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Stereochemical Studies. XLIX.[1] A Biogenetic-type Total Synthesis of Natural (+)-Maritidine from L-Tyrosine using highly Specific Asymmetric Cyclization[2]

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A first biogenetic-type asymmetric synthesis of natural (+)-maritidine from L-tyrosine is described. Phenolic oxidative coupling of monophenol (**10b**) with thallium(III) trifluoroacetate afforded the corresponding spiro dienone (**11b**) in 66.5% yield. Asymmetric cyclization of dienone (**14**) was found to occur highly selectively to give one diastereomer (**15**) preferentially. Removal of the carboxamide group in **15** was effected by reductive decyanization of the intermediate amino nitrile (**18**) by sodium in liquid ammonia to (+)-epimaritidine (**19**), which was epimerized to the objective (+)-maritidine by the known method.

Keywords——biogenetic-type synthesis; total synthesis; (+)-maritidine; alkaloid; asymmetric synthesis; oxidative coupling; thallium(III) trifluoroacetate; reductive decyanization

(+)-Maritidine (**1**) is a representative of the 5,10b-ethanophenanthridine class of Amaryllidaceae alkaloids.[4] Many radioactive tracer experiments have verified that alkaloids of this class are biosynthesized from L-tyrosine (**2**) *via* the intramolecular phenolic oxidative coupling of O-methylnorbelladine (**3**).[5] It is also important to note that these alkaloids are optically active. *In vivo*, the intermediate optically active enone (**5**) is considered to be synthesized asymmetrically from the achiral dienone (**4**).

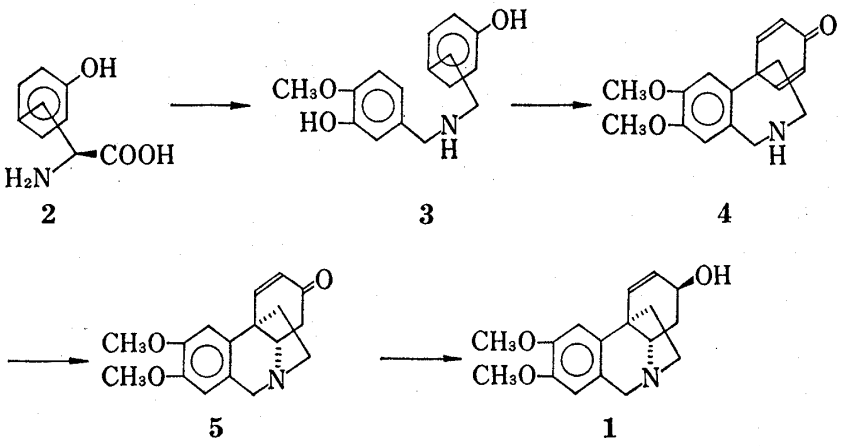
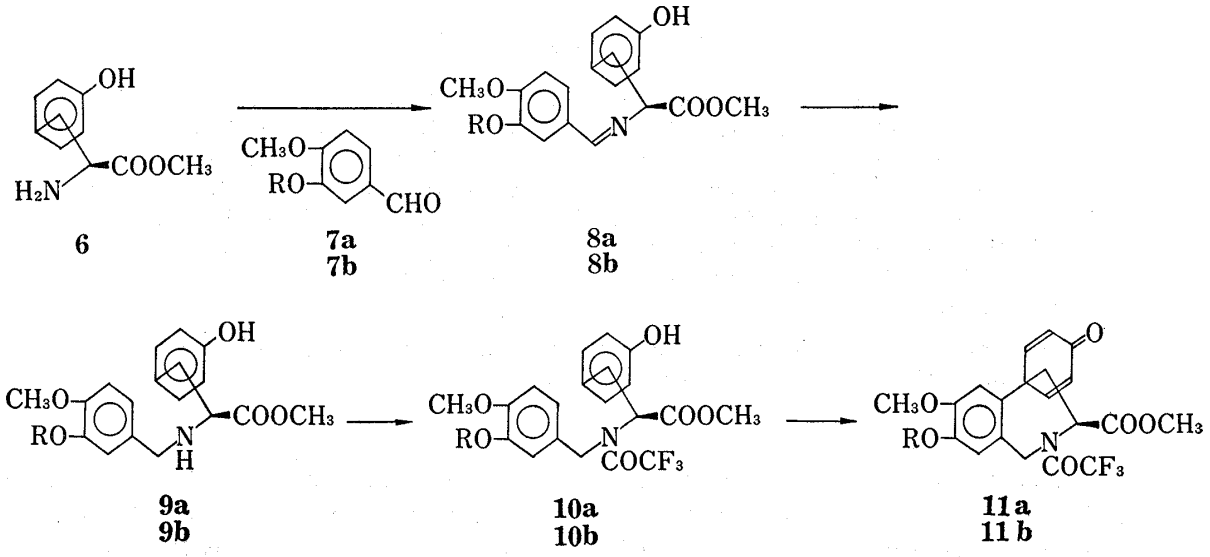


Chart 1

1) Part XLVIII: M. Ohzeki, T. Mizoguchi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **25**, 2676 (1977).
2) Preliminary communication: S. Yamada, K. Tomioka, and K. Koga, *Tetrahedron Lett.*, **1976**, 57.
3) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) *a*) F. Sandberg and K.H. Michel, *Lloydia*, **26**, 78 (1963); *b*) W.C. Wildman, "The Alkaloids," Vol. XI, ed. by R.H.F. Manske and H.L. Holmes, Academic Press, New York, 1968, p. 308; *c*) G.G. De Angelis and W.C. Wildman, *Tetrahedron Lett.*, **1969**, 729; *d*) C. Fuganti, "The Alkaloids," Vol. XV, ed. by R.H.F. Manske and H.L. Holmes, Academic Press, New York, 1975, p. 83.
5) *a*) W.C. Wildman, H.M. Fales, and A.R. Battersby, *J. Am. Chem. Soc.*, **84**, 681 (1962); *b*) D.H.R. Barton, G.W. Kirby, J.B. Taylor, and G.M. Thomas, *J. Chem. Soc.*, **1963**, 4545.

