Synthesis of an Azasteroid Using an Acyl Iminium Ion-Initiated Tandem Cyclization

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An acyl iminium ion-initiated tandem cyclization gave an unexpected dienone product, a seco-azasteroid (**2**). The factors governing the formation of **2** were investigated in an attempt to optimize its formation. The reaction was applied to a more elaborate system, resulting in the synthesis of the full steroid skeleton of 13-azaandrosta-1,4-diene-3,17-dione (**3**), which contains the unusual substitution of a chlorine atom for the axial 19-methyl.

Heterocyclic azasteroids are of continuing interest, particularly due to their diverse range of biological activities. Many of these activities are thought to be due to the formation of stable substrate−enzyme complexes, facilitated by the presence of the nitrogen atom. These activities include inhibition of steroid biosynthesis, which includes the use of A-ring azasteroids to inhibit the enzyme 5α-reductase in the conversion of testosterone to 5α-dihydrotestosterone, leading to a treatment for benign prostatic hypertrophy[1] and possibly acne and male pattern baldness.[2] Other 4-azasteroids have been shown to inhibit the 3β-hydroxy-Δ^5-steroid dehydrogenase and/or 3-keto-Δ^5-steroid isomerase conversion of pregnenolone to progesterone.[3] Similarly, azasteroid antimycotic[4] activity is postulated to be a consequence of the inhibition of fungal 14,15-sterol reductase. Further antifungal,[5] antibacterial,[4,6] hypochlosterolemic,[4] hypotensive,[4] and neuromuscular blocking[7] activities have also been attributed to azasteroids.

In the course of an investigation into the utility of using *N*-acyl iminium ion[8]-initiated tandem cyclizations to afford substituted octahydrobenz[*f*]isoquinoline adducts

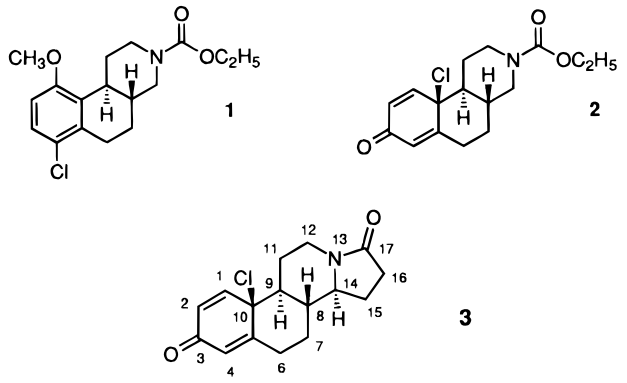

Figure 1.

(**1**) for further conversion into compounds of biological interest, we obtained an unexpected product (**2**), which can be described as a seco-azasteroid adduct (Figure 1). This came about during the treatment of **4** with paraformaldehyde in formic acid at 55 °C, where, in addition to the anticipated tandem cyclization to the site *ortho* to to the methoxy group leading to **1** (path a, Figure 2), we observed a competing cyclization occurring to the chlorine substituted position to give **2** (path b), via loss of the methyl on the *para*-substituted oxonium group contained in indermediate **6**. The yield of **2** (34%) is remarkable considering the number of chemical bonds both broken and formed, as well as the other reaction manifolds available, leading to **1** and **16**.[9]

Herein are reported the details of this reaction and the subsequent elaboration of this methodology to obtain the complete ring skeleton of androsta-1,4-diene-3,17-dione, with the bioisostere substitution of a nitrogen in place of C-13, and a chlorine replacing the axial 19-methyl (**3**).[10] It is noteworthy that besides the possibility for enzyme deactivation resulting from substitution with the aza group, the A-ring of this compound can serve as a mildly electrophilic chlorinating group, another possible mechanism for enzyme inhibition which has received attention.[11]

The cyclization substrates were easily obtained (Scheme 1). 4-Chloro-3-methylphenol (**7**) was protected as the *tert*-

[⊗] Abstract published in *Advance ACS Abstracts*, September 1, 1996.

(1) Rasmusson, G. H.; Reynolds, G. F.; Utne, T.; Jobson, R. B.; Primka, R. L.; Berman, C.; Brooks, J. R. Azasteroids as inhibitors of rat prostatic 5α-reductase. *J. Med. Chem.* **1984**, *27*, 1690−1701. Rasmusson, G. H.; Reynolds, G.; Steinberg, N. G.; Walton, E.; Patel, G. F.; Liang, T.; Cascieri, M. A.; Cheung, A. H.; Brooks, J. R.; Berman, C. Azasteroids: structure activity relationships for inhibition of 5α-reductase and of androgen receptor binding. *J. Med. Chem.* **1986**, *29*, 2298−2315.

(2) Brooks, J. R.; Berman, C.; Primka, R. L.; Reynolds, G. F.; Rasmusson, G. H. 5α-Reductase inhibitory and anti-androgenic activities of some 4-azasteroids in the rat. *Steroids* **1986**, *47*, 1−19. Brooks, J. R.; Berman, C.; Garnes, D.; Giltinan, D.; Gordon, L. R.; Malatesta, P. F.; Primka, R. L.; Reynolds, G. F.; Rasmusson, G. H. Prostatic effects induced in dogs by chronic or acute oral administration of 5α-reductase inhibitors. *Prostate* **1986**, *9*, 65−75.

(3) Brandt, M.; Levy, M. A. 3β-Hydroxy-Δ^5-steroid dehydrogenase/3-keto-Δ^5-steroid isomerase from bovine adrenals: mechanism of inhibition by 3-oxo-4-aza steroids and kinetic mechanism of the dehydrogenase. *Biochemistry* **1989**, *28*, 140−148.

(4) Dolle, R. E.; Allaudeen, H. S.; Kruse, L. I. Design and synthesis of 14α-methyl-15-aza-D-homosterols as novel antimycotics. *J. Med. Chem.* **1990**, *33*, 877−880.

(5) Solomons, W. E.; Doorenbos, N. J. Synthesis and antimicrobial properties of 17β-amino-4-aza-5α-androstane and derivatives. *J. Pharm. Sci.* **1974**, *63*, 19−23. Doorenbos, N. J.; Solomons, W. E. Synthesis and antimicrobial properties of 17β-isopentyloxy-4-aza-5α-androstane and the 4-methyl derivative. *J. Pharm. Sci.* **1973**, *62*, 638−640.

(6) Chesnut, R. W.; Durham, N. N.; Brown, R. A.; Mawdsley, E. A.; Berlin, R. A. Antibacterial activity of 15-azasteroids alone and in combination with antibiotics. *Steroids* **1976**, 525−541.

