[Chem. Pharm. Bull. 26(4)1123—1129(1978)]

DC 547.568.1.02 : 541.63.04

Absolute Configurations of Four Isomers of 3-Formamido-4-hydroxy-α-[[N-(*p*-methoxy-α-methylphenethyl)amino]methyl]benzyl Alcohol, a Potent β-Adrenoreceptor Stimulant

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(Received September 3, 1977)

The two pairs of enantiomers (**1A** and **1B**) of 3-formamido-4-hydroxy-α-[[N-(*p*-methoxy-α-methylphenethyl)amino]methyl]benzyl alcohol (**1**) were resolved into four isomers ((−)-**1A**, (+)-**1A**, (−)-**1B** and (+)-**1B**). Two isomers ((−)-**1A** and (−)-**1B**) were also obtained from (−)-N-(*p*-methoxy-α-methylphenethyl)amine (**5**) and 4′-benzyloxy-3′-nitro-2-bromoacetophenone by several steps. The configurations of the enantiomers of **5** were determined by chemical correlation with those of N-(*p*-hydroxy-α-methylphenethyl)-amine, whose configuration is known. The configurations of the asymmetric carbon (α) carrying the OH group and the asymmetric carbon (β) located in the amine moiety of (+)-**1A** were respectively determined by correlation with (+)-4-methoxy-3-nitrobenzoic acid (**7**) and (+)-**5**, whose configurations are known, through (+)-3-amino-4-methoxy-α-[[N-(*p*-methoxy-α-methylphenethyl)amino]methyl]benzyl alcohol (**12**). On the basis of these experiments the configurations of the four isomers were shown as follows: (−)-**1A**=α*R*,β*R*, (+)-**1A**=α*S*,β*S*, (−)-**1B**=α*S*,β*R* and (+)-**1B**=α*R*,β*S*. Bronchodilator activity of these compounds was found to decrease in the order (−)-**1A**>(+)-**1B**>(+)-**1A**>(−)-**1B**.

Keywords——bronchodilator; β-adrenoreceptor stimulant; BD40A; benzyl alcohol; phenethylamine; optical resolution; configuration; diastereomer; isolated trachea of guinea-pig

We have previously reported the synthesis and biological properties of a series of β-adrenoreceptor stimulants with the general structure 3-acylamino-4-hydroxy-α-((N-substituted amino)methyl) benzyl alcohol.[2] Among the compounds synthesized was 3-formamido-4-hydroxy-α-[[N-(*p*-methoxy-α-methylphenethyl)amino]methyl]benzyl alcohol(**1**). Like many other members of the series, **1** has two asymmetric carbons in its molecule and is a mixture of two pairs of enantiomers 1A and 1B. These were separated by selective crystallization[2] and one of them (**1A**), whose fumarate was coded BD40A, was found to be highly promising as a potent and selective bronchodilator.[2,3]

We have now succeeded in separating **1A** and **1B** further into their respective optical isomers and determining the absolute configurations of these four isomers. Preliminary investigation of their biological activity has also been made.

1A, **1B** and N-(*p*-methoxy-α-methylphenethyl)amine (**5**)[4] were resolved using (+)- and (−)-form of tartaric acid as resolving agents into their optical isomers as shown in Table I. (+)-N-(*p*-Methoxy-α-methylphenethyl)amine (**5**) was acetylated by acetic anhydride to (−)-N-acetyl-(*p*-methoxy-α-methylphenethyl)amine (**4**), which was found to be identical with the compound obtained from (+)-N-(*p*-hydroxy-α-methylphenethyl)amine (**2**),[5] whose

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2) K. Murase, T. Mase, H. Ida, K. Takahashi, and M. Murakami, *Chem. Pharm. Bull.* (Tokyo), **25**, 1368 (1977).
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configuration (*S*) is known, by acetylation with acetic anhydride followed by methylation with methyl iodide.

