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Stereochemical Studies. LIII.[1] An Asymmetric Synthesis of (3*S* 15*S* 20*R*)-Yohimbone from L-Tryptophan by 1,3-Transfer of Asymmetry

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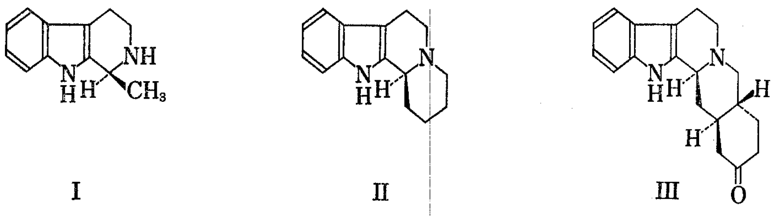
The asymmetric synthesis of (3*S* 15*S* 20*R*)-(—)-yohimbone (III) was accomplished. The key reactions in the process are: (i) the asymmetric Pictet-Spengler reaction of L-tryptophan (IV) with sodium 3-(*m*-methoxyphenyl)glycidate (V) (1,3-asymmetric induction), and (ii) the elimination of the chiral center derived from IV (1,3-transfer of asymmetry). The latter was conveniently achieved by converting the cyclic α-amino acid amide (XIIIa) to the pentacyclic α-amino nitrile (XIV), followed by reductive decyanization with sodium borohydride. Thus, the indole alkaloids, natural yohimbol (XX) and natural corynantheine (XXI), may be synthesized from L-tryptophan.

Keywords——asymmetric synthesis of (3*S* 15*S* 20*R*)-(—)-yohimbone; asymmetric Pictet-Spengler reaction; 1,3-transfer of asymmetry; 1,3-asymmetric induction; reductive decyanization; indole alkaloids; L-tryptophan

In a previous publication[3] we proposed a new approach to the synthesis of optically active indole and isoquinoline alkaloids, 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 cyclic α-amino acid derivatives. The latter was conveniently achieved by the conversion of α-amino acids to α-amino nitriles, followed by reductive decyanization with sodium borohydride.

Using 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 satisfactorily synthesized from L-tryptophan.[3]

To provide further support for this method and to develop a new asymmetric synthesis based on the 1,3-transfer of asymmetry, efforts were made to synthesize (3*S* 15*S* 20*R*)-(—)-yohimbone (III), starting with L-tryptophan.



I II III

Chart 1

(3*S* 15*S* 20*R*)-(—)-Yohimbone (III) was prepared by the Oppenauer oxidation of natural yohimbine.[4] Although there is a report on the synthesis of III in its recemic modification,[5]

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1) Part LII: K. Koga, T.M. Juang, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **26**, 178 (1978).

2) Location: *a*) *1-3-32, Ukima, Kita-ku, Tokyo 115, Japan*; *b*) *7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan.*

3) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikukawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 2619 (1974).

4) B. Witkop, *Ann.*, **554**, 83 (1943).

5) K. Mori, I. Takemoto, and M. Matsui, *Arg. Biol. Chem.*, **36**, 2605 (1972); T. Kametani, M. Kajiwara, and K. Fukumoto, *Tetrahedron*, **30**, 1053 (1974).

preparation of the optically active isomers of III has only been by optical resolution.[6] No attempt at asymmetric synthesis of optically active III has been.

The asymmetric Pictet-Spengler reaction of L-tryptophan (IV) with sodium 3-(*m*-methoxyphenyl)glycidate (V)[7] afforded a cyclic product (VI) in a 30% yield. In the process, the starting material, L-tryptophan was recovered in a 69% yield. The product (VI) was expected to have the more stable, 1,3-*cis* isomer with both ring substituents occupying equatorial positions.[3]

Support for this assignment was obtained by conversion of VI to III.

