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Quinolizidines. XI.[1] Structure Determination of the *Alangium* Alkaloid Desmethylpsychotrine through Synthetic Incorporation of Ethyl Cincholoiponate into (+)-9-Demethylpsychotrine

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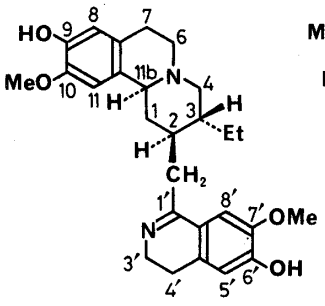
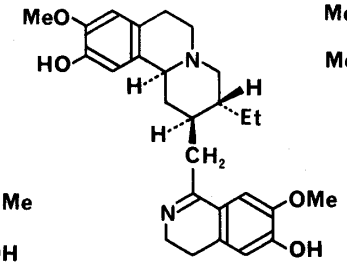
With a view to establishing the structure of the *Alangium* alkaloid desmethylpsychotrine, (+)-9-demethylpsychotrine [(+)-**1**] has been synthesized from ethyl cincholoiponate [(+)-**6**] and 3-benzyloxy-4-methoxyphenacyl bromide by the "cincholoipon-incorporating method" through the intermediates (+)-**7**, **8**, **10**—(+)-**14**, and (+)-**17**—(+)-**22**. The identity of synthetic (+)-**1** with natural desmethylpsychotrine unequivocally established the structure of this alkaloid.

Keywords——*Alangium* alkaloid desmethylpsychotrine; cincholoipon ethyl ester; mercuric acetate–edetic acid oxidation; regioselective lactam formation; thermal *cis–trans* isomerization; sodium borohydride reduction; catalytic hydrogenolysis; diethyl phosphorocyanidate amide formation; Bischler–Napieralski cyclization; (+)-9-demethylpsychotrine CD spectrum

The Indian medicinal plant *Alangium lamarckii* THWAITES (family Alangiaceae) is a rich source of a number of benzoquinolizidine alkaloids.[2] In 1967, Pakrashi and Ali[3] reported the isolation of desmethylpsychotrine, a new phenolic benzoquinolizidine alkaloid, from the root bark of this plant. They proposed two possible alternative structures (**1** and **2**) for the new base on the basis of mass spectral evidence and the chemical findings that it gave, on treatment with diazomethane, *O*-methylpsychotrine (**4**) *via* psychotrine (**3**), besides a third component presumed to be another monomethylated desmethylpsychotrine, and that desmethylpsychotrine was artificially obtainable from **3** by acid hydrolysis. Later on, we synthesized both of the alternative structures, (±)-9-demethylpsychotrine [(±)-**1**] and (±)-10-demethylpsychotrine [(±)-**2**], in racemic form through a "lactim ether route,"[1,4] and found that spectral



1



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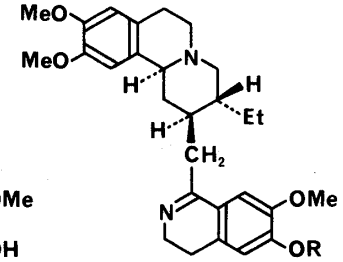
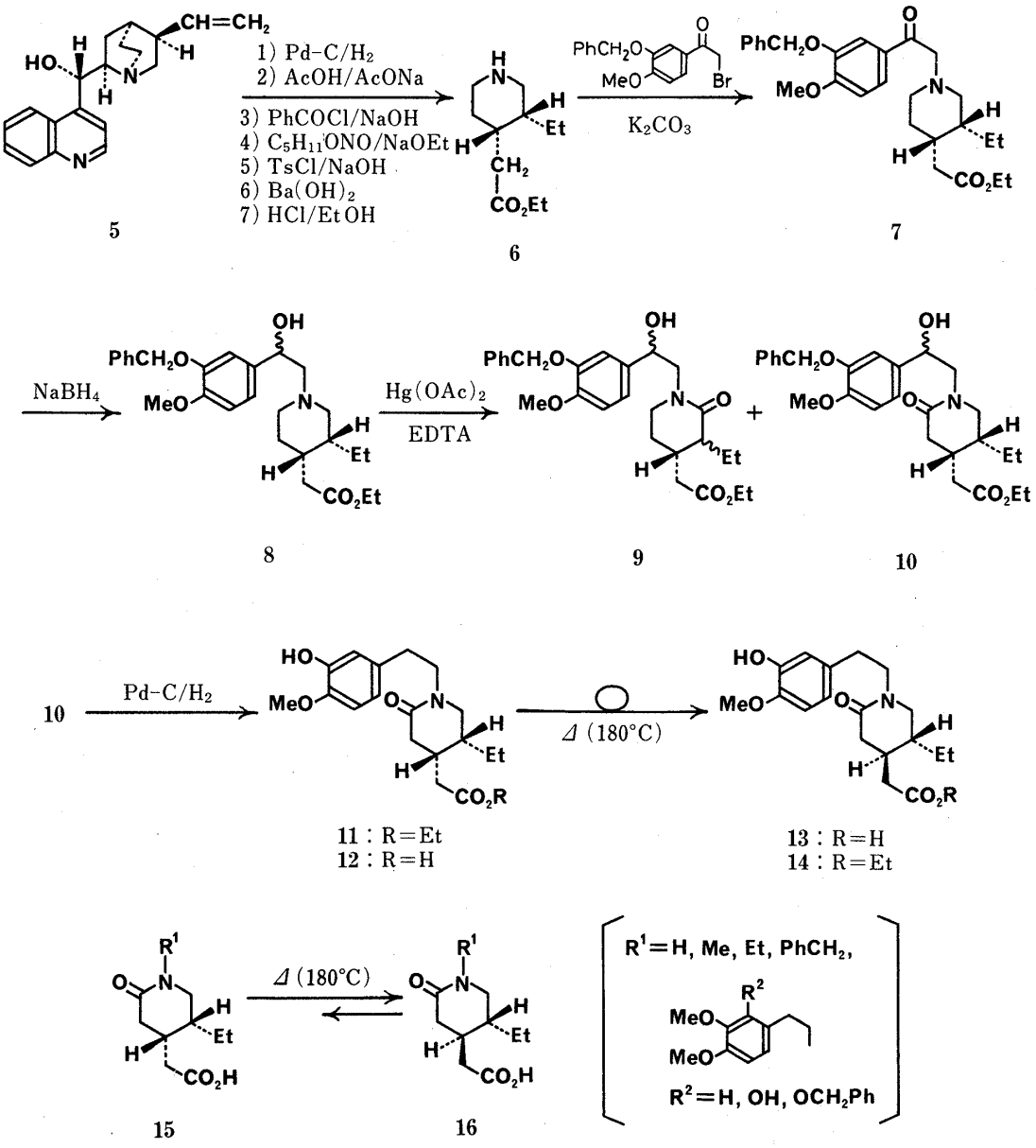


