Stereoselective Reactions. XXII.[1] Design and Synthesis of Chiral Chelated Lithium Amides for Enantioselective Reactions

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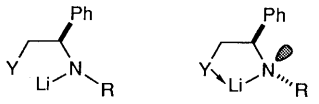
Chiral chelated lithium amides ((*R*))-1a—g) were designed and synthesized in optically pure forms starting from (*R*)-phenylglycine.

Keywords chiral lithium amide; chelation; chiral amide nitrogen; internal ligation site; (*R*)-phenylglycine

Lithium dialkylamides such as lithium diisopropylamide (LDA) are easily available by treating the corresponding secondary amines with alkyllithiums in aprotic solvents, and are currently used widely in organic synthesis as strong bases with low nucleophilicity. In recent years, a new area of asymmetric synthesis has been explored in which a chiral lithium amide is used as a base, and at the same time, as a chiral auxiliary in the reactions to give optically active products enantioselectively.[2] By employing chiral chelated lithium amides having the general structure **1**, we have already achieved several enantioselective reactions such as enantioselective deprotonation of prochiral cyclohexanones[3] and *meso*-type cycloalkanones,[4] kinetic reaction of racemic 2-substituted cyclohexanones,[5] regioselective enolization of optically active 3-keto steroids,[6] enantioselective aldol reaction,[7] enantioselective alkylation at α-position of cyclic ketones,[8] and enantioselective protonation.[9] The present paper describes the design and synthesis of the chiral chelated lithium amides ((*R*)-**1a**—**g**) that are useful for these enantioselective reactions.

Design of Chiral Lithium Amides ((*R*)-1a—g) Principles developed during the previous studies on diastereoselective asymmetric synthesis using chiral chelated lithioenamines[1,10] were applied to the design of chiral chelated lithium amides having the general structure **1** (Chart 1). The amides ((*R*)-**1a**—**d**) are structurally similar to LDA in that they carry a bulky alkyl group and an α-branched alkyl group on amide nitrogen, but are modified by introducing a chiral center at the α-carbon, and a substituent Y at the β-carbon of the amide nitrogen. We expected that the substituent Y would work as an internal ligation site for the lithium. We designed these chiral lithium amides as chiral versions of LDA based on the following four working hypotheses: (1) they exist as five-membered chelated forms that are stable in solution during the reaction; (2) they form aggregates in solution to satisfy the valency (tetravalency or trivalency) of lithium, the degree of aggregation being dependent on the solvent used; (3) the degree of aggregation in solution can be controlled by addition of a strong external ligand such as hexamethylphosphoric triamide (HMPA) to satisfy the valency of lithium; (4) the amide nitrogen in these lithium amides is chiral, because the alkyl substituent (R) on the amide nitrogen will orient itself exclusively *trans*, and therefore, the lone pair on amide nitrogen will be exclusively *cis* to the phenyl group on chiral carbon in the chelated monomeric ring, as shown in **2**. It is known that the basicity of lithium amides arises from the lone pair on amide nitrogen. It should be noted that the lone pair on amide nitrogen in ((*R*)-**1a**—**d**) is expected to reside on chiral amide nitrogen.



(*R*)-**1a**—**g** (*R*)-**2a**—**d**

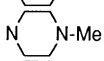
	Y	R
a		CH_2Bu-*tert*
b		iso-Pr
c		CH_2Bu-*tert*
d		CH_2CF_3
e		$CH_2CH_2OCH_2CH_2OMe$
f		$CH_2CH_2OCH_2CH_2NMe_2$
g		$CH_2CH_2N(Me)CH_2CH_2NMe_2$

Chart 1

The amides ((*R*)-**1e**—**g**) were designed as chiral chelated lithium amides having two additional ligation sites for the lithium.

Synthesis of Chiral Lithium Amides ((*R*)-1a—g) All chiral lithium amides ((*R*)-**1a**—**g**) were prepared from commercially available (*R*)-phenylglycine ((*R*)-**3**) as shown in Chart 2.[11] In the present synthesis, the amines ((*R*)-**7a** and (*R*)-**7b**) are pivotal intermediates from which various derivatives having a different substituent on nitrogen can be prepared. Thus, (*R*)-*Z*-phenylglycine ((*R*)-**4**) was converted to the corresponding acid amides ((*R*)-**5a** and (*R*)-**5b**) with piperidine and 1-methylpiperazine using diethylphosphorocyanidate (DEPC)[12] as a condensing reagent. After removal of the protecting group, (*R*)-**6a** and (*R*)-**6b** were subjected to lithium aluminum hydride reduction to give (*R*)-**7a** and (*R*)-**7b**, respectively. Monoalkylation at primary amino nitrogen

