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(54) Titre : TRAITEMENT D'UNE MALADIE DU PANCREAS A L'AIDE DE COMPOSES DE 15-CETO-PROSTAGLANDINE

(54) Title: TREATMENT OF PANCREATIC DISEASE WITH 15-KETO-PROSTAGLANDIN COMPOUNDS

(57) Abrégé/Abstract:
A pharmaceutical composition for treatment of a pancreatic disease comprising a 15-ketoprostaglandin compound in association with a pharmaceutically acceptable carrier, diluent or excipient.

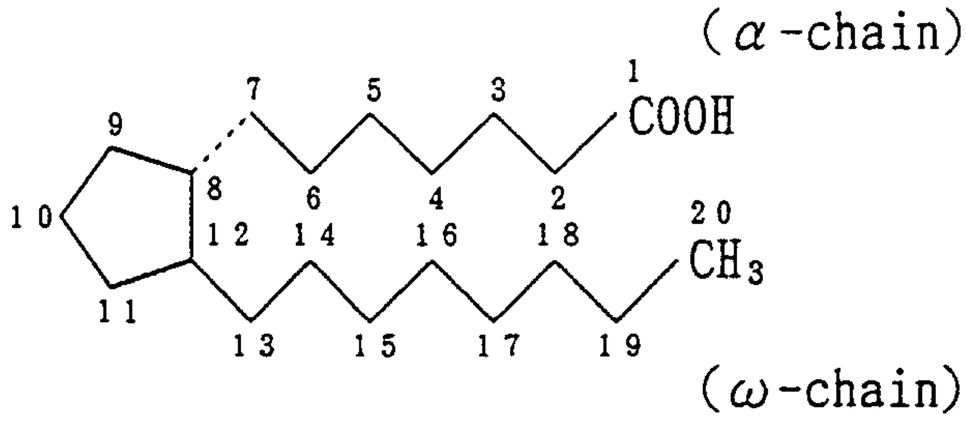
ABSTRACT

A pharmaceutical composition for treatment of a pancreatic disease comprising a 15-ketoprostaglandin compound in association with a pharmaceutically acceptable carrier, diluent or excipient.

TREATMENT OF PANCREATIC DISEASE WITH 15-KETO-PROSTAGLANDIN COMPOUNDS

The present invention relates to a treatment of a pancreatic disease with a 15-ketoprostaglandin compound.

Prostaglandins (hereinafter, prostaglandins are referred to as PGs) are members of a class of organic carboxylic acid 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 cycle 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 configration of hydroxy group at 9 into α(hydroxy group being in the alpha configration) and β(hydroxy group being in the beta configration).

PGE_1, PGE_2 and PGE_3 are known to have vasodilating, hypotensive, gastro-juice reducing, intestine-hyperkinetic, uterine contracting, diuretic, bronchodilating and anti-ulcer activities. Also, $PGF_{1\alpha}$, $PGF_{2\alpha}$ and $PGF_{3\alpha}$ are known to have hypertensive, vasocontracting, intestine-

hyperkinetic, uterine contracting, luteo-regressive and bronchocontracting activities.

USP 4,374,856 discloses the hepatocyte-protecting action of 15-methyl-PGE_2 and 16,16-dimethyl-PGE_2. JP-A-164512/1983 discloses the activity of 15-(3-propylcyclopentyl)-16,17,18,19,20-pentanor-6-oxo-PGE_1 methyl ester in the treatment of acute pancreatitis. JP-A-203911/1983 discloses the cell-protecting action of certain 6-oxo-PGE_1 and PGI_2 having methyl group(s) at one or two of positions 15, 16, 17 and 20 and specific 15-cyclopentyl-PGI_1. 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 catharitics.

In addition, some 15-keto (i.e. having an oxo group at position 15 in place of the hydroxy group) prostaglandins and 13,14-dihydro-15-ketoprostaglandins are known as substances naturally produced by enzymatic actions during metabolism of primary PGs (Acta Physiologica Scandinavica, 66, 509, 1966). It has also been described that 15-ketoprostaglandin $F_{2\alpha}$ has an antipregnant activity. However, it has not been reported that 15-ketoprostaglandin compounds are therapeutically effective in the treatment of a pancreatic disease.

The pancreatic disease includes acute

pancreatitis, acute pancreatic necrosis, chronic pancreatitis, hereditary pancreatitis, pancreatic cancer and pancreatic cysts, some of which are not etiologically clarified. Effective medicament has not been found and there is a continuous need for developing agents for treatment of pancreatic disease.

As a result of extensive studies about the biological properties of 15-ketoprostaglandin compounds, the present inventors have discovered that these compounds have an activity of improving or recovering injured pancreatic function in the experimental acute pancreatitis model and therefore useful as an agent for treating pancreatic disease.

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

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

In a third aspect, the present invention provides a pharmaceutical composition for treatment of a pancreatic disease comprising a 15-ketoprostaglandin compound in

association with a pharmaceutically acceptable carrier, diluent or excipient.

The term "pancreatic disease" includes specifically 1) acute pancreatitis and acute pancreatic necrosis originated in hepatobiliary disease, cardiovascular disease, drinking (of alcohol), allergy, trauma, infection, pregnancy, derivery, hyperparathyroidism, etc., 2) chronic pancreatitis originated in allergy, polyposis, cholelitiasis, acute pancreatitis, etc, 3) hereditary pancreatitis originated in existence of specific gene, 4) pancreatic cancer, 5) pancreatic cysts, etc.

As used herein, the term "treatment" or "treating" refers to any means of control of a disease in a mammal, 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 said ring starting from the carbon atom on which the α-chain is attached, and 13 to 20 on the ω-chain starting from the carbon atom adjacent to the ring. When the number of carbon atoms is decreased in the α-chain, the number is deleted in order starting from position 2 and when the number of carbon atoms is increased in the α-chain, compounds are named as substituted derivatives having respective substituents at position 1 in place of carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the ω-chain, the number is deleted in order starting from position 20 and when the number of carbon atoms is increased in the ω-chain, compounds are named as substituted derivatives having respective substituents at position 20. Stereochemistry of the compounds is the same as that of above formula (A) unless otherwise specified. Thus, 15-keto-PG compounds having 10 carbon atoms in the ω-chain are called

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 hydroxyl 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)-4-fluoro-3-oxo-1-octyl]-5-oxocyclopentyl}-hept-5-enic 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-oxo-cyclopentyl}-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-oxo-cyclopentyl}-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-enonate.

The 15-keto-PG compounds used in the present invention may be any derivatives of PG 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-dihydro-15-keto-PGE, and 13,14-dihydro-15-keto-PGF, wherein PG is as defined above as well as their derivatives.

Examples of substitution products or derivatives include esters at the carboxy group at 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.

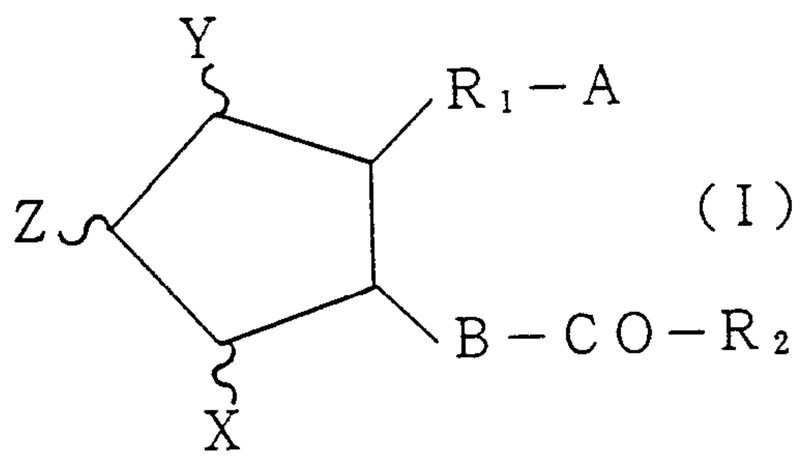
Examples of substituents present in preferred compounds are as follows: Substituents on the carbon atom at position 3, 17 and/or 19 include lower alkyl, for example, C_{1-4} alkyl, especially methyl and ethyl. Substituents on the carbon atom at position 16 include lower alkyl e.g. methyl, ethyl etc., hydroxy and halogen atom e.g. chlorine, fluorine, aryloxy e.g. trifluoromethylphenoxy, etc. Substituents on the carbon atom at position 17 include halogen atom 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 atom e.g. chlorine, fluorine, etc. Substituents on the carbon atom at position 6 include oxo group forming carbonyl. 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.

Said 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. chloro, fluoro 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.

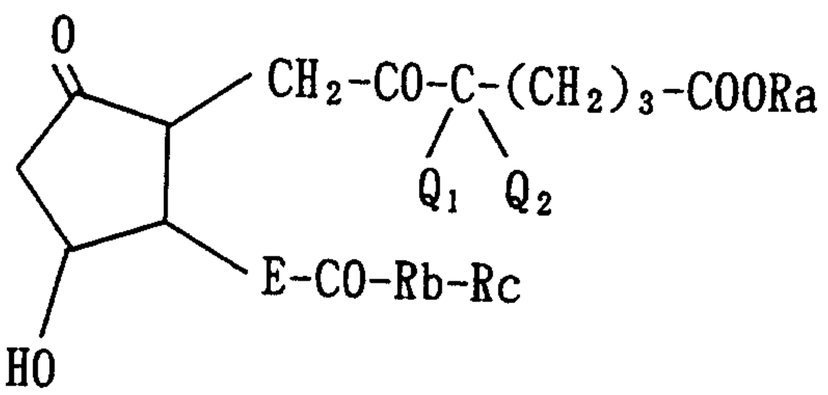
A group of preferred compounds used in the present invention has the formula



(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 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=C-, R_1 is 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.

Among the compounds of the above formula, the compounds represented by the following formula are novel.



(II)

wherein Q_1 is halogen, Q_2 is hydrogen or halogen, E is $-CH_2-CH_2-$ or -CH=CH-, Ra is hydrogen or lower alkyl, Rb

is single bond or lower alkylene, and Rc is lower alkyl which is unsubstituted or substituted with halogen, lower cycloalkyl which is unsubstituted or substituted with lower alkyl, monocyclic aryl which is unsubstituted or substituted with halogen or halo(lower) alkyl, or monocyclic aryloxy which is unsubstituted or substituted with halogen or halo(lower) alkyl

or a pharmaceutically acceptable salts in case of Ra is hydrogen.

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 individually, separately or serially present between carbon atoms of main and/or side chain. According to usual nomenclature, an unsaturation between two serial positions is represented by denoting the lower number of said two positions, and an 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 hydrocarboyl 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 2 to 10 carbon atoms for R_2.

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

The term "lower" 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, preferably 1 to 5 and more preferably 1 to 4 carbon atoms, such as 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.

The term "lower alkylene" refers to the group obtainable by removing a hydrogen atom from the lower alkyl group as defined above and includes e.g. methylene, ethylene, propylene, tetramethylene, 2-methyltetramethylene, pentamethylene, hexamethylene etc.

The term "halo(lower) alkyl" refers to lower alkyl group as defined above which is substituted with at least one and preferably 1 to 3 halogen atoms as defined above and includes e.g. chloromethyl, bromomethyl, fluoromethyl, trifluoromethyl, 1,2-dichloromethyl, 1,2,2-trichloroethyl, chloropropyl, chlorobutyl, chloropentyl, chlorohexyl etc.

The term "hydroxy(lower)alkyl" refers to alkyl as

defined above and substituted with at least one hydroxy group, such as 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 being as defined above.

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

The term "monocyclic aryl" includes phenyl unsubstituted or substituted with lower alkyl substituents, e.g phenyl, tolyl, xylyl, cumenyl etc.

The term "monocyclic aryloxy" refers to a group of the formula: m.Aro-wherein mAr is monocyclic aryl as defined above and includes e.g. phenoxy, tolyloxy, cumenyloxy etc.

The term "functional derivative" of carboxy as A includes salts (preferably pharmaceutically acceptable

salts), esters and amides.

Suitable "pharmaceutically acceptable salt" includes conventional non-toxic salt, and may be a salt with an inorganic base, for example a metal salt such as 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.), tetraalkylammonium salt and the like. These salts can be prepared by the conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the esters are aliphatic esters, for example, C_{1-6} alkyl ester such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, 1-cyclopropylethyl ester, etc., lower alkenyl ester such as vinyl ester, allyl ester, etc., lower alkynyl ester such as ethynyl ester, propynyl ester, etc., hydroxy(lower) alkyl ester such as hydroxyethyl ester, lower alkoxy(lower)-alkyl ester such as methoxymethyl ester,

1-methoxyethyl ester, etc., and aromatic esters, for example, optionally substituted aryl ester such as phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester, benzamidophenyl ester etc., aryl(lower)alkyl ester such as benzyl ester, trityl ester, benzhydryl ester, etc. Examples of the amides are mono- or di- lower alkyl amides such as methylamide, ethylamide, dimethylamide, etc., arylamide such as anilide, toluidide, and lower alkyl- or aryl-sulfonylamide such as methyl-sulfonylamide, ethylsulfonylamide, tolylsulfonylamide etc.

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

Examples of preferred R_1 are $-(CH_2)_2-$, $-(CH_2)_6-$, $-CH_2CO(CH_2)_2-$, $-CH_2CH=CH(CH_2)_3-$, $-CH_2CO(CH_2)_4-$, $-(CH_2)_2CH=CH(CH_2)_2-$, $-(CH_2)_4CH=CH-$, $-CH_2CH=C=CH(CH_2)_2-$ etc.

Examples of preferred R_2 are $-(CH_2)_2CO(CH_2)_4-CH_3$, $-(CH_2)_2CO(CH_2)_4-COOH$, $-(CH_2)_2COC(CH_3)_2(CH_2)_3-CH_3$, $-(CH_2)_2COCH_2O$-phenyl, $-(CH_2)_2COCH_2O$-methachlorophenyl, $-(CH_2)_2COCH_2O$-methatrifluorophenyl, $-(CH_2)_2COCH_2O$-3-thienyl, $-(CH_2)_2CO(CH_2)_2$-phenyl, $-(CH_2)_2COCH_2CH(CH_3)(CH_2)CH_3$, $-(CH_2)_2COC(CH_3)_2CH_2OCH_2CH_3$, $-(CH_2)_2COCH(CH=CH)(CH_2)_3CH_3$, $-(CH_2)_2CO$-cyclopentyl, $-(CH_2)_2CO$-cyclohexyl, $-(CH_2)_2CO(CH_2)_2$-cyclohexyl, $-(CH_2)_2COCH_2CH(CH_3)(CH_2)CH=C-(CH_3)_2$, $-(CH_2)_2COCH(CH_3)CH_2CC\equiv CH$, $-CH=CHCO(CH_2)_4-CH_3$, $-CH=CHCOC(CH_3)_2(CH_2)_3-CH_3$, $-CH=CHCOCH_2O$-phenyl, $-CH=CHCO-$

CH_2O-methachlorophenyl, -CH=CHCOCH$_2$O-methatrifluorophenyl, -CH=CHCOCH$_2$O-3-thienyl, -CH=CHCO$(CH_2)_2$-phenyl, -CH=CHCOCH$_2$CH$(CH_3)(CH_2)_3CH_3$, -CH=CHCOC$(CH_3)_2CH_2OCH_2CH_3$, -CH=CHCOCH(CH=CH)$(CH_2)_3CH_3$, -CH=CHCO-cyclopentyl, -CH=CHCO-cyclohexyl, -CH=CHCOCH$_2$CH$(CH_3)(CH_2)_2$CH=C$(CH_3)_2$, -CH=CHCOCH$(CH_3)CH_2$CC=CH, -CH=CHCOCH$(CH_3)(CH_2)_4CH_3$ etc.

