40-8; **19a**, 78012-40-5; *d*-**20**, 14917-83-0; **21**, 78012-41-6; **23**, 115115-25-8; 2-*epi*-**23**, 115115-28-1; **24**, 115047-41-1; **25**, 78012-44-9; *epi*-**25**, 115047-42-2; **26**, 40207-59-8; **27**, 115047-44-4; **28**, 115047-43-3; **28** (dimethylhydrazone), 115047-58-0; **29a**, 115047-45-5; **29b**, 115047-46-6; **37**, 5799-67-7; **40**, 115047-47-7; **43**, 101245-15-2; **45** (isomer 1), 115115-26-9; **45** (isomer 2), 115115-27-0; **46**, 115047-48-8; **47**, 115047-49-9; **49a**, 115115-29-2; **49b**, 115047-60-4; **51**, 115047-50-2; **52a**, 115047-61-5; **52b**, 115047-62-6; **53**, 1066-45-1; **54**, 115047-51-3; **55**, 115047-52-4; **56**, 115047-53-5; **57**, 115047-54-6; **57** (ketone), 115047-57-9; **58**, 115047-55-7; **59b**, 94616-76-9; **60**, 115047-37-5; **61**, 115047-38-6; **62**, 115047-39-7; CH_2=CHOEt, 109-92-2; 2-[(1′*S*,2′*R*,3′*S*,4′*R*)-1′-hydroxy-4′-methyl-3′-(phenylsulfonyl)cyclopent-2′-yl]-3-(1,3-dithian-2-ylidene)-(1*R*,6*S*)-7,7-dimethylbicyclo[4.1.0]heptane, 115047-59-1.

Supplementary Material Available: Crystal data and data collection parameters, positional parameters and their estimated standard deviations, general temperature factors, bond distances, and bond angles for compound **46** (12 pages). Ordering information is given on any current masthead page.

Octahydroquinoline Synthesis via Immonium Ion Based Diels–Alder Chemistry: Synthesis of (-)-8a-Epipumiliotoxin C

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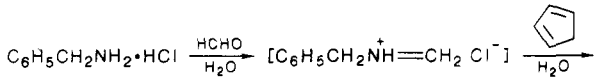
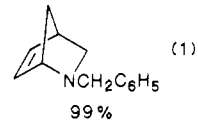
Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Received January 13, 1988

A total synthesis of (-)-8a-epipumiliotoxin C has been developed which features an intramolecular immonium ion based Diels–Alder reaction. Cyclocondensation of the immonium ion **8** derived from optically pure aldehyde **2** and ammonium chloride provided two octahydroquinolines **9** and **10**, in a ratio of 2.2:1. The formation of **9** and **10** is rationalized on the basis of the chair-like conformations **16** and **17** respectively. Reduction of the double bond in **9** afforded (-)-8a-epipumiliotoxin C.

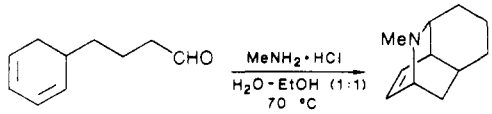
The ability of immonium ions to function as heterodienophiles in Diels–Alder reactons carried out under Mannich-like conditions holds considerable promise for the construction of nitrogen-containing ring systems. During our preliminary study, efforts were focused on probing the potential of utilizing immonium ions in simple intermolecular[2] (cf. eq 1) and intramolecular[3] (cf. eq 2) Diels–Alder cycloaddition reactions.





(1)

99%



(2)

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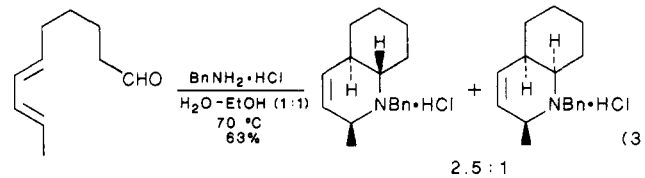
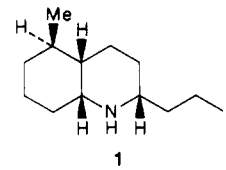
As an extension of our earlier work, we set out to investigate whether the intramolecular immonium ion based Diels–Alder reaction could be employed in the construction of substituted octahydroquinoline systems and, more importantly, to explore the stereochemical outcome of such processes wherein a substituent is located on the tether between diene and heterodienophile. Previous work during the early stages of our investigation had also established the feasibility of constructing octahydroquinoline ring systems[2] (cf. eq 3). Accordingly, we set out to explore the



(3)

2.5 : 1

possibility of elaborating octahydroquinolines which could serve as precursors to decahydroquinolines related to pumiliotoxin C (**1**),[4] a toxin isolated from the skin of Central American poison arrow frogs.



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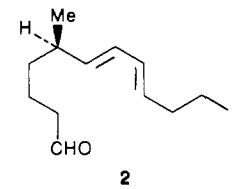
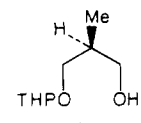


2

Our strategy for elaborating octahydroquinoline systems centered around intramolecular cyclocondensation of the immonium ion derived from aldehyde **2** and ammonium chloride. The known chiral alcohol **3**[5] conveniently served as a starting point for the preparation of **2**. Oxidation



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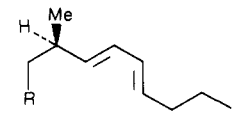

4, R = OH
5, R = I
6, R = CH_2COOMe
7, R = CH_2CH_2CN

(1) Procter and Gamble Predoctoral Fellow, 1987–1988.
(2) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.
(3) Larsen, S. D.; Grieco, P. A. *J. Org. Chem.* **1986**, *51*, 3553.
(4) Daly, J. W.; Tokuyama, T.; Habermehl, G.; Karle, I. L.; Witkop, B. *Justus Liebigs Ann. Chem.* **1969**, *729*, 198.
(5) Mori, K. *Tetrahedron* **1983**, *39*, 3107.

