FACILE DIASTEREOSELECTIVE REACTIONS OF CHIRAL 1,3-OXAZOLIDINES WITH GRIGNARD REAGENTS; ASYMMETRIC SYNTHESES OF 2-SUBSTITUTED AND 2,6-DISUBSTITUTED PIPERIDINES **

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Abstract —— (*S*)- and (*R*)-2-Phenylpiperidines, (*S*)- and (*R*)-2-methylpiperidines, *meso*- and (2*R*, 6*R*)-2,6-diphenylpiperidines, and *meso*- and (2*S*, 6*S*)-2,6-dimethylpiperidines were synthesized asymmetrically starting from the diastereoselective addition of Grignard reagents to chiral 1,3-oxazolidines, converting of 1-aza-4-oxabicyclo[4.3.0]nonane derivatives as pivotal intermediates.

INTRODUCTION

Chiral 1,3-oxazolidines can be simply synthesized by condensing (*R*)-*N*-alkyl-2-hydroxyethylamines with carbaldehydes.[1] These compounds react with various organometallic reagents in a highly diastereoselective way composing chiral amines in both high chemical and optical yields,[2] and finally provide a route to utilize such reactions for total syntheses of naturally occurring alkaloids.

It was pointed out in the previously report[3] that the syntheses of 2-substituted and 2,5-disubstituted pyrollidines have been achieved using 1,3-oxazolidines as starting point and bicyclo compounds, 1-aza-4-oxabicyclo[3.3.0]octane derivatives, as pivotal intermediates. This procedure is expandable to construct its six membered ring homologue piperidine, which has been found as a common structural element of numerous alkaloids. In particular, the 2-alkylpiperidines and 2,6-dialkylpiperidines include a number of products exhibiting notable biological activity.[4] In spite of their pharmacological properties, general methods to prepare them in enantiomerically pure form are still rare.

Herein, we wish to report the syntheses of both *R* and *S* configurations of 2-substituted piperidines, along with separable *cis*- and *trans*-2,6-disubstituted piperidines. The substituents in these experiments include a methyl group to represent the aliphatic substituent and a phenyl group to represent the aromatic one. The starting 1,3-oxazolidines in this work are those bearing *N*-2,4,6-trimethoxybenzyl substituent that it is so bulky enough to effect high selectivity in the reaction with Grignard reagents.

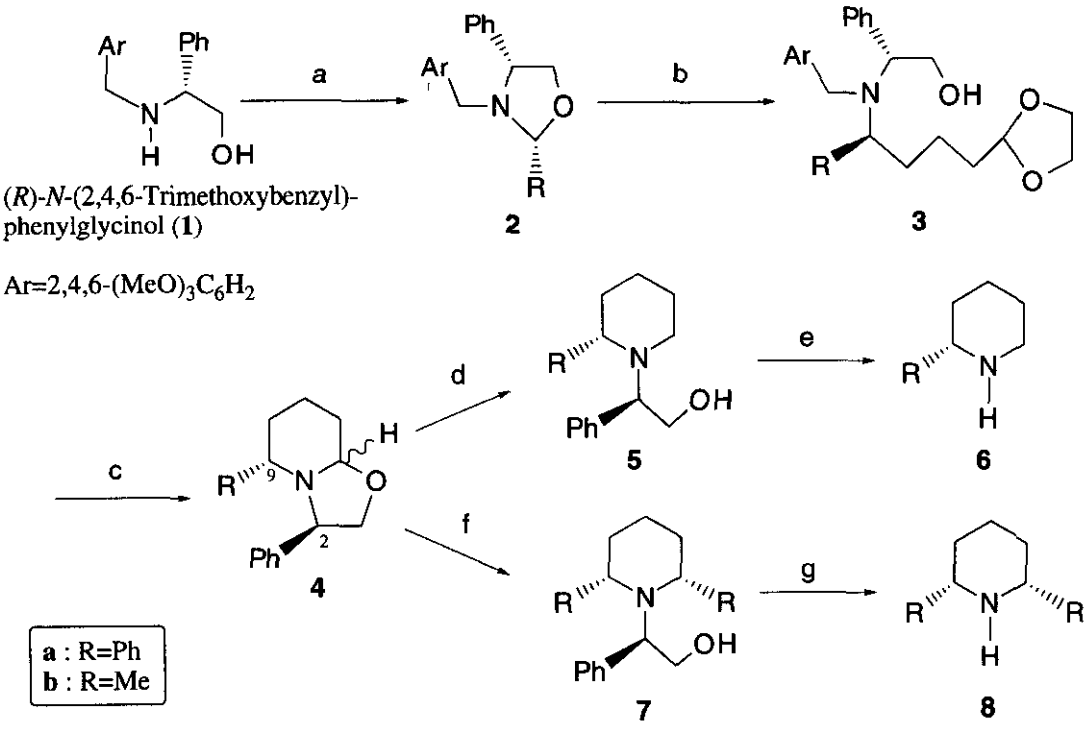
** This paper is dedicated on the memory of the late Professor Shun-ichi Yamada.

RESULTS AND DISCUSSION

Asymmetric Syntheses of (*S*)-2-Phenylpiperidine and *meso*-2,6-Diphenylpiperidine

We conducted preparation of methoxy-, dimethoxy- and trimethoxybenzylphenylglycinols to investigate their bulkiness effects toward selectivity of the products resulted from the reaction of oxazolidines with Grignard reagents. It was concluded that the *N*-benzylphenylglycinol bearing methoxy substituents at 2, 4 and 6 positions of benzene ring in its benzyl constituent gave highest selectivity.[5]

The condensation of (*R*)-*N*-(2,4,6-trimethoxybenzyl)phenylglycinol (**1**) and benzaldehyde in heating benzene with azeotropic removal of water gave oxazolidine (**2a**) which was deduced from ^{1}H-NMR spectral analysis to indicate nearly 100% diastereomeric excess and the presence of C-2 proton at 5.23 ppm. Purification of this product could not be performed due to the cleavage of 1,3-oxazolidine ring during column chromatography on silica gel.



(a) MeCHO or PhCHO, MS 3A, CH_2Cl_2; (b) $Br(CH_2)_3CH(OCH_2)_2$, Mg, THF;
(c) CF_3COOH, CH_2Cl_2; (d) $NaBH_4$, MeOH; (e) 5% Pd-C/H_2, MeOH;
(f) MeMgBr or PhMgBr, THF; (g) $Pb(OAc)_4$, HOAc or 5% Pd-C/H_2, MeOH.

Scheme 1.

The oxazolidine (**2a**) reacted with 4,4-ethylenedioxybutylmagnesium bromide, which was prepared *in situ* from 4,4-ethylenedioxybutyl bromide and magnesium turnings, to give a separable diastereomeric mixture in a ratio of 93.8 : 6.2 as indicated by ^{1}H-NMR spectra of the crude product. Completion of the reaction

was judged by the absence of C-2 proton of oxazolidine as starting compound and the presence of proton at carbon linked to ethylenedioxy substituent at 4.64 ppm. The major product could be isolated with simple column chromatography procedure affording acetal (**3a**). Under the condition caused by trifluoroacetic acid treatment of **3a** in CH_2Cl_2, the *N*-benzyl substituent was removed to generate secondary amine and at once the acetal was hydrolyzed to give free aldehyde, resulted in a cyclization reaction to provide the diastereomerically pure bicyclo compound (**4a**) which was confirmed as 1-aza-4-oxabicyclo[4.3.0]nonane derivative by ^{1}H-NMR spectral analysis. With just obtained **4a** as a precursor, we could be delivered both the 2-phenylpiperidine and 2,6-diphenylpiperidine. Utilizing sodium borohydride, **4a** was reduced to *N*-substituted 2-phenylpiperidine (**5a**) as a single diastereomeric compound determined from ^{1}H-NMR spectra analysis, and at the same time C-2 and C-1' protons were also detected at 3.28 ppm and 3.38 ppm, respectively. Elimination of *N*-alkyl substituent was thoroughly achieved by catalytic hydrogenation at atmospheric pressure with 5% palladium on carbon to afford the (*S*)-2-phenylpiperidine (**6a**). Its optical rotation, $[\alpha]^{20}_D$ -27.0° (*c* 0.43, MeOH), was compared with literature value {lit.,[6] (*R*)-2-phenylpiperidine : $[\alpha]_D$ +35.3° (MeOH)} to prove that this compound has (*S*)-configuration. On the other hand, the precursor (**4a**) reacted with phenylmagnesium bromide to give a separable diastereomeric mixture (82.1 : 17.9) of 2,6-disubstituted piperidine derivative as evidenced by ^{1}H-NMR spectra of the crude product mixture. The C-2, C-6 and C-1' protons were also detected at 3.53 ppm, 3.88 ppm and 4.04 ppm, respectively. The stereochemistry of newly formed asymmetric center (C-6) was confirmed to be *R* configuration based on the fact that its *N*-deprotected product (**8a**) was optically inactive. Simple column chromatography procedure provided major constituent (**7a**). Further, the removal of *N*-alkyl substituent in **7a** was accomplished upon oxidative cleavage with lead tetraacetate in glacial acetic acid, affording *cis*-2,6-diphenylpiperidine (**8a**) as a *meso* compound.

