

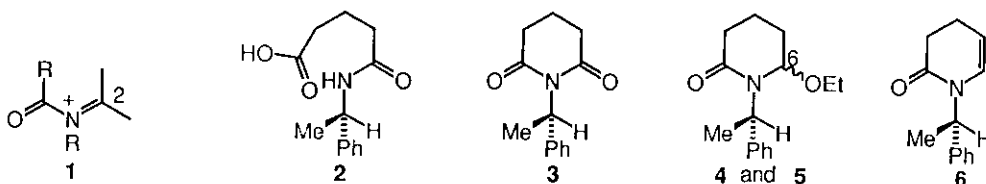
ASYMMETRIC SYNTHESIS OF (+)- AND (-)-CONIINES AND (-)-SEDAMINE
BY DIASTEREOSELECTIVE ALKYLATION REACTION OF ETHOXYPIPERIDINONE

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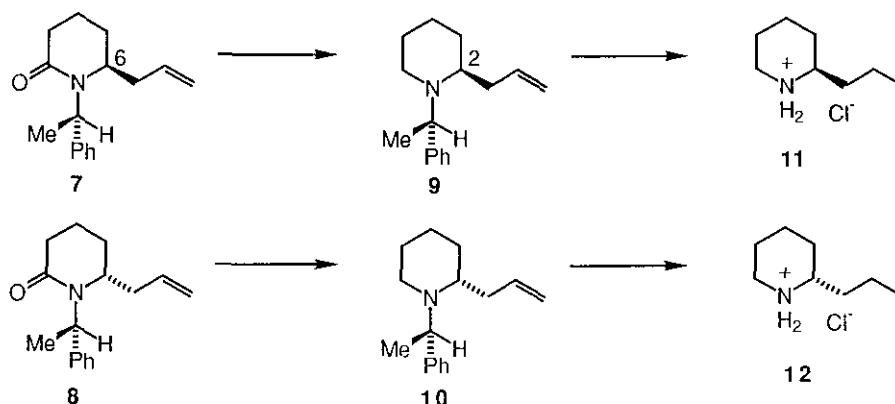
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Abstract—Diastereoselective alkylation reaction of the chiral 6-ethoxy-piperidinones (**4**) and (**5**) has been developed and successfully applied to the asymmetric synthesis of piperidine alkaloids, (+)- and (-)-coniines (**11**) and (**12**), (-)-sedamine (**21**), and (-)-allosedamine (**22**).

N-Acyliminium ions have emerged as an important class of electrophiles which react with appropriate nucleophiles to participate synthetically useful carbon-carbon bond forming reactions.¹ Expecting that the chiral protective group on the nitrogen in the N-acyliminium ion (**1**) would direct the approach of a nucleophile preferentially to one of two possible paths, one can achieve the stereoselective carbon-carbon bond formation at the C₂-position of piperidine skeleton to occur yielding a chiral 2-substituted piperidine after removing the chiral protective group. In this context, there have been two approaches, one is the route via N-acylpiperidine with a chiral acyl group and the other is that via N-alkyllactam with a chiral alkyl group. The former route has been recently studied by Wanner group^{2,3c} who have successfully achieved the application to the asymmetric synthesis of piperidine alkaloid (+)-sedamine.^{3c} Thus, we investigated the second approach which constitutes of the addition reaction of carbon atom-centered nucleophiles to the N-acyliminium ion derived from the ethoxylactam substituted with N-chiral alkyl group. (S)-(-)-1-Phenylethyl-