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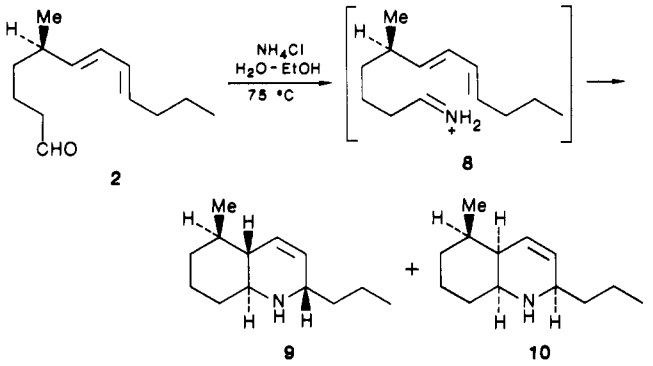
[pyridinium chlorochromate (PCC), NaOMe, CH_2Cl_2] of **3** followed by condensation of the resulting aldehyde with the ylide derived from (*E*)-2-hexenyltriphenylphosphonium bromide and subsequent cleavage of the tetrahydropyranyl ether employing pyridinium *p*-toluenesulfonate (PPTS)[6] in ethanol at 55 °C gave **4** in 73% overall yield as a 1.8:1 mixture of *E* and *Z* isomers respectively which were readily separated by preparative liquid chromatography. The enantiomeric purity of the (*E*,*E*)-dienyl alcohol **4** was confirmed by ^{19}F NMR analysis of the Mosher esters of **4** derived from (+)-MTPA and (−)-MTPA.[7] Alcohol **4** was transformed in a straightforward manner into iodide **5**, which was condensed with the anion derived from methyl (phenylsulfonyl)acetate in dimethyl sulfoxide. The alkylated product was smoothly desulfonylated with 3% sodium amalgam in methanol at −5 °C,[8] giving rise to ester **6** in 70% overall yield. Conversion of **6** into nitrile **7** was efficiently realized in an overall yield of 97% via a three-step sequence [(a) $LiAlH_4$, THF, 0 °C; (b) TsCl, Et_3N, CH_2Cl_2, DMAP; (c) NaCN, DMSO, 85 °C]. Nitrile **7** was subsequently reduced with diisobutylaluminum hydride in toluene at −78 °C, giving rise (99%) to enantiomerically pure aldehyde **2**.

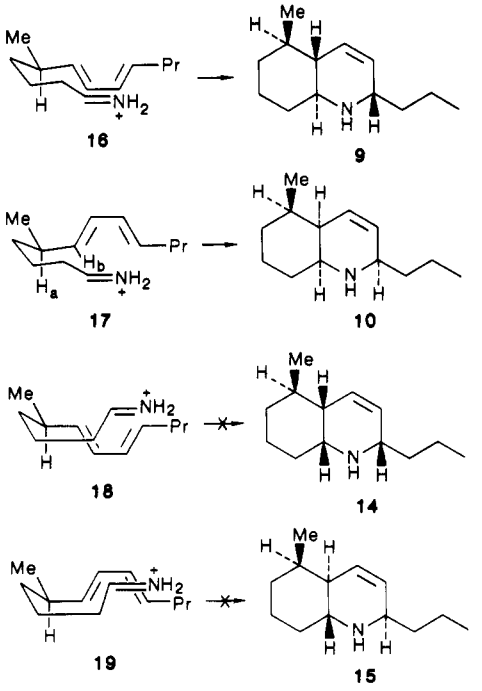
In order to probe the utility of dienyl aldehyde **2** in octahydroquinoline synthesis, we treated a 0.016 M solution of **2** in ethanol with an equal volume of a saturated aqueous ammonium chloride solution at ca. 75 °C for 48 h. Workup provided a 55% yield of two octahydroquinolines, **9** and **10**, in a ratio of 2.2:1. The structure of



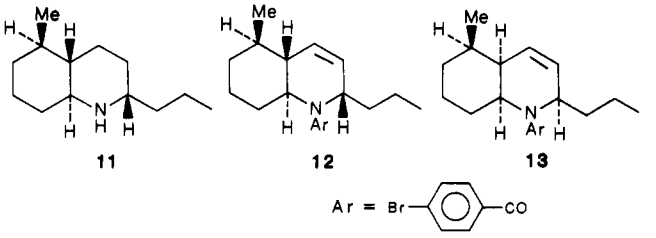
2 8 9 10

9 was initially established by ^1H NMR and its conversion upon reduction (H_2, 10% Pd/C, MeOH) into (−)-8a-epipumiliotoxin C (**11**).[9] The relative stereochemistry of octahydroquinolines **9** and **10** was unambiguously established by single-crystal X-ray analysis of the crystalline *p*-bromobenzamide derivatives **12**,[10] mp 110–112 °C, and **13**,[11] mp 142–143 °C, obtained from **9** and **10**. We were unable to detect, by employing a 360-MHz NMR spectrometer, any other octahydroquinoline including octahydroquinoline **14** with the pumiliotoxin C stereochemistry.

