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Stereochemical Studies. XL.[1] A Biomimetic Conversion of L-Lysine into optically Active 2-Substituted Piperidines. Syntheses of D- and L-Pipecolic Acid, and (*S*) (+)-Coniine from L-Lysine[2]

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In order to transform an optical integrity of L-lysine (L-**5c**) into simple piperidine alkaloids in a biomimetic sence, optically active pipecolic acids (D- or L-**10c**) or their derivatives ((*R*)- or (*S*)-**11**) were chosen as synthetic intermediates.

It was found that deamination of L-**5c**-HCl with a combination of sodium nitrite and aqueous hydrochloric acid, followed by the treatment with aqueous base, could give D-**10c** being more than 90% optically active. On the other hand, deamination of L-**5c**-$1/2H_2SO_4$ with sodium nitrite-aqueous sulfuric acid, followed by chlorination with thionyl chloride and pyridine and by cyclization with aqueous base, could afford L-**10c** which was about 80% optically pure. Precise estimation of retention for optical activity was carried out by isolating formed D- or L-**10c** as their derivatives ((*R*) (+)-**11a**, **b** or (*S*) (−)-**11b**).

Exploitations for other synthetic routes to L-**10c** from L-**5c** were also undertaken.

Based on the above-mentioned experimental results, almost optically pure (*S*) (+)-coniine, one of the simplest piperidine alkaloids, could be prepared from L-**5c**-HCl *via* D-**10c** and (*R*) (+)-**11a** or **b**.

Several kinds of piperidine alkaloids such as (*S*) (+)-coniine ((*S*) (+)-**1**), (2*S*, 1′*R*)-conhydrine ((*S*)-**2**), (*R*) (−)-pelletierine ((*R*) (−)-**3**), and (*S*) (−)-anabasine (*S*) (−)-**4**), have been isolated from natural sources,[4] and studies on the biosynthetic routes[5–7] present very fascinating aspects of these simple alkaloids.

As shown in Chart 1, it has been established that (*R*) (−)-**3** and (*S*) (−)-**4** are biosynthesized from L-lysine (L-**5c**) *via* 5-aminopentanal (**6**) and Δ^1-piperideine (**7**).[5–7] On the other hand, Leete[5] has suggested that the biosynthetic path way for the hemlock alkaloids such as (*S*) (+)-**1** and (*S*)-**2** is completely different from that described above, and that these alkaloids are biosynthesized from acetate (acetyl CoA) *via* poly-β-keto acid (**8**) and γ-coniceine (**9**) and L-**5c** can be also incorporated into these alkaloids by being catabolyzed to acetate. However, the source of the nitrogen atom is a problem for this novel biosynthetic route,[7] and the other path way to the hemlock alkaloids, by which **9** can be derived from **7**, has not yet been excluded completely.

Since L-**5c** can be actually incorporated into simple piperidine alkaloids *in vivo*, being apart from complexity of the biosynthetic route mentioned above, we paid attention to the

1) Part XXXIX: M. Shibasaki, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **24**, 315 (1976).
2) Presented at the 95th Annual Meeting of the Pharmaceutical Society of Japan, Nishinomiya, April, 1975.
3) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) *a*) L. Marion, "The Pyridine Alkaliods," in "The Alkaloids," Vol. I, Ed. by R.H.F. Manske and H.L. Holmes, Academic Press, New York, 1950, pp. 165—269; *b*) W.A. Ayer and T.E. Habgood, "The Pyridine Alkaloids," in "The Alkaloids," Vol. XI, Ed. by R.H.F. Manske, Academic Press, New York-London, 1968, pp. 459—510.
5) E. Leete, *Accounts Chem. Res.*, **4**, 100 (1971).
6) E. Leistner and I.D. Spencer, *J. Am. Chem. Soc.*, **95**, 4715 (1973).
7) T. Robinson, "The Biochemistry of Alkaloids," Springer-Verlag, Berlin, Heidelberg, New-York, 1968, pp. 24—40.

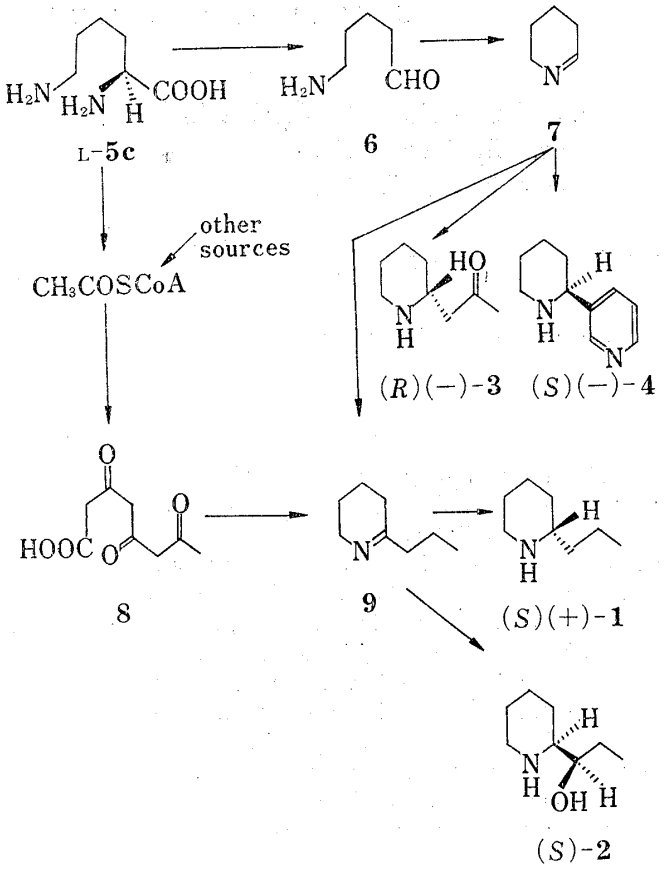
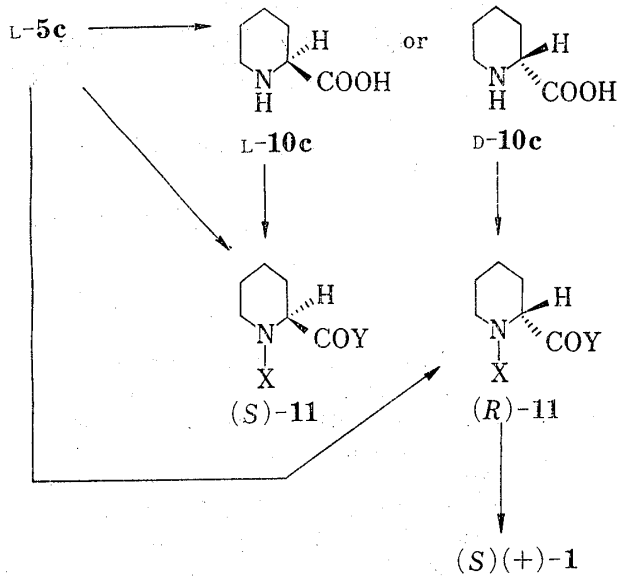


Chart 1



X=$COOCH_2C_6H_5$, $SO_2C_6H_4CH_3$ (*p*) (Tos), *etc.*
Y=OH, OMe, *etc.*

Chart 2

applicability of L-**5c** to the chemical synthesis of these alkaloids in their optically active forms in a biomimetic sence.[8]

In order to transform an optical integrity of L-**5c** into optically active piperidine alkaloids having (*R*) or (*S*)-configuration at the C_2-position, optically active D- or L-pipecolic acid (D- or L-**10c**),[9] or their derivatives ((*R*)- or (*S*)-**11**) were chosen as synthetic intermediates because true intermediates in biosynthesis such as **7** and **9**, had no chirality.

In this report, the authors first attempted to establish simple synthetic routes to D- or L-**10c** and (*R*)- or (*S*)-**11** from L-**5c**, then examined the conversion of D-pipecolic acid derivative ((*R*)-**11**) into one of the optically active simple piperidine alkaloids, (*S*) (+)-**1**, by extending alkyl chain from carboxyl group without racemization.

