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(71) Applicant
Farmitalia Carlo Erba SpA (Italy),
Via Carlo Imbonati 24, 20159 Milan, Italy

(72) Inventors
Nicola Mongelli,
Roberto Ceserani

(74) Agent and/or Address for Service
J. A. Kemp & Co.,
14 South Square, Gray's Inn, London WC1R 5EU

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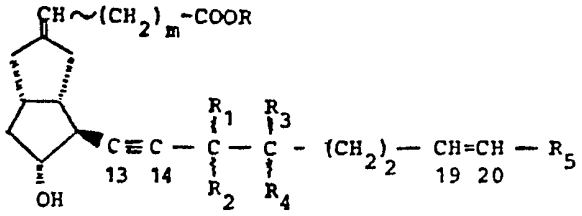
(58) Field of search
C2C

(54) 13,14,19,20-Tetradehydro derivatives of carboprostacyclins and process for their preparation

(57) Compounds of formulae (I)



(wherein
R=H or C_1-C_6 alkyl
m is 1 to 5,
one of R_1 and R_2 is H or C_1-C_6 alkyl and the other is OH,
one of R_3 and R_4 is H and the other is H or C_1-C_4 alkyl
R_5 is C_1-C_6 alkyl)
and their salts are useful in therapy.

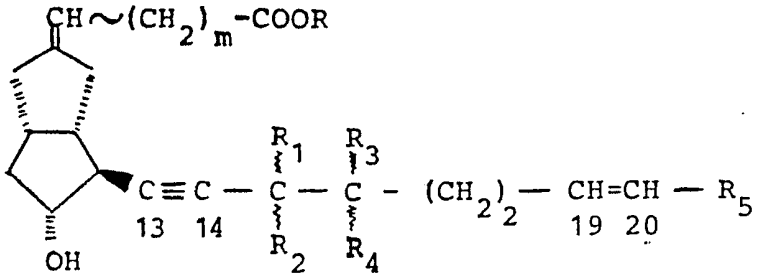
GB 2 156 342 A

SPECIFICATION

13,14,19,20-tetradehydro derivatives of carboprostacyclins and process for their preparation

The present invention relates to new 13,14,19,20-tetradehydro-carboprostacyclins, to a process for their preparation and to pharmaceutical and veterinary compositions containing them.

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



(I)

wherein R is hydrogen or C_1-C_6 alkyl;

m is an integer of 1 to 5;

one of R_1 and R_2 is hydrogen or C_1-C_6 alkyl and the other is hydroxy;

one of R_3 and R_4 is hydrogen and the other is hydrogen or C_1-C_4 alkyl; and

R_5 is C_1-C_6 alkyl, and the pharmaceutically or veterinarily acceptable salts thereof.

As indicated, the invention includes also the pharmaceutical and veterinary compositions containing a suitable carrier and/or diluent and, as an active principle, a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof. All the possible isomers of formula (I), both stereoisomers, e.g., *cis* (or Z) and *trans* (or E) isomers, and optical isomers, i.e. enantiomers, and diastereoisomers, and their mixtures, and the metabolites and the metabolic precursors or bioprecursors of the compounds of formula (I) are included in the scope of the invention.

In this application, a dashed line (‴) refers to a ring substituent in the α-configuration, that is, below the plane of the ring or to a bicyclo octane substituent in the endo configuration; a wedged line (◀) refers to a ring substituent in the β-configuration, that is above the plane of the ring, or to a bicyclo octane substituent in the exo-configuration; and a wavy line (⧘) indicates that a substituent may be both in the α- and in the β-configuration. The absolute "R" or "S" configurations of the chiral centers are assigned according to the sequence-rule procedure of IUPAC for the Nomenclature of Organic Chemistry (J.O.C. 35. 9 2849, 1970).

Where unspecified, "R,S" mixtures are intended. In the compounds of this invention, there are 2 possible geometric isomers arising from the configuration of the double bond exocyclic to the bicyclo octane ring depending on whether the chain linked to this double bond (chain α) is on the same side as or the opposite side from the other chain (chain ω) linked to the bicyclo octane ring: in the first case, the exocyclic double bond is defined as Z, i.e. cis; in the second, it is E, i.e. trans.

The symbol ~ in formula (I) means that both geometric isomers are covered by this invention, both separately and in mixtures.

Geometric isomers arise also from the Z or E configuration of the 19,20 double bond in formula (I): the invention includes both of them, either separately or in mixtures, though 19Z isomers are preferred.

Furthermore each Z or E or Z,E compound may be a racemic compound (±) or an optically active compound, i.e. a (+) or (−) enantiomer.

When unspecified a racemic compound is intended.

Pharmaceutically or veterinarily acceptable salts of the compounds of formula (I) are the salts of the compounds of formula (I) wherein R is hydrogen with a pharmaceutically or veterinarily acceptable inorganic or organic base. Acceptable inorganic bases may be, for example, the hydroxides of alkali, e.g. sodium or potassium, or alkaline earth, e.g. calcium or magnesium, metals, zinc and aluminium. Acceptable organic bases may be, for example, amines like methylamine, diethylamine, trimethylamine, ethylamine, dibutylamine, triisopropylamine, N-methylhexylamine, decylamine, dodecylamine, allylamine, crotylamine, cyclopentylamine, dicyclohexylamine, benzylamine, dibenzylamine, α-phenylethylamine, β-phenylethylamine, ethylenediamine, diethylenetriamine, and other similar aliphatic, aromatic and heterocyclic amines like piperidine, morpholine, pyrrolidine, piperazine, as well as substituted derivatives like 1-methylpiperidine, 4-ethylmorpholine, 1-isopropylpyrrolidine, 2-methylpyrrolidine, 1,4-dimethylpiperazine, 2-methylpiperidine, hydrophilic derivatives like mono-, di- and triethanolamine, 2-amino-2-butanol, 2-amino-1-butanol, 2-amino-2-ethyl-1,3-propanediol, 2-amino-2-methyl-1-propanol, tris-(hydroxymethyl)-aminomethane, N-phenylethanolamine, N-(p-tert-amylphenyl)-diethanolamine, ephedrine, procain, and α and β amino acids like lysine and arginine. In the above formula (I) the C_1-C_6 and C_1-C_4 alkyl groups may be branched or straight chain groups.

