Construction of Carbocyclic Arrays Containing Nitrogen via Intramolecular Imino Diels−Alder Reactions in Polar Media. A Comparative Study: 5.0 M Lithium Perchlorate−Diethyl Ether versus Water

Paul A. Grieco*,[1a] and Michael D. Kaufman[1b]

Department of Chemistry and Biochemistry, Montana State University, Bozeman, Montana 59717, and Department of Chemistry, Indiana University, Bloomington, Indiana 47405

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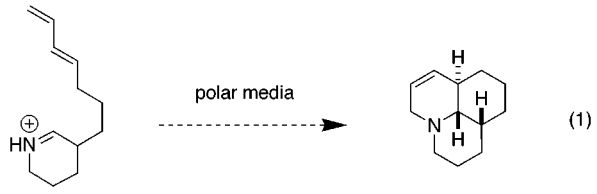
The intramolecular Diels−Alder reaction of iminium ions has been examined in polar media such as 5.0 M lithium perchlorate−diethyl ether and water. Cycloaddition of **3** in 5.0 M lithium perchlorate−diethyl ether containing 10 mol % camphorsulfonic acid proceeds, not by in situ generation of iminium ion **1**, but rather via *N*-(acyloxy)iminium ion **7** which subsequently cyclizes to tricyclic compounds **4** and **5**. Direct formation of imines **15** and **30** was realized by reduction of the corresponding lactams (**13** and **29**, respectively) followed by exposure to 2.0 equiv of tetra-*n*-butylammonium fluoride. Exposure of the trifluoroacetic acid salt **18** of imine **15** to 5.0 M lithium perchlorate−diethyl ether at ambient temperature gave rise to tricyclic amine **16** in which the diene underwent isomerization prior to [4+2] cycloaddition. In contrast, use of water provided tricyclic amine **19**. Similarly, exposure of iminium salt **31** to water afforded tricyclic amine **32**. The polar sovent of choice for intramolecular imino Diels−Alder reactions employing substrates such as **18** and **31** is water.

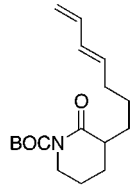
As an extension of our continued interest in solvent effects on chemical reactivity and selectivity,[2] we set out to examine the intramolecular [4+2] cycloaddition of iminium ion **1** in 5.0 M lithium perchlorate−diethyl ether in hopes of generating carbocyclic arrays containing nitrogen (cf. **2**) for use in alkaloid synthesis. We detail below the results of this investigation wherein both concentrated solutions of lithium perchlorate[3] in diethyl ether[4] and water were independently employed as polar media to effect transformations of the type illustrated in eq 1.



1 **2** (1)

Our preliminary efforts focused on examining substrate **3** as the precursor to iminium ion **1**. It was anticipated[5] that upon exposure of **3** to 5.0 M lithium perchlorate−diethyl ether containing 10 mol % camphorsulfonic acid, **3** would suffer loss of isobutylene and carbon dioxide, and give rise to protonated imine **1**. In an initial experiment, a 0.01 M solution of **3**[6] in 5.0 M $LiClO_4 \cdot Et_2O$ was exposed (ambient temperature, 2 h) to 10 mol % camphorsulfonic acid (CSA) (1.5 M in THF). Much to our surprise, none of the expected tricyclic amine **2** was isolated. Chromatography afforded a 63% yield of cycloadducts **4** and **5** in a ratio of ca. 5:1, accompanied by enamide **6**. Reexposure of **6** to 5.0 M $LiClO_4 \cdot Et_2O$ containing 10 mol % CSA provided after 26 h a 28% yield of **4** and **5** in a ratio of 4:1 along with recovered **6** (55%).

The structures assigned to cycloadducts **4** and **5** were confirmed by examination of their respective ^1H NMR spectra and extensive decoupling experiments. The results clearly reveal that cyclization of **3** proceeds, not by in situ generation of iminium ion **1**, but rather by



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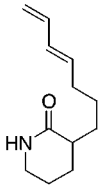

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(6) Substrate **3** was prepared via a one-pot procedure. Treatment of δ-valerolactone with 2.0 equiv of *n*-butyllithium followed by sequential addition of 1-iodo-hepta-4(*E*),6-diene (**33**) and di-*tert*-butyl dicarbonate provided lactam **34** (see the Experimental Section).

* To whom correspondence should be addressed.

(1) (a) Montana State University. (b) Indiana University.

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(5) We had previously observed that exposure of *N*-BOC lactam **34**[6] to 3.0 M lithium perchlorate in diethyl ether containing 10 mol % trifluroacetic acid gave rise to lactam **35** in 55% yield.

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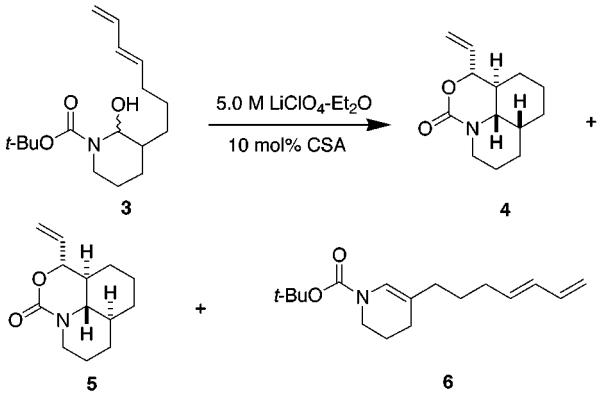
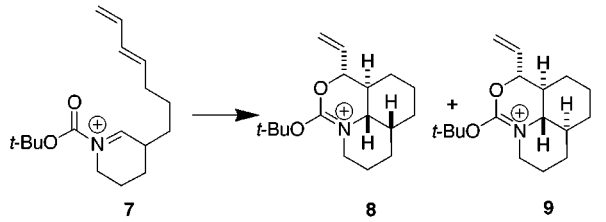


formation of the *N*-(acyloxy)iminium ion **7** and subsequent cyclization to dihydrooxazines **8** and **9** which give rise to **4** and **5**, respectively.[7]



The observance of the two diastereomeric cycloadducts **4** and **5**, derived from **8** and **9**, respectively, is of significance and suggests that the cycloaddition process is concerted. The selective formation of **4** and **5** with the complete exclusion of cycloadducts **10** and **11** can be

rationalized by transition-state analysis of *N*-(acyloxy)-iminium ion **7**. In the favored transition states leading to the observed products **4** and **5**, the carbon tethers can clearly adopt chairlike arrangements, thus minimizing nonbonded interactions (Figure 1). In contrast, the transition states leading to **10** and **11** necessitate that the carbon tethers adopt boatlike conformations possessing serious interactions (Figure 2).

At this point, the effect of decreasing the concentration of lithium perchlorate in diethyl ether was examined. It was hoped that a reduction in the solvent polarity would accelerate the formation of iminium ion **1** relative to *N*-(acyloxy)iminium ion **7**. Unfortunately, decreasing the concentration of lithium perchlorate in diethyl ether served to only increase the formation of **6** at the expense of **4** and **5** (Table 1). Once again, cycloadducts **10** and **11** were not detected.