3: R=H
4: R=Me

comparison of (±)-**1** and (±)-**2** with natural (+)-desmethylpsychotrine suggested formula **1** to be the most likely structure of this alkaloid.[1,4] However, the identity of (±)-**1** with natural desmethylpsychotrine could not be rigorously established because only insufficient natural alkaloid was obtained for solution infrared (IR) and/or nuclear magnetic resonance (NMR)

spectra. The frequent difficulty of comparing an enantiomer with a racemic modification in the solid state by means of IR spectroscopy is well known,[5] and this led us to synthesize the chiral target molecule **1** (absolute configuration shown[6]) for direct and unambiguous comparison with desmethylpsychotrine. A brief account of the synthetic work described below has been published in a preliminary form.[7]

Of the various routes conceivable for synthesis of the chiral target **1**, the one we selected was a "cincholoipon-incorporating route," which had been shown to work satisfactorily in our chiral syntheses of analogous *Alangium* alkaloids such as emetine,[8] ankorine,[9] alangicine,[10] alangimarckine,[11] demethylcephaeline,[12,13] 9-demethylprotoemetinol,[14] and 10-demethylprotoemetinol.[12,14] Thus, treatment of cincholoipon ethyl ester [(+)-**6**],[15] prepared from commercially available cinchonine (**5**)[16] in 50% overall yield according to the classical degradation procedure,[15a,17] with 3-benzyloxy-4-methoxyphenacyl bromide[18] and K_2CO_3 in benzene gave the amino ketone (+)-**7** in 71% yield. Reduction of (+)-**7** with $NaBH_4$ in EtOH afforded a diastereomeric mixture of the amino alcohol **8** in 94% yield. The mercuric acetate–



5 6 7

8 9 10

11 : R=Et
12 : R=H

13 : R=H
14 : R=Et

15 16

Chart 1

ethylenediaminetetraacetic acid (EDTA) oxidation of the mixture **8** in boiling aqueous AcOH followed by column chromatography produced the 6-piperidone **10** as a diastereomeric mixture (55% yield) together with an oily substance (20% yield) presumed[8,9] to be a diastereomeric mixture of the *cis*- and the *trans*-2-piperidones **9**. The two piperidone structures were assigned by analogy with the similar oxidation products of structurally related systems[8,9] and simpler 3-alkylpiperidine derivatives,[19] and the correctness of the 6-piperidone structure **10** was substantiated by the following self-consistent reaction sequence.