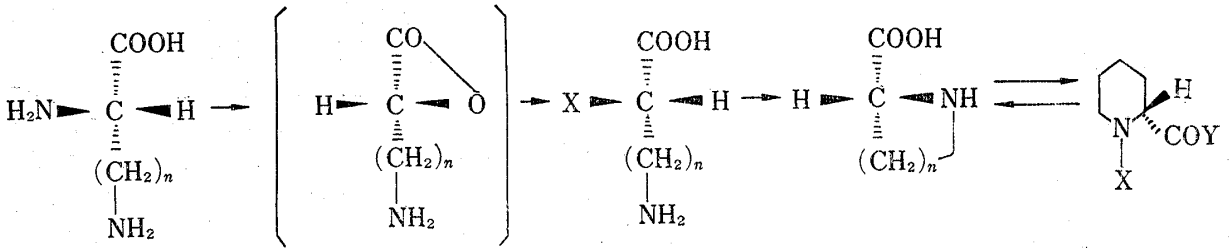
Result and Discussion

A. Preparations of D- and L-Pipecolic Acid (D- and L-10c) and Their Derivatives from L-Lysine (L-5c)

There have been reported that optically active D-azetidine-2-carboxylic acid (D-**10a**)[10] and D-proline (D-**10b**)[11,12] could be prepared respectively from L-γ-aminobutyrine (L-**5a**) and L-ornithine (L-**5b**) by deaminative halogenation followed by intramolecular cyclization. It

8) Naturally occurring piperidine alkaloids carry their side chain at the C_2-position in (*R*) or (*S*)-configuration. This is one of the interesting structural features of these alkaloids.
9) L-Pipecolic acid itself was reported to be biosynthesized from lysine *via* Δ^1-piperideine-2-carboxylic acid (see ref. 5).
10) L. Fowden, *Biochem. J.*, **64**, 323 (1956).
11) P.B. Hamilton, *J. Biol. Chem.*, **198**, 587 (1952).
12) S. Ohshiro, K. Kuroda, and T. Fujita, *Yakugaku Zasshi*, **87**, 1184 (1967).

is well established for this transformation that the deamination proceeds with net retention of configuration *via* α-lactone intermediate (**12**) and the α-halogen of (*S*)-α-halogenoacid (**13**) is substituted with intramolecular γ- or δ-amino group with net inversion. One report[13] also concerns with the preparation of D-**10c** from L-**5c** using nitrosyl bromide as a deamination reagent and barium hydroxide as a base for cyclization. In these attempts, since formed cyclic α-imino acids (D-**10**) were purified by recrystalization, precise estimation of the optical activity, which survived during the successive deamination and cyclization, could not be achieved.



L-**5** **12** **13** D-**10** (*R*)(+)-**11**

a: $n=2$
b: $n=3$
c: $n=4$

X=Cl or Br

a: $n=2$
b: $n=3$
c: $n=4$

a: X=$COOCH_2C_6H_5$, Y=OCH_3
b: X=$SO_2C_6H_4CH_3(p)$, (Tos) Y=OCH_3

Chart 3

As a method for preparing D-**10c** from L-**5c**, the authors also employed the above mentioned method using sodium nitrite–hydrochloric acid as a deamination reagent, and determined the presice value for retention of optical activity by isolating D-**10c** as (*R*) (+)-methyl N-benzyloxycarbonylpipecolate ((*R*) (+)-**11a**) or (*R*) (+)-methyl N-tosylpipecolate ((*R*) (+)-**11b**).

Deamination of L-lysine monohydrochloride (L-**5c**–HCl)[14] with sodium nitrite (1.2—1.4 equivalents) in a 1:1 mixture of concd. hydrochloric acid and water, followed by treating with barium hydroxide solution at reflux or with sodium hydroxide solution at room temperature, gave D-**10c**. Formed D-**10c** was isolated as (*R*) (+)-**11a**, $[\alpha]_D^{20}$ +42.2° (benzene), or (*R*) (+)-**11b**, $[\alpha]_D^{20}$ +33.9° (benzene). The chemical yields of (*R*) (+)-**11a** and (*R*) (+)-**11b** were 30% and 46% based on L-**5c**–HCl respectively. The optical purity of these esters could be calculated as more than 90% by comparing their optical activity with those of optically pure (*S*) (−)-**11a**, $[\alpha]_D^{20}$ −44.1° (benzene), and (*S*) (−)-**11b**, $[\alpha]_D^{20}$ −36.6° (benzene). Optically pure (*S*) (−)-**11a**, and (*S*) (−)-**11b** were independently prepared from optically pure L-**10c** by our hands because they had not been reported (see experimental). These results clearly disclosed that the chemical conversion of L-**5c** into D-**10c** proceeds with more than 90% retention of optical activity.

Acidic hydrolysis of (*R*) (+)-**11a**[15] regenerated D-**10c** in 68% yield after recrystallization.

Then we turned our effort to exploitation of the synthetic route to L-**10c** from L-**5c**.

Since it had been reported[12] that L-proline (L-**10b**) could be prepared from L-**5b** by deamination in aqueous sulfuric acid, followed by tosylation, esterification, chlorination and base-promoted cyclization, the same reaction scheme was first attempted using L-**5c** as shown in Chart 4.

Treatment of L-lysine-hemisulfate (L-**5c**-1/2H_2SO_4), prepared from L-**5c**–HCl, with 3.6 equivalents of sodium nitrite in 10% sulfuric acid gave a 54% yield of (*S*) (−)-6-amino-2-

13) U. Schiedt and H.G. Höss, *Hoppe-Seyler's Zeit. Phys. Chem.*, **308**, 179 (1957).
14) Commercially available optically pure L-**5c**-HCl, mp 261—264° (decomp.), $[\alpha]_D^{20}$ +12.5° ($c=2.02$, H_2O) and $[\alpha]_D^{20}$ +20.5° ($c=2.00$, 0.6 N HCl) was used throughout this work.
15) (*R*) (+)-**11a**, being 88% optically pure, was used for the reaction.

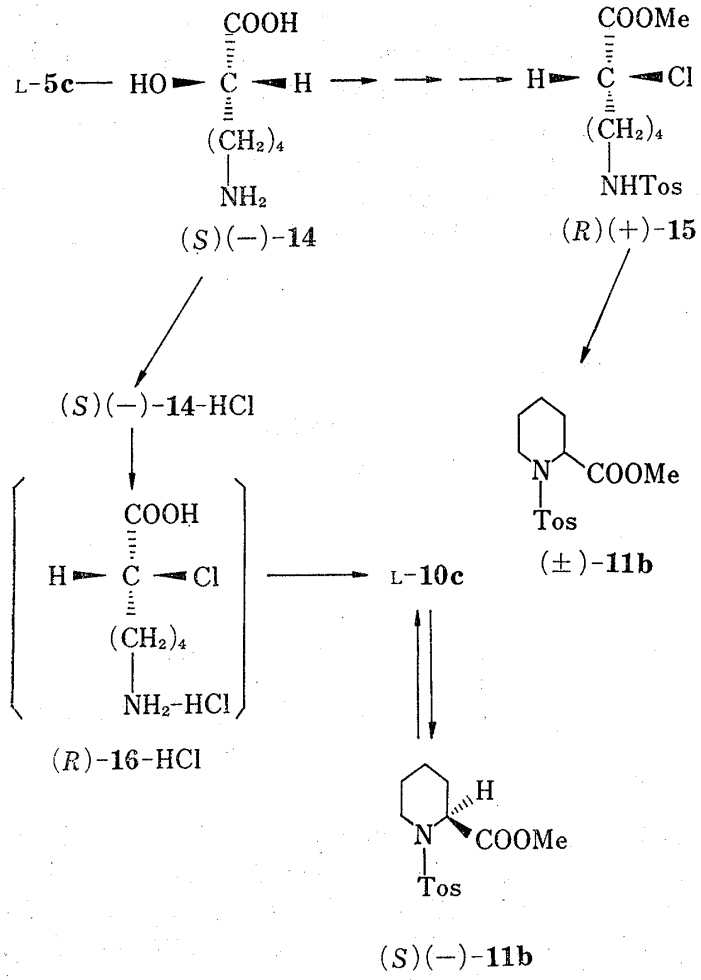


Chart 4

hydroxyhexanoic acid ((*S*) (−)-**14**), $[\alpha]_D^{20}$ −12.1° (water).[16] Tosylation according to the Schotten-Baumann procedure (69% yield), followed by esterification with diazomethane (97% yield) and chlorination with thionyl chloride and pyridine in chloroform (81% yield), afforded (*R*) (+)-methyl 2-chloro-6-tosylamidohexanoate ((*R*) (+)-**15**), $[\alpha]_D^{20}$ +11.1° (benzene).[17]

Cyclization of (*R*) (+)-**15** attempted under a similar condition to that for L-proline synthesis,[12] simply recovered the starting material. Under more forcing condition, that is, by refluxing a methanolic solution of (*R*) (+)-**15** in the presence of sodium methoxide or by stirring a tetrahydrofuran (THF) solution of (*R*) (+)-**15** and potassium *t*-butoxide at room temperature, (*R*) (+)-**15** was converted into completely racemized methyl N-tosylpipecolate ((±)-**11b**).

