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Scandium Triflate-Catalyzed Nucleophilic Additions to Indolylmethyl Meldrum's Acid Derivatives via a Gramine-Type Fragmentation: Synthesis of Substituted Indolemethanes

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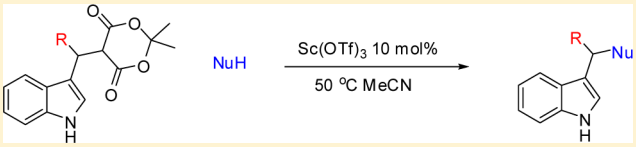
Supporting Information

ABSTRACT: Treatment of indolylmethyl Meldrum's acids with catalytic scandium triflate and a variety of nucleophiles results in the nucleophilic displacement of the Meldrum's acid moiety via a gramine-type fragmentation. The reaction is useful for the generation of heterocyclic compounds of significant molecular complexity.



The indolemethane moiety is abundant in a variety of marine and terrestrial natural products; has been shown to possess important biological activities such as antiviral, hemolytic, cytotoxic, insecticidal, antithrombotic, and anti-carcinogenic; and can also act as an enzymatic inhibitory agent.[1] The unique structural frameworks of three different marine-isolated indolemethane natural products are shown in Figure 1.[2] Because of the indole skeleton and the large array of

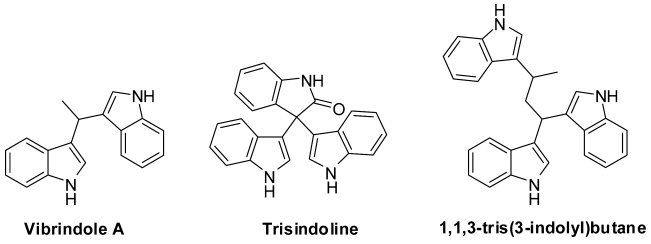


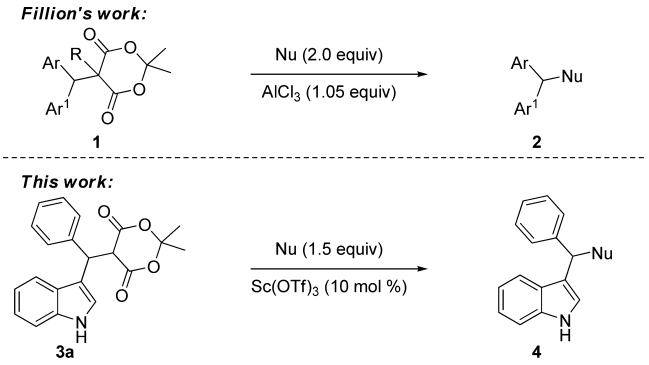
Figure 1. Indolemethane natural products.

biological activities that these molecules exhibit, it is not unexpected that research and development toward the synthesis of indolemethanes and related compounds are of ongoing interest in the scientific community.[3]

Our interest in the synthesis[4] and reactivity[5] of indole molecules along with their synthetic utility toward alkaloid total synthesis[6] was a vital factor in our decision to pursue a project devoted to the synthesis of indolemethanes. Inspired by the innovative work of the Fillion group[7] in the area of Meldrum's acid chemistry,[8] we envisioned that we could apply a similar strategy to indole-substituted Meldrum's acid molecule **3a** in order to access a variety of indolemethane adducts **4** (Scheme 1). The Fillion method employs relatively harsh Lewis acids (Me_3Al or $AlCl_3$), which would surely destroy the electron-rich indole.[9] Herein we present a complementary method that provides access to a variety of functionalized indolemethanes.[10]

To test our hypothesis, **3a** was prepared by a literature procedure[11] and subjected to a variety of reaction conditions in

Scheme 1. Use of Meldrum's Acid as a Leaving Group in Nucleophilic Additions



the presence of nucleophilic indole (Table 1). Initial attempts to optimize this transformation were performed in acetonitrile while varying the catalyst (entries 1–4). To our delight, we found that both $Yb(OTf)_3$ and $Sc(OTf)_3$ promoted the formation of diindolemethane **4a** in moderate yield, while at the sacrifice of the indole nucleophile due to what was suspected to be Lewis acid-catalyzed oligomerization. While both catalysts allowed for product formation, scandium triflate was ultimately chosen as the desired catalyst. In order to overcome the decomposition of the indole nucleophile, we next examined the effect of the indole stoichiometry and catalyst loading (entries 5–9). Gratifyingly, we discovered that using 3 equiv of indole with 10 mol % catalyst (entry 9) led to the desired product in quantitative yield. It should be noted that lower catalyst loadings (5 mol %) were tested, but the reaction time dramatically increased while the yield decreased.

Having achieved significant progress in the optimization of this transformation, we then set forth to perform a temperature study in hopes of lowering both the overall reaction time and

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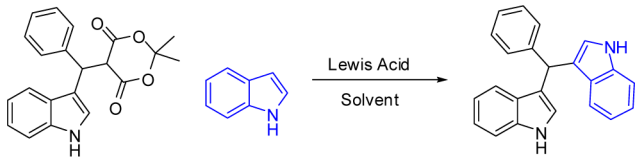
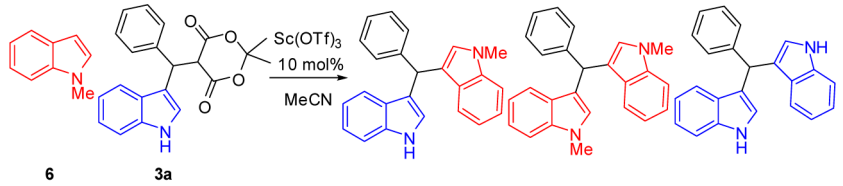
Table 1. Optimization of Indole Addition