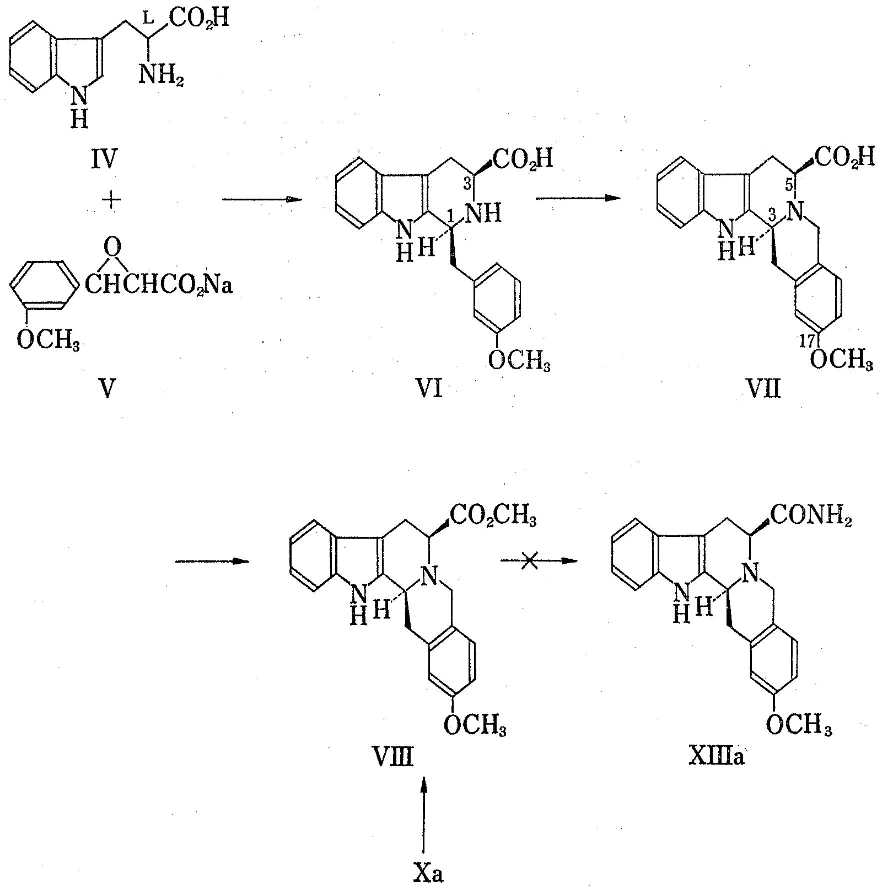

Chart 2

VI, on treatment with formalin, afforded a pentacyclic product (VII) in a 71% yield, which gave the methyl ester (VIII) in a 92% yield with methanolic hydrogen chloride. Attempt to prepare the amide (XIIIa) from VIII resulted in the recovery of VIII after one month of treatment with methanolic ammonia. The ester (VIII) was resistant to ammonolysis.

The asymmetric Pictet-Spengler reaction of L-tryptophan methyl ester hydrochloride (IX), prepared from L-tryptophan,[8] with V in 50% aqueous methanol under a gentle reflux afforded a diastereoisomeric mixture of 1,3-*cis* (Xa) and 1,3-*trans* (Xb) in a 27% yield. The ratio of Xa to Xb was 1.2: 1. These structures, Xa and Xb, were also supported by conversion of Xa to III and XIX. Treatment of Xa with formalin afforded VIII in a 65% yield. Treatment of VI with methanolic hydrogen chloride gave the methyl ester hydrochloride (Xa)

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6) A.G. Swan, *J. Chem. Soc.*, **1950**, 1534.
7) A.K.D. Gupta and J.K. Chakrabarti, *J. Sci. Ind. Res.* (India), **20B**, 394 (1961).
8) R.A. Boissonnas, S.T. Guttmann, R.L. Hugnenin, P.A. Jaquinoud, and Ed. Sandrin, *Helv. Chim. Acta*, **41**, 1867 (1958).

in an 87% yield. The ester (Xa) was treated with methanolic ammonia to give the amide (XIIa–HCl) in a 62.5% yield.

The asymmetric Pictet-Spengler reaction of L-tryptophan amide hydrochloride (XI), prepared from L-tryptophan,[9] with the glycidate (V) in 50% aqueous methanol under a gentle reflux afforded a diastereoisomeric mixture of 1,3-*cis* (XIIa) and 1,3-*trans* (XIIb) in a 67% yield. The ratio of XIIa to XIIb was 3:1. The assignment was made by assuming the main isomer to be the more stable *cis* isomer, according to previous experience.[3] The final support of XIIa was shown by conversion of XIIa to III and (—)-alloyohimbone (XIX). Treatment of XIIa with formalin afforded the pentacyclic amide (XIIIa) in an 84% yield. XIIb was also converted to XIIIb in an 85% yield.

The elimination of the chiral center derived from L-tryptophan was achived as follow: treatment of XIIIa with phosphorus oxychloride in pyridine and N,N-dimethylformamide afforded the nitrile (XIV) in a 70.3% yield and the resulting nitrile (XIV) was treated with sodium borohydride in ethanol and pyridine to give the decyanized product (XV) in an 82.8% yield.

The Birch reduction of XV with sodium in liquid ammonia afforded XVI in an 85.3% yield.

