# One-Pot Preparation of Quinolizidin-2-one and Indolizidin-7-one Ring Systems. Concise Total Syntheses of (±)-Myrtine, (±)-Lasubine II, and (−)-Indolizidine 223AB

Ronaldo A. Pilli,* Luiz Carlos Dias, and Adriano O. Maldaner

*Instituto de Química, Unicamp, Cx. Postal 6154, 13081-970 Campinas, SP, Brazil*

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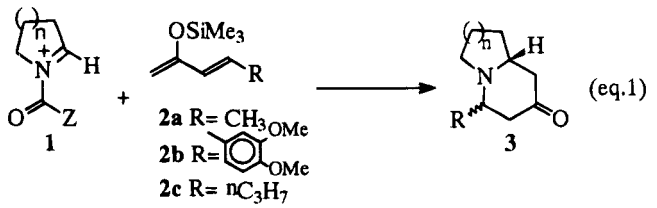
A highly efficient approach to the quinolizidine alkaloids (±)-myrtine (**4**) and (±)-lasubine II (**5**) and to the indolizidine alkaloid (−)-indolizidine 223AB (**6**) is described. The preparation of quinolizidin-2-ones **4/4a** and **11b/12b** and indolizidin-7-ones **16/17** is based on the addition of 2-((trimethylsilyl)oxy) 1,3-dienes **2a,b** and **2c** to cyclic *N*-acyliminium ions **10** and **15**, respectively. It encompasses five chemical transformations in the same pot yielding the axially oriented substituent at C-4 and C-5 as the major product in the quinolizidin-2-one and indolizidin-7-one systems, respectively. The thermodynamically more stable isomers **12b** and **17** were obtained after basic treatment.

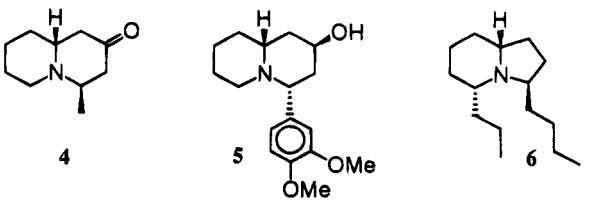
The addition of nucleophiles to *N*-acyliminium ions has established itself as a reliable tool for the preparation of nitrogen heterocycles.[1] In particular, the intramolecular reaction of cyclic iminium ions bearing endocyclic *N*-acyl groups and tethered nucleophiles has been successfully employed in the preparation of nitrogen-containing bicyclic compounds. Cyclic *N*-acyliminium ions with exocyclic *N*-acyl groups can adopt the s-cis conformation and react as a 4π-electron system with olefins and acetylenes in a Diels–Alder cycloaddition reaction with inverse electron demand.[2] Alternatively, they may behave as dienophiles in reactions with conjugated dienes.[3]

Although intramolecular cyclizations have been reported for iminium ions with exocyclic *N*-acyl groups and carbon-tethered nucleophiles,[4] it appeared to us that the reaction of cyclic iminium ion **1** bearing exocyclic acyl groups and activated dienes **2a–c** would significantly broaden the scope of this methodology provided that an *in situ* removable *N*-acyl group was in place (eq 1).




(eq.1)

We have previously reported on the trimethylsilyl trifluoromethanesulfonate (TMSOTf)-catalyzed addition of silylenol ethers to Schiff bases[5] and to cyclic *N*-acyliminium ions.[6] Herein we describe the successful application of the strategy depicted in eq 1 to the total syntheses of plant quinolizidine alkaloids (±)-myrtine (**4**)[7] and (±)-lasubine II (**5**),[8] isolated from *Vaccinium myrtillus* and *Lagerstroemia subcostata*, respectively, as well as (−)-indolizidine 223AB (**6**),[9] a 3,5-disubstituted indolizidine of amphibian origin found in minute amounts in the skin of *Dendrobates histrionicus*.




To reduce our plans into practice we started investigating the addition of silyloxydiene **2a** (R = $CH_3$) to the

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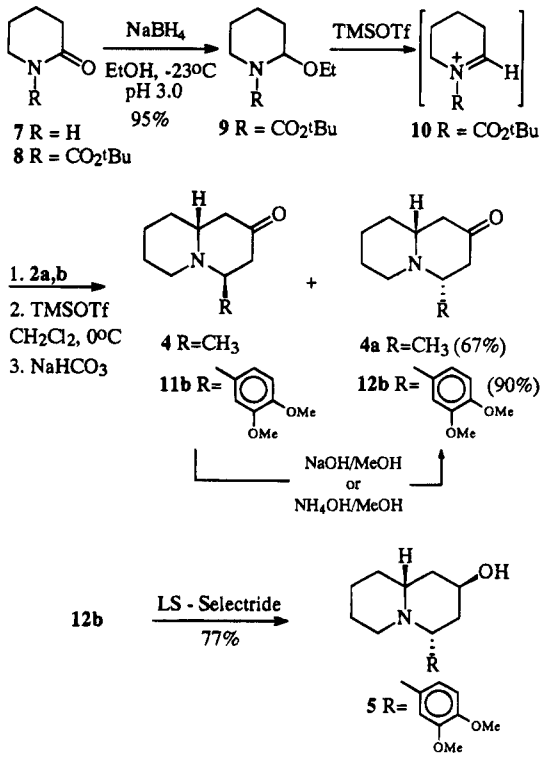
**Scheme 1**