Although several biogenetic-type syntheses of this class of alkaloids have been performed in racemic forms,[6] no reports have yet appeared on the synthesis in optically active forms. We have already reported a new method for the biogenetic-type asymmetric synthesis of some isoquinoline- and indole-alkaloids from L-DOPA and L-tryptophan, respectively.[7] Application of this method to the synthesis of natural (+)-maritidine (**1**) from L-tyrosine (**2**) is a subject of the present paper. The key steps in this synthesis are phenolic oxidative coupling to prepare dienone (**11b**), asymmetric cyclization of dienone (**14**), and reductive decyanization of amino nitrile (**18**) as described below.



a: R=H **b**: R=CH_3

Chart 2

The Schiff base (**8a**), prepared from L-tyrosine methyl ester (**6**) and isovanillin (**7a**), was reduced with sodium borohydride in methanol to give the amine (**9a**). Treatment of **9a** with trifluoroacetic anhydride in pyridine afforded the *N*-trifluoroacetyl derivative (**10a**). The results of phenolic oxidative coupling of **10a** to the *para–para* coupled spiro dienone (**11a**) with various reagents are given in Table I. The best yield (14%) was obtained when **10a** was treated with ferric chloride–dimethylformamide complex.[6c,8] Reactions with ferric chloride, iron (III) acetylacetonate, potassium ferricyanide, or vanadium oxytrichloride[6a] afforded **11a** in yields of less than 10%. With manganese (III) acetylacetonate[9] or thallium (III) trifluoroacetate[10] (abbreviated as TTFA in the following), **10a** was converted to **11a** in about 12% yield. The spiro dienone (**11a**) thus obtained was methylated with methyl iodide and potassium *t*-butoxide to O,O-dimethyl derivative (**11b**) in 25% yield. **11b** was therefore obtained from **10a** in a yield of not more than 3.5%.

This unsatisfactory result led us to try another approach to **11b**. The *N*-trifluoroacetyl derivative (**10b**) was prepared from **6** and veratraldehyde (**7b**) by the same procedure as with

6) *a*) M.A. Schwartz and R.A. Holton, *J. Am. Chem. Soc.*, **92**, 1090 (1970); *b*) T. Kametani, T. Kohno, S. Shibuya, and K. Fukumoto, *Tetrahedron*, **27**, 5441 (1971); *c*) E. Kotani, N. Takeuchi, and S. Tobinaga, *Tetrahedron Lett.*, **1973**, 2735; *d*) *Idem.*, *Chem. Commun.*, **1973**, 550.

7) *a*) S. Yamada and H. Akimoto, *Tetrahedron Lett.*, **1969**, 3105; *b*) S. Yamada, M. Konda, and T. Shioiri, *ibid.*, **1972**, 2215; *c*) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 2614 (1974); *d*) M. Konda, T. Shioiri, and S. Yamada, *ibid.*, **23**, 1025 (1975); *e*) *Idem*, *ibid.*, **23**, 1063 (1975).

8) S. Tobinaga and E. Kotani, *J. Am. Chem. Soc.*, **94**, 309 (1972).

9) M.J.S. Dewar and T. Nakaya, *J. Am. Chem. Soc.*, **90**, 7134 (1968).

10) *a*) A. McKillop, B.P. Swann, and E.C. Taylor, *Tetrahedron*, **26**, 4031 (1970); *b*) M.A. Schwartz, B.F. Rose, and B. Vishnuvajjala, *J. Am. Chem. Soc.*, **95**, 612 (1973).

Table I. Phenolic Oxidative Coupling of **10a** to **11a**

Run	Reagent	Molar ratio (reagent/**10a**)	Solvent	Concn. (M)	Temp.	Time (hr)	Yield[a] (%)
1	$FeCl_3$-DMF	5	Ether/H_2O	2.5×10^{-2}	Reflux	9	14.1
2	$FeCl_3$	5	Ether/H_2O	2.5×10^{-2}	Reflux	9.5	6.6
3	$Fe(acac)_3$	2	CH_3CN	2.5×10^{-3}	Reflux	48	0
4	$K_3Fe(CN)_6$–$NaHCO_3$	3	$CHCl_3/H_2O$	1.25×10^{-2}	Reflux	2	4
5	$K_3Fe(CN)_6$–$NaHCO_3$	1.5	Ether/H_2O	1.25×10^{-2}	Reflux	3	1
6	$VOCl_3$	3.5	Ether	2.5×10^{-3}	Reflux	15	8.5
7	$Mn(acac)_3$	2	CH_3CN	2.5×10^{-3}	Reflux	24	12.2
8	$Tl(OCOCF_3)_3$	1.2	CH_2Cl_2	10^{-2}	25°	22	12.2

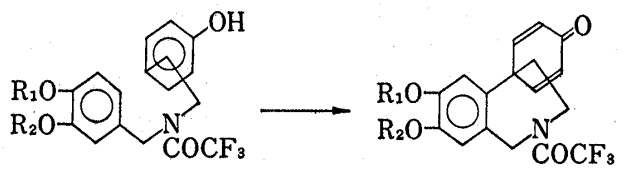
a) Isolated yield.

Table II. Phenolic Oxidative Coupling of **10b** to **11b** with TTFA[a]

Run	Molar ratio (TTFA/**10b**)	Solvent	Concn. (M)	Temp. (°C)	Time (hr)	Yield (%)
1[b]	1.2	CH_2Cl_2	10^{-2}	−78—25	24	trace
2	1.1	CH_2Cl_2	10^{-2}	−78—25	3	4.6
3	2	CH_2Cl_2–TFA(5:1)	10^{-2}	−23	1	19.1
4	2	CH_3CN	10^{-2}	−23—25	23	41.5
5	3	CH_3CN	10^{-2}	−23—25	16	43.1
6	3	CH_3CN	10^{-3}	−23—25	24	66.5

a) The solution of 1.1 mmoles of $Tl(OCOCF_3)_3$ (TTFA) in 1 ml of trifluoroacetic acid (TFA) was used.
b) Solid $Tl(OCOCF_3)_3$ was used.

