AN APPLIED STEREOCONTROLLED SYNTHESIS OF PIPERIDINE DERIVATIVE UTILIZING DIASTEREOSELECTIVE REACTION OF CHIRAL 1,3-OXAZOLIDINE WITH GRIGNARD REAGENT; ASYMMETRIC SYNTHESIS OF AN ALKALOID, (-) SEDAMINE **

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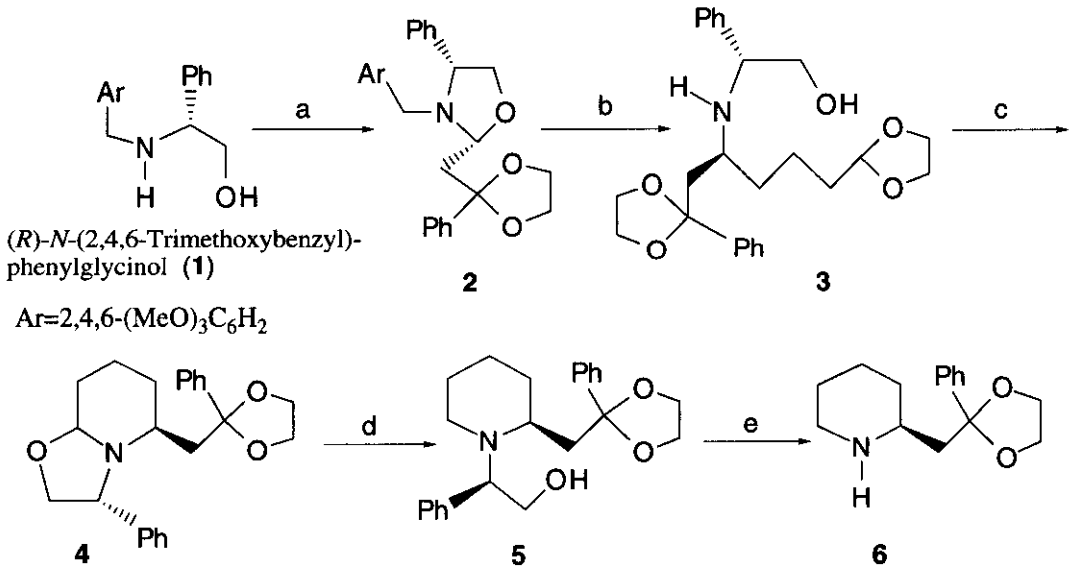
Abstract ——— A facile total synthesis of enantiomerically pure (-)-sedamine, known as a naturally occurring alkaloid, was accomplished by use of the diastereoselective addition of Grignard reagent to a chiral 1,3-oxazolidine, and utilizing of 1-aza-4-oxabicyclo[4.3.0]nonane derivative as a key intermediate. A diastereomeric pair, (-)-allosedamine, was also recovered as a minor product.

INTRODUCTION

Sedamine was the first alkaloid isolated from *Sedum acre*[1] and has been obtained later from a number of *Sedum* species;[2] both the levorotatory (-)-sedamine (**10a**) and the dextrorotatory enantiomeric form were found in all of *Sedum* species mentioned above. The solution conformation of (-)-sedamine was established by Hootele *et al.* using high resolution ^{1}H- and ^{13}C-NMR spectroscopy.[3] Stereocontrolled syntheses of sedamine have been reported either as racemic mixtures[4] or as single enantiomers.[5] In this research we attempted the optimization of enantioselective syntheses of (-)-sedamine to provide unequivocally pure enantiomer. It was known that chiral 1,3-oxazolidines, easily synthesized by condensing (*S*)- or (*R*)-*N*-alkyl-2-hydroxyethylamines such as (*R*)-*N*-alkylphenylglycinols with carbaldehydes,[6] react with various organometallic reagents in highly stereoselective manner providing chiral amines in high chemical and optical yields.[7] In our previous report the enantioselective syntheses of (*S*)-2-phenylpiperidine and (*R*)-2-methylpiperidine have been achieved to give optically pure products in moderate overall yield by utilization of 1,3-oxazolidines as starting point and bicyclo compounds, 1-aza-4-oxabicyclo[4.3.0]nonane derivatives, as pivotal intermediates.[8] This simple procedure constructed a chance to accomplish an enantioselective synthesis of (-)-sedamine, starting from a known versatile chiral amino acid derivative, (*R*)-*N*-(2,4,6-trimethoxybenzyl)phenylglycinol (**1**). It is worth noting that in the last step of our asymmetric synthesis of (-)-sedamine, (-)-allosedamine (**10b**) which is a long known constituent of *Lobelia inflata*,[9] was also recovered as a minor product.[10]

