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(54) **TRAITEMENT DE TROUBLES PULMONAIRES A L'AIDE DE COMPOSES DE 15-CETO-PROSTAGLANDINES**

(54) **TREATMENT OF PULMONARY DYSFUNCTION WITH 15-KETO-PROSTAGLANDIN COMPOUNDS**

(57) The present invention is directed to a pharmaceutical composition for the treatment of pulmonary dysfunction comprising a 15-ketoprostaglandin compound in association with a pharmaceutically acceptable carrier, diluent or excipient.

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Abstract

The present invention is directed to a pharmaceutical composition for the treatment of pulmonary dysfunction comprising a 15-ketoprostaglandin compound in association with a pharmaceutically acceptable carrier, diluent or excipient.

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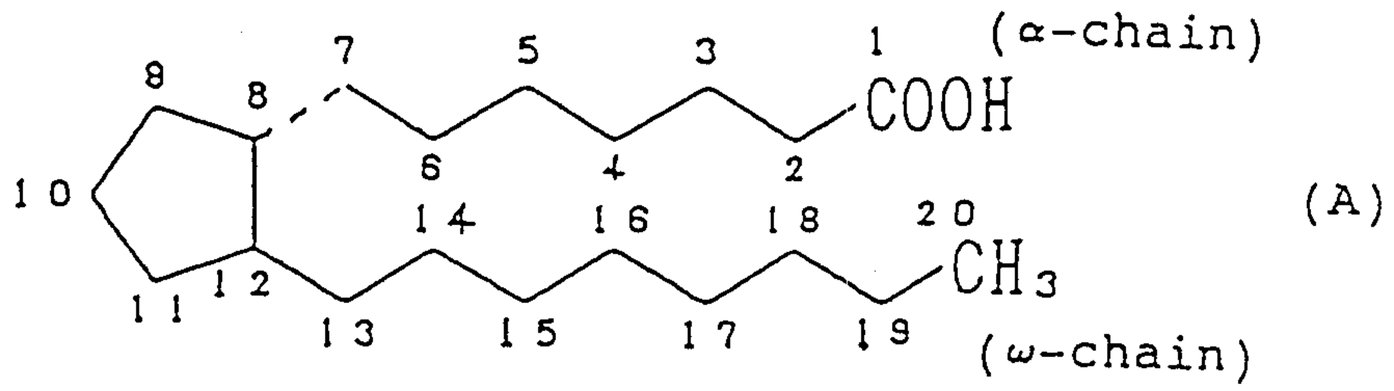
Treatment of Pulmonary Dysfunction With 15-Keto-Prostaglandin Compounds

The present invention relates to a pharmaceutical composition for treating pulmonary dysfunction comprising a 15-ketoprostaglandin compound.

Prostaglandins (hereinafter, prostaglandins are referred to as PGs) are members of a class of organic carboxylic acids that are contained in human and most other mammalian tissues or organs and that exhibit a wide range of physiological activities. Naturally occurring PGs possess as a common structural feature the prostanoic acid skeleton:



(A)

Some synthetic analogues have somewhat modified skeletons. The primary PGs are classified based on the structural feature of the five-membered cyclic moiety into PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs, and also on the presence or absence of unsaturation and oxidation in the chain moiety as:

Subscript 1 - - - 13,14-unsaturated-15-OH

Subscript 2 - - - 5,6- and 13,14-diunsaturated-15-OH

Subscript 3 - - - 5,6- 13,14-and 17,18-triunsaturated-15-OH

Further, PGFs are sub-classified according to the configuration of the hydroxy group at position 9 into α(hydroxy group being in the alpha configuration) and ß(hydroxy group being in the beta configuration).

JP-A-164512/1983 discloses the protecting action of 15-cycloalkyl-6-oxo-PGE_1, 15-cycloalkyl-PGI_1 and I_2, 15-cycloalkyl-6,9α-nitrilo-PGI_1 and 15-cycloalkyl-6,9α-thio-PGI_1

and I_2 in cells disorders. JP-A-203911/1983 discloses the cell-protecting action of certain 6-oxo-PGE_1 and PGI_1 having methyl group(s) at one or two of positions 15, 16, 17 and 20 and specific 15-cyclopentyl-PGI_1. JP-A-73522/1984 discloses that certain PGD_2 and PGE_1 derivatives may be used as an agent for treating anoxic disease of cranial nerves. All these compounds, however, do not belong to 15-keto-PGs or their derivatives.

European Patent Application No. 0,310,305 describes that 15-keto-PGs can be used as cathartics.

As a result of extensive studies on the biological properties of 15-ketoprostaglandin compounds, the present inventors have discovered that these compounds are useful as agents for treating damaged pulmonary function.

In a first aspect, the present invention provides a method for the treatment of pulmonary dysfunction which comprises administering, to a subject in need of such treatment, a 15-ketoprostaglandin compound in an amount effective in the treatment of pulmonary dysfunction.

In a second aspect, the present invention provides for the use of a 15-ketoprostaglandin compound in the manufacture of a medicament for the treatment of pulmonary dysfunction.

In a third aspect, the present invention provides for a pharmaceutical composition for the treatment of pulmonary dysfunction comprising a 15-ketoprostaglandin compound in association with a pharmaceutically acceptable carrier, diluent or excipient.

As used herein, the term "pulmonary dysfunction" means all conditions having etiology based on or accompanied by insufficiency of gas exchange function in the lungs, which are symptoms or diseases having connection with either permeation disorder of oxygen contained in expired gas into resorptive epithelium, permeation disorder from resorptive epithelium into the bloodstream via pulmonary capillary cells or disorder in uptake of oxygen into red cells (i.e. combination with hemoglobin). Examples of said symptoms or diseases include dyspnea or hypopnea resulting from a physiologically active

substance (e.g. narcotics, toxicants, etc.) foreign-body inhalation, anthracemia, bronchoconstriction attack in hypoxic condition (caused by smoke, dust, chemical irritant, etc.), bronco-pulmonary injury, pulmonary contusion or shock; pulmonary edema, atelectasis, pulmonary thrombosis, pulmonary infarction, pulmonary fibrosis, pulmonary emphysema, bronchitis, bronchial asthma, adult respiratory distress syndrome (ADRS), infantile respiratory distress syndrome (IRDS), pulmonary stenosis, pulmonary congestion, pulmonary hypertension, chronic obstructive lung disease, congenital heart disease, bilateral carotid body enucleation, sudden infant death syndrome, uremia and central inhibition caused by narcotic or anaesthetic.

As used herein, the term "treatment" or "treating" refers to any means of control of a disease in mammals, including preventing the disease, curing the disease, relieving the disease and arresting or relieving the development of the disease.

The term "15-ketoprostaglandin compounds", referred to as 15-keto-PG compounds, include any prostaglandin derivatives which have an oxo group in place of the hydroxy group at position 15 of the prostanoic acid nucleus irrespective of the presence or absence of the double bond between positions 13 and 14.

Nomenclature of 15-keto-PG compounds herein uses the numbering system of prostanoic acid represented in formula (A) shown above.

While formula (A) shows a basic skeleton having twenty carbon atoms, the 15-keto-PG compounds used in the present invention are not limited to those having the same number of carbon atoms. The carbon atoms in formula (A) are numbered 2 to 7 on the α-chain starting from the α-carbon atom adjacent to the carboxylic carbon atom which is numbered 1 and towards the five-membered ring, 8 to 12 on the ring starting from the carbon atom on which the α-chain is attached, and 13 to 20 on the ω-chain staring from the carbon atom adjacent to the ring. When the number of carbon atoms in the α-chain is decreased,

the number is lowered in order starting from position 2 and when the number of carbon atoms in the α-chain is increased, compounds are named as substituted derivatives having respective substituents at position 1 in place of the carboxy group (C-1). Similarly, when the number of carbon atoms in the ω-chain is decreased, the number is lowered in order starting from position 20 and when the number of carbon atoms in the ω-chain is increased, compounds are named as substituted derivatives having respective substituents at position 20. Stereochemistry of the compounds is the same as that of formula (A) above unless otherwise specified. Thus, 15-keto-PG compounds having 10 carbon atoms in the ω-chain is nominated as 15-keto-20-ethyl-PGs.

The above formula expresses a specific configuration which is the most typical one, and in this specification compounds having such a configuration are expressed without any specific reference to it.

In general, PGDs, PGEs and PGFs have a hydroxy group on the carbon atom at position 9 and/or 11 but in the present specification the term "15-keto-PG compounds" includes PGs having a group other than a hydroxy group at position 9 and/or 11. Such PGs are referred to as 9-dehydroxy-9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds.

