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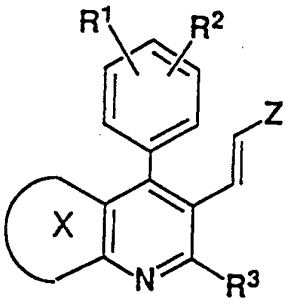
(54) Title: CONDENSED PYRIDINE TYPE MEVALONOLACTONE INTERMEDIATE AND PROCESS FOR ITS PRODUCTION

(57) Abstract

The present invention provides a synthetic condensed pyridine type mevalonolactone intermediate of formula (1), wherein Z is (a) or (b), each of R^{9a} and R^{9b} is a hydroxyl-protecting group, and R^{10} is methyl, ethyl, propyl, isopropyl, tert-butyl, tetrahydropyranyl, allyl, benzyl, triphenylmethyl, trimethylsilyl or tert-butyldimethylsilyl. The intermediate is useful for producing a 7-position substituted (E, 3R, 5S)-3,5-dihydroxy-6-heptenoic acid or its 1,5-lactone or its enantiomer which has an activity as an HMG-CoA reductase inhibitor and which is useful as a hypercholesterolemia therapeutic agent.



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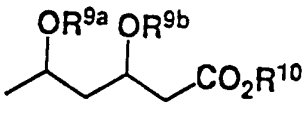
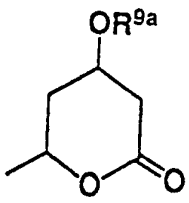


(a)



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SPECIFICATION

CONDENSED PYRIDINE TYPE MEVALONOLACTONE INTERMEDIATE AND PROCESS FOR ITS PRODUCTION

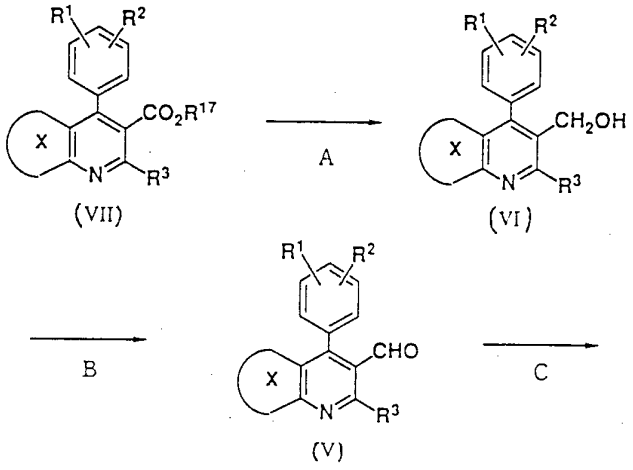
TECHNICAL FIELD

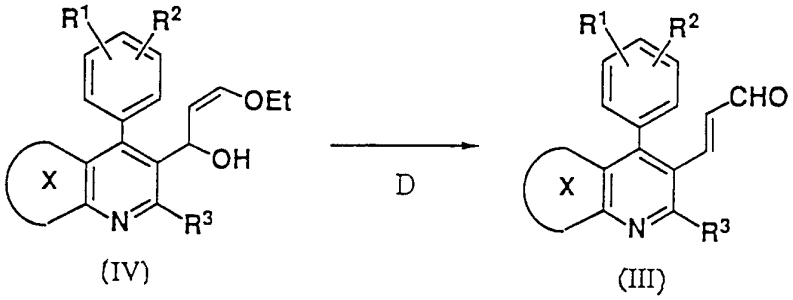
The present invention relates to a novel intermediate for a condensed pyridine type mevalonolactone derivative which is a HMG-CoA reductase inhibitor and which is useful as a hypercholesterolemia therapeutic agent or as an arteriosclerosis therapeutic agent, and a process for its production as well as a novel condensed pyridine derivative useful as the starting material thereof.

BACKGROUND ART

Heretofore, a condensed pyridine type mevalonolactone derivative has been synthesized by stepwisely extending the side chain of a condensed pyridine ring moiety, as disclosed in European Patent No. 535548 or Japanese Patent Application No. 257870/1991. (Scheme 1)

Scheme 1





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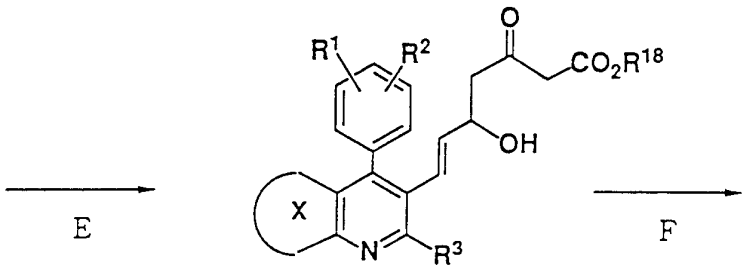
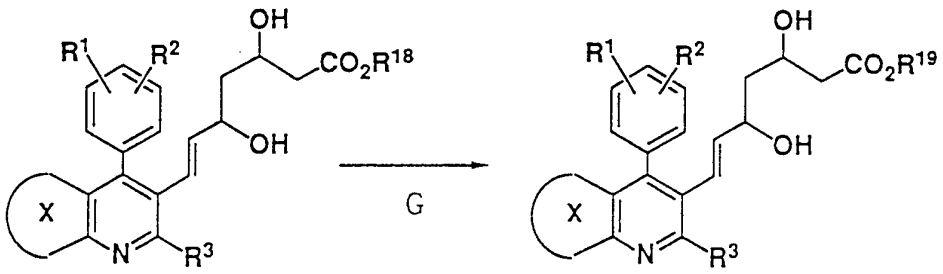
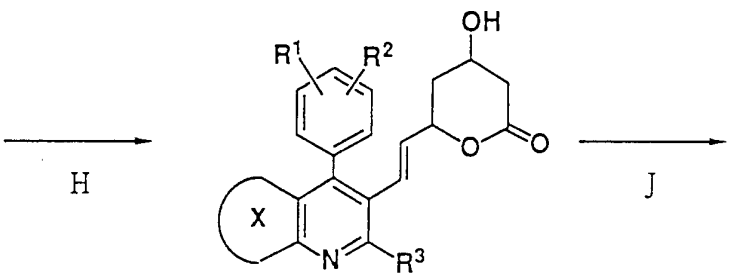


E (II) F

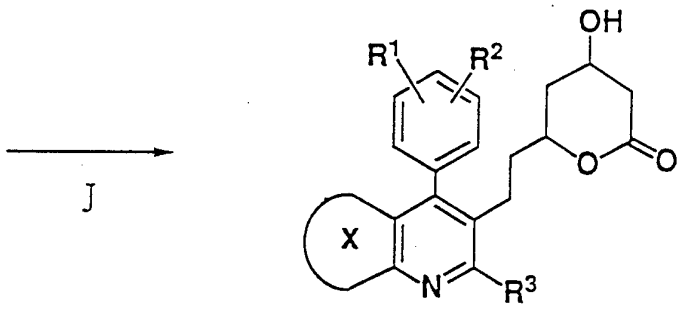


(I-1) G (I-2) (R^{19}=H)

(I-5) (R^{19}=pharmaceutically acceptable salt)



H (I-3) J



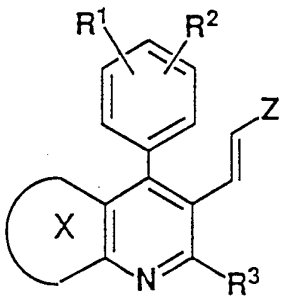
(I-4)

This method provides a relatively good yield in each step, but has drawbacks such that it is cumbersome including many steps, special conditions (an extremely low temperature, a borane reactant) are required to control the steric configuration of two hydroxyl groups (a syn-form is highly active), since the side chain is stepwisely extended, and a highly sophisticated asymmetrical synthetic method is required or an inefficient optical resolution has to be carried out to obtain an optically active substance (a (3R,5S)-form is highly active).

DISCLOSURE OF THE INVENTION

The present invention provides a novel process developed to solve such problems of the conventional method and a novel intermediate useful for the process.

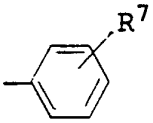
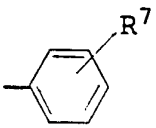
A condensed pyridine type mevalonolactone intermediate of the formula (1)



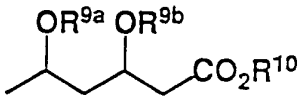
(1)

wherein ring X is a benzene ring, a substituted benzene ring or a substituted 5- or 6-membered heteroaromatic ring,

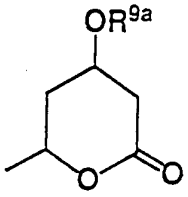
each of R^1 and R^2 which are independent of each other, is hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-3} alkoxy, butoxy, i-butoxy, sec-butoxy, tert-butoxy, $R^{20}R^{21}N$- (wherein each of R^{20} and R^{21} which are independent of each other, is hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy, hydroxymethyl or $-O(CH_2)_\ell OR^{22}$ (wherein R^{22} is hydrogen or C_{1-3} alkyl, and ℓ is 1, 2, or 3); or R^1 and R^2 together form -CH=CH-CH=CH- or methylenedioxy, when they are at the o-position to each other;

R^3 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl or  (wherein R^7 is hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-3} alkylthio, chloro, bromo, fluoro, chloromethyl, trichloromethyl, trifluoromethyl, trifluoromethoxy, trichloromethoxy, difluoromethoxy, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy or hydroxymethyl); or C_{1-3} alkyl substituted by one  (wherein R^7 is as defined above) and zero, one or two C_{1-3} alkyl;

Z is

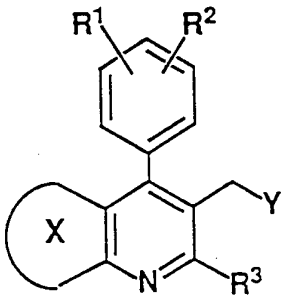


or



(each of R^{9a} and R^{9b} represents a hydroxyl-protecting group and is independently methoxymethyl, 2-methoxyethoxymethyl, tetrahydropyranyl, 4-methoxytetrahydropyranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, allyl, benzyl, p-methoxybenzyl, triphenylmethyl, trimethylsilyl, tert-butyldimethylsilyl or tert-butyldiphenylsilyl, or R^{9a} and R^{9b} together form isopropylidene, cyclopentylidene, cyclohexylidene or benzylidene; and

R^{10} is methyl, ethyl, propyl, isopropyl, tert-butyl, tetrahydropyranyl, allyl, benzyl, triphenylmethyl, trimethylsilyl or tert-butyldimethylsilyl), can be produced by reacting a condensed pyridine derivative of the formula (2):

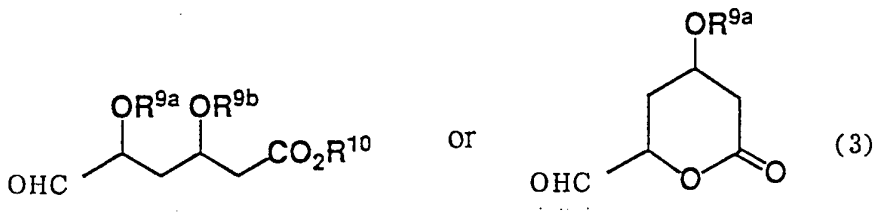


(2)

wherein ring X, R^1, R^2 and R^3 are as defined above:

Y is $P^+R^{11}R^{12}R^{13}Hal^-$ or $P(W)R^{14}R^{15}$ (wherein each of R^{11}, R^{12} and R^{13} which are independent of one another, is

methyl, ethyl, propyl, isopropyl, butyl, 2-chloroethyl, 2,2,2-trifluoroethyl, phenyl, methoxyphenyl, methylphenyl, pentafluorophenyl or benzyl, each of R^{14} and R^{15} which are independent of each other, is methyl, ethyl, propyl, isopropyl, butyl, 2-chloroethyl, 2,2,2-trifluoroethyl, phenyl, methoxyphenyl, methylphenyl, pentafluorophenyl, benzyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, 2-chloroethoxy, 2,2,2-trifluoroethoxy, phenoxy, methoxyphenyloxy, methylphenyloxy, pentafluorophenyloxy or benzyloxy, or R^{14} and R^{15} together form a 5- or 6-membered ring, Hal is chlorine, bromine or iodine, and W is O or S, with a base to form an anion, which is then condensed with a compound of the formula (3):

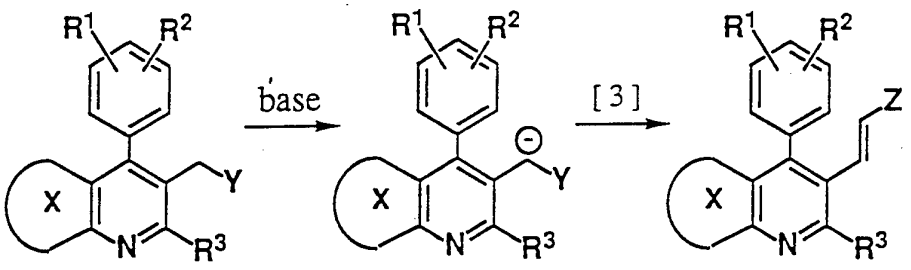


(3)

wherein R^{9a}, R^{9b} and R^{10} are as defined above.

Especially when Y in the formula (2) is $P(O)Ph_2$, the yield of the condensation reaction and the stereo selectivity (trans-selectivity) will be excellent, and the compound of the formula (1) can be obtained in good yield and with a high purity. (Scheme 2)

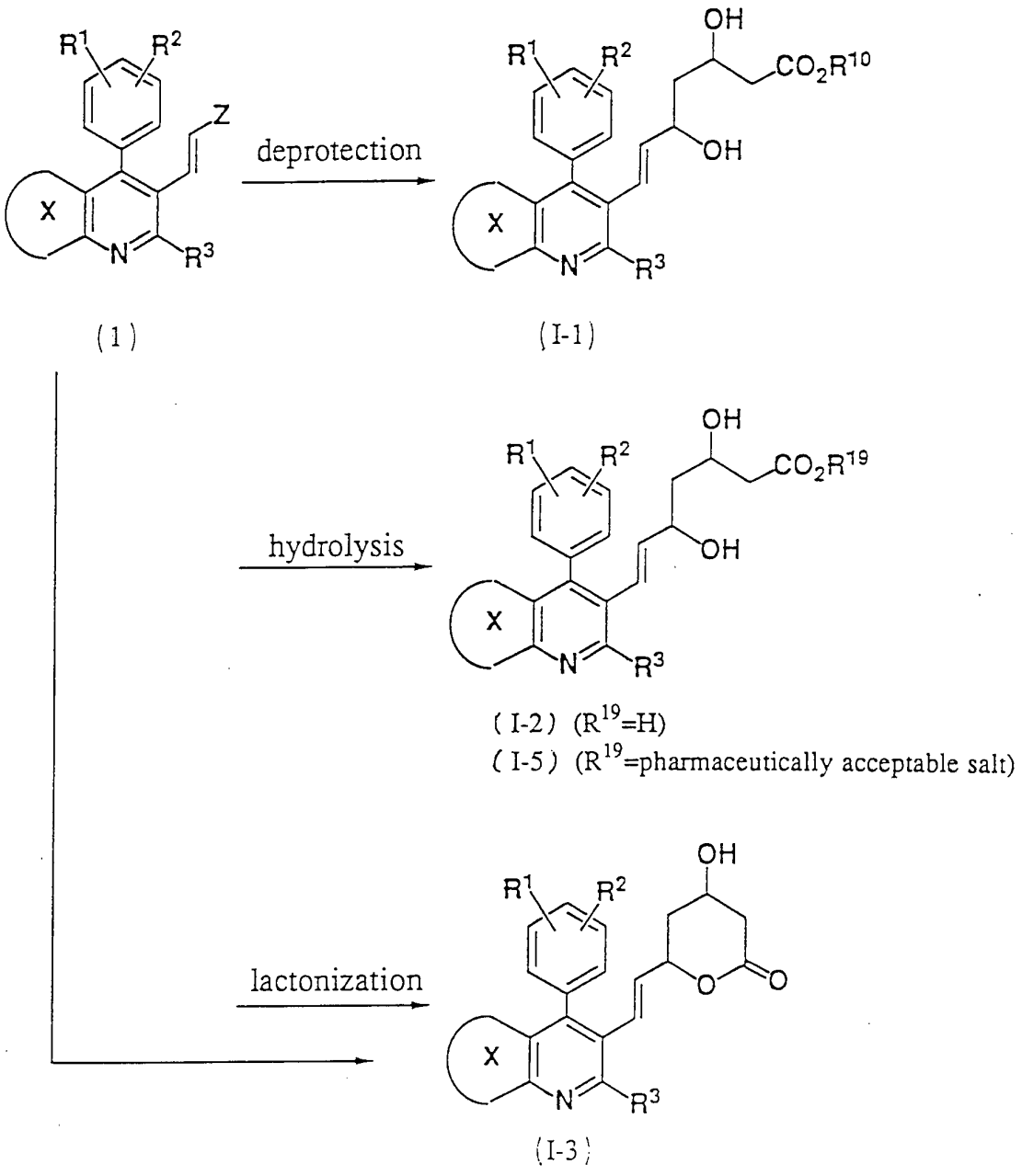
Scheme 2



(2) (VIII) (1)