To circumvent the problems associated with the cyclization of **7**, we set out to replace the BOC group of **3** with the fluoride labile β-trimethylsilylethoxycarbonyl (TEOC)[8] protecting group. In addition, to avoid potential

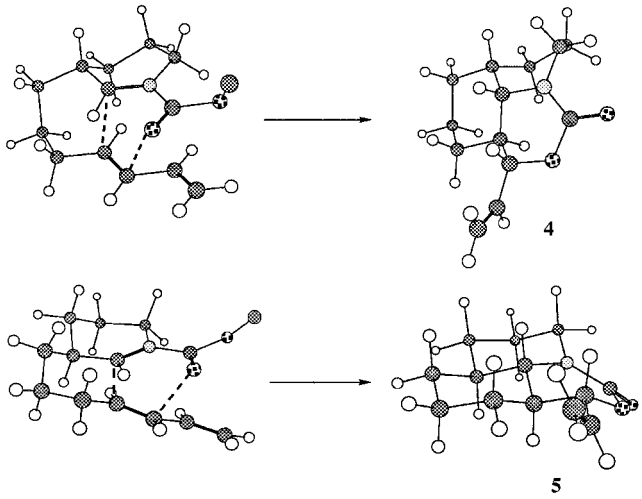


Figure 1. Favorable transition states in [4+2] cycloaddition of *N*-(acyloxy)iminium ion **7**.

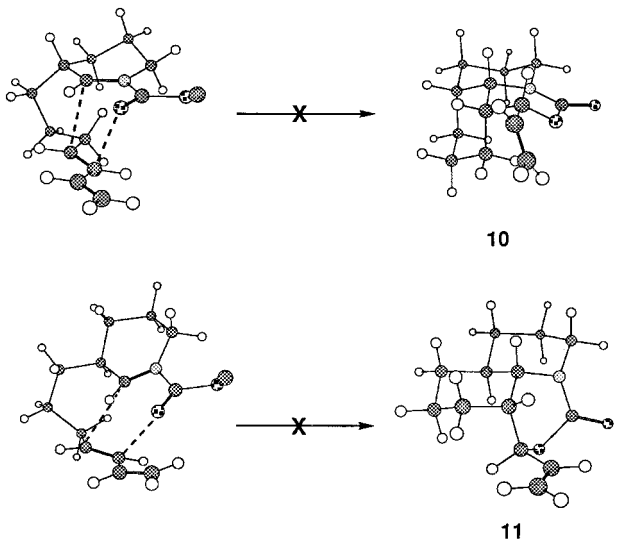


Figure 2. Disfavored transition states in [4+2] cycloaddition of *N*-(acyloxy)iminium ion **7**.

Table 1. Cycloaddition of *N*-(Acyloxy)iminium Ion 7[a]

		yield (%)[b]		
solvent	catalyst	**4**	**5**	**6**
3.0 M $LiClO_4 \cdot Et_2O$	10 mol % CSA	35	8	51
4.0 M $LiClO_4 \cdot Et_2O$	10 mol % CSA	44	11	44
5.0 M $LiClO_4 \cdot Et_2O$	10 mol % CSA	52	11	28

[a] All reactions were carried out at 0.01 M in the indicated solvent for 2 h. [b] Isolated yields.

complications due to imine−enamine tautomerization, the carbon atom adjacent to the imine carbon atom was quaternized. Thus, the dianion derived from 3-methyl-2-piperidone was alkylated with 1-iodo-hepta-4(*E*),6-diene, giving rise to lactam **12** in 61% yield. Subsequent introduction of the TEOC group employing 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate[9] provided **13** in 91% yield. Reduction [$Li(Et)_3BH$, −78 °C] of **13** afforded (98%) **14** as a 1:1 mixture of epimers. Exposure of **14** to 2.0 equiv of tetra-*n*-butylammonium fluoride provided, after chromatography, imine **15** as a colorless liquid in 83% yield.

(7) For an intermolecular *N*-(acyloxy)iminium ion−olefin cycloaddition, see: Ben-Ishai, D.; Hirsch, S. *Tetrahedron Lett.* **1983**, *24*, 955. For an intramolecular example see: Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447.

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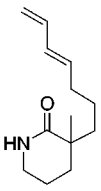

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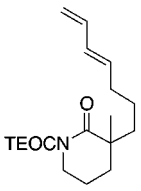

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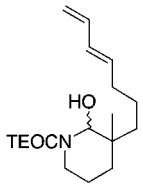

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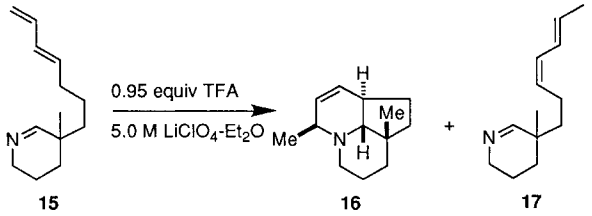
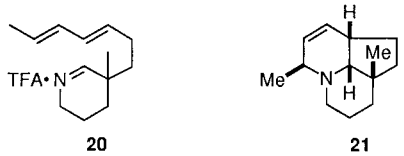
With the availability of imine **15**, the stage was set to examine the intramolecular cycloaddition. Thus, a 0.01 M solution of **15** in 5.0 M $LiClO_4$·Et_2O was treated at ambient temperature with 0.95 equiv of trifluoroacetic acid (TFA). Workup provided a 53% yield of a 1:1 mixture of the cyclized material **16** and the isomerized diene **17** which contained approximately 25% of imine **15**. When the preformed iminium salt **18** was exposed to 5.0 M $LiClO_4$·Et_2O, a 1:1 mixture of **16** and **17** was obtained in comparable yield. The anticipated cycloadduct **19** was not detected in either case.



15 **16** **17**

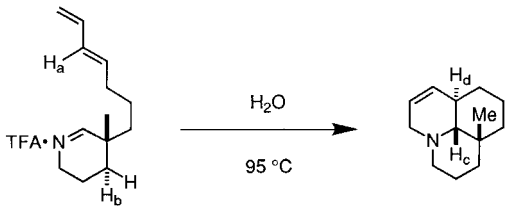
18 **19**

The formation of **16** undoubtedly arises from migration of the terminal diene, giving rise to **20** which undergoes a concerted cycloaddition. Cycloadduct **16** cannot arise from the TFA salt of diene **17** via a concerted process. While the formation of **16** from the TFA salt of **17** by way of a stepwise cycloaddition featuring discrete carbocation intermediates cannot be completely ruled out, the lack of products derived from "stepwise intermediates" and the stereochemical homogeniety of **16** lend no support to this hypothesis. A more reasonable proposal is that iminium ion **18** in highly polar media such as 5.0 M $LiClO_4$·Et_2O undergoes facile isomerizatiuon to a mixture of **20** and the TFA salt of imine **17**. Intermediate **20** undergoes [4+2] cycloaddition via a concerted process. In principle, the TFA salt of **17** can undergo a concerted cycloaddition, albeit via a highly strained transition state, to tricyclic amine **21**. However, we could not detect **21** in the crude reaction mixture.



