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Asymmetric synthesis of quinolizidine alkaloids (−)-lasubine I, (−)-lasubine II and (+)-subcosine II

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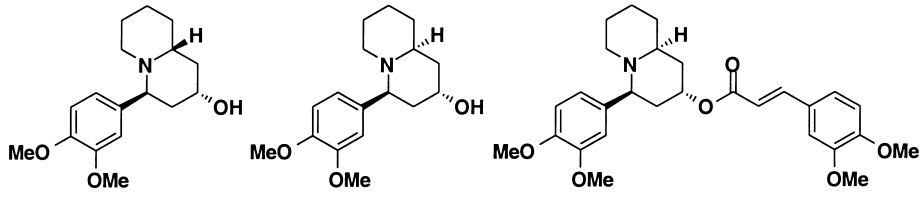
Abstract

The enantioselective synthesis of (−)-lasubine I **1** and the first asymmetric synthesis of (−)-lasubine II **2** and (+)-subcosine II **3** is described. The key step is the intramolecular cyclization of *N*-acyliminium ion **4** which is derived from (*S*)-aminoester **6**.

1. Introduction

The quinolizidine skeleton constitutes the backbone of many structurally interesting alkaloids.[1] Several quinolizidine alkaloids have been isolated from plants of the Lythraceae family. (−)-Lasubine I, (−)-lasubine II, (+)-subcosine I and (+)-subcosine II were isolated by Fuji et al. from the leaves of *Lagerstroemia subcostata* Koehne.[2] Numerous syntheses of these compounds in racemic form were described;[3] the first asymmetric syntheses of (−)-lasubine I **1** and (+)-subcosine I have recently been reported;[4] (−)-lasubine II **2** and (+)-subcosine II **3** have never been synthesized.



We have found that intramolecular cyclization of acyliminium ions substituted by an allylsilyl side chain as an internal π-nucleophile provided an excellent route to these structures.[5] By using this reaction, we have achieved the total synthesis of a variety of racemic quinolizidine alkaloids: (±)-myrtine and

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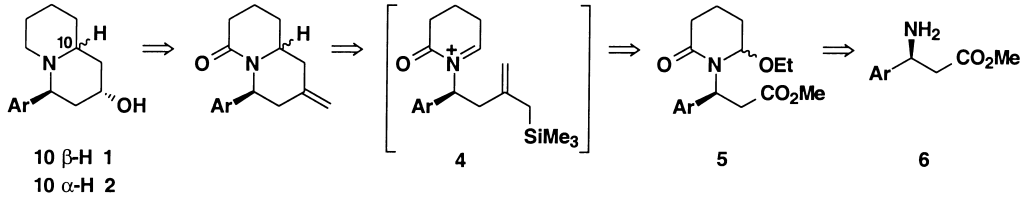
(±)-epimyrtine,[6] (±)-lasubine I and (±)-lasubine II.[3n] We have recently utilized this strategy for the synthesis of (+)-myrtine and (−)-epimyrtine starting from (*S*)-2-(2-hydroxypropyl)allyltrimethylsilane. In this paper, we describe a new approach to the quinolizidine alkaloids (−)-lasubine I **1**, (−)-lasubine II **2** and (+)-subcosine II **3**. Our synthetic sequence is illustrated in Scheme 1.

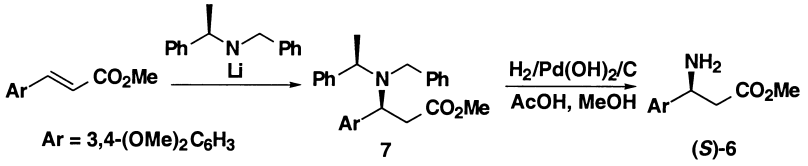


Scheme 1.

The key step is the intramolecular acyliminium ion–allylsilane cyclization of intermediate **4** generated from ethoxylactam **5**. Chirality is introduced with β-aminoester **6**.