The intermediate of the formula (1) is a novel compound, and it is a useful intermediate which can easily be led to a condensed pyridine type mevalonolactone derivative (I) which is a HMG-CoA reductase inhibitor and which is useful as a hypercholesterolemia therapeutic agent or as an arteriosclerosis therapeutic agent, stepwisely or in a single step by hydrolyzing R^{9a} and R^{9b} which are hydroxyl-protecting groups, and R^{10} which is an ester. (In the formulas, (I-1) represents a condensed pyridine type mevalonic acid ester, (I-2) represents a condensed pyridine type mevalonic acid, (I-5) represents a pharmaceutically acceptable salt of the condensed pyridine type mevalonic acid, and (I-3) represents a condensed pyridine type mevalonolactone.) (Scheme 3)

Scheme 3



(1)

(I-1)

(I-2) (R^{19}=H)

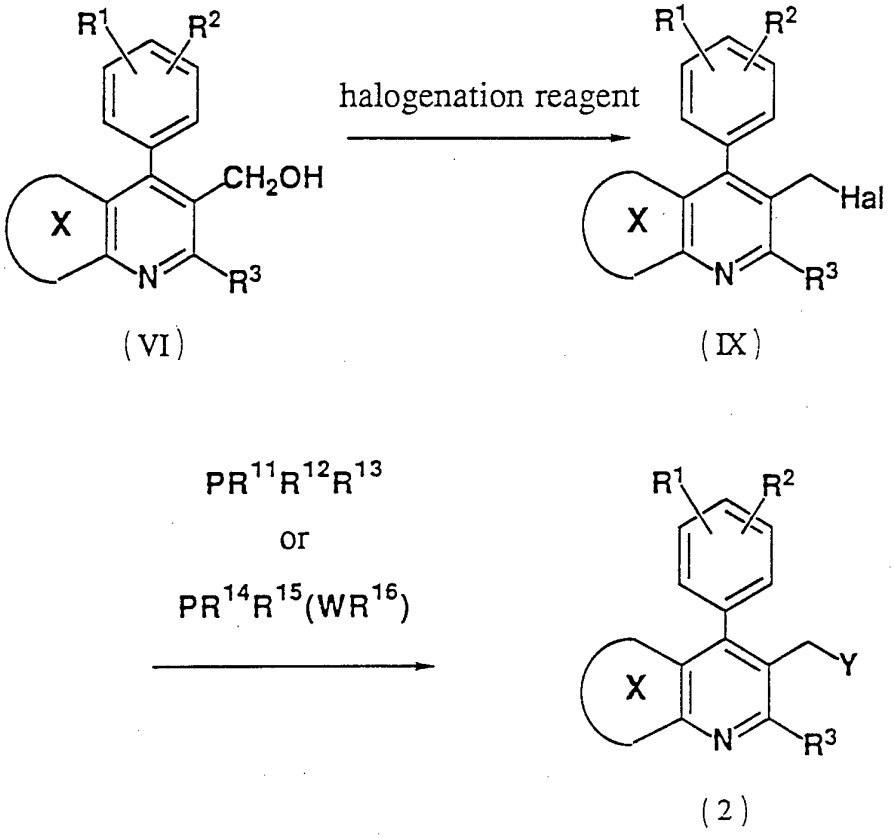
(I-5) (R^{19}=pharmaceutically acceptable salt)

(I-3)

These compounds respectively have four stereoisomers depending upon the steric configurations of hydroxyl groups of the compound of the formula (3) to be used, and they can be produced by the process of the present invention.

The compound of the formula (2) is also novel, and it can be synthesized from a conventional intermediate in accordance with Scheme 4.

Scheme 4

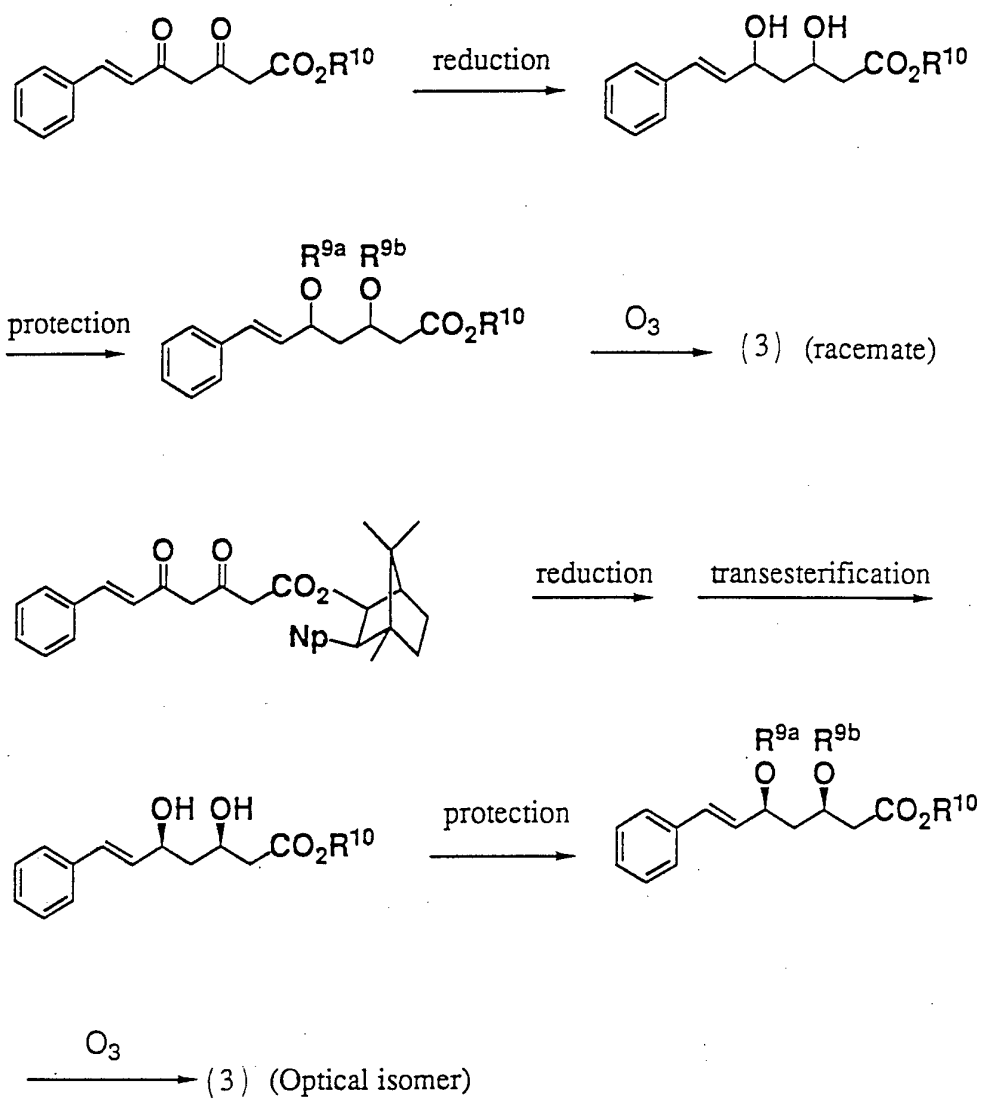


(VI) (IX) (2)

The hydroxyl group of the compound of the formula (VI) is treated by a halogenating agent such as PBr_3 to obtain a halogenated compound of the formula (IX). When the halogenated compound is reacted with $PR^{11}R^{12}R^{13}$ (wherein R^{11}, R^{12} and R^{13} are as defined above), a phosphonium salt (a compound of the formula (2) wherein Y is $P^{+}R^{11}R^{12}R^{13}Hal^{-}$) can be obtained. When the halogenated compound is subjected to an Arbusow reaction with $PR^{14}R^{15}(WR^{16})$ (wherein R^{14}, R^{15} and W are as defined above, and R^{16} is methyl, ethyl, propyl, isopropyl, butyl, 2-chloroethyl, 2,2,2-trifluoroethyl, phenyl, methoxyphenyl, methylphenyl, pentafluorophenyl or benzyl), or the above-mentioned phosphonium salt is hydrolyzed, a compound of the formula (2) wherein Y is $P(W)R^{14}R^{15}$ (wherein R^{14}, R^{15} and W are as defined above) can be prepared.

The compound of the formula (3) can be synthesized by the method of Scheme 5.

Scheme 5



The condensation reaction of the condensed pyridine derivative of the formula (2) with the aldehyde compound of the formula (3) is carried out by withdrawing a hydrogen atom adjacent to Y in the formula (2) by means of a base in an anhydrous inert solvent to form an anion, which is then reacted with the aldehyde compound of the formula (3).

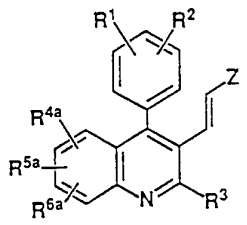
The inert solvent may, for example, be an aliphatic

hydrocarbon, an aromatic hydrocarbon or an ether type solvent. Preferred is an ether type solvent such as diethyl ether, 1,2-diethoxyethane, 1,2-dimethoxyethane or tetrahydrofuran. Further, as a stabilizer for the anion, a polar solvent such as hexamethylphosphoric acid triamide, dimethylsulfoxide or dimethylimidazolidone, may be employed, as the case requires.

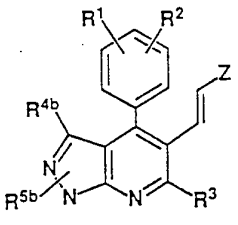
The base may, for example, be a sodium compound such as sodium hydride or sodium amide, a potassium compound such as tert-butoxypotassium, a lithium compound such as butyl lithium or phenyl lithium, or an amide lithium compound such as 2,2,6,6-tetramethylpiperidide lithium.

The reaction temperature varies to some extent depending upon the substrate. However, it is from -78 to 30°C at the time of the addition of the base, and the reaction with the aldehyde is conducted at a temperature of from -70°C to the refluxing temperature of the solvent.

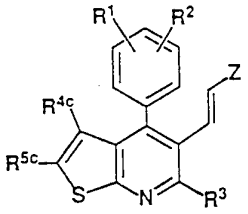
The compound of the formula (1) thus synthesized, can readily be led to a condensed pyridine type mevalonolactone derivative (I) by the method of the above-mentioned Scheme 3. The condensed pyridine type mevalonolactone intermediate of the formula (1) as the compound of the present invention includes compounds of the formulas (1a), (1b) and (1c):



(1a)

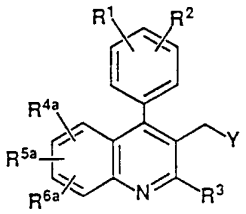


(1b)

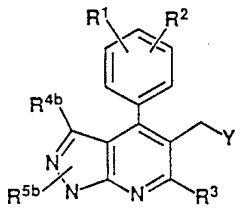


(1c)

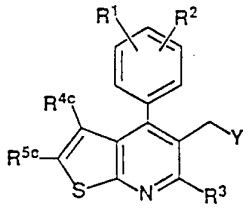
Further, the condensed pyridine type mevalonolactone intermediate of the formula (2) as the compound of the present invention includes compounds of the formulas (2a), (2b) and (2c):



(2a)



(2b)



(2c)

As the substituents of the above compounds, the following substituents may be mentioned. In any compounds, substituents R^1, R^2, R^3, Z and Y are as defined above.

Each of R^1 and R^2 is preferably hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, pentyl, i-pentyl, 1,2-dimethylpentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclohexyl, methoxy, ethoxy, propoxy, i-propoxy, butoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy or

hydroxymethyl.

R^3 is preferably hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, pentyl, i-pentyl, 1,2-dimethylpentyl, hexyl, heptyl, octyl, vinyl, 1-propenyl, 1-methylvinyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1,2-dimethyl-1-propenyl, cyclopropyl, cyclobutyl, cyclohexyl, 1-methylcyclopropyl, 2-methylcyclopropyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethylphenyl, 3,4-dichlorophenyl, 3-trifluoromethylphenyl, benzyl, 4-clorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, 2-phenethyl or 1-methylbenzyl.

In the quinoline type compounds of the formula (1a) and (2a), each of R^{4a}, R^{5a} and R^{6a} which are independent of one another, is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-3} alkoxy, butoxy, i-butoxy, sec-butoxy, $R^{26}R^{27}N$- (wherein R^{26} and R^{27} which are independent of each other, is hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy, hydroxymethyl or -$O(CH_2)_mOR^{28}$ (wherein R^{28} is hydrogen or C_{1-3} alkyl, and m is 1, 2 or 3); or

R^{4a} and R^{5a} together form -CH=CH-CH=CH-; or

R^{4a} and R^{5a} together form $-OC(R^{29})(R^{30})O-$ (wherein

each of R^{29} and R^{30} which are independent of each other, is hydrogen or C_{1-3} alkyl) when they are at the o-position to each other.

The following substituents may be mentioned as preferred substituents for R^{4a}, R^{5a} and R^{6a}.

Namely, when both R^{5a} and R^{6a} are hydrogen, R^{4a} is preferably hydrogen, 5-fluoro, 6-fluoro, 7-fluoro, 8-fluoro, 5-chloro, 6-chloro, 7-chloro, 8-chloro, 5-bromo, 6-bromo, 7-bromo, 8-bromo, 5-methyl, 6-methyl, 7-methyl, 8-methyl, 5-methoxy, 6-methoxy, 7-methoxy, 8-methoxy, 5-trifluoromethyl, 6-trifluoromethyl, 7-trifluoromethyl, 8-trifluoromethyl, 6-trifluoromethoxy, 6-difluoromethoxy, 8-hydroxyethyl, 5-hydroxy, 6-hydroxy, 7-hydroxy, 8-hydroxy, 6-ethyl, 6-butyl or 7-dimethylamino.

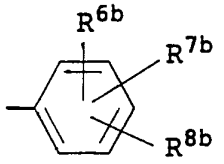
When R^{6a} is hydrogen, R^{4a} and R^{5a} may together represent 6-chloro-8-methyl, 6-bromo-7-methoxy, 6-methyl-7-chloro, 6-chloro-8-hydroxy, 5-methyl-2-hydroxy, 6-methoxy-7-chloro, 6-chloro-7-methoxy, 6-hydroxy-7-chloro, 6-chloro-7-hydroxy, 6-chloro-8-bromo, 5-chloro-6-hydroxy, 6-bromo-8-chloro, 6-bromo-8-hydroxy, 5-methyl-8-chloro, 7-hydroxy-8-chloro, 6-bromo-8-hydroxy, 6-methoxy-7-methyl, 6-chloro-8-bromo, 6-methyl-8-bromo, 6,7-difluoro, 6,8-difluoro, 6,7-methylenedioxy, 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo or 6,8-dibromo.

Further, R^{4a}, R^{5a} and R^{6a} may together represent 5,7-dimethoxy-8-hydroxy, 5,8-dichloro-6-hydroxy, 6,7,8-

trimethoxy, 6,7,8-trimethyl, 6,7,8-trichloro, 5-fluoro-6,8-dibromo or 5-chloro-6,8-dibromo.

Quinoline compounds of the formulas (1a) and (2a) wherein R^1 is p-fluoro, each of R^2, R^{4a}, R^{5a} and R^{6a} is hydrogen, and R^3 is cyclopropyl, are preferred.

