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Application of Furanyl Carbamate Cycloadditions Toward the Synthesis of Hexahydroindolinone Alkaloids

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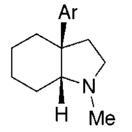
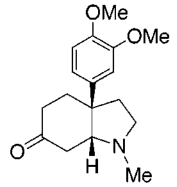
A convenient synthesis of various substituted hexahydroindolinones has been achieved by an intramolecular Diels−Alder cycloaddition reaction (IMDAF) of furanyl carbamates bearing tethered alkenyl groups. The initially formed [4 + 2]-cycloadduct undergoes nitrogen-assisted ring opening followed by deprotonation of the resulting zwitterion to give the rearranged ketone. The stereochemical outcome of the IMDAF cycloaddition has the sidearm of the tethered alkenyl group oriented syn with respect to the oxygen bridge. A synthetic route to (±)-mesembrane and (±)-crinane was accomplished using this methodology. It was possible to carry out a stereoselective reduction of the initially formed hexahydroindolinone ring to produce the *cis*-3a-aryl-hydroindole skeleton. A related [4 + 2]-cycloaddition/rearrangement sequence was also used for a formal synthesis of the Chinese ornamental orchid (±)-dendrobine. The tricyclic alkaloid core was formed stereoselectivity from the thermolysis of *N*-[(2-methyl-2-cyclopentenyl)methyl]-*N*-(4-isopropyl-furan-2-yl)carbamic acid *tert*-butyl ester. Kende's advanced intermediate **33** was prepared in seven additional steps by standard transformations, thereby completing a formal synthesis of (±)-dendrobine.

Introduction

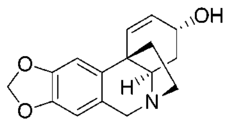
The *cis*-3a-arylhydroindole skeleton (**1**) is a basic structural element of the *Sceletium* alkaloids[1] and is also a key subunit of many crinine-type *Amaryllidaceae* alkaloids.[2] These alkaloids constitute a large family of natural products that have attracted considerable attention over the years due to their diverse and interesting structures.[3] The *Sceletium* alkaloid mesembrine[4] (**2**) can be regarded as a structural prototype for the more complex alkaloids of this structural type, such as crinine (**3**)[5] and pretazettine (**4**).[6] The sterically congested quaternary carbon center located at the hydroindolone bridgehead (C_{3a}) represents a particular challenge toward the synthesis of this family of natural products. A number of creative strategies have emerged over the years to address this problem. Total syntheses of members of this group of alkaloids were reported by many different groups,[7−13] as have a number of important approaches to the characteristic core ring system.[14] Despite the availability of many synthetic methods, there still exists a need to develop procedures more efficient than those currently in existence.



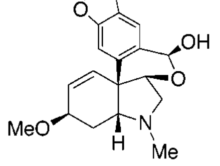
1; cis-3a-aryloctahydroindole ring system



2; mesembrine



3; crinine



4; pretazettine

Several years ago we began a synthetic program to provide general access to these alkaloids by [4 + 2]-cycloaddition chemistry of furanyl carbamates.[15] The plan for

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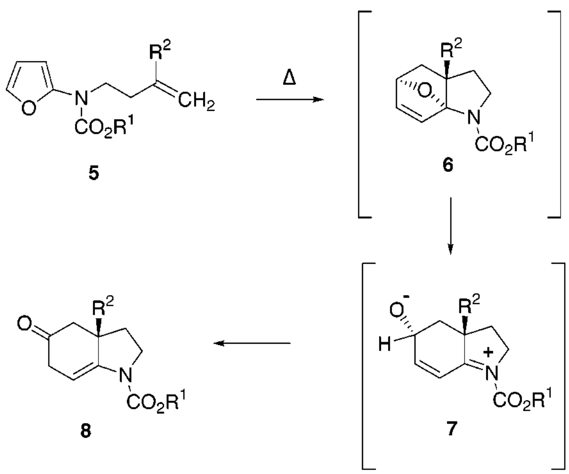
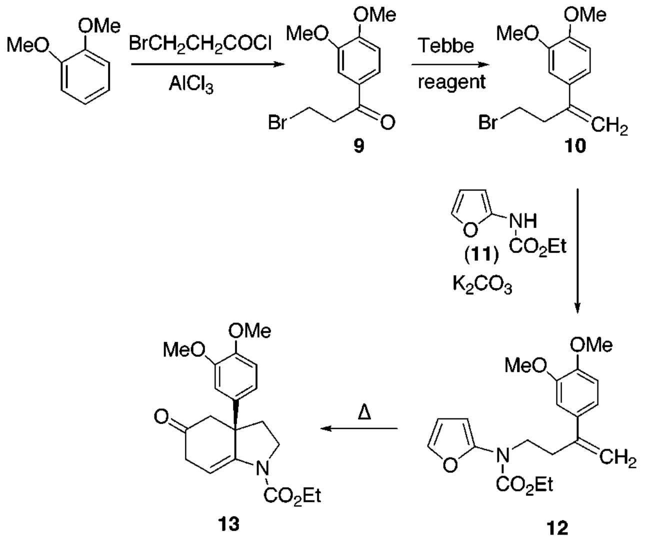
Scheme 1



Scheme 2



assembling the requisite *cis*-3*a*-arylhydroindole skeleton was to take advantage of an intramolecular Diels–Alder of an alkenyl-substituted 2-amidofuran derivative (IMDAF),[16] as had been outlined in earlier reports from these laboratories.[17] In our approach to the hexahydroindolinone core unit, we chose to explore the ring opening reaction of an aza-substituted oxabicyclo[2.2.1]heptene derivative. Oxabicyclic compounds are known to be valuable intermediates[18] for the synthesis of a variety of molecules of biological interest.[19] We found that the initially formed [4 + 2]-oxabicyclic adduct **6**, derived from the intramolecular Diels–Alder cycloaddition of a suitably substituted furanyl carbamate such as **5**, underwent a nitrogen-assisted ring opening. This was followed by a subsequent hydrogen shift of the resulting zwitterion **7** to give the hexahydroindolinone ring system **8** (Scheme 1). To highlight the method, the above synthetic strategy was applied to the synthesis of several different classes of alkaloids. The present paper documents the results of these studies.

Results and Discussion

(±)-Mesembrane. As the goal of our initial efforts, we chose the relatively simple synthetic problem posed by (±)-mesembrane (**18**). Although not naturally occurring, this substance possesses the basic structure of interest[20] and was selected as an optimal initial target to test the methodology. Preparation of the starting amidofuran (i.e., **12**) necessary for the mesembrane synthesis involved treating furan-2-ylcarbamic acid ethyl ester (**11**)[17] with base, followed by the addition of 4-[1-(2-bromoethyl)-vinyl]-1,2-dimethoxybenzene (**10**). Styryl bromide **10** was obtained in high yield from the reaction of 1,2-dimethoxybenzene with 3-bromopropionyl chloride[21] followed by treatment of the resulting aryl ketone **9** with Tebbe reagent[22] (Scheme 2). The IMDAF cycloaddition was performed by heating a solution of **12** in toluene at 155 °C for 20 h. Hexahydroindolinone **13** was obtained in 78% yield from this thermolysis according to the mechanism outlined in Scheme 1.

With keto-enamide **13** on hand, the stereoselective reduction of the enamide double bond into the requisite *cis*-fused hydroindole skeleton was next investigated. This turned out to be much more difficult than expected. A variety of conditions were examined to effect this transformation. These included several reductive protocols known to furnish saturated amides from enamides, such as the use of triethylsilane in the presence of TFA[23] or $NaBH_3CN$ in acetic acid.[24] In each case, however, the *trans*-fused hydroindolinone was obtained as the major product. Catalytic hydrogenation of **13** required forcing conditions. The reaction only proceeded at 80 atm using Pd/C at 50 °C in ethanol (7 days). Moreover, the only product isolated under these conditions corresponded to the 5-ethoxy-substituted *cis*-hydroindole **14** (77% yield). We suspect that the enamide π-bond is first reduced but that the transient *cis*-hydroindolinone reacts further with ethanol to give an enol ether that is subsequently hydrogenated to give **14**. Further reduction of **14** with LAH gave the corresponding *N*-methyl pyrrolidine **15** in 95% yield as a single diastereomer (Scheme 3). The *cis* ring-juncture stereochemistry of **15** was assigned by comparison with the ^1H NMR spectrum of mesembrane.[20] The *cis*-isomer shows a multiplet between δ 6.7–6.9 ppm for the three aromatic protons. In contrast, the NMR spectrum of the *trans*-substituted isomer generally shows

