A Stereoselective Synthesis of (±)-H_{12}-Histrionicotoxin and Related Photoaffinity-Labeled Congeners

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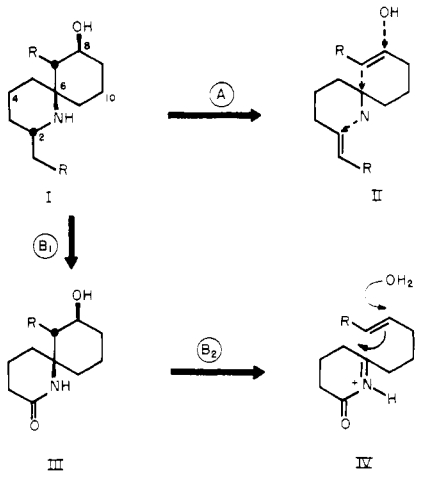
Abstract: A practical six-step stereoselective total synthesis of (±)-perhydrohistrionicotoxin (**4a**) (H_{12}-HTX) is reported. The desired azaspiro[5.5]undecane 6,6 ring system found in these alkaloid toxins has been constructed via the formic acid induced cyclization of either dihydropyridone **6** or carbinolamide **9**. The photoaffinity-labeled toxin analogue **4c** has also been prepared, which binds to *Torpedo californica* electroplax membrane fragments with binding affinities comparable with those of (±)-H_{12}-HTX (**4a**).

In recent years the tropical "arrow poison frogs", belonging to the genera *Dendrobates*, have been found to yield a host of new structurally unique alkaloids.[2,3] These bases, which are localized in the frog's defensive skin secretions, have been found to be highly active venoms as well as mucosal tissue irritants toward both mammals and reptiles. The meticulous investigations of Daly, Witkop, Karle, and co-workers have been instrumental in revealing the structures of many of these physiologically active alkaloids, which have attracted widespread interest as targets for total synthesis.[3] Three representative alkaloids, which have been isolated by the NIH group, are shown below to illustrate several common substructural relationships.

The C_{19} alkaloids histrionicotoxin (HTX)[2a-d] (**1**) and gephyrotoxin (**2**)[4] (*Dendrobates histrionicus*) share common cis enyne side chains while pumiliotoxin-C (**3**)[4] (*Dendrobates pumilio*) and gephyrotoxin (**2**) are both elaborated *cis*-decahydroquinolines. Other pumiliotoxin-C-class alkaloids of the C_{19} type possessing the cis enyne moiety have recently been tentatively identified.[4]

Both histrionicotoxin (**1**) and perhydrohistrionicotoxin (H_{12}-HTX) (**4a**) have attracted considerable interest from the standpoint of total synthesis, and while a total synthesis of HTX is yet to be accomplished, several different approaches to the construction of H_{12}-HTX have been reported.[5,6] The attention given to these objectives stems from their unique properties as neurotoxins in conjunction with the scarcity of HTX (ca. 200 μg per frog). It has been shown that both **1** and **4a** selectively bind to the acetylcholine receptor and interupt transsynaptic transmission of neuromuscular impulses.[7] Both **1** and **4a** block postsynaptic membrane depolarization while not interferring with acetylcholine binding. It has been postulated that these toxins prevent membrane depolarization by reversible binding to the receptor ion channel or "ion conductance modulator".[7]

Scheme I



The objectives of the current study have been to develop a highly practical laboratory synthesis of (±)-perhydrohistrionicotoxin (**4a**) as well as a suitably functionalized photoaffinity-labeled congener, e.g., **4c**, that might be employed to label that (those) polypeptide(s) that is the structural component(s) of the acetylcholine receptor ion channel.[8] The rationale for selecting the C_5 side chain terminus for photoaffinity labeling was predicated upon choosing a site distal to *both* the amine and C_8-hydroxyl functions, which are probably critical to toxin receptor binding. Accordingly, the

(1) (a) National Institutes of Health Postdoctoral Fellow. (b) Taken from the Ph.D. Thesis of R. E. Cherpeck, Department of Chemistry, California Institute of Technology, 1980.

(2) (a) Witkop, B. *Experientia* **1971**, *27*, 1121. (b) Daley, J. W.; Karle, I. L.; Meyers, W.; Tokuyama, T.; Walters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870. (c) Tokuyama, T.; Uenoyama, K.; Brown, G.; Daly, J. W.; Witkop, B. *Helv. Chim. Acta* **1974**, *57*, 2597. (d) Karle, I. L. *J. Am. Chem. Soc.* **1973**, *95*, 4036. (e) Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J.; Karle, I. L. *Ibid.* **1980**, *102*, 830.

(3) For recent reviews, see: (a) Inubushi, Y.; Ibuka, T. *Heterocycles* **1977**, *8*, 633. (b) Daly, J. W.; Brown, A. B.; Mensah-Dwumah, M.; Meyers, C. W. *Toxicon* **1978**, *16*, 163.

(4) Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128.

(5) (a) Aratani, M.; Dunkerton, L. V.; Fukuyama, T.; Kishi, Y.; Kakoi, H.;f Sugiura, S.; Inoue, S. *J. Org. Chem.* **1975**, *40*, 2009. (b) Fukuyama, T.; Dunkerton, L. V.; Aratani, M.; Kishi, Y. *Ibid.* **1975**, *40*, 2011. (c) Corey, E. J.; Arnett, J. F.; Widiger, G. N. *J. Am. Chem. Soc.* **1975**, *97*, 430. (d) Corey, E. J.; Petrzilka, M.; Ueda, Y. *Helv. Chim. Acta* **1977**, *60*, 2294 and references cited therein.

(6) For pertinent model studies directed toward the synthesis of the 1-azaspiro[5.5]undecane ring system, see: (a) Corey, E. J.; Balanson, R. D. *Heterocycles* **1976**, *5*, 445. (b) Bond, F. T.; Stemke, J. E.; Powell, D. W. *Synth. Commun.* **1975**, *5*, 427. (c) Gossinger, E.; Imhof, R.; Wehrli, H. *Helv. Chim. Acta* **1975**, *58*, 96. (d) Tufariello, J. J.; Trybulski, E. J. *J. Org. Chem.* **1974**, *39*, 3378.

(7) Elliott, J.; Raftery, M. A. *Biochemistry* **1979**, *18*, 1968 and references cited therein.

(8) For reviews on photoaffinity labeling, see: Bayler, H.; Knowles, J. R. *Methods Enzymol.* **1977**, *46*, 69. Chowdhry, V.; Westheimer, F. *Annu. Rev. Biochem.* **1979**, *48*, 293.

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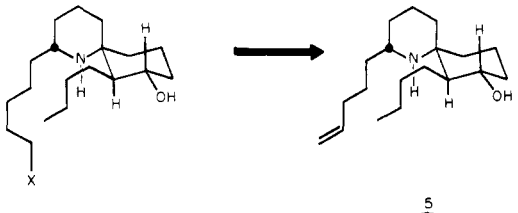
functionalized HTX derivative **5** was chosen as the penultimate objective for the present study.



