In a similar manner, starting from the corresponding 9-keto-11α,15α-bistetrahydropyranyloxy or 15α-monotetrahydropyranyloxy compounds of Example 18 there are obtained the following products:

9-oxo-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
4-methyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
6-methyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
4,6-dimethyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester and
4-propyl-6-methyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

EXAMPLE 26.

To a solution of 400 mg. of 9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester in 3 ml. of methanol is added a solution of 400 mg. of hydroxylamine hydrochloride and 500 mg. of sodium acetate in 10 ml. of methanol-water (1:1). The resulting reaction mixture is kept at room temperature for 18 hours under argon atmosphere and the solvent is then eliminated under reduced pressure. The residue is taken up in water and the mixture extracted with ethyl acetate, the organic phase is separated, washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under

vacuo, thus obtaining 9-hydroxyimino-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

In a similar manner, starting from the remaining respective 9-oxo compounds obtained in Example 25, there are obtained the corresponding oximes, i.e., 9-hydroxyimino-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester, 4-methyl-9-hydroxyimino-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester, 6-methyl-9-hydroxyimino-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,

4,6-dimethyl-9-hydroxyimino-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester, and
4-propyl-6-methyl-9-hydroxyimino-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

EXAMPLE 27.

To a solution of 250 mg. of 9-hydroxyimino-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester in 5 ml. of anhydrous tetrahydrofuran is added 1 g. of activated manganese dioxide, and the reaction mixture is stirred at room temperature for 6 hours, the manganese dioxide is filtered off and washed with acetone and the combined filtrates are evaporated to dryness under reduced pressure. The residue is redissolved in tetrahydrofuran and stirred with another 1 g. batch of manganese dioxide as above, repeating the operation twice. After final evaporation of the solvent and purification of the residue by chromatography on Florisil there is obtained the pure 9-hydroxyimino-11α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester.

By repeating the above procedure but using 9-hydroxyimino-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,

4-methyl-9-hydroxyimino-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
6-methyl-9-hydroxyimino-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
4,6-dimethyl-9-hydroxyimino-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester and
4-propyl-6-methyl-9-hydroxyimino-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester as starting materials there are respectively obtained:
9-hydroxyimino-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,
4-methyl-9-hydroxyimino-11α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,
6-methyl-9-hydroxyimino-11α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,
4,6-dimethyl-9-hydroxyimino-11α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester and
4-propyl-6-methyl-9-hydroxyimino-11α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester.

EXAMPLE 28.

A. To a stirred mixture of 3 ml. of hexamethyldisilazane and 0.6 ml. of trimethylchlorosilane there is added a solution of 200 mg. of 9-hydroxyimino-11α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester in 15 ml. of anhydrous tetrahydrofuran, under an argon atmosphere and the resulting mixture is stirred at room temperature, under anhydrous conditions for 16 hours. It is then evaporated to dryness under reduced pressure. The residue is dissolved in 10 ml. of toluene and the solvent eliminated under *vacuo*, repeating the operation several times, thus obtaining the crude 9-trimethylsilyloxyimino-11α-trimethylsilyloxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester.

B. The foregoing crude product is dissolved in 20 ml. of anhydrous diethyl ether, and the resulting solution is cooled to −78°C. in a dry ice-acetone bath. To the stirred cold solution is added dropwise a diethyl ether solution of 1.1 molar equivalents of methyl lithium (2.7 ml. of 0.22 M methyl lithium in diethyl ether) under stirring and under an argon atmosphere. The resulting stirred mixture is allowed to attain room temperature, and stirred 2 additional hours at this temperature. It is then poured into saturated ammonium chloride solution, the

ethereal phase is separated, washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under *vacuo*, thus obtaining the crude 9-trimethylsilyloxyimino-11α-trimethylsilyloxy-15ξ-hydroxy-15ξ-methyl-prosta-4,5,13-*trans*-trienoic acid methyl ester. (Mixture of 15α-hydroxy-15β-methyl and 15β-hydroxy-15α-methyl compounds).

C. A solution of 250 mg. of the crude 9-trimethylsilyloxyimino-11α-trimethylsilyoxy-15ξ-hydroxy-15ξ-methylprosta-4,5,13-*trans*-trienoic acid methyl ester in 10 ml. of 70% aqueous methanol is kept at room temperature for 18 hours under carbon dioxide atmosphere. The reaction mixture is then evaporated to dryness under reduced pressure and the residue purified by thin layer chromatography using ethyl acetate-ether (75:25) as eluant, thus obtaining the individual isomers, i.e., 9-hydroxyimino-11α,15α-dihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid methyl ester and 9-hydroxyimino-11α,15β-dihydroxy-15α-methylprosta-4,5,13-*trans*-trienoic acid methyl ester in pure form.

