

PATENT SPECIFICATION

(11) 1 414 881

- (21) Application No. 40736/73 (22) Filed 29 Aug. 1973
 (31) Convention Application No. 287 333 (32) Filed 8 Sept. 1972
 (31) Convention Application No. 379 127 (32) Filed 13 July 1973 in
 (33) United States of America (US)
 (44) Complete Specification published 19 Nov. 1975
 (51) INT CL² C07C 177/00; A61K 31/19, 31/215; C07C 61/38,
 69/74//C07D 307/93, 309/12, 407/12
 C07F 9/40



(52) Index at acceptance

C2C 121X 147X 167Z 200 201 204 20Y 213 215 225 227
 22Y 237 247 253 25Y 28X 292 29X 29Y 302 304
 305 306 30Y 311 31Y 322 32Y 351 352 353 355
 35Y 360 362 363 364 366 367 368 36Y 386 387
 388 389 409 40Y 431 435 43X 490 491 500 502
 506 507 509 50Y 620 623 624 625 628 633 635
 652 655 658 65X 662 672 67X 697 698 761 767
 770 771 790 79Y BJ BW NC TU UC UN WD
 C2P 3B11A 3B14A 3B19E 7

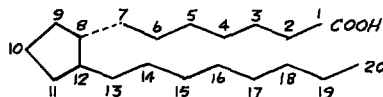
(54) DIFLUOROMETHYLENE SUBSTITUTED
PROSTAGLANDIN DERIVATIVES

(71) We, SYNTEX (U.S.A.) INC., a Corporation organised under the laws of the State of Delaware, United States of America, of 3401 Hillview Avenue, Palo Alto, California 94304, United States of America, 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.

In a further aspect, the present invention relates to antimeric and racemic prostaglandin derivatives and 5-*cis*-13-*trans*-dienoic acid derivatives having a difluoromethylene (difluorocyclopropyl) group attached to the C—11,12 positions, and oxygenated functions at C—9 and C—15 positions of the molecule, which may be further substituted at C—15 by a methyl or ethyl group, the C—20-nor or bisnor derivatives and certain C—20-alkyl derivatives thereof, the alkyl group containing from 1 to 4 carbon atoms inclusive, processes for the production of such compounds. Also included are the methyl esters of the carboxylic acid function and pharmaceutically acceptable salts thereof.

Prostaglandins are a group of chemically related 20-carbon chain hydroxy fatty acids having the basic skeleton of prostanic acid:



Prostanic Acid

The prostaglandins having a oxo group at the C—9 position are known as the PGE series, those having a hydroxyl group in place of the oxo group are known as the PGF series and are further designated by an α or β suffix to indicate the configuration of the hydroxyl group at said position. The natural compounds are the 9 α -hydroxy substituted compounds. They may contain different degrees of unsaturation in the molecule, particularly at C—5, C—13 and C—17, the unsaturation is also indicated by a suffix. 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.

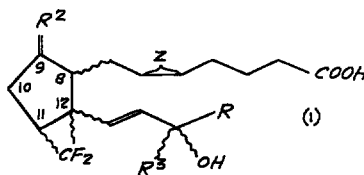
Prostaglandins are widely distributed in mammalian tissues and have been isolated from natural sources in very small amounts. In addition a number of the natural occurring prostaglandins have been prepared by chemical synthesis; note, for example, *J. Am. Chem. Soc.* 91, 5675 (1969), *J. Am. Chem. Soc.* 92, 2586 (1970) and *J. Am.*

[Price 33p]

Chem. Soc. 93, 1489—1493 (1971) and references cited therein, W. P. Schneider et al, *J. Am. Chem. Soc.* 90, 5895 (1968), U. Axen et al, *Chem. Commun.*, 303 (1969), and W. P. Schneider, *Chem. Commun.* 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 for preparing modified prostaglandins and derivatives thereof.

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



which comprises racemic mixtures and antimeric compounds wherein R represents a straight chain alkyl group of three to nine carbon atoms inclusive; R² represents an oxo group or the grouping.



and



R³ represents hydrogen, methyl or ethyl;

Z represents a single bond or a *cis* double bond; and

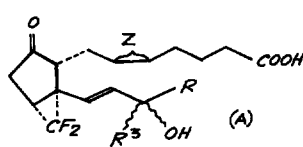
the wavy line ({} indicates the α or β configuration or mixtures thereof, provided that

a) when the side chain attached to the C—12 position is β , the difluoromethylene group at the C—11,12 positions is 11 α ,12 α only; and when the side chain attached at the C—12 position is α , the difluoromethylene group at the C—11,12 positions is 11 β ,12 β only; and

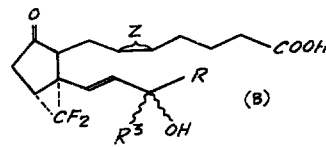
b) when R³ is α , the hydroxyl group, attached to the same carbon as R³, is β and when R³ is β , the hydroxyl group, attached to the same carbon as R³, is α ; and the pharmaceutically acceptable salts or methyl esters thereof.

The antimeric compounds encompassed by formula (I) above can be represented in further detail as follows:

The antimeric compounds wherein R² is oxo and the side chain attached at the C—12 position is β , can be represented by the subgeneric formulas:



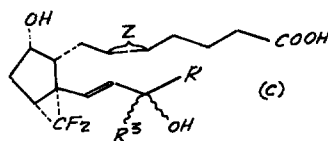
and



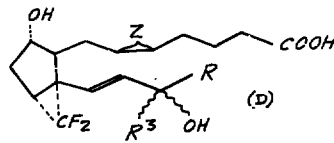
The antimeric compounds wherein R² is



and the side chain attached at the C—12 position is β , can be represented by the subgeneric formulas:



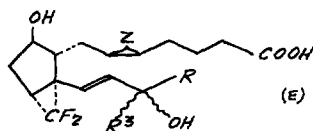
and



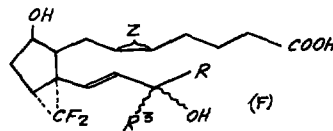
The antimeric compounds wherein R² is



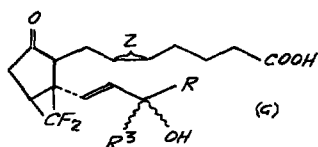
and the side chain attached at the C—12 position is β , can be represented by the subgeneric formulas:



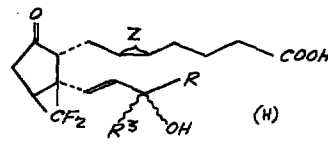
and



The antimeric compound wherein R^2 is oxo and the side chain attached at the C—12 position is α , can be represented by the subgeneric formulas:



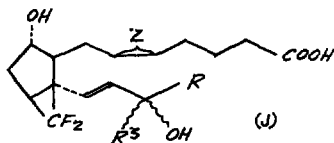
and



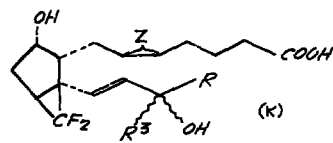
The antimeric compounds wherein R^2 is



and the side chain attached at the C—12 position is α , can be represented by the subgeneric formulas:



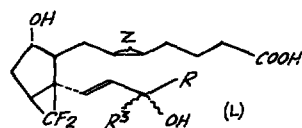
and



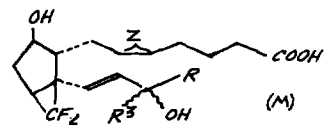
The antimeric compounds wherein R^2 is



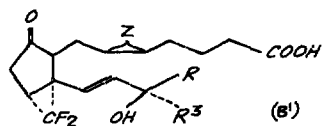
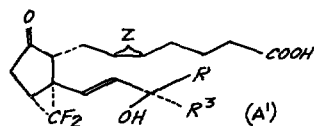
and the side chain attached at the C—12 position is α , can be represented by the subgeneric formulas:



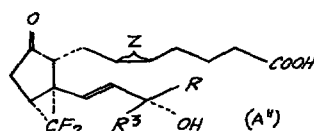
and



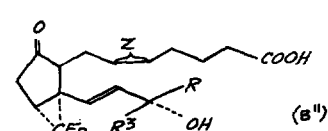
In turn, the antimeric compounds of Formula (A) and (B) wherein R^3 is α and the hydroxyl group, attached to the same carbon atom as R^3 , is β , can be represented by the formulas:



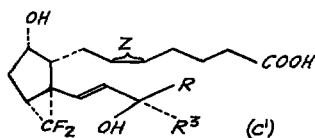
and those wherein R^3 is β and the hydroxyl group, attached to the same carbon atom as R^3 , is α , can be represented by the formulas:



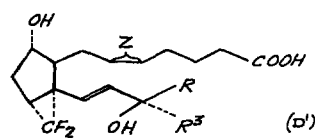
and



The antimeric compounds of formulas (C) and (D) wherein R^3 is α and the hydroxyl group, attached to the same carbon atom as R^3 , is β , can be represented by the formulas:



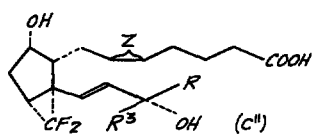
and



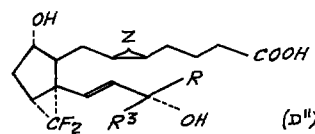
5

and those wherein R^3 is β and the hydroxyl group, attached to the same carbon atom as R^3 , is α , can be represented by the formulas:

5



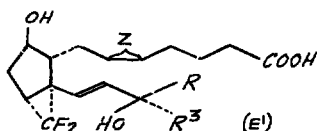
and



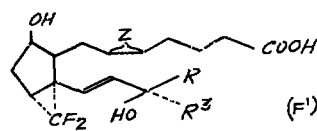
10

The antimeric compounds of formulas (E) and (F) wherein R^3 is α and the hydroxyl group, attached to the same carbon atom as R^3 , is β , can be represented by the formulas:

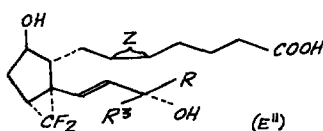
10



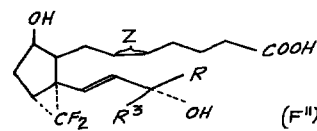
and



and those wherein R^3 is β and the hydroxyl group, attached to the same carbon atom as R^3 , is α , can be represented by the formulas:



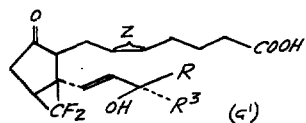
and



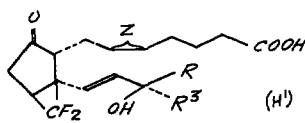
15

The antimeric compounds of Formulas (G) and (H) wherein R^3 is α and the hydroxyl group, attached to the same carbon atom as R^3 , is β can be represented by the formulas:

15



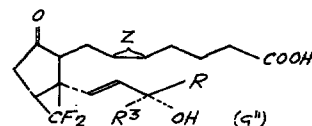
and



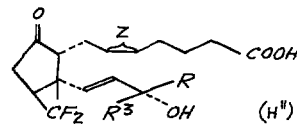
20

and those wherein R^3 is β and the hydroxyl group, attached to the same carbon atom as R^3 , is α can be represented by the formulas:

20

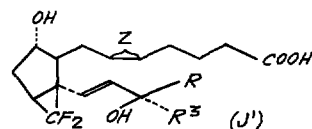


and

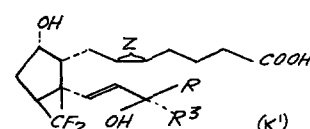


The antimeric compounds of Formulas (J) and (K) wherein R^3 is α and the hydroxyl group, attached to the same carbon atom as R^3 , is β , can be represented by the formulas:

25

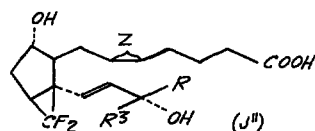


and

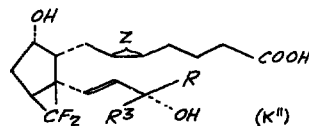


25

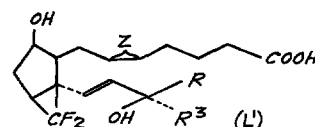
and those wherein R^3 is β and the hydroxyl group, attached to the same carbon atom as R^3 , is α , can be represented by the formulas:



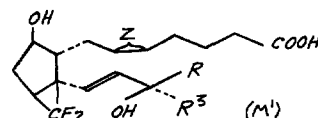
and



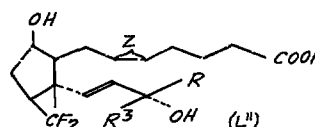
The antimeric compounds of formulas (L) and (M) wherein R^3 is α and the hydroxyl group, attached to the same carbon atom as R^3 , is β , can be represented by the formulas:



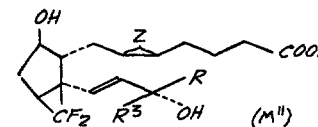
and



and those wherein R^3 is β and the hydroxyl group, attached to the same carbon atom as R^3 , is α , can be represented by the formulas:



and



The racemic mixtures encompassed by formula I above are mixtures in equal proportion of the following compounds:

(A')	and	(G'')
(B')	and	(H'')
(C')	and	(L'')
(D')	and	(M'')
(E')	and	(J'')
(F')	and	(K'')
(G')	and	(A'')
(H')	and	(B'')
(J')	and	(E'')
(K')	and	(F'')
(L')	and	(C'')
(M')	and	(D'')

and

The dotted lines shown in the above formulas and in the formulas below indicate that the substituents are in the α configuration, i.e., below the plane of the cyclopentane ring.

The compounds of formulas A, C and E possess the side chain at C—8 in α configuration and the side chain at C—12 in β configuration, thus the side chains are *trans* with respect to the cyclopentane nucleus, as in natural prostaglandins. The compounds of formulas G, J and L also have the side chains in *trans* configuration; however, the side chain at C—8 is β and the side chain at C—12 is α , i.e., they are opposite to the configuration of natural prostaglandins. The side chains in compounds of formulas B, D and F are (β, β) *cis* while the side chains in compounds of formulas H, K and M are (α, α) *cis* with respect to the cyclopentane nucleus.

The double bonds in the compounds of the present invention have the same configuration as in natural prostaglandins of the E_1 or E_2 or F_{1a} or F_{2a} series, i.e., the double bond at C—5,6 is in *cis* configuration and the double bond at C—13,14 is in *trans* configuration.

When the compounds of the present invention are racemic mixtures, they are produced starting from racemates, while when the compounds of the invention are individual antimers the compounds are preferably obtained starting from the appropriate individual antimer.

The use of the symbol "R" or "S" preceding a substituent designates the abso-

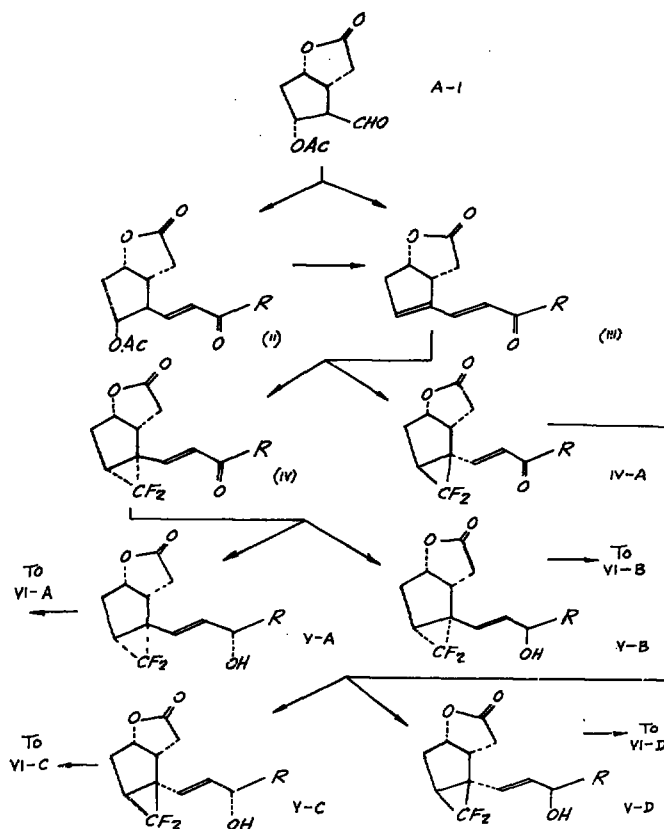
lute stereochemistry of that substituent according to the Cahn-Ingold-Prelog rules [see Cahn et al., *Angew. Chem. Inter. Edit.*, Vol 5, p. 385 (1966), errata p. 511; Cahn et al., *Angew. Chem.*, Vol. 78, p. 413 (1966); Cahn and Ingold, *J. Chem. Soc. (London)*, 1951, p. 612; Cahn et al., *Experientia*, Vol. 12, p. 81 (1956); Cahn, *J. Chem. Educ.*, Vol. 41, p. 116 (1964)]. Because of the interrelation of the designated substituent with the other substituents in the compound having α or β prefixes, the designation of the absolute configuration of one substituent fixes the absolute configuration of all substituents in the compound and thus the absolute configuration of the compound as a whole.

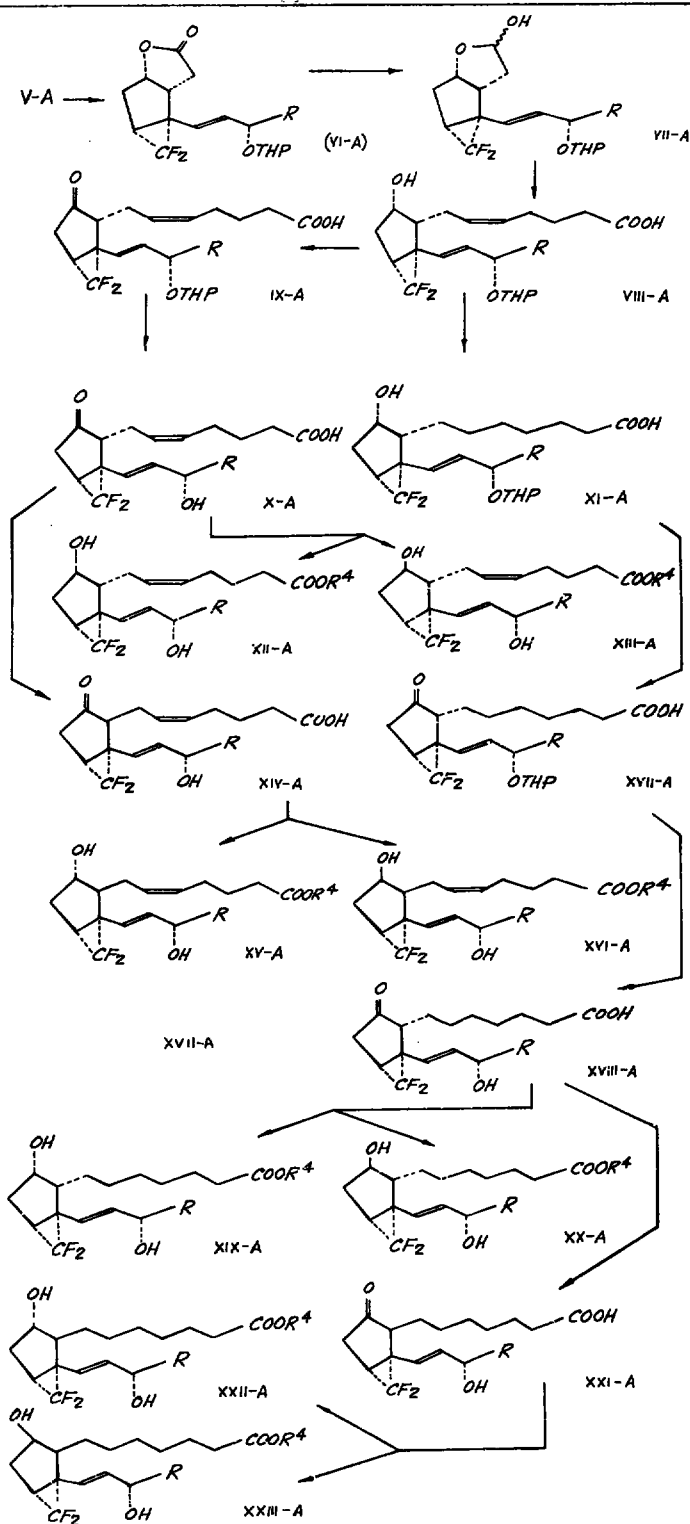
The preferred compounds of the present invention are those in which the side chain attached to the C-12 position has the same unit structure of natural prostaglandins, i.e., the compounds wherein R is the group n-pentyl.

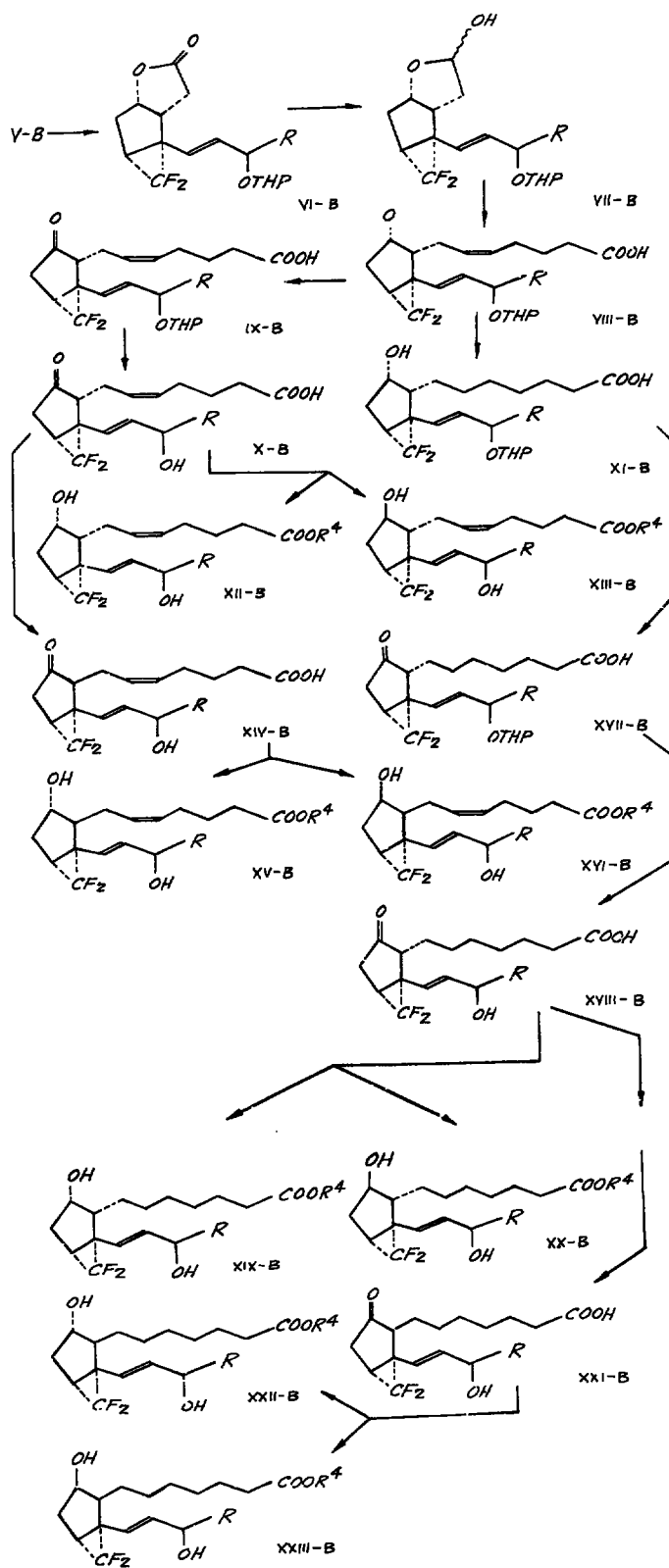
The numbering system and the stereochemistry nomenclature used herein for the compounds of the present invention is the art accepted numbering and stereochemistry nomenclature [see *Progress in the Chemistry of Fats and Other Lipids*, Vol. IX, Part 2, pages 233-236 (1968) Pergamon Press, New York, and *J. Lipids Research*, Vol. 10, pages 316 to 319 (1969)]. The α or β configuration for the side chains has been indicated only in the cases wherein one or both side chains are attached to the cyclopentane ring in opposite configuration to the configuration of natural prostaglandins, i.e., when the carboxylic side chain at C-8 is in β configuration and/or the alkyl side chain at C-12 is in α configuration.