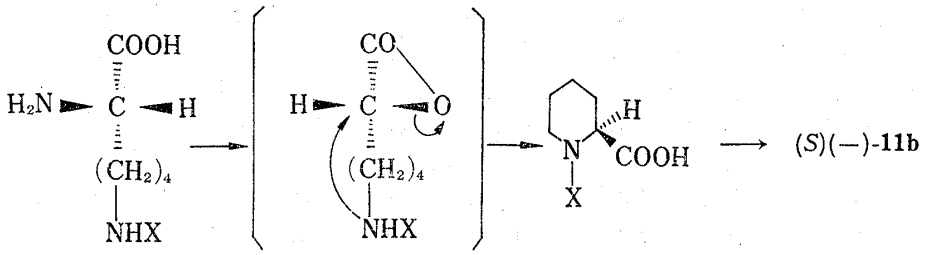
To circumvent difficulties which we encountered, modification of the reaction scheme was undertaken. (*S*) (−)-**14** was converted into its hydrochloride ((*S*) (−)-**14**–HCl), $[\alpha]_D^{20}$ −1.3° (water), by the usual manner. Chlorination of (*S*) (−)-**14**-HCl by the same method as that used before, followed by the basic treatment similarly to the case for the preparation of D-**10c** from L-**5c**–HCl, afforded L-**10c** *via* *R*-6-amino-2-chlorohexanoic acid hydrochloride (*R*-**16**–HCl). The cyclized product, isolated as (*S*) (−)-**11b** in 41% yield from (*S*) (−)-**14**–HCl, showed $[\alpha]_D^{20}$ −28.6° (benzene), and its optical purity was similarly calculated as 78%. Since it is clear that the cyclization of (*R*)-**16**–HCl to L-**10c** occurrs with more than 90% retention of optical activity when the preparation of D-**10c** from L-**5c**–HCl is taken into consideration, 20% racemization observed for (*S*) (−)-**11b**, seems due to the result that the deamination and/or the chlorination step proceeded with some racemization. Although some loss of optical activity might be accompanied, it is of interest from a synthetic point of view that the direct chlorination of the α-hydroxy acid such as (*S*) (−)-**14**–HCl with thionyl chloride–pyridine can afford the inverted α-chloro acid, (*R*)-**16**–HCl, with high retention of optical activity. Acidic hydrolysis of (*S*) (−)-**11b**[18] gave L-**10c**, $[\alpha]_D^{20}$ −16.1° (water), 61% optically pure, in 69% yield after recrystallization.

16) The absolute configuration of (−)-**14** was assumed to be (*S*)-configuration since the deamination of α-amino acid in aqueous sulfuric acid was reported to give α-hydroxy acid with net retention of configuration due to α-lactone intermediate (see ref. 12 and K. Koga, C.C. Wu, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 1272, 1282 (1972)).

17) The absolute configuration of (+)-**15** was assumed to be (*R*) series by considering the reported result.[12]

18) (*S*) (−)-**11b**, being 72% optically pure, was used for the reaction.

Aiming to improve the chemical and optical yields of L-pipecolic acid synthesis, direct ring closure of L-**5c** or Nε-tosyl-L-lysine (L-**17**)[19,20] under deamination condition was studied. As shown in Chart 5, deamination of L-**5c** or L-**17** is expected to afford α-lactone intermediate



L-**5c**: X=H
L-**17**: X=Tos

L-**10c**: X=H
L-**19** : X=Tos

Chart 5

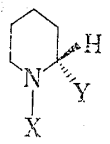
(**12** or **18**) and the subsequent ring opening by the attack of ε-amino or ε-tosylamido group in Walden inversion process, will give L-**10c** or N-tosyl-L-pipecolic acid (L-**19**). However, attempted deaminations using L-**5c** under various conditions[21] did not give the desired L-**10c**. On the other hand, when L-**17** was deaminated in a mixture of sodium trifluoroacetate (5 equivalents) and trifluoroacetic acid, desired L-**19** was found to be formed. L-**19** was similarly isolated as its methyl ester ((*S*) (−)-**11b**), $[\alpha]_D^{20}$ −32.9° (benzene), in *ca.* 1% yield based on L-**17**. The optical purity of this sample was determined as 90% by comparing its optical rotation with that of optically pure (*S*) (−)-**11b**, $[\alpha]_D^{20}$ −36.6° (benzene). That L-**19** could be obtained with more than 90% retention of optical activity suggests that the formation of L-**19** from L-**17** proceeded exclusively through **18**. However, further studies on this direct transformation was not undertaken since improvement of the chemical yield of L-**19** (isolated as (*S*) (−)-**11b**) was considered to be unpromising.

As it became possible to readily prepare D- or L-**10c** and their derivatives such as (*R*) (+)-**11a**, **b** and (*S*) (−)-**11b** from L-**5c**–HCl,[22] we next examined their conversion into optically active piperidine alkaloids, which is described in Section B.

B. Synthesis of optically Active Piperidine Alkaloid, (*S*) (+)-Coniine ((*S*) (+)-1), from D-Pipecolic Acid Derivatives (*R*-11)

As an optically active piperidine alkaloid which should be synthesized from (*R*)-**11**, (*S*) (+)-**1** was selected because it had the simplest structure among optically active piperidine alkaloids and synthesis of (*S*) (+)-**1** from (*R*)-**11** had not been reported.

Chemical scheme which was employed, was devised for protecting the asymmetric center from racemization.



	X	Y
(*R*)(+)-**20**	Tos	CH_2OTos
(*R*)(+)-**21**	Tos	$CH_2CH(COOEt)_2$
(*R*)(+)-**22**	Tos	CH_2CH_2COOEt
(*S*)(+)-**23**	Tos	$CH_2CH_2CH_3$
(*S*)(+)- **1**	H	$CH_2CH_2CH_3$

Chart 6

Reduction of (*R*) (+)-**11a**, $[\alpha]_D^{20}$ +39.8° (benzene), with 5% palladium on charcoal (92% yield), followed by reduction with lithium aluminium hydride (LAH) (73% yield)[23] and

19) R. Roeske, F.H.C. Stewart, R.J. Stedman, and V. du Vigneaud, *J. Am. Chem. Soc.*, **78**, 5883 (1956).
20) E.A. Morozova and S.M. Zhenodarova, *Zhur. Obshchei Khim.*, **31**, 45 (1961) [*C.A.*, **55**, 27121*e* (1961)].
21) Deaminations were carried out using sodium nitrite (2 equivalents) in the following mixtures: sodium acetate (1 equivalent) and acetic acid; sodium formate (1 equivalent) and formic acid; sodium trifluoroacetate (5 equivalents) and trifluoroacetic acid.
22) After our studies were completed, preparation of L-**10c** from L-**5c** by the deamination of Nα-tosyl-L-lysine was reported (T. Fujii, H. Sugano, and M. Miyoshi, "The 12th Sympodium on Peptide Chemistry," 1974, Kyoto, Abstract p. 75, and T. Fujii and M. Miyoshi, *Bull. Chem. Soc. Japan*, **48**, 1341 (1975)).
23) H. Ripperger and K. Schreiber, *Tetrahedron*, **21**, 1485 (1965).

ditosylation with tosyl chloride and pyridine (55% yield),[23] gave (*R*) (+)-1-tosyl-2-tosyloxymethylpiperidine ((*R*) (+)-**20**), $[\alpha]_D^{20}$ +42.3° (ethanol). The same compound, $[\alpha]_D^{20}$ +42.8° (ethanol), could be also prepared from (*R*) (+)-**11b**, $[\alpha]_D^{20}$ +35.9° (benzene), by the reduction with LAH (73% yield) and subsequent tosylation (quantitative yield). Treatment of (*R*) (+)-**20** with sodium iodide in dimethyl formamide (70% yield), followed by the substitution with diethyl malonate using potassium *t*-butoxide as a base (43% yield),[24,25] gave (*R*) (+)-diester ((*R*) (+)-**21**), $[\alpha]_D^{20}$ +34.5° (benzene). Heating (*R*) (+)-**21** with sodium chloride in wet dimethyl sulfoxide[26] yielded (*R*) (+)-monoester ((*R*) (+)-**22**), $[\alpha]_D^{20}$ +35.5° (benzene), in 91% yield. Reduction with LAH (60% yield), tosylation with tosyl chloride and pyridine (36% yield), and further reduction with LAH (73% yield) afforded (*S*) (+)-N-tosylconiine ((*S*) (+)-**23**), $[\alpha]_D^{20}$ +37.5° (benzene). The structure of (*S*) (+)-**23** was confirmed by comparing its spectral (infrared (IR) and nuclear magnetic resonance (NMR) spectra) and chromatographic (thin-layer chromatography(TLC)) behavior with those of authentic racemic compound prepared independently.[27] Removal of the tosyl group from (*S*) (+)-**23** with a mixture of acetic acid and 47% hydrobromic acid afforded (*S*) (+)-**1**, $[\alpha]_D^{27}$ +8.9° (chloroform) or its hydrobromide, $[\alpha]_D^{20}$ *ca.* +1° (ethanol), mp 206—208°. Since (*S*) (+)-**1** and its hydrobromide from natural source are reported to show $[\alpha]_D^{27}$ +9.0° (chloroform)[28] and mp 207°[29a] or 211°,[29b] it is evident that the optical activity of L-**5c**–HCl could be successfully transformed to (*S*) (+)-**1** without racemization, and that our initial objective that aimed to utilize L-**5c** for the synthesis of optically active simple piperidine alkaloids in a biomimetic sense was now accomplished.