As stated above, nomenclature of 15-keto-PG compounds is based upon the prostanoic acid. These compounds, however, can also be named according to the IUPAC naming system. For example, 13,14-dihydro-15-keto-16R,S-fluoro-PGE_2 is (Z)-7-{(1R,2R,3R)-3-hydroxy-2-[(4R,S)-fluoro-3-oxo-1-octyl]-5-oxocyclopentyl}-hept-5-enoic acid. 13,14-dihydro-15-keto-16,16-difluoro-PGE_2 is (Z)-7-[(1R,2R,3R)-2-(4,4-difluoro-3-oxo-1-octyl-3-hydroxy-5-oxocyclopentyl]-hept-5-enoic acid. 13,14-dihydro-15-keto-20-ethyl-11-dehydroxy-11R-methyl-PGE_2 methyl ester is methyl 7-{(1R,2S,3S)-3-methyl-2-[3-oxo-1-decyl]-5-oxocyclopentyl}-hept-5-enoate. 13,14-dihydro-6,15-diketo-19-methyl-PGE_2 ethyl ester is ethyl 7-{(1R,2S,3S)-3-hydroxy-2-(7-methyl-3-oxo-1-octyl)-5-oxocyclopentyl}-6-oxo-heptanoate. 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester is

isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-{3-oxo-1-decyl)-cyclopentyl]-hept-5-enoate. 13,14-dihydro-15-keto-20-methyl-$PGF_{2\alpha}$ methyl ester is methyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-{3-oxo-1-nonyl}-cyclopentyl]-hept-5-enoate.

The 15-keto-PG compounds used in the present invention may be any PG derivatives insofar as they have an oxo group at position 15 in place of the hydroxy group, and may have a double bond between positions 13 and 14 (15-keto-PG subscript 1 compounds), two double bonds between positions 13 and 14 as well as positions 5 and 6 (15-keto-PG subscript 2 compounds), or three double bonds between positions 13 and 14, positions 5 and 6 as well as positions 17 and 18 (15-keto-PG subscript 3 compounds), and may have a single bond between positions 13 and 14 (13,14-dihydro-15-keto-PG compounds).

Typical examples of the compounds used in the present invention are 15-keto-PGA, 15-keto-PGD, 15-keto-PGE, 15-keto-PGF, 13,14-dihydro-15-keto-PGA, 13,14-dihydro-15-keto-PGD, 13,14-dihdyro-15-keto-PGE, and 13,14-dihydro-15-keto-PGF, wherein PG is as defined above as well as their substitution products or derivatives.

Examples of substitution products or derivatives include esters at the carboxy group on the alpha chain, pharmaceutically or physiologically acceptable salts, unsaturated derivatives having a double bond or a triple bond between positions 2 and 3 or positions 5 and 6, respectively, substituted derivatives having substituent(s) on carbon atom(s) at position 3, 5, 6, 16, 17, 19 and/or 20 and compounds having lower alkyl or a hydroxy (lower) alkyl group at position 9 and/or 11 in place of the hydroxy group, of the above PGs.

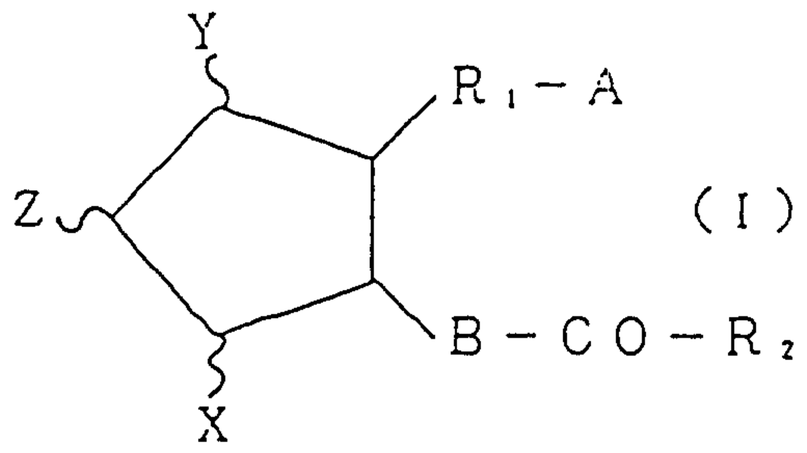
Examples of substituents present in preferred compounds are as follows: Substituents on the carbon atom at position 3, 17 and/or 19 include lower alkyl, for example, C_{1-4} alkyl, especially methyl and ethyl. Substituents on the carbon atom at position 16 include lower alkyl e.g. methyl, ethyl, etc., hydroxy and halogen atom e.g. chlorine, fluorine, aryloxy e.g. trifluoromethylphenoxy, etc. Substituents on the carbon atom

at position 17 include halogen atoms, e.g. chlorine, fluorine, etc. Substituents on the carbon atom at position 20 include saturated and unsaturated lower alkyl e.g. C_{1-4} alkyl, lower alkoxy e.g. C_{1-4} alkoxy and lower alkoxy (lower) alkyl e.g. C_{1-4} alkoxy-C_{1-4} alkyl. Substituents on the carbon atom at position 5 include halogen atoms, e.g. chlorine, fluorine, etc. Substituents on the carbon atom at position 6 include an oxo group forming a carbonyl. The stereochemistry of PGs having hydroxy, lower alkyl or lower (hydroxy) alkyl substituent on the carbon atom at position 9 and/or 11 may be alpha, beta or mixtures thereof.

Such derivatives may have an alkoxy, phenoxy or phenyl group at the end of the omega chain where the chain is shorter than the primary PGs.

Especially preferred compounds are those having a lower alkyl e.g. methyl, ethyl, etc., a halogen atom e.g. chloro, fluoro, etc. at position 16, those having a halogen atom e.g. chloro, fluoro, etc. at position 17, those having a lower alkyl e.g. methyl, ethyl, etc. at position 19, those having a halogen atom e.g. chlorine, fluorine, etc. at position 5, those having an oxo group at position 6, those having a lower alkyl, e.g. methyl, ethyl, etc. at position 20 and those having phenyl or phenoxy which are optionally substituted with halogen or haloalkyl at position 16 in place of the rest of the alkyl chain.

A group of preferred compounds used in the present invention has the formula



(I)

wherein X and Y are hydrogen, hydroxy, halo, lower alkyl, hydroxy(lower)alkyl, or oxo, with the proviso that at least one of X and Y is a group other than hydrogen, and the 5-

membered ring may have at least one double bond, Z is hydrogen or halo, A is $-CH_2OH$, $-COCH_2OH$, -COOH or its functional derivative, B is $-CH_2-CH_2$, -CH=CH- or $-C\equiv C-$, R_1 is a bivalent saturated or unsaturated, lower or medium aliphatic hydrocarbon residue which is unsubstituted or substituted with halo, oxo or aryl, R_2 is a saturated or unsaturated, lower or medium aliphatic hydrocarbon residue which is unsubstituted or substituted with halo, hydroxy, oxo, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, aryl or aryloxy.

In the above formula, the term "unsaturated" in the definitions for R_1 and R_2 is intended to include at least one and optionally more than one double bond and/or triple bond isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to usual nomenclature, unsaturation between two serial positions is represented by denoting the lower number of said two positions, and unsaturation between two distal positions is represented by denoting both of the positions. Preferred unsaturation is a double bond at position 2 and a double or triple bond at position 5.

The term "lower or medium aliphatic hydrocarbon residue" refers to a straight or branched chain hydrocarbyl group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms being preferred) and preferably 2 to 8 carbon atoms for R_1 and 6 to 12 carbon atoms for R_2.

The term "halo" denotes fluoro, chloro, bromo and iodo.

The term "lower" throughout the specification is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" as a group or a moiety in hydroxy(lower)alkyl includes saturated and straight or branched chain hydrocarbon radicals containing 1 to 6, carbon atoms, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to the group lower-alkyl-O- wherein lower alkyl is as defined above.

A

The term "hydroxy(lower)alkyl" refers to lower alkyl as defined above which is substituted with at least one hydroxy group, e.g. hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

The term "lower alkanoyloxy" refers to a group of the formula: RCO-O- wherein RCO- is an acyl group formed by oxidation of a lower alkyl group as defined above, e.g. acetyl.

The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above.

The term "aryl" includes unsubstituted or substituted aromatic carbocyclic or heterocyclic (preferably monocyclic) groups, e.g. phenyl, tolyl, xylyl and thienyl. Examples of substituents are halo and halo(lower)alkyl wherein halo and lower alkyl are as defined above.

The term "aryloxy" refers to a group of the formula: ArO- wherein Ar is aryl as defined above.

The term "functional derivative" of carboxy as A includes salts (preferably pharmaceutically acceptable salts), esters and amides.

Suitable "pharmaceutically acceptable salts" includes conventional non-toxic salts, and may be a salt with an inorganic base, for example an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), ammonium salt, a salt with an organic base, for example, an amine salt (e.g. methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)ethane salt, monomethyl-monoethanolamine salt, procaine salt, caffeine salt, etc.), a basic amino acid salt (e.g. arginine salt, lysine salt, etc.), tetraalkyl ammonium salt and the like. These salts can be prepared by conventional processes, for example from the corresponding acid and base, or by salt interchange.

Examples of the esters are aliphatic esters, for example, lower alkyl ester, e.g. methyl ester, ethyl ester, propyl

ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, 1-cyclopropylethyl ester, etc., lower alkenyl ester e.g. vinyl ester, allyl ester, etc., lower alkynyl ester e.g. ethynyl ester, propynyl ester, etc., hydroxy(lower)alkyl ester e.g. hydroxyethyl ester, lower alkoxy(lower)alkyl ester e.g. methyoxymethyl ester, 1-methoxyethyl ester, etc., and aromatic esters, for example, optionally substituted aryl ester e.g. phenyl ester, tosyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxy-phenyl ester, benzamidophenyl ester, etc., aryl(lower)alkyl ester e.g. benzyl ester, trityl ester, benzhydryl ester, etc. Examples of the amides are mono- or di- lower alkyl amides e.g. methylamide, ethylamide, dimethylamide, etc., arylamide e.g. anilide, toluidide, and lower alkyl- or aryl-sulfonylamide e.g. methylsufonylamide, ethylsulfonylamide, tolylsulfonylamide, etc.

