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# Design and Synthesis of Novel Quinone Inhibitors Targeted to the Redox Function of Apurinic/Apyrimidinic Endonuclease 1/Redox Enhancing Factor-1 (Ape1/Ref-1)

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The multifunctional enzyme apurinic endonuclease 1/redox enhancing factor 1 (Ape1/ref-1) maintains genetic fidelity through the repair of apurinic sites and regulates transcription through redox-dependent activation of transcription factors. Ape1 can therefore serve as a therapeutic target in either a DNA repair or transcriptional context. Inhibitors of the redox function can be used as either therapeutics or novel tools for separating the two functions for in vitro study. Presently there exist only a few compounds that have been reported to inhibit Ape1 redox activity; here we describe a series of quinones that exhibit micromolar inhibition of the redox function of Ape1. Benzoquinone and naphthoquinone analogues of the Ape1-inhibitor E3330 were designed and synthesized to explore structural effects on redox function and inhibition of cell growth. Most of the naphthoquinones were low micromolar inhibitors of Ape1 redox activity, and the most potent analogues inhibited tumor cell growth with $IC_{50}$ values in the 10−20 $\mu$M range.

## Introduction

Two fundamental concerns present in managing cellular homeostasis are maintaining DNA fidelity and regulating the expression of the genetic information contained therein. With regard to DNA fidelity, a major recurring event cells must overcome is the formation of apurinic or apyrimidinic (AP[a]) sites, formation of which takes place on the order of $10^4$ times per cell per day by spontaneous glycosidic hydrolysis.[1−3] AP sites in DNA have numerous deleterious ramifications, including prohibiting DNA replication, cytotoxicity, and mutagenicity. Spontaneous glycosidic hydrolysis is not the only route to forming AP sites; glycosylases as well as DNA damaging agents can induce AP site formation in DNA.[1] The ubiquitous enzyme apurinic/apyrimidic endonuclease 1 (Ape1) is a major component of the base excision repair (BER) pathway and has the responsibility of repairing AP sites throughout the genome. Ape1 possesses multiple enzymatic functions; the most relevant to BER is the 5′AP-endonuclease activity that initiates the removal of AP sites.

Gene expression is also controlled in part by Ape1. At the same time the BER function of Ape1 was being explored, another enzyme was identified that performed redox-dependent regulation of numerous transcription factors. This enzyme was named redox enhancing factor 1 (ref-1) and was linked to the regulation of transcription factors such as activator protein 1 (AP-1), hypoxia inducing factor 1alpha (HIF-1α), and nuclear factor kappa B (NFκB). It was subsequently determined that these were two distinct functions of the same protein, initially thought to reside in two nonoverlapping domains but later determined to have a minor degree of overlap.[1−5] However, redox or repair can be silenced independently using specific point mutations for each activity, indicating that each function can act independently.

Through both the redox and DNA repair functions, Ape1 supports cancer cell proliferation, and elevated expression levels have been shown to correlate to poor patient prognosis.[1−3] Ape1 is overexpressed in a number of cancers, where increased levels of DNA repair leads to resistance against DNA damaging agents, and increased redox activity is expected to enhance replication through redox cycling of transcription factors. Therefore Ape1 represents an interesting therapeutic target in different mechanistic contexts. Inhibitors of the BER function of Ape1 can be utilized as a complementary treatment option for those encountering resistance to DNA-damaging agents. Alternatively, inhibition of the redox function of Ape1 might interfere with regulation of transcription and alter a number of stress-induced responses of cancer cells. Recent data indicate that blocking the repair function of Ape1 leads to cell death, while redox activity inhibition leads to decreased cell growth and cytostatic effects.[6] Additionally, recent data indicate that blocking Ape1 redox function blocks angiogenesis.[6−8] Small molecule inhibitors of the redox function can also serve as tools to separate the two functions of Ape1 without the lethality of knocking out Ape1 completely.[9]

The design of inhibitors targeting the redox function of Ape1 is hindered by a lack of information regarding the redox active site. Mutation analysis has shown that cysteine 65 is necessary for redox activity; however, in every crystal structure C65 is buried, suggesting that a conformational change might be required to present the relevant redox-active

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[a] Abbreviations: AP, apurinic/apyrimidinic; Ape1, apurinic/apyrimidinic endonuclease 1; BER, base excision repair; EMSA, electrophoretic mobility shift assay; ref-1, redox-enhancing factor 1.

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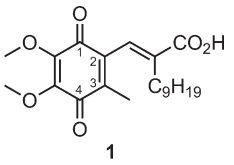


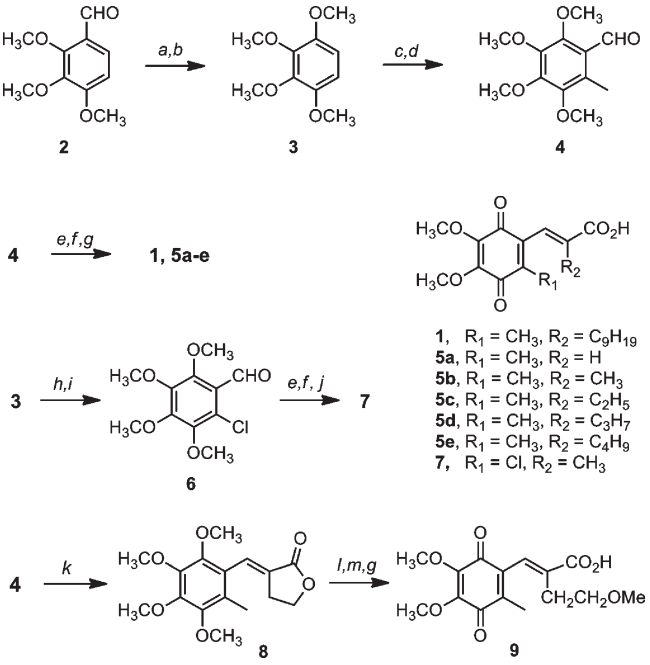
**Figure 1.** E3330, a reported inhibitor of Ape1 redox activity.[1]

structure.[10] Furthermore, there is only one known compound in the literature that has been shown to inhibit the redox function of Ape1.[1] To provide structural insight into potential inhibitor specificity for the redox active site, a series of benzoquinones and naphthoquinones has been synthesized based on the structure of (*E*)-3-(5,6-dimethoxy-3-methyl-1,4-dioxocyclohexa-2,5-dienyl)-2-nonylpropenoic acid (E3330, **1**), a known inhibitor of the redox function of Ape1.[1] (Figure 1) Analogues with improved physicochemical and binding profiles also have the potential to provide crystallographic data when complexed with the protein to elucidate the structure of the redox active site. The structure of **1** provides five regions for potential exploration in preliminary SAR studies, namely (1) the substituent on the 3-position of the quinone ring, (2) the benzoquinone structure, (3) the substituent α to the carboxyl group, (4) the carboxylate moiety, and (5) the saturation of the substituent at the quinone 2-position.

## Results and Discussion

**Chemistry.** The synthesis of benzoquinone **1** (E3330) has been reported in a patent, and key transformations have appeared separately in print.[11,12] The patent synthesis begins with the tribromination of *p*-cresol followed by a Cu(I)-mediated Ullmann reaction to generate 4-methyl-2,3,6-trimethoxyphenol that is alkylated in situ to provide 2,3,4,5-tetramethoxytoluene.[12] In our hands, the methanolysis of 4-methyl-2,3,6-tribromophenol resulted in a complex mixture that included products derived from reduction of the bromo substituents; these side products were very difficult to remove, and the resulting tetramethoxytoluene could not be obtained pure. To overcome these difficulties, we developed an alternative synthesis of **1** (Scheme 1) that was also used for the synthesis of several analogues.[10] Bayer−Villiger oxidation of 2,3,4-trimethoxybenzaldehyde **2** and subsequent hydrolysis in situ gave 2,3,4-trimethoxyphenol, which was then alkylated to provide 1,2,3,4-tetramethoxybenzene **3** in excellent yield.[13] Ring methylation was then performed to provide 2,3,4,5-tetramethoxytoluene in high yield and purity,[14] and the aldehyde moiety was introduced using α,α-dichloromethyl methyl ether and titanium(IV) chloride[15] to give **4** in 95% yield. The chloroaldehyde intermediate **6** was prepared by formylation of **3** using *N*-methyl formanilide and $POCl_3$, followed by chlorination with sulfuryl chloride.[16] The unsaturated ester moiety was introduced by Emmons condensation of aldehyde **4** or **6** and the appropriate phosphonate. All of the Emmons products derived from aldehyde **4** were formed exclusively as the *E* isomer. When using the chloro-substituted aldehyde **6**, however, the *E*:*Z* selectivity is 5:1 when the reaction is run at room temperature; performing the reaction in refluxing toluene provides 100% *E* isomer. The esters were hydrolyzed and the intermediate acids were oxidized to the benzoquinones **1**, **5a**−**e** and **7**. The 3-methyl analogues were easily oxidized with either nitric acid or ceric ammonium nitrate (CAN); however, successful oxidation of the 3-chloro analogue could only be accomplished using CAN. Finally, the methoxyethyl substituent was introduced by condensation of **4** with the Emmons reagent prepared from α-bromo-γ-butyrolactone to give lactone **8**. Treatment of **8** with trimethylorthoformate in acidic methanol generated the ring-opened methoxyethyl analogue;[17] hydrolysis of the methyl ester and oxidation afforded the quinone **9**.

**Scheme 1**[a]

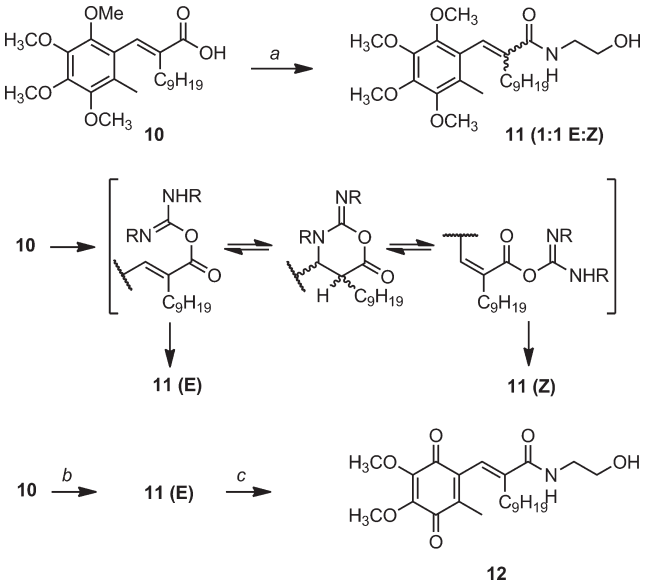


[a] Reagents and conditions: (a) $H_2O_2$, $H_2SO_4$, MeOH, reflux 3 h. (b) $K_2CO_3$, MeI, acetone, reflux 2 d. (c) (i) nBuLi, THF, 0 °C 1 h; (ii) MeI, 0 °C, 2 h. (d) $CHCl_2OCH_3$, $TiCl_4$, $CH_2Cl_2$, 0 °C to rt 4 h. (e) NaH, $(EtO)_2P(O)CHRCO_2Et$, THF, rt 12 h. (f) KOH, EtOH, reflux 30 min. (g) $HNO_3$, AcOH, EtOAc, rt 4 h. (h) NMFA, $POCl_3$, $CH_2Cl_2$, rt 2 d. (i) $SO_2Cl_2$, $CH_2Cl_2$, rt, 1 h. (j) CAN, MeCN, $H_2O$, 1 h. (k) α-Bromo-γ-butyrolactone, $(EtO)_3P$, then NaH, toluene, reflux 8 h. (l) $H_2SO_4$, $CH(OCH_3)_3$, MeOH, reflux 12 h. (m) KOH, EtOH, reflux 30 min.

