

FORM 1

592143

REGULATION 9

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

We, WARNER-LAMBERT COMPANY, a Corporation organised under the laws of the State of Delaware, United States of America, of 2800 Plymouth Road, Ann Arbor, Michigan, United States of America, hereby apply for the grant of a Standard Patent for an invention entitled:-

"IMPROVED PROCESS FOR THE RESOLUTION OF 1-AMINOINDANES"

which is described in the accompanying Complete Specification.

Details of basic application:-

Number: 824,988

Country: U.S.A.

Date: 3rd February, 1986

APPLICATION ACCEPTED AND AMENDMENTS

ALLOWED 26-10-89

Our address for service is:

SHELSTON WATERS

55 Clarence Street

SYDNEY, N.S.W. 2000.

DATED this 9th day of January, 1987

WARNER-LAMBERT COMPANY

by *Robert J. Shelston*

Fellow Institute of Patent Attorneys of Australia
of SHELSTON WATERS

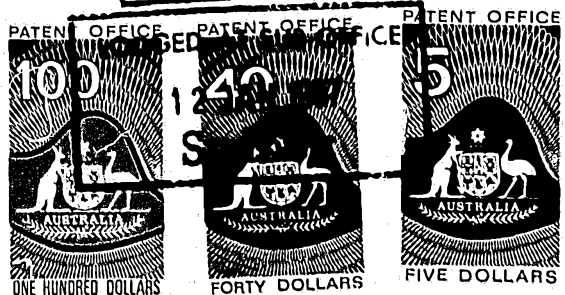
To: The Commissioner of Patents
WODEN A.C.T. 2606

File: D.B.5I

Fee: \$145.00
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12 JAN 1987
Sydney

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MAIL OFFICER: [Signature]



(CONVENTION - Company)

FORM 8 - REGULATION 12 (2)

COMMONWEALTH OF AUSTRALIA PATENTS ACT, 1952-1973
DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application No. ... made by (a) WARNER-LAMBERT COMPANY ...

(hereinafter referred to as "Applicant") for a patent for an invention entitled: (b) IMPROVED PROCESS FOR THE RESOLUTION OF 1-AMINOINDANES ...

(c) CHRISTINE A. TRAUTWEIN, ASSISTANT SECRETARY ...

(c) and (d) Here insert Full Name and Address of Company Official authorised to make declaration. of (d) WARNER-LAMBERT COMPANY, 2800 PLYMOUTH ROAD, ANN ARBOR, MICHIGAN 48105, U.S.A. ...

do solemnly and sincerely declare as follows:

- 1. I am authorised by Applicant to make this declaration on its behalf.
2. The basic Application(s) as defined by section 141 of the Act was/were made in (e) THE U.S.A. ... on the 3RD ... day of FEBRUARY ... 1986.
by (f) OM PRAKASH GOEL, 3995 HOLDEN DRIVE, ANN ARBOR, MI. 48103.
3. (g) OM PRAKASH GOEL, 3995 HOLDEN DRIVE, ANN ARBOR, MI. 48103

(e) Here insert Basic Country or Countries followed by date or dates of Basic Application(s).

(f) Here insert Full Name(s) of Applicant(s) in Basic Country.

(g) Here insert (In full) Name and Address of actual Inventor or Inventors.

of ... is/are the actual Inventor(s) of the invention and the facts upon which Applicant is entitled to make the Application are as follows:

Applicant is the Assignee of the said Inventor(s).

4. The basic Application(s) referred to in paragraph 2 of this Declaration was/were the first Application(s) made in a Convention country in respect of the invention, the subject of the Application.

DECLARED at WARNER-LAMBERT CO., ANN ARBOR, MICHIGAN ... this ... 19th ... day of DECEMBER ... 1986.

(h) Personal Signature of Declarant (c) (no seal, witness or legalisation).

(h) Christine A. Trautwein (Signature of Declarant) ASSISTANT SECRETARY

To THE COMMISSIONER OF PATENTS.

