

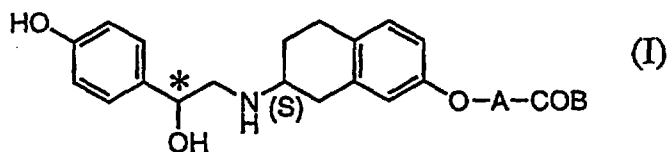
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PHENYLETHANOLAMINOTETRALINCARBOXAMIDE DERIVATIVES ✓

FIELD OF THE INVENTION

The present invention relates to novel phenylethanolamino-tetralincarboxamide derivatives which are useful as medicaments.

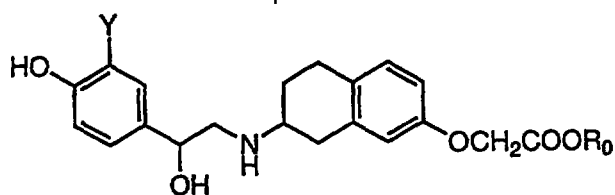
More particularly, the present invention relates to novel phenylethanolaminotetralincarboxamide derivatives represented by the general formula:



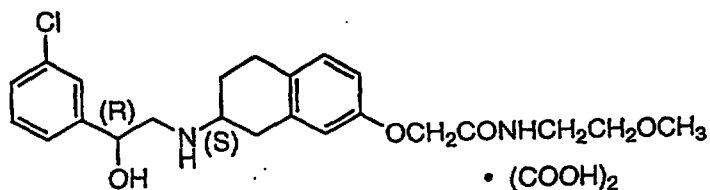
(wherein A represents a lower alkylene group, B represents an amino group, a di-lower alkylamino group, or a 3 to 7-membered alicyclic amino group which may contain an oxygen atom, the carbon atom marked with \* represents a carbon atom in (R) configuration, (S) configuration, or a mixture thereof, and the carbon atom marked with (S) represents a carbon atom in (S) configuration) and pharmaceutically acceptable salts thereof, which have a selective  $\beta_2$ -adrenergic receptor stimulating activity with reduced burdens on cardiovascular systems such as tachycardia.

BACKGROUND OF THE INVENTION

As substituted phenylethanaminotetralin derivatives, compounds having gut selective sympathomimetic and anti-pollakiuria activities have been disclosed, e.g., those represented by the general formula:



(wherein  $R_0$  represents a hydrogen atom or an ethyl group, and Y represents a hydrogen atom or a chlorine atom), hydrochloride or oxalate thereof, or single optical isomers thereof; and those represented by the formula:



(wherein the carbon atom marked with (R) represents a carbon atom in (R) configuration, and the carbon atom marked with (S) represents a carbon atom in (S) configuration) (cf. a published Japanese patent application (kohyo) No. Hei 6-506676 based on a PCT application and a published Japanese patent application (kohyo) No. Hei 6-506955 based on a PCT

application).

However, these compounds are  $\beta_3$ -adrenergic receptor stimulating agents having remarkable  $\beta_3$ -adrenergic receptor stimulating activity.

#### SUMMARY OF THE INVENTION

An object of the present invention is to provide novel phenylethanolaminotetralincarboxamide derivatives and pharmaceutically acceptable salts thereof which have a  $\beta_2$ -adrenergic receptor stimulating activity with higher selectivity in comparison with  $\beta_1$ -adrenergic receptor stimulating activity with reduced burdens on cardiovascular systems such as tachycardia.

Another object of the present invention is to provide a pharmaceutical composition containing, as an active ingredient, a phenylethanolaminotetralincarboxamide derivative or a pharmaceutically acceptable salt thereof.

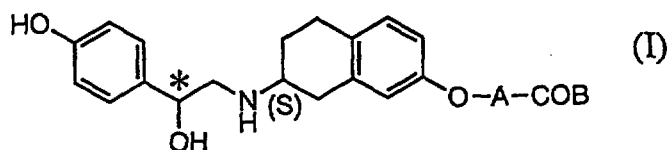
Other objects, features and advantages of the present invention will be apparent from the following description of the present invention.

#### DETAILED DESCRIPTION OF THE INVENTION

In order to find an excellent  $\beta_2$ -adrenergic receptor stimulating agent, the inventors of the present invention

made extensive studies and found that a certain phenylethanol-aminotetralincarboxamide derivative represented by the general formula (I) above has potent and selective  $\beta_2$ -adrenergic receptor stimulating activity and is remarkably useful as a  $\beta_2$ -adrenergic receptor stimulating agent, thereby resulting in the accomplishment of the present invention.

Accordingly, the present invention relates to novel phenylethanolaminotetralincarboxamide derivatives represented by the general formula:



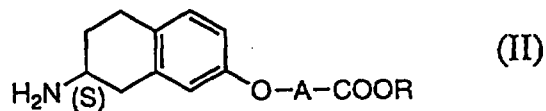
(wherein A represents a lower alkylene group, B represents an amino group, a di-lower alkylamino group, or a 3 to 7-membered alicyclic amino group which may contain an oxygen atom, the carbon atom marked with \* represents a carbon atom in (R) configuration, (S) configuration, or a mixture thereof, and the carbon atom marked with (S) represents a carbon atom in (S) configuration) and pharmaceutically acceptable salts thereof, which have a selective  $\beta_2$ -adrenergic receptor stimulating activity.

In the compounds represented by the general formula (I)

above of the present invention, the term "di-lower alkylamino group" means an amino group di-substituted with straight- or branched-chain alkyl group(s) having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl), such as a dimethylamino group, a diethylamino group, an ethylmethylamino group or the like. Also, the term "lower alkylene group" means a straight-chain alkylene group having 1 to 3 carbon atoms such as a methylene group, an ethylene group or a trimethylene group, and the term "3 to 7-membered alicyclic amino group which may contain an oxygen atom" means a 1-pyrrolidinyl group, a piperidino group, a morpholino group or the like.

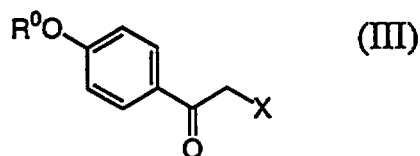
The compounds represented by the general formula (I) above of the present invention can be prepared by the following procedure.

For example, the compounds of the present invention can be prepared by subjecting an amine compound represented by the general formula:

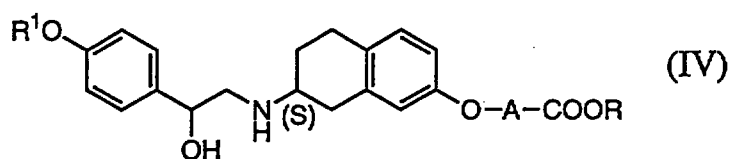


(wherein R represents a lower alkyl group, and A and the carbon atom marked with (S) have the same meanings as defined above) to N-alkylation using an alkylating agent represented

by the general formula:



(wherein  $R^0$  represents a hydroxy-protective group, and X represents a halogen atom), reducing the resulting compound in the usual way, removing the hydroxy-protective group as occasion demands to give a compound represented by the general formula:

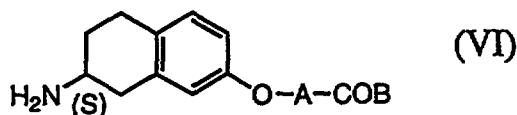


(wherein  $R^1$  represents a hydrogen atom or a hydroxy-protective group, and A, R and the carbon atom marked with (S) have the same meanings as defined above), subjecting the resulting compound to amidation in the usual way using an amine compound represented by the general formula:



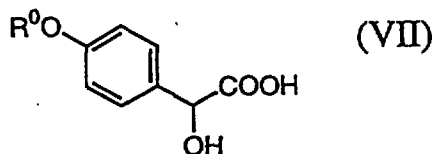
(wherein B has the same meaning as defined above), and removing the hydroxy-protective group as occasion demands.

The compounds represented by the general formula (I) above of the present invention can be also prepared by subjecting an amine compound represented by the general formula:

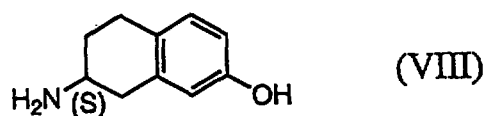


(wherein A, B and the carbon atom marked with (S) have the same meanings as defined above) to N-alkylation using an alkylating agent represented by the general formula (III) above, reducing the resulting compound in the usual way, and removing the hydroxy-protective group.

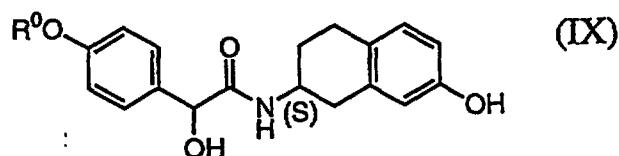
The compounds represented by the general formula (I) above of the present invention can be also prepared by allowing a mandelic acid derivative represented by the general formula:



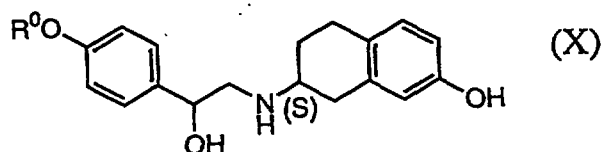
(wherein R<sup>0</sup> has the same meaning as defined above) to react with an amine compound represented by the general formula:



(wherein the carbon atom marked with (S) has the same meaning as defined above) in the presence of a condensing agent to give a compound represented by the general formula:



(wherein R<sup>0</sup> and the carbon atom marked with (S) have the same meanings as defined above), reducing the resulting compound using a reagent such as borane-dimethylsulfide complex to prepare a compound represented by the general formula:



(wherein R<sup>0</sup> and the carbon atom marked with (S) have the same meanings as defined above), protecting the alcoholic hydroxy group and amino group with a reagent such as trifluoroacetic anhydride as occasion demands, subjecting the resulting

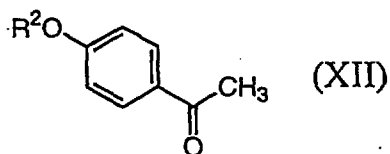
compound to O-alkylation using an alkylating agent represented by the general formula:



(wherein A, B and X have the same meanings as defined above), and removing the protective group.

