

PATENT SPECIFICATION

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 633 634 638 644 652 655 658 659 65X 662 668 672 67X
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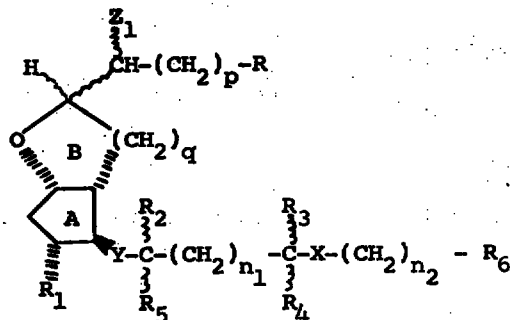
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(54) 5,9- OR 6,9-EPOXYPROSTAGLANDINS

(71) We, FARMITALIA CARLO ERBA S.p.A., formerly known as CARLO ERBA S.p.A., an Italian Body Corporate of Via Carlo Imbonati 24, 20159 Milan, Italy, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

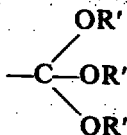
The present invention relates to 5,9- or 6,9-epoxy prostaglandins and to pharmaceutical and veterinary compositions containing them.

Subject to certain exclusions mentioned below, the compounds of the invention are of formula (I)

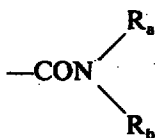


wherein

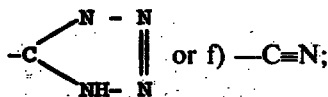
R is (a) a free or esterified carboxy group; (b)



wherein each of the R' groups, which may be the same or different, is C₁-C₆ alkyl or phenyl; (c) -CH₂OH; (d)



wherein R_a and R_b are independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkanoyl or phenyl; (e)



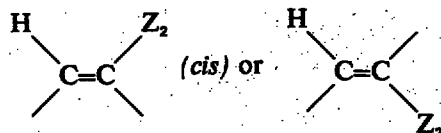
Z₁ is hydrogen or halogen;

p is zero or an integer of 1 to 7;

q is 1 or 2;

R₁ is hydrogen, hydroxy, C₁-C₆ alkoxy, aryl - C₁-C₆ - alkoxy or acyloxy;

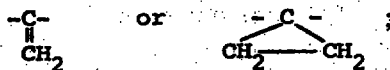
Y is -CH₂CH₂-, -C≡C-,



(trans), wherein Z₂ is hydrogen or halogen;

one of R₂ and R₃ is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or aryl, and the other is hydroxy, C₁-C₆ or aryl - C₁-C₆ - alkoxy or R₂ and R₃, taken together, form an oxo group;

Each of R₃ and R₄, which may be the same or different, is hydrogen, C₁-C₆ alkyl or fluorine or R₃ and R₄, taken together with the carbon atom to which they are linked, form the group



each of n₁ and n₂, which are the same or different, is zero or an integer of 1 to 6;

X is -O-, -S-, a single bond or -CH₂-;

R₆ is

(a') hydrogen;

(b') C₁-C₄ alkyl;

(c') a C₃-C₆ cycloaliphatic group, unsubstituted or substituted by one or more substituents selected from C₁-C₆ alkyl and C₁-C₆ alkoxy;

(d') aryl, unsubstituted or substituted by one or more substituents selected from halogen, halo - C₁-C₆ - alkyl, C₁-C₆ alkyl and C₁-C₆ alkoxy; or

(e') a saturated or unsaturated heterocyclic ring, unsubstituted or substituted by one or more substituents selected from halogen, halo - C₁-C₆ - alkyl, C₁-C₆ alkyl and C₁-C₆ alkoxy.

and the pharmaceutically or veterinarily acceptable salts thereof. The optical antipodes, i.e. the enantiomers, the racemic mixtures of the optical antipodes, the

geometric isomers and their mixtures and the mixtures of the diastereoisomers of the compounds of formula (I) are included in the scope of the present invention.

In the formulae of this specification the broken line (---) indicates that a substituent bound to the cyclopentane ring is in the α -configuration, i.e. below the plane of the ring, a substituent bound to the 2-oxa-bicyclic system in the *endo*-configuration and a substituent bound to a chain is in the *S*-configuration; the heavy solid line (—) indicates that a substituent bound to the cyclopentane ring is in the β -configuration, i.e. above the plane of the ring, a substituent bound to the 2-oxa-bicyclic system in the *exo*-configuration and a substituent bound to a chain is in the *R*-configuration; the wavy line attachment

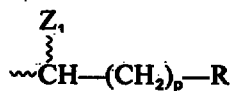
(ξ)

indicates that a substituent does not possess a definite stereochemical identity i.e. that a substituent bound to the cyclopentane ring may be both in the α - and in the β -configuration, a substituent bound to the 2-oxa-bicyclic system may be both in the *endo*- or in the *exo*-configuration and a substituent bound to a chain may be both in the *S*- and in the *R*-configuration.

In the compounds of the above formula (I) the heterocyclic ring B is *cis*-fused with the cyclopentane ring A and the two bonds indicated by the dotted lines (...) are both in the α -configuration with respect to the ring A.

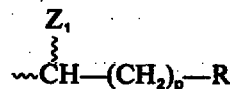
The side chain β -linked to the cyclopentane ring A is in *trans* configuration with respect to the α -fused heterocyclic ring B and consequently it is an *exo* substituent with respect to the 2-oxa-bicyclic system.

The carbon atom of the heterocyclic ring B bearing the side chain

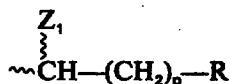


bears also an hydrogen atom.

When the side chain

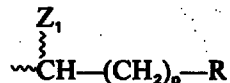


is in the *endo*-configuration with respect to the 2-oxa-bicyclic system, then said hydrogen atom is an *exo*-substituent and its absolute configuration is reported as β while when the chain

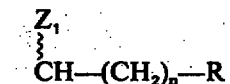


is in the *exo*-configuration, then said hydrogen atom is an *endo*-substituent and its absolute configuration is reported as α .

The compounds of the invention wherein the chain



is in the *exo*-configuration, the hydrogen atom linked to the same carbon atoms of the ring B having necessarily the α -absolute configuration, are reported as 6 α H-6,9 α -epoxy (formula I; q=1) and 5 α H-5,9 α -epoxy (formula I; q=2) prostanoic acid derivatives (prostaglandin numbering), while the compounds wherein the chain



is in the *endo*-configuration, the hydrogen atom linked to the same carbon atom of the ring B having necessarily the β -absolute configuration, are reported as 6 β H-

6,9 α -epoxy (formula I; q=1) and 5 β H - 5,9 α -epoxy (formula I; q=2) prostanoic acid derivatives (prostaglandin numbering). Alternatively the 6 α H - 6,9 α -epoxy prostanoic acid derivatives are reported as (2' - oxabicyclo[3.3.0]oct - 3' - *exo* - yl) - alkanolic acid derivatives, the 5 α H - 5,9 α - epoxyprostanoic acid derivatives as (2' - oxabicyclo[4.3.0]non - 3' - *exo* - yl) - alkanolic acid derivatives, the 6 β H - 6,9 α - epoxyprostanoic acid derivatives as (2' - oxabicyclo[3.3.0]oct - 3' - *endo* - yl) - alkanolic acid derivatives and the 5 β H - 5,9 α - epoxyprostanoic acid derivative as (2' - oxabicyclo[4.3.0]non - 3' - *endo* - yl) - alkanolic acid derivatives. The 6 α H - 6,9 α - oxide and 5 α H - 5,9 α - epoxyprostanoic acid derivatives have a higher chromatographic mobility (i.e. a higher R_f) and a less positive rotatory power ($[\alpha]_D$) than the corresponding 6 β H - 6,9 α - epoxy and 5 β H - 5,9 α - epoxy derivatives.

All the above notations refer to the natural compounds; the d,l - compounds are mixtures containing equimolar amounts of *nat*-compounds which possess the above-reported absolute stereochemistry and of *ent*-compounds which are mirror-like images of the former; in the *ent*-compounds the stereochemical configuration is the opposite at all the asymmetric centers with respect to the configuration of the natural compounds and the prefix *ent* indicates just this.

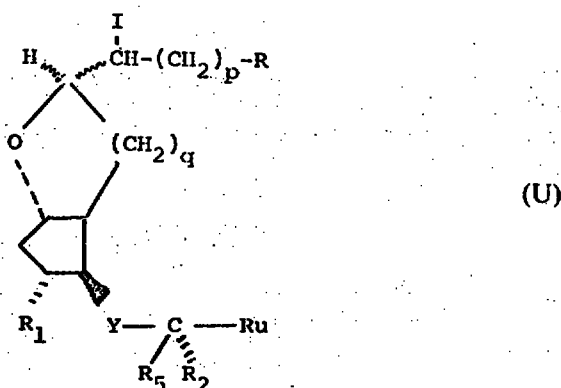
Some compounds falling within formula (I) as defined above are claimed in British Patents Nos. 1,554,044, 1,554,048 and 1,554,050 (all in the name of the Upjohn Company). Broadly, No. 1,554,044 claims generically some 4 - iodo - 5,9 α - and 5-iodo- 6,9 α - epoxyprostaglandins, No. 1,554,048 claims generically some 6,9 α - epoxyprostaglandins and some individual 6,9 α - epoxyprostaglandins. No. 1,554,050 claims some generically some 5,9 α - epoxyprostaglandins and some individual such prostaglandins. After taking into consideration these patents, the following compounds within formula (I) have been excluded from the scope of the present invention:

9 - deoxy - 6 ξ ,9 α - epoxy - PGF₁, otherwise termed 6,9 α - epoxy - 11 α ,15(S) - dihydroxyprost - *trans* - 13 - enoic acid, its salts and its methyl ester;
9 - deoxy - 6 ξ , 9 α - epoxy - 16,16 - dimethyl - PGF₁ and its salts;
9 - deoxy - 6 ξ , 9 α - epoxy - 17 - phenyl - 18,19,20 - trinor - PGF₁ methyl ester;

9 - deoxy - 6 ξ ,9 α - epoxy - 15(S) - 15 - methyl - PGF₁, otherwise termed 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 15 - methylprost - *trans* - 13 - enoic acid, and its salts;

9 - deoxy - 6 ξ ,9 α - epoxy - 2 - nor - PGF₁ methyl ester;

9 - deoxy - 6 ξ ,9 α - epoxy - 2,3,4 - trinor - PGF₁ methyl and ethyl esters; and certain 5 - iodo - epoxyprostaglandins. The excluded 5 - iodo - epoxyprostaglandins are those which are within the following definition (from claim 8 of British Patent 1,554,044) with reference to formula "U" but outside the definitions given in claims 6, 11, 13, 14 and 19 of the present specification. The iodo - epoxyprostaglandins of British Patent 1,554,044 referred to are of formula



wherein

R is (1) —CH₂OH, (2) —CH₂NR₁R₂ wherein R₁ and R₂ are each hydrogen or alkyl of one to 4 carbon atoms, (3) 5 - tetrazolyl, or (4) COOR₃ wherein R₃ is hydrogen; alkyl of one to 12 carbon atoms; cycloalkyl of 3 to 10 carbon atoms; aralkyl of 7 to 12 carbon atoms; phenyl; phenyl substituted one, 2 or 3 times by chlorine atoms or alkyl radicals of one to 4 carbon atoms;

p is zero or an integer of from 1 to 6;

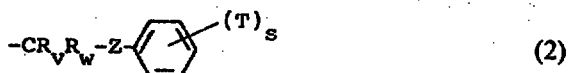
q is 1 or 2;

R₁ is hydroxy or hydrogen;

Y is *trans* —CH=CH—, *cis* —CH=CH—, —C≡C— or —CH₂—CH₂—;

R₅ and R₂ are both hydrogen or R₅ and R₂ together are oxo or one of R₅ and R₂ is hydrogen or alkyl of 1 to 4 carbon atoms and the other is hydroxy;

and R_u is (1) —CR_v—R_w—C₉H₂₀—CH₃, wherein R_v and R_w are each hydrogen, alkyl of one to 4 carbon atoms or fluorine with the proviso that —CR_vR_w— is not —CFAlkyl— and C₉H₂₀ is alkylene of one to 9 carbon atoms with one to 5 carbon atoms in the chain between —CR_vR_w— and the terminal methyl,



wherein Z is an oxygen atom, a valence bond or alkyl

wherein Z is an oxygen atom, a valence bond or alkylene of one to 9 carbon atoms with one to 6 carbon atoms in the chain between —CR_vR_w and the benzene ring, R_v and R_w are as defined above with the proviso that neither R_v nor R_w is fluorine when Z is an oxygen atom T is hydroxy, alkyl or alkoxy of one to 4 carbon atoms, fluorine, chlorine or trifluoromethyl and s is zero, one, 2 or 3 provided that when s is 2 or 3 not more than two T's are other than alkyl and the T's are the same or different, or (3) —CH₂—*cis*—CH=CH—C₂H₅;

The alkyl, alkenyl, alkynyl, alkoxy, and alkanoyloxy groups are branched or straight chain groups.

Preferably R is a free, salified or esterified carboxy group.

An aryl-C₁—C₆-alkoxy group is preferably benzyloxy.

An aryl group is preferably phenyl, α-naphthyl or β-naphthyl.

A halo-C₁—C₆-alkyl group is preferably trihalo-C₁—C₆-alkyl, most preferably trifluoromethyl.

A C₁—C₆ alkyl group is preferably methyl, ethyl or propyl.

A C₁—C₆ alkoxy group is preferably methoxy, ethoxy or propoxy.

A C₂—C₆ alkenyl radical is preferably vinyl.

A C₂—C₆ alkynyl radical is preferably ethynyl.

When R is an esterified carboxy group it is preferably a —COOR_e group wherein R_e is a C₁—C₁₂ alkyl radical, most preferably methyl, ethyl, propyl and heptyl, or a C₂—C₁₂ alkenyl radical, preferably allyl.

Preferably Z₁ is hydrogen.

When Z is halogen, it is preferably chlorine or bromine, or, slightly less preferably iodine.

The symbol p is preferably an integer of 1 to 3.

When R₁ is acyloxy, it is preferably C₂—C₁₂ alkanoyloxy (most preferably C₂—C₆ alkanoyloxy, e.g. acetoxy or propionyloxy) or benzoyloxy.

When Z₂ is halogen, it is preferably chlorine, bromine or iodine.

Preferably R₃ and R₄ are independently hydrogen, C₁—C₆ alkyl or fluorine.

n₁ is preferably zero or an integer of 1 to 3; n₂ is preferably an integer of 1 to 3.

When R₆ is a C₃—C₉ cycloaliphatic radical, it is preferably a C₃—C₉ cycloalkyl radical e.g. cyclopentyl, cyclohexyl and cycloheptyl or a C₃—C₉ cycloalkenyl radical, e.g. cyclopentenyl, cyclohexenyl and cycloheptenyl.

When R₆ is a heterocyclic ring, it may be either a heteromonocyclic ring or a heterobicyclic ring and contains at least one heteroatom selected from N, S and O. Examples of preferred heteromonocyclic radicals are tetrahydrofuryl, tetrahydropyranylyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl. Examples of preferred heterobicyclic radicals are 2-oxabicyclo[3.3.0]octyl, 2-oxabicyclo[3.4.0]nonyl, 2-thiabicyclo[3.3.0]octyl, 2-thiabicyclo[3.4.0]nonyl and their unsaturated analogs.

Pharmaceutically or veterinarily acceptable salts of the compounds of formula (I) are e.g. those with pharmaceutically and veterinarily acceptable bases. Pharmaceutically and veterinarily acceptable bases are either inorganic bases such as, for example, alkali metal hydroxides and alkaline-earth metal hydroxides as well as aluminium and zinc hydroxides or organic bases e.g. organic amines such as, for example, methylamine, dimethylamine, trimethylamine, ethylamine, dibutylamine,

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N - methylhexylamine, decylamine, dodecylamine, allylamine, cyclopentylamine, cyclohexylamine, benzylamine, dibenzylamine, α - phenylethylamine, β - phenylethylamine, ethylenediamine, diethylenetriamine, morpholine, piperidine, pyrrolidine, piperazine, as well as the alkyl derivatives of the latter four bases, mono-, di- and tri-ethanolamine, ethyl-diethanolamine, N-methylethanolamine, 2 - amino - 1 - butanol, 2 - amino - 2 - methyl - 1 - propanol, N - phenylethanolamine, galactamine, N - methylglucamine, N - methylglucosamine, ephedrine, procaine, dehydroabietylamine, lysine, arginine and other α or β amino acids. Preferred salts of the invention are those of the compounds of formula (I) wherein R is $-\text{COOR}_a$ wherein R_a is a pharmaceutically or veterinarily acceptable cation deriving from one of the above mentioned bases.

Particularly preferred compounds of the invention are $6\beta H$ - $6,9\alpha$ - epoxy and $5\beta H$ - $5,9\alpha$ - epoxy compounds of formula (I) wherein R is a free carboxy group and R_a is C_1-C_4 alkyl, C_5-C_7 cycloalkyl or optionally substituted phenyl.

The prefixes nor, dinor, trinor, tetranor- etc., are used to identify the compounds of formula (I) wherein the side chain bound to the cyclopentane ring A is one, two, three, four, etc. carbon atoms shorter than the analogous chain in the natural prostaglandins.

Specific examples of preferred compounds of the invention are the following:

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxyprost - 13 - ynoic acid;
 $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxyprostanoic acid;
 $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - methylprost - 13 - ynoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15$ - (S) - dihydroxy - 15 - methylprostanoic acid;
 $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15,20 - dimethylprost - *trans* - 13 - enoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15,20 - dimethylprost - 13 - ynoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15,20 - dimethylprostanoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 20 - methylprost - *trans* - 13 - enoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 20 - methylprost - 13 - ynoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 20 - methylprostanoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxyprost - *trans* - 13 - enoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxyprost - 13 - ynoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxyprostanoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxy - 15 - methyl - prost - *trans* - 13 - enoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxy - 15 - methylprost - 13 - ynoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxy - 15 - methylprostanoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxy - 15,20 - dimethylprost - *trans* - 13 - enoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxy - 15,20 - dimethylprost - 13 - ynoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxy - 15,20 - dimethylprostanoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxy - 20 - methylprost - *trans* - 13 - enoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxy - 20 - methylprostanoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 14 - bromoprost - *trans* - 13 - enoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 14 - chloroprost - *trans* - 13 - enoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 14 - bromo - 15 - methylprost - *trans* - 13 - enoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 14 - bromo - 20 - methylprost - *trans* - 13 - enoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 14 - bromo - 15,20 - dimethylprost - *trans* - 13 - enoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

$6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16(S,R) - fluoro - 17 -

cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid and the single 16(*S*)- and 16(*R*) - fluoro isomer;

6 β H - 6,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

6 β H - 6,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - 13 - ynoic acid;

6 β H - 6,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid and the *p* - fluoro-, *p* - chloro-, *p* - methoxy-, *o* - fluoro-, *m* - fluoro-, *m* - trifluoromethyl-, and *m* - chloro-phenoxy analogs thereof;

6 β H - 6,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 17 - (2' - tetrahydrofuryl) - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

6 β H - 6,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 17 - (2' - tetrahydrothienyl) - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

6 β H - 6,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 20 - ethylprost - *trans* - 13 - enoic acid;

6 β H - 6,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 16 - benzyloxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid and the *p* - fluoro-, *p* - chloro-, *p* - methoxy-, *o* - fluoro-, *m* - fluoro-, *m* - trifluoromethyl-, and *m* - chloro - benzyloxy analogs thereof;

5 β H - 5,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - prost - *trans* - 13 - enoic acid;

5 β H - 5,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - prostanoic acid;

5 β H - 5,9 α - epoxy - 11 α ,15(*S*) - dihydroxyprost - 13 - ynoic acid;

5 β H - 5,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 16(*S*) - methylprost - *trans* - 13 - enoic acid;

5 β H - 5,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 16(*R*) - methylprost - *trans* - 13 - enoic acid;

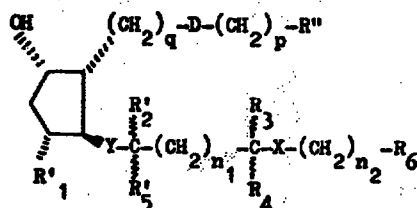
6 β H - 6,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 16(*S*) - methylprost - *trans* - 13 - enoic acid;

6 β H - 6,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 16(*R*) - methylprost - *trans* - 13 - enoic acid;

6 β H - 6,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 16(*S*) - methylprost - 13 - ynoic acid;

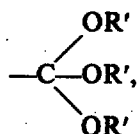
6 β H - 6,9 α - epoxy - 11 α ,15(*S*) - dihydroxy - 16(*R*) - methylprost - 13 - ynoic acid, as well as the 5 - bromo, the 5 - iodo, the 5 - chloro analogs of all the 6 β H - 6,9 α - epoxy derivatives above listed, as well as the 4 - bromo, the 4 - iodo, the 4 - chloro analogs of all the 5 β H - 5,9 α - epoxy derivatives above listed, as well as the 15(*R*) - epimers, the 15 - oxo - derivatives and the 6 α H- or 5 α H - diastereoisomers of all the compounds mentioned above.

The compounds of the invention can be prepared by a process comprising:
a) halocyclizing a compound of formula (II)



wherein

p, q, Y, n₁, n₂, R₃, R₄, X and R₆ are as defined above, D is *cis*- or *trans* -CH=CH-, R'' is (a'') a free or esterified carboxy group; (b'') a group



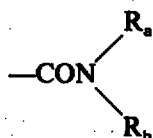
wherein each of the R' groups is as defined above; (C'') the group -CH₂-R₇, wherein R₇ is hydroxy or a known protecting group bound to the -CH₂- group by an ethereal oxygen atom; (d'')

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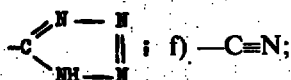
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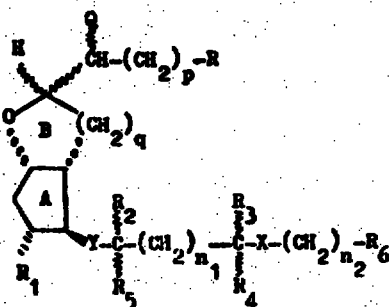


wherein R_a and R_b are as defined above; (c'') a radical of formula



R'_1 is hydrogen, hydroxy, C_1-C_6 alkoxy, aryl- C_1-C_6 -alkoxy, acyloxy or a known protecting group bound to the ring by an ethereal oxygen atom; one of R'_2 and R'_3 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl and the other is hydroxy, C_1-C_6 alkoxy, aryl- C_1-C_6 -alkoxy or a known protecting group bound to the chain by an ethereal oxygen atom, or R'_2 and R'_3 taken together, form an oxo group, so obtaining, after the removal of the known protecting groups, if present, a compound of formula (I) wherein Z_1 is halogen and, if necessary, dehalogenating a 1- and/or 11- and/or 15- ether group and/or, if desired, Z_1 is hydrogen; or

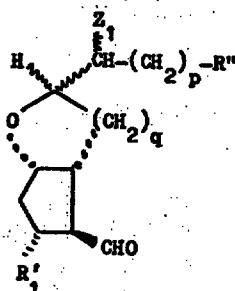
b) reducing a compound of formula (III)



(III)

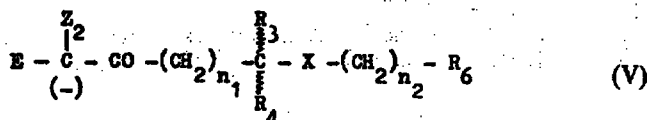
Q is halogen or a group $\sim Hg^{(++)}Z^{(-)}$, wherein $Z^{(-)}$ is $OH^{(-)}$ or the anion of an acid, R , p , q , R_1 , Y , R_2 , R_3 , R_4 , n_1 , n_2 , X and R_6 are as defined above, so obtaining a compound of formula (I) wherein Z_1 is hydrogen; or

c) reacting a compound of formula (IV)

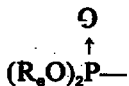


(IV)

wherein R'' , p , Z_1 , q , and R'_1 are as defined above, with a compound of formula (V)



wherein E is a group $(C_6H_5)_3P^{(+)}$ or a group



wherein each of the R_5 groups, which are the same or different, is alkyl or aryl and

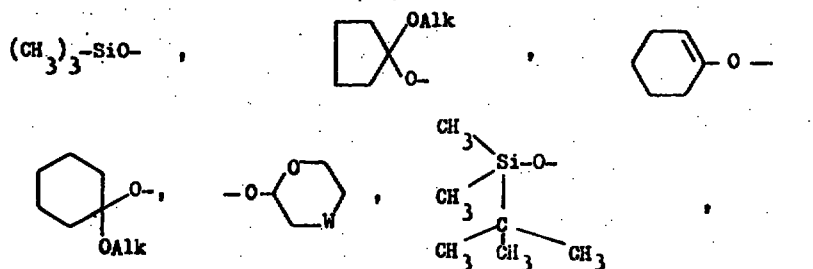
Z_2 , R_3 , R_4 , n_1 , n_2 , X and R_6 are as defined above, so obtaining, after the removal of the known protecting groups, if present, a compound of formula (I) wherein R_2 and R_5 , taken together, form an oxo group and Y is $-\text{CH}=\text{CZ}_2-$ wherein Z_2 is as defined above and, if desired, reducing a compound of formula (I) wherein R_2 and R_5 , taken together, form an oxo group and Y is $-\text{CH}=\text{CZ}_2-$ wherein Z_2 is as defined above, to give a compound of formula (I) wherein one of R_2 and R_5 is hydrogen and the other is hydroxy and Y is $-\text{CH}=\text{CZ}_2-$, wherein Z_2 is as defined above, or, if desired, converting a compound of formula (I) wherein R_2 and R_5 , taken together, form an oxo group and Y is $-\text{CH}=\text{CZ}_2-$ wherein Z_2 is as defined above, into a compound of formula (I) wherein one of R_2 and R_5 is hydroxy and the other is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl and, if desired, etherifying a compound of formula (I) wherein one of R_2 and R_5 is hydroxy and the other is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl and Y is $-\text{CH}=\text{CZ}_2-$ wherein Z_2 is as defined above, to give a compound of formula (I) wherein one of R_2 and R_5 is C_1-C_6 alkoxy or aryl- C_1-C_6 -alkoxy and the other is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl and Y is $-\text{CH}=\text{CZ}_2-$ wherein Z_2 is as defined above, and/or, if desired, hydrogenating a compound of formula (I) wherein Y is $-\text{CH}=\text{CZ}_2-$ wherein Z_2 is hydrogen, to give a compound of formula (I) wherein Y is $-\text{CH}_2\text{CH}_2-$ or, if desired, dehydrohalogenating a compound of formula (I) wherein Z_1 is hydrogen and Y is $-\text{CH}=\text{CZ}_2-$ wherein Z_2 is halogen, to give a compound of formula (I) wherein Y is $-\text{C}\equiv\text{C}-$ and Z_1 is hydrogen or, if desired, hydrogenating a compound of formula (I) wherein R_2 and R_5 , taken together, form an oxo group and Y is $-\text{CH}=\text{CZ}_2-$ wherein Z_2 is hydrogen, to give a compound of formula (I) wherein R_2 and R_5 , taken together, form an oxo group and Y is $-\text{CH}_2\text{CH}_2-$ or, if desired, dehydrohalogenating a compound of formula (I) wherein Z_1 is hydrogen, R_2 and R_5 , taken together, form an oxo group, and Y is $-\text{CH}=\text{CZ}_2-$ wherein Z_2 is halogen, to give a compound of formula (I) wherein Z_1 is hydrogen, R_2 and R_5 , taken together, form an oxo group and Y is $-\text{C}\equiv\text{C}-$ and, if desired, reducing a compound of formula (I) wherein R_2 and R_5 , taken together, form an oxo group, to give a compound of formula (I) wherein one of R_2 and R_5 is hydrogen and the other is hydroxy, or, if desired, converting a compound of formula (I) wherein R_2 and R_5 , taken together, form an oxo group, into a compound of formula (I) wherein one of R_2 and R_5 is hydroxy and the other is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl and, if desired, etherifying a compound of formula (I) wherein one of R_2 and R_5 is hydroxy and the other is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl, to give a compound of formula (I) wherein one of R_2 and R_5 is C_1-C_6 alkoxy or ar- C_1-C_6 -alkoxy and the other is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl; and/or, if desired, converting a compound of formula (I) into another compound of formula (I) and/or, if desired, salifying a compound of formula (I) and/or, if desired, obtaining a free compound of formula (I) from a salt thereof and/or, if desired, separating a mixture of isomers into the single isomers.

In the optional steps of the above processes when only one or a few substituents are specifically mentioned for a compound, it is understood that the other substituents have all the meanings previously indicated for formula (I). Conversion steps which are not more particularly defined can be carried out by methods *per se* known in prostaglandin chemistry.

The known protecting groups, i.e. ether groups, are convertible to hydroxy groups under mild reaction conditions, e.g. acid hydrolysis.

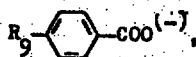
Examples are 1 - alkoxycycloalkoxy, 2 - oxacycloalkoxy groups (optionally containing a further ring oxygen atom), enol ethers and silyl ethers.

The preferred groups are

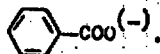


wherein W is $-\text{O}-$ or $-\text{CH}_2-$ and Alk is a C_{1-4} alkyl group.

When in the compound of formula (III) Q represents a group $\sim\text{Hg}^{(+)}\text{Z}^{(-)}$, wherein $\text{Z}^{(-)}$ is the anion of an acid, $\text{Z}^{(-)}$ is preferably $\text{Cl}^{(-)}$, $\text{Br}^{(-)}$, $\text{I}^{(-)}$, $\text{R}_8\text{—COO}^{(-)}$, wherein R_8 is an optionally halo-substituted $\text{C}_1\text{—C}_{12}$ alkyl group (preferably $\text{C}_1\text{—C}_6$ alkyl or trifluoromethyl) or



wherein R_9 is hydrogen, $\text{C}_1\text{—C}_6$ alkyl, halogen, e.g. bromine, or trifluoromethyl. Preferably $\text{Z}^{(-)}$ is $\text{Cl}^{(-)}$, $\text{Br}^{(-)}$, $\text{CH}_3\text{COO}^{(-)}$, $\text{CF}_3\text{COO}^{(-)}$ or



The halocyclization of a compound of formula (II) may be performed by reaction with either a stoichiometric amount or a small excess of a halogenating agent in an inert solvent, in either the presence or in absence of a base.

Preferred halogenating agents are, e.g., iodine, bromine, chlorine, dioxane dibromide, pyridine, perbromide, pyridinium hydrobromide perbromide KI_3 , pyrrolidone - 2 - hydrotribromide, an N - haloamide such as N - chlorosuccinimide, N - bromosuccinimide or N - iodosuccinimide, a cupric halide such as CuCl_2 or CuBr_2 , a mixed halide such as ICl or IBr , as well as a mixture of an alkali metal chloride with an alkali metal chlorate, a mixture of an alkali metal bromide with an alkali metal bromate or a mixture of an alkali metal iodide with an alkali metal iodate.

Suitable solvents are, for example, halogenated hydrocarbons such as CHCl_3 , CCl_4 , CH_2Cl_2 ; aliphatic hydrocarbons such as n-hexane, n-heptane; cycloaliphatic hydrocarbons such as cyclohexane; aromatic hydrocarbons such as benzene, toluene, pyridine, cyclic or linear ethers, e.g. dioxane, tetrahydrofuran, diethyl ether, 1,2 - dimethoxyethane; as well as mixtures thereof.

Preferred solvents are halogenated hydrocarbons, e.g. CH_2Cl_2 , since both the compound of formula (II) and the halogenating agent are usually soluble in these solvents.

A stoichiometric amount of a base is necessary when a hydrohalic acid is formed during the halocyclization reaction.

Such a base may be an inorganic base, e.g., an alkali metal oxide or an alkaline-earth metal oxide, carbonate or bicarbonate, e.g., CaO , CaCO_3 and K_2CO_3 , NaHCO_3 , Na_2CO_3 ; an organic base such as a tertiary amine, e.g., triethylamine; or an aromatic base, e.g. pyridine or an alkyl-substituted pyridine; or an anionic ion-exchange resin.

The halocyclization reaction is preferably carried out at temperatures ranging from -70°C to 100°C ; preferably the reaction is performed at room temperature.

The reaction times normally range from few minutes to several days, but usually do not exceed two hours and often a few minutes are sufficient to complete the reaction.

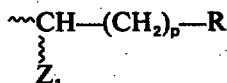
When other unsaturated bonds are present in the compound of formula (II) besides the double bond contained in the substituent D, those unsaturated bonds may add halogen during the halocyclization reaction. The added halogen may be easily removed to reobtain the original unsaturations, by treating the reaction product with an alkali metal iodide or alkaline-earth metal iodide in a suitable solvent such as, e.g., acetone at temperatures ranging from room temperature to reflux temperature but preferably at room temperature. Reaction time may range from 2—3 hours to 2—3 days.

The removal of the known protecting groups bound to the ring or to the chain by an ethereal oxygen atom can be performed, whenever required, under conditions of mild acid hydrolysis, for example with a mono- or poly-carboxylic acid such as formic, acetic, oxalic, citric and tartaric acid, and in a solvent, which may be water, acetone, tetrahydrofuran, 1,2 - dimethoxyethane or a lower aliphatic alcohol, or with a sulphonic acid, e.g., p - toluenesulphonic acid in a solvent such as a lower aliphatic alcohol, dry methanol or dry ethanol, for example, or with a polystyrene-sulphonic resin.

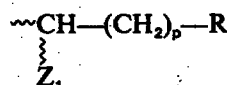
For example, 0.1 to 0.25 N poly-carboxylic acid (e.g., oxalic or citric acid) is used in the presence of a convenient low-boiling co-solvent which is miscible with water and which can be easily removed *in vacuo* at the end of the reaction.

All the cyclization reactions described in this specification such as e.g. the hereabove described halocyclization of a compound of formula (II) to give a

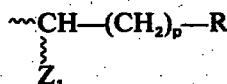
compound of formula (I) wherein Z_1 is halogen, the herebelow described cyclization of a compound of formula (II) to give a compound of formula (III) wherein Q is $\sim\text{Hg}^{(II)}\text{Z}^{(-)}$ and the below described cyclization of a compound of formula (VI) are identical reactions as to their mechanism and the number of the isomers contained in the reaction mixture is the same for all the above cyclizations. Thus for example the above halocyclization reaction of a compound of formula (II) can give to a mixture of four components, i.e. compounds of formula (I) wherein Z_1 is halogen, consisting in two diastereoisomers having the side chain



in the *exo*-configuration and differing from each other for the *S* or *R* configuration of the halogen Z_1 and two diastereoisomers having the side chain



in the *endo*-configuration and differing each other for the *S* or *R* configuration of the halogen Z_1 . While the chromatographic mobility (R_f) of the *endo*-isomer is clearly different from the chromatographic mobility of the *exo*-isomer, the difference of R_f between two *endo*- (or *exo*-) isomers differing from each other only for the *S* or *R* configuration of the Z_1 substituent, is very small. The two diastereoisomers wherein the chain



is in the *exo*-configuration may be separated from the two diastereoisomers wherein said chain is in the *endo*-configuration by fractional crystallization e.g. from diethyl ether, but preferably by thin layer preparative chromatography, by column chromatography or by high speed liquid chromatography. The separation by thin layer preparative chromatography or by column chromatography is preferably carried out on a support of silica gel or magnesium silicate with methylene chloride, diethylether, isopropylether, ethyl acetate, benzene, methyl acetate, cyclohexane or their mixtures as elution solvents.

