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Amino Acids and Peptides. XXIII.[1] An Asymmetric Synthesis of (*R*)-(—)-Laudanosine from L-3-(3,4-Dihydroxyphenyl)alanine

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Following the previous asymmetric syntheses of (*S*)-(+)-laudanosine (V) and (*S*)-(+)-reticuline (VI) from L-3-(3,4-dihydroxyphenyl)alanine (L-DOPA),[3a,b] (*R*)-(—)-laudanosine (XXIV) has been also synthesized from L-DOPA. A key step is an epimerization of (1*S*, 3*S*)-methyl 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (XIa), which was derived from a major product of the Pictet-Spengler reaction of the methyl ester of L-DOPA (Ia) and sodium 3-(3,4-dimethoxyphenyl)glycidate (IIa), to (1*R*,3*S*)-isomer (XIIa) under the hydrogenation condition using PtO_2 in MeOH–AcOH (100: 1). XIa and XIIa are interconvertible under this condition. Isomerization reactions of XIa and XIIa in a basic medium (MeONa in MeOH) have been also examined. Both compounds epimerize at C-3 position and afford the new (1*S*, 3*R*)-(XIII)- and (1*R*, 3*R*)-(XIV)-isomers, respectively.

Keywords——asymmetric synthesis; L-DOPA; decyanization; isomerization; isoquinoline alkaloid; (*R*)-(—)-laudanosine

We have observed that Pictet-Spengler reaction of the methyl ester of L-3-(3,4-dihydroxyphenyl)alanine (L-DOPA) (Ia) and sodium 3-(3,4-dimethoxyphenyl)glycidate (IIa) gave sterically favored (1*S*,3*S*)-methyl 1-(3,4-dimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (IIIa; 1,3-*cis*) in 31% yield, together with 13% yield of an unfavored (1*R*,3*S*)-isomer (IVa; 1,3-*trans*).[3a,b] A similar reaction of homologous Ib and IIb gave a (1*S*,3*S*)-isomer (IIIb) in 11.4% yield and a (1*R*,3*S*)-isomer (IVb) in 5.4% yield.[3c] Previous papers[3] also described the syntheses of optically pure (*S*)-(+)-laudanosine (V) and (*S*)-(+)-reticuline (VI) from the major products, IIIa and IIIb, in several steps, involving the conversion of 3-carboxyl group into the nitrile followed by reductive decyanization with sodium borohydride ($NaBH_4$).

With a little more improvement of the yield or the stereospecificity of the initial Pictet-Spengler reaction, this asymmetric synthesis of 1-(*S*)-substituted tetrahydroisoquinolines from L-DOPA by 1,3-transfer of chiral center could be generalized as a synthetic method for naturally occurring benzylisoquinoline alkaloids possessing an (*S*)-configuration at C-1.

On the other hand, the minor products, IVa and IVb, are also useful starting materials[4] for the synthesis of optically active morphine (VII)-series alkaloids, which have an (*R*)-configuration at C-9, the position corresponding to C-1 in IVa and IVb.

Continuing interest in the Pictet-Spengler reaction products led us to investigate the interrelation of 1,3-disubstituted tetrahydroisoquinolines (XI, XII, XIII, and XIV, shown in Chart 2) under several isomerization conditions. This report describes the results of the

1) Part XXII: K. Ninomiya, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **24**, 2711 (1976).
2) Location: *a) 2-2-50, Kawagishi, Toda-shi, Saitama, 335, Japan*; *b) 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
3) *a*) S. Yamada, M. Konda, and T. Shioiri, *Tetrahedron Letters*, **1972**, 2215; *b*) M. Konda, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 1025 (1975); *c*) M. Konda, T. Shioiri, and S. Yamada, *ibid.*, **23**, 1063 (1975).
4) A recent brilliant work by M.A. Schwartz and I.S. Mami has actualized the biogenetically patterned synthesis of (±)-thebaine from (±)-reticuline in a practical yield; *J. Am. Chem. Soc.*, **97**, 1239 (1975).

