Pergamon

Bioorganic & Medicinal Chemistry 9 (2001) 1213–1219

BIOORGANIC & MEDICINAL CHEMISTRY

Enantioselective Synthesis and Absolute Configuration of (−)-1-(Benzofuran-2-yl)-2-propylaminopentane, ((−)-BPAP), a Highly Potent and Selective Catecholaminergic Activity Enhancer

Takahiro Oka,[a] Takuya Yasusa,[a] Takashi Ando,[a] Mayumi Watanabe,[a] Fumio Yoneda,[a,*] Toshimasa Ishida[b] and Joseph Knoll[c]

[a]*Research Institute, Fujimoto Pharmaceutical Corporation, 1-3-40, Nishiotsuka, Matsubara, Osaka 580-8503, Japan*
[b]*Osaka Universzity of Pharmaceutical Science, 4-20-1, Nasahara, Takatsuki, Osaka 569-1094, Japan*
[c]*Department of Pharmacology, Semmelweis University of Medicine, P.O.B. 370, Budapest H-1445, Hungary*

Received 1 November 2000; accepted 8 December 2000

Abstract—Enantioselective synthesis and absolute configuration of (−)-1-(benzofuran-2-yl)-2-propylaminopentane ((−)-BPAP), which is a highly potent and selective catecholaminergic activity enhancer (CAE) substance, are described. The synthetic approach consists of the coupling reaction of benzofuran with (*R*)-*N*-tosyl-2-propylazirizine or (*R*)-*N*-methoxy-*N*-methylnorvaliamide, followed by appropriate modifications of the resulting coupling products. As the results, (−)-BPAP turned out to have the *R* configuration, which was finally confirmed by X-ray crystallographic analysis.

Introduction

The performance of catecholaminergic neurons in the brain has been proposed to be controlled according to the physiological need via a catecholaminergic activity enhancer (CAE) mechanism.[1] This novel CAE mechanism can reasonably elucidate the effects of the brain endogenous amines such as phenylethylamine (PEA) and tryptamine which significantly enhance the impulse mediated propagation release of catecholamines from the catecholaminergic neurons.[2] A PEA derivative, (−)-deprenyl (selegiline), known as a selective inhibitor of B-type monoamine oxidase (MAO-B),[3] is for the time being the only CAE substance in clinical use.[4] The unique effects of (−)-deprenyl such as the prolongation of the life of rats,[5] the neuroprotective effect,[6] the slowing of the functional decline of otherwise untreated subjects with early Parkinson's disease,[7] and the slowing of the progression of Alzheimer's disease,[8] were attributed to the CAE effect of this drug.[9]

To furnish a direct evidence that the CAE activity with a small dose of (−)-deprenyl is unrelated to MAO-B inhibition, (−)-1-phenyl-2-propylaminopentane ((−)-PPAP) devoid of MAO-B inhibition was synthesized. Actually (−)-PPAP showed the CAE activity by enhancing the impulse mediated propagation release of cathecholamines rather more potent than (−)-deprenyl. Aiming to develop a selective substance much more potent than (−)-deprenyl or (−)-PPAP, we have designed and synthesized a series of new 1-aryl-2-propylaminopentanes by changing the benzene ring of PPAP, and we have found that 1-(benzofuran-2-yl)-2-propylaminopentane (BPAP) was a highly potent and selective CAE substance devoid of the MAO-B inhibitory effect (Chart 1).[10a]

BPAP was originally synthesized as follows by starting from 1-(benzofuran-2-yl)-2-nitropentene (**2**) prepared by the condensation of benzofuran-2-carbaldehyde and 1-nitrobutane. Reduction of **2** with lithium aluminum hydride gave the corresponding 2-aminopentane (**3**), which was treated with propionyl chloride to afford the *N*-{2-[1-(benzofuran-2-yl)pentyl]}propionamide (**4**). The propionamide **4** was reduced with aluminum hydride to give BPAP (**1**) (Scheme 1).[10b]

As BPAP (**1**), however, contains an asymmetric carbon atom, the optical resolution into the corresponding (−)-

*Corresponding author. Tel.: +81-723-32-5151; fax: +81-723-32-8482; e-mail: soyaku@fujimoto-pharm.co.jp