RESULTS AND DISCUSSION

The oxazolidine (**2**) as a starting material was prepared by the condensation of the known phenylglycinol derivative (**1**)[8] with 3,3-ethylenedioxy-3-phenylpropanal in CH_2Cl_2 solution in the presence of Molecular sieve 3A to discharge eliminated water. The ^{1}H-NMR spectrum of crude **2** exhibited the presence of C-2 proton at 4.62 ppm supporting a single diastereomeric product. Because of the 1,3-oxazolidine ring cleavage during column chromatography, purification of this product could not be performed.

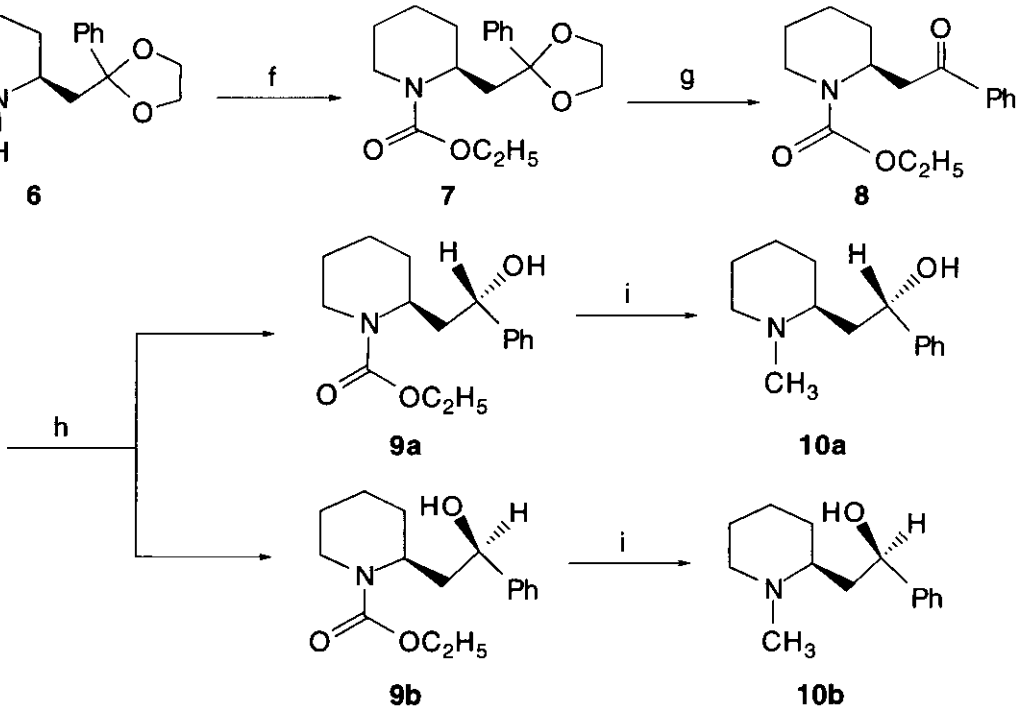


(a) $PhC(OCH_2)_2CH_2CHO$, MS 3A, CH_2Cl_2; (b) $Br(CH_2)_3CH(OCH_2)_2$, Mg, THF; (c) 1N HCl, MeOH; (d) $NaBH_4$, MeOH; (e) 20% $Pd(OH)_2$-C/H_2, 3-4 atm, MeOH.

Scheme 1.