On catalytic hydrogenolysis with hydrogen activated on Pd–C catalyst in EtOH in the presence of a little 70% perchloric acid, the diastereomeric mixture **10** furnished the lactam phenol (−)-**11** in 97% yield. Hydrolysis of (−)-**11** to give the lactam acid (−)-**12** was effected in 97% yield in EtOH containing 2 N aqueous NaOH at room temperature. Conversion of the *cis*-lactam acid (−)-**12** into the *trans* isomer was a crucial step in the present synthetic scheme. We have already found that *cis–trans* isomerization of structurally parallel systems **15**→**16** is possible under thermal (180 °C),[8,9,12,20] acidic (boiling aqueous HCl),[8,20] and alkaline (boiling 2.5 N aqueous KOH–EtOH)[21] conditions, among which the thermal conditions would be the first choice since they bring about fast isomerization with a good possibility of keeping other functional groups intact. Such thermal isomerization has also been found to proceed through *cis–trans* equilibration (**15** : **16** = 1 : 2),[8,9,20,22] presumably by a mechanism of intramolecular acidolysis of the lactam bond with the exocyclic carboxyl group.[20] The *cis*-lactam acid (−)-**12** was thus heated neat at 180 °C for 90 min to give a mixture of the *trans*

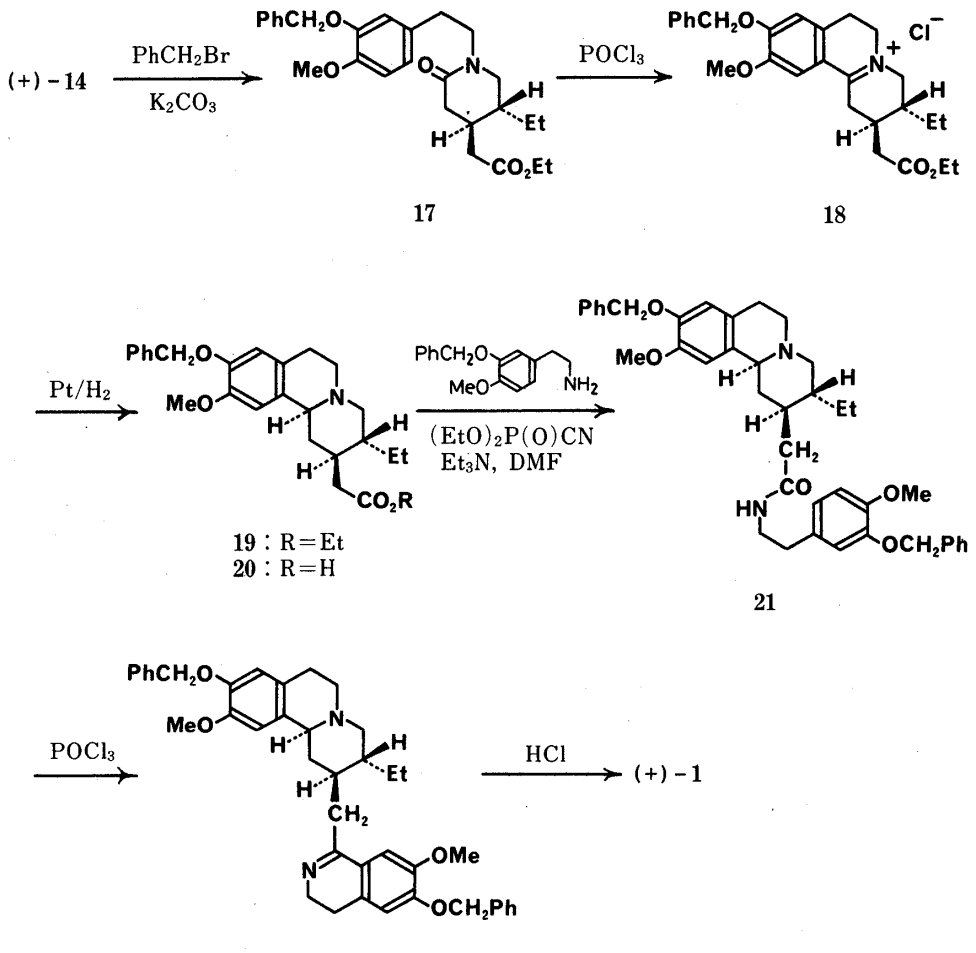


Chart 2

and *cis* isomers, from which the *trans*-lactam acid (+)-**13** was isolated by recrystallization. The yield of (+)-**13** was raised to 74% when the *cis*-lactam acid recovered from the reaction mixture was repeatedly subjected to the same thermal reaction. Esterification of (+)-**13** by the previously reported[23] Fischer–Speier method at room temperature provided the *trans*-lactam ester (+)-**14** in 96% yield. Spectral and thin-layer chromatographic (TLC) identity of (+)-**14** with the known racemic *trans*-lactam ester (±)-**14**[1] proved that stereochemical control in the synthetic operations proceeding from (+)-**6** to (+)-**14** had been secured as planned.