When R ic C_1-C_6 alkyl, methyl and ethyl are preferred. When one of R_1 and R_2 is C_1-C_6 alkyl, or one of R_3 and

R_4 is C_1-C_4 alkyl, preferred alkyl group is methyl. Preferred values for R_5 are methyl and ethyl.

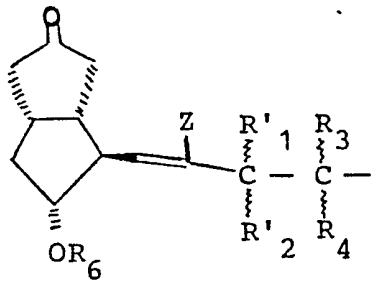
Preferred compounds of the invention are the compounds of the above formula (I) wherein R is hydrogen or C_1-C_6 alkyl; m is 3; one of R_1 and R_2 is hydrogen and the other is hydroxy; one of R_3 and R_4 is hydrogen and the other is hydrogen or methyl; and R_5 is methyl or ethyl, and the pharmaceutically or veterinarily acceptable salts thereof. The nomenclature used to identify the specific compounds falling within the invention is the same illustrated in U.K. patent 2013661B.

According to such a nomenclature, relating to the prostacyclanoic acid structure, the compounds of the invention are referred to as 9a-deoxy-9a-methylene-prostacyclanoic acid derivatives with the addition that the prefix "Z" or "E" or "(Z,E)" is used to identify the configuration of the double bond exocyclic to the bicyclooctane system, as well as the configuration of the 19,20 double bond.

As an example of this nomenclature, a compound of formula (I) wherein R is hydrogen; m is 3; R_1 is α-hydroxy; R_2, R_3 and R_4 are hydrogen, and R_5 is methyl, as a mixture of 5Z and 5E isomers with Z configuration of the 19,20 double bond, will be named (5Z,E)-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid.

Specific examples of preferred compounds under this invention are the following compounds, both as racemic compounds and as optically active compounds:
5(Z,E)-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid;
5Z-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid;
5E-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid;
5(Z,E)-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-16-S-16-methyl-20-methyl-prostacycla-5,19-dien-13-ynoic acid;
5Z-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-16-S-16-methyl-20-methyl-prostacycla-5,19-dien-13-ynoic acid;
5E-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-16-S-16-methyl-20-methyl-prostacycla-5,19-dien-13-ynoic acid, and the C_1-C_6 alkyl esters, and pharmaceutically or veterinarily acceptable salts thereof.

The compound of formula (I) are prepared by a process comprising reacting a compound of formula (II)



(II)

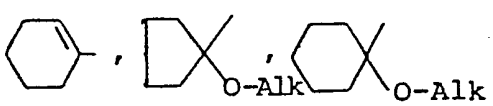
wherein R_3, R_4 and R_5 are as defined above;
Z is chlorine, bromine or iodine;
R_6 is hydrogen or a hydroxy protecting group; one of R'_1 and R'_2 is hydrogen or C_1-C_6 alkyl and the other is a group $-OR_6$ wherein R_6 is as defined above, with a compound of formula (III)

$$(R_7)_3P^{(+)} - CH^{(-)} - (CH_2)_m - COOR \qquad \text{(III)}$$

wherein R and m are as defined above and R_7 is an aryl or C_1-C_6 alkyl group, and, in any order, removing the protecting groups possibly present, converting, if desired, a possibly obtained salt into the corresponding free acid and, if desired, esterifying the obtained acid, and then, if desired, salifying a compound of formula (I) wherein R is hydrogen, or saponifying a compound of formula (I) wherein R is C_1-C_6 alkyl to give a compound of formula (I) wherein R is hydrogen or a salt thereof, and/or, if desired, separating a mixture of isomers of formula (I) into the single isomers.

In the compound of formula (II) the halogen Z is, preferably, bromine.

When in the compound of formula (II) R_6 is a hydroxy protecting group it is, for example, an ether or ester residue which may be readily split under mild conditions, for instance by acid hydrolysis. Preferred groups include silyl ether residues: for instance trialkysilyl like trimethyl, dimethyl-tert-butyl-isopropyl, or dimethylethyl-silyl; and also acetal and enol ether residues: for instance, tetrahydropyranyl, tetrahydrofuranyl, dioxanyl, oxathianyl, or groups such as



where Alk is C_1-C_6 alkyl.

When in the compound of formula (III) R_7 is aryl it is, preferably, phenyl; when R_7 is C_1-C_6 alkyl, ethyl is preferably, phenyl; when R_7 is C_1-C_6 alkyl, ethyl is preferred. The reaction between a compound of formula

(II) and a compound of formula (III) is preferably carried out in the presence of a solvent and, preferably, using an excess of the Wittig reagent of formula (III), e.g. from about 1.5 to about 5 moles of Wittig reagent per 1 mole of the compound of formula (II). The solvent may be any solvent which can, in general, be used for Wittig reactions. Preferably it is an inert organic solvent chosen from ethers, both linear and cyclic, e.g. diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; aliphatic or aromatic hydrocarbons, e.g. n-hexane, n-heptane, benzene, toluene or xylene; dialkysulphoxides, e.g. dimethylsulphoxide; aliphatic acid dialkylamides, e.g. dimethylformamide or dimethylacetamide; halogenated hydrocarbons, e.g. dichloromethane or chloroform; and phosphoric acid triamides, hexamethylphosphoramide for example. Dimethylsulphoxide is a particularly preferred solvent. The reaction temperature may range from about −10°C to the reflux temperature of the solvent used although room temperature is particularly preferred. The reaction is normally carried out in the presence of a base which may be, for example, potassium tert. butoxide or sodium hydride and, preferably, operating under nitrogen atmosphere.

The compound of formula (III) is usually generated "in situ", with the above reaction conditions, from a corresponding (carboxyalkyl)-triarylphosphonium bromide or (carboxyalkyl)-trialkyl-phosphonium bromide.

As both the triple bond formation and the alkylation with the Wittig reagent take place at the same time in an only one step, it is preferred to use not less than about two moles of compound (III) per mole of compound (II).