The oxazolidine (**2**) then reacted with 4,4-ethylenedioxybutylmagnesium bromide, which is generated *in situ* from 4,4-ethylenedioxybutyl bromide and magnesium turnings, to give diacetal product as a single diastereomeric compound deduced from ^{1}H-NMR spectrum of the crude product. The reaction was completely accomplished by determination of the absence of C-2 hydrogen of the starting oxazolidine which was substituted by the presence of proton of carbon linked to ethylenedioxy substituent at 4.68 ppm. Differ from the similar reaction described in the earlier report,[8] the *N*-2,4,6-trimethoxybenzyl substituent of **2** was eliminated at once to give a secondary amine, presumably because of two possible reasons as the following. First, reductive cleavage consequence of the Grignard reagent; and second, there are crowded bulky groups around the center nitrogen at the time of Grignard reagent attack to C-2 position of the oxazolidine so that the bulky *N*-2,4,6-trimethoxybenzyl substituent is effortlessly cleaved. The pure product could be isolated with simple column chromatography procedure to give **3** which has two ethylenedioxy substituents, but only one of them would be allowed to be hydrolyzed in the next step and the other one positioned γ from nitrogen remaining untouched. After careful investigation of suitable acidic conditions, we treated a solution

of **3** in MeOH with an aqueous solution of 1N hydrochloric acid in a 1 : 1 ratio of volume to afford the bicyclo product (**4**) as a single diastereomeric compound deduced from ^{1}H-NMR spectrum of the crude product, which was unstable and used without purification. It was supposed that phenyl group attached directly to the ketonic acetal of **3** is effective enough to make resistance toward acidic hydrolysis of acetal under weak acidic conditions.



(f) $ClCO_2Et$, DMAP, $(iso\text{-}Pr)_2NEt$; (g) 5% HCl, THF;
(h) $LiBH(Et)_3$, THF, -78°C; (i) $LiAlH_4$, THF, reflux.

Scheme 2.

By using sodium borohydride as hydride source, compound (**4**) was reduced to *N*-substituted piperidine (**5**) as a diastereomerically pure compound deduced from ^{1}H-NMR spectral analysis of the crude product. Catalytic hydrogenation using 20% palladium hydroxide on carbon as a catalyst under 3-4 atm pressure gave the secondary cyclic amine (**6**), which was so unstable that it was used immediately without further purification. Preventing racemization at C-2 position during acidic deprotection of ethylenedioxy substituent, we gave precedence to *N*-protection by reaction of **6** with ethyl chloroformate at a basic condition to give the *N*-ethoxycarbonylpiperidine (**7**). With *N*-protected compound in hand, the next reaction is providing deprotected ketone (**8**) by treating **7** with 5% hydrochloric acid in THF. To generate hydroxyl group, the *N*-substituted phenacylpiperidine (**8**) was treated with lithium triethylborohydride at -78°C to give a diastereomeric mixture in a ratio of 3 : 1, that are readily separable by column chromatography on silica gel. Lithium aluminium hydride reduction gave the same pair of diastereomers

only in a ratio of 1 : 1 as recounted by another publication.[11] The major product which has optical rotation of $[\alpha]^{20}_{D}$ -96.9° (*c* 1.51, $CHCl_3$) was confirmed as **9a** with (2*S*, 2'*S*) configuration by further conversion to the title compound (-)-sedamine as follows. The same treatment of the minor product (**9b**) having optical rotation of $[\alpha]^{20}_{D}$ -40.0° (*c* 0.80, $CHCl_3$) gave (-)-allosedamine as follows. Reduction of the *N*-ethoxycarbonylpiperidines (**9a**) with lithium aluminium hydride provided (-)-sedamine (**10a**) as colorless crystals, mp 58-59°C (lit.,[5c] : 59-61°C), $[\alpha]^{20}_{D}$ -88.4° (*c* 1.10, EtOH) {lit.,[5c] : $[\alpha]^{22}_{D}$ -87.8° (*c* 0.1, EtOH)}. Similar treatment of **9b** gave (-)-allosedamine (**10b**) as colorless crystals, mp 80-81°C (lit.,[5a] : 81-82°C), $[\alpha]^{20}_{D}$ -30.2° (*c* 1.05, MeOH) {lit.,[5a] : $[\alpha]^{20}_{D}$ -31.2° (*c* 5.0, MeOH)}.