Carboxamide analogues of the free acids were also of interest both for SAR and for the potential development of coupled products. However, all efforts to introduce a hydroxyethylamide moiety by reaction with the benzoquinone acids (e.g., **5a**) were unsuccessful. Therefore, acid **10** was converted to amide **11** and subsequently oxidized to give the desired quinone amide **12** (Scheme 2). The synthesis of **11** was initially attempted using DCC as a reagent; surprisingly, amide **11** was obtained as a 1:1 mixture of *E* and *Z* products. In contrast, the *E* stereochemistry was completely retained when **11** was synthesized using PyBOP in the coupling reaction. Further exploration of coupling conditions using a variety of unsaturated acids and amines showed that activation with either DCC or DIC leads to mixtures of *E* and *Z* products, but activation with PyBOP, methyl chloroformate, or oxalyl chloride do not. It is hypothesized that a reversible intramolecular cyclization of the activated carbodiimide intermediate is taking place that leads to loss of the stereochemical integrity of the double bond (Scheme 2). The amidation product *E*-**11** was then readily oxidized using nitric acid to provide hydroxyethylamide **12**.

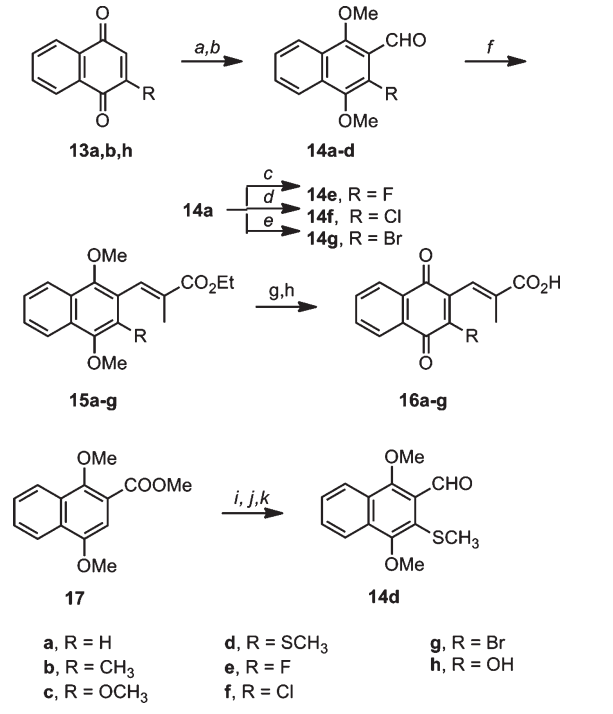
The naphthoquinone analogues were constructed via condensation of the appropriate aldehydes and phosphonates

**Scheme 2**[a]




[a] Reagents and conditions: (a) DCC, ethanolamine, $CH_2Cl_2$, rt; (b) PyBOP, $Et_3N$, rt 30 min, then ethanolamine, rt 4 h; (c) Ag(II)O, $HNO_3$, AcOH, EtOAc, rt 40 min.

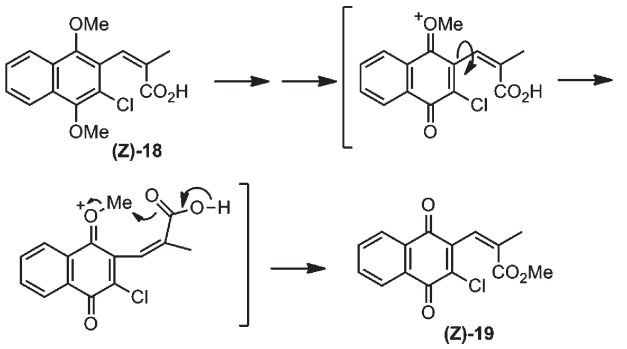
**Scheme 3**[a]




[a] Reagents and conditions: (a) (i) $H_2$, 10% Pd/C, THF, rt, 4 h; (ii) NaH, $Me_2SO_4$, 2 h, rt. (b) R = H, $CH_3$: $TiCl_4$, $CHCl_2OCH_3$, $CH_2Cl_2$, 0 °C, 4 h; R = $OCH_3$: (i) nBuLi, THF, −78 °C, 3 h; (ii) DMF, −78 °C. (c) Selectfluor, $CH_3CN$, reflux. (d) $SO_2Cl_2$, $CH_2Cl_2$, rt, 4 h. (e) $Br_2$, $CH_2Cl_2$, rt, 1 h. (f) R = H: NaH, $(EtO)_2P(O)CHR'CO_2$, Et, THF, rt, 12 h; R = $CH_3$, $OCH_3$, $SCH_3$, F, Cl, Br: NaH, $(EtO)_2P(O)CHR'CO_2Et$, PhMe, reflux, 12 h. (g) EtOH, KOH, reflux, 1 h. (h) R = H, $CH_3$, $OCH_3$, $SCH_3$: $HNO_3$, EtOAc, AcOH, rt, 3 h; R = F, Cl, Br: $HNO_3$, EtOAc, AcOH, Ag(II)O, rt, 2 h. (i) $LiAlH_4$, THF, rt, 12 h. (j) (i) nBuLi, THF, −78 °C; (ii) $(SCH_3)_2$, −78 °C. (k) PCC, $CH_2Cl_2$, rt, 8 h.

followed by ester hydrolysis and oxidation to the quinone. Synthesis of the requisite aldehydes is detailed in Scheme 3.

**Scheme 4**



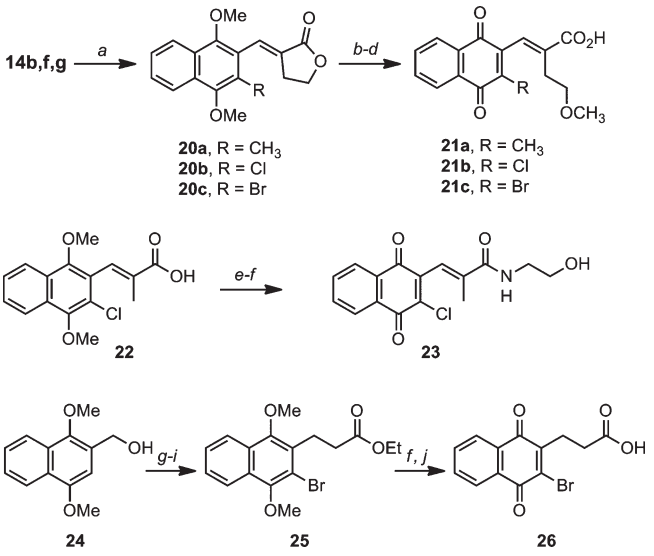

Aldehydes **14a**−**c** were prepared by dichloromethyl methyl ether formylation of the di- or trimethoxynaphthalenes. The methylthio substituent was introduced by lithiation of the hydroxymethylnaphthalene, followed by reaction with dimethyl disulfide and subsequent oxidation of the hydroxymethyl group to the aldehyde (**14d**). The 3-halo substituents in **14e**−**g** were introduced by electrophilic halogenation of **14a**. Emmons condensation with the naphthaldehydes showed reduced *E* selectivity relative to their benzaldehyde counterparts. The greatest *E* selectivity was observed with 3-methyl aldehyde **14b**, which afforded 100% *E* in refluxing toluene and an *E*:*Z* ratio of approximately 5:1 at room temperature. All other analogues produced a significant proportion of *Z* isomer (20−50%) even in refluxing toluene. The Emmons products **15a**−**g** were converted to the quinones **16a**−**g** by saponification and subsequent oxidation. Nitric acid was sufficient to oxidize the 3-methyl, 3-methoxy, and 3-methylthio analogues, but efficient oxidation of the 3-halo analogues required treatment with argentic oxide.

An interesting result was observed when a mixture of 3-chloro *E*- and *Z*-acids (resulting from hydrolysis of the crude Emmons product **15f**) was oxidized using nitric acid and argentic oxide; although the *E*-quinone product **16f** was produced from the *E*-acid as expected, the *Z*-quinone product following oxidation was recovered as a methyl ester. The oxidation was carried out on pure *Z*-acid **18**, and the *Z*-methyl ester **19** was the major product (Scheme 4). To rationalize the selective esterification of the *Z*-carboxylate group, an intramolecular esterification is hypothesized (Scheme 4) in which the *Z*-carboxylate attacks the methyl group of the oxonium ion intermediate generated in the oxidation reaction. The selective esterification of the *Z*-acids is fortuitous in that it provides a convenient strategy to purify otherwise difficult-to-separate *E* and *Z* products by generating easily separable *E*-acid and *Z*-methyl ester.

Finally, the naphthoquinone series was completed with the preparation of methoxyethyl side chain analogues **21a**−**c**, the amide **23**, and the bromoacid **26** in which the double bond at the 2-position was fully saturated (Scheme 5). Syntheses of **21** and **23** were accomplished via routes analogous to those previously described for the benzoquinone products. Alcohol **24** (the reduction product of **14a**) provided the starting material for the synthesis of **26**; conversion to the α,3-dibromide followed by displacement of the benzylic bromide afforded the saturated ester **25**. Oxidation and ester hydrolysis gave the desired product.

**Redox, Endonuclease, and Cell Growth Inhibition.** Compounds were tested for the ability to inhibit the redox function of Ape1 in a gel shift assay (EMSA), and $IC_{50}$ values were generated for each compound. Inhibition of Hey-C2 ovarian cancer cell growth was also assessed. Compounds were also evaluated as inhibitors of Ape1 endonuclease activity; all compounds were inactive at concentrations up to 100 $\mu$M. The redox and cell growth inhibition results are summarized in Tables 1 and 2; a representative EMSA assay is shown in Figure 2. Modification of the alkyl substituent on the double bond of the benzoquinones (Table 1) had only modest effects on the redox activity; replacement of the *n*-nonyl group (**1**, $IC_{50}$ = 10 $\mu$M) with a methyl group (**5b**, $IC_{50}$ = 3 $\mu$M) enhanced redox activity, whereas removal of the alkyl group (**5a**, $IC_{50}$ = 40 $\mu$M) reduced potency in the redox assay. In contrast, most of the structural modifications in the benzoquinone series diminished cell growth inhibitory activity compared to the lead compound **1**. The loss of cell-based activity relative to redox activity is especially dramatic for compounds **5a**, **5b**, and **9**. However, these compounds are significantly more hydrophilic than **1**, so they may be too polar to permeate the cell effectively. By comparison, most of the naphthoquinones (Table 2) were more potent than **1** as inhibitors of

**Scheme 5**[a]




[a] Reagents and conditions: (a) α-bromobutyrolactone, $(EtO)_3P$, then NaH, toluene, reflux 8 h; (b) $H_2SO_4$, $CH(OCH_3)_3$, MeOH, reflux 12 h; (c) KOH, EtOH, reflux 30 min; (d) R = $CH_3$: $HNO_3$, EtOAc, AcOH, rt 3 h; R = Cl or Br: $HNO_3$, EtOAc, AcOH, Ag(II)O, rt 2 h; (e) PyBOP, $Et_3N$, DMF:$CH_2Cl_2$ rt 30 min, then ethanolamine, rt 4 h; (f) Ag(II)O, $HNO_3$, AcOH, EtOAc, rt 30 min; (g) HBr, $CH_2Cl_2$ rt 30 min; (h) $Br_2$, $CH_2Cl_2$, rt 4 h; (i) $Li(SiMe_3)_2N$, $CH_3CO_2Et$, THF, −78 C to rt 4 h; (j) HCl, THF, reflux.

