Pergamon

Tetrahedron 56 (2000) 7751–7761

TETRAHEDRON

A Chiral Synthesis of the *Strychnos* and *Ophiorrhiza* Alkaloid Normalindine

Masashi Ohba,* Hiroyuki Kubo and Hiroyuki Ishibashi

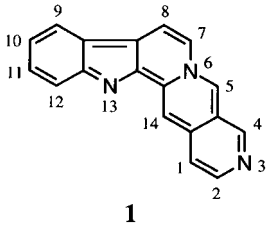
Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920-0934, Japan

Received 13 July 2000; accepted 7 August 2000

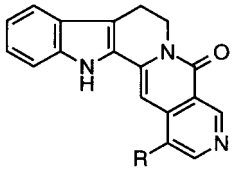
Abstract—A full account of the first chiral synthesis of (−)-normalindine [(−)-**4**], an indolopyridonaphthyridine alkaloid isolated from *Strychnos johnsonii* and *Ophiorrhiza filistipula*, is presented. Central features of the synthetic strategy include the conversion of L-alanine methyl ester (**13**) into the oxazole derivative **12** and the intramolecular Diels–Alder reaction of the oxazole–olefin derivatives **27a** and **30a**. The correctness of the absolute configuration proposed for normalindine has been unambiguously confirmed by the present synthesis.

Introduction

The pentacyclic system **1** represents the parent framework common to the indolo[2′,3′:3,4]pyrido[1,2-*b*][2,7]naphthyridine alkaloids, which have been known to occur in the genera, such as *Strychnos*, *Nauclea*, *Camptotheca*, *Mitragyna*, *Uncaria*, *Ophiorrhiza*, and *Anthocephalus*.[1–8] Although most of these alkaloids exist as lactams [e.g. nauclefine (**2**) and angustine (**3**)], some others including normalindine (**4**),[2,3] norisomalindine (**5**),[2] cadamine (**6**),[4] isocadamine (**7**),[4] malindine (**8**),[5,6] isomalindine (**9**),[6,7] and isomalindine-16-carboxylate (**10**)[8] are characterized by a stereogenic center at C(5).

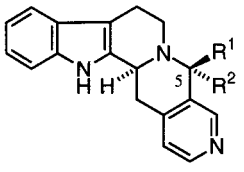


1

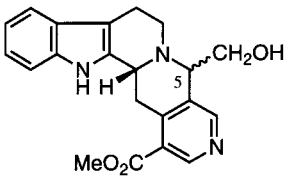


2: R = H
3: R = CH=CH$_2$

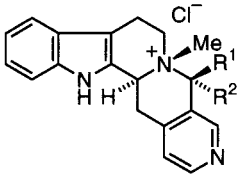
(−)-Normalindine (**4**) was reported for the first time as one of the 18 alkaloids isolated from the root bark of *Strychnos johnsonii* (Loganiaceae) by Massiot et al. in 1987.[2] The structure and relative stereochemistry suggested on the basis of its spectroscopic analysis were confirmed via racemic syntheses by two independent research groups.[9] Thereafter, Arbain et al. also announced the isolation of this alkaloid from the leaves of *Ophiorrhiza filistipula* (Rubiaceae) and proposed its absolute configuration to be (−)-**4** by CD spectral evidence.[3] In the present paper, we describe the details of the first chiral synthesis of (−)-normalindine [(−)-**4**], which have verified the correctness of this proposal. A brief account of the results reported here has been published in a preliminary form.[10]



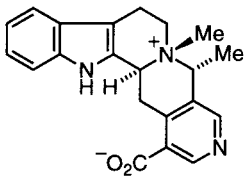
4: R^1 = Me, R^2 = H
5: R^1 = H, R^2 = Me



6, **7**: C(5)-epimers



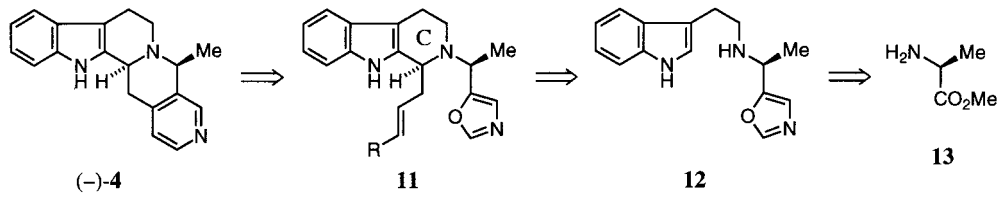
8: R^1 = Me, R^2 = H
9: R^1 = H, R^2 = Me



10

Keywords: amino acids and derivatives; Diels–Alder reactions; naphthyridines; oxazoles.
* Corresponding author. Tel.: +8-76-234-4475; fax: +8-76-234-1563; e-mail: ohba@dbs.p.kanazawa-u.ac.jp

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00695-5



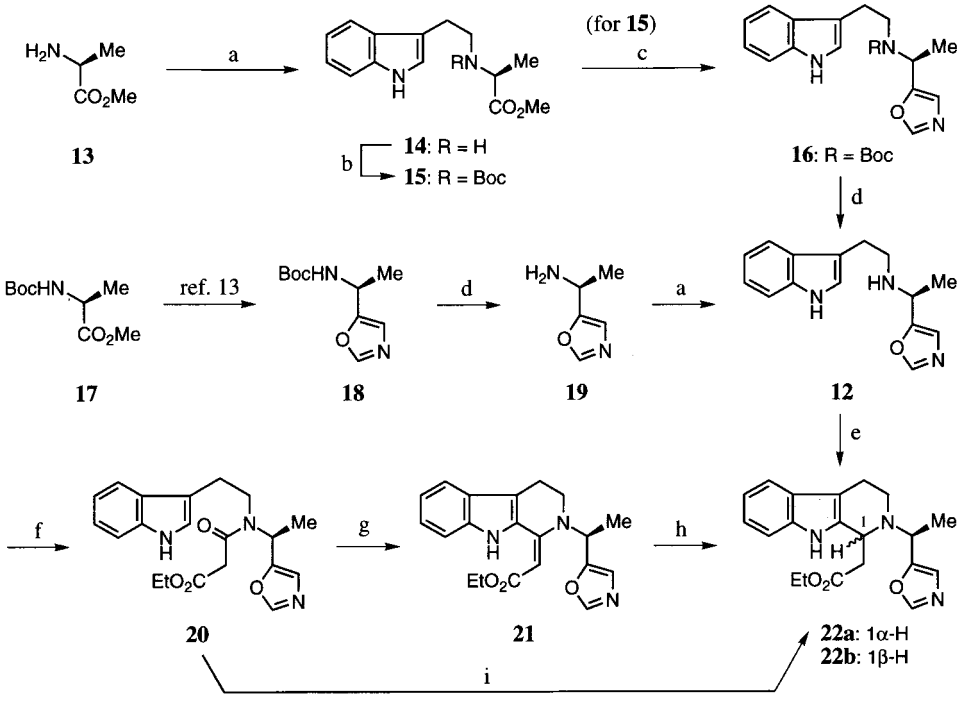
Scheme 1.

Results and Discussion

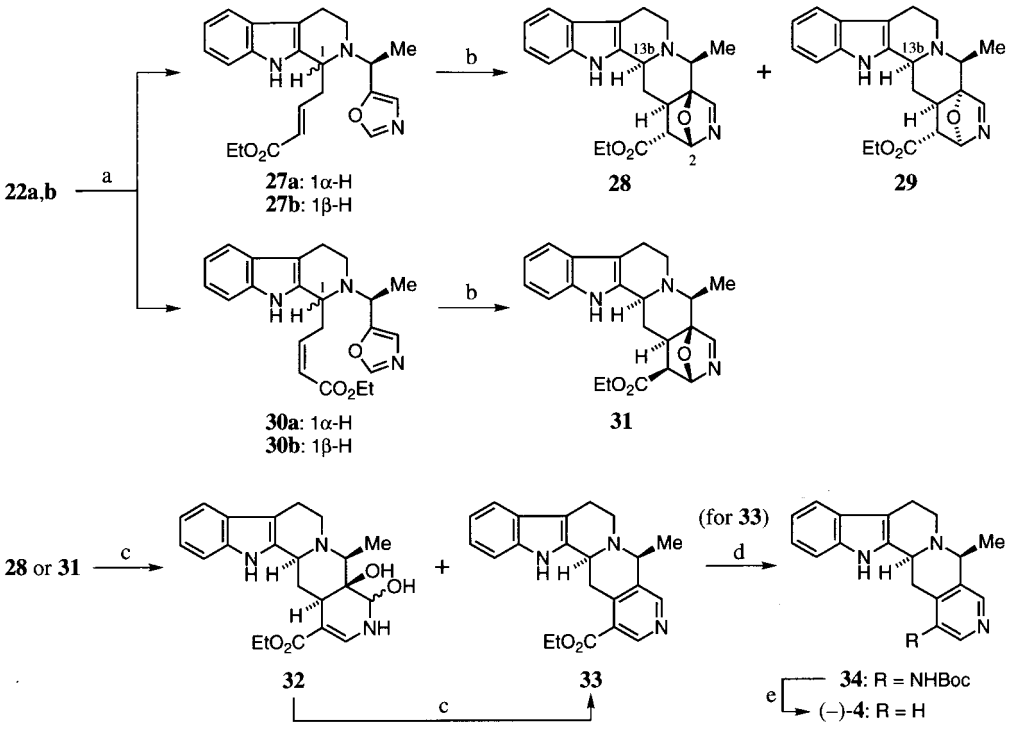
At the outset of the present synthesis, we planned to employ the intramolecular oxazole–olefin Diels–Alder reaction[11,12] of **11** toward an efficient construction of the naphthyridine skeleton of (−)-**4** (Scheme 1). The requisite oxazole–olefin derivative **11** would be obtainable from **12** via the formation of ring C and the subsequent introduction of an appropriate olefin moiety. In addition, our recent synthesis[13] of chiral 5-(aminomethyl)oxazole derivatives from α-amino esters is a reliable guide for the preparation of **12**.