Asymmetric Syntheses of (*R*)-2-Methylpiperidine and *meso*-2,6-Dimethylpiperidine

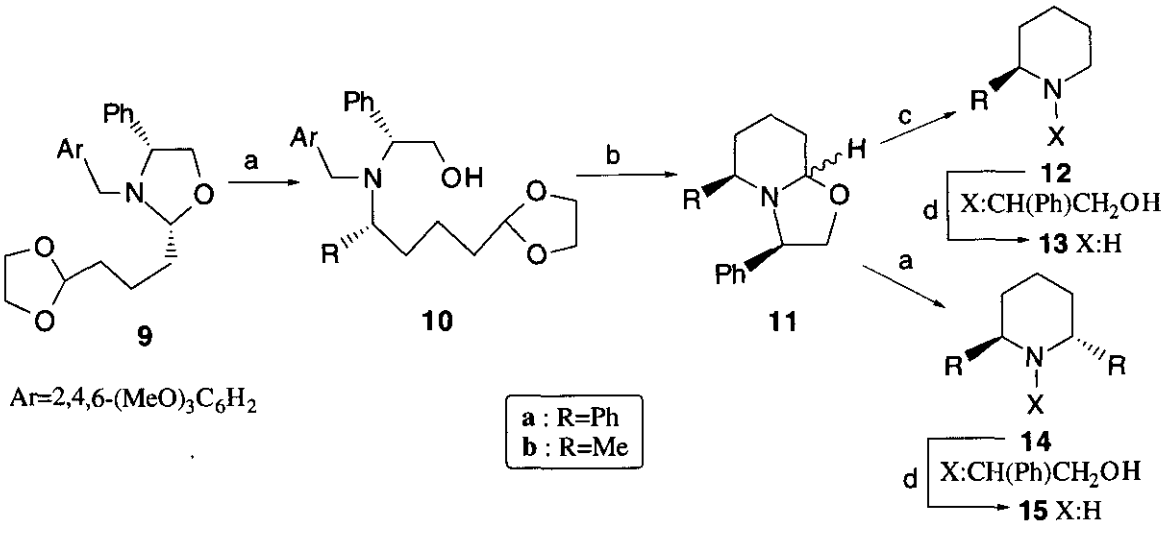
In the same manner as described for the syntheses of **6a** and **8a** by using acetaldehyde to substitute for benzaldehyde, the oxazolidine (**2b**) was obtained as a diastereomeric mixture (97 : 3) with the presence of C-2 proton at 4.41 ppm. Introducing a carbon chain by reacting **2b** with a Grignard reagent gave single diastereomer (**3b**) as determined by ^{1}H-NMR spectra of the crude product, which also showed the presence of proton at carbon linked to ethylenedioxy substituent at 4.82 ppm. Preparation of bicyclo compound from **3b** gave bicyclo compound (**4b**) as an inseparable diastereomeric mixture of C-5 epimeric cyclized product in a ratio of 41.7 : 58.3 as judged by ^{1}H-NMR spectra of the crude product, along with the presence of C-5 protons at 4.24 ppm (major component) and 4.34 ppm (minor component). Borohydride reduction of **4b** provided *N*-substituted piperidine (**5b**) as a sole compound, which later hydrogenated under atmospheric pressure of hydrogen with a catalyst of 5% palladium on carbon, and at once treated with ethanolic HCl to give the (*R*)-2-methylpiperidinium chloride (**6b**) as colorless crystals, mp 188-190°C (lit.,[7] mp 190°C). Comparison of its optical rotation, $[\alpha]^{20}_D$ +4.0° (*c* 0.31, EtOH), with literature value {lit.,[8] (*S*)-2-methylpiperidine-HCl : $[\alpha]^{15}_D$ -4.2° (*c* 6.9, EtOH)} revealed that it owns (*R*)-configuration. The same compound, HCl salt, with optical rotation $[\alpha]_D$ +2.53° (*c* 1.12, EtOH) has been reported as derived by another known method.[9] For the purpose of delivering the 2,6-disubstituted piperidine, **4b** reacted

smoothly with methylmagnesium bromide to give a single diastereomeric compound (**7b**). The facile removal of *N*-substituent followed by ethanolic HCl treatment afforded the *meso*-2,6-dimethylpiperidinium chloride (**8b**) as colorless crystals, mp 259-261°C (lit.,[10] mp 289-291°C). Its ^{1}H-NMR spectra are entirely identical with those of a commercial standard sample of optically inactive *cis*-(2,6)-dimethylpiperidine-HCl.

Asymmetric Syntheses of (*R*)-2-Phenylpiperidine and (2*R*, 6*R*)-2,6-Diphenylpiperidine

In the same way, by interchanging the sequence of functional groups of both the aldehydes and Grignard reagents as mentioned above, the syntheses of such piperidines derivatives with reverse configuration were attempted employing a starting chiral oxazolidine prepared from reaction between the bulky *N*-substituted phenylglycinol and a glutaric dialdehyde monoacetal.

The previously used chiral phenylglycinol derivative (**1**) condensed with 5,5-ethylenedioxy-1-pentanal in CH_2Cl_2 providing the oxazolidine (**9**) in a quantitative yield. The C-2 proton and the proton at carbon linked to ethylenedioxy substituent were detected at 4.37-4.40 ppm and 4.84 ppm, respectively, as indicated from ^{1}H-NMR spectral analysis. Consequently, the crude **9** was introduced with phenyl group of Grignard reagent in THF solution to give a diastereomeric mixture in a ratio of 96.8 : 3.2 evidenced by ^{1}H-NMR spectra of the crude product. With an easy chromatographically separation procedure the major **10a** was taken out.

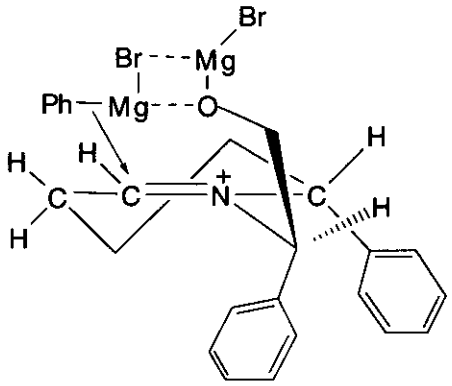


(a) MeMgBr or PhMgBr, THF; (b) CF_3COOH, CH_2Cl_2;
(c) $NaBH_4$, MeOH; (d) 5% Pd-C/H_2, MeOH or $Pb(OAc)_4$, HOAc.

Scheme 2.

Thereupon, by strong acid treatment the acetal (**10a**) underwent a cyclization to give bicyclo compound (**11a**) as an inseparable diastereomeric mixture in a ratio of 76 : 24 evidenced by ^{1}H-NMR spectra of the crude product which exhibited the presence of C-5 protons at 3.86 ppm (minor component) and 4.63 ppm

(major component). With the precursor in hand, the next reaction is hydroboration of **11a** to provide a single diastereomeric compound of *N*-substituted 2-phenylpiperidine (**12a**), followed by catalytic hydrogenation of **12a** to afford the (*R*)-2-phenylpiperidine (**13a**). Assignment of the configuration was completed by comparing its optical rotation, $[\alpha]^{20}_{D}$ +22.4° (*c* 1.4, MeOH), with literature values {lit., (*R*)-2-phenylpiperidine : $[\alpha]_{D}$ +35.3° (MeOH)[6], $[\alpha]_{D}$ +27.6° (*c* 1.0, MeOH)[11]}. Continuously, the pivotal compound (**11a**) was introduced with phenylmagnesium bromide to give a single diastereomeric product of 2,6-disubstituted piperidine derivative (**14a**) as confirmed by ^{1}H-NMR spectral analysis, which also showed the presence of C-2 and C-6 protons both at same chemical shift of 4.33 ppm. The stereochemistry of newly formed asymmetric center (C-6) was determined to be *R* configuration according to the fact that its *N*-deprotected form described later was optically active. The resulted diastereoselectivity of this reaction can be rationalized by assuming that the nucleophilic attack of phenyl substituent would occur from the *si* face of C=N bond of the intermediate as showed in Figure 1.[3]



Proposed transition state accounting for the diastereoselectivity

Figure 1.

The delivered *N*-substituted **14a** was subjected to oxidative cleavage with lead tetraacetate to afford (2*R*, 6*R*)-2,6-diphenylpiperidine (**15a**) which has *trans* configuration. The optical rotation, $[\alpha]^{20}_{D}$ +70.1° (*c* 4.63, EtOH), indicates that the absolute configuration of **15a** should be (*R*, *R*)-configuration, based on the fact that the chiral center at C-9 position of **11a** has (*R*)-configuration.

