

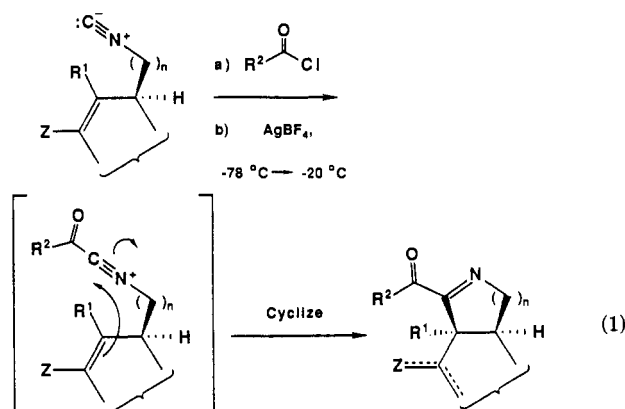
Acylnitrilium Ion Initiated Heteroannulations in Alkaloid Synthesis. An Efficient, Stereocontrolled, Total Synthesis of the *Orchidaceae* Alkaloid (±)-Dendrobine

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Abstract: A concise total synthesis of (±)-dendrobine is described that proceeds in eight steps from 2-methylcyclopent-2-en-1-one. The key transformation in this approach is the silver ion mediated cyclocondensation of the isonitrile **6** with the acyl chloride **5**. This highly convergent reaction proceeds in excellent (88%) overall yield to provide the Δ^1 -pyrroline **4**.

Background and Strategic Considerations. Cyclization reactions initiated by nitrogen-stabilized carbocations have continued to play a central role in synthetic approaches to numerous natural and unnatural heterocycles. Among the cationic species that have been employed for this purpose, iminium² and acyliminium ions³ have proven particularly useful for effecting selective carbon-carbon bond formation. Analogous cyclizations initiated by nitrilium ions are considerably more obscure and often proceed inefficiently.⁴ The latter processes are frequently complicated by the methods used to generate the parent nitrilium ion and various side reactions (e.g., facile proton loss α to the nitrilium moiety) that these intermediates undergo. In previous reports from these laboratories we have described the generation of transient C-acylnitrilium ions via the acylation of isonitriles as well as several types of cyclization reactions that involve these intermediates.⁵ The synthetic advantages inherent to acylnitrilium ion initiated cyclizations include (1) a high level of convergence with respect to the introduction of peripheral 2-acyl moieties, (2) the flexibility to construct heterocycles of varied annular dimension, (3) the presence of an endocyclic imine within the product that can serve as a site for further functionalization, and (4) the exceptionally mild reaction conditions ($\text{AgBF}_4\text{-ClCH}_2\text{CH}_2\text{Cl}$, $-78 \rightarrow 0^\circ\text{C}$) that are employed for effecting cyclization (eq 1).



The *Orchidaceae* alkaloid dendrobine (**1**) is the most abundant of the sesquiterpene bases isolated from the ornamental orchid "Jinchai Shihu" (*Dendrobium mobile* LINDL).⁶ This alkaloid is the principle component of the Chinese Folk medicine "Chin-Shih-Hu"⁷ and has been shown to exhibit antipyretic and hypotensive activity.⁸ The intricate molecular architecture of the isoprenoid *Orchidaceae* alkaloids is elaborated upon a densely clustered array of seven stereogenic centers. As a consequence, this family of compounds continues to represent a major challenge for efficient chemical synthesis. Studies directed toward the synthesis of dendrobine (**1**) have been conducted in several laboratories^{9–16} and have resulted in four successful total syntheses^{9–12} as well as a relay synthesis for this alkaloid.¹³ Despite the intensity of these efforts, dendrobine (**1**) has yet to succumb to total synthesis by a route that is both highly efficient and stereocontrolled.

Our approach to this molecule was designed around the possibility that the correct relative stereochemistry at C-6 and C-7 of **1** might arise as a consequence of syn delivery of hydrogen onto the convex α -face of the prospective intermediate **2**. Intermediate **2**, in turn, was envisaged to arise via an intramolecular reductive aldol- or phosphite anion-driven Horner-Wadsworth-Emmons-type coupling reaction involving the γ -keto enoate **3**. Dissection of the Δ^1 -pyrroline **4** corresponding to **3** implicated the isocyano silyl enol ether **6** and the acyl chloride **5**, which could potentially be united in a highly convergent manner by way of the acylnitrilium ion-siloxyalkene cyclization described previously by us^{5b} (Scheme 1). In this article we document the successful realization of this overall strategy that has culminated in an *unusually* efficient (eight linear steps, 6.2% cumulative yield) total synthesis of dendrobine (**1**).

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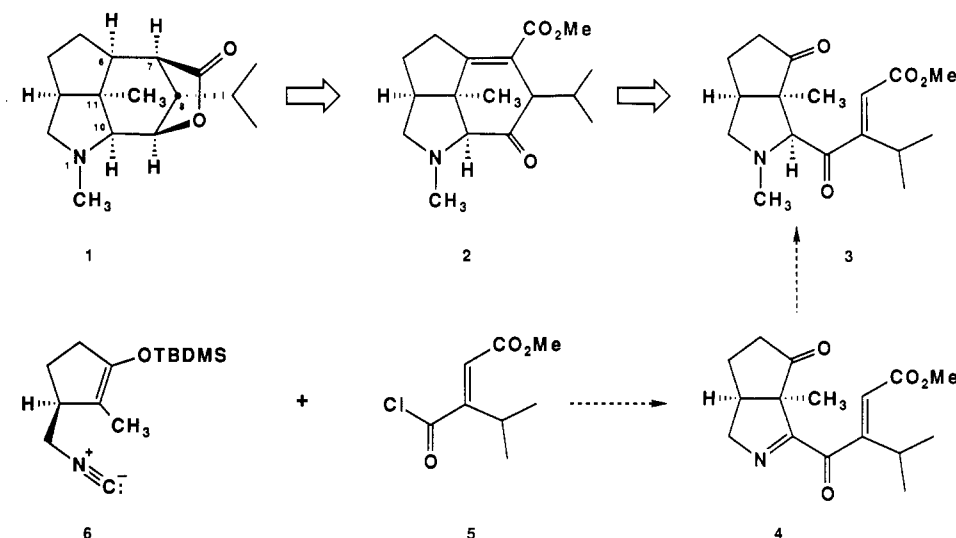
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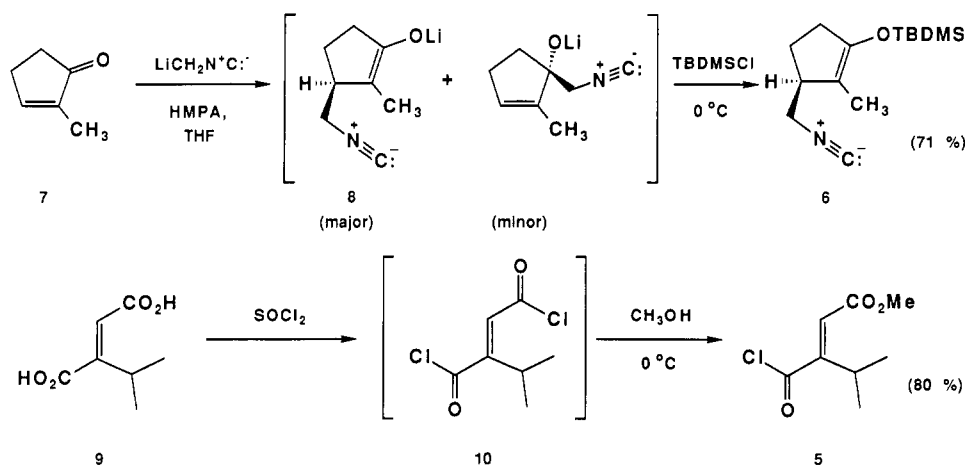
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Scheme I



