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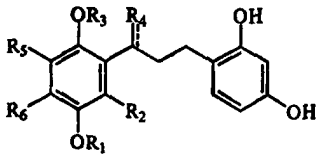
(54) Title: NOVEL 1,3-DIPHENYLPROPANE DERIVATIVES HAVING INHIBITORY ACTIVITY AGAINST TYROSINASE AND PROCESS FOR PREPARATION THEREOF



(I)

(57) Abstract

The present invention relates to a novel 1,3-diphenylpropane derivative having an inhibitory activity against tyrosinase represented by formula (I) and process for the preparation thereof: in which — represents double or single bond; R_1 represents hydrogen or C_1–C_{10} alkyl; R_2 represents C_1–C_5 alkyl or C_1–C_5 alkoxyalkyl, or R_1 and R_2 together represent a 5- to 6- membered heterocycle which can be substituted by C_1–C_5 alkyl and which contains oxygen as the hetero atom; R_3 represents hydrogen or C_1–C_7 alkyl; R_4 represents hydrogen, hydroxy, or oxo; and R_5 and R_6 independently of one another represent hydrogen or C_1–C_5 alkyl.

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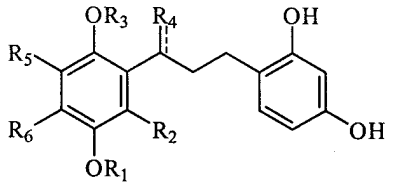
NOVEL 1,3-DIPHENYLPROPANE DERIVATIVES HAVING INHIBITORY ACTIVITY AGAINST TYROSINASE AND PROCESS FOR PREPARATION THEREOF

TECHNICAL FIELD

The present invention relates to a novel 1,3-diphenylpropane derivative having an inhibitory activity against tyrosinase represented by the following formula (I) :



(I)

in which

== represents double or single bond,

R_1 represents hydrogen or C_1-C_{10} alkyl,

R_2 represents C_1-C_5 alkyl or C_1-C_5 alkoxyalkyl, or

R_1 and R_2 together represent a 5 to 6 membered heterocycle which can be substituted by C_1-C_5 alkyl and which contains oxygen as the hetero atom,

R_3 represents hydrogen or C_1-C_7 alkyl,

R_4 represents hydrogen, hydroxy, or oxo, and

R_5 and R_6 independently of one another represent hydrogen or C_1-C_5 alkyl.

The present invention also relates to novel processes for preparation of the compound of formula (I) as defined above.

BACKGROUND ART

Melanin is prepared through the conversion of Tyrosine into DOPA,

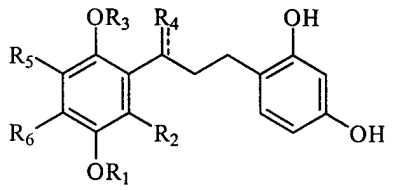
Dopaquinone by the action of Tyrosinase located in the chromatophore then through the non-enzymatic oxidation. Melanin is distributed over the skin and has an important function to protect the body from various stimuli. However, it has been reported that excess production of melanin is closely related to melanoma and may also induce melanistic skin, freckles, etc. Accordingly, a variety of cosmetics and medicaments for the prevention of excess production of melanin are actively developed in these days.

As the preventive agent for the excess production of melanin, hydroquinone has been mainly used heretofore. This compound, however, also exhibits side effects such as degeneration or lethal mutation of melanin, damage of the cellular function, etc., and therefore the use of hydroquinone in cosmetics is now prohibited in Korea, Japan, etc.(see, J. Soc. Cosmet. Chem., 42, 361, 1991). In addition, arbutin, a sugar derivative of hydroquinone, was commercialized but to have been identified as having little whitening effect, and ascorbic acid, kojic acid, etc. have so poor product stability that they can only be restrictively used. While, extracts from licorice root, mori cortex radicis, etc. have been widely known to have a skin-whitening effect since ancient times. But, those extracts occasionally represent so poor effect according to the place of production that it is difficult to keep the quality of the product constant(see, Fragrance J., 6, 59, 1990). Carzinol F extracted from a paper mulberry tree(see, Chem. Parm, Bull., 34(5), 1968, 1986; Cosmetics & Toiletries, 101, 51, 1995) was recently commercialized due to its good inhibitory activity against tyrosinase. However, this substance also has the problem that it is difficult to keep the quality of the product constant because carzinol F is an extract too. Particularly, sufficient data on stimulating property and stability of carzinol F are not available and it has a demerit that it cannot be easily synthesized because of the prenylcatechol group included therein.

DISCLOSURE OF INVENTION

Thus, the present inventors have intensively studied to develop a novel compound having an excellent inhibitory acitivity against tyrosinase in a small quantity. Further, the desired compound should be easily synthesized from the starting material and be stable. During the study, the present inventors analyzed the effect and structure of various natural substances known to have a whitening effect. As a result, we have developed a novel 1,3-diphenyl-propane derivative of formula (I), which satisfies the purpose as mentioned above, and thus completed the present invention.

Therefore, it is an object of the present invention to provide a novel 1,3-diphenylpropane derivative represented by the following formula (I) :



(I)

in which

= represents double or single bond,

R_1 represents hydrogen or C_1-C_{10} alkyl,

R_2 represents C_1-C_5 alkyl or C_1-C_5 alkoxyalkyl, or

R_1 and R_2 together represent a 5 to 6 membered heterocycle which can be substituted by C_1-C_5 alkyl and which contains oxygen as the hetero atom,

R_3 represents hydrogen or C_1-C_7 alkyl,

R_4 represents hydrogen, hydroxy, or oxo, and

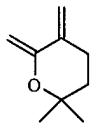
R_5 and R_6 independently of one another represent hydrogen or C_1-C_5 alkyl.

Among the foregoing definitions for the substituents of the compound of formula (I), the term "alkyl" defines straight or branched saturated

hydrocarbon radicals such as methyl, ethyl, n-propyl, isopropyl or several butyl isomers when it is used alone or in the composite form such as "alkyloxy" or "alkoxyalkyl".

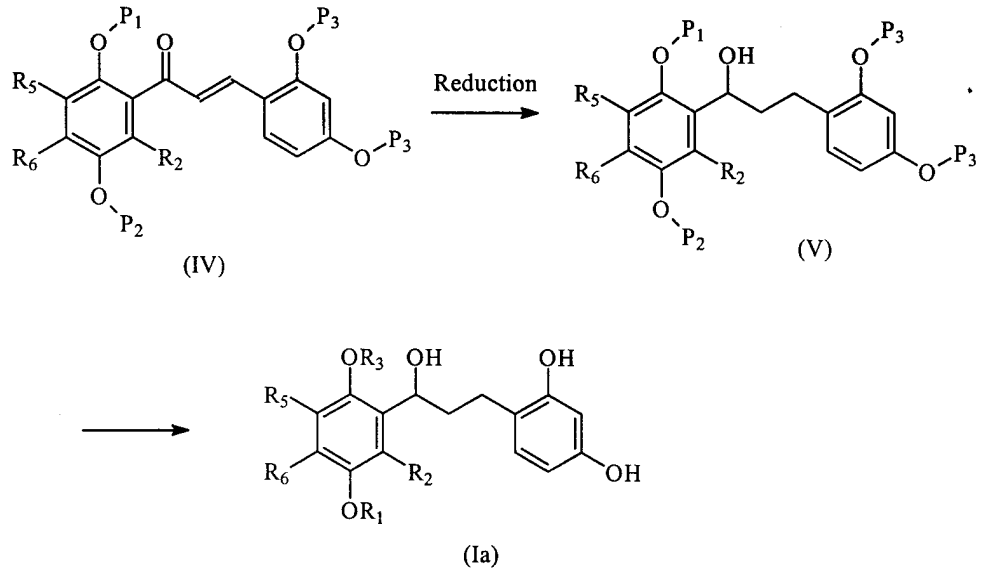
It is another object of the present invention to provide novel processes for preparing the compound of formula (I).

BEST MODE FOR CARRYING OUT THE INVENTION

Among the novel compound of formula (I), as defined above, the preferred compounds include those wherein R_1 represents hydrogen, methyl or ethyl, R_2 represents methyl, or R_1 and R_2 together represent  , R_3 represents hydrogen or methyl, R_4 represents hydrogen or hydroxy, R_5 and R_6 independently of one another represent methyl.

Among the compound of formula (I), a compound represented by the following formula (Ia) wherein R_4 is hydroxy can be prepared conveniently by reducing a compound represented by the following formula (IV) in a solvent to a compound represented by the following formula (V) then by removing the protecting groups, as depicted in the following reaction scheme 1.

Reaction Scheme 1



in which

P_1, P_2 and P_3 are hydroxy protecting groups, that is

P_1 represents benzyl, methyl, ethyl, tetrahydropyranyl, methoxymethyl, methoxyethoxymethyl or p-methoxybenzyl,

P_2 represents benzyl, methyl or ethyl,

P_3 represents benzyl, tetrahydropyranyl, methoxymethyl, methoxyethoxy methyl or p-methoxybenzyl,

R_1 to R_3, R_5 and R_6 are defined as previously described.