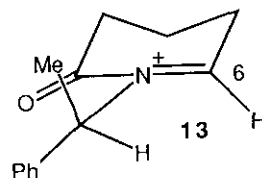


amine and either allyltrimethylsilane or silyl enol ether of acetophenone were employed as a chiral protective group and also as a nucleophile respectively. Heating glutaric anhydride with (S)-(-)-1-phenylethylamine in refluxing toluene gave the carboxylic acid (2) which was treated with acetyl chloride to afford the desired chiral imide (3) in 93% yield from the starting glutaric anhydride. According to the known procedure developed by Speckamp group,⁴ the imide (3) was readily reduced with sodium borohydride in ethanol containing 1 equiv. amount of hydrogen chloride and then subjected to ethanolysis of the resulting hydroxylactams in ethanol containing an excessive amount of hydrogen chloride to afford the ethoxylactams (4) and (5). Careful separation of the reduced product by medium-pressure column chromatography (MCC) gave two diastereomers (4) (61%) and (5) (20%) with a small amount of the enamide (6) (5%). These two ethoxylactams (4) and (5) were characterized by their spectral data though their absolute configurations at the 6-position were not established. Both the isolated ethoxylactams (4) and (5) were respectively treated with allyltrimethylsilane in the presence of titanium (IV) chloride in anhydrous dichloromethane at the temperature ranging from -30°C to room temperature to give 69-93% yield of a mixture of two allylated products (7) and (8) in the identical ratio (83:17) in addition to 1-3% yield of the undesired enamide (6). Two products (7) and (8) were inseparable by MCC though their ratio (83:17) was readily calculated by the nmr spectrum of the mixture. Under the same reaction conditions, a mixture of two lactams (4) and (5) gave the identical mixture of two products (7) and (8) in the same chemical yields. Of some Lewis acids tested (titanium (IV) chloride, stannic chloride, and boron trifluoride-etherate), titanium (IV) chloride was the reagent of choice in view of the optimum balance between chemical yield and stereoselectivity. A mixture of two lactams (7) and (8) was subjected to reduction with lithium aluminum hydride to give a mixture of two diastereomeric amine (9) and (10) which was readily separated by MCC. The ratio (83:17) of two amines (9) and (10) showed that the parent two ethoxylactams (4) and (5) were found to display moderate stereoselectivity (4.9:1) in their allylation reactions. Though absolute configurations of two products (9) and (10) were not determined yet at this stage, indirect deduction was made possible from their unambiguous chemical conversions to the respective known conines.⁵ Conventional catalytic hydrogenation of the allyl group in the amine (9) over 10% palladium on carbon in ethanol containing hydrochloric acid at 4 atm resulted in the formation of the

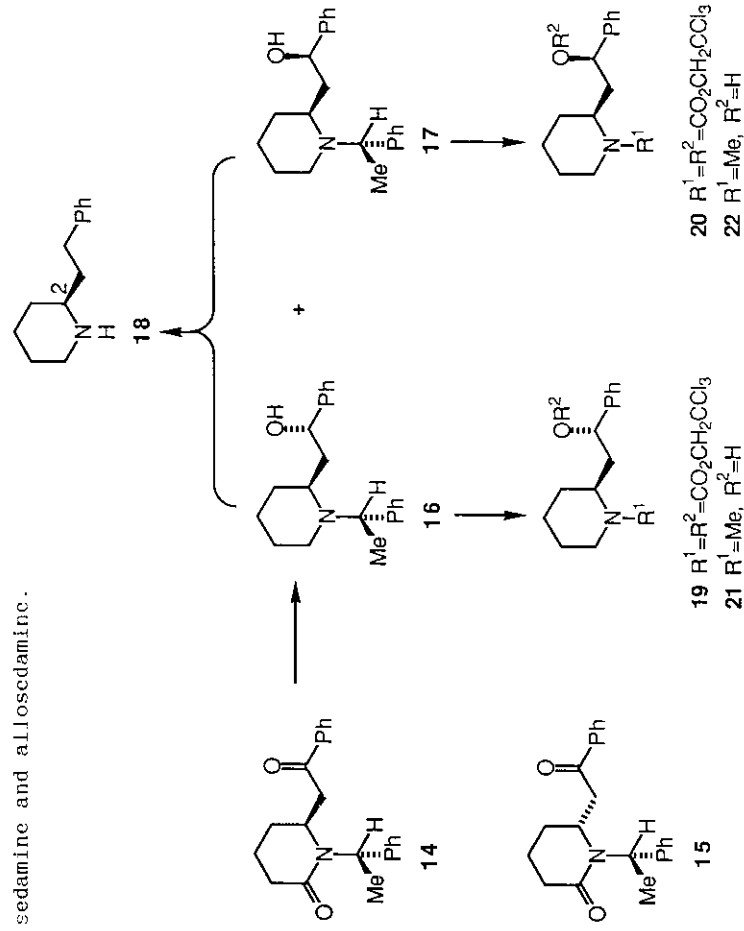


dealkylated (-)-amine hydrochloride (**11**) in 81% yield as a result of concomitant hydrogenolysis. The hydrochloride of the (-)-amine (**11**) showed the identical spectral data with those of (-)-coniine hydrochloride.^{5c,6} Optical purity of this product (**11**) was determined not only by comparisons of its optical rotation with the reported data^{5c} but also by the analysis of nmr spectra of the corresponding amide, prepared by the treatment with (R)-(+)- α -methoxy- α -(trifluoromethyl)phenylacetic acid ((+)-MTPA).⁷ Thus, absolute configurations at the 6-position of the lactam (**7**) and the 2-position of the amine (**9**) were indirectly established as (S). Similarly, catalytic hydrogenation and debenzylation reactions of the minor amine (**10**) proceeded smoothly to give the enantiomeric (+)-amine hydrochloride (**12**) in 65% yield, which showed the identical spectral data with those reported^{5c} on (+)-coniine hydrochloride and its optical purity was also established by the similar procedure to those of the (-)-amine hydrochloride (**11**) as described above.