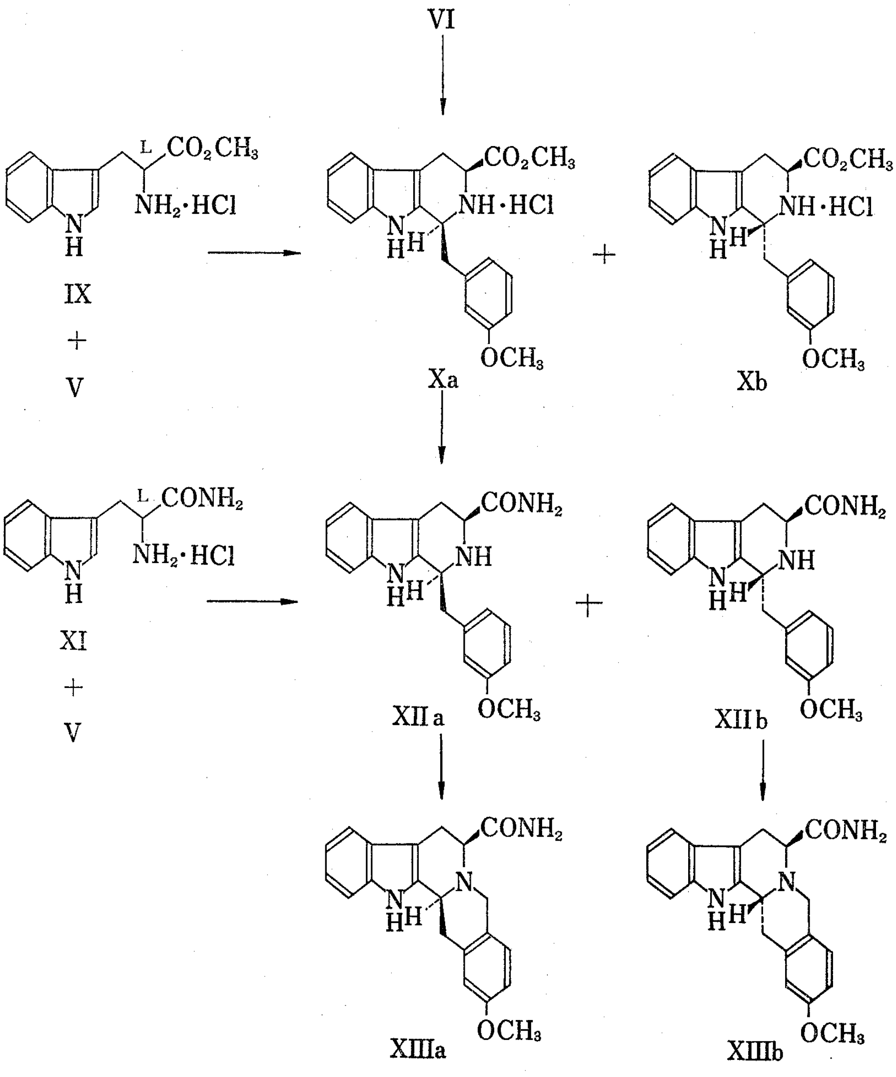

Chart 3

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[9] E.L. Smith and W.J. Polyluse, *J. Biol. Chem.*, **180**, 1209 (1949).

