Chem. Pharm. Bull.
32(10)3892—3899(1984)

Synthetic Studies on Lythraceae Alkaloids *via* [3+2]Cycloaddition. I. Total Synthesis of Some Simple Phenylquinolizidine Alkaloids and Ester Alkaloids[1,2]

SEIICHI TAKANO* and KOZO SHISHIDO

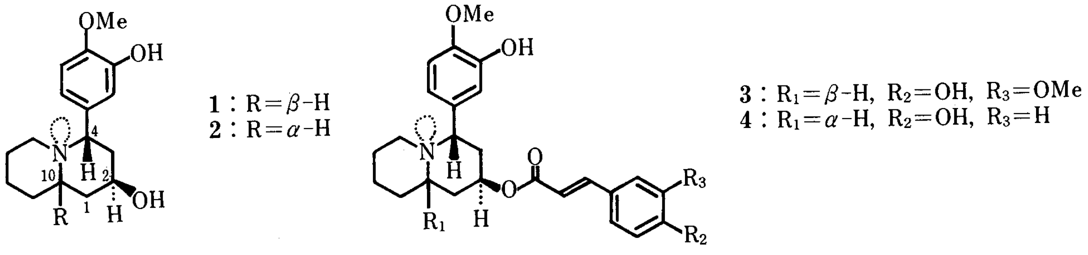
Pharmaceutical Institute, Tohoku University,
Aobayama, Sendai 980, Japan

(Received February 15, 1984)

A general synthetic route to Lythraceae alkaloids based on a regio- and stereoselective [3+2]cycloaddition reaction has been developed. The [3+2]cycloaddition of the nitrone **5** with the olefins **14** and **26** gave the adducts **15** and **27** which, upon treatment with methanesulfonyl chloride followed by reductive cleavage of the N–O bonds and acetylation, gave the *trans*-quinolizidines **18** and **30** and the *cis*-isomers **20** and **32** in reasonable yields. The *cis*-isomers were converted into the simple phenylquinolizidine alkaloid, (±)-**2**, and the ester alkaloid, (±)-10-*epi*-desmethoxyabresoline (**4**). On the other hand, (±)-**1**, (±)-lasubine II (**23**), and (±)-abresoline (**3**) were synthesized efficiently from the *trans*-isomers, after inversion of the configuration at the C-2 position by means of the Mitsunobu reaction.

Keywords——[3+2]cycloaddition reaction; Lythraceae alkaloid; (±)-lasubine II; (±)-abresoline; (±)-10-*epi*-desmethoxyabresoline; Mitsunobu reaction

Since the first isolation of the Lythraceae alkaloids[3] from *Decodon verticillatus* by Ferris[4] in 1962, more than forty alkaloids have been isolated from plants of the Lythraceae family. Most of these alkaloids possess a 2,4-disubstituted quinolizidine ring system, which can be divided into two groups, namely *trans* (*e.g.* **1** and **3**) and *cis* (*e.g.* **2** and **4**) series as shown in Fig. 1.



1 : R=β-H
2 : R=α-H

3 : R_1=β-H, R_2=OH, R_3=OMe
4 : R_1=α-H, R_2=OH, R_3=H

Fig. 1

Because the stereochemical interrelationships in **1**—**4** share a striking similarity, differing only in the configuration at C-10, we attempted to design a synthetic pathway to these natural products. Although both types of alkaloids have been synthesized so far, there is still a need for an efficient general route leading to the formation of both types from a single precursor.[5]

In planning access to these systems, we sought a convenient methodology not only for constructing both *trans*- and *cis*-quinolizidine frameworks from a common precursor but also for general application to synthesizing other Lythraceae alkaloids. The key features of the present synthesis involve regio-[6] and stereoselective[7] intermolecular [3+2]cycloaddition reaction of the cyclic nitrone **5**[8] with the 1-aryl-but-3-enol **6** and the subsequent internal Nalkylation of the adduct (**7**) by a proximally positioned electrophilic center, followed by reductive N–O bond fission of the presumed quaternary ammonium salt intermediate (**8**), affording both types of quinolizidines[9] (**11**, **12**) (Chart 1). We describe here the synthesis of three phenylquinolizidine alkaloids and two ester alkaloids of the Lythraceae group.

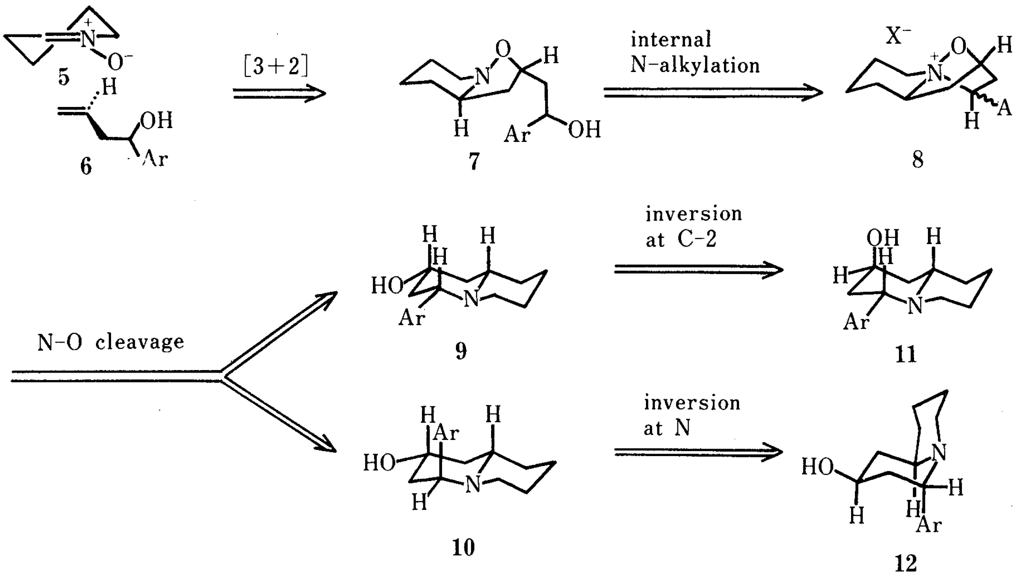


Chart 1

Synthesis of (±)-Phenylquinolizidine Alkaloids (1, 2) and (±)-Lasubine II (23)

In 1974, Rother and Schwarting isolated two isomeric phenylquinolizidines (**1**, **2**) from young seedlings of *Heimia salicifolia* plants.[10,11] Both alkaloids were absent in extracts of plants obtained at a later stage of growth,[12] and may be biogenetic intermediates in the formation of more complex products. For our initial synthetic target, we chose these isomeric alkaloids (**1**, **2**).