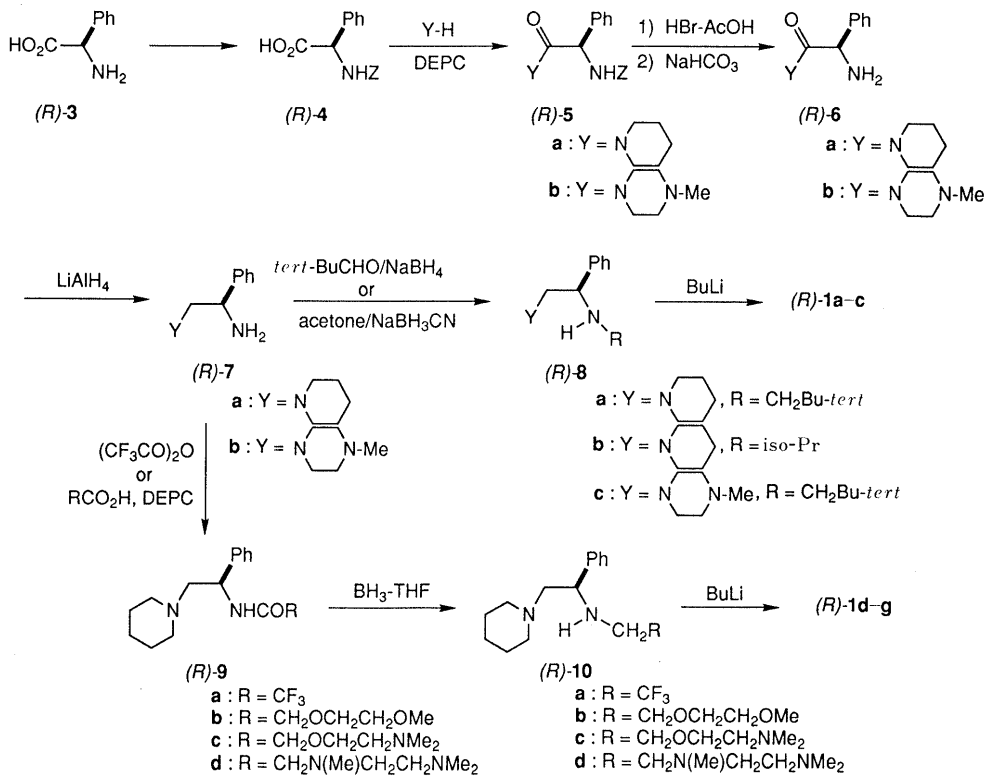


Chart 2

was carried out efficiently by the reductive amination of (*R*)-**7a**, **b** for (*R*)-**8a**—**c** or by the reduction of the corresponding acid amides ((*R*)-**9a**—**d**) for (*R*)-**10a**—**d**. Lithium amides ((*R*)-**1a**—**g**) were prepared as usual from the corresponding amines thus formed.

Since (*S*)-phenylglycine is also available commercially, (*S*)-**1a**—**g** can be prepared similarly.

Experimental

General All melting and boiling points are uncorrected. IR spectra were recorded on a JASCO IRA-1 or a JASCO DS-402G spectrometer. ^{1}H-NMR spectra were recorded on a Hitachi R-24B (60 MHz), a JEOL JNM-PS100 (100 MHz), a JEOL EX-270 (270 MHz), or a JEOL GSX-400 spectrometer. All spectra were recorded in $CDCl_3$, unless otherwise stated. The chemical shifts are given in δ (ppm) values using tetramethylsilane as an internal standard. Coupling constants (J) are given in hertz. The following abbreviations are used: br = broad, s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet. Mass spectra (MS) were recorded on a JEOL JMS-01 SG-Z spectrometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter.

(*R*)-1-[*N*-(Benzyloxycarbonyl)-2-phenylglycyl]piperidine ((*R*)-5a) Triethylamine (101 ml, 0.75 mol) was added dropwise during 30 min to an ice-cooled solution of (*R*)-**4** (mp 133—133.5 °C, $[\alpha]_D^{25}$ −117° (c = 4.21, EtOH), reported[13] mp 130—130.5 °C, $[\alpha]_D^{21}$ −119° (c = 4, EtOH)) (195 g, 0.68 mol), piperidine (76 ml, 0.75 mol), and DEPC[12] (136 g, 0.75 mol) in *N*,*N*-dimethylformamide (DMF) (730 ml), and the whole was stirred at room temperature for 25 h. The solution was diluted with a mixture of benzene (1.8 l) and ethyl acetate (3.6 l), and then washed successively with water (2 l × 4), 2.5% aqueous HCl (2 l × 3), water (4 l), saturated aqueous $NaHCO_3$ (2 l × 3), water (4 l), and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness *in vacuo* to give a pale yellow solid. Recrystallization from a mixture of ether (300 ml) and hexane (700 ml) gave (*R*)-**5a** (183 g, 76%) as colorless prisms of mp 75—76 °C, $[\alpha]_D^{25}$ −144° (c = 1.21, $CHCl_3$). IR (Nujol): 1730, 1645 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 0.9—1.7 (6H, m, $CH_2(CH_2)_3CH_2$), 3.2—3.8 (4H, m, CH_2NCH_2), 5.03, 5.11 (2H, ABq, J = 12, $C_6H_5CH_2O$), 5.58 (1H, d, J = 7, C_6H_5CHCO), 6.44 (1H, d, J = 7, NH). 7.3—7.4 (10H, m, $C_6H_5 \times 2$). *Anal.* Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.64; H, 6.84; N, 7.71.