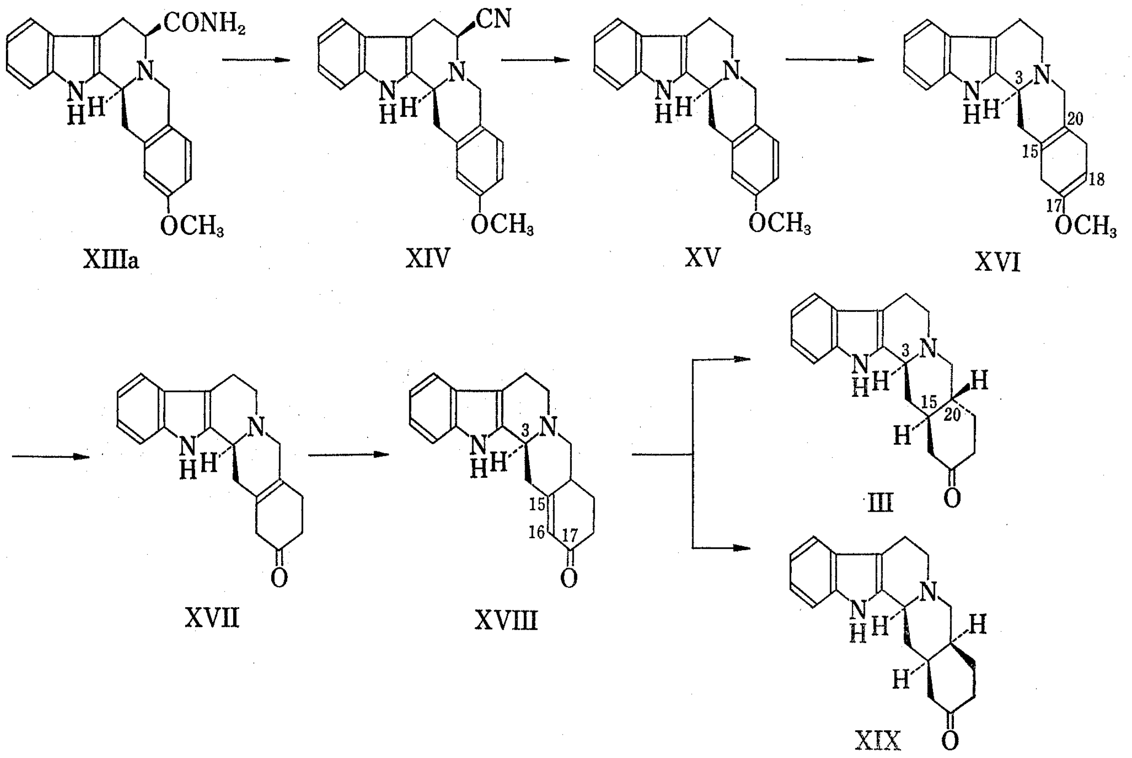

Chart 4

Hydrolysis of XVI in the same treatment as the racemic XVI[6] with 2N aqueous hydrochloric acid for 1.5 hr produced either a mixture of XVII and XVIII or the concomitant formation of some unknown products. Thus, XVI was warmed with a mixture of 2 N aqueous hydrochloric acid and methanol for 5 min to give only the *βγ*-unsaturated ketone (XVII) in an 80.6% yield.

The double bond migration of XVII to XVIII was found to be effected by heating XVII in pyridine for 2 hr. Thus, XVIII was isolated in an 80% yield. Its NMR spectrum showed a singlet at 5.83 ppm due to an olefin proton in the 16-position. XVIII was assumed to be a mixture of diastereoisomers but separation of each isomer was unsuccessful. The support of XVIII was shown by conversion of XVIII to III and XIX.

The *αβ*-unsaturated ketone (XVIII) was catalytically hydrogenated over 5% palladium-carbon to furnish a diastereoisomeric mixture of III and XIX in an 80% yield. The ratio of III to XIX was 4: 1. III was (3*S* 15*S* 20*R*)-(−)-yohimbone[4] and XIX was (3*S* 15*S* 20*S*)-(−)-yohimbone (alloyohimbone).[10] The physical constants of III and XIX coincided with those of the reported ones.[4,10] Spectra data also supported these structures.

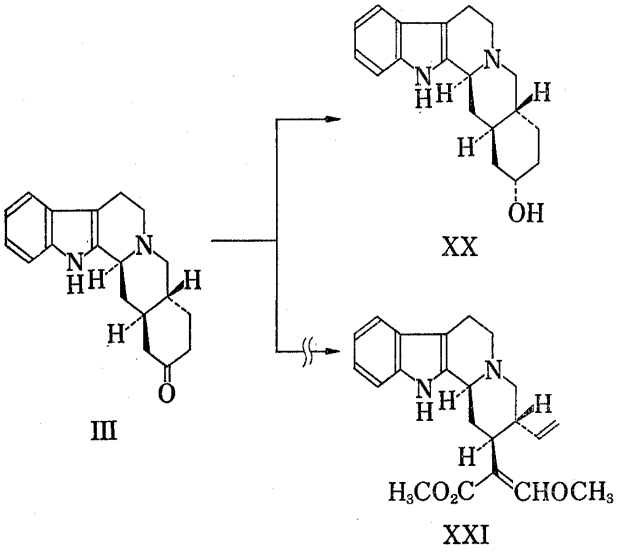

Chart 5

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[10] L. Bartlett, N.J. Dastoor, J. Hrbek Jr., H. Schmid, and G. Snatzke, *Helv. Chim. Acta*, **54**, 1238 (1971).

III has already been converted to the indole alkaloids, natural yohimbol (XX)[4] and natural corynantheine (XXI).[11]

Therefore, XX[12] and XXI[13] may be synthesized from L-tryptophan.

By applying the above 1,3-transfer of asymmetry, many indole alkaloids might be synthesized in their natural forms from optically active tryptophan.

Experimental

Unless stated all melting points were uncorrected. Infrared (IR) spectra were measured in KBr pellets. Nuclear magnetic resonance (NMR) spectra (100 MHz) were measured in deuterodimethylsulfoxide. Chemical shifts (δ) are given ppm relative to internal tetramethylsilane. Mass (MS) spectra were also measured. Organic solutions were dried over anhydrous sodium sulfate before vacuum evaporation.

(1*S* 3*S*)-(−)-1-(*m*-Methoxybenzyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (VI)——A mixture of sodium (*m*-methoxyphenyl)glycidate[7] (V, 3.5 g, 0.016 mol) in water (60 ml) and L-tryptophan (IV, 2.6 g, 0.013 mol) in 10% aqueous hydrochloric acid (7 ml) and water (200 ml) was adjusted to pH 4 with acetic acid and stirred at 10—15° for 4 days. The precipitates formed were collected by filtration, washed with ethyl acetate, and dried to give VI (1.44 g, 30.0%) as faint yellow crystals, mp 190—193°. For analysis a sample was recrystallized from a mixture of ethanol and water as colorless granules, mp 194—195°, $[\alpha]_D^{20}$ −142.4° (c=0.74, ethanol), IR: 3500, 3400, 1650, 1590 cm^{-1}. *Anal.* Calcd. for $C_{20}H_{20}N_2O_3 \cdot 3/2H_2O$: C, 66.10; H, 6.38; N, 7.71. Found: C, 66.27; H, 6.36; N, 7.66.

