Synthesis of (±)-Lasubine I and II and (±)-Subcosine I[1]

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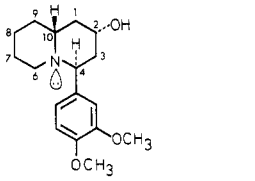
The first total synthesis of lasubine I and II and subcosine I has been achieved. A crucial step of this synthesis involves thermal [3 + 2] dipolar cycloaddition of 1-(3,4-dimethoxyphenyl)butadiene with 2,3,4,5-tetrahydropyridine 1-oxide, affording the *E* and *Z* isomers of 2-(3,4-dimethoxystyryl)-2,3,3a,4,5,6-hexahydropyrrolo[1,2-*b*]isoxazole favoring the exo adduct in each case. On treatment with hydrogen chloride followed by hydrogenation, the *E* isomer underwent in situ cyclization to furnish (±)-lasubine I and (±)-epilasubine II. When the same reaction was carried out on the *Z* isomer, (±)-lasubine I was obtained stereoselectively as a sole product. Alternatively, the *cis*- and *trans*-quinolizidin-2-ones, prepared by the Mannich reaction of isopelletierine with 3,4-dimethoxybenzaldehyde, led to (±)-lasubine I and to (±)-2-epilasubine II and (±)-lasubine II, respectively. Finally, the lithium salt of lasubine I was treated with 3,4-dimethoxycinnamic anhydride in the presence of 4-(dimethylamino)pyridine to afford (±)-subcosine I.

The leaves of *Lagerstroemia subcostata* Koehne have recently been found to contain four new quinolizidine alkaloids possessing both cis and trans ring junctures, namely, lasubine I (**1**) and II (**2**) and subcosine I (**3**) and II (**4**).[2] These alkaloids are structurally related to phenolic



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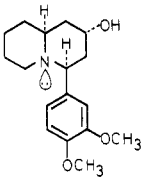

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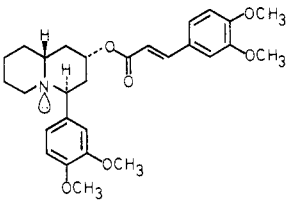

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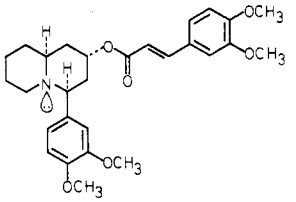

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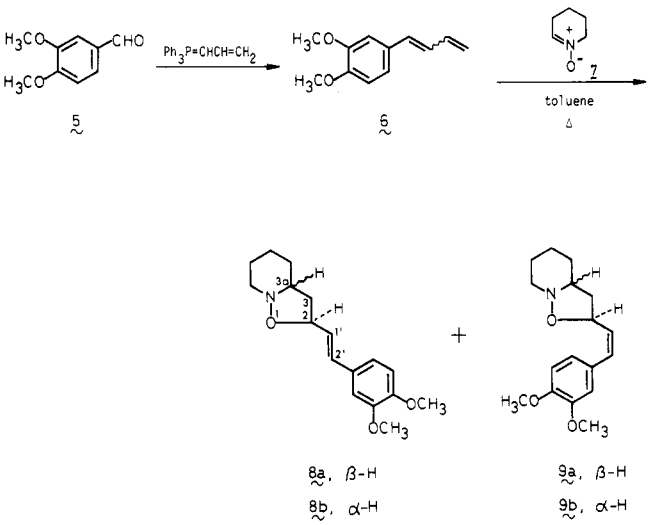
2-hydroxy-4-phenylquinolizidines which have been postulated as intermediates in the biosynthesis of the macrocyclic Lythraceae alkaloids classified into the two types, the lactonic biphenyl- and lactonic diphenylquinolizidines.[3,4] We now report the synthesis of lasubine and subcosine involving an efficient route based on 1,3-dipolar cycloaddition of a nitrone.[5]

The Wittig reaction of 3,4-dimethoxybenzaldehyde (**5**) with the phosphorane derived from allyltriphenylphosphonium bromide gave 1-(3,4-dimethoxyphenyl)butadiene (**6**) as a mixture of *E* and *Z* isomers (Scheme I). These isomers were inseparable by column chromatography on silica gel. However, GLC analysis indicated that the product was a 9:5 mixture of the *E* and *Z* isomers

