

A SYNTHESIS OF THE QUINOLIZIDINE ALKALOIDS (±)-LASUBINE I AND (±)-LASUBINE II

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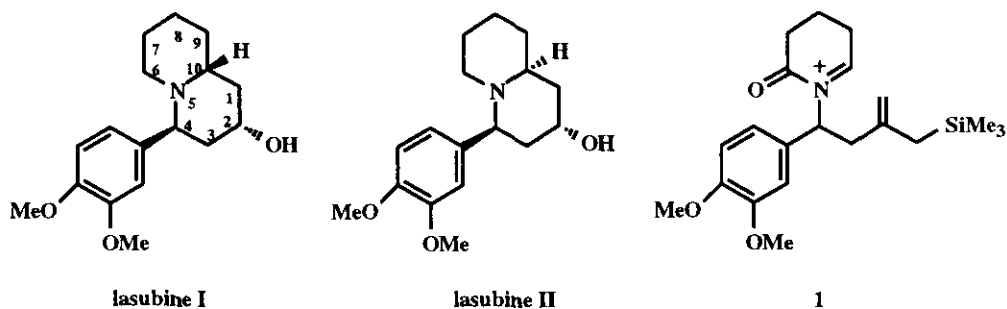
Abstract - A total synthesis of (±)-lasubine I and (±)-lasubine II has been achieved in six steps from a β -hydroxyallylsilane synthon using intramolecular cyclization of allylsilane on *N*-acyliminium ion as a key step.

The Lythraceae alkaloids are a large family of natural products, most of which contain 4-arylquinolizidine substructures. Among them are the quinolizidine alkaloids lasubine I and lasubine II which have been isolated from *Lagerstroemia subcostata* Koehne.¹ Several total syntheses of these alkaloids, including a chiral synthesis,¹³ have been described.²⁻¹⁶

We have shown that intramolecular cyclization of acyliminium ions substituted by an allylsilyl side chain as an internal π -nucleophile provided a route to the quinolizidine ring system, which has been used to prepare a variety of alkaloids including (±)-myrtine and (±)-epimyrtine.¹⁷

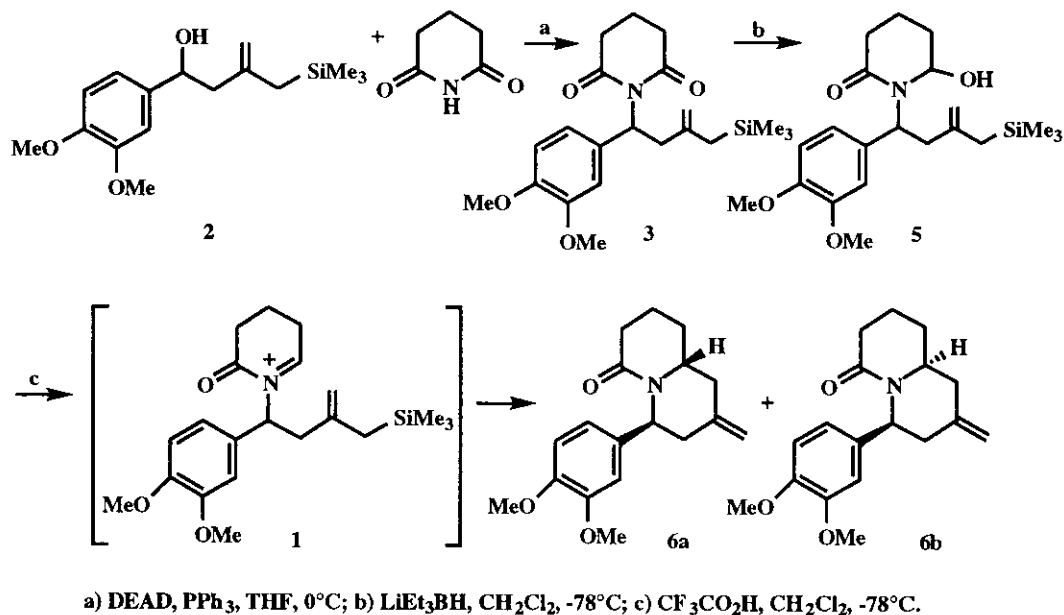
This cyclization produces an exocyclic methylene group which can be transformed into a keto group then into a secondary hydroxy function with control of the stereochemistry.

This article describes an application of this strategy to synthesis of (±)-lasubine I and (±)-lasubine II *via* the cyclization of *N*-acyliminium (**1**).



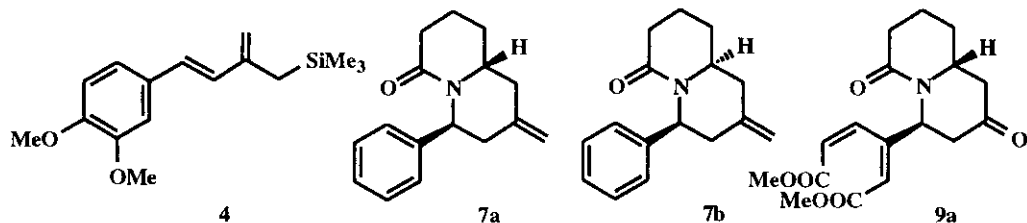
The first steps of our synthesis were carried out as shown in Scheme 1. The starting material was the 2-(2-hydroxyethyl)allylsilane (**2**) which was prepared in 86% yield by indium mediated allylsilylation of 3,4-dimethoxybenzaldehyde, as already described.¹⁸ Condensation of alcohol (**2**) with glutarimide under

Mitsunobu conditions led to imide (3) in 46% yield. In this reaction, ethylenic compound (4) resulting from the dehydration of alcohol (2) was also isolated, in an amount which could be reduced to 7% when diethyl azodicarboxylate addition was very slow.