0968-0896/01/$ - see front matter
PII: S0968-0896(00)00341-2

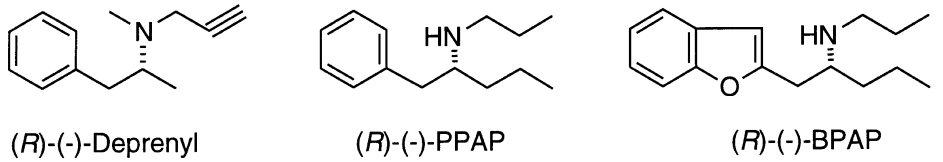
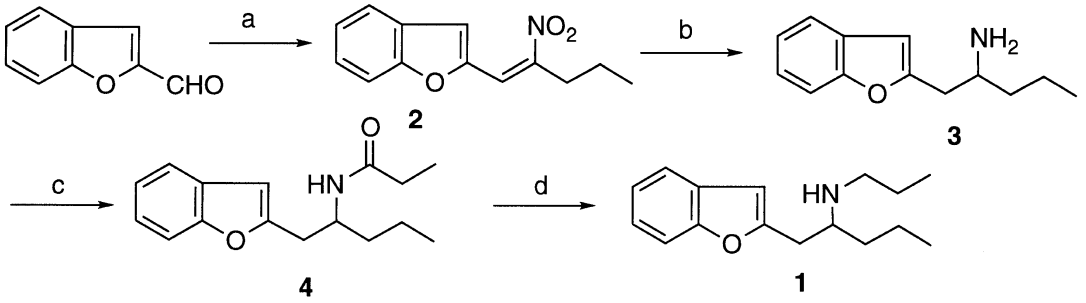
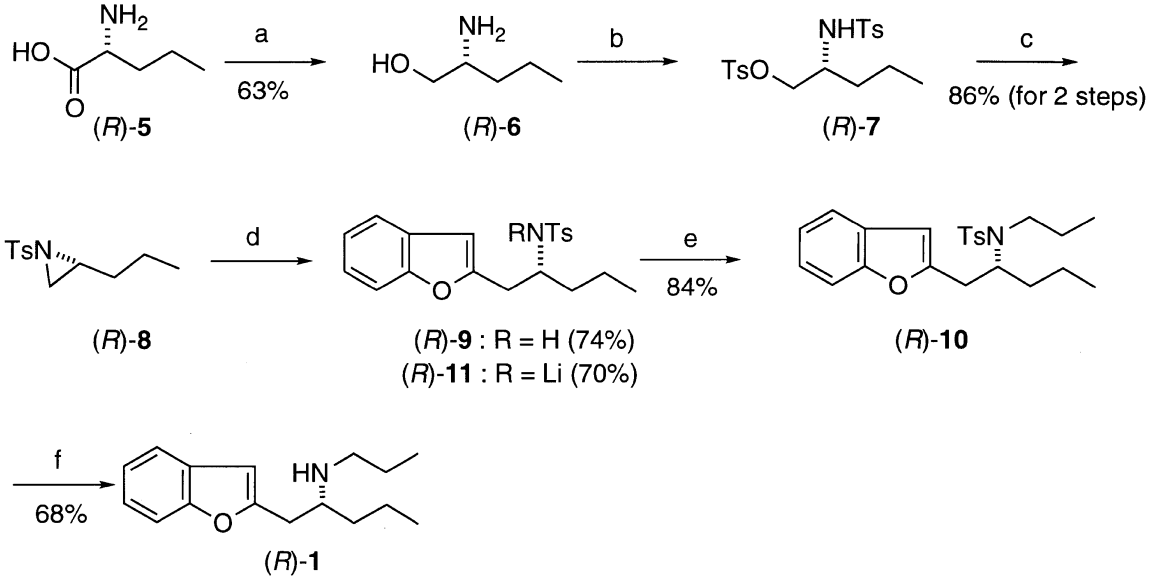


Chart 1.



Scheme 1. Reagents and conditions: (a) n-$BuNO_2$, $AcONH_4$, AcOH, 100 °C; (b) $LiAlH_4$, THF, rt; (c) EtCOCl, CH_2Cl_2, rt; (d) AlH_3, Et_2O, rt.



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, reflux; (b) TsCl, Py, 0 °C; (c) Et_2O, aq NaOH, 0 °C; (d) (1) n-BuLi, THF, benzofuran, 0 °C, (2) **8**; (e) NaH (via (*R*)-**9**), PrBr, DMF, 70 °C; (f) Sodium naphthalide, DME, −78 °C.

and (+)-enantiomer, ((−)-BPAP and (+)-BPAP), was carried out by HPLC on a chiral stationary phase. The (−)-BPAP thus obtained turned out to be about 50 times or more potent than (+)-BPAP, (−)-deprenyl or (−)-PPAP as a CAE substance.[10a] We report here a novel enantioselective synthesis of (−)-BPAP which is based on readily available norvaline as starting material and determination of the absolute configuration of (−)-BPAP.

Synthesis

Since the structure of BPAP (**1**) contains a 2-aminopentane unit, we considered the use of norvaline as a chiral building block in the synthesis of the respective (*R*)- and (*S*)-enantiomers. Thus, we have developed two synthetic approaches consisting of the coupling reaction of benzofuran with *N*-tosyl-2-propylaziridine (**8**) (Method A) and *N*-benzyloxycarbonylamino-*N*-methoxy-*N*-methyl norvalinamide (**13**) (Method B), followed by appropriate modifications of the resulting coupling products, as outlined in Schemes 2 and 3. Racemic **1** was obtained in the same way starting from *dl*-norvaline.

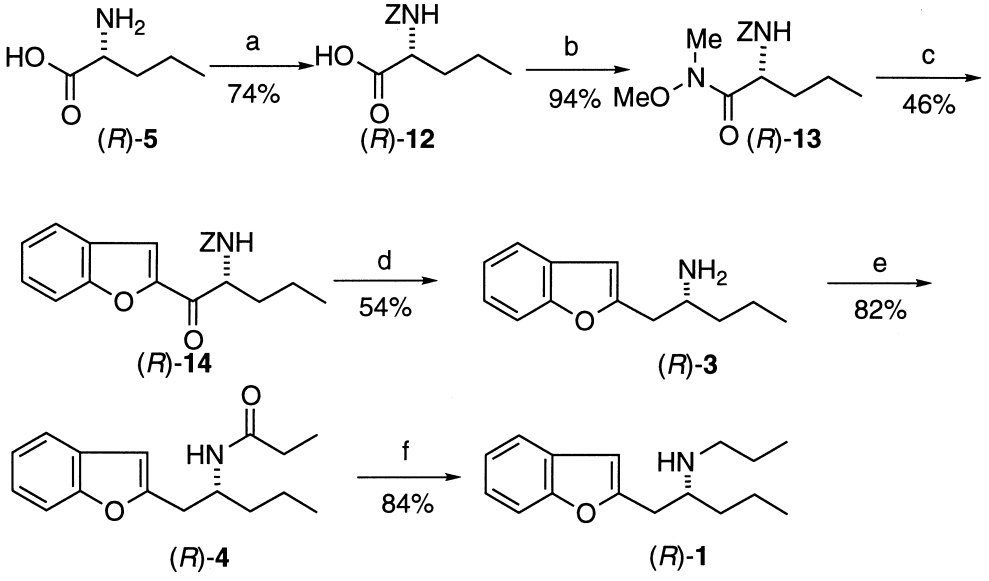
Method A. Condensed furans such as benzofuran can be lithiated at the α-position more readily than that at any other possible positions and treated with electrophiles to afford the corresponding α-substituted derivatives.[11] Thus, the coupling of lithiated benzofuran with *N*-tosyl-2-propylaziridine (**8**), prepared from norvaline (**5**) by the known methodology,[12] gave the desired 1-(benzofuran-2-yl)-2-(*p*-toluenesulfonyl)aminopentane (**9**). Treatment of the amide **9** with bromopropane in the presence of