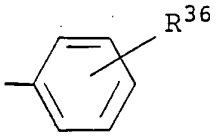
In the pyrazolopyridine type compounds of the formulas (1b) and (2b), R^{4b} is hydrogen, C_{1-8} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, C_{2-6} alkenyl, α- or β-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, fluoro, chloro, bromo,



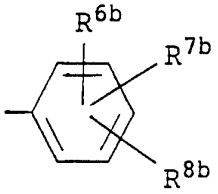
(wherein each of R^{6b}, R^{7b} and R^{8b} which are independent of one another, is hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-3} alkylthio, chloro, bromo, fluoro, $-NR^{31}R^{32}$ (wherein each of R^{31} and R^{32} which are independent of each other, is C_{1-3} alkyl), chloromethyl, trichloromethyl, trifluoromethyl, trifluoromethoxy, trichloromethoxy, difluoromethoxy, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy, hydroxymethyl or $-O(CH_2)_nOR^{33}$ (wherein R^{33} is hydrogen or C_{1-3} alkyl, and n is 1, 2 or 3), or

when R^{8b} is hydrogen, R^{6b} and R^{7b} together form $-OC(R^{34})(R^{35})O-$ when they are at the o-position to each other (wherein each of R^{34} and R^{35} which are independent of each other, is hydrogen or C_{1-3} alkyl group), or

when R^{7b} and R^{8b} are simultaneously hydrogen, R^{6b} is

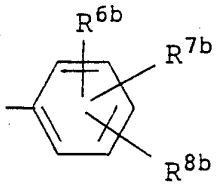


(wherein R^{36} is hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, trifluoromethyl, chloro, bromo or fluoro), phenyl-C_{2-3} alkenyl wherein the phenyl group may be substituted by C_{1-4} alkyl, C_{1-3} alkoxy, fluorine, chlorine or bromine, or C_{1-3} alkyl substituted by one member selected from C_{1-3} alkoxy, naphthyl and



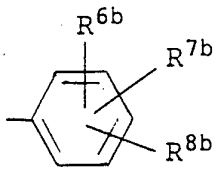
(wherein R^{6b}, R^{7b} and R^{8b} are as defined above) and zero, one or two C_{1-8} alkyl;

R^{5b} is bonded to nitrogen atom at the 1- or 2-position of the pyrazolopyridine ring, and such R^{5b} is hydrogen, C_{1-8} alkyl, C_{1-3} alkyl substituted by from one to three fluorine atoms, C_{3-7} cycloalkyl, α- or β-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl or



(wherein R^{6b}, R^{7b} and R^{8b} are as defined above); or

C_{1-3} alkyl substituted by one member selected from C_{1-3} alkoxy, hydroxy, naphthyl and



(wherein R^{6b}, R^{7b} and R^{8b} are as defined

above) and by zero, one or two C_{1-8} alkyl.

R^1, R^2, R^3 and Z are as defined with respect to the formula (1).

The following substituents may be mentioned as preferred substituents for R^{4b} and R^{5b}.

Namely, R^{4b} is preferably hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, cyclopropyl, cyclohexyl, phenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-bromophenyl, 2-, 3- or 4-tolyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-trifluoromethylphenyl, 2-, 3- or 4-chloromethylphenyl, 3- or 4-ethoxyphenyl, 4-(2-methylbutyl)phenyl, 4-heptylphenyl, 4-octylphenyl, 4-pentylphenyl, 4-hexylphenyl, 4-propylphenyl, 4-butylphenyl, 4-tert-butylphenyl, 4-butoxyphenyl, 4-pentyloxyphenyl, 4-hexyloxyphenyl, 4-heptyloxyphenyl, 4-octyloxyphenyl, 4-phenoxyphenyl, 4-biphenyl, 4-trichloromethoxyphenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 2,3-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 3,4-difluorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 2,3-dichlorophenyl, 2,5-dichlorophenyl, 3,5-dichlorophenyl, 3,4-dichlorophenyl, 2,3-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-

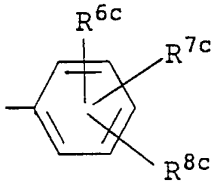
dimethoxyphenyl, 3,5-bis(trifluoromethyl)phenyl, 3,4-methylenedioxyphenyl, 2,4,6-trimethoxyphenyl, 3,4,5-trimethylphenyl or 2,4,6-triisopropylphenyl.

R^{5b} is preferably a group bonded to the nitrogen atom at the 1-position of the pyrazolopyridine ring and is methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, cyclohexyl, benzyl, 2-chlorobenzyl, 2-hydroxybenzyl, 3-trifluoromethylbenzyl, 2-phenylethyl, phenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-bromophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-tolyl, 2-, 3- or 4-trifluoromethylphenyl, 3- or 4-methoxyphenyl, 2-hydroxyphenyl, 4-isopropylphenyl, 4-tert-butylphenyl, 4-trifluoromethoxyphenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2,4,6-trichlorophenyl, 2,3,4-trichlorophenyl, 2,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3-chloro-4-tolyl, 3-chloro-6-tolyl, 4-chloro-2-tolyl, 2-chloro-6-tolyl, 2-chloro-6-fluorophenyl, 2-chloro-5-trifluoromethylphenyl, 3-chloro-4-fluorophenyl, 4-bromo-3-chlorophenyl, 2-chloro-4-trifluoromethylphenyl, 3-fluoro-6-tolyl, α-naphthyl, 2-pyridyl, 3-methyl-5-trifluoromethyl-2-pyridyl, 4-pyridyl or 2,6-dichloro-4-pyridyl.

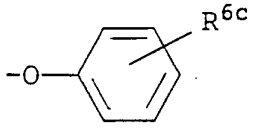
Pyrazolopyridine compounds of the formulas (1b) and (2b) wherein R^1 is p-fluoro, R^2 is hydrogen, each of R^{4b}

and R^{5b} is methyl and R^3 is cyclopropyl, are preferred.

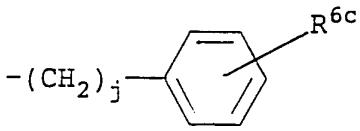
In the pyrazolopyridine type compounds of the formulas (1c) and (2c), each of R^{4c} and R^{5c} which are independent of each other, is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, fluoro, chloro, bromo,



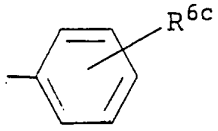
(wherein each of R^{6c}, R^{7c} and R^{8c} which are independent of one another, is hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl, trifluoromethyl, fluoro, chloro and bromo), 2-, 3- or 4-pyridyl, 2- or 5-pyrimidyl, 2- or 3-thienyl, 2- or 3-furyl,



(wherein R^{6c} is as defined above), $-NR^{37}R^{38}$ (wherein each of R^{37} and R^{38} which are independent of each other, is hydrogen, C_{1-4} alkyl,

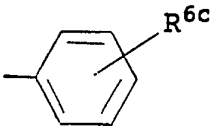


(wherein j is 1, 2 or 3, and R^{6c} is as defined above), or R^{37} and R^{38} together form $-(CH_2)_k-$ (wherein k is 3, 4 or 5)), C_{1-3} alkyl substituted by

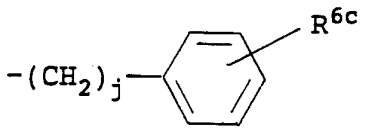


(wherein R^{6c} is as defined above), and by zero, one or two C_{1-3} alkyl, or α- or β-naphthyl; or

R^{4c} and R^{5c} together form C_{2-6} alkylene substituted by from zero to three members selected from C_{1-4} alkyl, C_{3-7} cycloalkyl, fluoro, chloro and bromo and by zero or one member selected from



(wherein R^{6c} is as defined above), or $-(CHR^{39})_p-A-(CHR^{40})_q-$ (wherein each of p and q is 0, 1, 2 or 3, A is $-C(R^{41})=C(R^{42})-$ (wherein each of R^{41} and R^{42} is hydrogen or C_{1-3} alkyl), -O-, -S- or $-N(R^{43})-$ (wherein R^{43} is hydrogen, C_{1-4} alkyl, or



(wherein R^{6c} and j are as defined above)), and each of R^{39} and R^{40} which are independent of each other, is hydrogen or C_{1-4} alkyl) or -CH=CH-CH=CH-.

The following substituents may be mentioned as preferred substituents for R^{4c} and R^{5c}.

Namely, each of R^{4c} and R^{5c} which are independent of each other, is preferably hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, pentyl, 1,2-dimethylpentyl, hexyl, heptyl, octyl, cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, 2-methylcyclohexyl, cycloheptyl, cyclopropylmethyl, vinyl, 1-methylvinyl, 1-propenyl, allyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-butenyl, 1-ethylvinyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-

propenyl, 1-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-1-butenyl, 1-i-propylvinyl, 1-methyl-1-pentenyl or phenyl; or

R^{4c} and R^{5c} together form ethylene, trimethylene, tetramethylene, pentamethylene, methyltetramethylene, chlorotetramethylene or phenyltetramethylene.

Thienopyridine compounds of the formula (1c) and (2c) wherein R^1 is p-fluoro, R^2 is hydrogen, R^{4c} is ethyl, R^{5c} is methyl and R^3 is cyclopropyl, are preferred.

BEST MODE FOR CARRYING OUT THE INVENTION

REFERENCE EXAMPLE 1

Preparation of methyl (3R*,5S*,6E)-7-phenyl-3,5-dihydroxy-6-heptenoate

Diethylmethoxyborane (1.07 ml, 8.13 mmol) was added at -78°C to a THF (20 ml)/methanol (5.0 ml) solution of methyl (E)-7-phenyl-3,5-dioxo-6-heptenoate (2.00 g, 8.12 mmol), and the mixture was stirred for 15 minutes to room temperature. The mixture was again cooled to -78°C, and sodium borohydride (1.54 g, 40.7 mmol) was added thereto. Then, the reaction mixture was stirred at -78°C for 4 hours and from -78°C to room temperature for 8 hours. Acetic acid (2.0 ml) was added to terminate the reaction, and the reaction mixture was poured into a saturated sodium hydrogencarbonate aqueous solution and extracted

with diethyl ether. The organic layer was washed with a saturated sodium chloride aqueous solution, then dried over sodium sulfate and concentrated. The residue was dissolved in methanol (10 ml) and then concentrated. This operation was repeated 10 times, and the organic boron compound was decomposed and distilled off. The product was purified by column chromatography (hexane:ethyl acetate = 2:1) to obtain methyl (3R*,5S*,6E)-7-phenyl-3,5-dihydroxy-6-heptenoate (1.16 g, 56%).

Rf = 0.08 (hexane:ethyl acetate = 2:1)

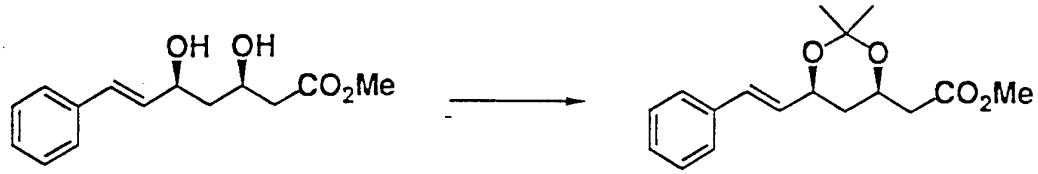
IR($CHCl_3$): 3475, 3005, 1720, 1490, 1435, 1205, 1110, 1070, 1030, 775, 730 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 7.38(d, J=7.2 Hz, 2H), 7.31(t, J=7.2 Hz, 2H), 7.24(tt, J=7.2, 1.3 Hz, 1H), 6.62(d, J=15.7 Hz, 1H), 6.21(dd, J=15.7, 6.4 Hz, 1H), 4.59(m,1H), 4.43(m, 1H), 3.74(s, 1H), 3.72(s, 3H), 3.24(s, 1H), 2.54(dd, J=19.8, 16.5 Hz, 1H), 2.52(dd, J=17.4, 16.5 Hz, 1H), 1.80(dt, J=14.3, 9.4 Hz, 1H), 1.73(dt, J=14.3, 3.1 Hz, 1H).

MS (m/z) 250(M^+, 2.5), 232(M^+-H_2O, 3.5), 218(4), 215(4), 200(15), 158(60), 104(100).

REFERENCE EXAMPLE 2

<u>Preparation of methyl (3R*,5S*,6E)-7-phenyl-3,5-isopropylidenedioxy-6-heptenoate</u>



Methyl (3R*,5S*,6E)-7-phenyl-3,5-dihydroxy-6-heptenoate (1.10 g, 4.39 mmol) obtained in Reference

Example 1 and p-toluenesulfonic acid (50 mg, catalytic amount) were dissolved in acetone dimethylacetal (10.0 ml), and the reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with diethyl ether, and the organic layer was washed with a saturated sodium hydrogencarbonate aqueous solution and a sodium chloride aqueous solution, then dried over anhydrous magnesium sulfate and concentrated. The product was purified by column chromatography (hexane:ethyl acetate = 10:1) to obtain methyl (3R*,5S*,6E)-7-phenyl-3,5-isopropylidenedioxy-6-heptenoate (1.17 g, 92%) as colorless oil.

Rf = 0.78 (hexane:ethyl acetate = 2:1)

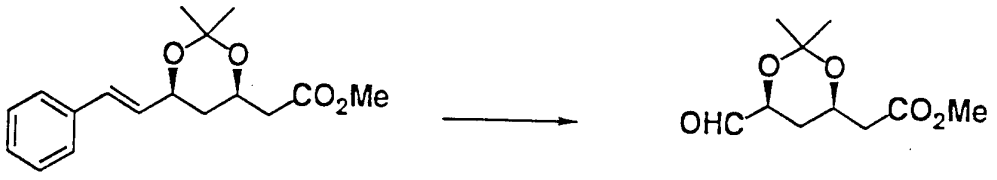
IR($CHCl_3$): 3000, 1735, 1440, 1380, 1200, 1160, 1085, 1030, 770, 740 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 7.37(d, J=7.2 Hz, 2H), 7.29(t, J=7.2 Hz, 2H), 7.24(tt, J=7.2, 1.3 Hz, 1H), 6.60(d, J=15.9 Hz, 1H), 6.16(dd, J=15.9, 6.2 Hz, 1H), 4.57(m,1H), 4.40(m, 1H), 3.70(s, 3H), 2.60(dd, J=15.6, 6.9 Hz, 1H), 2.52(dd, J=15.6, 6.2 Hz, 1H), 1.74(dt, J=12.3, 2.5 Hz, 1H), 1.54(s, 3H), 1.45(s, 3H), 1.40(dd, J=11.4, 10.2 Hz, 1H).

MS (m/z) 290(M^+, 3), 232(M^+-CO_2Me, 4), 215(15), 158(50), 104(100).

REFERENCE EXAMPLE 3

Preparation of methyl (3R*,5S*)-6-oxo-3,5-isopropylidenedioxy-6-heptenoate



Methyl (3R*,5S*,6E)-7-phenyl-3,5-isopropylidenedioxy-6-heptenoate (340 mg, 1.17 mmol) obtained in Reference Example 2 was dissolved in methanol (50 ml), and the solution was cooled to -78°C. A gas mixture of ozone and oxygen supplied from an ozone-generator, was introduced, and the introduction was continued until the reaction solution turned blue. Then, nitrogen gas was introduced to remove excess ozone gas. Then, dimethylsulfide (1.0 ml) was added thereto. The reaction mixture was stirred at room temperature for 12 hours and concentrated. The product was purified by column chromatography (hexane:ethyl acetate = 3:1) to obtain methyl (3R*,5S*)-6-oxo-3,5-isopropylidenedioxy-6-heptenoate (210 mg, 83%) as colorless crystals.

Rf = 0.14 (hexane:ethyl acetate = 2:1)

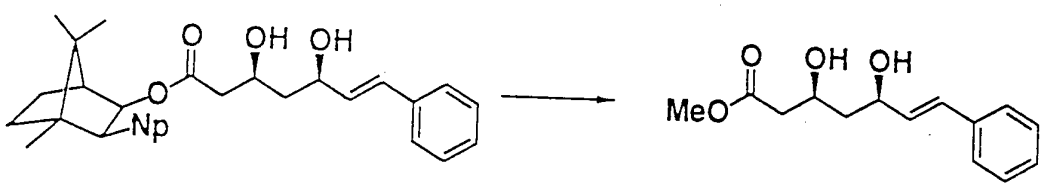
IR($CHCl_3$): 2950, 1735, 1435, 1380, 1080, 1030, 775, 730 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 9.58(s, 1H), 4.38(m,1H), 4.33(m, 1H), 3.70(s, 3H), 2.58(dd, J=15.8, 7.0 Hz, 1H), 2.44(dd, J=15.8, 6.0 Hz, 1H), 1.86(dt, J=12.9, 2.7 Hz, 1H), 1.50(s, 3H), 1.46(s, 3H), 1.35(dt, J=12.0, 12.0 Hz, 1H).