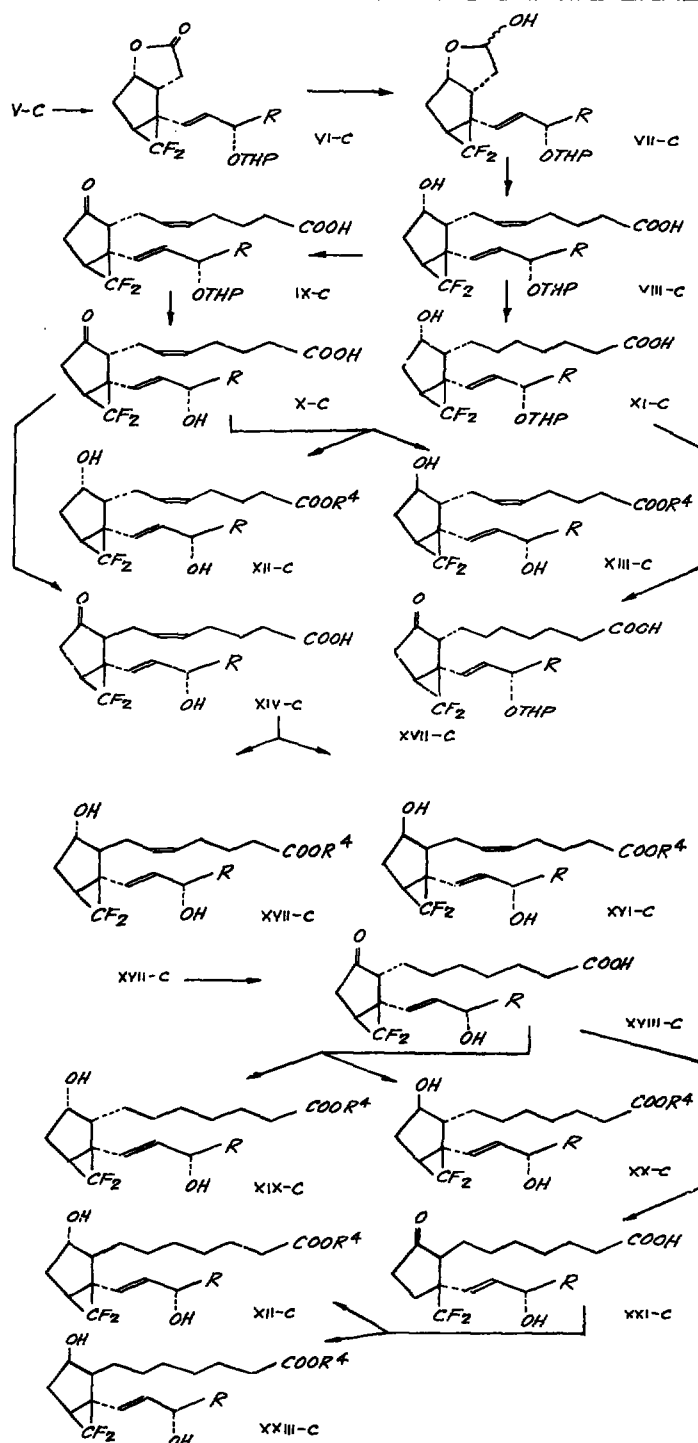
The term "pharmaceutically acceptable salts" refers to those salts which do not significantly adversely affect the pharmacological properties of the parent compound. Suitable pharmaceutically acceptable salts include, for example, metal salts such as sodium, potassium, calcium, magnesium and aluminium, as well as organic amine salts, such as ammonium, diethylamine, β -(dimethylamino) ethanol, β -(diethylamino) ethanol, lysine, arginine, caffeine, procaine and N-ethylpiperidine.

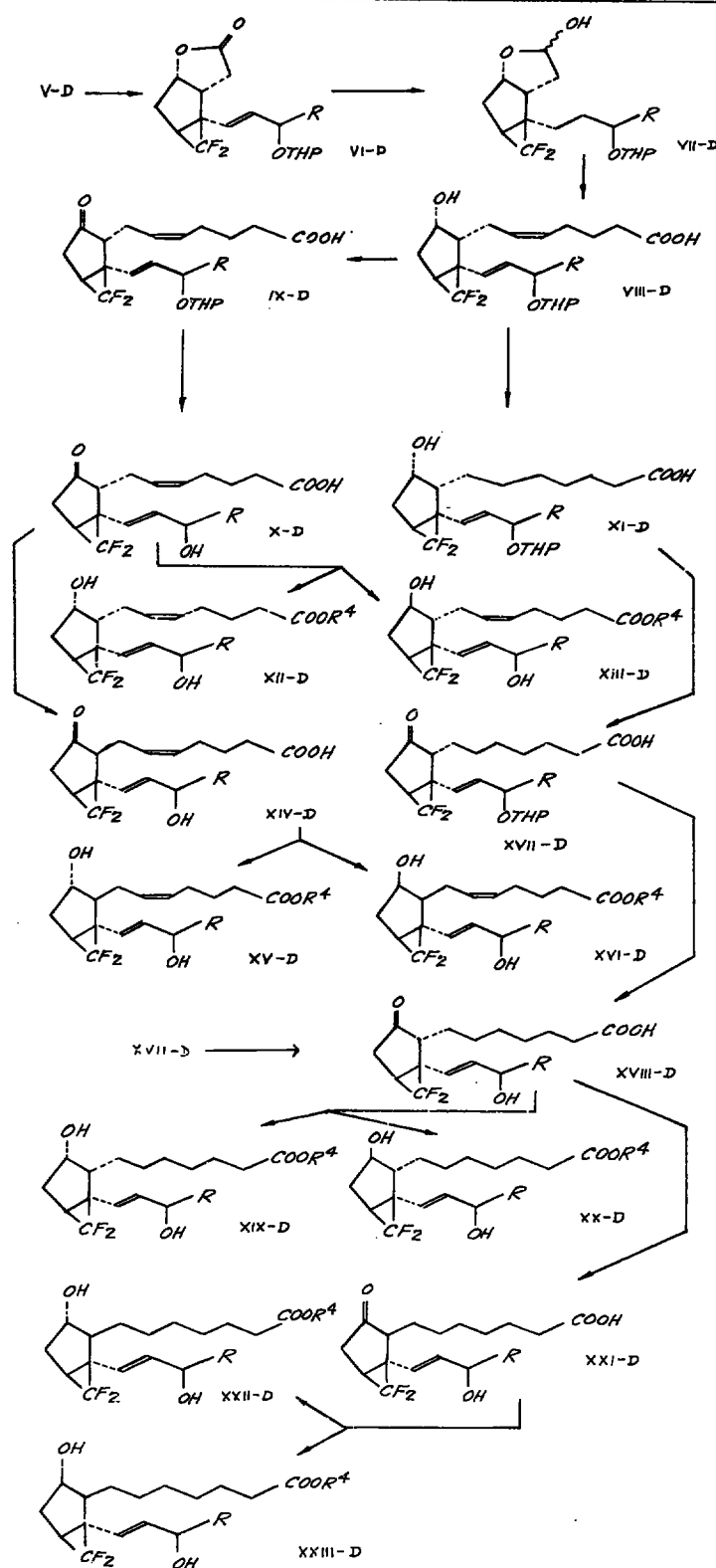
The individual antimeric compounds of the present invention, except those which are further substituted at C-15 by a methyl or ethyl group can be obtained by a process illustrated by the following scheme:





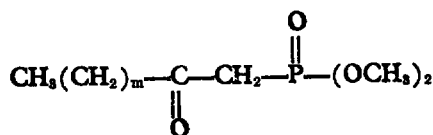






wherein R has the above-indicated meaning;
 R⁴ represents hydrogen or methyl;
 THP is 2-tetrahydropyranyl and Ac is acetyl.

In practicing the process illustrated above, the starting compound, namely 1'R-(2'α - hydroxy - 4'α - acetoxy - 5'β - formylcyclopent - 1'α - yl) - acetic acid 1,2'-lactone, represented by formula A—I is treated with the sodium anion of dimethyl 2-oxo-n-alkylphosphonate of the formula:



wherein m is an integer of from 2 to 8, in 1,2-dimethoxyethane solution to produce a mixture of the *trans* enone and dienone lactones of formulas II and III, respectively, which are separated by conventional techniques. In addition, acid or base treatment of II affords III, thus increasing the yield of the latter compound. This alkylation involves a modified Wittig reaction. Procedures for the Wittig reaction are well known in the art, see for example S. Trippet et al, *Adv. in Organic Chemistry*, Vol. 1, pages 83—102, S. Trippet, *Quarterly Reviews*, Vol. 17, pages 400—440. The sodium anion of a dimethyl 2-oxo-n-alkylphosphonate is prepared in accordance with the method described by E. J. Corey et al, *J. Am. Chem. Soc.*, 88, 5654 (1966), from dimethyl α-lithiomethanephosphonate and a methyl or ethyl ester of a n-alkanoic acid containing from 4 to 9 carbon atoms, e.g., ethyl *n*-butanoate, methyl-*n*-hexanoate, methyl *n*-octanoate and ethyl *n*-nonanoate. The reaction is preferably conducted under an inert atmosphere, e.g., under nitrogen or argon atmosphere at temperatures of 0°C to 40°C, preferably at room temperature or below, using at least one molar equivalent of the reagent per mol of aldehyde, and preferably 1.2 to 2 moles. This reaction is typically carried out for a period of one to four hours, depending on the temperature and concentration of the reaction mixture. In the preferred conditions, the reaction is conducted at room temperature for about two hours. The reaction product can be recovered from the reaction mixture by neutralization of the excess base with acetic acid to pH ~7, followed by evaporation of the solvent under high vacuum, at low temperature, or by adding water and extracting the product with an adequate solvent immiscible with water, e.g., methylene chloride and diethyl ether, followed by evaporation of the solvent. Compounds II and III are separated by conventional techniques, such as chromatography on silica gel or thin-layer chromatography (t.l.c.).

In the keystone step of our process the 1'R-antimeric dienone of formula III is then treated with a difluorocarbene generating source in a suitable organic solvent resulting in the addition of a difluorocyclopropyl group across the double bond most remote to the oxo group, i.e., the ring double bond, thus affording a mixture of the two epimeric difluoromethylene 1'S-antimeric compounds of formulas IV and IV—A in which the fused difluorocyclopropyl group is in α or β configurations, respectively. The side chain in compound of formula IV is in β configuration, i.e., it has the configuration required for natural prostaglandins, while the compound of formula IV—A has the side chain attached in α configuration. These compounds are readily separated by conventional techniques, known to the skilled in the art.

In the preferred embodiments, the reaction is conducted under anhydrous conditions, using sodium chlorodifluoroacetate as source of difluorocarbene, at a temperature above which the salt decomposes, using an inert non-aqueous solvent of sufficient polarity to dissolve the halo-acid salt. Suitable solvents include 1,2-dimethoxyethane, diethyleneglycol dimethyl ether (diglyme) and triethylene glycol dimethyl ether. Generally, the reaction is performed at temperatures in the range 80° to 180°C and preferably at the boiling point of the solvent used, for a period of time of five minutes to one hour. The course of the reaction can be monitored by thin-layer chromatography or by determination of the UV spectrum.

Alternatively, this difluorocyclopropyl addition can be effected with other reagents known to generate difluorocarbenes such as phenyl (trifluoromethyl) mercury and trimethyl (trifluoromethyl) tin in the presence of sodium iodide in an aromatic hydrocarbon solvent, at or near the boiling point of the solvent used for a period of time typically of from two to 18 hours.

The 1'S-antimeric difluoromethylene compounds of formulas IV and IV—A can be separated by conventional techniques such as fractional crystallization, column chromatography or thin-layer chromatography. The individual compounds are in turn submitted separately to the same sequence of reactions in order to obtain the difluoromethylene prostaglandin antimers of the invention.

Thus, the oxo group of the 1'S-antimeric enone lactones of formulas IV or IV—A

can be selectively reduced for example with a solution of zinc borohydride in an ether solvent such as 1,2-dimethoxyethane, to yield a mixture of the α -hydroxy compound and the β isomer thereof (V—A and V—B and V—C and V—D, respectively). The reaction is typically conducted at temperatures in the range 5° to 20°C for from 15 minutes to three hours, preferably using an excess of zinc borohydride. The zinc borohydride reagent solution can be prepared from freshly fused zinc chloride and sodium borohydride in 1,2-dimethoxyethane.

The isomeric α - and β -hydroxy compounds can be separated by conventional chromatography on silica gel or by thin-layer chromatography.

Alternatively, the reduction step can be carried out *via* treatment with a borohydride ion (conveniently prepared by reaction of a trialkylborane derivative from either racemic or (+)-limonene, t-hexylborane and t-butyllithium) in the presence of hexamethylphosphoramide, typically at from -130°C to -100°C and preferably -120°C. The predominant product of this treatment is the α -alcohol and only small or negligible amounts of the β -isomer is obtained.

A 1'S-antimeric α -hydroxy compound of formula V—A can be etherified with dihydropyran, preferably in methylene chloride, in the presence of catalytic amounts of an acid catalyst (e.g., *p*-toluenesulfonic acid), under anhydrous conditions, to produce the tetrahydropyranyloxy derivatives of formula VI—A. Typically the reaction is conducted at about room temperature for about 15 minutes, using about three molar equivalents of dihydropyran in an inert organic solvent, e.g., using methylene chloride as solvent. A larger excess of dihydropyran, or longer reaction periods, produce polymerization of this reagent.

The product can be isolated by adding a few drops of pyridine to the reaction mixture, followed by conventional extraction and evaporation of the organic extract.

The 1'S-isomeric lactol of formula VII—A can be prepared by reduction of the lactone of formula VI—A with from 1.1 to 3 molar equivalents of diisobutyl-aluminum hydride in a suitable inert organic solvent. Typically, the reduction is conducted at -30° to -70°C, preferably at about -60°C, for a period of from 10 to 30 minutes, preferably using about two molar equivalents of the diisobutylaluminum hydride. Suitable inert organic solvents for this reaction include, for example, aromatic hydrocarbons such as toluene or xylene.

The product can be isolated from the reaction mixture by conventional separation procedures and can be used for the next step with or without separation of the isomers.

The 8S-11 α ,12 α -difluoromethylene prostadienoic acid derivative of formula VIII—A can be prepared by condensation of the crude 8S-lactol VII—A with the Wittig reagent derived from 5-triphenylphosphoniopentanoic acid bromide and sodium methylsulfinylmethylide in dimethyl sulfoxide solution.

Typically, this reaction is conducted under anhydrous conditions for two to 24 hours at temperatures in the range of 15° to 50°C. This reaction is preferably carried out under an inert atmosphere, e.g., under argon or nitrogen atmosphere. Typically the triphenylphosphoniopentanoic acid is used in an amount varying from two to five moles per mol of starting lactol VII—A and the amount of sodium methylsulfinyl carbanion varies between two to 10 moles. In the preferred embodiments 2.5 molar equivalents of the acid reagent and five molar equivalents of the carbanion reagent are used per mol of lactol. The product is obtained as the sodium salt soluble in water, which can be converted to the free acid by acidification with oxalic acid or another weak acid to pH—2, followed by conventional extraction and evaporation. Preferably the prostaglandin derivative VIII—A is further purified by thin-layer chromatography. The 5-triphenylphosphoniopentanoic acid can be prepared according to the procedure described by R. Greenwald et al, in *J. Org. Chem.*, 28, page 1128 (1963), from 5-bromopentanoic acid and triphenylphosphine in acetonitrile. The sodium methylsulfinylmethylide can be obtained from sodium hydride and dimethyl sulfoxide, stirring the mixture at about 75°C until the evolution of gas ceases. Generally, it is preferred to prepare these reagents just prior to the reaction with the lactol of formula VII—A.

The 8R-prostadienoic acid compounds of formula IX—A can be prepared by oxidation of the corresponding 8S-9 α -hydroxylated compound of formula VIII—A with, for example, Jones' reagent, Collins' reagent or with aqueous chromic acid in diethyl ether [H. C. Brown et al, *J. Org. Chem.*, 36, page 387 (1971)]. This product can in turn be hydrolyzed under mild acidic conditions for example, by treatment with a weak acid (e.g., acetic acid, oxalic acid or tartaric acid) in the presence of water, to yield the 8R- compound of formula X—A. Preferably the starting material of formula IX—A is first dissolved in an inert water miscible organic solvent (e.g., tetrahydrofuran or dioxane) prior to treatment with the weak acid. This hydrolysis is preferably conducted using aqueous acetic acid, at a temperature in the range of 0° to 50°C for four to ten

hours. The preferred concentration of aqueous acetic acid is 65% wt./wt. however, other concentrations can, of course, also be used.

The 8S-monounsaturated compounds of formula XI—A can be conveniently prepared by selectively reducing the C—5(6)-olefin bond in the corresponding dienolic compounds of formula VIII—A. This can be conveniently effected by applying the procedure described by Koch et al, in the *Journal of Labelled Compounds*, Vol. VI, No. 4, page 395 (1970), with respect to the selective reduction of PGE₂ prostaglandins to PGE₁ prostaglandins, to the dienolic compounds of formula VIII—A.

By esterification of an 8R-compound of formula X—A with ethereal diazomethane, in a conventional manner, followed by reduction with sodium borohydride in a lower aliphatic alcohol such as methanol or ethanol, preferably at about room temperature for a period of time typically of 30 minutes to one hour, there is obtained a mixture of the corresponding 8S-9 α and 9 β -hydroxycompounds, (XII—A and XIII—A, R⁴=Me) which are separated by chromatography on silica gel, obtaining approximately equal amounts of each isomer. The alkyl ester group is then hydrolyzed by chemical or enzymatic methods, to yield the corresponding free acids (XII—A and XIII—A, R⁴=H).

When this hydrolysis is effected chemically, the methyl ester compound 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, typically of 30° to 50°C., preferably at about 40°C. for a period of time of 12 to 20 hours, preferably for about 16 hours, thus yielding, after acidification, the corresponding 8S-prostadienoic acid compound of formulas XII—A or XIII—A (R⁴=H). This hydrolysis is preferably conducted under an inert atmosphere i.e., under nitrogen or argon atmosphere.

Alternatively, the methyl ester group can be 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 or 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 the methyl ester group 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° to 30°C, preferably at 25° 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. The methyl ester compound is dissolved in the previously prepared buffered lipase aqueous solution by sonication at about 37°C. using typically from 0.5 ml. to 1 ml. of the lipase solution per milligram of substrate. The methyl ester group is readily hydrolyzed within a short period of time, typically 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 from the lipase have been obtained by column chromatography on Florisil (registered trade mark).

Alternatively, the 8S-antimeric compounds of formulas XII—A and XIII—A can be obtained from the 8R-antimeric compounds of formula IX—A, which are esterified with diazomethane, the alkyl esters reduced with sodium borohydride to yield a mixture of the 8S-9 α and 9 β -hydroxylated derivatives, which upon cleavage of the tetrahydropyranyloxy moiety and chemical or enzymatic hydrolysis of the alkyl ester group afford the respective compounds XII—A and XIII—A.

The 8R-antimeric compounds of formula X—A can be converted into the corresponding 8S-antimers of formula XIV—A by strong alkaline treatment, preferably by treatment with an alcoholic solution of an alkali metal alkoxide such as sodium methoxide or potassium methoxide in methanol solution. This reaction is preferably conducted under nitrogen or argon atmosphere using from 1.1 to 4 molar equivalents of the alkali metal alkoxide per mol of starting compound, at room temperature for a period of time of 10 minutes to 1 hour, followed by treatment with a strong mineral acid such as hydrochloric acid, to liberate the free prostadienoic acid from the alkaline salt formed during the reaction. In the preferred embodiments, the reaction is conducted using 2

molar equivalents of the alkali metal alkoxide per mol of compound X—A, for a period of time of about 25 minutes.

Upon esterification of an 8*S*-antimeric compound XIV—A with diazomethane followed by reduction with sodium borohydride as mentioned above in detail with regard to the transformation of compound X—A into XII—A and XIII—A there are obtained the corresponding 8*R*-9 α and 9 β -hydroxylated compounds of formulas XV—A and XVI—A respectively ($R^4 = \text{Me}$), which are converted into the corresponding free acids (XV—A and XVI—A, $R^4 = \text{H}$) by chemical or enzymatic hydrolysis methods.

A monounsaturated compound of formula XI—A can be converted into the corresponding 8*R*-11-keto compound of formula XVII—A by oxidation with an oxidizing reagent, e.g., using Jones' reagent or Collins' reagent and thereafter the tetrahydropyranloxy group cleaved by treatment with for example 65% w/w aqueous acetic acid, to yield an 8*R*-compound of formula XVIII—A. An 8*R*-antimeric compound of formula XVIII—A can be conventionally esterified with ethereal diazomethane, and the methyl ester thus obtained reduced with sodium borohydride in methanol solution to yield a mixture of the corresponding 8*S*-9 α and 9 β -hydroxylated compound of formulas XIX—A and XX—A, respectively ($R^4 = \text{Me}$), which are separated by chromatography and the individual isomers hydrolyzed by chemical or enzymatic methods, thus obtaining the free prostenoic acids (XIX—A and XX—A, $R^4 = \text{H}$).

The monounsaturated 8*R*-antimeric compounds of formula XVIII—A can be converted into the corresponding 8*S*-antimers of formula XXI—A by strong alkaline treatment, i.e., by treatment with sodium methoxide or potassium methoxide in methanol solution followed by acidification as described hereinbefore in detail with regard to the transformation of the corresponding dienic compounds (X—A into XIV—A). By conventional esterification of compounds of formula XXI—A with ethereal diazomethane followed by reduction of the methyl ester thus obtained with sodium borohydride in methanol solution there is obtained a mixture of the corresponding 8*R*-9 α and 9 β -hydroxy derivatives of formulas XXII—A and XXIII—A ($R^4 = \text{Me}$) which are separated by chromatography and the individual isomers hydrolyzed by chemical or enzymatic methods, to yield the corresponding free acids (XXII—A and XXIII—A, $R^4 = \text{H}$).

When the above-described reaction sequences (V—A through XXIII—A) are performed using the isomeric compound having the hydroxy group in β -configuration as starting material (V—B) there will be obtained in each and every step of the process the corresponding 15 β -substituted (prostaglandin numbering) derivative (VI—B through XXIII—B).

Similarly, when starting from the antimeric compounds having the difluoromethylene group in β -orientation and the hydroxyl group in α orientation (V—C) there will be produced in each and every step of the process the corresponding antimeric compounds (VI—C through XXIII—C). Also, starting from compounds of formula V—D, there will be produced in each and every step of the process the corresponding antimeric compounds (VI—D through XXIII—D).

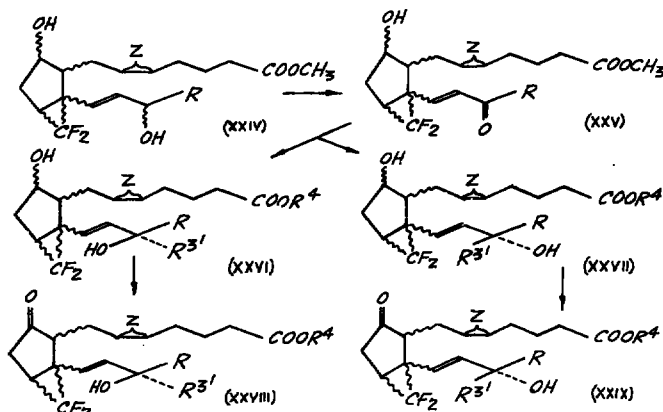
By substitution of racemic mixture of the compounds of Formula A—I corresponding to the individual antimeric compounds of Formula A—I depicted above there are obtained racemic mixtures at each and every stage of the process. Thus, carrying out the process using racemic (2' α -hydroxy-4' α -acetoxy-5' β -formylcyclopent-1' α -yl)-acetic acid 1,2'-lactone as starting material yields, for example, a racemic mixture of the compounds of formula X—A and its antimeric compounds of Formula XIV—D.