Scheme I



favoring the *E* isomer. The reaction of the mixture with 2,3,4,5-tetrahydropyridine 1-oxide (**7**) in refluxing toluene followed by chromatography on a silica gel column yielded the corresponding *E* and *Z* cycloadducts **8** and **9** in 49% and 22% yields, respectively. The geometries of the olefin moiety of these isomers were assigned on the basis of the ^{1}H NMR coupling constants, $J_{1'2'}$, of the C-2′ protons; for the *E* isomer **8**, J = 15.8 Hz, and for the *Z* isomer **9**, a somewhat smaller coupling constant of 11.2 Hz was observed. Furthermore, the *E* isomer was shown by GLC and ^{1}H NMR analyses to be a mixture of the trans and cis isomers **8a** and **8b** in a ratio of 10:3, and the *Z* isomer was shown to be a 5:1 mixture of trans and cis isomers **9a** and **9b**, with preference for formation of the trans isomers **8a** and **9a** in each case. The preponderant formation of the trans adducts can be rationalized in terms of a preference for an exo-oriented transition state involving the monosubstituted alkene and the cyclic nitrone.[6]

With the *E* isomer in hand, we attempted to transform it directly to lasubine. Thus **8** was treated with hydrogen chloride and then, without isolation of the products, subjected to hydrogenation over palladium on carbon in ethanol. This provided the desired racemic lasubine I (**1**) in 44% yield from **8** along with racemic 2-epilasubine II (**12**) as a minor product (14% yield).

The synthetic racemic lasubine I was found to be identical with natural (−)-lasubine I by ^{1}H NMR and ^{13}C NMR

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(2) Fuji, K.; Yamada, T.; Fujita, E.; Murata, H. *Chem. Pharm. Bull.* **1978**, *26*, 2515.

(3) Ferris, J. P.; Boyce, C. B.; Brinner, R. C. *Tetrahedron Lett.* **1966**, 5129.

(4) Rother, A.; Schwarting, A. E. *Lloydia* **1975**, *36*, 477.

(5) For some recent syntheses of Lythraceae alkaloids via nitrone cycloaddition, see: Takano, S.; Shishido, K. *J. Chem. Soc., Chem. Commun.* **1981**, 940. Takano, S.; Shishido, K. *Heterocycles* **1982**, *19*, 1439. Shishido, K.; Tanaka, K.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1983**, *24*, 2783.

(6) Tufariello, J. J.; Asrof Ali, Sk. *Tetrahedron Lett.* **1978**, 4647.

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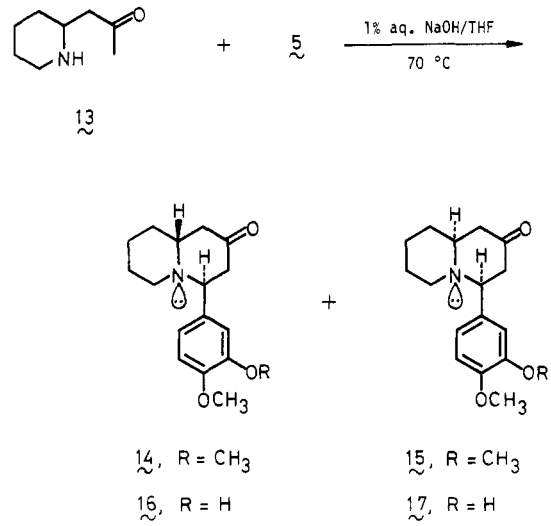
spectra as well as TLC behavior. The stereostructure of 2-epilasubine II (12) was assigned from its IR and ^{1}H NMR spectra as follows. The trans stereochemistry about the quinolizidine ring system of **12** was unambiguously shown by the presence of Bohlmann bands at 2785 and 2750 cm^{-1} in the IR spectrum. In the ^{1}H NMR spectrum of this compound the C-4 benzylic proton signal appears as a doublets at δ 2.93 with coupling constants of 11 and 2.5 Hz, which is characteristic of axial orientation.[4] Furthermore, an unresolved multiplet at δ 3.72 with $W_{1/4}$ = 33 Hz for the C-2 carbinol proton indicated that it is axial. Thus the relative orientation of the hydrogens at the 2 and 4 positions is cis which is unnatural since those in all naturally occuring lactonic Lythraceae alkaloids so far found are trans oriented.

Obviously both alkaloids **1** and **12** were formed from the major adduct **8a** because the cis relationship between 2-H and 10-H in these alkaloids corresponds to the configurational relationship (trans) of the hydrogens at the positions 2 and 3a in **8a**. Thus the formation of both alkaloids **1** and **12** must arise via both chlorides **10a** and **10b**, respectively, formed by addition of hydrogen chloride to **8a**.[7] Subsequent reductive N–O bond cleavage furnishing the amino alcohols **11a** and **11b** followed by in situ ring closure via S_N2 displacement may afford lasubine I (**1**) and 2-epilasubine II (**12**), respectively (Scheme II). In the case of the reaction leading to lasubine I, the initially formed conformer **1′**, which has a trans-fused quinolizidine ring and an axial aryl group should be thermodynamically disfavored because of strong nonbonded interactions between the aromatic hydrogens at 2′ and/or 6′ and the two axial quinolizidine hydrogens at C-2 and/or C-6.[4] Thus **1′** epimerizes to the thermodynamically more stable cis-fused quinolizidine conformation **1** by nitrogen inversion.

