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Quinolizidines. XII.¹⁾ Synthetic Incorporation of Ethyl Cincholoiponate into a Tricyclic Intermediate Adaptable to Chiral Syntheses of the 10-Hydroxy-9-methoxybenzo[*a*]quinolizidine-Type *Alangium* Alkaloids

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For the purpose of securing a key intermediate for chiral syntheses of the 10-hydroxy-9-methoxybenzo[*a*]quinolizidine-type *Alangium* alkaloids (type 4), the tricyclic ester (–)-15 has been synthesized from ethyl cincholoiponate [(+)-6] and 4-benzyloxy-3-methoxyphenacyl bromide by the “cincholoipon-incorporating method” through the intermediates (+)-7, 10, 8, (–)-11, (–)-12, (+)-13, (+)-14, (+)-17, and 16.

Keywords—*Alangium* alkaloid synthesis intermediate; cincholoipon ethyl ester; mercuric acetate–edetic acid oxidation; regioselective lactam formation; thermal *cis*–*trans* isomerization; sodium borohydride reduction; catalytic hydrogenolysis; Fischer–Speier esterification; phenolic *O*-benzylation; Bischler–Napieralski cyclization

Alangium lamarckii THWAITES (family Alangiaceae) is a deciduous shrub or small tree widely distributed throughout India, Burma, Ceylon, South China, Malaya, and the Philippines.^{2,3)} Various parts of this plant have been used in the indigenous Indian systems of medicine for a long time.^{2–4)} The plant has so far been found to contain seventeen benzo[*a*]quinolizidine alkaloids and nine other alkaloids.⁵⁾ These benzo[*a*]quinolizidine-type *Alangium* alkaloids fall into four categories according to their substitution patterns in the aromatic ring A: (a) 9,10-dimethoxy type (1) (*e.g.*, emetine, cephaeline, tubulosine, protoemetinol, *etc.*); (b) 8-hydroxy-9,10-dimethoxy type (2) (*i.e.*, ankorine, alangicine, and alangimarckine); (c) 9-hydroxy-10-methoxy type (3) (*e.g.*, desmethylpsychotrine, 9-demethylprotoemetinol, *etc.*); (d) 10-hydroxy-9-methoxy type (4) (*e.g.*, demethyltubulosine, 10-demethylprotoemetinol, *etc.*).⁵⁾ We have already shown that the racemic synthesis of all of these types of alkaloids is possible by the “lactim ether method”^{5–12)} and the chiral synthesis,

by the “cincholoipon-incorporating method”.^{1,5,9,12–16)} In this paper, we present the details of a study on the synthetic incorporation of ethyl cincholoiponate [(+)-6] into the tricyclic

ester (–)-**15**, a key intermediate for syntheses of the 4-type *Alangium* alkaloids. A preliminary account of this work has been reported.¹⁷⁾

Condensation of (+)-**6**,¹⁸⁾ prepared from commercially available cinchonine (**5**)¹⁹⁾ in 50% overall yield according to the classical degradation procedure,^{18a,20)} with 4-benzyloxy-3-methoxyphenacyl bromide in hot benzene containing K_2CO_3 furnished the amino ketone (+)-**7** in 98% yield. Reduction of (+)-**7** with $NaBH_4$ in EtOH gave a diastereomeric mixture of the amino alcohol **10** in 97% yield. Oxidation of the mixture **10** with mercuric acetate–

Chart 1

ethylenediaminetetraacetic acid (EDTA) in boiling 1% aqueous AcOH and column chromatographic separation of products afforded the 6-piperidone **8** as a diastereomeric mixture (53% yield) and an oily substance (15% yield) presumed^{1,13,14)} to be a diastereomeric mixture of the *cis*- and the *trans*-2-piperidones **9**. The two piperidone structures were assignable by analogy with the similar oxidation products of structurally analogous systems^{1,13,14)} and simpler 3-alkylpiperidine derivatives,²¹⁾ and the following self-consistent reaction sequence supported the correctness of these assignments.