10a. Phenolic oxidative coupling of **10b** using TTFA[10] as an oxidant under several conditions gave the results as shown in Table II. Treatment of **10b** with solid TTFA in methylene chloride afforded **11b** in trace yield. In a case where TTFA dissolved in trifluoroacetic acid was used in methylene chloride, **11b** was obtained in 4.6% yield. An increase in the ratio of trifluoroacetic acid to methylene chloride improved the yield of **11b**. Great improvement in the yield (up to 66.5%) was finally obtained when the oxidation with TTFA dissolved in trifluoroacetic acid was performed in acetonitrile. The utility of this reaction condition was also recognized in the oxidation of achiral monophenols (**12a** and **12b**) to the corresponding spiro dienones (**13a** and **13b**) in 42 and 22% yield, respectively.



12a **13a**
12b **13b**

a: $R_1=R_2=-CH_3$ **b**: R_1, $R_2=-CH_2-$

Chart 3

Amidation of **11b** with ammonia in methanol afforded the amide (**14**). Removal of trifluoroacetyl group from **14** with sodium hydroxide in aqueous methanol resulted in spontaneous Michael-type cyclization to give the enone (**15**) in 41% yield. The other diastereomer (**16**) was not obtained. This highly specific asymmetric cyclization of **14** to **15** can be explained as follows. There is a severe steric interaction between methylene group at C-6 and the amide group attached to C-12 in **16**, while such steric interaction does not exist in **15** as shown in Chart 4. The stereochemistry of **15** was confirmed by its conversion to natural (+)-maritidine.[11]

11) The absolute configuration of (+)-maritidine (**1**) has been determined by ORD study.[4c,6a]

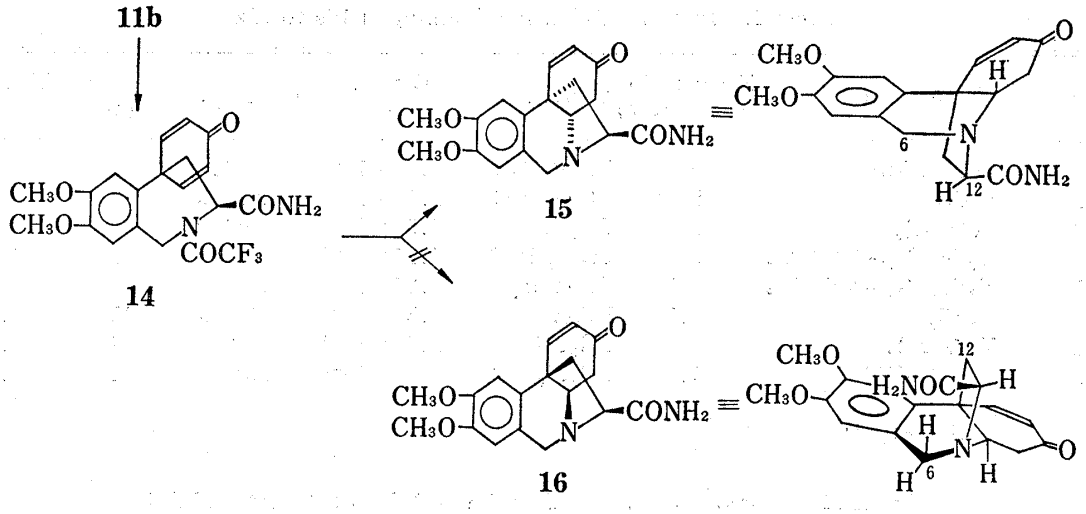


Chart 4

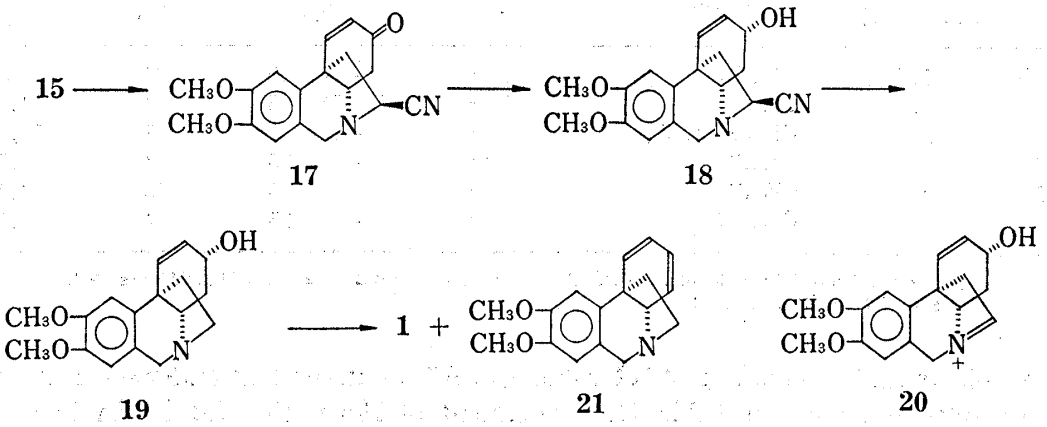


Chart 5

The next step is the removal of the amide group which became unnecessary after playing a key role in the asymmetric cyclization. Dehydration of **15** with phosphorus oxychloride in a mixture of pyridine and chloroform afforded the amino nitrile (**17**). Contrary to the previous results,[7] however, sodium borohydride reduction of **17** afforded the corresponding alcohol (**18**) as an only isolable product, and there was no evidence of the formation of the decyanized product. The alcohol (**18**) was also found to be recovered unchanged by treatment with sodium borohydride. The failure to get decyanized product in the present case seems to be due to the failure in forming the corresponding immonium salt (**20**).[12] To circumvent this problem, reductive decyanization of **18** by sodium metal in liquid ammonia was surveyed. It was found[13] that the reaction of **18** with sodium in liquid ammonia at −78° afforded (+)-epimaritidine (**19**) in optically pure state in 58% yield.[14] Epimerization[6a] at C-3 of **19** was accomplished by heating **19** in 10% hydrochloric acid for 1 hr to give, after preparative thin-layer chromatography (TLC), (+)-maritidine (**1**) in optically pure state in 17% yield,[14] accompanied with the dehydrated compound (**21**) in 5% yield. Melting point, optical rotation, and infrared (IR) spectrum of this synthetic (+)-maritidine agreed with those reported for the natural origin.[4a,b]

12) The amino nitrile (**17**) was recovered unchanged by the reaction with silver nitrate in ethanol, probably due to the effect known as Bredt's rule.

13) *a*) S. Yamada, K. Tomioka, and K. Koga, *Tetrahedron Lett.*, **1976**, 61; *b*) K. Tomioka, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **25**, 2689 (1977).

