FULL PAPER

2-(3-Pyrrolin-1-yl)-1,4-naphthoquinones: Photoactivated Alkylating Agents

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The preparation of 2-(3-pyrrolin-1-yl)-1,4-naphthoquinones and a study of their use as photoactivated alkylating agents is reported. The title compounds were easily synthesized by conjugate addition of the corresponding 3-pyrrolines to various naphthoquinones. Upon exposure to ambient room light, the compounds undergo an internal redox reaction to form 2-(pyrrol-1-yl)-1,4-hydroquinones, which are activated for nucleophilic addition by an S_N1 azafulvene mechanism. Control experiments demonstrated that the redox reaction is triggered by light and that the nucleophilic addition does not proceed before this activation occurs.

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Introduction

Many cancer chemotherapy strategies involve drugs that approach the toxicity level to be effective. Because cancerous cells proliferate more rapidly than normal cells, one general chemotherapeutic strategy is to stop the cell-division process by targeting DNA. During cell division, a DNA polymerase reads one strand, which it has separated from the double helix, then synthesizes its complement by relying on Watson–Crick base pairing of an incoming nucleotide triphosphate. Thus, if the two strands cannot be separated, replication is not possible. Reagents that react with DNA have been shown to form both inter- and intrastrand cross-links as well as interhelix cross-links and DNA–protein cross-links.[1] In general, interstrand cross-links are thought to be the most effective in disrupting this process.

An example of a natural product that cross-links DNA is illustrated in Scheme 1. Moncrotaline (**1**) is a carcinogenic pyrrolizidine alkaloid isolated from plant material in the pyrroline oxidation state.[2] Upon oxidation by P450 enzymes, the highly reactive pyrrole **2** is formed.[3] This species is the active cross-linker and after two elimination/addition sequences forms the ultimate adduct **3**. In addition to pyrrolizidine alkaloids like monocrotoline, other naturally occurring molecules such as mitomycin C metabolites and

synthetic molecules that share the reactive pyrrole core of **2**, generically represented by **4**, have been shown to cross-link DNA.[4] Unfortunately, these compounds (both synthetic and natural) often prove to be too reactive as they have the potential to alkylate a multitude of different chemical species.
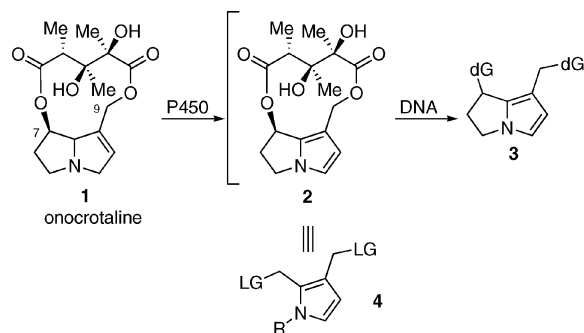
Scheme 1. DNA cross-linking by monocrotaline. LG = leaving group.

Toxicity also plagues these compounds because there is no specificity for tumor cells over healthy cells. Anderson, Hopkins, and several other groups, have tried to circumvent the problems of reactivity and stability in water by synthesizing various analogs, but this has met with only limited success.[5]

To solve these issues, nature has built in a control element with the P450 enzyme activation of monocrotaline (**1**) to activate the C-7 and C-9 positions. Chemists have also added their own control elements by modifying natural products to contain groups such as photolabile protecting

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groups that activate the molecule by deprotection of a reactive functional group. Two elegant examples of this have been reported by Williams in which reactive analogues of the natural products monocrotaline[6] and FR900482[7] are released after deprotection of a 6-nitroveratryl carbamate (NVOC). This concept retains the natural product-like structure that is responsible for the selective reaction with DNA, but is limited due to the necessity of a natural product starting material. An ideal molecule would be both selective and easily prepared so that the binding could be modified to select target different sequences.

We sought to combine the idea of a reactive pyrrole such as **4** with the notion of a triggering event (e.g., light) that would lead to its generation from a stable starting material. A search of the literature for the photochemical generation of pyrroles revealed several interesting examples.[8] Maruyama reported that irradiation of a benzene solution of the quinone **5** with a mercury arc lamp produced the hydroquinone **6** (Scheme 2).[8a] An internal redox reaction provided the hydroquinone with concomitant oxidation of the pyrroline moiety to the pyrrole as evidenced by trapping **6** as the diacetate in degassed solutions. In experiments where the solvent was not degassed, the hydroquinone **6** was oxidized to a pyrrole-bearing quinone. Franck reported the production of a pyrrole-bearing quinone from a benzoquinone and a 3-pyrroline, though the potential role of ambient light was not noted.[8c]
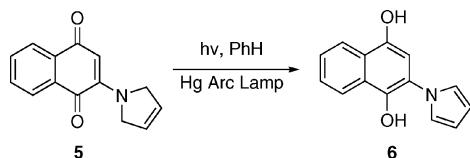
Scheme 2. Internal redox reactions of pyrroline-substituted quinones.

With evidence for a photochemically generated pyrrole, we surmised that the quinones **7**, with structures similar to **5** except now bearing one or more leaving groups (LG), could provide a platform to explore the preparation of simplified alkylating agents. Recent advances in the use of fiber optics and lasers in medicine[9] make photochemically activated alkylating agents attractive targets because they can be introduced in an inactive form and "turned on" at will. The quinones **7** should not be good alkylating agents until the photochemical redox reaction takes place to afford the pyrroles **4**. At this point, the deactivating quinone nucleus has been reduced to an electron-rich hydroquinone, and the pyrroline ring has been oxidized to a pyrrole, making substitution reactions facile by the intervention of azafulvene intermediates. In addition, the quinones **7** should be easily prepared by conjugate addition of the requisite 3-pyrroline to a quinone (Figure 1). This disconnection should lead to a facile assembly of a diverse array of compounds with varied 3-pyrroline and quinone fragments. Our initial studies to explore the preparation and reactivity of this potential scaffold are reported herein.
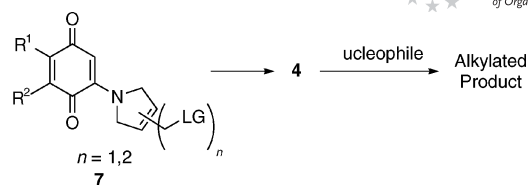

Figure 1. General design of potential photochemically triggered alkylating agents.

Results and Discussion

To prepare the target compounds, a variety of 3-pyrrolines (e.g., **8–15**) was necessary in order to find the best choices for the leaving group and its position on the ring for successful photochemically triggered alkylation chemistry. We examined both mono- and bis(alkylators) (Figure 2).
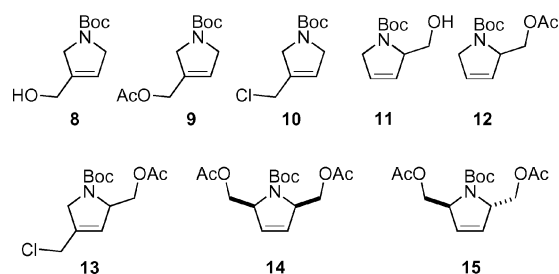

Figure 2. Desired substituted 3-pyrrolines.

The 3-substituted pyrrolines were prepared by a ring-closing metathesis (RCM) strategy (Scheme 3).[10] The necessary dienes were prepared in a straightforward manner starting with alkylation of N-Boc-allylamine (**16**) with commercially available 3-chloro-2-(chloromethyl)-1-propene (**17**). The chloride was then displaced with acetate in 89% yield, and both **18** and **19** were cyclized in good yield by using Grubbs' first-generation catalyst[10] without incident.
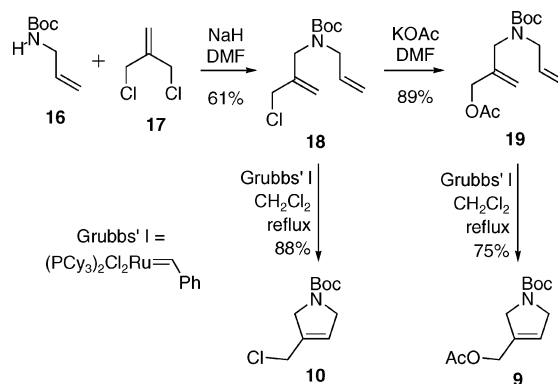
Scheme 3. Synthesis of 3-substituted-3-pyrrolines by RCM.

To prepare the 2-substituted 3-pyrroline **12**, the procedure of Blechert was applied to give **11**[11] starting with the known N-protected vinylglycine **20**[12] (Scheme 4). Re-

duction of the methyl ester **20** and formation of the oxazoli-dinone **22** proceeded in good yield. Hydrolysis and Boc protection then gave the necessary diene **23** in 82% yield. RCM by using Grubbs' first-generation ruthenium catalyst provided **11** and **12** after acylation.
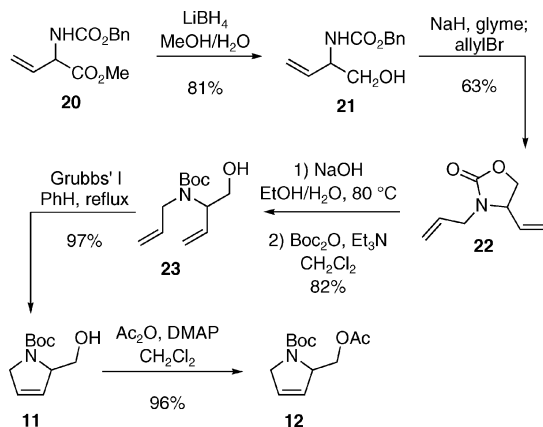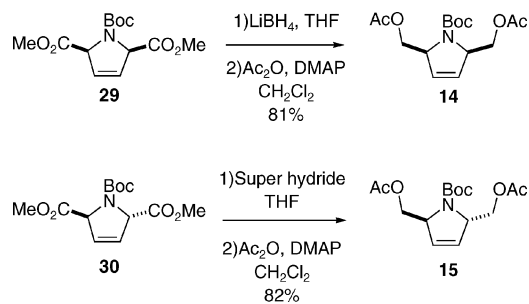

Scheme 4. Synthesis of 2-substituted-3-pyrrolines **11** and **12**.

The necessary disubstituted analogs were prepared in the following manner. *N*-Boc-vinylglycinol, derived from **21**, was protected as its triisopropylsilyl ether (Scheme 5). The second allyl unit was then introduced by alkylation with the allyl chloride **17**, and the TIPS group was removed with TBAF in THF, all in good yield. RCM with Grubbs' second generation catalyst[10] provided **28** in 98% yield and acylation provided the desired 3-pyrroline **13**.
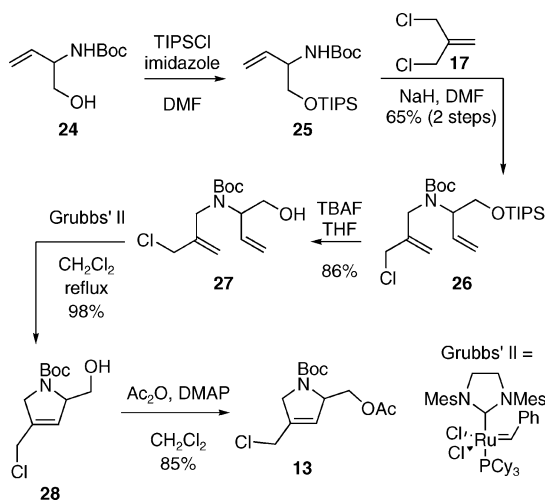
Scheme 5. Synthesis of 2,4-disubstituted-3-pyrrolines **28** and **13**.

