CHIRAL SYNTHESES OF BENZO[a]QUINOLIZIDINE-TYPE ALANGIUM ALKALOIDS

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Abstract —— Nineteen benzo[a]quinolizidine alkaloids isolated so far from Alangium plants are structurally classified into four types (I–IV), and studies on chiral syntheses of these I–IV-type alkaloids are reviewed with particular emphasis on the synthetic strategies and tactics employed. It has been found that chiral syntheses of all of these types of alkaloids are possible through the "cincholoipon-incorporating route" or the "lactim ether route", and the absolute configurations of four II-type, two III-type, and one IV-type alkaloids have been established by such syntheses. An extension of the "lactim ether route" to the synthesis of (−)-ochropposinine [(−)-**99g**] has unequivocally established the absolute stereochemistry of this Ochrosia alkaloid.

CONTENTS

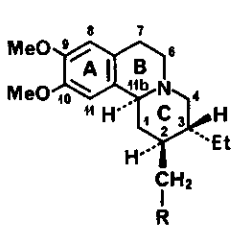
I. INTRODUCTION

It is known that 22 species of the genus Alangium constitute a monogeneric plant family, Alangiaceae.[1] Several of these species have been investigated chemically, and the Indian medicinal plant Alangium lamarckii Thwaites, a deciduous shrub or small tree widely distributed throughout India, Sri Lanka, Burma, South China, Malaya, and the Philippines,[1,2] was found to be a particularly rich source of alkaloids.[3] The chemical structures of all of the 19 benzo[a]quinolizidine alkaloids and 15 other alkaloids isolated so far from various parts of A. lamarckii and other species of the same genus are shown in formulas **1** – **34**[3–8] (see Table I and Fig. 1), where the alkaloids from A. lamarckii are marked with an asterisk and those from the other species with a dagger.

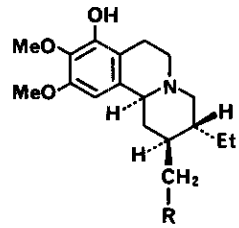
Of these Alangium alkaloids, the benzo[a]quinolizidine-type alkaloids **1** – **19** may be structurally classified into four groups according to their substitution patterns in the aromatic ring A: (i) 9,10-dimethoxy type (I), (ii) 8-hydroxy-9,10-dimethoxy type (II), (iii) 9-hydroxy-10-methoxy type (III), and (iv) 10-hydroxy-9-methoxy type (IV).[9] Thus, type I embraces nine alkaloids; type II, four; type III, four or three; and type IV, two or three (Table I). Among the I-type alkaloids are emetine (**1**), cephaeline (**2**), and psychotrine (**6**), which also occur in ipecacuanha plants (family Rubiaceae),[3] and synthetic routes to most of the I–IV-type alkaloids had been well established by the time when the ipecac alkaloids and β-carboline congeners were reviewed by us in 1983.[3a] In the present article, however, the unified chiral syntheses of all of these types of alkaloids, developed and utilized for the determination of the absolute configurations of most of the II–IV-type alkaloids, will be reviewed by placing major emphasis on the synthetic strategies and tactics employed, with coverage of the literature through the late part of 1987.

II. THE CINCHOLOIPON-INCORPORATING ROUTE

At the inception of our studies on unified chiral syntheses of the I–IV-type alkaloids, analysis of structural features in I–IV led to the recognition of the 3-ethyl-4-piperidineacetic acid skeleton **35** as one of the most efficient, common key synthons corresponding to the ring C moiety. An appropriate chiral form of this synthon would be cincholoipon ethyl ester [(+)-**36**],[10] a degradation product of the major Cinchona alkaloids (**37**),[11] because (i) it already carries the skeleton and side chains necessary for ring C of I–IV apart from the wrong configuration at C-4 and (ii) it is easily obtainable from commercial (+)-cinchonine (**38**), one of the major Cinchona alkaloids (**37**), as described in Section II, A.



I



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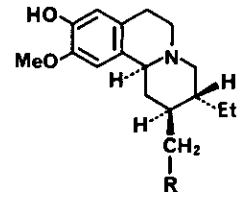

III

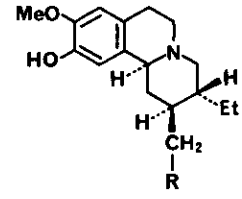

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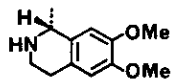
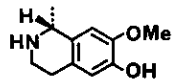
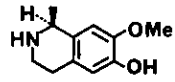
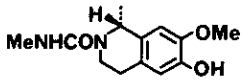
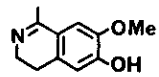
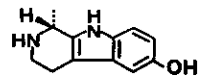
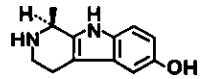
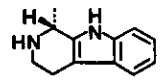
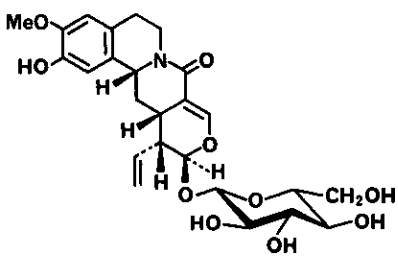
Table I. Benzo[a]quinolizidine-Type Alangium Alkaloids

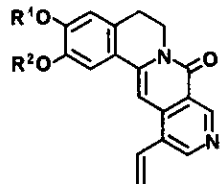
R	Type I	Type II	Type III	Type IV
	**1** Emetine*, a)	———	———	———
	**2** Cephaeline*, †	———	**3** Demethylcephaeline* (Type III or IV)	
	**4** Isocephaeline*	———	———	———
	**5** Alangamide*, b)	———	———	———
	**6** Psychotrine*, †	**7** Alangicine*	**8** 9-Demethyl-psychotrine*	———
	**9** Tubulosine*	———	**10** 9-Demethyl-tubulosine†	**11** 10-Demethyl-tubulosine*
	**12** Isotubulosine*	———	———	———
	**13** Deoxy-tubulosine*	**14** Alangi-marckine*	———	———
CH_2OH	**15** Protoemetinol*	**16** Ankorine*, †	**17** 9-Demethyl-protoemetinol*	**18** 10-Demethyl-protoemetinol*
CO_2H	———	**19** Alancine*	———	———

a) * A. lamarckii alkaloids, † Alkaloids from other species of Alangium.

b) Probably an artifact.

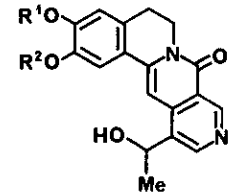


20 Alangiside*



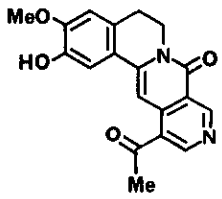
21 Alangimarine*
R^1 = Me, R^2 = H

22 Isoalangimarine*
R^1 = H, R^2 = Me

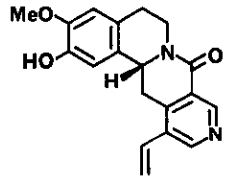


23 Alamarine* (racemic)
R^1 = Me, R^2 = H

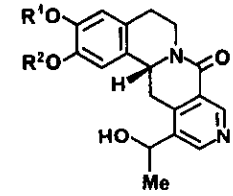
24 Isoalamarine*
R^1 = H, R^2 = Me



25 Alangimarinone*

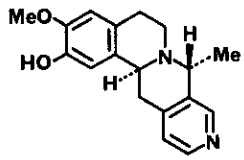


26 Alangimaridine*

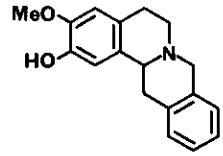


27 Dihydroalamarine*
R^1 = Me, R^2 = H

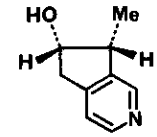
28 Dihydroisoalamarine*
R^1 = H, R^2 = Me



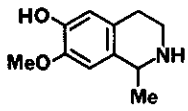
29 Alamaridine* (relative configuration shown)



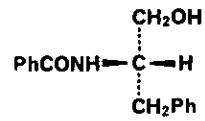
30 Bharatamine* (racemic)



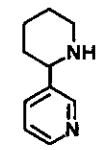
31 Venoterpine*,†



32 (±)-Salsoline*

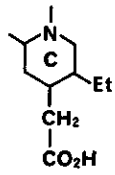


33 N-Benzoyl-L-phenylalaninol*

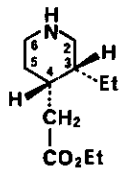


34 (±)-Anabasine†

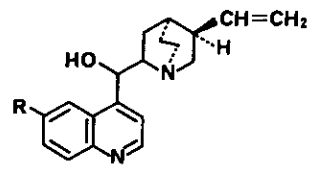
Fig. 1. Other Alangium Alkaloids (* A. lamarckii alkaloids, † Alkaloids from other species of Alangium)