The configuration of the ring and α- and/or ω-chain in the above formulas (I) and (II) may be the same as or different from that in the natural prostaglandins. However, the present invention also include a mixture of a compound having natural configuration and that of unnatural configuration.

Examples of the typical compounds of the present invention are 15-keto-PGs and 13,14-dihydro-15-keto-PGs and their derivatives such as 6-oxo-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.

In the 15-keto-PG compounds used in the present invention, when the bond between 13- and 14-positions is

saturated, a keto-hemiacetal equilibrium may sometimes be formed by the formation of a hemiacetal between the hydroxy group at 11-position and the keto group at 15-position.

When these tautomeric isomers are present, the ratio of the existing isomers will vary depending on the structure of other part of the molecule or the kind of possible substituents and in some cases one of the isomers is predominantly present. The present invention, however, includes both isomers, and while any compound of the invention may be represented by a structure or nomenclature of keto-type, this should be understood as a matter of mere convenience and should not be considered to be intended to exclude the compound in hemiacetal type isomer.

In the present invention, indivisional tautomeric isomers, a mixture thereof, or optical isomers, a mixture thereof, racemic mixture and other isomers such as stereoisomers can be used in the some purpose.

Some of the compounds used in the present invention are novel and may be prepared by the method disclosed in Japanese Patent Publications A-64-52753, A-1-104040, A-1-151519, A-2-131446 etc. Alternatively, these compounds may be prepared by a process analogous to that described herein or to known process.

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,β-unsaturated ketone (3), reduction of the α,β-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 ω-chain is a 13,14-dihydro-15-keto-alkyl group is prepared.

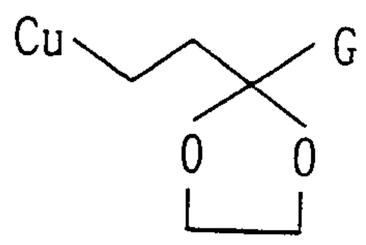
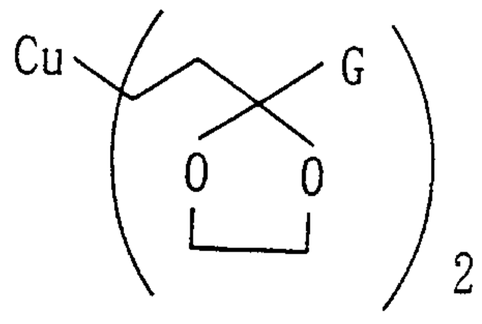
Using the above tetrahydropyranyl ether (7), 6-keto- PGE_1s (15) of which a group constituted with carbon atoms at positions 5, 6 and 7 is $-\overset{7}{CH_2}-\overset{6}{C}(O)-\overset{5}{CH_2}-$, may be prepared in the following steps; reduction of the tetrahydropyranyl ether (7) with, for example, 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 9-position 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 positions 5, 6 and 7 is $-\overset{7}{CH_2}-\overset{6}{CH}=\overset{5}{CH}-$ 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 the tetrahydropyranyl ether (7) as the starting material, the compound having $-\overset{7}{CH_2}-\overset{6}{CH_2}-\overset{5}{CH_2}-$ may be prepared by using the same process as that for preparing PGE_2 having $-CH_2CH=CH-$ and subjecting the resultant compound (18) to catalytic reduction for reducing the double bond between the positions 5 and 6 followed by removal of the protective groups.

Synthesis of 5,6-dehydro-PGE_2s having $-\overset{7}{CH_2}-\overset{6}{C}\equiv\overset{5}{C}-$ 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-β type PGEs can be prepared according to the Synthetic Chart III.

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

Alternatively, they can be prepared by protecting carbonyl of saturated ketone (4) produced by reduced 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 9-position to give PGA-type compound, and reacting the product with dimethyl copper complex in order to introduce a methyl group into position 11 to give 11-methyl-PGE-type compound, which on reduction with e.g. sodium borohydride gives 11-methyl-PGF-type compound. 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 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 the above one and may vary using different protecting, reducing and/or oxidizating methods.

Furthermore, the novel compounds of the formula III may be prepared by the following process, as summarized in Synthetic Charts V to VII, wherein P1, P2, P3, P4, P5, P6, P7, P8, Pa, Pb, Pc and Pd are protective groups, R'a is lower alkyl and Rb and Rc are the same as above.

Referring to Synthetic Chart V, a protected Corey® lactone (40) (commercially available) having a suitable protective group (e.g. 4-phenylbenzoyl) is oxidized (e.g. by Collins oxidation) and the produced aldehyde (41) is reacted with (2-oxoalkyl) phosphonic acid ester having desired R2 and R3 groups to give the compound (42). The oxo group is reduced to form (43), which is converted into (44) by protecting reaction. The acyl group at position 11 is removed to produce (45), to which another protective group (e.g. tetrahydropyramyl) is introduced to give (46). The lactone ring is opened with alkali to form a carboxylic acid which, on esterification, gives (47). A protective group

(e.g. tetrahydropyranyl) is introduced into (47) to give (48). After reducing the ester group by a reducing agent (e.g. by isobutylaluminum hydride) into an aldehyde group, the produced compound is reacted with an α-chain introducing agent (f) in the presence of a basic condensing agent (e.g. litium isopropyl amide) to form (49), of which the terminal group in α-chain is deprotected to produce (50). The obtained alcohol is oxidized (e.g. by Collins oxydation) and then esterified to give (51) and the group at position 5 is decarboxylated to afford (52). A protective group is removed by a method according to the nature of said group to form (53), which is reduced (e.g. catalytically) to form (54), which, on oxidation (e.g. by Collins oxidation) of position 15 gives (55). Deprotection of (55) produces (56), which, after protecting position 11 alone, is oxydized (e.g. by Collins oxydation) to give (57). This is deprotected to afford the desired (58). In the above process, when the reduction of (53) to (54) is omitted, an unsaturated compound is obtained. A compound wherein Ra is hydrogen can be obtained by hydrolyzing the compound (58).

The α-chain introducing agent (f) is prepared by a process shown in Synthetic Chart V. Thus, E-caprolactone (a) is ring-opened by an alcohol which can form the carboxy protective group Pa to give (b). The hydroxy group is protected to give (c), which is decarboxylated to (d),

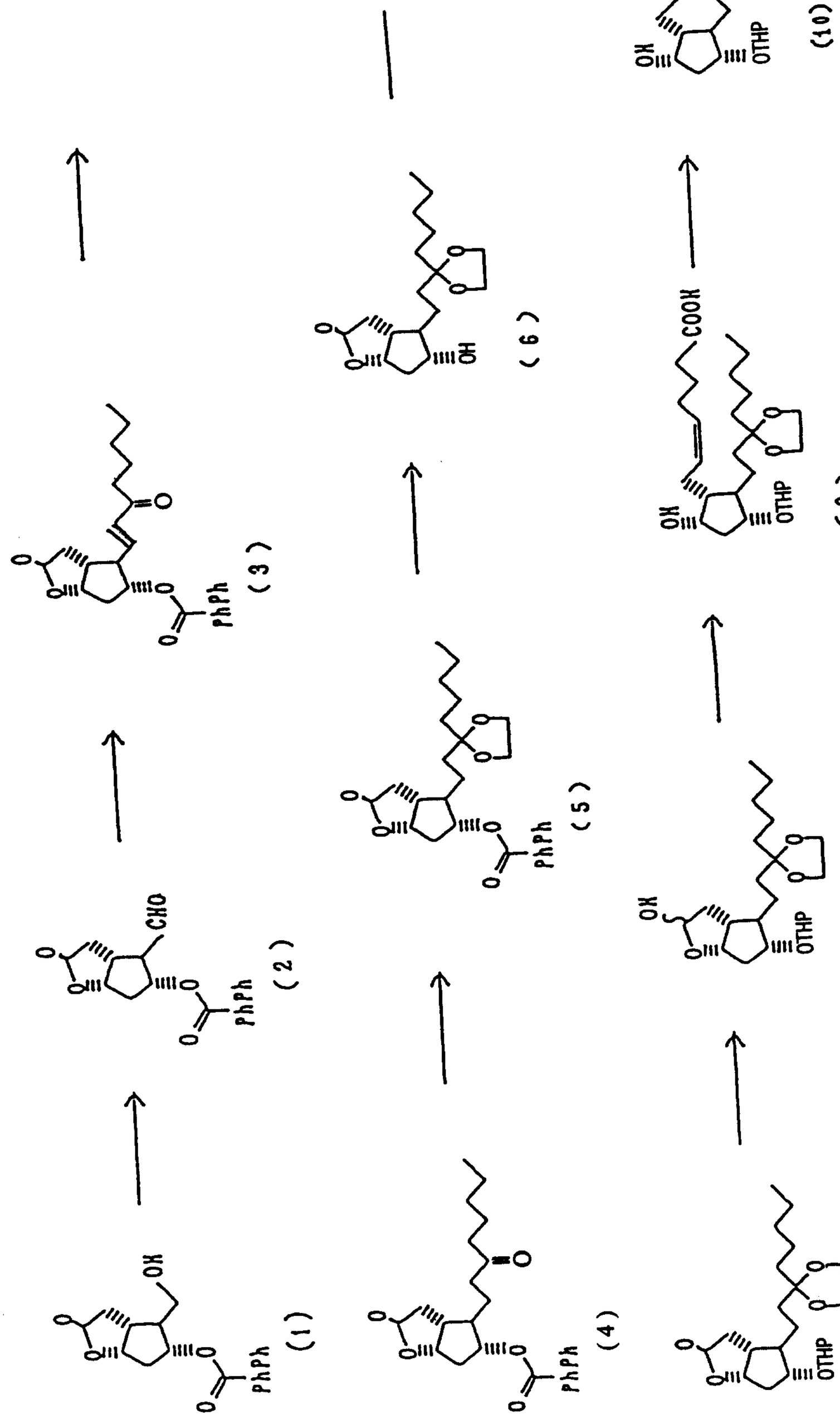
halogenated to (e) and then subjected to halogen exchange reaction to afford the compound (f).

In another process referring to Synthetic Chart VI, the protected Corey lactone (40) is converted into the compound (59) by reaction steps similar to that from (1) to (7) in synthetic Chart I. The compound (59) is hydrolyzed by alkali (e.g. sodium or potassium hydroxide) to form the free acid (60), which is esterified (e.g. with diazomethane) to give (61). After protecting the hydroxy group at position 9 giving (62), the ester group is reduced (e.g. by lithium aluminum hydride) to produce an alcohol (63) and newly formed hydroxy group is oxidized (e.g. by Swern oxidation) to an aldehyde (64). The aldehyde is reacted with an α-chain introducing agent (i) in the presence of zinc dust and mercuric chloride under ultrasonic irradiation to produce the compound (65). This is deprotected to form (66) and hydrogenated (e.g. over Pd/C) to afford (67), which is then oxidized in two steps (e.g. Swern oxidation and Jone's oxidation), via (68), to give (69). The acid (69) is deprotected either directly to (71) or via ester (70) to (72).

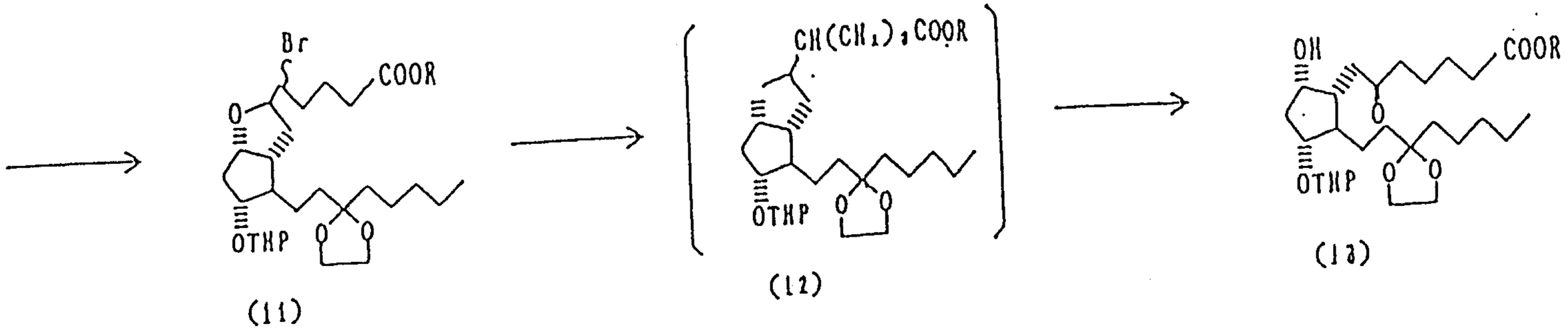
The α-chain introducing agent (i) is prepared by a process shown is synthetic Chart VIII. Thus, the acetylenic alcohol (g) is protected to form (h), which is reacted with difromodifluoromethane to produce (i).