The 3-pyrrolines **14** and **15** were obtained from **29** and **30** in a straightforward manner by reduction and acylation (Scheme 6). The known diesters **29** and **30** were prepared from the corresponding pyrroles by taking advantage of Donohoe's flexible partial reduction method.[13]
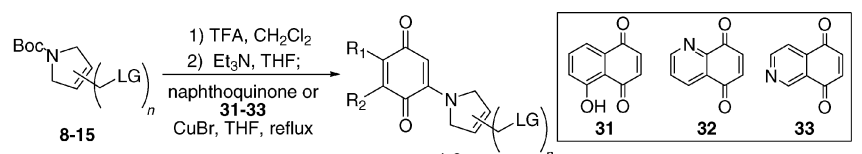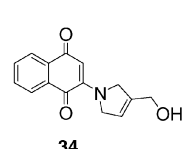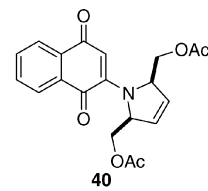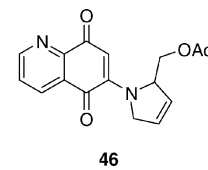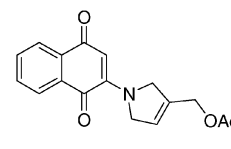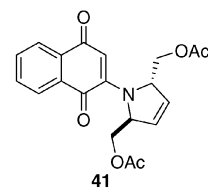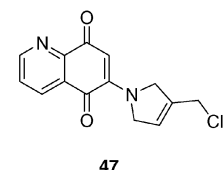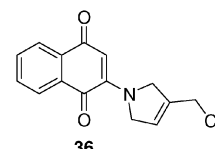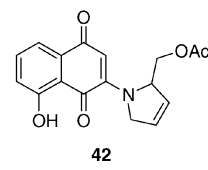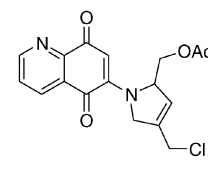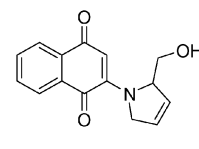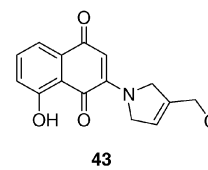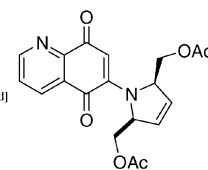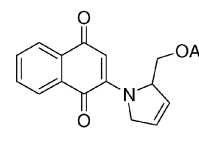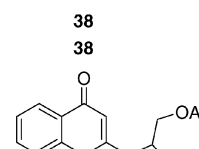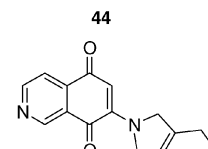

Scheme 6. Synthesis of 2-substituted-3-pyrrolines **14** and **15**.

With the 3-pyrrolines in hand we next set out to prepare a variety of the target quinones represented by the generic structure **7**. Deprotection of the *N*-Boc groups of the pyrrolines and in situ neutralization of the TFA salts followed by addition of the desired quinone and CuBr proceeded in reasonable yield (Table 1).[14] This reaction was used to prepare the naphthoquinones **34–41**, juglones **42–43**, isoquinolinequinones **44–45**, and the quinolinequinones **46–50**. It is important to note that these reactions were carried out in the absence of light to avoid unwanted redox reactions as the preparation of quinone **5** (Scheme 2) in our laboratories showed that the photochemical reaction proceeds in ambient room light and that the mercury arc lamp reported is unnecessary.

With a good indication that the photochemical redox reaction would proceed (vide supra), the next goal was to optimize the redox reaction and determine if the desired alkylation was possible. To this end, initial NMR-tube experiments were conducted in CDCl$_3$ as outlined in Scheme 7. It is desirable to avoid the use of a mercury arc lamp to trigger the redox reaction because it would be more convenient to use a sunlamp, but this would also provide less intense irradiation of the reaction. These irradiation conditions were tested, and when quinone **35** was irradiated with a sunlamp in the presence of ethanethiol, only the pyrrole **51** was observed by ^{1}H NMR spectroscopy. The internal redox reaction to **35a** had been successful, but presumably further oxidation by oxygen in the system had occurred instead of the desired alkylation.

It is known that the presence of electronegative substituents on the pyrrole nitrogen atom suppresses the azafulvene mechanism of substitution, which explains why the pyrroloquinones **51** and **52** do not react with ethanethiol.[15] Because the reaction had proceeded rapidly (15 min) and yielded no evidence of the hydroquinone, it was postulated that premature air oxidation of the desired hydroquinone to the quinone oxidation state was preventing alkylation. Experiments with ambient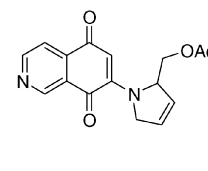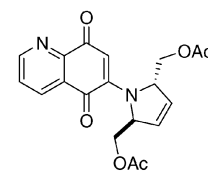 light were carried out with the hope that a less intense light source at lower temperature might lengthen the lifetime of the hydroquinone. Unfortunately, while the quinone **34** underwent the internal redox reaction, the resultant hydroquinone was again oxidized to the quinone **52** before alkylation could occur. Additionally, irradiation of degassed solutions of **34** yielded only intractable mixtures.

Table 1. Michael addition of 3-pyrrolines.

[a] Conditions: (1) TFA, CH$_2$Cl$_2$. (2) NH$_4$OH, MeOH; naphthoquinone, CuBr, Et$_2$O. [b] Conditions: (1) TFA, CH$_2$Cl$_2$. (2) Et$_3$N, THF; quinolinequinone, CeCl$_3$·7H$_2$O, EtOH. [c] The compound was found to be unstable to storage for prolonged periods. [d] Variable results were observed giving 0–12% yield, but in any case the reaction was not preparatively useful. [e] Decomposition.

Fortunately, a combination of a better leaving group and less intense irradiation provided an encouraging result. When the acetate **35** was treated with ethanethiol in the presence of ambient room light, a small amount of the desired alkylated product was isolated along with 53% of the non-alkylated product **51** (Scheme 8). Moving to a better leaving group, the (chloromethyl)-3-pyrroline **36** gave the desired sulfide **53** in 54% yield. In both cases, we did not observe the presumed hydroquinone species.

In order to determine whether the proposed hydroquinone–pyrroline intermediate was responsible for the successful alkylation, we carried out several experiments. Con-
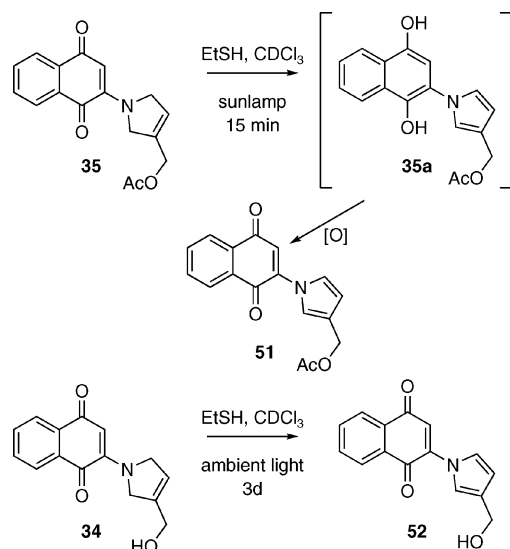
Scheme 7. Initial irradiation studies.

Table 2. Optimization studies.

Entry[a]	Solvent	Base	*hv*	Time	Yield
1	toluene	–	sunlamp	1 h	22%
2	CH₂Cl₂	–	sunlamp	1 h	26%
3	toluene	–	ambient	3 d	40%
4	CH₃CN	–	ambient	1 d	34%
5	CHCl₃	–	ambient	1 d	54%
6	CHCl₃	K₂CO₃	ambient	2 d	51%
7	CHCl₃	2,6-luti-dine	ambient	2 d	63%
8	MeOH	–	ambient	3 d	0%
9	MeOH	2,6-luti-dine	ambient	1 d	0%

[a] 10 mol-equiv. of EtSH employed.
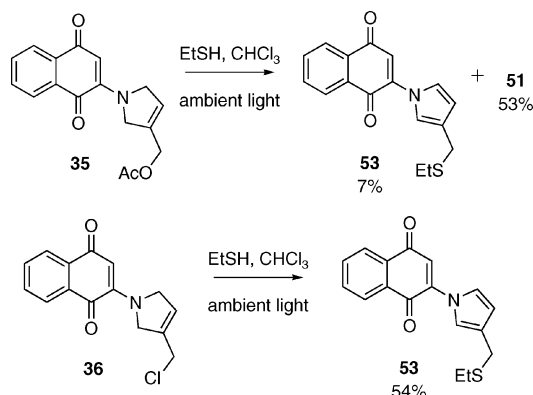
Scheme 8. Initial alkylation studies.

trol experiments excluding light from the reaction under conditions otherwise identical led to only the observation of the starting materials **35** and **36**, demonstrating that no chemistry can occur prior to light activation. To probe the issue of whether the alkylation occurs before or after oxidation of the hydroquinone to the quinone, the 3-pyrroline **36** was oxidized to the pyrrole **54** and exposed to the alkylation reaction conditions (Scheme 9). The pyrrole **54** failed to undergo a significant amount of alkylation (<10%) indicating that while **54** may participate in the reaction to some extent that it is likely a minor pathway and that the corresponding hydroquinone is the most likely reactive species.
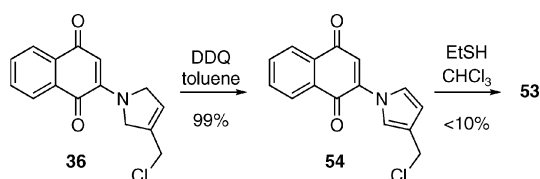
Scheme 9. Control experiment to determine when alkylation occurs.

Scheme 10. Light-triggered alkylation reactions of mono(electrophiles).

The reaction was next optimized for light source, solvent, time, and additive (Table 2). It was found that the best yield was obtained by using ambient light in chloroform with 2,6-lutidine as an additive to remove HCl generated during the reaction. To provide the best mimic for biological systems, it was hoped that the reaction would function in a polar protic solvent, but unfortunately the use of methanol provided no product.

With these conditions established, alkylation studies with the remaining monoalkylators are outlined in Scheme 10. Alkylation of the naphthoquinone **38** with the electrophilic group in the 2-position proceeded in 86% yield without any added base. Likewise, alkylation of the quinolinequinones **47** and **48** showed the same trend. The 2-substituted 3-pyrroline reacted substantially better, although it is interesting that the hydroquinone oxidation states of these compounds are stable enough to be isolated without further oxidation to the corresponding quinones, further validating our hypothesis that hydroquinones are involved in the alkylation. The juglone **42** also functioned in the reaction, but the isoquinolinequinones **44** and **45** failed to undergo even the initial internal redox reaction.

Alkylation of the bis(electrophiles) **39**, **40**, **48**, and **49** were studied with hopes that the sequence involving redox, two ionization/alkylation steps, and oxidation to the quinone would be as 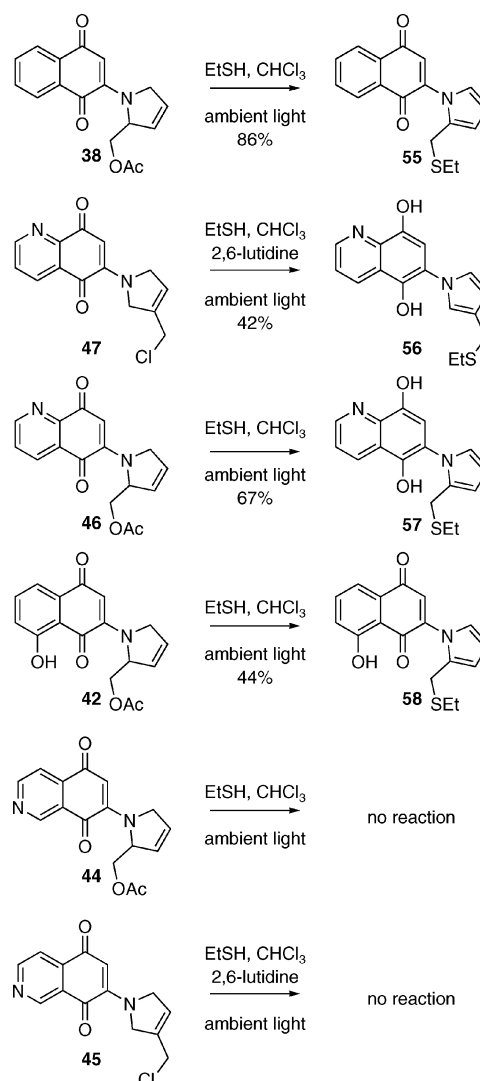efficient as the alkylation reactions described in Scheme 10. As outlined in Scheme 11, the chemistry worked as planned, but the products of the reactions employing naphthoquinones **39** and **40** were unusual in that

the hydroquinones **59** and **60** were isolated and characterized. These compounds were found to slowly undergo oxidation to the corresponding quinones, but were characterized in the hydroquinone oxidation state. It was gratifying that these two reactions proceeded in nearly 80% for each, demonstrating that the designed sequence could be very efficient.