This allylation reaction of the ethoxylactams (**4**) and (**5**) with stereoselectivity of 83:17 represents an example of 1,3-asymmetric induction and can be explained as follows. In the intermediary acyliminium ion, the conformation (**13**) would be most preferable since the alternate conformers would be destabilized by $\Delta^{1,3}$ -strain between methyl or phenyl group and hydrogen at the 6-position. Thus, a nucleophile would attack from the less hindered upper face which is occupied only by small methyl group. During the course of our synthesis, Polniaszek group⁸ have reported the stereoselective allylation reaction of analogous chiral N-acyliminium ions with the intermediacy of the identical chiral acyliminium ion (**13**).



Next, the same methodology was applied to the asymmetric synthesis of another piperidine alkaloid, sedamine, though diastereoselectivity was low in the alkylation reaction of the ethoxylactam (**4**). Treatment of the ethoxylactam (**4**) with silyl enol ether of acetophenone in the presence of titanium (IV) chloride from -20°C to room temperature gave three products, (**14**), (**15**), and (**6**) in 49, 37, and 14% yields respectively after chromatographic separation. The main product (**14**) was successively reduced with lithium aluminum hydride to give a 1:1 mixture of the amines (**16**) and (**17**) which without separation was subjected to hydrogenolysis over 10% palladium on carbon in ethanol containing hydrochloric acid to afford the (-)-phenylethylpiperidine (**18**) in 65% yield from the lactam (**14**). Comparison of the optical rotation of the (-)-amine (**18**) with that of the known compound^{2b} showed its (2S) configuration. In order to prepare (-)-sedamine (**21**) and (-)-allosedamine (**22**),³ the hydroxyamines (**16**) and (**17**) were separated by MCC and then each isomer was independently subjected to dealkylative carbamoylation with trichloroethyl chloroformate to give the carbamoylcarbonates (**19**) and (**20**), which without separation were reduced with lithium aluminum hydride to afford the (-)-N-methylalcohols (**21**) and (**22**) in 61 and 64% yields, respectively. They exhibited superimposable ir and nmr spectra with those^{3b} of the authentic enantiomers of sedamine and allosedamine.



ACKNOWLEDGMENT

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EXPERIMENTAL

The ^1H -nmr spectra were measured with JEOL PMX-60 (60 MHz) and Varian XL-200 (200 MHz) instruments for solutions in deuteriochloroform (with tetramethylsilane as an internal reference), and the ir spectra were measured with a Hitachi 215 machine for solutions in chloroform. Ms were taken with a Hitachi M-80 spectrometer and optical rotations on a JASCO DIP-181 digital polarimeter at room temperature. All melting points were determined with a Kofler-type hot-stage apparatus and are uncorrected. Reactions were performed under nitrogen atmosphere. Extracts from the reaction mixture were dried over anhydrous Na_2SO_4 , and evaporated under reduced pressure. Tlc was performed on pre-coated Silica gel 60F-254 (0.25 mm thick, Merck) and preparative-tlc (prep-tlc) on pre-coated Silica gel 60F-254 (0.5 mm thick, Merck) and spots were detected by uv irradiation of the plate at 254 and 300 nm. MCC was undertaken by 530-4-10V apparatus (Yamazen) using Lobar grosse B (310-25, Lichroprep Si60, Merck) as a column. Ether refers to diethyl ether.