entry	equiv of indole	catalyst (mol %)	solvent/temp. (°C)	time (h)	yield
		Catalyst Comparison			
1	1.1	$Cu(OTf)_2$ (20%)	CH_3CN/rt	48	no rxn
2	1.1	$Zn(NTf_2)_2$ (20%)	CH_3CN/rt	48	no rxn
3	1.1	$Yb(OTf)_3$ (20%)	CH_3CN/rt	48	41%[a]
4	1.1	$Sc(OTf)_3$ (20%)	CH_3CN/rt	48	58%[a]
		Reaction Stoichiometry			
5	1.5	$Sc(OTf)_3$ (20%)	CH_3CN/rt	48	60%
6	2	$Sc(OTf)_3$ (20%)	CH_3CN/rt	48	95%
7	3	$Sc(OTf)_3$ (20%)	CH_3CN/rt	48	quant.
8	2	$Sc(OTf)_3$ (10%)	CH_3CN/rt	48	95%
9	3	$Sc(OTf)_3$ (10%)	CH_3CN/rt	48	quant.
		Reaction Temperature			
10	3	$Sc(OTf)_3$ (10%)	CH_3CN/100 °C	1	decomp.
11	2	$Sc(OTf)_3$ (10%)	CH_3CN/100 °C	1	decomp.
12	2	$Sc(OTf)_3$ (10%)	CH_3CN/50 °C	3	quant.
13	1.1	$Sc(OTf)_3$ (10%)	CH_3CN/50 °C	3	73%
14	1.5	$Sc(OTf)_3$ (10%)	CH_3CN/50 °C	3	quant.
		Solvent Comparison			
15	1.5	$Sc(OTf)_3$ (10%)	benzene/50 °C	3	73%
16	1.5	$Sc(OTf)_3$ (10%)	THF/50 °C	3	79%
17	1.5	$Sc(OTf)_3$ (10%)	CH_2Cl_2/reflux	3	quant.
18	1.5	$Sc(OTf)_3$ (10%)	DMF/50 °C	3	no rxn[b]
19	1.5	no catalyst	CH_3CN/50 °C	3	no rxn[b]

[a]Incomplete reaction based on recovery of starting material **3a**. [b]Higher temperatures and indole loadings were examined with no success.

Scheme 2. Attempted Synthesis of Mixed Indolemethanes



the number of equivalents of indole required (entries 10−14). The best reaction conditions were determined to be 1.5 equiv of indole at 50 °C (entry 14). The increase in temperature and lowering of the indole excess allowed for quantitative product conversion in only 3 h, marking a significant decrease in the reaction time with no effect on the overall yield.

Finally, a selection of solvents was tested in order to identify alternative reaction media in the event of solubility issues in future applications (entries 15−19). With the use of dichloromethane as the solvent, we were pleased to see the reaction proceed to completion in quantitative yield, while both benzene and tetrahydrofuran afforded the product in lower yields. Not unexpectedly, the use of a polar aprotic solvent (DMF) led to no reaction, a result that could be explained by deactivation of the oxophilic catalyst through the oxygen of the solvent.[12]

With efficient conditions established, we then set out to examine the possibility of accessing dissymmetrical diindolemethanes. Scheme 2 summarizes our results for the addition of *N*-methylindole (**6**) to Meldrum's acid derivative **3a**. Under the standard reaction conditions, we were able to isolate mixed diindolemethane **4b** in 41% yield after column chromatography; however, both **4c** and **4a** were also isolated in smaller quantities. Compound **4c** is the result of addition of **6** to **4b** with the expulsion of indole (**5**) itself. The addition of **5** to **3a** or **4b** produces **4a**. To selectively promote the formation of only **4b**, the reaction temperature was lowered from 50 °C to rt and again to −10 °C. By lowering the temperature, we were successfully able to suppress access to compounds **4a** and **4c**, but at the consequence of unacceptable yields and impractical reaction times.

With the standard reaction conditions in hand, we set out to survey a range of nucleophiles that would efficiently undergo this transformation. Initial attempts at varying the indole *N*-position (**4b**) and the benzenoid portion (**4d**) of the

