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# Amino Acids and Peptides. XVII.[1] A Biogenetic-type, Asymmetric Synthesis of (*S*)-Laudanosine from L-3-(3,4-Dihydroxyphenyl) alanine by 1,3-Transfer of Asymmetry[2]

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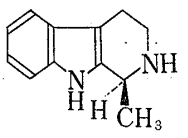
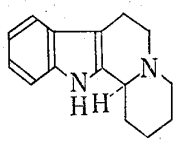
The asymmetric synthesis of a representative benzylisoquinoline alkaloid, (*S*)-(+)-laudanosine (III) was accomplished by means of the biogenetic-type, asymmetric Pictet-Spengler reaction of L-3-(3,4-dihydroxyphenyl)alanine methyl ester hydrochloride (IV) with sodium (3,4-dimethoxyphenyl)glycidate (V) (1,3-asymmetric induction) and the elimination of the chiral center derived from IV (1,3-transfer of asymmetry). The latter was conveniently achieved by conversion of the cyclized α-amino acid methyl ester (VIa) to the N-benzyl α-amino nitrile (XIII), followed by reductive decyanization with sodium borohydride.

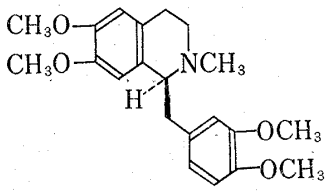
In our previous publication[4] we have proposed a new approach to the synthesis of optically active indole and isoquinoline alkaloids, which is based on the biogenetic-type, asymmetric Pictet-Spengler reaction of optically active α-amino acids with aldehydes, followed by laboratory simulation of decarboxylation from the cyclized α-amino acid derivatives. The latter was conveniently achieved by conversion of α-amino acids to α-amino nitriles, followed by reductive decyanization with sodium borohydride. By this new method, two indole alkaloids, (*S*)-(—)-tetrahydroharman (I) and (*S*)-(—)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (II) were synthesized from L-tryptophan in a satisfactory manner.[4] Application of this method to the synthesis of a natural isoquinoline alkaloid, (*S*)-(+)-laudanosine (III) is a subject of this paper.




I




II




III

Chart 1

(*S*)-(+)-Laudanosine (III) is one of the well-known, representative benzylisoquinoline alkaloids.[5] Although there are some reports on the synthesis of III in its racemic

1) Part XVI: T. Oguri, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 173 (1975).
2) Preliminary communication: S. Yamada, M. Konda, and T. Shioiri, *Tetrahedron Letters*, **1972**, 2215. Presented in part at the 16th Symposium on the Chemistry of Natural Products, Osaka, October 20, 1972, Symposium Papers, p. 264.
3) Location: *a*) *2-2-50, Kawagishi, Toda, Saitama, 335, Japan*; *b*) *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 2614 (1974).
5) (*S*)-(+)-Laudanosine has formerly been designated as L-(+)-laudanosine: *a*) A. Burger, "The Alkaloids," Vol. IV, ed. by R.H.F. Manske and H.L. Holmes, Academic Press, Inc., New York, 1954, p. 48; *b*) V. Deulofeu, J. Comin, and M.J. Vernengo, "The Alkaloids," Vol. X, ed. by R.H.F. Manske, Academic Press, Inc., New York, 1968, p. 427.

modification,[5] very few are concerned with the asymmetric synthesis. Recently Archer and his coworkers[6] tried the asymmetric synthesis of laudanosine by means of asymmetric reduction, but the efficiency of the asymmetric induction was quite bad. Furthermore, the main product was not a natural (*S*)-form, but an unnatural one.

The detailed biosynthetic pathways in this natural product area are still obscure. However, it is now known that the benzylisoquinoline alkaloids of type III are biosynthesized from two units of L-3-(3,4-dihydroxyphenyl)alanine (L-dopa).[5b] Thus we chose L-dopa as a starting material for the biogenetic-type, asymmetric synthesis of III.

The asymmetric Pictet-Spengler reaction of L-dopa methyl ester hydrochloride (IV), prepared from L-dopa,[7] with sodium 3-(3,4-dimethoxyphenyl)glycidate (V),[8] chemically equivalent to 3,4-dihydroxyphenylpyruvic acid derived from L-dopa *in vivo*,[5b] at pH 4 and 35° afforded a diastereoisomeric mixture of the cyclized products (VIa and VIb), which were separated by repeated silica gel column chromatography and recrystallizations into VIa, mp 173—174°, and VIb, mp 110—112°, the ratio of which was 3.2: 1.[9] The main product (VIa) was expected to have the more stable, 1,3-*cis* geometry with both ring substituents occupying equatorial positions.[4,10] Support for this assignment was obtained by conversion of VIa to (*S*)-(+)-laudanosine (III). Treatment of VIa with diazomethane afforded a mixture of the O,O-dimethylated product (VIIa, 87% yield) and the O,O,N-trimethylated product (VIIIa, 5% yield). Similar treatment of VIb analogously furnished VIIb in 68% yield and VIIIb in 16% yield.