The amine compounds represented by the general formulae (II) and (VIII) above which are used as starting materials in the above production process can be prepared according to a method described in a literature or analogous methods thereto (for example, *Eur. J. Med. Chem.*, No. 29, pp. 259-267 (1994); a published Japanese patent application (Kokai) No. Hei 3-14548).

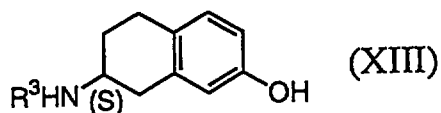
The compounds represented by the general formula (III) above which are used as starting materials in the above production process can be prepared by subjecting the ketone compound represented by the general formula:



(wherein R<sup>2</sup> represents a hydroxy-protective group suitable for this preparation) to halogenation using a halogenating agent according to a method described in a literature or analogous

methods thereto (e.g., *Bull. Chem. Soc. Jpn.*, Vol. 65, 295-297 (1992); *Synthesis*, No. 7, 545-546 (1988); *Synthesis*, No. 12, 1018-1020 (1982)), and converting the hydroxy-protective group of the resulting compound into other hydroxy-protective group as occasion demands.

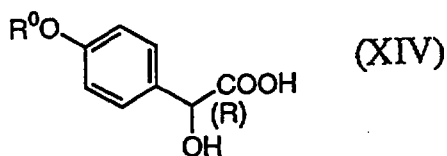
The amine compounds represented by the general formula (VI) above which are used as starting materials in the above production process can be prepared by subjecting a phenol compound represented by the general formula:



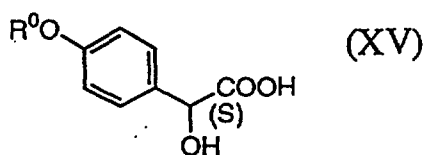
(wherein  $R^3$  represents an amino-protective group, and the carbon atom marked with (S) has the same meaning as defined above) to O-alkylation using an alkylating agent represented by the general formula (XI) above and then removing the amino-protective group, or by protecting the amino group of an amine compound represented by the general formula (II) above using an appropriate reagent, converting the resulting compound into free carboxylic acid or a reactive functional derivative thereof as occasion demands, subjecting the resulting compound to amidation using an amine compound represented by the general formula (V) above in the presence or absence of a condensing agent, and removing the amino-

protective group.

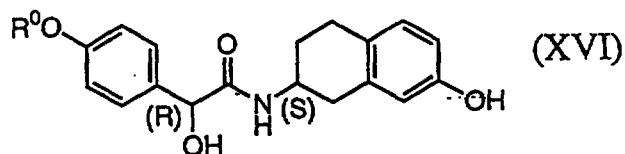
Among the compounds represented by the general formula (I) above of the present invention, single isomers can be prepared, for example, by subjecting a diastereomer mixture obtained by the above process to fractional recrystallization in the usual way, or by allowing an optically active mandelic acid derivative represented by the general formula:



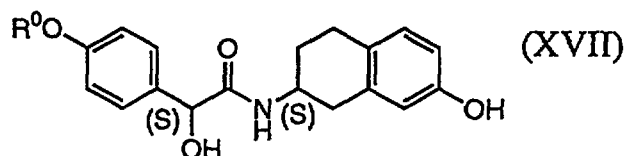
(wherein the carbon atom marked with (R) represents a carbon atom in (R) configuration, and  $R^0$  has the same meaning as defined above) or another optically active mandelic acid derivative represented by the general formula:



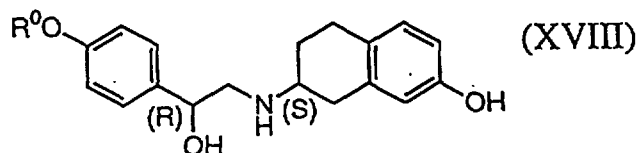
(wherein  $R^0$  and the carbon atom marked with (S) have the same meanings as defined above) to react with an amine compound represented by the general formula (VIII) above in the presence of a condensing agent to give a single isomer represented by the general formula:



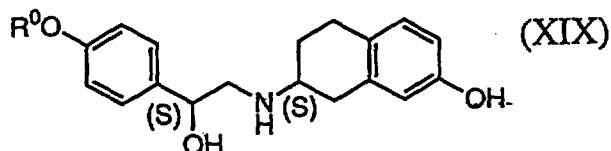
(wherein  $R^0$ , the carbon atom marked with (R) and the carbon atom marked with (S) have the same meanings as defined above) or another single isomer represented by the general formula:



(wherein  $R^0$  and the carbon atoms marked with (S) have the same meanings as defined above), reducing the resulting isomer using a reagent such as borane-dimethylsulfide complex to prepare a single isomer represented by the general formula:



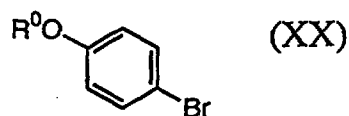
(wherein  $R^0$ , the carbon atom marked with (R) and the carbon atom marked with (S) have the same meanings as defined above) or another single isomer represented by the general formula:



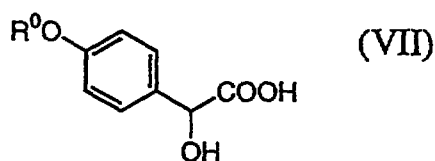
(wherein R<sup>0</sup> and the carbon atoms marked with (S) have the same meanings as defined above), protecting the alcoholic hydroxy group and amino group using a reagent such as trifluoroacetic anhydride, subjecting the resulting compound to O-alkylation using an alkylating agent represented by the general formula (XI) above, and removing the protective group.

Among the compounds represented by the general formula (I) above of the present invention, single isomers can be also prepared by subjecting a diastereomer mixture obtained as an intermediate by the above process to column chromatography or fractional recrystallization to isolate the corresponding single isomer and then carrying out the same reaction using said single isomer.

The mandelic acid compounds represented by the general formulae (VII), (XIV) and (XV) above which are used as starting materials in the above production process can be prepared by allowing a bromo-compound represented by the general formula:



(wherein  $R^0$  has the same meaning as defined above), which can be obtained according to a method described in a literature or analogous processes thereto, to react with diethyl oxalate, reducing the resulting phenylglyoxylic acid derivative using a reagent such as sodium borohydride, and hydrolyzing the ester compound to give a mandelic acid derivative represented by the general formula:



(wherein  $R^0$  has the same meaning as defined above) and, as occasion demands, subjecting the compound to optical resolution in the usual way using a resolving agent such as optically active 1-phenylethylamine.

The compounds of the present invention obtained by the above production process can be easily isolated and purified by conventional separation means such as fractional recrystallization, purification using column chromatography, solvent extraction and the like.

The phenylethanolaminotetralincarboxamide derivatives

represented by the general formula (I) above of the present invention can be converted into its pharmaceutically acceptable salts in the usual way. Examples of the such salts include acid addition salts with mineral acids (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like), acid addition salts with organic acids (e.g., formic acid, acetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, propionic acid, citric acid, succinic acid, tartaric acid, fumaric acid, butyric acid, oxalic acid, malonic acid, maleic acid, lactic acid, malic acid, carbonic acid, glutamic acid, aspartic acid and the like) and salts with inorganic bases such as sodium salt and potassium salt. The resulting salts have the same pharmacological activities as that of the free form.

In addition, the compounds represented by the general formula (I) above of the present invention also include its hydrates and solvates with pharmaceutically acceptable solvents (e.g., ethanol).

The compounds represented by the general formula (I) above of the present invention exist in two isomer forms of (R) configuration and (S) configuration based on the asymmetric carbon atom having a hydroxy group. Either one of the isomers or a mixture thereof can be employed in the present invention, and the (R) configuration isomer is preferable.

When the *in vitro* test for measuring  $\beta_2$ -adrenergic receptor stimulating activity was carried out in the usual way using isolated rat pregnant uterus, the compounds represented by the general formula (I) above of the present invention showed an activity to relax 50% of the spontaneous contractions of rat myometrium (i.e.,  $EC_{50}$ ) at an approximate molar concentration of  $5.0 \times 10^{-9}$  to  $5.0 \times 10^{-6}$ . For example, 2-[(2S)-2-[[[(2R)-2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yl]oxy]-N,N-dimethylacetamide showed the  $EC_{50}$  value at a molar concentration of  $1.5 \times 10^{-8}$ . Thus, the compounds of the present invention have markedly potent  $\beta_2$ -adrenergic receptor stimulating activity and therefore are remarkably useful as  $\beta_2$ -adrenergic receptor stimulating agents.

When the *in vitro* test for measuring  $\beta_1$ -adrenergic receptor stimulating activity was carried out in the usual way using isolated rat atrium, the compounds represented by the general formula (I) above of the present invention showed an activity to increase 20 beats per minute of rat heart rate ( $EC_{20}$  value) at an approximate molar concentration of  $1.0 \times 10^{-6}$  or more. For example, 2-[(2S)-2-[[[(2R)-2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yl]oxy]-N,N-dimethylacetamide showed the  $EC_{20}$  value at a molar concentration of  $1.6 \times 10^{-6}$ . Thus, the compounds of the

present invention have markedly weaker  $\beta_1$ -adrenergic receptor stimulating activity in comparison with the above  $\beta_2$ -adrenergic receptor stimulating activity.