Catalytic hydrogenolysis of the diastereomeric mixture of **8** with hydrogen activated on Pd–C catalyst in EtOH containing a little 70% perchloric acid produced the lactam phenol (–)-**11** in 99% yield. On hydrolysis with 2N aqueous NaOH in EtOH at 25 °C, (–)-**11** gave the *cis*-lactam acid (–)-**12** in 98% yield. Thermal isomerization of (–)-**12** to the *trans*-lactam acid (+)-**13** was patterned after those reported previously^{1,13,14,22)} for structurally parallel systems. Thus, (–)-**12** was heated neat at 180 °C for 90 min to form an equilibrated mixture of the *cis* and the *trans* isomers,²²⁾ from which the *trans*-lactam acid (+)-**13** was isolated by crystallization. The yield of (+)-**13** reached 74% when the *cis*-lactam acid recovered from the reaction mixture was repeatedly subjected to the same thermal reaction. On treatment with ethanolic HCl under the previously reported Fischer–Speier esterification conditions,²³⁾ (+)-**13** gave the lactam ester (+)-**14** in 99% yield. The structure of (+)-**14** was confirmed by the spectral and thin-layer chromatographic (TLC) identity of this chiral compound with the known racemic *trans*-lactam ester (±)-**14**.¹⁰⁾

Conversion of (+)-**14** into the benzyl ether (+)-**17** was effected in 96% yield by treatment of the former with benzyl bromide and K_2CO_3 in boiling acetone. Compound (+)-**17** was then cyclized with $POCl_3$ in boiling toluene, and the resulting iminium salt **16** was

hydrogenated in EtOH with hydrogen and Adams catalyst to produce the desired tricyclic ester (–)-**15** in 70% overall yield from (+)-**17**. The TLC behavior and the solution infrared (IR) and nuclear magnetic resonance (NMR) spectra of (+)-**17** and (–)-**15** thus obtained were identical with those of the corresponding racemic varieties,¹⁰⁾ substantiating the assigned structures and stereochemistry.

In conclusion, the key intermediate (–)-**15** for chiral syntheses of the 10-hydroxy-9-methoxybenzo[*a*]quinolizidine-type *Alangium* alkaloids (type **4**) has now become available from ethyl cincholoiponate [(+)-**6**] in 24% overall yield through the above “cincholoipon-incorporating route.” We have synthesized (–)-10-demethylcephaeline¹⁶⁾ and (–)-10-demethylprotoemetinol¹²⁾ from this intermediate, and the details will be reported elsewhere in the near future.

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 Na_2SO_4 and concentrated under reduced pressure. Spectra reported herein were recorded on a JASCO IRA-2 IR spectrophotometer, a JEOL JMS-01SG mass spectrometer, or a JEOL JNM-FX-100 NMR spectrometer at 24°C with Me_4Si as an internal standard. Optical rotations were measured with a JASCO DIP-SL polarimeter. 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-doubles, m = multiplet, q = quartet, s = singlet, t = triplet.

(3*R*,4*S*)-(+)-1-(4-Benzyloxy-3-methoxyphenacyl)-3-ethyl-4-piperidineacetic Acid Ethyl Ester [(+)-7**]**—A mixture of ethyl cincholoiponate [(+)-**6**]^{18a,20)} (4.98 g, 25 mmol), anhydrous K_2CO_3 (3.46 g, 25 mmol), 4-benzyloxy-3-methoxyphenacyl bromide²⁴⁾ (8.38 g, 25 mmol), and benzene (100 ml) was stirred at 50–55°C for 7 h. After cooling, the reaction mixture was washed successively with H_2O , 5% aqueous NaOH, and saturated aqueous NaCl, dried over anhydrous K_2CO_3 , and concentrated *in vacuo* to leave a reddish-brown oil (11.1 g, 98%). A portion of the oil was purified by column chromatography [alumina, hexane–AcOEt (3:1, v/v)] to give (+)-**7** as a pale yellow oil, $[\alpha]_{\text{D}}^{25} + 3.7^\circ$ ($c = 2.71$, EtOH); mass spectra (MS) m/e : 453 (M^+); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1726 (ester CO), 1670 (ArCO); NMR (CDCl_3) δ : 0.84 (3H, t, $J = 7.1$ Hz, CCH_2Me), 1.25 (3H, t, $J = 7.1$ Hz, OCH_2Me), 3.69 (2H, s, ArCOCH_2), 3.93 (3H, s, OMe), 4.13 (2H, q, $J = 7.1$ Hz, OCH_2Me), 5.22 (2H, s, OCH_2Ph), 6.87 (1H, d, $J = 9.0$ Hz, $\text{H}_{(5')}$), 7.25–7.5 (5H, m, Ph), 7.62 (1H, d, $J = 2.0$ Hz, $\text{H}_{(2')}$), 7.64 (1H, dd, $J = 9.0$ and 2.0 Hz, $\text{H}_{(6')}$).