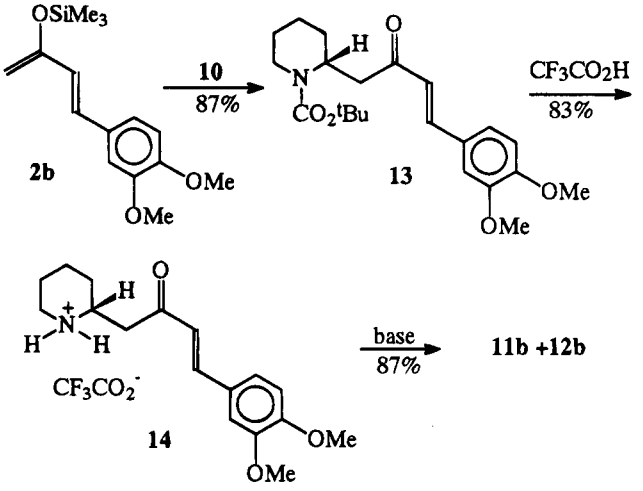

*N*-acyliminium ion **10** generated from *N*-carbo-*tert*-butoxy-2-ethoxypiperidine (**9**).[10,11] The propensity of silyloxy diene **2a** to regenerate the corresponding unsaturated ketone during chromatography on silica gel led us to explore its *in situ* formation.[12] In the event, the addition of TMSOTf to a solution of 3-penten-2-one and $Et_3N$, in $CH_2Cl_2$ at 0 °C, followed by the addition of ethoxypiperidine **9** and TMSOTf, afforded a 5.5:1.0 mixture of racemic myrtine (**4**) and epimyrtine (**4a**), in 67% yield (Scheme 1).

When the reaction sequence depicted in Scheme 1 was applied to silyloxy diene **2b** (R = 3,4-dimethoxyphenyl) a 3:2 mixture of quinolizidinones **11b** and **12b** was isolated, in 90% yield. However, when 0.6 equiv of TMSOTf was employed to promote the addition of silyloxy diene **2b** to **10** and the reaction was quenched with saturated $NH_4Cl$, after 1 h at 0 °C, carbamate **13** was isolated in 87% yield (Scheme 2).

Deprotection of carbamate **13** with trifluoroacetic acid in $CH_2Cl_2$ at 0 °C, followed by quenching with saturated $NaHCO_3$ until pH 6.0, led to the isolation of trifluoroacetate **14** in 83% yield. When its solution in $CH_2Cl_2$ was treated with base (saturated $NaHCO_3$, $Et_3N$, or DBU) at room temperature, a 3:2 mixture of quinolizidinones **11b** and **12b** was isolated, in 87% yield, supporting carbamate **13**[13] as an intermediate during the formation of the quinolizidinone ring system.

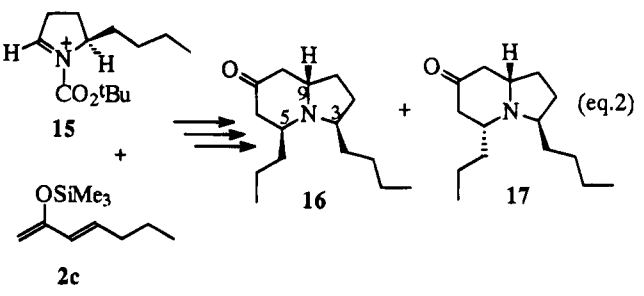
Upon treating a methanolic solution of a 3:2 mixture of **11b:12b** with 2 N NaOH or $NH_4OH$ (rt, 48 h), the thermodynamically more stable quinolizidinone **12b** was

**Scheme 2**




isolated in 90% yield probably through a retro Michael fragmentation–recyclization process.[14] Reduction with LS-Selectride (Aldrich) in THF at −78 °C[8f] followed by treatment of the crude reduction mixture with MeOH, evaporation, and column chromatography afforded (±)-lasubine II (**5**) in 77% yield, characterized by comparison of its spectroscopic data ($^1$H- and $^{13}$C-NMR, mass, and infrared spectra) with those reported in the literature.[8f]

Once the feasibility of our one-pot preparation of the quinolizidin-2-one ring system was established, our approach to (−)-indolizidine 223AB (**6**) required the preparation of homochiral *N*-acyliminium ion **15** (eq 2) which




upon addition of silyloxy diene **2c** would provide the ultimate precursor for the synthesis of indolizidine 223AB (**6**).

Despite some previous examples of cis addition of enol acetates and allylsilanes to substituted 5-membered *N*-acyliminium ions[15] we reasoned that the steric requirements of the *n*-butyl side chain would direct the approach of silyloxydiene to the *re* face of (*R*)-**15**. The stereochemical outcome at C-5 was expected to follow the same pattern as in the quinolizidinone series, e.g., axially oriented substituent at C-5, affording **16** as the major diastereoisomer. According to molecular mechanics (MM2) calculations **16** would preferentially adopt the cis-fused ring conformation and could conceivably be transformed to the thermodynamically more stable indolizidinone **17** (trans-fused ring) under basic conditions.[16]

The preparation of ethoxy carbamate **21**, the synthetic equivalent of *N*-acyliminium ion **15**, was accomplished starting from commercially available (*S*)-(−)-pyroglutam-

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(13) Carbamate **13** was also prepared, in 48% yield, using the boron enolate of 4-(3′,4′-dimethoxyphenyl)-3-buten-2-one ($^n$Bu$_2$BOTf, $^i$Pr$_2$NEt, $CH_2Cl_2$, −78 °C) and ethoxycarbamate **9**.