Conclusions

A diverse array of 2-(3-pyrrolin-1-yl)-1,4-naphthoquinones were prepared by Michael addition of the corresponding 3-pyrrolines with the requisite quinones. The reaction was found to be quite general and effective when carried out in the absence of light. The target compounds were observed to undergo an internal redox reaction triggered by ambient room light to generate reactive pyrroles that are then alkylated by ethanethiol. This provides a proof of principle for the potential use of these compounds as photoactivated alkylating agents.

Experimental Section

tert-Butyl Allyl[2-(chloromethyl)allyl]carbamate (18): *N*-Boc-Allylamine (**16**) (0.157 g, 1.00 mmol) and 3-chloro-2-(chloromethyl)-1-propene (0.125 g, 1.00 mmol) were dissolved in DMF (2.5 mL).
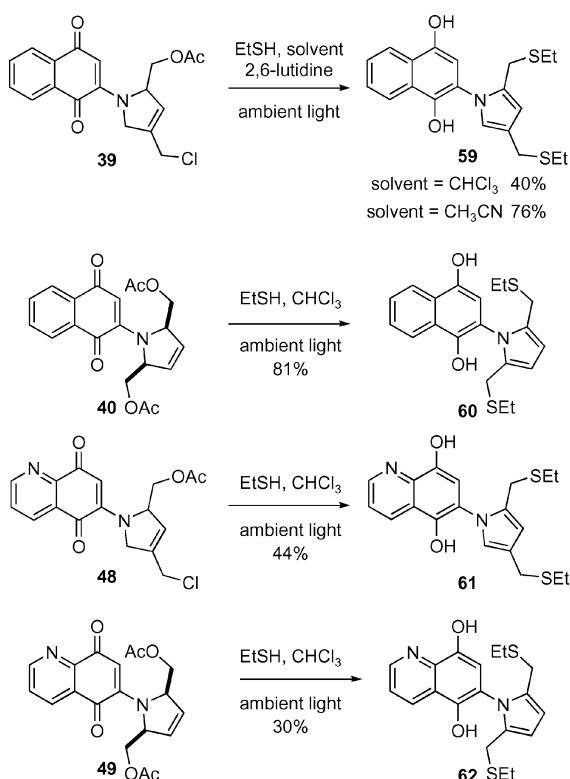
Scheme 11. Light-triggered alkylation reactions of bis(electrophiles).

NaH (0.06 g of a 60% dispersion in light mineral oil, 1.5 mmol) was added to the clear colorless solution which immediately turned to a cloudy pale yellow. After 1 h, the reaction was quenched by dropwise addition of H_2O (25 mL), then diluted with diethyl ether (ca. 25 mL). The layers were separated, and the organic layer was washed successively with three portions of H_2O, then brine, dried (MgSO_4), and the solvent removed in vacuo. Chromatography (0–6% EtOAc/hexane gradient) afforded 0.15 g (61%) of a colorless oil. R_f = 0.29 (10% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3): δ = 5.82–5.72 (m, 1 H), 5.27 (s, 1 H), 5.16–5.05 (m, 3 H), 4.03 (s, 2 H), 3.93 (s, 2 H), 3.82–3.78 (m, 2 H) 1.46 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 155.5, 141.3, 133.6, 116.9, 116.0, 80.0, 48.9, 48.3, 45.7, 28.4. IR (neat): $\tilde{v}$ = 3083 (w), 2978 (m), 2930 (m), 1697 (s), 1645 (m), 1457 (s), 1404 (s), 1366 (s) cm^{-1}. LRMS (EI, 70 eV): m/z (%) = 245 (0.036), 210 (2), 189 (17), 172 (19), 154 (100), 110 (32), 57 (78). HRMS (CI with NH_3): calcd. for $C_{12}H_{21}ClNO_2$ [M + H]$^+$ 246.1261; found 246.1249. $C_{12}H_{20}ClNO_2$ (245.12): calcd. C 58.65, H 8.20, N 5.70; found C 58.63, H 8.20, N 5.47.

***tert*-Butyl [2-(Acetoxymethyl)allyl]allylcarbamate (19):** Compound **18** (0.154 g, 0.630 mmol) was dissolved in DMF (1.6 mL), and to the solution was added KOAc (0.068 g, 0.69 mmol). The reaction mixture was heated to 65 °C for 3.5 h, cooled to room temp., then diluted with water (10 mL) and diethyl ether (10 mL). The layers were separated, and the organic layer was washed successively with three portions of H_2O, then brine, dried (MgSO_4), and the solvent removed in vacuo to yield 0.155 g (91%) of a clear colorless oil which was typically used without further purification. An analytically pure sample was obtained by chromatography (5% EtOAc/hexanes). R_f = 0.16 (10% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3): δ = 5.84–5.68 (m, 1 H), 5.18–5.04 (m, 4 H), 4.53 (s, 2 H), 3.90–3.75 (m, 4 H), 2.09 (s, 3 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 170.5, 155.5, 140.0, 133.7, 116.5, 114.6, 78.9, 65.0, 48.6, 48.3, 28.3, 20.8 ppm. IR (neat): $\tilde{v}$ = 3083 (w), 2977 (m), 2931 (m), 1745 (s), 1697 (s), 1456 (s), 1405 (s), 1366 (s) cm^{-1}. LRMS (CI with NH_3): m/z (%) = 270 (16), 231 (65), 214 (29), 170 (100). HRMS (CI with NH_3): calcd. for $C_{14}H_{24}NO_4$ [M + H]$^+$ 270.1714; found 270.1705. $C_{14}H_{23}NO_4$ (269.16): calcd. C 62.43, H 8.61, N 5.20; found C 62.63, H 8.39, N 5.15.

***tert*-Butyl Allyl[2-(hydroxymethyl)allyl]carbamate:** *tert*-Butyl [2-(acetoxymethyl)allyl]allylcarbamate (**19**) (0.155 g, 0.57 mmol) and methanol (2.9 mL) were mixed to form a cloudy solution. Potassium carbonate (0.079 g, 0.57 mmol) was dissolved in a minimal amount of H_2O (0.25 mL) and added to the solution. The reaction mixture was stirred for 2.5 h then diluted with H_2O (ca. 10 mL), and the methanol removed in vacuo. The mixture was extracted with three portions of CH_2Cl_2, and the combined organic extracts werer dried (MgSO_4). The solvent was removed in vacuo to yield 0.118 g (91%) of a clear colorless oil which was typically used without further purification. An analytically pure sample was obtained by chromatography (10–25% EtOAc/hexanes gradient). R_f = 0.30 (25% EtOAc/hexanes). ^1H NMR (300 MHz, CDCl_3): δ = 5.71–5.80 (m, 1 H), 5.17–5.08 (m, 3 H), 4.93 (s, 1 H), 4.01 (s, 2 H), 3.89 (s, 2 H), 3.74 (s, 2 H), 3.34 (br. s, 1 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 156.6, 144.9, 133.4, 116.8, 113.6, 80.4, 63.7, 49.0, 48.4, 28.3 ppm. IR (neat): $\tilde{v}$ = 3442 (m, br), 3082 (w), 2977 (w), 2929 (m), 1696 (s), 1675 (s), 1458 (s), 1410 (s), 1366 (s) cm^{-1}. LRMS (EI, 70 eV): m/z (%) = 227 (0.086), 171, (29), 154 (13), 126 (10), 100 (28), 57 (100). HRMS (CI, with NH_3): calcd. for $C_{12}H_{22}NO_3$ [M + H]$^+$ 228.1600; found 228.1597. $C_{12}H_{21}NO_3$ (227.15): calcd. C 63.41, H 9.31, N 6.16; found C 63.49, H 9.34, N 6.07.

***tert*-Butyl 3-(Hydroxymethyl)-2,5-dihydropyrrole-1-carbamate (11):** *tert*-Butyl allyl[2-(hydroxymethyl)allyl]carbamate (0.0564 g, 0.248

mmol) was dissolved in CH_2Cl_2 (5 mL). Grubb's catalyst (0.0102 g, 0.0124 mmol, 5 mol-%) was added and the mixture refluxed for 7 h. The reaction mixture was then cooled to room temp., opened to air, and stirred for 15 h. The crude reaction mixture was then adsorbed onto silica gel and immediately chromatographed (25–50% EtOAc/hexanes gradient) to give 0.0435 g (88%) of a brown oil. R_f = 0.30 (50% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3, –20 °C): δ = 5.56 (d, J = 9.2 Hz, 1 H), 4.29 (br. s, 1 H), 4.09 (s, 2 H), 4.02–4.00 (m, 4 H), 1.37 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl_3, –20 °C): δ = 154.4, 154.4, 139.5, 139.3, 119.6, 119.5, 79.6, 79.6, 59.2, 59.2, 53.1, 53.0, 52.7, 52.6, 28.2, 28.2 ppm. IR (neat): $\tilde{v}$ = 3429 (m, br.), 2970 (m), 2860 (m), 1702 (s), 1682 (s), 1657 (s), 1412 (s) cm^{-1}. LRMS (EI, 70 eV): m/z (%) = 199 (0.094), 184 (0.021), 142 (25), 126 (22), 112 (19), 98 (6), 80 (15), 68 (54), 57 (100). HRMS (CI, NH_3): calcd. for $C_{10}H_{18}NO_3$ [M + H]$^+$ 200.1287; found 200.1288. $C_{10}H_{17}NO_3$ (200.13): calcd. C 60.28, H 8.60, N 7.03; found C 60.41, H 8.60, N 6.97.

***tert*-Butyl 3-(Chloromethyl)-2,5-dihydropyrrole-1-carbamate (10):** (Benzylidene)dichloridobis(tricyclohexylphosphane)ruthenium (0.286 g, 0.35 mmol) was added to **18** (1.71 g, 6.96 mmol) in CH_2Cl_2 (130 mL), and the mixture was heated to reflux. After 16 h, the reaction was not progressing so an additional portion of the catalyst (60 mg, 73 μmol) was added. The reaction's progression had stopped again after 24 h, and another portion of the catalyst (60 mg, 73 μmol) was added. After a total of 3 d, the mixture was cooled to room temp., opened to air for 24 h, and then concentrated. The residue was chromatographed (5% to 20% ethyl acetate/hexanes, gradient) to yield 1.34 g (88%) of the title compound. R_f = 0.13 (10% ethyl acetate/hexanes). IR (neat): $\tilde{v}$ = 1700 (s) cm^{-1}. ^1H NMR (400 MHz, CDCl_3, containing rotamers): δ = 5.70 (d, J = 17.5 Hz, 1 H), 4.11–4.00 (m, 1 H), 4.06 (s, 2 H), 4.04 (s, 2 H), 1.38 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 153.96, 135.48, 135.41, 124.41, 124.38, 79.31, 79.26, 52.96, 52.80, 40.14, 40.08, 28.17 ppm. MS (EI, 70 eV): m/z (%) = 57 (100) [tBu]$^+$. HRMS (CI/NH_3): calcd. for $C_{10}H_{16}ClNO_2$ [M + H]$^+$ 218.0948; found 218.0943.