(*R*)-1-[*N*-(Benzyloxycarbonyl)-2-phenylglycyl]-4-methylpiperazine ((*R*)-5b) Triethylamine (1.54 ml, 111 mmol) was added dropwise during 10 min to an ice-cooled solution of (*R*)-**4** (30.0 g, 105 mmol), 1-methylpiperazine (11.6 g, 116 mmol), and DEPC[12] (21.0 g, 116 mmol) in DMF (200 ml), and the whole was stirred at room temperature for 4 h. The solution was diluted with a mixture of benzene (500 ml) and ethyl acetate (1 l), and then washed with water (1 l × 5) and brine (1 l × 3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness *in vacuo* to give (*R*)-**5b** (34.0 g, 98%) as a colorless caramel. This sample was used for the next step without further purification, $[\alpha]_D^{26}$ −96.8° (c = 1.02, EtOH). IR (film): 1715, 1650 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 2.15 (3H, s, N-CH_3), *ca.* 2.2 (4H, m, $CH_2N(Me)CH_2$), 3.1—3.7 (4H, m, CH_2NCH_2), 4.90 (2H, s, $C_6H_5CH_2O$), 5.40 (1H, d, J = 7, PhCHNH), 6.25 (1H, br, NH), 7.15 (5H, s, C_6H_5), 7.20 (5H, s, C_6H_5). MS *m/z*: 368 ($M^+ + 1$).

(*R*)-1-(2-Phenylglycyl)piperidine ((*R*)-6a) A solution of (*R*)-**5a** (182 g) in AcOH (95 ml) was mixed with 33% HBr–AcOH (366 ml) under ice-cooling, and the whole was stirred at room temperature overnight. The solution was poured into ice-water (1.7 l), and was washed with ether (1 l × 3). The aqueous layer was basified by addition of $NaHCO_3$, and was extracted with $CHCl_3$ (1.7 l × 3). The organic extracts were combined, washed with brine, dried over anhydrous K_2CO_3, and evaporated to dryness to give (*R*)-**6a** (120 g, quantitative) as a pale yellow oil. This sample was used for the next step without further purification. IR (film): 3400, 1645 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 0.9—1.6 (6H, m, $CH_2(CH_2)_3CH_2$), 2.04 (2H, br, NH_2), 3.2—3.8 (4H, m, CH_2NCH_2), 4.72 (1H, s, PhCHCO), *ca.* 7.3 (5H, m, C_6H_5).

(*R*)-4-Methyl-1-(2-phenylglycyl)piperazine ((*R*)-6b) Prepared from (*R*)-**5b** by a similar procedure to that for the preparation of (*R*)-**6a** described above to give (*R*)-**6b** as a pale yellow oil. This sample was used for the next step without further purification. IR (film): 3360, 1630 cm^{-1}. ^{1}H-NMR (60 MHz) δ: *ca.* 2.0 (2H, br, NH_2), 2.18 (3H, s, N-CH_3), *ca.* 2.3 (4H, m, $CH_2N(CH_3)CH_2$), 3.1—3.8 (4H, m, $CH_2N(CO)CH_2$), 4.71 (1H, s, PhCHCO), 7.31 (5H, s, C_6H_5).

(*R*)-1-Phenyl-2-piperidinoethylamine ((*R*)-7a) A solution of (*R*)-**6a** (81.3 g, 0.37 mol) in THF (800 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (30.0 g, 0.74 mol) in tetrahydrofuran (THF) (200 ml), and the whole was stirred under reflux for 2 h. Under stirring

and ice-cooling, water (30 ml), 15% aqueous NaOH (30 ml) and water (90 ml) were added successively to the reaction mixture, and the whole was filtered. The filtrate and THF washings were combined and evaporated to dryness *in vacuo* to give an oil, which was converted to the hydrochloride salt in the usual manner using HCl–EtOH. Recrystallization from EtOH (2 l) gave (*R*)-**7a**·2HCl (63 g, 76%) as colorless needles of mp 282 °C (dec.), $[\alpha]_D^{25}$ +10.3° (*c*=2.03, MeOH). *Anal.* Calcd for $C_{13}H_{20}N_2 \cdot 2HCl$: C, 56.32; H, 8.00; N, 10.10. Found: C, 56.40; H, 8.23; N. 9.81.