The reductive dehalogenation of a compound of formula (I) wherein Z_1 is halogen to give a compound of formula (I) wherein Z_1 is hydrogen, can be performed by reduction, e.g. with chromous acetate or a hydride such as tri(*n* - butyl)tin hydride, or by catalytic hydrogenation.

When it is desired to obtain a compound of formula (I) wherein Y is $-\text{C}\equiv\text{C}-$ or $-\text{CH}=\text{CZ}_2-$ wherein Z_2 is as defined above, the dehalogenation is carried out only by reduction, e.g., with tri(*n* - butyl)tin hydride or chromous acetate. When it is desired to obtain a compound of formula (I) wherein R_2 and R_3 taken together form an oxo group, by the dehalogenation of the compound of formula (I) wherein Z_1 is halogen, the reaction time should not exceed half an hour.

When the reductive dehalogenation is carried out with chromous acetate, the following procedure can be used. The chromous acetate reagent is added, with stirring, to a cooled solution of the compound of formula (I) wherein Z_1 is halogen, in a mixture of ethanol and aqueous sodium or potassium hydroxide under an atmosphere of nitrogen. The reaction mixture is then stirred one to three days at room temperature, according to the method described in J. Am. Chem. Soc. 76, 5499 (1954).

When the dehalogenation is carried out with tri(*n* - butyl)tin hydride, about 1.2 equivalents of the reducing agent are preferably used for each equivalent of the compound of formula (I) wherein Z_1 is halogen. Suitable solvents for the reaction are aromatic hydrocarbons such as benzene or toluene and the temperatures preferably are between room temperature and 70°C. Preferably the reaction is carried out at about 55°C in benzene and lasts about 12 hours.

The catalytic hydrogenation of a compound of formula (I) wherein Z_1 is halogen to give a compound of formula (I) wherein Z_1 is hydrogen and Y is $-\text{CH}_2\text{CH}_2-$ may be performed either at room temperature or by heating this compound, e.g., at

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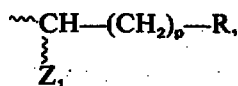
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30—60°C either at atmospheric pressure or under pressure, e.g., at 1.1-2 atm, in a solvent such as e.g., a lower aliphatic alcohol, tetrahydrofuran, dioxane, benzene, toluene in the presence of a catalyst such as palladium or platinum on charcoal or CaCO₃ and optionally in the presence of an ammonium salt, e.g., ammonium acetate or propionate.

The reductive dehalogenation converts a compound of formula (I) wherein Z₁ is halogen into a compound of formula (I) wherein Z₁ is hydrogen and therefore during the dehalogenation the carbon atom carrying the Z₁ substituent loses its asymmetry. The number of the possible diastereoisomers consequently contained in the dehalogenation reaction mixture is lower than the number of diastereoisomers contained in the halocyclization reaction mixture.

When the reductive dehalogenation is carried out directly on the mixture of four diastereoisomers obtained from the halocyclization process, a mixture of only two diastereoisomers of formula (I) wherein Z₁ is hydrogen is obtained, differing each other in the *exo*- or *endo*-configuration of the side chain $\sim\text{CH}_2-(\text{CH}_2)_p-\text{R}$.

When the reductive dehalogenation is carried out on a single pair of diastereoisomers of formula (I) having the side chain

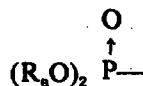


wherein Z₁ is halogen, in the *exo*- or in the *endo*-configuration and differing from each other for the *S* or *R* configuration of Z₁, then only one isomer of formula (I) wherein Z₁ is hydrogen is obtained wherein the side chain $\sim\text{CH}_2-(\text{CH}_2)_p-\text{R}$ is in the *exo*- or in the *endo*-configuration. If a mixture of the above diastereoisomers is obtained the single diastereoisomers may be easily separated by fractional crystallization or by column chromatography as described above for the separation of the diastereoisomers wherein Z₁ is halogen.

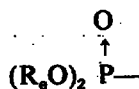
The reduction of the compound of formula (III) may be carried out by treatment with mixed hydrides such as alkali metal, e.g., sodium, potassium or lithium, borohydrides, with alkaline earth metal, e.g., calcium or magnesium, borohydrides in an inert solvent, preferably a solvent miscible with water, such as tetrahydrofuran, 1,2 - dimethoxyethane or lower aliphatic alcohols, e.g. methanol or ethanol; or with tri(n - butyl)tin hydride in benzene or toluene, preferably benzene; or also by treatment with hydrazine hydrate in a lower aliphatic alcohol, e.g., methanol or ethanol as solvent, at temperatures varying from room temperature to the reflux temperature of the solvent used. When it is desired to obtain compounds of formula (I) wherein Z₁ is hydrogen and R₂ and R₃ taken together form an oxo group, the reduction of the compound of formula (III) is preferably carried out with tri(n - butyl)tin hydride for a short reaction time, preferably a time varying from about 5 minutes to about half an hour.

During the above reduction of a compound of formula (III) the carbon atom carrying the Q substituent loses its asymmetry and therefore the number of the possible diastereoisomers contained in the reaction mixture at the end of the reduction process is half the number of the diastereoisomers contained in the starting material, analogously to what above reported with regards to dehalogenation of a compound of formula (I) wherein Z₁ is halogen.

When in the compound of formula (V) E is



wherein R_a is aryl, it is preferably phenyl; when R_a is alkyl, it is preferably C₁—C₆ alkyl. The reaction between an aldehyde of formula (IV) and a compound of formula (V) is carried out with an excess of the compound of formula (V), e.g., at least 1.01 molar equivalent of the compound of formula (V) for each mole of the compound of formula (IV). Any inert solvent can be used, such as linear and cyclic ethers, e.g. diethyl ether, tetrahydrofuran, dioxane, 1,2 - dimethoxyethane, aliphatic or aromatic hydrocarbons, e.g., n-heptane, n-hexane, benzene, toluene or halogenated hydrocarbons, e.g. methylene-chloride, tetrachloroethane and also mixtures of these solvents. The reaction temperature may vary between the freezing and the boiling points of the solvent. When the reaction is carried out with a compound of formula (V) wherein E is



the preferred temperature is the room temperature i.e. from 10°C to 25°C, when the reaction is carried out with a compound of formula (V) wherein E is



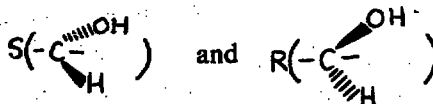
the preferred temperature is the reflux temperature of the solvent.

The product of the reaction between a compound of formula (IV) and a compound of formula (V) is a mixture of a compound of formula (I) wherein Y is *trans*-CH=CZ₂— wherein Z₂ is as defined above and a compound of formula (I) wherein Y is *cis*-CH=CZ₂— wherein Z₂ is as defined above, in a ratio varying between approximately 90:10 and 95:5. The compound of formula (I) wherein Y is *trans*-CH=CZ₂— wherein Z₂ is as defined above, may be separated from the mixture by crystallization with a suitable solvent, while the compound of formula (I) wherein Y is *cis*-CH=CZ₂— wherein Z₂ is as defined above, may be obtained by concentration of the mother liquor and subsequent chromatographic separation of the residue, either by column or preparative TLC chromatography using silica gel or magnesium silicate as support and e.g. methylene chloride, diethyl ether, diisopropyl ether, ethyl acetate, benzene, cyclohexane or their mixtures as elution solvents.

The removal of the protecting groups, if present, may be performed by mild acid hydrolysis as described above for the compounds obtained by the halocyclization and the reduction processes.

Both the optional reduction of a compound of formula (I) wherein R₂ and R₅, taken together form an oxo group, and Y is —CH=CZ₂—, wherein Z₂ is as defined above, to give a compound of formula (I) wherein Y is —CH=CZ₂—, wherein Z₂ is as defined above and wherein one of R₂ and R₅ is hydrogen and the other is hydroxy and the optional conversion of a compound of formula (I) wherein R₂ and R₅, taken together, form an oxo group and Y is —CH=CZ₂— wherein Z₂ is as defined above, into a compound of formula (I) wherein Y is —CH=CZ₂—, wherein Z₂ is as defined above, and wherein one of R₂ and R₅ is hydroxy and the other is C₁—C₈ alkyl, C₂—C₈ alkenyl, C₂—C₈ alkynyl or aryl can be regarded as 1,2 - polar additions to the carbonyl group.

The optional reduction of a ketone of formula (I) wherein R₂ and R₅ taken together form an oxo group, and Y is —CH=CZ₂—, wherein Z₂ is as defined above, to give a compound of formula (I) wherein Y is —CH=CZ₂—, wherein Z₂ is as defined above, and wherein one of R₂ and R₅ is hydrogen and the other is hydroxy, is preferably carried out with an alkali or alkaline earth metal borohydride, preferably sodium, lithium, calcium, magnesium or zinc borohydride, using from 0.5 to 6 moles of the reducing agent for each mole of the compound of formula (I). The reduction may be performed either in aqueous or anhydrous inert solvents such as linear or cyclic ethers, e.g. diethyl ether, tetrahydrofuran, 1,2 - dimethoxyethane, dioxane or aliphatic or aromatic hydrocarbons, e.g., n-heptane or benzene, or halogenated hydrocarbons, e.g. methylene dichloride, or hydroxylated solvents, e.g., ethyl, methyl or isopropyl alcohol, or mixtures of these solvents. The reaction temperature may vary between approximately -40°C and the boiling point of the solvent used, but the preferred temperature ranges from -20°C to 25°C. This reduction leads to a mixture of the two epimeric



alcohols from which the single epimers can be separated, if desired, by fractional crystallization, e.g. from di-diethyl ether, n-hexane, n-heptane, cyclohexane but preferably by chromatography either on silica gel or magnesium silicate columns or preparative TLC chromatography with, for example, silica gel, eluting, e.g., with CH₂Cl₂, diethyl ether, diisopropyl ether, ethyl acetate, methyl acetate, benzene, cyclohexane or mixtures of these, or by high speed liquid chromatography.

The optional conversion of a ketone of formula (I) wherein R₂ and R₅ taken

together form an oxo group and Y is $-\text{CH}=\text{CZ}_2-$, wherein Z_2 is as defined above, into a compound of formula (I) wherein one of R_2 and R_5 is hydroxy and the other is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl or aryl and Y is $-\text{CH}=\text{CZ}_2-$ wherein Z_2 is as defined above, may be carried out by treatment of the ketone with a Grignard reagent of formula $\text{R}'''-\text{MgHal}$, wherein Hal is halogen, preferably bromine or iodine and R''' is C_1-C_8 alkyl, C_2-C_8 alkynyl, C_2-C_8 alkenyl or aryl, preferably methyl, vinyl, ethynyl, phenyl. The Grignard reaction is carried out with 1.05 to 2 moles of the magnesium derivative for each mole of ketone, operating in anhydrous solvents which may be linear or cyclic ethers, e.g., diethyl ether, tetrahydrofuran, dioxane, 1,2 - dimethoxyethane or aliphatic or aromatic hydrocarbons, e.g., n-heptane, n-hexane, benzene, toluene, at temperatures varying from -70°C to the boiling point of the solvent used. The preferred temperatures range between -60°C and 10°C .

The optional etherification of an alcohol of formula (I) wherein Y is $-\text{CH}=\text{CZ}_2-$, wherein Z_2 is as defined above, and one of R_2 and R_5 is hydroxy and the other is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl or aryl to give a compound of formula (I) wherein Y is $-\text{CH}=\text{CZ}_2-$, wherein Z_2 is as defined above, and one of R_2 and R_5 is C_1-C_8 alkoxy or aralkoxy and the other is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl or aryl, may be carried out, for example, by reaction of the alcohol with an optionally aryl-substituted diazoalkane in the presence of a catalyst such as fluoroboric acid or boron trifluoride and in an organic solvent such as dichloromethane or by reaction of the free or saltified hydroxy group with an alkyl or aralkyl halide in the presence of a base, e.g. as silver oxide, and in a solvent e.g. dimethyl sulphoxide or dimethylformamide.

The optional hydrogenation of a compound of formula (I) wherein Y is $-\text{CH}=\text{CZ}_2-$, wherein Z_2 is hydrogen, to give a compound of formula (I) wherein Y is $-\text{CH}_2-\text{CH}_2-$ may be carried out, e.g., catalytically preferably in an alcoholic solvent, in the presence of platinum or palladium on charcoal as catalyst at temperatures varying from -40°C to the reflux temperature of the solvent. When it is desired to obtain compounds of formula (I) wherein Z_1 is halogen and Y is $-\text{CH}_2-\text{CH}_2-$ the hydrogenation is preferably carried out at temperatures ranging from -40°C to -20°C .

The optional dehydrohalogenation of a compound of formula (I) wherein Z_1 is hydrogen, and Y is $-\text{CH}=\text{CZ}_2-$, wherein Z_2 is halogen, so as to obtain the corresponding compounds of formula (I) wherein Z_1 is hydrogen and Y is $-\text{C}=\text{C}-$, may be carried out using a dehydrohalogenating agent preferably selected from a dimethylsulfinylcarbanion of formula $\text{CH}_3\text{SOCH}_2^-$, diazabicycloundecene, diazabicyclononene, the amide or the alkoxide of an alkali metal. From 1 to 5, and preferably from 1.5 to 1.8, molar equivalents of the basic dehydrohalogenating agent may be employed for each mole of the compound of formula (I) wherein Y is $-\text{CH}=\text{CZ}_2-$, wherein Z_2 is halogen. This dehydrohalogenation process is preferably carried out in the absence of atmospheric oxygen, in an inert solvent such as dimethyl sulphoxide, dimethylformamide, hexamethylphosphoramide; a linear or cyclic ether, e.g., 1,2 - dimethoxyethane, tetrahydrofuran, dioxane; an aromatic hydrocarbon, e.g., benzene, toluene; or liquid ammonia or a mixture of these solvents. The reaction temperature may vary between the liquefaction point of the ammonia and approximately 100°C , but the preferred temperature is room temperature. Depending on the solvent, the reaction temperature and the molar ratio used between the reagent and the compound, the reaction time may vary from a few minutes to several hours.

The optional reduction of a compound of formula (I) wherein R_2 and R_5 taken together form an oxo group and Y is $-\text{CH}_2-\text{CH}_2-$ or $-\text{C}=\text{C}-$ to give a compound of formula (I) wherein one of R_2 and R_5 is hydrogen and the other is hydroxy and Y is $-\text{CH}_2-\text{CH}_2-$ or $-\text{C}=\text{C}-$ may be carried out as described above for the analogous reduction of a compound of formula (I) wherein R_2 and R_5 taken together form an oxo group and Y is $-\text{CH}=\text{CZ}_2-$, wherein Z_2 is as defined above. The optional conversion of a compound of formula (I) wherein R_2 and R_5 taken together form an oxo group and Y is $-\text{CH}_2-\text{CH}_2-$ or $-\text{C}=\text{C}-$ into a compound of formula (I) wherein one of R_2 and R_5 is hydroxy and the other is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl or aryl may be effected under the same reaction conditions described above for the analogous conversion of the compounds of formula (I) wherein Y is $-\text{CH}=\text{CZ}_2-$, wherein Z_2 is as defined above.

Also the optional etherification of a compound of formula (I) wherein one of

R_2 and R_3 is hydroxy and the other is hydrogen or C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl and Y is $-CH_2-CH_2-$ or $-C\equiv C-$ may be carried out as described above for the etherification of a compound of formula (I) wherein one of R_2 and R_3 is hydroxy and the other is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkynyl or aryl and Y is $-CH=CZ_2-$, wherein Z_2 is as defined above.

The optional conversion of a compound of formula (I) into an other compound of formula (I) as well as the salification of a compound of formula (I), the preparation of a free compound from a salt and the separation of the isomers from a mixture may be carried out by known methods. Thus, for example, a compound of formula (I) wherein one of R_2 and R_3 is hydrogen and the other is hydroxy may be converted into a compound of formula (I) wherein R_2 and R_3 taken together form an oxo group by oxidation. The oxidation may be carried out by treatment with an excess of activated manganese dioxide in an inert solvent preferably a halogenated inert solvent such as dichloromethane or chloroform at room temperature for a reaction time varying between several hours and one or more days. Alternatively, the oxidation may be carried out by reaction with a 1.1-1.2 molar equivalent of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone (DDQ) in an inert solvent such as dioxane, tetrahydrofuran, benzene or a mixture of these at temperatures ranging from 40°C to the boiling point of the solvent.

A compound of formula (I) wherein R is a free carboxy group may be converted into a compound of formula (I) wherein R is an esterified carboxy group, e.g., a C_2-C_{13} alkoxycarbonyl group, by known methods, e.g. by reaction with the appropriate alcohol, e.g. a C_1-C_{12} aliphatic alcohol, in the presence of an acid catalyst, e.g. *p* - toluenesulphonic acid and also by treatment with a diazoalkane.

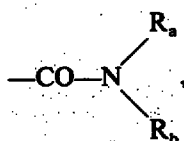
The optional conversion of a compound of formula (I) wherein R_1 is hydroxy into a compound of formula (I) wherein R_1 is acyloxy, if desired, may be performed in a conventional manner, e.g., by treatment with an anhydride or a halide, such as a chloride of the appropriate carboxylic acid in the presence of a base. When one of R_2 and R_3 is hydroxy, this hydroxy group may be protected before the acylation by one of the known protecting group mentioned above.

The optional conversion of a compound of formula (I) wherein R is an esterified carboxy group into a compound of formula (I) wherein R is a free carboxy group, if desired, may be carried out by the usual methods of saponification, e.g., by treatment with an alkali or alkaline earth metal hydroxide in aqueous or alcoholic aqueous solution followed by acidification. In a compound of formula (I) wherein R is an esterified carboxy and R_1 is acyloxy, the optional saponification may be carried out selectively with respect to the esterified carboxy, if desired, by transesterification, i.e., by reacting it in the same alcohol which esterifies the carboxy groups and in the presence of a base such as an alkali or alkaline earth metal alkoxide or K_2CO_3 .

The optional conversion of a compound of formula (I) wherein R_1 is hydroxy into a compound of formula (I) wherein R_1 is C_1-C_6 alkoxy or aralkoxy, if desired, may be carried out by the usual methods of the etherification, for example as described above for the etherification of a compound of formula (I) wherein one of R_2 and R_3 is hydroxy.

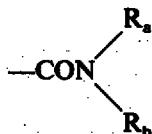
When it is desired to etherify only one of several hydroxyl groups present it is useful to protect before the etherification the hydroxy groups which it is desired to not etherify, e.g. with the known protecting groups above mentioned, then removing these at the end of the etherification by the procedures already described above. The optional conversion of a compound of formula (I) wherein R is a free or esterified carboxy group into a compound of formula (I) wherein R is $-CH_2-OH$, if desired, may be carried out, e.g. by reducing the ester with $LiAlH_4$ in diethyl ether or tetrahydrofuran at reflux temperature.

The optional conversion of a compound of formula (I) wherein R is a free carboxy group into a compound of formula (I) wherein R is



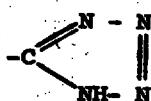
wherein R_a and R_b are as defined above, may be performed by treatment with an amine of formula NHR_aR_b in the presence of a condensing agent, e.g. a carbodiimide such as dicyclohexylcarbodiimide, and the optional conversion of a

compound of formula (I) wherein R is an esterified carboxy into a compound of formula (I) wherein R is



may be effected by treatment with an amine of formula NHR_aR_b in a suitable organic solvent at reflux temperature for 2—3 hours.

The optional conversion of a compound of formula (I) wherein R is a free carboxy group into a compound of formula (I) wherein R is a radical



may be carried out by converting the carboxy group into the corresponding halide, preferably chloride, e.g., by reaction with thionyl chloride or oxalyl chloride in dioxane or dichloroethane at reflux temperature, then reacting the halide, e.g., with ammonia, to give the amide, dehydrating the amide to nitrile, e.g., with *p*-toluenesulphonylchloride in pyridine at 90°C—100°C, and finally reacting the nitrile with sodium azide and ammonium chloride in dimethylformamide at a temperature varying between the room temperature and 100°C. But preferably the above-reported conversions of the carboxy group into a —CN or



are performed on the starting materials i.e. for example on the compounds of formula (II) and (VI).

The optional salification of a compound of formula (I) (Conversion of acid to salt) may be performed in a conventional manner.

Also the optional separation of the optically active compounds from a racemic mixture as well as the optional separation of the diastereoisomers or of the geometrical isomers from their mixtures may be effected by conventional methods.

The compounds of formula (II) are already known compounds and may be prepared, e.g., as described by E. J. Corey *et al.*, Ann. of New York Acad. of Sciences, 180, 24 (1971), by J. Fried *et al.*, J. Med. Chem. 16, 429 (1973), G. L. Bundy *et al.*, Amer. Chem. Soc. 94, 2124 (1972), by C. Gandolfi *et al.*, Il Farmaco Ed. Sc. 27, 1125 (1972), in the U.S. Patent No. 3,935,254, Derwent Farmdoc 20717 X, in the German Offenlegungsschrift No. 26 11 788 (Derwent Farmdoc 61615X), in the German Offenlegungsschrift No. 26 10 503 (Derwent Farmdoc 59715X), in the German Offenlegungsschrift No. 26 27 422 (Derwent Farmdoc 85028X), in the U.S. Patent No. 3,706,789, in the U.S. Patent No. 3,728,382, in the U.S. Patent No. 3,903,131, in the U.S. Patent No. 3,962,293, in the U.S. Patent No. 3,969,380, Derwent Farmdoc 73279U, Derwent Farmdoc 31279T, in the U.S. Patent No. 3,890,372, in the U.S. Patent No. 3,636,120, in the U.S. Patent No. 3,883,513, in the U.S. Patent No. 3,932,389, in the U.S. Patent No. 3,932,479, Derwent Farmdoc 19594W, Derwent Farmdoc 54179 U and in the British Patent No. 1,483,880.

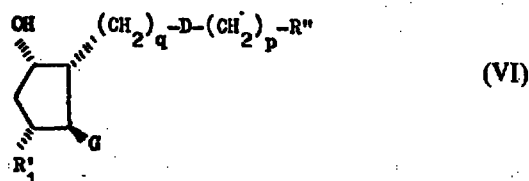
The compound of formula (III) wherein Q is halogen may be obtained by the same reaction described above for the synthesis of the compound of formula (I) wherein Z₁ is halogen.

The compound of formula (III) wherein Q is a group $\sim\text{Hg}^{(++)}\text{Z}^{(-)}$ wherein Z⁻ is as defined above may be prepared by cyclizing a compound of formula (II) in the presence of a source of Hg⁽⁺⁺⁾ ions. Suitable sources of Hg⁽⁺⁺⁾ ions may be, e.g., either compounds of formula Hg(Z)₂ or compounds of formula Hg(OH)Z. The above cyclization may be performed, e.g., using 1.01 to 1.5, preferably 1.2, equivalents of the mercuric compounds for each mole of the compound of formula (II), in an organic solvent miscible with water, e.g., tetrahydrofuran, methanol, ethanol or in a mixture of the organic solvent and water. The reaction temperature

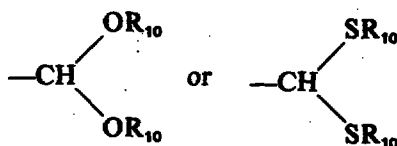
may vary between 0°C and the boiling point of the reaction mixture and the reaction time ranges from 5 minutes to 2 hours. The cyclization gives a mixture of four diastereoisomers of formula (III) differing from each other for the configuration (*endo* or *exo*) of the side chain linked to the heterocyclic ring B or for the configuration (S or R) of the Q substituent.

The separation of the diastereoisomers from their mixture, which may be carried out according to known methods, e.g. those already described above, may be effected at this point or, if desired, after the reduction of the compound of formula (III).

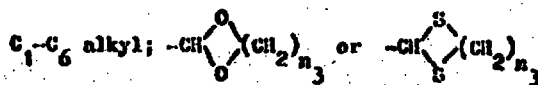
The compound of formula (IV) wherein Z₁ is halogen may be prepared by halocyclization of a compound of formula (VI)



wherein R'', p, q, D and R' are as defined above and G is a protected aldehyde group or a protected —CH₂OH group, preferably



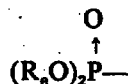
wherein R₁₀ is



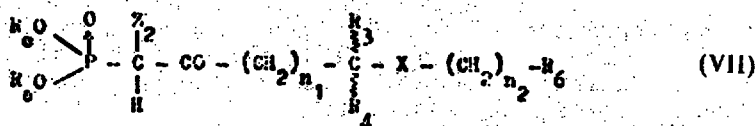
wherein n₃ is an integer of 2 to 4, preferably 2 or 3; —CH₂—O—CH₂—C₆H₅, or —CH₂—O—CH₂—SCH₃, followed by the removal of the protecting groups and by the selective oxidation of —CH₂OH, when obtained, to —CHO. The halocyclization of the compound of formula (VI) may be performed using the same reaction conditions described above for the conversion of a compound of formula (II) into a compound of formula (I) wherein Z₁ is halogen.

The removal of the protecting group from the aldehyde or hydroxy groups may be carried out by mild acid hydrolysis in the same conditions already described in this specification for the removal of the protecting groups (i.e. ether groups) of the hydroxyl group. The selective oxidation of —CH₂OH to —CHO may be effected in a conventional manner, e.g. by treatment with an excess of at least 3 moles per mole of the primary alcohol with dicyclohexylcarbodiimide in benzene-dimethyl sulphoxide and in the presence of an acid catalyst, e.g., pyridine trifluoroacetate or phosphoric acid.

The compound of formula (IV) wherein Z₁ is hydrogen may be prepared either by the dehalogenation of a compound of formula (IV) wherein Z₁ is halogen according to the method reported above for the conversion of a compound of formula (I) wherein Z₁ is halogen into a compound of formula (I) wherein Z₁ is hydrogen or by a process comprising the cyclization of a compound of formula (VI) in the presence of a source of Hg⁽⁺²⁾ ions [as already described for the preparation of a compound of formula (III) wherein Q is ~Hg⁽⁺²⁾Z⁽⁻¹⁾] and the subsequent reduction of the obtained compound using the same reaction conditions employed for the reduction of a compound of formula (III). The compound of formula (V) wherein E is

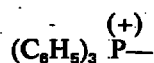


may be prepared by treatment of a phosphonate of formula (VII)

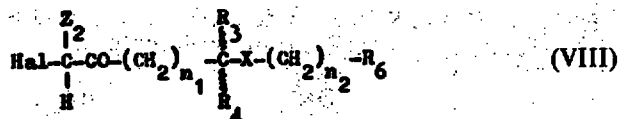


wherein R_3 , Z_2 , n_1 , R_3 , R_4 , X , n_2 and R_6 are as defined above, with at least an equivalent of a base preferably an alkali or alkaline earth metal hydride, e.g. sodium, potassium, lithium or calcium hydride; an alkali metal alkoxide, e.g. sodium or potassium *tert.* butoxide; an alkali or alkaline earth metal amide, e.g. sodium amide; an alkali or alkaline earth metal derivative of a carboxy-amide, e.g. sodium acetamide or sodium succinimide.

The compound of formula (V) wherein E is



may be prepared by reacting a compound of formula (VIII)



wherein

Z_2 , n_1 , R_3 , R_4 , X , n_2 , R_6 are as defined above and Hal is a halogen atom, with 1—1.2 molar equivalent of triphenylphosphine in an inert organic solvent such as e.g. benzene, acetonitrile, diethyl ether, then treating the triphenylphosphonium halide so obtained with an equivalent amount of an inorganic base such as, for example, NaOH, KOH, Na_2CO_3 , NaHCO_3 .

The compound of formula (VI) may be prepared, e.g. according to Tetrahedron Letters No. 42, 4307—4310 (1972). The compound of formula (VII) wherein Z_2 is hydrogen may be obtained by halogenating a compound of formula (VII) wherein Z_2 is hydrogen in a conventional manner, operating substantially as in the halogenation of β -ketoesters.

The compounds of formula (VII) wherein Z_2 is hydrogen may be prepared by known methods, e.g. according to E. J. Corey *et al.*, J. Am. Chem. Soc. 90, 3247 (1968) and E. J. Corey and G. K. Kwiatkowski, J. Am. Chem. Soc., 88, 5654 (1966).

The compounds of formula (VIII) are known compounds or may be prepared by known methods.

The compounds of the invention can be used, in general, for the same therapeutic indications as the natural prostaglandins in either human or veterinary medicine. In particular, those having a triple bond in the 13,14-position instead of an double bond and those with mono and di-substituents such as methyl and fluorine groups have the advantages of superior resistance to degradation by the 15-PG-dehydrogenase enzymes, which quickly inactivate natural compounds, and, of a more selective therapeutic action, as indicated below.

In order to obtain a preliminary biological profile, i.e. to assess whether the compounds of the invention possess PG-like or thromboxane (TXA_2)-like or PGI-like activity, they were at first tested by a superfusion cascade technique by the method of Piper and Vane, Nature 223, 29 (1969).

In order to increase the sensitivity of the bioassay, a mixture of antagonists [Gilmore *et al.*, Nature 218, 1135 (1968)] is added to the Krebs-Henseleit and indomethacin (4 $\mu\text{g}/\text{ml}$) is also added to prevent the endogenous biosynthesis of prostaglandins.

Contraction of rat colon (RC), rat stomach strip (RSS) and bovine coronary artery (BCA), and relaxation of rabbit mesentery artery (RbMA) are assumed to represent prostaglandin-like activity. TXA_2 -like activity is indicated when RbMA is contracted and must be confirmed by *in vitro* platelet pro-aggregation activity, since $\text{PGF}_{2\alpha}$ -like compounds also contract RbMA, as opposed to PGE. Finally, PGI-like activity is indicated by the relaxation of BCA, and is confirmed by *in vitro* platelet anti-aggregation activity. Synthetic PGE_2 and both the biosynthetic TXA_2 and PGI₂ are utilized as standard compounds.

They are active at a range of concentrations from 1—5 $\mu\text{g}/\text{ml}$. The compounds of the invention were dissolved in a few drops of ethanol just before testing; the

stock solution was prepared in 0.1 M tris-buffer, pH 9.0, (1 mg/ml) and diluted with Krebs-Henseleit to the required concentration.

The compound 11 α ,15(S) - dihydroxy - 6 β H - 6,9 α - epoxy - prost - *trans* - 13 - enoic acid was taken as the parent compound and is called 6 β H - 6,9 α - epoxy compound; the diastereoisomer -11 α ,15(S) - dihydroxy - 6 α H - 6,9 α - epoxy - prost - *trans* - 13 - enoic acid is then referred to as 6 α H - 6,9 α - epoxy compound. The chemical names of the other tested compounds are also referred to those of the parent compounds. The compounds were tested at concentrations up to 100 ng/ml. The results obtained showed that, in general, the 6 β H - diastereoisomers, e.g. the 6 β H - 6,9 α - epoxy compounds; dl - 6 β H - 5 - bromo - 6,9 α - epoxy compound, 6 β H - 6,9 α - epoxy - 16 - *m* - CF₃ - phenoxy - 17,18,19,20 - tetranor compound and 6 β H - 6,9 α - epoxy - 16 - *m* - chlorophenoxy - 17,18,19,20 - tetranor compound possess BCA-relaxing activity and therefore have PGI-like activity. Among the 6 β H - derivatives, only the dl - 6 β H - 6,9 α - epoxy - 16 - methyl - 16 - butoxy - 17,18,19,20 - tetranor compound showed a BCA-contracting activity. The 6 α H - derivatives, e.g. the 6 α H - 6,9 α - epoxy compound, dl - 6 α H - 5 - bromo - 6,9 α - epoxy compound; dl - 6 α H - 6,9 α - epoxy - 16 - methyl - 16 - butoxy - 17,18,19,20 - tetranor compound, 6 α H - 6,9 α - epoxy - 16 - *m* - CF₃ - phenoxy - 17,18,19,20 - tetranor compound and 6 α H - 6,9 α - oxide - 16 - *m* - chlorophenoxy - 17,18,19,20 - tetranor compound also showed BCA-contracting activity.

In general, the *exo*-configuration is associated with BCA contraction. Furthermore, the compounds of the invention have hypotensive activity in mammals as does the natural compound PGI₂. However, as compared to PGI₂, they have the great advantage of a higher chemical stability and can be used in pharmaceutical formulations. The hypotensive activity was demonstrated by the limb perfusion test. During the perfusion of the rat's left leg, through the left femoral artery, with a constant perfusion pressure, both the 6 β H- and 6 α H - 6,9 α - epoxy compounds caused a lowering of the values of the mean perfusion pressure at all the doses, over the range from 0.05—1 μ g (to -42.5% for 6 β H and -32% for 6 α H). Moreover, the systemic pressure, both systolic and diastolic, was depressed from 0.05 μ g/kg up to 5 μ g/kg (about -45%).

Because of their hypotensive and vasodilatory activity, the compounds of the invention are useful for treatment of cases of gangrene of the lower limbs. For this therapeutic use they have been found to be more active than PGE₁ and PGE₂. They are also useful in disturbances of the peripheral vasculature and, therefore in the prevention and treatment of diseases such as phlebitis, hepato-renal syndrome, ductus arteriosus, non-obstructive mesenteric ischemia, arteritis and ischemic ulcerations of the leg.

Among the compounds of the invention, in particular, the 6 β H - derivatives also have a high anti-aggregating activity. Among the 6 β H compounds, the more important ones are, in order of increasing potency, the dl - 6 β H - 5 - bromo - 6,9 α - epoxy compounds, 6 β H - 6,9 α - epoxy - 16 - *m* - CF₃ - phenoxy - 17,18,19,20 - tetranor compound dl - 6 β H - 6,9 α - epoxy compound, and 6 β H - 6,9 α - epoxy compound.

Using platelet-rich plasma (PRP) from healthy human donors who had not taken any drugs for at least one week, and monitoring platelet aggregation by continuous recording of light transmission in a Born aggregometer [Born G.V.R., Nature (London) 194, 927 (1962)] there is evidence that the 6 β H - 6,9 α - epoxy compound, dl - 6 β H - 5 - bromo - 6,9 α - epoxy compound, 6 β H - 6,9 α - epoxy - 16 - *m* - CF₃ - phenoxy - 17,18,19,20 - tetranor compound and 6 β H - 6,9 α - epoxy - 16 - *m* - chlorophenoxy - 17,18,19,20 - tetranor compound mimic the biosynthetic PGI₂ in its platelet-antiaggregating properties. The compounds investigated were incubated for 2—3 minutes at 37°C in the PRP prior to the addition of the aggregating agents, arachidonic acid (0.4 mM), ADP (10 μ M), collagen (38 μ M) or adrenaline (15 μ M). The potency ratio for the compound is, e.g., 1:10 for arachidonic acid-induced aggregation and 1:100 for ADP-induced aggregation, as compared with biosynthetic PGI₂.