MS (m/z) 201(M^+-Me, 24), 129(31), 97(36), 59(100).

REFERENCE EXAMPLE 4

Preparation of methyl (3S,5R,6E)-7-phenyl-3,5-dihydroxy-6-heptenoate



(4S)-4,7,7-trimethyl-3-exo-(1-naphthyl)bicyclo[2.2.1]heptan-2-exo-yl (3S,5R,6E)-7-phenyl-3,5-dihydroxy-6-heptenoate (210 mg, 0.42 mmol) prepared in accordance with a literature [J. Org. Chem., 56, 5752 (1991)] was dissolved in methanol, and a 1M sodium hydroxide aqueous solution (0.2 ml) was added thereto. The mixture was stirred at room temperature for 12 hours. Then, methanol was removed under reduced pressure. The residue was diluted with water, and (4S)-4,7,7-trimethyl-3-exo-(1-naphthyl)bicyclo[2.2.1]heptan-2-exo-ol was extracted with diethyl ether. The aqueous layer was acidified with hydrochloric acid, and the carboxylic acid was extracted with diethyl ether. The organic layer was treated with a diethyl ether solution of diazomethane to form a methyl ester. Acetic acid was added to consume excess diazomethane, and the organic layer was washed with a saturated sodium hydrogencarbonate aqueous solution, then dried over anhydrous magnesium sulfate and concentrated. The product was purified by column chromatography (hexane:ethyl acetate = 2:1) to obtain methyl (3S,5R,6E)-7-phenyl-3,5-dihydroxy-6-heptenoate (92 mg, 87%) as colorless oil.

Rf = 0.08 (hexane:ethyl acetate = 2:1)

IR($CHCl_3$): 3475, 3005, 1720, 1490, 1435, 1205, 1110, 1070, 1030, 775, 730 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 7.38(d, J=7.2 Hz, 2H), 7.31(t, J=7.2 Hz, 2H), 7.24(tt,

J=7.2 Hz, 1.3, 1H), 6.62(d, J=15.7 Hz, 1H), 6.21(dd, J=15.7, 6.4 Hz, 1H), 4.59(m,1H), 4.43(m, 1H), 3.74(s, 1H), 3.72(s, 3H), 3.24(s, 1H), 2.54(dd, J=19.8, 16.5 Hz, 1H), 2.52(dd, J=17.4, 16.5 Hz, 1H), 1.80(dt, J=14.3, 9.4 Hz, 1H), 1.73(dt, J=14.3, 3.1 Hz, 1H).

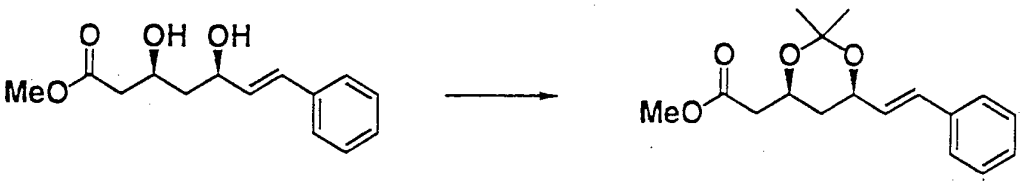
MS (m/z) 250(M^+, 2.5), 232(M^+-H_2O, 3.5), 218(4), 215(4), 200(15), 158(60), 104(100).

HRMS Calcd. for $C_{14}H_{18}O_4$; M^+ 250.1222, found m/z 250.1224.

$[\alpha]_D^{20}$ +8.23° (c 1.19, $CHCl_3$)

REFERENCE EXAMPLE 5

Preparation of methyl (3S,5R,6E)-7-phenyl-3,5-isopropylidenedioxy-6-heptenoate



Methyl (3S,5R,6E)-7-phenyl-3,5-dihydroxy-6-heptenoate (90 mg, 0.36 mmol) obtained in Reference Example 4 and p-toluenesulfonic acid (5 mg, catalytic amount) were dissolved in acetone dimethylacetal (1.0 ml). The reaction mixture was stirred at room temperature for 6 hours. Then, the mixture was diluted with diethyl ether, and the organic layer was washed with a saturated sodium hydrogencarbonate aqueous solution and a sodium chloride aqueous solution, then dried over anhydrous magnesium sulfate and concentrated. The product was purified by column chromatography (hexane:ethyl acetate = 10:1) to obtain methyl (3S,5R,6E)-7-phenyl-3,5-isopropylidenedioxy-6-heptenoate (97 mg, 92%) as

colorless oil.

Rf = 0.78 (hexane:ethyl acetate = 2:1)

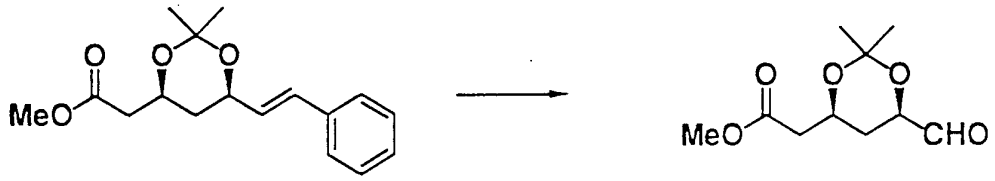
IR($CHCl_3$): 3000, 1735, 1440, 1380, 1200, 1160, 1085, 1030, 770, 740 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 7.37(d, J=7.2 Hz, 2H), 7.29(t, J=7.2 Hz, 2H), 7.24(tt, J=7.2, 1.3 Hz, 1H), 6.60(d, J=15.9 Hz, 1H), 6.16(dd, J=15.9, 6.2 Hz, 1H), 4.57(m,1H), 4.40(m, 1H), 3.70(s, 3H), 2.60(dd, J=15.6, 6.9 Hz, 1H), 2.52(dd, J=15.6, 6.2 Hz, 1H), 1.74(dt, J=12.3, 2.5 Hz, 1H), 1.54(s, 3H), 1.45(s, 3H), 1.40(dd, J=11.4, 10.2 Hz, 1H).

MS (m/z) 290(M^+, 3), 232(M^+-CO_2Me, 4), 215(15), 158(50), 104(100).
Milli MS Calcd. for $C_{17}H_{22}O_4$ M^+; 290.1498, found m/z; 290.1496.
$[\alpha]_D^{20}$ +6.66° (c 1.11, $CHCl_3$)

REFERENCE EXAMPLE 6

Preparation of methyl (3S,5R)-6-oxo-3,5-isopropylidenedioxy-6-heptenoate



Methyl (3S,5R,6E)-7-phenyl-3,5-isopropylidenedioxy-6-heptenoate (120 mg, 0.41 mmol) obtained in Reference Example 5 was dissolved in methanol (20 ml), and the solution was cooled to -78°C. A gas mixture of ozone and oxygen supplied from an ozone generator, was introduced, and the introduction was continued until the reaction solution turned blue. Then, nitrogen gas was introduced to remove excess ozone gas, and dimethyl sulfide (0.5 ml) was added thereto. The reaction mixture was stirred at

room temperature for 12 hours and concentrated. The product was purified column chromatography (hexane:ethyl acetate = 3:1) to obtain methyl (3S,5R)-6-oxo-3,5-isopropylidenedioxy-6-heptenoate (49 mg, 90%) as colorless oil.

Rf = 0.14 (hexane:ethyl acetate = 2:1)

IR($CHCl_3$): 2950, 1735, 1435, 1380, 1080, 1030, 775, 730 cm^{-1}.

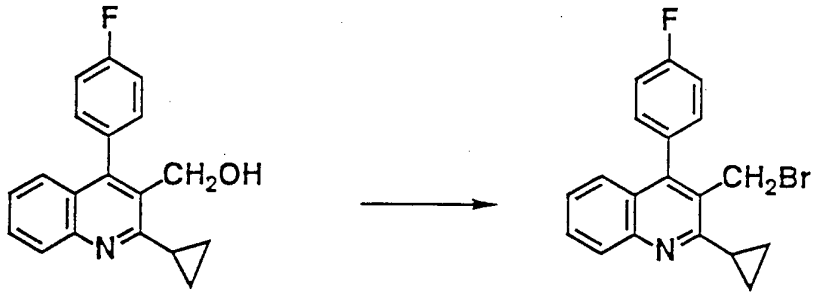
^{1}H-NMR($CDCl_3$): δ 9.58(s, 1H), 4.38(m,1H), 4.33(m, 1H), 3.70(s, 3H), 2.58(dd, J=15.8, 7.0, 1H), 2.44(dd, J=15.8, 6.0, 1H), 1.86(dt, J=12.9, 2.7, 1H), 1.50(s, 3H), 1.46(s, 3H), 1.35(dt, J=12.0, 12.0, 1H).

MS (m/z) 201(M^+-Me, 24), 129(31), 97(36), 59(100).

$[\alpha]_D^{20}$=20.00° (c 1.03, $CHCl_3$)

REFERENCE EXAMPLE 7

Preparation of 3-bromomethyl-2-cyclopropyl-4-(4-fluorophenyl)quinoline



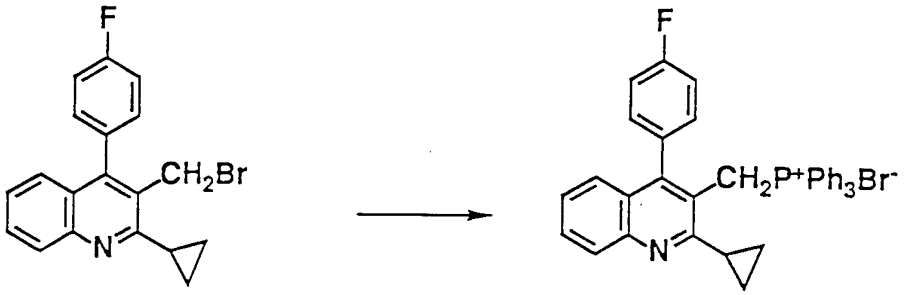
Phosphorus tribromide (4.0 ml, 42.1 mmol) was added at room temperature to a toluene (40 ml)-methylene chloride (20 ml) solution of 2-cyclopropyl-3-hydroxymethyl-4-(4-fluorophenyl)quinoline (6.0 g, 20.5 mmol). The reaction mixture was stirred at room temperature for 3 hours and then poured into an aqueous sodium hydrogencarbonate solution to terminate the

reaction. The mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (hexane:chloroform = 3:1) to obtain the desired product (6.54 g, 89%) as white crystals.

Melting point: 140°C

^{1}H-NMR($CDCl_3$): δ 7.97(d, J=8.9, 1H), 7.62(dd, J=6.8, 1.6 Hz, 1H), 7.40(m, 6H), 4.59(s, 2H), 2.51(m, 1H), 1.41-1.37(m, 2H), 1.16-1.12(m, 2H).

EXAMPLE 1



Triphenylphosphine (2.81 g, 10.7 mmol) was added to a toluene solution (50 ml) of 3-bromomethyl-2-cyclopropyl-4-(4-fluorophenyl)-quinoline (4.00 g, 10.2 mmol) obtained in Reference Example 7, and the mixture was refluxed under heating for 5 hours. The formed solid was collected by filtration, washed with toluene and then dried to obtain {2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl}methyltriphenylphosphonium bromide (6.80 g, quantitative yield) as white powder.

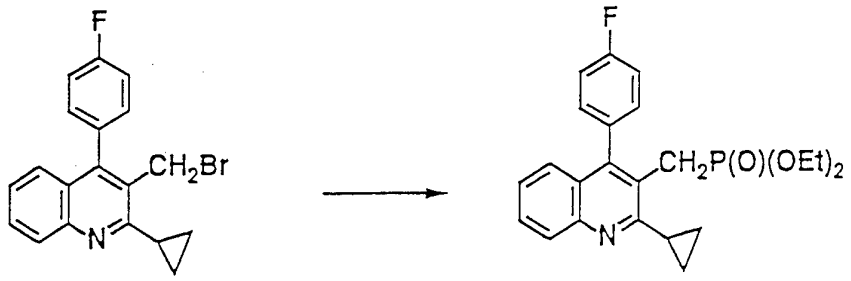
Melting point 245°C (decomposed)

IR($CHCl_3$): 3300, 3050, 1600, 1520, 1495, 1440, 1320, 1220, 1150, 920, 840 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 0.3-0.7 (m, 2H), 1.2-0.9 (m, 2H), 2.5-2.0 (m, 1H), 5.5(d, 2H, 14.4Hz), 8.0-6.8(m, 23H).

EXAMPLE 2

Preparation of diethyl {2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}methylphosphonate



Triethyl phosphite (3.50 ml, 20.4 mmol) was added to a toluene solution (30 ml) of 3-bromomethyl-2-cyclopropyl-4-(4-fluorophenyl)quinoline (4.00 g, 10.2 mmol) obtained in Reference Example 7, and the reaction mixture was refluxed under heating for 12 hours. The solvent was removed under reduced pressure, and the product was purified by column chromatography (hexane:ethyl acetate = 2:1) to obtain diethyl {2-cyclopropyl-4-(4-fluorophenyl-quinolin-3-yl}methylphosphonate (4.14 g, quantitative yield) as colorless crystals.

Melting point: 89°C

Rf = 0.09 (hexane:ethyl acetate = 5:1)

IR($CHCl_3$) 2950, 1600, 1510, 1490, 1435, 1240, 1145, 1020, 970, 830 cm^{-1}

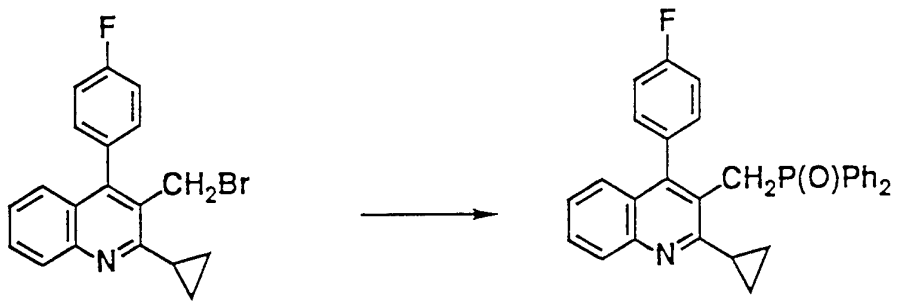
^{1}H-NMR($CDCl_3$): δ 8.95(d, J=8.4 Hz, 1H), 7.59(dt, 7.0, 1.2 Hz, 1H), 7.35-7.17(m, 6H), 4.01-3.84(m, 4H), 3.43(d, J=22.5 Hz, 2H), 2.67-2.61(m, 1H), 1.33-1.29(m, 2H), 1.19(t, J=7.0 Hz, 6H), 1.09(dd, J=8.0, 3.1

Hz, 2H).

MS (m/z) 413(M^+, 63), 385(4), 356(4), 328(5), 276(100).

EXAMPLE 3

Preparation of diphenyl {2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}methylphosphine oxide



Diphenylethoxyphosphorane (1.30 g, 5.65 mmol) was added to a toluene solution (20 ml) of 3-bromomethyl-2-cyclopropyl-4-(4-fluorophenyl)quinoline (1.00 g, 2.80 mmol) obtained in Reference Example 7, and the reaction mixture was refluxed under heating for 12 hours. The solvent was removed under reduced pressure, and the product was purified by column chromatography (hexane:ethyl acetate = 1:1) to obtain diphenyl {2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}methylphosphine oxide (1.38 g, quantitative yield) as colorless crystals.