Asymmetric Syntheses of (*S*)-2-Methylpiperidine and (2*S*, 6*S*)-2,6-Dimethylpiperidine

In the same manner, oxazolidine (**9**) was introduced with methylmagnesium bromide to provide a diastereomeric mixture in a ratio of 92.8 : 7.2 as indicated by ^{1}H-NMR spectra of the crude product. The major product was easily chromatographed to give acetal (**10b**), which contiguously cyclized to **11b** as inseparable diastereomers in a ratio of 77 : 23 indicated by ^{1}H-NMR of the crude mixture. The C-5 protons were detected at 4.31-4.42 ppm (major component) and 4.49 ppm (minor component). The diastereomeric mixture (**11b**) was simply reduced to *N*-substituted 2-methylpiperidine (**12b**) as a sole diastereomeric

compound, which soon afterward underwent catalytic hydrogenation and acidified with ethanolic HCl to provide (*S*)-2-methylpiperidinium chloride (**13b**) as colorless crystals, mp 192-193°C (lit.,[12] mp 192-194°C). Its optical rotation, $[\alpha]^{20}_{D}$ -4.6° (*c* 1.08, EtOH), was compared with literature value {lit.,[8] (*S*)-2-methylpiperidine-HCl : $[\alpha]^{15}_{D}$ -4.2° (*c* 6.9, EtOH)} to determine (*S*)-configuration. This compound has also been reported as an alkaloid of (+)-α-pipecoline, HCl salt[12] : $[\alpha]_{D}$ -3.9° (*c* 1.221, EtOH). Similar to those mentioned before, introduction of methyl group to the bicylo product (**11b**) gave 2,6-dimethylpiperidine derivative as a separable diastereomeric mixture in a ratio of 38 : 62. However, the expected compound having *trans* configuration could be isolated only as a minor product (**14b**). In the meantime, the diastereoselective mechanism of this reaction is still under investigation. After reductive cleavage of *N*-substituent followed by ethanolic HCl acidification, (2*S*, 6*S*)-2,6-dimethylpiperidinium chloride (**15b**) was obtained as colorless crystals, mp 242-244°C (lit.,[10] mp 240-242°C). Its optical rotation, $[\alpha]^{20}_{D}$ -13.2° (*c* 1.02, EtOH), indicates that the absolute configuration of this compound should be (*S*, *S*)-configuration, based on the fact that the chiral center at C-9 position of **11b** has (*S*)-configuration. Its enantiomeric pair, (2*R*, 6*R*)-2,6-lupetidine, exhibits optical rotation of $[\alpha]_{D}$ +12.8° (*c* 3.06, EtOH).[13]

EXPERIMENTAL SECTION

Melting points were measured with a Yanagimoto-Micro Melting Point apparatus without correction. Infra red (IR) spectra were recorded on a 215 Hitachi Grating IR spectrophotometer and major absorption are listed in wavenumber (cm^{-1}). Proton nuclear magnetic resonance (^{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. Mass spectra and High-Resolution mass spectra 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). Thin-layer chromatography (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. The following abbreviations are used: $CHCl_3$, chloroform; CH_2Cl_2, dichloromethane; ether, diethyl ether; EtOH, ethanol; EtOAc, ethyl acetate; MeOH, methanol; THF, tetrahydrofuran.

(*R*)-*N*-(2,4,6-Trimethoxybenzyl)phenylglycinol (1). A mixture of (*R*)-phenylglycinol (7.0 g, 51.03 mmol) and 2,4,6-trimethoxybenzaldehyde (10.01 g, 51.03 mmol) in benzene (150 mL) was refluxed for 1 h using Dean Stark trap to remove eliminated water. After being cooled, the mixture was concentrated

under reduced pressure, and the residue was dissolved in MeOH (150 mL). To this solution was added portionwise sodium borohydride (4.82 g, 127.43 mmol). After stirring at rt for 40 min, the reaction mixture was quenched with water (200 mL), then the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude solid. Recrystallization from EtOAc-hexane afforded colorless needles (16.03 g, 99%), mp 135°C. $[\alpha]^{20}_D$ -36.36° (*c* 0.99, $CHCl_3$). ^{1}H-NMR δ : 1.90 (br, 2H, NH, OH), 3.66-3.82 (m, 5H, NC<u>H</u>$_2$, C<u>H</u>$_2$OH, PhC<u>H</u>N), 3.76 (s, 6H, OCH_3 x 2), 3.80 (s, 3H, OCH_3), 6.08 (s, 2H, aromatic H), 7.22-7.35 (m, 5H, aromatic H). MS *m/z* : EI, 286 (M^+ -CH_2OH); CI, 318 (M^+ +1). IR ($CHCl_3$) : 3400 (OH and NH) cm^{-1}. *Anal.* Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found : C, 68.10; H, 7.34; N, 4.37.

(2*R*, 4*R*)-*N*-(2,4,6-Trimethoxybenzyl)-2,4-diphenyl-1,3-oxazolidine (2a). To a solution of **1** (8.50 g, 26.78 mmol) in benzene (100 mL) was added benzaldehyde (3.50 g, 32.98 mmol). The reaction mixture was refluxed for 15 h while carried on azeotropic removal of water using a Dean-Stark trap, then the organic solution was evaporated under reduced pressure and dried under vacuum to give **2a** as a colorless oil (8.80 g, 81%). $[\alpha]^{20}_D$ -16.48° (*c* 1.06, $CHCl_3$). ^{1}H-NMR δ : 3.55 (s, 6H, OCH_3 x 2), 3.68 (t, 1H, *J*=6.1 Hz, NC<u>H</u>C<u>H</u>$_2$O), 3.70 (s, 3H, OCH_3), 3.71 (d, 1H, *J*=14.0 Hz, ArC<u>H</u>HN), 3.76 (d, 1H, *J*=14.0 Hz, ArCH<u>H</u>N), 4.08 (t, 1H, *J*=6.1 Hz, NCHC<u>H</u>HO), 4.13 (t, 1H, *J*=6.1 Hz, NCHCH<u>H</u>O), 5.23 (s, 1H, NCHO), 5.84 (s, 2H, aromatic H), 7.19-7.61 (m, 10H, aromatic H). MS *m/z* : EI, 405 (M^+), 328 (M^+ -Ph); CI, 406 (M^+ +1). *Anal.* Calcd for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found : C, 74.22; H, 6.79; N, 3.39.

(1*S*,1'*R*)-1-[*N*-(2,4,6-Trimethoxybenzyl)-*N*-2'-hydroxy-1'-phenylethylamino]-5,5-ethylenedioxy-1-phenylpentane (3a). To a stirred solution of 4,4-ethylenedioxybutylmagnesium bromide in THF, derived from 4,4-ethylenedioxybutyl bromide (9.51 g, 48.75 mmol) and magnesium turnings (1.21 g, 49.78 mmol) in THF (25 mL), was added portionwise a solution of the oxazolidine (**2a**) (6.59 g, 16.25 mmol) in THF (25 mL) at rt under an atmosphere of nitrogen. After stirring at 0°C for 3 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), the organic extracts were combined, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a viscous oil (8.17 g, 96.4%) as a diastereomeric mixture (93.8 : 6.2) determined from ^{1}H-NMR of the crude mixture. The crude oil was subjected to column chromatography on silica gel with hexane-EtOAc (2:1) affording **3a** as an almost colorless solid, which was recrystallized from hexane-ether to provide colorless crystals, mp 106.5°C. $[\alpha]^{20}_D$ -196.8° (*c* 1.0, $CHCl_3$). ^{1}H-NMR δ : 0.97-1.59 (m, 6H, $CH_2CH_2CH_2$), 1.85 (br s, 1H, OH), 3.82 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3 x 2), 3.74-3.91 (m, 10H, OC<u>H</u>$_2$C<u>H</u>$_2$O, NC<u>H</u>C<u>H</u>$_2$OH, ArC<u>H</u>$_2$, NC<u>H</u>Ph), 4.64 [t, 1H, *J*=4.9 Hz, C<u>H</u>$(OCH_2)_2$], 6.15 (s, 2H, aromatic H), 6.82 (d, 2H, *J*= 6.7 Hz, aromatic H), 7.03-7.10 (m, 8H, aromatic H). MS *m/z* : EI, 490 (M^+ -CH_2OH); CI, 522 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}, 1140 (C-O-C) cm^{-1}. *Anal.* Calcd for $C_{31}H_{39}NO_6$: C, 71.37; H, 7.54; N, 2.69. Found : C, 71.52; H, 7.83; N, 2.71.