Scheme 1

Reduction of 3 with diisobutylaluminium hydride afforded hydroxylactam (5) isolated as a 1:1 mixture of isomers; higher yield and a single isomer were obtained when using lithium triethylborohydride as a reducing reagent. The reduction had to be performed at -78°C to prevent formation of ring opening products.¹⁹ Treatment of hydroxylactam (5) with trifluoroacetic acid in methylene chloride gave a mixture of isomeric bicyclic compounds (6a) and (6b) in a quantitative yield. These diastereomers were obtained in a 4:1 ratio when the reaction was performed at -78°C; this ratio was 0.55:1 at 20°C. Diastereomer separation was achieved easily by flash column chromatography.

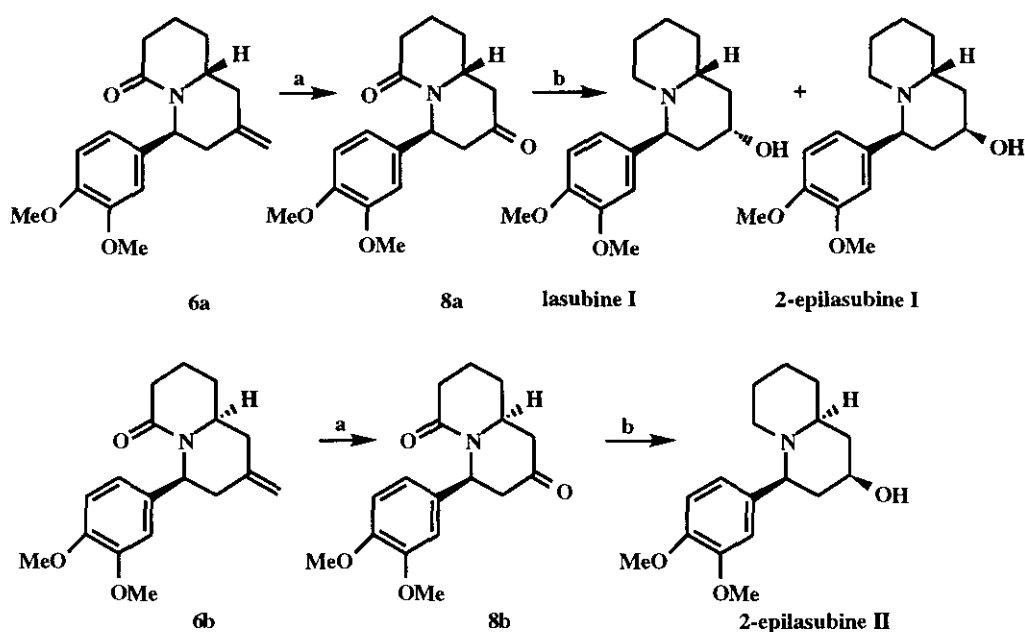


The 4,10-stereochemistry of 6a and 6b was deduced by comparison of their NMR spectra with those of the 4-phenyl analogues (7a) and (7b). The stereochemical assignment of 7a was indicated by X-Ray analysis. ¹³C-NMR spectra of 7a showed a high field chemical shift of C-10 relative to 7b. This upfield shift is

readily explained in terms of a γ -gauche effect between the aromatic ring and C-10 in **7a** and a γ -anti effect of these atoms in **7b**. Similar differences are found between the C-10 nuclei of isomers (**6a**) and (**6b**). In addition, chemical shifts were almost identical for H-4 and H-10 in **6a** compared to **7a** and in **6b** compared to **7b**. This stereorelationship was that expected from Hart's transition state model for a cyclization reaction via a chair conformation with a preference for the aryl group in axial position to minimize A(1,3) strain²⁰ between this substituent and the carbonyl group.

We examined two routes to the quinolizidine alkaloids lasubine I and lasubine II from methylenequinolizidinones (**6a**) and (**6b**); they involved oxidation of the methylene group into carbonyl which was then stereoselectively reduced to hydroxy group.

The shortest route (Scheme 2) consisted in the ozonolysis of the methylene group followed by the simultaneous reduction of the two carbonyl groups of keto lactams (**8a**) and (**8b**).

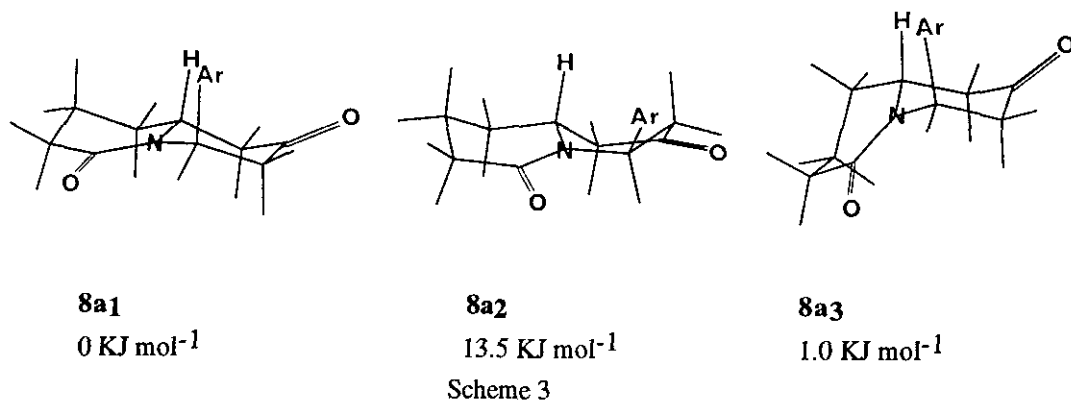


a) O_3 , Me_2S , CH_2Cl_2 - $MeOH$ (1-1), $-78^\circ C$; b) $LiAlH_4$, THF, reflux.