A stirred suspension of (*R*)-**7a**·2HCl (9.53 g) in ether (80 ml) was mixed with 20% aqueous K_2CO_3 (60 ml). After all had dissolved, the ether layer was separated, and the aqueous layer was extracted with ether (80 ml × 2). The ethereal extracts were combined, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residual oil was distilled to give (*R*)-**7a** (5.95 g, 85% from (*R*)-**7a**·2HCl) as a colorless oil of bp 210 °C (1.5 mmHg), $[\alpha]_D^{25}$ −64.2° (*c*=1.03, $CHCl_3$). IR (film): 3300 cm^{-1}. ^{1}H-NMR (100 MHz) δ: 1.15—1.9 (6H, m, $CH_2(C\underline{H}_2)_3CH_2$), 1.9 (2H, br, $N\underline{H}_2$), 1.9—2.8 (6H, m, $C\underline{H}_2N(C\underline{H}_2)C\underline{H}_2$), 4.07 (1H, dd, *J*=7, 6, $PhC\underline{H}CH_2$), 7.3—7.6 (5H, m, $C_6\underline{H}_5$).

(*R*)-1-Phenyl-2-(4-methylpiperazinyl)ethylamine ((*R*)-7b) Reduction of (*R*)-**6b** (24.6 g, 106 mmol) by $LiAlH_4$ (8.84 g, 233 mmol) was carried out by a similar procedure to that for the preparation of (*R*)-**7a** described above to give crude (*R*)-**7b** (21.8 g, 94 g) as a yellow solid of mp 50.5—52 °C. Recrystallization from ether gave colorless prisms of mp 52.5—54 °C, $[\alpha]_D^{25}$ −41.8° (*c*=1.27, MeOH). IR (Nujol): 3400 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 1.94 (2H, br, $N\underline{H}_2$), 2.30 (3H, s, N-$C\underline{H}_3$), 2.3—2.7 (10H, m, $C\underline{H}_2N(C\underline{H}_2C\underline{H}_2)_2NCH_3$), 4.12 (1H, dd, *J*=4, 11, $PhC\underline{H}CH_2$), 7.2—7.4 (5H, m, $C_6\underline{H}_5$). MS *m/z*: 220 (M^+). *Anal.* Calcd for $C_{13}H_{21}N_3$: C, 71.19; H, 6.95; N, 19.16. Found: C, 71.43; H, 9.68; N, 18.90.

(*R*)-*N*-(2,2-Dimethylpropyl)-1-phenyl-2-piperidnoethylamine ((*R*)-8a) A mixture of (*R*)-**7a** (5.87 g, 28.7 mmol), pivalaldehyde (3.6 ml, 33 mmol) and anhydrous Na_2SO_4 (10 g) in benzene (80 ml) was stirred at room temperature for 3 h. The reaction mixture was filtered, and the filtrate was evaporated to dryness *in vacuo*. The residual colorless oil was dissolved in EtOH (70 ml), $NaBH_4$ (2.5 g, 66 mmol) was added, and the whole was stirred under ice-cooling for 30 min. Evaporation of the solvent gave a residue, which was mixed with saturated aqueous $NaHCO_3$ (80 ml), and the whole was extracted with hexane (100 ml × 3). The organic extracts were combined, washed with brine (70 ml), dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo*. The residue was purified by column chromtography (silica gel, $CHCl_3$–MeOH (2 : 1)) to give a colorless oil. A solution of this oil in EtOH (10 ml) was mixed with a solution of picric acid (13.2 g, 57.6 mmol) in EtOH (270 ml). The resulting yellow precipitates were collected by filtration and recrystallized from MeOH (260 ml) to give (*R*)-**8a**·dipicrate (17.2 g, 82%) as yellow plates of mp 179.5—180.5 °C, $[\alpha]_D^{25}$ +7.14° (*c*=1.04, acetone). *Anal.* Calcd for $C_{31}H_{40}N_8O_5 \cdot CH_3OH$: C, 48.69; H, 5.27; N, 14.65. Found: C, 48.51; H, 5.18; N, 14.70.

