

[Chem. Pharm. Bull.]
33(12)5264—5269(1985)

Quinolizidines. XVI.¹⁾ Chiral Syntheses of 9-Demethylcephaeline and 10-Demethylcephaeline²⁾

TOZO FUJII* and MASASHI OHBA

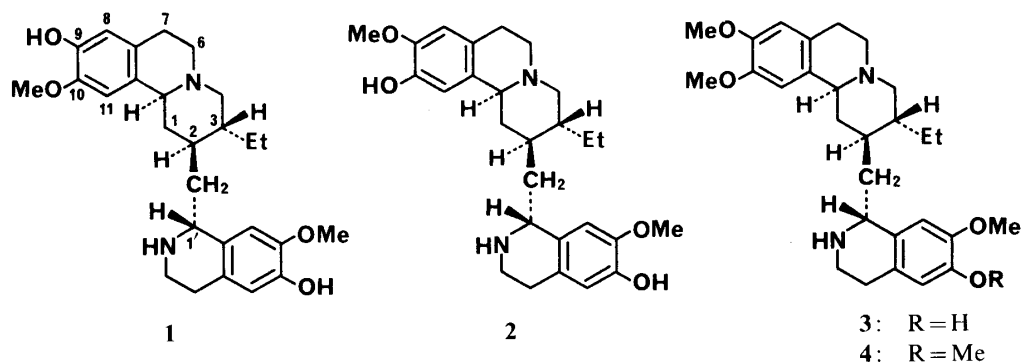
Faculty of Pharmaceutical Sciences, Kanazawa University,
Takara-machi, Kanazawa 920, Japan

(Received April 25, 1985)

In order to establish the structure of the *Alangium* alkaloid demethylcephaeline, chiral syntheses of the two possible alternative structures, (–)-9-demethylcephaeline (**1**) and (–)-10-demethylcephaeline (**2**), have been accomplished through a “cincholoipon-incorporating route.” The synthesis of (–)-**2** started with an initial condensation of the tricyclic acid (–)-**12b**, prepared from the ester (–)-**11b** by alkaline hydrolysis, with 3-benzyloxy-4-methoxyphenethylamine and proceeded through the intermediates (–)-**13b**, (+)-**15b**, and (–)-**14b**. The 1'-epimers (–)-**18b** and (–)-**17** were also produced in this reaction sequence. A parallel sequence of conversions starting with (+)-**15a** afforded (–)-**1** via the intermediate (–)-**14a**, together with the 1'-epimer (–)-**16** via (–)-**18a**. Unfortunately, however, lack of a sufficient amount of natural (–)-demethylcephaeline for a detailed and direct comparison precluded identification of either (–)-**1** or (–)-**2** with this alkaloid, leaving its chemistry incomplete.

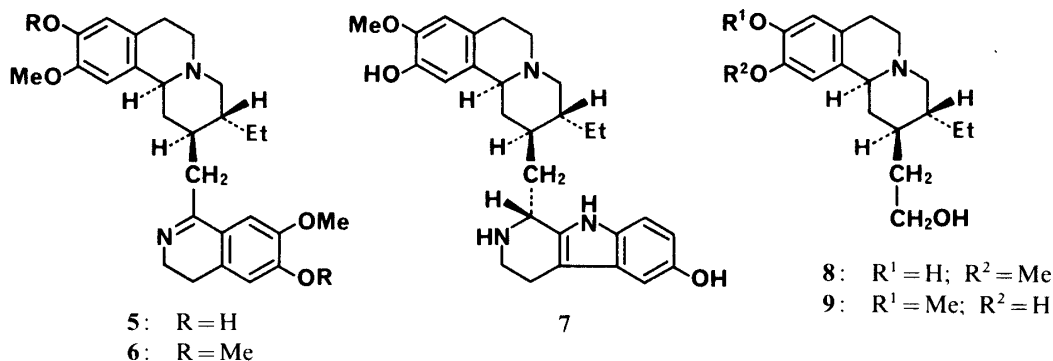
Keywords—demethylcephaeline; demethylisocephaeline; diethyl phosphorocyanidate amide formation; Bischler–Napieralski cyclization; carbon–nitrogen double-bond catalytic reduction; benzyl ether catalytic hydrogenolysis; TLC epimer differentiation; NMR epimer differentiation