NaH, followed by removement of *N*-tosyl group afforded **1**, which was converted into the corresponding hydrochloride. Furthermore, lithium salt of **9** (**11**) obtained directly in the coupling reaction also gave **1** by the treatment with bromopropane without NaH.

Method B. α-Lithiobenzofuran was treated with *N*-amino-*N*-methoxy-*N*-methylnorvalinamide (**13**), prepared by *N*-methoxy-*N*-methylamidation from norvaline (**5**),[13] gave the desired 1-(benzofuran-2-yl)-2-benzyloxycarbonylamino-1-pentanone (**14**). Treatment of the pentanone **14** with Et_3SiH in CF_3COOH[14] afforded 1-(benzofuran-2-yl)-2-aminopentane (**3**), which was treated with propionyl choloride to afford the desired *N*-{[2-(1-(benzofuran-2-yl))pentyl]}propionamide (**4**). The propionamide **4** thus obtained was reduced with lithium aluminum hydride ($LiAlH_4$) to give **1**, which was converted into the corresponding hydrochloride.

Determination of the absolute configuration

The syntheses of both enantiomers of BPAP (**1**) according to Schemes 2 and 3 were ascertained to preserve the chirality of the starting materials. Namely, the specific rotation of (*R*)-**1**·HCl was $[\alpha]_D^{20}$ −4.23° (*c* 4.40, methanol) and that of (*S*)-**1**·HCl was $[\alpha]_D^{20}$ +5.11° (*c* 0.440, methanol), which were identical with those of each enantiomers resoluted from racemic **1** by HPLC on a chiral stationary phase.[15] Accordingly, (−)-**1** was determined to have the *R* configuration. Finally, the structure of crystal of (−)-**1**·HCl obtained by recrystallization from ethanol and diethyl ether have



Scheme 3. Reagents and conditions: (a) ZCl, aq NaOH, aq Na_2CO_3, 0 °C→rt; (b) WSCDI, HOBt, CH_2Cl_2, MeONHMe·HCl, −10 °C→rt; (c) (1) *n*-BuLi, THF, benzofuram, −30–−25 °C; (2) **13**, (d) CF_3COOH, 50–55 °C; (e) EtCOCl, CH_2Cl_2, rt; (f) LAH, Et_2O, 0 °C→rt.

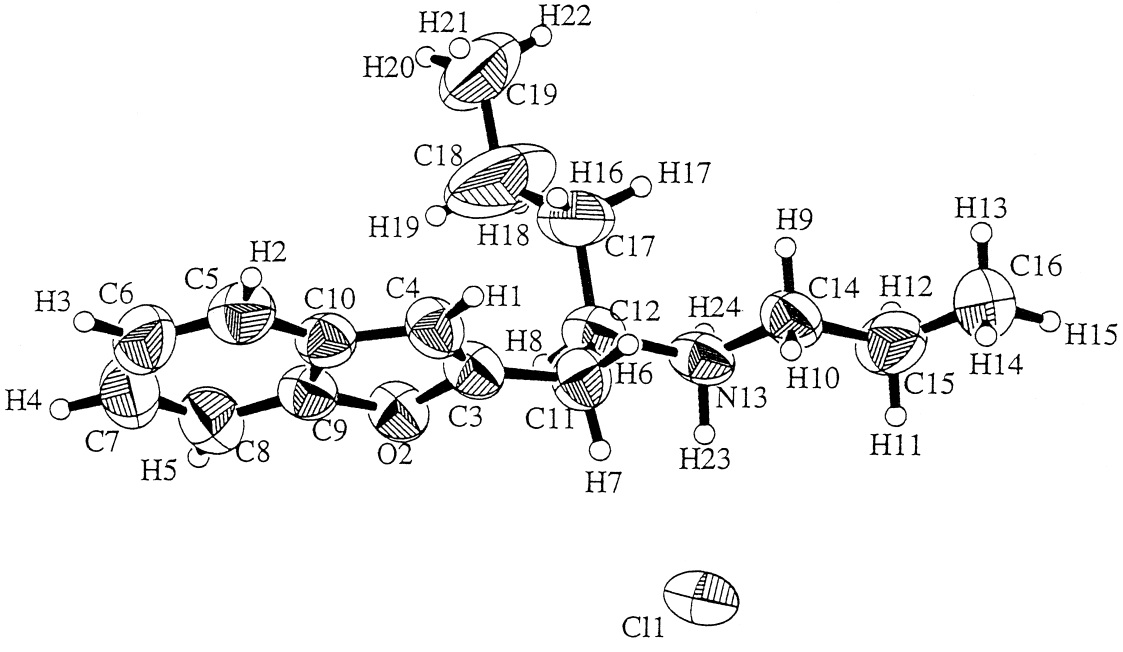


Figure 1. ORTEP drawing of (*R*)-(−)-**1**·HCl.

