

REPLACED SHEETS SG

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DESCRIPTION

Process for Producing Vitamin D Derivatives

TECHNICAL FIELD

The present invention relates to a process for
 5 synthesizing provitamin D compounds or provitamin D
 compounds in which the 5,7-diene structure is protected
 which are intermediates for synthesis of vitamin D
 derivatives having a substituent at the 2 β -position which
 have various physiological activities such as a calcium
 10 controlling activity in vivo and a differentiation deriving
 activity of tumor cells, etc.

More specifically, the present invention relates to
 a process for introducing a substituent into the 2 β -position
 by reacting a 1 α ,2 α -epoxy compound with an alcohol under
 15 a basic condition.

Background Art

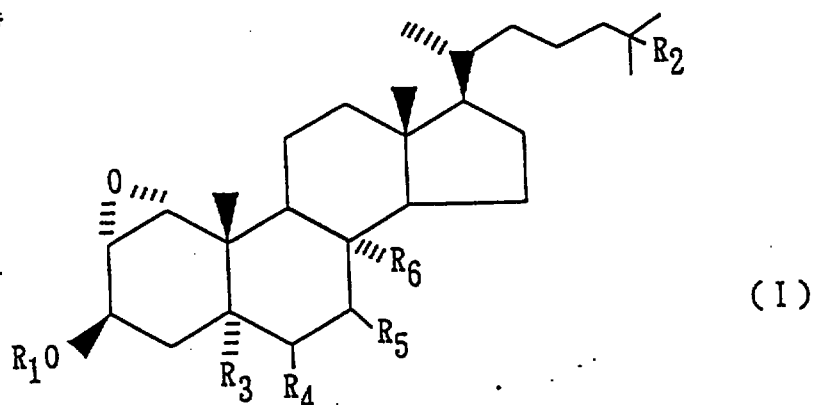
Hitherto, in introducing a substituted lower alkoxy
 group at the 2 β -position of vitamin D derivatives, a process
 in which the addition reaction of an alcohol to 1 α ,2 α -epoxy
 20 compound is carried out under an acidic condition has been
 known (Japanese Patent Application (Kokai) No. 61-267549),
 but this process is not satisfactory due to its low yield,
 etc.

Disclosure of Invention

25 As a result of extensive studies, the present
 inventors found that, in introducing a substituent at
 the 2 β -position by reacting a 1 α ,2 α -epoxy compound (1)
 represented by the formula (I):

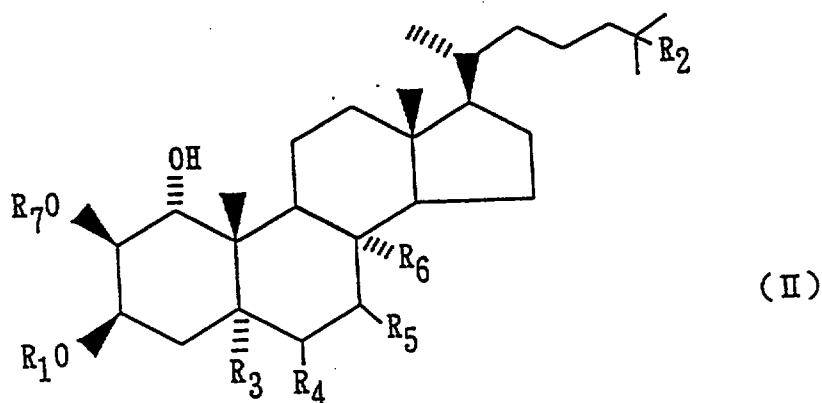
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(wherein R_1 represents a hydrogen atom or a protective group, R_2 represents a hydrogen atom or a hydroxyl group, R_3 , R_4 , R_5 and R_6 represent that each of R_3 and R_4 , and R_5 and R_6 forms a double bond, or R_4 and R_5 form a double bond, and