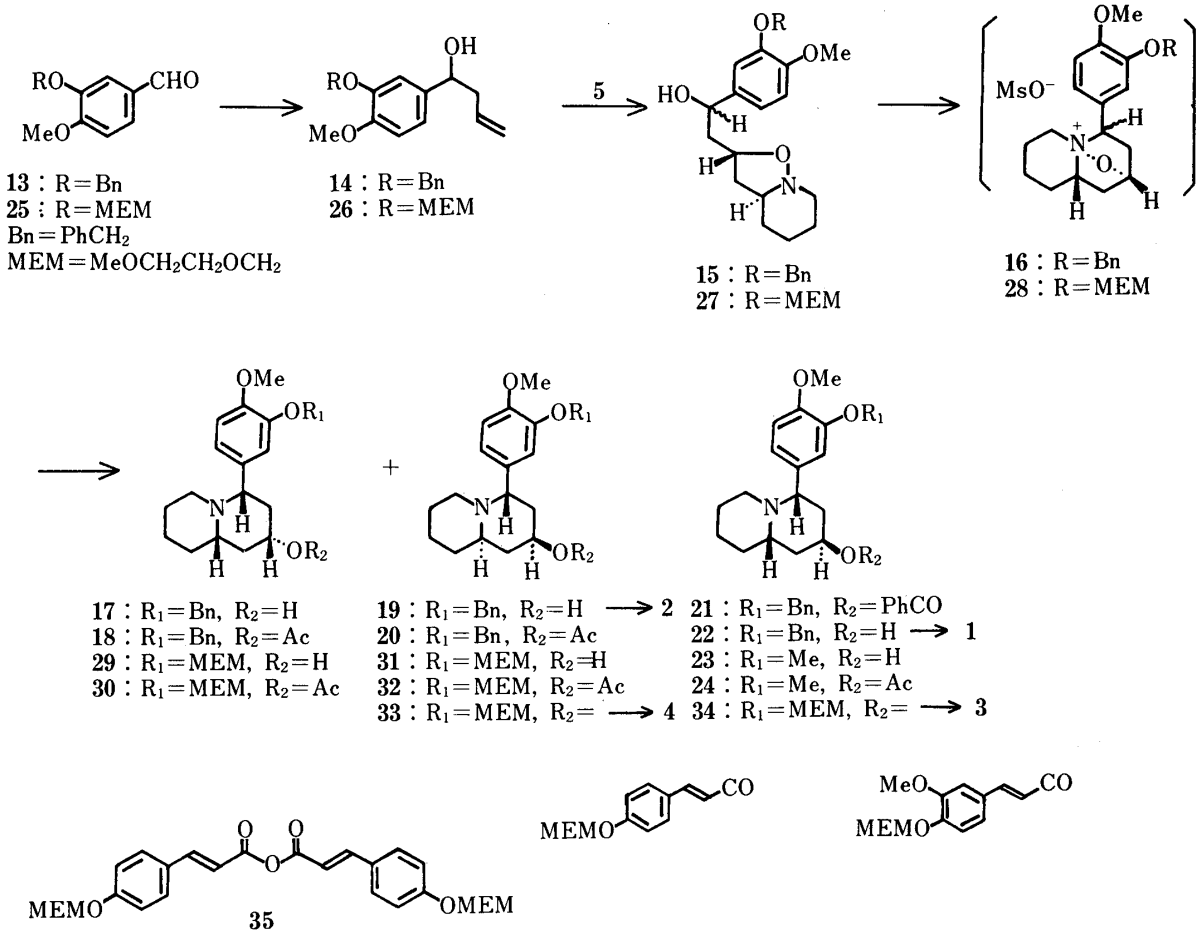
On heating of the homoallylic alcohol (**14**), readily derived from 3-benzyloxy-4-methoxybenzaldehyde (**13**) by treatment with allylmagnesium bromide, with 3,4,5,6-tetrahydropyridine 1-oxide (**5**) in toluene under reflux, the adduct (**15**) was obtained quantitatively as two inseparable diastereomers. Because of the absence of assignable characteristics in the spectral data, the relative stereochemistry shown in adduct (**15**) at the future C-2 and C-10 and the regiochemistry were determined from the eventual transformation of **15** into the alkaloids (**1**, **2**). Treatment of **15** with methanesulfonyl chloride in pyridine followed by reduction with zinc in 50% aqueous acetic acid in a one-pot operation gave the expected two alcohols (**17**, **19**) through the quaternary salt intermediate (**16**). These alcohols were separated and characterized as the acetates (**18**, **20**) in 37.5 and 25.3% yields, respectively. The quinolizidine ring of the acetate **18** should be *trans*-fused as indicated by the Bohlmann band[13] in the infrared (IR) spectrum and the nuclear magnetic resonance (NMR) absorption of the benzylic proton (C–4H) at δ 2.95 as double doublets ($J=11$ and 3 Hz). The axial orientation of C–2H was deduced from the NMR absorption at δ 4.86 with a half-height width of 19 Hz. On the other hand, the acetate **20** showed a mass spectrum similar to that of **18**. The absence of the Bohlmann band and the NMR chemical shift of C–4H (δ 4.14) demonstrated the presence of the *cis*-quinolizidine system.[18] Then **20** was converted into the alkaloid (**2**), mp 193—194 °C (lit.[11] 193—194 °C), with the *cis*-quinolizidine configuration by successive hydrolysis and hydrogenolysis. The overall yield of **2** from **13** was 15.5%.

For the conversion of the *trans*-acetate (**18**) into **1**, it is necessary to invert the configuration at C-2. Thus, the alcohol **17**, obtained by hydrolysis of **18**, was treated with diethyl azodicarboxylate and triphenylphosphine in the presence of benzoic acid[14] to give the benzoate (**21**). The expected inversion of the configuration at C-2 in **21** was confirmed by the NMR absorption of C-2H at δ5.38 with a half-height width of 10Hz, indicating the equatorial orientation. The alkaloid (±)-**1**, mp 94—95 °C (lit.[10] 94—95 °C), was then obtained in 19.2% overall yield from **13** by sequential methanolysis and hydrogenolysis. Further confirmation of the structure of the synthetic **1** was obtained as follows. Treatment of **1** with excess diazomethane gave the methylated alcohol (**23**) which was shown to be spectroscopically (IR and NMR) identical with lasubine II, isolated from *Lagerstroemia subcostata* by Fuji *et al.*[15] Then, **23** was further converted into the known acetate **24**[16] which was also shown to be identical with the authentic substance by comparison of IR and NMR spectra.

