Improved Synthesis of Indolyl Fulgides

Craig J. Thomas, Mason A. Wolak, Robert R. Birge, and Watson J. Lees*

Department of Chemistry and W. M. Keck Center for Molecular Electronics, Syracuse University, Syracuse, New York 13244-4100

wjlees@syr.edu

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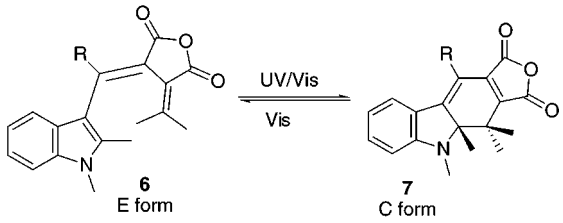
Introduction

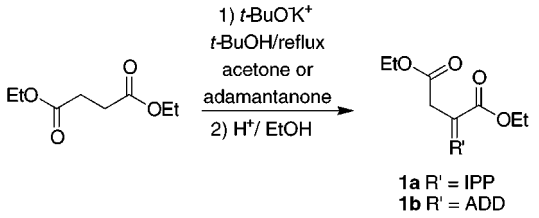
Manipulation of the structure of photochromic molecules to control their optical properties is central to the development of advanced materials.[1,2] Photochromic organic compounds undergo reversible structural changes upon illumination and currently find commercial success as dyes and inks and in ophthalmic lenses. One important potential application is utility as the photoactive medium in an erasable rewriteable optical memory. In the past decade, many dramatic strides in the engineering of such a device have been taken.[3] A significant hurdle that remains is the lack of a robust and efficient photochromic medium. Requirements for a photochromic molecule to be used for such a purpose include photochemical but not thermal reversibility of the photoreaction, ultrafast reaction rates, nondestructive readout, and suitable quantum yields. Further, for long-term data storage the material must have high photochemical and thermal stability. Finally, the wavelength maxima must match a commercially available light source and production of large amounts of material must be uncomplicated and cost-effective.

Fulgides have been identified as viable photochromic substances for a broad range of applications, including optical memory, due to the thermal stability of both forms of the molecule (Scheme 1).[2,4] Indolyl fulgides are of particular interest due to their enhanced photochemical and thermal stability and the shift of their E form wavelength maxima into the near visible region of the spectrum relative to other heteroaromatic fulgides.[5] Yokoyama et al. recently reported that the trifluoromethyl derivative of an indolyl-based fulgide, **6** ($R = CF_3$), possessed the most promising combination of photochromic properties recorded to date.[6] Among these properties were a large increase in photochemical stability relative to the methyl derivative ($R = CH_3$) and a red shift of the absorption maximum which places the absorbance of the E form further into the visible region (426 nm) than any other fulgide. While the discovery of this robust fulgide was of great importance, a simple and efficient method to produce it in large quantity was not available. Limited availability of **6** hinders photochemical characterization, eliminates it as a viable candidate for optical memory, and severely restricts the number of derivatives synthesizable directly from the fulgide. Difficulties in the synthesis of all fulgides, especially the most promising indolyl fulgides, have plagued their realization as useful and practical media for all manner of applications.

Scheme 1. Photochromism of an Indolyl Fulgide



Scheme 2. First Stobbe Condensation



Herein, we describe an improved synthetic route to Yokoyama's indolyl fulgide, including modification of reported techniques and development of new methodology, which increases the overall synthetic yield. Additionally, we have synthesized a number of novel fulgides to explore structure−activity relationships.

Results and Discussion

The most versatile synthetic route to the fulgides employs two Stobbe condensation reactions.[7] The synthetic strategies herein are based upon this sequence employing modifications and new methods. The first Stobbe condensation involves the reaction of diethyl succinate with either acetone or adamantanone to form isopropylidene (IPP, **1a**) or adamantylidene (ADD, **1b**) diethyl succinate derivatives,[8] respectively (Scheme 2). The succeeding Stobbe condensation combined either **1a** or **1b** with a series of acylindoles. The acetylindole **2a**

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10.1021/jo005722n CCC: $20.00
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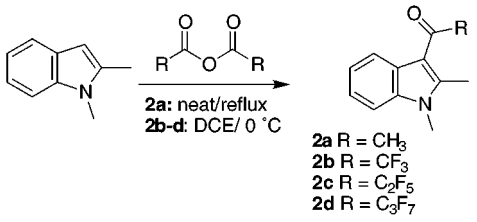
Scheme 3. Synthesis of 3-Acylindoles



Scheme 4. Second Stobbe Condensation

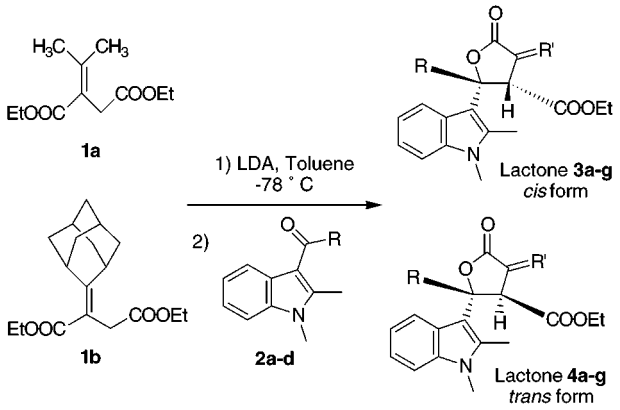


Table 1. Summary of Fulgide Synthesis

				yield (%) of **6a**−**g** from lactones		
compd	R	R′	cis/trans ratio **3**:**4**	KOH method only	NaH + KOH methods	% yield ratio
a	CH_3	IPP	1:2	18.2[a]	42.7[b]	2.3
b	CF_3	IPP	4:1	15.0[a]	81.4[c]	5.4
c	C_2F_5	IPP	3:1	19.7[a]	63.0[c]	3.2
d	C_3F_7	IPP	4:1	14.6[a]	44.5[c]	3
e	CF_3	ADD	>10:1	12.5[d,e]	56[d]	4.5
f	C_2F_5	ADD	>10:1	NA	28[d]	NA
g	C_3F_7	ADD	>10:1	NA	34[d]	NA

