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(54) **1-phenylpyrrolidone derivatives having optical activity**

Optisch aktive 1-Phenylpyrrolidonderivate

Dérivés optiquement actifs de 1-phényle-pyrrolidone

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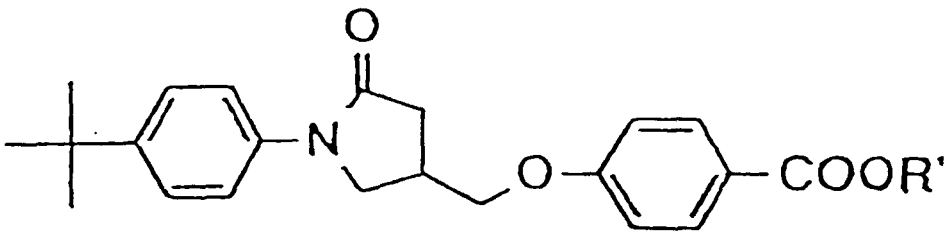
- **JEAN JACQUES, ANDR[1] COLLET, SAMUEL H. WILEN: "Enantiomers, Racemates and Resolutions" 1991 , KRIEGER , MALABAR, FLORIDA XP002096145 * page 263 - page 264 ***
- **DATABASE WPI Week 9432 Derwent Publications Ltd., London, GB; AN 94-260486 XP002096146 -& JP 06 192221 A (NAGASE SANGYO KK) , 12 July 1994**
- **S. WATANABE ET AL.: "Synthesis of 4-[1-(subsituted phenyl)-2-oxo-pyrrolidin-4-yl] methyloxyben zoic acids and related compounds, and their inhibitory capacities toward fatty-acid and sterol biosynthesis" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRYCHIMICA THERAPEUTICA., vol. 29, 1994, pages 675-686, XP002096144 PARIS FR**

EP 0 916 657 B9

Description

Field of the Invention

[0001] The present invention relates to a novel 1-phenylpyrrolidone derivative having optical activity, and there is described herein an intermediate for the preparation of the derivative, and processes for their preparation. The present invention provides an optically active form of a compound represented by the following formula (II) which is useful as an agent for treating hyperlipidemia which has an activity to inhibit the synthesis of fatty acids and an activity to inhibit the synthesis of cholesterol



(II)

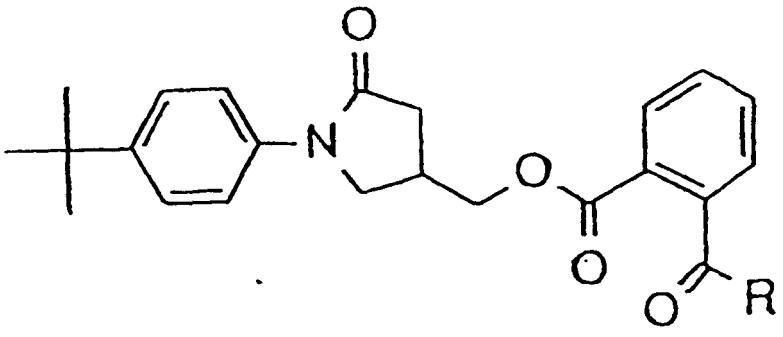
wherein R' is a hydrogen atom or a lower alkyl group such as an alkyl group having 1 to 6 carbon atoms.

Background Art

[0002] An optically inactive, racemic form of the compound of the formula (II) is disclosed in Japanese Unexamined Patent Publication (Kokai) Hei 3-275666 (European Patent Publication No. 393607), but no report has been made on the synthesis of an optically active form of the compound of the formula (II).

Disclosure of the Invention

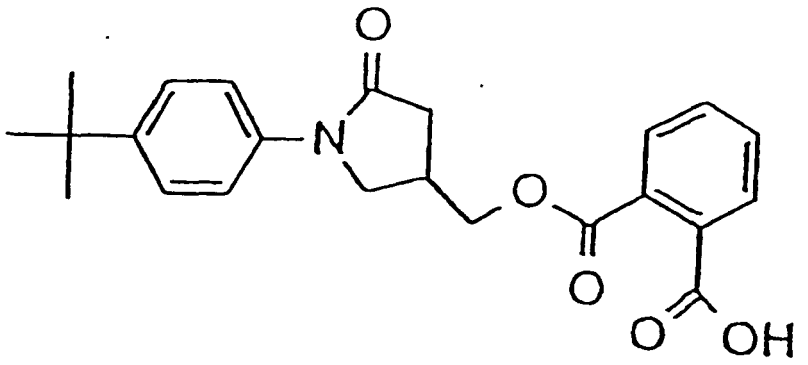
[0003] The present inventors conducted extensive research on processes for preparing the optically active form of the compound of the formula (II) and found that a 1-phenylpyrrolidone derivative having optical activity and represented by the formula (I), wherein R represents an optionally substituted optically active α-phenylethylamino group, which is a novel compound undisclosed in literature is useful as an intermediate for preparing the optically active form of the compound of the formula (II). The present inventors completed this invention on the basis of this finding.



(I)

[deletion(s)]

[0004] A 1-phenylpyrrolidone derivative represented by the formula (I-a)



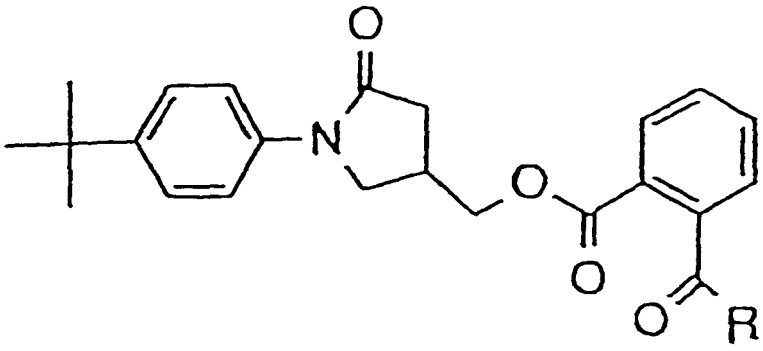
(I-a)

is an intermediate for preparing the 1-phenylpyrrolidone derivative of the formula (I) having optical activity.