35



(+)-36

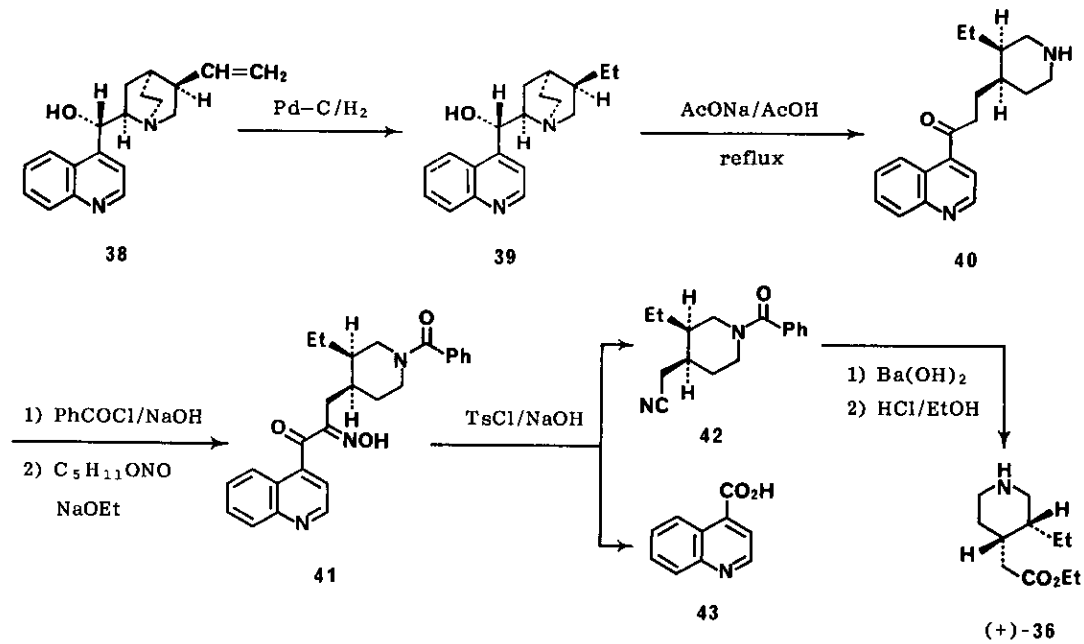


37 R = H or MeO

If chirality could be conserved at C-3 and C-4 in a reaction sequence starting with (+)-**36** (hence the sequence may be called the "cincholoipon-incorporating route"), many difficulties in stereochemical control and resolution of racemized intermediates could be avoided.[12] Such synthetic strategy required the following five main operations: (i) introduction of an appropriate phenethyl skeleton into (+)-**36** at N-1; (ii) generation of the lactam carbonyl function at C-6; (iii) alteration of the stereochemistry at C-4 to produce the 3,4-trans configuration that must match the relative and absolute configurations of the I–IV-type alkaloids at the 3- and 2-positions; (iv) cyclization to form the benzo[a]quinolizidine system; and (v) modification of the acetate side chain. The sequel will be marked under Subsections A–F.

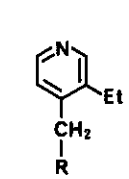
A. Preparation of Cincholoipon Ethyl Ester

As described above, cincholoipon ethyl ester [(+)-**36**] was selected as the common starting material



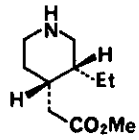
38 39 40 41 42 43 (+)-36

Scheme 1



44 R = H

45 R = CO_2Me



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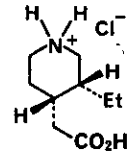

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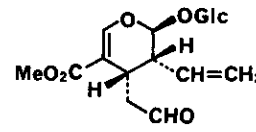


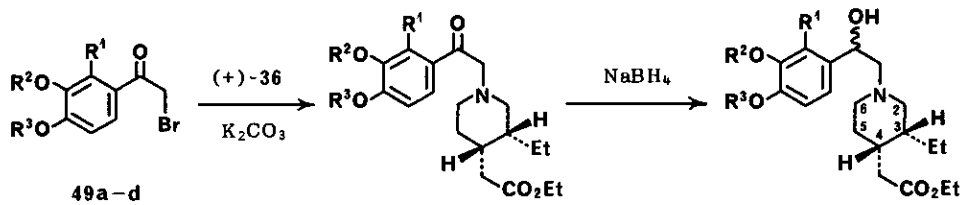
48

for unified chiral syntheses of the I–IV-type Alangium alkaloids. It was prepared in fairly large quantities from commercially available (+)-cinchonine (**38**) in 50% overall yield[13] according to the classical seven-step degradation procedure [**38** → **39** → **40** →→ **41** → **42** →→ (+)-**36** (Scheme 1)],[10a,14] which featured cleavage of the quinuclidine moiety by the so-called hydramine fission (**39** → **40**) as well as disconnection of the resulting piperidine moiety from the quinoline moiety by the "second-order" Beckmann rearrangement (**41** → **42** + **43**).

A few reports on the synthesis of related compounds have appeared: Uskoković's group[15] reported the preparation of cincholoipon methyl ester (**46**) from β-collidine (**44**) via a route involving methoxycarbonylation of **44**, catalytic hydrogenation of the resulting 4-pyridineacetate **45** to give (±)-cincholoipon methyl ester [(±)-**46**], and optical resolution of (±)-**46** with d-tartaric acid. Brown's group[16] reported an eight-step, stereoconservative synthesis of cincholoipon hydrochloride (**47**) from secologanin (**48**).

B. Introduction of a Phenethyl Skeleton at N-1

Operation i required for the "cincholoipon-incorporating strategy" is to introduce an appropriate phenethyl skeleton into (+)-**36** at N-1. Thus, the ring-oxygenated phenacyl bromides **49a–d**,[17] appropriate forms of the requisite phenethyl synthon, were condensed with (+)-**36** in benzene containing K_2CO_3



49a–d **50a–d** **51a–d**

a R^1 = H, R^2 = R^3 = Me **b** R^1 = OCH_2Ph, R^2 = R^3 = Me

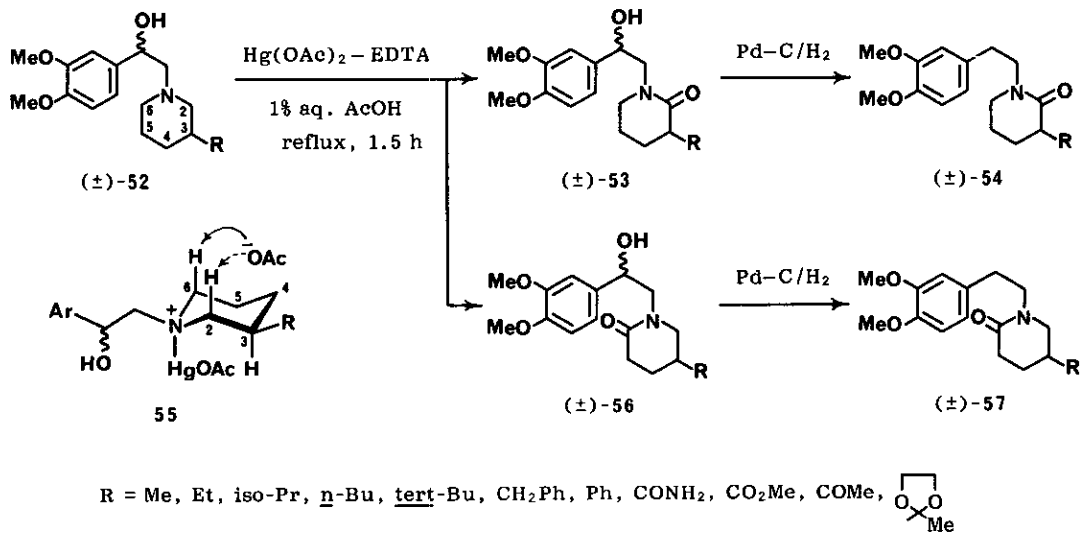
c R^1 = H, R^2 = CH_2Ph, R^3 = Me **d** R^1 = H, R^2 = Me, R^3 = CH_2Ph

Scheme 2

to give the amino ketones **50a-d** in good yields.[18–21] On reduction with $NaBH_4$ in EtOH, **50a-d** afforded diastereomeric mixtures of the amino alcohols **51a-d** in good yields.[18–21] As pointed out in the literature,[22] the presence of the benzylic hydroxy group constituting the 2-piperidinoethanol structure in **51a-d** was essential to the generation of the lactam carbonyl function in the subsequent mercuric acetate–edetic acid (EDTA) oxidation step.[23]

C. Generation of the Lactam Carbonyl Function at C-6

One of the key operations in the "cincholoipon-incorporating route" is the mercuric acetate–EDTA oxidation of the N-substituted cincholoipon ester derivatives **51a-d** to produce the 6-piperidone derivatives **59a-d** (operation ii). Because of the unsymmetrical structures of **51a-d** with respect to the piperidine ring, this operation required some preliminary experiments to determine the effect of the C(3)-ethyl group on the regioselectivity in such functionalization. Thus, the model compounds (±)-**52** were treated with mercuric acetate–EDTA in boiling 1% aqueous AcOH for 1.5 h, and a quantitative