D. To a stirred solution of 150 mg. of 9-hydroxyimino-11α,15α-dihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid methyl ester in 3 ml. of methanol is added a solution of 150 mg. of thallium (III) nitrate in 3 ml. of methanol. The reaction mixture is stirred at room temperature for 10 minutes, and the formed precipitate separated by filtration and washed with methanol. To the filtrate are added 5 ml. of dilute acetic acid and the mixture is stirred for 5 minutes, it is then extracted with diethyl ether and the organic extract washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue is purified by chromatography on Florisil. The fractions eluted with diethyl ether-ethyl acetate (9:1) afford the pure 9-oxo-11α,15α-dihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid methyl ester.

By repeating the procedures described in this Example but using as starting materials in part A the compounds listed below:

4-methyl-9-hydroxyimino-11α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,
6-methyl-9-hydroxyimino-11α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,
4,6-dimethyl-9-hydroxyimino-11α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester and
4-propyl-6-methyl-9-hydroxyimino-11α-hydroxy-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester,

there are obtained are final products, respectively:

4,15β-dimethyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester and 4,15α-dimethyl-9-oxo-11α,15β-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
6,15β-dimethyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester and 6,15α-dimethyl-9-oxo-11α,15β-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
4,6,15β-trimethyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester and 4,6,15α-trimethyl-9-oxo-11α,15β-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester, and
4-propyl-6,15β-dimethyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester and 4-propyl-6,15α-dimethyl-9-oxo-11α,15β-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

Similarly, by repeating the procedure of parts B and D, using 9-hydroxyimino-15-oxoprosta-4,5,13-*trans*-trienoic acid methyl ester as starting material there is obtained a mixture of 9-oxo-15α-hydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid methyl ester and the 15β-hydroxy-15α-methyl isomer, which is separated by chromatography on Florisil.

EXAMPLE 29.

In accordance with the method described in Example 24, 9-oxo-11α,15α-dihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid methyl ester is converted into 9-oxo-11α,15α-dihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid.

Likewise, the remaining compounds obtained as final products in Example 28 are converted into the corresponding free acids.

EXAMPLE 30.

To a solution of 100 mg. of 9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid in 5 ml. of methylene chloride is added an ethereal solution of diazomethane until the color of the reagent persists in the mixture. The reaction mixture is maintained at room temperature for 1 hour and is then evaporated to dryness under reduced pressure, thus obtaining 9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

In a similar manner, 9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid, 4-methyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, 4-ethyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, 4-methyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid, 9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, 4,6-dimethyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid, 6-methyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid and 4-propyl-6-methyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid are converted into the corresponding methyl esters.

Likewise, the ethyl esters of the foregoing acids are produced using diazoethane *in lieu* of diazomethane.

EXAMPLE 31.

To a solution of 100 mg. of 9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid in 10 ml. of methanol is added 2.6 ml. of a 0.1N solution of sodium hydroxide, and the mixture is stirred at room temperature for 1 hour. It is then evaporated to dryness under reduced pressure, to give the sodium salt of 9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid.

By employing 1.1 molar equivalents of potassium hydroxide (in the form of a 0.1 N solution) in place of sodium hydroxide in the above procedure the potassium salt of 9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid is obtained.

Similarly, the sodium and potassium salts of the other prostatrienoic acid derivatives obtained in Examples 5, 6, 8, 9, 14, 16, 17, 24 and 29, are produced.

EXAMPLE 32.

To a solution of 100 mg. of 9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid in 10 ml. of methanol is added a mixture of 3 ml. of concentrated ammonium hydroxide solution and 5 ml. of methanol. The resulting mixture is stirred for two hours at room temperature and then evaporated to dryness, to yield the ammonium salt of 9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid.

By employing dimethylamine, diethylamine or dipropylamine in place of ammonium hydroxide in the above process the corresponding salts of 9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid are obtained.