A greater excess of the Wittig reagent, up to 5 moles per mole of compound (II), may be, however, employed and in this way the reaction times can be considerably reduced. The time required by the reaction may vary, depending upon the used reaction conditions, within the range from 0.5 to 24 hours. The removal of the hydroxy protecting groups possibly present may be carried out following known conventional procedures. For example ether residue protecting groups may be removed by mild acid, hydrolysis, for instance with mono- or poly-carboxylic acids, such as, e.g., acetic, formic, citric, oxalic, or tartaric, in a solvent such as, e.g., water, acetone, tetrahydrofuran, dimethoxyethane or a low molecular weight alcohol, or with a sulfonic acid such as, e.g., p-toluenesulfonic, in a low molecular weight alcohol such as, e.g., anhydrous ethanol or methanol, or with a polystyrene-sulfonic resin. For example, a 0.1-0.25N polycarboxylic acid (like oxalic or citric) is used with a suitable low-boiling solvent miscible with water and readily removable under vacuum at the end of the reaction. Silyl ether residues may be selectively removed in the presence of other protecting groups with F^- ions in solvents such as, e.g., tetrahydrofuran and dimethyl-formamide.

Ester protecting groups may be removed by following typical saponification procedures.

The optional conversion of an obtained salt into the corresponding free acid may be carried out by acidification in a conventional way.

The optional esterification of an obtained acid may be carried out following the usual and known esterification procedures of the organic chemistry.

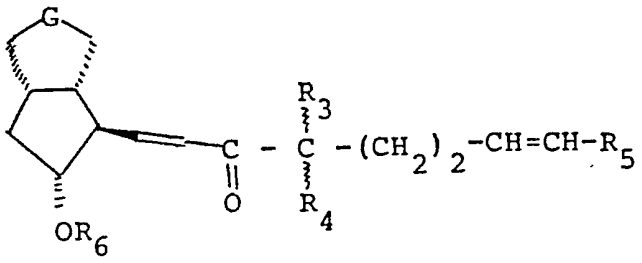
Thus, for example, the esterification may be carried out using the appropriate diazoalkane in an inert organic solvent, e.g. diethylether, ethylacetate, methylene chloride, or their mixtures at temperatures from about −10°C to about 20°C, preferably at about 0°C; or using the appropriate alkylhalide, for example in acetone or N,N-dimethyl-formamide in the presence of a base which may be, for instance, sodium or potassium carbonate or bicarbonate. Also the optional saponification of a compound of formula (I) wherein R is C_1-C_6 alkyl may be carried out by conventional procedures, for example by reaction with an aqueous solution of an alkali metal, e.g. sodium or potassium, hydroxide or carbonate in the presence of a water miscible solvent, e.g. dioxane, tetrahydrofuran, methanol or ethanol, preferably at room temperature. The saponification product may be recovered as a salt, e.g. alkali metal salt, or, previous possible acidification, as a free acid.

The optional salification of a compound of formula (I) as well as the optional separation of a mixture of isomers into the single isomers may be carried out by usual methods known *per se.* In particular, for example, single isomers may be obtained from their mixture by means of, e.g., fractional crystallization from a suitable solvent or by chromatography, either thin layer, column or liquid-liquid at low, medium or high pressure. For column and thin layer chromatography, for instance, silica gel or magnesium silicate may be used as support with a solvent such as, e.g., cyclohexane, n-hexane, benzene, methylene chloride, diethyl ether, isopropyl ether, ethyl acetate or methyl acetate as the mobile phase.

Thus, for example, the above illustrated reaction between a compound (II) and a compound (III) gives a mixture of geometric isomers in that the new exocyclic double bond formed in the reaction may be Z or E: if desired, the individual geometric isomers may be separated by one of the above reported techniques.

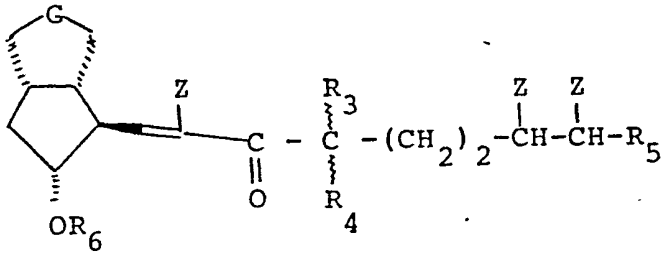
The compounds of formula (II) may be prepared by a procedure involving:

a) halogenation of a compound of formula (IV)



(IV)

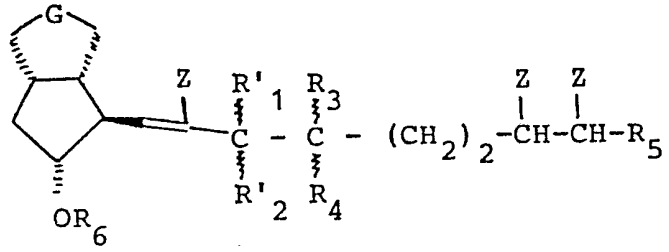
wherein R_3, R_4, R_5 and R_6 are as defined above, and G is a protected carbonyl group, so obtaining a compound of formula (V)



(V)

wherein R_3, R_4, R_5, R_6, G and Z are as defined above;

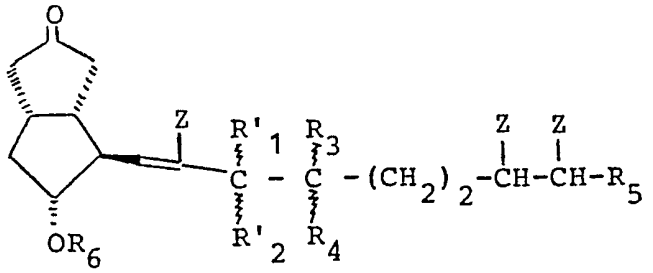
b) reduction or nucleophilic addition on the free oxo group of the compound of formula (V) followed by optional separation of the obtained mixture of the S and R alcohols and optional protection of the newly formed hydroxy group, so obtaining a compound of formula (Va)



(Va)

wherein R'_1, R'_2, R_3, R_4, R_5, R_6, G and Z are as defined above;

c) removal of the carbonyl protecting group from G and optional removal of the hydroxy protecting groups possibly present in a compound of formula (Va), so obtaining a compound of formula (Vb)