Table 1. Crystallographic data

Formula	$C_{16}H_{23}N_1O_1 \cdot HCl$
Mr	281.83
Crystal system	Monoclinic
Space group	$P2_1$
Cell constant	
a (Å)	10.411(1)
b (Å)	7.533(1)
c (Å)	11.029(2)
α (°)	90.00
β (°)	105.98(1)
γ (°)	90.00
Volume (Å^3)	831.6(1)
Z	2
D (calc), g cm^{-3}	1.125
μ (Cu Kα) (mm^{-1})	1.97
F (000)	304
Crystal size (mm)	0.5×0.2×1.0
Data collection method	ω-2θ scan
Scan spped in ω, ° min^{-1}	12
Scan range in ω, °	1.600 + 0.3tanθ
Data range measured	$0 \le h \le 12$, $-9 \le k \le 0$, $-13 \le l \le 13$
θ_{max},°	67.61
No. of independent reflections	1608
No. of observed reflections	1478
Criterion for observed reflections	$I > 2\sigma(I)$
No. of parameters	172
Goodness of fit	1.308
R; R_w	0.041; 0.145

been revealed by X-ray crystallography. The ORTEP drawing is illustrated in Figure 1, and the crystallographic data are summarized in Table 1. From the X-ray crystallographic analysis of (−)-**1**•HCl, by means of anomalous dispersion effect of the chlorine atom, it has been confirmed that (−)-**1** has the *R* configuration.

Conclusion

Two efficient enantioselective routes toward (−)-BPAP ((−)-**1**) have been developed starting from commercially available (*R*)-norvaline. Thus, the productibity of (−)-BPAP was much improved by use of these routes in comparison with the previous synthetic route[10b] by the optical resolution of racemic **1**. The absolute configuration of (−)-BPAP has been determined to be *R* by the enantioselective synthesis and X-ray crystallographic analysis. It is interesting to note that the known CAE substances such as (−)-deprenyl, (−)-PPAP, and (−)-BPAP have all the *R* configurations. This fact suggests that the CAE substances would interact with a specific bioactive point of catecholaminergic neurons in the brain. Utilization of these routes for mass production and development of methods using further asymmetric induction are currentry underway in our laboratory.

Experimental

Instruments. Melting points (mp) were obtained on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260–50 spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL GX-270 (270 MHz) spectrometer with tetramethylsilane as internal reference and all shifts are indicated in ppm. Electron impact (EI) mass spectra and high resolution mass (HRMS) spectra were recorded on a Hitachi M-80B mass spectrometer. Elemental analyses were performed using a Yanagimoto MT-3 elemental analyzer. Optical rotations were measured on a Horiba SEPA-200 digital polarimeter. Column chromatography was performed on silica gel (Fuji Silysia Chemical, particle size 0.053–0.150 mm).

Materials. Organic reagents and solvents were purchased from Tokyo Kasei Kogyo Co. Ltd., Nakarai Tesque, Inc., Wako Pure Chemical Industries, Ltd., and Aldrich Chemical Co., and used as received.

All of the respective (*R*), (*S*), and *dl* products were sythesized, but only preparation of (*R*) products are described below.

(*R*)-2-Amino-1-pentanol (*R*)-6. D-Norvaline (*R*)-**5** (15.0 g, 128 mmol) was added in portions into a suspension of lithium aluminum hydride (7.3 g, 192 mmol) in tetrahydrofuran (230 mL) under stirring at 0 °C, and the mixture was refluxed for 2 h. After being cooled, water was added to the mixture until finishing the evolution of hydrogen. The insoluble matter was filtrated off and washed with ethyl acetate (150 mL×4). The combined filtrate was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The oily residue was distilled (115 °C/ 34 mmHg) to give (*R*)-**6**. (8.3 g, 63%) as colorless needles: (lit.[16] (*S*): mp 45–47 °C) $[\alpha]_D^{20}$ −4.1° (*c* 1.4, methanol); ^{1}H NMR($CDCl_3$) 0.93 (t, *J* = 6.7 Hz, 3H), 1.12–1.54 (m, 4H), 1.90–2.40 (br, 3H), 2.76–2.90 (m, 1H), 3.26 (dd, *J* = 10.8, 8.1 Hz, 1H), 3.58 (dd, *J* = 10.8, 4.0 Hz, 1H); IR (KBr) 3320, 2940, 1460 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_5H_{13}NO$ (M^+), 103.0997; found 103.0948.

(*R*)-2-Amino-1-pentanol-bis-*p*-tolenesulfonate (*R*)-7. To a solution of (*R*)-**6** (8.2 g, 79 mmol) in pyridine (50 mL) was added *p*-toluenesulfonyl chloride (36.4 g, 191 mmol) at 0 °C under stirring, and the mixture was stirred at 0 °C for 2.5 h. Diethyl ether (250 mL) was added to the reaction mixture, and the organic phase was washed with 4 M HCl aq solution (70 mL×3), and then water (50 mL). The organic layer was used for the next reaction without purification.

Colorless needles; mp 58–60 °C (from chloroform); $[\alpha]_D^{20}$ +51° (*c* 1.0, methanol), ^{1}H NMR ($CDCl_3$) 0.72 (t, *J* = 7.1 Hz, 3H), 0.90–1.50 (m, 4H), 2.42 (s, 3H),2.46 (s, 3H), 3.30–3.40 (m, 1H), 3.82 (dd, *J* = 10.1, 4.4 Hz, 1H), 3.95 (dd, *J* = 10.1, 3.3 Hz, 1H), 4.79 (d, *J* = 8.4 Hz, 1H), 7.25–7.37 (m, 4H), 7.71 (t, *J* = 8.1 Hz, 4H); IR (KBr) 3275, 2880, 1595, 1365, 1310, 1180, 1160 cm^{-1}; MS 410 (M^+–1), 365, 329, 299, 255, 225, 183. Anal. calcd for $C_{19}H_{25}NO_5S_2$: C, 55.45; H, 6.12; N 3.40%. Found: C, 55.23; H, 6.10; N 3.12%.

