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PATENT SPECIFICATION (11) 1 596 510

(21) Application No. 48955/77 (22) Filed 24 Nov. 1977
(31) Convention Application No. 2653564
(32) Filed 25 Nov. 1976
(31) Convention Application No. 2702369
(32) Filed 21 Jan. 1977 in
(33) Federal Republic of Germany (DE)
(44) Complete Specification published 26 Aug. 1981
(51) INT CL³ C07C 177/00 A61K 31/557//C07D 317/10 319/06 339/00 407/00
(52) Index at acceptance
C2C 1175 1492 1520 1672 1691 1692 200 211 215 21X 220 221 225 226 227 22Y 246 248 253 254 259 25Y 28X 295 304 305 30Y 311 313 31Y 338 350 351 353 355 35Y 360 361 362 363 364 366 367 368 36Y 37X 386 387 388 389 401 407 409 40Y 43X 46X 490 491 500 507 509 50Y 54X 623 624 625 628 633 634 638 648 652 655 658 65X 662 665 672 694 697 699 778 779 802 80Y AA BJ BW TA TC UF UL WJ

(54) 16-HYDROXYPROSTENOIC ACID DERIVATIVES AND PROCESSES FOR THEIR MANUFACTURE

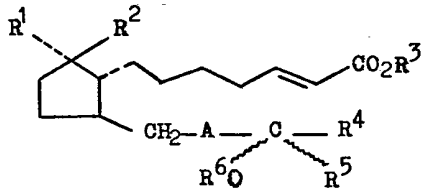
(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt/Main 80, Postfach 80 03 20, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The natural prostaglandins are a group of fatty acids which occur in numerous tissues and organs of humans and animals. The basic structure of the naturally occurring prostaglandins comprises 20 carbon atoms, which are arranged in the form of a five-membered ring and two adjacent linear side chains.

The pharmacological effects of the prostaglandins extend, *inter alia,* over the fields of reproduction, bronchial muscular tone, blood pressure and gastroenterology. These pharmacological properties are the subject of numerous review articles, for example N. H. Andersen and P. W. Ramwell in Arch. Internal Med. 133, 30 (1974); R. L. Jones in Pthobiology Ann. *1972,* 359; J. Pike in Scient. American *225,* 84 (1971) or M. P. L. Caton in Progress in Med. Chem., volume 8, edition: Butterworth, London, 1971.

The syntheses of analogues of prostanoic acids, which analogues are not naturally occurring and in which the multiplicity of pharmacological actions of the naturally occurring prostaglandins are differentiated, are becoming increasingly important.

The present invention provides a cyclopentane derivative of the general formula



I

wherein:

one of R^1 and R^2 represents a hydrogen atom and the other represents a hydroxyl group, or R^1 and R^2 together represent an oxygen atom;

R^3 represents a hydrogen atom; an aliphatic or cycloaliphatic hydrocarbon group having up to 8 carbon atoms; an alkoxyalkyl group having from 3 to 10 carbon atoms; an araliphatic hydrocarbon group having from 7 to 10 carbon atoms; a metal ion; an ammonium ion; or a substituted ammonium ion derived from a primary, secondary or tertiary amine;

R^4 represents an aliphatic hydrocarbon group having from 1 to 10 carbon atoms or a cycloaliphatic hydrocarbon group having from 3 to 7 carbon atoms, which aliphatic or cycloaliphatic group may be unsubstituted or substituted by one or more of the same or different substituents selected from: (a) aliphaticoxy or aliphatictho groups having from 1 to 7 carbon atoms;

(b) phenoxy groups which may be unsubstituted or substituted by one or two of the same or different substituents selected from alkyl groups having from 1 to 3 carbon atoms, which alkyl groups may be unsubstituted or substituted by one or more of the same or different halogen atoms; halogen atoms; phenoxy groups which may be unsubstituted or substituted by one or more of the same or different halogen atoms; and alkoxy groups having from 1 to 4 carbon atoms;

(c) furyloxy, thienyloxy, benzyloxy, phenyl, thienyl or furyl groups, which may be unsubstituted or substituted by one or two of the same or different substituents selected from alkyl groups having from 1 to 3 carbon atoms which may be unsubstituted or substituted by one or more of the same or different halogen atoms; halogen atoms; and alkoxy groups having from 1 to 4 carbon atoms;

(d) fluorine atoms, trifluoromethyl or pentafluoroethyl groups; and

(e) cycloalkyl groups having from 3 to 7 carbon atoms;

R^5 represents an alkyl group having from 1 to 5 carbon atoms; an alkenyl or alkynyl group having from 2 to 5 carbon atoms; or a hydrogen atom;

R^6 represents a hydrogen atom or a group of the general formula R^7CO, wherein R^7 represents a hydrogen atom or an alkyl group having up to 10 carbon atoms; and A represents a *trans*—CH=CH— group or a $—CH_2—CH_2—$ group with the proviso that if A represents a $—CH_2—CH_2—$ group, R^5 may only represent a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms.

Preferably if R^3 represents an ion, the ion is such that the resulting compound of the general formula I is physiologically tolerable. If the aliphatic or cycloaliphatic group represented by R^4 is substituted, it is preferably monosubstituted by any one of the substituents listed or disubstituted by two fluorine atoms.

Amongst the substituents mentioned, the following are preferred:

for R^3: a hydrogen atom, an alkyl group having from 1 to 8 carbon atoms, an alkoxyalkyl group having a total of from 3 to 10 carbon atoms, an alkenyl group having from 2 to 4 carbon atoms, a cycloalkyl group having from 5 to 7 carbon atoms, an aralkyl group having 7 or 8 carbon atoms, an ammonium ion, a physiologically tolerable metal ion or substituted ammonium ion which is derived from a primary, secondary or tertiary amine;

for R^4: an aliphatic hydrocarbon group having from 1 to 8 carbon atoms or a cycloaliphatic hydrocarbon group having from 5 to 7 carbon atoms, which groups may be unsubstituted or substituted by:

(a) an alkoxy, alkylthio, alkenyloxy or alkenylthio group having from 1 to 5 carbon atoms;

(b) a phenoxy group which may be unsubstituted or substituted by one or two of the same or different substituents selected from alkyl groups having from 1 to 3 carbon atoms; trifluoromethyl groups; halogen atoms; phenoxy groups which may be unsubstituted or substituted by one or more of the same or different halogen atoms; and methoxy and ethoxy groups;

(c) a thienyloxy, benzyloxy, phenyl or thienyl group which may be unsubstituted or substituted by one or two of the same or different substitutents selected from alkyl groups having from 1 to 3 carbon atoms; trifluoromethyl groups; halogen atoms; and methoxy and ethoxy groups;

(d) one or two fluorine atoms or a trifluoromethyl groups; or

(e) a cycloalkyl or cycloalkylidene group having from 5 to 7 carbon atoms.

for R^5: an alkyl group having from 1 to 5 carbon atoms or an alkenyl or alkynyl group having from 2 to 4 carbon atoms; and

for R^6: a hydrogen atom or a group of the general formula R^7CO, wherein R^7 represents a hydrogen atom or an alkyl group having up to 4 carbon atoms.

The following substituents are especially preferred:

for R^3: a hydrogen atom; a straight chain alkyl group having from 1 to 6 carbon atoms; a branched alkyl group having from 3 to 5 carbon atoms;

An alkoxyalkyl group; a straight chain alkenyl group having from 2 to 4 carbon atoms; a cyclopentyl, cyclohexyl or benzyl group; or a physiologically acceptable metal ion, ammonium ion or substituted ammonium ion which is derived from a primary, secondary or tertiary amine; and

for R^4: an alkyl group having from 1 to 6 carbon atoms, an alkenyl group

having from 3 to 5 carbon atoms or a cycloalkyl group having from 5 to 7 carbon atoms, which alkyl, alkenyl or cycloalkyl group may be unsubstituted or substituted by:

(a) an alkoxy, alkylthio, alkenyloxy or alkenylthio group having from 1 to 4 carbon atoms;

(b) a phenoxy group which may be unsubstituted or substituted by one or two of the same or different substituents selected from methyl, trifluoromethyl and methoxy groups; chlorine or fluorine atoms; and phenoxy groups which may be unsubstituted or substituted by one or more fluorine and/or chlorine atoms;

(c) a thienyloxy, benzyloxy, phenyl or thienyl group which may be unsubstituted or substituted by one or two of the same or different substituents selected from methyl, trifluoromethyl and methoxy groups and chlorine and fluorine atoms;

(d) one or two fluorine atoms or a trifluoromethyl group; or

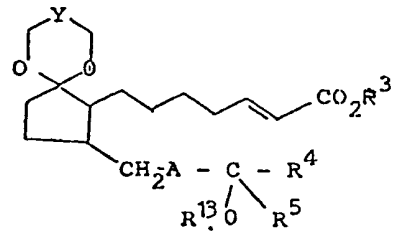
(e) a cycloalkyl group having from 5 to 7 carbon atoms.

R^4 especially represents one of the groups listed in Table A.

TABLE A

n - butyl, n - pentyl, n - hexyl, n - heptyl, 2,2 - dimethylhexyl, 3,3 - dimethylhexyl, 4,4 - dimethylhexyl, 3 - ethylpentyl, 1,1 - dimethyl - 4 - pentenyl, 5 - methyl - 4 - hexenyl, 1 - methyl - 5 - cyclohexylpentyl, 4 - cycloheptylidenebutyl, 4 - trifluoromethylbutyl, 5 - trifluoromethylheptyl, 1,1 - dimethyl - 6 - trifluoromethylhexyl, 1 - methyl - 5 - trifluoromethylpentyl, 1,1 - difluoro - 4,4 - dimethylpentyl, 4,4 - difluorocyclohexyl, 4 - trifluoromethylcyclohexyl, 3 - trifluoromethylcyclohexyl, 2 - trifluoromethylcycloheptyl, 3 - trifluoromethylcyclopentyl, 3,3 - dimethyl - 2 - oxapentyl, 3 - methyl - 2 - oxahexyl, 4,4 - dimethyl - 2 - oxapentyl, 1,1,4 - trimethyl - 2 - oxapentyl, 3,4 - dimethyl - 2 - oxapentyl, 5 - methyl - 2 - oxa - 4 - hexenyl, 2,2 - dimethyl - 3 - oxaheptyl, 1,1 - dimethyl - 3 - oxahexyl, 1,1 - dimethyl - 3 - oxaoctyl, 1,1,5,5 - tetramethyl - 3 - oxahexyl, 1 - methyl - 3 - oxahexyl, 1 - methyl - 3 - oxaoctyl, 1,1,6 - trimethyl - 3 - oxa - 5 - heptenyl, 1,1,6 - trimethyl - 3 - oxaheptyl, 7 - methyl - 4 - oxaoctyl, 1,1 - dimethyl - 4 - oxa - 6 - heptenyl, 4 - methoxycyclohexyl, 3 - butoxycyclohexyl, 2 - ethoxycyclohexyl, 3 - ethoxycyclopentyl, 4 - methoxycycloheptyl, 2 - thiapentyl, 2 - thiahexyl, 2 - thiaheptyl, 4,4 - dimethyl - 2 - thiapentyl, 5 - methyl - 2 - thia - 4 - hexenyl, 3 - thiapentyl, 3 - thiahexyl, 5,5 - dimethyl - 3 - thiahexyl, 1,1 - dimethyl - 3 - thiapentyl, 1,1 - dimethyl - 4 - thiapentyl, 4 - chlorophenoxymethyl, 3 - chlorophenoxymethyl, 2,3 - dichlorophenoxymethyl, 2,4 - dichlorophenoxymethyl, 2,5 - dichlorophenoxymethyl, 2,6 - dichlorophenoxymethyl, 3,4 - dichlorophenoxymethyl, 3,5 - dichlorophenoxymethyl, 2 - chloro - 6 - methylphenoxymethyl, 2 - chloro - 4 - methylphenoxymethyl, 3 - chloro - 2 - methylphenoxymethyl, 4 - chloro - 2 - methylphenoxymethyl, 5 - chloro - 2 - methylphenoxy, 4 - trifluoromethylphenoxymethyl, 3 - trifluoromethylphenoxymethyl, 2 - methyl - 5 - trifluoromethylphenoxymethyl, 3 - methyl - 5 - trifluoromethylphenoxymethyl, 3 - fluorophenoxymethyl, 2 - fluorophenoxymethyl, 3 - (4 - fluorobenzyloxy)propyl, 4 - (3 - chlorophenoxy)cyclohexyl, 4 - (3 - trifluoromethylphenoxy)cyclohexyl, 2 - phenoxycyclohexyl, 4 - (2 - chlorobenzyloxy)cyclohexyl, benzyl, 3 - trifluoromethylbenzyl, 4 - methylbenzyl, 3 - chlorophenethyl, 4 - fluorophenethyl, 1,1 - dimethylphenethyl, 1,1 - dimethyl - 4 - phenylbutyl, 2 - methyl - 3 - thienyloxymethyl, 2 - chloro - 3 - thienyloxymethyl, 2 - chloro - 4 - thienyloxymethyl, 3 - chloro - 4 - thienyloxymethyl, 2,5 - dimethyl - 3 - thienyloxymethyl, 2 - chloro - 3 - methyl - 4 - thienyloxymethyl, 2 - thienyloxymethyl, 4 - methyl - 2 - thienyloxymethyl, 5 - chloro - 2 - thienyloxymethyl, 5 - chloro - 2 - methyl - 3 - thienyloxymethyl, 5 - chloro - 3 - methyl - 2 - thienyloxymethyl, 3,5 - dimethyl - 2 - thienyloxymethyl, 2 - (3 - thienyl) - 1,1 - dimethylethyl, 3 - (3 - thienyl) - 1 - methylpropyl, 3 - (2 - methoxy - 4 - thienyl)propyl, 3 - thienyl, 2 - chloro - 4 - thenyl, 2 - methyl - 5 - thenyl, (2- or 3 - thienyl)butyl, 3 - (1,1 - dimethyl - 3 - thienyl)propyl and 2 - (4 - methoxy - 2 - thienyl)ethyl.