The later part of the synthetic scheme followed essentially the same route that used recently for the racemic series.[1] Treatment of (+)-**14** with benzyl bromide in boiling acetone containing K_2CO_3 gave the benzyl ether (+)-**17** in 98% yield. The Bischler–Napieralski cyclization of (+)-**17** was carried out with $POCl_3$ in boiling toluene, and the resulting iminium salt **18** was hydrogenated in EtOH with hydrogen and Adams catalyst to afford the tricyclic ester (−)-**19** in 73% overall yield from (+)-**17**. On hydrolysis with aqueous NaOH in EtOH at room temperature, (−)-**19** furnished the amino acid (−)-**20** (82% yield), which was coupled with 3-benzyloxy-4-methoxyphenethylamine in *N*,*N*-dimethylformamide (DMF) at room temperature *via* the agency of diethyl phosphorocyanidate[24] in the presence of Et_3N. The resulting amide (−)-**21** (87% yield) was then treated with $POCl_3$ in boiling toluene to give the penultimate base (+)-**22** in 81% yield. Debenzylation of (+)-**22** in boiling aqueous HCl–EtOH for 15 h produced the desired phenolic base (+)-**1** (82% yield), which was characterized as an ethanolate [mp 166—170 °C (sintered at 148 °C); $[\alpha]_D^{16}$ +58.6° (MeOH)]. The IR (Nujol), ultraviolet (UV) (EtOH, 0.1 N aqueous HCl, or 0.1 N aqueous NaOH), and mass spectra of the synthetic (+)-**1** were identical with those of natural (+)-desmethylpsychotrine [mp 166—168 °C (crystallized from EtOH); $[\alpha]_D$ +67.9° (c=0.50, MeOH)].[3] Conformity of the synthetic (+)-**1** with the racemic base (±)-**1** that was prepared recently by a different stereospecific synthesis[1] was also confirmed by TLC and spectroscopic means. In EtOH, synthetic (+)-**1** exhibited a characteristic circular dichroism (CD) curve, as shown in Fig. 1, which was very similar to those[10] of psychotrine (**3**) and alangicine (8-hydroxypsychotrine). These observations further supported the stereospecificity of the synthetic operations in the present "cincholoipon-incorporating route."

In conclusion, the above results have thus established the structure of the *Alangium* alkaloid desmethylpsychotrine[3] as 9-demethylpsychotrine [(+)-**1**]. A noteworthy structural feature of this benzoquinolizidine alkaloid is that the positions of the hydroxy and the methoxy groups in the two isoquinoline moieties are identical. Apart from the structure problem, it should also be emphasized that the present synthesis of (+)-**1** has extended the scope of the "cincholoipon-incorporating route"[8-14] to cover the 9-hydroxy-10-

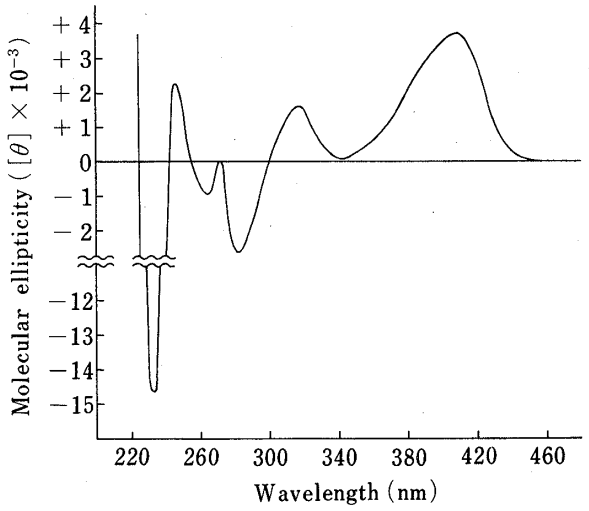


Fig. 1. The CD Curve of (+)-9-Demethylpsychotrine [(+)-**1**] in EtOH at 25 °C

methoxybenzo[*a*]quinolizidine type of *Alangium* alkaloids.

Experimental

General Notes——Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. All melting points were determined with a Yamato MP-1 capillary melting point apparatus and are corrected. See refs. 1, 9, and 10 for details of instrumentation and measurements. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

(3*R*,4*S*)-(+)-1-(3-Benzyloxy-4-methoxyphenacyl)-3-ethyl-4-piperidineacetic Acid Ethyl Ester [(+)-7]——A mixture of ethyl cincholoiponate [(+)-**6**][17] (3.99 g, 20 mmol), anhydrous K_2CO_3 (2.77 g, 20 mmol), 3-benzyloxy-4-methoxyphenacyl bromide[18] (6.71 g, 20 mmol), and benzene (80 ml) was stirred at 50—55 °C for 15 h. After cooling, the reaction mixture was washed sequentially with H_2O, 5% aqueous KOH, and H_2O, dried over anhydrous K_2CO_3, and concentrated to leave a reddish brown oil. The oil was purified by column chromatography [alumina, hexane–AcOEt (3 : 1, v/v)] to give (+)-**7** (6.42 g, 71%) as a yellow oil, $[\alpha]_D^{13}$ +2.1° (c = 2.39, EtOH); MS *m/e*: 453 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1724 (ester CO), 1670 (ArCO); ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, t, J = 7 Hz, $CCH_2\underline{Me}$), 1.24 (3H, t, J = 7 Hz, $OCH_2\underline{Me}$), 3.64 (2H, s, $ArCOC\underline{H}_2$), 3.93 (3H, s, OMe), 4.12 (2H, q, J = 7 Hz, $OC\underline{H}_2Me$), 5.14 (2H, s, $OC\underline{H}_2Ph$), 6.85 (1H, d, J = 10 Hz, $H_{(5')}$), 7.2—7.55 (5H, m, Ph), 7.68 (1H, d, J = 1.5 Hz, $H_{(2')}$), 7.72 (1H, dd, J = 10 and 1.5 Hz, $H_{(6')}$).