(-)-1-((1S)-1-Phenylethyl)glutarimide (**3**). According to the reported procedure,⁹ a solution of (S)-(-)-1-phenylethylamine (7.89 g, 0.065 mol) in toluene (30 ml) was added to a solution of glutaric anhydride (7.4 g, 0.065 mol) in toluene (150 ml) and the resulting solution was heated under reflux for 6 h. (At this time, the residue which was obtained by removing the solvent, was characterized as **2**, ^1H -nmr (60 MHz) δ : 8.58 (1H, br s, COOH), 6.78 (1H, br d, $J=7$ Hz, NH), 4.95 (1H, quint, $J=7$ Hz, CHMePh), 1.38 (3H, d, $J=7$ Hz, CHMePh). Acetyl chloride (21 ml, 0.29 mol) was added to the reaction mixture and the solution was heated under reflux for 5 h. The solvent was removed, and the residue was dissolved in benzene and the mixture was washed with 10% aqueous HCl, 5% aqueous NaOH, and water. The organic layer was dried and evaporated to give the residue which was recrystallized from benzene to give the imide (**3**) (13.1 g, 93%) as colorless crystals, mp 124-127.5°C. $[\alpha]_D -143^\circ$ ($c=1.0$, EtOH) (lit.,^{3a} enantiomer of **3**, $[\alpha]_D +142.6^\circ$ ($c=1.0$, EtOH)). Ir ν_{max} cm^{-1} : 1718 (CO), 1666 (NCO). ^1H -Nmr (200 MHz) δ : 7.45-7.20 (5H, m, ArH), 6.10 (1H, q, $J=7$ Hz, CHMePh), 2.66 (4H, br t, $J=6.5$ Hz, 3- and 5- H_2), 1.95 (2H, quint, $J=6.5$ Hz, 4- H_2), 1.78 (3H, d, $J=7$

Hz, CHMePh). High-resolution ms m/z : 217.1102. Calcd for $C_{13}H_{15}NO_2$ (M^+). Found: 217.1112.

Reduction of the Imide (3) with Sodium Borohydride. Sodium borohydride (405 mg, 10.7 mmol) was added to a solution of the imide (3) (390 mg, 1.8 mmol) in ethanol (20 ml) at 0-5°C. At regular intervals (mostly 10 min) 2-3 drops of 2N HCl in EtOH (0.9 ml) were added. After 3 h, the reaction mixture was cooled to -30°C and the excess sodium borohydride was destroyed by adding 2N HCl in EtOH till pH=3. The mixture was stirred for an additional 0.5 h at room temperature and poured into saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane, and the extract was dried and evaporated. The crude residue was separated by MCC (AcOEt-*n*-hexane =1:1) to give (-)-6-ethoxy-1-((1S)-1-phenylethyl)-2-piperidinones (4) (270 mg, 61%) and (5) (90 mg, 20%) and (-)-3,4-dihydro-1-((1S)-1-phenylethyl)-2-pyridinone (6) (19 mg, 5%). The major isomer (4) (less polar isomer): a colorless oil. $[\alpha]_D -93.5^\circ$ ($c=1.0$, EtOH). $Ir \nu_{max} cm^{-1}$: 1630 (NCO). 1H -Nmr (60 MHz) δ : 5.86 (1H, q, $J=7$ Hz, CHMePh), 4.20 (1H, br s, 6-H), 1.59 (3H, d, $J=7$ Hz, CHMePh), 1.27 (3H, t, $J=7$ Hz, OCH_2CH_3). High-resolution ms m/z : 247.1571. Calcd for $C_{15}H_{21}NO_2$ (M^+). Found: 247.1565. The minor isomer (5) (polar isomer): a colorless oil. $[\alpha]_D -80^\circ$ ($c=1.0$, EtOH). $Ir \nu_{max} cm^{-1}$: 1632 (NCO). 1H -Nmr (60 MHz) δ : 5.61 (1H, q, $J=7$ Hz, CHMePh), 4.53 (1H, br s, 6-H), 1.54 (3H, d, $J=7$ Hz, CHMePh), 0.80 (3H, t, $J=7$ Hz, OCH_2CH_3). High-resolution ms m/z : 247.1571. Calcd for $C_{15}H_{21}NO_2$ (M^+). Found: 247.1554. The enamide (6): colorless crystals from ether-petroleum ether, mp 41-42°C. $[\alpha]_D -171.6^\circ$ ($c=1.0$, EtOH). $Ir \nu_{max} cm^{-1}$: 1658 (NCO). 1H -Nmr (200 MHz) δ : 7.45-7.24 (5H, m, ArH), 6.06 (1H, q, $J=7$ Hz, CHMePh), 5.92 (1H, dt, $J=7.5, 1.5$ Hz, 6-H), 5.16 (1H, m, 5-H), 2.62 (2H, t, $J=8$ Hz, 3-H₂), 2.44-2.24 (2H, m, 4-H₂), 1.56 (3H, d, $J=7$ Hz, CHMePh). High-resolution ms m/z : 201.1152. Calcd for $C_{13}H_{15}NO$ (M^+). Found: 201.1136.