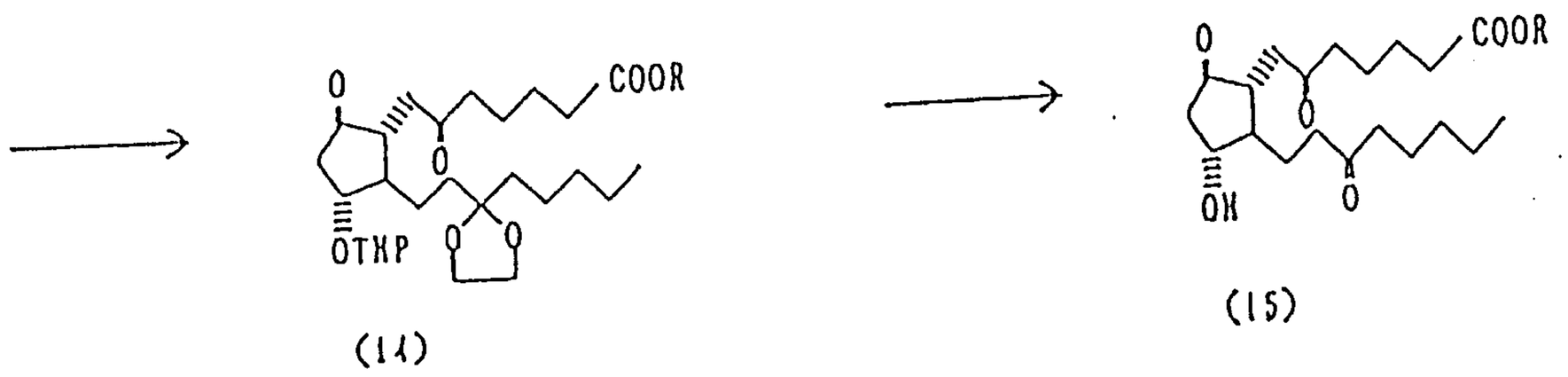
Corresponding other PG compounds can be prepared analogously.

Synthetic Chart I

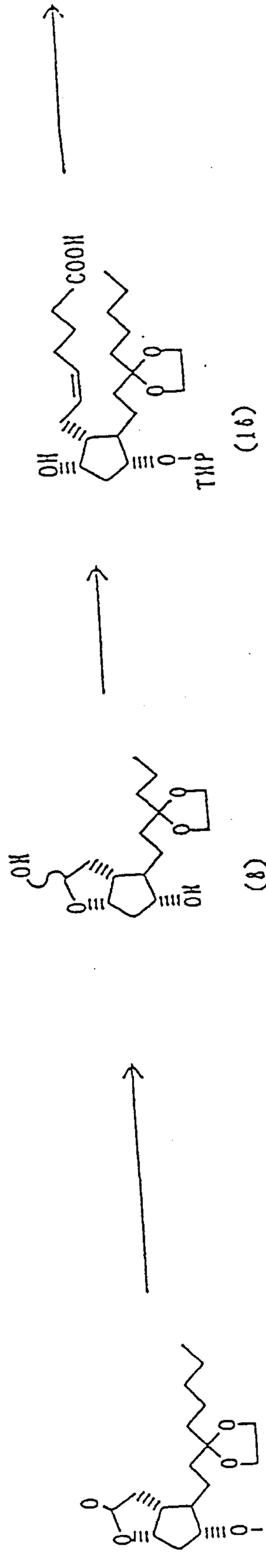


Synthetic Chart I (continued)



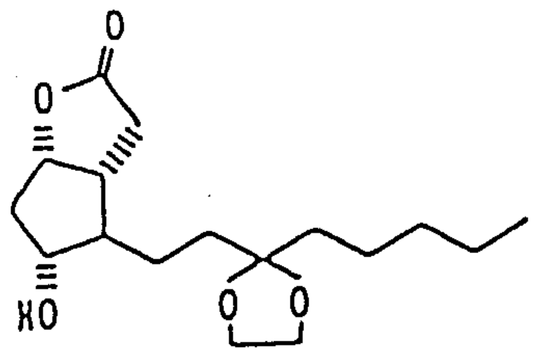


Synthetic Chart II



(1) (16) (19) (8) (18) (1) (17)

Syhthetic Chart III



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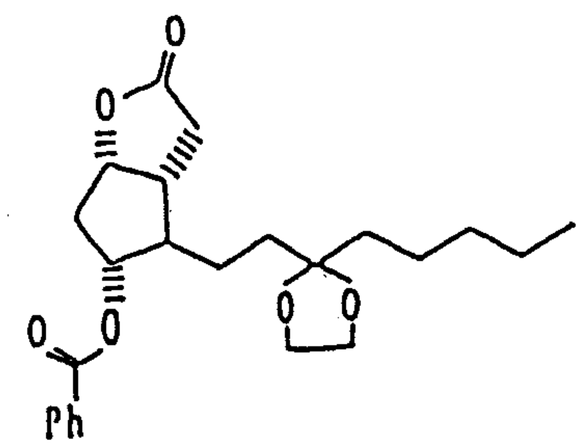

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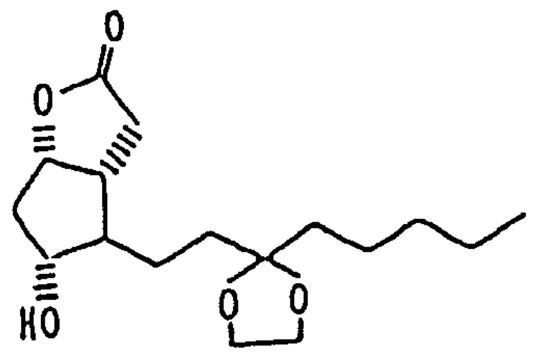

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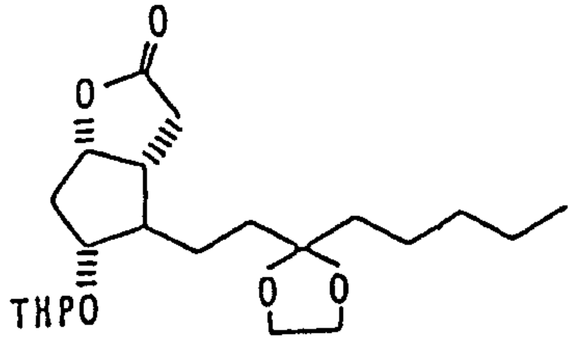

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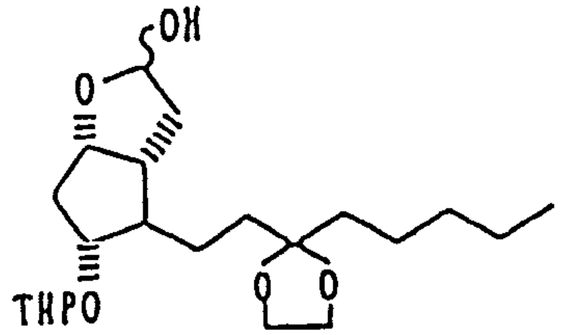

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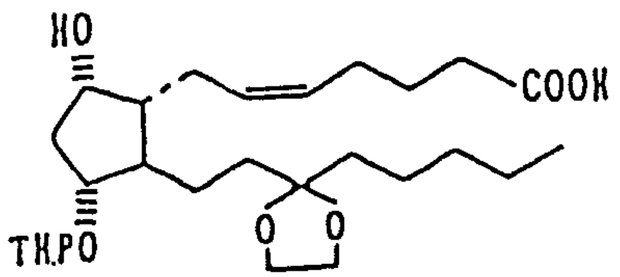

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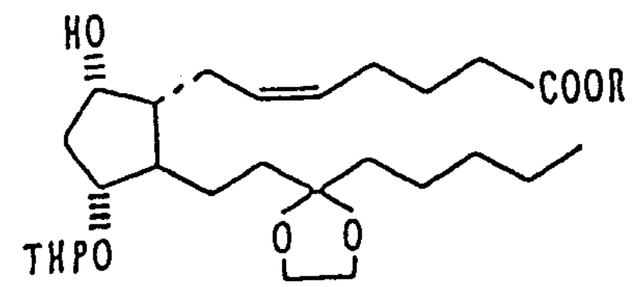

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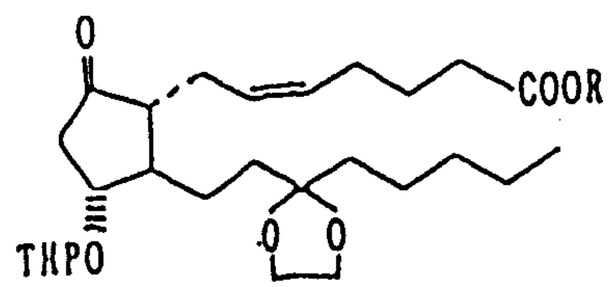

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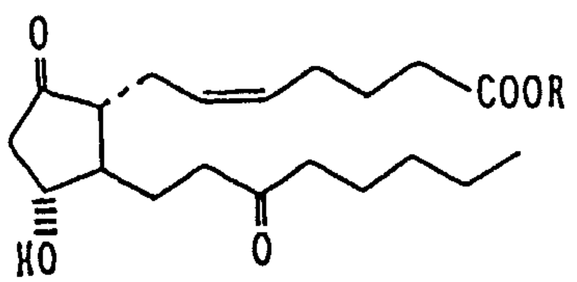

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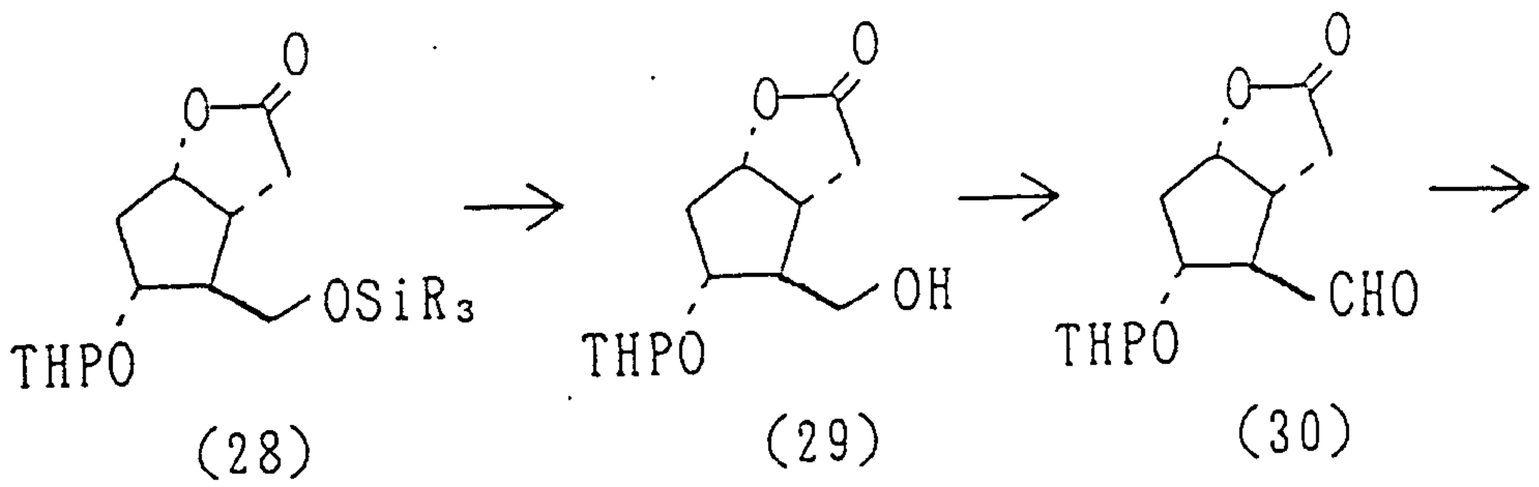
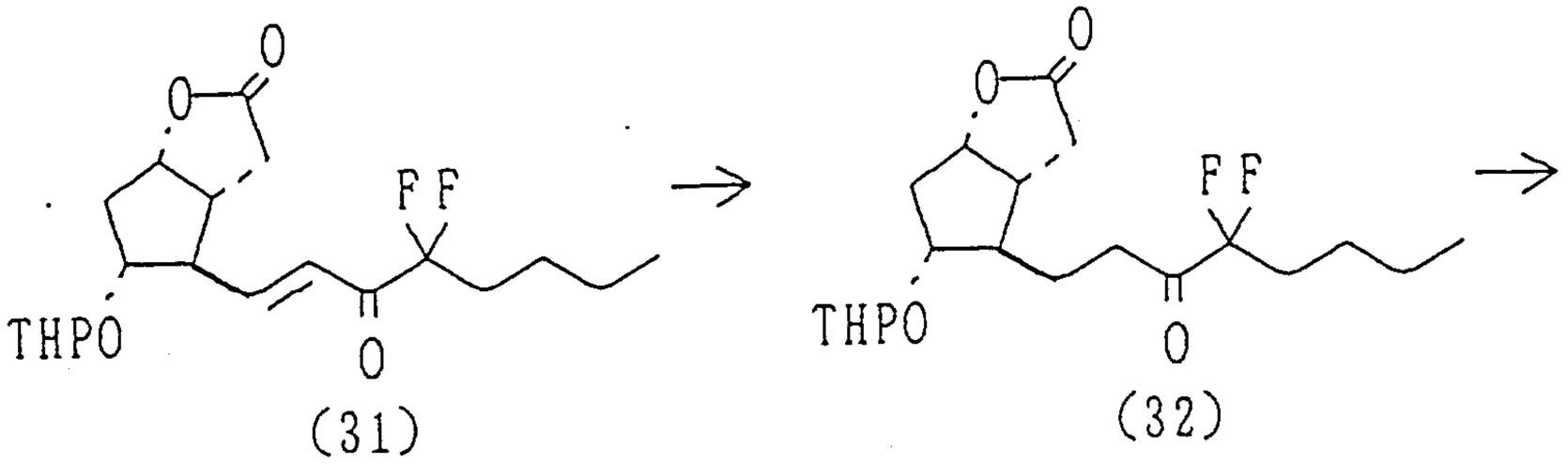
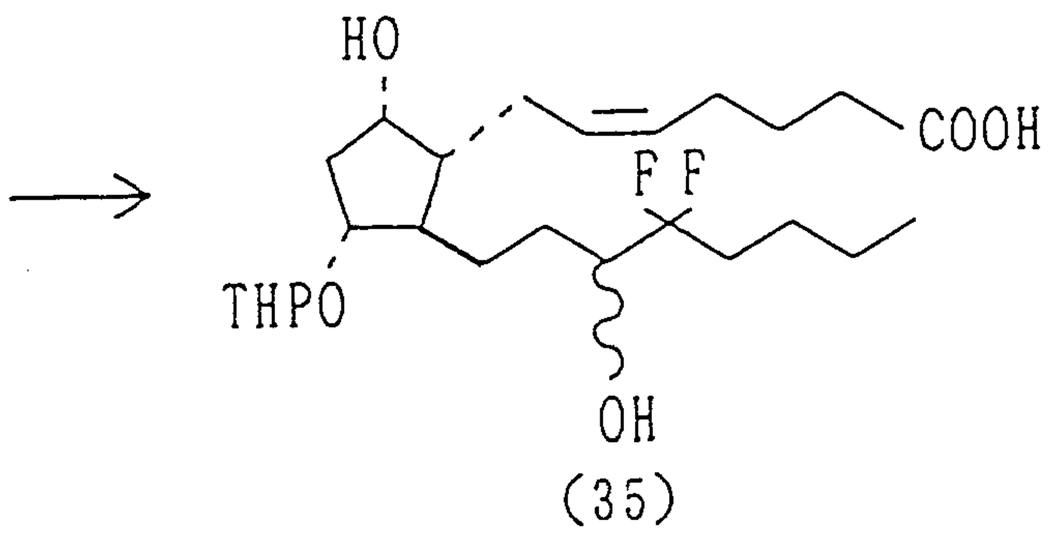
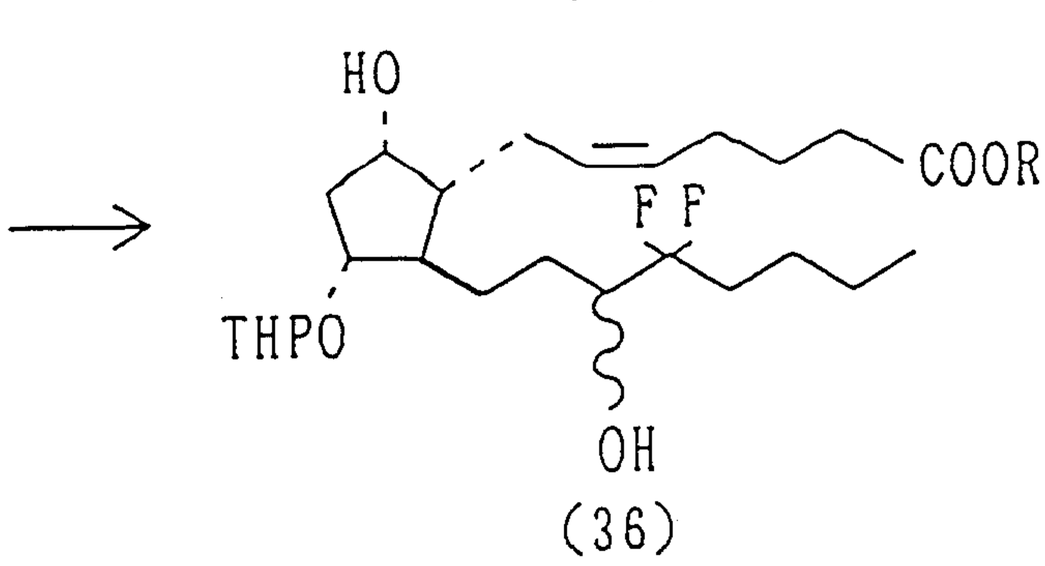
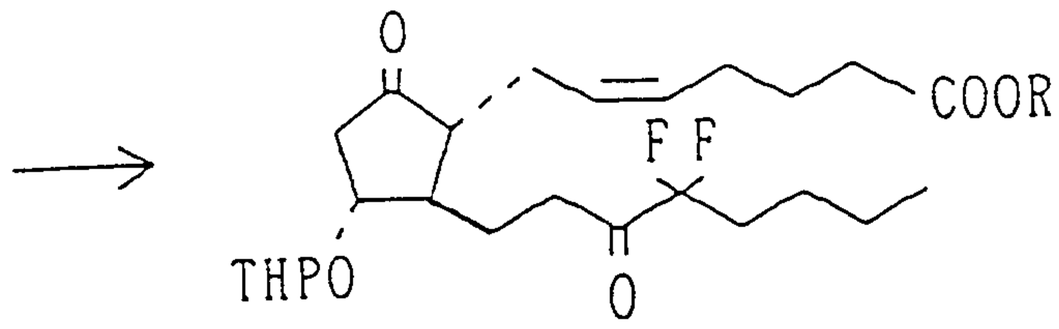
Synthetic Chart Ⅳ