Scheme II



Results and Discussion

Synthesis of the Cyclization Substrate 3. The point of departure for our synthetic effort was 2-methylcyclopent-2-en-1-one (7). This substance possesses all of the carbons required for the intact B ring of the *Orchidaceae* alkaloids. Exposure of 7 to 1.17 equiv of isocyanomethylthallium^{5a,17,18} in the presence of HMPA (THF, -78°C) led to regioselective 1,4-addition to afford a solution of the corresponding enolate 8 along with a small amount of the tertiary alkoxide resulting from 1,2-addition.^{5a} Direct treatment of this mixture with *tert*-butyldimethylchlorosilane ($-78 \rightarrow 0^{\circ}\text{C}$) led to *selective* trapping of the less hindered enolate 8 to provide isocyanosilyl enol ether 6 in 71% overall yield after chromatography. The requisite acyl chloride 5 was prepared in an exceedingly straightforward manner from the known 2-butenedioic acid¹⁹ 9. Accordingly, treatment of 9 with thionyl chloride gave the corresponding acyl chloride 10, which was *directly* treated with methanol under carefully controlled reaction conditions. We were gratified to find that the methanolysis of 10 proceeded with *complete* specificity for esterification of the least sterically encumbered carbonyl to furnish 5 in 80% overall yield (Scheme II).

With abundant quantities of the essential precursors 5 and 6 in hand, we were suitably positioned for the execution of the crucial acylnitrilium ion-initiated heteroannulation. The reaction of isocyanide moieties with acyl chlorides is typically quite rapid, even at 25°C .^{5c} However, due to the sterically congested nature of the chlorocarbonyl function of 5, slightly elevated temperatures

(e.g., 40°C) were required for the facile acylation of 6. To this end, exposure of 6 to 1.17 equiv of 5 (CH_2Cl_2 , reflux 3.5 h) in the presence of 4-Å molecular sieves (for the sequestration of adventitious HCl) provided the α -ketoimidoil chloride 11 quantitatively. Direct transfer of the solution of 11 prepared in the above manner to 1.45 equiv of AgBF_4 dissolved in 1:1 $\text{ClCH}_2\text{CH}_2\text{Cl}$ at -78°C followed by warming to -20°C resulted in the generation of the transient acylnitrilium ion 12 and its ultimate cyclization to the essential Δ^1 -pyrroline 4 in 88% yield. It should be strongly emphasized that the gratifyingly high yield obtained in the case of 4 is quite representative for acylnitrilium ion-initiated heteroannulations.^{5a,20} This characteristic has provided the impetus for the ongoing application of this methodology to a wide range of synthetically challenging problems in these laboratories.^{5a}

In principle, the stereoselective conversion of Δ^1 -pyrroline 4 to the contrathermodynamic 2-acylpyrrolidine 3 should be most readily accomplished by a sequence involving consecutive N-methylation-hydride reduction. The successful implementation of this experimental protocol initially proved quite challenging. Although N-methylation of 4 could be achieved quantitatively via the agency of $\text{CH}_3\text{O}_3\text{SCF}_3$, attempts to effect *selective* reduction of the corresponding iminium salt 13 with the usual types of reagents [e.g., $(\text{Ph}_3\text{P})_2\text{CuBH}_4$,²¹ NaBH_3CN , etc.] gave capricious results. It was ultimately discovered that the direct

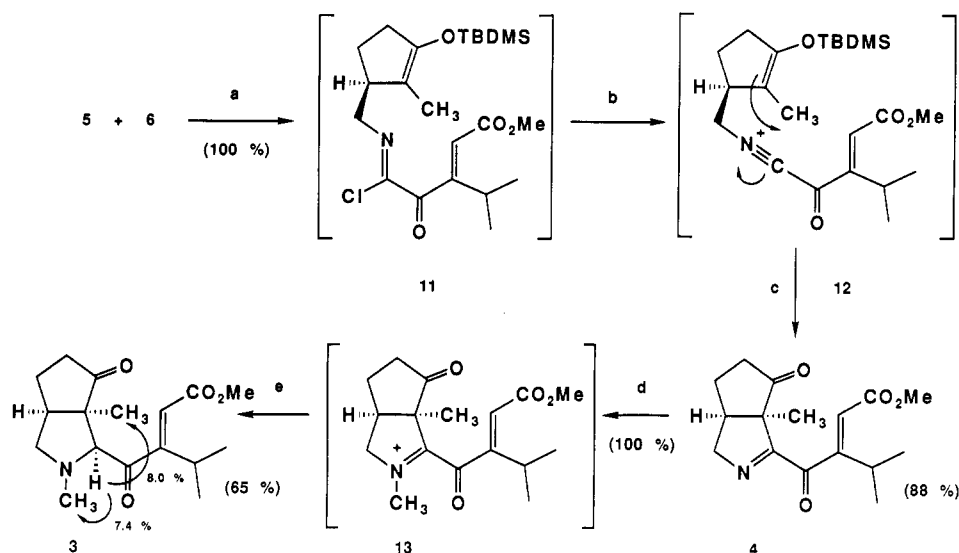
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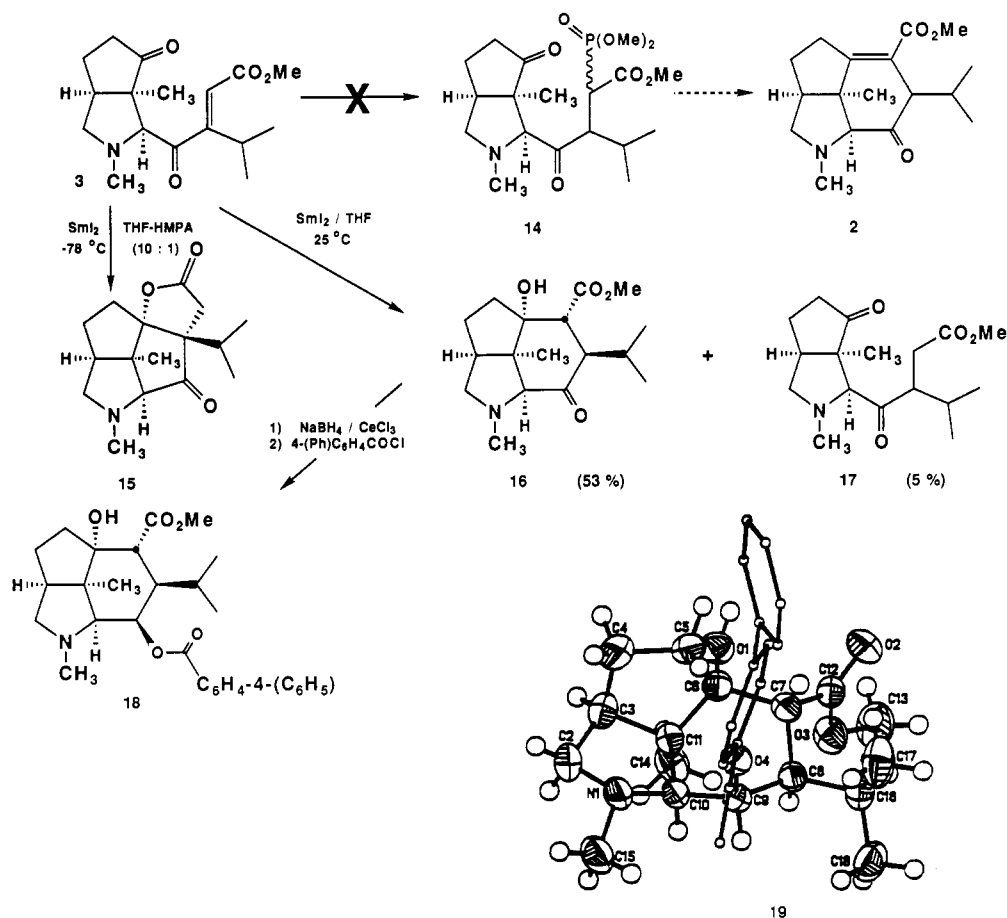
(20) It should be noted that Δ^1 -pyrrolines of this general variety are readily adsorbed onto silica gel. Rigorous purification of these substances by chromatography on this medium results in decreased yields unless special care is taken.^{5a}

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Scheme III^a

^a 4-Å sieves, 40 °C; (b) AgBF₄, -78 °C; (c) -78 → -20 °C; (d) CH₃O₃SCF₃; (e) K⁺HB⁻(O-*t*-Bu)₃.