In 1970, Pakrashi and Achari³⁾ reported the isolation of (–)-demethylcephaeline, a new phenolic benzoquinolizidine alkaloid, from the stem bark of the Indian medicinal plant *Alangium lamarkii* THWAITES (Alangiaceae). On the basis of its chemical correlation with cephaeline (**3**) and emetine (**4**), as well as ultraviolet (UV), infrared (IR), and mass spectral evidence, they assigned either structure **1** (absolute configuration shown⁴⁾) or **2** to the new base, with their preference for **2**.³⁾ However, differentiation between the 9- and the 10-demethyl structures was not possible at that time. With the aim of determining which



structure is correct, we tried to synthesize both of the possible alternative structures, 9-demethylcephaeline (**1**) and 10-demethylcephaeline (**2**), through a “cincholoipon-incorporating route.”⁵⁾ The simultaneous setting of the two synthetic targets is reasonable since we have recently shown that (+)-desmethylpsychotrine, another phenolic *A. lamarkii*

alkaloid,⁶⁾ has the 9-demethyl structure **5**,⁷⁾ whereas (–)-demethyltubulosine, yet another phenolic *A. lamarckii* alkaloid,^{6,8)} is not a 9-demethylated base,⁹⁾ but 10-demethyltubulosine (**7**).^{1,10)} The occurrence of both 9-demethylprotoemetinol (**8**) and 10-demethylprotoemetinol (**9**) in the seeds of *A. lamarckii* has also been reported quite recently.¹¹⁾



For the synthesis of the first target, 9-demethylcephaeline (**1**), we selected (+)-*O,O*-dibenzyl-9-demethylpsychotrine (**15a**) as a key intermediate. When the present work was commenced, this intermediate had already been prepared from (+)-ethyl cincholoiponate (**10**), a degradation product from the *Cinchona* alkaloid cinchonine, by a 13-step synthesis [through (–)-**11a**, (–)-**12a**, and (–)-**13a**] and utilized by us for the synthesis of (+)-9-demethylpsychotrine (**5**).^{7a,c)} Catalytic hydrogenation of (+)-**15a** in EtOH over Adams catalyst and chromatographic separation of the products furnished (–)-*O,O*-dibenzyl-9-demethylcephaeline (**14a**) and its 1'-epimer [(–)-**18a**] in 47% and 30% yields, respectively. On debenzylation using hydrogen and Pd–C catalyst, (–)-**14a** gave the first target molecule (–)-**1**

TABLE I. ¹³C Chemical Shifts of (–)-*O,O*-Dibenzyl-9-demethylcephaeline (**14a**), (–)-*O,O*-Dibenzyl-10-demethylcephaeline (**14b**), and Their 1'-α-H Isomers (–)-**18a, b** in CDCl₃

Carbon	Chemical shift ^{a)}				Carbon	Chemical shift ^{a)}			
	(–)- 14a	(–)- 14b	(–)- 18a	(–)- 18b		(–)- 14a	(–)- 14b	(–)- 18a	(–)- 18b
C(1)	36.9	36.7	39.4	39.2	C(4')	29.2	29.4	29.4 ^{b)}	29.2
C(2)	36.9	36.7	38.9	39.0	C(4'a)	127.0	127.0	127.2	127.0
C(3)	41.7	41.9	42.9	42.9	C(5')	114.8	114.8	114.8	114.8
C(4)	61.4	61.4	61.6	61.5	C(6')	146.8 ^{c)}	146.7 ^{d)}	146.7 ^{e)}	146.7 ^{f)}
C(6)	52.3	52.4	52.5	52.5	C(7')	148.0 ^{c)}	148.0 ^{d)}	147.8 ^{e)}	147.8 ^{f)}
C(7)	29.2	29.4	29.1 ^{b)}	29.2	C(8')	110.0	110.1	110.4	110.4
C(7a)	127.0	127.6	126.7	127.3	C(8'a)	132.7	132.9	132.7	132.6
C(8)	114.5	112.1 ^{g)}	114.4	112.1 ^{h)}	9-OMe	—	56.0	—	56.0
C(9)	146.6 ^{c)}	148.3 ^{d)}	146.7 ^{e)}	148.2 ^{f)}	10-OMe	56.6	—	56.3	—
C(10)	147.9 ^{c)}	146.1 ^{d)}	147.8 ^{e)}	146.2 ^{f)}	7'-OMe	56.2	56.2	56.3	56.3
C(11)	109.7	112.4 ^{g)}	109.1	111.8 ^{h)}	9-OCH ₂	71.0	—	71.1	—
C(11a)	131.0	130.3	130.8	130.1	10-OCH ₂	—	71.7	—	71.6
C(11b)	62.4	62.3	62.8	62.6	6'-OCH ₂	71.2	71.2	71.1	71.0
C(12)	40.2	40.3	40.7	40.7	Ph	137.3	137.6	137.2	137.4
C(13)	23.5	23.5	24.0	24.0	—	—	137.3	—	137.2
C(14)	11.2	11.2	11.3	11.3	—	128.4	128.5	128.4	128.3
C(1')	51.9	51.8	55.3	55.2	—	127.6	127.6	127.6	127.6
C(3')	40.7	40.7	41.1	41.0	—	127.2	127.3	127.2	127.2

a) In ppm downfield from internal Me₄Si. b–h) Assignments indicated by a given superscript may be interchanged.