A suspension of (*R*)-**8a**·dipicrate (9.8 g) in hexane (250 ml) was mixed with 10% aqueous NaOH (1600 ml) under stirring. After all had dissolved, the organic layer was separated, and the aqueous layer was extracted with hexane (250 ml). The organic layer was combined with organic extracts, washed with brine (100 ml × 2), and dried over anhydrous K_2CO_3. Evaporation of the solvent gave (*R*)-**8a** (3.8 g, quantitative) as a colorless oil. A small sample was further purified by bulb-to-bulb distillation (150—160 °C (bath temperature), 3—5 mmHg) as a colorless oil, $[\alpha]_D^{25}$ −113.2° (*c*=1.19, benzene). IR (film): 3300 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 0.92 (9H, s, $C(C\underline{H}_3)_3$), 1.4—1.6 (6H, m, $CH_2(C\underline{H}_2)_3CH_2$), 2.1—2.6 (9H, m, $C\underline{H}_2N(C\underline{H}_2)C\underline{H}_2$, $N\underline{H}C\underline{H}_2$), 3.67 (1H, dd, *J*=11, 4, $PhC\underline{H}CH_2$), 7.1—7.4 (5H, m, $C_6\underline{H}_5$). *Anal.* Calcd for $C_{18}H_{30}N_2$: C, 78.78; H, 11.02; N, 10.21. Found: C, 78.58; H, 11.12; N, 9.97.

(*R*)-*N*-Isopropyl-1-phenyl-2-piperidinoethylamine ((*R*)-8b) A solution of (*R*)-**7a** (15.0 g, 73.4 mmol), concentrated aqueous HCl (7.4 ml, 89 mmol), and acetone (5.75 ml, 78 mmol) in MeOH (170 ml) was mixed with $NaBH_3CN$ (90%, 5.59 g, 89 mmol), and the whole was stirred at the room temperature for 11 h. Evaporation of the solvent gave a residue, which was mixed with 6% aqueous NH_3 (130 ml), and the whole was extracted with $CHCl_3$ (500 ml × 3). The organic extracts were combined, dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo*. The residue was converted to the salt with picric acid as above. Recrystallization from MeOH (5.2 l) gave (*R*)-**8b**·dipicrate (36.4 g, 71%) as yellow needles of mp 193.5 °C, $[\alpha]_D^{25}$ −43.3° (*c*=0.54, acetone). *Anal.* Calcd for $C_{28}H_{32}N_8O_{14}$: C, 47.73; H, 4.58; N, 15.90. Found: C, 47.58; H, 4.52; N, 15.88.

The free amine ((*R*)-**8b**) (1.63 g, 93%) was obtained from (*R*)-**8b**·dipicrate (5.00 g) as a colorless liquid by a similar procedure to that used for the preparation of (*R*)-**8a** described above. A small sample was subjected to bulb-to-bulb distillation (150—160 °C (bath temperature), 0.5 mmHg) to give a colorless liquid, $[\alpha]_D^{25}$ −91.0° (*c*=0.95, EtOH). IR (film): 3320 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 0.94 (3H, d, *J*=6, $CHC\underline{H}_3$), 1.05 (3H, d, *J*=6, $CHC\underline{H}_3$), 1.3—2.0 (6H, m, $CH_2(C\underline{H}_2)_3CH_2$), 2.0—2.8 (8H, m, $C\underline{H}_2N(C\underline{H}_2)C\underline{H}_2$, $N\underline{H}C\underline{H}$), 3.84 (1H, dd, *J*=9, 6, $PhC\underline{H}CH_2$), 7.3 (5H, m, $C_6\underline{H}_5$).

(*R*)-*N*-(2,2-Dimethylpropyl)-1-phenyl-2-(4-methylpiperazinyl)ethylamine ((*R*)-8c) Treatment of (*R*)-**7b** (11.6 g) according to the procedure described above for the preparation of (*R*)-**8a** gave crude (*R*)-**8c** as a solid, which was converted to the salt with HCl using HCl–EtOH. Recrystallization from EtOH gave (*R*)-**8c**·3HCl (15.3 g, 72%) as colorless prisms of mp 236—240 °C (dec.), $[\alpha]_D^{20}$ −18.0° (*c*=1.20, MeOH). *Anal.* Calcd for $C_{18}H_{34}Cl_3N_3 \cdot H_2O$: C, 51.86; H, 8.70; N, 10.08. Found: C, 51.56; H, 8.60; N, 9.87.