2. Results and discussion

(*S*)-β-Aminoester **6** was prepared according to Davies' procedure (Scheme 2).[7]



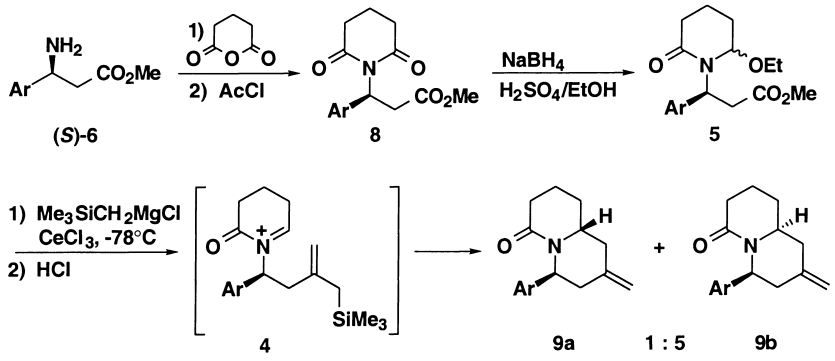
Scheme 2.

Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to methyl 3,4-dimethoxyphenylcinnamate afforded the tertiary amine **7** with excellent diastereoselectivity (>92%). Debenzylation of **7** with Pearlman's catalyst and hydrogen gave the aminoester **6** in 90% yield. The enantiomeric excess of **6** was determined by deuterium NMR of its *N*-trideuteroacetyl derivative in a chiral solvent [dichloromethane solution of γ-benzyl L-glutamate (PBLG)] as described previously by Courtieu et al.[8] and was found to be 92%. The absolute configuration of **6** was assigned as *S* by analogy with related experiments of Davies et al.[7]

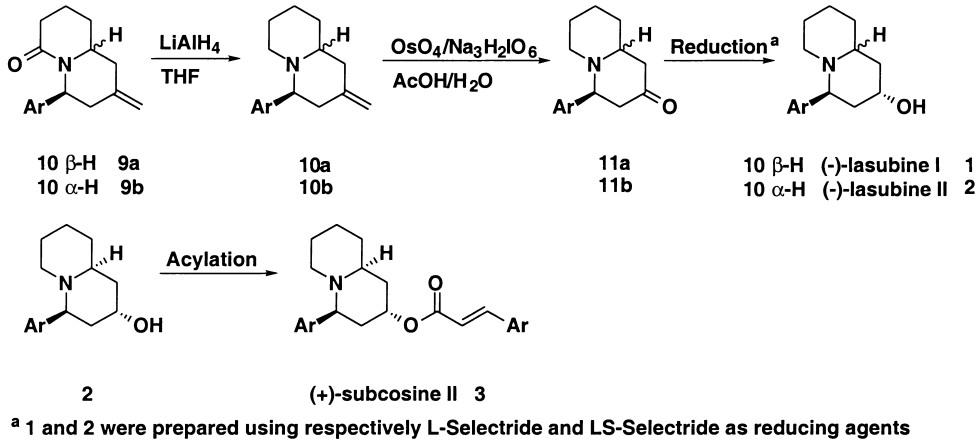
The synthesis of the quinolizidine skeleton is illustrated in Scheme 3. Reaction of **6** with glutaric anhydride then with acetyl chloride[9] in refluxing toluene gave imide **8** in 86% yield. Its enantiomeric purity was determined to be >90% by chiral column HPLC analysis. Imide **8** was reduced[10] into ethoxylactam **5** which was isolated as a mixture of two diastereomers. The reduction had to be performed at −10°C to prevent formation of ring opening products.[11] In the next step, ethoxylactam **5** was treated with the cerium reagent[12] derived from $CeCl_3$ and trimethylsilylmethylmagnesium chloride. The mixture was then hydrolyzed with 1 N HCl, to give methylenequinolizidinones **9a** and **9b** in a 1:5 ratio and 60% yield. These isomers were separated by flash column chromatography. The enantiomeric excess of **9b** was found to be >90%.

This reaction involved formation of acyliminium ion (*S*)-**4** which cyclized spontaneously. The structure and 4,10-stereochemistry of **9a** and **9b** were established by comparison of their NMR data with literature values of the racemic compounds.[3n]

Lasubine I and lasubine II were synthesized from methylenequinolizidinones **9a** and **9b** as outlined in Scheme 4.



Scheme 3.



Scheme 4.