In a similar manner, the ammonium dimethylamine diethylamine and dipropylamine salts of the other prostanoic acid derivatives of the previous Examples can be prepared e.g., the amine salts of 9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid,

4-ethyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid,
9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid,
4-methyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid,
4-propyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid,
6-methyl-9-oxo-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid,
4,6-dimethyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid,
4-methyl-6-ethyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid,
9α,15α-dihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid,
9-oxo-11α,15α-dihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid and
6-methyl-9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid.

EXAMPLE 33.

A mixture of 100 mg. of 9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester, 0.4 ml. of pyridine and 0.8 ml. of acetic anhydride is kept at room temperature for 1 hour. The reaction mixture is then evaporated to dryness under reduced pressure and the residue is dissolved in ethyl acetate. Fifty milligrams of sodium bisulfate are added and the solution is filtered through Celite,

diatomaceous earth. The filtrate is evaporated to dryness under reduced pressure to yield 9α,11α,15α-triacetoxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

By the same process but using propionic, caproic and cyclopentylpropionic anhydrides as esterifying agents there are produced the corresponding triesters of the methyl ester of 9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid.

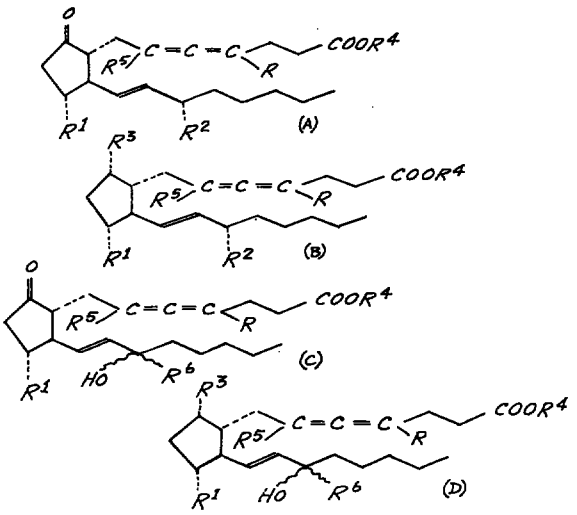
In a similar manner, other prostatrienoic acid derivatives obtained in Examples 6, 8, 9, 14, 16, 17 and 30 are converted into the corresponding diesters or triesters.

Representative compounds thus obtained are:

9-oxo-11α,15α-diacetoxyprosta-4,5,13-*trans*-trienoic acid,
9-oxo-11α,15α-diacetoxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
9-oxo-11α,15α-dipropionoxy-4,5,13-*trans*-trienoic acid ethyl ester,
9α,15α-diacetoxyprosta-4,5,13-*trans*-trienoic acid,
9α,11α,15α-triacetoxy-4-methylprosta-4,5,13-*trans*-trienoic acid,
9α,11α,15α-tripropionoxy-4-ethylprosta-4,5,13-*trans*-trienoic acid,
9α,11α,15α-tricaproxy-4-propylprosta-4,5,13-*trans*-trienoic acid,
9-oxo-11α,15α-diacetoxy-4-methylprosta-4,5,13-*trans*-trienoic acid methyl ester,
9-oxo-11α,15α-diacetoxy-4-ethylprosta-4,5,13-*trans*-trienoic acid methyl ester,
6-methyl-9-oxo-11α,15α-diacetoxyprosta-4,5,13-*trans*-trienoic acid,
4-methyl-6-ethyl-9-oxo-11α,15α-dipropionoxyprosta-4,5,13-*trans*-trienoic acid,
4,6-dimethyl-9α,11α,15α-triacetoxyprosta-4,5,13-*trans*-trienoic acid, and
4-propyl-6-methyl-9α,11α,15α-tricaproxyprosta-4,5,13-*trans*-trienoic acid.

WHAT WE CLAIM IS:—

1. A compound selected from racemic mixtures represented by the following formulas:



wherein

each of R and R^5 represents hydrogen, methyl, ethyl or propyl;

R^1 represents hydrogen, hydroxy, or esterified or etherified hydroxy;

each of R^2 and R^3 represents hydroxy, or esterified or etherified hydroxy;

R^6 represents methyl, ethyl or propyl,

R^4 represents hydrogen, a C_{1-4} alkyl group or the pharmaceutically acceptable, non-toxic salts of compounds in which R^4 is hydrogen and the wavy

diatomaceous earth. The filtrate is evaporated to dryness under reduced pressure to yield 9α,11α,15α-triacetoxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

By the same process but using propionic, caproic and cyclopentylpropionic anhydrides as esterifying agents there are produced the corresponding triesters of the methyl ester of 9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid.