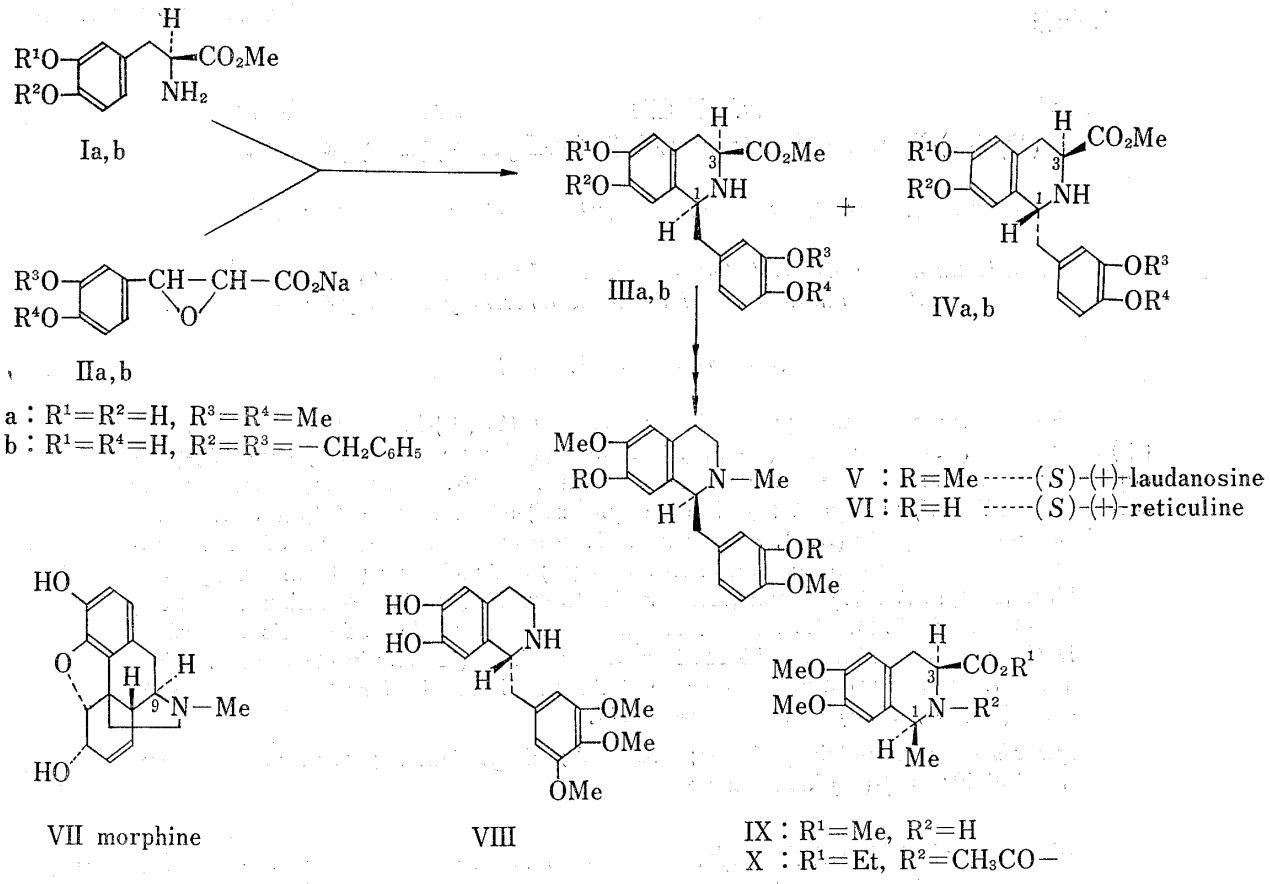


Chart 1

attempted isomerization reactions and also the conversion of IVa into (*R*)-(−)-laudanosine (XXIV) as a model for an approach to the asymmetric synthesis of morphine alkaloids.

Isomerization Reactions

Procedure A: With Heating——Yamato and Kawanishi observed that the hydrochloride of (1*R*)-(+)-1-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (VIII) readily racemized by heating to melt at 200°.[5] Accordingly, the hydrochloride of IVa was heated at 200°, but this procedure resulted in complete decomposition of the starting compound giving only tarry materials.