5 R_3 and R_6 bond to dienophile which is capable of protecting a conjugated double bond), with an alcohol, the reaction proceeds even under a basic condition whereby a ring-cleaved product represented by the following formula (II) can be obtained in a high yield:



10 (wherein R_1 represents a hydrogen atom or a protective group, R_2 represents a hydrogen atom or a hydroxyl group, R_3 , R_4 , R_5 and R_6 represent that each of R_3 and R_4 , and R_5 and R_6 forms a double bond, or R_4 and R_5 form a double bond, and



R₃ and R₆ bond to dienophile which is capable of protecting a conjugated double bond, and R₇ represents a lower alkyl group, a cycloalkyl group or a lower hydroxyalkyl group wherein the hydroxyl group may be protected.)

5 In the above reaction, protection of some functional groups which has been considered necessary in a conventional ring-cleaving reaction under an acidic condition becomes to be unnecessary, but the reaction may be carried out while protected. Further, in the process of this invention, the
10 ring-cleaved product can be obtained in a high yield as compared with the reaction under an acidic condition.

 The provitamin D₃ derivatives prepared according to the process of this invention can be converted into the corresponding vitamin D₃ derivatives by subjecting
15 the provitamin D₃ derivatives to the conventional thermal isomerization after irradiation with U.V. light.

 In the present invention, examples of the protective groups in the formula include an acyl group such as an acetyl group, a pivaloyl group, a methoxycarbonyl group,
20 a benzyloxycarbonyl group and a p-toluenesulfonyl group, an alkyl group which may be substituted such as a methyl group and a methoxymethyl group, and a substituted silyl group such as a trimethylsilyl group, a triethylsilyl group and a t-butyldimethylsilyl group, and, preferably,
25 a trimethylsilyl group, a triethylsilyl group and a t-butyldimethylsilyl group.

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The alcohol compound means an aliphatic monohydric or polyhydric alcohol having from 1 to 7 carbon atoms, and some of the hydroxyl groups thereof other than any one hydroxyl group thereof may be protected. Examples of the alcohol
5 compound include propanol, butanol, pentanol, hexanol, cyclopropanol, cyclobutanol, cyclopentanol, cyclohexanol, ethylene glycol, 1,3-propanediol, 1,4-butanediol, 1,5-pentanediol, etc.

The lower alkyl group means a straight chain or
10 a branched alkyl group having from 1 to 6 carbon atoms, for example, a methyl group, an ethyl group, an n-propyl group, an i-propyl group, an n-butyl group, an s-butyl group, a t-butyl group, etc. The cycloalkyl group means a cycloalkyl group having from 3 to 8 carbon atoms, for example, a cyclo-
15 propyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, a cyclooctyl group, etc. The lower hydroxyalkyl group means an alkyl group having from 1 to 7 carbon atoms wherein at least one hydrogen atom is substituted with a hydroxyl group, for
20 example, a 2-hydroxyethyl group, a 3-hydroxypropyl group, a 4-hydroxybutyl group, etc., preferably a 3-hydroxypropyl group.

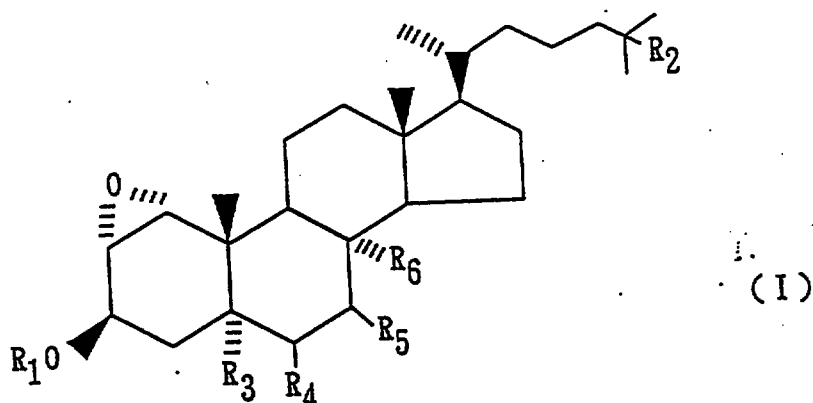
The ring cleaving reaction according to the present invention can be carried out with or without using a
25 solvent, and, when the solvent is used, examples thereof include ether type solvents such as tetrahydrofuran and dioxane, and aromatic type solvents such as benzene and toluene. Preferably, the reaction is carried out with