[0005] A process for preparing the foregoing 1-phenylpyrrolidone derivative having optical activity and represented by the formula (I), comprises the steps of:

i) reacting the foregoing compound of the formula (I-a) with a chlorinating agent in a solvent which does not participate in the reaction to convert the compound to the acid chloride thereof,

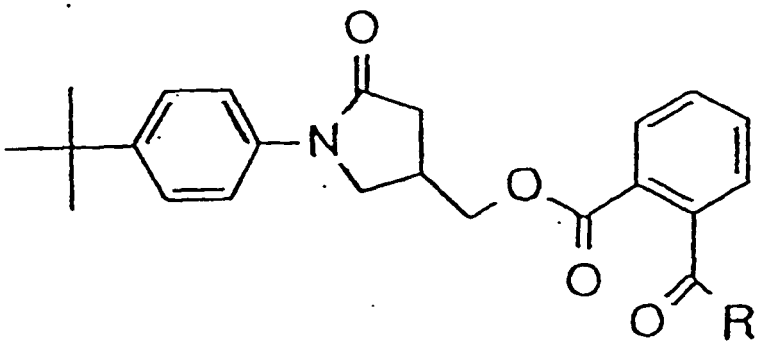
ii) reacting the acid chloride prepared in the step i) with an optionally substituted optically active α-phenylethylamine in the presence of a basic compound in a solvent which does not participate in the reaction to give a mixture of diastereomers of a compound represented by the formula (I-b)



(I-b)

wherein R is as defined above, and

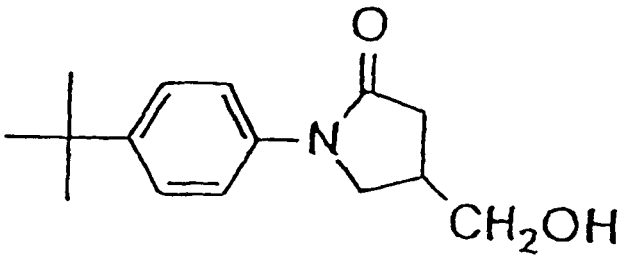
iii) optionally conducting resolution of the diastereomer mixture obtained in the step ii) to give an optically active compound represented by the formula (I-b')



(I-b')

wherein R is as defined above.

[0006] A process for preparing the foregoing compound of the formula (I-a), comprises the step of reacting a racemic mixture represented by the formula (III)



(III)

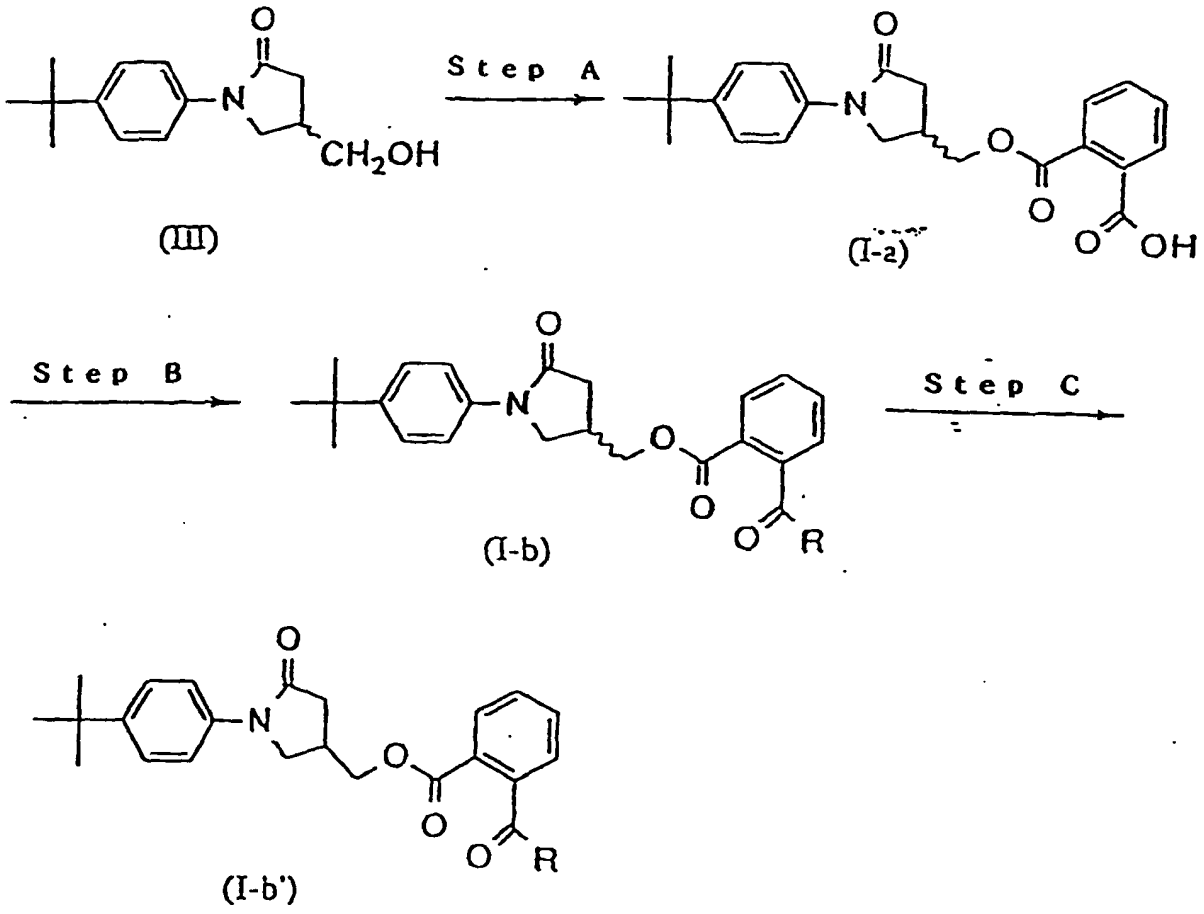
with phthalic anhydride for esterification in the presence of a basic compound in a solvent which does not adversely affect the reaction.