[a] After precipitating out the cis lactone, the resulting mixture of cis and trans lactones was converted to fulgide with the KOH method. Treatment of the initial mixture of lactones with ethanolic KOH resulted in lower overall yields. [b] The mixture of cis and trans lactones was converted to fulgide with the NaH method.[c] A combined yield from using the NaH and KOH methods on the cis and trans lactones, respectively. [d] Only the cis isomer was isolated from the condensation reaction. [e] The cis lactone was converted to fulgide with the KOH method.

was synthesized by refluxing 1,2-dimethylindole in neat acetic anhydride (Scheme 3).[9] The fluorinated acylindoles **2b**−**d** were synthesized by quantitative acylation of 1,2-dimethylindole with the corresponding perfluorinated anhydride in 1,2-dichloroethane at 0 °C,[10] an improvement upon previous fulgide syntheses which used the mixed anhydride of trifluoroacetic acid and trifluoromethanesulfonic acid.[6] The second Stobbe condensation was accomplished by enolization of the succinate derivatives **1a** and **1b** and subsequent coupling with acylindoles **2a**−**d** (Scheme 4).[11] This reaction afforded a mixture of the cis (**3a**−**g**) and trans (**4a**−**g**) indole lactone intermediates. The cis to trans ratios varied from 1:2 to greater than 10:1 depending on the substrate (Table 1) as determined by NMR spectroscopy.

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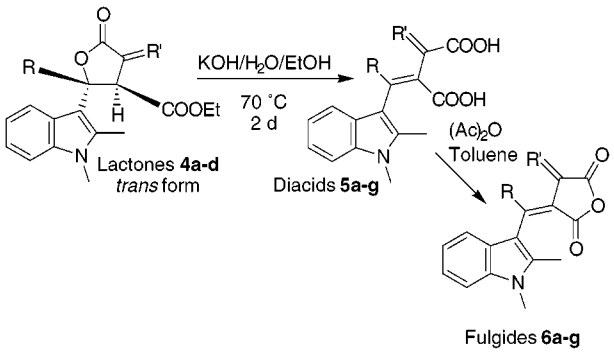
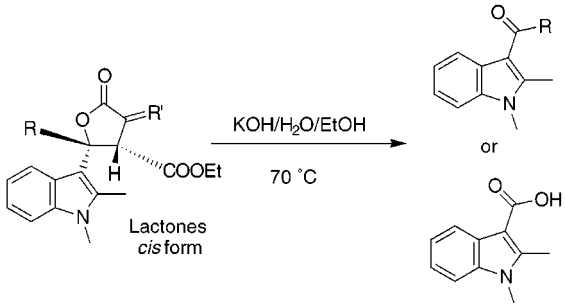
(10) Cipiciani, A.; Clementi, S.; Giulietti, G.; Marino, G.; Savelli, G.; Linda, P. *J. Chem. Soc. Perkin Trans. 2* **1982**, 523.
(11) Janicki, S. Z; Schuster, G. B. *J. Am. Chem. Soc.* **1995**, *117*, 8524.

Scheme 5. Synthesis of Fulgides Using the KOH Method



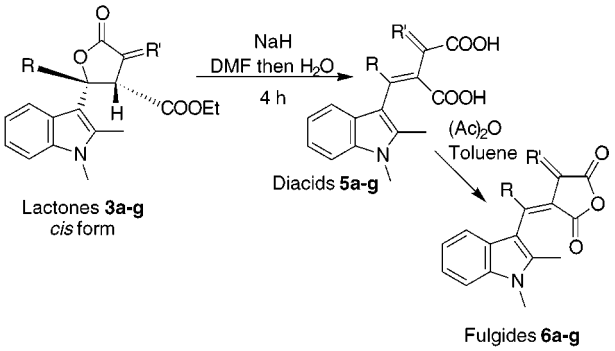
Scheme 6. Unwanted Decompositions of *cis*-Indole Lactones



In previous synthetic endeavors involving the CH_3 analogue, only the trans lactone derivatives had been carried on to the final product.[11] In accordance with previous efforts, treatment of trans indole lactones **4a**−**d** with aqueous ethanolic potassium hydroxide at 70 °C opened the lactone via an elimination reaction and afforded hydrolysis of the ethyl ester. The resulting diacids **5a**−**d** were dehydrated with acetic anhydride to produce the corresponding fulgides (Scheme 5). Yields of the combined elimination/hydrolysis of the trans indole lactone to diacid and subsequent dehydration to fulgide generally exceeded 70%. Under the same reaction conditions for the opening of the trans isopropylidene indole lactones **4a**−**d**, the cis isopropylidene indole lactones **3a** and **3b** decomposed to the starting acylindole or to 3-carboxyl-1,2-dimethylindole, respectively (Scheme 6). Historically, the decomposition of the cis indole lactone derivatives and low overall yields of fulgide were common difficulties. For the fluorinated analogues, the cis indole lactone comprised at least 75% of the product formed, making these difficulties unmanageable. Additionally, the ratio of cis to trans indole lactone for the adamantylidene derivatives proved to be so great that it was not feasible to isolate the trans derivatives. The cis adamantylidene indole lactones were found to open to diacid via the aqueous ethanolic potassium hydroxide method; however, yields were consistently low. While production of fulgide from the trans indole lactones occurred in equivalent or better yields than previous reports, the need for chemistry to make use of the cis isomer of the lactones was imperative.