This route began with the reduction of lactams **9a** and **9b** with lithium aluminium hydride in refluxing THF for 12 h to give methylenequinolizidines **10a** and **10b** in 83% and 92% yields, respectively. Osmium tetroxide catalyzed periodate oxidation of the olefinic bond of **10a** and **10b** under carefully controlled conditions led to quinolizidin-2-ones **11a** {$[\alpha]_D^{25}$ +9.5 (*c* 3.1, $CHCl_3$); lit.[4] $[\alpha]_D^{23}$ +10.8 (*c* 1.31, $CHCl_3$)} and **11b** in 70 and 90% yields. The final step is a reduction of the carbonyl group. Stereoselective reduction of **11a** with L-Selectride provided (−)-lasubine I **1** in 62% yield {$[\alpha]_D^{25}$ −6.5 (*c* 2.6, MeOH); lit.[2] $[\alpha]_D^{22}$ −8.8 (*c* 0.34, MeOH); lit.[4] $[\alpha]_D^{23}$ −7.03 (*c* 0.37, MeOH)}. Quinolizidin-2-one **11b** was selectively converted to (−)-lasubine II (**2**) with LS-Selectride in 65% yield {*ee* >90%; $[\alpha]_D^{25}$ −41.0 (*c* 3.7, MeOH); lit.[2] $[\alpha]_D^{22}$ −34.7 (*c* 0.32, MeOH)}. Acylation of **2** with 3,4-dimethoxycinnamic anhydride gave (+)-subcosine II **3** in 60% yield {$[\alpha]_D^{25}$ +121 (*c* 3.5, MeOH); lit.[2] $[\alpha]_D^{22}$ +85.3 (*c* 0.64, MeOH)}. These three alkaloids exhibited IR, ^1H and ^{13}C NMR spectral data in agreement with the reported values for the natural products.[2]

In conclusion, we describe the total synthesis of (−)-lasubine I **1**, (−)-lasubine II **2** and (+)-subcosine II (**3**) using intramolecular cyclization of *N*-acyliminium ion (*S*)-**4**. Alkaloids **1** and **2** were obtained in six steps with overall yields of 7 and 14%, respectively. Subcosine **3** was prepared in seven steps with an overall yield of 9%. These three compounds were obtained with a high enantiomeric purity. These results constitute the first total synthesis of naturally occurring (−)-lasubine II and (+)-subcosine II and unambiguously establish their absolute configuration as 2*S*,4*S*,10*S*.

3. Experimental section

3.1. General methods

NMR spectra were recorded on a Bruker AC 400 spectrometer operating at 400.13 MHz for ^{1}H NMR, at 46.07 MHz for ^{2}H NMR and 100.61 MHz for ^{13}C NMR. Chemical shifts are recorded as δ values (ppm). A Perkin–Elmer 377 instrument was used to determine IR spectra. TLC analyses were performed on Merck 60 F_{254} silica gel plates and were visualized using iodine. Column chromatography was carried out using Merck silica gel (grade 60, 70–230 mesh) and Merck silica gel (grade 60, 230–400 mesh) for flash column chromatography. The enantiomeric purity was determined by HPLC using a Chiracel OJ column (J. T. Baker, Inc., Phillipsburg, NJ).

3.2. Methyl 3-(N-methylbenzyl-N′-benzylamino)-3-(3,4-dimethoxyphenyl)propanoate **7**

To a stirred solution of (+)-(*R*)-*N*-benzyl-*N*-α-methylbenzylamine (7.7 g, 36.5 mmol) in dry THF (160 ml) at 0°C under argon was slowly added *n*-BuLi (1.6 M, 22.8 ml, 36.5 mmol). After 1 h, methyl 3,4-dimethoxycinnamate (7 g, 31.4 mmol) in dry THF (60 ml) was added. The mixture was stirred for 3 h at 0°C then ammonium chloride (60 ml) was added. The aqueous layer was extracted with diethyl ether (3×60 ml). The combined organic phases were dried over $MgSO_4$ and the solvent removed in vacuo. The resulting crude product was purified by flash column chromatography (ethyl acetate:hexane 1:1) to give **7** (11.0 g, 81% yield) as a yellow oil: $[\alpha]_D^{25}$ +2 (*c* 5.3, $CHCl_3$); *de* >92%; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 3H, J=7.0 Hz), 2.62 (ABX system, 2H, J_{AB}=14.8, J_{AX}=5.4, J_{BX}=9.5 Hz), 3.50 (s, 3H), 3.75 (s, 2H), 3.88 (s, 3H) 3.94 (s, 3H), 4.05 (q, 1H, J=7.0 Hz), 4.40 (dd, 1H, J_{AX}=5.4, J_{BX}=9.5 Hz), 6.80–7.04 (m, 3H), 7.15–7.50 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 16.6, 37.2, 50.7, 51.5, 55.9, 56.1, 57.1, 59.0, 110.7, 111.7, 119.7, 126.6, 126.9, 127.8, 127.9, 128.1, 128.2, 134.3, 141.5, 144.2, 148.1, 148.7, 172.3; IR (NaCl neat) 1743, 1601, 1593 cm^{-1}. Anal. calcd for $C_{28}H_{33}NO_4$: C, 74.31; H, 7.35; N, 3.23. Found: C, 74.79; H, 7.21, N, 3.35.