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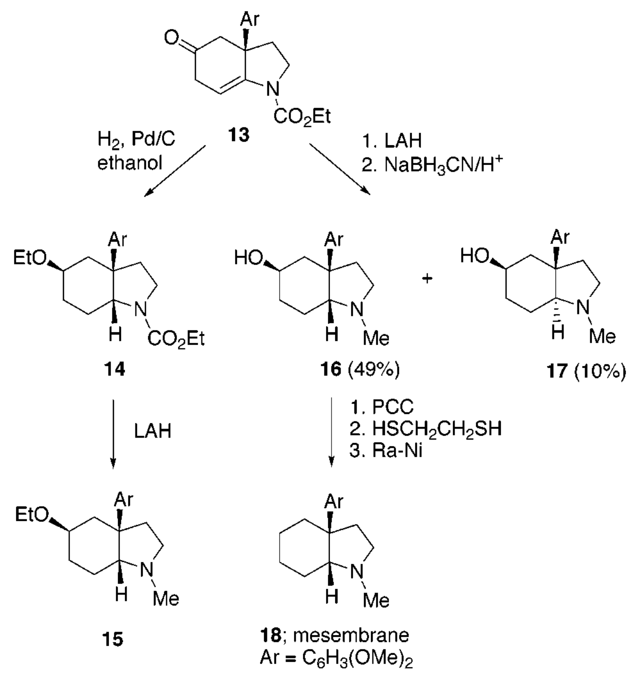
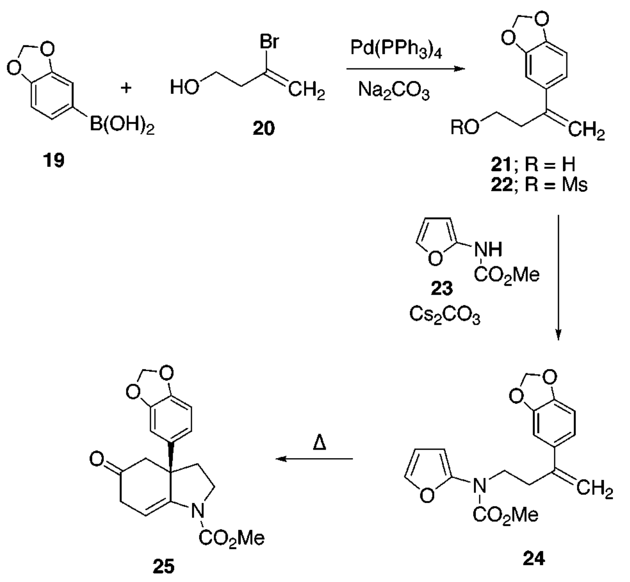
Scheme 3



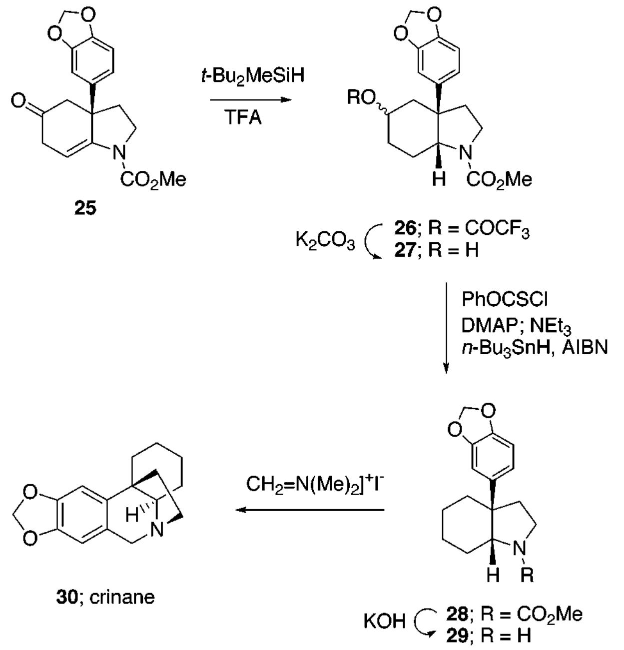
three distinct signals at δ 6.8, 7.3, and 7.5. Unfortunately, all of our attempts to cleave the ethoxy group from the 5-position led to the decomposition of starting material. After considerable experimentation, we ultimately found that sequential reduction of **13** with LAH followed by reaction with $NaBH_3CN/H^+$ afforded a 5:1 mixture of diastereomers, which could readily be separated by silica gel chromatography. The major diastereomer corresponded to the desired *cis*-3a-arylhydroindole ring stereochemistry (i.e., **16**) as evidenced by its ^1H NMR. This isomer was subjected to oxidation using PCC to furnish the expected ketone in quantitative yield. Further reaction with 1,2-ethylenedithiol afforded the corresponding thioketal which was reduced with Raney nickel to give (±)-mesembrane in 85% overall yield.

(±)-Crinane. The successful preparation of (±)-mesembrane encouraged us to also apply the IMDAF reaction of the related carbamate **24** to the synthesis of (±)-crinane (**30**).[25] The plan for assembling the requisite amidofuran **24** was to carry out the *N*-alkylation of furan-2-ylcarbamic acid methyl ester (**23**) with styryl mesylate **22**, as had been outlined in earlier reports from these laboratories.[26] The synthesis of **24** begins with a Pd(0)-catalyzed coupling of the commercially available boronic acid **19** and 3-bromo-but-3-en-1-ol. Suzuki coupling[27] of these two substrates gave alcohol **21** in 54% yield. Conversion of **21** into mesylate **22** followed by reaction with furanyl carbamate **23** and Cs_2CO_3 furnished **24** in 61% yield (Scheme 4). Heating a sample of **24** at 180 °C for 15 h provided the rearranged cycloadduct **25** in 85% yield. Reduction of **25** with di-*tert*-butylmethyl silane in TFA[28] afforded a 10:1 mixture of the *cis*- (major) and *trans*-trifluoroacetoxy hydroindoles **26** in 75% yield.

Scheme 4



Scheme 5



Conversion of **26** to the desired amine **29** requires removal of the trifluoroacetoxy group and hydrolysis of the carbamate functionality. The transformation of **26** to the corresponding alcohol **27** was accomplished without incident by reaction with potassium carbonate (95%). The Barton–McCombie deoxygenation procedure[29] was used to convert **27** into **28**, and this was followed by carbamate cleavage using KOH in aqueous ethylene glycol to give amine **29** in 78% yield (Scheme 5). For completion of the synthesis of (±)-crinane, it remained only to subject amine **29** to Pictet–Spengler cyclization according to the published procedure.[30] Thus, heating a sample of amine **29** with Eschenmoser's salt at 40 °C in THF yielded (±)-crinane (**30**).

(±)-Dendrobine. As an extension of these studies, we came to recognize that the cycloaddition/rearrangement

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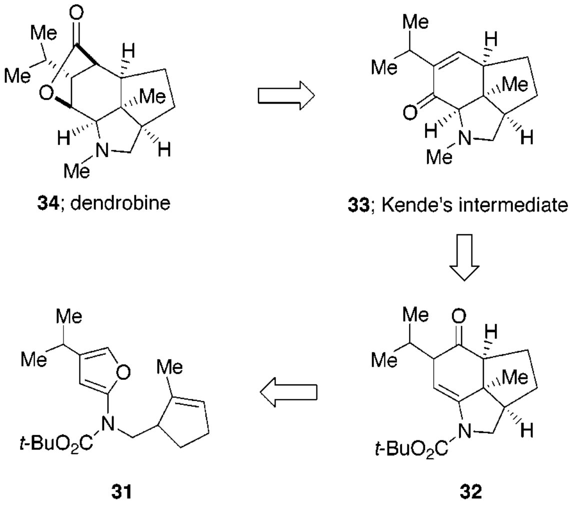
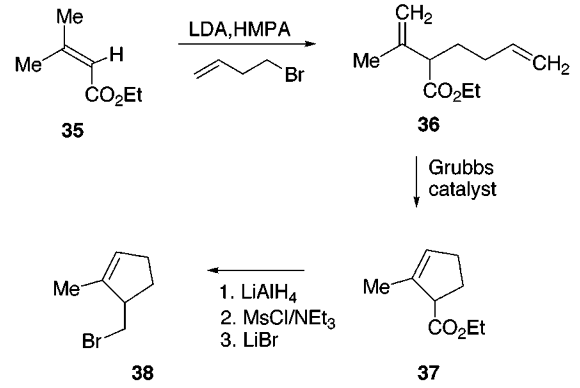
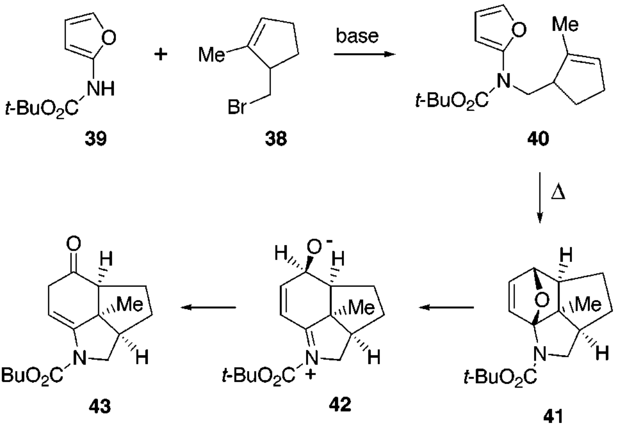
Scheme 6



Scheme 7



Scheme 8



cascade of furanyl carbamates could also be used for a concise and stereocontrolled synthesis of the tricyclic core of the alkaloid (±)-dendrobine.[31] Dendrobine (**34**) is the major component of the Chinese ornamental orchid *Dendrobium nobile* and exhibits antipyretic, hypotensive, and convulsant activity.[32,33] This alkaloid is a challenging synthetic target owing to the presence of seven asymmetric centers on a compact carbon skeleton and continues to represent a major challenge for efficient chemical synthesis. Total syntheses of dendrobine were first completed by several research groups in the early 70s.[34] As a consequence of its intricate architecture and biological activity, it is not surprising that dendrobine has been the subject of more recent synthetic investigations. Indeed, a number of additional total and formal syntheses[35] employing a wide range of strategies[36] have been reported in recent years. We present here another approach to dendrobine based on our recently described *amidofuran cycloaddition–rearrangement* methodology.[15,26]

Our retrosynthetic analysis is outlined in Scheme 6. The key step in our plan involves the intramolecular Diels–Alder[16] reaction of 2-amidofuran **31** followed by a subsequent rearrangement to give hexahydroindolinone **32**. The attractiveness of this strategem involves the possibility of establishing four of the asymmetric centers in one step. We envisioned that a few functional group manipulations would convert **32** into enone **33**, which was a key advanced intermediate in Kende's total synthesis of dendrobine.[34c]