EXPERIMENTAL SECTION

Melting points were measured with a Yanagimoto-Micro Melting Point apparatus without correction. IR spectra were recorded on a 215 Hitachi Grating IR spectrophotometer and major absorption are listed in wavenumber (cm^{-1}). ^{1}H-NMR spectra were recorded on a JEOL GSX-270 spectrometer. Each signal is described in terms of its chemical shift in ppm from tetramethylsilane (TMS) as internal standard. All spectra were run in $CDCl_3$ unless otherwise noted. Multiplicity and coupling constants are then given. Abbreviations used to denote NMR spectral signals are s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. MS and HMRS were recorded on a JEOL JMS D-300 spectrometer in the chemical ionization (CI) with isobutane and electron impact (EI) methods. Elemental analyses were performed on a Perkin-Elmer 240-B instrument. Optical rotations were performed on a JASCO DIP-360 and DIP-370; concentrations reported are in g/100 mL. Sibata Glass Tube Oven GTO-350RD was used as distillation apparatus. Column chromatography was performed on silica gel (45~75 mm, Wakogel C-300). TLC was carried out on glass plates coated with silica gel F_{254} (Merck). Spot detection was performed with UV 254 nm or Iodium vapor; and with a solution mixture of *p*-anisaldehyde, sulfuric acid, acetic acid and ethanol (2.5 : 3.5 : 1 : 93). The reaction solvents were prepared as the following. Tetrahydrofuran and dichloromethane were distilled over potassium metal and phosphorus pentoxide, respectively.

(2*R*, 4*R*)-*N*-(2,4,6-Trimethoxybenzyl)-2-(2,2-ethylenedioxy-2-phenylethyl)-4-phenyl-1,3-oxazolidine (2). To a solution of **1** (13.5 g, 42.54 mmol) in CH_2Cl_2 (100 mL) were added 3,3-ethylenedioxy-3-phenylpropanal (10.0 g, 52.03 mmol) and an equal amount of Molecular sieve 3A. After being stirred at rt for 18 h, the reaction mixture was filtered through a pad of Celite. The reaction flask was rinsed twice with CH_2Cl_2, and then the combined organic solutions were evaporated under reduced pressure to give an almost colorless solid. The crude solid was recrystallized from EtOAc-hexane to yield **2** as colorless crystals (19.11 g, 91.4%), mp 100-101°C. $[\alpha]^{20}_{D}$ -28.4° (*c* 2.03, $CHCl_3$). ^{1}H-NMR δ : 2.19 [dd, 1H, *J*=7.9, 14.7 Hz, C<u>H</u>HC$(OCH_2)_2$], 2.27 [dd, 1H, *J*=1.8, 14.7 Hz, CH<u>H</u>C$(OCH_2)_2$], 3.61 (s, 6H, OCH_3 x 2), 3.76 (s, 3H, OCH_3), 3.55-3.80 (m, 5H, NC<u>H</u>CH_2O, OC<u>H_2CH_2</u>O), 3.89 (t, 1H, *J*=7.6 Hz, NCHC<u>H</u>HO), 4.02-4.12 (m, 3H, Ar<u>CH_2</u>N, NCHCH<u>H</u>O), 4.62 (dd, 1H, *J*=1.8, 7.9 Hz, NCHO), 5.92 (s, 2H, aromatic H), 7.12-7.21 (m, 3H, aromatic H), 7.25-7.36 (m, 5H, aromatic H), 7.45 (dd, 2H, *J*=1.5, 7.6 Hz, aromatic H). MS *m/z* : EI, 491 (M^+), 328 [M^+ -$CH_2C(OCH_2)_2Ph$]; CI, 492 (M^+ +1). IR

($CHCl_3$) : 1140 (C-O-C) cm^{-1}. *Anal.* Calcd for $C_{29}H_{33}NO_6$: C, 70.85; H, 6.77; N, 2.85. Found : C, 71.13; H, 6.48; N, 2.88.