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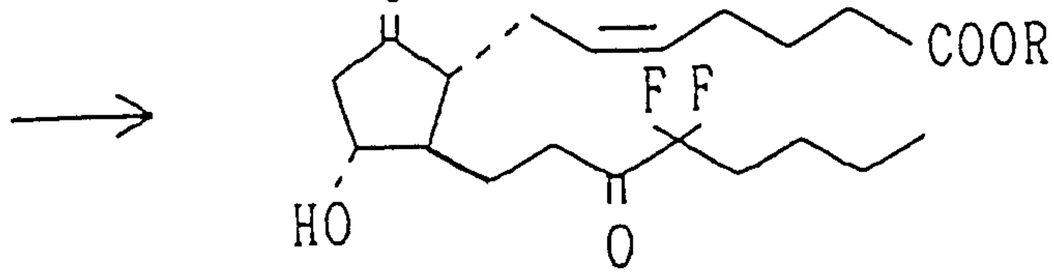

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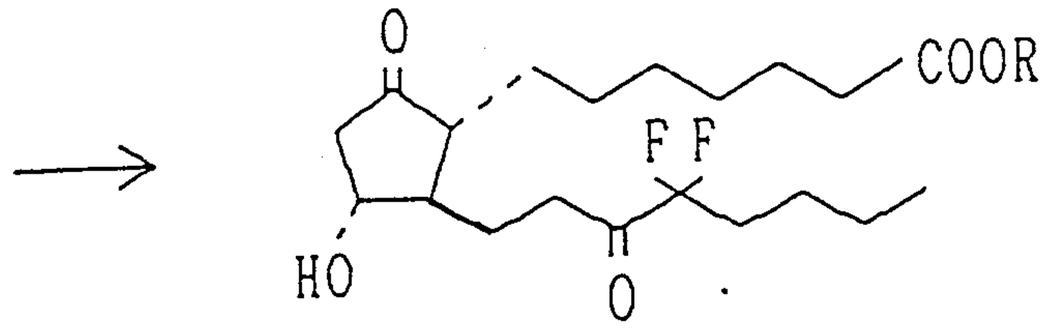

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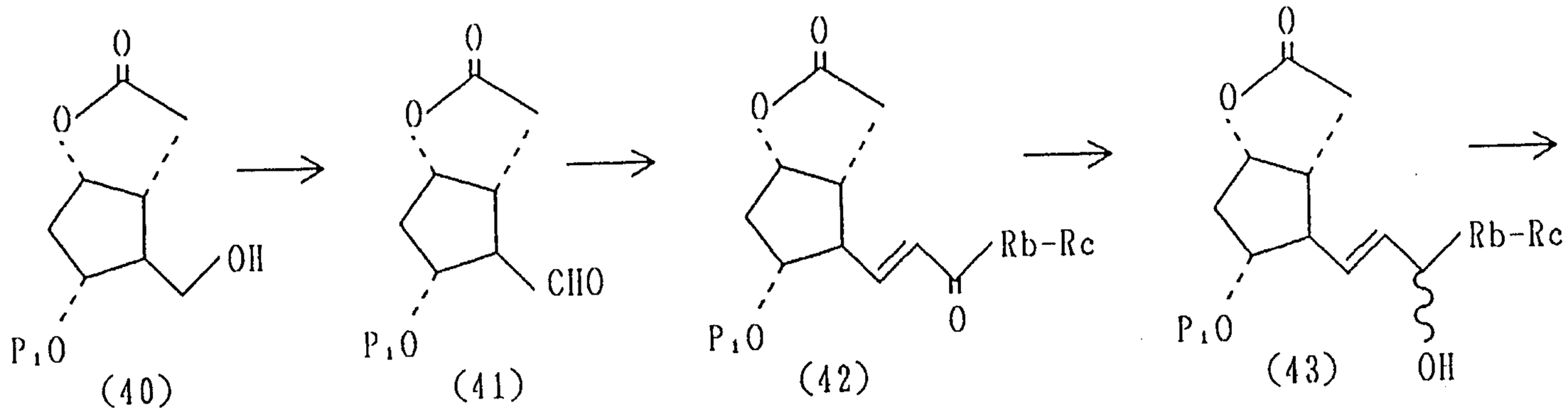
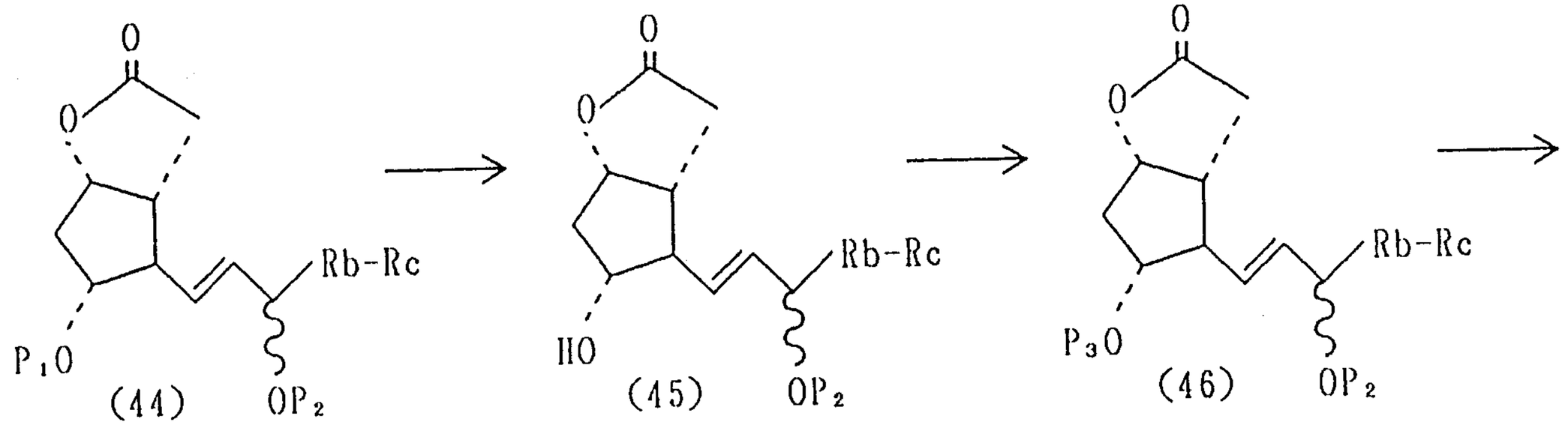
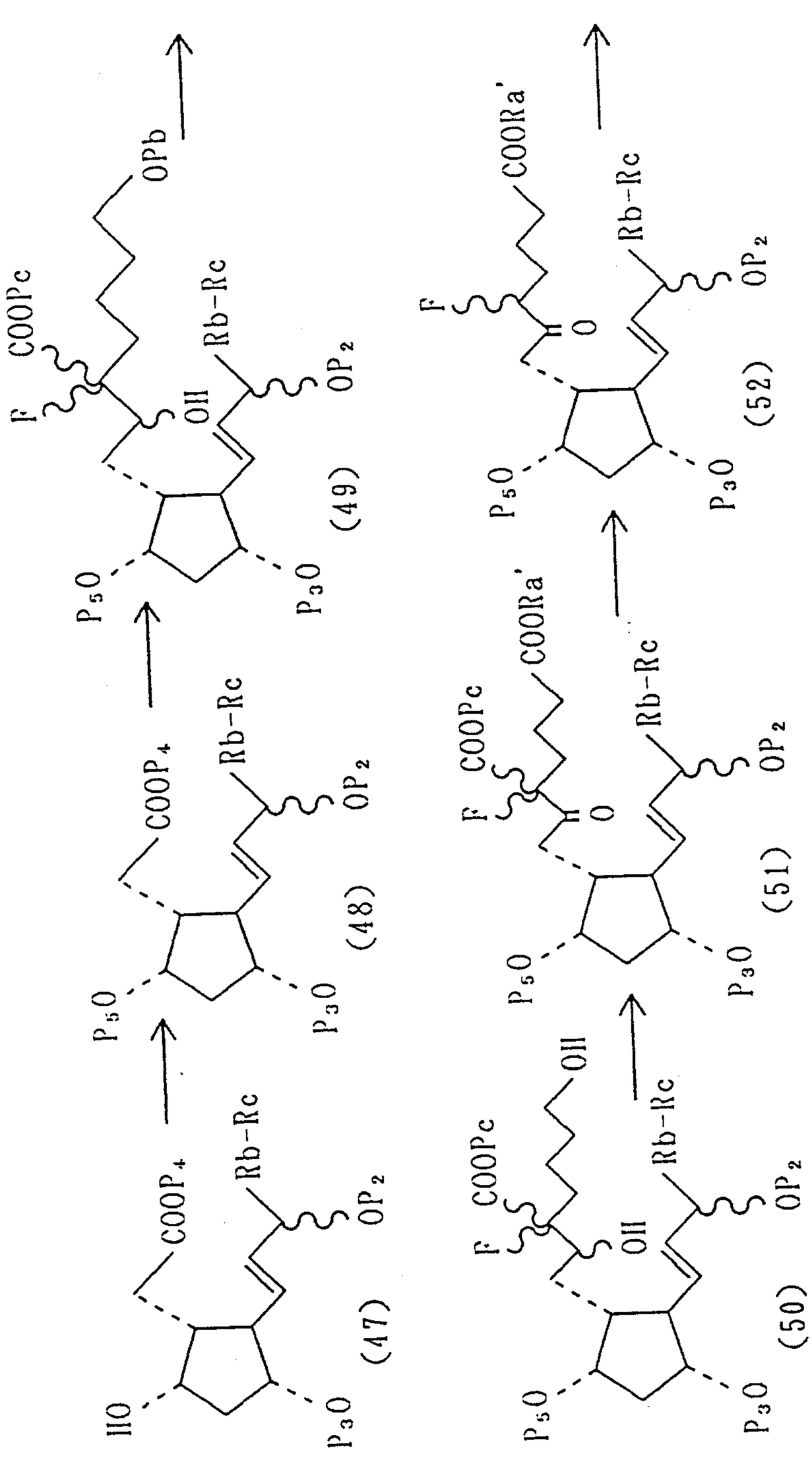
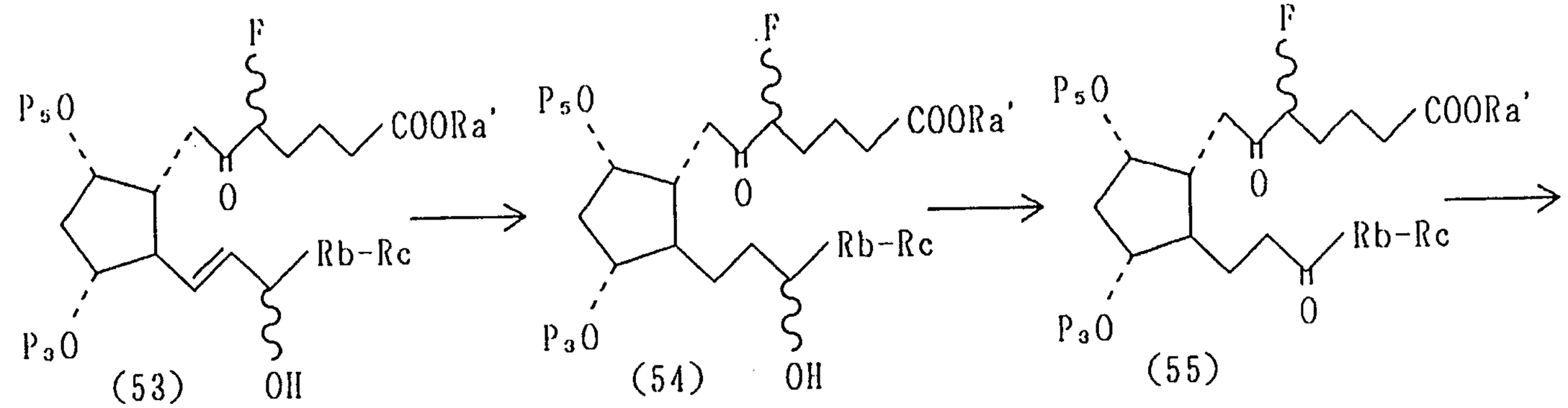
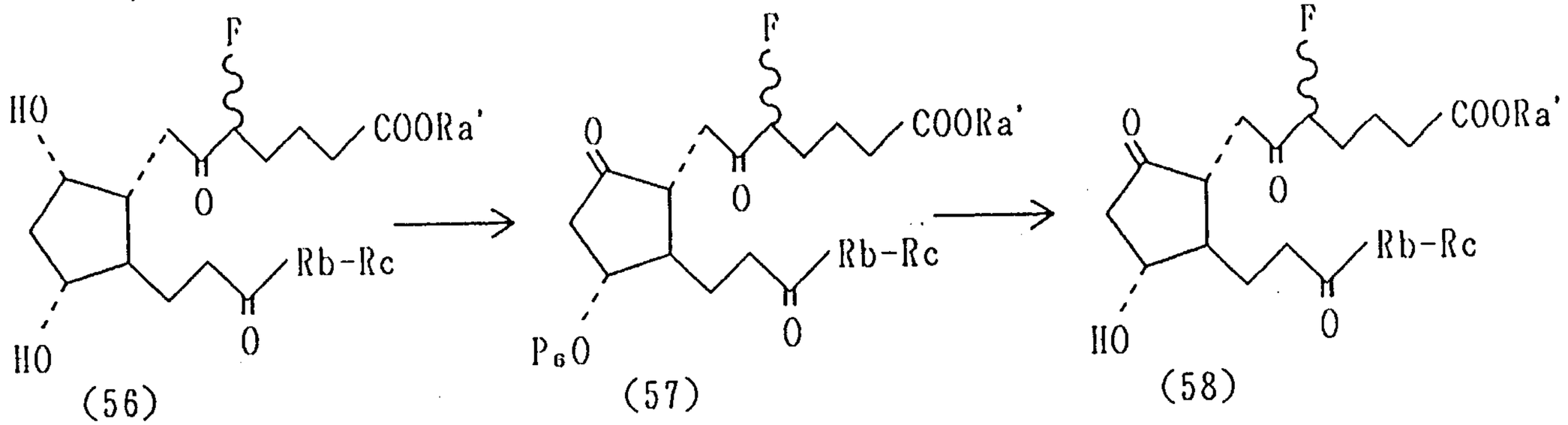
Synthetic Chart V