***tert*-Butyl 2-(Acetoxymethyl)-2,5-dihydropyrrole-1-carbamate (12):** Acetic anhydride (0.161 mL, 1.71 mmol) was added to *tert*-butyl 2-(hydroxymethyl)-2,5-dihydropyrrole-1-carboxylate (**11**) (0.113 g, 0.57 mmol) in CH_2Cl_2 (12 mL), followed by the addition of 4-(dimethylamino)pyridine (0.209 g, 1.71 mmol). After 16 h, the mixture was diluted with ethyl acetate, washed (saturated NaHCO_3, then brine), dried (Na_2SO_4), and concentrated. The residue was chromatographed (10% ethyl acetate/hexanes) to yield 0.133 g (96%) of the title compound. R_f = 0.12 (10% ethyl acetate/hexanes). IR (neat): $\tilde{v}$ = 1745 (s), 1698 (s) cm^{-1}. ^1H NMR (400 MHz, CDCl_3, containing rotamers): δ = 5.80 (s, 0.56 H), 5.73 (s, 0.43 H), 5.62 (s, 1 H), 4.64 (s, 0.43 H), 4.53 (s, 0.56 H), 4.29 (dd, J = 20.7, 10.6 Hz, 1 H), 4.16–3.94 (m, 3 H), 1.94 (s, 3 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 170.68, 154.00, 153.86, 127.13, 126.93, 79.84, 79.47, 64.34, 63.86, 63.04, 62.82, 53.57, 53.42, 28.21, 20.57, 20.56 ppm. MS (EI, 70 eV): m/z (%) = 168 (44) [M – OtBu]$^+$, 126 (44) [M – C_2H_2O – OtBu]$^+$, 112 (100) [M + H – tBu – CH_2O_2CCH_3]$^+$. HRMS (ESI): calcd. for $C_{12}H_{19}NO_4$ [M + Na]$^+$ 264.1212; found 264.1217.

***tert*-Butyl 1-[(Triisopropylsilyloxy)methyl]allylcarbamate (25):** Imidazole (19.8 mg, 0.29 mmol) was added to *tert*-butyl 1-(hydroxymethyl)allylcarbamate (**24**) (18.1 mg, 97.0 μmol) and triisopropylsilyl chloride (30 μL, 0.14 mmol) in DMF (0.25 mL). After 2 h, the mixture was diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed (1% to 5% ethyl acetate/hexanes, gradient) to yield 33.3 mg (100%)

of the title compound. R_f = 0.32 (5% ethyl acetate/hexanes). IR (neat): ṽ = 3354 (br.), 1720 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.83 (ddd, J = 17.2, 10.4, 5.4 Hz, 1 H), 5.18 (d, J = 17.2 Hz, 1 H), 5.10 (dt, J = 10.2, 1.5 Hz, 1 H), 4.84 (s, 1 H), 4.14 (s, 1 H), 3.74 (dd, J = 9.5, 4.4 Hz, 1 H), 3.68 (dd, J = 9.7, 4.4 Hz, 1 H), 1.41 (s, 9 H), 1.04 (s, 3 H), 1.02 (s, 18 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 155.50, 136.72, 115.46, 79.16, 65.64, 54.36, 28.26, 17.80, 11.77 ppm. MS (EI, 70 eV): m/z (%) = 270 (8) [M – OtBu]$^+$, 244 (100) [M – OtBu – C$_2$H$_2$]$^+$. HRMS (ESI): calcd. for C$_{18}$H$_{37}$NO$_3$Si [M + Na]$^+$ 366.2440; found 366.2430.

***tert*-Butyl [2-(Chloromethyl)allyl]{1-[(triisopropylsilyloxy)methyl]-allyl}carbamate (26):** Sodium hydride (0.296 g of 60 wt.-% suspension in mineral oil, 7.4 mmol) was added to **25** (1.27 g, 3.7 mmol) and 3-chloro-2-(chloromethyl)-1-propene (0.856 mL, 7.4 mmol) in DMF (9 mL). After 4 h, water (3 mL), was slowly added, and the mixture was extracted with diethyl ether, washed with water, dried (MgSO$_4$) and concentrated. The residue was chromatographed (1% to 5% ethyl acetate/hexanes, gradient) to yield 1.04 g (65%) of the title compound. R_f = 0.36 (5% ethyl acetate/hexanes). IR (neat): ṽ = 1699 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.90 (s, 1 H), 5.19–5.07 (m, 4 H), 4.34–4.15 (m, 1 H), 4.07–3.83 (m, 1 H), 4.05 (d, J = 13.2 Hz, 1 H), 4.00 (s, 2 H), 3.85 (d, J = 16.8 Hz, 1 H), 3.76 (dd, J = 10.1, 5.5 Hz, 1 H), 1.40 (s, 9 H), 1.02 (s, 18 H), 1.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 155.18, 141.82, 134.69, 117.33, 115.33, 79.75, 70.28, 64.04, 61.40, 48.73, 45.93, 28.20, 17.82, 11.74 ppm. MS (EI, 70 eV): m/z (%) = 332 (100) [M + H – tBu – iPr]$^+$, 188 (58) [M + H – CH$_2$OTips – tBu]$^+$, 144 (72) [M – CH$_2$OTIPS – OtBu – C$_2$H$_3$]$^+$, 57 (91) [tBu]$^+$. HRMS (ESI): calcd. for C$_{22}$H$_{42}$ClNO$_3$Si [M + Na]$^+$ 454.2520; found 454.2530.

***tert*-Butyl [2-(Chloromethyl)allyl][1-(hydroxymethyl)allyl]carbamate (27):** Tetrabutylammonium fluoride (4.4 mL of a 1.0 M solution in THF, 4.4 mmol) was added slowly to **26** (0.968 g, 2.20 mmol) in THF (44 mL). After 15 min, ethyl acetate was added, and the mixture was washed with brine. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated. The residue was chromatographed (5% to 30% ethyl acetate/hexanes, gradient) to yield 0.523 g (86%) of the title compound. R_f = 0.32 (30% ethyl acetate/hexanes). IR (neat): ṽ = 3450 (br), 1693 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.89 (ddd, J = 17.0, 10.2, 6.6 Hz, 1 H), 5.26 (s, 2 H), 5.23 (d, J = 10.6 Hz, 1 H), 5.16 (d, J = 17.2 Hz, 1 H), 5.12 (s, 1 H), 4.23 (q, J = 6.2 Hz, 1 H), 4.10–3.76 (m, 4 H), 4.04 (s, 2 H), 2.05 (s, 1 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 156.16, 142.08, 133.69, 117.86, 115.83, 80.59, 63.40, 61.68, 51.28, 48.25, 45.74, 28.11 ppm. MS (EI, 70 eV): m/z (%) = 188 (52) [M + H – tBu – CH$_2$OH]$^+$, 144 (64) [M – CH$_2$OH – C$_2$H$_3$ – OtBu]$^+$, 57 (100) [tBu]$^+$. HRMS (ESI): calcd. for C$_{13}$H$_{22}$ClNO$_3$ [M + Na]$^+$ 298.1186; found 298.1190.

***tert*-Butyl 4-(Chloromethyl)-2-(hydroxymethyl)-2,5-dihydropyrrole-1-carbamate Acid (28):** [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichlorido(phenylmethylene)(tricyclohexylphosphane)-ruthenium (Grubbs' catalyst, 2nd generation) (0.144 g, 0.17 mmol) was added to **27** (0.937 g, 3.40 mmol) in CH$_2$Cl$_2$ (68 mL), and the mixture was heated to reflux. After 10 h, the reaction was not progressing so an additional portion of the catalyst (62 mg, 73 μmol) was added. After a total of 15 h, the mixture was cooled to room temp. and then concentrated. The residue was chromatographed (20% to 30% ethyl acetate/hexanes, gradient) to yield 0.830 g (98%) of the title compound. R_f = 0.42 (40% ethyl acetate/hexanes). IR (neat): ṽ = 3409 (br.), 1698 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, containing rotamers): δ = 5.63 (s, 1 H), 4.74 (s, 1 H), 4.50 (d, J = 7.4 Hz, 1 H), 4.23 (d, J = 15.0 Hz, 1 H), 4.12 (d, J =

15.0 Hz, 1 H), 4.10 (s, 2 H), 3.74 (dd, J = 11.4, 5.1 Hz, 1 H), 3.58 (dd, J = 11.4, 7.3 Hz, 1 H), 1.48 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ = 156.25, 136.49, 125.23, 80.79, 67.77, 66.51, 54.13, 39.86, 28.25 ppm. MS (EI, 70 eV): m/z (%) = 57 (100) [tBu]$^+$. HRMS (ESI): calcd. for C$_{11}$H$_{18}$ClNO$_3$ [M + H]$^+$ 248.1053; found 248.1055.

***tert*-Butyl 2-(Acetoxymethyl)-4-(chloromethyl)-2,5-dihydropyrrole-1-carbamate (13):** Acetic anhydride (0.164 mL, 1.74 mmol) was added to **28** (0.145 g, 0.580 mmol) in CH$_2$Cl$_2$ (12 mL), followed by the addition of 4-(dimethylamino)pyridine (0.212 g, 1.74 mmol). After 1.5 h, the mixture was diluted with ethyl acetate, washed (saturated NaHCO$_3$, then brine), dried (Na$_2$SO$_4$), and concentrated. The residue was chromatographed (10% to 20% ethyl acetate/hexanes, gradient) to yield 0.143 g (85%) of the title compound. R_f = 0.32 (10% ethyl acetate/hexanes). IR (neat): ṽ = 1743 (s), 1701 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, containing rotamers): δ = 5.71 (d, J = 5.9 Hz, 1 H), 4.74 (s, 0.5 H), 4.62 (s, 0.5 H), 4.40 (ddd, J = 23.2, 10.8, 2.9 Hz, 1 H), 4.28 (d, J = 15.0 Hz, 1 H), 4.21–4.07 (m, 4 H), 2.02 (s, 3 H), 1.48 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.74, 153.87, 137.17, 136.93, 125.80, 125.59, 80.23, 79.91, 78.16, 63.57, 53.69, 53.55, 39.91, 39.80, 28.26, 20.60 ppm. MS (EI, 70 eV): m/z (%) = 160 (72) [M + H – tBu – CH$_2$OAc]$^+$, 57 (100) [tBu]$^+$. HRMS (ESI): calcd. for C$_{13}$H$_{20}$ClNO$_4$ [M + Na]$^+$ 312.0979; found 312.0987.

***tert*-Butyl (2R*,5S*)-2,5-Bis(acetoxymethyl)-2,5-dihydropyrrole-1-carbamate (14):** The ester **29**[13] (0.147 g, 0.515 mmol) in THF (1.25 mL) was added slowly to LiBH$_4$ (33.7 mg, 1.54 mmol) in THF (3.75 mL). After 1 h, 1 M HCl (4 mL) was added dropwise, and the mixture was extracted with ethyl acetate, dried (MgSO$_4$), and concentrated. The residue was dissolved in CH$_2$Cl$_2$ (10 mL), and acetic anhydride (0.243 mL, 2.57 mmol) and 4-(dimethylamino)pyridine (0.189 g, 1.54 mmol) were added in succession. After 2 h, the mixture was diluted with ethyl acetate, washed (saturated NaHCO$_3$, then brine), dried (Na$_2$SO$_4$), and concentrated. The residue was chromatographed (20% ethyl acetate/hexanes) to yield 0.131 g (81%) of the title compound. R_f = 0.22 (20% ethyl acetate/hexanes). IR (neat): ṽ = 1743 (s), 1700 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.75 (d, J = 6.6 Hz, 1 H), 5.70 (d, J = 6.2 Hz, 1 H), 4.67 (q, J = 2.2 Hz, 1 H), 4.55 (dd, J = 5.1, 4.8 Hz, 1 H), 4.47 (dd, J = 10.8, 5.1 Hz, 1 H), 4.38 (dd, J = 11.0, 2.2 Hz, 1 H), 4.34 (dd, J = 11.0, 5.1 Hz, 1 H), 4.20 (dd, J = 11.0, 5.1 Hz, 1 H), 2.05 (s, 3 H), 1.48 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.89, 154.17, 128.65, 80.57, 65.20, 64.72, 63.75, 63.53, 28.32, 20.79 ppm. MS (EI, 70 eV): m/z (%) = 124 (94) [M – tBu – CH$_2$OAc – OAc]$^+$, 80 (100) [M – Boc – CH$_2$OAc – OAc]$^+$, 57 (52) [tBu]$^+$. HRMS (ESI): calcd. for C$_{15}$H$_{23}$NO$_6$ [M + Na]$^+$ 336.1423; found 336.1419.