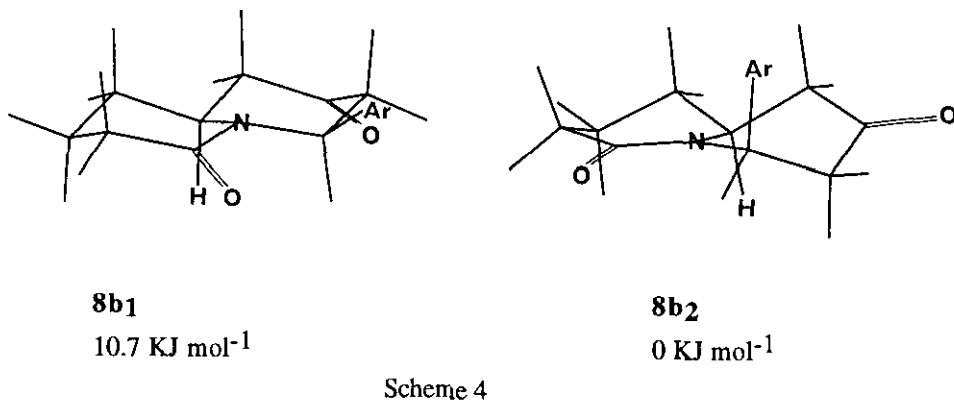
Scheme 2

Thus, treatment of **6a** with ozone then with dimethyl sulfide²¹ afforded the expected keto lactam (**8a**)¹⁴ in 91% yield provided that a very short ozonization time (5 min) was used. Otherwise, with a longer ozonization time (7 min or more), compound (**9a**) was produced in 90% yield, presumably from ozone attack of the double bond connected to the two electron donating groups of the veratryl ring, as already observed by Woodward and coll.²² in the total synthesis of strychnine. Ozonolysis of **6b** led to keto lactam (**8b**) in 63% yield. Reduction of **8a** with lithium aluminium hydride afforded in 60% yield a 1:1.2 mixture of lasubine I¹ and 2-epilasubine I² which were separated as their acetates.² In the same way, reduction of **8b** gave 2-epilasubine II^{7,10} in 70% yield.

In order to explain the stereochemical outcome of these reactions, none of which led exclusively to lasubine I or lasubine II, we investigated the conformational analysis of **8a** and **8b**.



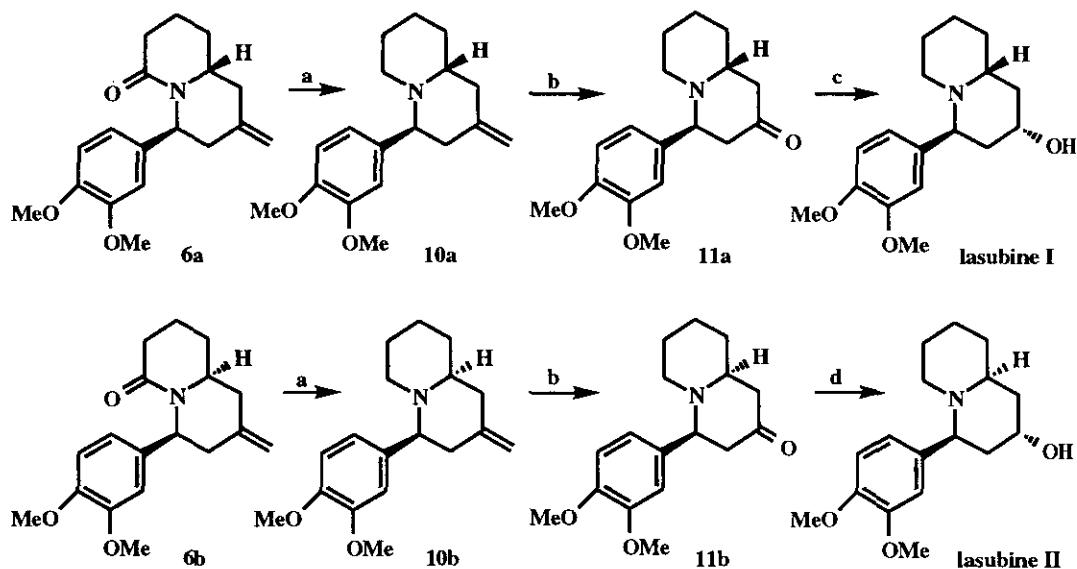
The major conformers of **8a** are **8a1** and **8a3** (Scheme 3) in which the upper face of the carbonyl group is crowded by the axial aromatic ring. As a consequence, reduction with LiAlH₄ gave an important amount of the undesired axial alcohol. Use of a more bulky reagent should increase this amount.



The isomer (**8b**) exists predominantly as conformer (**8b2**) (> 98%) (Scheme 4) in which the upper face of the piperidin-2-one ring is crowded by the aromatic ring; in consequence, reduction of the carbonyl group occurred by the lower face yielding exclusively the undesired axial hydroxy group. Utilisation of a more bulky reagent could not improve the yield of the equatorial hydroxy group.

In order to circumvent the stereochemical difficulty we decided to reduce first the lactam group to obtain quinolizidines whose conformation should not be distorted by the junction with the piperidone ring. Lactams (**6a**) and (**6b**) were reduced with lithium aluminium hydride to give methylenequinolizidines (**10a**) and (**10b**) in respectively 92% and 78% yields (Scheme 5). Osmium tetroxide catalyzed periodate oxidation^{23,24} of the olefinic bond of methylenequinolizidines (**10a**) and (**10b**) under carefully controlled conditions led to already described 2-oxoquinolizidines (**11a**)^{7,13} and (**11b**)^{3,7,11} in respectively 79%