Synthesis of (±)-Abresoline (3) and (±)-10-*epi*-Desmethoxyabresoline (4)

Three minor alkaloids have been isolated from *Heimia salicifolia* by Schwarting *et al.*[17,18] Two of those are abresoline (**3**) and 10-*epi*-desmethoxyabresoline (**4**), the structural features of which seem to be the same as those of phenylquinolizidines (**1**, **2**) except that both **3** and **4** are the C-2 cinnamate derivatives. In evaluating these alkaloids (**3**, **4**) as a target for total synthesis, attention should be paid to the cinnamate formation and the protection of phenolic hydroxyl groups.

We began with β-methoxyethoxymethyl(MEM)-protected[19] isovanillin (**25**). The MEM protection technique for phenolic hydroxyl groups has already been applied in the first total synthesis of (±)-abresoline by Quick *et al.*[20] The aldehyde **25** was transformed to the



13 : R=Bn
25 : R=MEM
Bn=$PhCH_2$
MEM=$MeOCH_2CH_2OCH_2$

14 : R=Bn
26 : R=MEM

15 : R=Bn
27 : R=MEM

16 : R=Bn
28 : R=MEM

17 : R_1=Bn, R_2=H
18 : R_1=Bn, R_2=Ac
29 : R_1=MEM, R_2=H
30 : R_1=MEM, R_2=Ac

19 : R_1=Bn, R_2=H → 2
20 : R_1=Bn, R_2=Ac
31 : R_1=MEM, R_2=H
32 : R_1=MEM, R_2=Ac
33 : R_1=MEM, R_2= → 4

21 : R_1=Bn, R_2=PhCO
22 : R_1=Bn, R_2=H → 1
23 : R_1=Me, R_2=H
24 : R_1=Me, R_2=Ac
34 : R_1=MEM, R_2= → 3

35

Chart 2

[3+2]cycloadduct (**27**), *via* the homoallylalcohol (**26**), which was then subjected to the quinolizidine-forming sequence as described for **15** to afford the two isomeric acetates (**30**, **32**). These structures were supported by the spectral features, and the MEM group remained intact under the conditions of zinc-50% aqueous acetic acid treatment.

For completion of the total synthesis of 10-*epi*-desmethoxyabresoline (**4**), the esterification of the hydroxyl group at C-2 in **31**, prepared by basic hydrolysis of **32**, with *p*-MEMoxycinnamic acid with retention of the configuration is necessary. Since the usual esterification conditions (*e.g.* dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP); acid chloride, pyridine; *etc.*) gave no satisfactory results (less than 20% yield), recourse was taken to the anhydride method.[21] Thus, treatment of **31** with the anhydride **35** (prepared from the corresponding cinnamic acid[19] with DCC) in pyridine in the presence of a catalytic amount of DMAP gave the desired cinnamate (**33**) in 72.7% yield. The structure of **33** was supported by IR absorptions of cinnamate at 1700 and 1630 cm^{-1}, NMR absorptions of olefinic protons at δ 6.28 and 7.57 each as a doublet ($J=16$ Hz), and the molecular ion peak at *m*/*z* 599 in the mass spectrum (MS). Subsequent exposure of **33** to trifluoroacetic acid[20] in methylene chloride provided (±)-10-*epi*-desmethoxyabresoline (**4**) as colorless prisms, mp 220—222 °C (lit.[18] 221—223 °C), in 12.2% overall yield from **25**. The identity of synthetic **4** was confirmed by comparison of the IR, NMR and ultraviolet (UV) spectra with those of an authentic sample. Meanwhile, the conversion of the *trans*-acetate (**30**) into abresoline (**3**) was completed as follows. The alcohol **29**, prepared by basic hydrolysis of **30**, was subjected to Mitsunobu conditions in the presence of 3-methoxy-4-MEMoxycinnamic acid to afford the inverted cinnamate (**34**) in 85.6% yield on the basis of consumed **29**. In the NMR spectrum of **34**, the C-2 equatorial proton and the olefinic protons were observed at 5.24 as a multiplet and at δ 6.48 and 7.75 each as a doublet ($J=16$ Hz), respectively. The Bohlmann band in IR and the molecular ion peak at *m*/*z* 629 in the MS supported the structure. In the Mitsunobu reaction using the cinnamic acid, which has not previously appeared in the literature, the reaction always seemed to be accompanied by recovery of the starting alcohol (**29**) in a series of experiments under various reaction conditions. Finally, **34** was treated under the same conditions as described for the synthesis of **4** to afford (±)-abresoline (**3**),[17] which was shown to be identical with an authentic sample by comparison of the IR, NMR and UV spectra, as a yellow amorphous solid in 15.9% overall yield from **25**.

Thus, we completed efficient total syntheses of two types of Lythraceae alkaloids. The methodology described herein is considered to hold considerable promise as a general procedure for syntheses of 2,4-disubstituted quinolizidine alkaloids.

Experimental

Melting points were determined on a Yanagimoto MP-S2 apparatus and are uncorrected. IR spectra were obtained on a Shimadzu IR 400 instrument or a Hitachi 125 grating spectrometer, and UV spectra on a Hitachi 124 spectrophotometer in methanol. NMR spectra were recorded on JEOL PMX-60, JEOL PS-100 and Varian XL-200 spectrometers with tetramethylsilane as an internal standard. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broadened. Ordinary mass spectra were measured with a Hitachi M-52G instrument, while high resolution mass spectroscopy was performed on a JEOL TMS-OISG-2 spectrometer. Unless otherwise specified, all reactions were carried out under an atmosphere of dry argon or nitrogen and solutions were dried over anhydrous Na_2SO_4. Column chromatography was carried out with Wako gel C-200. Preparative thin layer chromatography (prep. TLC) was performed on 20 × 20 cm plates coated with 1-mm thickness of Merck Kieselgel 60 containing PF 254 indicator.