(7) Singh, H.; Paul, D.; Parashar, V. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1204. Singh, H.; Paul, D. *Ibid.* **1974**, 1475. Singh, H.; Bhardwaj, T. R.; Ahuja, N. K.; Paul, D. Steroids and related studies. Part 44. 17a-Methyl-3β-(N-pyrrolidinyl)-17a-aza-D-homo-5α-androstane bis-(methiodide) (Dihydrochandonium iodide) and certain other analogues of chandonium iodide. *Ibid.* **1979**, 305−307.

(8) Review of intramolecular cyclizations of *N*-acyliminium ions: Speckamp, W. N.; Heimstra, H. Intramolecular reactions of N-acyliminium intermediates. *Tetrahedron* **1985**, *41*, 4367−4416.

(9) Compound **16** arises from formic acid serving as a nucleophile, intercepting **5** after the first cyclization. This is probably a synchronous mechanism since only *trans*-substituted **16** is obtained.

(10) Steroid numbering system.

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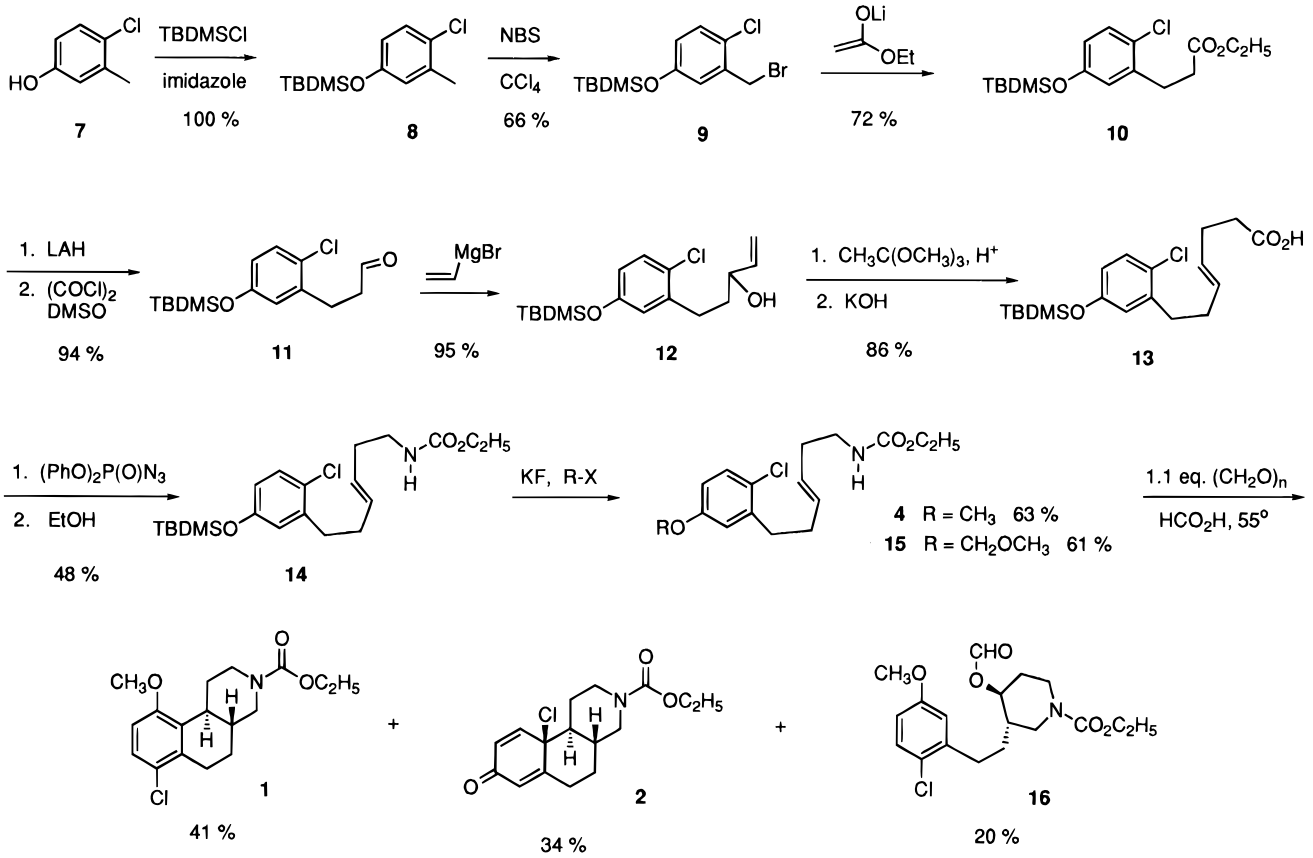
Scheme 1. Synthesis of Seco-Steroid Precursors (4, 14, and 15) and Subsequent Acyl Iminium Ion-Initiated Tandem Cyclization of 4.



butyldimethylsilyl ether (**8**) in order to provide flexibility to examine how varying the aryl ether substituent would affect the cyclization product ratios. Benzylic bromination of **8** with NBS, followed by enolate alkylation afforded ester **10** in good yield. LAH reduction followed by Swern oxidation gave aldehyde **11**. Treatment with vinylmagnesium bromide afforded allylic alcohol **12** which underwent a Claisen rearrangement when treated with triethylorthoacetate. Saponification of the ester followed by a diphenyl phosphorazidate-mediated Curtius rearrangement[12] gave the isocyanate which was condensed with ethanol to provide the carbamate **14**. At this stage the silyl ether could be converted into either methyl ether **4** or MOM ether **15**, using a one-pot procedure with potassium fluoride/methyl iodide or chloromethyl methyl ether, respectively.[13] Methyl ether **4** was cyclized with 1.1 equiv of paraformaldehyde in formic acid at 55 °C for 2 h to afford **1**, **2**, and **16** (41%, 34%, and 20% isolated yields, respectively).

Several variables were examined in an effort to optimize the formation of **2** as well as to gain mechanistic information. Silyl ether **14** and MOM ether **15** were subjected to the cyclization conditions used for **4** in an attempt to demonstrate whether enhancing the ability of the oxonium ion to be neutralized would increase the amount of **2** obtained. Interestingly, these variations had no effect on the product ratios. In a separate experiment, compound **4** was treated with boron trifluoride etherate to observe the effect of acid catalysis without the nucleophilic component present in formic acid.[14] Under the influence of this Lewis acid, **1** was the only product obtained, in excellent yield.