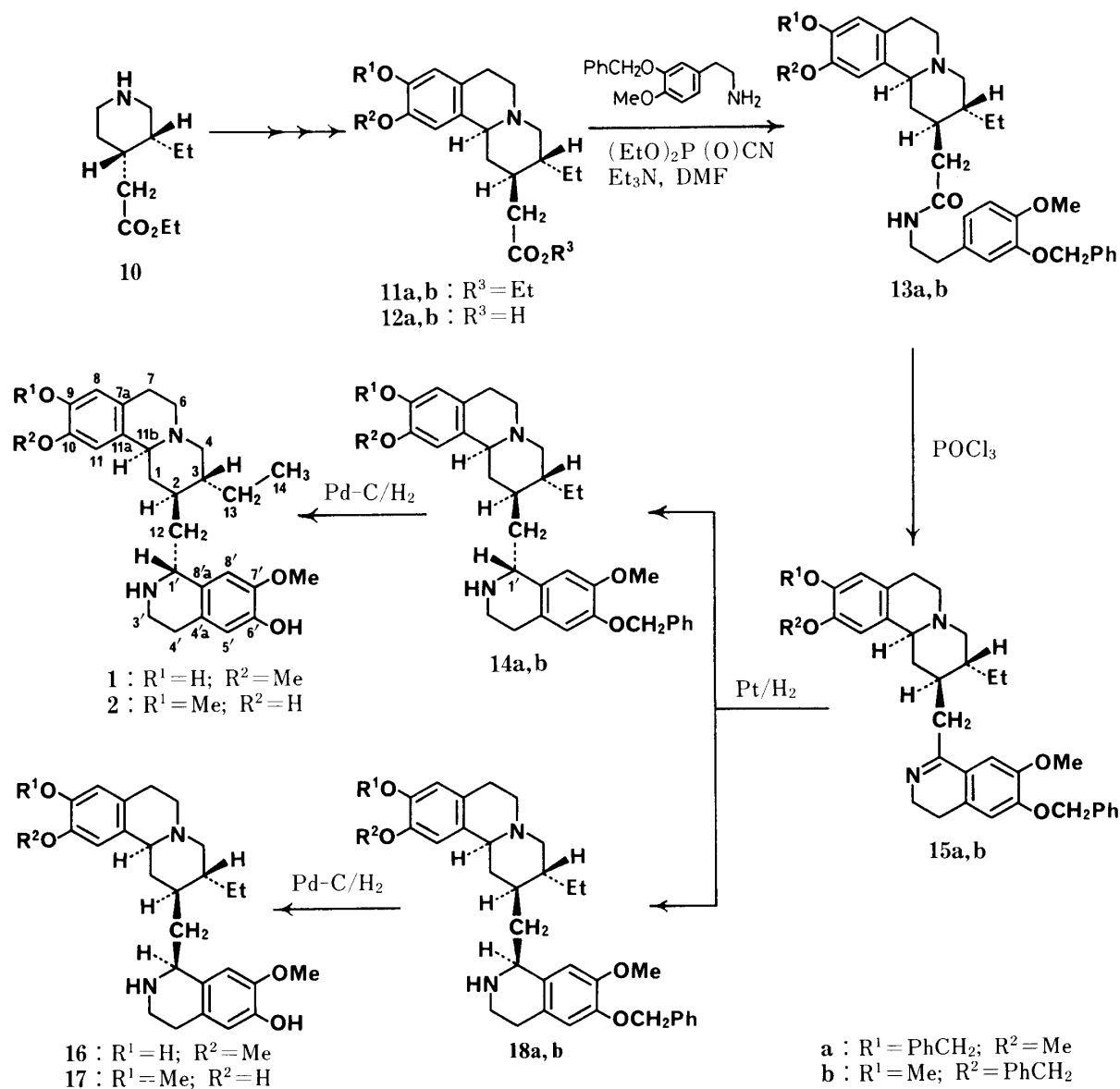


Chart 1

[mp 147 °C; $[\alpha]_D^{12} - 55.0^\circ$ (CHCl₃)] in 82% yield. A similar hydrogenolysis of the epimeric base (–)-**18a** afforded the corresponding phenolic base (–)-**16** in 73% yield.