1-(3-Benzyloxy-4-methoxyphenyl)-3-buten-1-ol (14)——A solution of allyl bromide (5.2 ml) and 3-benzyloxy-4-methoxybenzaldehyde (**13**) (12.0 g) in dry THF (80 ml) was added dropwise to a stirred mixture of Mg (1.81 g) in dry THF (40 ml) at room temperature (RT). The reaction mixture was stirred for 45 min, then sat. NH_4Cl solution was added and the whole was extracted with benzene. The extract was washed with sat. NaCl solution, then dried, and the solvent was evaporated off to give **14** (10.8 g, 76.6%) as colorless needles, mp 68—69 °C, after recrystallization from benzene–*n*-hexane. NMR ($CDCl_3$) δ: 2.07 (1H, d, $J=3$ Hz, –O$\underline{H}$, D_2O disappeared), 2.45 (1H, t, $J=7$ Hz, $-CH_2-$), 3.88 (3H, s, –OMe), 4.65 (1H, dd, $J=7$ and 3 Hz, $-\overset{\text{OH}}{\overset{|}{\text{C}}}-\underline{\text{H}}$), 5.19 (1H, s, $-O-CH_2-Ph$), 4.92—6.17 (3H, m, $-CH=CH_2$), 6.98 (3H, m, Ar–H), 7.47 (5H, m, Ar–H). MS *m/z*: 284 (M^+). High resolution MS (*m/z*): Calcd for $C_{18}H_{20}O_3$: 284.1413. Found: 284.1418.

The Isoxazolidine 15——A mixture of 1-hydroxypiperidine (0.65 g) and HgO (yellow) (2.8 g) in dry CH_2Cl_2 (20 ml) was stirred at −10—0 °C for 1.5 h, then filtered. Dry toluene (10 ml) was added to the filtrate and the CH_2Cl_2 was evaporated off. The resulting solution of the nitrone **5** in toluene was refluxed with a solution of the homoallylalcohol **14** (0.91 g) in toluene (15 ml) for 2 h. The organic layer was washed with sat. NaCl solution, dried and evaporated to give a residue, which was subjected to chromatography. Elution with $CHCl_3$–MeOH (99 : 1, v/v) afforded **15** (1.27 g, 100%) as a colorless oil, which was an inseparable epimeric mixture at the hydroxy-bearing carbon. NMR ($CDCl_3$) δ: 3.83 (3H, s, –OMe), 4.78 (1H, m, $\text{Ar}-\overset{\text{OH}}{\langle}\underline{\text{H}}$), 5.13 (2H, s, $Ph-CH_2-$). MS *m/z*: 383 (M^+), 256 (100%). High resolution MS (*m/z*): Calcd for $C_{23}H_{29}NO_4$: 383.2095. Found: 383.2084.

The *trans*-Quinolizidine Acetate 18 and the *cis*-Acetate 20——Methanesulfonyl chloride (1.64 ml) was added dropwise to a stirred solution of **15** (2.7 g) in dry pyridine (30 ml) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min and at for 2.5 h. After removal of the pyridine and the excess reagent by evaporation, the residue was taken up in 50% aqueous AcOH (30 ml) and the solution was treated with Zn dust (6.9 g) at RT for 2.5 h. The mixture was filtered with the aid of celite and the filtrate was concentrated to give a pale yellow oil, which was then treated with Ac_2O (20 ml) and pyridine (20 ml) at RT for 15 h. Removal of the solvent gave a residue, which was subjected to chromatography. Elution with $CHCl_3$ afforded **18** (1.08 g, 37.5%) as colorless needles, mp 89—90 °C, after recrystallization from MeOH. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1}: 2785 and 2740 (Bohlmann band), 1725 ($-O-\underset{\text{O}}{\underset{\|}{\text{C}}}-CH_3$). NMR ($CDCl_3$) δ: 2.02 (3H, s, $-O-\underset{\text{O}}{\underset{\|}{\text{C}}}-CH_3$), 2.95 (1H, dd, $J=11$ and 3 Hz, C–4H), 4.86 (1H, m, $W_{1/2}=19$ Hz, C–2H). MS *m/z*: 409 (M^+). *Anal.* Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 73.37; H, 7.68; N, 3.42. From the fraction eluted with $CHCl_3$–MeOH (99 : 1, v/v), the *cis*-isomer (**20**) (0.73 g, 25.3%) was collected as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1}: 1730. NMR ($CDCl_3$) δ: 2.05 (3H, s, $-O-\underset{\text{O}}{\underset{\|}{\text{C}}}-CH_3$), 4.14 (1H, t, $J=6$ Hz, C–4H), 5.20 (1H, m, C–2H). MS *m/z*: 409 (M^+). High resolution MS (*m/z*): Calcd for $C_{25}H_{31}NO_4$: 409.2253. Found: 409.2269.

Hydrolysis of 20——A solution of **20** (120 mg) and NaOH (27.6 mg) in aqueous MeOH (H_2O 0.5 ml, MeOH 3 ml) was stirred at RT for 15 h, then evaporated to dryness. The residue was extracted with CH_2Cl_2. The extract was washed with sat. NaCl solution, dried and evaporated to give a residue, which was purified by prep. TLC developed with $CHCl_3$–MeOH, (90 : 10, v/v) to give **19** (103 mg, 95.7%) as colorless prisms, mp 136—137 °C, after recrystallization from MeOH. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1}: 3575 and 3400 (–OH). NMR ($CDCl_3$) δ: 3.90 (3H, s, –OMe), 4.05 (2H, m, C-2, 4H), 5.23 (2H, s, $Ph-C\underline{H}_2-$). MS *m/z*: 367 (M^+). *Anal.* Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.24; H, 8.12; N, 3.85.

The *cis*-Quinolizidine Alkaloid 2——A solution of **19** (550 mg) in MeOH (10 ml) was hydrogenated over 10% Pd–C (20 mg) at atmospheric pressure for 2 h at RT. The catalyst was removed by filtration and the filtrate was concentrated to give **2** (347 mg, 83.5%) as colorless prisms, mp 193—194 °C, (lit.[11]) 193—194 °C), after recrystallization from MeOH–Et_2O. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1}: 3350 (–OH). NMR ($CDCl_3+CF_3CO_2H$) δ: 3.95 (3H, s, –OMe), 4.25—5.00 (2H, m, C-2, 4H), 7.04 (3H, m, Ar–H). MS *m/z*: 277 (M^+). High resolution MS (*m/z*): Calcd for $C_{16}H_{23}NO_3$: 277.1677. Found: 277.1674.