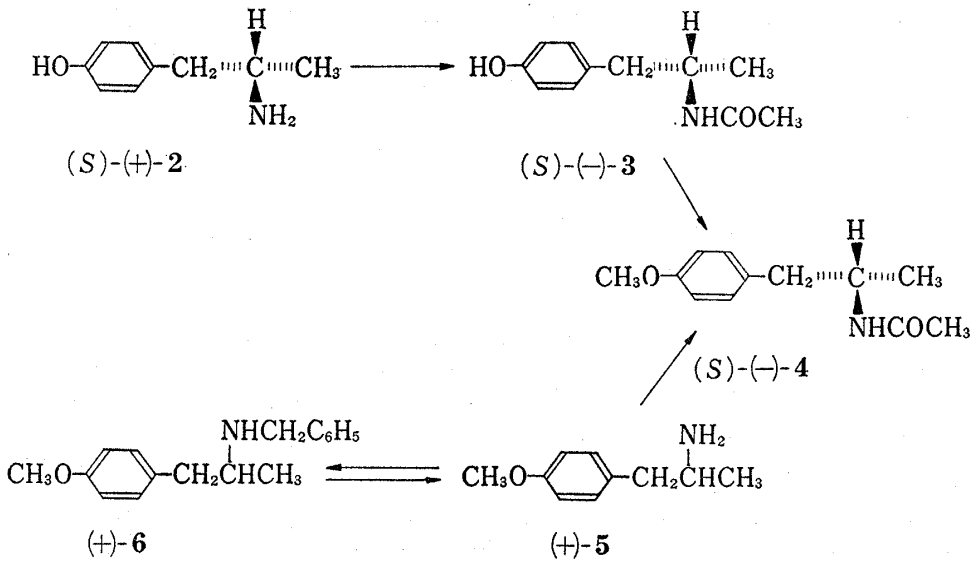

Chart 1

(*R*)-(−)-**6** was synthesized from (*R*)-(−)-**5** by reductive benzylation. A mixture of two isomers of 1 was obtained from 4′-benzyloxy-3′-nitro-2-bromoacetophenone and (*R*)-(−)-**6** in the same sequense used in the preparation of 1 and its analog. The mixture of diastereomers thus obtained was separated by selective crystallization into (−)-**1A** and (−)-**1B**, which were found to be identical with those obtained by resolution of **1A** and **1B**.

On the basis of these facts the β-asymmetric centers located in the amine moieties of (−)-**1A** and (−)-**1B** are determined to have the *R* configuration and those of their antipodes, (+)-**1A** and (+)-**1B**, have the *S* configuration.

The absolute configurations at α-asymmetric centers carrying the OH groups of these isomers were determined chemically by correlation with (+)-4-methoxy-3-nitromandelic acid,[6] of which the configuration (*S*) was known, through (+)-3-amino-4-methoxy-α-[[N-(p-methoxy-α-methylphenethyl)amino]methyl]benzyl alcohol (**12**). (*S*)-(+)-5-(4-methoxy-3-nitrophenyl)-1,3-dioxane-2,4-dione (**8**) was obtained by the reaction of (*S*)-(+)-4-methoxy-3-nitromandelic acid (**7**) and carbonyl chloride. The condensation of (*S*)-(+)-**8** and (*S*)-(+)-**5** gave (*S,S*)-(+)-4-methoxy-3-nitro-N-(p-methoxy-α-methylphenethyl)mandelamide (**10**) and its diastereoisomer which appeared to isomerize partially at α-asymmetric center. These isomers were separated into two spots, (*S,S*)-(+)-**10**: Rf=0.41 and its isomer: Rf=0.29, by thin-layer chromatography (TLC) (EtOAc–C_6H_6 2:3). Therefore (*S*)-(+)-**8** was transformed into the activated ester, N-succinimide ester (**9**), by the reaction of (*S*)-(+)-**8** and N-hydroxy succinimide in tetrahydrofurane (THF). The ester (**9**) was condensed with (*S*)-(+)-amine (**5**) without isolation giving (*S,S*)-(+)-**10**, which was free from its diastereomer. The nitro group of (*S,S*)-(+)-**10** was catalytically hydrogenated to the corresponding amine (*S,S*)-(+)-**11**, which was reduced by lithium aluminium hydride[7] in THF to give (*S,S*)-(+)-3-amino-4-methoxy-α-[[N-(p-methoxy-α-methylphenethyl)amino]methyl]benzyl alcohol (**12**) as a gum, $[\alpha]_D^{20}$ +30.2 (c=1, MeOH).

It was next necessary to convert (+)-1A into (+)-**12**. (+)-**1A** was treated with benzyl chloride to give (+)-3-formamido-4-hydroxy-α-[[N-benzyl-N-(p-methoxy-α-methylphenethyl)-amino]methyl]benzyl alcohol (**13**). (+)-**13** was methylated with methyliodide giving (+)-

6) P. Pratesi, A. La Manna, A. Campiglio, and V. Ghislandi, *J. Chem. Soc.*, **1958**, 2069.
7) In ref. 6, it is reported that optically active mandelamides were reduced to the corresponding amines without appreciable racemization.