Other racemic mixtures which may be noted, in addition to the compounds of formulas X—A and XIV—D, are, for example, the compounds of formulas:

			X—B	and	XIV—C	
	XII—A	and	XVI—D	XII—B	and	XVI—C
	XIII—A	and	XV—D	XIII—B	and	XV—C
	XIV—A	and	X—D	XIV—B	and	X—C
55	XV—A	and	XIII—D	XV—B	and	XIII—C
	XVI—A	and	XII—D	XVI—B	and	XII—C
	XVIII—A	and	XXI—D	XVIII—B	and	XXI—C
	XXI—A	and	XVIII—D	XXI—B	and	XVIII—C
	XXII—A	and	XX—D	XXII—B	and	XX—C
60	XXIII—A	and	XIX—D	XXIII—B	and	XIX—C
	XIX—A	and	XXIII—D	XIX—B	and	XXIII—C
	XX—A	and	XXII—D	XX—B	and	XXII—C

The compounds of the present invention further substituted by a methyl or ethyl group at the C—15 position can be obtained by a process illustrated by the following

sequence of reactions in which, to avoid undue prolixity, each formula covers antimeric compounds and racemic mixtures as well:



wherein R, R⁴ and Z and the wavy lines () have the above-indicated meaning and R^{3'} is methyl or ethyl, provided that when the side chain attached to the C—12 position is β , the difluoromethylene group at C—11,12 is in α -configuration only and when the side chain attached to the C—12 position is α , the difluoromethylene group at C—11,12 is in β -configuration only.

Formula XXIV is a composite of antimeric compounds of formulas:

XII—A, XIII—A, XV—A, XVI—A, XIX—A, XX—A, XXII—A and XXIII—A; and XII—B, XIII—B, XV—B, XVI—B, XIX—B, XX—B, XXII—B and XXIII—B; and XII—C, XIII—C, XV—C, XVI—C, XIX—C, XX—C, XXII—C and XXIII—C; and XII—D, XIII—D, XV—D, XVI—D, XIX—D, XX—D, XXII—D and XXIII—D.

When the compounds of formula XXIV are racemic mixtures, for example, a racemic mixture of the compounds of formulas XII—A and XVI—D rather than an individual antimer, it is to be understood that racemic mixtures of the compounds of formulas XXV, XXVI, XXVII, XXVIII and XXIX are thereby obtained.

In practicing the process illustrated above, a compound of formula XXIV (racemic or individual antimer) is selectively oxidized at C—15 with an excess of manganese dioxide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in a suitable inert organic solvent, e.g., chloroform, tetrahydrofuran and dioxane to produce the corresponding 15-oxo compound of formula XXV. When manganese dioxide is used as reagent, this reaction is preferably conducted at room temperature, for a period of time of 18 to 40 hours, under vigorous stirring, using preferably chloroform or tetrahydrofuran as solvents. The oxidizing agent is added portionwise at 4—6 hours intervals. When the oxidation is effected using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone as reagent, the reaction is preferably conducted at 50°C. using particularly dioxane as solvent, for a period of time of 14 to 20 hours, preferably for about 18 hours. In any case 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.

Upon reaction of a compound of formula XXV with methyl- or ethyllithium or the corresponding alkylmagnesium halide, there is obtained a mixture of the corresponding 15 α -alkyl-15 β -hydroxy and 15 β -alkyl-15 α -hydroxy compounds of formulas XXVI and XXVII, respectively, in which R⁴ is methyl. In the preferred embodiments, the reaction is carried out using preferably 1.1 to 1.2 molar equivalents of the alkylolithium, or from 6 to 12 molar equivalents of the alkyl-magnesium halide per molar equivalent of starting compound, using diethyl ether or tetrahydrofuran as solvent, at a temperature of -78°C to room temperature, for a period of time of 2 to 10 hours and under an inert atmosphere, preferably under argon atmosphere. The mixture of 15 α -hydroxy-15 β -alkyl- and 15 β -hydroxy-15 α -alkyl compounds thus obtained is separated by thin layer chromatographic techniques, and the methyl ester group in compounds XXVI and XXVII (R⁴ = Me) is in turn saponified preferably by enzymatic methods to yield the corresponding 15 α -hydroxy-15 β -alkyl and 15 β -hydroxy-15 α -alkyl-prostadienoic or prostenoic acids (XXVI and XXVII, R⁴ = H).

The 9-oxo compounds of formulas XXVIII and XXIX (R⁴ = H) are obtained by

oxidation of compounds XXVI and XXVII ($R^4 = \text{Me}$ or H), respectively, using particularly chromium trioxide-dipyridine complex (Collins' reagent) or an 8N chromic acid in acetone solution (Jones' reagent) followed by enzymatic hydrolysis of the methyl ester group, when required.

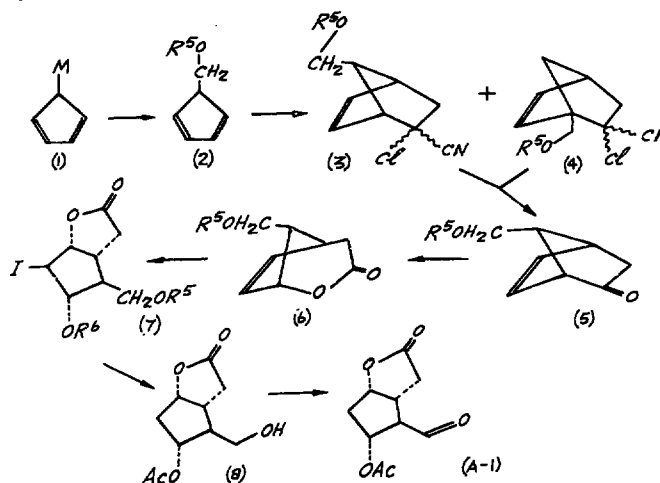
The salts of the prostadienoic and prostenoic acids of the present invention (individual antimers or racemic mixtures) can be prepared by treating the corresponding free acids with about one molar equivalent of a pharmaceutically acceptable base per molar equivalent of free acid. Suitable pharmaceutically acceptable bases include, for example, sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, trimethylamine, triethylamine, tripropylamine, β -(dimethylamino) ethanol, β -(diethylamino) ethanol, arginine, lysine, caffeine or procaine. Typically, the reaction is conducted in an aqueous solution, alone or in combination with an inert, water miscible organic solvent, at a temperature typically of 0° to 30°C , preferably at room temperature.

Typical inert, water miscible organic solvents include methanol, ethanol, isopropanol, butanol, dioxane or tetrahydrofuran. 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.

In conducting the aforescribed processes, it is generally preferred to separate or isolate the respective products of each reaction step prior to their use as starting materials in subsequent steps. Illustrative non-limiting separation and isolation procedures can be had by reference to the appropriate Example set forth herein below.

Also although the above processes, for purposes of simplicity, have been described with respect to tetrahydropyran and acetate protecting groups, other conventional suitable ether and ester protecting groups could, of course, also be used.

The starting materials used in the above described process, i.e., 1' R -(2' α -hydroxy-4' α -acetoxy-5' β -formylcyclopent-1' α -yl)-acetic acid 1,2'-lactone, or its racemate are prepared in accordance with the methods described, for example, by E. J. Corey et al, in *J. Am. Chem. Soc.*, 91, page 5675 (1969); *J. Am. Chem. Soc.*, 92, page 397 (1970); *J. Am. Chem. Soc.*, 93, pages 1489, 1490 and 1491 (1971) and references cited therein, as illustrated by the following sequence of reactions:



wherein R^5 represents methyl or benzyl;
 R^6 represents hydrogen or acetyl; 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, page 1489 (1971) with a slight excess of chloromethylmethylether or chloromethylbenzylether is tetrahydrofuran at approximately -55°C , to yield respectively the 5-methoxymethyl-1,3-cyclopentadiene (2, $R^5 = \text{methyl}$) or 5-benzyl-oxymethyl-1,3-cyclopentadiene (2, $R^5 = \text{benzyl}$) 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) ($R^5 = \text{methyl}$ 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

(R⁵ = methyl) or 7-*syn*-benzyloxymethyl-2-norbornen-5-one (R⁵ = benzyl) respectively, which upon reaction with a slight molar excess of *m*-chloroperbenzoic acid in methylene chloride in the presence of sodium bicarbonate result in selective Baeyer-Villiger oxidation to form the corresponding lactone (6), namely 2-oxa-8-*syn*-methoxymethylbicyclo (3.2.1)-oct-5-en-3-one, (R⁵ = methyl) and 2-oxa-8-*syn*-benzyl-oxymethylbicyclo (3.2.1) oct 5-en-3-one (R⁵ = 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° to 5°C produce the respective racemic hydroxyiodo-lactones of formula (7). The 1'*R*-antimers of (7), namely 1'*R*-(2' α ,4' α -dihydroxy-3' β -iodo-5' β -benzyloxymethylcyclopent-1' α -yl)-acetic acid 1,2'-lactone (7, R⁵ = benzyl, R⁶ = H) and 1'*R*-(2' α ,4' α -dihydroxy-3' β -iodo-5' β -methoxymethylcyclopent-1' α -yl)-acetic acid 1,2'-lactone (7, R⁵ = methyl, R⁶ = H) are obtained as described by E. J. Corey et al, in *J. Am. Chem. Soc.* 93, 1491 (1971) and in *J. Am. Chem. Soc.* 92, 397 (1970) respectively, *via* base catalyzed hydrolysis of the corresponding lactone (6) to the hydroxyacid, resolution of the hydroxyacid as the (+)-amphetamine salt of the benzyloxymethyl compound or as the (-)-ephedrine salt for the methoxymethyl compound and iodolactonization of the respective 1'*R*-antimeric acid. The racemic compounds of formula (7) or the 1'*R*-antimers thereof are then esterified with acetic anhydride in pyridine, under conventional conditions to yield the corresponding acetoxy compound, (7, R⁶ = acetyl). The racemic compound or the 1'*R*-antimer is 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 -benzyl-oxymethyl or 5' β -methoxymethyl group to produce the hydroxymethyl compound (8) (Racemic or 1'*R*-antimer).

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 typically of -78°C to 0°C.

Oxidation of a hydroxymethyl compound (8) (racemic or 1'*R*-antimer) with chromium trioxide-dipyridine complex (prepared as described by J. C. Collins et al. in *Tetrahedron Letters*, page 3363 (1968) in methylene chloride solution at about 0°C, affords respectively the racemic or 1'*R*-antimeric aldehyde of formula A—I.

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 preservatives 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 from 0.01 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.

A further understanding of the invention can be had from the following Preparations and Examples, however they are not intended to limit its scope. Further, when individual antimers are used as starting materials, antimeric compounds are obtained as products, while when racemic mixtures are used as starting materials, the products obtained are racemates. Also where needed, Examples are repeated to provide starting materials for subsequent Examples. Examples 1 to 6, 8 and 26 relate to intermediate steps in the process of the invention.

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 (1, M = thallium).

B. A mixture of 216.28 g. of benzyl alcohol, 61.44 g. of paraformaldehyde, 481.6 g. of anhydrous magnesium sulfate and 1200 ml. of methylene chloride is cooled to a temperature of between -50° 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° 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 then 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 $3\frac{1}{2}$ 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 fluoroborate, 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-benzyloxy-methylbicyclo-(2.2.1)-hept-2-ene [mixture of (3) and (4), $\text{R}^5 = \text{benzyl}$].

PREPARATION 2.

To a well-stirred slurry of 74.1 g. of cyclopentadienylthallium in 100 ml. of anhydrous ether cooled to -20° 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) 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 aqueous sodium chloride solution is then added and the reaction mixture extracted with 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 2-chloro-2-cyano- Δ^5 -7-syn-methoxymethylbicyclo-(2.2.1)-heptane [mixture of (3) and (4), $\text{R}^5 = \text{Me}$] 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 dimethyl sulfoxide 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 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 (5, R^s = benzyl), homogeneous on thin-layer chromatography.

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 (5, R^s = methyl).

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-5-en-3-one (6, R^s = benzyl) as a homogeneous 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-5-en-3-one (6, R^s = Me).

PREPARATION 5.

To a solution of 60 g. of 2-oxa-8-*syn*-benzyloxymethylbicyclo-(3.2.1)-oct-5-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 ether to eliminate the unsaponified 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 sulfite 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 ether-methylene chloride, to yield the pure (2',4',4'-dihydroxy-3'β-iodo-5'β-benzyloxy-methylcyclopent-1'α-yl)-acetic acid 1,2'-lactone (7, R^s = benzyl; R^e = H).

By the same procedure, 2-oxa-8-*syn*-methoxymethylbicyclo-(3.2.1)-oct-5-ene-3-one is converted into (2',4',4'-dihydroxy-3'β-iodo-5'β-methoxymethylcyclopent-1'α-yl)-acetic acid 1,2'-lactone.

PREPARATION 6.

A mixture of 2.5 g. of (2',4',4'-dihydroxy-3'β-iodo-5'β-benzyloxymethylcyclopent-1'α-yl)-acetic acid 1,2'-lactone, 2.5 ml. of pyridine and 5 ml. of acetic anhydride is kept at room temperature for 30 minutes. The solvents are then evaporated under reduced pressure and the residue crystallized from ether, to yield (2'-hydroxy-4'-acetoxy-3'β-iodo-5'β-benzyloxymethylcyclopent-1'α-yl)-acetic acid 1,2'-lactone (7, R^s = benzyl, R^e = acetyl).

In a similar manner (2',4',4'-dihydroxy-3'β-iodo-5'β-methoxymethylcyclopent-1'α-yl)-acetic acid 1,2'-lactone is converted into the corresponding 4'-acetoxy derivative.

Substituting 1'R-(2',4',4'-dihydroxy-3'β-iodo-5'β-benzyloxymethylcyclopent-1'α-yl)-acetic acid 1,2'-lactone obtained as described by E. J. Corey et al, in *J. Am. Chem. Soc.* 93, 1491 (1971), for (2',4',4'-dihydroxy-3'β-iodo-5'β-benzyloxymethylcyclopent-1'α-yl)-acetic acid 1,2'-lactone in the above procedure is productive of 1'R-(2'-hydroxy-4'-acetoxy-3'β-iodo-5'β-benzyloxymethylcyclopent-1'α-yl)-acetic acid 1,2'-lactone, (1'R-antimer of 7, R^s = benzyl, R^e = acetyl).

Likewise acetylation of 1'R-(2',4',4'-dihydroxy-3'β-iodo-5'β-methoxymethylcyclopent-1'α-yl)-acetic acid 1,2'-lactone [obtained as described by E. J. Corey et al, in *J. Am. Chem. Soc.* 92, 397 (1970)], gives rise to 1'R-(2'-hydroxy-4'-acetoxy-3'β-iodo-5'β-methoxymethylcyclopent-1'α-yl)-acetic acid 1,2'-lactone, (1'R-antimer of 7, R^s = methyl, R^e = acetyl).

PREPARATION 7.

To a solution of 6.2 g. of (2'-hydroxy-4'-acetoxy-3'-iodo-5'-benzyloxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone in 80 ml. of anhydrous benzene (dried over molecular sieves) are added 4.0 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, page 1216 (1961) and 20 mg. of azobisisobutyronitrile. The reaction mixture is stirred at 50°C for three hours then the benzene is removed by evaporation under reduced pressure, the oily residue is dissolved in 150 ml. of 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 dissolved in hexane and filtered through synthetic magnesium silicate, sold under the trademark Florisil by the Floridin Company, to remove nonpolar by-products, and the filtrate is purified by thin-layer chromatography using hexane-ethyl acetate (60:40) as eluant, to yield (2'-hydroxy-4'-acetoxy-5'-benzyloxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone.

In a similar manner, (2'-hydroxy-4'-acetoxy-3'-iodo-5'-methoxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone,

1'R - (2'-hydroxy-4'-acetoxy-3'-iodo-5'-methoxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone and

1'R - (2'-hydroxy-4'-acetoxy-3'-iodo-5'-benzyloxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone,

are converted respectively into:

(2'-hydroxy-4'-acetoxy-5'-methoxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone,

1'R - (2'-hydroxy-4'-acetoxy-5'-methoxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone and

1'R - (2'-hydroxy-4'-acetoxy-5'-benzyloxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone.

PREPARATION 8.

A. To a prehydrogenated suspension of 600 mg. of 10% palladium charcoal catalyst in 20 ml. of ethyl acetate is added 6 g. of (2'-hydroxy-4'-acetoxy-5'-benzyloxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone and the mixture is stirred under hydrogen atmosphere until the absorption of hydrogen ceases. The catalyst is then separated by filtration and washed with ethyl acetate. The combined organic filtrates are evaporated to dryness under reduced pressure and the residue is purified by thin-layer chromatography using hexane-ethyl acetate (30:70) as eluant, to yield (2'-hydroxy-4'-acetoxy-5'-hydroxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone (8).

In a similar manner 1'R-(2'-hydroxy-4'-acetoxy-5'-benzyloxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone is converted into 1'R-(2'-hydroxy-4'-acetoxy-5'-hydroxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone (1'R-antimer of 8).

B. A stirred solution of 15 g. of (2'-hydroxy-4'-acetoxy-5'-methoxymethylcyclopent-1'-yl)-acetic acid 1,2'-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 resulting solution is added 270 ml. of diethyl ether to decompose excess boron tribromide, maintaining the reaction mixture at 0°C. The mixture is then poured into a vigorously stirred slurry of 95 g. of sodium bicarbonate in 500 ml. of a saturated aqueous 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 under reduced pressure. The residue is purified by crystallization from chloroform to afford (2'-hydroxy-4'-acetoxy-5'-hydroxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone, identical to that obtained in part A.

By using 1'R-(2'-hydroxy-4'-acetoxy-5'-methoxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone as starting material there is obtained 1'R-(2'-hydroxy-4'-acetoxy-5'-hydroxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone, identical to that obtained in part A.

C. To a suspension of 60 g. of diatomaceous earth (dried for 24 hours at 105°C) and 60 g. of chromium trioxide-dipyridine complex (prepared as described by J. C. Collins et al, *Tetrahedron Letters*, 3363 (1968)) in 800 ml. of anhydrous methylene chloride, cooled to 0° to 2°C is added under stirring 4.7 g. of (2'-hydroxy-4'-acetoxy-5'-hydroxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone dissolved in 500 ml. of methylene chloride and the mixture is stirred for 20 minutes further, maintaining the temperature at about 0°C; 20.8 g. of sodium bisulfate are then added and the mixture

is stirred for an additional 10 minute period, the solids are separated by filtration and washed with methylene chloride. The combined filtrates are evaporated to dryness under reduced pressure, at a temperature below 0°C, obtaining (2'-hydroxy-4'-acetoxy-5'-β-formylcyclopent-1'-yl)-acetic acid 1,2'-lactone, A—I, as a homogeneous oil.

In a similar manner, 1'R-(2'-hydroxy-4'-acetoxy-5'-β-hydroxymethylcyclopent-1'-yl)-acetic acid 1,2'-lactone is converted into 1'R-(2'-hydroxy-4'-acetoxy-5'-β-formylcyclopent-1'-yl)-acetic acid 1,2'-lactone (1'R-antimer of A—I).

EXAMPLE 1.

A. Preparation of dimethyl 2-oxoalkylphosphonates. 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 is added dropwise under stirring and under an argon atmosphere, 495 ml. of 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 vacuum. 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.

In a similar manner but using methyl n-butanoate, methyl n-pentanoate, ethyl n-heptanoate, ethyl n-octanoate and methyl n-decanoate in place of methyl caproate, there are respectively obtained: dimethyl 2-oxopentylphosphonate, dimethyl 2-oxohexylphosphonate, dimethyl 2-oxooctylphosphonate, dimethyl 2-oxononylphosphonate and dimethyl 2-oxoundecylphosphonate.

B. To a suspension of 1.8 g. of sodium hydride (previously washed with pentane, under argon) in 200 ml. of 1,2-dimethoxyethane freshly distilled from lithium aluminium hydride is added, under stirring and under an atmosphere of argon, a solution of 8.1 g. of dimethyl 2-oxoheptylphosphonate in 100 ml. of anhydrous 1,2-dimethoxyethane. The reaction mixture is stirred for 30 minutes at room temperature and 4.5 g. of 1'R-(2'-hydroxy-4'-acetoxy-5'-β-formylcyclopent-1'-yl)-acetic acid 1,2'-lactone dissolved in 120 ml. of 1,2-dimethoxyethane 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 using an 80 x 20 cm. silica plate and a benzenedioxane (90:10 mixture as eluant, to obtain 1'R-[2'-hydroxy-4'-acetoxy-5'-β-(3''-oxo-oct-1''(t)-enyl)-cyclopent-1'-yl]-acetic acid 1,2'-lactone, (II, R = nC₈H₁₇), [2'-hydroxy-5'-(3''-oxo-oct-1''(t)-enyl)-cyclopent-4'-en-1'-yl]-acetic acid 1,2'-lactone (III, R = nC₈H₁₇) and a small amount of dimethyl 2-oxoheptylphosphonate.

In a similar manner but using dimethyl 2-oxopentylphosphonate, dimethyl 2-oxohexylphosphonate, dimethyl 2-oxooctylphosphonate, dimethyl 2-oxononylphosphonate and dimethyl 2-oxoundecylphosphonate in lieu of dimethyl 2-oxoheptylphosphonate there are respectively obtained:

1'R-[2'-hydroxy-4'-acetoxy-5'-β-(3''-oxohex-1''(t)-enyl)-cyclopent-1'-yl]-acetic acid 1,2'-lactone and 1'R-[2'-hydroxy-5'-(3''-oxohex-1''(t)-enyl)-cyclopent-4'-en-1'-yl]-acetic acid 1,2'-lactone;

1'R-[2'-hydroxy-4'-acetoxy-5'-β-(3''-oxohept-1''(t)-enyl)-cyclopent-1'-yl]-acetic acid 1,2'-lactone and 1'R-[2'-hydroxy-5'-(3''-oxohept-1''(t)-enyl)-cyclopent-4'-en-1'-yl]-acetic acid 1,2'-lactone;

1'R-[2'-hydroxy-4'-acetoxy-5'-β-(3''-oxonon-1''(t)-enyl)-cyclopent-1'-yl]-acetic acid 1,2'-lactone and 1'R-[2'-hydroxy-5'-(3''-oxonon-1''(t)-enyl)-cyclopent-4'-en-1'-yl]-acetic acid 1,2'-lactone;

1'R-[2'-hydroxy-4'-acetoxy-5'-β-(3''-oxodec-1''(t)-enyl)-cyclopent-1'-yl]-acetic acid 1,2'-lactone and 1'R-[2'-hydroxy-5'-(3''-oxodec-1''(t)-enyl)-cyclopent-4'-en-1'-yl]-acetic acid 1,2'-lactone; and

1'R-[2'-hydroxy-4'-acetoxy-5'-β-(3''-oxododec-1''(t)-enyl)-cyclopent-1'-yl]-acetic acid 1,2'-lactone and 1'R-[2'-hydroxy-5'-(3''-oxododec-1''(t)-enyl)-cyclopent-4'-en-1'-yl]-acetic acid 1,2'-lactone.

Likewise, starting from racemic (2'-hydroxy-4'-acetoxy-5'-β-formylcyclopent-1'-yl)-acetic acid 1,2'-lactone there are obtained the corresponding racemates in place of the above-mentioned 1'R-antimers.

EXAMPLE 2.

A solution of 1.1 g. of 1'R - [2'α - hydroxy - 5' - (3'' - oxo - oct - 1''(t) - enyl) - cyclopent - 4' - en - 1'α - yl] - acetic acid 1,2'-lactone in 40 ml. of diglyme is heated to the boiling point and about 10 ml. or distilled off to remove moisture. To the stirred refluxing solution are added, dropwise and under continuous distillation, 22 g. of sodium chlorodifluoroacetate dissolved in 40 ml. of diglyme. After completion of the addition, the reaction mixture is refluxed for ten additional minutes. It is then evaporated to dryness under reduced pressure, the oily residue is dissolved in methylene chloride and filtered through alumina. The filtrate is evaporated to dryness and the residue purified by thin-layer chromatography using hexane-ethyl acetate (60:40) as eluant, to obtain two isomeric difluoromethylene compounds, namely, 1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3'' - oxo - oct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone (IV, R = nC₈H₁₇) and 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3'' - oxo - oct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone (IV—A, R = nC₈H₁₇) which are recrystallized from methylene chloride-diethyl ether and diethyl ether-hexane, respectively.