Scheme IV



reduction of 13 to 3 could be realized in a highly stereocontrolled manner (selectivity = 98:2) by employing potassium tri-*tert*-butoxy borohydride²² as the reducing agent at -78 °C. To our knowledge this is the first example of an iminium cation reduction employing this useful reagent.²³ Evidence for the relative stereochemistry

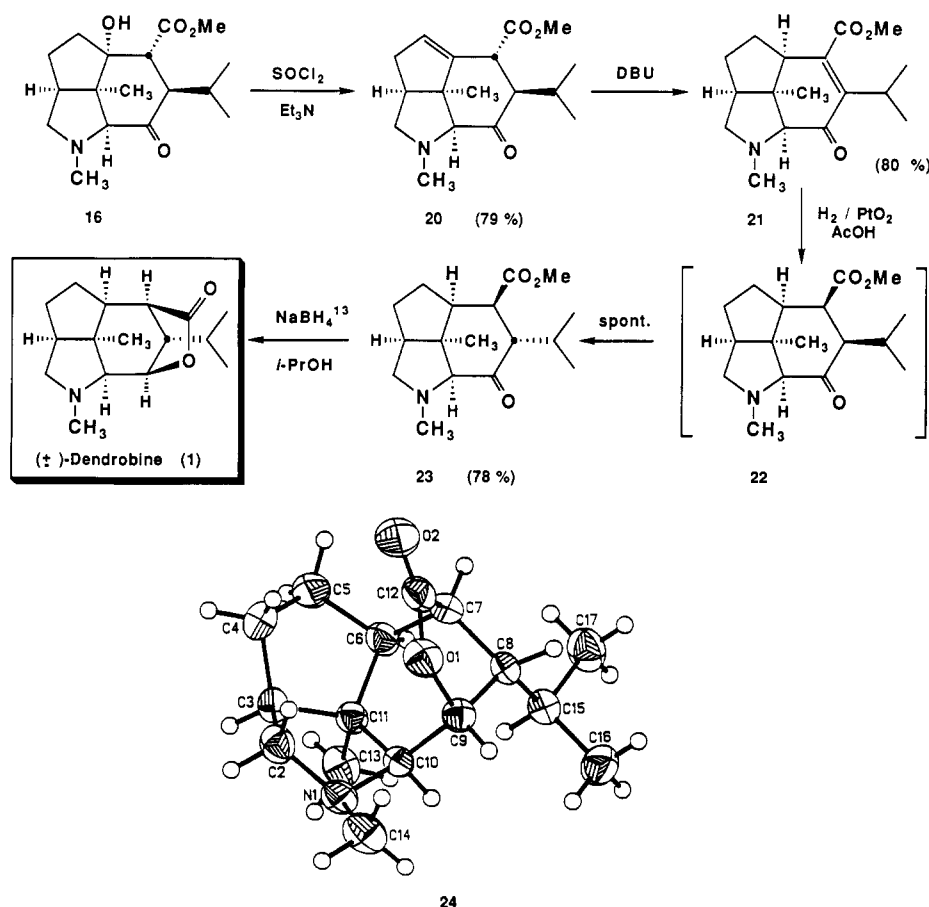
of 3 was provided by nuclear Overhauser difference (NOED) spectroscopy. Specifically, irradiation of the C-10 methine led to an 8.0% enhancement in the signal corresponding to the C-11 methyl substituent and a 7.4% enhancement of the *N*-methyl singlet (Scheme III).

Studies on the Cyclization of the Octahydrocyclopenta[*c*]pyrrole 3. Samarium Iodide-Mediated Closure of Ring C. Having achieved the synthesis of 2-acylpyrrolidine 3 in three overall steps from 2-methylcyclopent-2-en-1-one (7), our attention was directed toward the essential task of effecting the annulation of ring C. It was our original intention to employ a phosphite anion-driven Horner–Wadsworth–Emmons coupling reaction for this purpose.

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(23) (a) Tri-*n*-butyltin hydride^{23b} was also examined as a reducing agent for the preparation of 3. In this instance 3 was produced along with its C-10 epimer in a ratio of 93:7. In addition, the reaction was not amenable to scale up: (b) Palmisano, G.; Lesma, G.; Nali, M.; Rindone, B.; Tollari, S. *Synthesis* **1985**, 1072.

Scheme V



Unfortunately, the γ -keto enoate moiety of **3** proved inert toward 1,4-addition of phosphite-derived reagents under a wide range of reaction conditions. Even trimethylaluminum-promoted addition of dimethyl phosphite²⁴ was ineffective in this regard. In a series of elegant papers Enholm,²⁵ Curran,²⁶ and Molander²⁷ have described several provocative applications of samarium(II) iodide-promoted ketyl-alkene couplings. These cyclization procedures typically lead to the preferential formation of five-membered rings, as would be expected for free radical cyclizations.²⁸ It was our hope, however, that the steric deceleration created by the presence of the obstructive isopropyl substituent at C-2 of the acyl moiety would override this inherent kinetic preference. Unfortunately, treatment of **3** with SmI_2 in THF-HMPA (10:1) at -78°C led to the exclusive formation of the tetracyclic γ -lactone **15** formally derived from the 5-exo mode of ring closure. Through experimentation it was rapidly established that the mode selectivity of cyclization was *strongly* coupled to reaction temperature. Accordingly, addition of **3** to SmI_2 (4 equiv) in THF at 25°C provided **16** as the exclusive cyclized product in 53% yield after chromatography. In addition, 5% of the reduction product **17** was formed in this reaction (Scheme IV). The relative stereochemistry of **16** was readily established by single-crystal X-ray diffraction analysis of the derivative **18** prepared by sequential Luche reduction²⁹ and 4-phenylbenzoylation of the C-9 carbonyl. The results of this study are depicted in representation **19**. The stereochemical outcome of the $\text{Sm}(\text{II})$ -mediated annulation is con-

sistent with both a chelation-controlled diyl cyclization and an intramolecular aldol condensation involving a samarium(III) enolate intermediate. Experiments have not been conducted that would distinguish between these two mechanistic possibilities.