If the isomerization of 1,3-*trans* isomers (VIb, VIIb, and VIIIb) to 1,3-*cis* isomers (VIa, VIIa, and VIIIa) could be achieved, the ratio of 1,3-asymmetric induction in the Pictet-Spengler reaction would amount to 100% theoretically. To attempt this, the hydrochloride of VIb was heated at 200°, resulting in the formation of resinous materials. VIIb and VIIIb were respectively shaken over platinum oxide in alcoholic solvent in the presence of hydrogen,[11] but no isomerization occurred.

The ester (VIIa) was treated with methanolic ammonia to give the amide (IX) in 94% yield. On the other hand, the N-methyl ester (VIIIa) was resisted to aminolysis and furnished the N-methyl amide (X) in 41% yield after 2 weeks' treatment with methanolic ammonia. Reductive N-methylation of IX with sodium borohydride and formalin occurred to the extent of 71% with the formation of the desired N-methyl amide (X), with concomitant formation of some unknown products. However, IX quantitatively yielded X by refluxing with a mixture of methyl iodide and potassium carbonate in methanol without occurring quaternization.

After several trials, it was found that dehydration of the amide (X) to the nitrile (XI) could be effected by treatment with a mixture of phosphorus pentoxide and hyflo-supercel in pyridine at 105° for 25 min, followed by a silica gel column chromatography, though not efficiently. As the nitrile (XI) was so labile that it changed upon standing at room temperature, it was immediately, without further purification, subjected to the decyanization with sodium borohydride in a mixture of ethanol and pyridine[4] to afford (*S*)-(+)-laudanosine (III) in very low yield.

6) J.F. Archer, D.R. Boyd, W.R. Jackson, M.F. Grundon, and W.A. Khan, *J. Chem. Soc.* (*C*), **1971**, 2560.
7) K. Vogler and H. Baumgartner, *Helv. Chim. Acta*, **35**, 1776 (1952).
8) Y. Ban and T. Oishi, *Chem. Pharm. Bull.* (Tokyo), **6**, 574 (1958).
9) The ratio of VIa to VIb was reported to be 2.4: 1 in our communication.[2] However, the further investigation revealed that crystals of VIb contained chloroform as solvate, hence the ratio should be corrected to be 3.2: 1.
10) N. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **13**, 1231 (1965).
11) T. Kametani and M. Ihara, *J. Chem. Soc.* (*C*), **1968**, 191; T. Kametani, M. Ihara, and K. Shima, *ibid.*, **1968**, 1619.