In line with the above discussion the other isomers, lasubine II (**2**) and 4-epilasubine II, would have been expected to be formed from the minor cis adduct **8b**; however, in fact, no products other than **1** and **12** could be isolated in pure forms.

When the *Z* isomer mixture **9a,b** was subjected to the same series of transformations the reaction proceeded very sluggishly and the only product isolated in pure form was lasubine I (**1**) in lower yield (35%).

In order to confirm the above stereochemical assignments, an alternative synthesis of 2-epilasubine II (**12**) was examined, which was based on the Mannich reaction of isopelletierine (**13**) with aromatic aldehydes, originally described by Matsunaga et al.[9] and is generally utilized for the synthesis of Lythraceae alkaloids.[10] Thus condensation of **13** with 3,4-dimethoxybenzaldehyde (**5**) under alkaline conditions afforded the *cis*- and *trans*-quinolizidinones **14** and **15** in 46% and 22% yields, respectively. The stereochemistry of these isomers was determined by spectral analysis and by comparison of the spectral data with those reported for the analogous compounds **16** and **17** with the *cis*- and *trans*-quinolizidine ring systems, respectively.[4]



Reduction of the *cis*-quinolizidinone **14** with sodium borohydride stereoselectively gave lasubine I (**1**) in 83% yield, then providing an alternative synthesis of lasubine I. On the other hand, reduction of *trans*-quinolizidinone **15** gave lasubine II (**2**) and 2-epilasubine II (**12**) in 19% and 70% yields, respectively. The latter material was identical in all respects with the sample previously prepared by the [3 + 2] cycloaddition reaction.

Finally for conversion of lasubine I (**1**) to subcosine I (**3**), we first examined direct esterification with 3,4-dimethoxycinnamic acid using a proton-donor catalyst, DCC, and Mukaiyama's reagent, i.e., 2-chloro-1-methylpyridinium iodide (CMPI),[11] and also the Schotten–Baumann reaction with 3,4-dimethoxycinnamoyl chloride. While these attempts were unsuccessful, a procedure based on Narasaka's method[12] was effective. The lithium salt of lasubine I generated by treatment with *n*-butyllithium in THF at –78 °C was treated with 3,4-dimethoxycinnamic anhydride **18**, prepared from 3,4-dimethoxycinnamic acid by treatment with Mukaiyama's reagent, in the presence of 4-(dimethylamino)pyridine (DMAP) in dioxane at room temperature for 24 h. This gave (±)-subcosine I (**3**) in 48% yield, which was identical with natural (+)-subcosine I spectroscopically. Similarly, (±)-2-episubcosine II (**19**) was obtained from 2-epilasubine II (**12**).

Thus the first total synthesis of (±)-subcosine I has been achieved by utilizing [3 + 2] dipolar cycloaddition of the nitrone as a key step. We believe that the present methodology will provide an efficient access to lactonic Lythraceae alkaloids.

Experimental Section

Melting points were determined on a Yanagimoto micro apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 215 spectrophotometer. ^{1}H NMR spectra were recorded on Varian EM-390 (90 MHz) and JEOL JNM-FX-270 (270 MHz) spectrometers using tetramethylsilane as an internal standard and $CDCl_3$ as solvent. ^{13}C NMR spectra were measured with a JOEL JNM-FX 270 spectrometer at 67.8 MHz using tetra-

(7) The predominant formation of **1** is probably related to the preference of **10a** in the addition of hydrogen chloride to **8a**. The ionic addition of hydrogen halide to the styrenic system is believed to proceed by the formation of the benzyl cation followed by predominant cis addition of halide ion.[8] However, the explanation for the preferential formation of **10a** based on this mechanism appears to be difficult since the prediction of conformational preference for **8a** (and cationic intermediate generated from **8a**) is difficult because of possible rotations about the C_2–$C_{1'}$ bond (and the $C_{1'}$–$C_{2'}$ bond).