Reaction of the Ethoxylactams (4) and (5) with Allyltrimethylsilane.

From the major isomer (4): The lactam (4) (113 mg, 0.45 mmol) was dissolved in dichloromethane (1.5 ml) and cooled to -30°C. Allyltrimethylsilane (390 mg, 3.4 mmol) in dichloromethane (0.3 ml) and titanium (IV) chloride (0.1 ml, 0.9 mmol) were added sequentially, and the mixture was stirred at room temperature for 3.5 h. Water was added to the reaction mixture and the mixture was extracted with dichloromethane. The organic layer was dried and evaporated. The residue was

separated by MCC (AcOEt-*n*-hexane=1:1) to give the enamide (6) (1 mg, 1%) and a mixture of (6*S*)-(-)-1-((1*S*)-1-phenylethyl)-6-(1-prop-2-enyl)-2-piperidinone (7) and (6*R*)-1-((1*S*)-1-phenylethyl)-6-(1-prop-2-enyl)-2-piperidinone (8) (93 mg, 84%). The ratio of 7 and 8 was determined as 83:17 by the ^1H -nmr spectrum on the crude reaction mixture. The major isomer (8) was partly separated by repeated MCC as a colorless oil. $[\alpha]_D^{25} -42^\circ$ ($c=1.0$, EtOH). Ir ν_{max} cm^{-1} : 1618 (NCO). ^1H -Nmr (200 MHz) δ : 7.48-7.24 (5H, m, ArH), 5.85 (1H, q, $J=7$ Hz, CHMePh), 5.44 (1H, m, $\text{CH}=\text{CH}_2$), 4.95 (1H, br d, $J=10$ Hz, $\text{CH}=\text{CH}_2$), 4.81 (1H, br d, $J=17$ Hz, $\text{CH}=\text{CH}_2$), 3.49 (1H, m, 6-H), 2.58-2.42 (2H, m, 3-H₂), 2.05-1.46 (6H, m, 4-H₂, 5-H₂, and $\text{CH}_2\text{CH}=\text{CH}_2$), 1.60 (3H, d, $J=7$ Hz, CHMePh). High-resolution ms m/z : 243.1622. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}$ (M^+). Found: 243.1630. From the ^1H -nmr (200 MHz) spectrum of a mixture of the lactams (7) and (8), the following peaks were assignable for the minor isomer (8), δ : 5.96 (1H, q, $J=7.5$ Hz, CHMePh), 5.60 (1H, m, $\text{CH}=\text{CH}_2$), 5.14-5.00 (2H, m, $\text{CH}=\text{CH}_2$), 3.16 (1H, m, 6-H), 1.63 (3H, d, $J=7.5$ Hz, CHMePh). From the minor isomer (5): The lactam (5) (111 mg) was treated with allyltrimethylsilane and titanium (IV) chloride in the same way as above to give the enamide (6) (2 mg, 2%) and a mixture of 7 and 8 (74 mg, 69%) in the ratio of 83:17. From a mixture of 4 and 5: A mixture of the lactams (4) and (5) (1 g) was treated with allyltrimethylsilane and titanium (IV) chloride in the same way as above to give the enamide (6) (22 mg, 3%) and a mixture of 7 and 8 (913 mg, 93%) in the ratio of 83:17.

Reduction of a Mixture of the Lactams (7) and (8) with Lithium Aluminum Hydride.

Lithium aluminum hydride (520 mg, 13.7 mmol) was added to a solution of a mixture of the lactams (7) and (8) (648 mg, 2.66 mmol) in anhydrous ether (260 ml), and the resulting solution was heated under reflux for 1 h. The cooled mixture was quenched with water and extracted with ether. The organic layer was dried and evaporated to give the residue which was separated by MCC (AcOEt-*n*-hexane=3:2) to afford (2*S*)-(-)-1-((1*S*)-1-phenylethyl)-2-(1-prop-2-enyl)piperidine (9) (462 mg, 76%) and (2*R*)-(-)-1-((1*S*)-1-phenylethyl)-2-(1-prop-2-enyl)piperidine (10) (97 mg, 16%). The amine (9): a colorless oil. $[\alpha]_D^{25} -42^\circ$ ($c=1.0$, EtOH). Ir ν_{max} cm^{-1} : 1638 (C=C). ^1H -Nmr (200 MHz) δ : 7.48-7.20 (5H, m, ArH), 5.65 (1H, m, $\text{CH}=\text{CH}_2$), 5.09-4.91 (2H, m, $\text{CH}=\text{CH}_2$), 4.08 (1H, br q, $J=7$ Hz, CHMePh), 2.76 (1H, m, 2-H), 2.60-1.20 (10H, m, 3-6-H₂ and $\text{CH}_2\text{CH}=\text{CH}_2$), 1.42 (3H, d, $J=7$ Hz, CHMePh). High-resolution ms m/z : 228.1750. Calcd for $\text{C}_{16}\text{H}_{22}\text{N}$ (M^+-H). Found: 228.1733. The amine (10): a colorless oil. $[\alpha]_D^{25} -29^\circ$ ($c=1.0$, EtOH). Ir ν_{max} cm^{-1} :