3.3. Methyl (3S)-3-amino-3-(3,4-dimethoxyphenyl)propanoate **6**

A mixture of **7** (11.3 g, 26.1 mmol) in methanol (120 ml), acetic acid (3.1 ml) and water (12 ml) was treated with 20% palladium hydroxide on activated carbon (2.7 g). The mixture was stirred under a hydrogen atmosphere (4 bar) for 3 days. The reaction mixture was filtered through Celite, then washed with methanol and the filtrate was concentrated under reduced pressure to give a residue which was treated with saturated aqueous bicarbonate solution (200 ml) and then extracted with dichloromethane (3×200 ml). The combined organic extracts were dried over anhydrous K_2CO_3. Evaporation under reduced pressure provided **6** (5.6 g, 90% yield) as a clear oil: $[\alpha]_D^{25}$ −9.8 (*c* 1.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.95 (br s, 2H), 2.65 (d, 2H, J=6.8 Hz), 3.65 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 4.40 (t, 1H, J=6.8 Hz), 6.78–6.93 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 44.1, 51.7, 52.3, 55.8, 55.9, 109.2, 111.1, 118.2, 137.2, 148.2, 149.0, 172.5; IR (NaCl neat) 3391, 1737, 1609–1590 cm^{-1}. Anal. calcd for $C_{12}H_{17}NO_4$: C, 60.22; H, 7.16; N, 5.86. Found: C, 59.89; H, 7.28; N, 5.79.

3.4. Methyl (3S)-3-amino-3-(3,4-dimethoxyphenyl)-N-trideuteroacetyl)propanoate

To a stirred solution of **6** (196 mg, 0.82 mmol) and triethylamine (0.137 ml, 0.98 mmol) in anhydrous diethyl ether (6 ml), was added trideuteroacetyl chloride (73 mg, 0.9 mmol) and the mixture stirred for 10

min. The solvent was removed in vacuo and the resulting mixture was dissolved with ethyl acetate:hexane 7:3 (10 ml). The mixture was filtered and concentrated. The crude product was chromatographed over silica gel (eluted with ethyl acetate:hexane 7:3) to give the *N*-trideuteroacetyl compound (148 mg, 63% yield) as a pale yellow oil: *ee* >92%; ^{1}H NMR ($CDCl_3$) δ 2.80 (ABX system, 2H, J_{AB}=15.2 Hz, J_{AX}=6.2, J_{BX}=6.25 Hz), 3.70 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 5.30 (m, 1H), 6.75 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 39.9, 49.4, 51.7, 55.7, 110.0, 111.1, 118.2, 133.2, 148.3, 148.9, 169.3, 171.7; IR (NaCl neat) 3435, 1740, 1680 cm^{-1}.

3.5. (S)-N-*[1-(3,4-Dimethoxyphenyl)-2-methoxycarbonylethyl]glutarimide* ***8***

A solution of **5** (4.0 g, 16.7 mmol) and glutaric anhydride (2.1 g, 18.4 mmol) in toluene (160 ml) was refluxed for 12 h. The solvent was removed and the mixture was refluxed with acetyl chloride (5.4 ml, 75.3 mmol) in toluene (160 ml) for 3 h. The solvent was removed in vacuo and the resulting mixture was taken up with 50 ml of dichloromethane and washed with 10% HCl (20 ml) then with water (20 ml). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed over silica gel (eluted with ethyl acetate:hexane 9:1) to afford **8** (4.8 g, 86% yield) as a white solid: mp 113°C; $[\alpha]_D^{25}$ −84 (*c* 1.46, $CHCl_3$); *ee* >90% (HPLC, eluted with hexane:ethanol 1:9); ^{1}H NMR ($CDCl_3$) δ 1.60 (q, 2H, *J*=6.5 Hz), 2.61 (t, 4H, *J*=6.5 Hz), 3.15 (dd, 1H, *J*=16.0, 5.9 Hz), 3.60 (dd, 1H, *J*=16.0, 9.8 Hz), 3.65 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 6.27 (dd, 1H, *J*=9.8, 5.9 Hz), 6.74–7.04 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 17.1, 33.6 (×2), 35.4, 50.6, 51.9, 55.9, 56.0, 110.7, 111.8, 120.8, 131.3, 148.6, 148.7, 171.6 (×2), 172.8; IR (NaCl neat) 1741, 1688, 1680 cm^{-1}. Anal. calcd for $C_{17}H_{21}NO_6$: C, 60.87; H, 6.31; N, 4.18. Found: C, 61.03; H, 6.45; N, 4.08.

