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

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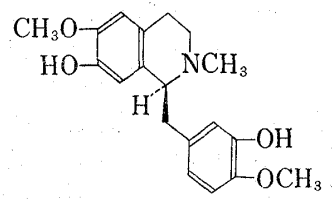
The asymmetric synthesis of (*S*)-reticuline (I) was accomplished by means of the biogenetic-type, asymmetric Pictet-Spengler reaction of 3-(3-hydroxy-4-benzyloxyphenyl)-L-alanine methyl ester hydrochloride (XXIII) with sodium 3-benzyloxy-4-methoxyphenylglycidate (XXIV) (1,3-asymmetric induction) and the elimination of the chiral center derived from XXIII (1,3-transfer of asymmetry), the latter of which was achieved by conversion of the cyclized α-amino acid methyl ester (XXVa) to the N-benzyl α-amino nitrile (XXVIII), followed by reductive decyanization with sodium borohydride.

The position of the benzyl group of XXIII which was prepared from L-dopa by monobenzylation was proved by the alternate synthesis of XXIII starting from L-tyrosine.

By this success, morphinanedienone, aporphine and protoberberine alkaloids, (−)-pallidine (XXXII), (+)-isoboldine (XXXIII), (−)-coreximine (XXXIV), and (−)-scoulerine (XXXV) are formally to have been synthesized from L-dopa.

Reticuline[4] (I), one of typical benzylisoquinoline alkaloids, enjoys considerable importance as a versatile synthetic intermediate as well as a biosynthetic precursor of several other alkaloids with benzylisoquinoline structures such as morphinanedienone, aporphine, and protoberbeline alkaloids.[4,5]

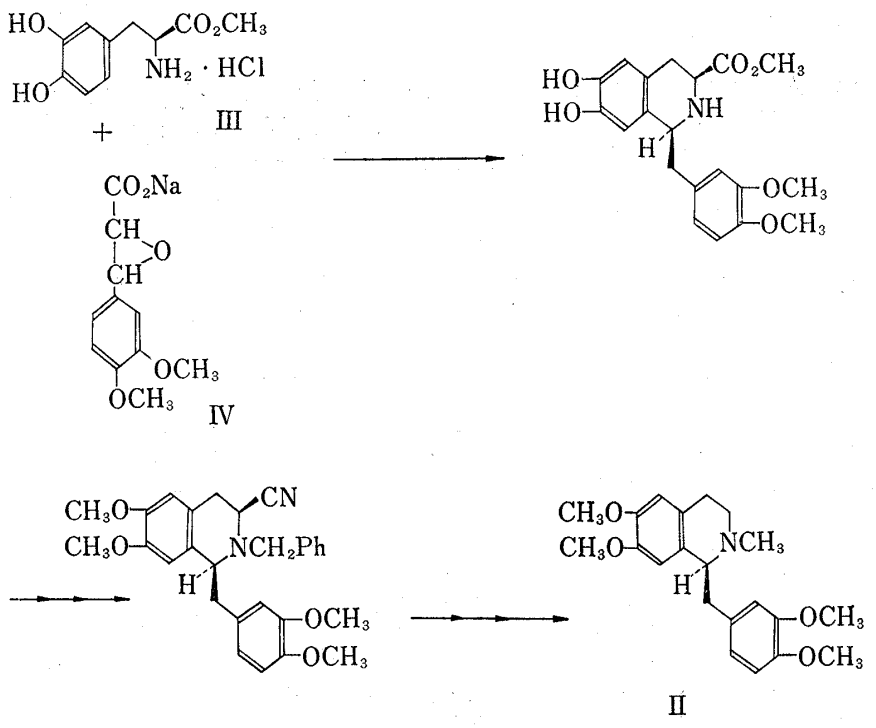
Although several syntheses of racemic reticuline (I) have been described,[4] the preparation of the optical isomers of I has been done only by optical resolution.[6] No attempt of asymmetric synthesis of optically active I has been recorded. As described in our preceding paper,[1] the synthesis of (*S*)-laudanosine (II) was accomplished by means of the biogenetic-type, asymmetric Pictet-Spengler reaction of L-3-(3,4-dihydroxyphenyl)alanine methyl ester hydrochloride (III) with sodium (3,4-dimethoxyphenyl) glycidate (IV) (1,3-asymmetric induction), and the elimination of the chiral center derived from III by reductive decyanization as a key step (1,3-tranfer of asymmetry).



(*S*)-I

In order to provide further support for the principle and to develop the new biogenetic-type, asymmetric synthesis based on 1,3-transfer of asymmetry, efforts were made to realize the synthesis of reticuline (I) in its (*S*)-form, started with L-3-(3,4-dihydroxyphenyl) alanine (L-dopa, V).

1) Part XVII: M. Konda, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 1025 (1975).
2) Presented in part at the 93rd Annual Meeting at Pharmaceutical Society of Japan, Tokyo, April 1973, Abstracts, II, p. 239.
3) Location: *a) 2-2-50, Kawagishi, Toda, Saitama, 335, Japan; b) Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) 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. 419.
5) A.R. Battersby, "Oxidative Coupling of Phenols," ed. by A.R. Battersby and W.I. Taylor, Marcel Dekker Inc., New York, 1967, p. 119; K.L. Stuart, *Chem. Rev.*, **71**, 47 (1971); E. Brochmann-Hanssen, "Pharmacognosy and Phytochemistry," Springer-Verlag, Berlin, 1971, p. 347.
6) A.R. Battersby, D.M. Foules, and R. Binks, *J. Chem. Soc.*, **1965**, 3323.



Ph=phenyl

Chart 1

The most obvious task in the project planned along the synthesis of (*S*)-laudanosine (II) was how to differentiate two phenolic hydroxyl functions of L-dopa. The C-3 hydroxyl function para to the position of the Pictet-Spengler cyclization will be indispensable for the smooth ring closure,[7] and the C-4 hydroxyl function should be protected during the ring closure by an easily removable group. The group chosen was benzyl.

Initial experiments were designed to produce L-3-(3-hydroxy-4-benzyloxyphenyl) alanine benzyl ester (VI) by selective benzylation of L-dopa (V). Treatment of L-dopa with 2 equivalents of benzyl bromide in a mixture of aqueous sodium hydroxide and dimethyl sulfoxide[8] resulted in the formation of a small amount of the N,N-dibenzyl benzyl ester (VII) as the only identifiable product. Refluxing a mixture of L-dopa and benzyl chloride with potassium carbonate in ethanol raised the yield of VII to 56%, but none of the desired VI was detected. These preparative difficulties prompted that protection of amino acid moiety of L-dopa was necessary before benzylation of phenolic hydroxyl function. The N-formyl methyl ester (VIII) was thus selected, and was prepared by esterification of L-dopa,[1] followed by N-formylation.

Selective monobenzylation of the N-formyl ester (VIII) was tried with benzyl chloride in refluxing methanol in the presence of potassium carbonate, resulting in the recovery of the starting material (VIII). By replacement of methanol with ethanol, the benzylation reaction proceeded with ester exchange and partial racemization to give a mixture of the C-4-benzylated product (IXa, 30% yield), the C-3-benzylated one (IXb, 33%), and the dibenzylated one (IXc, 10%). A possible intermediate for this reaction might be the oxazolone derivative[9] (X) since the recovered VIII was almost racemized when the above benzylation was carried out under the same reaction conditions in methanol. To avoid ester exchange and racemiza-

7) W.M. Whaley and T.R. Govindachari, *Org. Reactions*, **6**, 151 (1951).
8) *cf.* S.L. Solar and R.R. Schumaker, *J. Org. Chem.*, **31**, 1996 (1966).
9) M. Bodanszky and M.A. Ondetti, "Peptide Synthesis," Interscience Publishers, New York, 1966, Chapter VI.

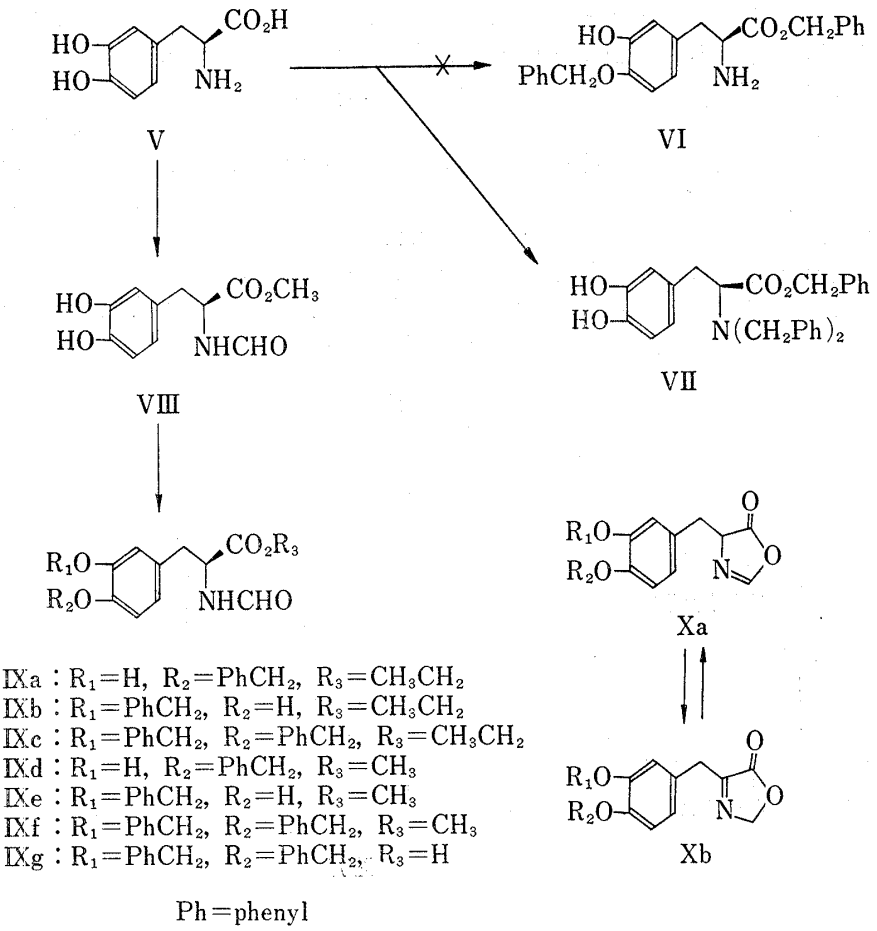


Chart 2

tion, the reaction was run in dimethyl sulfoxide at room temperature using benzyl chloride and potassium carbonate. The desired C-4-benzylated product (IXd) with good optical purity was obtained in 27% yield. Lithium carbonate in sharp contrast with potassium carbonate was not effective in both ethanol and dimethyl sulfoxide. Benzylation of VIII with phenyldiazomethane afforded IXd without racemization. Either procedure furnished a mixture of monobenzylated products (IXd and IXe) in approximately equal amounts. The dibenzylated product (IXf) was obtained only when the reaction temperature of the benzylation in dimethylsulfoxide was rather high. Attempted mono-debenzylation of IXf with sodium in liquid ammonia failed, and only the carboxylic acid (IXg) was obtained in low yield.