14) TLC behavior and NMR spectrum of this sample agreed with those of the corresponding racemic modification prepared by the reported method.[6a]

The first successful conversion of L-tyrosine to natural (+)-maritidine holds promise for the biogenetic-type asymmetric syntheses of various optically active Amaryllidaceae alkaloids from optically active hydroxy phenylalanine derivatives. The investigations along this line are now in progress.

Experimental[15]

L-(+)-*N*-(3′-Hydroxy-4′-methoxy)benzyltyrosine Methyl Ester (9a)——A solution of L-tyrosine methyl ester (**6**) (mp 134.5—135.5°, $[\alpha]_D^{20}$ +26.7° (c=1.97, MeOH); reported[16] mp 135—136°, $[\alpha]_D^{20}$ +25.97° (MeOH)) (13.7 g, 0.07 mol) and isovanillin (**7a**) (10.7 g, 0.07 mol) in MeOH (210 ml) was stirred in the presence of molecular sieve 4A (10 g) at room temperature for 5 hr. After filtration, MeOH (190 ml) was added to the filtrate. To this solution was added $NaBH_4$ (7.95 g, 0.21 mol) slowly under ice bath cooling, and the whole was stirred at 15° for 3 hr. Evaporation of the solvent gave a residue, which was mixed with AcOEt (600 ml) and water (140 ml). The resulting mixture was neutralized to pH 7—8 by addition of conc. HCl, the AcOEt layer was separated and the aq. layer was extracted twice with AcOEt (400 ml and 200 ml). The AcOEt extracts were combined and washed with satd. aq. NaCl, dried over $MgSO_4$ and evaporated *in vacuo* to dryness to give **9a** as a white solid (19.6 g, 84.5%). Recrystallization from MeOH–ether–hexane afforded colorless needles of mp 124.5—125.5°, $[\alpha]_D^{20}$ +3.89° (c=1.08, MeOH), IR ν_{max}^{KBr} cm^{-1}: 3260, 1737, 1615, 1590. *Anal.* Calcd. for $C_{18}H_{21}NO_5$: C, 65.25; H, 6.39; H, 4.23. Found: C, 65.16; H, 6.40; N, 4.22.

L-(−)-*N*-(3′-Hydroxy-4′-methoxy)benzyl-*N*-trifluoroacetyltyrosine Methyl Ester (10a)——Trifluoroacetic anhydride (12.7 ml, 90 mmol) was added to a solution of **9a** (6.60 g, 20 mmol) in pyridine (66 ml) at −30°. After stirring for 1 hr at −30° and for 2 hr at room temperature, water (66 ml) was added to the reaction mixture under ice bath cooling and the whole was stirred at room temperature for 30 min. AcOEt (250 ml) was added and the mixture was acidified with conc. HCl to pH 1. The AcOEt layer was separated and the aq. layer was extracted with AcOEt twice (100 and 50 ml). The combined extracts were washed successively with water, satd. aq. $NaHCO_3$, water, satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent gave a yellow glass (7.29 g), which was purified by silica gel column chromatography using hexane–ether (4: 1) to give **10a** as a slightly yellow glass (6.06 g, 71%) of $[\alpha]_D^{20}$ −75.6° (c=1.15, MeOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560, 3500, 1745, 1687, NMR ($CDCl_3$) δ: 3.21 (2H, d, J=7 Hz, $C\underline{H}_2$), 3.42 and 4.42 (each 1H, each d, J=16 Hz, $C_6H_5C\underline{H}_2N$), 3.62 (3H, s, $OC\underline{H}_3$), 3.82 (3H, s, $OC\underline{H}_3$), 5.98 (1H, broad s, O$\underline{H}$), 6.4—7.0 (4H, aromatic protons), 6.60 and 6.82 (each 2H, each d, J=13 Hz, aromatic protons). MS m/e: 427 (M^+). *Anal.* Calcd. for $C_{20}H_{20}F_3NO_6 \cdot H_2O$: C, 53.94; H, 4.98; N, 3.14. Found: C, 53.71; H, 4.61; N, 3.15.

(3*S*)-(+)-8-Hydroxy-7-methoxy-4′-oxo-2-trifluoroacetyl-1,2,3,4-tetrahydro-5H-benz[*c*]azepine-5-spiro-1′-cyclohexa-2′,5′-diene-3-carboxylic Acid Methyl Ester (11a)——a) Run 1 Using $FeCl_3$–DMF Complex[6c,8]: A mixture of **10a** (105 mg, 0.25 mmol) in ether (10 ml) and $FeCl_3$–DMF complex (1.35 g, 2.5 mmol) in water (27 ml) was stirred mechanically under reflux for 9 hr. After cool, ether (20 ml) was added to the reaction mixture. The ether layer was separated, washed with water, satd. aq. $NaHCO_3$, satd. aq. NaCl successively and dried over $MgSO_4$. Evaporation of the ether left a brown glass (85 mg), which was fractionated by silica gel preparative TLC using hexane–ether (1: 9) to afford starting material (**10a**) (4 mg, recovery yield 3.8%) and **11a** (15 mg, 14.1%) of $[\alpha]_D^{20}$ +146° (c=0.544, MeOH), UV λ_{max}^{MeOH} nm: 213, 236, 280, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3515, 1753, 1692, 1667, 1627, NMR ($CDCl_3$): 2.40 (1H, double d, J=4 and 16 Hz, $C\underline{H}_2$–CH), 2.83 (1H, double d, J=13 and 16 Hz, $C\underline{H}_2$–CH), 3.72 (3H, s, $OC\underline{H}_3$), 3.76 (3H, s, $OC\underline{H}_3$), 4.66 and 4.88 (2H, AB-quartet, J=18 Hz, $C\underline{H}_2N$), 5.60 (1H, double d, J=4 and 13 Hz, CH_2–C$\underline{H}$–), 6.04 (1H, broad s, O$\underline{H}$), 6.7—7.0 (6H, m, olefinic and aromatic protons), MS m/e 425 (M^+), 366, 328, High MS: molecular ion at m/e 425.1087, Calcd. 425.1031.