The free amine ((*R*)-**8c**) (10.5 g, 97%) was obtained from (*R*)-**8c**·3HCl (15.3 g) as a solid. Recrystallization from aqueous EtOH gave colorless needles of mp 78.5—80 °C, $[\alpha]_D^{25}$ −104° (*c*=1.18, $CHCl_3$). IR (Nujol): 3330 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 0.92 (9H, s, $C(C\underline{H}_3)_3$), 2.29 (3H, s, $NC\underline{H}_3$), 2.1—2.7 (13H, m, $C\underline{H}_2N(C\underline{H}_2C\underline{H}_2)_2NCH_3$, $N\underline{H}C\underline{H}_2$), 3.68 (1H, dd, *J*=11, 4, $PhC\underline{H}CH_2$), 7.2—7.4 (5H, m, $C_6\underline{H}_5$). *Anal.* Calcd for $C_{18}H_{31}N_3$: C, 74.69; H, 10.79; N, 14.52. Found: C, 74.75; H, 10.84; N, 14.55.

(*R*)-*N*-(1-Phenyl-2-piperidinoethyl)trifluoroacetamide ((*R*)-9a) Trifluoroacetic anhydride (1.80 ml, 12.7 mmol) was added dropwise at −10 °C to a solution of (*R*)-**7a** (1.73 g, 8.47 mmol) and triethylamine (1.77 ml, 12.7 mmol) in CH_2Cl_2 (8.5 ml), and the whole was allowed to stand at room temperature overnight. The reacion mixture was diluted with CH_2Cl_2 (50 ml), washed with saturated aqueous $NaHCO_3$ (10 ml) and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* gave a residue, which was purified by column chromatography (silica gel, hexane–acetone (8 : 1)) to give (*R*)-**9a** (1.95 g, 77%) as a pale yellow oil, $[\alpha]_D^{25}$ −74.2° (*c*=0.97, MeOH). IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.4—1.7 (6H, m, $CH_2(C\underline{H}_2)_3CH_2$), 2.0—2.5 (4H, m, $CH_2C\underline{H}_2NC\underline{H}_2CH_2$), 2.60 (2H, d, *J*=7, N-$C\underline{H}_2CH$), 4.83 (1H, t, *J*=7, $NCH_2C\underline{H}$), 7.2—7.4 (5H, m, $C_6\underline{H}_5$), 7.7 (1H, br, $N\underline{H}$). *Anal.* Calcd for $C_{15}H_{19}F_3N_2O$: C, 60.00; H, 6.38; N, 9.33. Found: C, 60.29; H, 6.43; N, 9.07.

(*R*)-*N*-(1-Phenyl-2-piperidinoethyl)-2-(2-methoxyethyloxy)acetamide ((*R*)-9b) Triethylamine (17.7 g, 175 mmol) was added dropwise under ice-cooling to a solution of (*R*)-**7a** (32.4 g, 159 mmol), methoxyethoxyacetic acid[14] (23.4 g, 175 mmol), and DEPC[12] (95%, 28.6 g, 167 mmol) in DMF (300 ml), and the whole was stirred at room temperature for 12 h. The solution was diluted with a mixture of ethyl acetate (500 ml) and benzene (250 ml), washed successively with water (500 ml × 3), saturated aqueous $NaHCO_3$ (100 ml), and brine (100 ml), and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was dissolved in ether (100 ml), and extracted with 8% aqueous HCl (100 ml × 4). The aqueous extracts were combined, washed with ether (100 ml), and then basified with $NaHCO_3$ to pH *ca.* 9. The alkaline aqueous mixture was extracted with ether (200 ml × 3). The ethereal extracts were combined, washed with brine (100 ml), and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a pale yellow oil, which was distilled to give (*R*)-**9b** (42.1 g, 83%) as a pale yellow oil of bp 150—180 °C (0.7 mmHg). This sample was used for the next step without further purification. IR (film): 1680 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.2—1.7 (6H, m, $CH_2(C\underline{H}_2)_3CH_2$), 2.3—2.7 (6H, m, $C\underline{H}_2N(C\underline{H}_2)C\underline{H}_2$), 3.42 (3H, s, $OC\underline{H}_3$), 3.6—3.8 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 4.0—4.1 (2H, m, $COC\underline{H}_2O$), 5.09 (1H, dd, *J*=8, 7, $PhC\underline{H}CH_2$), 7.2—7.4 (5H, m, $C_6\underline{H}_5$), 7.8 (1H, br, $N\underline{H}$). MS *m/z*: 321 ($M^+ + 1$).