The filtrate was washed well with ethyl acetate and concentrated to a small volume. Ethanol was added to the residual solution to recover IV (1.8 g, 69.0%) as a white powder, mp 260° (dec.). Recrystallization from a mixture of ethanol and water afforded colorless leaflets, mp 265° (dec.), $[\alpha]_D^{22}$ +4.3° (c=1, 0.5 N HCl) (lit.[14] mp 289° (dec.), $[\alpha]_D^{20}$ +2.4° (c=1, 0.5 N HCl)). *Anal.* Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.53; H, 6.13; N, 13.58.

(1*S* 3*S*)-(−)-Methyl 1-(*m*-Methoxybenzyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylate Hydrochloride (Xa)——A mixture of VI (1.5 g, 4.1 mmol) and 10% (w/v) of methanolic hydrogen chloride (50 ml) was refluxed for 3 hr. Concentration of the mixture afforded yellow crystals, which were recrystallized from a mixture of methanol and diethyl ether to give Xa (1.4 g, 87.0%) as colorless needles, mp 164—166°, $[\alpha]_D^{20}$ −111.9° (c=0.52, methanol), IR: 1750 cm^{-1}. *Anal.* Calcd. for $C_{21}H_{23}ClN_2O_3 \cdot H_2O$: C, 62.29; H, 6.22; N, 6.92. Found: C, 62.49; H, 6.29; N, 6.72.

(1*S* 3*S*)-(−)-1-(*m*-Methoxybenzyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxamide Hydrochloride (XIIa-HCl)——An ice-cooled solution of Xa (1.4 g, 3.5 mmol) in methanol (50 ml) was saturated with ammonia gas. The mixture was allowed to stand at room temperature for 10 days after which it was evaporated to give XIIa-HCl (1.0 g, 62.5%) as faint yellow crystals. For analysis a sample was recrystallized from methanol as colorless needles, mp 203°, $[\alpha]_D^{18}$ −136.9° (c=1, methanol), IR: 1690 cm^{-1}. *Anal.* Calcd. for $C_{20}H_{22}ClN_3O_2 \cdot H_2O$: C, 61.61; H, 6.20; N, 10.78. Found: C, 61.87; H, 6.18; N, 10.52.

(3*S* 5*S*)-(−)-15,16,17,18,19,20-Hexadehydro-17-methoxyyohimbane-5-carboxylic Acid (VII)——Thirty seven percent formalin (1 ml) was added to a mixture of VI (0.336 g, 1 mmol), 50% aqueous ethanol (20 ml) and 1 N aqueous hydrochloric acid (1 ml). The mixture was refluxed for 3 hr. Evaporation gave faint yellow crystals, which were dissolved in 28% aqueous ammonia. Concentration afforded VII (0.26 g, 71.0%) as a faint yellow powder, mp 195°. Recrystallization from aqueous ethanol furnished colorless crystals, mp 205°, $[\alpha]_D^{21}$ −220.9° (c=0.708, methanol), IR: 1620 cm^{-1}. *Anal.* Calcd. for $C_{21}H_{20}N_2O_3 \cdot 1/2H_2O$: C, 70.57; H, 5.92; N, 7.84. Found: C, 70.34; H, 5.86; N, 7.94.

(3*S* 5*S*)-(−)-Methyl 15,16,17,18,19,20-Hexadehydro-17-methoxyyohimbane-5-carboxylate Hydrochloride (VIII)——A mixture of VII (0.26 g, 0.73 mmol) and 10% (w/v) of methanolic hydrogen chloride (50 ml) was refluxed for 2.5 hr. Evaporation gave VIII (0.28 g, 92.0%), which was recrystallized from methanol as colorless needles, mp 185°, $[\alpha]_D^{22}$ −149.5° (c=0.38, methanol), IR: 1750 cm^{-1}, MS *m/e*: 362 (M^+ of VIII). *Anal.* Calcd. for $C_{22}H_{23}ClN_2O_3 \cdot H_2O$: C, 63.53; H, 6.06; N, 6.74. Found: C, 63.53; H, 6.30; N, 6.64.