The configurations at C-1' of (–)-**14a** and (–)-**18a** and hence those of (–)-**1** and (–)-**16** were assigned on the basis of the following evidence. The above formation of a 1.6: 1 mixture of (–)-**14a** and (–)-**18a** from (+)-**15a** is comparable to that¹²⁾ of a 1.7: 1 mixture of emetine (**4**) and its 1'-epimer (isoemetine) in a similar hydrogenation of *O*-methylpsychotrine (**6**). On thin-layer chromatographic (TLC) analysis, (–)-**14a** moved faster than (–)-**18a**. In the ¹³C nuclear magnetic resonance (¹³C-NMR) spectra in CDCl₃ (see Table I), the C(1), C(2), and C(1') carbon signals of (–)-**14a** appeared upfield from the corresponding signals of the 1'-epimer (–)-**18a** by 2.0–3.4 ppm. In the ¹H-NMR spectra in CDCl₃, the C(1')H proton of (–)-**14a** resonated at δ 4.11 as a doublet with *J* = 10.5 Hz, whereas that of (–)-**18a** resonated at δ 4.04 as an indistinct triplet with *J* = 5 Hz. These chemical TLC, and NMR spectral features of (–)-**14a** and (–)-**18a** fulfilled all the recently reported criteria^{1,9b,13)} for distinguishing between the 1'β-H and 1'α-H isomers in such unique ring systems.

We next proceeded to the synthesis of the second target, 10-demethylcephaeline (2).

Alkaline hydrolysis of the tricyclic ester (–)-**11b**, prepared from (+)-**10** in 24% overall yield through the recently reported synthetic route (“cincholoipon-incorporating route”),¹⁴⁾ gave the amino acid (–)-**12b** in 98% yield. Condensation of (–)-**12b** with 3-benzyloxy-4-methoxyphenethylamine in *N,N*-dimethylformamide (DMF) by the diethyl phosphorocyanidate method¹⁵⁾ produced the amide (–)-**13b** (90% yield), which was then cyclized with POCl₃ in boiling toluene to provide (+)-*O,O*-dibenzyl-10-demethylpsychotrine (**15b**) in 87% yield. The correctness of the structures of (–)-**12b**, (–)-**13b**, and (+)-**15b** was verified by their spectral identity with the corresponding racemic modifications which had been obtained in the course of our recent synthesis^{7b)} of (±)-10-demethylpsychotrine. The subsequent steps to **2** were essentially the same as described above for the 9-demethyl series, giving an epimeric pair of (–)-**14b** [48% yield from (+)-**15b**] and (–)-**18b** (29% yield) first, and then the desired second target (–)-**2** [mp 148 °C; $[\alpha]_D^{17} - 53.0^\circ$ (CHCl₃); 73% yield from (–)-**14b**] and its 1'-epimer (–)-**17** [77% yield from (–)-**18b**]. The stereochemistry at C-1' of (–)-**14b** and (–)-**18b** [and hence that of (–)-**2** and (–)-**17**] was confirmed as in the case of the above 9-demethyl congeners (see also Table I).

With the two candidate compounds (–)-**1** and (–)-**2** in hand, we now proceeded to the problem of identification with natural (–)-demethylcephaeline [mp 147–149 °C;³⁾ $[\alpha]_D - 53.5^\circ$ (CHCl₃)³⁾]. The UV (in EtOH or 0.1 N ethanolic NaOH), IR (in Nujol), and mass spectra of all three were so closely similar that they were impracticable as a means of identification. Although the ¹H-NMR spectra (in CDCl₃) of (–)-**1** and (–)-**2** were clearly differentiated from one another, that of the natural alkaloid had not been measured at that time. Unfortunately, no sample of natural (–)-demethylcephaeline was available for obtaining a ¹H-NMR spectrum and/or for a mixture melting point test, and this precluded identification of either (–)-**1** or (–)-**2** with the *Alangium* alkaloid, thus leaving its chemistry incomplete. Since (–)-demethylcephaeline has been shown to be a constituent of an amorphous alkaloidal mixture (AL 60, isolated from *A. lamarckii*) exerting dose-dependent biphasic action on blood pressure,³⁾ further isolation of this alkaloid from the natural source in a sufficient quantity for a detailed and direct comparison with the synthetic samples is necessary before chemical and pharmacological investigations can continue.

Experimental

General Notes—All melting points were determined with a Yamato MP-1 capillary melting point apparatus and are corrected. Unless otherwise stated, the organic solutions obtained after extraction were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. See refs. 1 and 14b for details of instrumentation and measurements. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: d = doublet, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

(2R,3R,11bS)-10-Benzyloxy-3-ethyl-1,3,4,6,7,11b-hexahydro-9-methoxy-2H-benzo[*a*]quinolizine-2-acetic Acid [(–)-12b**]**—A solution of the tricyclic ester (–)-**11b**¹⁴⁾ (875 mg, 2 mmol) and 2 N aqueous NaOH (2 ml) in EtOH (15 ml) was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, and H₂O (15 ml) was added to the residual oil. The resulting aqueous solution was neutralized with 2 N aqueous HCl (2 ml) to deposit a pale yellowish gum, which was extracted with CHCl₃. The CHCl₃ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave (–)-**12b** (802 mg, 98%) as an almost colorless glass, $[\alpha]_D^{18} - 56.8^\circ$ (*c* = 0.50, EtOH); MS *m/e*: 409 (M⁺). The IR (CHCl₃) and ¹H-NMR (CDCl₃) spectra of this sample were identical with those of authentic (±)-**12b**.^{7b)}