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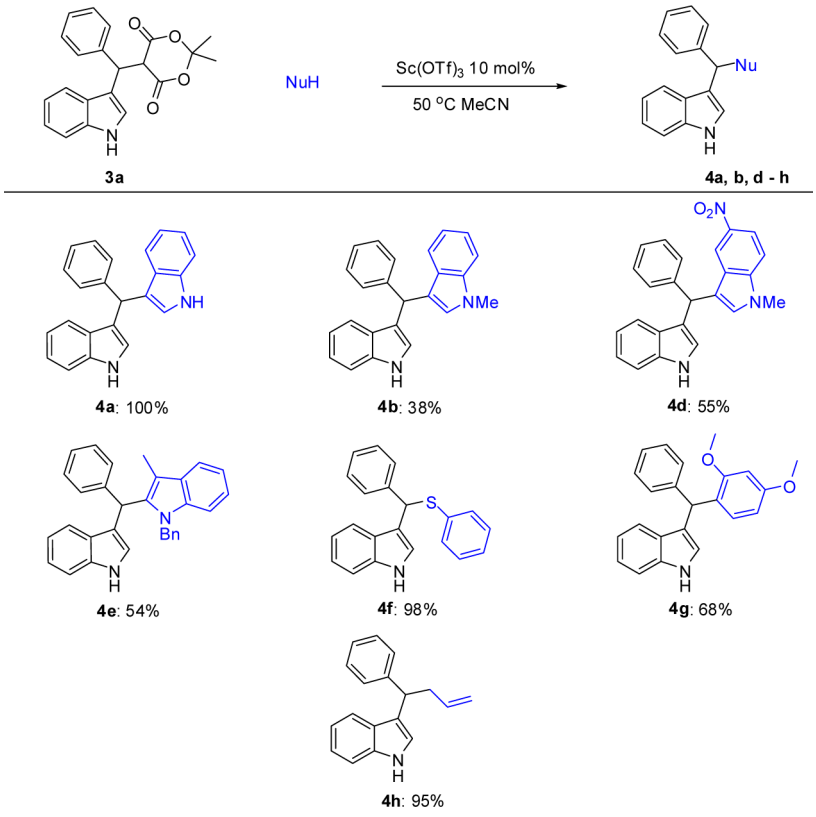
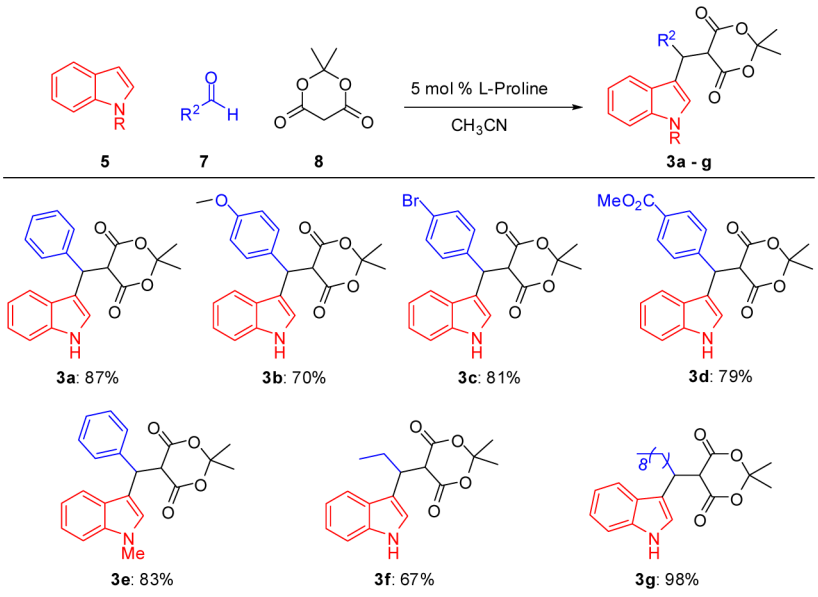
Scheme 3. Nucleophile Scope



Scheme 4. Synthesis of Electrophiles



nucleophile allowed access to dissymmetric diindolemethanes in moderate isolated yields. However, other crossover products were also isolated (Scheme 3). Interestingly, when *N*-benzylskatole was subjected to the reaction conditions, indolemethane **4e** was isolated as the sole identifiable product (albeit in modest yield). With the difficulty in achieving high yields of the dissymmetric diindolemethane, we turned our attention to the use of alternative nucleophiles for the formation of substituted indolemethane molecules. It was suspected and ultimately realized that soft nucleophiles would perform best for this transformation. Thiophenol and allyltrimethylsilane led to nearly quantitative yields of **4f** and **4h**, respectively.The electron-rich aromatic ring of 1,3-dimethoxybenzene led to a moderate yield of **4g**, with a minimal amount of the alternative regioisomer. A variety of other nucleophiles were attempted, including alkyl thiols, styrene, and morpholine, but all led to quick decomposition of the Meldrum's acid starting material.

We next set out to explore the role of the electrophile in the reaction. A library of electrophiles was prepared (Scheme 4)

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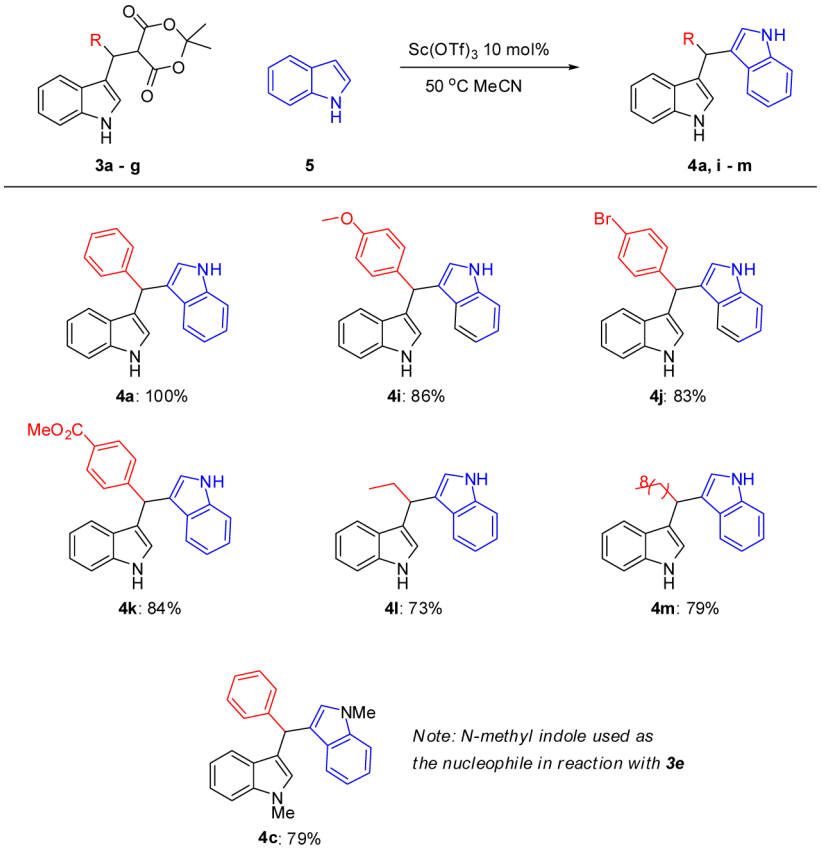
Scheme 5. Electrophile Substrate Scope