Preferred examples of A include -COOH, $-COOCH_3$, $-COOCH_2CH_3$, $-COOCH(CH_3)_2$ and $-CONHSO_2CH_3$.

The configuration of the ring and the α- and/or omega chain in the above formula (I) may be the same as or different from that in the primary PGs. However, the present invention also includes a mixture of a compound having a primary configuration and that of a nonprimary configuration.

Examples of typical compounds of the present invention are 15-keto-PGs, 13,14-dihydro-15-keto-PGs and their 6-keto-derivatives, Δ^2-derivatives, 3R,S-methyl-derivatives, 5R,S-fluoro-derivatives, 5,5-difluoro-derivatives, 16R,S-methyl-derivatives, 16,16-dimethyl-derivatives, 16R,S-fluoro-derivatives, 16,16-difluoro-derivatives, 17S-methyl-derivatives, 17R,S-fluoro-derivatives, 17,17-difluoro-derivatives, 19-methyl-derivatives, 20-methyl-derivatives, 20-ethyl-derivatives, 19-desmethyl-derivatives and 16-desbutyl-16-phenoxy derivatives.

When 15-keto-PG compounds of the present invention have a saturated bond between positions 13 and 14, these compounds may be in the keto-hemiacetal equilibrium by forming a

hemiacetal between the hydroxy group at position 11 and the ketone at position 15.

The proportion of both tautomeric isomers, when present, varies depending on the structure of the rest of the molecule or type of any substituent present and, sometimes, one isomer may predominate in comparison with the other. However, in this invention, it is to be appreciated that the compounds used in the invention include both isomers. Further, while the compounds used in the invention may be represented by a structure or name based on the keto-form regardless of the presence or absence of the isomers, it is to be noted that such structure or name is not intended to eliminate the hemiacetal type of compounds.

In the present invention, any of the individual tautomeric isomers, a mixture thereof, or optical isomers, a mixture thereof, a racemic mixture, and other isomers, e.g. steric isomers can be used for the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in Japanese Patent Publications (unexamined) No. A-52753/1989, A-104040/1989, A-151519/1989.

Alternatively, these compounds may be prepared by a process analogous to that described herein or to known processes.

A practical preparation of the 15-keto compounds involves the following steps; referring to the Synthetic Charts I to III, reaction of the aldehyde (2) prepared by the Collins oxidation of commercially available (-)-Corey lactone (1) with dimethyl (2-oxoheptyl)phosphate anion to give α,ß-unsaturated ketone (3), reduction of the α,ß-unsaturated ketone (3) to the corresponding saturated ketone (4), protection of the carbonyl group of the ketone (4) with a diol to the corresponding ketal (5), and deprotection of the p-phenylbenzoyl group to give the corresponding alcohol (6) followed by protection of the newly derived hydroxy group with dihydropyrane to give the corresponding tetrahydropyranyl ether (7). According to the

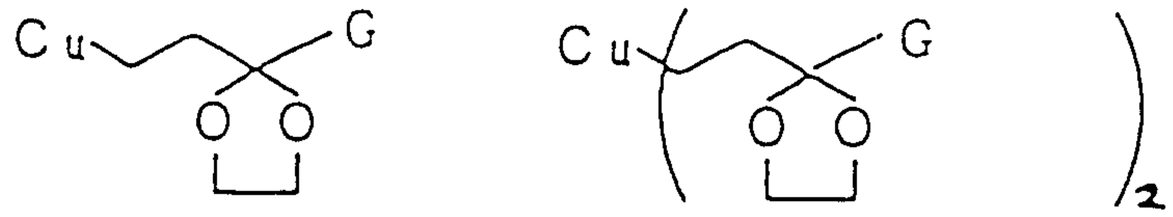
above process, a precursor of PGEs wherein the ω-chain is a 13,14-dihydro-15-keto-alkyl group is prepared.

Using the above tetrahydropyranyl ether (7), 6-keto-PGE_1s (15) of which a group constituted with carbon atoms at positions 5, 6 and 7 is $-\overset{5}{C}H_2-\overset{6}{C}(O)-\overset{7}{C}H_2-$, may be prepared in the following steps; reduction of the tetrahydropyranyl ether (7) with, for example, diisobutyl aluminum hydride to give the corresponding lactol (8), reaction of the lactol (8), with the ylide generated from (4-carboxybutyl)triphenyl phosphonium bromide followed by esterification (10), cyclization between the 5,6-double bond and the hydroxyl group at position 9 with NBS or iodine to give the halogenated compound (11), dehydrohalogenation of the compound (11) with, for example, DBU to give the 6-keto compound (13) followed by Jones oxidation and removal of the protecting groups.

Furthermore, PGE_2s (19) of which a group constituted with carbon atoms at positions 5, 6 and 7 is $-\overset{7}{C}H_2-\overset{6}{C}H=\overset{5}{C}H-$ may be prepared in the following steps; as shown in the Synthetic Chart II, reduction of the above tetrahydropyranyl ether (7) to give the lactol (8), reaction of the resultant lactol (8) with the ylide derived from (4-carboxybutyl)triphenyl phosphonium bromide to give the carboxylic acid (16) followed by esterification to give ester (17), Jones oxidation of the esters (17) to give the compound (18), and removal of the protecting groups.

Using the above tetrahydropyranyl ether (7) as the starting material, a compound having $-\overset{7}{C}H_2-\overset{6}{C}H_2-\overset{5}{C}H_2-$ may be prepared by using the same process as that for preparing PGE_2 having $-CH_2-CH=CH-$ and subjecting the resultant compound (18) to catalytic reduction to reduce the double bond between the positions 5 and 6 followed by removal of the protective groups.

Synthesis of 5,6-dehydro-PGE_2s having $-\overset{7}{C}H_2-\overset{6}{C}\equiv\overset{5}{C}-$ may be carried out by capturing a copper enolate formed by 1,4-addition of a monoalkylcopper complex or a dialkylcopper complex of the following formulae:



wherein G is alkyl,

to 4R-t-butyldimethylsilyloxy-2-cyclopenten-1-one with 6-alkoxycarbonyl-1-iodo-2-hexyne or the derivatives.

The 11-ß type PGEs can be prepared according to the Synthetic Chart III.

PGE derivatives having a methyl group at position 11 in place of hydroxy can be prepared by reacting a dimethyl copper complex with a PGA-type compound obtained by subjecting 9-hydroxy-11-tosylate to the Jones oxidation.

Alternatively, they can be prepared by protecting the carbonyl of saturated ketone (4) produced by reducing unsaturated ketone (3), eliminating p-phenylbenzoyl and tosylating the produced alcohol, treating with DBU to form a lactol, introducing the alpha-chain by Wittig reaction, oxidizing the alcohol at position 9 to give a PGA-type compound, and reacting the product with dimethyl copper complex in order to introduce a methyl group into position 11 to give an 11-methyl-PGE-type compound, which on reduction with e.g. sodium borohydride gives an 11-methyl-PGF-type compound. An 11-hydroxymethyl-PGE-type compound, is obtained by a benzophenone-sensitized photoaddition of methanol of PGA-type compound, which is reduced with, e.g. sodium borohydride, to give an 11-hydroxymethyl-PGF-type compound. The 16-mono- or 16,16-di-halo type PGEs can be prepared according to the synthetic chart IV. The synthetic route for the compounds used in the present invention is not limited to that described above, and may vary using different protecting, reducing and/or oxidizing methods.

Other corresponding PG compounds can be produced analogously.