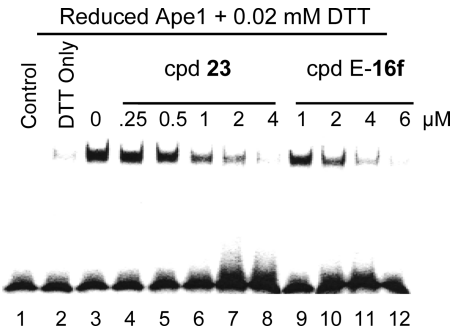



**Figure 2.** Inhibition of Ape1 redox activity measured by electrophoretic mobility shift assay. See Experimental Section for details.

**Table 1.** Redox and Growth Inhibition of Benzoquinone Analogues

| compd | $R_1$ | $R_2$ | $R_3$ | redox inhibition $IC_{50}$, $\mu$M[a] | growth inhibition $GI_{50}$, $\mu$M[b] |
|---|---|---|---|---|---|
| **1** | $CH_3$ | $C_9H_{19}$ | OH | 10 | 35 |
| **5a** | $CH_3$ | H | OH | 40 | 250 |
| **5b** | $CH_3$ | $CH_3$ | OH | 3 | 130 |
| **5e** | $CH_3$ | $C_4H_9$ | OH | 15 | 85 |
| **7** | Cl | $CH_3$ | OH | 3 | 45 |
| **9** | $CH_3$ | $C_2H_4OCH_3$ | OH | 10 | 200 |
| **12** | $CH_3$ | $C_9H_{19}$ | $NH(CH_2)_2OH$ | 10 | 35 |

[a] Determined in a gel shift EMSA assay; see Experimental Section for details. [b] Hey-C2 cells treated with drug for 72 h. Values represent the average of three experiments.

**Table 2.** Redox and Growth Inhibition of Naphthoquinone Analogues

| compd | $R_1$ | $R_2$ | $R_3$ | redox inhibition $IC_{50}$, $\mu$M[a] | growth inhibition $GI_{50}$, $\mu$M[b] |
|---|---|---|---|---|---|
| **16a** | H | $CH_3$ | OH | 3 | 20 |
| **16b** | $CH_3$ | $CH_3$ | OH | 15 | 45 |
| **16c** | $OCH_3$ | $CH_3$ | OH | 1 | 40 |
| **16d** | $SCH_3$ | $CH_3$ | OH | 1 | 30 |
| **16e** | F | $CH_3$ | OH | 4 | 50 |
| **16f(*E*)** | Cl | $CH_3$ | OH | 1 | 15 |
| **16f(*Z*)** | Cl | $CH_3$ | OH | 2 | 30 |
| **16g** | Br | $CH_3$ | OH | 2 | 13 |
| **21a** | $CH_3$ | $C_2H_4OCH_3$ | OH | 10 | 30 |
| **21b** | Cl | $C_2H_4OCH_3$ | OH | 3 | 30 |
| **21c** | Br | $C_2H_4OCH_3$ | OH | 1 | 25 |
| **23** | Cl | $CH_3$ | $NH(CH_2)_2OH$ | 1 | 8 |
| **26** | Br | H (saturated) | OH | 5 | 15 |

[a] Determined in a gel shift EMSA assay; see Experimental Section for details. [b] Hey-C2 cells treated with drug for 72 h. Values represent the average of three experiments.

Ape1 redox activity, with $IC_{50}$ values in the 1−5 $\mu$M range. Compounds with electronegative substituents in the 3-position of the naphthoquinone ring generally had the highest redox inhibitory activity; in contrast, the 3-methyl compounds were the least active in this assay. The best of the naphthoquinones were 2−4 fold more potent than **1** in growth inhibitory activity and, although the most potent compounds were generally 3-chloro or 3-bromo analogues, the structural modifications investigated here had only modest effects on growth inhibition. It is interesting to note that functionalization of the carboxylic acid as the hydroxyethyl amide did not affect either redox or cell growth inhibitory activity significantly (compounds *E*-**16f** and **23**).

## Conclusion

The goal of this work was to exploit **1** as a lead to develop more potent and druggable inhibitors of Ape1 redox activity. Analogues based on the benzoquinone core showed little improvement in enzymatic activity, and most were less effective cell growth inhibitors, presumably because of significant changes in physicochemical properties. Most of the naphthoquinone analogues were highly potent inhibitors of Ape1 redox activity. All of these compounds had favorable physicochemical properties, with cLogP values in the 1−3 range. The most potent compounds have an electron-withdrawing substituent at the 3-position of the naphthoquinone ring. Several of these compounds exhibited $IC_{50}$ values of ~1 $\mu$M in the Ape1 redox assay and $< 20$ $\mu$M in the cell growth inhibition assay.

## Experimental Procedures

**Materials and Methods.** All NMR spectra were recorded using a 300 MHz Bruker spectrometer equipped with a 5 mm multinuclear probe. $^1$H chemical shifts are reported in parts per million using tetramethylsilane as internal standard. $^{31}$P NMR spectra were obtained using broadband $^1$H decoupling, and chemical shifts are reported in parts per million using 1% triphenylphosphine oxide/benzene-$d_6$ as the coaxial reference (triphenylphosphine oxide/benzene-$d_6$ has a chemical shift of +24.7 ppm relative to 85% phosphoric acid). Mass spectral data were obtained from the Purdue University Mass Spectrometry Service, and elemental analyses were performed by the Purdue University Microanalysis Lab. Purity of all tested compounds was assessed by either combustion analysis or HPLC (C18 reverse phase) and found to be 95% or greater. Silica gel grade 60 (230−400 mesh) was used to carry out all flash chromatographic separations. Thin layer chromatography was performed using Analtech glass plates precoated with silica gel (250 $\mu$m). Visualization of the plates was accomplished using UV and/or the following stains: 1% 4-(*p*-nitrobenzyl)pyridine in acetone followed by heating and subsequent treatment with 3% KOH in methanol or *p*-anisaldehyde dip (1.85% *p*-anisaldehyde, 20.5% sulfuric acid, 0.75% acetic acid in 95% ethanol) followed by heating. All anhydrous reactions were carried out under an atmosphere of argon. Tetrahydrofuran was distilled prior to use from sodium using benzophenone ketyl as an indicator. Dichloromethane, triethylamine, pyridine, and acetonitrile were distilled from calcium hydride prior to use. Unless otherwise noted, all other solvents were purchased from Fisher or VWR and used as received. All chemical reagents were purchased from Aldrich, unless otherwise noted.

**Enzymatic Redox Assay.** Inhibition of Ape1 redox activity was measured using an electrophoretic mobility shift assay (EMSA).[18] Briefly, purified Ape1 protein (10 mg/mL) was reduced with DTT (1.0 mM) at 37 °C for 10 min and then diluted with PBS buffer to final concentrations of Ape1 and DTT of 2 mg/mL and 0.2 mM, respectively. A final volume of 18 mL was prepared from EMSA buffer (10 mM Tris [pH 7.5], 50 mM NaCl, 1 mM $MgCl_2$, 1 mM EDTA, 5% [vol/vol] glycerol) to which was added 2 mL of reduced Ape1 protein and 6 mg of oxidized nuclear extracts (Hey-C2 cells, treated with 0.01 mM diamide for 10 min), and the reaction was incubated at room temperature for 30 min. One mL of poly(dI-dC)·poly(dI-dC) (1 mg/L, Amersham Biosciences, Piscataway, NJ) was added for 5 min followed by 1 mL of the 5′ hexachlorofluorescein phosphoramidite (HEX)-labeled double-stranded oligonucleotide DNA (0.1 pmol, The Midland Certified Reagent Company, Midland, TX) containing the AP-1 consensus sequence (5′CGCTTGATGACTCAGCCGGAA-3′), and the mixture was further incubated for 30 min at room temperature. The final concentration of DTT in the redox reactions was 0.02 mM. Samples were loaded on a 5% nondenaturing polyacrylamide gel and subjected to electrophoresis in 0.5X TBE buffer (200 V for 1 h at 4 °C) and detected using the Hitachi FMBio II fluorescence imaging system (Hitachi Genetic Systems, South San Francisco, CA). The HEX fluorophore is excited by a solid-state laser at 532 nm (Perkin-Elmer) and emits a fluorescent light signal at 560 nm, which is then measured using a 585 nm filter.

**Growth Inhibition Assay.** Growth inhibition was tested in vitro using the MTS assay following the procedure of Fishel et al.[19] Hey-C2 ovarian cancer cells were cultured in RPMI 1640 medium containing 10% fetal calf serum. Cells (2−4000) were aliquoted into each well of a 96-well plate in triplicate and allowed to adhere overnight. Cells were incubated with drug for 72 h at 37 °C. After 72 h, 0.05 mg/mL MTS reagent was added to each well and incubated at 37 °C for 4 h, followed by absorbance measurement at 490 nm. The values were standardized to wells containing media alone.

**Synthetic Procedures. (*E*)-3-(5,6-Dimethoxy-3-methyl-14-dioxocyclohexa-25-dienyl)-2-nonylpropenoic Acid (1).** According to the modified procedure of Murphy et al.,[20] NaH (0.135 g, 3.38 mmol) was added to a flame-dried 50 mL 3-neck round-bottom flask connected to a water-jacketed reflux condenser. The flask was purged with argon, and THF (20 mL) was added to the flask followed by triethyl 2-phosphonoundecanoate (1.08 g, 3.09 mmol) at room temperature. The reaction was stirred at room temperature for 30 min, and then **4** (0.581 g, 2.42 mmol) dissolved in THF (10 mL) was added rapidly at room temperature. The reaction was stirred for another 12 h at room temperature and then acidified with 2 M HCl, diluted with ethyl acetate, and washed with brine. The organic layer was dried, filtered, and condensed. The resulting oil was purified via flash column chromatography (3:17 EtOAc:hexanes) to provide ethyl (*E*)-3-(6-methyl-2,3,4,5-trimethoxyphenyl)-2-nonylpropenoate (0.603 g, 57%) as a colorless oil. $R_f$ = 0.40 (3:17 EtOAc:hexanes). $^1$H NMR ($CDCl_3$): $\delta$ 0.84 (t, 3H, $J$ = 7.2 Hz), 1.08−1.22 (m, 11H), 1.24−1.35 (m, 3H), 1.33 (t, 3H), 2.03 (s, 3H), 2.12 (m, 2H), 3.69 (s, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 4.25 (q, 2H), 7.37 (s, 1H).

The ethyl ester (1.57 g, 3.60 mmol) was dissolved in EtOH (12.0 mL), and then KOH (0.41 g, 7.3 mmol) was added and the solution was refluxed for 1 h. The reaction was then acidified with 2 M HCl, extracted with ethyl acetate, washed two times with saturated brine, dried, filtered, and condensed. The product was obtained as a light-yellow oil (1.43 g, 97%) following flash chromatography (2:3 $Et_2O$:hexanes 0.5% AcOH). $R_f$ = 0.36 (2:3 $Et_2O$:hexanes 0.5% AcOH). $^1$H NMR ($CDCl_3$): $\delta$ 0.84 (t, 3H), 1.13 (m, 12H), 1.36 (m, 2H), 2.04 (s,3H), 2.14 (m, 2H), 3.70 (s, 3H), 3.79 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 7.537 (s,1H).

Following modifications to the procedures by Shinkawa et al. and Flader et al.,[11,21] the unsaturated acid (1.13 g, 2.77 mmol) was dissolved in ethyl acetate (15 mL) at room temperature.

$HNO_3$ (0.75 mL) and AcOH (6 drops) were added at room temperature, and the reaction was stirred for 4 h. The reaction was then diluted with EtOAc (20.0 mL), washed with brine, dried over $MgSO_4$, filtered, and condensed. The red oil was then purified by flash chromatography (2:3 $Et_2O$:hexanes 0.5% AcOH), followed by recrystallization from $Et_2O$/hexanes to afford **1** (0.443 g, 42%) as a red solid. $R_f$ = 0.16 (2:3 $Et_2O$: hexanes 0.5% AcOH); mp = 56−57 °C (lit. 68 °C).[5] $^1$H NMR ($CDCl_3$): $\delta$ 0.84 (t, 3H), 1.18 (bs, 14H), 1.39 (bs, 2H), 1.94 (d, 3H), 2.09 (t, 3H,), 3.99 (s, 3H), 4.02 (s, 3H), 7.26 (d, 1H).