In order to prove the position of benzylation, other routes to IXd from L-tyrosine (XI) were investigated. Thus, N-trifluoroacetyl-3-(3-nitro-4-benzyloxyphenyl) alanine methyl ester (XII) prepared from XI according to the literatures[10] was treated with phenyldiazomethane[10b] to give the O-benzyl derivative (XIII). As the yield was not good and purification of the product was troublesome, benzylation was carried out with benzyl chloride and potassium carbonate in refluxing acetone, giving XIII in 95% yield. Interestingly the reaction did not proceed at all when acetone was replaced with methanol. Reduction of XIII with zinc in aqueous calcium chloride afforded the amino derivative (XIV), which was converted to the diazonium salt (XV) with sodium nitrite in aqueous tetrafluoroboric acid. Attempts to prepare the phenol (XVI) or its acetylated product from the diazonium salt (XV) resulted

10) *a*) B. Johnson and E.F. Kohlmann, *J. Am. Chem. Soc.*, **37**, 1863 (1918); *b*) R.W. Hanson and H.D. Law, *J. Chem. Soc.*, **1965**, 7297.

in either recovery of the starting material or formation of the tarry products. The direct conversion of XIV to XVI by treatment with sodium nitrite in a mixture of hydrochloric acid and acetic acid followed by standing at ambient temperature or at higher temperature was again unsuccessful.

Next the project in which the Fries rearrangement or the Friedel-Crafts reaction followed by the Baeyer-Villiger oxidation was key steps[11] was investigated. N-Formyl-L-tyrosine methyl ester (XVII) obtained from L-tyrosine (XI) was converted to its O-benzyl ethyl ester (XVIII) and acetyl derivative (XIX). In spite of many attempts to carry out the Friedel-Crafts reaction on XVII, XVIII, or XIX, the desired C-3-acetyl derivative could not be obtained. However, Fries rearrangement of XIX with 2 equivalents of aluminum chloride

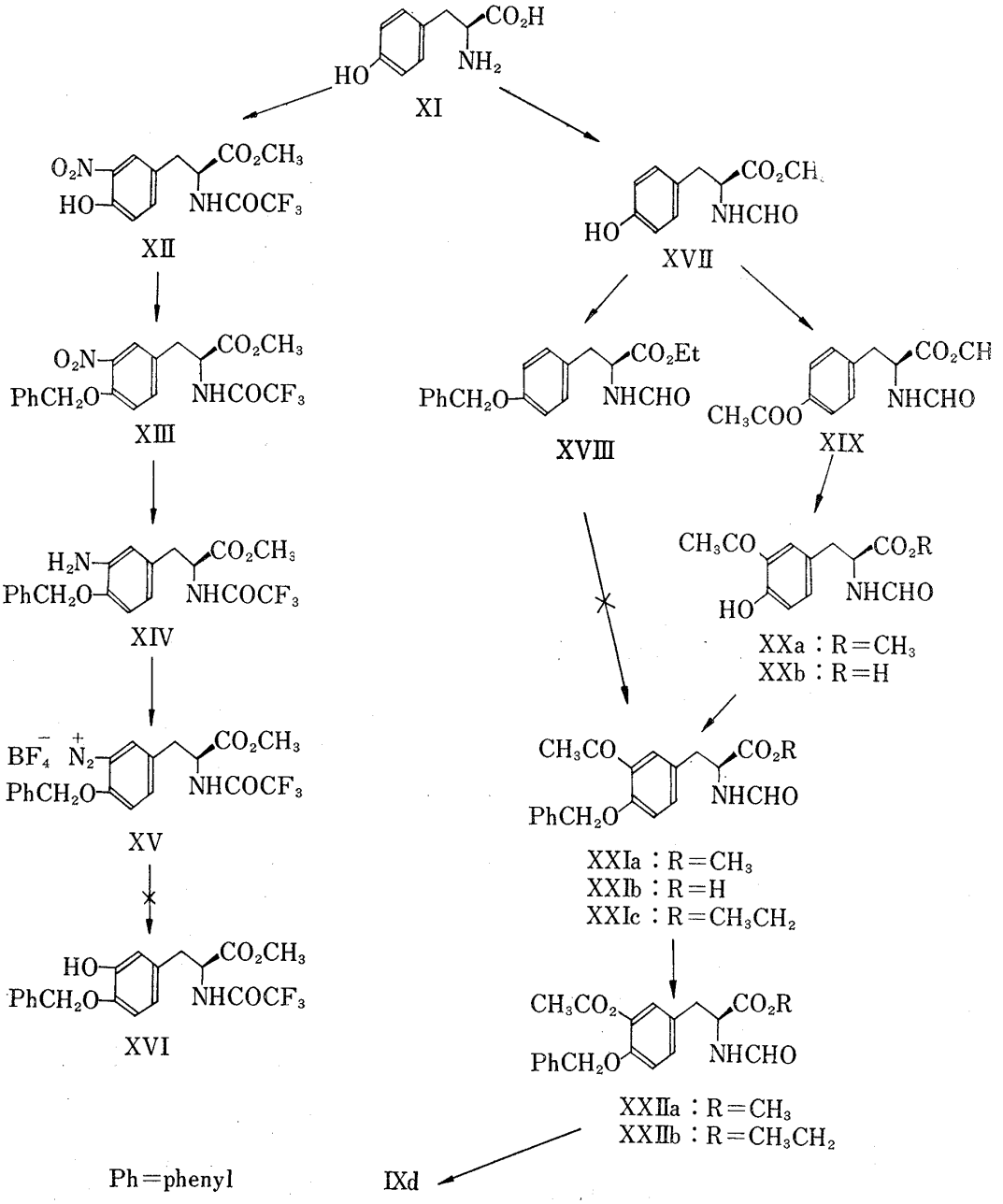


Chart 3

11) Efficient conversion of L-tyrosine to L-dopa using the Fries rearrangement or the Friedel-Crafts reaction followed by the Baeyer-Villiger oxidation was recently reported: H. Bretschneider, K.H.-Oehringen, A. Kaiser, and U. Wölcke, *Helv. Chim. Acta*, **56**, 2857 (1973).

in tetrachloroethane afforded the C-3-acetyl ester (XXa) and the corresponding carboxylic acid (XXb) in 13 and 31% yields, respectively. Increase of amounts of aluminum chloride from 2 to 3 equivalents yielded XXa in 1% yield but XXb in 77% yield. The latter was easily converted to the former by two-step process (methanolic hydrogen chloride and formic acid-acetic anhydride).

Refluxing XXa with benzyl chloride and potassium carbonate in methanol afforded the O-benzyl methyl ester (XXIa) in 31% yield in company with the carboxylic acid (XXIb) in 56% yield. Treatment of the latter with diazomethane easily furnished the former. Changing the solvent of the benzylation from methanol to ethanol under the above conditions