Scheme I



16 9 17 10 18 14 19 15

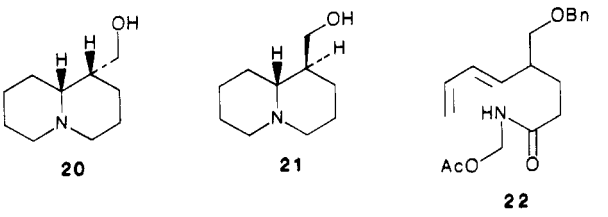


11 12 13

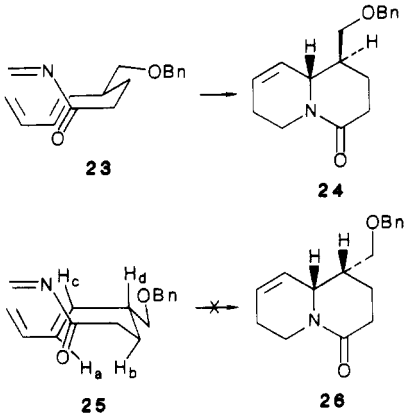
A priori, intramolecular cyclocondensation of intermediate immonium ion **8** can lead to four possible octahydroquinolines (Scheme I). Examination of Dreiding models of immonium ion **8** reveals two chair-like and two boat-like Diels–Alder transition states. Adducts **9** and **10** arise from the chair-like conformations **16** and **17** respectively. The formation of **9** as the major product was anticipated in view of the fact that conformation **17** leading to octahydroquinoline **10** is destabilized by a serious eclipsing interaction between H_a and H_b. The absence of isomers **14** and **15** is not surprising in view of the fact that these adducts are derived from boat-like conformations.

It is of interest to note that in the intramolecular imino Diels–Alder reaction where *N*-acyl imines are employed as heterodienophiles, Weinreb[12] found exclusive preference for boat-like transition states wherein the carbonyl group of the *s-cis*-*N*-acyl imine is endo to the diene. For example, in Weinreb's application of the intramolecular acyl imine Diels–Alder reacton to the synthesis of the quinolizidine alkaloids lupinine (**20**) and epilupinine (**21**),[13] it was found that thermolysis of methylol acetate **22** in refluxing *o*-dichlorobenzene provided bicyclic lactam **24** as the sole product. None of the epimeric lactam **26** could be detected. These results were rationalized by consideration of the two endo transition states **23** and **25**. The quasi-boat

(6) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
(7) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(8) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
(9) For a synthesis of pumiliotoxin C, see: Habermehl, G.; Andres, H.; Miyahara, K.; Witkop, B.; Daly, J. W. *Justus Liebigs Ann. Chem.* **1976**, 1577.
(10) Compound **12** crystallizes in the unique space group $P2_1/a$ with a = 14.355 (2) Å, b = 19.394 (4) Å, c = 13.398 (1) Å, and β = 91.62 (0)° at −155 °C; D_{calcd} = 1.341 g/cm^3 for Z = 8. A continuous θ–2θ scan at a rate of 4°/min over a range of 2° + dispersion and 5-s background counts was used to collect the 4877 unique intensities on a Picker goniostat. The structure was solved by direct methods and refined by full-matrix best squares to yield final residuals of R_F = 0.0740 and R_{WF} = 0.0722.
(11) Compound **13** crystallizes in the noncentrosymmetric space group $P2_12_12_1$ with a = 9.587 (3) Å, b = 12.480 (5) Å, and c = 15.313 (6) Å at −155 °C; D_{calcd} = 1.365 g/cm^3 for Z = 4. A continous θ–2θ scan at a rate of 4°/min over a range of 2° + dispersion and 5-s background counts was used to collect the 1406 unique intensities on a Picker goniostat. The structure was solved by direct methods and refined by full-matrix least squares to yield final residuals of R_F = 0.0426 and R_{WF} = 0.0414.
(12) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16.
(13) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661.



transition state **23** gives rise to cycloadduct **24**. The selectivity observed is attributed to an unfavorable, 1,4-nonbonded interaction between H_a and H_b and, more importantly, to an eclipsing interaction between H_c and H_d in the chair-like conformation **25** leading to the transition state.



In summary, it appears that the immonium-based intramolecular Diels–Alder reaction complements the intramolecular acyl imine methodology developed by Weinreb and co-workers. Application of the immonium ion based Diels–Alder reaction to the preparation of increasingly more demanding systems is under investigation.

Experimental Section

Melting points were determined on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. Infrared spectra (IR) were determined on a Perkin-Elmer 298 grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded at 360 MHz (Nicolet NT-360). Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ 0.00) as an internal standard. High-resolution mass spectra were recorded on a Kratos MS-80 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

All solvents are reagent grade unless otherwise stated. "Dry" solvents were dried immediately before use. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dimethyl sulfoxide (Me_2SO), triethylamine, and diisopropylamine were distilled from calcium hydride. Methylene chloride was dried by passing through a column of alumina (Woelm, basic activity I) and was stored over molecular sieves (type 3A). Thin-layer chromatography (TLC) was carried out on Analtech (Uniplate) glass plates precoated with silica gel GF (250 μm). Column chromatographic separations were performed on Merck silica gel 60, 70–230 mesh ASTM, whereas Merck silica gel 60, 230–400 mesh, was used for flash chromatography. Purity of all samples was estimated (>95%) on the basis of 360-MHz NMR, TLC, and HPLC analyses.