1638 (C=C). $^1\text{H-Nmr}$ (200 MHz) δ : 7.50-7.18 (5H, m, ArH), 5.90 (1H, m, $\text{CH}=\text{CH}_2$), 5.16-5.00 (2H, m, $\text{CH}=\text{CH}_2$), 4.06 (1H, q, $J=7$ Hz, CHMePh), 2.88 (1H, m, 2-H), 2.54-1.20 (10H, m, 3-6- H_2 and $\text{CH}_2\text{CH}=\text{CH}_2$), 1.30 (3H, d, $J=7$ Hz, CHMePh). High-resolution ms m/z : 228.1751. Calcd for $\text{C}_{16}\text{H}_{22}\text{N}$ (M^+-H). Found: 228.1767.

(-)-Coniine HCl (11). A solution of the amine (9) (406 mg) in ethanol (30.5 ml) containing concentrated HCl (3 ml) was catalytically hydrogenated over 10% palladium on carbon (580 mg) under 4 atm at room temperature for 15 h. After filtration off of catalyst, the solvent was evaporated to give the residue which was recrystallized from iso-PrOH to afford (-)-coniine HCl (11) (234 mg, 81%) as colorless needles, mp 221-222°C (lit.,⁶ mp 221°C). $[\alpha]_D -5.5^\circ$ ($c=1.0$, EtOH) (lit.,^{5c} $[\alpha]_D -5.8^\circ$ ($c=1.0$, EtOH)). High-resolution ms m/z : 127.1360. Calcd for $\text{C}_8\text{H}_{17}\text{N}$ (M^+-HCl). Found: 127.1364. The ir spectrum of (-)-(11) was found to be identical with that reported⁶ on (-)-coniine HCl.

(+)-Coniine HCl (12). According to the hydrogenation procedure described for 9, treatment of the amine (10) (110 mg) with 10% palladium on carbon (157 mg) gave (+)-coniine HCl (12) (51 mg, 65%), mp 223-228°C (colorless needles from iso-PrOH). $[\alpha]_D +4.8^\circ$ ($c=0.5$, EtOH) (lit.,^{5c} $[\alpha]_D +5.2^\circ$ ($c=1.0$, EtOH)). High-resolution ms m/z : 127.1360. Calcd for $\text{C}_8\text{H}_{17}\text{N}$ (M^+-HCl). Found: 127.1371.

Reaction of the Ethoxylactam (4) with Silyl Enol Ether of Acetophenone. The lactam (4) (0.966 g, 3.9 mmol) was dissolved in dichloromethane (12 ml) and cooled to -20°C. Silyl enol ether of acetophenone (1.5 g, 7.8 mmol) in dichloromethane (3 ml) and titanium (IV) chloride (0.56 ml, 5.1 mmol) were added sequentially, and the mixture was stirred at room temperature for 5 h. Water was added to the reaction mixture and the mixture was extracted with dichloromethane, and the extract was dried and evaporated. The residue was separated by MCC (AcOEt- n -hexane =2:1) to give the enamide (6) (109 mg, 14%), (6S)-(-)-6-(2-oxo-2-phenylethyl)-1-((1S)-1-phenylethyl)-2-piperidinone (14) (615 mg, 49%), and (6R)-(-)-6-(2-oxo-2-phenylethyl)-1-((1S)-1-phenylethyl)-2-piperidinone (15) (465 mg, 37%). The lactam (14): a colorless oil. $[\alpha]_D -109^\circ$ ($c=0.8$, EtOH). Ir ν_{max} cm^{-1} : 1682 (CO), 1618 (NCO). $^1\text{H-Nmr}$ (200 MHz) δ : 7.60-7.10 (10H, m, ArH), 6.12 (1H, q, $J=7.5$ Hz, CHMePh), 4.31 (1H, m, 6-H), 2.89 (1H, dd, $J=17.5, 10$ Hz, CH_2COPh), 2.56 (2H, br t, $J=5.5$ Hz, 3- H_2), 2.32 (1H, dd, $J=17.5, 3$ Hz, CH_2COPh), 1.95-1.70 (4H, m, 4- and 5- H_2), 1.59 (3H, d, $J=7.5$ Hz, CHMePh). High-resolution