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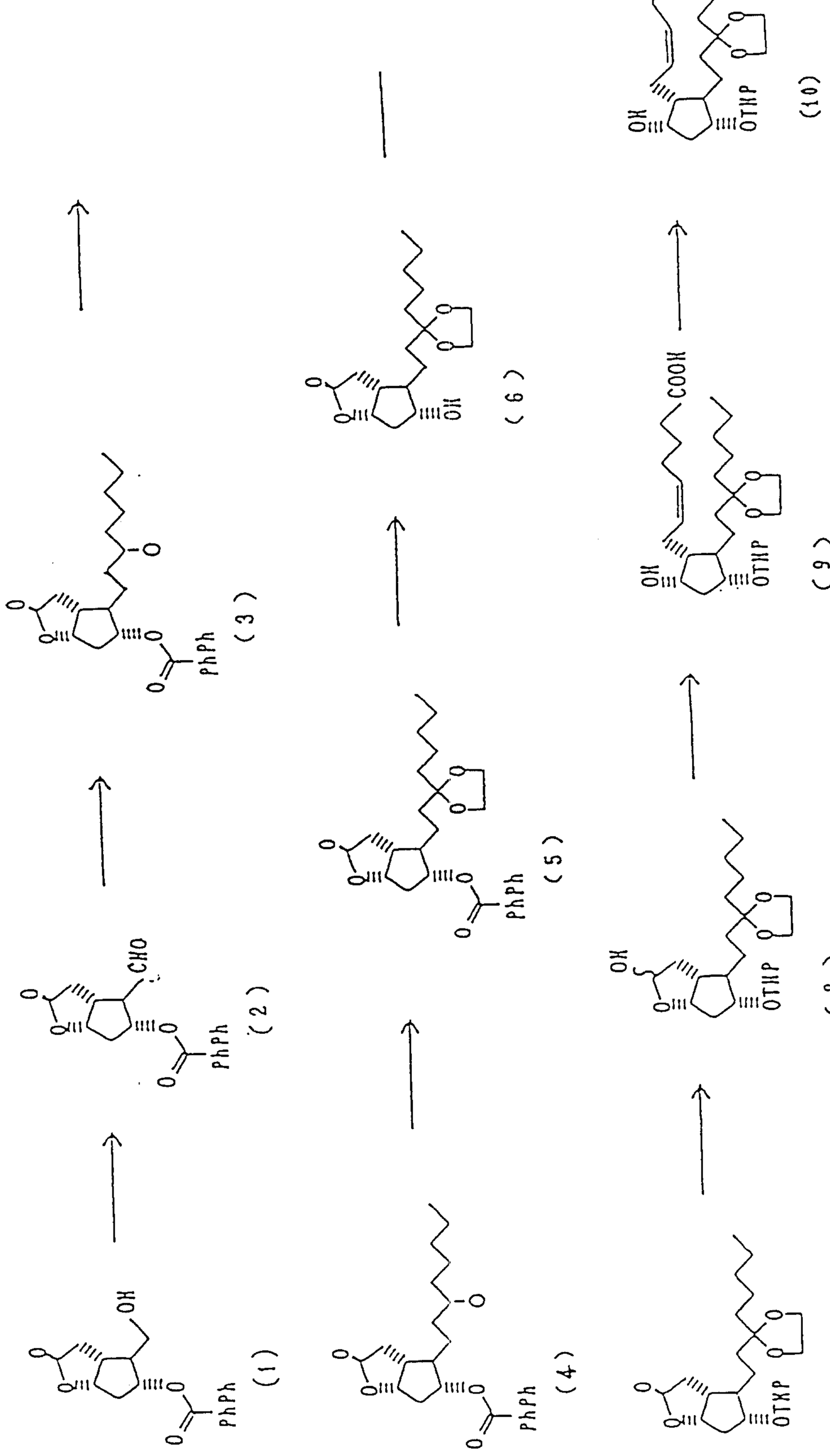
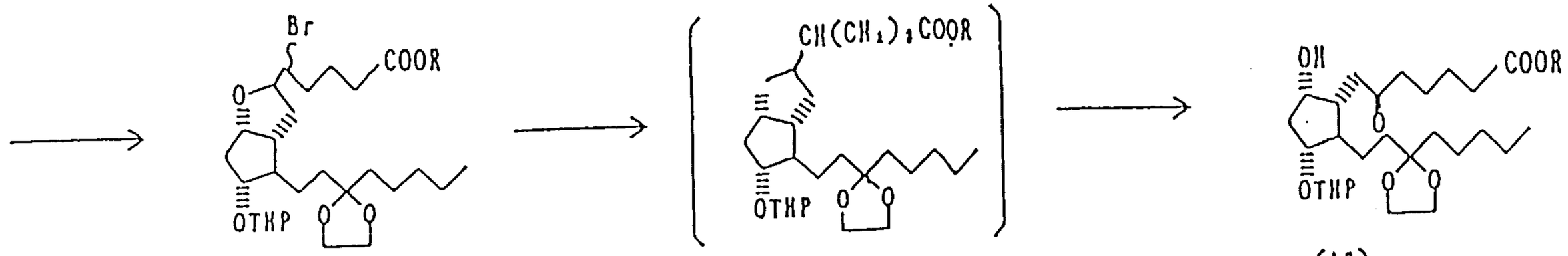
Synthetic Chart I



Synthetic Chart I (continued)



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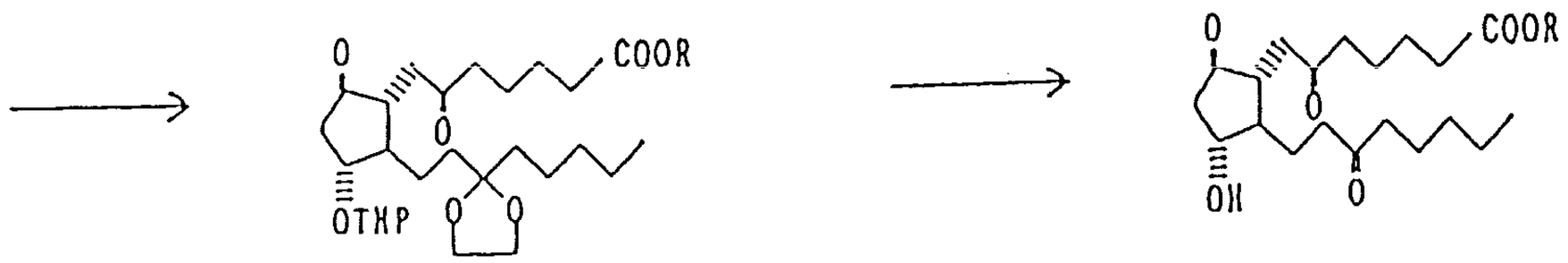

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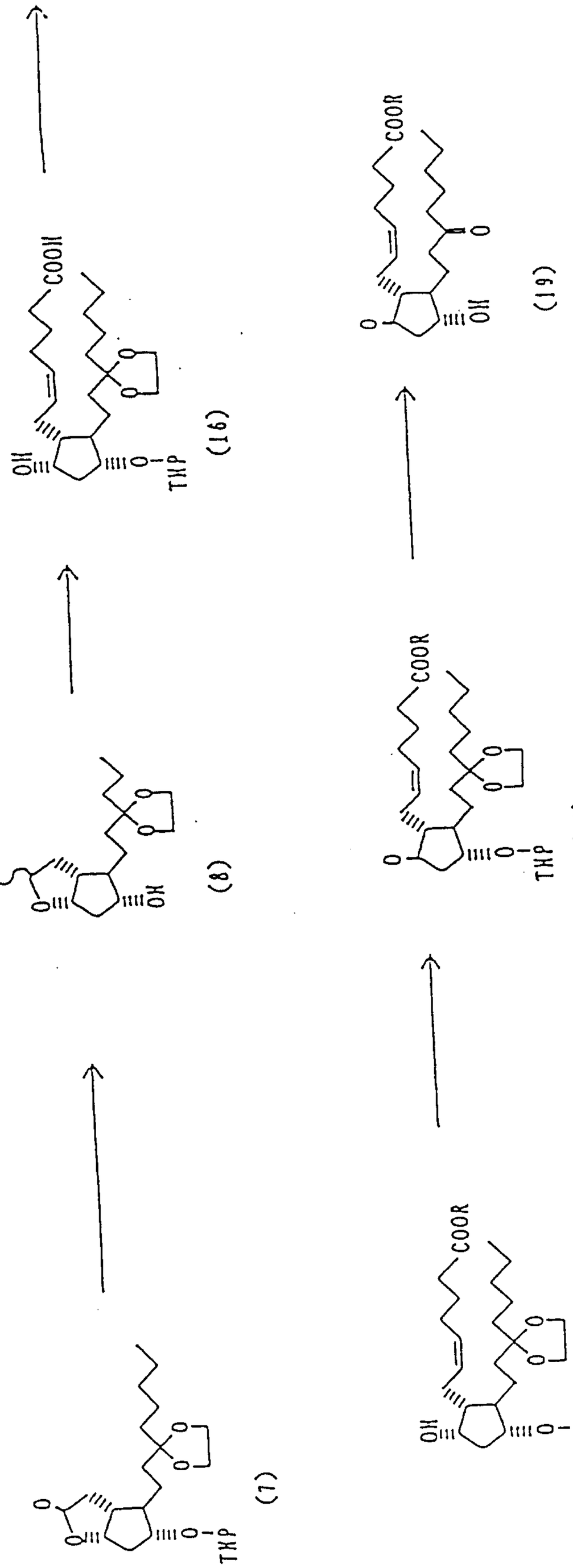
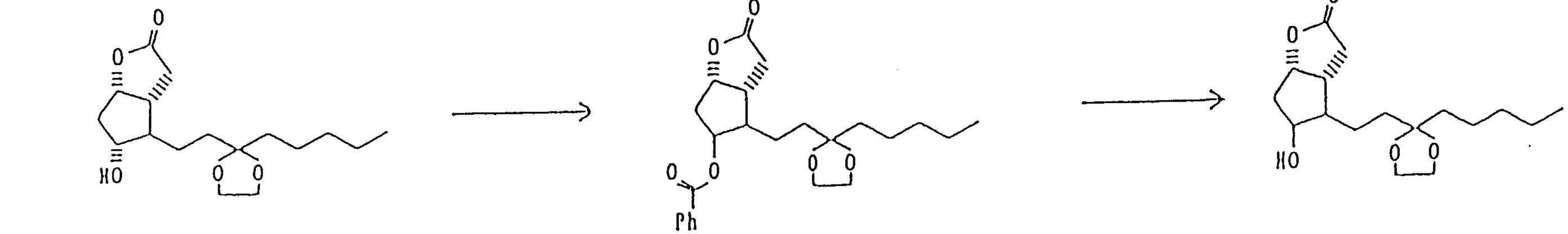
Synthetic Chart II