For a more elaborate demonstration of this unusual cyclization, the full ring skeleton of 13-aza-androsta-1,4-diene-3,17-dione (**3**) was synthesized, where the D-ring portion of the azasteroid skeleton was obtained by proceeding through a Speckamp cyclization[8] of the cyclic imide (Scheme 2). To carry this out, **4** was saponified to the primary amine (**17**) and acylated with succinic anhydride, followed by cyclization with acetyl chloride to obtain imide **18**. Selective reduction of the imide with sodium borohydride in ethanol afforded cyclization precursor **19**. Subjecting **19** to *N*-acyl iminium ion cyclization conditions, formic acid, and paraformaldehyde at 25 °C, afforded **3** in 30% yield, with four contiguous stereocenters.[15] The remainder of the mass balance was accounted for by cyclization *ortho* to the methoxy group and by formic acid trapping the partially cyclized product, analogously to **4**.

The *trans-anti-trans* ring fusions of compound **3** were proven by examining several NMR proton−proton cou-

(11) Steroidal *N*-chloro amides have been synthesized for this purpose: Back, T. G.; Lai, E. K. Y.; Morzycki, J. W. A convenient new synthesis of 17-azasteroids. Preparation of some novel N-chloro-17-aza- and N-chloro-17A-aza-17A-homosteroids as potential affinity labels and enzyme inhibitors. *Heterocycles* **1991**, *32*, 481−488.

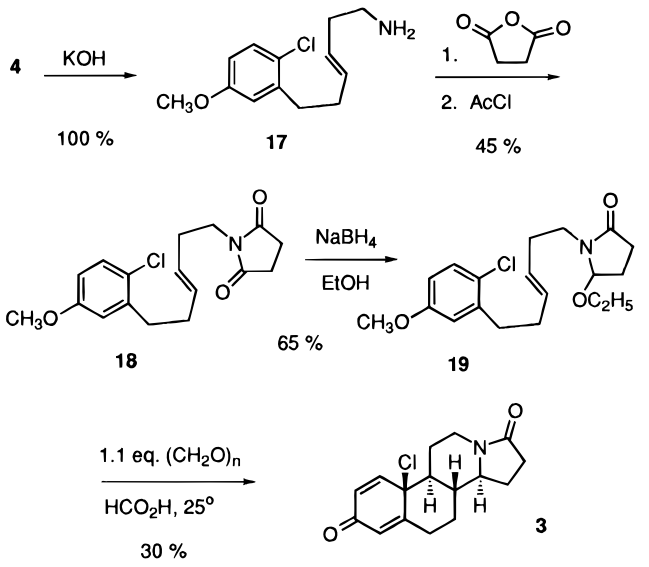
(12) Ninomiya, K.; Shioiri, T.; Yamada, S., Phosphorus in organic synthesis-VII. Diphenyl phosphorazidate (DPPA). A new convenient reagent for a modified Curtius reaction. *Tetrahedron* **1974**, *30*, 2151−2157.

(13) Sinhababu, A. S.; Kawase, M.; Borchardt, R. T. *tert*-Butyldimethylsilyl ethers of phenols: their one step conversion to benzyl or methyl ethers and utility in regioselective *ortho* lithiation. *Tetrahedron Lett.* **1987**, 4139−4142.

(14) One equivalent of boron trifluoride etherate was added to a slurry of **4** and 1.1 equivalent of paraformaldehyde in methylene chloride at 25 °C. The reaction was complete in several minutes. Other Lewis acids, such as titanium tetrachloride, were much inferior.

(15) Repeating this procedure with a MOM ether substituted for the methyl ether afforded a similar yield and product mixture.

Scheme 2. Synthesis of Speckamp-Type Acyl Iminium Ion Initiator 19 and Cyclization to Azasteroid 3.



pling constants. The indicated *trans*-diaxial relationship between the chlorine and the C-9 proton results in the "B"-ring assuming a pseudo-chair conformation; the C-6 proton resonances support this with axial C-6/axial C-7, equatorial C-6/axial C-7, and equatorial C-6/equatorial C-7 couplings of 13.7, 4.4, and 2.5 Hz, respectively.[16] The relative stereochemistry of the remaining ring fusions are supported by the axial proton on C-9 exhibiting a 10.9 Hz coupling to the axial C-8 proton and a 11.0 Hz coupling to the axial C-11 proton, the axial C-7 proton exhibiting a 12.0 Hz coupling to the axial C-8 proton, and the pseudo-axial C-14 proton exhibiting a 9.8 Hz coupling to the axial C-8 proton. Similar arguments support the stereochemical assignment of **2**.[17]

Discussion

While Friedel−Crafts cyclization of *p*-methoxy-substituted benzene rings to give geminally disubstituted dienones is not uncommon, these are usually systems which for steric reasons are constrained to cyclize to the *ipso* position giving spirocycles.[18] These specialized systems contrast with the ability of **4** to undergo "normal" cyclization to an unsubstituted *ortho*-position (path a, Figure 2), leading to **1**. The question arises as to whether **1** and **2** are generated as a result of a synchronous

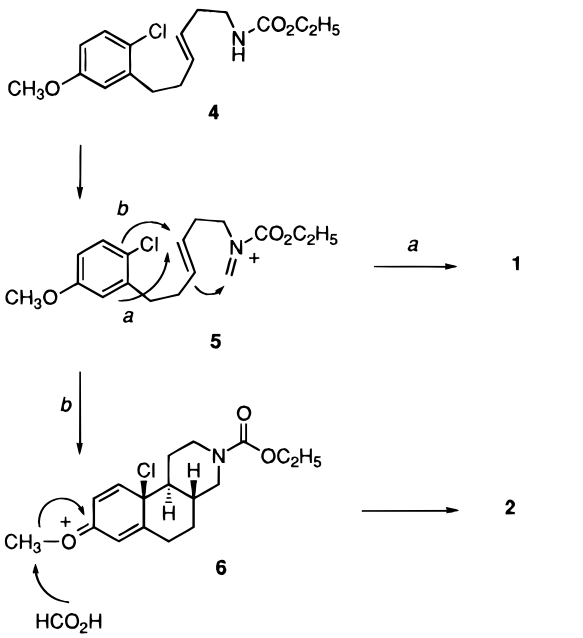


Figure 2. Cyclization by pathways a and b to give **1** and **2**, respectively.