benzene or without any solvent.

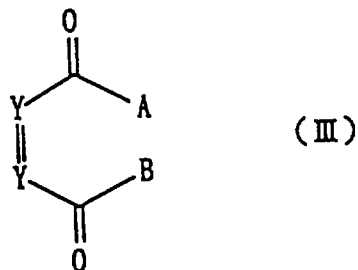
The reaction temperature can be from 50 to 150°C preferably from 80 to 120°C.

The compound represented by the formula (I):



5 (wherein R_1 represents a hydrogen atom or a protective group, R_2 represents a hydrogen atom or a hydroxyl group, R_3 , R_4 , R_5 and R_6 represent that each of R_3 and R_4 , and R_5 and R_6 forms a double bond, or R_4 and R_5 form a double bond, and R_3 and R_6 bond to dienophile which is capable of protecting
10 a conjugated double bond) which can be used in the present invention, can be synthesized by the process described in, for example, Japanese Patent Application (Kokai) Nos. 50-84555 and 50-84560, and J. Org. Chem., 57, 5019-5020(1992).

The dienophile which is capable of protecting
15 a conjugated double bond used in the present invention includes a compound represented by the formula (III):



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(wherein A, and B, which may be the same or different, each represents an alkoxy group having from 1 to 4 carbon atoms, or A and B, when taken together, represent a phenylimino group or an o-phenylene group, and Y represents a nitrogen atom or a methine (=CH-) group), and preferably, 4-phenyl-1,2,4-triazoline-3,5-dione, diethyl maleate, etc.

The basic condition means that a base is present in the reaction system.

The base which can be used in the present invention includes a metal base such as a metal alkoxide, a metal hydride and the like, for example, potassium t-butoxide and sodium hydride, preferably potassium t-butoxide. The base may be used alone or in combination with an additive such as a Crown ether, and examples of the combination with the additive include sodium hydride + 15-Crown-5, potassium t-butoxide + 18-Crown-6, potassium t-butoxide + dibenzo 18-Crown-6 and the like, and preferably, potassium t-butoxide + dibenzo 18-Crown-6.

The present invention is further illustrated by the following Examples and Reference Example in more detail.

Reference Example 1

Synthesis of 3 β ,25-dihydroxy-1 α ,2 α -epoxy-5,7-cholestadiene

A solution of 49 mg (8.3×10^{-5} mol) of 1 α ,2 α -epoxy-5 α ,8 α -(3,5-dioxo-4-phenyl-1,2,4-triazolidino)-6-cholestene-3 β ,25-diol) in DMI (5 ml) was stirred in an argon atmosphere at 140°C (bath temperature) for 5 hours. The reaction mixture was poured into water, and the resulting mixture



was extracted twice with ethyl acetate, and then washed once with water. After drying the ethyl acetate layer over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure, and the resulting residue was
5 purified by fractional thin layer chromatography (silica gel:ethyl acetate:n-hexane = 55:45) to obtain 21 mg (62% yield) of the titled compound as a white powder.