Synthetic Chart III



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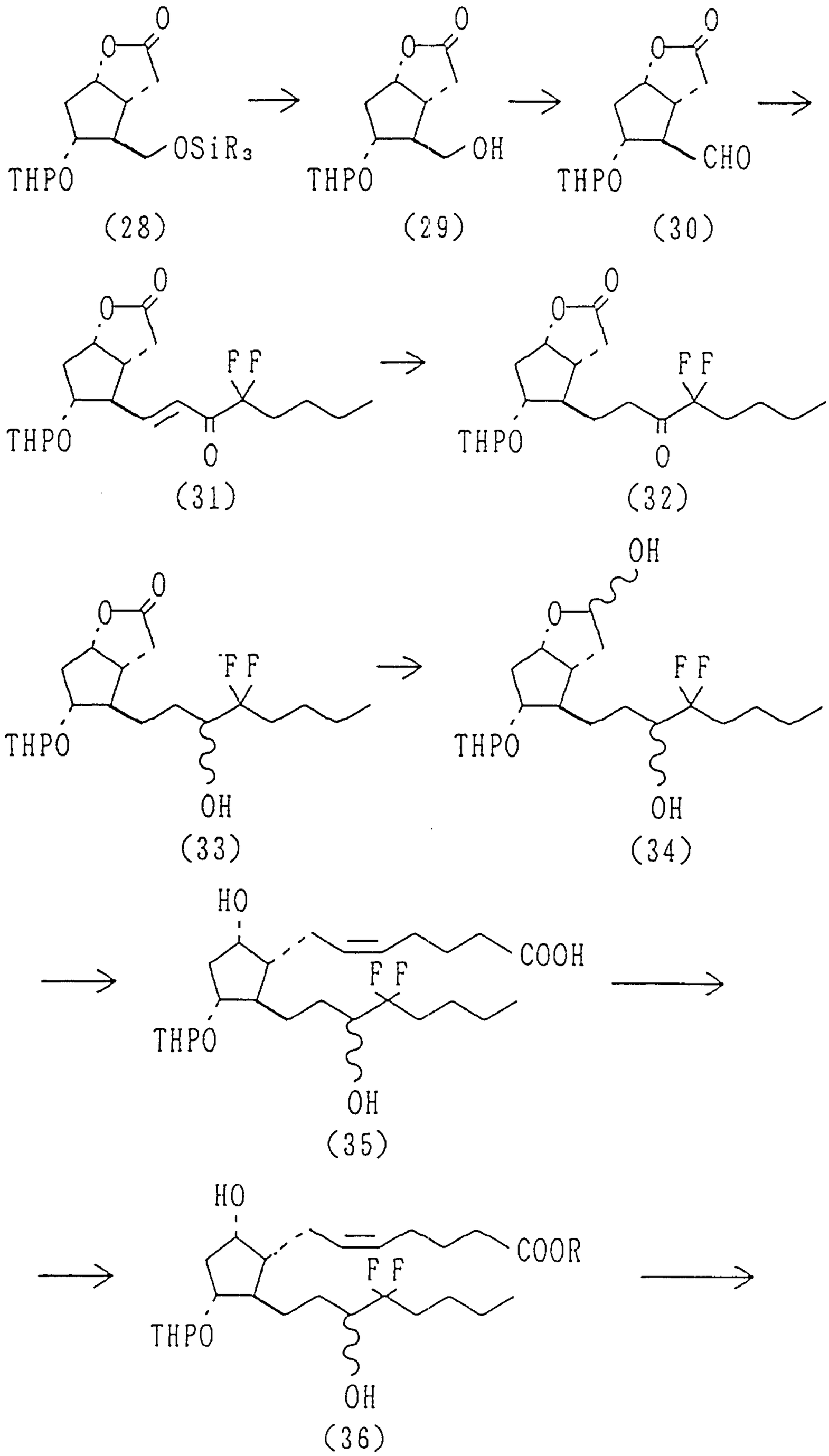
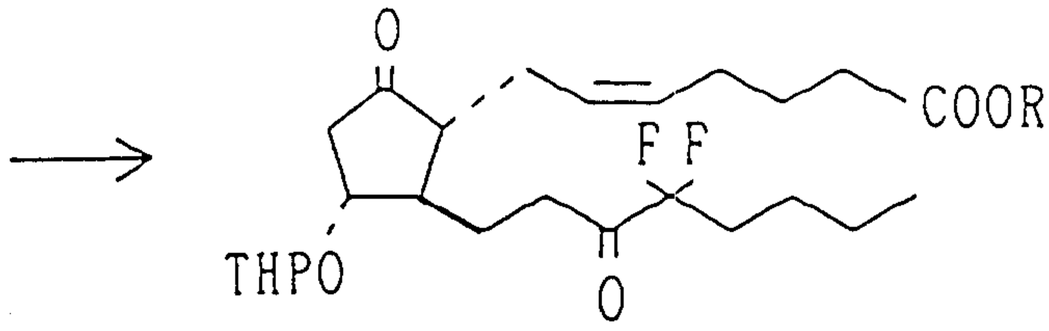
Synthetic Chart Ⅳ





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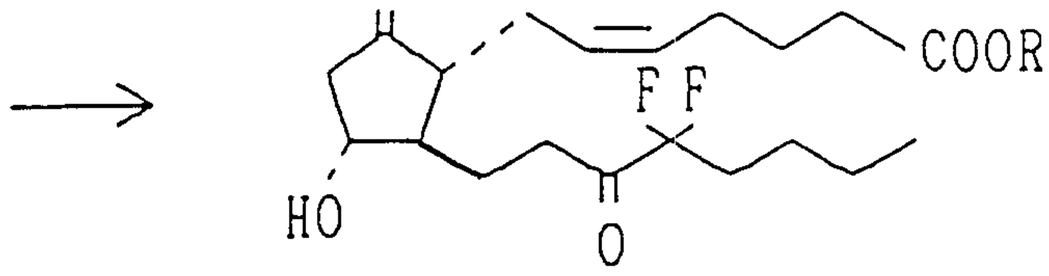

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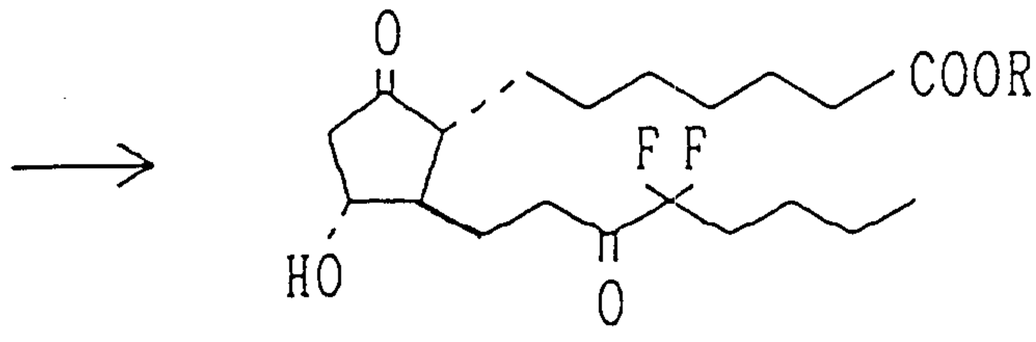

(39)

Since the compounds used in the present invention have an activity useful in the prevention or therapy of gas exchange function insufficiency in lungs and improving defensive ability of cells thereto, or preventing death of cells therefrom, these can be used for preparing a medicament for treating pulmonary dysfunction. Such activities can be measured by standard methods, e.g. potassium cyanide induced cytotoxic hypoxia model or dyspnea model.

The compounds used in the present invention may be used as a medicine for animals and human beings and are usually applied systemically or locally by such methods as oral administration, intravenous injection (including instillation), subcutaneous injection, suppository and the like. While the dosage will vary depending on the particular animal or human patient, age, body weight, symptoms to be treated, desired therapeutic effect, administration route, term of treatment and the like, satisfactory effects will be obtained with a dosage of 0.001 - 500 mg/kg administered in 2 to 4 divided doses a day or as a sustained form.

As a solid composition of this invention for oral administration, tablets, troches, buccals, capsules, pills, powders, granules and the like are included. The solid composition containing one or more active substances is mixed with at least an inactive diluent, e.g. lactose, mannitol, glucose, hydroxypropyl cellulose, fine crystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate. The composition may contain additives other than the inactive diluent, for example, lubricants e.g., magnesium stearate, a disintegrator e.g. cellulose calcium gluconates, stabilizers e.g. α-, ß- or γ-cyclodextrins, etherated cyclodextrins (e.g. dimethyl-α-, dimethyl-ß-, trimethyl-ß-, or hydroxypropyl-ß-cyclodextrins), branched cyclodextrins (e.g. glucosyl- or maltosyl-cyclodextrins), formyl cyclodextrins, sulfur-containing cyclodextrins, misoprotols or phospholipids. Such cyclodextrins may increase the stability of the compounds by forming inclusion compounds. The stability may often be increased by forming lyposomes with

phospholipids. Tablets and pills may be coated with an enteric or gastroenteric film e.g. white sugar, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalates and the like, if necessary, and furthermore they may be covered with two or more layers. Additionally, the composition may be in the form of capsules made of a substance easily adsorbed e.g. gelatin. The composition may be in the form of buccals, when an immediate effect is desired. For this purpose, a base e.g. glycerine or lactose, may be used.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs and the like and contain a generally used inactive diluent e.g. purified water or ethyl alcohol. The composition may contain additives e.g. wetting agents, suspending agents, sweeteners, flavours, perfumes and preservatives.