The invention also provides a process for the preparation of a compound of the general formula I into another compound of the general formula I by any general formula



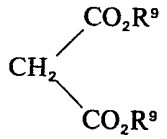
XXII

wherein R^3, R^4, R^5 and A have the meanings given for the general formula I, R^{13} represents a hydrogen atom or a protecting group which can be eliminated by acid solvolysis; Y represents a single bond, a $-CH_2-$ group or an isopropylidene group, to give a compound of the general formula I wherein R^1 and R^2 together represent an oxygen atom; and if desired, converting the resulting compound of the general formula I into another compound of the general formula I by any suitable method.

The compound of the general formula XXII may be prepared as described in the following reaction scheme. The present invention also provides a process for the preparation of a compound of the general formula I wherein there is used as starting material any one of the compounds of the general formula II, IV, V, VI, VII, VIII, X, XII, XIII, XV XVI, XVIII, XIX or XX, and the subsequent steps in the following reaction scheme are performed.

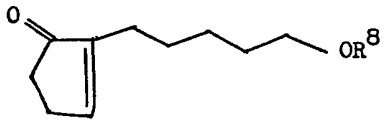
The reaction may begin by:

(a) reacting a malonate of the general formula



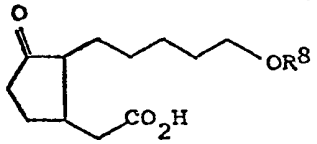
III

wherein each R^9, which may be the same or different, represents an alkyl group having from 1 to 5 carbon atoms or an aralkyl group having from 7 to 9 carbon atoms, with a cyclopentenone of the general formula



II

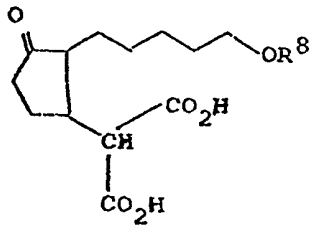
in which R^8 represents a hydrogen atom or an aliphatic carboxylic acyl group having from 2 to 6 carbon atoms, to form a compound of the general formula



IV

wherein a R^8 and R^9 have the meanings given above;

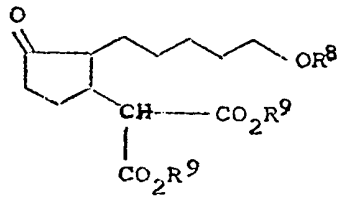
(b) a compound of the general formula IV is converted by any suitable method into a compound of the general formula



V

wherein R^8 has the meaning given for formula II;

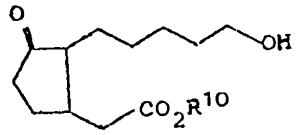
(c) a compound of the general formula V is converted by any suitable method into a compound of the general formula



VI

wherein R^8 has the meaning given for formula II;

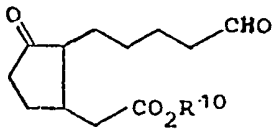
(d) a compound of the general formula VI is converted, using an alkanol having from 1 to 5 carbon atoms in acid solution, into a compound of the general formula



VII

wherein R^{10} represents an alkyl group having from 1 to 5 carbon atoms;

(e) an alcohol of the general formula VII is oxidized to give an aldehyde of the general formula



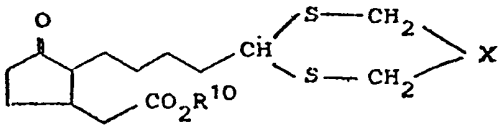
VIII

wherein R^{10} has the meaning given for formula VII;

(f) an aldehyde of the general formula VIII is selectively converted, using a dithiol of the general formula

$$HS—CH_2—X—CH_2—SH \qquad IX$$

wherein X represents a single bond, a $—CH_2—$ group or an isopropylidene group, in the presence of an acid catalyst, into a dithioacetal of the general formula



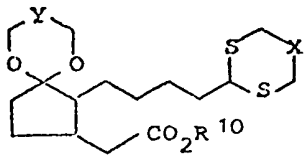
X

wherein R^{10} and X have the meanings given for formulae VII and IX respectively;

(g) a dithioacetal of the general formula X is reacted with a diol of the general formula

$$HOCH_2—Y—CH_2OH \qquad XI$$

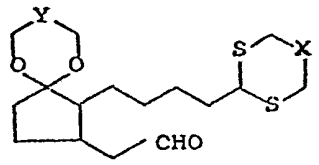
wherein Y represents a single bond, a $—CH_2—$ group or an isopropylidene group, in the presence of an acid catalyst, to give an acetal of the general formula



XII

wherein X has the meaning given for formula IX, Y has the meaning given for formula XI and R^{10} has the meaning given for formula VII;

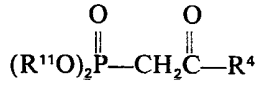
(h) an ester of the general formula XII is reduced to give an aldehyde of the general formula



XIII

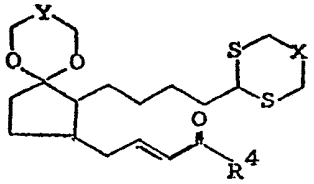
wherein X and Y have the meanings given for formulae IX and XI respectively;

(i) an aldehyde of the general formula XIII is reacted with a phosphonate of the general formula



XIV

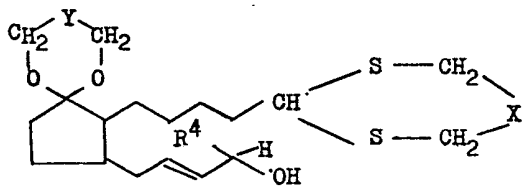
wherein R^4 has the meaning given for formula I and each R^{11}, which may be the same or different, represents an unbranched alkyl group having from 1 to 4 carbon atoms, to give an unsaturated ketone of the general formula



XV

wherein X has the meaning given for formula IX and Y has the meaning given for formula XI;

(j) an unsaturated ketone of the general formula XV is reduced to give a compound of the general formula



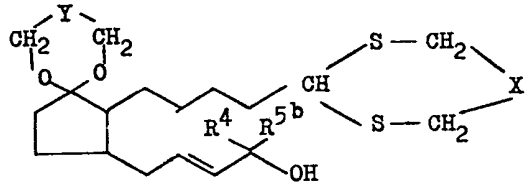
XVI(a)

wherein R^4 has the meaning given for formula I, X has the meaning given for formula IX, Y has the meaning given for formula XI; or if desired,

(j') the unsaturated ketone of the general formula XV is reacted with an organometallic compound of the general formula

$$R^{5b}M \qquad \text{XVII}$$

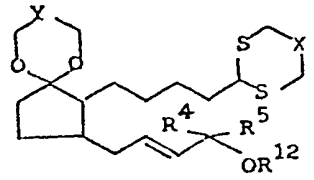
wherein R^{5b} represents an alkyl group having from 1 to 5 carbon atoms or an alkenyl or alkynyl group having from 2 to 5 carbon atoms, and M represents an alkali metal or a group of the general formula HalMg, in which Hal represents a chlorine, bromine or iodine atom, to give a compound of the general formula



XVI(b)

wherein R^4 has the meaning given for formula I, R^{5b} has the meaning given for formula XVII, X has the meaning given for formula IX and Y has the meaning given for formula XI.

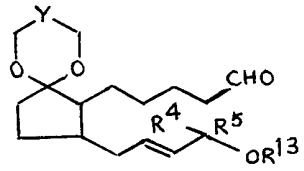
(k) the hydroxyl group of a compound of the general formula XVI(b) or XVI(a) is protected by means of a group which can be removed easily by acid solvolysis, to give a compound of the general formula



XVIII

wherein R^4 and R^5 have the meanings given for formula I, X has the meaning given for formula IX, Y has the meaning given for formula XI, and R^{12} represents a protecting group which can be removed easily by acid solvolysis;

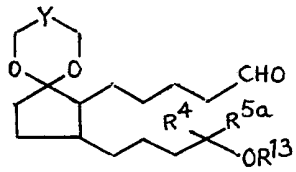
(l) the thioacetal group in a compound of the general formula XVI(a) or (b) or XVIII is removed under mild conditions, for example in the presence of a heavy metal salt, $HgCl_2$ or an alkyl halide in a mixture of an organic solvent and water, to form an aldehyde of the general formula



XIX

wherein R^4 and R^5 have the meanings given for formula I, Y has the meaning given for formula XI and R^{13} represents a hydrogen atom or a protecting group which can be removed easily by acid solvolysis;

(m) if desired, an aldehyde of the general formula XIX is hydrogenated in the presence of a suitable catalyst to form a compound of the general formula



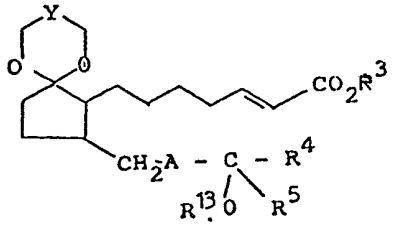
XX

wherein R^4 has the meaning given for formula I, R^{13} has the meaning given for formula XIX, Y has the meaning given for formula XI and R^{5a} represents a hydrogen atom or an alkyl group having from one to five carbon atoms;

(n) a compound of the general formula XIX or XX is reacted with an ylid of the general formula

$$R_3^{14}P{=}CH{-}CO_2R^3 \qquad \text{XXI}$$

in which each R^{14}, any two or three of which may be the same or different, represents a straight chain alkyl group having from 1 to 4 carbon atoms or a phenyl group, and R^3 has the meaning given for formula I, to give a compound of the general formula



XXII

where R^3, R^4, R^5 and A have the meanings given for formula I, R^{13} has the meaning given for formula XIX and Y has the meaning given for formula XI;

(o) if desired, a compound of the general formula XXII wherein R^{13} represents a hydrogen atom is prepared by mild acid solvolysis of a compound of the general

formula XXII in which R^{13} represents a protecting group which can be removed easily;

(p) the acetal protective group and also, if R^{13} does not denote a hydrogen atom, the protecting group R^{13}, are removed from a compound of the general formula XXII by acid solvolysis, to give a compound of the general formula I, wherein R^1 and R^2 together represent an oxygen atom, R^6 represents a hydrogen atom, and R^3, R^4, R^5 and A have any one of the meanings given for formula I; and, if desired, one or more of the following reactions is carried out in any appropriate order:

(q) a compound of the general formula I wherein R^1 and R^2 together represent an oxygen atom, R^6 represents a hydrogen atom, R^3 has any one of the meanings given for formula I except that it is not a hydrogen atom, R^4, R^5 and A have any one of the meanings given for formula I is converted by saponification into the corresponding free acid;

(r) a compound of the general formula I wherein R^1 and R^2 together represent an oxygen atom, R^6 represents a hydrogen atom, R^3 has any one of the meanings given for formula I except that it is not a hydrogen atom, and R^4, R^5 and A have any one of the meanings given for formula I is converted by transesterification into another ester of the general formula I;

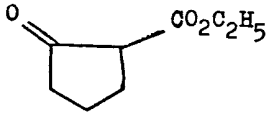
(s) a compound of the general formula I wherein R^1 and R^2 together represent an oxygen atom, R^6 represents a hydrogen atom, R^3 represents a hydrogen atom and R^4, R^5 and A have any one of the meanings given for formula I, is esterified to give a compound of the general formula I wherein R^1 and R^2 together represent an oxygen atom, R^6 represents a hydrogen atom, R^3 represents an aliphatic or cycloaliphatic hydrocarbon group having from 1 to 8 carbon atoms, an alkoxyalkyl group having from 3 to 10 carbon atoms or an araliphatic hydrocarbon group having from 7 to 9 carbon atoms, and R^4, R^5 and A have any one of the meanings given for formula I;

(t) a compound of the general formula I, wherein R^1 and R^2 together represent an oxygen atom, R^6 represents a hydrogen atom and R^3, R^4 and R^5 have any one of the meanings given for formula I, is reacted with an acylating agent to give a compound of the general formula I in which R^1 and R^2 together represent an oxygen atom and R^3 to R^5 have any one of the meanings given for formula I and R^6 represents a group of the general formula R^7CO, wherein R^7 is as hereinbefore defined;

(u) a compound of the general formula I, wherein R^1 and R^2 together represent an oxygen atom and R^3, R^4, R^5, R^6 and A have any one of the meanings given for formula I, is reduced to give a compound of the general formula I wherein one of R^1 and R^2 represents a hydrogen atom and the other represents a hydroxyl group, and R^3, R^4, R^5, R^6 and A have any one of the meanings given for formula I;

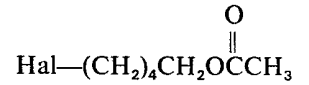
(v) a compound of the general formula I wherein R^3 represents a hydrogen atom and R^1, R^2, R^4, R^5, R^6 and A have any one of the meanings given for formula I, is converted into a compound of the general formula I, wherein R^3 represents a metal ion, an ammonium ion or a substituted ammonium ion derived from a primary, secondary or tertiary amine.