(*R*)-*N*-(1-Phenyl-2-piperidinoethyl)-2-(2-dimethylaminoethyloxy)acetamide ((*R*)-9c) Prepared from (*R*)-**7a** (5.90 g, 28.9 mmol) and [2-(dimethylamino)ethoxy]acetic acid[15] (5.18 g, 28.2 mmol) by a similar procedure to that described above for the preparation of (*R*)-**9b**. The crude product was purified by column chromatography (silica gel, ethyl acetate, hexane, and then hexane–iso-$PrNH_2$ (20 : 1)) to give (*R*)-**9c** (8.44 g, 90%) as a pale yellow oil. This sample was used for the next step without further purification. A small sample was further purified by bulb-to-bulb distillation (280 °C (bath temperature), 0.6 mmHg), $[\alpha]_{365}^{25}$ −38.4° (*c*=2.0, benzene). IR (film): 1670 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.4—1.6 (6H, m, $CH_2(C\underline{H}_2)_3CH_2$), 2.29 (6H, s, $N(C\underline{H}_3)_2$),

2.2—2.7 (8H, m, $CH_2N(CH_2)CH_2$, CH_2NMe_2), 3.5—3.7 (2H, m, OCH_2CH_2N), 3.9—4.0 (2H, m, OCH_2CO), 5.01 (1H, dd, $J=15$, 6, $PhCHCH_2$), 7.2—7.3 (5H, m, C_6H_5), 7.8 (1H, br, NH). MS *m/z*: 333 (M^+).

(*R*)-*N*-(1-Phenyl-2-piperidinoethyl)-2[*N*-(2-dimethylaminoethyl)-*N*-methylamino]acetamide ((*R*)-9d) Reaction of (*R*)-**7a** (2.96 g, 14.5 mmol) and *N*-(2-dimethylaminoethyl)-*N*-methylglycine[16] (3.73 g, 16 mmol) by a similar procedure to that described above for the preparation of (*R*)-**9b** afforded a crude product, which was purified by column chromatography (silica gel, hexane–iso-$PrNH_2$ (20 : 1)) to give (*R*)-**9d** (3.45 g, 69%) as a pale yellow oil. This sample was used for the next step without further purification. A small sample was further purified by bulb-to-bulb distillation (290 °C (bath temperature), 0.7 mmHg), $[\alpha]_{365}^{20}$ −33.9° (*c*=2.0, benzene). IR (film): 1680 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.3—1.6 (6H, m, $CH_2(CH_2)_3CH_2$), 2.25 (6H, s) and 2.37 (3H, s) ($N(CH_3)_2$, NCH_3), 2.3—2.6 (10H, m, $CH_2N(CH_2)CH_2$, NCH_2CH_2N), 3.0—3.1 (2H, m, NCH_2CO), 5.02 (1H, dd, $J=15$, 6, $PhCHCH_2$), 7.2—7.4 (5H, m, C_6H_5), 8.0 (1H, br, NH). MS *m/z*: 246 (M^+).

(*R*)-*N*-(2,2,2-Trifluoroethyl)-1-phenyl-2-piperidinoethylamine ((*R*)-10a) A 1 M solution of BH_3 in THF (76 ml, 76 mmol) was added dropwise to a solution of (*R*)-**9a** (7.65 g, 25.5 mmol) in THF (30 ml), and the whole was heated under reflux for 10 h. The reaction mixture was quenched with MeOH (10 ml) under ice-cooling, and was then evaporated to dryness. The residue was mixed with 37% HCl–MeOH (70 ml), and the whole was heated under reflux for 4.5 h. Evaporation of the solvent gave a residue, which was dissolved in water (70 ml). After addition of K_2CO_3 (13.8 g, 100 mmol), the whole was extracted with hexane (100 ml, 50 ml). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness *in vacuo* to give a pale yellow oil. Purification by column chromatography (silica gel, ethyl acetate–hexane (1 : 10)) gave (*R*)-**10a** (6.98 g, 96%) as a colorless oil. Further purification by bulb-to-bulb distillation (150—160 °C (bath temperature), 0.3 mmHg) gave a colorless oil, $[\alpha]_D^{25}$ −82.7° (*c*=1.20, MeOH). ^{1}H-NMR (270 MHz) δ: 1.4—1.65 (6H, m, $CH_2(CH_2)_3CH_2$), 2.2—2.6 (6H, m, $CH_2N(CH_2)CH_2$), 3.0 (1H, br, NH), 3.04 (2H, q, $J=9$, NCH_2CF_3), 3.94 (1H, dd, $J=11$, 3, $PhCHCH_2$), 7.2—7.4 (5H, m, C_6H_5). *Anal.* Calcd for $C_{15}H_{21}F_3N_2$: C, 62.92; H, 7.39; N, 9.78. Found: C, 62.66; H, 7.41; N, 9.58.