(3*S*, 1'*R*)-3-(*N*-2'-Hydroxy-1'-phenylethylamino)-1,1,7,7-bis(ethylenedioxy)-1-phenylheptane (3). To a stirred solution of 4,4-ethylenedioxybutylmagnesium bromide, derived from 4,4-ethylenedioxybutyl bromide (12.0 g, 61.52 mmol) and magnesium turnings (1.53 g, 62.94 mmol) in THF (25 mL), was added portionwise a solution of **2** (10.0 g, 20.34 mmol) in THF (25 mL) at rt under an atmosphere of nitrogen. After being stirred at 0°C for 2 d, the reaction mixture was quenched with water and the organic solution was decanted from the insoluble solid. The residue was extracted with ether (2 x 50 mL), then the organic extracts were combined, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a viscous oil as a single diastereomeric compound indicated from ^{1}H-NMR of the crude product. Purification of the crude oil was performed by column chromatography on silica gel with CH_2Cl_2-MeOH (11 : 1) to yield **3** as a pale yellow oil (8.33 g, 95.8%). $[\alpha]^{20}_D$ -44.3° (*c* 1.09, $CHCl_3$). ^{1}H-NMR δ : 1.23-1.35 (m, 6H, $CH_2CH_2CH_2$), 2.02 (m, 2H, NCHC$\underline{H}_2$CPh), 2.66 (m, 1H, NC$\underline{H}$CH_2CPh), 3.47 (1H, dd, *J*=8.6, 10.4 Hz, NCHC$\underline{H}$HOH), 3.59-3.97 (m, 10H, OC$\underline{H}_2$C$\underline{H}_2$O x 2, NC$\underline{H}$CH$\underline{H}$OH), 4.68 [t, 1H, *J*=4.6 Hz, C$\underline{H}$(OCH_2)$_2$] , 7.18-7.35 (m, 8H, aromatic H), 7.43 (dd, 2H, *J*= 1.5, 7.6 Hz, aromatic H) MS *m/z* : EI, 396 (M^+ -CH_2OH); CI, 428 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}, 1140 (C-O-C) cm^{-1}. *Anal.* Calcd for $C_{25}H_{33}NO_5$: C, 70.23; H, 7.78; N, 3.28. Found : C, 69.90; H, 8.01; N, 3.11.

(2*R*, 9*S*)-9-(2,2-Ethylenedioxy-2-phenylethyl)-2-phenyl-1-aza-4-oxabicyclo[4.3.0]nonane (4). 1 N Hydrochloric acid (20 mL) was added to a stirred solution of **3** (3.30 g, 7.72 mmol) in MeOH (20 mL). The reaction mixture was stirred at rt for 2 h, followed by quenching with the addition of 10% solution of sodium carbonate. The resulting mixture was extracted with ether (3 x 20 mL), then the remaining aqueous layer was also extracted with ether (2 x 20 mL). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give **4** as a yellow oil, which was unstable and used immediately in the next reaction without further purification. ^{1}H-NMR δ : 1.37-1.75 (m, 5H, OCHC$\underline{H}$HC$\underline{H}_2$C$\underline{H}_2$), 1.86 (dd, 1H, *J*=7.9, 14.7 Hz, NCHC$\underline{H}$HCPh), 1.98 (br d, 1H, *J*=9.8 Hz, OCHCH$\underline{H}$CH_2CH_2), 2.10 (dd, 1H, *J*=1.8, 14.7 Hz, NCHCH$\underline{H}$CPh), 3.11 (br d, 1H, *J*=5.5 Hz, NC$\underline{H}$CH_2CPh), 3.50-3.72 (m, 4H, OCH_2CH_2O), 3.75 (m, 1H, NCHO), 3.88 (t, 1H, *J*=7.9 Hz, NC$\underline{H}$CH_2O), 4.02-4.09 (m, 2H, NCHC$\underline{H}_2$O), 7.18-7.35 (m, 10H, aromatic H). MS *m/z* : EI, 365 (M^+), 203 [M^+ -$CH_2C(OCH_2)_2Ph$]; CI, 366 (M^+ +1).

(2*S*, 1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2-(2,2-ethylenedioxy-2-phenylethyl)piperidine (5). To a stirred solution of **4** in MeOH (15 mL) was added portionwise sodium borohydride (1.61 g, 42.56 mmol). The reaction mixture was stirred at rt for 40 min, followed by quenching with water and extraction with CH_2Cl_2 (3 x 20 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a yellow oil. The crude oil was purified by column chromatography on silica gel with CH_2Cl_2-MeOH-NH_3 (190 : 9 : 1) to afford **5** as a pale yellow oil (2.50 g, 88.0% overall yield from **3**). $[\alpha]^{20}_D$ -81.1° (*c* 0.65, $CHCl_3$). ^{1}H-NMR δ : 1.17-1.54 (m, 5H,