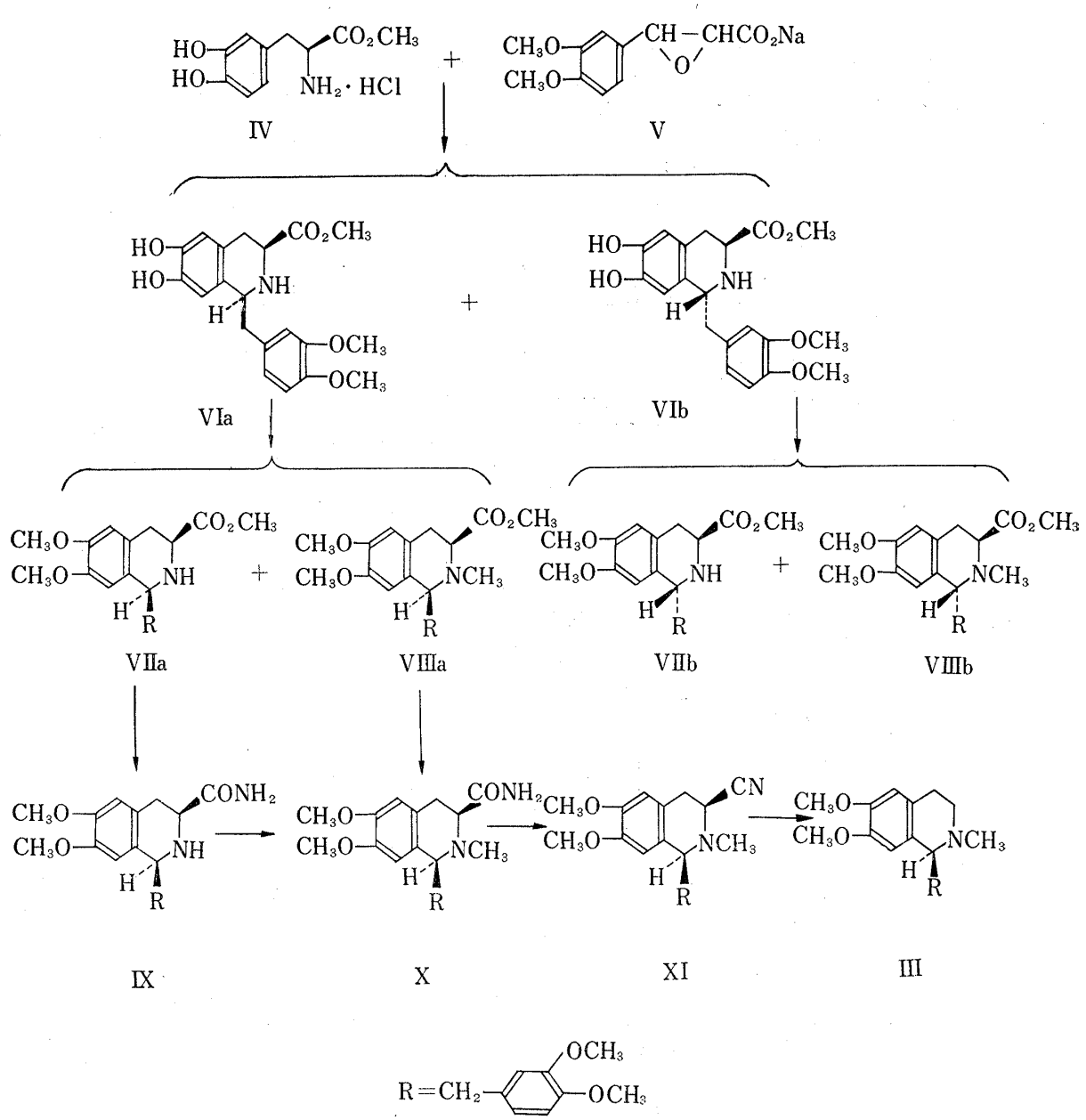



Chart 2

This unsatisfactory result led us to replace the more basic N-methyl function with the less basic N-benzyl one, which could be easily converted to N-methyl function by catalytic debenzylation followed by N-methylation. Thus, the amide (IX) was converted to the N-benzyl amide (XII) with benzyl chloride, which was dehydrated under reaction conditions similar to above to yield the N-benzyl nitrile (XIII) in 55% yield. XIII was also labile, and hardly exhibited the nitrile absorption in its infrared spectrum. However, high peaks at *m/e* 432, 307, and 280 (base peak) were observed in its mass spectrum, which could be explained as shown in Chart 3 and supports the structure of the α-amino nitrile (XIII).

The crude nitrile (XIII) was immediately decyanized with sodium borohydride to give the decyanized product (XIV) in 87% yield. Reductive debenzylation of XIV with 5% palladium carbon afforded the known (*S*)-(+)-norlaudanosine hydrochloride (XV).[12] In contrast to conversion of IX to X, refluxing XV with a mixture of methyl iodide and potas-

12) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **39**, 889 (1956).