***tert*-Butyl (2S*,5S*)-2,5-Bis(acetoxymethyl)-2,5-dihydropyrrole-1-carbamate (15):** 1-*tert*-Butyl 2,5-dimethyl *trans*-2,5-dihydropyrrole-1,2,5-tricarboxylate (**30**) (106 mg, 0.371 mmol) in THF (0.5 mL) was added slowly to super hydride (1.86 mL of a 1.0 M solution in THF, 1.86 mmol) in THF (1.5 mL). After 20 h, 1 M HCl (1.5 mL) was added dropwise, and the mixture was extracted with ethyl acetate, dried (MgSO$_4$), and concentrated. The residue was dissolved in CH$_2$Cl$_2$ (7.5 mL), and acetic anhydride (0.175 mL, 1.85 mmol) and 4-(dimethylamino)pyridine (136 mg, 1.11 mmol) were added in succession. After 1 h, the mixture was diluted with ethyl acetate, washed (saturated NaHCO$_3$, then brine), dried (Na$_2$SO$_4$), and concentrated. The residue was chromatographed (20% ethyl acetate/hexanes) to yield 95.0 mg (82%) of the title compound. R_f = 0.20 (20% ethyl acetate/hexanes). IR (neat): ṽ = 1743 (s), 1698 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.75 (d, J = 6.6 Hz, 1 H), 5.70

(d, J = 6.2 Hz, 1 H), 4.67 (q, J = 2.2 Hz, 1 H), 4.55 (dd, J = 6.8, 5.1 Hz, 1 H), 4.47 (dd, J = 10.8, 2.6 Hz, 1 H), 4.39 (dd, J = 11.0, 2.2 Hz, 1 H), 4.34 (dd, J = 11.0, 5.1 Hz, 1 H), 4.20 (dd, J = 11.0, 5.1 Hz, 1 H), 1.99 (s, 3 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.68, 153.21, 128.56, 128.42, 80.46, 65.19, 63.71, 63.57, 62.65, 28.29, 20.61 ppm. MS (EI, 70 eV): m/z (%) = 124 (95) [M – tBu – CH$_2$OAc – OAc]$^+$, 80 (100) [M – Boc – CH$_2$OAc – OAc]$^+$, 57 (56) [tBu]$^+$. HRMS (ESI): calcd. for C$_{15}$H$_{23}$NO$_6$ [M + Na]$^+$ 336.1423; found 336.1423.

2-[3-(Hydroxymethyl)-2,5-dihydropyrrol-1-yl]-1,4-naphthoquinone (34): *tert*-Butyl 3-(hydroxymethyl)-2,5-dihydropyrrole-1-carboxylate (**8**) (0.1197 g, 0.6013 mmol) was dissolved in CH$_2$Cl$_2$ (1.4 mL), and trifloroacetic acid (0.46 mL, 6.013 mmol) was added dropwise. The reaction mixture was stirred for 1 h, at which time the solvent and excess trifluoroacetic acid were removed in vacuo to leave the trifloroacetic acid salt of the free amine which was used without purification. The crude amine salt was neutralized by the addition of a 0.2 M solution of NH$_4$OH in methanol (3.1 mL, 0.62 mmol). A second solution containing naphthoquinone (0.0951 g, 0.6013 mmol) and copper(I) bromide (0.0086 g, 0.06013 mmol) in diethyl ether (3 mL) was prepared, and the flask wrapped in aluminum foil to protect it from ambient light. In a dark fume hood, the amine solution was added dropwise to the solution of the quinone. Upon addition of the first few drops, the solution turned from a deep gold color to red. The reaction mixture, open to air, was stirred for 15 h, then the solvent removed in vacuo. The residue was taken up in water and CH$_2$Cl$_2$, the layers were separated, the organic layer was extracted with 3 portions of CH$_2$Cl$_2$. The combined organic extracts were dried (MgSO$_4$), and the solvent was removed in vacuo to yield an orange solid. Chromatography (50–100% EtOAc/hexanes gradient) afforded 0.0930 g of an orange crystalline solid. R_f = 0.23 (EtOAc). M.p. 163–164 °C. ^{1}H NMR (400 MHz, CDCl$_3$, 3 drops of CD$_3$OD): δ = 8.04 (dd, J = 7.6, 1.2 Hz, 1 H), 8.01 (dd, J = 7.6, 1.2 Hz, 1 H), 7.71 (dd, J = 7.6, 1.2 Hz, 1 H), 7.62 (dd, J = 7.6, 1.2 Hz, 1 H), 5.83 (s, 1 H), 5.69 (s, 1 H), 4.78 (s, 2 H), 4.28 (s, 2 H), 4.21 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 183.0, 182.7, 148.0, 134.2, 133.1, 131.9, 131.7, 126.5, 125.6, 105.1, 59.7, 58.5–57.5 (br., 2 C) ppm. As further proof of structure, a low-temperature NMR spectrum was recorded to "freeze out" the vinylogous amide rotamers: ^{1}H NMR (400 MHz, CDCl$_3$, 3 drops of CD$_3$OD, –20 °C): δ = 8.00–8.03 (m, 2 H), 7.74 (d, J = 7.5 Hz, 1 H), 7.65 (d, J = 7.5 Hz, 1 H), 5.84 (d, J = 20 Hz, 1 H), 5.67 (s, 1 H), 4.78 (d, J = 14.4 Hz, 2 H), 4.30–4.19 (m, 5 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, –20 °C): δ = 183.0, 182.8, 182.3, 147.9, 147.8, 141.0, 136.7, 134.3, 132.7, 132.01, 132.0, 131.1, 126.5, 126.5, 125.2, 121.2, 116.6, 104.0, 103.8, 58.8, 58.6, 58.4, 58.0, 57.5, 57.2 ppm. IR (neat): $\tilde{v}$ = 3364 (m, br.), 2918 (m), 2849 (m), 1672 (m), 1608 (m), 1589 (s), 1539 (s), 1454 (m), 1420 (m) cm^{-1}. UV (CHCl$_3$): λ_{max} = 247, 277, 464, 642, 729 nm (log ε = 3.91, 3.99, 3.53, 3.29, 3.21). LRMS (CI, NH$_3$): m/z (%) = 256 (100), 238 (38), 225 (21). HRMS (CI, NH$_3$): calcd. for C$_{15}$H$_{14}$NO$_3$ [M + H]$^+$ 256.0974; found 256.0961. C$_{15}$H$_{13}$NO$_3$ (255.09): calcd. C 70.58, H 5.13, N 5.49; found C 70.61, H 5.03, N 5.27.

2-[3-(Acetoxyoxymethyl)-2,5-dihydropyrrol-1-yl]-1,4-naphthoquinone (35): 2-[3-(Hydroxymethyl)-2,5-dihydropyrrol-1-yl]-1,4-naphthoquinone (**34**) (0.0700 g, 0.275 mmol) was dissolved in pyridine (1 mL) in a flask wrapped in aluminum foil (to protect the contents from light). The solution was cooled in an ice bath, and acetic anhydride (0.2800 g, 2.77 mmol) was added. After 5 min, the bath was removed and stirring continued for 4 h. The reaction mixture was then diluted with EtOAc (ca. 10 mL) and aqueous NaOH (10 mL of a 15% w/v solution). The layers were then separated,

and the organic layer was washed with NaOH solution (20 mL), followed by H$_2$O (2 × 20 mL). The extract was dried (MgSO$_4$) and the solvent removed in vacuo. Chromatography (0–30% EtOAc/hexanes gradient) afforded 0.0817 g (quantitative yield) of a red solid. R_f = 0.045 (20% EtOAc/hexanes). M.p. 119.5–121 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.07 (dd, J = 7.8, 1.2 Hz, 1 H), 8.04 (dd, J = 7.8, 1.2 Hz, 1 H), 7.71 (dt, J = 7.8, 1.2 Hz, 1 H), 7.62 (dt, J = 7.8, 1.2 Hz, 1 H), 5.91 (s, 1 H), 5.73 (s, 1 H), 5.17–4.58 (m, 4 H), 4.19 (br. s, 2 H), 2.11 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 182.7, 182.5, 170.5, 147.6, 136.2, 134.1, 133.0, 131.9, 131.6, 126.4, 125.5, 120.7, 105.3, 60.5, 57.8 (br., 2 C), 20.7 ppm. IR (neat): $\tilde{v}$ = 3067 (w), 2919 (w), 2848 (w), 1738 (s), 1673 (s), 1622 (s), 1593 (s), 1565 (s), 1267 (s) cm^{-1}. UV (CHCl$_3$): λ_{max} = 246, 276, 464, 642 nm (log ε = 4.04, 4.15, 3.56, 2.81). LRMS (CI, NH$_3$): m/z (%) = 298 (24), 240 (100), 224 (21), 82 (19). HRMS (CI, NH$_3$): calcd. for C$_{17}$H$_{16}$NO$_4$ [M + H]$^+$ 298.1079; found 298.1073. C$_{17}$H$_{15}$NO$_4$ (297.10): calcd. C 68.66, H 5.09, N 4.71; found C 68.67, H 5.07, N 4.47.

2-[3-(Chloromethyl)-2,5-dihydropyrrol-1-yl]-1,4-naphthoquinone (36): Trifluoroacetic acid (0.619 mL, 8.0 mmol) was added to **10** (175 mg, 0.800 mmol) in CH$_2$Cl$_2$ (8 mL). After 2 h, the mixture was concentrated and exposed to high vacuum for 1 h. The residue was dissolved in THF (8 mL), and triethylamine (123 µL, 0.88 mmol) was added. After 10 min, this mixture was added to 1,4-naphthoquinone (126 mg, 0.800 mmol) and copper(I) bromide (23.0 mg, 0.160 mmol) in THF (4 mL) in the dark. The mixture was heated to reflux open to air in the dark. After 16 h, it was cooled to room temp. and concentrated. The residue was chromatographed (20% to 40% ethyl acetate/hexanes, gradient) to yield 111 mg (51%) of the title compound. R_f = 0.11 (25% ethyl acetate/hexanes). IR (neat): $\tilde{v}$ = 1668 (s), 1617 (s), 1591 (m), 1557 (s) cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.05 (dd, J = 7.6, 0.7 Hz, 1 H), 8.02 (dd, J = 7.7, 0.7 Hz, 1 H), 7.70 (td, J = 7.6, 1.5 Hz, 1 H), 7.61 (td, J = 7.7, 1.5 Hz, 1 H), 5.96 (s, 1 H), 5.69 (s, 1 H), 4.81 (s, 2 H), 4.22 (s, 4 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 182.81, 182.63, 147.86, 134.27, 132.99, 132.01, 131.58, 126.49, 125.58, 105.33, 58.11, 39.85 ppm. MS (EI, 70 eV): m/z (%) = 273 (38) [M]$^+$, 238 (100) [M – Cl]$^+$, 224 (42) [M – H – CH$_2$Cl]$^+$. HRMS (EI, 70 eV): calcd. for C$_{15}$H$_{12}$ClNO$_2$ [M]$^+$ 273.0557; found 273.0556.

2-[2-(Acetoxymethyl)-2,5-dihydropyrrol-1-yl]-1,4-naphthoquinone (38): Trifluoroacetic acid (123 µL, 1.6 mmol) was added to **12** (39.7 mg, 0.160 mmol) in CH$_2$Cl$_2$ (2 mL). After 2 h, the mixture was concentrated and exposed to high vacuum for 1 h. The residue was dissolved in THF (2 mL), and triethylamine (24.5 µL, 0.176 mmol) was added. After 10 min, this mixture was added to 1,4-naphthoquinone (25.3 mg, 0.160 mmol) and copper(I) bromide (4.6 mg, 32 µmol) in THF (1 mL) in the dark. The mixture was heated to reflux open to air in the dark. After 2 d, it was cooled to room temp. and concentrated. The residue was chromatographed (10% to 40% ethyl acetate/hexanes, gradient) to yield 23.6 mg (50%) of the title compound. R_f = 0.05 (30% ethyl acetate/hexanes). IR (neat): $\tilde{v}$ = 1741 (s), 1674 (m), 1626 (m), 1592 (m), 1557 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.03 (dd, J = 7.5, 1.1 Hz, 1 H), 8.00 (dd, J = 7.7, 1.1 Hz, 1 H), 7.68 (td, J = 7.5, 1.5 Hz, 1 H), 7.60 (td, J = 7.5, 1.5 Hz, 1 H), 6.02 (dd, J = 6.6, 1.8 Hz, 1 H), 5.88 (s, 1 H), 5.88–5.85 (m, 1 H), 5.51 (s, 1 H), 4.40 (s, 1 H), 4.32–4.17 (m, 1 H), 4.31 (dd, J = 11.5, 2.9 Hz, 1 H), 4.19 (dd, J = 11.7, 4.4 Hz, 1 H), 1.97 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 183.39, 182.95, 170.74, 148.58, 134.35, 132.58, 131.80, 127.43, 126.73, 125.66, 106.53, 65.51, 63.62, 58.06, 20.62 ppm. MS (EI, 70 eV): m/z (%) = 297 (6) [M]$^+$, 237 (36) [M –HOAc]$^+$, 224 (100) [M – CH$_2$OAc]$^+$. HRMS (EI, 70 eV): calcd. for C$_{17}$H$_{15}$NO$_4$ [M]$^+$ 297.1001; found 297.1006.