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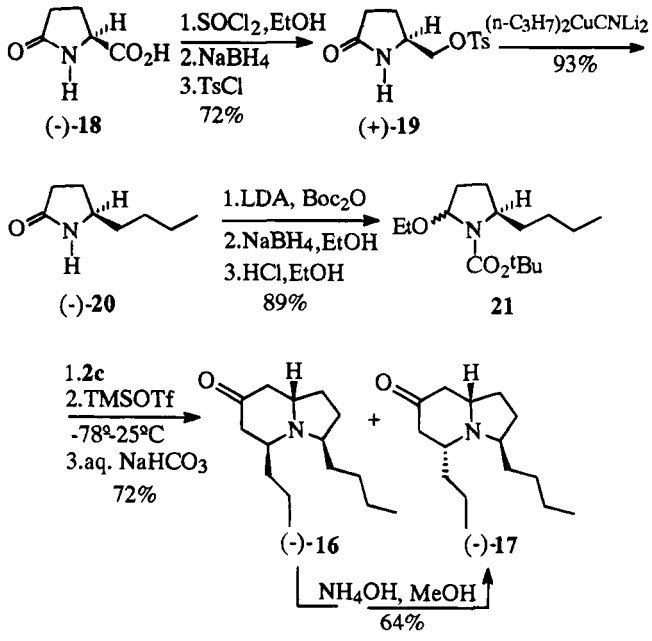
**Scheme 3**




ic acid (**18**) which was uneventfully converted to (+)-**19**, in 72% overall yield, according to a previously described procedure.[17] The three-carbon homologation necessary to prepare (−)-**20** was examined under several different conditions[18] and could only be performed in good yield when an excess (5.0 equiv) of $(n\text{-}C_3H_7)_2CuCNLi_2$ was employed. After 3.0 h at −40 °C, the reaction mixture was allowed to warm to room temperature and stirred overnight to afford (−)-**20** (93% yield), which was converted to ethoxy carbamate **21** (Scheme 3).[10]

The key event was the addition of silyloxy diene **2c**, prepared *in situ* after addition of TMSOTf to a $CH_2Cl_2$ solution of 3-hepten-2-one and triethylamine, to N-acyliminium ion **15** which afforded a 3:2 mixture of indolizidinones (−)-**16** and (−)-**17**, in 72% yield. The $^1H$- and $^{13}C$-NMR data for the major diastereoisomer isolated by column chromatography on silica gel were identical to those reported by Cordero and co-workers[9k] for racemic indolizidinone **17**. However, when the *p*-toluenesulfonyl hydrazone of our major indolizidinone was subjected to reduction with $NaBH_4$ in EtOH we were not able to isolate (−)-indolizidine 223AB (**6**), but its C-5 epimer was isolated instead (65% yield), as shown by comparison of its $^1H$ and $^{13}C$-NMR data with those reported by Hart and Tsai.[9g]

Homo- and heteronuclear correlation spectroscopies and differential NOE experiments allowed us to unambiguously establish the stereochemical pattern of our major indolizidinone. The double doublet at $\delta$ 2.66 ppm ($^3J$ = 13.1 and 6.1 Hz) was assigned to one of the protons at C-6, and the multiplets at $\delta$ 3.03, 3.37, and 3.58 ppm were attributed to H-3, H-5, and H-9, respectively. Upon irradiation of the multiplet at $\delta$ 3.03 ppm (H-3), no enhancement was observed for the multiplet at $\delta$ 3.58 ppm (H-9) while 1% and 5% enhancements were observed for the multiplets at $\delta$ 3.37 (H-5) and $\delta$ 2.66 (H-6) ppm, respectively. These observations could only be accounted for by assuming a cis ring-fused conformation for the indolizidinone ring and a cis relationship for the side chains at C-3 and C-5, supporting indolizidinone **16** as the major isomer isolated in our work.

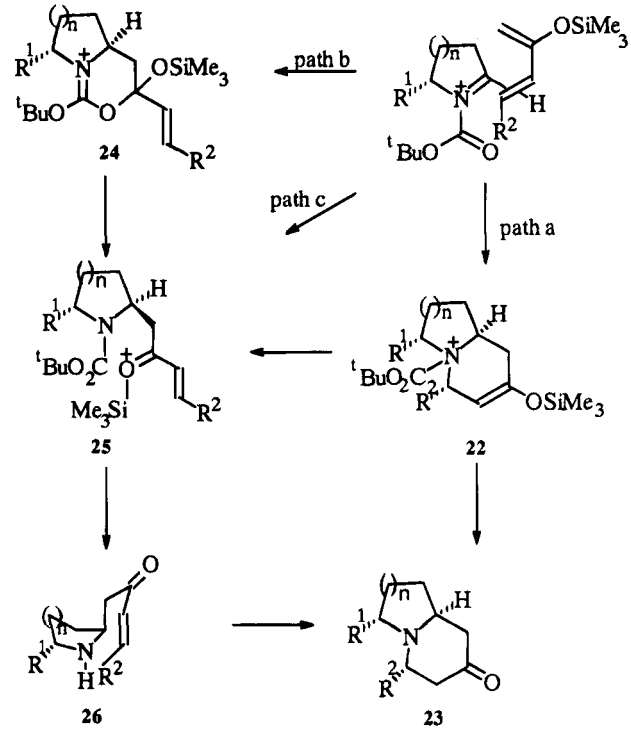
Along the same line, the multiplet at $\delta$ 3.32 ppm of the minor indolizidinone was assigned to H-3 and the multiplet at $\delta$ 2.79 ppm to H-5 and H-9 in the trans ring-fused **17**: upon irradiation of H-3 no enhancement was observed for H-5, H-9, or H-6/H-8 protons while irradiation of the multiplet at $\delta$ 2.79 ppm (H-5 and H-9) resulted in a 1.7% enhancement of the H-6 and H-8 protons.