3.6. *6-Ethoxy*-N-*[1-(3,4-dimethoxyphenyl)-2-methoxycarbonylethyl]piperidin-2-one* ***5***

$NaBH_4$ (3.2 g, 84.8 mmol) was slowly added to a solution of **8** (4 g, 11.9 mmol) in anhydrous ethanol (90 ml) at −10°C under argon. After stirring for 15 min, 10 drops of a 4 N solution of H_2SO_4 in ethanol were added every 15 min during 2 h. The $NaBH_4$ excess was destroyed by adding a 12 N solution of H_2SO_4 in ethanol until pH 2. The solution was then poured into 300 ml of saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layers were dried over K_2CO_3 and concentrated in vacuo. The resulting pale yellow oil was purified by column chromatography on silica gel (ethyl acetate:hexane 8:2) to give **5** (3.4 g, 77% yield) as a pale yellow oil which was isolated as a mixture of two diastereomers in a 4:1 ratio: ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 0.6H, *J*=6.9 Hz), 1.19 (t, 2.4H, *J*=7.0 Hz), 1.33 (tt, 1H, *J*=13.7, 3.0 Hz), 1.55 (m, 1H), 1.85–2.00 (m, 2H), 2.20–2.35 (m, 1H), 2.43–2.53 (m, 1H), 3.08–3.35 (m, 4H), 3.56 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 4.22 (br s, 0.8H), 4.57 (br s, 0.2H), 5.87 (t, 0.8H, *J*=7.7 Hz), 6.15 (t, 0.2H, *J*=7.7 Hz), 6.72–6.86 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.9, 15.1, 15.4, 19.8, 26.1, 26.8, 31.6, 32.5, 32.6, 36.7, 37.5, 51.3, 51.6, 53.9, 55.7, 56.1, 62.1, 62.9, 83.7, 85.1, 110.3, 110.8, 111.6, 111.9, 130.5, 130.7, 148.4, 148.6, 148.9, 149.0, 169.1, 170.0, 170.7, 171.6; IR (NaCl neat) 1737, 1658 cm^{-1}. Anal. calcd for $C_{19}H_{27}NO_6$: C, 62.44; H, 7.45; N, 3.83. Found: C, 62.31; H, 7.63; N, 3.73.

3.7. *2-Methylene-4-(3,4-dimethoxyphenyl)quinolizidin-6-ones* ***9a*** *and* ***9b***

$CeCl_3 \cdot 7H_2O$ (20 g, 53 mmol) was dried by stirring under 0.01 mbar, for 4 h at 150°C, then overnight at room temperature. The flask was flushed with argon, then dry THF (60 ml) was added and the white suspension was stirred at room temperature for 2 h. This slurry was cooled to −78°C under argon and trimethylsilylmethylmagnesium chloride in THF [prepared from chloromethyltrimethylsilane (7.4 ml, 53

mmol) and magnesium pellets (1.3 g, 54 mmol) in dry THF (20 ml)] was added dropwise over a period of 40–60 min. The cold mixture was stirred for 2 h and a solution of **7** (4.3 g, 12 mmol) in 50 ml of dry THF was added. The resulting mixture was allowed to warm to room temperature and stirred for 3 days. The reaction mixture was then cooled to 0°C and a 1 N HCl solution (200 ml) was added. The aqueous layer was extracted with $CHCl_3$ (3×150 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting crude mixture was purified by column chromatography on silica gel (ethyl acetate:hexane 1:1) to give **9a** (0.6 g, 16% yield) and **9b** (1.7 g, 44% yield) as pale yellow oils.