(*R*)-*N*-[2-(2-Methoxyethyloxy)ethyl]-1-phenyl-2-piperidinoethylamine ((*R*)-10b) Reduction of (*R*)-**9b** (40.4 g, 0.126 mol) by $LiAlH_4$ (14.0 g, 0.346 mol) was carried out by a similar procedure to that described above for the preparation of (*R*)-**7a** to give crude (*R*)-**10b** as a pale yellow oil. A solution of this oil in MeOH was mixed with a solution of picric acid (73 g, 0.32 mol) in MeOH to give yellow precipitates, which were collected by filtration and recrystallized from MeOH (2.5 l) to give (*R*)-**10b**·dipicrate (71.3 g, 74%) as yellow leaflets of mp 140 °C, $[\alpha]_D^{20}$ −25.9° (*c*=2.07, acetone). *Anal.* Calcd for $C_{30}H_{36}N_8O_{16}$: C, 47.12; H, 4.75; N, 14.65. Found: C, 47.71; H, 4.71; N, 14.63.

The free amine ((*R*)-**10b**) was obtained from (*R*)-**10b**·dipicrate in quantitative yield by the usual way as a colorless oil of bp 142—146 °C (0.03 mmHg), $[\alpha]_D^{25}$ −70.4° (*c*=2.17, benzene). IR (film): 3320 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.4—1.7 (6H, m, $CH_2(CH_2)_3CH_2$), 2.2—2.7 (8H, m, $CH_2N(CH_2)CH_2$, $NHCH_2$), 2.8 (1H, br, NH), 3.39 (3H, s, OCH_3), 3.5—3.7 (6H, m, OCH_2CH_2O, OCH_2CH_2N)), 3.78 (1H, dd, $J=11$, 4, $PhCHCH_2$), 7.2—7.4 (5H, m, C_6H_5). MS *m/z*: 307 ($M^+ + 1$).

(*R*)-*N*-[2-(2-Dimethylaminoethyloxy)ethyl]-1-phenyl-2-piperidinoethylamine ((*R*)-10c) Reduction of (*R*)-**9c** (8.44 g, 25.3 mmol) with $LiAlH_4$ (3.30 g, 87 mmol) was carried out by a similar procedure to that described above for the preparation of (*R*)-**7a**. The crude product was purified by column chromatography (silica gel, hexane–iso-$PrNH_2$ (30 : 1)) to give (*R*)-**10c** (6.64 g, 73%) as a pale yellow oil. A small sample was further purified by bulb-to-bulb distillation (280 °C (bath temperature), 0.8 mmHg) as a colorless oil, $[\alpha]_D^{25}$ −64.9° (*c*=2.15, benzene). ^{1}H-NMR (270 MHz) δ: 1.4—1.6 (6H, m, $CH_2(CH_2)_3CH_2$), 2.28 (6H, s, $N(CH_3)_2$), 2.2—2.7 (10H, m, $CH_2N(CH_2)CH_2$, $NHCH_2$, CH_2NMe_2), 2.9 (1H, br NH), 3.4—3.6 (4H, m, CH_2OCH_2), 3.77 (1H, dd, $J=11$, 4, $PhCHCH_2$), 7.2—7.4 (5H, m, C_6H_5). *Anal.* Calcd for $C_{19}H_{33}N_3O$: C, 71.43; H, 10.41; N, 13.15. Found: C, 71.14; H, 10.37; N, 12.87.

(*R*)-*N*-[2-[*N*-(2-Dimethylaminoethyl)-*N*-methylamino]ethyl]-1-phenyl-2-piperidinoethylamine ((*R*)-10d) Reduction of (*R*)-**9d** (3.39 g, 9.78 mmol) with BH_3 (1 M solution in THF, 80 ml, 80 mmol) was carried out by a similar procedure to that described above for the preparation of (*R*)-**10a**. The crude product was purified by column chromatography (silica gel, $CHCl_3$–MeOH (9 : 1) and then $CHCl_3$–iso-$PrNH_2$ (20 : 1)) to give (*R*)-**10d** (2.06 g, 63%) as a pale yellow oil. A small sample was further purified by bulb-to-bulb distillation (290 °C (bath temperature), 0.8 mmHg) as a colorless oil, $[\alpha]_D^{25}$ −57.1° (*c*=2.03, benzene). ^{1}H-NMR (270 MHz) δ: 1.4—1.6 (6H, m, $CH_2(CH_2)_3CH_2$), 2.21 (3H, s) and 3.30 (6H, s) ($N(CH_3)_2$, NCH_3), 2.2—2.6 (14H, m, $CH_2N(CH_2)CH_2$, $NHCH_2CH_2NCH_2CH_2N$), 2.9 (1H, br, NH), 3.73 (1H, dd, $J=11$, 4, $PhCHCH_2$), 7.2—7.4 (5H, m, C_6H_5). *Anal.* Calcd for $C_{20}H_{36}N_4$: C, 72.24; H, 10.91; N, 16.85. Found: C, 71.98; H, 10.78; N, 16.59.

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