Procedure B: Under Hydrogenation Conditions[6]——Pure XIa in MeOH–AcOH (100: 1)[7] was stirred with PtO_2 in hydrogen atmosphere at room temperature for 40 hr to give a mixture of XIa and XIIa in 1: 3.8 ratio. Similar treatment starting with XIIa gave a mtixure of XIa and XIIa in 1: 2.7 ratio. The 1,3-*trans* isomer (XIIa) was found to predominate over the 1,3-*cis* isomer (XIa) under this condition. The composition of the products was determined by gas–liquid chromatography (GLC), and each product was identified after isolation by thin-layer chromatography (TLC). The trans predominance, on treatment under the same condition, was more remarkable with N-methyl compounds, XIb and XIIb, both of which gave almost exclusively the 1,3-*trans* isomer (XIIb) (more than 95% yield), and the 1,3-*cis* isomer (XIb) was sparingly detected in the reaction mixture by GLC. Any compound epimerized

5) Unpublished results. The (1*S*)-enantiomer of VIII is an efficient bronchodilator, Trimetoquinol or Inolin.

6) Racemization of optically active protoberberine alkaloids and 1-benzyl-tetrahydroisoquinolines under the conditions of catalytic hydrogenation has been described; *a*) T. Kametani and M. Ihara, *J. Chem. Soc.* (*C*), **1968**, 191; *b*) T. Kametani, M. Ihara, and K. Shima, *ibid.*, **1968**, 1619.

7) Without addition of a small amount of AcOH, only starting XIa was quantitatively recovered.

at C-3 was not obtained in the above experiments, and isomerization of (1*S*,3*S*)-methyl 1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (IX)[8] did not take place by this procedure. These facts indicate that epimerization at C-1 in XI and XII might proceed through the abstraction of hydrogen atoms from C-1 and the active benzylic position of the 1-substituent forming intermediary XV, followed by recombination of hydrogens to the double bond from the less hindered side.

We also attempted isomerization of XIIb with PtO_2, using AcOH as a solvent. Methyl 1-cyclohexyl-(XVI), 1-monomethoxycyclohexyl-(XVII), and 1-dimethoxycyclohexyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (XVIII) were isolated from the reaction mixture in 23%, 26.5%, and 23.6% yield, respectively. Although the stereochemistry of these compounds could not be established, the structures were confirmed on the basis of NMR and mass spectrometries. Treatment of the isolated XVIII under the same condition gave rise to no further demethoxylation. The demethoxylation producing XVI and XVII might take place at the stage of dihydro- or tetrahydro-benzene.