The initial step was *N*-alkylation of L-alanine methyl ester (**13**) with 2-(3-indolyl)ethyl bromide, reported by Waldmann et al.,[14] which was effected with a slight modification, giving **14** in 66% yield (Scheme 2). After protection of **14** with di-*tert*-butyl dicarbonate, the resulting *N*-Boc-α-amino ester **15** was converted into the oxazole **16** in 76% yield by treatment with α-lithiated methyl isocyanide at −78°C according to our previous procedure.[13] Deprotection of **16** with trifluoroacetic acid afforded the desired amino oxazole **12** in 98% yield. Alternatively, **12** was also obtained from **18**[13] through deprotection (97% yield) followed by direct *N*-alkylation (55%) of the primary amine **19** with 2-(3-indolyl)ethyl bromide. In an attempt to improve the efficiency of the conversion of **19** to **12**, reduction of the amide **23**, derived from **19** in 94% yield, was tried under various conditions, but without satisfactory results.

With the amino oxazole **12** in hand, we next turned our attention to the construction of ring C in the intermediate **11**. Condensation of **12** with monoethyl malonate using diethyl phosphorocyanidate[15] provided the amide **20** (98% yield), which was then submitted to the Bischler–Napieralski cyclization with $POCl_3$ in boiling CH_3CN followed by the $NaBH_4$ reduction of the resulting iminium salt **24**, giving the amino esters **22a** and **22b** as a 2:1 diastereoisomeric mixture in 31% yield from **20**. In accordance with the interpretation of Polniaszek,[16] we postulated the hydrogen at C(1) in the major isomer **22a** as the α configuration because the hydride attack would prefer the sterically less hindered iminium ion diastereoface of the conformer **24** with minimized allylic 1,3-strain. On basification with Na_2CO_3, the iminium salt **24** was transformed to the (*E*)-ester **21** (46% yield from **20**), whose geometry of the exocyclic double bond was assigned on the basis of the fact that the $N_{(a)}$ proton resonated at δ 13.05 ($CDCl_3$) and the ester $\nu_{C=O}$

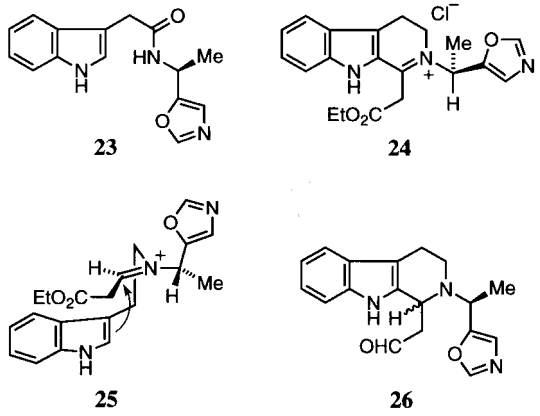


Scheme 2. *Reagents and conditions:* (a) 2-(3-indolyl)ethyl bromide, *i*-Pr_2NEt, THF, reflux, 10 days for **13**; 7 days for **19**; (b) $(Boc)_2O$, $CHCl_3$, rt, 24 h; (c) $LiCH_2NC$, THF, −78°C, 6 h; (d) CF_3CO_2H, CH_2Cl_2, 0°C, 2 h for **16**; rt, 1 h for **18**; (e) 1) $HC{\equiv}CCO_2Et$, $CHCl_3$, rt, 40 h; 2) CF_3CO_2H, rt, 1 h; (f) $HO_2CCH_2CO_2Et$, $(EtO)_2P(O)CN$, Et_3N, DMF, rt, 2 h; (g) 1) $POCl_3$, CH_3CN, reflux, 4 h; 2) 10% aqueous Na_2CO_3; (h) 10% Pd–C, H_2, AcOEt, rt, 5 h; (i) 1) $POCl_3$, CH_3CN, reflux, 4 h; 2) $NaBH_4$, MeOH, 0°C, 1.5 h.



Scheme 3. *Reagents and conditions:* (a) 1) DIBALH, CH_2Cl_2, −78°C, 20 min; 2) $Ph_3P{=}CHCO_2Et$, rt, 3 h; (b) toluene, reflux, 24 h; (c) AcOH–xylene (1:5), reflux, 8 h; (d) 1) LiOH, THF–MeOH–H_2O, rt, 1.5 h; 2) $(PhO)_2P(O)N_3$, Et_3N, *tert*-BuOH, reflux, 5 h; (e) 1) CF_3CO_2H, CH_2Cl_2, rt, 5 h; 2) BuONO, DMF, 70°C, 30 min.

appeared at 1663 cm^{-1} ($CHCl_3$), suggesting the existence of intramolecular hydrogen bonding between the NH and ester carbonyl groups. Catalytic hydrogenation of **21** over Pd–C in AcOEt was found to increase the diastereoselectivity of **22a** and **22b** to 3:1. On the other hand, the modified Pictet–Spengler cyclization[17] of **12** by treatment with ethyl propiolate followed by trifluoroacetic acid furnished a 1:2 mixture of **22a** and **22b** in 78% yield. By analogy to an analysis given by Waldmann et al.[14] for related systems, we assumed that this cyclization predominantly proceeded via the preferred conformation **25** of the iminium intermediate.



With a view to introducing an olefinic dienophile into the amino esters **22a,b**, the above 3:1 mixture was treated with diisobutylaluminum hydride (DIBALH) at −78°C in CH_2Cl_2. Initial attempts to execute methylenation of the aldehyde **26**, assumed to be prepared, leading to the olefin **11** (R=H) proved fruitless because of the lability of the aldehyde. However, when the DIBALH reduction of **22a,b** followed by the Wittig reaction with ethyl (triphenylphosphoranylidene)acetate was performed in a one-pot procedure without isolating **26**, a 3:1 mixture of the (*E*)-esters **27a** and **27b** [*J*=15.5 Hz (olefinic protons)] and a 3:1 mixture of the (*Z*)-esters **30a** and **30b** (*J*=11.5 Hz) were obtained in 59 and 26% overall yields from **22a,b**, respectively (Scheme 3).

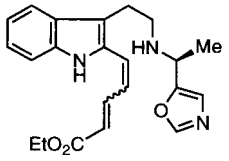
Having succeeded in the syntheses of the oxazole–olefin derivatives **27a,b** and **30a,b**, we set out to explore their intramolecular Diels–Alder reactions. The results are listed in Table 1. The best result was obtained by heating the 3:1 mixture of the (*E*)-isomers **27a** and **27b** in boiling toluene for 24 h: under these conditions, the adducts **28** and **29**, both embracing α configuration for their C(13b)–H, were produced in 53 and 5% yields, respectively. Addition of a Lewis acid, such as $Eu(fod)_3$[12e,f] and $Yb(OTf)_3$,[18] failed to improve the yields of the adducts **28** and **29**. Treatment of **27a,b** in *o*-dichlorobenzene (*o*-DCB) at 150°C in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), an application of Weinreb's procedure,[12a–c] resulted in a retro-Michael reaction, providing the diene **35** in 53% yield. In order to examine this reaction in further detail, the adduct **28** was treated in boiling toluene for 24 h. Two products obtained together with unaltered **28** (60%) were the oxazole–olefin derivative **27a** (18% yield), produced via a retro-Diels–Alder reaction, and another adduct **29** (6%), suggesting that **27a** came to equilibrium with the adducts **28** and **29** after 24 h under the conditions employed and no epimerization between **27a** and **27b** occurred. In a similar fashion, the 3:1 mixture of the (*Z*)-isomers **30a** and **30b** afforded the adduct **31** in 40% yield. None of adducts arising

Table 1. Intramolecular oxazole–olefin Diels–Alder reaction of the (*E*)-isomers **27a,b** (a 3:1 mixture of **27a** and **27b** was used)

Entry	Solvent	Additive (mol %)	Temp (°C)	Time (h)	Yield (%)[a]	
					28	**29**
1	Toluene	–	80	17	25	–
2	Toluene	–	Reflux	17	40	4
3	Toluene	–	Reflux	24	53	5
4	Toluene	–	Reflux	36	53	5
5	Toluene	$Eu(fod)_3$ (7)	Reflux	17	38	5
6	Toluene	$Yb(OTf)_3$ (10)	Reflux	24	48	4
7	*o*-DBC	–	150	24	20	6

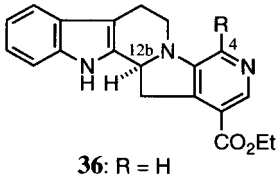
[a] Isolated yield based on the mixture of **27a** and **27b** after purification by flash chromatography.

from the minor diastereoisomers **27b** and **30b** were obtained. The stereochemistries of **28**, **29**, and **31** were determined by the appearance of absorption bands assignable to a *trans*-quinolizidine ring[19] in their IR spectra and the results of detailed NOE experiments shown in Fig. 1.

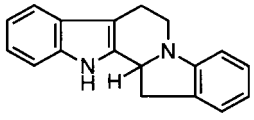


35

Conversion of three adducts **28**, **29**, and **31** into pyridine derivatives was next investigated. On treatment with DBN in boiling toluene for 10 h,[12a–c] the adduct **28** gave **27a** (10% yield) and **35** (25%) via retro-Diels–Alder reaction and subsequent retro-Michael reaction, respectively, together with recovered **28** (38%), but no product possessing the desired skeleton was obtained. However, the C(2)–O bond cleavage of **28** was found to be ready upon exposure to AcOH at room temperature for 1 h, affording the diol **32** in 77% yield with concomitant addition of H_2O to the imino group. The desired naphthyridine ester **33** was eventually obtained in 18% yield along with the diol **32** (64% yield) by heating **28** in boiling AcOH–xylene (1:5) for 8 h. Similar treatment of **32** provided **33** in 13% yield, accompanied by recovered **32** (62%). Under these conditions, the adduct **31** gave the results analogous to those obtained from **28**, whereas **29** exhibited unpredictable behavior. The adduct **29** disappeared within 1 h on treatment in boiling AcOH–xylene (1:2), and two compounds **36** and **37** containing a pyrrolo[2,3-*c*]pyridine skeleton were obtained in 46 and 44% yields, respectively. The structures **36** and **37** were assigned on the basis of their spectral properties in conjunction with their elemental analyses. Thus, the ^{1}H NMR spectrum of **36** in $CDCl_3$ displayed two pyridine ring proton signals at δ 8.20 and 8.53 and a C(12b)–H signal at δ 5.20, the latter of which is comparable to the corresponding signal (δ 5.03) of **38**.[20] On the other hand, the ^{1}H NMR spectrum of **37** showed newly the signals arising from the C(4)-ethyl group with disappearance of the signal at δ 8.20 on that of **36**. The formations of **36** and **37** may be presumed to proceed through the aziridinium ion **40** derived from the tertiary alcohol **39** as depicted in Scheme 4.