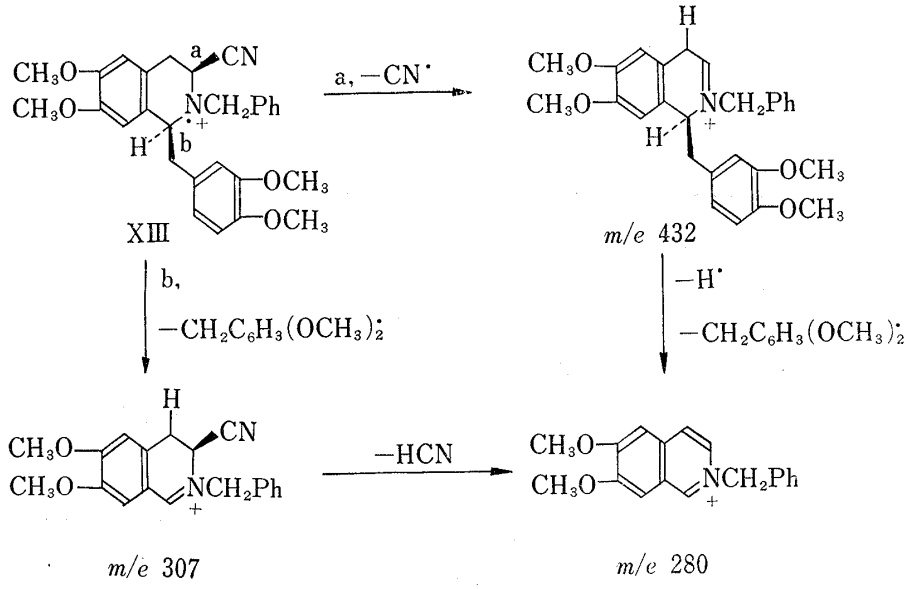



Chart 3

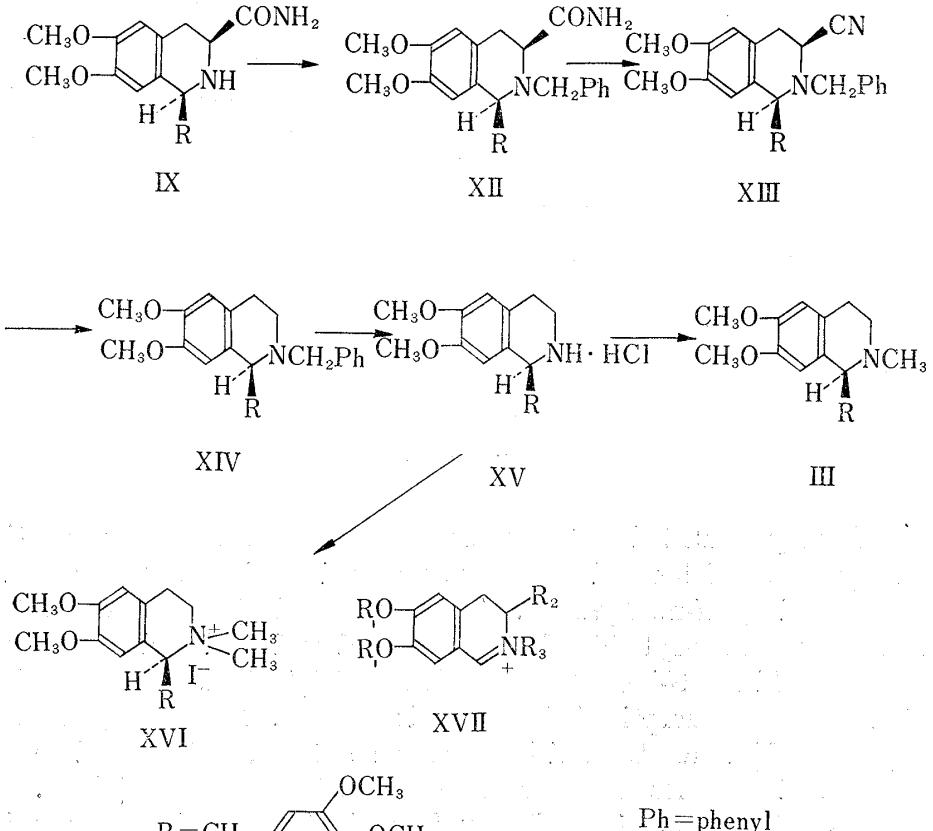



Chart 4

sium carbonate in methanol caused the formation of the quaternary salt (XVI) instead of the desired (*S*)-(+)-laudanosine (III). However, a free base of XV was conveniently converted

to III with a mixture of sodium borohydride and formalin. The physical constants of III[13] and its quaternary salt[12] (XVI) were coincident with those of the reported ones, and their spectral data also supported their structures. The all compounds after VI had base peaks corresponding to the general structure XVII, typical of 1-benzylisoquinoline derivatives.[14]

The synthesis of (*S*)-(+)-laudanosine may open the way for the biogenetic-type, asymmetric synthesis of many important benzylisoquinoline alkaloids.[5] The investigation along this line is now being continued.

## Experimental

Unless otherwise stated, melting points were uncorrected; infrared (IR) spectra were measured either in nujol mulls (for crystals) or in liquid films (for oils); nuclear magnetic resonance (NMR) spectra (60 MHz) were measured in deuterochloroform, and chemical shifts ($\delta$) are given in ppm relative to internal tetramethylsilane. Wakogel C-200 was used for silica gel column chromatography. The organic solutions were dried over sodium sulfate before vacuum evaporation.

**(1*S*,3*S*)-(−)-Methyl 1-(3,4-Dimethoxybenzyl)-6,7-dihydroxy-1,2-3,4-tetrahydroisoquinoline-3-carboxylate (VIa) and (1*R*,3*S*)-(−)-Methyl 1-(3,4-Dimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (VIb)**——A mixture of sodium 3-(3,4-dimethoxyphenyl)glycidate[8] (V, 7.4 g, 0.03 mole) in water (60 ml) and L-dopa methyl ester hydrochloride[7] (IV, 5.0 g, 0.02 mole) in methanol (80 ml) was adjusted to pH 4 with acetic acid (8 ml) and stirred at 35° (bath temperature) for 24 hr. After evaporation of methanol, ethyl acetate was added, and the organic layer was extracted with 10% aqueous hydrochloric acid. The combined extracts were neutralized with potassium carbonate, and extracted with ethyl acetate. The ethyl acetate extracts were washed with water, dried, and evaporated. The resultant red brown viscous oil was fractionated by repeating silica gel column chromatography with a mixture of chloroform and ethyl acetate (3: 2) and recrystallizations from a mixture of ethyl acetate and *n*-hexane (or chloroform).