A very interesting increase in the anti-aggregating potency follows 20-methyl substitution in both the 6 β H- and 6 α H-6,9 α -epoxy parent compounds. Similarly, 6 β H - 5 - bromo - 20 - methyl, 6 β H - 5,14 - dibromo, 6 β H - 13,14 - didehydro - 20 - methyl and finally 6 β H - 5 - bromo - 13,14 - didehydro compounds and their 6 β H - 5 - iodo (but not 6 α H - 5 - iodo isomers) are very active compounds as anti-aggregating agents. The compounds of the invention are, therefore, particularly useful in mammals for inhibiting platelet aggregation, for preventing and inhibiting

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thrombus formation and for decreasing the adhesiveness of platelets. Therefore, they are useful in treatment and prevention of thromboses and myocardial infarct in treatment of atherosclerosis, and in general in all syndromes etiologically based on or associated with lipid imbalance or hyperlipidemia, as well as in treatment of

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geriatric patients for prevention of cerebral ischemic episodes, and in long-term treatment after myocardial infarct.

When the compounds of the invention are given as anti-aggregating agents, the routes of administration are the usual ones, oral, intravenous, subcutaneous, intramuscular. In emergency situations, the preferred route is intravenous, with

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doses that can vary from 0.005 to 10 mg/kg/day. The exact dose will depend on the condition of the patient, his weight, his age and the route of administration.

The compounds of the invention were also studied for their uterine contractile activity, both *in vitro* and *in vivo*, against $\text{PGF}_{2\alpha}$ as standard. For example, *in vitro*, on the uterus of the estrogenized rat $6\alpha H$ - $6,9\alpha$ - epoxy - 16 - *m* - chlorophenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid and $6\beta H$ - $6,9\alpha$ - epoxy - 16 - *m* - CF_3 - phenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid, were 1.3 and 3.1 times as active as $\text{PGF}_{2\alpha}$. In the *in vivo* assay, measuring the intrauterine pressure of the ovariectomized rabbit, the same compounds of the invention were 5.9 and 8.25 times as active as $\text{PGF}_{2\alpha}$ (see the following Table). The compounds of the invention are referred to in the Table as "A" and "B" for brevity

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TABLE

	<i>in vitro</i>		<i>in vivo</i>
	Uterus	Ileum	
$\text{PGF}_{2\alpha}$	1	1	1
Compound A	1.3	0.05	5.9
Compound B	3.1	0.1	8.25

The Table shows that the compounds have greater activity on the uterus than on the gastrointestinal tract. These compounds, which are useful for induction of labor, for expulsion of dead fetuses from the pregnant female, in either human or veterinary medicine, are without the undesirable side effects of the natural prostaglandins, such as vomiting and diarrhoea. For this purpose the compounds of the invention can be given by intravenous infusion, at a dose of about 0.01 $\mu\text{g/kg/minute}$ until the end of labor. At the same dosage, the compounds of the invention dilate the uterine cervix, facilitating therapeutic abortion and, in that situation are given preferably in the form of vaginal tablets or suppositories.

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The compounds of the invention, in particular dl - $6\beta H$ - $6,9\alpha$ - epoxy - 16 - *m* - chlorophenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid, also have luteolytic activity and are therefore of use for control of fertility.

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The $6\beta H$ - $6,9\alpha$ - epoxy and their $6\alpha H$ - isomers were also investigated for their action on the gastrointestinal tract, in order to know: (a) cytoprotective activity against lesions induced by non-steroid anti-inflammatory drugs; (b) ability to prevent the ulcers induced by the method of Togagi-Okabe [(Japan J. Pharmac. vol. 18, 9 (1968))] and (c) antisecretory activity, according to Shay et al Gastroenter. 26, 906 (1954). The cytoprotective ability is a common feature of all the compounds. For example, given subcutaneously, the $6\beta H$ - $6,9\alpha$ - epoxy is slightly more active (1.5—2 times) than the standard PGE_2 as a gastric antisecretory agent.

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In general, the cytoprotective activity of the $6\beta H$ compounds is doubled when an triple bond is present in the 13,14-position; it is quadrupled when a 16-alkyl group, usually a methyl, is positioned in the 16(*S*)-configuration. As an ulcer-preventing substance, the parent $6\beta H$ - $6,9\alpha$ - epoxy analog is at least equipotent with PGE_2 and the following substitutions, 13,14-Triple bond; 16(*S*) or (*R*) methyl; 16(*S*) or (*R*) fluoro, highly increase (up to 30 times) the potency ratio.

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Furthermore a significant oral antisecretory activity appears when a methyl group is in the C-15-position of the parent $6\beta H$ - $6,9\alpha$ - epoxy compound or in the 16,16 - dimethyl or 16 - methy, 16 - alkoxy compounds, such as the $6\beta H$ - $6,9\alpha$ -

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epoxy - 16 - methyl - 16 - butoxy - 17,18,19,20 - tetranor derivative. For this purpose the compounds are preferably given by intravenous injection or infusion, subcutaneously or intramuscularly. For intravenous infusion, the doses vary from 0.1 μ g to 500 μ g/kg/body weight/minute. The total daily dose, either by injection or by infusion, is of the order of 0.1 to 20 mg/kg, the exact dose depending on the age, weight and condition of the patient or of the animal being treated and on the route of administration.

In addition, the compounds of the invention are also useful for treatment of obstructive pulmonary diseases such as bronchial asthma, since they have considerable bronchodilatory activity.

For treatment of the obstructive pulmonary disorders, for example bronchial asthma, the compounds of the invention can be given by different routes; orally, in the form of tablets, capsules, coated tablets or in liquid form as drops or syrups; rectally in suppositories; intravenously, intramuscularly or subcutaneously; by inhalation, as aerosols or solutions for the nebulizer; by insufflation, in powdered form.

Doses of the order of 0.01—4 mg/kg can be given from 1 to 4 times a day, with the exact dose depending on the age, weight, and condition of the patient and on the route of administration. For use as an antiasthmatic, the compounds of the invention can be combined with other antiasthmatic agents, such as sympathicomimetic drugs like isoproterenol, ephedrine,, xanthine derivatives, such as theophylline and aminophylline, or corticosteroids.

The dosages when used as hypotensive and vasodilatory agents are about the same as those used for the anti-aggregating effects.

As previously stated, the compounds of the invention can be given, either to humans or animals in a variety of dosage forms, e.g., orally in the form of tablets, capsules or liquids; rectally, in the form of suppositories, parenterally, subcutaneously or intramuscularly, with intravenous administration being preferred in emergency situations; by inhalation in the form of aerosols or solutions for nebulizers; in the form of sterile implants for prolonged action; or intravaginally in the form, e.g., of bougies.

The invention includes pharmaceutical and veterinary compositions containing a compound of the invention and a pharmaceutical or veterinarily acceptable carrier and/or diluents. The carrier or diluent and the form of the compositions can be any conventionally used. For example, for intravenous injection or infusion, sterile aqueous isotonic solutions are preferred. For subcutaneous or intramuscular injection, sterile solutions or suspensions in aqueous or non-aqueous media may be used; for tissue implants, a sterile tablet or silicone rubber capsule containing or impregnated with the compound is used.

Conventional carriers or diluents are, for example, water, gelatine, lactose, dextrose, saccharose, mannitol, sorbitol, cellulose, talc, steric acid, calcium or magnesium stearate, glycol, starch, gum arabic, tragacanth gum, alginic acid or alginates, lecithin, polysorbate, vegetable oils.

For administration by nebulizer, a suspension or a solution of the compound of the invention, preferably in the form of a salt, such as the sodium salt in water, can be used. Alternatively, the pharmaceutical preparation can be in the form of a suspension or of a solution of the compound of the invention in one of the usual liquefied propellants, such as dichloro - difluoromethane or dichlorotetrafluoroethane, administered from a pressurized container such as an aerosol bomb. When the compound is not soluble in the propellant it may be necessary to add a co-solvent, such as ethanol, dipropylene glycol and/or a surfactant to the pharmaceutical formulation.

The invention is illustrated by the following examples, wherein the abbreviations "THF", "DME", "DMSO", "THP", "Et₂O" refer to tetrahydrofuran, 1,2 - dimethoxyethane, dimethyl sulphoxide, 2 - tetrahydropyranyl, and diethyl ether, respectively.

The following Examples illustrate but do not limit the present invention. Examples 1—41, 75, 76 and 77 describe the preparation of intermediates. Optical rotations were measured at room temperature by a Perkin Elmer 141 automatic polarimeter having microcells of 100 mm. path length. 1% (1 g./100 ml. solvent) solutions were used. Where no solvent is specifically mentioned in the test, it is chloroform (CHCl₃). The values indicated as $[\alpha]_D$ were determined using a sodium vapour lamp as light source (589 nm wavelengths) and the values indicated as $[\alpha]_{365}$ were determined using a high pressure mercury vapour lamp (365 nm wavelength).

Example 1

To a solution of 1.0 g of dl - 5 β - hydroxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - acetic acid γ - lactone - 4 - *p* - phenylbenzoate in 8 ml of benzene/DMSO (75/25) is added with stirring 0.89 g of dicyclohexylcarbodiimide. At room temperature, 1.42 ml of a solution of pyridinium trifluoroacetate is added (prepared from 1 ml of trifluoroacetic acid and 2 ml of pyridine brought to 25 ml with 75/25 benzene/DMSO). After 3 hours 19 ml of benzene is added and the mixture is treated dropwise with an oxalic acid dihydrate solution, 0.3 g in 3.8 ml of water. After approximately 15 minutes of stirring, the mixture is filtered, and the organic phase is washed with water until neutral, concentrated to 2 ml, and then diluted with 5 ml of isopropyl ether. The product is isolated by filtration and crystallized from diisopropyl ether to give 0.8 g of dl - 5 β - formyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - acetic acid γ - lactone 4 - *p* - phenylbenzoate, m.p.=129—131°C. A solution of 800 mg of this in 2.8 ml of anhydrous methanol is treated with 0.62 ml of methyl orthoformate and 18 mg of *p* - toluenesulfonic acid monohydrate. After 1 hour, 0.01 ml of pyridine is added and the solution is evaporated to dryness. The residue is dissolved in ethyl acetate; it is washed with 1.0 N NaOH and then saturated NaCl until neutral. The solvent is removed at reduced pressure and the residue is crystallized from methanol to give 800 mg of dl - 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - acetic acid γ - lactone 4 - *p* - phenylbenzoate, m.p.=108—110°C.

60 mg of K₂CO₃ is added to a solution of this in 5.6 ml of anhydrous methanol. After 4 hours of stirring at room temperature, the solution is filtered; it is then reduced to small volume and acidified with a saturated NaH₂PO₄ solution. The methanol is removed and the residue taken up in ethyl acetate. This is washed with saturated NaCl until neutral, is dried over anhydrous Na₂SO₄, is filtered, and evaporated under reduced pressure to give 480 mg of dl - 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - acetic acid γ - lactone.

A solution of this in 4 ml of CH₂Cl₂ is treated with 0.32 ml of 2,3 - dihydropyran and 4.8 mg of *p* - toluenesulfonic acid. After 4 hours at room temperature, pyridine is added and the solution is evaporated at reduced pressure. The crude reaction product is filtered on 5 g of silica gel, with cyclohexane:ethyl-ether (50:50) as eluent, to give 380 mg of dl - 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxy - cyclopentane - 1 α - acetic acid γ - lactone 4 - (2 - tetrahydropyranyl ether). Starting from a 4-ester of 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxy - cyclopentane - 1 α - acetic acid γ - lactone (for example: 4 - *p* - phenylbenzoate, m.p. 128—130°C, [α]_D=+85°) or from a 4-ester of 5 α - hydroxymethyl - 2 β ,4 β - dihydroxycyclopentane - 1 β - acetic acid γ - lactone (for example: the 4 - *p* - phenylbenzoate, m.p.=127—129°C, [α]=+84.5), the same procedure was used to prepare the following compounds: 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - acetic acid γ - lactone 4 - (2 - tetrahydropyranyl ether) and 5 α - dimethoxymethyl - 2 β ,4 β - dihydroxycyclopentane - 1 β - acetic acid γ - lactone 4 - (2 - tetrahydropyranyl ether). If 1,4 - diox - 2 - ene is used instead of 2,3 - dihydropyran, the corresponding 4 - (1,4 - dioxan - 2 - yl ether) derivatives are obtained.

Example 2

A solution of 216 mg of 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxy - cyclopentane - 1 α - acetic acid γ - lactone [α]_D=-16°, [α]₃₆₅=-48° (c=1% CHCl₃) in 1.6 ml of dimethylformamide is treated with 0.3 ml of triethylamine followed by 291 mg of dimethyl - *tert* - butylchlorosilane. After one hour, the mixture is diluted with 8.3 ml of water and extracted with hexane. The organic phase is washed with water and dried over Na₂SO₄ to give 310 mg of 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - acetic acid γ - lactone 4 - dimethyl - *tert* - butylsilyl ether.

Example 3

To a solution of dl - 5 β - hydroxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - propionic acid δ - lactone 4 - *p* - phenylbenzoate (1 g) in 8 ml of benzene: DMSO (75:25) is added 0.86 g of dicyclohexylcarbodiimide followed by 1.37 ml of a freshly prepared pyridinium trifluoroacetate (see Example 1). After three hours, 18 ml of benzene is added; a solution of 0.29 g of oxalic acid dihydrate in 3.7 ml of water is then added dropwise. After 15 minutes of stirring, the dicyclohexylurea is removed by filtration and the organic phase is washed with water until neutral. This is then reduced to volume to approximately 2 ml and diisopropyl ether is added. One obtains 0.793 g of dl - 5 β - formyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - propionic acid δ - lactone 4 - *p* - phenylbenzoate.

A solution of 780 mg of this in 2.7 ml of anhydrous methanol is treated with 0.59 ml of methyl orthoformate and 17.3 mg of *p* - toluenesulfonic acid. After approximately one hour, 0.01 ml of pyridine is added and the solution is evaporated to dryness. The residue is taken up in ethyl acetate; the organic phase is washed with 1N NaOH and then saturated NaCl until neutral. Evaporation to dryness gives 769 mg of dl - 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - propionic acid δ - lactone 4 - *p* - phenylbenzoate. This is then dissolved in 5.4 ml of anhydrous methanol and 75 mg of K₂CO₃ is added. After four hours of stirring at room temperature and filtration, the solution is reduced in volume and acidified with a saturated solution of NaH₂PO₄. The methanol is evaporated and the aqueous phase treated with ethyl acetate; the organic phase is then washed with a saturated NaCl solution until neutral, dried over Na₂SO₄, and evaporated under vacuum to give crude dl - 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - propanoic acid δ - lactone. A solution of this in 4 ml of CH₂Cl₂ is treated with 0.3 ml of 2,3 - dihydropyran and 4.5 mg of *p* - toluenesulfonic acid. After four hours at room temperature, 0.01 ml of pyridine is added and the solution is evaporated to dryness. The reaction product is purified on silica gel with cyclohexane:ethyl ether (50:50) as eluent to give 480 mg of dl - 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - propanoic acid δ - lactone 4 - (2 - tetrahydropyranyl ether).

From a 4-ester of 5 β - hydroxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - propanoic acid δ - lactone and from a 4 - ester of 5 α - hydroxymethyl - 2 β ,4 β - dihydroxycyclopentane - 1 β - propanoic acid δ - lactone (for example, the 4 - *p* - phenylbenzoate), using the same procedure, the following compounds were obtained: 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - propanoic acid δ - lactone 4 - (2 - tetrahydropyranyl ether); 5 α - dimethoxymethyl - 2 β ,4 β - dihydroxycyclopentane - 1 β - propanoic acid δ - lactone 4 - (2 - tetrahydropyranyl ether). If 1,4 - diox - 2 - ene is used instead of 2,3 - dihydropyran, the corresponding 3 - (1,4 - dioxan - 2 - yl ether) derivatives are obtained.

Example 4

A solution of 1 g of 5 β - formyl - 2 α - hydroxycyclopentane - 1 α - acetic acid γ - lactone in 6.5 ml of anhydrous methanol is treated with 1.74 ml of methyl orthoformate and 52 mg of *p* - toluenesulfonic acid. After approximately one hour, 0.04 ml of pyridine is added and the solution is evaporated to dryness. The residue is taken up in ethyl acetate, and the washed with 1N NaOH and then saturated NaCl until neutral. Evaporation under vacuum gives 1 g of 5 β - dimethoxymethyl - 2 α - hydroxycyclopentane - 1 α - acetic acid γ - lactone, $[\alpha]_D^{25} = -16^\circ$.

The same procedure gave 5 β - dimethoxymethyl - 2 α - hydroxycyclopentane - 1 α - propionic acid δ - lactone and its dl derivatives from 5 β - formyl - 2 α - hydroxycyclopentane - 1 α - propionic acid δ - lactone.

Example 5

To a solution of 960 mg of dl - 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - acetic acid γ - lactone 4 - (2 - tetrahydropyranyl ether) in 16 ml of toluene, cooled to -70°C , is added 8.5 ml of a 0.5N toluene solution of di - *iso* - butylaluminum hydride, over a 30 minute period. After a further 30 minutes of stirring at -70°C , 10 ml of a 2M toluene solution of *iso* - propanol is added dropwise. The solution is warmed to 0°C and treated with 3 ml of a 30% solution of NaH₂PO₄. After 1 hour of stirring, 12 g of anhydrous Na₂SO₄ is added. Filtration and evaporation of solvent gives 900 mg of dl - 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - ethanal γ - lactol 4 - (2 - tetrahydropyranyl ether).

Example 6

Following the procedure of Example 5, a solution of 400 mg of 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - acetic acid γ - lactone 4 - dimethyl - *tert* - butylsilyl ether in 11 ml of toluene, cooled to -70°C , is treated dropwise with 5.9 ml of a 0.5 N toluene solution of di - *iso* - butylaluminum hydride to give 0.43 g of 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - ethanol γ - lactol 4 - dimethyl - *tert* - butylsilyl ether.

Example 7

Under a nitrogen atmosphere, a solution of 628 mg of 5 β - dimethoxymethyl - 2 α ,4 α - dihydroxycyclopentane - 1 α - propanoic acid δ - lactone 4 - (2 -

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tetrahydropyranyl ether) in 11 ml of toluene, cooled to -70°C , is treated dropwise with 5.9 ml of a 0.5M toluene solution of di-*iso*-butylaluminium hydride. After 30 minutes at -70°C , 10.9 ml of a 2M toluene solution of isopropanol is added dropwise. The temperature is allowed to rise to 0°C and 2 ml of 30% NaH_2PO_4 is added. After one hour of stirring, 8.3 g of anhydrous Na_2SO_4 is added and the mixture is filtered. Evaporation of the organic phase under vacuum gives 620 mg of 5 β -dimethoxymethyl-2 α ,4 α -dihydroxycyclopentane-1 α -propanal δ -lactol 4-(2-tetrahydropyranyl ether).

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Example 8

Using one of the procedures outlined in Examples 5, 6 and 7, 4-(2-tetrahydropyranyl ether); 4-(1,4-dioxan-2-yl ether) and 4-dimethylbutylsilyl ether of the following compounds are prepared:

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5 β -dimethoxymethyl-2 α ,4 α -dihydroxycyclopentane-1 α -ethanal γ -lactol, in its dl and optically active form (or *nat*-);

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5 α -dimethoxymethyl-2 β ,4 β -dihydroxycyclopentane-1 β -ethanal γ -lactol (or *ent*- form);

5 β -dimethoxymethyl-2 α ,4 α -dihydroxycyclopentane-1 α -propanal δ -lactol, in its dl and optically active form (or *nat*-);

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5 α -dimethoxymethyl-2 β ,4 β -dihydroxycyclopentane-1 β -propanal δ -lactol (or *ent*- form).

Example 9

0.29 ml of absolute ethanol in 3.5 ml of toluene is added dropwise to a solution of 5×10^{-3} mol of sodium (2-methoxyethoxy)aluminium hydride (1.4 ml of a 70% benzene solution diluted with 5 ml of toluene) cooled to 0°C . 8.2 ml of the alanate solution so prepared is added, at -30°C , to 0.98 g of dl-5 β -benzyloxymethyl-2 α -hydroxycyclopentane-1 α -propionic acid δ -lactone in 22 ml of toluene. After 45 minutes, excess reagent is quenched with 6 ml of a 0.5M toluene solution of isopropanol. The mixture is warmed to 0°C , 4 ml of 30% NaH_2PO_4 is added, and the resulting mixture is stirred for 2 hours. The inorganic salts are removed by filtration and the solution is evaporated to dryness to give 0.94 g of dl-5 β -benzyloxymethyl-2 α -hydroxycyclopentane-1 α -propanal δ -lactol.

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Using the procedure reported above, or one of those from Examples 4 to 7, the following compounds were prepared from their corresponding γ -lactones:

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5 β -benzyloxymethyl-2 α -hydroxycyclopentane-1 α -ethanal γ -lactol;

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5 β -benzyloxymethyl-2 α -hydroxycyclopentane-1 α -propanal δ -lactol;

5 β -benzyloxymethyl-2 α -hydroxycyclopentane-1 α -ethanal δ -lactol;

5 β -dimethoxymethyl-2 α -hydroxycyclopentane-1 α -propanal δ -lactol.

Example 10

With stirring and external cooling to maintain a reaction temperature of $20-22^{\circ}\text{C}$, a solution of 1.05 g of potassium *tert*-butylate in 10 ml of DMSO is added dropwise to a solution of 1.8 g of 4-carboxybutyl-triphenylphosphonium bromide and 0.38 g of 5 β -dimethoxymethyl-2 α ,4 α -dihydroxycyclopentane-1 α -ethanal γ -lactol 4-(2-tetrahydropyranyl ether). After the addition, the mixture is held at room temperature for 1 hour and then diluted with 16 ml of ice/water. The aqueous phase is extracted with ether (5 $\times$ 8 ml) and diethyl ether:benzene (70:30, 5 $\times$ 6 ml); the organic layers, after re-extraction with 0.5 M NaOH (2 $\times$ 10 ml), are discarded. The combined alkaline aqueous phase is acidified to pH 4.8 with 30% NaH_2PO_4 and then extracted with ethyl ether:pentane (1:1, 5 $\times$ 15 ml); from the combined organic phases, after drying over Na_2SO_4 and solvent removal, one obtains 0.45 g of 7-(2' α ,4' α -dihydroxy-5' β -dimethoxymethylcyclopent-1' α -yl)-hept-*cis*-5-enoic acid 4'-(2-tetrahydropyranyl ether). This in turn is converted to the corresponding methyl ester upon treatment with diazomethane in diethyl ether. An analytic sample is prepared by adsorbing 100 mg of the crude product on 1 g of silica gel and eluting with benzene:diethyl ether (85:15). N.M.R.:

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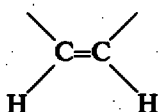
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5.46 p.p.m. multiplet.

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Example 11

In an anhydrous nitrogen atmosphere, a suspension of 0.39 g of a 75% oil dispersion of NaH in DMSO (13.5 ml) is heated to 60–65°C for 3½ hours; after cooling to room temperature and while maintaining the reaction mixture at 20–22°C, the following are added, in order: 2.66 g of (3-carboxypropyl) - triphenylphosphonium bromide in 6 ml of DMSO and 0.6 g of 5β - dimethoxymethyl - 2α,4α - dihydroxycyclopentane - 1α - propanal δ - lactol 4 - (2 - tetrahydropyranyl ether) in 3 ml of DMSO. The mixture is stirred for 3 hours, and then diluted with 35 ml of water.

The aqueous phase is extracted with diethyl ether (5×12 ml) and diethyl ether:benzene (70:30, 7×12 ml); the combined organic extract, after re-extraction with 0.5 N NaOH (2×15 ml), is discarded. The combined alkaline aqueous extract is acidified to pH 4.3 with 30% aqueous NaH₂PO₄ and extracted with ethyl ether:pentane (1:1) to give, after washing until neutral, drying over Na₂SO₄, and removal of the solvent, 0.71 g of 7 - (2'α,4'α - dihydroxy - 5'β - dimethoxymethyl - cyclopent - 1'α - yl) - hept - cis - 4 - enoic acid. 4' - (2' - tetrahydropyranyl ether). Treatment with diazomethane affords the corresponding methyl ester.

Example 12

The methyl esters of the following acids were prepared from lactols made according to the procedures of Examples 4 to 8 by treatment with a Wittig reagent (prepared from (4 - carboxybutyl) - triphenylphosphonium bromide or (3 - carboxypropyl) - triphenylphosphonium bromide) and successive esterification with diazomethane, in their optically active or dl forms:

7 - (2'α - hydroxy - 5'β - benzyloxymethylcyclopent - 1'α - yl) - hept - cis - 4 - enoic;

7 - (2'α - hydroxy - 5'β - dimethoxymethyl - cyclopent - 1'α - yl) - hept - cis - 4 - enoic;

7 - (2'α - hydroxy - 5'β - dimethoxymethyl - cyclopent - 1'α - yl) - hept - cis - 5 - enoic;

7 - (2'α - hydroxy - 5'β - benzyloxymethyl - cyclopent - 1'α - yl) - hept - cis - 5 - enoic;

7 - (2'α,4'α - dihydroxy - 5'β - dimethoxymethyl - cyclopent - 1'α - yl) - hept - cis - 5 - enoic and its 4' - (1,4 - dioxan - 2 - yl), (2 - tetrahydropyranyl) and 4' - (dimethyl - tert - butylsilyl) - ethers;

7 - (2'α,4'α - dihydroxy - 5'β - dimethoxymethyl - cyclopent - 1'α - yl) - hept - cis - 4 - enoic and its 4' - (1,4 - dioxan - 2 - yl, - 4' - (2 - tetrahydropyranyl) and 4' - dimethyl - tert - butylsilyl) - ethers;

6 - (2'α,4'α - dihydroxy - 5'β - dimethoxymethyl - cyclopent - 1'α - yl) - hex - cis - 4 - enoic and its 4' - (2 - tetrahydropyranyl ether);

8 - (2'α,4'α - dihydroxy - 5'β - dimethoxymethyl - cyclopent - 1'α - yl) - oct - cis - 5 - enoic and its 4' - (2 - tetrahydropyranyl ether).

Example 13

A solution of 1.06 g of the methyl ester of 7 - (2'α,4'α - dihydroxy - 5'β - dimethoxymethyl - cyclopent - 1'α - yl) - hept - cis - 5 - enoic acid 4' - (2 - tetrahydropyranyl ether) in 5 ml of methanol is added to 0.84 g of mercuric acetate in methanol. After 30 minutes at room temperature, a solution of 250 mg of sodium borohydride in 2 ml of water is added with stirring and external cooling. After 20 minutes of stirring, the mixture is acidified to pH 6.5 with aqueous monosodium phosphate, the methanol is removed under vacuum, and the residue is taken up in water diethyl ether. The organic phase, upon removal of the solvent, affords 1.02 g of 5 - (6' - exo - dimethoxymethyl - 7' - endo - hydroxy - 2' - oxobicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester (7' - tetrahydropyranyl ether).

Example 14

A solution of 1.59 g of 7 - (2'α,4'α - dihydroxy - 5'β - dimethoxymethyl - cyclopent - 1'α - yl) - hept - cis - 4 - enoic methyl ester 4' - (2 - tetrahydropyranyl ether) in 6 ml of THF is added to a solution of 1.26 g of mercuric acetate in 4 ml of water diluted with 4 ml of THF. The mixture is stirred for 1½ hours until precipitation is complete. 180 mg of sodium borohydride (in 2.5 ml of water) is then added and the resulting mixture is stirred for 30 minutes. The solution is decanted from the precipitate, which is then washed with THF. The

aqueous/organic decanted solution is concentrated under reduced pressure and the residue extracted with ethyl acetate. The combined organic extract, after washing with water until neutral, affords upon removal of the solvent 0.98 g of 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester 8' - (2 - tetrahydropyranyl ether).

Example 15

Starting from the esters prepared as described in Examples 9 to 11, by reaction with a mercuric salt and subsequent reductive demercuration as described in the procedures in Examples 13 and 14, the following bicyclic derivatives are obtained:

5 - (6' - *exo* - benzyloxymethyl - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester;

5 - (6' - *exo* - dimethoxymethyl - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester;

4 - (7' - *exo* - benzyloxymethyl - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester;

4 - (7' - *exo* - dimethoxymethyl - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester;

the 7' - (2 - tetrahydropyranyl ether), (1,4 - dioxan - 2 - yl ether), and 7' - (dimethyl - *tert* - butylsilyl ether) of 5 - (6' - *exo* - dimethoxy - methyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester;

the 8' - (2 - tetrahydropyranyl ether), (1,4 - dioxan - 2 - yl ether) and 8' - (dimethyl - *tert* - butylsilyl ether) of 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester;

4 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]octan - 3'ξ - yl) - butanoic acid methyl ester 7' - (2 - tetrahydropyranyl ether);

5 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - pentanoic acid methyl ester 8' - (2 - tetrahydropyranyl ether).

All these compounds are obtained in the *dl*-, *nat*- and *ent*-forms.

Example 16

A solution of 0.48 g of bromine in 5 ml of methylene chloride is added dropwise, with stirring, to a solution of 0.27 g of pyridine and 1.2 g of 7 - (2'α,4'α - dihydroxy - 5'β - dimethoxymethyl - cyclopent - 1'α - yl) - hept - *cis* - 5 - enoic acid methyl ester 4' - (2 - tetrahydropyranyl ether) in 6 ml of methylene chloride, cooled to 0°C. Stirring is continued for ten minutes following the addition. The organic phase is washed with 5 ml of a pH 7 buffer solution 10% in sodium thiosulfate and then with water until neutral. After drying over Na₂SO₄, removal of the solvent affords 1.38 g of 5 - bromo - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester 7' - (2 - tetrahydropyranyl ether).

Example 17

1.24 g of N - iodosuccinimide is added to a solution of 2 g of 7 - (2'α,4'α - dihydroxy - 5'β - dimethoxymethyl - cyclopent - 1'α - yl) - hept - *cis* - 5 - enoic acid methyl ester 4' - (2 - tetrahydropyranyl ether) in 15 ml of carbon tetrachloride. The mixture is stirred for 3 hours and 30 ml of diethyl ether is added. The organic phase is washed with 1N Na₂S₂O₃ and then with water until neutral. Removal of the solvent affords 2.48 g of 5 - iodo - 5' - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3'ξyl) - pentanoic acid methyl ester 7' - (2 - tetrahydropyranyl ether).

Example 18

422 mg of N - bromosuccinimide is added with stirring to a solution of 0.78 g of 7 - (2'α,4'α - dihydroxy - 5'β - dimethoxy methyl - cyclopent - 1'α - yl) - hept - *cis* - 4 - enoic acid methyl ester 4 - (2 - tetrahydropyranyl ether) in 11 ml of CCl₄. After four hours of stirring, diethyl ether is added; the solution is then washed with water, 1N Na₂S₂O₃, and water until neutral. Evaporation to dryness gives 0.98 g of 4 - bromo - 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester 8' - (2 - tetrahydropyranyl ether).

Example 19

To a suspension of 0.25 g of dry CaCO_3 in a solution of 346 mg of 7 - (2' α - hydroxy - 5' β - benzyloxymethylcyclopent - 1' α - yl) - hept - *cis* - 5 - enoic acid methyl ester in 10 ml of CCl_4 cooled to 0–5°C is added with stirring a solution of 75 mg of chlorine in 3 ml of CCl_4 . After stirring for 2 hours, the inorganic salts are removed by filtration. The solution is washed with a 7% aqueous solution of KI and $\text{Na}_2\text{S}_2\text{O}_3$ and then with water until neutral. The residue upon evaporation to dryness is adsorbed on silica gel and eluted with cyclohexane:diethyl ether (80:20) to give 0.27 g of 5 - chloro - 5 - (6' - *exo* - benzyloxymethyl - 2' - oxabicyclo[3.3.0]oct - 3' ξ - yl) - pentanoic acid methyl ester.

Example 20

A solution of 0.39 g of 7 - (2' α ,4' α - dihydroxy - 5' β - dimethoxymethylcyclopent - 1' α - yl) - hept - *cis* - 5 - enoic acid methyl ester 4' - (1,4 - dioxan - 2 - yl ether) and 98 mg of pyridine in 10 ml of dichloromethane is cooled to –40°C. A solution of 81 mg of chlorine in 6 ml of CH_2Cl_2 is then added over a period of 30 minutes. After 10 minutes of stirring, the mixture is heated to room temperature. The organic phase is washed with a 7% solution of KI and $\text{Na}_2\text{S}_2\text{O}_3$ and then with water until neutral. Removal of the solvent affords 0.39 g of 5 - chloro - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' ξ - yl) - pentanoic acid methyl ester 4' - (1,4 - dioxan - 2 - yl ether).

Example 21

280 mg of iodine in CCl_4 is added to a solution of 0.39 g of 7 - (2' α ,4' α - dihydroxy - 5' β - dimethoxymethyl - cyclopent - 1' α - yl) - hept - *cis* - 4 - enoic acid methyl ester 4' - (2 - tetrahydropyranyl ether) and 82 mg of pyridine in 10 ml of CCl_4 . Stirring is continued until the color disappears; 30 ml of diethyl ether is then added. The organic phase is washed with water, then a solution 7% in KI and $\text{Na}_2\text{S}_2\text{O}_3$, and then water until neutral. Removal of the solvent affords 0.48 g of 4 - iodo - 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3' ξ - yl) - butanoic acid methyl ester 8' - (2 - tetrahydropyranyl ether).

Example 22

To a solution of 0.34 g of 7 - (2' α - hydroxy - 5' β - benzyloxymethylcyclopent - 1' α - yl) - hept - *cis* - 5 - enoic acid methyl ester in 6 ml of methanol is added with stirring a solution of 0.325 g of mercuric acetate in water:methanol (1:9, 6 ml). The mixture is stirred for 15 minutes, reduced to 3 ml under vacuum, and then added to 5 ml of a saturated solution of NaCl in water. The precipitate is then extracted with methylene chloride. The organic phase is washed with water and evaporated to dryness to give 0.52 g of crude 5 - chloromercurio - 5 - (6' - *exo* - benzyloxymethyl - 2' - oxabicyclo[3.3.0]oct - 3' ξ - yl) - pentanoic acid methyl ester. A solution of this in methylene chloride (10 ml) is treated with 80 mg of pyridine in 2 ml of CH_2Cl_2 and then dropwise with stirring with a solution of 150 mg of Br_2 in CH_2Cl_2 . After 20 minutes of stirring at room temperature, the organic phase is washed with water, then 7% KI and $\text{Na}_2\text{S}_2\text{O}_3$, and water until neutral. Evaporation to dryness gives 0.34 g of 5 - bromo - 5 - (6' - *exo* - benzyloxymethyl - 2' - oxabicyclo[3.3.0]oct - 3' ξ - yl) - pentanoic acid methyl ester.

Mass spectrum M^+ 424, 426 m/e $\text{M}^+ - \text{HBr}$ 344 m/e $\text{M}^+ - \text{CHBr}(\text{CH}_2)_3\text{CO}_2\text{CH}_3 = 231$ m/e.