[0007] The optically active 1-phenylpyrrolidone derivatives of the formula (I) may exist as four different optical isomers.

[0008] The substituent for the "optionally substituted optically active α-phenylethylamino group" which is represented by R is one introduced to the o-position, m-position or p-position of the phenyl group of the α-phenylethylamino group. Particularly preferable among them is one introduced to the p-position thereof. Examples of the substituent are a lower alkyl group having 1 to 4 carbon atoms, a halogen atom such as fluorine, chlorine, bromine, iodine, etc., nitro group, and so on. Preferred p-substituted phenyl groups are p-tolyl group, p-bromophenyl group, p-nitrophenyl group, etc.

[0009] The optically active 1-phenylpyrrolidone derivative of the formula (I) (I-b, I-b') can be synthesized in accordance with Reaction Scheme (i) illustrated below from a compound of the formula (III) in the form of racemic mixture via the compound of the formula (I-a) in the form of racemic mixture as the intermediate.

Reaction Scheme (i)



[0010] In the formulas, R is as defined above.

[0011] In Reaction Scheme (i), the steps are conducted as described below in greater detail.

Step A

[0012] The known racemic mixture represented by the formula (III) is reacted with phthalic anhydride (esterification reaction) in a suitable solvent in the presence of a basic compound, giving the compound of the formula (I-a).

[0013] Solvents useful for the reaction are not specifically limited insofar as they do not adversely affect the reaction. Examples of useful solvents are ethers such as diethyl ether, tetrahydrofuran, dioxane, etc., halogenated hydrocarbons such as dichloromethane, chloroform, etc., aromatic hydrocarbons such as benzene, toluene, xylene, etc., amines such as pyridine, piperidine, triethylamine, etc., and aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, etc. These solvents can be used singly or at least two of them are usable in mixture.

[0014] Examples of the basic compound are organic basic compounds such as tertiary amines, e.g. triethylamine, pyridine, etc. and inorganic basic compounds such as sodium hydride, etc. When triethylamine, pyridine or other basic compound is used as a solvent, they can act also as a basic compound, and therefore an additional basic compound is not necessarily used.

[0015] As to the proportions of the starting materials to be used in the esterification reaction, about 1 to about 2 moles of phthalic anhydride and about 1 to about 3 moles of the basic compound are used per mole of the compound of the formula (III). The reaction temperature is in the range of approximately 0°C to the boiling point of the solvent, preferably about 0 to about 80°C. The reaction time is in the range of about 0.5 to about 48 hours, preferably about 2 to about 24 hours.

[0016] The compound of the formula (I-a) from the reaction mixture prepared by the foregoing reaction is used as a starting material in the subsequent reaction step after isolation or without isolation.

Step B

[0017] The compound of the formula (I-a) prepared in step A is reacted with a chlorinating agent (chlorination reaction) in a suitable solvent to thereby convert the compound to the acid chloride thereof. The acid chloride is then reacted with an optionally substituted optically active α-phenylethylamine in a suitable solvent in the presence of a basic compound, giving the compound of the formula (I-b) in the form of a diastereomer mixture.

[0018] Solvents for use in the conversion to the acid chloride are not specifically limited insofar as they do not participate in the reaction. Useful solvents include, for example, halogenated hydrocarbons such as dichloromethane, chloroform, etc. and aromatic hydrocarbons such as benzene, toluene, xylene, etc. These solvents can be used singly or at least two of them are usable in mixture.

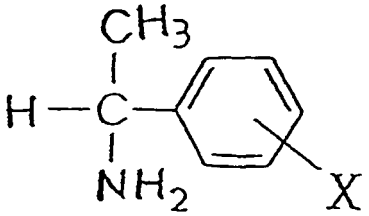
[0019] Useful chlorinating agents include, for example, thionyl chloride, phosphorus pentachloride, etc.

[0020] As to the proportions of the starting materials to be used in the chlorination reaction, about 1 to about 3 moles of the chlorinating agent is used per mole of the compound of the formula (I-a). The reaction temperature is in the range of approximately 0°C to the boiling point of the solvent, preferably about 10 to about 80°C. The reaction time is in the range of about 0.5 to about 12 hours, preferably about 1 to about 3 hours.

[0021] After completion of the chlorination reaction, the solvent alone or the solvent and the excess chlorinating agent is (are) evaporated off whereby the acid chloride of the compound of the formula (I-a) can be quantitatively obtained.

[0022] Next, the obtained acid chloride is reacted with an optionally substituted optically active α-phenylethylamine (reaction for the introduction of α-phenylethylamine).

[0023] The optionally substituted optically active α-phenylethylamine which is used in this reaction is a compound represented by the formula (IV)



(IV)

wherein X is a hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms, a halogen atom or nitro group. Examples of such compounds are (S)-(-)-α-phenylethylamine, (S)-(-)-4-methyl-α-phenylethylamine, (S)-(-)-4-bromo-α-phenylethylamine, (S)-(-)-4-nitro-α-phenylethylamine, (R)-(+)-α-phenylethylamine, (R)-(+)-4-methyl-α-phenylethylamine, (R)-(+)-4-bromo-α-phenylethylamine or (R)-(+)-4-nitro-α-phenylethylamine, etc. These compounds of the formula (IV), which are all known compounds, are readily available or can be synthesized according to known processes.