Treatment of the cis indole lactones **3a**−**g** with sodium hydride in DMF at 0 °C followed by the addition of at least 2 equiv of water resulted in the elimination of the lactone and hydrolysis of the ethyl ester (Scheme 7). The diacids **5a**−**g** were then dehydrated as previously mentioned to form the fulgide. The ability to carry the cis as

Scheme 7. Synthesis of Fulgides Using the NaH Method



well as the trans lactone on to fulgide improved the overall yield of the initial CF_3 isopropylidene fulgide **6b** to 29% from 1,2-dimethylindole. The previously reported yield was 1.3%.[6] Table 1 summarizes the yield enhancements achieved by incorporation of this new methodology. Use of aqueous sodium hydroxide with DMF as the solvent in place of sodium hydride followed by water produced similar results with slightly lower yields. Replacing DMF with DMSO or acetonitrile achieved elimination of the lactone but did not efficiently hydrolyze the ester. The same reaction protocols gave little or no reaction in THF or toluene. LDA and *n*-butyllithium in THF or toluene provided no product.

In conclusion, we have developed a method to enhance the overall synthetic yields of fulgides and demonstrated that the procedure has broad applicability. The method has been shown to improve the yields of both fluorinated and nonfluorinated indole fulgide derivatives. It is expected that the scope of this reaction will include most, if not all, cis lactone derivatives. The new methodology will provide for the production of large quantities of numerous derivatives of fluorinated and nonfluorinated indolyl fulgides, including the robust trifluoromethyl derivative. These advances will afford the materials necessary to thoroughly study the photochromic properties of the fulgides, in turn making major progress toward new and exciting applications.

Experimental Section

General Procedures and Materials. All commercially available materials were used without further purification. NMR spectra were recorded on a Bruker 300 MHz NMR spectrometer. ^1H and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm). ^{19}F NMR samples were externally referenced to fluorotrichloromethane (0.00 ppm). Flash chromatography was performed with 230−400 mesh silica gel. E&R Microanalytical Laboratory Inc. (Parsippany. NJ) performed all elemental analyses. Synthesis of **2a**, **3a**/**4a**, and **6a** was accomplished in accordance with previous reports.[9,11]

Isopropylidene Diethyl Succinate (1a).[8] To a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (250 mL, 1.0 M) was added diethyl succinate (43.0 g, 0.247 mol). After 5 min, acetone (14.2 g, 0.245 mol) was added and the solution refluxed for 24 h. The reaction was then quenched with aqueous HCl (50 mL, 50% solution) and extracted with diethyl ether (2 × 100 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and solvent was removed in vacuo. The resulting brown syrup was dissolved in ethanol (1 L) and acidified with conc HCl (20 mL). After 48 h the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL) and extracted with diethyl ether (3 × 200 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and solvent was removed in vacuo. Vacuum distillation afforded isopropylidene diethyl succinate (39.6 g, 75%) as a clear colorless oil: ^1H NMR ($CDCl_3$) δ 4.07 (q, J_{HH} = 7.1 Hz, 2H), 4.06 (q, J_{HH} = 7.1 Hz, 2H), 3.28 (s, 2H), 2.06 (s, 3H), 1.78 (s, 3H), 1.17 (t, J_{HH} = 7.1 Hz, 3H), 1.16 (t, J_{HH} = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.2, 167.6, 148.6, 120.7, 60.4, 60.0, 35.3, 23.0, 14.0. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.39; H, 8.66.

Adamantylidene Diethyl Succinate (1b).[8] Synthesis was accomplished in a manner similar to that for **1a** (54% yield): ^1H NMR ($CDCl_3$) δ 4.13 (q, J_{HH} = 7.1 Hz, 2H), 4.08 (q, J_{HH} = 7.1 Hz, 2H), 3.63 (s, 1H), 3.31 (s, 2H), 2.78 (s, 1H), 1.98−1.75 (m, 12H), 1.23 (t, J_{HH} = 7.1 Hz, 3H), 1.21 (t, J_{HH} = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.5, 168.6, 162.4, 114.3, 60.5, 60.1, 39.1, 38.9, 36.6, 35.0, 34.6, 34.5, 27.5, 14.2, 14.1.

General Preparation of Acylindoles 2b−d.[10] To a stirred solution of fluorinated anhydride at 0 °C was added over 30 min a solution of 1 equiv of 1,2-dimethylindole dissolved in dichloroethane. After 2 h at room temperature, the now purple reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$) and filtered. The solvent was removed in vacuo to afford the acylindole as a pale yellow solid.

1,2-Dimethyl-3-trifluoroacetylindole (2b):[10] 96% yield; ^1H NMR ($CDCl_3$) δ 8.08−8.02 (m, 1H), 7.33−7.21 (m, 3H), 3.57 (s, 3H), 2.66 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −74.5 (s); ^{13}C NMR ($CDCl_3$) δ 174.8 (q, J_{CCF} = 36 Hz), 150.1, 136.8, 125.1, 123.1, 123.0, 120.6 (q, J_{CCCF} = 4 Hz), 117.3 (q, J_{CF} = 290 Hz), 109.8, 107.7, 29.7, 12.9. Anal. Calcd for $C_{12}H_{10}F_3NO$: C, 59.75; H, 4.18; F, 23.63; N, 5.81. Found: C, 59.59; H, 3.88; F, 23.32; N, 5.65.

1,2-Dimethyl-3-pentafluoropropionylindole (2c): 95% yield; ^1H NMR ($CDCl_3$) δ 8.10−8.02 (m, 1H), 7.33−7.19 (m, 3H), 3.57 (s, 3H), 2.62 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −82.8 (s), −118.8 (s); ^{13}C NMR ($CDCl_3$) δ 178.2 (t, J_{CCF} = 28 Hz), 150.2, 136.7, 125.0, 123.2, 123.1, 121.1 (t, J_{CCCF} = 7 Hz), 118.8 (qt, J_{CF} = 286 Hz, J_{CCF} = 35 Hz), 109.7, 108.7 (tq, J_{CF} = 270 Hz, J_{CCF} = 35 Hz), 108.4, 29.6, 13.0. Anal. Calcd for $C_{13}H_{10}F_5NO$: C, 53.62; H, 3.46; F, 32.62; N, 4.81. Found: C, 53.76; H, 3.28; F, 32.48; N, 4.76.