The composition of the present invention may be in the form of sprays which may contain one or more active ingredients and which can be prepared according to well known methods.

An injection of this invention for non-oral administration includes sterile aqueous or nonaqueous solutions, suspensions, and emulsions. Diluents for the aqueous solution or suspension include, for example, distilled water for injection, physiological saline and Ringer's solution. Diluents for the nonaqueous solution and suspension include, for example, propylene glycol, polyethylene glycol, vegetable oils e.g. olive oil, alcohols, e.g. ethanol and polysorbates. The composition may contain other additives, e.g. preservatives, wetting agents, emulsifying agents, dispersing agents and the like. These are sterilized by filtration through, e.g. a bacteria-retaining filter, compounding with a sterilizer, gas sterilization or radiation sterilization. These can be prepared by producing a sterilized water or a sterilized solvent for injection before use.

Another formulation according to the present invention is a rectal or vaginal suppository. This can be prepared by mixing at least one active compound according to the invention with a suppository base e.g. cacao butter and optionally containing a nonionic surfactant to improve absorption.

The above pharmaceutical preparation can be used to treat toxic headache, increased irritability, confusion, vertigo, paropsia, nausea, syncope, coma, spasm, hypopnea, hyperidrosis, pyrexia, leucocytosis, bleeding tendency, albuminurea, tremor, drowsiness, hypertension, etc.

The present invention also provides a method for treating disorders of oxygen uptake into the bloodstream through the lungs.

A more complete understanding of the present invention can be obtained by reference to the following Preparation Examples, Formulation Examples and Test Examples which are provided herein for the purpose of illustration only and are not intended to limit the scope of the invention.

Preparation Example 1

Preparation of 16,16-difluoro-13,14-dihydro-15-keto-PGE_1 methyl ester (39)

1-1) Preparation of (1S,5R,6R,7R)-6-hydroxymethyl-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octan-3-one (29)

A solution (1.0 M, 300 ml) of tetrabutylammonium fluoride in tetrahydrofuran was added to a solution of commercial Corey lactone (THP-form, 37.9 g) in tetrahydrofuran, and the resulting mixture was stirred at room temperature for 3 hours.

The reaction mixture was then concentrated under reduced pressure and the residue was subjected to column chromatography to give the title compound (29).

Yield: 21.70 g (82.8%)

1-2) Preparation of (1S,5R,6R,7R)-6-{(E)-4,4-difluoro-5-oxo-2-octenyl}-7-tetrahydropyranyloxy-2-oxabicyclo-[3.3.0]octan-3-one (31)

A solution (2.0 M, 45.5 ml) of oxalyl chloride in methylene chloride was diluted with methylene chloride under an argon atmosphere at -78°C. To this solution was added

dropwise dimethylsulfoxide (12.9 ml) and the resulting mixture was stirred for 10 minutes. A solution of (1S,5R,6R,7R)-6-hydroxymethyl-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octan-3-one (29) (11.65 g) in methylene chloride was added dropwise and the mixture was stirred for 30 minutes. Then, triethylamine (56 ml) was added dropwise and stirring was continued for a further hour. The reaction mixture was treated in a conventional manner to give the aldehyde (30) as a crude product.

Dimethyl 3,3-difluoro-2-oxoheptylphosphonate (11.9 g) was added under an argon atmosphere to a solution of thallium ethoxide (3.26 ml) in methylene chloride and the resulting mixture was stirred for 1 hour. After cooling the solution to 0°C, a solution of the aldehyde (30) obtained above in methylene chloride was added dropwise to said solution and the mixture was stirred at room temperature for 14 hours. The reaction mixture was treated with acetic acid, Celite* and a saturated aqueous potassium iodide solution and filtered. The filtrate was treated in a conventional manner and the crude product was subjected to column chromatography to give the title compound (31).

Yield: 7.787 g (44.3%).

1-3) Preparation of (1S,5R,6R,7R)-6-(4,4-difluoro-5-oxo-2-octyl)-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octan-3-one (32)

To a solution of (1S,5R,6R,7R)-6-{(E)-4,4-difluoro-5-oxo-2-octenyl}-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octan-3-one (31) (5.57 g) in ethyl acetate was added 5% Pd/C (catalytic amount) and the resulting mixture was shaken under a hydrogen atmosphere at room temperature for 7 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the title compound (32) as a crude product.

Yield: 5.48 g (97.8%)

* Trademark

1-4) Preparation of (1S,5R,6R,7R)-6-{4,4-difluoro-5(RS)-hydroxyoctyl}-7-tetrahydropyranyloxy-2-oxabicyclo-[3.3.0]octan-3-one (33)

Sodium borohydride (0.800 g) at 0°C was added to a solution of (1S,5R,6R,7R)-6-(4,4-difluoro-5-oxoctyl)-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octan-3-one (32) (5.48 g) in methanol, and the resulting mixture was stirred for 10 minutes. The reaction mixture was treated in a conventional manner and the resulting crude product was subjected to column chromatography to give the title compound (33).

Yield: 5.46 g (99.5%).

1-5) Preparation of 16,16-difluoro-13,14-dihydro-11-0-tetrahydropyranyl-$PGF_{2\alpha}$ methyl ester (36)

A solution of (1S,5R,6R,7R)-6-{4,4-dihydro-5(RS)hydroxyoctyl}-7-tetrahydropyranyloxy-2-oxabicyclo-[3.3.0]octan-3-one (33) (2.579 g) in toluene was cooled to -78°C under an argon atmosphere. To this solution was added dropwise a solution (1.5 M, 9.6 ml) of diisobutylaluminum hydride in toluene and stirred for 30 minutes. The reaction mixture was treated with methanol and a saturated aqueous Rochelle salt solution. Then the solution was treated in a conventional manner to give the lactol (34) as a crude product.

A solution (1.0 M, 52.84 ml) of potassium tert-butoxide in tetrahydrofuran was added dropwise under an argon atmosphere to a suspension of 4-carboxybutyl triphenyl phosphine bromide (11.72 g) in tetrahydrofuran and the resulting mixture was stirred for 20 minutes. The solution was cooled to 0°C and combined with a solution of lactol (34) in tetrahydrofuran. The resulting mixture was stirred at room temperature for 15 hours and then treated in a conventional manner to give the carboxylic acid (35) as a crude product.

To a solution of the carboxylic acid (35) in acetonitrile was added under an argon atmosphere 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (4.0 ml) and methyl iodide (1.7 ml) and the resulting solution was stirred at 60°C for 30 hours. The

solution was treated in a conventional manner and the product was subjected to column chromatography to give the title compound (36).

Yield: 2.737 g (84.5%).

1-6) Preparation of 16,16-difluoro-13,14-dihydro-15-keto-11-O-tetrahydropyranyl-PGE_2 methyl ester (37)

A solution of 16,16-difluoro-13,14-dihydro-11-O-tetrahydropyranyl-$PGF_{2\alpha}$ methyl ester (36) (2.646 g) in methylene chloride under an argon atmosphere at -20°C was added to a solution of Collins reagent, prepared from chromic anhydride (16.18 g) and pyridine (26.2 ml) in a conventional process, in methylene chloride. The resulting mixture was stirred at the same temperature for 2 hours and at -5°C for 9 hours. The solution was treated with ether and sodium hydrogen sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography to give the title compound (37).

Yield: 1.890 g (64.4 %).

1-7) Preparation of 16,16-difluoro-13,14-dihydro-15-keto-PGE_2 methyl ester (38).

Into a mixed solvent of acetic acid : water : tetrahydrofuran (3:1:1) was dissolved 16,16-difluoro-13,14-dihydro-15-keto-11-O-tetrahydroxypyranyl-PGE_2 methyl ester (37) (2.809 g) and the resulting solution was stirred at 60°C for 5 hours. The reaction mixture was concentrated under reduced pressure and the residue was subjected to chromatography to give the title compound (38).

Yield: 1.755 g (75.5%).

1-8) Preparation of 16,16-difluoro-13,14-dihydro-15-keto-PGE_1 methyl ester (39)

To a solution of 16,16-difluoro-13,14-dihydro-15-keto-PGE_2 methyl ester (38) (1.755 g) in ethyl acetate was added Pd/C (catalytic amount) and the mixture was shaken under a hydrogen atmosphere at room temperature for 6 hours. The reaction mixture was filtered, the filtrate concentrated, and the residue was subjected to column chromatography to give the title compound (39).

Yield: 1.655 g (93.8%).