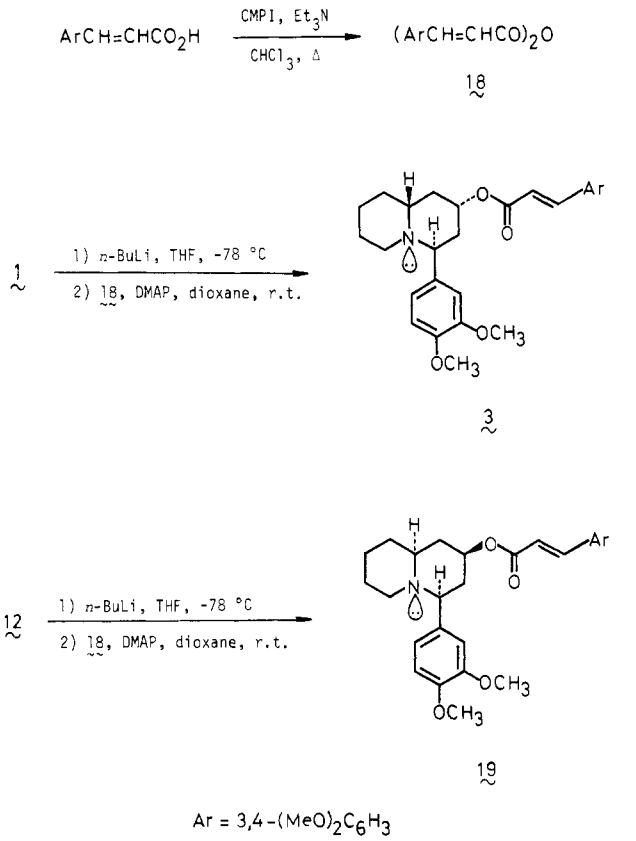
(8) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; pp 446–447.

(9) Matsunaga, T.; Kawasaki, I.; Kaneko, T. *Tetrahedron Lett.* **1967**, 2471.

(10) For synthesis of lactonic Lythraceae alkaloids, see the following. Decaline: Hanaoka, M.; Ogawa, N.; Arata, Y. *Tetrahedron Lett.* **1973**, 2355. Hanaoka, M.; Ogawa, N.; Arata, Y. *Chem. Pharm. Bull.* **1975**, *23*, 2140. Wrobel, J. T.; Golebiewski, W. M. *Tetrahedron Lett.* **1973**, 4293. Vertaline: Hanaoka, M.; Ogawa, N.; Arata, Y. *Chem. Pharm. Bull.* **1974**, *22*, 973. Hanaoka, M.; Ogawa, N.; Arata, Y. *Ibid.* **1976**, *24*, 1045. Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555. Lagerine: Hanaoka, M.; Kamei, M.; Arata, Y. *Chem. Pharm. Bul.*. **1975**, *23*, 2191. Decaline: Lantos, I.; Loev, B. *Tetrahedron Lett.* **1975**, 2011. Decamine: Lantos, I.; Razgaitis, C.; VanHoeven, H.; Loev, B. J. *J. Org. Chem.* **1977**, *42*, 228.

(11) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707.

(12) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Morimoto, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 455.



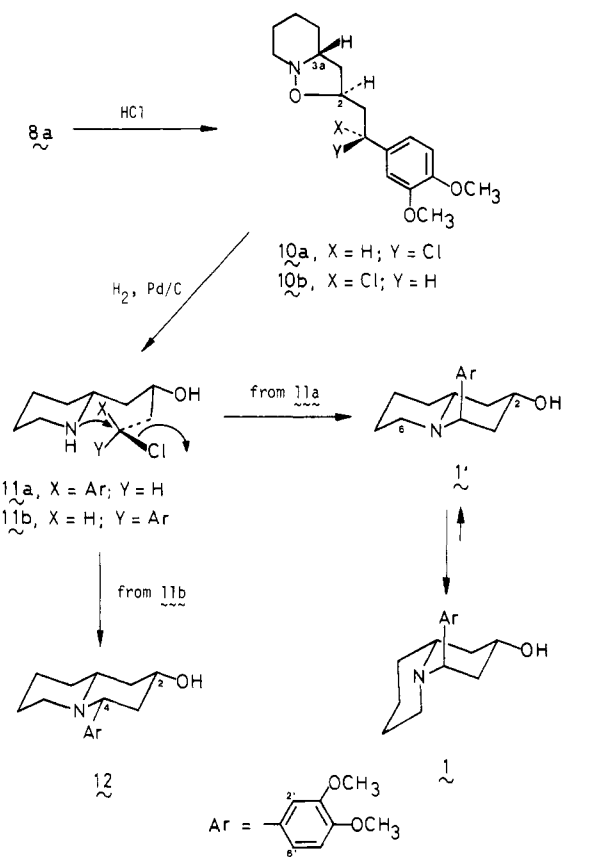
methylsilane as an internal standard and $CDCl_3$ as a solvent. Mass spectra were obtained with Hitachi RMU-7L and M-80 (equiped with a Hitachi M-003 data processing system) double-focusing mass spectrometers at an ionizing potential of 70 eV. Gas chromatographic analyses were conducted on a Shimazu GC-7AG instrument with a 1-m column of silicone 2% OV-1 on Chromosorb W AW DMCS (60–80 mesh). HPLC was carried out by using a Kusama KP-6H micro pump with a Kusano CIG column (silica gel, 10-μm particle size, 15 mm i.d. × 30 cm). TLC was run on Merck precoated silica gel F-254 plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography.