b) Run 6 with Vanadium Oxytrichloride: Vanadium oxytrichloride (605 mg, 3.5 mmol) was added to a solution of **10a** (210 mg, 0.5 mmol) in ether (200 ml) at −78° under N_2 atmosphere. The mixture was stirred for 3 hr at −78° and for 15 hr at reflux. After cool, the reaction mixture was washed with water, satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent gave a brown oil (400 mg), which was fractionated by silica gel preparative TLC using hexane–ether (2: 3) to give starting material (**10a**) (96 mg, recovery yield 45.7%) and **11a** (18 mg, 8.5%) as a yellow glass.

c) Run 7 with Manganese Trisacetylacetonate: A mixture of **10a** (107 mg, 0.25 mmol) and manganese trisacetylacetonate (352 mg, 1.0 mmol) in CH_3CN (100 ml) (bubbled with N_2 before use) was stirred under reflux for 24 hr. After evaporation of the solvent, ether (100 ml) was added to the residue. The ether layer

15) Melting points are not corrected. Optical rotations were taken with a Yanagimoto Photo Direct Reading Polarimeter, Model OR-50. Infrared (IR) spectra were taken with a Jasco Infrared Spectrometer Model DS-402G. Nuclear magnetic resonance (NMR) spectra were taken with a JNM-PS 100 Spectrometer at 100 MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Ultraviolet (UV) spectra were taken with a Hitachi UV Spectrometer Model 323. MS were taken with a JEOL-01 SG-2 Mass Spectrometer.

16) E. Fischer and B. Schrauth, *Ann.*, **354**, 34 (1907).

was washed successively with water, 10% aq. HCl, water, satd. aq. $NaHCO_3$, water, satd. aq. NaCl, and dried over $MgSO_4$. Evaporation of the solvent gave a yellow glass (79 mg), which was fractionated by silica gel preparative TLC using hexane–ether (1 : 2) to give starting material (**10a**) (22 mg, recovery yield 20.6%) and **11a** (13 mg, 12.2%).

L-(−)-*N*-(3′,4′-Dimethoxy)benzyltyrosine Methyl Ester (**9b**)——A mixture of **6** (19.5 g, 0.1 mol) and veratraldehyde (**7b**) (mp 44.5—45°, reported[17] mp 43—44.5°) (16.6 g, 0.1 mol) in MeOH (300 ml) in the presence of molecular sieve 4A (20 g) was stirred for 16 hr at room temperature. After filtration, MeOH (200 ml) was added to the filtrate. To this solution at −78°, $NaBH_4$ (7.57 g, 0.2 mol) was added and the whole was stirred at −78° for 1 hr and at room temperature for 2 hr. The reaction mixture was evaporated to dryness, AcOEt (500 ml) and water (200 ml) was added to the residue, and the whole was neutralized to pH 7.5 with conc. HCl at −10°. The AcOEt layer was separated and the aq. layer was extracted twice with AcOEt (500 ml each). The extracts were combined, washed with satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent afforded **9a** (31.5 g, 91.0%) as a yellow glass of $[\alpha]_D^{20}$ −1.98° (c=3.44, MeOH), IR ν_{max}^{film} cm^{-1}: 3400, 1740, NMR (CD_3OD) δ: 2.89 (2H, d, J=7 Hz, $C\underline{H}_2$), 3.60 (3H, s, $OC\underline{H}_3$), 3.75 (6H, s, two $OC\underline{H}_3$), 6.4—7.0 (7H, m, aromatic protons), MS m/e: 345 (M^+).

L-(−)-*N*-(3′,4′-Dimethoxy)benzyl-*N*-trifluoroacetyltyrosine Methyl Ester (**10b**)——Trifluoroacetic anhydride (33 ml, 0.24 mol) was added to a solution of **9b** (31.5 g, 0.09 mol) in pyridine (200 ml) at −30° during 10 min. After stirring at −30° for 1 hr and at room temperature for 16 hr, water (200 ml) was added to the reaction mixture at −10° and the whole was stirred at the same temperature for 30 min. AcOEt (1 l) was added and the mixture was acidified with conc. HCl. The AcOEt layer was separated, and the aq. layer was extracted three times with AcOEt (500 ml each). The extracts were combined and washed successively with water, satd. aq. $NaHCO_3$, water, satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent gave a brown glass (45.3 g), which was purified by silica gel column chromatography using hexane–ether (2: 3) to give **10b** (32.1 g, 80.8%) as a pale yellow glass of $[\alpha]_D^{20}$ −65.9° (c=1.06, MeOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560, 1747, 1688, NMR ($CDCl_3$) δ: 3.25 (2H, d, J=7 Hz, $C\underline{H}_2$–CH), 3.44 and 4.52 (2H, AB-quartet, J=16 Hz, $C\underline{H}_2$–N), 3.66 (3H, s, $OC\underline{H}_3$), 3.78 (3H, s, $OC\underline{H}_3$), 3.83 (3H, s, two $OC\underline{H}_3$), 6.64 and 6.86 (4H, AB-quartet, J=16 Hz, aromatic protons), MS m/e: 441 (M^+), 344, 151.

(3*S*)-(+)-7,8-Dimethoxy-4′-oxo-2-trifluoroacetyl-1,2,3,4-tetrahydro-5H-benz[*c*]azepine-5-spiro-1′-cyclohexa-2′,5′-diene-3-carboxylic Acid Methyl Ester (**11b**)——a) O-Methylation of **11a**: Potassium *t*-butoxide (25 mg, 0.22 mmol) was added to a solution of **11a** (85 mg, 0.2 mmol) in DMF (2 ml) at −23° under N_2 atmosphere. After the mixture was stirred for 7 min at −23°, a solution of MeI (56 mg, 0.4 mmol) in dimethyl formamide (DMF) (1 ml) was added at the same temperature, and the resulting solution was stirred for 3 hr at room temperature. Ether (20 ml) was added and the whole was washed successively with 10% aq. HCl, water, satd. aq. $NaHCO_3$, water, and satd. aq. NaCl. Drying over $MgSO_4$ followed by evaporation of the solvent afforded a pale yellow oil (42 mg). Trituration in ether–hexane afforded **11b** (22 mg, 25%) as pale yellow needles of mp 176.5—177.5°, $[\alpha]_D^{20}$ +216° (c=0.317, MeOH). This sample was shown to be identical to that obtained in b) below.