(Vb)

wherein R'_1, R'_2, R_3, R_4, R_5, R_6, G and Z are as defined above; and

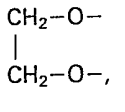
d) dehalogenation of a compound of formula (Vb). The halogenation of a compound of formula (IV) to give a compound of formula (V) may be carried out with any suitable halogenating agent following conventional methods. According to a preferred procedure the halogenation may be, e.g., performed with bromine or with pyridinium tribromide in pyridine, preferably operating at room temperature, to give a compound of formula (V) wherein Z is bromine: preferred Z value in the compound (V) is, indeed, bromine. The reduction of the free oxo group in a compound of formula (V) leading to a mixture of secondary S and R alcohols, may be performed by conventional methods, e.g. by treatment with a mixed hydride such as, for instance, $NaBH_4$ or $LiAlH_4$, preferably $NaBH_4$, with the usual reaction conditions reported in the organic chemistry for this kind of reduction. The nucleophilic addition on the free oxo group of a compound of formula (V), leading to a mixture of tertiary S and R alcohols, may be carried out in a conventional way too, for example by reaction with a Grignard reagent of formula R_X MgZ wherein R_X is C_1-C_6 alkyl and Z is a halogen atom as defined

above, according to the standard reaction conditions. The separation of the obtained mixture of either secondary or tertiary S and R alcohols may be carried out by the already indicated fractional crystallization or chromatography techniques.

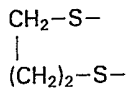
The optional protection of the newly formed hydroxy group may be carried out by any known conventional etherification or esterification procedure.

Conventional procedures too may be followed also for removing the carbonyl protecting group, and, if desired, the hydroxy protecting groups, in a compound of formula (Va).

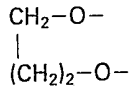
In the above formulae the protected carbonyl group G is a carbonyl group preferably protected as acetal or thioacetal, for example a dimethoxyacetyl, a diethyoxyacetal, a dimethylthioacetal, a diethylthioacetal, preferably a dimethoxyacetal, or as ketal or thioketal, for example an ethylendioxyketal



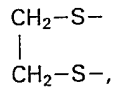
a propylendithioketal



a propylendioxyketal



an ethylendithioketal

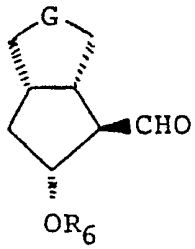


preferably an ethylendioxyketal.

The dehalogenation of a compound of formula (Vb) to give a compound of formula (II) may be carried out following known methods, for example by treatment with an alkali metal, e.g. sodium, iodide in a conventional way, or, preferably, with chromium^{II}sulphate operating at room temperature in a suitable solvent, preferably chosen from aqueous acetone and aqueous dimethylformamide.

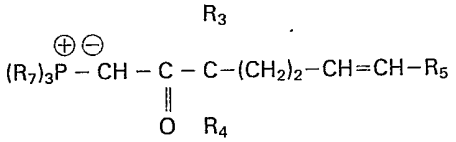
The compounds of formula (III) are known compounds and may be prepared, for instance, as described in UK patent 2 013 661B.

The compounds of formula (IV) may be prepared too following known procedures, e.g. those described in U.K. patent 2 013 661B for the preparation of analogous compounds. In particular, for example, a compound of formula (IV) may be obtained by reaction of a compound of formula (VI)



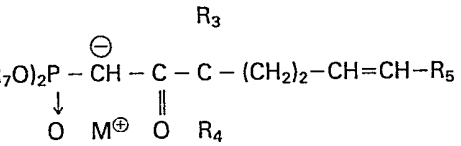
(VI)

wherein R_6 and G are as defined above, with a Wittig reagent of formula (VII)



(VII)

or with a modified Wittig reagent of formula (VIIa)



(VIIa)

wherein R_3, R_4, R_5 and R_7 are as defined above an M is a cation.

In a compound of formula (VII) R_7 is, preferably, a phenyl group.

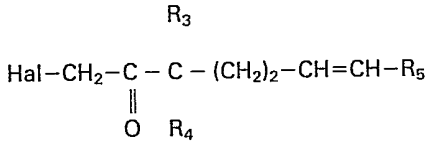
In a compound of formula (VIIa) R_7 is, preferably, a methyl group, and the cation M is, preferably, an alkali metal cation, sodium or potassium in particular.

The reaction between a compound of formula (VI) and a compound of formula (VII) or (VIIa) may be carried out using, approximately, the same reaction conditions reported above for the reaction between a compound of formula (II) and a compound of formula (III).

The compounds of formula (VI) are known compounds and may be prepared by known methods e.g. those described in UK patent 2 013 661B.

The compounds of formula (VII) and (VIIa) may be prepared by a procedure analogous to that used to obtain a compound of formula (III), e.g. as described in UK patent 2 013 661B for the preparation of analogous compounds.

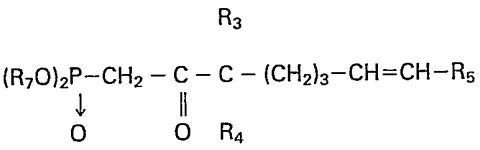
In particular, for example, a compound of formula (VII) may be prepared reacting a compound of formula (VIII)



(VIII)

wherein R_3, R_4 and R_5 are as defined above and Hal is a halogen atom, with an excess amount of a compound of formula $(R_7)_3P$ wherein R_7 is as defined above, triphenylphosphine for instance, in an organic solvent such as, e.g., benzene, acetonitrile or diethylether, and then treating the product phosphonium salt with an equivalent amount of an inorganic base, e.g. NaOH or KOH.

Analogously, a compound of formula (VIIa) may be prepared from a compound of formula (IX)



(IX)

wherein

R_3, R_4, R_5 and R_7 are as defined above, with a suitable base carrying the M^+ cation, which base may be, for instance, an alkali metal hydride such as, e.g., sodium or potassium hydride, an alkali metal alkoxide such as, e.g., sodium or potassium tert. butoxide, an alkali metal salt of a carboxamide such as, e.g., N-sodioacetamide and N-sodiosuccinimide.