Melting point: 170°C

Rf = 0.11 (hexane:ethyl acetate = 2:1)

IR($CHCl_3$) 2950, 1605, 1510, 1490, 1435, 1210, 1110, 1025, 830 cm^{-1}

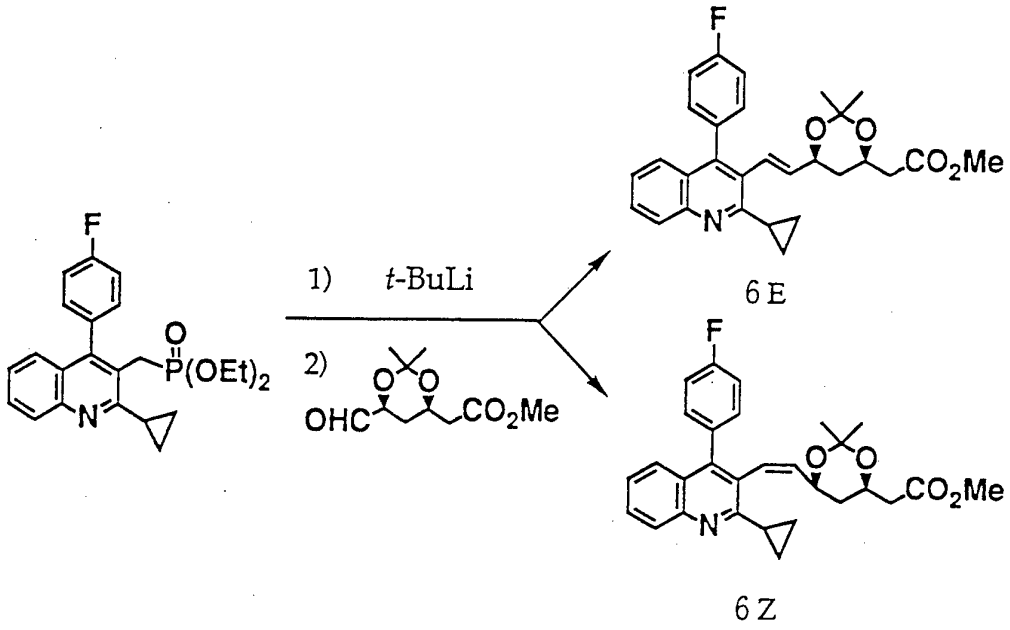
^{1}H-NMR($CDCl_3$): δ 7.95(d, J=8.3 Hz, 1H), 7.57(t, J=7.2 Hz, 1H), 7.51-7.33(m, 1H), 7.24(td, J=7.0, 1.2 Hz, 1H), 7.05(d, J=8.4 Hz, 1H), 6.99(d, J=8.7 Hz, 1H), 6.97(d, J=8.7 Hz, 1H), 6.80(d, J=5.5 Hz, 1H), 6.78(d,

J=5.5 Hz, 1H), 4.04(d, J=14.0 Hz, 2H), 2.61-2.55(m, 1H), 1.24-1.20(m, 2H), 0.89(dd, J=8.8, 3.1 Hz, 2H).

MS (m/z) 477(M^+, 3), 449(0.1), 352(4), 246(8), 201(50), 124(25), 77(100).

EXAMPLE 4

Preparation of methyl (3R*,5S*)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate



t-Butyl lithium (0.15 ml, 1.60M pentane solution, 0.24 mmol) was added at -78°C to a THF solution (3.0 ml) of diethyl {2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}methylphosphonate (100 mg, 0.24 mmol) obtained in Example 2, and the mixture was stirred at -78°C for 30 minutes. A THF solution (2.0 ml) of methyl (3R*,5S*)-6-oxo-3,5-isopropylidenedioxy-6-heptenoate (50 mg, 0.23 mmol) obtained in Reference Example 3, was added at -78°C, and reaction mixture was stirred for 3 hours from

-78°C to 0°C and further stirred for 2 hours at room temperature. A saturated sodium hydrogencarbonate aqueous solution was added to terminate the reaction, and the reaction mixture was extracted with diethyl ether. The organic layer was washed with a sodium chloride aqueous solution, then dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (hexane:ethyl acetate = 10:1) to obtain methyl (3R*,5S*,6Z)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate (14 mg, 12%) as colorless crystals and (6E)-form (31 mg, 29%) as colorless crystals.

6Z-form

Rf = 0.40 (hexane:ethyl acetate = 5:1)

IR($CHCl_3$) : 3000, 1730, 1600, 1510, 1490, 1380, 1230, 1160, 1090, 840 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 7.96(d, J=8.2 Hz, 1H), 7.62(dd, J=6.7, 1.5 Hz, 1H), 7.37-7.15(m, 6H), 6.42(d, J=11.4 Hz, 1H), 5.61(dd, J=11.4, 8.2 Hz, 1H), 4.38-4.30(m, 1H), 4.13-4.06(m, 1H), 3.64(s, 3H), 2.48(dd, J=15.5, 6.8 Hz, 1H), 2.46-2.41(m, 1H), 2.29(dd, J=15.5, 6.3 Hz, 1H), 1.46(s, 3H), 1.40-1.35(m, 4H), 1.37(s, 3H), 1.31-1.25(m, 2H), 1.04(dd, J=8.1, 3.3 Hz, 2H).

MS (m/z) 475(M^+, 6), 416(8), 400(5), 344(21), 288(100), 275(43)

6E-form

Melting point: 133°C

Rf = 0.33 (hexane:ethyl acetate = 5:1)

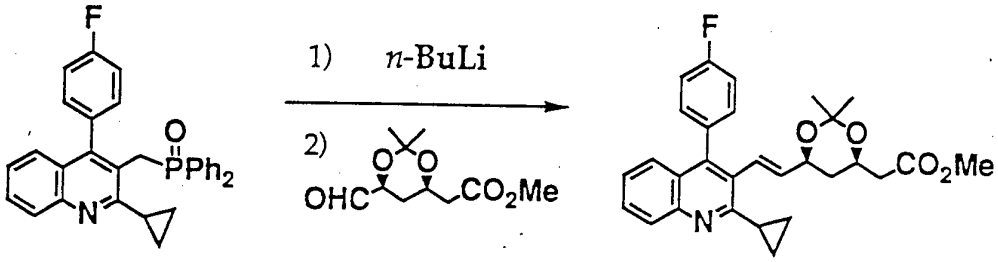
IR($CHCl_3$) : 3000, 1730, 1605, 1510, 1490, 1380, 1230, 1160, 1090, 840 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 7.95(d, J=8.4 Hz, 1H), 7.58(dd, J=6.6, 1.6 Hz, 1H), 7.37-7.15(m, 6H), 6.55(dd, J=16.3, 1.2 Hz, 1H), 5.57(dd, J=16.3, 6.1 Hz, 1H), 4.38-4.33(m, 1H), 4.32-4.25(m, 1H), 3.71(s, 3H), 2.54(dd, J=15.6, 6.7 Hz, 1H), 2.43(m, 1H), 2.35(dd, J=15.6, 6.4 Hz, 1H), 1.46(s, 3H), 1.40-1.35(m, 4H), 1.37(s, 3H), 1.31-1.25(m, 2H), 1.04(dd, J=8.1, 3.3 Hz, 2H).

MS (m/z): 475(M^+, 6), 416(8), 400(5), 344(21), 288(100), 275(43).

EXAMPLE 5

Preparation of methyl (3R*,5S*,6E)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate



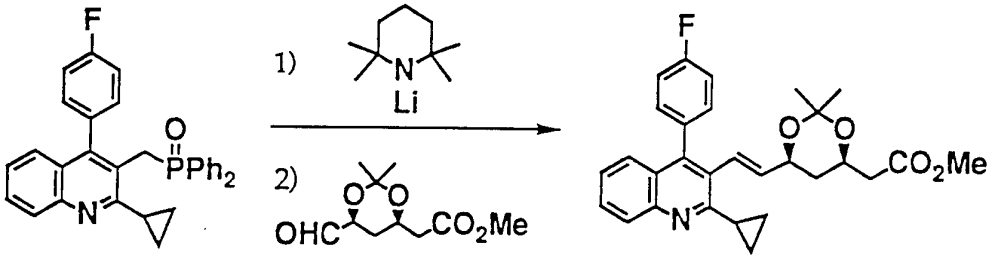
A THF solution (6 ml) of diphenyl {2-cyclopropyl-4-(4-fluorophenyl-3-yl}methylphosphine oxide (115 mg, 0.24 mmol) obtained in Example 3, was cooled to -78°C. Then, butyl lithium (0.16 ml, 0.26 mmol) was added thereto, and the mixture was stirred for 30 minutes. A THF solution (2.0 ml) of methyl (3R*,5S*)-6-oxo-3,5-isopropylidenedioxy-6-heptenoate (50 mg, 0.23 mmol) obtained in Reference Example 3 was stirred at -78°C for 4 hours, and then the temperature was raised to room temperature overnight with stirring. The mixture was

treated in the same manner as in Example 4 to obtain methyl (3R*,5S*,6E)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate (71 mg, 64%) as colorless crystals. The E/Z ratio was 99:1 as measured by ^{1}H-NMR.

The melting point, Rf, IR, ^{1}H-NMR and MS agreed to 6E-form of Example 4.

EXAMPLE 6

Preparation of methyl (3R*,5S*,6E)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate



Butyl lithium (0.16 ml, 1.62M hexane solution, 0.26 mmol) was added at -78°C to a THF solution (2.0 ml) of 2,2,6,6-tetramethylpiperidine (37 mg, 0.26 mmol), and the mixture was stirred at -78°C for 15 minutes. A THF solution (4.0 ml) of diphenyl {2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}methylphosphine oxide (115 mg, 0.24 mmol) obtained in Example 3, was added thereto at -78°C, and the mixture was stirred at room temperature for 30 minutes. A THF solution (2.0 ml) of methyl (3R*,5S*)-6-oxo-3,5-isopropylidenedioxy-6-heptenoate (50 mg, 0.23 mmol) obtained in Reference Example 3, was added

thereto at room temperature, and the reaction mixture was stirred at room temperature for 3 hours. The mixture was treated in the same manner as in Example 4 to obtain methyl (6E)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate (84 mg, 76%) as colorless crystals. The E/Z ratio was 98:2 as measured by ^{1}H-NMR.

The melting point, Rf, IR, ^{1}H-NMR and MS agreed to 6E-form of Example 4.

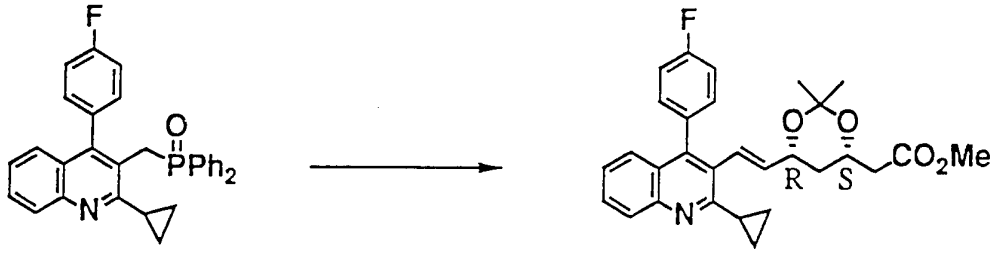
EXAMPLES 7 to 10

Using the following amines instead of 2,2,6,6-tetramethylpiperidine in Example 6, the reaction was conducted in the same manner to obtain the following results.

Examples	Amines	Yield of 6E-form (%)	E/Z
7	Diisopropylamine	54	98:2
8	Bistrimethylsilylamine	47	98:2
9	Dicyclohexylamine	60	97:3
10	Isopropylcyclohexylamine	64	95:5

EXAMPLE 11

Preparation of methyl (3S,5R,6E)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate



Butyl lithium (0.125 ml, 1.62M hexane solution, 0.20 mmol) was added at -78°C to a THF solution (2.0 ml) of 2,2,6,6-tetramethylpiperidine (29 mg, 0.20 mmol), and the mixture was stirred at -78°C for 15 minutes. A THF solution (4.0 ml) of diphenyl {2-cyclopropyl-4-(4-fluorophenyl)isoquinolin-3-yl}-methylphosphine oxide (98 mg, 0.20 mmol) obtained in Example 3, was added thereto at -78°C, and the mixture was stirred at room temperature for 30 minutes. Then, a THF solution (2.0 ml) of methyl (3S,5R)-6-oxo-3,5-isopropylidenedioxy-6-heptenoate (38 mg, 0.18 mmol) obtained in Reference Example 6, was added thereto at room temperature, and the reaction mixture was stirred at room temperature for 3 hours. Then, a saturated sodium hydrogencarbonate aqueous solution was added to terminate the reaction, and the mixture was extracted with diethyl ether. The organic layer was washed with a sodium chloride aqueous solution, then dried over anhydrous magnesium sulfate and concentrated. The product was purified by column chromatography (hexane:ethyl acetate = 5:1) to obtain methyl (3S,5R,6E)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate (62 mg, 74%) as colorless oil. The E/Z ratio was 98:2 as confirmed by

^{1}H-NMR.

$[\alpha]_D^{20}$ = 19.16° (c 0.96, $CHCl_3$)

Rf = 0.33 (hexane:ethyl acetate = 5:1)

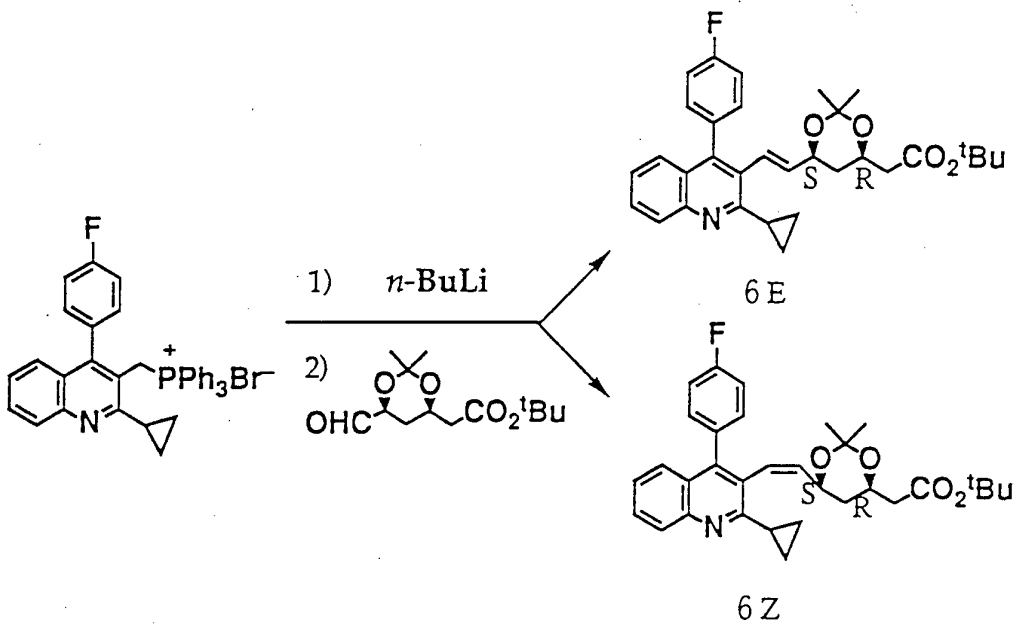
IR($CHCl_3$): 3000, 1730,1605, 1510, 1490, 1380, 1230, 1160, 1090, 840 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 7.95(d, J=8.4Hz, 1H), 7.58(dd, J=6.6, 1.6 Hz, 1H), 7.37-7.15(m, 6H), 6.55(dd, J=16.3, 1.2 Hz, 1H), 5.57(dd, J=16.3, 6.1 Hz, 1H), 4.38-4.33(m,1H), 4.32-4.25(m,1H), 3.71(s, 3H), 2.54(dd, J=15.6, 6.7Hz, 1H), 2.43(m,1H), 2.35(dd, J=15.6, 6.4Hz, 1H), 1.46(s,3H), 1.40-1.35(m,4H), 1.37(s,3H), 1.31-1.25(m,2H), 1.04(dd, J=8.1, 3.3Hz, 2H).

MS (m/z) 475(M^+, 6), 416(8), 400(5), 344(21), 288(100), 275(43).

HRMS(Calcd. for $C_{29}H_{30}O_4NF$; M^+ 475.2149, found m/z 475.2157.

EXAMPLE 12



Preparation of t-butyl (3R,5S)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate

Butyl lithium (0.42 ml, 0.67 mmol) was added at -70°C

to a THF solution (15 ml) of {2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}methyltriphenylphosphonium bromide obtained in Example 1, and the mixture was stirred at -78°C for 30 minutes. A THF solution (5 ml) of t-butyl (3R,5S)-6-oxo-3,5-isopropylidenedioxy-6-heptenoate (208 mg, 0.78 mmol) separately prepared, was added thereto at -78°C, and the mixture was stirred for 2 hours at -78°C and further overnight while raising the temperature to room temperature. The mixture was treated and purified in the same manner as in Example 4 to obtain t-butyl (3R,5S,6Z)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate (140 mg, 40%) as colorless oil and 6E-form (200 mg, 58%) as colorless crystals.