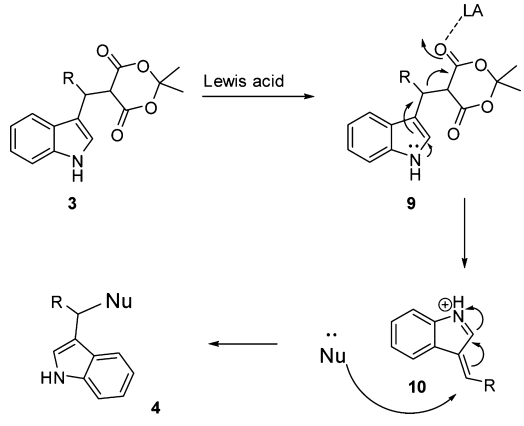
using a modification of the Oikawa procedure.[9] All of the Meldrum's acid derivatives (**3a**–**g**) were synthesized in moderate to excellent yields.

With a variety of Meldrum's acid derivatives **3** in hand, we were able to explore the reactivity of these substrates toward indole (**5**) (Scheme 5). Interestingly when the R group in **3** was aryl, the nature of the substitution on the aryl ring did not seem to greatly affect the product yield. However, it should be noted that *p*-cyano and *p*-nitro derivatives failed to produce significant yields of products. Notably, diindolemethane product formation was achieved readily when nonaromatic substitution was placed on the Meldrum's acid derivative, as both ethyl- and nonyl-substituted electrophiles gave the desired products in yields of 73% (**4l**) and 79% (**4m**), respectively. Reaction of Meldrum's acid derivative **3e** with *N*-methylindole as the nucleophile gave compound **4c** in 79% yield. The reduced yield compared with **4a** is consistent with our previous observations in which the unprotected indole behaved better as a nucleophile compared with *N*-methylindole.[5a]

A simple proposed mechanism for this transformation is shown in Scheme 6. Coordination of the Lewis acid to the carbonyl oxygen in **3** allows the Meldrum's acid moiety to become a better leaving group in a presumed gramine-style fragmentation of **9**. The putative iminium ion **10** may subsequently undergo reaction with a variety of nucleophiles, leading to adducts **4**.

In conclusion, we have developed an expedient and efficient method for the synthesis of indolemethane derivatives. The one-pot gramine-type fragmentation/nucleophilic trapping has been shown to be versatile with a variety of nucleophiles and should be applicable to the synthesis of a variety of interesting natural and unnatural products.

Scheme 6. Proposed Mechanism



EXPERIMENTAL SECTION

General Information. All of the solvents for routine isolation of products and chromatography were reagent grade. Flash chromatography was performed using silica gel (230–400 mesh) with the indicated solvents. All of the reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (60F-254) visualized with UV light and developed using acidic anisaldehyde. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on either a 400 or 600 MHz NMR spectrometer. The ^{1}H NMR data are reported as the chemical shift in parts per million, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz, and number of protons. HRMS was performed with electron impact (EI) ionization and a quadrupolar mass analyzer.

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General Experimental Procedure for the Synthesis of Substituted Indolemethanes 4a−m. To a solution of Meldrum's acid derivative **3** (1.0 equiv) in anhydrous MeCN was added the nucleophile (1.5 equiv). The solution was stirred under argon for 20 min. Scandium triflate (10 mol %) was added, and the reaction mixture was stirred at 50 °C until the reaction was complete (as determined by TLC analysis). The reaction was quenched with sodium bicarbonate, and the mixture was extracted with EtOAc (three times). The organic layers were then combined and dried with magnesium sulfate. Following filtration, the solvent was removed under reduced pressure, and the crude mixture was purified by flash chromatography (EtOAc/hexanes) to yield the desired product **4a−m**.

*3,3′-(Phenylmethylene)bis(1H-indole) (**4a**).* Reagents employed: 5-((1*H*-indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**) (0.100 g, 0.286 mmol), indole (0.050 g, 0.430 mmol), scandium triflate (0.014 g, 0.0284 mmol), and 5 mL of anhydrous MeCN at 50 °C for 3 h. Yield: 100% (92 mg) as a pink foam. R_f = 0.30, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 2H), 7.44−7.15 (m, 11H), 7.05 (dt, J = 6.7, 2.6 Hz, 2H), 6.57 (s, 2H), 5.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 136.56, 128.6, 128.1, 126.9, 126.1, 123.6, 121.8, 119.8, 119.5, 119.1, 111.0, 40.1; IR (thin film) 3414, 1635, 1492, 1455, 1417, 1336, 1216, 1092, 743, 700, 667, 596 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{18}N_2$ 322.1470, found 322.1461.

*3-((1H-Indol-3-yl)(phenyl)methyl)-1-methyl-1H-indole (**4b**).* Reagents employed: 5-((1*H*-indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**) (0.100 g, 0.286 mmol), *N*-methylindole (0.0563 g, 0.429 mmol), scandium triflate (0.014 g, 0.0286 mmol), and 10 mL of anhydrous MeCN at 50 °C for 3 h. Yield: 38% (37 mg) as a pink foam. R_f = 0.20, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H) 7.41−7.34 (m, 5H), 7.30−7.26 (m, 3H), 7.23−7.16 (m, 3H), 7.03−6.98 (m, 2H), 6.67 (s, 1H), 6.51 (s, 1H), 5.89 (s, 1H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 137.4, 136.6, 128.7, 128.2, 128.1, 127.4, 127.0, 126.1, 123.6, 121.9, 121.4, 120.0, 119.9, 119.8, 119.2, 118.6, 118.1, 110.9, 106.0, 40.11, 32.6; IR (thin film) 3413, 3055, 2928, 1600, 1482, 1455, 1419, 1371, 1329, 1217, 1153, 1091, 1050, 1028, 741, 703 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{20}N_2$ 336.1626, found 336.1627.