1,2-Dimethyl-3-heptafluorobutyrylindole (2d): 93% yield; ^1H NMR ($CDCl_3$) δ 8.07−8.01 (m, 1H) 7.34−7.18 (m, 3H) 3.53 (s, 3H) 2.61 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −80.1 (s), −116.0 (s), −125.5 (s); ^{13}C NMR ($CDCl_3$) δ 178.6 (t, J_{CCF} = 28 Hz), 150.1, 136.7, 125.0, 123.1, 123.0, 121.0 (t, J_{CCCF} = 7 Hz), 118.1 (qt, J_{CF} = 288 Hz, J_{CCF} = 34 Hz), 109.7, 109.5 (t of sextet, J_{CF} = 254 Hz, J_{CCF} = 33 Hz), 109.4, 109.3 (tt, J_{CF} = 260 Hz, J_{CCF} = 34 Hz), 29.6, 12.9. Anal. Calcd for $C_{14}H_{10}F_7NO$: C, 49.28; H, 2.95; F, 38.97; N, 4.10. Found: C, 49.50; H, 3.02; F, 38.94; N, 4.11.

General Preparation of Indole Lactones (3a−d/4a−g).[11] To a stirred solution of either isopropylidene or adamantylidene diethyl succinate in toluene at −78 °C was added 1.1 equiv of a 2.0 M solution of lithium diisopropylamide in toluene. The resulting mixture was allowed to warm to 0 °C and then recooled to −78 °C. The appropriate acylindole (1.0 equiv) was added, and the mixture was allowed to warm to room temperature. After 24 h, the reaction was quenched with a 10% H_2SO_4 solution and extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and solvent was removed in vacuo. Purification was accomplished via flash chromatography (2:1 hexane/ethyl acetate or 1:1 hexane/ethyl ether) and multiple crystallizations from ethanol to yield pure cis indole lactone (**3a−g**) as a mixture of atropisomers. The trans indole lactone (**4a−d**) was isolated via supplementary flash chromatography (CH_2Cl_2) as an oil, often containing a small portion of the cis isomer. Note: the trans indole lactone was only collected for the isopropylidene derivatives (**3a−d**).

CF_3 isopropylidene indole lactone (3b/4b): 36% yield (80% cis (**3b**), 20% trans (**4b**)). **4b** (determined from mixture): ^1H NMR ($CDCl_3$) δ 8.00 (d, J_{HH} = 8.3 Hz, 1H), 7.33−7.02 (m, 3H), 4.89 (s, 1H), 4.42−4.25 (m, 2H), 3.66 (s, 3H), 2.61 (s, 3H), 2.24 (s, 3H), 1.73 (s, 3H), 1.37 (t, J_{HH} = 7.0 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ −75.3 (s). **3b**: ^1H NMR ($CDCl_3$) δ 8.27 (d, J_{HH} = 7.4 Hz, 0.3H), 7.60 (d, J_{HH} = 7.4 Hz, 0.7H), 7.22−7.04 (m, 3H), 4.81 (s, 0.7H), 4.62 (s, 0.3H), 3.75−3.68 (m, 1.4H), 3.58 (s, 2.1H), 3.54 (s, 0.9H), 3.52−3.43 (m, 0.6H), 2.65 (s, 2.1H), 2.42 (s, 0.9H), 2.33 (s, 3H), 2.07 (s, 2.1H), 2.02 (s, 0.9H), 0.59 (t, J_{HH} = 7.1 Hz, 2.1H), 0.35 (t, J_{HH} = 7.1 Hz, 0.9H); ^{19}F NMR ($CDCl_3$) δ −79.7 (s); ^{13}C NMR ($CDCl_3$) δ 168.1, 167.9, 166.7, 166.6, 154.5, 153.8, 137.5, 136.7, 136.5, 133.7, 127.1, 125.0 (q, J_{CF} = 288 Hz), 124.2, 121.9, 121.5,

121.1, 120.4 (q, J_{CCCF} = 3 Hz), 120.2, 119.2, 118.5, 118.4, 108.9, 108.5, 103.2, 102.0, 83.3 (q, J_{CCF} = 30 Hz), 82.7 (q, J_{CCF} = 30 Hz), 61.2, 61.0, 58.1, 53.0, 51.8, 29.3, 29.2, 24.1, 20.4, 20.2, 12.9, 12.7, 11.9. Anal. Calcd for $C_{21}H_{22}F_3NO_4$: C, 61.61; H, 5.42; F, 13.92; N, 3.42. Found: C, 61.79; H, 5.73; F, 13.75; N, 3.41.