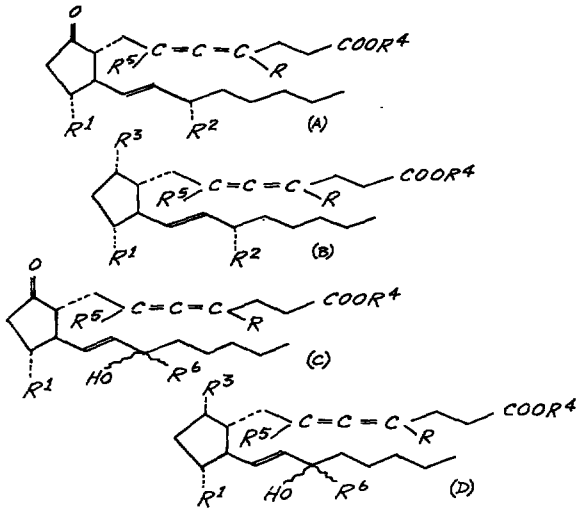
In a similar manner, other prostatrienoic acid derivatives obtained in Examples 6, 8, 9, 14, 16, 17 and 30 are converted into the corresponding diesters or triesters.

Representative compounds thus obtained are:

9-oxo-11α,15α-diacetoxyprosta-4,5,13-*trans*-trienoic acid,
9-oxo-11α,15α-diacetoxyprosta-4,5,13-*trans*-trienoic acid methyl ester,
9-oxo-11α,15α-dipropionoxy-4,5,13-*trans*-trienoic acid ethyl ester,
9α,15α-diacetoxyprosta-4,5,13-*trans*-trienoic acid,
9α,11α,15α-triacetoxy-4-methylprosta-4,5,13-*trans*-trienoic acid,
9α,11α,15α-tripropionoxy-4-ethylprosta-4,5,13-*trans*-trienoic acid,
9α,11α,15α-tricaproxy-4-propylprosta-4,5,13-*trans*-trienoic acid,
9-oxo-11α,15α-diacetoxy-4-methylprosta-4,5,13-*trans*-trienoic acid methyl ester,
9-oxo-11α,15α-diacetoxy-4-ethylprosta-4,5,13-*trans*-trienoic acid methyl ester,
6-methyl-9-oxo-11α,15α-diacetoxyprosta-4,5,13-*trans*-trienoic acid,
4-methyl-6-ethyl-9-oxo-11α,15α-dipropionoxyprosta-4,5,13-*trans*-trienoic acid,
4,6-dimethyl-9α,11α,15α-triacetoxyprosta-4,5,13-*trans*-trienoic acid, and
4-propyl-6-methyl-9α,11α,15α-tricaproxyprosta-4,5,13-*trans*-trienoic acid.

WHAT WE CLAIM IS:—

1. A compound selected from racemic mixtures represented by the following formulas:



wherein

each of R and R^5 represents hydrogen, methyl, ethyl or propyl;

R^1 represents hydrogen, hydroxy, or esterified or etherified hydroxy;

each of R^2 and R^3 represents hydroxy, or esterified or etherified hydroxy;

R^6 represents methyl, ethyl or propyl,

R^4 represents hydrogen, a C_{1-4} alkyl group or the pharmaceutically acceptable, non-toxic salts of compounds in which R^4 is hydrogen and the wavy

lines (ξ) indicate the α or β configuration or mixtures thereof; provided that if R^1 is not hydrogen it is the same as R^2 and R^3.

2. A racemic compound according to Claim 1 wherein R^1, R^2 and R^3 are hydroxy and R, R^4 and R^5 are hydrogen.

3. A racemic compound according to Claim 1 wherein R, R^1, R^4 and R^5 are hydrogen and R^2 and R^3 are hydroxy.

4. A racemic compound according to Claim 1 wherein R is methyl, ethyl or propyl, R^1, R^2 and R^3 are hydroxy and R^4 and R^5 are hydrogen.

5. A racemic compound according to Claim 1 wherein R is methyl, ethyl or propyl, R^2 and R^3 are hydroxy and R^1, R^4 and R^5 are hydrogen.

6. A racemic compound according to Claim 1 wherein R^5 is methyl, ethyl or propyl, R^1, R^2 and R^3 are hydroxy and R and R^4 are hydrogen.

7. A racemic compound according to Claim 1 wherein R^5 is methyl, ethyl or propyl, R^2 and R^3 are hydroxy and R, R^1 and R^4 are hydrogen.