*3,3′-(Phenylmethylene)bis(1-methyl-1H-indole) (**4c**).* Reagents employed: 5-((1*H*-indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**) (0.100 g, 0.286 mmol), *N*-methylindole (0.0563 g, 0.429 mmol), scandium triflate (0.014 g, 0.0286 mmol), and 10 mL of anhydrous MeCN at 50 °C for 3 h. Yield: 25% (25 mg) as a red foam. R_f = 0.56, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.34 (m, 4H), 7.31−7.25 (m, 4H), 7.23−7.19 (m, 3H), 7.02−6.98 (m, 2H), 6.53 (s, 2H), 5.89 (s, 1H), 3.69 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 137.4, 128.7, 128.3, 128.2, 127.4, 125.9, 121.4, 120.0, 118.6, 118.2, 109.0, 40.1, 32.7; IR (thin film) 3446, 3055, 2930, 2360, 2340, 1635, 1549, 1472, 1423, 1370, 1327, 1224, 1153, 1011, 739, 762, 667, 576, 539 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{22}N_2$ 350.1783, found 350.1784.

*3-((1H-Indol-3-yl)(phenyl)methyl)-5-nitro-1H-indole (**4d**).* Reagents employed: 5-((1*H*-indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**) (0.100 g, 0.286 mmol), 1-methyl-5-nitro-1*H*-indole (76 mg, 0.430 mmol), scandium triflate (0.014 g, 0.0286 mmol), and 5 mL of anhydrous MeCN at 50 °C for 3 h. Yield: 55% (60 mg) as an orange foam. R_f = 0.24, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.10, (dd, J = 9.5, 2.1 Hz, 1H), 8.03 (s, 1H), 7.39−7.28 (m, 7H), 7.23−7.17 (m, 2H), 7.02 (t, J = 7.3 Hz, 1H), 6.7 (s, 1H), 6.65 (s, 1H), 5.91 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 140.1, 136.7, 131.2, 129.7, 128.5, 128.4, 126.7, 126.6, 126.5, 123.4, 122.1, 121.1, 119.7, 119.4, 118.9, 117.3, 117.2, 111.2, 111.1, 39.9, 33.1; IR (thin film) 3419, 2923, 2361, 1617, 1512, 1485, 1455, 1392, 1331, 1094, 1033, 742, 707 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{19}N_3O_2$ 381.1477, found 381.1478.

*2-((1H-Indol-3-yl)(phenyl)methyl)-1-benzyl-3-methyl-1H-indole (**4e**).* Reagents employed: 5-((1*H*-indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**) (0.100 g, 0.286 mmol), 1-benzyl-3-methyl-1*H*-indole (0.095g, 0.4293 mmol), scandium triflate (0.014 g, 0.0286 mmol), and 5 mL of anhydrous MeCN at 50 °C for 3 h. Yield: 54% (66 mg) as a purple foam. R_f = 0.43, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.62 (dd, J = 7.4, 1.6 Hz, 1H) 7.34 (d, J = 8.1 Hz, 1H), 7.30−7.26 (m, 7H), 7.24−7.15 (m, 6H), 7.05−6.98 (m, 3H), 6.52 (s, 1H), 5.89 (s, 1H), 5.27 (q, J = 17.2 Hz, 2H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 138.3, 136.6, 136.5, 136.3, 129.1, 128.7, 128.6, 128.3, 127.1, 127.0, 126.4, 126.0, 124.0, 122.2, 122.1, 121.4, 119.5, 119.4, 118.8, 118.3, 117.0, 111.0, 109.3, 109.0, 46.8, 40.17; IR (thin film) 3852, 3820, 3743, 3648, 3413, 357, 2999, 2360, 2340, 1733, 1683, 1652, 1558, 1540, 1465, 1456, 1418, 1353, 1070, 1029, 741, 699 cm^{-1}; HRMS (EI) calcd for $C_{31}H_{26}N_2$ 426.2096, found 426.2104.

*3-(Phenyl(phenylthio)methyl)-1H-indole (**4f**).* Reagents employed: 5-((1*H*-indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**) (0.100 g, 0.286 mmol), benzenethiol (0.047 g, 0.429 mmol), scandium triflate (0.014 g, 0.0286 mmol), and 5 mL of anhydrous MeCN at 50 °C for 3 h. Yield: 98% (88 mg) as a yellow foam. R_f = 0.58, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 8.9 Hz, 2H), 7.23−6.96 (m, 12H), 5.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 136.7, 136.6, 130.2, 128.6, 128.4, 127.1, 126.3, 126.2, 123.8, 128.3, 122.3, 119.6, 116.2, 111.2, 49.7 (missing one carbon, presumably because of overlap); IR (thin film) 3853, 3750, 3675, 3628, 3420, 3056, 2924, 2360, 1716, 1616, 1581, 1479, 1455, 1437, 1417, 1353, 1337, 1223, 1177, 1124, 1089, 1073, 1025, 740, 697, 473 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{17}NS$ 314.1009, found 314.1009 (M − H).