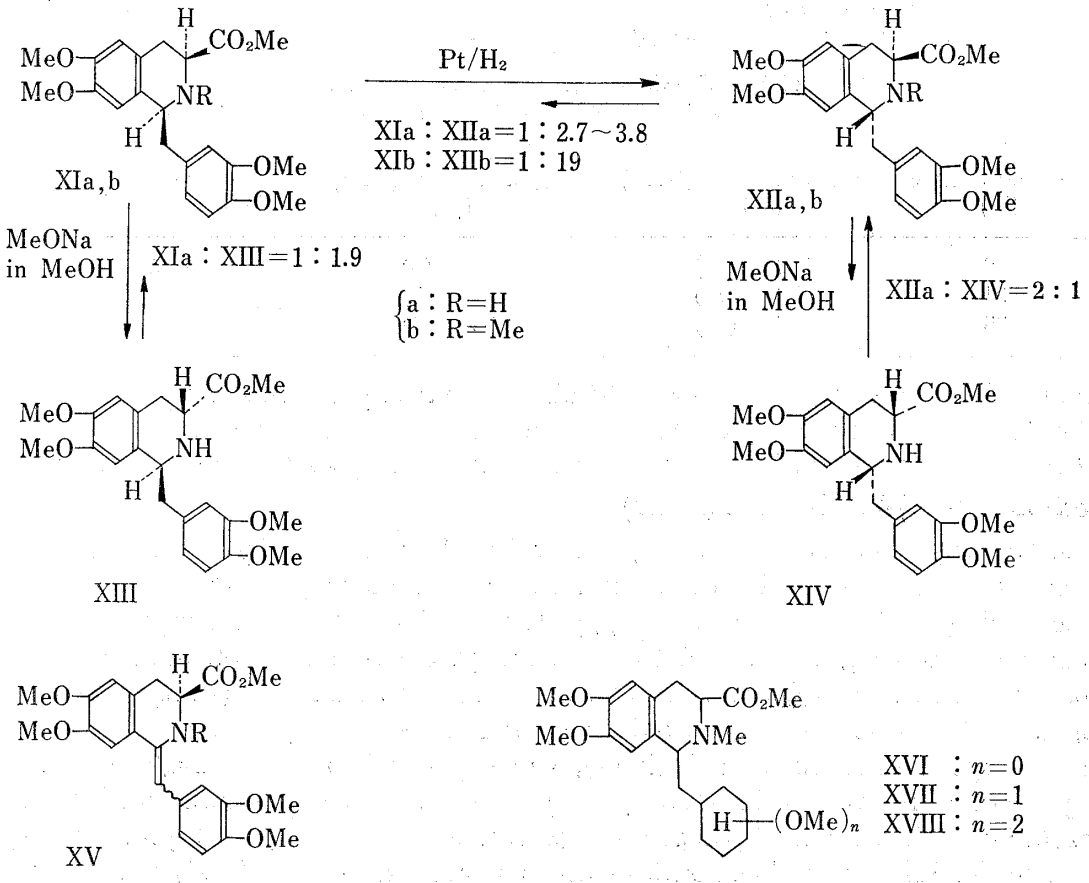


Chart 2

Procedure C: With Sodium Methoxide (MeONa)——Isomerization of XIa and XIIa in a basic medium was also examined. Heating of a methanolic solution of XIa and MeONa at 50° gave an equilibrium mixture in 95 hr, which consisted of XIa (35%) and XIII (65%). XIIa was similarly treated to attain an equilibration of XIIa (67%) and XIV (33%) in 95 hr. The product ratio during the reactions was monitored by GLC and measurement of their optical rotations (Table I). The structures of new isomers, XIII and XIV, were readily

8) (1*S*,3*S*)-(−)-6,7-Dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid was synthesized by the method reported by A. Brossi, A. Focella, and S. Teitel, *Helv. Chim. Acta*, **55**, 15 (1972). Esterification of the acid with MeOH–HCl and methylation with diazomethane gave IX as an oil; HCl-salt, mp 226—228° (decomp.), $[\alpha]_D^{20}$ −20.4° (MeOH).

determined by comparing the physical properties (infrared (IR) spectra, NMR, melting points, and optical rotations) with those of their enantiomers, XIa and XIIa. By this procedure, epimerization occurred exclusively at C-3 position, and 1,3-*trans* isomers (XIII and XIIa) were found more favorable than 1,3-*cis* isomers (XIa and XIV) in a basic medium.

Table I-a. The Compositions of XIa and XIII during the Isomerization Reaction in a Basic Medium

Reaction time (hr)	1,3-*cis* Isomer (XIa) (%)	1,3-*trans* Isomer (XIII) (%)	$[\alpha]_D$ of the reaction mixture
1	100[a] (100)[b]	0[a] (0)[b]	−112.5°
3	94 (—)	6 (—)	—
6	77 (76)	23 (24)	−70.0°
21	54 (53)	46 (47)	−27.8°
95	35 (37)	65 (63)	0

a) determined by GLC
b) Values in parentheses were calculated from the optical rotation

Table I-b. The Composition of XIIa and XIV during the Isomerization Reaction in a Basic Medium

Reaction time (hr)	1,3-*trans* Isomer (XIIa) (%)	1,3-*cis* Isomer (XIV) (%)	$[\alpha]_D$ of the reaction mixture
0	100 (100)	0 (0)	−67.0°
21	73 (75)	27 (25)	−22.3°
95	67 (67)	33 (33)	−8.5°

Similar base catalyzed equilibration studies of optically active 2-acetyl-6,7-dimethoxy-1-methyl-tetrahydroisoquinolinecarboxylic esters (X) were recently reported by Bruderer, *et al.*,[9] who also showed that the equilibration mixtures mainly contained the 1,3-*trans* isomer.