[0024] Solvents which can be used in the reaction for the introduction of α-phenylethylamine are not specifically limited insofar as they do not participate in the reaction. Useful solvents include, for example, halogenated hydrocarbons such

as dichloromethane, chloroform, etc., and aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, etc. These solvents can be used singly or at least two of them are usable in mixture.

[0025] Examples of the basic compound are organic basic compounds such as tertiary amines, e.g. triethylamine, pyridine, etc.

[0026] As to the proportions of the starting materials to be used in the reaction for the introduction of α-phenylethylamine, about 1 to about 2 moles of the optionally substituted optically active α-phenylethylamine, and about 1 to about 5 moles of the basic compound are used per mole of the acid chloride. The reaction temperature is in the range of approximately 0°C to the boiling point of the solvent, preferably about 0 to about 80°C. The reaction time is in the range of about 0.5 to about 12 hours, preferably about 1 to about 3 hours.

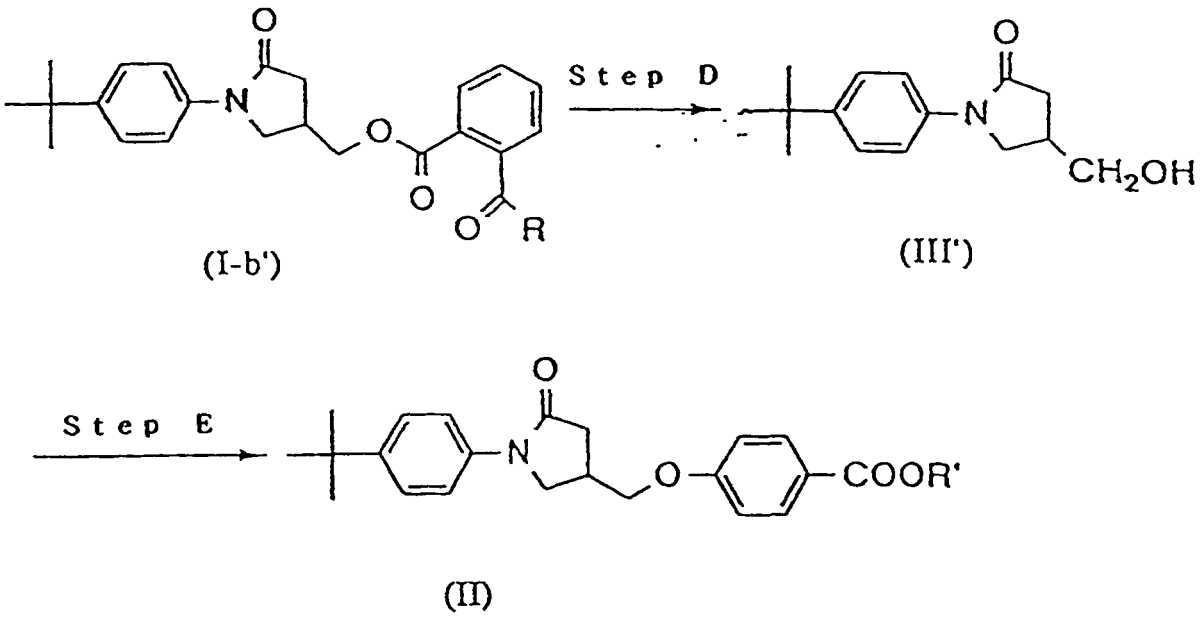
[0027] The diastereomer mixture represented by the formula (I-b) can be easily isolated and purified by conventional separation methods such as silica gel column chromatography, extraction, etc. from the reaction mixture obtained by the foregoing reaction.

Step C

[0028] An optically active compound of the formula (I-b') can be prepared from the diastereomer mixture represented by the formula (I-b) by conventional methods such as fractional recrystallization using a suitable solvent, e.g. ethyl acetate, methanol, hexane-ethyl acetate mixture, silica gel column chromatography etc.

[0029] The optically active form of the compound of the formula (II) can be synthesized from the compound of the formula (I-b') of the present invention according to Reaction Scheme (ii) illustrated below.

Reaction Scheme (ii)



[0030] In the above formulas, R' and R are as defined above.

[0031] In Reaction Scheme (ii), the steps are conducted as described below in greater detail.

Step D

[0032] An optically active form of the compound of the formula (III') can be produced by hydrolyzing in the presence of an alkali a (+)- form or (-)- form of the compound of the formula (I-b') prepared in Reaction Scheme (i).

[0033] Useful alkalis include, for example, hydroxides of alkali metals such as sodium hydroxide, potassium hydroxide, etc. Useful solvents include, for example, alcohols such as methanol, ethanol and isopropanol, water, etc.

[0034] As to the proportions of the starting materials to be used in the hydrolysis reaction, about 1 to about 2 moles of the alkali is used per mole of the compound of the formula (I-b'). The reaction temperature is in the range of approximately 0°C to the boiling point of the solvent, preferably about 0 to about 80°C. The reaction time is in the range of about 0.2

to about 12 hours, preferably about 0.5 to about 3 hours.

Step E

[0035] The compound of the formula (II) having optical activity can be prepared from the compound of the formula (III') obtained in step D by following the same procedure as the method disclosed in Japanese Unexamined Patent Publication (Kokai) No. Hei 3-275666 (European Patent Publication No.393607). The details of the synthesis of the compound of the formula (II) will be given in Reference Examples to be described later.