(*E*)-2-Hexenyltriphenylphosphonium Bromide. To a heterogeneous mixture of 6.69 g (19.5 mmol) of triphenylphosphonium bromide in 120 mL of benzene at room temperature was added dropwise 1.50 g (15.0 mmol) of (*E*)-2-hexen-1-ol. The mixture was heated at reflux for 10 h, using a Dean–Stark trap. Upon cooling (0 °C) of the homogeneous reaction mixture, the product crystallized. The crystals were filtered and washed several times with ether. There was obtained 6.36 g (100%) of the pure phosphonium bromide, mp 178–180 °C, which was dried under vacuum over P_2O_5 in a drying pistol heated at 78 °C: IR ($CHCl_3$) 3060, 2940, 1595, 1490, 1440, 1220, 1115, 1000, 965, 685, 600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.80–7.60 (m, 15 H), 5.82 (m, 1 H), 5.21 (m, 1 H), 4.54 (dd, 2 H, J = 14.8, 7.2 Hz), 1.85 (m, 2 H), 1.15 (sextet, 2 H, J = 7.4 Hz), 0.66 (t, 3 H, J = 7.4 Hz); high-resolution MS calcd for $C_{24}H_{26}BrP$-Br m/e 345.1795, found 345.1798.

(*R*)-2-Methyl-(*E*,*E*)-4,6-nonadienol (4). To a suspension of 128 g of dry Celite, 39.0 g (0.47 mol) of anhydrous sodium acetate, and 51.2 g (0.238 mol) of pyridinium chlorochromate in 0.7 L of methylene chloride was added 20.7 g (0.119 mol) of **3**.[5] The reaction mixture was mechanically stirred for 1.5 h at room temperature. The reaction mixture was diluted with 1 L of ether, filtered through Celite and a small amount of silica gel, and dried over anhydrous sodium sulfate. The clear filtrate was concentrated under reduced pressure at room temperature. A portion of the crude unstable aldehyde (18.8 g, 91%) [R_f 0.33 (20% ethyl acetate–hexane); IR (neat) 2940, 2885, 1720, 1465, 1450, 1380, 1345, 1260, 1200, 1180, 1120, 1070, 1020, 970, 905, 870, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.70 (d, 1 H, J = 1.4 Hz), 4.60–4.55 (m, 1 H), 3.95–3.40 (m, 4 H), 2.66–2.57 (m, 1 H), 1.78–1.41 (m, 6 H), 1.11 (d, 1.5 H, J = 6.8 Hz), 1.09 (d, 1.5 H, J = 6.8 Hz)] was used directly in the next reaction.

To a suspension of 41.0 g (96.4 mmol) of (*E*)-2-hexenyltriphenylphosphonium bromide in 500 mL of tetrahydrofuran at 0 °C was added dropwise 63.0 mL (96.4 mmol) of a 1.53 M solution of *n*-butyllithium in hexanes. The reaction mixture was mechanically stirred at room temperature for 45 min. The deep red solution was cooled to −78 °C, and a solution of 13.8 g (80.3 mmol) of the above crude aldehyde in 150 mL of tetrahydrofuran was added dropwise over a 30-min period. The reaction mixture was warmed to room temperature and stirred for 3 h. The orange reaction mixture was quenched by the addition of 15 mL of methanol. The homogeneous solution was concentrated under reduced pressure and the residue taken up in hexane. The resulting heterogeneous solution was filtered, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The thick dark brown oil was subjected to flash chromatography. Elution with 10% ether–hexane afforded 16.0 g (84%) of a mixture of cis and trans isomers as a clear oil, which was used directly in the next reaction.

To a solution of 12.7 g (53.3 mmol) of the above Wittig product in 100 mL of absolute ethanol was added 1.34 g (5.33 mmol) of pyridinium *p*-toluenesulfonate. The reaction mixture was stirred at 55 °C (bath temperature) for 4.5 h. The solvent was removed under reduced pressure. The residue was directly purified by flash chromatography (10% ethyl acetate–hexane) on 400 g of silica gel, affording 7.81 g (95%) of a clear oil. The ratio of *E*,*E* to *Z*,*E* isomers was 1.8:1 as determined by ^{1}H NMR. The isomeric dienes were separated on a Waters Associates Prep/LC system 500A using 2% ethyl acetate–hexane with one recycle. *Z*,*E* isomer: R_f 0.30 (10% ethyl acetate–hexane, 2 developments); IR (neat) 3700–3100, 3000, 2960, 2930, 2870, 1650, 1455, 1380, 1335, 1260, 1220, 1030, 980, 945, 910, 820, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.30 (ddd, 1 H, J = 14.8, 11.1, 1.1 Hz), 6.05 (t, 1 H, J = 11.0 Hz), 5.68 (dt, 1 H, J = 14.8, 7.2 Hz), 5.05 (t, 1 H, J = 10.3 Hz), 3.51–3.43 (m, 1 H), 3.37–3.31 (m, 1 H), 2.89–2.77 (m, 1 H), 2.05 (q, 2 H, J = 6.8 Hz), 1.91 (br s, 1 H), 1.39 (sextet, 2 H, J = 7.3 Hz), 0.95 (d, 3 H, J = 6.5 Hz), 0.88 (t, 3 H, J = 7.2 Hz); high-resolution MS calcd for $C_{10}H_{18}O$ m/e 154.1357, found 154.1356. *E*,*E* isomer: R_f 0.28; $[\alpha]^{23}_D$ −39.33° (*c*, 3.580, $CHCl_3$); IR (neat) 3700–3100, 3020, 2960, 2930, 2870, 1460, 1380, 1340, 1100, 1030, 985, 945 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.14–5.97 (m, 2 H), 5.63 (dt, 1 H, J = 14.8, 6.9 Hz), 5.42 (dd, 1 H, J = 14.8, 7.9 Hz), AB q centered at δ 3.45, $\Delta\nu_{AB}$ = 33.5 Hz (H_A, dt, 1 H, J = 10.4, 6.0 Hz and H_B, ddd, 1 H, J = 10.4, 7.6, 3.2 Hz), 2.37 (heptet, 1 H, J = 7.2 Hz), 2.04 (q, 2 H, J = 7.0 Hz), 1.52 (t, 1 H, J = 4.5 Hz), 1.40 (sextet, 2 H, J = 7.3 Hz), 1.01 (d, 3 H, J = 6.5 Hz), 0.90 (t, 3 H, J = 7.4 Hz); high-resolution MS calcd for $C_{10}H_{18}O$ m/e 154.1357, found 154.1356.