VIa was obtained as yellow prisms by recrystallization from a mixture of ethyl acetate and *n*-hexane (2.30 g, 30.8%), mp 173—174°, $[\alpha]_D^{21}$ −124.6° ($c$=1.0, methanol). IR: 1740, 1723 $cm^{-1}$. IR: in chloroform 1740 $cm^{-1}$. NMR: 3.64 (3H, singlet, $CO_2CH_3$), 3.72 and 3.76 (each 3H, singlet, $OCH_3$), 6.6 (2H, broad, OH). Mass Spectrum *m/e*: 222. *Anal.* Calcd. for $C_{20}H_{23}O_6N$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.25; H, 6.21; N, 3.81. Hydrochloride, colorless pillars, mp 144—147°, $[\alpha]_D^{20}$ −96.5° ($c$=0.51, methanol).

VIb was obtained as colorless needles by recrystallization from a mixture of ethyl acetate and chloroform (0.97 g, 9.9%), mp 110—112°, $[\alpha]_D^{20}$ −38.4° ($c$=1.0, methanol). IR 1725 $cm^{-1}$.: NMR: in hexadeuterodimethyl sulfoxide 3.65 (3H, singlet, $CO_2CH_3$), 3.77 (6H, singlet, $2\times OCH_3$), 8.05 (1H, singlet, $CHCl_3$ as solvate). Mass Spectrum *m/e*: 222. *Anal.* Calcd. for $C_{20}H_{23}O_6N\cdot CHCl_3$: C, 51.22; H, 4.91; N, 2.84. Found: C, 51.55; H, 5.00; N, 2.79. Hydrochloride, colorless needles, mp 185—188°, $[\alpha]_D^{20}$ −83.3° ($c$=0.50, methanol).

If chloroform was not used for the separation of the diastereoisomeric mixture, VIb was obtained as colorless needles by recrystallization from a mixture of ethyl acetate and diethyl ether, mp 98—100°. *Anal.* Calcd. for $C_{20}H_{23}O_6N\cdot 1/2H_2O$: C, 62.81; H, 6.33; N, 3.66. Found: C, 62.59; H, 6.38; N, 3.94. The crystals afforded colorless needles containing chloroform as solvate by recrystallization from a mixture of ethyl acetate and chloroform.

**(1*S*,3*S*)-(−)-Methyl 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (VIIa) and (1*S*,3*S*)-(−)-Methyl 1-(3,4-Dimethoxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (VIIIa)**——To a stirred diazomethane (prepared from 7 mmole of nitrosomethylurea[15]) in diethyl ether (65 ml) was added VIa (0.37 g, 1.0 mmole) in methanol (12 ml) with ice-cooling. The mixture was allowed to stand at room temperature for 24 hr. After evaporation at room temperature, the residue was solidified with diethyl ether. Filtration afforded VIIa (0.25 g) as colorless crystals, mp 124—125°. For analysis a sample was recrystallized from a mixture of ethyl acetate and *n*-hexane to give colorless needles, mp 126—128°, $[\alpha]_D^{23}$ −106.8° ($c$=0.5, methanol). IR: 1750 $cm^{-1}$. NMR: 2.15 (1H, singlet, NH), 3.73 (3H, singlet, $CO_2CH_3$), 3.80—3.82 (12H, $4\times OCH_3$). Mass Spectrum *m/e*: 250. *Anal.* Calcd. for $C_{22}H_{27}O_6N$: 65.65; H, 6.78; N, 3.49. Found: C, 65.56; H, 6.69; N, 3.56.

The above filtrate was evaporated to an oily residue, which was fractionated by a silica gel column chromatography with a mixture of benzene and ethyl acetate (4: 1). The first fraction to be eluted was VIIIa (0.02 g, 5%) as colorless prisms (chloroform and *n*-hexane), mp 70—71°, $[\alpha]_D^{26}$ −47.3° ($c$=0.69, methanol). IR: 1725 $cm^{-1}$. NMR: 2.45 (3H, singlet, $NCH_3$), 3.65 (3H, singlet, $CO_2CH_3$), 3.74 and 3.76 (each,

13) K. Ito and T. Aoki, *Yakugaku Zasshi*, **79**, 325 (1959).
14) H. Budzikiewicz, C. Djerassi, and D.H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, Holden-Day, San Francisco, 1964, p. 173.
15) F. Arndt, "Org. Syntheses," Coll. Vol. 2, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, 1943, p. 165.

3H, singlet, $OCH_3$), 3.80 (6H, singlet, $2\times OCH_3$). Mass Spectrum *m/e*: 264. *Anal.* Calcd. for $C_{23}H_{29}O_6N$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.17; H, 6.96; N, 3.16.