The compounds of formula (VIII) and (IX) are in turn prepared using standard methods, for example those described by Corey et al. in J.Amer.Chem.Socl *90*, 3247 (1968) and *88*, 5654 (1966).

The compounds of formula (I) exhibit substantially the same pharmacological activities known for carboprostacyclins and illustrated, for instance, in UK patent 2 013 661B and in European patent 11591.

The present compounds of formula (I) form a class of carboprostacyclins which is not disclosed in UK patent 2 013 661B and European patent 11591. No mention or characterization is given in these patents of any specific compound within the scope of formula (I).

Furthermore the compounds of the present invention possess higher activity than the prior art compounds and so they may be administered at lower dosages with a consequent lower incidence of undesired possible side effects. In particular, for example, the compounds of formula (I) show high platelet antiaggregating and disaggregating activity in that they inhibit, prevent and reverse the blood platelet aggregation.

The high platelet anti-aggregation and disaggregating activity exhibited by the compounds of formula (I) indicates their use to inhibit platelet aggregation, to decrease adhesion, to prevent clot formation, and to dissolve recently-formed clots. The platelet anti-aggregating activity is also associated with a relaxation of the coronary arteries. Thus the compounds of formula (I) can be useful, e.g., in preventing and treating myocardial infactions, and, in general, in treating and preventing thromboses, in treating conditions like atherosclerosis, arteriosclerosis, and, more generally, hyperlipidemia. The compounds of the invention also exhibit vasodilatory, i.e. hypotensive or anti-hypertensive, activity and so they may be useful for treating the syndromes caused by arterial hypertension.

While the compounds of formula (I) have particular utility as anti-aggregating and/or disaggregating agents and, in addition, as vasodilating, i.e. hypotensive or anti-hypertensive, agents, they may also be used for treating obstructive pulmonary diseases such as, e.g., bronchial asthma, or to take advantage of their anti-ulcerogenic and antisecretory activities, as is shown, e.g. by the fact that they have been found to be active in the bronchodilation test on the awake or anaesthetized guinea-pig [Prostaglandins and Medicine vol. 2, 459-466 (1979)], in preventing ethanol-induced, stress-induced or ASA-induced gastric ulcers and indomethacin-induced intestinal ulcers [Gastroenterology *77*, 761-767 (1979), and Prostaglandins and Medicine vol. 5, 131-139 (1980)], and in inhibiting gastric secretion according to the method of Shay et al. [Gastroenterology *26*, 906 (1954)].

When the compounds of the invention are given as anti-aggregating or disaggregating agents, the routes of administration can be the usual ones, oral, intravenous, subcutaneous, intramuscular. In emergency situations, the preferred route is intravenous, with doses that can vary, for adult humans, from 0.001 to 1.5 mg/kg/day. The exact dose will depend on the condition of the patient, his weight, his age and the route of administration. The dosages and methods of administration of the compounds, when used as vasodilatory, i.e. hypotensive or anti-hypertensive, agents, are about the same as those used for the anti-aggregating application.

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

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

For the anti-ulcerogenic and anti-secretory applications the compound of the invention can be administered, for example, by intravenous infusion or by intravenous, subcutaneous or intramuscular injection; doses for intravenous infusion range from 0.1 μg to 500 μg/kilo/minute. The total daily dose for both injection and infusion is about 0.1-20 mg/kg depending on the age, weight and condition of the patient and on the administration method. Also rectal administration and oral administration are useful for these kinds of applications.

The toxicity of the compounds of the invention is quite negligible, so that they can be safely used in therapy.

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

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

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

For administration by suppositories suitable carriers may be, e.g., cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

For administration by nebulizer, a suspension or a solution of the compound of the invention, preferably in the form of a salt, such as the sodium salt in water, can be used. Alternatively, the pharmaceutical preparation can be in the form of a suspension or of a solution of the compound of the invention in one of the usual liquefied propellants, such as dichloro- difluoromethane or dichlorotetrafluoroethane, administered from a pressurized container as an aerosol.

When the compound is not soluble in the propellant it may be necessary to add a cosolvent, such as ethanol, dipropylene glycol and/or surfactant, to the pharmaceutical formulation.

The abbrevations DMSO and SMF used in the examples stand, respectively, for dimethylsulphoxide and dimethylformamide.

The following examples illustrate but do not limit in any way the invention. Percentages are by weight.

Example 1

To a solution of 3,3-ethylenedioxy-3-oxo-6-exo-formyl-7-endo-(2'-tetrahydropyranyloxy)-bicyclo[3,3,0]octane (3 g) in toluene (100 ml), 1.01 molar equivalents of (hex-5'-cis-5'-en-1'-yl)carbonylmethylidenetriphenylphosphorane (4.1 g) were added. The resulting solution was refluxed under

nitrogen for 24 hours.

The reaction mixture was concentrated under vacuum and the residue was adsorbed on silica gel column and eluted with n-hexane:ethylacetate (6:4) affording 3-oxo-3,3-ethylenedioxy-6-exo[1'-trans-3'-oxo-7'-cis-non-1',7'-dienyl]-7-endo-(2"-tetrahydropyranyloxy)-bicyclo[3,3,0]octane.

In similar way 3-oxo-3,3-ethylenedioxy-6-exo-[1'-trans-3'-oxo-4'-S-4'-methyl-7'-xis-non-1'-,7-dienyl]-7-endo-(2"-tetrahydropyranyloxy)-bicyclo[3,3,0]octane was prepared.

Example 2

A solution of 3-oxo-3,3-ethylenedioxy-6-exo-(1'-trans-3'-oxo-7'-cis-non-1',7'-dienyl)-7-endo-(2"-tetrahydropyranyloxy)-bicyclo[3,3,0]octane (1 g) in pyridine (10 ml) was treated under stirring with pyridinehydrotribromide (2.4 g) for 2 hours. The mixture was diluted with aqueous 30% NaH_2PO_4 solution (60 ml) and exhaustively extracted with ethylacetate. The collected organic phases were washed with water, dried and evaporated to dryness. After SiO_2 column chromatography (n-hexane:ethylacetate 40:60) 3-oxo-3,3-ethylenedioxy-6-exo-(1'-trans-2'-bromo-3'-oxo-7',8'-dibromo-non-1'-enyl)-7-endo-(2"-tetrahydropyranyloxy)-bicyclo[3,3,0]octane (1 g) was obtained. In similar way 3-oxo-3,3-ethylenedioxy-6-exo-(1'-trans-2'-bromo-3'-oxo-4'-S-4'-methyl-7',8-dibromo-non-1'-enyl)-7-endo-(2"-tetrahydropyranyloxy)-bicyclo[3,3,0]octane was prepared.