6Z-form

Rf = 0.40 (hexane:ethyl acetate = 5:1)

IR($CHCl_3$): 3450, 3000, 1720, 1595, 1560, 1510, 1490, 1380, 1310, 1260, 1220, 1200, 1160, 1100, 1030, 970, 950, 920, 840 cm^{-1}

^{1}H-NMR($CDCl_3$): δ 7.0-8.1(m, 8H), 6.4(d, J=11Hz, 1H), 5.6(dd, J=11, 8Hz, 1H), 3.7-4.2(m,2H), 2.1-2.7(m,3H), 0.8-1.7(m, 21H).

MS (m/z) 518(M^+H, 100), 462, 404, 386, 344, 316, 288, 274, 262, 220, 173, 154, 136.

6E-form

Melting point: 46°C

$[\alpha]_D^{25}$ = +10.4° (c 1.0, $CHCl_3$)

Rf = 0.33 (hexane:ethyl acetate = 5:1)

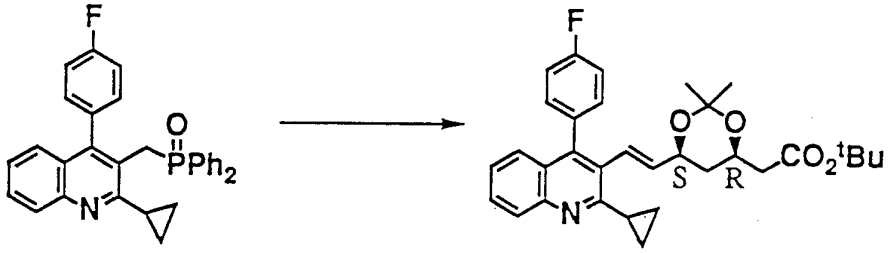
IR(KBr): 3450, 3000, 1720, 1600, 1560, 1510, 1490, 1380, 1310, 1260, 1220, 1200, 1160, 1100, 1030, 970, 950, 920, 840 cm^{-1}.

^{1}H-NMR($CDCl_3$):60MHz, δ 7-8(m,8H), 6.5(d, J=16Hz, 1H), 5.5(dd, J=16, 6Hz, 1H), 4.0-4.5(m, 2H), 2.2-2.6(m, 3H), 0.85-1.7(m, 21H).

MS (m/z) 518(M^+H, 100), 462, 404, 386, 344, 316, 288, 274, 262, 220, 173, 154, 136.

EXAMPLE 13

Preparation of t-butyl (3R,5S,6E)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate



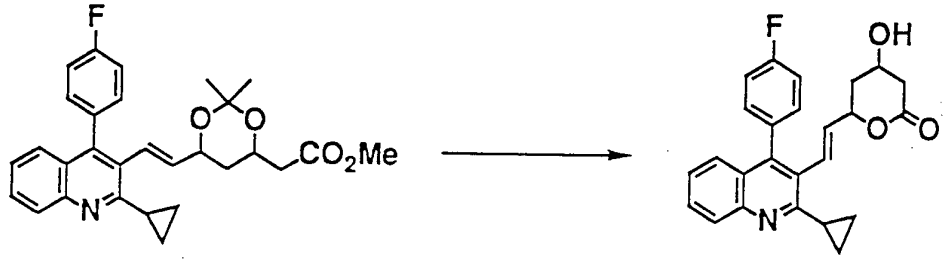
Butyl lithium (1.24 ml, 2.0 mmol) was added at 0°C to a THF solution (5 ml) of 2,2,6,6-tetramethylpiperidine (161 mg, 1.1 mmol), and the mixture was stirred for 15 minutes. The mixture was cooled to -78°C. Then, a THF solution (5 ml) of diphenyl {2-cyclopropyl-4-(4-fluorophenyl)isoquinolin-3-yl}methylphosphine oxide (419 mg, 0.86 mmol) obtained in Example 3, was added thereto, and the mixture was stirred for 30 minutes. Then, a THF solution (5 ml) of t-butyl (3R,5S)-6-oxo-3,5-isopropylidenedioxy-6-heptenoate (294 mg, 1.1 mmol) separately prepared, was added thereto, and the mixture was stirred for 4 hours at -78°C and then overnight to room temperature. The mixture was treated in the same

manner as in Example 6 to obtain t-butyl (3R,5S,6E)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate (378 mg, 83%) as white crystals. The E/Z ratio was 95:5 as confirmed by high performance liquid chromatography.

The melting point, $[\alpha]_D^{25}$, Rf, IR, ^{1}H-NMR and MS agreed to 6E-form of Example 12.

REFERENCE EXAMPLE 8

Preparation of (4R*,6S*)-6-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl-E-ethenyl}-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one



A methyl chloride solution (2 ml) of trifluoroacetic acid (170 mg, 1.5 mmol) was added to a methylene chloride solution (5 ml) of methyl (3R*,5S*,6E)-7-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylidenedioxy-6-heptenoate (48 mg, 0.1 mmol) obtained in Example 5, and the mixture was stirred at room temperature for 24 hours. The reaction solution was cooled with ice, and then a 5% sodium hydrogencarbonate aqueous solution was added, and the mixture was extracted with methyl chloride. Then, the organic layer was washed with a saturated sodium chloride aqueous solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced

pressure, and the residue was purified by column chromatography (hexane:ethyl acetate = 5:1) to obtain ($4R^*$,$6S^*$)-6-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl-E-ethenyl}-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (30 mg, 75%) as white crystals.

Melting point: 201°C

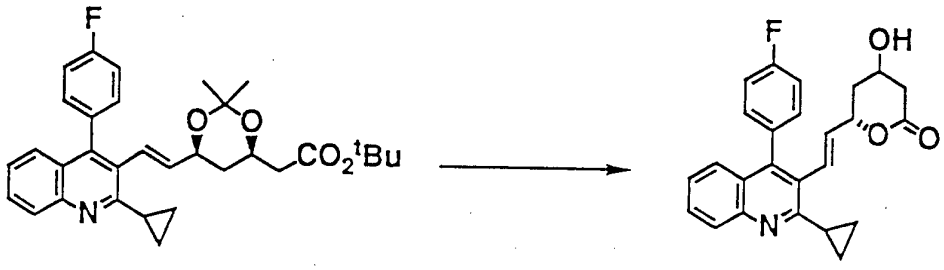
IR($CHCl_3$): 3440, 3005, 1730, 1600, 1560, 1510, 1490, 1410, 1230, 1155, 1060, 970, 830, 730 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 1.03-1.08(m,2H), 1.30-1.40(m, 2H), 1.56-1.60(m, 1H), 1.78(m, 1H), 2.38(m, 1H), 2.60(ddd, J=7.4, 4.0, 1.5Hz, 1H), 2.70(dd, J=13.0, 4.8 Hz, 1H), 4.25(m, 1H), 5.18 and 4.66(m, 1H, ratio 64:36), 5.62(dd, J=16.1, 6.2Hz, 1H), 6.72(dd, J=16.1, 1.4Hz, 1H), 7.17-7.25(m, 4H), 7.30-7.37(m, 2H), 7.61(dd, J=6.1, 2.1Hz, 1H), 7.96(d, J=8.3Hz, 1H).

MS (m/z) 403(M^+, 9), 316(11), 288(100), 274(12).

REFERENCE EXAMPLE 9

<u>Preparation of (4R,6S)-6-{2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl-E-ethenyl}-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one</u>



t-Butyl (3R,5S,6E)-7-{2-cycloropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-isopropylideneoxy-6-heptenoate (259 mg, 0.5 mmol) obtained in Example 13, was reacted in the same manner as in Reference Example 8 to obtain (4R,6S)-6-{2-cyclopropyl-4-(4-

fluorophenyl)quinolin-3-yl-E-ethenyl}-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (151 mg, 75%) as white crystals.

Melting point: 139°C

$[\alpha]_D^{20}$ = +9.0° (c 1.0, $CHCl_3$)

Rf = 0.19 (hexane:ethyl acetate = 2:1)

IR($CHCl_3$):3440, 3005, 1730, 1600, 1560, 1510, 1490, 1410, 1230, 1155, 1060, 970, 830, 730 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 1.03-1.08(m,2H), 1.30-1.40(m, 2H), 1.56-1.60(m, 1H), 1.78(m, 1H), 2.38(m, 1H), 2.60(ddd, J=7.4, 4.0, 1.5Hz, 1H), 2.70(dd, J=13.0, 4.8 Hz, 1H), 4.25(m, 1H), 5.18 and 4.66(m, 1H, ratio 64:36), 5.62(dd, J=16.1, 6.2Hz, 1H), 6.72(dd, J=16.1, 1.4Hz, 1H), 7.17-7.25(m, 4H), 7.30-7.37(m, 2H), 7.61(dd, J=6.1, 2.1Hz, 1H), 7.96(d, J=8.3Hz, 1H).

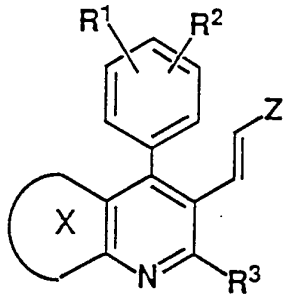
MS (m/z) 403(M^+, 9), 316(11), 288(100), 274(12).

INDUSTRIAL APPLICABILITY

The present invention provides a novel intermediate for a condensed pyridine type mevalonolactone derivative which is a HMG-CoA reductase inhibitor and which is useful as a hypercholesterolemia therapeutic agent or as an arteriosclerosis therapeutic agent and a process for its production as well as a novel condensed pyridine derivative useful as a starting material therefor.

CLAIMS:

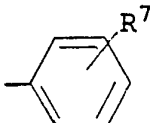
1. A condensed pyridine type mevalonolactone intermediate of the formula (1):

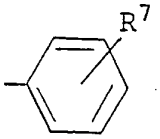


(1)

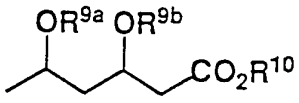
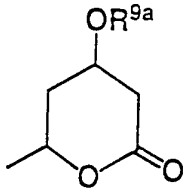
wherein ring X is a benzene ring, a substituted benzene ring or a substituted 5- or 6-membered heteroaromatic ring,

each of R^1 and R^2 which are independent of each other, is hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-3} alkoxy, butoxy, i-butoxy, sec-butoxy, tert-butoxy, $R^{20}R^{21}N$- (wherein each of R^{20} and R^{21} which are independent of each other, is hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy, hydroxymethyl or $-O(CH_2)_\ell OR^{22}$ (wherein R^{22} is hydrogen or C_{1-3} alkyl, and ℓ is 1, 2, or 3); or R^1 and R^2 together form -CH=CH-CH=CH- or methylenedioxy, when they are at the o-position to each other;

R^3 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl or  (wherein R^7 is hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-3} alkylthio, chloro,

bromo, fluoro, chloromethyl, trichloromethyl, trifluoromethyl, trifluoromethoxy, trichloromethoxy, difluoromethoxy, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy or hydroxymethyl); or C_{1-3} alkyl substituted by one  (wherein R^7 is as defined above) and zero, one or two C_{1-3} alkyl;

Z is

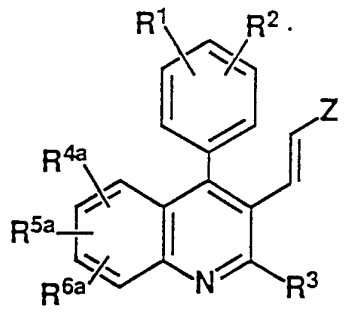
 or 

(each of R^{9a} and R^{9b} represents a hydroxyl-protecting group and is independently methoxymethyl, 2-methoxyethoxymethyl, tetrahydropyranyl, 4-methoxytetrahydropyranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, allyl, benzyl, p-methoxybenzyl, triphenylmethyl, trimethylsilyl, tert-butyldimethylsilyl or tert-butyldiphenylsilyl, or R^{9a} and R^{9b} together form isopropylidene, cyclopentylidene, cyclohexylidene or benzylidene; and

R^{10} is methyl, ethyl, propyl, isopropyl, tert-butyl, tetrahydropyranyl, allyl, benzyl, triphenylmethyl, trimethylsilyl or tert-butyldimethylsilyl).

2. The intermediate according to Claim 1, which is a quinoline type mevalonolactone intermediate of the

formula (1a)



(1a)

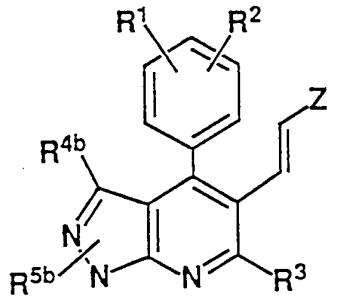
wherein each of R^{4a}, R^{5a} and R^{6a} which are independent of one another, is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-3} alkoxy, butoxy, i-butoxy, sec-butoxy, $R^{26}R^{27}N$- (wherein each of R^{26} and R^{27} which are independent of each other, is hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy, hydroxymethyl or $-O(CH_2)_mOR^{28}$ (wherein R^{28} is hydrogen or C_{1-3} alkyl, and m is 1, 2, or 3); or

R^{4a} and R^{5a} together form -CH=CH-CH=CH-; or

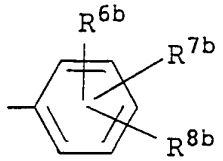
R^{4a} and R^{5a} together form $-OC(R^{29})(R^{30})O-$ when they are at the o-position to each other (wherein each of R^{29} and R^{30} which are independent of each other, is hydrogen or C_{1-3} alkyl); and

R^1, R^2, R^3 and Z are as defined with respect to the formula (1).

3. The intermediate according to Claim 1, which is a pyrazolopyridine type mevalonolactone intermediate of the formula (1b):

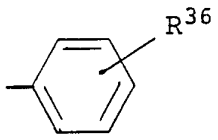


(1b)

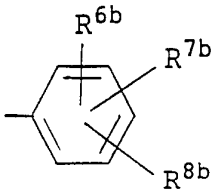
wherein R^{4b} is hydrogen, C_{1-8} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, C_{2-6} alkenyl, α- or β-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, fluoro, chloro, bromo,  (wherein each of R^{6b}, R^{7b} and R^{8b} which are independent of one another, is hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-3} alkylthio, chloro, bromo, fluoro, $-NR^{31}R^{32}$ (wherein each of R^{31} and R^{32} which are independent of each other, is C_{1-3} alkyl), chloromethyl, trichloromethyl, trifluoromethyl, trifluoromethoxy, trichloromethoxy, difluoromethoxy, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy, hydroxymethyl or $-O(CH_2)_nOR^{33}$ (wherein R^{33} is hydrogen or C_{1-3} alkyl, and n is 1, 2 or 3), or

when R^{8b} is hydrogen, R^{6b} and R^{7b} together form $-OC(R^{34})(R^{35})O-$ when they are at the o-position to each other (wherein each of R^{34} and R^{35} which are independent of each other, is hydrogen or C_{1-3} alkyl group), or

when R^{7b} and R^{8b} are simultaneously hydrogen, R^{6b} is

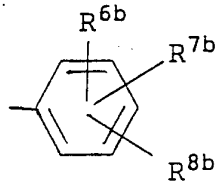


(wherein R^{36} is hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, trifluoromethyl, chloro, bromo or fluoro), phenyl-C_{2-3} alkenyl wherein the phenyl group may be substituted by C_{1-4} alkyl, C_{1-3} alkoxy, fluorine, chlorine or bromine, or C_{1-3} alkyl substituted by one member selected from C_{1-3} alkoxy, naphthyl and



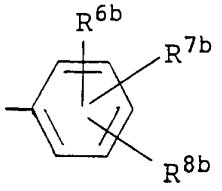
(wherein R^{6b}, R^{7b} and R^{8b} are as defined above) and zero, one or two C_{1-8} alkyl;

R^{5b} is bonded to nitrogen atom at the 1- or 2-position of the pyrazolopyridine ring, and such R^{5b} is hydrogen, C_{1-8} alkyl, C_{1-3} alkyl substituted by from one to three fluorine atoms, C_{3-7} cycloalkyl, α- or β-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl or



(wherein R^{6b}, R^{7b} and R^{8b} are as defined above); or

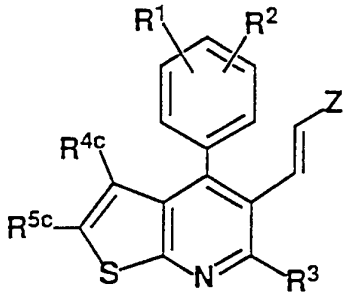
C_{1-3} alkyl substituted by one member selected from C_{1-3} alkoxy, hydroxy, naphthyl and



(wherein R^{6b}, R^{7b} and R^{8b} are as defined above) and zero, one or two C_{1-8} alkyl; and

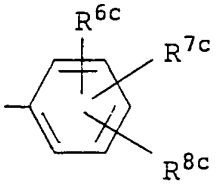
R^1, R^2, R^3 and Z are as defined with respect to the formula (1).