Example 23

10.5 mg of *p* - toluenesulfonic acid monohydrate is added to a solution of 0.26 g of 5 - iodo - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' ξ - yl) - pentanoic acid methyl ester 7' - (2 - tetrahydropyranyl ether) and the resulting mixture is left at room temperature for 30 minutes. 10 mg of pyridine is then added and the solution is evaporated to dryness. The residue is taken up in diethyl ester/water. After drying over Na_2SO_4 , the organic phase gives upon solvent evaporation 0.23 g of crude 5 - iodo - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' ξ - yl) - pentanoic acid methyl ester. Separation by chromatography on silica gel with methylene chloride: diethyl ether (75:25) as eluent affords 84 mg of 5 - iodo - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - *endo* - yl) - pentanoic acid methyl ester and 55 mg of the 3' - *exo* isomer.

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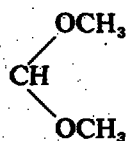
Referring to the spectrometric data, the prostaglandin numbering will be used; thus the above diastereoisomers can be named as follows: the *endo* diastereoisomer: 6 β H - 6,9 α - epoxy - 11 α - hydroxy - 13,13 - dimethoxy - 14,15,16,17,18,19,20 - heptanor prostanoic acid methyl ester and the *exo* diastereoisomer 6 α H - 6,9 α - epoxy - 11 α - hydroxy - 13,13 - dimethoxy - 14,15,16,17,18,19,20 - heptanor prostanoic acid methyl ester.

Analytical data:

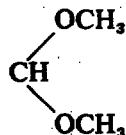
endo diastereoisomer: TLC more polar-one spot

Mass spectrum (m/e; % intensity fragment):

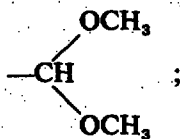
442 0.002 M⁺; 412 4 M⁺-CH₂O, 315/314 3 M⁺-iodine/HI 283 11 315-CH₃OH, 75 100



N.M.R. (solvent CDCl₃, TMS internal standard) p.p.m.: 3.49 and 3.52 s, 3H/3H,



3.64 s, 3H, CO₂CH₃; 4.00 m, 3H (protons at C₅, C₉, C₁₁); 4.29 d, 1H,



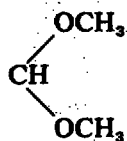
4.60 m, 1H, 6 β H

¹³C-MR (at 20 MHz in C₂D₆ solution, TMS int. standard) p.p.m. 172.9, 36.5, 33.1, 25.6, 41.8, 81.0, 38.1, 55.5, 83.1, 41.5, 74.2, 44.6, 108.0, 54.2, 54.1, 51.0.

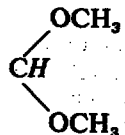
exo diastereoisomer: TLC less polar-one spot

Mass spectrum: 442 0.01 M⁺, 366 3 M⁺ CH₂CH(OCH₃)₂, 315 4 M⁺-1; 283 10 M⁺-1-CH₃OH; 75 100 CH(OCH₃)₂⁺

N.M.R.: p.p.m. 3.34 and 3.37 3H/3H s



3.5 and 4.1 m 1H and 2H protons at C₅, C₉, C₁₁ uncertain assignment, 3.65, s 3H, CO₂CH₃; 4.21, d1H,



4.35 m, 1H, 6 α H

¹³CMR; p.p.m. 173.0, 37.0, 33.1, 25.5, 40.1, 84.4, 39.7, 57.2, 83.7, 40.5, 75.9, 44.0, 107.3, 54.0, 53.8, 51.1.

Example 24

A solution of 980 mg of 4 - bromo - 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - *oxa* - bicyclo[3.4.0]non - 3' ξ - yl) - butanoic acid methyl

ester 8' - (2 - tetrahydropyranyl ether) in 6 ml of anhydrous methanol is treated at room temperature for 30 minutes with 48 mg of *p* - toluenesulfonic acid. 2% aqueous NaHCO₃ is added and the mixture is extracted with diethyl ether. From the organic phase, after washing until neutral and evaporation of the solvent, one obtains 0.68 g of a crude product which after purification on silica gel with methylene chloride:ethyl ether (80:20) as eluent affords 0.30 g of 4 - bromo - 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3' - *exo* - yl) - butanoic acid methyl ester and 0.29 g of the 3' - *endo* isomer.

Example 25

Starting from acids prepared according to the procedure of Example 11 and performing their halocyclization as described in one of the Examples 16 to 22, the following halobicyclic compounds are prepared:

- 5 - chloro - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester 7' - (2 - tetrahydropyranyl ether) (and 7' - (1,4 - dioxan - 2 - yl ether) and 7' - dimethyl - *tert* - butylsilyl ether);
- 4 - chloro - 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester 8' - (2 - tetrahydropyranyl ether) (and 8' - (1,4 - dioxan - 2 - yl ether) and 8' - dimethyl - *tert* - butylsilyl ether);
- 5 - chloro - 5 - (6' - *exo* - dimethoxymethyl - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester;
- 5 - chloro - 5 - (6' - *exo* - benzyloxymethyl - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester;
- 4 - chloro - 4 - (7' - *exo* - dimethoxymethyl - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester;
- 4 - chloro - 4 - (7' - *exo* - benzyloxymethyl - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester;
- 5 - bromo - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester 7' - (2 - tetrahydropyranyl ether) (and 7' - (1,4 - dioxan - 2 - yl ether and 7' - dimethyl - *tert* - butylsilyl ether);
- 4 - bromo - 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester 8' - (2 - tetrahydropyranyl ether) (and 8' - (1,4 - dioxan - 2 - yl ether) and 8' - (dimethyl - *tert* - butylsilyl ether);
- 5 - bromo - 5 - (6' - *exo* - dimethoxymethyl - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester;
- 5 - bromo - 5 - (6' - *exo* - benzyloxymethyl - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester;
- 4 - bromo - 4 - (7' - *exo* - dimethoxymethyl - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester;
- 4 - bromo - 4 - (7' - *exo* - benzyloxymethyl - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester;
- 5 - iodo - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]octan - 3'ξ - yl) - pentanoic acid methyl ester 7' - (2 - tetrahydropyranyl ether) (and 7' - (1,4 - dioxan - 2 - yl ether) and 7' - (dimethyl - *tert* - butylsilyl ether);
- 4 - iodo - 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester 8' - (2 - tetrahydropyranyl ether) (and 8' - (1,4 - dioxan - 2 - yl ether) and 8' - dimethyl - *tert* - butylsilyl ether);
- 5 - iodo - 5 - (6' - *exo* - dimethoxymethyl - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester;
- 5 - iodo - 5 - (6' - *exo* - benzyloxymethyl - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester;
- 4 - iodo - 4 - (7' - *exo* - benzyloxymethyl - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester;
- 4 - iodo - 4 - (7' - *exo* - dimethoxymethyl - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester.

Example 26

Selective deetherification of the ethers described in Example 25, according to the procedure in Examples 23 and 24 affords the hydroxy derivatives, which give the following upon separation of isomers:

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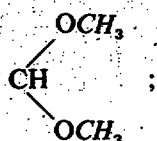
30

5 - chloro - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester, and its individual 3' - *exo* and 3' - *endo* isomers;

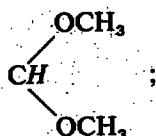
5 4 - chloro - 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester, and its individual 3' - *exo* - and 3' - *endo* isomers;

10 5 - bromo - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester, and its individual 3' - *exo* and 3' - *endo* isomers;

10 *endo* isomer: TLC on SiO₂ more polar one spot N.M.R.: (CDCl₃) p.p.m. 3.4 d, 6H,



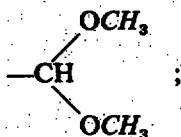
3.65, s, 3H CO₂CH₃ 4.00 m, 4H (proton at C₄, C₅, C₉, C₁₁); 4.17 d, 1,



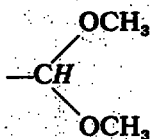
15 4.5 m, 1H, 6βH.

¹³CMR: 173.0, 35.0, 33.3, 23.6, 59.4, 80.6, 36.4, 55.6, 83.3, 41.6, 74.3, 44.5, 108.0, 54.4, 54.2, 51.1

exo isomer: TLC on SiO₂ less polar isomer one spot N.M.r.: (CDCl₃) p.p.m.: 3.37 d, 6H



3.66 s, 3H, CO₂CH₃ 4.00 m 4H, protons at C₄, C₅, C₉, C₁₁; 4.2 d, 1,



4.32 m, 1H, 6αH

¹³CMR: 173.0, 35.5, 33.3, 23.6, 57.7, 84.2, 38.2, 57.9, 83.6, 40.5, 76.0, 43.9, 107.2, 53.8, 53.8, 51.0

4 - bromo - 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester and its individual isomers, 3' - *exo* and 3' - *endo*;

5 - iodo - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester and its individual 3' - *exo* and 3' - *endo* isomers;

4 - iodo - 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester and its individual 3' - *exo* and 3' - *endo* isomers.

Example 27

With stirring under nitrogen, a benzene solution (30 ml) of 2.8 g of 5 - iodo - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester 7' - (2 - tetrahydropyranyl ether) is treated with a solution of 2.8 g of tributyltin hydride in 8

ml of benzene. The mixture is held at 55°C for 8 hours and then overnight at room temperature. The benzene layer is washed with 2x10 ml of a 5% NaHCO₃ solution and then with water until neutral. The residue upon solvent evaporation is adsorbed on 10 g of silica gel and eluted with benzene and benzene:ethyl ether (85:15) to give 1.94 g of 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxa - bicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester 7' - (2 - tetrahydropyranyl ether).

Example 28

60 mg of *p* - toluenesulfonic acid is added to a solution of 1.98 g of 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]octan - 3'ξ - yl) - pentanoic acid methyl ester - 7' - (2 - tetrahydropyranyl ether) in 10 ml of anhydrous methanol. After 30 minutes at room temperature, this is added to 20 ml of 20% aqueous NaHCO₃. The mixture is extracted with ethyl ether; the combined ether extract, after drying over Na₂SO₄, is evaporated to dryness. The residue is adsorbed on 100 g of silica gel and eluted with methylene chloride:diethyl ether (94:6) to give 0.64 g of 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - *exo* - yl) - pentanoic acid methyl ester, 0.52 g of the 3' - *endo* - isomer and 0.12 g of the 3'ξ - yl.

N.M.R. (CDCl₃) *endo* isomer 4.6 p.p.m. m, 1H 6βH, T.L.C. more polar;
exo isomer 4.3 p.p.m. m, 1H 6αH, T.L.C. less polar.

0.32 g of the 3' - *endo* isomer is dissolved in pyridine (0.8 ml) and treated for 8 hours at room temperature with 0.3 ml of acetic anhydride. The mixture is then poured into ice/water, and, after acidifying to pH 4.2, is extracted with ethyl ether. The combined extract, after washing until neutral, is evaporated to give 0.315 g of 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]octan - 3' - *endo* - yl) - pentanoic acid methyl ester 7' - acetate.

Example 29

A solution of 1.32 g of 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester 8' - (*tert* - butyldimethylsilyl ether) in 10 ml of anhydrous methanol is treated with 55 mg of *p* - toluenesulfonic acid for 2 hours at room temperature. 0.1 ml of pyridine is added, the solvent is removed under vacuum, and the residue is taken up in water/diethyl ether. The organic phase gives, upon removal of the solvent, 1.1 g of the crude 8' - hydroxy - 3'ξ - yl derivative. Chromatography of this on silica gel with benzene:diethyl ether (80:20) as eluent separates this into 4 - (7' - *exo* - dimethoxymethyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3' - *endo* - yl) - butanoic acid methyl ester (0.42 g) and the 3' - *exo* isomer (0.34 g).

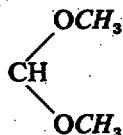
Example 30

Using the procedure in Examples 28 and 29, hydrolysis of the ethers described in Example 15 gives the corresponding free alcohols.

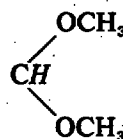
Example 31

Upon acetylation with pyridine (0.6 ml) and acetic anhydride (0.3 ml) 0.2 g of 5 - iodo - 5 - (6' - *exo* - dimethoxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - *endo* - yl) - pentanoic acid methyl ester gives 0.21 g of the corresponding 7' - acetoxy derivative.

N.M.R. (CDCl₃) p.p.m.: 2.03 s, 3H OCOCH₃; 3.36—3.40 s, s 3H/3H



3.66 s 3H CO₂CH₃; 4.00 m 2H protons at C₅, C₉; 4.27 d 1H



4.6 m 1H 6βH 5.0 m 1H proton at C₁₁

[The spectrometric data for the 6*aH* isomer acetate are respectively the following 2.03; 3.34—338, 3.66 s+m 4H CO₂CH₃ and one of C₅, C₉ protons 4.1 m 1H, other of C₅, C₉ protons 4.2, 4.4 m 1H 6*aH*, 5.1]. A solution of the 5 - iodo - 3' - endo - acetate in benzene (5 ml) is treated with 0.4 g of tributyltin hydride for 10 hours at 50°C. After the benzene phase is washed with 5% NaHCO₃ and water, evaporation of the solvent and purification on silica gel (10 g) with a benzene:diethyl ether (80:20) eluent afford 0.105 g of 5 - (6' - *exo* - dimethoxymethyl - 7' - endo - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' endo - yl) - pentanoic acid methyl ester 7' - acetate, identical in all respects with a sample prepared by the procedure in Example 28.

Example 32

Using the procedure of Examples 27 and 31, the reduction with tributyltin hydride of one of the halo-derivatives synthesized in Examples 16—26 gives the corresponding derivative in which halogen is replaced by hydrogen. These are identical in every way with the compounds prepared according to the procedures of Examples 15, 28, 29 and 30.

Example 33

5.4 mg of hydroquinone and a solution of 1.63 g of oxalic acid in 48 ml of water are added to a solution of 4 g of 5 - (6' - *exo* - dimethoxymethyl - 7' - endo - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' ξ - yl) - pentanoic acid methyl ester in 180 ml of acetone. After 12 hours at 40°C, the acetone is removed at reduced pressure and the mixture is extracted with ethyl acetate (3×25 ml). The combined organic extract is washed until neutral with a 10% ammonium sulfate solution and dried over Na₂SO₄. Removal of the solvent affords 3.21 g of 5 - (6' - *exo* - formyl - 7' - endo - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' ξ - yl) - pentanoic acid methyl ester. The 6' - *exo* - formyl - 3' - endo and the 6' - *exo* - formyl - 3' - *exo* - derivatives are prepared from the corresponding individual isomers.

Example 34

Using the procedure of Example 33, starting from the corresponding bicyclo[3.3.0]oct - 6' - *exo* - dimethoxymethyl and bicyclo[3.4.0]non - 7' - *exo* - dimethoxymethyl derivatives, the following compounds are prepared, either as individual 3' - *exo* - and 3' - endo or 3' ξ isomers:

5 - (6' - *exo* - formyl - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester;

4 - (7' - *exo* - formyl - 2' - oxabicyclo[3.4.0]non - 3' - yl) - butanoic acid methyl ester;

5 - (6' - *exo* - formyl - 7' - endo - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester;

4 - (7' - *exo* - formyl - 8' - endo - hydroxy - 2' - oxabicyclo[3.4.0]nonan - 3' - yl) - butanoic acid methyl ester;

5 - chloro - 5 - (6' - *exo* - formyl - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester;

4 - chloro - 4 - (7' - *exo* - formyl - 2' - oxabicyclo[3.4.0]non - 3' - yl) - butanoic acid methyl ester;

5 - chloro - 5 - (6' - *exo* - formyl - 7' - endo - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester;

4 - chloro - 4 - (7' - *exo* - formyl - 8' - endo - hydroxy - 2' - oxabicyclo[3.4.0]nonan - 3' - yl) - butanoic acid methyl ester;

5 - bromo - 5 - (6' - *exo* - formyl - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester;

4 - bromo - 4 - (7' - *exo* - formyl - 2' - oxabicyclo[3.4.0]non - 3' - yl) - butanoic acid methyl ester;

5 - bromo - 5 - (6' - *exo* - formyl - 7' - endo - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester;

4 - bromo - 4 - (7' - *exo* - formyl - 8' - endo - hydroxy - 2' - oxabicyclo[3.4.0]non - 3' - yl) - butanoic acid methyl ester;

5 - iodo - 5 - (6' - *exo* - formyl - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester;

4 - iodo - 4 - (7' - *exo* - formyl - 2' - oxabicyclo[3.4.0]non - 3' - yl) - butanoic acid methyl ester;

5 - iodo - 5 - (6' - *exo* - formyl - 7' - endo - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester;

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4 - iodo - 4 - (7' - *exo* - formyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3' - yl) - butanoic acid methyl ester;

5 - (6' - *exo* - formyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester 7' - acetate;

5 5 - iodo - 5 - (6' - *exo* - formyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0] - oct - 3' - yl) - pentanoic acid methyl ester 7' - acetate;

5 - (7' - *exo* - formyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3' - yl) - pentanoic acid methyl ester;

10 4 - (6' - *exo* - formyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - butanoic acid methyl ester.

Example 35

15 To a solution of 1.2 g of 5 - (6' - *exo* - benzyloxymethyl - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester in methanol:methyl acetate (10 ml:10 ml) is added 2 ml of a 0.1N methanol solution of HCl. After 0.15 g of PtO₂ is added, the mixture is hydrogenated at ambient temperature and pressure until 1 molar equivalent of hydrogen is absorbed. After the removal of the gas under vacuum and washing with nitrogen, the suspension is filtered, neutralized, and evaporated to dryness. The residue is taken up in water/ethyl acetate, and the organic phase yields 0.84 g of 5 - (6' - *exo* - hydroxymethyl - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester. This is then oxidized to the 6' - *exo* - formyl derivative by the procedure in Example 1, using dicyclohexylcarbodiimide in DMSO:benzene (25:75).

Example 36

25 To a solution of 18.1 g of 5 β - [(2' - tetrahydropyranyloxy)methyl] - 2 α ,4 α - dihydroxycyclopentane - 1 α - acetic acid *p*-lactone 4 - (2 - tetrahydropyranyl ether) in 150 ml of toluene cooled to -70°C is added in 30 minutes 128 ml of a 5M solution of di - *iso* - butyl - aluminium hydride (1.2 M/M). After 30 minutes at -70°C, 128 ml of a 2M toluene solution of isopropanol is added and the solution is brought to 0°C. Then 10 ml of a saturated aqueous solution of NaH₂PO₄ is added and the mixture is stirred for four hours. Following the addition of 10 g of anhydrous Na₂SO₄ and 10 g of filtering earth, the solution is filtered and evaporated to dryness to give 18.1 g of 5 β - [(2' - tetrahydropyranyloxy)methyl] - 2 α ,4 α - dihydroxy - cyclopentane - 1 α - ethanal *p*-lactol 4 - (2 - tetrahydropyranyl ether). A solution of this in 24 ml of anhydrous DMSO is added dropwise to a solution of the ylide prepared as follows: 9.6 g of 80% sodium hydride in 300 ml of DMSO is heated for four hours at 60°C. Then after the mixture is brought to 18-20°C, 67 g of (4 - carboxybutyl)triphenylphosphonium bromine dissolved in 80 ml of anhydrous DMSO is added while maintaining a temperature of 20-22°C to generate a bright red color. After four hours of stirring, 600 ml of water is added and the mixture is extracted with diethyl ether:benzene (70:30) to remove the triphenylphosphine oxide. The benzene organic phase is re-extracted with 0.1 N NaOH and then with water until neutral; it is then discarded. The alkaline aqueous phase is acidified to pH 5-4.8 and then extracted with ethyl ether:pentane (1:1) to give 21.6 g of -7 - (2' α ,4' α - dihydroxy - 5' β - tetrahydropyran - 2' - yloxymethylcyclopent - 1 α - yl) - hept - *cis* - 5 - enoic acid 4' - (2 - tetrahydropyranyl ether), which may be converted to its methyl ester by treatment with diazomethane in diethyl ether. 7.72 g of this ester in 28 ml of tetrahydrofuran is added dropwise to a yellow-brown suspension formed by adding 28 ml of THF to a solution of 6.13 g of mercuric acetate in 28 ml of water. After the mixture is stirred for 20 minutes at room temperature, it is cooled in an ice:water bath and 810 mg of NaBH₄ in 14 ml of water is added dropwise. Elemental mercury precipitates out, the suspension is decanted, the tetrahydrofuran is evaporated at reduced pressure and the residue is extracted with diethyl ether. Removal of the solvent affords 7.5 g of 5 - (6' - *exo* - tetrahydropyran - 2' - yloxymethyl - 7' - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester 7' - (2 - tetrahydropyranyl ether); 0.42 g of *p* - toluenesulfonic acid is then added to a solution of this in 30 ml of methanol. After 2 hours at room temperature, the solution is concentrated under vacuum and water is added. After extraction with ether and chromatography on silica gel with diethyl ether as eluent, one obtains 2.4 g of 5 - (6' - *exo* - hydroxymethyl - 7' - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - *exo* - yl) - pentanoic acid methyl ester and 2.6 g of the 3' - *endo* isomer.

Example 37

2.5 g of N - iodosuccinimide is added to a solution of 4.26 g of -7 - (2' α ,4' α -

dihydroxy - 5'β - tetrahydropyran - 2' - yloxymethylcyclopent - 1'α - yl) - hept - cis - 5 - enoic acid 4' - (2 - tetrahydropyranyl ether) in CH₂Cl₂:CCl₄ (10 ml:10 ml) and the resulting mixture is stirred for four hours. 30 ml of anhydrous methanol containing 130 mg of *p* - toluenesulfonic acid is added and stirring is continued for another 2 hours. 0.2 ml of pyridine is added, the mixture is reduced to small volume, and the residue is taken up in water/ethyl acetate. After washing with Na₂S₂O₃ and then water until neutral, the organic phase is evaporated to dryness to give a residue that is adsorbed on silica gel and eluted with diethyl ether to give 2.2 g of 5 - iodo - 5 - (6' - *exo* - hydroxymethyl - 7' - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - *exo* - yl) - pentanoic acid methyl ester and 1.85 g of the 3' - *endo* isomer.

Example 38

Following the procedure of Example 37, but using the methyl ester instead of the acid and N - bromoacetamide instead of N - iodosuccinimide, the 5 - bromo - 5 - (6' - *exo* - hydroxymethyl - 7' - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester is prepared. Silica gel chromatography allows the separation into the 3' - *exo* and 3' - *endo* isomers.

Example 39

A solution of 0.86 g of pyridine and 2.2 g of 7 - (2'α,4'α - dihydroxy - 5'β - tetrahydropyran - 2' - yloxymethylcyclopent - 1'α - yl) - hept - cis - 5 - enoic acid methyl ester 4' - (2 - tetrahydropyranyl ether) in dichloromethane (20 ml) is cooled to -30°C and 0.38 g of chlorine in 10 ml of CCl₄:CH₂Cl₂ (1:1) is added. The mixture is stirred for 2 hours, warmed to room temperature, and washed with 2N H₂SO₄ and then water until neutral. After evaporation of the solvent, the residue is dissolved in methanol (10 ml) and treated with 0.1 g of *p* - toluenesulfonic acid. The solution is then concentrated, diluted with water, and extracted with ethyl acetate. Removal of the solvent and purification of the residue on silica gel afford 0.6 g of 5 - chloro - 5 - (6' - *exo* - hydroxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - *exo* - yl) - pentanoic acid and 0.71 g of the 3' - *endo* isomer.

Example 40

To a solution of 0.356 g of 5 - iodo - 5 - (6' - *exo* - hydroxymethyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - *exo* - yl) - pentanoic acid methyl ester in 4.8 ml of benzene:DMSO (75:25) are added, in order, 0.28 g of dicyclohexylcarbodiimide and 0.4 ml of a pyridinium trifluoroacetate solution (see example 1). After 3 hours of stirring, 8 ml of benzene and then aqueous oxalic acid (94 mg in 1.2 ml) are added. The precipitate is removed by filtration and the benzene solution is washed with water until neutral. Removal of the solvent affords 0.32 g of 5 - iodo - 5 - (6' - *exo* - formyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - *exo* - yl) - pentanoic acid methyl ester.

Example 41

Upon oxidation of the 6' - *exo* - hydroxymethyl - 7' - *endo* - hydroxy derivatives prepared according to Examples 36—39, following the procedure of Example 40, the corresponding 6' - *exo* - formyl derivatives are prepared.

Example 42

A solution of 3.4 g of dimethyl (2 - oxoheptyl)phosphonate in 50 ml of 2 - dimethoxyethane is added dropwise to a suspension of 0.45 g of 80% NaH (mineral oil dispersion). After stirring for 1 hour, a solution of 2.7 g of 5 - (6' - *exo* - formyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester in 40 ml of 1,2 - dimethoxyethane is added. In 10 minutes this is diluted with 50 ml of a 30% aqueous solution of monobasic sodium phosphate. The organic phase is separated, the aqueous phase is re-extracted, and the combined organic extract is evaporated. Purification of the crude product on 50 g of silica gel (cyclohexane diethyl ether, 50:50) gives 1.1 g of 5 - [6' - *exo* - (3'' - oxo - oct - 1'' - *trans* - en - 1'' - yl) - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - *endo* - yl] - pentanoic acid methyl ester or 6βH - 6,9α epoxy - 11α - hydroxy - 15 - oxo - prost - *trans* - 13 - enoic acid methyl ester (designated compound 42/1) and 0.98 g of 5 - [6' - *exo* - (3'' - oxo - oct - 1'' - *trans* - en - 1'' - yl) - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0] - oct - 3' - *exo* - yl] - pentanoic acid methyl ester or 6αH - 6,9α - epoxy - 11α - hydroxy - 15 - oxoprost - *trans* - 17 - enoic acid

methyl ester (42/2), plus 0.9 g of a 1:1 mixture of these two isomers (3' - *exo* and 3' - *endo*, or 6 α H and 6 β H). This last mixture is separated into its two isomeric components by thin layer chromatography with diethyl ether. They show the following absorptions, respectively:

$\lambda_{\text{max}}^{\text{MeOH}}=230 \text{ m}\mu$, $\epsilon=13,070$; $\lambda_{\text{max}}^{\text{MeOH}}=228 \text{ m}\mu$, $\epsilon=12,200$.

N.M.R. (CDCl_3) 0.9 t 3H $\text{C}_{20}-\text{CH}_3$, 3.68 s 3H CO_2CH_3 , 6.16

d 1H vinylic proton at C_{14} ($J_{\text{H}_{14}-\text{H}_{15}}$ 16 Hz);

6.71 q 1H vinylic proton at C_{13} ($J_{\text{H}_{13}}$ 9 Hz).

By the same procedure, starting from the corresponding 5-H and 5-halo compounds, the following prostenoic acid derivatives are prepared:

42/3. 6 α H-6, 9 α - epoxy - 5 - oxoprost - *trans* - 13 - enoic acid methyl ester;
42/4. 6 α H-6, 9 α - epoxy - 5 - chloro - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;

42/5. 6 α H-6, 9 α - epoxy - 5 - bromo - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;

42/6. 6 α H-6, 9 α - epoxy - 5 - iodo - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;

42/7. 6 α H-6, 9 α - epoxy - 5 - chloro - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;

42/8. 6 α H-6, 9 α - epoxy - 5 - bromo - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester, N.M.R.=3.67 s 3H CO_2CH_3 ; 3.95 m 4H C_5 , C_9 , C_{11} protons and Hx/Hy proton at C_4 ; 4.3 m 1H 6 α H; 6.15 d 1H C_{14} proton; 6.63 q 1H C_{13} proton;

42/9. 6 α H-6, 9 α - epoxy - 5 - iodo - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester, N.M.R. 0.9 s 3H C_{20}CH_3 , 3.53 m 1H proton at C_5 , 3.6 s 3H CO_2CH_3 , 3.9 m H proton at C_4 , 4.1 m 2H proton at C_9 , C_{11} ; 4.4 m 1H 6 α H; 6.2 d 1H proton at C_{14} , 6.75 q 1H proton at C_{13} ;

42/10. 6 β H-6, 9 α - epoxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
42/11. 6 β H - 6, 9 α - epoxy - 5 - chloro - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;

42/12. 6 β H - 6, 9 α - epoxy - 5 - bromo - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;

42/13. 6 β H - 6, 9 α - epoxy - 5 - iodo - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;

42/14. 6 β H - 6, 9 α - epoxy - 5 - chloro - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;

42/15. 6 β H - 6, 9 α - epoxy - 5 - bromo - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester, N.M.R.: 3.65 s 3H CO_2CH_3 ; 4.00 m 3H proton at C_5 , C_9 , C_{11} , 4.6 m 1H 6 β H; 6.2 d 1H proton at C_{14} ; 6.64 q 1H proton at C_{13} ;

42/16. 6 β H - 6, 9 α - epoxy - 5 - iodo - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester; N.M.R. 3.66 s 3H CO_2CH_3 , 3.96 m 3H protons at C_9 , C_{11} and C_5 , 4.6 m 1H 6 β H, 6.21 d 1H proton at C_{14} , 6.75 q 1H proton at C_{13} .

Example 43

A solution of 2.16 g of dimethyl 2 - oxo - heptylphosphonate in 20 ml of benzene is added dropwise to a suspension of 292 mg of NaH (75% mineral oil dispersion) in 30 ml of benzene. After 30 minutes of stirring, a solution of 2.6 g of 4 - bromo - 4 - (7' - *exo* - formyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'yl) - butanoic acid methyl ester in 20 ml of benzene is added drop by drop. Stirring is continued for another 30 minutes, and 24 ml of a 30% aqueous solution of NaH_2PO_4 is added. The organic phase is separated, and the aqueous phase is re-extracted with benzene. The organic layers are combined and evaporated to dryness. The residue is purified on silica gel (50 g) with CH_2Cl_2 diethyl ether (120:40) as eluent to give 0.52 g of 4 - bromo - 4 - [7' - *exo* - (3'' - oxo - oct - 1'' - *trans* - enyl) - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3' - *endo* - yl] - butanoic acid methyl ester or 4 - bromo - 5 β H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester (43/1); and 1.45 g of 4 - bromo - 4 - [7' - *exo* - (3'' - oxo - oct - 1'' - *trans* - enyl) - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3' - *exo* - yl] - butanoic acid methyl ester or 4 - bromo - 5 α H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester (43/2). Methanolic solutions of these two compounds absorb in the UV at $\lambda_{\text{max}}^{\text{MeOH}}=230 \text{ m}\mu$, $\epsilon=10,640$, and $\lambda_{\text{max}}^{\text{MeOH}}=229 \text{ m}\mu$, $\epsilon=11,600$, respectively.

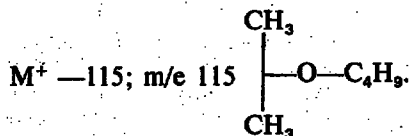
The same procedure, starting from the 4-H and 4-halo bicyclo derivatives, gives the following prostenoic acids:

- 43/3. 5 β H - 5,9 α - epoxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/4. 5 β H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/5. 4 - chloro - 5 β H - 5,9 α - epoxy - 15 - prost - *trans* - 13 - enoic acid methyl ester;
 43/6. 4 - chloro - 5 β H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/7. 4 - bromo - 5 β H - 5,9 α - epoxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/8. 4 - bromo - 5 β H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/9. 4 - iodo - 5 β H - 5,9 α - epoxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/10. 4 - iodo - 5 β H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/11. 5 α H - 5,9 α - epoxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/12. 5 α H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/13. 4 - chloro - 5 α H - 5,9 α - epoxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/14. 4 - chloro - 5 α H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/15. 4 - bromo - 5 α H - 5,9 α - epoxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/16. 4 - bromo - 5 α H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/17. 4 - iodo - 5 α H - 5,9 α - epoxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester;
 43/18. 4 - iodo - 5 α H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester.

Example 44

By the procedure of Example 42, the reaction of 620 mg of dimethyl (2 - oxo - 3 - methyl - 3 - butoxybutyl)phosphonate with 74 mg of NaH (75%) and 0.43 g of 5 - (6' - *exo* - formyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' ξ - yl) - pentanoic acid methyl ester in 1,2 - dimethoxyethane gives, after chromatography on silica gel (25 g) with 1:1 ethyl ether:hexane as eluent, 0.15 g of 6 α H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (44/1) (λ_{max} = 238 m μ , ϵ = 14,500) and 300 mg of the 6 β H-isomer (44/2) (λ_{max} = 237 m μ , ϵ = 12,280).

Mass spectrum: m/e 410 M⁺; m/e 392 M⁺ - H₂₀; m/e 379 m⁺ - OCH₃; m/e 295



The two isomers present similar spectra with minimal differences at level of secondary fragmentation.

Using the same procedure the 5-chloro, 5-bromo and 5 - iodo - 6 ξ H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl esters (44/3, 44/4 and 44/5) were prepared.