By the same method, starting from

1'R - [2'α - hydroxy - 5' - (3'' - oxohex - 1''(t) - enyl) - cyclopent - 4' - en - 1'α - yl] - acetic acid 1,2'-lactone,
 1'R - [2'α - hydroxy - 5' - (3'' - oxohept - 1''(t) - enyl) - cyclopent - 4' - en - 1'α - yl] - acetic acid 1,2'-lactone,
 1'R - [2'α - hydroxy - 5' - (3'' - oxonon - 1''(t) - enyl) - cyclopent - 4' - en - 1'α - yl] - acetic acid 1,2'-lactone,
 1'R - [2'α - hydroxy - 5' - (3'' - oxodec - 1''(t) - enyl) - cyclopent - 4' - en - 1'α - yl] - acetic acid 1,2'-lactone and
 1'R - [2'α - hydroxy - 5' - (3'' - oxododec - 1''(t) - enyl) - cyclopent - 4' - en - 1'α - yl] - acetic acid 1,2'-lactone,
 there are respectively obtained:

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3'' - oxohex - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3'' - oxohex - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone;

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3'' - oxohept - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3'' - oxohept - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone;

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3'' - oxonon - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3'' - oxonon - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone;

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3'' - oxodec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3'' - oxodec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3'' - oxododec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3'' - oxododec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone.

Likewise but using as starting materials the corresponding racemic compounds in place of the 1'R-antimers there are produced the corresponding racemic 4'α,5'α-difluoromethylene- and 4'β,5'β-difluoromethylene derivatives thereof.

EXAMPLE 3.

To a stirred solution of 400 mg. of 1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3'' - oxo - oct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone in 5 ml. of 1,2-dimethoxyethane, freshly distilled from lithium aluminium hydride, are added 1.2 ml. of zinc borohydride reagent (prepared from 0.025 mol of fused zinc chloride, 0.050 mol of sodium borohydride in 50 ml. of 1,2-dimethoxyethane, stirring the mixture for 16 hours and filtering the insoluble material under argon atmosphere). The reaction mixture is stirred for 90 minutes at room temperature, and then treated with a saturated solution of sodium bitartrate until the resulting 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 1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - hydroxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone (V—A, R = nC₈H₁₇) in mixture with

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''β - hydroxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] acetic acid 1,2'-lactone (V—B, R=nC₈H₁₁).

This oily mixture is separated into the individual isomers by thin-layer chromatography using a mixture of methylene chloride-acetone (75:25) as eluant.

In a similar fashion, starting from 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - oxo - oct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone, there is obtained a mixture of 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - hydroxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone (V—C, R=NC₈H₁₁) and 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''β - hydroxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone (V—D, R=nC₈H₁₁), which are separated into the individual isomers by t.l.c.

Likewise, the remaining 3''-oxo compounds obtained in Example 3 are converted into the corresponding 3''-hydroxyderivatives, namely:

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - hydroxyhex - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''β - hydroxyhex - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone;

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - hydroxyhept - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''β - hydroxyhept - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone;

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - hydroxynon - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''β - hydroxynon - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone;

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - hydroxydec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''β - hydroxydec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone;

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - hydroxydodec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''β - hydroxydodec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone;

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - hydroxyhex - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''β - hydroxyhex - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone;

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - hydroxyhept - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''β - hydroxyhept - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone;

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - hydroxynon - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''β - hydroxynon - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone;

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - hydroxydec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''β - hydroxydec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone;

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - hydroxydodec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone and 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''β - hydroxydodec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone.

When using racemic mixtures in lieu of the 1'S-antimers as starting materials there are produced the corresponding racemates in place of the above-mentioned 1'S-antimeric compounds.

EXAMPLE 4.

To a solution of 2 g. of 1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - hydroxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone in 20 ml. of methylene chloride are added 20 mg. of *p*-toluenesulfonic acid, and 2 ml. of freshly distilled dihydropyran. 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 aqueous sodium chloride solution. The organic phase is separated,

dried over magnesium sulfate and evaporated to dryness under reduced pressure, at approximately 0°C. The oily residue is purified by thin-layer chromatography using chloroform-methanol (9:1) as eluant, to produce the pure 1'S - 2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - tetrahydropyran - 2''' - yloxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone (VI—A, R = nC₈H₁₇).

By the same method 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - hydroxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone is converted into the corresponding 3''-tetrahydropyran-2'''-yl ether (VI—C, R = nC₈H₁₇).

In a similar manner, the remaining compounds obtained in Example 3 are converted into the corresponding 3''-tetrahydropyran-2'''-yl ethers.

EXAMPLE 5.

One gram of 1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - tetrahydropyran - 2''' - yloxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetic acid 1,2'-lactone is dissolved in 20 ml. of anhydrous toluene. The solution is cooled to -60°C and to the cold solution is added a solution of 650 mg. of diisobutylaluminum hydride in 2.7 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 diethyl 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 1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - tetrahydropyran - 2''' - yloxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal (VII—A, R = nC₈H₁₇).

By the same method, 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - tetrahydropyran - 2''' - yloxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] acetic acid 1,2'-lactone is converted into 1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - tetrahydropyran - 2''' - yloxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal (VII—C, R = nC₈H₁₇).

In a similar manner, the following compounds are produced, starting from the corresponding lactones:

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''β - tetrahydropyran - 2''' - yloxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal (VII—B, R = nC₈H₁₇),

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''β - tetrahydropyran - 2''' - yloxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal (VII—D, R = nC₈H₁₇),

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - tetrahydropyran - 2''' - yloxyhex - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal,

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - tetrahydropyran - 2''' - yloxyhept - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal,

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - tetrahydropyran - 2''' - yloxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal,

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - tetrahydropyran - 2''' - yloxydec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal,

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - tetrahydropyran - 2''' - yloxydodec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal,

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - tetrahydropyran - 2''' - yloxyhex - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal,

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - tetrahydropyran - 2''' - yloxyhept - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal,

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - tetrahydropyran - 2''' - yloxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal,

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - tetrahydropyran - 2''' - yloxydec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal,

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''α - tetrahydropyran - 2''' - yloxydodec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal;

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''β - tetrahydropyran - 2''' - yloxyhex - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal,

1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''β - tetrahydropyran - 2''' - yloxydec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal,

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''β - tetrahydropyran - 2''' - yloxydec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal,

1'S - [2'α - hydroxy - 4'β,5'β - difluoromethylene - 5'α - (3''β - tetrahydropyran - 2''' - yloxydodec - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal.

Likewise but using racemic compounds in place of 1'S-antimers there are produced the corresponding racemates of the above-mentioned compounds.

EXAMPLE 6.

A stirred suspension of 440 mg. of sodium hydride in 5 ml. of anhydrous dimethylsulfoxide is heated to 80°C for half an hour under an argon atmosphere; 1.4 ml. of the resulting solution are added to a solution of 380 mg. of dried 5-triphenylphosphoniopentanoic acid bromide in 0.8 ml. of anhydrous dimethyl sulfoxide, under an argon atmosphere, and under stirring. The reaction mixture is stirred for 5 minutes, 150 mg. of 1'S - [2'α - hydroxy - 4'α,5'α - difluoromethylene - 5'β - (3''α - tetrahydropyran-2''' - yloxyoct - 1''(t) - enyl) - cyclopent - 1'α - yl] - acetaldehyde 1,2'-hemiacetal dissolved in 1 ml. of dimethyl sulfoxide is added, and the reaction mixture is stirred at room temperature for 18 hours. The solvent is then evaporated under reduced pressure at a temperature below 35°C and the residue is dissolved in 10 ml. of water. The neutral products are extracted with ethyl acetate:ether (1:1) (4 × 4 ml.). The aqueous phase is acidified with saturated aqueous oxalic acid solution to pH 2, and extracted several times with a mixture of pentane:diethyl ether (1:1). The combined organic extracts are washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated to dryness at a temperature not higher than 20°C. Purification of the residue by thin-layer chromatography, using chloroform:methanol, (9:1) as eluant, affords the pure 8S - 9α - hydroxy - 11α,12α - difluoromethylene - 15α - tetrahydropyran - 2' - yloxyprosta - 5 - cis,13 - trans - dienoic acid (VIII—A, R = nC₅H₁₁).

The 5-triphenylphosphoniopentanoic acid bromide used as reagent is prepared by reflux of a mixture of 9.5 g. of 5-bromopentanoic acid, 14.4 g. of triphenylphosphine and 100 ml. of acetonitrile for about 70 hours. The insoluble material is separated by filtration and the filtrate is concentrated to a small volume. The product is crystallized by addition of diethyl ether, and is further purified by two subsequent recrystallizations from acetonitrile-ether.

In a similar manner, starting from the corresponding lactols obtained in Example 5 there are produced the following prostadienoic acid derivatives:

8S - 9α - hydroxy - 11β,12β - difluoromethylene - 15α - tetrahydropyran - 2'-yloxy - 12α - prosta - 5 - cis,13 - trans - dienoic acid (VIII—C, R = nC₅H₁₁),

8S - 9α - hydroxy - 11α,12α - difluoromethylene - 15β - tetrahydropyran - 2' - yloxyprosta - 5 - cis,13 - trans - dienoic acid (VIII—B, R = nC₅H₁₁),

8S - 9α - hydroxy - 11β,12β - difluoromethylene - 15β - tetrahydropyran - 2'-yloxy - 12α - prosta - 5 - cis,13 - trans - dienoic acid (VIII—D, R = nC₅H₁₁),

8S - 9α - hydroxy - 11α,12α - difluoromethylene - 15α - tetrahydropyran - 2' - yloxy - 19,20 - bisnorprosta - 5 - cis,13 - trans - dienoic acid,

8S - 9α - hydroxy - 11α,12α - difluoromethylene - 15α - tetrahydropyran - 2' - yloxy - 20 - norprosta - 5 - cis,13 - trans - dienoic acid,

8S - 9α - hydroxy - 11α,12α - difluoromethylene - 15α - tetrahydropyran - 2' - yloxy - 20 - methylprosta - 5 - cis,13 - trans - dienoic acid,

8S - 9α - hydroxy - 11α,12α - difluoromethylene - 15α - tetrahydropyran - 2' - yloxy - 20 - ethylprosta - 5 - cis,13 - trans - dienoic acid,

8S - 9α - hydroxy - 11α,12α - difluoromethylene - 15α - tetrahydropyran - 2' - yloxy - 20 - butylprosta - 5 - cis,13 - trans - dienoic acid,

8S - 9α - hydroxy - 11β,12β - difluoromethylene - 15α - tetrahydropyran - 2' - yloxy - 19,20 - bisnor - 12α - prosta - 5 - cis,13 - trans - dienoic acid,

8S - 9α - hydroxy - 11β,12β - difluoromethylene - 15α - tetrahydropyran - 2' - yloxy - 20 - nor - 12α - prosta - 5 - cis,13 - trans - dienoic acid,

8S - 9α - hydroxy - 11β,12β - difluoromethylene - 15α - tetrahydropyran - 2' - yloxy - 20 - methyl - 12α - prosta - 5 - cis,13 - trans - dienoic acid,

8S - 9α - hydroxy - 11β,12β - difluoromethylene - 15α - tetrahydropyran - 2' - yloxy - 20 - ethyl - 12α - prosta - 5 - cis,13 - trans - dienoic acid,

8S - 9α - hydroxy - 11β,12β - difluoromethylene - 15α - tetrahydropyran - 2' - yloxy - 20 - butyl - 12α - prosta - 5 - cis,13 - trans - dienoic acid,

8S - 9α - hydroxy - 11α,12α - difluoromethylene - 15β - tetrahydropyran - 2' - yloxy - 19,20 - bisnorprosta - 5 - cis,13 - trans - dienoic acid,

8S - 9α - hydroxy - 11α,12α - difluoromethylene - 15β - tetrahydropyran - 2' - yloxy - 20 - ethylprosta - 5 - cis,13 - trans - dienoic acid,

8S - 9α - hydroxy - 11β,12β - difluoromethylene - 15β - tetrahydropyran - 2' - yloxy - 20 - nor - 12α - prosta - 5 - cis,13 - trans - dienoic acid, and

8S - 9α - hydroxy - 11β,12β - difluoromethylene - 15β - tetrahydropyran - 2' - yloxy - 20 - butyl - 12α - prosta - 5 - cis,13 - trans - dienoic acid.

Likewise, starting from racemic [2'α - hydroxy - 4'α,5'α - difluoromethylene-

5' β - (3'' α - tetrahydropyran - 2''' - yloxyoct - 1''(t) - enyl) - cyclopent - 1' α - yl]-acetaldehyde hemiacetal there is obtained racemic 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxyprosta - 5 - *cis*,13 - *trans* - dienoic acid.

EXAMPLE 7.

5 A. A solution of 100 mg. of 8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene 15 α - tetrahydropyran - 2' - yloxyprosta - 5 - *cis*,13 - *trans* - dienoic acid in 4 ml. of purified acetone is cooled to -10°C and treated under an atmosphere of nitrogen and with stirring, with 0.15 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 30 minutes further at -10°C, 0.15 ml. 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 give 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxyprosta - 5 - *cis*,13 - *trans* - dienoic acid (IX—A, R = nC₅H₁₁), which is purified by thin-layer chromatography using chloroform:methanol (9:1) as eluant.

20 B. A mixture of 173 mg. of 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxyprosta - 5 - *cis*,13 - *trans* - dienoic acid, 0.45 ml. of tetrahydrofuran and 4.5 ml. of 65% aqueous acetic acid is stirred at 40°C for four hours, cooled to 0°C and evaporated to dryness under reduced pressure; the oily residue is purified by thin-layer chromatography using chloroform:methanol (9:1) as eluant, thus yielding the pure 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid (X—A, R = nC₅H₁₁).

25 In another experiment the reaction mixture is kept at room temperature for 18 hours, obtaining the same results.

By repeating the procedures described in Parts A and B of this Example using as starting materials the remaining compounds obtained in Example 6, there are produced as final products respectively:

30 8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid (X—C, R = nC₅H₁₁),

8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - hydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid (X—B, R = nC₅H₁₁),

35 8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid (X—D, R = nC₅H₁₁),

8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 19,20 - bis - norprosta - 5 - *cis*,13 - *trans* - dienoic acid,

8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - norprosta - 5 - *cis*,13 - *trans* - dienoic acid,

40 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - methylprosta - 5 - *cis*,13 - *trans* - dienoic acid,

8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - ethylprosta - 5 - *cis*,13 - *trans* - dienoic acid,

45 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - butylprosta - 5 - *cis*,13 - *trans* - dienoic acid,

8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 19,20 - bisnor - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid,

8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - nor - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid,

50 8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - methyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid,

8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - ethyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid,

55 8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - butyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid,

8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - hydroxy - 19,20 - bis - norprosta - 5 - *cis*,13 - *trans* - dienoic acid,

8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - hydroxy - 20 - ethylprosta - 5 - *cis*,13 - *trans* - dienoic acid,

60 8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 20 - nor - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid, and

8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 20 - butyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid.

Likewise, starting from racemic 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxyprosta - 5 - *cis*,13 - *trans* - dienoic acid there is

obtained as final product racemic 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α -hydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid.

EXAMPLE 8.

Fifteen milligrams of 8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 α -tetrahydropyran - 2' - yloxyprosta - 5 - *cis*,13 - *trans* - dienoic acid is dissolved in a mixture of 2 ml. of benzene and 3 ml. of acetone containing 5 mg. of freshly prepared tris-(triphenylphosphine) chlororhodium, at room temperature. The resulting mixture is stirred in a hydrogen atmosphere and aliquots are removed at periodic intervals. The aliquots are esterified with diazomethane and analyzed by gas liquid chromatography to determine whether hydrogenation has been completed. When the hydrogenation is determined to be essentially complete (ca. six hours), the reaction mixture is applied to 20% wt. silver nitrate impregnated silica gel (G) preparative plates developing with chloroform:methanol:acetic acid:water in a 95:75:1:0.6 parts by volume ratio. The zone corresponding to the desired monounsaturated compound is eluted with a 90:10, by volume, of a mixture of chloroform and methanol yielding pure 8S - 9 α - hydroxy-11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxyprost - 13 - *trans*-enoic acid (XI—A, R = nC₅H₁₁).

Similarly by following the same procedure using as starting materials the corresponding prosta - 5 - *cis*,13 - *trans* - dienoic acid derivatives obtained in Example 6, the following compounds are respectively prepared:

8S - 9 α - hydroxy - 11 β ,12 β - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxy - 12 α - prost - 13 - *trans* - enoic acid (XI—C, R = nC₅H₁₁),

8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 β - tetrahydropyran - 2' - yloxyprost - 13 - *trans* - enoic (XI—B, R = nC₅H₁₁),

8S - 9 α - hydroxy - 11 β ,12 β - difluoromethylene - 15 β - tetrahydropyran - 2' - yloxy - 12 α - prost - 13 - *trans* - enoic acid (XI—D, R = nC₅H₁₁).

8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxy - 19,20 - bisnorprost - 13 - *trans* - enoic acid,

8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxy - 20 - norprost - 13 - *trans* - enoic acid,

8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxy - 20 - methylprost - 13 - *trans* - enoic acid,

8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxy - 20 - ethylpros - 13 - *trans* - enoic acid,

8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxy - 20 - butylprost - 13 - *trans* - enoic acid,

8S - 9 α - hydroxy - 11 β ,12 β - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxy - 19,20 - bisnor - 12 α - prost - 13 - *trans* - enoic acid,

8S - 9 α - hydroxy - 11 β ,12 β - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxy - 20 - nor - 12 α - prost - 13 - *trans* - enoic acid,

8S - 9 α - hydroxy - 11 β ,12 β - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxy - 20 - methyl - 12 α - prost - 13 - *trans* - enoic acid,

8S - 9 α - hydroxy - 11 β ,12 β - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxy - 20 - ethyl - 12 α - prost - 13 - *trans* - enoic acid,

8S - 9 α - hydroxy - 11 β ,12 β - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxy - 20 - butyl - 12 α - prost - 13 - *trans* - enoic acid,

8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 β - tetrahydropyran - 2' - yloxy - 19,20 - bisnorprost - 13 - *trans* - enoic acid,

8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 β - tetrahydropyran - 2' - yloxy - 20 - ethylprost - 13 - *trans* - enoic acid,

8S - 9 α - hydroxy - 11 β ,12 β - difluoromethylene - 15 β - tetrahydropyran - 2' - yloxy - 20 - nor - 12 α - prost - 13 - *trans* - enoic acid, and

8S - 9 α - hydroxy - 11 β ,12 β - difluoromethylene - 15 β - tetrahydropyran - 2' - yloxy - 20 - butyl - 12 α - prost - 13 - *trans* - enoic acid.

Likewise, racemic 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxyprosta - 5 - *cis*,13 - *trans* - dienoic acid is converted into racemic 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxyprost-13 - *trans* - enoic acid.

EXAMPLE 9.

To a solution of 100 mg. of 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α -hydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid in 5 ml. of methylene chloride is added 1 ml. of an ethereal solution of diazomethane and the reaction mixture is maintained at room temperature for 30 minutes. The solvents and excess reagent are eliminated

under reduced pressure, to yield 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester.

In a similar manner, the remaining prostadienoic acid compounds obtained in Example 7 are converted into the corresponding methyl esters.

EXAMPLE 10.

- 5 A solution of 100 mg. of 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester in 5 ml. of methanol is cooled to 0°C and treated with 50 mg. of sodium borohydride; the reaction mixture is stirred at room temperature for 30 minutes and then evaporated to dryness under reduced pressure, water is added to the oily residue and the product extracted with ethyl acetate. The organic extract is washed with dilute hydrochloric acid solution and water to neutral, dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue is purified by chromatography on silica gel using methylene chloride-ethyl acetate mixtures to thus obtain 8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester (XII—A, R = nC₈H₁₇; R⁴ = Me) and 8S - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester (XIII—A, R = nC₈H₁₇; R⁴ = Me) in approximately equal amounts.
- 10 In a similar manner, starting from the corresponding methyl esters of the 9-oxo prostadienoic acid compounds of Example 7, there are produced:
- 15 8S - 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxyprosta - 5 - *cis* - 13 - *trans* - dienoic acid methyl ester (XII—B, R = nC₈H₁₇; R⁴ = Me) and 8S - 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxyprosta - 5 - *cis* - 13 - *trans* - dienoic acid methyl ester (XIII—B, R = nC₈H₁₇; R⁴ = Me);
- 20 8S - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester (XII—C, R = nC₈H₁₇; R⁴ = Me) and 8S - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester (XIII—C, R = nC₈H₁₇; R⁴ = Me);
- 25 8S - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester (XII—D, R = nC₈H₁₇; R⁴ = Me) and 8S - 11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester (XIII—D, R = nC₈H₁₇; R⁴ = Me);
- 30 8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 19,20 - bisnorprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and 8S - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 19,20 - bisnorprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester;
- 35 8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - norprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and 8S - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - norprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester;
- 40 8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - methylprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and 8S - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - methylprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester;
- 45 8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethylprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and 8S - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethylprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester;
- 50 8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - butylprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and 8S - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - butylprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester;
- 55 8S - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 19,20 - bisnor - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and 8S - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 19,20 - bisnor - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester;
- 60 8S - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - methyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and 8S - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - methyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester;
- 8S - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and 8S - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester;

8S - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - butyl - 12 α - prosta-5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8S - 11 β ,12 β - difluoromethylene-9 β ,15 α - dihydroxy - 20 - butyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester;

8S - 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy - 19,20 - bisnorprosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8S - 11 α ,12 α - difluoromethylene-9 β ,15 β - dihydroxy - 19,20 - bisnorprosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester;

8S - 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy - 20 - ethylprosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8S - 11 α ,12 α - difluoromethylene-9 β ,15 β - dihydroxy - 20 - ethylprosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester;

8S - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 20 - nor - 12 α - prosta-5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8S - 11 β ,12 β - difluoromethylene-9 β ,15 β - dihydroxy - 20 - nor - 12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester;

8S - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 20 - butyl - 12 α - prosta-5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8S - 11 β ,12 β - difluoromethylene-9 β ,15 β - dihydroxy - 20 - butyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester.

Likewise, starting from racemic 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester there are obtained racemic 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester and racemic 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester.

EXAMPLE 11.

Twenty milligrams of 8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester are dissolved in a mixture of 2 ml. 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 2N hydrochloric acid to pH—2 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 8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid (XII—A, R = nC₅H₁₁; R⁴ = H).

In a similar manner, the remaining prostadienolic acid methyl ester compounds obtained in Example 10 are converted into the corresponding free acids, e.g.:

8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid (XII—B, R = nC₅H₁₁; R⁴ = H),

8S - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid (XII—C, R = nC₅H₁₁; R⁴ = H),

8S - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid (XII—D, R = nC₅H₁₁; R⁴ = H),

8S - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid (XIII—A, R = nC₅H₁₁; R⁴ = H),

8S - 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid (XIII—B, R = nC₅H₁₁; R⁴ = H),

8S - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid (XIII—C, R = nC₅H₁₁; R⁴ = H),

8S - 11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid (XIII—D, R = nC₅H₁₁; R⁴ = H),

8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 19,20 - bisnorprosta - 5 - *cis*,13 - *trans* - dienolic acid,

8S - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethylprosta - 5 - *cis*,13 - *trans* - dienolic acid,

8S - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - nor - 12 α - prosta-5 - *cis*,13 - *trans* - dienolic acid,

8S - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - methyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid, and

8S - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 12 α - prosta-5 - *cis*,13 - *trans* - dienolic acid.

EXAMPLE 12.

To a solution of 80 mg. of 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid in 2 ml. of anhydrous methanol is added,

- at room temperature and under argon atmosphere, 0.22 ml. of a 2N solution of sodium methoxide in methanol. The reaction mixture is kept under the same conditions for 25 minutes, it is then acidified with dilute hydrochloric acid to pH—2 and extracted with ethyl acetate. The organic extract is washed with 50% saturated sodium chloride solution dried over magnesium sulfate and evaporated to dryness under reduced pressure. Purification of the residue by thin layer chromatography using a methylene chloride-ether-acetic acid mixture (58:40:2) affords the pure 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid (XIV—A, R = nC₅H₁₁).
- 5 In a similar manner but using as starting materials the corresponding 8R-9-oxo compounds obtained in Example 7, there are produced the following 8S-antimers:
- 10 8S - 9 - oxo - 11 β ,12 β - difluoroethylene - 15 α - hydroxy - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid (XIV—C, R = nC₅H₁₁),
- 15 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - hydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid (XIV—B, R = nC₅H₁₁),
- 15 8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid, (XIV—D, R = nC₅H₁₁),
- 20 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 19,20 - bisnor - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid,
- 20 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - nor - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid,
- 25 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - methyl - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid,
- 25 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - butyl - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid,
- 30 8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 19,20 - bisnor - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid,
- 30 8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - nor - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid,
- 35 8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - methyl - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid,
- 35 8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - ethyl - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid,
- 40 8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - butyl - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid,
- 40 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - hydroxy - 20 - ethyl - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid,
- 45 8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 20 - nor - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid, and
- 45 8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 20 - butyl - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid.
- Likewise, racemic 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid is converted into racemic 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* dienolic acid.