(1*S* 3*S*)-(−)-Methyl 1-(*m*-Methoxybenzyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylate Hydrochloride (Xa) and (1*R* 3*S*)-(+)-Methyl 1-(*m*-Methoxybenzyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylate Hydrochloride (Xb)——A mixture of L-tryptophan methyl ester hydrochloride[8] (IX, 2.5 g, 0.01 mol), V (3.0 g, 0.014 mol), 1 N aqueous hydrochloric acid (14 ml), methanol (44 ml), and water (30 ml) was refluxed for 20 hr. After the evaporation of methanol, 10% aqueous hydrochloric acid was added to the residue. The precipitates

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11) R.L. Autrey and P.W. Schullard, *Chem. Commun.*, **1966**, 841.

12) J.D.M. Asher, J.M. Robertson, G.A. Sim, M.F. Bartlett, R. Sklar, and W.I. Taylor, *Proc. Chem. Soc.*, **1962**, 72; M.F. Bartlett, B. Korzum, R. Sklar, A.F. Smith, and W.I. Taylor, *J. Org. Chem.*, **28**, 1445 (1963).

13) P. Karrer and P. Euslin, *Helv. Chim. Acta*, 32, 1390 (1949); R. Hamet, *Comp. Rend.*, **197**, 860 (1933).

14) "The Merck Index," ninth edition, 1976, p. 1256.

formed were collected by filtration and washed well with cold water and ethyl acetate. Colorless needles of Xa (0.2 g), mp 164° (dec.), $[\alpha]_D^{22}$ $-110°$ ($c=1$, methanol), IR: 1750 cm^{-1}, were obtained. The ethyl acetate washings were washed with water and saturated sodium chloride solution, then dried and evaporated, after which they were treated with methanolic hydrogen chloride to give colorless needles (0.3 g), mp 161° (dec.), $[\alpha]_D^{22}$ $-111.5°$ ($c=1$, methanol), IR: 1750 cm^{-1}. The IR spectrum and optical rotation were superimposable on those of Xa, prepared from VI. The total yield of Xa was 0.5 g (14%). For analysis a sample was recrystallized from a mixture of methanol and diethyl ether to afford colorless needles, mp 160—162° (dec.), $[\alpha]_D^{22}$ $-111°$ ($c=1$, methanol), MS *m/e*: 350 (M^+ of Xa). *Anal.* Calcd. for $C_{21}H_{23}ClN_2O_3 \cdot H_2O$: C, 62.29; H, 6.22; N, 6.92. Found: C, 62.39; H, 6.43; N, 7.11.

The aqueous filtrate and the water washings were evaporated to dryness and the crystalline residue was recrystallized from a mixture of ethyl acetate and diethyl ether to afford Xb (0.47 g, 13%) as colorless crystals, mp 194° (dec.), $[\alpha]_D^{21}$ $+22.1°$ ($c=1$, methanol), IR: 1750 cm^{-1}, MS *m/e*: 350. *Anal.* Calcd. for $C_{21}H_{23}ClN_2O_3 \cdot H_2O$: C, 62.29; H, 6.22; N, 6.92. Found: C, 62.49; H, 6.29; N, 6.74.

Preparation of VIII from Xa——Thirty seven percent formalin (1 ml) was added to a mixture of Xa (0.23 g, 0.57 mmol) in 50% aqueous methanol (20 ml) and the mixture was refluxed for 3 hr. Evaporation gave crude crystals, which were recrystallized from a mixture of methanol and diethyl ether to afford VIII (0.15 g, 65.0%) as colorless needles, mp 191°, $[\alpha]_D^{21}$ $-152.1°$ ($c=0.37$, methanol), IR: 1750 cm^{-1}, MS *m/e*: 362.

(1*S* 3*S*)-(−)-1-(*m*-Methoxybenzyl)-1,2,3,4-tetrahydro-*β*-carboline-3-carboxamide (XIIa) and (1*R* 3*S*)-(−)-1-(*m*-Methoxybenzyl)-1,2,3,4-tetrahydro-*β*-carboline-3-carboxamide (XIIb)——A mixture of XI[9] (113 g, 0.472 mol) and V (142 g, 0.658 mol) in 50% aqueous methanol (4 l) was gently refluxed under stirring for 23 hr. Concentration gave crude crystals, which were filtered and washed well with ethyl acetate to afford faint yellow crystals (78 g, 40%). Recrystallization from a mixture of methanol and diethyl ether furnished XIIa-HCl (63 g, 32.3%) as colorless needles, mp 205—206.5°, $[\alpha]_D^{17}$ $-137.8°$ ($c=1.39$, methanol), IR: 1690 cm^{-1}, MS *m/e*: 335 (M^+ of XIIa). *Anal.* Calcd. for $C_{20}H_{22}ClN_3O_2 \cdot H_2O$: C, 61.61; H, 6.20; N, 10.78. Found: C, 61.83; H, 6.48; N, 10.86. The IR spectrum and optical rotation were superimposable on those of XIIa-HCl, prepared from Xa. XIIa-HCl was converted to XIIa as usual. Recrystallization from acetonitrile afforded colorless rods, mp 222—225°, $[\alpha]_D^{26}$ $-200.7°$ ($c=1.98$, methanol), IR: 3430, 3300, 3120, 1655, 1607, 1580 cm^{-1}, MS *m/e*: 335, NMR: 3.36 (3H, singlet, OCH_3). *Anal.* Calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.50; H, 6.32; N, 12.58.

