# New Tools for Studying Vesicular-Mediated Protein Trafficking: Synthesis and Evaluation of Ilimaquinone Analogs in a Non-Radioisotope-Based Antisecretory Assay

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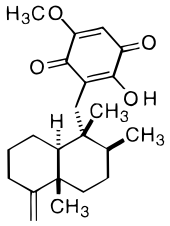
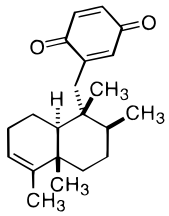
Structural variants of the marine sponge metabolite ilimaquinone, with comparable biological activity, have been prepared. These analogs, as well as related natural products, were screened for their effects on the Golgi apparatus through a novel, non-radioisotope-based secretion assay. The assay has identified a variant of ilimaquinone that contains a versatile linker group yet retains the natural product's cellular activity. This functional ilimaquinone analog will be a valuable tool for studying intracellular protein trafficking.

## Introduction

Ilimaquinone[3] (**1**) and related sesquiterpene quinones, such as avarone[4] (**2**), are reported to have interesting biological effects including antimicrobial, anti-HIV, anti-inflammatory, and antimitotic activity.[5] More recently, ilimaquinone's ability to inhibit the cytotoxicity of ricin and diphtheria toxin,[6] as well as to reversibly disrupt the Golgi apparatus, has also been noted.[7] Considering the proven value of using natural products as probes of cellular processes,[8] our plan is to exploit ilimaquinone's unique activity for the study of intracellular vesicular trafficking.

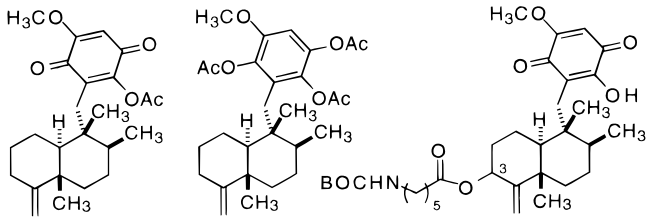


ilimaquinone (**1**)



avarone (**2**)

A crucial element in our plan is the design and preparation of an active variant of ilimaquinone that contains a versatile linker group. Such a compound will allow us to probe vesicular trafficking through a variety of protein isolation techniques including affinity chromatography, photoaffinity labeling, and ligand blotting experiments.[9] In this regard, our studies on the synthesis of (−)-ilimaquinone and related compounds are reported herein. In addition, the development of a novel, non-radioisotope-based antisecretion assay to evaluate the ilimaquinone analogs is also described. The combined synthetic and biochemical effort has allowed for the identification of an active analog possessing the functionality required to study ilimaquinone's role in vesicular trafficking.



**3** **4** **5**

**Figure 1.** Modifications to ilimaquinone.

## Results and Discussion

**Synthesis.** Given that the shortest route to a compound with the functionality required for our studies might be realized through direct modification of ilimaquinone, our initial chemical efforts focused on derivatizing the natural product. This strategy was supported by the fact that several variants of ilimaquinone's quinone moiety have already been reported (Figure 1, **3** and **4**).[3a,5a] Nevertheless, to increase the likelihood of identifying a useful compound, additional analogs were sought. To this end, (−)-ilimaquinone was oxidized with $SeO_2$/*t*-BuOOH to introduce a hydroxyl at the C3 position

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(4) Minale, L.; Riccio, R.; Sodano, G. *Tetrahedron Lett.* **1974**, *38*, 3401.

(5) (a) Loya, S.; Tal, R.; Kashman, Y.; Hizi, A. *Antimicrob. Agents Chemother.* **1990**, *34*, 2009. (b) Kushlan, D. M.; Faulkner, D. J.; Parkanyi, L.; Clardy, J. C. *Tetrahedron* **1989**, *45*, 3307. (c) Bourguet-Kondracki, M.-L.; Longeon, A.; Morel, E.; Guyot, M. *Int. J. Immunopharmacol.* **1991**, *13*, 393. (d) Schröder, H. C.; Wenger, R.; Gerner, H.; Reuter, P.; Kuchino, Y.; Sladic, D.; Müller, W. E. G. *Cancer Res.* **1989**, *49*, 2069. (e) Sarin, P. S.; Sun, D.; Thornton, A.; Müller, W. E. G. *J. Natl. Cancer Inst.* **1987**, *78*, 663. (f) Belisario, M. A.; Maturo, M.; Pecce, R.; De, R. S.; Villani, G. R. D. *Toxicology* **1992**, *72*, 221. (g) Müller, W. E. G.; Dogovic, N.; Zahn, R. K.; Maidhof, A.; Diehl, S. B.; Bedker, C.; Sachsse, W.; Gasic, M. J.; Schroeder, H. C. *Basic Appl. Histochem.* **1985**, *29*, 321.

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(8) (a) Schreiber, S. L.; Albers, M. W.; Brown, E. J. *Acc. Chem. Res.* **1993**, *26*, 412. (b) Schreiber, S. L. *Chem. Eng. News* **1992**, *70* (Oct. 26), 22.

(9) For example, see: (a) Jones, K. *Am. Biotechnol. Lab.* **1990**, *8*, 26. (b) Fretz, H.; Albers, M. W.; Galat, A.; Standaert, R. F.; Lane, W. S.; Burakoff, S. J.; Bierer, B. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 1409. (c) Wilchek, M.; Bayer, E. A. *Methods Enzymol.* **1990**, *184*, 243. (d) Wade, D. P.; Knight, B. L.; Soutar, A. K. *Biochem. J.* **1985**, *229*, 785. (e) Morris, D. I.; Robbins, J. D.; Ruoho, A. E.; Sutkowski, E. M.; Seamon, K. B. *J. Biol. Chem.* **1991**, *266*, 13377. For additional experiments, see: (f) Handschumacher, R. E.; Harding, M. W.; Rice, J.; Drugge, R. J.; Speicher, D. W. *Science* **1984**, *226*, 544. (g) Shen, G. K.; Zukoski, C. F.; Montgomery, D. W. *Int. J. Immunopharmacol.* **1992**, *14*, 63. (h) Siekierka, J. J.; Staruch, M. J.; Hung, S. H.; Sigal, N. H. *J. Immunol.* **1989**, *143*, 1580.

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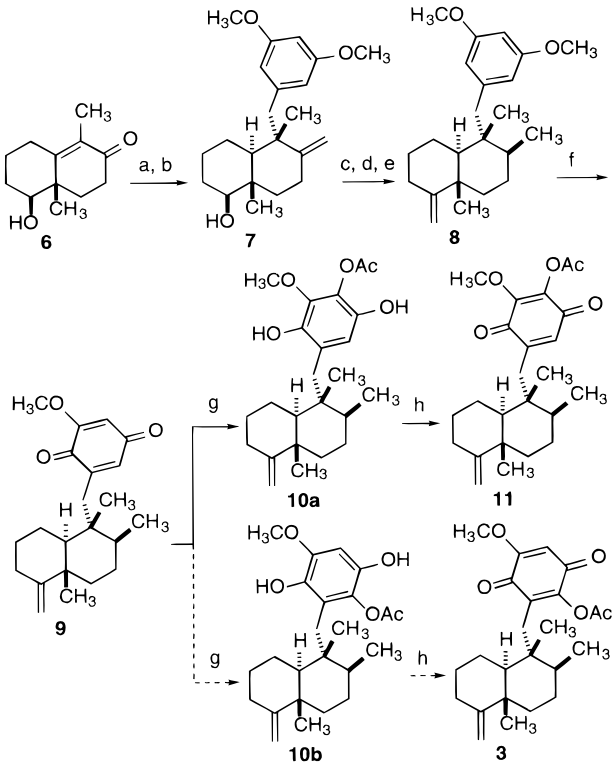
**Scheme 1**[a]



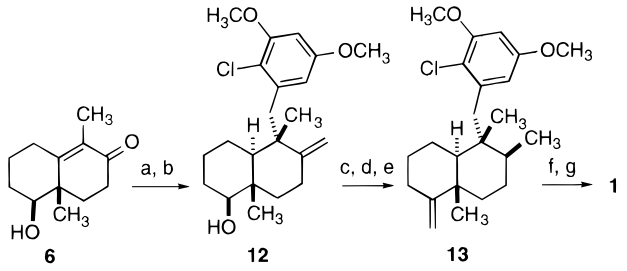

[a] Key: (a) $Li^0$, $NH_3$, 3,5-dimethoxybenzyl bromide (57%); (b) $Ph_3P{=}CH_2$, DMSO (60%); (c) $H_2$, Pd/C (84%); (d) PCC, $CH_2Cl_2$ (94%); (e) $Ph_3P{=}CH_2$, DMSO (71%); (f) $CrO_3$ (68%); (g) AcOH, NaOAc, $H_2O$ (86%); (h) $FeCl_3$, $H_2O$.

(94% yield). The C3 hydroxyl group was then esterified with BOC-protected 6-aminohexanoic acid (84% yield) to provide compound **5**. If active, this variant of ilimaquinone (**5**) with a tethered linker group should be an effective tool for our studies. Unfortunately, our activity assay (see assay results) indicated that **5** retains none of ilimaquinone's influence on protein trafficking (*i.e.*, vesicular-mediated protein secretion). While additional modifications to ilimaquinone are possible, insufficient supplies of the natural product precluded further synthetic investigations.