SHELSTON WATERS PATENT ATTORNEYS 55 CLARENCE STREET, SYDNEY AUSTRALIA Cables: 'Valid' Sydney Telex: 24422

(12) PATENT ABRIDGMENT (11) Document No. AU-B-67506/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 592143

(54) Title
PROCESS FOR RESOLUTION OF 1-AMINOINDANES

International Patent Classification(s)
(51) C07C 087/457 C07H 019/167

(21) Application No. : 67506/87 (22) Application Date : 12.01.87

(30) Priority Data

(31) Number (32) Date (33) Country
824988 03.02.86 US UNITED STATES OF AMERICA

(43) Publication Date : 06.08.87

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(71) Applicant(s)
WARNER-LAMBERT COMPANY

(72) Inventor(s)
OM PRAKASH GOEL

(74) Attorney or Agent
SHELSTON WATERS

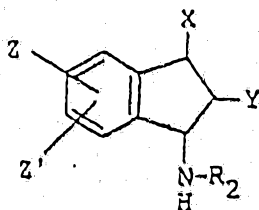
(57) In the present invention the resolving agent used is R-N-acetyl-3,4-dimethoxyphenylalanine which is disclosed in US 3,734,952 but not used as a resolving agent.

The process of the present invention may be used for producing intermediates in the synthesis of indanyl-adenosines which compounds are described in US 4,501,735 herein incorporated by reference.

The present process gives greatly improved yield, 83% yield of R(-)-1-aminoindane compared to very low yields in the process described above.

CLAIM

1. A process for the preparation of the R isomer of a compound of the formula



wherein X is hydrogen, lower alkyl or lower alkyl terminally substituted by hydroxy, lower alkoxy or carboxyl, Y is hydrogen, lower alkyl or lower alkyl

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(10) 592143

-2-

terminally substituted by hydroxy, lower alkoxy, OR where R is hydrogen, lower alkyl, lower alkanoyl, or benzoyl, Z and Z' are each independently hydrogen, halogen, nitro, trifluoromethyl, lower alkyl, hydroxy or lower alkoxy, R₂ is hydrogen or lower alkyl which comprises

- (a) reacting R-N-acetyl-3,4-dimethoxyphenyl alanine in an alcohol with an (R,S) mixture of a compound of the above formula as defined above;
- (b) removing the precipitated (R,S) salt;
- (c) concentrating the filtrate containing the (R,R) salt, treating with base, separating and isolating according to known means the desired R isomer of the compound above.

592143

COMMONWEALTH OF AUSTRALIA

FORM 10

PATENTS ACT 1952

COMPLETE SPECIFICATION

FOR OFFICE USE:

Application Number: 67506/87. Class Int. Class Lodged:

Complete Specification Lodged: Accepted: Published:

Priority: Related Art:

This document contains the amendments made under Section 49 and is correct for printing.

Name of Applicant: WARNER-LAMBERT COMPANY

Address of Applicant: 2800 PLYMOUTH ROAD, ANN ARBOR, MICHIGAN 48105, U.S.A.

Actual Inventor: OM PRAKASH GOEL

Address for Service: SHELSTON WATERS, 55 Clarence Street, Sydney

Complete Specification for the Invention entitled:

"IMPROVED PROCESS FOR THE RESOLUTION OF 1-AMINOINDANES"

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

BACKGROUND OF THE INVENTION

The process of the present invention is an efficient method of resolving 1-aminoindanes into the R-isomer. The process is a simple method which gives high yields of the desired isomer.

In contrast the method in the literature gives a low yield. That resolution uses N-acetylleucine as the resolving agent and uses an aqueous solution. In 100 consecutive crystallizations of the salt obtained by combining equimolar quantities of DL-1-aminoindane and L-(-)-N-acetylleucine it was possible to obtain the R(-)-1-aminoindane L-(-)-N-acetylleucine from which R(-)-1-aminoindane and the R(+) hydrochloride were obtained. Low yield prompted attempts to recover and fractionally crystallize the salts present in the mother liquors of the resolution. Bull Chim e Farm 115:489-500 (1976).

In the present invention the resolving agent used is R-N-acetyl-3,4-dimethoxyphenylalanine which is disclosed in US 3,734,952 but not used as a resolving agent.

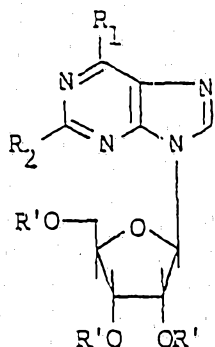
The process of the present invention may be used for producing intermediates in the synthesis of indanyl-adenosines which compounds are described in US 4,501,735 herein incorporated by reference.