The synthetic sequence depicted above relies on a stereoselective [4 + 2]-cycloaddition of a 3-substituted amidofuran (i.e., **31**) across an unactivated cyclopentenyl π-bond. Before attempting the more challenging Diels–Alder reaction of **31**, a simpler model system (i.e., **40**) was investigated so as to test the feasibility of this approach (Scheme 8). The desired starting material was easily synthesized by the alkylation of furan-2-yl carbamic acid *tert*-butyl ester (**39**) with 5-bromomethyl-1-methylcyclopent-ene (**38**). Cyclopentenyl bromide **38** was prepared by treating ethyl 3-methyl-2-butenoate (**35**) with LDA in the presence of HMPA followed by reaction with 4-bromo-1-butene to give ester **36** in 82% yield (Scheme 7). Ring closing metathesis (RCM) is a well-established process allowing the synthesis of a wide variety of cyclic systems from the corresponding acyclic diene.[37] This reaction can be catalyzed by a number of metallocarbene complexes, among the most popular of which is the ruthenium benzylidene complex $(Cy_3P)_2Ru(=CHPh)Cl_2$.[38] When diene **36** was treated with an excess of Grubbs catalyst in dichloromethane at 30 °C for 18 h, cyclopentenyl ester **37** was formed in 63% yield. This metathesis reaction was followed by reduction of the ester

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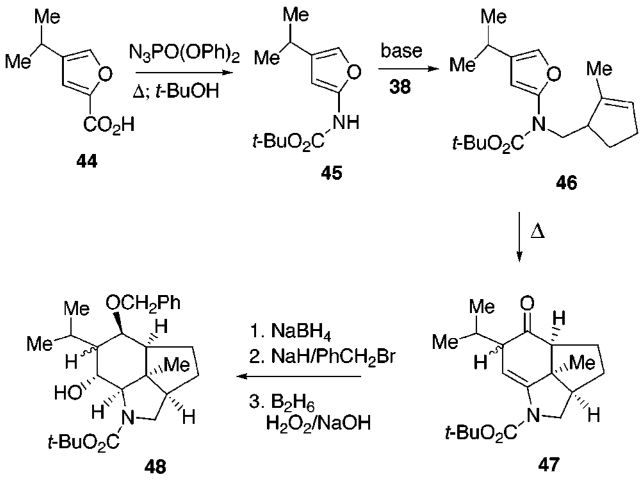
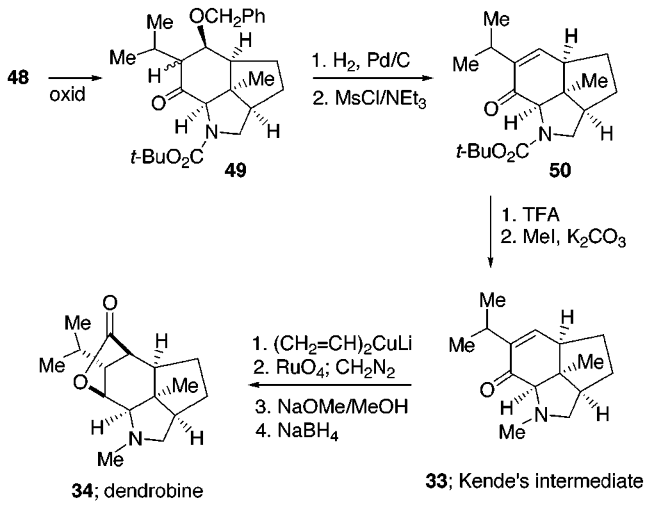
Scheme 9



Scheme 10



group to the alcohol, conversion to the mesylate, and then bromide ion displacement to give **38** in 70% overall yield.

Attachment of the cyclopentenyl tether to the furanyl carbamate was accomplished by treating **39** with potassium carbonate/sodium hydroxide tetrabutylammonium hydrogen sulfate in benzene followed by the addition of bromide **38**, which gave **40** in 79% yield. The thermal IMDAF reaction of **40** occurred at 165 °C to furnish **43** in 78% yield as a single diastereomer (Scheme 8). The initially formed oxa-bridge cycloadduct **41** was not detected, as it readily underwent ring opening followed by a subsequent proton shift of the transient acyl iminium ion intermediate **42**. The ring-opened hexahydroindolinone **43** is derived from a transition state where the sidearm of the tethered cyclopentenyl group is oriented *syn* (*exo*) with respect to the oxygen bridge. This stereochemical result is consistent with other reports in the literature involving related furanyl systems that possess short tethered alkenyl side chains.[39]

At this juncture, we turned our attention to the more complex [4 + 2]-cycloaddition of furan carbamate **46**, which bears the isopropyl group necessary for a synthesis of dendrobine (**34**). Carbamate **45** was prepared by heating a sample of the known 4-isopropyl-furan-2-carboxylic acid (**44**)[40] with diphenyl phosphorylazidate[41] in *tert*-butyl alcohol, which effected a Curtius rearrangement to give **45** in 83% yield. Subjection of **45** to the previously used alkylation conditions furnished **46** in 71% yield. We were gratified to find that the thermolysis of **46** proceeded in 74% yield to produce the tricyclic indolinone **47** as a 2:1 mixture of diastereomers (Scheme 9).[42] Reduction of the keto group in **47** was effectively accomplished by treatment of the mixture with sodium borohydride in methanol. Protection of the hydroxyl group as the benzyl ether was followed by hydroboration/oxidation to deliver the tricyclic alcohol **48** as a 2:1 mixture of stereoisomers. Fortunately, the two diastereomers were easily separated by silica gel chromatography and were formed in 50% and 22% overall yield, respectively, from hexahydroindolinone **46**. Thus, the three-step sequence (reduction, protection, and oxidative hydroboration) was quite efficient (i.e., a 72% overall yield after separation). Delivery of hydride to the keto group as well as hydroboration of the enamide double bond occurred from the sterically less hindered convex face of the tricyclic core, which is on the same face as the methyl group.[35d,e]

Exposure of the major diastereomer of **48** to Dess–Martin periodinane afforded a mixture of epimers of **49**, most likely the result of epimerization at C(6) during the oxidation. Attempts to form Kende's intermediate **33** via the elimination of benzyl alcohol directly from **49** were unsuccessful. Instead, **49** was subjected to hydrogenolysis using a Pd/C catalyst to cleave the benzylic-oxygen bond. Without purification, the resulting alcohol was treated with mesyl chloride/NEt$_3$ and the resulting mesylate underwent spontaneous elimination to furnish enone **50** in 62% overall yield from alcohol **48** (Scheme 10). Finally, cleavage of the BOC group in **50** with dilute trifluoroacetic acid in CH$_2$Cl$_2$ followed by methylation of the resulting secondary amine with methyl iodide furnished Kende's intermediate **33** in 65% yield for the two steps. The spectroscopic data of **33** were identical to those reported in the literature.[43]

In summary, a concise formal synthesis of several *Amaryllidaceae* alkaloids, as well as the Chinese ornamental orchid (±)-dendrobine, have been carried out using the IMDAF cycloaddition/rearrangement sequence of furanyl carbamates previously reported from our laboratories. Our formal synthesis of (±)-dendrobine involved the preparation of Kende's advanced intermediate **33** and was accomplished in 11 steps from readily available starting materials. All synthetic steps of this sequence proceeded in good yield, and the stereogenic centers from the cycloaddition were established with high stereoselectivity. Further application of this methodology to other alkaloids is currently underway in our laboratories and will be reported in due course.

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(43) Mori and co-workers report additional details for the characterization and conversion of **33** into (±)-dendrobine.[35e]

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column using an ethyl acetate/hexane mixture as the eluent unless specified otherwise. All solids were recrystallized from ethyl acetate/hexane for analytical data.

4-[1-(2-Bromoethyl)vinyl]-1,2-dimethoxybenzene (10). A mixture containing 9.3 g (70 mmol) of aluminum trichloride and 6.7 mL (52 mmol) of 1,2-dimethoxy-benzene in 300 mL of carbon disulfide at 25 °C was treated dropwise with 10 g (58 mmol) of 3-bromopropionyl chloride in 100 mL of carbon disulfide. After the addition was complete, the mixture was heated at reflux for 3 h and cooled to 25 °C, and a 50% HCl solution was slowly added. The organic layer was separated, washed with water, 10% NaOH, and brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude solid was recrystallized from MeOH to give 11 g (86%) of 3-bromo-1-(3,4-dimethoxyphenyl)propan-1-one (**9**)[44] as a white solid: mp 110−111 °C; IR (KBr) 3060, 2934, 1652, and 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.53 (t, 2H, $J = 7.2$ Hz), 3.74 (t, 2H, $J = 6.8$ Hz), 3.93 (s, 3H), 3.95 (s, 3H), 6.89 (d, 1H, $J = 8.4$ Hz), 7.51 (d, 1H, $J = 2.0$ Hz), and 7.55 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3, 42.0, 57.1, 57.2, 111.0, 111.1, 123.9, 130.6, 150.2, 154.7, and 196.6. Anal. Calcd for $C_{11}H_{13}O_3Br$: C, 48.37; H, 4.80. Found: C, 48.48; H, 4.77.