(2*R*, 9*S*)-2,9-Diphenyl-1-aza-4-oxabicyclo[4.3.0]nonane (4a). Trifluoroacetic acid (9.90 g, 86.83 mmol) was added to a dilute solution of the acetal (**3a**) (5.61 g, 10.75 mmol) in CH_2Cl_2 (300 mL). After being stirred at rt for 3 d, the reaction mixture was quenched with the addition of water and potassium carbonate, respectively. The organic solution was separated, washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a viscous oil. The crude oil was subjected twice to column chromatography on silica gel with CH_2Cl_2 and hexane-ether (20 : 1), respectively, to afford **4a** as an almost colorless solid, which was recrystallized from hexane to provide colorless crystals (1.49 g, 49.6%), mp 86.8°C. $[\alpha]^{20}_D$ -168.5° (*c* 1.0, $CHCl_3$). ^{1}H-NMR δ : 1.23-1.66 (m, 4H, $OCHCH_2C\underline{H}_2C\underline{H}_2$), 1.76-1.84 (m, 1H, $OCHC\underline{H}HCH_2CH_2$), 2.09-2.14 (m, 1H, $OCHCH\underline{H}CH_2CH_2$), 3.0 (dd, 1H, *J*=3.1, 9.8 Hz, $NC\underline{H}CH_2CH_2$), 4.09 (d, 1H, *J*=5.5 Hz, $NC\underline{H}CH_2O$), 4.29-4.37 (m, 3H, $NCHC\underline{H}_2O$, $NC\underline{H}O$), 6.76 (dd, 2H, *J*=1.5, 7.6 Hz, aromatic H), 7.08-7.33 (m, 8H, aromatic H). MS *m/z* : EI, 279 (M^+), 202 (M^+ - Ph); CI, 280 (M^+ +1). *Anal.* Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found : C, 81.78; H, 7.79; N, 4.99.

(2*S*,1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2-phenylpiperidine (5a). To a stirred solution of **4a** (0.598 g, 2.14 mmol) in MeOH (10 mL) was added portionwise sodium borohydride (0.25 g, 6.61 mmol). The reaction mixture was stirred at rt for 40 min, then it was quenched with water, and extracted with CH_2Cl_2 (2 x 15 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a viscous oil. The crude oil was subjected to column chromatography on silica gel with hexane-ether (2 : 1) affording **5a** as an almost colorless solid, which was recrystallized from hexane-ether to provide colorless crystals (0.59 g, 98.0%), mp 60.9°C. $[\alpha]^{20}_D$ -165.9° (*c* 1.0, $CHCl_3$). ^{1}H-NMR δ : 1.12-1.25 (m, 1H, $NCHCH_2C\underline{H}HCH_2$), 1.53-1.75 (m, 5H, $NCHC\underline{H}_2CH\underline{H}C\underline{H}_2$), 1.91 (dt, 1H, *J*=2.1, 11.6 Hz, $NC\underline{H}HCH_2$), 3.12 (br d, 1H, *J*=11.6 Hz, $NCH\underline{H}CH_2$), 3.28 (dd, 1H, *J*=2.7, 10.7 Hz, $NC\underline{H}CH_2CH_2$), 3.38 (dd, 1H, *J*=3.4, 8.2 Hz, $NC\underline{H}CH_2OH$), 3.54 (br s, 1H, OH), 4.00 (dd, 1H, *J*=3.4, 11.3 Hz, $NCHC\underline{H}HOH$), 4.03 (dd, 1H, *J*=8.2, 11.3 Hz, $NCHCH\underline{H}OH$), 6.99-7.06 (m, 2H, aromatic H), 7.25-7.44 (m, 8H, aromatic H). MS *m/z* : EI, 250 (M^+ -CH_2OH); CI, 282 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}. *Anal.* Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found : C, 80.86; H, 8.33; N, 4.91.

(*S*)-2-Phenylpiperidine (6a). A solution of **5a** (0.349 g, 1.24 mmol) in MeOH (10 mL) was hydrogenated under 1 atm pressure of hydrogen with 5% palladium on carbon (0.1 g) at rt for 2 d. The catalyst was separated through a pad of Celite, then the reaction flask was rinsed with MeOH (2 x 15 mL). The organic solutions were combined and evaporated under reduced pressure to give a pale yellow oil, which was subjected to column chromatography on silica gel with CH_2Cl_2-MeOH-NH_3 (200 : 10 : 1) to provide **6a** as a colorless oil (0.12 g, 60.0%). $[\alpha]^{20}_D$ -27.0° (*c* 0.43, MeOH); {lit.,[6] (*R*)-2-phenylpiperidine : $[\alpha]_D$ +35.3° (MeOH)}. ^{1}H-NMR δ : 1.43-1.49 (m, 3H, C3-H_{ax}, C4-H_{ax}, C5-H_{ax}), 1.64 (br s, 1H, NH), 1.77-1.90 (m, 3H, C3-H_{eq}, C4-H_{eq}, C5-H_{eq}), 2.79 (dt, 1H, *J*=3.1, 11.6 Hz, $NC\underline{H}HCH_2$), 3.19 (br d, 1H, *J*=11.6 Hz, $NCH\underline{H}CH_2$), 3.58 (dd, 1H, *J*=2.4, 10.4 Hz, $NC\underline{H}CH_2$), 7.19-7.38 (m, 5H, aromatic H).

(2*S*, 6*R*,1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2,6-diphenylpiperidine (7a). To a stirred solution of **4a** (0.492 g, 1.76 mmol) in THF (10 mL) was added dropwise a 2 mol/L solution of phenylmagnesium bromide in THF (2.7 mL, 5.4 mmol). After being stirred at 0°C for 3 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 15 mL), then the organic extracts were combined, dried over anhydrous Na_2SO_4 and evaporated to give a pale yellow oil (0.63 g, 100%) as a diastereomeric mixture (82.1 : 17.9) determined from ^{1}H-NMR of the crude mixture. The crude oil was subjected to column chromatography on silica gel with CH_2Cl_2-hexane (1 : 1) to provide **7a** as a colorless oil. $[\alpha]^{20}_D$ -129.1° (*c* 1.47, $CHCl_3$). ^{1}H-NMR δ : 1.21-1.29 (m, 1H, $CH_2C\underline{H}HCH_2$), 1.56-1.84 (m, 5H, $C\underline{H}_2CH\underline{H}C\underline{H}_2$), 1.99 (br s, 1H, OH), 3.06 (dd, 1H, *J*=7.3, 11.0 Hz, NCHC$\underline{H}$HOH), 3.18 (t, 1H, *J*=11.0 Hz, NCHCH$\underline{H}$OH), 3.53 (t, 1H, *J*=7.0 Hz, NC$\underline{H}CH_2CH_2$), 3.88 (dd, 1H, *J*=3.4, 11.3 Hz, NC$\underline{H}CH_2CH_2$), 4.04 (dd, 1H, *J*=7.3, 11.0 Hz, NC$\underline{H}CH_2$OH), 7.08 (d, 2H, *J*=7.9 Hz, aromatic H), 7.23-7.48 (m, 11H, aromatic H), 7.58 (d, 2H, *J*=7.9 Hz, aromatic H). MS *m/z* : EI, 326 (M^+ -CH_2OH); CI, 358 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}. *Anal.* Calcd for $C_{25}H_{27}NO$: C, 83.99; H, 7.61; N, 3.92. Found : C, 83.81; H, 7.91; N, 3.74.

***cis*-2,6-Diphenylpiperidine (8a).** To a solution of **7a** (0.30 g, 0.84 mmol) in glacial acetic acid (10 mL) was added lead tetraacetate (0.56 g, 1.26 mmol). The reaction mixture was stirred at 60°C for 14 h, then it was quenched with the addition of water (20 mL) and 1 N sodium hydroxide solution (40 mL), respectively. The resulted basic mixture was extracted with ether (3 x 15 mL), the organic extracts were combined and evaporated under reduced pressure to give a pale yellow oil. The crude oil was subjected to column chromatography on silica gel with hexane-EtOAc (14 : 1) to provide **8a** as a colorless oil (0.15 g, 75.0%). $[\alpha]^{20}_D$ 0° (*c* 1.03, MeOH). ^{1}H-NMR δ : 1.52-2.01 (m, 6H, $CH_2CH_2CH_2$), 3.83 (dd, 2H, *J*=2.4, 7.9 Hz, NC$\underline{H}CH_2$ x 2), 7.20-7.38 (m, 6H, aromatic H), 7.46 (dd, 4H, *J*=1.8, 6.7 Hz, aromatic H).

(2*R*, 4*R*)-*N*-(2,4,6-Trimethoxybenzyl)-2-methyl-4-phenyl-1,3-oxazolidine (2b). To a solution of **1** (5.80 g, 18.28 mmol) in CH_2Cl_2 (50 mL) was added acetaldehyde (1.0 g, 22.7 mmol) and an equal amount of Molecular sieve 3A. The reaction mixture was stirred at rt for 15 h, then it was filtered through a pad of Celite and the reaction flask was rinsed with CH_2Cl_2 (2 x 50 mL). The combined organic solutions were evaporated under reduced pressure and dried under vacuum to give **2b** as a yellow oil (6.28 g, 100%) of a mixture (97 : 3) determined from ^{1}H-NMR of the crude mixture. $[\alpha]^{20}_D$ -77.12° (*c* 1.35, $CHCl_3$). ^{1}H-NMR δ : major component : 1.34 (d, 3H, *J*=4.9 Hz, NCHC$\underline{H}_3$), 3.54 (t, 1H, *J*=7.3 Hz, NC$\underline{H}CH_2O$), 3.66 (s, 6H, OCH_3 x 2), 3.75 (s, 2H, $ArCH_2N$), 3.77 (s, 3H, OCH_3), 3.89 (t, 1H, *J*=7.3 Hz, NCHC$\underline{H}$HO), 3.99 (t, 1H, *J*=7.3 Hz, NCHCH$\underline{H}$O), 4.43 (q, 1H, *J*=4.9 Hz, NCHO), 6.00 (s, 2H, aromatic H), 7.18-7.40 (m, 5H, aromatic H). MS *m/z* : EI, 343 (M^+), 328 (M^+ -CH_3); CI, 344 (M^+ +1). *Anal.* Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.08. Found : C, 69.91; H, 7.43; N, 3.95.