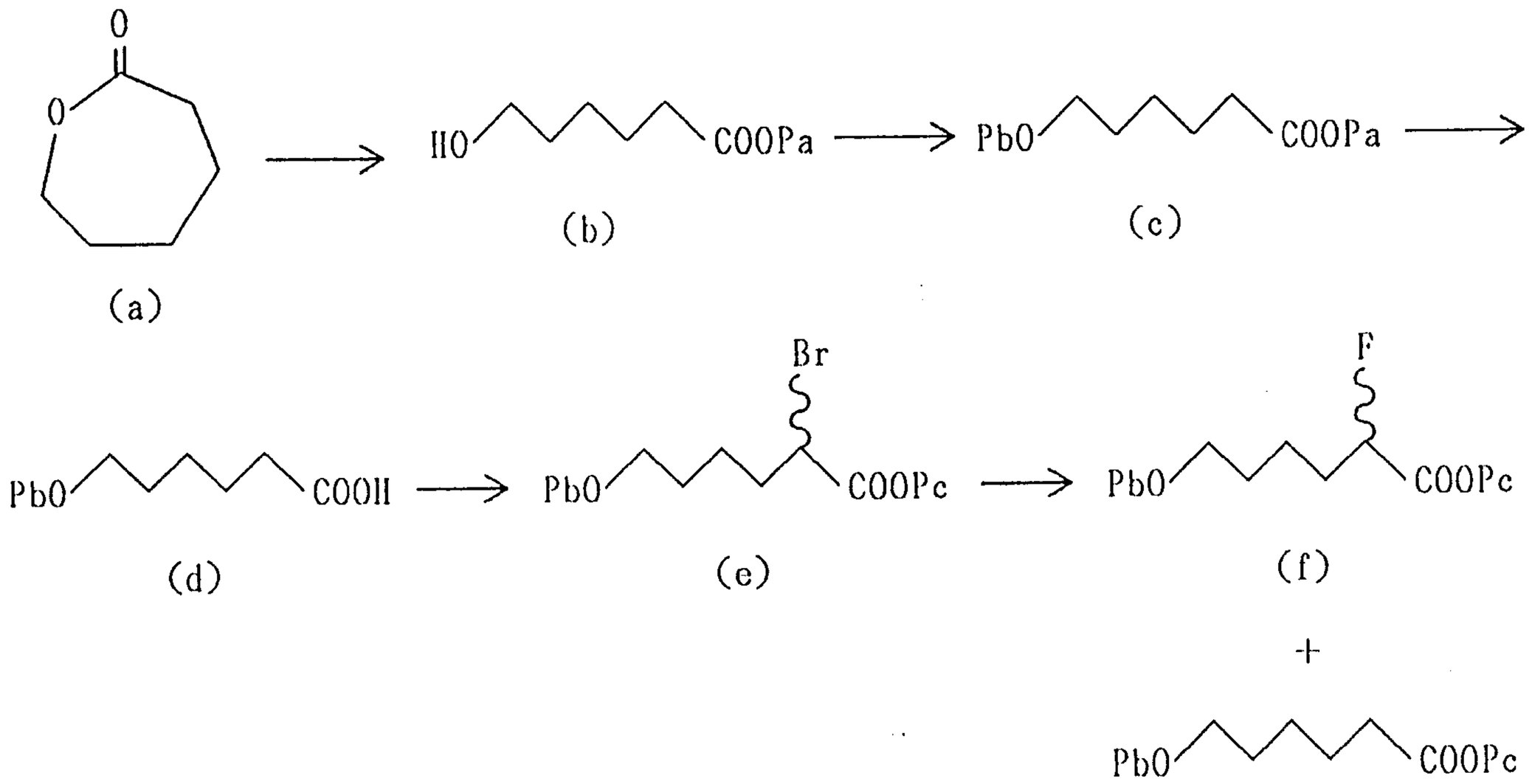



OPb
F COOPc
OH
Rb-Rc
OP2
P5O
P3O
(49)
COOP4
(48)
H2O
(47)
F COOPa'
O
(52)
(51)
(50)


F
P₅O
COORa'
O
Rb-Rc
P₃O
(53)
OH
(54)
(55)


F
HO
COORa'
O
Rb-Rc
HO
(56)
P₆O
(57)
(58)

Synthetic Chart VI



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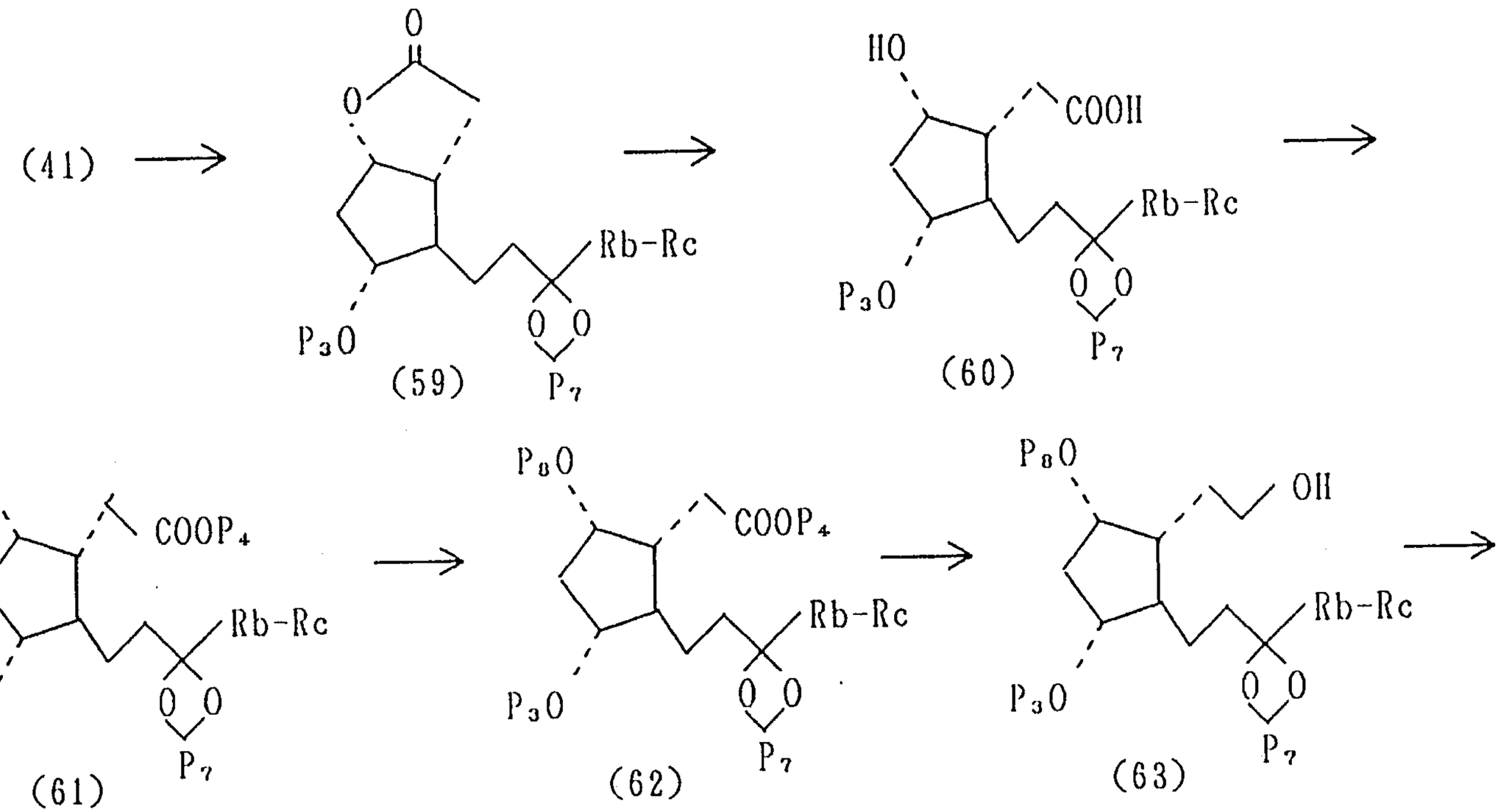
Synthetic Chart VII



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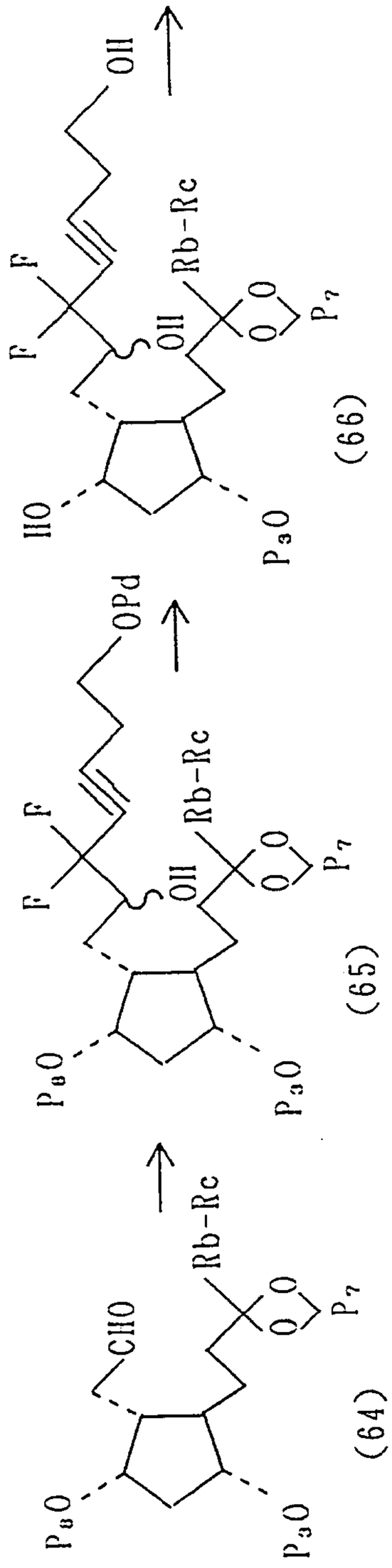
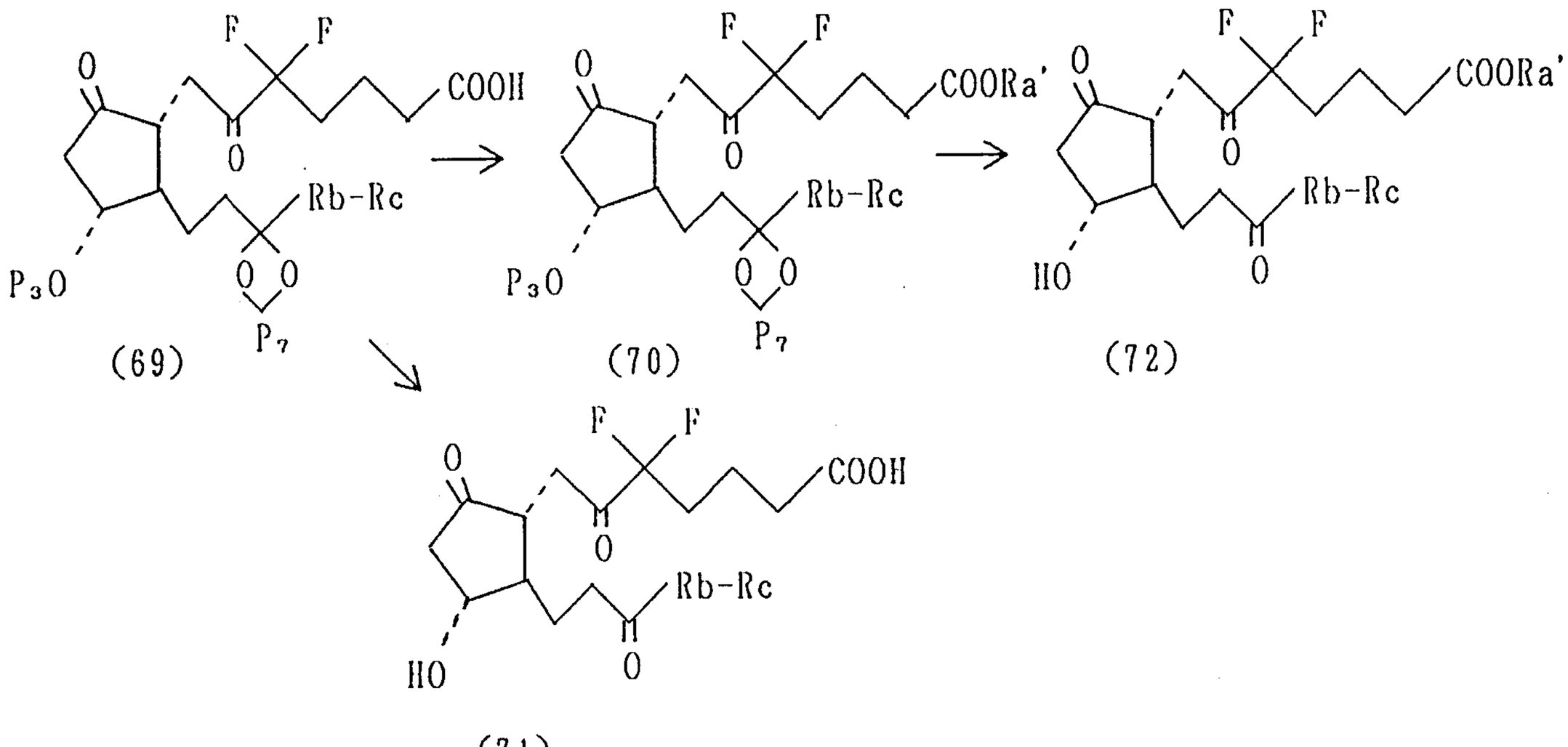