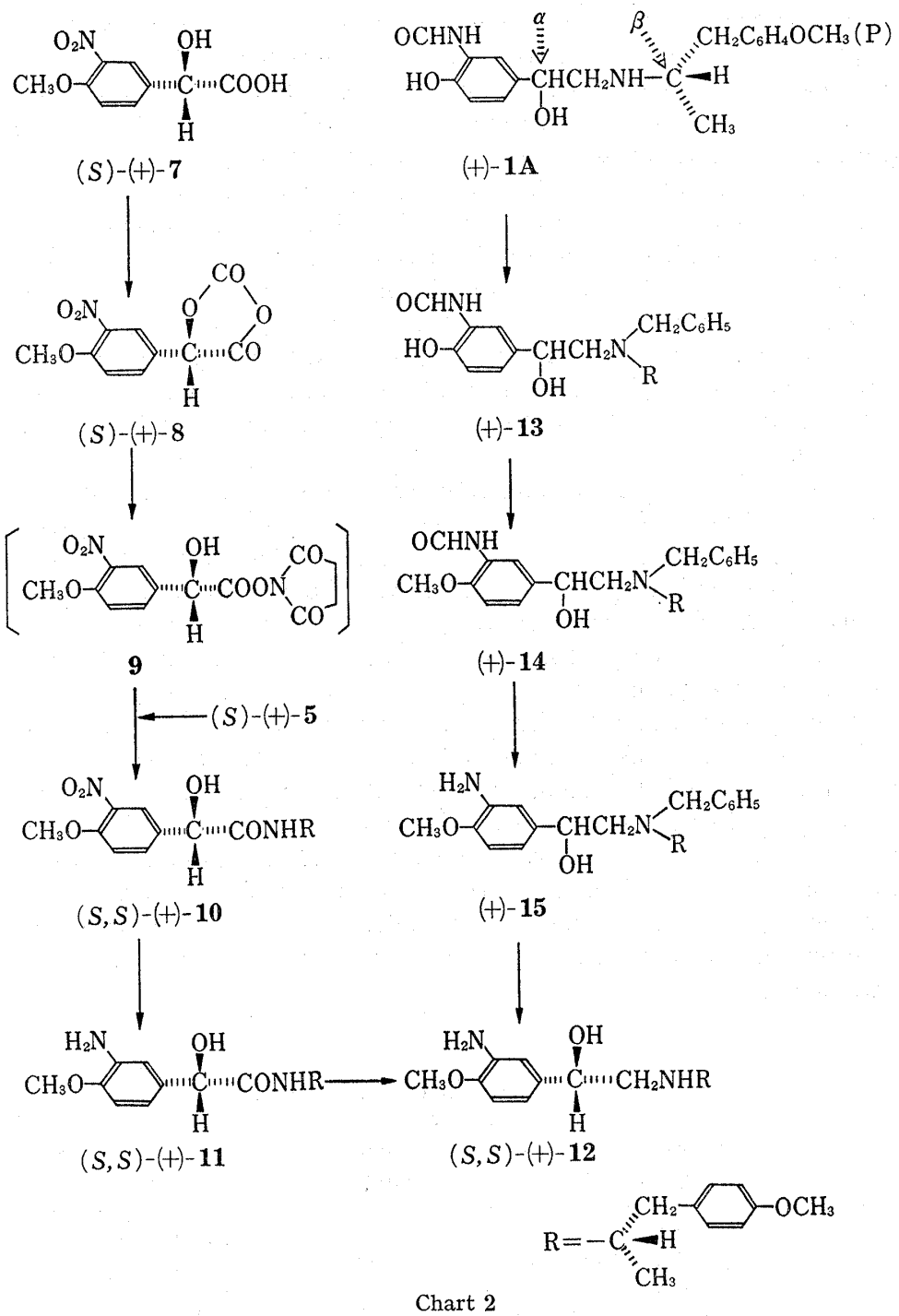

Chart 2

3-formamido-4-methoxy-α-[[N-benzyl-N-(*p*-methoxy-α-methylphenethyl)amino]methyl]benzyl alcohol (**14**). (+)-**14** was hydrolyzed in 1 N HCl aq. 80% methanol and then debenzylated by catalytic hydrogenation yielding (+)-**12** as a gum, $[\alpha]_D^{20}$ +29.4 (c=1, MeOH), identical with the sample [(*S*,*S*)-(+)-**12**] obtained above from (*S*)-(+)-**7** and (*S*)-(+)-**5**.

It was verified by gas-liquid chromatographic (GLC) analysis[8] that both samples ((+)-**12**) prepared by the different sequences of reactions were completely free from its diastereomer.

8) Before GLC analysis, the samples (1.5 mg) were dissolved in a mixture of trimethylsilylimidazole–EtOAc (1: 4) (0.05 ml) and then a mixture of heptafluorobutyryl imidazole–EtOAc (1: 9) (0.2 ml) was added to the above solution. Conditions: glass column, 80—100 mesh Diasolid ZS, 1.8 m×1.8 mm i.d.; temperature, column 200°, inject. 300°, detector FID 250°; carrier gas, He 34 ml/min. The retention times of (+)-**12** and its diastereomer were respectively 11.73 min and 12.75 min.

On the basis of these experiments the configuration of the four isomers were shown as follows: (+)-**1A**=$\alpha S,\beta S$, (−)-**1A**=$\alpha R,\beta R$, (+)-**1B**=$\alpha R,\beta S$, and (−)-**1B**=$\alpha S,\beta R$.

The bronchodilator activity of the isomers was compared using isolated tracheal preparations of guinea-pigs. The data are summarized in Table II. (−)-**1A** and (+)-**1B**, which have the *R* configuration at the α-carbon, were more potent than the corresponding isomers (−)-**1B** and (+)-**1A**, respectively, which have the S configuration. These data are in general agreement with those reported for sympathomimetic amines such as norepinephrine,[9] epinephrine,[6] isoproterenol[10] and salbutamol,[11] the activiry of which is known to reside almost exclusively in one of their isomers having the *R* configuration.[12] However, the difference in potency between the isomers of 1 was far smaller than might have been expected from that of the sympathomimetic amines cited above. (−)-**1A** with $\alpha R,\beta R$ configuration was only 14 times more potent than (−)-**1B** which has $\alpha S,\beta R$ configuration and the difference in potency between (+)-**1B** and (+)-**1A** which have the configuration $\alpha R,\beta S$ and $\alpha S,\beta S$, respectively, was only marginal.