(2*R*, 1'*R*)-2-[*N*-(2,4,6-Trimethoxybenzyl)-*N*-2'-hydroxy-1'-phenylethylamino]-6,6-

ethylenedioxyhexane (3b). To a stirred solution of 4,4-ethylenedioxybutylmagnesium bromide in THF, derived from 4,4-ethylenedioxybutyl bromide (8.51 g, 43.63 mmol) and magnesium turnings (1.09 g, 44.85 mmol) in THF (25 mL), was added portionwise a solution of the oxazolidine (**2b**) (4.99 g, 14.53 mmol) in THF (25 mL) at rt under an atmosphere of nitrogen. After being stirred at 0°C for 3 d, the reaction mixture was worked up in the same manner as described for the preparation of **3a** to give a viscous oil. The crude oil was subjected to column chromatography on silica gel with hexane-ether-MeOH (100 : 100 : 5) to afford **3b** as an almost colorless oil (6.44 g, 96.4%). $[\alpha]^{20}_{D}$ -136.6° (*c* 1.14, $CHCl_3$). ^{1}H-NMR δ : 0.47 (d, 3H, *J*=6.7 Hz, NCHC<u>H</u>$_3$), 1.26-1.70 (m, 6H, $CH_2CH_2CH_2$), 2.76-2.81 (m, 1H, NC<u>H</u>CH_3), 3.35 (d, 1H, *J*=6.1 Hz, NC<u>H</u>CH_2OH), 3.82 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3 x 2), 3.72-3.98 (m, 8H, OC<u>H</u>$_2$C<u>H</u>$_2$O, NCHC<u>H</u>$_2$OH, ArC<u>H</u>$_2$), 4.82 [t, 1H, *J*=4.6 Hz, C<u>H</u>$(OCH_2)_2$)], 6.16 (s, 2H, aromatic H), 7.26-7.43 (m, 5H, aromatic H). MS *m/z* : EI, 428 (M^+ -CH_2OH); CI, 460 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}, 1140 (C-O-C) cm^{-1}. *Anal.* Calcd for $C_{26}H_{37}NO_6$: C, 67.95; H, 8.12; N, 3.05. Found : C, 67.69; H, 7.90; N, 3.02.

(2*R*, 9*R*)-9-Methyl-2-phenyl-1-aza-4-oxabicyclo[4.3.0]nonane (4b). Trifluoroacetic acid (9.30 g, 81.56 mmol) was added to a dilute solution of the acetal (**3b**) (4.62 g, 10.05 mmol) in CH_2Cl_2 (300 mL). After being stirred at rt for 3 d, the reaction mixture was worked up in the same manner as described for the preparation of **4a** to give a yellow oil. The crude oil was subjected twice to column chromatography on silica gel with CH_2Cl_2-MeOH (98 : 2) and hexane-ether (3 : 1), respectively, to afford **4b** as a pale yellow oil (1.38 g, 63.1%), which exhibited a mixture (41.7 : 58.3) of C-5 epimeric 1-aza-4-oxabicyclo[4.3.0]nonane. $[\alpha]^{20}_{D}$ -131.9° (*c* 1.15, $CHCl_3$). ^{1}H-NMR δ : major component : 0.92 (d, 3H, *J*=7.3 Hz, NCHC<u>H</u>$_3$), 1.40-1.80 (m, 5H, OCHC<u>H</u>HC<u>H</u>$_2$C<u>H</u>$_2$), 1.99-2.05 (m, 1H, OCHCH<u>H</u>CH_2CH_2), 3.10-3.19 (m, 1H, NC<u>H</u>CH_3), 3.57 (dd, 1H, *J*=6.7, 7.9 Hz, NC<u>H</u>CH_2O), 3.92 (t, 1H, *J*=7.9 Hz, NCHC<u>H</u>HO), 4.11 (t, 1H, *J*=7.6 Hz, NCHCH<u>H</u>O), 4.24 (dd, 1H, *J*=2.7, 9.4 Hz, NCHO), 7.24-7.41 (m, 5H, aromatic H); minor component : 1.09 (d, 3H, *J*=6.1 Hz, NCHC<u>H</u>$_3$), 1.16-1.80 (m, 5H, OCHC<u>H</u>HC<u>H</u>$_2$C<u>H</u>$_2$), 1.99-2.05 (m, 1H, OCHCH<u>H</u>CH_2CH_2), 2.25-2.32 (m, 1H, NC<u>H</u>CH_3), 4.01 (dd, 1H, *J*=2.4, 7.9 Hz, NCHC<u>H</u>HO), 4.34 (dd, 1H, *J*=3.1, 9.2 Hz, NCHO), 4.39 (dd, 1H, *J*=6.7, 7.9 Hz, NCHCH<u>H</u>O), 4.54 (dd, 1H, *J*=2.4, 6.7 Hz, NC<u>H</u>CH_2O), 7.24-7.41 (m, 10H, aromatic H). MS *m/z* : EI, 217 (M^+), 202 (M^+ -CH_3); CI, 218 (M^+ +1). *Anal.* Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found : C, 77.08; H, 9.03; N, 6.39.

(2*R*, 1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2-methylpiperidine (5b). To a stirred solution of **4b** (0.277 g, 1.27 mmol) in MeOH (10 mL) was added portionwise sodium borohydride (0.15 g, 3.96 mmol). The reaction mixture was stirred at rt for 40 min, then it was worked up in the same manner as described for the preparation of **5a** to give a pale yellow oil. The crude oil was subjected to column chromatography on silica gel with CH_2Cl_2-MeOH (98 : 2) to afford **5b** as an almost colorless oil (0.27 g, 96.5%). $[\alpha]^{20}_{D}$ -83.3° (*c* 1.16, $CHCl_3$). ^{1}H-NMR δ : 1.02-1.65 (m, 6H, $CH_2CH_2CH_2$), 1.70 (dt, 1H, *J*=2.4, 11.6 Hz, NC<u>H</u>HCH_2), 1.27 (d, 3H, *J*=6.1 Hz, NCHC<u>H</u>$_3$), 2.37-2.48 (m, 1H, NC<u>H</u>CH_3), 2.87 (br d, 1H, NCH<u>H</u>CH_2), 3.54 (dd, 1H, *J*=4.9, 11.0 Hz, NC<u>H</u>CH_2OH), 3.55 (br s, 1H, OH), 3.98 (t, 1H, *J*=11.0

Hz, NCHC<u>H</u>HOH), 4.31 (dd, 2H, *J*=4.9, 11.0 Hz, NCHCH<u>H</u>OH), 7.17 (dd, 2H, *J*=1.5, 7.6 Hz, aromatic H), 7.21-7.37 (m, 3H, aromatic H). MS *m/z* : EI, 188 (M^+ -CH_2OH); CI, 220 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}. HRMS Calcd for $C_{14}H_{21}NO$: 219.1624. Found : 219.1624.

(*R*)-2-Methylpiperidinium chloride (6b·HCl). A solution of **5b** (0.196 g, 0.89 mmol) in MeOH (10 mL) was hydrogenated under 1 atm pressure of hydrogen with 5% palladium on carbon (60 mg) at rt for 2 d. The catalyst was separated through a pad of Celite, then the reaction flask was rinsed with MeOH (2 x 15 mL). The organic solutions were combined, a few drops of ethanolic HCl was added, and evaporated under reduced pressure to give a colorless solid. The crude solid was recrystallized from EtOAc-hexane to afford **6b·HCl** as colorless crystals (0.10 g, 82.3%), mp 188-190°C (lit.,[7] mp 190°C). $[\alpha]^{20}_D$ +4.0° (*c* 0.31, EtOH); {lit.,[8] (*S*)-2-methylpiperidine-HCl : $[\alpha]^{15}_D$ -4.2° (*c* 6.9, EtOH)}. ^{1}H-NMR (CD_3OD) δ : 1.32 (d, 3H, *J*=6.1 Hz, NCHC<u>H</u>$_3$), 1.45-1.70 (m, 3H, C3-H_{ax}, C4-H_{ax}, C5-H_{ax}), 1.85-1.95 (m, 3H, C3-H_{eq}, C4-H_{eq}, C5-H_{eq}), 2.96 (br t, 1H, *J*=11.9 Hz, NC<u>H</u>HCH$_2$), 3.12-3.24 (m, 1H, NC<u>H</u>CH$_3$), 3.34 (br d, 1H, *J*=12.8 Hz, NCH<u>H</u>CH$_2$) . MS *m/z* : EI, 99 (M^+), 84 (M^+ -CH_3); CI, 100 (M^+ +1).