OPd
F
F
OH
Rb-Rc
O
O
P7
HO
P3O
(65)
ClHO
(64)
ClIO
(66)
O
(68)
OH
(67)



Synthetic Chart Ⅷ

$HC\equiv CCH_2CH_2OH$ (g) $\longrightarrow$ $HC\equiv CCH_2CH_2OPd$ (h) $\longrightarrow$ $BrCF_2C\equiv CCH_2OPd$ (i)

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Since the above 15-keto-PG compounds have pancreatic metabolism activating action and pancreatic function protecting action, they are useful in treatment of pancreatic disease such as actue pancreatitis. Such activities can be measured by the standard methods, for example, methods using experimental acute pancreatitis model.

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

As solid composition of this invention for oral administration, tablets, torches, buccals, capsule, 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 such as lactose, mannitol, glucose, hydoxypropyl cellulose, micro crystalline cellulose, starch, polyvinyl pyrolidone, magnesium aluminate

metasilicate. The composition may contain additives other than the inactive diluent, such as lubricants e.g., magnesium stearate, a disintegrator e.g. cellulose calcium gluconates, stabilizers e.g. α, β- or γ-cyclodextrins, etherated cyclodextrins (e.g. dimethyl-α-, dimethyl-β-, trimethyl-β-, or hydroxypropyl-β-cyclodextrins), branched cyclodextrins (e.g. glucosyl- or maltosyl-cyclodextrins), formyl cyclodextrins, sulfur-containing cyclodextrins, misoprotols or phospholipids. Such cyclodextrins may form complex to increase the stability of the compounds. The stability may be often increased by forming lyposome with phospholipids. Tablets and pills may be coated with an enteric or gastroenteric film such as 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 substance easily absorbed such as gelatin. Further, when rapid effect is required, it may be in the form of buccal, in which glycerol, lactose etc are used as a base.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs and the like and contain a generally used inactive diluent such as purified water or ethyl alcohol. The composition may contain additives such

as wetting agents, suspending agents, sweeteners, flavors, perfumes and preservatives.

The compositions for oral administration may be sprays which contain one or more active substance and can be prepared according to a well known method.

The 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 such as olive oil, alcohols such as ethanol and polysorbates. The composition may contain other additives such as 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 also be prepared by producing a sterilized solid composition and dissolving in sterilized water or a sterilized solvent for injection before use.

Another formulation according to the present invention is the rectal or vaginal suppository. This can be prepared by mixing at least one active compound according to

the invention with a suppository base which may be softened at body temperature, optionally containing non-ion surfactant having appropriate softening temperature for improving absorption.

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 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)

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

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

Yield: 21.70g (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 (1S,5R,6R,7R)-6-hydroxymethyl-7-tetrahydropyranyloxy-2-oxabicylo[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 further 1 hour. The reaction mixture was treated in the conventional manner to give the aldehyde (30) as a crude product.

To a solution of thallium ethoxide (3.26 ml) in methylene chloride was added under an argon atmosphere dimethyl 3,3-difluoro-2-oxoheptylphosphonate (11.9 g) 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 idodide solution and filtered. The filtrate was treated in the 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-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%).

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)

To a solution of (1S,5R,6R,7R)-6-(4,4-difluoro-5-oxooctyl)-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octan-3-one (32) (5.48 g) in methanol was added sodium borohydride (0.800 g) at 0°C and the resulting mixture was stirred for 10 minutes. The reaction mixture was treated in the conventional manner and the obtained 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-tetrahydropyranyloxy-$PGF_{2\alpha}$ 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 diisobutylalmium 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 the conventional manner to give the lactol (34) as a crude product.

To a suspension of 4-carboxybutyl triphenyl phosphine bromide (11.72 g) in tetrahydrofuran was added dropwise under an argon atmosphere a solution (1.0 M, 52.84 ml) of potassium tert-butoxide 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 the 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 the 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-tetrahydropyranyloxy-PGE_2 methyl ester (37)

To a solution of Collins reagent, prepared from chromic anhydride (16.18 g) and pyridine (26.2 ml) in the conventional process, in methylene chloride was added a solution of 16,16-difluoro-13,14-dihydro-11-tetrahydropyranyloxy-$PGF_{2\alpha}$ methyl ester (36) (2.646 g) in methylene chloride under an argon atmosphere at -20°C. 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-tetrahydroxypyranyloxy-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 was concentrated and the residue was subjected to column chromatography to give the title compound (39).

Yield: 1.655 g (93.8%).

^1H NMR($CDCl_3$) δ0.87(3H,t,J=7Hz), 1.15-2.05(23H,m), 2.11-2.30(3H,m), 2.50(1H,dd,J=7.5 and 17Hz), 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-O-tetrahydropyranyl-$PGF_{2\alpha}$ benzyl ester (36)

To a solution of 16,16-difluoro-13,14-dihydro-11-O-tetrahydropyranyl-$PGF_{2\alpha}$ (35) (2.33 g) in dichloromethane

(300 ml) were added DBU (2.1 ml) and benzyl bromide (2.2 ml) and the resulting mixture was stirred at room temperature for 1.5 hour. The reaction mixture was treated in the 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-O-tetrahydropyranyl-PGE_2 benzyl ester (37)

Collins reagent was prepared by 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-O-tetrahydropyranyl-$PGF_{2\alpha}$ benzyl ester (36) (2.550 g). The reaction mixture was treated in the 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 the conventional manner and the crude product was purified by silica-gel column chromatography to give the title compound (38).

Yield: 1.225g (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_2 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 the 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)

Preparation Example 3

Preparation of 5(RS)-fluoro-13,14-dihydro-6,15-diketo-PGE_1 methyl ester [IUPAC nomenclature: 5(RS)-fluoro-7-{(1R,2s,3S)-3-hydroxy-2-(3-oxooctyl-5-oxocyclopentyl}-6-oxoheptanoate]

3-1) Preparation of (1S,5R,6R,7R)-6-[(E)-3-oxo-1-octenyl]-7-(4-phenyl)benzoyloxy-2-oxabicyclo[3.3.0]octan-3-one (42)

Commercial (-)-Corey lactone (40) (10.0g) in dichloromethane was subjected to Collins oxidation to give the aldehyde (41), which was reacted with an anion prepared from dimethyl (2-oxoheptyl)phosphonate (6.21g). The

reaction mixture was treated in the conventional manner and the obtained crude product was subjected to column chromatography to give the title compound (42).

Yield: 7.45g (60 %)

3-2) Preparation of (1S,5R,6R,7R)-6-[(E)-3(RS)-hydroxy-1-octenyl]-7-(4-phenyl)benzoyloxy-2-oxabicyclo-[3.3.0]-octan-3-one (43)

To a solution of (1S,5R,6R,7R)-6-[(E)-3-oxo-1-octenyl]-7-(4-phenyl)benzoyloxy-2-oxabicyclo-[3.3.0]-octan-3-one (42) (7.45g) in methanol were added cerium chloride (III) heptahydrate (6.84g) at -20 °C and sodium borohydride (0.69g) and the mixture was stirred for 1 hour.

The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to the column chromatography to give the title compound (43) as a mixture of the diastereomers.

Yield: 7.64g (theoretical)

3-3) Preparation of (1S,5R,6R,7R)-6-[(E)-3(RS)-t-butyl-dimethylsilyloxy-1-octenyl]-7-(4-phenyl)benzoyloxy-2-oxabicyclo[3.3.0]octan-3-one (44)

To a solution of (1S,5R,6R,7R)-6-[(E)-3(RS)-hydroxy-1-octenyl]-7-(4-phenyl)benzoyloxy-2-oxabicyclo-[3.3.0]octan-3-one (43) (7.65g) in dimethyl formamide were added imidazol (2.27g) and t-butyldimethylsilyl chloride (3.78g) and the mixture was stirred for 1 hour.

The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to the silica gel column chromatography to give the title compound (44) as a mixture of the diastereomers.

Yield: 7.49g (80 %)

3-4) Preparation of (1S,5R,6R,7R)-6-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one (45)

A mixture of (1S,5R,6R,7R)-6-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-7-(4-phenyl)benzoyloxy-2-oxabicyclo[3.3.0]octane-3-one (44) (7.49g), potassium carbonate (1.10g) and methanol was stirred at room temperature for 16 hours. The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to the silica gel column chromatography to give the title compound (45) as a mixture of the diastereomers.

Yield: 4.69g (92 %)

3-5) Preparation of (1S,5R,6R,7R)-6-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octan-3-one (46)

To a solution of (1S,5R,6R,7R)-6-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one (45) (4.69g) in methylene chloride were added dihydropyran (5.17g), and pyridinium p-toluenesufonate (0.77g), and the resultant mixture was stirred at room

temperature for 16 hours. The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to the silica gel column chromatography to give the title compound (46) as a mixture of the diastereomers.

Yield: 5.37g (94 %)

3-6) Preparation of methyl 2-{(1R,2R,3R,5S)-2-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-5-hydroxy-tetrahydropyranyloxy-cyclopentyl}acetate (47)

To a solution of (1S,5R,6R,7R)-6-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octan-3-one (46) (1.85g) in a mixed solvent of methanol and water (4:1) was added lithium hydroxyde (0.33g). The resultant mixture was stirred at room temperature for 16 hours. The reaction mixture was neutralized and extracted with ethyl acetate.

Then, the organic layer was separated and an ether solution of diazomethane was added thereto. The resultant mixture was stirred at room temperature for 1 hour. The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to the silica gel column chromatography to give the title compound (47) as a mixture of the diastereomers.

Yield: 1.82g (92 %)

3-7) Preparation of methyl 2-{(1R,2R,3R,5S)-2-[(E)-3(RS)-

t-butyldimethylsilyloxy-1-octenyl]-3,5-bis-tetrahydro-pyranyl-oxy-cyclopentyl}acetate (48)

To a solution of methyl 2-{(1R,2R,3R,5S)-2-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-5-hydroxy-tetrahydropyranyloxy-cyclopentyl}acetate (47)(4.45g) in methylene chloride were added dihydropyran (3.75g) and pyridinium p-toluenesufonate (0.56g), and the resultant mixture was stirred at room temperature for 16 hours. The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to the silica gel column chromatography to give the title compound (48) as a mixture of the diastereomers.

Yield: 4.24g (74 %)

3-8) Preparation of methyl 6-benzoyloxy-2(RS)-{2-[(1R,2R,3R,5S)-2-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-3,5-bis-tetrahydropyranyloxy-cyclopentyl]-1(RS)-hydroxyethyl}-2(SR)-fluorohexaneacetate (49)

To a toluene solution of methyl 2-{(1R,2R,3R,5S)-2-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-3,5-bis-tetrahydropyranyloxy-cyclopentyl}acetate (48) (0.5g) was added a toluene solution of DIBAL-H (1.5M, 1.43ml) at -78°C and the resultant mixture was stirred for 1 hour. The reaction mixture was treated in the conventional manner to give the aldehyde as a crude product.

The solution of LDA, prepared in the conventional

manner, in terahydrofuran (0.94 mmol) was cooled to -78°C, and methyl 6-benzoyloxy-2(RS)-fluorohexanoate (f) (0.23g) was added thereto. The resultant mixture was stirred for 10 minutes and the solution of the crude aldehyde in tetrahydrofran was added thereto. The reaction mixture was heated to room temperature and stirred at the same temperature for 1 hour, The crude product obtained in the conventional manner was subjected to the silica gel column chromatography to give the title compound (49) as a mixture of the diastereomers.

Yield: 0.51g (74 %)

3-9) Preparation of methyl 2(RS)-{2-[(1R,2R,3R,5S)-2-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-3,5-bis-tetrahydropyranyloxy-cyclopentyl]-1(RS)-hydroxyethyl}-2(SR)-fluoro-6-hydroxyhexanoate (50)

To a solution of methyl 6-benzoyloxy-2(RS)-{2-[(1R,2R,3R,5S)-2-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-3,5-bis-tetrahydropyranyloxy-cyclopentyl]-1(RS)-hydroxyethyl-2(SR)-fluorohexaneacetate (49) (2.48g) in methanol was added potassium carbonate (2.47g) in methanol and the resultant mixture was stirred at room temperature for 24 hours. The crude product obtained in the conventional manner was subjected to the silica gel column chromatography to give the title compound (50).