Conversion of 16 into (\pm)-Dendrobine (1). The direct conversion of **3** to **16**, although quite pleasing in a practical sense, presented the obvious strategic obstacles of correcting the oxidation state at C-6 and the stereochemical incongruencies at C-7 and C-8. These transformations were expediently achieved as follows. Treatment of **16** with SOCl_2 (3 equiv) and Et_3N (30 equiv) in EtOAc ($0 \rightarrow 25^\circ\text{C}$) led to *regiospecific* dehydration in the Hofmann sense to provide the β,γ -enoate **20** in 79% yield. The regiochemical preference observed for this reaction is not surprising in light of the sterically shielded nature and low kinetic acidity of the hydrogen at C-7. Isomerization of **20** to γ -ketoenoate **21** was cleanly achieved in 81% yield by exposure to DBU (4 equiv) in refluxing dioxane. Reduction of the tetrasubstituted double bond within **21** was most readily accomplished by hydrogenation over PtO_2 in AcOH at 40 psi pressure (25°C). Fortuitously under these conditions, the anticipated *cis* isomer **22**, which was initially produced via *syn* hydrogenation, underwent quantitative isomerization to furnish the required *trans* isomer **23** directly in 78% yield. Presumably, AcOH is sufficiently acidic to promote the observed epimerization at C-8. Final reduction of **23** according to the procedure of Roush¹² (NaBH_4 , *i*-PrOH, 20°C) gave (\pm)-dendrobine (**1**) in 58% yield after recrystallization. Synthetic (\pm)-dendrobine (**1**), mp $129\text{--}131^\circ\text{C}$ (lit.⁸ mp $130\text{--}132^\circ\text{C}$), prepared in this manner was identical in all respects (300-MHz ^1H and ^{13}C NMR spectra) except optical rotation with an authentic sample of the natural material, which was kindly provided by Professor K. Yamada. An X-ray crystal structure of synthetic (\pm) **1** appears in representation **24** (Scheme V).

Conclusion

An *acylnitrilium ion*-initiated heteroannulation has been employed as the central transformation in uniting an eight-carbon

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isonitrile with a seven-carbon acyl chloride to secure a 2-acyl- Δ^1 -pyrroline possessing *all* of the carbons contained within the contiguous carbocyclic framework of the *Orchidaceae* alkaloid (\pm)-dendrobine (**1**). It is noteworthy that this transformation exhibits the highest efficiency (88%) among the eight linear steps used to prepare **1** from 2-methylcyclopent-2-en-1-one (**7**). The overall yield of dendrobine (**1**) from this commercially available material is 6.2%.

The efficient synthesis of (\pm)-dendrobine (**1**) using this methodology serves as the most vivid illustration to date of the potential that acylnitrilium ion-initiated cyclizations hold for the synthesis of structurally complex azacycles of natural and unnatural origin.

Experimental Section³⁰

(E)-3-Carbomethoxy-2-(1-methylethyl)prop-2-en-1-yl Chloride (5). An oven-dried flask was charged with 6.4 g (40.0 mmol) of isopropyl fumaric acid, 3 drops of DMF, and 64 mL of CH_2Cl_2 . To this solution was added 8.9 mL (120.0 mmol) of thionyl chloride at room temperature. After refluxing for 6 h, the reaction mixture was cooled to 0 °C and then treated with 6.5 mL (160.0 mmol) of methanol. The mixture was stirred for 30 min at 0 °C and for an additional 3 h at room temperature. After removing the volatile components under reduced pressure, the residue was distilled (58–60 °C at 1 Torr) to give 6.1 g (79.7%) of the acyl chloride **5** as a colorless oil: ^1H NMR (CDCl_3) δ 6.83 (1 H, s, CH), 3.79 (3 H, s, CH_3), 3.75 (1 H, m, CH), 1.19 (6 H, d, $J = 7.0$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 167.31 (s), 165.13 (s), 156.12 (s), 130.22 (d), 52.09 (q), 29.33 (d), 20.28 (2 \times q); IR (CDCl_3) 2970, 2880, 1730, 1765, 1640, 1235, 1175, 795 cm^{-1} ; mass spectrum (EI) 191, 159, 154, 131, 126, 111, 95, 81, 67, 59, 53, 50. High-resolution mass spectrum calcd for $\text{C}_8\text{H}_{11}\text{ClO}_3$: 191.0475. Found: 191.0463.

1-[(*tert*-Butyldimethylsilyl)oxy]-3-(isocyanomethyl)-2-methylcyclopent-1-ene (6). An oven-dried flask fitted with a thermometer, an addition funnel, a N_2 adaptor, a rubber septum, and a magnetic stirring bar was charged with 4.5 mL (45.0 mmol) of *n*-BuLi (10 M in hexane) and 120 mL of THF and was then cooled to -78 °C. To this solution was added 2.2 mL (42.0 mmol) of methyl isocyanide in 20 mL of THF so that the temperature did not exceed -60 °C. The resultant white suspension was stirred at -78 °C for 20 min, and 20 mL of HMPA in 20 mL of THF was added dropwise followed by 3.5 mL (36.0 mmol) of 2-methylcyclopent-2-en-1-one in 20 mL of THF at -78 °C. The reaction mixture was stirred at -78 °C for 2 h and then 6.2 g (42.0 mmol) of *tert*-butyldimethylchlorosilane in 50 mL of pentane was added. The reaction mixture was stirred for an additional 30 min at -78 °C and then allowed to warm to 0 °C and maintained at this temperature for 30 min. The reaction mixture was poured into saturated NH_4Cl ; the organic layer was separated, washed with brine, and dried over anhydrous MgSO_4 . After filtration through Florisil, the solvents were removed under reduced pressure to give the crude isonitrile **6** as an oil, which was subjected to chromatography on silica gel (2% ethyl acetate–hexane for elution) to afford 6.4 g (71%) of the pure isonitrile **6** as a pale yellow oil: ^1H NMR (CDCl_3) δ 3.45 (1 H, ddt, $J = 14.67, 5.74, 1.73$ Hz, CH_2), 3.30 (1 H, ddt, $J = 14.67, 6.42, 1.73$ Hz, CH_2), 2.73 (1 H, br s, CH), 2.43 (1 H, m, CH_2), 2.34 (1 H, m, CH_2), 2.20 (1 H, m, CH_2), 1.70 (1 H, m, CH_2), 1.52 (3 H, t, $J = 1.20$ Hz, CH_3), 0.94 (9 H, s, CH_3), 0.13 (3 H, s, CH_3), 0.12 (3 H, s, CH_3); ^{13}C NMR (CDCl_3) δ 156.45 (s), 149.89 (s), 111.03 (s), 45.15 (t), 44.8 (d), 32.24 (t), 25.62 (q), 24.10 (t), 18.02 (s), 9.87 (q), 4.10 (q), 4.04 (q); IR (CDCl_3) 2995, 2930, 2860, 2150, 1690, 1260, 845 cm^{-1} ; mass spectrum (EI) 251, 211, 194, 167, 73, 59. High-resolution

mass spectrum calcd for $\text{C}_{14}\text{H}_{25}\text{NOSi}$: 251.1702. Found: 251.1705. Anal. Calcd for $\text{C}_{14}\text{H}_{25}\text{NOSi}$: C, 66.87; H, 10.02. Found: C, 66.70; H, 10.19.