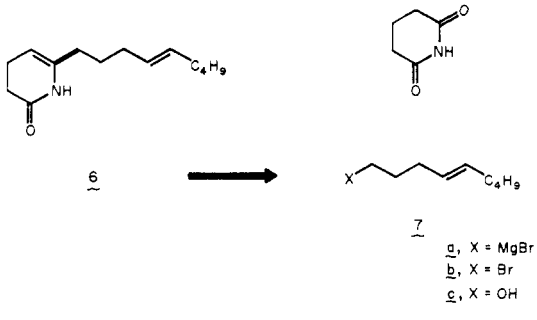
5

4a, X = H
b, X = OH
c, X = O-(2-NO2, 4-N3-C6H3)

The two basic approaches to the synthesis of histrionicotoxin (**1**), perhydrohistrionicotoxin (**4a**), and related congeners under investigation in these laboratories are illustrated in Scheme I. Both **1** and **4a** (R = HC=CHC≡CH or *n*-C_4H_9), as depicted in I, possess a latent skeletal symmetry element that is revealed when the N–C_1, C_6–C_7, and C_8–OH bonds are disconnected as in transform A. In principle, the requisite stereocenters at C_6 C_7, and C_8 can be constructed in a single step via electrophilic olefin addition. In the present study the less-symmetric toxin congeners **4** were derived by a variant on this approach from spirolactam III (R = *n*-C_4H_9), which had been prepared earlier by Kishi[5a,b] and Corey[5c] in a successful synthesis of **4a**. The choice of this latter route becomes compelling in the face of the uncertainties surrounding the construction of photoaffinity-labeled toxin analogues that might retain high receptor binding affinities. The following discussion describes the viability of employing the acylimmonium ion approach, IV → III, in a practical synthesis of histrionicotoxin congeners **4** and **5**.[9]

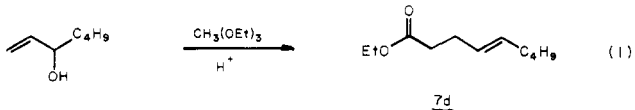
Results and Discussion

The synthesis of the dihydropyridone **6**, a suitable precursor to acylimmonium ion IV (R = *n*-C_4H_9), was efficiently carried out from glutarimide and the Grignard reagent **7a**. Following



6 **7**

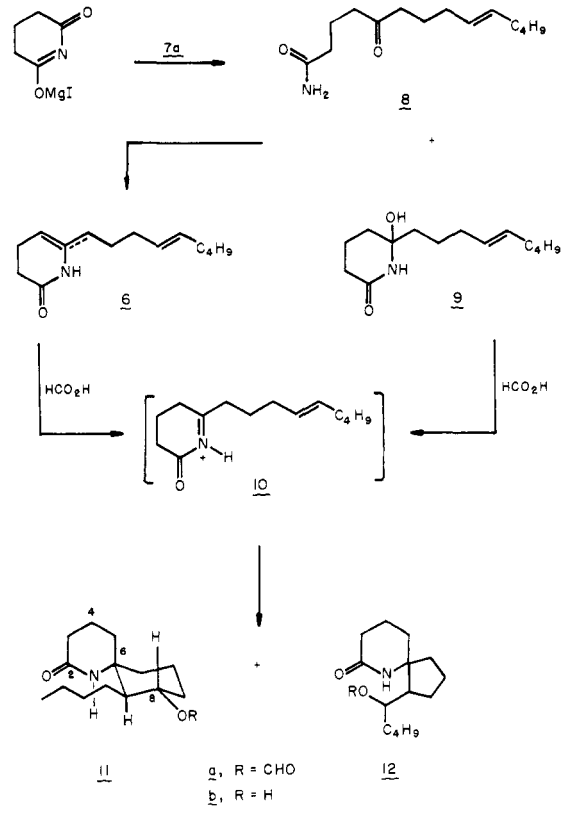
a, X = MgBr
b, X = Br
c, X = OH



7d (1)

conventional lines, 1-hepten-3-ol was transformed into the unsaturated ester **7d** (eq 1) in 95% yield via the orthoester Claisen rearrangement.[10] Lithium aluminum hydride reduction of **7d** and subsequent conversion of **7c** to the corresponding unsaturated bromide was carried out in a 66% overall yield from the heptenol starting material. Following established precedent,[11] the addition

Scheme II



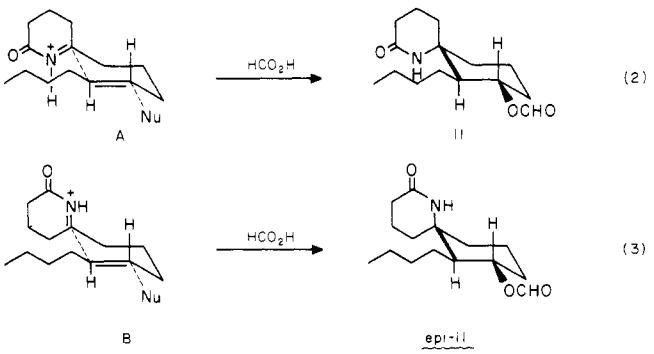
8 **6** **9** **10** **11** **12**

a, R = CHO
b, R = H

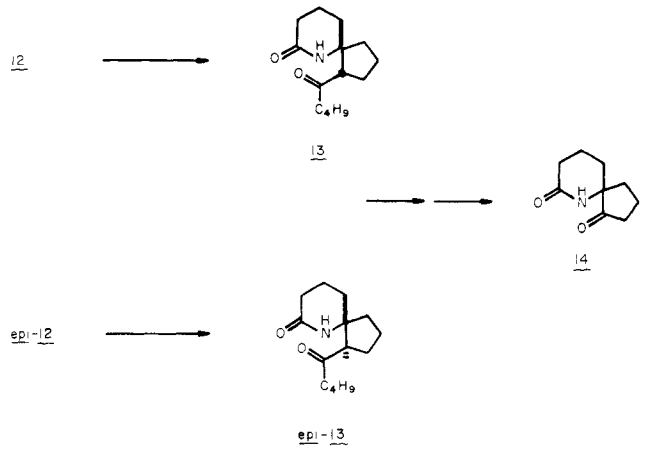
of Grignard reagent **7a** to the iodomagnesium salt of glutarimide in diethyl ether afforded a 62% yield of *both* ketoamide **8** and carbinolamide **9** as a 1:1 mixture (Scheme II). Although **8** and **9** could not be effectively separated, the mixture could be efficiently transformed to the dihydropyridone **6** accompanied by minor amounts of its exocyclic olefinic isomer (K_{eq}(endo ⇄ exo) = 9) in 75% yield by acid catalysis with azeotropic removal of water. In exploring conditions to improve the overall efficiency of the Grignard addition step, we found that if a solution of the glutarimide salt was prepared in *dichloromethane*, the addition of Grignard reagent **7a** proceeded in nearly quantitative yield to afford the carbinolamide **9** uncontaminated by ketoamide **8**. After exploring a range of acid-catalyzed cyclization conditions, we found that 0.1 M solutions of **6** in anhydrous formic acid (25 °C, 32 h) afforded a mixture of lactam cyclization products from which the nicely crystalline lactam **11a** was isolated in 40% yield after chromatography. Hydrolysis of the formate ester (MeOH, MeONa) afforded hydroxylactam 11b, mp 133–136 °C, which was found to be identical in all respects with a independently prepared sample provided by Professor Kishi.[5a] An experimentally simplified procedure for the synthesis of the desired lactam **11a** was developed once the technical details for the synthesis of carbinolamide **9** had been refined. Direct acid-catalyzed cyclization of the *unpurified* carbinolamide **9** afforded the desired lactam formate ester **11a**, which could be purified by direct crystallization from diisopropyl ether. By this procedure a 33% yield of **11a** was realized for the combined two steps from glutarimide. These complementary sets of experiments confirm that either enamide **6** or carbinolamide **9** are effective acylimmonium ion precursors. However, this was shown *not* to be the case for ketoamide **8**, which may be recovered intact after the usual formic acid treatment.