**(*E*)-3-(5,6-Dimethoxy-3-methyl-1,4-dioxocyclohexa-2,5-dienyl)-propenoic Acid (5a).** Following the method used for the synthesis of **1**, the Emmons condensation was performed with **4** (0.323 g, 1.34 mmol) to provide ethyl (*E*)-3-(6-methyl-2,3,4,5-trimethoxyphenyl)-propenoate (0.343 g, 83%) as a pale-yellow oil following chromatography ($CH_2Cl_2$ to 1:19 EtOAc:$CH_2Cl_2$). $R_f$ = 0.17 ($CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 1.32 (t, 3H), 2.26 (s, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 4.24 (q, 2H), 6.52 (d, 1H), 7.77 (d, 1H).

The ethyl ester (0.066 g, 0.21 mmol) was hydrolyzed (KOH, EtOH) to provide the unsaturated acid (0.046 g, 78%) as a light-tan solid following flash chromatography (2:3 $Et_2O$:hexanes 0.5% AcOH) or recrystallization from $Et_2O$/hexanes. $R_f$ = 0.16 (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 96−97 °C. $^1$H NMR ($CDCl_3$): $\delta$ 3.77 (s, 3H), 3.81 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 6.59 (d, 1H), 7.90 (d, 1H).

The unsaturated acid (0.089 g, 0.31 mmol) was then oxidized to provide **5a** (0.024 g, 57%) as a red solid following flash chromatography (1:1 $Et_2O$:hexanes 0.5% AcOH) and subsequent recrystallization from $Et_2O$/hexanes. $R_f$ = 0.06 (2:3 $Et_2O$: hexanes 0.5% AcOH); mp = 116−125 °C. $^1$H NMR ($CDCl_3$): $\delta$2.19 (s, 3H), 4.00 (s, 6H), 6.76 (d, 1H), 7.60 (d, 1H).

**(*E*)-3-(5,6-Dimethoxy-3-methyl-1,4-dioxocyclohexa-2,5-dienyl)-2-methylpropenoic Acid (5b).** Following the method used for the synthesis of **1**, the Emmons condensation was performed with **4** (0.569 g, 2.37 mmol) to provide ethyl (*E*)-3-(6-methyl-2,3,4,5-trimethoxyphenyl)-2-methylpropenoate (0.674 g, 88%) as a pale-yellow oil following chromatography (1:3 EtOAc:hexanes). $R_f$ = 0.48 (1:3 EtOAc:hexanes). $^1$H NMR ($CDCl_3$): $\delta$1.31 (t, 3H), 1.71 (d, 3H), 2.01 (s, 3H), 3.67 (s, 3H), 3.77 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 4.24 (q, 2H), 7.47 (d, 1H).

The ethyl ester (0.156 g, 0.481 mmol) was hydrolyzed (KOH, EtOH) to provide the unsaturated acid (0.121 g, 85%) as a light-yellow solid following flash chromatography (2:3 $Et_2O$:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.16 (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 98−102 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.76 (d, 3H, $J$ = 1.2 Hz), 2.05 (s, 3H), 3.69 (s, 3H), 3.79 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 7.64 (d, 1H).

The unsaturated acid (0.057 g, 0.19 mmol) was then oxidized to provide **5b** (0.016 g, 31%) as a red solid following flash chromatography (1:1 $Et_2O$:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.06 (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 134−136 °C. $^1$H NMR ($CDCl_3$): $\delta$1.77 (d, 3H, $J$ = 1.2 Hz), 1.95 (d, 3H, $J$ = 1.2 Hz), 4.01 (s, 3H), 4.03 (s, 3H), 7.39 (s, 1H).

**(*E*)-3-(5,6-Dimethoxy-3-methyl-1,4-dioxocyclohexa-2,5-dienyl)-2-ethylpropenoic acid (5c).** Following the method used for the synthesis of **1**, the Emmons condensation was performed with **4** (0.437 g, 1.82 mmol) to provide ethyl (*E*)-3-(6-methyl-2,3,4,5-trimethoxyphenyl)-2-ethylpropenoate (0.258 g, 42%) as a colorless oil following chromatography (1:3 EtOAc:hexanes). $R_f$ = 0.50 (1:3 EtOAc:hexanes). $^1$H NMR ($CDCl_3$): $\delta$ 0.94 (t, 3H), 1.33 (t, 3H), 2.02 (s, 3H), 2.15 (q, 2H), 3.69 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 4.26 (q, 2H), 7.36 (s, 1H).

The ethyl ester (0.041 g, 0.12 mmol) was then hydrolyzed to provide the unsaturated acid (0.010 g, 27%) as a gold oil following flash chromatography (2:3 $Et_2O$:hexanes 0.5% AcOH). $R_f$ = 0.16 (2:3 $Et_2O$:hexanes 0.5% AcOH). $^1$H NMR ($CDCl_3$): $\delta$ 0.98 (t, 3H), 2.04 (s, 3H), 2.18 (q, 2H), 3.70 (s, 3H), 3.79 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 7.53 (s, 1H).

The unsaturated acid (0.010 g, 0.033 mmol) was then oxidized to provide **5c** (0.003 g, 32%) as a red solid following flash chromatography (1:1 $Et_2O$:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.10 (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 124−131 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.01 (t, 3H), 1.94 (d, 3H), 2.12 (q, 2H), 3.99 (s, 3H), 4.01 (s, 3H), 7.23 (d, 1H).

**(*E*)-3-(4,5-Dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)-2-propylpropenoic Acid (5d).** Following the method used for the synthesis of **1**, the Emmons condensation was performed with **4** (0.437 g, 1.82 mmol) to provide ethyl (*E*)-3-(6-methyl-2,3,4,5-trimethoxyphenyl)-2-propylpropenoate (0.275 g, 43%) as a colorless oil following chromatography (1:3 EtOAc:hexanes). $R_f$ = 0.52 (1:3 EtOAc:hexanes). $^1$H NMR ($CDCl_3$): $\delta$ 0.75 (t, 3H, $J$ = 7.2 Hz), 1.33 (t, 3H, $J$ = 7.2 Hz), 1.35 (m, 2H), 2.03 (s, 3H), 2.11 (m, 2H), 3.69 (s, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 4.25 (q, 2H, $J$ = 7.2 Hz), 7.38 (s, 1H).

The ethyl ester (0.034 g, 0.098 mmol) was then hydrolyzed (KOH, EtOH) to provide the unsaturated acid (0.029 g, 92%) as a gold oil following flash chromatography (2:3 $Et_2O$:hexanes 0.5% AcOH). $R_f$ = 0.18 (2:3 $Et_2O$:hexanes 0.5% AcOH). $^1$H NMR ($CDCl_3$): $\delta$ 0.77 (t, 3H), 1.41 (m, 2H), 2.04 (s, 3H), 2.13 (m, 2H), 3.70 (s, 3H), 3.79 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 7.55 (s, 1H).

The unsaturated acid (0.029 g, 0.090 mmol) was then oxidized to provide **5d** (0.016 g, 59%) as a red solid following flash chromatography (1:1 $Et_2O$:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.12 (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 95−99 °C. $^1$H NMR ($CDCl_3$): $\delta$ 0.76 (t, 3H), 1.41 (m, 2H), 1.91 (d, 3H), 2.04 (m, 2H), 3.95 (s, 3H), 3.98 (s, 3H), 7.24 (s, 1H).

**(*E*)-3-(5,6-Dimethoxy-3-methyl-1,4-dioxocyclohexa-2,5-dienyl)-2-butylpropenoic Acid (5e).** Following the method used for the synthesis of **1**, the Emmons condensation was performed with **4** (0.650 g, 2.71 mmol) to provide ethyl (*E*)-3-(6-methyl-2,3,4,5-trimethoxyphenyl)-2-butylpropenoate (0.484 g, 49%) as a yellow oil following chromatography (1:9 EtOAc:hexanes). $R_f$ = 0.54 (1:3 EtOAc:hexanes). $^1$H NMR ($CDCl_3$): $\delta$ 0.73 (t, 3H), 1.12 (m, 2H), 1.29 (m, 2H), 1.32 (t, 3H), 2.03 (s, 3H), 2.13 (m, 2H), 3.69 (s, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 4.25 (q, 2H), 7.37 (s, 1H).

The ethyl ester (0.166 g, 0.453 mmol) was then hydrolyzed (KOH, EtOH) to provide the unsaturated acid (0.144 g, 94%) as a yellow amorphous solid following flash chromatography (2:3 $Et_2O$:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.26 (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 70−85 °C. $^1$H NMR ($CDCl_3$): $\delta$ 0.74 (t, 3H), 1.19 (m, 4H), 2.04 (s, 3H), 2.15 (m, 2H), 3.70 (s, 3H), 3.79 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 7.53 (s, 1H).

The unsaturated acid (0.015 g, 0.044 mmol) was then oxidized to provide **5e** (0.005 g, 40%) as a red solid following flash chromatography (1:1 $Et_2O$:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.12 (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 54−55 °C. $^1$H NMR ($CDCl_3$): $\delta$ 0.82 (t, 3H), 1.22 (m, 2H), 1.39 (m, 2H), 1.95 (d, 3H), 2.10 (m, 2H), 3.99 (s, 3H), 4.02 (s, 3H), 7.24 (s, 1H).

**2-Chloro-3,4,5,6-tetramethoxybenzaldehyde (6).** According to a general aryl chlorination procedure by Lopez-Alvarado,[22] 2,3,4,5-tetramethoxybenzaldehyde (0.767 g, 3.39 mmol) was dissolved in $CH_2Cl_2$ (10 mL) at room temperature and then $SO_2Cl_2$ (neat, 0.31 mL, 3.7 mmol) was added at room temperature. The reaction was stirred for 1 h and monitored by $^1$H NMR for completion. The reaction was then diluted with $CH_2Cl_2$, washed with brine, dried over $MgSO_4$, filtered, and condensed. The resulting oil was then purified by flash column chromatography (1:4 $Et_2O$:hexanes) to provide **6** (0.861 g, 97%) as a colorless oil. $R_f$ = 0.27 (1:4 $Et_2O$:hexanes). $^1$H NMR ($CDCl_3$): $\delta$ 3.84 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 4.02 (s, 3H), 10.34 (s, 1H).

**(*E*)-3-(3-Chloro-5,6-dimethoxy-1,4-dioxocyclohexa-2,5-dienyl)-2-methylpropenoic Acid (7).** Following the method used for the synthesis of **1**, the Emmons condensation was performed in

refluxing toluene with **6** (0.861 g, 3.30 mmol) to provide ethyl (*E*)-3-(2-chloro-3,4,5,6-trimethoxyphenyl)-2-methylpropenoate (0.559 g, 49%) as a colorless oil following chromatography (1:9 $^{i}Pr_2O$:hexanes). $R_f = 0.29$ (1:4 $Et_2O$:hexanes); *E*:*Z* = 1:0 in refluxing toluene. $^1H$ NMR ($CDCl_3$): $\delta$ 1.34 (t, 3H), 1.78 (d, 3H), 3.69 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 4.26 (q, 2H), 7.42 (q, 1H).

The ethyl ester (0.255 g, 0.740 mmol) was then hydrolyzed (KOH, EtOH) to provide the unsaturated acid (0.222 g, 95%) as a red amorphous solid following flash chromatography (2:3 $Et_2O$:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f = 0.20$ (2:3 $Et_2O$:hexanes 0.5% AcOH). $^1H$ NMR ($CDCl_3$): $\delta$ 1.81 (s, 3H), 3.71 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 7.57 (d, 1H).