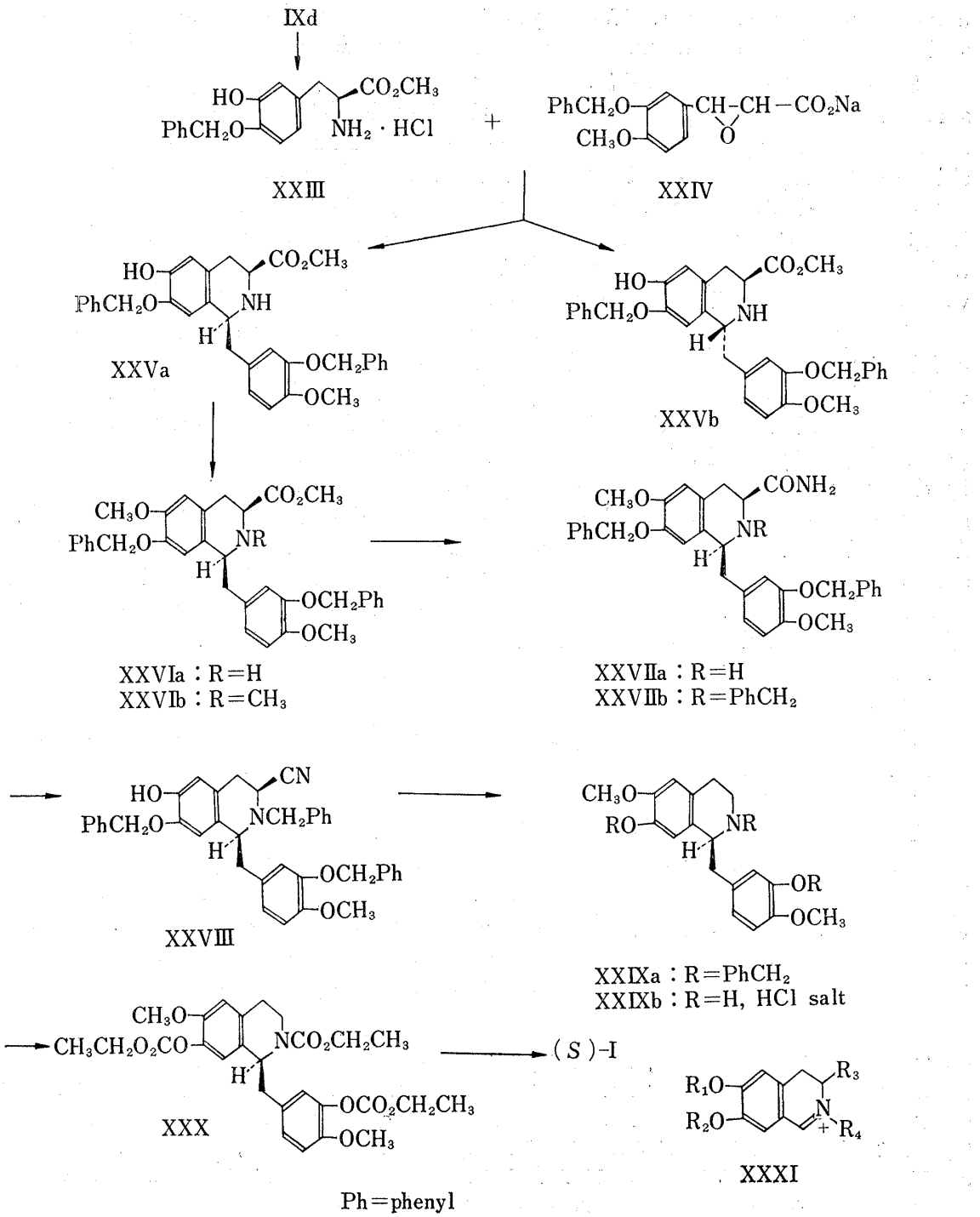


Chart 4

yielded the ethyl ester (XXIc) in 83% yield together with XXIb in 13% yield. Easy exchange of ester portion will be due to the oxazolone formation as in the benzylation of VIII, and the products (XXI) might be partially racemized. Baeyer-Villiger oxidation of XXIa with *m*-chloroperbenzoic acid afforded a 1: 1 mixture of the starting XXIa and the oxidation product (XXIIa), the ratio of which was determined by integrated intensities of two methyl proton signals at δ 2.25 and 2.58 ppm on the nuclear magnetic resonance spectrum. Similar oxidation of XXIc furnished a 1: 2 mixture of XXIc and XXIIb, which was treated with potassium hydrogen carbonate in aqueous acetone and methanol. Purification of the crude products by a silica gel column chromatography afforded the partially racemized methyl ester (IXd), which was identified with IXd prepared from VIII by comparisons of infrared and nuclear magnetic resonance spectra. The ethyl ester (IXa) also underwent analogous ester exchange and racemization to give the methyl ester (IXd) under the same reaction conditions.

Since the structure of IXd was amply confirmed, optically pure IXd was subjected to acidic deformylation to give the amine hydrochloride (XXIII). The biogenetic-type, asymmetric Pictet-Spengler reaction of XXIII with sodium 3-benzyloxy-4-methoxyphenylglycidate[12] (XXIV) at pH 4 and 40° afforded a diastereoisomeric mixture of 1,3-*cis*-XXVa, mp 114—116°, and 1,3-*trans*-XXVb, mp 157.5—158.5°, in 17% yield. The ratio of 1,3-*cis*-XXVa to 1,3-*trans*-XXVb was 2.1: 1. The assignment was made by assuming the main isomer to be the more stable *cis* isomer, according to our previous experience.[1] This assumption was further confirmed by the conversion of XXVa to (*S*)-reticuline (I).

The synthesis of (*S*)-reticuline after this was relatively straightforward. Treatment of XXVa with diazomethane afforded the dimethylated ester (XXVIa) in 83% yield together with its N-methyl derivative (XXVIb) in 5% yield. XXVIa on treatment with methanolic ammonia yielded the amide (XXVIIa) in 84% yield, which afforded the N-benzylamide (XXVIIb) in 89% yield with benzyl chloride. Removal of C_1-unit from XXVIIb was achieved by dehydration with a mixture of phosphorus pentoxide and hyflo-super-cel in pyridine to give the nitrile (XXVIII), which was immediately reduced with sodium borohydride.[1] The decyanized product (XXIXa) thus obtained in 52% yield was catalytically hydrogenated over 5% palladium-carbon to produce (*S*)-norreticuline hydrochloride (XXIXb), whose physical data coincided with those of the reported one.[13] XXIXb was converted to the triethoxycarbonyl derivative[14] (XXX), which was finally reduced with lithium aluminum hydride to give (*S*)-reticuline (I). Its physical data and those of its perchlorate supported the structure[4,15] as shown in Experimental.

The mass spectra of all tetrahydroisoquinoline derivatives prepared in these experiments showed base peaks due to the ions (XXXI),[1,16] which made valid the structure of the synthetic intermediates.

The synthesis of (*S*)-norreticuline (XXIXb) and (*S*)-reticuline (I) from L-dopa represents the formal synthesis of some natural morphinanedienone alkaloids whose absolute configuration belongs to sinomenine series, aporphine and protoberberine alkaloids, such as (−)-pallidine[17] (XXXII), (+)-isoboldine[17] (XXXIII), (−)-coreximine[13] (XXXIV), and (−)-scoulerine[13] (XXXV). If D-dopa or the minor isomer (XXVb) from L-dopa was chosen as the starting material, analogous series of experiments should give (*R*)-reticuline, which was already con-

12) T. Kametani, K. Fukumoto, and M. Fujihara, *Bioorg. Chem.*, **1**, 40 (1971).
13) A.R. Battersby, R. Southgate, J. Staunton, and M. Hirst, *J. Chem. Soc.* (*C*), **1966**, 1052.
14) T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *Tetrahedron*, **25**, 3667 (1969).
15) K.W. Gopinath, T.R. Govindachari, B.R. Pai, and N. Viswanathan, *Chem. Ber.*, **92**, 776 (1959).
16) 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.
17) T. Kametani, K. Fukumoto, K. Kigasawa, and K. Wakisaka, *Chem. Pharm. Bull.* (Tokyo), **19**, 714 (1971).

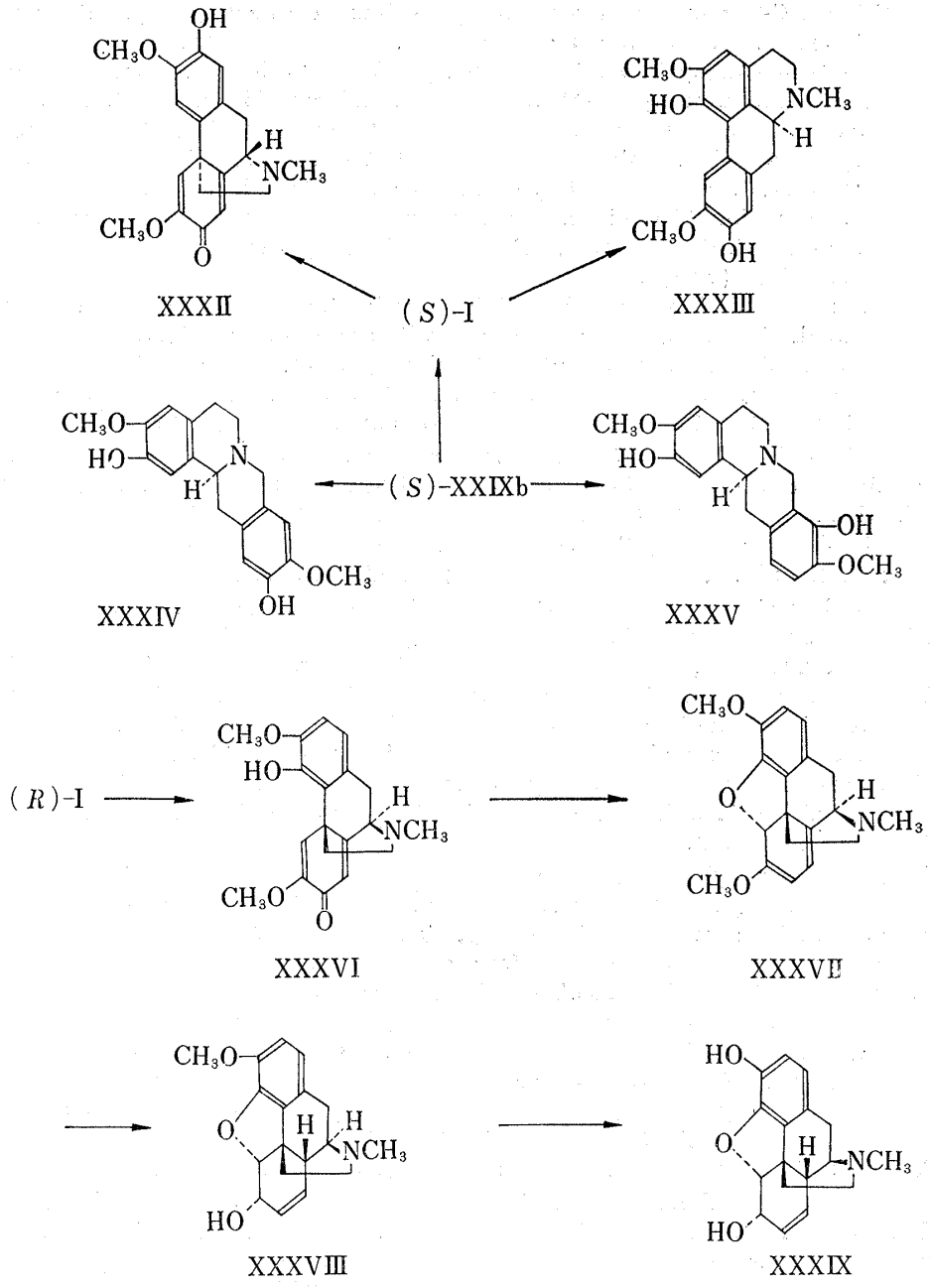


Chart 5

verted[18] to natural morphine (XXXIX) *via* salutaridine (XXXVI), thebaine (XXXVII), and codeine (XXXVIII) as shown in Chart 5.