A more plentiful source of analogs should be available through synthesis from readily available starting materials. Our initial approach to (−)-ilimaquinone, which was modeled after Sarma's preparation of (±)-avarone[10] (**2**), is illustrated in Scheme 1. Unfortunately, reactions to install the necessary quinone functionality did not provide the expected results.[11]

We anticipated that a Thiele−Winter acetoxylation of **9**[12] followed by treatment of the resulting triacetoxyaryl moiety with LAH and mild oxidation would provide (−)-ilimaquinone.[13] Unfortunately, the acetoxylation reaction resulted in low mass recovery which, in part,

**Scheme 2**[a]




[a] Key: (a) $Li^0$, $NH_3$, 2-chloro-3,5-dimethoxybenzyl bromide (75%); (b) $Ph_3P{=}CH_2$, DMSO (71%); (c) $H_2$, $PtO_2$, $CH_2Cl_2$ (60%); (d) PCC, $CH_2Cl_2$ (95%); (e) $Ph_3P{=}CH_2$, DMSO (82%); (f) CAN, $CH_3CN$, $H_2O$ (72%); (g) $Pd(Ph_3P)_4$, THF, $H_2O$, $NaHCO_3$ (33%).

involved a migration of the $\Delta^{4,11}$ olefin.[14] In retrospect, this is not surprising given the strong acidic conditions of the Thiele−Winter acetoxylation ($H_2SO_4$).

When the acidity problem was circumvented by treating **9** with sodium acetate in acetic acid, clean addition of acetate into the quinone system was observed. However, subsequent acetylation of this acetate addition product (**10a**) did not yield compound **3**, an intermediate derived from the natural product. A NOE study of the quinone/aromatic protons in the unidentified product, as well as in compound **9**, indicated that the compound obtained in the acetate addition is **10a**, not the required acetate regioisomer **10b**. Apparently, steric factors override the electronic biases in the addition of an acetate into the quinone functionality of compound **9**.

Fortunately, as reported in a preliminary communication, modifications to the quinone formation strategy provided a synthesis of the desired natural product.[15] The solution is realized through the incorporation of a chlorine onto the dimethoxyaryl moiety (Scheme 2, **6** → **12**). Compound **13** is prepared from **12** in a similar fashion to our initial studies (*cf.* Scheme 1). Interestingly, this dimethoxychloroarene **13** undergoes a regioselective oxidation to an appropriately functionalized chloroquinone which is then hydrolyzed to provide ilimaquinone (**13** → **1**).

This successful pathway to (−)-ilimaquinone can now be altered at various intermediates to yield a series of potentially useful structural analogs. For example, as illustrated in Scheme 3, the preparation of analog **16** originates with the synthetic intermediate **12**. Hydroboration of the $\Delta^{8,13}$ olefin in **12** followed by oxidative workup yields a 2:1 ratio of epimeric hydroxymethyl-containing substrates (**14**:**17**) in 74% yield. Attachment of a linker group to the newly formed C13 hydroxyl group of **14** provides compound **15**. The subsequent steps then follow the reaction sequence developed for the natural product (→**16**). An analogous sequence was carried out on the epimeric hydroxymethyl product (**17** → **19**). In a similar fashion, compound **13** can be stereoselectively hydroborated in 88% yield to provide **20**. After attachment of a linker (**20** → **21**) the quinone functionality is introduced in a straightforward manner to yield ilimaquinone analog **22**.

Efforts were also directed toward the synthesis of avarone (**2**) and related analogs to investigate the role of ilimaquinone's functionality on vesicular trafficking, as well as to determine if related sesquiterpene quinones

(10) (a) Sarma, A. S.; Gayen, A. K. *Tetrahedron Lett.* **1983**, *24*, 3385. (b) Sarma, A. S.; Chattopadhyay, P. *J. Org. Chem.* **1982**, *47*, 1727. (c) Sharma, A. S.; Gayen, A. K. *Tetrahedron* **1985**, *41*, 4581.

(11) For successful preparations of the quinone portion, see: (a) Danheiser, R. L.; Cha, D. D. *Tetrahedron Lett.* **1990**, *31*, 1527. (b) Yadav, J. S.; Upender, V.; Rao, A. V. R. *J. Org. Chem.* **1992**, *57*, 3242. (c) Reinaud, O.; Capdevielle, P.; Maumy, M. *Tetrahedron* **1987**, *43*, 4167.

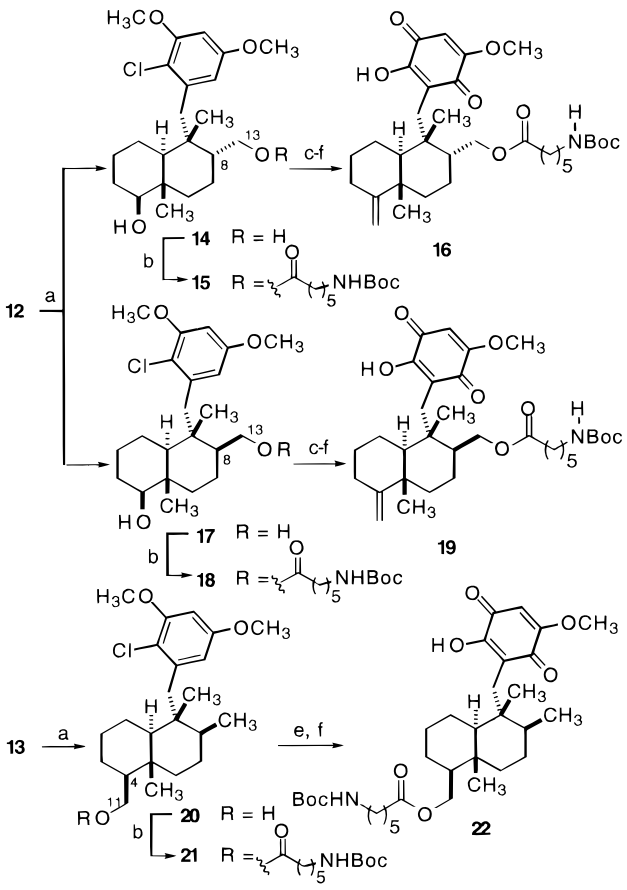
(12) McOmie, J. F. W.; Blatchly, J. M. *Org. React.* **1972**, *19*, 199.

(13) For recent examples of this sequence in related systems, see: (a) Sargent, M. V.; Wangchareontrakul, S. *J. Chem. Soc. Perkin Trans. I* **1990**, 1429. (b) Almeida, W. P.; Correia, C. R. D. *Tetrahedron Lett.* **1994**, *35*, 1367.

(14) Capon, R. J. *J. Nat. Prod.* **1990**, *53*, 753.

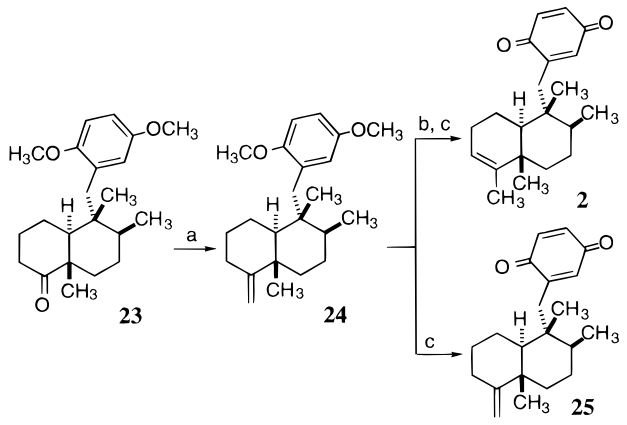
(15) Bruner, S. D.; Radeke, H. S.; Tallarico, J. A.; Snapper, M. L. *J. Org. Chem.* **1995**, *60*, 1114.

**Scheme 3**[a]



[a] Key: (a) $BH_3$·DMS, $H_2O_2$, NaOH; (b) $HO_2C(CH_2)_5NHBOC$, EDCI, DMAP; (c) PCC, $CH_2Cl_2$; (d) $Ph_3P{=}CH_2$, DMSO; (e) CAN, $CH_3CN$, $H_2O$; (f) $Pd(Ph_3P)_4$, THF, $H_2O$, $NaHCO_3$.

**Scheme 4**[a]

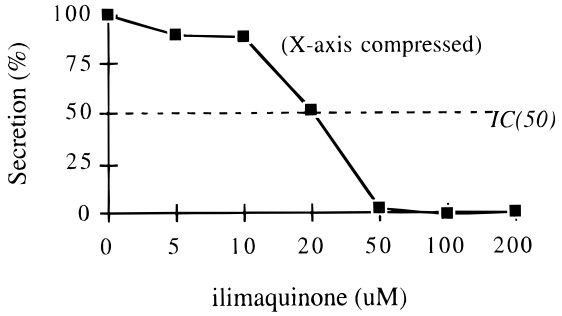


[a] Key: (a) $Ph_3P{=}CH_2$, DMSO (87%); (b) $RhCl_3$·$H_2O$, EtOH, $CHCl_3$ (84%); (c) CAN, $H_2O$, AcOH.

share ilimaquinone's cellular activity. While the preparation of compound **23** (Scheme 4) has been described in Sarma's synthesis of **2**, a shortened, enantioselective route is realized with the sequence illustrated in Scheme 4.[16] The desired natural product (**2**) is prepared through a three-step sequence from **23**. Wittig olefination of **23** yields compound **24**; olefin isomerization[17] of **24** followed by CAN oxidation then delivers avarone (**2**). In a related

(16) Also see: An, J.; Wiemer, D. F. *J. Org. Chem.* **1996**, *61*, 8775.
(17) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc. Perkin Trans. I* **1977**, 359.