Yield: 1.50g (69%)

3-10) Preparation of 7-{(1R,2R,3R,5S)-2-[(E)-3(RS)-t-butyl-dimethylsilyloxy-1-octenyl]-3,5-bis-tetrahydropyranyl-oxycyclopentyl]-5(RS)-methoxycarbonyl-5(SR)-fluoro-6-oxoheptanoate (51)

Methyl 2(RS)-{2-[(1R,2R,3R,5S)-2-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-3,5-bis-tetrahydro-pyranyloxycyclopentyl]-1(RS)-hydroxyethyl}-2(SR)-fluoro-6-hydroxyhexanoate (50) (1.23g) was subjected to Collins oxidation at -50°C under an argon atmosphere for 4.5 hours. The crude product obtained in the conventional manner was dissolved into ether, and a solution of diazomethane in ether was added thereto. The resultant mixture is stirred at room temperature for 1 hour. The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to the silica gel column chromatography to give the title compound (51) in the form of diastereomeric mixture. Unreacted starting material (50) was recovered (0.41g, Recovery: 33%).

Yield: 0.60g (47%)

3-11) Preparation of methyl 7-{(1R,2R,3R,5S)-2-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-3,5-bis-tetrahydro-pyranyloxycyclopentyl]-5(RS)-fluoro-6-oxo-heptanoate (52)

Methyl 7-{(1R,2R,3R,5S)-2-[(E)-3(RS)-t-butyldi-methylsilyloxy-1-octenyl]-3,5-bis-tetrahydropyranyloxy-

cyclopentyl]-5(RS)-methoxycarbonyl-5(SR)-fluoro-6-oxoheptanoate (51) (0.80g) was dissolved into a mixture of dimethyl sulfoxide, sodium chloride and water (50:2.8:1) and the resultant mixture was stirred at 135-140°C under an argon atmosphere for 1.5 hours. The crude product obtained by treating in the conventional manner was subjected to silica gel column chromatography to give the title compound (12) as a mixture of diastereomers.

Yield: 0.55g (75 %)

3-12) Preparation of methyl 5(RS)-fluoro-7-{(1R,2R,3R,5S)-2-[(E)-3(RS)-t-hydroxy-1-octenyl]-3,5-bis-tetrahydropyranyloxycyclopentyl]-6-oxoheptanoate (53)

To a solution of methyl 7-{(1R,2R,3R,5S)-2-[(E)-3(RS)-t-butyldimethylsilyloxy-1-octenyl]-3,5-bis-tetrahydropyranyloxy-cyclopentyl]-5(RS)-fluoro-6-oxo-heptanoate (52) (0.52g) in tetrahydrofuran was added a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1M, 23ml), and the resultant mixture was stirred at room temperature for 40 hours. The crude product obtained by treating in the conventional manner was subjected to silica gel chromatography to give the title compound (53).

Yield: 0.34g (67%)

3-13) Preparation of methyl 5(RS)-fluoro-7-{(1R,2R,3R,5S)-2-[3(RS)-hydroxy-1-octyl]-3,5-bistetra-hydropyranyloxy-

cyclopentyl]-6-oxoheptanoate (54)

To a solution of methyl 5(RS)-fluoro-7-{(1R,2R,3R,5S)-2-[(E)-3(RS)-t-hydroxy-1-octenyl]-3,5-bis-tetrahydropyranyloxycyclopentyl]-6-oxoheptanoate (53) in ethyl acetate was added 5% of Pd/C (0.06g), and the resultant mixture was stirred at room temperature under a hydrogen atmosphere for 16 hours. The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to silica gel column chromatography to give the title compound (54) as a mixture of diastereomers.

Yield: 0.30g (88%)

3-14) Preparation of methyl 5(RS)-fluoro-7-{(1R,2R,3R,5S)-2-[3-oxo-octyl]-3,5-bistetrahydropyranyloxy-cyclopentyl]-6-oxoheptanoate (55)

To a solution of methyl 5(RS)-fluoro-6-oxo-7-{(1R,2R,3R,5S)-2-[3(RS)-hydroxy-1-octyl]-3,5-bis-tetrahydropyranyloxy-cyclopentyl]-6-oxo-heptanoate (54) (0.30g) in acetone was added Jones reagent (2.60 M, 0.6ml) and the resultant mixture was stirred at -30°C for 1.5 hours. The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to silica gel column chromatography to give the title compound (55) as a mixture of diastereomers.

Yield: 0.24g (80%)

3-15) Preparation of methyl 5(RS)-fluoro-7-{(1R,2R,3R)-

3-t-butyldimethylsilyloxy-5-oxo-2-(3-oxo-octyl)-cyclopentyl]-6-oxoheptanoate (57)

Methyl 5(RS)-fluoro-6-oxo-7-{(1R,2R,3R,5S)-2-[3-oxo-octyl]-3,5-bis-tetra-hydropyranyloxy-cyclopentyl]-6-oxo-heptanoate (55) (0.24g) was dissolved into a mixed solvent of acetic acid, tetrahydrofuran and water (3:1:1), and the resultant mixture was stirred at 45°C for 4.5 hours. The crude product obtained by treating in the conventional manner was subjected to silica gel column chromatography to give a diol product (56) (0.15g).

To a solution of diol product (56) (0.15g) in dimethylformamide were added imidazol (0.35g) and t-butyl-dimethylsilyl chloride (0.38g) and the resultant mixture was stirred at room temperature for 5 hours. The crude product obtained by treating in the conventional manner was subjected to silica gel column chromatography to give monosilyl product (0.135g).

The monosilyl product (0.135g) was subjected to Collins oxidation in methylene chloride at room temperature for 15 minutes. The crude product obtained by treating in the conventional manner was subjected to silica gel column chromatography to give the title compound (57).

Yield: 0.10g (49%, starting from Compound (55))

3-16) Preparation of 5(RS)-fluoro-13,14,-dihydro-6,15-diketo-PGE_1 methyl ester (58)

To a solution of methyl 5(RS)-fluoro-7-{(1R,2R,3R)-3-t-butyldimethylsilyloxy-5-oxo-2-(3-oxo-octyl)-cyclopentyl]-6-oxoheptanoate (57) (0.05 g) in dichloromethane was added a solution of hydrogen fluoride-pyridine (70:30, 0.40ml), and the resultant mixture was stirred at room temperature for 7 hours. The crude product obtained by treating in the conventional manner was subjected to silica gel column chromatography to give the title compound (58).

Yield: 0.38 g (98%)

^{1}H NMR ($CDCl_3$): δ 0.87(3H,t,J=6.8Hz), 1.16-2.05(14H,m), 2.23-3.15(11H,m), 3.66(3H,s), 3.98-4.12(1H,m), 4.62-4.70(0.5H,m), 4.85-4.95(0.5H,m).

Preparation of Starting Material: Methyl 6-benzoyloxy-2(RS)-fluoro-hexanoate (f)

1) Preparation of benzyl 6-hydroxyhexanoate (b)

A mixture of ϵ-caprolactone (a) (40 g), benzyl alcohol and p-toluenesulfonic acid monohydrate (0.7 g) was stirred at 100°C for 16 hours. The reaction mixture was treated in the conventional manner and was distilled under reduced pressure (1 mmHg, 140-154°C) to give the title compound (b).

Yield: 27.37g (35%)

2) Preparation of benzyl 6-benzoyloxyhexanoate (c)

To a solution of benzyl 6-hydroxyhexanoate (b)

(27.37 g) in methylene chloride were added 4-dimethyl amino pyridine (19.5g) and benzoyl chloride (19.53 g), and the resultant mixture was stirred for 2 hours. The reaction mixture was treated in the conventional manner and was distilled under reduced pressure (1 mmHg, 190-215°C) to give the title compound (c).

Yield: 38.09g (95%)

3) Preparation of 6-benzoyloxy-hexanoic acid (d)

To a solution of benzyl 6-benzoyloxy-hexanoate (c) (38.09 g) in ethyl acetate was added 5% Pd/C (3 g) and the resultant mixture was stirred under a hydrogen atmosphere for 24 hours. The crude product obtained by treating in the conventional manner was distilled under reduced pressure (1 mmHg, 182-192°C) to give the title compound (d).

Yield: 4.92g (90%)

4) Preparation of methyl 6-benzoyloxy-2(RS)-bromo-hexanoate (e)

Thionyl chloride (22ml) was added dropwise to 6-benzoyloxyhexanoic acid (d) (14.92 g), and the resultant mixture was stirred at 65°C for 1 hour. To the reaction mixture were added carbon tetrachloride (50ml), N-bromo-succinimide (22.5 g) and 48% hydrobromic acid (5 drops), and the resultant mixture was stirred at 85°C for 20 hours. The reaction mixture was allowed to cool, and was filtered to remove solid product. The filtrate was concentrated under

reduced pressure. The obtained residue was dissolved into methanol and the resultant mixture was stirred at room temperature. The crude product obtained by treating in the conventional manner was subjected to silica gel chromatography to give the title compound (e).

Yield: 14.02g (67%)

5) Preparation of methyl 6-benzoyloxy-2(RS)-fluoro-hexanoate (f)

A mixture of methyl 6-benzoyloxy-2(RS)-bromo-hexanoate (e) (14.02 g), potassium fluoride (12.59 g) and acetamide (12.3 g) was stirred at 105°C for 6 hours. The crude product obtained by treating in the conventional manner was subjected to silica gel chromatography to give the title compound (f) and methyl 6-benzoyloxyhexanoate (g) (3.11 g, yield: 29%).

Yield: 5.28g (46%)

^{1}H NMR ($CDCl_3$) δ: 1.55-2.18 (6H,m), 3.79(3H,s), 4.33(2H,t,J=7Hz), 4.77-4.86(0.5H,m), 5.05-5.12(0.5H,m), 7.40-7.62(3H,m), 8.00-8.10(2H,m).

Preparation Example 4

Preparation of 5,5-difluoro-13,14-dihydro-6,15-diketo-PGE_1 methyl ester (72)

4-1) Preparation of (1S,5R,6R,7R)-6-[(E)-3-oxo-1-octenyl]-7-(4-phenylbenzoyloxy)-2-oxabicyclo[3.3.0]-octan-3-one (42)

Corey-lactone (40) (10.0 g) dissolved in dichloromethane (160ml) was subjected to Moffatt oxidation using DMSO (79.2 g), dicyclohexylcarbodiimide (24.0 g), pyridine (2.3 ml) and trifluoroacetic acid (1.1ml) to give Corey-lactone aldehyde (2a). Separately, dimethyl (2-oxoheptyl)phosphonate anion was prepared from dimethyl-(2-oxoheptyl)phosphonate (6.31 g) and sodium hydride (60%, 0.13 g) in dichloromethane, and the solution of the previously obtained aldehyde (160ml) was added dropwise thereto, and the resultant mixture was stirred at room temperature for 11.5 hours. The crude product obtained by treating in the conventional manner was subjected to silica gel chromatography to give the title compound (42).

Yield: 10.8g (85.3%)

4-2) Preparation of (1S,5R,6R,7R)-6-(3-oxo-1-octenyl)-7-(4-phenylbenzoyloxy)-2-oxabicyclo[3.3.0]octan-3-one (4a)

A mixture of (1S,5R,6R,7R)-6-[(E)-3-oxo-1-octenyl]-7-(4-phenylbenzoyloxy)-2-oxabicycloctan[3.3.0]-3-one (42) (10.8 g) and 5% Pd/C (1.02 g) in ethyl acetate (150ml) was stirred under a hydrogen atmosphere for 3 hours. The reaction mixture was treated in the conventional manner to give the title compound (4a).

Yield: 8.20 g

4-3) Preparation of (1S,5R,6R,7R)-6-(3,3-ethylene-

dioxyoctyl-7-(4-phenylbenzoyloxy)-2-oxabicyclo[3.3.0]-octan-3-one (5)

To a solution of (1S,5R,6R,7R)-6-(3-oxo-1-octenyl)-7-(4-phenylbenzoyloxy)-2-oxabicyclo[3.3.0]octan-3-one (4a) (8.20 g) in toluene (100 ml) were added ethylene glycol (23.0 g) and p-toluenesulfonic acid (0.41 g), and the resultant mixture was refluxed for 4 hours. Water formed in the reaction was removed by azeotropic distillation. The reaction mixture was treated in the conventional manner and was subjected to silica gel column chromatography to give the title compound (5a).

Yield: 8.23g (91.3%)

4-4) Preparation of (1S,5R,6R,7R)-6-(3,3-ethylene-dioxyoctyl)-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one (6a)

To a solution of (1S,5R,6R,7R)-6-(3,3-ethylene-dioxyoctyl-7-(4-phenylbenzoyloxy)-2-oxabicyclo[3.3.0]octan-3-one (5a) (8.20 g) in methanol (200 ml)was added potassium carbonate (1.15g) and the resultant mixture was stirred overnight, and acetic acid (1ml) was added thereto. The crude product obtained by treating in the conventional manner was subjected to silica gel column chromatography to give the title compound (6a).

Yield: 4.70g (90.0%)

4-5) Preparation of (1S,5R,6R,7R)-6-(3,3-ethylenedioxy-

octyl)-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octan-3-one (59)

A solution of (1S,5R,6R,7R)-6-(3,3-ethylenedioxyoctyl)-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one (6a) (4.70g) in dichloromethane (200 ml) was cooled on ice and dihydropyran (2.41g) and p-toluenesulfonic acid (0.23g) were added thereto and the resultant mixture was stirred for 1,5 hours. The crude product obtained by treating in the conventional manner was subjected to silica gel column chromatography to give the title compound (59).

Yield: 5.54g (93%)

4-6) Preparation of methyl 2-[(1S,2R,3R,5S)-2-(3,3-ethylenedioxyoctyl)-3-(tetrahydropyranyloxy)-5-hydroxycyclopentyl]acetate (61)

(1S,5R,6R,7R)-6-(3,3-ethylenedioxyoctyl)-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octan-3-one (59) (5.54g) was dissolved into methanol (61ml), and 5% aqueous potassium hydroxyde (37ml) was added thereto. The resultant mixture was stirred at 50°C for 30 minutes. While cooling on ice, the reaction mixture was neutralized with aqueous 0.5 N hydrochloric acid and the acid (60) obtained by treating in the conventional manner was treated with diazomethane to give the title compound (61).

Yield: 5.74g

4-7) Preparation of methyl 2-[(1S,2R,3R,5S)-2-(3,3-ethylene

dioxyoctyl)-3-(tetrahydropyranyloxy)-5-(t-butylsilyl-oxy)-cyclopentyl]acetate (62)

To a solution of methyl 2-[(1S,2R,3R,5S)-2-(3,3-ethylenedioxyoctyl)-3-(tetrahydropyranyloxy)-5-hydroxycyclopentyl]acetate (61) in DMF (80ml) were added t-butyldimethylsilyl chloride (2.11g) and imidazol (0.95g), and the resultant mixture was stirred. The crude product obtained by treating in the conventional manner was subjected to silica gel column chromatography to give the title compound (62).