NCHC<u>H</u>HC<u>H</u>$_2$C<u>H</u>$_2$), 1.84-1.98 (m, 2H, NCHCH<u>H</u>CH$_2$CH$_2$, NCHC<u>H</u>HCPh), 2.10 (m, 1H, NC<u>H</u>HCH$_2$), 2.53 (dd, 1H, *J*=2.8, 14.9 Hz, NCHCH<u>H</u>CPh), 2.65-2.89 (m, 2H, NCH<u>H</u>CH$_2$, NC<u>H</u>CH$_2$CPh), 3.62-3.88 (m, 4H, OCH$_2$CH$_2$O), 3.94-4.03 (m, 2H, NCHC<u>H</u>$_2$O), 4.08 (m, 1H, NC<u>H</u>CH$_2$O), 7.18-7.42 (m, 8H, aromatic H), 7.45 (dd, 2H, *J*=1.8, 7.9 Hz, aromatic H). MS *m/z* : EI, 336 (M^+ -CH_2OH); CI, 368 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}. *Anal.* Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found : C, 75.03; H, 8.22; N, 3.64.

(*S*)-2-(2,2-Ethylenedioxy-2-phenylethyl)piperidine (6). To a solution of **5** (2.50 g, 6.8 mmol) in MeOH (50 mL), which was placed in a pressure bottle of an apparatus for catalytic reduction, was added carefully palladium hydroxide on carbon (Pearlman's catalyst) (1.40 g). After the bottle had been alternately evacuated and filled with hydrogen twice, the mixture was reduced by shaking with hydrogen under 3-4 atm pressure for 2 d. The reaction mixture was filtered through a pad of Celite to remove the catalyst, then the reaction flask was rinsed with MeOH (2 x 25 mL). The organic solution were combined and evaporated under reduced pressure to give **6** as a yellow oil, which was unstable and used immediately in the next reaction without further purification.

(*S*)-*N*-Ethoxycarbonyl-2-(2,2-ethylenedioxy-2-phenylethyl)piperidine (7). To a solution of **6** in CH_2Cl_2 (40 mL) were added diisopropylethylamine (2.64 g, 20.4 mmol), ethyl chloroformate (1.47 g, 13.5 mmol) and 4-(dimethylamino)pyridine (0.4 g, 3.3 mmol). After stirring at rt for 4 h under an argon atmosphere, the volatiles were removed under reduced pressure, and the residual material was subjected to column chromatography on silica gel with hexane-EtOAc (7 : 1) to provide **7** as a pale yellow oil (1,58 g, 72.8 % overall yield from **5**). $[\alpha]^{20}_D$ -37.3° (*c* 1.51, $CHCl_3$). ^{1}H-NMR δ : 1.20 (t, 3H, *J*=7.3 Hz, OCH$_2$C<u>H</u>$_3$), 1.26-1.70 (m, 6H, CH$_2$CH$_2$CH$_2$), 2.05-2.25 (m, 2H, NCHC<u>H</u>$_2$CPh), 2.78 (dt, 1H, *J*=2.7, 13.1 Hz, NC<u>H</u>HCH$_2$), 3.66-3.82 (m, 2H, OC<u>H</u>HC<u>H</u>HO), 3.92-4.09 (m, 5H, OCH<u>H</u>CH<u>H</u>O, OC<u>H</u>$_2$CH$_3$, NCH<u>H</u>CH$_2$), 4.50 (br s, 1H, NC<u>H</u>CH$_2$CPh), 7.25-7.36 (m, 3H, aromatic H), 7.45 (dd, 2H, *J*=1.8, 7.9 Hz, aromatic H). MS *m/z* : EI, 319 (M^+), 276 (M^+ -OCH_2CH_3); CI, 320 (M^+ +1). IR ($CHCl_3$) : 1670 (C=O) cm^{-1}. *Anal.* Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found : C, 67.46; H, 8.09; N, 4.21.