Treatment of a methanolic solution of the major indolizidinone **16** or a 3:2 mixture of **16**/**17** with aqueous $NH_4OH$ afforded, after 48 h at room temperature, (−)-indolizidinone **17** as the major isomer (64% yield) together with recovered (−)-indolizidinone **16** (30% yield).

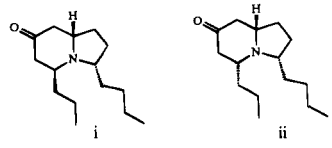
Accordingly, reduction of the tosylhydrazone corresponding to indolizidinone **17** with $NaBH_4$ in EtOH afforded (−)-indolizidine 223AB (**6**), in 70% yield, as shown by comparison of its $^1H$- and $^{13}C$-NMR spectroscopic data with those reported by Machinaga and Kibayashi.[9e]

Two possible rationalizations may be advanced for the preference for the kinetic product **23** (Scheme 4): (a) a [4 + 2] cycloaddition with an *endo* approach of the *tert*-butoxycarbonyl group (path a), followed by dealkoxycarbonylation and hydrolysis of silylenol ether **22** to afford the *cis* relationship between the hydrogen at the ring junction and $R^2$ group, or (b) a [4 + 2] cycloaddition

**Scheme 4**




(16) MM2 calculations have shown the products i and ii to adopt a trans-fused ring junction and to be more stable (relative steric energies 0.0 and 1.78 kcal·mol$^{-1}$) than **16** (cis-fused ring junction, steric energy: 6.60 kcal·mol$^{-1}$) and **17** (trans-fused ring junction, steric energy: 5.74 kcal·mol$^{-1}$).



i ii

(17) (a) Rosset, S.; Célerier, J. P.; Lhommet, G. *Tetrahedron Lett.* **1991**, *32*, 7521. (b) Reference 9m.

(18) The use of CuBr·DMS, CuI, or lithium 2-thienylcyanocuprate and propyllithium (1.1 M solution in hexanes) was also explored without success. For related transformations see ref 17.

followed by fragmentation to **25** (paths a and b) and/or a Mannich reaction (path c) to afford **25** which after dealkoxycarbonylation[19] undergoes an intramolecular Michael reaction with the initial formation of a cis-fused bicyclic system (**26** → **23**).

Although definitive mechanistic evidence is still lacking, the isolation of carbamate **13** and its conversion to quinolizidinones **11b/12b** support the intermediacy of monocyclic adduct **25**.

## Conclusion

A one-pot preparation of the quinolizidin-2-one and indolizidin-7-one ring systems has been described. The reaction of 2-ethoxy carbamates (**9** and **21**) with 2-(silyloxy) 1,3-dienes **2a–c** afforded the corresponding kinetic products as the major isomer which were shown, in two cases, to undergo retro Michael reaction to the thermodynamically more stable isomer under mild conditions ($NH_4OH$, MeOH, rt).

The concise and efficient total syntheses of the racemic form of the quinolizidine alkaloids myrtine (**4**) and lasubine II (**5**) were accomplished in 57% and 73% yield, respectively, from ethoxypiperidine **9**. (−)-Indolizidine 223B (**6**) was prepared in 27% overall yield starting from (−)-pyroglutamic acid (**18**) and 2-((trimethylsilyl)oxy))-1,3-heptadiene (**2c**).

## Experimental Section

Unless otherwise noted materials were obtained from commercial suppliers and were used without further purification. THF and ether were distilled from Na–benzophenone ketyl immediately prior to use. Diisopropylamine, $Et_3N$, and $CH_2Cl_2$ were distilled from calcium hydride. *n*-Hexane was distilled from Na and EtOH from $Mg(OMe)_2$. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was distilled immediately prior to use. All reactions involving organometallic reagents or TMSOTf were carried out under an argon atmosphere with flame-dried glassware. The normal processing of organic extracts consisted of drying over $MgSO_4$, filtration, and concentration with a rotary evaporator. Melting points are uncorrected. $^1$H-NMR spectra were recorded in $CDCl_3$ solution at 300 MHz and $^{13}$C-NMR spectra in $CDCl_3$ solution at 75.2 MHz unless otherwise noted. $J$ values are given in Hz. Optical rotations were determined at $\lambda = 546$ nm using a Hg lamp. Data are reported as follows: $[\alpha]^{25}_{546}$ = (concentration g/100 mL, solvent).