(*R*)-*N*-(*p*-Toluenesulfonyl)-2-propylaziridine (*R*)-8. To the above ether solution of (*R*)-**7** (250 mL) was added 2.5 M NaOH aq solution (250 mL) dropwise at 0 °C,

and the mixture was stirred at 0 °C for 1.5 h. The reaction mixture was allowed to stand to separate the organic phase. The organic phase was washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate = 6:1) to give (*R*)-**8** (16.4 g, 86%) as colorless oil: $[\alpha]_D^{20}$ −15° (*c* 1.3, chloroform) (lit.[17] (*S*): $[\alpha]_D^{20}$ +12°(*c* 0.97, $CHCl_3$)); ^1H NMR ($CDCl_3$) 0.87 (t, *J* = 7.1 Hz, 3H),1.23–1.61 (m, 4H), 2.06 (d, *J* = 4.7 Hz, 1H), 2.45 (s, 3H), 2.63 (d, *J* = 7.1 Hz, 1H), 2.67–2.83 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H); IR (neat) 2960, 1592, 1459, 1323 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{12}H_{17}NSO_2$ (M^+), 239.0980; found 239.1027.

(*R*)-1-(Benzofuran-2-yl)-2-(*p*-toluenesulfonyl)aminopentane (*R*)-9. To a solution of benzofuran (2.68 g, 22.8 mmol) in diethyl ether (20 mL) was added *n*-butyllithium (1.54 M in hexane, 14.8 mL, 22.8 mmol) at 0 °C under argon atomosphere, and the mixture was refluxed for 30 min. (*R*)-**8** (1.82 g, 7.60 mmol) in diethyl ether (15 mL) was added herein at 0 °C and the mixture was stirred at room temperature for 2 h. After adding water (30 mL) at 0 °C, the organic phase was separated, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate = 5:1) to give (*R*)-**9** (2.01 g, 74%) as colorless needles: mp 83–84 °C(from *n*-hexane); $[\alpha]_D^{20}$ −38° (*c* 1.0, methanol), ^1H NMR ($CDCl_3$) 0.83 (t, *J* = 7.1 Hz, 3H), 1.26–1.65 (m, 4H), 2.33 (s, 3H), 2.77 (dd, *J* = 15.1, 6.1 Hz, 1H), 2.84 (dd, *J* = 15.1, 5.4 Hz, 1H), 3.55–3.70 (m, 1H), 4.55 (d, *J* = 8.4 Hz, 1H), 6.33 (s, 1H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.14–7.30 (m, 2H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.44 (dd, *J* = 6.4, 2.0 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 2H); IR (KBr) 3290, 2925, 1602, 1453, 1409, 1323 cm^{-1}; MS 357(M^+), 226, 186, 155. Anal. calcd for $C_{20}H_{23}NO_3S$:C, 67.20; H, 6.49; N 3.92%. Found: C, 67.45; H, 6.55; N, 3.59%.

(*R*)-1-(2-Benzofuran-2-yl)-2-*N*-propyl-*p*-toluenesulfonylaminopentane (*R*)-10. To a solution of (*R*)-**9** (9.60 g, 26.9 mmol) in dimethylformamide (100 mL) was added NaH (1.61 g, 40.3 mmol) under stirring at 0 °C. Bromopropane (3.7 mL, 40.3 mmol) was added to the mixture and then stirred at 70 °C for 1 h. The reaction mixture was poured over ice water (200 mL) and stirred at room temperature for 15 min. The precipitate was collected by filtration, and washed with water (50 mL) to give (*R*)-**10**. The filtrate was extracted with diethyl ether (150 mL), and the etheral solution was separated, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate = 9:1) to give (*R*)-**10**, which was combined with the previous (*R*)-**10** to give the sum (*R*)-**10** (8.97 g, 84%) as colorless needles; mp 92.5–93.5 °C (from *n*-hexane); $[\alpha]_D^{20}$ −104° (*c* 1.11, methanol); ^1H NMR ($CDCl_3$) 0.83 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H), 1.15–1.86 (m, 6H), 2.31 (s, 3H), 2.72–2.88 (m, 1H), 2.98–3.16 (m, 1H), 4.14–4.27 (m, 1H), 6.35 (s, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.13–7.30 (m, 2H), 7.39 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.44 (dd, *J* = 6.7, 2.0 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 2H); IR (KBr) 2950, 1593, 1450, 1325 cm^{-1}; MS 399(M^+), 269, 226, 155, 130. Anal. calcd for $C_{23}H_{29}NO_3S$: C, 69.14; H, 7.32; N 3.51%. Found: C, 69.02; H, 7.25; N 3.15%.