A solution containing 3.2 g (12 mmol) of the above ketone in 50 mL of THF at −40 °C was treated dropwise with 40 mL of Tebbe reagent[22] (0.5 M in toluene). The solution was stirred at −40 °C for 30 min, allowed to warm to room temperature, and maintained there for 1 h. The mixture was diluted with 50 mL of THF and cooled to −10 °C, and a solution of 15% NaOH was added with an accompanying evolution of methane. The mixture was stirred at room temperature for another 10 min and filtered through Celite, the solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography to give 2.5 g (80%) of **10**[21] as a colorless oil: IR (neat) 3063, 2981, 1432, and 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.03 (t, 2H, $J = 7.2$ Hz), 3.44 (t, 2H, $J = 7.2$ Hz), 3.88 (s, 3H), 3.90 (s, 3H), 5.08 (d, 1H, $J = 1.2$ Hz), 5.32 (d, 1H, $J = 1.2$ Hz), 6.83 (d, 1H, $J = 8.4$ Hz), 6.91 (d, 1H, $J = 2.0$ Hz) and 6.93 (d, 1H, $J = 2.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.1, 39.9, 55.9, 109.4, 110.9, 113.5, 113.6, 118.4, 132.5, 145.0, and 148.8. Anal. Calcd for $C_{12}H_{15}O_2Br$: C, 53.15; H, 5.58. Found: C, 53.08; H, 5.66.

[3-(3,4-Dimethoxyphenyl)-but-3-enyl]-furan-2-yl-carbamic Acid Ethyl Ester (12). A suspension containing 1.7 g (11 mmol) of carbamate **11**,[17] 1.8 g (32 mmol) of powdered KOH, 1.5 g (11 mmol) of powdered K_2CO_3, and 1.9 g (5.5 mmol) of Bu_4NHSO_4 in 50 mL of benzene was stirred at room temperature for 1 h. To this mixture was added 2.9 g (11 mmol) of bromide **10**. After 40 h of stirring at 50 °C, the mixture was filtered through a pad of silica gel. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 1.1 g (55%) of carbamate **12** as a pale yellow oil: IR (neat) 1723, 1272, and 1018 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, 3H, $J = 6.8$ Hz), 2.80 (m, 2H), 3.72 (m, 2H), 3.88 (s, 6H), 4.18 (q, 2H, $J = 6.8$ Hz), 5.04 (d, 1H, $J = 1.0$ Hz), 5.30 (d, 1H, $J = 1.0$ Hz), 6.08 (brs, 1H), 6.37 (dd, 1H, $J = 3.2$ and 2.0 Hz), 6.82 (d, 1H, $J = 8.4$ Hz), 6.95−7.06 (m, 2H), and 7.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 34.4, 48.6, 55.7, 55.8, 62.1, 101.8, 109.1, 110.8, 111.0, 112.6, 118.2, 132.9, 138.4, 144.3, and 148.6. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.06; H, 6.72; N, 4.06. Found: C, 66.13; H, 6.62; N, 4.04.

3a-(3,4-Dimethoxyphenyl)-5-oxo-2,3,3a,4,5,6-hexahydroindole-1-carboxylic Acid Ethyl Ester (13). A solution containing 1.0 g (3 mmol) of carbamate **12** in 15 mL of toluene was heated in a sealed tube at 155 °C for 20 h. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.77 g (78%) of **13** as a thick yellow oil: IR (neat) 1714, 1518, 1417, and 1333 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (brs, 3H), 2.10−2.16 (m, 1H), 2.31 (dd, 1H, $J = 1.6$ and 1.2 Hz), 2.71−2.82 (m, 2H), 2.92−3.08 (m, 2H), 3.24 (dt, 1H, $J = 11.2$ and 1.6 Hz), 3.79 (t, 1H, $J = 6.2$ Hz), 3.83 (s, 3H), 3.84 (s, 3H), 4.24 (brs, 2H), 6.40 (brs, 1H), and 6.74−6.82 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 37.6, 38.6, 46.3, 51.3, 53.5, 55.8, 55.9, 61.4, 101.0, 109.3, 111.1, 118.7, 132.9, 142.0, 148.2, 149.2, 153.2, and 208.6. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.06; H, 6.72; N, 4.06. Found: C, 65.97; H, 6.59; N, 3.85.

3a-(3,4-Dimethoxyphenyl)-5-ethoxy-2,3,3a,4,5,6,7,7a-octahydroindole-1-carboxylic Acid Ethyl Ester (14). A mixture containing 0.18 g (0.5 mmol) of **13** and 0.03 g of 5% palladium on charcoal in 10 mL of ethanol was hydrogenated under 1200 psi (80 atm) at 50 °C for 7 days. The mixture was filtered through a pad of Celite. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.15 g (77%) of **14** as a pale yellow oil whose NMR consisted of a 1:1 mixture of rotamers: IR (neat) 1697, 1514, and 1411 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16−1.33 (m, 8H), 1.52 (t, 1H, $J = 2.6$ Hz), 2.06 (brs, 2H), 2.21−2.41 (m, 2H), 2.41−2.44 (m, 1H), 2.90−3.13 (m, 1H), 3.30−3.42 (m, 1H), 3.44−3.60 (m, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.04−4.32 (m, 3H), and 6.79−6.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7 (14.9), 15.6, 27.0 (27.6), 29.5 (29.6), 32.4 (33.6), 41.9 (42.0), 43.0 (43.2), 48.5 (49.2), 55.8, 58.9 (59.1), 60.7 (60.8), 63.4 (63.5), 74.4 (74.5), 108.8 (108.9), 110.8 (110.9), 117.2 (117.3), 139.3 (139.4), 147.2 (147.3), 148.6 (148.7), and 154.7 (154.8). Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.80; H, 8.28; N, 3.71. Found: C, 66.93; H, 8.19; N, 3.66.

3a-(3,4-Dimethoxyphenyl)-5-ethoxy-1-methyl-2,3,3a,4,5,6,7,7a-octahydroindole (15). To a suspension of 0.02 g (0.4 mmol) of lithium aluminum hydride in 8 mL of ether at 0 °C was added dropwise a solution containing 0.07 g (0.18 mmol) of carbamate **14** in 2 mL of ether. After the addition was complete, the mixture was stirred at room temperature for 17 h, diluted with ether, quenched with sodium sulfate decahydrate, filtered through a pad of Celite, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.06 g (95%) of **15** as a colorless oil: IR (neat) 2932, 1515, and 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, 3H, $J = 7.0$ Hz), 1.46−1.51 (m, 1H), 1.68−1.74 (m, 1H), 1.84−1.95 (m, 3H), 2.01−2.16 (m, 3H), 2.32 (s, 3H), 2.32−2.39 (m, 1H), 2.70 (t, 1H, $J = 3.6$ Hz), 3.05−3.21 (m, 3H), 3.55−3.60 (m, 1H), 3.86 (s, 3H), 3.89 (s, 3H), and 6.77−6.92 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.2, 19.8, 25.8, 39.7, 40.3, 47.0, 53.8, 55.8, 55.9, 62.6, 67.5, 73.3, 110.2, 110.6, 117.9, 142.6, 146.5, and 148.2. Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.43; H, 9.16; N, 4.39. Found: C, 71.28; H, 9.08; N, 4.27.

3a-(3,4-Dimethoxyphenyl)-1-methyl-2,3,3a,4,5,6,7,7a-octahydroindole-5-ol (16). To a suspension of 0.18 g (4.7 mmol) of lithium aluminum hydride in 60 mL of ether was added dropwise a solution containing 0.55 g (1.6 mmol) of hexahydroindole **13** in 40 mL of ether. After 4 h of stirring at room temperature, the mixture was heated at reflux for 1 h, cooled, diluted with ether, filtered through a pad of Celite, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude mixture was used in the next step without further purification.

To a solution containing 0.16 g (0.55 mmol) of the above mixture and a small amount of bromocresol green in 25 mL of methanol was added dropwise a 2 N HCl in methanol solution until the color became yellow. To this mixture was added 0.04 g (0.6 mmol) of $NaBH_3CN$. The mixture was stirred at room temperature, and periodically a 2 N HCl in methanol solution was slowly added to keep the mixture at pH 3. When the yellow color persisted, the mixture was stirred at room temperature for an additional 5 h. The solution was quenched with 5% NaOH, extracted with ether, and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.08 g (49%) of *cis*-3a-

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[44] Kratzl, E. *Chem. Ber.* **1943**, *76*, 895.

(3,4-dimethoxyphenyl)-1-methyl-octahydroindole-5-ol (**16**) and 0.02 g (10%) of *trans*-3a-(3,4-dimethoxyphenyl)-1-methyl-octahydroindole-5-ol (**17**). The stereochemistry of each isomer was assigned on the basis of their characteristic NMR spectra.

The major *cis*-diastereoisomer **16** consisted of a yellow oil that exhibited the following spectral properties: IR (neat) 3364, 1520, and 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.50−2.00 (m, 8H), 2.20−2.23 (m, 1H), 2.30−2.37 (m, 1H), 2.33 (s, 3H), 2.55 (s, 1H), 3.27 (dt, 1H, $J = 9.2$ and 4.8 Hz), 3.46−3.55 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), and 6.79−6.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.1, 29.7, 40.3, 41.0, 44.6, 49.2, 54.1, 55.8, 55.9, 67.5, 67.8, 110.1, 110.6, 118.2, 139.4, 147.0, and 148.7. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.06; H, 8.65; N, 4.81. Found: C, 69.83; H, 8.79; N, 4.68.

The minor *trans*-stereoisomer **17** consisted of a yellow oil that exhibited the following spectral properties: IR (neat) 3562, 1513, and 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40−2.28 (m, 10H), 2.39 (s, 3H), 2.95−3.03 (m, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 3.96−4.02 (m, 1H), 6.81 (d, 1H, $J = 8.6$ Hz), 7.38 (dd, 1H, $J = 8.6$ and 1.8 Hz), and 7.57 (d, 1H, $J = 1.8$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3, 33.4, 41.5, 41.6, 43.9, 46.5, 52.7, 55.7, 55.9, 67.8, 76.0, 110.7, 112.8, 120.8, 136.7, 146.8, and 148.3; HRMS calcd for $C_{17}H_{25}NO_3$ 291.1835, found 291.1844.