36: R = H
37: R = Et



38

Alkaline hydrolysis of **33** with LiOH followed by the modified Curtius rearrangement using diphenyl phosphoroazidate[21] furnished the carbamate **34** in 64% yield. Finally, conversion of **34** into the target compound (−)-**4** was achieved in 40% yield by treatment with CF_3CO_2H and subsequent reductive deamination of the resulting arylamine with butyl nitrite in DMF.[22] The synthetic (−)-**4** [mp 122–126°C, $[\alpha]_D^{22}=-212°$ (*c* 0.29, $CHCl_3$)] proved to be virtually identical with a natural sample of normalindine [mp 131–136°C, $[\alpha]_D=-210°$ (*c* 0.1, $CHCl_3$)][3] by comparison of the UV, IR, ^{1}H NMR, and mass spectra and TLC mobility (three solvent systems).

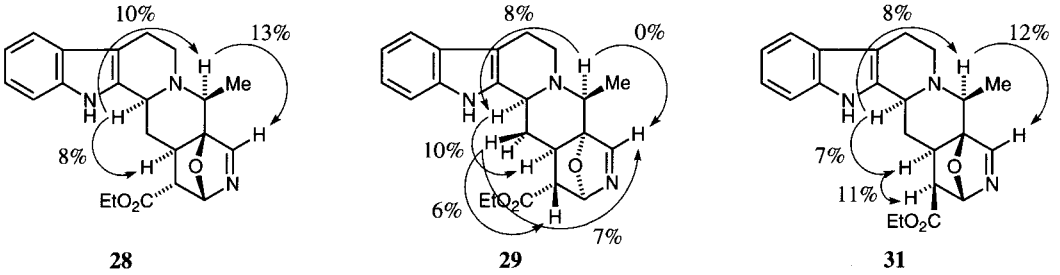
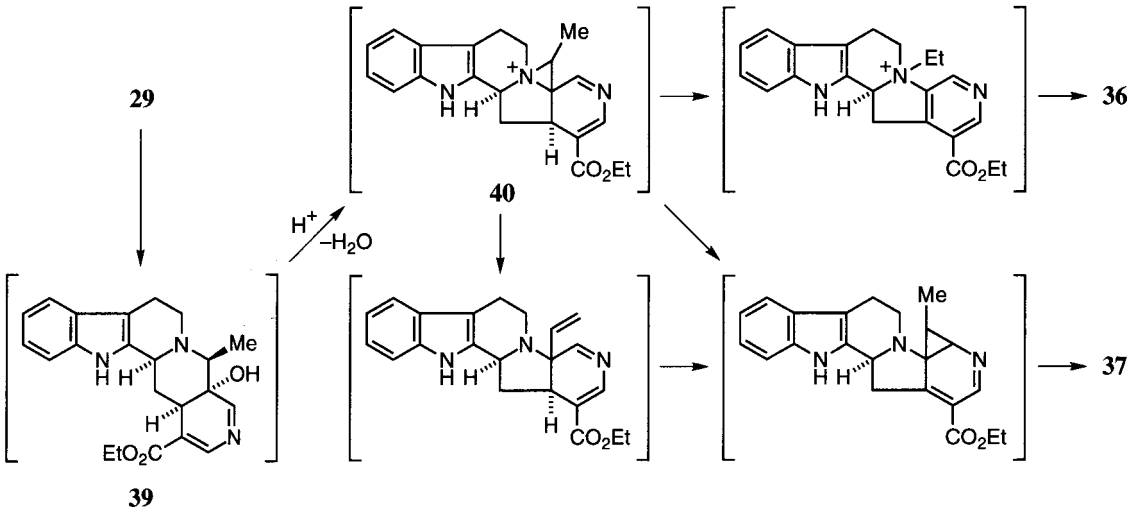


Figure 1. NOE data of the adducts **28**, **29** and **31**.



Scheme 4.

In conclusion, the first chiral synthesis of the *Strychnos* and *Ophiorrhiza* alkaloid normalindine has been accomplished via the intramolecular Diels–Alder reaction of the chiral oxazole–olefin derivatives **27a** and **30a**. The present results have not only unequivocally established the absolute configuration of normalindine to be (5*S*,13b*S*)-form on the basis of L-alanine methyl ester (**13**) employed as a starting material, but also suggest that the intramolecular oxazole–olefin Diels–Alder reaction would be applicable to the synthesis of various bicyclic systems comprising a pyridine skeleton.

Experimental

General method

All melting points were determined on a Büchi model 530 capillary melting point apparatus and are corrected. Flash chromatography[23] was carried out by using Merck silica gel 60 (No. 9385). Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The ratios of solvents in mixtures are shown in v/v. Spectra reported herein were recorded on a JEOL JMS-SX102A mass spectrometer, a Shimadzu FTIR-8100 IR spectrophotometer, and either a JEOL JNM-GSX-500 (^{1}H 500 MHz, ^{13}C 125 MHz) or a JEOL JNM-EX-270 (^{1}H 270 MHz, ^{13}C 67.8 MHz) NMR spectrometer. Chemical shifts are reported in δ values relative to internal Me_4Si. Optical rotations were measured with a Horiba SEPA-300 polarimeter using a 1-dm sample tube. Elemental analyses and MS measurements were performed by Dr M. Takani and co-workers at Kanazawa University.

***N*-[2-(1*H*-Indol-3-yl)ethyl]-L-alanine methyl ester (14).** A solution of 2-(3-indolyl)ethyl bromide[24] (8.66 g, 38.6 mmol), L-alanine methyl ester (**13**) (7.17 g, 69.5 mmol), and *N*-ethyldiisopropylamine (5.00 g, 38.7 mmol) in THF (100 ml) was heated under reflux in an atmosphere of N_2 for 10 days. After cooling, the precipitate that resulted was filtered off and washed with ether. The filtrate and washings were combined, washed successively with H_2O and saturated aqueous NaCl, dried, and concentrated to leave an orange oil. Purification by flash chromatography (AcOEt) afforded **14** (6.27 g, 66%) as a slightly yellow oil, $[\alpha]_D^{24}=-23.1°$ (*c* 1.01, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (NH), 1732 (ester CO). The ^{1}H NMR ($CDCl_3$) spectral data for this sample were in agreement with those reported in the literature.[14]

***N*-(*tert*-Butoxycarbonyl)-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-alanine methyl ester (15).** A mixture of **14** (41.4 g, 0.168 mol) and di-*tert*-butyl dicarbonate (40.3 g, 0.185 mol) in $CHCl_3$ (300 ml) was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo, and the residual solid was recrystallized from MeOH, giving a first crop (46.9 g) of **15**. Concentration of the mother liquor and recrystallization of the residue from MeOH afforded a second crop (5.04 g) of **15**. A further crop (2.94 g) was obtained by concentration of the mother liquor of the second recrystallization and subsequent purification of the residue by flash chromatography [hexane–AcOEt (2:1)]. Total yield of **15** was 54.88 g (94%). Further recrystallization from MeOH provided an analytical sample as colorless prisms, mp 136.5–137°C; $[\alpha]_D^{21}=-21.7°$ (*c* 1.01, $CHCl_3$); MS *m/z*: 346 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3315 (NH), 1746 (ester CO), 1674 (carbamate CO); ^{1}H NMR ($CDCl_3$) δ: 1.42 and 1.44 (3H, d each, *J*=6.8 Hz, CH*Me*), 1.46 and 1.49 (9H, s each, *tert*-Bu), 2.9–3.7 (4H, m, two CH_2's), 3.71 (3H, s, OMe), 4.11 and 4.60 (1H, q each, *J*=6.8 Hz, C*H*Me), 7.01 and 7.04 [1H, br s each, C(2)–H], 7.12 and 7.19 [1H each, dd, *J*=7, 7 Hz, C(5)–H and C(6)–H], 7.36 (1H, d, *J*=7 Hz) and 7.62 and 7.66 (1H, d each, *J*=7 Hz) [C(4)–H and C(7)–H], 8.02 (1H, s, NH). Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.88; H, 7.56; N, 8.09. Found: C, 65.87; H, 7.57; N, 8.01.

(*S*)-[2-(1*H*-Indol-3-yl)ethyl][1-(5-oxazoyl)ethyl]carbamic acid *tert*-butyl ester (16). A solution of methyl isocyanide (16.4 g, 0.40 mol) in THF (400 ml) was cooled to −78°C in an atmosphere of N_2, and a 1.6 M solution (250 ml, 0.40 mol) of BuLi in hexane was added dropwise over 1.5 h. After the mixture had been stirred for 30 min, a

solution of **15** (27.7 g, 80.0 mmol) in THF (230 ml) was introduced dropwise over 30 min. Stirring was then continued at −78°C for 6 h. The reaction was quenched by adding AcOH (23 ml), and the mixture was brought to room temperature during 30 min. After concentration of the mixture, the residue was partitioned between H_2O and ether. The ethereal extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a yellow oil. Purification by flash chromatography [AcOEt–hexane (1:1)] furnished **16** (21.6 g, 76%) as a colorless solid. Recrystallization from AcOEt–hexane (1:1) gave an analytical sample as colorless prisms, mp 116–117°C; $[\alpha]_D^{17}=-29.2°$ (*c* 1.00, $CHCl_3$); MS *m/z*: 355 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3225 (NH), 1682 (carbamate CO); ^1H NMR ($CDCl_3$) δ: 1.50 (3H, d, *J*=7.3 Hz, CH*Me*), 1.53 (9H, s, *tert*-Bu), 2.75–3.45 (4H, m, two CH_2's), 5.22 and 5.60 (1H, br each, C*H*Me), 6.90 and 6.95 [2H, br each, C(2)–H and C(4′)–H], 7.10 and 7.18 [1H each, dd, *J*=7.5, 7.5 Hz, C(5)–H and C(6)–H], 7.34 (1H, d, *J*=7.5 Hz) and 7.53 (1H, br) [C(4)–H and C(7)–H], 7.81 [1H, s, C(2′)–H], 8.00 (1H, s, NH).[25] Anal. Calcd for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.50; H, 7.17; N, 11.74.