The process described in the reaction scheme 1 above will be more specifically explained in the following.

In the reaction step for preparing the compound (V) by reducing the compound (IV), ethers such as diethylether, tetrahydrofuran(THF), etc. can be preferably used as the solvent and lithium aluminum hydride(LAH) can be preferably used as the reducing agent. It is desirable to carry out the reaction at temperatures ranging from -30 to 30℃. After the reduction is completed,

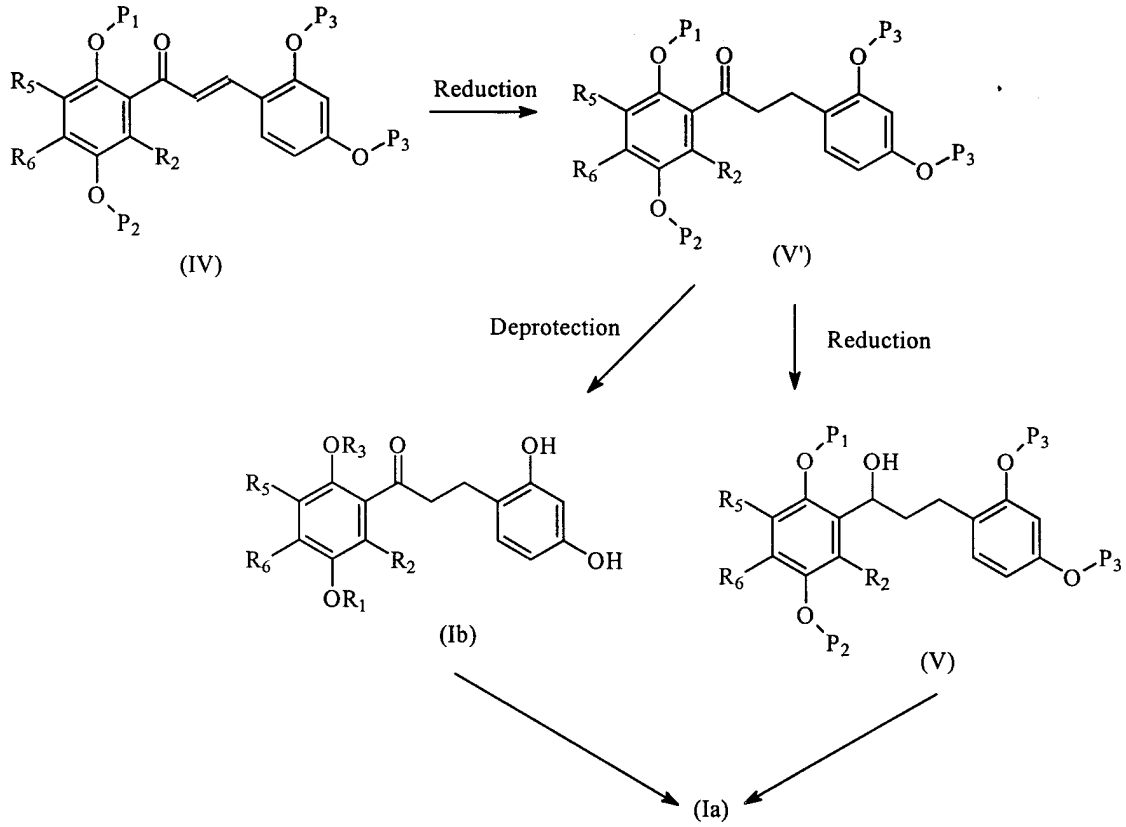
protecting groups included in the compound (V) are eliminated to produce the compound (Ia). The protecting groups may be readily removed by conventionally known processes depending on the protecting groups to be removed. The selection of an appropriate deprotection condition can be made by a person having ordinary skill in this art. Particularly, when the protecting group is benzyl, the compound (Ia) can be prepared by carrying out a hydrogenation reaction in ethylacetate or by refluxing in a solvent mixture of hydrochloric acid and acetic acid.

Reduction of the compound (IV) to the compound (V) may be commonly carried out according to the aforementioned processes. However, the compound (V) can also be prepared by reducing in advance the double bond of the compound (IV) through a hydrogenation(H_2, Pd-C) to obtain a ketone compound represented by the following formula (V') and then by converting the ketone group of the compound (V') to an alcohol group of the compound (V).

On the other hand, a compound represented by the following formula (Ib) wherein R_4 is oxo can be prepared by removing the protecting groups contained in the compound (V') instead of reducing the same. The compound (Ib) can also be reduced into the compound (Ia) in the presence of sodium borohydride or lithium aluminum hydride.

The processes as explained above are summarized in the reaction scheme 2 below.

Reaction Scheme 2



in which

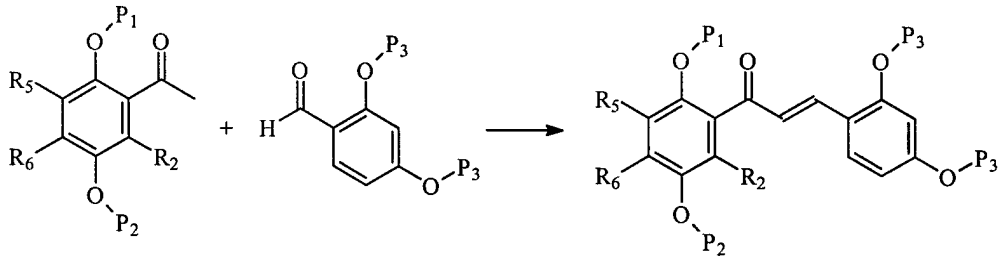
P_1, P_2, P_3, R_1 to R_3, R_5 and R_6 are defined as previously described.

In the above reaction scheme 2, the reduction from the compound (IV) to the compound (V') is achieved by hydrogenating the double bond contained in the compound (IV) for 2 hours under normal temperature and pressure in a solvent such as ethylacetate. The ketone compound (V') is reduced to the alcohol compound (V) through a treatment by sodium borohydride or lithium aluminum hydride. The process for obtaining the compound (Ib) by carrying out a deprotection on the compound (V') is identical to that explained for the reaction scheme 1 above. Particularly, when the protecting group is benzyl, the compound (Ib) can be prepared from the compound (V') by hydrogenating (i) in a solvent of ethylacetate for 10 to 15 hours under normal temperature

and 2 to 4 atms, or (ii) in a solvent mixture of ethylacetate and a lower alcohol (methanol, ethanol, isopropanol, etc.) for 20 minutes to one hour under temperatures ranging from 35 to 55℃ and normal pressure, or it is also possible to obtain the compound (Ib) directly from the compound (IV) by the hydrogenation under the condition (i) or (ii).

The compound (IV) used as a starting material in the reaction scheme 1 can be prepared by condensing a compound of formula (II) with a compound of formula (III) in a solvent in the presence of a base, as depicted in the following reaction scheme 3.

Reaction Scheme 3



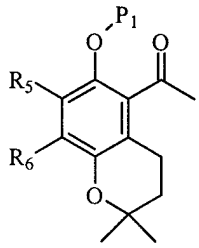
(II) (III) (IV)

in which

P_1, P_2, P_3, R_2, R_5 and R_6 are defined as previously described.

In this reaction, it is preferable to use one or more selected from a group consisting of ethanol, tetrahydrofuran and dimethylformamide as the solvent, and to use one or more selected from a group consisting of sodium hydroxide, potassium hydroxide and sodium hydride as the base. The desired product is obtained by stirring the reactants for about 5 to 24 hours. When P_1 and P_2 are different from each other, the compound of formula (II) can readily be prepared from the existing compounds(see, Chem. Ber., 95, 1413, 1962; J. Med. Chem., 34, 2152, 1991).