(2*R*, 6*S*, 1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2,6-dimethylpiperidine (7b). To a stirred solution of **4b** (0.37 g, 1.70 mmol) in THF (10 mL) was added dropwise a 3 mol/L solution of methylmagnesium bromide in ether (1.7 mL, 5.1 mmol). After being stirred at 0°C for 3 d, the reaction mixture was worked up in the same manner as described for the preparation of **7a** to give a pale yellow oil. The crude oil was subjected to column chromatography on silica gel with CH_2Cl_2-MeOH (98 : 2) to provide **7b** as a colorless oil (0.324 g, 81.6%). $[\alpha]^{20}_D$ -24.9° (*c* 1.29, $CHCl_3$). ^{1}H-NMR δ : 1.08 (t, 3H, *J*=6.7 Hz, NCHC<u>H</u>$_3$), 1.16 (t, 3H, *J*=6.7 Hz, NCHC<u>H</u>$_3$), 1.21-1.41 (m, 4H, C<u>H</u>HC<u>H</u>$_2$C<u>H</u>H), 1.59-1.68 (m, 2H, CH<u>H</u>CH$_2$CH<u>H</u>), 2.86-2.92 (m, 1H, NC<u>H</u>CH$_3$), 2.99-3.07 (m, 1H, NC<u>H</u>CH$_3$), 3.78 (dd, 1H, *J*=6.1, 9.8 Hz, NCHC<u>H</u>HOH), 3.87 (dd, 1H, *J*=8.5, 9.8 Hz, NCHCH<u>H</u>OH), 4.23 (dd, 1H, *J*=6.1, 8.5 Hz, NC<u>H</u>CH$_2$OH), 7.24-7.37 (m, 5H, aromatic H). MS *m/z* : EI, 202 (M^+ -CH_2OH); CI, 234 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}. HRMS Calcd for $C_{15}H_{23}NO$: 233.1781. Found : 233.1776.

***cis*-2,6-Dimethylpiperidinium chloride (8b·HCl).** A solution of **7b** (0.23 g, 0.99 mmol) in MeOH (10 mL) was hydrogenated under 1 atm pressure of hydrogen with 5% palladium on carbon (0.1 g) at rt for 2 d. Then, it was worked up in the same manner as described for the preparation of **6b** to give a colorless solid. The crude solid was recrystallized twice from MeOH-ether and CH_2Cl_2-hexane, respectively, to provide **8b·HCl** as colorless crystals (0.11 g, 75.0%), mp 259-261°C (lit.,[10] mp 289-291°C). $[\alpha]^{20}_D$ 0° (*c* 1.1, EtOH). ^{1}H-NMR (CD_3OD) δ : 1.33 (d, 6H, *J*=6.7 Hz, NCHC<u>H</u>$_3$ x 2), 1.37-1.67 (m, 3H, C3-H_{ax}, C4-H_{ax}, C5-H_{ax}), 1.83-1.93 (m, 3H, C3-H_{eq}, C4-H_{eq}, C5-H_{eq}), 3.10-3.24 (m, 2H, NC<u>H</u>CH$_3$ x 2). MS *m/z* : *EI, 113* (M^+), *98* (M^+ -CH_3); *CI, 114* (M^+ +1).

(2*R*, 4*R*)-*N*-(2,4,6-Trimethoxybenzyl)-2-(4,4-ethylenedioxybutyl)-4-phenyl-1,3-oxazolidine (9). To a solution of **1** (11.9 g, 37.5 mmol) in CH_2Cl_2 (100 mL) was added 5,5-ethylenedioxypentanal (6.5 g, 45.08 mmol) and an equal amount of dried Na_2SO_4. The reaction mixture

was stirred at rt for 2d, then it was worked up in the same manner as described for the preparation of **2b** to give **9** as a colorless oil (16.63 g, 100%). $[\alpha]^{20}_{D}$ -47.6° (*c* 1.84, $CHCl_3$). ^{1}H-NMR δ : 1.53-1.73 (m, 6H, $CH_2CH_2CH_2$), 3.51 (t, 1H, *J*=7.3 Hz, NC<u>H</u>CH_2O), 3.67 (s, 6H, OCH_3 x 2), 3.75 (s, 2H, $ArCH_2N$), 3.78 (s, 3H, OCH_3), 3.81-3.98 (m, 4H, OCH_2CH_2O), 3.91 (t, 1H, *J*=7.3 Hz, NCHC<u>H</u>HO), 4.01 (t, 1H, *J*=7.3 Hz, NCHCH<u>H</u>O), 4.37-4.40 (m, 1H, NCHO), 4.84 [t, 1H, *J*=4.6 Hz, C<u>H</u>$(OCH_2)_2$], 6.0 (s, 2H, aromatic H), 7.16-7.24 (m, 3H, aromatic H), 7.38 (dd, 2H, *J*=1.5, 8.2 Hz, aromatic H). MS *m/z* : EI, 443 (M^+), 328 [M^+ -$(CH_2)_3CH(OCH_2)_2$]; CI, 444 (M^+ +1). IR ($CHCl_3$) : 1140 (C-O-C) cm^{-1}. *Anal.* Calcd for $C_{25}H_{33}NO_6$: C, 67.70; H, 7.50; N, 3.16. Found : C, 67.49; H, 7.53; N, 3.13.

(1*R*, 1'*R*)-2-[*N*-(2,4,6-Trimethoxybenzyl)-*N*-2'-hydroxy-1'-phenylethylamino]-5,5-ethylenedioxy-1-phenylpentane (10a). To a stirred solution of **9** (5.46 g, 12.31 mmol) in THF (25 mL) was added dropwise a 2 mol/L solution of phenylmagnesium bromide in THF (18.5 mL, 37.0 mmol). After being stirred at 0°C for 3 d, the reaction mixture was worked up in the same manner as described for the preparation of **7a** to give a pale yellow oil (6.0 g, 93.4%) as a diastereomeric mixture (96.8 : 3.2) determined from ^{1}H-NMR of the crude mixture. The crude mixture was subjected to column chromatography on silica gel with EtOAc-hexane-MeOH (100: 100 : 2) providing **10a** as a colorless oil. $[\alpha]^{20}_{D}$ -118.3° (*c* 1.08, $CHCl_3$). ^{1}H-NMR δ : 0.79-1.86 (m, 6H, $CH_2CH_2CH_2$), 3.28 (dt, 1H, *J*=4.3, 11.0 Hz, NCHC<u>H</u>HOH), 3.60 (d, 1H, *J*=11.0 Hz, OH), 3.69 (s, 6H, OCH_3 x 2), 3.81 (s, 3H, OCH_3), 3.71-3.88 (m, 7H, OC<u>H</u>$_2$C<u>H</u>$_2$O, ArC<u>H</u>HN, NCHCH<u>H</u>OH, NC<u>H</u>Ph), 4.02 (t, 1H, *J*=10.7 Hz, NC<u>H</u>CH_2OH), 4.07 (d, 1H, *J*=12.2 Hz, ArCH<u>H</u>N), 4.58 [t, 1H, *J*=4.6 Hz, C<u>H</u>$(OCH_2)_2$], 6.12 (s, 2H, aromatic H), 7.18-7.38 (m, 8H, aromatic H), 7.44 (dd, 2H, *J*=1.5, 7.6 Hz, aromatic H). MS *m/z* : EI, 490 (M^+ - CH_2OH); CI, 522 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}, 1140 (C-O-C) cm^{-1}. *Anal.* Calcd for $C_{31}H_{39}NO_6$: C, 71.37; H, 7.54; N, 2.69. Found : C, 71.07; H, 7.56; N, 2.75.