In consequence, the compounds of the present invention have markedly potent  $\beta_2$ -adrenergic receptor stimulating activity with markedly high selectivity in comparison with  $\beta_1$ -adrenergic receptor stimulating activity, so that these are extremely useful highly selective  $\beta_2$ -adrenergic receptor stimulating agents of in which burdens on cardiovascular systems are reduced due to suppression of side effects upon the heart (e.g., tachycardia) caused by  $\beta_1$ -adrenergic receptor stimulating activity.

The compounds of present invention are selective  $\beta_2$ -adrenergic receptor stimulating agents which are extremely useful as, for example, an agent for the prevention of threatened abortion, premature labor, as an agent for the treatment or prevention of diseases associated with bronchiostenosis or airway obstruction (bronchodilator) and as an agent for pain remission or stone removal in urolithiasis.

Also, the compounds represented by the general formula (I) above of the present invention are an extremely stable compound and therefore have excellent storage stability.

When the phenylethanolaminotetralincarboxamide

derivatives represented by the general formula (I) above of the present invention and pharmaceutically acceptable salts thereof are employed in the practical treatment, they are administered orally or parenterally in the form of appropriate pharmaceutical compositions such as tablets, powders, fine granules, granules, capsules, injections, and the like. These pharmaceutical compositions can be formulated in accordance with conventional methods using conventional pharmaceutical carriers, excipients and other additives.

The dosage is appropriately decided depending on the sex, age, body weight, degree of symptoms and the like of each patient to be treated, which is approximately within the range of from 1 to 1,000 mg per day per adult human in the case of oral administration and approximately within the range of from 0.01 to 100 mg per day per adult human in the case of parenteral administration, and the daily dosage can be divided into one to several doses per day.

EXAMPLES

The present invention is further illustrated in more detail by way of the following Reference Examples, Examples and Test Examples. However, the present invention is not limited thereto.

Reference Example 1

Ethyl 2-[(2*S*)-2-[[ (2*RS*)-2-hydroxy-2-(4-hydroxyphenyl)-ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetate

To a stirred solution of 2-bromo-4'-hydroxyacetophenone (860 mg) in dichloromethane (20 ml) were added 3,4-dihydro-2H-pyran (550  $\mu$ l) and pyridinium p-toluenesulfonate (100 mg) at room temperature. After the mixture was stirred at room temperature for 17 hours, the reaction mixture was washed with water, dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: hexane /ethyl acetate = 10/1) gave 2-bromo-4'-((2*RS*)-2-tetrahydropyranyloxy)acetophenone (1.01 g) having a melting point of 102-104°C.

IR (KBr): 1687  $\text{cm}^{-1}$

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.50-2.10 (6H, m), 3.55-3.65 (1H, m), 3.75-3.90 (1H, m), 4.41 (2H, s), 5.54 (1H, t,  $J=3.1\text{Hz}$ ), 7.11 (2H, d,  $J=9.0\text{Hz}$ ),

7.96 (2H, d, J=9.0Hz)

To a stirred solution of ethyl (S)-(2-amino-1,2,3,4-tetrahydronaphthalen-7-yloxy)acetate (1.14 g) in *N,N*-dimethylformamide (15 ml) was added 2-bromo-4'-((2RS)-2-tetrahydropyranyloxy)acetophenone (600 mg) under ice-cooling. After the mixture was stirred at room temperature for an hour, sodium borohydride (380 mg) and ethanol (10 ml) were added to the reaction mixture under ice-cooling. After the mixture was still stirred for an hour, the reaction mixture was poured into ice-water, and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The resulting residue was dissolved in tetrahydrofuran (20 ml), triethanolamine (2 ml) was added to the solution and the mixture was heated under reflux for 17 hours. After cooling, water was poured into the reaction mixture and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: ethyl acetate) gave ethyl 2-[(2S)-2-[[[(2RS)-2-hydroxy-2-[4-((2RS)-2-tetrahydropyranyloxy)phenyl]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetate (780 mg) as an oil.

IR (neat): 3304, 1760  $\text{cm}^{-1}$

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.15-1.65 (8H, m), 1.80-2.10 (4H, m), 2.50-3.05 (7H, m), 3.55-3.65 (1H, m), 3.85-3.95 (1H, m), 4.20-4.30 (2H, m), 4.55-4.70 (3H, m), 5.41 (1H, t,  $J=3.2\text{Hz}$ ), 6.61 (1H, s), 6.69 (1H, dd,  $J=8.4, 2.7\text{Hz}$ ), 6.95-7.10 (3H, m), 7.25-7.35 (2H, m)

To a stirred solution of ethyl 2-[(2S)-2-[[ (2RS)-2-hydroxy-2-[4-((2RS)-2-tetrahydropyranyloxy)phenyl]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetate (780 mg) in ethanol (20 ml) was added 1N hydrochloric acid (34 ml) under ice-cooling. After the mixture was stirred for an hour, the reaction was quenched with a saturated aqueous sodium bicarbonate solution and then the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated *in vacuo*.

Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: ethyl acetate) gave ethyl 2-[(2S)-2-[[ (2RS)-2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydro-naphthalen-7-yloxy]acetate (238 mg) as an amorphous.

IR (film): 3294, 1754  $\text{cm}^{-1}$

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.15-1.25 (3H, m), 1.50-1.65 (1H, m), 1.95-2.10 (1H, m),

2.45-2.60 (1H, m), 2.65-3.05 (6H, m), 3.73 (3H, br), 4.20-4.30 (2H, m), 4.50-4.70 (3H, m), 6.50-6.60 (1H, m), 6.67 (1H, dd,  $J=8.4, 2.6\text{Hz}$ ), 6.75 (2H, d,  $J=8.4\text{Hz}$ ), 6.97 (1H, d,  $J=8.4\text{Hz}$ ), 7.17 (2H, d,  $J=8.4\text{Hz}$ )

#### Reference Example 2

4-[(2*S*)-2-[[ (2*RS*)-2-(4-Benzoyloxyphenyl)-2-hydroxy-ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylbutyramide

To a stirred solution of (*S*)-2-(*tert*-butoxycarbonylamino)-7-hydroxytetralin (400 mg) in *N,N*-dimethylformamide (8 ml) were added cesium carbonate (3.16 g) and ethyl 4-bromo-butyrate (650  $\mu\text{l}$ ) at room temperature. After the mixture was stirred at room temperature for 1.5 hours, water was poured into the reaction mixture and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated *in vacuo*.

Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: hexane/ethyl acetate = 1/1) gave ethyl (*S*)-4-[2-(*tert*-butoxycarbonylamino)-1,2,3,4-tetrahydronaphthalen-7-yloxy]butyrate (488 mg) having a melting point of 96-98°C.

IR (KBr): 3360, 1723, 1680  $\text{cm}^{-1}$

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.26 (3H, t,  $J=7.1\text{Hz}$ ), 1.45 (9H, s), 1.65-1.80 (1H, m), 2.00-2.15 (3H, m), 2.50 (2H, t,  $J=7.3\text{Hz}$ ), 2.59 (1H, dd,  $J=16.5, 7.9\text{Hz}$ ), 2.75-2.85 (2H, m), 3.07 (1H, dd,  $J=16.5, 4.6\text{Hz}$ ), 3.90-4.05 (3H, m), 4.14 (2H, q,  $J=7.1\text{Hz}$ ), 4.50-4.65 (1H, m), 6.58 (1H, d,  $J=2.6\text{Hz}$ ), 6.68 (1H, dd,  $J=8.4, 2.6\text{Hz}$ ), 6.99 (1H, d,  $J=8.4\text{Hz}$ )

Optical rotation:  $[\alpha]_D^{25} = -50.7^\circ$  ( $c=1.03$ , MeOH)

To a stirred solution of ethyl (S)-4-[2-(*tert*-butoxycarbonylamino)-1,2,3,4-tetrahydronaphthalen-7-yloxy]butyrate (988 mg) in methanol (15 ml) and ethanol (15 ml) was added a 2N aqueous sodium hydroxide solution (3.0 ml) at room temperature. After the mixture was stirred at room temperature for 2 hours, the reaction mixture was concentrated *in vacuo*. To the resulting residue was added a 10% aqueous citric acid solution and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous magnesium sulfate. Concentration of the solution *in vacuo* gave (S)-4-[2-(*tert*-butoxycarbonylamino)-1,2,3,4-tetrahydronaphthalen-7-yloxy]-butyric acid (914 mg) having a melting point of 150-153°C.

IR (KBr): 3452, 3365, 1691  $\text{cm}^{-1}$

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.45 (9H, s), 1.65-1.80 (1H, m), 2.00-2.20 (3H, m),

2.55-2.70 (3H, m), 2.75-2.85 (2H, m), 3.00-3.15 (1H, m), 3.90-4.10 (3H, m), 4.55-4.70 (1H, m), 6.58 (1H, d,  $J=2.6\text{Hz}$ ), 6.68 (1H, dd,  $J=8.4, 2.6\text{Hz}$ ), 6.99 (1H, d,  $J=8.4\text{Hz}$ )

Optical rotation:  $[\alpha]_D^{25} = -53.5^\circ$  ( $c=0.52$ , MeOH)

To a stirred solution of (*S*)-4-[2-(*tert*-butoxycarbonylamino)-1,2,3,4-tetrahydronaphthalen-7-yloxy]butyric acid (399 mg) in tetrahydrofuran (5 ml) was added 1,1'-carbonyldiimidazole (204 mg) under ice-cooling. After the mixture was still stirred for 2 hours. A solution of dimethylamine (1.40 g) in tetrahydrofuran (2 ml) was added to the reaction mixture under ice-cooling with stirring. After the mixture was still stirred for 45 minutes and then at room temperature for 45 minutes, the reaction mixture was concentrated *in vacuo*. Water was added to the resulting residue and the mixture was extracted with diethyl ether. The extract was washed with a 10% aqueous citric acid solution, water, a saturated aqueous sodium bicarbonate solution and water successively, and dried over anhydrous magnesium sulfate. Concentration of the solution *in vacuo* gave (*S*)-4-[2-(*tert*-butoxycarbonylamino)-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylbutyramide (396 mg) having a melting point of 97-101°C.