**Chart 1. Phosphatase Activity versus Ilimaquinone Concentration ($\mu$M)**




fashion, direct CAN oxidation of compound **24** provides isoavarone (**25**), a hybrid structure comprised of ilimaquinone's decalin system and avarone's quinone functionality.

**Activity Assay.** Since structural modifications may annul ilimaquinone's unique effects on the Golgi apparatus and protein trafficking, an assay to screen structural variants for antisecretory activity is required. A common method for examining the effect of agents on secretory function is through pulse−chase radiolabeling experiments.[18] Choosing to minimize the use of radioactive compounds for safety and environmental reasons, we sought instead to employ an enzymatic assay. Specifically, we adapted a system originally designed in the Crabtree and Schreiber laboratories to study signal transduction events.[19]

In this system a plasmid encoding for secreted alkaline phosphatase (AP) under the control of the interleukin-2 NFAT enhancer region is introduced into Jurkat T-lymphocytes.[20] These transiently transfected cells can then be selectively activated to express and secrete alkaline phosphatase upon treatment with phorbol ester (PMA) and ionomycin. The amount of alkaline phosphatase secreted is determined spectroscopically by measuring AP-catalyzed hydrolysis of *p*-nitrophenyl phosphate. With this secreted reporter gene system, the effects of various compounds on protein secretion can provide a convenient assessment of secretory function.

Chart 1 represents the measured activity of secreted alkaline phosphatase from activated Jurkat cells treated with various concentrations of (−)-ilimaquinone. The lack of cytotoxicity at the ilimaquinone concentrations tested (≤250 $\mu$M) suggests that general inhibition of protein synthesis is not a factor and that these levels of phosphatase activity reflect ilimaquinone's noncytotoxic inhibition of vesicle-mediated trafficking. According to these results, 50% inhibition of AP activity ($IC_{50}$) is observed at 19 $\mu$M (±3 $\mu$M) ilimaquinone.

In a fashion similar to the study with ilimaquinone, other compounds were examined for inhibition of secreted alkaline phosphatase activity. Chart 2 displays the 50% inhibition concentration ($IC_{50}$) for ilimaquinone (**1**), as well as variants of this natural product. The structures of these analogs are illustrated in Figure 2. It is not

(18) For example, see: (a) Ulmer, J. B.; Palade, G. E. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 6992. (b) Misumi, Y.; Misumi, Y.; Miki, K.; Takatsuki, A.; Tamura, G.; Ikehara, Y. *J. Biol. Chem.* **1986**, *261*, 11398. (c) Sampath, D.; Varki, A.; Freeze, H. H. *J. Biol. Chem.* **1992**, *267*, 4440.
(19) Spencer, D. M.; Wandless, T. J.; Schreiber, S. L.; Crabtree, G. R. *Science* **1993**, *262*, 1019.
(20) The Jurkat cells were modified to constituitively express the T-antigen. This allows for replication of the plasmid through its SV40 promoter (Mr. Peter Belshaw, Harvard University).

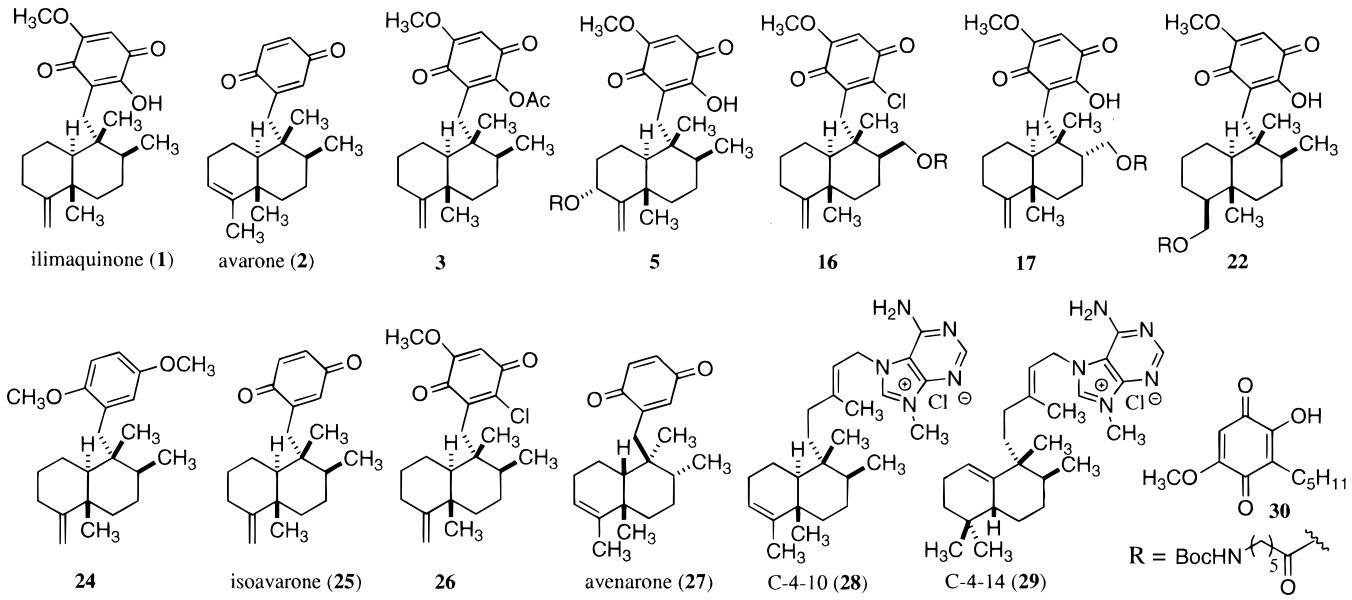
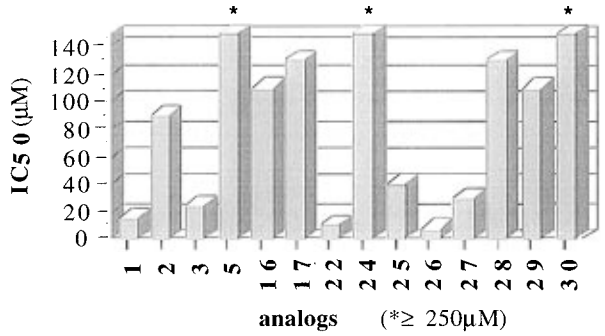



**Figure 2.** Structural variants of ilimaquinone and related natural products.

**Chart 2. Concentrations ($\mu$M) of Analogs Required To Inhibit Alkaline Phosphatase Secretion by 50%**




surprising that two of the more active compounds tested are chloroquinone **26** ($IC_{50}$ 7 $\mu$M) and ilimaquinone monoacetate **3** ($IC_{50}$ 22 $\mu$M), since both of these compounds can readily serve as *in vivo* precursors to ilimaquinone. Because of this possibility, it is unclear whether these variants will lead to useful probes of ilimaquinone's cellular function.

More pertinent to the goal of our studies, however, are the effects of compound **22** ($IC_{50}$ 8 $\mu$M).[21] This analog, with all of ilimaquinone's activity and a protected amine group attached through a tether, can serve well as a versatile tool for studying ilimaquinone's cellular interactions. For example, deprotection of the amine group followed by attachment to biotin, a fluorescing group, or a photoaffinity label will provide useful tools for studying ilimaquinone's cellular effects. In fact, preliminary affinity chromatography experiments with **22** immobilized on a solid support have already yielded selective cellular interactions.[22]

## Conclusions

This work presents three key advancements in a program to decipher ilimaquinone's cellular effects. First, the applicability of total synthesis toward the construction of ilimaquinone structural variants is demonstrated. Second, the development of a non-radioisotope-based secretion assay to identify agents that effect intracellular protein trafficking is described. Finally, the combination of analog syntheses with the employment of a novel secretion assay has identified a tether-containing ilimaquinone analog (**22**) with all the antisecretory activity of the natural product. With this versatile analog in hand, our future studies are directed at isolating and identifying the target responsible for ilimaquinone's cellular activities.

## Experimental Section

**General.** Starting materials and reagents were purchased from commercial suppliers and used without further purification except the following. THF and $Et_2O$ were distilled over sodium and benzophenone under $N_2$. DMSO, $CH_2Cl_2$, and $CH_3CN$ were distilled from $CaH_2$ under $N_2$. Cerium ammonium nitrate (CAN, $(NH_4)_2Ce(NO_3)_6$) was recrystallized from dilute nitric acid. Hexanes and EtOAc were distilled before use.