1-[3-Carbomethoxy-2-(1-methylethyl)propenyl]-3,3a,4,5,6,6a-hexahydro-6a-methylcyclopenta[*c*]pyrrol-6-one (4). An oven-dried flask was charged with 0.22 g (0.88 mmol) of isonitrile **7**, 2 mL of CH_2Cl_2 , 0.11 g of 4-Å molecular sieves, and 0.17 mL (1.03 mmol) of acyl chloride **5**. After refluxing for 3.5 h, the mixture was allowed to cool to room temperature and was then diluted with 2 mL of CH_2Cl_2 and 4 mL of 1,2-dichloroethane. The resultant mixture was cooled to -78 °C, and the supernatant was added dropwise, via cannula, to a solution of 2.5 mL (1.28 mmol) of AgBF_4 (0.51 M in 1,2-dichloroethane) and 2.5 mL of CH_2Cl_2 maintained at -78 °C. The reaction mixture was stirred for 1.5 h at -78 °C and subsequently kept at -20 °C for 16 h. The mixture was then poured into 20 mL of 10% aqueous KHCO_3 , and the organic layer was separated. The aqueous layer was extracted with 15 mL of 10% ethyl acetate–hexane and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . The solvents were removed under reduced pressure to provide 224 mg (88%) of crude **4** (92.4% purity by NMR). This crude product was used in the next step without further purification. For an analytical sample, this material was purified by flash column chromatography (35% ethyl acetate–hexane for elution) to afford pure **4**: ^1H NMR (CDCl_3) δ 6.06 (1 H, s, CH), 4.31 (1 H, dd, $J = 17.9, 7.1$ Hz, CH_2), 4.03 (1 H, dd, $J = 17.9, 2.64$ Hz, CH_2), 3.72 (3 H, s, CH_3), 3.73 (1 H, septet, $J = 7.0$ Hz, CH), 2.69 (1 H, tt, $J = 7.6, 7.1$ Hz, CH_2), 2.34 (2 H, dt, $J = 7.6, 5.6$ Hz, CH_2), 2.19 (1 H, q, $J = 7.6$ Hz, CH_2), 1.59 (1 H, m, CH_2), 1.37 (3 H, s, CH_3), 1.17 (6 H, d, $J = 6.97$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 212.85 (s), 193.45 (s), 170.67 (s), 165.53 (s), 158.91 (s), 126.09 (d), 68.47 (s), 67.25 (t), 51.53 (q), 47.48 (d), 36.68 (t), 28.57 (d), 25.12 (t), 20.46 (2 \times q), 18.76 (q); IR (CDCl_3) 2990, 2880, 1735, 1680, 1635, 1460, 1215, 1045, 920 cm^{-1} ; mass spectrum (EI) 291, 276, 259, 244, 232, 216, 204, 188, 176, 155, 137, 127, 108, 95, 81, 67, 59, 53, 41. High-resolution mass spectrum calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4$: 291.1471. Found: 291.1464. Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.02; H, 7.55; N, 4.58.

1-[3-Carbomethoxy-2-(1-methylethyl)propenyl]-1a,2,3,3a,4,5,6,6a-octahydro-2,6a-dimethylcyclopenta[*c*]pyrrol-6-one (3). An oven-dried flask fitted with a N_2 inlet adaptor, a rubber septum, and a magnetic stirring bar was charged with 240 mg (0.8 mmol) of pyrroline **4** in 5 mL of CH_2Cl_2 . The solution was cooled to 0 °C and 120 mg (0.1 mmol) of methyl trifluoromethanesulfonate was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for an additional 4 h. The volatile components were removed in vacuo to give the corresponding iminium triflate in a quantitative yield as a yellow foam: ^1H NMR (CDCl_3) δ 6.76 (1 H, s, CH), 5.01 (1 H, dd, $J = 15.3, 9.1$ Hz, CH_2), 4.50 (1 H, dd, $J = 15.3, 4.7$ Hz, CH_2), 3.80 (3 H, s, CH_3), 3.62 (3 H, s, CH_3), 3.48 (1 H, m, CH), 3.32 (1 H, m, CH), 2.81 (1 H, m, $J = 9.1$ Hz, CH_2), 2.53 (1 H, m, CH_2), 2.29 (1 H, m, CH_2), 2.14 (1 H, m, CH_2), 1.53 (3 H, s, CH_3), 1.24 (6 H, d, $J = 7.1$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 207.74 (s), 187.33 (s), 164.63 (s), 159.00 (s), 151.82 (s), 140.27 (d), 68.05 (t), 52.51 (q), 43.70 (d), 40.42 (s), 36.67 (t), 28.42 (d), 23.93 (t), 20.94 (q), 20.71 (q), 19.90 (q), 19.78 (q).

To a vigorously stirring solution of 374 mg (0.8 mmol) of the iminium triflate obtained in the above manner in 6 mL of THF maintained at -78 °C was added 0.85 mL (0.8 mmol) of potassium tri-*tert*-butoxy borohydride (0.97 M in THF). After 5 min at -78 °C, the reaction mixture was quenched with 1 mL of methanol and allowed to warm to 0 °C. The mixture was poured into cold water and extracted with 3 \times 15 mL of ethyl acetate. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4 . The solvents were removed under reduced pressure to give 218 mg (94.9%) of crude products, which were purified by chromatography on silica gel (40% ethyl acetate–hexane for elution) to give 150 mg (65.2%) of the mixture of **3** and its C-10 epimer in a ratio of 98:2: ^1H NMR (CDCl_3) δ 6.50 (1 H, s, CH), 3.75 (3 H, s, OCH_3), 3.52 (1 H, septet, $J = 7.1$ Hz, CH), 3.29 (1 H, s, CH), 3.02 (1 H, dd, $J = 9.5, 1.3$ Hz, CH_2), 2.65 (1 H, dd, $J = 9.5, 7.4$ Hz, CH_2), 2.51 (1 H, app pentet, 9.5 Hz, CH), 2.45 (1 H, m, CH_2), 2.24 (1 H, m, CH_2), 2.20 (3 H, s, NCH_3), 2.02 (1 H, m, CH_2), 1.91 (1 H, m, CH_2), 1.26 (3 H, s, CH_3), 1.22 (3 H, d, $J = 7.1$ Hz, CH_3), 1.18 (3 H, d, $J = 7.1$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 219.70 (s), 201.23 (s), 166.40 (s), 160.85 (s), 124.49 (d), 82.15 (d), 62.61 (t), 59.88 (s), 51.63 (q), 47.58 (d), 40.87 (q), 38.70 (t), 29.11 (d), 25.92 (t), 22.56 (q), 21.17 (q), 20.60 (q); IR (CDCl_3) 2960, 2880, 1740, 1680, 1445, 1215, 1115, 745 cm^{-1} ; mass spectrum (EI) 293, 262, 218, 165, 152, 137, 108, 97, 81, 69, 53. High-resolution mass spectrum calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_4$: 308.1862. Found: 308.1863.

5-Carbomethoxy-2,2a,3,4,4a,5b,6a,7,7a,7ba-decahydro-1,7b-dimethyl-4a-hydroxy-6-(1-methylethyl)-1H-cyclopent[*cd*]indol-7-one (16). An oven-dried flask fitted with a thermometer, an addition funnel, a N_2 inlet adapter, a rubber septum, and a magnetic stirring bar was charged

(30) General experimental details: Tetrahydrofuran (THF) and Et_2O were distilled from K metal and Na–benzophenone, respectively. Dimethylformamide (DMF) was distilled from CaH_2 at 20 mmHg, while CH_2Cl_2 , benzene, toluene, and diisopropylamine were distilled from CaH_2 at atmospheric pressure. The molarities indicated for organolithium reagents were established by titration with 2-butanol. ^1H NMR and ^{13}C NMR were measured at 250 and 63 and 300 and 75 MHz, respectively, with Bruker WM-250 and Bruker AC-300 spectrometers. ^1H NMR chemical shifts are reported as δ values in parts per million relative to TMS. ^1H NMR coupling constants are reported in hertz and refer to apparent multiplicities and not true coupling constants. Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); app d (apparent doublet); app t (apparent triplet); dd (doublet of doublets); etc. High-resolution mass spectra were measured on a VG Analytical 7070E spectrometer. Infrared spectra were recorded with a Nicolet SDX FTIR spectrometer. Microanalyses were performed by Desert Analytics, Tucson, AZ. TLC and column chromatography were done with E. Merck silica gel. Radial chromatography was done with a Harrison Research Chromatotron. All reactions were run under an argon or nitrogen atmosphere and concentrations were performed under reduced pressure with a Büchi rotary evaporator.