(*E* and *Z*)-1-(3,4-Dimethoxyphenyl)butadiene (6). To a stirred, cooled (ice/water) suspension of triphenyl propenylphosphonium bromide (3.83 g, 10 mmol) in dry ether (50 mL) was added dropwise *n*-butyllithium (20 mmol in hexane (2 mL)) under N_2 at 0 °C with stirring. After being stirred at room temperature for 4 h, a solution of 3,4-dimethoxybenzaldehyde (5) (1.69 g, 10 mmol) in dry ether (50 mL) was added dropwise to the mixture under N_2. The mixture was heated at reflux overnight. After removal of an insoluble material by filtration, the ethereal solution was washed with water, dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (10:1) as eluent to give a pale yellow oil (6) (0.86 g, 45%). GLC analysis of this product indicated two peaks in a ratio of 9:5 at a column temperature of 160 °C. These isomers appeared on TLC as almost overlapping two spots: IR ($CHCl_3$) 1595 cm^{-1}; ^1H NMR δ 3.85 (s, 3 H), 3.88 (s, 3 H), 5.04–5.38 (unresolved, 2 H), 6.28–6.74 (m, 3 H), ~6.8–7.1 (m, 3 H); mass spectrum, *m/z* (relative intensity) 190 (M^+, 100), 159 (82), 115 (47); exact mass calcd for $C_{12}H_{14}O_2$ *m/z* 190.0994, found *m/z* 190.0998.

Cyclization of 1-Arylbutadiene 6 with 2,3,4,5-Tetrahydropyridine 1-Oxide (7). A mixture of 6 (2.60 g, 13.7 mmol) described above and 7[13] (1.36 g, 13.7 mmol) in toluene (50 mL) was heated at reflux for 4 h. After removal of the solvent by evaporation at reduced pressure, the residual oily product was chromatographed on silica gel with hexane/ethyl acetate (5:1) as eluent. The first fraction contained 2(*Z*)-(3,4-dimethoxystyryl)-3,3a,4,5,6,7-hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine (9) (860 mg, 22%) as a pale yellow oil: IR ($CHCl_3$) 1600, 1140, 1025, 910 cm^{-1}; ^1H NMR δ ~1.15–3.2 (series of m, 9 H), 3.44 (br m, 1 H), ~3.8–4.2 (m, 1 H?, with s (3 H) at δ 3.875, s (3 H) at δ 3.883), 4.90 and 5.18 (dd, *J* = 20, 11.2 Hz,and t, *J* = 11.2 Hz, respectively, total 1 H , (5:1 ratio)), 5.62 and 5.85 (dd, *J* = 11.2, 8.9 Hz, and t, *J* = 11 Hz, respectively, total 1 H (5:1 ratio)), 6.51 and 6.57 (d, *J* = 11 Hz each, total 1 H (1:5 ratio)), 6.82–6.93 (m, 3 H); mass spectrum, *m/z* (relative intensity) 289 (M^+, 24), 190 (100), 159 (63); exact mass calcd for $C_{17}H_{23}NO_3$ *m/z* 289.1678, found *m/z* 289.1655.

(13) Iwashita, T.; Kusumi, T.; Kakisawa, H. *J. Org. Chem.* **1982**, *47*, 230.

Scheme II



The second fraction contained 2(*E*)-(3,4-dimethoxystyryl)-3,3a,4,5,6,7-hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine (8) (1.94 g, 49%) as a pale yellow oil: IR ($CHCl_3$) 1140, 1025, 965 cm^{-1}; ^1H NMR δ ~1.15–3.2 (series of m, 9 H), 3.47 and 3.60 (br d and br m, respectively, total 1 H (10:3 ratio)), ~3.75–4.15 (m, 1 H? with s (3 H) at δ 3.872, s (3 H) at δ 3.890), 4.63 and 4.92 (br m and br s, respectively, total 1 H (10:3 ratio)), 6.04 (dd, 1 H, *J* = 15.8, 7.9 Hz), 6.55 (d, 1 H, *J* = 15.8 Hz), 6.79–6.95 (m, 3 H); mass spectrum, *m/z* (relative intensity) 289 (M^+, 11), 190 (100), 159 (66); exact mass calcd for $C_{17}H_{23}NO_3$ *m/z* 289.1678, found *m/z* 289.1669.