IR (KBr): 3325, 1709, 1624  $\text{cm}^{-1}$

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.45 (9H, s), 1.65-1.80 (1H, m), 2.00-2.15 (3H, m), 2.51 (2H, t,  $J=7.2\text{Hz}$ ), 2.59 (1H, dd,  $J=16.5, 8.1\text{Hz}$ ), 2.75-2.85 (2H, m), 2.95 (3H, s), 3.00-3.10 (4H, m), 3.90-4.00 (3H, m), 4.58 (1H, br s), 6.59 (1H, d,  $J=2.6\text{Hz}$ ), 6.69 (1H, dd,  $J=8.4, 2.6\text{Hz}$ ), 6.98 (1H, d,  $J=8.4\text{Hz}$ )

Optical rotation:  $[\alpha]_D^{25} = -50.0^\circ$  ( $c=0.50$ , MeOH)

To a stirred solution of (S)-4-[2-(*tert*-butoxycarbonyl-amino)-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethyl-butylamide (396 mg) in dichloromethane (5 ml) was added a solution of trifluoroacetic acid (5 ml) in dichloromethane (5 ml) under ice-cooling. After the mixture was still stirred for 15 minutes and then at room temperature for 15 minutes, the reaction mixture was concentrated *in vacuo*. Dichloromethane, water and sodium bicarbonate were added to the resulting residue and the mixture was stirred at room temperature for 30 minutes. The organic layer was separated and dried over anhydrous magnesium sulfate. Concentration of the solution *in vacuo* gave (S)-4-(2-amino-1,2,3,4-tetrahydronaphthalen-7-yloxy)-*N,N*-dimethyl-butylamide (263 mg) as an oil.

IR (neat): 3404, 1618  $\text{cm}^{-1}$

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.75-1.90 (1H, m), 2.00-2.25 (3H, m), 2.45-2.55 (2H, m), 2.65-2.90 (3H, m), 2.94 (3H, s), 3.00 (3H, s), 3.05-3.20 (1H,

m), 3.30-3.50 (1H, m), 3.96 (2H, t,  $J=5.9\text{Hz}$ ), 5.89 (2H, br s), 6.60 (1H, d,  $J=2.3\text{Hz}$ ), 6.68 (1H, dd,  $J=8.4, 2.3\text{Hz}$ ), 6.96 (1H, d,  $J=8.4\text{Hz}$ )

Optical rotation:  $[\alpha]_{\text{D}}^{25} = -46.2^\circ$  ( $c=0.45$ , MeOH)

To a stirred solution of (*S*)-4-(2-amino-1,2,3,4-tetrahydronaphthalen-7-yloxy)-*N,N*-dimethylbutyramide (196 mg) and triethylamine (270  $\mu\text{l}$ ) in *N,N*-dimethylformamide (3 ml) was added a solution of 4'-benzyloxy-2-bromoacetophenone (195 mg) in *N,N*-dimethylformamide (2 ml) under ice-cooling. After the mixture was stirred under ice-cooling for 15 minutes, sodium borohydride (240 mg) and ethanol (3 ml) were added to the reaction mixture under ice-cooling. After the mixture was still stirred for 2 hours, the reaction mixture was poured into ice-water, and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. To the resulting residue was added a solution of triethanolamine (200 mg) in tetrahydrofuran (5 ml) and the mixture was heated under reflux for 16 hours. After cooling, water was poured into the reaction mixture and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the residue by medium pressure liquid column

chromatography on silica gel (eluent: ethyl acetate/ethanol = 6/1) gave 4-[(2*S*)-2-[[ (2*RS*)-2-(4-benzyloxyphenyl)-2-hydroxy-ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylbutyramide (85 mg) as an amorphous.

IR (film): 3348, 1639  $\text{cm}^{-1}$

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.55-1.65 (1H, m), 1.80-2.30 (5H, m), 2.45-2.85 (6H, m), 2.90-3.10 (9H, m), 3.95-4.05 (2H, m), 4.67 (1H, dd,  $J=9.1$ , 3.3Hz), 5.07 (2H, s), 6.60 (1H, s), 6.68 (1H, dd,  $J=8.4$ , 2.7Hz), 6.90-7.05 (3H, m), 7.20-7.50 (7H, m)

#### Reference Example 3

2-[(2*S*)-2-[[ (2*R*)-2-(4-benzyloxyphenyl)-2-hydroxyethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylacetamide

To a stirred solution of (*R*)-4-hydroxymandelic acid (2.02 g) in *N,N*-dimethylformamide (24 ml) were added benzyl bromide (3.57 ml) and potassium carbonate (3.65 g) at room temperature. After the mixture was stirred at room temperature for 12 hours, ice-water was poured into the reaction mixture and the resulting precipitates were collected. The precipitates were suspended in methanol (24 ml) and a 1*N* aqueous sodium hydroxide solution (12 ml) was added to the suspension under ice-cooling. After the mixture was stirred at room temperature for 2 hours,

the reaction mixture was acidified with 1N hydrochloric acid (12 ml) under ice-cooling with stirring. Collection of the resulting precipitates gave (R)-4-benzyloxy-mandelic acid (2.43 g) having a melting point of 161-163°C.

IR (KBr): 3439, 1733  $\text{cm}^{-1}$

$^1\text{H}$ -NMR (DMSO- $d_6$ )

$\delta$  ppm: 4.96 (1H, s), 5.10 (2H, s), 5.75 (1H, br), 6.95-7.05 (2H, m), 7.25-7.50 (7H, m), 12.52 (1H, br)

Optical rotation :  $[\alpha]_D^{25} = -100.5^\circ$  ( $c=1.00$ , MeOH)

To a stirred solution of (R)-4-benzyloxymandelic acid (2.43 g), (S)-2-amino-7-hydroxytetralin hydrobromide (2.87 g) and triethylamine (2.88 ml) in dichloromethane (38 ml) was added benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (4.58 g) at room temperature. After the mixture was stirred at room temperature for 15 hours, the reaction mixture was diluted with ethyl acetate. The resulting mixture was washed with water, 1N hydrochloric acid, a saturated aqueous sodium bicarbonate solution and brine successively, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: chloroform/ethyl acetate = 1/1) and following recrystallization from ethyl acetate-hexane gave (2R)-2-(4-benzyloxyphenyl)-2-hydroxy-N-((2S)-7-

hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (3.48 g)  
having a melting point of 137-139°C.

IR (KBr): 3374, 1630  $\text{cm}^{-1}$

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.60-1.75 (1H, m), 1.90-2.00 (1H, m), 2.53 (1H, dd,  $J=16.3, 8.3\text{Hz}$ ), 2.60-2.80 (2H, m), 2.97 (1H, dd,  $J=16.3, 5.0\text{Hz}$ ), 3.43 (1H, br), 4.15-4.30 (1H, m), 4.97 (1H, s), 5.03 (2H, s), 5.70 (1H, br), 6.34 (1H, d,  $J=8.1\text{Hz}$ ), 6.43 (1H, d,  $J=2.6\text{Hz}$ ), 6.59 (1H, dd,  $J=8.3, 2.6\text{Hz}$ ), 6.88 (1H, d,  $J=8.3\text{Hz}$ ), 6.93 (2H, d,  $J=8.7\text{Hz}$ ), 7.20-7.50 (7H, m)

Optical rotation:  $[\alpha]_{\text{D}}^{25} = -89.4^\circ$  ( $c=1.06$ , MeOH)

To a stirred solution of (2R)-2-(4-benzyloxyphenyl)-2-hydroxy-*N*-((2S)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (605 mg) in tetrahydrofuran (7.5 ml) was added 2M borane-dimethylsulfide complex in tetrahydrofuran (2.25 ml) at room temperature. After the mixture was heated under reflux for 3 hours, a solution of triethanolamine (1.12 g) in tetrahydrofuran (2.5 ml) was added to the reaction mixture at room temperature and the mixture was heated under reflux for 15 hours. After cooling, water was poured into the reaction mixture and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated in vacuo.

Recrystallization of the residue from ethyl acetate gave (1*R*)-1-(4-benzyloxyphenyl)-2-[(*2S*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)amino]ethanol (350 mg) having a melting point of 132-134°C.

IR (KBr): 3250 cm<sup>-1</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

δ ppm: 1.20-2.10 (2H, m), 2.50-3.05 (7H, m), 3.50 (1H, br), 4.60-4.70 (1H, m), 5.06 (2H, s), 6.50-6.55 (1H, m), 6.60 (1H, dd, *J*=8.2, 2.7Hz), 6.90-7.00 (3H, m), 7.25-7.50 (7H, m)

Optical rotation: [α]<sub>D</sub><sup>25</sup> = -63.1° (c=0.98, MeOH)

To a stirred suspension of (1*R*)-1-(4-benzyloxyphenyl)-2-[(*2S*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)amino]-ethanol (350 mg) and *N,N*-diisopropylethylamine (0.78 ml) in dichloromethane (3.6 ml) was added trifluoroacetic anhydride (0.38 ml) at -15°C. After the mixture was stirred at -15°C for 30 minutes, the reaction mixture was washed with water, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The resulting residue was dissolved in *N,N*-dimethylformamide (4.5 ml) and 2-bromo-*N,N*-dimethylacetamide (0.11 ml), cesium carbonate (880 mg) and molecular sieves 4A powder (350 mg) were added to the solution at room temperature. After the mixture was stirred at room temperature for 2 hours, diethylamine (0.11 ml) was added to the reaction mixture at room temperature and

the resulting mixture was still stirred for 20 minutes. Water (3.5 ml) and methanol (3.5 ml) were added to the reaction mixture under ice-cooling and the mixture was stirred at room temperature for 1.5 hours. Brine was poured into the reaction mixture and the resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*.