By the application of the above 1,3-tranfer of asymmetry, many important alkaloids (*e.g.*, the other benzylisoquinoline, phenethylisoquinoline, erythrina, and ochotensine alkaloids) might be synthesized in their natural forms from optically active amino acids.

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 (δ) are given in ppm relative to internal tetra-

18) D.H.R. Barton, G.W. Kirby, W. Steglich, and G.M. Thomas, *Proc. Chem. Soc.*, **1963**, 203; D.H.R. Barton, D.S. Bhakuni, R. James, and G.W. Kirby, *J. Chem. Soc.* (*C*), **1967**, 128; D.H.R. Barton, G.W. Kirby, W. Steglich, G.M. Thomas, A.R. Battersby, T.A. Dobson, and H. Ramuz, *J. Chem. Soc.*, **1965**, 2423.

methylsilane. Wakogel C-200 was used for silica gel column chromatography. The organic solutions were dried over sodium sulfate before vacuum evaporation.

N,N-Dibenzyl-3-(3,4-dihydroxyphenyl)alanine Benzyl Ester (VII)——i) With Sodium Hydroxide: L-Dopa (2.0 g, 0.01 mole) in a mixture of 50% aqueous sodium hydroxide (1.6 ml, 0.02 mole) and dimethylsulfoxide (100 ml) was heated at 120° (bath temperature) for 0.5 hr. After benzyl bromide (3.4 g, 0.02 mole) was added to the mixture at 65°, the mixture was stirred at 120° for 3 hr, and poured onto ice (100 g). Extraction with diethyl ether, drying, followed by evaporation afforded a black oil, which was extracted with 10% aqueous hydrochloric acid. The acid extracts were washed with diethyl ether, neutralized with aqueous ammonia, and extracted with diethyl ether. The ethereal extracts were washed with water, dried, and evaporated to give a black oil (0.25 g).

On the other hand the insoluble material obtained during the above acid treatment was dissolved in acetone, and evaporated. The residue was neutralized with aqueous ammonia, and extracted with diethyl ether. Drying followed by evaporation afforded a black oil (0.52 g). The combined black oil (0.77 g) was subjected to a silica gel column chromatography with a mixture of ethyl acetate and benzene (4: 96) to give VII (0.22 g) as an oil, IR 3400, 1735 cm^{-1}. Mass Spectrum *m/e*: 467 (M^+), 344 ($M^+-C_7H_7O_2$), 123 ($C_7H_7O_2$).

The hydrochloride of VII (0.15 g, 4.7% yield) was prepared as usual, mp 92—94° (decomp.). Recrystallization from a mixture of acetone and diethyl ether furnished colorless needles, mp 102—105° (decomp.). NMR 1.20 (6H, triplet, $J=7$ Hz, $2\times CH_3$), 3.45 (4H, quartet, $2\times CH_2$ of diethyl ether), 4.30 (4H, broad, $2\times NCH_2$), 4.95 (2H, singlet, CO_2CH_2), 7.25 (15H, broad, $3\times C_6H_5$). *Anal.* Calcd. for $C_{30}H_{29}O_5N\cdot HCl\cdot C_2H_5OC_2H_5$: C, 70.64; H, 6.98; N, 2.43. Found: C, 70.51; H, 6.93; N, 2.69.

ii) With Potassium Carbonate: A mixture of L-dopa (2.0 g, 0.01 mole) and potassium carbonate (1.4 g, 0.01 mole) in ethanol was stirred at reflux for 1 hr. After the addition of sodium iodide (0.5 g) and benzyl chloride (2.6 g, 0.02 mole), the mixture was refluxed for 5 hr, filtered, and evaporated. The residue was extracted with diethyl ether, and the extracts were washed with water, and treated with 10% aqueous hydrochloric acid to give the hydrochloride of VII as white precipitates (0.90 g). The aqueous solution was neutralized with aqueous ammonia and extracted with diethyl ether. The ethereal extracts were washed with water, dried, and evaporated to give an oily product which was purified by a silica gel column chromatography as in (i) to furnish VII, which was converted to its hydrochloride (0.85 g). Total yield was 1.75 g (56.3%), mp 102—105° (decomp.).

N-Formyl-3-(3,4-dihydroxyphenyl)-L-alanine Methyl Ester (VIII)——To a stirred mixture of L-dopa methyl ester hydrochloride[19] (2.5 g, 0.01 mole) and sodium formate (0.75 g, 0.011 mole) in formic acid (25 ml) was added acetic anhydride (10 ml) with ice-cooling. The mixture was stirred at room temperature for 3 hr. After addition of methanol (15 ml) with ice-cooling, the mixture was stirred at room temperature for 1 hr, and evaporated. The residue was dissolved in ethyl acetate, and filtered to remove insoluble materials. The filtrates were washed with a small amount of 10% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. Drying and evaporation afforded VIII (2.3 g, 100%) as colorless crystals. For analysis a sample was recrystallized from a mixture of ethyl acetate and *n*-hexane to give colorless crystals, mp 119—121°, $[\alpha]_D^{27}$ +36.5° ($c=0.8$, MeOH). IR: 1730, 1635 cm^{-1}. NMR in tetradeuteromethanol, 3.55 (3H, singlet, CO_2CH_3), 7.9 (1H, singlet, NHC<u>H</u>O). *Anal.* Calcd. for $C_{11}H_{13}O_5N$: C, 55.22; H, 5.46; N, 5.86. Found: C, 55.07; H, 5.39; N, 5.81.

Benzylation of VIII——i) With Potassium Carbonate in Ethanol: A mixture of VIII (1.6 g, 6.7 mmole), benzyl chloride (0.89 g, 7.0 mmole), potassium carbonate (0.47 g, 3.4 mmole) and sodium iodide (catalytic amount) in ethanol (40 ml) was stirred at reflux for 4 hr. Filtration followed by evaporation afforded a red brown viscous oil, which was fractionated by a silica gel column with chloroform. The first fraction gave colorless crystals of N-formyl-3-(3,4-dibenzyloxyphenyl)-L-alanine ethyl ester (IXc, 0.30 g, 10%), which was recrystallized from a mixture of ethyl acetate and *n*-hexane to give colorless needles, mp 94°, $[\alpha]_D^{25}$ +11.0° ($c=1.0$, methanol). IR: 1745, 1655 cm^{-1}. NMR: 1.25 (3H, triplet, $J=7$ Hz, CH_3), 4.15 (2H, quartet, $J=7$ Hz, $C\underline{H}_2CH_3$), 5.15 (4H, singlet, $OC\underline{H}_2C_6H_5$), 5.90 (1H, broad, NH), 7.35 (10H, singlet, $2\times C_6H_5$), 8.0 (1H, singlet, CHO). *Anal.* Calcd. for $C_{26}H_{27}O_5N$: C, 72.04; H, 6.28; N, 3.23. Found: C, 72.11; H, 6.36; N, 3.37.

The second fraction gave colorless crystals of N-formyl-3-(3-benzyloxy-4-hydroxyphenyl)-L-alanine ethyl ester (IXb, 0.75 g, 33%), which was recrystallized from a mixture of ethyl acetate and *n*-hexane to give colorless prisms, mp 107—108° or mp 138—140° (both were identified by infrared spectral comparison in chloroform), $[\alpha]_D^{20}$ +8.5° ($c=0.4$, methanol). IR: 1725, 1675 or 1710, 1675 cm^{-1}. NMR: 1.25 (3H, triplet, $J=7$ Hz, CH_3), 4.15 (2H, quartet, $J=7$ Hz, $C\underline{H}_2CH_3$), 5.05 (2H, singlet, $OC\underline{H}_2C_6H_5$), 6.05 (1H, broad, NH), 7.30 (5H, singlet, $OCH_2C_6\underline{H}_5$), 8.00 (1H, singlet, CHO). *Anal.* Calcd. for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.46; H, 6.17; N, 4.12.

The third fraction gave colorless crystals of N-formyl-3-(3-hydroxy-4-benzyloxyphenyl)-L-alanine ethyl ester (IXa, 0.68 g, 30% yield), which was recrystallized from a mixture of ethyl acetate and *n*-hexane to give

19) K. Vogler and H. Baumgartner, *Helv. Chim. Acta*, 35, 1776 (1952).

colorless needles, mp 86—87°, $[\alpha]_D^{26}$ +15.5° (c=0.4, methanol). IR: 1730, 1635 cm^{-1}. NMR: 1.20 (3H, triplet, J=7 Hz, CH_3), 4.10 (2H, quartet, J=7 Hz, $C\underline{H}_2CH_3$), 5.00 (2H, singlet, $OC\underline{H}_2C_6H_5$), 6.10 (1H, broad, NH), 7.30 (5H, singlet, $OCH_2C_6\underline{H}_5$), 8.06 (1H, singlet, CHO). *Anal.* Calcd. for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.42; H, 6.27; N, 4.27.