Synthesis of (*R*)-(—)-Laudanosine (XXIV)

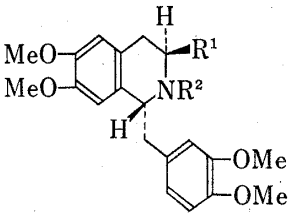
The starting 1,3-*trans* ester (XIIa) was supplied sufficiently by the above-mentioned isomerization method of the Pictet-Spengler reaction products (Procedure B).

The amide (XIX) was obtained in 97% yield from XIIa by its treatment with methanolic ammonia under cooling, and benzylated with benzyl chloride and potassium carbonate in ethanol to give XX in 92.5% yield. Dehydration of XX to the nitrile (XXI) was effected by heating at 100° with phosphorus pentoxide and Hyflo-super-cel in pyridine. After separation from Hyflo-super-cel the crude nitrile (XXI), which appeared to be unstable,[10] was subjected to decyanization reaction with $NaBH_4$ to give XXII in 58% overall yield from XX. Debenzylation of XXII with hydrogen and palladium on carbon (Pd-C) gave (*R*)-(—)-norlaudanosine (XXIII), the hydrochloride of which showes $[\alpha]_D$ −36.8° (H_2O) and the identical NMR and mass spectra with those of (*S*)-(+)-norlaudanosine prepared by us earlier.[3a,b]

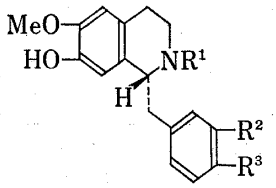
The final product, (*R*)-(—)-laudanosine (XXIV) was prepared quantitatively from XXIII by methylation with formaline and $NaBH_4$. The physical data (melting point and IR, NMR and Mass spectra) of XXIV are coincident with those of authentic (*S*)-(+)-laudanosine (V).[3a,b] The optical purity of XXIV was established by the rotation of a similar magnitude but with an opposite sign to that of optically pure V.

Application of the above method, using the compound with appropriate substituents, would similarly provide the other (*R*)-1-benzylisoquinoline alkaloids, such as (*R*)-(—)-reticuline (XXV) and D-(+)-coclaurine (XXVI), from L-DOPA.

9) H. Bruderer, A. Brossi, A. Focella, and S. Teitel, *Helv. Chim. Acta*, **58**, 795 (1975).
10) *cf.* Ref. 3*a*, *b*. No attempt was made to purify XXI in the present study.



XIX : $R^1=CONH_2$, $R^2=H$
XX : $R^1=CONH_2$, $R^2=-CH_2C_6H_5$
XXI : $R^1=CN$, $R^2=-CH_2C_6H_5$
XXII : $R^1=H$, $R^2=-CH_2C_6H_5$
XXIII : $R^1=R^2=H$
XXIV : $R^1=H$, $R^2=Me$ ··· (*R*)-(−)-laudanosine



XXV : $R^1=Me$, $R^2=OH$, $R^3=OMe$
XXVI : $R^1=H$, $R^2=H$, $R^3=OH$

Chart 3

Experimental

All the melting points were uncorrected. Infrared (IR) spectra were taken with a Hitachi 215 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded at 60 Mc on a Model JNM-MH-60 II spectrophotometer with tetramethylsilane as an internal standard. Mass spectra were determined on a Hitachi Mass spectrometer, Model RMS-4. Optical rotations were measured with a JASCO DIP 180 automatic polarimeter. GLC was carried out on a Shimazu Model GC-4B (1.5 meter, 1.5% OV-1). The organic solutions were dried over Na_2SO_4 prior to vacuum evaporation.