ms m/z : 321.1727. Calcd for $C_{21}H_{23}NO_2$ (M^+). Found: 321.1717. The lactam (15): colorless crystals from AcOEt-ether, mp 138-138.5°C. $[\alpha]_D -33^\circ$ ($c=1.0$, EtOH). Ir $\nu_{\max} \text{ cm}^{-1}$: 1682 (CO), 1620 (NCO). $^1\text{H-Nmr}$ (200 MHz) δ : 7.95-7.24 (10H, m, ArH), 5.98 (1H, q, $J=7.5$ Hz, CHMePh), 4.05 (1H, m, 6-H), 3.40 (1H, dd, $J=17$, 9.5 Hz, CH_2COPh), 3.23 (1H, dd, $J=17$, 3.5 Hz, CH_2COPh), 2.57 (2H, t, $J=7$ Hz, 3-H₂), 2.06-1.40 (4H, m, 4- and 5-H₂), 1.62 (3H, d, $J=7.5$ Hz, CHMePh). High-resolution ms m/z : 321.1727. Calcd for $C_{21}H_{23}NO_2$ (M^+). Found: 321.1724.

Reduction of the Lactam (14) with Lithium Aluminum Hydride. Lithium aluminum hydride (80 mg, 2.1 mmol) was added to a solution of the lactam (14) (220 mg, 0.7 mmol) in anhydrous ether (50 ml), and the resulting solution was heated under reflux for 0.5 h. Usual work-up gave the crude residue which was separated by MCC (AcOEt-*n*-hexane=9:1) to afford (2S)-(-)-2-((2S)-2-hydroxy-2-phenylethyl)-1-((1S)-1-phenylethyl)piperidine (16) (93 mg, 44%) and (2S)-(-)-2-((2R)-2-hydroxy-2-phenylethyl)-1-((1S)-1-phenylethyl)piperidine (17) (96 mg, 45%). The amine (16): a colorless oil. $[\alpha]_D -58.7^\circ$ ($c=0.63$, EtOH). Ir $\nu_{\max} \text{ cm}^{-1}$: 3130 (OH). $^1\text{H-Nmr}$ (200 MHz) δ : 7.60-7.20 (10H, m, ArH), 5.05 (1H, br d, $J=11$ Hz, CHOH), 4.24 (1H, q, $J=7$ Hz, CHMePh), 3.77 (1H, m, 2-H), 3.00 (1H, td, $J=12$, 2.5 Hz, 6-H), 2.60-2.34 (2H, m, CH_2CHOHPh and 6-H), 1.97 (1H, m, CH_2CHOHPh), 1.80-1.06 (6H, m, 3-5-H₂), 1.53 (3H, d, $J=7$ Hz, CHMePh). High-resolution ms m/z : 309.2091. Calcd for $C_{21}H_{27}NO$ (M^+). Found: 309.2100. The amine (17): a colorless oil. $[\alpha]_D -8.2^\circ$ ($c=2.0$, EtOH). Ir $\nu_{\max} \text{ cm}^{-1}$: 3150 (OH). $^1\text{H-Nmr}$ (200 MHz) δ : 7.60-7.20 (10H, m, ArH), 5.23 (1H, dd, $J=6$, 5 Hz, CHOH), 4.45 (1H, q, $J=7$ Hz, CHMePh), 3.20-3.00 (2H, m, 2- and 6-H), 2.42 (1H, ddd, $J=15$, 8, 5 Hz, CH_2CHOHPh), 2.22 (1H, m, 6-H), 2.10 (1H, ddd, $J=15$, 6, 3.5 Hz, CH_2CHOHPh), 1.88-1.23 (6H, m, 3-5-H₂), 1.38 (3H, d, $J=7$ Hz, CHMePh). High-resolution ms m/z : 309.2091. Calcd for $C_{21}H_{27}NO$ (M^+). Found: 309.2102.