The aqueous layer was neutralized with sodium carbonate and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residual viscous oil was solidified with acetonitrile, then filtered to give faint brown crystals (45.3 g, 27%). Recrystallization from acetonitrile afforded XIIb (17 g, 10.4%) as colorless needles, mp 180—183°, $[\alpha]_D^{26}$ $-35.1°$ ($c=1.92$, methanol), IR: 3360, 3170, 1657, 1580 cm^{-1}, MS *m/e*: 335, NMR: 3.70 (3H, singlet, OCH_3). *Anal.* Calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.90; H, 6.15; N, 12.67.

(3*S* 5*S*)-(−)-15,16,17,18,19,20-Hexadehydro-17-methoxyyohimbane-5-carboxamide (XIIIa)——A mixture of XIIa-HCl (0.446 g, 1.2 mmol) and 37% formalin (5 ml) in water (50 ml) was stirred at 50—60° for 2 hr. The reaction mixture was allowed to stand at room temperature overnight, then neutralized with 10% aqueous sodium carbonate to give XIIIa (0.345 g, 84%) as faint yellow crystals, mp 240° (dec.). For analysis a sample was recrystallized from a mixture of ethanol and water as colorless leaflets, mp 243° (dec.), $[\alpha]_D^{19}$ $-267°$ ($c=1.19$, methanol), IR: 3450, 3300, 1690, 1615 cm^{-1}, MS *m/e*: 347 (M^+ of XIIIa). *Anal.* Calcd. for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.74; H, 5.79; N, 12.14.

(3*S* 5*S*)-(−)-15,16,17,18,19,20-Hexadehydro-17-methoxyyohimbane-5-carbonitrile (XIV)——Phosphorus oxychloride (1.84 g, 0.012 mol) was added to a stirred mixture of XIIIa (3.47 g, 0.01 mol) and dry pyridine (9.5 g, 0.1 mol) in N,N-dimethylformamide (150 ml) below 5°. The mixture was stirred at room temperature for 2.5 hr., diluted with chloroform (300 ml) under cooling and poured into ice-water, then it neutralized with 10% aqueous sodium carbonate. The separated chloroform layer was washed with water, dried, and evaporated. The residue was purified by silica gel column chromatography using a mixture of methylene chloride and benzene to give XIV (2.2 g, 70.3%) as faint brown crystals, mp 178—180°. Recrystallization from methylene chloride afforded colorless fine needles, mp 181—183°, $[\alpha]_D^{26}$ $-275°$ ($c=1.23$, methanol), IR: 2240 cm^{-1}, MS *m/e*: 329 (M^+ of XIV). *Anal.* Calcd. for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.54; H, 5.54; N, 12.73.

(3*S*)-(−)-15,16,17,18,19,20-Hexadehydro-17-methoxyyohimbane (XV)——(i) At 35°. Sodium borohydride (0.2 g, 5 mmol) was added to an ice-cold mixture of XIV (0.33 g, 1 mmol), pyridine (10 ml) and ethanol (20 ml) with stirring. The reaction mixture was stirred at 35° for 24 hr, then evaporated. The residue was diluted with saturated sodium chloride (15 ml) and extracted with benzene. The extract was dried and evaporated to give a faint brown oil, which was purified by silica gel column chromatography with methylene chloride. The fractional product was recrystallized from a mixture of benzene and *n*-hexane to afford XV (0.2 g, 66%) as colorless needles, mp 103°, $[\alpha]_D^{18}$ $-235°$ ($c=0.85$, methanol), MS *m/e*: 304 (M^+ of XV). *Anal.* Calcd. for $C_{20}H_{20}N_2O \cdot H_2O$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.68; H, 7.13; N, 8.62. Hydrochloride: colorless needles (recrystallized from a mixture of methanol and diethyl ether), mp 235° (dec.). *Anal.* Calcd. for $C_{20}H_{21}ClN_2O$: C, 70.46; H, 5.91; N, 8.22. Found: C, 70.72; H, 6.25; N, 8.12.

The starting material (XIV, 0.07 g, 20%) was recovered as colorless fine needles, mp 180°, $[\alpha]_D^{19}$ $-269°$ ($c=1$, methanol).

(ii) At 50°. Sodium borohydride (0.6 g, 0.015 mol) was added to an ice-cold mixture of XIV (0.99 g, 3 mmol), pyridine (30 ml) and ethanol (60 ml) with stirring. The mixture was stirred at 50° for 24 hr and treated as in (i) to furnish XV (0.75 g, 82.8%) as colorless needles, mp 100°, $[\alpha]_D^{20}$ $-237°$ ($c=1.2$, methanol).