with 3.6 g (24 mmol) of samarium metal powder and 120 mL of THF. To this slurry was added 3.4 g (12 mmol) of 1,2-diiodoethane at room temperature. The mixture was stirred for 1 h at which time the reaction color had changed from olive-green to deep blue. To the resulting samarium(II) iodide solution was added 0.9 g (4 mmol) of 2-acylpyrrolidine (3) in 30 mL of THF over 15 min while maintaining the temperature between 22 and 25 °C. After it was stirred for 1 h, the mixture was poured into 100 mL of saturated aqueous K_2CO_3 and the organic layer was separated. The aqueous layer was extracted with 3 \times 30 mL of ethyl acetate and the combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4 . Evaporation of solvents and filtration of the residue through florisil with 50% ethyl acetate-hexane for elution gave 1.1 g (89%) of the crude product, which was purified by flash chromatography (15% ethyl acetate-hexane for elution) to afford 660 mg (53.3%) of pure tricyclic β -hydroxy ester 16: 1H NMR ($CDCl_3$) δ 3.97 (1 H, d, J = 12.1 Hz, CH), 3.72 (3 H, s, OCH_3), 3.60 (1 H, s, OH), 2.79 (1 H, d, J = 8.5 Hz, CH_2), 2.73 (1 H, d, J = 8.5 Hz, CH_2), 2.58 (1 H, dd, J = 12.1, 4.4 Hz, CH), 2.22 (1 H, app pentet, J = 8.5 Hz, CH), 2.08 (3 H, s, NCH_3), 2.07 (1 H, s, CH), 1.94 (2 H, m, CH_2), 1.78 (1 H, q, J = 8.5 Hz, CH_2), 1.57 (1 H, q, J = 8.5 Hz, CH_2), 1.47 (1 H, m, CH), 1.04 (3 H, s, CH_3), 0.99 (3 H, d, J = 6.9 Hz, CH_3), 0.87 (3 H, d, J = 6.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 201.98 (s), 176.49 (s), 82.50 (d), 79.75 (s), 62.68 (t), 57.62 (s), 51.85 (q), 51.45 (d), 51.12 (d), 46.41 (d), 41.52 (q), 38.96 (t), 30.44 (d), 29.14 (t), 23.62 (q), 20.44 (q), 20.12 (q); IR ($CDCl_3$) 3500, 2960, 2790, 1710, 1455, 1255, 1205, 1170, 1045, 895 cm^{-1} ; mass spectrum (EI) 310, 281, 238, 205, 190, 153, 138, 125, 108, 96, 57. High-resolution mass spectrum calcd for $C_{17}H_{27}NO_4$: 309.1940. Found: 309.1949.

5-Carbomethoxy-2,2 α ,3,4,4 α ,5 β ,6 α ,7 α ,7 β α -decahydro-1,7b-dimethyl-4a-hydroxy-6-(1-methylethyl)-1H-cyclopent[cd]indol-7-yl 4-Phenylbenzoate (18). An oven-dried flask fitted with a N_2 inlet adaptor, a rubber septum, and a magnetic stirring bar was charged with 100 mg (32×10^{-2} mmol) of tricyclic β -hydroxy ester 16 in 5 mL of methanol. The solution was cooled to 0 °C and 240 mg (64×10^{-2} mmol) of cerium(III) chloride heptahydrate was added followed by 30 mg (80 mmol) of sodium borohydride. The reaction mixture was stirred for 30 min at 0 °C and 2 h at room temperature and was then poured into saturated sodium bicarbonate and extracted with 3 \times 30 mL of CH_2Cl_2 . The combined extracts were dried over anhydrous sodium sulfate and the solvent was then removed under reduced pressure to give 100 mg (99.0%) of the corresponding dihydroxy ester. To a stirred solution of 76 mg (24×10^{-2} mmol) of the crude dihydroxy ester in 4 mL of acetonitrile was added 37 mg (31×10^{-2} mmol) of DMAP and 66 mg (31×10^{-2} mmol) of 4-phenylbenzoyl chloride at 0 °C. The resultant mixture was then allowed to warm to room temperature and stirred for 4 h. The reaction mixture was poured into ice and extracted with ethyl acetate. The combined extracts were washed sequentially with water and brine and dried over anhydrous sodium sulfate. The solvents were evaporated under reduced pressure to give 106 mg (88.4%) of biphenyl ester 18, which was recrystallized from ethyl ether-hexane to provide a pure crystal for X-ray analysis: mp 136–137 °C; 1H NMR ($CDCl_3$) δ 7.68–7.35 (9 H, m, ArH), 5.80 (1 H, dd, J = 7.8, 3.6 Hz, CH), 3.73 (3 H, s, OCH_3), 3.69 (1 H, d, J = 11.8 Hz, CH), 3.25 (1 H, s, OH), 2.76 (1 H, d, J = 9.4 Hz, CH), 2.36 (3 H, s, NCH_3), 1.21 (3 H, s, CH_3), 1.06 (3 H, d, J = 7.0 Hz, CH_3), 0.91 (3 H, d, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 177.04 (s), 165.83 (s), 145.72 (s), 140.03 (s), 130.12 (d), 129.30 (d), 128.92 (d), 128.13 (d), 127.25 (d), 127.20 (d), 80.92 (s), 75.42 (d), 70.87 (d), 63.15 (t), 55.46 (s), 51.67 (q), 49.13 (d), 46.62 (d), 43.00 (q), 41.98 (d), 39.83 (t), 29.50 (t), 27.31 (d), 23.41 (q), 21.85 (q), 19.27 (q); IR ($CDCl_3$) 3505, 2950, 2795, 1715, 1605, 1275, 1105, 750, 700 cm^{-1} ; mass spectrum (EI) 491, 460, 448, 394, 293, 250, 193, 181, 152, 100, 96. High-resolution mass spectrum calcd for $C_{30}H_{37}NO_5$: 491.2672. Found: 491.2676. Anal. Calcd for $C_{30}H_{37}NO_5$: C, 73.29; H, 7.59; N, 2.85. Found: C, 73.21; H, 7.60; N, 2.82.

5-Carbomethoxy-2,2 α ,3,4,4 α ,5 β ,6 α ,7,7 α ,7 β α -decahydro-1,7b-dimethyl-6-(1-methylethyl)-1H-cyclopent[cd]indol-4-en-7-one (20). An oven-dried flask fitted with a N_2 inlet adaptor, a rubber septum, and a magnetic stirring bar was charged with 0.27 g (0.87 mmol) of tricyclic β -hydroxy ester 16 in 15 mL of ethyl acetate. The solution was cooled to 0 °C and 3.65 mL (26.2 mmol) of triethylamine was added. To this solution was added 0.19 mL (2.6 mmol) of thionyl chloride at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, allowed to warm to room temperature, and stirred for an additional 6 h. The resulting mixture was poured into ice water and extracted with 3 \times 20 mL of CH_2Cl_2 . The combined extracts were washed with saturated sodium bicarbonate and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure to give crude 20, which was purified by chromatography on silica gel (40% ethyl acetate-hexane for elution) to afford 200 mg (79.4%) of pure β , γ -unsaturated keto ester 20 as an oil: 1H NMR ($CDCl_3$) δ 5.64 (1 H, app t, J = 2.4 Hz, CH), 3.66 (3 H, s, OCH_3), 3.61

(1 H, d, J = 5.7 Hz, CH), 2.84 (1 H, dd, J = 9.0, 5.7 Hz, CH), 2.77 (1 H, dd, J = 9.5, 2.4 Hz, CH_2), 2.71 (1 H, app t, J = 8.4 Hz, CH_2), 2.53 (1 H, dd, J = 9.5, 7.8 Hz, CH_2), 2.46 (1 H, s, CH), 2.33 (3 H, s, NCH_3), 2.31 (1 H, app t, J = 8.4 Hz, CH_2), 2.17 (1 H, m, CH), 1.29 (3 H, s, CH_3), 1.16 (1 H, m, CH), 0.87 (3 H, d, J = 7.0 Hz, CH_3), 0.84 (3 H, d, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 201.26 (s), 173.33 (s), 138.33 (s), 129.78 (d), 82.30 (d), 64.75 (t), 61.77 (s), 55.25 (d), 52.18 (q), 49.18 (d), 46.08 (d), 41.96 (q), 38.77 (t), 27.83 (d), 24.92 (q), 21.23 (q), 19.80 (q); IR ($CDCl_3$) 2950, 2795, 1740, 1645, 1460, 1245, 1210, 1170, 805, 735 cm^{-1} ; mass spectrum (EI) 292 ($m + 1$)⁺, 263, 248, 220, 204, 96. High-resolution mass spectrum calcd for $C_{17}H_{25}NO_3$: 291.1834. Found: 291.1828.