The 2 - (5 - acetoxypentyl)cyclopent - 2 - en - 1 - one of the general formula II (R^8 represents an acetyl group), which may be used as a starting material in the process of the invention, may be prepared by various processes. A suitable route comprises reacting 2 - oxocyclopentancarboxylic acid ethyl ester of the formula



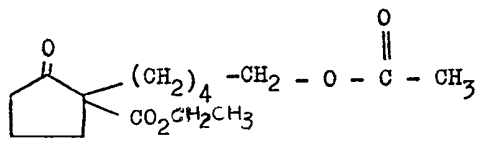
XXIII

with a 5 - acetoxypentyl halide of the general formula XXIV



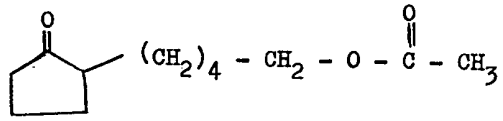
XXIV

wherein Hal represents a chlorine, bromine or iodine atom, to give a 2 - oxocyclopentancarboxylic acid ethyl ester which is substituted in the 1-position and of the general formula



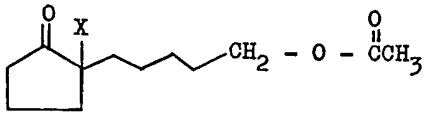
XXV

saponifying and decarboxylating the compound of the general formula XXV with glacial acetic acid/H_2O/H_2SO_4, to give the compound of the formula



XXVI

and obtaining the compound of the general formula II via a compound of the general formula



XXVII

wherein X represents a halogen atom, analogously to the process described in German Offenlegungsschrift No. 2,430,700.

The process of the invention may begin by adding a malonate of the general formula III to a cyclopentenone of the general formula II. This addition reaction is preferably carried out using an alcohol as solvent and a small amount of the corresponding alkoxide is preferably added as a basic catalyst. An alcohol which produces an alkoxide ion which, while it has good basicity, is only slightly nucleophilic, for example a tertiary alcohol, is preferred. The reaction temperature is suitably in the range of from +20° to +80°C.

A preferred process uses dibenzyl malonate as the compound of the general formula III in *t* - butanol as the solvent.

The malonate of the general formula IV which is thus obtained may then be converted into the corresponding substituted malonic acid of the general formula V. Alkaline saponification is especially suitable for this purpose. When R^8 represents an aliphatic carboxylic acyl group, alkaline saponification leads to a acid of the general formula V in which the radical R^8 represents a hydrogen atom.

A process which has proved especially useful for the manufacture of the free malonic acid of the general formula V is hydrogenolytic debenzylation of those malonates of the general formula IV in which each R^9 represents a benzyl group. Those malonic acids in which R^8 represents an aliphatic carboxylic acyl radical are also preparable by this means.

For decarboxylation, the free malonic acid of the general formula V are preferably warmed in an aqueous lower carboxylic acid as the solvent, with the addition of a mineral acid, until the evolution of CO_2 has ceased. If malonic acids in which R^8 represents an aliphatic carboxylic acyl radical are used, it is advantageous to use the corresponding carboxylic acid as the solvent. A 3 - oxocyclopentaneacetic acid of the general formula VI which can readily be purified by distillation is obtained.

The conversion of the compound of the general formula VI into the ester-alcohol of the general formula VII is suitably effected by acid-catalysed alcoholysis in an alcohol of the general formula $R^{10}OH$ as the solvent, at a temperature in the range of from +20 to +100°C. During this reaction both an esterification of the carboxy group and elimination of any aliphatic carboxylic acyl radical R^8 which may be present, take place.

In the next step of the process of the invention, an alcohol of the general formula VII is oxidised to give the corresponding aldehyde of the general formula VIII. Any suitable oxidising agent customarily used for the oxidation of aliphatic alcohols to aldehydes may be used.

Several methods are described for example, in Houben Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), volume 7/1, Georg Thieme Verlag, Stuttgart 1954, page 159 *et seq.*

Further suitable oxidizing agents include the complex formed from thioanisole

and chlorine (J. Org. Chem. *38*, 1233 (1973)), the chromium trioxide/pyridine complex (J. Org. Chem. *35*, 4000 (1970) and J. Org. Chem. *26*, 4814 (1961)), and dimethyl sulphoxide with various coreactants (J. Amer. Chem. Soc. 87, 5661 (1965), *88*, 1762 (1966), *89*, 5505 (1967), Chem. Rev. *67*, 247 (1967) and J. Amer. Chem. Soc. *94*, 7586 *(1972)*).

An especially preferred process is an oxidation using the complex formed from dimethyl sulphoxide and chlorine. For this reaction the instructions of E. J. Corey and C. K. Kim (Tetrahedron Letters *1973*, 919) are suitably followed.

The aldehyde of the general formula VIII may be purified by distillation or by chromatography; however it is advantageous to react the crude aldehyde direct and selectively in the presence of an acid catalyst in an inert solvent with a dithiol of the general formula IX to give a dithioacetal of the general formula X.

The selective protection of the aldehyde group in the compound of the general formula VIII in preference to the oxo group which is also present, may be achieved by working with a stoichiometric amount of the dithiol of the general formula IX and carrying out the reaction at a temperature in the range of from −10°C to −30°C.

A preferred embodiment of this process comprises allowing the crude aldehyde of the general formula VIII to react, at a temperature in the range of from −5 to +10°C, with a slight excess of a dithiol of the general formula IX in the presence of boron trifluoride etherate and, if desired, a water-binding agent, for example magnesium sulphate, in benzene or methylene chloride.

The dithioacetal of the general formula X thus formed may be purified by distillation or chromatography or, alternatively, reacted directly with a diol of the general formula XI in the presence of an acid catalyst in an inert solvent, for example benzene or toluene, if desired in the presence of a water-binding agent, to give an acetal of the general formula XII. Preferably the dithioacetal of the general formula X is heated to boiling point with somewhat more than the stoichiometric amount of the diol of the general formula XI, in benzene or toluene, with an acid catalyst, for example *p* - toluenesulphonic acid, with a water separator and subsequently the reaction mixture is worked up in any suitable manner.

The acetal of the general formula XII may be purified by distillation under a high vacuum or by chromatography, and then reduced by any suitable method to give an aldehyde of the general formula XIII. Suitable reducing agents are reducing agents known for the reduction of esters to aldehydes, preferably complex metal hydrides, for example lithium triethoxyaluminium hydride. Diisobutylaluminium hydride in an inert solvent for example an aliphatic or aromatic hydrocarbon or an anhydrous ether, tetrahydrofuran or 1,2 - dimethoxyethane, is especially preferred.

The reduction is suitably carried out at a temperature in the range of from −80° to −30°C, especially from −80 to −50°C.

The reduction of the compound of the general formula XII may, for example, be carried out by adding the equimolar amount, or a slight excess, of diisobutylaluminium hydride dropwise, at about −78°C, to a solution of the compound of the general formula XII in toluene. The reduction is generally complete after two to three hours.

The aldehydes of the general formula XIII may be used in the next process step without further purification, or it may, if desired, be purified by column chromatography. The reaction of a phosphonate of the general formula XIV with a compound of the general formula XIII may be carried out under the conditions usual for the Horner reaction, for example in an ether at room temperature. Ethers which are preferably used include diethyl ether, tetrahydrofuran and 1,2 - dimethoxyethane. The phosphonate is used in excess in order to bring the reaction to completion more readily.

The reaction has usually ended after 3 to 24 hours at a temperature in the range of from 20 to 50°C. The reaction product of the general formula XV is then isolated from the reaction mixture, and purified by any suitable method. Details of the procedure for carrying out this reaction are described in J. Amer. Chem. Soc. *83*, 1733 (1961).

The phosphonates of the general formula XIV are either known (J. Org. Chem. *30*, 680 (1965)) or can be manufactured analogously to known processes (for example J. Amer. Chem. Soc. *88*, 5654 (1966)).

A compound of the general formula XVI(a) may be obtained by treating a compound of the general formula XV with a reducing agent. The reduction may be carried out with any reducing agent which permits selective reduction of a carbonyl

group to a hydroxyl group in the presence of an olefinic double bond. Preferred reducing agents are complex metal hydrides, especially the complex borohydrides, for example potassium borohydride, sodium borohydride, zinc borohydride or lithium perhydro - 9b - boraphenalkyl hydride (J. Amer. Chem. Soc. *92*, 709 (1970)), or aluminium hydrides, for example sodium bis(2 - methoxyethoxy)aluminium hydride or diisobutylamuminium hydride. The reduction is usually carried out at a temperature in the range of from −10° to 50°C in a solvent which is inert towards the hydride, for example an ether, for example diethyl ether, 1,2 - dimethoxyethane, dioxane, tetrahydrofuran or diethylene glycol dimethyl ether, or a hydrocarbon, for example benzene, or in an alcohol/water mixture, for example ethanol/water.

In order to prepare an alkylated compound of the general formula XVI(b), a ketone of the general formula XV is reacted with an organometallic compound of the general formula XVII. Suitable organometallic compounds are, especially, organolithium or organomagnesium (Gridnard) compounds.

This reaction is carried out in a solvent which is inert under the reaction conditions, for example in a hydrocarbon or, preferably, an ether, for example diethyl ether, tetrahydrofuran or 1,2 - dimethoxyethane. The reaction may be carried out at a temperatures in the range of from −60 to +30°C, preferably from −30 to −10°C.

The isomeric α- and β - hydroxy compounds of the general formulae XVI(a) or XVI(b) which are formed during the reduction or the reaction with the organometallic compound may be separated into the two isomers using chromatographic methods. The subsequent reactions may, however, be carried out successfully with a mixture of two isomers, so that separation into α- and β - hydroxy compounds can be carried out at any desired stage in the process after the reduction.

In principle, the hydroxyl group in a compound of the general formula XVI(a) or XVI(b) may be protected by any protecting group which can be easily removed. Protecting groups which are especially suitable for converting the compound of the general formula XVI(a) or XVI(b) into a compound of the general formula XVIII are those which are introduced by acid catalysis, and usually by reaction with an enol-ether. Especially suitable enolethers are 2,3-dihydropyran, ethyl vinyl ether and methyl isopropenyl ether, and especially suitable acid catalysts, are, for example, *p* - toluenesulphonic acid and sulphuric acid. The reaction is suitably carried out in an aprotic solvent, for example diethyl ether, dioxane or benzene, and a temperature in the range of from −20°C to +40°C is suitably maintained.

The liberation of an aldehyde of the general formula XIX from the dithioacetal of the general formula or XVIII, XVI(a), XVI(b) or XVIII, be effected in the presence of a heavy metal salt, $HgCl_2$, or an alkyl halide, in a mixture of an organic solvent and water. Organic solvents which may be used are preferably water-miscible solvents, for example tetrahydrofuran or dioxane, and preferably dipolar aprotic solvents, for example acetonitrile, dimethylformamide or dimethyl sulphoxide. The elimination of the protecting group is advantageously carried out in the presence of an acid-binding agent. The reaction temperature is suitably in the range of from 0 to +100°C, preferably +10 to +60°C.

Preferably the dithioacetal of the general formula XVI(a), XVI(b) or XVIII is stirred in a dimethyl sulphoxide/water mixture with excess methyl iodide and calcium carbonate for 2 to 5 hours at 30 to 50°C. After removal of the inorganic salt and the solvent, the resulting aldehyde of the general formula XIX may be reacted further directly or purified by chromatography.

The unsaturated aldehyde of the general formula XIX may, if desired, be hydrogenated to give a saturated aldehyde of the general formula XX. Any process which will selectively reduce an isolated olefin is double bond without attacking an aldehyde group is suitable. Catalytic hydrogenation using nickel, palladium or platinum catalysts, if desired on a support material for example active charcoal or $CaCO_3$, is especially suitable. Suitable solvents are the usual solvents for catalytic hydrogenation reactions, for example low-molecular weight alcohols, esters or ethers, for example methanol, ethyl acetate, tetrahydrofuran or 1,2 - dimethoxyethane. Preferably the compound of the general formula XX is hydrogenated in an aprotic solvent, for example tetrahydrofuran, dioxane, 1,2 - dimethoxyethane, ethyl acetate or acetone, using Raney nickel, or palladium on active charcoal, a temperature in the range of from 20 to 80°C and a hydrogen pressure of from 1 to 20 atmospheres being maintained. If the group represented by R^5 contains a multiple bond, this is also hydrogenated.

The aldehyde of the general formula XIX or XX is converted into a compound of the general formula XXII by reaction with a phosphonium ylid of the general formula XXI, in which R^{14} preferably represents a phenyl group, in a suitable solvent. The phosphonium ylid and the phosphonium salt from which it is derived, may be prepared analogously to methods described in the literature (for example Organic Reactions, volume 14, (1965), page 270 et seq., edition John Wiley and Sons, New York, London, Sidney). Suitably, a solution of the resonance stabilized ylid of the general formula XXI is added in a slight excess to a solution of the aldehyde of the general formula XIX or XX and the reaction mixture is heated to a temperature in the range of from 40 to 100°C for between 2 and 12 hours. Examples of suitable solvents are ethers, for example diethyl ether, tetrahydrofuran and diethylene glycol dimethyl ether, di(lower alkyl)sulphoxides, for example dimethyl sulphoxide, amides of carboxylic acids, for example dimethylformamide and N,N - dimethyl acetamide, hexamethylphosphoric acid triamide (HMPT) or hydrocarbons, especially benzene, toluene or xylene.

Preferably a solution of methoxycarbonylmethylenetriphenylphosphorane in toluene is added dropwise, in a slight excess, to a solution of the aldehyde of the general formula XIX or XX in toluene, and reaction mixture is heated to 40 to 80°C for between 4 and 6 hours in an inert gas atmosphere, for example argon; the end of the reaction may be determined using thin layer chromatography. In general, the resulting compound of the general formula XXII is purified by chromatography after working up. However, the compound may also be used further in the form of the crude product.

The protecting group for the hydroxyl group and the acetal protecting group may be removed either successively, or together in a one stage reaction. Under mild conditions, for example in an alcohol/water mixture which contains about 1% by weight of oxalic acid, and preferably in ethylene glycol in the presence of an acid catalyst, for example dichloroacetic acid boron trifluoride etherate or oxalic acid, predominantly compounds of the general formula XXII wherein R^{11} represents a hydrogen atom are obtained, at temperatures between 0 and 30°C.