Melting point : 173 - 175°C

¹H-NMR(CDCl₃)δ : 0.64(3H,s), 0.97(3H,d,J=6.3Hz),
10 1.05(3H,s), 1.22(6H,s),
3.04(1H,d,J=3.4Hz), 3.33(1H,d,J=3.4Hz),
3.90(1H,dd,J=10.7,6.1Hz), 5.36-5.42(1H,m),
5.70-5.72(1H,m)

MS(m/z) : 414(M⁺), 59(100%)

15 UV λ_{max}(nm) : 290, 278, 268

Example 1

Synthesis of 2β-(3-hydroxypropoxy)-1α,3β,25-trihydroxycholesta-5,7-diene

A mixture of 21 mg (5.1×10^{-5} mol) of 3β,25-
20 dihydroxy-1α,2α-epoxy-5,7-cholestadiene, 294 μl (4.1×10^{-3} mol) of 1,3-propanediol, 19 mg (1.5×10^{-4} mol) of potassium t-butoxide and 4.8 mg (1.3×10^{-5} mol) of dibenzo-18-Crown-6 was stirred in an argon atmosphere at 110°C (bath temperature) for 4 hours. The reaction mixture was poured
25 into water, and the resulting mixture was extracted twice with ethyl acetate and washed once with a saturated aqueous sodium chloride solution. After drying the ethyl acetate layer over anhydrous magnesium sulfate, the solvent was



distilled off under reduced pressure, and the resulting residue was purified by fractional thin layer chromatography (silica gel:dichloromethane:ethanol = 100:15) to obtain 18 mg (72% yield) of the titled compound as a white powder.

5 Melting point : 118 - 120°C

$^1\text{H-NMR}(\text{CDCl}_3)_\delta$: 0.62(3H,s), 0.96(3H,d,J=6.3Hz),
1.06(3H,s), 1.22(6H,s), 5.32-5.42(1H,m),
5.64-5.73(1H,m)

MS(m/z) : 490(M^+), 131(100%)

10 UV $\lambda_{\text{max}}(\text{nm})$: 293, 281.5, 271, 262(shoulder)

Example 2

Synthesis of 2 β -(3-hydroxypropoxy)-1 α ,3 β -dihydroxy-5,7-cholestadiene

A mixture of 275 mg (6.9×10^{-4} mol) of 1 α ,2 α -epoxy-
15 3 β -hydroxy-5,7-cholestadiene, 4 ml (5.5×10^{-2} mol) of
1,3-propanediol, and 258 mg (2.1×10^{-3} mol) of potassium
t-butoxide was stirred in an argon atmosphere at 110°C
(bath temperature) for 4.5 hours. The reaction mixture was
poured into water, and the resulting mixture was extracted
20 twice with diethyl ether and washed three times with water.
Sodium chloride was added to the aqueous layer, and the
mixture was extracted twice with ethyl acetate and washed
once with a saturated aqueous sodium chloride solution.
After drying the combined organic layer over anhydrous
25 magnesium sulfate, the solvent was distilled off under
reduced pressure, and the resulting residue was purified
by flash column chromatography (silica gel:dichloro-
methane:ethanol = 10:1) to obtain 229 mg (70% yield) of



the titled compound as a white powder.

Melting point : 114 - 116°C

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 0.62(3H,s), 0.87(6H,d,J=6.3Hz),
0.94(3H,d,J=6.8Hz), 5.32-5.39(1H,m),
5.63-5.73(1H,m)

MS(m/z) : 474(M^+), 380(100%)

UV $\lambda_{\text{max}}(\text{nm})$: 293, 282, 271, 262(shoulder)

Examples 3 to 8

The following compounds were synthesized in the same manner as described in Example 2 except for using various alcohols in place of 1,3-propanediol.