All oxygen- or moisture-sensitive reactions were carried out under $N_2$ or Ar in oven-dried (140 °C, ≥4 h) glassware. Air- or moisture-sensitive liquids were transferred by syringe or cannula and introduced into the reaction flasks through rubber septa. Air- or moisture-sensitive solids were transferred in a glovebag. Unless otherwise stated, reactions were stirred with a Teflon-covered stir bar and carried out at rt. Concentration refers to the removal of solvent using a Büchi rotatory evaporator at 40−100 Torr followed by use of a vacuum pump at approximately 1 Torr. Silica gel column chromatography was performed using Baxter brand silica gel 60 Å (230−400 Mesh ASTM). The term "brine" refers to saturated NaCl.

Proton nuclear magnetic resonance spectra ($^1$H NMR) were measured at 300 MHz on a Varian Unity-300 instrument or at 400 MHz on a Varian Gemini-400 instrument. Chemical shifts are reported in ppm downfield from tetramethylsilane. Infrared spectra (IR) were measured on a Nicolet 510 FT-IR spectrometer and are reported in wavenumbers ($cm^{-1}$). Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a 1 dm cell. UV−vis absorbances were measured on a Varian Cary 1 E and are reported as $\lambda$ ($\epsilon$), nm.

Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Mass spectral analyses were performed by the Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign.

(21) Analog **22** has also been shown to vesiculate the Golgi apparatus in a manner similar to ilimaquinone (C. Jamora and V. Malhotra, UCSD).

(22) Radeke, H. S.; Bruner, S. D.; Digits, C. A.; Snapper, M. L. Manuscript in preparation.

**(+)-3α-(6-BOC-aminohexanoic acid ester)ilimaquinone (5).** Ilimaquinone (**1**) (5.0 mg, 0.014 mmol) was dissolved in dry $CH_2Cl_2$ (1 mL). $SeO_2$ (0.77 mg, 0.007 mmol) and *t*-BuOOH (3.0 μL, 0.028 mmol, 90% in $H_2O$) were added to the stirring solution. The reaction mixture was stirred for 6 h at 25 °C, upon which it was diluted with 1 mL of saturated $NH_4Cl$. The organic layer was washed with saturated $NH_4Cl$ (3×) and brine, dried over $Na_2SO_4$, filtered through Celite, and concentrated to yield a crude oil. Silica gel chromatography (98:2 $Et_2O$:AcOH) afforded 3-hydroxyilimaquinone (5.0 mg, 94%) as a clear yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.48 (1H, s), 5.86 (1H, s), 4.80 (1H, d, *J* = 1.5 Hz), 4.73 (1H, d, *J* = 1.5 Hz), 4.23 (1H, s), 3.86 (3H, s), 2.59 (1H, d, *J* = 13.6 Hz), 2.48 (1H, d, *J* = 13.7 Hz), 2.00 (1H, d, *J* = 11.9 Hz), 1.81−1.58 (4H, m), 1.38 (2H, m), 1.25 (6H, s), 0.98 (3H, d, *J* = 6.4 Hz), 0.88 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 181.4, 179.8, 162.7, 159.8, 150.1, 128.8, 101.3, 99.4, 55.5, 50.0, 48.7, 44.1, 41.5, 38.1, 37.9, 31.2, 30.5, 28.6, 27.7, 26.0, 22.2, 18.5; IR (thin film, NaCl) 3436, 2925, 2855, 1653, 1644, 1611, 1456, 1378, 1351, 1260, 1238, 1094, 1039 cm$^{-1}$; HRMS calcd for $C_{22}H_{30}O_5$ 374.2090, found 374.2093; MS (70 eV) *m*/*z* (rel int) 374($M^+$, 4), 356(5), 319(3), 295(3), 281(3), 221(6), 205(7), 189(55), 168(100), 147(13), 133(18), 119(29), 95(47), 83(37), 69(53), 57(62); [α]$^{25}_D$ = −15 (*c* 0.1, $CHCl_3$).

The 3-hydroxyilimaquinone (5 mg, 0.014 mmol) was dissolved in $CH_2Cl_2$ (1 mL). DMAP (2.7 mg, 0.014 mmol), 6-BOC-aminohexanoic acid (3.2 mg, 0.014 mmol), and EDCI (2.7 mg, 0.014 mmol) were added to the stirring solution. The reaction mixture was allowed to stir for 2 days, the reaction quenched with $Et_2O/H_2O$, and the mixture acidified with AcOH. The organic solution was separated, washed with saturated $NH_4Cl$ and brine, and dried over $Na_2SO_4$. The crude mixture of product and starting material was purified by using silica gel chromatography (gradient of hexanes, $Et_2O$, and AcOH) to yield **5** (1.7 mg, 84% yield at 75% conversion): $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.49 (1H, s), 5.86 (1H, s), 4.96 (1H, d, *J* = 1.4 Hz), 4.80 (1H, d, *J* = 1.5 Hz), 4.73 (1H, d, *J* = 1.3 Hz), 4.55 (1H, br s), 3.86 (3H, s), 3.12 (2H, dt, *J* = 6.8, 7.3 Hz), 2.59 (1H, d, *J* = 13.7 Hz), 2.48 (1H, d, *J* = 13.9 Hz), 2.36 (2H, t, *J* = 7.5 Hz), 1.99 (2H, d, *J* = 10.8 Hz), 1.80 (2H, d, *J* = 10.8 Hz), 1.67−1.52 (9H, m), 1.43 (9H, s), 1.24 (3H, s), 0.98 (3H, d, *J* = 6.2 Hz), 0.88 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 183.7, 181.2, 174.3, 161.1, 159.0, 153.7, 142.2, 113.8, 107.7, 100.2, 79.7, 67.9, 66.6, 56.6, 56.0, 53.8, 50.0, 46.1, 43.1, 39.6, 39.3, 37.3, 35.9, 34.4, 29.6, 28.2, 26.3, 22.2, 24.2, 17.8, 14.8; IR (thin film, NaCl)-3351, 2926, 2855, 1713, 1698, 1650, 1608, 1557, 1538, 1505, 1456, 1261, 1166 cm$^{-1}$; HRMS calcd for $C_{33}H_{50}NO_8$ 588.3536, found 588.3537; MS (70 eV) *m*/*z* (rel int) 588($M^+$, <1), 477(<1), 374(7), 356(6), 319(6), 207(5), 189(64), 168(100), 140(12), 119(26), 59(26); [α]$^{25}_D$ = +70 (*c* 0.1, $CHCl_3$).

**(+)-*trans*-Octahydro-1α-[(3,5-dimethoxyphenyl)methyl]-1*β*,4a*β*-dimethyl-5α-hydroxy-2(1*H*)-naphthalenone (6a).** Liquid $NH_3$ (100 mL) was distilled from a flask containing $Li^0$ into a 250 mL two-neck round bottom flask equipped with a dry ice condenser. $Li^0$ (0.212 g, 30.5 mmol) was added to the $NH_3$, and the resulting blue solution was refluxed for 30 min. The keto alcohol **6** (1.49 g, 7.5 mmol), dissolved in THF (10 mL), was added dropwise over 30 min to the blue solution. After the addition was complete, the reaction mixture was refluxed for an additional 30 min. 2,5-Dimethoxybenzyl bromide (17.0 g, 73.0 mmol) dissolved in THF (15 mL) was added to the stirring solution quickly. The white slurry stirred for 30 min followed by addition of saturated $NH_4Cl$ (50 mL) and dilution with $Et_2O$ (150 mL). The dry ice condenser was replaced with a water condenser, and the $NH_3$ was allowed to evaporate. $Et_2O$ and HCl (5% aq) were added to the remaining crude solid, the layers were separated, and the aq layer was extracted with $Et_2O$ (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting orange oil was purified by silica gel chromatography (4:1 hexane:EtOAc) to afford **6a** (1.58 g, 57%) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) δ 6.30 (1H, s), 6.21 (2H, s), 3.74 (6H, s), 3.42 (1H, d, *J* = 8.2 Hz), 3.32 (1H, d, *J* = 13.6 Hz), 3.05 (1H, dd, *J* = 10.2, 5.0 Hz), 2.84 (1H, br s), 2.68 (1H, d, *J* = 13.0 Hz), 2.51 (1H, ddd, *J* = 18.6, 12.0, 7.2 Hz), 2.44 (1H, dd, *J* = 9.3, 5.1 Hz), 2.38 (1H, d, *J* = 13.6 Hz), 2.30 (1H, ddd, *J* = 17.4, 5.9, 2.6 Hz), 1.98 (1H, ddd, *J* = 13.3, 6.3, 2.2 Hz), 1.67 (2H, m), 1.34−1.22 (4H, m), 1.12 (3H, s), 0.96 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 216.3, 160.3, 141.1, 121.1, 108.4, 108.2, 98.3, 79.3, 55.0, 45.2, 43.8, 35.1, 34.1, 30.1, 24.0, 23.2, 22.6, 11.5; IR (thin film, NaCl) 3484, 2949, 2867, 2842, 1703, 1665, 1602, 1457, 1425, 1319, 1205, 1148, 1067 cm$^{-1}$; [α]$^{25}_D$ = +15 (*c* 5.0, EtOAc). Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.80; H, 8.73.