Another interesting feature to be noted from Table II is the effect of configuration around the β-carbon on the potency of the isomers. The isomer (−)-**1A** with $\alpha R,\beta R$ configuration was about 3 times as potent as (+)-**1B** whose configuration is $\alpha R,\beta S$. On the other hand, the potency of (+)-**1A** with $\alpha S,\beta S$ configuration was about 3 times that of (−)-**1B** whose configuration is $\alpha S,\beta R$. These data show that the configuration at the β-carbon also influences the bronchodilator potency of compound **1**, although it is impossible to correlate a particular configuration with the increase in potency. In this connection, it is pertinent to quote the β-blocking activity reported for the four isomers of 2-(α-methyl-2-phenethylamino)-1-(2-naphthyl)ethanol, which, like compound 1, has two asymmetric carbons α and β, the former neighboring the naphthyl group and the latter carrying the amine moiety. The β-blocking activity of the isomers, as reported, decrease in the order $\alpha R,\beta R > \alpha R,\beta S \gg \alpha S,\beta R > \alpha S,\beta S$.[13] This shows that with this compound, the *R* configuration at the β-carbon, as well as at the α-carbon seems to be the preferred configuration for the potency. The relationship between the stereochemistry and the β-stimulant activity of the series of compounds including **1** seems more complicated and much remains to be elucidated before a general rule can be worked out.

Table I. Optical Rotations and Melting Points of Isomers of **1**

Compound	mp (°C)	$[\alpha]_D^{20}$ b)
(+)-**1A**	a	+29.3
(+)-**1A** (+)-tartrate	184	+40.4
(−)-**1A**	a	+30.1
(−)-**1A** (−)-tartrate	185	−42.6
(+)-**1B**	150	+8.9
(+)-**1B** (+)-tartrate	172	+12.2
(−)-**1B**	150	−9.0
(−)-**1B** (−)-tartrate	172	−12.3

a) An amorphous solid.
b) The rotations of the tartrates were measured as aqueous solutions and those of the bases as methanolic solution.

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11) D. Hartley and D. Middlemiss, *J. Med. Chem.*, **14**, 895 (1971).
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13) R. Howe and B.S. Rao, *J. Med. Chem.*, **11**, 1118 (1968).

Table II. Relative Potencies of the Isomers of I on Tracheobronchial Muscle

Compound	Configurations α	Configurations β	Relative bronchodilator potencies[a] dose ratios, Isoproterenol=1
Isoproterenol			1.0
Racemic **1A**[b]			0.1
(−)-**1A**[b]	*R*	*R*	0.08
(+)-**1A**[b]	*S*	*S*	0.31
Racemic **1B**[b]			0.91
(−)-**1B**[b]	*S*	*R*	1.1
(+)-**1B**[b]	*R*	*S*	0.2

a) Based on the effective dose required to give 50% relaxation of histamine-induced constriciton of isolated guinea-pig tracheal preparations.
b) The compound was used as its fumarate; the molar ratio of the compound to fumaric acid was 2:1.

Experimental

All melting points were uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded with JEOL MH-100 spectrometer (100 MHz) using $(CH_3)_4Si$ as internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet, dd=double doublet. Infrared (IR) spectra were run on a Hitachi Model 215 spectrometer. TLC plates, silica gel 60 F_{254} Merck, were used. For the column chromatography, silica gel [Wakogel C-200, 74—149 μ] was used. GLC analyses were obtained on a Hewlett packard GC-5830A. The organic solutions were dried over $MgSO_4$ and all evaporations were carried out under reduced pressure. Optical rotations were determined with Perkin-Elmer 241 polarimeter.

Resolution of Racemic N-(*p*-Methoxy-α-methylphenethyl)amine[4] (**5**)——Racemic-**5** (100 g) and (+)-tartaric acid (102 g), were dissolved in 70% aq. iso-PrOH (650 ml) and kept overnight at room temperature. The crystals which separated were collected by filtration and the filtrate was retained for further examination. The crystals (58 g), mp 140—143°, $[\alpha]_D^{20}$ +13.7° (*c*=1, MeOH), was recrystallized from 80% aq. iso-PrOH until the rotaion became constant. (−)-**5** (+)-tartrate was obtained. Yield 9 g, mp 153—154°, $[\alpha]_D^{20}$ +9.3° (*c*=1, MeOH). *Anal.* Calcd. for $C_{14}H_{21}NO_7$: C, 53.33; H, 6.71; N, 4.44. Found: C, 53.19; H, 6.52; N, 4.01. The free base was obtained by shaking a mixture of (−)-**5** (+)-tartrate (9 g) and 25% aq. NaOH (10 ml) with toluene. The toluene solution was dried and evaporated yielding (−)-**5**, $[\alpha]_D^{20}$ −29.5° (*c*=1, MeOH). The filtrate retained in the above experiment was concentrated. To the residue was added 20% aq. KOH (300 ml) and the mixture was extracted with toluene. The extract was dried and evaporated to give a crude product (63 g). The crude product (63 g) and (−)-tartaric acid (63 g) were dissolved in 85%aq. iso-PrOH (500 ml) at room temperature. After standing for 2 hr, the crystals which separated were collected by filtration. The crystals (50 g), mp 145—147°, $[\alpha]_D^{20}$ −12.7° (*c*=1, MeOH), were recrystallized from 80% aq. iso-PrOH until the rotation became constant. (+)-**5** (−)-tartrate was obtained. Yield 15.5 g, mp 153—154°, $[\alpha]_D^{20}$ −9.3° (*c*=1, MeOH). *Anal.* Calcd. for $C_{14}H_{21}NO_7$: C, 53.33; H, 6.71; N, 4.44. Found: C, 53.26; H, 6.61; N, 4.11. (+)-5, $[\alpha]_D^{20}$ +30.2° (*c*=1, MeOH), was obtained from its (−)-tartrate by the same procedure described above.