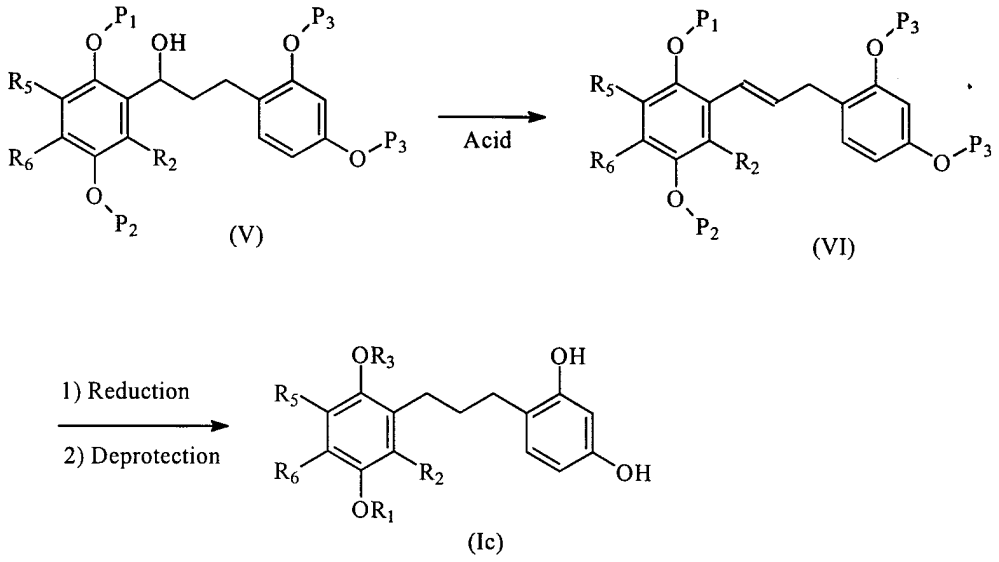
Among the compounds of formula (Ia), the compound wherein R_1 and R_2 together form a heterocycle can be prepared according to the same procedure as explained above using a compound represented by the following formula (IIa)(see, J. Chem. Soc. Perkin Trans I, 1437, 1981) instead of the compound of formula (II).



(IIa)

Finally, a compound represented by the following formula (Ic) wherein R_4 is hydrogen can be prepared, as depicted in the following reaction scheme 4, by dehydrating the compound (V) in a solvent in the presence of an acid to produce a compound represented by the following formula (VI) and then by reducing and deprotecting the compound (VI) thus produced.

Reaction Scheme 4



in which

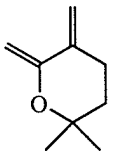
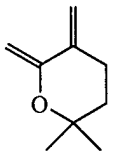
P_1 to P_3, R_1 to R_3, R_5 and R_6 are defined as previously described.

The process described in reaction scheme 4 will be specifically explained below.

The compound (V) is dehydrated in one or more solvents selected from a group consisting of benzene, toluene and xylene in the presence of one or more acids selected from a group consisting of sulfuric acid, phosphoric acid and p-toluenesulfonic acid to produce the compound (VI). This dehydration reaction is preferably carried out at temperatures ranging from 80 to 100℃. The desired compound (Ic) is obtained by reducing the compound (VI) through a hydrogenation reaction and then by removing the protecting groups. Process for removing the protecting groups is carried out according to the same procedure as reaction scheme 1.

Typical examples of the compound (I) prepared according to the processes as explained above are represented in the following Table 1.

Table 1.

COM. NO.	R_1	R_2	R_3	R_4	R_5	R_6
1	-H	-Me	-H	-OH	-Me	-Me
2	-H	-Me	-H	-H	-Me	-Me
3	-H	-Me	-Me	-OH	-Me	-Me
4	-H	-Me	-Me	-H	-Me	-Me
5	-Me	-Me	-H	-OH	-Me	-Me
6	-Me	-Me	-H	-H	-Me	-Me
7	-Et	-Me	-H	-OH	-Me	-Me
8			-H	-OH	-Me	-Me
9			-H	-H	-Me	-Me

Next, the present inventors have identified the inhibitory activity against tyrosinase of the compound (I) of the present invention according to the following procedure. That is, a sample is introduced into a microplate, to which are added a phosphate buffer solution(pH 6.8) and a L-tyrosine solution. Enzymatic reaction is started by the addition of a tyrosinase enzyme solution to the above mixture and then absorbance at 475nm was measured to calculate the inhibition(%) against tyrosinase(see, Experimental Example 1).

In addition, in order to determine the inhibitory activity of the compound (I) againt melanin biosynthesis, this compound is added to a culture media comprising B-16 melanoma cells and incubated. Then, the cells are

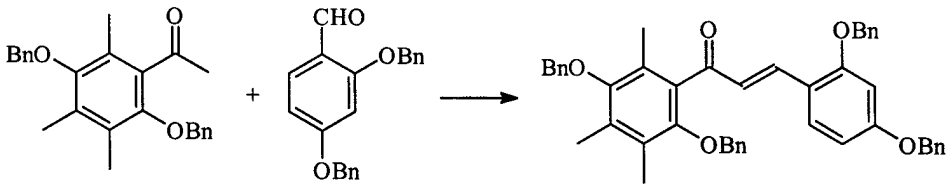
centrifuged to extract melanin and the amount of melanin produced is measured based on the absorbance(see, Experimental Example 2).

As a result, the compound of formula (I) according to the present invention is identified to have a superior or similar inhibitory effect against tyrosinase activity and melanin biosynthesis to that of the existing whitening substances. Therefore, it is possible to apply the compound of the present invention having such an effect to medicaments, non-medicinal supplies and cosmetics. The applying dosage of the compound (I) can be varied with the formulation type, purpose of use, etc.

The present invention will be more specifically explained by the following preparations, examples and experimental examples. However, it should be understood that the examples are intended to illustrate but not to in any manner limit the scope of the present invention.

Preparation 1

Synthesis of 3-(2,4-dibenzyloxy-phenyl)-1-(2,5-dibenzyloxy-3,4,6-trimethyl-phenyl)-propenone



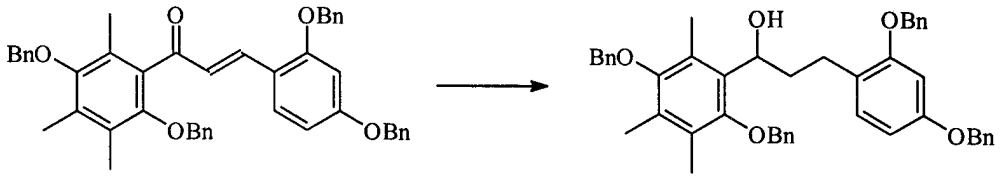
1.7g(4.54mmol) of 1-(2,5-dibenzyloxy-3,4,6-trimethyl-phenyl)-ethanone and 2.9g(9.08mmol) of 2,4-dibenzyloxy-benzaldehyde were dissolved in 32㎖ of a solvent mixture of ethanol and tetrahydrofuran(1/1, v/v), to which was slowly added dropwise 6㎖ of 50% aqueous sodium hydroxide solution. After the addition was completed, the reaction mixture was stirred for 16 hours at normal temperature. The solvent was removed by distillation under reduced

pressure and the resulting residue was diluted with 25㎖ of water, which was then neutralized to pH 7 with 10% aqueous HCl solution. This reaction solution was extracted with ethylacetate and then the solvent contained therein was removed by distillation under reduced pressure. The resulting mixture having a high viscosity was subjected to a silica gel column chromatography (eluent: n-hexane/ethylacetate=7/1, v/v) to obtain 1.8g(2.61mmol, Yield 58%) of the title compound.

Example 1

Synthesis of 4-[3-hydroxy-3-(2,5-dihydroxy-3,4,6-trimethyl-phenyl)-propyl]-benzene-1,3-diol

Step 1: Preparation of 3-(2,4-dibenzyloxy-phenyl)-1-(2,5-dibenzyloxy-3,4,6-trimethyl-phenyl)-propan-1-ol



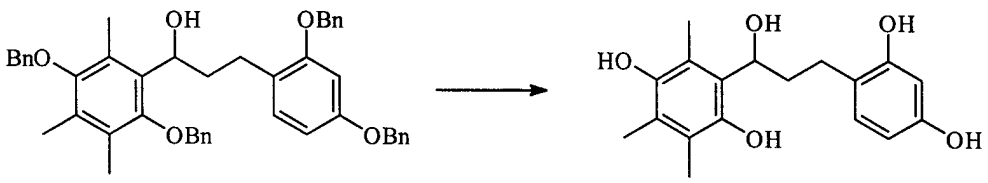
Method 1

0.57g(0.83mmol) of 3-(2,4-dibenzyloxy-phenyl)-1-(2,5-dibenzyloxy-3,4,6-trimethyl-phenyl)-propenone prepared in Preparation 1 was dissolved in 5㎖ of dry tetrahydrofuran and 0.1g(2.52mmol) of lithium aluminum hydride(LAH) was added thereto little by little while stirring at -30℃. The reaction solution was stirred for one hour, 0.1㎖ of water, 0.1㎖ of 15% aqueous NaOH solution and 0.3㎖ of water were added to the solution in order and then the whole mixture was stirred for further 30 minutes. The resulting precipitate was filtered off and the filtrate was distilled to obtain a white solid, which was then purified by a silica gel column chromatography(eluent: n-hexane/ethylacetate=5/1, v/v) to obtain 0.56g(Yield 98%) of the title compound.