R = Me, Et, iso-Pr, n-Bu, tert-Bu, CH_2Ph, Ph, $CONH_2$, CO_2Me, COMe,

Scheme 3

analytical work to determine the isomer ratios of the 3-substituted 2- [type (±)-**53**] and 6-piperidones [type (±)-**56**] that formed was carried out. The structures of (±)-**53** and (±)-**56** were confirmed by hydrogenolysis using hydrogen and Pd–C catalyst, which led to the known 2- [type (±)-**54**] and 6-piperidone derivatives [type (±)-**57**]. The results[24–28] are summarized in Table II. It may be seen that all the hydrocarbon groups at the 3-position orient the oxidation to both the 2- and 6-positions, but with advantage to the 6-position. A bulkier alkyl substituent tends to cause the extent of the 6-oxidation to increase. Comparison of the results from the 3-isopropyl derivative [(±)-**52** (R = iso-Pr)]

Table II. The Mercuric Acetate–EDTA Oxidation of 1,3-Disubstituted Piperidines [(±)-**52**]

Starting material [(±)-52] R	Product: Combined yield (%)	Product: % 2-oxidation (±)-53	Product: % 6-oxidation (±)-56	Reference
Me	75	45	55	*24*
Et	76	46	54	*24*
n-Bu	82	41	59	*25*
iso-Pr	86	29	71	*25*
$PhCH_2$	84	26	74	*25*
Ph	71	15	85	*25*
tert-Bu	79	2	98	*27*
$CONH_2$	71[a]	4	96	*26*
CO_2Me	80[a]	0	100	*26*
COMe	90	10[b]	90	*26, 28*
	66	0	100[c]	*26*

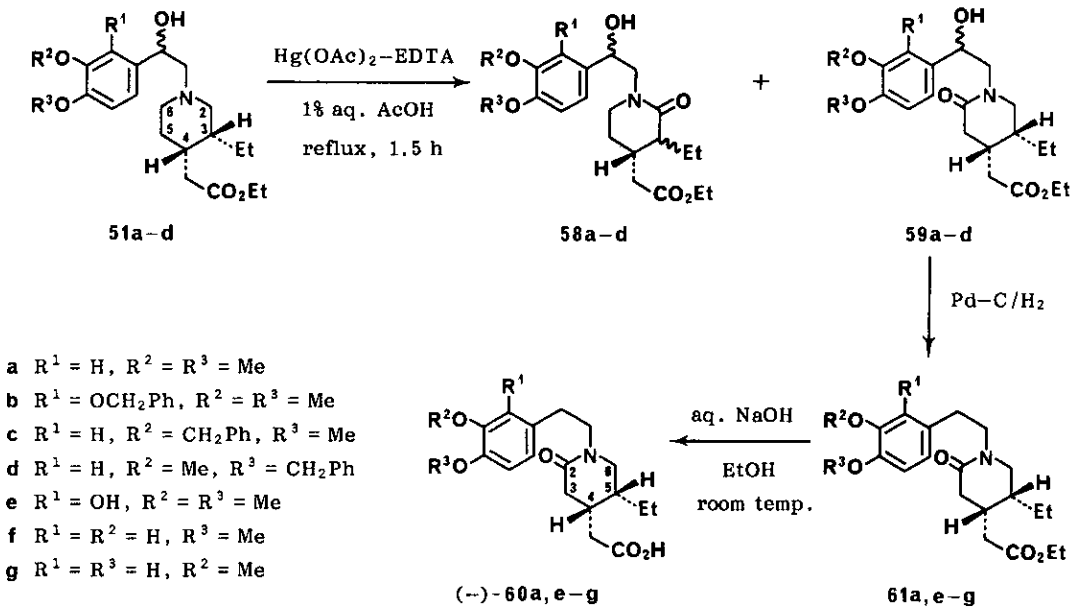
a) Overall yield from the piperidinoethanol stage [type (±)-52] to the lactam stage [(±)-54, (±)-57] through the lactam alcohol stage [(±)-53, (±)-56].

b) The product isolated was not the piperidone (±)-53 (R = COMe), but 1-[2-(3,4-dimethoxyphenyl)-2-hydroxyethyl]-1,2,3,4-tetrahydro-5-pyridyl methyl ketone.[28]

c) Obtained as a mixture of the ketone derivative [(±)-56 (R = COMe)] and the ketal derivative.

with those from the 3-phenyl derivative [(±)-**52** (R = Ph)] suggests that an electrostatic factor may be also important. In the carbonyl function series, a 3-substituent orients the oxidation almost exclusively to the 6-position, suggesting the importance of an electrostatic factor as well as a steric factor. On the basis of the postulated mechanism of the mercuric acetate oxidation of cyclic amines[29] and piperidinoalcohols,[22] we have proposed that in the above oxidation of (±)-**52** the possible factors involved in determining its regioselectivity may be steric and electrostatic repulsions, which should be operative between the 3-substituent and the acetate ion approaching the axial C(2)-H atom of the mercurated complex **55** formed at the first stage.[25,26]

The regioselectivity observed for the oxidation of the 3-ethyl derivative [(±)-**52** (R = Et)] was not sufficiently high, but it was still encouragingly in favor of the desired 6-oxidation. To our surprise,

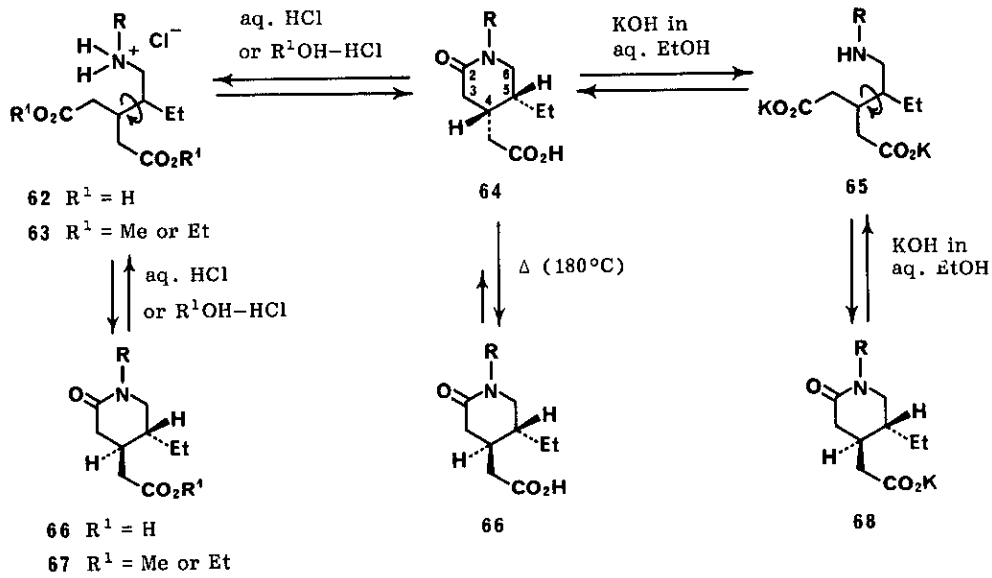


Scheme 4

such regioselectivity was enhanced when the same oxidation method was applied to the 3-ethyl analogues with a benzyloxy group in the aryl moiety and to the original compounds **51a–d** which carried the cis acetate chain at the 4-position.[30] Thus, **51a–d** were separately oxidized with mercuric acetate–EDTA in boiling 1% aqueous AcOH for 1.5 h to afford the 6-piperidones **59a–d** (as diastereomeric mixtures) in moderate yields, together with small amounts of oily substances presumed to be diastereomeric mixtures of the cis- and trans-2-piperidones **58a–d**.[18–21] Catalytic hydrogenolysis of **59a–d** with hydrogen activated on Pd–C catalyst gave the cis lactam esters **61a,e–g**, which were converted into the cis lactam acids (–)-**60a,e–g** by alkaline hydrolysis at room temperature.[18–21]