**(+)-*trans*-Octahydro-1α-[(3,5-dimethoxyphenyl)methyl]-1*β*,4a*β*-dimethyl-5*β*-hydroxy-2(1*H*)-naphthalene (7).** Sodium hydride (60% oil dispersion; 2.8 g, 0.070 mol) was washed with several portions of anhydrous $Et_2O$ to remove the mineral oil. The flask was purged with $N_2$ after each washing. The system was then equipped with a rubber septum, a reflux condenser, and a magnetic stir bar. Dry DMSO (56 mL) was introduced, and the reaction mixture was heated at 75 °C for 1 h. The resulting aqua blue methylsulfinyl carbanion was cooled to 0−5 °C. $CH_3PPh_3Br$ (32.2 g, 0.09 mol) in warm DMSO (152 mL) was added through a cannula. The resulting dark yellow solution of the methyltriphenylphosphorane ($Ph_3PCH_2$) was stirred at 25 °C for 1 h before being used.

$Ph_3PCH_2$ (63 mL, 0.4 M, 28 mmol) was transferred with a cannula into a two-neck round bottom flask fitted with a water condenser and a Schlenk adapter. The ketone **6a** (0.95 g, 2.8 mmol) was added dropwise to the ylide at rt. Upon completion of addition, the solution was stirred at 75 °C for 4 h and monitored by TLC (1:1 hexane:EtOAc). The reaction was quenched with $NH_4Cl$ (20 mL), and the aq layer was extracted with $Et_2O$ (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (4:1 hexane:EtOAc) to yield compound **7** (510 mg, 60%) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) δ 6.31 (3H, s), 4.89 (1H, s), 4.64 (1H, s), 3.74 (6H, s), 3.18 (1H, dd, *J* = 10.2, 5.0 Hz), 2.73 (1H, d, *J* = 13.6 Hz), 2.56 (1H, d, *J* = 13.6 Hz), 2.24 (2H, m), 1.75 (1H, dt, *J* = 12.5, 2.9 Hz), 1.60 (2H, m), 1.51 (2H, m), 1.39−1.17 (3H, m), 0.99 (3H, s), 0.91 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 160.4, 153.7, 141.7, 109.7, 109.4, 98.5, 81.5, 55.8, 47.7, 47.5, 43.7, 39.8, 38.1, 31.0, 29.7, 24.8, 23.4, 15.3 cm$^{-1}$; IR (thin film, NaCl) 3434, 2935, 2862, 1596, 1460, 1428, 1344, 1321, 1293, 1151; [α]$^{25}_D$ = +18 (*c* 3.5, EtOAc). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.41; H, 9.13.

**(+)-*trans*-Octahydro-5α-[(3,5-dimethoxyphenyl)methyl]-5*β*,6*β*,8a*β*-trimethyl-1*β*-naphthalenol (7c).** Compound **7** (10.0 mg, 0.29 mmol), dissolved in $CH_2Cl_2$ (0.5 mL), was syringed into a flask containing $PtO_2$ (61 mg, 0.27 mmol). A Schlenk adapter was fitted with a double balloon. The flask was evacuated and flushed with $N_2$ (3×) and then with $H_2$. Hydrogenation was complete in 2 days as determined by NMR. The solution was filtered through a silica gel plug (3 cm). Silica gel chromatography (4:1 hexane:EtOAc) was used to separate the 13:1 mixture of diastereoisomers to provide the major product **7c** (8.4 mg, 84%): $^1$H NMR ($CDCl_3$, 400 MHz) δ 6.33 (1H, s), 6.26 (2H, s), 3.77 (6H, s), 3.00 (1H, dd, *J* = 10.9, 3.5 Hz), 2.63 (1H, d, *J* = 14.1 Hz), 2.47 (1H, d, *J* = 14.1 Hz), 1.82 (2H, m), 1.61 (3H, m), 1.32 (6H, m), 1.13 (1H, d, *J* = 13.8 Hz), 1.12 (1H, d, *J* = 15.3 Hz), 0.98 (3H, d, *J* = 6.2 Hz), 0.88 (3H, s), 0.80 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 160.0, 141.1, 109.9, 97.7, 80.6, 55.2, 45.8, 43.2, 40.6, 39.4, 36.8, 35.5, 29.9, 26.7, 23.9, 21.6, 17.7, 16.7, 12.6; IR (thin film, NaCl) 3459, 2917, 1596, 1457, 1382, 1287, 1073, 954, 828 cm$^{-1}$; [α]$^{25}_D$ = +2.3 (*c* 1.5, EtOAc). Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.01; H, 10.17.

**(−)-*trans*-Octahydro-5α-[(3,5-dimethoxyphenyl)methyl]-5*β*,6*β*,8a*β*-trimethyl-1(2*H*)-naphthalenone (7d).** Alcohol **7c** (167 mg, 0.482 mmol) dissolved in $CH_2Cl_2$ (5 mL) was added dropwise to a stirring solution of PCC (0.103 g, 0.482 mmol) in $CH_2Cl_2$ (25.0 mL) at 0 °C. The reaction was monitored by TLC (1:1 hexane:EtOAc) for completion, and after 12 h silica gel was added. The reaction mixture was filtered and concentrated. The resulting oil was purified by passing it through a plug of silica gel (1 cm) that was presaturated with $Et_2O$ to afford compound **7d** (152 mg, 92%) as a clear oil: $^1$H NMR ($CDCl_3$, 400 MHz) δ 6.30 (1H, s), 6.20 (2H, s), 3.74 (6H, s), 2.63 (1H, d, *J* = 13.9 Hz), 2.52 (1H, d, *J* = 13.9 Hz), 2.11 (3H, m), 1.81 (4H, dd, *J* = 12.8, 3.0 Hz), 1.35 (5H, m), 1.14 (3H, s),

0.99 (3H, d, $J$ = 7.2 Hz), 0.89 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 216.4, 160.9, 140.9, 123.2, 109.4, 98.1, 55.5, 47.4, 43.7, 42.1, 37.7, 35.5, 32.8, 26.8, 25.8, 22.0, 19.3, 18.3, 16.8; IR (thin film, NaCl) 2962, 1709, 1596, 1596, 1464, 1426, 1187, 1162 cm$^{-1}$; $[\alpha]^{25}_D = -24$ (*c* 1.1, EtOAc). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 77.80; H, 9.24.

**(−)-*trans*-Octahydro-5α-[(3,5-dimethoxyphenyl)methyl]-5*β*,6*β*,8a*β*-trimethyl-1(2*H*)-naphthalene (8).** Compound **7d** (80 mg, 0.23 mmol), dissolved in DMSO (1.0 mL), was added dropwise to $Ph_3PCH_2$ (4.0 mL, 0.4 M, 1.6 mmol). The solution was refluxed at 80 °C for 15 h and monitored by TLC (4:1 hexane:EtOAc). Purification with Ag-impregnated silica gel (17%, w/w) chromatography (98:2 hexanes:EtOAc) afforded compound **8** as a clear oil (57 mg, 71%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.31 (1H, s), 6.25 (2H, s), 4.41 (1H, t, $J$ = 1.4 Hz), 4.39 (1H, t, $J$ = 1.7 Hz), 3.76 (6H, s), 2.64 (1H, d, $J$ = 13.6 Hz), 2.46 (1H, d, $J$ = 13.6 Hz), 2.32 (2H, td, $J$ = 13.8, 5.0 Hz), 2.09 (1H, d, $J$ = 11.8 Hz), 1.95 (2H, m), 1.59 (1H, qd, $J$ = 13.7, 3.2 Hz), 1.50−1.29 (2H, m), 1.06 (3H, s), 0.99 (3H, d, $J$ = 5.7 Hz), 0.83 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 160.1, 160.7, 141.8, 109.5, 103.5, 98.4, 55.9, 48.1, 44.1, 42.2, 40.8, 37.3, 36.4, 33.7, 28.7, 28.0, 23.5, 21.4, 18.4, 17.8; IR (thin film, NaCl) 2924, 2861, 1585, 1457, 1426, 1211, 1155, 1067, 897, 834 cm$^{-1}$; $[\alpha]^{25}_D = -40$ (*c* 0.1, EtOAc). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.46; H, 9.62.