[0036] Conventional process for preparing the compound (racemate) of the formula (II) is intended to produce the compound of the formula (II) directly from the compound (racemate) of the formula (III). On the other hand, an attempt may be made to subject the compound (racemate) of the formula (II) directly to optical resolution in order to obtain the compound of the formula (II) having an optical activity. However, it is very difficult to achieve the optical resolution of the compound (racemate) of the formula (II) without resort to the techniques described herein. Contrastedly, the compound of the formula (II) having optical activity can be easily produced from the compound of the formula (I-b) (diastereomer mixture) via the compound of the formula (I-b') having optical activity.

Effects of the Invention

[0037] When the 1-phenylpyrrolidone derivative of the formula (I) of the present invention having optical activity is used as an intermediate, 4-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxybenzoic acid or a lower alkyl ester thereof of the formula (II) which is useful as an agent for treating hyperlipidemia can be easily produced by using known method.

[0038] That is to say, the compound of the formula (I-b) of the present invention, which is prepared by reacting the intermediate compound (I-a) with an optionally substituted optically active α-phenylethylamine, can be easily resolved into isomers, and therefore the compound (I-b') having optical activity can be easily recovered. Using the compound (I-b') having optical activity as the starting material, an optically active form of 4-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl] methoxybenzoic acid or a lower alkyl ester thereof of the formula (II) can be easily prepared by utilizing the known methods.

[0039] An optically active compound of the formula (II) has a higher absorption and a higher therapeutic effect and involves less side effects than a racemic form.

EXAMPLES

[0040] Examples and Reference Examples are given below to illustrate the synthetic route in detail.

Example 1

Synthesis of phthalic acid mono-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methyl ester (I-a)

[0041] A 8.3 ml (60 mmol) quantity of triethylamine was added to a solution of 12.35 g (50 mmol) of [1-(4-t-butylphenyl)-2-pyrrolidone-4-yl)methyl alcohol (III) and 7.4 g (50 mmol) of phthalic anhydride in dichloromethane (150 ml), and the mixture was refluxed with heating for 24 hours. The reaction mixture was washed with a dilute hydrochloric acid, dried over magnesium sulfate and concentrated under reduced pressure to give 19.8 g (quantitative yield) of the title compound.
Melting point: 155°C-157°C
NMR spectrum ($CDCl_3$) δ
2.66 (1H, dd, J=16.8, 6.3 Hz), 2.8-3.0 (2H, m), 3.72 (1H, dd, J=9.9, 5.3 Hz), 3.99(1H, dd, J=9.9, 8.0 Hz), 4.39 (2H, d, J=6.0Hz), 7.33 (2H, d, J=8.9Hz), 7.46 (2H, d, J=8.9Hz), 7.50-7.60 (2H, m), 7.65-7.73 (2H, m), 7.84-7.90 (2H, m)
MASS spectrum (FAB) 394 (M^+-1)

Example 2

Synthesis of (-)-2-[(S)-1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxycarbonyl benzoic acid (S)-α-phenylethylamide (I-b')

[0042] A benzene (100 ml) solution of 19.8 g (50 mmol) of phthalic acid mono-[l-(4-t-butylphenyl)-2-pyrrolidone-4-yl] methyl ester obtained in Example 1 and 7.3 ml (0.1 mol) of thionyl chloride was refluxed with heating for 2 hours. The reaction mixture was concentrated under reduced pressure and 100 ml of dichloromethane was added thereto. To the mixture was added dropwise a solution of 6.05 g (50 mmol) of (S)-(-)-α-phenylethylamine and 10.4 ml (75 mmol) of triethylamine in dichloromethane (50 ml) over a period of 10 minutes with ice-cooling, and the resulting mixture was stirred at the room temperature for 1.5 hours.

[0043] The reaction mixture was concentrated under reduced pressure and 100 ml of ethyl acetate was added thereto.

The mixture was washed with a dilute hydrochloric acid and with water, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and purified by chloroform-ethyl acetate gradient elution to give 17.93 g of a diastereomer mixture (I-b) of the title compound as an oil (yield 72%).

[0044] Further, hexane-ethyl acetate mixed solvent was added to the mixture for crystallization, and recrystallization from ethyl acetate was conducted twice. Thus, 5.5 g of the title compound as one of the diastereomers was obtained (>99% d.e. (diastereomer excess)).

Melting point: 184°C-186°C

Specific rotation: $[\alpha]_D^{25} = -33.0°$ (c=1.0, CH_2Cl_2)

NMR spectrum ($CDCl_3$)δ

1.59 (3H, d, J=6.9Hz), 2.27-2.41 (1H, m), 2.55-2.71 (2H, m), 3.68 (1H, dd, J=10.2, 5.3 Hz), 3.92 (1H, dd, J=10.2, 7.9 Hz), 4.18-4.31 (2H, m), 5.29 (1H, dq, J=7.9, 7.0 Hz), 6.11 (1H, d, J=7.9Hz), 7.25-7.88 (13H, m)

MASS spectrum (EI)498 (M^+)

Elementary analysis (for $C_{31}H_{34}N_2O_4$)			
	C	H	N
Calculated	74.67	6.87	5.62
Found	74.76	6.94	5.52

Example 3

Synthesis of (+)-2-[(R)-1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxycarbonylbenzoic acid (R)-α-phenylethylamide (I-b')

[0045] A reaction was conducted in the same manner as in Example 2 except that (R)-(+)-α-phenylethylamine was used in place of (S)-(-)-α-phenylethylamine to give a diastereomer mixture (I-b) of the title compound (yield 68%).

[0046] Further, a hexane-ethyl acetate mixed solvent was added to the mixture for crystallization, and recrystallization from methanol was conducted twice. Thus, the title compound as one of the diastereomers was obtained (>99% d.e.).