A priori, there are four completing cyclization modes that are accessible to acylimmonium ion **10**; two of these result in the formation of the C_6 diastereoisomeric 1-azaspiro[5.5]undecane lactams (eq 2 and 3), while the other two lead to the 1-azaspi-

(9) For a preliminary account of this study, see: Evans, D. A.; Thomas, E. W. *Tetrahedron Lett.* **1979**, 411.
(10) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksonn, T. J.; Faulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
(11) Sekiya, M.; Terao, Y. *Chem. Pharm. Bull.* **1971**, *19*, 391. Wrobel, J. T.; Cybulski, J.; Dabrowski, Z. *Synthesis* **1977**, 686.



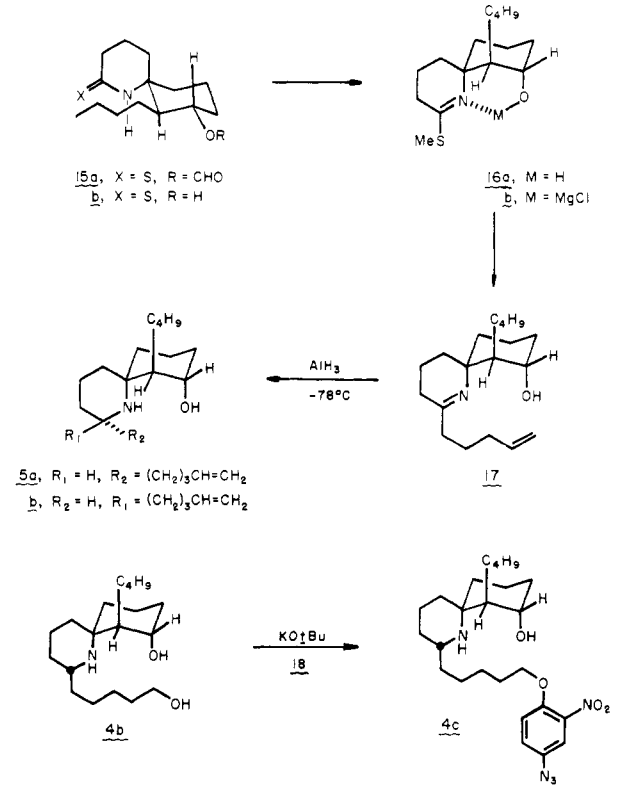
ro[5.4]decane ring system (cf. **12**). The logic that had been employed for predicting that transition state A, leading to the desired lactam **11**, would be preferred over transition state B rested on two tenuous points: it was assumed that the C_4H_9 side chain would prefer to eclipse trigonal rather than tetrahedral atoms ($\Delta H_A^{\ddagger} < \Delta H_B^{\ddagger}$), and transition-state NH-solvent hydrogen-bonding reorganization would be *greater* for B than A ($\Delta S_B^{\ddagger} < \Delta S_A^{\ddagger}$). For provision of information pertaining to the relative energetics of the competing cyclization modes accessible to acylimmonium ion **10**, a careful analysis of all reaction products was undertaken by high-pressure liquid chromatography. The isolated products were found to be 10% recovered enamide **6**, 10% enamide dimer,[12] 40% desired lactam **11a**, 20% 6,5-spirolactam **12a**, and 10% diastereoisomeric 6,5-spirolactam *epi*-**12a**. The structures of both **12a** and *epi*-**12a** were determined in the following manner. Jones oxidation of both **12b** and *epi*-**12b** afforded the respective ketones **13** and *epi*-**13**, each of which was equili-



brated (MeOH, MeONa) to a 1:1 mixture. The HPLC retention volumes of both **13** and *epi*-**13** were *different* from those observed for the corresponding retention volumes of the two C_7 epimeric ketones derived from the 6,6 lactam **11b**.[5a,b] Hence, neither **12** n or *epi*-**12** possessed the 6,6 azaspirane skeleton. Successive Baeyer–Villiger and chromate oxidation of **13** afforded keto lactam **14**, which confirmed the presence of the 6,5-azaspirane skeleton in both **12** and *epi*-**12**. Within the error limits of ca. 5%, it is concluded that: (a) 6,6 spirocyclization is preferred over 6,5 spirocyclization by a ratio of 4:3, and (b) the observed diastereoselection in the 6,6 spirocyclization manifold to produce the desired lactam **11** (eq 2 vs. 3) is very large. During the course of this study, Speckamp and co-workers disclosed a similar synthesis of **11a** (23%) via the same strategy.[13a] It is noteworthy that these workers did *not* observe any of the alternate cyclization mode (e.g., **10** → **12**) in their investigation, but this path becomes dominant in closely related analogues.[13b]

The elaboration of lactam **11a** to the HTX skeleton is illustrated in Scheme III. Transformation of **11a** to the crystalline hydroxy

Scheme III



thioamide **15b** was accomplished in 91% yield by successive treatment with phosphorus pentasulfide and sodium hydroxide. Subsequent methylation (MeI) afforded a quantitative yield of methylthioimidate **16a**, which existed predominantly, if not exclusively, in the depicted hydrogen-bonded conformation as evidenced by both high-dilution infrared and ^1H NMR studies. Both of the above transformations were based upon analogous reactions executed by Kishi on **15** (X = O, R = $C(O)CH_3$).[5a,b] Pretreatment of hydroxy thioimidate **16a** with anhydrous magnesium chloride (CH_2Cl_2) to form the presumed chelate **16b**,[14] followed by the addition of 4-pentenylmagnesium chloride, afforded a 67% yield of imine **17**.[15] The success of this reaction was found to be critically dependent upon the *preformation* of the magnesium–imide complex in methylene chloride; direct treatment of **16a** with an excess of desired Grignard reagent led only to apparent enolization.

On the basis of established precedent, aluminum hydride reduction of imine **17** in toluene (−70 °C) proceeded stereoselectively to the desired HTX congener **5a** along with minor amounts of the C_2 epimer **5b** (**5a**:**5b** = 93:7).[5a,16] The structure of H_{10}-HTX (**5a**) was confirmed by catalytic hydrogenation (Pd–C, THF) to H_{12}-HTX (**4a**) in quantitative yield. H_{12}-HTX prepared via this route proved to be identical in all respects [^1H NMR, IR, mmp (HCl salt), HPLC, biological activity] with an authentic sample of (±)-H_{12}-HTX provided to us by Professor Y. Kishi.[5a,b]

The elaboration of H_{10}-HTX (**5a**) to the photoaffinity-labeled toxin congener **4c** is illustrated in Scheme III. Hydroboration (BH_3·SMe_2, CH_2Cl_2) of **5a** with excess reagent followed by basic peroxide treatment afforded amino diol **4b**. Treatment of **4b** (THF) with 2.5 equiv of potassium *tert*-butoxide followed by 1 equiv of 4-fluoro-3-nitrophenylazide (**18**)[18] selectively formed the

(12) For related dimerizations, see: Wijnberg, J. B. P. A.; Speckamp, W. N.; deBoer, J. J. J. *Tetrahedron Lett.* **1974**, 4077.