Under more vigorous hydrolysis conditions, the acetal protecting group in the compound of the general formula XXII is removed as well as the hydroxyl protecting group, and a compound of the general formula I wherein R^1 and R^2 together represent an oxygen atom, and R^6 represents a hydrogen atom, is obtained. If a lower alcohol which has a low water content and contains a small amount of a strong acid is chosen as the solvent, an ester of the general formula I is obtained, transesterification taking place in some cases.

The removal of the protecting group is suitable effected at a temperature in the range of from 20 to 50°C with a reaction time of 3 to 24 hours. After evaporating off the solvent at low temperature, the keto-acid is suitably purified by a chromatographic method. However, it may also be directly reacted further after removing the acid catalyst, for example by partitioning the crude product between water or a saturated solution of sodium chloride and a non-polar solvent, for example benzene.

In general, the α,β-unsaturated esters of the general formula I wherein R^1 and R^2 together represents an oxygen atom, R^3 does not represent a hydrogen atom and A, R^4 and R^5 have any of the given meanings, are not readily saponified under these conditions. In order to obtain compounds of the general formula I in which R^3 represents a hydrogen atom, this reaction is suitably followed by alkaline saponification with an alkali metal hydroxide in aqueous alcoholic solution. Starting from a compound of the general formula I in which R^1 and R^2 together represent an oxygen atom and R^3 represents a hydrogen atom, it is possible to prepare the corresponding esters. This may be effected in a simple way by reacting the carboxylic acid with the diazoalkane in a solvent such as diethyl ether or THF. Aromatic solvents, for example benzene, or a halogenated hydrocarbon, for example chloroform, are also suitable for this reaction.

The reaction of a salt of the carboxylic acid with an alkyl halide also provides a route to the corresponding esters. Suitable solvents for this reaction are, especially, dipolar, aprotic solvents, for example acetonitrile, dimethylformamide or dimethyl sulphoxide, and the reaction temperatures may be, for example between −10° and +100°C, preferably between +20 and +60°C.

In principle, any carboxylic acid of the general formula I (R^3 represents a hydrogen atom) can be converted into one of the corresponding esters by these methods.

An ester obtained in this way may subsequently be reacted with a suitable acylating agent.

Acylating agents which may be used include free carboxylic acids and their reactive derivatives. When the free carboxylic acid is used, the reaction is preferably carried out using this acid as the solvent, at a temperature in the range of from 0° to 70°. In some cases it is advantageous to buffer the reaction solution in order to avoid secondary reactions (compare J. E. Pike, F. H. Lincoln and W. P. Schneider, H. Org. Chem. *34,* 3553 (1969)).

The corresponding carboxylic acid halide or carboxylic acid anhydride may also be used for the acylation. The reaction is then preferably carried out in an aprotic solvent in the presence of a base at a temperature in the range of from 0° to 80°. Furthermore, the reaction of the alcohol with the corresponding ketene can also be used for the acylation. This reaction is suitably carried out in an aprotic solvent at room temperature.

By reducing the carbonyl group in the compound of the general formula I wherein R^1 and R^2 together represent an oxygen atom, it is possible to prepare the corresponding alcohol of the general formula I wherein one of R^1 and R^2 represents a hydrogen atom and the other represents a hydroxyl group. Reducing agents which may be used are those which reduce a carbonyl group in preference to an ester or acid group and do not attack olefinic double bonds. Complex metal hydrides, for example sodium borohydride, zinc borohydride or lithium perhydro - 9b - boraphenalkyl hydride, are preferred. However, reducing agents, for example lithium aluminum hydride, which are able to reduce a carboxyl group, can also be used for this reduction if they are not used in excess and if low temperatures are employed. The reaction conditions are suitably essentially those described for the manufacture of a compound of the general formula XVI from a compound of the general formula XV.

The reduction of the carbonyl group in the 1-position of the cyclopentane range usually does not proceed stereospecifically. A mixture of α- and β-isomers relative to the position of the resulting hydroxyl group, is formed.

The same applies both for the reduction of the carbonyl group in the 3-position of the lower side chain (reaction of a compound of the general formula XV to give a compound of general formula XVI) and for the reaction thereof with an organometallic compound.

The stereoisomers may be separated directly after they are formed or after any of the subsequent reaction steps. This means that all of the reactions described can be carried out either with the pure α- or β-isomer, or with a mixture of the α- and β-isomers.

Compounds of the general formula I wherein R^3 represents a hydrogen atom may be converted into the corresponding metal salts or ammonium salts by adding the equimolar amount of a base, for example an alkali, a carbonate or an amine. Amines which are especially useful are physiologically tolerable primary, secondary or tertiary amines, tris(hydroxymethyl)aminomethane, piperidine or 4 - ethylmorpholine. Suitable metal ions include those of the alkali metals and alkaline earth metals.

In the compounds of the general formulae IV to VII, X, XII, XIII, XV, XVI, XVIII to XX and XXII, the side chains in the 2- and 3-position of the cyclopentane ring may be *cis* or *trans* relative to one another. However, after the acetal protecting group in the 1-position of the cyclopentane ring has been removed, the two side chains generally assume the *trans*-configuration which is favoured thermodynamically. Therefore, if a compound of the general formula I wherein R^1 and R^2 together represent an oxygen atom is treated with a base, the compound obtained is generally one having the *trans*-configuration in respect of the linking of the side chains to the five-membered ring. The *trans*-configuration of the side chains is usually already obtained when these compounds are manufactured and purified.

The reactions for the introduction of double bonds do not proceed completely stereospecifically. In general, however, it can be assumed that, in the main, a *trans*-linkage is obtained from the Horner reaction and the corresponding *cis*-product is formed to only a slight extent; it may be removed by a chromatographic purification. Similarly, with the Witting reaction for the introduction of the carboxyl side chain, in the main the corresponding *trans*-olefin is formed. In this case also, the *cis*-olefin, which is formed to a slight extent as a by-product, may be separated off by purification operations.

If the individual reaction products are not obtained in a sufficiently pure form

to be used directly in the subsequent reaction step, purification by means of, for example, column chromatography, thin layer chromatography or high pressure liquid chromatography, is advisable.

The compounds of the general formula I are usually obtained in the form of racemates. These may, if desired, be obtained in the form of the optically active antipodes by any suitable method of resolving the racemate.

Compounds which can be manufactured by the processes according to the invention are, in addition to those mentioned in the Examples, especially those listed in Table B.

TABLE B

9 - oxo - 16ξ - hydroxy - 20 - methylprosta - *trans* 2, *trans* 14 - dienoic acid benzyl ester, 9 - oxo - 16ξ - hydroxyprosta - *trans* 2, *trans* 14 - dienoic acid benzyl ester, 9 - oxo - 16ξ - hydroxy - 20 - methylprosta - *trans* 2, *trans* 14 - dienoic acid phenethyl ester, 9 - oxo - 16ξ - hydroxyprosta - *trans* 2, *trans* 14 - dienoic acid phenethyl ester, 9 - oxo - 16ξ - hydroxy - 20 - methylprosta - *trans* 2, *trans* 14 - dienoic acid butyl ester, 9 - oxo - 16ξ - hydroxyprosta - *trans* 2, *trans* 14 - dienoic acid butyl ester, 9 - oxo - 16ξ - hydroxy - 17,17,20 - trimethyl - 19 - oxoprosta - *trans* 2, *trans* 14-dienoic acid propyl ester, 9 - oxo - 16ξ - hydroxy - 17,17 - dimethyl - 19 - oxaprosta - *trans* 2, *trans* 14 - dienoic acid propyl ester, 9 - oxo - 16,20 - dimethyl - 16ξ - hydroxyprosta - *trans* 2, *trans* 14 - dienoic acid hexyl ester, 9 - oxo - 16 - methyl - 16ξ - hyxroxyprosta - *trans* 2, *trans* 14 - dienoic acid hexyl ester, 9 - oxo - 16 - hydroxy - 17 - (*m* - trifluoromethylphenyloxy) - 18,19,20 - trinorprosta - *trans* 2, *trans* 14 - dienoic acid heptyl ester, 9ξ,16ξ - dihydroxy - 17 - (*m* - chlorophenoxy) - 18,19,20 - trinorprosta - *trans* 2, *trans* 14 - dienoic acid ethyl ester, 9ξ,16ξ - dihydroxy - 17 - phenoxy - 18,19,20 - trinorprosta - *trans* - 2, *trans* 14 - dienoic acid 2 - ethoxyethyl ester, 9ξ,16ξ - dihydroxy - 17 - (*p* - fluorophenoxy) - 18,19,20 - trinorprosta - *trans* 2, *trans* 14 - dienoic acid 2 - n - butoxy - ethyl ester and 9ξ,16ξ - dihydroxy - 17 - phenoxy - 18,19,20 - trinorprosta - *trans* 2, *trans* 14 - dienoic acid 4 - ethoxybutyl ester.

The compounds of the invention generally have spasmogenic, bronchodilating, gastric juice secretion-inhibiting, luteolytic and abortive and, especially, hypotensive, properties. The present invention therefore provides a pharmaceutical preparation which comprises a compound of the general formulu I in admixture or conjunction with a pharmaceutically suitable carrier. The pharmaceutical preparation contains a compound of the general formula I in the form of a free acid, physiologically tolerable salt, or an ester.

The pharmaceutical preparation may contain an acid, salt or ester in the form of an aqueous solution or suspension, or in the form of a solution or suspension in a pharmaceutically suitable organic solvent, for example a monohydric or polyhydric alcohol, for example ethanol, ethylene glycol or glycerol, an oil, for example sunflower oil or cod-liver oil, an ether, for example diethylene glycol dimethyl ether, or a polyether, for example a polyethylene glycol; pharmaceutically suitable polymeric excipients, for example polyvinylpyrrolidone, may be used.

The pharmaceutical preparation may have any suitable formulation; it may for example, be a galenic infusion solution, an injectable solution or oral dosage units, for example tablets; it may also be a formulation which can be applied locally, for example a cream, an emulsion or suppositories, and, especially, an aerosol.

The compound of the general formula I may be used in combination with other active ingredients, for example fertility-regulating hormones or releasing hormones, for example LH, FSH, oestradiol and LH-RH; diuretic agents, for example Furosemide; antidiabetic agents, for example Glycodiazine, Tolbutamide, Glibenclamide, Phenformin, Buformin and Metformin; preparations for the treatment of diseases of the circulatory system in general for example agents which dilate the coronary vessels, for example Chromonar or Prenylamine; hypotensive agents, for example reserpine, α-Methyldopa or Clonidine, or antiarrhythmic agents; agents which lower the lipid level; agents for use in geriatric medicine and other formulations which have an action on the metabolism; psychopharmacological agents, for example Chlordiazepoxide, Diazepam or Meprobamate; prostaglandins or prostaglandin-like compounds, prostaglandin antagonists or agents which inhibit prostaglandin biosynthesis, for example non-steroid antiphlogistic agents.

The dosage unit is preferably in the range of from 0.05 to 150 mg, the daily dose suitably ranging from 0.1 to 750 mg.

The following Examples illustrate the invention. The proportions of solvents, mentioned with regard to chromatography hereinafter, are given on a volume basis; ether, when used hereinafter, is used to denote diethyl ether.

Example 1

2-(5-acetoxypentyl)-3-carboxymethylcyclopentan-1-one

200 g of dibenzyl malonate and 105 g of 2 - (5 - acetoxypentyl)cyclopent - 2 - en - 1 - one were added successively to a solution of 0.1 mol of sodium *tert* - butoxide in 250 ml of *tert* - butanol. The reaction solution is stirred for 72 hours at 50°C. It was then cooled, the solution was neutralised by adding glacial acetic acid and the bulk of the solvent was then evaporated off *in vacuo*. The crude residue was taken up in ether. The ether phase was washed with semi-saturated sodium chloride solution and $NaHCO_3$ solution. The ether phase was dried and evaporated. The mixture of dibenzyl malonate and dibenzyl[2 - (5 - acetoxypentyl) - 3 - oxocyclopent - 1 - yl]malonate, which was thus obtained, was hydrogenated, without further purification, in glacial acetic acid (1000 ml) using Pd/C as the catalyst, at room temperature and without excess pressure.

After the absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate was heated for 12 hours under reflux in order to decarboxylate the [2 - (5 - acetoxypentyl) - 3 - oxocyclopent - 1 - yl]malonic acid obtained. The solvent was then distilled off *in vacuo*. The residue was taken up in 1 l of toluene and the solution was again evaporated in order to remove the excess glacial acetic acid. The residue was again taken up in ether and the ether solution was extracted several times with 10% w/v ice-cold $KHCO_3$ solution. The combined alkaline, aqueous extracts were immediately acidified with solid sodium bisulphate and extracted several times with ethyl acetate. The combined ethyl acetate extracts were dried and evaporated and the residue was distilled under a high vacuum.

94 g of the desired product were obtained at a boiling $point_{0.05}$ of ~190°C.

NMR (60 MH_z $CDCl_3$)
δ9.4 ppm 1H singlet
4.1 ppm 2H triplet
2.8—1.0 ppm multiplet
2.0 ppm singlet.

Example 2

2-(5-hydroxypentyl)-3-ethoxycarbonylmethyl-cyclopentanone

7.0 g of 2 - (5 - acetoxypentyl) - 3 - carboxymethyl - cyclopentan - 1 - one were dissolved in 250 ml of absolute methanol and the solution, together with 1 ml of concentrated H_2SO_4, was boiled for one hour under reflux. The mixture was left to stand overnight and on the next day the product taken up in ether. The ether solution was washed with semi-saturated $NaHCO_3$ solution and with semi-saturated NaCl solution, dried and evaporated. This gave 6.4 g of an end product which according to thin layer chromatography is a single compound.