Example 3

To a stirred solution of $NaBH_4$ (0.041 g) in MeOh (20 ml) cooled to −10°C a solution of 3-oxo-3,3-ethylenedioxy-6-exo-(1'-trans-2'-bromo-3'-oxo-7',8'-dibromo-non-1'-enyl)-7-endo-(2"-tetrahydropyranyloxy)-bicyclo[3,3,0] octane (0.7 g) in MeOH (10 ml) was added.

After 1 hour the reaction mixture was diluted with 30% aqueous NaH_2PO_4 (150 ml) and extracted with ethyl acetate. The organic phases were collected, dried and, after evaporation in vacuo of the solvent, the residue was taken up with acetone (20 ml). After addition of aqueous 1N oxalic acid solution (20 ml), the mixture was heated at 40°C for 15 hours. The acetone was then removed in vacuo and the aqueous emulsion was extracted with ethylacetate. The organic extracts were collected, washed with water, dried over M_gSO_4 and the solvent was evaporated.

The residue was chromatographed on silica gel with ethylacetate: n-hexane 80:20 as eluant, affording in the order 3-oxo-6-exo-(1'-trans-2'-bromo-3'-S-3'-hydroxy-7',8'-dibromo-non-1'-enyl)-7-endo-hydroxy-bicyclo[3,3,0]octane (0.17 g) and 3-oxo-6-exo-(1'-trans-2'-bromo-3'-R-3'-hydroxy-7',8'-dibromo-non-1'-enyl)-7-endo-hydroxy-bicyclo[3,3,0]octane (0.17 g).

In similar way 3-oxo-6-exo-(1'-trans-2'-bromo-3'-S-3'-hydroxy-4'-S-4'-methyl-7',8'-dibromo-non-1'-enyl)-7-endo-hydroxy-bicyclo]3,3,0]octane and 3-oxo-6-exo-(1'-trans-2'-bromo-3'-R-3'-hydroxy-4'-S-4'-methyl-7',8'-dibromo-non-1'-enyl)-7-endo-hydroxy-bicyclo[3,3,0]octane were prepared.

Example 4

To a solution of 0.79 g of $Cr_2(SO_4)_2$ in 25 ml of H_2O, 0.062 g of Zn were added and the suspension was magnetically stirred under nitrogen. After 5' a catalytic amount of H_gCl_2 was added and the mixture, warmed to 40°C, became blue. The whole was filtered through a small pad of glass wool, under nitrogen atmosphere, directly into a dropping funnel connected with a reaction flask containing a solution of 3-oxo-6-exo-(1'-trans-2'-bromo-3'-S-3'-hydroxy-7',8'-dibromo-non-1'-enyl)-7-endo-hydroxy-bicyclo[3,3,0]octane (0.07 g) in 4 ml of a 1:1 mixture of water and DMF. The chromous sulphate solution was added dropwise and the reaction mixture was stirred at room temperature for 2 hours. The whole was poured into 100 ml of water and extracted with diethyl ether. The organic extracts were collected, washed with water, dried over $MgSO_4$ and the solvent was evaporated to yield 0.04 g of 3-oxo-6-exo-(1'-trans-2'-bromo-3'-S-3'-hydroxy-7'-cis-non-1',7'-dienyl)-7-endo-hydroxy-bicyclo[3,3,0]octane.

By proceeding analogously the following compounds were prepared:

3-oxo-6-exo-(1'-trans-2'-bromo-3'-R-3'-hydroxy-7'-cis-non-1',7-dienyl)-7-endo-hydroxy-bicyclo[3,3,0]octane;

3-oxo-6-exo-(1'-trans-2'-bromo-3'-S-3'-hydroxy-4'-S-4'-methyl-7'-cis-non-1',7'-dienyl)-7-endo-hydroxy-bicyclo[3,3,0]octane, and

3-oxo-6-exo-(1'-trans-2'-bromo-3'-R-3'-hydroxy-4'-S-4'-methyl-7'-cis-non-1',7'-dienyl)-7-endo-hydroxy-bicyclo[3,3,0]octane.

Example 5

Under nitrogen atmosphere, 4-carboxy-butyl-triphenyl-phosphonium bromide (0.3 g) was added to a mixture of potassium tert.butoxide (0.15 g) and dry DMSO (2 ml); this mixture was then treated with a solution of 3-oxo-6-exo-(1'-trans-2'-bromo-3'-S-3'-hydroxy-7'-cis-non-1'-7'-dienyl)-7-endo-hydroxy-bicyclo[3,3,0]octane (0.04 g) in DMSO (2 ml). After 2 hours the reaction mixture was diluted with water, acidified with 2N H_2SO_4 and extracted with diethyl ether.

The ethereal phase was extracted with 1N NaOH aqueous solution; the aqueous alkaline extracts were collected, acidified to pH 5 and extracted with n-pentane:diethyl ether (20:80). The final organic extracts were collected, washed with water, dried and evaporated to dryness to give, after purification,

5(Z,E)-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid (0.02 g) [NMR ($CDCl_3$) 90 MH_z δ p.p.m.: 3.94 (m,1H); 4.38 (m,1H); 5.10-5.50 (m,3H); 5.36 (bs,3H)] which was chromatographed on silica gel (eluant:ethyl acetate 70:n-hexane 30:acetic acid 4) so obtaining in the order 5Z-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid (0.006 g) [NMR ($CDCl_3$) 90 MH_z δ p.p.m.: 3.95 (m,1H); 4.39 (m,1H); 5.10-5.50 (m.3H); 5.37 (bs,3H)] and 5E-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid (0.011 g) [NMR ($CDCl_3$ 90 MH_z δ p.p.m.: 3.95 (m, 1H); 4.39 (bt,1H); 5.0-5.6 (m,3H); 5.3 (bs,3H).