Example 45

By the procedure of Example 44, from 4 - (7' - *exo* - formyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3' ξ - yl) - butanoic acid methyl ester and the 4 - iodo bicyclic derivative the following are obtained:

- 45/1. 5 β H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester;

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- 45/2. 4 - iodo - 5 β H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester;
 45/3. 5 α H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester;
 5 45/4. 4 - iodo - 5 α H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester. 5

Example 46

10 To a suspension of 80% NaH in 10 ml of benzene is added to a solution of 375 mg of dimethyl (2 - oxo - 3,3 - dimethylheptyl) - phosphonate in 10 ml of benzene, followed 30 minutes later by a solution of 0.305 g of 5 - iodo - 5 - (6' - *exo* - formyl - 2' - oxabicyclo[3.3.0]oct - 3' ξ - yl) - pentanoic acid methyl ester. After stirring for 45 minutes, the mixture is diluted with 10% aqueous NaH₂PO₄. The organic phase is washed until neutral, dried and concentrated to small volume. Adsorption on silica gel and elution with cyclohexane:diethyl ether (90:10) give 0.12 g of 5 - iodo - 6,9 α - epoxy - 15 - oxo - 16 - dimethylprost - *trans* - 13 - enoic acid methyl ester (46/1) and 0.095 g of 5 - iodo - 6 α H - 6,9 α - epoxy - 15 - oxo - 16,16 - dimethylpost - *trans* - 13 - enoic acid methyl ester (46/2). 15

Example 47

20 By substituting in the procedure of Example 46 the formyl derivatives prepared according to Example 34, the following 16,16 - dimethyl derivatives are prepared: 20

- 47/1. 6 β H - 6,9 α - epoxy - 15 - oxo - 16,16 - dimethyl - prost - *trans* - 13 - enoic acid methyl ester;
 25 47/2. 6 β H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethyl - prost - *trans* - 13 - enoic acid methyl ester; 25
 47/3. 5 β H - 5,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 47/4. 5 β H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 30 47/5. 5 - chloro - 6 β H - 6,9 α - epoxy - 15 - oxo - 16,16 - dimethyl - prost - *trans* - 13 - enoic acid methyl ester; 30
 47/6. 5 - chloro - 6 β H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 35 47/7. 4 - chloro - 5 β H - 5,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester; 35
 47/8. 4 - chloro - 5 β H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 47/9. 5 - bromo - 6 β H - 6,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 40 47/10. 5 - bromo - 6 β H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester; 40
 47/11. 4 - bromo - 5 β H - 5,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 45 47/12. 4 - bromo - 5 β H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester; 45
 47/13. 5 - iodo - 6 β H - 6,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 47/14. 5 - iodo - 6 β H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 50 47/15. 4 - iodo - 5 β H - 5,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester; 50
 47/16. 4 - iodo - 5 β H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester.
 47/17. 6 α H - 6,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 55 47/18. 6 α H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethyl - prost - *trans* - 13 - enoic acid methyl ester; 55
 47/19. 5 α H - 5,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 60 47/20. 5 α H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethyl - prost - *trans* - 13 - enoic acid methyl ester; 60

- 47/21. 5 - chloro - 6 α H - 6,9 α - epoxy - 15 - oxo - 16,16 - dimethyl - prost - *trans* - 13 - enoic acid methyl ester;
 47/22. 5 - chloro - 6 α H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 5 47/23. 4 - chloro - 5 α H - 5,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 47/24. 4 - chloro - 5 α H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 10 47/25. 5 - bromo - 6 α H - 6,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 47/26. 5 - bromo - 6 α H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 47/27. 4 - bromo - 5 α H - 5,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 15 47/28. 4 - bromo - 5 α H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 47/29. 5 - iodo - 6 α H - 6,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 20 47/30. 5 - iodo - 6 α H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 47/31. 4 - iodo - 5 α H - 5,9 α - epoxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;
 47/32. 4 - iodo - 5 α H - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16,16 - dimethylprost - *trans* - 13 - enoic acid methyl ester;

Example 48

To a suspension of 178 mg of NaH (75% mineral oil dispersion) in 15 ml of benzene is added dropwise a solution of 1.55 g of dimethyl[2 - oxo - 3(S,R) - fluoro - 4 - cyclohexylbutyl] - phosphonate in 10 ml of anhydrous benzene. After 30 minutes of stirring, a solution of 1 g of 5 - (6' - *exo* - formyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester is added and stirring is continued for another hour. The mixture is neutralized with 30% aqueous NaH₂PO₄, and the organic phase is separated, concentrated and adsorbed on silica gel. Elution with CH₂Cl₂-Et₂O (90:10) gives 0.62 g of 6 α H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16(S,R) - fluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (48/1) ($\lambda_{\text{max}}^{\text{MeOH}}=238 \text{ m}\mu$, $\epsilon=12,765$) and 0.31 g of the 6 β H isomer (48/2) ($\lambda_{\text{max}}^{\text{MeOH}}=238 \text{ m}\mu$, $\epsilon=9,870$).

The N.M.R. data for the former compound are the following (CDCl₃) p.p.m. 3.64 s 3H CO₂CH₃, 3.8 m 1H C₉ proton, 4.03 q 1H proton at C₁₁, 4.3 m 1H 6 α H, 5.00 and 5.55 t, t, 1H, 1H proton at C₁₈, J_{HF} 55 Hz, 6.54 q 1H proton at C₁₄, 6.9 q 1H proton at C₁₃, J_{H14-H12} 3.5 Hz, J_{H13-H12} 7.5 Hz, J_{H13-H14} 15.5 Hz.

Treating this compound with pyridine and acetic anhydride it is converted into the 6 α H - 11 α - acetoxy derivative (48/3), for which the N.M.R. data are: (CHCl₃) p.p.m. 2.02 s 3H OCOCH₃, 3.64 s 3H CO₂CH₃, 3.8 proton at C₉, 4.25 m 1H 6 α H, 4.66, 5.22 t, t, 1H, 1H proton at C₁₈, 4.97 q 1H proton at C₁₁, 6.51 proton at C₁₄, 6.90 proton at C₁₃.

For the diastereoisomeric hydroxy ketones the mass spectrum shows the following masses:

M⁺ 424 m/e and then M⁺-H₂O, M⁺-HF, M⁺-CH₃OH/CH₂O, M⁺-CH₂=CHOH (basis ion) M⁺-115 M⁺-44-59 and M⁺-(CHF-CH₂-C₆H₁₁).

In the mass spectrum of the *exo* - diastereoisomer the following masses are predominant: M⁺-CH₃OH and M⁺-44-28; in that of *endo* - diastereoisomer the predominant ones are M⁺-CH₃O and M⁺-44-18.

From the 5 - bromo derivative, 5 - bromo - 6 β H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16(S,R) - fluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (48/4) is prepared.

Example 49

Substituting in the procedure of Example 48 a phosphonate chosen from dimethyl (2 - oxo - 4 - cyclohexylbutyl)phosphonate and dimethyl (2 - oxo - 4 - phenylbutyl)phosphonate, the following were prepared:

6 β H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (49/1), 6 β H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 17 - phenyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (49/2) and their 6 α H isomers (49/3 and 49/4 resp.).

Example 50

To a suspension of 178 mg of NaH (75% mineral oil dispersion) in anhydrous tetrahydrofuran at 0°C is added dropwise with stirring a solution of 1.63 g of dimethyl 2 - oxo - 3 - (*m* - chlorophenoxy) - propyl phosphonate in 10 ml of anhydrous THF. After 30 minutes of stirring, a solution of 1 g of 5 - (6' - *exo* - formyl - 7' - *endo* - 2' - oxabicyclo[3.3.0]oct - 3' - yl) - pentanoic acid methyl ester is added and stirring is continued for another hour. The mixture is acidified with aqueous NaH₂PO₄, the organic phase is separated, and the aqueous phase is re-extracted with benzene. From the combined organic extract, after chromatography on silic gel with CH₂Cl₂:Et₂O (95:5) as eluent, one obtains 0.43 g of 6 α H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16 - *m* - chlorophenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid methyl ester (50/1) ($\lambda_{\text{max}}^{\text{MeOH}}=227$ m μ , $\epsilon=16,800$) and 0.11 g of the 6 β H isomer (50/2) ($\lambda_{\text{max}}=224$ m μ , $\epsilon=16,900$).

Both the diastereoisomers show the mass peak *m/e* 436 in according to C₂₂H₂₉ClO₆. This ion is involved in the following fragmentation: M⁺—H₂O, M⁺—OCH₂/CH₂OH, M⁺—44, M⁺—(O—C₆H₄Cl), M⁺—H₂O—(O—C₆H₄Cl) and M⁺—(CH₂)₄—CO₂CH₃, so furthermore confirming the proposed structure.

The following differences are between the two diastereoisomers: the *exo*(6 α H) isomer shows a peak at M⁺—32 and a little intense peak at M⁺—44 on the other hand the *endo* (6 β H) isomer shows a peak at M⁺—31 and an intense peak at M⁺—44.

Example 51

The substitution of a phosphonate chosen from dimethyl 2 - oxo - 3 - (*m* - trifluoromethylphenoxy) - propylphosphonate and dimethyl 2 - oxo - 3 - (*p* - fluorophenoxy) - propylphosphonate in the procedure of Example 50 leads to the following compounds, respectively:

6 β H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16 - *m* - trifluoromethyl - phenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid methyl ester (51/1), 6 β H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16 - *p* - fluorophenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid methyl ester (51/2), and their 6 α H isomers (51/3 and 51/4 resp.).

The mass spectra of all the compounds agree with the proposed structure for example showing the mass peak M⁺—115, an interesting difference between the *endo*- and *exo*-trifluoromethyl analogous is that the mass peaks M⁺—CH₂OH and M⁺—CF₃—C₆H₄—OH are in the *exo*-isomer and the mass peak M⁺—CH₂O and M⁺—CF₃—C₆H₄—O are in the *endo*-isomer.

Example 52

The substitution of dimethyl (2 - oxo - 3(*S*) - methylheptyl)phosphonate for the phosphonate in the procedure of Example 48 gave 6 β H - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16(*S*) - methylprost - *trans* - 13 - enoic acid methyl ester (52/1) and its 6 α H isomer (52/2). To a solution of 2.2 g of the 6 β H isomer in 2.6 ml of pyridine, cooled to 0°C, is added 1.05 ml of acetic anhydride. The solution is held at 0°C overnight and then added to an excess of cold 0.05 N sulfuric acid. Extraction with diethyl ether and evaporation to dryness give 2.3 g of 6 β H - 6,9 α - epoxy - 11 α - acetoxo - 15 - oxo - 16(*S*) - methylprost - *trans* - 13 - enoic acid methyl ester (52/3) ($\lambda_{\text{max}}^{\text{MeOH}}=229$ m μ , $\epsilon=12,050$).

875 mg of bromine in glacial acetic acid is added dropwise to a solution of the latter compound (52/3) in 10 ml of glacial acetic acid, until a light orange color appears. 1.52 g of anhydrous potassium carbonate is then added and the resulting mixture is held at 80°C for 4—5 hours to complete the precipitation of potassium bromide. Excess acetic acid is removed under vacuum, water is added, and the pH is brought to pH 6.8 with alkali metal hydroxide. This is then extracted with diethyl ether and the organic phase is reduced in volume.

Adsorption on silica gel and elution with methylene chloride:ethyl ether (70:30) gives 2.01 g of 6 β H - 6,9 α - epoxy - 11 α - acetoxo - 14 - bromo - 15 - oxo - 16(*S*) - methylprost - *trans* - 13 - enoic acid methyl ester (52/4), $\lambda_{\text{max}}^{\text{MeOH}}=249$ m μ , $\epsilon=11,450$.

The 14 - bromo - 6 α H isomer (52/5) is similarly prepared.

Example 53

A solution of 2.06 g of dimethyl (2 - oxo - 3(*S*) - methylheptyl)phosphonate in 20 ml of 1,2 - dimethoxyethane is added dropwise to a suspension of 0.265 g of NaH (80% mineral oil dispersion) in DME (10 ml). After stirring for 30 minutes, 1.6 g of *N* - bromosuccinimide is added and vigorous stirring is continued for 10

minutes. 1.35 g of 5 - (6' - *exo* - formyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester in 5 ml of 1,2 - dimethoxyethane is then added. The mixture is stirred for 1 hour and 20 ml of 30% NaH₂PO₄ is added. After the usual work-up, crude 14 - bromoenone is obtained. Separation on silica gel with methylene chloride:ethyl ether (85:15) gives 0.9 g of 6βH - 6,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 16(S) - methylprost - *trans* - 13 - enoic acid methyl ester (53/1) and 0.92 g of the 6αH isomer (53/2). Upon treatment with 0.4 ml of pyridine and 0.2 ml of acetic anhydride, 0.2 g of the 6βH isomer gives 0.205 g of the 11 - acetoxo derivative (52/4), identical in all respects with that made by the procedure of Example 52.

Example 54

A solution of 0.43 g of dimethyl (2 - oxo - octyl)phosphonate in 10 ml of benzene is added dropwise to a suspension of 54 mg of NaH (80% mineral oil dispersion) in 5 ml of benzene. After 1 hour, when the evolution of H₂ has ceased, 0.32 g of N - bromo - succinimide is added all at once. To the carbanion thus prepared, of dimethyl (1 - bromo - 2 - oxooctyl)phosphonate, is added a solution of 270 mg of 5 - (6' - *exo* - formyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester in 8 ml of benzene. After 30 minutes, the reaction is quenched by the addition of 20 ml of a 10% solution of NaH₂PO₄. The organic phase, after being washed until neutral, gives 0.31 g of 6ξH - 6,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 20 - methylprost - *trans* - 13 - enoic acid methyl ester; this is then separated into the 6αH and 6βH isomers (54/1 and 54/2 resp.).

Example 55

Upon substitution of the dimethyl (2 - oxooctyl)phosphonate in the procedure of Example 54 with dimethyl (2 - oxo - 4 - cyclohexylbutyl)phosphonate and dimethyl (2 - oxo - 4 - phenyl - butyl)phosphonate, the following compounds were prepared:

6βH - 6,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (55/1)
6βH - 6,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 17 - phenyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (55/2).

Example 56

By substituting the formyl derivatives in Examples 53, 54 and 55 by 5 - iodo - 5 - (6' - *exo* - formyl - 7' - *endo* - hydroxy - 2' - oxabicyclo[3.3.0]oct - 3'ξ - yl) - pentanoic acid methyl ester, 4 - iodo - 4 - (7' - *exo* - formyl - 8' - *endo* - hydroxy - 2' - oxabicyclo[3.4.0]non - 3'ξ - yl) - butanoic acid methyl ester, and the corresponding 4-H derivative, the following compounds were prepared:

56/1. 5 - iodo - 6βH - 6,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 16(S) - methylprost - *trans* - 13 - enoic acid methyl ester;
56/2. 4 - iodo - 5βH - 5,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 16(S) - methylprost - *trans* - 13 - enoic acid methyl ester;
56/3. 5βH,5,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 16(S) - methylprost - *trans* - 13 - enoic acid methyl ester;
56/4. 5 - iodo - 6βH - 6,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 20 - methylprost - *trans* - 13 - enoic acid methyl ester;
56/5. 4 - iodo - 5βH - 5,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 20 - methylprost - *trans* - 13 - enoic acid methyl ester;
56/6. 5βH - 5,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 20 - methylprost - *trans* - 13 - enoic acid methyl ester;
56/7. 5 - iodo - 6βH - 6,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester;
56/8. 5βH - 5,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester;
56/9. 5 - iodo - 6βH - 6,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 17 - phenyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester;
56/10. 5βH - 5,9α - epoxy - 11α - hydroxy - 14 - bromo - 15 - oxo - 17 - phenyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester.

Example 57

A solution of 0.61 g of (2 - oxooctyl) - triphenylphosphonium bromide in 6 ml

of DMSO is added to a solution of 0.15 g of potassium *t*-butoxide in 3 ml of DMSO while keeping the reaction temperature at 16–19°C. 0.27 g of 5-(6'-*exo*-formyl-7'-*endo*-hydroxy-2'-oxabicyclo[3.3.0]oct-3'-yl)-pentanoic acid methyl ester in 8 ml of anhydrous tetrahydrofuran is then added. After 30 minutes of stirring, an equal volume of water is added and the mixture is extracted with diethyl ether. The combined organic extract is washed until neutral and the solvent is evaporated. Chromatography on silica gel (cyclohexane:diethyl ether (40:60) gives 0.21 g of 6 α H-6,9 α -epoxy-11 α -hydroxy-15-oxo-20-methylprost-*trans*-13-enoic acid methyl ester. Subsequent preparative thin layer chromatography (SiO₂-Et₂O) allows separation of the 6 α H and 6 β H isomers (57/1 and 57/2).

Example 58

A solution of d,l-6 α H-6,9 α -epoxy-11 α -hydroxy-15-oxo-prost-*trans*-13-enoic acid methyl ester (*exo*-isomer at greatest R_f), (0.9 g), in dry diethyl ether (30 ml) is dripped on to a stirred 0.1 M solution of Zn(BH₄)₂ in dry diethyl ether (30 ml), over 15 minutes. After 2 hours, the excess reagent is decomposed by cautious addition of saturated NaCl solution and aqueous 2N sulfuric acid. The organic layer is separated, washed to neutral and evaporated to dryness affording a residue which is adsorbed on silica gel and eluted with diethyl ether to yield 0.38 g of d,l-6 α H-6,9 α -epoxy-11 α -15(R)-dihydroxyprost-*trans*-13-enoic acid methyl ester, as an oil, and 0.42 g of d,l-6 α H-6,9 α -epoxy-11 α ,15(S)-dihydroxyprost-*trans*-13-enoic acid ester, m.p. 69–71°C (mass spectrum m/e 350 M⁺—18, 319 M⁺—18—CH₃O; 318 M⁺—18—CH₃OH). A solution in methanol (4 ml) of this ester is treated with 60 mg of lithium hydroxide and water (0.8 ml) for 8 hours at room temperature. The methanol is removed in vacuum, the residue is diluted with water and extracted with diethyl ether to remove neutral impurities. The alkaline phase is treated with aqueous saturated NaH₂PO₄ solution until to pH 5 and then extracted with diethyl ether. The later organic phases are collected to yield after evaporation of the solvents the free acid d,l-6 α H-6,9 α -epoxy-11 α ,15(S)-dihydroxyprost-*trans*-13-enoic acid, m.p. 105–106°C. The 15(R)-hydroxy compound is a non-crystallizable oil and is designated compound 58/1. In the same way using *nat*-oxo compound in the reduction reaction with Zn(BH₄)₂ we obtained besides the 15-*epi* alcohol, the *nat*-6 α H-6,9 α -epoxy-11 α -15(S)-dihydroxyprost-*trans*-13-enoic acid methyl ester, m.p. 71–72°C [α]_D²⁰=+10.2°, [α]₃₆₅²⁰=+32.2° (CHCl₃) and after saponification the free acid m.p. 101–102°C [α]_D²⁰=+6.34° [α]₃₆₅²⁰=+33.2° (CHCl₃).

Starting from the *endo*-diastereoisomers (more polar compounds), the following esters were obtained:

6 β H-6,9 α -epoxy-11 α ,15(R)-dihydroxyprost-*trans*-13-enoic acid methyl ester (d, l, *nat*-, *ent*- oils) (58/2);

6 β H-6,9 α -epoxy-11 α ,15(S)-dihydroxyprost-*trans*-13-enoic acid methyl ester (d, l, *nat*-, [α]_D²⁰=+24.5°, [α]₃₆₅²⁰=+52.9° (CHCl₃) oil; *ent*- [α]_D²⁰=–22°, oil), and after saponification the following free acids:

6 β H-6,9 α -epoxy-11 α ,15(R)-dihydroxyprost-*trans*-13-enoic acid (d, l, *nat*-, *ent*- oils) (58/3);

6 β H-6,9 α -epoxy-11 α ,15(S)-dihydroxyprost-*trans*-13-enoic acid (d, l oil, *nat*-, m.p. 78–80°C [α]_D²⁰=+32.5°, [α]₃₆₅²⁰=+11.6° (EtOH), *ent*- m.p. 78–79°C, [α]_D²⁰=–31° (EtOH).

The 15(S) hydroxy compounds in this Example are outside the scope of the present invention.

Example 59

With the temperature of the reaction mixture kept at around –5° to –8°C, a solution of 159 mg of NaBH₄ in 7 ml of propan-2-ol, is gradually added to a solution of 0.332 g of anhydrous CaCl₂ in propan-2-ol (7 ml); then, under stirring, a solution of 0.38 g of 6 α H-6,9 α -epoxy-11 α -hydroxy-15-oxo-16(S,R)-fluoro-17-cyclohexyl-18,19,20-trinorprost-*trans*-13-enoic acid methyl ester (48/1) in 3 ml of propan-2-ol is added to the above prepared Ca(BH₄)₂ in a period of 40 minutes. The reaction mixture is kept under stirring at a temperature ranging at $\pm$ 5°C, then the excess reagent is destroyed by addition of 5 ml of acetone and 2 ml of water. The solvent is evaporated under vacuum and the residue is partitioned between water, 0.1N H₂SO₄ and ethyl acetate. The organic extracts are collected, washed until neutral and after evaporation of solvent the residue chromatographed on silica gel (30 g) using CH₂Cl₂-diethyl ether 70:30 as eluent. The eluate yields 0.21 g of 6 α H-6,9 α -epoxy-11 α ,15(R)-dihydroxy-

16(*S,R* - fluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (59/1), and 0.14 g of the 15(*S*) - epimer (59/2), m.p. 83°C—84°C (from diethyl ether). In the same way, reduction of the 6 β *H* - 6,9 α - epoxy - 11 α ,15(*R*) - dihydroxy - 16(*S,r*) - fluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (59/3) m.p. 63—64°C (from diisopropyl ether), and 60 mg of 15(*S*) - alcohol (59/4).

Example 60

A solution of 0.15 g of 6 α *H* - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (44/1) in methanol (5 ml) is cooled at -5+—10°C and reduced by addition of a solution of NaBH₄ (30 mg) in water (0.5 ml). The reaction mixture is neutralized by addition of 15% aqueous NaH₂PO₄ solution after 15 minutes and then evaporated in vacuum. The aqueous residue is extracted with ethyl ether to yield a crude mixture of epimeric 15(*R*),15(*S*) - alcohols. Chromatographic separation on silica gel (CH₂Cl₂ - diethyl ether 70:30 as eluent) affords respectively 6 α *H* - 6,9 α - epoxy - 11 α ,15(*R*) - dihydroxy - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (compound 60/1; 45 mg) and 15(*S*) - hydroxy - epimer (compound 60/2; 62 mg).

Example 61

By reduction of 5 α *H* - 5,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester, under the same conditions as in the procedure of Example 60 followed by chromatographic separation of the epimeric alcohols (300 mg) on silica gel (12 g) with methylene chloride-diethyl ether 75:25 eluent, we respectively obtained 100 mg of 5 α *H* - 5,9 α - epoxy - 11 α ,15(*R*) - dihydroxy - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (61/1), and 110 mg of 15(*S*) - epimer (61/2). These are then saponified to yield the corresponding free acids, designated 61/3 and 61/4.

Example 62

Dropwise, to a stirred 0.12 M solution of zinc borohydride in diethyl ether (8 ml) a solution of 0.135 g of 5 - bromo - 6 α *H* - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - prost - *trans* - 13 - enoic acid methyl ester in 2 ml of anhydrous Et₂O is added. The mixture is stirred for 2 hours and the excess reagent is decomposed with water—2N H₂SO₄. The organic phase is separated, washed to neutral and evaporated to dryness. After TLC on silica gel with ethyl ether-ethyl acetate 90:10, 38 mg of 5 - bromo - 6 α *H* - 6,9 α - epoxy - 11 α ,15(*R*) - dihydroxyprost - *trans* - 13 - enoic acid methyl ester (62/1) and 46 mg of 15(*S*) - epimer (62/2) were obtained.

Example 63

Starting from 5,14 - dibromo - 6 α *H* - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester (0.2 g) and using a mixture of CH₂Cl₂ - diethyl ether 60:40, during the chromatographic separation on silica gel, we obtained 0.056 g of 5,14 - dibromo - 6 α *H* - 6,9 α - epoxy - 11 α ,15(*R*) - dihydroxyprost - *trans* - 13 - enoic acid methyl ester (63/1) and 0.098 g of 15(*S*) - isomer (63/2). A solution of this product in methanol is then hydrolyzed with aqueous LiOH to yield 72 mg of 5,14 - dibromo - 6 α *H* - 6,9 α - epoxy - 11 α ,15(*S*) - dihydroxyprost - *trans* - 13 - enoic acid (63/3).

Example 64

Using, in the procedure of Example 60, isopropanol as solvent and NaBH₄ (45 mg), the reduction of 6 β *H* - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxo - 16 - *m* - trifluoromethyl - phenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid methyl ester (0.47 g) yields 0.20 g of 6 β *H* - 9 α - epoxy - 11 α ,15(*s*) - dihydroxy - 16 - *m* - trifluoromethyl - phenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid methyl ester (64/1), [α]_D²⁰ = +33.3° (MeOH) and 0.18 g of 15(*R*) - epimer (64/2). The 6 α *H* - 15(*S*) - alcohol epimer (64/3) is an oil with [α]_D²⁰ = +12° (MeOH).

Example 65

A solution in dry diethyl ether (20 ml) of *trans* - 16(*S*) - methyl - 6 α *H* - 6,9 α - epoxy - 11 α - hydroxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester (0.002 M, 0.72 g) is added to a stirred ethereal solution of zinc borohydride (0.01 M, 100 ml). The excess reagent is destroyed, after 30—45 minutes, by addition of 2N-

5 sulphuric acid in NaCl saturated aqueous solution. The organic phase is washed until neutral and evaporated to dryness. The residue is chromatographed on silica gel (25 g) using methylene-chloride:diethyl ether (80:20) as eluent, affording (7.5.10⁻⁴ M, 0.27 g) of the 15(R) - hydroxy - isomer (65/1) and (1.1.10⁻⁴ M; 0.38 g) of the 15(S) - alcohol:6 α H,6,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxyprost - *trans* - 13 - enoic acid methyl ester (65/2), using this procedure, the methyl esters of the following acids were obtained:

- | | | |
|----|--|----|
| 10 | 65/3. 6 β H - 6,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxy - prost - <i>trans</i> - 13 - enoic acid; | 10 |
| 15 | 65/4. 6 β H - 6,9 α ,epoxy - 16(R) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | 15 |
| 20 | 65/5. 6 α H - 6,9 α - epoxy - 20 - methyl - 11 α ,15(S) - dihydroxy - prost - <i>trans</i> - 13 - enoic acid, m.p. 57—59°C [α] _D ²⁰ = +14°, [α] ₃₆₅ ²⁰ = +47° (CHCl ₃); | 20 |
| 25 | 65/6. 6 β H - 6,9 α - epoxy - 20 - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid, m.p. 38—39°C, [α] _D ²⁰ = +21.7°, [α] ₃₆₅ ²⁰ = +77° (CHCl ₃); | 25 |
| 30 | 65/7. 5 - bromo - 6 β H - 6,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | 30 |
| 35 | 65/8. 5 - bromo - 6 β H - 6,9 α - epoxy - 16(R) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | 35 |
| 40 | 65/9. 5 - bromo - 6 β H - 6,9 α - epoxy - 16,16 - dimethyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | 40 |
| 45 | 65/10. 5 - bromo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 20 - methylprost - <i>trans</i> - 13 - enoic acid, [α] _D ²⁰ = +38°; | 45 |
| 50 | 65/11. 5 - iodo - 6 β H - 6,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxyprost - 13 - enoic acid; | 50 |
| 55 | 65/12. 5 - iodo - 6 β H - 6,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | 55 |
| 60 | 65/13. 5 - iodo - 6 β H - 6,9 α - epoxy - 16(R) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | 60 |
| | 65/14. 5 - iodo - 6 β H - 6,9 α - epoxy - 16,16 - dimethyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/15. 5 - iodo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 20 - methylprost - <i>trans</i> - 13 - enoic acid, [α] _D ²⁰ = +23°, [α] ₃₆₅ ²⁰ = +78° (CHCl ₃); | |
| | 65/16. 5 - chloro - 6 β H - 6,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/17. 5 β H - 5,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/18. 5 β H - 5,9 α - epoxy - 16,16 - dimethyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/19. 4 - bromo - 5 β H - 5,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxy - prost - <i>trans</i> - 13 - enoic acid; | |
| | 65/20. 4 - bromo - 5 β H - 5,9 α - epoxy - 16(R) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/21. 4 - bromo - 5 β H - 5,9 α - epoxy - 16,16 - dimethyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/22. 4 - iodo - 5 β H - 5,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/23. 4 - chloro - 5 β H - 5,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/24. 6 β H - 6,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxy - 14 - bromoprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/25. 6 β H - 6,9 α - epoxy - 16(R) - methyl - 11 α ,15(S) - dihydroxy - 14 - bromoprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/26. 6 β H - 6,9 α - epoxy - 20 - methyl - 11 α ,15(S) - dihydroxy - 14 - bromoprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/27. 6 β H - 6,9 α - epoxy - 16(S,R),20 - dimethyl - 11 α ,15(S) - dihydroxy - 14 - bromoprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/28. 5 β H - 5,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxy - 14 - bromoprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/29. 5 β H - 5,9 α - epoxy - 16(R) - methyl - 11 α ,15(S) - dihydroxy - 14 - bromoprost - <i>trans</i> - 13 - enoic acid; | |
| | 65/30. 5 β H - 5,9 α - epoxy - 20 - methyl - 11 α ,15(S) - dihydroxy - 14 - bromoprost - <i>trans</i> - 13 - enoic acid; | |

	65/31. 5 β H - 5,9 α - epoxy - 16(S,R),20 - dimethyl - 11 α ,15(S) - dihydroxy - 14 - bromoprost - <i>trans</i> - 13 - enoic acid;	
	65/32. 5,14 - dibromo - 6 β H - 6,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid;	
5	65/33. 5,14 - dibromo - 6 β H - 6,9 α - epoxy - 16(R) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid;	5
	65/34. 5,14 - dibromo - 6 β H - 6,9 α - epoxy - 20 - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid;	
10	65/35. 5,14 - dibromo - 6 β H - 6,9 α - 16(S,R),20 - dimethyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid;	10
	65/36. 4,14 - dibromo - 5 β H - 5,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid;	
	65/37. 4,14 - dibromo - 5 β H - 5,9 α - epoxy - 16(R) - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid;	
15	65/38. 4,14 - dibromo - 5 β H - 5,9 α - epoxy - 20 - methyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid;	15
	65/39. 4,14 - dibromo - 5 β H - 5,9 α - epoxy - 16(S,R),20 - dimethyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid;	
20	65/40. 6 β H - 6,9 α - epoxy - 16,16 - dimethyl - 11 α ,15(S) - dihydroxyprost - <i>trans</i> - 13 - enoic acid;	20

together with their 15(R) - epimeric alcohols (65/41 to 65/78 respectively), when the corresponding 15 - oxo compounds are submitted to reduction followed by chromatographic separation. Starting from 6 α H and 5 α H diastereoisomeric 15 - oxo compounds we prepare the corresponding 15(S) alcohols (compounds 65/79 to 65/116) and 15(R) - alcohols (compounds 65/117 to 65/154). All these methyl esters except 65/40 and its 6 α H, diastereoisomer 65/116 are then saponified to yield the corresponding free acids. The acids of esters 65/3 to 65/39 are designated 65/155 to 65/191. The acids of the 15(R) - hydroxy methyl esters 65/41 to 65/78 are designated 65/192 to 65/229. The acids of the 15(S) - hydroxy methyl ester α H diastereoisomers 65/79 to 65/115 are designated 65/230 to 65/266. Those of the 15(R) - hydroxy methyl ester α H - diastereoisomers are designated 65/267 to 65/304. The acids of the esters (65/1) and (65/2) are designated 65/305 and 65/306.

Example 66

A solution of 5 - iodo - 6 β H - 6,9 α - epoxy - 16(R) - methyl - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester (0.32 g) in diethyl ether (8 ml) is added to a stirred solution of zinc borohydride in diethyl ester (25 ml). After 30 minutes, the excess reagent was destroyed by addition of a saturated solution of NaCl and normal H₂SO₄. After the usual work-up, the organic phase is separated and the crude residue is chromatographed on SiO₂ (eluent (CH₂Cl₂ - diethyl ether) to yield 0.16 g of 5 - iodo - 6 β H - 6,9 α - epoxy - 16(R) - methyl - 15(S) - hydroxyprost - *trans* - 13 - enoic acid methyl ester (66/1) and 0.095 g of 15(R) - hydroxy epimer (66/2). Using this procedure the methyl esters of the following acids were obtained:

45	66/3. 6 β H - 6,9 α - epoxy - 15(S) - hydroxy - 16(S) - methylprost - <i>trans</i> - 13 - enoic acid;	45
	66/4. 6 β H - 6,9 α - epoxy - 15(S) - hydroxy - 16(R) - methylprost - <i>trans</i> - 13 - enoic acid;	
	66/5. 6 β H - 6,9 α - epoxy - 15(S) - hydroxy - 16,16 - dimethylprost - <i>trans</i> - 13 - enoic acid;	
50	66/6. 5 β H - 5,9 α - epoxy - 15(S) - hydroxy - 16(S) - methylprost - <i>trans</i> - 13 - enoic acid;	50
	66/7. 5 β H - 5,9 α - epoxy - 15(S) - hydroxy - 16(R) - methylprost - <i>trans</i> - 13 - enoic acid;	
55	66/8. 5 β H - 5,9 α - epoxy - 15(S) - hydroxy - 16,16 - dimethylprost - <i>trans</i> - 13 - enoic acid;	55
	66/9. 5 - bromo - 6 β H - 6,9 α - 15(S) - hydroxy - 16(S) - methylprost - <i>trans</i> - 13 - enoic acid;	
	66/10. 5 - bromo - 6 β H - 6,9 α - epoxy - 15(S) - hydroxy - 16(R) - methylprost - <i>trans</i> - 13 - enoic acid;	
60	66/11. 5 - bromo - 6 β H - 6,9 α - epoxy - 15(S) - hydroxy - 16,16 - dimethylprost - <i>trans</i> - 13 - enoic acid	60

66/12. 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxy - 20 - methylprost - *trans* - 13 - enoic acid;

66/13. 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxy - 16(*S*), 20 - dimethylprost - *trans* - 13 - enoic acid;

together with their $15(R)$ - epimeric alcohols (66/14 to 66/24), when the corresponding 15 - oxo compounds are submitted to reduction followed by chromatographic separation.

Starting from $6\alpha H$ and $5\alpha H$ diastereoisomeric 15-oxo compounds we prepare the corresponding $15(S)$ - and (*R*)-alcohols. The $6\alpha H$ - diastereoisomers of the $15(S)$ alcohol-66/1 and $15(R)$ -alcohol 66/2 are designated 66/25 and 66/26. The αH - diastereoisomers of the $15(S)$ -alcohols 66/3 to 66/13 are designated compounds 66/27 to 66/37. The αH diastereoisomers of the $15(R)$ alcohols 66/14 to 66/24 are designated 66/38 to 66/48.