Rf~0.18 (silica gel/cyclohexane, ethyl acetate, glacial acetic acid, 60/40/1).

NMR (60 MH_z, $CDCl_3$)
3.8 ppm singlet 3H
3.7 ppm triplet 2H
2.8—1.0 ppm multiplet 19H
Singlet at 2.1 ppm.

Example 3

5-(5-oxo-2-methoxycarbonylmethylcyclopentyl)valeraldehyde

A solution of 4.1 g of chlorine in 80 ml of absolute methylene chloride was prepared at 0°C, with the exclusion of moisture. This solution was cooled to −45°C and a mixture of 20 g of absolute dimethyl sulphoxide and 22 ml of absolute methylene chloride was added dropwise, whilst stirring well. The temperature did not rise above −30°C during the addition. The mixture was stirred for a further 10 minutes and 5 g of 2 - (5 - hydroxypentyl) - 3 - methoxycarbonylmethyl-cyclopentanone in 7 ml of absolute methylene chloride were then added dropwise. The mixture was stirred for a further one hour at −50°C and for three hours at −30°C. A solution of 12 g of freshly distilled triethylamine in 10 ml of absolute methylene chloride was then added dropwise to the reaction mixture. The mixture

was stirred for a further 5 minutes and 200 ml of carbon tetrachloride were then added. The solution thus obtained was washed with 50 ml of saturated sodium chloride solution and 50 ml of semi-saturated sodium bicarbonate solution. The organic solution was then dried and concentrated to about 100 ml *in vacuo* at temperatures below 40°C. The solution of 5 - (5 - oxo - 2 - methoxycarbonylmethylcyclopentyl)valeraldehyde which was thus obtained was used, without further purification, for the preparation of the thioacetal described in Example 4. Thin layer chromatography (silica gel).

Rf~0.38 (cyclohexane/ethyl acetate/glacial acetic acid, 60/40/1), can be stained with 2,4 - dinitrophenyl - hydrazine.

Example 4

2-[4-(1,3-dithiolan-2-yl)-butyl]-3-methoxycarbonylmethylcyclopentanone

15 g of anhydrous magnesium sulphate, 2.1 g of dithioglycol and 1 ml of boron trifluorode-etherate solution (45% by weight in ether) were added to the aldehyde solution obtained in Example 3. The mixture was stirred for 1 hour at room temperature and a further 1 ml of dithioglycol and 0.5 ml of boron trifluoride-etherate were then added and the mixture left to stand overnight. The next morning the mixture was poured into 200 ml of ice water, the organic phase was separated off and the aqueous phase was washed with carbon tetrachloride. The combined organic extracts were washed, at −10°C, which 100 ml of 1N NaOH and then with twice 100 ml of water. The organic phase was dried and evaporated. The residue was chromatographed on silica gel using toluene/ethyl acetate, 10/1. 2.3 g of the desired thioacetal are obtained.

Rf~0.204 (toluene 10/ethyl acetate 1).

NMR (60 MH_z, $CDCl_3$)
- δ4.5 ppm, 1H, triplet
- 3.6 ppm, 3H, singlet
- 3.2 ppm, 4H, singlet
- 2.6—1.0 ppm, 16H, multiplet.

Example 5

6-[4-(1,3-dithiolon-2-yl)butyl]-7-methoxycarbonylmethyl-1,4-dioxaspiro[4,4]nonane

7.5 g of 2 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 3 - methoxycarbonylmethylcyclopentanone were dissolved in 200 ml of toluene and, after adding 15 g of ethylene glycol and 2 ml of a 45% w/v solution of boron trifluoride-etherate, the mixture was boiled for 4 hours with a water-separator. It was allowed to cool and 50 ml of water were added. The toluene phase was separated off, washed with sodium bicarbonate solution and saturated sodium chloride solution, dried and evaporated. 7.2 g of crude product were obtained.

Thin layer chromatography (silica gel/cyclohexane, 60/ethyl acetate, 40/glacial acetic acid, 1).

Rf~0.51.

NMR ($CDCl_3$/60 MH_z)
- δ 3.9 ppm, 4H, multiplet.

Example 6

6-[4-(1,3-dithiolon-2-yl)butyl]-7-formylmethyl-1,4-dioxaspiro[4,4]nonane

7.2 g of 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - methoxycarbonylmethyl - 1,4 - dioxaspiro[4,4]nonane were dissolved in 150 ml of absolute toluene. This solution is cooled to −70°C and 23 ml of a 20% w/v solution of diisobutylaluminum hydride in toluene was added dropwise. After 3.5 hours, 10 g of glacial acetic acid in 40 ml of toluene were added at −70°C. The temperature was allowed to rise to 0°C and 50 ml of water were then added to the mixture. The organic phase was separated off and the aqueous phase was extracted several times with toluene. The combined organic phases were washed once with semi-saturated sodium chloride solution and once with semi-saturated bicarbonate solution, dried over magnesium sulphate and evaporated to dryness. 6.9 g of the desired aldehyde were obtained.

Thin layer chromatography (silica gel/cyclohexane:ethyl acetate:glacial acetic acid, 60/40/1).

Rf~0.42.
NMR (60 MH_z, $CDCl_3$)
δ 9.85 ppm, 1H triplet
4.50 ppm, 1H triplet
3.95 ppm, 4H singlet
3.30 ppm, 4H singlet
2.4—1.1 ppm, 16H multiplet.

Example 7a

6-[4-(1,3-dithiolon-2-yl)butyl]-7-(4-oxonon-*trans*-2-enyl)-1,4-dioxaspiro[4,4]nonane

420 mg of 80% by weight sodium hydride suspension (in mineral oil) were initially introduced into 45 ml of absolute 1,2 - dimethoxyethane and 2.66 g of dimethyl - 2 - oxo - heptylphosphonate in 60 ml of 1,2 - dimethoxyethane were added, under argon. The mixture was stirred for a further hour at room temperature and a solution of 3.2 g of the aldehyde from Example 6 then added. The mixture was stirred for a further 3 hours at room temperature, neutralised with glacial acetic acid, clarified with a little animal charcoal and chromatographed on silica gel using toluene/ethyl acetate, 10/1, as the running agent.

Thin layer chromatography (silica gel/toluene/ethyl acetate, 1:1).
Rf~0.68.
NMR ($CDCl_3$/60 MH_z)
δ6.6—7.2 ppm, 1H multiplet
6.1 ppm, 1H doublet
4.5 ppm, 1H triplet
3.9 ppm, 4H singlet
3.2 ppm. 4H singlet
2.8—1.1 ppm, multiplet, other protons.

In an analogous manner, starting from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - formylmethyl - 1,4 - dioxaspiro[4,4]nonane, the following compounds were prepared:

Example 7b

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxooct - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.
NMR
δ 5.8—7.0 ppm, 2H multiplet
by reaction with dimethyl 2 - oxohexylphosphonate,

Example 7c

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxoundec - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.
NMR
δ5.8—6.1 ppm, multiplet
by reaction with dimethyl 1,2 - oxohexylphosphonate.

Example 7d

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxo - 4 - cyclohexylbut - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.
NMR
δ5.8—7.1 ppm, 2H multiplet
by reaction with dimethyl - 2 - cyclohexyl - 2 - oxoethylphosphonate.

Example 7e

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxo - 5,5 - dimethyl - 7 - oxanon - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.
NMR
δ5.8—7.1 ppm, 2H, multiplet
3.4 ppm, 2H, quartet
3.1 ppm, 2H, singlet
1.1 ppm, singlet for $(CH_3)_2$
by reaction with dimethyl - 2 - oxo - 3,3 - dimethyl - 5 - oxaheptylphosphonate.

Example 7f

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxo - 5,5 - dimethylnon - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.
NMR
5.8—7.2 ppm, 2H,
by reaction with dimethyl - 2 - oxo - 3,3 - dimethylheptylphosphonate.

Example 7g

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxo - 5 - *m* - chlorophenoxypent - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

NMR

Multiplet at 6.0—7.6 ppm (6H)

by reaction with dimethyl - 2 - oxo - 3 - *m* - chlorophenoxypropylphosphonate.

Example 7h

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxo - 5 - phenoxypent - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

NMR

5.8—7.6 ppm, multiplet, 7H

by reaction with dimethyl - 2 - oxo - 3 - phenoxypropylphosphonate and

Example 7i

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - oxo - 5 - (*m* - trifluoromethylphenoxy)pent - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

NMR

5.8—7.7 ppm, multiplet (6H)

by reaction with dimethyl - 2 - oxo - 3 - (*m* - trifluoromethylphenoxy)propylphosphonate.

Example 8a

6-[4-(1,3-dithiolon-2-yl)butyl]-7-(4-hydroxynon-*trans*-2-enyl)-1,4-dioxaspiro[4,4]nonane

4.1 g of the α,β-unsaturated ketone described in Example 7a were dissolved in 30 ml of tetrahydrofuran and 30 ml of methanol and the solution was added dropwise, at 0° to 5°C, to a solution of 1.8 g of sodium borohydride in 20 ml of methanol and 2 ml of water. The mixture was stirred for a further one hour at 10°C, neutralised with glacial acetic acid and evaporated *in vacuo*. The residue was taken up in water and the aqueous solution was then extracted several times with ether. The combined ether phases were washed with sodium bicarbonate solution, dried and evaporated. 4.1 g of the desired alcohol were obtained.

Thin layer chromatography (silica gel, toluene/ethyl acetate, 1:1).

Rf~0.60.

NMR (60 MH_7, $CDCl_3$)

δ5.5—5.7 ppm, 2H, multiplet

IR ν(OH)~3500 cm^{-1}

In a completely analogous manner the following compounds were prepared:

Example 8b

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxyoct - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

NMR

5.5—5.9 ppm, 2H, multiplet

IR ν(OH)~3500 cm^{-1}

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxooct - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Example 8c

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxyundec - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

NMR

δ5.5—5.9 ppm, 2H, multiplet

IR ν(OH)~3500 cm^{-1}

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxoundec - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Example 8d

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxy - 4 - cyclohexylbut - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

NMR

5.5—5.8 ppm, 2H, multiplet

IR ν(OH)~3500 cm^{-1}

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxo - 4 - cyclohexylbut - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Example 8e

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxy - 5,5 - dimethyl - 7 - oxanon - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

NMR

5.5—5.9 ppm, 2H, multiplet

IR ν(OH)~3450 cm^{-1}

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxo - 5,5 - dimethyl - 7 - oxanon - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Example 8f

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxy - 5,5 - dimethylnon - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

NMR

δ 5.4—5.8 ppm, 2H, multiplet

IR ν(OH)~3500 cm^{-1}

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxo - 5,5 - dimethylnon - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Example 8g

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxy - 5 - *m* - chlorophenoxypent - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

NMR

δ5.4—6.1 ppm, multiplet, 2H

IR ν(OH)~3500 cm^{-1}

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxo - 5 - *m* - chlorophenoxypent - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Eample 8h

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxy - 5 - phenoxypent - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

NMR

δ5.4—6.0 ppm

IR ν(OH)~3500 cm^{-1}

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - oxo - 5 - phenoxypent - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane, and

Example 8i

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - hydroxy - 5 - (*m* - trifluoromethylphenoxy)pent - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

NMR

δ5.4—6.1 ppm

IR ν(OH)~3500 cm^{-1}

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - oxo - 5 - (*m* - trifluoromethylphenoxy)pent - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Example 9a

6-[4-(1,3-dithiolon-2-yl)butyl]-7-[4-(tetrahydropyran-2-yloxy)-non-*trans*-2-enyl]-1,4-dioxaspiro[4,4]nonane

4.1 g of the alcohol obtained in Example 8a were dissolved in 120 ml of absolute ether, 7 ml of 2,3 - dihydropyran and 100 mg of *p* - toluenesulphonic acid were added and the mixture stirred for 5 hours at room temperature. For working up, the reaction solution was shaken with semi-saturated sodium chloride solution and semi-saturated sodium bicarbonate solution, dried with magnesium sulphate and evaporated. For purification, the residue was chromatographed on silica gel using toluene/ethyl acetate, 10/1.

3.8 g of the desired end product were obtained.

Thin layer chromatography (silica gel/toluene:ethyl acetate, 1:1).

Rf~0.70.

NMR (60 MH_z, $CDCl_3$)

δ5.2—5.8 ppm, 2H, multiplet

4.3—4.8 ppm, 2H, multiplet and triplet

3.9 ppm, 4H, singlet

3.25 ppm, 4H, singlet

In an analogous manner the following compounds were prepared:

Example 9b

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy)oct - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane

NMR

δ4.3—4.8 ppm, 2H, multiplet with triplet

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxyoct - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Example 9c

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy)undec - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

NMR

δ4.3—4.8 ppm, 2H, multiplet with triplet

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxyundec - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Example 9d

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 4 - cyclohexylbut - *trans* - 2 - enyl)] - 1,4 - dioxaspiro[4,4]nonane.