(2R,3R,11bS)-10-Benzyloxy-*N*-(3-benzyloxy-4-methoxyphenethyl)-3-ethyl-1,3,4,6,7,11b-hexahydro-9-methoxy-2H-benzo[*a*]quinolizine-2-acetamide [(–)-13b**]**—The tricyclic acid (–)-**12b** was allowed to react with 3-benzyloxy-4-methoxyphenethylamine¹⁶⁾ by the diethyl phosphorocyanidate method¹⁵⁾ in a manner similar to that carried out in the recent synthesis^{7a,c)} of (–)-**13a** from (–)-**12a**, giving (–)-**13b** in 90% yield as a colorless solid. Recrystallization of the solid from EtOH produced an analytical sample as colorless minute needles, mp 149–151 °C; $[\alpha]_D^{20} - 22.2^\circ$ (*c* = 0.50, EtOH). *Anal.* Calcd for C₄₁H₄₈N₂O₅: C, 75.90; H, 7.46; N, 4.32. Found: C, 75.79; H, 7.45; N, 4.13. The IR (CHCl₃) and ¹H-NMR (CDCl₃) spectra and TLC mobility of this sample were identical with those of authentic (±)-**13b**.^{7b)}

(2*R*,3*R*,11*bS*)-10-Benzyloxy-2-(6-benzyloxy-3,4-dihydro-7-methoxy-1-isoquinolyl)methyl-3-ethyl-1,3,4,6,7,11*b*-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizines [(+)-15*b*]—Crude (+)-15*b* was obtained from (–)-13*b* and POCl₃ as described recently for (+)-15*a*^{7a,c} and purified by column chromatography [alumina, AcOEt–hexane (1:1, v/v)] to give a faintly yellowish glass (87% yield), $[\alpha]_D^{26} + 39.9^\circ$ ($c=0.96$, EtOH); MS m/e : 630 (M^+). The IR (CHCl₃) and ¹H-NMR (CDCl₃) spectra of this sample were superimposable on those of authentic (±)-15*b*.^{7b}

[2*S*-[2*α*(*S),3*β*,11*bβ*]]- and [2*S*-[2*α*(*R**),3*β*,11*bβ*]]-9-Benzyloxy-2-(6-benzyloxy-7-methoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl-3-ethyl-1,3,4,6,7,11*b*-hexahydro-10-methoxy-2*H*-benzo[*a*]quinolizines [(–)-14*a* and (–)-18*a*]**—A solution of (+)-15*a*^{7a,c} (1.01 g, 1.6 mmol) in EtOH (30 ml) was hydrogenated over Adams catalyst (120 mg) at atmospheric pressure and 18 °C for 1 h. Removal of the catalyst by filtration and evaporation of the filtrate under reduced pressure left a yellow oil, which was dissolved in CHCl₃ (80 ml). The CHCl₃ solution was washed successively with 5% aqueous NaOH and saturated aqueous NaCl, dried, and concentrated to leave an orange glass (972 mg). This material was chromatographed successively on a Merck Lobar column (LiChroprep Si 60) and a silica gel column using CHCl₃–MeOH (10:1, v/v) as the eluent, and then on preparative TLC plates [silica gel, CHCl₃–MeOH (10:1, v/v)]. The fractions with higher TLC mobility (R_f 0.61) gave (–)-*O*,*O*-dibenzyl-9-demethylcephaeline [(–)-14*a*] (478 mg, 47%) as a faintly yellowish glass, $[\alpha]_D^{26} - 18.7^\circ$ ($c=0.82$, EtOH); MS m/e : 632 (M^+); IR $\nu_{\max}^{\text{CHCl}_3}$ 2760 cm^{–1} (*trans*-quinolizidine ring);¹⁷ ¹H-NMR (CDCl₃) δ : 0.89 (3H, t, $J=6.6$ Hz, CCH₂Me), 3.81 and 3.85 (3H each, s, two OMe's), 4.11 (1H, d, $J=10.5$ Hz, H₍₁₁₎), 5.10 (4H, s, two OCH₂Ph's), 6.56 and 6.80 (1H each, s, aromatic protons), 6.62 (2H, s, two aromatic protons), 7.1–7.5 (10H, m, two OCH₂Ph's); ¹³C-NMR (Table I).