20 **21**

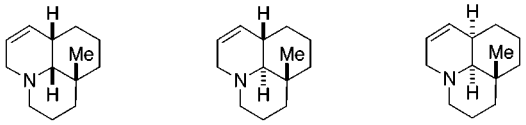
It is clear from these results that diene **18** is not electron rich enough to facilitate cycloaddition at ambient temperature in 5.0 M $LiClO_4$·Et_2O at a rate which is competitive with acid-catalyzed diene isomerization. The more rapid cyclization of **20** versus **18** can be rationalized both on entropic (five- versus six-membered ring formation) as well as on electronic (more electron-rich nature of the isomerized diene) grounds. To avoid the problems associated with migration of the terminal diene due to the enhanced acidity of normally weak acids in highly polar media such as 5.0 M $LiClO_4$·Et_2O, we set out to investigate the [4+2] cycloaddition of **18** in an aqueous medium.[4] No cycloaddition was observed upon prolonged standing of a 0.02 M solution of **18** in water at ambient temperature. In contrast, heating (95 °C) a 0.02 M solution of **18** in water for 38 h gave rise to a 55% yield of **19** along with 18% recovered imine.



18 **19**

The structure of **19** was confirmed by analysis of its ^1H NMR spectrum. The central methine proton H_c appears as a doublet (J = 10.6 Hz) which is coupled to the allylic methine proton H_d. This large coupling constant is only consistent with a trans-diaxial relationship for these two protons. The syn relationship between H_c and the angular methyl group was confirmed by the observance of a strong (9.7%) NOE enhancement of H_c upon irradiation of the angular methyl group.

The exclusive formation of **19** is significant since, in principle, three additional cycloadducts, **22**−**24**, are potential products in the above reaction. The absence of **23** and **24** is not all that surprising since their formation would necessitate approach of the diene to the iminium ion syn to the angular methyl group, thus setting up very serious steric interactions in both the exo and endo transition states.



22 **23** **24**

The formation of **19** and the total absence of cycloadduct **22** can be rationalized by examination of transition states **25** and **26**, respectively (Figure 3). As illustrated, the carbon tethers in both transition states can adopt chairlike arrangements that easily place the diene within bonding distance of the iminium ion. However, in transition state **26** there exists a serious interaction between the axial C(4) proton H_b on the tetrahydropyridine ring and the olefinic proton H_a located on the diene (cf. structure **18** and transition state **26**). This interaction is alleviated in transition state **25**, leading to the observed product **19**.

To examine the effect on the cycloaddition process of introducing substitution at the terminus of the tethered diene, we set out to prepare the trifluoroacetic acid salt **31** of imine **30**. The synthesis of imine **30** commenced with δ-valerolactam. Alkylation of the dianion of δ-valerolactam with 1-iodoocta-4(*E*),6(*E*)-diene (**36**) at −78 °C provided lactam **27** in 85% yield. The conversion of **27** into imine **30** proceeded along the lines described above for the preparation of imine **15**. Thus, lactam **27** was

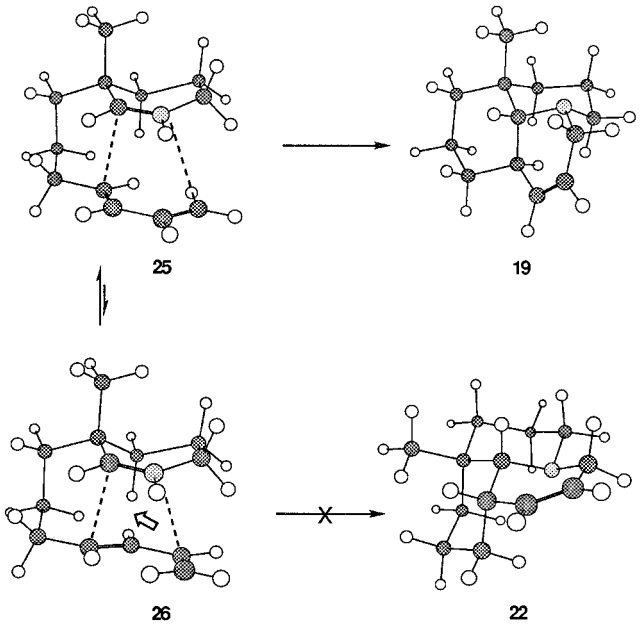
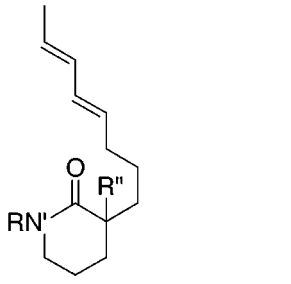
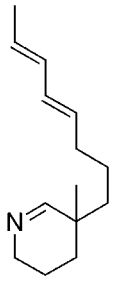


Figure 3. Transition states leading to the formation of **19** and **22**.

deprotonated with lithium bis(trimethylsilyl)amide and subsequently treated with 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate, giving rise (91%) to the *N*-protected lactam **28** which, upon methylation, afforded **29**. Selective reduction of the lactam carbonyl provided the corresponding hydroxy carbamate which upon exposure to tetra-*n*-butylammonium fluoride gave imine **30**. Treatment of **30** with 0.95 equiv of trifluoroacetic acid afforded iminium salt **31**.

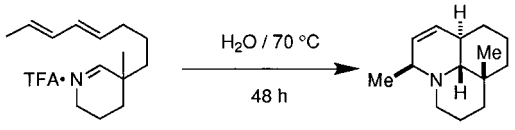


27 R' = R" = H
28 R' = TEOC, R" = H
29 R' = TEOC, R" = Me



30

With the availability of iminium salt **31**, efforts were focused on examining the intramolecular Diels−Alder reaction of **31** in both water and 5.0 M $LiClO_4 \cdot Et_2O$. Heating (70 °C) a 0.02 M solution of **31** in water for 48 h gave rise to an 80% yield of tricyclic amine **32** as the sole



31 **32**

reaction product after basic workup. The crude ^1H NMR spectrum revealed the lack of any starting imine **30** and confirmed the presence of a single cycloadduct. The structure of **32** was established by examination of its ^1H NMR spectrum and NOE experiments. The increased yield and lower reaction temperature for the transformation of **31** into **32** relative to the cycloaddition of **18** in water is clearly a testament to the greater reactivity of the methyl-substituted diene present in **31**.

In contrast to the above results in water, exposure of iminium salt **31** to 5.0 M lithium perchlorate in diethyl ether at ambient temperature for 66 h afforded only a 13% yield of tricyclic amine **32**. Imine **30** was recovered in ca. 80% yield; however, 15% of the olefinic geometry was a mixture of *E* and *Z* isomers.

In conclusion, it would appear that the polar solvent of choice for intramolecular imino Diels−Alder reactions of the type discussed above is water. The major problem associated with the use of 5.0 M lithium perchlorate in diethyl ether stems from the fact that weak acids in highly polar media such as 5.0 M $LiClO_4 \cdot Et_2O$ become strong acids and protonation of the tethered dienes with concomitant diene isomerization is competitive with cycloaddition. The activation energy for intramolecular cycloaddition in the above constrained systems is sufficiently high that cyclization is very slow at ambient temperature. In addition the highly acidic nature of the medium promotes other acid-catalyzed processes including diene isomerization and polymerization which compete effectively with the desired cycloadditions. Despite the disappointing results employing 5.0 M $LiClO_4 \cdot Et_2O$ as a medium for facilitating aza Diels−Alder reactions of the type illustrated above, the studies clearly demonstrate the potential of water to provide tricyclic amines in good to excellent yield with outstanding stereocontrol.