When the above benzylation reaction was carried out in methanol instead of ethanol, only the starting material (VIII) was recovered with racemization, mp 142—144°, $[\alpha]_D^{23}$ +4.7° (c=0.85, methanol).

ii) With Potassium Carbonate in Dimethyl Sulfoxide: A mixture of VIII (2.5 g, 0.01 mole), benzyl chloride (1.95 g, 0.015 mole), potassium carbonate (2.8 g, 0.02 mole) and sodium iodide (catalytic amount) in dimethyl sulfoxide (30 ml) was stirred at 15° for 48 hr. The mixture was poured into ice-water, followed by extraction with ethyl acetate. The extracts were washed with water and dried. Evaporation afforded a black brown oil, which was fractionated by a silica gel column chromatography with chloroform. The first fraction gave N-formyl-3-(3-benzyloxy-4-hydroxyphenyl)-L-alanine methyl ester (IXe, 0.84 g, 26%), which was recrystallized from a mixture of ethyl acetate and n-hexane to give colorless needles, mp 155—156°, $[\alpha]_D^{23}$ +27.9° (c=0.6, methanol). Although its melting point and infrared spectrum in nujol were different from those of IXe prepared in (iii), their thin-layer chromatograms and nuclear magnetic resonance spectra were identical (see (iii)).

The second fraction gave N-formyl-3-(3-hydroxy-4-benzyloxyphenyl)-L-alanine methyl ester (IXd, 0.89 g, 27%), which was recrystallized from a mixture of ethyl acetate and n-hexane to give colorless needles, mp 120—121°, $[\alpha]_D^{23}$ +43.5° (c=0.82, methanol), identified with IXd prepared in (iii).

When the above reaction was carried out at 30°, N-formyl-3-(3,4-dibenzyloxyphenyl)-L-alanine methyl ester (IXf) was obtained as the first fraction in the column chromatography. Recrystallization from a mixture of ethyl acetate and n-hexane afforded colorless needles, mp 99—101°, $[\alpha]_D^{23}$ +28.7° (c=0.78, methanol), IR: 1760, 1650 cm^{-1}. NMR: 3.65 (3H, singlet, CO_2CH_3), 5.12 (4H, singlet, $2\times OC\underline{H}_2C_6H_5$), 7.35 (10H, singlet, $2\times C_6H_5$), 8.00 (1H, singlet, CHO). *Anal.* Calcd. for $C_{25}H_{25}O_5N$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.64; H, 5.97; N, 3.53.

iii) With Phenyldiazomethane: A mixture of VIII (17.0 g, 0.67 mole) in methanol (100 ml) and phenyldiazomethane (prepared from N-nitroso-p-poluenesulfonylbenzylamide (58 g, 0.2 mole) according to Hanson and Law[10b]) in dioxane (80 ml) was stirred at 60° (bath temperature) for 20 hr. Evaporation gave a red black viscous oil, which was fractionated by a silica gel column chromatography with chloroform. The first fraction afforded IXe (3.30 g, 15%) as colorless prisms (recrystallized from a mixture of ethyl acetate and n-hexane), mp 99—101°, $[\alpha]_D^{23}$ +32.5° (c=0.65, methanol). IR: 1740, 1660 cm^{-1}. NMR: 3.85 (3H, singlet, CO_2CH_3), 5.10 (2H, singlet, $OC\underline{H}_2C_6H_5$), 6.10 (1H, broad, OH), 7.40 (5H, singlet, C_6H_5), 8.04 (1H, singlet, CHO). *Anal.* Calcd. for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.59; H, 5.87; N, 4.28.

The second fraction afforded IXd (2.81 g, 13%) as colorless needles (recrystallized from a mixture of ethyl acetate and n-hexane), mp 120—122°, $[\alpha]_D^{23}$ +44.7° (c=0.68, methanol). IR: 1735, 1655 cm^{-1}. NMR 3.75 (3H, singlet, CO_2CH_3), 5.05 (2H, singlet, $OC\underline{H}_2C_6H_5$), 6.15 (1H, broad, OH), 7.34 (5H, singlet, C_6H_5), 8.08 (1H, singlet, CHO). *Anal.* Calcd. for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.45; H, 5.81; N, 4.33.

Further elution of the column with ethyl acetate furnished the starting VIII (9.5 g, 56%).

N-Formyl-3-(3,4-dibenzyloxyphenyl)-L-alanine Ethyl Ester (IXc)——A mixture of VIII (5.4 g, 0.023 mole) and potassium carbonate (4.7 g, 0.034 mole) in ethanol (150 ml) was refluxed for 0.5 hr, followed by the addition of benzyl chloride (6.3 g, 0.068 mole) and sodium iodide (catalytic amount). The mixture was refluxed for 2.5 hr, and evaporated. The residue was extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated to give a colorless oil, which was crystallized by tritulation with a mixture of ethyl acetate and n-hexane. The yield of IXc was 8.1 g (83%), mp 92—94°, $[\alpha]_D^{21.5}$ +11.0° (c=1.0, methanol).

N-Formyl-3-(3,4-dibenzyloxyphenyl)-L-alanine (IXg)——To sodium (0.18 g, 7.6 matom) in liquid ammonia (20 ml) was added IXc (1 g, 2.3 mmole) with stirring. The mixture was stirred for 6 hr to evaporate ammonia. The residue was treated with ice-water and ethyl acetate. The ethyl acetate layer was dried and evaporated to give an oil (0.18 g), which was purified over silica gel with a mixture of benzene and ethyl acetate (9: 1) to furnish the starting IXc (0.03 g, 3%).

The aqueous layer was acidified with 10% aqueous hydrochloric acid and extracted with ethyl acetate. The extracts were dried and evaporated to give IXg (0.25 g, 26%) as a slightly yellow crystals, mp 139—143°. Recrystallization from a mixture of ethyl acetate and n-hexane afforded a slightly yellow needles, mp 144—147°. IR: 1700 cm^{-1}, NMR: 4.70 and 4.75 (each, 2H, singlet, $OC\underline{H}_2C_6H_5$), 7.00 and 7.03 (each, 5H, singlet, $OCH_2C_6\underline{H}_5$), 7.65 (1H, singlet, CHO). *Anal.* Calcd. for $C_{24}H_{23}O_5N$: C, 70.81; H, 5.69; N, 3.50. Found: C, 71.09; H, 5.72; N, 3.45.

N-Trifluoroacetyl-3-(3-nitro-4-benzyloxyphenyl)-L-alanine Methyl Ester (XIII)——i) With Phenyldiazomethane: Benzylation of XII with phenyldiazomethane was carried out according to the literature[10b] to give XIII in 36% yield.

ii) With Benzyl Chloride in Ethanol: A mixture of XII (7.0 g, 21 mmole), benzyl chloride (5.2 g, 42 mmole), potassium carbonate (2.8 g, 21 mmole), and sodium iodide (catalytic amount) in acetone (300 ml) was refluxed for 5 hr. Filtration, washing with acetone, and evaporation afforded the solid residue, which

was extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated to give XIII (8.4 g, 95%) as colorless crystals, mp 89—92°. For analysis a sample was recrystallized from a mixture of ethyl acetate and *n*-hexane to furnish colorless needles, mp 91—93° (lit.[10b] 94—95°). IR: 1750, 1710, 1540, 1350 cm^{-1}. NMR: 3.83 (3H, singlet, CO_2CH_3), 5.23 (2H, singlet, OCH_2), 7.40 (5H, singlet, C_6H_5). *Anal.* Calcd. for $C_{19}H_{17}O_6N_2F_3$: N, 6.56. Found: N, 6.51.

N-Trifluoroacetyl-3-(3-amino-4-benzyloxyphenyl)-L-alanine Methyl Ester (XIV)——To a mixture of XIII (8.5 g, 0.02 mole) in methanol (150 ml) and calcium chloride (5.5 g, 0.05 mole) in water (150 ml) was added zinc powder (60 g), and the mixture was stirred at reflux for 1.5 hr. After filtration and washing the residue with methanol, the combined solution was evaporated to give the residue, which was extracted with chloroform. The extracts were washed with saturated aqueous sodium chloride, dried, and evaporated to give a red brown oil of XIV, which was, as usual, converted to its hydrochloride (5.5 g, 64%) as an amorphous powder, mp 158—160°. For analysis a sample was recrystallized from a mixture of methanol and diethyl ether to give a colorless amorphous powder, mp 159—160°. *Anal.* Calcd. for $C_{19}H_{19}O_4N_2F_3 \cdot HCl$: N, 6.47. Found: N, 6.42. Free base, IR: 3360, 1750—1715 (broad) cm^{-1}, NMR: 3.50 (2H, singlet, NH_2), 3.75 (3H, singlet, CO_2CH_3).

L-2-Benzyloxy-5-(2-trifluoroacetamide-2-methoxycarbonylethyl)-benzene Diazonium Fluoroborate (XV)——To a suspension of the hydrochloride of XIV (0.80 g, 1.85 mmole) in a mixture of water (4 ml) and *N* hydrochloric acid (4 ml) was added dropwise sodium nitrite (0.16 g, 2.2 mmole) in water (2 ml) with ice-cooling. After stirring at room temperature for 5 min, a yellow oil was separated by the addition of tetrafluoroboric acid (9 ml), followed by dissolving the oil in methanol (2 ml) after decantation. Addition of diethyl ether gave slightly yellow needles, which were filtered and washed with diethyl ether. The yield of XV was 0.80 g (87%), mp 139—141° (decomp.). IR: 2300, 1750, 1730 cm^{-1}.

Solvolysis of XV was attempted by (i) refluxing in acetic acid, (ii) treatment with a mixture of acetic acid and concentrated hydrochloric acid, or (iii) refluxing in water to result in either recovery of XV or formation of the tarry products.