Hydrolysis of 18——A solution of **18** (1.9 g) and NaOH (0.43 g) in aqueous MeOH (H_2O 4 ml, MeOH 40 ml) was stirred at RT for 1 h, then evaporated to dryness. The residue was extracted with $CHCl_3$. The extract was washed with sat. NaCl solution, dried and evaporated to give the alcohol **17** (1.7 g, 100%) as colorless prisms, mp 124—125 °C, after recrystallization from MeOH–Et_2O. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1}: 3600 and 3400 (–OH), 2790 and 2745 (Bohlmann band). NMR ($CDCl_3$) δ: 2.90 (1H, dd, $J=11$ and 3 Hz, C–4H), 3.75 (1H, m, C–2H), 3.90 (1H, s, –OMe), 5.21 (2H, s, $Ph-C\underline{H}_2-$). MS *m/z*: 367 (M^+). *Anal.* Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 74.90; H, 7.89; N, 3.88.

The Mitsunobu Reaction of 17——A solution of diethyl azodicarboxylate (0.12 ml) in dry THF (1.5 ml) was added dropwise to a stirred solution of **17** (200 mg), triphenylphosphine (200 mg) and benzoic acid (93 mg) in dry THF (1.5 ml) at RT. The resulting mixture was stirred at the same temperature for 2.5 h. After removal of the solvent, the residue was extracted with $CHCl_3$. The extract was washed with sat. $NaHCO_3$ solution and H_2O, then dried. Evaporation of the solvent gave a pale yellow oil which was subjected to chromatography. Elution with $CHCl_3$ afforded **21** (240 mg, 93.4%) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1}: 2800 and 2750 (Bohlmann band), 1710 ($Ph-\underset{\text{O}}{\underset{\|}{\text{C}}}-O-$). NMR ($CDCl_3$) δ: 3.35 (1H, dd, $J=10$ and 5 Hz, C–4H), 3.87 (3H, s, –OMe), 5.20 (2H, s, $Ph-C\underline{H}_2-$), 5.38 (1H, m, $W_{1/2}=10$ Hz, C–2H), 6.93 (2H, s, Ar–H), 7.60 (1H, s, Ar–H), 7.50 (8H, m, Ar–H), 8.25 (2H, m, Ar–H). MS *m/z*: 471 (M^+). High resolution MS (*m/z*): Calcd for $C_{30}H_{33}NO_4$: 471.2408. Found: 471.2367.

Methanolysis of 21——A solution of **21** (0.95 g) and NaOMe (1.1 g) in dry MeOH (20 ml) was stirred at RT for

10.5 h, then evaporated to dryness. The residue was extracted with CH_2Cl_2 and the extract was washed with H_2O, dried and evaporated to give a brownish oil, which was subjected to chromatography. Elution with $CHCl_3$ afforded **22** (0.67 g, 91.8%) as a colorless oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3600 and 3400 (–OH), 2790 and 2750 (Bohlmann band). NMR ($CDCl_3$) δ: 3.40 (1H, m, C–4H), 3.89 (3H, s, –OMe), 4.16 (1H, m, C–2H), 5.20 (2H, s, Ph–CH_2–), 6.93 (2H, s, Ar–H), 7.08 (1H, s, Ar–H), 7.50 (5H, m, Ar–H). MS *m/z*: 367 (M^+). High resolution MS (*m/z*): Calcd for $C_{23}H_{29}NO_3$: 367.2147. Found: 367.2175.

The *trans*-Quinolizidine Alkaloid (1)——A solution of **22** (120 mg) in MeOH (3 ml) was hydrogenated over 10% Pd–C (10 mg) at atmospheric pressure for 38 h at RT. The catalyst was removed by filtration and the filtrate was concentrated to give **1** (70 mg, 77.8%) as colorless prisms, mp 94—95 °C (lit.[10] 94—95 °C), after recrystallization from AcOEt. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3350 (–OH), 2800 and 2760 (Bohlmann band). NMR ($CDCl_3$) δ: 3.35 (1H, m, $W_{1/4}=18$ Hz, C–4H), 3.90 (3H, s, –OMe), 4.18 (1H, m, $W_{1/4}=11$ Hz, C–2H), 6.90 (2H, s, Ar–H), 7.06 (1H, s, Ar–H). MS *m/z*: 277 (M^+). High resolution MS (*m/z*): Calcd for $C_{16}H_{23}NO_3$: 277.1677. Found: 277.1651.

Lasubine II (23)——A solution of CH_2N_2 (large excess, prepared from 5 g of *p*-toluenesulfonyl-*N*-methyl-*N*-nitrosamide) was added to a solution of **1** (120 mg) in MeOH (1 ml) at 0 °C and the mixture was left at the same temperature for 15 h, then evaporated to dryness. The residue was extracted with CH_2Cl_2 and the extract was washed with sat. NaCl solution, dried and evaporated. The resulting crude oil was purified by prep. TLC (developed with MeOH–$CHCl_3$–NH_4OH, 10 : 9 : 1, v/v) to give **23**[14] (110 mg, 87.3%) as a colorless oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3600 (–OH), 2800 and 2750 (Bohlmann band). NMR (200 MHz, $CDCl_3$) δ: 3.34 (1H, m, C–4H), 3.87, 3.90 (3H each, s, –OMe), 4.16 (1H, m, $W_{1/2}=8$ Hz, C–2H), 6.82 (2H, br s, Ar–H), 6.92 (1H, br s, Ar–H). MS *m/z*: 291 (M^+, 100%).

Acetylation of 23——A solution of **23** (100 mg) in Ac_2O (1 ml) and pyridine (1 ml) was stirred at RT for 15 h. After removal of the excess reagents, the residue was extracted with CH_2Cl_2. The extract was washed with H_2O, sat. $NaHCO_3$ solution and H_2O, then dried. Removal of the solvent gave a residue, which was purified by prep. TLC (developed with $CHCl_3$–MeOH, 95 : 5, v/v) to give **24**[15] (80 mg, 70.2%) as a colorless oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2800 and 2750 (Bohlmann band), 1730 ($-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{OCH_3}$). NMR ($CDCl_3$) δ: 2.14 (3H, s, $-\mathrm{O}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{CH_3}$), 3.27 (1H, m, $W_{1/4}=18$ Hz, C–4H), 3.90, 3.93 (3H each, s, –OMe), 5.15 (1H, m, $W_{1/2}=8$ Hz, C–2H), 6.92 (2H, s, Ar–H), 7.01 (1H, s, Ar–H). MS *m/z*: 333 (M^+).