Example 3

2 β -Butoxy-1 α ,3 β -dihydroxycholesta-5,7-diene

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 0.63(3H,s), 0.87(6H,d,J=6.6Hz),
0.94(3H,d,J=6.9Hz), 1.07(3H,s),
3.41-3.50(1H,m), 3.66-3.74(2H,m),
3.83-3.99(2H,m), 5.34-5.42(1H,m),
5.68-5.74(1H,m)

MS(m/z) : 472(M^+), 57(100%)

UV $\lambda_{\text{max}}(\text{nm})$: 293, 281, 270

IR(cm^{-1}) : 3450, 2980, 2900, 1480, 1400, 1110,
1060, 750

Example 4

2 β -Cyclohexyloxy-1 α ,3 β -dihydroxycholesta-5,7-diene

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 0.63(3H,s), 0.87(6H,d,J=6.6Hz),
3.39-3.96(4H,m), 5.31-5.41(1H,m),
5.56-5.63(1H,m)

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MS(m/z) : 498(M⁺), 55(100%)
UV λ_{max}(nm) : 290, 279, 269
IR(cm⁻¹) : 3450, 2950, 2900, 1090,

Example 5

5 2β-Cyclohexyloxy-1α,3β,25-trihydroxycholesta-5,7-diene

¹H-NMR(CDCl₃)δ : 0.63(3H,s), 0.96(3H,d,J=6.3Hz),
1.09(3H,s), 1.22(6H,s), 3.38-3.50(1H,m),
3.73-3.83(2H,m), 3.87-3.93(1H,m),
5.32-5.40(1H,m), 5.67-5.73(1H,m)

10 MS(m/z) : 514(M⁺), 55(100%)
UV λ_{max}(nm) : 293, 281, 271
IR(cm⁻¹) : 3400, 2940, 2850, 1450, 1380, 990, 760

Example 6

15 2β-(4-Hydroxybutoxy)-1α,3β,25-trihydroxycholesta-5,7-diene

¹H-NMR(CDCl₃)δ : 0.63(3H,s), 0.96(3H,d,J=6.3Hz),
1.06(3H,s), 1.22(6H,s), 3.41-4.00(7H,m),
5.33-5.40(1H,m), 5.68-5.73(1H,m)

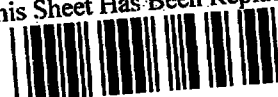
MS(m/z) : 504(M⁺), 55(100%)
20 UV λ_{max}(nm) : 293, 281, 270
IR(cm⁻¹) : 3420, 2950, 2900, 1480, 1390, 770

Example 7

2β-Butoxy-1α,3β,25-trihydroxycholesta-5,7-diene

25 ¹H-NMR(CDCl₃)δ : 0.63(3H,s), 0.93(3H,t,J=7.3Hz),
0.96(3H,d,J=6.3Hz), 1.07(3H,s),
1.21(6H,s), 3.40-3.52(1H,m), 3.66-
3.77(2H,m), 3.84-4.00(2H,m), 5.33-
5.41(1H,m), 5.67-5.74(1H,m)

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MS(m/z) : 488(M⁺), 59(100%)
UV λ_{max}(nm) : 292, 281, 271
IR(cm⁻¹) : 3450, 2950, 2900, 1490, 1390, 1100

Example 8

5 2β-(5-Hydroxypentoxy)-1α,3β,25-trihydroxycholesta-5,7-diene

¹H-NMR(CDCl₃)δ : 0.63(3H,s), 0.96(3H,d,J=6.3Hz),
1.06(3H,s), 1.22(6H,s), 3.41-4.00(7H,m),
5.33-5.40(1H,m), 5.68-5.73(1H,m)

10 MS(m/z) : 518(M⁺), 59(100%)
UV λ_{max}(nm) : 293, 281, 270
IR(cm⁻¹) : 3400, 2950, 2880, 1380, 1140, 970, 760

Examples 9 to 14

The following vitamin D₃ derivatives were synthesized
15 from the products of Examples 3 to 8 by thermal isomerization after irradiation of U.V. light under the conventional conditions.