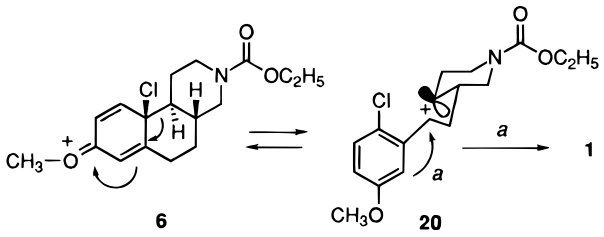


Figure 3. Alternate explanation for the formation of **1** from **6**, by fragmentation of oxonium intermediate **20**. This mechanism is less likely than a direct partitioning of **5** to **1** and **2**.

tandem cyclization mechanism which directly partitions **5** between the observed products via paths a and b. At first it would appear that the role of the acid catalyst is solely to catalyze the condensation of paraformaldehyde with the carbamate nitrogen to generate the highly reactive acyl iminium species which immediately cyclizes to give the product(s). However, this explanation does not account for the dramatic difference in product ratios observed upon going from formic acid to boron trifluoride etherate as the catalyst. An alternative mechanism can be considered, although less likely than irreversible direct partitioning. This would require the kinetically generated oxonium species **6** to either lose a methyl to give **2** or undergo fragmentation to give **20**, which could then recyclize to the unsubstituted *ortho* position to provide **1** (Figure 3). In this instance the ratio of **1** to **2** would be a reflection of the relative rate of demethylation of **6** versus the overall rate of fragmentation of **6** to **20** and subsequent cyclization of **20** to give **1**. Thus, assuming a kinetic cyclization to **6** occurred first, regardless of the acid catalyst, the inability of boron trifluoride etherate to demethylate **6** would eventually result in fragmentation to **20**.

However, several pieces of evidence argue against the intermediacy of **20**. Only *trans*-fused (**1** and **2**) or substituted (**16**) products are obtained with either acid catalyst; it is unlikely that **20** could exhibit this high level of stereospecificity, requiring exclusive pseudo-equatorial attack on the secondary carbocation. Furthermore, the

(16) Examination of a model of the alternative pseudo-boat conformation indicates that it would result in both of the C-6 protons eclipsing a vicinal C-7 proton, resulting in *syn*-periplanar coupling constants for both of the C-6 protons. This is not supported by the ^{1}H NMR. Furthermore, a *cis*-ring fusion between C-9 and C-10 would require the chlorine to eclipse the C-9 proton, resulting in an upfield shielding of this proton. However, the resonance of this proton (1.55 ppm) shows it is not undergoing shielding, again supporting the *trans*-fusion of these rings.

(17) A full tabulation of proton resonances for compounds **2** and **3**, including assignments and coupling partners, as well as ^{13}C resonances, including assignments and multiplicities, are included in the supporting information. Copies of the spectra used to assign the resonances, including HETCOR, DEPT, and COSY studies, are also included.

(18) Some recent examples: Boyle, F. T.; Matusiak, Z. S.; Hares, O.; Whiting, D. A. Synthesis of tricyclospirodienones via spiroannulation: methodology for synthesis of aromatase inhibitors. *J. Chem. Soc., Chem. Commun.* **1990**, 518−519. Haack, R. A.; Beck, K. R. Synthesis of substituted spiro[4.5]deca-3,6,9-triene-2,8-diones: an expeditious route to the spiro[4.5]decane terpene skeleton. *Tetrahedron Lett.* **1989**, 1605−1608.

inability to influence the ratio of products **1**, **2**, and **16** by varying the ability of cationic oxonium intermediates such as **6** to be neutralized, by substituting a silyl (**14**) or MOM (**15**) ether in place of the methyl ether (**4**) in the formic acid-catalyzed reaction, suggests that the reaction is proceeding through an early transition state, leading to direct partitioning to the observed products. This is in agreement with prior work where results from biomimetic cationic polyene cyclizations[19] and biomimetic tandem heterocyclizations[20] suggest a very high degree of synchronicity in the tandem cyclizations.

Therefore it is likely that the change in catalyst from formic acid to boron trifluoride etherate results in different rates for path a versus path b and that intermediate **6** is not being generated in the presence of boron trifluoride etherate. Implicit in this explanation is that the acid catalysts are performing more of a role than simply catalyzing the formation of the acyl iminium ion **5**.

In conclusion, this unusual selectivity allows for the synthesis of a full azasteroid skeleton, wherein four contiguous asymmetric centers are generated in one step. With the ability to substitute a chlorine for the C-19 axial methyl, resulting in a mildly electrophilic oxidizing species, this approach may prove useful in the rapidly developing field of drug inhibition of steroid biosynthesis pathways.

Experimental Section

General. Analytical TLC was performed on Analtech 10 × 20 cm (250 μm) silica gel prescored glass plates. Flash column chromatography was performed with silica gel 60 (230−400 mesh) from EM Science. THF and dioxane were distilled from benzophenone ketyl prior to use. All reactions were performed under nitrogen atmosphere. Melting points are uncorrected. Elemental analyses reported for the tandem cyclization products are within 0.4% of the calculated values, except for compound **3** which degraded upon storing. The structures of compounds **2** and **3** were determined using ^{1}H NMR, carbon−hydrogen correlation (HETCOR), carbon multiplicity (DEPT), and hydrogen−hydrogen correlation (COSY) experiments. Copies of these experimental spectra and tabulated NMR assignments are included in the supporting information.

4-Chloro-3-methylphenyl *tert*-Butyldimethylsilyl Ether (8). *tert*-Butyldimethylchlorosilane (5.9 g, 38.2 mmol) was added to 4-chloro-3-methylphenol (5.0 g, 34.71 mmol) and imidazole (5.2 g, 76.4 mmol) in DMF (70 mL, 0 °C). The ice bath was removed and the solution stirred overnight. After cooling to 0 °C, the solution was quenched with water and extracted with ether. The ether layer was washed with hydrochloric acid (2 N), water, aqueous sodium bicarbonate, and brine and then dried over sodium sulfate, removing the solvent under vacuum to yield 8.92 g (100%) of a clear oil. MS (EI) *m*/*z*: 256, 199. High resolution calculated: 256.1050; found: 256.1052. IR (thin film): 2958, 1598, 1577, 1480, 1464 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 6.98 (d, 1H, J = 8.6), 6.53 (d, 1H, J = 2.8), 6.42 (dd, 1H, J = 8.6, 2.8), 2.12 (s, 3H), 0.79 (s, 9H), 0.00 (s, 6H). Anal. Calcd for $C_{13}H_{21}ClOSi$ C: 60.79, H: 8.24. Found: C: 60.99, H: 8.07.