NMR

δ4.3—4.8 ppm, 2H, multiplet with triplet

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxy - 4 - cyclohexylbut - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

Example 9e

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5,5 - dimethyl - 7 - oxanon - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

NMR

δ4.3—4.8 ppm, 2H, multiplet with triplet

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxy - 5,5 - dimethyl - 7 - oxanon - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

Example 9f

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5,5 - dimethylnon - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

NMR

δ4.3—4.8 ppm, 2H, multiplet with triplet

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxy - 5,5 - dimethylnon - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

Example 9g

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5 - *m* - chlorophenoxypent - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

NMR

δ4.3—4.8 ppm, 2H, multiplet with triplet

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxy - 5 - *m* - chlorophenoxypent - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

Example 9h

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5 - phenoxypent - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

NMR

δ4.3—4.8 ppm, 2H, multiplet with triplet

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - (4 - hydroxy - 5 - phenoxypent - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane, and

Example 9i

6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5 - (*m* - trifluoromethylphenoxy)pent - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

NMR

δ4.3—4.8 ppm, 2H, multiplet with triplet

from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - hydroxy - 5 - (*m* - trifluoromethylphenoxy)pent - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Example 10a

6-(4-formylbutyl)-7-[4-(tetrahydropyran-2-yloxy)non-*trans*-2-enyl]-1,4-dioxaspiro[4,4]nonane

2.3 g of 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy)non - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane were dissolved in 23 ml of dimethyl sulphoxide, 3.6 g of powdered calcium carbonate, 0.65 ml of water and 1.95 ml of methyl iodide were added and the mixture was stirred for 3 hours at 60°C.

After cooling, ether was added and the solids were filtered off. Ice water was added to the filtrate. The ether phase was separated off and the aqueous phase was extracted several times with ether. The combined either phases were washed with aqueous sodium thiosulphate solution and evaporated. The residue was purified by filtration through a short column containing silica gel, using ether. 1.7 g of the desired aldehyde are obtained.

Thin layer chromatography (silica gel/toluene/ethyl acetate, 1/1).
Rf~0.32, can be stained with 2,4 - dinitrophenylhydrazine.
NMR (60 MH_z, $CDCl_3$)
δ9.85 ppm, 1H, triplet
5.4—5.8 ppm, 2H, multiplet.

In an analogous manner the following compounds were prepared:

Example 10b

6 - (4 - formylbutyl) - 7 - [4 - (tetrahydropyran - 2 - yloxy)oct - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.
Thin layer chromatography (silica gel//toluene/ethyl acetate, 1/1).
Rf~0.35, can be stained with 2,4 - dinitrophenylhydrazine.
NMR
δ9.8 ppm, 1H
from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl - 7 - [4 - (tetrahydropyran - 2 - yloxy)oct - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

Example 10c

6 - (4 - formylbutyl) - 7 - [4 - (tetrahydropyran - 2 - yloxy)undec - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.
Thin layer chromatography (silica gel//toluene/ethyl acetate, 1/1).
Rf~0.31, can be stained with 2,4 - dinitrophenylhydrazine.
NMR
δ9.8 ppm, 1H, triplet
from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy)undec - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Example 10d

6 - (4 - formylbutyl) - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 4 - cyclohexylbut - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.
Thin layer chromatography (toluene/ethyl acetate, 1/1).
Rf~0.35, can be stained with 2,4 - dinitrophenylhydrazine.
NMR
δ9.8 ppm, 1H, triplet
from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 4 - cyclohexylbut - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Example 10e

6 - (4 - formylbutyl) - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5,5 - dimethyl - 7 - oxanon - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.
Thin layer chromatography (toluene/ethyl acetate, 1/1).
Rf~0.35, can be stained with 2,4 - dinitrophenylhydrazine
NMR
δ9.8 ppm, 1H, triplet
from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5,5 - dimethyl - 7 - oxanon - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane.

Example 10f

6 - (4 - formylbutyl) - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5,5 - kvmethylnon - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

Thin layer chromatography (toluene/ethyl acetate, 1/1).
Rf~0.35, can be stained with 2,4 - dinitrophenylhydrazine.
NMR
δ9.8 ppm, 1H, triplet
from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5,5 - dimethylnon - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

Example 10g

6 - (4 - formylbutyl) - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5 - *m* - chlorophenoxypent - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.
Thin layer chromatography (toluene/ethyl acetate, 1/1).
Rf~0.30, can be stained with 2,4 - dinitrophenylhydrazine.
NMR
δ~9.8 ppm, 1H, triplet
from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5 - *m* - chlorophenoxypent - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

Example 10h

6 - (4 - formylbutyl) - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5 - phenoxypent - *trans* - 2 - enyl]1,4 - dioxaspiro[4,4]nonane.
Thin layer chromatography (toluene/ethyl acetate).
Rf~0.3, can be stained with 2,4 - dinitrophenylhydrazine.
NMR
δ~9.8 ppm, 1H, triplet
from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5 - phenoxypent - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane, and

Example 10i

6 - (4 - formylbutyl) - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5 - (*m* - trifluoromethylphenoxy)pent - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.
Thin layer chromatography (toluene/ethyl acetate, 1/1).
Rf~0.35, can be stained with 2,4 - dinitrophenylhydrazine.
NMR
δ~9.8 ppm
from 6 - [4 - (1,3 - dithiolon - 2 - yl)butyl] - 7 - [4 - (tetrahydropyran - 2 - yloxy) - 5 - (*m* - trifluoromethylphenoxy)pent - *trans* - 2 - enyl] - 1,4 - dioxaspiro[4,4]nonane.

Example 11a

9,9-ethylenedioxy-16-(tetrahydropyran-2-yloxy)-20-methylprosta-*trans*-2-*trans*-14-dienoic Acid Methyl Ester

470 mg of 6 - (4 - formylbutyl) - 7 - [4 - (tetrahydropyran - 2 - yloxy)non - *trans* - 2 - enyl) - 1,4 - dioxaspiro[4,4]nonane were dissolved in 25 ml of absolute toluene and the solution was boiled, together with 550 mg of methoxycarbonylmethylenetriphenylphosphorane, for 5 hours under reflux. The solution was evaporated *in vacuo*, the residue was taken up in ether and the solution was filtered through a column containing silica gel.
490 mg of 9,9 - ethylenedioxy - 16 - (tetrahydropyran - 2 - yloxy) - 20 - methylprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester were obtained.
NMR
6.8—7.4 ppm, 1H, multiplet
5.4—6.2 ppm, 3H, multiplet
3.8 ppm, 3H, singlet
In an analogous manner, the following compounds were obtained by reacting the aldehydes obtained in Examples 10b—10i with methoxycarbonylmethylenetriphenylphosphorane.

Example 11b

9,9 - ethylenedioxy - 16 - (tetrahydropyran - 2 - yloxy)prosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.
NMR
6.8—7.4 ppm, 1H, multiplet
5.4—6.2 ppm, 3H, multiplet
3.8 ppm, 3H, singlet.

Example 11c

9,9 - ethylenedioxy - 16 - (tetrahydropyran - 2 - yloxy) - 20 - propylprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

NMR

6.8—7.5 ppm, 1H, multiplet
5.4—6.3 ppm, 3H, multiplet
3.8 ppm, 3H, singlet.

Example 11d

9,9 - ethylenedioxy - 16 - (tetrahydropyran - 2 - yloxy) - 16 - cyclohexyl - 17,18,19,20 - tetranorprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

NMR

6.8—7.5 ppm, 1H, multiplet
5.4—6.3 ppm, 3H, multiplet
3.9 ppm, 3H, singlet.

Example 11e

9,9 - ethylenedioxy - 16 - (tetrahydropyran - 2 - yloxy) - 17,17,20 - trimethyl - 19 - oxaprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

NMR

6.8—7.4 ppm, 1H, multiplet
5.4—6.4 ppm, 3H, multiplet
3.8 ppm, 3H, singlet.

Example 11f

9,9 - ethylenedioxy - 16 - (tetrahydropyran - 2 - yloxy) - 17,17,20 - trimethylprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

NMR

6.8—7.4 ppm, 1H, multiplet
5.4—6.4 ppm, 3H, multiplet
3.8 ppm, 3H, singlet.

Example 11g

9,9 - ethylenedioxy - 16 - (tetrahydropyran - 2 - yloxy) - 17 - *m* - chlorophenoxy - 18,19,20 - trinorprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

NMR

5.4—7.6 ppm, 8H, multiplet
3.8 ppm, 3H, singlet.

Example 11h

9,9 - ethylenedioxy - 16 - (tetrahydropyran - 2 - yloxy) - 17 - phenoxy - 18,19,20 - trinorprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

5.4—7.6 ppm, 9H, multiplet
3.8 ppm, 3H, singlet.

Example 11i

9,9 - ethylenedioxy - 16 - (tetrahydropyran - 2 - yloxy) - 17 - (*m* - trifluoromethylphenoxy) - 18,19,20 - trinorprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

5.4—7.6 ppm, 8H, multiplet
3.8 ppm, 3H, singlet.

Example 12a

9-oxo-16ξ-hydroxy-20-methylprosta-*trans*-2-*trans*-14-dienoic Acid Methyl Ester

258 mg of 9,9 - ethylenedioxy - 16 - (tetrahydropyran - 2 - yloxy) - 20 - methylprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester were dissolved in 50 ml of absolute methanol and 2 ml of aqueous 10% w/v oxalic acid were added. The reaction mixture was warmed to 50°C for 3 hours and left to stand overnight at room temperature. The next morning, the mixture was substantially evaporated *in vacuo*, the residue was taken up in ether and the ether solution was washed once with semi-saturated sodium bicarbonate solution. The reaction solution was dried with magnesium sulphate and then evaporated. The residue was chromatographed on silica gel using toluene/ethyl acetate, 60/40, as the running agent.

Thin layer chromatography (Merck ready-to-use plates//toluene/ethyl acetate/glacial acetic acid, 40/60/1).

Rf~0.37.

NMR: The signals at δ=4.6 ppm and δ=3.9 ppm, which were typical for the THP group and the ketal bridge, had disappeared.

δ3.7 ppm, singlet, 3H
3.7—4.0 ppm, multiplet, 1H
5.4—6.0 ppm, multiplet, 3H
6.6—7.4 ppm, multiplet, 1H.

The following compounds were obtained in an analogous manner from the compounds obtained in Example 11b to 11i:

Example 12b

9 - oxo - 16 - hydroxyprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

Thin layer chromatography Rf~0.36.

Example 12c

9 - oxo - 16 - hydroxy - 20 - propylprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

Thin layer chromatography Rf~0.38.

Example 12d

9 - oxo - 16ξ - hydroxy - 16 - cyclohexyl - 17,18,19,20 - tetranorprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

Thin layer chromatography Rf~0.38.

Example 12e

9 - oxo - 16ξ - hydroxy - 17,17,20 - trimethyl - 19 - oxaprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

Thin layer chromatography Rf~0.36.

Example 12f

9 - oxo - 16ξ - hydroxy - 17,17,20 - trimethylprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

Thin layer chromatography Rf~0.35.

Example 12g

9 - oxo - 16ξ - hydroxy - 17*m* - chlorophenoxy - 18,19,20 - trinorprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

Thin layer chromatography Rf~0.35.

Example 12h

9 - oxo - 16ξ - hydroxy - 17 - phenoxy - 18,19,20 - trinorprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

Thin layer chromatography Rf~0.38, and

Example 12i

9 - oxo - 16ξ - hydroxy - 17 - (*m* - trifluoromethylphenoxy) - 18,19,20 - trinorprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester.

Thin layer chromatography Rf~0.38.

The thin layer chromatography data given relates to Merck ready-to-use plates and the running agent toluene/ethyl acetate, 1/1.

Example 13a

9-oxo-16ξ-hydroxy-20-methylprosta-*trans*-2-*trans*-14-dienoic Acid

480 g of 9 - oxo - 16ξ - hydroxy - 20 - methylprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester were dissolved in 10 ml of methanol, 2 ml of 1N sodium hydroxide solution were added and the mixture was stirred at room temperature. After 3 hours the bulk of the methanol was removed in a rotary evaporator and the residue was taken up in 5 ml of water. The aqueous solution was extracted twice with ether.

The aqueous solution was then acidified with 10% w/v citric acid solution and extracted several times with ether. The combined acid ether extracts were dried and evaporated. The residue is purified by column chromatography on silica gel using ethyl acetate, 40/cyclohexane, 60/glacial acetic acid, 1 as the running agent.

Thin layer chromatography (silica gel//toluene, 40/ethyl acetate, 60/glacial acetic acid, 1).

Rf~0.33.
NMR (60 MH_z, $CDCl_3$)
δ6.6—7.5 ppm, 1H, multiplet
δ4.8—5.0 ppm, 2H, multiplet
δ5.4—6.0 ppm, 3H, multiplet
δ3.9—4.3 ppm, 1H, multiplet

The acids indicated in Examples 13b to 13i were prepared in an analogous manner from the esters obtained in Examples 12b—12i. The thin layer chromatographic data relate to ethyl acetate/cyclohexane/glacial acetic acid, 60/40/1, as the running agent (Merck ready-to-use plates).

Example 13b

9 - oxo - 16ξ - hydroxyprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.35.

Example 13c

9 - oxo - 16ξ - hydroxy - 20 - propylprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.32.

Example 13d

9 - oxo - 16ξ - hydroxy - 16 - cyclohexyl - 17,18,19,20 - tetranorprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.32.

Example 13e

9 - oxo - 16ξ - hydroxy - 17,17,20 - trimethyl - 19 - oxaprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.37.

Example 13f

9 - oxo - 16ξ - hydroxy - 17,17,20 - trimethylprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.38.

Example 13g

9 - oxo - 16ξ - hydroxy - 17 - *m* - chlorophenoxy - 18,19,20 - trinorprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.32.

Example 13h

9 - oxo - 16ξ - hydroxy - 17 - phenoxy - 18,19,20 - trinorprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.35.

Example 13i

9 - oxo - 16ξ - hydroxy - 17 - (*m* - trifluoromethylphenoxy) - 18,19,20 - trinorprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.34.

Example 14a

9ξ,16ξ-dihydroxy-20-methylprosta-*trans*-2-*trans*-14-dienoic Acid

180 mg of 9 - oxo - 16 - hydroxy - 20 - methylprosta - *trans* - 2 - *trans* - 14 - dienoic acid were dissolved in 10 ml of methanol and 480 mg of sodium borohydride were added in small portions at 0°C.