The unsaturated acid (0.124 g, 0.391 mmol) was dissolved in acetonitrile (10 mL) at room temperature, then ceric ammonium nitrate (0.970 g, 1.77 mmol) dissolved in water (8 mL) was added at room temperature. The reaction was stirred for 30 min and then extracted with $CH_2Cl_2$. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and condensed. The red oil was then purified by either flash column chromatography (1:1 $Et_2O$:hexanes 0.5% AcOH) or recrystallization from $Et_2O$/hexanes to afford **7** (0.026 g, 22%) as a red solid. $R_f = 0.32$ (1:1 $Et_2O$:hexanes 0.5% AcOH); mp = 183−185 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 1.83 (d, 3H), 4.03 (s, 3H), 4.05 (s, 3H), 7.28 (d, 1H).

**(*E*)-4′-(6-Methyl-2,3,4,5-tetramethoxyphenyl)-3-ethylidenetetrahydrofuran-2-one (8).** NaH (0.210 g, 5.25 mmol) was added to a flame-dried 100 mL 3-neck round-bottom flask connected to a water-jacketed reflux condenser.[20] The flask was purged with argon, and a drying tube was attached to the top. Toluene (30 mL) was added to the flask, followed by 2-diethylphosphono-$\gamma$-butyrolactone (1.83 g, 8.2 mmol) dissolved in toluene (10 mL) at room temperature. The reaction was heated under reflux for 30 min, and the aldehyde (**4**, 0.501 g, 2.09 mmol) was dissolved in toluene (5 mL) and added slowly at reflux. The reaction was heated for another 8 h under reflux before being cooled to room temperature, diluted with ethyl acetate, and washed with brine. The organic layer was dried, filtered, and condensed. The resulting oil was purified via flash column chromatography (1:3 EtOAc:hexanes) to provide **8** (0.429 g, 66%) as a white solid. $R_f = 0.18$ (1:3 EtOAc:hexanes); *E*:*Z* = 20:1 in refluxing toluene; mp = 78−79 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 2.12 (s, 3H), 2.85 (dt, 2H), 3.65 (s, 3H), 3.78 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 4.35 (t, 2H), 7.48 (t, 1H).

**(*E*)-3-(5,6-Dimethoxy-3-methyl-1,4-dioxocyclohexa-2,5-dienyl)-2-methoxyethylpropenoic Acid (9).** According to a modified procedure of King,[17] **8** (0.084 g, 0.27 mmol) was added to a flame-dried 10 mL round-bottom flask under argon and a water-jacketed reflux condenser was attached. Anhydrous MeOH (2 mL) was then added, followed by $H_2SO_4$ (4 drops) and trimethyl orthoformate (0.31 mL, 4.0 mmol) at room temperature. The reaction was then heated under reflux for 12 h, cooled to room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc, washed with saturated brine, dried over $MgSO_4$, filtered, and condensed. The resulting crude product was purified via flash column chromatography (1:3 EtOAc:hexanes) to provide the methyl ester (0.073 g, 76%) as a pale-yellow solid. $R_f$ = 0.25 (1:3 EtOAc:hexanes); mp = 35−37 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 2.02 (s, 3H), 2.47 (t, 2H), 3.17 (s, 3H), 3.37 (t, 2H), 3.69 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 7.49 (s, 1H).

The methyl ester (0.074 g, 0.21 mmol) was hydrolyzed following the method for **1** to provide the unsaturated acid (0.070 g, 100%) as a tan solid following flash chromatography (2:3 $Et_2O$: hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f = 0.16$ (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 97−99 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 2.07 (s, 3H), 2.45 (t, 2H), 3.20 (s, 3H), 3.68 (s, 3H), 3.69 (q, 2H), 3.76 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 7.59 (s, 1H).

The resulting unsaturated acid (0.070 g, 0.21 mmol) was oxidized following the procedure for **1** to provide **9** (0.012 g, 19%) as a red solid following flash chromatography (2:3 $Et_2O$:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f = 0.06$ (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 104−106 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 1.95 (d, 3H), 2.40 (t, 2H), 3.24 (s, 3H), 3.44 (t, 2H), 3.99 (s, 3H), 4.01 (s, 3H), 7.35 (d, 1H).

**(*E*)-*N*-(2-Hydroxyethyl)-3-(6-methyl-2,3,4,5-tetramethoxyphenyl)-2-nonylpropenamide (11).** Dicyclohexylcarbodiimide (0.106 g, 0.514 mmol) was added to a flame-dried 10 mL round-bottom flask under argon, and then $CH_2Cl_2$ (2 mL) was added at room temperature. In a second flame-dried flask under argon, a solution of acid (*E*)-**10** (0.167 g, 0.409 mmol) and 1-hydroxybenztriazole (0.008 g, 0.06 mmol) was prepared using DMF (3 mL) and $CH_2Cl_2$ (1 mL). The acid/HOBt solution was then added and stirred for 2 h. Ethanolamine (0.040 mL, 0.66 mmol) was then added rapidly at room temperature. The reaction was stirred for an additional 12 h, diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and condensed. The resulting white solid, a mixture of dicyclohexylurea, DCC, and product, was first suspended in approximately 5 mL of $CH_2Cl_2$. The suspension was then filtered through a pipet containing a cotton plug, and the pipet was washed two times with 2 mL of $CH_2Cl_2$. The combined fractions were then purified via flash chromatography (1:4 EtOAc:hexanes) to provide two compounds that appeared to be isomers: (*E*)-**11** (0.088 g, 48%, 2:3 EtOAc:hexanes $R_f$ = 0.36) and (*Z*)-**11** (0.063 g, 33%, 2:3 EtOAc:hexanes $R_f = 0.71$, coeluted with DCC), both as colorless oils. (*E*)-**11**: $^1H$ NMR ($CDCl_3$): $\delta$ 0.83 (t, 3H), 1.13 (m, 12H), 1.32 (m, 2H), 2.03 (s, 3H), 2.13 (m, 2H), 2.70 (t, 1H), 3.55 (m, 2H), 3.69 (s, 3H), 3.78 (s, 3H), 3.80 (m, 2H), 3.88 (s, 3H), 3.92 (s, 3H), 6.31 (bs, 1H), 6.92 (s, 1H). (*Z*)-**11**: $^1H$ NMR ($CDCl_3$): $\delta$ 3.19 (s, 3H), 2.14 (m, 2H), 2.42 (m, 2H), 3.68 (m, 1H), 3.75 (s, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 4.07 (m, 1H), 6.64 (s, 1H), 8.53 (d, 1H).

**(*E*)-*N*-(2-Hydroxyethyl)-3-(5,6-dimethoxy-3-methyl-1,4-dioxocyclohexa-2,5-dienyl)-2-nonylpropenamide (*E*-12).** Amide (*E*)-**11** (0.088 g, 0.20 mmol) was added to a flame-dried round-bottom flask and dissolved in EtOAc (7.0 mL). Then AcOH (5 drops) and $HNO_3$ (0.5 mL) were added and the reaction was stirred for 3 h at room temperature. The colorless oil easily dissolved in EtOAc, and the reaction turned orange upon addition of $HNO_3$. The reaction was then diluted with EtOAc (40.0 mL), washed three times with brine, dried over $MgSO_4$, filtered, and condensed to provide an orange oil. The oil was then purified using flash chromatography (1:2−1:1 EtOAc: hexanes) and recrystallized from acetone/hexane to provide (*E*)-**12** (0.037 g, 45%) as a red oil. $R_f = 0.24$ (2:3 EtOAc:hexanes). $^1H$ NMR ($CDCl_3$): $\delta$ 0.84 (t, 3H), 1.17 (m, 12 H), 1.33 (m, 2H), 1.93 (d, 3H), 2.09 (t, 2H), 2.51 (t, 1H), 3.52 (q, 2H), 3.79 (dd, 2H), 3.98 (s, 3H), 4.02 (s, 3H), 6.48 (bs, 1H), 6.53 (s, 1H).

**1,4-Dimethoxy-2-naphthaldehyde (14a).** Following the procedure of Evans et al.,[23] 1,4-naphthoquinone (**13a**, 10.00 g, 63.20 mmol) and Pd/C (10 wt %, 0.994 g) were added to a flame-dried 500 mL round-bottom flask at room temperature under argon. THF (250.0 mL) was then added at room temperature, the reaction vessel was covered in foil, and then was purged with hydrogen gas for 10 min. A balloon filled with $H_2$ was attached and the reaction stirred for 4 h at room temperature. The reaction was then purged with argon before adding NaH (5.66 g, 142 mmol) slowly at 0 °C. After 10 min, dimethyl sulfate (13.0 mL, 137 mmol) was added slowly at 0 °C. The reaction mixture then became too thick to stir, so THF (50 mL) was added. The dark-green mixture was allowed to stir at room temperature for 4 h. The reaction was then filtered through celite, washed with brine, dried over $MgSO_4$, and condensed. The resulting solid was then purified by flash chromatography (EtOAc:hexanes) or recrystallized from $Et_2O$:hexanes to provide 1,4-dimethoxynaphthalene (11.74 g, 99%) as pink needles. $R_f = 0.76$ ($CH_2Cl_2$); mp = 74−78 °C (lit. 84−86 °C).[18] $^1H$ NMR ($CDCl_3$): $\delta$ 3.95 (s, 6H), 6.69 (s, 2H), 7.50 (m, 2H), 8.20 (m, 2H).

Following a modified procedure of Ito et al.,[24] to a flame-dried 50 mL round-bottom flask was added 1,4-dimethoxynaphthalene (1.34 g, 7.12 mmol) dissolved in $CH_2Cl_2$ (10.0 mL) and then cooled to 0 °C under argon. Then $TiCl_4$ (1 M in $CH_2Cl_2$, 8.0 mL, 8.0 mmol) was added slowly at 0 °C followed by α,α-dichloromethyl methyl ether (0.71 mL, 8.0 mmol) at 0 °C. The reaction was stirred at 0 °C for 3 h, poured into water, and stirred for 10 min at room temperature. The reaction was then extracted with EtOAc, washed with saturated brine, dried over $MgSO_4$, filtered, and condensed. The resulting oil was purified using flash chromatography ($CH_2Cl_2$) to provide **27** (1.43 g, 93%) as a white solid that was recrystallized from $Et_2O$:hexanes to provide white needles. $R_f = 0.62$ ($CH_2Cl_2$); mp = 108−109 °C (lit. 120−121 °C).[22] $^1$H NMR ($CDCl_3$): δ 4.01 (s, 3H), 4.08 (s, 3H), 7.11 (s, 1H), 7.62 (m, 2H), 8.23 (m, 2H), 10.56 (s, 1H).

**1,4-Dimethoxy-3-methyl-2-naphthaldehyde (14b).** 1,4-Dimethoxy-2-methylnaphthalene was prepared from **13b** (1.90 g, 9.39 mmol) as described above for **14a** to give 1.490 g (69%) of the product as a white solid that was recrystallized from $Et_2O$/hexanes to provide white needles. $R_f$ = 0.57 (3:7 EtOAc:hexanes); mp = 78−80 °C (lit. 83.5−83.7 °C).[22] $^1$H NMR ($CDCl_3$): δ 2.63 (s, 3H), 3.85 (s, 3H), 4.05 (s, 3H), 7.59 (dt, 2H), 8.14 (dd, 2H).