*3-((2,4-Dimethoxyphenyl)(phenyl)methyl)-1H-indole (**4g**).* Reagents employed: 5-((1*H*-indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**) (0.100 g, 0.286 mmol), 1,3-dimethoxybenzene (0.059 g 0.429 mmol), scandium triflate (0.014 g, 0.0286 mmol), and 5 mL of anhydrous MeCN at 50 °C for 3 h. Yield: 68% (67 mg) as a pink foam. R_f = 0.63, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.29−7.15 (m, 6H), 7.00 (dt, J = 7.5, 1.08 Hz, 2H), 6.91 (d, J = 2.4 Hz, 1H), 6.54 (q, J = 1.2 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.8 Hz, 1H), 6.00 (s, 1H), 3.79 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 157.8, 144.3, 136.7, 130.2, 128.9, 127.9, 127.1, 125.8, 124.9, 123.9, 121.9, 120.1, 120.0, 119.2, 110.9, 103.8, 98.5, 55.6, 55.2, 40.6; IR (thin film) 3418, 2931, 2361, 1771, 1733, 1669, 1652, 1609, 1586, 1558, 1503, 1456, 1436, 1417, 1291, 1258, 1207, 1175, 1156, 1114, 1033, 924, 833, 742, 700 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{21}NO_2$ 343.1572, found 343.1576.

*3-(1-Phenylbut-3-en-1-yl)-1H-indole (**4h**).* Reagents employed: 5-((1*H*-indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**) (0.100 g, 0.286 mmol), allyltrimethylsilane (0.049 g 0.429 mmol), scandium triflate (0.014 g, 0.0286 mmol), and 5 mL of anhydrous MeCN at 50 °C for 3 h. Yield: 95% (67 mg) as a gray foam. R_f = 0.63, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.23−7.12 (m, 5H), 7.11−7.03 (m, 2H), 6.93 (dt, J = 8.1, 1.1 Hz, 2H), 5.79−5.66 (m, 1H), 4.98 (dq, J = 10.2, 1.9 Hz, 1H), 4.88 (dq, J = 10.2, 1.1 Hz, 1H), 4.19 (t, J = 7.63 Hz, 1H), 2.98−2.88 (m, 1H), 2.81−2.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 137.3, 136.4, 128.2, 127.9, 126.9, 126.0, 121.9, 121.2, 119.6, 119.5, 119.2, 115.9, 110.9, 42.9, 40.5; IR (thin film) 3419, 3058, 3025, 2974, 2924, 2859, 1638, 1600, 1490, 1455, 1417, 1337, 1222, 1096, 1074, 1011, 993, 912, 741, 700, 583, 474 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{17}N$ 247.1361, found 247.1368.

*3,3′-((4-Methoxyphenyl)methylene)bis(1H-indole) (**4i**).* Reagents employed: 5-((1*H*-indol-3-yl)(4-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3b**) (0.040 g, 0.105 mmol), indole (0.0185 g, 0.158 mmol), scandium triflate (0.005 g, 0.0105 mmol), and anhydrous MeCN at 50 °C for 3 h. Yield: 86% (32 mg) as an orange foam. R_f = 0.38, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 2H), 7.39 (d, J = 9.3 Hz, 2H), 7.34 (d, J = 9.3 Hz, 2H), 7.27−7.24 (m, 2H), 7.17 (t, J = 7.8 Hz, 2H), 7.01 (t, J = 7.4 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.64 (s, 2H), 5.85 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 136.7, 136.2, 129.6, 127.1, 123.5, 121.9, 120.0, 119.9, 119.2, 113.6, 110.0, 55.2, 39.2; IR (thin film) 3411, 2925, 2360, 2340, 1652, 1558, 1507, 1456, 1418, 1338, 1243, 1173, 1032, 742, 667 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{20}N_2O$ 352.1576, found 352.1580.

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*3,3′-((4-Bromophenyl)methylene)bis(1H-indole) (**4j**).* Reagents employed: 5-((4-bromophenyl)(1*H*-indol-3-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3c**) (0.050 g, 0.116 mmol), indole (0.0205 g, 0.175 mmol), scandium triflate (0.006 g, 0.0122 mmol), and anhydrous MeCN at 50 °C for 3 h. Yield: 83% (39 mg) as a red foam. R_f = 0.41, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 2H), 7.39−7.34 (m, 6H), 7.22−7.20 (m, 4H), 7.02 (t, J = 7.9 Hz, 2H), 6.64 (s, 2H), 5.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 136.6, 131.3, 130.5, 126.8, 123.6, 122.1, 119.8, 119.3, 119.1, 111.5, 111.1, 39.7; IR (thin film) 3852, 3748, 3648, 3410, 2922, 2210, 1652, 1558, 1540, 1485, 1456, 1418, 1338, 1216, 1223, 1093, 1009, 743 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{17}BrN_2$ 400.0575, found 400.0569.

*Methyl 4-(Bis(1H-indol-3-yl)methyl)benzoate (**4k**).* Reagents employed: methyl 4-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)(1*H*-indol-3-yl)methyl)benzoate (**3d**) (0.050 g, 0.122 mmol), indole (0.0216 g, 0.184 mmol), scandium triflate (0.006 g, 0.0122 mmol), and anhydrous MeCN at 50 °C for 3 h. Yield: 84% (39 mg) as a red foam. R_f = 0.41, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 2H), 7.96 (d, J = 7.9, 2H), 7.43−7.35 (m, 7H), 7.18 (t, J = 8.0 Hz, 2H), 7.01 (t, J = 7.7 Hz, 2H), 6.67 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 149.6, 136.7, 129.7, 128.8, 128.2, 126.9, 123.7, 122.1, 119.8, 119.4, 118.8, 111.2, 52.6, 40.3; IR (thin film) 3405, 2923, 2852, 2285, 1719, 1609, 1457, 1435, 1376, 113, 1018, 724 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{20}N_2O_2$ 380.1525, found 380.1530.