2-[2-(Acetoxymethyl)-4-(chloromethyl)-2,5-dihydropyrrol-1-yl]-1,4-naphthoquinone (39): Trifluoroacetic acid (0.185 mL, 2.40 mmol) was added to **13** (69.5 mg, 0.240 mmol) in CH_2Cl_2 (2.5 mL). After 3 h, the mixture was concentrated and exposed to high vacuum for 1 h. The residue was dissolved in THF (2.5 mL), and triethylamine (36.8 µL, 0.264 mmol) was added. After 10 min, this mixture was added to 1,4-naphthoquinone (37.9 mg, 0.240 mmol) and copper(I) bromide (6.9 mg, 48 µmol) in THF (1 mL) in the dark. The mixture was heated to reflux open to air in the dark. After 16 h, it was cooled to room temp. and concentrated. The residue was chromatographed (30% ethyl acetate/hexanes) to yield 28.2 mg (34%) of the title compound. R_f = 0.25 (50% ethyl acetate/hexanes). IR (neat): ṽ = 1739 (s), 1670 (s), 1626 (m), 1592 (m), 1556 (s) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.05 (dd, J = 8.4, 1.5 Hz, 1 H), 8.02 (dd, J = 7.6, 1.1 Hz, 1 H), 7.71 (td, J = 7.6, 1.4 Hz, 1 H), 7.63 (td, J = 7.6, 1.4 Hz, 1 H), 5.89 (s, 1 H), 5.87 (s, 1 H), 5.52 (s, 1 H), 4.52 (s, 1 H), 4.38 (dd, J = 11.5, 2.7 Hz, 1 H), 4.32–4.23 (m, 1 H), 4.23 (s, 2 H), 4.20 (dd, J = 11.7, 4.1 Hz, 1 H), 2.00 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 182.98, 179.85, 170.56, 147.86, 134.26, 132.53, 132.23, 131.76, 126.57, 125.57, 107.25, 96.18 94.50, 84.63, 65.96, 58.08, 39.56, 20.70 ppm. MS (EI, 70 eV): m/z (%) = 117 (97), 49 (100). HRMS (ESI): calcd. for C$_{18}$H$_{16}$ClNO$_4$ [M + Na]$^+$ 368.0666; found 368.0663.

2-[cis-2,5-Bis(acetoxymethyl)-2,5-dihydropyrrol-1-yl]-1,4-naphthoquinone (40): Trifluoroacetic acid (92 µL, 1.2 mmol) was added to **14** (39.0 mg, 0.120 mmol) in CH_2Cl_2 (1.5 mL). After 2.5 h, the mixture was concentrated and exposed to high vacuum for 1 h. The residue was dissolved in THF (1.5 mL), and triethylamine (19.5 µL, 0.140 mmol) was added. After 10 min, this mixture was added to 1,4-naphthoquinone (19.0 mg, 0.120 mmol) and copper(I) bromide (3.4 mg, 24 µmol) in THF (1 mL) in the dark. The mixture was heated to reflux open to air in the dark. After 3 d, it was cooled to room temp. and concentrated. The residue was chromatographed (10% to 40% ethyl acetate/hexanes, gradient) to yield 23.3 mg (52%) of the title compound. R_f = 0.10 (30% ethyl acetate/hexanes). IR (neat): ṽ = 1741 (s), 1674 (s), 1631 (m), 1592 (m), 1550 (s) cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.04 (td, J = 7.6, 1.0 Hz, 2 H), 7.72 (td, J = 7.6, 1.5 Hz, 1 H), 7.64 (td, J = 7.6, 1.5 Hz, 1 H), 6.09 (s, 1 H), 6.00 (s, 2 H), 5.19 (dd, J = 5.2, 3.7 Hz, 2 H), 4.47 (dd, J = 11.3, 3.7 Hz, 2 H), 4.24 (dd, J = 11.2, 5.9 Hz, 2 H), 2.11 (s, 6 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 183.41, 170.70, 148.00, 134.27, 132.37, 132.14, 128.42, 126.76, 125.44, 107.29, 66.56, 64.39, 20.77 ppm. MS (EI, 70 eV): m/z (%) = 236 (100) [M − HOAc − CH$_2$OAc]$^+$. HRMS (ESI): calcd. for C$_{20}$H$_{19}$NO$_6$ [M + Na]$^+$ 392.1110; found 392.1100.

2-(2-Acetoxymethyl-2,5-dihydropyrrol-1-yl)-8-hydroxy-1,4-naphthoquinone (42): Trifluoroacetic acid (97 µL, 1.3 mmol) was added to **12** (30.5 mg, 0.126 mmol) in CH_2Cl_2 (2 mL). After 1.5 h, the mixture was concentrated and exposed to high vacuum for 1 h. The residue was dissolved in THF (2 mL), and triethylamine (19.3 µL, 0.139 mmol) was added. After 10 min, this mixture was added to juglone (21.9 mg, 0.126 mmol) and copper(I) bromide (3.6 mg, 25 µmol) in THF (1 mL) in the dark. The mixture was heated to reflux open to air in the dark. After 2 d, it was cooled to room temp. and concentrated. The residue was chromatographed (10% to 40% ethyl acetate/hexanes, gradient) to yield 17.7 mg (45%) of the title compound. R_f = 0.09 (40% ethyl acetate/hexanes). IR (neat): ṽ = 1740 (s), 1625 (s), 1557 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 11.84 (s, 1 H), 7.56 (d, J = 5.1 Hz, 1 H), 7.55 (d, J = 4.0 Hz, 1 H), 7.12 (t, J = 4.8 Hz, 1 H), 6.01 (dd, J = 6.6, 1.8 Hz, 1 H), 5.85 (dd, J = 6.6, 2.2 Hz, 1 H), 5.79 (s, 1 H), 5.47 (s, 1 H), 4.38 (s, 1 H), 4.28 (dd, J = 11.5, 3.3 Hz, 1 H), 4.23–4.18 (m, 1 H), 4.19 (dd, J = 11.4, 4.4 Hz, 1 H), 1.96 (s, 3 H) ppm. ^{13}C NMR (100 MHz,

CDCl$_3$): δ = 188.06, 182.16, 170.55, 161.88, 147.56, 137.13, 132.77, 127.40, 126.07, 122.70, 118.03, 115.02, 107.98, 65.58, 63.97, 58.26, 29.67, 20.69 ppm. MS (EI, 70 eV): m/z (%) = 253 (46) [M − HOAc]$^+$, 57 (100). HRMS (ESI): calcd. for C$_{17}$H$_{15}$NO$_5$ [M + Na]$^+$ 336.0848; found 336.0849.

7-(2-Acetoxymethyl-2,5-dihydropyrrol-1-yl)isoquinoline-5,8-dione (44): Trifluoroacetic acid (0.11 mL, 1.4 mmol) was added to **12** (33.8 mg, 0.140 mmol) in CH_2Cl_2 (2 mL). After 1 h, the mixture was concentrated and exposed to high vacuum for 1 h. The residue was dissolved in THF (2.5 mL), and triethylamine (22 µL, 0.15 mmol) was added. After 10 min, this mixture was added to isoquinoline-5,8-dione (22.3 mg, 0.140 mmol) and copper(I) bromide (4.0 mg, 28 µmol) in THF (1 mL) in the dark. The mixture was heated to reflux open to air in the dark. After 16 h, it was cooled to room temp. and concentrated. The residue was chromatographed (30% to 60% ethyl acetate/hexanes, gradient) to yield 21.4 mg (51%) of the title compound. R_f = 0.13 (60% ethyl acetate/hexanes). IR (neat): ṽ = 1740 (s), 1679 (m), 1627 (s), 1586 (m), 1548 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.25 (s, 1 H), 8.98 (d, J = 4.8 Hz, 1 H), 7.86 (d, J = 5.1 Hz, 1 H), 6.05 (dd, J = 6.6, 1.8 Hz, 1 H), 5.92–5.88 (m, 1 H), 5.91 (s, 1 H), 5.52 (s, 1 H), 4.40 (s, 1 H), 4.33–4.24 (m, 3 H), 1.99 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 182.49, 180.94, 170.49, 155.53, 153.96, 148.28, 147.98, 147.83, 138.15, 125.46, 118.09, 107.56, 65.61, 58.07, 29.66, 20.69 ppm. MS (EI, 70 eV): m/z (%) = 298 (3) [M]$^+$, 238 (45) [M − HOAc]$^+$, 225 (100) [M − CH$_2$OAc]$^+$. HRMS (EI, 70 eV): calcd. for C$_{16}$H$_{14}$N$_2$O$_4$ [M]$^+$ 298.0954; found 298.0965.

7-[3-(Chloromethyl)-2,5-dihydropyrrol-1-yl]isoquinoline-5,8-dione (45): Trifluoroacetic acid (0.41 mL, 5.3 mmol) was added to **10** (106 mg, 0.530 mmol) in CH_2Cl_2 (7.5 mL). After 2 h, the mixture was concentrated and exposed to high vacuum for 1 h. The residue was dissolved in THF (7.5 mL), and triethylamine (81 µL, 0.58 mmol) was added. After 10 min, this mixture was added to isoquinoline-5,8-dione (84.3 mg, 0.530 mmol) and copper(I) bromide (15.2 mg, 106 µmol) in THF (3 mL) in the dark. The mixture was heated to reflux open to air in the dark. After 1.5 h, it was cooled to room temp. and concentrated. The residue was chromatographed (40% to 65% ethyl acetate/hexanes, gradient) to yield 80.5 mg (55%) of the title compound. R_f = 0.10 (50% ethyl acetate/hexanes). IR (neat): ṽ = 1676 (m), 1631 (m), 1586 (m), 1554 (s) cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.27 (s, 1 H), 9.00 (d, J = 4.9 Hz, 1 H), 7.89 (dd, J = 4.9, 0.7 Hz, 1 H), 6.00 (s, 1 H), 5.82 (s, 1 H), 4.90 (s, 1 H), 4.25 (s, 4 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 180.43, 155.53, 153.78, 148.15, 138.44, 125.11, 121.16, 118.09, 118.03, 105.74, 58.16, 57.56, 39.68 ppm. MS (EI, 70 eV): m/z (%) = 274 (53) [M]$^+$, 239 (100) [M − Cl]$^+$, 225 (56) [M − CH$_2$Cl]$^+$. HRMS (EI, 70 eV): calcd. for C$_{14}$H$_{11}$ClN$_2$O$_2$ [M]$^+$ 274.0509; found 274.0504.