Experimental Section

Infrared spectra were recorded as 5−10% solutions in chloroform or carbon tetrachloride as indicated. High-resolution mass spectra were performed using either chemical ionization (CI) or electron impact ionization (EI) as indicated. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded at 400 or 500 MHz as indicated. ^1H NMR spectra were obtained in deuterated solvents. ^{13}C NMR spectra were obtained in deuteriochloroform solution. Melting points are uncorrected. Elemental analyses were performed by Robertson Laboratory, Inc., Madison, NJ.

Unless otherwise stated, all experiments were run in oven-dried glassware under an argon atmosphere using anhydrous solvents. The solvents were dried and distilled as indicated below. Tetrahydrofuran, diethyl ether, benzene, and toluene were purified by distillation from sodium benzophenone ketyl. Diisopropylamine, triethylamine, diisopropylethylamine, hexamethylphosphoramide, dimethylformamide, and dichloromethane were purified by distillation from calcium hydride. Chloroform was purified by washing with water, drying with anhydrous magnesium sulfate, and distilling from phosphorus pentoxide. Lithium perchlorate was purchased anhydrous and was further dried at 180 °C under high vacuum for 24 h prior to use. Other reagents and solvents were reagent grade and were used as received.

E. Merck silica gel no. 9385 (230−400 mesh) was used for flash chromatography. Kieselgel 60 F_{254} silica plates (0.25 mm, EM Science) were used for analytical thin-layer chromatography. The plates were visualized by immersion in *p*-anisaldehyde solution, phosphomolybdic acid solution, ninhydrin solution, or cobalt(II) thiocyanate solution.

PCMODEL 4.0 Molecular Modeling Software was used for all calculations. For a discussion of the MMX enhanced version of MM2, see ref 12.

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(1α,6a*β*,9aα,9b*β*)-1-Vinyl-4,5,6,6a,7,8,9,9a-octahydro-2-oxa-3a-aza-phenalen-3-one (4), (1α,6aα,9aα,9b*β*)-1-Vinyl-4,5,6,6a,7,8,9,9a-octahydro-2-oxa-3a-aza-phenalen-3-one (5), and 5-(Hepta-4(*E*),6-dienyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (6). A solution of lactam **35** (199 mg, 0.678 mmol) in 3.0 mL of tetrahydrofuran at −78 °C was treated with a 1.0 M solution of lithium triethylborohydride in tetrahydrofuran (0.9 mL, 0.9 mmol). After 10 min, a few drops of water were added. The reaction was poured into water and was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on 20 g of silica gel. Elution with hexanes−ethyl acetate (3:1) afforded 175 mg (87%) of **3** as a mixture of epimers which was not characterized but used directly in the next reaction.

To a solution of **3** (55.8 mg, 0.189 mol) in freshly prepared 5.0 M lithium perchlorate in diethyl ether (18.9 mL) was added a 1.46 M solution of camphorsulfonic acid in tetrahydrofuran (13 μL, 0.019 mmol). The reaction was stirred for 2 h at ambient temperature. Triethylamine (15 μL, 0.10 mmol) was added, and the reaction was quenched with water. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with saturated aqueous brine solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was chromatographed on 10 g of silica gel. Elution with hexanes−ethyl acetate (1:1) afforded 15.0 mg (28%) of enamide **6** as a colorless oil: R_f 0.37 (hexanes−ether, 9:1); IR ($CHCl_3$) 1690, 1670, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 0.42 H), 6.51 (s, 0.58 H), 6.31 (m, 1 H), 6.04 (m, 1 H), 5.70 (dt, J = 15.4, 6.9 Hz, 1 H), 5.08 (d, J = 17.0 Hz, 1 H), 4.95 (d, J = 10.1 Hz, 1 H), 3.49 (m, 2 H), 2.07 (m, 2 H), 2.03−1.93 (m, 4 H), 1.80 (m, 2 H), 1.56−1.47 (m, 11 H); high-resolution MS (EI) calcd for $C_{17}H_{27}NO_2$ (M^+) *m/e* 277.20431, found 277.20464.

Further elution with hexanes−ethyl acetate (1:1) afforded 4.6 mg (11%) of cycloadduct **5** as a white solid: R_f 0.42 (hexanes−ethyl acetate, 1:1); IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddd, J = 17.0, 10.4, 7.5 Hz, 1 H), 5.34 (dt, J = 17.0, 1.1 Hz, 1 H), 5.30 (dt, J = 10.4, 1.0 Hz, 1 H), 4.43 (dm, J = 13.2 Hz, 1 H), 4.28 (dd, J = 10.4, 7.5 Hz, 1 H), 2.70 (td, J = 13.1, 2.8 Hz, 1 H), 2.59 (t, J = 10.1 Hz, 1 H), 1.84−1.69 (m, 5 H), 1.65−1.47 (m, 2 H), 1.40 (qt, J = 13.2, 4.1 Hz, 1 H), 1.23 (m, 1 H), 1.14−0.97 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 133.9, 119.4, 81.3, 63.3, 44.4, 42.2, 41.1, 31.8, 30.3, 27.0, 24.7, 24.5. Recrystallization from pentane−ether afforded colorless needles: mp 101−102.5 °C; high-resolution MS (EI) calcd for $C_{13}H_{19}NO_2$ (M^+) *m/e* 221.14167, found 221.14195. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.66; H, 8.69; N, 6.11.

Continued elution with hexanes−ethyl acetate afforded 21.7 mg (52%) of cycloadduct **4** as a white solid: R_f 0.21 (hexanes−ethyl acetate, 1:1); IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddd, J = 17.3, 10.4, 7.5 Hz, 1 H), 5.32 (dt, J = 17.3, 0.9 Hz, 1 H), 5.27 (br d, J = 10.4 Hz, 1 H), 4.32 (dd, J = 10.4, 7.5 Hz, 1 H), 4.10 (ddd, J = 13.8, 8.2, 0.8 Hz, 1 H), 3.46 (dd, J = 10.2, 6.1 Hz, 1 H), 3.05 (ddd, J = 13.8, 12.0, 6.0 Hz, 1 H), 2.27 (m, 1 H), 1.91 (m, 1 H), 1.75−1.52 (m, 7 H), 1.50−1.28 (m, 2 H), 0.87 (qd, J = 12.6, 3.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 134.9, 119.1, 84.1, 57.1, 37.3, 37.1, 30.0, 28.9, 25.7, 21.4, 20.5, 19.5. Recrystallization from pentane−ether afforded colorless needles: mp 83.0−84.0 °C; high-resolution MS (EI) calcd for $C_{13}H_{19}NO_2$ (M^+) *m/e* 221.14167, found 221.14114. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33; Found: C, 70.75; H, 70.65; N, 6.12.