Experimental[30]

(*S*) (−)-**Methyl N-Benzyloxycarbonylpipecolate** ((*S*) (−)-**11a**)——Usual benzyloxycarbonylation of optically pure L-**10c** (mp 261—263°, $[\alpha]_D^{20}$ −27.0° (*c*=0.20, H_2O)) (lit.,[31] mp 266° (decomp.), $[\alpha]_D$ −25.4° ±1° (*c*=2.85, H_2O); lit.,[32] $[\alpha]_D^{21}$ −25.0° ±0.5° (*c*=2.2, H_2O)) according to the Schotten-Baumann procedure,[33]

24) Detailed studies on the malonate synthesis using N-protected β-amino alcohol derivatives will be published separately (C.C. Tseng, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), in preparation.

25) Attempted substitutions of the iodide with lithium salt of 1,3-dithian or that of 2-methyl-1,3-dithian (*cf.* D. Seebach, *Synthesis*, **1969**, 17, and E.J. Corey and D. Seebach, *Angew. Chem.*, **77**, 1134, 1135 (1965).) were completely unsuccessful for affording the substituted products, and simple recovery of the starting iodide was observed. This is considered due to the steric hindrance caused by the piperidine ring system.

26) A.P. Krapcho and A.J. Lovey, *Tetrahedron Letters*, **1973**, 957.

27) K.B. Prasad and S.C. Shaw, *Ber.*, **98**, 2823 (1965).

28) T.P. Hilditch, *J. Chem. Soc.*, **93**, 700 (1908).

29) *a*) A. Ladenburg, *Ber.*, **17**, 1676 (1884); *b*) R. Wolffenstein, *ibid.*, **27**, 2615 (1894).

30) All melting and boiling points are uncorrected. IR spectra measurements were performed with spectrometers, JASCO Infrared Spectrometer Model DS-402G and JASCO IRA-1 Grating Infrared Spectrometer. NMR spectra were measured with Hitachi R-24 High Resolution NMR Spectrometer. All signals are expressed by the ppm downfield from tetramethylsilane as an internal standard. Following abbreviations are used: singlet (s); doublet (d); triplet (t); quartet (q); multiplet (m); broad (b). Optical rotations were recorded with YANACO OR-50 Automatic Polarimeter. Mass spectra measurements were carried out with JEOL JMS-01 SG-2 Mass Spectrometer.

31) H.C. Beyermann, *Rec. Trav. Chim.*, **78**, 134 (1959).

32) *a*) J.P. Greenstein and M. Winitz, "Chemistry of the Amino Acid," John-Wiley & Sons, Inc., New York-London, 1961, pp. 2533—2535; *b*) G. Harris and J.R.A. Pollack, *Chem. Ind.*, **1953**, 462.

33) Acylating reagent (1.0 equivalent) (neat benzyloxycarbonyl chloride or an acetone solution of tosyl chloride) and 4N NaOH solution (1.2 equivalents) were simultaneously added to a vigorously stirred aqueous solution of sodium salt of amino acid (1.0 equivalent) in an ice-bath. During the addition of reagents, pH of the reaction mixture was kept weakly basic. After the addition was over, the cooling bath was removed and the whole solution was stirred for 1 hr at room temperature. Excess acylating reagent was removed by extraction with ether (×2), and the aqueous phase was made acidic (pH<2) by adding aqueous hydrochloric acid, then extracted with ethyl acetate (×2). Combined ethyl acetate extracts were washed with satd. NaCl solution (×2), and dried over anhyd. $MgSO_4$ or anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* afforded the crude N-acylated amino acid.

followed by esterification with diazomethane and purification with column chromatography (silica gel, solvent benzene: ethyl acetate 6: 1), gave optically pure (*S*) (−)-**11a** as a colorless oil, $[\alpha]_D^{20}$ −44.1° (*c*=0.78, benzene). IR ν_{max}^{film} cm^{-1}: 1760 (ester), 1720 (amide). NMR (in $CDCl_3$): 1.0—2.5 (6H, bm, NCH_2 ($C\underline{H}_2$)$_3$), 2.5—4.5 (2H, bm, $NC\underline{H}_2$), 3.64 (3H, s, $COOC\underline{H}_3$), 4.5—5.0 (1H, bm, $NC\underline{H}$), 5.05 (2H, s, $C\underline{H}_2C_6H_5$), 7.20 (5H, s, $C_6\underline{H}_5$).

(*R*) (+)-Methyl N-Benzyloxycarbonylpipecolate ((*R*) (+)-**11a**)——An aqueous solution (6 ml) of sodium nitrite (1.04 g, 15 mmole) was added to a solution of L-**5c**-HCl[14] (1.97 g, 11 mmole) in a mixture of H_2O (10 ml) and concd. HCl (10 ml) over a period of 3 hr at room temperature. After the addition was over, the whole mixture was stirred overnight at room temperature, then was neutralized by the addition of aqueous NaOH solution. A solution of barium hydroxide octahydrate (1.58 g, 5 mmole) in H_2O (20 ml) was added to the neutralized solution, and the whole solution was refluxed for 20 min. After cooling, the mixture was again neutralized with aqueous sulfuric acid, then was poured on to a column of ion exchanger (Amberlite IR-120, H^+ form, 100 ml). The column was first thoroughly washed with H_2O, and then eluted with aqueous NH_4OH (concd. NH_4OH: H_2O 1: 3). Fractions being positive to ninhydrin test, were combined and evaporated *in vacuo* to give a yellow oily residue. Treatment of the residue in a similar manner to the case for the preparation of (*S*) (−)-**11a**, afforded (*R*) (+)-**11a** as a colorless oil (0.89 g, 30% yield based on L-**5c**-HCl), $[\alpha]_D^{20}$ +42.2° (*c*=1.80, benzene), 93% optically pure.[34] Spectral (IR and NMR) and chromatographic (TLC) behavior of this oil were identical with those of authentic (*S*) (−)-**11a** measured in the same states.

(*S*) (−)-Methyl N-Tosylpipecolate ((*S*) (−)-**11b**)——This compound was prepared from optically pure L-**10c** (mp 261—263°, $[\alpha]_D^{20}$ −27.0° (*c*=0.20, H_2O)) (lit.,[31] mp 266° (decomp.), $[\alpha]_D$ −25.4° ±1° (*c*=2.85, H_2O); lit.,[32] $[\alpha]_D$ −25.0° (H_2O)) by tosylation by the Schotten-Baumann procedure,[33] followed by esterification with diazomethane and purification by column chromatography (silica gel, solvent benzene: ethyl acetate 6: 1). (*S*) (−)- **11b** obtained as a pale yellow oil, showed $[\alpha]_D^{20}$ −36.6° (*c*=0.58, benzene). IR ν_{max}^{film} cm^{-1}: 1750 (ester), 1320, 1160 (SO_2). NMR (in $CDCl_3$): 1.0—2.3 (6H, bm, NCH_2 ($C\underline{H}_2$)$_3$), 2.40 (3H, s, $C\underline{H}_3C_6H_4$), 2.8—3.9 (2H, bm, NCH_2), 3.53 (3H, s, $COOC\underline{H}_3$), 3.9—4.5 (1H, bm, $NC\underline{H}$), 7.30 (2H, d, *J*=9 Hz, aromatic protons *ortho* to CH_3), 7.70 (2H, d, *J*=9 Hz, aromatic protons *meta* to CH_3). Mass Spectrum *m/e*: 297 (M^+), 238, 155, 142, 91.

(*R*) (+)-Methyl N-Tosylpipecolate ((*R*) (+)-**11b**)——A solution of sodium nitrite (17.0 g, 0.24 mole) in H_2O (100 ml) was gradually added to a solution of L-**5c**-HCl[14] (36.5 g, 0.20 mole) in a mixture of H_2O (80 ml) and concd. HCl (180 ml) over a period of 3 hr at room temperature. After the addition was over, the mixture was stirred for an additional 3 hr. An excess amount of nitrous acid present in the reaction mixture, was decomposed by the addition of urea. The whole solution was poured on to a column of ion exchanger (Amberlite IR-120, H^+ form, 500 ml). The column was first washed with H_2O until the eluate became neutral, then was eluted with aqueous NH_4OH. Fractions which were positive to ninhydrin test, were combined, and evaporated *in vacuo* to afford a brown oil. The oil was added to a solution of NaOH (8.6 g, 0.22 mole) in H_2O (50 ml). and the solution was vigorously stirred at 20—30° for several hours. The aqueous mixture was directly tosylated with tosyl chloride,[33] and then treated in a similar manner to the case for (*S*) (−)-**11b**, to give pure (*R*) (+)-**11b** as a pale yellow oil (27.2 g, 46% based on L-**5c**-HCl), $[\alpha]_D^{20}$ +33.9° (*c*=1.38, benzene), 93% optically pure.[35] The structure of (*R*) (+)-**11b** was comfirmed by comparing its spectral (IR and NMR) and chromatographic (TLC) properties with those of authentic (*S*) (−)-**11b**.