Isomerization Reactions under Hydrogenation Conditions——i) XIa in MeOH–AcOH: XIa (0.2 g) was dissolved in MeOH (20 ml) and AcOH (0.2 ml). The mixture was stirred over PtO_2 (0.2 g) in hydrogen atmosphere at room temperature for 40 hr. After removing the catalyst, the solution was neutralyzed with 12 M NH_4OH and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried and evaporated to give an oil (0.16 g), which consisted of XIa and XIIa in a ratio of 1: 2.7 (GLC).[11] Isolation by preparative TLC (silica gel, 2: 1 $CHCl_3$–AcOEt) gave XIa (45 mg), mp 123—124°, $[\alpha]_D^{20}$ −108.9° (c=0.420, MeOH) and XIIa (70 mg), mp 95—97°, $[\alpha]_D^{20}$ −71.0° (c=0.388, MeOH).[12]

ii) XIIa in MeOH–AcOH: The same procedure was followed as for the *cis* isomer (XIa). XIIa (0.15 g) gave an oily mixture (0.13 g) of XIa and XIIa in a ratio of 1: 3.8 (GLC).[11] Isolated XIa (27 mg) had mp 121—122°, $[\alpha]_D^{20}$ −100° (c=0.160, MeOH), and XIIa (60 mg) had mp 96—98°, $[\alpha]_D^{20}$ −61.5° (c=0.436, MeOH)[12]

iii) XIb in MeOH–AcOH: The same procedure as for XIa gave crude XIIb, mp 90—112°, $[\alpha]_D^{20}$ −6.4° (c=0.480, MeOH),[12] in 85% yield. GLC indicated that this material contained 3% of XIb.

iv) XIIb in MeOH–AcOH: The same procedure as for XIa gave crude XIIb quantitatively, mp 105—116°, $[\alpha]_D^{20}$ −8.4° (c=0.400, MeOH).[12] This material was also found to contain 4% of XIb by GLC analysis.

v) XIb in AcOH: XIb (0.2 g) in AcOH (20 ml) was stirred over PtO_2 (0.2 g) in hydrogen atmosphere at room temperature for 40 hr. After removing the catalyst, the solution was diluted with H_2O, neutralized with 12 M NH_4OH and extracted with AcOEt. Work-up as usual gave a yellow viscous oil (175 mg). The preparative TLC (silica gel, 1: 1 benzene–AcOEt) gave three oily compounds. XVI (50 mg, 23%) was obtained from the highest fraction; NMR ($CDCl_3$) δ: 2.40 (3H, s, N–CH_3), 3.77 (3H, s, –CO_2CH_3), 3.90 (6H, s, 2×Ar-OCH_3), 6.62 (1H, s, aromatic proton), 6.67 (1H, s, aromatic proton); Mass Spectrum m/e: 361 (M^+), 264 (base). XVII (40 mg, 26.5%) was obtained from the middle fraction; NMR ($CDCl_3$) δ: 2.40 (3H, s, NCH_3), 3.35 (3H, s, –OCH_3), 3.78 (3H, s, –CO_2CH_3), 3.89 (6H, s, 2×ArOCH_3), 6.61 (1H, s, aromatic proton), 6.67 (1H, s, aromatic proton); Mass Spectrum m/e: 391 (M^+), 264 (base). XVIII (48 mg, 23.6%) was obtained from the bottom fraction; NMR ($CDCl_3$) δ: 2.40 (3H, s, NCH_3), 3.37 (3H, s, –OCH_3), 3.41 (3H, s, –OCH_3), 3.75 (3H, s, –CO_2CH_3), 3.86 (6H, s, 2×ArOCH_3), 6.57 (1H, s, aromatic proton), 6.64 (1H, s, aromatic proton); Mass Spectrum m/e: 421 (M^+), 264 (base).