(13) (a) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, 4841. (b) Schoemaker, H. S.; Kruk, C.; Speckamp, W. N. *Ibid.* **1979**, 2437.

(14) Mukaiyama, T.; Yamaguchi, M.; Narasaka, K. *Chem. Lett.* **1978**, 689.

(15) For previous work on the addition of Grignard reagents to imidates, see: (a) Rogers, R.; Neilson, D. *Chem. Rev.* **1961**, *61*, 179. (b) Glushkov, R. G.; Granik, V. G. *Adv. Heterocycl. Chem.* **1970**, *12*, 185.

(16) For some recent examples in the use of chelation to direct hydride delivery, see: (a) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129. (b) Asami, M.; Ohno, H.; Kabayashi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1869. (c) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567.

toxin-labeled phenoxy azide **4c** in 80% yield (based upon H_{12}-HTX (**5a**) after purification by chromatography). It is presumed that this reaction proceeded via the bis potassium alkoxide derived from **4b**. The origin of the demonstrated greater reactivity of the primary alkoxide in this reaction was anticipated since the C_8 alkoxide could be stabilized via nitrogen chelation. In earlier abortive experiments designed to derivatize diol **4b** with acid chloride derived photoaffinity labels, it was found that acylation (PhC(O)Cl, 2,6-lutidine) proceeded selectively at the C_8-hydroxyl function from which acyl transfer to the secondary amine was observed. This result is compatible with the normally observed nucleophilic enhancement of alcohols proximal to amine functions. The binding affinity of the potoaffinity-labeled toxin **4c**, carried out on *Torpedo californica* electroplax membrane fragments by a competition assay, revealed that the presence of the phenoxyazide moiety on the C_5 terminus in **4c** does *not* significantly alter toxin-binding properties (for **5a**, $K_I = 1 \times 10^{-6}$ M; for **4c**, $K_I = 5 \times 10^{-6}$ M).[17] Receptor polypeptide labeling studies will be reported in due course.

Experimental Section

Infrared spectra were recorded on a Beckman 4210 spectrophotometer. ^{1}H magnetic resonance spectra were recorded on a Varian Associates EM-390 (90 MHz) spectrometer and are reported in ppm from internal trimethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant (Hz), and interpretation. ^{13}C magnetic resonance spectra were recorded on a JEOL FX-90Q (22.5 MHz) and are reported in ppm from trimethylsilane on the δ scale. Melting points were taken on a Büchi SMP-20 melting-point apparatus and are reported uncorrected. Mass spectra were recorded on a Kratos MS-9 spectrometer at 70 eV by the Mass Spectrometry Laboratory at the University of California, Los Angeles. Combustion analyses were performed by Spang Micronalytical Laboratory.

When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran and diethyl ether were distilled from benzophenone ketyl. Toluene and benzene were distilled from sodium. Dichloromethane was dried by passing through a column of activity I aluminum oxide. Grignard reagents were prepared from 1 equiv of alkyl halide and 1 equiv of magnesium in diethyl ether, decanted, and titrated.[19] All temperatures refer to the reaction itself.

Ethyl (*E*)-4-nonenoate (7d). A solution of 1-hepten-3-ol (45.6 g, 0.4 mole, triethyl orthoacetate (453.6 g, 2.8 mol), and propionic acid (1.7 g, 24 mmol) was heated between 120 and 150 °C for 1 h, until ethanol ceased to distill from the mixture. After removal of the remaining solvent by distillation under 1 atm, the crude product was distilled to afford 69.7 g (95%) of **7d** as a colorless liquid, bp 83–86 °C (2 mmHg) (lit.[20] 60 bp °C (0.3 mmHg)). The distilled product was homogeneous by gas chromatography [5% FFAP (9 ft)/120 °C]: ^{1}H NMR ($CDCl_3$) δ 5.39 (m, 2 H, =C—H), 4.10 (q, 2 H, J = 6.1 Hz, OCH_2), 2.20–2.35 (m, 4 H), 1.62–2.11 (m, 2 H), 1.10–1.45 (m, 7 H), 0.88 (t, 3 H, J = 5.5 Hz, CH_3); IR (neat) 2950, 2920, 1728, 1728, 1362, 1157, 962 cm^{-1}.

(*E*)-4-Nonen-1-ol (7c). Ester **7d** (60.9 g, 0.33 mol) and lithium aluminum hydride (12.5 g, 0.33 mol) in diethyl ether (1.0 L) were stirred for 14 h at 25 °C under nitrogen. The reaction mixture was quenched by the slow addition of water (12.5 mL), sodium hydroxide (12.5 mL, 15% aqueous), and then water (37.5 mL). The white precipitate was removed by filtration, and the organic phase dried (Na_2SO_4). Filtration, removal of the solvent in vacuo, and distillation afforded 42.0 g (90%) of **7c**: bp 55 °C (0.4 mmHg) (lit.[20] 83 °C (0.3 mmHg)); ^{1}H NMR ($CDCl_3$) δ 5.37 (m, 2 H, =CH), 3.55 (t, 2 H, J = 6.0 Hz, OCH_2), 1.78–2.50 (m, 5 H), 1.42–1.78 (m, 2 H), 1.03–1.42 (m, 4 H), 0.88 (t, 3 H, J = 5.5 Hz, CH_3); IR (neat) 3360, 2950, 2920, 1045, 962 cm^{-1}.

(*E*)-1-Bromo-4-nonene (7b). Methanesulfonyl chloride (34.4 g, 0.3 mol) was added over 10 min to a magnetically stirred solution of alcohol **7c** (39.0 g, 0.27 mol), triethylamine (40.4 g, 0.4 mol), and dichloromethane (1 L) cooled to 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 45 min. The organic phase was washed with water (500 mL), saturated aqueous sodium bicarbonate (250 mL), and saturated aqueous sodium chloride (250 mL), dried (Na_2SO_4), and filtered. Removal of the solvent in vacuo afforded the crude mesylate: ^{1}H NMR ($CDCl_3$) δ 5.43 (m, 2 H, =CH), 4.23 (t, 2 H, CH_2O), 3.00 (s, 3 H, CH_3SO_2), 0.87–2.00 (7, 13 H, alkyl); IR (neat) 2920, 1460, 1350, 1171, 970, 928, 830, 733 cm^{-1}. The crude mesylate and lithium bromide (94.0 g, 1.08 mol) in acetone (500 mL) were stirred at 25 °C for 14 h under nitrogen. The reaction was filtered, concentrated, and diluted with ether (500 mL). The ether layer was extracted with water (2 × 100 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Distillation afforded 45.7 g (82%) as a colorless oil: bp 93–95 °C (10 mmHg) (lit.[20] 50 °C (0.2 mmHg)); ^{1}H NMR ($CDCl_3$) δ 5.08–5.65 (m, 2 H, =CH), 3.34 (t, 2 H, J = 6.0 Hz, $BrCH_2$), 1.65–2.21 (m, 6 H), 1.02–1.45 (m, 4 H), 0.70–0.95 (m, 3 H).