*3,3′-(Propane-1,1-diyl)bis(1H-indole) (**4l**).* Reagents employed: 5-(1-(1*H*-indol-3-yl)propyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3f**) (0.050 g, 0.166 mmol), indole (0.0292 g, 0.249 mmol), scandium triflate (0.008 g, 0.0166 mmol), and anhydrous MeCN at 50 °C for 3 h. Yield: 73% (33 mg) as a clear red oil. R_f = 0.36, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.17 (dt, J = 7.4, 1.2 Hz, 2H), 7.06 (dt, J = 7.5, 1.0 Hz, 2H), 6.96 (d, J = 2.3 Hz, 2H), 4.40 (t, J = 7.0, 1H), 2.27−2.12 (m, 2H), 1.03 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 127.2, 121.7, 121.4, 120.2, 119.7, 118.9, 111.0, 35.8, 26.7,13.1; IR (thin film) 3412, 3054, 2957, 2926, 2869, 1616, 1455, 1485, 1418, 1337, 1218, 1093, 1010, 742, 581, 494 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{18}N_2$ 274.1470, found 274.1472.

*3,3′-(Decane-1,1-diyl)bis(1H-indole) (**4m**).* Reagents employed: 5-(1-(1*H*-indol-3-yl)decyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3g**) (0.050 g, 0.125 mmol), indole (0.0220 g, 0.188 mmol), scandium triflate (0.006 g, 0.0122 mmol), and anhydrous MeCN at 50 °C for 3 h. Yield: 79% (37 mg) as a black oil. R_f = 0.56, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.61 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.15 (dt, J = 7.2, 1.2 Hz, 3H), 7.03 (dt, J = 7.5, 1.0 Hz, 3H), 7.00 (d, J = 2.0 Hz, 2H), 4.47 (t, J = 7.5 Hz, 1H), 2.25−2.15 (m, 2H), 1.45−1.15 (m, 12H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 127.1, 121.7, 121.3, 120.6, 119.7, 118.9, 111.0, 35.8, 33.9, 31.8, 29.8, 29.7, 29.3, 28.3, 22.6, 20.8, 14.1; IR (thin film) 3852, 3749, 3674, 3412, 2923, 2852, 2361, 1733, 1699, 1652, 1616, 1456, 1418, 1337, 1069, 1032, 740, 533, 521 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{32}N_2$ 372.2565, found 372.2577.

General Experimental Procedure for the Synthesis of Electrophiles 3a−g. Indole (1.0 equiv) and aldehyde (2.0 equiv) were added to a solution of Meldrum's acid (1.0 equiv) in anhydrous MeCN. The mixture was stirred for 10 min, and then L-proline (5 mol %) was added. The reaction mixture was allowed to stir at room temperature until the reaction was complete (as determined by TLC analysis). Water was then added, and the organic layer was extracted with EtOAc (three times). The organic layers were then combined and dried with magnesium sulfate. Following filtration, the solvent was removed under reduced pressure, and the crude mixture was purified by flash chromatography (EtOAc/hexanes) to yield the desired product **3a−g**.

*5-((1H-Indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**).* Reagents employed: indole (5.00 g, 42.7 mmol), benzaldehyde (9.05 g, 85.4 mmol), Meldrum's acid (6.15 g, 42.7 mmol), L-proline (0.246 g, 2.13 mmol), and anhydrous MeCN at room temperature for 24 h. Yield: 83% (12.38 g) as a pink powder. R_f = 0.20, 30% EtOAc in hexanes. Spectral analysis matched that for the known literature compound.[9]

*5-((1H-Indol-3-yl)(4-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3b**).* Reagents employed: indole (0.081 g, 0.694 mmol), 4-methoxybenzaldehyde (0.189 g, 1.388 mmol), Meldrum's acid (0.100 g, 0.694 mmol), L-proline (0.0204 g, 0.035 mmol), and anhydrous MeCN at room temperature for 24 h. Yield: 70% (184 mg) as a light-orange foam. R_f = 0.11, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.35−7.31 (m, 4H), 7.18 (dt, J = 6.7, 1.1, 1H), 7.06 (dt, J = 7.72, 1.2, 1H), 6.82−6.78 (m, 2H), 5.6 (d, J = 2.4 Hz, 1H), 4.29 (d, J = 2.63 Hz, 1H), 3.76 (s, 3H), 1.69 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 164.7, 158.5, 135.8, 131.7, 130.2, 126.8, 123.7, 122.1, 119.5, 118.9, 115.2, 113.6, 111.1, 105.1, 55.1, 51.9, 41.1, 28.1, 27.8; IR (thin film) 3416, 3003, 2932, 2837, 1779, 1743, 1610, 1511, 1458, 1383, 1297, 1249, 1205, 1179, 1094, 1011, 902, 833, 747 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{21}NO_5$ 379.1420, found 379.1410.

*5-((4-Bromophenyl)(1H-indol-3-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3c**).* Reagents employed: indole (0.163 g, 1.388 mmol), *p*-bromobenzaldehyde (0.514 g, 2.775 mmol), Meldrum's acid (0.200 g, 1.388 mmol), L-proline (0.008 g, 0.069 mmol), and anhydrous MeCN at room temperature for 24 h. Yield: 81% (478 mg) as a light-yellow foam. R_f = 0.20, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.41−7.32 (m, 5H), 7.31−7.25 m, 2H), 7.19 (t, J = 7.7 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 5.62 (d, J = 2.5 Hz, 1H), 4.27 (d, J = 2.1 Hz, 1H), 1.74 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 164.4, 138.8, 135.8, 131.4, 130.9, 126.8, 123.9, 122.5, 121.1, 119.9, 118.9, 114.5, 111.2, 105.2, 51.8, 40.5, 28.2, 27.7; IR (thin film) 3852, 3784, 3648, 3419, 3003, 2923, 2360, 2340, 1741, 1699, 1652, 1558, 1488, 1457, 1394, 1297, 1204, 1074, 1010, 903, 745, 667 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{18}BrNO_4$ 427.0419, found 427.0411.