The hydrochloride of XIV was treated with sodium nitrite in a mixture of *N* hydrochloric acid and acetic acid to give the result similar to above.

N-Formyl-L-tyrosine Methyl Ester (XVII)——To a mixture of L-tyrosine methyl ester hydrochloride (20.9 g, 0.9 mole) and sodium formate (6.8 g, 0.1 mole) in formic acid (200 ml) was added dropwise acetic anhydride (72 ml) with stirring and ice-cooling. After stirring at room temperature for 0.5 hr, methanol (90 ml) was added with ice-cooling, followed by stirring at room temperature for 0.5 hr. The mixture was evaporated, and the residue was extracted with ethyl acetate. The extracts were filtered, and the filtrate was washed with 10% aqueous hydrochloric acid and saturated aqueous sodium chloride. Drying and evaporation afforded an oil, which was tritulated with chloroform to give colorless crystals. Recrystallization with a mixture of ethyl acetate and diethyl ether afforded XVII (16.4 g, 82%) as colorless needles, mp 147—148°, $[\alpha]_D^{25}$ +47.4° (c=1.1, methanol). IR: 1750, 1670 cm^{-1}. NMR in tetradeuteromethanol 3.55 (3H, singlet, CO_2CH_3), 7.90 (1H, singlet, CHO). *Anal.* Calcd. for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.13; H, 5.75; N, 6.34.

N-Formyl-O-benzyl-L-tyrosine Ethyl Ester (XVIII)——A mixture of XVII (2.9 g, 0.013 mole), benzyl chloride (3.8 g, 0.03 mole), and potassium carbonate (2.1 g, 0.015 mole) in ethanol (30 ml) was refluxed for 1.5 hr. Filtration and evaporation gave the residue, which was extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated to furnish an oil (3.9 g), which was purified by a silica gel column chromatography with a mixture of benzene and ethyl acetate (20: 1) to give XVIII (3.3 g, 79%) as colorless crystals, mp 82—84°. For analysis a sample was recrystallized from a mixture of ethyl acetate and *n*-hexane to furnish colorless needles, mp 88—89°, $[\alpha]_D^{23}$ +27.0° (c=1.0, methanol). IR: 1745, 1660 cm^{-1}. NMR: 1.25 (3H, triplet, CH_3), 4.20 (2H, quartet, $C\underline{H}_2CH_3$), 5.05 (2H, singlet, $OC\underline{H}_2C_6H_5$), 6.20 (1H, broad, NH), 7.40 (5H, singlet, C_6H_5), 8.15 (1H, singlet, CHO). *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.76; H, 6.39; N, 4.20.

N-Formyl-O-acetyl-L-tyrosine Methyl Ester (XIX)——To a suspension of XVII (2.2 g, 0.01 mole) in chloroform (30 ml) was added dropwise acetic anhydride (1.5 g, 0.015 mole) and triethylamine (1.5 g, 0.015 mole) with ice-cooling, and the mixture was stirred at room temperature for 4 hr. Washing the mixture with water, drying, followed by evaporation afforded an oil, which was treated with *n*-hexane to give colorless crystals. Recrystallization from a mixture of ethyl acetate and *n*-hexane furnished XIX (2.6 g, 100%) as colorless prisms, mp 96—98°, $[\alpha]_D^{23}$ +39.0° (c=1.0, methanol). IR: 1740, 1670 cm^{-1}. NMR: 2.25 (3H, singlet, CH_3CO), 3.70 (3H, singlet, CO_2CH_3), 6.30 (1H, broad, NH), 7.95 (1H, singlet, CHO). *Anal.* Calcd. for $C_{13}H_{15}O_5N$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.90; H, 5.68; N, 5.34.

The Friedel-Crafts reaction on XVII, XVIII or XIX using a mixture of aluminum chloride and acetyl chloride under various conditions failed to give the C-3-acetyl derivative.

Fries Rearrangement of XIX——i) With 3 Equivalents of Aluminum Chloride: A suspension of XIX (10.6 g, 0.04 mole) and aluminum chloride (16.0 g, 0.12 mole) in tetrachloroethane (250 ml) was stirred at 130°. Hydrogen chloride gas vigorously evolved with appearance of insoluble oily products. After 1.5 hr, ice (4.5 g) and concentrated hydrochloric acid (28 ml) was added with ice-cooling and the mixture was stirred

at room temperature for 1 hr. The tetrachloroethane layer was separated, and the aqueous layer was extracted with chloroform and ethyl acetate. The ethyl acetate extracts were washed with water, dried, and evaporated to give an amorphous powder (9.7 g), which was recrystallized from a mixture of ethyl acetate and *n*-hexane to give N-formyl-3-(3-acetyl-4-hydroxyphenyl)-L-alanine (XXb, 7.1 g) as an amorphous powder, mp 156—157°, $[\alpha]_D^{25}$ +138.7° (c=2.0, methanol). IR: 1735, 1645, 1610 cm^{-1}. NMR in tetradeuteromethanol 2.65 (3H, singlet, CO_2CH_3), 8.10 (1H, singlet, CHO). *Anal.* Calcd. for $C_{12}H_{13}O_5N$: C, 57.36; H, 5.21; N, 5.58. Found: C, 56.89; H, 5.13; N, 5.70.

Evaporation of the combined tetrachloroethane and chloroform layer gave the residue, which was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate. The aqueous layer was neutralized with 10% aqueous hydrochloric acid, followed by extraction with ethyl acetate and washing with water. Drying and evaporation afforded the amorphous powder of XXb (0.6 g). Total yield of XXb was 7.7 g (77%).

The ethyl acetate layer separated from the sodium bicarbonate layer was washed with water, and dried. Evaporation followed by a silica gel column chromatography with a mixture of benzene and ethyl acetate (4: 1) afforded N-formyl-3-(3-acetyl-4-hydroxyphenyl)-L-alanine methyl ester (XXa, 0.12 g, 1.2%) as colorless crystals, mp 93—95°. Recrystallization from a mixture of ethyl acetate and *n*-hexane furnished colorless needles, mp 110—112°, $[\alpha]_D^{24}$ +31.0° (c=1.0, methanol). IR: 1750, 1650, 1620 cm^{-1}. NMR: 2.60 (3H, singlet, CH_3CO), 3.78 (3H, singlet, CO_2CH_3), 6.40 (1H, broad, NH), 8.15 (1H, singlet, CHO). *Anal.* Calcd. for $C_{13}H_{15}O_5N$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.86; H, 5.73; N, 5.12.

ii) With 2 Equivalents of Aluminum Chloride: The use of 2 equivalents of aluminum chloride under the same conditions as above gave XXa in 13% yield and XXb in 31% yield.

3-(3-Acetyl-4-hydroxyphenyl)-L-alanine Methyl Ester Hydrochloride——A mixture of XXb (4.20 g, 17 mmole) in 24% methanolic hydrogen chloride (80 ml) was refluxed for 2.5 hr. Evaporation afforded an oil, which was treated with a mixture of acetone and diethyl ether to give colorless crystals (2.8 g, 60%), mp 183—184°. For analysis a sample was recrystallized from a mixture of methanol and diethyl ether to give colorless needles, mp 183—186°. IR: 1760, 1640 cm^{-1}: NMR in deuterium oxide 2.60 (3H, singlet, CH_3CO), 3.80 (3H, singlet, CO_2CH_3). *Anal.* Calcd. for $C_{12}H_{15}O_4N \cdot HCl$: C, 52.65; H, 5.90; N, 5.12. Found: C, 52.28; H, 5.87; N, 5.09.

N-Formyl-3-(3-acetyl-4-hydroxyphenyl)-L-alanine Methyl Ester (XXa)——To a mixture of the above hydrochloride (3.4 g, 12.5 mmole) and sodium formate (1.0 g, 15 mmole) in formic acid (35 ml) was added dropwise acetic anhydride (12 ml) with ice-cooling. After stirring at room temeprature for 2 hr, evaporation gave the residue, which was extracted with ethyl acetate. The extracts were washed with 10% aqueous hydrochloric acid and saturated aqueous sodium chloride. Drying and evaporation afforded an oil, which was purified by a silica gel column chromatography with ethyl acetate to give XXa (1.53 g, 46%) as colorless needles, mp 110—111°, identical with a sample obtained by the Fries rearrangement of XIX.

Benzylation of XXa——i) Using Methanol as Solvent: A mixture of XXa (0.32 g, 1.2 mmole), benzyl chloride (0.30 g, 2.4 mmole), potassium carbonate (0.16 g, 1.2 mmole), and sodium iodide (catalytic amount) in methanol (20 ml) was refluxed for 5 hr. Filtration and evaporation gave the residue, which was treated with ethyl acetate and water. The organic layer was dried and evaporated to furnish an oil, which was purified by a silica gel column chromatography with benzene to give N-formyl-3-(3-acetyl-4-benzyloxyphenyl)alanine methyl ester (XXIa, 0.13 g, 31%) as colorless crystals. Recrystallization from a mixture of ethyl acetate and *n*-hexane afforded colorless needles, mp 78—79°, $[\alpha]_D^{23}$+ 4.0° (c=1, methanol). IR: 1745, 1665 cm^{-1}. NMR: 2.60 (3H, singlet, CH_3CO), 3.75 (3H, singlet, CO_2CH_3), 5.10 (2H, singlet, OCH_2), 7.35 (5H, singlet, C_6H_5), 8.1 (1H, singlet, CHO). *Anal.* Calcd. for $C_{20}H_{21}O_5N$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.67; H, 5.99; N, 3.99.