The second fraction to be eluted was VIIa (0.10 g). Total yield of VIIa was 0.35 g (87%).

**(1*R*,3*S*)-(−)-Methyl 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (VIIb) and (1*R*,3*S*)-(−)-Methyl 1-(3,4-Dimethoxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (VIIIb)**——To a stirred diazomethane (prepared from 3.8 mmole of nitrosomethylurea[15]) in diethyl ether (35 ml) was added VIb (0.20 g, 0.54 mmole) in methanol (8 ml) with ice-cooling. The mixture was allowed to stand at room temperature for 24 hr. After evaporation at room temperature, the residue was solidified with diethyl ether. Filtration afforded VIIb (0.05 g) as slightly yellow crystals, mp 95—96°. For analysis a sample was recrystallized from a mixture of ethyl acetate and *n*-hexane to furnish faintly yellow needles, mp 95—96°, $[\alpha]_D^{19}$ −53.6° (*c*=0.36, methanol). IR: 1720 $cm^{-1}$. NMR: 2.33 (1H, singlet, NH), 3.69 (3H, singlet, $CO_2CH_3$), 3.75 (3H, singlet, $OCH_3$), 3.90 (9H, singlet, $3\times OCH_3$). Mass Spectrum *m/e*: 250. *Anal.* Calcd. for $C_{22}H_{27}O_6N$: C, 65.65; H, 6.78 N, 3.49. Found: C, 65.88; H, 6.82; N, 3.69.

The above filtrate was evaporated and fractionated by a silica gel column chromatography with a mixture of benzene and ethyl acetate (4: 1) to give VIIIb (0.035 g, 16%) as the first fraction. Recrystallization of VIIIb from chloroform and *n*-hexane afforded colorless needles, mp 113—114°, $[\alpha]_D^{26}$ −4.8° (*c*=0.54, methanol). IR: 1720 $cm^{-1}$. NMR: 2.50 (3H, singlet, $NCH_3$), 3.59 (3H, singlet, $CO_2CH_3$), 3.61 (3H, singlet, $OCH_3$), 3.69 (3H, singlet, $OCH_3$), 3.76 (6H, singlet, $2\times OCH_3$). Mass Spectrum *m/e*: 264. *Anal.* Calcd. for $C_{23}H_{29}O_6N$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.27; H, 7.02; N, 3.18.

The second fraction to be eluted was VIIb (0.095 g). Total yield of VIIb was 0.145 g (68%).

**(1*S*,3*S*)-(−)-1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (IX)**——An ice-cooled solution of VIIa (5.2 g, 0.013 mole) in methanol (300 ml) was saturated with ammonia gas. The mixture was allowed to stand at room temperature for 24 hr, and evaporated to give IX (4.85 g, 94%) as slightly yellow crystals. For analysis a sample was recrystallized from a mixture of chloroform and diethyl ether to give colorless needles, mp 196—198°, $[\alpha]_D^{20.5}$ −124.8° (*c*=0.5, chloroform). IR: 3400, 3300, 1685 $cm^{-1}$. NMR: 3.76 (3H, singlet, $OCH_3$), 3.80 (3H, singlet, $OCH_3$), 3.82 (6H, singlet, $2\times OCH_3$), 4.96 (2H, doublet, $CONH_2$). Mass Spectrum *m/e*: 235. *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, 63.98; H, 6.60; N, 6.99.

**(1*S*,3*S*)-(−)-1-(3,4-Dimethoxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (X)**——(i) From IX by reductive methylation. A mixture of IX (4.1 g, 0.01 mole) and formalin (8.4 ml) in methanol (300 ml) was stirred at room temperature for 1 hr. After ice-cooling, sodium borohydride (3.2 g, 0.08 mole) was added, followed by stirring at room temperature for 1 hr. After further addition of formalin (8.4 ml) and sodium borohydride (3.2 g), the mixture was stirred at room temperature overnight, and evaporated. The residue was extracted with chloroform. The extracts were washed with water, dried and evaporated to give slightly yellow crystals, which were purified by a silica gel column chromatography with a mixture of chloroform and ethyl acetate (9: 1) to give X (3.3 g, 71%) as colorless crystals, mp 151—152°. A sample was recrystallized from a mixture of chloroform and diethyl ether to give colorless needles, mp 149—151°, $[\alpha]_D^{20}$ −46.7° (*c*=0.5, chloroform), IR: 3400, 3300, 1690 $cm^{-1}$. NMR: 2.36 (3H, singlet, $NCH_3$), 3.68 (3H, singlet, $OCH_3$), 3.72 (3H, singlet, $OCH_3$), 3.80 (6H, singlet, $2\times OCH_3$), 6.35 (2H, doublet, $CONH_2$). Mass Spectrum *m/e*: 249. *Anal.* Calcd. for $C_{22}H_{28}O_5N_2$: C, 65.98; H, 7.05; N, 7.01. Found: C, 65.84; H, 7.15; N, 7.26.