Resolution of Racemic 3-Formamido-4-hydroxy-α-[[N-(*p*-methoxy-α-methylphenethyl)amino]methyl]-benzyl Alcohol (1A)——**1A** (22.5 g), which was prepared as described previously,[2] and (+)-tartaric acid (11 g) were dissolved in 400 ml of hot 90% aq. iso-PrOH and kept at room temperature overnight. The crystals which separated were collected by filtration and the filtrate was retained for further examination. The crystals (11.6 g), mp 175°, $[\alpha]_D^{20}$ +22.0° (*c*=1, H_2O), were recrystallized from aq. 80% iso-PrOH until the rotation became constant. (+)-**1A** (+)-tartrate was obtained. Yield 1.6 g, mp 184°, $[\alpha]_D^{20}$ +40.4° (*c*=1, H_2O). *Anal.* Calcd. for $C_{23}H_{30}N_2O_{10}$; C, 55.87; H, 6.11; N, 5.67. Found: C, 55.62; H, 6.04; N, 5.23. The free base was obtained by shaking a mixture of (+)-**1A** (+)-tartrate and saturated aq. $NaHCO_3$ with EtOAc. The EtOAc solution was dried and evaporated giving (+)-**1A**, an amorphous solid, $[\alpha]_D^{20}$ +29.3° (*c*=1, MeOH). The filtrate retained in the above experiment was evaporated. To the residue was added saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc. The extract was dried and evaporated to give a crude product (10 g). A solution of the crude product (10 g) and (−)-tartaric acid (5 g) in 90% aq. iso-PrOH was kept at room temperature overnight. The crystals, 4.3 g, $[\alpha]_D^{20}$ −15.4° (*c*=1, H_2O), which separated were recrystallized from 80% aq. iso-PrOH until the rotation became constant. (−)-**1A** (−)-tartrate was obtained. Yield 1 g, mp 185°, $[\alpha]_D^{20}$ −42.6° (*c*=1, H_2O). *Anal.* Calcd. for $C_{23}H_{30}N_2O_{10}$: C, 55.87; H, 6.11; N, 5.67. Found: C, 55.78; H, 6.08; N, 5.30. (−)-**1A**, an amorphous solid, $[\alpha]_D^{20}$ −30.1° (*c*=1, MeOH), was obtained from its tartrate by the same procedure as (+)-**1A**.

Resolution of Racemic 3-Formamido-4-hydroxy-α-[[N-(*p*-methoxy-α-methylphenethyl)amino]methyl]-benzyl Alcohol (1B)——**1B** (1.6 g), which was prepared as described previously,[2] and (−)-tartaric acid (0.7 g) were dissolved in 80% aq. iso-PrOH (20 ml) and kept at room temperature overnight. The crystals

which separated were isolated by filtration and the filtrate was retained for further examination. The crystals (0.65 g), $[\alpha]_D^{20}$ −6.8° (c=1, H_2O), were recrystallized from 95% aq. EtOH until the rotation became constant giving (−)-**1B** (−)-tartrate (0.27 g), mp 170—172°; $[\alpha]_D^{20}$ −12.3° (c=1, H_2O). *Anal.* Calcd. for $C_{23}H_{30}N_2O_{10}$: C, 55.87; H, 6.11; N, 5.67. Found: C, 55.71; H, 6.03; N, 5.39. (−)-**1B**, mp 150°, $[\alpha]_D^{20}$ −9.0° (c=1, MeOH), was obtained from (−)-**1B** (−)-tartrate by the same procedure as (+)-**1A**. *Anal.* Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.45; H, 7.26; N, 8.20. The filtrate retained in the above experiment was evaporated. To the residue was added saturated aq. $NaHCO_3$ (20 ml) and the mixture was extracted with EtOAc. The extract was dried and evaporated to give a crude product (1.05 g), $[\alpha]_D^{20}$ +1.6° (c=1, MeOH). A solution of the crude product (0.95 g) and (+)-tartaric acid (0.45 g) in 95% aq. EtOH (10 ml) was kept at room temperature overnight. The crystals, $[\alpha]_D^{20}$ +11.2° (c=1, H_2O), which separated were recrystallized from 95% aq. EtOH until the rotation became constant and gave (+)-**1B** (+)-tartrate (0.28 g), mp 170—172°, $[\alpha]_D^{20}$ +12.2° (c=1, H_2O). *Anal.* Calcd. for $C_{23}H_{30}N_2O_{10}$: C, 55.87; H, 6.11; N, 5.67. Found: C, 55.90; H, 6.13; N, 5.29. (+)-**1B**, mp 150°, $[\alpha]_D^{20}$ −8.9° (c=1, MeOH) was obtained from its (+)-tartrate by the same procedure as (+)-**1A**.