(*R*)-1-(Benzofuran-2-yl)-2-propylaminopentane (*R*)-1 hydrochloride. To a solution of naphthalene (17.8 g, 139 mmol) in ethylene glycol dimethylether (90 mL) was added sodium (3.26 g, 139 mmol) at room temperature under argon atomosphere, and the mixture was sonicated for 2 h. The solution was added dropwise into a solution of (*R*)-**10** (13.9 g, 34.8 mmol) in ethylene glycol dimethylether (70 mL) at −78 °C, and was stirred at −78 °C for 30 min. To the solution was added water until the color of the solution changes to orange. To the solution was added diethyl ether (300 mL) and the organic phase was separated. The organic phase was extacted with 2 M HCl aq solution (120 mL×5). After washing the aq layer with diethyl ether (100 mL), the layer was made basic to litmus with 28% aqueous NH_3. The aqueous mixture was extracted with diethyl ether (400 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo to give (*R*)-**1** (5.84 g, 68%), which was treated with HCl in diethyl ether to give (*R*)-**1** hydrochloride (5.97 g, 61%) as colorless needles: mp 167–168 °C (from ethanol-diethyl ether); $[\alpha]_D^{20}$ −4.23° (*c* 4.40, methanol); ^1H NMR ($CDCl_3$) 0.91 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H), 1.35–1.72 (m, 2H), 1.72–2.15 (m, 4H), 2.75–3.05 (m, 2H), 3.20–3.35 (m, 1H), 3.45–3.64 (m, 2H), 6.65 (s, 1H), 7.10–7.38 (m, 2H), 7.38–7.65 (m, 2H), 9.62 (br, 2H), IR(KBr) 2960, 2750, 2510, 2430, 1608, 1595, 1457 cm^{-1}; MS 245(M^+). Anal. calcd for $C_{16}H_{23}NO{\cdot}HCl$:C, 68.19; H, 8.58; N:4.97%. Found: C:68.36; H, 8.42; N: 5.06%.

Lithium (*R*)-1-(Benzofuran-2-yl)-2-*N*-propyl-*p*-toluenesulfonylaminopentane (*R*)-11. To a solution of benzofuran (6.86 g, 59.4 mmol) in tetrahydrofuran (20 mL) was added *n*-butyllithium (1.50 M in hexane, 39.6 mL, 59.4 mmol) at 0 °C under argon atomosphere, and the mixture was refluxed for 30 min. To the solution was added (*R*)-**8** (11.8 g, 49.5 mmol) in tetrahydrofuran (17 mL) for 20 min, and the mixture was stirried at 0 °C. After 10 min, the precipitate was resulted and diethyl ether (20 mL) was added to the mixture at 0 °C. The mixture was filtered and washed with diethyl ether (50 mL×4) to give (*R*)-**11** (12.5 g, 70%) as yellow solid: mp 230 °C-(decompose); ^1H NMR ($CDCl_3$) 0.83 (t, *J* = 7.1 Hz, 3H), 1.20–1.55 (m, 4H), 2.32 (s, 3H), 2.75 (dd, *J* = 15.1, 6.4 Hz, 1H), 2.85 (dd, *J* = 15.1, 5.7 Hz, 1H), 3.54–3.69 (m, 1H), 6.33 (s, 1H), 7.08 (d, *J* = 8.1 Hz, 2H), 7.14–7.49 (m, 4H), 7.64 (d, *J* = 8.1 Hz, 2H); IR(KBr) 2970, 1600, 1460, 1325 cm^{-1}; MS 363 (M^+), 357, 226, 155, 130.

(*R*)-*N*-(Benzyloxycarbonyl)-norvaline (*R*)-12. D-Norvaline (*R*)-**5** (7.00 g, 59.8 mmol) was dissolved in 2M NaOH aq solution (35 mL) under stirring at 0 °C. To the solution was benzyl chloroformate (10.2 g, 60 mmol) and 2M Na_2CO_3 aq solution (53 mL). The mixture was stirred for 30 min at 0 °C and further stirred overnight at room temperature. The reaction solution was acidified with concentrated HCl, and extracted with diethyl ether. The etheral phase was washed with water and brine, dried over anhydrous sodium sulfate, and

concentrated in vacuo to give (*R*)-**12** (11.1 g, 74%) as white solid: mp 84–85 °C (from ethyl acetate) (lit.[18] (*S*): mp 86 °C); $[\alpha]_D^{20}$ +1.6° (*c* 9.1, methanol) (lit.[18] (*S*): $[\alpha]_D^{12}$ −4.2° (*c* 2, acetone)); ^{1}H NMR ($CDCl_3$) 0.94 (t, *J* = 7.1 Hz, 3H), 1.60–2.00 (m, 4H), 4.30–4.50 (m, 1H), 5.12 (s, 1H), 5.20–5.30 (m, 1H), 7.35 (s, 1H). IR(KBr) 3330, 1745, 1725, 1690, 1650 cm^{-1}; MS 251(M^+), 206, 162, 110. HRMS (EI) *m*/*z* calcd for $C_{13}H_{17}NO_4$ (M^+) 251.1157; found 251.1195.

(*R*)-*N*-Benzyloxycarbonylamino-*N*-methoxy-*N*-methyl norvalinamide (*R*)-13. 1-Hydroxybenzotriazole hydrate (1.88 g, 13.9 mmol) and 4-methylmorpholine (1.49 g, 14.7 mmol) were added to a −10 °C solution of 1-ethyl-3-[3-(diethylamino)propyl]carbodimide hydrochloride (2.66 g, 13.9 mmol) in dichlomethane (70 mL). After the reaction mixture was warmed to room temperatue, to the mixture was added a solution of (*R*)-**12** (3.50 g, 13.9 mmol) in dodichloromethane (28 mL). The mixture was stirred at room temperature for 30 min and cooled to −10 °C. A mixture of *N*-methyl-*O*-methylhydroxylamine hydrochloride (1.37 g, 14.1 mmol) and 4-methylmorpholine (1.62 mL, 14.7 mmol) in dichloromethane (28 mL) was added dropwise, and stirred at room temperature overnight. The reaction mixture was evaporated and partitioned between water and ethyl acetate. The organic layer was washed with 10% HCl, saturated $NaHCO_3$ and brine, then dried over anhydrous magnessium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 40:1) to give (*R*)-**12** (3.86 g, 94%) as colorless oil: $[\alpha]_D^{20}$ +20° (*c* 1.3, methanol); ^{1}H NMR ($CDCl_3$) 0.92 (t, *J* = 7.1 Hz, 3H), 1.35–1.75 (m, 4H), 3.21 (s, 1H), 3.78 (s, 3H), 4.70–4.80 (m, 1H), 5.00–5.15 (m, 2H), 5.40–5.50 (m, 1H), 7.25–7.34 (m, 5H); IR(neat) 3300, 2955, 1720, 1660, 1520 cm^{-1}; MS 295($M^+ + 1$), 234, 206, 187, 162, 110, HRMS (EI) *m*/*z* calcd for $C_{15}H_{22}N_2O_4$ $(M+H)^+$ 295.1658; found 295.1617.