(*R*)-2-Methyl-1-iodo-(*E*,*E*)-4,6-nonadiene (5). To a solution of 940 mg (6.10 mmol) of alcohol **4** in 25 mL of methylene chloride at 0 °C were added 934 μL (6.71 mmol) of triethylamine, 1.28 g (6.71 mmol) to tosyl chloride, and 73 mg (0.60 mmol) of 4-(dimethylamino)pyridine, respectively. The mixture was stirred at 0 °C for 3 h and at room temperature for 5 h. The resulting heterogeneous mixture was diluted with methylene chloride (50 mL) and washed with 5% aqueous hydrochloric acid solution (2 × 25 mL). The aqueous phase was separated and extracted with methylene chloride (1 × 20 mL). The organic layers were combined, washed with brine solution (1 × 25 mL), dried over an-

hydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting light amber oil was purified by flash chromatography on 100 g of silica gel. Elution with 5% ethyl acetate–hexane afforded 1.72 g (91.4%) of a clear oil [R_f 0.36 (10% ethyl acetate–hexane); $[\alpha]^{23}_D$ + 14.4° (c 1.675, $CHCl_3$); IR (neat) 3020, 2960, 2930, 2880, 1660, 1600, 1500, 1460, 1365, 1310, 1295, 1215, 1190, 1180, 1125, 1100, 1040, 1010, 990, 970, 830, 810, 790, 705, 690, 665, 620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (AB q, 4 H, J = 8.3 Hz, $\Delta\nu_{AB}$ = 157.7 Hz), 6.02–5.87 (m, 2 H), 5.60 (dt, 1 H, J = 14.4, 6.8 Hz), 5.29 (dd, 1 H, J = 14.4, 7.2 Hz), AB portion of ABX system centered at δ 3.85, $\Delta\nu_{AB}$ = 28.6 Hz (H_A, dd, 1 H, J = 9.4, 6.5 Hz and H_B, dd, 1 H, J = 9.4, 6.8 Hz), 2.57–2.48 (m, 1 H), 2.44 (s, 3 H), 2.02 (q, 2 H, J = 7.2 Hz), 1.39 (sextet, 2 H, J = 7.2 Hz), 1.00 (d, 3 H, J = 6.8 Hz), 0.89 (t, 3 H, J = 7.2 Hz)], which was used directly in the next reaction.

To a solution of 2.93 g (9.49 mmol) of tosylate obtained from two experiments in 65 mL of acetone was added 7.11 g (47.4 mmol) of sodium iodide. The reaction mixture was heated at 45–50 °C for 20 h. The resulting red solution was concentrated under reduced pressure. The dark red residue was directly chromatographed on 200 g of silica gel. Elution with 1% ethyl acetate–hexane afforded 2.33 g (92%) of iodide **5** as a clear oil: R_f 0.78 (10% ethyl acetate–hexane); $[\alpha]^{23}_D$ −31.1° (c 1.61, $CHCl_3$); IR (neat) 3020, 2960, 2930, 2870, 1660, 1455, 1425, 1375, 1285, 1280, 1195, 1170, 1140, 985, 950, 800, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08–6.94 (m, 2 H), 6.65 (dt, 1 H, J = 14.4, 7.0 Hz), 6.44 (dd, 1 H, J = 14.4, 7.6 Hz), AB portion of ABX system centered at δ 4.14, $\Delta\nu_{AB}$ = 32.8 Hz (H_A, dd, 1 H, J = 9.5, 5.6 Hz and H_B, dd, 1 H, J = 9.5, 7.0 Hz), 3.39 (heptet, 1 H, J = 6.5 Hz), 3.03 (q, 2 H, J = 7.2 Hz), 2.40 (sextet, 2 H, J = 7.3 Hz), 2.12 (d, 3 H, J = 6.5 Hz), 1.90 (t, 3 H, J = 7.4 Hz); high-resolution MS calcd for $C_{10}H_{17}I$ m/e 264.0375, found 264.0388. The iodide was found to be unstable and was used immediately.

Methyl (*R*)-4-Methyl-(*E*,*E*)-5,7-undecadienoate (6). To a solution of dimsyl sodium [prepared from 1.04 g (24.5 mmol) of sodium hydride (56.8% oil dispersion) and 80 mL of dimethyl sulfoxide] was added 5.63 g (26.3 mmol) of solid methyl (phenylsulfonyl)acetate. After the mixture was stirred at 60 °C for 1 h, a solution of 2.32 g (8.75 mmol) of iodide **5** in 20 mL of dimethyl sulfoxide was added at 60 °C. After the solution was stirred for an additional 2 h, the reaction was quenched by the addition of 400 mL of brine. The mixture was extracted with ether (5 × 100 mL). The ether layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting yellow residue was purified by flash chromatography on 250 g of silica gel. Elution with 5% ethyl acetate–hexane afforded 2.15 g (70%) of the corresponding sulfone as a clear viscous oil [R_f 0.16 (10% ethyl acetate–hexane); IR (neat) 3070, 3030, 3010, 2970, 2940, 2880, 1745, 1590, 1480, 1450, 1440, 1380, 1335, 1325, 1310, 1270, 1230, 1205, 1155, 1150, 1085, 1045, 1020, 995, 955, 850, 840, 830, 760, 745, 725, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84 (d, 2 H, J = 7.6 Hz), 7.67 (t, 1 H, J = 7.4 Hz), 7.56 (t, 2 H, J = 7.6 Hz), 5.24–5.14 (m, 1 H), 4.01–3.90 (m, 1 H), 3.65 and 3.55 (2 s, 3 H), 2.25–2.16 (m, 1 H), 2.09–1.84 (m, 4 H), 1.45–1.31 (m, 2 H), 1.02–0.98 (m, 3 H), 0.92–0.84 (m, 3 H); high-resolution MS calcd for $C_{19}H_{26}O_4S$ (M^+) m/e 350.1552, found 350.1549], which was employed directly in the next reaction.