(−)-N-Acetyl-N-(*p*-hydroxy-α-methylphenethyl)amine (3)——(+)-N-(*p*-Hydroxy-α-methylphenethyl)-amine (2) (0.5 g), $[\alpha]_D^{20}$ +33.0° (c=1, MeOH), which was obtained by the same procedure used by J. van Dijk *et al.*[5] was acetylated with Ac_2O (1 ml) in pyridine (2 ml). The mixture was evaporated. The residue was dissolved in a mixture of K_2CO_3 (1 g) and 90% aq. MeOH (10 ml), and stirred at room temperature for 1 hr. The reaction mixture was evaporated and the residue was extracted with EtOAc. The extract was washed with water, dried and evaporated to give crystals. The crystals were recrystallized from EtOAc. Yield 0.4 g, mp 152°, $[\alpha]_D^{20}$ −10.6° (c=2, EtOH). *Anal.* Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.21; H, 7.91; N, 7.12.

(−)-N-Acetyl-N-(*p*-methoxy-α-methylphenethyl)amine (4)——a) A mixture of (*S*)-(−)-3 (0.3 g), methyl iodide (0.3 g), K_2CO_3 (0.3 g) and methyl ethyl ketone (5 ml) was refluxed for 3 hr. After cooling, the mixture was evaporated and the residue was extracted with toluene. The extract was washed with 5% KOH (10 ml), then with water, dried and evaporated to give a solid. The solid was crystallized from *n*-hexane–C_6H_6 giving crystals of (−)-4 (0.17 g). mp 91°, $[\alpha]_D^{20}$ −14.9° (c=1, MeOH). *Anal.* Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.39; H, 8.30; N, 6.61.

b) (+)-**5** (1 g) was dissolved in pyridine (5 ml). To the solution was added Ac_2O (2 ml) and the mixture was stirred at room temperature for 1 hr. The mixture was evaporated and the residue was extracted with toluene. The extract was washed with 5% aq. HCl (10 ml), water successively, then dried and evaporated to give a solid. The solid was crystallized from *n*-hexane–C_6H_6 giving crystals (0.6 g) of (−)-4, mp 91°, $[\alpha]_D^{20}$ −15.3° (c=1, MeOH). The IR spectrum of this sample identical with that of the sample obtained above from (+)-**2**.

(+)-N-Benzyl-N-(*p*-methoxy-α-methylphenethyl)amine (6)——A solution of (+)-**5** (6 g) and benzaldehyde (4.3 g) in MeOH (30 ml) was hydrogenated in the presence of Pt-black (0.3 g) at room temperature under ordinary pressure until H_2-uptake had ceased. The catalyst was filtered off, and the filtrate was evaporated. To the residue was added 10% aq. HCl (20 ml). The crystals which separated were collected and washed with iso-PrOH giving (+)-**6** hydrochloride (8.5 g), mp 199°. The hydrochloride (8.5 g) was added to 10% methanolic KOH (15 ml) and the mixture was evaporated. The residue was extracted with toluene. The extract was washed with water, dried and evaporated giving (+)-**6** (6 g), as an oil $[\alpha]_D^{20}$ +36.3 (c=1, MeOH). NMR ($CDCl_3$) δ: 1.04 (3H, d, >CHC$\underline{H}_3$), 2.61 (2H, dd, -C$\underline{H}_2$-CH<), 2.82 (1H, m, >C$\underline{H}$NH-), 3.67, 3.84 (2H, AB-q, >NC$\underline{H}_2C_6H_5$), 3.72 (3H, s, -OCH_3), 6.79, 7.05 (4H, AB-q, -$C_6\underline{H}_4$OCH_3), 7.20 (5H, s, -C_6H_5). (−)-N-benzyl-N-(*p*-methoxy-α-methylphenethyl)amine (**6**), $[\alpha]_D^{20}$ −38.3 (c=1, MeOH), was obtained from (−)-**5** by the same procedure as (+) **6**.