3-(Bromomethyl)-4-chlorophenyl *tert*-Butyldimethylsilyl Ether (9). Benzoyl peroxide (0.43 g, 1.74 mmol) was added to **8** (8.9 g, 34.71 mmol) and *N*-bromosuccinimide (6.9 g, 38.18 mmol) in carbon tetrachloride (25 mL) and refluxed for 2 h. The mixture was filtered through diatomaceous earth, and the solvent was removed under vacuum. The residue was flash chromatographed on a 19.5 × 7 cm silica gel column and eluted with hexane to yield 7.74 g (66%) of a pale oil. MS (EI) *m*/*z*: 334, 277. High resolution calculated: 334.0156. Found: 334.0153. IR (thin film): 2957, 1597, 1574, 1479, 1464, 1410 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.22 (d, 1H, J = 8.6), 6.90 (d, 1H, J = 2.9), 6.72 (dd, 1H, J = 8.7, 2.9), 4.51 (s, 2H), 0.97 (s, 9H), 0.19 (s, 6H). Anal. Calcd for $C_{13}H_{20}BrClOSi$: C: 46.51, H: 6.00, Cl: 10.56, Br: 23.80. Found: C: 46.15, H: 6.11, Cl: 10.24, Br: 23.92.

Ethyl 3-[5-(*tert*-Butyldimethylsiloxy)-2-chlorophenyl]-propionate (10). Ethyl acetate (8.4 mL, 86 mmol) was added to LDA (1 equiv) in THF (100 mL) at −78 °C. After 10 min, **9** (29 g, 86 mmol) in THF (50 mL) was added. The solution was allowed to warm to −35 °C and stir for 3 h. The reaction was quenched with aqueous HCl and extracted with diethyl ether. The organic layer was washed successively with water, aqueous sodium bicarbonate, and brine and was dried over sodium sulfate. The product was flash chromatographed on a 22 × 7 cm silica gel column and eluted with 5% methylene chloride in hexane to yield 21 g (72%) of an oil. MS (EI) *m*/*z*: 342, 297, 239. High resolution calculated: 242.1418; found: 342.1417. IR (thin film): 1738, 1598, 1574, 1477 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 7.00 (d, 1H, J = 8.6), 6.55 (d, 1H, J = 2.9), 6.46 (dd, 1H, J = 8.6, 2.9), 3.96 (q, 2H, J = 7.2), 2.81 (t, 2H, J = 7.8), 2.43 (t, 2H, J = 7.8), 1.07 (t, 3H, J = 7.1), 0.79 (s, 9H), 0.00 (s, 6H). Anal. Calcd for $C_{17}H_{27}ClO_3Si$: C: 59.45, H: 7.94. Found: C: 59.51, H: 8.03.

3-[5-(*tert*-Butyldimethylsiloxy)-2-chlorobenzene]propionaldehyde (11). Ester **10** (28.7 g, 83.71 mmol) in diethyl ether (100 mL) was added to lithium aluminum hydride (3.34 g, 83.71 mmol) in diethyl ether (50 mL) at 0 °C. The ice bath was removed, and after 90 min, it was reapplied. Water (3 mL), 15% aqueous sodium hydroxide (3 mL), and water (10 mL) were added and the slurry stirred at 25 °C for 10 min. The slurry was filtered and dried over sodium sulfate, and the solvent was removed under vacuum to yield 23.7 g (94%) of the alcohol as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): 6.99 (d, 1H, J = 8.6), 6.54 (d, 1H, J = 2.9), 6.44 (dd, 1H, J = 8.6, 2.9), 3.51 (m, 2H), 2.57 (m, 2H), 1.69 (m, 2H), 1.21 (s, 1H), 0.80 (s, 9H), 0.00 (s, 6H). Oxalyl chloride (7.6 g, 86.64 mmol) was added to DMSO (12.3 mL, 173.3 mmol) in methylene chloride in a −78 °C bath. After 15 min, the alcohol (23.7 g, 78.8 mmol) was added, followed by triethylamine (54.9 mL, 393.9 mmol), and the slurry was allowed to warm to 25 °C. The solution was partitioned between water and diethyl ether. The organic layer was washed with 2 N hydrochloric acid, water, aqueous sodium bicarbonate, and brine. It was dried over sodium sulfate, and the solvent was removed under vacuum to yield 23.6 g (100% crude) of a pale yellow oil. High resolution calculated: 300.1312; found: 300.1312. IR (thin film): 3346, 2931, 1597, 1573, 1477, 1448 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 9.64 (s, 1H), 7.00 (d, 1H, J = 8.6), 6.54 (d, 1H, J = 2.9), 6.46 (dd, 1H, J = 8.6, 2.9), 2.80 (t, 2H, J = 7.5), 2.60 (t, 2H, J = 7.4), 0.79 (s, 9H), 0.00 (s, 6H). Anal. Calcd for $C_{15}H_{25}ClO_2Si$: C: 59.88, H: 8.37. Found: C: 59.84, H: 8.53.

5-(*tert*-Butyldimethylsilyloxy)-2-chloro-α-ethenylbenzenepropanol (12). Aldehyde **11** (23.6 g, 78.8 mmol) in THF (25 mL) was added to vinylmagnesium bromide (168 mL, 118.1 mmol, 0.70 M in THF) at 0 °C. The ice bath was removed and after 2 h replaced, and aqueous ammonium chloride was added. The mixture was partitioned between diethyl ether and 2 N hydrochloric acid. The organic layer was washed with water, aqueous sodium bicarbonate, and brine. It was dried over sodium sulfate, and the solvent was removed under vacuum to yield 24.4 g (95%) of a dark yellow oil. MS (EI) *m*/*z*: 326, 291, 269. IR (thin film): 3363, 1597, 1573, 1477 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 6.99 (d, 1H, J = 8.6), 6.55 (d, 1H, J = 2.9), 6.44 (dd, 1H, J = 8.6, 2.9), 5.74 (ddd, 1H, J = 17.0, 10.4, 6.1), 5.12 (dt, 1H, J = 17.1, 0.7), 4.97 (dt, 1H, J = 10.4, 0.6), 3.98 (q, 1H, J = 6.2), 2.58 (m, 2H), 1.64 (m, 2H), 1.48 (s, 1H), 0.79 (s, 9H), 0.00 (s, 6H).