Isomerization Reaction of XIa with CH_3ONa——To XIa (0.60 g, 1.5 mmole) in MeOH (11 ml) was added CH_3ONa (17.2 mg, 0.3 mmole) in MeOH (1 ml) under ice-cooling. Then the mixture was stirred at 50°. During the reaction, samplings were made at intervals shown in Table I-a. Each sample (3 ml) was taken up in AcOEt after neutralization with AcOH, washed with saturated $NaHCO_3$ aqueous solution and H_2O, dried and freed from the solvent by evaporation to give a viscous oil in more than 90% yield, and analyzed by GLC[11] and measurement of optical rotations. The results were summarized in Table I. In order to isolate

11) The sample was N-trifluoroacetylated and then analyzed by GLC.
12) Melting points and optical rotations of the analytical samples. *cf.* lit. 3*a*, *b*. XIa; mp 126—128°, $[\alpha]_D^{20}$ −112.5° (MeOH). XIb; mp 95—96°, $[\alpha]_D^{20}$ −67.0° (MeOH). XIIa; mp 76—78°, $[\alpha]_D^{20}$ −47.3° (MeOH). XIIb; mp 118—120°, $[\alpha]_D^{20}$ −4.8° (MeOH).

the products the final sample after 95 hr was worked up in the similar manner and subjected to preparative TLC (silica gel, 2: 1 $CHCl_3$–AcOEt). From the band with higher *Rf* value, XIa was isolated as colorless crystals, mp 124—125°, $[\alpha]_D^{20}$ −114.5° (c=0.234, MeOH).[12] From the band with lower *Rf* value, XIII was isolated as colorless crystals, mp 94—97°, $[\alpha]_D^{20}$ +67.0° (c=0.254, MeOH) and exhibited the identical IR spectrum with that of XIIa. Analysis could not be made because of the shortage of the sample.

Isomerization Reaction of XIIa with CH_3ONa——This experiment was run in the same way as described for the *cis*-isomer (XIa), and the results were summarized in Table I-b. The final products after 95 hr were also separated into each component by preparative TLC (silica gel, 2: 1 $CHCl_3$–AcOH). XIIa (lower *Rf*) had mp 97—98° and $[\alpha]_D^{20}$ −73.5° (c=0.808, MeOH).[12] XIV (higher *Rf*) was colorless needles from AcOEt–*n*-hexane, mp 123—125°, $[\alpha]_D^{20}$ +120° (c=0.400, MeOH) and exhibited the identical IR spectrum with that of XIa. *Anal.* Calcd. for $C_{22}H_{27}O_6N$ (XIV): C, 65.65; H, 6.78; N, 3.49. Found: C, 65.91; H, 6.73; N, 3.51.

(1*R*,3*S*)-(−)-1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (XIX)——An ice-cooled solution of XIIa (2.0 g) in MeOH (400 ml) was saturated with ammonia gas. The mixture was allowed to stand at room temperature for 24 hr and evaporated to give XIX (1.90 g, 96.0%). A sample for analysis was obtained as colorless needles by recrystallization from $CHCl_3$–AcOEt and melted at 206—208°, $[\alpha]_D^{20}$ −77.2° (c=0.500, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3440, 3310, 3270, 1675. NMR ($CDCl_3$) δ: 3.65 (3H, s, $-OCH_3$), 3.80 (9H, s, $3\times OCH_3$), 7.10 (2H, s, $-CONH_2$). Mass Spectrum *m/e*: 235 (base). *Anal.* Calcd. for $C_{21}H_{26}O_5N_2\cdot 1/2H_2O$: C, 63.77; H, 6.88; N, 7.08. Found: C, 64.23; H, 6.55; N, 7.13.

(1*R*,3*S*)-(−)-1-(3,4-Dimethoxybenzyl)-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (XX)——A mixture of XIX (1.9 g, 4.7 mmole), benzyl chloride (3.6 g, 28.1 mmole), K_2CO_3 (3.9 g, 28.1 mmole) and EtOH (150 ml) was refluxed for 4 hr. Removal of the insoluble materials by filtration and evaporation of the solvent gave a residue, which was dissolved in 10% HCl. The acidic solution was washed with AcOEt, basified with K_2CO_3 and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried and evaporated to give XX as colorless crystals (2.1 g, 92.5%). Recrystallization from $CHCl_3$–$(C_2H_5)_2O$ gave needles, mp 140°, $[\alpha]_D^{20}$ −47.0° (c=0.540, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3460, 3340, 1695. Mass Spectrum *m/e*: 325 (base). *Anal.* Calcd. for $C_{28}H_{32}O_5N_2\cdot 1/2H_2O$: C, 69.26; H, 7.06; N, 5.77. Found: C, 69.50; H, 6.77; N, 5.66.