^{1}H NMR($CDCl_3$) δ0.87(3H,t,J=7 Hz), 1.15-2.05(23H,m), 2.11-2.30(3H,m), 2.50(1H,dd,J=7.5 and 17 Hz), 3.10-3.20(1H,br), 3.71(3H,s), 4.05-4.20(1H,m)

MS(DI-EI) m/z 404(M^+), 355($M^+-H_2O-CH_3O$), 297($M^+-C_5H_9F_2$)

Preparation Example 2

Preparation of 16,16-difluoro-13,14-dihydro-15-keto-PGE_1 (39').

2-1) Preparation of (15RS)-16,16-difluoro-13,14-dihydro-11-0-tetrahydropyranyl-$PGF_{2\alpha}$ benzyl ester (36)

DBU (2.1 ml) and benzyl bromide (2.2 ml) were added to a solution of 16,16-difluoro-13,14-dihydro-11-0-tetrahydropyranyl-$PGF_{2\alpha}$ (35) (2.33 g) in dichloromethane (300 ml), and the resulting mixture was stirred at room temperature for 1.5 hours. The reaction mixture was treated in a conventional manner and the crude product was purified by silica gel column chromatography to give the title compound (36).

Yield: 2.522 g (96.1%)

2-2) Preparation of 16,16-difluoro-13,14-dihydro-15-keto-11-0-tetrahydropyranyl-PGE_2 benzyl ester (37)

Collins reagent was prepared using chromic anhydride (13.5 g) and pyridine (21.8 ml) in dichloromethane (300 ml), and to this were added Celite (40 g) and (15RS)-16,16-difluoro-13,14-dihydro-11-0-tetrahydropyranyl-$PGF_{2\alpha}$ benzyl ester (36) (2.550 g). The reaction mixture was treated in a conventional manner and the crude product was purified by silica gel column chromatography to give the title compound (37).

Yield: 1.991 g (78.6%)

2-3) Preparation of 16,16-difluoro-13,14-dihydro-15-keto-PGE_2 benzyl ester (38)

Into a mixed solvent of acetic acid:THF:water (3:1:1, 50 ml) was dissolved 16,16-difluoro-13,14-dihydro-15-keto-11-O-tetrahydropyranyl-PGE_2 benzyl ester (37) (1.550 g) and the solution was kept at 50°C for 4 hours. The reaction mixture was treated in a conventional manner and the crude product was

purified by silica gel column chromatography to give the title compound (38).

Yield: 1.225 g (92.9%)

2-4) Preparation of 16,16-difluoro-13,14-dihydro-15-keto-PGE_1 (39')

To a solution of 16,16-difluoro-13,14-dihydro-15-keto-PGE_1-tetrahydropyranyl-PGF_1 benzyl ester (38) (0.844 g) in ethyl acetate (30 ml) was added 5% Pd/C and the mixture was shaken under a hydrogen atmosphere. The reaction mixture was treated in a conventional manner and the crude product was purified by silica gel column chromatography to give the title compound (43).

Yield: 0.404 g

^1H NMR ($CDCl_3$) δ0.94 (t,3H,J=7.5 Hz), 1.20-2.70(m, 26H), 4.19(m,1H), 4.80(br,2H).

MS(DI-EI) m/z 390(M^+), 372(M^+-H_2O), 354(M^+-2H_2O)

Formulation Example 1

(Powders for injection)

	(Parts by weight)
13,14-dihydro-15-keto-16,16-difluoro-PGE_2	1
mannitol	5
distilled water	0.4

The above ingredients were mixed, stirred, sterilized, filtered and lyophilized to give powders for injection.

Formulation Example 2

(Injectable solution)

	(Parts by weight)
13,14-dihydro-15-keto-16,16-difluoro-PGE_1	0.2
nonionic surfactant	2
distilled water	98

The above ingredients were mixed and sterilized to give an injectable solution.

Formulation Example 3

(Enteric capsules)

13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGE_2 (50 mg) dissolved in methanol (10 ml) was mixed with mannitol (18.5g). The mixture was screened (with a sieve having a pore size of

30 mm in diameter), dried at 30°C for 90 minutes and screened again. The powders thus obtained were mixed with fine-grain silica gel (Aerosil*, 200 g) and No. 3 hard gelatin capsules (100) were filled with the powder to give enteric capsules which contain 0.5 mg of 13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGE_2 per capsule.

Formulation Example 4

(Powders for oral administration)

	(Parts by weight)
13,14-dihydro-15-keto-16,16-difluoro-$PGF_{2\alpha}$ methyl ester	5
light anhydrous silicic acid	5
Abicel*	20
lactose	70

The above ingredients were mixed to give powders for oral administration.

Formulation Example 5

(Soft gelatine capsules)

	(Parts by weight)
13,14-dihydro-15-keto-20-methyl-PGE_2 methyl ester	1
light anhydrous silicic acid	899
Panasate*	20

The above ingredients were mixed and soft gelatine capsules were filled with the mixture.

Formulation Example 6

(Enteric capsules)

16,desbutyl-13,14-dihydro-15-keto-16-m-trifluoromethylphenoxy-$PGF_{2\alpha}$ methyl ester (50 mg) dissolved in methanol (10 ml) was mixed with mannitol (18.5 g). The mixture was screened (with a sieve having a pore size of 30 mm in diameter), dried at 30°C for 90 minutes and screened again. The powders thus obtained were mixed with fine-grain silica gel (Aerosil*, 200 g) and No. 3 hard gelatin capsules (100) were filled with the powder to give enteric capsules which

*Trade mark

contain 0.5 mg of 13,14-dihydro-15-keto-16-desbutyl-16-m-trifluoromethylphenoxy-$PGF_{2\alpha}$ methyl ester per capsule.

Formulation Example 7

(Powders for injection)

	(Parts by weight)
13,14-dihydro-15-keto-16,16-difluoro-PGE_1	1
mannitol	5
distilled water	0.4

The above ingredients were mixed, stirred, sterilized, filtered and lyophilized to give powders for injection.

Formulation Example 8

(Injectable solution)

	(Parts by weight)
13,14-dihydro-6,15-diketo-5R,S-fluoro-PGE_1	0.2
nonionic surfactant	2
distilled water	98

The above ingredients were mixed and sterilized to give an injectable solution.

Formulation Example 9

(Powders for oral administration)

	(Parts by weight)
13,14-dihydro-15-keto-16,16-difluoro-19-desmethyl-PGE_2 methyl ester	5
light anhydrous silicic acid	5
Abicel *	20
lactose	70

The above ingredients were mixed to give powders for oral administration.

Formulation Example 10

(Soft gelatine capsules)

	(Parts by weight)
13,14-dihydro-15-keto-16-desbutyl-16-m-trifluoromethylphenoxy-PGE_2 methyl ester	1
light anhydrous silicic acid	899
Panasate *	20

*Trade mark

The above ingredients were mixed and soft gelatine capsules were filled with the mixture.

In the above formulation examples, the active ingredient can be replaced by any other compound within the scope of the compounds used in the invention.

Test Example 1

As the test animals, 10-12/group male Slc-ddY mice (5 weeks old, 27-30 g) were used.

For subcutaneous administration, the test compound was dissolved in Ringer's solution in such an amount that the obtained solution can be administered at 10 ml/kg body weight.

The mice were divided according to their weight into groups with even mean weight, each group consisting of 12 animals.

The mice received the test compound in solution and after 5 minutes, 4 mg/kg KCN intravenously and survival time was measured based on heartbeat as an index.

The results are shown in Table 1.

Table 1

	Dose (mg/kg, s.c.)	Number of Animals	Survival Time (min.-sec.) Mean ± S.D.
Control	0	12	9-32±1-48
Compound 1	0.3	10	**16-42±3-36
	0.1	10	**13-09±2-10
	0.03	10	8-45±1-16

t-test: **p<0.01 v.s. Control

Test Compound: 13,14-dihydro-15-keto-16,16-difluoro-PGE_2

Test Example 2

As the test animals, 5/group male Crj:Wistar rats (7 weeks old, 200-250 g) were used.

For subcutaneous administration, the test compound was dissolved in physiological saline in such an amount that the resulting solution can be administered at 5 ml/kg body weight.

The test compound was subcutaneously administered at the dorsal skin.

After 30 minutes, ammonium sulfate [$(NH_4)_2SO_4$] was intraperitoneally administered at a dose of 600 mg/kg and survival rate after 30 minutes was measured. The results are shown in Table 2.

The control animals received the physiological saline. In this case, tonic convulsion derived from dyspnea was observed after about 10 minutes and all animals died within 30 minutes of administration.

Table 2

	Dose (μg/kg)	Survival Rate (%)
Control	0	0
Compound 1	1	20
	10	80

T-test: **p<0.01 v.s. Control

Compound 1: The same as in Test Example 1

Test Example 3

The procedure of Test Example 2 was repeated using other Test Compounds. The results are shown in Tables 3 and 4.

Table 3

	Dose (μg/kg)	Survival Rate (%)
Control	0	0
Compound 2	100	40

Compound 2: 13,14-dihydro-15-keto-16,16-difluoro-PGE_2 methyl ester

Table 4

	Dose (μg/kg)	Survival Rate (%)
Control	0	30
Compound 2	100	60

Compound 3: 13,14-dihydro-15-keto-16,16-difluoro-PGE_1

Test Example 4

As the test animals, 5/group male Crj:Wistar rats (7 weeks old, 200-250 g) were used.