EXAMPLE 13.

- 50 In accordance with the method of Example 9, 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid is converted into its methyl ester.
- 55 A solution of 100 mg. of 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester in 5 ml. of methanol is cooled to 0°C and treated with 50 mg. of sodium borohydride, the reaction mixture is stirred at room temperature for 30 minutes; water is then added and the product extracted with ethyl acetate. The organic extract is washed with dilute hydrochloric acid solution and water to neutral, dried and evaporated to dryness under vacuo.
- 60 The residue is purified by chromatography on silica gel using methylene chloride-ethyl acetate mixtures to thus obtain 8R - 11 α ,12 α - difluoromethylene - 9 α 15 α - dihydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester (XV—A, R = nC₅H₁₁; R⁴ = Me) and 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester (XVI—A, R = nC₅H₁₁; R⁴ = Me).

Similarly, the remaining 8S-9-oxo compounds of Example 12 are esterified with diazomethane and thereafter reduced with sodium borohydride, to yield respectively:

- 5 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy - 8 β - prosta - 5 - *cis*,13-*trans* - dienolic acid methyl ester (XV—B, R = nC₅H₁₁; R⁴ = Me) and 8R-11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxy - 8 β - prosta - 5 - *cis*,13 - *trans*-dienolic acid methyl ester (XVI—B, R = nC₅H₁₁; R⁴ = Me);
- 10 8R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β ,12 α - prosta - 5-*cis*,13 - *trans* - dienolic acid methyl ester, (XV—C, R = nC₅H₁₁; R⁴ = Me) and 8R-11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans*-dienolic acid methyl ester (XVI—C, R = nC₅H₁₁; R⁴ = Me);
- 15 8R - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 8 β ,12 α - prosta - 5-*cis*,13 - *trans* - dienolic acid methyl ester (XV—D, R = nC₅H₁₁; R⁴ = Me) and 8R-11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans*-dienolic acid methyl ester (XVI—D, R = nC₅H₁₁; R⁴ = Me);
- 20 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 19,20 - bisnor - 8 β -prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 19,20 - bisnor - 8 β - prosta - 5 - *cis*,13 - *trans*-dienolic acid methyl ester;
- 25 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - nor - 8 β - prosta - 5-*cis*,13 - *trans* - dienolic acid methyl ester and 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - nor - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester;
- 30 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - methyl - 8 β -prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - methyl - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester;
- 35 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 8 β - prosta-5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethyl - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester;
- 40 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - butyl - 8 β - prosta-5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - butyl - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester;
- 45 8R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 19,20 - bisnor - 8 β ,12 α -prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8R - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 19,20 - bisnor - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans*-dienolic acid methyl ester;
- 50 8R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - nor - 8 β ,12 α -prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8R - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - nor - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester;
- 55 8R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - methyl - 8 β ,12 α -prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8R - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - methyl - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans*-dienolic acid methyl ester;
- 60 8R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 8 β ,12 α -prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8R - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethyl - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester;
- 8R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 8 β - prosta-5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxy - 19,20 - bisnor - 8 β - prosta - 5 - *cis*,13 - *trans*-dienolic acid methyl ester;
- 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy - 19,20 - bisnor - 8 β -prosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxy - 19,20 - bisnor - 8 β - prosta - 5 - *cis*,13 - *trans*-dienolic acid methyl ester;
- 8R - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 20 - ethyl - 8 β - prosta-5 - *cis*,13 - *trans* - dienolic acid methyl ester and 8R - 11 β ,12 β - difluoro-

methylene - 9 β ,15 β - dihydroxy - 20 - nor - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester;

5 8R - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 20 - butyl - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and 8R - 11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 20 - butyl - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans*-dienoic acid methyl ester.

10 Likewise, starting from racemic 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α -hydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester there are obtained racemic 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and racemic 11 α ,12 α - difluoromethylene-9 β ,15 α - dihydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester.

EXAMPLE 14.

15 A. A suspension of 4 g. of crude pancreatic lipase (Sigma L—3126) in 40 ml. of a 0.1M sodium chloride and 0.05M 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 1N sodium hydroxide solution to pH 7.2 to 7.4 and used directly for the hydrolysis of the prostaglandin derivatives of the invention.

20 B. Forty-two milligrams of 8R - 11 α ,12 α - difluoromethylene 9 α ,15 α - dihydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienoic 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 27°C, adjusting constantly the pH at 7.2 to 7.4 during the reaction period with 1N sodium hydroxide solution. The reaction mixture is then acidified using a 0.2N hydrochloric acid solution and the product extracted several times from the solution with ethyl acetate and 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 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienoic acid (XV—A, R = nC₅H₁₁; R⁴ = H).

35 In a similar manner by following the above procedure or the procedure described in Example 11 the remaining alkyl ester compounds obtained in Example 13 as final products are converted into the corresponding free acids. Representative compounds thus obtained are:

40 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy - 8 β - prosta - 5 - *cis*,13-*trans* - dienoic acid (XV—B, R = nC₅H₁₁; R⁴ = H),

8R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid (XV—C, R = nC₅H₁₁; R⁴ = H),

8R - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid (XV—D, R = nC₅H₁₁; R⁴ = H),

45 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β - prosta - 5 - *cis*,13-*trans* - dienoic acid (XVI—A, R = nC₅H₁₁; R⁴ = H),

8R - 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxy - 8 β - prosta - 5 - *cis*,13-*trans* - dienoic acid (XVI—A, R = nC₅H₁₁; R⁴ = H),

8R - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid (XVI—C, R = nC₅H₁₁; R⁴ = H),

50 8R - 11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid (XVI—D, R = nC₅H₁₁; R⁴ = H),

8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 8 β - prosta-5 - *cis*,13 - *trans* - dienoic acid,

55 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxy - 20 - butyl - 8 β - prosta-5 - *cis*,13 - *trans* - dienoic acid,

8R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 19,20 - bisnor - 8 β ,12 α -prosta - 5 - *cis*,13 - *trans* - dienoic acid and

8R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 8 β ,12 α -prosta - 5 - *cis*,13 - *trans* - dienoic acid.

60

EXAMPLE 15.

To a suspension of 2 g. of Celite (registered Trade Mark), diatomaceous earth (dried for 24 hours at 105°C) and 1 g. of chromium trioxide-dipyridine complex [prepared as described by J. C. Collins et al, in *Tetrahedron Letters*, 3363 (1968)] in

60

15 ml. of methylene chloride cooled to -5°C is added, under stirring, a solution of 130 mg. of 8*S* - 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran-2' - yloxyprost - 13 - *trans* - enoic acid in 5 ml. of methylene chloride and the mixture is stirred for 15 minutes further at 0° to 5°C ; 300 mg. of sodium bisulfate monohydrate are then added and the reaction mixture is stirred for an additional 10 minute period. The insoluble material is separated by filtration and washed well with methylene chloride. The combined organic filtrates are evaporated to dryness under vacuo and the residue purified by thin-layer chromatography, thus obtaining 8*R* - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxyprost - 13 - *trans* - enoic acid (XVII—A, $\text{R} = \text{nC}_5\text{H}_{11}$).

Same results are obtained when using 8*N* chromic acid in acetone solution, in accordance with the method of Example 7, part A.

Upon hydrolysis of the tetrahydropyranyloxy group with 65% aqueous acetic acid, in accordance with the method of Example 7, part B, there is produced 8*R* - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprost - 13 - *trans* - enoic acid (XVIII—A, $\text{R} = \text{nC}_5\text{H}_{11}$).

In a similar manner, starting from the remaining compounds obtained in Example 8, there are produced as final products, respectively:

8*R* - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 12 α - prost - 13 - *trans* - enoic acid (XVIII—C, $\text{R} = \text{nC}_5\text{H}_{11}$),

8*R* - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - hydroxyprost - 13 - *trans* - enoic acid (XVIII—B, $\text{R} = \text{nC}_5\text{H}_{11}$),

8*R* - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 12 α - prost - 13 - *trans* - enoic acid (XVIII—D, $\text{R} = \text{nC}_5\text{H}_{11}$),

8*R* - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 19,20 - bisnorprost-13 - *trans* - enoic acid,

8*R* - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - norprost - 13 - *trans* - enoic acid,

8*R* - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - methylprost-13 - *trans* - enoic acid,

8*R* - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - ethylprost - 13 - *trans* - enoic acid,

8*R* - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - butylprost - 13 - *trans* - enoic acid,

8*R* - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 19,20 - bisnor - 12 α - prost - 13 - *trans* - enoic acid,

8*R* - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - nor - 12 α - prost - 13 - *trans* - enoic acid,

8*R* - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - methyl - 12 α - prost - 13 - *trans* - enoic acid,

8*R* - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - ethyl - 12 α - prost - 13 - *trans* - enoic acid,

8*R* - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - butyl - 12 α - prost - 13 - *trans* - enoic acid,

8*R* - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - hydroxy - 19,20 - bisnorprost-13 - *trans* - enoic acid,

8*R* - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - hydroxy - 20 - ethylprost - 13 - *trans* - enoic acid,

8*R* - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 20 - nor - 12 α - prost - 13 - *trans* - enoic acid and

8*R* - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 20 - butyl - 12 α - prost - 13 - *trans* - enoic acid.

Likewise, racemic 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxyprost - 13 - *trans* - enoic acid is converted into racemic 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprost - 13 - *trans* - enoic acid.

EXAMPLE 16.

By following the method of Example 9, 200 mg. of 8*R* - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprost - 13 - *trans* - enoic acid are converted into the corresponding methyl ester.

A solution of 200 mg. of 8*R* - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprost - 13 - *trans* - enoic acid methyl ester in 10 ml. of methanol is cooled to 0°C and treated with 100 mg. of sodium borohydride. The reaction mixture is stirred at room temperature for 30 minutes, and thereafter the solvent eliminated under vacuo. Water is added to the oily residue and the product extracted with ethyl acetate; the

organic extract is washed with dilute hydrochloric acid solution and water to neutral, dried over magnesium sulfate and evaporated to dryness under *vacuo*. Purification of the residue by chromatography on silica gel using methylene chloride-ethyl acetate mixtures affords the pure 9α and 9β -hydroxy compounds i.e., $8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\alpha,15\alpha$ -dihydroxyprost-13-*trans*-enoic acid methyl ester (XIX—A, $R=nC_5H_{11}$; $R^4=Me$) and $8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\beta,15\alpha$ -dihydroxyprost-13-*trans*-enoic acid methyl ester (XX—A, $R=nC_5H_{11}$; $R^4=Me$).

In a similar manner, the remaining $8R$ -9-oxo-prostenoic acid derivatives obtained in Example 15 are converted into the corresponding methyl esters, which are in turn reduced with sodium borohydride to yield the respective $8S$ - 9α and 9β -hydroxylated compounds, namely:

$8S$ - $11\beta,12\beta$ -difluoromethylene- $9\alpha,15\alpha$ -dihydroxy- 12α -prost-13-*trans*-enoic acid methyl ester (XIX—C, $R=nC_5H_{11}$; $R^4=Me$) and $8S$ - $11\beta,12\beta$ -difluoromethylene- $9\beta,15\alpha$ -dihydroxy- 12α -prost-13-*trans*-enoic acid methyl ester (XX—C, $R=nC_5H_{11}$; $R^4=Me$);

$8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\alpha,15\beta$ -dihydroxyprost-13-*trans*-enoic acid methyl ester (XIX—B, $R=nC_5H_{11}$; $R^4=Me$) and $8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\beta,15\beta$ -dihydroxyprost-13-*trans*-enoic acid methyl ester (XX—B, $R=nC_5H_{11}$; $R^4=Me$);

$8S$ - $11\beta,12\beta$ -difluoromethylene- $9\alpha,15\beta$ -dihydroxy- 12α -prost-13-*trans*-enoic acid methyl ester (XIX—D, $R=nC_5H_{11}$; $R^4=Me$) and $8S$ - $11\beta,12\beta$ -difluoromethylene- $9\beta,15\beta$ -dihydroxy- 12α -prost-13-*trans*-enoic acid methyl ester (XX—D, $R=nC_5H_{11}$; $R^4=Me$);

$8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\alpha,15\alpha$ -dihydroxy-19,20-bisnorprost-13-*trans*-enoic acid methyl ester and $8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\beta,15\alpha$ -dihydroxy-19,20-bisnorprost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\alpha,15\alpha$ -dihydroxy-20-norprost-13-*trans*-enoic acid methyl ester and $8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\beta,15\alpha$ -dihydroxy-20-norprost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\alpha,15\alpha$ -dihydroxy-20-methylprost-13-*trans*-enoic acid methyl ester and $8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\beta,15\alpha$ -dihydroxy-20-methylprost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\alpha,15\alpha$ -dihydroxy-20-ethylprost-13-*trans*-enoic acid methyl ester and $8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\beta,15\alpha$ -dihydroxy-20-ethylprost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\alpha,15\alpha$ -dihydroxy-20-butylprost-13-*trans*-enoic acid methyl ester and $8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\beta,15\alpha$ -dihydroxy-20-butylprost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\beta,12\beta$ -difluoromethylene- $9\alpha,15\alpha$ -dihydroxy-19,20-bisnor- 12α -prost-13-*trans*-enoic acid methyl ester and $8S$ - $11\beta,12\beta$ -difluoromethylene- $9\beta,15\alpha$ -dihydroxy-20-bisnor- 12α -prost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\beta,12\beta$ -difluoromethylene- $9\alpha,15\alpha$ -dihydroxy-20-nor- 12α -prost-13-*trans*-enoic acid methyl ester and $8S$ - $11\beta,12\beta$ -difluoromethylene- $9\beta,15\alpha$ -dihydroxy-20-nor- 12α -prost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\beta,12\beta$ -difluoromethylene- $9\alpha,15\alpha$ -dihydroxy-20-methyl- 12α -prost-13-*trans*-enoic acid methyl ester and $8S$ - $11\beta,12\beta$ -difluoromethylene- $9\beta,15\alpha$ -dihydroxy-20-methyl- 12α -prost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\beta,12\beta$ -difluoromethylene- $9\alpha,15\alpha$ -dihydroxy-20-ethyl- 12α -prost-13-*trans*-enoic acid methyl ester and $8S$ - $11\beta,12\beta$ -difluoromethylene- $9\beta,15\alpha$ -dihydroxy-20-ethyl- 12α -prost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\beta,12\beta$ -difluoromethylene- $9\alpha,15\alpha$ -dihydroxy-20-butyl- 12α -prost-13-*trans*-enoic acid methyl ester and $8S$ - $11\beta,12\beta$ -difluoromethylene- $9\beta,15\alpha$ -dihydroxy-20-butyl- 12α -prost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\alpha,15\beta$ -dihydroxy-19,20-bisnorprost-13-*trans*-enoic acid methyl ester and $8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\beta,15\beta$ -dihydroxy-19,20-bisnorprost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\alpha,15\beta$ -dihydroxy-20-ethylprost-13-*trans*-enoic acid methyl ester and $8S$ - $11\alpha,12\alpha$ -difluoromethylene- $9\beta,15\beta$ -dihydroxy-20-ethylprost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\beta,12\beta$ -difluoromethylene- $9\alpha,15\beta$ -dihydroxy-20-nor- 12α -prost-13-*trans*-enoic acid methyl ester and $8S$ - $11\beta,12\beta$ -difluoromethylene- $9\beta,15\beta$ -dihydroxy-20-nor- 12α -prost-13-*trans*-enoic acid methyl ester;

$8S$ - $11\beta,12\beta$ -difluoromethylene- $9\alpha,15\beta$ -dihydroxy-20-butyl- 12α -prost-13-*trans*-enoic acid methyl ester and $8S$ - $11\beta,12\beta$ -difluoromethylene- $9\beta,15\beta$ -dihydroxy-20-butyl- 12α -prost-13-*trans*-enoic acid methyl ester.

Likewise starting from racemic 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprost - 13 - *trans* - enoic acid there are produced racemic 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprost - 13 - *trans* - enoic acid methyl ester and racemic 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxyprost - 13 - *trans* - enoic acid methyl ester.

EXAMPLE 17.

By following the method of Example 11, the 9 α and 9 β -hydroxylated methyl ester compounds obtained in Example 16 are converted into the corresponding free acids, e.g.,

8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprost - 13 - *trans* - enoic acid (XIX—A, R = nC₈H₁₁; R⁴ = H),

8S - 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxyprost - 13 - *trans* - enoic acid (XIX—B, R = nC₈H₁₁; R⁴ = H),

8S - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 12 α - prost - 13 - *trans* - enoic acid (XIX—C, R = nC₈H₁₁; R⁴ = H),

8S - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 12 α - prost - 13 - *trans* - enoic acid (XIX—D, R = nC₈H₁₁; R⁴ = H),

8S - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxyprost - 13 - *trans* - enoic acid (XX—A, R = nC₈H₁₁; R⁴ = H);

8S - 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxyprost - 13 - *trans* - enoic acid (XX—B, R = nC₈H₁₁; R⁴ = H),

8S - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 12 α - prost - 13 - *trans* - enoic acid (XX—C, R = nC₈H₁₁; R⁴ = H),

8S - 11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 12 α - prost - 13 - *trans* - enoic acid (XX—D, R = nC₈H₁₁; R⁴ = H),

8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethylprost - 13 - *trans* - enoic acid, and

8S - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethyl - 12 α - prost - 13 - *trans* - enoic acid.

EXAMPLE 18.

To a solution of 120 mg. of 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprost - 13 - *trans* - enoic acid in 3 ml. of anhydrous methanol is added, at room temperature and under argon atmosphere, 0.33 ml. of 2N solution of sodium methoxide in methanol, and the reaction mixture is maintained at room temperature for 30 minutes. It is then acidified with dilute hydrochloric acid to pH—2 and extracted with methylene chloride. The organic extract is washed with 50% saturated sodium chloride solution, dried and evaporated to dryness under vacuo. The residue is purified by thin layer chromatography, to obtain the pure 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 8 β - prost - 13 - *trans* - enoic acid (XXI—A, R = nC₈H₁₁).

By the same method, the remaining 8R prostenoic acid compounds of Example 15 are converted into the corresponding 8S-antimers, namely:

8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid (XXI—C, R = nC₈H₁₁),

8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - hydroxy - 8 β - prost - 13 - *trans* - enoic acid (XII—B, R = nC₈H₁₁),

8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid (XXI—D, R = nC₈H₁₁),

8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - bisnor - 8 β - prost - 13 - *trans* - enoic acid,

8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 19,20 - nor - 8 β - prost - 13 - *trans* - enoic acid,

8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - methyl - 8 β - prost - 13 - *trans* - enoic acid,

8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - ethyl - 8 β - prost - 13 - *trans* - enoic acid,

8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - butyl - 8 β - prost - 13 - *trans* - enoic acid,

8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 19,20 - bisnor - 8 β ,12 α - prost - 13 - *trans* - enoic acid,

8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - nor - 8 β ,12 α - prost - 13 - *trans* - enoic acid,

8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - methyl - 8 β ,12 α - prost - 13 - *trans* - enoic acid,

8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - ethyl - 8 β ,12 α - prost - 13 - *trans* - enoic acid,

- 8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - butyl - 8 β ,12 α -prost - 13 - *trans* - enoic acid,
 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - hydroxy - 19,20 - bis - nor-8 β - prost - 13 - *trans* - enoic acid,
 5 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - hydroxy - 20 - ethyl - 8 β -prost - 13 - *trans* - enoic acid,
 8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 20 - nor - 8 β ,12 α -prost - 13 - *trans* - enoic acid, and
 10 8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 20 - butyl - 8 β ,12 α -prost - 13 - *trans* - enoic acid.
 Likewise racemic 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprost-13 - *trans* - enoic acid is converted into racemic 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 8 β - prost - 13 - *trans* - enoic acid.

EXAMPLE 19.

- 15 In accordance with the method of Example 9, 200 mg. of 8S - 9 - oxo-11 α ,12 α - difluoromethylene - 15 α - hydroxy - 8 β - prost - 13 - *trans* - enoic acid is esterified with diazomethane, to yield the corresponding methyl ester.
 A solution of 200 mg. of 8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α -hydroxy - 8 β - prost - 13 - *trans* - enoic acid methyl ester in 10 ml. of methanol
 20 is cooled to 0°C and treated with 100 mg. of sodium borohydride. The reaction mixture is stirred at room temperature for 30 minutes and thereafter the solvent is eliminated under *vacuo*. Water is added to the oily residue and the product extracted with ethyl acetate. The organic extract is washed with dilute hydrochloric acid solution and water
 25 to neutral, dried over magnesium sulfate and evaporated to dryness under *vacuo*. Purification of the residue by chromatography on silica gel, using methylene chloride-ethyl acetate mixtures affords the pure 9 α and 9 β -hydroxy compounds i.e., 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β - prost - 13 - *trans* - enoic acid methyl ester (XXII—A, R = nC₅H₁₁; R⁴ = Me) and 8R - 11 α ,12 α - difluoromethylene-9 β ,15 α - dihydroxy - 8 β - prost - 13 - *trans* - enoic acid methyl ester (XXIII—A, R = nC₅H₁₁; R⁴ = Me).
 30 In a similar manner the remaining 8S-9-oxo-prostenoic acid derivatives obtained in Example 18 are converted into the corresponding methyl esters, which are in turn reduced with sodium borohydride to yield the respective 8R-9 α and 9 β -hydroxylated compounds, namely:
 35 8R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β ,12 α - prost - 13-*trans* - enoic acid methyl ester (XXII—C, R = nC₅H₁₁; R⁴ = Me) and 8R-11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester (XXIII—C, R = nC₅H₁₁; R⁴ = Me);
 40 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy - 8 β - prost - 13 - *trans*-enoic acid methyl ester (XXII—B, R = nC₅H₁₁; R⁴ = Me) and 8R - 11 α ,12 α -difluoromethylene - 9 β ,15 β - dihydroxy - 8 β - prost - 13 - *trans* - enoic acid methyl ester (XXIII—B, R = nC₅H₁₁; R⁴ = Me);
 45 8R - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 8 β ,12 α - prost - 13-*trans* - enoic acid methyl ester (XXII—D, R = nC₅H₁₁; R⁴ = Me) and 8R-11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester (XXIII—D, R = nC₅H₁₁; R⁴ = Me).
 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 19,20 - bisnor - 8 β -prost - 13 - *trans* - enoic acid methyl ester and 8R - 11 α ,12 α - difluoromethylene-9 β ,15 α - dihydroxy - 19,20 - bisnor - 8 β - prost - 13 - *trans* - enoic acid methyl ester;
 50 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - nor - 8 β - prost-13 - *trans* - enoic acid methyl ester and 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 α -dihydroxy - 20 - nor - 8 β - prost - 13 - *trans* - enoic acid methyl ester;
 55 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - methyl - 8 β - prost-13 - *trans* - enoic acid methyl ester and 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 α -dihydroxy - 20 - methyl - 8 β - prost - 13 - *trans* - enoic acid methyl ester;
 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 8 β - prost-13 - *trans* - enoic acid methyl ester and 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 α -dihydroxy - 20 - ethyl - 8 β - prost - 13 - *trans* - enoic acid methyl ester;
 60 8R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - butyl - 8 β - prost-13 - *trans* - enoic acid methyl ester and 8R - 11 α ,12 α - difluoromethylene - 9 β ,15 α -dihydroxy - 20 - butyl - 8 β - prost - 13 - *trans* - enoic acid methyl ester;
 8R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 19,20 - bisnor - 8 β ,12 α -prost - 13 - *trans* - enoic acid methyl ester and 8R - 11 β ,12 β - difluoromethylene-

- 9 β ,15 α - dihydroxy - 19,20 - bisnor - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester;
- 5 8 R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - nor - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester and 8 R - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - nor - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester;
- 10 8 R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - methyl - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester and 8 R - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - methyl - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester;
- 15 8 R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester and 8 R - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethyl - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester;
- 20 8 R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - butyl - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester and 8 R - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - butyl - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester;
- 25 8 R - 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy - 19,20 - bisnor - 8 β - prost - 13 - *trans* - enoic acid methyl ester and 8 R - 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxy - 19,20 - bisnor - 8 β - prost - 13 - *trans* - enoic acid methyl ester;
- 30 8 R - 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy - 20 - ethyl - 8 β - prost - 13 - *trans* - enoic acid methyl ester and 8 R - 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxy - 20 - ethyl - 8 β - prost - 13 - *trans* - enoic acid methyl ester;
- 35 8 R - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 20 - nor - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester and 8 R - 11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 20 - nor - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester;
- 40 8 R - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 20 - butyl - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester and 8 R - 11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 20 - butyl - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester.
- Likewise, starting from racemic 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 8 β - prost - 13 - *trans* - enoic acid there are produced racemic 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β - prost - 13 - *trans* - enoic acid methyl ester and racemic 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester.