**(−)-2-Methoxy-6-[(*trans*-octahydro-5*β*,6*β*,8a*β*-trimethyl-1(2*H*)-naphthalenyl)methyl]-2,5-cyclohexadiene-1,4-dione (9).** $CrO_3$ (36.0 mg, 0.36 mmol) dissolved in $H_2O$ (100 $\mu$L) and AcOH (600 $\mu$L) was added dropwise to compound **8** (36.3 mg, 0.114 mmol) in AcOH (600 $\mu$L) at 0 °C. The reaction mixture was monitored by TLC (4:1 hexanes:EtOAc). After 30 min, ice water was added, and the aq layer was extracted with EtOAc (7×). The combined organic layers were washed with (saturated) $NH_4Cl$, dried over $MgSO_4$, filtered, and concentrated. Purification through silica gel chromatography (4:1 hexanes:EtOAc) afforded compound **9** (21.0 mg, 68%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.38 (1H, d, $J$ = 4.0 Hz), 5.87 (1H, d, $J$ = 4.0 Hz), 4.43 (1H, t, $J$ = 2.5 Hz), 4.47 (1H, t, $J$ = 1.9 Hz), 3.81 (3H, s), 2.56 (1H, d, $J$ = 13.5 Hz), 2.4 (1H, d, $J$ = 13.5 Hz), 2.30 (2H, td, $J$ = 16.0, 4.0 Hz), 2.09 (2H, d, $J$ = 12.1 Hz), 1.88 (2H, d, $J$ = 12.1 Hz), 1.54 (2H, d, $J$ = 11.0 Hz), 1.41−1.14 (4H, m), 1.05 (3H, s), 0.94 (3H, d, $J$ = 6.6 Hz), 0.88 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 209.9, 196.3, 160.7, 145.8, 137.7, 122.1, 108.0, 104.1, 57.3, 50.1, 43.8, 41.3, 38.1, 37.7, 36.0, 33.8, 29.0, 28.4, 23.6, 21.6, 18.7, 17.8; IR (thin film, NaCl) 2936, 1678, 1646, 1596, 1457, 1388, 1325, 1224, 1055, 897 cm$^{-1}$; HRMS calcd for $C_{22}H_{30}O_3$ 342.2195, found 342.2180; MS (70 eV) *m*/*z* (rel int) 342(6, M$^+$), 191(37), 175(12), 151(51), 135(22), 108(28), 95(100), 79(27); $[\alpha]^{25}_D = -15$ (*c* 2.0, EtOAc).

**(−)-3-Acetyl-6-[(*trans*-decahydro-5*β*,6*β*,8a*β*-trimethyl-1(2*H*)-naphthalenyl)methyl]-2-methoxyhydroquinone (10a).** Quinone **9** (8.0 mg, 0.048 mmol) was dissolved in AcOH (400 $\mu$L) saturated with NaOAc. The reaction mixture was stirred at rt under $N_2$ and monitored by TLC (6:4 hexanes: EtOAc, product $R_f$ = 0.57) for consumption of quinone. After 7 days, the reaction mixture was diluted with $Et_2O$ (1 mL) and $H_2O$ (1 mL), and the reaction was quenched with saturated $NH_4Cl$ (1 mL) and 5% citric acid. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. Purification through silica gel chromatography (3:2 hexanes: EtOAc) provided compound **10a** as a clear oil (6.0 mg, 86%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.4 (1H, s), 5.54 (1H, s), 5.30 (1H, s), 4.42 (2H, t, $J$ = 1.9 Hz), 4.38 (1H, t, $J$ = 1.3 Hz), 3.87 (3H, s), 2.64 (1H, d, $J$ = 14.3 Hz), 2.47 (1H, d, $J$ = 14.5 Hz), 2.32 (3H, s), 2.04 (3H, t, $J$ = 5.9 Hz), 1.85 (2H, m), 1.81 (2H, d, $J$ = 1.5 Hz), 1.46 (1H, d, $J$ = 13.0 Hz), 1.40 (1H, d, $J$ = 8.1 Hz), 1.25 (2H, m), 1.04 (3H, s), 0.97 (3H, d, $J$ = 5.7 Hz), 0.87 (1H, m), 0.82 (3H, s); $^{13}$C NMR ($CDCl_3$, 400 MHz) $\delta$ 175.4, 160.6, 135.8, 120.7, 117.5, 103.2, 61.7, 48.7, 42.4, 40.7, 37.2, 37.1, 36.7, 33.5, 30.1, 28.8, 28.2, 23.4, 21.4, 21.1, 18.1, 17.9; IR (thin film, NaCl) 3427, 2936, 2856, 1772, 1659, 1514, 1464, 1376, 1332, 1193, 1332, 1056, 1023, 973, 891 cm$^{-1}$; HRMS calcd for $C_{24}H_{34}O_5$ 402.2406, found 402.2406; MS (70 eV) *m*/*z* (rel int) 402(12, M$^+$), 360(7), 212(66), 191(26), 170(100), 135(15), 121(20), 95(59), 79(13), 67(11).

**(−)-*trans*-Octahydro-5α-[(2-chloro-3,5-dimethoxyphenyl)methyl]-5*β*,8a*β*-dimethyl-6*β*-(hydroxymethyl)-1-naphthalenol (17).** Olefin **12** (616 mg, 1.63 mmol) dissolved in THF (5 mL) was cooled to 0 °C. $BH_3$·$SMe_2$ (0.96 mL, 10 M, 8.8 mmol) was added dropwise to the cooled solution over 30 min. Once the borane addition was complete, the reaction mixture was heated to reflux. After 3 h the reaction mixture was allowed to cool to rt. $H_2O$ (2.5 mL) and EtOH (10 mL) were added; then after 30 min $H_2O_2$ (30%, 3.4 mL) and NaOH (39 mL, 1 M) were added. After an additional 1 h, $K_2CO_3$ (100 mg) was added. The reaction mixture was washed with $Et_2O$ (3×), and the organic layer was dried over $Na_2SO_4$ and concentrated. The diastereomers were separated by silica gel chromatography (3:2 hexanes:EtOAc) to provide **14** and **17** in an overall yield of 74% (**14**:**17** = 2:1).

**17**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.42 (1H, d, $J$ = 2.7 Hz), 6.33 (1H, d, $J$ = 2.7 Hz), 4.13 (1H, d, $J$ = 11.4 Hz), 3.87 (3H, d, $J$ = 1.2 Hz), 3.80 (3H, d, $J$ = 1.2 Hz), 3.23 (1H, dd, $J$ = 10.3, 5.3 Hz), 3.06 (1H, d, $J$ = 10.5 Hz), 2.93 (1H, d, $J$ = 13.7 Hz), 2.75 (1H, d, $J$ = 14.1 Hz), 1.92−1.65 (6H, m), 1.51−1.17 (7H, m), 1.07 (1H, d, $J$ = 11.5 Hz), 0.93 (3H, s), 0.84 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 158.5, 156.4, 139.4, 109.8, 98.6, 81.1, 66.1, 56.7, 56.1, 47.7, 45.7, 41.9, 41.7, 40.1, 36.5, 30.6, 24.4, 22.9, 22.3, 18.6, 13.2, 13.1; IR (thin film, NaCl) 3404, 2936, 2863, 1591, 1453, 1415, 1202, 1163 cm$^{-1}$; MS (70 eV) *m*/*z* (rel int) 398(7, M$^{2+}$), 396(16, M$^+$), 359(3), 314(4), 290(6), 270(3), 251(4), 193(25), 186(100), 175(30), 163(14), 151(14), 133(25), 119(27), 109(58), 95(65), 81(83), 67(54), 55(84), 41(78); $[\alpha]^{25}_D = -9.8$ (*c* 12.0, $CHCl_3$).

**14**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.59 (1H, d, $J$ = 2.6 Hz), 6.35 (1H, d, $J$ = 2.6 Hz), 4.02 (1H, dd, $J$ = 9.9, 3.3 Hz), 3.81 (3H, s), 3.74 (3H, s), 3.18 (1H, d, $J$ = 13.9 Hz), 3.15 (1H, dd, $J$ = 10.9, 4.1 Hz), 2.36 (1H, d, $J$ = 13.9 Hz), 2.26 (2H, br s), 1.73−1.66 (3H, m), 1.56 (2H, m), 1.59−1.33 (5H, m), 0.92 (3H, s), 0.91 (3H, s) (partial); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 158.6, 156.2, 140.0, 109.7, 108.3, 98.0, 81.6, 62.1, 56.7, 56.0, 47.6, 44.9, 40.9, 40.4, 39.1, 32.5, 30.7, 24.8, 22.2, 21.1, 19.5, 15.3; IR (thin film, NaCl) 3400, 2960, 2872, 1596, 1458, 1344, 1208, 1162, 1041, 932, 748 cm$^{-1}$; MS (70 eV) *m*/*z* (rel int) 398(2, M$^{2+}$), 396(7, M$^+$), 362(1), 221(1), 211(5), 205(24), 193(28), 186(100), 175(32), 163(8), 152(25), 133(12), 121(18), 109(31), 95(26), 81(30), 69(18), 55(29), 43(22); $[\alpha]^{25}_D = +7.7$ (*c* 19.0, $CHCl_3$).