D-Pipecolic Acid (D-**10c**)——A solution of (*R*) (+)-**11a** ($[\alpha]_D^{20}$ +38.9° (*c*=1.30, benzene), 88% optically pure[34]) (3.05 g, 11 mmole) in a mixture of acetic acid (20 ml) and 47% HBr (20 ml) was heated at reflux for 3 hr. After cooling, the mixture was diluted with H_2O, and treated with charcoal. The decolorized aqueous solution was poured on to a column of ion exchanger (Amberlite IR-120, H^+ form), then the column was washed with H_2O until the eluate became neutral. The column was eluted with aqueous NH_4OH, and fractions which were positive to ninhydrin test, were combined. Evaporation of the combined solution *in vacuo*, followed by recrystallization from methanol–ether, afforded pure D-**10c** as a colorless powder (0.96 g, 68%), mp 268—271° (decomp.), $[\alpha]_D^{20}$ +24.6° (*c*=1.30, H_2O), 91% optically pure.[36] IR ν_{max}^{Nujol} cm^{-1}: 2700—2200, 1600. This spectrum was superimposable on that of optically pure L-**10c**.

(*S*) (−)-6-Amino-2-hydroxyhexanoic Acid ((*S*) (−)-**14**)——An aqueous solution of L-**5c**-HCl[14] (18.3 g, 0.10 mole) was passed through a column of ion exchanger (Amberlite IR-45, OH^- form, 500 ml), and the column was eluted with H_2O. Eluates which were positive to ninhydrin test, were combined and neutralized with 10% H_2SO_4. Evaporation *in vacuo*, followed by recrystallization from ethanol–H_2O, afforded L-**5c**-1/2H_2SO_4 as colorless crystals (19.0 g, 97%), mp 289—294° (decomp.), which was immediately used for the next reaction.

An aqueous solution (100 ml) of sodium nitrite (25.9 g, 0.36 mole) was gradually added to a solution of L-**5c**-1/2H_2SO_4 (19.0 g, 0.097 mole) in 10% H_2SO_4 (250 g) over a period of 2 hr with stirring at 45—50°. After the addition was over, the whole solution was stirred at the same temperature for 3 hr. An excess amount of nitrous acid present in the reaction mixture, was decomposed with urea, and the aqueous solution was poured on to a column of ion exchanger (Amberlite IR-120, H^+ form, 200 ml). After the column was thoroughly washed with H_2O, it was eluted with aqueous NH_4OH until the eluate became negative to ninhydrin test.

34) (*S*) (−)-**11a** showing $[\alpha]_D^{20}$ −44.1° (*c*=0.78, benzene), was assumed to be optically pure.
35) (*S*) (−)-**11b** which showed $[\alpha]_D^{20}$ −36.6° (*c*=0.58, benzene), was assumed to be optically pure.
36) Optically pure L-**10c** showed $[\alpha]_D^{20}$ −27.0° (*c*=0.20, H_2O).

Combined eluates were evaporated *in vacuo*, giving a pale yellow semisolid which was recrystallized from ethanol–H_2O to afford (*S*) (−)-**14** as a colorless powder (7.9 g, 54% based on L-**5c**-HCl), mp 203—206°, $[\alpha]_D^{20}$ −12.1° (*c*=1.16, H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3400—3000 (NH_3^+, OH), 1620, 1560, 1530 (NH_3^+, COO^-), 1090 (OH). *Anal.* Calcd. for $C_6H_{13}O_3N$: C, 48.97; H, 8.90; N, 9.51. Found: C, 48,33; H, 8.90; N, 9.54.

(*S*) (−)-**2-Hydroxy-6-tosylamidohexanoic Acid**——Usual tosylation of (*S*) (−)-**14** (4.41 g, 30 mmole) according to the Schotten-Baumann procedure,[33] afforded the crude tosylate as a colorless solid (6.21 g, 69%), mp 113—120°. Recrystallization from ethyl acetate gave an analytical sample, mp 125—127°, $[\alpha]_D^{20}$ −1.4° (*c*=0.70, EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3410 (OH), 3240 (NH), 1735 (COOH), 1310, 1155 (SO_2). *Anal.* Calcd. for $C_{13}H_{19}O_5NS$: C, 51.79; H, 6.36; N, 4.65. Found: C, 51.58; H, 6.44 N, 4.69.

(*S*)-**Methyl 2-Hydroxy-6-tosylamidohexanoate**——Esterification of (*S*) (−)-2-hydroxy-6-tosylamidohexanoic acid (1.00 g, 3.3 mmole) with diazomethane gave the desired product as a pale yellow oil (1.01 g, 97%) after usual work up, $[\alpha]_D^{20}$ 0° (*c*=0.94, benzene). IR ν_{max}^{film} cm^{-1}: 3500 (OH), 3280 (NH), 1740 (ester), 1320, 1160 (SO_2). NMR (in $CDCl_3$): 1.2—2.0 (6H, bm, $NCH_2(C\underline{H}_2)_3$), 2.40 (3H, s, $C\underline{H}_3C_6H_4$), 2.6—3.5 (3H, $NC\underline{H}_2$ and O<u>H</u>), 3.70 (3H, s, $COOC\underline{H}_3$), 4.10 (1H, bm, C<u>H</u>OH), 5.22 (1H, t, *J*=6 Hz, N<u>H</u>), 7.20 (2H, d, *J*=9 Hz, aromatic protons *ortho* to CH_3), 7.65 (2H, d, *J*=9 Hz, aromatic protons *meta* to CH_3).

(*R*) (+)-**Methyl 2-Chloro-6-tosylamidohexanoate** ((*R*) (+)-**15**)——A chloroform solution (15 ml) of (*S*)-methyl 2-hydroxy-6-tosylamidohexanoate (3.06 g, 9.7 mmole) was added to a refluxing solution of thionyl chloride (1.67 g, 19 mmole) and pyridine (1.50 g, 19 mmole) in chloroform (20 ml) over a period of 15 min with stirring. After reflux with stirring was continued for 2 hr, chloroform was removed *in vacuo* to give a residue which was dissolved in an ice-water. The aqueous mixture was extracted with ethyl acetate, and the combined organic extracts were washed with H_2O, and dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave a dark brown oil which was purified by column chromatography (silica gel, solvent benzene: ethyl acetate 6: 1) to give pure (*R*) (+)-**15** as a pale brown oil (2.62 g, 81%), $[\alpha]_D^{20}$ +11.1° (*c*=1.24, benzene). IR ν_{max}^{film} cm^{-1}: 3240 (NH), 1750 (ester), 1320, 1160 (SO_2). NMR (in $CDCl_3$): 1.0—2.3 (6H, bm, $NCH_2(C\underline{H}_2)_3$), 2.40 (3H, s, $C\underline{H}_3C_6H_4$), 2.95 (2H, m, $NC\underline{H}_2$), 3.70 (3H, s, $COOC\underline{H}_3$), 4.13 (1H, t, *J*=6 Hz, C<u>H</u>–Cl), 5.23 (1H, t, *J*=6 Hz, N<u>H</u>), 7.23 (2H, d, *J*=9 Hz, aromatic protons *ortho* to CH_3), 7.68 (2H, d, *J*=9 Hz, aromatic protons *meta* to CH_3).

Attempted Cyclization of (*R*) (+)-**Methyl 2-Chloro-6-tosylamidohexanoate** ((*R*) (+)-**15**)——A mixture of (*R*) (+)-**15** (0.83 g, 2.5 mmole) and sodium methoxide (prepared from Na (0.07 g, 3.0 mg atom)) in methanol (*ca.* 10 ml) was stirred at room temperature for 30 min. TLC analysis (silica gel, solvent benzene: ethyl acetate 6: 1) showed no cyclization had occurred. Then, the whole mixture was refluxed for 2 hr. Evaporation *in vacuo*, afforded a residue which was diluted with H_2O. The aqueous solution was extracted with ethyl acetate, and the combined organic extracts were washed with H_2O, and dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave the crude cyclized product ((±)-**11b**) as a red oil (0.26 g), $[\alpha]_D^{20}$ 0° (*c*=1.20, benzene).[35] IR and NMR spectra of this oil were almost the same as those of authentic (*S*) (−)-**11b** recorded in the same states.