(3*R*,4*S*)-1-[2-(4-Benzyloxy-3-methoxyphenyl)-2-hydroxyethyl]-3-ethyl-4-piperidineacetic Acid Ethyl Ester (10**)**

—A solution of (+)-7 (6.26 g, 13.8 mmol) in EtOH (60 ml) was stirred under ice-cooling, and NaBH₄ (522 mg, 13.8 mmol) was added portionwise over a period of 10 min. After stirring was continued at 0–5 °C for 2 h and then at room temperature for 6 h, acetone (3 ml) was added and the mixture was concentrated *in vacuo*. The residual yellow jelly was partitioned between H₂O and benzene. The benzene extracts were washed with saturated aqueous NaCl, dried over anhydrous K₂CO₃, and concentrated to leave a diastereomeric mixture of **10** (6.07 g, 97%) as a faintly yellowish solid, mp 45–70 °C; $[\alpha]_D^{18} -1.6^\circ$ ($c=2.55$, EtOH); MS m/e : 455 (M⁺); IR $\nu_{\max}^{\text{CHCl}_3} \text{ cm}^{-1}$: 3430 (OH), 1726 (ester CO); NMR (CDCl₃) δ : 0.93 (3H, t, $J=7.1$ Hz, CCH₂Me), 1.26 (3H, t, $J=7.1$ Hz, OCH₂Me), 3.1 (1H, br, OH), 3.90 (3H, s, OMe), 4.14 (2H, q, $J=7.1$ Hz, OCH₂Me), 4.55–4.75 [1H, m, ArCH(OH)], 5.14 (2H, s, OCH₂Ph), 6.7–7.0 (3H, m, aromatic protons), 7.2–7.5 (5H, m, Ph). Recrystallization of the solid from hexane–AcOEt (10:1, v/v) yielded an analytical sample, whose diastereomeric purity was undetermined, as colorless plates, mp 92–93 °C; $[\alpha]_D^{22} +16.0^\circ$ ($c=1.50$, EtOH); IR $\nu_{\max}^{\text{Nujol}} \text{ cm}^{-1}$: 3420 (OH), 1724 (ester CO). Anal. Calcd for C₂₇H₃₇NO₅: C, 71.18; H, 8.19; N, 3.07. Found: C, 70.92; H, 8.16; N, 3.34.