Compound **14b** was prepared from 1,4-dimethoxy-2-methylnaphthalene (3.54 g, 20.6 mmol) as described above for **14a** to give 4.02 g (97%) of the product as a low melting white solid following flash chromatography (1:19 EtOAc:hexanes). $R_f$ = 0.60 (3:7 EtOAc:hexanes); mp = 29−31 °C (lit. 35.9−36.3 °C).[22] $^1$H NMR ($CDCl_3$): δ 2.43 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 7.45 (dt, 2H), 8.09 (dd, 2H).

**1,3,4-Trimethoxy-2-naphthaldehyde (14c).** 1,2,4-Trimethoxynaphthalene was prepared from **13h** (5.23 g, 33.3 mmol) as described above for **14a** to give 5.19 g (71%) of the product as a red oil that solidified in the freezer. $R_f$ = 0.17 (1:9 EtOAc:hexanes), 0.50 ($CH_2Cl_2$); mp = oil (lit. 38−40 °C).[20] $^1$H NMR ($CDCl_3$): δ 3.91 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.63 (s, 1H), 7.40 (m, 2 H), 8.09 (dd, 2H).

According to the procedure by Syper et al.,[25] 1,2,4-trimethoxynaphthalene (1.07 g, 4.90 mmol) was dissolved in THF (20.0 mL) at 0 °C under argon, and then nBuLi (1.6 M in hexanes, 4.0 mL, 10.0 mmol) was added at 0 °C. The reaction was stirred at 0 °C for 5 h before DMF (0.850 mL, 11.0 mmol) was added at 0 °C. The reaction was stirred for another 30 min at room temperature before quenching with water. The reaction was diluted with ethyl ether and washed with saturated brine. The organic layer was dried over $MgSO_4$, filtered, and condensed. Following purification via column chromatography ($CH_2Cl_2$ to 1:9 EtOAc:$CH_2Cl_2$), pure aldehyde **14c** (1.07 g, 89%) was obtained as a yellow solid. $R_f$ = 0.25 (1:9 EtOAc:hexanes), 0.20 ($CH_2Cl_2$); mp = 43−45 °C (lit. 53 °C d).[23] $^1$H NMR ($CDCl_3$): δ 3.99 (s, 3H), 4.00 (s, 3H), 4.03 (s, 3H), 7.55 (m, 2H), 8.15 (dd, 2H), 10.57 (s, 1H).

**1,4-Dimethoxy-3-methylthio-2-naphthaldehyde (14d).** Pyridinium chlorochromate (PCC, 1.03 g, 4.78 mmol) was added to a flame-dried 250 mL round-bottom flask followed by dry $CH_2Cl_2$ (90 mL) at room temperature under argon. 1,4-Dimethoxy-2-hydroxymethyl-3-methylthionaphthalene, synthesized following the procedure of Flader et al.,[21] (0.514 g, 1.94 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and added slowly at room temperature. The reaction was stirred for a further 12 h at room temperature before being poured into a slurry of florisil, $MgSO_4$, and $CH_2Cl_2$. After stirring, the suspension was filtered through celite and condensed. Purification by flash chromatography (1:9 EtOAc:hexanes) gave **14d** (0.308 g, 1.17 mmol, 62%) as an amorphous yellow solid. $R_f$ = 0.26 (1:9 EtOAc:hexanes). $^1$H NMR ($CDCl_3$): δ 2.47 (s, 3H), 4.01 (s, 3H), 4.04 (s, 3H), 7.62 (m, 2H), 8.13 (d, 1H), 8.21 (d, 1H), 10.70 (s, 1H).

**1,4-Dimethoxy-3-fluoro-2-naphthaldehyde (14e).** Aldehyde **14a** (0.517 g, 2.39 mmol) and MeCN (20 mL) were added to a flame-dried 50 mL round-bottom flask under argon and Selectfluor (1.25 g, 3.37 mmol) was added. The reaction was then heated to reflux for 8 h, then cooled and extracted with EtOAc. The organic layer was washed three times with brine, dried over $MgSO_4$, filtered, and condensed to provide the crude aldehyde as a yellow solid. Following flash chromatography (3:1 $CH_2Cl_2$:hexanes), aldehyde **14e** (0.254 g, 45%) was obtained as a yellow solid. $R_f$ = 0.36 (3:1 $CH_2Cl_2$:hexanes); mp = 69−71 °C. $^1$H NMR ($CDCl_3$): δ 4.07 (s, 3H), 4.09 (d, 3H), 7.54 (t, 1H), 7.66 (t, 1H), 8.18 (m, 2H), 10.54 (s, 1H).

**3-Chloro-1,4-dimethoxy-2-naphthaldehyde (14f).** Following a general aromatic chlorination procedure reported by Lopez-Alvarado,[22] aldehyde **14a** (2.12 g, 9.81 mmol) was dissolved in $CH_2Cl_2$ (15 mL) at room temperature in a flame-dried 50 mL round-bottom flask under argon. Neat $SO_2Cl_2$ (0.92 mL, 11 mmol) was added at room temperature, and the argon line was replaced with a drying tube. After 20 h, the reaction was complete by NMR, and the solution was diluted with $CH_2Cl_2$ (50 mL), washed with brine, dried over $MgSO_4$, and filtered. The resulting solid was purified by flash chromatography (1:1 $CH_2Cl_2$:hexanes) to provide **14f** (1.63 g, 66%) as white needles. $R_f$ = 0.21 (1:1 $CH_2Cl_2$:hexanes); mp = 94−96 °C. $^1$H NMR ($CDCl_3$): δ 3.99 (s, 3H), 4.05 (s, 3H), 7.64 (m, 2H), 8.17 (dd, 2H), 10.61 (s, 1H).

**Ethyl (*E*)-3-(1,4-Dimethoxynaphthalen-2-yl)-2-methylpropenoate (15a).** NaH (0.303 g, 7.59 mmol) was added to a flame-dried 50 mL round-bottom flask connected to a water-jacketed reflux condenser. The flask was purged with argon, and a drying tube was attached to the top of the condenser. Toluene (20 mL) was added to the flask followed by triethyl 2-phosphonopropionate (1.0 mL, 4.6 mmol) at room temperature. The reaction was heated under reflux for 30 min, and aldehyde **14a** (0.542 g, 2.51 mmol) was dissolved in toluene (5 mL) and added slowly at reflux. The reaction was heated for another 8 h under reflux. The reaction was then cooled to room temperature, acidified with 2 M HCl, diluted with ethyl acetate, and washed with brine. The organic layer was dried, filtered, and condensed. The resulting oil was purified via flash column chromatography (1:19 $^i$Pr$_2$O:hexanes) to provide **15a** (0. 554 g, 73%) as a colorless oil. $R_f$ = 0.30 (1:19 $^i$Pr$_2$O:hexanes, 4 developments); *E*:*Z* = 20:1. $^1$H NMR ($CDCl_3$): δ 1.36 (t, 3H), 2.10 (d, 3H), 3.91 (s, 3H), 3.96 (s, 3H), 4.29 (q, 2H), 6.70 (s, 1H), 7.51 (m, 2H), 7.96 (d, 1H), 8.15 (m, 2H).

**Ethyl (*E*)-3-(1,4-Dimethoxy-3-methylnaphthalen-2-yl)-2-methylpropenoate (15b).** Compound **15b** was prepared from **14b** (0.506 g, 2.20 mmol) as described above for **15a** to give 0.541 g (1.42 mmol, 65%) of the product as a colorless oil following flash chromatography (1:19 $^i$Pr$_2$O:hexanes). $R_f$ (*E*)-**15b** = 0.22, (*Z*)-**15b** = 0.15 (1:19 $^i$Pr$_2$O:hexanes, 4 developments); *E*:*Z* = 20:1. (*E*)-**15b**. $^1$H NMR ($CDCl_3$): δ 1.36 (t, 3H), 1.79 (s, 3H), 2.28 (s, 3H), 3.73 (s, 3H), 3.87 (s, 3H), 4.30 (q, 2H), 7.49 (m, 2H), 7.70 (s, 1H), 8.07 (m, 2H).

**Ethyl (*E*)-3-(1,3,4-Trimethoxynaphthalen-2-yl)-2-methylpropenoate (15c).** Compound **15c** was prepared from **14c** (0.330 g, 1.33 mmol) as described above for **15a** to give 0.119 g (27%) of the product as a yellow oil following flash chromatography (1:9 $Et_2O$:hexanes). $R_f$ = (*E*)-**15c** = 0.17, (*Z*)-**15c** = 0.11 (1:19 $^i$Pr$_2$O:hexanes, 4 developments); *E*:*Z* = 11:9 in refluxing toluene. $^1$H NMR ($CDCl_3$): δ 1.36 (t, 3H), 1.87 (d, 3H), 3.75 (s, 3H), 3.87 (s, 3H), 3.98 (s, 3H), 4.29 (q, 2H), 7.47 (m, 2H), 7.73 (d, 1H), 8.09 (m, 2H).

**Ethyl (*E*)-3-(1,4-Dimethoxy-3-methylsulfanylnaphthalen-2-yl)-2-methylpropenoate (15d).** Compound **15d** was prepared from **14d** (0.308 g, 1.17 mmol) as described above for **15a** to give 0.231 g (55%) of the product as an amorphous yellow solid following flash chromatography (1:9 EtOAc:hexanes) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.26 (1:9 EtOAc:hexanes); *E*:*Z* = 7:3. $^1$H NMR ($CDCl_3$): δ 1.37 (t, 3H), 1.82 (s, 3H), 2.37 (s, 3H), 3.72 (s, 3H), 4.00 (s, 3H), 4.30 (q, 2H), 7.54 (m, 2H), 7.86 (s, 1H), 8.10 (m, 2H).

**Ethyl (*E*)-3-(1,4-Dimethoxy-3-fluoronaphthalen-2-yl)-2-methylpropeonoate (15e).** Compound **15e** was prepared from **14e** (0.216 g,

0.922 mmol) as described above for **15a** to give 0.226 g (77%) of the product as a yellow oil following flash chromatography (1:19 $Et_2O$:hexanes). (0.093 g pure *E*, 0.128 g *E*/*Z* mixture). $R_f$ (*E*)-**15e** 0.26, (*Z*)-**15e** = 0.17 (1:19 $Et_2O$:hexanes, 3 developments); *E*:*Z* = 5:1. $^1$H NMR ($CDCl_3$): $\delta$ 1.36 (t, 3H), 1.91 (t, 3H), 3.80 (s, 3H), 4.05 (d, 3H), 4.30 (q, 2H), 7.51 (m, 2H), 7.67 (s, 1H), 8.09 (dd, 1H), 8.14 (dd, 1H).

**Ethyl (*E*)-3-(3-Chloro-1,4-dimethoxynaphthalen-2-yl)-2-methylpropenoate (15f).** Compound **15f** was prepared from **14f** (2.93 g, 11.7 mmol) as described above for **15a** to give 2.56 g (65%) of the product as a yellow solid following flash chromatography (1:19 $Et_2O$:hexanes) and recrystallization from $Et_2O$/hexanes (1.50 g *E*, yellow solid; 0.960 g *E*/*Z* mixture, gold oil; 0.101 g *Z*, gold solid). $R_f$ (*E*)-**15f** = 0.32, (*Z*)-**15f** = 0.24 (1:19 $^i Pr_2O$:hexanes, 4 developments); *E*:*Z* = 15:5; mp = 108−109 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.37 (t, 3H), 1.83 (s, 3H), 3.75 (s, 3H), 3.98 (s, 3H), 4.30 (q, 2H), 7.55 (m, 2H), 7.68 (s, 1H), 8.11 (m, 2H).