(*S*)-*N*-Ethoxycarbonyl-2-phenacylpiperidine (8). Compound (**7**) (0.86 g, 2.7 mmol) was dissolved in 20 mL of THF containing 10 mL of 5% hydrochloric acid. After being stirred at rt for 18 h, the reaction mixture was evaporated under reduced pressure to give crude keto derivative, which was purified by column chromatography on silica gel with hexane-ether (4 : 1) to afford **8** as a colorless viscous oil (0.73 g, 97.6%). $[\alpha]^{20}_D$ +29.4° (*c* 1.08, $CHCl_3$). ^{1}H-NMR δ : 1.18 (t, 3H, *J*=7.3 Hz, OCH$_2$C<u>H</u>$_3$), 1.26-1.75 (m, 6H, CH$_2$CH$_2$CH$_2$), 2.92 (dt, 1H, *J*=2.7, 13.6 Hz, NC<u>H</u>HCH$_2$), 3.19 (dd, 1H, *J*=5.5, 14.7 Hz, NCHC<u>H</u>HCPh), 3.25 (dd, 1H, *J*=8.5, 14.7 Hz, NCHCH<u>H</u>CPh), 4.04-4.11 (m, 3H, OC<u>H</u>$_2$CH$_3$, NCH<u>H</u>CH$_2$), 4.87 (br s, 1H, NC<u>H</u>CH$_2$CPh), 7.28-7.60 (m, 3H, aromatic H), 8.00 (d, 2H, *J*=7.3 Hz, aromatic H). MS *m/z* : EI, 275 (M^+), 230 [M^+ -OCH_2CH_3]; CI, 276 (M^+ +1). IR ($CHCl_3$) : 1670 (C=O) cm^{-1}. *Anal.* Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found : C, 69.61; H, 7.84; N, 5.00.

(2*S*, 2'*S*)- and (2*S*, 2'*R*)-*N*-Ethoxycarbonyl-2-(2-hydroxy-2-phenylethyl)piperidine (9a and 9b). To a stirred solution of **8** (0.61 g, 2.2 mmol) in THF (15 mL) at -78°C and under an atmosphere of nitrogen was added dropwise a 1.0 M solution of lithium triethylborohydride in THF (3.9 mL, 3.9 mmol). After stirring at -78°C for 4 h, the reaction mixture was quenched by the addition of water and allowed to warm up to rt and extracted with ether (3 x 15 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The remaining oil containing a pair of diastereomers was subjected to column chromatography on silica gel with CH_2Cl_2-ether (30 : 1) to provide **9a** (0.44 g, 72%) and **9b** (0.16 g, 26%) as colorless oil. Major product, (2*S*, 2'*S*)-**9a** : $[\alpha]^{20}_D$ -96.9° (*c* 1.51, $CHCl_3$). ^{1}H-NMR δ : 1.23 (t, 3H, *J*=7.0 Hz, $OCH_2C\underline{H}_3$), 1.29-1.60 (m, 6H, $CH_2C\underline{H}_2C\underline{H}_2$), 1.88 (ddd, 1H, *J*=5.5, 11.0, 14.0 Hz, NCHC$\underline{H}$HCHPh), 2.16 (dt, 1H, *J*=7.5, 14.0 Hz, NCHCH$\underline{H}$CHPh), 2.78 (br t, 1H, *J*=12.8 Hz, NC$\underline{H}$HCH$_2$), 3.89 (br s, 1H, NCH$\underline{H}$CH$_2$), 4.10 (q, 2H, *J*=7.0 Hz, $OC\underline{H}_2CH_3$), 4.42 (br s, 1H, NC$\underline{H}$CH$_2$CHPh), 4.74 (br s, 1H, NCHCH$_2$C$\underline{H}$Ph), 7.21-7.38 (m, 5H, aromatic H). MS *m/z* : EI, 277 (M^+), 232 [M^+ -OCH_2CH_3]; CI, 278 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}, 1670 (C=O) cm^{-1}. *Anal.* Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found : C, 69.12; H, 8.61; N, 4.97. Minor product, (2*S*, 2'*R*)-**9b** : $[\alpha]^{20}_D$ -40.0° (*c* 0.80, $CHCl_3$). ^{1}H-NMR δ : 1.29 (t, 3H, *J*=7.0 Hz, $OCH_2C\underline{H}_3$), 1.42-1.78 (m, 7H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$, NCHC$\underline{H}$HCHPh), 2.22 (dt, 1H, *J*=1.8, 13.1 Hz, NCHCH$\underline{H}$CHPh), 2.83 (dt, 1H, *J*=3.1, 12.8 Hz, NC$\underline{H}$HCH$_2$), 4.09 (br d, 1H, *J*=12.8 Hz, NCH$\underline{H}$CH$_2$), 4.19 (q, 2H, *J*=7.0 Hz, $OC\underline{H}_2CH_3$), 4.46 (br d, 1H, *J*=8.6 Hz, NC$\underline{H}$CH$_2$CHPh), 4.60 (br s, 1H, NCHCH$_2$C$\underline{H}$Ph), 7.21-7.39 (m, 5H, aromatic H). MS *m/z* : EI, 277 (M^+), 232 [M^+ -OCH_2CH_3]; CI, 278 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}, 1670 (C=O) cm^{-1}. *Anal.* Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found : C, 69.24; H, 8.58; N, 4.97.