Method 2

0.15g(0.22mmol) of 3-(2,4-dibenzyloxy-phenyl)-1-(2,5-dibenzyloxy-3,4,6-trimethyl-phenyl)-propenone prepared in Preparation 1 was dissolved in 4㎖ of ethylacetate(EtOAc). To this solution was slowly added 5㎎ of 10% palladium-carbon catalyst, which was reacted for 30minutes under pressurized hydrogen atmosphere(2atm). The reaction solution was diluted with 50㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure to produce 0.17g of 3-(2,4-dibenzyloxy-phenyl)-1-(2,5-dibenzyloxy-3,4,6-trimethyl-phenyl)-propanone. 0.17g(0.22mmol) of the compound thus produced was dissolved in 2㎖ of methanol, 20㎎(0.53mmol) of sodium boro hydride($NaBH_4$) was added thereto little by little at 0℃. The mixture was stirred for 10minutes at 0℃ and then the solvent was eliminated by distillation under reduced pressure. The residue was diluted with 10㎖ of water, extracted with ethylacetate and dried over anhydrous sodium sulfate. The solvent was distilled under reduced pressure and the residue was subjected to a silica gel column chromatography(eluent: n-hexane/ethylacetate=1/1, v/v) to obtain 0.1g (Yield 66%) of the title compound.

Step 2: Preparation of 4-[3-hydroxy-3-(2,5-dihydroxy-3,4,6-trimethyl-phenyl)-propyl]-benzene-1,3-diol

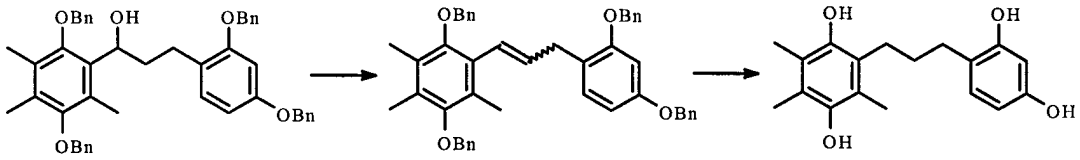


0.31g(0.45mmol) of 3-(2,4-dibenzyloxy-phenyl)-1-(2,5-dibenzyloxy-3,4,6-trimethyl-phenyl)-propan-1-ol was dissolved in 6㎖ of ethylacetate. To this solution was slowly added 10㎎ of 10% palladium-carbon catalyst, which was reacted for 12.5hours under pressurized hydrogen atmosphere(4atm). The

reaction solution was diluted with 50㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure to obtain 0.14g (Yield 100%) of the title compound.

Example 2

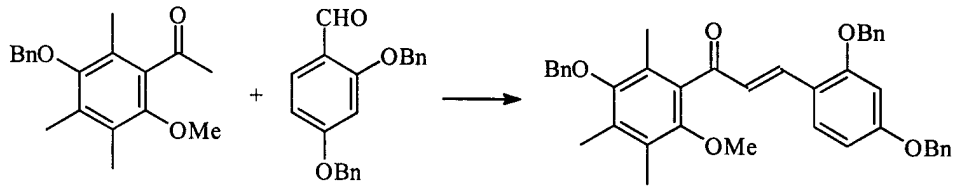
Synthesis of 4-[3-(2,5-dihydroxy-3,4,6-trimethyl-phenyl)-propyl]-benzene-1,3-diol



2.39g(3.46mmol) of 3-(2,4-dibenzyloxy-phenyl)-1-(2,5-dibenzyloxy-3,4,6-trimethyl-phenyl)-propan-1-ol was diluted with 100㎖ of dry benzene and 30㎎ of p-toluenesulfonic acid was added thereto. The mixture was stirred for 4hours while refluxing to eliminate water. The solution thus produced was cooled down to room temperature and washed once(x1) with saturated aqueous sodium hydrogen carbonate solution. The washings was extracted with dichloromethane and the extract was combined with the original organic layer. Then, the combined mixture was dried, distilled under reduced pressure and subjected to a silica gel column chromatography(eluent: n-hexane/ethylacetate= 10/1, v/v) to obtain 2.1g(Yield 90%) of 4-[3-(2,5-dibenzyloxy-3,4,6-trimethyl-phenyl)-allyl]-1,3-dibenzyloxy-benzene. 2.1g(3.12mmol) of the compound thus obtained was diluted with 30㎖ of ethylacetate, to which was slowly added 45 ㎎ of 10% palladium catalyst. The resulting solution was stirred for 72hours under hydrogen atmosphere of 60psi, diluted with 50㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure and subjected to a silical gel column chromatography(eluent: n-hexane/ethylacetate =1/1, v/v) to obtain 0.74g (Yield 79%) of the title compound.

Preparation 2

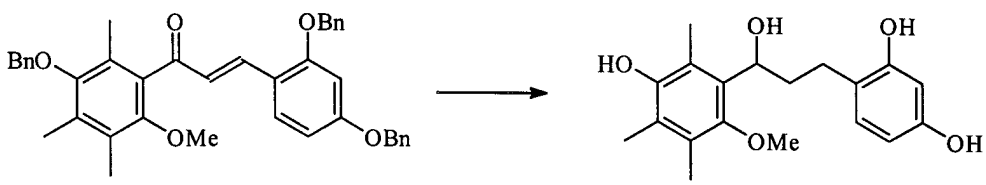
Synthesis of 3-(2,4-dibenzyloxy-phenyl)-1-(5-benzyloxy-2-methoxy-3,4,6-trimethyl-phenyl)-propenone



0.23g(0.77mmol) of 1-(5-benzyloxy-2-methoxy-3,4,6-trimethyl-phenyl)-ethanone and 0.62g(1.94mmol) of 2,4-dibenzyloxybenzaldehyde were dissolved in 7㎖ of a solvent mixture of ethanol and tetrahydrofuran(1/1, v/v) and then 1.5㎖ of 50% aqueous sodium hydroxide solution was slowly added dropwise thereto. After the addition was completed, the mixture was stirred for 16hours at normal temperature. The solvent contained therein was removed, the residue was diluted with water and neutralized to pH 7 using 10% aqueous hydrochloric acid solution. This solution was extracted with ethylacetate and the solvent was removed by distillation under reduced pressure. The residue having a high viscosity was subjected to a silica gel column chromatography (eluent: n-hexane/ethylacetate=7/1, v/v) to obtain 0.30g(Yield 65%) of the title compound.

Example 3

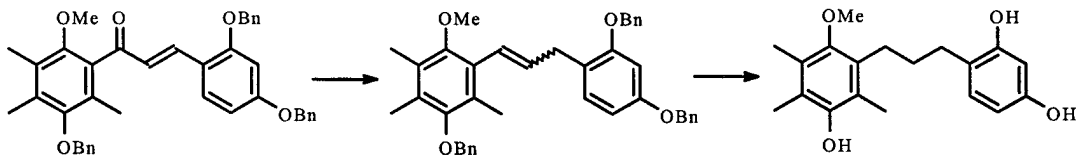
Synthesis of 4-[3-hydroxy-3-(5-hydroxy-2-methoxy-3,4,6-trimethyl-phenyl)-propyl]-benzene-1,3-diol



290㎎(0.48mmol) of 3-(2,4-dibenzyloxy-phenyl)-1-(5-benzyloxy-2-methoxy-3,4,6-trimethyl-phenyl)-propenone prepared in Preparation 2 was dissolved in 5㎖ of ethylacetate. To this solution was slowly added 15㎎ of 10% palladium-carbon catalyst, which was reacted for 12 hours under pressurized hydrogen atmosphere(4atm). The reaction solution was diluted with 100㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure to obtain 160㎎(0.48mmol, Yield 98%) of 3-(2,4-dihydroxy-phenyl)-1-(5-hydroxy-2-methoxy-3,4,6-trimethyl-phenyl)-propanone. 160㎎(0.48mmol) of the compound thus obtained was dissolved in 2㎖ of diethylether and 160㎎ (4.21mmol) of lithium aluminum hydride was added thereto little by little at 0 ℃. After stirring for one hour, 0.1㎖ of water, 0.1㎖ of 15% aqueous NaOH solution and 0.3㎖ of water were added thereto in order and the mixture was stirred for further 30 minutes. The resulting precipitate was filtered off and the filtrate was distilled to obtain a white solid which was then subjected to a silical gel column chromatography(eluent: n-hexane/ethylacetate=5/1, v/v) to obtain 158㎎(Yield 98%) of the title compound.