(*E*)-6-[5-(*tert*-Butyldimethylsilyloxy)-2-chlorophenyl]-hex-3-enecarboxylic Acid (13). Triethyl orthoacetate (44.6 mL, 235.8 mmol), propionic acid (0.35 mL, 4.72 mmol), and **12** (25.7 g, 78.6 mmol) were heated for 1 h while ethanol was

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distilled off. The solution was heated at 160 °C for another 1 h. The reaction was partitioned between ether and water, the ether layer was washed with saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate, and the solvent was removed under vacuum to yield 30 g (96%) of the ester as a yellow oil. MS (EI) *m/z*: 396, 351, 339; IR (thin film): 1738, 1597, 1573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 6.98 (d, 1H, J = 8.5), 6.49 (d, 1H, J = 2.9), 6.43 (dd, 1H, J = 8.6, 2.9), 5.30 (m, 2H), 3.95 (q, 2H, J = 7.1), 2.51 (m, 2H), 2.15 (m, 4H), 1.08 (t, 3H, J = 7.1), 0.79 (s, 9H), 0.00 (s, 6H). Potassium hydroxide (14.6 g, 226.7 mmol), methanol (150 mL), water (15 mL), THF (35 mL), and the ester (30.0 g, 75.6 mmol) were stirred at room temp for 4 h, and the solvents were removed under vacuum. The residue was partitioned between water and diethyl ether. The water layer was acidified with hydrochloric acid to pH 2 at 0 °C and extracted with diethyl ether. The ether layer was washed with water and brine and dried over sodium sulfate. The solvent was removed under vacuum to yield a yellow solid. ^1H-NMR analysis of the crude material indicated that a significant amount of the *tert*-butyldimethylsilyl protecting group had come off. The crude product was combined with imidazole (22.8 g, 332.4 mmol) and DMF (150 mL), and *tert*-butyldimethylsilyl chloride (25.8 g, 166.2 mmol) was added at 0 °C, the ice bath was removed, and the reaction was stirred overnight at 25 °C. Ice was then added, followed by water and diethyl ether. The ether layer was washed with 2 N hydrochloric acid, water, and brine. It was dried over sodium sulfate, and the solvent was removed under vacuum. Methanol (150 mL) was added and stirred 2 days. The solvent was removed under vacuum to yield 25.2 g (90%) of an amber oil. MS (FAB) *m/z*: 369, 353, 351. IR (thin film): 3001, 1712, 1597, 1573, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 6.98 (d, 1H, J = 8.6), 6.49 (d, 1H, J = 2.9), 6.43 (dd, 1H, J = 8.6, 2.9), 5.30 (m, 2H), 2.52 (m, 2H), 2.23 (m, 2H), 2.14 (m, 4H), 0.79 (s, 9H), 0.00 (s, 6H).

(*E*)-[6-[5-(*tert*-Butyldimethylsilyloxy)-2-chlorophenyl]-3-hexenyl]carbamic Acid, Ethyl Ester (14). Triethylamine (9.5 mL, 68.2 mmol) was added to **13** (25.2 g, 68.2 mmol) and diphenyl phosphorazidate (15.0 mL, 68.2 mmol) in 1,4-dioxane (225 mL). After 30 min at room temp, it was refluxed for 40 min, and ethanol (40 mL, 682 mmol) was added. Refluxing continued overnight after which the solvent was removed under vacuum. The residual oil was partitioned between diethyl ether and water. The ether layer was washed with water, 2 N hydrochloric acid, aqueous sodium bicarbonate, and brine. It was dried over sodium sulfate, and the solvent was removed under vacuum. The residue was flash chromatographed on a 20 × 4.7 cm silica gel column and eluted with 10% ethyl acetate in hexane to yield a light amber oil, 13.45 g (48%). MS (EI) *m/z*: 411, 383, 354. IR (thin film): 3429, 3343, 1710, 1596, 1573 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 6.99 (d, 1H, J = 8.6), 6.50 (d, 1H, J = 2.9), 6.44 (dd, 1H, J = 8.5, 2.9), 5.34 (m, 1H), 5.21 (M, 1H), 4.44 (br, 1H), 3.93 (q, 2H, J = 7.1), 3.00 (q, 2H, J = 6.2), 2.53 (m, 2H), 2.12 (q, 2H, J = 7.7), 2.00 (q, 2H, J = 6.7), 1.06 (t, 3H, J = 7.1), 0.79 (s, 9H), 0.00 (s, 6H).

(*E*)-[6-(2-Chloro-5-methoxyphenyl)-3-hexenyl]carbamic Acid, Ethyl Ester (4). Iodomethane (0.84 mL, 13.35 mmol) was added to potassium fluoride (1.42 g, 24.27 mmol), **14** (5.0 g, 12.13 mmol), and DMF (25 mL) at 0 °C. After 15 min, the ice bath was removed and after 27 h, diethyl ether and water were added. The ether layer was washed with water and brine and dried over sodium sulfate to yield a yellow oil, 3.65 g. The oil was flash chromatographed on a 19 × 2.0 cm silica gel column, eluting successively with 10%, 15%, and 20% ethyl acetate in hexane to yield 2.39 g (63%) of a pale oil. ^1H NMR (300 MHz, $CDCl_3$): 7.24 (d, 1H, J = 8.7), 6.74 (d, 1H, J = 3.0), 6.69 (dd, 1H, J = 8.7, 3.0), 5.55 (m, 1H), 5.39 (m, 1H), 4.62 (br, 1H), 4.11 (m, 2H), 3.78 (s, 3H), 3.19 (m, 2H), 2.75 (m, 2H), 2.32 (m, 2H), 2.21 (m, 2H), 1.24 (t, 3H, J = 7.1). IR (thin film): 3341, 1719, 1597 cm^{-1}. MS (EI) *m/z*: 311, 276. Anal. Calcd for $C_{16}H_{22}NO_3Cl$ C: 61.63, H: 7.11, N: 4.49. Found: C: 61.97, H: 7.35, N: 4.17.

(*E*)-[6-[2-Chloro-5-(methoxymethyloxy)phenyl]-3-hexenyl]carbamic Acid, Ethyl Ester (15). Potassium fluoride (2.0 g, 34.12 mmol), **14** (7.0 g, 17.06 mmol), and DMF (35 mL) were stirred for 45 min, and then chloromethyl methyl ether (1.36 mL, 17.91 mmol) was slowly added (0 °C) to the mixture. After 10 min, the ice bath was removed and after 21.5 h, diethyl ether, and water were added. The ether layer was washed with water and brine and dried over sodium sulfate to yield an amber oil, 6.01 g. The oil was flash chromatographed on a 20 × 2.0 cm silica gel column, eluting with 12% ethyl acetate in hexane to yield 3.57 g (61%) of a pale oil. MS (EI) *m/z*: 341, 309, 274. IR (thin film): 3419, 3345, 1707, 1478 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.24 (d, 1H, J = 8.7), 6.89 (d, 1H, J = 2.9), 6.83 (dd, 1H, J = 8.7, 2.9), 5.52 (m, 1H), 5.40 (m, 1H), 5.14 (s, 2H), 4.67 (br, 1H), 4.10 (m, 2H), 3.47 (s, 3H), 3.19 (m, 2H), 2.75 (m, 2H), 2.32 (m, 2H), 2.18 (m, 2H), 1.24 (t, 3H, J = 7.1).