4. The intermediate according to Claim 1, which is a thienopyridine type mevalonolactone intermediate of the formula (1c):

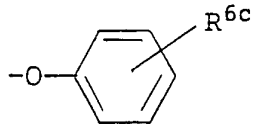


(1c)

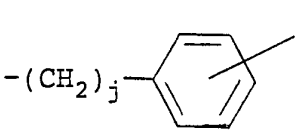
wherein each of R^{4c} and R^{5c} which are independent of each other, is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, fluoro, chloro, bromo,



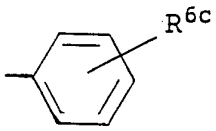
(wherein each of R^{6c}, R^{7c} and R^{8c} which are independent of one another, is hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl, trifluoromethyl, fluoro, chloro and bromo), 2-, 3- or 4-pyridyl, 2- or 5-pyrimidyl, 2- or 3-thienyl, 2- or 3-furyl,



(wherein R^{6c} is as defined above), $-NR^{37}R^{38}$ (wherein each of R^{37} and R^{38} which are independent of each other, is hydrogen, C_{1-4} alkyl,

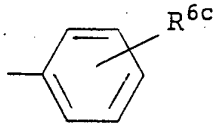


(wherein j is 1, 2 or 3, and R^{6c} is as defined above), or R^{37} and R^{38} together form $-(CH_2)_k-$ (wherein k is 3, 4 or 5)), C_{1-3} alkyl substituted by

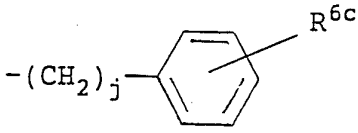


(wherein R^{6c} is as defined above), and zero, one or two C_{1-3} alkyl, or α- or β-naphthyl; or

R^{4c} and R^{5c} together form C_{2-6} alkylene substituted by from zero to three members selected from C_{1-4} alkyl, C_{3-7} cycloalkyl, fluoro, chloro and bromo and zero or one member selected from



(wherein R^{6c} is as defined above), or $-(CHR^{39})_p-A-(CHR^{40})_q-$ (wherein each of p and q is 0, 1, 2 or 3, A is $-C(R^{41})=C(R^{42})-$ (wherein each of R^{41} and R^{42} is hydrogen or C_{1-3} alkyl), -O-, -S- or $-N(R^{43})-$ (wherein R^{43} is hydrogen, C_{1-4} alkyl, or



(wherein R^{6c} and j are as defined

above)), and each of R^{39} and R^{40} which are independent of each other, is hydrogen or C_{1-4} alkyl) or -CH=CH-CH=CH-; and

R^1, R^2, R^3 and Z are as defined with respect to the formula (I).

5. The quinoline type mevalonolactone intermediate according to Claim 2, wherein in the formula (Ia),

R^3 is hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, pentyl, i-pentyl, 1,2-dimethylpentyl, hexyl, heptyl, octyl, vinyl, 1-propenyl, 1-methylvinyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1, 2-dimethyl-1-propenyl, cyclopropyl, cyclobutyl, cyclohexyl, 1-methylcyclopropyl, 2-methylcyclopropyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethylphenyl, 3,4-dichlorophenyl, 3-trifluoromethylphenyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, 2-phenethyl or 1-methylbenzyl;

when R^{5a} and R^{6a} are simultaneously hydrogen, R^{4a} is hydrogen, 5-fluoro, 6-fluoro, 7-fluoro, 8-fluoro, 5-chloro, 6-chloro, 7-chloro, 8-chloro, 5-bromo, 6-bromo, 7-bromo, 8-bromo, 5-methyl, 6-methyl, 7-methyl, 8-methyl, 5-methoxy, 6-methoxy, 7-methoxy, 8-methoxy, 5-trifluoromethyl, 6-trifluoromethyl, 7-trifluoromethyl, 8-trifluoromethyl, 6-trifluoromethoxy, 6-difluoromethoxy,

8-hydroxyethyl, 5-hydroxy, 6-hydroxy, 7-hydroxy, 8-hydroxy, 6-ethyl, 6-butyl or 7-dimethylamino; or

when R^{6a} is hydrogen, R^{4a} and R^{5a} together represent 6-chloro-8-methyl, 6-bromo-7-methoxy, 6-methyl-7-chloro, 6-chloro-8-hydroxy, 5-methyl-2-hydroxy, 6-methoxy-7-chloro, 6-chloro-7-methoxy, 6-hydroxy-7-chloro, 6-chloro-7-hydroxy, 6-chloro-8-bromo, 5-chloro-6-hydroxy, 6-bromo-8-chloro, 6-bromo-8-hydroxy, 5-methyl-8-chloro, 7-hydroxy-8-chloro, 6-bromo-8-hydroxy, 6-methoxy-7-methyl, 6-chloro-8-bromo, 6-methyl-8-bromo, 6,7-difluoro, 6,8-difluoro, 6,7-methylenedioxy, 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo or 6,8-dibromo; or

R^{4a}, R^{5a} and R^{6a} together represent 5,7-dimethoxy-8-hydroxy, 5,8-dichloro-6-hydroxy, 6,7,8-trimethoxy, 6,7,8-trimethyl, 6,7,8-trichloro, 5-fluoro-6,8-dibromo or 5-chloro-6,8-dibromo.

6. The pyrazolopyridine type mevalonolactone intermediate according to Claim 3, wherein in the formula (1b),

R^3 is hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, pentyl, i-pentyl, 1,2-dimethylpentyl, hexyl, heptyl, octyl, vinyl, 1-propenyl, 1-methylvinyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1,2-dimethyl-1-propenyl, cyclopropyl, cyclobutyl, cyclohexyl, 1-methylcyclopropyl, 2-methylcyclopropyl, phenyl, 2-methylphenyl, 3-

methylphenyl, 4-methylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethylphenyl, 3,4-dichlorophenyl, 3-trifluoromethylphenyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, 2-phenethyl or 1-methylbenzyl;

R^{4b} is hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, cyclopropyl, cyclohexyl, phenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-bromophenyl, 2-, 3- or 4-tolyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-trifluoromethylphenyl, 2-, 3- or 4-chloromethylphenyl, 3- or 4-ethoxyphenyl, 4-(2-methylbutyl)phenyl, 4-heptylphenyl, 4-octylphenyl, 4-pentylphenyl, 4-hexylphenyl, 4-propylphenyl, 4-butylphenyl, 4-tert-butylphenyl, 4-butoxyphenyl, 4-pentyloxyphenyl, 4-hexyloxyphenyl, 4-heptyloxyphenyl, 4-octyloxyphenyl, 4-phenoxyphenyl, 4-biphenyl, 4-trichloromethoxyphenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 2,3-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 3,4-difluorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 2,3-dichlorophenyl, 2,5-dichlorophenyl, 3,5-dichlorophenyl, 3,4-dichlorophenyl, 2,3-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,5-

bis(trifluoromethyl)phenyl, 3,4-methylenedioxyphenyl, 2,4,6-trimethoxyphenyl, 3,4,5-trimethylphenyl or 2,4,6-triisopropylphenyl;

R^{5b} is a group bonded to the nitrogen atom at the 1-position of the pyrazolopyridine ring and is methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, cyclohexyl, benzyl, 2-chlorobenzyl, 2-hydroxybenzyl, 3-trifluoromethylbenzyl, 2-phenylethyl, phenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-bromophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-tolyl, 2-, 3- or 4-trifluoromethylphenyl, 3- or 4-methoxyphenyl, 2-hydroxyphenyl, 4-isopropylphenyl, 4-tert-butylphenyl, 4-trifluoromethoxyphenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2,4,6-trichlorophenyl, 2,3,4-trichlorophenyl, 2,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3-chloro-4-tolyl, 3-chloro-6-tolyl, 4-chloro-2-tolyl, 2-chloro-6-tolyl, 2-chloro-6-fluorophenyl, 2-chloro-5-trifluoromethylphenyl, 3-chloro-4-fluorophenyl, 4-bromo-3-chlorophenyl, 2-chloro-4-trifluoromethylphenyl, 3-fluoro-6-tolyl, α-naphthyl, 2-pyridyl, 3-methyl-5-trifluoromethyl-2-pyridyl, 4-pyridyl or 2,6-dichloro-4-pyridyl.

7. The thienopyridine type mevalonolactone intermediate according to Claim 4, wherein in the formula (1c),

R^3 is hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, pentyl, i-pentyl, 1,2-dimethylpentyl, hexyl, heptyl, octyl, vinyl, 1-propenyl, 1-methylvinyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1,2-dimethyl-1-propenyl, cyclopropyl, cyclobutyl, cyclohexyl, 1-methylcyclopropyl, 2-methylcyclopropyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethylphenyl, 3,4-dichlorophenyl, 3-trifluoromethylphenyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, 2-phenethyl or 1-methylbenzyl;

each of R^{4c} and R^{5c} which are independent of each other, is hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, pentyl, 1,2-dimethylpentyl, hexyl, heptyl, octyl, cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, 2-methylcyclohexyl, cycloheptyl, cyclopropylmethyl, vinyl, 1-methylvinyl, 1-propenyl, allyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-butenyl, 1-ethylvinyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-1-butenyl, 1-i-propylvinyl, 1-methyl-1-pentenyl or phenyl; or

R^{4c} and R^{5c} together form ethylene, trimethylene, tetramethylene, pentamethylene, methyltetramethylene,

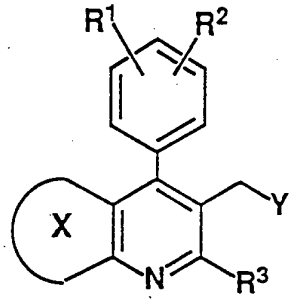
chlorotetramethylene or phenyltetramethylene.

8. The quinoline type mevalonolactone intermediate according to Claim 2, wherein in the formula (1a), R^1 is p-fluoro, each of R^2, R^{4a}, R^{5a} and R^{6a} is hydrogen, and R^3 is cyclopropyl.

9. The pyrazolopyridine type mevalonolactone intermediate according to Claim 3, wherein in the formula (1b), R^1 is p-fluoro, R^2 is hydrogen, each of R^{4b} and R^{5b} is methyl, and R^3 is cyclopropyl.

10. The thienopyridine type mevalonolactone intermediate according to Claim, 4, wherein in the formula (1c), R^1 is p-fluoro, R^2 is hydrogen, R^{4c} is ethyl, R^{5c} is methyl, and R^3 is cyclopropyl.

11. A condensed pyridine derivative of the formula (2):

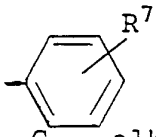
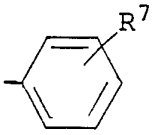


(2)

wherein ring X is a benzene ring, a substituted benzene ring or a substituted 5- or 6-membered heteroaromatic ring,

each of R^1 and R^2 which are independent of each other, is hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-3} alkoxy, butoxy, i-butoxy, sec-butoxy, tert-butoxy, $R^{20}R^{21}N$- (wherein each of R^{20} and R^{21} which are independent of each other, is hydrogen or C_{1-3} alkyl),

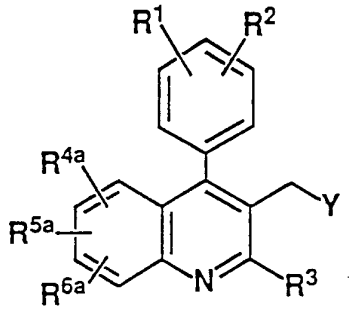
trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy, hydroxymethyl or $-O(CH_2)_\ell OR^{22}$ (wherein R^{22} is hydrogen or C_{1-3} alkyl, and ℓ is 1, 2, or 3); or R^1 and R^2 together form -CH=CH-CH=CH- or methylenedioxy, when they are at the o-position to each other;

R^3 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl or  (wherein R^7 is hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-3} alkylthio, chloro, bromo, fluoro, chloromethyl, trichloromethyl, trifluoromethyl, trifluoromethoxy, trichloromethoxy, difluoromethoxy, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy or hydroxymethyl); or C_{1-3} alkyl substituted by one  (wherein R^7 is as defined above) and zero, one or two C_{1-3} alkyl;

Y is $P^+R^{11}R^{12}R^{13}Hal^-$ or $P(W)R^{14}R^{15}$ (wherein each of R^{11}, R^{12} and R^{13} which are independent of one another, is methyl, ethyl, propyl, isopropyl, butyl, 2-chloroethyl, 2,2,2-trifluoroethyl, phenyl, methoxyphenyl, methylphenyl, pentafluorophenyl or benzyl, each of R^{14} and R^{15} which are independent of each other, is methyl, ethyl, propyl, isopropyl, butyl, 2-chloroethyl, 2,2,2-trifluoroethyl, phenyl, methoxyphenyl, methylphenyl,

pentafluorophenyl, benzyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, 2-chloroethoxy, 2,2,2-trifluoroethoxy, phenoxy, methoxyphenyloxy, methylphenyloxy, pentafluorophenyloxy or benzyloxy, or R^{14} and R^{15} together form a 5- or 6-membered ring, Hal is chlorine, bromine or iodine, and W is O or S.

12. The derivative according to Claim 11, which is a quinoline derivative of the formula (2a):



(2a)

wherein each of R^{4a}, R^{5a} and R^{6a} which are independent of one another, is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-3} alkoxy, butoxy, i-butoxy, sec-butoxy, $R^{26}R^{27}N$- (wherein each of R^{26} and R^{27} which are independent of each other, is hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy, hydroxymethyl or $-O(CH_2)_mOR^{28}$ (wherein R^{28} is hydrogen or C_{1-3} alkyl, and m is 1, 2, or 3); or

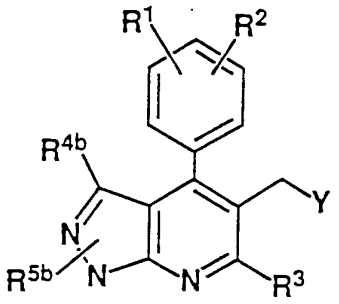
R^{4a} and R^{5a} together form -CH=CH-CH=CH-; or

R^{4a} and R^{5a} together form $-OC(R^{29})(R^{30})O-$ when they are at the o-position to each other (wherein each of R^{29} and R^{30} which are independent of each other, is hydrogen

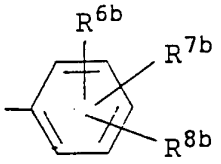
or C_{1-3} alkyl); and

R^1, R^2, R^3 and Y are as defined with respect to the formula (2).