*Methyl 4-((2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)(1H-indol-3-yl)methyl)benzoate (**3d**).* Reagents employed: indole (0.163 g, 1.388 mmol), methyl 4-formylbenzoate (0.456 g, 2.775 mmol), Meldrum's acid (0.200 g, 1.388 mol), L-proline (0.008 g, 0.070 mmol), and anhydrous MeCN at room temperature for 24 h. Yield: 79% (0.445 g) as an orange foam. R_f = 0.21, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.90 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.49−7.30 (m, 3H), 7.19 (t, J = 7.7 Hz, 1H), 7.06 (t, J = 7.0 Hz, 1H), 5.71 (d, J = 2.0 Hz, 1H), 4.33 (d, J = 2.4 Hz, 1H), 3.88 (s, 3H), 1.74 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 165.1, 164.4, 145.3, 135.7, 129.6, 128.8, 128.7, 126.8, 124.2, 122.4, 119.6, 118.9, 114.1, 111.2, 105.2, 52.1, 51.7, 40.9, 28.1, 27.7; IR (thin film) 3408, 3002, 2951, 1779, 1744, 1719, 1610, 1574, 1458, 1435, 1383, 1286, 1199, 1112, 1064, 1019, 905, 749 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{21}NO_6$ 430.1266, found 430.1267 (M + Na^+).

*2,2-Dimethyl-5-((1-methyl-1H-indol-3-yl)(phenyl)methyl)-1,3-dioxane-4,6-dione (**3e**).* Reagents employed: *N*-methylindole (0.930 g, 7.091 mmol), benzaldehyde (1.505 g, 14.182 mmol), Meldrum's acid (1.022 g, 7.091 mmol), L-proline (0.040 g, 0.355 mmol), and anhydrous MeCN at room temperature for 24 h. Yield: 83% (2.13 g) as a light-pink foam. R_f = 0.24, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.39 (m, 3H), 7.28−7.19 (m, 6H), 7.04 (dt, J = 7.6, 1.4 Hz, 1H), 5.63 (d, J = 2.3 Hz, 1H), 4.28 (d, J = 2.7 Hz, 1H), 3.75 (s, 3H), 1.68 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 164.6, 140.0, 136.5, 128.9, 128.8, 128.3, 127.4, 127.0, 121.8, 119.1, 118.9, 109.1, 105.0, 52.0, 41.2, 39.4, 32.8, 28.1, 27.8; IR (thin film) 3465, 3003, 2942, 1780, 1747, 1652, 1615, 1473, 1382, 1295, 1076, 1014, 898, 745, 719 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{21}NO_4$ 363.1471, found 363.1473.

*5-(1-(1H-Indol-3-yl)propyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3f**).* Reagents employed: indole (0.163 g, 1.388 mmol), propanal (0.161 g, 2.775 mmol), Meldrum's acid (0.200 g, 1.388 mmol), L-proline (0.008 g, 0.069 mmol), and anhydrous MeCN at room temperature for 24 h. Yield: 67% (280 mg) as a yellow foam. R_f = 0.22, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.21−7.10 (m, 3H), 4.11−4.04 (m, 1H), 3.79 (d, J = 2.9 Hz, 1H), 2.34−2.25 (m, 1H),

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2.12−2.04 (m, 1H), 1.61 (s, 3H), 1.19 (s, 3H), 0.99 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.7, 135.6, 127.0, 123.4, 122.1, 119.7, 118.9, 114.7, 111.0, 105.2, 50.6, 38.8, 28.0, 27.9, 26.6, 12.8; IR (thin film) 3411, 2967, 2874, 2360, 2339, 1739, 1618, 1457, 1382, 1293, 1241, 1204, 1095, 1000, 745 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{19}NO_4$ 301.1314, found 301.1317.

*5-(1-(1H-Indol-3-yl)decyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3g**).* Reagents employed: indole (0.163 g, 1.388 mmol), decanal (0.434 g, 2.775 mmol), Meldrum's acid (0.200 g, 1.388 mmol), L-proline (0.008 g, 0.007 mmol), and anhydrous MeCN. Yield: 98% (543 mg) as a clear red oil. R_f = 0.27, 30% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.33 (d, J = 7.4 Hz, 1H), 7.21−7.11 (m, 3H), 4.21−4.14 (m, 1H), 3.79 (d, J = 3.0 Hz, 1H), 2.29−2.25 (m, 1H), 2.09−1.99 (m, 1H), 1.61 (s, 3H), 1.37−1.23 (m, 14H), 1.20 (s, 3H), 0.89 (t, J = 6.71 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.6, 135.6, 126.9, 123.4, 122.1, 119.7, 119.0, 114.9, 111.0, 105.1, 50.9, 41.8, 37.0, 33.5, 31.8, 29.5, 29.4, 29.2, 28.2, 28.0, 27.9, 22.6, 14.0; IR (thin film) 3412, 3057, 2924, 2854, 1740, 1619, 1457, 1425, 1392, 1384, 1293, 1247, 1205, 1124, 1095, 907, 897, 743, 765, 646, 599, 515 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{33}NO_4$ 399.2410, found 399.2425.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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