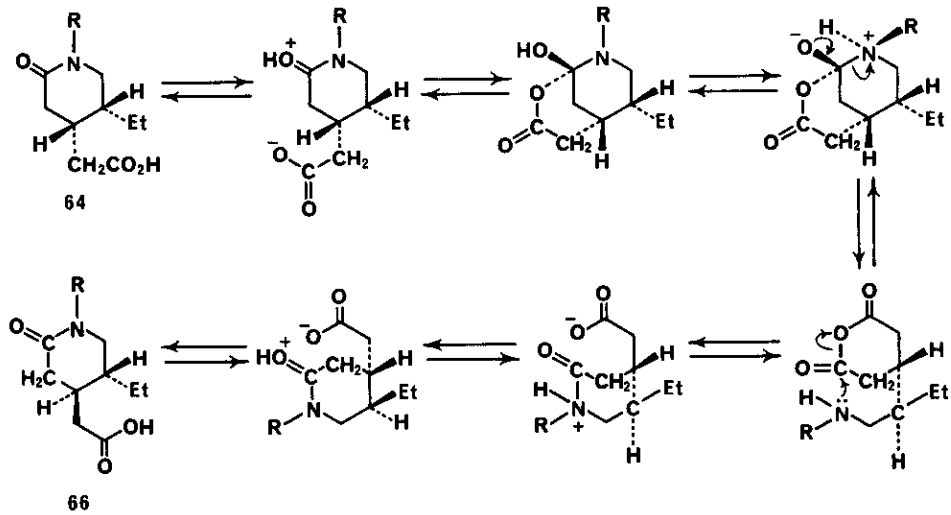
D. Alteration of the Stereochemistry at C-4

Another key operation in the "cincholoipon-incorporating strategy" is to alter the absolute configurations of the cis lactam acids (–)-**60a,e–g** at C-4 from (S) to (R) (operation iii). Each of these molecules contains two acetic acid units joined through the C(4) atom in a potentially symmetrical manner, and utilization of such latent molecular symmetry for the required cis→trans isomerization would offer the key to operation iii. We found that cis→trans isomerization in the 5-ethyl-2-oxo-4-piperidineacetic acid system (type **64**) was feasible through the cis–trans equilibration (e.g., **64** ⇌ **66**) under acid hydrolytic conditions,[13,18,31] or less efficiently under Fischer–Speier esterification conditions at high temperature [in the case of the N-unsubstituted analogue (±)-**64a**],[32] or under alkaline hydrolytic



a R = H **b** R = Me **c** R = Et
d R = CH_2Ph

Scheme 5



Scheme 6

Table III. Thermal Cis–Trans Equilibration of the Lactam Acids **60**, **64**, **66**, and **69** at 180°C

Lactam acid		Reaction conditions			Composition at equilibrium	
Cis	Trans	Solvent	Concn. (M)	Time (min)	Cis (%)	Trans (%)
(±)-64a		Nil[a)]	———	5	33	67
	(±)-66a	Nil	———	8	33	67
(±)-64b	(±)-66b	Nil	———	28	34	66
(±)-64c	(±)-66c	Nil	———	40	33	67
(±)-64d	(±)-66d	Nil	———	50	33	67
		Tetralin	0.2	70	33	67
		Tetralin	0.005	250	—[b)]	—[b)]
(±)-60a	(±)-69a	Nil	———	75	33	67
(–)-60f	(+)-69f	Nil	———	90	32	68
(–)-60g	(+)-69g	Nil	———	90	33	67
(–)-60e	(+)-69e	Nil	———	90	33	67
(–)-60b	(+)-69b	Nil	———	130	34	66

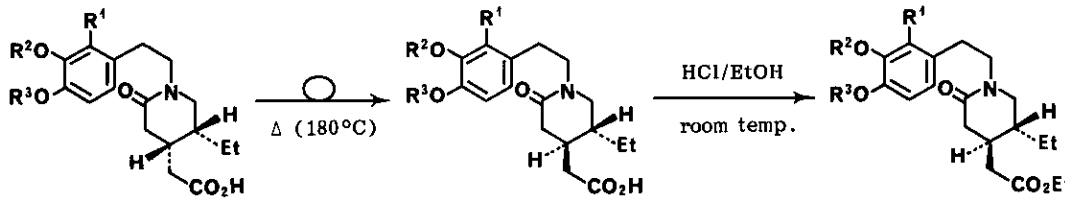
a) At 210°C. *b*) Although the cis/trans ratio was close to 1 : 2, the two isomers had not been equilibrated.

conditions,[33] or most efficiently under thermal conditions (e. g., heating at 180°C without using any solvent).[13,31,34] The cis→trans isomerization under hydrolytic or esterification conditions is considered to occur through ring opening by hydrolysis or alcoholysis (**64** ⟶ **62**, **65**, or **63**) followed by rotation and recyclization with another carboxy or alkoxycarbonyl group (**62** or **65** ⟶ **66** or **68**, **63** ⟶ **67**) (Scheme 5).[13,18,32,33]

On the other hand, the thermal cis→trans isomerization is assumed to proceed by intramolecular acidolysis of the lactam bond with the exocyclic carboxy group, as shown in Scheme 6.[13,34] The importance of activation of the lactam carbonyl group by inter- or intramolecular protonation with a proton dissociated from the exocyclic carboxy group in the first step (Scheme 6) may be supported by the unsusceptibility of the methyl esters of the cis lactam acids **64a,d** and the trans lactam acids **66a,d** to cis–trans isomerization under similar thermal conditions.[13] It may be seen from Table III that the thermal reaction comes to equilibrium within 8–130 min, when the cis and trans isomers exist in a ratio of 1:2.[34] A higher and/or bulkier N-substituent obviously causes the rate of isomerization to decrease. In the proposed isomerization mechanism (Scheme 6), all steps must be reversible. Therefore, the observed 1:2 ratio of the cis to the trans isomer in the equilibrated mixtures should reflect the relative thermo-

dynamic stabilities of the two isomers, which are probably dependent on steric repulsion between the 4- and 5-substituents regardless of the presence or absence of a remote N-substituent. However, a bulky N-substituent should cause the rates of the second and subsequent steps to decrease since these steps are most likely influenced by the steric nature of the lactam moiety. In addition, the slower isomerization of the N-benzyl analogue (±)-**64d** or (±)-**66d** observed in tetralin solutions at 0.2 and 0.005 M concentrations (Table III) suggests the importance of intermolecular rather than intramolecular protonation of the lactam carbonyl group with a proton dissociated from the exocyclic carboxy group in the first step of the cis–trans equilibration (Scheme 6).

Of the four isomerization conditions, the thermal conditions would be the first choice since they bring about fast isomerization with a good possibility of keeping other functional groups intact. On the basis of the above preliminary experiments, the cis lactam acids (−)-**60a,e–g** were separately heated neat at 180°C for 90 min [80 min for (−)-**60a**] to give equilibrated 1:2 mixtures of the cis and trans isomers, from which the trans lactam acids (+)-**69a,e–g** were isolated by recrystallization. The yields of



(−)-**60a,e–g** (+)-**69a,e–g** (+)-**70a,e–g**

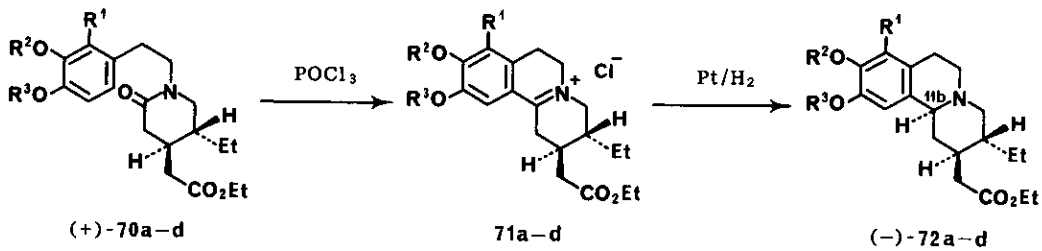
a R^1 = H, R^2 = R^3 = Me **b** R^1 = OCH_2Ph, R^2 = R^3 = Me
c R^1 = H, R^2 = CH_2Ph, R^3 = Me **d** R^1 = H, R^2 = Me, R^3 = CH_2Ph
e R^1 = OH, R^2 = R^3 = Me **f** R^1 = R^2 = H, R^3 = Me
g R^1 = R^3 = H, R^2 = Me

Scheme 7

(+)-**69a,e–g** were raised to 83%, 73%, 74%, and 74%, respectively, when the cis lactam acids recovered from the mixtures were separately subjected to the same reactions.[18–21] Esterifications of (+)-**69a,e–g** with ethanolic HCl were effected at room temperature for 20–24 h to afford the lactam esters (+)-**70a,e–g** in excellent yields.[18–21] For protection of the phenolic hydroxy group, (+)-**70e–g** were treated with benzyl bromide in boiling acetone containing K_2CO_3 for 20–26 h, providing the benzyl ethers (+)-**70b–d** in 96–98% yields.[19–21]

E. Cyclization to Form the Benzo[a]quinolizidine System

This transformation constitutes operation iv and was achieved by conventional means. Thus, the



(+)-70a–d 71a–d (–)-72a–d

a R^1 = H, R^2 = R^3 = Me **b** R^1 = OCH_2Ph, R^2 = R^3 = Me
c R^1 = H, R^2 = CH_2Ph, R^3 = Me **d** R^1 = H, R^2 = Me, R^3 = CH_2Ph