Example 67

The methyl esters of the following $15(S)$ - hydroxy - 5 or $6,9\alpha$ - epoxy - prostenoic acids together with their $15(R)$ - epimeric alcohols are obtained after reduction of the corresponding 15-oxo compounds using one of the procedures described in Examples 58 to 66:

67/1. 14 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - *trans* - 13 - prostenoic acid;

67/2. 14 - chloro - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - *trans* - 13 - prostenoic acid;

67/3. 5 - iodo - 14 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 20 - methylprost - *trans* - 13 - enoic acid;

67/4. 14 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16(*S,R*) - fluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/5. 5,14 - dibromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16(*S,R*) - fluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/6. 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16(*S,R*) - fluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/7. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16,16 - difluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/8. 14 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16,16 - difluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/9. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16(*S,R*) - fluoro - 17 - phenyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/10. 14 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16(*S,R*) - fluoro - 17 - phenyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/11. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 17 - cyclopentyl - 18,19,20 - trinorprost - *trans* - enoic acid;

67/12. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/13. 14 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/14. 5,14 - dibromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/15. 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/16. 5 - chloro - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/17. 5 - iodo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/18. 5 - iodo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16 - methyl - 16 - propoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/19. 5 - iodo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16 - methyl - 16 - amyloxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/20. 5 - iodo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 17 - cycloheptyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid;

67/21. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16 - *p* - fluoro - phenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid;

67/22. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid;

67/23. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 16 - cyclohexyloxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid;

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	67/24.	6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - m - chlorophenoxy - 17,18,19,20 - tetranorprost - <i>trans</i> - 13 - enoic acid;	
	67/25.	14 - bromo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - p - fluorophenoxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	
5	67/26.	14 - bromo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	5
	67/27.	14 - bromo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - m - chlorophenoxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	
10	67/28.	14 - bromo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - m - trifluoromethylphenoxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	10
	67/29.	5 - iodo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - p - fluorophenoxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	
15	67/30.	5 - iodo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	15
	67/31.	5 - iodo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - cyclohexyloxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	
	67/32.	5 - iodo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - m - chlorophenoxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	
20	67/33.	5 - iodo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - m - trifluoromethylphenoxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	20
	67/34.	5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - <i>trans</i> - 13 - prostenoic acid;	
25	67/35.	14 - bromo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - <i>trans</i> - 13 - prostenoic acid;	25
	67/36.	14 - chloro - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - <i>trans</i> - 13 - prostenoic acid;	
	67/37.	4,14 - dibromo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - <i>trans</i> - 13 - prostenoic acid;	
30	67/38.	5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 20 - methyl - <i>trans</i> - 13 - prostenoic acid;	30
	67/39.	4 - iodo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 20 - methyl - <i>trans</i> - 13 - prostenoic acid;	
35	67/40.	4 - iodo - 14 - bromo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 20 - methyl - <i>trans</i> - 13 - prostenoic acid;	35
	67/41.	14 - bromo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S,R) - fluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - <i>trans</i> - 13 - enoic acid;	
40	67/42.	4,14 - dibromo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S,R) - fluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - <i>trans</i> - 13 - enoic acid;	40
	67/43.	4 - bromo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S,R) - fluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - <i>trans</i> - 13 - enoic acid;	
	67/44.	5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S,R) - fluoro - 17 - phenyl - 18,19,20 - trinorprost - <i>trans</i> - 13 - enoic acid;	
45	67/45.	14 - bromo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S,R) - fluoro - 17 - phenyl - 18,19,20 - trinorprost - <i>trans</i> - 13 - enoic acid;	45
	67/46.	5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 17 - cyclopentyl - 18,19,20 - trinorprost - <i>trans</i> - 13 - enoic acid;	
50	67/47.	5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - <i>trans</i> - 13 - enoic acid;	50
	67/48.	14 - bromo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - <i>trans</i> - 13 - enoic acid;	
	67/49.	4,14 - dibromo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - <i>trans</i> - 13 - enoic acid;	
55	67/50.	5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	55
	67/51.	4 - iodo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	
60	67/52.	4 - iodo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - cyclohexyloxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	60
	67/53.	4 - iodo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - m - chlorophenoxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	
65	67/54.	4 - iodo - 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - m - trifluoromethylphenoxy - 17,18,19,20 - tetranor - <i>trans</i> - 13 - prostenoic acid;	65

In a similar way the corresponding 15(R) - alcohols, designated compounds 67/55 to 67/108, are prepared. Also the diastereoisomeric αH - diastereoisomers are prepared when αH -5 or 6,9 α -epoxy, 15-oxo diastereoisomers were used as starting materials. The αH -15(S) - alcohols are designated 67/109 to 67/162. The αH -15(R) - alcohols are designated 67/163 to 67/216. Further, the 6 βH - diastereoisomer of the 6 αH - compound 63/1 and the 15(R) - alcohol epimers of both diastereoisomers (compounds 67/217 to 67/219) are prepared. All these esters are then saponified to obtain the free acids, which are designated 67/220 to 67/438.

Example 68

0.46 g of 5 βH - 5,9 α - epoxy - 16(S) - methyl - 11 α - hydroxy - 15 - oxo - prost - *trans* - 13 - enoic acid methyl ester are treated with pyridine (2 ml) and acetic anhydride (1 ml). After 6 hours at room temperature the mixture is diluted with brine, acidified to pH 4.5—4.8 and extracted with diethyl ether. The combined organic phases are then evaporated to dryness yielding 0.48 g of 11 - acetoxy derivative ($\lambda_{max}^{MeOH}=229\text{ m}\mu$, $\epsilon=11.058$), designated compound 68/1. A solution of this compound in diethyl ether is then added dropwise to a solution of $Zn(BH_4)_2$ in diethyl ether. After 30 minutes the excess reagent is decomposed with a N solution of H_2SO_4 and after the usual work-up, 0.47 g of 5 βH - 5,9 α - epoxy - 16(S) - methyl - 11 α - acetoxy - 15(S,R) - hydroxy - *trans* - 13 - prostenoic acid methyl ester (68/2) are obtained. A solution of this mixture in CH_2Cl_2 (5 ml) cooled to about $-5^\circ C$ to $-10^\circ C$, is treated with a solution of BF_3 etherate ($1.2 \times 10^{-4} M$) in CH_2Cl_2 and then with a 5% solution of diazomethane in CH_2Cl_2 until a persistent yellow coloration. The reaction mixture is evaporated to half volume under vacuum, washed with a 5% aqueous $NaHCO_3$ solution and water to neutral, and evaporated to dryness to yield 0.47 g of 5 βH - 5,9 α - epoxy - 16(S) - methyl - 11 α - acetoxy - 15(S,R) - methoxyprost - *trans* - 13 - enoic acid (68/3) which is separated into its individual isomers by chromatography on SiO_2 using benzene - diethyl ether (85:15) as eluent. The 15(S) - methoxy isomer is designated compound 68/4 and the 15(R) - methoxy isomer 68/5. 0.21 g of the mixture of 15(S,R) - methoxy - derivatives (68/3) is dissolved in dry methanol (4 ml) and selectively deacetylated by treatment with 20 mg of K_2CO_3 for 4 hours at room temperature. After neutralization by dilution with aqueous NaH_2PO_4 , the methanol is evaporated under vacuum and the residue is extracted with diethyl ether (2x5 ml.) and ethyl acetate (2x6 ml). The combined organic phases are evaporated to dryness to yield 180 mg of the crude 5 βH - 5,9 α - epoxy - 16(S) - methyl - 11 α - hydroxy - 15(S,R) - methoxy - *trans* - prostenoic acid methyl ester (68/6) which is then readily separated by means of a silica gel column chromatograph using CH_2Cl_2 - ethyl ether 80:20 as eluent to yield the two pure isomers: 15(S) - methoxy (68/7) and 15(R) - methoxy (68/8).

Using the same procedure the methyl esters of the following acids were obtained:

- 68/9. 6 βH - 6,9 α - epoxy - 16(S) - methyl - 11 α - hydroxy - 15(S) - methoxyprost - *trans* - 13 - enoic acid;
- 68/10. 6 βH - 6,9 α - epoxy - 16(R) - methyl - 11 α - hydroxy - 15(S) - methoxyprost - *trans* - 13 - enoic acid;
- 68/11. 6 βH - 6,9 α - epoxy - 20 - methyl - 11 α - hydroxy - 15(S) - methoxy - prost - *trans* - 13 - enoic acid;
- 68/12. 5 - bromo - 6 βH - 6,9 α - epoxy - 20 - methyl - 11 α - hydroxy - 15(S) - methoxyprost - *trans* - 13 - enoic acid;
- 68/13. 5 - bromo - 6 βH - 6,9 α - epoxy - 11 α - hydroxy - 15(S) - methoxyprost - *trans* - 13 - enoic acid;
- 68/14. 5 - bromo - 6 βH - 6,9 α - epoxy - 16(S) - methyl - 11 α - hydroxy - 15(S) - methoxyprost - *trans* - 13 - enoic acid,

and their epimeric 15(R) - methoxy compounds designated 68/15 to 68/20, are obtained starting from the corresponding 11 - acetoxy - 15 - oxo compounds designated 68/21 to 68/26, via 11 - acetoxy - 15(S,R) - hydroxy compounds designed 68/27 to 68/32 and 11 α - hydroxy - 15(S,R) - methoxy compounds 68/33 to 68/38.

Using in this procedure the αH - diastereoisomer instead of the βH , the corresponding αH - 15 - methoxy compounds are also obtained. The αH compounds corresponding to 68/1 to 68/38 are designated 68/39 to 68/76. The same procedure can be also utilized for any 15-oxo compound, previously described and analogously another diazoalkane can be used inside of diazomethane.

Example 69

To a solution of 0.26 g of 6 β H - 6,9 α - epoxy - 15(S,R) - hydroxy - 16(S) - methyl - prost - *trans* - 13 - enoic acid methyl ester in methylene chloride, treated with 0.3 ml of a solution of BF₃ etherate in methylene chloride, cooled at -10 to 8°C, a solution of diazoethane in methylene chloride, is added until a persistent yellow coloration is formed. The solvent is evaporated under vacuum and the residue chromatographed on silica gel using diethyl ether-methylene chloride 10:90 as eluent to yield 0.115 g of 6 β H - 6,9 α - epoxy - 15(S) - ethoxy - 16(S) - methylprost - *trans* - 13 - enoic acid methyl ester (69/1), and 0.1 g of 15(R) - ethoxy isomer (69/2). When a mixture of 15(S), 15(R) - alcohols, for example, 6 β H - 6,9 α - epoxy - 11 α , 15(S,R) - dihydroxy - 16(S) - methylprost - *trans* - 13 - enoic acid, containing a free 11-hydroxy group is submitted to the procedure of the Examples 68 and 69, the simultaneous alkylation of the 11-hydroxy group also occurs yielding with diazomethane, for example, after chromatographic separation of the 15(S) and 15(R) epimers (69/3), 6 β H - 6,9 α - epoxy - 11 α , 15(S) - dimethoxy - 16(S) - methylprost - *trans* - 13 - enoic acid methyl ester (69/4) and the 15(R) - epimeric derivative (69/5).

In a similar way the methyl esters of the following 15(S) - alkoxy - prostenoic derivatives were obtained:

- 69/6. 5 β H - 5,9 α - epoxy - 11 α , 15(S) - dimethoxyprost - *trans* - 13 - enoic acid;
- 69/7. 6 β H - 6,9 α - epoxy - 11 α , 15(S) - dimethoxyprost - *trans* - 13 - enoic acid;
- 69/8. 5 - bromo - 6 β H - 6,9 α - epoxy - 11 α , 15(S) - dimethoxyprost - *trans* - 13 - enoic acid;
- 69/9. 5 - iodo - 6 β H - 6,9 α - 11 α , 15(S) - dimethoxyprost - *trans* - 13 - enoic acid;
- 69/10. 5 β H - 5,9 α - epoxy - 15(S) - methoxy - 16(S) - methylprost - *trans* - 13 - enoic acid;
- 69/11. 6 β H - 6,9 α - epoxy - 15(S) - methoxy - 16(S) - methylprost - *trans* - enoic acid;
- 69/12. 6 β H - 6,9 α - epoxy - 15(S) - methoxy - 16(R) - methylprost - *trans* - 13 - enoic acid;
- 69/13. 6 β H - 6,9 α - epoxy - 15(S) - methoxy - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid,

and their corresponding 15(R) - epimers (69/14 to 69/21) are obtained and when they are saponified with LiOH in methanol the free acids are prepared.

The same procedure can be used to obtain diastereoisomeric α H-5 or 6,9 α -oxo derivatives. α H isomers corresponding to 69/1 to 96/5 are designated 69/22 to 69/26. The α H isomers corresponding to 69/6 to 69/21 are designated 69/27 to 69/42.

Example 70

To a stirred solution of 1.33 g of 6 α H - 6,9 α - epoxy - 11 α - acetoxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester in 6 ml of toluene and 54 ml of benzene, cooled at +4°C, a solution of 1.67 g of methyl-magnesium iodide in diethyl ether is added. After 20 minutes, the excess reagent is decomposed with an iced 20% solution of ammonium chloride in water.

After dilution with one volume of diethyl ether the organic phase is washed with water, sodium bicarbonate and water, dried over magnesium sulphate, treated with 0.1 ml of pyridine and evaporated to dryness to yield 1.2 g of 6 α H - 6,9 α - epoxy - 11 α - acetoxy - 15(S,R) - hydroxy - 15 - methylprost - *trans* - 13 - enoic acid methyl ester (70/1) of which 0.2 g are separated into the pure 15(S)- and 15(R) - alcohol isomers (70/2 and 70/3) by thin layer chromatography on silica gel, with benzene - diethyl ether 60:40 eluent. 1 g of the mixture of the two alcohols (70/1) is dissolved in anhydrous methanol (20 ml) and stirred for 4 hours with 0.25 g of K₂CO₃. The mixture is evaporated to dryness, the residue is partitioned between diethyl ether and aqueous 15% NaH₂PO₄. The organic phase is evaporated in vacuum and the residue is absorbed on silica gel (200 g). Elution with diethyl ether - diisopropyl ether 80:20 affords 0.20 g of 6 α H - 6,9 α - epoxy - 11 α , 15(R) - dihydroxy - 15 - methylprost - *trans* - 13 - enoic acid methyl ester (70/4), and 0.36 g of 15(S) - alcohol epimer, designated compound (70/5), 0.16 g of this compound are dissolved in 12 ml of methanol and treated with 0.8 ml of water and 0.2 g of K₂CO₃. After 5 hours at room temperature the methanol is evaporated under vacuum, the residue is treated with 20% NaH₂PO₄ and ethyl acetate. The organic phase yields 0.14 g of 6 α H - 6,9 α - epoxy - 11 α , 15(S) - dihydroxy - 15 -

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methylprost - *trans* - 13 - enoic acid, which is not part of the present invention. The corresponding $6\beta H$ - isomers are prepared in the same way: the methyl esters corresponding to 70/1 to 70/5 are designated 70/6 to 70/10.

Example 71

5 To 1.79 g of $5\alpha H$ - $5,9\alpha$ - epoxy - 11α - acetoxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester in 20 ml of anhydrous tetrahydrofuran 50 ml of 0.3 M ethynylmagnesium bromide in anhydrous tetrahydrofuran is added. The mixture is shaken for one hour, the excess reagent is eliminated by treating with a saturated NH_4Cl solution, and the organic phase is concentrated under vacuum, and taken up in diethyl ether to yield 1.62 g of $5\alpha H$ - $5,9\alpha$ - epoxy - 11α - acetoxy - 15(*S,R*) - hydroxy - 15 - ethynylprost - *trans* - 13 - enoic acid methyl ester (71/1), which is dissolved in anhydrous methanol, treated with 250 mg of anhydrous potassium carbonate for 3 hours under shaking, evaporated under vacuum and diluted with 20% aqueous NaH_2PO_4 and diethyl ether. After separating the organic phase and evaporating solvent therefrom, the organic phase yielded 1.41 g of $5\alpha H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S,R)$ - dihydroxy - 15 - ethynylprost - 13 - *trans* - enoic acid methyl ester (71/2), which is separated into the two pure 15(*S*) - hydroxy (71/3) and 15(*R*) - hydroxy (71/4) epimers by silica gel chromatography with benzene - diethyl ether 1:1 as eluent, and after saponification of the 15(*S*) - hydroxy epimer with K_2CO_3 in methanol, there is yielded the $5\alpha H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - ethynylprost - *trans* - 13 - enoic acid, designated 71/5. 10 15 20

Example 72

25 To a solution of anhydrous tetrahydrofuran (25 ml) of 1.41 g of 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - 15 - oxoprost - *trans* - 13 - enoic acid methyl ester, a 0.5 M solution of magnesium-vinyl bromide in tetrahydrofuran (25 ml) is added at 0—5°C and allowed to stand for 4 hours at room temperature. The excess reagent is decomposed with a saturated solution of ammonium chloride, the tetrahydrofuran distilled off under vacuum and the residue taken up in diethyl ether. 30 The organic phase is adsorbed on silica gel and eluted with methylene chloride-diethyl ether to yield 0.41 g of 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - 15(*R*) - hydroxy - 15 - vinylprost - *trans* - 13 - enoic acid methyl ester (72/1), and 0.62 g of 15(*S*)-isomer (72/2), which after saponification with LiOH in methanol yields 0.49 g of pure 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - 15(*S*) - hydroxy - 15 - vinylprost - *trans* - 13 - enoic acid (72/3). 35

Example 73

A solution of 0.98 g of 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - 11α - acetoxy - 15 - oxo - 20 - methylprost - *trans* - 13 - enoic acid methyl ester in 30 ml of benzene-toluene (85:15) is cooled at 3—4°C and to this a solution of 0.92 g of phenylmagnesium bromide in diethyl ether-benzene (1:1) is added, and the mixture is allowed to stand for 5 hours at room temperature. Then the excess reagent is decomposed with an iced solution of 15% NH_4Cl , the organic phase is washed repeatedly with water to neutral, then evaporated. The crude 15 - phenyl - 15(*S,R*) - hydroxy derivative is dissolved in anhydrous methanol to which is 0.25 g of K_2CO_3 is added, shaken for 2 hours, evaporated to dryness, diluted with aqueous 20% NaH_2PO_4 and diethyl ether, and from the organic phase after evaporation of the solvent, 0.81 g of 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S,R)$ - dihydroxy - 15 - phenyl - 20 - methylprost - *trans* - 13 - enoic acid methyl ester (73/1) is obtained, which after separation on silica gel, with diethyl ether elution, yields the individual 15(*S*) and 15(*R*) isomers (73/2) and (73/3). 40 45 50

Example 74

By reaction of the corresponding 15-oxo-derivative with a reagent selected from a halide of methylmagnesium, ethylmagnesium, vinylmagnesium, ethynylmagnesium and phenylmagnesium, working according to one of the procedures given in Examples 70 to 73, the following methyl esters of the following acids were prepared: 55

- 74/1. $6\beta H$ - $6,9\alpha$ - epoxy - 15(*S*) - hydroxy - 15 - methylprost - *trans* - 13 - enoic acid;
74/2. $6\beta H$ - $6,9\alpha$ - epoxy - 15(*S*) - hydroxy - 15,20 - dimethylprost - *trans* - 13 - enoic acid; 60

57

- 74/3. $6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxy - 15 - ethylprost - *trans* - 13 - enoic acid;
- 74/4. $6\beta H$ - $6,9\alpha$ - epoxy - $15(S)$ - hydroxy - 15 - ethynylprost - *trans* - 13 - enoic acid;
- 5 74/5. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - methyl - prost - *trans* - 13 - enoic acid; 5
- 74/6. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - ethylprost - *trans* - 13 - enoic acid;
- 10 74/7. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - vinylprost - *trans* - 13 - enoic acid; 10
- 74/8. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - ethynylprost - *trans* - 13 - enoic acid;
- 74/9. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - phenylprost - *trans* - 13 - enoic acid;
- 15 74/10. $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15,20 - dimethylprost - *trans* - 13 - enoic acid; 15
- 74/11. 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - methylprost - *trans* - 13 - enoic acid;
- 20 74/12. 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - vinylprost - *trans* - 13 - enoic acid; 20
- 74/13. 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - ethynylprost - *trans* - 13 - enoic acid;
- 74/14. 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - ethyl - prost - *trans* - 13 - enoic acid;
- 25 74/15. 5 - bromo - $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - phenyl - prost - *trans* - 13 - enoic acid; 25
- 74/16. 4 - bromo - $5\beta H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - methylprost - *trans* - 13 - enoic acid;
- 30 74/17. 4 - bromo - $5\beta H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15,20 - dimethylprost - *trans* - 13 - enoic acid; 30
- 74/18. 5 - bromo - $5\beta H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - ethynyl - prost - *trans* - 13 - enoic acid;
- 74/19. $5\beta H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - methylprost - *trans* - 13 - enoic acid;
- 35 74/20. $5\beta H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15,20 - dimethylprost - *trans* - 13 - enoic acid; 35
- 74/21. $5\beta H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - phenyl - prost - *trans* - 13 - enoic acid;
- 40 74/22. $5\beta H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - ethynyl - prost - *trans* - 13 - enoic acid; 40
- 74/23. $5\beta H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - vinyl - prost - *trans* - 13 - enoic acid;
- 74/24. $5\beta H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - methyl - prost - *trans* - 13 - enoic acid;
- 45 and their $15(R)$ - hydroxy epimers, designated 74/25 to 74/48. Analogously, starting from the αH -5, or $6,9\alpha$ - epoxy - 15 - oxo - compounds we obtained the corresponding αH -5, or $6,9\alpha$ - epoxy - 15 - substituted alcohols. The αH -isomers of the βH - $15(S)$ -hydroxy epimers 74/5 and 74/22 are already designated 70/5 and 71/3 respectively. The αH -isomers of the other listed βH - $15(S)$ -hydroxy epimers are designated 74/49 to 74/70 respectively. The αH -isomers of the βH - $15(R)$ -hydroxy epimers 74/29 and 74/46 are 70/4 and 71/4 respectively. The αH -isomers of the other designated βH - $15(R)$ -hydroxy epimers are therefore designated 74/71 to 74/92 respectively.
- 50

Example 75

- 55 To a solution of 0.5 g of $6\beta H$ - $6,9\alpha$ - epoxy - 11α - acetoxy - hydroxy - 14 - bromo - $16(S)$ - methylprost - *trans* - 13 - enoic acid, methyl ester in 2 ml. of dimethylformamide, dimethyl - t - butyl silyl chloride (0.21 g) and triethylamine (0.16 g) are added. The mixture was shaken for 2 hours, then diluted with 4 volumes of water and extracted with diethyl ether. The organic phase, after the usual washings, evaporation of the solvent, and filtration through silica gel with cyclohexane-diethyl ether 90:10 eluent, yields 0.57 g of $6\beta H$ - $6,9\alpha$ - epoxy - 11α - acetoxy - $15(S)$ - dihydroxy - 14 - bromo - $16(S)$ - methylprost - *trans* - 13 - enoic acid methyl ester, 15 - dimethyl - t-butylsilyl ether, from which, by
- 60

transesterification in anhydrous methanol and 0.5 molar equivalents of K_2CO_3 yields the corresponding 11-hydroxy-derivative.

Example 76

To 0.52 g of 5,14 - dibromo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxyprost - *trans* - 13 - enoic acid methyl ester in 10 ml of dichloromethane, 2,3 - dihydropyran (0.27 g) and *p* - toluenesulphonic acid (4 mg) are added. The mixture is kept at room temperature for 3 hours, then washed with a 5% solution of $KHCO_3$ and water to neutral, and evaporated to dryness. Filtration through silica gel with cyclohexane-diethyl ether 90:10 as eluent yields 0.59 g of 5,14 - dibromo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxyprost - *trans* - 13 - enoic acid methyl ester, 11,15 - bis - (2 - tetrahydropyranyl ether).

Example 77

The 14-bromo-alcohols yielded by the foregoing Examples, when treated with dimethyl-t.butylchlorosilane in dimethylformamide while, working to the procedures as in Example 75, or with 2,3 - dihydropyran, 1,4 - diox - 2 - ene, or ethyl vinyl ether, and working to the procedure of Example 76, are then converted into the corresponding ethers.

Example 78

Under an atmosphere of inert gas, to a stirred solution of 0.46 g of 14 - bromo - 6 β H - 6,9 α - epoxy - 15(S) - methoxy - 16(S) - methylprost - *trans* - 13 - enoic acid methyl ester in anhydrous dimethyl sulfoxide (5 ml), potassium *tert*-butoxide (0.15 g) is added and stirring is continued for 30 minutes. The reaction mixture is diluted with 2 volumes of water and stirred for 15 minutes, then extracted with diethyl ether. The organic phases are re-extracted with 2x5 ml of 0.2N NaOH and then with water until neutral and evaporated to dryness to give 30 mg of 6 β H - 6,9 α - epoxy - 15(S) - methoxy - 16(S) - methylprost - 13 - ynoic acid methyl ester (78/1). The combined aqueous phases are acidified to pH 5.1 and extracted with diethyl ether. After evaporation of the solvent, 0.28 g of 6 β H - 6,9 α - epoxy - 15(S) - methoxyprost - 13 - ynoic acid (78/2) is obtained.

Example 79

Under an atmosphere of inert gas, with stirring and rigorous exclusion of moisture, 0.84 g of trimethylsilylimidazole is added to an anhydrous dimethyl sulfoxide solution of 0.445 g of 5 α H - 5,9 α - epoxy - 14 - bromo - 11 α ,15(S) - dihydroxy - 16(R) - methylprost - *trans* - 13 - enoic acid. Stirring is continued for 30 minutes and then a solution of 0.19 g of potassium - *tert* - butoxide is added. After 30 minutes stirring, the mixture is diluted with 3 volumes of water and stirred for 2 more hours. After acidification to pH 5.2, it is extracted with diethyl ether:hexane 80:20 and the organic extracts are dried and evaporated to dryness to give 0.31 g of 5 α H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(R) - methylprost - 13 - ynoic acid, compound 79.

Example 80

To a solution of sodium methylsulfinylcarbanion, obtained by heating at 60°C for 3 hours and 30 minutes a suspension of 50 mg of 80% NaH in 8 ml of anhydrous dimethyl sulfoxide, a solution of 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dimethoxy - 14 - bromo - 16(S,R) - fluoro - 20 - methylprost - *trans* - 13 - enoic acid methyl ester (0.86 g) in 5 ml of dimethyl sulfoxide is added with stirring under an atmosphere of inert gas, at a temperature of 18–20°C. After 40 minutes of stirring an excess of 25% NaH_2PO_4 is poured in and the mixture extracted with ethyl ether to give 0.51 g of 6 β H - 6,9 α - epoxy - 11 α ,15(S)dimethoxy - 16(S,R) - fluoro - 20 - methylprost - 13 - ynoic acid methyl ester, compound 80.

Example 81

To a solution of 80 mg of sodium amide in 10 ml of dimethyl sulfoxide a solution of 14 - bromo - 5 α H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - *m* - trifluoromethylphenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid 11,15 - bis - (2 - tetrahydropyranyl - ether) (0.65 g) in 5 ml of dimethyl sulfoxide is added. It is stirred for 2 hours and then diluted with water and extracted with diethyl ether. The ethereal extracts, after re-extraction with alkali are discarded. The aqueous alkaline extracts are acidified to pH 5.4 and extracted with ethyl ether to give 0.54 of 5 α H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - *m* - trifluoro-

5 methylphenoxy - 17,18,19,20 - tetranorprost - 13 - ynoic acid 11,15 - bis - (2 -
 tetrahydropyranyl ether). A solution of this compound (0.23 g) in anhydrous
 ethanol (5 ml) and 2,2 - diethoxypropane (3 ml) is treated with 20 mg of *p* -
 toluenesulfonic acid. After 5 hours at room temperature it is neutralized with
 10 aqueous NaHCO₃, evaporated under vacuum and the residue partitioned between
 water and diethyl ether. The organic phase is evaporated and, after passing the
 residue through silica gel, 0.1 g of 5 α H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy -
 16 - *m* - trifluoromethylphenoxy - 17,18,19,20 - tetranorprost - 13 - ynoic acid
 ethyl ester (81/1) is obtained. De-esterification is carried out on another 0.2 g of
 15 product dissolved in 5 ml of acetone and treated with 3.5 ml of 0.2N oxalic acid for
 8 hours at 40°C; after evaporation of the acetone under vacuum, extraction of the
 aqueous phase with diethyl ether and chromatography on silica gel with diethyl
 ether:ethyl acetate 95:5 the free acid (95 mg) is obtained and is designated
 compound 81/2. In the same way, starting from 14 - chloro - 6 α H - 6,9 α - epoxy -
 11 α ,15(S) - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 -
 enoic acid 11,15 - bis - (1,4 - dioxan - 2 - yl ether), 6 α H - 6,9 α - epoxy -
 11 α ,15(S) - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - 13 - ynoic acid
 (81/3) is obtained.

Example 82

20 To a solution of 0.48 g of 14 - bromo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) -
 dihydroxy - 16 - cyclohexyloxy - 17,18,19,20 - tetranor - prost - *trans* - 13 -
 enoic acid methyl ester in 3 ml of anhydrous dimethyl sulfoxide is added after 30
 minutes a solution of 1,5 - diazabicyclo[5.4.0]undec - 5 - ene (0.25 g) in 2 ml of
 25 anhydrous dimethylformamide and the reaction mixture maintained for 6 hours at
 65°C. It is diluted with water acidified to pH 4.5, and extracted with diethyl ether.
 From the organic phase, after evaporation of the solvent and purification on silica
 gel (eluted with benzene-diethyl ether 80:20), 6 β H - 6,9 α - epoxy - 11 α ,15(S) -
 dihydroxy - 16 - cyclohexyloxy - 17,18,19,20 - tetranorprost - 13 - ynoic acid
 methyl ester (0.29 g) is obtained and designated compound 82.

Example 83

30 Using one of the procedures described in Examples 78 to 82 and starting from
 the corresponding 14 - halo - prost - *trans* - 13 - enoic acids, the following prost -
 13 - ynoic acids are prepared:

- 35 83/1. 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxyprost - 13 - ynoic acid;
- 83/2. 6 β H - 6,9 α - epoxy - 11 α ,15(R) - dihydroxyprost - 13 - ynoic acid;
- 83/3. 6 β H - 6,9 α - epoxy - 15(S,R) - methoxyprost - 13 - ynoic acid;
- 83/4. 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S) - methylprost - 13 -
 ynoic acid;
- 40 83/5. 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S),20 - dimethylprost -
 13 - ynoic acid;
- 83/6. 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(R) - methylprost - 13 -
 ynoic acid;
- 83/7. 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S) - fluoroprost - 13 -
 ynoic acid;
- 45 83/8. 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16,16 - difluoroprost - 13 -
 ynoic acid;
- 83/9. 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 20 - methylprost - 13 - ynoic
 acid;
- 50 83/10. 6 β H - 6,9 α - 11 α ,15(S) - dihydroxy - 17 - cyclohexyl - 18,19,20 -
 trinorprost - 13 - ynoic acid;
- 83/11. 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - fluoro - 17 -
 cyclohexyl - 18,19,20 - trinorprost - 13 - ynoic acid;
- 83/12. 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - *p* - fluorophenoxy -
 17,18,19,20 - tetranorprost - 13 - ynoic acid;
- 55 83/13. 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 17 - phenyl - 18,19,20 -
 trinorprost - 13 - ynoic acid;
- 83/14. 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 15(S) - methylprost - 13 -
 ynoic acid;
- 83/15. 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S),20 - dimethyl - prost -
 13 - ynoic acid;
- 60 83/16. 5 β H - 5,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(R) - methylprost - 13 -
 ynoic acid;

60

83/17. $5\beta H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - $16(S)$ - fluoroprost - 13 - ynoic acid;

83/18. $5\beta H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxyprost - 13 - ynoic acid;

83/19. $5\beta H$ - $5,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 20 - methylprost - 13 - ynoic acid, and their methyl esters designated 83/20 to 83/38, respectively.

Starting from the αH - diastereoisomers and using the same procedure, the $5\alpha H$ or $6\alpha H$ - 13 - ynoic compounds are prepared. The αH - epimers corresponding to compounds 83/16 and 83/10 are already designated 79 and 81/3 respectively. The αH - epimers corresponding to the other acids are designated 83/39 to 83/55 and those corresponding to the methyl esters 83/20 to 83/38 are designated 83/56 to 83/74, respectively.

Example 84

A solution of 0.35 g of mercuric acetate in methanol is added at room temperature, with stirring, to a solution of 0.54 g of $9\alpha,11\alpha,15(S)$ - trihydroxyprosta - *cis* - $5,trans$ - 13 - dеноic acid methyl ester $11,15$ - bis - THP ether ($PGF_{2\alpha}$ - methyl ester $11,15$ - bis - THP ether). After stirring for 15 minutes, 50 mg of sodium borohydride is added in small portions, the elemental mercury generated is removed by filtration and the methanol is evaporated under vacuum. The residue is partitioned between dichloromethane/water; the organic phase, after washing with sodium bicarbonate and water until neutral, is evaporated to give 0.51 g of crude $11\alpha,15(S)$ - dihydroxy - $6\beta H$ - $6,9\alpha$ - epoxyprost - *trans* - 13 - enoic acid methyl ester $11,15$ - bis - THP - ether. A solution of this in 10 ml of acetone added to 8 ml of 0.2N oxalic acid is heated to $40-45^\circ C$ for 6 hours. After the removal of the acetone under vacuum, the aqueous suspension is extracted with ethyl acetate (3×15 ml). The organic phase is washed until neutral and evaporated to dryness. The residue (approximately 0.45 g) is adsorbed on silica gel (50 g) and eluted with diethyl ether, collecting fractions of 20 ml. From fractions 11 to 50, $6\alpha H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxyprost - *trans* - 13 - enoic acid methyl ester (0.11 g; m.p. $67-69^\circ$), is obtained. Then, after obtaining a mixture of diastereoisomers as 5-10% of ethyl acetate is added to ethyl ether $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxyprost - *trans* - 13 - enoic acid methyl ester, (0.16 g; $[\alpha]_D^{25} = +19.62^\circ$ ($CHCl_3$)) is collected.

A sample of the latter compound, after crystallization, shows m.p. $40-41^\circ C$, $[\alpha]_D^{25} = +25.2^\circ$, $[\alpha]_{385}^{25} = +83.8^\circ$ ($CHCl_3$). The crude free acid has $[\alpha]_D^{25} = +18.3^\circ$ (EtOH).

A sample is crystallized from pentane-diether ether affording pure crystalline $6\beta H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - prost - *trans* - 13 - enoic acid, m.p. $80-81^\circ C$, $[\alpha]_D^{25} = +32.5^\circ$, $[\alpha]_{385}^{25} = +11.6^\circ$ (EtOH). The mass spectrum of the compound shows the following peaks (m/e, intensity, structure):

336 7% $[M-H_2O]^+$, 318 3% $[M-2H_2]^+$; 292 100% $[M-H_2]-44]^+$; 264 30% $[M-H_2O-CH_2CHCO_2H]^+$; 235 4% $[M-H_2]-(CH_2)_4CO_2H$.

The mass spectrum of the $6\alpha H$ - diastereoisomer is substantially similar. These free acids and esters are not part of the present invention.

Example 85

A solution of 0.19 g of 15 - methyl - $PGF_{2\alpha}$ methyl ester in 2.5 ml of THF is added to 0.3 g of mercuric acetate in 1.5 ml water/3.0 ml THF. After 30 minutes of stirring, 60 mg of sodium borohydride in 1.2 ml of water is added to the deep yellow suspension. After the mercury is separated, the THF is removed under vacuum and the aqueous suspension is extracted repeatedly with ethyl acetate. The organic phase, when washed until neutral and evaporated to dryness, yields 0.16 g of product which is purified by thin layer chromatography to give 0.04 g of $6\alpha H$ - $6,9\alpha$ - epoxy - $11\alpha,15(S)$ - dihydroxy - 15 - methylprost - *trans* - 13 - enoic acid methyl ester, compound 70/5, otherwise termed $6\alpha H$ - $6,9\alpha$ - epoxy - 9 - deoxy - 15 - methyl - $PGF_{1\alpha}$ methyl ester, $[\alpha]_D^{25} = +6.2^\circ$ ($CHCl_3$) and 0.034 g of the $6\beta H$ - $6,9\alpha$ - epoxy isomer (70/10), $[\alpha]_D^{25} = +19.62^\circ$ ($CHCl_3$).

Example 86

0.43 g of $9\alpha,15(S)$ - dihydroxy - $16R$ - methylprosta - *cis* - $5,trans$ - 13 - dienenoic acid methyl ester 15 - (1,4 - dioxan - 2 - yl ether) in methanol (2.5 ml) is reacted with a solution of 0.38 g of mercuric bromide in methanol. The reaction mixture is held at room temperature for 15 minutes and overnight at $0^\circ C$. The crystalline precipitate which forms is isolated by filtration to give 0.36 g of $6\beta H$ - $6,9\alpha$ - epoxy - 5 - bromomercurio - $15(S)$ - hydroxy - $16(R)$ - methyl - prost - *trans* - 13 - enoic acid methyl ester, from which the mercury is removed upon

61 54 treatment with sodium borohydride to give 0.12 g of 6 β H - 6,9 α - epoxy - 15(S) - hydroxyl - 16(R) - methylprost - *trans* - 13 - enoic acid methyl ester. Column chromatography on silica gel effects the separation into the 6 α H - 6,9 α - epoxy and 6 β H - 6,9 α - epoxy diastereoisomers (66/28 and 66/4 respectively).