Grignard Addition of 7a to Glutarimide in Diethyl Ether. Grignard reagent **7a** was formed from **7b** (11.52 g, 72 mmol) and magnesium turnings (1.92 g, 0.08 mol) in diethyl ether (100 mL) under nitrogen. In a separate flask glutarimide (6.78 g, 60 mmol) and methylmagnesium iodide (27.2 mL, 60 mmol) were heated at reflux in diethyl ether (100 mL) for 0.5 h. Grignard reagent **7a** was added to the iodomagnesium salt of glutarimide and the entire mixture was heated at reflux for 0.5 h; the reaction mixture was cooled to 0 °C and quenched with saturated aqueous ammonium chloride (100 mL). The resultant suspension was filtered, the organic and aqueous layers were separated, and the aqueous layer was extracted with chloroform (5 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo to give a mixture of **8** and **9** (1:1 by NMR). Chromatography (Waters Prep 500 chromatograph, silica gel, ethyl acetate, retention volumes: **9**, 13.88 mL; **8**, 15.06 mL) afforded 8.95 g (62%) of a mixture of endocyclic and exocyclic enamides **6**, ketoamide **8**, and carbinolamide **9**.

Ketoamide **8**: mp 90–91 °C; ^{1}H NMR ($CDCl_3$) δ 5.65 (br s, 2 H, NH_2), 5.24–5.30 (m, 2 H, =CH), 1.40–2.56 (m, 14 H, alkyl), 1.12–1.40 (m, 4 H), 0.76–0.96 (m, 3 H, CH_3); IR (Nujol) 3382, 3190, 2920, 1700, 1655, 1640, 960 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 210.6 (C_5), 174.7 (C_1), 131.5, 128.9 (C_9, C_{10}), 42.1, 41.4, 34.7, 32.2, 32.0, 31.7, 23.6, 19.6, 19.5, 14.0.

Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53. Found: C, 69.94; H, 10.11.

Carbinolamide **9**: ^{1}H NMR ($CDCl_3$) δ 8.04 (br s, 1 H, NH), 5.10–5.57 (m, 2 H, =CN), 2.83–0.69 (m, 22 H); IR (neat) 3320, 3240, 3180, 2930, 1670, 1640, 1465, 970 cm^{-1}.

Endocyclic and Exocyclic Enamide 6. A mixture of ketoamide **8** and carbinolamide **9** (2.0 g, 8.4 mmol), toluene (50 mL), dimethylformamide (1 mL) and *p*-toluenesulfonic acid (5 mg) was heated at reflux for 48 h under nitrogen. The mixture was concentrated, diluted with diethyl ether (50 mL), and extracted with saturated aqueous sodium bicarbonate (1 × 100 mL). The organic portion was dried ($MgSO_4$), evaporated in vacuo, and chromatographed (silica gel, 50% hexane/50% ethyl acetate) to yield enamide **6** (9:1 ratio by ^{1}H NMR of endocyclic:exocyclic, 75%).

Endocyclic enamide **6**: ^{1}H NMR ($CDCl_3$) δ 5.28–5.42 (m, 2 H, =CH), 4.68–4.86 (m, 1 H, N—CΔbdCH), 1.00–2.52 (m, 16 H, alkyl), 0.78–1.00 (m, 3 H, CH_3); IR (neat) 3220, 3140, 3100, 2930, 1687, 1665, 1378, 1167, 966 cm^{-1}.

Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.90; H, 10.35; N, 6.30.

Exocyclic enamide **6**: ^{1}H NMR ($CDCl_3$) δ 7.48 (bs, 1 H, NH), 5.21–5.41 (m, 2 H, =CH), 4.32 (t, 1 H, J = 6.0 Hz, N—C=CH), 2.16–2.50 (m, 3 H), 1.52–2.16 (m, 6 H), 1.00–1.52 (m, 7 H), 0.74–1.00 (m, 3 H, CH_3); IR (neat) 3220, 2960, 2930, 1682, 1665, 1380, 1182, 965 cm^{-1}.

***rel*-(6*S*,7*S*,8*S*)-8-(7-Butyl-1-azaspiro[5.5]undecane-2-one) Formate (11a). i. From Enamide 6.** Enamide **6** (1.29 g, 5.8 mmol) was dissolved in anhydrous formic acid (60 mL) and stirred at 25 °C for 32 h. The solvent was removed in vacuo, and the residue dissolved in toluene. Removal of the sovlent in vacuo followed by chromatography [Waters Prep 500 chromatograph (silica gel, ethyl acetate)] afforded 0.70 g (40%) of **11a** as a white crystalline solid: mp 148–149 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 1 H, OCH), 6.89 (s, 1 H, NH), 4.78–5.16 (m, 1 H), CHO), 2.10–2.44 (m, 2 H), 0.72–2.10 (m, 20 H, alkyl); IR ($CHCl_3$) 3400, 2900, 1716, 1650, 1185 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 171.9 (C_2), 160.1 (formate), 73.9 (C_8), 58.5 (C_6), 50.7 (C_7), 36.1 (C_3), 32.2, 31.4, 29.5, 27.8, 26.7, 23.0, 18.5, 16.9, 13.9.

Anal. Calcd for $C_{15}H_{25}NO_3$: C, 37.38; H, 9.43; N, 5.24. Found: C, 67.48; H, 9.16; N, 5.25.

ii. From Glutarimide. Methylmagnesium bromide (26 mL, 2.9 M in ether) was added to a magnetically stirred solution of glutarimide (9.31 g, 82.3 mmol) in dichloromethane (1400 mL) under argon. A white precipitate formed and the reaction was heated to reflux for 30 min. The reaction mixture was cooled to 25 °C, and the (*Z*)-4-nonenylmagnesium bromide **7a** (90 mL, 1.2 M ether) was added. The reaction mixture was heated at reflux for 18 h, cooled to 0 °C, and quenched with saturated

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aqueous ammonium chloride (520 mL). The resultant suspension was filtered, and the organic and aqueous layers were separated. The aqueous phase was extracted with dichloromethane (4 × 250 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo to give the carbinolamide **9**, which was carried on without purification. Cyclization of **9** was carried out in anhydrous formic acid (850 mL) at 25 °C for 48 h. The solvent was removed in vacuo, and the residue dissolved in toluene (500 mL). Removal of the sovlent in vacuo and recrystallization (isopropyl ether) afforded 7.3 g (33%) of **11a** as a white crystalline solid, mp 148–150 °C.

Product Analysis of Formic Acid Cyclization of 6 or 9. Chromatographic separation (Waters Prep 500 chromatograph, silica gel, ethyl acetate) of the formic acid cyclization products from enamide **6** or carbinolamide **9** afforded **11a** (40%), **12a** (20%), and *epi*-**12a** (10%). Observed retention volumes: [analytical HPLC, μ-Poracil (30 cm), ethyl acetate, 6 mL/min] **11a** (14.3 mL), **12a** (11.2 mL), *epi*-**12a** (13.1 mL). Compound **12a** was isolated as a white crystalline solid: mp 118–120 °C; IR ($CHCl_3$) 3190, 3040, 2958, 1708, 1650, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (s, 1 H, O=CH), 7.45 (s, 1 H, NH), 5.13 (dd, 1 H, J_1 = 5.4 Hz, J_2 = 10.8 Hz, OCH), 2.10–2.42 (m, 2 H), 1.0–2.10 (m, 17 H, alkyl), 0.70–1.00 (m, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.0 (C_7), 160.3 (formate), 72.8 (C_{11}), 64.2 (C_5), 52.2 (C_1), 40.0 (C_8), 33.5, 31.3, 27.4, 26.7, 24.5, 22.4, 19.9, 17.8, 13.9.

Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43. Found: C, 67.27; H, 9.31.

Compound *epi*-**12a** was isolated as an oil; IR (neat) 3200, 3064, 2940, 1715, 1650, 1180 cm^{-1}.

***rel*-(6*S*,7*S*,8*S*)-7-Butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (11b).** Formate **11a** (1.0 g, 3.75 mmol) was added to a magnetically stirred solution of sodium methoxide (270 mg, 5 mmol) and methanol (150 mL) under nitrogen. The solution was stirred at 25 °C for 0.5 h. The solvent was removed in vacuo and the residue was diluted with dichloromethane (250 mL). The organic portion was extracted with water (25 mL), dried (Na_2SO_4), and concentrated to give crude **11b** as a white solid. Recrystallization (diethyl ether/ethyl) acetate) gave 855 mg (95%) of a white, crystalline, solid: mp 133–136 °C (lit.[5a] mp 133–134 °C); ^1H NMR ($CDCl_3$) δ 8.60 (s, 1 H, NH), 5.50–5.68 (m, 1 H, OH), 4.00 (bs, 1 H, OCH), 2.03–2.32 (m, 2 H, O=C—CH_2), 0.68–2.03 (m, 20 H, alkyl); IR ($CHCl_3$) 3360, 2951, 1623, 1462, 970, 828, 658 cm^{-1}; ^{13}C NMR ($CHCl_3$) δ 171.4 (C_2), 69.7 (C_8), 57.4 (C_6), 49.3 (C_7), 33.1 (C_3), 32.5, 31.1, 30.4, 28.4, 27.3, 22.9, 16.5, 16.0, 14.0.

Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.35; H, 10.67; N, 5.57.

***rel*-(6*S*,7*S*)-7-Butyl-1-azaspiro[5.5]undecane-2,8-dione.** A solution of **11b** (70 mg, 0.29 mmol) and acetone (5 mL) was cooled to 0 °C and Jones reagent was added dropwise until the red color persisted. The reaction was quenched with 2-propanol, filtered, concentrated, diluted with dichloromethane (20 mL), extracted with saturated aqueous sodium bicarbonate (2 × 2 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a ketone (70 mg, 100%): ^1H NMR ($CDCl_3$) δ 7.19. (s, 1 H, NH), 1.00–2.48 (m, 19 H), 0.72–1.00 (m, 3 H); IR (neat) 3200, 2950, 1720, 1650, 1400, 1038, 730 cm^{-1}; anal. HPLC (μ-Poracil, 97% ethyl acetate/3% methanol, 6 mL/min), retention volume 10.7 mL.

1-(1-Hydroxypentyl)-6-azaspiro[4.5]decan-7-one (12b). In a manner similar to the methanolysis of **11b**, **12a** (400 mg, 1.5 mmol) was converted to **12b** (370 mg, 100%): ^1H NMR ($CDCl_3$) δ 6.45 (s, 1 H, NH), 3.74 (bs, 1 H, OCH), 1.04–2.65 (m, 20 H), 0.76–1.04 (m, 3 H, CH_3); IR (neat) 3360, 2950, 1640, 1460, 1400, 905, 730 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 172.2 (C_7), 69.6 (C_{11}), 64.7 (C_5), 54.6 (C_1), 40.1 (C_8), 37.2, 31.5, 28.2, 27.4, 22.7, 22.4, 20.3, 18.1, 14.0.

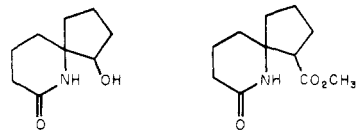
epi-**12b.** In a manner similar to the methanolysis of **11b**, *epi*-**12a** (70 mg, 0.27 mmol) was converted to *epi*-**12b** (61 mg, 92%); IR (neat 3200, 2940, 1650, 1450, 1400 cm^{-1}.

1-(1-Oxopentyl)-6-azaspiro[4.5]decan-7-one (13). Performed Collins' reagent [CrO_3 (1.0 g, 10 mmol); pyridine (1.6 g, 20 mmol); CH_2Cl_2 (25 mL)] was employed to oxidize **12b** (239 mg, 1.0 mmol) in dichloromethane (20 mL) for 15 min. The ketone was isolated by decantation of the reaction mixture, concentration, and dilution with ether (100 mL). This solution was filtered through Florisil and the solvent removed in vacuo to yield 170 mg (72%) of ketone **13**: ^1H NMR ($CDCl_3$) δ 7.80 (s, 1 H, NH), 2.98, (t, 1 H, J = 8.1 Hz, O=C—CH), 2.03–2.54 [m, 4 H, O=C—CH_2, O=C(N)—sCH_2], 1.06–2.01 (m, 16 H), 0.74–1.00 (m, 3 H, CH_3); IR (neat) 3200, 2945, 1697, 1650, 1400 cm^{-1}; anal. HPLC (97% ethyl acetate/3% methanol, 6 mL/min), retention volume 8.4 mL. After equilibration with base, two compounds were present in a 1:1 ratio with retention volumes of 8.4 and 8.6 mL.

epi-**13.** In a similar manner to the oxidation of **11b**, *epi*-**12b** (61 mg, 0.25 mmol) was oxidized to *epi*-**13** (50 mg, 82%): IR (neat) 3320, 1700, 1650 cm^{-1}; anal. HPLC (97% ethyl acetate/3% methanol, 6 mL/min); retention volume 8.6 mL.

6-Azaspiro[4.5]decane-1,7-dione (14). i. Baeyer–Villiger oxidation of **13** was done with trifluoroperacetic acid formed from hydrogen peroxide (0.8 mL, 90% aqueous) and trifluoroacetic anhydride (0.5 mL, 3.6 mmol) in dichloromethane (0.5 mL). The peracid was added to a magnetically stirred solution of the preceding ketoamide (40 mg, 0.18 mol) and Na_2HPO_4 (300 mg) in dichloromethane (1.5 mL). The reaction mixture was stirred at 25 °C for 2 h followed by refluxing for 2 h. The mixture was filtered, and the solid salts were washed with dichloromethane (20 mL). The organic portion was extracted with saturated aqueous sodium bicarbonate (1 × 3 mL), dried (Na_2SO_4), filtered, and concentrated. Chromatography (silica gel, diethyl ether) afforded 14 mg (31%) of a mixture of two esters: ^1H NMR ($CDCl_3$) δ 6.48 (s, 1 H, NH), 6.22 (s, 1 H, NH), 4.98 (m, 1 H, oCH), 4.08 (t, 2 H, J = 6.1 Hz, OCH_2); IR (neat) 1726, 1732, 1652 cm^{-1}.

ii. In a manner similar to the methanolysis of **11a**, the esters in the preceeding mixture (14 mg, 0.055 mmol) were converted to alcohols. Recrystallization (pentane) afforded 4.9 mg of E as a semisolid; IR ($CHCl_3$) 3260, 2958, 1646 cm^{-1}. F was recovered (6.9 mg) by concentration of the pentane fraction; IR (neat) 3240, 1720, 1650, 1400, 800 cm^{-1}.