The starting ester (+)-**6** was prepared from commercially available cinchonine (**5**)[16] in 50% overall yield according to the literature procedure[15a,17] and was characterized as reported previously.[20]

(3*R*,4*S*)-1-[2-(3-Benzyloxy-4-methoxyphenyl)-2-hydroxyethyl]-3-ethyl-4-piperidineacetic Acid Ethyl Ester (8)——A solution of (+)-**7** (6.12 g, 13.5 mmol) in EtOH (60 ml) was stirred under ice-cooling, and $NaBH_4$ (386 mg, 10.2 mmol) was added portionwise over a period of 10 min. After stirring had been continued at 0—5 °C for 6 h and then at room temperature overnight, acetone (3 ml) was added and the mixture was concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of H_2O and benzene. The benzene extracts were washed with H_2O, dried over anhydrous K_2CO_3, and concentrated to leave a diastereomeric mixture of **8** (5.76 g, 94%) as a faintly yellow oil, $[\alpha]_D^{13}$ −2.5° (c = 1.63, EtOH); MS *m/e*: 455 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (OH), 1725 (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J = 7 Hz, $CCH_2\underline{Me}$), 1.25 (3H, t, J = 7 Hz, $OCH_2\underline{Me}$), 3.86 (3H, s, OMe), 4.13 (2H, q, J = 7 Hz, $OC\underline{H}_2Me$), 4.5—4.7 [1H, m, $ArC\underline{H}(OH)$], 5.12 (2H, s, $OC\underline{H}_2Ph$), 6.8—7.05 (3H, m, aromatic protons), 7.2—7.55 (5H, m, Ph).

(4*S*,5*R*)-1-[2-(3-Benzyloxy-4-methoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (10)——A stirred mixture of **8** (5.47 g, 12 mmol), 1% aqueous AcOH (88 ml), disodium ethylenediaminetetraacetate dihydrate (11.2 g, 30 mmol), and $Hg(OAc)_2$ (9.56 g, 30 mmol) was heated under reflux for 1.5 h, precipitating metallic Hg and a reddish-brown oil. After cooling, the reaction mixture was extracted with $CHCl_3$, and the $CHCl_3$ extracts were washed successively with 5% aqueous HCl, H_2O, 5% aqueous NaOH, and H_2O, dried, and evaporated to leave a brown oil. The residue was dissolved in a little $CHCl_3$, and the solution was passed through a column packed with alumina (36 g). The column was eluted with $CHCl_3$ and the eluate was evaporated *in vacuo* to give an orange oil (5.76 g), shown to be impure by the detection of four spots on TLC analysis [alumina, hexane–AcOEt (1 : 1, v/v) or silica gel, hexane–AcOEt (1 : 2, v/v)]. For hydrolysis of substances presumed to be the acetates of **9** and **10**,[25] a solution of the total amount of the oil in EtOH (60 ml) containing anhydrous Na_2CO_3 (3 g) was stirred at room temperature for 24 h and then, after addition of H_2O (6 ml), at 50—55 °C for 10 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ and the solution was washed with H_2O, dried, and evaporated to leave an orange oil, which was chromatographed on silica gel. Earlier fractions eluted with hexane–AcOEt (1 : 2, v/v) gave small amounts of substances presumed to be the unchanged acetates of **9** and **10**, and the middle fractions afforded a yellow oil (1.11 g, 20%) presumed[8,9] to be a diastereomeric mixture of the *cis*- and *trans*-2-piperidones **9**, $[\alpha]_D^{18}$ +15.1° (c = 2.00, EtOH); MS *m/e*: 469 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH), 1726 (ester CO), 1611 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J = 7 Hz, $CCH_2\underline{Me}$), 1.25 (3H, t, J = 7 Hz, $OCH_2\underline{Me}$), 3.87 (3H, s, OMe), 4.12 (2H, q, J = 7 Hz, $OC\underline{H}_2Me$), 4.8—4.95 [1H, m, $ArC\underline{H}(OH)$], 5.13 (2H, s, $OC\underline{H}_2Ph$), 6.8—7.0 (3H, m, aromatic protons), 7.2—7.5 (5H, m, Ph). Later fractions eluted with the same solvent system yielded the 6-piperidone **10** (3.09 g, 55%) as an orange, glassy gum, $[\alpha]_D^{18}$ −11.8° (c = 2.00, EtOH); MS *m/e*: 469 (weak, M^+), 451 ($M^+ - H_2O$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (OH), 1727 (ester CO), 1617 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.77 and 0.80 (3H, t each, J = 6.5 Hz, diastereomeric $CCH_2\underline{Me}$'s), 1.23 (3H, t, J = 7 Hz, $OCH_2\underline{Me}$), 3.85 (3H, s, OMe), 4.10 (2H, q, J = 7 Hz, $OC\underline{H}_2Me$), 4.8—4.95 [1H, m, $ArC\underline{H}(OH)$], 5.12 (2H, s, $OC\underline{H}_2Ph$), 6.8—7.0 (3H, m, aromatic protons), 7.2—7.5 (5H, m, Ph).