Purification of the residue by medium pressure liquid column chromatography on aminopropylated silica gel (eluent: chloroform/methanol = 50/1) gave 2-[(2*S*)-2-[[ (2*R*)-2-(4-benzyl-oxyphenyl)-2-hydroxyethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylacetamide (283 mg) as an amorphous.

IR (KBr): 3430, 1651  $\text{cm}^{-1}$

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.35-1.70 (2H, m), 2.00-2.10 (1H, m), 2.50-3.15 (13H, m), 3.50 (1H, br), 4.60-4.70 (3H, m), 5.07 (2H, s), 6.65 (1H, d,  $J=2.5\text{Hz}$ ), 6.73 (1H, dd,  $J=8.4, 2.5\text{Hz}$ ), 6.90-7.05 (3H, m), 7.25-7.50 (7H, m)

Optical rotation:  $[\alpha]_{\text{D}}^{25} = -61.0^\circ$  ( $c=0.62$ , MeOH)

#### Reference Example 4

According to the procedure described in Reference Example 3, the following compounds were prepared using 1-(2-bromoacetyl)piperidine and 4-(2-bromoacetyl)morpholine instead of 2-bromo-

*N,N*-dimethylacetamide.

1-[2-[(2*S*)-2-[[ (2*R*)-2-(4-Benzylloxyphenyl)-2-hydroxyethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]-piperidine

amorphous

IR (KBr): 3420, 1645 cm<sup>-1</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

δ ppm: 1.50-1.70 (7H, m), 2.00-2.10 (1H, m), 2.50-2.65 (1H, m), 2.70-2.85 (3H, m), 2.95-3.10 (3H, m), 3.45-3.60 (4H, m), 4.63 (2H, s), 4.66 (1H, dd, J=9.0, 3.5Hz), 5.07 (2H, s), 6.65 (1H, d, J=2.7Hz), 6.73 (1H, dd, J=8.4, 2.7Hz), 6.95-7.05 (3H, m), 7.25-7.50 (7H, m)

Optical rotation: [α]<sub>D</sub><sup>25</sup> = -53.0° (c=0.54, MeOH)

4-[2-[(2*S*)-2-[[ (2*R*)-2-(4-Benzylloxyphenyl)-2-hydroxyethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]-morpholine

amorphous

IR (film): 3365, 1653 cm<sup>-1</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

δ ppm: 1.55-1.70 (1H, m), 2.00-2.10 (1H, m), 2.50-3.10 (7H, m), 3.55-3.75 (9H, m), 4.60-4.70 (3H, m), 5.06 (2H, s), 6.64 (1H, d, J=2.6Hz), 6.72 (1H, dd, J=8.4, 2.6Hz), 6.96 (2H, d,

$J=8.6\text{Hz}$ ), 7.00 (1H, d,  $J=8.4\text{Hz}$ ), 7.25-7.50 (7H, m)

Optical rotation:  $[\alpha]_D^{25} = -49.8^\circ$  ( $c=0.59$ , MeOH)

#### Reference Example 5

2-[(2*S*)-2-[[[(2*S*)-2-(4-Benzoyloxyphenyl)-2-hydroxyethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylacetamide

To a solution of 4-benzoyloxymandelic acid (40.8 g) in methanol (405 ml) and ethyl acetate (405 ml) was added a solution of (*S*)-1-phenylethylamine (20.4 ml) in methanol (200 ml). After the mixture was allowed to stand at room temperature, the resulting precipitates were collected. Recrystallization of the precipitates (37.9 g) from methanol (926 ml) gave (*S*)-1-phenylethylamine (*S*)-4-benzoyloxymandelate (24.8 g) having a melting point of 174-180°C.

IR (KBr): 3301, 3036, 1609  $\text{cm}^{-1}$

$^1\text{H-NMR}$  (DMSO- $d_6$ )

$\delta$  ppm: 1.42 (3H, d,  $J=6.7\text{Hz}$ ), 4.27 (1H, q,  $J=6.7\text{Hz}$ ), 4.50 (1H, s), 5.07 (2H, s), 6.85-6.95 (2H, m), 7.20-8.00 (14H, m)

Optical rotation:  $[\alpha]_D^{25} = +36.2^\circ$  ( $c=0.50$ , MeOH)

To a stirred suspension of (*S*)-1-phenylethylamine (*S*)-4-benzoyloxymandelate (1.0 g) in ethyl acetate (20 ml) and water (20 ml) was added 1N hydrochloric acid (3.0 ml) under ice-

cooling. After the mixture was stirred under ice-cooling for 30 minutes, the organic layer was separated, washed with water and dried over anhydrous magnesium sulfate. Concentration of the resulting solution *in vacuo* gave (*S*)-4-benzyloxymandelic acid (595 mg) having a melting point of 158-162°C.

IR (KBr): 3440, 1734  $\text{cm}^{-1}$

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ).

$\delta$  ppm: 4.95 (1H, s), 5.09 (2H, s), 5.70 (1H, br), 6.90-7.00 (2H, m), 7.25-7.50 (7H, m), 12.30 (1H, br)

Optical rotation:  $[\alpha]_D^{25} = +99.9^\circ$  ( $c=1.00$ , MeOH)

To a stirred solution of (*S*)-4-benzyloxymandelic acid (1.80 g), (*S*)-2-amino-7-hydroxytetralin hydrobromide (1.87 g) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (3.39 g) in *N,N*-dimethylformamide (21 ml) was added triethylamine (2.03 ml) under ice-cooling. After the mixture was stirred at room temperature for an hour, diethyl ether and water were added to the reaction mixture. Collection of the resulting precipitates gave (2*S*)-2-(4-benzyloxyphenyl)-2-hydroxy-*N*-((2*S*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (2.64 g) as powders.

IR (KBr): 3487, 3402, 1652  $\text{cm}^{-1}$

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.65-1.80 (1H, m), 1.95-2.10 (1H, m), 2.53 (1H, dd,

$J=16.3$ ,  $8.6\text{Hz}$ ),  $2.65\text{--}2.85$  (2H, m),  $3.00$  (1H, dd,  $J=16.3$ ,  $5.1\text{Hz}$ ),  $4.15\text{--}4.20$  (1H, m),  $4.99$  (1H, s),  $5.06$  (2H, s),  $6.32$  (1H, d,  $J=8.0\text{Hz}$ ),  $6.48$  (1H, d,  $J=2.6\text{Hz}$ ),  $6.62$  (1H, dd,  $J=8.3$ ,  $2.6\text{Hz}$ ),  $6.85\text{--}7.00$  (3H, m),  $7.20\text{--}7.50$  (7H, m)  
Optical rotation:  $[\alpha]_D^{25} = -6.8^\circ$  ( $c=1.00$ , MeOH)

To a stirred solution of (2*S*)-2-(4-benzyloxyphenyl)-2-hydroxy-*N*-((2*S*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (2.50 g) in tetrahydrofuran (31 ml) was added borane-dimethylsulfide complex (1.76 ml) at room temperature. After the mixture was heated under reflux for 4 hours, a solution of triethanolamine (4.62 g) in tetrahydrofuran (4.6 ml) was added to the reaction mixture at room temperature and the mixture was heated under reflux for 11 hours. After cooling, water was poured into the reaction mixture and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: ethyl acetate/ethanol = 7/1) gave (1*S*)-1-(4-benzyloxyphenyl)-2-(((2*S*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)amino)ethanol (1.63 g) as an amorphous.

IR (KBr):  $3290\text{ cm}^{-1}$

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.55-1.70 (1H, m), 1.95-2.10 (1H, m), 2.50-3.05 (7H, m), 3.40 (2H, br), 4.67 (1H, dd,  $J=9.1, 3.5\text{Hz}$ ), 5.06 (2H, s), 6.50 (1H, d,  $J=2.6\text{Hz}$ ), 6.60 (1H, dd,  $J=8.2, 2.6\text{Hz}$ ), 6.93 (1H, d,  $J=8.2\text{Hz}$ ), 6.96 (2H, d,  $J=8.7\text{Hz}$ ), 7.20-7.50 (7H, m)  
Optical rotation:  $[\alpha]_{\text{D}}^{25} = -11.9^\circ$  ( $c=1.00$ ,  $\text{CHCl}_3$ )

To a stirred suspension of (1S)-1-(4-benzyloxyphenyl)-2-[[((2S)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)amino]-ethanol (1.30 g) and *N,N*-diisopropylethylamine (2.91 ml) in dichloromethane (16.7 ml) was added trifluoroacetic anhydride (1.41 ml) at  $-15^\circ\text{C}$ . After the mixture was stirred at  $-15^\circ\text{C}$  for 20 minutes, water was poured into the reaction mixture and the resulting mixture was extracted with dichloromethane. The extract was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The resulting residue was dissolved in *N,N*-dimethylformamide (8.6 ml) and 2-bromo-*N,N*-dimethylacetamide (571 mg), cesium carbonate (2.52 g) and molecular sieves 4A powder (860 mg) were added to the solution at room temperature. After the mixture was still stirred for 2.5 hours, water and methanol were added to the reaction mixture under ice-cooling and the resulting mixture was stirred at room temperature for 12 hours. The insoluble materials were filtered off and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in ethyl

acetate, and the solution was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. Recrystallization of the residue from diethyl ether gave 2-[(2*S*)-2-[[ (2*S*)-2-(4-benzyloxyphenyl)-2-hydroxyethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylacetamide (437 mg) having a melting point of 103-106°C.