**(4*RS*,10*RS*)-4-Methylquinolizidin-2-one (4).** To a solution of 3-penten-2-one (0.210 g, 2.5 mmol) and $CH_2Cl_2$ (5.0 mL) at 0 °C was added $Et_3N$ (0.64 mL, 4.55 mmol), followed by dropwise addition of TMSOTf (0.830 g, 3.73 mmol). The reaction mixture was stirred for 45 min at 0 °C when a solution of (±)-**9**[11] (0.474 g, 2.07 mmol) in $CH_2Cl_2$ (4.0 mL) was added dropwise, followed by additional TMSOTf (0.467 g, 2.10 mmol). The reaction mixture was stirred at rt for 30 min and then it was quenched by the addition of saturated $NaHCO_3$ solution (10 mL). After 36 h of vigorous stirring at rt it was extracted with $CH_2Cl_2$ (3 × 10 mL), and the organic extracts were combined and concentrated. Chromatography on neutral alumina (1:9 EtOAc–hexanes) afforded a 6:1 mixture of **4**:**4a** (0.232 g, 1.38 mmol, 67% yield). Preparative TLC afforded an analytically pure sample of (±)-myrtine (**4**): $^1$H NMR $\delta$ 0.97 (d, 3H, $J$ = 6.3), 1.15–1.45 (m, 2H), 1.55–1.90 (m, 4H), 2.18–2.40 (m, 3H), 2.49 (dt, 1H, $J$ = 11.5 and 3.0), 2.62–2.72 (m, 1H), 2.74–2.90 (m, 2H), 3.39 (dqt, 1H, $J$ = 6.3 and 2.4); $^{13}$C NMR $\delta$ 11.1, 23.5, 25.9, 34.3, 48.1, 48.8, 51.5, 53.6, 57.2, 210.0; MS $m/z$ 167 ($M^+$, 39), 152 (100); IR (film) 1714 cm$^{-1}$.

**(4*RS*,10*RS*)- and (4*SR*,10*RS*)-4-(3′,4′-Dimethoxyphenyl)-quinolizidin-2-one (11b and 12b). (a) From Ethoxy Carbamate 9.** To a solution of (*E*)-4-(3′,4′-dimethoxyphenyl)-3-buten-2-one (0.206 g, 1.0 mmol) and $CH_2Cl_2$ (3.0 mL) at 0 °C were added $Et_3N$ (0.202 g, 2.0 mmol) and TMSOTf (0.333 g, 1.5 mmol). The reaction mixture was stirred for 1 h at 0 °C, and a solution of **9**[11] (0.252 g, 1.1 mmol) in $CH_2Cl_2$ (2.0 mL) was added, followed by additional TMSOTf (0.229 g, 1.0 mmol). The reaction mixture was stirred at rt during 30 min and quenched with saturated $NaHCO_3$ solution (10 mL). After being stirred for 36 h at rt it was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were normally processed to yield 0.300 g of crude material (3:2 mixture of **11b**:**12b**) which was taken up in MeOH (2.0 mL), treated with 2 N NaOH (2.0 mL) or $NH_4OH$ (2.0 mL), and stirred for 48 h at rt. The reaction mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), normally processed, and chromatographed on silica gel (1:30 MeOH–$CHCl_3$) to afford (±)-**12b**[8f] (0.260 g, 0.90 mmol), in 90% yield. **(b) From Trifluoroacetate** (±)-**14**. A solution of (±)-**14** (0.383 g, 0.95 mmol) and $CH_2Cl_2$ (2.0 mL) was treated with base (saturated $NaHCO_3$, DBU, or $Et_3N$) at rt for 24 h. The reaction mixture was extracted with $CH_2Cl_2$ (3 × 5 mL), and the combined organic extracts were processed. The oily residue was chromatographed on silica gel (1:30 MeOH–$CHCl_3$) to afford a 3:2 mixture of **11b/12b** (0.240 g, 0.83 mmol), in 87% yield. Preparative TLC afforded a pure sample of **11b**: $^1$H NMR $\delta$ 1.15–1.77 (m, 6H), 2.20 (dt, 1H, $J$ = 11.7 and 3.3), 2.38 (dd, 1H, $J$ = 14.5 and 8.7), 2.61 (m, 2H), 2.90 (m, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.25 (dd, 1H, $J$ = 6.3 and 4.2), 6.68 (m, 2H), 6.81 (d, 1H, $J$ = 8.7); $^{13}$C NMR $\delta$ 23.4, 24.0, 31.9, 46.8, 47.6, 51.4, 54.5, 55.9, 56.0, 63.9, 110.9, 112.0, 121.2, 131.6, 148.7, 149.0, 209.8; MS $m/z$ 289 ($M^+$, 68), 246 (16), 206 (31), 164 (100); IR (film) 1713 cm$^{-1}$. **12b**:[8f] $^1$H NMR $\delta$ 1.27 (m, 1H), 1.40–1.78 (m, 6H), 2.22–2.55 (m, 4H), 2.68 (t, 1 H, $J$ = 13.0), 2.79 (d, 1H, $J$ = 10.6), 3.21 (dd, 1H, $J$ = 12.1 and 3.2), 3.87 (s, 3H), 3.90 (s, 3H), 6.83 (m, 2H), 6.92 (s br, 1H); $^{13}$C NMR $\delta$ 24.2, 25.9, 34.4, 48.8, 50.9, 52.9, 56.0, 56.1, 62.6, 70.1, 110.0, 111.3, 119.7, 135.3, 148.6, 149.6, 208.3; MS $m/z$ 289 ($M^+$, 62), 246 (24), 206 (34), 164 (100) ; IR (film) 1712 cm$^{-1}$.