Addition of Hydrogen Chloride–Reductive Ring Closure of (*E*)-Isoxazolidine 8. Gaseous hydrogen chloride was passed through a solution of 8 (350 mg, 1.21 mmol) in chloroform (20 mL) with stirring and cooling at 0–5 °C for 3 h. After evaporation of the solvent in vacuo, the residue was dissolved in ethanol (30 mL) and basified by addition of pyridine. To this solution was added 10% Pd/C (60 mg), and the mixture was hydrogenated at atmospheric pressure and temperature for 15 h. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel with chloroform/methanol (10:1) and elution of the fast moving component afforded (±)-2-epilasubine II (12) (48 mg, 14%) as a colorless solid, which was recrystallized from chloroform/hexane to give colorless crystals: mp 141–142 °C; IR ($CHCl_3$) 3600, 2785 and 2750 sh cm^{-1} (Bohlmann bands); ^1H NMR δ 1.15–2.05 (series of m, 12 H), 2.36 (br s, 1 H), 2.68 (br d, 1 H, *J* = 10.5 Hz), 2.93 (dd, 1 H, *J* = 11, 2.5 Hz), 3.72 (m, $W_{1/4}$ = 33 Hz, 1 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 6.78 (s, 2 H), 6.91 (br s, 1 H); ^{13}C NMR δ 149.1 (s), 148.0 (s), 136.2 (s), 119.7 (d), 110.8 (d), 68.3 (2 × d), 61.1 (d), 56.0 (q), 55.8 (q), 52.9 (t), 44.9 (t), 42.6 (t), 33.5 (t), 25.9 (t), 24.5 (t); mass spectrum, *m/z* (relative intensity 291 (M^+, 100), 164 (93), 154 (92); exact

mass calcd for $C_{17}H_{25}NO_3$ m/z 291.1834, found m/z 291.1826. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.77; H, 8.67; N, 4.69.

Elution of the slow moving component yielded (±)-lasubine I (1) (156 mg, 44%) as a pale yellow oil: IR (neat film) 3350 cm^{-1}; ^1H NMR δ ~1.2–2.3 (series of m, 12 H), 2.72 (br d, 1 H, J = ~13 Hz), 2.97 (br s, 1 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 4.10 (m, 1 H), 4.18 (m, overlapped with m at δ 4.10, 1 H), 6.79 and 6.82 (s each, total 1 H (1:2.5 ratio)), 6.87 and 6.89 (s, each, total 2 H (4:1 ratio)); ^{13}C NMR δ 148.7 (s), 147.8 (s), 135.4 (s), 120.5 (d), 112.1 (d), 110.8 (d), 64.9 (d), 61.9 (d), 55.9 (q), 55.8 (q), 53.9 (d), 51.1 (t), 40.3 (t), 40.1 (t), 32.8 (t), 24.5 (t), 24.0 (t); mass spectrum, m/z (relative intensity) 291 (M^+, 75), 164 (100), 154 (98); exact mass calcd for $C_{17}H_{25}NO_3$ m/z 291.1832, found m/z 291.1812.

Addition of Hydrogen Chloride–Reductive Ring Closure of (*Z*)-Isoxazolidine 9. Gaseous hydrogen chloride was passed through a solution of **9** (955 mg, 3.30 mmol) in chloroform (50 mL) with cooling at 0–5 °C for 3 h. After workup similar to that described above for **8**, hydrogenation over 10% Pd/C (150 mg) in ethanol followed by column chromatography on silica gel with chloroform/methanol (10:1) afforded (±)-lasubine I (1) (335 mg, 35%), which was identical in all respects with the sample obtained from **8**.

Mannich Reaction of Isopelletierine (13) with 3,4-Dimethoxybenzaldehyde (5). To a solution of **13**[14] (4.38 g, 31 mmol) and **5** (5.15 g, 31 mmol) in THF (140 mL) was added 1% aqueous NaOH (50 mL) under N_2 with stirring. The mixture was heated with stirring under N_2 at 70 °C for 4 h. After cooling, the mixture was neutralized by adding 10% HCl and concentrated at reduced pressure. The residue was dissolved in chloroform and the solution was washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel with chloroform/methanol (20:1) as eluent. Elution of the fastest moving component gave 4-(4,5-dimethoxphenyl)-(*E*)-*trans*-quinolizidin-2-one (**15**) (1.97 g, 22%) as a colorless solid, which was recrystallized from methanol to give colorless crystals: mp 83–84 °C; IR ($CHCl_3$) 2770 and 2725 (Bohlmann bands), 1710 cm^{-1}; ^1H NMR δ ~1.15–2.9 (series of m, 13 H), 3.20 (dd, 1 H, J = 11, 4 Hz), 3.85 (s, 3 H), 3.89 (s, 3 H), 6.83 (s, 3 H), 6.93 (s, 1 H); mass spectrum, m/z (relative intensity) 289 (M^+, 18), 206 (6), 164 (26), 83 (100); exact mass calcd for $C_{17}H_{23}NO_3$ m/z 289.1678, found m/z 289.1681.