The mixture was stirred for a further 15 minutes at room temperature, glacial acetic acid and semi-saturated sodium chloride solution were then added carefully at 0°C and the solution thus obtained was extracted several times with ether. The combined ether phases were dried and evaporated. The desired product was obtained as a pale yellow oil.

Thin layer chromatography (running agent: ethyl acetate/cyclohexane/glacial acetic acid, 60/40/1).

Two isomeric products
less polar product Rf~0.29
polar product Rf~0.22.
NMR ($CDCl_3$)
δ6.5—7.5 ppm, 1H, multiplet
5.2—6.0 ppm, 3H, multiplet
4.8 ppm, 3H, broad singlet (3 acid H)
3.6—4.3 ppm, 2H, multiplet.

The 9ξ - hydroxyacids indicated in Examples 14b—14i which follow were preparated in an analogous manner from the compounds obtained in Example 13b—13i. The thin layer chromatography data given relate to Merck ready-to-use plates; running agent mixture:ethyl acetate/cyclohexane/glacial acetic acid, 60/40/1.

Example 14b

9ξ,16ξ - dihydroxyprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.28 and 0.21.

Example 14c

9ξ,16ξ - dihydroxy - 20 - propylprosta - *trans* - 2 - *trans* - 14 - dienoic acid
Thin layer chromatography Rf~0.29 and 0.23.

Example 14d

9ξ,16ξ - dihydroxy - 16 - cyclohexyl - 17,18,19,20 - tetranorprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.27 and 0.21.

Example 14e

9ξ,16ξ - dihydroxy - 17,17,20 - trimethyl - 19 - oxaprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.29/0.22.

Example 14f

9ξ,16ξ - dihydroxy - 17,17,20 - trimethylprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.28/0.21.

Example 14g

9ξ,16ξ - dihydroxy - 17 - *m* - chlorophenoxy - 18,19,20 - triprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.29/0.23.

Example 14h

9ξ,16ξ - dihydroxy - 17 - phenoxy - 18,19,20 - trinorprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
Thin layer chromatography Rf~0.28/0.21.

Example 14i

9ξ,16ξ - dihydroxy - 17 - (*m* - trifluoromethylphenoxy) - 18,19,20 - trinorprosta - *trans* - 2 - *trans* - 14 - dienoic acid.
This layer chromatography Rf~0.29/0.22.

Example 15

9-oxo-16ξ-acetoxy-17,17,20-trimethyl-19-oxaprosta-*trans*-2-*trans*-14-dienoic Acid Methyl Ester

60 mg of 9 - oxo - 16ξ - hydroxy - 17,17,20 - trimethyl - 19 - oxaprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester were dissolved in 2 ml of pyridine, 0.02 ml of acetic anhydride was added and the mixture was warmed to 65°C for 8 hours. The reaction solution was then evaporated to dryness *in vacuo* and the residue was chromatographed through a silica gel column using cyclohexane/ethyl acetate, 8/2, as the running agent. 34 mg of the desired product were obtained.

Thin layer chromatography (Merck ready-to-use plates, cyclohexane/ethyl acetate/glacial acetic acid, 60/40/1).

Rf~0.57.
NMR (60 MH_z, $CDCl_3$)
δ7.2—6.6 ppm, 1H, multiplet
6.0—5.3 ppm, 3H, multiplet
5.3—5.0 ppm, 1H, multiplet
3.7 ppm, 3H, singlet
3.4 ppm, 2H, quartet
3.1 ppm, 2H, singlet
2.6—0.7 ppm, remaining protons with
2.0 ppm, singlet
1.1 ppm, triplet
0.8 and 0.9 ppm, singlet.

Example 16

9-oxo-16ξ-formyloxy-17,17,20-trimethyl-19-oxaprosta-*trans*-2-*trans*-14-dienoic Acid Methyl Ester

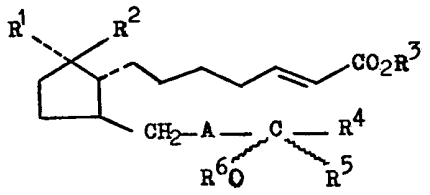
50 mg of 9 - oxo - 16ξ - hydroxy - 17,17,20 - trimethyl - 19 - oxaprosta - *trans* - 2 - *trans* - 14 - dienoic acid methyl ester were dissolved in 5 ml of 100% formic acid in which 130 mg of potassium carbonate had previously been dissolved. This solution was left to stand overnight at 0°C. The next morning the solution was evaporated to dryness *in vacuo* at room temperature. The residue was taken up in 10 ml of ether and 2 ml of water. The mixture was shaken round well and the ether phase was separated off. The aqueous phase was again extracted with ether. The combined ether phases were washed with semi-saturated sodium bicarbonate solution, dried and evaporated. 47 mg of the desired compound were obtained.

Thin layer chromatography (Merck ready-to-use plates, cyclohexane/ethyl acetate/glacial acetic acid, 60/40/1).

Rf=0.56.
NMR (60 MH_z, $CDCl_3$)
8.1 ppm, 1H, singlet
7.2—6.6 ppm, 1H, multiplet
6.0—5.1 ppm, 4H, multiplet
3.7 ppm, 3H, singlet
3.4 ppm, 2H, quarter
3.1 ppm, 2H, singlet
2.8—0.7 ppm, remaining protons, including
1.1 ppm, triplet
0.9 and 0.95 ppm, singlet.

WHAT WE CLAIM IS:—

1. A compound of the general formula



I

where one R^1 and R^2 represents a hydrogen atom and the other represents a hydroxyl group, or R^1 and R^2 together represent an oxygen atom;

R^3 represents a hydrogen atom; an aliphatic or cycloaliphatic hydrocarbon group having up to 8 carbon atoms; an alkoxyalkyl group having from 3 to 10 carbon atoms; an araliphatic hydrocarbon group having from 7 to 10 carbon atoms; a metal ion; an ammonium ion; or a substituted ammonium ion derived from a primary, secondary or tertiary amine;

R^4 represents an aliphatic hydrocarbon group having from 1 to 10 carbon atoms or a cycloaliphatic hydrocarbon group having from 3 to 7 carbon atoms, which aliphatic or cycloaliphatic group may be unsubstituted or substituted by one or more of the same or different substituents selected from: (a) aliphaticoxy or aliphaticthio groups having from 1 to 7 carbon atoms;

(b) phenoxy groups which may be unsubstituted or substituted by one or two of the same or different substituents selected from alkyl groups having from 1 to 3 carbon atoms, which alkyl groups may be unsubstituted or substituted by one or

more of the same or different halogen atoms; halogen atoms; phenoxy groups which may be unsubstituted or substituted by one or more of the same or different halogen atoms; and alkoxy groups having from 1 to 4 carbon atoms;

(c) furyloxy, thienyloxy, benzyloxy, phenyl, thienyl or furyl groups, which may be unsubstituted or substituted by one or two of the same or different substituents selected from alkyl groups having from 1 to 3 carbon atoms which may be unsubstituted or substituted by one or more of the same or different halogen atoms; halogen atoms; and alkoxy groups having from 1 to 4 carbon atoms;

(d) fluorine atoms, trifluoromethyl or pentafluoroethyl groups; and

(e) cycloalkyl groups having from 3 to 7 carbon atoms;

R^5 represents an alkyl group having from 1 to 5 carbon atoms; an alkenyl or alkynyl group having from 2 to 5 carbon atoms; or a hydrogen atom;

R^6 represents a hydrogen atom or a group of the general formula R^7CO, wherein R^7 represents a hydrogen atom or an alkyl group having up to 10 carbon atoms; and A represents a *trans*- —CH=CH— group or a —CH_2—CH_2— group with the proviso that if A represents a —CH_2—CH_2— group, R^5 may only represent a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms.

2. A compound as claimed in Claim 1, wherein R^3 represents a hydrogen atom, an alkyl group having from 1 to 8 carbon atoms, an alkoxyalkyl group having a total of from 3 to 10 carbon atoms, an alkenyl group having from 2 to 4 carbon atoms, a cycloalkyl group having from 5 to 7 carbon atoms, an aralkyl group having 7 or 8 carbon atoms, an ammonium ion, a physiologically tolerable metal ion or substituted ammonium ion which is derived from a primary, secondary or tertiary amine.

3. A compound as claimed in Claim 2, wherein R^3 represents a hydrogen atom; a straight-chain alkyl group having from 1 to 6 carbon atoms; a branched alkyl group having from 3 to 5 carbon atoms; an alkoxyalkyl group; a straight-chain alkenyl group having from 2 to 4 carbon atoms; a cyclopentyl, cyclohexyl or benzyl group; or a physiologically acceptable metal ion, ammonium ion or substituted ammonium ion which is derived from a primary, secondary or tertiary amine;

4. A compound as claimed in any one of Claims 1 to 3, wherein R^4 represents an aliphatic hydrocarbon group having from 1 to 8 carbon atoms or a cycloaliphatic hydrocarbon group having from 5 to 7 carbon atoms, which groups may be unsubstituted or substituted by:

(a) an alkoxy, alkylthio, alkenyloxy or alkenylthio group having from 1 to 5 carbon atoms;

(b) a phenoxy group which may be unsubstituted or substituted by one or two of the same or different substituents selected from alkyl group having from 1 to 3 carbon atoms; trifluoromethyl groups; halogen atoms; phenoxy groups which may be unsubstituted or substituted by one or more of the same or different halogen atoms; and methoxy and ethoxy groups;

(c) a thienyloxy, benyloxy, phenyl or thienyl group which may be unsubstituted or substituted by one or two of the same or different substituents selected from alkyl groups having from 1 to 3 carbon atoms; trifluoromethyl groups; halogen atoms; methoxy and ethoxy groups;

(d) one or two fluorine atoms or a trifluoromethyl group; or

(e) a cycloalkyl or cycloalkylidene group having from 5 to 7 carbon atoms.

5. A compound as claimed in Claim 4, wherein R^4 represents an alkyl group having from 1 to 6 carbon atoms, an alkenyl group having from 3 to 5 carbon atoms or a cycloalkyl group having from 5 to 7 carbon atoms, which alkyl, alkenyl or cycloalkyl group may be unsubstituted or substituted by:

(a) an alkoxy, alkylthio, alkenyloxy or alkenylthio group having from 1 to 4 carbon atoms;

(b) a phenoxy group which may be unsubstituted or substituted by one or two of the same or different substitutent selected from methyl, trifluoromethyl and methoxy groups; chlorine or fluorine atoms; and phenoxy groups which may be unsubstituted or substituted by one or more fluorine and/or chlorine atoms;

(c) a thienyloxy, benzyloxy, phenyl or thienyl group which may be unsubstituted or substituted by one or two of the same or different substituents selected from methyl, trifluoromethyl and methoxy groups and chlorine and fluorine atoms;

(d) one or two fluorine atoms or a trifluoromethyl group; or

(e) a cycloalkyl group having from 5 to 7 carbon atoms.

6. A compound as claimed in Claim 5, whersin R^4 represents any one of the groups listed in Table A herein.

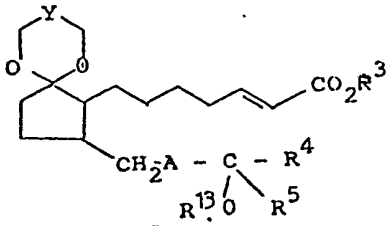
7. A compound as claimed in any one of Claims 1 to 6, wherein R^5 represents an alkyl group having from 1 to 5 carbon atoms or an alkenyl or alkynyl group having from 2 to 4 carbon atoms.

8. A compound as claimed in any one of Claims 1 to 7, wherein R^6 represents a hydrogen atom or a group of the general formula R^7CO, wherein R^7 represents a hydrogen atom or an alkyl group having up to 4 carbon atoms.

9. A compound as claimed in Claim 1 and listed in Table B herein.

10. A compound as claimed in Claim 1 and named in any one of Examples 12 to 16 herein.

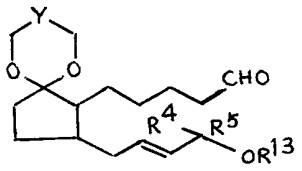
11. A process for the preparation of a compound as claimed in Claim 1, which comprises the acid solvolysis of a compound of the general formula



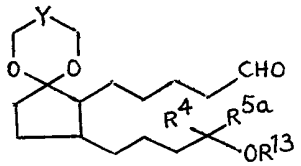
XXII

wherein R^3, R^4, R^5 and A have the meanings given for the general formula I, with the proviso that if A represents a $—CH_2—CH_2—$ group, R^5 represents a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms; R^{13} represents a hydrogen atom or a protective group which can be eliminated by acid solvolysis; and Y represents a single bond, a $—CH_2—$ group or an isopropylidene group, to give a compound of the general formula I wherein R^1 and R^2 together represent an oxygen atom, and R^6 represents a hydrogen atom; and if desired, converting the resulting compound of the general formula I into another compound of the general formula I by any suitable method.

12. A process as claimed in Claim 11, wherein the compound of the general formula XXII is prepared by reacting a compound of the general formula



XIX or



XX

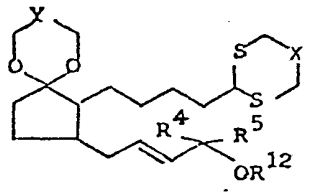
wherein R^4 and R^5 have the meanings given in Claim 1, Y represents a single bond, a $—CH_2—$ group or an isopropylidene group, R^{5a} represents a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms, and R^{13} represents a hydrogen atom or a protecting group which can be removed easily by acid solvolysis, with a compound of the general formula

$$R^{14}_3P=CH—CO_2R^3 \qquad \text{XXI}$$

wherein each R^{14}, any two or three of which may be the same or different, represents a straight-chain alkyl group having from 1 to 4 carbon atoms or a phenyl group, and R^3 has the meaning given in Claim 1.