Yield: 5.41g (71.2g)

4-8) Preparation of 2-[(1S,2R,3R,5S)-2-(3,3-ethylenedioxy-octyl)-3-(tetrahydropyranyloxy)-5-(t-butyldimethyl-silyloxy)cyclopentyl]ethanol (63)

Methyl 2-[(1S,5R,6R,7R)-2-(3,3-ethylenedioxy-octyl)-3-(tetrahydropyranyloxy)-5-(t-butyldimethylsiloxy)-cyclopentyl]acetate (62) was reduced with lithium aluminium hydride in ether (150ml). The crude product obtained by treating in the conventional manner was subjected to silica gel column chromatography to give the title compound (63).

Yield: 4.81g (93.8%)

4-9) Preparation of 2-[(1S,5R,6R,7R)-2-(3,3-ethylenedioxy-octyl)-3-(tetrahydropyranyloxy)-5-(t-butyldimethyl-silyloxy)cyclopentyl]acetaldehyde (64)

A solution of 2-[(1S,5R,6R,7R)-2-(3,3-ethylene-

dioxy-octyl)-3-(tetrahydropyranyloxy)-5-(t-butylsiloxy) cyclopentyl]ethanol (63) in dichloromethane (50 ml) was subjected to Swan oxidation using oxalyl chloride (1.78g), DMSO (2.19g) and triethylamine (4.37g) to give the title compound (12).

Yield: 4.60g (96.0%)

4-10) Preparation of 1-[(1R,2R,4S,5R)-2-tetrahydropyranyl-oxy-4-t-butylsilyloxy-5-{2(RS)-hydroxy-3,3-difluoro-7-t-butyldimethylsilyloxy-4-heptynyl}-cyclopentyl]-3,3-ethylenedioxy-octane (65)

To a solution of 2-[(1S,2R,3R,5S)-2-(3,3-ethylenedioxyoctyl)-3-(tetrahydropyranyloxy)-5-(t-butylsiloxy)cyclopentyl]acetaldehyde (64) (1.00 g) in THF (25 ml) was added activated zinc powder (2.54g), and while cooling on ice, the solution of 1-bromo-1,1-difluoro-5-(t-butyl-dimethylsilyloxy)-2-pentyne (i) (0.92g) in THF (5ml) was added dropwise to the resultant mixture. To the resultant solution was added mercury chloride (0.11g) and the resultant mixture was stirred under ultrasonic irradiation. The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to silica gel column chromatography to give the title compound (65).

Yield: 1.40g (95.9%)

4-11) Preparation of 1-[(1R,2R,4S,5R)-2-tetrahydropyranyl-

oxy-4-hydroxy-5-{2(RS),7-dihydroxy-3,3-difluoro-4-heptyl}cyclopentyl]-3,3-ethylenedioxyoctane (67)

A solution of 1-[(1R,2R,4S,5R)-2-tetrahydropyranyloxy-4-t-butylsilyloxy-5-{2(RS)-hydroxy-3,3-difluoro-7-t-butyldimethylsilyloxy-4-heptynyl}cyclopentyl]-3,3-ethylenedioxy-octane (65) (0.96g) in THF (15 ml) was cooled on ice and tetrabutyl ammonium fluoride (1M, 0.57ml) was added thereto and the resultant mixture was stirred for 12 hours. The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to silica gel chromatography to give the triol (66) (0.492g).

The triol (66) was subjected to catalytic hydrogenation over 5% Pd/C (0.06g) in ethyl acetate (50ml). The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to silica gel chromatography to give the title compound (67).

Yield: 0.487g (98.6%)

4-12) Preparation of 5,5-difluoro-6-keto-11-pyranyloxy-15,15-ethylenedioxy-13,14-dihydro-PGE_1 methyl ester (70)

A solution of 1-[(1R,2R,4S,5R)-2-tetrahydropyranyloxy-4-hydroxy-5-{2(RS),7-dihydroxy-3,3-difluoro-4-heptynyl}cyclopentyl]-3,3-ethylenedioxyoctane (67) (0.487 g) in dichloromethane (18 ml) was subjected to Swan oxidation using oxalyl chloride (1.17g), DMSO (1.51g) and triethylamine (3.1g) to give the

diketoaldehyde (68) (0.321g, Y: 67.3%).

The obtained diketoaldehyde (68) (0.212g) was subjected to Jones oxidation using Jones reagent (2.67M 153.6μ) at a temperature between -50°C and -40°C to give the carboxylic acid (69), which was reacted with diazomethane in order to obtain methyl ester. The obtained crude product was subjected to silica gel column chromatography to give the title compound (70).

Yield: 0.152g (67.8%)

4-13) Preparation of 5,5-difluoro-13,14-diketo-PGE_1 methyl ester (72)

A solution of 5,5-difluoro-6-keto-11-pyranyloxy-13,14-dihydro-15,15-ethylenedioxy-PGE_1 methyl ester (70) (0.152g) in a mixed solvent of acetic acid/THF /water (2/1/1) (6ml) was kept at 45-50° for 2.5 hours. The reaction mixture was treated in conventional manner and the obtained crude product was subjected to silica gel column chromatography to give the title compound (72).

Yield: 0.101g (87.0%)

* 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($C_6H_{11}CO^+$)

Preparation of Starting Material:5-(t-butyl-dimethylsiloxy)-1-bromo-1,1-difluoro-3-pentyne (i)

1) Preparation of 5-(t-butyldimethylsiloxy)-3-pentyne (h)

To a solution of 3-butyn-1-ol (g) (10.0g) in DMF (80ml) were added t-butyldimethylsilyl chloride (21.5g) and imidazol (10.6g), and the resultant mixture was kept at 35°C for 7 hours. The reaction mixture was treated in the conventional manner and the obtained crude product was distilled to give the title compound (h).

Yield: 17.4g (66%)

2) Preparation of 5-(t-butyl-dimethylsiloxy-1-bromo-1,1-difluoro-3-pentyne) (i)

A solution of 5-(t-butyldimethylsiloxy)-3-pentyne (h) (8.00g) in THF (100ml)was cooled to -20°C and n-butyl lithium (1.6M, 27.1ml) was added dropwise thereto. The resultant mixture was stood at 0°C and a solution of dibromodifluoromethane in THF (5ml) was added, and the mixture was stirred for 2 hours. The reaction mixture was treated in the conventional manner and the obtained crude product was subjected to silica gel column chromatography to give the title compound (i).

Yield: 3.67g (27%)

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-dimethyl-PGE_2	0.2
nonion surfactant	2
distilled water	98

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

Formulation Example 3

13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGE_2 (50mg) dissolved in methanol (10ml) was mixed with mannitol (18.5g). The mixture was screened (with a sieve, the pore size of which being 30 mm in diameter), dried and screened again. The powders thus obtained were mixed with fine-grain silica gel (Aerosil*, 200g) and filled in No.3 hard gelatin capsules (100) to give enteric capsules which contain 0.5mg

of 13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGE_2 per capsule.

* Trade Mark

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.

* Trade Mark

Formulation Example 5

(Soft gelatine capsules)

	(Parts by weight)
13,14-dihydro-15-keto-16,16-difluoro-20-methyl-PGE_1 methyl ester	1
Panasate*	20

The above ingredients were mixed and filled in soft gelatine capsules.

* Trade Mark

Formulation Example 6

(Enteric capsules)

16-desbutyl-13,14-dihydro-15-keto-16-(m-trifluoromethyl)phenoxy-$PGF_{2\alpha}$ methyl ester (50mg) dissolved in methanol (10ml) was mixed with mannitol (18.5g). The mixture was screened (with a sieve, the pore size of which being 30 mm in diameter), dried for 90 minutes at 30°C and screened again. The powders thus obtained were mixed with fine-grain silica gel (Aerosil*, 200g) and filled in No.3 hard gelatin capsules (100) to give enteric capsules which contain 0.5mg of 13,14-dihydro-15-keto-16-desbutyl-16-m-trifluoromethylphenoxy-$PGF_{2\alpha}$ methyl ester per capsule.

* Trade Mark

Formulation Example 7

(Injectable solution)

	(Parts by weight)
13,14-dihydro-6,15-diketo-5,5-difluoro-PGE_1	0.2
nonion surfactant	2
distilled water	98

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

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

Formulation Example 8

(Soft gelatine capsules)

(Parts by weight)

13,14-dihydro-15-keto-16-desbutyl-16-m-trifluoromethylphenoxy-PGE_2 methyl ester	1
Panasate*	899

The above ingredients were mixed and filled in soft gelatine capsules.

* Trade Mark

Test Example 1

(Method)

As the test animals, male Crj-Wistar rats (weight: 240-270g, 7-8 weeks old), fasted overnight, were used.

The rats were anesthetized by administration of pentobarbital (35 mg/kg). After shaving, the abdominal skin was incised along the median line and the duodenal opening of the bile duct was exposed. A mixed solution of 3ml of 10% sodium taurocholic acetate and a solution of trypsin (Cryst. Type III) 1mg in 0.3ml water (hereinafter, this mixed solution is refered simply to as "mixed solution") was antidromically infused at 0.1 ml/body in the duodenal opening of the bile duct through a polyethylene tube. The bile duct was blocked at the hepatic side with forceps during the infusion in order to prevent flowing-in of the mixed solution into the liver and duodenum. After the

infusion was completed, the forceps and cannula were removed.

The test compound was dissolved in the physiological saline and administred subcutaneously at the dorsal skin in a dose of 1ml/kg before 30 minutes, after 2 hours and after 4 hours of the operation. After 6 hours of the operation, the animals were exsanguinated and amylase activity in the serum was dertermined. As the test compound, 13,14-dihydro-15-keto-16,16-difluoro-PGE_2 was used. The grouping of animals was as follows:

Group	Drug	Dose	Mixed Solution	number
1	Vehicle	1ml/kg	0	6
2	Vehicle	1ml/kg	yes	8
3	Test Compound	10μg/kg	yes	8
4	Test Compound	100μg/kg	yes	9

(Vehicle : Physiological saline)

(Results)

The results are shown in the following Table 1.

Table 1

Group	Amylase activity (Somogyi U)
1	1308 ± 292
2	10564 ± 3226
3	7736 ± 2297
4	6368* ± 1673

(Dunnet test, * : $P<0.01$)

From the above results, it can be clearly seen that the test compound has a pancreatic function improving activity in the experimental acute pancreatitis.

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.

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

^1H NMR ($CDCl_3$) δ 0.93(t,3H,J=7.5 Hz), 1.20-2.70(m,2H), 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-PGE_1 isopropyl ester

^1H NMR ($CDCl_3$) δ 0.93(t,3H,J=7.5 Hz), 1.23(d,J=7.5 Hz), 1.20-2.70(m,26H), 3.15(s,1H), 4.18(m,1H), 5.00(ht,1H,J=7.5 Hz)

MS (DI-EI) m/z 432(M^+), 414(M^+-H_2O)

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

^1H NMR ($CDCl_3$) δ 0.93(t,3H,J=7.5 Hz), 1.23(d,6H,J=7.5 Hz), 1.30-2.70(m,22H), 2.78(,1H), 4.20(m,1H), 5.00(ht,1H,J=7.5 Hz)

MS (DI-EI) m/z 430(M^+), 412(M^+-H_2O)

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

^1H NMR ($CDCl_3$) δ 0.98(t,3H,J=7.5 Hz), 1.50-2.70(m,20H), 2.94 (s,1H), 3.68(s,3H), 4.20(m,1H), 5.40(m,2H)

MS (DI-EI) m/z 388(M^+), 370(M^+-H_2O), 357($M^+-H_2O-CH_3O$), 355($M^+-H_2O-CH_3$)

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

^1H NMR ($CDCl_3$) δ 0.98(t,3H,J=7.5 Hz), 1.40-2.70(m,22H), 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-11-dehydroxy-11-methyl-PGE_2 methyl ester

^1H NMR ($CDCl_3$) δ 0.93(t,3H,J=7.5 Hz), 1.14(d,3H,J=6 Hz), 1.25-2.80(m,22H), 3.63(s,3H), 5.38(m,2H)

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

* 13,14-dihydro-15-keto-16,16-difluoro-PGD_2 methyl ester

^1H NMR ($CDCl_3$) δ 0.91(t,3H,J=7.5 Hz), 1.20-3.20(m,23H), 3.68 (s,3H), 4.44(m,1H,J=1.2 Hz), 5.49(m,2H)

MS (DI-EI) m/z 402(M^+), 384(M^+-H_2O), 353($M^+-H_2O-CH_3O$)

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

^{1}H NMR ($CDCl_3$) δ 0.90(t,3H,J=7.5 Hz), 1.20-2.70(m,26H), 4.20 (m,1H), 5.41(m,2H)

MS (DI-EI) m/z 402(M^+), 384(M^+-H_2O), 366(M^+-2H_2O)

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

^{1}H NMR ($CDCl_3$) δ 0.89(t,3H,J=7.5 Hz), 1.20-2.70(m,26H), 2.93 (s,1H), 3.68(s,3H), 4.20(m,1H), 5.41(m,2H)

MS (DI-EI) m/z 430(M^+), 412(M^+-H_2O), 399(M^+-CH_3O), 381($M^+-H_2O-CH_3O$)

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

^{1}H NMR ($CDCl_3$) δ 0.94(t,3H,J=7.5 Hz), 1.20-2.70(m,27H), 4.21 (m,1H), 5.43(m,2H)

MS (DI-EI) m/z 416(M^+), 398(M^+-H_2O), 380(M^+-2H_2O)

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for treatment of a pancreatic disease comprising a 15-ketoprostaglandin compound in association with a pharmaceutically acceptable carrier, diluent or excipient.

2. The composition according to claim 1, wherein said 15-keto-prostaglandin compound is a 16-mono- or di-halo-15-keto-prostaglandin compound.

3. The composition according to claim 1, wherein said 15-keto-prostaglandin compound is a 13,14-dihydro-16-mono- or di-halo-15-keto-prostaglandin compound.

4. The composition according to claim 1, wherein said 15-keto-prostaglandin compound is a 13,14-dihydro-16-mono- or di-fluoro-15-keto-prostaglandin compound.

5. The composition according to claim 1, wherein said 15-keto-prostaglandin compound is a 6,15-diketo-prostaglandin compound.

6. The composition according to claim 1, wherein said 15-keto-prostaglandin compound is a 13,14-dihydro-6,15-diketo-prostaglandin compound.

7. The composition according to claim 1, wherein said 15-keto-prostaglandin compound is a 15-keto-20-alkyl-prostaglandin compound.

8. The composition according to claim 1, wherein said 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-

20-alkyl-prostaglandin compound.

9. The composition according to claim 1, wherein said 15-keto-prostaglandin compound is a 13,14-dihydro-6,15-diketo-5-mono or di-halo-prostaglandin compound.

10. The use of a composition according to any one of claims 1 to 9, for the treatment of pancreatic disease.