**Ethyl (*E*)-3-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)-2-methylpropenoate (15g).** Compound **15g** was prepared from **14g** (0.515 g, 1.75 mmol) as described above for **15a** to give 0.373 g (56%) of the product as a white solid following flash chromatography (1:19 $^i Pr_2O$:hexanes) and recrystallization from $Et_2O$/hexanes (0.314 g *E*; 0.059 g *Z*). $R_f$ (*E*)-**15g** = 0.26, (*Z*)-**15g** = 0.19 (1:19 $^i Pr_2O$: hexanes, 4 developments); *E*:*Z* = 17:3; mp = 102−103 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.37 (t, 3H), 1.81 (d, 3H), 3.74 (s, 3H), 3.97 (s, 3H), 4.31 (q, 2H), 7.56 (m, 2H), 7.65 (d, 1H), 8.11 (m, 2H).

**(*E*)-3-(1,4-Naphthoquinon-2-yl)-2-methylpropenoic acid (16a).** Emmons ester **15a** (0.231 g, 0.769 mmol) was dissolved in EtOH (10 mL), and then KOH (0.40 g, 7.13 mmol) was added to the reaction. The reaction was heated to reflux and stirred at this temperature for 30 min. The reaction was then cooled, acidified, and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and condensed. The resulting acid was then used without further purification in the next step. Alternatively, it can be purified via flash chromatography (1:3 EtOAc:hexanes 0.5% AcOH) or by recrystallization from $Et_2O$/hexanes to provide (*E*)-3-(1,4-dimethoxynaphthalen-2-yl)-2-methylpropenoic acid (0.175 g, 83%) as a white solid. $R_f$ = 0.24 (1:3 EtOAc:hexanes 0.5% AcOH); mp = 149−155 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.16 (d, 3H), 3.86 (s, 3H), 3.99 (s, 3H), 6.75 (s, 1H), 7.53 (m, 2H), 8.15 (d, 1H), 8.17 (m, 2H).

The crude acid (0.114 g, 0.419 mmol) was dissolved in ethyl acetate (10 mL) at room temperature and then $HNO_3$ (1 mL) and AcOH (3 drops) were added at room temperature. The reaction was stirred at room temperature for 4 h and then diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and condensed. The yellow oil was then purified by either flash column chromatography (2:3 $Et_2O$:hexanes 0.5% AcOH) or recrystallization from $Et_2O$/hexanes to afford **16a** (0.059 g, 58%) as a yellow solid. $R_f$ = 0.43 (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 205 °C d. $^1$H NMR ($CDCl_3$): $\delta$ 2.13 (d, 3H,), 6.99 (s, 1H), 7.79 (m, 3H), 8.11 (m, 2H).

**(*E*)-3-(3-Methyl-1,4-naphthoquinon-2-yl)-2-methylpropenoic Acid (16b).** (*E*)-3-(1,4-Dimethoxy-3-methylnaphthalen-2-yl)-2-methylpropenoic acid was prepared from **15b** (0.176 g, 0.560 mmol) as described above for **16a** to give 0.134 g (83%) of the product as a light-yellow solid following flash chromatography (3:17 acetone:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.20 (1:3 EtOAc:hexanes 0.5% AcOH); mp = 153−155 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.80 (s, 3H), 3.75 (s, 3H), 3.89 (s, 3H), 7.51 (m, 2H), 7.72 (s, 1H), 8.09 (m, 2H).

Compound **16b** was prepared from (*E*)-3-(1,4-dimethoxy-3-methylnaphthalen-2-yl)-2-methylpropenoic acid (0.083 g, 0.29 mmol) as described above for **16a** to give 0.048 g (0.19 mmol, 65%) of the product as a yellow solid following flash chromatography (3:17 acetone:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.30 (2:3 $Et_2O$:hexanes); mp = 195−196 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.81 (bs, 3H), 2.11 (bs, 3H), 7.58 (m, 1H), 7.73 (m, 2H), 8.09 (m, 2H).

**(*E*)-3-(3-Methoxy-1,4-naphthoquinon-2-yl)-2-methylpropenoic Acid (16c).** (*E*)-3-(1,3,4-Trimethoxynaphthalen-2-yl)-2-methylpropenoic acid was prepared from **15c** (0.073 g, 0.22 mmol) as described above for **16a** to give 0.067 g (100%) of the product as a tan solid following flash chromatography (1:3 EtOAc:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.13 (1:3 EtOAc:hexanes 0.5% AcOH); mp = 119−123 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.91 (s, 3H), 3.77 (s, 3H), 3.89 (s, 3H), 3.99 (s, 3H), 7.49 (m, 2H), 7.91 (s, 1H), 8.10 (t, 2H).

Compound **16c** was prepared from (*E*)-3-(1,3,4-trimethoxynaphthalen-2-yl)-2-methylpropenoic acid (0.060 g, 0.20 mmol) as described above for **16a** to give 0.015 g (27%) of the product as a yellow solid following flash chromatography (2:3 $Et_2O$: hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.43 (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 205 °C d. $^1$H NMR ($CDCl_3$): $\delta$ 1.83 (d, 3H), 4.15 (s, 3H), 7.53 (d, 1H), 7.73 (m (5), 2H), 8.08 (m, 2H).

**(*E*)-3-(3-Methylthio-1,4-naphthoquinon-2-yl)-2-methylpropenoic Acid (16d).** (*E*)-3-(1,4-Dimethoxy-3-methylthionaphthalen-2-yl)-2-methylpropenoic acid was prepared from **15d** (0.165 g, 0.476 mmol) as described above for **16a** to give 0.152 g (100%) of the product as an orange solid following flash chromatography (1:3 EtOAc:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.18 (1:3 EtOAc:hexanes 0.5% AcOH). $^1$H NMR ($CDCl_3$): $\delta$ 1.82 (d, 3H), 2.37 (s, 3H), 3.72 (s, 3H), 4.00 (s, 3H), 7.51 (m, 2H), 7.99 (d, 1H), 8.07 (m, 2H).

Compound **16d** was prepared from (*E*)-3-(1,4-dimethoxy-3-methylthionaphthalen-2-yl)-2-methylpropenoic acid (0.180 g, 0.565 mmol) as described above for **16a** to give 0.063 g (38%) of the product as a red fluffy solid following flash chromatography (2:3 $Et_2O$:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.45 (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 195−196 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.81 (d, 3H), 2.58 (s, 3H), 7.56 (d, 1H), 7.72 (m, 2H), 8.09 (m, 2H).

**(*E*)-3-(3-Fluoro-1,4-naphthoquinon-2-yl)-2-methylpropenoic Acid (16e).** (*E*)-3-(1,4-Dimethoxy-3-fluoronaphthalen-2-yl)-2-methylpropenoic acid was prepared from **15e** (0.128 g, 0.402 mmol) as described above for **16a** to give 0.097 g (83%) of the product as a white solid following flash chromatography (1:4 acetone:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.13 (1:4 acetone:hexanes 0.5% AcOH) mp = 157−158.5 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.93 (d, 3H), 3.82 (s, 3H), 4.06 (d, 3H), 7.52 (m, 2H), 7.83 (d, 1H), 8.10 (d,1H), 8.15 (d, 1H). $^{19}$F NMR ($CDCl_3$): $\delta$ −137.38.

(*E*)-3-(1,4-Dimethoxy-3-fluoronaphthalen-2-yl)-2-methylpropenoic acid (0.097 g, 0.33 mmol) was dissolved in ethyl acetate (10 mL) at room temperature and then $HNO_3$ (1 mL) and AcOH (6 drops) are added at room temperature. Silver(II) oxide (0.309 g, 2.49 mmol) was then added, and the reaction was stirred vigorously at room temperature for 1 h. The mixture was filtered through a Pasteur pipet and cotton plug, the plug was washed with ethyl acetate, and the combined organic layers were washed with brine. The organic layer was dried over $MgSO_4$, filtered, and condensed. The yellow oil was then purified by either flash column chromatography (1:1 $Et_2O$: hexanes 0.5% AcOH) or recrystallization from $Et_2O$/hexanes to afford **16e** (0.020 g, 23%) as a yellow solid. $R_f$ = 0.08 (1:4 EtOAc:hexanes 0.5% AcOH); mp = 185−190 °C d. $^1$H NMR ($CDCl_3$): $\delta$ 1.94 (d, 3H), 7.45 (s, 1H), 7.80 (m, 2H), 8.15 (m, 2H). $^1$H NMR (DMSO): $\delta$ 1.83 (d, 3H), 7.15 (s, 1H), 7.91 (m, 2H), 8.06 (m, 2H).

**(*E*)-3-(3-Chloro-1,4-naphthoquinon-2-yl)-2-methylpropenoic Acid (16f).** Emmons ester **15f** (0.959 g, 2.90 mmol) was hydrolyzed as described for **16a** to provide (*E*)-3-(3-chloro-1,4-dimethoxynaphthalen-2-yl)-2-methylpropenoic acid (0.872 g, 98%) as a tan solid following flash chromatography (3:17 acetone:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.08 (3:17 acetone:hexanes 0.5% AcOH); mp = 155−157 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.88 (s, 3H), 3.77 (s, 3H), 3.99 (s, 3H), 7.58 (m, 2H), 7.85 (s, 1H), 8.123 (m, 2H).

Following the procedure for **16e**, (*E*)-3-(3-chloro-1,4-dimethoxynaphthalen-2-yl)-2-methylpropenoic acid (0.146 g, 0.476 mmol) was oxidized to provide **16f** (0.087 g, 0.32 mmol, 67%) as a yellow solid following flash chromatography (2:3 acetone:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.44 (2:3 acetone:hexanes 0.5% AcOH); mp = 229−230 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.87 (d, 3H), 7.45 (d, 1H), 7.79 (m, 2H), 8.13 (m, 1H), 8.19 (m, 1H).

**(*E*)-3-(3-Bromo-1,4-naphthoquinon-2-yl)-2-methylpropenoic Acid (16g).** (*E*)-3-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)-2-methylpropenoic acid was prepared from **15g** (0.314 g, 0.828 mmol) as described above for **16a** to give 0.291 g (100%) of the product as a white solid following recrystallization from $Et_2O$/hexanes. $R_f$ = 0.32 (1:1 $Et_2O$:hexanes 0.5% AcOH); mp = 143−145 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.86 (d, 3H), 3.77 (s, 3H), 3.99 (s, 3H), 7.57 (m, 2H), 7.82 (d, 1H), 8.13 (m, 2H).

Following the procedure for **16e**, (*E*)-3-(3-bromo-1,4-dimethoxynaphthalen-2-yl)-2-methylpropenoic acid (0.291 g, 0.829 mmol) was oxidized to provide **16g** (0.122 g, 46%) as a yellow solid following flash chromatography (1:1 $Et_2O$:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$=0.32 (1:1 $Et_2O$:hexanes 0.5% AcOH); mp = 186−189 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.85 (d, 3H), 7.33 (m, 1H), 7.91 (m, 2H), 8.14 (m, 2H).

**(*E*)-4′-(1,4-dimethoxy-2-methylnaphthalen-2-yl)-3-ethylidenetetrahydrofuran-2-one (20a).** Lactone **20a** was prepared following the procedure for **8** using aldehyde **14b** (0.486 g, 2.11 mmol) to provide 0.629 g (100%) of product as a white solid following flash chromatography (1:4 EtOAc:hexanes) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.32 (1:3 EtOAc:hexanes); *E*:*Z* = 100:0; mp = 105−107 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.37 (s, 3H), 2.92 (dt, 2H), 3.70 (s, 3H), 3.87 (s, 3H), 4.40 (t, 2H), 7.52 (m, 2H), 7.69 (t, 1H), 8.09 (m, 2H).

**(*E*)-4′-(3-Chloro-1,4-dimethoxynaphthalen-2-yl)-3-ethylidenetetrahydrofuran-2-one (20b).** Lactone **20b** was prepared following the procedure for **8** using aldehyde **14f** (0.484 g, 1.94 mmol) to provide 0.311 g (51%) of the product as a colorless oil following flash chromatography (1:9 EtOAc:hexanes). $R_f$ = 0.13 (3:37 EtOAc:hexanes, developed 4×); *E*:*Z* = 9:1. $^1$H NMR ($CDCl_3$): $\delta$ 2.94 (dt, 2H), 3.73 (s, 3H), 3.99 (s, 3H), 4.41 (t, 2H), 7.58 (m, 2H), 7.77 (t, 1H, 3 Hz), 8.12 (m, 2H).