Example 87

5 A solution of 0.55 g of 9 α ,11 α ,15(S) - trihydroxyprost - *cis* - 5 - enoic acid methyl ester in 2.5 ml of DME is added to a solution of 0.5 g of mercuric acetate in 2 ml of water/4 ml of DME. After 15 minutes, the reaction mixture is treated with a solution of 0.08 g of sodium borohydride in 1.2 ml of water, the mercury is separated, the DME is removed under vacuum, and the residue is extracted several times with dichloromethane. The organic phase is evaporated to dryness, adsorbed on silica gel and eluted with ethyl ether/ethyl acetate to give 0.21 g of 6 α H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy prostanoic acid methyl ester (87/1) and 0.18 g of the 6 β H - 6,9 α - epoxy isomer (87/2).

Example 88

15 A solution of 116 mg of 9 α ,11 α ,15(S) - trihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - *cis* - 5 - en - 13 - ynoic acid methyl ester 11,15 - bis - THP ether in 1.5 ml of methanol is treated with 64 mg of mercuric acetate in 1.5 ml of methanol. After 10 minutes, 25 mg of sodium borohydride is added. Methanol is removed under vacuum, the mercury is separated and the product is dissolved in water/ethyl acetate. Evaporation of the organic phase to dryness affords crude 20 11 α ,15(S) - dihydroxy - 6 β H - 6,9 α - epoxy - 17 - cyclohexyl - 18,19,20 - trinorprost - 13 - ynoic acid methyl ester 11,15 - bis - THP ether (100 mg); this is treated in acetone (4 ml) with 2.5 ml of 0.2N oxalic acid overnight at 40°C. After removal of the acetone under vacuum, the mixture is extracted with ethyl acetate. Evaporation of the solvent gives a residue which is purified on silica gel (eluent, diethyl ether) to give 28 mg of 6 α H - 6,9 - epoxy - 11 α ,15(S) - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - 13 - ynoic acid methyl ester (83/65) 25 [α]_D²⁰ = +17.2°, [α]_D³⁸⁵ = +54°, and 12.5 mg of the 6 β H - 6,9 α - epoxy - isomer, 83/29, [α]_D²⁰ = +26.5°, [α]_D³⁸⁵ = +84° (EtOH); M⁺ 406, M - H₂O⁺ 388.

30 Under the same conditions, 9 α ,11 α ,15(S) - trihydroxy - 16(S) - methylprost - *cis* - 5 - en - 13 - ynoic acid methyl ester 11,15 - bis - THP ether gives 6 α H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S) - methylprost - 13 - ynoic acid methyl ester (83/59) and its 6 β H - 6,9 α - epoxy isomer, 83/23.

Example 89

35 0.24 g of 6 α H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester and 0.13 g of the 6 β H - 6,9 α - epoxy isomer are obtained from the reaction of 1.01 molar equivalent of mercuric acetate (636 mg) in 10 ml of methanol and 1.1 g of 40 9 α ,11 α ,15(S) - trihydroxy - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *cis* - 5 - *trans* - 13 - dienenoic acid methyl ester 11,15 - bis - THP ether in 5 ml of methanol. The mercury compound so prepared is reduced *in situ* by the cautious addition of 85 mg of sodium borohydride in small portions. The methanolic solution is then decanted from the solid residue and reduced in volume. 10 ml of 45 0.2N aqueous oxalic acid and 20 ml of acetone are added, and the resulting mixture is held at 50°C for 12 hours. The organic solvents are removed under vacuum, and the resulting solution is saturated with sodium sulfate and extracted with ethyl acetate. The organic phase is washed with 30% ammonium sulfate (2x5 ml) and 2.5 ml of water; after drying over NaSO₄, it is evaporated to give a crude residue which 50 is purified on silica gel using an eluent containing an increasing fraction of benzene-methyl acetate, to give the isomeric 6 α H - 6,9 α - epoxy- and 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - methyl - 16 - butoxy - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl esters designated respectively 60/2 and 89 respectively. From the above reaction with 16 - *m* - chlorophenoxy, 16 - *p* - fluorophenoxy, and 16 - *m* - trifluoromethyl - phenoxy - 9 α ,11 α ,15S-trihydroxy - 55 17,18,19,20 - tetranorprost - *cis* - 5, *trans* - 13 - dienenoic acid methyl ester 11,15 - bis - THP ether and the following compounds were obtained respectively:

60 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - *m* - chlorophenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid methyl ester (67/24), [α]_D²⁰ = +31°;
6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - *p* - fluorophenoxy -

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17,18,19,20 - tetranorprost - trans - 13 - enoic acid methyl ester (67/21), $[\alpha]_D^{25} = +30^\circ$;

6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16 - m - trifluoromethyl - phenoxy - 17,18,19,20 - tetranorprost - trans - 13 - enoic acid methyl ester, (64/1) $[\alpha]_D^{25} = +33^\circ$;

and their 6 α H - 6,9 α - epoxy isomers 67/132, 67/129 and 64/3 respectively which show $[\alpha]_D$ ranging between $+8^\circ$ and 12° in CHCl_3 .

Example 90

Using the 16(S) - fluoro - 17 - cyclohexyl - 9 α ,11 α ,15(S) - trihydroxy - 18,19,20 - trinorprosta - cis - 5, trans - 13 - dienolic acid methyl ester 11,15 - bis - THP ether, in the procedure of Example 89, the 6 α H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S) - fluoro - 17 - cyclohexyl - 18,19,20 - trinorprost - trans - 13 - enoic acid methyl ester (90/1) and its 6 β H - 6,9 α - epoxy diastereoisomer (90/2) are obtained.

Example 91

0.12 g of 6 β H - 6,9 α - epoxyprost - trans - 13 - enoic acid methyl ester in 6 ml of methanol is reacted with a 0.5 N aqueous solution of lithium hydroxide (2 ml). After six hours, the methanol is removed under vacuum. The residue is diluted with water (2 ml) and extracted with diethyl ether to remove neutral impurities. The alkaline aqueous phase is acidified by treatment with 4 ml of 30% aqueous NaH_2PO_4 and extracted several times with diethyl ether. The later combined ether extracts are washed with water (2x1 ml) and dried; removal of the solvent affords 91 mg of 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - prost - trans - 13 - enoic acid, m.p. $78-80^\circ\text{C}$, $[\alpha]_D^{25} = +31^\circ$ (EtOH). This procedure is used for saponification of the esters from the preceding Examples to the corresponding free acids. The acids 9 - deoxy - 6,9 α - epoxy - 11 α ,15(S) - dihydroxyprost - trans - 13 - enoic acid, its 16,16 - dimethyl and 15 - methyl derivatives are not part of the present invention. Other acids corresponding to the esters mentioned hereinbefore in these Examples by a numerical designation are part of the invention. Those not already assigned a designation number are designated as follows:—

Ester	Free Acid
42/1 to 42/16	91/1 to 91/16
43/1 to 43/18	91/16 to 91/33
44/1 to 44/5	91/34 to 91/38
45/1 to 45/4	91/39 to 91/43
46/1 to 46/2	91/44 and 91/45
47/1 to 47/32	91/46 to 91/77
48/1 to 48/4	91/78 to 91/81
49/1 to 49/4	91/82 to 91/85
50/1 and 50/2	91/86 and 91/87
51/1 to 51/4	91/88 to 91/91
52/1 to 52/5	91/92 to 91/96
53/1 and 53/2	91/97 and 91/98
54/1 and 54/2	91/99 and 91/100
55/1 and 55/2	91/101 and 91/102
56/1 to 56/10	91/103 to 91/112
57/1 and 57/2	91/113 and 91/114
58/1 to 58/3	91/115 to 91/117
59/1 to 59/4	91/118 to 91/121
60/1 and 60/2	91/122 and 91/123
61/1 and 61/2	91/124 and 91/125
62/1 and 62/2	91/125 and 91/126
63/1 and 63/2	91/127 and 91/129
64/1 to 64/3	91/130 to 91/132
66/1 to 66/48	91/133 to 91/180
68/1 to 68/76	91/181 to 91/256
69/1 to 69/42	91/257 to 91/298
70/1 to 70/10	91/299 to 91/308
71/1 to 71/4	91/303 to 91/312
72/1 and 72/2	91/313 and 91/314
73/1 to 73/3	91/315 to 91/317
74/1 to 74/4	91/318 to 91/321
74/6 to 74/92	91/322 to 91/408

Ester	Free acid
80	91/409
82	91/410
87/1 and 87/2	91/411 and 91/412
89	91/413
90/1 and 90/2	91/414 and 91/415

Example 92

6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S) - methylprost - 13 - ynoic acid (83/4) (0.11 g) in methylene chloride is treated with 1.5 molar equivalent of diazomethane in methylene chloride. After 15 minutes, solvent is removed under vacuum and the residue adsorbed on silica gel. Elution with diethyl ether/benzene (70:30) gives, in the following order, 12 mg of 6 β H - 6,9 α - epoxy - 11 α - hydroxy - 15(S) - methoxy - 16(S) - methylprost - 13 - ynoic acid methyl ester (92/1) and 78 mg of 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S) - methylprost - 13 - ynoic acid methyl ester (83/23).

Using in this procedure diazoethane in place of the diazomethane, 11 α - hydroxy - 15(S) - ethoxy - 6 β H - 6,9 α - epoxy - 16(S) - methylprost - 13 - ynoic acid ethyl ester (compound 92/2) is obtained.

Example 93

A solution of I₂ (0.33 g) in methylene chloride is added to a suspension of finely divided calcium carbonate in 6 ml of methylene chloride containing 0.54 g of 9 α ,11 α ,15(S) - trihydroxyprosta - cis - 5, trans - 13 - dienolic acid methyl ester 11,15 - bis - (2 - tetrahydropyranyl ether) (PGF_{2a} bis - 2 - tetrahydropyranyl ether methyl ester). The reaction mixture is cooled in an ice/water bath and kept in darkness. After three hours of stirring, inorganic compounds are removed by filtration and the organic phase is washed with 0.25 N sodium thiosulfate and water. Removal of the solvent affords 0.66 g of crude 5 - iodo - 6H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - prost - trans - 13 - enolic acid methyl ester 11,15 - bis - (2 - tetrahydropyranyl ether).

A solution of this in 10 ml of acetone is added to 8 ml of 0.1N oxalic acid and heated to 45–46°C for 4 hours. The acetone is then removed at reduced pressure and the aqueous suspension is extracted with ethyl acetate (3×12 ml); the organic phase is washed until neutral and evaporated to dryness. The residue (0.42 g) is separated on silica gel with diethyl ether eluent. Elution of the high R_f fraction with acetone gives 0.14 g of 5 - iodo - 6 α H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxyprost - trans - 13 - enolic acid methyl ester (93/1), while the low R_f portion is 0.20 g of 5 - iodo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxyprost - trans - 13 - enolic acid methyl ester (93/2).

The methyl esters of the following acids were prepared analogously:

65/12. 5 - iodo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 16(S) - methylprost - trans - 13 - enolic acid;

65/15. 5 - iodo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 20 - methylprost - trans - 13 - enolic acid, $[\alpha]_D^{25} = +23^\circ$, $[\alpha]_{365}^{25} = +78^\circ$ (CHCl₃);

93/3. 5 - iodo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - trans - 13 - enolic acid;

93/4. 5 - iodo - 6 α H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - trans - 13 - enolic acid;

93/5. 5 - iodo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 18,19,20 - trinor - 17 - phenoxyprost - trans - 13 - enolic acid;

93/6. 5 - iodo - 6 α H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxy - 18,19,20 - trinor - 17 - phenoxyprost - trans - 13 - enolic acid;

93/7. 5 - iodo - 6 β H - 6,9 α - epoxy - 15(S) - hydroxyprost - trans - 13 - enolic acid;

93/8. 5 - iodo - 6 α H - 6,9 α - epoxy - 15(S) - hydroxyprost - trans - 13 - enolic acid;

93/9. 5 - iodo - 6 β H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxyprost - 13 - ynoic acid;

93/10. 5 - iodo - 6 α H - 6,9 α - epoxy - 11 α ,15(S) - dihydroxyprost - 13 - ynoic acid;

93/11. 5 - iodo - 6 β H - 6,9 α - epoxy - 16(S) - methyl - 11 α ,15(S) - dihydroxyprost - 13 - ynoic acid;

93/12. 5 - iodo - 6 β H - 6,9 α - epoxy - 20 - methyl - 11 α ,15(S) - dihydroxyprost - 13 - ynoic acid, $[\alpha]_D^{25} = +20^\circ$ (CHCl₃).

(64)

Example 94

To a solution of 0.22 g of 15 - methyl - PGF_{2α} methyl ester in 10 ml of CH₂Cl₂ and 0.1 ml of pyridine is added dropwise a solution of 180 mg of iodine in methylene chloride. The resulting mixture is stirred for 1 hour. After dilution with water and washing of the organic phase with 0.1N sodium thiosulfate and water until neutral, the solution is evaporated in vacuum to a small volume and adsorbed on a silica gel plate 0.5 mm in thickness. After development with diethyl ether and elution with acetone, 0.052 g of 5 - iodo - 6βH - 6,9α - epoxy - 11α,15(S) - dihydroxy - 15 - methylprost - *trans* - 13 - enoic acid methyl ester (94/1) and 0.021 g of the isomeric 5 - iodo - 6αH - 6,9α - epoxy compound (94/2) are obtained.

Example 95

0.288 g of 9α,11α,15(S) - trihydroxy - 16,16 - dimethylprost - *cis* - 5 - enoic acid methyl ester in a solution of 60 mg of pyridine in methylene chloride (8 ml) is reacted with 115 ml of bromine in methylene chloride. After 30 minutes, starting material has completely disappeared; the organic phase is washed with water, then 5% aqueous metabisulfite, and then water until neutral to give, after removal of the solvent and purification by TLC on silica gel with diethyl ether as eluent, 0.083 g of 5 - bromo - 6βH - 6,9α - epoxy - 11α,15(S) - dihydroxy - 16,16 - dimethyl prostanoic acid methyl ester (95/1) and 0.04 g of 6αH - diastereoisomer (95/2).

The following compounds were prepared analogously:

65/9. 5 - bromo - 6βH - 6,9α - epoxy - 11α,15(S) - dihydroxy - 16,16 - dimethyl - prost - *trans* - 13 - enoic acid;

65/87. 5 - bromo - 6αH - 6,9α - epoxy - 11α,15(S) - dihydroxy - 16,16 - dimethyl - prost - *trans* - 13 - enoic acid.

Example 96

To a solution of pyrrolidone - 2 - hydrotribromide (1.1 molar equivalents) in anhydrous tetrahydrofuran (6 ml) is added a solution of 9α,11α,15(S) - trihydroxy - 18,19,20 - trinor - 17 - cyclohexylprost - *cis* - 5 - *trans* - 13 - dienolic acid methyl ester 11,15 - bis - (2 - tetrahydropyranyl ether) (0.7 g) in 6 ml of tetrahydrofuran. The mixture is stirred for 12 hours, the precipitate which forms is removed by filtration, and the tetrahydrofuran solution is diluted with 2 volumes of acetone and treated with 4 g of potassium iodide.

After 4 hours at room temperature, the iodine liberated is decomposed with sodium metabisulfate. 1.5 volumes of 0.1N aqueous oxalic acid is then added and the mixture heated to 48°C for 4 hours. The mixture is reduced under vacuum and extracted with ethyl acetate.

Separation on TLC gives 0.14 g of 5 - bromo - 6αH - 6,9α - epoxy - 11α,15(S) - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - *trans* - 13 - enoic acid methyl ester (67/123) and 0.11 g of the 5 - bromo - 6βH - 6,9α - epoxy compound (67/15).

Using the procedures of the Examples 95 and 96, the following 6,9α-epoxy compounds were obtained:

96/1. 5 - bromo - 6βH - 6,9α - epoxy - 11α,15(S) - dihydroxy - 17 - cyclohexyl - 18,19,20 - trinorprost - 13 - enoic acid methyl ester;

96/2. 5 - bromo - 6βH - 6,9α - epoxy - 11α,15(S) - dihydroxyprostanoic acid;

96/3. 5 - bromo - 6βH - 6,9α - epoxy - 11α,15(S) - dihydroxyprost - *trans* - 13 - enoic acid;

65/10. 5 - bromo - 6βH - 6,9α - epoxy - 11α,15(S) - dihydroxy - 20 - methylprost - *trans* - 13 - enoic acid;

74/11. 5 - bromo - 6βH - 6,9α - epoxy - 11α,15(S) - dihydroxy - 15 - methylprost - *trans* - 13 - enoic acid;

74/58. 5 - bromo - 6αH - 6,9α - epoxy - 11α,15(S) - dihydroxy - 15 - methylprost - *trans* - 13 - enoic acid;

65/7. 5 - bromo - 6βH - 6,9α - oxide - 11α,15(S) - dihydroxy - 16(S) - methylprost - *trans* - 13 - enoic acid;

96/4. 5 - bromo - 6βH - 6,9α - epoxy - 11α,15(S) - dihydroxy - 16 - *m* - trifluoromethyl - phenoxy - 17,18,19,20 - tetranorprost - *trans* - 13 - enoic acid.

Example 97

A solution of 0.1×10⁻³ M of a methyl ester, prepared according to Examples 93 to 96 in 2 ml of methanol is treated with 1 ml of an aqueous solution of lithium hydroxide (0.2×10⁻³ moles). The mixture is stirred for 3 hours, evaporated nearly to dryness, diluted with 5 ml of water, and extracted with diethyl ether. The organic

phase is washed with 0.1N LiOH (2N) and water, and is then discarded. The aqueous phase is acidified to pH 4.8 with 30% aqueous NaH_2PO_4 and extracted with diethyl ether to give the free acid.

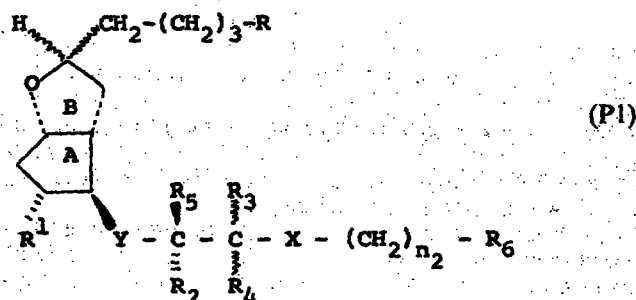
The free acids not already designated by a number are designated as follows:

5	Methyl ester	Free acid	5
	93/1 to 93/12	97/1 to 97/12	
	94/1 to 94/2	97/13 to 97/14	
	96/1 to 96/4	97/15 to 97/18	
	95/1 and 95/2	97/19 and 97/20	

10 In the following claims some shorthand notations have been used. Where it is desired to refer in a claim to the whole of a definition in terms of a generic formula, in an earlier claim, reference is made to compounds *defined* in the formula. Where, however, it is desired to repeat the drawing of the formula appearing in an earlier claim but not the definitions of the symbols used therein reference is made to a formula *drawn* in the earlier claim.

15 Each claim 76 to 1,778 is to be construed as a distinct and separate claim from each other such claim, for all purposes (including particularly the allocation of priority dates). Shorthand notation is used for these claims in the interests of economy and convenience.

20 WHAT WE CLAIM IS:—
1. Compounds of formula (P1)



wherein:

- 25 R is a carboxy group or an alkoxycarbonyl group having 2 to 13 carbon atoms;
R₁ is hydrogen or hydroxy;
- 25 Y is $-\text{CH}_2\text{CH}_2-$, $-\text{C}\equiv\text{C}-$, or *cis-* or *trans-* $-\text{CH}=\text{CH}-$;
- 25 R₂ is hydroxy or alkoxy having 1 to 6 carbon atoms;
R₅ is hydrogen or alkyl having 1 to 6 carbon atoms;
- 30 each of R₃ and R₄, which are the same or different, is hydrogen, alkyl having 1 to 6 carbon atoms or fluorine;
- 30 X is $-\text{O}-$, $-\text{S}-$, $-\text{CH}_2-$, or a single bond;
n₂ is 0 or an integer of 1 to 6; and
R₆ is:
- 35 (a') hydrogen
- 35 (b') methyl
- 35 (c') a cycloalkyl group having 3 to 9 ring atoms, which is unsubstituted or is substituted by one or more substituents selected from alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms;
- 40 (d') aryl, unsubstituted or ring-substituted by one or more substituents selected from halogen, trifluoromethyl, alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms; and
- 40 (e') a saturated or unsaturated heterocyclic ring group which is unsubstituted or substituted by one or more substituents selected from halogen, trifluoromethyl, alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms;
- 45

and the pharmaceutically or veterinarily acceptable salts of the above compounds in which R is carboxy, but excluding the following:

9 - deoxy - 6 β ,9 α - epoxy - PGF₁, its salts and its methyl ester;

phase is washed with 0.1N LiOH (2N) and water, and is then discarded. The aqueous phase is acidified to pH 4.8 with 30% aqueous NaH_2PO_4 and extracted with diethyl ether to give the free acid.

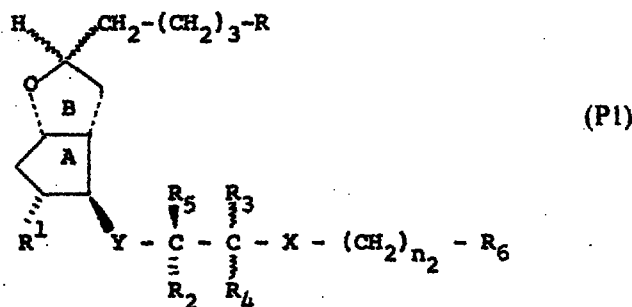
The free acids not already designated by a number are designated as follows:

5	Methyl ester	Free acid	5
	93/1 to 93/12	97/1 to 97/12	
	94/1 to 94/2	97/13 to 97/14	
	96/1 to 96/4	97/15 to 97/18	
	95/1 and 95/2	97/19 and 97/20	

10 In the following claims some shorthand notations have been used. Where it is desired to refer in a claim to the whole of a definition in terms of a generic formula, in an earlier claim, reference is made to compounds *defined* in the formula. Where, however, it is desired to repeat the drawing of the formula appearing in an earlier claim but not the definitions of the symbols used therein reference is made to a formula *drawn* in the earlier claim.

15 Each claim 76 to 1,778 is to be construed as a distinct and separate claim from each other such claim, for all purposes (including particularly the allocation of priority dates). Shorthand notation is used for these claims in the interests of economy and convenience.

20 WHAT WE CLAIM IS:—
1. Compounds of formula (P1)



wherein: -

- 25 R is a carboxy group or an alkoxycarbonyl group having 2 to 13 carbon atoms;
- R₁ is hydrogen or hydroxy;
- Y is $-\text{CH}_2\text{CH}_2-$, $-\text{C}\equiv\text{C}-$, or *cis-* or *trans-* $-\text{CH}=\text{CH}-$;
- R₂ is hydroxy or alkoxy having 1 to 6 carbon atoms;
- R₅ is hydrogen or alkyl having 1 to 6 carbon atoms;
- 30 each of R₃ and R₄, which are the same or different, is hydrogen, alkyl having 1 to 6 carbon atoms or fluorine;
- X is $-\text{O}-$, $-\text{S}-$, $-\text{CH}_2-$, or a single bond;
- n₂ is 0 or an integer of 1 to 6; and
- R₆ is:
 - 35 (a') hydrogen
 - (b') methyl
 - (c') a cycloalkyl group having 3 to 9 ring atoms, which is unsubstituted or is substituted by one or more substituents selected from alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms;
 - 40 (d') aryl, unsubstituted or ring-substituted by one or more substituents selected from halogen, trifluoromethyl, alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms; and
 - (e') a saturated or unsaturated heterocyclic ring group which is unsubstituted or substituted by one or more substituents selected from halogen, trifluoromethyl, alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms;

45 and the pharmaceutically or veterinarily acceptable salts of the above compounds in which R is carboxy, but excluding the following:

9 - deoxy - 6 ξ ,9 α - epoxy - PGF₁, its salts and its methyl ester;



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9 - deoxy - 6 ξ ,9 α - epoxy - 16,16 - dimethyl - PGF₁, and its salts;
9 - deoxy - 6 ξ ,9 α - epoxy - 17 - phenyl - 18,19,20 - trinor - PGF₁, methyl ester; and

5

9 - deoxy - 6 ξ ,9 α - epoxy - 15(S) - 15 - methyl - PGF₁, and its salts.
2. Compounds of formula (PI) defined in claim 1 excluding those in which simultaneously;

5

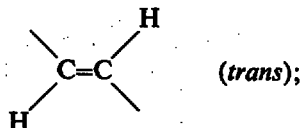
R is a carboxy group or an alkoxycarbonyl group having from 2 to 5 carbon atoms;

10

R₁ is hydroxy;

Y is

10



R₂ is hydroxy;

R₃, R₄ and R₅ are hydrogen; and

15

X—(CH₂)_n—R₆ is —(CH₂)₃—CH₃; and the pharmaceutically acceptable or veterinarily acceptable salts of the non-excluded compounds of formula (PI) in which R is carboxy.

15

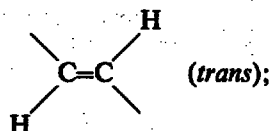
3. Compounds of formula (PI) defined in claim 1 excluding those in which simultaneously;

20

R is a carboxy group or an alkoxycarbonyl group having from 2 to 9 carbon atoms;

20

Y is



R₂ is hydroxy;

25

R₅ is hydrogen or alkyl having from 1 to 4 carbon atoms; each of R₃ and R₄, which are the same or different, is hydrogen, alkyl having 1 to 4 carbon atoms or fluorine; and either (a)

25

X is a single bond, n₂ is an integer of 1 to 5 and R₆ is methyl, in which case one of R₃ and R₄ can be fluoro only when the other is hydrogen or fluoro,

or (b)

30

X is a single bond, n₂ is an integer from 1 to 6, and R₆ is phenyl unsubstituted or ring-substituted by one to three substituents selected from fluoro, chloro, trifluoromethyl, alkyl having 1 to 4 carbon atoms or alkoxy having 1 to 4 carbon atoms provided that no more than two such substituents are other than alkyl;

30

or (c)

35

X is —O—, n₂ is 0, R₆ is phenyl unsubstituted or ring-substituted as defined above and neither R₃ nor R₄ is fluoro when X is —O—; and the pharmaceutically or veterinarily acceptable salts of the non-excluded compounds of formula (PI).

35

4. Compounds of formula (PI) drawn in claim 1 wherein:

40

Y is —C≡C— and all other symbols are as defined in claim 1; and the pharmaceutically or veterinarily acceptable salts of the above compounds in which R is carboxy.

40

5. Compounds according to claim 1, 2 or 3 wherein:

45

R is —COOH or —COOCH₃;

Y is —C≡C—;

R₂ is hydroxy and R₅ is hydrogen or methyl;

45

R₃ is hydrogen or methyl;

R₄ is hydrogen or methyl; and

X—(CH₂)_{n₂}—R₆ represents n-butyl, n-butoxy, phenyl, phenoxy, or benzyl.

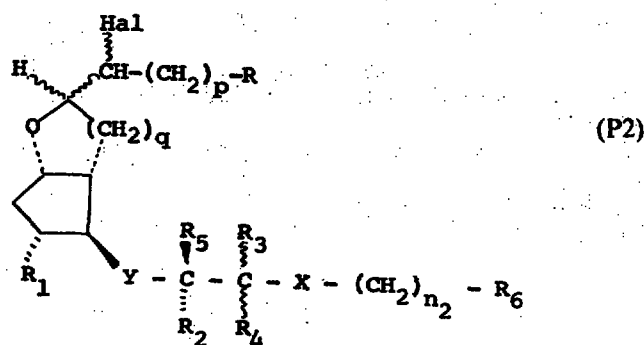
6. Compounds of formula (P2)



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wherein:

R is a carboxy group or an alkoxycarbonyl group having 2 to 13 carbon atoms;
p is an integer from 1 to 7;

Hal is a halogen atom;

R₁ is hydrogen or hydroxy;

q is 1 or 2;

Y is —CH₂CH₂—, —C=C— or *cis*- or *trans*- —CH=CH—;

R₂ is hydroxy or alkoxy having 1 to 6 carbon atoms;

R₃ is hydrogen or alkyl having 1 to 6 carbon atoms;
each of R₃ and R₄, which are the same or different, is hydrogen, alkyl having 1 to 6 carbon atoms or fluorine;

X is —O—, —S—, —CH₂— or a single bond;

n₂ is 0 or an integer of from 1 to 6; and

R₅ is:

(a') hydrogen

(b') methyl

(c') a cycloalkyl group having 3 to 9 ring atoms, which is unsubstituted or is substituted by one or more substituents selected from alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms;

(d') aryl, unsubstituted or ring-substituted by one or more substituents selected from halogen, trifluoromethyl, alkyl having 1 to 6 carbon atoms, and alkoxy having 1 to 6 carbon atoms; and

(e') a saturated or unsaturated heterocyclic ring group which is unsubstituted or substituted by one or more substituents selected from halogen, trifluoromethyl, alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms;

and the pharmaceutically or veterinarily acceptable salts of the above compounds in which R is carboxy.

7. Compounds of formula (P2) defined in claim 6 excluding those in which simultaneously:

R is a carboxy group or an alkoxycarbonyl group having from 2 to 5 carbon atoms;

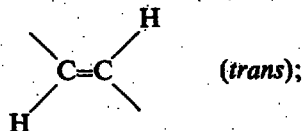
Hal is bromo or iodo;

p is 3;

R₁ is hydroxy;

q is 1;

Y is



R₃, R₄ and R₅ are hydrogen; and

X—(CH₂)_{n2}—R₆ is —(CH₂)₃—CH₃;

and the pharmaceutically or veterinarily acceptable salts of the non-excluded compounds of formula (P2).

8. Compounds of formula (P2) defined in claim 6 excluding those in which simultaneously:

p is an integer from 1 to 6;

Hal is iodo;



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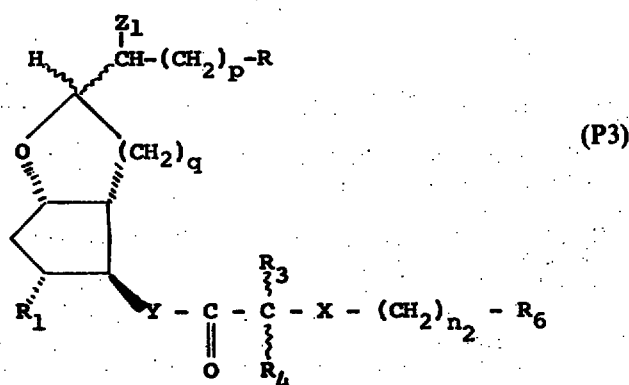
61

R_2 is hydroxy;
 R_5 is hydrogen or alkyl having 1 to 4 carbon atoms;
each of R_3 and R_4 which are the same or different, is hydrogen, alkyl having from 1 to 4 carbon atoms or fluorine; and
5 X , n_2 and R_6 are as defined in the exclusion clause of claim 3;
and the pharmaceutically or veterinary acceptable salts of the non-excluded compounds of formula (P2) in which R is carboxy.

9. Compounds of formula (P2) defined in claim 6 in which q is 1 subject to exclusions as in claim 8 in respect of the meanings of the other symbols, and their pharmaceutically or veterinarily acceptable salts.

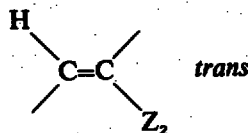
10. Compounds according to claim 6 wherein Hal is chlorine or bromine.

11. Compounds of formula (P3)



wherein:

R is a carboxy group or an alkoxycarbonyl group having 2 to 13 carbon atoms;
 p is an integer from 1 to 7;
 Z_1 is hydrogen or a halogen atom;
 R_1 is acyloxy;
 q is 1 or 2;
20 Y is



where Z_2 is hydrogen or halogen;
each of R_3 and R_4 , which are the same or different, is hydrogen, alkyl having 1 to 6 carbon atoms or fluorine;

X is $-O-$, $-S-$, $-CH_2-$ or a single bond;
 n_2 is 0 or an integer of from 1 to 6; and

R_6 is:

(a') hydrogen

(b') methyl

(c') a cycloalkyl group having 3 to 9 ring atoms, which is unsubstituted or is substituted by one or more substituents selected from alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms;

(d') aryl, unsubstituted or ring-substituted by one or more substituents selected from halogen, trifluoromethyl, alkyl having 1 to 6 carbon atoms, and alkoxy having 1 to 6 carbon atoms; and

(e') a saturated or unsaturated heterocyclic ring group which is unsubstituted or substituted by one or more substituents selected from halogen, trifluoromethyl, alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms;
and the pharmaceutically or veterinarily acceptable salts of the above compounds in which R is carboxy.

12. Compounds of formula (P3) drawn in claim 11 wherein:

R_1 is hydrogen, hydroxy or acyloxy;

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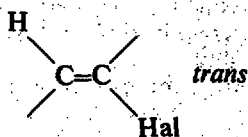


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Y is



and all other symbols are as defined in claim 11; and pharmaceutically or
veterinarily acceptable salts of the above compounds wherein R is carboxy.

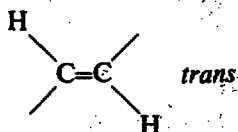
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13. Compounds of formula (P3) drawn in claim 11 wherein:

5

R₁ is hydrogen or hydroxy;

Y is



10

Z₁ is halogen as defined in claim 11 and all other symbols are as defined in
claim 11;

10

excluding those in which simultaneously:

p is an integer from 1 to 6;

Hal is iodo;

15

each of R₃ and R₄, which are the same or different, is hydrogen, alkyl having 1 to 4
carbon atoms or fluorine; and

15

X, n₂ and R₆ are as defined in the exclusion clause of claim 3;

and the pharmaceutically or veterinarily acceptable salts of the non-excluded
compounds of formula (P3) defined above wherein R is carboxy.

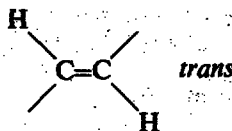
20

14. Compounds of formula (P3) drawn in claim 11 wherein:

20

R₁ is hydrogen or hydroxy

Y is



25

Z₁ is hydrogen and all other symbols are as defined in claim 11;
and the pharmaceutically or veterinarily acceptable salts of the compounds defined
above wherein R is carboxy.

25

15. Compounds according to claim 14 wherein q is 1.

16. Compounds according to claim 15 excluding those in which
simultaneously:

30

R₃, R₄, X, n₂ and R₆ are as defined in the exclusion clause of claim 3.