(2S)-(-)-2-(2-Phenylethyl)piperidine (18). A solution of a mixture of the amine (16) and (17) (55 mg) in ethanol (5 ml) containing concentrated HCl (0.5 ml) was catalytically hydrogenated over 10% palladium on carbon (60 mg) under 4 atm at room temperature for 15 h. After filtration off of catalyst, the solvent was evaporated. The saturated aqueous NaHCO_3 was added to the residue and the mixture was extracted with dichloromethane. The organic layer was dried and evaporated to give the residue which was purified by prep-tlc (dichloromethane-methanol=9:1) to afford the (-)-amine (18) (20 mg, 65% from 14) as a colorless

oil. $[\alpha]_{577} -7^\circ$ ($c=0.6$, EtOH) (lit.,^{2b} enantiomer of **18**, $[\alpha]_{578} +7^\circ$ ($c=0.19$, MeOH)). $^1\text{H-Nmr}$ (200 MHz) δ : 7.40-7.12 (5H, m, ArH), 3.12 (1H, br d, $J=12$ Hz, 2-H), 2.80-2.10 (5H, m, NH, 6-H₂, and CH₂Ph), 1.90-1.50 (8H, m, 3-5-H₂ and CH₂CH₂Ph). High-resolution MS m/z : 189.1517. Calcd for C₁₃H₁₉N (M⁺). Found: 189.1535.

(-)-Sedamine (21). 2,2,2-Trichloroethyl chloroformate (0.1 ml, 0.73 mmol) and KHC₃O₃ (150 mg, 1.5 mmol) were added to a solution of the amine (**16**) (70 mg, 0.23 mmol) in 1,2-dichloroethane (10 ml) and the resulting solution was heated under reflux for 5 h. Water was added to the cooled reaction mixture and the mixture was extracted with dichloromethane. The extract was dried and evaporated, and further the residue was heated at 100°C in vacuo for removing the residual 2,2,2-trichloroethyl chloroformate to give the crude carbamate (**19**). $^1\text{H-Nmr}$ (60 MHz) δ : 5.53 (1H, t, $J=7$ Hz, CHOC₂CH₂CCl₃), 4.80-4.58 (4H, m, CH₂CCl₃×2), 4.70-3.93 (2H, m, 2- and 6-H). Without purification, lithium aluminum hydride (70 mg, 1.8 mmol) was added to a solution of **19** in anhydrous ether (10 ml), and the solution was heated under reflux for 0.5 h. Usual work-up gave the residue which was purified by prep-tlc (dichloromethane-methanol=9:1) to afford (-)-sedamine (**21**) (30 mg, 61%), mp 61-62°C (colorless crystals from *n*-hexane) (lit.,¹⁰ mp 61-62°C). $[\alpha]_D -88^\circ$ ($c=0.45$, EtOH) (lit.,¹⁰ $[\alpha]_D -92.5^\circ$ (EtOH)). High-resolution ms m/z : 219.1622. Calcd for C₁₄H₂₁NO (M⁺). Found: 219.1624. The ir and $^1\text{H-nmr}$ spectra of (-)-(**21**) were found to be identical with those of (+)-sedamine.^{3b}

(-)-Allosedamine (22). According to the procedure given for the preparation of **21**, treatment of the amine (**17**) (36 mg, 0.12 mmol) with 2,2,2-trichloroethyl chloroformate (0.05 ml, 0.37 mmol) and KHC₃O₃ (75 mg, 0.75 mmol) in 1,2-dichloroethane (5 ml) gave the crude carbamate (**20**). $^1\text{H-Nmr}$ (60 MHz) δ : 5.46 (1H, dd, $J=8, 5$ Hz, CHOC₂CH₂CCl₃), 5.00-4.50 (4H, m, CH₂CCl₃×2), 4.60-3.86 (2H, m, 2- and 6-H). Without purification, lithium aluminum hydride reduction of **20** gave (-)-allosedamine (**22**) (16 mg, 64%), mp 81-82°C (colorless needles from *n*-hexane) (lit.,¹⁰ mp 79-80°C). $[\alpha]_D -17.8^\circ$ ($c=0.56$, EtOH) (lit.,¹⁰ $[\alpha]_D -18.9^\circ$ (EtOH)). High-resolution ms m/z : 219.1621. Calcd for C₁₄H₂₁NO (M⁺). Found: 219.1615. The ir and $^1\text{H-nmr}$ spectra of (-)-(**22**) were found to be identical with those of (+)-allosedamine.^{3b}

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