To a solution of 5.67 g (16.1 mmol) of sulfone obtained from three experiments in 100 mL of anhydrous methanol were added 11.4 g (80.6 mmol) of disodium hydrogen phosphate and 22.5 g of 3% sodium–mercury amalgam at −5 °C. The contents were mechanically stirred at −5 °C for 1 h. After filtration, the solution was diluted with 250 mL of brine and extracted with ether (4 × 150 mL). The ether extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on 500 g of silica gel. Elution with 8% ethyl acetate–hexane afforded 3.41 g (100%) of ester **6** as a light yellow oil: R_f 0.40 (10% ethyl acetate–hexane); $[\alpha]^{23}_D$ −21.4° (c = 1.20, $CHCl_3$); IR (neat) 3020, 2960, 2930, 2870, 1740, 1455, 1440, 1380, 1365, 1325, 1260, 1200, 1170, 1090 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.02–5.92 (m, 2 H), 5.63–5.55 (m, 1 H), 5.40–5.33 (m, 1 H), 3.65 (s, 3 H), 2.32–2.25 (m, 2 H), 2.14 (quintet, 1 H, J = 7.2 Hz), 2.03 (q, 2 H, J = 7.2 Hz), 1.72–1.52 (m, 2 H), 1.49 (quintet, 2 H, J = 7.2 Hz), 1.01 (d, 3 H, J = 6.8 Hz), 0.90 (t, 3 H, J = 7.2 Hz); high-resolution MS calcd for $C_{13}H_{22}O_2$ (M^+) m/e 210.1620, found 210.1615.

(*R*)-1-Cyano-4-methyl-(*E*,*E*)-5,7-undecadiene (7). To a suspension of 481 mg (12.6 mmol) of lithium aluminum hydride in 4 mL of tetrahydrofuran at 0 °C was added dropwise a solution of 268 mg (1.26 mmol) of diene ester **6** in 2 mL of tetrahydrofuran. The reacton mixture was stirred at 0 °C for 45 min. The reaction was quenched at 0 °C by sequential addition of 480 μL of water, 480 μL of 15% sodium hydroxide aqueous solution, and 1.5 mL of water. The resulting white suspension was filtered through Celite, and the salts were thoroughly washed with ether. The filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The diene alcohol (225 mg, 97%) was sufficiently pure for the subsequent reaction step. An analytical sample was obtained by flash chromatography (10% ethyl acetate–hexane) on 5 g of silica gel: R_f 0.10 (10% ethyl acetate–hexane); $[\alpha]^{23}_D$ −20.8° (c 1.264, $CHCl_3$); IR (neat) 3700–3100, 3020, 2960, 2930, 2880, 1455, 1380, 1340, 1060, 1030, 985, 950, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.04–5.89 (m, 2 H), 5.64–5.52 (m, 1 H), 5.43 (dd, 1 H, J = 13.8, 7.9 Hz), 3.62 (t, 2 H, J = 6.5 Hz), 2.19–2.10 (m, 1 H), 2.03 (q, 2 H, J = 7.2 Hz), 1.63–1.50 (m, 3 H), 1.45–1.27 (m, 4 H), 1.00 (d, 3 H, J = 6.5 Hz), 0.90 (t, 3 H, J = 7.2 Hz); high-resolution MS calcd for $C_{12}H_{22}O$ (M^+) m/e 182.1671, found 182.1677.

To a solution of 88 mg (0.48 mmol) of the above diene alcohol in 2 mL of methylene chloride were added 73.8 μL (0.53 mmol) of triethylamine, 101 mg (0.53 mmol) of tosyl chloride, and 6.0 mg (0.048 mmol) of 4-(dimethylamino)pyridine, respectively. The solution was stirred at room temperature for 2 h. The resulting heterogeneous mixture was washed with 5% aqueous hydrochloric acid (2 × 1 mL). The aqueous layers were extracted with methylene chloride (2 × 3 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on 8 g of silica gel. Elution with 10% ether–hexane afforded 166 mg (100%) of tosylate [R_f 0.20 (10% ethyl acetate–hexane); $[\alpha]^{23}_D$ −11.9° (c 1.05, $CHCl_3$); IR (neat) 3030, 2980, 2940, 2880, 1610, 1505, 1460, 1370, 1330, 1220, 1195, 1180, 1125, 1105, 1044, 1025, 995, 975, 925, 830, 820, 799, 740, 710, 695, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (AB q, 4 H, J = 8.3 Hz, $\Delta\nu_{AB}$ = 159.1 Hz), 6.00–5.85 (m, 2 H), 5.57 (quintet, 1 H, J = 7.2 Hz), 5.32 (dd, 1 H, J = 14.4, 7.9 Hz), 4.00 (t, 2 H, J = 6.5 Hz), 2.50 (s, 3 H), 2.13–1.99 (m, 3 H), 1.68–1.51 (m, 2 H), 1.45–1.24 (m, 4 H), 0.94 (d, 3 H, J = 6.5 Hz), 0.90 (t, 3 H, J = 7.2 Hz); high-resolution MS calcd for $C_{19}H_{28}O_3S$ (M^+) m/e 336.1759, found 336.1742], which was used directly in the next reaction.