Melting point: 186°C-187°C

Specific rotation: $[\alpha]_D^{25} = +32.4°$ (c=1.0, CH_2Cl_2)

NMR spectrum ($CDCl_3$) δ

1.59 (3H, d, J=6.9Hz), 2.27-2.41 (1H, m), 2.55-2.71 (2H, m), 3.68 (1H, dd, J=10.2, 5.3 Hz), 3.92 (1H, dd, J=10.2, 7.9 Hz), 4.18-4.31 (2H, m), 5.29(1H, dq, J=7.9, 7.0 Hz), 6.11-(1H, d, J=7.9Hz), 7.25-7.88 (13H, m)

MASS spectrum (EI)498(M^+)

Elementary analysis (for $C_{31}H_{34}N_2O_4$)			
	C	H	N
Calculated	74.67	6.87	5.62
Found	74.73	7.06	5.60

Reference Example 1

Synthesis of (S)-(-)-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methyl alcohol (III')

[0047] A 4% aqueous solution of sodium hydroxide (18 ml) was added dropwise at 60°C to a suspension of 4.47 g (8.98 mmol) of (-)-2-[(S)-1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxycarbonylbenzoic acid (S)-α-phenylethylamide (I-b') obtained in Example 2 in 35 ml of ethanol, and the mixture was stirred for 30 minutes.

[0048] The reaction mixture was concentrated under reduced pressure and extracted with ether twice. The extract was washed with water, with a dilute hydrochloric acid and with water, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give 2.12 g of the title compound (yield 96%, >99% e.e.(enantiomer excess)).

Melting point: 83°C-84°C

Specific rotation: $[\alpha]_D^{25} = -10.8°$ (c=1.0, CH_2Cl_2)

Elementary analysis (for $C_{15}H_{21}NO_2$)			
	C	H	N
Calculated	72.84	8.56	5.66
Found	72.91	9.02	5.47

Reference Example 2

Synthesis of (R)-(+)-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methyl alcohol (III')

[0049] A reaction was conducted in the same manner as in Reference Example 1 except that (+)-2-[(R)-1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxycarbonylbenzoic acid (R)-α-phenylethylamide obtained in Example 3 was used in place of (-)-2-[(S)-1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxycarbonylbenzoic acid (S)-α-phenylethylamide to give the title compound (yield 96%, >99% e.e.).
Melting point: 83°C-84°C

Specific rotation: $[\alpha]_D^{25} = +9.9°$ (c=1.0, CH_2Cl_2)

Elementary analysis (for $C_{15}H_{21}NO_2$)			
	C	H	N
Calculated	72.84	8.56	5.66
Found	72.91	8.92	5.50

Reference Example 3

Synthesis of (R)-(-)-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methyl methanesulfonate

[0050] A 0.83 ml (1.08 mmol) quantity of methanesulfonyl chloride was added dropwise with ice-cooling to a solution of 2.42 g (9.80 mmol) of (R)-(+)-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methyl alcohol (III') obtained in Reference Example 2 and 1.5 ml (1.08 mmol) of triethylamine in dichloromethane (20 ml), and the mixture was stirred at the room temperature for 30 minutes.

[0051] The reaction mixture was diluted with ethyl acetate, washed with an aqueous solution of ammonium chloride and with an aqueous solution of sodium chloride, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give 3.12 g of the title compound (yield 98%).
Melting point: 108°C-109°C

Specific rotation: $[\alpha]_D^{25} = -1.7°$ (c=1.0, CH_2Cl_2)

Elementary analysis (for $C_{16}H_{23}NO_4S$)			
	C	H	N
Calculated	59.05	7.12	4.30
Found	58.62	7.34	4.44

Reference Example 4

Synthesis of (S)-(+)-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methyl methanesulfonate

[0052] A reaction was conducted in the same manner as in Reference Example 3 except that (S)-(-)-[1-(4-t-butylphenyl)-

2-pyrrolidone-4-yl]methyl alcohol (III') obtained in Reference Example 1 was used in place of (R)-(+)-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methyl alcohol to give the title compound (yield 99%).
Melting point: 108°C-109°C

Specific rotation: $[\alpha]_D^{25}=+2.0°$ (c=1.0, CH_2Cl_2)

Elementary analysis (for $C_{16}H_{23}NO_4S$)			
	C	H	N
Calculated	59.05	7.12	4.30
Found	58.64	7.38	4.38

Reference Example 5

Synthesis of methyl (R)-(-)-4-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxybenzoate (II)

[0053] A suspension of 3.0 g (9.23 mmol) of (R)-(-)-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methyl methanesulfonate, 1.4 g (9.23 mmol) of methyl p-hydroxybenzoate and 1.53 g (11.1 mmol) of potassium carbonate in 30 ml of N,N-dimethylformamide was stirred at 70°C for 15 hours.
[0054] The reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate. The extract was washed with water and with an aqueous solution of sodium chloride, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and recrystallized from methanol to give 2.68 g of the title compound (yield 72%, >99% e.e.).
Melting point: 126°C-128°C

Specific rotation: $[\alpha]_D^{25}=-18.1°$ (c=1.0, CH_2Cl_2)

MASS spectrum (FAB) 382 (M^+ +1)

Elementary analysis (for $C_{23}H_{27}NO_4$)			
	C	H	N
Calculated	72.42	7.13	3.67
Found	72.49	7.30	3.64

Reference Example 6

Synthesis of methyl (S)-(+)-4-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl] methoxybenzoate (II)

[0055] A reaction was conducted in the same manner as in Reference Example 5 except that (S)-(+)-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methyl methanesulfonate obtained in Reference Example 4 was used in place of (R)-(-)-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methyl methanesulfonate to give the title compound (yield 67%, >99% e.e.).
Melting point: 130°C-131°C

Specific rotation: $[\alpha]_D^{25}=+16.4°$ (c=1.0, CH_2Cl_2)

MASS spectrum (FAB)382(M^++1)

Elementary analysis (for $C_{23}H_{27}NO_4$)			
	C	H	N
Calculated	72.42	7.13	3.67
Found	72.49	7.39	3.70

Reference Example 7

Synthesis of (R)-(-)-4-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxybenzoic acid (II)

[0056] A 5.7 ml quantity of an 8% aqueous solution of sodium hydroxide was added dropwise at 60°C to a suspension of 2.18 g (5.72 mmol) of methyl (R)-(-)-4-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxybenzoate obtained in Reference Example 5 in 55 ml of ethanol, and the mixture was stirred for 16 hours.