8. A racemic compound according to Claim 1 wherein each of R and R^3 are methyl, ethyl or propyl, R^1, R^2 and R^3 are hydroxy and R^4 is hydrogen.

9. A racemic compound according to Claim 1 wherein each of R and R^5 are methyl, ethyl or propyl, R^2 and R^3 are hydroxy and R^1 and R^4 are hydrogen.

10. Racemic 9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, and the nontoxic, pharmaceutically acceptable salts thereof.

11. Racemic 9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

12. Racemic 9-oxo-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid, and the non-toxic, pharmaceutically acceptable salts thereof.

13. Racemic 4-methyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid and the non-toxic, pharmaceutically acceptable salts thereof.

14. Racemic 4-methyl-9-oxo-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid, and the non-toxic, pharmaceutically acceptable salts thereof.

15. Racemic 6-methyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid and the non-toxic, pharmaceutically acceptable salts thereof.

16. Racemic 6-methyl-9-oxo-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid, and the non-toxic, pharmaceutically acceptable salts thereof.

17. Racemic 4,6-dimethyl-9-oxo-11α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, and the non-toxic, pharmaceutically acceptable salts thereof.

18. Racemic 4,6-dimethyl-9-oxo-15α-hydroxyprosta-4,5,13-*trans*-trienoic acid, and the non-toxic, pharmaceutically acceptable salts thereof.

19. Racemic 9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid, and the non-toxic, pharmaceutically acceptable salts thereof.

20. Racemic 9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid methyl ester.

21. Racemic 9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, and the non-toxic, pharmaceutically acceptable salts thereof.

22. Racemic 4-methyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid and the non-toxic, pharmaceutically acceptable salts thereof.

23. Racemic 4-methyl-9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, and the non-toxic, pharmaceutically acceptable salts thereof.

24. Racemic 6-methyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid, and the non-toxic, pharmaceutically acceptable salts thereof.

25. Racemic 6-methyl-9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid, and the non-toxic, pharmaceutically acceptable salts thereof.

26. Racemic 4,6-dimethyl-9α,11α,15α-trihydroxyprosta-4,5,13-*trans*-trienoic acid and the non-toxic, pharmaceutically acceptable salts thereof.

27. Racemic 4,6-dimethyl-9α,15α-dihydroxyprosta-4,5,13-*trans*-trienoic acid and the non-toxic, pharmaceutically acceptable salts thereof.

28. A racemic compound according to Claim 1 formulas (C) and (D) wherein the hydroxy group at C—15 is in α-configuration and the alkyl group at said position is in β-configuration.

29. A racemic compound according to Claim 1 formulas (C) and (D) wherein the hydroxy group at C—15 is in β-configuration and the alkyl group at said position is in α-configuration.

30. Racemic 9-oxo-11α,15α-dihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid, and the non-toxic pharmaceutically acceptable salts thereof.

31. Racemic 9-oxo-15α-hydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid, and the non-toxic, pharmaceutically acceptable salts thereof.

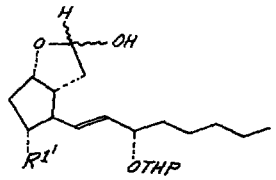
* C L M S *

32. Racemic 9α,11α,15α-trihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid and the non-toxic, pharmaceutically acceptable salts thereof.

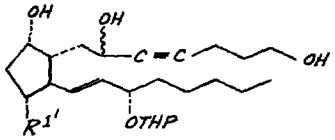
33. Racemic 9α,15α-dihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid and the non-toxic, pharmaceutically acceptable salts thereof.

34. A process for producing a racemic compound of claim 1 of formula A or formula B, which comprises the steps of:

a) treating a compound of the formula:



wherein $R^{1'}$ is hydrogen or tetrahydropyran-2-yloxy, with an excess of the dilithium salt of pent-4-yn-1-ol in an inert organic solvent to obtain a trihydroxy-acetylenic compound of the formula:

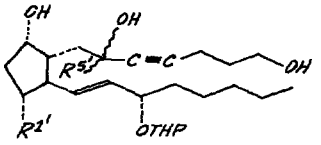


wherein $R^{1'}$ is as defined above;

b) converting the acetylenic compound of step a) into a triester, or

c) selectively oxidizing the hydroxyl group at C—6;