**(±)-1-(*N*-(*tert*-Butoxycarbonyl)-2-piperidinyl)-4-(3′,4′-dimethoxyphenyl)-3-buten-2-one (13).** To a solution of (*E*)-4-(3′,4′-dimethoxyphenyl)-3-buten-2-one (0.206 g, 1.0 mmol) and $CH_2Cl_2$ (3.0 mL), at 0 °C, was added $Et_3N$ (0.202 g, 2.0 mmol) followed by dropwise addition of TMSOTf (0.333 g, 1.5 mmol). After 5 min at 0 °C, a solution of **9**[11] (0.229 g, 1.0 mmol) in $CH_2Cl_2$ (2.0 mL) was added dropwise, followed by additional TMSOTf (0.133 g, 0.6 mmol). The reaction mixture was stirred for 30 min at 0 °C, quenched by the addition of saturated $NH_4Cl$ solution (10 mL), and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were processed, and the crude material was purified by chromatography on silica gel (1:9 EtOAc–hexanes) to yield (±)-**13** (0.338 g, 0.87 mmol), in 87% yield, as a pale green oil. $^1$H NMR $\delta$ 1.43 (s, 10H), 1.63 (s, br, 5H), 2.80–2.90 (m, 3H), 3.92 (s, 6H), 4.0 (m, 1H), 4.79 (m, 1H), 6.67 (d, 1H, $J$ = 16.0), 6.88 (d, 1H, $J$ = 8.3), 7.09 (d, 1H, $J$ = 1.7), 7.14 (dd, 1H, $J$ = 8.3 and 1.9), 7.56 (d, 1H, $J$ = 16.0); $^{13}$C NMR $\delta$ 18.9, 25.3, 28.1, 28.4, 39.5, 41.5, 48.0, 55.9, 56.0, 79.6, 109.8, 111.1, 123.2, 124.1, 127.5, 143.1, 149.3, 151.4, 154.8, 198.3; IR (film) 1682, 1596 cm$^{-1}$.

Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.86; H, 7.97; N, 3.60. Found: C, 67.78; H, 8.14; N, 3.32.

**(±)-Trifluoroacetate 14.** To a solution of (±)-**13** (0.389 g, 1.0 mmol) and $CH_2Cl_2$ (3.0 mL) at 0 °C was added $CF_3CO_2H$ (4.0 mL) dropwise. After 1 h at 0 °C the reaction mixture was quenched with saturated $NaHCO_3$ solution until pH 6.5 and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were processed, and the residue was crystallized from $CH_2Cl_2$–hexanes to afford (±)-**14** (0.334 g, 0.83 mmol), in 83% yield, as colorless crystals (mp 144.8–146.3 °C): $^1$H NMR $\delta$ 1.40–1.60 (m, 1H), 1.70–2.00 (m, 5H), 2.80–3.00 (m, 1H), 3.03 (dd, 1H, $J$ = 17.6 and 6.2), 3.27 (dd, 1H, $J$ = 17.6 and 6.2), 3.40–3.60 (m, 2H), 3.90 (s, 3H), 3.91 (s, 3H), 6.57 (d, 1H, $J$ = 16.0), 6.85 (d, 1H, $J$ = 8.3), 7.04 (d, 1H, $J$ = 1.9), 7.11 (dd, 1H, $J$ = 8.4 and 1.9), 7.54 (d, 1H, $J$ = 16.0) 8.93 (s br, 1H), 9.60 (s

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br, 1H); $^{13}$C NMR $\delta$ 22.2, 22.4, 28.5, 42.6, 45.1, 53.7, 56.0, 56.1, 110.3, 111.4, 123.6, 123.8, 127.1, 145.2, 149.6, 152.2, 162.4, 197.1; IR (KBr) 3456, 1690, 1608. Anal. Calcd for $C_{19}H_{24}F_3NO_5$: C, 56.57; H, 5.99; N, 3.47. Found: C, 56.70; H, 6.05; N, 3.14.

**(±)-Lasubine II (5).** To a 1.0 M solution of LS-Selectride (0.31 mL, 0.31 mmol) and THF (2.0 mL) at −78 °C was added dropwise a solution of (±)-**12b** (0.072 g, 0.25 mmol) in THF (1.0 mL). After 30 min at −78 °C, 1.0 M phosphate buffer (pH 7.0, 1.0 mL) was added, the reaction mixture was allowed to warm up to rt and extracted with ether (2 × 25 mL). The combined organic extracts were processed as usual, and the residue was taken up in MeOH (2.0 mL) and stirred at rt for 12 h. It was poured into 5% aqueous $NaHCO_3$ (5 mL), the organic solvent was removed under reduced pressure, and the aqueous phase was extracted with ether (2 × 25 mL). The combined organic extracts were processed, and the crude product was purified by chromatography on silica gel (1:30 MeOH−$CHCl_3$) to yield 0.055 g (0.19 mmol) of (±)-lasubine II (**5**),[8f] in 77% yield: $^1$H NMR $\delta$ 1.22−1.96 (m, 12H), 2.37−2.50 (d br, 1H), 2.70 (d br, 1H, $J$ = 11.7), 3.35 (dd, 1H, $J$ = 11.7 and 2.29), 3.86 (s, 3H), 3.89 (s, 3H), 4.16 (t, 1H, $J$ = 2.7), 6.78−6.94 (m, 3H); $^{13}$C NMR $\delta$ 24.7, 25.9, 33.4, 40.2, 42.6, 53.1, 55.8, 55.9, 56.5, 63.4, 64.9, 110.5, 110.9, 119.8, 137.1, 147.9, 149.1; IR (film) 3404, 1593 cm$^{-1}$; MS $m/z$ 291 ($M^+$, 59), 164 (55), 154 (51), 84 (100).