(ii) From IX by methylation with methyl iodide. A mixture of IX (2.50 g, 6.3 mmole), methyl iodide (15 ml), and potassium carbonate (5.0 g) in methanol (300 ml) was refluxed for 3 hr. Evaporation gave the residue, which was extracted with ethyl acetate. The organic extracts were washed with water, dried, and evaporated to give X (2.52 g, 97%) as colorless needles, mp 148—151°.

(iii) From VIIIa. An ice-cooled solution of VIIIa (1.0 g, 2.41 mmole) in methanol (50 ml) was saturated with ammonia. The mixture was allowed to stand at room temperature for 2 weeks, during which ammonia was saturated at the 3rd day and the 5th day. Evaporation followed by tritulation of the residue with a mixture of methanol and diethyl ether afforded X (0.39 g, 41%) as colorless crystals, mp 135—140°. Recrystallization from a mixture of chloroform and diethyl ether afforded colorless needles, mp 148—150°.

**(1*S*,3*S*)-(−)-1-(3,4-Dimethoxybenzyl)-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (XII)**——A mixture of IX (0.79 g, 2 mmole), benzyl chloride (0.48 g, 3.8 mmole), potassium carbonate (0.31 g, 2.2 mmole), and sodium iodide (trace) was refluxed in ethanol (80 ml) for 4 hr. Evaporation afforded the residue, which was dissolved in 10% aqueous hydrochloric acid. The acidic solution was washed with ethyl acetate, basified with potassium carbonate, and extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated to give a yellow amorphous powder of XII (0.90 g, 95%), $[\alpha]_D^{22}$ −71.6° (*c*=1, chloroform). IR in chloroform 3400, 3300, 1680 $cm^{-1}$. NMR: 3.58 (3H, singlet, $OCH_3$), 3.60 (3H, singlet, $OCH_3$), 3.70 (2H, singlet, $NC\underline{H}_2C_6H_5$), 3.78 (3H, singlet, $OCH_3$), 3.84 (3H, singlet, $OCH_3$), 6.75 (2H, doublet, $CONH_2$), 7.26 (5H, singlet, $C_6H_5$). Mass Spectrum *m/e*: 326. Picrate (recrystallized from ethanol), yellow needles, mp 109—111°. *Anal.* Calcd. for $C_{28}H_{32}O_5N_2\cdot C_6H_3O_7N_3\cdot H_2O$: C, 56.41; H, 4.88; N, 9.92. Found: C, 56.39; H, 5.12; N, 10.06.

**(1*S*,3*S*)-(−)-1-(3,4-Dimethoxybenzyl)-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carbonitrile (XIII)**——To a stirred suspension of phosphorus pentoxide (8.5 g, 60 mmole) and dry hyflo-super-cel (15 g) in pyridine (150 ml) was added XII (1.9 g, 4 mmole) at 80°, followed by stirring at 100° for 20 min. The mixture was filtered, and washed with chloroform. Evaporation of the combined filtrates afforded a black brown viscous oil, which was purified by a silica gel column chromatography with chloroform to furnish XIII (1.0 g, 55%) as a brown viscous oil. Mass Spectrum *m/e*: 432, 307, 280 (base peak). XIII was immediately used for the next step.

**(*S*)-(+)-1-(3,4-Dimethoxybenzyl)-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XIV)**——To an ice-cooled XIII (0.90 g, 2 mmole) in a mixture of pyridine (7 ml) and ethanol (15 ml) was added sodium borohydride (0.36 g, 9.5 mmole) with stirring. The mixture was stirred at room temperature for 20 hr, and evaporated. The residue was extracted with diethyl ether. The ethereal extracts were washed with saturated aqueous sodium chloride, dried over potassium carbonate, and evaporated to furnish a yellow viscous oil, which was purified by a silica gel column chromatography with chloroform to give XIV (0.75 g, 87%) as a yellow viscous oil, $[\alpha]_D^{21}$ +37.2° (*c*=0.54, methanol). IR: 1610, 1595 $cm^{-1}$. NMR: 3.67 (3H, singlet, $OCH_3$), 3.74 (3H, singlet, $OCH_3$), 3.77 (2H, singlet, $NC\underline{H}_2C_6H_5$), 3.83 (6H, singlet, $2\times OCH_3$), 7.26 (5H, singlet, $C_6H_5$). Mass Spectrum *m/e*: 433.