Preparation of 3-Formamido-4-hydroxy-α-[[N-(*p*-methoxy-α-methylphenethyl)amino]methyl]benzyl Alcohol ((−)-1A and (−)-1B) from (*R*)-(−)-N-Benzyl-N-(*p*-methoxy-α-methylphenethyl)amine (6)——A mixture of diastereomers of I was obtained using (−)-N-benzyl-N-(*p*-methoxy-α-methylphenethyl)amine (**6**), of which the configuration (*R*) was known, in the same sequence as the preparation of I and its analog.[2] A mixture of diastereomers of I (2.1 g), an amorphous solid, $[\alpha]_D^{20}$ −17.9° (c=1, MeOH), and (+)-tartaric acid (0.92 g) were dissolved in 85% aq. iso-PrOH (10 ml) and kept at room temperature overnight. The crystals which separated as tartrate were isolated by filtration and the filtrate was retained for further examination. The crystals (1.6 g), mp 183—184°, $[\alpha]_D^{20}$ −19.2° (c=1, H_2O), were recrystallized from 85% aq. iso-PrOH until the rotation became constant and gave (−)-**1A** (+)-tartrate (0.3 g) melting at 192—194°. $[\alpha]_D^{20}$ −26.3° (c=1, H_2O). The base was obtained from the (+)-tartrate by the same procedure as (+)-**1A**. The base, an amorphous solid, $[\alpha]_D^{20}$ −29.2° (c=1, MeOH), was identical with (−)-**1A** described above in IR. The filtrate retained in the above experiment was evaporated. To the residue was added saturated aq. $NaHCO_3$ (10 ml) and the mixture was extracted with EtOAc. The extract was dried and evaporated to give a crude product (0.4) as an amorphous solid. A solution of this crude product (0.4 g) and (−)-tartaric acid (0.19 g) in 85% aq. iso-PrOH (5 ml) was kept at room temperature for 3 days. The crystals which separated were collected to give (−)-**1B** (−)-tartrate, mp 170—172°, $[\alpha]_D$ −12.2° (c=1, H_2O), which was identical with (−)-**1B** (−)-tartrate obtained above in IR and TLC (EtOAc–C_6H_6–MeOH-aq. NH_3=20: 10: 5: 1).

(+)-5-(4-Methoxy-3-nitrophenyl)-1,3-dioxane-2,4-dione (8)——(*S*)-(+)-4-Methoxy-3-nitromandelic acid (**7**) (3 g), which was obtained by resolution of racemic-**7**,[6] was dissolved in a mixture of carbonyl chloride (2.5 ml) and dry THF (20 ml) at 5—10°. The solution was kept at room temperature for 15 hr and then heated at 40—45° for 3 hr. The solvent was evaporated to give (+)-**8** as crystals, mp 134°, $[\alpha]_D^{20}$ +23.8° (c=1, THF). *Anal.* Calcd. for $C_{10}H_7NO_7$: C, 47.44; H, 2.79; N, 5.53. Found: C, 47.55; H, 2.77; N, 5.50.

(+)-4-Methoxy-3-nitro-N-(*p*-methoxy-α-methylphenethyl)mandelamide (10)——N-Hydroxy succinimide (1.4 g) was added to a solution of (+)-**8** (2.9 g) in dry THF (20 ml) and the mixture was stirred at room temperature for 2 hr. To the mixture, a solution of (+)-**5** (1.8 g) in dry THF (5 ml) was added gradually at 0—10°. After stirring at room temperature overnight, the mixture was evaporated and the residue was extracted with toluene. The extract was washed with 5% aq. HCl, 5% aq. $NaHCO_3$ successively, then dried and evaporated giving (+)-**10** (3.8 g), a gum, $[\alpha]_D^{20}$ +32.2° (c=1.43, EtOH). NMR ($CDCl_3$) δ: 1.05 (3H, d, >CHC$\underline{H}_3$), 2.64 (2H, d, >CH–C$\underline{H}_2$–), 3.71 (3H, s, –C_6H_4OC$\underline{H}_3$), 3.87 (3H, s, –$C_6H_3(NO_2)$OC$\underline{H}_3$), 4.06 (1H, m, >NC$\underline{H}$(CH_3)–), 6.65 (1H, d, >N$\underline{H}$), 6.65, 6.96 (4H, AB-q, –$C_6\underline{H}_4OCH_3$), 6.95 (1H, dd, 5-H), 7.46 (1H, dd, 6-H), 7.83 (1H, d, 2-H).

(+)-3-Amino-4-methoxy-N-(*p*-methoxy-α-methylphenethyl)mandelamide (11)——A solution of (+)-**10** (3.6 g) in EtOH (30 ml) was hydrogenated in the presence of Pt-black (0.2 g) at room temperature under ordinary pressure until the theoretical amount of H_2 had been absorbed. The catalyst was filtered off, and the filtrate was evaporated. The residue was chromatographed on silica gel using EtOAc–C_6H_6 (2: 3) as an eluent giving (+)-**11** (2.0 g), $[\alpha]_D^{20}$ +23.0° (c=1, EtOH). NMR ($CDCl_3$) δ: 1.04 (3H, d, >CHC$\underline{H}_3$), 2.61 (2H, >CH–C$\underline{H}_2$–), 3.74, 3.80 (each 3H, both s, 2×–OCH_3), 4.13 (1H, m, >N–C$\underline{H}$(CH_3)–), 4.74 (1H, s, >C$\underline{H}$OH), 6.36 (1H, d, >N$\underline{H}$), 6.6—7.3 (7H, m, aromatic protons).