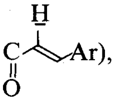
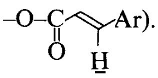
1-[3-(β-Methoxyethoxymethyloxy)-4-methoxyphenyl]-3-buten-1-ol (26)——A solution of allyl bromide (3.1 ml) and 3-(β-methoxyethoxymethyloxy)-4-methoxybenzaldehyde (**25**)[18] (7.0 g) in dry THF (20 ml) was added dropwise to a stirred mixture of Mg (1.1 g) in dry THF (50 ml) at RT. Stirring was continued for 0.5 h, then the same treatment as described for **14** was carried out. The resulting crude residue was chromatographed, and elution with *n*-hexane–AcOEt (1 : 1, v/v) afforded **26** (6.3 g, 89.4%) as a colorless oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3580 and 3425 (–OH), 1635 (–CH=CH_2). NMR ($CDCl_3$) δ: 3.37 (3H, s, –OCH_3), 3.88 (3H, s, Ar–OCH_3), 5.25 (2H, s, –O–CH_2–O–), 6.93—7.30 (3H, m, Ar–H). MS *m/z*: 282 (M^+). High resolution MS (*m/z*): Calcd for $C_{15}H_{22}O_5$: 282.1466. Found: 282.1463.

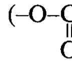
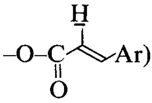
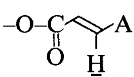
The Isoxazolidine (27)——A mixture of 1-hydroxypiperidine (1.72 g) and HgO (yellow) (7.37 g) in dry CH_2Cl_2 (60 ml) was stirred at -8—0 °C for 1.5 h, then filtered. Dry toluene (60 ml) was added to the filtrate and the CH_2Cl_2 was evaporated off. Then, **26** (2.4 g) was added to the resulting solution of the nitrone (**5**), and the mixture was refluxed for 2.5 h. The same work-up and purification as described for **15** afforded **27** (3.21 g, 99.1%) as a colorless oil (an epimeric mixture at the hydroxy-bearing carbon). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3500 (–OH). NMR ($CDCl_3$) δ: 3.38 (3H, s, –OCH_3), 3.87 (3H, s, Ar–O–CH_3), 4.87 (1H, m, Ar–$\underline{\mathrm{H}}$), 5.34 (2H, s, –O–CH_2–O–). MS *m/z*: 381 (M^+). High resolution MS (*m/z*): Calcd for $C_{20}H_{31}NO_6$: 381.2149. Found: 381.2126.

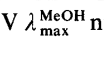
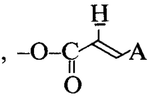
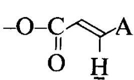
The *trans*-Quinolizidine Acetate 30 and the *cis*-Acetate 32——Methanesulfonyl chloride (1.65 ml) was added dropwise to a stirred solution of **27** (2.7 g) in dry pyridine (30 ml) at 0 °C. The mixture was stirred at 0 °C for 40 min and at RT for 1.5 h. After evaporation of the solvent, the residue was taken up in 50% aqueous AcOH (30 ml). This solution was treated with Zn dust (6.95 g) at RT for 2 h, then filtered. The filtrate was evaporated to dryness to give a residue, which was extracted with $CHCl_3$. The extract was washed with H_2O, sat. $NaHCO_3$ solution and H_2O, then dried. Removal of the solvent gave a pale yellow oil, which was treated with Ac_2O (20 ml) and pyridine (20 ml) at RT for 15 h. After removal of the excess reagent by evaporation, the residue was subjected to chromatography. Elution with $CHCl_3$ and $CHCl_3$–MeOH (99 : 1, v/v) afforded **30** (1.25 g, 43.3%) as a colorless oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2785 and 2740 (Bohlmann band), 1728 ($-\mathrm{O}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{CH_3}$). NMR ($CDCl_3$) δ: 2.00 (3H, s, $-\mathrm{O}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{CH_3}$), 3.02 (1H, dd, $J=12$ and 3 Hz, C–4H), 3.40 (3H, s, –OCH_3), 3.87 (Ar–OCH_3), 4.87 (1H, m, $W_{1/2}=24$ Hz, C–2H), 5.34 (2H, s, –O–CH_2–O–), 6.92 (2H, br s, Ar–H), 7.25 (1H, br s, Ar–H). MS *m/z*: 407 (M^+, 100%). High resolution MS (*m/z*): Calcd for $C_{22}H_{33}NO_6$: 407.2308. Found: 407.2289. From the fraction eluted with $CHCl_3$–MeOH (98 : 2, v/v), the *cis*-isomer (**32**) (0.93 g, 32.3%) was obtained as a colorless oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1725 ($-\mathrm{O}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{CH_3}$). NMR ($CDCl_3$) δ: 2.05 (3H, s, $-\mathrm{O}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{CH_3}$), 3.36 (3H, s, –$OCH_3$), 3.86 (3H, s, Ar–$OCH_3$), 4.02 (1H, m, C–4H), 5.25 (1H, m, C–2H), 5.35 (2H, s, –O–CH_2–O–), 6.80—7.30 (3H, m, Ar–H). MS *m/z*: 407 (M^+, 100%). High resolution MS (*m/z*): Calcd for $C_{22}H_{33}NO_6$: 407.2308. Found: 407.2317.

Hydrolysis of 32——A solution of **32** (250 mg) and LiOH·H_2O (53 mg) in aqueous MeOH (H_2O 1 ml, MeOH

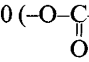
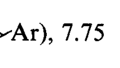
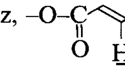
3 ml) was stirred at RT for 3 h. After removal of the solvent, the residue was extracted with $CHCl_3$. The extract was washed with H_2O and dried. Evaporation of the solvent gave a residue, which was subjected to chromatography. Elution with $CHCl_3$–MeOH (98 : 2, v/v) afforded **31** (192 mg, 85.7%) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 3400 (–OH). NMR ($CDCl_3$) δ: 3.33 (3H, s, $-OCH_3$), 3.83 (3H, s, Ar–OCH_3), 4.07 (2H, m, C-2, 4H), 5.25 (2H, s, $-O-CH_2-O-$), 6.67—7.20 (3H, m, Ar–H). MS m/z: 365 (M^+). High resolution MS (m/z): Calcd for $C_{20}H_{31}NO_5$: 365.2203. Found: 365.2238.