(3*S*)-(−)-15,17,18,20-Tetradehydro-17-methoxyyohimbane (XVI)—Sodium (2.3 g, 0.1 mol) and *tert*-buthanol (9 ml) were alternately added in six portions at −20° over a period of 1 hr to a mixture of XV (1.12 g, 4 mmol) in liquid ammonia (300 ml). This mixture to which methanol (20 ml) was added was stirred at −20° for 1 hr. The whole was allowed to stand for several hours until all the ammonia was removed, then it was poured into ice-water to precipitate. Filtration afforded XVI (1.09 g, 85.3%) as a faint yellow solid, mp 180° (dec.). For analysis a sample was recrystallized from benzene as colorless crystals, mp 195° (decomp.), IR: 3300, 1650—1670 cm^{-1}, $[\alpha]_D^{25}$ $-251.6°$ ($c=0.636$, methanol), MS *m/e*: 306 (M$^+$ of XVI), NMR: 4.66 (1H, singlet, an olefin proton of 18 position). *Anal.* Calcd. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.64; H, 7.06; N, 9.01.

(3*S*)-(−)-15,20-Dehydroyohimbone (XVII)——2 N Aqueous hydrochloric acid (20 ml) was added to a mixture of XVI (1.0 g, 3.3 mmol) in methanol (50 ml). The mixture was heated under stirring for 5 min. Evaporation produced a crystalline residue, which was neutralized with 10% aqueous sodium carbonate and extracted with chloroform. The extract was washed with water, dried and evaporated to give crude crystals. Recrystallization from methanol afforded XVII (0.78 g, 80.6%) as colorless needles, mp 235°, $[\alpha]_D^{24}$ $-266°$ ($c=0.534$, methanol), IR: 3370, 1705, 1657 cm^{-1}, MS *m/e*: 292 (M$^+$ of XVII). *Anal.* Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 77.80; H, 6.89; N, 9.58.

(3*S*)-(+)-15,16-Dehydroyohimbone (XVIII)——A mixture of XVII (0.97 g, 3.3 mmol) in dry pyridine (50 ml) was refluxed for 2 hr and evaporated. The residue was purified by silica gel column chromatography with a mixture of chloroform and benzene producing faint yellow crystals. Recrystallization from methanol furnished XVIII (0.77 g, 80.0%) as colorless needles, mp 249—253°, $[\alpha]_D^{24}$ $+26.3°$ ($c=0.28$, pyridine), MS *m/e*: 292, NMR: 5.83 (1H, singlet, an olefin proton of 16 position). *Anal.* Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 77.84; H, 7.14; N, 9.66.

(3*S* 15*S* 20*R*)-(−)-Yohimbone (III) and (3*S* 15*S* 20*S*)-(−)-Alloyohimbone (XIX)——A mixture of XVIII (0.7 g, 2.4 mmol) in acetic acid (30 ml) was catalytically hydrogenated over 5% Pd-C under atmospheric pressure at room temperature for 4 hr. Filtration and evaporation gave a crystalline residue, which was dissolved in water and neutralized with 10% aqueous sodium carbonate, then extracted with chloroform. The extract was washed with water, dried and evaporated to afford a solid, which was purified by alumina column chromatography with a mixture of methylene chloride and benzene to give a mixture of III and XIX (0.56 g, 80.0%) as faint yellow crystals, mp 230—260°, $[\alpha]_D^{20}$ $-95.5°$ ($c=0.4$, pyridine), IR: 1704 cm^{-1}, MS *m/e*: 294 (M$^+$). These crystals were repeatedly recrystallized from methanol as XIX (0.03 g, 4.3%) in colorless prism form, mp 240—244° (lit.[10] mp 235.5—236°), $[\alpha]_D^{20}$ $-92.1°$ ($c=0.39$, pyridine) (lit.[10] $[\alpha]_D^{22}$ $-96.5\pm0.3°$ ($c=0.5$, pyridine)), IR: 3350, 2810, 2750, 1704 cm^{-1}, MS *m/e*: 294 (M$^+$). *Anal.* Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.68; H, 7.61; N, 9.62.

The filtrate was collected and cooled in ice-water giving faint yellow needles, mp 270—273°, which were repeatedly recrystallized from a mixture of methanol and chloroform to furnish III (0.12 g, 17.5%) as colorless needles, mp 302° (lit.[4] mp 305—306°), $[\alpha]_D^{21.5}$ $-108.8°$ ($c=0.34$, pyridine) (lit.[4] $[\alpha]_D^{18}$ $-106°$ ($c=2.585$, pyridine)), IR: 3340, 2791, 2740, 1704 cm^{-1}, MS *m/e*: 294 (M$^+$). *Anal.* Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.63; H, 7.55; N, 9.56.