13. The derivative according to Claim 11, which is a pyrazolopyridine derivative of the formula (2b):



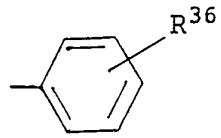
(2b)

wherein R^{4b} is hydrogen, C_{1-8} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, C_{2-6} alkenyl, α- or β-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, fluoro, chloro, bromo,  (wherein each of R^{6b}, R^{7b} and R^{8b} which are independent of one another, is hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-3} alkylthio, chloro, bromo, fluoro, $-NR^{31}R^{32}$ (wherein each of R^{31} and R^{32} which are independent of each other, is C_{1-3} alkyl), chloromethyl, trichloromethyl, trifluoromethyl, trifluoromethoxy, trichloromethoxy, difluoromethoxy, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-tert-butylsilyloxy, hydroxymethyl or $-O(CH_2)_nOR^{33}$ (wherein R^{33} is hydrogen or C_{1-3} alkyl, and n is 1, 2 or 3), or

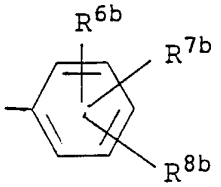
when R^{8b} is hydrogen, R^{6b} and R^{7b} together form $-OC(R^{34})(R^{35})O-$ when they are at the o-position to each

other (wherein each of R^{34} and R^{35} which are independent of each other, is hydrogen or C_{1-3} alkyl group), or

when R^{7b} and R^{8b} are simultaneously hydrogen, R^{6b} is

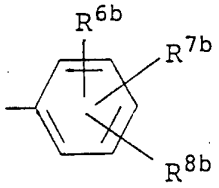


(wherein R^{36} is hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, trifluoromethyl, chloro, bromo or fluoro), phenyl-C_{2-3} alkenyl wherein the phenyl group may be substituted by C_{1-4} alkyl, C_{1-3} alkoxy, fluorine, chlorine or bromine, or C_{1-3} alkyl substituted by one member selected from C_{1-3} alkoxy, naphthyl and



(wherein R^{6b}, R^{7b} and R^{8b} are as defined above) and zero, one or two C_{1-8} alkyl;

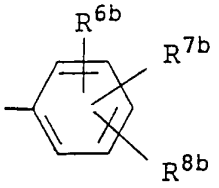
R^{5b} is bonded to nitrogen atom at the 1- or 2-position of the pyrazolopyridine ring, and such R^{5b} is hydrogen, C_{1-8} alkyl, C_{1-3} alkyl substituted by from one to three fluorine atoms, C_{3-7} cycloalkyl, α- or β-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl or



(wherein R^{6b}, R^{7b} and R^{8b} are as defined above); or

C_{1-3} alkyl substituted by one member selected from

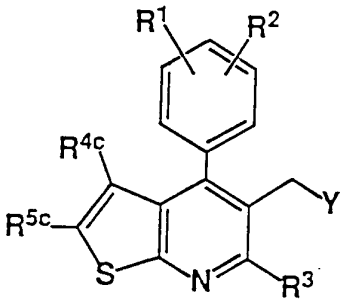
C_{1-3} alkoxy, hydroxy, naphthyl and



(wherein R^{6b}, R^{7b} and R^{8b} are as defined above) and zero, one or two C_{1-8} alkyl; and

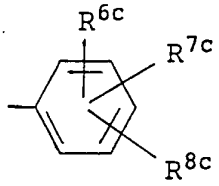
R^1, R^2, R^3 and Y are as defined with respect to the formula (2).

14. The derivative according to Claim 11, which is a thienopyridine derivative of the formula (2c):

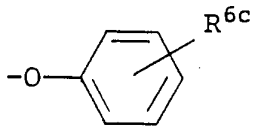


(2c)

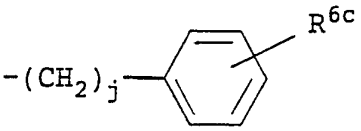
wherein each of R^{4c} and R^{5c} which are independent of each other, is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, fluoro, chloro, bromo,



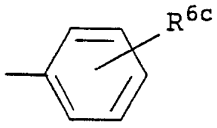
(wherein each of R^{6c}, R^{7c} and R^{8c} which are independent of one another, is hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl, trifluoromethyl, fluoro, chloro and bromo), 2-, 3- or 4-pyridyl, 2- or 5-pyrimidyl, 2- or 3-thienyl, 2- or 3-furyl,



(wherein R^{6c} is as defined above), $-NR^{37}R^{38}$ (wherein each of R^{37} and R^{38} which are independent of each other, is hydrogen, C_{1-4} alkyl,

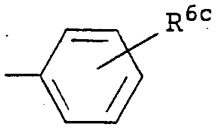


(wherein j is 1, 2 or 3, and R^{6c} is as defined above), or R^{37} and R^{38} together form $-(CH_2)_k-$ (wherein k is 3, 4 or 5)), C_{1-3} alkyl substituted by

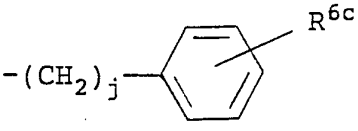


(wherein R^{6c} is as defined above), and zero, one or two C_{1-3} alkyl, or α- or β-naphthyl; or

R^{4c} and R^{5c} together form C_{2-6} alkylene substituted by from zero to three members selected from C_{1-4} alkyl, C_{3-7} cycloalkyl, fluoro, chloro and bromo and zero or one member selected from



(wherein R^{6c} is as defined above), or $-(CHR^{39})_p-A-(CHR^{40})_q-$ (wherein each of p and q is 0, 1, 2 or 3, A is $-C(R^{41})=C(R^{42})-$ (wherein each of R^{41} and R^{42} is hydrogen or C_{1-3} alkyl), -O-, -S- or $-N(R^{43})-$ (wherein R^{43} is hydrogen, C_{1-4} alkyl, or



(wherein R^{6c} and j are as defined

above)), and each of R^{39} and R^{40} which are independent of each other, is hydrogen or C_{1-4} alkyl) or -CH=CH-CH=CH-; and

R^1, R^2, R^3 and Y are as defined with respect to the formula (2).

15. The quinoline derivative according to Claim 12, wherein in the formula (2a),

R^3 is hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, pentyl, i-pentyl, 1,2-dimethylpentyl, hexyl, heptyl, octyl, vinyl, 1-propenyl, 1-methylvinyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1, 2-dimethyl-1-propenyl, cyclopropyl, cyclobutyl, cyclohexyl, 1-methylcyclopropyl, 2-methylcyclopropyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethylphenyl, 3,4-dichlorophenyl, 3-trifluoromethylphenyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, 2-phenethyl or 1-methylbenzyl;

when R^{5a} and R^{6a} are simultaneously hydrogen, R^{4a} is hydrogen, 5-fluoro, 6-fluoro, 7-fluoro, 8-fluoro, 5-chloro, 6-chloro, 7-chloro, 8-chloro, 5-bromo, 6-bromo, 7-bromo, 8-bromo, 5-methyl, 6-methyl, 7-methyl, 8-methyl, 5-methoxy, 6-methoxy, 7-methoxy, 8-methoxy, 5-trifluoromethyl, 6-trifluoromethyl, 7-trifluoromethyl, 8-trifluoromethyl, 6-trifluoromethoxy, 6-difluoromethoxy,

8-hydroxyethyl, 5-hydroxy, 6-hydroxy, 7-hydroxy, 8-hydroxy, 6-ethyl, 6-butyl or 7-dimethylamino; or

when R^{6a} is hydrogen, R^{4a} and R^{5a} together represent 6-chloro-8-methyl, 6-bromo-7-methoxy, 6-methyl-7-chloro, 6-chloro-8-hydroxy, 5-methyl-2-hydroxy, 6-methoxy-7-chloro, 6-chloro-7-methoxy, 6-hydroxy-7-chloro, 6-chloro-7-hydroxy, 6-chloro-8-bromo, 5-chloro-6-hydroxy, 6-bromo-8-chloro, 6-bromo-8-hydroxy, 5-methyl-8-chloro, 7-hydroxy-8-chloro, 6-bromo-8-hydroxy, 6-methoxy-7-methyl, 6-chloro-8-bromo, 6-methyl-8-bromo, 6,7-difluoro, 6,8-difluoro, 6,7-methylenedioxy, 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo or 6,8-dibromo; or

R^{4a}, R^{5a} and R^{6a} together represent 5,7-dimethoxy-8-hydroxy, 5,8-dichloro-6-hydroxy, 6,7,8-trimethoxy, 6,7,8-trimethyl, 6,7,8-trichloro, 5-fluoro-6,8-dibromo or 5-chloro-6,8-dibromo.

16. The pyrazolopyridine derivative according to Claim 13, wherein in the formula (2b),

R^3 is hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, pentyl, i-pentyl, 1,2-dimethylpentyl, hexyl, heptyl, octyl, vinyl, 1-propenyl, 1-methylvinyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1,2-dimethyl-1-propenyl, cyclopropyl, cyclobutyl, cyclohexyl, 1-methylcyclopropyl, 2-methylcyclopropyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-chlorophenyl, 3-

chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethylphenyl, 3,4-dichlorophenyl, 3-trifluoromethylphenyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, 2-phenethyl or 1-methylbenzyl;

R^{4b} is hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, cyclopropyl, cyclohexyl, phenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-bromophenyl, 2-, 3- or 4-tolyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-trifluoromethylphenyl, 2-, 3- or 4-chloromethylphenyl, 3- or 4-ethoxyphenyl, 4-(2-methylbutyl)phenyl, 4-heptylphenyl, 4-octylphenyl, 4-pentylphenyl, 4-hexylphenyl, 4-propylphenyl, 4-butylphenyl, 4-tert-butylphenyl, 4-butoxyphenyl, 4-pentyloxyphenyl, 4-hexyloxyphenyl, 4-heptyloxyphenyl, 4-octyloxyphenyl, 4-phenoxyphenyl, 4-biphenyl, 4-trichloromethoxyphenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 2,3-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 3,4-difluorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 2,3-dichlorophenyl, 2,5-dichlorophenyl, 3,5-dichlorophenyl, 3,4-dichlorophenyl, 2,3-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,5-bis(trifluoromethyl)phenyl, 3,4-methylenedioxyphenyl,

2,4,6-trimethoxyphenyl, 3,4,5-trimethylphenyl or 2,4,6-triisopropylphenyl;

R^{5b} is a group bonded to the nitrogen atom at the 1-position of the pyrazolopyridine ring and is methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, cyclohexyl, benzyl, 2-chlorobenzyl, 2-hydroxybenzyl, 3-trifluoromethylbenzyl, 2-phenylethyl, phenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-bromophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-tolyl, 2-, 3- or 4-trifluoromethylphenyl, 3- or 4-methoxyphenyl, 2-hydroxyphenyl, 4-isopropylphenyl, 4-tert-butylphenyl, 4-trifluoromethoxyphenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2,4,6-trichlorophenyl, 2,3,4-trichlorophenyl, 2,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3-chloro-4-tolyl, 3-chloro-6-tolyl, 4-chloro-2-tolyl, 2-chloro-6-tolyl, 2-chloro-6-fluorophenyl, 2-chloro-5-trifluoromethylphenyl, 3-chloro-4-fluorophenyl, 4-bromo-3-chlorophenyl, 2-chloro-4-trifluoromethylphenyl, 3-fluoro-6-tolyl, α-naphthyl, 2-pyridyl, 3-methyl-5-trifluoromethyl-2-pyridyl, 4-pyridyl or 2,6-dichloro-4-pyridyl.

17. The thienopyridine derivative according to Claim 14, wherein in the formula (2c),

R^3 is hydrogen, methyl, ethyl, propyl, i-propyl,

butyl, i-butyl, sec-butyl, tert-butyl, pentyl, i-pentyl, 1,2-dimethylpentyl, hexyl, heptyl, octyl, vinyl, 1-propenyl, 1-methylvinyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1,2-dimethyl-1-propenyl, cyclopropyl, cyclobutyl, cyclohexyl, 1-methylcyclopropyl, 2-methylcyclopropyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethylphenyl, 3,4-dichlorophenyl, 3-trifluoromethylphenyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, 2-phenethyl or 1-methylbenzyl;

each of R^{4c} and R^{5c} which are independent of each other, is hydrogen, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, tert-butyl, pentyl, 1,2-dimethylpentyl, hexyl, heptyl, octyl, cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, 2-methylcyclohexyl, cycloheptyl, cyclopropylmethyl, vinyl, 1-methylvinyl, 1-propenyl, allyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-butenyl, 1-ethylvinyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-1-butenyl, 1-i-propylvinyl, 1-methyl-1-pentenyl or phenyl; or

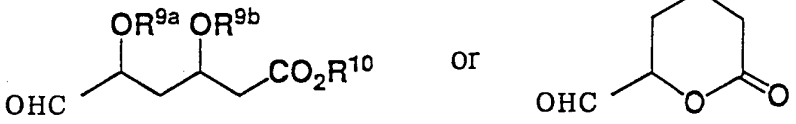
R^{4c} and R^{5c} together form ethylene, trimethylene, tetramethylene, pentamethylene, methyltetramethylene, chlorotetramethylene or phenyltetramethylene.

18. The quinoline derivative according to Claim 12, wherein in the formula (2a), R^1 is p-fluoro, each of R^2, R^{4a}, R^{5a} and R^{6a} is hydrogen, and R^3 is cylcopropyl.

19. The pyrazolopyridine derivative according to Claim 13, wherein in the formula (2b), R^1 is p-fluoro, R^2 is hydrogen, each of R^{4b} and R^{5b} is methyl, and R^3 is cyclopropyl.

20. The thienopyridine derivative according to Claim 14, wherein in the formula (2c), R^1 is p-fluoro, R^2 is hydrogen, R^{4c} is ethyl, R^{5c} is methyl, and R^3 is cylcopropyl.

21. A process for producing a compound of the formula (1) as defined in Claim 1, which comprises reacting a compound of the formula (2) as defined in Claim 11 with a base to form an anion, which is then condensed with a compound of the formula (3):



(3)

wherein each R^{9a} and R^{9b} is a hydroxyl-protecting group, and is independently methoxymethyl, 2-methoxyethoxymethyl, tetrahydropyranyl, 4-methoxytetrahydropyranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, allyl, benzyl, p-methoxybenzyl, triphenylmethyl, trimethylsilyl, tert-butyldimethylsilyl

or tert-butyldiphenylsilyl, or R^{9a} and R^{9b} together form isopropylidene, cyclopentylidene, cyclohexylidene or benzylidene; and

R^{10} is methyl, ethyl, propyl, isopropyl, tert-butyl, tetrahydropyranyl, allyl, benzyl, triphenylmethyl, trimethylsilyl or tert-butyldimethylsilyl.

22. A process for producing a compound of the formula (1a) as defined in Claim 2, which comprises reacting a compound of the formula (2a) as defined in Claim 12, with a base to form an anion, which is then condensed with a compound of the formula (3) as defined in Claim 21.

23. A process for producing a compound of the formula (1b) as defined in Claim 3, which comprises reacting a compound of the formula (2b) as defined in Claim 13 with a base to form an anion, which is then condensed with a compound of the formula (3) as defined in Claim 21.

24. A process for producing a compound of the formula (1c) as defined in Claim 4, which comprises reacting a compound of the formula (2c) as defined in Claim 14 with a base to form an anion, which is then condensed with a compound of the formula (3) as defined in Claim 21.

25. A process for producing a quinoline type mevalonolactone intermediate as defined in Claim 5, which comprises reacting a quinoline derivative as defined in Claim 15 with a base to form an anion, which is then condensed with a compound of the formula (3) as defined in Claim 21.

26. A process for producing a pyrazolopyridine type mevalonolactone intermediate as defined in Claim 6, which comprises reacting a pyrazolopyridine derivative as defined in Claim 16 with a base to form an anion, which is then condensed with a compound of the formula (3) as defined in Claim 21.

27. A process for producing a thienopyridine type mevalonolactone intermediate as defined in Claim 7, which comprises reacting a thienopyridine derivative as defined in Claim 17 with a base to form an anion, which is then condensed with a compound of the formula (3) as defined in Claim 21.

28. A process for producing a quinoline type mevalonolactone intermediate as defined in Claim 8, which comprises reacting a quinoline derivative as defined in Claim 18 with a base to form an anion, which is then condensed with a compound of the formula (3) as defined in Claim 21.

29. A process for producing a pyrazolopyridine type mevalonolactone intermediate as defined in Claim 9, which comprises reacting a pyrazolopyridine derivative as defined in Claim 19 with a base to form an anion, which is then condensed with a compound of the formula (3) as defined in Claim 21.

30. A process for producing a thienopyridine type mevalonolactone intermediate as defined in Claim 10, which comprises reacting a thienopyridine derivative as

defined in Claim 20 with a base to form an anion, which is then condensed with a compound of the formula (3) as defined in Claim 21.

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/JP 93/01551

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/06 A61K31/47 C07F9/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 822 799 (SANDOZ PHARM. CORP.) 18 April 1989 * complete document; column 6, line 20-31 * ---	1,11,21
Y	TETRAHEDRON LETTERS vol. 33, no. 49 , 1992 , OXFORD GB pages 7525 - 7526 TATSUYA MINAMI ET AL. 'A novel enantioselective synthesis of HMG Co-A reductase inhibitor NK-104 and a related compound.' * complete document * --- -/--	21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 1994	12.07.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	US,A,4 870 199 (SANDOZ PHARM. CORP.) 26 September 1989 * the Wittig reaction *	21
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A	US,A,4 939 159 (SANDOZ PHARM. CORP.) 3 July 1990 * the Wittig reaction *	21
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E	CHEMICAL ABSTRACTS, vol. 120, 9 May 1994, Columbus, Ohio, US; abstract no. 244704v, HYAMA, TAMEJIRO ET AL. 'Preparation of pyridine-type mevalonolactone intermediates' see abstract & JP,A,93 310 700 (NISSAN CHEMICAL IND LTD)	1,11,21

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/JP 93/01551

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JP-A-93310700		NONE		