(4*S*,5*R*)-(−)-5-Ethyl-1-(3-hydroxy-4-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid Ethyl Ester [(−)-11]——A solution of **10** (14.6 g, 31 mmol) in EtOH (200 ml) containing 70% perchloric acid (3 ml) was hydrogenated over 10% Pd–C (4.0 g) at atmospheric pressure and room temperature for 34 h. The catalyst was removed by filtration and

the filtrate was concentrated *in vacuo*. The oily residue was dissolved in $CHCl_3$ (300 ml), and the solution was washed successively with H_2O, saturated aqueous $NaHCO_3$, and H_2O, dried, and concentrated to leave (−)-**11** (11.0 g, 97%) as a faintly orange oil, $[\alpha]_D^{20}$ −4.2° (*c*=2.00, EtOH); MS *m/e*: 363 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570 (OH), 1726 (ester CO), 1625 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, *J*=7 Hz, $CH_2\underline{Me}$), 1.25 (3H, t, *J*=7 Hz, $OCH_2\underline{Me}$), 3.85 (3H, s, OMe), 4.12 (2H, q, *J*=7 Hz, $OC\underline{H}_2Me$), 5.98 (1H, s, OH), 6.68 (1H, dd, *J*=8.5 and 1.5 Hz, $H_{(6')}$), 6.74 (1H, d, *J*=8.5 Hz, $H_{(5')}$), 6.78 (1H, d, *J*=1.5 Hz, $H_{(2')}$).

(4*S*,5*R*)-(−)-5-Ethyl-1-(3-hydroxy-4-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid [(−)-12]——A solution of (−)-**11** (1.89 g, 5.2 mmol) and 2 N aqueous NaOH (10 ml) in EtOH (20 ml) was stirred at room temperature for 30 h. The solvent was removed by vacuum distillation and the residue was dissolved in H_2O (20 ml). The aqueous solution was washed with benzene, made acidic with aqueous HCl, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and evaporated to leave (−)-**12** (1.69 g, 97%) as an orange, glassy gum. Crystallization of the gum from AcOEt gave an analytical sample as colorless prisms, mp 127—129 °C; $[\alpha]_D^{30}$ −0.2° (*c*=2.00, EtOH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (OH), 1711 (CO_2H), 1624 (sh), 1598 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t, *J*=7 Hz, $CH_2\underline{Me}$), 3.82 (3H, s, OMe), 6.64 (1H, dd, *J*=8 and 1.5 Hz, $H_{(6')}$), 6.71 (1H, d, *J*=8 Hz, $H_{(5')}$), 6.74 (1H, d, *J*=1.5 Hz, $H_{(2')}$), 7.9 (2H, br, OH and CO_2H). *Anal.* Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.44; H, 7.62; N, 4.19.

(4*R*,5*R*)-(+)-5-Ethyl-1-(3-hydroxy-4-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid [(+)-13]——The *cis*-lactam acid (−)-**12** (10.0 g, 29.8 mmol) was placed in a small flask and heated neat in an oil bath kept at 180 °C for 90 min. After cooling, the oily reaction mixture was dissolved in AcOEt (30 ml), and the solution was kept in a refrigerator for 2 d. The pale brownish prisms (mp 118—122 °C) that resulted were filtered off and recrystallized from AcOEt to yield (+)-**13**, mp 128—130 °C. The filtrates, which were obtained when the crude and recrystallized samples were isolated, were combined and concentrated *in vacuo*, and the residue was again heated at 180 °C for 90 min and worked up as described above. Repetition of this procedure 5 times raised the yield of (+)-**13** to 74%. For analysis, the crystals (mp 128—130 °C) were further recrystallized from AcOEt to produce faintly brownish prisms, mp 130—132 °C; $[\alpha]_D^{31}$ +72.0° (*c*=0.50, EtOH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (OH), 1711 (CO_2H), 1600 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, t, *J*=7 Hz, $CH_2\underline{Me}$), 3.84 (3H, s, OMe), 6.64 (1H, dd, *J*=8 and 1.5 Hz, $H_{(6')}$), 6.72 (1H, d, *J*=8 Hz, $H_{(5')}$), 6.74 (1H, d, *J*=1.5 Hz, $H_{(2')}$). *Anal.* Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.27; H, 7.46; N, 4.09.