The aqueous layer separated from ethyl acetate was neutralized with 10% aqueous hydrochloric acid, and extracted with ethyl acetate. The organic extracts were washed with water, dried, and evaporated to give N-formyl-3-(3-acetyl-4-benzyloxyphenyl)alanine (XXIb, 0.23 g, 56%) as colorless crystals. Recrystallization from a mixture of ethyl acetate and *n*-hexane afforded colorless needles, mp 155—158°, $[\alpha]_D^{23}$ 0° (c=1.0, methanol). IR: 1720, 1675, 1635 cm^{-1}. NMR in tetradeuteromethanol 2.50 (3H, singlet, CH_3CO), 5.10 (2H, singlet, OCH_2), 7.50 (5H, singlet, C_6H_5), 8.00 (1H, singlet, CHO). *Anal.* Calcd. for $C_{20}H_{21}O_5N$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.67; H, 5.62; N, 4.25.

ii) Using Ethanol as Solvent: A mixture of XXa (0.74 g, 2.8 mmole), benzyl chloride (0.89 g, 7 mmole), potassium carbonate (0.49 g, 3.5 mmole), and sodium iodide (catalytic amount) in ethanol (50 ml) was refluxed for 2.5 hr, and worked up as in (i). From the ethyl acetate extracts an oil was obtained, which was purified by a silica gel column chromatography with a mixture of benzene and ethyl acetate (9: 1) to give N-formyl-3-(3-acetyl-4-benzyloxyphenyl) alanine ethyl ester (XXIc, 0.85 g, 83%) as colorless crystals, mp 80—82°. For analysis a sample was recrystallized from a mixture of ethyl acetate and *n*-hexane to give colorless needles, mp 83—85°, $[\alpha]_D^{21}$ +6.0° (c=1.0, methanol). IR: 1750, 1660 cm^{-1}. NMR: 1.30 (3H, triplet, J=7 Hz, $C\underline{H}_3$-CH_2), 2.60 (3H, singlet, CH_3CO), 4.20 (2H, quartet, J=7 Hz, $CH_3C\underline{H}_2$), 5.15 (2H, singlet, $OC\underline{H}_2C_6H_5$), 6.30 (1H, broad, NH), 8.15 (1H, singlet, CHO). *Anal.* Calcd. for $C_{21}H_{23}O_5N$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.28; H, 6.28; N, 3.74.

From the aqueous layer XXIb (0.13 g, 13%) was obtained as colorless crystals, mp 154—156°.

Preparation of XXIa from XXIb——To XXIb (0.43 g, 1.26 mmole) in ethanol (20 ml) was added dropwise diazomethane (11 mmole) in diethyl ether (20 ml) with ice-cooling. After stirring at room temperature for 1 hr, evaporation gave a brown viscous oil, which was treated with a mixture of ethyl acetate and *n*-hexane to give XXIa (0.34 g) as colorless crystals, mp 78—80°. An oily substance from the mother liquor was purified by a silica gel column chromatography with benzene to give another crop (0.10 g) of XXIa. Total yield of XXIa was 0.44 g (100%).

Baeyer-Villiger Oxidation of XXIa——A mixture of XXIa (0.15 g, 0.42 mmole) and *m*-chloroperbenzoic acid (purity more than 85%, 0.22 g, 1.09 mmole) in chloroform (10 ml) was refluxed for 48 hr, and washed with saturated aqueous sodium bicarbonate and water. Drying and evaporation gave an oil, which was passed over silica gel with a mixture of benzene and ethyl acetate (9: 1) to give an oily substance (0.10 g). This was proved to be a 1: 1 mixture of XXIa and N-formyl-3-(3-acetoxy-4-benzyloxyphenyl)alanine methyl ester (XXIIa) by its NMR spectrum: 2.25 (3H, singlet, CH_3CO_2), 2.58 (3H, singlet, CH_3CO).

Baeyer-Villiger Oxidation of XXIc——A mixture of XXIc (1.1 g, 3 mmole) and *m*-chloroperbenzoic acid (1.1 g, 5.1 mmole) in chloroform (30 ml) was refluxed for 48 hr, and washed with saturated aqueous sodium bicarbonate and water. Drying and evaporation afforded an oil (1.13 g), which was purified by a silica gel column chromatography with a mixture of benzene and ethyl acetate (9: 1) to give a colorless viscous oil (0.72 g). Treatment of the oil with a mixture of ethyl acetate and *n*-hexane afforded colorless crystals (0.62 g), mp 78—90°, which was proved to be a 1: 2 mixture of XXIc and N-formyl-3-(3-acetoxy-4-benzyloxyphenyl)alanine ethyl ester (XXIIb) by its NMR spectrum: 2.25 (singlet, CH_3CO_2), 2.58 (singlet, CH_3CO). Recrystallization from a mixture of ethyl acetate and *n*-hexane furnished a 1: 3 mixture of XXIc and XXIIb as colorless needles, mp 100—102°. IR: 1765, 1750, 1660 cm^{-1}. *Anal.* Calcd. for $C_{21}H_{23}O_6N$ (XXIIb): C, 65.44; H, 6.01; N, 3.64. Found: C, 65.01; H, 6.07; N, 3.70.

N-Formyl-3-(3-hydroxy-4-benzyloxyphenyl)alanine Methyl Ester (IXd)——i) From a Mixture of XXIc and XXIIb: A solution of the foregoing mixture (0.51 g) of XXIc and XXIIb (1: 2) and potassium bicarbonate (0.55 g) in acetone (30 ml)-methanol (50 ml)-water (10 ml) was stirred at 30° (bath temperature) for 3 hr. Evaporation gave the residue, which was extracted with ethyl acetate. The organic extracts were washed with saturated aqueous sodium chloride, dried, and evaporated. The residual oil (0.33 g) was purified by a silica gel column chromatography with a mixture of benzene and ethyl acetate (9: 1) to give IXd (0.28 g) as colorless crystals, mp 109—111°. Recrystallization from a mixture of ethyl acetate and *n*-hexane afforded colorless needles, mp 113—115°, $[\alpha]_D^{18}$ +7.7° (c=0.6, methanol). IR: 1735, 1650 cm^{-1}. Its IR and NMR spectra in chloroform were identical with those of IXd obtained from VIII.

ii) From IXa: A solution of IXa (0.25 g, 0.73 mmole) and potassium bicarbonate (0.30 g, 3 mmole) in acetone (20 ml)-methanol (30 ml)-water (6 ml) was stirred at 35° (bath temperature) for 4 hr, and worked up as in (i) to give IXd (0.16 g, 67%) as colorless crystals, mp 95—106°. Recrystallization from a mixture of ethyl acetate and *n*-hexane afforded colorless needles, mp 113—115°, $[\alpha]_D^{12}$ +14.3° (c=0.6, methanol).

3-(3-Hydroxy-4-benzyloxyphenyl)-L-alanine Methyl Ester Hydrochloride (XXIII)——A solution of optically pure IXd (0.13 g, 0.40 mmole) in 4.5% methanolic hydrogen chloride (6 ml) was allowed to stand at room temperature overnight. Evaporation at room temperature gave the residue, which was treated with diethyl ether to give XXIII (0.12 g, 90%) as colorless crystals, mp 176—179°. For analysis a sample was recrystallized from a mixture of methanol and diethyl ether to give colorless needles, mp 179.5—180°, $[\alpha]_D^{23}$ +13.0° (c=0.6, methanol.) IR: 1760 cm^{-1}. *Anal.* Calcd. for $C_{17}H_{19}O_4N \cdot HCl$: C, 60.44; H, 5.97; N, 4.15. Found: C, 60.00, H, 5.97; N, 4.23.

(1*S*, 3*S*)-Methyl 1-(3-Benzyloxy-4-methoxybenzyl)-6-hydroxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (XXVa) and (1*R*, 3*S*)-Methyl 1-(3-Benzyloxy-4-methoxybenzyl)-6-hydroxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (XXVb)——A mixture of XXIII (13.8 g, 0.041 mole) and sodium 3-benzyloxy-4-methoxyphenylglycidate[12] (XXIV) in methanol (800 ml)-water (400 ml) was adjusted to pH 4 with acetic acid (55 ml). The mixture was stirred at 40° (bath temperature) for 48 hr. Evaporation at 40° gave the residue, which was extracted with ethyl acetate. The organic extracts were washed with 10% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, and water. Drying and evaporation gave a reddish brown oil, which was fractionated by a silica gel column chromatography with chloroform.

The first fraction to be eluted was XXVa (2.5 g, 11.4%) as yellow crystals, mp 94—97°. For analysis a sample was passed over alumina column, followed by recrystallization from a mixture of ethyl acetate and *n*-hexane to give slightly yellow needles, mp 114—116°, $[\alpha]_D^{20}$ −85.3° (c=0.54, chloroform). IR: 1750 cm^{-1}. NMR: 3.70 (3H, singlet, CO_2CH_3), 3.83 (3H, singlet, $ArOCH_3$), 4.80 (2H, singlet, OCH_2), 5.05 (2H, singlet, OCH_2), 7.30 (10H, singlet, $2 \times C_6H_5$). Mass Spectrum *m/e*: 312. *Anal.* Calcd. for $C_{33}H_{33}O_6N$: C, 73.45; H, 6.21; N, 2.60. Found: C, 73.23; H, 6.21; N, 2.57.

The second fraction to be eluted was XXVb (1.20 g, 5.4%) as colorless crystals, mp 151—154°. For analysis a sample was recrystallized from a mixture of ethyl acetate and *n*-hexane to give colorless needles, mp 157.5—158.5°, $[\alpha]_D^{20}$ −49.3° (c=0.43, chloroform). IR: 1740 cm^{-1}. NMR: 3.69 (3H, singlet, CO_2CH_3), 3.85 (3H, singlet, $ArOCH_3$), 4.90 (2H, singlet, OCH_2), 5.05 (2H, singlet, OCH_2), 7.30 (10H, singlet, $2 \times C_6H_5$).