**(+)-*trans*-Decahydro-5α-[(2-chloro-3,5-dimethoxyphenyl)methyl]-5*β*,8a*β*-dimethyl-6*β*-(hydroxymethyl)-1*β*-naphthalenol 6-(*N*-*t*-BOC-amino)hexanoate (18).** Alcohol **17** (165 mg, 0.42 mmol), 6-(*N*-*t*-BOC-amino)hexanoic acid (96 mg, 0.42 mmol), and DMAP (61 mg, 0.50 mmol) were placed in a flask and cooled (0−5 °C). EDCI (120 mg, 0.63 mmol) dissolved in $CH_2Cl_2$ (4.5 mL) was then added dropwise to the flask. The reaction mixture was stirred for 2 h at 0 °C and then allowed to warm to 25 °C. After 12 h the reaction mixture was quenched with saturated $NH_4Cl$. The aqueous layer was washed (2×) with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The crude product was purified by silica gel chromatography (7:3 hexanes:EtOAc) to yield ester **18** (169 mg, 66%) as a clear yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.41 (1H, d, $J$ = 2.6 Hz), 6.31 (1H, d, $J$ = 2.7 Hz), 4.56 (1H, s), 4.42 (1H, dd, $J$ = 10.4, 2.2 Hz), 3.87 (2H, m), 3.86 (3H, s), 3.78 (3H, s), 3.11 (2H, dt, $J$ = 6.6, 6.2 Hz), 3.05 (1H, dd, $J$ = 10.8, 4.0 Hz), 2.90 (1H, d, $J$ = 14.3 Hz), 2.78 (1H, d, $J$ = 14.3 Hz), 2.30 (2H, t, $J$ = 7.5 Hz), 1.81−1.47 (11H, m), 1.43 (9H, s), 1.35 (4H, m), 1.07 (2H, d, $J$ = 9.7 Hz), 0.92 (3H, s), 0.90 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 174.7, 158.2, 156.6, 156.5, 139.1, 116.7, 109.6, 98.6, 81.2, 68.1, 56.9, 56.2, 47.8, 42.2, 41.7, 41.6, 41.1, 41.0, 40.1, 36.3, 34.9, 30.7, 30.5, 29.1, 27.0, 25.4, 24.5, 23.1, 22.5, 18.9, 13.1; IR (thin film, NaCl) 3403, 2937, 2865, 1730, 1727, 1707, 1692, 1590, 1454, 1201, 1166 cm$^{-1}$; HRMS calcd for $C_{33}H_{51}NO_7Cl$ 608.3354, found 608.3352; MS (70 eV) *m*/*z* (rel int) 610(42, M$^{2+}$), 608(5, M$^+$), 553(88), 555(51), 517(100), 499(71), 472(59), 458(64), 406(25), 192(30), 132(18), 91(23); $[\alpha]^{25}_D = +18$ (*c* 11.0, $CHCl_3$).

**(−)-*trans*-Octahydro-5α-[(2-chloro-3,5-dimethoxyphenyl)methyl]-6*β*,8a*β*-dimethyl-6α-(hydroxymethyl)-1*β*-naphthalenol 6-(*N*-*t*-BOC-amino)hexanoate (15b):** see compound **18** for similar experimental; $^1$H NMR ($CDCl_3$, 300

MHz) δ 6.52 (1H, d, *J* = 2.7 Hz), 6.35 (1H, d, *J* = 2.7 Hz), 4.65 (1H, br s), 4.55 (1H, dd, *J* = 11.2, 4.2 Hz), 4.23 (1H, t, *J* = 10.3 Hz), 3.81 (3H, s), 3.74 (3H, s), 3.25 (1H, d, *J* = 14.4 Hz), 3.20 (1H, dd, *J* = 11.2, 4.2 Hz), 3.06 (2H, dt, *J* = 6.5, 6.4 Hz), 2.32 (2H, t, *J* = 6.8 Hz), 2.29 (1H, d, *J* = 14.6 Hz), 1.94 (2H, dd, *J* = 8.8, 3.7 Hz), 1.63−1.44 (9H, m), 1.39 (9H, s), 1.35−1.22 (7H, m), 0.94 (3H, s), 0.90 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 174.2, 158.8, 156.4, 139.6, 116.9, 108.1, 98.4, 81.4, 64.5, 56.8, 56.1, 47.5, 41.5, 41.0, 40.6, 39.0, 34.9, 32.2, 30.8, 30.6, 30.2, 29.1, 28.4, 26.9, 25.3, 22.4, 22.2, 20.8, 19.9, 15.3; IR (thin film, NaCl) 3327, 2924, 2848, 1734, 1652, 1552, 1451, 1262, 1155 cm$^{-1}$; [α]$^{25}_D$ = −20 (*c* 2.0, $CHCl_3$).

**(−)-*trans*-Octahydro-5α-[(2-chloro-3,5-dimethoxyphenyl)methyl]-5*β*,8a*β*-dimethyl-6*β*-(hydroxymethyl)-1*β*-naphthalenone 6-(*N*-*t*-BOC-amino)hexanoate (18c).** To a stirring solution of PCC (58.8 mg, 0.26 mmol) in $CH_2Cl_2$ (8.8 mL) was added alcohol **18** (107.2 mg, 0.18 mmol) dissolved in $CH_2Cl_2$ (8.8 mL) dropwise. The reaction mixture was stirred for 3 h. The brown mixture was filtered through silica gel, which was prewashed with 1:1 hexanes:EtOAc, to yield the ketone **18c** (104 mg, 97%) as a clear yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 6.40 (1H, d, *J* = 2.6 Hz), 6.26 (1H, d, *J* = 2.7 Hz), 4.56 (1H, br s), 4.41 (1H, dd, *J* = 10.8, 2.4 Hz), 3.86 (2H, m), 3.85 (3H, s), 3.75 (3H, s), 3.11 (2H, dt, *J* = 6.2, 6.0 Hz), 2.89 (1H, d, *J* = 14.4 Hz), 2.83 (1H, d, *J* = 14.5 Hz), 2.60 (1H, dt, *J* = 14.1, 7.1 Hz), 2.31 (2H, t, *J* = 7.5 Hz), 2.2 (1H, dd, *J* = 14.5, 4.8 Hz), 2.05 (2H, m), 1.75 (2H, m), 1.62 (4H, m), 1.51−1.31 (6H, m), 1.43 (9H, s), 1.17 (3H, s), 0.99 (3H, s); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 216.1, 174.7, 158.6, 156.7, 138.4, 116.4, 109.7, 98.4, 79.8, 74.7, 67.6, 56.9, 56.1, 49.7, 48.7, 42.7, 42.1, 41.3, 41.1, 38.0, 34.9, 32.1, 30.5, 29.1, 27.0, 25.9, 25.4, 22.8, 22.6, 19.4, 19.3; IR (thin film, NaCl) 3380, 2932, 2865, 1708, 1577, 1451, 1158 cm$^{-1}$; HRMS calcd for $C_{33}H_{50}NO_7Cl$ 607.3272, found 607.3276; MS (70 eV) *m*/*z* (rel int) 609(6, $M^{2+}$), 607(14, $M^+$), 533(7), 471(9), 377(7), 348(5), 322(84), 191(41), 186(100), 185(29), 173(30), 163(13), 151(13), 149(31), 147(16), 140(11), 135(28), 132(21), 114(20), 107(16), 85(15), 69(25), 57(92), 55(18); [α]$^{25}_D$ = −3.5 (*c* 13.0, $CHCl_3$).

**(+)-*trans*-Octahydro-5α-[(2-chloro-3,5-dimethoxyphenyl)methyl]-5*β*,8a*β*-dimethyl-6α-(hydroxymethyl)-1(2*H*)-naphthalenone 6-(*N*-*t*-BOC-amino)hexanoate (15c):** see compound **18e** for similar experimental; $^1$H NMR ($CDCl_3$, 300 MHz) δ 6.55 (1H, d, *J* = 2.6 Hz), 6.40 (1H, d, *J* = 2.5 Hz), 4.61 (1H, dd, *J* = 11.2, 5.8 Hz), 4.62 (1H, br s), 4.14 (1H, t, *J* = 11.8 Hz), 3.84 (2H, m), 3.78 (3H, s), 3.28 (1H, d, *J* = 14.3 Hz), 3.09 (2H, dt, *J* = 6.1, 6.0 Hz), 2.54 (1H, dd, *J* = 10.0, 6.0 Hz), 2.38 (1H, d, *J* = 14.6 Hz), 2.32 (2H, t, *J* = 7.0 Hz), 2.23 (1H, d, *J* = 14.0 Hz), 2.00 (2H, br s), 1.78−1.56 (10H, m), 1.42 (9H, s), 1.33 (5H, m), 1.33 (3H, s), 0.99 (3H, s); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 215.3, 174.1, 159.0, 156.6, 139.2, 108.2, 98.6, 64.3, 56.8, 56.2, 50.0, 48.2, 42.1, 41.4, 41.1, 39.0, 37.8, 37.7, 34.9, 30.4, 30.3, 29.0, 28.8, 27.5, 27.0, 26.2, 25.2, 22.2, 21.7, 21.1, 19.7; IR (thin film, NaCl) 3300, 2961, 2930, 1734, 1641, 1598, 1353, 1200, 1133 cm$^{-1}$; [α]$^{25}_D$ = +2.6 (*c* 16.0, $CHCl_3$).