EXAMPLE 20.

- By following the methods of Examples 11 or 14 the 9 α and 9 β -hydroxylated-methyl ester 8 R -antimeric compounds obtained in Example 19 are converted into the corresponding free acids. Representative compounds thus obtained are:
- 8 R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β - prost - 13 - *trans* - enoic acid (XXII—A, R = nC₅H₁₁; R⁴ = H);
- 40 8 R - 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy - 8 β - prost - 13 - *trans* - enoic acid (XXII—B, R = nC₅H₁₁; R⁴ = H);
- 8 R - 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid (XXII—C, R = nC₅H₁₁; R⁴ = H);
- 45 8 R - 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid (XXII—D, R = nC₅H₁₁; R⁴ = H);
- 8 R - 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β - prost - 13 - *trans* - enoic acid (XXIII—A, R = nC₅H₁₁; R⁴ = H);
- 50 8 R - 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxy - 8 β - prost - 13 - *trans* - enoic acid (XXIII—B, R = nC₅H₁₁; R⁴ = H);
- 8 R - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid (XXIII—C, R = nC₅H₁₁; R⁴ = H);
- 55 8 R - 11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid (XXIII—D, R = nC₅H₁₁; R⁴ = H),
- 8 R - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 8 β - prost - 13 - *trans* - enoic acid and
- 8 R - 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethyl - 8 β ,12 α - prost - 13 - *trans* - enoic acid.

EXAMPLE 21.

- By following the hydrolysis methods of Examples 11 or 14, using as starting materials the methyl esters of the racemic prostadienoic and prostenoic acid derivatives obtained in Examples 10, 13, 16 and 19, there are produced the corresponding free acids, namely:
- 60 Racemic 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13-*trans* - dienenoic acid,

- racemic 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxyprosta - 5 - *cis*,13-*trans* - dienoic acid,
 racemic 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β - prosta - 5-*cis*,13 - *trans* - dienoic acid,
 5 racemic 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β - prosta - 5-*cis*,13 - *trans* - dienoic acid,
 racemic 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprost - 13 - *trans* - enoic acid,
 10 racemic 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - prost - 13 - *trans*-*enoic acid*,
 racemic 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β - prost - 13-*trans* - enoic acid and
 racemic 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β - prost - 13-*trans* - enoic acid.
- 15 **EXAMPLE 22.**
 Examples 6, 7 and 12 are repeated starting from racemic [2' α - hydroxy-4' β ,5' β - difluoromethylene - 5' α - (3'' α - tetrahydropyran - 2''' - yloxyoct - 1''(t)-en - 1'' - yl) - cyclopent - 1' α - yl] acetaldehyde 1,2'-hemiacetal, thus obtaining successively:
 20 racemic 9 α - hydroxy - 11 β ,12 β - difluoromethylene - 15 α - tetrahydropyran - 2'-yloxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid,
 racemic 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - tetrahydropyran - 2' - yl-*oxy* - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid,
 25 racemic 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 12 α - prosta - 5-*cis*,13 - *trans* - dienoic acid and
 racemic 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 8 β ,12 α - prosta-5 - *cis*,13 - *trans* - dienoic acid.
- EXAMPLE 23.**
 In accordance with the methods of Examples 8, 15 and 18, racemic 9 α -hydroxy - 11 β ,12 β - difluoromethylene - 15 α - tetrahydropyran - 2' - yloxy - 12 α -prosta - 5 - *cis*,13 - *trans* - dienoic acid is converted successively into:
 racemic 9 α - hydroxy - 11 β ,12 β - difluoromethylene - 15 α - tetrahydropyran - 2'-yloxy - 12 α - prost - 13 - *trans* - enoic acid,
 35 racemic 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - tetrahydropyran - 2' - yl-*oxy* - 12 α - prost - 13 - *trans* - enoic acid,
 racemic 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 12 α - prost-13 - *trans* - enoic acid and
 racemic 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 8 β ,12 α - prost-13 - *trans* - enoic acid.
- 40 **EXAMPLE 24.**
 By following the method of Example 9, racemic 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid,
 racemic 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 8 β ,12 α - prosta-5 - *cis*,13 - *trans* - dienoic acid,
 45 racemic 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 12 α - prost - 13-*trans* - enoic acid and
 racemic 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 8 β ,12 α - prost-13 - *trans* - enoic acid.
 are converted into the corresponding methyl esters.
- 50 **EXAMPLE 25.**
 Example 10 is repeated using as starting materials the racemic methyl ester compounds of Example 24, thus obtaining respectively:
 racemic 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 12 α - prosta - 5-*cis*,13 - *trans* - dienoic acid methyl ester and racemic 11 β ,12 β - difluoromethylene-9 β ,15 α - dihydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester;
 55 racemic 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β ,12 α - prosta - 5-*cis*,13 - *trans* - dienoic acid methyl ester and
 racemic 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β ,12 α - prosta - 5-*cis*,13 - *trans* - dienoic acid methyl ester;
 60 racemic 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 12 α - prost - 13-*trans* - enoic acid methyl ester and racemic 11 β ,12 β - difluoromethylene - 9 β ,15 α -dihydroxy - 12 α - prost - 13 - *trans* - enoic acid methyl ester and

racemic 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β ,12 α - prost - 13-*trans* - enoic acid methyl ester and racemic 11 β ,12 β - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester.

Upon saponification of the methyl ester group, in accordance with the methods of Examples 11 or 14 there are produced the corresponding racemic free acids, i.e.,

racemic 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 12 α - prosta - 5-*cis*,13 - *trans* - dienoic acid,

racemic 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β ,12 α - prosta - 5-*cis*,13 - *trans* - dienoic acid,

racemic 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 12 α - prost - 13-*trans* - enoic acid,

racemic 11 β ,12 β - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β ,12 α - prost - 13-*trans* - enoic acid, and the corresponding 9 β -isomers.

EXAMPLE 26.

This Example illustrates the methods according to the invention for converting the compounds of formula XXIV into the compounds of formula XXV.

A. A mixture of 80 mg. of 8S - 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester, 2 ml. of dioxane and 160 mg. of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone is stirred at room temperature for 18 hours. The reaction mixture is then evaporated to dryness under reduced pressure and the residue is dissolved in methylene chloride and chromatographed on Florisil. The fractions eluted with methylene chloride-diethyl ether-methanol (78:20:2) afford 8S-9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 - oxoprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester in pure form.

B. To a solution of 100 mg. of 8S - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester in 5 ml. of anhydrous tetrahydrofuran are added 400 mg of activated manganese dioxide, and the reaction mixture is stirred at room temperature for 6 hours. The manganese dioxide is then 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 400 mg. 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 8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 - oxoprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester, identical to the compound obtained in part A.

By the above-described methods, starting from the corresponding 8R- or 8S-anti-metric 9,15-dihydroxylated prostaglandin derivatives obtained in Examples 10, 13, 16 and 19, in which the hydroxyl group at C-15 may be in α or β configuration, there are produced the following compounds:

8S - 11 α ,12 α - difluoromethylene - 9 β - hydroxy - 15 - oxoprosta - 5 - *cis*,13-*trans* - dienoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 9 α - hydroxy - 15 - oxo - 12 α - prosta - 5-*cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 9 β - hydroxy - 15 - oxo - 12 α - prosta - 5-*cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 α ,12 α - difluoromethylene - 9 α - hydroxy - 15 - oxo - 19,20 - bisnorprosta-5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 α ,12 α - difluoromethylene - 9 β - hydroxy - 15 - oxo - 20 - methylprosta-5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 α ,12 α - difluoromethylene - 9 α - hydroxy - 15 - oxo - 20 - ethylprosta - 5-*cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 9 β - hydroxy - 15 - oxo - 20 - nor - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 9 α - hydroxy - 15 - oxo - 20 - ethyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 9 β - hydroxy - 15 - oxo - 20 - butyl - 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8R - 11 α ,12 α - difluoromethylene - 9 α - hydroxy - 15 - oxo - 8 β - prosta - 5-*cis*,13 - *trans* - dienoic acid methyl ester,

8R - 11 β ,12 β - difluoromethylene - 9 α - hydroxy - 15 - oxo - 8 β ,12 α - prosta - 5-*cis*,13 - *trans* - dienoic acid methyl ester,

8R - 11 α ,12 α - difluoromethylene - 9 β - hydroxy - 15 - oxo - 8 β - prosta - 5-*cis*,13 - *trans* - dienoic acid methyl ester,

	8R - 11 β ,12 β - difluoromethylene - 9 β - hydroxy - 15 - oxo - 8 β ,12 α - prosta-5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid methyl ester,	
	8R - 11 α ,12 α - difluoromethylene - 9 α - hydroxy - 15 - oxo - 20 - ethyl - 8 β -prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid methyl ester,	
5	8R - 11 α ,12 α - difluoromethylene - 9 β - hydroxy - 15 - oxo - 19,20 - bisnor - 8 β -prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid methyl ester,	5
	8R - 11 β ,12 β - difluoromethylene - 9 α - hydroxy - 15 - oxo - 20 - methyl - 8 β ,12 α -prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid methyl ester,	
10	8S - 11 α ,12 α - difluoromethylene - 9 α - hydroxy - 15 - oxoprost - 13 - <i>trans</i> - enoic acid methyl ester,	10
	8S - 11 α ,12 α - difluoromethylene - 9 β - hydroxy - 15 - oxoprost - 13 - <i>trans</i> - enoic acid methyl ester.	
	8S - 11 β ,12 β - difluoromethylene - 9 α - hydroxy - 15 - oxo - 12 α - prost - 13- <i>trans</i> - enoic acid methyl ester,	
15	8S - 11 α ,12 α - difluoromethylene - 9 α - hydroxy - 15 - oxo - 19,20 - bisnorprost-13 - <i>trans</i> - enoic acid methyl ester,	15
	8S - 11 α ,12 α - difluoromethylene - 9 α - hydroxy - 15 - oxo - 20 - ethylprost - 13- <i>trans</i> - enoic acid methyl ester,	
20	8S - 11 β ,12 β - difluoromethylene - 9 β - hydroxy - 15 - oxo - 12 α - prost - 13- <i>trans</i> - enoic acid methyl ester,	20
	8S - 11 β ,12 β - difluoromethylene - 9 β - hydroxy - 15 - oxo - 20 - butyl - 12 α -prost - 13 - <i>trans</i> - enoic acid methyl ester,	
	8R - 11 α ,12 α - difluoromethylene - 9 α - hydroxy - 15 - oxo - 8 β - prost - 13- <i>trans</i> - enoic acid methyl ester,	
25	8R - 11 α ,12 α - difluoromethylene - 9 β - hydroxy - 15 - oxo - 8 β - prost - 13- <i>trans</i> - enoic acid methyl ester,	25
	8R - 11 α ,12 α - difluoromethylene - 9 α - hydroxy - 15 - oxo - 20 - ethyl - 8 β -prost - 13 - <i>trans</i> - enoic acid methyl ester,	
	8R - 11 α ,12 α - difluoromethylene - 9 β - hydroxy - 15 - oxo - 20 - nor - 8 β - prost-13 - <i>trans</i> - enoic acid methyl ester,	
30	8R - 11 β ,12 β - difluoromethylene - 9 α - hydroxy - 15 - oxo - 8 β ,12 α - prost - 13- <i>trans</i> - enoic acid methyl ester,	30
	8R - 11 β ,12 β - difluoromethylene - 9 β - hydroxy - 15 - oxo - 8 β ,12 α - prost - 13- <i>trans</i> - enoic acid methyl ester,	
35	8R - 11 β ,12 β - difluoromethylene - 9 α - hydroxy - 15 - oxo - 20 - bisnor - 8 β ,12 α -prost - 13 - <i>trans</i> - enoic acid methyl ester, and	35
	8R - 11 β ,12 β - difluoromethylene - 9 α - hydroxy - 15 - oxo - 20 - ethyl - 8 β ,12 α -prost - 13 - <i>trans</i> - enoic acid methyl ester.	
40	Likewise, racemic 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprosta - 5- <i>cis</i> ,13 - <i>trans</i> - dienoic acid methyl ester and racemic 11 β ,12 β - difluoromethylene-9 β ,15 α - dihydroxy - 12 α - prost - 13 - <i>trans</i> - enoic acid methyl ester are converted into the corresponding 15-oxo derivatives.	40

EXAMPLE 27.

This Examples illustrates the methods, according to the invention, for converting the compounds of formula XXV into the methyl ester compounds of formulas XXVI and XXVII.

A. A solution of 60 mg. of 8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene-15 - oxoprost - 5 - *cis*,13 - *trans* - dienoic acid methyl ester in 10 ml. of anhydrous diethyl ether is cooled to -78°C and treated dropwise, under stirring and under argon atmosphere with 6 molar equivalents of methylmagnesium bromide (using a 3N ethereal solution of this reagent). The temperature of the reaction mixture is allowed to rise to -25°C., 6 additional molar equivalents of methylmagnesium bromide solution are added, and the resulting mixture is stirred for 2 hours more, at the end of which time there are added 5 ml. of methanol. The resulting mixture is diluted with ether and washed several times with saturated sodium chloride solution. The ethereal extract is then dried over magnesium sulfate and evaporated to dryness under reduced pressure. The oily residue is purified by thin layer chromatography, using a mixture of methylene chloride-diethyl ether-methanol (88:10:2) as gradient to produce 8S - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and 8S - 11 α ,12 α - difluoromethylene - 15 α - methyl - 9 α ,15 β -dihydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester in pure form.

In a similar manner but using ethylmagnesium bromide in place of methylmagnesium bromide, there are obtained 8S - 11 α ,12 α - difluoromethylene - 15 β - ethyl-9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and 8S-

11 α ,12 α - difluoromethylene - 15 α - ethyl - 9 α ,15 β - dihydroxyprosta - 5 - *cis*,13 - *trans*-dienoic acid methyl ester, which are separated by t.l.c.

B. One hundred milligrams of 8S - 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 - oxoprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester are dissolved in 10 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 1.4 ml. of 0.22M methyllithium 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. Purification of the residue by thin layer chromatography, as described in part A of this Example affords 8S - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester and 8S - 11 α ,12 α - difluoromethylene - 15 α - methyl - 9 α ,15 β - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester, identical to the products obtained in part A of this Example.

Similarly, by following the methods described in parts A or B, using methyl magnesium bromide or methyllithium as reagents, and the corresponding 15-oxo compounds obtained in Example 26 as starting materials there are produced:

8S - 11 α ,12 α - difluoromethylene - 15{ - methyl - 9 β ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 15{ - methyl - 9 α ,15{ - dihydroxy - 12 α -prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 15{ - methyl - 9 β ,15{ - dihydroxy - 12 α -prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 α ,12 α - difluoromethylene - 15{ - methyl - 9 α ,15{ - dihydroxy - 19,20-bisnorprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 α ,12 α - difluoromethylene - 15{ - methyl - 9 β ,15{ - dihydroxy - 20 - ethylprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 α ,12 α - difluoromethylene - 15{ - methyl - 9 α ,15{ - dihydroxy - 20 - ethylprosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 15{ - methyl - 9 β ,15{ - dihydroxy - 20 - nor-12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 15{ - methyl - 9 α ,15{ - dihydroxy - 20 - ethyl-12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 15{ - methyl - 9 β ,15{ - dihydroxy - 20 - butyl-12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8R - 11 α ,12 α - difluoromethylene - 15{ - methyl - 9 α ,15{ - dihydroxy - 8 β -prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8R - 11 β ,12 β - difluoromethylene - 15{ - methyl - 9 α ,15{ - dihydroxy - 8 β ,12 α -prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8R - 11 α ,12 α - difluoromethylene - 15{ - methyl - 9 β ,15{ - dihydroxy - 8 β -prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8R - 11 β ,12 β - difluoromethylene - 15{ - methyl - 9 β ,15{ - dihydroxy - 8 β ,12 α -prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8R - 11 α ,12 α - difluoromethylene - 15{ - methyl - 9 α ,15{ - dihydroxy - 20 - ethyl-8 β - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8R - 11 α ,12 α - difluoromethylene - 15{ - methyl - 9 β ,15{ - dihydroxy - 19,20-bisnor - 8 β - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8R - 11 β ,12 β - difluoromethylene - 15{ - methyl - 9 α ,15{ - dihydroxy - 20-methyl - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid methyl ester,

8S - 11 α ,12 α - difluoromethylene - 15{ - methyl - 9 α ,15{ - dihydroxyprost - 13-*trans* - enoic acid methyl ester,

8S - 11 α ,12 α - difluoromethylene - 15{ - methyl - 9 β ,15{ - dihydroxyprost - 13-*trans* - enoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 15{ - methyl - 9 α ,15{ - dihydroxy - 12 α -prost - 13 - *trans* - enoic acid methyl ester,

8S - 11 α ,12 α - difluoromethylene - 15{ - methyl - 9 α ,15{ - dihydroxy - 19,20-bisnorprost - 13 - *trans* - enoic acid methyl ester,

8S - 11 α ,12 α - difluoromethylene - 15{ - methyl - 9 α ,15{ - dihydroxy - 20 - ethylprost - 13 - *trans* - enoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 15{ - methyl - 9 β ,15{ - dihydroxy - 12 α -prost - 13 - *trans* - enoic acid methyl ester,

8S - 11 β ,12 β - difluoromethylene - 15{ - methyl - 9 β ,15{ - dihydroxy - 20 - butyl-12 α - prost - 13 - *trans* - enoic acid methyl ester,

- 8R - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 β - dihydroxy - 8 β -prost - 13 - *trans* - enoic acid methyl ester,
 8R - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 β ,15 β - dihydroxy - 8 β -prost - 13 - *trans* - enoic acid methyl ester,
 5 8R - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 β - dihydroxy - 20 - ethyl-8 β - prost - 13 - *trans* - enoic acid methyl ester,
 8R - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 β ,15 β - dihydroxy - 20 - nor-8 β - prost - 13 - *trans* - enoic acid methyl ester,
 10 8R - 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 α ,15 β - dihydroxy - 8 β ,12 α -prost - 13 - *trans* - enoic acid methyl ester,
 8R - 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 β ,15 β - dihydroxy - 8 β ,12 α -prost - 13 - *trans* - enoic acid methyl ester,
 15 8R - 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 α ,15 β - dihydroxy - 19,20-bisnor - 8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester, and
 8R - 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 α ,15 β - dihydroxy - 20 - ethyl-8 β ,12 α - prost - 13 - *trans* - enoic acid methyl ester.
 Likewise racemic 9 α - hydroxy - 11 α ,12 α - difluoromethylene - 15 - oxoprost-5 - *cis*,13 - *trans* - dienolic acid methyl ester and racemic 9 β - hydroxy - 11 β ,12 β -difluoromethylene - 15 - keto - 12 α - prost - 13 - *trans* - enoic acid methyl ester are converted respectively into racemic 11 α ,12 α - difluoromethylene - 15 β - methyl-9 α ,15 β - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester and racemic 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 β ,15 β - dihydroxy - 12 α - prost - 13 - *trans* - enoic acid methyl ester.
 The individual 15 α -hydroxy-15 β -methyl and 15 β -hydroxy-15 α -methyl isomers are separated by thin layer chromatographic techniques.
 The corresponding 15-ethyl compounds are produced when using ethylmagnesium bromide or ethyllithium as reagents in place of methylmagnesium bromide or methyl-lithium, respectively, in the procedures described in parts A and B of this Example.

EXAMPLE 28.

- This Example illustrates the method according to the invention, for converting the methyl ester compounds of formulas XXVI and XXVII into the corresponding free prostadienoic and prostenoic acids.
 Eighty milligrams of 8S - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 α -dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid methyl ester are dissolved by sonication at 37°C for 20 minutes in 60 ml. of the lipase solution prepared as described in part A of Example 16. The reaction mixture is magnetically stirred for 15 minutes at 25° to 27°C, adjusting constantly the pH at 7.2 to 7.4 during the reaction period with 1N sodium hydroxide solution. The reaction mixture is then acidified to pH 5 using a 0.2N hydrochloric acid solution and the product extracted several times from the solution with ethyl acetate and 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 6 g. of Florisil. The fractions eluted with ethyl acetate containing 20% of methanol yield the pure 8S - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid,
 By the same procedure, the remaining methyl ester compounds obtained in Example 27 are hydrolyzed to produce the corresponding free acids. Representative compounds thus obtained are:
 8S - 11 α ,12 α - difluoromethylene - 15 β - ethyl - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid,
 8S - 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy - 12 α -prosta - 5 - *cis*,13 - *trans* - dienolic acid,
 8S - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid,
 8S - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy - 20 - ethylprosta - 5 - *cis*,13 - *trans* - dienolic acid,
 8S - 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxy - 12 α -prosta - 5 - *cis*,13 - *trans* - dienolic acid,
 8S - 11 β ,12 β - difluoromethylene - 15 α - methyl - 9 α ,15 β - dihydroxy - 12 α -prosta - 5 - *cis*,13 - *trans* - dienolic acid,
 8R - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy - 8 β -prosta - 5 - *cis*,13 - *trans* - dienolic acid,
 8R - 11 α ,12 α - difluoromethylene - 15 β - ethyl - 9 β ,15 α - dihydroxy - 8 β - prosta-5 - *cis*,13 - *trans* - dienolic acid,

	8R - 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy - 8 β ,12 α - prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid,	
	8R - 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxy - 8 β ,12 α - prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid,	
5	8S - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxyprost - 13- <i>trans</i> - enoic acid,	5
	8S - 11 α ,12 α - difluoromethylene - 15 β - ethyl - 9 α ,15 α - dihydroxyprost - 13- <i>trans</i> - enoic acid,	
10	8S - 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy - 12 α - prost - 13 - <i>trans</i> - enoic acid,	10
	8S - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxyprost - 13- <i>trans</i> - enoic acid,	
15	8S - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy - 20 - ethyl- prost - 13 - <i>trans</i> - enoic acid,	15
	8S - 11 β ,12 β - difluoromethylene - 15 α - ethyl - 9 β ,15 β - dihydroxy - 12 α - prost - 13 - <i>trans</i> - enoic acid,	
20	8S - 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxy - 12 α - prost - 13 - <i>trans</i> - enoic acid,	20
	8R - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy - 8 β - prost - 13 - <i>trans</i> - enoic acid,	
25	8R - 11 α ,12 α - difluoromethylene - 15 β - ethyl - 9 β ,15 α - dihydroxy - 8 β - prost- 13 - <i>trans</i> - enoic acid,	25
	8R - 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy - 8 β ,12 α - prost - 13 - <i>trans</i> - enoic acid, and	
30	8R - 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxy - 8 β ,12 α - prost - 13 - <i>trans</i> - enoic acid.	30
	Likewise, racemic 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 α - di- hydroxyprosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid methyl ester and racemic 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxy - 12 α - prost - 13 - <i>trans</i> - enoic acid methyl ester are converted into the corresponding free acids.	

EXAMPLE 29.

This Example illustrates the methods according to the invention, for converting compounds of formulas XXVI and XXVII into compounds of formulas XXVIII and XXIX respectively.