9a: $[\alpha]_D^{25}$ −118 (*c* 1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.45–1.70 (m, 2H), 1.75–2.00 (m, 2H), 2.10–2.35 (m, 2H), 2.40–2.50 (m, 2H), 2.54 (dd, 1H, *J*=15.5, 6.5 Hz), 2.86 (d, 1H, *J*=14.5 Hz), 3.25–3.33 (m, 1H), 3.78 (s, 3H), 3.81 (s, 3H), 4.87 (d, 1H, *J*=1.5 Hz), 4.91 (d, 1H, *J*=1.5 Hz), 6.70–6.95 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 18.4, 29.8, 33.3, 35.7, 42.0, 50.0, 51.2, 55.8, 110.8, 111.2, 111.7, 120.1, 133.1, 142.7, 147.9, 148.8, 169.8; IR (NaCl neat) 1640, 1517 cm^{-1}.

9b: $[\alpha]_D^{25}$ +49 (*c* 1.6, $CHCl_3$); *ee* >90% (HPLC, hexane:2-propanol 8:2, 0.1% Et_3N); ^{1}H NMR ($CDCl_3$) δ 1.45–1.65 (m, 1H), 1.75–2.00 (m, 3H), 2.30–2.55 (m, 4H), 2.75 (dd, 1H, *J*=15.9, 2.4 Hz), 2.95 (br d, 1H, *J*=15.9 Hz), 3.73 (m, 1H), 3.79 (s, 3H), 3.83 (s, 3H), 4.71 (br s, 1H), 4.74 (br s, 1H), 5.50 (m, 1H), 6.65–6.80 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 20.4, 31.0, 32.3, 36.3, 37.1, 53.4, 55.7, 55.8, 109.6, 110.9, 111.4, 117.6, 135.2, 139.8, 147.5, 148.6, 170.3; IR (NaCl neat) 1649, 1517 cm^{-1}.

These spectral data are in agreement with reported values.[3n]

*3.8. (4S,10R)-4-(3,4-Dimethoxyphenyl)-2-methylenequinolizidine **10a***

A mixture of **9a** (64 mg, 0.21 mmol) and $LiAlH_4$ (16 mg, 0.43 mmol) in dry THF (5 ml) was refluxed for 12 h. Ether was added, followed by water (0.05 ml), 15% NaOH (0.05 ml) and water (0.250 ml).The aqueous layer was extracted with CH_2Cl_2 (3×2 ml) and the combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give **10a** (50 mg, 83% yield) as a clear oil: $[\alpha]_D^{25}$ +57 (*c* 3.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.15–1.37 (m, 2H), 1.39–1.62 (m, 3H), 1.66–1.75 (m, 1H), 2.02–2.17 (m, 2H), 2.42 (ABX system, 2H, J_{AB}=13.4, J_{AX}=4.0, J_{BX}=5.4 Hz), 2.62–2.73 (m, 2H), 2.79 (m, 1H), 3.80 (s, 3H), 3.85 (s, 3H), 3.90 (t, 1H, *J*=5.4 Hz), 4.70 (br s, 1H), 4.75 (br s, 1H), 4.75 (br s, 1H), 6.70–6.95 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 23.0, 24.5, 30.2, 41.4, 41.5, 51.7, 55.5, 55.7, 55.9, 62.3, 109.1, 110.3, 111.9, 121.2, 134.6, 144.4, 147.9, 148.4; IR (NaCl neat) 1650, 1604, 1592 cm^{-1}. These spectral data are in agreement with reported values.[3n]

*3.9. (4S,10S)-4-(3,4-Dimethoxyphenyl)-2-methylenequinolizidine **10b***

Using the above procedure, **9b** (0.93 g, 3.1 mmol) gave **10b** (0.79 g, 89% yield) as a clear oil: $[\alpha]_D^{25}$ −15 (*c* 2.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.15–1.35 (m, 2H), 1.35–1.55 (m, 3H), 1.62–1.75 (m, 2H), 1.85–2.00 (m, 1H); 2.10–2.40 (m, 4H), 2.70 (d, 1H, *J*=11.3 Hz), 2.85 (dd, 1H, *J*=11.3, 3.2 Hz), 3.85 (s, 3H), 3.90 (s, 3H); 4.63 (br s, 1H), 4.66 (br s, 1H), 6.80–6.95 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 24.7, 26.2, 34.0, 42.3, 44.8, 53.3, 55.9, 56.0, 64.2, 71.3, 106.9, 110.3, 110.9, 119.7, 137.2, 146.3, 147.8, 148.7; IR (NaCl neat) 1655, 1604, 1592 cm^{-1}. These spectral data are in agreement with reported values.[3n]