Mass Spectrum *m/e*: 312. *Anal.* Calcd. for $C_{33}H_{33}O_6N$: C, 73.45; H, 6.16; N, 3.60. Found: C, 73.26; H, 6.41; N, 3.86.

(1*S*, 3*S*)-Methyl 1-(3-Benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (XXVIa) and (1*S*, 3*S*)-Methyl 1-(3-Benzyloxy-4-methoxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-terahydroisoquinoline-3-carboxylate (XXVIb)——To diazomethane (13 mmole) in diethyl ether (50 ml) was added dropwise XXVa (2.4 g, 4.4 mmole) in methanol (30 ml) with ice-cooling. The mixture was stirred at room temperature overnight, and evaporated to the residue, which was treated with diethyl ether to give XXVIa (2.05 g, 83%) as slightly yellow crystals, mp 76—80°. For analysis a sample was recrystallized from a mixture of ethyl acetate and *n*-hexane to furnish slightly yellow needles, mp 83—84°, $[\alpha]_D^{20}$ −84.8° (*c*=0.64, chloroform). IR: 1750 cm^{-1}. NMR: 2.65 (1H, singlet, NH), 3.70 (3H, singlet, CO_2CH_3), 3.83 (6H, singlet, 2×$ArOCH_3$), 5.00 (2H, singlet, OCH_2), 5.02 (2H, singlet, OCH_2). Mass Spectrum *m/e*: 326. *Anal.* Calcd. for $C_{34}H_{35}O_6N$: C, 73.36; H, 6.37; N, 2.53. Found: C, 73.49; H, 6.26; N, 2.52.

An oil obtained from the mother liquor was fractionated by a silica gel column chromatography with chloroform to give the starting XXVa (0.16 g, 4%) and XXVIb (0.13 g, 5%) as a yellow oil, $[\alpha]_D^{20}$ −5.0° (*c*=0.28, chloroform). IR: 1745 cm^{-1}. NMR: 2.46 (3H, singlet, NCH_3), 3.78 (3H, singlet, CO_2CH_3), 3.85 (6H, singlet, 2×$ArOCH_3$), 4.95 (2H, singlet, OCH_2), 5.10 (2H, singlet, OCH_2). Mass Spectrum *m/e*: 340.

(1*S*, 3*S*)-1-(3-Benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (XXVIIa)——An ice-cooled solution of XXVIa (1.9 g, 3.3 mmole) in methanol (90 ml) and chloroform (30 ml) was saturated with ammonia gas. The mixture was allowed to stand at room temperature for 38 hr, and evaporated to give a reddish yellow viscous oil, which was purified by a silica gel column chromatography with a mixture of chloroform and ethyl acetate (1: 1) to give XXVIIa (1.47 g, 84%) as colorless crystals, mp 78—82°. For analysis a sample was recrystallized from a mixture of chloroform and diethyl ether to give colorless crystals, mp 94—95°, $[\alpha]_D^{20}$ −99.5° (*c*=0.43, chloroform). IR: 1700 cm^{-1}. NMR: 1.74 (2H, singlet, $CONH_2$), 3.82 (6H, singlet, 2×$ArOCH_3$), 5.01 (2H, singlet, OCH_2), 5.07 (2H, singlet, OCH_2), 5.30 (1H, broad, NH). Mass Spectrum *m/e*: 311. *Anal.* Calcd. for $C_{33}H_{34}O_5N_2$: C, 73.58; H, 6.36; N, 5.20. Found: C, 73.70; H, 6.33; N, 5.04.

(1*S*, 3*S*)-1-(3-Benzyloxy-4-methoxybenzyl)-2-benzyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (XXVIIb)——A mixture of XXVIIa (1.4 g, 2.6 mmole), benzyl chloride (0.49 g, 3.9 mmole), potassium carbonate (1.1 g, 7.8 mmole), and sodium iodide (catalytic amount) in ethanol (100 ml) was refluxed for 2 hr. Evaporation gave the residue, which was extracted with chloroform. The extracts were washed with water, dried, and evaporated to give a yellow oil, which was purified by a silica gel column chromatography with a mixture of benzene and ethyl acetate (1: 1), followed by an alumina column chromatography with ethyl acetate to give XXVIIb (1.45 g, 89%) as colorless crystals, mp 62—64°. For analysis a sample was recrystallized from a mixture of chloroform and diethyl ether to give colorless needles, mp 63—65°, $[\alpha]_D^{20}$ −24.4° (*c*=0.40, chloroform). IR: 1705 cm^{-1}. NMR: 2.00 (2H, broad, $CONH_2$), 3.75 (2H, singlet, NCH_2), 3.80 (6H, singlet, 2×$ArOCH_3$), 4.80 (4H, singlet, OCH_2). Mass Spectrum *m/e*: 401. *Anal.* Calcd. for $C_{40}H_{40}O_5N_2$: C, 76.41; H, 6.36; N, 4.46. Found: C, 75.98; H, 6.66; N, 4.67.

(*S*)-1-(3-Benzyloxy-4-methoxybenzyl)-2-benzyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (XXIXa)——To a stirred suspension of phosphorus pentoxide (4.8 g, 35 mmole) and dry hyflo-super-cel (10 g) in pyridine (50 ml) was added XXVIIb (1.45 g, 2.35 mmole) in pyridine (20 ml) at 80° (bath temperature), followed by stirring at 100° for 20 min. The mixture was filtered, and washed with chloroform. Evaporation of the combined filtrates afforded a reddish black oil, containing mainly (1*S*, 3*S*)-1-(3-benzyloxy-4-methoxybenzyl)-2-benzyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline-3-carbonitrile (XXVIII), which was dissolved in a mixture of pyridine (18 ml) and ethanol (35 ml) and treated with sodium borohydride (0.36 g, 9.5 mmole) with ice-cooling. The mixture was stirred at 15—20° overnight, and at 35° for 3 hr. Evaporation gave the residue, which was extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated. The residue was purified by a silica gel column chromatography with chloroform, followed by passing over an alumina column with benzene to give XXIXa (0.71 g, 52%) as a yellow oil, $[\alpha]_D^{25}$ +35.5° (*c*=0.85, chloroform). NMR: 3.79 (2H, singlet, $NC\underline{H}_2C_6H_5$), 3.88 (6H, singlet, 2×$ArOCH_3$), 4.85 (2H, singlet, OCH_2), 5.03 (2H, singlet, OCH_2), 7.29 (5H, singlet, $NCH_2C_6\underline{H}_5$), 7.37 (10H, singlet, 2×$OCH_2C_6\underline{H}_5$). Mass Spectrum *m/e*: 358.

(*S*)-1-(3-Hydroxy-4-methoxy-4-methoxybenzyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride=(*S*)-Norreticuline Hydrochloride (XXIXb)——A mixture of XXIXa (0.62 g, 1.06 mmole) and 15% aqueous hydrochloric acid (5 ml) in ethanol (90 ml) was catalytically hydrogenated over 5% palladium carbon (0.35 g) at room temperature. Filtration and evaporation afforded a slightly green oil, which was treated with a mixture of ethanol and diethyl ether to give slightly yellow crystals (0.33 g), mp 155—160°. Recrystallization from a mixture of methanol, ethanol, and diethyl ether afforded XXIXb (0.235 g, 63%) as colorless crystals, mp 237—240° (lit.[13] 228—230°), $[\alpha]_D^{20}$ −13.0° (*c*=0.66, methanol) (lit.[13] $[\alpha]_D^{25}$ −13.3° (methanol)). IR: 1605, 1595 cm^{-1}. NMR in tetradeuteromethanol 5.84 (6H, singlet, $ArOCH_3$). Mass Spectrum *m/e*: 178. *Anal.* Calcd. for $C_{18}H_{21}O_4N\cdot HCl$: C, 61.45; H, 6.31; N, 3.98. Found: C, 61.02; H, 6.13; N, 3.89.

(*S*)-1-(3-Hydroxy-4-methoxybenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline=(*S*)-Reticuline (I)——To a mixture of XXIXb (0.180 g, 0.51 mmole) and triethylamine (0.258 g, 2.55 mmole)

in chloroform (30 ml) was added dropwise ethyl chloroformate (0.200 g, 1.84 mmole) with ice-cooling. The mixture was stirred at room temperature for 1 hr, washed with water, dried over potassium carbonate, and evaporated to give XXX (0.28 g) as a blue-brown viscous oil, IR: 1760, 1680 cm^{-1}. The oil (XXX) in tetrahydrofuran (120 ml) was refluxed with lithium aluminum hydride (0.30 g) for 14 hr. Ammonium chloride (3.0 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 0.5 hr. Filtration and evaporation gave the residue, which was treated with chloroform and water. After filtration, the chloroform layer was washed with water and dried. Evaporation afforded a slightly brown oil (0.15 g), which was purified by a silica gel column with a mixture of ethyl acetate and methanol (12: 1) to give (*S*)-I (0.08 g, 46%) as a viscous oil. IR: in chloroform 3560 cm^{-1}. NMR: 2.5 (3H, singlet, NCH_3), 3.8 (6H, singlet, $2 \times OCH_3$), 5.7 (2H, singlet, $2 \times OH$). The free base of (*S*)-I was converted to its perchlorate, colorless prisms (recrystallized from ethanol), mp 203—204° (lit.[15] 203—204°), $[\alpha]_D^{18}$ +88.3° (c=0.21, ethanol) (lit.[15] $[\alpha]_D^{31}$ +87.5° (ethanol)). Mass Spectrum *m/e*: 192. *Anal.* Calcd. for $C_{19}H_{23}O_4N \cdot HClO_4$: C, 53.08; H, 5.59; N, 3.26. Found: C, 52.90; H, 5.65; N, 3.23.