(2*R*, 9*R*)-2,9-Diphenyl-1-aza-4-oxabicyclo[4.3.0]nonane (11a). Trifluoroacetic acid (7.20 g, 63.15 mmol) was added to a dilute solution of **10a** (4.07 g, 7.80 mmol) in CH_2Cl_2 (300 mL). After being stirred at rt for 3 d, the reaction mixture was worked up in the same manner as described for the preparation of **4a** to give a yellow oil. The crude oil was subjected to column chromatography on silica gel with CH_2Cl_2 to afford **11a** as a pale yellow oil (1.25 g, 57.3%), which exhibited a mixture (76 : 24) of C-5 epimeric 1-aza-4-oxabicyclo[4.3.0]nonane. $[\alpha]^{20}_{D}$ -21.0° (*c* 0.98, $CHCl_3$). ^{1}H-NMR δ : major component : 1.48-1.99 (m, 5H, OCHC<u>H</u>HC<u>H</u>$_2$C<u>H</u>$_2$), 2.13 (br d, 1H, *J*=12.8 Hz, OCHCH<u>H</u>CH_2CH_2), 3.63 (dd, 1H, *J*=2.4, 11.0 Hz, NC<u>H</u>CH_2CH_2), 3.85 (dd, 1H, *J*=3.1, 7.9 Hz, NCHC<u>H</u>HO), 4.21 (dd, 1H, *J*=3.1, 7.9 Hz, NC<u>H</u>CH_2O), 4.38 (t, 1H, *J*=7.9 Hz, NCHCH<u>H</u>O), 4.63 (br t, 1H, *J*=2.7 Hz, NCHO), 6.79-7.30 (m, 8H, aromatic H), 7.45 (dd, 2H, *J*=1.2, 6.7 Hz, aromatic H); minor component : 1.48-1.99 (m, 5H, OCHC<u>H</u>HC<u>H</u>$_2$C<u>H</u>$_2$), 2.13 (br d, 1H, *J*=12.8 Hz, OCHCH<u>H</u>CH_2CH_2), 3.30 (dd, 1H, *J*=3.1, 10.4 Hz, NC<u>H</u>CH_2CH_2), 3.48 (dd, 1H, *J*=6.1, 8.6 Hz, NCHC<u>H</u>HO), 3.75 (dd, 1H, *J*=6.1, 8.6 Hz, NC<u>H</u>CH_2O), 3.86 (t, 1H, *J*=4.9 Hz, NCHO), 4.14 (t, 1H, *J*=8.6 Hz, NCHCH<u>H</u>O), 6.79-7.30 (m, 10, aromatic H). MS *m/z* : EI, 279 (M^+), 202 (M^+ -Ph); CI, 280 (M^+ +1). *Anal.* Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found : C, 81.64; H, 7.63; N, 4.93.

(2*R*, 1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2-phenylpiperidine (12a). To a stirred solution of **11a** (0.47 g, 1.68 mmol) in MeOH (10 mL) was added portionwise sodium borohydride (0.20 g, 5.29 mmol). The reaction mixture was stirred at rt for 40 min, then it was worked up in the same manner as described for the preparation of **5a** to give a viscous oil. The crude oil was subjected to column chromatography on silica gel with hexane-EtOAc (3 : 1) affording an almost colorless solid, which was recrystallized from hexane to provide **12a** as colorless crystals (0.44 g, 92.6%), mp 78.0°C. $[\alpha]^{20}_{D}$ -30.3° (*c* 1.08, $CHCl_3$). ^{1}H-NMR δ : 1.30-1.80 (m, 7H, $CH_2CH_2CH_2$, OH), 2.51 (dt, 1H, *J*=2.7, 11.3 Hz, NCHHCH$_2$), 2.89-2.96 (m, 1H, NCHHCH$_2$), 3.76 (dd, 1H, *J*=3.1, 9.8 Hz, NCHCH$_2$CH$_2$), 3.83 (t, 1H, *J*=6.4 Hz, NCHCHHOH), 3.98-4.09 (m, 2H, NCHCHHOH), 7.19-7.42 (m, 10H, aromatic H). MS *m/z* : EI, 250 (M^+ -CH_2OH); CI, 282 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}. *Anal.* Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found : C, 80.90; H, 8.37; N, 4.95.

(*R*)-2-Phenylpiperidine (13a). A solution of **12a** (0.32 g, 1.14 mmol) in MeOH (10 mL) was hydrogenated under 1 atm pressure of hydrogen with 5% palladium on carbon (0.1 g) at rt for 2 d. Then, it was worked up in the same manner as described for the preparation of **6a** to give a pale yellow oil. The crude oil was subjected to column chromatography on silica gel with hexane-EtOAc-MeOH (100 : 100 : 6) to provide **13a** as a colorless oil (0.17 g, 92.6%). $[\alpha]^{20}_{D}$ +22.4° (*c* 1.4, MeOH); {lit.,[6] (*R*)-2-phenylpiperidine : $[\alpha]_D$ +35.3° (MeOH)}. ^{1}H-NMR δ : 1.42-1.90 (m, 6H, $CH_2CH_2CH_2$), 2.80 (br t, 1H, *J*=7.3 Hz, NCHHCH$_2$), 3.19 (br d, 1H, *J*=8.9 Hz, NCHHCH$_2$), 3.58 (dd, 1H, *J*=2.8, 10.7 Hz, NCHCH$_2$), 7.19-7.38 (m, 5H, aromatic H). MS *m/z* : EI, 161(M^+), 84 (M^+ -Ph); CI, 162 (M^+ +1).

(2*R*, 6*R*, 1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2,6-diphenylpiperidine (14a). To a stirred solution of **11a** (0.506 g, 1.81 mmol) in THF (10 mL) was added dropwise a 2 mol/L solution of phenylmagnesium bromide in THF (2.8 mL, 5.6 mmol). After being stirred at 0°C for 3 d, the reaction mixture was worked up in the same manner as described for the preparation of **7a** to give a pale yellow oil. The crude oil was subjected to column chromatography on silica gel with CH_2Cl_2-hexane (1 : 1) to provide **14a** as a colorless oil (0.59 g, 91.0%). $[\alpha]^{20}_{D}$ -21.2° (*c* 0.34, $CHCl_3$). ^{1}H-NMR δ : 1.45-1.55 (m, 2H, $CH_2CH_2CH_2$), 1.61-1.69 (m, 2H, CHHCH$_2$CHH), 1.80-1.92 (m, 2H, CHHCH$_2$CHH), 1.93 (s, 1H, OH), 3.31 (dd, 1H, *J*=6.4, 10.7 Hz, NCHCHHOH), 3.77 (dd, 1H, *J*=8.2, 10.7 Hz, NCHCHHOH), 3.95 (dd, 1H, *J*=6.4, 8.2 Hz, NCHCH$_2$OH), 4.33 (dd, 2H, *J*=4.0, 7.0 Hz, NCHCH$_2$CH$_2$ x 2), 7.24-7.43 (m, 11H, aromatic H), 7.53 (d, 4H, *J*=7.3 Hz, aromatic H). MS *m/z* : EI, 326 (M^+ -CH_2OH); CI, 358 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}. *Anal.* Calcd for $C_{25}H_{27}NO$: C, 83.99; H, 7.61; N, 3.92. Found : C, 83.69; H, 7.83; N, 3.74.

(2*R*, 6*R*)-2,6-Diphenylpiperidine (15a). To a solution of **14a** (0.45 g, 1.26 mmol) in glacial acetic acid (10 mL) was added lead tetraacetate (0.84 g, 1.89 mmol). The reaction mixture was stirred at 60°C for 14 h, then it was worked up in the same manner as described for the preparation of **8a** to give a pale yellow oil. The crude oil was subjected to column chromatography on silica gel with hexane-EtOAc (14 : 1) to

provide **15a** as a colorless oil (0.21 g, 70.5%). $[\alpha]^{20}_D$ +70.1° (*c* 4.63, EtOH). ^{1}H-NMR δ : 1.65-1.74 (m, 2H, $CH_2C\underline{H}_2CH_2$), 1.86-2.06 (m, 4H, $C\underline{H}_2CH_2C\underline{H}_2$), 2.10 (br s, 1H, NH), 4.12 (dd, 2H, *J*=4.9, 6.1 Hz, $NC\underline{H}CH_2$ x 2), 7.21-7.43 (m, 10H, aromatic H).

(2*S*, 1'*R*)-2-[*N*-(2,4,6-Trimethoxybenzyl)-*N*-2'-hydroxy-1'-phenylethylamino]-6,6-ethylenedioxyhexane (10b). To a stirred solution of **9** (8.01 g, 18.06 mmol) in THF (25 mL) was added dropwise a 3 mol/L solution of methylmagnesium bromide in ether (18.1 mL, 54.3 mmol). After being stirred at 0°C for 3 d, the reaction mixture was worked up in the same manner as described for the preparation of **7a** to give a pale yellow oil (7.45 g, 89.7%) as a diastereomeric mixture (92.8 : 7.2) determined from ^{1}H-NMR of the crude mixture. The crude oil was subjected to column chromatography on silica gel with EtOAc-hexane-MeOH (20 : 30 : 4) to provide **10b** as a colorless oil. $[\alpha]^{20}_D$ -146.6° (*c* 1.45, $CHCl_3$). ^{1}H-NMR δ : 0.82-1.01 (m, 3H, $NCHC\underline{H}HC\underline{H}_2CH_2$), 1.12 (d, 3H, *J*=6.7 Hz, $NCHC\underline{H}_3$), 1.16-1.33 (m, 3H, $NCHCH\underline{H}CH_2C\underline{H}_2$), 2.74-2.79 (m, 1H, $NC\underline{H}CH_3$), 3.35 (dd, 1H, *J*=3.4, 8.8 Hz, $NC\underline{H}CH_2OH$), 3.81 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3 x 2), 3.74-3.97 (m, 8H, $OC\underline{H}_2C\underline{H}_2O$, $NCHC\underline{H}_2OH$, $ArC\underline{H}_2N$), 4.61 [t, 1H, *J*=4.9 Hz, $C\underline{H}(OCH_2)_2$], 6.15 (s, 2H, aromatic H), 7.25-7.37 (m, 3H, aromatic H), 7.40 (dd, 2H, *J*=1.8, 7.9 Hz, aromatic H). MS *m/z* : EI, 428 (M^+ -CH_2OH); CI, 460 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}, 1140 (C-O-C) cm^{-1}. *Anal.* Calcd for $C_{26}H_{37}NO_6$: C, 67.95; H, 8.12; N, 3.05. Found : C, 67.81; H, 8.24; N, 3.12.