6-[2-(Acetoxymethyl)-2,5-dihydropyrrol-1-yl]quinoline-5,8-dione (46): Trifluoroacetic acid (0.16 mL, 2.1 mmol) was added to **12** (50.7 mg, 0.210 mmol) in CH_2Cl_2 (2 mL). After 3 h, the mixture was concentrated and exposed to high vacuum for 1 h. The residue was dissolved in THF (1 mL), and triethylamine (32 µL, 0.23 mmol) was added. After 10 min, this mixture was added to quinoline-5,8-dione (33.4 mg, 0.210 mmol) and cerium(III) chloride heptahydrate (78.2 mg, 0.210 mmol) in ethanol (4 mL) in the dark. After stirring for 18 h open to air in the dark, water was added, and the mixture was extracted with ethyl acetate (5×), dried (Na$_2$SO$_4$) and concentrated. The residue was chromatographed (0% to 5% methanol/ethyl acetate, gradient) to yield 33.2 mg (53%) of the title compound. R_f = 0.18 (5% methanol/ethyl acetate). IR (neat): ṽ = 1738 (s), 1683 (m), 1627 (m), 1552 (s) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.01 (d, J = 3.7 Hz, 1 H), 8.36 (dd, J = 8.0, 1.5 Hz, 1 H), 7.60 (dd, J = 7.7, 4.8 Hz, 1 H), 6.05 (s, 1 H), 6.04 (dd, J = 6.6, 1.8 Hz, 1 H), 5.88 (dd, J = 6.6, 2.2 Hz, 1 H), 5.58 (s, 1 H), 4.42 (s, 1 H), 4.32–4.22 (m, 1 H), 4.30 (dd, J = 11.5, 2.9 Hz, 1 H), 4.24 (dd, J = 11.7, 4.0 Hz, 1 H), 1.98 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 182.04, 181.48, 170.89, 154.40, 148.43, 148.08, 135.05, 128.27, 126.79, 125.86, 106.98, 65.75, 63.54, 58.22, 20.28 ppm. MS (EI, 70 eV): m/z (%) = 298 (1) [M]$^+$, 238 (100) [M – HOAc]$^+$. HRMS (ESI): calcd. for C$_{16}$H$_{14}$N$_2$O$_4$ [M + Na]$^+$ 321.0851; found 321.0846.

6-[3-(Chloromethyl)-2,5-dihydropyrrol-1-yl]quinoline-5,8-dione (47): Trifluoroacetic acid (0.146 mL, 1.9 mmol) was added to **10** (41.4 mg, 0.190 mmol) in CH$_2$Cl$_2$ (2 mL). After 1.5 h, the mixture was concentrated and exposed to high vacuum for 1 h. The residue was dissolved in THF (1 mL), and triethylamine (29.3 µL, 0.21 mmol) was added. After 10 min, this mixture was added to quinoline-5,8-dione (30.4 mg, 0.190 mmol) and cerium(III) chloride heptahydrate (70.8 mg, 0.190 mmol) in ethanol (4 mL) in the dark. After stirring for 16 h open to air in the dark, water was added, and the mixture was extracted with ethyl acetate (4×), dried (Na$_2$SO$_4$) and concentrated. The residue was chromatographed (0% to 5% methanol/ethyl acetate, gradient) to yield 38.2 mg (73%) of the title compound. R_f = 0.14 (5% methanol/ethyl acetate). IR (neat): $\tilde{v}$ = 1682 (s), 1623 (s), 1555 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.98 (dd, J = 4.6, 1.5 Hz, 1 H), 8.32 (dd, J = 8.0, 1.5 Hz, 1 H), 7.55 (dd, J = 8.0, 4.8 Hz, 1 H), 5.92 (s, 2 H), 4.81 (s, 2 H), 4.20 (s, 4 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 182.18, 181.05, 154.85, 148.77, 147.56, 134.62, 128.10, 126.32, 106.32, 57.87, 39.58 ppm. MS (EI, 70 eV): m/z (%) = 274 (41) [M]$^+$, 239 (100) [M – Cl]$^+$, 225 (58) [M – CH$_2$Cl]$^+$. HRMS (EI, 70 eV): calcd. for C$_{14}$H$_{11}$ClN$_2$O$_2$ [M]$^+$ 274.0509; found 274.0500.

6-[2-(Acetoxymethyl)-4-(chloromethyl)-2,5-dihydropyrrol-1-yl]quinoline-5,8-dione (48): Trifluoroacetic acid (0.205 mL, 2.7 mmol) was added to **13** (77.0 mg, 0.266 mmol) in CH$_2$Cl$_2$ (3 mL). After 2.5 h, the mixture was concentrated and exposed to high vacuum for 1 h. The residue was dissolved in THF (1.5 mL), and triethylamine (40.7 µL, 0.292 mmol) was added. After 10 min, this mixture was added to quinoline-5,8-dione (42.3 mg, 0.266 mmol) and cerium(III) chloride heptahydrate (99.1 µg, 0.266 mmol) in ethanol (5 mL) in the dark. After stirring for 16 h open to air in the dark, the mixture was diluted with ethyl acetate and washed with brine. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated. The residue was chromatographed (0% to 5% methanol/ethyl acetate, gradient) to yield 49.9 mg (54%) of the title compound. R_f = 0.19 (5% methanol/ethyl acetate). IR (neat): $\tilde{v}$ = 1738 (s), 1683 (s), 1627 (m), 1552 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.98 (d, J = 3.7 Hz, 1 H), 8.33 (dd, J = 7.9, 1.5 Hz, 1 H), 7.56 (dd, J = 8.0, 4.8 Hz, 1 H), 6.03 (s, 1 H), 5.87 (s, 1 H), 5.48 (s, 1 H), 4.54 (s, 1 H), 4.52–4.17 (m, 1 H), 4.32 (dd, J = 11.5, 2.9 Hz, 1 H), 4.23 (dd, J = 11.7, 4.4 Hz, 1 H), 4.20 (s, 2 H), 1.98 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 183.12, 181.96, 171.12, 155.47, 148.92, 148.18, 135.30 129.00, 127.08, 126.07, 108.74, 66.80, 64.00, 58.79, 39.90, 21.07 ppm. MS (EI, 70 eV): m/z (%) = 237 (59) [M – H – CH$_2$OAc – Cl]$^+$, 43 (100) [COCH$_3$]$^+$. HRMS (ESI): calcd. for C$_{17}$H$_{15}$ClN$_2$O$_4$ [M + Na]$^+$ 369.0618; found 369.0607.

6-[*cis*-2,5-Bis(acetoxymethyl)-2,5-dihydropyrrol-1-yl]quinoline-5,8-dione (49): Trifluoroacetic acid (0.223 mL, 2.9 mmol) was added to **14** (92.1 mg, 0.290 mmol) in CH$_2$Cl$_2$ (3 mL). After 2.5 h, the reaction was not complete, so an additional portion of trifluoroacetic acid (50 µL, 0.65 mmol) was added. After 3 h, the mixture was concentrated and exposed to high vacuum for 1 h. The residue was

dissolved in THF (1.5 mL), and triethylamine (44.6 µL, 0.32 mmol) was added. After 10 min, this mixture was added to quinoline-5,8-dione (46.8 mg, 0.290 mmol) and cerium(III) chloride heptahydrate (0.108 g, 0.290 mmol) in ethanol (6 mL) in the dark. After stirring for 2 d open to air in the dark, water and brine were added, and the mixture was extracted with ethyl acetate (4×), dried (Na$_2$SO$_4$) and concentrated. The residue was chromatographed (0% to 5% methanol/ethyl acetate, gradient) to yield 40.6 mg (38%) of the title compound. R_f = 0.20 (5% methanol/ethyl acetate). IR (neat): $\tilde{v}$ = 1742 (s), 1684 (s), 1547 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.98 (dd, J = 4.8, 1.5 Hz, 1 H), 8.34 (dd, J = 7.9, 1.5 Hz, 1 H), 7.58 (dd, J = 8.0, 4.8 Hz, 1 H), 6.25 (s, 1 H), 5.99 (s, 1 H), 5.79 (s, 1 H), 5.16 (t, J = 3.7 Hz, 1 H), 4.43 (dd, J = 11.3, 3.7 Hz, 1 H), 4.36 (t, J = 4.8 Hz, 1 H), 4.23 (dd, J = 11.3, 5.9 Hz, 1 H), 4.00 (dd, J = 9.5, 5.3 Hz, 1 H), 2.09 (s, 3 H), 2.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 181.85, 171.18, 170.66, 154.84, 147.67, 135.13, 128.28, 127.76, 126.88, 107.72, 93.99, 66.87, 64.97, 64.05, 62.53, 20.71, 20.37 ppm. MS (EI, 70 eV): m/z (%) = 252 (100) [M – 2 OAc]$^+$. HRMS (ESI): calcd. for C$_{19}$H$_{18}$N$_2$O$_6$ [M + Na]$^+$ 393.1063; found 393.1068.

2-[3-(Hydroxymethyl)pyrrol-1-yl]-1,4-naphthoquinone (52): An NMR sample of the pyrroline **34** in CDCl$_3$ was allowed to stand under ambient laboratory light until the starting material was consumed (approximately 3 d): R_f = 0.17 (30% acetone/hexanes). ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 8.20–8.11 (m, 2 H), 7.83–7.76 (m, 2 H), 7.31–7.29 (m, 1 H), 7.27–7.25 (m, 1 H), 6.82 (s, 1 H), 6.46–6.45 (m, 1 H), 4.63 (s, 2 H), 1.25 (s, 1 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 184.4, 181.1, 142.7, 134.5, 133.9, 131.5, 131.7, 128.9, 127.2, 126.1, 122.5, 122.4, 119.6, 112.6, 58.6 ppm. UV (CHCl$_3$): λ_{max} = 257, 307, 643, 400 nm (log ε = 4.17, 3.90, 3.45, 3.69).

2-{3-[(Ethylsulfanyl)methyl]pyrrol-1-yl}-1,4-naphthoquinone (53): Ethanethiol (24 µL, 0.32 mmol) was added to **36** (8.80 mg, 32.0 µmol) and 2,6-lutidine (3.7 µL, 32 µmol) in chloroform (2 mL). After being exposed to ambient light and open to air for 2 d, there was no **36** remaining so the mixture was adsorbed on silica gel, while the solvent was removed in a rotavapor, and chromatographed (10% to 20% ethyl acetate/hexanes, gradient) to yield 6.0 mg (63%) of the title compound. R_f = 0.34 (20% ethyl acetate/hexanes). IR (neat): $\tilde{v}$ = 1679 (s), 1646 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.14–8.12 (m, 1 H), 8.08–8.06 (m, 1 H), 7.76–7.73 (m, 2 H), 7.24 (s, 1 H), 7.19 (s, 1 H), 6.76 (s, 1 H), 6.36 (s, 1 H), 3.61 (s, 2 H), 2.48 (q, J = 7.3 Hz, 2 H), 1.23 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 184.41, 181.05, 142.58, 134.40, 133.80, 131.98, 131.52, 127.16, 126.01, 125.38, 122.30, 121.91, 119.65, 113.77, 27.70, 25.38, 14.40 ppm. MS (EI, 70 eV): m/z (%) = 297 (17) [M]$^+$, 236 (100) [M – SEt]$^+$. HRMS (EI, 70 eV): calcd. for C$_{17}$H$_{15}$NO$_2$S [M – H]$^+$ 296.0745; found 296.0747.

2-{2-[(Ethylsulfanyl)methyl]pyrrol-1-yl}-1,4-naphthoquinone (55): Ethanethiol (26 µL, 0.35 mmol) was added to **38** (10.3 mg, 35.0 µmol) in chloroform (3 mL). After being exposed to ambient light and open to air for 24 h, there was no **38** remaining so the mixture was adsorbed on silica gel, while the solvent was removed in a rotavapor, and chromatographed (10% to 20% ethyl acetate/hexanes, gradient) to yield a mixture of quinone and hydroquinone products. The mixture was dissolved in CH$_2$Cl$_2$, and silica gel was added. After stirring for 2 h, the only product present was the quinone product. Filtration and concentration yielded 9.0 mg (86%) of the title compound. R_f = 0.22 (10% ethyl acetate/hexanes). IR (neat): $\tilde{v}$ = 1678 (s), 1659 (s), 1280 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.16 (dd, J = 5.8, 3.5 Hz, 1 H), 8.12 (dd, J = 5.6, 3.5 Hz, 1 H), 7.78 (dd, J = 5.1, 4.0 Hz, 2 H), 6.85 (s, 1 H), 6.78 (dd, J = 2.9, 1.8 Hz, 1 H), 6.24–6.21 (m, 2 H), 3.78 (s, 2 H), 2.20

(q, J = 7.3 Hz, 2 H), 1.06 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 184.85, 180.23, 145.94, 134.22, 134.04, 131.98, 130.00, 127.91, 127.21, 126.33, 123.88, 121.98, 113.34, 109.96, 28.04, 25.01, 13.95 ppm. MS (EI, 70 eV): m/z (%) = 297 (15) [M]$^+$, 236 (100) [M – SEt]$^+$. HRMS (EI, 70 eV): calcd. for C$_{17}$H$_{15}$NO$_2$S [M]$^+$ 297.0824; found 297.0833.