Acyl Iminium Ion Cyclization of (*E*)-[6-(2-Chloro-5-methoxyphenyl)-3-hexenyl]carbamic Acid, Ethyl Ester (4). Paraformaldehyde (0.095 g, 3.2 mmol) was added to a solution of **4** (0.90 g, 2.89 mmol) in formic acid (6 mL). The solution was heated to 55 °C and stirred for 2 h. Most of the formic acid was removed *in vacuo*, and the residue was flash chromatographed on a 22 × 2 cm silica gel column, eluting with 10% and then 15% ethyl acetate in hexane to afford 0.37 g (41%) of **1**, 0.32 g (34%) of **2**, and 0.21 g (20%) of **16**. **(4aα,10bβ)-7-Chloro-10-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenz[*f*]isoquinoline-3-carbamic acid, ethyl ester (1)**: MS (EI) *m/z*: 323, 294, 288, 250. High resolution calculated: 323.1288; found: 323.1288. IR (Nujol): 1693, 1441, 1431 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.18 (d, 1H, J = 8.7), 6.65 (d, 1H, J = 8.7), 4.22 (m, 4H), 3.79 (s, 3H), 2.96 (m, 3H), 2.62 (m, 3H), 1.83 (m, 1H), 1.50 (m, 1H), 1.27 (m, 4H), 1.09 (m, 1H). ^{13}C NMR DEPT (75 MHz, $CDCl_3$): 157.33 C, 155.53 C, 136.74 C, 129.26 C, 126.90 CH, 126.20 C, 109.03 CH, 61.08 CH_2, 55.06 CH_3, 50.08 CH_2, 44.80 CH_2, 41.82 CH, 40.84 CH, 30.27 CH_2, 28.94 CH_2, 25.67 CH_2, 14.63 CH_3. Anal. Calcd for $C_{17}H_{22}ClNO_3$ C: 63.06, H: 6.85, N: 4.33, Cl: 10.95. Found: C: 62.97, H: 6.93, N: 4.28, Cl: 10.99. **(4aα,10aα,10bβ)-10a-Chloro-1,4,4a,5,6,8,10a,10b-octahydro-8-oxobenzo[*f*]isoquinoline-3(2*H*)-carbamic acid, ethyl ester (2)**: MS (EI) *m/z*: 309, 274, 263. IR (Nujol): 1683, 1670, 1663, 1449, 1439 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 50 °C): 7.08 (d, 1H, J = 10.1), 6.23 (dd, 1H, J = 10.1, 2.0), 6.10 (d, 1H, J = 2.0), 4.30 (br, 2H), 4.15 (q, 2H, J = 7.1), 2.91 (m, 1H), 2.72 (br, 1H), 2.45 (m, 1H), 2.37 (br, 1H), 1.82−2.08 (m, 4H), 1.46 (m, 1H), 1.28 (t, 3H, J = 7.1), 1.19 (m, 1H). ^{13}C NMR DEPT (75 MHz, $CDCl_3$): 184.6 C, 159.8 C, 155.1 C, 146.4 CH, 127.1 CH, 124.3 CH, 66.2 C, 61.4 CH_2, 50.9 CH, 48.75 CH_2, 43.2 CH_2, 35.4 CH, 31.4 CH_2, 31.0 CH_2, 26.3 CH_2, 14.6 CH_3. Anal. Calcd for $C_{16}H_{20}ClNO_3$: C: 62.03, H: 6.51, Cl: 11.44, N: 4.52. Found: C: 61.72, H: 6.45, Cl: 11.52, N: 4.62. ***trans*-4-(Formyloxy)-3-[(2-chloro-5-methoxyphenyl)ethyl]piperidine-1-carbamic acid, ethyl ester (16)**: MS (EI) *m/z*: 334, 324, 288, 250. High resolution calculated: 369.1343; found: 369.1350. IR (thin film): 1723, 1698, 1478, 1435 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 8.09 (s, 1H), 7.23 (d, 1H, J = 8.7), 6.75 (d, 1H, J = 2.9), 6.69 (dd, 1H, J = 8.7, 3.0), 4.87 (m, 1H), 4.15 (q, 2H, J = 7.1), 3.88 (m, 1H), 3.78 (s, 3H), 3.20 (br, 1H), 3.02 (br, 1H), 2.78 (m, 1H), 2.69 (m, 1H), 1.99 (m, 1H), 1.77 (m, 2H), 1.52 (m, 2H), 1.28 (t, 3H, J = 7.1). Anal. Calcd for $C_{18}H_{24}ClNO_5$: C: 58.57, H: 6.55, N: 3.79, Cl: 9.60. Found: C: 58.48, H: 6.73, N: 3.82, Cl: 9.56.

(*E*)-[6-(2-Chloro-5-methoxyphenyl)-3-hexenyl]amine (17). Carbamate **4** (2.4 g, 7.66 mmol) was refluxed with potassium hydroxide (2.97 g, 46.0 mmol), ethanol (20 mL), and water (2 mL) for 48 h. The solvent was removed under vacuum and the residue partitioned between diethyl ether and water. The ether layer was washed with water and brine and dried over sodium sulfate to yield 1.85 g (100%, crude) of a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): 7.23 (d, 1H, J = 8.7), 6.74 (d, 1H, J = 3.0), 6.68 (dd, 1H, J = 8.7, 3.0), 5.53 (m, 1H), 5.40 (m, 1H), 3.77 (s, 3H), 2.72 (m, 4H), 2.34 (q, 2H, J = 7.3), 2.12 (q, 2H, J = 6.6), 1.18 (br, 2H).

(*E*)-1-[6-(2-Chloro-5-methoxyphenyl)-3-hexenyl]-2,5-pyrrolidinedione (18). Succinic anhydride (0.87 g, 8.43 mmol) was added to **17** (1.84 g, 7.66 mmol) in THF (20 mL) at 0 °C. After the succinic anhydride was fully dissolved, the ice bath was removed and after 2.75 h, 1,3-dicyclohexylcarbodi-