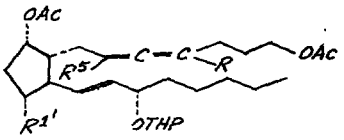
d) treating the dihydroxy oxo acetylenic compound of step c) with an alkyl lithium or an alkyl magnesium halide in which the alkyl group is methyl, ethyl or propyl in an inert organic solvent to produce a compound of the formula:



wherein $R^{1'}$ is as defined above and $R^{5'}$ is methyl, ethyl or propyl;

e) converting the 6-alkyl acetylenic compound of step d) into a triester;

f) treating a triester of steps b) or e) with a lithium dialkyl copper reagent, in which the alkyl radicals are the same and are methyl, ethyl or propyl, under an inert atmosphere, in an ether solvent, using about 4 molar equivalents of lithium dialkyl copper at −50°C. to −78°C. or about 1 molar equivalent of lithium dialkyl copper at about 0°C., to produce a compound of the formula:



wherein $R^{1'}$ is as defined above, and R and R^5 are as defined in claim 1, Ac is an acyl group of 1 to 4 carbon atoms;

g) hydrolyzing the compound of step f) under alkaline conditions;

h) oxidizing the mono- or dihydroxylated compound obtained in step g);

i) hydrolyzing the protected hydroxyl groups which remain in the molecule and

j) optionally esterifying or etherifying the hydroxyl groups and/or converting the carboxylic acid group into an alkyl ester or a pharmaceutically acceptable salt thereof.

35. A process in accordance with Claim 34 in which in step a) are used from 5 to 15 molar equivalents of the dilithium salt of pent-4-yn-1-ol in diethyl ether solution, conducting the reaction under substantially anhydrous conditions and under inert atmosphere, at about room temperature.

* C L M S *

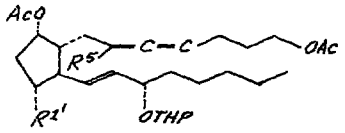
36. A process in accordance with Claim 34 wherein the reagent used in step b) is acetyl chloride.

37. A process in accordance with Claim 34 wherein the oxidation of step c) is effected with manganese dioxide.

38. A process in accordance with Claim 34 wherein the esterification of step e) is effected using methyl lithium and acetyl chloride as reagents.

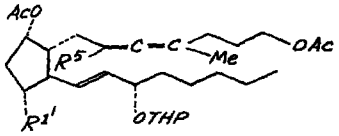
39. A process in accordance with Claim 34 wherein the reagent used in step f) is lithium dimethyl copper.

40. A process in accordance with Claim 39 wherein there are used four molar equivalents of lithium dimethyl copper in diethyl ether solution, conducting the reaction at a temperature between −78°C. to −50°C. for a period of time of 3 to 7 hours and under an inert atmosphere, obtaining as intermediate a compound of the formula:



wherein $R^{1'}$, R^5 and Ac are as defined above.

41. A process in accordance with Claim 39 wherein there is used one molar equivalent of lithium dimethyl copper in diethyl ether solution, conducting the reaction at about 0°C. for a period of time of 3 to 7 hours and under an inert atmosphere, obtaining as intermediate a compound of the formula:



wherein $R^{1'}$, R^5 and Ac are as defined above.

42. A process in accordance with Claim 34 wherein the basic hydrolysis of step g) is effected using an excess of anhydrous potassium carbonate in methanol at room temperature or below to hydrolyze both acyloxy groups present at C—1 and C—9.

43. A process in accordance with Claim 34 wherein the basic hydrolysis of step g) is effected using 1.1 molar equivalent of anhydrous potassium carbonate in methanol solution at about 0°C., to hydrolyze selectively the primary acyloxy group at C—1.

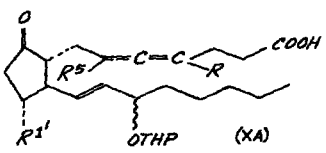
44. A process in accordance with Claim 34 wherein the reagent used for the oxidation of step h) is an 8 N solution of chromic acid in acetone solution in the presence of sulfuric acid, using stoichiometric amounts of this reagent, conducting the reaction at about −10°C. for about 2 hours.

45. A process in accordance with Claim 34 wherein in step i) the tetrahydropyranyloxy groups are hydrolyzed using aqueous solutions of acetic acid, oxalic acid or tartaric acid.