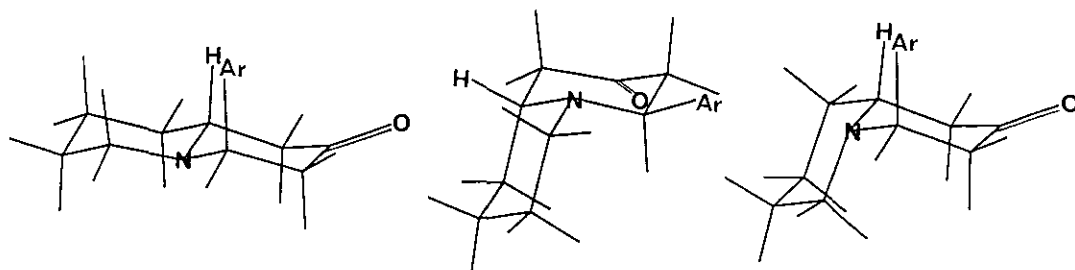
and 89% yields. The final step is a reduction of the carbonyl group. The use of sodium borohydride in the reduction of **11a** has been described to give lasubine I in an excellent yield.^{7,14} In our hands, this reaction afforded a 1:1 mixture of (\pm)-lasubine I and (\pm)-2-epilasubine I. Stereoselective reduction of quinolizidin-2-one (**11a**) to (\pm)-lasubine I was achieved in 50% yield with lithium tri-*sec*-butylborohydride (L-selectride).^{2,3,13} Quinolizidinone (**11b**) was selectively converted to (\pm)-lasubine II^{1,10} with lithium trisiamylborohydride (LS-selectride)¹¹ in 60% yield.



a) LiAlH_4 , THF, reflux; b) OsO_4 , $\text{Na}_3\text{H}_2\text{IO}_6$, 80% AcOH, 8°C; c) L-Selectride, THF, -78°C; d) LS-Selectride, THF, -78°C.

Scheme 5

Molecular modelling studies provide a better comprehension of the stereochemical outcome of these reactions.



11a1
4.1 KJ mol⁻¹

11a2
0 KJ mol⁻¹

11a3
6.9 KJ mol⁻¹

Scheme 6

obtained were submitted to AM1 calculations (MOPAC version 5.0)²⁶ to optimize their geometry using the key word "mmok" for **8a** and **8b** that contains an amide function. The energies were calculated after optimization of all parameters and compared.

***N*-[1-(3,4-Dimethoxyphenyl)-3-(trimethylsilylmethyl)but-3-enyl]glutarimide (3).**

To a stirred solution of alcohol (**2**)¹⁸ (3.0 g; 10.2 mmol), glutarimide (1.65 g; 14.3 mmol) and triphenylphosphine (3.36 g; 13 mmol) in anhydrous THF (40 mL) at 0°C under argon was added dropwise a solution of diethyl azodicarboxylate (2.26 g; 13 mmol) in THF (10 mL) during 3 h. The reaction mixture was stirred for 1 h at rt and concentrated. The residue was chromatographed over silica gel using ethyl acetate-hexane (2:8) as eluent to give imide (**3**) (1.69 g, 46% based on consumed starting material) and ethylenic product (**4**) (0.2 g, 7%).

Imide (**3**): IR (cm⁻¹) 1765, 1727 and 1677; ¹H-NMR (CDCl₃) δ 7.05-6.75 (3H, m), 6.07 (1H, dd, J = 5.1, 11.2 Hz), 4.56 (2H, s), 3.86 (3H, s), 3.84 (3H, s), 3.28 (1H, dd, J = 13.5, 11.2 Hz), 2.58 (4H, t, J = 6.0 Hz), 2.52 (1H, dd, J = 13.5, 5.1 Hz), 1.84 (2H, quintet, J = 6.5 Hz), 1.50 (2H, s), 0.05 (9H, s); ¹³C-NMR (CDCl₃) δ 172.8, 148.3, 148.1, 144.4, 132.3, 120.7, 111.7, 110.6, 108.9, 55.8, 55.7, 51.8, 38.6, 33.6, 26.2, 17.2, -1.3. Anal. Calcd for C₂₁H₃₁NO₄Si: C, 64.75; H, 8.03. Found: C, 64.65; H, 8.21.

1-(3,4-dimethoxyphenyl)-3-(trimethylsilylmethyl)but-1,3-diene (**4**): ¹H-NMR (CDCl₃) δ 7.05-6.80 (3H, m), 6.70 (1H, d, J = 16.0 Hz), 6.40 (1H, d, J = 16.0 Hz), 5.05 (1H, s), 4.82 (1H, s), 3.89 (3H, s), 3.85 (3H, s), 1.85 (2H, s), 0.05 (9H, s); ¹³C-NMR (CDCl₃) δ 149.3, 148.7, 132.0, 130.3, 128.7, 119.8, 114.0, 111.2, 108.6, 55.9, 55.8, 22.2, -1.1.

6-Hydroxy-1-[1-(3,4-dimethoxyphenyl)-3-(trimethylsilyl)but-3-enyl]piperidin-2-one (5)

a) Reduction with DIBAL-H:

To a stirred solution of imide (**3**) (0.3 g; 0.77 mmol) in anhydrous toluene (3 mL) at -78°C under argon was added dropwise a solution of 1.5M DIBAL-H in toluene (1.0 mL; 1.2 mmol). The reaction mixture was stirred for 30 min at -78°C, then poured into a mixture of chloroform and 5% H₂SO₄. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with ethyl acetate:hexane (4:6)) to give hydroxylactam (**5**) (0.09 g, 30%) isolated as a 1:1 mixture of two isomers; ¹H-NMR (CDCl₃) δ 7.28-6.77 (5H, m), 6.05 (0.5H, dd J = 5.6, 12.2 Hz), 5.95 (0.5H, t, J = 7.9 Hz), 5.14 (0.5H, m), 4.85 (0.5H, m), 4.74 (0.5H, s), 4.65 (0.5H, s), 4.60 (1H, s), 3.80 (3H, s), 3.70 (3H, s), 2.90-1.49 (11H, m), 0.05 (9H, s); ¹³C-NMR (CDCl₃) δ 170.7 and 170.6, 149.4 and 148.9, 148.4, 145.9 and 144.1, 132.6, 119.7 and 119.3, 111.8 and 111.6, 111.3 and 110.7, 110.6 and 110.4, 75.7, 55.9, 55.8, 54.0 and 52.0, 40.2 and 39.5, 32.2 and 32.0, 30.5 and 29.6, 26.3 and 25.9, 15.3 and 15.1, -1.3.

b) Reduction with lithium triethylborohydride:

To a stirred solution of imide (**3**) (0.65g; 1.67 mmol) in anhydrous methylene chloride (5.5 mL) at -78°C under argon was added dropwise a solution of 1M lithium triethylborohydride in THF (2.0 mL; 2.2 mmol). The reaction mixture was stirred for 3 h at -78°C and hydrolysed with a saturated aqueous ammonium chloride solution (1.3 mL). The reaction mixture was allowed to warm to rt and extracted with methylene chloride. The combined organic layers were dried over MgSO₄, concentrated and chromatographed over

silica gel (eluted with ethyl acetate-hexane (4:6)) to give hydroxylactam (**5**) (0.39 g, 60%) isolated as a single isomer : mp 90-92°C; IR (cm⁻¹) 3518 and 1649; ¹H-NMR (CDCl₃) δ 6.95-6.77 (3H, m), 5.97 (1H, dd, J = 6.6, 9.30 Hz), 4.86 (1H, m), 4.75 (1H, s), 4.66 (1H, s), 3.80 (3H, s), 3.70 (3H, s), 2.88-1.40 (11H, m), 0.00 (9H, s); ¹³C-NMR (CDCl₃) δ 170.7, 149.4, 148.4, 144.1, 132.6, 119.3, 111.6, 110.7, 110.4, 75.7, 55.9, 55.8, 52.0, 39.5, 32.0, 29.6, 26.0, 15.3, 1.3. Anal. Calcd for C₂₁H₃₃NO₄Si : C, 64.41; H, 8.49; N, 3.58; Si, 7.17. Found : C, 64.53; H, 8.62; N, 3.64; Si, 7.10.

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

To a stirred solution of hydroxylactam (**5**) (0.2 g; 0.50 mmol) in anhydrous methylene chloride (1 mL) at -78°C under argon was added dropwise trifluoroacetic acid (0.15 mL; 2 mmol). The reaction mixture was stirred for 5 h and saturated aqueous sodium bicarbonate (1.5 mL) was added. The aqueous layer was extracted with methylene chloride. The combined organic layers were dried over MgSO₄ and concentrated to give **6a** and **6b** in a 4:1 ratio (0.15 g, 99% overall yield). They were separated by chromatography over silica gel (eluted with ethyl acetate).

6a : mp 92-93°C; IR (cm⁻¹) 1639 and 1517; ¹H-NMR (CDCl₃) δ 6.93-6.68 (3H, Ar, m), 6.14 (1H, H-4, d, J = 6.4 Hz), 4.91 (1H, s), 4.88 (1H, s), 3.81 (3H, s), 3.78 (3H, s), 3.34-3.24 (1H, H-10, m), 2.79 (1H, H-3, d, J = 14.5 Hz), 2.53 (1H, H-3, dd, J = 14.5, 6.4 Hz), 2.45 (2H, H-7, m), 2.20 (2H, H-1, m), 1.94-1.70 (2H, H-9, H-8, m), 1.65-1.45 (2H, H-9, H-8, m); ¹³C-NMR (CDCl₃) δ 170.8 (C-6), 148.6 (Ar), 147.8 (Ar), 142.5 (C-2), 132.6 (Ar), 120.1 (Ar), 111.8 (CH₂), 111.0 (Ar), 110.7 (Ar), 55.8 (CH₃), 51.1 (C-10), 50.3 (C-4), 41.7 (C-1), 35.3 (C-3), 32.8 (C-7), 29.4 (C-9), 17.9 (C-8); (¹H, ¹H and ¹H, ¹³C COSY experiments provided the signal assignment). Anal. Calcd for C₁₈H₂₃NO₃ : C, 71.73; H, 7.70; N, 4.65. Found : C, 71.53; H, 7.76; N, 4.88.

6b : IR (cm⁻¹) 1649 and 1516; ¹H-NMR (CDCl₃) δ 6.78-6.62 (3H, m), 5.50 (1H, H-4, d, J = 2.5 Hz), 4.72 (1H, s), 4.69 (1H, s), 3.80 (3H, s), 3.78 (3H, s), 3.67 (1H, H-10, m), 2.93 (1H, H-3, d, J = 16.1 Hz), 2.70 (1H, H-3, dd, J = 2.5, 16.1 Hz), 2.50-2.28 (4H, H-1, H-7, m), 1.99-1.65 (3H, H-8, H-8, H-9, m), 1.58-1.43 (1H, H-9, m); ¹³C-NMR (CDCl₃) δ 171.2 (C-6), 148.5 (Ar), 147.3 (Ar), 139.6 (C-2), 134.9 (Ar), 117.5 (Ar), 111.3 (CH₂), 110.6 (Ar), 109.4 (Ar), 55.7 (CH₃), 55.6 (CH₃), 53.4 (C-4), 53.3 (C-10), 36.8 (C-1), 36.1 (C-3), 31.8 (C-7), 30.7 (C-9), 19.9 (C-8); (¹H, ¹H and ¹H, ¹³C COSY experiments provided the signal assignment). Exact MS calcd for C₁₈H₂₃NO₃ m/z 301.1678. Found m/z 301.1689.

4-(3,4-Dimethoxyphenyl)quinolizidine-2,6-dione (**8a**)

A solution of methylenelactam (**6a**) (0.038 g; 0.13 mmol) in methylene chloride:methanol (1:1) (3 mL) at -78°C was ozonized for 5 min. The solution was then purged with N₂ and dimethyl sulfide (0.1 mL) was added. The solution was allowed to warm to rt and was washed twice with water and once with brine. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. The residue was chromatographed over silica gel (eluted with ethyl acetate) to give **8a** (0.036 g; 91%) as a solid : mp 166-167°C; IR (cm⁻¹) 1719 and 1644; ¹H-NMR (CDCl₃) δ 6.77 (3H, m), 6.53 (1H, m), 3.89 (3H, s), 3.86 (3H, s), 3.54 (1H, m), 3.00 (1H, d, J = 15.3 Hz), 2.79 (1H, dd, J = 7.2, 15.3 Hz), 2.65-2.31 (4H, m), 2.02-1.52 (4H, m); ¹³C-NMR (CDCl₃) δ 207.6, 169.8, 149.3, 148.6, 131.9, 119.6, 110.8, 110.6, 55.9, 50.9, 49.5, 48.1, 43.3,

33.1, 29.3, 18.1. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.29; H, 6.98; N, 4.62. Found: C, 67.27; H, 6.92; N, 4.47.