The fractions with lower TLC mobility (R_f 0.54) in the above chromatography afforded the 1' α -H isomer (–)-18*a* (308 mg, 30%) as a yellow glass, $[\alpha]_D^{26} - 25.6^\circ$ ($c=0.66$, EtOH); MS m/e : 632 (M^+); IR $\nu_{\max}^{\text{CHCl}_3}$ 2760 cm^{–1} (*trans*-quinolizidine ring);¹⁷ ¹H-NMR (CDCl₃) δ : 0.94 (3H, t, $J=6.6$ Hz, CCH₂Me), 3.80 and 3.83 (3H each, s, two OMe's), 4.04 (1H, dull t, $J=5$ Hz, H₍₁₁₎), 5.07 (4H, s, two OCH₂Ph's), 6.59 and 6.69 (1H each, s, aromatic protons), 6.61 (2H, s, two aromatic protons), 7.1–7.5 (10H, m, two OCH₂Ph's); ¹³C-NMR (Table I).

[2*S*-[2*α*(*S),3*β*,11*bβ*]]- and [2*S*-[2*α*(*R**),3*β*,11*bβ*]]-10-Benzyloxy-2-(6-benzyloxy-7-methoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl-3-ethyl-1,3,4,6,7,11*b*-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizines [(–)-14*b* and (–)-18*b*]**—These two isomers were prepared from (+)-15*b* by a catalytic reduction similar to that described above for (–)-14*a* and (–)-18*a*, and by subsequent chromatographic separation on an alumina column [hexane–AcOEt (2:1, v/v)] and on a silica gel column [CHCl₃–MeOH (10:1, v/v)].

(–)-*O*,*O*-Dibenzyl-10-demethylcephaeline [(–)-14*b*] was isolated as a faintly yellowish glass (48% yield), TLC R_f 0.55 [silica gel, CHCl₃–MeOH (10:1, v/v)] or 0.49 [alumina, hexane–AcOEt (2:1, v/v)]; $[\alpha]_D^{30} - 33.2^\circ$ ($c=0.50$, EtOH); MS m/e : 632 (M^+); IR $\nu_{\max}^{\text{CHCl}_3}$ 2760 cm^{–1} (*trans*-quinolizidine ring);¹⁷ ¹H-NMR (CDCl₃) δ : 0.87 (3H, t, $J=6.6$ Hz, CCH₂Me), 3.82 and 3.85 (3H each, s, two OMe's), 3.96 (1H, d, $J=10.5$ Hz, H₍₁₁₎), 5.05 and 5.16 (2H, AB type d's, $J=12$ Hz, OCH₂Ph), 5.10 (2H, s, OCH₂Ph), 6.52, 6.60, 6.62, and 6.74 (1H each, s, aromatic protons), 7.1–7.5 (10H, m, two OCH₂Ph's); ¹³C-NMR (Table I).

The 1' α -H isomer (–)-18*b* was obtained as a faintly orange glass (29% yield), TLC R_f 0.47 [silica gel, CHCl₃–MeOH (10:1, v/v)] or 0.25 [alumina, hexane–AcOEt (2:1, v/v)]; $[\alpha]_D^{30} - 30.9^\circ$ ($c=0.50$, EtOH); MS m/e : 632 (M^+); IR $\nu_{\max}^{\text{CHCl}_3}$ 2760 cm^{–1} (*trans*-quinolizidine ring);¹⁷ ¹H-NMR (CDCl₃) δ : 0.93 (1H, t, $J=6.6$ Hz, CCH₂Me), 3.82 (6H, s, two OMe's), 3.99 (1H, dull t, $J=5.8$ Hz, H₍₁₁₎), 5.05 and 5.07 (2H each, s, two OCH₂Ph's), 6.58, 6.61, 6.66, and 6.68 (1H each, s, aromatic protons), 7.1–7.5 (10H, m, two OCH₂Ph's); ¹³C-NMR (Table I).

[2*S*-[2*α*(*S),3*β*,11*bβ*]]-3-Ethyl-1,3,4,6,7,11*b*-hexahydro-9-hydroxy-2-(6-hydroxy-7-methoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl-10-methoxy-2*H*-benzo[*a*]quinolizines [(–)-9-Demethylcephaeline] [(–)-1]**—A solution of (–)-14*a* (443 mg, 0.7 mmol) in MeOH–AcOH (1:1, v/v) (30 ml) was hydrogenated over 10% Pd–C (350 mg) at atmospheric pressure and 18 °C for 3 h. The catalyst was filtered off and washed with MeOH (20 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave a yellow oil, which was dissolved in H₂O (10 ml). The aqueous solution was made alkaline with 10% aqueous Na₂CO₃ and extracted with CHCl₃. The CHCl₃ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a yellowish-brown solid (306 mg). Purification of the solid by column chromatography [alumina, CHCl₃–EtOH (10:1, v/v)] gave (–)-1 (260 mg, 82%) as a yellowish solid. The solid was then recrystallized from benzene, producing an analytical sample as faintly yellowish minute needles, mp 147 °C (sintered at 124 °C); $[\alpha]_D^{12} - 55.0^\circ$ ($c=0.50$, CHCl₃); MS m/e (relative intensity): 453 ($M^+ + 1$) (19), 452 (M^+) (60), 275 (12), 274 (27), 272 (18), 261 (15), 260 (18), 259 (21), 258 (51), 232 (23), 230 (23), 192 (53), 191 (28), 179 (12), 178 (100), 177 (18); UV $\lambda_{\max}$ (EtOH) 225 nm (sh) (ϵ 14300), 284.5 (7770), 288 (7800); $\lambda_{\max}$ (0.1 N aqueous NaOH) 243 (17200), 299 (10100); $\lambda_{\max}$ (0.1 N aqueous HCl) 223.5 (13800), 284 (6980); ¹H-NMR (CDCl₃) δ : 0.89 (3H, t, $J=6.5$ Hz, CCH₂Me), 3.81 and 3.84 (3H each, s, two OMe's), 4.10 (1H, d, $J=11$ Hz, H₍₁₁₎), 6.50 and 6.72 (1H each, s, aromatic protons), 6.63 (2H, s, two aromatic protons). *Anal.* Calcd for C₂₇H₃₆N₂O₄: C, 71.65; H, 8.02; N, 6.19. Found: C, 71.72; H, 7.89; N, 5.89.