By analogous procedure the following compounds were obtained:

5(Z,E)-19Z-9a-deoxy-9a-methylene-11α, 15S-dihydroxy-16-S-16-methyl-20-methyl-prostacycla-5,19-dien-13-ynoic acid, NMR ($CDCl_3$) 90 MH_z δp.p.m.: 0.95 (d,3H); 3.93 (m, 1H); 4.38 (m, 1H); 5.10-5.50 (m,3H); 5.35 (bs,3H);

5Z-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-16-S-16-methyl-20-methyl-prostacycla-5,19-dien-13-ynoic acid, NMR ($CDCl_3$) 90 MH_z δ p.p.m.: 0.96 (d,3H); 3.92 (m,1H); 4.38 (m,1H); 5.10-5.50 (m,3H); 5.36 (bs,3H);

5E-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-16-S-16-methyl-20-methyl-prostacycla-5,19-dien-13-ynoic acid, NMR ($CDCl_3$) 90 MH_z δ p.p.m.: 0.95 (d,3H); 3.91 (m,1H); 4.37 (m, 1H); 5.10-5.50 (m,3H); 5.34 (bs,3H);

5(Z,E)-19Z-9a-deoxy-9a-methylene-11α,15R-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid, NMR ($CDCl_3$) 90 MH_z δ p.p.m.: 3.94 (m,1H); 4.37 (m,1H); 5.10-5.50 (m,3H); 5.37 (bs,3H);

5Z-19Z-9a-deoxy-9a-methylene-11α,15R-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid, NMR ($CDCl_3$) 90 MH_zδ p.p.m.: 3.95 (m,1H); 4.38 (m,1H); 5.10-5.50 (m,3H); 5.36 (bs,3H);

5E-19Z-9a-deoxy-9a-methylene-11α,15R-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid, NMR ($CDCl_3$) 90 MH_z δ p.p.m.: 3.95 (m,1H); 4.38 (bt,1H); 5.0-5.6 (m,3H); 5.29 (bs,3H);

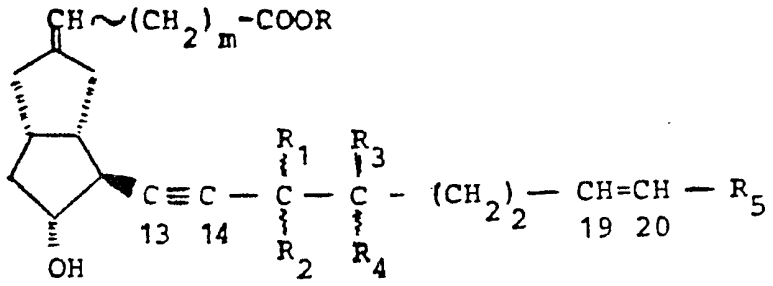
5(Z,E)-19Z-9a-deoxy-9a-methylene-11α,15R-dihydroxy-16-S-16-methyl-20-methyl-prostacycla-5,19-dien-13-ynoic acid, NMR ($CDCl_3$) 90 MH_z δ p.p.m.: 0.95 (d,3H); 3.92 (m,1H); 4.38 (m,1H); 5.10-5.50 (m,3H); 5.34 (bs,3H);

5Z-19Z-9a-deoxy-9a-methylene-11α,15R-dihydroxy-16-S-16-methyl-20-methyl-prostacycla-5,19-dien-13-ynoic acid, NMR ($CDCl_3$) 90 MH_z δ p.p.m.: 0.96 (d, 3H); 3.91 (m,1H); 4.38 (m,1H); 5.10-5.50 (m,3H); 5.35 (bs,3H); and

5E-19Z-9a-deoxy-9a-methylene-11α,15R-dihydroxy-16-S-16-methyl-20-methyl-prostacycla-5,19-dien-13-ynoic acid, NMR ($CDCl_3$) 90 MH_z δ p.p.m.: 0.94 (d,3H); 3.91 (m,1H); 4.37 (m,1H); 5.10-5.50 (m,3H); 5.33 (bs,3H).

CLAIMS

1. An optically active or racemic compound of the following formula (I)



(I)

wherein R is hydrogen or C_1-C_6 alkyl;

m is an integer of 1 to 5;

one of R_1 and R_2 is hydrogen or C_1-C_6 alkyl and the other is hydroxy;

one of R_3 and R_4 is hydrogen and the other is hydrogen or C_1-C_4 alkyl; and

R_5 is C_1-C_6 alkyl, and the pharmaceutically or veterinarily acceptable salts thereof.

2. A compound of formula (I) according to claim 1 wherein R is hydrogen or C_1-C_6alkyl; m is 3; one of R_1 and R_2 is hydrogen and the other is hydroxy; one of R_3 and R_4 is hydrogen and the other is hydrogen or methyl; and R_5 is methyl or ethyl, and the pharmaceutically or veterinarily acceptable salts thereof.

3. A compound selected from the group consisting of:

5(Z,E)-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid;

5Z-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid;

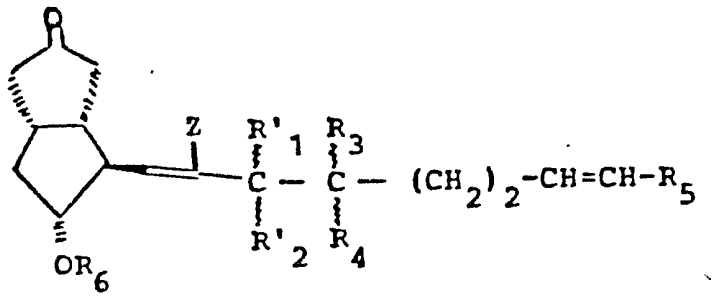
5E-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-20-methyl-prostacycla-5,19-dien-13-ynoic acid;

5(Z,E)-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-16-S-16-methyl-20-methyl-prostacycla-5,19-dien-13-ynoic acid;

5Z-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-16-S-16-methyl-20-methyl-prostacycla-5,19-dien-13-ynoic acid;

5E-19Z-9a-deoxy-9a-methylene-11α,15S-dihydroxy-16-S-16-methyl-20-methyl-prostacycla-5,19-dien-13-ynoic acid, and the C_1-C_6 alkyl esters and pharmaceutically or veterinarily acceptable salts thereof.