E F

iii. Compound E (14 mg, 0.023 mmol) was heated to reflux with chromic acid on a polymer (100 mg, 0.25 mmol) in dichloromethane (2 mL) for 4 h. The reaction mixture was filtered and the solvent removed in vacuo to afford 3 mg (75%) of **14**: IR ($CHCl_3$) 3380, 1718, 1650 cm^{-1}; exact mass calcd for $C_9H_{13}NO_3$ 167.093, found 167.095.

***rel*-(6*S*,7*S*,8*S*)-7-Butyl-8-hydroxy-1-azaspiro[5.5]undecane-2-thione (15b).**[56] A magnetically stirred solution of amide **11a** (1.0 g, 3.74 mmol) and phosphorus pentasulfide (0.6. g, 3.11 mmol) in benzene (95 mL) was heated at reflux for 1.5 h under argon. The reaction mixture was dissolved in dichloromethane (200 mL), extracted with saturated sodium bicarbonate (3 × 75 mL), and dried ($MgSO_4$), and the solvent was removed in vacuo to give 0.95 g of **15a** as a yellow-orange oil. The oil was dissolved in methanol (95 mL), and sodium hydroxide (4.86 mmol, 1 N in water) was added. The solution was stirred at 25 °C for 3 h. Acetic acid (1.6 mL) was added to the reaction mixture and the solvent removed in vacuo. The residue was dissolved in dichloromethane (200 mL) and extracted with saturated sodium bicarbonate (1 × 75 mL) and saturated sodium chloride (1 × 75 mL). The organic phase was dried (Na_2SO_4) and the solvent removed in vacuo to give **15b** as a yellow-orange solid. Recrystallization (toluene) gave 0.87 g (91%) of **15b** as a white crystalline solid: mp 157–159 °C (lit.[5b] mp 166–168 °C); ^1H NMR ($CDCl_3$) δ 10.6 (br s, 1 H, NH), 4.03 (br s, 1 H, CHO), 3.73 (br s, 1 H, OH), 3.16–0.80 (m, 22 H, alkyl); IR ($CHCl_3$) 3600, 3440–3100, 2960, 2880, 2860, 1540, 1520, 1460, 1160, 1090 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 199.7 (C_2), 69.9 (C_8), 60.7 (C_6), 49.2 (C_7), 38.5 (C_3), 32.9, 31.0, 30.8, 28.6, 27.1, 22.7, 16.7, 16.0, 13.7.

Anal. Calcd for $C_{14}H_{25}NO_5$: C, 65.83; H, 9.87; N, 5.48. Found: C, 65.45; H, 9.93; N, 5.32.

***rel*-(6*S*,7*S*,8*S*)-7-Butyl-8-hydroxy-2-(methylthio)-1-azaspiro[5.5]undec-1-ene (16a).** Methyl iodide (1.8 mL, 28.4 mmol) was added to a magnetically stirred solution of **15b** (0.73 g, 2.84 mmol) in dichloromethane (23.0 mL) under argon. The solution was stirred at room temperature for 18 h, and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (200 mL) and extracted with saturated sodium bicarbonate (1 × 100 mL). The aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), and the solvent was removed in vacuo to give 0.77 g (100%) of **16** as a light-yellow oil: ^1H NMR ($CDCl_3$) δ 6.71 (d, 1 H, J = 9.0 Hz, OH), 3.97 (dm, 1 H, J = 9.0 Hz, CHO), 2.27 (s, 3 H, SCH_3), 2.33–0.78 (m, 22 H, alkyl); IR (neat) 3560–3060, 2940, 2860, 1625, 1450, 1420, 1130, 1070, 1020 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 164.3 (C_2), 70.3 (C_8), 61.7 (C_6), 49.6 (C_7), 39.1 (C_3), 33.3, 32.6, 30.7, 28.2, 27.2, 22.6, 16.0, 15.8, 13.6, 12.0; exact mass calcd for $C_{15}H_{27}NO_5$ 269.1814, found 269.1835.

***rel*-(6*S*,7*S*,8*S*)-7-Butyl-8-hydroxy-2-(4-pentenyl)-1-azaspiro[5.5]undecane (17).** 4-Pentenylmagnesium chloride (2.0 mL, 1.9 M in ether) was added to a magnetically stirred solution of thioimidate **16a** (67.8 mg, 0.25 mmol) and anhydrous magnesium chloride (210 mg, 2.21 mmol) in dichloromethane (10 mL). The light red solution was heated at reflux for 24 h under argon and cooled to 0 °C, and saturated ammonium chloride (1 mL) was added. The slurry was filtered through Celite, and

the residue was washed with dichloromethane (50 mL). The organic phase was extracted with saturated sodium bicarbonate (1 × 25 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo to give a yellow oil. Flash chromatography[21] (silica gel, 97% toluene/2.8% 2-propanol/0.2% saturated aqueous ammonium hydroxide) gave 48.9 mg (67%) of **17** as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.00–5.33 (m, 1 H, CH=C), 5.10–4.82 (m, 2 H, C=CH_2), 3.93 (br s, 1 H, CHO), 2.30–0.77 (m, 29 H, alkyl); IR (neat) 3560–3060, 2960, 2860, 1660, 1630, 1450, 1260, 1020, 800 cm^{-1}; exact mass calcd for $C_{19}H_{33}NO$ 291.2562, found 291.2594.

***rel*-(2*R*,6*R*,7*S*,8*S*)-7-Butyl-8-hydroxy-2-(4-pentenyl)-1-azaspiro[5.5]undecane (5a).** A magnetically stirred solution of imine **17** (50.0 mg, 0.17 mmol) and toluene (8 mL) was cooled to −72 °C under argon. Aluminum hydride[22] (5.4 mL, 0.16 M suspension in toluene) was added over 10 min, and the suspension was stirred for an additional 5 h at −72 °C. The reaction was warmed slowly to 25 °C and stirred for 14 h. The mixture was cooled to 0 °C and quenched with saturated aqueous ammonium chloride (1.0 mL) over 15 min. The toluene was evaporated in vacuo and the residue diluted with ether (50 mL). The organic phase was washed with aqueous 1 N sodium hydroxide (25 mL), saturated sodium bicarbonate (25 mL), and saturated sodium chloride (25 mL), dried (Na_2SO_4), and filtered. Removal of the solvent in vacuo afforded a 93:7 mixture of **5a**:**5b** as analyzed by HPLC [alumina (4 ft) column, $CHCl_3$, 1 mL/min]. Chromatography (silica gel, 90% chloroform/9.3% 2-propanol/0.7% saturated aqueous ammonium hydroxide) or recrystallization of the hydrochloride salt (diethyl ether/2-propanol) gave 35.8 mg (71%) of **5a** as a colorless oil: mp (hydrochloride salt) 168–169.5 °C; ^{1}H NMR ($CDCl_3$) δ 6.03–5.53 (m, 1 H, C*H*=C), 5.08–4.82 (m, 2 H, C=CH_2), 3.87 (br s, 1 H, CHO), 3.07–2.73 (m, 1 H, CHN), 2.30–0.80 (m, 30 H, alkyl); IR (neat) 3560–3100, 3080, 2930, 2860, 1640, 1445, 1130, 910 cm^{-1}; exact mass calcd for $C_{19}H_{35}NO$ 293.2718, found 293.2717.