[2*S*-[2*α*(*S),3*β*,11*bβ*]]-3-Ethyl-1,3,4,6,7,11*b*-hexahydro-10-hydroxy-2-(6-hydroxy-7-methoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl-9-methoxy-2*H*-benzo[*a*]quinolizines [(–)-10-Demethylcephaeline] [(–)-2]**—Hydrogenolysis of (–)-14*b* and work-up of the reaction mixture were carried out as described above for (–)-1, affording (–)-2·H₂O (73% yield) as a yellow solid. Recrystallization of the solid from benzene and drying over P₂O₅ at 2 mmHg and

50 °C for 20 h gave an analytical sample as faintly yellowish minute needles, mp 148 °C (sintered at 129–130 °C); $[\alpha]_D^{17}$ –53.0° ($c=0.50$, CHCl_3); MS m/e (relative intensity): 453 ($M^+ + 1$) (14), 452 (M^+) (46), 275 (17), 274 (29), 272 (14), 261 (12), 260 (17), 259 (17), 258 (40), 232 (21), 230 (20), 192 (32), 191 (22), 179 (12), 178 (100), 177 (12); UV λ_{max} (EtOH) 225 nm (sh) (ϵ 15100), 286 (7730); λ_{max} (0.1 N aqueous NaOH) 243 (15700), 299 (9940); λ_{max} (0.1 N aqueous HCl) 223.5 (13900), 284 (6650); $^1\text{H-NMR}$ (CDCl_3) δ : 0.88 (3H, t, $J=6.5$ Hz, CCH_2Me), 3.81 and 3.85 (3H each, s, two OMe's), 4.06 (1H, d, $J=11.2$ Hz, $\text{H}_{(11)}$), 6.47, 6.55, 6.61, and 6.81 (1H each, s, aromatic protons). *Anal.* Calcd for $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_4 \cdot \text{H}_2\text{O}$: C, 68.91; H, 8.14; N, 5.95. Found: C, 69.03; H, 7.88; N, 5.61.

[2S-[2 α (R*)-3 β ,11 β]]-3-Ethyl-1,3,4,6,7,11b-hexahydro-9-hydroxy-2-(6-hydroxy-7-methoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl-10-methoxy-2H-benzo[*a*]quinolizine [(–)-9-Demethylisocephaline] [(–)-16]—Debenzylation of (–)-**18a** was effected as described above for (–)-**1**, and crude (–)-**16** was obtained in 73% yield as a yellowish solid. Recrystallization of the solid from EtOH–hexane (1:1, v/v) and drying over P_2O_5 at 2 mmHg and 50 °C for 10 h yielded an analytical sample of (–)-**16**·1/2EtOH as colorless minute needles, mp 178–180 °C; $[\alpha]_D^{12}$ –94.0° ($c=0.36$, CHCl_3); MS m/e : 452 (M^+); UV λ_{max} (EtOH) 225 nm (sh) (ϵ 14000), 285 (7780), 288 (7790); λ_{max} (0.1 N aqueous NaOH) 243 (16800), 299 (10100); λ_{max} (0.1 N aqueous HCl) 223.5 (13700), 284 (6760); $^1\text{H-NMR}$ (CDCl_3) δ : 0.94 (3H, t, $J=6.5$ Hz, CCH_2Me), 1.24 (1.5H, t, $J=7.0$ Hz, MeCH_2OH), 3.71 (1H, q, $J=7.0$ Hz, MeCH_2OH), 3.78 and 3.80 (3H each, s, two OMe's), 4.07 (1H, dull t, $J=5.2$ Hz, $\text{H}_{(11)}$), 6.45, 6.56, 6.61, and 6.63 (1H each, s, aromatic protons). *Anal.* Calcd for $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_4 \cdot 1/2\text{C}_2\text{H}_5\text{OH}$: C, 70.71; H, 8.26; N, 5.89. Found: C, 70.79; H, 8.25; N, 5.69.