6-{3-[(Ethylsulfanyl)methyl]pyrrol-1-yl}quinoline-5,8-diol (56): Ethanethiol (52 µL, 0.70 mmol) was added to **47** (19.3 mg, 70.0 µmol) and 2,6-lutidine (8.2 µL, 70 µmol) in chloroform (3.5 mL). After being exposed to ambient light and open to air for 18 h, there was no **47** remaining so the mixture was adsorbed on silica gel, while the solvent was removed in a rotavapor, and chromatographed (20% to 30% ethyl acetate/hexanes, gradient) to yield 8.8 mg (42%) of the title compound. R_f = 0.19 (20% ethyl acetate/hexanes). IR (neat): $\tilde{\nu}$ = 3390 (br.) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.81 (dd, J = 4.4, 1.3 Hz, 1 H), 8.58 (dd, J = 7.8, 1.3 Hz, 1 H), 7.50 (dd, J = 8.5, 4.4 Hz, 1 H), 7.05 (s, 1 H), 6.88–6.87 (m, 2 H), 6.41 (t, J = 1.9 Hz, 1 H), 3.72 (s, 2 H), 2.57 (q, J = 7.4 Hz, 2 H), 1.29 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 148.59, 146.17, 137.44, 131.88, 123.44, 122.71, 122.18, 121.73, 120.10, 111.64, 107.89, 29.62, 27.80, 25.63, 14.38 ppm. MS (EI, 70 eV): m/z (%) = 239 (100) [M – SEt]$^+$, 238 (99) [M – HSEt]$^+$. HRMS (ESI): calcd. for C$_{16}$H$_{16}$N$_2$O$_2$S [M + H]$^+$ 301.1011; found 301.1010.

6-{2-[(Ethylsulfanyl)methyl]pyrrol-1-yl}quinoline-5,8-diol (57): Ethanethiol (21 µL, 0.28 mmol) was added to **46** (8.4 mg, 28 µmol) in chloroform (3 mL). After being exposed to ambient light and open to air for 16 h, there was no **46** remaining so the mixture was adsorbed on silica gel, while the solvent was removed in a rotavapor, and chromatographed (20% ethyl acetate/hexanes) to yield 5.6 mg (67%) of the title compound. R_f = 0.25 (30% ethyl acetate/hexanes). IR (neat): $\tilde{\nu}$ = 3398 (br.) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.85 (dd, J = 4.2, 1.6 Hz, 1 H), 8.64 (dd, J = 8.4, 1.6 Hz, 1 H), 7.88 (s, 1 H), 7.52 (dd, J = 8.5, 4.1 Hz, 1 H), 6.97 (s, 1 H), 6.75 (dd, J = 2.7, 1.9 Hz, 1 H), 6.30 (dd, J = 3.6, 2.7 Hz, 1 H), 6.26 (dd, J = 3.6, 1.6 Hz, 1 H), 5.97 (s, 1 H), 3.64 (s, 1 H), 3.52 (s, 1 H), 2.45 (q, J = 7.4 Hz, 2 H), 1.16 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 149.03, 146.24, 140.19, 138.49, 132.36, 130.37, 123.55, 122.02, 121.70, 120.80, 110.00, 109.83, 109.52, 26.85, 25.50, 14.12 ppm. MS (EI, 70 eV): m/z (%) = 238 (100) [M – HSEt]$^+$. HRMS (ESI): calcd. for C$_{16}$H$_{16}$N$_2$O$_2$S [M + H]$^+$ 301.1011; found 301.1008.

2-{2-[(Ethylsulfanyl)methyl]pyrrol-1-yl}-8-hydroxy-1,4-naphthoquinone (58): Ethanethiol (24 µL, 0.32 mmol) was added to **42** (10.2 mg, 32.0 µmol) in chloroform (1.6 mL). After being exposed to ambient light and open to air for 2 d, there was no **42** remaining so the mixture was adsorbed on silica gel, while the solvent was removed in a rotavapor, and chromatographed (10% to 20% ethyl acetate/hexanes, gradient) to yield 4.4 mg (44%) of the title compound. R_f = 0.47 (30% ethyl acetate/hexanes). IR (neat): $\tilde{\nu}$ = 1642 (s), 1606 (s), 1277 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 11.73 (s, 1 H), 7.65 (d, J = 4.4 Hz, 2 H), 7.29 (t, J = 4.8 Hz, 1 H), 6.85 (s, 1 H), 6.75 (t, J = 2.9 Hz, 1 H), 6.22–6.20 (m, 2 H), 3.76 (s, 2 H), 2.20 (q, J = 7.3 Hz, 2 H), 1.05 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 184.58, 162.76, 137.71, 132.71, 131.70, 130.58, 125.35, 124.73, 119.89, 115.34, 113.79, 110.52, 94.62, 28.42, 25.57, 14.60 ppm. MS (EI, 70 eV): m/z (%) = 313 (19) [M]$^+$, 252 (100) [M – SEt]$^+$. HRMS (EI, 70 eV): calcd. for C$_{17}$H$_{15}$NO$_3$S [M]$^+$ 313.0773; found 313.0775.

2-{2,4-Bis[(ethylsulfanyl)methyl]pyrrol-1-yl}naphthalene-1,4-diol (59): Ethanethiol (120 µL, 1.6 mmol) was added to **39** (53.8 mg, 160 µmol) and 2,6-lutidine (18 µL, 0.16 mmol) in acetonitrile (8 mL). After being exposed to ambient light and open to air for

2 d, there was no **39** remaining so the mixture was adsorbed on silica gel, while the solvent was removed in a rotavapor, and chromatographed (10% to 20% ethyl acetate/hexanes, gradient) to yield 45.2 mg (76%) of the title compound. Although characterized as the hydroquinone, this compound was found to be relatively unstable, converting over time to the quinone product. R_f = 0.38 (30% ethyl acetate/hexanes). IR (neat): $\tilde{\nu}$ = 3388 (br.) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.28 (dd, J = 6.2, 3.3 Hz, 1 H), 8.16 (dd, J = 5.9, 3.3 Hz, 1 H), 7.58 (dd, J = 6.3, 3.3 Hz, 2 H), 6.64 (s, 2 H), 6.23 (s, 1 H), 5.77 (s, 2 H), 3.65 (s, 4 H), 2.55 (q, J = 7.4 Hz, 2 H), 2.45 (q, J = 7.4 Hz, 2 H), 1.27 (t, J = 7.4 Hz, 3 H), 1.15 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 145.10, 141.97, 130.88, 126.64, 126.60, 125.93, 125.35, 122.98, 121.88, 121.68, 121.40, 119.69, 110.25, 108.60, 27.87, 26.63, 25.61, 25.49, 14.43, 14.10 ppm. MS (EI, 70 eV): m/z (%) = 311 (63) [M – HSEt]$^+$, 250 (100) [M – HSEt – SEt]$^+$. HRMS (ESI): calcd. for C$_{20}$H$_{23}$NO$_2$S$_2$ [M + Na]$^+$ 396.1068; found 396.1068.

2-{2,5-Bis[(ethylsulfanyl)methyl]pyrrol-1-yl}naphthalene-1,4-diol (60): Ethanethiol (47 µL, 0.63 mmol) was added to **40** (23.3 mg, 63.0 µmol) in chloroform (3 mL). After being exposed to ambient light and open to air for 2 d, there was no starting material remaining so the mixture was adsorbed onto silica gel and chromatographed (10% to 20% ethyl acetate/hexanes, gradient) to yield 19.0 mg (81%) of the title compound. R_f = 0.29 (20% ethyl acetate/hexanes). IR (neat): $\tilde{\nu}$ = 3391 (br.), 1598 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.32–8.29 (m, 1 H), 8.18–8.15 (m, 1 H), 7.57 (td, J = 4.9, 1.5 Hz, 2 H), 6.60 (s, 1 H), 6.15 (s, 2 H), 5.80 (s, 1 H), 5.32 (s, 1 H), 3.44 (d, J = 2.9 Hz, 4 H), 2.40 (q, J = 7.3 Hz, 4 H), 1.11 (t, J = 7.3 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 145.28, 142.92, 130.98, 126.77, 126.60, 125.70, 123.24, 121.69, 118.27, 109.43, 108.70, 27.10, 25.50, 14.16 ppm. MS (EI, 70 eV): m/z (%) = 311 (66) [M – HSEt]$^+$, 250 (100) [M – HSEt – SEt]$^+$. HRMS (ESI): calcd. for C$_{20}$H$_{23}$NO$_2$S$_2$ [M + Na]$^+$ 396.1068; found 396.1082.

6-{2,4-Bis[(ethylsulfanyl)methyl]pyrrol-1-yl}quinoline-5,8-diol (61): Ethanethiol (47 µL, 0.64 mmol) was added to **48** (22.3 mg, 64.0 µmol) in chloroform (3 mL). After being exposed to ambient light and open to air for 18 h, there was no **48** remaining so the mixture was adsorbed on silica gel, while the solvent was removed in a rotavapor, and chromatographed (20% to 30% ethyl acetate/hexanes, gradient) to yield 10.6 mg (44%) of the title compound. R_f = 0.14 (20% ethyl acetate/hexanes). IR (neat): $\tilde{\nu}$ = 3390 (br.) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.85 (dd, J = 4.1, 1.4 Hz, 1 H), 8.63 (dd, J = 8.5, 1.4 Hz, 1 H), 7.87 (s, 1 H), 7.52 (dd, J = 8.5, 4.1 Hz, 1 H), 6.95 (s, 1 H), 6.66 (d, J = 1.6 Hz, 1 H), 6.24 (d, J = 1.6 Hz, 1 H), 6.02 (s, 1 H), 3.66 (s, 4 H), 2.55 (q, J = 7.4 Hz, 2 H), 2.46 (q, J = 7.4 Hz, 2 H), 1.27 (t, J = 7.4 Hz, 3 H), 1.16 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 149.03, 146.26, 140.16, 138.48, 132.35, 130.94, 121.99, 121.86, 121.72, 120.82, 110.62, 109.79, 27.97, 26.88, 25.64, 25.55, 14.46, 14.14 ppm. MS (EI, 70 eV): m/z (%) = 312 (53) [M – HSEt]$^+$, 251 (100) [M – HSEt – SEt]$^+$. HRMS (ESI): calcd. for C$_{19}$H$_{22}$N$_2$O$_2$S$_2$ [M + H]$^+$ 375.1201; found 375.1199.

6-{2,5-Bis[(ethylsulfanyl)methyl]pyrrol-1-yl}quinoline-5,8-diol (62): Ethanethiol (17 µL, 0.23 mmol) was added to **49** (8.5 mg, 23 µmol) in chloroform (1 mL). After being exposed to ambient light and open to air for 16 h, there was no **49** remaining so the mixture was adsorbed on silica gel, while the solvent was removed in a rotavapor, and chromatographed (50% ethyl acetate/hexanes) to yield 2.6 mg (30%) of the title compound. R_f = 0.17 (30% ethyl acetate/hexanes). IR (neat): $\tilde{\nu}$ = 3392 (br.) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.86 (dd, J = 4.4, 1.5 Hz, 1 H), 8.69 (dd, J = 8.4,

1.5 Hz, 1 H), 7.54 (dd, J = 8.4, 4.4 Hz, 1 H), 6.95 (s, 1 H), 6.16 (s, 2 H), 6.06 (s, 1 H), 3.52 (d, J = 14.6 Hz, 2 H), 3.40 (d, J = 14.3 Hz, 2 H), 2.41 (q, J = 7.3 Hz, 4 H), 1.11 (t, J = 7.3 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 148.73, 146.15, 142.50, 141.10, 133.29, 131.03, 121.94, 121.63, 120.81, 111.26, 108.95, 27.14, 25.39, 14.16 ppm. MS (EI, 70 eV): m/z (%) = 312 (32) [M – HSEt]$^+$, 251 (100) [M – HSEt – SEt]$^+$. HRMS (ESI): calcd. for C$_{19}$H$_{22}$N$_2$O$_2$S$_2$ [M + H]$^+$ 375.1201; found 375.1184.

Supporting Information (see footnote on the first page of this article): Spectra for all new compounds.

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