[0057] The reaction mixture was concentrated under reduced pressure, and a dilute hydrochloric acid was added thereto and the crystals precipitated were collected by filtration. Thus, 2.04 g of the title compound was obtained (yield 97%, >99% e.e.).

Melting point: 247°C-248°C

Specific rotation: $[\alpha]_D^{25} = -27.9°$ (c=1.0, DMF)

MASS spectrum (FAB)366(M^+-1)

Elementary analysis (for $C_{22}H_{25}NO_4$)			
	C	H	N
Calculated	71.91	6.86	3.81
Found	71.92	6.94	3.65

Reference Example 8

Synthesis of (S)-(+)-4-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxybenzoic acid (II)

[0058] A reaction was conducted in the same manner as in Reference Example 7 except that methyl (S)-(+)-4-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxybenzoate (II) obtained in Reference Example 6 was used in place of methyl (R)-(-)-4-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxybenzoate to obtain the title compound (yield 98%, >99% e-e.).

Melting point: 247°C-248°C

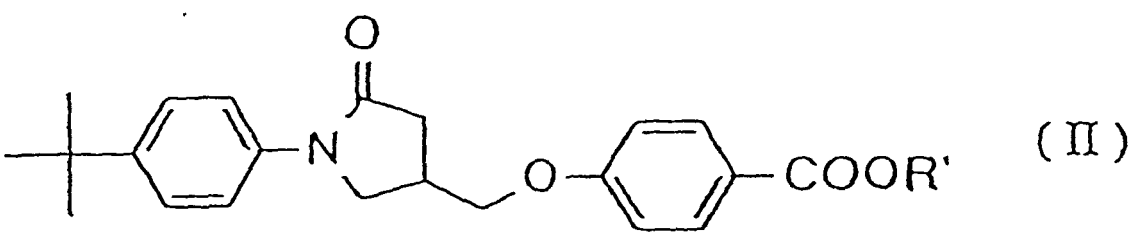
Specific rotation: $[\alpha]_D^{25} = +27.0°$ (c=1.0, DMF)

MASS spectrum (FAB) 366 (M^+-1)

Elementary analysis (for $C_{22}H_{25}NO_4$)			
	C	H	N
Calculated	71.91	6.86	3.81
Found	71.76	6.93	3.60

Claims

1. S)-(+)-4-[1-(4-t-Butylphenyl)-2-pyrrolidone-4-yl]methoxybenzoic acid, or a lower alkyl ester thereof, represented by the formula (II)



(II)

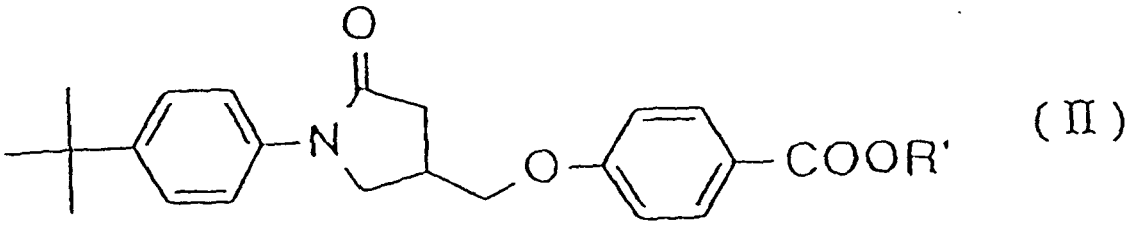
wherein R' is a hydrogen atom or a lower alkyl group.

2. Methyl (S)-(+)-4-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxybenzoate.

3. S)-(+)-4-[1-(4-t-Butylphenyl)-2-pyrrolidone-4-yl] methoxybenzoic acid.

4. A pharmaceutical composition for treating hyperlipidemia comprising as an active ingredient (S)-(+)-4-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxybenzoic acid, or a lower alkyl ester thereof as defined in any one of claims 1 to 3 in combination with a pharmaceutically acceptable carrier.

5. Use of (S)-(+)-4-[1-(4-t-butylphenyl)-2-pyrrolidone-4-yl]methoxybenzoic acid, or a lower alkyl ester thereof, represented by the formula (II)

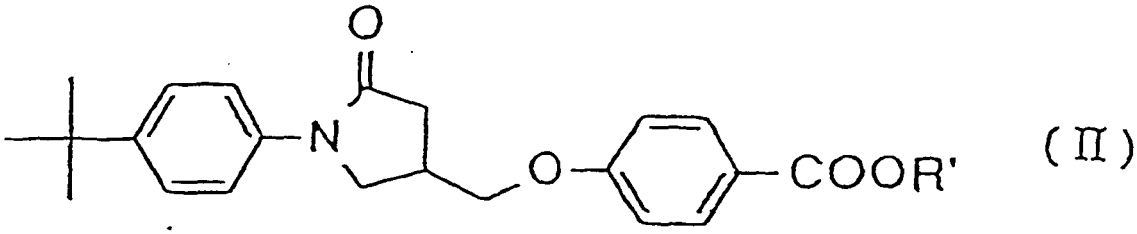


(II)

where R' is a hydrogen atom or a lower alkyl group for the preparation of a pharmaceutical composition for treating hyperlipidemia.