**(*E*)-4′-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)-3-ethylidenetetrahydrofuran-2-one (20c).** Lactone **20c** was prepared following the procedure for **8** using aldehyde **14g** (0.588 g, 1.99 mmol) to provide 0.307 g (42%) of the product as a colorless oil following flash chromatography (3:17 EtOAc:hexanes). $R_f$ = 0.09 (1:9 EtOAc:hexanes); *E*:*Z* = 3:1. $^1$H NMR ($CDCl_3$): $\delta$ 2.92 (dt, 2H, *J* = 3, 7.2 Hz), 3.73 (s, 3H), 3.98 (s, 3H), 4.41 (t, 2H, *J* = 7.2 Hz), 7.59 (m, 2H), 7.74 (t, 1H), 8.12 (m, 2H).

**(*E*)-3-(3-Methyl-1,4-naphthoquinon-2-yl)-2-methoxyethylpropenoic acid (21a).** The methyl ester was prepared from lactone **20a** (0.243 g, 0.815 mmol) following the procedure for **9** to provide 0.249 g (59%) as tan crystals following flash chromatography (1:3 EtOAc:hexanes) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.43 (1:3 EtOAc:hexanes); mp = 64−65 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.28 (s, 3H), 2.55 (t, 2H), 3.07 (s, 3H), 3.37 (t, 2H), 3.75 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 7.48 (m, 2H), 7.71 (s, 1H), 8.07 (m, 2H).

The resulting methyl ester (0.104 g, 0.302 mmol) was hydrolyzed following the procedure for **9** to provide (*E*)-3-(1,4-dimethoxy-3-methylnaphthalen-2-yl)-2-methoxyethylpropenoic acid (0.076 g, 77%) as a tan solid following flash chromatography (1:3 EtOAc:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.10 (1:3 EtOAc:hexanes 0.5% AcOH); mp = 145−148 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.30 (s, 3H), 2.57 (t, 2H), 3.17 (s, 3H), 3.44 (t, 2H), 3.77 (s, 3H), 3.88 (s, 3H), 7.50 (m, 2H), 7.86 (s, 1H), 8.08 (dt, 2H).

Compound **21a** was prepared from (*E*)-3-(1,4-dimethoxy-3-methylnaphthalen-2-yl)-2-methoxyethylpropenoic acid (0.076 g, 0.23 mmol) following the procedure for **9** to provide 0.049 g (70%) of the product as a yellow solid following flash chromatography (2:3 $Et_2O$:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.45 (2:3 $Et_2O$:hexanes 0.5% AcOH); mp = 147−148 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.12 (d, 3H), 2.45 (t, 2H), 3.20 (s, 3H), 3.44 (t, 2H), 7.53 (d, 1H), 7.73 (m, 2H), 8.09 (m, 2H).

**(*E*)-3-(3-Chloro-1,4-naphthoquinon-2-yl)-2-methoxyethylpropenoic Acid (1b).** The methyl ester was prepared from lactone **20b** (0.098 g, 0.30 mmol) following the procedure for **9** to provide 0.064 g (58%) as tan crystals following flash chromatography (1:3 EtOAc:hexanes) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.44 (1:3 EtOAc:hexanes); mp = 61−62 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.59 (t, 2H), 3.12 (s, 3H), 3.39 (t, 2H), 3.78 (s, 3H), 3.39 (s, 3H), 3.98 (s, 3H), 7.55 (m, 2H), 7.68 (s, 1H), 8.10 (m, 2H).

The methyl ester (0.064 g, 0.17 mmol) was hydrolyzed following the procedure for **9** to provide (*E*)-3-(3-chloro-1,4-dimethoxynaphthalen-2-yl)-2-methoxethylpropenoic acid (0.067 g, quantitative) of the product as a tan solid following flash chromatography (1:3 EtOAc:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.12 (1:3 EtOAc:hexanes 0.5% AcOH); mp = 145−146 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.60 (t, 2H), 3.21 (s, 3H), 3.45 (t, 2H), 3.80 (s, 3H), 3.98 (s, 3H), 7.56 (m, 2H), 7.80 (s, 1H), 8.11 (m, 2H).

Compound **21b** was prepared from (*E*)-3-(3-chloro-1,4-dimethoxynaphthalen-2-yl)-2-methoxethylpropenoic acid (0.067 g, 0.19 mmol) as described for **16e** to provide 0.032 g (53%) of the product as a yellow solid following flash chromatography (2:3 acetone:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$=0.48 (2:3 acetone:hexanes 0.5% AcOH); mp=160 °C d. $^1$H NMR ($CDCl_3$): $\delta$ 2.52 (t, 2H), 3.17 (s, 3H), 3.45 (t, 2H), 7.47 (s, 1H), 7.78 (m, 2H), 8.12 (m, 1H), 8.18 (m, 1H).

**(*E*)-3-(3-Bromo-1,4-naphthoquinon-2-yl)-2-methoxyethylpropenoic Acid (21c).** The methyl ester was prepared from lactone **20c** (0.257 g, 0.708 mmol) following the procedure for **9** to provide 0.290 g (100%) of the product as tan crystals following flash chromatography (1:3 EtOAc:hexanes) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.42 (1:3 EtOAc:hexanes); mp = 66−67 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.57 (t, 2H), 3.12 (s, 3H), 3.39 (t, 2H), 3.77 (s, 3H), 3.86 (s, 3H), 3.97 (s, 3H), 7.42 (m, 2H), 7.65 (s, 1H), 8.10 (m, 2H).

The methyl ester (0.179 g, 0.437 mmol) was hydrolyzed following the procedure for **9** to provide (*E*)-3-(3-bromo-1,4-dimethoxynaphthalen-2-yl)-2-methoxyethylpropenoic acid (0.060 g, 35%) of the product as a tan solid following flash chromatography (1:3 EtOAc:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.12 (1:3 EtOAc:hexanes 0.5% AcOH); mp = 158−160 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.57 (t, 3H), 3.27 (s, 3H), 3.45 (t, 3H), 3.79 (s, 3H), 3.98 (s, 3H), 7.57 (m, 2H), 7.72 (s, 1H), 8.12 (m, 2H).

Compound **21c** was prepared from (*E*)-3-(3-bromo-1,4-dimethoxynaphthalen-2-yl)-2-methoxyethylpropenoic acid (0.060 g, 0.15 mmol) as described for **16e** to provide 0.029 g (53%) of the product as a yellow solid following flash chromatography (2:3 acetone:hexanes 0.5% AcOH) and recrystallization from $Et_2O$/hexanes. $R_f$ = 0.45 (2:3 acetone:hexanes 0.5% AcOH); mp = 168−172 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.52 (t, 2H), 3.18 (s, 3H), 3.46 (t, 2H), 7.41 (s, 1H), 7.78 (m, 2H), 8.12 (m, 1H), 8.19 (m, 1H).

**(*E*)-*N*-(2-Hydroxyethyl)-3-(3-chloro-1,4-dioxonaphthoquinon-2-yl)-2-methylpropenamide (23).** Compound **22** (0.117 g, 0.381 mmol) was converted to the hydroxyethylamide prepared as described for **11** to provide 0.110 g (83%) of the intermediate as a white solid following flash chromatography (2:3 EtOAc:hexanes). $R_f$ = 0.38 (1:1 acetone:hexanes); mp = 165−167 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.86 (d, 3H), 2.68 (bs, 1H, OH), 3.60 (q, 2H), 3.75 (s, 3H), 3.84 (t, 2H), 3.98 (s, 3H), 6.42 (bs, 1H, NH), 7.43 (s, 1H), 7.55 (m, 2H), 8.10 (m, 2H).

The dimethoxynaphthalene intermediate (0.050 g, 0.14 mmol) was then oxidized following the procedure for **16e** to provide **23** (0.027 g, 60%) as a yellow solid following flash

chromatography (2:3 EtOAc:hexanes) and recrystallized from acetone/hexane. $R_f = 0.25$ (1:1 acetone:hexanes); mp = 120 °C d. $^1$H NMR ($CDCl_3$): $\delta$ 1.87 (s, 3H), 2.51 (bs, 1H, OH), 3.56 (q, 2H), 3.81 (m, 2H), 6.46 (bs, 1H, NH), 7.03 (s, 1H), 7.77 (m, 2H), 8.10 (m, 1H), 8.17 (m, 1H).

**Ethyl 3-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)-propionate (25).** Following a modified procedure of Clegg et al.,[26] lithium hexamethyldisilazide (LiHMDS, 1 M in THF, 1.5 mL, 1.5 mmol) was added to a flame-dried round-bottom flask containing THF (20 mL) at −78 °C. Ethyl acetate (0.15 mL, 1.5 mmol) was then added slowly at −78 °C and stirred at −78 °C for 30 min. 2-Bromo-3-bromomethyl-1,4-dimethoxynaphthalene (0.415 g, 1.15 mmol) was then dissolved in THF (10 mL) and added at −78 °C, at which point the reaction was allowed to warm to room temperature and then stirred for 4 h. The reaction was monitored by TLC ($CH_2Cl_2$) for disappearance of the less polar starting material. Additional LiHMDS (2.0 mL, 2.0 mmol) and EtOAc (0.70 mL, 0.70 mmol) were added and the reaction was monitored for the disappearance of starting material. When no starting material was present (ca. 10 h), the reaction was poured into water, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and condensed. The product was the purified by column chromatography ($CH_2Cl_2$ to 1:19 EtOAc:$CH_2Cl_2$) to provide **25** (0.361 g, 86%) as a yellow oil. $R_f = 0.43$ ($CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 1.26 (t, 3H), 2.62 (m, 2H), 3.29 (m, 2H), 3.91 (s, 3H), 3.95 (s, 3H), 4.17 (q, 2H), 7.51 (m, 2H), 8.02 (m, 1H), 8.07 (m, 1H).

**3-(3-Bromo-1,4-naphthoquinon-2-yl)-propionic Acid (26).** Compound **25** (0.361 g, 0.983 mmol) was oxidized following the procedure for **16e** to provide ethyl (3-bromo-1,4-naphthoquinon-2-yl)-propionate (0.135 g, 41%) as a yellow solid following recrystallization from acetone/hexanes. $R_f = 0.44$ (1:4 acetone:hexanes); mp = 78−79 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.23 (t, 3H), 2.59 (t, 2H), 3.16 (t, 2H, $J$ = 7.8 Hz), 4.12 (q, 2H), 7.74 (m, 2H), 8.13 (m, 2H).

The resulting ethyl ester (0.108, 0.320 mmol) was dissolved in THF (5 mL) at room temperature and then 2 M HCl (4 mL) was added at room temperature. The homogeneous solution was then stirred vigorously and heated under reflux for 24 h, or until no starting material was observed by TLC (1:4 EtOAc:hexanes). The reaction was then cooled and diluted with EtOAc (30 mL) and then washed 2 times with saturated brine, dried over $MgSO_4$, filtered, and condensed. If any starting ester was still present, the resulting yellow oil was first purified via flash column chromatography (1:4 acetone:hexanes 0 to 0.5% AcOH) followed by recrystallization from $Et_2O$/hexanes to provide **26** (0.077 g, 78%) as fine yellow needles. $R_f = 0.14$ (1:3 EtOAc:hexanes 0.5% AcOH); mp = 156−157 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.65 (t, 2H), 3.15 (m, 2H), 7.74 (m, 2H), 8.13 (m, 2H).

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