3-(Hepta-4(*E*),6-dienyl)-3-methyl-2-piperidone (12). To a stirred solution of 3-methyl-2-piperidone[10] (425 mg, 3.75 mmol) in 10 mL of tetrahydrofuran at −78 °C was added *n*-butyllithium (3.0 mL, 7.5 mmol) as a 2.50 M solution in hexanes. The resultant solution was allowed to warm to ambient temperature for 30 min. After the solution of dianion was cooled to −78 °C, iodide **33** (808 mg, 3.64 mmol) was added in 1.0 mL of tetrahydrofuran, and the reaction mixture was stirred for an additional 20 min at −78 °C. Saturated aqueous ammonium chloride was added, and the resultant solution was warmed to room temperature and poured into water. The aqueous solution was extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed on 20 g of silica gel. Elution with ethyl acetate afforded 478 mg (61%) of lactam **12** as a colorless oil: R_f 0.40 (ethyl acetate); IR ($CHCl_3$) 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (dt, J = 17.0, 10.4 Hz, 1 H), 6.04 (dd, J = 15.1, 10.4 Hz, 1 H), 5.81 (br s, NH), 5.69 (dt, J = 15.1, 6.9 Hz, 1 H), 5.08 (d, J = 17.0 Hz, 1 H), 4.95 (d, J = 10.4 Hz, 1 H), 3.27 (m, 2 H), 2.07 (m, 2 H), 1.83−1.74 (m, 3 H), 1.71 (td, J = 12.2, 4.7 Hz, 1 H), 1.59−1.24 (m, 4 H), 1.19 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 137.2, 135.0, 131.1, 114.8, 42.8, 41.3, 39.2, 33.0, 32.5, 25.7, 23.8, 19.5; high-resolution MS (EI) calcd for $C_{13}H_{21}NO$ (M^+) *m/e* 207.1624, found 207.1630.

3-(Hepta-4(*E*),6-dienyl)-3-methyl-2-oxopiperidine-1-carboxylic Acid [2-(Trimethylsilyl)ethyl] Ester (13). A solution of lactam **12** (478 mg, 2.30 mmol) in 15 mL of tetrahydrofuran cooled to −78 °C was treated with a 1.0 M solution of lithium bis(trimethylsilyl)amide (2.50 mL, 2.50 mmol) in tetrahydrofuran. After 15 min, 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (681 mg, 2.40 mmol) was added in 5 mL of tetrahydrofuran. The resultant solution was stirred for 15 min at −78 °C and 1 h at room temperature. The reaction was partitioned between ether and water, and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on 30 g of silica gel. Elution with hexanes−ether (3:1) afforded 739 mg (91%) of amide **13** as a colorless oil: R_f 0.39 (hexanes−ether, 3:1); IR ($CHCl_3$) 1765, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (dt, J = 16.8, 10.4 Hz, 1 H), 6.03 (dd, J = 15.2, 10.4 Hz, 1 H), 5.66 (dt, J = 15.2, 6.8 Hz, 1 H), 5.08 (d, J = 16.8 Hz, 1 H), 4.95 (d, J = 10.4 Hz, 1 H), 4.30 (m, 2 H), 3.72 (m, 1 H), 3.59 (m, 1 H), 2.06 (m, 2 H), 1.85−1.78 (m, 3 H), 1.69 (m, 1 H), 1.59 (m, 1 H), 1.51 (td, J = 12.8, 4.4 Hz, 1 H), 1.43−1.31 (m, 2 H), 1.21 (s, 3 H), 1.09 (m, 2 H), 0.03 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 155.2, 137.1, 134.7, 131.3, 114.9, 65.3, 47.6, 44.7, 39.6, 33.3, 32.9, 25.7, 23.7, 19.8, 17.5, 1.6; high-resolution MS (CI) calcd for $C_{19}H_{34}NO_3Si$ (M + 1) *m/e* 352.23092, found 352.23523.

5-(Hepta-4(*E*),6-dienyl)-5-methyl-2,3,4,5-tetrahydropyridine (15). A solution of lactam **13** (471 mg, 1.34 mmol) in 10 mL of tetrahydrofuran at −78 °C was treated with a 1.0 M solution of lithium triethylborohydride in tetrahydrofuran (1.6 mL, 1.6 mmol). After 15 min, the excess hydride reagent was quenched by dropwise addition of water. The reaction mixture was warmed to room temperature and was diluted with water. The aqueous layer was extracted with dichloromethane. The combined organics were washed with saturated aqueous brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 465 mg (98%) of α-hydroxy carbamate **14** as a mixture of epimers. Crude **14** was redissolved in 5 mL of tetrahydrofuran and was treated with a 1.0 M solution of tetrabutylammonium fluoride (2.6 mL, 2.6 mmol) in tetrahydrofuran. The resultant solution was stirred for 12 h at ambient temperature and then partitioned between ether and water. The aqueous layer was extracted with ether, and the combined organic layers were washed with saturated aqueous brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue oil was chromatographed on 25 g of silica gel. Elution with ether (containing 0.1% v/v of 30% aqueous ammonium hydroxide) afforded 207 mg (83%) of imine **15** as a colorless oil: R_f 0.23 (ethyl acetate); IR ($CHCl_3$) 1655, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1 H), 6.30 (dt, J = 17.0, 10.1 Hz, 1 H), 6.04 (dd, J = 15.1, 10.4 Hz, 1 H), 5.67 (dt, J = 15.1, 6.9 Hz, 1 H), 5.09 (d, J = 17.0 Hz, 1 H), 4.96 (d, J = 10.1 Hz, 1 H), 3.55 (m, 1 H), 3.37 (m, 1 H), 2.04 (m, 2 H), 1.64−1.54 (m, 3 H), 1.47−1.29 (m, 6 H), 0.99 (s, 3 H); ^{13}C NMR δ 170.2, 137.1, 134.6, 131.3, 115.0,

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49.4, 39.6, 36.5, 33.0, 30.7, 24.5, 23.4, 19.3; high-resolution MS (CI) calcd for $C_{13}H_{21}N$ (M^+) *m/e* 191.1675, found 191.1622.

5-(Hepta-4(*E*),6-dienyl)-5-methyl-2,3,4,5-tetrahydro-1*H*-pyridinium Trifluoroacetate (18). A solution of imine **15** (34.4 mg, 0.180 mmol) in 1.0 mL of ether was cooled to −78 °C. Trifluoroacetic acid (19.8 mg, 0.174 mmol) was added, and the resultant solution was stirred for 30 min at −78 °C and 30 min at ambient temperature. The solvent was removed in vacuo to afford 53.3 mg (98%) of imine−trifluoraocacetic acid salt **18** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1 H), 6.25 (dt, J = 17.0, 10.2 Hz, 1 H), 6.02 (dd, J = 15.2, 10.2 Hz, 1 H), 5.59 (dt, J = 15.2, 6.8 Hz, 1 H), 5.08 (d, J = 17.0 Hz, 1 H), 4.95 (d, J = 10.2 Hz, 1 H), 2.06 (m, 2 H), 1.91−1.24 (m, 9 H), 1.19 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 136.7, 133.1, 132.0, 115.5, 44.8, 38.2, 37.7, 32.4, 28.8, 23.3, 22.9, 17.3.