On the other hand, when a mixture of (*R*) (+)-**15** (0.71 g, 2.0 mmole) and potassium *t*-butoxide (0.20 g, 1.8 mmole) in THF (10 ml) was stirred at room temperature overnight, the pure cyclized product, which was obtained by a similar extractive isolation to that for the above case, followed by purification with preparative TLC (silica gel, solvent benzene: ethyl acetate 6: 1), weighed 0.15 g and showed $[\alpha]_D^{20}$ −1.3° (*c*=0.80, benzene).[35] This sample was also comfirmed by spectral comparison with authentic (*S*) (−)-**11b**.

(*S*) (−)-**6-Amino-2-hydroxyhexanoic Acid Hydrochloride** ((*S*) (−)-**14-HCl**)——A solution of (*S*) (−)-**14** (2.94 g, 20 mmole) in 10% HCl (8 ml) was evaporated *in vacuo* to afford a crystalline residue. Addition of benzene, followed by evaporation *in vacuo*, was twice repeated to remove H_2O completely, to give crude (*S*) (−)-14-HCl as a white solid (4.05 g), mp 126—136°. Recrystallization from a mixture of H_2O, ethanol, and ether afforded pure (*S*) (−)-14-HCl as colorless prisms (3.17 g, 86%), mp 132—138°, $[\alpha]_D^{20}$ −1.3° (*c*=1.50, H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3500 (NH_3^+, OH), 1690 (COOH), 1590 (NH_3^+), 1070 (OH). *Anal.* Calcd. for $C_6H_{13}O_3N$–HCl: C, 39.24; H, 7.68; N, 7.63. Found: C, 38.94; H, 7.72; N, 7.58.

(*S*) (−)-**Methyl N-Tosylpipecolate** ((*S*) (−)-**11b**) **from** (*S*) (−)-**6-Amino-2-hydroxyhexanoic Acid Hydrochloride** ((*S*) (−)-**14-HCl**)——Crude (*S*) (−)-**14**-HCl (2.03 g) prepared from (*S*) (−)-**14** (1.47 g, 10 mmole), was added to a stirred solution of thionyl chloride (3.54 g, 49 mmole) and pyridine (3.16 g, 40 mmole) in chloroform (20 ml) at room temperature. Stirring was continued for 40 hr at room temperature, then chloroform was removed *in vacuo* to give a residue, to which was added H_2O (*ca.* 30 ml). The aqueous solution was extracted with benzene (50 ml×1), and the benzene layer was re-extracted with H_2O (50 ml×2). The combined aqueous layers were poured on to a column of ion exchanger (Amberlite IR-120, H^+ form, 200 ml). The column was thoroughly washed with H_2O until the eluate became neutral, then eluted with aqueous NH_4OH. Fractions which were positive to ninhydrin test, were evaporated *in vacuo* to give a dark brown oil (1.90 g). This oil was treated in a similar way to the case for the preparation of (*R*) (+)-**11b** from L-**5c**-HCl, to give pure (*S*) (−)-**11b** as a pale yellow oil (1.21 g, 41% based on (*S*) (−)-**14**) after purification by column chromatography, $[\alpha]_D^{20}$ −28.6° (*c*=2.04, benzene), 78% optically pure.[35] This sample was identified with authentic (*S*) (−)-**11b** by spectra (IR and NMR) and TLC comparisons.

L-Pipecolic Acid (L-**10c**)——A solution of (*S*) (−)-**11b** ($[\alpha]_D^{20}$ −26.2° (*c*=1.42, benzene), 72% optically pure[35]) (0.81 g, 2.7 mmole) in a mixture of acetic acid (10 ml) and 47% HBr (10 ml) was heated at reflux for

3 hr. After cooling, the reaction mixture was worked up in a similar manner to the case for the preparation of D-**10c** from (*R*) (+)-**11b**, to give L-**10c** as a pale brown powder (0.24 g, 69%) after recrystallization from methanol–ether, mp 258—268° (decomp.), $[\alpha]_D^{20}$ −16.0° (*c*=2.00, H_2O), 61% optically pure.[36] IR spectrum of this sample was identical with that of authentic L-**10c**.

(+)-Nε-Tosyl-L-lysine (L-**17**)——This compound was prepared in 50% yield as a colorless powder, according to the reported procedure,[19] and showed mp 212—215° (decomp.), $[\alpha]_D^{20}$ +15.2° (*c*=1.84, 2NHCl) (lit.,[19] mp 237—238°, $[\alpha]_D^{20}$ +13.6° (*c*=3.0, 2NHCl); lit.,[20] mp 217—219°). IR ν_{max}^{Nujol} cm^{-1}: 1585 (NH_3^+ and COO^-), 1350, 1140 (SO_2).

Deamination of (+)-Nε-Tosyl-L-lysine (L-**17**)——To a solution of L-**17** (0.90 g, 3 mmole) and sodium trifluoroacetate (2.66 g, 15 mmole) in trifluoroacetic acid (20 ml) was added sodium nitrite (0.32 g, 4.5 mmole) with stirring at room temperature. The whole solution was stirred overnight at room temperature, then evaporated *in vacuo* to give a pale green solid which was dissolved in H_2O. The aqueous solution was extracted with ethyl acetate (30 ml×2), and the combined organic extracts were washed with H_2O, and dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave a brown oil (0.53 g), which was directly treated with diazomethane. Successive purifications by column chromatography (silica gel, solvent benzene: ethyl acetate 6: 1) and preparative TLC (silica gel, solvent benzene: ethyl acetate 6: 1) gave (*S*) (−)-**11b** as a pale yellow oil (7 mg, 0.8%), $[\alpha]_D^{20}$ −32.9° (*c*=0.14, benzene), 90% optically pure.[35] Spectral (IR and NMR) and chromatographic (TLC) properties of this oil were identical with those of authentic (*S*) (−)-**11b** measured in the same states.

(*R*) (+)-1-Tosyl-2-tosyloxymethylpiperidine ((*R*) (+)-**20**)——a) (*R*) (+)-**20** from (*R*) (+)-**11a**: (+)-Methyl D-Pipecolate: Hydrogen gas was passed through a methanolic solution (50 ml) of (*R*) (+)-**11a** ($[\alpha]_D^{20}$ +39.8° (*c*=2.48, benzene)) (7.76 g, 28 mmole) and 5% palladium on charcoal (0.78 g) at room temperature for 5 hr. Filtration and evaporation *in vacuo* gave crude (+)-methyl D-pipecolate as a pale yellow oil (3.68 g, 92%). $[\alpha]_D^{20}$ +13.5° (*c*=1.38, MeOH) (lit.,[37] $[\alpha]_D$ +11.6° (*c*=8.5, MeOH)). IR ν_{max}^{film} cm^{-1}: 1740 (ester). NMR (in $CDCl_3$): 1.0—2.0 (6H, bm, NCH_2 ($C\underline{H}_2$)$_3$), 2.13 (1H, s, N<u>H</u>), 2.3—3.1 (2H, m, $NC\underline{H}_2$), 3.1—3.5 (1H, m, NC<u>H</u>), 3.70 (3H, s, $COOC\underline{H}_3$).

(*R*) (−)-2-Hydroxymethylpiperidine: A THF solution of crude (+)-methyl D-pipecolate (0.53 g, 3.7 mmole) was added to a suspension of LAH (0.70 g, 18.5 mmole) in THF (20 ml).[23] The whole solution was heated at reflux for 4 hr. After cooling, the formed metal complex was decomposed by the successive addition of ether saturated with H_2O (20 ml) and 10% NaOH (3 ml). The whole suspension was dried over anhyd. K_2CO_3, and filtered. A solid mass thus obtained, was washed with ether (50 ml). Ethereal filtrate and washings were combined, and dried over anhyd. K_2CO_3. Filtration and evaporation *in vacuo* gave crude (*R*) (−)-2-hydroxymethylpiperidine as a colorless oil (0.31 g, 73%), $[\alpha]_D^{21}$ −15.3° (*c*=0.90, EtOH) (lit.,[23] $[\alpha]_D^{21}$ −16.0° (*c*=2.34, EtOH)). IR ν_{max}^{film} cm^{-1}: 3400—3200, 1150 (OH).