**(*R*)-5-*n*-Butyl-2-pyrrolidinone (20).** To a stirred suspension of CuCN (1.88 g, 21.0 mmol) in dry THF (10 mL) at −40 °C was added dropwise over 1 h a 1.13 M solution of *n*-propyllithium in *n*-hexane (37.2 mL, 42.0 mmol). A solution of the tosylate (+)-**19**[17] (1.13 g, 4.2 mmol) in dry THF (10 mL) was cannulated to the cuprate at −40 °C, and the resulting solution was maintained at −40 °C for 4 h and then overnight at rt. Saturated $NH_4Cl$ solution (20 mL) was added, and the mixed solution was separated. The upper organic layer was washed with a further 10 mL of a saturated $NH_4Cl$ solution, and the aqueous washings were extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic extracts were processed to give a pale yellow oil. Purification by flash chromatography on silica gel (70:30 *n*-hexane−EtOAc) gave 0.552 g (3.91 mmol) of **20** as a pale yellow oil, in 93% yield: $[\alpha]^{25}_{546}$ = −0.72° (*c* 11.8, $CH_2Cl_2$); IR (film) 3240, 1685 cm$^{-1}$; $^1$H-NMR $\delta$ 0.91 (t, $J$ = 6.75, 3H), 1.33 (m, 4H), 1.50 (m, 2H), 1.68 (m, 1H), 2.20 (m, 1H), 2.33 (m, 2H), 3.63 (q, 1H, $J$ = 6.6), 7.18 (br, 1H); $^{13}$C-NMR $\delta$ 14.0, 22.6, 27.3, 28.0, 30.5, 36.5, 54.9, 179.0 ppm; MS $m/z$: 141 (11, $M^+$), 85 (12), 84 (100). Anal. Calcd for $C_8H_{15}NO$: C, 68.08; H, 10.64; N, 9.93. Found: C, 68.25; H, 10.94; N, 9.96.

**(−)-(*R*)-*N*-(*tert*-Butoxycarbonyl)-5-*n*-butyl-2-pyrrolidinone.** To a solution of diisopropylamine (1.32 mL, 9.40 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (3.76 mL of a 2.5 M solution in hexanes, 9.40 mmol). After 15 min, a solution of **20** (1.327g, 9.40 mmol) in THF (5 mL) was added dropwise. The resulting solution was maintained at −78 °C for 15 min, at which time di-*tert*-butyl dicarbonate (2.26 g, 10.34 mmol) was added in one portion. After 2 h at −78 °C, the resulting mixture was allowed to warm to rt, diluted with ether (20 mL), and washed with water and brine. The organic phase was processed and the crude product was purified on silica gel (90:10 *n*-hexane−EtOAc) to give 2.18 g (9.02 mmol, 96%) of the title compound as a pure clear oil: $[\alpha]^{25}_{546}$ = −70.9° (*c* 3.0, $CH_2Cl_2$); IR (film) 1785, 1750, 1713 cm$^{-1}$; $^1$H-NMR $\delta$ 0.92 (t, 3H, $J$ = 6.9), 1.34 (m, 4H), 1.47−1.59 (m, 1H), 1.53 (s, 9H), 1.75 (m, 2H), 2.10 (m, 1H), 2.58 (ddd, 1H, $J$ = 17.7, 11.0, and 9.1), 2.42 (ddd, 1H, $J$ = 17.7, 9.3, and 2.7), 4.11 (tdd, 1H, $J$ = 8.83, 3.12, and 1.94); $^{13}$C-NMR $\delta$ 14.1, 22.5, 22.6, 27.8, 28.1, 31.5, 33.5, 58.2, 82.7, 150.3, 174.6 ppm; MS $m/z$: 241 ($M^+$, 1), 185 (13), 168 (12), 84 (100). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.73; H, 9.54; N, 5.81. Found: C, 64.92; H, 9.71; N, 5.88.

**(2*RS*,5*R*)-*N*-(*tert*-butoxycarbonyl)-2-ethoxy-5-*n*-butylpyrrolidine (21).** To a stirred solution of *N*-((*R*)-*tert*-butoxycarbonyl)-5-*n*-butyl-2-pyrrolidinone (2.20 g, 9.13 mmol) in absolute EtOH (70 mL) at −23 °C was added $NaBH_4$ (1.38 g, 36.51 mmol) in one portion. This mixture was kept at −23 °C for 4 h and then quenched with 2 N solution of HCl in EtOH until pH 4.0 and stirred for an additional 1 h period at −23 °C when it was neutralized with 1% KOH in EtOH. This mixture was poured into water (20 mL) and extracted with $CH_2Cl_2$ (2 × 50 mL), and the organic extracts were washed with water and brine and processed. Purification by flash chromatography on silica gel (90:10:1 *n*-hexane−EtOAc−$Et_3N$) gave 2.30 g (8.49 mmol, 93%) of **21** as a clear oil: IR (film) 1700, cm$^{-1}$; $^1$H-NMR $\delta$ 0.91 (t, 3H, $J$ = 6.9), 1.17 (t, 3H, $J$ = 7.05), 1.30 (m, 5H), 1.47 (s, 9H), 1.83 (m, 4H), 2.03 (m, 1H), 3.40−3.82 (m, 3H), 5.30 (m, 1H); $^{13}$C-NMR $\delta$ 14.2, 15.3, 15.6, 22.8, 28.0, 28.5, 28.7, 28.9, 29.4, 30.4, 32.0, 32.4, 33.23, 36.1, 53.4, 57.4, 58.0, 62.2, 62.7, 63.7, 64.5, 79.5, 154.8 ppm; MS $m/z$ 231 (12), 218 (4), 174 (33), 59 (100). Anal. Calcd for $C_{15}H_{29}NO_3$: C, 66.42; H, 10.70; N, 5.17. Found: C, 66.22; H, 10.38; N, 4.97.