Example 4

Synthesis of 4-[3-(2-methoxy-5-hydroxy-3,4,6-trimethyl-phenyl)-propyl]-benzene-1,3-diol

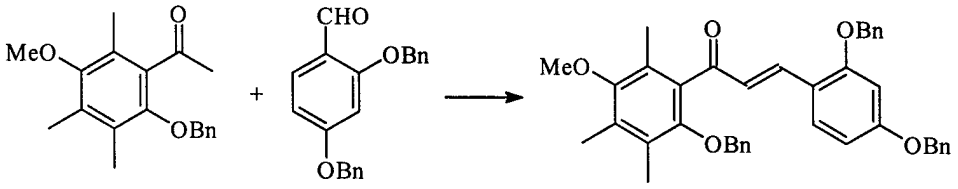


550㎎(0.92mmol) of 3-(2,4-dibenzyloxy-phenyl)-1-(5-benzyloxy-2-methoxy-3,4,6-trimethyl-phenyl)-propenone was dissolved in 7㎖ of ethylacetate. To this solution was slowly added 15㎎ of 10% palladium-carbon catalyst, and reacted for 2 hours under hydrogen atmosphere of normal pressure(1atm). The reaction solution was diluted with 15㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure to obtain 552㎎(Yield 100%) of

3-(2,4-dibenzyloxy-phenyl)-1-(2-methoxy-5-benzyloxy-3,4,6-trimethyl-phenyl)-propanone. 225㎎(0.37mmol) of the compound thus obtained was reduced by $NaBH_4$ to an alcohol compound which was then diluted with 10㎖ of dry benzene. 30㎎ of p-toluenesulfonic acid was added thereto and the mixture was stirred for 4hours while refluxing. The reaction solution was cooled down to room temperature and then washed with saturated aqueous sodium hydrogen carbonate solution once(x1). The washings was extracted again with dichloromethane and the extract was combined with the original organic layer. Then, the combined mixture was dried, distilled under reduced pressure and subjected to a silica gel column chromatography(eluent: n-hexane/ethylacetate =10/1, v/v) to obtain 169㎎(0.29mmol, Yield 78%) of 4-[3-(2-methoxy-5-benzyloxy-3,4,6-trimethyl-phenyl)-allyl]-1,3-dibenzyloxy-benzene. 160㎎(0.27 mmol) of the compound thus obtained was diluted with 30㎖ of ethylacetate, to which was slowly added 45㎎ of 10% palladium catalyst. The resulting mixture was stirred for 48 hours under hydrogen atmosphere of 60psi, diluted with 10㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure and the residue was subjected to a silica gel column chromatography(eluent: n-hexane/ethylacetate=1/1, v/v) to obtain 74㎎(0.234 mmol, Yield 86%) of the title compound.

Preparation 3

Synthesis of 3-(2,4-dibenzyloxy-phenyl)-1-(2-benzyloxy-5-methoxy-3,4,6-trimethyl-phenyl)-propenone

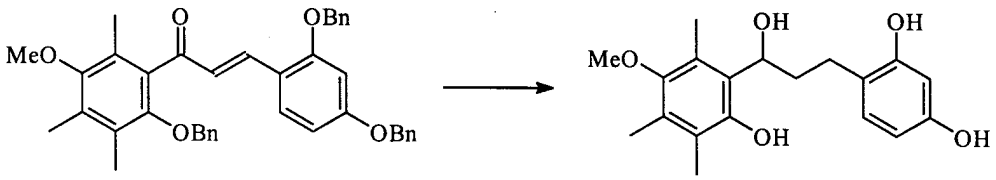


1.22g(4.09mmol) of 1-(2-benzyloxy-5-methoxy-3,4,6-trimethyl-phenyl)-ethanone and 2.8g(9mmol) of 2,4-dibenzyloxy-benzaldehyde were dissolved in

40㎖ of a solvent mixture of ethanol and tetrahydrofuran(1/1, v/v), to which was slowly added dropwise 10㎖ of 50% aqueous sodium hydroxide solution. After the addition was completed, the mixture was stirred for 16hours at normal temperature. The solvent contained in the reaction solution was removed by distillation under reduced pressure, the resulting residue was diluted with 40㎖ of water and then neutralized to pH 7 using 10% aqueous hydrochloric acid solution. This solution was extracted with ethylacetate and the solvent contained in the extract was removed by distillation under reduced pressure. The resulting mixture having a high viscosity was subjected to a silica gel column chromatography(eluent: n-hexane/ethylacetate= 7/1, v/v) to obtain 2.37g(Yield 97%) of the title compound.

Example 5

Synthesis of 4-[3-hydroxy-3-(2-hydroxy-5-methoxy-3,4,6-trimethyl-phenyl)-propyl]-benzene-1,3-diol

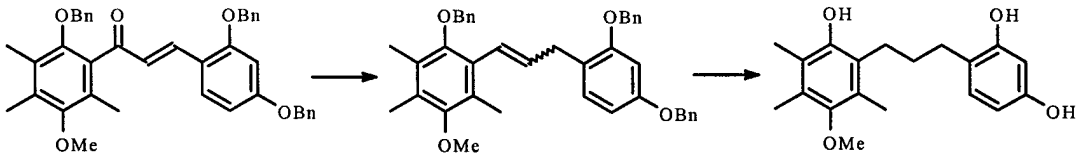


1.28g(0.21mmol) of 3-(2,4-dibenzyloxy-phenyl)-1-(2-benzyloxy-5-methoxy-3,4,6-trimethyl-phenyl)-propenone prepared in Preparation 3 was dissolved in 6㎖ of ethylacetate. To this solution was slowly added 45㎎ of 10% palladium-carbon catalyst, which was reacted for 12 hours under pressurized hydrogen atmosphere(4atm). The reaction solution was diluted with 50㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure to obtain 660㎎(Yield 95%) of 3-(2,4-dihydroxy-phenyl)-1-(2-hydroxy-5-methoxy-3,4,6-trimethyl-phenyl)-propanone. 660㎎(2mmol) of the compound thus obtained was dissolved in 12㎖ of diethylether, 750㎎ of lithium aluminum hydride was added thereto little by little at 0℃ and then the mixture was stirred for one hour. After 1㎖ of water, 1㎖ of 15% aqueous NaOH

solution and 3㎖ of water were added to the reaction solution in order, the resulting solution was stirred for further 30 minutes. The precipitate produced was filtered off and the filtrate was distilled to obtain a white solid which was then subjected to a silica gel column chromatography(eluent: n-hexane/ ethylacetate=5/1, v/v) to obtain 524㎎(1.58mmol, Yield 79%) of the title compound.

Example 6

Synthesis of 4-[3-(2-hydroxy-5-methoxy-3,4,6-trimethyl-phenyl)-propyl]-benzene-1,3-diol



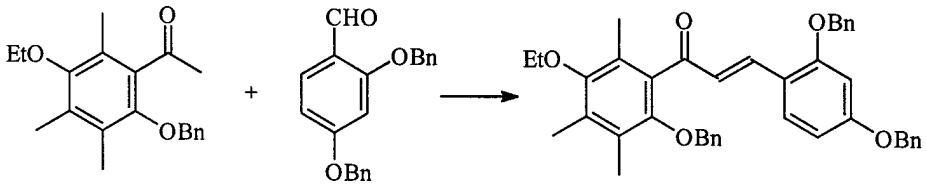
300㎎(0.50mmol) of 3-(2,4-dibenzyloxy-phenyl)-1-(2-benzyloxy-5-methoxy-3,4,6-trimethyl-phenyl)-propenone was dissolved in 3㎖ of ethylacetate. To this solution was slowly added 15㎎ of 10% palladium-carbon catalyst, which was reacted for 3 hours under hydrogen atmosphere of normal pressure (1atm). The reaction solution was diluted with 20㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure to obtain 3-(2,4-dibenzyloxy-phenyl)-1-(2-benzyloxy-5-methoxy-3,4,6-trimethyl-phenyl)-propanone. The compound thus obtained was not further purified and reduced by 40㎎ of $NaBH_4$ in 5㎖ of methanol to an alcohol compound. The reaction solution containing the alcohol compound was distilled under reduced pressure to remove methanol and extracted with dichloromethane to obtain 277㎎(Yield 92%) of the alcohol compound, which was then diluted with 10㎖ of dry benzene. 30㎎ of p-toluenesulfonic acid was added thereto and the mixture was stirred for 4 hours while refluxing. The reaction solution was cooled down to room temperature and then washed with saturated aqueous sodium hydrogen carbonate solution once(x1). The washings was extracted again

with dichloromethane and the extract was combined with the original organic layer. Then, the combined mixture was dried, distilled under reduced pressure and subjected to a silica gel column chromatography(eluent: n-hexane/ethylacetate=10/1, v/v) to obtain 244㎎(0.42mmol, Yield 91%) of 4-[3-(2-benzyloxy-5-methoxy-3,4,6-trimethyl-phenyl)-allyl]-1,3-dibenzyloxy-benzene.

The compound thus obtained was diluted with 30㎖ of ethylacetate, to which was slowly added 45㎎ of 10% palladium catalyst. The resulting mixture was stirred for 20 hours under hydrogen atmosphere of 60psi, diluted with 10 ㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure and the residue was subjected to a silica gel column chromatography (eluent: n-hexane/ethylacetate=1/1, v/v) to obtain 118㎎(Yield 88%) of the title compound.