The present process gives greatly improved yield, 83% yield of R(-)-1-aminoindane compared to very low yields in the process described above.

DETAILED DESCRIPTION

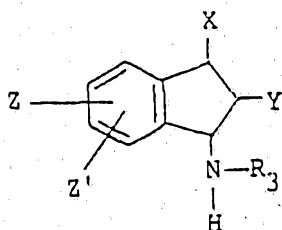
The present invention is a greatly improved process for the resolution of 1-aminoindanes into the R-isomer.

These are intermediates in the synthesis of indanyladenosines of the formula



I

wherein R_1 is of the formula



II

wherein X is hydrogen, lower alkyl or lower alkyl terminally substituted by hydroxy, lower alkoxy or carboxyl, or OR where R is hydrogen, lower alkyl, lower alkanoyl or benzoyl, phenyl or phenyl substituted by halogen, hydroxy, lower alkoxy or trifluoromethyl; Y is hydrogen, lower alkyl or lower alkyl substituted by hydroxy, lower alkoxy, OR where R is hydrogen, lower alkyl, lower alkanoyl or benzoyl; Z and Z' are independently hydrogen, halogen, nitro, trifluoromethyl, lower alkyl, hydroxy, or lower alkoxy; R_3 is hydrogen or lower alkyl; R' is hydrogen, acetyl or benzoyl, R_2 is hydrogen or halogen, and the diastereomers or mixtures thereof, or a pharmaceutically acceptable acid addition salt thereof.



In the compounds of Formula I and II, the term lower alkyl means a straight or branched alkyl group having from one to six carbon atoms such as, for example, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tertiarybutyl, amyl, isoamyl, neopentyl, hexyl, and the like.

Lower alkoxy is O-alkyl of from one to six carbon atoms as defined above for lower alkyl.

Preferable halogens are fluorine, chlorine, or bromine.

Compounds of Formula I are useful both in the free base form and in the form of acid addition salts.

Pharmaceutically acceptable salts are those derived from mineral acids such as hydrochloric acid and sulfuric acid, and organic acids such as methanesulfonic acid, benzenesulfonic acid, P-toluenesulfonic acid and the like.

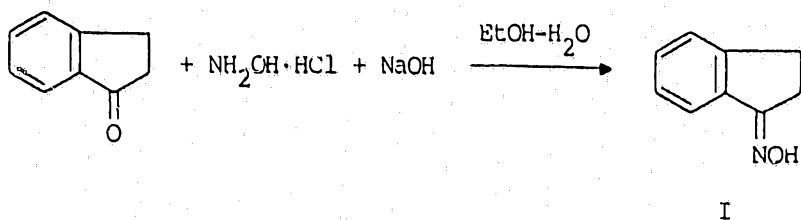
The compound of Formula I may contain more asymmetric carbon atoms at the N⁶ side chain.

Steps 3 and 4 of synthetic Scheme I are illustrative of the present invention.

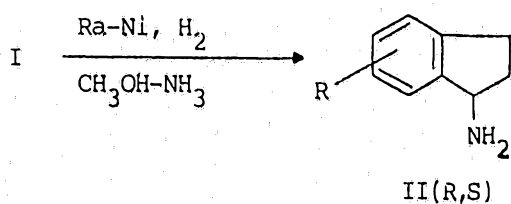
The essential feature of the present invention is the discovery that the resolving agent R-N-acetyl-3,4-dimethoxyphenylalanine obtained as a by product of the L-DOPA synthesis in US 3,734,952, improves the resolution which results in greater overall yields of the desired enantiomeric form of the final product.