5-Carbomethoxy-1,7b-dimethyl-6-(1-methylethyl)-2,2 α ,3,4,4 α ,7,7 α ,7 β α -octahydro-1H-cyclopent[cd]indol-7-one (21). An oven-dried flask fitted with a reflux condenser, a N_2 inlet adaptor, a rubber septum, and a magnetic stirring bar was charged with 125 mg (0.4 mmol) of β , γ -unsaturated keto ester 20 in 4 mL of dioxane. To this solution was added 0.3 mL (1.8 mmol) of DBU. After refluxing for 24 h, the reaction mixture was allowed to cool to room temperature, diluted with 10 mL of CH_2Cl_2 , and poured into saturated sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with 2 \times 5 mL of CH_2Cl_2 . The combined organic layers were washed with water and brine and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure to give 125 mg (100%) of crude product, which was purified by chromatography on florisil (15% ethyl acetate-hexane for elution) to afford 101 mg (81%) of α , β -unsaturated keto ester 21: 1H NMR ($CDCl_3$) δ 3.77 (3 H, s, OCH_3), 2.71 (1 H, app t, J = 8.4 Hz, CH_2), 2.70 (1 H, septet, J = 7.0 Hz, CH), 2.45 (H, app t, J = 9.1 Hz, CH_2), 2.43 (H, dd, J = 7.5 Hz, CH), 2.23 (1 H, s, CH), 2.17 (1 H, m, CH), 2.10 (3 H, s, NCH_3), 1.86 (1 H, m, CH_2), 1.83 (1 H, app t, J = 5.7 Hz, CH_2), 1.77 (1 H, m, CH_2), 1.69 (1 H, app t, J = 5.7 Hz, CH_2), 1.17 (3 H, s, CH_3), 1.17 (3 H, d, J = 7.0 Hz, CH_3), 1.10 (3 H, d, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 200.35 (s), 169.56 (s), 145.14 (s), 138.00 (s), 80.12 (d), 64.42 (t), 53.55 (s), 51.74 (q), 50.02 (d), 48.98 (d), 41.14 (q), 33.48 (t), 33.36 (t), 30.10 (d), 25.87 (q), 21.66 (q), 19.77 (q); IR ($CDCl_3$) 2960, 2790, 1730, 1675, 1660, 1455, 1245, 795 cm^{-1} ; mass spectrum (EI) 291, 276, 248, 220, 204, 122, 109, 108, 96, 81, 40. High-resolution mass spectrum calcd for $C_{17}H_{25}NO_3$: 291.18344. Found: 291.18338.

5-Carbomethoxy-2,2 α ,3,4,4 α ,5 α ,6 β ,7,7 α ,7 β α -decahydro-1,7b-dimethyl-6-(1-methylethyl)-1H-cyclopent[cd]indol-7-one (23). To a solution of 50 mg (0.17 mmol) of α , β -unsaturated keto ester 21 in 2 mL of glacial acetic acid was added 10 mg of platinum(IV) oxide. This reaction mixture was hydrogenated at a hydrogen pressure of 50 psi. After it was stirred under H_2 for 20 h at room temperature, the mixture was filtered through Celite and washed with CH_2Cl_2 . The solvents were evaporated under reduced pressure and the residue was dissolved in 10 mL of CH_2Cl_2 . This solution was poured into 25 mL of saturated sodium bicarbonate and extracted with 3 \times 15 mL of CH_2Cl_2 . The combined extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to provide 39 mg (78%) of methyl ketodendrobinate (23) as a pale yellow crystalline solid: 1H NMR ($CDCl_3$) δ 3.67 (3 H, s, CH_3), 3.17 (1 H, dd, J = 4.9, 11.4 Hz, CH), 2.99 (1 H, dd, J = 4.1, 11.4 Hz, CH), 2.79 (1 H, dd, J = 1.4, 9.3 Hz, CH_2), 2.54 (1 H, app t, J = 9.3 Hz, CH_2), 2.23 (1 H, s, CH), 2.20 (3 H, s, NCH_3), 2.14 (1 H, m, CH), 1.99 (1 H, app pentet, J = 9.3 Hz, CH), 1.97 (1 H, m, CH_2), 1.87 (1 H, d septet, J = 6.9 Hz, CH), 1.70 (1 H, m, CH_2), 1.60 (1 H, m, CH_2), 1.44 (1 H, m, CH_2), 1.24 (3 H, s, CH_3), 0.98 (3 H, d, J = 6.9 Hz, CH_3), 0.93 (3 H, d, J = 6.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 213.83 (s), 173.52 (s), 82.44 (d), 64.46 (t), 57.49 (s), 51.70 (q), 50.82 (d), 48.71 (d), 48.07 (d), 46.80 (d), 41.30 (q), 31.94 (t), 29.43 (d), 28.34 (t), 26.32 (q), 20.49 (q), 18.04 (q); IR ($CDCl_3$) 2960, 2890, 1740, 1680, 1460, 1375, 1260, 1170, 920, 810, 740 cm^{-1} ; mass spectrum (EI) 293, 265, 250, 222, 206, 137, 122, 109, 96, 81, 44. High-resolution mass spectrum calcd for $C_{17}H_{27}NO_3$: 293.1991. Found: 293.1974.

(\pm)-Dendrobine (1). An oven-dried flask fitted with a N_2 inlet adaptor, a rubber septum, and a magnetic stirring bar was charged with 25 mg (85×10^{-3} mmol) of methyl ketodendrobinate (23) in 2 mL of 2-propanol. To this solution was added 12 mg (0.32 mmol) of sodium borohydride and the resultant mixture was stirred for 3 days at 20 °C. The reaction mixture was cooled to 0 °C and quenched by the addition of 2.5 mL of 1 N hydrochloric acid. After 30 min at room temperature, the mixture was poured into 25 mL of saturated sodium bicarbonate and extracted with 3 \times 10 mL of CH_2Cl_2 . The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 20 mg (89%) of crude synthetic (\pm)-dendrobine (1), which was purified by recrystallization from ethyl ether to afford 13 mg (58%) of pure crystalline (\pm)-dendrobine (1): mp 129–131 °C (lit.^{12b} mp 130–132 °C); 1H NMR ($CDCl_3$) δ 4.84 (1 H, dd, J = 5.5, 3.0 Hz, CH) 3.15 (1 H, app t, J = 8.7 Hz, CH_2), 2.69 (1 H, app t, J = 8.7 Hz, CH_2), 2.66