For subcutaneous administration, test compounds were dissolved in physiological saline in such an amount that the resulting solution can be administered at 5 ml/kg body weight.

The test compound was subcutaneously administered at the dorsal skin.

After 30 minutes, ammonium sulfate [$(NH_4)_2SO_4$] was intraperitoneally administered at a dose of 600 mg/kg. After 30 minutes, the surviving animals were sacrificed with chloroform and immediately the lungs of the animal were removed and weighed. The control animals received the physiological saline and the lungs were weighed similarly.

Rate of inhibiting increase in lung weight was calculated comparing the weights of lungs from the animals treated with the test compounds with those from the control animals. The results are shown in Table 5-13.

Table 5

	Dose (μg/kg)	Rate of Inhibiting Increase in Lung Weight (%)
Compound 1	10	48.2
	100	66.1

Table 6

	Dose (μg/kg)	Rate of Inhibiting Increase in Lung Weight (%)
Compound 2	100	102.8

Table 7

	Dose (μg/kg)	Rate of Inhibiting Increase in Lung Weight (%)
Compound 3	10	49.0

Table 8

	Dose (μg/kg)	Rate of Inhibiting Increase in Lung Weight (%)
Compound 4	100	75.2

Table 9

	Dose (μg/kg)	Rate of Inhibiting Increase in Lung Weight (%)
Compound 5	100	79.8

Table 10

	Dose (μg/kg)	Rate of Inhibiting Increase in Lung Weight (%)
Compound 6	100	46.5

Table 11

	Dose (μg/kg)	Rate of Inhibiting Increase in Lung Weight (%)
Compound 7	100	46.5

Table 12

	Dose (μg/kg)	Rate of Inhibiting Increase in Lung Weight (%)
Compound 8	100	45.7

Table 13

	Dose (μg/kg)	Rate of Inhibiting Increase in Lung Weight (%)
Compound 9	100	47.3

Test Compound:

1: The same as above.

2: The same as above.

3: The same as above.

4: 13,14-dihydro-15-keto-16,16-difluoro-PGE_1 methyl ester

5: 13,14-dihydro-15-keto-16,16-difluoro-19-desmethyl-PGE_2

6: 13,14-dihydro-15-keto-16,16-difluoro-20-methyl-PGE_2

7: 13,14-dihydro-15-keto-16,16-difluoro-11-dehydroxy-11-methyl-PGE_2 methyl ester

8: 13,14-dihydro-6,15-diketo-5,5-difluoro-PGE_1 methyl ester

9: 13,14-dihydro-15-keto-16,16-difluoro-$PGF_{2\alpha}$ methyl ester

In the following data, NMR spectra were measured in $CDCl_3$ using HITACHI R-90H** and mass spectra were measured by EI method at an ionization potential of 70eV using HITACHI M-80B.**

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*13,14-dihydro-15-keto-16,16-difluoro-PGE_2

^1H NMR ($CDCl_3$) δ0.93(t,3H, J=7.5 Hz), 1.20-2.70(m,24H), 4.20 (m, 1H), 5.40(m,2H)

MS(DI-EI) m/z 388(M^+), 370(M^+-H_2O),352(M^+-2H_2O)

*13,14-dihydro-15-keto-16,16-difluoro-19-desmethyl-PGE_2

^1H NMR ($CDCl_3$) δ0.98(t,3H,J=7.5 Hz), 1.40-2.70(m,26H), 4.20 (m,1H), 5.40(m,2H)

MS(DI-EI) m/z 374(M^+), 356(M^+H_2O), 338(M^+-2H_2O),

*13,14-dihydro-15-keto-16,16-difluoro-20-methyl-PGE_2

^1H NMR ($CDCl_3$) δ0.90(t,3H,J=7.5 Hz), 1.20-2.70(m,24H), 4.20 (m,1H), 5.41(m,2H)

MS(DI-EI) m/z 402(M^+), 384(M^+-H_2O), 368(M^+-2H_2O)

*13,14-dihydro-15-keto-16,16-difluoro-11-dehydroxy-11-methyl-PGE_2 methyl ester

^1H NMR ($CDCl_3$) δ0.93(t,3H,J=7.5 Hz), 1.14(d,3H,J=6 Hz), 1.25-2.80(m,22H), 3.68(s,3H), 5.38(m,2H)

MS(DI-EI) m/z 400(M^+), 369(M^+-CH_3O)

*13,14-dihydro-6,15-diketo-5,5-difluoro-PGE_1 methyl ester

^1H NMR ($CDCl_3$) δ0.88(t,3H,J=6.6 Hz), 1.10-1.40(m,4H), 1.45-2.20(m,10H), 2.20-3.15(m,11H), 3.67(s, 3H), 4.00-4.18(m,1H)

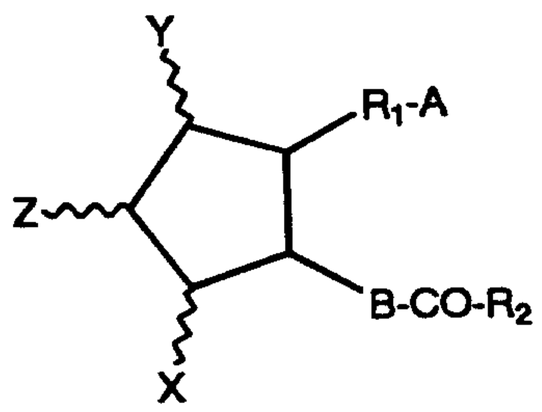
MS(DI-EI) m/z 418(M^+), 400(M^+H_2O), 360(M^+-HF-H_2O), 99($C_6H_{11}CO^+$)

Claims:

1. A pharmaceutical composition for the treatment of pulmonary dysfunction comprising a 15-ketoprostaglandin compound having a halogen atom at least at one of positions 5 and 16 in association with a pharmaceutically acceptable carrier, diluent, or excipient.

2. A composition according to Claim 1, in which the 15-ketoprostaglandin compound is a 15-ketoprostaglandin A compound, a 15-ketoprostaglandin D compound or a 15-ketoprostaglandin E compound.

3. A composition according to Claim 1, in which the 15-ketoprostaglandin compound is represented by the formula (I):



(I)

wherein X and Y are hydrogen, hydroxy, halo, lower alkyl, hydroxy(lower)alkyl, or oxo, with the proviso that at least one of X and Y is a group other than hydrogen, and the 5-membered ring may have at least one double bond, Z is hydrogen or halo, A is $-CH_2OH$, $-COCH_2OH$, -COOH or its functional derivative, B is $-CH_2-CH_2-$, -CH=CH- or $-C\equiv C-$, R_1 is a bivalent saturated or unsaturated, lower or medium aliphatic hydrocarbon residue which is unsubstituted or substituted with halo, oxo or aryl, R_2 is saturated or unsaturated, lower or medium aliphatic hydrocarbon residue which is unsubstituted or substituted with halo, hydroxy, oxo, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, aryl or aryloxy, and said compound represented by formula (I) having a halogen atom at least at one of positions 5 and 16.

4. A composition according to Claim 1, 2 or 3, in which the pulmonary dysfunction is based on cytotoxic hypoxia or dyspnea.

5. A composition according to any one of Claims 1 to 4, in which said 15-ketoprostaglandin compound is a 16-mono- or di-halo-15-ketoprostaglandin compound.

6. A composition according to any one of Claims 1 to 4, in which said 15-ketoprostaglandin compound is a 13,14-dihydro-16-mono- or di-halo-15-ketoprostaglandin compound.

7. A composition according to any one of Claims 1 to 4, in which said 15-ketoprostaglandin compound is a 13,14-dihydro-16-mono- or di-fluoro-15-ketoprostaglandin compound.

8. A composition according to any one of Claims 1 to 7, in which said 15-ketoprostaglandin compound is a 6,15-diketo-prostaglandin compound.

9. A composition according to any one of Claims 1 to 8 for the treatment of gas exchange function insufficiency.

10. A composition according to any one of claims 1 to 8 for the treatment of pulmonary edema.

11. The use of a 15-ketoprostaglandin compound for the treatment of pulmonary dysfunction.

12. The use of a 15-ketoprostaglandin compound for the manufacture of a medicament for the treatment of pulmonary dysfunction.

13. The use according to Claim 11 or 12 wherein said pulmonary dysfunction is based on cytotoxic hypoxia or dyspnea.

14. The use of a 15-ketoprostaglandin compound for the treatment of gas exchange function insufficiency.

15. The use of a 15-ketoprostaglandin compound for the treatment of pulmonary edema.

16. The use according to Claim 11, 14 or 15 wherein said 15-ketoprostaglandin compound is a 16-mono- or di-halo-15-ketoprostaglandin compound.

17. The use according to Claim 11, 14 or 15 wherein said 15-ketoprostaglandin compound is a 13,14-dihydro-16-mono- or di-halo-15-ketoprostaglandin compound.

18. The use according to Claim 11, 14 or 15 wherein said 15-ketoprostaglandin compound is a 13,14-dihydro-16-mono- or di-fluoro-15-ketoprostaglandin compound.

19. The use according to Claim 11, 14 or 15 wherein said 15-ketoprostaglandin compound is a 6,15-diketoprostaglandin compound.