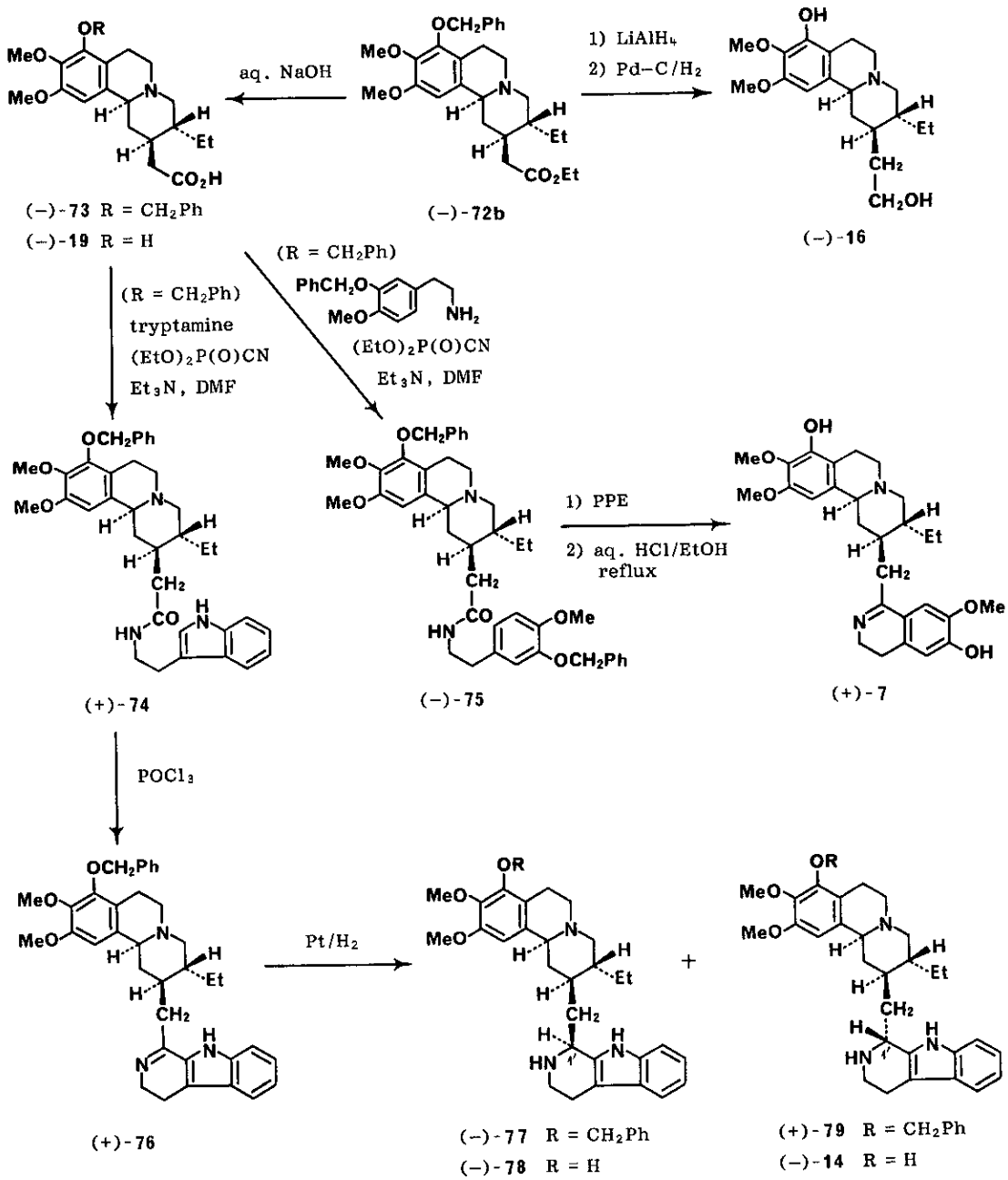
Scheme 8

Bischler–Napieralski cyclization of (+)-**70a–d** was carried out with $POCl_3$ in boiling toluene, and the resulting iminium salts **71a–d** were hydrogenated in EtOH with hydrogen and Adams catalyst to furnish the tricyclic base (–)-**72a–d** in 55–82% overall yields from (+)-**70a–d**.[18–21] Since catalytic hydrogenation of similar systems provides the more stable isomer,[35] the hydrogen at C-11b was assigned the α configuration. The correctness of the stereochemical outcome of the above chiral syntheses started from (+)-**36** was supported by the identity of (–)-**72a** with an authentic sample.[18]

F. Modification of the Acetate Side Chain

Operation v, the last operation in the "cincholoipon-incorporating route", is to modify the acetate side chain in (–)-**72a–d** to a methylene group linked to CH_2OH, CO_2H, or a second heterocyclic ring. Since (–)-**72a** has been shown to lead to emetine (**1**),[36] cephaeline (**2**),[37] isocephaeline (**4**),[37] psychotrine (**6**),[38] tubulosine (**9**),[39] isotubulosine (**12**),[39] deoxytubulosine (**13**),[39] and protoemetinol (**15**),[37,40] the above preparation of (–)-**72a** from cincholoipon ethyl ester [(+)-**36**] formally concluded syntheses of these I-type Alangium alkaloids.[3,41]

Scheme 9 delineates the routes that concluded the syntheses of the II-type alkaloids. Reduction of (–)-**72b** with $LiAlH_4$ and removal of the benzyl group by catalytic hydrogenolysis afforded (–)-**16**, which was identical with natural ankorine.[19] On the other hand, treatment of (–)-**72b** with NaOH in aqueous EtOH at room temperature gave the tricyclic amino acid (–)-**73**.[42] Debenzylation of (–)-**73** with hydrogen and Pd–C catalyst furnished alancine [(–)-**19**], which was converted into the hydrochloride (–)-**19**·HCl by conventional means.[5b,c] The synthetic (–)-**19**·HCl was found to be identical with a sample isolated from the stem bark of A. lamarckii, indicating that the natural sample, previously considered to be in the free base form [(–)-**19**],[5a] was actually in the hydrochloride salt form.[5b,c] Condensation of (–)-**73** with 3-benzyloxy-4-methoxyphenethylamine in N,N-dimethylformamide (DMF) at 25°C using the coupling reagent diethyl phosphorocyanidate[43] in the presence of Et_3N gave the


aq. NaOH
1) LiAlH4
2) Pd–C/H2
(–)-73 R = CH2Ph
(–)-19 R = H
(–)-72b
(–)-16
(R = CH2Ph)
tryptamine
(EtO)2P(O)CN
Et3N, DMF
(R = CH2Ph)
(EtO)2P(O)CN
Et3N, DMF
1) PPE
2) aq. HCl/EtOH
reflux
(+)-74
(–)-75
(+)-7
POCl3
Pt/H2
(+)-76
(–)-77 R = CH2Ph
(–)-78 R = H
(+)-79 R = CH2Ph
(–)-14 R = H

Scheme 9

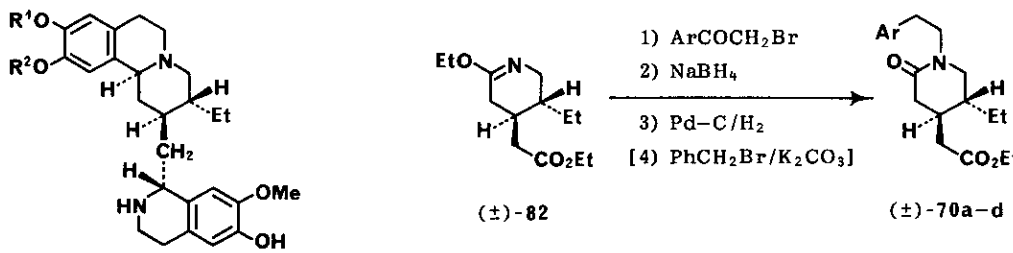
amide (−)-**75**.[42] Cyclization of (−)-**75** with polyphosphate ester (PPE) in boiling $CHCl_3$, followed by debenzylation with boiling 10% aqueous HCl–EtOH, yielded (+)-**7**, which was identical with natural alangicine.[42]

A parallel sequence of conversions starting with (−)-**73** and tryptamine provided (+)-**76** through (+)-**74**.[44] Catalytic hydrogenation of (+)-**76** in dioxane over Adams catalyst followed by column chromatography produced (+)-8-benzyloxydeoxytubulosine [(+)-**79**] (25% yield) and its 1'-epimer [(−)-**77**] (48% yield).[44] Catalytic hydrogenolyses of (+)-**79** and (−)-**77** with hydrogen and Pd–C catalyst furnished (−)-**14** and (−)-**78** in 96% and 95% yields, respectively. The synthetic (−)-**14** was found to be identical with natural alangimarckine.[44] The assignments of the configuration at C-1' of (−)-**77**, (+)-**79**, (−)-**78**, and (−)-**14** were based on five criteria, namely, the ratio of products from the reduction of (+)-**76**, tlc mobility, and ^1H and ^{13}C nmr and cd spectroscopic features.[44]