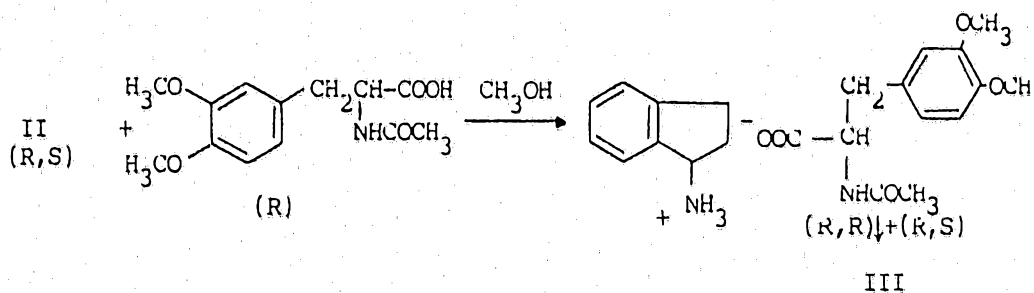
Step 1



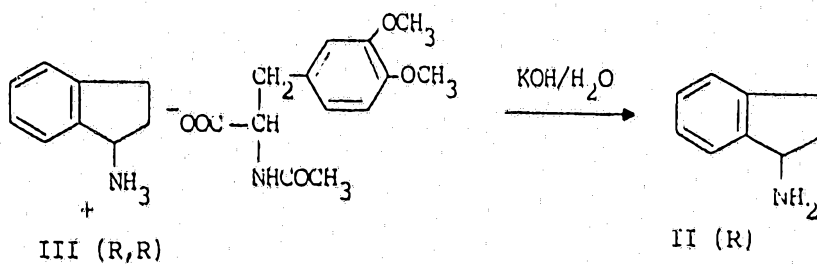
Step 2



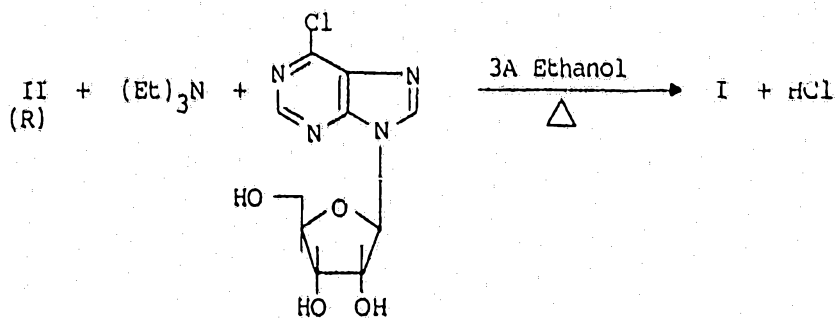
Step 3



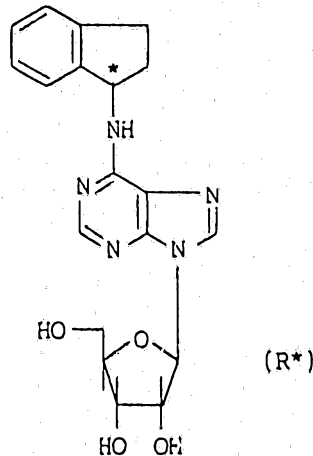
Step 4



Step 5



In Step 1 a 1-indanone is treated with a hydroxyl-
amine and a base to produce a 1-indanone oxime. In
Step 2 the oxime is hydrogenated to produce a correspond-
ing primary amine, both R and S forms. In Step 3 the
5 primary amine is then added to D-N-acetyl-3,4-dimethoxy-
phenylalanine in alcohol to produce the (R,R) and (R,S)
salts of the primary amine. The (R,S) salt crystallizes
first and the (R,R) salt is soluble. These are
separated by filtration. The mother liquor, on
10 concentrating and cooling precipitates the desired R,R
isomer in high yield and optical purity. In Step 4 a
solution of R,R isomer is treated with a base to produce
the R form of the primary amine. In Step 5 the R
primary amine is reacted with a tertiary amine and
15 6-chloropurineriboside to produce the adenosine
compounds of Formula I of the present invention, for
example, N⁶-[1-(R)-indanyl]adenosine.



A preferred embodiment of the present invention is
the use of methanol in Step 3 in producing the salts of
20 the primary amine by which the R,S and R,R diastereomers
are cleanly separated in high yield.

Another preferred embodiment is the use of the base
potassium hydroxide for treating the filtrate.

Still another preferred embodiment is the process
25 wherein the R form of Compound II in which X, Y, Z, and
Z' are hydrogen is produced.

A particular preferred embodiment is the process whereby the compound of Formula I is N⁶-[1-(R)-indanyl]-adenosine or a pharmaceutically acceptable salt thereof which is obtained by the process wherein the resolving agent is R-N-acetyl-3,4-dimethoxyphenylalanine.

The compounds of Formula 1 have been found to possess differing affinities at adenosine receptors. These compounds are active in animal tests which are predictive of neuroleptic activity for the treatment of major psychoses such as schizophrenia. These compounds also have sedative and hypnotic properties and, as such, are useful for the treatment of sleep disorders.