Patentansprüche

1. (S)-(+)-4-[1-(4-t-Butylphenyl)-2-pyrrolidon-4-yl]methoxybenzoesäure oder ein Niederalkylester davon, dargestellt durch die Formel (II)



(II)

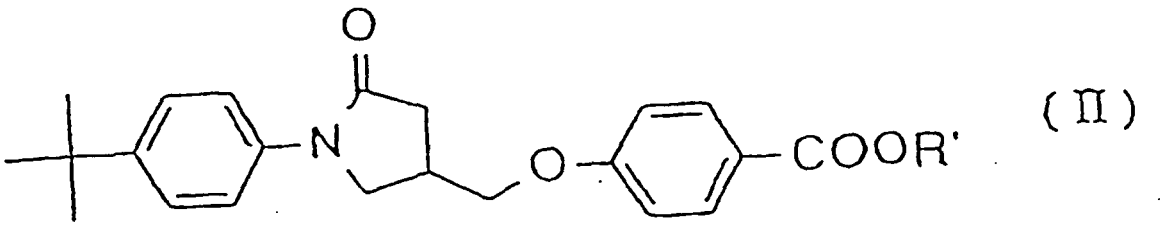
wobei R' ein Wasserstoffatom oder ein Niederalkylrest ist.

2. Methyl-(S)-(+)-4-[1-(4-t-butylphenyl)-2-pyrrolidon-4-yl]methoxybenzoat.

3. (S)-(+)-4-[1-(4-t-Butylphenyl)-2-pyrrolidon-4-yl]methoxybenzoesäure.

4. Arzneimittel zur Behandlung von Hyperlipidämie, umfassend als Wirkstoff (S)-(+)-4-[1-(4-t-Butylphenyl)-2-pyrrolidon-4-yl]methoxybenzoesäure oder einen Niederalkylester davon nach einem der Ansprüche 1 bis 3 in Verbindung mit einem pharmazeutisch verträglichen Träger.

5. Verwendung von (S)-(+)-4-[1-(4-t-Butylphenyl)-2-pyrrolidon-4-yl]methoxybenzoesäure oder eines Niederalkylesters davon, dargestellt durch die Formel (II)

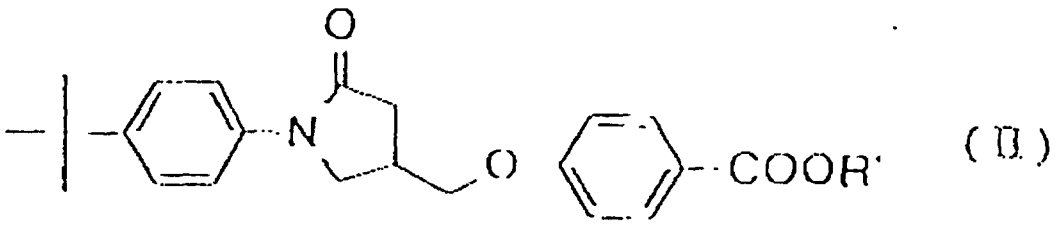


(II)

wobei R' ein Wasserstoffatom oder ein Niederalkylrest ist, zur Herstellung eines Arzneimittels zur Behandlung von Hyperlipidämie.

Revendications

1. Acide (S)-(+)-4-[1-(4-t-butylphényl)-2-pyrrolidone-4-yl]méthoxybenzoïque, ou un ester d'alkyle inférieur de cet acide, représenté par la formule (II)



(II)

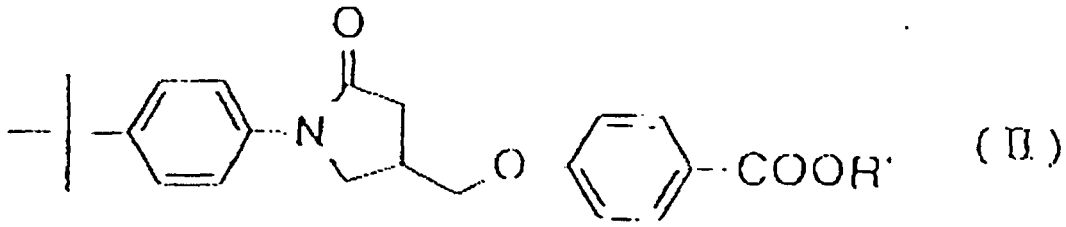
dans laquelle R' représente un atome d'hydrogène ou un groupe alkyle inférieur.

2. (S)-(+)-4-[1-(4-t-butylphényl)-2-pyrrolidone-4-yl]méthoxybenzoate de méthyle.

3. Acide (S)-(+)-4-[1-(4-t-butylphényl)-2-pyrrolidone-4-yl]-méthoxybenzoïque.

4. Composition pharmaceutique permettant de traiter l'hyperlipidémie comprenant en tant que principe actif l'acide (S)-(+)-4-[1-(4-t-butylphényl)-2-pyrrolidone-4-yl]méthoxybenzoïque, ou un ester d'alkyle inférieur de cet acide, tel que défini dans l'une quelconque des revendications 1 à 3, en combinaison avec un véhicule pharmaceutiquement acceptable.

5. Utilisation de l'acide (S)-(+)-4-[1-(4-t-butylphényl)-2-pyrrolidone-4-yl]-méthoxybenzoïque, ou d'un ester d'alkyle inférieur de cet acide, représenté par la formule (II)



(II)

dans laquelle R' représente un atome d'hydrogène ou un groupe alkyle inférieur, afin de préparer une composition pharmaceutique permettant de traiter l'hyperlipidémie.