b) Run 6 in CH_3CN: A solution of TTFA in trifluoroacetic acid (0.7 ml, 0.75 mmol for TTFA) was added to a solution of **10b** (110 mg, 0.25 mmol) in CH_3CN (250 ml) at −23° under N_2 atmosphere. Shielding from light, the mixture was stirred at −23° for 3 hr and at room temperature for 21 hr. The mixture was diluted with ether (200 ml) and the whole was basified with satd. aq. $NaHCO_3$. The ether layer was separated and the aq. layer was extracted twice with ether (100 and 50 ml). The ether extracts were combined and washed with water, satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent gave a pale brown glass (121 mg), which was purified by silica gel column chromatography using ether–hexane (3: 1) to give **11b** (73 mg, 66.5%) as a colorless glass. Recrystallization from ether–hexane afforded colorless needles of mp 175.5—176.5°, $[\alpha]_D^{20}$ +213° (c=1.07, MeOH), UV λ_{max}^{MeOH} nm (log ε): 213 (4.66), 238 (4.33), 280 (3.27), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1695, 1665, 1625, NMR ($CDCl_3$) δ: 2.38 (1H, double d, J=5 and 15 Hz, $C\underline{H}_2$–CH), 2.84 (1H, double d, J=13 and 15 Hz, $C\underline{H}_2$–CH), 3.69 (3H, s, $OC\underline{H}_3$), 3.75 (3H, s, $OC\underline{H}_3$), 3.84 (3H, s, $OC\underline{H}_3$), 4.69 and 4.93 (2H, AB-quartet, J=17 Hz, N–$C\underline{H}_2$), 5.06 (1H, double d, J=5 and 13 Hz, C$\underline{H}$), 6.0—7.0 (6H, m, aromatic protons), High MS: molecular ion at m/e 439.1242, Calcd. 439.1224. *Anal.* Calcd. for $C_{21}H_{20}F_3NO_6$: C, 57.41; H, 4.59; N, 3.19. Found: C, 57.44; H, 4.67; N, 3.37.

c) Run 3 in a Mixture of CH_2Cl_2–Trifluoroacetic Acid (5: 1): A solution of TTFA in trifluoroacetic acid (5.70 ml, 6.30 mmol for TTFA) was added to a solution of **10b** (1.39 g, 3.15 mmol) in CH_2Cl_2 (300 ml) and trifluoroacetic acid (60 ml) at −23° under N_2 atmosphere. After stirring at the same temperature for 1 hr, the reaction mixture was basified with satd. aq. $NaHCO_3$, and the whole was extracted with CH_2Cl_2 (100 ml). The extract was washed successively with water, satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent left a brown caramel (1.07 g), which was fractionated by silica gel column chromatography using hexane–ether (1: 3) to give **11b** (264 mg, 19.1%) as a pale yellow glass. Recrystallization from ether–hexane afforded colorless needles of mp 175.5—76.5°. This sample was found to be identical with that obtained in b) above.

17) J.S. Buck, "Organic Syntheses," Coll. Vol. 2, p. 619.

4-Hydroxy-*N*-(3′,4′-dimethoxy)benzyl-*N*-trifluoroacetylphenethylamine (12a)——This compound was prepared from tyramine and **7b** by the procedure analogous to the preparation of **10b** as pale yellow needles of mp 129.5—130.5°, IR ν_{max}^{KBr} cm^{-1}: 3380, 2820, 1685, 1614, 1595. *Anal.* Calcd. for $C_{19}H_{20}F_3NO_4$: C, 59.53; H, 5.26; N, 3.65. Found: C, 59.68; H, 5.40; N, 3.38.

4-Hydroxy-*N*-(3′,4′-methylenedioxy)benzyl-*N*-trifluoroacetylphenethylamine (12b) ——This compound was prepared from tyramine and piperonal by the procedure analogous to the preparation of **10b** as crystals of mp 117—118°, IR ν_{max}^{KBr} cm^{-1}: 3350, 2770, 1670, 1615, 1598.

7′,8′-Dimethoxy-4′-oxo-2′-trifluoroacetyl-1,2,3,4-tetrahydro-5H-benz[*c*]azepine-5-spiro-1′-cyclohexa-2′,5′-diene (13a)——To a solution of **12a** (380 mg, 1 mmol) in CH_3CN (100 ml) was added TTFA in trifluoroacetic acid (2 ml, 2.2 mmol for TTFA) at −23° under N_2 atmosphere. The mixture was stirred at −23° for 2 hr and at room temperature for 14 hr. After neutralization with satd. aq. $NaHCO_3$, the mixture was extracted three times with ether (100, 60 and 20 ml). The combined extracts were washed with water, satd. aq. NaCl, dried over $MgSO_4$ and evaporated to dryness to give a brown oil, which was purified by silica gel preparative TLC using ether–$CHCl_3$ (1: 9) to **13a** (160 mg, 42%) as a pale yellow solid. Recrystallization from ether–hexane afforded colorless needles of mp 152—154° (reported[6d] mp 159—160°), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685, 1665, 1620, NMR ($CDCl_3$) δ: 2.40 (2H, t, J=6 Hz, C<u>H</u>$_2$–CH_2), 3.73 (3H, s, OC<u>H</u>$_3$), 3.90 (3H, s, OC<u>H</u>$_3$), 4.82 (2H, s, C<u>H</u>$_2$–N), 6.40 (2H, d, J=10 Hz, =C<u>H</u>–CO–C<u>H</u>=), 6.65 (1H, s, aromatic proton), 6.8—6.95 (1H, aromatic proton), 7.07 (1H, d, J=10 Hz, C<u>H</u>=CH–CO), 7.18 (1H, d, J=10 Hz, C<u>H</u>=CH–CO).