(7aα,10aβ,10bβ)-10a-Methyl-2,3,7a,8,9,10,10a,10b-octahydro-1*H*,5*H*-benzo[*ij*]quinolizine (19). A 10 mL round-bottomed flask was charged with iminium salt **18** (24 mg, 0.078 mmol). Doubly distilled, deionized water (4.0 mL) was added, and the reaction was heated to 95 °C for 38 h. The cooled reaction mixture was poured into 3 N sodium hydroxide, and the product was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to afford 10.9 mg of a yellow oil. ^{1}H NMR analysis of the crude reaction mixture revealed a 3:1 ratio of cycloadduct **19** and imine **15**. A pure sample of **19** was obtained by chromatography on alumina (Brockman basic, activity IV). Elution with hexanes−ether (19:1) afforded pure **19** as a colorless oil: IR ($CHCl_3$) 2940, 2875, 1455, 1440, 1110 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (dm, J = 10.2 Hz, 1 H), 5.50 (dm, J = 10.2 Hz, 1 H), 3.63 (br d, J = 18.3 Hz, 1 H), 2.95 (br d, J = 18.3 Hz, 1 H), 2.78 (td, J = 12.4, 3.2 Hz, 1 H), 2.48 (dd, J = 11.4, 4.4 Hz, 1 H), 2.42 (m, 1 H), 2.22 (d, J = 10.6 Hz, 1 H), 1.91 (qt, J = 13.0, 4.9 Hz, 1 H), 1.81 (dd, J = 13.0, 4.6 Hz, 1 H), 1.74 (m, 1 H), 1.57−1.43 (m, 4 H), 1.27 (m, 1 H), 1.11 (s, 3 H), 1.03 (m, 1 H), 0.96 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 125.2, 66.4, 54.6, 47.3, 40.8, 33.5, 32.6, 28.3, 27.5, 27.3, 22.7, 22.2; high-resolution MS (CI) calcd for $C_{13}H_{21}N$ (M^+) *m/e* 191.1675, found 191.1679.

(7aα,9aβ,9bβ)-5,9a-Dimethyl-2,3,5,7a,8,9,9a,9b-octahydro-1*H*-cyclopenta[*ij*]quinolizine (16). To a solution of imine **15** (27.0 mg, 0.141 mmol) in 5.0 M lithium perchlorate−diethyl ether (14 mL) was added trifluoroacetic acid (10.3 μL, 0.134 mmol). The resultant solution was stirred for 74 h at ambient temperature. The reaction mixture was poured into an ice-cold solution of water and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed on 20 g of basic alumina (Brockman, activity IV). Elution with hexanes−ether (19:1) afforded 7.0 mg (26%) of cycloadduct **16** as a colorless oil: IR ($CHCl_3$) 2940, 2880, 2810, 1495, 1375, 1120, 1145 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dt, J = 9.9, 1.6 Hz, 1 H), 5.56 (dt, J = 9.9, 3.0 Hz, 1 H), 3.03 (m, 1 H), 2.70−2.59 (m, 2 H), 2.56 (br d, J = 9.9 Hz, 1 H), 2.35 (d, J = 10.9 Hz, 1 H); 1.79 (m, 1 H), 1.70 (m, 1 H), 1.59−1.39 (m, 4 H), 1.31 (m, 1 H), 1.18−1.10 (m, 1 H), 1.14 (s, 3 H), 1.13 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2, 128.6, 66.5, 58.4, 48.7, 38.9, 35.4, 35.3, 29.4, 25.5, 25.0, 23.8, 21.6; high-resolution MS (CI) calcd for $C_{13}H_{22}N$ (M + 1) *m/e* 192.17536, found 192.17558.

Further elution with ether afforded 7.3 mg (27%) of imines **17** [IR ($CHCl_3$) 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1 H), 6.28 (ddt, J = 14.9, 11.0, 1.6 Hz, 1 H), 5.93 (t, J = 11.0 Hz, 1 H), 5.54 (dq, J = 14.8, 6.9 Hz, 1 H), 5.24 (dt, J = 10.7, 7.2 Hz, 1 H), 3.62−3.33 (m, 2 H), 2.22−2.04 (m, 2 H), 1.77 (d, J = 6.9 Hz, 3 H), 1.64−1.22 (m, 6 H), 1.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 129.7, 128.8 (2 C), 126.6, 49.4, 40.0, 30.6, 29.7, 24.5, 22.2, 19.3, 18.3] and **15** as a 2:1 mixture, respectively.

3-(Octa-4(*E*),6(*E*)-dienyl)-2-piperidone (27). A solution of δ-valerolactam (325 mg, 3.27 mmol) in 4 mL of anhydrous tetrahydrofuran at −78 °C was treated with a 2.5 M solution of *n*-butyllithium (2.4 mL, 6.0 mmol) in hexane. The resultant solution was stirred for 5 min at −78 °C and then warmed to 0 °C for 30 min. After cooling to −78 °C, 1-iodooct-4(*E*),6(*E*)-diene (634 mg, 2.68 mmol) was added neat via cannula. After 30 min at −78 °C, the reaction was quenched by the addition of saturated aqueous ammonium chloride. The reaction mixture was diluted with ether and washed with water and saturated brine solution. The combined aqueous washings were extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The product was purified by chromatography on 30 g of silica gel. Elution with ethyl acetate afforded 475 mg (85%) of lactam **27** as a white powder: R_f 0.29 (chloroform−methanol, 25:1); IR ($CHCl_3$) 3420, 3300, 3200, 1700, 990 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (br s, NH), 5.95 (m, 2 H), 5.52 (m, 2 H), 3.24 (m, 2 H), 2.21 (m, 1 H), 2.05 (m, 2 H), 1.94−1.76 (m, 3 H), 1.72 (d, J = 6.4 Hz, 3 H), 1.64 (m, 1 H), 1.51−1.33 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 131.5, 131.4, 130.3, 126.6, 42.1, 40.8, 32.5, 31.1, 26.8, 25.9, 21.2, 17.9. Recrystallization from pentane−ether afforded fine white needles: mp 73.5−75.0 °C. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.19; H, 10.26; N, 6.74.

3-(Octa-4(*E*),6(*E*)-dienyl)-2-oxopiperidine-1-carboxylic Acid [2-(Trimethylsilyl)ethyl] Ester (28). Lactam **27** (451 mg, 2.17 mmol) was dissolved in 5.0 mL of tetrahydrofuran, and the resultant solution was cooled to −78 °C. A 1.0 M solution of lithium bis(trimethylsilyl)amide (2.4 mL, 2.4 mmol) in tetrahydrofuran was added, and the reaction was stirred for 20 min. A solution of 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (623 mg, 2.20 mmol) was added in 5.0 mL of tetrahyrofuran, and the reaction was stirred for 2.5 h. The reaction was quenched with saturated aqueous ammonium chloride, warmed to room temperature, and concentrated in vacuo. Chromatography on 30 g of silica gel, eluting with hexanes−ethyl acetate (12:1), afforded 696 mg (91%) of **28** as a colorless oil: R_f 0.53 (hexanes−ethyl acetate, 4:1); IR ($CHCl_3$) 1765, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.98 (m, 2 H), 5.54 (m, 2 H), 4.31 (m, 2 H), 3.78 (ddd, J = 12.6, 7.6, 4.8 Hz, 1 H), 3.64 (ddd, J = 12.4, 7.2, 4.8 Hz, 1 H), 2.40 (m, 2 H), 2.10−1.95 (m, 3 H), 1.92−1.75 (m, 3 H), 1.71 (d, J = 6.4 Hz, 3 H), 1.55−1.39 (m, 4 H), 1.10 (m, 2 H), 0.03 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 154.6, 131.5, 131.3, 130.6, 126.9, 65.4, 45.8, 43.7, 32.5, 30.7, 26.8, 26.0, 21.6, 18.0, 17.6, −1.6; high-resolution MS (EI) calcd for $C_{19}H_{33}NO_3Si$ (M^+) *m/e* 351.2231, found 351.2239.