IR (KBr): 3438, 1672, 1653 cm<sup>-1</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

δ ppm: 1.50-1.70 (1H, m), 2.00-2.15 (1H, m), 2.55-3.10 (13H, m), 4.60-4.70 (3H, m), 5.07 (2H, s), 6.64 (1H, d, J=2.8Hz), 6.74 (1H, dd, J=8.4, 2.8Hz), 6.97 (2H, d, J=8.8Hz), 6.99 (1H, d, J=8.4Hz), 7.20-7.50 (7H, m)

Optical rotation: [α]<sub>D</sub><sup>25</sup> = -14.2° (c=1.00, CHCl<sub>3</sub>)

#### Reference Example 6

According to the procedure described in Reference Example 5, the following compounds were prepared using 1-(2-bromoacetyl)piperidine and 4-(2-bromoacetyl)morpholine instead of 2-bromo-*N,N*-dimethylacetamide.

1-[2-[(2*S*)-2-[[ (2*S*)-2-(4-Benzyloxyphenyl)-2-hydroxyethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]piperidine oil

IR (neat): 3304, 1638 cm<sup>-1</sup>

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )

$\delta$  ppm : 1.50-1.70 (7H, m), 2.00-2.15 (1H, m), 2.50-3.05 (7H, m), 3.40-3.60 (4H, m), 4.60-4.70 (3H, m), 5.07 (2H, s), 6.64 (1H, d,  $J=2.7\text{Hz}$ ), 6.73 (1H, dd,  $J=8.4, 2.7\text{Hz}$ ), 6.90-7.05 (3H, m), 7.25-7.60 (7H, m)

Optical rotation:  $[\alpha]_{\text{D}}^{25} = -12.1^\circ$  ( $c=1.00$ ,  $\text{CHCl}_3$ )

4-[2-[(2*S*)-2-[[ (2*S*)-2-(4-Benzoyloxyphenyl)-2-hydroxyethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]morpholine  
amorphous

IR (KBr): 3438, 1651  $\text{cm}^{-1}$

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.50-1.70 (1H, m), 2.00-2.10 (1H, m), 2.50-3.10 (7H, m), 3.55-3.75 (9H, m), 4.60-4.70 (3H, m), 5.07 (2H, s), 6.64 (1H, d,  $J=2.7\text{Hz}$ ), 6.72 (1H, dd,  $J=8.4, 2.7\text{Hz}$ ), 6.97 (2H, d,  $J=8.7\text{Hz}$ ), 6.98 (1H, d,  $J=8.4\text{Hz}$ ), 7.25-7.50 (7H, m)

Optical rotation:  $[\alpha]_{\text{D}}^{25} = -26.3^\circ$  ( $c=0.50$ , MeOH)

#### Example 1

2-[(2*S*)-2-[[ (2*RS*)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethyl-acetamide

To a solution of ethyl 2-[(2*S*)-2-[[ (2*RS*)-2-hydroxy-2-(4-

hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetate (250 mg) in tetrahydrofuran (5 ml) was added dimethylamine (1 ml) under ice-cooling. After the mixture was stirred in sealed tube at 60°C for 60 hours, the reaction mixture was concentrated in vacuo. Purification of the residue by medium pressure liquid column chromatography on aminopropylated silica gel (eluent: ethyl acetate/ethanol = 10/1) gave 2-[(2*S*)-2-[[*(2RS)*-2-hydroxy-2-(4-hydroxyphenyl)-ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylacetamide (189 mg) as an amorphous.

IR (KBr): 3290, 1651 cm<sup>-1</sup>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ ppm: 1.35-1.70 (2H, m), 1.80-2.00 (1H, m), 2.35-3.05 (13H, m), 4.45-4.55 (1H, m), 4.65-4.75 (2H, m), 5.06 (1H, br s), 6.55-6.75 (4H, m), 6.93 (1H, d, J=8.4Hz), 7.14 (2H, d, J=8.3Hz), 9.19 (1H, br s)

#### Example 2

According to the procedure described in Example 1, the following compounds were prepared using piperidine, morpholine and pyrrolidine instead of dimethylamine.

1-[2-[(2*S*)-2-[[*(2RS)*-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]piperidine

amorphous

IR (KBr) : 3397, 1638  $\text{cm}^{-1}$

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.40-1.70 (7H, m), 2.00-2.10 (1H, m), 2.45-3.10 (7H, m),  
3.40-3.70 (4H, m), 4.60-4.70 (3H, m), 6.62 (1H, d,  $J=2.6\text{Hz}$ ),  
6.65-6.85 (3H, m) , 6.97 (1H, d,  $J=8.4\text{Hz}$ ), 7.20-7.25 (2H, m)

4-[2-[(2*S*)-2-[[ (2*RS*)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-  
amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]morpholine  
amorphous

IR (KBr): 3402, 1651  $\text{cm}^{-1}$

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.50-1.65 (1H, m), 1.95-2.10 (1H, m), 2.40-2.55 (1H, m),  
2.60-3.00 (6H, m), 3.55-3.75 (8H, m), 4.60-4.70 (3H, m), 6.55-  
6.65 (1H, m), 6.69 (1H, dd,  $J=8.4, 2.7\text{Hz}$ ), 6.79 (2H, d,  
 $J=8.5\text{Hz}$ ), 6.97 (1H, d,  $J=8.4\text{Hz}$ ), 7.19 (2H, d,  $J=8.5\text{Hz}$ )

1-[2-[(2*S*)-2-[[ (2*RS*)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-  
amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]pyrrolidine  
amorphous

IR (KBr): 3403, 1643  $\text{cm}^{-1}$

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )

$\delta$  ppm: 1.45-1.65 (1H, m), 1.70-2.05 (6H, m), 2.10-3.00 (9H, m),  
3.45-3.55 (4H, m), 4.55-4.70 (3H, m), 6.58 (1H, dd,  $J=8.2,$

2.7Hz), 6.65-6.75 (1H, m), 6.80 (2H, d, J=8.4Hz), 6.96 (1H, d, J=8.2Hz), 7.18 (2H, d, J=8.4Hz)

### Example 3

2-[(2S)-2-[[ (2R)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-N,N-dimethylacetamide

To a solution of 2-[(2S)-2-[[ (2R)-2-(4-benzyloxyphenyl)-2-hydroxyethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-N,N-dimethylacetamide (273 mg) in ethanol (5.5 ml) was added 10% palladium on activated carbon (60 mg). After the mixture was vigorously stirred at room temperature for 12 hours under hydrogen atmosphere, the catalyst was filtered off and the filtrate was concentrated in vacuo. Recrystallization of the resulting residue from methanol gave 2-[(2S)-2-[[ (2R)-2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-N,N-dimethylacetamide (200 mg) having a melting point of 169-172°C.

IR (KBr): 3255, 1656 cm<sup>-1</sup>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ ppm: 1.70-1.85 (1H, m), 2.20-2.30 (1H, m), 2.60-2.90 (6H, m), 2.98 (3H, s), 3.00-3.25 (3H, m), 3.35-3.50 (1H, m), 4.73 (2H, s), 4.80-4.95 (1H, m), 6.02 (1H, br s), 6.65 (1H, d, J=2.6Hz), 6.70 (1H, dd, J=8.4, 2.6Hz), 6.78 (2H, d, J=8.5Hz), 6.99 (1H, d, J=8.4Hz), 7.22 (2H, d, J=8.5Hz), 8.80 (1H, br), 9.47 (1H, br)

s)

Optical rotation (hydrochloride):  $[\alpha]_D^{25} = -69.3^\circ$  (c=1.01, H<sub>2</sub>O)

#### Example 4

According to the procedure described in Example 3, the following compounds were prepared using the corresponding amide derivatives instead of 2-[(2*S*)-2-[[ (2*R*)-2-(4-benzyloxyphenyl)-2-hydroxyethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylacetamide.

1-[2-[(2*S*)-2-[[ (2*R*)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]piperidine  
amorphous

IR (KBr): 3309, 1638 cm<sup>-1</sup>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

$\delta$  ppm: 1.35-1.65 (6H, m), 1.70-1.90 (1H, m), 2.20-2.35 (1H, m), 2.60-2.90 (3H, m), 3.00-3.50 (8H, m), 4.71 (2H, s), 4.85-5.00 (1H, m), 6.02 (1H, br s), 6.66 (1H, s), 6.71 (1H, dd, J=8.4, 2.2Hz), 6.78 (2H, d, J=8.4Hz), 6.99 (1H, d, J=8.4Hz), 7.22 (2H, d, J=8.4Hz), 8.90 (1H, br), 9.50 (1H, s).