7′,8′-Methylenedioxy-4′-oxo-2′-trifluoroacetyl-1,2,3,4-tetrahydro-5H-benz[*c*]azepine-5-spiro-1′-cyclohexa-2′,5′-diene (13b)——To a solution of **12b** (367 mg, 1 mmol) in CH_3CN (100 ml) was added TTFA in trifluoroacetic acid (2.7 ml, 3 mmol for TTFA) at −23° under N_2 atmosphere. The reaction mixture was stirred at −23° for 2 hr and at room temperature for 22 hr. Ether (200 ml) and satd. aq. $NaHCO_3$ (30 ml) was added to the reaction mixture and the organic layer was separated. The aq. layer was extracted twice with ether (100 and 50 ml). The extracts were combined, washed successively with water, 10% aq. HCl, water, satd. aq. $NaHCO_3$, water, satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent left a brown glass, which was fractionated by silica gel preparative TLC using MeOH–$CHCl_3$ (1: 99) to give **13b** (80 mg, 22%) as pale yellow solid. Recrystallization from aq. MeOH gave colorless powder-like crystals of mp 133—135° (reported[10b] mp 138—142°), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690, 1668, 1628.

(3*S*)-(+)-7,8-Dimethoxy-4′-oxo-2′-trifluoroacetyl-1,2,3,4-tetrahydro-5H-benz[*c*]azepine-5-spiro-1′-cyclohexa-2′,5′-diene-3-carboxamide (14)——An ice-cooled solution of **11b** (440 mg, 1 mmol) in MeOH (40 ml) was saturated with NH_3 gas, the whole was allowed to stand under ice-bath cooling for 6 hr, and then evaporated to dryness. The residue was purified by silica gel column chromatography using MeOH–AcOEt (1: 99) to give **14** (333 mg, 78.5%) as a pale brown glass. Crystallization from AcOEt–hexane afforded colorless fine needles of mp 226—229° (dec.), $[\alpha]_D^{20}$ +198° (c=0.420, MeOH), IR ν_{max}^{Nujol} cm^{-1}: 1695, 1685, 1665, NMR (CD_3OD–$CDCl_3$) δ: 2.19 (1H, double d, J=14 and 4 Hz, C<u>H</u>$_2$–CH), 3.06 (1H, double d, J=14 and 13 Hz, C<u>H</u>$_2$–CH), 3.73 (3H, s, OC<u>H</u>$_3$), 3.86 (3H, s, OC<u>H</u>$_3$), 4.68 and 5.17 (2H, AB-quartet, C<u>H</u>$_2$–N), 4.96 (1H, double d, J=13 and 4 Hz, CH_2–C<u>H</u>). MS m/e: 424 (M^+). *Anal.* Calcd. for $C_{20}H_{19}F_3N_2O_5 \cdot 1/2H_2O$: C, 55.43; H, 4.65; N, 6.46. Found: C, 55.31; H, 4.59; N, 6.47.

(4a*S*,10b*R*,12*S*)-(+)-8,9-Dimethoxy-3-oxo-3,4,4a,5,6,10b-hexahydro-5,10b-ethanophenanthridine-12-carboxamide (15)——To an ice-cooled solution of **14** (127 mg, 0.3 mmol) in MeOH (12 ml) was added a solution of 2 N NaOH (0.3 ml, 0.6 mmol). The resulting solution was stirred for 2.5 hr at room temperature. After addition of excess NH_4Cl and water (10 ml) to the reaction mixture, the whole was condensed to a half volume and extracted three times with $CHCl_3$ (60, 40 and 20 ml). The combined extracts were washed with satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent afforded a pale yellow glass (136 mg), which was fractionated by silica gel column chromatography using MeOH–AcOEt (3: 97) to give **15** (40 mg, 40.5%) as a colorless glass. Recrystallization from benzene–hexane afforded colorless needles of mp 114—115°, $[\alpha]_D^{20}$ +98.6° (c=0.720, MeOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680, 1610, NMR ($CDCl_3$) δ: 3.81 (3H, s, OC<u>H</u>$_3$), 3.89 (3H, s, OC<u>H</u>$_3$), 4.44 (1H, d, J=17 Hz, N–C<u>H</u>$_2$-arom.), 6.07 (1H, d, J=10 Hz, C<u>H</u>=CH–CO), 6.34 (1H, CON<u>H</u>$_2$), 6.52 (1H, s, aromatic proton at C-7), 6.91 (1H, s, aromatic proton at C-10), 7.42 (1H, CON<u>H</u>$_2$), 7.59 (1H, d, J=10 Hz, =C<u>H</u>–CO). High MS: molecular ion at m/e 328.1436. Calcd. 328.1423. *Anal.* Calcd. for $C_{18}H_{20}N_2O_4 \cdot 1/6C_6H_6$: C, 66.86; H, 6.16; N, 7.04. Found: C, 66.64; H, 6.24; N, 7.30.

(4a*S*,10b*R*,12*S*)-(+)-8,9-Dimethoxy-3-oxo-3,4,4a,5,6,10b-hexahydro-5,10b-ethanophenanthridine-12-carbonitrile (17)——To a solution of **15** (1.07 g, 3.26 mmol) in a mixture of $CHCl_3$ (30 ml) and pyridine (3 ml) was added $POCl_3$ (0.45 ml, 4.9 mmol) at −23°. The mixture was stirred for 15 min at −23° and for 20 min under reflux. After cool, $CHCl_3$ (200 ml) was added and the whole was washed successively with satd. aq. $NaHCO_3$, water satd. aq. $CuSO_4$, water, satd. aq. $NaHCO_3$, satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography using MeOH–AcOEt (1: 9) to give **17** (0.63 g, 62%) as a colorless viscous oil of $[\alpha]_D^{20}$ +45.0° (c=1.05 MeOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2230, 1680, 1610, NMR ($CDCl_3$) δ: 2.4—3.0 (4H, m, two C<u>H</u>$_2$), 3.82 (3H, s, OC<u>H</u>$_3$), 3.88 (3H, s, OC<u>H</u>$_3$), 4.45 (1H, d, J=17 Hz, N–C<u>H</u>$_2$), 6.16 (1H, d, J=10 Hz, =C<u>H</u>–CO), 6.52 (1H, s, aromatic proton at C-7), 6.88 (1H, s, aromatic proton at C-10), 7.56 (1H, d, J=10 Hz, C<u>H</u>=CH–CO), MS m/e: 310 (M^+).