Example 9

20 2β-butoxy-1α,3β-dihydroxy-9,10-secocholesta-5,7,10(19)-triene

¹H-NMR(CDCl₃)δ : 0.55(3H,s), 0.86(6H,d,J=6.6Hz),
0.92(3H,d,J=6.0Hz), 0.94(3H,t,J=7.4Hz),
3.22(1H,dd,J=9.1,2.8Hz), 3.47-3.58(1H,m),
3.65-3.77(1H,m), 4.23(1H,brs),
25 4.29(1H,d,J=6.6Hz), 5.08(1H,s),
5.49(1H,s), 6.06(1H,d,J=11.2Hz),
6.36(1H,d,J=11.2Hz)

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MS(m/z) : 472(M⁺), 109(100%)
UV λ_{max}(nm) : 264, λ_{min}(nm) : 228
IR(cm⁻¹) : 3400, 2950, 2860, 1460, 1380, 1100

Example 10

5 2β-cyclohexyloxy-1α,3β-dihydroxy-9,10-secocholesta-
5,7,10(19)-triene

¹H-NMR(CDCl₃)δ : 0.55(3H,s), 0.86(6H,d,J=6.6Hz),
0.92(3H,d,J=6.3Hz),
3.35(1H,dd,J=9.4,2.5Hz), 3.39-3.50(1H,m),
10 4.12-4.18(1H,m), 4.19-4.30(1H,m),
5.07(1H,s), 5.49(1H,s),
6.06(1H,d,J=11.4Hz), 6.36(1H,d,J=11.4Hz)

MS(m/z) : 498(M⁺), 56(100%)
UV λ_{max}(nm) : 264, λ_{min}(nm) : 229

15 Example 11

2β-cyclohexyloxy-1α,3β,25-trihydroxy-9,10-secocholesta-
5,7,10(19)-triene

¹H-NMR(CDCl₃)δ : 0.55(3H,s), 0.94(3H,d,J=6.3Hz),
1.21(6H,s), 3.32-3.39(1H,m), 3.40-
20 3.45(1H,m), 4.11-4.17(1H,m), 4.22-
4.29(1H,m), 5.07(1H,s), 5.49(1H,s),
6.06(1H,d,J=11.3Hz), 6.34(1H,d,J=11.3Hz)

MS(m/z) : 514(M⁺), 55(100%)
UV λ_{max}(nm) : 264, λ_{min}(nm) : 228

25 Example 12

2β-(4-hydroxybutoxy)-1α,3β,25-trihydroxy-9,10-
secocholesta-5,7,10(19)-triene

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$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 0.55(3H,s), 0.59(3H,d,J=5.9Hz),
1.21(6H,s), 3.15-3.20(1H,m), 3.45-
4.38(6H,m), 5.08(1H,s), 5.48(1H,s),
6.05(1H,d,J=11.6Hz), 6.36(1H,d,J=11.6Hz)

5 MS(m/z) : 504(M^+), 59(100%)
UV $\lambda_{\text{max}}(\text{nm})$: 263, $\lambda_{\text{min}}(\text{nm})$: 229

Example 13

2 β -butoxy-1 α ,3 β ,25-trihydroxy-9,10-secocholesta-
5,7,10(19)-triene

10 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 0.55(3H,s), 0.91-0.99(6H,m), 1.22(6H,s),
3.18-3.26(1H,m), 3.47-3.77(2H,m),
4.23(1H,brs), 4.29(1H,d,J=6.6Hz),
5.08(1H,s), 5.50(1H,s),
6.08(1H,d,J=12.2Hz), 6.34(1H,d,J=12.2Hz)

15 MS(m/z) : 488(M^+), 59(100%)
UV $\lambda_{\text{max}}(\text{nm})$: 264, $\lambda_{\text{min}}(\text{nm})$: 228

Example 14

2 β -(5-hydroxypentoxy)-1 α ,3 β ,25-trihydroxy-9,10-
secocholesta-5,7,10(19)-triene