(*S*)-α-Methyl-5-oxazolemethanamine (19). A solution of **18**[13] (850 mg, 4.0 mmol) in CH_2Cl_2 (12 ml) was cooled to 0°C, and CF_3CO_2H (12 ml) was added. After stirring at room temperature for 1 h, the reaction mixture was concentrated in vacuo. The residual pale yellow oil was dissolved in a small amount of H_2O, made basic with K_2CO_3, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried over anhydrous K_2CO_3 and concentrated to leave **19** (436 mg, 97%) as a slightly yellow oil, $[\alpha]_D^{28}=-13.0°$ (*c* 1.01, MeOH); CIMS *m/z*: 113 (MH^+); IR ν_{max}^{film} cm^{-1}: 3360, 3295 (NH_2); ^1H NMR ($CDCl_3$) δ: 1.46 (3H, d, *J*=6.8 Hz, Me), 1.70 (2H, s, NH_2), 4.17 (1H, q, *J*=6.8 Hz, C*H*Me), 6.87 [1H, s, C(4)–H], 7.80 [1H, s, C(2)–H].

(*S*)-*N*-[1-(5-Oxazoyl)ethyl]-1*H*-indole-3-ethanamine (12). *(i) From **16**:* A mixture of **16** (1.21 g, 3.4 mmol), CF_3CO_2H (5 ml), and CH_2Cl_2 (5 ml) was stirred at 0°C for 2 h. The reaction mixture was then concentrated in vacuo, and the residue was dissolved in H_2O (20 ml). The aqueous solution was made basic with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over anhydrous K_2CO_3 and concentrated to leave a yellow oil, which was purified by flash chromatography [AcOEt–EtOH (5:1)] to give **12** (855 mg, 98%) as a pale yellow oil, $[\alpha]_D^{22}=-39.5°$ (*c* 1.00, $CHCl_3$); MS *m/z*: 255 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (NH); ^1H NMR ($CDCl_3$) δ: 1.40 (3H, d, *J*=6.8 Hz, Me), 1.59 (1H, br, CH_2NH), 2.85–3.0 (4H, m, two CH_2's), 3.95 (1H, q, *J*=6.8 Hz, C*H*Me), 6.85 [1H, s, C(4′)–H], 7.01 [1H, d, *J*=2.5 Hz, C(2)–H], 7.10 and 7.19 [1H each, dd, *J*=7.5, 7.5 Hz, C(5)–H and C(6)–H], 7.36 and 7.56 [1H each, d, *J*=7.5 Hz, C(4)–H and C(7)–H], 7.73 [1H, s, C(2′)–H], 8.06 [1H, s, N(1)–H];[25] HRMS *m/z* calcd for $C_{15}H_{17}N_3O$: 255.1371, found: 255.1390.

*(ii) From **19**:* A mixture of **19** (2.54 g, 22.7 mmol), 2-(3-indolyl)ethyl bromide[24] (5.09, 22.7 mmol), *N*-ethyldiisopropylamine (2.93 g, 22.7 mmol), and THF (50 ml) was heated under reflux in an atmosphere of N_2 for 7 days. The reaction mixture was diluted with ether, washed with saturated aqueous NaCl, dried over anhydrous K_2CO_3, and concentrated in vacuo. Purification of the residual oil by flash chromatography [AcOEt–EtOH (5:1)] afforded **12** (3.17 g, 55%) as a pale yellow oil. This sample was identical (by comparison of the IR and ^1H NMR spectra, TLC mobility, and specific rotation) with the one obtained by method-(i).

(*S*)-*N*-[1-(5-Oxazoyl)ethyl]-1*H*-indole-3-acetamide (23). A stirred mixture of **19** (252 mg, 2.25 mmol), indole-3-acetic acid (473 mg, 2.7 mmol), and diethyl phosphorocyanidate (734 mg, 4.5 mmol) in DMF (6 ml) was cooled to 0°C, and a solution of Et_3N (401 mg, 4.0 mmol) in DMF (1 ml) was added. After having been stirred at 0°C for 30 min and at room temperature for 2 h, the reaction mixture was diluted with H_2O (20 ml) and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated. Purification of the residual oil by flash chromatography [acetone–hexane (1:2)] gave **23** (569 mg, 94%) as a slightly yellow solid. Recrystallization from AcOEt–hexane (1:1) provided an analytical sample as colorless needles, mp 118.5–119.5°C; $[\alpha]_D^{25}=-67.5°$ (*c* 0.99, MeOH); MS *m/z*: 269 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3435, 3300 (NH), 1624 (amide CO); ^1H NMR ($CDCl_3$) δ: 1.35 (3H, d, *J*=7 Hz, Me), 3.77 (2H, s, CH_2CO), 5.33 (1H, dq, *J*=8.5, 7 Hz, C*H*Me), 5.88 (1H, d, *J*=8.5 Hz, NHCO), 6.73 [1H, s, C(4′)–H], 7.14 [1H, s, C(2)–H], 7.14 and 7.24 [1H each, dd, *J*=7.5, 7.5 Hz, C(5)–H and C(6)–H], 7.40 and 7.52 [1H each, d, *J*=7.5 Hz, C(4)–H and C(7)–H], 7.69 [1H, s, C(2′)–H], 8.36 [1H, s, N(1)–H].[25] Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.93; H, 5.55; N, 15.67.

(*S*)-3-[[2-(1*H*-Indol-3-yl)ethyl][1-(5-oxazoyl)ethyl]amino]-3-oxopropanoic acid ethyl ester (20). Diethyl phosphorocyanidate (4.05 g, 24.8 mmol) and Et_3N (2.51 g, 24.8 mmol) were successively added to a chilled, stirred solution of **12** (3.17 g, 12.4 mmol) and monoethyl malonate (2.46 g, 18.6 mmol) in DMF (100 ml). The mixture was stirred at room temperature for 2 h and concentrated in vacuo. The residue was partitioned between H_2O and $CHCl_3$, and the $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated. Purification of the residual oil by flash chromatography (AcOEt) furnished **20** (4.50 g, 98%) as a slightly yellowish oil, $[\alpha]_D^{28}=-38.8°$ (*c* 1.00, $CHCl_3$); MS *m/z*: 369 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (NH), 1736 (ester CO), 1646 (amide CO); ^1H NMR ($CDCl_3$) δ: 1.27 (2H) and 1.33 (1H) (t each, *J*=7 Hz, CH_2Me), 1.60 (3H, d, *J*=6.8 Hz, CH*Me*), 2.64 (2/3H), 2.75 (1/3H), 2.84 (2/3H), and 2.98 (1/3H) (ddd each, *J*=13.5, 11, 5.5 Hz, CH_2CH_2N), 3.40 and 3.42 (2/3H each, AB type d's, *J*=15.5 Hz) and 3.63 and 3.72 (1/3H each, AB type d's, *J*=15.5 Hz) (CH_2CO), 3.3–3.5 (2H, m, CH_2CH_2N), 4.20 (4/3H) and 4.27 (2/3H) (q each, *J*=7 Hz, CH_2Me), 5.10 (1/3H) and 5.99 (2/3H) (br q each, *J*=6.8 Hz, C*H*Me), 6.91 (2/3H) and 6.95 (1/3H) [d each, *J*=2 Hz, C(2)–H], 7.00 (1/3H) and 7.09 (2/3H) [d each, *J*=1 Hz, C(4′)–H], 7.10 (1/3H), 7.13 (2/3H), 7.17 (1/3H), and 7.20 (2/3H) [dd each, *J*=8, 8 Hz, C(5)–H and C(6)–H], 7.33 (1/3H), 7.37 (2/3H), 7.44 (2/3H), and 7.59 (1/3H) [d each, *J*=8 Hz, C(4)–H and C(7)–H], 7.82 (1/3H) and 7.87 (2/3H) [s each, C(2′)–H], 8.04 (1/3H) and 8.16 (2/3H)

(s each, NH);[25] HRMS *m/z* calcd for $C_{20}H_{23}N_3O_4$: 369.1689, found: 369.1693.