[2S-[2 α (R*),3 β ,11 β]]-3-Ethyl-1,3,4,6,7,11b-hexahydro-10-hydroxy-2-(6-hydroxy-7-methoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl-9-methoxy-2H-benzo[*a*]quinolizine [(–)-10-Demethylisocephaline] [(–)-17]—The benzyl ether (–)-**18b** was debenzylated as described above for (–)-**1**, furnishing crude (–)-**17** in 77% yield as a faintly yellow solid. Recrystallization of the solid from EtOH and drying over P_2O_5 at 2 mmHg and 50 °C for 20 h gave (–)-**17**· H_2O as colorless needles, mp 114–116 °C; $[\alpha]_D^{17}$ –50.0° ($c=0.34$, CHCl_3); MS m/e : 452 (M^+); UV λ_{max} (EtOH) 225 nm (sh) (ϵ 14900), 286 (7770); λ_{max} (0.1 N aqueous NaOH) 243 (15700), 299.5 (10200); λ_{max} (0.1 N aqueous HCl) 224 (13800), 284 (6760); $^1\text{H-NMR}$ (CDCl_3) δ : 0.93 (3H, t, $J=6.8$ Hz, CCH_2Me), 3.83 and 3.84 (3H each, s, two OMe's), 3.97 (1H, dull t, $J=5.8$ Hz, $\text{H}_{(11)}$), 6.53, 6.61, 6.64, and 6.67 (1H each, s, aromatic protons). *Anal.* Calcd for $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_4 \cdot \text{H}_2\text{O}$: C, 68.91; H, 8.14; N, 5.95. Found: C, 68.86; H, 8.17; N, 5.67.

Acknowledgment The authors are grateful to Dr. S. C. Pakrashi (Calcutta) for a generous gift of copies of the UV, IR, and mass spectra of natural demethylcephaline, to Professor S. Yamada (Tokyo) for financial assistance in the form of a grant from the Japan Research Foundation for Optically Active Compounds, and to Professor T. Shioiri (Nagoya) for a gift of diethyl phosphorocyanidate.

References and Notes

- 1) Paper XV in this series, T. Fujii and M. Ohba, *Chem. Pharm. Bull.*, **33**, 4314 (1985).
- 2) A preliminary account of this work has been published: T. Fujii and M. Ohba, *Heterocycles*, **19**, 857 (1982).
- 3) S. C. Pakrashi and B. Achari, *Experientia*, **26**, 933 (1970).
- 4) Unless otherwise noted, the structural formulas of optically active compounds in this paper represent their absolute configurations.
- 5) For the "cincholoipon-incorporating route" leading to the chiral synthesis of the benzo[*a*]quinolizidine-type *Alangium* alkaloids, see references cited in refs. 7c and 14.
- 6) S. C. Pakrashi and E. Ali, *Tetrahedron Lett.*, **1967**, 2143.
- 7) a) T. Fujii, M. Ohba, S. C. Pakrashi, and E. Ali, *Tetrahedron Lett.*, **1979**, 4955; b) T. Fujii and M. Ohba, *Chem. Pharm. Bull.*, **33**, 144 (1985); c) *Idem, ibid.*, **33**, 583 (1985).
- 8) A. Popelak, E. Haack, and H. Spingler, *Tetrahedron Lett.*, **1966**, 1081.
- 9) a) M. Ohba, M. Hayashi, and T. Fujii, *Heterocycles*, **14**, 299 (1980); b) *Idem, Chem. Pharm. Bull.*, **33**, 3724 (1985).
- 10) T. Fujii, M. Ohba, A. Popelak, S. C. Pakrashi, and E. Ali, *Heterocycles*, **14**, 971 (1980).
- 11) a) E. Ali, R. R. Sinha, B. Achari, and S. C. Pakrashi, *Heterocycles*, **19**, 2301 (1982); b) T. Fujii, M. Ohba, H. Suzuki, S. C. Pakrashi, and E. Ali, *ibid.*, **19**, 2305 (1982).
- 12) A. R. Battersby and J. C. Turner, *J. Chem. Soc.*, **1960**, 717.
- 13) T. Fujii, H. Kogen, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.*, **33**, 1946 (1985).
- 14) a) T. Fujii, M. Ohba, and H. Suzuki, *Heterocycles*, **19**, 705 (1982); b) *Idem, Chem. Pharm. Bull.*, **33**, 1023 (1985).
- 15) T. Shioiri, Y. Yokoyama, Y. Kasai, and S. Yamada, *Tetrahedron*, **32**, 2211 (1976).
- 16) M. Tomita and H. Yamaguchi, *Yakugaku Zasshi*, **72**, 1219 (1952).
- 17) a) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); b) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).