3a-(3,4-Dimethoxyphenyl)-1-methyl-octahydroindole-5-one. A mixture containing 0.02 g (0.06 mmol) of the *cis* hydroindole **16**, 0.02 g (0.1 mmol) of PCC, and 0.02 g of silica gel in 10 mL of CH_2Cl_2 was stirred at room temperature overnight. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.015 g (99%) of the title compound as a pale yellow oil: IR (neat) 2941, 1712, 1525, and 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.68−1.79 (m, 1H), 1.87−2.03 (m, 2H), 2.06−2.21 (m, 2H), 2.39 (s, 3H), 2.50−2.61 (m, 3H), 2.79 (d, 2H, $J = 3.6$ Hz), 3.29 (dt, 1H, $J = 8.8$ and 3.6 Hz), 3.86 (s, 3H), 3.88 (s, 3H), and 6.79−6.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9, 35.1, 40.0, 40.1, 50.2, 52.3, 54.5, 55.8, 55.9, 70.8, 110.0, 110.9, 118.5, 138.9, 147.4, 148.7, and 212.5. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.55; H, 8.02; N, 4.84. Found: C, 70.48; H, 7.92; N, 4.77.

(±)-Mesembrane (18). A mixture containing 0.02 g (0.06 mmol) of the above ketone, 13 μL (0.1 mmol) of $BF_3 \cdot OEt_2$, and 8 μL (0.1 mmol) of 1,2-ethylene dithiol in 10 mL of CH_2Cl_2 was stirred at room temperature for 16 h. The solution was quenched with a 5% NaOH solution and extracted with ether. The combined organic layers was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.02 g (99%) of the dithiolane derivative of 3*a*-(3,4-dimethoxyphenyl)-1-methyl-octahydroindole-5-one as a white solid: mp 115−116 °C; IR (neat) 2931, 1520, 1470, and 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.67−1.82 (m, 2H), 1.92−2.03 (m, 2H), 2.16−2.28 (m, 3H), 2.31 (s, 3H), 2.51 (dd, 1H, $J = 13.8$ and 1.4 Hz), 2.67 (s, 1H), 2.75 (d, 1H, $J = 13.8$ Hz), 2.95−3.22 (m, 5H), 3.88 (s, 3H), 3.89 (s, 3H), and 6.80−6.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6, 37.1, 37.2, 39.2, 40.2, 41.3, 49.0, 49.9, 53.4, 55.7, 55.9, 64.6, 67.4 110.3, 110.9, 118.9, 139.0, 147.2, and 148.3. Anal. Calcd for $C_{19}H_{27}NO_2S_2$: C, 62.44; H, 7.45; N, 3.83. Found: C, 62.41; H, 7.32; N, 3.66.

A suspension containing 0.02 g (0.05 mmol) of the above dithiolane and excess Raney nickel in 8 mL of ethanol was heated at reflux for 6 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.15 g (87%) of (±)-mesembrane (**18**)[20] as a colorless oil: IR (neat) 2936, 1525, and 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08−1.65 (m, 5H), 1.74−1.98 (m, 5H), 2.26−2.32 (m, 1H), 2.33 (s, 3H), 2.58 (brs, 1H), 3.25 (dt, 1H, $J = 9.2$ and 4.4 Hz), 3.87 (s, 3H), 3.89 (s, 3H), 6.81 (d, 1H, $J = 8.4$ Hz), and 6.89−6.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.4, 22.9, 23.7, 36.1, 40.6, 41.1, 47.5, 54.4, 55.8, 55.9, 68.7, 110.5, 110.7, 118.8, 140.3, 146.7, and 148.5. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.13; H, 9.16; N, 5.09. Found: C, 74.08; H, 9.11; N, 4.93.

3-(Benzo[1,3]dioxol-5-yl)but-3-en-1-ol (21). To a mixture containing 1.0 mL (10 mmol) of 3-bromobut-3-en-1-ol,[45] 0.35 g (0.3 mmol) of tetrakis(triphenylphosphine)palladium, 10 mL of a 2.0 M sodium carbonate solution, and 20 mL of benzene was added a slurry containing 1.8 g (11 mmol) of 3,4-methylene-dioxyphenylboronic acid (**19**) in 10 mL of ethanol. The mixture was heated at reflux for 12 h under an argon atmosphere. After cooling, the mixture was treated with 1 mL of hydrogen peroxide for 30 min. The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give 1.0 g (54%) of alcohol **21** as a yellow oil: IR (neat) 3360, 1503, 1490, and 1441 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.03 (brs, 1H), 2.73 (t, 2H, $J = 6.4$ Hz), 3.71 (t, 2H, $J = 6.4$ Hz), 5.07 (d, 1H, $J = 0.8$ Hz), 5.31 (d, 1H, $J = 0.8$ Hz), 5.96 (s, 2H), 6.77 (d, 1H, $J = 8.4$ Hz), and 6.88−6.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.9, 61.1, 101.3, 106.8, 108.3, 113.8, 119.8, 134.7, 144.4, 147.4, and 148.0. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.49; H, 6.37.

***N*-[3-(Benzo[1,3]dioxol-5-yl)but-3-enyl]-*N*-(furan-2-yl)-carbamic Acid Methyl Ester (24).** To a solution containing 1.0 g (5.4 mmol) of alcohol **21** and 0.9 mL (6.4 mmol) of triethylamine in 20 mL of dry CH_2Cl_2 was added 0.5 mL (5.9 mmol) of methanesulfonyl chloride at 0 °C. The mixture was stirred at room temperature overnight, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to give 1.4 g (95%) of crude mesylate **22**, which was used in next step reaction without further purification.

To a stirred suspension containing 0.76 g (5.4 mmol) of furan-2-ylcarbamic acid methyl ester (**23**)[26] and 2.6 g (8.0 mmol) of cesium carbonate in 4 mL of dry DMF at 60 °C was added dropwise a solution containing the above mesylate in 1 mL of dry THF. The resulting mixture was stirred at 60 °C for 12 h. The mixture was diluted with water, extracted with ether, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 1.02 g (64%) of carbamate **24** as a pale yellow oil: IR (neat) 1719, 1609, 1503, 1442, and 1300 cm^{-1}; ^1H NMR (DMSO-d_6, 70 °C, 400 MHz) δ 2.68 (t, 2H, $J = 7.6$ Hz), 3.61 (t, 2H, $J = 7.6$ Hz), 3.63 (s, 3H), 5.00 (s, 1H), 5.29 (s, 1H), 6.00 (s, 2H), 6.15 (d, 1H, $J = 3.2$ Hz), 6.43−6.47 (m, 1H), 6.84 (d, 1H, $J = 8.0$ Hz), 6.90 (dd, 1H, $J = 8.0$ and 1.6 Hz), 6.97 (d, 1H, $J = 1.6$ Hz), and 7.42 (d, 1H, $J = 1.6$ Hz); ^{13}C NMR (DMSO-d_6, 70 °C, 100 MHz) δ 33.6, 48.0, 52.7, 100.7, 101.9, 105.8, 105.9, 107.7, 110.8, 112.6, 119.0, 133.8, 138.9, 143.6, 146.6, 147.2, and 154.4. Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 65.03; H, 5.39; N, 4.47.

3a-(Benzo[1,3]dioxol-5-yl)-5-oxo-2,3,3a,4,5,6-hexahydroindole-1-carb-oxylic Acid Methyl Ester (25). A 0.6 g (1.9 mmol) sample of carbamate **24** in 10 mL of dry toluene was heated in a sealed tube under an argon atmosphere at 180 °C for 15 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.5 g (85%) of ketoenamide **25** as a pale yellow solid: mp 114−115 °C; IR (KBr) 1716, 1671, 1502, and 1386 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.07−2.15 (m, 1H), 2.25−2.30 (m, 1H), 2.70−3.03 (m, 5H), 3.24 (m, 1H), 3.78 (brs, 3H), 5.92 (s, 2H), 6.38 (brs, 1H), and 6.69−6.75 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 37.7, 38.9, 46.3, 52.7, 53.7, 60.5, 101.3, 106.9, 108.4, 119.7, 134.5, 146.9, 148.3, and 208.6. Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.46; H, 5.39; N, 4.29.

***cis*-3a,7a-(Benzo[1,3]dioxol-5-yl)-5-(2,2,2-trifluoro-ethanoyloxy)-2,3,3a,4,5,6,7,7a-octahydroindole-1-carboxylic Acid Methyl Ester (26).** A mixture containing 0.63 g (2.0 mmol) of keto-enamide **25** and 0.63 g (4.0 mmol) of bis-(*tert*-butyl)methylsilane[28] in 6 mL of trifluoroacetic acid was

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[45] Barton, T. J.; Lin, J.; Ijadi-Maghsoodi, S.; Power, M. D.; Zhang, X. *J. Am. Chem. Soc.* **1995**, *117*, 11695.

heated at reflux for 3 h under an argon atmosphere. After cooling to room temperature, the mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give a 1:10 mixture of diastereomers. The minor *trans*-isomer contained 0.05 g (6%) and exhibited the following spectral properties: IR (neat) 1782, 1699, 1450, and 1226 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.80−2.42 (m, 8H), 3.35−3.41 (m, 1H), 3.46−3.52 (m, 1H), 3.71 (brs, 3H), 4.15 (brs, 1H), 5.08 (brs, 1H), 5.95 (s, 2H), and 6.76−6.84 (m, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 22.6, 26.0, 27.9, 37.6, 44.7, 48.4, 52.6, 59.9, 74.9, 101.4, 106.7, 108.4, 114.6, 118.9, 138.1, 146.5, 148.4, 156.1, and 157.0. Anal. Calcd for $C_{19}H_{20}F_3NO_6$: C, 54.94; H, 4.85; N, 3.37. Found: C, 54.78; H, 4.91; N, 3.23.