4-[2'-(1',4'-Dimethoxycarbonyl)buta-1',3'-dienyl]quinolizidine-2,6-dione (9a)

Methylenelactam (6a) (0.03 g; 0.1 mmol) was ozonized for 7 min as previously described to give 9a (0.019 g; 90%) as an oil; IR (cm^{-1}) 1723 and 1640; 1H -NMR ($CDCl_3$) δ 6.67 (1H, H-3', ddd, $J = 0.8, 1.9, 12.2$ Hz), 6.26 (1H, H-4, br d, $J = 7.3$ Hz), 5.95 (1H, H-4', d, $J = 12.2$ Hz), 5.75 (1H, H-1', t, $J = 1.9$ Hz), 3.85 (1H, H-10, m), 3.66 (3H, s), 3.61 (3H, s), 2.81 (1H, H-3, dd, $J = 1.8, 15.7$ Hz), 2.62 (1H, H-3, dd, $J = 7.3, 15.7$ Hz), 2.45-2.35 (4H, H-1, H-9, m), 2.07-1.56 (4H, H-8, H-7, m); ($^1H, ^1H$ COSY experiment provided the signal assignment); ^{13}C -NMR ($CDCl_3$) δ 205.9, 169.6, 165.7, 165.3, 152.3, 141.1, 122.4, 119.2, 52.1, 51.6, 51.5, 50.6, 47.7, 42.2, 32.8, 29.1, 17.8; Exact MS calcd for $C_{17}H_{21}NO_6$ m/z 335.1369. Found m/z 335.1366.

4-(3,4-Dimethoxyphenyl)quinolizidine-2,6-dione (8b)

Methylenelactam (6b) (0.035 g; 0.12 mmol) was ozonized for 2 min as previously described to give 8b (0.019 g; 63%) as an oil; IR (cm^{-1}) 1734 and 1655; 1H -NMR ($CDCl_3$) δ 6.81-6.64 (3H, m), 5.87 (1H, dd, $J = 1.1, 4.1$ Hz), 4.11-4.00 (1H, m), 3.86 (3H, m), 3.84 (3H, s), 3.13 (1H, dd, $J = 6.0, 16.7$ Hz), 2.97 (1H, dd, $J = 2.3, 16.7$ Hz), 2.70-1.65 (8H, m); ^{13}C -NMR ($CDCl_3$) δ 206.5, 170.3, 148.9, 148.3, 133.8, 117.1, 111.2, 109.2, 56.0, 55.9, 53.1, 52.4, 45.3, 44.9, 32.2, 30.9, 20.5.

4-(3,4-Dimethoxyphenyl)-2-methylenequinolizidine (10a)

To a stirred solution of lactam (6a) (0.16 g; 0.53 mmol) in anhydrous THF (5.3 mL) at rt under argon was added lithium aluminium hydride (0.04 g; 1.06 mmol). The reaction mixture was refluxed for 6 h, then allowed to warm to rt. Water (0.04 mL) was added, followed by 15% NaOH (0.04 mL) and water (0.12 mL). After filtration, the organic layer was concentrated to give 10a (0.14 g; 92%); IR (cm^{-1}) 1650, 1604 and 1592; 1H -NMR ($CDCl_3$) δ 7.04-6.75 (3H, Ar, m), 4.78 (1H, s), 4.74 (1H, s), 3.90 (1H, H-4, t, $J = 5.4$ Hz), 3.85 (3H, s), 3.83 (3H, s), 2.80 (1H, H-10, m), 2.75-2.62 (2H, H-1, H-6, m), 2.53 (1H, H-3, dd, $J = 4.1, 13.4$ Hz), 2.39 (1H, H-3, dd, $J = 5.4, 13.4$ Hz), 2.17-2.02 (2H, H-6, H-1, m), 1.78-1.65 (1H, H-8, m), 1.62-1.40 (3H, H-9, H-9, H-7, m), 1.36-1.15 (2H, H-8, H-7, m); ^{13}C -NMR ($CDCl_3$) δ 148.4 (Ar), 147.9 (Ar), 144.4 (C-2), 134.5 (Ar), 121.2 (Ar), 111.8 (Ar), 110.2 (Ar), 109.1 (CH_2), 62.3 (C-4), 55.8 (CH_3), 55.7 (CH_3), 55.5 (C-10), 51.7 (C-6), 41.5 (C-3), 41.4 (C-1), 30.2 (C-9), 24.5 (C-8), 23.0 (C-7); ($^1H, ^1H$ and $^1H, ^{13}C$ COSY experiments provided the signal assignment). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.21; H, 8.77; N, 4.88. Found: C, 75.26; H, 8.83; N, 4.84.

4-(3,4-Dimethoxyphenyl)-2-methylenequinolizidine (10b)

Lactam (6b) (0.19 g; 0.63 mmol) was reduced with lithium aluminium hydride according to the previously described procedure to give 10b (0.13 g; 78%); IR (cm^{-1}) 2790, 2753 (Bohlmann bands), 1655, 1606 and 1591; 1H -NMR ($CDCl_3$) δ 6.94-6.76 (3H, Ar, m), 4.65 (1H, s), 4.62 (1H, s), 3.89 (3H, s), 3.85 (3H, s), 2.87 (1H, H-4, dd $J = 3.3, 11.3$ Hz), 2.70 (1H, H-6, br d, $J = 11.2$ Hz), 2.40-2.10 (4H, H-3, H-3, H-1, H-1, m), 1.96-1.89 (1H, H-10, m), 1.75-1.60 (2H, H-8, H-7, m), 1.57 (1H, H-6, dd, $J = 2.7, 11.7$ Hz), 1.52-1.34 (3H, H-9, H-9, H-7, m), 1.30-1.16 (1H, H-8, m); ^{13}C -NMR ($CDCl_3$) δ 149.0 (Ar), 147.9 (Ar), 146.2 (C-2), 137.1 (Ar), 119.6 (Ar), 110.8 (Ar), 110.1 (Ar), 106.8 (CH_2), 71.2 (C-4), 64.1 (C-10), 55.9 (CH_3), 55.8 (CH_3), 53.2 (C-6), 44.7 (C-3), 42.2 (C-1), 33.8 (C-7), 26.1 (C-9), 24.6 (C-8);

(^1H , ^1H and ^1H , ^{13}C COSY experiments provided the signal assignment). Exact MS calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_2$ m/z 287.1885. Found m/z 287.1897.