(+)-3-Amino-4-methoxy-α-[[N-(*p*-methoxy-α-methylphenethyl)amino]methyl]benzyl Alcohol (12)——a) A solution of (+)-**11** (1.3 g) in THF (40 ml) was added gradually with stirring to a mixture of $LiAlH_4$ (0.8 g) and THF (30 ml), and the resulting mixture was refluxed for 5 hr with stirring. After cooling, to the mixture was added dropwise water (3 ml) with stirring. The mixture was filtered and the filtrate was evaporated. The residue was extracted with toluene. The extract was washed with water, dried and evaporated. The residue was chromatographed on silica gel using C_6H_6–EtOAc–MeOH–aq. NH_3 (80: 80: 10: 1) to give (+)-**12** (0.3 g). $[\alpha]_D^{20}$ +32.5° (c=1, EtOH). NMR ($CDCl_3$) δ: 1.03 (3H, d, >CHC$\underline{H}_3$), 2.5—3.0 (5H, m, –C$\underline{H}_2$–NHC$\underline{H}$–(CH_3)C$\underline{H}_2$–), 3.76, 3.80 (each 3H, both s, 2×–OCH_3), 4.48 (1H, t, >C$\underline{H}$OH), 6.7—7.3 (7H, m, aromatic protons). (+)-**12** showed a single peak at t_R 11.75 min by GLC.

b) A solution of (+)-**15** (0.56 g) in MeOH (30 ml) was hydrogenated in the presence of 10% Pd–C (0.2 g) at room temperature under ordinary pressure until H_2-uptake had ceased. The catalyst was filtered off and the filtrate was evaporated giving a gum, $[\alpha]_D^{20}$ +29.4° (c=1, EtOH). This sample was identical with the sample ((+)-**12**) obtained above in all respects [NMR, GLC, TLC: solvent=EtOAc–C_6H_6–MeOH–aq. NH_3 (20: 10: 5: 1)].

(+)-Formamido-4-hydroxy-α-[[N-benzyl-N-(*p*-methoxy-α-methylphenethyl)amino]methyl]benzyl Alcohol (13)——A mixture of (+)-**1A** (0.5 g), benzyl chloride (0.19 g), K_2CO_3 (0.2 g), NaI (0.1 g) and methyl ethyl ketone (10 ml) was refluxed overnight with stirring. After cooling the mixture was filtered and the filtrate was evaporated. The residue was chromatographed on silica gel using EtOAc–toluene (1: 5) to give (+)-**13** (0.45 g) as an amorphous solid. $[\alpha]_D^{20}$ +80.3° (c=1, EtOH). NMR ($CDCl_3$) δ: 1.02 (3H, d, >CHC$\underline{H}_3$), 2.4—2.8 (4H, m, –C$\underline{H}_2$–NCH(CH_3)C$\underline{H}_2$–), 3.13 (1H, m, >N–C$\underline{H}$(CH_3)–), 3.46, 3.85 (2H, AB-q, >NC$\underline{H}_2C_6H_5$), 3.72 (3H, s, –OCH_3) 4.44 (1H, t, >C$\underline{H}$OH), 6.7—7.4 (12H, m, aromatic, protons), 8.07 (1H, s, –CHO).

(+)-3-Formamido-4-methoxy-α-[[N-benzyl-N-(*p*-methoxy-α-methylphenethyl)amino]methyl]benzyl Alcohol (14)——A mixture of (+)-**13** (1.2 g), K_2CO_3 (0.76 g), CH_3I (0.59 g) and methyl ethyl ketone (10 ml) was refluxed for 3 hr with stirring. After cooling the mixture was evaporated and the residue was extracted with toluene. The extract was washed with 10% aq. K_2CO_3, dried and evaporated giving (+)-**14** (1.22 g), a gum. $[\alpha]_D^{20}$ +69.0° (c=1, EtOH). NMR ($CDCl_3$) δ: 0.96 (3H, d, >CHC$\underline{H}_3$), 2.4—2.7 (4H, m, –CH_2NCH(CH_3)C$\underline{H}_2$–), 3.08 (1H, m, >NC$\underline{H}$(CH_3)–), 3.45, 3.85 (2H, AB-q, >N–C$\underline{H}_2C_6H_5$), 3.72, 3.99 (each 3H, both s, 2×–OCH_3), 4.50 (1H, m, >C$\underline{H}$OH), 8.42 (1H, s, –CHO).

(+)-3-Amino-4-methoxy-α-[[N-benzyl-N-(*p*-methoxy-α-methylphenethyl)amino]methyl]benzyl Alcohol (15)——A solution of (+)-14 (1.2 g) in 1 N HCl aq. 80% MeOH (60 ml) was refluxed for 1 hr. After cooling, to the solution was added 2 N KOH (30 ml), and the mixture was evaporated. The residue was extracted with toluene. The extract was washed with water, dried and evaporated. The residue was chromatographed on silica gel using toluene–EtOAc (9: 1) as an eluent giving (+)-**15** (0.6 g), a gum. $[\alpha]_D^{20}$ +88.36 (c=0.84, EtOH). NMR ($CDCl_3$) δ: 0.98 (3H, d, >CHC$\underline{H}_3$), 2.5—2.7 (4H, m, –C$\underline{H}_2$–N–CH(CH_3)C$\underline{H}_2$–), 3.10 (1H, m, >C$\underline{H}$$CH_3$), 3.46, 3.89 (2H, AB-q, >NC$\underline{H}_2C_6H_5$), 3.76—3.80 (each 3H, both s, 2×–OCH_3), 4.46 (1H, t, >C$\underline{H}$–OH), 6.6—7.3 (12H, m, aromatic protons).

Acknowledgement The authors are indebted to Mr. M. Shimizu for GLC analysis and to the members of the Measurement Division in their Laboratories for NMR spectral measurement and for elemental analysis.