(4S,5R)-1-[2-(4-Benzyloxy-3-methoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (8)—A stirred mixture of **10** (1.02 g, 2.24 mmol), 1% aqueous AcOH (16 ml), disodium ethylenediaminetetraacetate dihydrate (2.09 g, 5.6 mmol), and Hg(OAc)₂ (1.79 g, 5.6 mmol) was heated under reflux for 90 min. After cooling, the reaction mixture was extracted with CHCl₃, and the CHCl₃ extracts were washed sequentially with 5% aqueous HCl, H₂O, saturated aqueous NaHCO₃, and saturated aqueous NaCl, dried, and concentrated to leave a reddish oil. The residue was dissolved in a little CHCl₃, and the solution was passed through a column packed with alumina (10 g). The column was eluted with CHCl₃ and the eluate was evaporated *in vacuo* to leave a reddish-brown oil (965 mg), shown to be a mixture of at least three components on TLC analysis [silica gel, hexane–AcOEt (1:3, v/v)]. The oil was then chromatographed on silica gel using hexane–AcOEt (1:3, v/v) as eluent. Earlier fractions gave an orange oil (94 mg, 8.2%) presumed²⁵ to be a mixture of the diastereomeric acetates of **9**, $[\alpha]_D^{25} +12.4^\circ$ ($c=1.71$, EtOH); MS m/e : 511 (M⁺); IR $\nu_{\max}^{\text{CHCl}_3} \text{ cm}^{-1}$: 1730 (ester CO), 1632 (lactam CO); NMR (CDCl₃) δ : 0.83, 0.91, and 0.99 (3H, t each, $J=7.5$ Hz, diastereomeric *cis*- and *trans*-CCH₂Me's), 1.26 (3H, t, $J=7.2$ Hz, OCH₂Me), 2.06 (3H, s, OCOMe), 3.90 (3H, s, OMe), 4.14 (2H, q, $J=7.2$ Hz, OCH₂Me), 5.13 (2H, s, OCH₂Ph), 5.9–6.1 [1H, m, ArCH(OAc)], 6.75–6.95 (3H, m, aromatic protons), 7.2–7.5 (5H, m, Ph). The middle fractions afforded an orange oil (231 mg), which produced, after repeated chromatography under different conditions [alumina, hexane–CHCl₃ (1:3, v/v)], a yellow oil (41 mg, 3.6%) presumed²⁵ to be a diastereomeric mixture of the acetate of **8**, $[\alpha]_D^{25} +2.1^\circ$ ($c=1.58$, EtOH); MS m/e : 511 (M⁺); IR $\nu_{\max}^{\text{CHCl}_3} \text{ cm}^{-1}$: 1730 (ester CO), 1635 (lactam CO); NMR (CDCl₃) δ : 0.90 (3H, t, $J=7.0$ Hz, CCH₂Me), 1.26 (3H, t, $J=7.2$ Hz, OCH₂Me), 2.07 (3H, s, OCOMe), 3.90 (3H, s, OMe), 4.13 (2H, q, $J=7.2$ Hz, OCH₂Me), 5.14 (2H, s, OCH₂Ph), 5.9–6.1 [1H, m, ArCH(OAc)], 6.75–6.95 (3H, m, aromatic protons), 7.2–7.5 (5H, m, Ph), and yet another yellow oil (157 mg, 15%) presumed^{1,13,14} to be a diastereomeric mixture of the *cis*- and the *trans*-2-piperidones **9**, $[\alpha]_D^{18} +10.3^\circ$ ($c=2.00$, EtOH); MS m/e : 469 (M⁺); IR $\nu_{\max}^{\text{CHCl}_3} \text{ cm}^{-1}$: 3350 (OH), 1726 (ester CO), 1610 (lactam CO); NMR (CDCl₃) δ : 0.92 and 1.01 (3H, t each, $J=7.2$ and 7.4 Hz, diastereomeric CCH₂Me's), 1.26 (3H, t, $J=7.1$ Hz, OCH₂Me), 3.89 (3H, s, OMe), 4.13 (2H, q, $J=7.1$ Hz, OCH₂Me), 4.8–5.0 [1H, m, ArCH(OH)], 5.14 (2H, s, OCH₂Ph), 6.7–7.0 (3H, m, aromatic protons), 7.2–7.5 (5H, m, Ph).