Preparation 4

Synthesis of 3-(2,4-dibenzyloxy-phenyl)-1-(2-benzyloxy-5-ethoxy-3,4,6-trimethyl-phenyl)-propenone

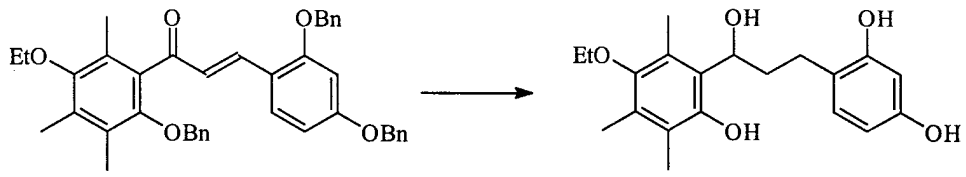


310㎎(1mmol) of 1-(2-benzyloxy-5-ethoxy-3,4,6-trimethyl-phenyl)-ethanone and 650㎎(2.1mmol) of 2,4-dibenzyloxy-benzaldehyde were dissolved in 15㎖ of a solvent mixture of ethanol and tetrahydrofuran(1/1, v/v), to which was slowly added dropwise 5㎖ of 50% aqueous sodium hydroxide solution. After the addition was completed, the mixture was stirred for 24 hours at normal temperature. The solvent contained in the reaction solution was removed by distillation under reduced pressure, the resulting residue was diluted with 10㎖ of water and then neutralized to pH 7 using 10% aqueous hydrochloric acid solution. This solution was extracted with ethylacetate and

the solvent contained in the extract was removed by distillation under reduced pressure. The residue was subjected to a silica gel column chromatography (eluent: n-hexane/ethylacetate=7/1, v/v) to obtain 440㎎(Yield 72%) of the title compound.

Example 7

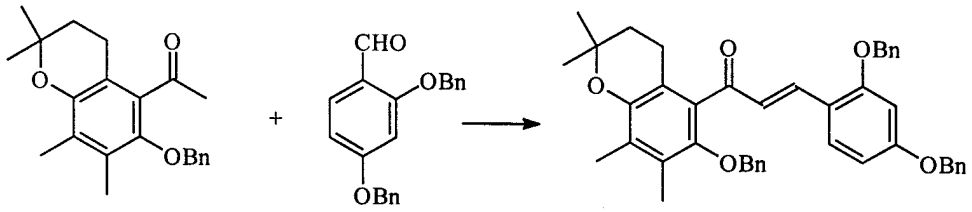
Synthesis of 4-[3-hydroxy-3-(2-hydroxy-5-ethoxy-3,4,6-trimethyl-phenyl)-propyl]-benzene-1,3-diol



440㎎(0.72mmol) of 3-(2,4-dibenzyloxy-phenyl)-1-(2-benzyloxy-5-ethoxy-3,4,6-trimethyl-phenyl)-propenone prepared in Preparation 4 was dissolved in 6 ㎖ of ethylacetate. To this solution was slowly added 15㎎ of 10% palladium-carbon catalyst, which was then reacted for 15 hours under pressurized hydrogen atmosphere(4atm). The reaction solution was diluted with 30㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure to obtain 205㎎(Yield 91%) of 3-(2,4-dihydroxy-phenyl)-1-(2-hydroxy-5-ethoxy-3,4,6-trimethyl-phenyl)-propanone. 205㎎(0.66mmol) of the compound thus obtained was dissolved in 12㎖ of diethylether, 200㎎ of lithium aluminum hydride was added thereto little by little at 0℃ and then the mixture was stirred for one hour. After 0.2㎖ of water, 0.2㎖ of 15% aqueous NaOH solution and 0.6㎖ of water were added to the reaction solution in order, the resulting solution was stirred for further 30minutes. The precipitate produced was filtered off and the filtrate was distilled to obtain a white solid, which was then subjected to a silica gel column chromatography(eluent: n-hexane/ ethylacetate=5/1, v/v) to obtain 160㎎(Yield 70%) of the title compound.

Preparation 5

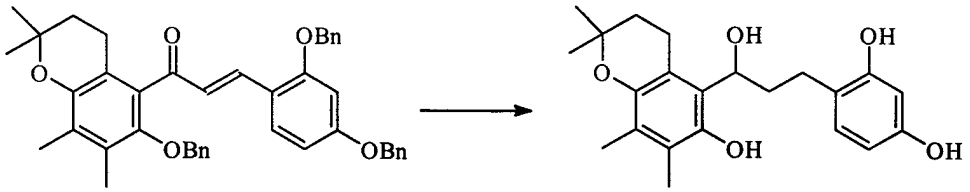
Synthesis of 3-(2,4-dibenzyloxy-phenyl)-1-(6-benzyloxy-2,2,7,8-tetramethyl-chroman-5-yl)-propenone



1.69g(5mmol) of 1-(6-benzyloxy-2,2,7,8-tetramethyl-chroman-5-yl)-ethanone and 3.2g(10.5mmol) of 2,4-dibenzyloxy-benzaldehyde were dissolved in 50 mℓ of a solvent mixture of ethanol and tetrahydrofuran(1/1, v/v), to which was slowly added dropwise 10mℓ of 50% aqueous sodium hydroxide solution. After the addition was completed, the mixture was stirred for 16 hours at normal temperature. After the solvent contained in the reaction solution was removed by distillation under reduced pressure, the residue was diluted with 50 mℓ of water and then neutralized to pH 7 using 10% aqueous hydrochloric acid solution. This solution was extracted with ethylacetate and the solvent contained in the extract was removed by distillation under reduced pressure. The residue was subjected to a silica gel column chromatography(eluent: n-hexane/ethylacetate=7/1, v/v) to obtain 2.13g(Yield 68%) of the title compound.

Example 8

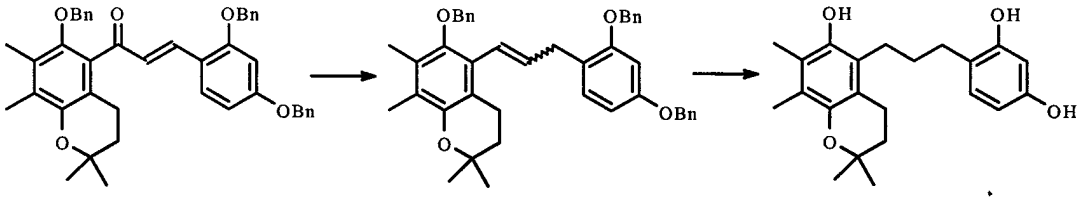
Synthesis of 4-[3-hydroxy-3-(6-hydroxy-2,2,7,8-tetramethyl-chroman-5-yl)-propyl]-benzene-1,3-diol



2.13g(3.33mmol) of 3-(2,4-dibenzyloxy-phenyl)-1-(6-benzyloxy-2,2,7,8-tetramethyl-chroman-5-yl)-propenone prepared in Preparation 5 was dissolved in 5㎖ of ethylacetate. To this solution was slowly added 30㎎ of 10% palladium-carbon catalyst, which was then reacted for 12 hours under pressurized hydrogen atmosphere(4atm). The reaction solution was diluted with 50㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure to obtain 1.14g(0.31mmol, Yield 94%) of 3-(2,4-dihydroxy-phenyl)-1-(6-hydroxy-2,2,7,8-tetramethyl-chroman-5-yl)-propanone. 1.14g of the compound thus obtained was dissolved in 10㎖ of diethylether, 1.0g of lithium aluminum hydride was added thereto little by little at 0℃ and then the mixture was stirred for one hour. After 1㎖ of water, 1㎖ of 15% aqueous NaOH solution and 3㎖ of water were added to the reaction solution in order, the resulting solution was stirred for further 30minutes. The precipitate produced was filtered off and the filtrate was distilled to obtain a white solid, which was then subjected to a silica gel column chromatography(eluent: n-hexane/ethylacetate=1/1, v/v) to obtain 1.04g(2.80mmol, Yield 90%) of the title compound.