(*R*) (+)-**20**: A mixture of crude (*R*) (−)-2-hydroxymethylpiperidine (1.05 g, 9.1 mmole) and tosyl chloride (4.20 g, 22 mmole) in pyridine (12 ml) was kept at 4° overnight, then poured into cold water, and extracted with ether (50 ml×2). Combined ethereal extracts were successively washed with 1N-HCl and satd. $NaHCO_3$ solutions, and dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave a brown oil (2.93 g), which was purified by column chromatography (alumina, solvent benzene) to afford pure (*R*) (+)-**20** as a pale yellow oil (2.12 g, 55%), $[\alpha]_D^{18}$ +42.3° (*c*=1.04, EtOH) (lit.,[23] $[\alpha]_D^{18}$ +56.6° (*c*=1.03, EtOH)). IR ν_{max}^{film} cm^{-1}: 1180, 1160 (SO_2). NMR (in $CDCl_3$): 0.8—2.1 (6H, bm, NCH_2 ($C\underline{H}_2$)$_3$), 2.40, 2.42 (6H, two s, 2×$C\underline{H}_3C_6H_4$), 2.3—4.5 (5H, bm, $C\underline{H}_2NHC\underline{H}C\underline{H}_2O$), 7.20, 7.30 (4H, two d, *J*=9 Hz, aromatic protons *ortho* to CH_3), 7.65, 7.72 (4H, two d, *J*=9 Hz, aromatic protons *meta* to CH_3). Mass Spectrum *m/e*: 424 (M+1), 252, 238, 155, 91.

b) (*R*) (+)-**20** from (*R*) (+)-**11b**: (*R*) (+)-2-Hydroxymethyl-1-tosylpiperidine: A THF solution (5 ml) of (*R*) (+)-**11b** ($[\alpha]_D^{20}$ +35.9° (*c*=1.08, benzene)) (1.26 g, 4.2 mmole) was added to a suspension of LAH (0.16 g, 4.2 mmole) in THF (15 ml). The whole solution was heated at reflux for 2 hr. After cooling, the formed metal complex was decomposed by the successive addition of ether saturated with H_2O (5 ml), H_2O (5 ml), and 10% NaOH (0.2 ml). The mixture was directly dried over anhyd. K_2CO_3 for 2 hr. Filtration and evaporation *in vacuo* gave the crude product as a colorless oil (0.83 g, 73%). This oil solidified when kept at room temperature, and showed mp 55—70°, $[\alpha]_D^{20}$ +36.1° (*c*=1.40, benzene). Repeated recrystallizations from benzene–hexane gave pure sample as colorless needles, mp 80—83°, $[\alpha]_D^{20}$ +40.4° (*c*=1.46, benzene). IR ν_{max}^{Nujol} cm^{-1}: 3560, 1060 (OH), 1310, 1150 (SO_2). NMR (in $CDCl_3$): 1.0—2.0 (6H, bm, NCH_2 ($C\underline{H}_2$)$_3$), 2.42 (4H, s, $C\underline{H}_3C_6H_4$ and O<u>H</u>), 2.6—4.3 (5H, bm, $C\underline{H}_2NC\underline{H}C\underline{H}_2O$), 7.25 (2H, d, *J*=9 Hz, aromatic protons *ortho* to CH_3), 7.73 (2H, d, aromatic protons *meta* to CH_3). *Anal.* Calcd. for $C_{13}H_{19}O_3NS$: C, 57.97; H, 7.11; N, 5.20. Found: C, 57.96; H, 7.17; N, 5.09.

(*R*) (+)-**20**: A mixture of (*R*) (+)-2-hydroxymethyl-1-tosylpiperidine (8.92 g, 33 mmole) and tosyl chloride (12.6 g, 66 mmole) in pyridine (35 ml) was kept overnight at room temperature. The whole was poured into an ice-water (50 ml), and extracted with ethyl acetate (50 ml×3). Combined organic extracts were successively washed with dil. HCl, satd. $CuSO_4$, H_2O, satd. $NaHCO_3$, and satd. NaCl solutions, then

37) V. Franzen, *Ber.*, **90**, 2036 (1957).

dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave a red oil which was purified by column chromatography (silica gel, solvent benzene: ethyl acetate 9: 1) to afford pure (*R*) (+)-**20** as a yellow oil (14.9 g, quantitative yield (106%)), $[\alpha]_D^{20}$ +42.8° (*c*=0.92, EtOH). Spectral (IR and NMR) properties of this oil were completely identical with those of (*R*) (+)-**20** independently prepared from (*R*) (+)-**11a**.

(*R*) (+)-2-Iodomethyl-1-tosylpiperidine——A dimethyl formamide solution (30 ml) of (*R*) (+)-**20** (17.8 g, 66 mmole) and sodium iodide (30.0 g, 0.20 mole) was heated at 90—100° with stirring. After diluted with ethyl acetate (100 ml), the whole mixture was successively washed with H_2O, dil. HCl, 0.1N $Na_2S_2O_3$, H_2O, satd. $NaHCO_3$, and satd. NaCl solutions, and finally dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave crude product as a reddish brown oil (21.6 g, 87%), which gradually solidified on standing, mp 60—70°, $[\alpha]_D^{20}$ +22.9° (*c*=1.40, benzene). Recrystallization from benzene–hexane gave pale brown prisms (17.5 g, 70%), mp 82—87°, $[\alpha]_D^{20}$ +25.4° (*c*=1.40, benzene). Further two recrystallizations from the same solvent system gave an analytical sample as colorless prisms, mp 86—88.5°, $[\alpha]_D^{20}$ +26.7° (*c*=1.16, benzene). IR ν_{max}^{Nujol} cm^{-1}: 1320, 1150 (SO_2). NMR (in $CDCl_3$): 1.0—2.3 (6H, bm, NCH_2 ($C\underline{H}_2$)$_3$), 2.40 (3H, s, $C\underline{H}_3C_6H_4$), 2.6—4.0 (4H, m, $C\underline{H}_2NCHC\underline{H}_2I$), 4.0—4.6 (1H, m, $NC\underline{H}$), 7.25 (2H, d, *J*=9 Hz, aromatic protons *ortho* to CH_3), 7.66 (2H, d, *J*=9 Hz, aromatic protons *meta* to CH_3). Mass Spectrum *m/e*: 379 (M^+), 238, 155, 91. *Anal.* Calcd. for $C_{13}H_{18}O_2NSI$: C, 41.17; H, 4.79; N, 3.69. Found: C, 40.78; H, 4.71; N, 3.39

(*R*) (+)-2-[2,2-Bis(ethoxycarbonyl)ethyl]-1-tosylpiperidine ((*R*) (+)-**21**)——A dimethyl formamide solution (5 ml) of diethyl malonate (0.48 g, 3 mmole) was added to a solution of potassium *t*-butoxide (0.34 g, 3 mmole) in dimethyl formamide (5 ml). (*R*) (+)-2-Iodomethyl-1-tosylpiperidine (0.34 g, 0.9 mmole) was added to the dimethyl formamide solution prepared above. The mixture was heated at reflux for 4.5 hr, then diluted with H_2O and extracted with ethyl acetate (20 ml×2). Combined organic extracts were successively washed with dil. HCl (20 ml×3) and satd. NaCl (20 ml×1) solutions, and dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* afforded a yellow oil (0.29 g), which was purified by preparative TLC (silica gel, solvent benzene: ethyl acetate 6: 1) to give (*R*) (+)-**21** as a pale yellow oil (0.16 g, 43%), $[\alpha]_D^{20}$ +34.5° (*c*=1.10, benzene). IR ν_{max}^{film} cm^{-1}: 1740, 1250 (ester), 1320, 1150 (SO_2). NMR (in $CDCl_3$): 1.0—2.0 (6H, bm, NCH_2 ($C\underline{H}_2$)$_3$), 1.26 (6H, t, *J*=7 Hz, 2×$CH_2C\underline{H}_3$), 2.0—4.6 (6H, bm, $C\underline{H}_2NC\underline{H}C\underline{H}_2C\underline{H}$), 2.40 (3H, s, $C\underline{H}_3C_6H_4$), 4.21 (4H, q, *J*=7 Hz, 2×$C\underline{H}_2CH_3$), 7.25 (2H, d, *J*=9 Hz, aromatic protons *ortho* to CH_3), 7.65 (2H, d, *J*=9 Hz, aromatic protons *meta* to CH_3).

(*R*) (+)-2-(2-Ethoxycarbonylethyl)-1-tosylpiperidine ((*R*) (+)-**22**)——A mixture of (*R*) (+)-**21** (0.16 g, 0.4 mmole) and H_2O (27 mg, 1.5 mmole) in dimethyl sulfoxide (2 ml) was heated at 160° for 1 hr, then refluxed at 170° for 1 hr.[26] After diluted with H_2O, the mixture was extracted with ethyl acetate (×3). Combined organic extracts were successively washed with dil. HCl (×3), and satd. NaCl (×2) solutions, and dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave crude (*R*) (+)-**22** as a pale brown oil (115 mg, 91%), $[\alpha]_D^{20}$ +35.5° (*c*=0.40, benzene). IR ν_{max}^{film} cm^{-1}: 1740, 1180 (ester), 1330, 1150 (SO_2). NMR (in $CDCl_3$): 0.5—1.7 (6H, bm, NCH_2 ($C\underline{H}_2$)$_3$), 1.25 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 1.7—4.5 (7H, bm, $C\underline{H}_2NC\underline{H}C\underline{H}_2C\underline{H}_2CO$), 2.40 (3H, s, $C\underline{H}_3C_6H_4$), 4.07 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 7.25 (2H, d, *J*=9 Hz, aromatic protons *ortho* to CH_3), 7.65 (2H, d, *J*=9 Hz, aromatic protons *meta* to CH_3). This crude oil was directly used for the next step.