Later fractions eluted in the first chromatography [silica gel, hexane–AcOEt (1:3, v/v)] furnished the 6-piperidone **8** (559 mg, 53%) as a faintly orange oil, $[\alpha]_D^{25} -9.6^\circ$ ($c=2.00$, EtOH); MS m/e : 469 (M⁺); IR $\nu_{\max}^{\text{CHCl}_3} \text{ cm}^{-1}$: 3350 (OH), 1726 (ester CO), 1618 (lactam CO); NMR (CDCl₃) δ : 0.83 and 0.86 (3H, t each, $J=6.5$ Hz, diastereomeric CCH₂Me's), 1.26 (3H, t, $J=7.1$ Hz, OCH₂Me), 3.90 (3H, s, OMe), 4.14 (2H, q, $J=7.1$ Hz, OCH₂Me), 4.50 and 4.66 (1H, d each, $J=4.4$ Hz, diastereomeric OH's), 4.8–5.0 [1H, m, ArCH(OH)], 5.14 (2H, s, OCH₂Ph), 6.7–7.05 (3H, m, aromatic protons), 7.2–7.5 (5H, m, Ph).

(4S,5R)-(-)-5-Ethyl-1-(4-hydroxy-3-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid Ethyl Ester [(–)-11]—A solution of **8** (15.4 g, 32.8 mmol) in EtOH (200 ml) containing 70% perchloric acid (3.3 ml) was hydrogenated over 10% Pd–C (5.0 g) at atmospheric pressure and 35 °C for 16 h. The reaction mixture was worked up as described recently¹ for the 1-(3-hydroxy-4-methoxyphenethyl) isomer, giving (–)-**11** (11.8 g, 99%) as an orange oil, $[\alpha]_D^{25} -5.7^\circ$ ($c=2.00$, EtOH); MS m/e : 363 (M⁺); IR $\nu_{\max}^{\text{CHCl}_3} \text{ cm}^{-1}$: 3570 (OH), 1726 (ester CO), 1625 (lactam CO); NMR (CDCl₃) δ : 0.88 (3H, t, $J=7.1$ Hz, CCH₂Me), 1.26 (3H, t, $J=7.2$ Hz, OCH₂Me), 3.87 (3H, s, OMe), 4.13 (2H, q, $J=7.2$ Hz, OCH₂Me), 5.75 (1H, s, OH), 6.68 (1H, dd, $J=7.8$ and 1.7 Hz, H_(6r)), 6.75 (1H, d, $J=1.7$ Hz, H_(2r)), 6.85 (1H, d, $J=7.8$ Hz, H_(5r)).

(4S,5R)-(-)-5-Ethyl-1-(4-hydroxy-3-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid [(–)-12]—A solution of (–)-**11** (11.7 g, 32.2 mmol) and 2N aqueous NaOH (55 ml) in EtOH (110 ml) was stirred at 25 °C for 24 h. The reaction mixture was then worked up as reported recently¹ for the 1-(3-hydroxy-4-methoxyphenethyl) isomer, and (–)-**12** (10.6 g, 98%) was obtained as an orange, glassy gum, $[\alpha]_D^{24} -0.2^\circ$ ($c=2.00$, EtOH); MS m/e : 335 (M⁺); IR $\nu_{\max}^{\text{CHCl}_3} \text{ cm}^{-1}$: 3570 (OH), 1711 (CO₂H), 1598 (lactam CO); NMR (CDCl₃) δ : 0.87 (3H, t, $J=7.0$ Hz, CCH₂Me), 3.86 (3H, s, OMe), 6.67 (1H, dd, $J=7.8$ and 2.0 Hz, H_(6r)), 6.74 (1H, d, $J=2.0$ Hz, H_(2r)), 6.84 (1H, d, $J=7.8$ Hz, H_(5r)), 7.8 (2H, br, OH and CO₂H).

(4R,5R)-(+)-5-Ethyl-1-(4-hydroxy-3-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 (25 ml), and the solution was kept in a