[*S*-(*E*)]-[2,3,4,9-Tetrahydro-2-[1-(5-oxazoyl)ethyl]-1*H*-pyrido[3,4-*b*]indol-1-ylidene]acetic acid ethyl ester (21). A mixture of **20** (443 mg, 1.2 mmol), $POCl_3$ (1.84 g, 12 mmol), and CH_3CN (10 ml) was heated under reflux for 4 h. After cooling, the solvent and excess $POCl_3$ were distilled off in vacuo. The residual oil, after washing with hexane, was dissolved in $CHCl_3$, and the $CHCl_3$ solution was poured into 10% aqueous Na_2CO_3 (10 ml). The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2. The CH_2Cl_2 extracts and the above organic layer were combined, washed successively with 10% aqueous Na_2CO_3 and saturated aqueous NaCl, dried over anhydrous K_2CO_3, and concentrated. Purification of the residual oil by flash chromatography [AcOEt–hexane (1:1)] provided **21** (192 mg, 46%) as a pale yellow oil, $[\alpha]_D^{28}=-24.0°$ (*c* 0.50, $CHCl_3$); MS *m/z*: 351 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200 (NH), 1663 (ester CO); ^1H NMR ($CDCl_3$) δ: 1.33 (3H, t, *J*=7 Hz, CH_2*Me*), 1.65 (3H, d, *J*=6.8 Hz, CH*Me*), 2.86 [2H, dd, *J*=6.5, 6.5 Hz, C(4)–H's], 3.24 and 3.44 [1H each, ddd, *J*=12, 6.5, 6.5 Hz, C(3)–H's], 4.21 (2H, q, *J*=7 Hz, CH_2Me), 5.17 (1H, s, C*H*CO_2Et), 5.33 (1H, q, *J*=6.8 Hz, C*H*Me), 7.07 [1H, s, C(4′)–H], 7.09 and 7.26 [1H each, dd, *J*=8, 8 Hz, C(6)–H and C(7)–H], 7.47 and 7.52 [1H each, d, *J*=8 Hz, C(5)–H and C(8)–H], 7.87 [1H, s, C(2′)–H], 13.05 (1H, s, NH);[25] HRMS *m/z* calcd for $C_{20}H_{21}N_3O_3$: 351.1583, found: 351.1592.

[*S*-(*R,*R**)]- and [*R*-(*R**,*S**)]-2,3,4,9-Tetrahydro-2-[1-(5-oxazoyl)ethyl]-1*H*-pyrido[3,4-*b*]indole-1-acetic acid ethyl ester (22a and 22b).** *(i) Via catalytic hydrogenation of **21**:* A solution of **21** (2.96 g, 8.42 mmol) in AcOEt (150 ml) was hydrogenated over 10% Pd–C (3.0 g) at room temperature and atmospheric pressure for 5 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to leave a pale yellow oil. Purification by flash chromatography (AcOEt) afforded a 3:1 mixture[26] (2.76 g, 93%) of **22a** and **22b** as a pale yellow oil, MS *m/z*: 353 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (NH), 1717 (ester CO); ^1H NMR ($CDCl_3$) δ: 1.25 (9/4H) and 1.28 (3/4H) (t each, *J*=7 Hz, CH_2*Me*), 1.45 (3/4H) and 1.48 (9/4H) (d each, *J*=6.8 Hz, CH*Me*), 2.5–3.35 [6H, m, C(3)–H's, C(4)–H's, and CH_2CO_2Et], 4.1–4.25 (3H, m, C*H*Me and CH_2Me), 4.28 (3/4H, dd, *J*=8.8, 5 Hz) and 4.46 (1/4H, dd, *J*=8.8, 3.5 Hz) [C(1)–H], 6.89 (3/4H) and 6.93 (1/4H) [s each, C(4′)–H], 7.08 and 7.15 [1H each, dd, *J*=7.5, 7.5 Hz, C(6)–H and C(7)–H], 7.30 (3/4H) and 7.31 (1/4H) (d each, *J*=7.5 Hz) and 7.466 (1/4H) and 7.474 (3/4H) (d each, *J*=7.5 Hz) [C(5)–H and C(8)–H], 7.77 (3/4H) and 7.81 (1/4H) [s each, C(2′)–H], 8.47 (3/4H) and 8.50 (1/4H) (s, NH);[25] HRMS *m/z* calcd for $C_{20}H_{23}N_3O_3$: 353.1739, found: 353.1746.

*(ii) Via reduction of the iminium salt **24**:* The iminium salt **24**, prepared from **20** (100 mg, 0.27 mmol) in a manner similar to that described above for **21** without treatment with 10% aqueous Na_2CO_3, was dissolved in MeOH (4 ml). $NaBH_4$ (40 mg, 1.1 mmol) was added to the MeOH solution under ice-cooling, and the mixture was then stirred at 0°C for 1.5 h. After addition of acetone (1 ml), the reaction mixture was concentrated in vacuo, and the residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated. Purification of the residual oil by flash chromatography [AcOEt–hexane (4:1)] yielded a 2:1 mixture[26] (30 mg, 31% from **20**) of **22a** and **22b**.

*(iii) Via the modified Pictet–Spengler reaction of **12**:* A solution of **12** (682 mg, 2.67 mmol) and ethyl propiolate (288 mg, 2.9 mmol) in $CHCl_3$ (10 ml) was stirred at room temperature for 40 h. After addition of trifluoroacetic acid (0.52 ml, 6.7 mmol), stirring was continued for a further 1 h. The reaction mixture was concentrated in vacuo, and the residue was partitioned between $CHCl_3$ and 10% aqueous Na_2CO_3. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a yellow oil. Purification by flash chromatography (AcOEt) gave a 1:2 mixture[26] (736 mg, 78%) of **22a** and **22b**.

[*S*-[*R,*R**-(*E*)]]- and [*R*-[*R**,*S**-(*E*)]]-4-[2,3,4,9-Tetrahydro-2-[1-(5-oxazoyl)ethyl]-1*H*-pyrido[3,4-*b*]indol-1-yl]-2-butenoic acid ethyl ester (27a and 27b) and [*S*-[*R**,*R**-(*Z*)]]- and [*R*-[*R**,*S**-(*Z*)]]-4-[2,3,4,9-tetrahydro-2-[1-(5-oxazoyl)ethyl]-1*H*-pyrido[3,4-*b*]indol-1-yl]-2-butenoic acid ethyl ester (30a and 30b).** A stirred solution of a 3:1 mixture (1.55 g, 4.39 mmol) of **22a** and **22b** in CH_2Cl_2 (40 ml) was cooled to −78°C in an atmosphere of N_2, and a 0.98 M solution (8.9 ml, 8.7 mmol) of DIBALH in hexane was added dropwise over 5 min. After the mixture had been stirred at −78°C for 20 min, the reaction was quenched by adding MeOH (4 ml). Stirring was continued for a further 20 min, and a solution of ethyl (triphenylphosphoranylidene)acetate (1.68 g, 4.8 mmol) in CH_2Cl_2 (30 ml) was added. After having been brought to room temperature during 1.5 h and stirred for 3 h, the reaction mixture was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous K_2CO_3, and concentrated to leave a brown oil, which was then subjected to flash chromatography [AcOEt–hexane (2:1)]. Earlier fractions furnished a 3:1 mixture[26] (426 mg, 26%) of **30a** and **30b** as a pale yellow glass, MS *m/z*: 379 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 1705 (ester CO); ^1H NMR ($CDCl_3$) δ: 1.27 (9/4H) and 1.29 (3/4H) (t each, *J*=7 Hz, CH_2*Me*), 1.46 (9/4H) and 1.47 (3/4H) (d each, *J*=6.8 Hz, CH*Me*), 2.5–2.8 and 3.0–3.4 [6H, m each, C(1)-CH_2, C(3)–H's, and C(4)–H's], 4.06 (3/4H, dd, *J*=7, 3.5 Hz) and 4.1–4.2 (1/4H, m) [C(1)–H], 4.16 (3/2H) and 4.20 (1/2H) (q each, *J*=7 Hz, CH_2Me), 4.24 (3/4H) and 4.32 (1/4H) (q each, *J*=6.8 Hz, C*H*Me), 5.77 (1/4H) and 5.78 (3/4H) (d each, *J*=11.5 Hz, CH=C*H*CO_2Et), 6.34 (1/4H) and 6.44 (3/4H) (dt each, *J*=11.5, 8 Hz, C*H*=CHCO_2Et), 6.88 (3/4H) and 6.93 (1/4H) [s each, C(4′)–H], 7.07 (1/4H), 7.08 (3/4H), 7.12 (1/4H), and 7.14 (3/4H) [dd each, *J*=7.5, 7.5 Hz, C(6)–H and C(7)–H], 7.30 (1/4H), 7.31 (3/4H), 7.45 (1/4H), and 7.46 (3/4H) [d each, *J*=7.5 Hz, C(5)–H and C(8)–H], 7.79 (3/4H) and 7.82 (1/4H) [s each, C(2′)–H], 8.30 (1H, s, NH);[25] HRMS *m/z* calcd for $C_{22}H_{25}N_3O_3$: 379.1896, found: 379.1895.

Later fractions in the above chromatography gave a 3:1 mixture[26] (990 mg, 59%) of **27a** and **27b** as a pale yellow glass, MS *m/z*: 379 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 1709 (ester CO); ^1H NMR ($CDCl_3$) δ: 1.26 (3/4H) and 1.29

(9/4H) (t each, J=7 Hz, CH_2Me), 1.41 (3/4H) and 1.48 (9/4H) (d each, J=6.8 Hz, $CHMe$), 2.55–2.9 and 3.15–3.3 [6H, m each, C(1)–CH_2, C(3)–H's, and C(4)–H's], 3.87 (3/4H) and 4.05 (1/4H) [t each, J=6.5 Hz, C(1)–H], 4.08–4.22 (3H, m, C*H*Me and CH_2Me), 5.80 (3/4H) and 5.85 (1/4H) (d each, J=15.5 Hz, CH=C*H*CO_2Et), 6.84 (3/4H) and 6.91 (1/4H) [s each, C(4′)–H], 6.90 (1/4H) and 6.95 (3/4H) (dt each, J=15.5, 7.5 Hz, C*H*=$CHCO_2$Et), 7.08 (1/4H), 7.09 (3/4H), 7.14 (1/4H), and 7.15 (3/4H) [dd each, J=7.5, 7.5 Hz, C(6)–H and C(7)–H], 7.28 (1H), 7.46 (1/4H), and 7.48 (3/4H) [d each, J=7.5 Hz, C(5)–H and C(8)–H], 7.77 (3/4H) and 7.81 (1/4H) [s each, C(2′)–H], 8.14 (1/4H) and 8.23 (3/4H) (s each, NH);[25] HRMS *m/z* calcd for $C_{22}H_{25}N_3O_3$: 379.1896, found: 379.1909.