(3*R*,4a*S*,10b*R*,12*S*)-(+)-8,9-Dimethoxy-3-hydroxy-3,4,4a,5,6,10b-hexahydro-5,10b-ethanophenanthridine-12-carbonitrile (18)——$NaBH_4$ (85 mg, 2.24 mmol) was added to a solution of **17** (0.58 g, 1.87 mmol) in MeOH

(20 ml) at −23°. After stirring for 1 hr at the same temperature, satd. aq. NaCl (40 ml) was added. The reaction mixture was extracted three times with $CHCl_3$ (200, 100 and 50 ml). The extracts were combined, washed with satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent afforded a pale yellow viscous oil, which was purified by silica gel column chromatography using MeOH–AcOEt (1: 99) to **18** (389 mg, 66.7%) as a colorless glass of $[\alpha]_D^{20}$ +27.4° (c=1.03, MeOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570, 2860, 2240, 1612, 1511, 1035, NMR ($CDCl_3$) δ: 1.8—2.8 (4H, m, two C<u>H</u>$_2$), 3.2—3.6 (2H, C<u>H</u>–N and O<u>H</u>), 3.78 (3H, s, OCH_3), 3.83 and 4.42 (2H, AB-quartet, J=17 Hz, N–C<u>H</u>$_2$-arom.), 3.84 (3H, s, OC<u>H</u>$_3$), *ca.* 4.4 (1H, m, C<u>H</u>–OH), 5.86 (1H, d, J= 10 Hz, C<u>H</u>–CO), 6.37 (1H, double d, J=10 and 2 Hz, C<u>H</u>=CH–CO), 6.46 (1H, s, aromatic proton at C-7), 6.76 (1H, s, aromatic proton at C-10), MS *m/e*: 312 (M^+).

(+)-Epimaritidine (19)——A solution of **18** (300 mg, 0.96 mmol) in THF (10 ml) was added to a deep blue-colored solution of Na (330 mg, 14.4 mg atom) in liquid ammonia (20 ml) at −78° under N_2 atmosphere. The mixture was stirred for 15 min at the same temperature, and then excess NH_4Cl was added to decolorize. After the addition of $CHCl_3$ (20 ml) and satd. aq. $NaHCO_3$ (10 ml), NH_3 was allowed to evaporate at room temperature. The resulting mixture was extracted three times with $CHCl_3$ (100, 100 and 50 ml). The extracts were combined, washed with satd. aq. NaCl, and dried over $MgSO_4$. Evaporation of the solvent afforded a pale brown viscous oil, which was purified by alumina column chromatography using MeOH–$CHCl_3$ (2: 98) to **19** (160 mg, 58%) as colorless needles.[14] Recrystallization from EtOH-hexane afforded colorless needles of mp 235.5—236.5°, $[\alpha]_D^{20}$ +136° (c=0.210, MeOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2540, 1610, 1510, 1467, 1405, 1330, 1315, 1257, 1135, 1030, NMR ($CDCl_3$): 3.79 (3H, s, OC<u>H</u>$_3$), 3.85 (3H, s, OC<u>H</u>$_3$), *ca.* 4.4 (1H, m, C<u>H</u>–OH), 4.40 (1H, d, J=17 Hz, N–C<u>H</u>$_2$–arom.), 5.76 (1H, d, J=10 Hz, C<u>H</u>–CO), 6.43 (1H, double d, J=10 and 2 Hz, C<u>H</u>=CH–CO), 6.47 (1H, s, aromatic proton at C-7), 6.75 (1H, s, aromatic proton at C-10). High MS: molecular ion at *m/e* 287.1511. Calcd. 287.1521. *Anal.* Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.77; H, 7.46; N, 4.90.

(+)-Maritidine (1)——Epimerization at C-3 of **19** was performed as follows according to the reported method.[6a] A solution of **19** (121 mg, 0.42 mmol) in 10% aq. HCl (42 ml) was stirred under reflux for 1 hr. After cool, the reaction mixture was made alkaline with conc. NH_4OH, and then extracted three times with $CHCl_3$ (150, 100 and 50 ml). The combined extracts were washed with satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent afforded a pale yellow viscous oil, which was fractionated by alumina preparative TLC using MeOH–$CHCl_3$ (1.5: 98.5) to give the dehydrated compound (**21**) (6 mg, 5.3%) as a semi-solid of IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1610, 1510, 1466, 1325, 1255, NMR ($CDCl_3$) δ: 2.0—2.3 (2H, m, C<u>H</u>$_2$–C<u>H</u>$_2$–N), 2.6—3.4 (3H, m, C<u>H</u>–N and C<u>H</u>$_2$–C<u>H</u>$_2$–N), 3.80 (3H, s, OC<u>H</u>$_3$), 3.88 (3H, s, OC<u>H</u>$_3$), 4.44 (1H, d, J=17 Hz, N–C<u>H</u>$_2$–arom.), 5.6—6.1 (3H, m, olefinic protons), 6.50 (1H, s, aromatic proton at C-7), 6.6—6.8 (1H, m, olefinic proton), 6.91 (1H, s, aromatic proton at C-10), starting material (**19**) (35 mg, 29%) as a colorless solid, and (+)-maritidine (**1**) (21 mg, 17%) as a colorless solid. Recrystallization of **1** thus obtained from EtOH–hexane afforded colorless small prisms[14] of mp 253—256° (reported mp 253—255°,[4a] mp 263—265°[4b]), $[\alpha]_D^{20}$ +25.1° (c=0.216, MeOH) (reported[4b] $[\alpha]_D^{20}$ +26° (MeOH)), IR ν_{max}^{KBr} cm^{-1}: 3380, 3100, 1607, 1510, 1467, 1460, 1445, 1400, 1330, 1317, 1260, 1240, 1223, 1140, 1047, 1033, 1005, 875, 852, 813, 767, 738, 730 (these values agree well with those reported[4a]), NMR (DMSO-d_6) δ: 3.67 and 4.24 (2H, AB-quartet, J=17 Hz, N–C<u>H</u>$_2$–arom.), 3.67 (3H, s, OC<u>H</u>$_3$), 3.72 (3H, s, OC<u>H</u>$_3$), *ca.* 4.6 (1H, m, C<u>H</u>–OH), 5.75 (1H, double d, J=10 and 2 Hz, C<u>H</u>–CHOH), 6.56 (1H, s, aromatic proton at C-7), 6.62 (1H, d, J=10 Hz, C<u>H</u>=CH–CHOH), 6.88 (1H, s, aromatic proton at C-10), High MS: molecular ion at *m/e* 287.1500. Calcd. 287.1521. *Anal.* Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.61; H, 7.44; N, 4.90.