C_2F_5 isopropylidene indole lactone (3c/4c): 21% yield (76% cis (**3c**), 26% trans (**4c**)). **4c** (determined from mixture): ^{1}H NMR ($CDCl_3$) δ 7.98−7.88 (m, 1H), 7.28−7.00 (m, 3H), 4.91 (s, 1H), 4.40 (q, J_{HH} = 7.0 Hz, 2H), 3.60 (s, 3H), 2.54 (s, 3H), 2.19 (s, 3H), 1.99 (s, 3H), 1.45 (t, J_{HH} = 7.0 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ −82.3 (s), −120.4 (m). **3c**: ^{1}H NMR ($CDCl_3$) δ 8.24 (d, J_{HH} = 7.8 Hz, 0.3H), 7.61 (t, J_{HH} = 7.8 Hz, 0.7H), 7.19−7.03 (m, 3H), 4.91 (s, 0.7H), 4.73 (s, 0.3H), 3.67−3.57 (m, 1.4H), 3.61 (s, 2.1H), 3.58 (s, 0.9H), 3.49−3.35 (m, 0.6H), 2.64 (s, 2.1H), 2.41 (d, J_{HH} = 2.9 Hz, 0.9H), 2.32 (s, 3H), 2.05 (s, 2.1H), 2.00 (s, 0.9H), 0.55 (t, J_{HH} = 7.0 Hz, 2.1H), 0.26 (t, J_{HH} = 7.0 Hz, 0.9H); ^{19}F NMR ($CDCl_3$) δ −79.7 (s), −121.3 (m); ^{13}C NMR ($CDCl_3$) δ 168.1, 167.8, 166.5, 166.3, 154.0, 153.2, 137.0, 136.8, 136.4, 134.1, 126.9, 124.2, 122.1, 121.4, 121.2, 120.9, 120.7, 120.2, 119.1, 118.8, 118.7 (qt, J_{CF} = 289 Hz, J_{CCF} = 36 Hz), 118.6 (qt, J_{CF} = 289 Hz, J_{CCF} = 36 Hz), 114.2 (tq, J_{CF} = 266 Hz, J_{CCF} = 35 Hz), 114.1 (tq, J_{CF} = 266 Hz, J_{CCF} = 35 Hz), 108.7, 108.4, 103.0, 101.8, 83.5 (m), 83.0 (m), 61.2, 60.9, 53.3, 52.0, 29.4, 29.3, 24.1, 24.0, 20.4, 20.2, 13.6, 12.9, 12.5, 11.9. Anal. Calcd for $C_{22}H_{22}F_5NO_4$: C, 57.52; H, 4.83; F, 20.68; N, 3.05. Found: C, 57.68; H, 4.98; F, 20.50; N, 3.03.

C_3F_7 isopropylidene indole lactone (3d/4d): 10% yield (83% cis (**3d**), 17% trans (**4d**)). **4d** (determined from mixture): ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J_{HH} = 8.0 Hz, 1H), 7.32−7.01 (m, 3H), 4.91 (s, 1H), 4.42−4.27 (m, 2H), 3.64 (s, 3H), 2.63 (s, 3H), 2.31 (s, 3H), 1.84 (s, 3H), 1.34 (t, J_{HH} = 8.0 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ −80.9 (s), −113.0 (m), −124.8 (m). **3d**: ^{1}H NMR ($CDCl_3$) δ 8.24 (d, J_{HH} = 8.2 Hz, 0.3H), 7.60 (dd, J_{HH} = 8.2 Hz, J_{HH} = 3.8 Hz, 0.7H), 7.26−7.03 (m, 3H), 4.90 (s, 0.7H), 4.71 (s, 0.3H), 3.66 (s, 2.1H), 3.62 (s, 0.9H), 3.61−3.49 (m, 1.4H), 3.48−3.33 (m, 0.6H), 2.66 (s, 2.1H), 2.42 (d, J_{HH} = 4.0 Hz, 0.9H), 2.34 (s, 3H), 2.04 (s, 2.1H), 2.00 (s, 0.9H), 0.56 (t, J_{HH} = 7.1 Hz, 2.1H), 0.24 (t, J_{HH} = 7.1 Hz, 0.9H); ^{19}F NMR ($CDCl_3$) δ −81.3 (s), −115.0 (m), −122.5 (m); ^{13}C NMR ($CDCl_3$) δ 168.0, 167.7, 166.6, 166.4, 153.9, 153.2, 137.1, 136.8, 134.2, 127.0, 124.3, 122.3, 121.4, 121.1, 120.9, 120.8, 120.2, 119.2, 118.8, 118.7, 117.7 (qt, J_{CF} = 289 Hz, J_{CCF} = 35 Hz), 117.6 (qt, J_{CF} = 289 Hz, J_{CCF} = 35 Hz), 109.1 (t of sextet, J_{CF} = 231 Hz, J_{CCF} = 37 Hz), 108.9 (t of sextet, J_{CF} = 231 Hz, J_{CCF} = 37 Hz), 108.7, 108.4, 108.3 (tt, J_{CF} = 243 Hz, J_{CCF} = 36 Hz), 108.1 (tt, J_{CF} = 243 Hz, J_{CCF} = 36 Hz), 103.0, 101.6, 84.2 (m), 84.1 (m), 61.2, 60.9, 53.6, 52.3, 29.3, 29.2, 24.0, 20.3, 20.1, 13.6, 13.4, 12.9, 12.4, 12.0. Anal. Calcd for $C_{23}H_{22}F_7NO_4$: C, 54.23; H, 4.35; F, 26.11; N, 2.75. Found: C, 54.65; H, 3.99; F, 26.33; N, 2.71.