(*R*)-1-(Benzofuran-2-yl)-2-benzyloxycarbonylamino-1-pentanone (*R*)-14. To a −35 °C solution of benzofuran (2.64 g, 25.4 mmol) in tetrahydrofuran (90 mL) was added dropwise *n*-butyllithium (1.54 M in hexane, 33.0 mL, 50.8 mmol) under argon atomosphere, and the mixture was stirred at −30 to −25 °C for 10 min and then refluxed for 30 min. To the solution was added quickly (*R*)-**13** (3.00 g, 10.2 mmol) in tetrahydrofuran (36 mL) within 1 min, and the mixture was stirried at −30 °C for 2 h. The reaction mixture was poured into saturated NH_4Cl. The aqueous phase was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane:dichloromethane = 1:1) to give (*R*)-**14** (1.63 g, 46%) as colorless needles; mp 91–92 °C (from diethyl ether); $[\alpha]_D^{20}$ −48° (*c* 1.0, methanol); ^{1}H NMR ($CDCl_3$) 0.94 (t, *J* = 7.1 Hz, 3H), 1.40–2.10 (m, 4H), 5.12 (s, 2H), 5.26–5.30 (m, 1H), 5.60–5.64 (m,1H), 7.25–7.36 (m, 5H), 7.48-7.75 (m, 5H); IR(KBr) 3320, 1685, 1665, 1610, 1530 cm^{-1}, MS 352 ($M^+ + 1$), 308, 244, 207, 173, 145; HRMS (EI) *m*/*z* calcd for $C_{21}H_{21}NO_4$ (M^+) 351.1470; found 351.1487.

(*R*)-1-(Benzofuran-2-yl)-2-aminopentane (*R*)-3 hydrochloride. To a solution of (*R*)-**14** (1.50 g, 4.26 mmol) in trifluoroacetic acid (6.60 mL) was added triethylsilane (2.18 g, 18.8 mmol) at 0 °C under stirring. The mixture was stirred at 50–55 °C for 2 h. The reaction mixture was cooled to room temperature, to which a mixture of water (1.0 mL) and methanol (1.0 mL) was added and stirred overnight. The mixture was neutralized with $NaHCO_3$ and extracted with ethyl acetate (100 mL×3). Combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane:dichloromethane = 1:1) to give (*R*)-**3** (0.47 g, 54%), which was treated with HCl in diethyl ether to give (*R*)-**3** hydrochloride (0.42 g, 41%) as colorless needles: mp 143–144 °C (from acetone); $[\alpha]_D^{20}$ −15° (*c* 1.0, methanol); ^{1}H NMR ($CDCl_3$) 0.91 (t, *J* = 7.0 Hz, 3H), 1.35–1.80 (m, 4H), 3.10–3.40 (m, 2H), 3.68 (m, 1H), 6.56 (s, 1H), 7.10–7.42 (m, 2H), 7.47–7.51 (m, 2H), 7.64 (br, 2H); IR(KBr) 2800, 2680, 1585, 1510 cm^{-1}; MS 204($M^+ + 1$), 160, 131, 103, 72. Anal. calcd for $C_{13}H_{17}NO$:C, 65.13; H, 7.57; N 5.84%. Found: C, 65.46; H, 7.49; N 5.96%.

(*R*)-*N*-{2-[(1-(Benzofurane-2-yl))-pentyl]}propionamide (*R*)-4. (*R*)-**3** (0.47 g, 2.31 mmol) and triethylamine (0.48 mL, 3.44 mmol) were dissolved in dichloromethane (4.00 mL). To the solution was added propionyl chloride (0.43 g, 4.60 mmol) and the mixture was stirred at room temperature for 4 h, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane:dichloromethane = 40:1) to give (*R*)-**4** (0.49 g, 82%) as colorless needles: mp 84–85 °C (from diethyl ether); $[\alpha]_D^{20}$ −21° (*c* 1.0, methanol); ^{1}H NMR ($CDCl_3$) 0.91 (t, *J* = 6.7 Hz, 3H), 1.15 (t, *J* = 7.7 Hz, 3H), 1.40–1.55 (m, 4H), 2.19 (q, *J* = 7.7 Hz, 2H), 2.80–3.10 (m, 2H), 4.32 (m, 1H), 5.43 (m, 1H), 6.47 (s, 1H), 7.10–7.40 (m, 2H),7.40-7.52 (m, 2H); IR(KBr) 3295, 1640, 1605, 1540 cm^{-1}; MS 260($M^+ + 1$), 202, 186, 160, 144, 128,103; HRMS (EI) *m*/*z* calcd for $C_{16}H_{20}NO_2$ $(M-H)^+$ 258.1494; found 258.1460

(*R*)-1-(Benzofuran-2-yl)-2-propylaminopentane (*R*)-1 hydrochloride. A solution of (*R*)-**4** (1.76 g, 6.79 mmol) in diethyl ether (20 mL) was added to a suspension of lithium aluminum hydride (1.03 g, 27.1 mmol) in diethyl ether (20 mL). The mixture was stirred at 0 °C for 30 min and then refluxed for 2 h with stirring. After being cooled, sodium fluoride (4.56 g, 10.9 mmol) was added to the solution at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (1.47 mL), and washed with dichloromethane:ethanol (95:5 mL), and ethyl acetate:ethanol (95:5 mL). The combined filtrates were concentrated in vacuo. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 10:1) to give (*R*)-**1** (1.40 g, 84%), which was treated with HCl in diethyl ether to give (*R*)-**1** hydrochloride (1.24 g, 64%).