[1*R*-(1α,2β,4aβ,5β,13bα,14aα)]- and [1*R*-(1α,2α,4aα,5β,13bα,14aα)]-1,2,7,8,13,13b,14,14a-Octahydro-5-methyl-5*H*-2,4a-epoxyindolo[2′,3′:3,4]pyrido[1,2-*b*][2,7]naphthyridine-1-carboxylic acid ethyl ester (28 and 29). (Entry 3 in Table 1.) A solution of a 3:1 mixture (650 mg, 1.71 mmol) of **27a** and **27b** in toluene (65 ml) was heated under reflux in an atmosphere of N_2 for 24 h. The reaction mixture was concentrated in vacuo to leave a brown glass, which was purified by flash chromatography [AcOEt–hexane (1:1) and then AcOEt]. The first fractions to elute afforded **29** (31 mg, 5%) as a pale brown solid. Recrystallization from EtOH gave an analytical sample as colorless needles, mp 181–182°C (dec); $[\alpha]_D^{20}$=−52.3° (*c* 0.51, $CHCl_3$); MS *m/z*: 379 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (NH), 2835, 2810, 2735 (*trans*-quinolizidine ring[19]), 1730 (ester CO); ^1H NMR ($CDCl_3$) δ: 1.14 (1H, ddd, J=13, 13, 11 Hz) and 2.46 (1H, ddd, J=13, 4, 2.5 Hz) [C(14)–H's], 1.33 (3H, t, J=7 Hz, CH_2Me), 1.39 [3H, d, J=6.5 Hz, C(5)-Me], 2.16 [1H, ddd, J=13, 6, 4 Hz, C(14a)–H], 2.21 [1H, d, J=6 Hz, C(1)–H], 2.52 (1H, ddd, J=11, 11, 4 Hz) and 3.63 (1H, ddd, J=11, 5.5, 2 Hz) [C(7)–H's], 2.79 (1H, dddd, J=15, 4, 2, 2 Hz) and 2.92 (1H, dddd, J=15, 11, 5.5, 2.5 Hz) [C(8)–H's], 3.11 [1H, q, J=6.5 Hz, C(5)–H], 3.70 [1H, dddd, J=11, 2.5, 2.5, 2 Hz, C(13b)–H], 4.24 and 4.26 (1H each, dq, J=10.5, 7 Hz, CH_2Me), 6.12 [1H, s, C(2)–H], 7.11 and 7.15 [1H each, dd, J=7.5, 7.5 Hz, C(10)–H and C(11)–H], 7.29 and 7.50 [1H each, d, J=7.5 Hz, C(9)–H and C(12)–H], 7.69 (1H, s, NH), 8.16 [1H, s, C(4)–H]; ^{13}C NMR ($CDCl_3$) δ: 14.3 (q), 15.1 (q), 22.4 (t), 34.7 (t), 42.7 (d), 46.9 (t), 49.5 (d), 58.2 (d), 60.5 (d), 61.4 (t), 90.2 (s), 97.6 (d), 109.0 (s), 110.8 (d), 118.3 (d), 119.7 (d), 121.8 (d), 127.0 (s), 133.9 (s), 136.1 (s), 171.8 (s), 171.9 (d). Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.29; H, 6.62; N, 10.97.

A mixture of **27a** and **27b** was recovered (129 mg, 20%) from the second fractions to elute in the above chromatography. The third fraction provided **28** (342 mg, 53%) as a pale brown solid. Recrystallization of the solid from MeOH yielded an analytical sample as colorless needles, mp 208–211°C (dec); $[\alpha]_D^{20}$=+136° (*c* 0.49, $CHCl_3$); MS *m/z*: 379 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (NH), 2850, 2805, 2760 (*trans*-quinolizidine ring[19]), 1732 (ester CO); ^1H NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz, CH_2Me), 1.38 [3H, d, J=6.5 Hz, C(5)-Me], 1.65 (1H, ddd, J=12, 12, 12 Hz) and 2.42 (1H, ddd, J=12, 6, 1 Hz) [C(14)–H's], 2.20 [1H, ddd, J=12, 6, 3.5 Hz, C(14a)–H], 2.43 (1H, ddd, J=11, 10.5, 4 Hz) and 3.48 (1H, ddd, J=11, 5.5, 2.5 Hz) [C(7)–H's], 2.76 (1H, ddd, J=15.5, 4, 2.5 Hz) and 2.95 (1H, dddd, J=15.5, 10.5, 5.5, 2 Hz) [C(8)–H's], 2.83 [1H, dd, J=4, 3.5 Hz, C(1)–H], 3.30 [1H, q, J=6.5 Hz, C(5)–H], 3.60 [1H, ddd, J=12, 2, 1 Hz, C(13b)–H], 4.13 and 4.17 (1H each, dq, J=11, 7 Hz, CH_2Me), 6.12 [1H, d, J=4 Hz, C(2)–H], 7.09 and 7.14 [1H each, dd, J=7.5, 7.5 Hz, C(10)–H and C(11)–H], 7.30 and 7.48 [1H each, d, J=7.5 Hz, C(9)–H and C(12)–H], 7.67 (1H, s, NH), 7.91 [1H, s, C(4)–H]; ^{13}C NMR ($CDCl_3$) δ: 14.2 (q), 16.8 (q), 21.9 (t), 34.1 (t), 34.8 (d), 46.5 (t), 52.7 (d), 56.1 (d), 58.4 (d), 61.3 (t), 91.5 (s), 95.4 (d), 109.2 (s), 110.8 (d), 118.3 (d), 119.5 (d), 121.6 (d), 127.2 (s), 133.6 (s), 136.2 (s), 169.9 (s), 171.4 (d). Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.62; H, 6.63; N, 10.93.

[1*S*-(1α,2α,4aα,5α,13bβ,14aβ)]-1,2,7,8,13,13b,14,14a-Octahydro-5-methyl-5*H*-2,4a-epoxyindolo[2′,3′:3,4]-pyrido[1,2-*b*][2,7]naphthyridine-1-carboxylic acid ethyl ester (31). A solution of a 3:1 mixture (100 mg, 0.26 mmol) of **30a** and **30b** in toluene (10 ml) was heated under reflux in an atmosphere of N_2 for 24 h. The reaction mixture was concentrated in vacuo to leave a brown glass, which was subjected to flash chromatography (AcOEt). From earlier fractions, a mixture of **30a** and **30b** was recovered (42 mg, 42%). Later fractions furnished **31** (40 mg, 40%) as a pale brown solid. Recrystallization from AcOEt gave an analytical sample as colorless minute needles, mp 208–210°C (dec); $[\alpha]_D^{25}$=−4.3° (*c* 0.50, $CHCl_3$); MS *m/z*: 379 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 2850, 2805 (*trans*-quinolizidine ring[19]), 1724 (ester CO); ^1H NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, CH_2Me), 1.40 [3H, d, J=6.5 Hz, C(5)-Me], 1.51 (1H, ddd, J=12, 12, 12 Hz) and 2.21 (1H, ddd, J=12, 6, 1 Hz) [C(14)–H's], 2.08 [1H, ddd, J=12, 8, 6 Hz, C(14a)–H], 2.44 (1H, ddd, J=11, 10.5, 4 Hz) and 3.46 (1H, ddd, J=11, 5.5, 2.5 Hz) [C(7)–H's], 2.62 [1H, d, J=8 Hz, C(1)–H], 2.75 (1H, ddd, J=15.5, 4, 2.5 Hz) and 2.94 (1H, dddd, J=15.5, 10.5, 5.5, 2 Hz) [C(8)–H's], 3.29 [1H, q, J=6.5 Hz, C(5)–H], 3.57 [1H, ddd, J=12, 2, 1 Hz, C(13b)–H], 4.11 and 4.21 (1H each, dq, J=10.7, 7 Hz, CH_2Me), 6.20 [1H, s, C(2)–H], 7.09 and 7.14 [1H each, dd, J=7.5, 7.5 Hz, C(10)–H and C(11)–H], 7.30 and 7.48 [1H each, d, J=7.5 Hz, C(9)–H and C(12)–H], 7.69 (1H, s, NH), 7.80 [1H, s, C(4)–H]; ^{13}C NMR ($CDCl_3$) δ: 14.3 (q), 16.6 (q), 21.9 (t), 30.4 (t), 34.5 (d), 46.3 (t), 48.3 (d), 56.0 (d), 58.3 (d), 61.2 (t), 89.3 (s), 96.0 (d), 109.3 (s), 110.8 (d), 118.3 (d), 119.5 (d), 121.6 (d), 127.2 (s), 133.6 (s), 136.2 (s), 170.6 (s), 170.6 (d). Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.39; H, 6.60; N, 10.92.

Retro-Michael reaction of 27a,b. A solution of a 3:1 mixture (40 mg, 0.11 mmol) of **27a** and **27b** in *o*-DCB (10 ml) was heated with DBN (12 mg, 0.10 mmol) at 150°C in an atmosphere of Ar for 2.5 h. After cooling, the reaction mixture was concentrated in vacuo to leave a brown oil. Purification of the oil by preparative TLC (silica gel, AcOEt) afforded **35** (21 mg, 53%) as a yellow foam, MS *m/z*: 379 (M^+); ^1H NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7 Hz, CH_2Me), 1.39 (3H, d, J=6.8 Hz, $CHMe$), 2.8–3.05 (4H, m, two CH_2's), 3.94 (1H, q, J=6.8 Hz, C*H*Me), 4.23 (2H, q, J=7 Hz, CH_2Me), 5.94 (1H, d, J=15.1 Hz, CH=C*H*CO_2Et), 6.61 (1H, dd, J=15.6, 11.2 Hz, ArCH=C*H*), 6.82 [1H, s, C(4′)–H], 7.00 (1H, d, J=15.6 Hz, ArC*H*=CH), 7.07 and 7.21 [1H each, dd, J=7.5, 7.5 Hz, C(5)–H and C(6)–H], 7.29 and 7.52 [1H each, d,

J=7.5 Hz, C(4)–H and C(7)–H], 7.46 (1H, dd, J=15.1, 11.2 Hz, C*H*=CHCO$_2$Et), 7.73 [1H, s, C(2′)–H], 8.54 [1H, s, N(1)–H];[25] HRMS *m/z* calcd for $C_{22}H_{25}N_3O_3$: 379.1896, found: 379.1895. On the basis of the ^{1}H NMR spectrum, this sample is presumed to be a mixture of the four possible isomers based on two olefinic double bond. The signals arising from the (*E*,*E*)-isomer comprising 70% of the isomers are described above.