CF_3 adamantylidene indole lactone (3e): 45% yield (100% cis (**3e**)); ^{1}H NMR ($CDCl_3$) δ 8.27 (d, J_{HH} = 7.6 Hz, 0.3H), 7.55 (d, J_{HH} = 7.8 Hz, 0.7H), 7.24−7.02 (m, 3H), 4.81 (s, 0.7H), 4.61 (s, 0.3H), 4.34 (s, 1H), 3.73−3.66 (m, 1.4H), 3.65 (s, 2.1H), 3.62 (s, 0.9H), 3.60−3.47 (m, 0.6H), 3.01 (s, 0.7H), 2.86 (s, 0.3H), 2.67 (s, 2.1H), 2.42 (s, 0.9H), 2.07−1.83 (m, 12H), 0.64 (t, J_{HH} = 7.1 Hz, 2.1H), 0.41 (t, J_{HH} = 7.1 Hz, 0.9H); ^{19}F NMR ($CDCl_3$) δ −120.2 (s); ^{13}C NMR ($CDCl_3$) δ 169.9, 169.3, 168.5, 168.4, 166.9, 166. 7, 137.4, 136.6, 136.4, 133.5, 127.1, 124.9 (q, J_{CF} = 289 Hz), 124.2, 122.0, 121.4, 120.9, 120.3, 120.1, 119.0, 111.8, 111.7, 108.7, 108.2, 103.5, 102.2, 83.2 (q, J_{CCF} = 30 Hz), 82.7 (q, J_{CCF} = 30 Hz), 60.96, 60.88, 52.0, 50.7, 39.4, 39.2, 39.1, 39.0, 37.1, 37.0, 36.3, 31.8, 31.7, 29.3, 27.3, 27.2, 13.4, 13.1, 12.8, 11.9. Anal. Calcd for $C_{28}H_{30}F_3NO_4$: C, 67.05; H, 6.03; F, 11.36; N, 2.79. Found: C, 66.91; H, 6.25; F, 11.30; N, 2.64.

C_2F_5 adamantylidene indole lactone (3f): 29% yield (100% cis (**3f**)); ^{1}H NMR ($CDCl_3$) δ 8.24 (d, J_{HH} = 7.9 Hz, 0.3H), 7.59−7.56 (m, 0.7H), 7.26−7.01 (m, 3H), 4.93 (s, 0.7H), 4.74 (s, 0.3H), 4.32 (s, 1H), 3.73−3.49 (m, 0.6H), 3.65 (s, 2.1H), 3.62 (s, 0.9H), 3.49−3.36 (m, 1.4H), 2.97 (s, 0.7H), 2.84 (s, 0.3H), 2.65 (s, 2.1H), 2.41 (d, J_{HH} = 3.5 Hz, 0.9H), 2.16−1.78 (m, 12H), 0.59 (t, J_{HH} = 7.1 Hz, 2.1H), 0.32 (t, J_{HH} = 7.1 Hz, 0.9H); ^{19}F NMR ($CDCl_3$) δ −119.0 (s), −184.5 (m); ^{13}C NMR ($CDCl_3$) δ 169.9, 169.2, 168.7, 168.6, 166.8, 166.6, 137.0, 136.7, 136.3, 134.0, 126.4, 124.3, 122.2, 121.4, 121.2, 120.8, 120.7, 120.2, 119.0, 118.7 (qt, J_{CF} = 289 Hz, J_{CCF} = 36 Hz), 118.6 (qt, J_{CF} = 289 Hz, J_{CCF} = 36 Hz), 114.4 (tq, J_{CF} = 265 Hz, J_{CCF} = 35 Hz), 114.3 (tq, J_{CF} = 265 Hz, J_{CCF} = 35 Hz), 112.1, 111.9, 108.7, 108.3, 103.2, 102.1, 83.5 (m), 83.2 (m), 61.1, 60.9, 52.3, 51.0, 39.3, 39.2, 39.1, 39.0, 38.9, 37.2, 37.0, 36.3, 36.2, 31.9, 31.7, 29.5, 29.4, 27.3, 27.2, 13.7, 13.5, 13.1, 12.7, 12.0. Anal. Calcd for $C_{29}H_{30}F_5NO_4$: C, 63.15; H, 5.48; F, 17.22; N, 2.54. Found: C, 62.97; H, 5.75; F, 17.51; N, 2.31.

C_3F_7 adamantylidene indole lactone (3g): 24% yield (100% cis (**3g**)); ^{1}H NMR ($CDCl_3$) δ 8.27 (d, J_{HH} = 7.8 Hz, 0.3H), 7.62−7.58 (m, 0.7H), 7.26−7.01 (m, 3H), 4.96 (s, 0.7H), 4.77 (s, 0.3H), 4.34 (s, 1H), 3.63 (s, 2.1H), 3.61 (s, 0.9H), 3.60−3.50 (m, 1.4H), 3.48−3.35 (m, 0.6H), 2.97 (s, 0.7H), 2.84 (s, 0.3H), 2.66 (s, 2.1H), 2.41 (d, J_{HH} = 4.0 Hz· 0.9H), 2.02−1.60 (m, 12H), 0.58 (t, J_{HH} = 7.1 Hz, 2.1H), 0.31 (t, J_{HH} = 7.1 Hz, 0.9H); ^{19}F NMR ($CDCl_3$) δ −122.3 (s), −176.5 (m), −187.2 (m); ^{13}C NMR ($CDCl_3$) δ 169.7, 169.0, 168.6, 168.5, 166.8, 166.7, 137.1, 136.7, 136.3, 134.1, 126.9, 124.3, 122.4, 121.4, 121.1, 120.9, 120.7, 120.2, 120.0, 119.0, 117.9 (qt, J_{CF} = 290 Hz, J_{CCF} = 34 Hz), 117.7 (qt, J_{CF} = 290 Hz, J_{CCF} = 34 Hz), 112.1, 111.8, 109.7 (t of sextet, J_{CF} = 271 Hz, J_{CCF} = 38 Hz), 109.6 (t of sextet, J_{CF} = 271 Hz, J_{CCF} = 38 Hz), 108.9 (tt, J_{CF} = 258 Hz, J_{CCF} = 34 Hz), 108.7 (tt, J_{CF} = 258 Hz, J_{CCF} = 34 Hz), 108.6, 108.3, 103.2, 101.9, 84.2 (m), 84.1 (m), 61.1, 60.9, 52.6, 51.3, 39.3, 39.2, 39.1, 39.0, 38.9, 37.2, 37.1, 36.3, 31.8, 31.7, 29.4, 29.3, 27.3, 27.2, 13.6, 13.5, 13.1, 12.7, 12.1, 12.0. Anal. Calcd for $C_{30}H_{30}F_7NO_4$: C, 59.90; H, 5.03; F, 22.11; N, 2.33. Found: C, 59.79; H, 4.99; F, 21.81; N, 2.26.