(1 H, d, $J = 3.0$ Hz, CH), 2.50 (3 H, s, NCH_3), 2.45 (1 H, dd, $J = 9.5$, 4.0 Hz, CH), 2.36 (1 H, app pentet, $J = 8.7$ Hz, CH), 2.12 (1 H, m, CH), 2.05 (1 H, m, CH_2), 2.02 (1 H, m, CH), 1.85 (1 H, m, CH_2), 1.76 (1 H, septet, $J = 6.5$ Hz, CH), 1.55 (1 H, m, CH_2), 1.38 (3 H, s, CH_3), 0.97 (3 H, d, $J = 6.5$ Hz, CH_3), 0.96 (3 H, d, $J = 6.5$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 178.99 (s), 79.31 (d), 67.05 (d), 61.95 (t), 53.88 (d), 52.49 (s), 51.64 (d), 44.03 (d), 43.11 (d), 36.60 (q), 32.85 (t), 32.78 (q), 30.75 (t), 24.52 (d), 21.10 (q), 20.42 (q); IR (CDCl_3) 2970, 2920, 2860, 1765, 1435, 1420, 1365, 1125, 975 cm^{-1} ; mass spectrum (EI) 263, 220,

206, 178, 136, 108, 40. High-resolution mass spectrum calcd for $\text{C}_{16}\text{H}_{25}\text{NO}_2$: 263.1885. Found: 263.1887.

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Emerimicins III and IV and Their Ethylalanine¹² Epimers. Facilitated Chemical-Enzymatic Synthesis and a Qualitative Evaluation of Their Solution Structures

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Abstract: The peptaibol antibiotics, emerimicin III and IV ($\text{Ac-Phe}^1\text{-MeA}^2\text{-MeA}^3\text{-MeA}^4\text{-Val}^5\text{-Gly}^6\text{-Leu}^7\text{-MeA}^8\text{-MeA}^9\text{-Hyp}^{10}\text{-Gln}^{11}\text{-R-EtA}^{12}\text{-Hyp}^{13}\text{-Xxx}^{14}\text{-Phol}^{15}$, where Xxx = Ala for emerimicin III and Xxx = MeA for emerimicin IV) and their EtA¹² epimers have been synthesized using a combined approach involving solution-phase fragment condensation with a final papain-mediated coupling of the 1-6 and 7-15 fragments. The yield of this final step, ranging from 62 to 80% for the four peptides, was a dramatic improvement over efforts to couple these fragments chemically using DCC/HOBt. A qualitative evaluation of the solution structures of these peptides in DMSO is consistent with a right-handed, predominantly 3_{10} helical conformation throughout the length of the sequence. The antibacterial activity of synthetic emerimicins III and IV was found to be comparable to the native material. The absolute stereochemistry at position 12 has minimal effect on either the biological activity or the solution conformation of the emerimicins.

Introduction

The emerimicins, produced by *Emericellopsis microspora* in the presence of *trans*-4-propyl-L-proline,² belong to the class of peptaibol antibiotics commonly found in filamentous fungi.³ Structurally, these compounds are characterized by several residues of α,α -dialkyl amino acids such as α -methylalanine (MeA or Aib, aminoisobutyric acid⁴) and α -ethylalanine (EtA, or Iva, isovaline⁴),

the presence of a C-terminal amino alcohol, and an N-terminal acetyl group. The main interest in peptaibols stems from their ability to form voltage-dependent ion-conducting pores in lipid bilayer membranes, and alamethicin, a 20-residue peptaibol discovered in 1967,⁵ is the most intensively studied model for voltage-gated channels. Employing mainly various gas chromatography-mass spectrometry techniques, Rinehart et al.^{6,7} determined the sequences of the emerimicins to be $\text{Ac-Phe}^1\text{-MeA}^2\text{-MeA}^3\text{-MeA}^4\text{-Val}^5\text{-Gly}^6\text{-Leu}^7\text{-MeA}^8\text{-MeA}^9\text{-Hyp}^{10}\text{-Gln}^{11}\text{-S-EtA}^{12}\text{-Hyp}^{13}\text{-Xxx}^{14}\text{-Phol}^{15}$ where Xxx = MeA for emerimicin IV,⁷ the principal component, and Xxx = Ala for emerimicin III, the minor component. The configuration of EtA¹², originally assigned as *S*, was subsequently revised to *R*, based on chiral gas chromatography⁸ and X-ray analysis.⁹ As part of our long-standing interest in the conformational attributes of α,α -dialkyl amino acids and the molecular mechanisms by which peptaibols

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(2) Argoudelis, A. D.; Johnson, L. E. *J. Antibiot.* **1974**, *27*, 274-282.

(3) For the natural occurrence of peptaibols, see: (a) Brückner, H.; Reinecke, C. In *Meeting on Peptides Forming Voltage Dependent Channels, Structure and Function*; Museum d'Histoire Naturelle, Centre National de la Recherche Scientifique: Paris, 1988; Symposium Book, p 7. (b) Brückner, H.; Reinecke, C. *J. High Resolut. Chromatogr.* **1989**, *113*-116. (c) Fujita, T.; Iida, A.; Uesato, S.; Takaishi, Y.; Shingu, T.; Saito, M.; Morita, M. *J. Antibiot.* **1988**, *XLI*, 814-817. (d) Brückner, H.; Wunsch, P.; Kussin, C. In *Second Forum on Peptides*; Aubry, A.; Marraud, M.; Vitoux, B., Eds.; J. Libbey Eurotext Ltd.: Montrouge, France, 1989; Vol. 174, pp 103-106.

(4) In the literature, the names aminoisobutyric acid (Aib) and isovaline (Iva) are prevalent. The abbreviation Iva is confusing because it is used also to denote the isovaleryl residue. In the first systematic synthetic studies on α,α -disubstituted amino acids by Kenner's group (refs 32 and 34), the names α -methylalanine and α -ethylalanine were introduced. We support this self-explanatory nomenclature and we have proposed abbreviations (ref 10) consisting of Me or Et to designate an α -alkyl substituent and the one letter code used for the amino acid i.e., MeA or EtA. The abbreviations of other amino acids correspond to IUPAC-IUB rules (*Eur. J. Biochem.* **1984**, *138*, 9-37). Other abbreviations: Phol, L-phenylalaninol; DCC, *N,N'*-dicyclohexylcarbodiimide; HOBt, 1-hydroxybenzotriazole; DMF, dimethylformamide; DABS, 4-(dimethylamino)azobenzene-4'-sulfonyl group; Piv, pivaloyl; Ox, oxazolone residue; Bzl, benzyl; Z, benzyloxycarbonyl; Boc, (*tert*-butoxy)carbonyl.

(5) Meyer, C. E.; Reusser, F. *Experientia* **1967**, *23*, 85-86.

(6) Pandey, R. C.; Cook, J. C., Jr.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 5205-5206.

(7) Rinehart, K. L., Jr.; Cook, J. C., Jr.; Meng, H.; Olson, K. L.; Pandey, R. C. *Nature* **1977**, *269*, 832-853. In an earlier publication (ref 6), the authors denoted emerimicin containing MeA in position 14 as emerimicin IV and emerimicin with Ala¹⁴ as emerimicin III. In ref 7, the same authors used the reverse numbering and this led to confusion in denoting both emerimicins by others. We use the numbering originally proposed by the Rinehart group, i.e. emerimicin IV = MeA¹⁴-emerimicin and emerimicin III = Ala¹⁴-emerimicin.

(8) Brückner, H.; Nicholson, G. J.; Jung, G.; Kruse, K.; König, W. A. *Chromatographia* **1980**, *13*, 209-214. Correction: *Chromatographia* **1980**, *13*, 516.

(9) Bosch, R.; Brückner, H.; Jung, G.; Winter, W. *Tetrahedron* **1982**, *38*, 3579-3583.