(5*S*-*trans*)-5,7,8,13,13b,14–Hexahydro-5-methylindolo-[2′,3′:3,4]pyrido[1,2-*b*][2,7]naphthyridine-1-carboxylic acid ethyl ester (33). *(i) From 28:* A solution of **28** (374 mg, 1.0 mmol) in AcOH (3 ml) and xylene (15 ml) was heated under reflux in an atmosphere of Ar for 8 h. After concentration of the reaction mixture, the residual brown glass was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated to leave a brown glass, which was then subjected to flash chromatography [hexane–acetone (2:1)]. Earlier fractions furnished **33** (65 mg, 18%) as a yellow solid. Recrystallization from EtOH afforded an analytical sample as colorless needles, mp 198–200°C; $[\alpha]_D^{24}$=−268° (*c* 0.35, $CHCl_3$); MS *m/z*: 361 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 2810, 2760 (*trans*-quinolizidine ring[19]), 1717 (ester CO); ^{1}H NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz, CH$_2$*Me*), 1.62 [3H, d, J=6.5 Hz, C(5)–Me], 2.55 (1H, ddd, J=11, 11, 4 Hz) and 3.58 (1H, dd, J=11, 5 Hz) [C(7)–H's], 2.84 (1H, dd, J=15, 4 Hz) and 3.00 (1H, dddd, J=15, 11, 5, 2 Hz) [C(8)–H's], 3.14 (1H, dd, J=17, 11 Hz) and 3.84 (1H, dd, J=17, 2.5 Hz) [C(14)–H's], 3.70 [1H, br d, J=11 Hz, C(13b)–H], 3.87 [1H, q, J=6.5 Hz, C(5)–H], 4.40 (2H, q, J=7 Hz, C*H*$_2$Me), 7.11 and 7.17 [1H each, dd, J=7.5, 7.5 Hz, C(10)–H and C(11)–H], 7.33 and 7.52 [1H each, d, J=7.5 Hz, C(9)–H and C(12)–H], 8.03 (1H, s, NH), 8.63 [1H, s, C(4)–H], 8.99 [1H, s, C(2)–H]; ^{13}C NMR ($CDCl_3$) δ: 14.3 (q), 21.9 (t), 22.8 (q), 33.2 (t), 48.9 (t), 54.8(d), 57.4 (d), 61.3 (t), 109.0 (s), 110.9 (d), 118.3 (d), 119.5 (d), 121.7 (d), 124.2 (s), 127.0 (s), 134.1 (s), 136.4 (s), 136.6 (s), 144.8 (s), 148.9 (d), 151.9 (d), 166.0 (s). Anal. Calcd for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63. Found: C, 72.83; H, 6.40; N, 11.60.

Later fractions in the above chromatography provided **32** (251 mg, 64%) as a yellow glass, MS *m/z*: 397 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH), 1669 (ester CO); ^{1}H NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz, CH$_2$*Me*), 1.27 [3H, d, J=7 Hz, C(5)-Me], 1.62 [1H, ddd, J=13.5, 12, 12 Hz, C(14)–Hβ], 2.50 (1H, br) and 3.45 (1H, dd, J=11, 4 Hz) [C(7)–H's], 2.75–2.85 [3H, m, C(5)–H, C(14)–Hα, and C(14a)–H], 2.87 (1H, m) and 3.37 (1H, ddd, J=13.5, 4, 3.5 Hz) [C(8)–H's], 3.65 [1H, br, C(13b)–H], 4.11 (2H, q, J=7 Hz, C*H*$_2$Me), 4.71 [1H, d, J=4.5 Hz, C(4)–H], 5.53 [1H, br, N(3)–H], 7.08 and 7.13 [1H each, dd, J=7.5, 7.5 Hz, C(10)–H and C(11)–H], 7.30 and 7.46 [1H each, d, J=7.5 Hz, C(9)–H and C(12)–H], 7.43 [1H, br d, J=5.5 Hz, C(2)–H], 8.19 [1H, br, N(13)–H]; HRMS *m/z* calcd for $C_{22}H_{27}N_3O_4$: 397.2002, found: 397.2003.

(ii) From 32: A stirred solution of **32** (251 mg, 0.63 mmol) in AcOH (2 ml) and xylene (10 ml) was heated under reflux in an atmosphere of Ar for 8 h. Work-up of the reaction mixture in a manner similar to that described above under method-(i) provided **33** (30 mg, 13%) as a pale yellow solid together with unaltered **32** (155 mg, 62%).

(iii) From 31: A solution of **31** (50 mg, 0.13 mmol) in AcOH (1 ml) and xylene (5 ml) was heated under reflux in an atmosphere of Ar for 8 h. The reaction mixture was worked up as described above under method-(i), giving **33** (6.0 mg, 13%) as a pale yellow solid and **32** (27 mg, 52%) as a yellow glass.

Degradation of the adduct 29. A solution of **29** (50 mg, 0.13 mmol) in AcOH (1 ml) and xylene (2 ml) was heated under reflux in an atmosphere of N_2 for 1 h. After cooling, the reaction mixture was concentrated in vacuo and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed successively with 10% aqueous Na_2CO_3 and saturated aqueous NaCl, dried, and concentrated in vacuo to leave a brown oil, which was submitted to flash chromatography [AcOEt–hexane (1:1)]. Earlier fractions provided **37** (21 mg, 44%) as a pale yellow solid. Recrystallization from EtOH furnished an analytical sample as colorless prisms, mp 180–181.5°C; $[\alpha]_D^{22}$=−184° (*c* 0.25, $CHCl_3$); MS *m/z*: 361 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3140 (NH), 1709 (ester CO); ^{1}H NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7 Hz, OCH$_2$*Me*), 1.36 (3H, t, J=7.5 Hz, ArCH$_2$*Me*), 2.73 (1H, ddd, J=15.5, 4, 2 Hz) and 2.80 (1H, ddd, J=15.5, 11, 4.5 Hz) [C(7)–H's], 3.03 and 3.06 (1H each, dq, J=15, 7.5 Hz, ArC*H*$_2$Me), 3.50 (1H, ddd, J=14.5, 11, 4 Hz) and 4.25 (1H, ddd, J=14.5, 4.5, 2 Hz) [C(6)–H's], 3.53 (1H, dd, J=17.5, 9.5 Hz) and 3.78 (1H, dd, J=17.5, 2.5 Hz) [C(13)–H's], 4.32 (2H, q, J=7 Hz, OC*H*$_2$Me), 5.16 [1H, dd, J=9.5, 2.5 Hz, C(12b)–H], 7.07 and 7.15 [1H each, dd, J=7.5, 7.5 Hz, C(9)–H and C(10)–H], 7.31 and 7.42 [1H each, d, J=7.5 Hz, C(8)–H and C(11)–H], 7.98 (1H, s, NH), 8.51 [1H, s, C(2)–H]; ^{13}C NMR ($CDCl_3$) δ: 12.1 (q), 14.3 (q), 20.0 (t), 29.1 (t), 35.4 (t), 44.6 (t), 60.0 (d), 60.8 (t), 109.8 (s), 110.9 (d), 118.1 (d), 119.8 (d), 121.4 (s), 122.1 (d), 126.9 (s), 134.2 (s), 136.2 (s), 141.5 (d), 142.2 (s), 144.6 (s), 148.4 (s), 166.0 (s). Anal. Calcd for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63. Found: C, 73.18; H, 6.42; N, 11.55.

Later fractions in the above chromatography afforded **36** (20 mg, 46%) as a pale yellow solid, which was recrystallized from EtOH to give an analytical sample as colorless minute needles, mp 224–227°C; $[\alpha]_D^{25}$=−41.7° (*c* 0.20, $CHCl_3$); MS *m/z*: 333 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3155 (NH), 1715 (ester CO); ^{1}H NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7 Hz, OCH$_2$*Me*), 2.69 (1H, dd, J=15.5, 4.5 Hz) and 2.97 (1H, ddd, J=15.5, 12, 5 Hz) [C(7)–H's], 3.47 (1H, ddd, J=14.5, 12, 4.5 Hz) and 4.09 (1H, dd, J=14.5, 5 Hz) [C(6)–H's], 3.61 (1H, dd, J=17.5, 9.5 Hz) and 3.77 (1H, dd, J=17.5, 2 Hz) [C(13)–H's], 4.34 (2H, q, J=7 Hz, OC*H*$_2$Me), 5.20 [1H, dd, J=9.5, 2 Hz, C(12b)–H], 7.07 and 7.15 [1H each, dd, J=7.5, 7.5 Hz, C(9)–H and C(10)–H], 7.31 and 7.42 [1H each, d, J=7.5 Hz, C(8)–H and C(11)–H], 8.12 (1H, s, NH), 8.20 [1H, s, C(4)–H], 8.53 [1H, s, C(2)–H]; ^{13}C NMR ($CDCl_3$) δ: 14.3 (q), 17.4 (t), 35.7 (t), 42.3 (t), 59.4 (d), 61.0 (t), 109.1 (s), 110.9 (d), 118.2 (d), 119.8 (d), 122.3 (d), 123.4 (s), 126.9 (s), 132.5 (d), 133.9 (s), 136.2 (s), 141.5 (d), 141.7 (s), 147.6 (s), 165.7 (s). Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.80; H, 5.74; N, 12.49.