The Anhydride 35——DCC (0.5 g) was added to a stirred solution of p-MEMoxy-cinnamic acid[18] (1.0 g) at RT. The resulting mixture was stirred at the same temperature for 15 h. The mixture was cooled at 0 °C for a while, then the resulting precipitate was filtered off with the aid of celite and the filtrate was concentrated to give **35** (0.85 g, 87.8%) as a colorless solid which was used for the next reaction without further purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 and 1695 (anhydride). NMR ($CDCl_3$) δ: 3.25 (3H, s, $-OCH_3$), 5.18 (2H, s, $-O-CH_2-O-$), 6.25 (1H, d, J = 16 Hz, –O–  $\mathrm{\underset{\overset{\|}{O}}{C}-\overset{\underline{H}}{C}{=}CH-Ar}$), 7.65 (1H, d, J = 16 Hz,  $\mathrm{-O-\underset{\overset{\|}{O}}{C}-CH{=}\underset{\underline{H}}{C}-Ar}$).

The Cinnamate 33——A solution of **31** (47 mg) and **35** (90 mg) in pyridine (1 ml) containing a catalytic amount of 4-dimethylaminopyridine was stirred at RT for 14 h. After removal of the pyridine, the residue was extracted with CH_2Cl_2. The extract was washed with H_2O, sat. $NaHCO_3$ solution and H_2O, then dried. Evaporation of the solvent gave a residue, which was subjected to chromatography. Elution with $CHCl_3$–MeOH (98 : 2, v/v) gave **33** (56 mg, 72.7%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 ( $\mathrm{-O-\underset{\overset{\|}{O}}{C}-}$), 1630 (–HC=CH–). NMR ($CDCl_3$) δ: 3.33 (6H, s, $-OCH_3 \times 2$), 3.83 (3H, s, Ar–OCH_3), 5.26, 5.29 (2H each, s, $-O-CH_2-O-$), 5.30 (1H, m, C–2H), 6.28 (1H, d, J = 16 Hz,  $\mathrm{-O-\underset{\overset{\|}{O}}{C}-\overset{\underline{H}}{C}{=}CH-Ar}$), 7.57 (1H, d, J = 16 Hz,  $\mathrm{-O-\underset{\overset{\|}{O}}{C}-CH{=}\underset{\underline{H}}{C}-Ar}$). MS m/z: 599 (M^+). High resolution MS (m/z): Calcd for $C_{33}H_{45}NO_9$: 599.3093. Found: 599.3113.

(±)-10-*epi*-Desmethoxyabresoline (4)——CF_3CO_2H (1 ml) was added dropwise to a stirred solution of **33** (58 mg) in dry CH_2Cl_2 (1.7 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h then at RT for 2 h, and was neutralized with sat. $NaHCO_3$ solution under ice-water cooling. The whole were extracted with CH_2Cl_2, and the organic layer was washed with H_2O, then dried. Removal of the solvent gave an oil, which was purified by prep. TLC (developed with $CHCl_3$–MeOH, 90 : 10, v/v) to give **4** (28 mg, 68.5%) as colorless prisms, mp 220—222 °C (lit.[17] 221—223 °C), after recrystallization from $CHCl_3$. IR ν_{max}^{KBr} cm^{-1}: 3390 (–OH), 1710 ( $\mathrm{-O-\underset{\overset{\|}{O}}{C}-}$), 1635 (–HC=CH–). UV λ_{max}^{MeOH} nm: 313, 298 (sh), 288 (sh), 227. NMR (100 MHz, DMSO-d_6): 3.78 (3H, s, –OMe), 5.13 (1H, br s, $W_{1/4}$ = 28 Hz), 6.35 (1H, d, J = 16 Hz,  $\mathrm{-O-\underset{\overset{\|}{O}}{C}-\overset{\underline{H}}{C}{=}CH-Ar}$), 7.52 (1H, d, J = 16 Hz,  $\mathrm{-O-\underset{\overset{\|}{O}}{C}-CH{=}\underset{\underline{H}}{C}-Ar}$). MS m/z: 423 (M^+), 259 (100%), 218, 177. High resolution MS (m/z): Calcd for $C_{25}H_{29}NO_5$: 423.2045. Found: 423.2060.

Hydrolysis of 30——A solution of **30** (0.7 g) and NaOH (0.16 g) in aqueous MeOH (H_2O 1.5 ml, MeOH 15 ml) was stirred at RT for 45 min. The same work-up as described for **18** was carried out to afford **29** (0.61 g, 97.3%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 and 3420 (–OH), 2780 and 2745 (Bohlmann band). NMR ($CDCl_3$) δ: 2.91 (1H, dd, J = 11 and 3 Hz, C–4H), 3.37 (3H, s, $-OCH_3$), 3.85 (3H, s, Ar–OCH_3), 5.33 (2H, s, $-O-CH_2-O-$). MS m/z: 365 (M^+, 100%). High resolution MS (m/z): Calcd for $C_{20}H_{31}NO_5$: 365.2201. Found: 365.2201.

The Mitsunobu Reaction of 29——A solution of diethyl azodicarboxylate (0.64 ml) in dry THF (5 ml) was added dropwise to a stirred solution of **29** (0.6 g), triphenylphosphine (0.86 g) and 3-methoxy-4-MEMoxycinnamic acid (0.93 g) in dry THF (20 ml) at RT. The mixture was stirred at the same temperature for 7 h, then the solvent was evaporated off to give a residue, which was subjected to chromatography. Elution with $CHCl_3$–MeOH (99 : 1, v/v) afforded **34** (0.59 g, 57.3%, 85.6% based on consumed **29**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800 and 2750 (Bohlmann band), 1700 ( $\mathrm{-O-\underset{\overset{\|}{O}}{C}-}$), 1630 (–HC=CH–). NMR ($CDCl_3$) δ: 3.37 (6H, s, $-OCH_3 \times 2$), 3.86, 3.96 (3H each, s, Ar–OCH_3), 5.24 (1H, m, C–2H), 5.36, 5.39 (2H each, s, $-O-CH_2-O-$), 6.48 (1H, d, J = 16 Hz,  $\mathrm{-O-\underset{\overset{\|}{O}}{C}-\overset{\underline{H}}{C}{=}CH-Ar}$), 7.75 (1H, d, J = 16 Hz,  $\mathrm{-O-\underset{\overset{\|}{O}}{C}-CH{=}\underset{\underline{H}}{C}-Ar}$). MS m/z: 629 (M^+). High resolution MS (m/z): Calcd for $C_{34}H_{47}NO_{10}$: 629.3199. Found: 629.3179. From the fraction eluted with $CHCl_3$–MeOH (96 : 4, v/v), starting alcohol (**29**) (0.2 g) was recovered.