4. A process for the preparation of a compound of formula (I) according to claim 1, or a pharmaceutically or veterinarily acceptable salt thereof, comprising reacting a compound of formula (II)



(II)

wherein R_3, R_4 and R_5 are as defined in claim 1; Z is chlorine, bromine or iodine; R_6 is hydrogen or a hydroxy protecting group; one of R'_1 and R'_2 is hydrogen or C_1-C_6 alkyl and the other is a group $-OR_6$ wherein R_6 is as defined above, with a compound of formula (III)

$$(R_7)_3P^{(+)} - CH^{(-)}-(CH_2)_m-COOR \qquad \text{(III)}$$

wherein R and m are as defined in claim 1 and R_7 is an aryl or C_1-C_6 alkyl group, and, in any order, removing the protecting groups possibly present, converting, if desired, a possibly obtained salt into the corresponding free acid and, if desired, esterifying the obtained acid, and then, if desired, salifying a compound of formula (I) wherein R is hydrogen, or saponifying a compound of formula (I) wherein R is C_1-C_6 alkyl to give a compound of formula (I) wherein R is hydrogen or a pharmaceutically or veterinarily acceptable salt thereof, and/or, if desired, separating a mixture of isomers of formula (I) into the single isomers.

5. A pharmaceutical or veterinary composition containing a compound of formula (I) according to claim 1 or a pharmaceutically or veterinarily acceptable salt thereof and a pharmaceutically or veterinarily acceptable carrier and/or diluent.

6. A compound of formula (I), as defined in claim 1, hereinbefore specified other than a compound of formula (I) claimed in claim 3.

7. A compound of formula (I) as defined in claim 1, or a pharmaceutically or veterinarily acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

8. A compound of formula (I) or salt thereof according to claim 7 for use as a platelet anti-aggregation and disaggregating agent.

9. A compound of formula (I) or salt thereof according to claim 7 for use as a hypotensive or anti-hypertensive agent.

10. A compound of formula (I) or salt thereof according to claim 7 for use in treating obstructive pulmonary diseases.

11. A compound of formula (I) or salt thereof according to claim 7 for use as an anti-ulcer or anti-secretory agent.

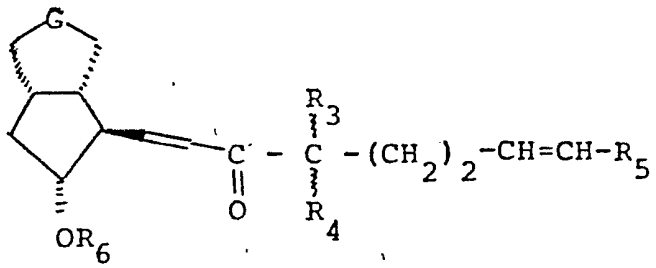
12. A process for the preparation of a compoiund of formula (I) as defined in claim 1, said process being substantially as hereinbefore described in Example 5.

13. A compound of formula (II) as defined in claim 4.

14. A compound of formula (II) as defined in claim 4 hereinbefore specified.

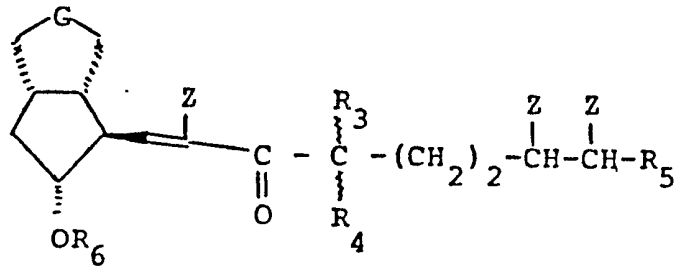
15. A process for the preparation of a compound of formula (II) as defined in claim 4, which process comprises:

a) halogenation of a compound of formula (IV)



(IV)

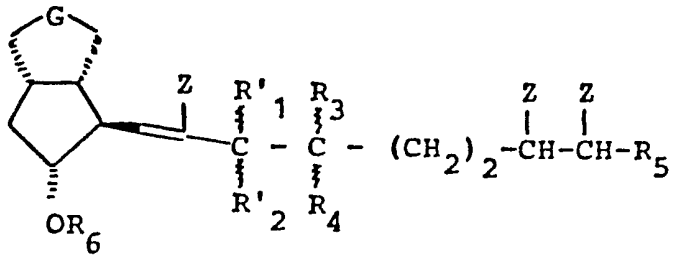
wherein R_3, R_4 and R_5 are as defined in claim 1 and R_6 as defined in claim 4, and G is protected carbonyl group, so obtaining a compound of formula (V)



(V)

wherein R_3, R_4, R_5, R_6 and G are as defined above and Z is as defined in claim 4;

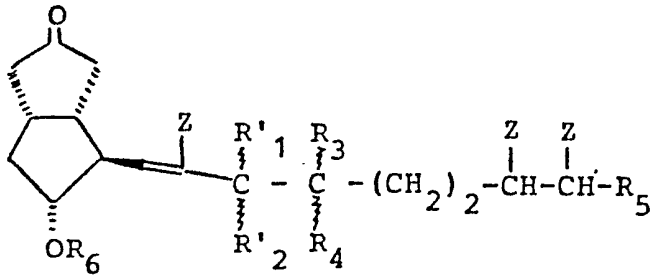
b) reduction of or nucleophilic addition to the free oxo group of the compound of formula (V) followed by optional separation of the obtained mixture of the S and R alcohols and optional protection of the newly formed hydroxy group, so obtaining a compound of formula (Va)



(Va)

wherein R_3, R_4, R_5, R_6, G and Z are as defined above and R'_1 and R'_2 are as defined in claim 4;

c) removal of the carbonyl protecting group from G and optional removal of the hydroxy protecting groups which may be present in a compound of formula (Va), so obtaining a compound of formula (Vb)



(Vb)

wherein R'_1, R'_2, R_3, R_4, R_5, R_6, G and Z are as defined above; and

d) dehalogenation of a compound of formula (Vb).

16. A process for the preparation of a compound of formula (II) as defined in claim 4, said process being substantially as hereinbefore described in Example 4.

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