Similar side chain modifications starting from (−)-**72c,d** with or without 3-benzyloxy-4-methoxyphenethylamine gave the III- and IV-type alkaloids such as 9-demethylpsychotrine (**8**),[20] 9-demethylcephaeline [(−)-**80**],[45] 10-demethylcephaeline [(−)-**81**],[45] 9-demethylprotoemetinol (**17**),[46] and 10-demethylprotoemetinol (**18**).[46] In the synthetic work of (−)-**80** and (−)-**81**, lack of a sufficient amount of natural (−)-demethylcephaeline (**3**) for a detailed and direct comparison precluded identification of either (−)-**80** or (−)-**81** with this alkaloid, leaving its chemistry incomplete. A similar situation was also encountered in the case of 9-demethylprotoemetinol (**17**).[46] Yet another parallel sequence of conversions starting with (−)-**72c** and 5-benzyloxytryptamine yielded the A. vitiense alkaloid 9-demethyltubulosine (**10**).[47] The chiral synthesis of the A. lamarckii alkaloid 10-demethyltubulosine (**11**) via a similar route was not attempted because its absolute configuration had already been established as a result of its racemic synthesis by us[48] and the previous chemical correlation[49] with O-methyltubulosine through tubulosine (**9**) by Popelak et al.

III. THE LACTIM ETHER ROUTE

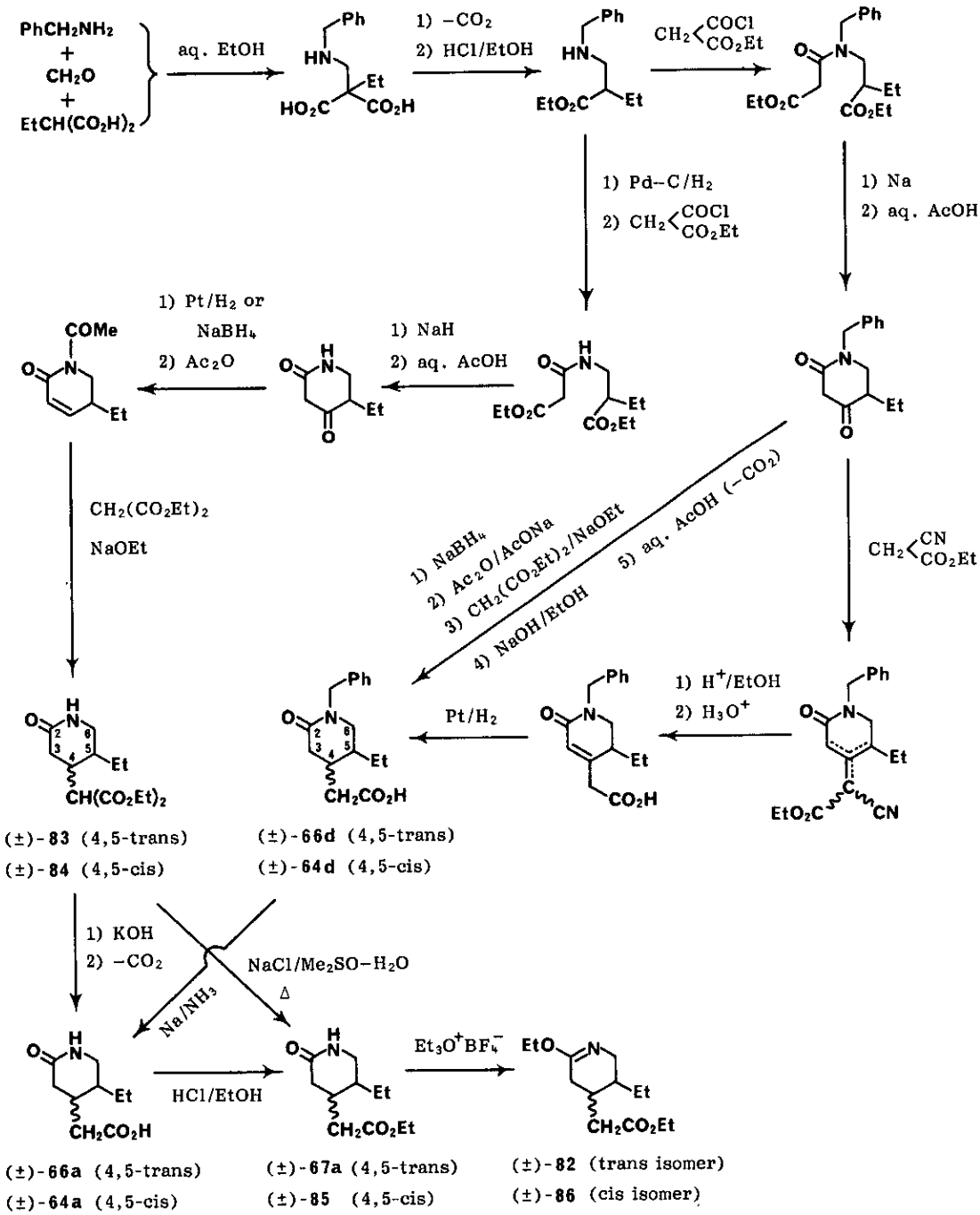
This route was originally designed,[50] together with the "3-acetylpyridine route",[28,51] for unified