(*R*)-(−)-1-(3,4-Dimethoxybenzyl)-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XXII)——To a stirred suspension of P_2O_5 (8.8 g, 63 mmole) and dry Hyfro-super-cel (18 g) in pyridine (90 ml) was added a solution of XIX (2.0 g, 4.1 mmole) in pyridine (10 ml) at 80°, and then stirring was continued at 100° for 4 hr. The insoluble materials were removed by filtration and rinsed well with $CHCl_3$. The mother liquor and the $CHCl_3$ washings were combined and evaporated to give 3-cyano derivative (XXI), which was directly used in the next reaction without further purification. Crude XXI was dissolved in pyridine (30 ml) and EtOH (70 ml). To this was added $NaBH_4$ (0.64 g, 16.8 mmole) with stirring. The mixture was stirred at room temperature for 20 hr and evaporated to give a residue, which was taken up in AcOEt. The AcOEt solution was washed with saturated NaCl aqueous solution, dried and evaporated to give a yellow viscous oil. Purification by preparative TLC (silica gel, 8: 1 $CHCl_3$–AcOEt) gave XXII (1.03 g, 57.9%) as a yellow viscous oil, $[\alpha]_D^{20}$ −52.9° (c=0.386, MeOH), whose IR and NMR spectra were identical with those of the known (*S*)-(+)-isomer.[3a,b]

(*R*)-(−)-1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline=(*R*)-(−)-Norlaudanosine (XXIII)——XXII (0.92 g, 2.12 mmole) in 15% HCl (5 ml) and EtOH (50 ml) was catalytically hydrogenated over 10% Pd–C (0.80 g) at room temperature. Filtration and evaporation gave a colorless oil, which was solidified by trituration with $(C_2H_5)_2O$. Crystallization from MeOH–$(C_2H_5)_2O$ gave XXIII–HCl (0.49 g, 60%) as colorless needles, mp 147—154°, $[\alpha]_D^{20}$ −36.2° (c=0.420, H_2O),[13] whose IR spectrum was identical with that of (*S*)-(+)-norlaudanosine–HCl·1/2H_2O. Recrystallization from MeOH–$(C_2H_5)_2O$ gave colorless needles, mp 136—137°, $[\alpha]_D^{20}$ −36.8° (c=0.316, H_2O). *Anal.* Calcd. for $C_{20}H_{25}O_4N\cdot HCl\cdot H_2O$: C, 60.37; H, 6.84; N, 3.52. Found: C, 60.02; H, 6.68; N, 3.55. Although this material showed a slightly different IR spectrum in nujol with that of (*S*)-(+)-isomer, NMR and Mass spectra were superimposable to those of (*S*)-(+)-isomer. These crystals were found to contain 1 mole of water of crystallization by analysis.

(*R*)-(−)-Laudanosine (XXIV)——To a solution of the free base (XXIII) from XXIII-HCl (0.25 g, 0.64 mmole) in MeOH (40 ml) was added 37% formalin (0.8 ml, 10 mmole). To this mixture was added $NaBH_4$ (0.30 g, 8 mmole) with ice-cooling. The mixture was stirred at room temperature for 2 hr and evaporated to give a residue, which was taken up in AcOEt. The AcOEt solution was washed with saturated NaCl aqueous solution, dried and evaporated to give XXIV (0.23 g, 100%) as colorless crystals. Recrystallization from EtOH furnished colorless needles, mp 83—85°, $[\alpha]_D^{20}$ −84.8° (c=0.446, EtOH).[13] *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.39; H, 7.70; N, 3.77. IR Spectrum of XXIV was identical with that of (*S*)-(+)-laudanosine (V).[3a,b]

13) *cf.* lit. 3*a*, *b*. (*S*)-(+)-norlaudanosine·HCl·1/2H_2O, mp 164—167°, $[\alpha]_D^{20}$ +37.4° (H_2O). (*S*)-(+)-laudanosine (V), mp 84—88°, $[\alpha]_D^{20}$ +82.5° (EtOH).