(2*R*, 9*S*)-9-Methyl-2-phenyl-1-aza-4-oxabicyclo[4.3.0]nonane (11b). Trifluoroacetic acid (10.8 g, 94.72 mmol) was added to a dilute solution of **10b** (5.40 g, 11.75 mmol) in CH_2Cl_2 (300 mL). After being stirred at rt for 3 d, the reaction mixture was worked up in the same manner as described for the preparation of **4a** to give a yellow oil. The crude oil was subjected to column chromatography on silica gel with CH_2Cl_2 to afford **11b** as a pale yellow oil (1.33 g, 52.1%), which exhibited a mixture (77 : 23) of C-5 epimeric 1-aza-4-oxabicyclo[4.3.0]nonane. $[\alpha]^{20}_D$ -47.1° (*c* 1.45, $CHCl_3$). ^{1}H-NMR δ : major component : 0.66 (d, 3H, *J*=6.1 Hz, $NCHC\underline{H}_3$), 1.18-1.88 (m, 5H, $OCHC\underline{H}HC\underline{H}_2C\underline{H}_2$), 1.98-2.08 (m, 1H, $OCHCH\underline{H}CH_2CH_2$), 2.36-2.45 (m, 1H, $NC\underline{H}CH_3$), 3.60-3.67 (m, 2H, $NCHC\underline{H}_2O$), 3.74-3.78 (m, 1H, $NC\underline{H}CH_2O$), 4.31-4.42 (m, 1H, NCHO), 7.18-7.43 (m, 5H, aromatic H); minor component : 1.15 (d, 3H, *J*=5.5 Hz, $NCHC\underline{H}_3$), 1.18-1.88 (m, 5H, $OCHC\underline{H}HC\underline{H}_2C\underline{H}_2$), 1.98-2.08 (m, 1H, $OCHCH\underline{H}CH_2CH_2$), 2.59-2.68 (m, 1H, $NC\underline{H}CH_3$), 3.70-3.72 (m, 1H, $NC\underline{H}CH_2O$), 4.10-4.20 (m, 2H, $NCHC\underline{H}_2O$), 4.49 (br s, 1H, NCHO), 7.18-7.43 (m, 5H, aromatic H). MS *m/z* : EI, 217 (M^+), 202 (M^+ - CH_3); CI, 218 (M^+ +1). *Anal.* Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found : C, 77.10; H, 8.92; N, 6.31.

(2*S*, 1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2-methylpiperidine (12b). To a stirred solution of **11b** (0.31 g, 1.43 mmol) in MeOH (10 mL) was added portionwise sodium borohydride (0.17 g, 4.49 mmol). The reaction mixture was stirred at rt for 40 min, then it was worked up in the same manner as described for the preparation of **5a** to give a pale yellow oil. The crude oil was subjected to column chromatography on silica gel with EtOAc to provide **12b** as a colorless oil (0.28 g, 89.3%). $[\alpha]^{20}_D$

+0.91° (*c* 1.89, $CHCl_3$). ^{1}H-NMR δ : 0.99 (d, 3H, *J*=6.7 Hz, NCHC<u>H</u>$_3$), 1.41-1.55 (m, 5H, NCHC<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>H), 1.72-1.80 (m, 1H, NCHCH$_2$CH$_2$CH<u>H</u>), 2.46-2.61 (m, 2H, NC<u>H</u>$_2$CH$_2$), 2.74 (br s, 1H, OH), 3.10-3.21 (m, 1H, NC<u>H</u>CH$_3$), 3.66-3.82 (m, 3H, NC<u>H</u>C<u>H</u>$_2$OH), 7.22-7.36 (m, 5H, aromatic H). MS *m/z* : EI, 188 (M^+ -CH_2OH); CI, 220 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}. *Anal.* Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found : C, 76.56; H, 9.77; N, 6.29.

(*S*)-2-Methylpiperidinium chloride (13b·HCl). A solution of **12b** (0.168 g, 0.76 mmol) in MeOH (10 mL) was hydrogenated under 1 atm pressure of hydrogen with 5% palladium on carbon (60 mg) at rt for 2 d. Then, it was worked up in the same manner as described for the preparation of **6b** to give a colorless solid. The crude solid was recrystallized from EtOAc-hexane to provide **13b·HCl** as colorless crystals (92.6 mg, 89.3%), mp 192-193°C (lit.,[12] mp 192-194°C). $[\alpha]^{20}_D$ -4.6° (*c* 1.08, EtOH); {lit.,[8] (*S*)-2-methylpiperidine-HCl : $[\alpha]^{15}_D$ -4.2° (*c* 6.9, EtOH)}. ^{1}H-NMR δ : 1.42-1.54 (m, 1H, NCHCH$_2$C<u>H</u>HCH$_2$), 1.51 (d, 3H, *J*=6.1 Hz, NCHC<u>H</u>$_3$), 1.66-2.05 (m, 5H, NCHC<u>H</u>$_2$CH<u>H</u>C<u>H</u>$_2$), 2.84 (br q, 1H, *J*=12.2 Hz, NC<u>H</u>HCH$_2$), 3.02-3.20 (m, 1H, NC<u>H</u>CH$_3$), 3.43 (br d, 1H, *J*=12.2 Hz, NCH<u>H</u>CH$_2$), 9.21 (br s, 1H, N$^+$<u>H</u>H), 9.62 (br s, 1H, N$^+$H<u>H</u>). MS *m/z* : EI, 99 (M^+), 84 (M^+ -CH_3); CI, 100 (M^+ +1).

(2*S*, 6*S*, 1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2,6-dimethylpiperidine (14b). To a stirred solution of **11b** (0.546 g, 2.51 mmol) in THF (10 mL) was added dropwise a 3 mol/L solution of methylmagnesium bromide in ether (2.5 mL, 7.5 mmol). After being stirred at 0°C for 3 d, the reaction mixture was worked up in the same manner as described for the preparation of **7a** to give a pale yellow oil (0.57 g, 97.4%) as a diastereomeric mixture (38 : 62) determined from ^{1}H-NMR of the crude mixture. The crude mixture was subjected to column chromatography on silica gel with hexane-EtOAc (3 : 1) to provide the minor product (**14b**) as a colorless oil. $[\alpha]^{20}_D$ -26.1° (*c* 2.05, $CHCl_3$). ^{1}H-NMR δ : 1.02-1.08 (m, 4H, C<u>H</u>HC<u>H</u>$_2$C<u>H</u>H), 1.23 (d, 6H, *J*=6.7 Hz, NCHC<u>H</u>$_3$ x 2), 1.39-1.48 (m, 2H, CH<u>H</u>CH$_2$CH<u>H</u>), 3.29-3.38 (m, 2H, NC<u>H</u>CH$_3$ x 2), 3.53 (dd, 1H, *J*=5.5, 9.8 Hz, NCHC<u>H</u>HOH), 3.86 (t, 1H, *J*=9.8 Hz, NCHCH<u>H</u>OH), 4.20 (dd, 1H, *J*=5.5, 9.8 Hz, NC<u>H</u>CH$_2$OH), 7.26-7.37 (m, 5H, aromatic H). MS *m/z* : EI, 202 (M^+ -CH_2OH); CI, 234 (M^+ +1). IR ($CHCl_3$) : 3400 (OH) cm^{-1}. HRMS Calcd for $C_{15}H_{23}NO$: 233.1781. Found : 233.1779.

(2*S*, 6*S*)-2,6-Dimethylpiperidinium chloride (15b·HCl). A solution of **14b** (0.132 g, 0.56 mmol) in MeOH (10 mL) was hydrogenated under 1 atm pressure of hydrogen with 5% palladium on carbon (50 mg) at rt for 2 d. Then, it was worked up in the same manner as described for the preparation of **6b** to give a colorless solid. The crude solid was recrystallized from EtOAc-hexane to provide **15b·HCl** as colorless crystals (69.5 mg, 82.1%), mp 242-244°C (lit.,[10] mp 240-242°C). $[\alpha]^{20}_D$ -13.2° (*c* 1.02, EtOH). ^{1}H-NMR δ : 1.48 (d, 6H, *J*=6.7 Hz, NCHC<u>H</u>$_3$ x 2), 1.55-1.73 (m, 4H, C<u>H</u>HC<u>H</u>$_2$C<u>H</u>H), 1.95-2.00 (m, 2H, CH<u>H</u>CH$_2$CH<u>H</u>), 3.54 (m, 2H, NC<u>H</u>CH$_3$ x 2), 9.39 (br s, 2H, N$^+$H$_2$). MS *m/z* : EI, 113 (M^+), 98 (M^+ -CH_3); CI, 114 (M^+ +1).

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