30

17. Compounds according to claim 14 wherein q is 2.

18. Compounds according to claim 17 wherein:

R₁ is —COOH or —COOCH₃;

R₃ is hydrogen or methyl;

R₄ is hydrogen or methyl; and

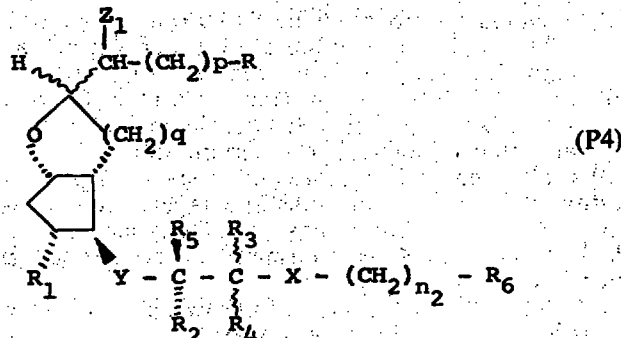
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X—(CH₂)_{n₂}—R₆

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represents n-butyl, n-butoxy, phenyl, phenoxy, or benzyl.

19. Compounds of formula:

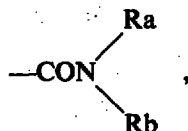


wherein:



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R is carboxy, alkoxycarbonyl having 2 to 13 carbon atoms or



Ra and Rb being independently hydrogen, alkyl having 1 to 6 carbon atoms or phenyl;

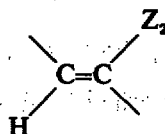
p is 1 to 7;

Z₁ is hydrogen or halogen;

q is 1 or 2;

R₁ is hydrogen, hydroxy, alkoxy having 1 to 6 carbon atoms, atoms, aralkoxy having 1 to 6 carbon atoms in the alkoxy part thereof, or acyloxy;

Y is



Z₂ being hydrogen or halogen;

one of R₂ and R₃ is hydrogen, alkyl having 1 to 6 carbon atoms, alkenyl or alkynyl having 2 to 6 carbon atoms or aryl, and the other is hydroxy, alkoxy having 1 to 6 carbon atoms, or aralkoxy having 1 to 6 carbon atoms in the alkoxy part thereof; each of R₃ and R₄ is independently hydrogen, alkyl having 1 to 6 carbon atoms or fluorine;

X is —O—, —S—, a single bond or —CH₂—;

n₂ is 0 or an integer of 1 to 6;

R₅ is:

(a') hydrogen,

(b') methyl,

(c') a cycloalkyl group having 3 to 9 ring atoms, which is unsubstituted or is substituted by one or more substituents selected from alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms;

(d') aryl, unsubstituted or ring-substituted by one or more substituents selected from halogen, trifluoromethyl, alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms; and

(e') a saturated or unsaturated heterocyclic ring group which is unsubstituted or substituted by one or more substituents selected from halogen, trifluoromethyl, alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms;

and the pharmaceutically or veterinarily acceptable salts of the above compounds in which R is carboxy,

with the proviso that when R is carboxy or alkoxy carbonyl having 2 to 13 carbon atoms:

(a) when Z₁ is hydrogen, p is 1, 2, 4, 5, 6 or 7 or q is 2 or R₁ is a said alkoxy, aralkoxy or acyloxy group or R₂ is hydrogen, or a said alkyl, alkenyl, alkynyl, aryl or aralkoxy group or R₅ is a said alkenyl, alkynyl, aryl, hydroxy, alkoxy or aralkoxy group; and

(b) when Z₁ is halogen, Z₂ is halogen, or R₁ is alkoxy having 1 to 6 carbon atoms or R₂ is hydrogen, or a said alkyl, alkenyl, alkynyl, aryl or aralkoxy group or R₅ is a said alkenyl, alkynyl, aryl, hydroxy, alkoxy or aralkoxy group,

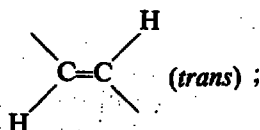
excluding compounds in which simultaneously:

Z₁ is iodo;

p is an integer from 1 to 6;

R₁ is hydrogen or hydroxy;

Y is



R₂ and R₅ are both hydrogen



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or one of R_2 and R_5 is hydrogen or alkyl having 1 to 4 carbon atoms and the other is hydroxy;

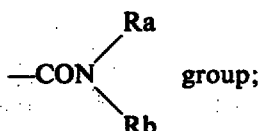
each of R_3 and R_4 which are the same or different is hydrogen, alkyl having from 1 to 4 carbon atoms or fluorine; and

5 X , n_2 and R_6 are as defined in the exclusion clause of claim 13; and also excluding

9 - deoxy - 6 β ,9 α - epoxy - 2 - nor PGF₁ methyl ester.

20. Compounds of Formula (P4) defined in claim 19 in which Z_1 is hydrogen excluding those in which simultaneously:

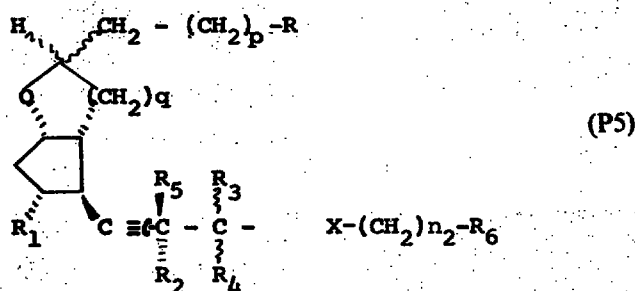
10 R is a carboxyl group, an alkoxycarbonyl group having from 2 to 9 carbon atoms or a said



15 q is 1; and Y , R_2 , R_5 , R_3 , R_4 , X , n_2 and R_6 are as defined in the exclusion clause of claim 3;

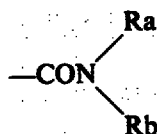
and the pharmaceutically or veterinarily acceptable salts of the non-excluded compounds of formula (P4).

21. Compounds of formula:



wherein:

20 R is carboxy, alkoxycarbonyl having 2 to 13 carbon atoms or



R_a and R_b being independently hydrogen, alkyl having 1 to 6 carbon atoms or phenyl;

25 p is 1 to 7;

q is 1 or 2;

R_1 is hydrogen, hydroxy, alkoxy having 1 to 6 carbon atoms, aralkoxy having 1 to 6 carbon atoms in the alkoxy part thereof, or acyloxy;

30 one of R_2 and R_5 is hydrogen, alkyl having 1 to 6 carbon atoms, alkenyl or alkynyl having 2 to 6 carbon atoms or aryl, and the other is hydroxy, alkoxy having 1 to 6 carbon atoms, or aralkoxy having 1 to 6 carbon atoms in the alkoxy part thereof;

each of R_3 and R_4 is independently hydrogen, alkyl having 1 to 6 carbon atoms of fluorine;

35 X is $-\text{O}-$, $-\text{S}-$, a single bond or $-\text{CH}_2-$;

n_2 is 0 or an integer of 1 to 6;

R_6 is:

(a') hydrogen

(b') methyl

40 (c') a cycloalkyl group having 3 to 9 ring atoms which is unsubstituted or substituted by one or more substituents selected from alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms;

(d') aryl, unsubstituted or ring-substituted by one or more substituents



selected from halogen, trifluoromethyl, alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms; and

(e') a saturated or unsaturated heterocyclic ring group which is unsubstituted or substituted by one or more substituents selected from halogen, trifluoromethyl, alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms;

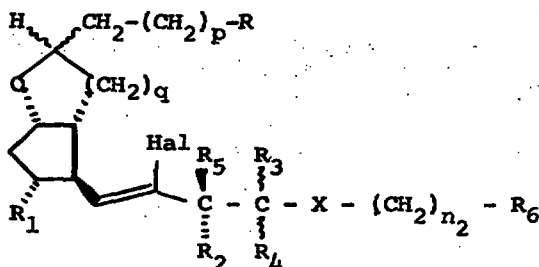
and the pharmaceutically or veterinarily acceptable salts of the above compounds in which R is carboxy,

with the proviso that when R is carboxy or alkoxy-carbonyl having 2 to 13 carbon atoms, p is 1, 2, 4, 5, 6, or 7 or q is 2 or R₁ is a said alkoxy, aryloxy or acyloxy group or R₂ is hydrogen or a said alkyl, alkenyl, alkynyl, aryl or aralkoxy group or R₅ is a said alkenyl, alkynyl, aryl, hydroxy, alkoxy or aralkoxy group.

22. Compounds according to claim 21 wherein q is 1.

23. Compounds of formula (P5) drawn in claim 21 wherein:

R, p, q, R₁, R₅, X, N₂ and R₆ are as defined in Formula (P5) in claim 21 (but are not subject to the proviso of claim 21) and the pharmaceutically or veterinarily acceptable salts of the above compounds in which R is carboxy, when prepared by a process which comprises dehydrohalogenating a compound of general formula:



Hal representing a halogen atom and all other symbols being as defined in formula (P5) in claim 21) but are not subject to the proviso of claim 21).

24. Compounds according to claim 23 wherein in formula (P5):

R is -COOH or -COOCH₃;

R₂ is hydroxy and R₅ is hydrogen or methyl;

R₃ is hydrogen or methyl;

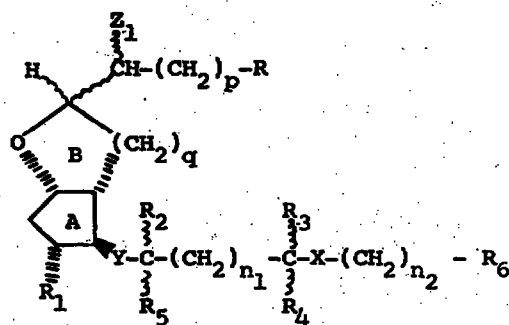
R₄ is hydrogen or methyl;

and X-(CH₂)_{n2}-R₆ represents n-butyl, n-butoxy, phenyl, phenoxy or benzyl.

25. Compounds according to claim 24 wherein q is 1.

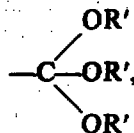
26. Compounds according to claim 24 wherein q is 2.

27. Compounds of formula (I)



wherein

R is (a) a free or esterified carboxy group; (b)



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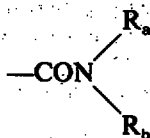


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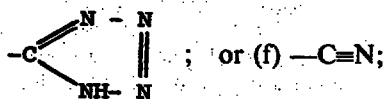
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wherein each of the R' groups, which are the same or different, is alkyl having 1 to 6 carbon atoms or phenyl; (c) $-\text{CH}_2\text{OH}$; (d)



wherein R_a and R_b are independently selected from hydrogen, alkyl having 1 to 6 carbon atoms, alkanoyl having 2 to 6 carbon atoms and phenyl; (e) a group of formula:



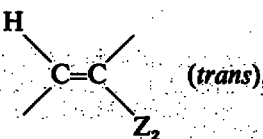
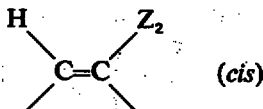
Z₁ is hydrogen or halogen;

p is zero or an integer of 1 to 7;

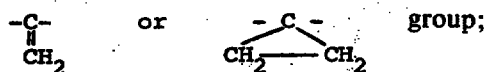
q is 1 or 2;

R₁ is hydrogen, hydroxy, alkoxy having 1 to 6 carbon atoms, aralkoxy having 1 to 6 carbon atoms in the alkoxy part, acyloxy;

Y is $-\text{CH}_2\text{CH}_2-$, $-\text{C}\equiv\text{C}-$,



wherein Z₂ is hydrogen or halogen; one of R₂ and R₃ is hydrogen, alkyl having 1 to 6 carbon atoms, alkenyl or alkynyl having 2 to 6 carbon atoms or aryl, and the other is hydroxy having 1 to 6 carbon atoms, alkoxy or aralkoxy having 1 to 6 carbon atoms or R₂ and R₃, taken together, form an oxo group; each of R₃ and R₄, which are the same or different, is hydrogen, C₁-C₆ alkyl or fluorine or R₃ and R₄, taken together with the carbon atom to which they are attached, form a



each of n₁ and n₂, which are the same or different, is 0 or an integer of 1 to 6;

X is $-\text{O}-$, $-\text{S}-$, a single bond, or $-\text{CH}_2-$;

R₅ is selected from:

(a') hydrogen

(b') alkyl, having 1 to 4 carbon atoms

(c') a cycloaliphatic group having 3 to 9 carbon atoms unsubstituted or substituted by one or more substituents selected from alkyl and alkoxy having 1 to 6 carbon atoms,

(d') aryl, unsubstituted or substituted by one or more substituents selected from halogen and haloalkyl, alkyl and alkoxy having 1 to 6 carbon atoms,

(e') a saturated or unsaturated heterocyclic ring, unsubstituted or substituted by one or more substituents selected from halogen and haloalkyl, alkyl and alkoxy and having 1 to 6 carbon atoms; and

the pharmaceutically or veterinarily acceptable salts therefore, but *excluding* compounds (i) which are claimed in any one of the above claims 1, 6, 11 to 14, 19, 21 and 23; (ii) compounds (u) as hereinbefore defined (i) compounds defined in the exclusion clause of claim 1 above, and (iv) 9 - deoxy - 6 ξ ,9 α - epoxy - 2 - nor - PGF₁₁, methyl ester and 9 - deoxy - 6 ξ ,9 α - epoxy - 2,3,4 - trinor - PGF₁₁, methyl and ethyl esters.



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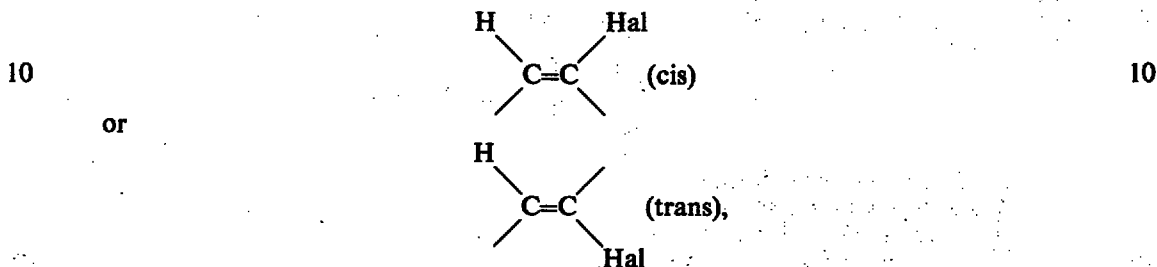
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28. Compounds of formula (I) drawn in claim 27 wherein R has meaning (b) or (f) set out in claim 27; and the other symbols are as defined in claim 27; and the pharmaceutically or veterinarily acceptable salts thereof.

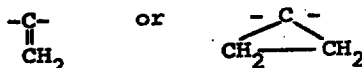
29. Compounds of formula (I) drawn in claim 27 wherein
5 R₁ is an alkoxy group having 1 to 6 carbon atoms or an aralkoxy group having 1 to 6 carbon atoms in the alkoxy part thereof; and the other symbols are as defined in claim 27; and the pharmaceutically or veterinarily acceptable salts thereof.

30. Compounds of formula (I) drawn in claim 27 wherein Y is



Hal representing a halogen atom and the other symbols are as defined in claim 27; and the pharmaceutically or veterinarily acceptable salts thereof.

31. Compounds of formula (I) drawn in claim 27 wherein
15 R₃ and R₄ together with the carbon atom to which they are attached form a

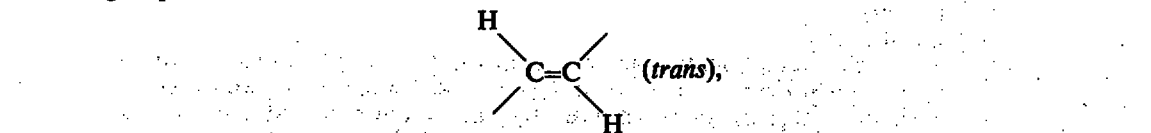


group; and the other symbols are as defined in claim 27; and the pharmaceutically or veterinarily acceptable salts thereof.

32. Compounds of formula (I) drawn in claim 27 wherein
20 R₅ has the meaning (c') or (e') defined in claim 27; and the other symbols are as defined in claim 27; and the pharmaceutically or veterinarily acceptable salts thereof.

33. Compounds of formula (I) drawn in claim 27 wherein
25 R₆ is aryl substituted by one or more haloalkyl substituents, and the other symbols are as defined in claim 27; and the pharmaceutically or veterinarily acceptable salts thereof.

34. Compounds of formula (I) drawn in claim 27 wherein Z₁ is chlorine or bromine; and the other symbols are as defined in claim 27; and the pharmaceutically or veterinarily acceptable salts thereof, excluding compounds in which simultaneously Z₁ is bromine, p is 3, q is 1, R is a free or esterified carboxy group, Y is



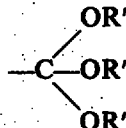
35 R₁ is hydroxy, R₂ is 15(S)-hydroxy, R₃ is hydrogen, n₁ is 0, R₅ and R₄ are both hydrogen and X-(CH₂)_{n₂}-R₆ is an n-butyl group.

35. Compounds according to any one of claims 28 to 33 wherein
Z₁ is fluorine, chlorine or bromine.

36. Compounds according to any one of claims 28 to 33 wherein
q is 2 and Z₁ is hydrogen.

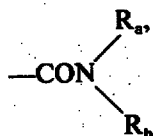
37. Compounds of formula (I) drawn in claim 27 wherein
40 q is 2;

R is (a) a free or esterified carboxy group; (b)

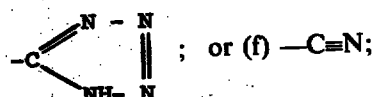




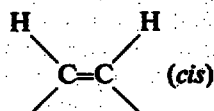
wherein each of R' groups, which are the same or different, is C_1-C_6 alkyl or phenyl; (c) $-CH_2OH$; (d)



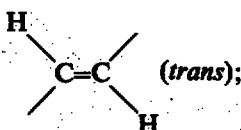
wherein R_a and R_b are independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkanoyl and phenyl; (e) a group of formula



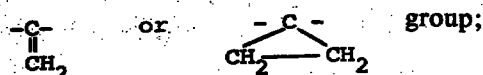
Z_1 is bromine, or chlorine;
 p is zero or an integer of 1 to 7;
 R_1 is hydrogen or hydroxy; and
 Y is $-CH_2-CH_2-$, $-C \equiv C-$,



or



one of R_2 and R_3 is hydrogen or C_1-C_6 alkyl and the other is hydroxy or R_2 and R_3 taken together, form an oxo group; each of R_4 and R_5 , which are the same or different, is hydrogen, C_1-C_6 alkyl or fluorine or R_4 and R_5 , taken together with the carbon atom to which they are attached form a



each of n_1 and n_2 , which are the same or different, is 0 or an integer of 1 to 6;
 X is $-O-$, $-S-$, a single bond or $-CH_2-$;

R_6 is

(a') hydrogen;

(b') C_1-C_6 alkyl;

(c') a C_3-C_9 cycloaliphatic radical, unsubstituted or substituted by one or more substituents selected from C_1-C_6 alkyl and C_1-C_6 alkoxy;

(d') aryl, unsubstituted or substituted by one or more substituents selected from halogen, halo- C_1-C_6 -alkyl, C_1-C_6 alkyl and C_1-C_6 alkoxy; and

(e') a saturated or unsaturated heterocyclic ring, unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, halo- C_1-C_6 -alkyl, C_1-C_6 alkyl and C_1-C_6 alkoxy; and

the pharmaceutically or veterinarily acceptable salts thereof.

38. Compounds of formula (I) drawn in claim 27 wherein

R_1 is C_1-C_6 alkoxy, aryl- C_1-C_6 -alkoxy or acyloxy; and all other symbols are as defined in claim 27 (but are not subject to the exclusion clauses of claim 27) and the pharmaceutically or veterinarily acceptable salts thereof.

39. Compounds of formula (I) drawn in claim 27 wherein

R_1 is hydrogen or hydroxy;

one of R_2 and R_3 is C_1-C_6 alkoxy or ar- C_1-C_6 -alkoxy and the other is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl; and all other symbols are as defined in claim 27 (but are not subject to the exclusion clause of claim 27);

the pharmaceutically and veterinarily acceptable salts thereof.



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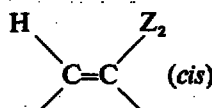
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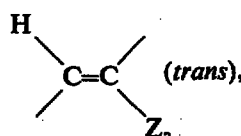
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40. Compounds of formula (I) drawn in claim 27 wherein R_1 is hydrogen or hydroxy; and one of R_2 and R_5 is C_2-C_6 alkenyl, C_2-C_6 alkynyl or aryl and the other is hydroxy; and all other symbols are as defined in claim 27 (but are not subject to the exclusion clause of claim 27) and the pharmaceutically or veterinarily acceptable salts thereof.

41. Compounds of formula (I) drawn in claim 27 wherein R_1 is hydrogen or hydroxy; Y is



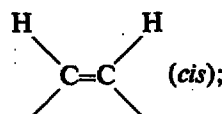
or



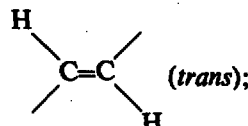
wherein Z_2 is halogen; and

one of R_2 and R_5 is hydroxy and the other is hydrogen or C_1-C_6 alkyl, or R_2 and R_5 taken together form an oxo group; and the other symbols are as defined in claim 27 (but are not subject to the exclusion clause of claim 27); and the pharmaceutically or veterinarily acceptable salts thereof.

42. Compounds according to claim 27 wherein X is $-S-$; q is 1; R_1 is hydrogen or hydroxy; Y is $-CH_2-CH_2-$; $C=C-$;



or



and

one of R_2 and R_5 is hydroxy and the other is hydrogen or C_1-C_6 alkyl or R_2 and R_5 taken together form an oxo group.

43. Compounds according to claim 1, 2, 3 or 4 wherein X is $-S-$, R_2 is hydroxy and R_5 is hydrogen or C_1-C_6 alkyl.

44. Compounds according to claim 6, 7, 8, 9 or 10 wherein X is $-S-$; q is 1; R_2 is hydroxy; and R_5 is hydrogen or C_1-C_6 alkyl.

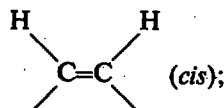
45. Compounds according to claim 13 or 15 wherein X is $-S-$; q is 1; and Z_2 is hydrogen.

46. Compounds according to claim 19 or 20 wherein X is $-S-$; q is 1; R_1 is hydrogen or hydroxy; Z_2 is hydrogen and one of R_2 and R_5 is hydroxy and the other is hydrogen or C_1-C_6 alkyl.

47. Compounds according to claim 21, 22 or 23 wherein X is $-S-$; q is 1; R_1 is hydrogen or hydroxy; and R_2 and R_5 are as defined in claim 46.

48. Compounds according to claim 27 wherein X is $-O-$; R_6 has any of meanings (a'), (b'), (c') and (e'); q is 1;

R_1 is hydrogen or hydroxy; Y is $-CH_2-CH_2-$; $C=C-$;



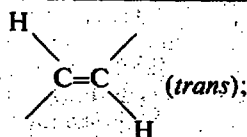
or



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and

one of R_2 and R_5 is hydroxy and the other is hydrogen or C_1-C_6 alkyl or R_2 and R_5 taken together form an oxo group.

5 49. Compounds according to claim 1, 2, 3 or 4 wherein X is $-\text{O}-$; R_6 has any of meanings (a'), (b'), (c') and (e'); R_2 is hydroxy and R_5 is hydrogen or C_1-C_6 alkyl. 5

10 50. Compounds according to claim 6, 7, 8, 9 or 10 wherein X is $-\text{O}-$; R_6 has any of meanings (a'), (b'), (c') and (e'); q is 1; R_2 is hydroxy; and R_5 is hydrogen or C_1-C_6 alkyl. 10

51. Compounds according to claim 13 or 15 wherein X is $-\text{O}-$; R_6 has any of meanings (a'), (b'), (c') and (e'); q is 1; and Z_2 is hydrogen.

15 52. Compounds according to claim 19 or 20 wherein X is $-\text{O}-$; R_1 is hydrogen or hydroxy; R_6 has any of meanings (a'), (b'), (c') and (e'); q is 1; Z_2 is hydrogen and one of R_2 and R_5 is hydroxy and the other is hydrogen or C_1-C_6 alkyl. 15

20 53. Compounds according to claim 21, 22 or 23 wherein X is $-\text{O}-$; R_1 is hydrogen or hydroxy; R_6 has any of meanings (a'), (b'), (c') and (e'); q is 1; and R_2 and R_5 are as defined in claim 51. 20

54. Compounds according to claim 27 wherein X is $-\text{O}-$;

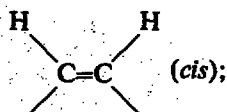
R_6 has meaning (d'); 20

q is 1;

R_1 is hydrogen or hydroxy;

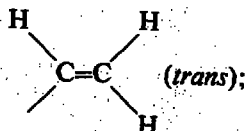
Y is $-\text{CH}_2\text{CH}_2-$, $-\text{C}\equiv\text{C}-$;

25



25

or



30 one of R_2 and R_5 is hydroxy and the other is hydrogen or C_1-C_6 alkyl or R_2 and R_5 , taken together, form an oxo group; and at least one of n_1 and n_2 is an integer of 1 to 6. 30

35 55. Compounds according to claim 6, 7, 8, 9 or 10 wherein X is $-\text{O}-$; R_6 has meaning (d'); q is 1; R_2 is hydroxy; R_5 is hydrogen or C_1-C_6 alkyl; and at least one of n_1 and n_2 is an integer of 1 to 6. 35

56. Compounds according to claim 13 or 15 wherein X is $-\text{O}-$; R_6 has meaning (d'); q is 1; and at least one of n_1 and n_2 is an integer of 1 to 6. 35

40 57. Compounds according to claim 19 or 20 wherein X is $-\text{O}-$; R_6 has meaning (d'); q is 1; R_1 is hydrogen or hydroxy; Z_2 is hydrogen; one of R_2 and R_5 is hydroxy and the other is hydrogen or C_1-C_6 alkyl; and at least one of n_1 and n_2 is an integer of 1 to 6. 40

58. Compounds according to claim 21, 22 or 23 wherein X is $-\text{O}-$; R_1 is hydrogen or hydroxy; R_6 has meaning (d'); q is 1; R_2 and R_5 are as defined in claim 57; and at least one of n_1 and n_2 is an integer of 1 to 6. 40

59. Compounds according to claim 27 wherein R is a carboxy group, alkoxy carbonyl group having 2 to 13 carbon atoms or has meaning (b), (d) or (f); 45

Z_1 is hydrogen;

q is 1;

R_1 is hydrogen or hydroxy;

Y is $\text{C}=\text{C}-$;

one of R_2 and R_5 is hydroxy and the other is hydrogen or C_1-C_6 alkyl;

50 n_1 and n_2 are zero;

X is $-\text{O}-$; and 50



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R_6 is aryl, unsubstituted or substituted by one or more substituents selected from halogen, halo- C_1-C_6 -alkyl, C_1-C_6 alkyl and C_1-C_6 alkoxy.

60. Compounds of formula (P5) drawn in claim 21 wherein q is 1, R_1 is hydrogen or hydroxy, one of R_2 and R_5 is hydroxy and the other is hydrogen or C_1-C_6 alkyl, n_2 is 0, X is $-O-$ and R_6 is aryl, unsubstituted or substituted by one or more substituents selected from halogen, halo- C_1-C_6 alkyl, C_1-C_6 -alkyl and C_1-C_6 alkyl; and all other symbols are as defined in formula (P5) in claim 21 (but are not subject to the proviso clause of claim 21) and the pharmaceutically or veterinarily acceptable salts thereof.

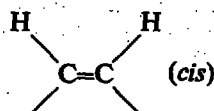
61. Compounds according to claim 27 wherein R is a carboxy group or an alkoxy carbonyl group having 2 to 13 carbon atoms,

Z_1 is bromine or chlorine;

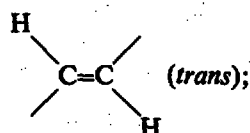
q is 1;

R_1 is hydrogen or hydroxy;

Y is $-CH_2CH_2-$, $-C\equiv C-$,



or



one of R_2 and R_5 is hydroxy and the other is hydrogen or C_1-C_6 alkyl;

n_1 and n_2 are zero;

X is $-O-$; and

R_6 is aryl, unsubstituted or substituted by one or more substituents selected from halogen, halo- C_1-C_6 -alkyl, C_1-C_6 alkyl and C_1-C_6 alkoxy.

62. Compounds according to claim 10 wherein q is 1 one of R_2 and R_5 is hydroxy and the other is hydrogen or C_1-C_6 alkyl, n_2 is 0, X_2 is $-O-$ and R_6 is aryl, unsubstituted or substituted by one or more substituents selected from halogen, halo- C_1-C_6 -alkyl, C_1-C_6 -alkyl and C_1-C_6 alkoxy.

63. Compounds according to claim 27

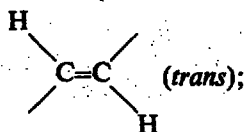
R is a carboxy group or an alkoxy carbonyl group having 2 to 13 carbon atoms;

Z_1 is hydrogen, chlorine or bromine;

q is 1;

R_1 is hydrogen or hydroxy;

Y is



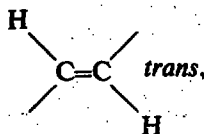
R_2 and R_5 , taken together, form an oxo group;

n_1 and n_2 are zero;

X is $-O-$; and

R_6 is aryl, unsubstituted or substituted by one or more substituents selected from halogen, halo- C_1-C_6 -alkyl, C_1-C_6 alkyl and C_1-C_6 alkyl and C_1-C_6 alkoxy.

64. Compounds according to claim 13 wherein Y is



Z_1 is hydrogen, chlorine or bromine.

q is 1,

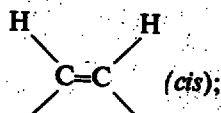


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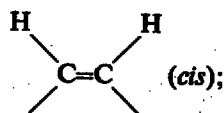
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n_2 is 0;
 X is $-\text{O}-$ and
 R_6 is aryl, unsubstituted or substituted by one or more substituents selected
 5 from halogen, halo- C_1-C_6 -alkyl, C_1-C_6 alkyl and C_1-C_6 alkyl and C_1-C_6 alkoxy.
 65. Compounds according to claim 1 wherein Y is $-\text{CH}_2\text{CH}_2-$ or

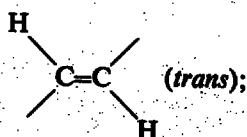


one of R_2 and R_5 is hydroxy and the other is hydrogen or C_1-C_6 alkyl;
 n_2 is 0;
 X is $-\text{O}-$; and
 10 R_6 is aryl, unsubstituted or substituted by one or more substituents selected
 from halogen, halo- C_1-C_6 -alkyl, C_1-C_6 alkyl and C_1-C_6 alkoxy;
 66. Compounds according to claim 27 wherein

X is a single bond or $-\text{CH}_2-$;
 R_6 has meaning (c') or (e');
 15 q is 1;
 R_1 is hydrogen or hydroxy;
 Y is $-\text{CH}_2-\text{CH}_2-$, $-\text{C}\equiv\text{C}-$;



or



and

one of R_2 and R_5 is hydroxy and the other is hydrogen, C_1-C_6 alkyl or R_2 and
 R_5 , taken together, form an oxo group.

67. Compounds according to claim 1, 2, 3 or 4 wherein
 X and R_6 are as defined in claim 66, R_2 is hydroxy and R_5 is hydrogen or C_1-
 C_6 alkyl.

68. Compounds according to claim 6, 7, 8, 9 or 10 wherein
 X and R_6 are as defined in claim 66,

q is 1;
 R_2 is hydroxy; and
 R_5 is hydrogen or C_1-C_6 alkyl;

69. Compounds according to claim 13 wherein
 X and R_6 are as defined in claim 66,

q is 1; and
 Z_2 is hydrogen.

70. Compounds according to claim 19 or 20 wherein

R_1 is hydrogen or hydroxy;
 X and R_6 are as defined in claim 66;

q is 1;
 Z_2 is hydrogen and one of R_2 and R_5 is hydroxy and the other is hydrogen or
 C_{1-6} alkyl.

71. Compounds according to claim 21, 22 or 23 wherein
 R_1 is hydrogen or hydroxy;

X and R_6 are as defined in claim 66;
 q is 1; and

R_2 and R_5 are as defined in claim 70.

72. Compounds according to claim 4 wherein R_2 is hydroxy, X is $-\text{O}-$, n_2 is 0
 and R_6 is aryl, unsubstituted or substituted by one or more substituents selected
 from halogen, trifluoromethyl, C_{1-6} alkyl and C_{1-6} alkoxy.

73. Compounds according to claim 4 wherein R_2 is hydroxy, X is $-\text{CH}_2-$ or a
 single bond, and R_6 has meaning (a'), (b') or (d') given in claim 1.



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74. Compounds according to claim 21 wherein q is 1; R₁ is hydrogen or hydroxy; one of R₂ and R₃ is hydrogen or C₁₋₆ alkyl and the other is hydroxy; X is —CH₂— or a single bond and R₆ has meaning (a'), (b') or (d') given in claim 21.

5 75. Compounds according to claim 10 wherein q is 1; Y is —C≡C—; R₂ is hydroxy; R₃ is hydrogen or C₁₋₆ alkyl; X is —CH₂— or a single bond; and R₆ has meaning (a'), (b') or (d') given in claim 6. 5

76. Compounds according to claim 1 wherein X is —O—; R₆ has meaning (d'); R₂ is hydroxy and R₃ is hydrogen or C₁₋₆ alkyl.

10 77 to 1,778. These claims are to be construed for all purposes as 1,702 separate, independent claims, each claim defining one only of the following 1,702 compounds hereinbefore mentioned: 10

	42/1 to 42/16	59/1 to 59/4	79	
	43/1 to 43/18	60/1 and 60/2	80	
	44/1 to 44/5	61/1 to 61/4	81/1 to 81/3	
15	45/1 to 45/4	62/1 and 62/2	82	15
	46/1 and 46/2	63/1 to 63/3	83/1 to 83/74	
	47/1 to 47/32	64/1 to 64/3		
	48/1 to 48/4	65/1 to 65/306	87/1 and 87/2	
	49/1 to 49/4	66/1 to 66/48	89	
20	50/1 and 50/2	67/1 to 67/438	90/1 and 90/2	20
	51/1 to 51/4	68/1 to 68/76	91/1 to 91/415	
	52/1 to 52/5	69/1 to 69/42	92/1 and 92/2	
	53/1 and 53/2			
	54/1 and 54/2	70/1 to 70/10	93/1 to 93/12	
25	55/1 and 55/2	71/1 to 71/5	94/1 and 94/2	25
	56/1 and 56/10	72/1 to 72/3	95/1 and 95/2	
	57/1 and 57/2	73/1 to 73/3	96/1 to 96/4	
	58/1 to 58/3	74/1 to 74/92	97/1 to 97/20	
		78/1 and 78/2		

30 1779. Each of the compounds according to any one of claims 1, 6, 11 to 14, 19, 21 and 23, other than claimed in claims 77 to 1778 hereinbefore mentioned. 30

1780. A pharmaceutical or veterinary composition comprising a compound claimed in any preceding claim in association with a pharmaceutically or veterinarily acceptable diluent or carrier.

35 1781. Use of a compound claimed in any one of claims 1 to 1779 in veterinary treatment. 35

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