(±)-**82** (±)-**70a–d**

(−)-**80** $R^1 = H$, $R^2 = Me$
(−)-**81** $R^1 = Me$, $R^2 = H$

Scheme 10

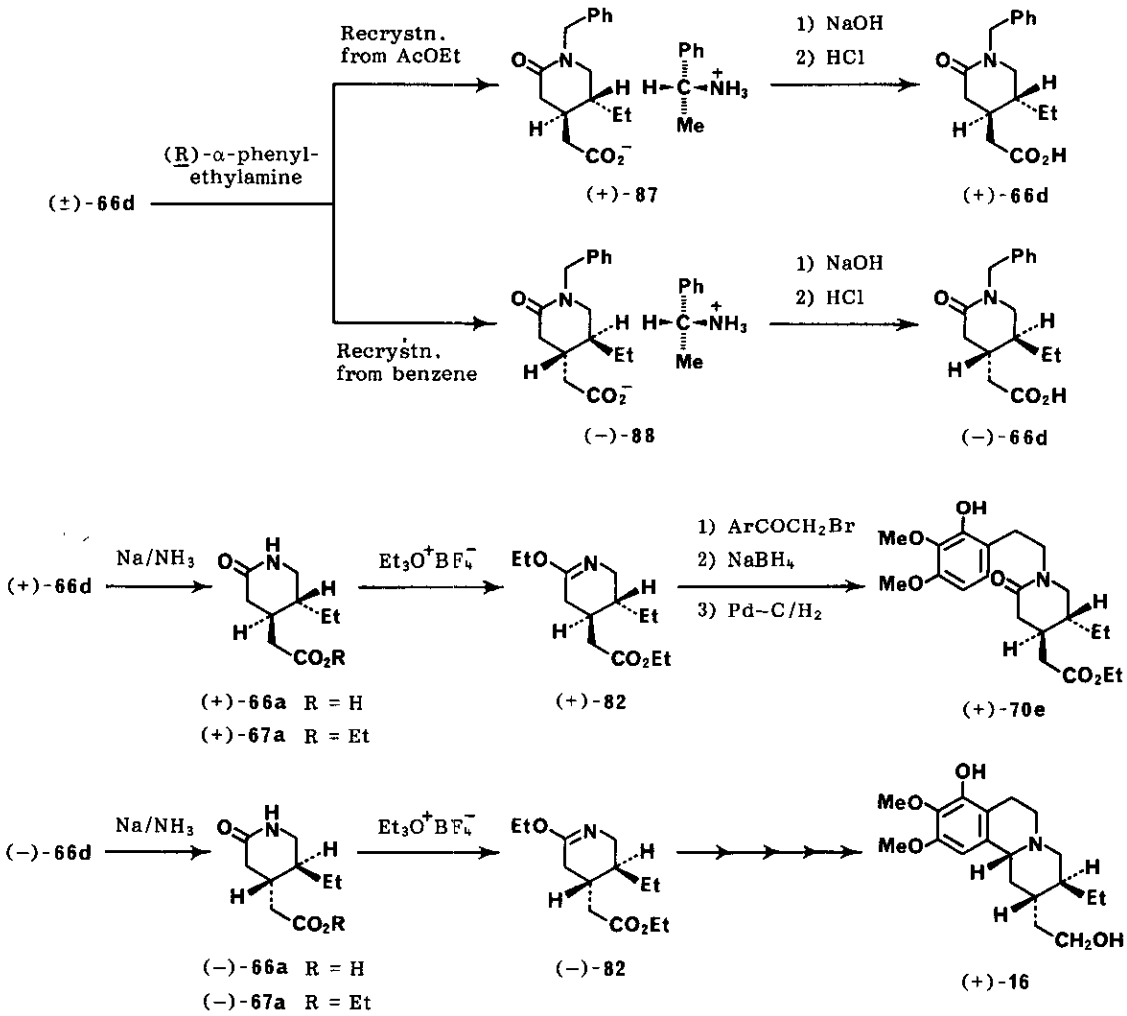

PhCH2NH2 + CH2O + EtCH(CO2H)2
aq. EtOH
1) −CO2
2) HCl/EtOH
CH2(COCl)(CO2Et)
1) Na
2) aq. AcOH
1) Pd–C/H2
2) CH2(COCl)(CO2Et)
1) Pt/H2 or NaBH4
2) Ac2O
1) NaH
2) aq. AcOH
CH2(CO2Et)2
NaOEt
1) NaBH4
2) Ac2O/AcONa
3) CH2(CO2Et)2/NaOEt
4) NaOH/EtOH
5) aq. AcOH (−CO2)
CH2(CN)(CO2Et)
1) H+/EtOH
2) H3O+
Pt/H2
(±)-83 (4,5-trans)
(±)-84 (4,5-cis)
(±)-66d (4,5-trans)
(±)-64d (4,5-cis)
1) KOH
2) −CO2
NaCl/Me2SO–H2O
Δ
Na/NH3
HCl/EtOH
Et3O+BF4−
(±)-66a (4,5-trans)
(±)-64a (4,5-cis)
(±)-67a (4,5-trans)
(±)-85 (4,5-cis)
(±)-82 (trans isomer)
(±)-86 (cis isomer)

Scheme 11

racemic synthesis of the I–IV-type alkaloids.[3a,b,5b,c,46,48,52–57] It featured the introduction of an adequate phenethyl skeleton into the racemic trans lactim ether [(±)-**82**], a common key intermediate generated from the already discussed 3-ethyl-4-piperidineacetic acid synthon (**35**) (Section II), as shown in Scheme 10. The synthetic route to (±)-**82** from benzylamine, formaldehyde, and ethylmalonic acid is outlined in Scheme 11.[13,15a,31,32,52,58–62] With the aim of extending this "lactim ether route" to cover chiral syntheses of the I–IV-type alkaloids, the enantiomers of **82** were prepared by the following two methods (Subsections A and B).

A. The Optical Resolution Method

In view of the instability of the lactim ether (±)-**82**, optical resolution was tried at a suitable precursor stage.[63] Thus, the resolution of (±)-**66d** was effected with (R)-(+)-α-phenylethylamine through



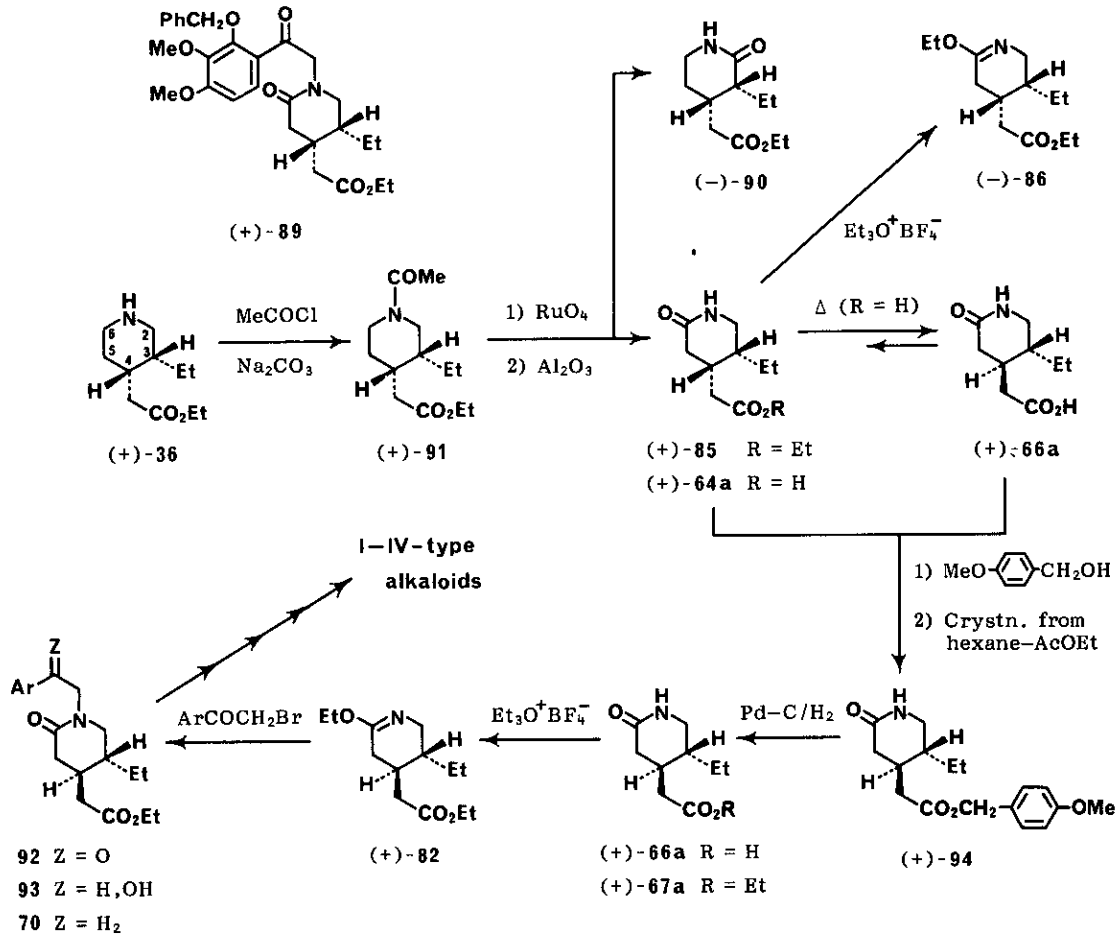
Scheme 12

formation of the diastereomeric salts (+)-**87** and (−)-**88** (Scheme 12). Conversion of (+)-**66d** into (+)-**82** proceeded via a route involving debenzylation of (+)-**66d** with Na in liquid NH_3, esterification of the resulting (+)-**66a** to give the ethyl ester (+)-**67a**, and ethylation of the ethyl ester (+)-**67a** with triethyloxonium fluoroborate.[63] Condensation of (+)-**82** with the phenacyl bromide **49b**, followed by $NaBH_4$ reduction and catalytic hydrogenolysis, gave the lactam phenol (+)-**70e**.[64] Since (+)-**70e** had already been converted into (−)-ankorine (**16**),[19] alangicine (**7**),[42] alangimarckine (**14**),[44] and alancine (**19**),[5b,c] the above sequence of conversions starting from (+)-**66d** formally constitutes alternative chiral syntheses of these Alangium alkaloids.

A parallel series of conversions starting with (−)-**66d** and proceeding through (−)-**82** produced the antipode [(+)-**16**] of natural ankorine.[63,64]

B. The Modified Cincholoipon-Incorporating Method

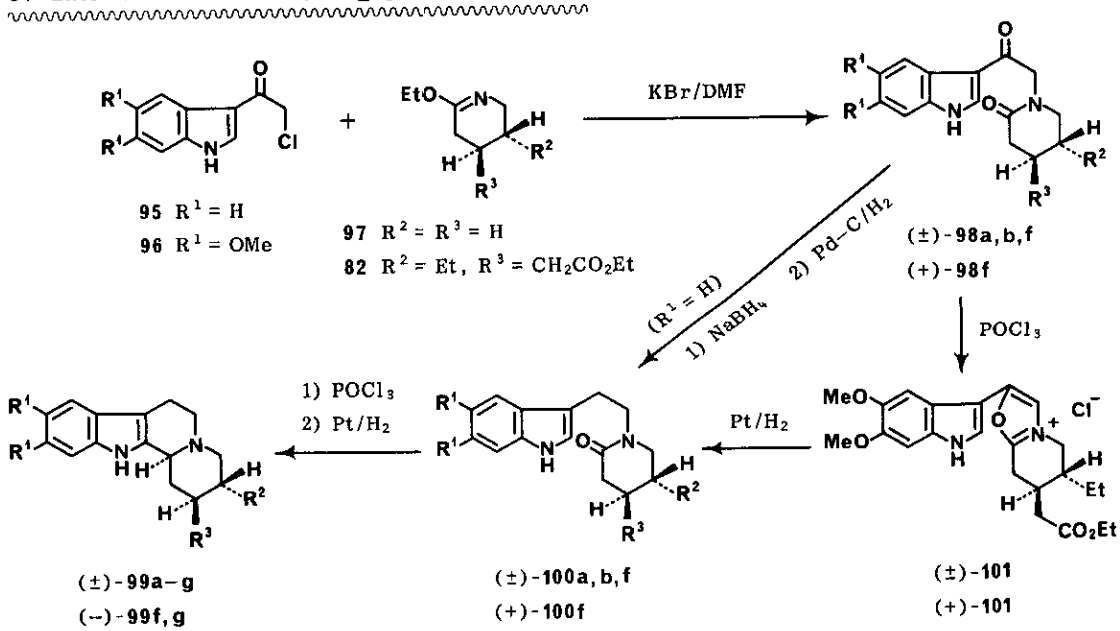
A hybrid of the "cincholoipon-incorporating route" and the "lactim ether route" has made it possible