Optical rotation:  $[\alpha]_D^{25} = -85.2^\circ$  (c=0.58, MeOH)

4-[2-[(2*S*)-2-[[ (2*R*)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]morpholine

melting point: 98-101°C (CHCl<sub>3</sub>-Et<sub>2</sub>O)

IR (KBr): 3393, 1643 cm<sup>-1</sup>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ ppm: 1.65-1.80 (1H, m), 2.10-2.25 (1H, m), 2.60-3.20 (6H, m), 3.25-3.65 (10H, m), 4.70-4.90 (3H, m), 5.88 (1H, br), 6.66 (1H, d, J=2.5Hz), 6.71 (1H, dd, J=8.5, 2.5Hz), 6.77 (2H, d, J=8.5Hz), 6.99 (1H, d, J=8.5Hz), 7.21 (2H, d, J=8.5Hz), 9.45 (1H, br s)

Optical rotation: [α]<sub>D</sub><sup>25</sup> = -68.4° (c=0.98, MeOH)

2-[(2*S*)-2-[[*(2S)*-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylacetamide  
melting point: 181-183°C (EtOH-EtOAc)

IR (KBr): 3156, 1652 cm<sup>-1</sup>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ ppm: 1.35-1.55 (1H, m), 1.85-2.00 (1H, m), 2.30-3.05 (14H, m), 4.45-4.55 (1H, m), 4.69 (2H, s), 5.10 (1H, br s), 6.59 (1H, d, J=2.6Hz), 6.63 (1H, dd, J=8.4, 2.6Hz), 6.69 (2H, d, J=8.5Hz), 6.93 (1H, d, J=8.4Hz), 7.14 (2H, d, J=8.5Hz), 9.22 (1H, s)

Optical rotation: [α]<sub>D</sub><sup>25</sup> = -24.1° (c=1.00, AcOH)

1-[2-[(2*S*)-2-[[*(2S)*-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-

amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]piperidine  
amorphous

IR (KBr): 3374, 1634  $\text{cm}^{-1}$

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )

$\delta$  ppm: 1.45-1.70 (7H, m), 1.95-2.00 (1H, m), 2.40-2.55 (1H, m),  
2.65-3.00 (8H, m), 3.45-3.60 (4H, m), 4.60-4.70 (3H, m), 6.58  
(1H, d,  $J=2.7\text{Hz}$ ), 6.69 (1H, dd,  $J=8.4, 2.7\text{Hz}$ ), 6.78 (2H, d,  
 $J=8.5\text{Hz}$ ), 6.96 (1H, d,  $J=8.4\text{Hz}$ ), 7.15 (2H, d,  $J=8.5\text{Hz}$ )

Optical rotation:  $[\alpha]_{\text{D}}^{25} = -14.2^\circ$  ( $c=1.00$ ,  $\text{CHCl}_3$ )

4-[2-[(2*S*)-2-[[ (2*S*)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-  
amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]morpholine  
amorphous

IR (KBr): 3402, 1649  $\text{cm}^{-1}$

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )

$\delta$  ppm: 1.40-1.75 (2H, m), 1.85-2.00 (1H, m), 2.30-2.95 (7H, m),  
3.40-3.65 (8H, m), 4.45-4.55 (1H, m), 4.72 (2H, s), 5.10 (1H,  
d,  $J=4.1\text{Hz}$ ), 6.61 (1H, d,  $J=2.6\text{Hz}$ ), 6.65 (1H, dd,  $J=8.3,$   
2.6Hz), 6.69 (2H, d,  $J=8.5\text{Hz}$ ), 6.94 (1H, d,  $J=8.3\text{Hz}$ ), 7.13 (2H,  
d,  $J=8.5\text{Hz}$ ), 9.22 (1H, s)

Optical rotation:  $[\alpha]_{\text{D}}^{25} = -15.5^\circ$  ( $c=0.49$ , MeOH)

4-[(2*S*)-2-[[ (2*RS*)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-

amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethyl-  
butyramide

amorphous

IR (film): 3220, 1616  $\text{cm}^{-1}$

$^1\text{H}$ -NMR ( $\text{DMSO}-d_6$ )

$\delta$  ppm: 1.35-1.75 (2H, m), 1.80-2.00 (3H, m), 2.35-3.00 (14H, m), 3.31 (1H, s), 3.85-3.95 (2H, m), 4.45-4.55 (1H, m), 5.10 (1H, br s), 6.55-6.75 (4H, m), 6.93 (1H, d,  $J=7.4\text{Hz}$ ), 7.13 (2H, d,  $J=8.4\text{Hz}$ ), 9.22 (1H, s)

#### Example 5

2-[(2*S*)-2-[[*(2R)*-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylacetamide hydrochloride

To a suspension of 2-[(2*S*)-2-[[*(2R)*-2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylacetamide (210 mg) in ethanol (10.5 ml) was added 1*N* hydrochloric acid (546  $\mu\text{l}$ ) and the mixture was heated until homogeneous on a steam bath. After cooling, collection of the resulting crystals gave 2-[(2*S*)-2-[[*(2R)*-2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylacetamide hydrochloride (100 mg) having a melting point of 165-168°C.

IR (KBr): 2433, 1652  $\text{cm}^{-1}$

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ ppm: 1.70-1.90 (1H, m), 2.15-2.30 (1H, m), 2.60-3.60 (13H, m), 4.74 (2H, s), 4.80-4.95 (1H, m), 6.06 (1H, d, J=2.8Hz), 6.66 (1H, d, J=2.6Hz), 6.72 (1H, dd, J=8.4, 2.6Hz), 6.79 (2H, d, J=8.6Hz), 7.01 (1H, d, J=8.4Hz), 7.24 (2H, d, J=8.6Hz), 8.65-9.00 (2H, m), 9.48 (1H, s)

Optical rotation:  $[\alpha]_{D^{25}} = -69.3^{\circ}$  (c=1.01, H<sub>2</sub>O)

#### Example 6

According to the procedure described in Example 5, the following compounds were prepared using L-tartaric acid and a 1N aqueous sulfuric acid solution instead of 1N hydrochloric acid.

2-[(2S)-2-[[ (2R)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-N,N-dimethylacetamide 0.5 L-tartrate

melting point: 178-181°C (EtOH)

IR (KBr): 3634, 3360, 2440, 1659, 1616 cm<sup>-1</sup>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ ppm: 1.50-1.70 (1H, m), 1.95-2.15 (1H, m), 2.40-3.20 (14H, m), 3.40 (2H, br), 3.79 (1H, s), 4.60-4.80 (3H, m), 5.60 (1H, br), 6.63 (1H, d, J=2.6Hz), 6.67 (1H, dd, J=8.3, 2.6Hz), 6.73 (2H, d, J=8.5Hz), 6.96 (1H, d, J=8.3Hz), 7.18 (2H, d, J=8.5Hz),

9.30 (1H, br)

Optical rotation:  $[\alpha]_D^{25} = -64.7^\circ$  ( $c=1.03$ ,  $H_2O$ )

2-[(2*S*)-2-[[*(2R)*-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylacetamide hemisulfate

melting point: 202-205°C (decomposition) (EtOH)

IR (KBr): 2429, 1638  $cm^{-1}$

$^1H$ -NMR (DMSO- $d_6$ )

$\delta$  ppm: 1.50-1.70 (1H, m), 1.95-2.15 (1H, m), 2.30-3.30 (15H, m), 4.60-4.80 (3H, m), 5.60 (1H, br), 6.63 (1H, d,  $J=2.6Hz$ ), 6.67 (1H, dd,  $J=8.4, 2.6Hz$ ), 6.74 (2H, d,  $J=8.5Hz$ ), 6.96 (1H, d,  $J=8.4Hz$ ), 7.18 (2H, d,  $J=8.5Hz$ ), 9.34 (1H, br s)

Optical rotation:  $[\alpha]_D^{25} = -65.2^\circ$  ( $c=0.50$ , DMSO)

#### Example 7

According to the procedure described in Example 5, the following compounds were prepared using 1-[2-[(2*S*)-2-[[*(2R)*-2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]piperidine, L-tartaric acid and D-tartaric acid.

1-[2-[(2*S*)-2-[[*(2R)*-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]piperidine

0.5 L-tartrate

melting point: 208-210°C (EtOH)

IR (KBr): 3373, 1645 cm<sup>-1</sup>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ ppm: 1.30-1.70 (7H, m), 2.00-2.15 (1H, m), 2.50-3.25 (7H, m),  
3.30-3.50 (4H, m), 3.85 (1H, s), 4.60-4.75 (3H, m), 6.64 (1H,  
d, J=2.6Hz), 6.67 (1H, dd, J=8.4, 2.6Hz), 6.73 (2H, d,  
J=8.5Hz), 6.96 (1H, d, J=8.4Hz), 7.19 (2H, d, J=8.5Hz), 9.20  
(1H, br)

Optical rotation:  $[\alpha]_D^{25} = -66.9^\circ$  (c=0.55, MeOH)

1-[2-[(2S)-2-[[ (2R)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-  
amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]piperidine

0.5 D-tartrate

melting point: 206-208°C (EtOH)

IR (KBr): 3395, 1645 cm<sup>-1</sup>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ ppm: 1.35-1.70 (7H, m), 2.00-2.15 (1H, m), 2.50-3.20 (7H, m),  
3.30-3.50 (4H, m), 3.82 (1H, s), 4.60-4.75 (3H, m), 5.70 (1H,  
br), 6.63 (1H, d, J=2.7Hz), 6.67 (1H, dd, J=8.4, 2.7Hz), 6.73  
(2H, d, J=8.5Hz), 6.96 (1H, d, J=8.4Hz), 7.18 (2H, d, J=8.5Hz),  
9.30 (1H, br)

Optical rotation:  $[\alpha]_D^{25} = -82.8^\circ$  (c=0.50, MeOH)

Example 8

According to the procedure described in Example 5, the following compounds were prepared using 4-[2-[(2*S*)-2-[[2-*R*)-2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]morpholine, L-tartaric acid, D-tartaric acid and fumaric acid.