refrigerator. The pale brownish pillars that resulted were collected by filtration to give (+)-**13** (3.96 g). The filtrate was concentrated to dryness *in vacuo*, and the residue was again heated at 180°C for 90 min and worked up as described above. This procedure was repeated 3 more times to raise the yield of (+)-**13** to 74%. Recrystallization of the above pillars from AcOEt yielded an analytical sample as faintly brownish pillars, mp 122.5–123°C; $[\alpha]_D^{16} + 68.0^\circ$ ($c=0.500$, EtOH); IR $\nu_{\max}^{\text{CHCl}_3}$ cm⁻¹: 3570 (OH), 1714 (CO₂H), 1601 (lactam CO); NMR (CDCl₃) δ : 0.81 (3H, t, $J=7.0$ Hz, CCH₂Me), 3.87 (3H, s, OMe), 6.67 (1H, dd, $J=8.1$ and 2.0 Hz, H_(6')), 6.73 (1H, d, $J=2.0$ Hz, H_(2')), 6.84 (1H, d, $J=8.1$ Hz, H_(5')). *Anal.* Calcd for C₁₈H₂₅NO₅: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.46; H, 7.57; N, 4.16.

(4R,5R)-(+)-5-Ethyl-1-(4-hydroxy-3-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-14**]**—A solution of (+)-**13** (6.20 g, 18.5 mmol) in 10% (w/w) ethanolic HCl (120 ml) was stirred at 15°C for 24 h. The reaction mixture was worked up as described recently¹⁾ for the 1-(3-hydroxy-4-methoxyphenethyl) isomer, producing (+)-**14** (6.65 g, 99%) as an orange oil, $[\alpha]_D^{16} + 66.8^\circ$ ($c=0.500$, EtOH); MS m/e : 363 (M⁺). The IR (CHCl₃) and NMR (CDCl₃) spectra and TLC behavior of this sample were identical with those of authentic (±)-**14**.¹⁰⁾

(4R,5R)-(+)-1-(4-Benzoyloxy-3-methoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-17**]**—A stirred mixture of (+)-**14** (6.40 g, 17.6 mmol), anhydrous K₂CO₃ (2.92 g, 21.1 mmol), benzyl bromide (3.60 g, 21.0 mmol), and acetone (80 ml) was heated under reflux for 26 h. The reaction mixture was then worked up as described recently¹⁰⁾ for the corresponding racemic variety, and (+)-**17** (7.64 g, 96%) was obtained as a yellow oil, $[\alpha]_D^{15} + 55.0^\circ$ ($c=0.500$, EtOH); MS m/e : 453 (M⁺). The IR (CHCl₃) and NMR (CDCl₃) spectra and TLC behavior of this oil were identical with those of authentic (±)-**17**.¹⁰⁾

(2R,3R)-10-Benzoyloxy-2-ethoxycarbonylmethyl-3-ethyl-1,2,3,4,6,7-hexahydro-9-methoxybenzo[*a*]quinolizinium Chloride (16**)**—A solution of (+)-**17** (2.04 g, 4.5 mmol) and POCl₃ (3.45 g, 22.5 mmol) in dry toluene (21 ml) was heated under reflux for 90 min. The reaction mixture was worked up as described recently¹⁰⁾ for the racemic series, giving **16** (2.48 g) as a brown oil. This oil was directly used in the next hydrogenation step without further purification.

(2R,3R,11bS)-(-)-10-Benzoyloxy-3-ethyl-1,3,4,6,7,11b-hexahydro-9-methoxy-2H-benzo[*a*]quinolizine-2-acetic Acid Ethyl Ester [(-)-15**]**—A solution of the total amount of crude **16** described above in EtOH (35 ml) was hydrogenated over Adams catalyst (180 mg) at atmospheric pressure and room temperature for 60 min. The reaction mixture was then worked up in a manner similar to that described recently¹⁾ for the 9-benzoyloxy-10-methoxy isomer, and the resulting brown solid (1.63 g) was recrystallized from ether to give (-)-**15** (1.38 g, 70%). Further recrystallization from ether furnished an analytical sample as faintly yellow needles, mp 99–99.5°C; $[\alpha]_D^{16} - 46.0^\circ$ ($c=0.500$, EtOH). *Anal.* Calcd for C₂₇H₃₅NO₄: C, 74.11; H, 8.06; N, 3.20. Found: C, 74.02; H, 8.08; N, 3.22. The IR (CHCl₃) and NMR (CDCl₃) spectra and TLC behavior of this sample were identical with those of authentic (±)-**15**.¹⁰⁾

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