**(3*R*,5*S*,9*S*)-3-*n*-Butyl-5-*n*-propyloctahydroindolizin-7-one (16) and (3*R*,5*R*,9*S*)-3-*n*-Butyl-5-*n*-propyloctahydroindolizin-7-one (17).** To a stirred solution of 3-hepten-2-one (0.292 g, 2.61 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C was added $Et_3N$ (0.73 mL, 0.528 g, 5.22 mmol), followed by dropwise addition of TMSOTf (0.76 mL, 0.87 g, 3.91 mmol). The resulting solution was stirred for 30 min at 0 °C and cooled to −78 °C. A solution of **21** (0.596 g, 2.20 mmol) in $CH_2Cl_2$ (5 mL) was prepared in a separate flask and cooled to −78 °C. This solution was transferred to the reaction flask via cannula over 1 min, followed by the dropwise addition of additional TMSOTf (0.42 mL, 0.49 g, 2.2 mmol) at −78 °C. The resulting solution was allowed to warm to rt, stirred for an additional 30 min period, and quenched with saturated aqueous $NaHCO_3$ (15 mL). The resulting mixture was stirred for 24 h at rt and extracted with $CH_2Cl_2$ (2 × 15 mL). The organic extracts were processed to yield 0.514 g of a 3:2 mixture of indolizidinones **16** and **17** which was purified by flash chromatography on silica gel (70:30 *n*-hexane−EtOAc). Elution of the fastest moving component gave 0.260 g (1.1 mmol, 50%) of the pure indolizidinone **16**, $[\alpha]^{25}_{546}$ = −53° (*c* 4.1, $CH_2Cl_2$), as a pale yellow oil: IR (film) 1710 cm$^{-1}$; $^1$H-NMR $\delta$ 0.88 (t, 3H, $J$ = 7.20), 0.92 (t, 3H, $J$ = 6.90), 1.20−1.65 (m, 12H), 1.98−2.22 (m, 5H), 2.66 (dd, 1H, $J$ = 6.1 and 13.1), 3.03 (m, 1H), 3.37 (m, 1H), 3.58 (qt, 1H, $J$ = 5.34); $^{13}$C-NMR $\delta$ 13.9, 14.2, 18.7, 23.2, 28.2, 28.6, 29.7, 35.6, 36.7, 41.2, 44.9, 56.4, 58.1, 58.6, 211.2 ppm; MS $m/z$ 237 ($M^+$, 2), 194 (54), 180 (100). Elution of the slowest moving component gave 0.115 g (0.48 mmol, 22%) of the pure indolizidinone **17**, $[\alpha]^{25}_{546}$ = −51° (*c* 6.5, $CH_2Cl_2$), as a pale yellow oil: IR (film) 1721 cm$^{-1}$; $^1$H-NMR $\delta$ 0.91 (t, 3H, $J$ = 7.10), 0.94 (t, 3H, $J$ = 7.20), 1.05−1.80 (m, 12H), 2.02 (m, 2H), 2.20 (m, 2H), 2.44 (m, 2H), 2.79 (m, 2H), 3.32 (m, 1H); $^{13}$C-NMR $\delta$ 14.2, 14.3, 18.3, 22.9, 25.7, 27.1, 29.1, 30.0, 36.4, 45.9, 48.5, 54.9, 58.0, 58.9, 210.4 ppm; MS $m/z$ 237 ($M^+$, 5), 194 (100). Anal. Calcd for $C_{15}H_{27}NO$: C, 75.90; H, 11.46; N, 5.90. Found: C, 76.12; H, 11.75; N, 5 .53.

A solution of a 3:2 mixture of indolizidinones **16/17** (0.120 g, 0.5 mmol) in MeOH (2.0 mL) was treated with aqueous $NH_4OH$ (1.0 mL) at rt for 48 h. The reaction mixture was diluted with $CH_2Cl_2$ (10 mL), and the organic phase was washed with water (2 × 10 mL) and processed. Flash chromatography as described above yielded (−)-**17** (0.077 g, 0.32 mmol), in 64% yield, and (−)-**16** (0.035 g, 0.15 mmol).

**(3*R*,5*R*,9*R*)-3-*n*-Butyl-5-*n*-propyloctahydroindolizine (Indolizidine 223AB, 6).** To a stirred solution of (−)-**17** (0.092 g, 0.39 mmol) in absolute EtOH (5 mL) was added (*p*-toluenesulfonyl)hydrazine (0.106 g, 0.56 mmol). The resulting solution was stirred for 5 h at rt and cooled to 0 °C. $NaBH_4$ (0.303 g, 9.95 mmol) was added during 1 h under ice cooling (0 °C), and the resulting mixture was heated at reflux for 3.5 h. The reaction mixture was quenched with saturated $NH_4Cl$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were processed, and the oily residue was purified by flash chromatography on silica gel eluting with EtOAc/$Et_3N$ (99/1), yielding (−)-**6**[9e] (0.061 g, 0.27 mmol) as a pale yellow oil in 70% yield: $[\alpha]^{25}_{546}$ = −88° (*c* 0.56, MeOH); $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 0.91 (t, 3H, $J$ = 7.3), 0.93 (t, 3H, $J$ = 7.0), 1.00−1.98 (m, 14H), 1.60−1.93 (m, 6H), 2.36−2.42 (m, 2H), 3.30 (br t, 1H, $J$ = 8.7); $^{13}$C-NMR ($CDCl_3$, 75.5 MHz)

δ 14.1, 14.5, 19.0, 23.0, 24.6, 24.9, 26.4, 29.1, 30.0, 30.9, 32.3, 35.8, 56.7, 58.6, 59.1 ppm.

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**Supplementary Material Available:** Copies of $^{1}H$, $^{13}C$ NMR and differential NOE spectra for (−)-**16** and (−)-**17** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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