3-Methyl-3-(octa-4(*E*),6(*E*)-dienyl)-2-oxopiperidine-1-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (29). A solution of lactam **28** (700 mg, 1.99 mmol) in 10 mL of tetrahydrofuran at −78 °C was treated with a 1.0 M solution of lithium bis(trimethylsilyl)amide (2.2 mL, 2.2 mmol). The resultant solution was stirred for 10 min at −78 °C and 30 min at −42 °C. A solution of methyl iodide (1.0 mL, 16.0 mmol) and hexamethylphosporamide (1.0 mL, 5.75 mmol) was added, and the reaction was stirred for 10 min at −42 °C. The reaction was quenched with saturated aqueous ammonium chloride, and the product was isolated by extraction with ether. The combined organic layers were washed with water and saturated brine solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on 30 g of silica gel. Elution with hexanes−ether (5:1) afforded 501 mg (69%) of **29** as a colorless oil: R_f 0.40 (hexanes−ether, 3:1); IR ($CHCl_3$) 1765, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (m, 2 H), 5.53 (m, 2 H), 4.30 (m, 2 H), 3.77 (m, 1 H), 3.60 (m, 1 H), 2.03 (q, J = 7.4 Hz, 2 H), 1.87−1.76 (m, 3 H), 1.72 (d, J = 6.4 Hz, 3 H), 1.71−1.56 (m, 2 H), 1.50 (td, J = 12.6, 4.8 Hz, 1 H), 1.43−1.26 (m, 2 H), 1.20 (s, 3 H), 1.09 (m, 2 H), 0.03 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 155.2, 131.5, 131.3, 130.7, 127.0, 65.3, 47.6, 44.7, 39.6, 33.3, 32.9, 25.7, 23.9, 19.8, 18.0, 17.5, −1.6; high-resolution MS (CI) calcd for $C_{20}H_{36}NO3Si$ (M + 1) *m/e* 366.2466, found 366.2480.

3-Methyl-3-(octa-4(*E*),6(*E*)-dienyl)-2,3,4,5-tetrahydropyridine (30). A solution of **29** (205 mg, 0.56 mmol) in 10 mL of tetrahydrofuran at −78 °C was treated with a 1.0 M solution of lithium triethylborohydride (0.675 mL, 0.675 mmol) in tetrahydrofuran. After 10 min, saturated aqueous ammonium

chloride was added. The reaction mixture was diluted with ether and washed with water and saturated aqueous brine. The combined aqueous washings were extracted with ether. The combined organic layers were dried over anhydrous magnesium sulfate, concentrated in vacuo, and chromatographed on silica gel. Elution with hexanes−ether (3:1) afforded 192 mg (93%) of the corresponding alcohol as a mixture of epimers. This mixture was redissolved in 5.0 mL of tetrahydrofuran. A 1.0 M solution of tetrabutylammoium fluoride (2.0 mL, 2.0 mmol) in tetrahydrofuran was added, and the reaction was stirred for 11 h at ambient temperature. The reaction mixture was diluted with ether and washed with water and saturated brine. The combined aqueous washings were extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on 10 g of silica gel. Elution with ether containing 0.2% of aqueous ammonium hydroxide (30%) afforded 103 mg (98%) of imine **30** as a colorless oil: R_f 0.23 (ethyl acetate); IR (CCl_4) 1655, 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1 H), 6.00 (m, 2 H), 5.54 (m, 2 H), 3.55 (m, 1 H), 3.38 (m, 1 H), 2.04 (m, 2 H), 1.72 (d, J = 6.4 Hz, 3 H), 1.62−1.56 (m, 3 H), 1.46−1.31 (m, 5 H), 0.99 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 131.5, 131.3, 130.7, 127.1, 49.4, 39.6, 36.5, 33.1, 30.7, 24.5, 23.6, 19.3, 18.0; high-resolution MS (CI) calcd for $C_{14}H_{24}N$ (M + 1) *m/e* 206.1910, found 206.1900.

(7aα,10aβ,10bβ)-5,10a-Dimethyl-2,3,7a,8,9,10,10a,10b-octahydro-1*H*,5*H*-benzo[*ij*]quinolizine (32). A suspension of imine **30** (24.7 mg, 0.12 mmol) in 1.0 mL of ether was cooled to −78 °C and trifluoroacetic acid (0.85 μL, 0.11 mmol) was added. After 30 min, a vacuum of 0.5 Torr was applied, and the reaction was allowed to slowly warm to room temperature. After the visible removal of solvent was complete, the vacuum was maintained for 3 h. The resulting iminium salt was used directly in the cylization reaction.

Cyclization of 31 in Water. A 20 mL Pyrex culture tube with a Teflon-lined cap was charged with iminium salt **31** (39 mg, 0.12 mmol) and 6.0 mL of doubly distilled water. The tube was capped and heated in an oil bath at 70 °C for 48 h. The cooled reaction mixture was poured into saturated aqueous sodium bicarbonate solution and extracted with ether. The combined extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford 20 mg (80%) of **32** as a yellow oil. Distillation (bp 25 °C at 50 Torr) afforded a colorless oil: IR ($CHCl_3$) 1455, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.59 (dt, J = 9.8, 3.0 Hz, 1 H), 5.46 (dt, J = 9.8, 1.6 Hz, 1 H), 2.93 (m, 1 H), 2.72 (td, J = 11.6, 3.0 hz, 1 H), 2.44 (m, 1 H), 2.36 (m, 1 H), 2.20 (d, J = 10.4 Hz, 1 H), 1.95−1.78 (m, 2 H), 1.77−1.70 (m, 1 H), 1.54−1.42 (m, 4 H), 1.31−1.21 (m, 1 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.08 (s, 3 H), 1.04−0.93 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.9, 129.3, 61.3, 57.5, 48.1, 40.9, 33.1, 32.5, 29.1, 27.4, 26.9, 22.8, 22.2, 21.1; high-resolution MS (CI) calcd for $C_{14}H_{24}N$ (M + 1) *m/e* 206.19102, found 206.19187.

Cyclization of 31 in 5.0 M Lithium Perchlorate−Diethyl Ether. A solution of imine **30** (14.3 mg, 0.070 mmol) in 0.5 mL of ether was chilled to −78 °C, and trifluoroacetic acid (4.8 μL, 0.068 mmol) was added. After 30 min, a vacuum of 0.5 Torr was applied, and the reaction was allowed to slowly warm to room temperature. After the visible removal of solvent was complete, the vacuum was maintained for 3 h. The residual oil was redissolved in 2.5 mL of a 5.0 M solution of lithium perchlorate in diethyl ether and was allowed to stand for 66 h. The reaction mixture was diluted with ether and was washed with 3 N sodium hydroxide solution. The combined aqueous washings were extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to afford 13.2 mg (92%) of a yellow oil. ^1H NMR analysis indicated the presence of imine **30** and cycloadduct **32** in a ca. 6:1 ratio.