46. A process in accordance with Claim 45 wherein the hydrolyzing agent is 65% V/V aqueous acetic acid.

47. A process for producing a racemic compound of Claim 1 of formula C, which comprises the steps of:

a) converting a compound of the formula:



wherein

each of R and R^5 is as defined in claim 1; and

$R^{1'}$ is hydrogen or tetrahydropyran-2-yloxy, into an alkyl ester;

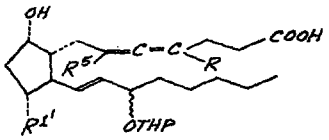
b) hydrolyzing the tetrahydropyranyloxy groups,

c) protecting the 9-oxo group as the oxime,

* C L M S *

d) selectively oxidizing the hydroxyl group at C—15,
e) protecting the hydroxyl group at C—11α when present as the trimethylsilyl ether;
f) treating the 15-oxo-compound with a slight molar excess of an alkylmagnesium halide in which the alkyl group is methyl, ethyl or propyl to produce the corresponding 15ξ-hydroxy-15ξ-alkyl derivatives,
g) hydrolyzing the trimethylsilyloxy group when present,
h) optionally separating the 15α-hydroxy-15β-alkyl and 15β-hydroxy-15α-alkyl isomers;
i) hydrolyzing the oxime to the corresponding oxo compound,
j) hydrolyzing the alkyl ester group by chemical or enzymatic methods and
k) optionally esterifying or etherifying the secondary hydroxyl group when present and/or converting the carboxylic acid function into the pharmaceutically acceptable salts.

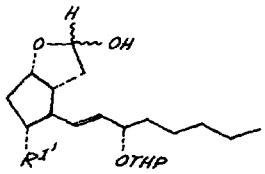
48. A process for producing a racemic compound of Claim 1 of formula D, which comprises the steps of:
a) converting a compound of the formula:



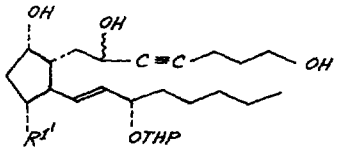
(XIVA)

wherein each of R and R^5 is as defined in Claim 1 and $R^{1'}$ is hydrogen or tetrahydropyran-2-yloxy into an alkyl ester,
b) hydrolyzing the tetrahydropyranyloxy groups,
c) selectively oxidizing the hydroxyl group at C—15,
d) protecting the hydroxyl groups present as the trimethylsilyl ethers,
e) treating the trimethylsilyloxy-15-oxo compound with a slight molar excess of an alkyl lithium or an alkylmagnesium halide in which the alkyl group is methyl, ethyl or propyl, to produce the corresponding 15ξ-hydroxy-15ξ-alkyl derivative,
f) hydrolyzing the trimethylsilyloxy groups present;
g) optionally separating the 15α-hydroxy-15β-alkyl and 15β-hydroxy-15α-alkyl isomers;
h) hydrolyzing the alkyl ester group by chemical or enzymatic methods, and
i) optionally esterifying or etherifying the secondary hydroxyl groups present, and/or converting the carboxylic acid function into the pharmaceutically acceptable salts.

49. A process for producing a racemic compound of Claim 1 which process comprises
A for the production of the compounds of the formulas A and B, the steps of:
a) treating a compound of the formula:



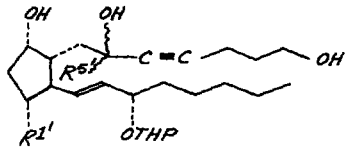
wherein $R^{1'}$ is hydrogen or tetrahydropyran-2-yloxy with an excess of the dilithium salt of pent-4-yn-1-ol in an inert organic solvent to obtain a trihydroxyacetylenic compound of the formula:



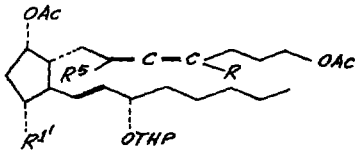
wherein $R^{1'}$ is as defined above;
b) converting the acetylenic compound of step a) into a triester, or
c) selectively oxidizing the hydroxyl group at C—6;

* C L M S *

d) treating the dihydroxy oxo acetylenic compound of step c) with an alkyl lithium or an alkyl magnesium halide in which the alkyl group is methyl, ethyl or propyl in an inert organic solvent to produce a compound of the formula:

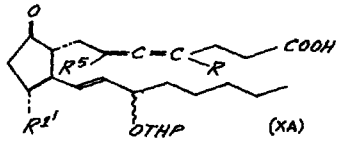


wherein $R^{1'}$ is as defined above and $R^{5'}$ is methyl, ethyl or propyl;
e) converting the 6-alkyl acetylenic compound of step d) into a triester;
f) treating a triester of steps b) or e) with a lithium dialkyl copper reagent in which the alkyl radicals are the same and are methyl, ethyl or propyl, under an inert atmosphere, in an ether solvent, using about 4 molar equivalents of lithium dialkyl copper about 1 molar equivalent of lithium dialkyl copper at about 0°C., to produce a compound of the formula:



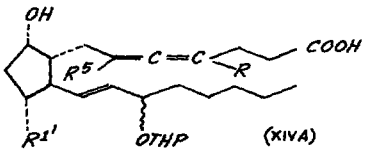
wherein $R^{1'}$ is as defined above, and R and R^5 are as defined in Claim 1,
Ac is an acyl group of 1 to 4 carbon atoms;
g) hydrolyzing the compound of step f) under alkaline conditions;
h) oxidizing the mono- or dihydroxylated compound obtained in step g);
i) hydrolyzing the protected hydroxyl groups which remain in the molecule and
j) optionally esterifying or etherifying the hydroxyl groups and/or converting the carboxylic acid group into an alkyl ester or a pharmaceutically acceptable salt thereof;

B for the production of the compounds of the formula C, the steps of:
a) converting a compound of the formula:



wherein
each of R and R^5 is as defined in Claim 1; and
R^1 is hydrogen or tetrahydropyran-2'-yloxy, into an alkyl ester;
b) hydrolyzing the tetrahydropyranyloxy groups,
c) protecting the 9-oxo group as the oxime,
d) selectively oxidizing the hydroxyl group at C—15,
e) protecting the hydroxyl group at C—11α when present as the trimethylsilyl ether;
f) treating the 15-oxo-compound with a slight molar excess of an alkyl lithium or an alkylmagnesium halide in which the alkyl group is methyl, ethyl or propyl to produce the corresponding 15ξ-hydroxy-15ξ-alkyl derivatives,
g) hydrolyzing the trimethylsilyloxy group when present,
h) separating the 15α-hydroxy-15β-alkyl and 15β-hydroxy-15α-alkyl isomers;
i) hydrolyzing the oxime to the corresponding oxo compound,
j) hydrolyzing the alkyl ester group by chemical or enzymatic methods and
k) optionally esterifying or etherifying the secondary hydroxyl group when present and/or converting the carboxylic acid function into the pharmaceutically acceptable salts;

C for the production of the compounds of the formula D, the steps of:
a) converting a compound of the formula:



* C L M S *

wherein each of R and R^3 is as defined in Claim 1 and R^{11} is hydrogen or tetrahydropyran-2-yloxy into an alkyl ester,
b) hydrolyzing the tetrahydropyranyloxy groups,
c) selectively oxidizing the hydroxyl group at C—15,
d) protecting the hydroxyl groups present as the trimethylsilyl ethers,
e) treating the trimethylsilyloxy-15-oxo compound with a slight molar excess of an alkyl lithium or an alkylmagnesium halide in which the alkyl group is methyl, ethyl or propyl, to produce the corresponding 15ξ-hydroxy-15ξ-alkyl derivative,
f) hydrolyzing the trimethylsilyloxy groups present;
g) optionally separating the 15α-hydroxy-15β-alkyl and 15β-hydroxy-15α-alkyl isomers;
h) hydrolyzing the alkyl ester group by chemical or enzymatic methods, and
i) optionally esterifying or etherifying the secondary hydroxyl groups present, and/or converting the carboxylic acid function into the pharmaceutically acceptable salts.

50. The mixture of racemic 9α,11α,15α-trihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid methyl ester and racemic 9α,11α,15β-trihydroxy-15α-methylprosta-4,5,13-*trans*-trienoic acid methyl ester.

51. Racemic 9α,11α,15α-trihydroxy-15β-methylprosta-4,5,13-*trans*-trienoic acid methyl ester.

52. Racemic 9α,11α,15β-trihydroxy-15α-methylprosta-4,5,13-*trans*-trienoic acid methyl ester.

53. A racemic compound according to Claim 1 substantially as herein described and exemplified.

54. A process according to any one of Claims 34, 47, 48 and 49, substantially as herein described and exemplified.

55. The product of the process of any one of Claims 34 to 49 and 54.

56. A pharmaceutical composition comprising a compound of any one of Claims 1 to 33, 50 to 53 and 55 and an excipient therefor.

MEWBURN, ELLIS & CO.,
Chartered Patent Agents,
70/72 Chancery Lane,
London, WC2A 1AD.
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1975.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