Synthesis of (-)-Sedamine (10a). A solution of (2*S*, 2'*S*)-**9a** (0.28 g, 1.0 mmol) in THF (5 mL) was added dropwise to a stirred solution of lithium aluminium hydride (76 mg, 2.0 mmol) in THF (5 mL). After refluxing for 20 h, the reaction mixture was quenched by the addition of water (1 mL) and 15% aqueous sodium hydroxide (1 mL), respectively. The resulting mixture was washed with water (3 mL) and extracted with ether (3 x 10 mL). The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residual material was subjected to column chromatography on silica gel with CH_2Cl_2-MeOH (12 : 1) to give (2*S*, 2'*S*)-**10a** as a colorless solid (0.21 g, 95.7%), which was recrystallized from petroleum ether to yield colorless crystals, mp 58-59°C (lit.,[5c] : 59-61°C). $[\alpha]^{20}_D$ -88.4° (*c* 1.10, EtOH); {lit.,[5c] : $[\alpha]^{22}_D$ -87.8° (*c* 0.1, EtOH)}. ^{1}H-NMR δ : 1.29-1.80 (m, 7H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$, NCHC$\underline{H}$HCHPh), 2.12 (m, 1H, NCHCH$\underline{H}$CHPh), 2.51 (s, 3H, NCH_3), 2.53-2.62 (m, 1H, NC$\underline{H}$HCH$_2$), 2.84-2.93 (m, 1H, NC$\underline{H}$CH$_2$CHPh), 3.04-3.14 (m, 1H, NCH$\underline{H}$CH$_2$), 4.90 (dd, 1H, *J*=2.7, 10.7 Hz, NCHCH$_2$C$\underline{H}$Ph), 6.36 (br s, 1H, OH), 7.20-7.40 (m, 5H, aromatic H). MS *m/z* : EI, 219 (M^+), 98 [M^+ - $CH_2CH(OH)Ph$]; CI, 220 (M^+ +1). IR ($CHCl_3$) : 3200 (OH) cm^{-1}.

Synthesis of (-)-Allosedamine (10b). In the same manner as described for the synthesis of **10a**; (2*S*, 2'*R*)-**9b** (0.16 g) was subjected to reductive *N*-methylation. The same work up provided colorless

needles of (2*S*, 2'*R*)-**10b** (0.11 g, 88.6%), mp 80-81°C (lit.,[5a] : 81-82°C). $[\alpha]^{20}_{D}$ -30.2° (*c* 1.05, MeOH); {lit.,[5a] : $[\alpha]^{20}_{D}$ -31.2° (*c* 5.0, MeOH)}. ^{1}H-NMR δ : 1.26-1.39 (m, 1H, $NCHCH_2C\underline{H}HCH_2$), 1.51-1.71 (m, 4H, $NCHC\underline{H}HCH\underline{H}C\underline{H}_2$), 1.80-1.95 (m, 2H, $NCHCH\underline{H}CH_2CH_2$, $NCHC\underline{H}HCHPh$), 2.04 (dt, 1H, *J*=3.7, 11.6 Hz, $NC\underline{H}HCH_2$), 2.15 (ddd, 1H, *J*=3.9, 10.4, 14.7 Hz, $NCHCH\underline{H}CHPh$), 2.21-2.30 (m, 1H, $NC\underline{H}CH_2CHPh$), 2.42 (s, 3H, NCH_3), 2.97 (br d, 1H, *J*=12.2 Hz, $NCH\underline{H}CH_2$), 5.13 (dd, 1H, *J*=3.4, 10.7 Hz, $NCHCH_2C\underline{H}Ph$), 6.59 (br s, 1H, OH), 7.20-7.40 (m, 5H, aromatic H). MS *m/z* : EI, 219 (M^+), 98 [M^+ - $CH_2CH(OH)Ph$]; CI, 220 (M^+ +1). IR ($CHCl_3$) : 3200 (OH) cm^{-1}.

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REFERENCES AND NOTES

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