Elution of the middle moving component gave 4-(4,5-dimethoxyphenyl)-(*E*)-*cis*-quinolizidine-2-one (**14**) (4.10 g, 46%) as a yellow oil: IR ($CHCl_3$) 1700 cm^{-1}; ^1H NMR δ ~1.1–3.1 (series of m, 13 H), 3.85 (s, 6 H), 4.22 (dd, 1 H, J = 6, 4 Hz), 6.71 (s with weak absorptions at the base, 2 H), 6.78 (s with weak absorptions at the base, 1 H); mass spectrum, m/z (relative intensity) 289 (M^+, 18), 206 (6), 164 (26), 83 (100); exact mass calcd for $C_{17}H_{23}NO_3$ m/z 289.1678, found m/z 289.1675.

Elution of the slowest moving component gave recovered starting material **5** (1.15 g, 22%).

Reduction of *cis*-Quinolizidinone 14 with Sodium Borohydride. To a cooled (ice/water), stirred solution of **14** (2.57 g, 8.88 mmol) in methanol (45 mL) was added $NaBH_4$ (0.52 g, 13.7 mmol) in small portions. The mixture was stirred at ambient temperature for 15 h and poured into water (100 mL). The resulting oily product was extracted with chloroform and the organic layer was washed with water and dried ($MgSO_4$). Evaporation of the solvent left a viscous oil, which was purified by column chromatography on silica gel with chloroform/methanol (20:1) to give (±)-lasubine I (1) (2.15 g, 83%). This material was identical in all respects with the authentic sample described above.

Reduction of *trans*-Quinolizidinone 15 with Sodium Borohydride. A solution of **15** (821 mg, 2.84 mmol) in methanol (15 mL) was treated with $NaBH_4$ (170 mg, 4.50 mmol) in the same manner as described above for **14**. After workup, column chromatography on silica gel with chloroform/methanol (20:1) gave (±)-2-epilasubine II (**12**) (576 mg, 70%) as a colorless crystalline powder: mp 141–142 °C (chloroform/hexane). This was identical in all respects with the sample prepared from **8**.

Further elution of the slow moving component afforded (±)-lasubine II (**2**) (161 mg, 19%) as a colorless oil: IR ($CHCl_3$) 3600, 2780 and 2750 sh cm^{-1} (Bohlmann bands); ^1H NMR δ ~1.2–2.8 (series of m, 13 H), 3.32 (dd, 1 H, J = 9, 6 Hz), 3.85 (s, 3 H), 3.88 (s, 3 H), 4.13 (m, 1 H, $W1/2$ = 8 Hz), 6.82 (s with s at δ 6.85 with less intensity, 2 H), 6.93 (s, 1 H); mass spectrum, m/z (relative intensity) 291 (M^+, 80), 164 (81), 154 (77); exact mass calcd for $C_{17}H_{25}NO_3$ m/z 291.1832, found m/z 291.1843.

3,4-Dimethoxycinnamic Anhydride (18). To a stirred solution of 2-chloro-1-methylpyridinium iodide (4.4 g, 17 mmol) in chloroform (5 mL) was added dropwise a solution of 3,4-dimethoxycinnamic acid (2.7 g, 13 mmol) in chloroform (50 mL) followed by triethylamine (1.8 g, 18 mmol) at room temperature, and the mixture was heated at reflux. After 4 h, it was cooled, washed with water and saturated $NaHCO_3$, and dried ($MgSO_4$). Evaporation of the solvent and recrystallization from chloroform/hexane gave **18** (3.75 g, 65%) as colorless needles: mp 177–178 °C; IR ($CHCl_3$) 1760, 1615 cm^{-1}; ^1H NMR δ 3.92 (s, 12 H), 6.39 (d, 2 H, J = 16 Hz), 6.89 (d, 2 H, J = 8 Hz), 7.09 (d, 2 H, J = 2 Hz), 7.17 (dd, 2 H, J = 8, 2 Hz), 7.80 (d, 2 H, J = 16 Hz); mass spectrum, m/z (relative intensity) 398 (M^+, 8), 208 (100), 191 (37). Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57; O, 28.11. Found: C, 66.17; H, 5.57; O, 28.25.