Scheme 13

to establish an alternative synthetic route to all of the I–IV-type alkaloids from cincholoipon ethyl ester [(+)-**36**].[64,65] In a recent synthesis of (−)-ankorine (**16**),[64] the N-acetyl derivative (+)-**91**, obtained from (+)-**36** by acetylation, was oxidized with a mixture of RuO_2 and 10% aqueous $NaIO_4$ to give the 6-piperidone (+)-**85** and the 2-piperidone (−)-**90** in 55% and 27% yields, respectively. Alkaline hydrolysis of (+)-**85** and thermal cis→trans isomerization of the resulting cis lactam acid (+)-**64a** at 190°C for 15 min produced an equilibrated 66 : 34 mixture of (+)-**66a** and (+)-**64a**. However, separation of the desired trans isomer [(+)-**66a**] from the mixture was so difficult that the alteration of stereochemistry in (+)-**85** had to be done at a later stage. This led us to follow the synthetic route (+)-**85**→(−)-**86**→(+)-**89**→**59b**→**61e**→(−)-**60e**→(+)-**69e**→→→(−)-**16**. In quite a recent work,[65] however, the trans lactam acid (+)-**66a** was isolated in good yield in the form of the 4-methoxybenzyl ester (+)-**94** from the above equilibrated mixture, as shown in Scheme 13. Catalytic hydrogenolysis of (+)-**94** with hydrogen and Pd–C catalyst afforded (+)-**66a** in 97% yield, and this opened a new synthetic route to the I–IV-type Alangium alkaloids from cincholoipon ethyl ester [(+)-**36**] through (+)-**66a**, the ethyl ester (+)-**67a**, the lactim ether (+)-**82**, **92**, **93**, and **70**.[65]

C. Extension to the Indolo[2,3-a]quinolizidine Series



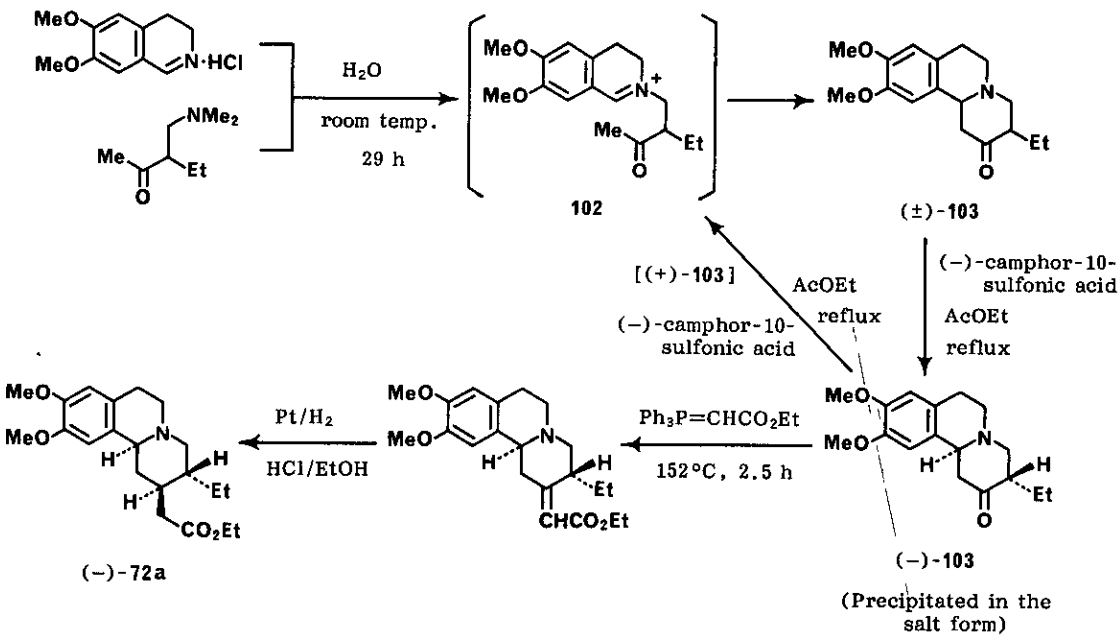
a $R^1 = R^2 = R^3 = H$
b $R^1 = H$, $R^2 = Et$, $R^3 = CH_2CO_2Et$
c $R^1 = H$, $R^2 = Et$, $R^3 = CH_2CH_2OH$
d $R^1 = H$, $R^2 = Et$, $R^3 = C(CO_2Me)=CHOMe$
e $R^1 = H$, $R^2 = Et$, $R^3 = CH(CO_2Me)CH_2OH$
f $R^1 = OMe$, $R^2 = Et$, $R^3 = CH_2CO_2Et$
g $R^1 = OMe$, $R^2 = Et$, $R^3 = CH_2CH_2OH$

Scheme 14

The tetracycle **99a** is the simplest among a number of indoloquinolizidine alkaloids.[66] We have found that the "lactim ether route" (as shown in Scheme 14) also worked well for synthesizing the racemic modifications of this parent framework and more complex indoloquinolizidine alkaloids, such as dihydrocorynantheol (**99c**), dihydrocorynantheine (**99d**), dihydrositsirikine (**99e**), and ochropposinine (**99g**).[67–69] Now that the optically active lactim ether (+)-**82** became available (see Section III, A and B), (−)-**99g** was synthesized from (+)-**82** and **96** via the intermediates (+)-**98f**, (+)-**101**, (+)-**100f**, and (−)-**99f**. The identity of the synthetic (−)-**99g** with natural ochropposinine unequivocally established the absolute stereochemistry of this Ochrosia alkaloid.[68]

IV. OTHER ROUTES

The tricyclic ester (−)-**72a**, a precursor for chiral syntheses of the I-type alkaloids,[36–40,70–72] was prepared by Openshaw and Whittaker[36,73–75] through an elegant and commercially applicable route, as shown in Scheme 15. The highlight of this route is that the formation of the insoluble camphorsulfonate salt of the ketone (−)-**103** from (±)-**103**[76] and recycling of the enantiomer (+)-**103** to (±)-**103** by acid-catalyzed racemization proceeding through **102** were all effected with (−)-camphor-10-sulfonic acid in boiling AcOEt in a one-pot reaction manner.



Scheme 15

Stereoconservative, multistep syntheses of emetine (**1**), cephaeline (**2**), isocephaeline (**4**), and deoxytubulosine (**13**) from secologanin (**48**) by Brown's group[77] have been treated in a recent review.[3a] (−)-Emetine (**1**) has been obtained by optical resolution of (±)-**1** with a variety of resolving agents

such as (+)-camphor-10-sulfonic acid,[78] N-acetyl-L-leucine,[79] and (+)-O,O-dibenzoyltartaric acid,[80] or at the precursor level [(±)-O-methylpsychotrine] with (−)-O,O-dibenzoyltartaric acid.[81]

V. CONCLUDING REMARKS

As a result of the above chiral syntheses of the II–IV-type Alangium alkaloids, the absolute configurations of all of them were established unequivocally, except for the cases where the difficulty of obtaining adequate supplies of natural samples of alkaloid for direct comparison was encountered [demethylcephaeline (**3**) and 9-demethylprotoemetinol (**17**)] or the absolute configuration had already been determined by chemical conversion into a known compound [10-demethyltubulosine (**11**)]. This provides a fine example in support of the statement that synthesis can still be an important tool for structure elucidation even in this new era of highly refined spectroscopic studies. The synthetic routes described in Sections II and III emphasize the utility of the 3-ethyl-4-piperidineacetic acid synthon **35** in the unified syntheses of the I–IV-type alkaloids as well as structurally related indoloquinolizidine alkaloids. They may also serve as valid vehicles for chiral syntheses of the analogous alkaloids which remain to be synthesized or to be catalogued newly in the blank in Table I.

ACKNOWLEDGMENT

We acknowledge with gratitude the contributions of our co-workers, whose names appear in the individual literature citations. Financial support provided by the Ministry of Education, Science and Culture, Japan (in the form of Grants-in-Aid for Scientific Research), the Foundation for the Promotion of Research on Medicinal Resources, the Fugaku Trust for Medicinal Research, and the Japan Research Foundation for Optically Active Compounds is deeply appreciated. Finally, T. F. wishes to thank Emeritus Professor Dr. Shigehiko Sugasawa (University of Tokyo), who planted the seed 35 years ago for the body of work described herein.

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