The major *cis*-isomer contained 0.57 g (69%) and exhibited the following spectral properties: IR (neat) 1781, 1699, 1450, and 1390 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.56 (m, 2H), 1.79 (q, 1H, J = 12.0 Hz), 2.08−2.45 (m, 5H), 3.10 (m, 1H), 3.40 (m, 1H), 3.69 (d, 3H, J = 20 Hz), 4.23 (dt, 1H, J = 20 and 7.2 Hz), 5.14 (m, 1H), 5.95 (s, 2H), and 6.76−6.82 (m, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 26.5, 28.1, 33.2, 40.2, 43.4, 49.2, 52.7, 58.7, 75.1, 101.4, 106.2, 108.4, 114.5, 118.3, 139.4, 146.5, 148.3, 155.5, and 157.2. Anal. Calcd for $C_{19}H_{20}F_3NO_6$: C, 54.94; H, 4.85; N, 3.37. Found: C, 54.99; H, 4.98; N, 3.14.

***cis*-3a-(Benzo[1,3]dioxol-5-yl)-2,3,3a,4,5,6,7,7a-octahydroindole-1-carboxylic Acid Methyl Ester (28).** A mixture containing 0.54 g (1.3 mmol) of the *cis*-isomer **26** and 0.25 g of potassium carbonate in 30 mL of methanol was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure, diluted with water, and extracted with ether. The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure to give 0.4 g (95%) of *cis*-3a,7a-(benzo[1,3]-dioxol-5-yl)-5-hydroxyloctahydroindole-1-carboxylic acid methyl ester (**27**), which was used in next step without further purification.

To a solution containing a 0.16 g (0.5 mmol) sample of the above alcohol, 0.12 g (1.0 mmol) of 4-(dimethylamino)pyridine (DMAP), and 0.2 mL (1.5 mmol) of triethylamine in 9 mL of CH$_2$Cl$_2$ was added a solution of 0.15 g (0.89 mmol) of phenyl chlorothionocarbonate in 1 mL of CH$_2$Cl$_2$.[29] The mixture was stirred at room temperature for 4 h and then poured into a mixture of 10 mL of a 2 M Na$_2$CO$_3$ aqueous solution and 20 mL of CH$_2$Cl$_2$. After phase separation, the aqueous phase was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was taken up in 10 mL of dry benzene, and then 0.27 mL of tributyltin hydride and 20 mg of AIBN were added under an argon atmosphere. The mixture was heated at reflux for 2 h, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.1 g (67%) of carbamate **28** as a colorless oil: IR (neat) 1698, 1488, 1451, and 1390 cm^{-1}; ^{1}H NMR (DMSO-d_6, 60 °C, 400 MHz) δ 1.38−1.61 (m, 5H), 1.90−2.02 (m, 3H), 2.28−2.36 (m, 1H), 3.02 (q, 1H, J = 8.4 Hz), 3.20 (s, 1H), 3.31 (t, 1H, J = 8.4 Hz), 3.54 (s, 3H), 4.40 (dd, 1H, J = 9.2 and 6.0 Hz), 5.96 (s, 2H), 6.82 (s, 2H), and 6.97 (s, 1H); ^{13}C NMR (DMSO-d_6, 60 °C, 100 MHz) δ 21.5, 22.5, 27.5, 31.7, 35.4, 42.9, 47.2, 51.5, 59.7, 100.6, 106.3, 107.6, 118.1, 141.3, 145.1, 147.3, and 154.1. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.29; H, 6.98; N, 4.62. Found: C, 67.33; H, 6.81; N, 4.72.

(±)-Crinane (30). To a solution containing 0.08 g (0.26 mmol) of carbamate **28** in 2 mL of ethylene glycol was added a solution containing 0.15 g (2.6 mmol) of potassium hydroxide in 1 mL of water. The resulting mixture was heated at reflux for 24 h, cooled to room temperature, diluted with water, extracted with chloroform, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH$_2$Cl$_2$/NEt$_3$/MeOH 20:2:2) to give 0.05 g (78%) of *cis*-3a-(benzo-[1,3]dioxol-5-yl)octahydroindole (**29**)[30] as a yellow oil: IR (neat) 3346, 1506, 1488, and 1232 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.22−2.05 (m, 10H), 2.97 (dt, 1H, J = 11.1 and 4.5 Hz), 3.11 (m, 1H), 3.34 (brs, 1H), 5.92 (s, 2H), 6.75 (d, 1H, J = 8.1 Hz), 6.81 (d, 1H, J = 8.1 Hz), and 6.87 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 21.3, 22.3, 26.4, 34.0, 41.4, 43.2, 48.1, 61.1, 100.9, 107.6, 107.8, 119.4, 140.7, 145.3, and 147.6. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.43; H, 7.81; N, 5.71. Found: C, 73.41; H, 7.71; N, 5.52. The HCl salt was also prepared and exhibited the same spectral features as described in the literature:[30] ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.20 (m, 1H), 1.61 (brs, 2H), 1.81 (t, 1H, J = 13.6 Hz), 1.91−2.19 (m, 6H), 3.43 (brs, 1H), 3.67 (m, 1H), 4.02 (brs, 1H), 5.97 (s, 2H), 6.73−6.80 (m, 3H), 9.33 (brs, 1H), and 10.34 (brs, 1H).

A solution of 0.03 g (0.12 mmol) of amine **29** in 8 mL of THF was treated with 0.035 g (0.18 mmol) of Eschenmoser's salt according to the procedure of Keck[30] to give (±)-crinane **30** in 87% yield.

2-Isopropenylhex-5-enoic Acid Ethyl Ester (36). To 100 mL (80 mmol) of a LDA solution (0.8 M in THF) was added 14 mL (80 mmol) of anhydrous hexamethylphosphoramide (HMPA) at −78 °C, followed by the dropwise addition of 8.6 g (67 mmol) of ethyl 3-methyl-2-butenoate (**35**) in 10 mL of THF. After stirring for 15 min, the mixture was treated with 10 g (74 mmol) of 4-bromo-1-butene at −78 °C. The resultant mixture was stirred at −78 °C for 1 h and was allowed to warm to room temperature. The mixture was quenched with a saturated NH$_4$Cl solution, diluted with water, and extracted with ether. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was distilled under vacuum to give 10 g (82%) of **36** as a colorless oil: bp 78−81 °C (5 mm) (lit.[44] 85−87 °C (10 mm); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.23 (t, 3H, J = 6.8 Hz), 1.64−1.67 (m, 1H), 1.73 (s, 3H), 1.87−1.92 (m, 1H), 1.98 (q, 2H, J = 6.8 Hz), 3.02 (t, 1H, J = 7.2 Hz), 4.12 (q, 2H, J = 6.8 Hz), 4.86−5.02 (m, 4H), and 5.73−5.80 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.2, 20.1, 29.1, 31.4, 52.3, 60.4, 113.8, 115.2, 137.7, 142.3, and 173.5.

5-Bromomethyl-1-methylcyclopentene (38). To a degassed solution of 3.5 g (4.0 mmol) of bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride[38] in 3 L of dry CH$_2$Cl$_2$ at room temperature was added 3.0 g (16 mmol) of **36** under an argon atmosphere. The mixture was stirred at room temperature for 18 h, and the solvent was removed under reduced pressure. The residue was distilled to give 1.6 g (63%) of ethyl 2-methyl-2-cyclopent-ene-1-carboxylate (**37**)[46] as a colorless oil: IR (neat) 2954, 1730, 1445, 1161 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.25 (t, 3H, J = 7.2 Hz), 1.72 (s, 3H), 2.12−2.16 (m, 2H), 2.22−2.34 (m, 1H), 2.38−2.50 (m, 1H), 3.31 (m, 1H), 4.08−4.18 (m, 2H), and 5.49 (t, 1H, J = 2.0 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.3, 15.2, 28.3, 31.6, 53.9, 60.3, 128.4, 137.6, and 175.0. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.27; H, 9.23.

A solution containing 5.6 g (36 mmol) of ester **37** in 50 mL of dry ether at 0 °C was treated with 1.4 g (36 mmol) of lithium aluminum hydride portionwise. The mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature, and then stirred for an additional 30 min. The mixture was treated with a 2 N NaOH solution until gas evolution had ceased. The solution was washed with a saturated NH$_4$Cl solution, and the organic layer was separated, washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography gave 3.7 g (91%) of (2-methyl-2-cyclopentenyl)methanol as a colorless oil: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.37 (brs, 1H), 1.71 (s, 3H), 1.72−1.80 (m, 1H), 2.03 (m, 1H), 2.17−2.37 (m, 2H), 2.63 (brs, 1H), 3.62 (m, 2H), and 5.47 (brs, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.9, 27.2, 31.1, 50.7, 64.5, 127.6, and 139.2.

To a solution of 3.8 g (34 mmol) of the above alcohol in 50 mL of CH$_2$Cl$_2$ at 0 °C was added 5.2 mL (37 mmol) of triethylamine followed by 2.9 mL (37 mmol) of methanesulfonyl chloride. The mixture was stirred at 0 °C for 5 h, and then water was added. The organic layer was separated, and the aqueous layer was extracted with ether. The combined ethereal extracts were dried over MgSO$_4$, and the solvent was removed under reduced pressure to give 6.4 g (98%) of 2-methyl-2-cyclopentenyl methanesulfonate, which was used in the next step without further purification: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.71 (s, 3H), 1.73 (m, 1H), 2.08 (m, 2H), 2.22 (m, 2H), 3.00

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(46) For the related methyl ester, see: Martin, S. F.; Li, W. *J. Org. Chem.* **1991**, *56*, 642.