4-(3,4-Dimethoxyphenyl)quinolizidin-2-one (11a)

To a stirred solution of **10a** (0.05 g; 0.17 mmol) in 80% acetic acid (5 mL) at 0°C was added sodium paraperiodate (0.11 g; 0.37 mmol) and osmium tetroxide (0.0015 g; 0.006 mmol). The reaction mixture was stirred for 14 h at 8°C . Acetic acid was evaporated to give a residue which was partitioned between methylene chloride and 5% sodium bicarbonate solution. The aqueous layer was extracted with methylene chloride. The combined organic layers were dried over MgSO_4 and concentrated to give aminoketone (**11a**) (0.039 g; 79%); IR (cm^{-1}) 1718; ^1H -NMR (CDCl_3) δ 6.81 (1H, d, $J = 8.7$ Hz), 6.68 (2H, m), 4.25 (1H, H-4, dd, $J = 6.3, 4.0$ Hz), 3.87 (3H, s), 3.86 (3H, s), 2.90 (3H, H-3, H-6, H-10, m), 2.61 (2H, H-1, H-3, m), 2.38 (1H, H-1, dd, $J = 14.9, 8.9$ Hz), 2.19 (1H, H-6, td, $J = 11.8, 3.0$ Hz), 1.77-1.15 (6H, H-7, H-7, H-9, H-9, H-8, H-8, m); (^1H , ^1H COSY experiment provided the signal assignment); ^{13}C -NMR (CDCl_3) δ 209.8, 148.6, 148.4, 131.4, 120.9, 111.7, 110.6, 63.9, 55.9, 55.8, 54.2, 51.4, 47.6, 46.8, 31.9, 24.0, 23.4; this is in agreement with reported spectra.^{7,13}

4-(3,4-Dimethoxyphenyl)quinolizidin-2-one (11b)

Methylenequinolizidine (**10b**) (0.057 g; 0.2 mmol) was oxidized with sodium paraperiodate and osmium tetroxide according to the previously described procedure to give aminoketone (**11b**) (0.05 g; 89%); IR (cm^{-1}) 2755 and 2794 (Bohlmann bands), 1725; ^1H -NMR (CDCl_3) δ 6.92 (1H, br s), 6.83 (2H, m), 3.90 (3H, s), 3.87 (3H, s), 3.21 (1H, H-4, dd, $J = 12.1, 3.2$ Hz), 2.79 (1H, H-6, d, $J = 11.5$ Hz), 2.67 (1H, H-3, t, $J = 12.7$ Hz), 2.54-2.22 (4H, H-1, H-1, H-3, H-10, m), 1.78-1.40 (6H, H-9, H-9, H-8, H-8, H-6, H-7, m), 1.26 (1H, H-7, m); ^{13}C -NMR (CDCl_3) δ 207.9 (C-2), 149.4 (Ar), 148.3 (Ar), 135.1 (Ar), 119.5 (Ar), 111.0 (Ar), 109.7 (Ar), 70.0 (C-4), 62.5 (C-10), 56.0 (CH_3), 55.9 (CH_3), 52.8 (C-6), 50.8 (C-3), 48.7 (C-1), 34.3 (C-8), 25.8 (C-9), 24.2 (C-7); this is in agreement with reported spectra.^{3,7,11} (^1H , ^1H and ^1H , ^{13}C COSY experiments provided the signal assignment).

(\pm)-Lasubine I

To a stirred solution of aminoketone (**11a**) (0.029 g; 0.1 mmol) in anhydrous THF (3 mL) at -78°C under argon was added 1M L-selectride in THF (0.15 mL; 0.15 mmol). The reaction mixture was stirred for 2 h at -78°C and saturated aqueous ammonium chloride (1 mL) was added. The aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 , concentrated and chromatographed over silica gel (eluted with chloroform:methanol (95:5)) to give (\pm)-lasubine I (0.015 g; 50%); ^1H -NMR (CDCl_3) δ 7.05-6.78 (3H, m), 4.19 (2H, H-2 and H-4, m), 3.87 (3H, s), 3.86 (3H, s), 3.13 (1H, H-10, m), 2.75 (1H, H-6, d, $J = 14.2$ Hz), 2.25 (1H, H-6, td, $J = 12.0, 3.2$ Hz), 2.11-1.20 (11H, m); ^{13}C -NMR (CDCl_3) δ 148.8, 147.9, 135.6, 118.5, 111.2, 109.8, 64.7, 62.1, 56.1, 55.9, 54.0, 51.2, 40.4, 40.2, 32.6, 24.5, 24.2. This is in agreement with reported spectra.¹