Additionally, these compounds are useful as anti-hypertensive agents for the treatment of high blood pressure. They also increase coronary blood flow and as such are useful in the treatment of angina and myocardial ischemia.

The following examples are illustrative of the invention but are not meant to limit the invention in any way.

EXAMPLE 1

Preparation of 1-Indanone Oxime

In a 12 l four-necked flask fitted with a mechanical stirrer, a reflux condenser and a thermometer was placed 3.6 l of deionized water. Hydroxylamine hydrochloride was added. A clear, colorless solution formed (pH 2.5) to which was added 475 ml of 50% sodium hydroxide which had been diluted to 2.4 l with deionized water (pH 6.2). 1-Indanone was dissolved in 2.4 l of 3A anhydrous ethanol and added to the flask. The slightly turbid solution was heated at reflux for 15 minutes. A white solid started to precipitate at 39°C. The mixture was cooled to room temperature and then in an ice-water bath. The product was filtered off and washed with three 2 l portions of chilled water. The product was

dried in a vacuum oven at 46°C. A white fluffy solid was obtained.

Weight = 522.4 g

Yield 98.6%

5 mp 142-144°C

HPLC (18170X142A): 99.5%

IR (KBr) N 1841.950, satisfactory

NMR (d₆ DMSO) X 284.A883, satisfactory

Microanalysis: Calcd. for C₉H₉NO: C, 73.45; H, 6.16;

10 N, 9.52

Found: C, 73.33; H, 6.21; N, 9.50

EXAMPLE 2

Preparation of 1-Aminoindane

The oxime (160 g, 1.087 mole) was dissolved in cold
15 1.6 l of methanol containing 16% of anhydrous ammonia.
Raney nickel catalyst (12 g) was added and the mixture
hydrogenated at a constant pressure of 50 psi. A nearly
theoretical amount of hydrogen had been absorbed after
24.5 hours. The temperature range during hydrogenation
20 was 15-40°C. The filtered methanol solution was
concentrated on the rotary evaporator (maximum bath
temperature, 40°C). The residue was distilled through a
short four inch column packed with Goodloe teflon
packing. The main fraction of 125 g was collected at
25 57°C (0.35 mm).

Yield 86.4%

GC (18096X135) 99.3%

HPLC (18170X146C) 99.6%

EXAMPLE 3

30 Resolution of (R,S) 1-Aminoindane into the (R,R) and (R,S) Salts of R-N-acetyl-3,4-dimethoxyphenylalanine

To a 5 l, three-necked flask fitted with a mechanical stirrer, a nitrogen blanket adapter, a reflux

condenser and a thermometer was added D-N-acetyl-3,4-dimethoxyphenylalanine and 2.5 l of methanol. The solution was heated to 60°C and a solution of (R,S)-1-aminoindane in 250 ml of methanol was added slowly to keep refluxing under control. A white solid precipitated which was the (R,S) salt. The (R,R) salt remained in solution. After stirring and cooling to room temperature, the mixture was stored in the cold room overnight. The solid was filtered off, washed with small portions of cold methanol and dried in a vacuum oven at 10 mm pressure for 24 hours. There was obtained 200 g (97.5%) of the R,S salt.

mp 212.5-214.5°C

$[\alpha]_D^{23} = -53.1^\circ$ (1.03% in CH₃OH)

15 Microanalysis: Calcd. for C₂₂H₂₈N₂O₅: C, 65.98; H, 7.05; N, 6.99

Found: C, 65.96; H, 7.01; N, 7.11

The filtrate from above was charcoaled, filtered, and reduced in volume to 1.8 l on a rotary evaporator. A small amount of precipitate was filtered off, weight = 1.54 g, mp 189-190°C.

The filtrate was stored in the refrigerator overnight. The white solid was filtered and washed with three 50 ml portions of cold methanol. The product was dried in a vacuum oven at 68°C to give 140 g of the R,R isomer.

Yield 68.2%

mp 194.5-195.8°C

$[\alpha]_D^{23} = -52.8^\circ$ (1.09% in methanol)

30 The filtrate from above was concentrated to approximately 900 ml and further stored in the refrigerator overnight to afford a second crop of the R,R isomer.