General Preparation of Fulgides 6a−d via KOH/H_2O/EtOH Methodology.[11] To the cis/trans mixture of indole lactone (**3a−d**/**4a−d**) dissolved in ethanol was added a saturated aqueous potassium hydroxide solution (4:1 ratio of ethanol to base solution). The clear yellow solution immediately tinted brown. After being stirred for 2 d at 70 °C, the solution was allowed to cool to room temperature, diluted with water, and extracted with ethyl ether (3 × 50 mL). The aqueous solution was then acidified with a 20% H_2SO_4 solution and extracted with ethyl acetate (3 × 50 mL). The combined ethyl acetate layers were dried ($MgSO_4$) and filtered, and solvent was removed in vacuo producing a brown solid. The product was suspended in toluene and allowed to stir. Acetic anhydride (2 equiv) was then added. The solid immediately dissolved and the solution turned dark orange. The solution was allowed to stir for at least 10 min and then solvent was removed in vacuo. The resulting dark slurry was purified by flash chromatography (2:1 hexane/ethyl acetate). Fulgides **6a−d** were recrystallized from 2-propanol.

General Preparation of Fulgides 6a−g via NaH/DMF Methodology. To a stirred solution of cis indole lactone **3a−g** dissolved in *N*,*N*-dimethylformamide at 0 °C was added sodium hydride (at least 2 equiv). The solution was stirred and allowed to warm to room temperature over 1 h. The mixture was recooled to 0 °C, and 4−5 equiv of water was added to the mixture. Hydrogen gas evolved, and the solution was allowed to warm to room temperature and stirred overnight. The reaction was carefully monitored by TLC to ensure complete elimination and hydrolysis. Solvent was removed in vacuo to yield a white powder. The product was suspended in toluene and stirred. At least 3 equiv of acetic anhydride was then added. The solid immediately dissolved, and the solution turned dark orange. After the solution was stirred for 10 min, the solvent was removed in vacuo. The resulting product was extracted from water with dichloromethane (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and solvent was removed in vacuo. The product was purified via flash chromatography (CH_2Cl_2 or 2:1 hexane/ethyl acetate). Crystallization of the fulgides was accomplished using 2-propanol for isopropylidene fulgides **6a−d** and toluene/ligroin for adamantylidene fulgides **6e−g**.

CF_3 isopropylidene fulgide (6b):[6] KOH/H_2O/EtOH method, 75% yield; NaH/DMF method, 83% yield; overall, fulgide **6b** from acylindole **2b**, 29% yield; ^{1}H NMR ($CDCl_3$) δ 7.37−7.11 (m, 4H), 3.71 (s, 3H), 2.28 (s, 3H), 2.16 (s, 3H), 0.97 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −58.2 (s); ^{13}C NMR ($CDCl_3$) δ 161.8, 160.8 159.7, 138.0, 136.9, 132.8 (q, J_{CCF} = 36 Hz), 127.9, 124.6, 122.4, 122.0 (q, J_{CF} = 278 Hz), 121.3, 119.5, 119.4, 109.6, 106.9, 31.0, 26.7, 23.2, 12.2. Anal. Calcd for $C_{19}H_{16}F_3NO_3$: C, 62.81; H, 4.44; F, 15.69; N, 3.86. Found: C, 62.58; H, 4.06; F, 15.52; N, 3.77.

C_2F_5 isopropylidene fulgide (6c): KOH/H_2O/EtOH method, 76% yield; NaH/DMF method, 57% yield; overall; fulgide **6c** from acylindole **2c**, 13% yield; ^{1}H NMR ($CDCl_3$) δ 7.35−7.12 (m, 4H), 3.69 (s, 3H), 2.24 (s, 3H), 2.12 (s, 3H), 1.09 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −80.9 (s), −103.4 (m); ^{13}C NMR ($CDCl_3$) δ 161.6, 161.3,

158.9, 137.4, 137.0, 132.1 (t, J_{CCF} = 27 Hz), 124.9, 122.2, 121.4, 120.8, 119.5, 119.6, 119.3 (qt, J_{CF} = 289 Hz, J_{CCF} = 37 Hz), 113.0 (tq, J_{CF} = 273 Hz, J_{CCF} = 38 Hz), 109.4, 107.4, 30.1, 27.2, 23.1, 11.9. Anal. Calcd for $C_{20}H_{16}F_5NO_3$: C, 58.12; H, 3.90; F, 22.98; N, 3.39. Found: C, 58.09; H, 3.60; F, 23.11; N, 3.31.

C_3F_7 isopropylidene fulgide (6d): KOH/H_2O/EtOH method, 86% yield; NaH/DMF method, 36% yield; overall, fulgide **6d** from acylindole **2d**, 5% yield; ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J_{HH} = 7.7 Hz, 1H), 7.29 (d, J_{HH} = 8.0 Hz, 1H), 7.25 (td, J_{HH} = 7.8 Hz, J_{HH} = 0.9 Hz, 1H), 7.12 (dt, J_{HH} = 7.8 Hz, J_{HH} = 0.9 Hz, 1H), 3.69 (s, 3H), 2.25 (s, 3H), 2.13 (s, 3H), 1.09 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −81.2 (s), −100.4 (m), −121.6 (s); ^{13}C NMR ($CDCl_3$) δ 161.7, 161.3, 159.0, 137.4, 137.0, 132.0 (t, J_{CCF} = 26 Hz), 124.9, 122.2, 121.4, 120.8, 119.8, 119.7, 117.9 (qt, J_{CF} = 287 Hz, J_{CCF} = 32 Hz), 115.2 (tt, J_{CF} = 260 Hz, J_{CCF} = 32 Hz), 109.4 (t of sextet, J_{CF} = 267 Hz, J_{CCF} = 39 Hz), 109.3, 107.5, 30.1, 27.3, 23.1, 11.9. Anal. Calcd for $C_{21}H_{16}F_7NO_3$: C, 54.44; H, 3.48; F, 28.70; N, 3.02. Found: C, 54.36; H, 3.22; F, 28.65; N, 2.98.