(4*R*,5*R*)-(+)-5-Ethyl-1-(3-hydroxy-4-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-14]——A solution of (+)-**13** (470 mg, 1.4 mmol) in 10% (w/w) ethanolic HCl (10 ml) was stirred at 24—28 °C for 20 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between H_2O and $CHCl_3$. The $CHCl_3$ extracts were washed successively with H_2O, saturated aqueous $NaHCO_3$, and H_2O, dried, and evaporated to furnish (+)-**14** (490 mg, 96%) as an orange oil, $[\alpha]_D^{31}$ +69.3° (*c*=0.50, EtOH). The IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra and TLC behavior of this sample were identical with those of authentic (±)-**14**.[1)]

(4*R*,5*R*)-(+)-1-(3-Benzyloxy-4-methoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-17]——A stirred mixture of (+)-**14** (6.36 g, 17.5 mmol), anhydrous K_2CO_3 (2.90 g, 21.0 mmol), benzyl bromide (3.59 g, 21.0 mmol), and acetone (70 ml) was heated under reflux for 24 h. The reaction mixture was worked up as described previously[1)] for a similar benzylation of (±)-**14**, giving an orange oil (7.81 g, 98%), which was shown to be virtually homogeneous on a TLC plate. A portion of the oil was purified by column chromatography [alumina, hexane–AcOEt (2:1, v/v)] to afford (+)-**17** as a faintly yellowish oil, $[\alpha]_D^{33}$ +52.8° (*c*=0.50, EtOH); MS *m/e*: 453 (M^+); IR ($CHCl_3$), ^{1}H-NMR ($CDCl_3$), and TLC behavior identical with those of authentic (±)-**17**.[1)]

(2*R*,3*R*)-9-Benzyloxy-2-ethoxycarbonylmethyl-3-ethyl-1,2,3,4,6,7-hexahydro-10-methoxybenzo[*a*]quinolizinium Chloride (18)——A solution of (+)-**17** (454 mg, 1.0 mmol) and $POCl_3$ (770 mg, 5.0 mmol) in dry toluene (5 ml) was heated under reflux for 1.5 h. The reaction mixture was worked up as described previously[1)] for the corresponding racemic modification, yielding crude **18** (561 mg) as a brown glass. This sample was directly used in the next hydrogenation step without further purification.

(2*R*,3*R*,11b*S*)-(−)-9-Benzyloxy-3-ethyl-1,3,4,6,7,11b-hexahydro-10-methoxy-2*H*-benzo[*a*]quinolizine-2-acetic Acid Ethyl Ester [(−)-19]——The total amount of crude **18** described above was dissolved in EtOH (10 ml), and the solution was hydrogenated over Adams catalyst (40 mg) at atmospheric pressure and room temperature for 40 min. The reaction mixture was then worked up in a manner similar to that described previously[1)] for the corresponding racemic modification, affording (−)-**19** [321 mg, 73% overall yield from (+)-**17**] as an orange solid, mp 57—59 °C. Recrystallization of the solid from hexane gave an analytical sample as colorless needles, mp 61.5—62.5 °C; $[\alpha]_D^{25}$ −56.4°. (*c*=0.44, EtOH); IR ($CHCl_3$), ^{1}H-NMR ($CDCl_3$), and TLC behavior identical with those of authentic (±)-**19**.[1)] *Anal.* Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20. Found: C, 73.85; H, 8.01; N, 3.39.

(2*R*,3*R*,11b*S*)-(−)-9-Benzyloxy-3-ethyl-1,3,4,6,7,11b-hexahydro-10-methoxy-2*H*-benzo[*a*]quinolizine-2-acetic Acid [(−)-20]——A solution of (−)-**19** (4.38 g, 10 mmol) and 2 N aqueous NaOH (10 ml) in EtOH (80 ml) was stirred at room temperature for 20 h. The reaction mixture was concentrated *in vacuo*, and H_2O (50 ml) was added to the residue. The resulting solution was neutralized with 2 N aqueous HCl (10 ml) and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave an orange glass, which was triturated with ether. The insoluble solid that resulted was filtered off and dried to furnish (−)-**20** (3.38 g, 82%), mp

142—146 °C; $[\alpha]_D^{25}$ −30.7° (c=0.50, EtOH); ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7 Hz, CCH_2Me), 3.82 (3H, s, OMe), 5.05 (2H, s, OCH_2Ph), 6.59 (1H, s, $H_{(8)}$ or $H_{(11)}$), 6.67 (1H, s, $H_{(11)}$ or $H_{(8)}$), 7.3—7.55 (5H, m, Ph); IR ($CHCl_3$) identical with that of authentic (±)-**20**.[1] Since this sample was difficult to purify by recrystallization, it was directly used in the next amidation step.