20 $^1\text{H-NMR}(\text{CDCl}_3)\delta$: 0.55(3H,s), 0.94(3H,d,J=6.6Hz),
1.22(6H,s), 3.17-3.27(1H,m), 3.45-
4.40(6H,m), 5.08(1H,s), 5.50(1H,s)

MS(m/z) : 518(M^+), 69(100%)
UV $\lambda_{\text{max}}(\text{nm})$: 264, $\lambda_{\text{min}}(\text{nm})$: 228

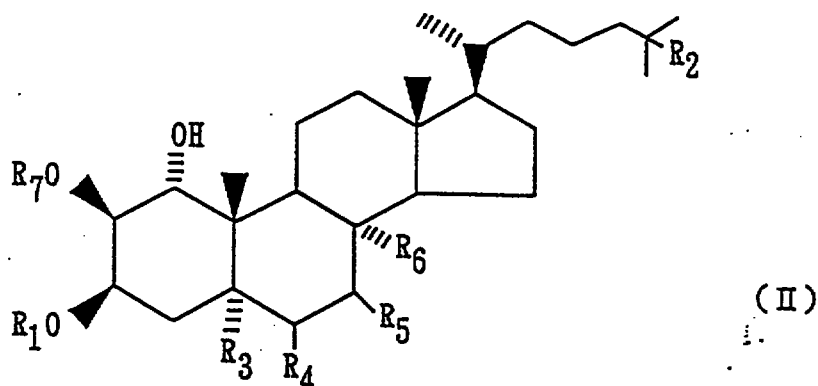
25 IR(cm^{-1}) : 3400(br), 2930, 2860, 1460, 1380,
1100, 980, 740



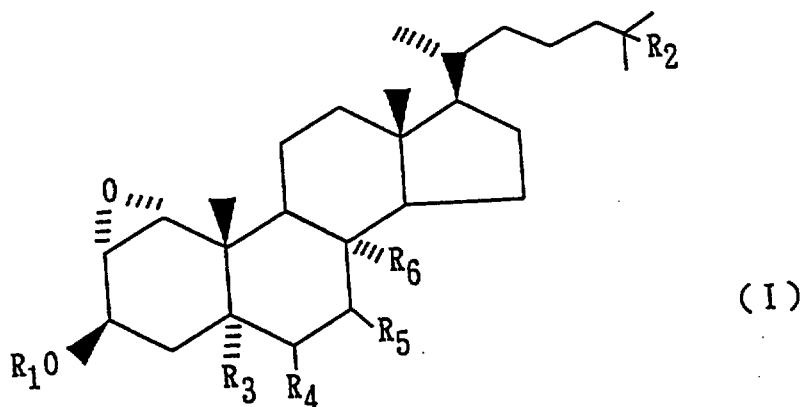


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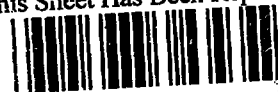
A process for producing a compound represented by the formula (II):



(wherein R_1 represents a hydrogen atom or a protective group,
5 R_2 represents a hydrogen atom or a hydroxyl group, R_3 , R_4 ,
 R_5 and R_6 represent that each of R_3 and R_4 , and R_5 and R_6
forms a double bond, or R_4 and R_5 form a double bond, and
 R_3 and R_6 bond to dienophile which is capable of protecting
a conjugated double bond, and R_7 represents a lower alkyl
10 group, a cycloalkyl group or a lower hydroxyalkyl group
wherein the hydroxyl group may be protected), which
comprises reacting an epoxy compound represented by the
formula (I):



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(wherein R_1 represents a hydrogen atom or a protective group, R_2 represents a hydrogen atom or a hydroxyl group, R_3 , R_4 , R_5 and R_6 represent that each of R_3 and R_4 , and R_5 and R_6 forms a double bond, or R_4 and R_5 form a double bond, and
5 R_3 and R_6 bond to dienophile which is capable of protecting a conjugated double bond), with an alcohol, wherein the reaction is carried out under a basic condition.

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