Synthesis of (±)-Subcosine I (3). To a solution of (±)-lasubine I (**1**) (1.00 g, 3.43 mmol) in THF (10 mL) was added *n*-butyllithium (3.43 mmol in hexane (1.5 mL)) with stirring and cooling at −78 °C under nitrogen. After 30 min, 4-(dimethylamino)pyridine (42 mg, 0.34 mmol) was added to this mixture followed by a solution of **18** (1.37 g, 3.44 mmol) in dioxane (70 mL), and the mixture was allowed to warm to room temperature. After the mixture was stirred for another 24 h, the solvent was evaporated at reduced pressure. The residual oil was dissolved in chloroform, and the solution was washed with water and saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Removal of the solvent at reduced pressure followed by HPLC of the residue on silica gel using chloroform/methanol (40:1) at 3 mL/min flow rate allowed to provide (±)-subcosine I (**3**) (742 mg, 48%) as a pale yellow oil:[15] IR ($CHCl_3$) 1685, 1625 cm^{-1}; ^1H NMR δ ~1.2–2.4 (series of m, 11 H), 2.78 (near d, 1 H, $W_{1/2}$ = 20.5 Hz), 3.04 (br m, 1 H, $W_{1/2}$ = 20.2 Hz), 3.88 (s, 3 H), 3.91 (s, 6 H), 3.92 (s, 3 H), 4.12 (m, 1 H, $W_{1/2}$ = 12.5 Hz), 5.35 (br m, 1 H, $W_{1/2}$ = 19.0 Hz), 6.32 (d, 1 H, J = 15.8 Hz), 6.82–7.14 (m, 6 H), 7.62 (d, 1 H, J = 15.8 Hz); mass spectrum, m/z (relative intensity) 481 (M^+, 53), 398 (18), 287 (27), 273 (100), 191 (75), 133 (48); exact mass calcd for $C_{28}H_{35}NO_6$ m/z 481.2464, found m/z 481.2437.

(±)-2-Episubcosine II (19). A solution of (±)-epilasubine II (**12**) (470 mg, 1.61 mmol) in THF (2 mL) was treated with *n*-butyllithium (1.61 mmol in hexane (0.6 mL)) followed by 4-(dimethylamino)pyridine (20 mg, 0.16 mmol) and **18** (643 mg, 1.61 mmol) in a manner similar to that described above for the esterification of lasubine I (**1**) to give subcosine I (**3**). Workup and HPLC[15] afforded (±)-2-episubcosine II (**19**) (350 mg, 45% (73% based on starting material **12** recovered)) as a colorless oil: IR ($CHCl_3$) 2780 and 2750 sh (Bohlmann bands), 1690, 1630 cm^{-1}; ^1H NMR δ ~1.2–2.3 (series of m, 12 H), 2.72 (unresolved, 1 H), 3.02 (dd, 1 H, J = 12, 2.5 Hz), 3.84 (s, 3 H), 3.89 (s, 9 H), 4.96 (m, 1 H), 6.27 (d, 1 H, J = 16 Hz), 6.82–7.16 (m, 6 H), 7.61 (d, 1 H, J = 16 Hz); mass spectrum, m/z (relative intensity) 481 (M^+, 37), 273 (68), 191 (100), 136 (37); exact mass calcd for $C_{28}H_{35}NO_6$ m/z 481.2464, found m/z 481.2437.

Further elution contained (±)-2-epilasubine II (**12**) (180 mg, 38%) unchanged.

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Registry No. (±)-**1**, 88931-04-8; (±)-**2**, 89771-49-3; (±)-**3**, 88931-06-0; **5**, 120-14-9; (*E*)-**6**, 75560-74-6; (*Z*)-**6**, 88909-06-2; **7**, 34418-91-2; (±)-**8a**, 88931-07-1; (±)-**8b**, 88909-04-0; (±)-**9a**, 88931-09-3; (±)-**9b**, 88931-08-2; (±)-**12**, 88931-05-9; (±)-**13**, 539-00-4; (±)-**14**, 89690-19-7; (±)-**15**, 89690-20-0; **18**, 88909-07-3; (±)-**19**, 89771-50-6; triphenylpropenylphosphonium bromide, 1560-54-9; (*E*)-3,4-dimethoxycinnamic acid, 14737-89-4.

(14) Hanaoka, M.; Ogawa, N.; Arata, Y. *Yakugaku Zasshi* **1974**, *94*, 531.

(15) A small amount of *n*-butyl 3,4-dimethoxycinnamate was isolated as a component of the initial elution on HPLC.