CF_3 adamantylidene fulgide (6e): NaH/DMF method, 56% yield; overall, fulgide **6e** from acylindole **2b**, 25% yield; ^{1}H NMR ($CDCl_3$) δ 7.30−7.13 (m, 4H), 4.09 (s, 1H), 3.68 (s, 3H), 2.29 (s, 3H), 2.23 (s, 1H), 1.91 (dq J_{HH} = 12.7 Hz, J_{HH} = 2.6 Hz, 1H), 1.76 (dq J_{HH} = 12.7 Hz, J_{HH} = 2.6 Hz, 1H), 1.65−1.54 (m, 5H), 1.42 (dq J_{HH} = 12.4 Hz, J_{HH} = 2.4 Hz, 1H), 1.25 (dq J_{HH} = 12.7 Hz, J_{HH} = 2.7 Hz, 1H), 1.04 (dq J_{HH} = 12.7 Hz, J_{HH} = 2.6 Hz, 1H), 0.64 (d J_{HH} = 12.3 Hz, 1H), 0.39 (d J_{HH} = 12.6 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ − 87.7 (s); ^{13}C NMR ($CDCl_3$) δ 177.8, 161.7, 159.8, 137.2, 137.0, 131.9 (q, J_{CCF} = 36 Hz), 125.2, 122.3, 121.9 (q, J_{CF} = 278 Hz), 121.8, 121.2, 120.9, 119.2, 109.5, 106.7, 40.5, 39.5, 38.8, 38.7, 38.1, 35.6, 34.1, 29.9, 26.7, 26.6, 12.0. Anal. Calcd for $C_{26}H_{24}F_3NO_3$: C, 68.56; H, 5.31; F, 12.51; N, 3.08. Found: C, 68.36; H, 5.25; F, 12.70; N, 3.07.

C_2F_5 adamantylidene fulgide (6f): NaH/DMF method, 28% yield; overall, fulgide **6f** from acylindole **2c**, 8% yield; ^{1}H NMR ($CDCl_3$) δ 7.33−7.13 (m, 4H), 4.04 (s, 1H), 3.68 (s, 3H), 2.37 (s, 1H), 2.26 (s, 3H), 1.89 (dq, J_{HH} = 12.7 Hz, J_{HH} = 2.6 Hz, 1H), 1.77 (dq, J_{HH} = 12.7 Hz, J_{HH} = 2.7 Hz, 1H), 1.67−1.43 (m, 6H), 1.30 (d, J_{HH} = 12.8 Hz, 1H), 0.89 (d, J_{HH} = 12.5 Hz, 2H), 0.07 (d, J_{HH} = 12.6, 1H); ^{19}F NMR ($CDCl_3$) δ −121.3 (s), −154.8 (m); ^{13}C NMR ($CDCl_3$) δ 177.7, 161.5, 159.1, 137.1, 136.8, 131.0 (t, J_{CCF} = 26.9 Hz), 125.8, 122.1, 121.3, 119.5, 119.4, 119.3 (qt, J_{CF} = 289 Hz, J_{CCF} = 39 Hz), 119.3, 112.9 (tq, J_{CF} = 259 Hz, J_{CCF} = 38 Hz), 109.4, 107.0, 40.1, 39.6, 39.2, 38.3, 37.8, 35.5, 34.0, 30.0, 26.7, 26.6, 11.9. Anal. Calcd for $C_{27}H_{24}F_5NO_3$: C, 64.16; H, 4.79; F, 18.79; N, 2.77. Found: C, 63.87; H, 4.74; F, 18.48; N, 2.56.

C_3F_7 adamantylidene fulgide (6g): NaH/DMF method, 34% yield; overall, fulgide **6g** from acylindole **2d**, 8% yield; ^{1}H NMR ($CDCl_3$) δ 7.34−7.13 (m, 4H), 4.06 (s, 1H), 3.67 (s, 3H), 2.39 (s, 1H), 2.28 (s, 3H), 1.90 (dq, J_{HH} = 12.7 Hz, J_{HH} = 2.6 Hz, 1H), 1.77 (dq, J_{HH} = 12.6 Hz, J_{HH} = 2.6 Hz, 1H), 1.68−1.49 (m, 6H), 1.29 (d, J_{HH} = 12.9 Hz, 1H), 0.88 (d, J_{HH} = 12.8 Hz, 2H), 0.07 (d, J_{HH} = 12.8 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ −121.9 (s), −149.9 (m), −183.9 (s); ^{13}C NMR ($CDCl_3$) δ 177.8, 161.5, 159.1, 137.2, 137.0, 130.9 (t, J_{CCF} = 27 Hz), 125.8, 122.2, 121.3, 119.5, 119.4, 119.3, 117.7 (qt, J_{CF} = 288 Hz, J_{CCF} = 34 Hz), 115.1 (tt, J_{CF} = 259 Hz, J_{CCF} = 33 Hz), 109.7 (t of sextet, J_{CF} = 266 Hz, J_{CCF} = 39 Hz), 109.4, 107.2, 40.1, 39.6, 39.2, 38.3, 37.9, 35.5, 34.1, 29.9, 26.7, 26.6, 11.9. Anal. Calcd for $C_{28}H_{24}F_7NO_3$: C, 60.54; H, 4.35; F, 23.94; N, 2.52. Found: C, 60.54; H, 4.01; F, 23.81; N, 2.38.

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