(s, 3H), 4.09 (dd, 1H, J = 9.4 and 6.8 Hz), 4.25 (dd, 1H, J = 9.4 and 4.8 Hz), and 5.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.9, 27.3, 30.6, 37.2, 47.7, 71.6, 128.2, and 137.8.

A solution containing 6.4 g (34 mmol) of the above mesylate in 70 mL of acetone was treated with 8.8 g (102 mmol) of lithium bromide. The mixture was heated at reflux for 6 h, cooled to room temperature, diluted with water, and extracted with ether, and the combined ethereal extracts were dried over $MgSO_4$. Removal of the solvent under reduced pressure gave 4.6 g (78%) of 5-bromomethyl-1-methylcyclopentene (**38**), which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.69 (s, 3H), 1.77 (m, 1H), 2.02−2.36 (m, 3H), 2.95 (brs, 1H), 3.35 (dd, 1H, J = 10.0 and 7.2 Hz), 3.55 (dd, 1H, J = 10.0 and 3.2 Hz), and 5.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 29.2, 30.5, 38.0, 50.1, 127.8, and 139.5.

***tert*-Butyl *N*-[(2-Methyl-2-cyclopentyl)methyl]-*N*-(2-furyl) Carbamate (40).** A mixture containing 1.1 g (6.3 mmol) of *N*-(furan-2-yl)carbamic acid *tert*-butyl ester (**39**),[26] 0.9 g (22 mmol) of powdered sodium hydroxide, 1.7 g (13 mmol) of potassium carbonate, and 0.2 g (0.6 mmol) of tetrabutylammonium hydrogen sulfate in 60 mL of benzene was heated at reflux for 20 min, and then 1.1 g (6.3 mmol) of bromide **38** was added dropwise to this mixture. The resulting mixture was maintained at reflux for an additional 2 h, quenched with water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 1.4 g (79%) of carbamate **40** as a colorless oil: IR (neat) 2975, 1716, 1374, and 1168 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H), 1.64 (m, 1H), 1.66 (s, 3H), 1.94 (m, 1H), 2.13 (m, 1H), 2.18 (m, 1H), 2.62 (brs, 1H), 3.41 (dd, 1H, J = 13.6 and 9.6 Hz), 3.73 (dd, 1H, J = 13.6 and 4.4 Hz), 5.37 (s, 1H), 6.00 (brs, 1H), 6.33 (dd, 1H, J = 3.2 and 2.0 Hz), and 7.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 28.1, 28.4, 30.5, 47.7, 51.4, 80.9, 101.4, 110.8, 126.4, 126.5, 138.8, 140.6, and 148.6. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.16; H, 8.47; N, 5.00.

7b-Methyl-5-oxo-2,2a,3,4,4a,5,6,7b-octahydro-1-aza-cyclopenta[*cd*]-indene-1-carboxylic Acid *tert*-Butyl Ester (43). A solution of 1.1 g (0.56 mmol) of furan **40** in 12 mL of toluene was heated in a sealed tube at 165 °C for 12 h under an argon atmosphere. After cooling to room temperature, the solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give 0.82 g (78%) of ketoenamide **43** as a pale yellow solid: mp 117−118 °C; IR (neat) 2974, 1709, 1364, and 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (s, 3H), 1.33 (m, 1H), 1.46 (s, 9H), 1.84 (m, 2H), 1.97 (m, 1H), 2.22 (m, 1H), 2.55 (m, 1H), 2.76 (dd, 1H, J = 20.0 and 6.8 Hz), 3.06 (dd, 1H, J = 20.0 and 2.4 Hz), 3.48 (d, 1H, J = 11.2 Hz), 3.72 (dd, 1H, J = 11.2 and 5.6 Hz), and 5.65 (d, 1H, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 27.2, 27.7, 30.3, 36.1, 45.5, 52.2, 54.6, 57.0, 79.7, 95.9, 143.4, 151.7, and 210.2. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.40; H, 8.37; N, 5.04.

4-Isopropylfuran-2-carbaldehyde. To a suspension containing 200 g (1.5 mol) of aluminum chloride in 1.0 L of carbon disulfide was added 120 g (1.3 mol) of 2-furaldehyde. To the mixture was added dropwise 103 mL (1.3 mol) of isopropyl chloride, and the resulting solution was stirred at room temperature for 24 h. The dark mixture was carefully poured over 2 kg of ice, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and saturated $NaHCO_3$ solution, dried over Na_2SO_4, filtered through a pad of silica gel, and concentrated under reduced pressure. The residue was distilled under vacuum to give 27 g (20%) of 4-isopropyl-furan-2-carbaldehyde as a yellow oil: bp 85−86 °C (10 mm) (lit.[47] 101−103 °C (21 mm)); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, 6H, J = 6.9 Hz), 2.85 (m, 1H), 7.17 (s, 1H), 7.47 (s, 1H), and 9.60 (s, 1H).

4-Isopropylfuran-2-carboxylic Acid (44). To a suspension containing 50 g (0.29 mol) of silver nitrate in 150 mL of 50% ethanol was added a solution of 18 g (0.13 mol) of the above aldehyde in 80 mL of ethanol, followed by the dropwise addition of 12 g (0.3 mol) of NaOH in 50 mL of water. During the addition, the internal temperature was maintained at 40−50 °C. The mixture was stirred at room temperature for 12 h, and the resulting suspension was filtered through a pad of Celite. After removal of the ethanol under reduced pressure, the aqueous layer was washed with ether, acidified with 1 M HCl, and extracted with ether. Removal of the solvent under reduced pressure afforded 19 g (95%) of **44** as a pale yellow solid: mp 75−76 °C (lit.[40] mp 76−77 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, 6H, J = 6.9 Hz), 2.83 (m, 1H), 7.26 (s, 1H), 7.41 (s, 1H), and 10.03 (brs, 1H).

4-Isopropylfuran-2-ylcarbamic Acid *tert*-Butyl Ester (45). A solution containing 2.0 (13 mmol) of furan **44**, 3.6 mL (26 mmol) of triethylamine, and 5.6 mL (26 mmol) of diphenylphosphoryl azide in 40 mL of *tert*-butyl alcohol was heated at reflux for 12 h. After cooling, the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 2.4 g (83%) of carbamate **45** as a pale yellow oil: IR (KBr) 3281, 1702, 1547, and 1157 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (d, 6H, J = 6.8 Hz), 1.50 (s, 9H), 2.71 (m, 1H), 6.00 (brs, 1H), 6.62 (brs, 1H), and 6.80 (t, 1H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 22.8, 25.3, 28.2, 44.7, 130.4, 134.0, 145.3, and 151.7. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 69.98; H, 8.50; N, 6.21. Found: C, 69.84; H, 8.25; N, 6.04.

***N*-[(2-Methyl-2-cyclopentyl)methyl]-*N*-(4-isopropylfuran-2-yl)carbamic Acid *tert*-Butyl Ester (46).** A 2.3 g (10 mmol) sample of carbamate **45**, 3.3 g (10 mmol) of tetrabutylammonium bromide, and 2.1 g (12 mmol) of bromide **38** in 25 mL of CH_2Cl_2 at 0 °C was treated dropwise with 10 mL of a 50% NaOH solution. The mixture was heated at reflux for 14 h, cooled to room temperature, and diluted with water, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 2.3 g (71%) of **46** as a pale yellow oil: IR (neat) 3080, 2964, 1704, and 1545 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 1H, J = 2.8 Hz), 1.17 (d, 6H, J = 6.8 Hz), 1.26 (m, 6H), 1.46 (s, 9H), 1.67 (s, 3H), 2.68 (m, 1H, J = 6.8 Hz), 5.28 (s, 1H), 5.95 (brs, 1H), and 6.97 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.9, 21.1, 22.8, 25.3, 27.3, 28.2, 28.3, 31.1, 44.7, 50.6, 127.6, 130.4, 134.0, 139.2, 145.3, and 151.7. Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.28; H, 9.09; N, 4.30.

3-(*tert*-Butoxycarbonyl)-6-isopropyl-11-methyl-3-aza-tricyclo[6.2.1.0^{4,11}]-undec-4-en-7-one (47). A 1.0 g (3.1 mmol) sample of carbamate **46** in 10 mL of toluene was heated in a sealed tube under an argon atmosphere at 165 °C for 15 h. After cooling to room temperature, the solution was concentrated under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.74 g (74%) of **47** as a pale yellow oil, which consisted of a 2:1 mixture of diastereomers that proved to be inseparable: IR (KBr) 2968, 1709, 1381, and 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) major δ 0.77 (d, 3H, J = 6.8 Hz), 0.92 (d, 3H, J = 6.8 Hz), 1.22 (s, 3H), 1.42 (s, 9H), 1.70−1.90 (m, 3H), 2.16 (m, 2H), 2.50 (m, 2H), 2.83 (dd, 1H, J = 4.8 and 2.4 Hz) 3.43 (d, 1H, J = 11.2 Hz) 3.68 (dd, 1H, J = 11.2 and 6.0 Hz), and 5.59 (s, 1H); ^{1}H NMR ($CDCl_3$, 400 MHz) minor δ 0.76 (d, 3H, J = 6.8 Hz), 0.91 (d, 3H, J = 6.8 Hz), 1.08 (s, 3H), 1.42 (s, 9H), 1.90−2.02 (m, 3H), 2.25 (m, 2H), 2.50 (m, 2H), 2.71 (t, 1H, J = 5.2 Hz), 3.40 (d, 1H, J = 11.2 Hz), 3.65 (dd, 1H, J = 11.2 and 6.0 Hz), and 5.70 (d, 1H, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) major δ 18.0, 20.1, 21.1, 26.7, 27.7, 30.1, 46.1, 50.0, 51.8, 56.5, 58.0, 79.7, 97.9, 142.5, 144.4, 151.7, and 210.1; ^{13}C NMR ($CDCl_3$, 100 MHz) minor δ 18.7, 20.1, 23.1, 26.1, 27.7, 28.3, 30.1, 46.1, 50.8, 51.7, 54.2, 79.5, 97.7, 100.8, 144.4, 151.7, and 211.5. Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.38; H, 9.18; N, 4.36.