35	To a suspension of 2 g. of Celite, diatomaceous earth (dried for 24 hours at 105°C) and 1 g. of chromium trioxide-dipyridine complex [prepared as described by J. C. Collins et al, in <i>Tetrahedron Letters</i> , 3363 (1968)] in 15 ml. of methylene chloride cooled to -5°C is added, under stirring, a solution of 130 mg. of 8S - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxyprosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid methyl ester in 5 ml. of methylene chloride and the mixture is stirred for 15 minutes further at 0°C to 5°C; 300 mg. of sodium bisulfate monohydrate are then added and the reaction mixture is stirred for an additional 10 minute period. The insoluble material is separated by filtration and washed well with methylene chloride. The combined organic filtrates are evaporated to dryness under vacuo and the residue purified by thin-layer chromatography, thus obtaining 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxyprosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid methyl ester.	35
40	Upon hydrolysis of the methyl ester group, by following the method of Example 28 there is produced 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxyprosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid.	40

50	The latter compound can also be obtained by oxidation of 8S - 11 α ,12 α - difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxyprosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid or its 9 β -hydroxy-isomer.	50
----	--	----

55	In a similar manner, starting from the corresponding 9 α - or 9 β -hydroxylated compounds of Example 27 there are produced the following compounds as final products, <i>via</i> the corresponding methyl esters:	55
----	--	----

	8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - methyl - 15 β - hydroxyprosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid,	
	8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - methyl - 15 α - hydroxy - 12 α - prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid,	
60	8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - methyl - 15 β - hydroxy - 19,20- bisorprosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid,	60
	8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxy - 20- methylprosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid,	

	8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxy - 20-ethylprosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid,	
	8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - methyl - 15 β - hydroxy - 20-nor - 12 α - prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid,	
5	8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - methyl - 15 β - hydroxy - 20-ethyl - 12 α - prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid,	5
	8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - ethyl - 15 β - hydroxy - 20-butyl - 12 α - prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid,	
10	8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxy - 8 β -prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid,	10
	8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - methyl - 15 α - hydroxy-8 β ,12 α - prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid,	
	8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxy - 20-ethyl - 8 β - prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid,	
15	8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - ethyl - 15 α - hydroxy - 19,20-bisnor - 8 β - prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid,	15
	8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 15 α ,20 - dimethyl-8 β ,12 α - prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid,	
20	8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxyprost-13 - <i>trans</i> - enoic acid,	20
	8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - methyl - 15 α - hydroxy - 12 α -prost - 13 - <i>trans</i> - enoic acid,	
	8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - ethyl - 15 α - hydroxyprost-13 - <i>trans</i> - enoic acid,	
25	8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - methyl - 15 β - hydroxy - 20-ethylprost - 13 - <i>trans</i> - enoic acid,	25
	8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - ethyl - 15 α - hydroxy - 20-nor - 12 α - prost - 13 - <i>trans</i> - enoic acid,	
30	8R - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - methyl - 15 α - hydroxy - 20-butyl - 12 α - prost - 13 - <i>trans</i> - enoic acid,	30
	8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxy - 8 β -prost - 13 - <i>trans</i> - enoic acid,	
	8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxy - 20-ethyl - 8 β - prost - 13 - <i>trans</i> - enoic acid,	
35	8S - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - ethyl - 15 α - hydroxy - 20-nor - 8 β - prost - 13 - <i>trans</i> - enoic acid,	35
	8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - methyl - 15 α - hydroxy-8 β ,12 α - prost - 13 - <i>trans</i> - enoic acid,	
40	8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α - methyl - 15 β - hydroxy - 19,20-bisnor - 8 β ,12 α - prost - 13 - <i>trans</i> - enoic acid and	40
	8S - 9 - oxo - 11 β ,12 β - difluoromethylene - 15 α ,20 - diethyl - 15 β - hydroxy-8 β ,12 α - prost - 13 - <i>trans</i> - enoic acid.	

EXAMPLE 30.

45	In accordance with the oxidation method of Example 29, racemic 11 α ,12 α -difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxyprosta - 5 - <i>cis</i> ,13 - <i>trans</i> -dienoic acid and racemic 11 β ,12 β - difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxy - 12 α - prost - 13 - <i>trans</i> - enoic acid are converted respectively into racemic 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxyprosta - 5 - <i>cis</i> ,13- <i>trans</i> - dienoic acid and racemic 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - methyl-15 α - hydroxy - 12 α - prost - 13 - <i>trans</i> - enoic acid.	45
50		50

EXAMPLE 31.

55	To a solution of 100 mg of 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α -hydroxyprosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid in 10 ml. of methanol is added 3 ml. of a 0.1N solution of sodium hydroxide, and the mixture is stirred at room temperature for one hour. It is then evaporated to dryness under reduced pressure, to give the sodium salt of 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprosta-5 - <i>cis</i> ,13 - <i>trans</i> - dienoic acid.	55
----	--	----

60	By employing 1.1 molar equivalents of potassium hydroxide (in the form of a 0.1N solution) in place of sodium hydroxide in the above procedure, the potassium salt of 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprosta - 5 - <i>cis</i> ,13 - <i>trans</i> -dienoic acid is obtained.	60
----	--	----

Similarly, the sodium and potassium salts of the other free antimeric 8R- and 8S-11 α ,12 α - or 11 β ,12 β -difluoromethylene prostaglandin derivatives, or the racemic mixtures thereof, obtained in the previous Examples, are produced.

EXAMPLE 32.

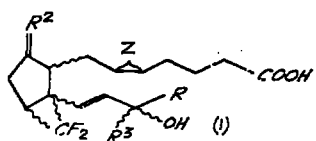
To a solution of 100 mg. of 8*R* - 11*β*,12*β* - difluoromethylene - 9*α*,15*α* - dihydroxy - 12*α* - prosta - 5 - *cis*,13 - *trans* - dienoic acid in 10 ml. of methanol is added a mixture of 3 ml. of concentrated ammonium hydroxide solution and 5 ml. of methanol. The resulting mixture is stirred for two hours at room temperature and then evaporated to dryness under vacuo, to yield the ammonium salt of 8*R* - 11*β*,12*β* - difluoromethylene - 9*α*,15*α* - dihydroxy - 12*α* - prosta - 5 - *cis*,13 - *trans* - dienoic acid.

By employing dimethylamine, diethylamine or dipropylamine in place of ammonium hydroxide in the above process, the corresponding salts of 8*R* - 11*β*,12*β* - difluoromethylene - 9*α*,15*α* - dihydroxy - 12*α* - prosta - 5 - *cis*,13 - *trans* - dienoic acid are obtained.

In a similar manner, the ammonia, dimethylamine, diethylamine and dipropylamine salts of the other antimers, 8*R* and 8*S*-11*α*,12*α*- or 11*β*,12*β*-difluoromethylene free prostenoic or prostadienoic acids or the racemic mixtures thereof, obtained in the previous Examples, are produced.

WHAT WE CLAIM IS:—

1. A compound selected from antimers and racemic mixtures of the formula:



wherein R represents a straight chain alkyl of three to nine carbon atoms;
R² represents an oxo group or the grouping



and



R³ represents hydrogen, methyl or ethyl;

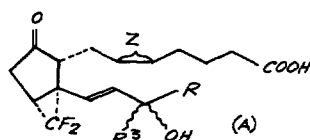
Z represents a single bond or a *cis* double bond; and

the wavy line () represents the *α* or *β* configuration or mixtures thereof, provided that

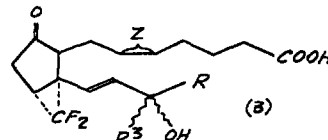
(a) when the side chain attached at the 12-position is *β*, the difluoromethylene group at the 11,12-positions is 11*α*,12*α* only; and when the side chain attached at the 12 position is *α*, the difluoromethylene group at the 11,12-positions is 11*β*,12*β* only; and

(b) when R³ is *α* the hydroxyl group, attached to the same carbon as R³ is *β*; and when R³ is *β* the hydroxyl group, attached to the same carbon as R³, is *α*; and the pharmaceutically acceptable salts or methyl esters thereof.

2. The antimeric compounds as claimed in Claim 1 of the formulas:

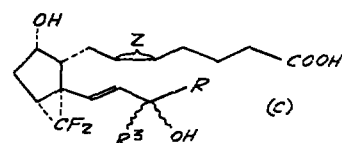


and

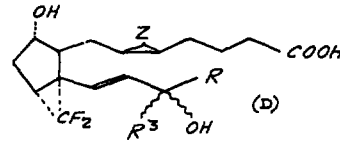


where R, R³, Z and the wavy lines are as defined in claim 1.

3. The antimeric compounds as claimed in Claim 1 of the formulas:

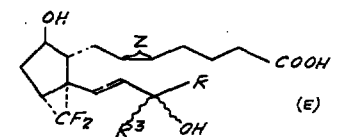


and

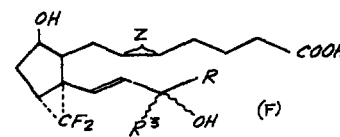


where R, R³, Z and the wavy lines are as defined in claim 1.

4. The antimeric compounds as claimed in Claim 1 of the formulas:



and



where R, R³, Z and the wavy lines are as defined in claim 1.

EXAMPLE 32.

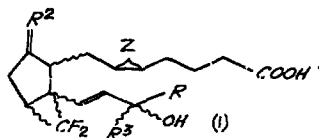
To a solution of 100 mg. of 8*R* - 11*β*,12*β* - difluoromethylene - 9*α*,15*α* - dihydroxy - 12*α* - prosta - 5 - *cis*,13 - *trans* - dienoic acid in 10 ml. of methanol is added a mixture of 3 ml. of concentrated ammonium hydroxide solution and 5 ml. of methanol. The resulting mixture is stirred for two hours at room temperature and then evaporated to dryness under vacuo, to yield the ammonium salt of 8*R* - 11*β*,12*β* - difluoromethylene - 9*α*,15*α* - dihydroxy - 12*α* - prosta - 5 - *cis*,13 - *trans* - dienoic acid.

By employing dimethylamine, diethylamine or dipropylamine in place of ammonium hydroxide in the above process, the corresponding salts of 8*R* - 11*β*,12*β* - difluoromethylene - 9*α*,15*α* - dihydroxy - 12*α* - prosta - 5 - *cis*,13 - *trans* - dienoic acid are obtained.

In a similar manner, the ammonia, dimethylamine, diethylamine and dipropylamine salts of the other antimers, 8*R* and 8*S*-11*α*,12*α*- or 11*β*,12*β*-difluoromethylene free prostenoic or prostadienoic acids or the racemic mixtures thereof, obtained in the previous Examples, are produced.

WHAT WE CLAIM IS:—

1. A compound selected from antimers and racemic mixtures of the formula:



wherein R represents a straight chain alkyl of three to nine carbon atoms;
R³ represents an oxo group or the grouping



and



R³ represents hydrogen, methyl or ethyl;

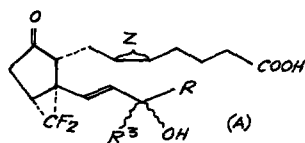
Z represents a single bond or a *cis* double bond; and

the wavy line () represents the *α* or *β* configuration or mixtures thereof, provided that

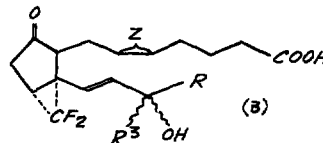
(a) when the side chain attached at the 12-position is *β*, the difluoromethylene group at the 11,12-positions is 11*α*,12*α* only; and when the side chain attached at the 12 position is *α*, the difluoromethylene group at the 11,12-positions is 11*β*,12*β* only; and

(b) when R³ is *α* the hydroxyl group, attached to the same carbon as R³ is *β*; and when R³ is *β* the hydroxyl group, attached to the same carbon as R³, is *α*; and the pharmaceutically acceptable salts or methyl esters thereof.

2. The antimeric compounds as claimed in Claim 1 of the formulas:

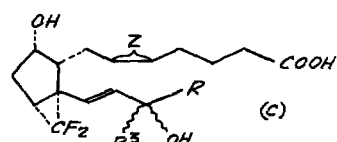


and

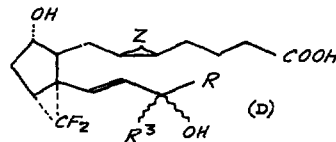


where R, R³, Z and the wavy lines are as defined in claim 1.

3. The antimeric compounds as claimed in Claim 1 of the formulas:

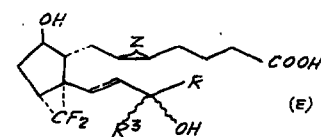


and

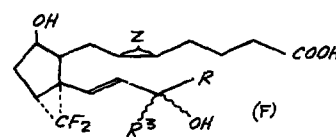


where R, R³, Z and the wavy lines are as defined in claim 1.

4. The antimeric compounds as claimed in Claim 1 of the formulas:



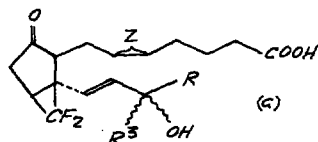
and



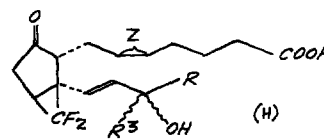
where R, R³, Z and the wavy lines are as defined in claim 1.



5. The antimeric compounds as claimed in Claim 1 of the formulas:



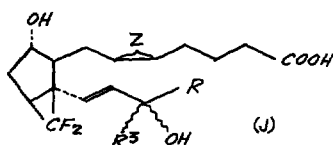
and



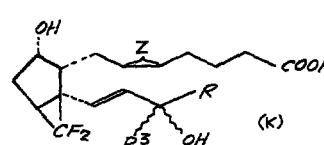
where R, R³, Z and the wavy lines are as defined in claim 1.

6. The antimeric compounds as claimed in Claim 1 of the formulas:

5



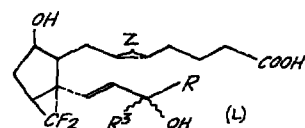
and



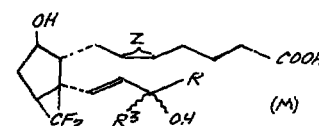
5

where R, R³, Z and the wavy lines are as defined in claim 1.

7. The antimeric compounds as claimed in Claim 1 of the formulas:



and

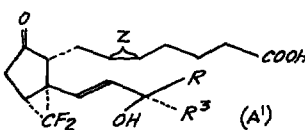


10

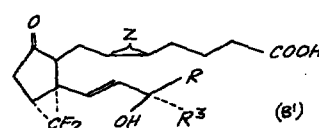
where R, R³, Z and the wavy lines are as defined in claim 1.

8. The antimeric compounds as claimed in Claim 2 of the formulas:

10

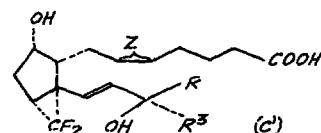


and

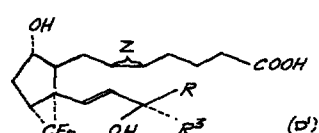


where R, R³ and Z are as defined in claim 1.

9. The antimeric compounds as claimed in Claim 3 of the formulas:



and

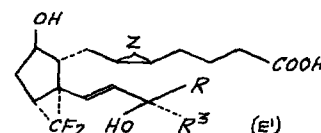


15

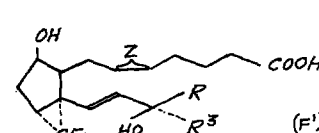
where R, R³ and Z are as defined in claim 1.

15

10. The antimeric compounds as claimed in Claim 4 of the formulas:



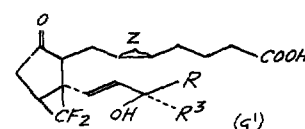
and



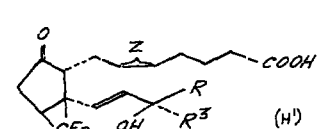
where R, R³ and Z are as defined in claim 1.

11. The antimeric compounds as claimed in Claim 5 of the formulas:

20



and

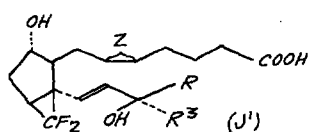


20

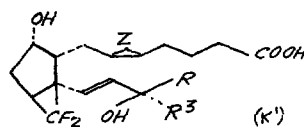
where R, R³ and Z are as defined in claim 1.



12. The antimeric compounds as claimed in Claim 6 of the formulas:

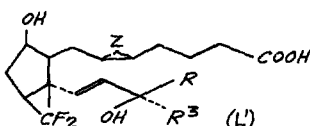


and

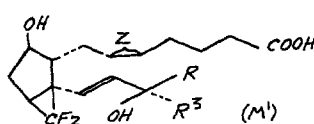


where R, R³ and Z are as defined in claim 1.

13. The antimeric compounds as claimed in Claim 7 of the formulas:

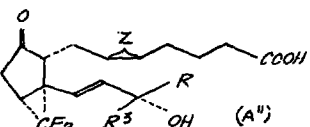


and

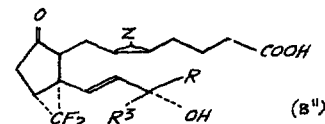


where R, R³ and Z are as defined in claim 1.

14. The antimeric compounds as claimed in Claim 2 of the formulas:

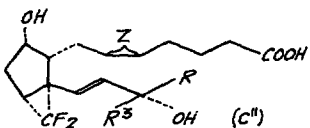


and

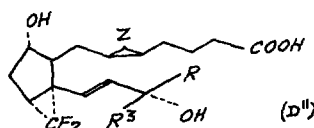


where R³, R and Z are as defined in claim 1.

15. The antimeric compounds as claimed in Claim 3 of the formulas:

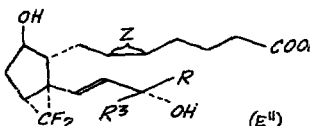


and

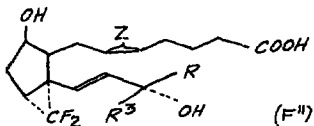


where R, R³ and Z are as defined in claim 1.

16. The antimeric compounds as claimed in Claim 4 of the formulas:

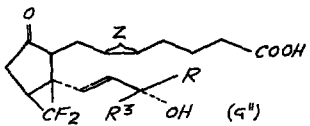


and

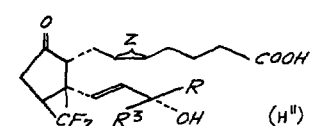


where R, R³ and Z are as defined in claim 1.

17. The antimeric compounds as claimed in Claim 5 of the formulas:

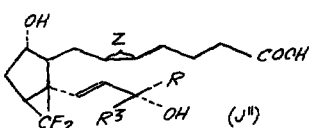


and

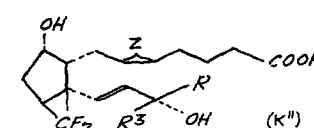


where R, R³ and Z are as defined in claim 1.

18. The antimeric compounds as claimed in Claim 6 of the formulas:



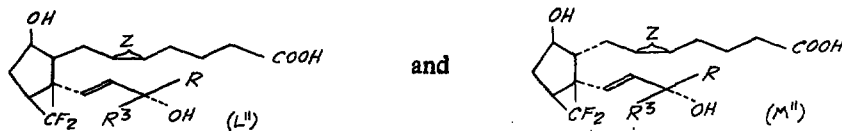
and



wherein R, R³ and Z are as defined in claim 1.



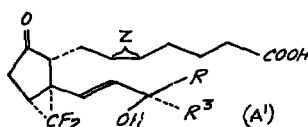
19. The antimeric compounds as claimed in Claim 7 of the formulas:



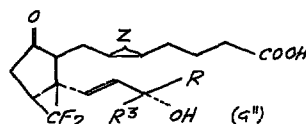
wherein R, R³ and Z are as defined in claim 1.

20. The racemic mixture of the compounds of Formula (A') of Claim 8,

5



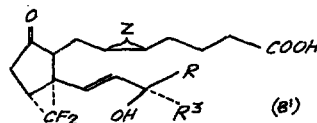
and its antimers, the compounds of the formula:



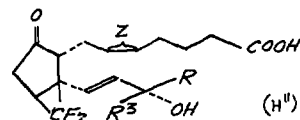
where R, R³ and Z are as defined in claim 1.

21. The racemic mixture of the compounds of Formula (B') of Claim 8,

10



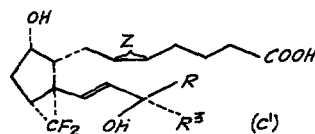
and its antimers, the compounds of the formula:



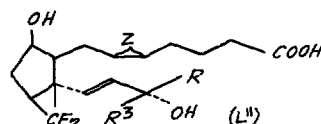
where R, R³ and Z are as defined in claim 1.

22. The racemic mixture of the compounds of Formula (C') of Claim 9,

15



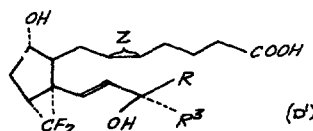
and its antimers, the compounds of the formula:



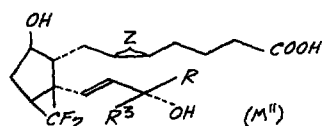
where R, R³ and Z are as defined in claim 1.

23. The racemic mixture of the compound of Formula (D') of Claim 9,

20

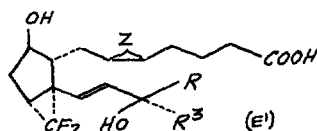


and its antimers, the compounds of the formula:

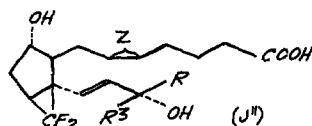


where R, R³ and Z are as defined in claim 1.

24. The racemic mixture of the compounds of Formula (E') of Claim 10,

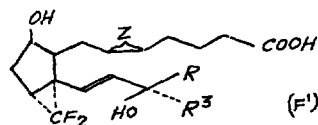


and its antimers, the compounds of the formula:

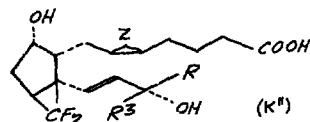


where R, R³ and Z are as defined in claim 1.

25. The racemic mixture of the compounds of Formula (F') of Claim 10,

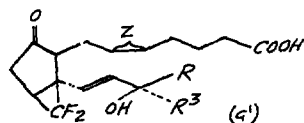


and its antimers, the compounds of the formula:

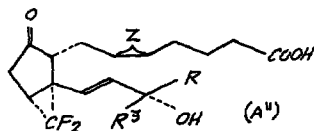


where R, R³ and Z are as defined in claim 1.

26. The racemic mixture of the compounds of Formula (G') of Claim 11,

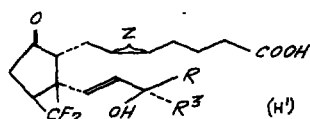


and its antimers, the compounds of the formula:

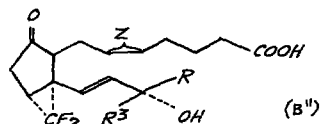


where R, R³ and Z are as defined in claim 1.

27. The racemic mixture of the compounds of Formula (H') of Claim 11,

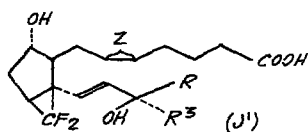


and its antimers, the compounds of the formula:

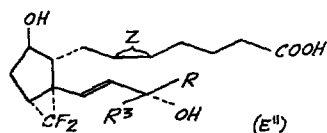


where R, R³ and Z are as defined in claim 1.

28. The racemic mixture of the compounds of Formula (J') of Claim 12,

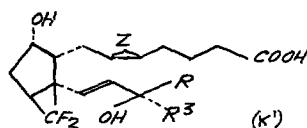


and its antimers, the compounds of the formula:

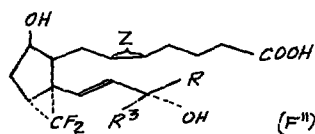


where R, R³ and Z are as defined in claim 1.

29. The racemic mixture of the compounds of Formula (K') of Claim 12,

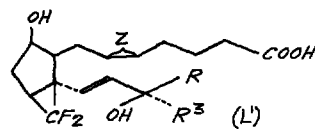


and its antimers, the compounds of the formula:

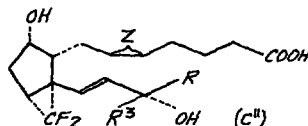


where R, R³ and Z are as defined in claim 1.

30. The racemic mixture of the compounds of Formula (L') of Claim 13,

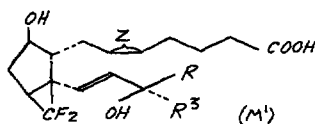


and its antimers, the compounds of the formula:

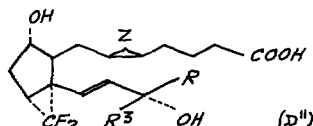


where R, R³ and Z are as defined in claim 1.

31. The racemic mixture of the compounds of Formula (M') of Claim 13,



and its antimers, the compounds of the formula:



where R, R³ and Z are as defined in claim 1.

32. 8R - 9 - Oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprosta - 5 - *cis*,13-*trans* - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.

33. 8R - 9 - Oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprost - 13 - *trans*-enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

34. 8R - 9 - Oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid and the methyl ester of pharmaceutically acceptable salts thereof.