(\pm)-Lasubine II

To a stirred solution of aminoketone (**11b**) (0.05 g; 0.173 mmol) in anhydrous THF (4 mL) at -78°C under argon was added 1M LS-selectride in THF (0.26 mL; 0.26 mmol). The reaction mixture was stirred for 2 h at -78°C and saturated aqueous ammonium chloride (1 mL) was added. The aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 , concentrated and chromatographed over

silica gel (eluted with chloroform:methanol (95:5)) to give (\pm)-lasubine II (0.03 g; 60%); IR (cm^{-1}) 3620, 2797 and 2762 (Bohlmann bands); $^1\text{H-NMR}$ (CDCl_3) δ 7.00-6.70 (3H, m), 4.12 (1H, H-2, t, $J = 2.3$ Hz), 3.87 (3H, s), 3.85 (3H, s) 3.30 (1H, H-4, dd, $J = 12.5, 1.5$ Hz), 2.65 (1H, H-6, d, $J = 11.1$ Hz), 2.40 (1H, H-10, q, $J = 7.5$ Hz), 1.87 (1H, H-3, t, $J = 12.5$ Hz) 1.80 (1H, H-3, d, $J = 14.0$ Hz) 1.75-1.60 (6H, H-8, H-8, H-6, H-1, H-1, OH, m) 1.55 (1H, H-9, m), 1.50 (1H, H-7, m) 1.45-1.25 (2H, H-9, H-7, m); $^{13}\text{C-NMR}$ (CDCl_3) δ 149.0 (Ar), 147.8 (Ar), 137.2 (Ar), 119.8 (Ar), 110.8 (Ar), 110.5 (Ar), 65.0 (C-2), 63.5 (C-4), 56.6 (C-10), 56.0 (CH_3), 55.9 (CH_3), 53.3 (C-6), 42.7 (C-3), 40.4 (C-1), 33.6 (C-9), 26.2 (C-7), 24.6 (C-8); this is in agreement with reported spectra.^{1,10} (^1H , ^1H and ^1H , ^{13}C COSY experiments provided the signal assignment).

Reduction of ketolactam (8a) with lithium aluminium hydride :

Ketolactam (8a) (0.016 g; 0.054 mmol) was treated with lithium aluminium hydride (0.006 g; 0.15 mmol) according to the previously described procedure to give 0.009 g of a mixture of (\pm)-lasubine I (44%) and (\pm)-2-epilasubine I (56%) in 60% overall yield.

2-epilasubine I : $^1\text{H-NMR}$ (CDCl_3) δ 7.05-6.78 (3H, m), 4.05-3.90 (1H, H-4, m), 3.97 (1H, H-2, dd, $J = 2.8, 11.4$ Hz), 3.90 (3H, s), 3.86 (3H, s) 3.30 (1H, H-10, m), 2.55 (1H, H-6, d, $J = 12.6$ Hz), 2.11-1.20 (12H, m); this is in agreement with the reported spectrum;² $^{13}\text{C-NMR}$ (CDCl_3) δ 149.4, 148.2, 136.1, 119.8, 111.4, 109.5, 65.2, 62.7, 57.6, 56.8, 53.5, 49.6, 45.3, 40.7, 30.0, 26.0, 18.4.

A solution of the preceding mixture (0.0094 g; 0.03 mmol) in acetic anhydride (0.2 mL) and pyridine (0.2 mL) was stirred at rt overnight. After removal of the excess reagents, the residue was extracted with chloroform. The extracts were washed with saturated aqueous sodium bicarbonate, dried over MgSO_4 and concentrated. The residue was chromatographed over silica gel (eluted with chloroform:methanol (49:1)).

Lasubine I acetate : IR (cm^{-1}) 1725; $^1\text{H-NMR}$ (CDCl_3) δ 6.97-6.80 (3H, m) 5.22 (1H, H-2, m) 4.09 (1H, H-4, m) 3.89 (3H, s) 3.86 (3H, s) 3.03 (1H, H-10, m) 2.77 (1H, H-6, d, $J = 12.3$ Hz) 2.34 (1H, H-6, t, $J = 12.2$ Hz) 2.06 (3H, s) 2.16-1.20 (10H, m); this is in agreement with reported spectrum;² $^{13}\text{C-NMR}$ (CDCl_3) δ 170.6, 149.0, 148.1, 134.8, 120.5, 111.7, 111.0, 68.2, 60.4, 56.3, 56.0, 53.8, 50.8, 36.1, 35.7, 31.1, 24.4, 24.1, 21.6.

2-epilasubine I acetate : IR (cm^{-1}) 1725; $^1\text{H-NMR}$ (CDCl_3) δ 7.00-6.75 (3H, m) 5.06 (1H, H-2, m), 4.05 (1H, H-4, m) 3.89 (3H, s) 3.86 (3H, s) 3.35 (1H, H-10, m) 2.78 (1H, H-6, d, $J = 13.4$ Hz), 2.60 (1H, H-6, m), 2.00 (3H, s), 2.3-0.90 (10H, m); this is in agreement with reported spectrum;² $^{13}\text{C-NMR}$ (CDCl_3) δ 170.7, 149.4, 148.3, 135.4, 119.9, 110.9, 110.0, 68.6, 57.4, 56.3, 56.3, 55.9, 49.5, 41.2, 36.7, 25.8, 24.4, 24.1, 18.4.

Reduction of ketolactam (8b) with lithium aluminium hydride :

Ketolactam (8b) (0.018 g; 0.05 mmol) was treated with lithium aluminium hydride (0.006 g; 0.15 mmol) according to the previously described procedure to give (\pm)-2-epilasubine II (0.012 g; 70%); IR (cm^{-1}) 3620, 2785 (Bohlmann band); $^1\text{H-NMR}$ (CDCl_3) δ 6.88-6.80 (3H, m) 3.89 (3H, s) 3.86 (3H, s) 3.77-3.69 (1H, H-2, m), 2.91 (1H, H-4, dd, $J = 2.6, 11.6$ Hz), 2.68 (1H, H-6, br d, $J = 11.3$ Hz), 2.05-1.90 (3H, H-10, H-3, H-1, m) 1.75-1.20 (10H, m); $^{13}\text{C-NMR}$ (CDCl_3) δ 149.2, 148.0, 136.9, 119.6, 111.2, 110.9, 68.4 (C-2), 68.2 (C-4), 61.0 (C-10), 56.0 (CH_3), 55.9 (CH_3), 53.0 (C-6), 45.3 (C-3), 42.9 (C-

1), 33.8 (C-9), 26.1 (C-7), 24.7 (C-8); this is in agreement with reported spectra.^{7,10} (¹H, ¹H and ¹H, ¹³C COSY experiments provided the signal assignment).

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