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[47] (a) Gilman, H.; Calloway, N. O. *J. Am. Chem. Soc.* **1933**, *55*, 4197. (b) Gilman, H.; Calloway, N. O. *J. Am. Chem. Soc.* **1935**, *57*, 906. (c) Divald, S.; Chun, M. C.; Joullie, M. M. *J. Org. Chem.* **1976**, *41*, 2835.

7-Benzyloxy-3-(*tert*-butoxycarbonyl)-6-isopropyl-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]undecan-5-ol (48). To a solution containing 0.15 g (0.47 mmol) of ketoenamide **47** in 10 mL of methanol was added an aqueous solution containing 0.02 g (0.47 mmol) of sodium borohydride in 1 mL of water at 0 °C. The mixture was allowed to warm to room temperature and was maintained at that temperature for 1 h. The mixture was concentrated under reduced pressure, diluted with water, and extracted with ether. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure to give 0.14 g (93%) of crude 3-(*tert*-butoxycarbonyl)-6-isopropyl-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]undec-4-en-7-ol as a yellow oil, which was used in next step without further purification.

The above 2:1 mixture of alcohols was taken up into 5 mL of dry THF, and the resulting solution was added dropwise to a stirred suspension containing 0.02 g (0.94 mmol) of sodium hydride in 5 mL of dry THF at 0 °C. After 15 min of stirring, 0.17 g (0.47 mmol) of tetrabutylammonium iodide and 0.1 g (0.6 mmol) of benzyl bromide were added to the yellow mixture. The resulting mixture was heated at reflux for 20 h, cooled to room temperature, and quenched by the slow addition of water. The mixture was extracted with ether, and the combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure to give 7-benzyloxy-3-(*tert*-butoxycarbonyl)-6-iso-propyl-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]undec-4-ene as a pale yellow oil that was used in the next step reaction without further purification.

The above oil was taken up in 5 mL of dry THF and 0.5 mL (0.5 mmol) of a 1.0 M borane/THF solution was added at 0 °C under an argon atmosphere. The mixture was allowed to stir at room temperature for 4 h and cooled to 0 °C, and then 0.9 mL of a 3.0 M NaOH aqueous solution was added dropwise to destroy the excess borane, followed by 1 mL of a 30% hydrogen peroxide solution. The resulting mixture was stirred at 50 °C for 2 h, cooled to room temperature, diluted with water, extracted with ether, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.08 g (40%) of the major diastereomer and 0.04 g (20%) of the minor stereoisomer as a pale yellow oils. The major stereoisomer **48a** exhibited the following spectral properties: IR (neat) 3402, 1666, 1403, 1365, and 1110 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.99 (d, 3H, J = 7.2 Hz), 1.07 (d, 3H, J = 7.2 Hz), 1.26 (s, 3H), 1.48 (s, 9H), 1.54−2.25 (m, 8H), 2.94 (dd, 1H, J = 10.8 and 7.2 Hz), 3.54−3.59 (m, 1H), 3.64 (d, 1H, J = 3.6 Hz), 3.84 (brs, 1H), 4.14−4.60 (m, 4H), and 7.23−7.34 (m, 5H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 19.4, 21.6, 27.3, 27.4, 28.2, 28.6, 28.7, 33.7, 49.0, 51.0, 51.6, 51.9, 52.2, 72.5, 73.4, 74.7, 79.7, 126.4, 127.1, 128.3, 139.2, and 156.1; HRMS calcd for C$_{26}$H$_{39}$NO$_4$ + Li 436.3039, found 436.3020.

The minor stereoisomer **48b** exhibited the following spectral properties: IR (neat) 3400, 1666, 1403, 1365, and 1112 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.87 (d, 3H, J = 6.4 Hz), 1.00 (d, 3H, J = 6.4 Hz), 1.37 (s, 3H), 1.47 (s, 9H), 1.28−1.82 (m, 5H), 2.10−2.34 (m, 3H), 2.76 (dd, 1H, J = 11.6 and 8.8 Hz), 3.76−3.85 (m, 3H), 4.34 (d, 1H, J = 11.6 Hz), 4.40 (s, 2H), 4.71 (d, 1H, J = 11.6 Hz), and 7.27−7.34 (m, 5H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 21.1, 21.2, 24.7, 28.0, 28.7, 31.1, 33.7, 41.3, 47.3, 48.0, 51.8, 52.4, 69.4, 70.2, 71.8, 79.2, 79.8, 127.9, 128.1, 128.7, 137.7, and 154.7; HRMS calcd for C$_{26}$H$_{39}$NO$_4$ + Li 436.3039, found 436.3028.

3-(*tert*-Butoxycarbonyl)-6-isopropyl-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]-undec-6-en-5-one (50). To a solution containing 0.06 g (0.14 mmol) of **48a** in 5 mL of dry CH$_2$Cl$_2$ was added 0.07 g (0.17 mmol) of Dess−Martin's periodinane, and the mixture was stirred at room temperature for 4 h. To this solution was added 1 mL of a 3 M NaOH aqueous solution, and the resulting mixture was stirred at room temperature for 1 h. The mixture was diluted with water and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure to give 7-benzyloxy-3-(*tert*-butoxycarbonyl)-6-isopropyl-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]undecan-5-one (**49**) as a pale yellow oil, which was used in the next step reaction without further purification: IR (neat) 1734, 1702, 1450, and 1397 cm^{-1}.

A mixture containing ketone **49** and 0.2 g of 5% palladium on charcoal in 5 mL of ethyl acetate was stirred under a hydrogen atmosphere overnight. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give 7-hydroxy-3-(*tert*-butoxycarbonyl)-6-isopropyl-11-methyl-3-azatri-cyclo[6.2.1.0^{4,11}]undecan-5-one as a colorless oil, which was used in the next step reaction without further purification: IR (neat) 3509, 1728, 1699, and 1371 cm^{-1}.

To a solution containing the above alcohol and 0.06 g (0.56 mmol) of triethylamine in 5 mL of dry CH$_2$Cl$_2$ was added 0.03 g (0.28 mmol) of methanesulfonyl chloride at 0 °C. The mixture was stirred at room temperature for 12 h and then heated at reflux for 2 h. The cooled mixture was diluted with water and extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.02 g (52%) of enone **50** as a colorless oil: IR (neat) 2961, 1703, 1391, 1365, and 1173 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.00 (d, 3H, J = 8.8 Hz), 1.05 (d, 3H, J = 8.8 Hz), 1.20−1.28 (m, 1H), 1.32 (s, 3H), 1.46 (s, 9H), 1.60 (s, 1H), 1.67−1.79 (m, 1H), 2.02−2.57 (m, 3H), 2.84 (pent, 1H, J = 8.0 Hz), 2.99 (dd, 1H, J = 15.2 and 6.8 Hz), 3.71 (t, 1H, J = 9.6 Hz), 3.85 (brs, 1H), and 6.31 (dd, 1H, J = 6.8 and 2.0 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 22.1, 27.9, 28.6, 29.4, 30.4, 35.2, 44.7, 49.6, 79.7, 140.5, 144.6, 155.3, and 198.0. Anal. Calcd for C$_{19}$H$_{29}$NO$_3$: C, 71.43; H, 9.16; N, 4.39. Found: C, 71.25; H, 9.08; N, 4.49.

6-Isopropyl-3,11-dimethyl-3-azatricyclo[6.2.1.0^{4,11}]undec-6-en-5-one (33). To a solution containing 0.02 g (0.07 mmol) of enone **50** in 1 mL of dry CH$_2$Cl$_2$ was added 0.2 mL of trifluoroacetic acid (TFA). The mixture was stirred at room temperature for 2 h, and the solvent was removed under reduced pressure. The residue was taken up into 1 mL of dry DMF, and 0.2 g (1.4 mmol) of potassium carbonate and 0.1 g (0.7 mmol) of iodomethane were added. The resulting mixture was stirred at room temperature for 4 h, diluted with water, and extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.01 g (65%) of Kende's intermediate **33**[34c] as a colorless oil: IR (neat) 1669, 1368, 1260, and 1092 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.01 (d, 3H, J = 7.2 Hz), 1.06 (d, 3H, J = 7.2 Hz), 1.18 (s, 3H), 1,60−2.00 (m, 4H), 2.14 (s, 3H), 2.14−2.23 (m, 1H), 2.28 (s, 1H), 2.30−2.39 (m, 1H), 2.47 (t, 1H, J = 8.8 Hz), 2.76 (d, 1H, J = 8.8 Hz), 2.84−2.94 (m, 1H), and 6.46 (d, 1H, J = 4.8 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 21.3, 22.0, 26.4, 26.8, 33.8, 34.1, 41.3, 48.2, 50.2, 53.4, 64.6, 79.9, 141.0, 142.0, and 199.2; HRMS calcd for C$_{15}$H$_{23}$NO 233.1780, found 233.1782.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for new compounds lacking elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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