(5*S*-*trans*)-(5,7,8,13,13b,14–Hexahydro-5-methylindolo-[2′,3′:3,4]pyrido[1,2-*b*][2,7]naphthyridin-1-yl)carbamic acid *tert*-butyl ester (34). To a stirred solution of **33** (79.5 mg, 0.22 mmol) in THF (3 ml) and MeOH (1.5 ml) in an atmosphere of Ar was added a solution of LiOH (32 mg, 1.3 mmol) in H_2O (1 ml). The resulting mixture was stirred at room temperature for 1.5 h and then concentrated in vacuo. After addition of 1N aqueous HCl (1.3 ml), the precipitate was filtered off, washed with H_2O, and dried. The slightly yellow solid (73.6 mg) thus obtained was dissolved in *tert*-BuOH (2.5 ml), and the solution was then heated under reflux with diphenyl phosphoroazidate (90 mg, 0.33 mmol) and Et_3N (35 mg, 0.35 mmol) in an atmosphere of Ar for 5 h. The reaction mixture was then concentrated in vacuo to leave a yellow oil, which was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated. Purification of the residual oil by flash chromatography (AcOEt) afforded **34** (56.8 mg, 64% from **33**) as a colorless solid. Recrystallization from AcOEt–hexane (1:1) and drying over P_2O_5 at 2 mmHg and 50°C for 5 h produced an analytical sample as colorless minute prisms, mp 183–185°C (dec); $[\alpha]_D^{21}=-205°$ (*c* 0.11, $CHCl_3$); MS *m*/*z*: 404 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3330, 3170 (NH), 1696 (carbamate CO); ^1H NMR ($CDCl_3$) δ: 1.57 (9H, s, *tert*-Bu), 1.58 [3H, d, *J*=6.5 Hz, C(5)–Me], 2.49 (1H, ddd, *J*=11.5, 11, 4 Hz) and 3.52 (1H, ddd, *J*=11.5, 5, 2 Hz) [C(7)–H's], 2.57 (1H, dd, *J*=16, 11 Hz) and 2.96 (1H, d, *J*=16 Hz) [C(14)–H's], 2.80 (1H, ddd, *J*=15, 2, 2 Hz) and 2.93 (1H, m) [C(8)–H's], 3.56 [1H, br d, *J*=11 Hz, C(13b)–H], 3.77 [1H, q, *J*=6.5 Hz, C(5)–H], 6.71 [1H, br, C(1)-NH], 7.13 and 7.21 [1H each, dd, *J*=7.5, 7.5 Hz, C(10)–H and C(11)–H], 7.36 and 7.50 [1H each, d, *J*=7.5 Hz, C(9)–H and C(12)–H], 8.14 [1H, br, N(13)–H], 8.28 [1H, s, C(4)–H], 8.81 [1H, s, C(2)–H]; HRMS *m*/*z* calcd for $C_{24}H_{28}N_4O_2$: 404.2212, found: 404.2210. Anal. Calcd for $C_{24}H_{28}N_4O_2 \cdot 1/5H_2O$: C, 70.63; H, 7.01; N, 13.73. Found: C, 70.75; H, 6.95; N, 13.67.

(5*S*-*trans*)-5,7,8,13,13b,14–Hexahydro-5-methylindolo-[2′,3′:3,4]pyrido[1,2-*b*][2,7]naphthyridine [(−)-normalindine] [(−)-4]. A mixture of **34** (25.7 mg, 0.064 mmol) and CF_3CO_2H (0.15 ml) in CH_2Cl_2 (1.5 ml) was stirred at room temperature for 5 h. The reaction mixture was then poured into cold 10% aqueous Na_2CO_3 (2 ml) and extracted with $CHCl_3$ containing a small amount of EtOH. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous K_2CO_3, and concentrated to leave an orange glass (19.5 mg), which was taken up in DMF (0.7 ml). After addition of butyl nitrite (65 mg, 0.63 mmol), the mixture was stirred at 70°C under Ar atmosphere for 30 min and concentrated in vacuo. The residual oil was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$, and the $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous K_2CO_3, and concentrated to leave a brown oil. Purification by two successive preparative TLC [silica gel, ether–MeOH (10:1); silica gel, AcOEt] provided (−)-**4** (7.4 mg, 40% from **34**) as a yellow solid. Recrystallization of the solid from AcOEt furnished pale yellow prisms, mp 122–126°C; $[\alpha]_D^{22}=-212°$ (*c* 0.29, $CHCl_3$); MS *m*/*z* (relative intensity): 290 (21), 289 (M^+) (100), 288 (65), 275 (20), 274 (100), 273 (14), 272 (44), 246 (12), 245 (21), 170 (21), 169 (58), 144 (18), 143 (14), 137 (17), 115 (12); UV λ_{max}^{MeOH} nm (ϵ): 224 (38600), 269 (8230), 282 (7870), 290 (6390); IR ν_{max}^{KBr} cm^{-1}: 3410, 3180, 2980, 2855, 2814, 1601, 1572, 1499, 1460, 1412, 1391, 1371, 1324, 1315, 1300, 1269, 1061, 741; HRMS *m*/*z* calcd for $C_{19}H_{19}N_3$: 289.1579, found: 289.1578. The ^1H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) spectral data for this sample were in agreement with those reported for natural sample[3] and for (±)-**4**,[9b] respectively.

Acknowledgements

We are grateful to Professors M. V. Sargent (University of Western Australia) and D. Arbain (University of Andalas) for providing us with a sample and spectral copies of natural normalindine and to Emeritus Professor T. Fujii (Kanazawa University) for his interest and encouragement.

References

1. (a) Jahangir; Brook, M. A.; MacLean, D. B.; Holland, H. L. *Tetrahedron* **1987**, *43*, 5761–5768 and references cited therein. (b) Phillipson, J. D.; Hemingway, S. R.; Bisset, N. G.; Houghton, P. J.; Shellard, E. J. *Phytochemistry* **1974**, *13*, 973–978. (c) Lin, L.-Z.; Cordell, G. A. *Phytochemistry* **1990**, *29*, 2744–2746. (d) Erdelmeier, C. A. J.; Regenass, U.; Rali, T.; Sticher, O. *Planta Med.* **1992**, *58*, 43–48. (e) Abreu, P.; Pereira, A. *Heterocycles* **1998**, *48*, 885–891.

2. Massiot, G.; Thépenier, P.; Jacquier, M.-J.; Le Men-Olivier, L.; Verpoorte, R.; Delaude, C. *Phytochemistry* **1987**, *26*, 2839–2846.

3. Arbain, D.; Putra, D. P.; Sargent, M. V. *Aust. J. Chem.* **1993**, *46*, 977–985.

4. Brown, R. T.; Chapple, C. L. *Tetrahedron Lett.* **1976**, 1629–1630.

5. Olaniyi, A. A.; Rolfsen, W. N. A.; Verpoorte, R. *Planta Med.* **1981**, *43*, 353–359.

6. Caprasse, M.; Tavernier, D.; Anteunis, M. J. O.; Angenot, L. *Planta Med.* **1984**, *50*, 27–30.

7. Arbain, D.; Lajis, N. H.; Putra, D. P.; Sargent, M. V.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1993**, *46*, 969–976.

8. Arbain, D.; Byrne, L. T.; Dachriyanus; Sargent, M. V. *Aust. J. Chem.* **1997**, *50*, 1109–1110.

9. (a) Maiti, B. C.; Giri, V. S.; Pakrashi, S. C. *Heterocycles* **1990**, *31*, 847–850. (b) Rey, A. W.; Szarek, W. A.; MacLean, D. B.; *Heterocycles* **1991**, *32*, 1143–1151.

10. Ohba, M.; Kubo, H.; Fujii, T.; Ishibashi, H.; Sargent, M. V.; Arbain, D. *Tetrahedron Lett.* **1997**, *38*, 6697–6700.

11. For reviews on the Diels–Alder reaction of oxazoles, see Hassner, A.; Fischer, B. *Heterocycles* **1993**, *35*, 1441–1465 and references cited therein.

12. For the intramolecular oxazole–olefin Diels–Alder reactions, see (a) Levin, J. I.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 1397–1398. (b) Levin, J. I.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 4325–4332. (c) Subramanyam, C.; Noguchi, M.; Weinreb, S. M. *J. Org. Chem.* **1989**, *54*, 5580–5585. (d) Shimada, S.; Tojo, T. *Chem. Pharm. Bull.* **1983**, *31*, 4247–4258. (e) Levin, J. I. *Tetrahedron Lett.* **1989**, *30*, 2355–2358. (f) Jung, M. E.; Dansereau, S. M. K. *Heterocycles* **1994**, *39*, 767–778. (g) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595–3607.

13. Ohba, M.; Kubo, H.; Seto, S.; Fujii, T.; Ishibashi, H. *Chem. Pharm. Bull.* **1998**, *46*, 860–862.
14. Waldmann, H.; Schmidt, G.; Jansen, M.; Geb, J. *Tetrahedron* **1994**, *50*, 11865–11884.
15. Shioiri, T.; Yokoyama, Y.; Kasai, Y.; Yamada, S. *Tetrahedron* **1976**, *32*, 2211–2217.
16. (a) Polniaszek, R. P.; McKee, J. A. *Tetrahedron Lett.* **1987**, *28*, 4511–4514. (b) Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc*. **1989**, *111*, 4859–4863.
17. (a) Vercauteren, J.; Lavaud, C.; Lévy, J.; Massiot, G. *J. Org. Chem.* **1984**, *49*, 2278–2279. (b) Bailey, P. D.; Hollinshead, S. P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 739–745.
18. Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195–1202.
19. (a) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157–2167. (b) Wenkert, E.; Roychaudhuri, D. K. *J. Am. Chem. Soc.* **1956**, *78*, 6417–6418.
20. Gribble, G. W.; Pelcman, B. *J. Org. Chem.* **1992**, *57*, 3636–3642.
21. Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157.
22. Doyle, M. P.; Dellaria Jr., J. F.; Siegfried, B.; Bishop, S. W. *J. Org. Chem.* **1977**, *42*, 3494–3498.
23. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
24. Hoshino, T.; Shimodaira, K. *Justus Liebigs Ann. Chem.* **1935**, *520*, 19–30.
25. For convenience, each position of the oxazole ring is indicated by a primed number.
26. The diastereoisomeric ratio was estimated on the basis of ^{1}H NMR spectral analysis.