(±)-Abresoline (3)——CF_3CO_2H (5 ml) was added dropwise to a stirred solution of **34** (300 mg) in dry CH_2Cl_2 (8 ml) at 0 °C. The mixture was stirred at 0 °C for 2.5 h, then treated as described in the case of **4**. The resulting crude pale yellow oil was purified by prep. TLC (developed with $CHCl_3$–MeOH, 92 : 8 × 1, 90 : 10 × 1, v/v) to give the starting material (**34**) (20 mg) and **3**$^{16)}$ (100 mg, 46.3%, 49.5% based on consumed **34**) as a yellow amorphous solid. IR ν_{max}^{KBr} cm^{-1}: 3400 (–OH), 1700 ($-\mathrm{O}-\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-$), 1630 (–HC=CH–); $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520 (–OH), 2780 and 2750 (Bohlmann band), 1690 ($-\mathrm{O}-\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-$), 1623 (–HC=CH–). UV λ_{max}^{MeOH} nm: 326, 287. NMR ($CDCl_3$) δ: 3.22 (1H, dd, J= 10 and 1.5 Hz, C–4H), 3.90, 3.98 (3H each, s, –OMe), 5.13 (1H, brs, $W_{1/2}$=8 Hz, C–2H), 6.33 (1H, d, J= 16 Hz, $-\mathrm{O}-\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-\overset{\underline{\mathrm{H}}}{\mathrm{C}}=\mathrm{C}-\mathrm{Ar}$), 7.67 (1H, d, J=16 Hz, $-\mathrm{O}-\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-\mathrm{C}=\underset{\underline{\mathrm{H}}}{\mathrm{C}}-\mathrm{Ar}$). MS m/z: 453 (M^+), 259, 177. High resolution MS (m/z): Calcd for $C_{26}H_{31}NO_6$: 453.2150. Found: 453.2142.

Acknowledgement We are grateful to Professor J. M. Edwards and Dr. A. Rother of The University of Connecticut, Professor M. Hanaoka of Kanazawa University and Professor K. Fuji of Kyoto University for supplying us with the spectral data for abresoline (IR, NMR), 10-*epi*-desmethoxyabresoline (IR, NMR, UV), the acetate **24** (IR, NMR), and lasubine II (IR, NMR). We also thank Professor E. Fujita of Kyoto University for valuable information and Dr. K. Ogasawara of our Institute for helpful discussions.

References and Notes

1) Preliminary reports of parts of this work appeared in *J. Chem. Soc., Chem. Commun.*, **1981**, 940 and in *Heterocycles*, **19**, 1439 (1982).
2) Presented at the 9th International Congress of Heterocyclic Chemistry, Tokyo, August 1983.
3) For reviews, see *a*) E. Fujita and K. Fuji, "International Review of Science, Organic Chemistry Series Two," Vol. 9, ed. by K. Wiesner, Butterworths, London, 1976, p. 119; *b*) W. M. Golebiewski and J. T. Wrobel, "The Alkaloids," Vol. XVIII, ed. by R. H. F. Manske and R. G. A. Rodrigo, Academic Press, New York, 1981, p. 263.
4) J. P. Ferris, *J. Org. Chem.*, **27**, 2985 (1962).
5) T. Matsunaga, I. Kawasaki, and T. Kaneko, *Tetrahedron Lett.*, **1967**, 2471; M. Hanaoka, N. Ogawa, K. Shimizu, and Y. Arata, *Chem. Pharm. Bull.*, **23**, 1573 (1975).
6) *a*) R. Huisgen, *Angew. Chem. Int. Ed. Engl.*, **2**, 565, 633 (1963); *b*) *Idem*, *J. Org. Chem.*, **41**, 403 (1976); *c*) D. S. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, **1975**, 205; *d*) S. A. Ali, P. A. Senaratne, C. R. Illig, H. Mecker, and J. J. Tufariello, *Tetrahedron Lett.*, **1979**, 4167, and references cited therein.
7) J. J. Tufariello and S. A. Ali, *Tetrahedron Lett.*, **1978**, 4647.
8) For reviews, see *a*) J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964); *b*) G. R. Delpierre and M. Lamchen, *Q. Rev., Chem. Soc.*, **19**, 329 (1965); *c*) D. S. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, **1975**, 205; *d*) J. J. Tufariello, *Acc. Chem. Res.*, **1979**, 396; *e*) H. Iida and C. Kibayashi, *J. Syn. Org. Chem.* (Japan), **41**, 652 (1983).
9) A synthesis of the quinolizidine nucleus as *trans*- and *cis*-forms *via* unsymmetrical diene-nitrone cycloadditions has been reported: J. J. Tufariello and R. C. Gatrone, *Tetrahedron Lett.*, **1978**, 2753.
10) A. Rother and A. E. Schwarting, *Experientia*, **30**, 22 (1974).
11) A. Rother and A. E. Schwarting, *Lloydia*, **38**, 477 (1975).
12) R. H. Dobberstein, J. M. Edwards, and A. E. Schwarting, *Phytochemistry*, **14**, 1769 (1975).
13) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).
14) For a review, see O. Mitsunobu, *Synthesis*, **1981**, 1.
15) K. Fuji, T. Yamada, E. Fujita, and H. Murata, *Chem. Pharm. Bull.*, **26**, 2515 (1978).
16) M. Hanaoka, N. Ogawa, and Y. Arata, *Chem. Pharm. Bull.*, **23**, 2140 (1975).
17) R. B. Horhammer, A. E. Schwarting, and J. M. Edwards, *J. Org. Chem.*, **40**, 656 (1975).
18) A. Rother and A. E. Schwarting, *Phytochemistry*, **17**, 305 (1978).
19) Phenolic hydroxyl group protection was achieved by employing the Quick procedure.$^{20)}$ The protected products exhibited satisfactory spectroscopic and analytical (high-resolution mass spectral) data consistent with the structures shown.
20) J. Quick and R. Ramachandra, *Synth. Commun.*, **8**, 511 (1978).
21) C.-T. Hsu, N.-Y. Wang, L. H. Latimer, and C. J. Sih, *J. Am. Chem. Soc.*, **105**, 593 (1983).