*3.10. (4S,10R)-4-(3,4-Dimethoxyphenyl)quinolizidin-2-one **11a***

To a stirred solution of **10a** (0.2 g, 0.70 mmol) in 80% acetic acid (15 ml) at 0°C was added sodium paraperiodate (0.45 g, 1.54 mmol) and osmium tetroxide (0.006 g, 0.024 mmol). The reaction mixture was stirred for 18 h at 10°C. Acetic acid was evaporated to give a residue which was partitioned

between CH_2Cl_2 (10 ml) and saturated sodium bicarbonate solution (10 ml). The aqueous layer was extracted with CH_2Cl_2 (15 ml). The combined organic layers were dried over $MgSO_4$, concentrated and chromatographed over silica gel (eluted with ethyl acetate) to afford **11a** (140 mg, 70% yield) as a yellow oil: $[\alpha]_D^{25}$ +9.5 (*c* 3.1, $CHCl_3$) {lit.[4] $[\alpha]_D^{25}$ +10.8 (*c* 1.31, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$) δ 1.10–1.24 (m, 1H), 1.34–1.70 (m, 5H), 2.17 (td, 1H, *J*=11.8, 3.0 Hz), 2.35 (dd, 1H, *J*=14.9, 8.7 Hz), 2.58 (m, 2H), 2.87 (m, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.25 (dd, 1H, *J*=6.1, 3.9 Hz), 6.64–6.68 (m, 2H), 6.79 (d, 1H, *J*=8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 23.2, 23.9, 31.7, 46.7, 47.4, 51.2, 54.0, 55.6, 55.7, 63.7, 110.4, 111.5, 120.7, 131.3, 148.2, 148.5, 209.6; IR (NaCl neat) 1715 cm^{-1}. These spectral data are in agreement with reported values.[3n]

*3.11. (4S,10S)-4-(3,4-Dimethoxyphenyl)quinolizidin-2-one **11b***

Using the above procedure, **10b** (147 mg, 0.51 mmol) gave **11b** (130 mg, 90% yield) as a yellow oil: $[\alpha]_D^{25}$ −63 (*c* 1.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 1H), 1.35–1.70 (m, 6H), 2.19–2.50 (m, 4H), 2.64 (t, 1H, *J*=12.8 Hz), 2.73 (d, 1H, *J*=11.4 Hz), 3.15 (dd, 1H, *J*=12.1, 3.1 Hz), 3.82 (s, 3H), 3.85 (s, 3H), 6.75 (m, 2H), 6.93 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.1, 25.7, 34.2, 48.6, 50.7, 52.7, 55.8, 55.9, 62.3, 69.8, 109.7, 110.9, 119.4, 135.0, 148.2, 149.2, 207.7; IR (NaCl neat): 2793, 2755 (Bohlmann bands), 1725 cm^{-1}. These spectral data are in agreement with reported values.[3n]

*3.11.1. (−)-Lasubine I **1***

To a solution of **11a** (47 mg, 0.16 mmol) in anhydrous THF (5 ml) at −78°C under argon was added L-Selectride (1 M solution in THF, 0.244 ml, 0.244 mmol). The reaction mixture was stirred for 2 h at −78°C, then it was warmed to 0°C and water (3.1 ml) was added. The mixture was concentrated and saturated sodium bicarbonate (5 ml) was added. The aqueous layer was extracted with $CHCl_3$ (3×5 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed over alumina (eluted with ethyl acetate:hexane 1:1) to give (−)-lasubine I **1** (29 mg, 62% yield) as a pale yellow oil: $[\alpha]_D^{25}$ −6.5 (*c* 2.6, MeOH) {lit.[2] $[\alpha]_D^{22}$ −8.8 (*c* 0.34, MeOH), lit.[4] $[\alpha]_D^{23}$ −7.03 (*c* 0.37, MeOH)}; ^{1}H NMR ($CDCl_3$) δ 1.18–2.12 (m, 11H), 2.24 (td, 1H, *J*=11.7, 2.6 Hz), 2.69 (br d, 1H, *J*=4.7 Hz), 2.96 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 4.08 (t, 1H, *J*=4.7 Hz), 4.18 (heptuplet, 1H, *J*=4.4 Hz), 6.77–6.89 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 24.1, 24.5, 32.4, 40.2, 40.3, 51.2, 54.0, 55.8, 55.9, 61.9, 65.0, 110.7, 111.9, 120.6, 135.3, 147.8, 148.7; IR (NaCl neat): 3382, 1513 cm^{-1}. These spectral data are in agreement with reported values.[3n]