***rel*-(2*R*,6*R*,7*S*,8*S*)-7-Butyl-8-hydroxy-2-pentyl-1-azaspiro[5.5]undecane (4a).** Olefin **5a** (33.0 mg, 0.11 mmol) was dissolved in tetrahydrofuran (8.3 mL) containing 5% Pd/C (82.5 mg) and was reduced with hydrogen at atmospheric pressure for 4 h. The slurry was filtered through Celite and the residue washed with ether (20 mL). Removal of the solvents in vacuo gave 33.0 mg (100%) of **4a** as a colorless oil: mp (hydrochloride salt) 158–160 °C (lit.[5a] mp 159–161 °C); ^{1}H NMR ($CDCl_3$) δ 3.89 (br s, 1 H, CHO), 2.89–2.52 (m, 1 H, CHN), 2.33–0.70 (m, 35 H, alkyl); IR ($CHCl_3$) 2930, 2860, 1460, 1450 cm^{-1}; mmp 158–160 °C; exact mass calcd for $C_{19}H_{37}NO$ 295.2875, found 295.2878.

Anal. (hydrochloride salt) Calcd for $C_{19}H_{38}ClON$: C, 68.74; H, 11,54; N, 3.90. Found: C, 68.54; H, 11.31; N, 3.90.

***rel*-(2*R*,6*R*,7*S*,8*S*)-7-Butyl-8-hydroxy-2-(5-hydroxypentyl)-1-azaspiro[5.5]undecane (4b).** Borane methyl sulfide (0.35 mmol, 9.3 M) was added to a magnetically stirred solution of **5a** (20.7 mg, 0.071 mmol) and dichloromethane (2.0 mL) under argon. The solution was stirred at room temperature for 5 h. Sulfuric acid (0.25 mL, 10% in water) was added slowly and the reaction mixture was stirred at room temperature for 1 h. Sodium hydroxide (0.75 mL, 15% in water) was added, followed by hydrogen peroxide (0.50 mL, 30% in water). The solution was stirred for 13 h at room temperature and was diluted with ether (40 mL). The organic phase was extracted with sodium tartrate (3 × 20 mL, 10% in water) and saturated sodium chloride (1 × 20 mL). The organic phase was dried (Na_2SO_4) and the solvent removed in vacuo to give **4a** as a colorless oil homogeneous by TLC (silica gel, 90% chloroform/9.3% 2-propanol/0.7% saturated aqueous ammonium hydroxide). Streaking normally accompanied chromatography under these conditions, which resulted in loss of material. Normally the crude **4b** was carried directly on to the next experient. ^{1}H NMR ($CDCl_3$) δ 3.88 (br s, 1 H, CHO), 3.60 (br t, 2 H, CH_2O), 3.13–2.58 (m, 1 H, CHN), 2.32–0.77 (m, 33 H, alkyl); Ir ($CHCl_3$) 3620, 3500–3010, 2930, 2860, 1445 cm^{-1}; exact mass calcd for $C_{19}H_{37}NO_2$ 311.2824, found 311.2805.

***rel*-(2*R*,6*R*,7*S*,8*S*)-7-Butyl-8-hydroxy-2-[5-(2-nitro-4-azidophenoxy)pentyl]-1-azaspiro[5.5]undecane (4c).** Potassium *tert*-butoxide (12.6 mg, 0.112 mmole was added to a magnetically stirred solution of **4b** (14.0 mg, 0.045 mmol) and tetrahydrofuran (2.0 mL) in a flask wrapped in aluminum foil under nitrogen. The solution turned yellow as the potassium alkoxides formed. 4-Fluoro-3-nitrophenylazide (8.2 mg, 0.045 mmol) was added, and the solution was stirred at room temperature for 14 h. A reddish-brown precipitate formed. The reaction was diluted with ether (35 mL) and extracted with water (2 × 20 mL) and saturated sodium chloride (1 × 20 mL). The organic phase was dried (Na_2SO_4) and the solvent removed in vacuo to give a yellow oil. Chromatography (silica gel, chloroform followed by 90% chloroform/9.3% 2-propanol/0.7% saturated aqueous ammonium hydroxide) gave 17.0 mg of **4c** (80%) based on olefin **5a**. ^{1}H NMR ($CDCl_3$) δ 7.48–6.97 (m, 3 H, aromatic), 4.05 (t, 2 H, J = 6.5 Hz, CH_2O), 3.87 (br s, 1 H, CHO), 3.07–2.67 (m, 1 H, CHN), 2.37–0.73 (m, 32 H, alkyl); IR ($CHCl_3$) 2940, 2860, 2120, 1525, 1490, 1406, 1350 cm^{-1}; exact mass calcd for $C_{25}H_{39}N_5O_4$ 473.3001, found 473.2983.

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Registry No. (±)-**4a**, 55254-30-3; (±)-**4a** HCl, 81521-83-7; (±)-**4b**, 81497-07-6; (±)-**4c**, 81497-08-7; (±)-**5a**, 81521-84-8; (±)-**5a** HCl, 81570-14-1; (±)-**5b**, 81521-85-9; **6** endocyclic, 71046-42-9; **6** exocyclic, 81497-09-8; **7a**, 16695-35-5; **7c**, 16695-34-4; **7c** mesylate, 81497-10-1; **7d**, 69361-38-2; **8**, 81497-11-2; (±)-**9**, 81521-86-0; (±)-**11a**, 71075-39-3; (±)-**11b**, 55228-76-7; **12a**, 71046-44-1; **12b**, 71046-45-2; (±)-**13**, 81497-12-3; (±)-*epi*-**13**, 81497-13-4; (±)-**13** ester, 81497-14-5; (±)-*epi*-**13** ester, 81497-15-6; (±)-**14**, 71046-46-3; (±)-**15a**, 81497-16-7; (±)-**15b**, 81521-87-1; (±)-**16a**, 81497-17-8; (±)-**17**, 81497-18-9; E, 81497-19-0; F, 81497-20-3; 1-hepten-3-ol, 4938-52-7; triethyl orthoacetate, 78-39-7; glutarimide iodomagnesium salt, 81505-46-6; methyl bromide, 74-83-9; glutarimide, 1121-89-7; (±)-(6*S*,7*S*)-7-butyl-1-azaspiro[5.5]undecane-2,8-dione, 56459-13-3; 4-pentenyl chloride, 16435-50-0; 4-fluoro-3-nitrophenylazide, 28166-06-5.

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(22) A solution of aluminum hydride in ether was prepared by method 2 of Ashby et al. (Ashby, E. C.; Sanders, J. R.; Claudy, P.; Schwartz, R. *J. Am. Chem. Soc.* **1973**, *95*, 6485). For preparation of a suspension in toluene the ether was removed in vacuo and the resultant white solid (**Caution**: pyrophoric) placed under high vacuum for 15 h. Toluene was then added with stirring under argon.