(*R*) (+)-2-(3-Hydroxypropyl)-1-tosylpiperidine——A THF solution (30 ml) of (*R*) (+)-**22** (6.69 g, 20 mmole) was added to a suspension of LAH (0.75 g, 20 mmole) in THF (60 ml). The whole mixture was heated at reflux for 4 hr, then the formed complex was decomposed by the addition of 10% NaOH (5 ml) and ether (30 ml). After refluxing for 1 hr, the heterogeneous solution was filtered. The filtrate was dried over anhyd. K_2CO_3, and filtration and evaporation *in vacuo* gave a colorless turbid oil (3.82 g), which was purified by column chromatography (silica gel, solvent benzene: ethyl acetate 1: 1) to give the pure product as a pale yellow oil (3.50 g, 60%), $[\alpha]_D^{20}$ +42.1° (*c*=0.38, benzene). IR ν_{max}^{film} cm^{-1}: 3600—3200, 1030 (OH), 1320, 1150 (SO_2): NMR (in $CDCl_3$): 0.5—2.2 (10H, bm, NCH_2 ($C\underline{H}_2$)$_3$$C\underline{H}$($C\underline{H}_2$)$_2$$CH_2OH$), 2.00 (1H, s, O$\underline{H}$), 2.40 (3H, s, $C\underline{H}_3C_6H_4$), 2.6—4.3 (5H, bm, $C\underline{H}_2NC\underline{H}(CH_2)_2C\underline{H}_2OH$), 7.25 (2H, d, *J*=9 Hz, aromatic protons *ortho* to CH_3), 7.65 (2H, d, *J*=9 Hz, aromatic protons *meta* to CH_3). Mass Spectrum *m/e*: 298 (M^+), 238, 155, 91.

(*R*) (+)-1-Tosyl-2(3-tosyloxypropyl)piperidine——A mixture of (*R*) (+)-2-(3-hydroxypropyl)-1-tosylpiperidine (0.48 g, 1.6 mmole) and tosyl chloride (0.61 g, 3.2 mmole) in pyridine (5.0 ml) was kept at room temperature overnight, then poured on to an ice-water (50 ml) and extracted with ethyl acetate (×2). Combined organic extracts were successively washed with dil. HCl, satd. $CuSO_4$, satd. $NaHCO_3$, and satd. NaCl solutions, and finally dried over anhyd. $MgSO_4$. Filtration and evaporation *in vacuo* gave a pale brown oil (0.50 g), which was purified by preparative TLC (silica gel, solvent benzene: ethyl acetate 6: 1) to give the pure ditosylate as a pale yellow oil (0.26 g, 36%), $[\alpha]_D^{20}$ +31.9° (*c*=0.54, benzene). IR ν_{max}^{film} cm^{-1}: 1320, 1150 (SO_2). NMR (in $CDCl_3$): 0.8—2.2 (10H, bm, $NCH_2(C\underline{H}_2)_3C\underline{H}(C\underline{H}_2)_2$), 2.42, 2.46 (6H, two s, 2×$C\underline{H}_3C_6H_4$), 2.6—4.3 (5H, bm, $C\underline{H}_2NC\underline{H}(CH_2)_2C\underline{H}_2O$), 7.20, 7.25 (4H, two d, *J*=9 Hz, aromatic protons *ortho* to CH_3), 7.65, 7.75 (4H, two d, *J*=9 Hz, aromatic protons *meta* to CH_3). Mass Spectrum *m/e*: 451 (M^+), 238, 155, 91.

(*S*) (+)-N-Tosylconiine ((*S*) (+)-**23**)——A THF solution (15 ml) of (*R*) (+)-1-tosyl-2-(3-tosyloxypropyl)-piperidine (2.80 g, 6.2 mmole) was added to a suspension of LAH (0.71 g, 19 mmole) in THF (20 ml). The mixture was heated at reflux for 4 hr, then the formed complex was decomposed with 10% NaOH (0.5 ml) and ether (10 ml) after cooling. The heterogeneous solution was refluxed for 1 hr, and then filtered. The filtrate was dried over anhyd. K_2CO_3, and filtration and evaporation *in vacuo* gave (*S*) (+)-**23** as a pale yellow oil (1.28 g, 73%), $[\alpha]_D^{20}$ +37.5° (*c*=0.98, benzene). IR ν_{max}^{film} cm^{-1}: 1320, 1150 (SO_2). NMR (in $CDCl_3$): 0.6—

1.1 (3H, bt, $C\underline{H}_3$), 1.1—1.8 (10H, bm, $NCH_2(C\underline{H}_2)_3CH(C\underline{H}_2)_2CH_3$), 2.40 (3H, s, $C\underline{H}_3C_6H_4$), 2.6—4.3 (3H, bm, $C\underline{H}_2NC\underline{H}CH_2$), 7.25 (2H, d, $J=9$ Hz, aromatic protons *ortho* to CH_3), 7.65 (2H, d, $J=9$ Hz, aromatic protons *meta* to CH_3). Mass Spectrum *m/e*: 281 (M^+), 238, 155, 91. TLC analysis of this sample showed a single spot whose *Rf* value was *ca.* 0.6 (silica gel, solvent benzene: ethyl acetate 6: 1).

(±)-N-Tosylconiine ((±)-**23**)——This compound was synthesized from crude (±)-**1** by tosylation with tosyl chloride and pyridine, followed by purification by preparative TLC (silica gel, solvent benzene: ethyl acetate 6: 1). Crude (±)-**1** was independently prepared from 2-cyanopyridine according to the published procedure.[27] (±)-**23** obtained as a pale yellow oil, showed complete the same spectral (IR and NMR) and chromatographic (TLC) behavior as those of (*S*) (+)-**23**.

(*S*) (+)-Coniine ((*S*) (+)-**1**)——A solution of (*S*) (+)-**23** (1.14 g, 4.1 mmole) in a mixture of acetic acid (10 ml) and 47% HBr (10 ml) was heated at reflux for 6 hr. The whole solution was diluted with H_2O (20 ml), and treated with charcoal. Filtration and evaporation *in vacuo* gave a residue, to which was added dil. aqueous NaOH. The alkaline solution was extracted with ether (30 ml×2). Combined ethereal extracts were washed with satd. NaCl solution (×1), and dried over anhyd. K_2CO_3. Filtration and concentration under atmospheric pressure gave an oily residue, which was submitted to fractional distillation to give pure (*S*) (+)-**1** as a colorless oil (0.28 g, 54%), bp 190—200° (760 mmHg) (bath temperature), $[\alpha]_D^{27}$ +8.9° ($c=0.54$, $CHCl_3$) (lit.,[28] $[\alpha]_D^{27}$ +9.0° ($c=1.00$, $CHCl_3$)). IR ν_{max}^{film} cm^{-1}: 3400—3200, 1650 (NH), 1120. NMR (in $CDCl_3$): 0.85 (3H, bt, $J=6$ Hz, $C\underline{H}_3$), 1.0—2.0 (10H, bm, $NCH_2(C\underline{H}_2)_3CH(C\underline{H}_2)_2CH_3$), 1.46 (1H, s, $N\underline{H}$), 2.0—3.3 (3H, bm, $C\underline{H}_2NC\underline{H}$). When the oily residue, obtained by concentration of the ethereal extract under atmospheric pressure, was dissolved in a mixture of 47% HBr (1 ml) and H_2O (3 ml), and the aqueous solution was evaporated *in vacuo* to afford crude (*S*) (+)-**1**-HBr as a pale brown semi-solid. Repeated recrystallizations from ethanol-ethyl acetate gave an analytical sample as colorless fine needles, mp 206—208° (lit.,[29a] mp 207°; lit.,[29b] mp 211°), $[\alpha]_D^{20}$ *ca.* +1° ($c=0.96$, EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1590 (NH_2^+). NMR (in $CDCl_3$): 0.97 (3H, bt. $J=6$ Hz, $C\underline{H}_3$), 1.0—2.5 (10H, bm, NCH_2 $(C\underline{H}_2)_3CH(C\underline{H}_2)_2CH_3$), 2.5—3.9 (3H, bm, $C\underline{H}_2NC\underline{H}$), 8.90 (2H, bs, $N\underline{H}_2^+$). *Anal.* Calcd. for $C_8H_{17}NHBr$: C, 46.16; H, 8.72; N, 6.73. Found: C, 45.52; H, 8.66; N, 6.63.

(±)-Coniine ((±)-**1**)——Similar treatment of (±)-**23** to that for (*S*) (+)-**23** gave pure (±)-**1** as a colorless oil, bp 200—210° (760 mmHg) (bath temperature), and its hydrobromide as colorless fine needles, mp 195—197 (lit.,[38] mp 199—200°). NMR spectra of these racemic compounds were respectively identical with those of (*S*) (+)-**1** and (*S*) (+)-**1**-HBr.

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