*3.11.2. (−)-Lasubine II **2***

To a solution of **12b** (241 mg, 0.83 mmol) in dry THF (7 ml) at −78°C under argon was added LS-Selectride (1 M solution in THF, 1.24 ml, 1.24 mmol). The reaction mixture was stirred for 12 h at −78°C, then it was warmed to 0°C and water (5 ml) was added. The mixture was concentrated and saturated aqueous sodium bicarbonate (7 ml) was added. The aqueous layer was extracted with $CHCl_3$ (3×15 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed over silica gel (eluted with ethyl acetate:methanol 9:1) to give (−)-lasubine II **2** (140 mg, 60% yield) as a pale yellow oil: $[\alpha]_D^{25}$ −41.0 (*c* 3.7, MeOH) {lit.[2] $[\alpha]_D^{22}$ −34.7 (*c* 0.32, MeOH)}; *ee* >90% (HPLC, hexane:2-propanol 8:2, 0.1% Et_3N); ^{1}H NMR ($CDCl_3$) δ 1.20–1.43 (m, 2H), 1.48 (m, 2H), 1.53 (m, 1H), 1.61–1.73 (m, 4H), 1.74–1.92 (m, 3H), 2.38 (m, 1H), 2.67 (d, 1H, *J*=10.9 Hz), 3.32 (br d, 1H, *J*=10.5 Hz), 3.84 (s, 3H), 3.87 (s, 3H), 4.12 (br s, 1H), 6.74–6.95 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 24.9, 26.1, 33.6, 40.3, 42.8, 53.2, 55.8, 55.9, 56.5, 63.5, 64.9, 110.8, 119.5, 119.7, 137.2, 147.8, 148.9; IR (NaCl): 3620, 2797, 2762 cm^{-1}. These spectral data are in agreement with reported values.[3n]

*3.11.3. (+)-Subcosine II **3***

trans-3,4-Dimethoxycinnamic anhydride (0.100 g, 0.25 mmol) was added to a solution of (−)-lasubine II (68 mg, 0.23 mmol) and DMAP (2.5 g, 0.023 mmol) in pyridine (10 ml) under argon. The mixture was refluxed for 3 h, then cooled to room temperature. The solvent was removed in vacuo and saturated aqueous sodium bicarbonate (10 ml) was added. The aqueous layer was extracted with CH_2Cl_2 (3×15 ml). The combined organic layers were dried over K_2CO_3 and concentrated. The resulting crude product was chromatographed over silica gel (eluted with ethyl acetate) to give (+)-subcosine II **3** (65 mg, 60% yield) as a pale yellow oil: $[\alpha]_D^{25}$ +121 (*c* 3.5, MeOH) {lit.[2] $[\alpha]_D^{22}$ +85.3 (*c* 0.64, MeOH)}; ^{1}H NMR ($CDCl_3$) δ 1.20–1.80 (m, 8H), 1.85–2.20 (m, 3H), 2.36 (t, 1H, *J*=10.5 Hz), 2.72 (t, 1H, *J*=11.4 Hz), 3.28 (d, 1H, *J*=8.4 Hz), 3.85 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 5.20 (m, 1H), 6.40 (d, 1H, *J*=15.9 Hz), 6.75–6.93 (m, 4H), 7.08–7.18 (m, 2H), 7.67 (d, 1H, *J*=15.9 Hz); ^{13}C NMR ($CDCl_3$) δ 24.9, 26.2, 33.6, 37.4, 39.8, 53.2, 55.8, 55.9, 56.0, 56.1, 57.2, 64.2, 68.4, 109.6 (×2), 111.0 (×2), 116.3 (×2), 122.8, 127.5, 137.0, 147.9, 149.2 (×2), 151.1 (×2), 166.7; IR (NaCl neat) 1709, 1634, 1599 cm^{-1}. These spectral data are in agreement with reported values.[2]

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