(2*R*,3*R*,11b*S*)-(−)-9-Benzyloxy-*N*-(3-benzyloxy-4-methoxyphenethyl)-3-ethyl-1,3,4,6,7,11b-hexahydro-10-methoxy-2*H*-benzo[*a*]quinolizine-2-acetamide [(−)-21]——To a chilled, stirred solution of (−)-**20** (2.29 g, 5.6 mmol) and 3-benzyloxy-4-methoxyphenethylamine[26] (2.16 g, 8.4 mmol) in $HCONMe_2$ (25 ml) were added sequentially diethyl phosphorocyanidate[27] (1.82 g, 11.2 mmol) and Et_3N (1.13 g, 11.2 mmol). The mixture was stirred at room temperature for 6 h and worked up as described previously[1] for the corresponding racemic modification, giving (−)-**21** (3.16 g, 87%) as a colorless solid. Recrystallization of the solid from EtOH produced an analytical sample as colorless granules, mp 152—154 °C; $[\alpha]_D^{17}$ −20.8° (c=0.50, EtOH); IR ($CHCl_3$), ^{1}H-NMR ($CDCl_3$), and TLC behavior identical with those of authentic (±)-**21**.[1] *Anal.* Calcd for $C_{41}H_{48}N_2O_5$: C, 75.90; H, 7.46; N, 4.32. Found: C, 75.62; H, 7.62; N, 4.26.

(2*R*,3*R*,11b*S*)-(+)-9-Benzyloxy-2-(6-benzyloxy-3,4-dihydro-7-methoxy-1-isoquinolyl)methyl-3-ethyl-1,3,4,6,7,11b-hexahydro-10-methoxy-2*H*-benzo[*a*]quinolizine [(+)-22]——The tricyclic amide (−)-**21** was cyclized with $POCl_3$ as reported previously[1] for (±)-**21**, yielding (+)-**22** (81% yield) as a pale orange glass, $[\alpha]_D^{24}$ +45.6° (c=1.37, EtOH); MS m/e: 630 (M^+); IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) identical with those of authentic (±)-**22**.[1]

(2*R*,3*R*,11b*S*)-(+)-2-(3,4-Dihydro-6-hydroxy-7-methoxy-1-isoquinolyl)methyl-3-ethyl-1,3,4,6,7,11b-hexahydro-9-hydroxy-10-methoxy-2*H*-benzo[*a*]quinolizine [(+)-9-Demethylpsychotrine; Desmethylpsychotrine] [(+)-1]——A solution of (+)-**22** (145 mg, 0.23 mmol) and 10% aqueous HCl (8 ml) in 10% ethanolic HCl (3 ml) was heated under reflux for 15 h. After cooling, the reaction mixture was washed with benzene, neutralized with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated to leave an orange glass, which was triturated with EtOH. The insoluble solid that resulted was filtered off to provide (+)-**1**·5/2EtOH (107 mg, 82%) as a yellow powder. Recrystallization of the solid from EtOH and drying over P_2O_5 at 2 mmHg and room temperature for 24 h gave an ethanolate as yellowish minute needles, mp 166—170 °C (sintered at 148 °C); $[\alpha]_D^{16}$ +58.6° (c=0.50, MeOH); MS m/e (relative intensity): 450 (M^+) (40), 435 (M^+−Me) (2.0), 421 (M^+−Et) (1.2), 272 (22), 260 (26), 259 (71), 258 (58), 257 (13), 256 (25), 244 (20), 231 (19), 230 (100), 228 (14), 225 (8.2), 216 (20), 192 (34), 191 (53), 190 (28), 178 (23), 177 (25), 176 (19); UV λ_{max} (99% aqueous EtOH) 226 nm (ε 17800), 277 (11500), 312 (4300), 408 (19800); UV λ_{max} (0.1 N aqueous HCl) 244.5 (15800), 291.5 (8200), 307 (9100), 356 (9500); UV λ_{max} (0.1 N aqueous NaOH) 243 (19300), 306 (sh) (14200), 327 (15900); ^{1}H-NMR (Me_2SO-d_6) and ^{13}C-NMR (Me_2SO-d_6) identical with those of authentic (±)-**1**·5/2EtOH.[1] *Anal.* Calcd for $C_{27}H_{34}N_2O_4 \cdot 5/2C_2H_5OH$: C, 67.94; H, 8.73; N, 4.95. Found: C, 67.92; H, 8.59; N, 5.07. The UV, IR (Nujol), and mass spectra of this sample were identical with those of natural desmethylpsychotrine [mp 166—168 °C (crystallized from EtOH); $[\alpha]_D$ +67.9° (c=0.50, MeOH)].[3]

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