13. A process as claimed in Claim 12, wherein the compound of the general formula XX is prepared by hydrogenating a compound of the general formula XIX in the presence of a suitable catalyst.

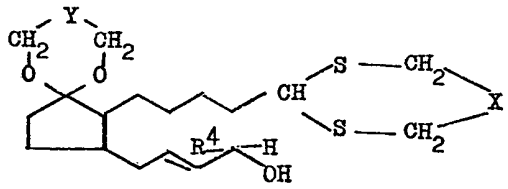
14. A process as claimed in either Claim 12 or Claims 13, wherein the compound of the general formula XIX is prepared by removing the thioacetal group in a compound of the general formula



XVIII

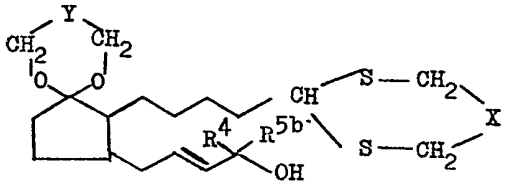
wherein R^4 and R^5 have the meanings given in Claim 1, X represents a single bond, a $—CH_2—$ group or an isopropylidene group, Y has the meaning given in Claim 12 and R^{12} represents a protecting group which can be removed easily by acid solvolysis, in the presence of a heavy metal salt, $HgCl_2$ or an alkyl halide in a mixture of organic solvent and water.

15. A process as claimed in Claim 14, wherein the compound of the general formula XVIII is produced by protecting the hydroxyl group in a compound of the general formula



XVI(a)

or



XVI(b)

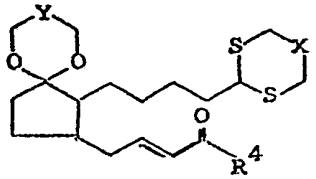
in which X has the meaning given in Claim 14, Y has the meaning given in Claim 12, R^4 has the meaning given in Claim 1 and R^{5b} represents an alkyl group having from 1 to 5 carbon atoms or an alkenyl or alkynyl group having from 2 to 5 carbon atoms.

16. A process as claimed in Claim 15, wherein the compound of the general formula XVI(b) is produced by reacting a compound of the general formula XV with an organometallic compound of the general formula

$$R^{5b}M \qquad \text{XVII}$$

wherein R^{5b} has the meaning given in Claim 15 and M represents an alkali metal or a group of the general formula HalMg, wherein Hal represents a chlorine, fluorine or bromine atom.

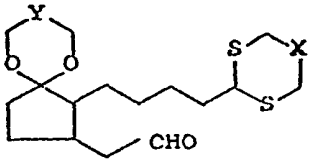
17. A process as claimed in either Claim 15 or Claim 16, wherein the compound of the general formula XVI(a) is produced by reducing a compound of the general formula



XV

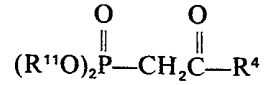
wherein R^4 has the meaning given in claim 1, X has the meaning given in Claim 14 and Y has the meaning given in Claim 12.

18. A process as claimed in Claim 17, wherein the compound of the general formula XV is produced by reacting a compound of the general formula



XIII

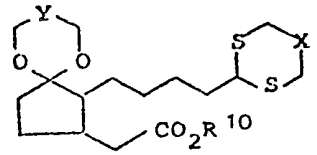
wherein X has the meaning given in Claim 14 and Y has the meaning given in Claim 12, with a compound of the general formula



XIV

wherein R^4 has the meaning given in Claim 1 and each R^{11}, which may be the same or different represents an unbranched alkyl group having from 1 to 4 carbon atoms.

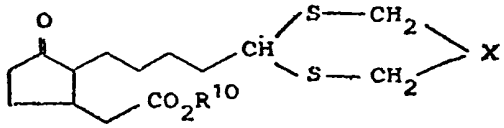
19. A process as claimed in Claim 18, wherein the compound of the general formula XII is produced by reducing a compound of the general formula



XII

wherein X has the meaning given in Claim 14, Y has the meaning given in Claim 12, and R^{10} represents an alkyl group having from 1 to 5 carbon atoms.

20. A process as claimed in Claim 19, wherein the compound of the general formula XII is produced reacting a compound of the general formula



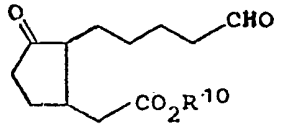
X

wherein X has the meaning given in Claim 14 and R^{10} has the meaning given in Claim 19, with a compound of the general formula

$$HOCH_2—Y—CH_2OH \qquad XI$$

wherein Y has the meaning given in Claim 12.

21. A process as claimed in Claim 20, wherein the compound of the general formula X is produced by reacting a compound of the general formula



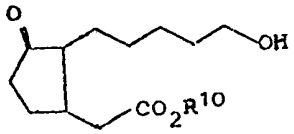
VIII

wherein R^{10} has the meaning given in Claim 19, with a compound of the general formula

$$HS—CH_2—X—CH_2—SH \qquad IX$$

wherein X has the meaning given in Claim 14.

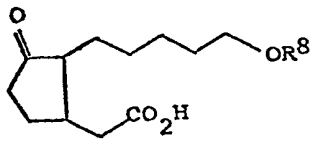
22. A process as claimed in Claim 21, wherein the compound of the general formula VIII is produced by oxidizing a compound of the general formula



VII

wherein R^{10} has the meaning given in Claim 19.

23. A process as claimed in Claim 22, wherein the compound of the general formula VII is produced by reacting a compound of the general formula

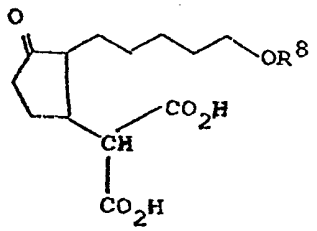


VI

wherein R^8 represents a hydrogen atom or an aliphatic acyl group having from 2 to 6 carbon atoms, in acid solution, with a alkanol having from 1 to 5 carbon atoms.

24. A process as claimed in Claim 23, wherein the compound of the general

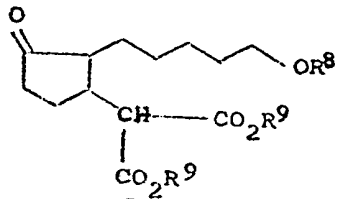
formula VI is prepared by any suitable method from a compound of the general formula



V

wherein R^8 has the meaning given in Claim 23.

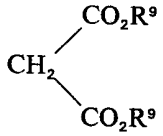
25. A process as claimed in Claim 24, wherein the compound of the general formula V is prepared by any suitable method from a compound of the general formula



IV

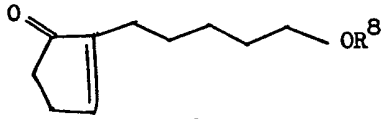
wherein R^8 has the meaning given in Claim 23 and each R^9, which may be the same or different, represents an alkyl group having from 1 to 5 carbon atoms or an aralkyl group having from 7 to 9 carbon atoms.

26. A process as claimed in Claim 25, wherein the compound of the general formula IV is prepared by reacting a compound of the general formula



III

wherein R^9 has the meaning given in Claim 25, with a compound of the general formula



II

wherein R^8 has the meaning given in Claim 23.

27. A process as claimed in Claim 11, carried out substantially as described in Example 12 herein in combination, if desired, with a process substantially as described in Example 13, and if desired Example 14, and if desired Example 15, and if desired Example 16.

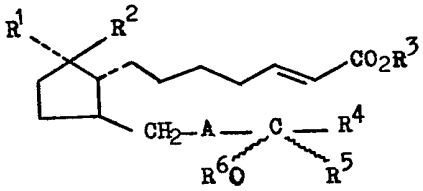
28. A process as claimed in Claim 27, carried out substantially as described in any one of Examples 1 to 11 herein in combination with all subsequent Examples up to Example 12.

29. A compound as claimed in Claim 1, whenever prepared by a process as claimed in one of Claims 11 to 28.

30. A pharmaceutical preparation which comprises a compound as claimed in any one of Claims 1 to 10 and 29, in admixture or conjunction with a pharmaceutically suitable carrier.

31. A pharmaceutical preparation as claimed in Claim 30, in dosage unit form, each unit containing in the range of from 0.1 to 750 mg of the compound of the general formula I.

32. A compound of the general formula

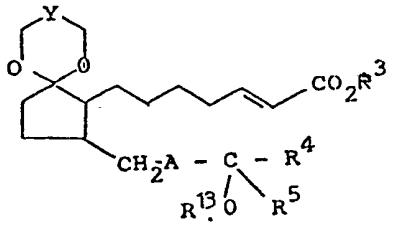


I

in which R^1 and R^2 together represent an oxygen atom or one represents a hydrogen atom and the other a hydroxyl group, R^3 represents a hydrogen atom or a straight chain, branched chain, saturated or unsaturated, aliphatic or cycloaliphatic hydrocarbon radical having from 1 to 8 carbon atoms or a straight chain or branched chain alkoxyalkyl radical having from 3 to 10 carbon atoms, or an araliphatic hydrocarbon radical having from 7 to 9 carbon atoms, or a physiologically tolerable metal ion, ammonium ion or substituted ammonium ion which is derived from a primary, secondary or tertiary amine, and R^4 represents a straight chain, branched chain, saturated or unsaturated aliphatic hydrocarbon radical having from 1 to 10 carbon atoms or a cycloaliphatic hydrocarbon radical having from 3 to 7 carbon atoms, it being possible for each of the said radicals to be substituted by a) a straight chain, branched chain, saturated or unsaturated alkoxy or alkylthio radical with 1 to 7 carbon atoms, b) a phenoxy radical which, itself, may be monosubstituted or disubstituted by an optionally halogen-substituted alkyl group having from 1 to 3 carbon atoms, by halogen atoms or by an optionally halogen-substituted phenoxy radical or an alkoxy radical having from 1 to 4 carbon atoms, it being possible in the case of disubstitution, for the substituents to be the same or different, c) a furyloxy, thienyloxy or benzyloxy radical, each of which may be monosubstituted or disubstituted by an alkyl group having from 1 to 3 carbon atoms, which, itself, may be halogen-substituted, by halogen atoms or by an alkoxy group having from 1 to 4 carbon atoms, it being possible in the case of disubstitution, for the substituents to be the same or different, d) one or two fluorine atoms or a trifluoromethyl or pentafluoroethyl group, e) a cycloalkyl radical having from 3 to 7 carbon atoms or f) a phenyl, thienyl or furyl radical, each of which may be monosubstituted or disubstituted by an optionally halogen-substituted alkyl group having from 1 to 3 carbon atoms, by halogen atoms or by an alkoxy group having from 1 to 4 carbon atoms, it being possible, in the case of disubstitution, for the substituents to be the same or different, and R^5 represents an alkyl radical having from 1 to 5 carbon atoms, an alkenyl or alkynyl group having from 2 to 5 carbon atoms or a hydrogen atom, R^6 represents a hydrogen atom or a R^7CO group, in which R^7 may be a hydrogen atom or a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, and A represents a *trans* —CH=CH— group or a $—CH_2—CH_2—$ group with the provisio that if A represents a $—CH_2—CH_2—$ group, R^5 may only represent a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms.

33. A process for the preparation of a compound as claimed in Claim 1, wherein

a) the acetal protective group and also, if R^{13} does not represent a hydrogen atom, the protective group R^{13}, are split off, by acid solvolysis, from a compound of the general formula



XXII

wherein R^{13} represents a hydrogen atom or a protective group which can be split off easily by acid solvolysis and Y represents a single bond, a $—CH_2—$ group or an isopropylidene group and R^3, R^4, R^5 and A have the meaning indicated under formula I to produce a compound of the general formula I, wherein R^1 and R^2 together represent an oxygen atom, and R^6 represents a hydrogen atom, and, if desired, one or more of the following reactions is carried out in any appropriate order:

b) a compound of the general formula I, wherein R^1 and R^2 together represent an oxygen atom, R^6 represents a hydrogen atom and R^3, R^4, R^5 and A have the meaning indicated under formula I in Claim 1, with the proviso that R^3 does not represent a hydrogen atom, is converted, by saponification, into the free acid,

c) a compound of the general formula I, wherein R^1 and R^2 together represent an oxygen atom, R^3, R^4, R^5 and A have the meaning indicated under formula I in Claim 1, R^6 represents a hydrogen atom with the proviso that R^3 does not represent a hydrogen atom is converted, by transesterification, into another ester of the general formula I,

d) a compound of the general formula I, wherein R^3 represents a hydrogen atom and R^1 and R^2 together represent an oxygen atom, R^4, R^5 and A have the meaning indicated under formula I in Claim 1 and R^6 represents a hydrogen atom, is esterified,

e) the compound of the general formula I, wherein R^1 and R^2 together represent an oxygen atom, R^3, R^4, R^5 and A have the meaning indicated under formula I in Claim 1, and R^6 represents a hydrogen atom, is reacted with an acylating agent,

f) a compound of the general formula I, wherein R^1 and R^2 together represent an oxygen atom and R^3, R^4, R^5, R^6 and A have the meaning indicated under formula I in Claim 1, is reduced to a compound of the general formula I wherein R^1 and R^2 are different one representing a hydrogen atom and the other representing a hydroxyl group, and

g) a compound of the general formula I, wherein R^3 represents a hydrogen atom and R^1, R^2, R^4, R^5, R^6 and A have the meaning indicated under formula I in Claim 1, is converted into a compound of the general formula I wherein R^3 represents a metal ion, an ammonium ion or a substituted ammonium ion derived from a primary, secondary or tertiary amine.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1981
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.