35. 8R - 9 - Oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxyprost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

36. 8R - 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - ethylprosta - 5 - *cis*,13 - *trans* - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.

37. 8R - 9 - Oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - ethylprost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

38. 8S - 9 - Oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.

39. 8S - 9 - Oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 8 β - prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

40. 8S - 9 - Oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.

41. 8S - 9 - Oxo - 11 α ,12 α - difluoromethylene - 15 β - methyl - 15 α - hydroxy - 8 β - prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

42. 8S - 9 - Oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - ethyl - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.

43. 8S - 9 - Oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 20 - ethyl - 8 β - prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

44. 8S - 11 α ,12 α - Difluoromethylene - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13-*trans* - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.

45. 8S - 11 α ,12 α - Difluoromethylene - 9 α ,15 α - dihydroxyprost - 13 - *trans*-enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

46. 8S - 11 α ,12 α - Difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.

47. 8S - 11 α ,12 α - Difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxyprost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

48. 8S - 11 α ,12 α - Difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethylprosta - 5 - *cis*,13 - *trans* - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.

49. 8S - 11 α ,12 α - Difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethylprost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

50. 8R - 11 α ,12 α - Difluoromethylene - 9 α ,15 α - dihydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.

51. 8R - 11 α ,12 α - Difluoromethylene - 9 α ,15 α - dihydroxy - 8 β - prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

52. 8R - 11 α ,12 α - Difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.

53. 8R - 11 α ,12 α - Difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy - 8 β -



	prost - 13 - <i>trans</i> - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.	
5	54. 8 <i>R</i> - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 8 β -prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.	5
	55. 8 <i>R</i> - 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 8 β -prost - 13 - <i>trans</i> - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.	
10	56. 8 <i>S</i> - 11 α ,12 α - Difluoromethylene - 9 β ,15 α - dihydroxyprosta - 5 - <i>cis</i> ,13- <i>trans</i> - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.	10
	57. 8 <i>S</i> - 11 α ,12 α - Difluoromethylene - 9 β ,15 α - dihydroxyprost - 13 - <i>trans</i> -enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.	
15	58. 8 <i>S</i> - 11 α ,12 α - Difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxyprosta-5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.	15
	59. 8 <i>S</i> - 11 α ,12 α - Difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxyprost-13 - <i>trans</i> - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.	
20	60. 8 <i>S</i> - 11 α ,12 α - Difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethylprosta - 5- <i>cis</i> ,13 - <i>trans</i> - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.	20
	61. 8 <i>S</i> - 11 α ,12 α - Difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethylprost - 13- <i>trans</i> - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.	
25	62. 8 <i>R</i> - 11 α ,12 α - Difluoromethylene - 9 β ,15 α - dihydroxy - 8 β - prosta - 5- <i>cis</i> ,13 - <i>trans</i> - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.	25
	63. 8 <i>R</i> - 11 α ,12 α - Difluoromethylene - 9 β ,15 α - dihydroxy - 8 β - prost - 13- <i>trans</i> - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.	
30	64. 8 <i>R</i> - 11 α ,12 α - Difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxy - 8 β -prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.	30
	65. 8 <i>R</i> - 11 α ,12 α - Difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxy - 8 β -prost - 13 - <i>trans</i> - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.	
35	66. 8 <i>R</i> - 11 α ,12 α - Difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethyl - 8 β -prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.	35
	67. 8 <i>R</i> - 11 α ,12 α - Difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethyl - 8 β -prost - 13 - <i>trans</i> - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.	
40	68. 8 <i>S</i> - 9 - Oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 8 β ,12 α - prosta-5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.	40
	69. 8 <i>S</i> - 9 - Oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 8 β ,12 α - prost-13 - <i>trans</i> - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.	
45	70. 8 <i>S</i> - 9 - Oxo - 11 β ,12 β - difluoromethylene - 15 β - methyl - 15 α - hydroxy-8 β ,12 α - prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.	45
	71. 8 <i>S</i> - 9 - Oxo - 11 β ,12 β - difluoromethylene - 15 β - methyl - 15 α - hydroxy-8 β ,12 α - prost - 13 - <i>trans</i> - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.	
50	72. 8 <i>S</i> - 9 - Oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - ethyl-8 β ,12 α - prosta - 5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.	50
	73. 8 <i>S</i> - 9 - Oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - ethyl-8 β ,12 α - prost - 13 - <i>trans</i> - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.	
55	74. 8 <i>R</i> - 9 - Oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 12 α - prosta-5 - <i>cis</i> ,13 - <i>trans</i> - dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.	55
	75. 8 <i>R</i> - 9 - Oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 12 α - prost-13 - <i>trans</i> - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.	
60	76. 8 <i>R</i> - 9 - Oxo - 11 β ,12 β - difluoromethylene - 15 β - methyl - 15 α - hydroxy-	60
65		65

- 12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 5 77. 8R - 9 - Oxo - 11 β ,12 β - difluoromethylene - 15 β - methyl - 15 α - hydroxy-12 α - prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof. 5
78. 8R - 9 - Oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - ethyl - 12 α -prosta - 5 - *cis*,13 - *trans* - dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 10 79. 8R - 9 - Oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 20 - ethyl - 12 α -prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof. 10
80. 8R - 11 β ,12 β - Difluoromethylene - 9 α ,15 α - dihydroxy - 8 β ,12 α - prosta - 5-*cis*,13 - *trans* - dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 15 81. 8R - 11 β ,12 β - Difluoromethylene - 9 α ,15 α - dihydroxy - 8 β ,12 α - prost - 13-*trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof. 15
82. 8R - 11 β ,12 β - Difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy-8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 20 83. 8R - 11 β ,12 β - Difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy-8 β ,12 α - prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof. 20
84. 8R - 11 β ,12 β - Difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 8 β ,12 α -prost - 5 - *cis*,13 - *trans* - dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 25 85. 8R - 11 β ,12 β - Difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 8 β ,12 α -prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof. 25
86. 8S - 11 β ,12 β - Difluoromethylene - 9 α ,15 α - dihydroxy - 12 α - prosta - 5-*cis*,13 - *trans* - dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 30 87. 8S - 11 β ,12 β - Difluoromethylene - 9 α ,15 α - dihydroxy - 12 α - prost - 13-*trans* - enoic acid and the methylester or pharmaceutically acceptable salts thereof. 30
88. 8S - 11 β ,12 β - Difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy - 12 α -prosta - 5 - *cis*,13 - *trans* - dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 35 89. 8S - 11 β ,12 β - Difluoromethylene - 15 β - methyl - 9 α ,15 α - dihydroxy - 12 α -prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof. 35
90. 8S - 11 β ,12 β - Difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 12 α -prosta - 5 - *cis*,13 - *trans* - dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 40 91. 8S - 11 β ,12 β - Difluoromethylene - 9 α ,15 α - dihydroxy - 20 - ethyl - 12 α -prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof. 40
92. 8R - 11 β ,12 β - Difluoromethylene - 9 β ,15 α - dihydroxy - 8 β ,12 α - prosta-5 - *cis*,13 - *trans* - dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 45 93. 8R - 11 β ,12 β - Difluoromethylene - 9 β ,15 α - dihydroxy - 8 β ,12 α - prost - 13-*trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof. 45
94. 8R - 11 β ,12 β - Difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxy-8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 50 95. 8R - 11 β ,12 β - Difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxy-8 β ,12 α - prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof. 50
96. 8R - 11 β ,12 β - Difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethyl - 8 β ,12 α -prosta - 5 - *cis*,13 - *trans* - dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 55 97. 8R - 11 β ,12 β - Difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethyl - 8 β ,12 α -prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof. 55
98. 8S - 11 β ,12 β - Difluoromethylene - 9 β ,15 α - dihydroxy - 12 α - prosta - 5-*cis*,13 - *trans* - dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 60 65 65





- 5 99. 8S - 11 β ,12 β - Difluoromethylene - 9 β ,15 α - dihydroxy - 12 α - prost - 13-
trans - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 5 100. 8S - 11 β ,12 β - Difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxy-
12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid and the methyl ester or pharmaceu-
tically acceptable salts thereof.
- 10 101. 8S - 11 β ,12 β - Difluoromethylene - 15 β - methyl - 9 β ,15 α - dihydroxy-
12 α - prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically
acceptable salts thereof.
- 10 102. 8S - 11 β ,12 β - Difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethyl - 12 α -
prosta - 5 - *cis*,13 - *trans* - dienolic acid and the methyl ester or pharmaceutically
acceptable salts thereof.
- 15 103. 8S - 11 β ,12 β - Difluoromethylene - 9 β ,15 α - dihydroxy - 20 - ethyl - 12 α -
prost - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable
salts thereof.
- 15 104. The racemic mixture of 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β -
hydroxyprosta - 5 - *cis*,13 - *trans* - dienolic acid and its mirror image, 9 - oxo-
11 β ,12 β - difluoromethylene - 15 α - hydroxy - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans*-
dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 20 105. The racemic mixture of 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β -
hydroxyprost - 13 - *trans* - enoic acid and its mirror image, 9 - oxo - 11 β ,12 β -
difluoromethylene - 15 α - hydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid and the
methyl ester or pharmaceutically acceptable salts thereof.
- 25 106. The racemic mixture of 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β -
hydroxy - 8 β - prosta - 5 - *cis* - 13 - *trans* - dienolic acid and its mirror image, 9-
oxo - 11 β ,12 β - difluoromethylene - 15 α - hydroxy - 12 α - prosta - 5 - *cis*,13 - *trans*-
dienolic acid and the methyl ester or pharmaceutically acceptable salts thereof.
- 25 107. The racemic mixture of 9 - oxo - 11 α ,12 α - difluoromethylene - 15 β -
hydroxy - 8 β - prost - 13 - *trans* - enoic acid and its mirror image, 9 - oxo-
11 β ,12 β - difluoromethylene - 15 α - hydroxy - 12 α - prost - 13 - *trans* - enoic acid and
the methyl ester or pharmaceutically acceptable salts thereof.
- 30 108. The racemic mixture of 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy-
prosta - 5 - *cis*,13 - *trans* - dienolic acid and its mirror image, 11 β ,12 β - difluoro-
methylene - 9 β ,15 α - dihydroxy - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid
and the methyl ester or pharmaceutically acceptable salts thereof.
- 35 109. The racemic mixture of 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy-
prost - 13 - *trans* - enoic acid and its mirror image, 11 β ,12 β - difluoromethylene-
9 β ,15 α - dihydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid and the methyl ester
or pharmaceutically acceptable salts thereof.
- 40 110. The racemic mixture of 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy-
8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid and its mirror image, 11 β ,12 β - di-
fluoromethylene - 9 β ,15 α - dihydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid
and the methyl ester or pharmaceutically acceptable salts thereof.
- 45 111. The racemic mixture of 11 α ,12 α - difluoromethylene - 9 α ,15 β - dihydroxy-
8 β - prest - 13 - *trans* - enoic acid and its mirror image, 11 β ,12 β - difluoromethyl-
ene - 9 β ,15 α - dihydroxy - 12 α - prost - 13 - *trans* - enoic acid and the methyl ester
or pharmaceutically acceptable salts thereof.
- 50 112. The racemic mixture of 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxy-
prosta - 5 - *cis*,13 - *trans* - dienolic acid and its mirror image, 11 β ,12 β - difluoro-
methylene - 9 α ,15 α - dihydroxy - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid
and the methyl ester or pharmaceutically acceptable salts thereof.
- 50 113. The racemic mixture of 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxy-
prost - 13 - *trans* - enoic acid and its mirror image, 11 β ,12 β - difluoromethylene-
9 α ,15 α - dihydroxy - 8 β ,12 α - prost - 13 - *trans* - enoic acid and the methyl ester
or pharmaceutically acceptable salts thereof.
- 55 114. The racemic mixture of 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxy-
8 β - prosta - 5 - *cis*,13 - *trans* - dienolic acid and its mirror image, 11 β ,12 β - di-
fluoromethylene - 9 α ,15 α - dihydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid
and the methyl ester or pharmaceutically acceptable salts thereof.
- 60 115. The racemic mixture of 11 α ,12 α - difluoromethylene - 9 β ,15 β - dihydroxy-
8 β - prost - 13 - *trans* - enoic acid and its mirror image, 11 β ,12 β - difluoromethyl-
ene - 9 α ,15 α - dihydroxy - 12 α - prost - 13 - *trans* - enoic acid and the methyl ester
or pharmaceutically acceptable salts thereof.
- 65 116. The racemic mixture of 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β -
hydroxy - 8 β ,12 α - prosta - 5 - *cis*,13 - *trans* - dienolic acid and its mirror image,
9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprosta - 5 - *cis*,13 - *trans*-

dienoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

117. The racemic mixture of 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 8 β ,12 α - prosta - 13 - *trans* - enoic acid and its mirror image, 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxyprosta - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

118. The racemic mixture of 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienioic acid and its mirror image, 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienioic acid and the methyl ester or pharmaceutically acceptable salts thereof.

119. The racemic mixture of 9 - oxo - 11 β ,12 β - difluoromethylene - 15 β - hydroxy - 12 α - prosta - 13 - *trans* - enoic acid and its mirror image, 9 - oxo - 11 α ,12 α - difluoromethylene - 15 α - hydroxy - 8 β - prosta - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

120. The racemic mixture of 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 8 β ,12 α - prosta - 5 - *cis* - 13 - *trans* - dienioic acid and its mirror image, 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienioic acid and the methyl ester or pharmaceutically acceptable salts thereof.

121. The racemic mixture of 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 8 β ,12 α - prosta - 13 - *trans* - enoic acid and its mirror image, 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxyprosta - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

122. The racemic mixture of 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 12 α - prosta - 5 - *cis*,13 - *trans* - dienioic acid and its mirror image, 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienioic acid and the methyl ester or pharmaceutically acceptable salts thereof.

123. The racemic mixture of 11 β ,12 β - difluoromethylene - 9 α ,15 β - dihydroxy - 12 α - prosta - 13 - *trans* - enoic acid and its mirror image, 11 α ,12 α - difluoromethylene - 9 β ,15 α - dihydroxy - 8 β - prosta - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

124. The racemic mixture of 11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 8 β ,12 α - prosta - 5 - *cis* - 13 - *trans* - dienioic acid and its mirror image, 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprosta - 5 - *cis*,13 - *trans* - dienioic acid and the methyl ester or pharmaceutically acceptable salts thereof.

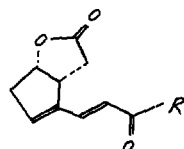
125. The racemic mixture of 11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 8 β ,12 α - prosta - 13 - *trans* - enoic acid and its mirror image, 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxyprosta - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

126. The racemic mixture of 11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 12 α - prosta - 5 - *cis* - 13 - *trans* - dienioic acid and its mirror image, 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β - prosta - 5 - *cis*,13 - *trans* - dienioic acid and the methyl ester or pharmaceutically acceptable salts thereof.

127. The racemic mixture of 11 β ,12 β - difluoromethylene - 9 β ,15 β - dihydroxy - 12 α - prosta - 13 - *trans* - enoic acid and its mirror image, 11 α ,12 α - difluoromethylene - 9 α ,15 α - dihydroxy - 8 β - prosta - 13 - *trans* - enoic acid and the methyl ester or pharmaceutically acceptable salts thereof.

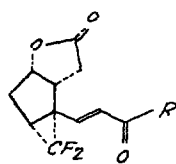
128. A process for producing a compound of claim 1 which comprises:

a) treating a 1'*R*-antimeric or racemic compound of the formula:

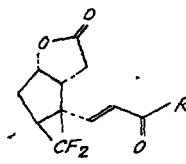


wherein R is as defined above;

with a difluorocarbene generating source in an organic solvent to yield a mixture of 1'*S*-antimeric or racemic compounds of the formulas:



and

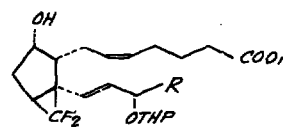
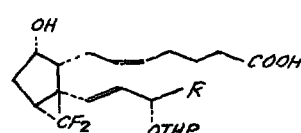
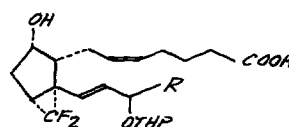
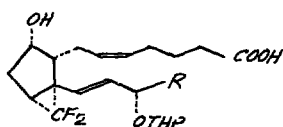


wherein R is as defined above;



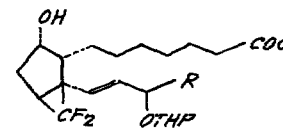
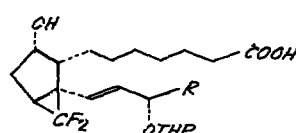
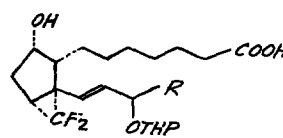
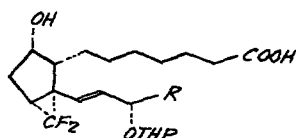


- b) separating the 1'S-11 α ,12 α - and 1'S-11 β ,12 β -difluoromethylene compounds of step a) and selectively reducing the 3''-oxo group in the separated 1'S-11 α ,12 α - and 1'S-11 β ,12 β -difluoromethylene compounds, thereby yielding mixtures of the 1'S-11 α ,12 α -difluoromethylene-3'' α - and 3'' β -hydroxy and 1'S-11 β ,12 β -difluoromethylene-3'' α - and 3'' β -hydroxy derivatives;
- c) separating the respective 3'' α - and 3'' β -hydroxy compounds obtained in step b) and reacting the separated compounds with dihydropyran in the presence of a catalytic amount of an acid thereby yielding the corresponding tetrahydropyranyloxy derivatives;
- d) reducing the lactone oxo group in the 1'S-antimeric or racemic etherified compounds of step c) with 1.1 to 3 molar equivalents of diisobutylaluminum hydride in an inert organic solvent, thereby yielding the corresponding lactol;
- e) condensing a lactol of step d) with the Wittig reagent derived from 5-triphenylphosphoniopentanoic acid bromide and sodium methylsulfinylmethylide in dimethyl sulfoxide, thereby yielding the corresponding 8S-antimeric or racemic compounds represented by the formulas:



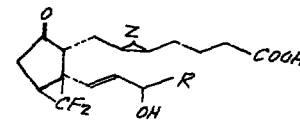
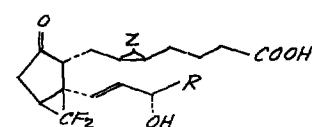
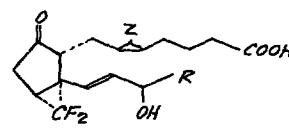
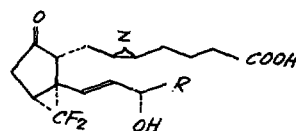
wherein R is as defined above and OTHP is 2-tetrahydropyranyloxy.

- f) selectively reducing the *cis* double bond at C-5 in the compounds of step e) thereby yielding the corresponding 8S-antimeric or racemic compounds of the formulas:



wherein R and OTHP are as defined above;

- g) oxidizing the hydroxyl group in the compounds of steps e) and f) thereby yielding the corresponding 8R-antimeric or racemic 9-oxo derivatives;
- h) hydrolyzing the tetrahydropyranyloxy group in the compounds of step g) under mild acidic conditions thereby yielding the corresponding 8R-antimeric or racemic compounds of the formulas:

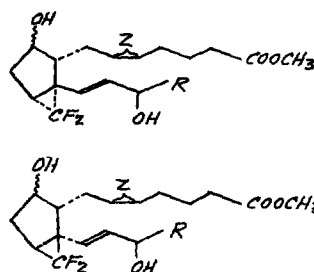
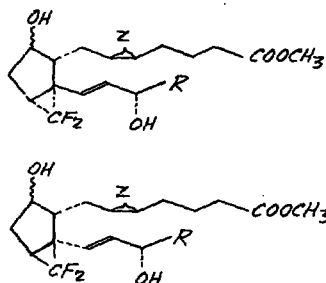


wherein R and Z are as defined above;

- i) converting the compounds of step h) into the corresponding methyl esters;

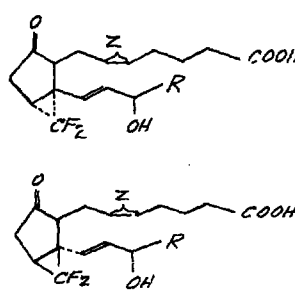
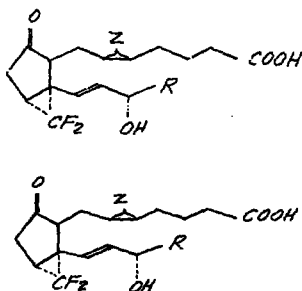


- j) reducing the oxo group in the methyl ester compounds of step i) with sodium borohydride in a lower aliphatic alcohol thereby yielding the corresponding 8*S*-antimeric or racemic 9 α and 9 β hydroxylated compounds of the formulas:



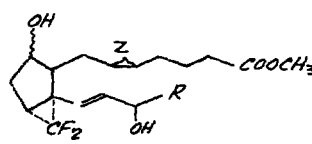
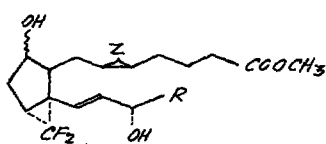
wherein R, Z and the wavy lines ({}) are as defined above, and, if desired, hydrolysing the methyl ester group thereby yielding the corresponding antimeric or racemic free acid;

- k) treating the 8*R*-antimeric or racemic compounds of step h) with an alcoholic solution of an alkali metal alkoxide to invert the configuration of the carboxylic acid chain followed by treatment with a strong mineral acid thereby yielding the corresponding 8*S*-antimeric or racemic compounds of the formulas:



wherein R and Z are as defined above;

- l) converting the compounds of step k) into the corresponding methyl esters;
m) reducing the oxo group in the methyl ester compounds of step l) with sodium borohydride in a lower aliphatic alcohol thereby yielding the corresponding 8*R*-antimeric or racemic 9 α and 9 β -hydroxylated compounds of the formulas:



wherein R, Z and the wavy lines ({}) are as defined above and, if desired, hydrolysing the methyl ester group thereby yielding the corresponding antimeric or racemic free acid;

- n) separating the individual 9 α and 9 β -hydroxy isomers in the antimeric or racemic compounds of steps j) and m);
o) selectively oxidizing the 15-hydroxy group in the individual 9 α ,15 α -, 9 α ,15 β -, 9 β ,15 α - and 9 β ,15 β -dihydroxylated compounds of step n) with an excess of manganese dioxide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in an inert organic solvent, thereby yielding the corresponding antimeric or racemic 15-oxo derivatives;

- p) treating the 15-oxo compounds of step n) with an alkylmagnesium halide or an alkyllithium in which the alkyl group is methyl or ethyl, thereby yielding the corresponding 15 β -hydroxy-15 α -alkyl compounds and separating the individual antimeric or racemic 15 α -hydroxy-15 β -alkyl and 15 β -hydroxy-15 α -alkyl compounds;
- 5 q) oxidizing the 9-hydroxy group in the compounds of step p) thereby yielding the corresponding antimeric or racemic 9-oxo derivatives; 5
- r) hydrolyzing the methyl ester group in the compounds of steps p) and q) thereby yielding the corresponding antimeric or racemic free acids and
- 10 s) converting the antimeric or racemic free acids of step h), j), k), m) and r) into the pharmaceutically acceptable salts thereof. 10
129. The process of Claim 128 wherein the difluorocarbene generating source in step a) is sodium chlorodifluoroacetate and wherein said treatment is conducted under anhydrous conditions in an inert organic solvent.
- 15 130. The process of Claim 129 wherein said treatment is conducted at temperatures in the range of from 80°C to 120°C for from five minutes to one hour. 15
131. The process of Claim 129 wherein said inert solvent is 1,2-dimethoxyethane, diethylene glycol dimethyl ether, or triethylene glycol dimethyl ether.
132. The process of Claim 128 wherein said compounds are antimeric compounds.
133. The process of Claim 128 wherein said compounds are racemic mixtures.
- 20 134. A compound according to claim 1, substantially as exemplified herein. 20
135. A process according to claim 128, substantially as described herein.
136. A compound according to claim 1 when prepared by a process according to any one of claims 128 to 133 and 135.
- 25 137. A pharmaceutical composition, comprising a compound of any one of claims 1 to 127, 134 and 136 with a suitable excipient. 25

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