Weight = 29.9 g

Yield 14.6%

35 mp 191-193°C

$[\alpha]_D^{23} = -49.2^\circ$

Microanalysis: Satisfactory

Total yield of first and second crops = 82.8%.
Both first and second crops were combined for subsequent reactions.

EXAMPLE 4

5 Preparation of R-(-)-aminoindane

The R-1-aminoindane free base was isolated by dissolving 187 g of the R,R salt in 1.4 l of deionized water, and adding sufficient 50% KOH solution to reach a pH of 12.9. The mixture was extracted with three 1.4 l portions of diethyl ether. The combined extracts were dried over anhydrous $MgSO_4$ and the solvent removed as much as possible on a rotary evaporator (bath temperature 36°C). The vacuum on the flask was released with nitrogen to avoid the carbonate formation. A 0.5 ml portion of R-1-aminoindane obtained in this manner was converted to the hydrochloride salt for identification purpose.

mp 237-238°C

$[\alpha]_D^{23} = +3.5^\circ C$ (1% solution in methanol)

20 Microanalysis: Calcd. for $C_9H_{11}N.HCl$: C, 63.72;

H, 7.13; N, 8.26

Found, C, 63.83; H, 7.21; N, 8.25

The residual liquid was diluted with 200 ml of anhydrous 3A ethanol and kept under a nitrogen atmosphere.

EXAMPLE 5

Preparation of N^6 -[1-(R)-indanyl]adenosine

A 5 l, four-necked flask was fitted with a sealed mechanical stirrer, a thermometer, a reflux condenser, and a N_2 blanket adapter. To this flask was added 150 ml of 3A anhydrous ethanol, 126.8 g of 6-chloro-purineriboside, 65.4 ml of dry triethylamine and the alcoholic solution of R-1-aminoindane obtained above. The slightly green suspension was heated at reflux for

24 hours, cooled to room temperature, and then stored in the refrigerator overnight.

The product was collected by filtration, washed with three 100 ml portions of cold 3A alcohol, and dried in a vacuum oven at a maximum temperature of 88°C. There was obtained 121.8 g of a white crystalline solid. Yield 74.9%

mp 186.7-188.5°C (clear melt)

A mixture melting point with an authentic sample was underpressed.

HPLC (18643X2C) 99.7%

IR (KBr) N 1842 482, satisfactory

NMR (d_6 DMSO 11840772 and D_2O exchange), satisfactory

Rotation A-26628 $[\alpha]_D^{23} = +4.3^\circ$ (1.07% in DMF)

Water (K-F) None

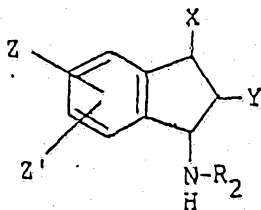
Microanalysis: Calcd. for $C_{19}H_{21}N_5O_4$: C, 59.52;

H, 5.52; N, 18.27

Found, C, 59.21; H, 5.56; N, 18.62

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A process for the preparation of the R isomer of a compound of the formula



wherein X is hydrogen, lower alkyl or lower alkyl terminally substituted by hydroxy, lower alkoxy or carboxyl, Y is hydrogen, lower alkyl or lower alkyl terminally substituted by hydroxy, lower alkoxy, OR where R is hydrogen, lower alkyl, lower alkanoyl, or benzoyl, Z and Z' are each independently hydrogen, halogen, nitro, trifluoromethyl, lower alkyl, hydroxy or lower alkoxy, R₂ is hydrogen or lower alkyl which comprises

(a) reacting R-N-acetyl-3,4-dimethoxyphenyl alanine in an alcohol with an (R,S) mixture of a compound of the above formula as defined above;

(b) removing the precipitated (R,S) salt;

(c) concentrating the filtrate containing the (R,R) salt, treating with base, separating and isolating according to known means the desired R isomer of the compound above.

2. The process of claim 1, wherein in step (a) the alcohol is a lower alkanol.

3. The process in claim 2, wherein in step (a) the alcohol is methanol.

4. The process in claim 1, wherein the R-isomer of the compound wherein X, Y, Z, and Z' are hydrogen is produced.



5. The process according to claim 4 wherein R_2 is hydrogen.

DATED this 4th day of OCTOBER, 1989

WARNER-LAMBERT COMPANY

Attorney: IAN T. ERNST

Fellow Institute of Patent Attorneys of Australia
of SHELSTON WATERS