Example 9

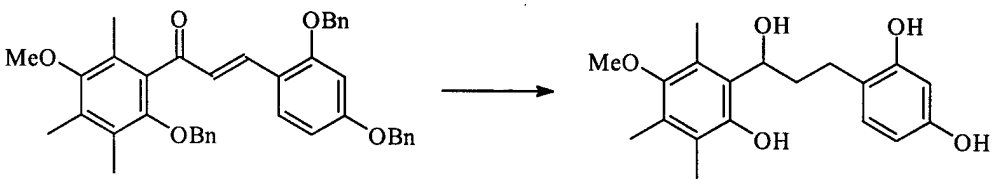
Synthesis of 4-[3-(6-hydroxy-2,2,7,8-tetramethyl-chroman-5-yl)-propyl]-benzene-1,3-diol



550㎎(0.86mmol) of 3-(2,4-dibenzyloxy-phenyl)-1-(6-benzyloxy-2,2,7,8-tetramethyl-chroman-5-yl)-propenone prepared in Preparation 5 was dissolved in 7㎖ of ethylacetate. To this solution was slowly added 10㎎ of 10% palladium-carbon catalyst, which was then reacted for 2hours under hydrogen atmosphere of normal pressure(1atm). The reaction solution was diluted with 50㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure to obtain 478㎎(0.75mmol, Yield 87%) of 3-(2,4-dibenzyloxy-phenyl)-1-(6-benzyloxy-2,2,7,8-tetramethyl-chroman-5-yl)-propanone. 200㎎(0.31 mmol) of the compound thus obtained was reduced by 125㎎ of $NaBH_4$ to an alcohol compound, which was then diluted with 10㎖ of dry benzene. 30㎎ of p-toluenesulfonic acid was added thereto and the mixture was stirred for 4hours while refluxing. The reaction solution was cooled down to room temperature and then washed with saturated aqueous sodium hydrogen carbonate solution once(x1). The washings was extracted again with dichloromethane and the extract was combined with the original organic layer. Then, the combined mixture was dried, distilled under reduced pressure and subjected to a silica gel column chromatography(eluent: n-hexane/ethylacetate=10/1, v/v) to obtain 169㎎(0.271mmol, Yield 88%) of an olefin compound. 160㎎ (0.26mmol) of this olefin compound thus obtained was diluted with 30㎖ of ethylacetate, to which was slowly added 4.5㎎ of 10% palladium catalyst. The resulting mixture was stirred for 48hours under hydrogen atmosphere of 60psi, diluted with 10㎖ of ethylacetate and then filtered. The filtrate was distilled under reduced pressure and the residue was subjected to a silica gel column chromatography(eluent: n-hexane/ethylacetate=3/1, v/v) to obtain 74㎎ (0.21mmol, Yield 80%) of the title compound.

Example 10

Synthesis of 4-[3-hydroxy-3-(2-hydroxy-5-methoxy-3,4,6-trimethyl-phenyl)-propyl]-benzene-1,3-diol



5.5g(9.2mmol) of 3-(2,4-dibenzyloxy-phenyl)-1-(2-benzyloxy-5-methoxy-3,4,6-trimethyl-phenyl)-propenone prepared in Preparation 3 was dissolved in 20 mℓ of a solvent mixture of ethanol and ethylacetate(1/3, v/v), to which was slowly added 50mg of 10% palladium-carbon catalyst. The temperature of the mixture was raised to 40℃ and then hydrogenation was carried out for 0.5hours at normal pressure. The reaction solution was diluted with 60mℓ of ethylacetate, filtered and then the filtrate was distilled under reduced pressure. The residue was diluted with diethylether, washed with aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate and then filtered. The filtrate was distilled under reduced pressure to obtain 2.88g(8.73mmol, Yield 95%) of 3-(2,4-dihydroxy-phenyl)-1-(2-hydroxy-5-methoxy-3,4,6-trimethyl-phenyl)-propanone. 2.88g(8.73mmol) of the compound thus obtained was dissolved in 12mℓ of methanol and 165mg(4.37mmol) of sodium borohydride was added thereto at 0℃ little by little. The reaction solution was stirred for one hour at normal temperature, distilled under reduced pressure, diluted with 10mℓ of ethylacetate and then washed with 10mℓ of water three times(x3). The organic layer separated was dried over anhydrous sodium sulfate and then filtered. The filtrate was distilled under reduced pressure and the residue was subjected to silica gel column chromatography (eluent: n-hexane/ethylacetate=5/1, v/v) to obtain 767mg(2.31mmol, Yield 80%) of the title compound.

The compounds represented in Table 1 were synthesized according to

the Preparations and Examples above, and their physico-chemical properties are represented in the following Table 2.

Table 2.

COM. NO.	^{1}H NMR ppm(solvent)	m.p. (℃)
1	6.90(d,1H), 6.35(d,1H), 6.25(dd,1H), 5.06(dd,1H), 2.72~2.82(m, 1H), 2.55~2.70(m,1H), 2.10(s,3H), 2.04(s,3H), 1.94(s,3H), 1.82 ~1.94(m,2H) (acetone d-6)	202
2	6.87(d,1H), 6.37(d,1H), 6.25(dd,1H), 2.58(t,2H), 2.51(t,2H), 2.06 (s,3H), 2.04(s,3H), 1.95(s,3H), 1.69(m,2H) (acetone d-6)	194
3	6.86(d,1H), 6.26(d,1H), 6.20(dd,2H), 5.12(dd,1H), 3.56(s,3H), 2.60~2.72(m,1H), 2.42~2.55(m,1H), 2.25(s,3H), 2.15(s,3H), 2.13 (s,3H), 1.80~1.95(m,2H) ($CDCl_3$)	63
4	6.89(d,1H), 6.20~6.26(m,2H), 3.53(s,3H), 2.60(t,2H), 2.53(t,2H), 2.28(s,3H), 2.20(s,3H), 2.17(s,3H), 1.70~1.80(m,2H) ($CDCl_3$)	58
5	6.93(d,1H), 6.40(d,1H), 6.29(dd,1H), 5.07(dd,1H), 3.51(s,3H), 2.85(m,1H), 2.68(m,1H), 2.10(s,3H), 2.06(m,1H), 1.95(s,3H), 1.85(m,1H) (acetone-d_6)	202
6	6.88(d,1H), 6.38(d,1H), 6.25(dd,1H), 3.54(s,3H), 2.60~2.80 (m,4H), 2.12(s,9H), 1.75~1.95(m,2H) (acetone-d_6)	153
7	6.96(d,1H), 6.39(d,1H), 6.28(dd,1H), 5.08(dd,1H), 3.65(q,2H), 2.69~2.75(m,1H), 2.78~2.85(m,1H), 2.10(s,3H), 2.06(s,3H), 2.00 (s,3H), 1.80~1.95(m,2H), 1.31(t,3H) (acetone-d-6)	132
8	7.00(d,1H), 6.36(d,1H), 6.27(m,1H), 5.10(dd,1H), 2.72~2.82 (1H,m), 2.56~2.70(m,3H), 2.14(s,3H), 2.12(s,3H), 1.70~1.95 (m,4H), 1.36(s,3H), 1.28(s,3H) ($CDCl_3$)	156
9	6.97(d,1H), 6.31~6.36(m,2H), 5.10~5.20(br,s,1H), 4.80~4.90 (br,s,1H), 2.55~2.65(m,6H), 2.13(s,3H), 2.09(s,3H), 1.65~1.85 (m,4H), 1.28(s,6H) ($CDCl_3$)	134

The inhibitory effects against tyrosinase and melanin biosynthesis of the compound (I) of the present invention was measured according to the procedures described in the following Experimental Examples 1 and 2.

Experimental Example 1

Inhibitory activity against tyrosinase

Enzyme tyrosinase extracted from mushrooms(manufactured by Sigma) was used in the present experiment. First, a substrate L-tyrosine was dissolved in phosphate buffer solution(0.05M, pH 6.8) to a concentration of 1.5mM and then 0.01㎖ of this solution was introduced to a 0.3㎖ cuvette in a spectrophotometry. Dopa as a cofacter was prepared as a solution in a concentration of 0.06mM and 0.01㎖ of this dopa solution was added to the substrate solution. To the resulting mixture were added the inhibitor of formula (I) and phosphate buffer solution to a total volume of 0.31㎖. The reaction was started by adding 0.1㎖ of an enzyme solution in which tyrosinase was dissolved in phosphate buffer solution in a concentration of 60U/㎖. 0.1㎖ of phosphate buffer solution instead of the enzyme solution was added to the blank sample. The reaction was carried out for 10 minutes at 37℃ and then absorbance at 475nm was measured using Spectrophotometer (Beckman DU-7500).

Inhibition(%) against tyrosinase of the compound (I) is calculated based on the absorbance at 475nm and IC_{50} value is determined as the concentration of the inhibitor when the inhibition(%) against enzyme activity reaches 50%. The Inhibition(%) can be calculated according to the following formula and the results are represented in the following Table 3.

$$\text{Inhibition}(\%) = \frac{(A-B)}{A} \times 100$$

in the above formula

A represents absorbance at 475nm when the inhibitor is added, and

B represents absorbance at 475nm when the inhibitor is not added.

Table 3.

Inhibitory activity against tyrosinase

Compound No.	$IC_{50}(\mu g/m\ell)$
1	0.5
2	1
3	50
4	20
5	0.1
6	0.1
7	1.0
8	0.3
9	0.3
Arbutin	113
Kojic acid	3.1
Hydroquinone	0.5

As can be seen from the results in Table 3 above, the compound of formula (I) according to the present invention shows a similar or superior inhibitory activity against tyrosinase to the existing inhibitors. Thus, the present compounds can be used advantageously for such a purpose.

Experiment 2

Inhibitory effect against melanin biosynthesis in B-16 mouse melanoma cell

The compound according to the present invention was added to a culture media of B-16 mouse melanoma cell and observed in order to examine its whitening effect in cellular level.