4-[2-[(2*S*)-2-[[2-*R*)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]morpholine  
0.5 L-tartrate

melting point: 199-201°C (EtOH)

IR (KBr): 3430, 1652 cm<sup>-1</sup>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ ppm: 1.50-1.70 (1H, m), 2.00-2.15 (1H, m), 2.50-3.20 (7H, m), 3.30-3.70 (8H, m), 3.82 (1H, s), 4.66 (1H, d, J=6.2Hz), 4.74 (2H, s), 5.70 (1H, br), 6.65 (1H, d, J=2.5Hz), 6.68 (1H, dd, J=8.4, 2.5Hz), 6.73 (2H, d, J=8.5Hz), 6.97 (1H, d, J=8.4Hz), 7.18 (2H, d, J=8.5Hz), 9.30 (1H, br)

Optical rotation: [α]<sub>D</sub><sup>25</sup> = -62.6° (c=0.54, MeOH)

4-[2-[(2*S*)-2-[[2-*R*)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]morpholine  
0.5 D-tartrate

melting point: 202-204°C (EtOH)

IR (KBr): 3423, 1655 cm<sup>-1</sup>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ ppm: 1.50-1.70 (1H, m), 2.00-2.20 (1H, m), 2.55-3.25 (7H, m), 3.35-3.65 (8H, m), 3.85 (1H, s), 4.68 (1H, dd, J=9.3, 3.0Hz), 4.74 (2H, s), 5.90 (1H, br), 6.65 (1H, d, J=2.6Hz), 6.68 (1H, dd, J=8.4, 2.6Hz), 6.73 (2H, d, J=8.5Hz), 6.97 (1H, d, J=8.4Hz), 7.18 (2H, d, J=8.5Hz), 9.20 (1H, br)

Optical rotation: [α]<sub>D</sub><sup>25</sup> = -71.5° (c=0.54, MeOH)

4-[2-[(2*S*)-2-[[ (2*R*)-2-Hydroxy-2-(4-hydroxyphenyl)ethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]morpholine hemifumarate

melting point: 193-197°C (EtOH)

IR (KBr): 3459, 1643 cm<sup>-1</sup>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)

δ ppm: 1.50-1.65 (1H, m), 2.00-2.15 (1H, m), 2.55-3.20 (7H, m), 3.35-3.70 (8H, m), 4.67 (1H, dd, J=9.3, 3.2Hz), 4.74 (2H, s), 6.46 (1H, s), 6.64 (1H, d, J=2.6Hz), 6.68 (1H, dd, J=8.3, 2.6Hz), 6.73 (2H, d, J=8.5Hz), 6.96 (1H, d, J=8.3Hz), 7.17 (2H, d, J=8.5Hz), 9.30 (1H, br)

Optical rotation: [α]<sub>D</sub><sup>25</sup> = -67.0° (c=0.54, MeOH)

Test Example 1

Action of the agent on the spontaneous contractions of isolated rat myometrium

The uterus of a pregnant SD rat (21 days of pregnancy) was isolated. A uterine muscle strip (15 mm long, 5 mm wide) was longitudinally dissected and suspended vertically in a 10 ml chamber and prepared for recording of isometric contractions. The endometrium and placenta-attached part were carefully removed from the uterus with a fine forceps, and the test was carried out in accordance with the Magnus method. The sample was set in Locke-Ringer solution at 37°C aerated with a mixed gas containing 95% of oxygen and 5% of carbon dioxide, and 1 g of load was applied. Spontaneous contractions of isolated rat myometrium were induced isometrically via a pressure transducer and recorded on a rectigram. The efficacy was evaluated by comparing the total degree of uterine contraction during 5 minutes before the addition of the agent with the total degree of uterine contraction during 5 minutes after the addition of the agent and calculating the 50% inhibitory concentration as  $EC_{50}$ .

Test Example 2

Action of the agent on the heart rate of isolated rat atrium

The atrium of an SD male rat (350 to 400 g in body weight)

was isolated and the test was carried out in accordance with the Magnus method. The sample was set in a Krebs-Henseleit solution at 37°C aerated with a mixture gas containing 95% of oxygen and 5% of carbon dioxide, and 1.g of load was applied. The atrial contraction was induced isometrically via a pressure transducer and recorded on a rectigram. After addition of the agent, its efficacy was evaluated by calculating EC<sub>20</sub> value which is the agent concentration which increases 20 beats per minute of heart rate.

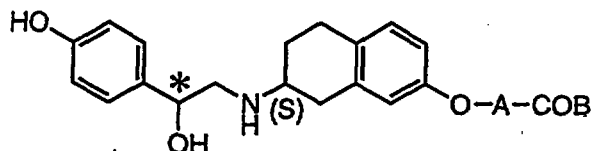
#### Test Example 3

##### Acute Toxicity

To 4 female ICR mice of 4 weeks age was administered intravenously 2-[(2*S*)-2-[[ (2*R*)-2-hydroxy-2-(4-hydroxyphenyl)-ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N,N*-dimethylacetamide in saline at dose of 50 mg/kg. No death of animals was observed during 24 hours after the administration.

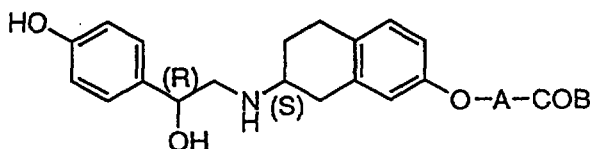
CLAIMS

1. A phenylethanolaminotetralincarboxamide derivative represented by the general formula:



(wherein A represents a lower alkylene group, B represents an amino group, a di-lower alkylamino group, or a 3 to 7-membered alicyclic amino group which may contain an oxygen atom, the carbon atom marked with \* represents a carbon atom in (R) configuration, (S) configuration, or a mixture thereof, and the carbon atom marked with (S) represents a carbon atom in (S) configuration) and a pharmaceutically acceptable salt thereof.

2. A phenylethanolaminotetralincarboxamide derivative as claimed in claim 1, represented by the general formula:

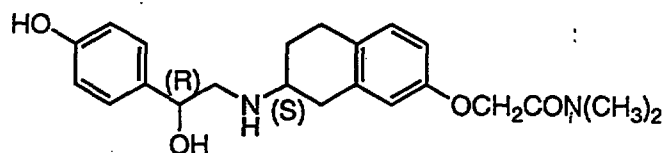


(wherein A represents a lower alkylene group, B represents an



amino group, a di-lower alkylamino group, or a 3 to 7-membered alicyclic amino group which may contain an oxygen atom, the carbon atom marked with (R) represents a carbon atom in (R) configuration, and the carbon atom marked with (S) represents a carbon atom in (S) configuration) and a pharmaceutically acceptable salt thereof.

3. A phenylethanolaminotetralincarboxamide derivative as claimed in claim 2, represented by the formula:

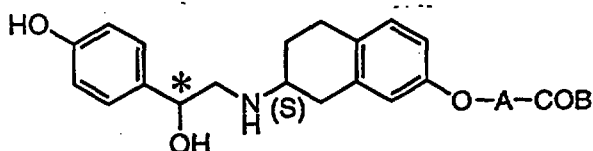


(wherein the carbon atom marked with (R) represents a carbon atom in (R) configuration, and the carbon atom marked with (S) represents a carbon atom in (S) configuration) and a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition for the prevention of threatened abortion, premature labor, for the treatment or prevention of diseases associated with bronchostenosis or airway obstruction and pain remission, stone removal in urolithiasis containing, as an active ingredient, a

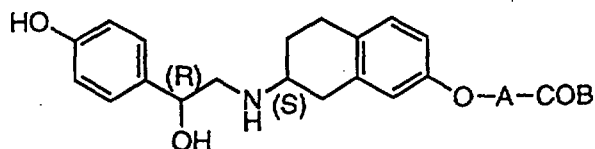


phenylethanolaminotetralincarboxamide derivative represented by the general formula:



(wherein A represents a lower alkylene group, B represents an amino group, a di-lower alkylamino group, or a 3 to 7-membered alicyclic amino group which may contain an oxygen atom, the carbon atom marked with \* represents a carbon atom in (R) configuration, (S) configuration, or a mixture thereof, and the carbon atom marked with (S) represents a carbon atom in (S) configuration) or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition as claimed in claim 4, wherein said active ingredient is represented by the general formula:

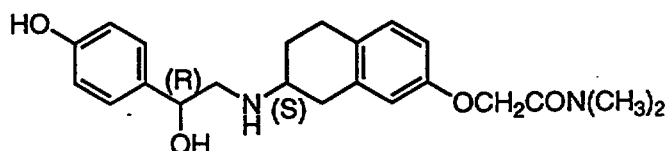


(wherein A represents a lower alkylene group, B represents an amino group, a di-lower alkylamino group, or a 3 to 7-membered



alicyclic amino group which may contain an oxygen atom, the carbon atom marked with (R) represents a carbon atom in (R) configuration, and the carbon atom marked with (S) represents a carbon atom in (S) configuration) or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition as claimed in claim 5, wherein said active ingredient is represented by the formula:



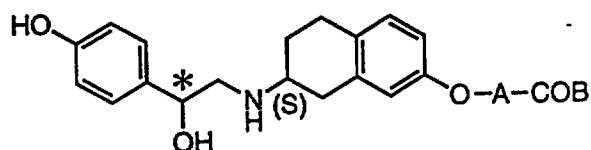
(wherein the carbon atom marked with (R) represents a carbon atom in (R) configuration, and the carbon atom marked with (S) represents a carbon atom in (S) configuration) or a pharmaceutically acceptable salt thereof.



## PHENYLETHANOLAMINOTETRALINCARBOXAMIDE DERIVATIVES

### ABSTRACT

A novel phenylethanolaminotetralincarboxamide derivative having potent  $\beta_2$ -adrenergic receptor stimulating activity, which is represented by the general formula:



(wherein A represents a lower alkylene group, B represents an amino group, a di-lower alkylamino group, or a 3 to 7-membered alicyclic amino group which may contain an oxygen atom, the carbon atom marked with \* represents a carbon atom in (*R*) configuration, (*S*) configuration, or a mixture thereof, and the carbon atom marked with (*S*) represents a carbon atom in (*S*) configuration) and a pharmaceutically acceptable salt thereof. The compounds are selective  $\beta_2$ -adrenergic receptor stimulating agents with reduced burdens on cardiovascular systems, which are useful as an agent for preventing threatened abortion or premature labor, as a bronchodilator, and the like.