**(*S*)-(+)-1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride=(*S*)-(+)-Norlaudanosine Hydrochloride (XV)**——A mixture of XIV (0.93 g, 2.15 mmole) and 15% aqueous hydrochloric acid (5 ml) in ethanol (50 ml) was catalytically hydrogenated over 5% palladium-carbon (0.80 g) at room temperature. Filtration and evaporation afforded a colorless viscous oil, which was solidified by tritulation with diethyl ether. Colorless crystals of XV (0.55 g, 66%), mp 150—155°, were obtained by filtration. For analysis a sample was recrystallized from a mixture of methanol and diethyl ether to give colorless needles, mp 164—167° (lit.[12] 167°), $[\alpha]_D^{20}$ +37.4° (*c*=0.4, water) (lit.[12] $[\alpha]_D$ +38° (water)). IR: 1610, 1590 $cm^{-1}$. NMR in deuterium oxide (internal reference: sodium 3-(trimethylsilyl)propanesulfonate) 3.67 (3H, singlet, $OCH_3$), 3.80 (3H, singlet, $OCH_3$), 3.87 (6H, singlet, $2\times OCH_3$). Mass Spectrum *m/e*: 178. *Anal.* Calcd. for $C_{20}H_{25}O_4N\cdot HCl\cdot 1/2H_2O$: C, 61.70; H, 6.99; N, 3.60. Found: C, 61.25; H, 6.67; N, 3.64.

**(*S*)-(+)-Laudanosine (III)**——(i) From XV. To a mixture of the free base of XV (0.32 g, 0.93 mmole) and formalin (0.8 ml, 10 mmole) in methanol (40 ml) was added sodium borohydride (0.30 g, 8 mmole) with ice-cooling. The mixture was stirred at room temperature for 12 hr, and evaporated. The residue was extracted with ethyl acetate. The extracts were washed with saturated aqueous sodium chloride and dried. Evaporation afforded III (0.27 g, 81%) as colorless crystals. Recrystallization from ethanol furnished colorless needles, mp 84—88° (lit.[13] 90—91°), $[\alpha]_D^{21}$ +82.5° (*c*=0.4, ethanol) (lit.[13] $[\alpha]_D$ +83.4° (ethanol)). IR: 1603, 1518 $cm^{-1}$. NMR: 2.50 (3H, singlet, $NCH_3$), 3.55 (3H, singlet, $OCH_3$), 3.78 (3H, singlet, $OCH_3$), 3.81 (6H, singlet, $2\times OCH_3$). Mass Spectrum *m/e*: 192. *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.30; H, 7.59; N, 3.97.

(ii) From X. To a stirred suspension of phosphorus pentoxide (1.4 g, 10 mmole) and dry hyflo-super-cel (25 g) in pyridine (150 ml) was added X (1.6 g, 4 mmole) at 80°, followed by stirring at 105° for 25 min. The mixture was filtered and washed with chloroform. Evaporation of the combined filtrates afforded a black viscous oil, which furnished an unstable brown oil (0.10 g, containing mainly the nitrile (XI)) by purification over a silica gel column using a mixture of benzene and ethyl acetate (1: 1).

The oily unstable product (0.10 g) was immediately dissolved in a mixture of ethanol (3 ml) and pyridine (1.5 ml), and sodium borohydride (0.10 g, 2.6 mmole) was added. The mixture was stirred at room temperature for 20 hr. After evaporation, the residue was extracted with diethyl ether. The ethereal extracts were washed with saturated aqueous sodium chloride and dried over potassium carbonate. Evaporation followed by purification over a silica gel column using a mixture of ethyl acetate and methanol (1: 1) gave III (8 mg), which was identified with the foregoing sample of III.

**(*S*)-(+)-Laudanosine Methiodide (XVI)**——A stirred mixture of XV (0.30 g, 0.79 mmole), methyl iodide (2 ml), and potassium carbonate (0.83 g, 6 mmole) in methanol (50 ml) was refluxed for 3 hr, and evaporated. The residue was extracted with chloroform. The extracts were washed with water, dried, and evaporated to give XVI (0.30 g, 77%) as colorless crystals, mp 213—222°. Recrystallization from a mixture of methanol and diethyl ether afforded colorless needles. mp 225—227° (lit.[12] 218—221°), $[\alpha]_D^{20.5}$ +121.0° (*c*=0.4, methanol) (lit.[12] $[\alpha]_D$ +120° (*c*=1, methanol)). IR: 1615, 1592 $cm^{-1}$. NMR: 3.38 (3H, singlet, $NCH_3$), 3.50 (3H, singlet, $NCH_3$), 3.70—4.0 (12H, $4\times OCH_3$). Mass Spectrum *m/e*: 206, 372 ($M^+$). *Anal.* Calcd. for $C_{22}H_{30}O_4NI$: C, 52.91; H, 6.06; N, 2.81. Found: C, 53.25; H, 6.16; N, 2.90.