B-16 mouse melanoma cells were cultured to a density of 10^6cells/dish in culture media, compounds in various concentrations were respectively added thereto and then cultured for 3days. The cells were separated from the culture dish by the treatment with trypsin and then centrifuged to extract melanin(wherein a pellet was extracted using 2N perchloric acid). 1㎖ of 1N aqueous sodium hydroxide solution was added to the melanin extracted and the resulting mixture was heated to dissolve melanin. The absorbance at 400nm was measured by a spectrophotometer and the amount of the melanin produced was represented by the absorbance per unit cell numbers(10^6 cell). IC_{50} value is determined as the concentration of the inhibitor when the inhibition(%) against enzyme activity reaches 50% and the results are represented in the following Table 4.

Table 4.

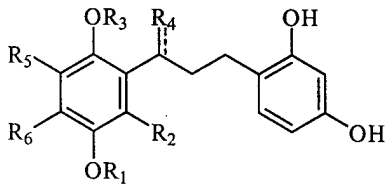
Compound No.	IC_{50}(㎍/㎖)
1	10
2	5
3	40
4	45
5	5
6	10
7	20
8	2
9	3
Arbutin	300
Kojic acid	15

The results of Table 4 shows that the compound according to the present invention exhibits an excellent inhibitory activity against melanin

biosynthesis in mouse melanoma cell. Therefore, it is recognized that the compound of the present invention exhibits a distinguished whitening effect through the prevention of melanin synthesis which is fundamentally due to the inhibition against tyrosinase.

WHAT IS CLAIMED IS:

1. 1,3-diphenylpropane derivative represented by the following formula (I):



(I)

in which

= represents double or single bond,

R_1 represents hydrogen or C_1-C_{10} alkyl,

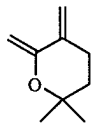
R_2 represents C_1-C_5 alkyl or C_1-C_5 alkoxyalkyl, or

R_1 and R_2 together represent a 5 to 6 membered heterocycle which can be substituted by C_1-C_5 alkyl and which contains oxygen as the hetero atom,

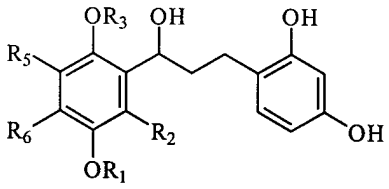
R_3 represents hydrogen or C_1-C_7 alkyl,

R_4 represents hydrogen, hydroxy, or oxo, and

R_5 and R_6 independently of one another represent hydrogen or C_1-C_5 alkyl.

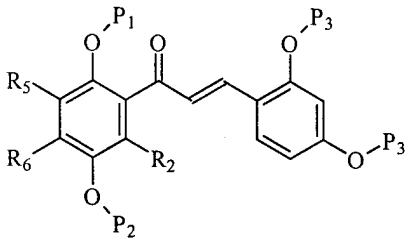
2. The compound of claim 1, wherein R_1 represents hydrogen, methyl or ethyl, R_2 represents methyl, or R_1 and R_2 together represent  , R_3 represents hydrogen or methyl, R_4 represents hydrogen or hydroxy, and R_5 and R_6 independently of one another represent methyl.

3. A process for preparing a compound represented by the following formula (Ia),



(Ia)

in which R_1 to R_3, R_5 and R_6 are as defined in claim 1, which comprises reducing a compound represented by the following formula (IV),



(IV)

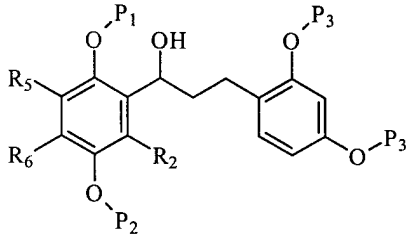
in which

P_1 represents benzyl, methyl, ethyl, tetrahydropyranyl, methoxymethyl, methoxyethoxymethyl or p-methoxybenzyl,

P_2 represents benzyl, methyl or ethyl,

P_3 represents benzyl, tetrahydropyranyl, methoxymethyl, methoxyethoxy methyl or p-methoxybenzyl, and

R_2, R_5 and R_6 are as defined in claim 1, in a solvent to produce a compound represented by the following formula (V),



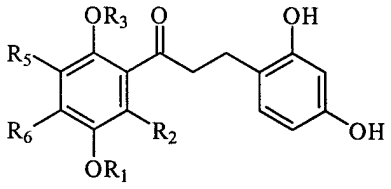
(V)

in which P_1 to P_3 are defined as above and R_2, R_5 and R_6 are as defined in claim 1, and then removing the protecting groups in the compound of formula (V).

4. The process of claim 3, wherein the reduction is carried out in a solvent selected from a group consisting of diethylether and tetrahydrofuran (THF) in the presence of lithium aluminum hydride(LAH).

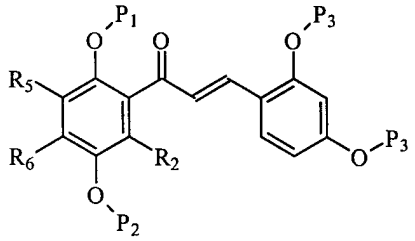
5. The process of claim 4, wherein the reduction is carried out at temperatures ranging from -30 to 30℃.

6. A process for preparing a compound represented by the following formula (Ib),



(Ib)

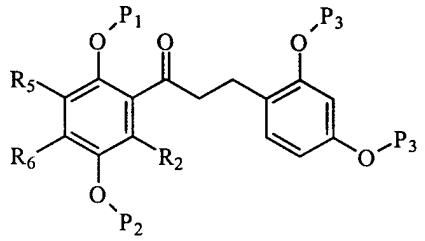
in which R_1 to R_3, R_5 and R_6 are as defined in claim 1, which comprises hydrogenating the double bond in a compound represented by the following formula (IV),



(IV)

in which P_1 to P_3 are as defined in claim 3 and R_2, R_5 and R_6 are as defined in claim 1, in a solvent to produce a compound represented by the following

formula (V'),



(V')

in which P_1 to P_3 are as defined in claim 3 and R_2, R_5 and R_6 are as defined in claim 1, and then removing the protecting groups in the compound of formula (V').

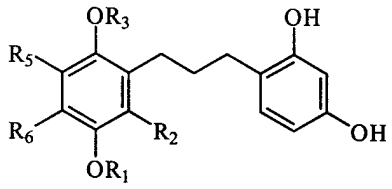
7. The process of claim 6, wherein the solvent is ethylacetate.

8. The process of claim 6, wherein the protecting group is benzyl and the compound of formula (Ib) is produced from the compound of formula (V') or directly produced from the compound of formula (IV) by carrying out the hydrogenation in ethylacetate or a solvent mixture of ethylacetate and a lower alcohol.

9. The process of claim 8, wherein the solvent is ethylacetate and the hydrogenation is carried out for 10 to 15 hours under normal temperature and pressures ranging from 2 to 4atms.

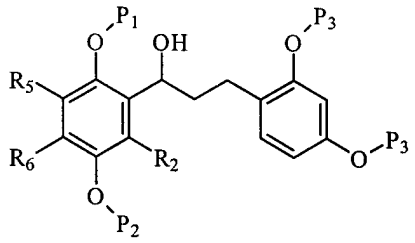
10. The process of claim 8, wherein the solvent is a mixture of ethylacetate and a lower alcohol and the hydrogenation is carried out for 20 minutes to one hour under temperatures ranging from 35 to 55℃ and normal pressure.

11. A process for preparing a compound represented by the following formula (Ic),



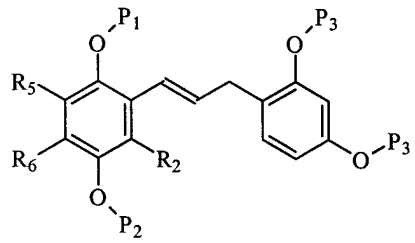
(Ic)

in which R_1 to R_3, R_5 and R_6 are as defined in claim 1, which comprises dehydrating a compound represented by the following formula (V),



(V)

in which P_1 to P_3 are as defined in claim 3 and R_2, R_5 and R_6 are as defined in claim 1, in a solvent in the presence of an acid to produce a compound represented by the following formula (VI),



(VI)

in which P_1 to P_3 are as defined in claim 3 and R_2, R_5 and R_6 are as defined in claim 1, and then reducing and deprotecting the compound of formula (VI) thus produced.

12. The process of claim 11, wherein the dehydration is carried out in a solvent selected from a group consisting of benzene, toluene and xylene in the presence of an acid selected from a group consisting of sulfuric acid, phosphoric acid and p-toluenesulfonic acid.

13. The process of claim 12, wherein the dehydration is carried out at temperatures ranging from 80 to 100℃.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 98/00039

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 C 39/12, 43/23, 49/83, 49/84; C 07 D 311/20

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]: C 07 C 39/00, 43/00, 49/00; C 07 D 311/00

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 practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search	Date of mailing of the international search report
03 April 1998 (03.04.98)	15 April 1998 (15.04.98)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Reif Telephone No. 1/53424/323

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 98/00039

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Information on patent family members

International application No.
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