1-Iodohepta-4(*E*),6-diene (33). Hepta-4(*E*),6-dien-1-ol (4.95 g, 44.1 mmol),[11] triphenylphoshine (13.90 g, 52.9 mmol), and imidazole (3.65 g, 53.6 mmol) were combined in 90 mL of dichloromethane. After complete dissolution, the reaction mixture was cooled to 0 °C. Iodine (12.8 g, 50.4 mmol) was added in four portions during 30 min, after which the reaction was allowed to warm to ambient temperature overnight. The reaction was diluted with hexanes and washed with water, saturated aqueous sodium sulfite, and saturated aqueous brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residual liquid was chromatographed on 300 g of silica gel. Elution with pentane afforded 8.26 g (84%) of iodide **33** as a colorless liquid: R_f 0.53 (hexanes); IR ($CHCl_3$) 1005, 955, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (dt, J = 17.0, 10.4 Hz, 1 H), 6.10 (dd, J = 15.2, 10.4 Hz, 1 H), 5.63 (dt, J = 15.2, 6.8 Hz, 1 H), 5.13 (d, J = 17.0 Hz, 1 H), 5.00 (d, J = 10.4 Hz, 1 H), 3.19 (t, J = 6.8 Hz, 2 H), 2.20 (q, J = 6.8 Hz, 2 H), 1.92 (quintet, J = 7.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 132.5, 132.3, 115.6, 33.0, 32.6, 6.3; high-resolution MS (EI) calcd for $C_7H_{11}I$ (M^+) *m/e* 221.99063, found 221.99003.

3-(Hepta-4(*E*),6-dienyl)-2-oxopiperidine-1-carboxylic Acid *tert*-Butyl Ester (34). To a solution of δ-valerolactam (625 mg, 6.30 mmol) in 10.0 mL of tetrahydrofuran cooled to −78 °C under an atmosphere of argon was added a 2.45 M solution of *n*-butyllithium in hexanes (5.15 mL, 12.6 mmol). The resultant solution was stirred for 15 min at −78 °C and for 45 min at 0 °C. The reaction was again cooled to −78 °C, and a solution of iodide **33** (1.27 g, 5.70 mmol) in 5.0 mL of tetrahydrofuyran was added. After an additional 15 min at −78 °C, di-*tert*-butyl dicarbonate (1.68 g, 7.67 mmol) was added in 5.0 mL of tetrahydrofuran, and the reaction mixture was stirred for an additional 15 min at −78 °C. The reaction was quenched by the addition of saturated aqueous ammonium chloride, and the resultant aqueous solution was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by chromatography on 75 g of silica gel. Elution with hexanes−ethyl acetate (9:1) afforded 640 mg (35%) of **34** as a colorless oil: R_f 0.70 (hexanes−ethyl acetate, 3:1); IR ($CHCl_3$) 1765, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (dt, J = 17.0, 10.2 Hz, 1 H), 6.02 (dd, J = 15.1, 10.4 Hz, 1 H), 5.69 (dt, J = 15.1, 6.9 Hz, 1 H), 5.08 (d, J = 16.7 Hz, 1 H), 4.95 (d, J = 10.1 Hz, 1 H), 3.73 (ddd, J = 12.7, 7.5, 5.0 Hz, 1 H). 3.57 (ddd, J = 12.4, 7.4, 5.0 Hz, 1 H), 2.37 (m, 1 H), 2.10 (q, J = 6.9 Hz, 2 H), 1.99 (m, 1 H), 1.94−1.73 (m, 3 H), 1.51 (s, 9 H), 1.51−1.43 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 153.0, 137.1, 134.8, 131.2, 114.8, 82.6, 46.0, 43.6, 32.5, 30.7, 28.0, 26.6, 26.0, 21.6; high-resolution MS (EI) calcd for $C_{17}H_{27}NO_3$ (M^+) *m/e* 293.19921, found 293.19877.

3-(Hepta-4(*E*),6-dienyl)-2-piperidone (35). A solution of δ-valerolactam (580 mg, 5.85 mmol) in 10.0 mL of tetrahydrofuran was cooled to −78 °C under an atmosphere of argon. To this solution was added, dropwise over 5 min, a 2.45 M solution of *n*-butyllithium in hexanes (4.70 mL, 11.7 mmol). The resultant solution was stirred for 15 min at −78 °C and 30 min at 0 °C. The reaction mixture was again cooled to −78 °C, and a solution of iodide **33** (1.07 g, 4.83 mmol) in 3.0 mL of tetrahydrofuran was added. After 15 min, the reaction was poured into saturated aqueous ammonium chloride, and the resultant aqueous solution was extracted with dichloromethane. The combined organics were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by chromatography on 50 g of silica gel. Elution with ethyl acetate afforded 350 mg (33%) of lactam **35** as a colorless oil that solidified upon standing at −20 °C: R_f 0.28 (ethyl acetate); IR ($CHCl_3$) 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (br s, NH), 6.24 (dt, J = 17.0, 10.1 Hz, 1 H), 5.99 (dd, J = 15.1, 10.3 Hz, 1 H), 5.65 (dt, J = 15.1, 6.9 Hz, 1 H), 5.03 (d, J = 17.0 Hz, 1 H), 4.89 (d, J = 10.1 Hz, 1 H), 3.23 (m, 2 H), 2.20 (m, 1 H), 2.05 (m, 2 H), 1.94−1.75 (m, 3 H), 1.64 (m, 1 H), 1.51−1.37 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 137.1, 134.8, 131.0, 114.6, 42.1, 40.8, 32.5, 31.1, 26.5, 26.0, 21.2. Recrystallization from pentane−ether afforded colorless needles, mp 54.5−55.5 °C. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.58; H, 10.27; N, 7.19.

1-Iodoocta-4(*E*),6(*E*)-diene (36). A solution of octa-4(*E*),6(*E*)-dien-1-ol[13] (528 mg, 4.18 mmol), triphenylphosphine (1.66 g, 6.35 mmol), and imidazole (835 mg, 12.3 mmol) in 20 mL of dichloromethane was cooled to 0 °C. Iodine (1.34 g, 5.28 mmol) was added, and the resultant solution was allowed to warm to ambient temperature. After 1 h, ether was added, and the reaction was poured into a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with pentane afforded 914 mg (93%) of 1-iodoocta-4(*E*),6(*E*)-diene (**36**) as a colorless oil: R_f 0.67 (pentane); IR ($CHCl_3$) 995 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.09−5.97 (m, 2 H), 5.60 (m, 1 H), 5.47 (m, 1 H), 3.18 (t, J = 6.9 Hz, 2 H), 1.90 (quintet, J = 6.9 Hz, 2 H), 1.73 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 131.3, 129.1, 127.7, 33.1, 32.9, 18.0, 6.4; high-resolution MS (EI) calcd for $C_8H_{13}I$ (M^+) *m/e* 236.00629, found 236.00558.

(13) Lithium aluminum hydride reduction of 4(*E*),6(*E*)-octadienoic acid (Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020) provided octa-4(*E*),6(*E*)-dienol in 98% yield.

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Supporting Information Available: Copies of the ^1H and ^{13}C NMR spectra for compounds **4**, **5**, **12**, **13**, **15**, **16**, **18**, **19**, **27**−**30**, and **32**−**36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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