Crystallographic studies. Crystal of (−)-**1**·HCl was grown from ethanol and diethyl ether by slow evaporation at room temperature. A summary of the crystallographic data is given in Table 1. The unit-cell

dimensions were determined by a least-squares fit of 2θ angles for 25 reflections, measured by graphite-monochromated Cu-K_α radiation ($\lambda = 1.5418$ Å) on an automated Rigaku AFC-5 diffractometer. Intensity data were collected in a ω-2θ scan mode using the same diffractometer; the back-grounds were countered for 5 s at both extreams of each reflection peak. Four standard reflections were monitored for every 100 reflection intervals throughout the data collection, showing a random variation of ±2% with no significant trends. The observed intensities were corrected for the Lorentz and polarization effects, but not for the absorption effect.

The structure of (−)-**1**·HCl was solved by the direct method using the SHELXS 97 program[19] and refined by the full-matrix least squares method with anisotropic thermal parameters. The atomic factors and terms of anomalous dispersion corrections were taken from ref 20.

References and Notes

1. Knoll, J.; Miklya, I. *Life Sci.* **1995**, *56*, 611.
2. (a) Knoll, J. *Pharmacol. Toxicol.* **1994**, *75*, 65. (b) Knoll, J. *Biomed. & Pharmacother.* **1995**, *49*, 187. (c) Knoll, J. *Exp. Gerontol* **1997**, *32*, 539. (d) Knoll, J. *Neurobiology* **2000**, *8*, 179.
3. Knoll, J.; Magyar, K. *Adv. Bioch. Psychopharmacol.* **1972**, *5*, 393.
4. Knoll, J.; Knoll, B.; Török, Z.; Timár, J.; Yasar, S. *Arch. int. Pharmacodyn. Thér.* **1992**, *316*, 5.
5. Knoll, J. *Mech. Ageing & Dev.* **1988**, *46*, 237.
6. Tatton, W. G.; Grenwood, C. E. *J. Neurosci. Res.* **1991**, *30*, 666.
7. (a) Terud, J. W.; Langston, J. W. *Science* **1989**, *245*, 519. (b) Parkinson Study Group *New. Engl. J. Med.* **1989**, *321*, 1364.
8. Sano, M.; Ernesto, C.; Thomas, R. G.; Klauber, M. R.; Schafer, K.; Grundman, M.; Woodbury, P.; Growdon, J.; Cotman, C. W.; Pfeiffer, E.; Schneider, L. S.; Thal, L. *J. New Engl. J. Med.* **1997**, *336*, 1216.
9. Knoll, J. *Pharmacol. Toxicol.* **1998**, *82*, 57.
10. (a) Knoll, J.; Yoneda, F.; Knoll, B.; Ohde, H.; Miklya, I. *British J. Pharm.* **1999**, *128*, 1723. (b) Yoneda, F.; Moto, T.; Sakae, M.; Ohde, H.; Knoll, B.; Miklya, I.; Knoll, J. *Bioorg. Med. Chem.* **2001**, *9*, in press.
11. Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1972**, *26*, 1.
12. (a) Oppolzer, W.; Flaskamp, E. *Hel. Chim. Acta* **1977**, *22*, 204. (b) Farmer, J. J.; Attygalle, A. B.; Smedley, S. R.; Eisner, T.; Meinwald, J. *Tetrahedron Lett.* **1997**, *38*, 2787.
13. Edwards, P. D.; Wolanin, D. J.; Andisk, D. W.; Davis, M. W. *J. Med. Chem.* **1995**, *38*, 76.
14. Sun, G.; Slavica, M.; Uretsky, N. J.; Wallace, L. J.; Shams, G.; Weinstein, D. M.; Miller, J. C.; Millar, D. D. *J. Med. Chem.* **1998**, *41*, 1034.
15. Conditions for analytical chromatography of **1**: column, CHIRALPAK AD-RH (0.46 cm×1.5 cm); eluent, 20 mM phosphate buffer (pH 8.0):acetonitrile = 3:2; flow rate, 1.0 mL/min; detection, UV 249 nm; retention times 35 (*R*) and 39 min (*S*). The (*R*)-**1**·HCl obtained by two methods was in high optical purity (> 98% ee).
16. Dina, G. D.; Otto, M. J.; Treasurywala, A. M.; McKinlay, M. A.; Oglesby, R. C.; Maliski, E. G.; Rossmann, M. G.; Smith, T. J. *J. Med. Chem.* **1988**, *31*, 540.
17. Davis, F. A.; Zhou, P.; Liang, C.-H; Reddy, R. E. *Tetrahedron: Asymmetry* **1995**, *6*, 1511.
18. Izumiya, N.; Yamashita, T. *J. Biochem.* **1959**, *46*, 19.
19. Sheldrick, G. M., SHELXS 97. *Programs for the Solution of Crystral Structure*, University of Göttingen, Germany, 1997.
20. International Tables for X-ray Crystallography, Vol. C, Kluwer Academic Publishers, 1992.