To a solution of 151 mg (0.449 mmol) of the above tosylate in 4 mL of dimethyl sulfoxide was added 110 mg (2.24 mmol) of sodium cyanide. The mixture was heated at 80–85 °C for 3.5 h. The reaction mixture was diluted with 20 mL of water. The product was extracted with hexane (3 × 30 mL). The extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (10% ethyl acetate–hexane) on 20 g of silica gel afforded 86 mg (100%) of nitrile **7** as a clear oil: R_f 0.52 (50% methylene chloride–hexane; 2 developments); $[\alpha]^{23}_D$ −20.1° (c 1.01, $CHCl_3$); IR (neat) 3020, 2960, 2930, 2970, 2250, 1460, 1430, 1380, 1335, 990, 955, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.02–5.93 (m, 2 H), 5.66–5.54 (m, 1 H), 5.41–5.32 (m, 1 H), 2.32 (t, 2 H, J = 7.2 Hz), 2.23–2.10 (m, 1 H), 2.04 (q, 2 H, J = 7.2 Hz), 1.70–1.34 (m, 6 H), 1.01 (d, 3 H, J = 6.8 Hz), 0.90 (t, 3 H, J = 7.2 Hz); high-resolution MS calcd for $C_{13}H_{21}N$ (M^+) m/e 191.1674, found 191.1699.

(*R*)-5-Methyl-(*E*,*E*)-6,8-dodecadienal (2). To a solution of 128.0 mg (0.669 mmol) of nitrile **7** in 4 mL of hexane at −78 °C was added 3.35 mL (3.34 mmol) of a 1 M diisobutylaluminum hydride solution in toluene. The reaction mixture was stirred at −78 °C for 15 min and was carefully quenched with excess methanol. The reaction mixture was filtered through a small amount of Celite, and the salts were washed with ether. The filtrate was concentrated under reduced pressure at 10 °C. The resulting volatile oil was purified by flash chromatography on 6 g of silica gel. Elution with 5% ether–hexane afforded 129 mg (99%) of aldehyde **2** as a volatile clear oil: R_f 0.61 (50% methylene chloride–hexane); $[\alpha]^{23}_D$ −21.7° (c 1.34, $CHCl_3$); IR ($CHCl_3$) 3020, 2980, 2940, 2740, 1725, 1465, 1385, 1235, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.74 (t, 1 H, J = 1.8 Hz), 6.05–5.91 (m, 2 H), 5.58 (td, 2 H, J = 7.2, 1.8 Hz), 2.14 (quintet, 1 H, J = 6.8 Hz), 2.03 (q, 2 H, J = 7.2 Hz), 1.68–1.24 (m, 8 H), 0.99 (d, 3 H, J = 6.8 Hz), 0.90

(t, 3 H, J = 7.2 Hz); high-resolution MS calcd for $C_{13}H_{22}O$ (M^+) m/e 194.1671, found 194.1689.

Octahydroquinoline Synthesis via Intramolecular Diels–Alder Reaction. To a solution of 254 mg (1.31 mmol) of dienyl aldehyde **2** in 100 mL of ethanol was added 100 mL of a saturated aqueous ammonium chloride solution. The reaction mixture was heated at 75 °C. After 48 h, the reaction mixture was cooled to room temperature and diluted with 150 mL of water. The reaction mixture was washed with hexane (5 × 75 mL), basified with solid potassium hydroxide, and extracted with ether (5 × 100 mL). The combined organic extracts were concentrated under reduced pressure to a 50-mL volume and washed with water (2 × 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo, leaving 195 mg of crude product. ^{1}H NMR ($CDCl_3$) analysis of the crude product indicated a 2.2:1 ratio of Diels–Alder adducts. The isomeric octahydroquinolines were separated by flash chromatography on 60 g of silica gel. Elution with 2% methanol–chloroform provided, in order of elution, 87 mg of octahydroquinoline **9** [R_f 0.49 (chloroform–methanol–concentrated ammonium hydroxide, 85:15:1); **9**·HCl $[\alpha]^{23}_D$ +37.3° (c 2.92, MeOH); IR (**9**·HCl) (CCl_4) 3030, 2960, 2930, 2870, 2860, 2810, 2730, 2690, 2520, 1615, 1605, 1585, 1455, 1450, 1375, 1330, 1295, 1290, 1235, 1165, 1135, 1100, 710 cm^{-1}; ^{1}H NMR (free amine, $CDCl_3$) δ 5.87 (d, 1 H, J = 10.4 Hz), 5.68 (dt, 1 H, J = 10.4, 3.2 Hz), 3.33–3.24 (m, 1 H), 2.37 (ddd, 1 H, J = 11.9, 9.4, 3.6 Hz), 2.33–2.20 (m, 1 H), 1.80–1.65 (m, 3 H), 1.51–0.90 (m, 15 H); ^{1}H NMR (hydrochloride, $CDCl_3$) δ 6.04–5.78 (m, 3 H), 5.67 (dt, 1 H, J = 10.4, 3.1 Hz), 3.56–3.48 (m, 1 H), 2.54 (ddd, 1 H, J = 12.5, 9.4, 3.3 Hz), 1.95 (br d, 1 H, J = 7.2 Hz), 1.80–1.00 (m, 10 H), 0.96 (d, 3 H, J = 6.5 Hz), 0.92 (t, 3 H, J = 7.2 Hz); high-resolution MS calcd for $C_{13}H_{23}N$ m/e 193.1830, found 193.1816] and 42 mg of octahydroquinoline **10** [R_f 0.43; $[\alpha]^{23}_D$ −7.5° (c 0.80, MeOH); IR (**10**·HCl) (CCl_4) 3030, 2970, 2940, 2880, 2800, 2790–2200, 1585, 1460, 1390, 1330, 1280, 1130, 1110, 970, 825, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.79–5.69 (m, 1 H), 3.67–3.56 (m, 1 H), 3.28 (ddd, 1 H, J = 8.6, 4.4, 4.4 Hz), 2.51 (br s, 1 H), 1.86–1.08 (m, 12 H), 1.02 (d, 3 H, J = 7.2 Hz), 0.95 (t, 3 H, J = 7.2 Hz); high-resolution MS calcd for $C_{13}H_{23}N$ m/e 193.1830, found 193.1836].