imide (1.60 g, 7.66 mmol) was added. The mixture was stirred overnight and then was filtered through diatomaceous earth, and the solvent was removed under vacuum to yield an amber semisolid. This was flash chromatographed through a 23 × 2.2 cm silica gel column and eluted with 66% ethyl acetate in hexane followed by 90% methylene chloride in methanol. The seco-imide was obtained as a solid, 1.69 g (65%), mp 86.0−87.0 °C. MS (EI) *m*/*z*: 339, 222, 155. IR (Nujol): 3300, 1695, 1639, 1555, 1478 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 7.24 (d, 1H, $J = 8.7$), 6.75 (d, 1H, $J = 3.0$), 6.69 (dd, 1H, $J = 8.7, 3.0$), 5.82 (br, 1H), 5.54 (m, 1H), 5.35 (m, 1H), 3.78 (s, 3H), 3.26 (q, 2H, 6.3), 2.75 (t, 2H, 7.6), 2.69 (t, 2H, 6.6), 2.47 (t, 2H, 6.5), 2.34 (q, 2H, 7.5), 2.19 (t, 2H, 6.5). Anal. Calcd for $C_{17}H_{22}ClNO_4$: C, 60.09; H, 6.53; N, 4.12. Found: C, 60.26; H, 6.68; N, 4.20. To effect cyclization to the imide, acetyl chloride (40 mL), and the seco-imide (1.18 g, 3.47 mmol) were refluxed 20 h. Another 40 mL portion of acetyl chloride was added and the solution refluxed an additional 4 h. Solvents were removed under vacuum, and the residue was flash chromatographed on a 23 × 2.2 cm silica gel column, eluting with 33% ethyl acetate in hexane to yield 0.78 g (70%) of the imide. MS (EI) *m*/*z*: 321, 286, 222, 207. ^1H NMR (300 MHz, $CDCl_3$): 7.23 (d, 1H, $J = 8.6$), 6.73 (d, 1H, $J = 2.9$), 6.68 (dd, 1H, $J = 8.7, 2.9$), 5.52 (m, 1H), 5.40 (m, 1H), 3.78 (s, 3H), 3.54 (t, 2H, $J = 7.2$), 2.70 (m, 2H), 2.68 (s, 4H), 2.28 (q, 4H, $J = 7.0$). Anal. Calcd for $C_{17}H_{20}NO_3$: C: 71.31, H: 7.04, N: 4.89. Found: C: 71.72, H: 7.43, N: 4.66.

***(E)*-1-[6-(2-Chloro-5-methoxyphenyl)-3-hexenyl]-5-hydroxy-2-pyrrolidinone (19).** Sodium borohydride (0.55 g, 14.14 mmol) was added to **18** (0.65 g, 2.02 mmol) in ethanol (50 mL) at 0 °C followed by chlorotrimethylsilane (2.6 mL in 7.4 mL ethanol, five drops every 15 min over a period of 4 h). The remaining amount of the chlorotrimethylsilane in ethanol was then added and stirred 75 min. The white slurry was poured into aqueous sodium bicarbonate and extracted with chloroform (4 × 400 mL). The organic layer was washed with water and brine and then dried over sodium sulfate to yield 0.65 g of pale amber oil. This oil was flash chromatographed on a 1.2 × 22 cm silica gel column, eluted with 33% and 50% ethyl acetate in hexane to yield 0.46 g (65%) of a clear oil. MS (EI) *m*/*z*: 351, 306, 222, 196. IR (thin film): 1699, 1597, 1576 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.23 (d, 1H, $J = 8.7$), 6.74 (d, 1H, $J = 3.0$), 6.68 (dd, 1H, $J = 8.7, 3.0$), 5.54 (m, 1H), 5.43 (m, 1H), 4.96 (d, 1H, $J = 5.0$), 3.78 (s, 3H), 3.56 (m, 1H), 3.46 (q, 2H, $J = 7.0$), 3.08 (m, 1H), 2.73 (m, 2H), 2.49 (m, 1H), 2.4−2.0 (m, 6H), 1.96 (m, 1H), 1.23 (t, 3H, $J = 7.0$).

(4aα,4bβ,10aβ,10bα)-4a-Chloro-4a,4b,5,6,9,10,10a,10b,-11,12-decahydrobenzo[*f*]pyrrolo[2,1-*a*]isoquinoline-2,8-dione (3). Formic acid (7 mL) was added to **19** (0.46 g, 1.3 mmol) at 25 °C. After 18 h, solvents were removed under vacuum and the residue was partitioned between diethyl ether and saturated aqueous sodium bicarbonate. The organic layer was washed with brine and dried over sodium sulfate to yield 0.40 g of white foam. This was flash chromatographed on a 22 × 1.2 cm silica gel column, eluting with 10% methanol (saturated with ammonia) in methylene chloride to yield 0.11 g (30% yield) of the title compound as a white foam, mp 112 °C dec. MS (FAB) *m*/*z*: 294, 292, 258. High resolution calculated: 292.1104; found: 292.1090. IR (Nujol): 1686, 1666, 1633, 1609 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.10 (d, 1H, $J = 10.1$), 6.24 (dd, 1H, $J = 10.1, 1.9$), 6.12 (dd, 1H, $J = 1.8, 1.8$), 4.26 (ddd, 1H, $J = 13.4, 5.0, 2.0$), 3.07 (dt, 1H, $J = 9.8, 7.3$), 2.89 (dddd, 1H, $J = 13.7, 13.7, 5.2, 1.7$), 2.67 (ddd, 1H, $J = 13.3, 13.3, 3.7$), 2.49 (ddd, 1H, $J = 13.5, 4.4, 2.5$), 2.43 (m, 1H), 2.37 (ddd, 1H, $J = 17.0, 9.1, 1.5$), 2.28 (dddd, 1H, $J = 9.0, 7.3, 7.3, 3.8$), 2.07 (dddd, 1H, $J = 13.0, 5.4, 3.7, 2.6$), 1.95 (dddd, 1H, $J = 13.0, 3.4, 3.4, 2.0$), 1.83 (dddd, 1H, $J = 12.9, 12.9, 11.0, 5.0$), 1.76−1.66 (m, 2H), 1.58 (ddd, 1H, $J = 11.0, 10.9, 3.3$), 1.20 (dddd, 1H, $J = 13.3, 13.3, 12.0, 4.4$). ^{13}C NMR DEPT (75 MHz, $CDCl_3$): 184.38 C, 173.20 C, 159.21 C, 146.32 CH, 127.22 CH, 124.37 CH, 66.06 C, 60.64 CH, 49.98 CH, 42.52 CH, 38.43 CH_2, 31.13 CH_2, 30.19 CH_2, 29.39 CH_2, 25.37 CH_2, 23.85 CH_2.

Supporting Information Available: Two charts containing the assignment of all of the proton chemical shifts, *J* values, coupling assignments, and ^{13}C NMR assignments of compounds **2** and **3**, as well as reproductions of the spectra from the NMR experiments (^1H, ^{13}C, HETCOR, and COSY NMR) used in this determination. Reproductions of the ^1H NMR spectra for compounds **1**, **4**, **16**, **18**, and **19** are also included (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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