***trans*-Octahydroquinoline Derivative 12.** To a solution of 23.2 mg (0.120 mmol) of *trans*-octahydroquinoline in 1.5 mL of methylene chloride were added 51 μL (0.36 mmol) of triethylamine, 80.0 mg (0.361 mmol) of *p*-bromobenzoyl chloride, and 7.4 mg (0.060 mmol) of 4-(dimethylamino)pyridine, respectively. The reaction mixture was stirred for 8.5 h at room temperature. The solution was concentrated under reduced pressure, and the residue was directly subjected to flash chromatography (10% ethyl acetate–hexane) on 20 g of silica gel. Recrystallization from hexanes provided 37.2 mg (82.4% yield) of amide **12** as colorless crystals, mp 110–112 °C: R_f 0.31 (10% ethyl acetate–hexane); ^{1}H NMR ($CDCl_3$) δ 7.40 (AB q, 4 H, J = 9.6 Hz, $\Delta\nu_{AB}$ = 76.8 Hz), 5.88 (d, 1 H, J = 10.2 Hz), 5.67–5.56 (m, 1 H), 4.07–3.90 (br s, 1 H), 3.04–2.93 (m, 1 H), 2.78–2.48 (br s, 1 H), 2.30–2.15 (br t, 1 H), 1.90–1.08 (m, 10 H), 1.04 (d, 3 H, J = 7.1 Hz), 0.90 (t, 3 H, J = 7.1 Hz). Anal. Calcd for $C_{20}H_{26}BrNO$: C, 63.83; H, 6.96. Found: C, 63.90; H, 6.79.

***cis*-Octahydroquinoline Derivative 13.** To a solution of 22.3 mg (0.116 mmol) of *cis*-octahydroquinoline in 1.5 mL of methylene chloride were added 57 μL (0.404 mmol) of triethylamine, 76.0 mg (0.058 mmol) of *p*-bromobenzoyl chloride, and 7.0 mg (0.058 mmol) of 4-(dimethylamino)pyridine, respectively. The reaction mixture was stirred for 8.5 h at room temperature. The solution was concentrated under reduced pressure and directly subjected to flash chroamtography (10% ethyl acetate–hexane) on 25 g of silica gel. Recrystallization from hexanes provided 36.5 mg (83.8 % yield) of the amide **13** as colorless needles, mp 142–143 °C: R_f 0.16 (10% ethyl acetate–hexane); ^{1}H NMR ($CDCl_3$) δ 7.40 (AB q, 4 H, J = 9.6 Hz, $\Delta\nu_{AB}$ = 110.4 Hz), 5.94–5.85 (m, 1 H), 5.74–5.65 (d, 1 H, J = 10.2 Hz), 4.88–4.77 (m, 1 H), 3.67–3.56 (m, 1 H), 2.37 (br s, 1 H), 1.93–0.80 (m, 17 H). Anal. Calcd for $C_{20}H_{26}BrNO$: C, 63.83; H, 6.96. Found: C, 63.69; H, 6.76.

8a-Epipumiliotoxin C (11). A suspension of 40.0 mg of 10% palladium on carbon in 1.0 mL of methanol was repeatedly evacuated and flushed with hydrogen. To this suspension was added a solution of 79.5 mg (0.411 mmol) of *trans*-octahydroquinoline **9** in 2.0 mL of methanol. The contents were vigorously stirred under 1 atm of hydrogen for 30 min at room temperature. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo, affording 78.6 mg (98%) of **11** as a yellow oil: R_f 0.35 (85:15:1 chloroform–methanol–concentrated ammonium hydroxide); $[\alpha]^{23}_D$ −30.8° (c 1.327, MeOH); IR (free amine, CCl_4) 2930, 2860, 1740, 1455, 1380, 1140, 720, 640 cm^{-1}; IR (hydrochloride, CCl_4) 2930, 2860, 2700–2240, 1730, 1590, 1455, 1380, 1130, cm^{-1}; ^{1}H NMR (free amine, $CDCl_3$) δ 2.96 (dd, 1 H, J = 6.1, 5.8 Hz), 2.37 (td, 1 H, J = 10.5, 3.2 Hz), 1.77–0.95 (m, 17 H), 0.92 (t, 3 H, J = 7.2 Hz), 0.84 (d, 3 H, J = 6.2 Hz); ^{1}H NMR (hydrochloride, $CDCl_3$) δ 3.40 (ddd, 1 H, J = 9.4, 4.7, 4.7 Hz), 2.72 (td, 1 H, J = 10.7, 3.4 Hz), 2.17 (br d, 1 H, J = 10.4 Hz), 2.12–1.97 (m, 1 H), 1.90–1.01 (m, 14 H), 0.95 (t, 3 H, J = 7.2 Hz), 0.89 (d, 3 H, J = 6.0 Hz); high-resolution MS calcd for $C_{13}H_{25}N$ (M^+) m/e 195.1986, found 195.1962.

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