**(+)-*trans*-Octahydro-5α-[(2-chloro-3,5-dimethoxyphenyl)methyl]-5*β*,8a*β*-dimethyl-6*β*-(hydroxymethyl)-1(2*H*)-naphthalenyl 6-(*N*-*t*-BOC-amino)hexanoate (18d).** A solution of $Ph_3PCH_2$ (0.4 M, 1.53 mmol, 3.84 mL) was placed in a round bottom flask. Ketone **18c** (103.7 mg, 0.17 mmol) dissolved in DMSO (1.8 mL) was added dropwise to the stirring ylide solution. The reaction mixture was heated to 75 °C for 30 min and then the reaction quenched with saturated $NH_4Cl$. The crude reaction mixture was extracted several times with $Et_2O$ (3×). The combined organic layers were washed with saturated $NH_4Cl$ and brine, dried over $Na_2SO_4$, and concentrated. The crude product was purified by silica gel chromatography (7:3 hexanes:EtOAc) to afford olefin **18d** (30.0 mg, 75%) as a clear oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 6.39 (1H, d, *J* = 3.3 Hz), 6.28 (1H, d, *J* = 2.9 Hz), 4.56 (1H, br s), 4.47 (1H, s), 4.43 (1H, s), 4.41 (1H, dd, *J* = 10.8, 2.2 Hz), 3.89 (2H, m), 3.85 (3H, s), 3.76 (3H, s), 3.11 (2H, d, *J* = 6.6, 7.3 Hz), 2.88 (1H, d, *J* = 14.3 Hz), 2.76 (1H, d, *J* = 14.5 Hz), 2.30 (2H, t, *J* = 7.5 Hz), 2.38 (1H, dd, *J* = 12.7, 5.0 Hz), 2.11 (1H, d, *J* = 13.0 Hz), 1.91 (2H, d, *J* = 9.7 Hz), 1.75 (1H, dd, *J* = 12.6, 4.0 Hz), 1.64−1.50 (5H, m), 1.43 (9H, s), 1.38−1.25 (8H, m), 1.19 (1H, d, *J* = 10.2 Hz), 1.08 (3H, s), 0.92 (3H, s): $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 174.7, 160.0, 158.5, 156.4, 139.1, 109.4, 103.9, 98.7, 68.1, 56.8, 56.2, 49.4, 42.5, 42.2, 42.8, 41.1, 40.7, 36.2, 35.0, 33.6, 30.4, 29.1, 28.8, 27.1, 25.9, 25.3, 22.7, 22.5, 19.4, 19.3; IR (thin film, NaCl) 3390, 2934, 2873, 1720, 1592, 1456, 1251, 1173 cm$^{-1}$; HRMS calcd for $C_{34}H_{52}NO_6Cl$ 605.3479, found 605.3483; MS (70 eV) *m*/*z* (rel int) 607(4, $M^{2+}$), 605(10, $M^+$), 459(5), 375(7), 320(21), 189(100), 186(33), 176(23), 147(8), 133(15), 119(10), 107(13), 95(41), 93(12), 69(10), 57(36) 55(8); [α]$^{25}_D$ = +58 (*c* 15.0, $CHCl_3$).

**(−)-*trans*-Octahydro-5α-[(2-chloro-3,5-dimethoxyphenyl)methyl]-5*β*,8a*β*-dimethyl-6α-(hydroxymethyl)-1(2*H*)-naphthalenyl 6-(*N*-*t*-BOC-amino)hexanoate (15d):** see compound **18d** for similar experimental; $^1$H NMR ($CDCl_3$, 300 MHz) δ 6.62 (1H, d, *J* = 2.4 Hz), 6.38 (1H, d, *J* = 2.5 Hz), 4.66 (1H, dd, *J* = 11.0, 2.1 Hz), 4.52 (1H, s), 4.50 (1H, s), 4.29 (1H, t, *J* = 11.2 Hz), 3.85 (3H, s), 3.78 (3H, s), 3.31 (1H, d, *J* = 14.4 Hz), 3.09 (2H, dt, *J* = 6.6, 6.1 Hz), 2.35 (1H, d, *J* = 15.1 Hz), 2.32 (1H, d, *J* = 14.6 Hz), 1.94 (2H, dd, *J* = 8.8, 3.7 Hz), 1.63−1.44 (9H, m), 1.39 (9H, s), 1.35−1.22 (6H, m), 0.94 (3H, s), 0.90 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 174.2, 160.4, 159.0, 156.4, 139.8, 108.0, 103.2, 98.4, 64.4, 57.0, 56.2, 49.6, 41.9, 41.4, 41.2, 41.1, 40.9, 38.8, 35.0, 33.5, 30.9, 30.3, 29.1, 27.0, 25.3, 23.0, 22.8, 20.5, 20.2; IR (thin film, NaCl) 3400, 2960, 2872, 1730, 1710, 1596, 1458, 1344, 1208, 1162, 1041, 932, 748 cm$^{-1}$; [α]$^{25}_D$ = −60 (*c* 2.0, $CHCl_3$).

**(+)-2-Methoxy-5-chloro-6-[[*trans*-octahydro-5*β*,8a*β*-dimethyl-6*β*-[[[6-(*N*-*t*-BOC-amino)hexanoyl]oxy]methyl]-1(2*H*)-naphthalenyl]methyl]-1,4-cyclohexadiene-1,4-dione (18e).** Arene **18d** (9.1 mg, 0.015 mmol) was dissolved in acetonitrile (0.63 mL). CAN (73.6 mg, 0.13 mmol) dissolved in $H_2O$ (0.13 mL) was added dropwise to the stirring solution over 1.25 h. The reaction mixture was allowed to stir for 4 h; then the reaction mixture was partitioned between $H_2O$ and $Et_2O$. The aqueous layer was separated and washed with $Et_2O$ (3×). The combined organic layers were washed with brine, filtered, and concentrated. The resulting oil was purified by silica gel chromatography (1:1 hexanes:EtOAc) to yield the quinone **18e** (8.5 mg, 94%) as a bright yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 6.03 (1H, br s), 4.60 (1H, s), 4.51 (2H, d, *J* = 5.7 Hz), 4.24 (1H, dd, *J* = 11.2, 2.2 Hz), 3.84 (3H, s), 3.70 (2H, dd, *J* = 10.5, 9.0 Hz), 3.12 (2H, dt, *J* = 7.6, 6.0 Hz), 2.84 (1H, d, *J* = 13.4 Hz), 2.79 (1H, d, *J* = 13.0 Hz), 2.35 (1H, dd, *J* = 13.9, 8.2 Hz), 2.28 (2H, t, *J* = 7.3 Hz), 2.11 (1H, d, *J* = 9.2 Hz), 1.83 (2H, m), 1.66−1.48 (7H, m), 1.43 (9H, s), 1.35−1.25 (6H, m), 1.06 (3H, s), 0.89 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 180.7, 179.4, 174.5, 160.0, 159.8, 156.7, 144.4, 144.0, 110.2, 107.4, 104.2, 79.7, 67.9, 57.4, 53.6, 44.81, 44.77, 41.1, 39.6, 36.4, 34.9, 33.4, 30.5, 30.4, 29.1, 29.0, 27.0, 25.3, 24.1, 21.0, 18.0; IR (thin film, NaCl) 3398, 2929, 2861, 1359, 2341, 1716, 1683, 1653, 1629, 1259, 1163 cm$^{-1}$; HRMS calcd for $C_{33}H_{50}NO_7Cl$ 607.3273, found 607.3275; MS (70 eV) *m*/*z* (rel int) 609(<1, $M^{2+}$), 607(1, $M^+$), 533(2), 507(9), 469(2), 375(9), 320(12), 189-(100), 133(19), 95(46), 56(54); [α]$^{25}_D$ = +11 (*c* 10, $CHCl_3$).

**(−)-2-Methoxy-5-chloro-6-[[*trans*-octahydro-5*β*,8a*β*-dimethyl-6α-[[[6-(*N*-*t*-BOC-amino)hexanoyl]oxy]methyl]-1(2*H*)-naphthalenyl]methyl]-1,4-cyclohexadiene-1,4-dione (15e):** see compound **18e** for similar experimental; $^1$H NMR ($CDCl_3$, 300 MHz) δ 6.52 (1H, d, *J* = 2.7 Hz), 6.35 (1H, d, *J* = 2.7 Hz), 4.65 (1H, br s), 4.55 (2H, dd, *J* = 11.2, 4.2 Hz), 4.23 (1H, t, *J* = 10.3 Hz), 3.81 (3H, s), 3.74 (3H, s), 3.25 (1H, d, *J* = 14.4 Hz), 3.20 (1H, dd, *J* = 11.2, 4.2 Hz), 3.06 (2H, dt, *J* = 6.5, 6.4 Hz), 2.32 (2H, t, *J* = 6.8 Hz), 2.29 (1H, d, *J* = 14.6 Hz), 2.26 (1H, m), 1.94 (2H, dd, *J* = 8.8, 3.7 Hz), 1.63−1.44 (9H, m), 1.39 (9H, s), 1.35−1.22 (7H, m), 0.94 (3H, s), 0.90 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 174.2, 158.8, 156.4, 139.6, 116.9, 108.1, 98.4, 81.4, 64.5, 56.8, 56.1, 47.5, 41.5, 41.0, 40.6, 39.0, 34.9, 32.2, 30.8, 30.6, 30.2, 29.1, 28.4, 26.9, 25.3, 22.4, 22.2, 20.8, 19.9, 15.3; IR (thin film, NaCl) 3327, 2924, 2848, 1734, 1652, 1552, 1451, 1262, 1155 cm$^{-1}$; [α]$^{25}_D$ = −9 (*c* 2.0, $CHCl_3$).

**(+)-2-Methoxy-5-hydroxy-6-[[*trans*-octahydro-5*β*,8a*β*-dimethyl-6α-[[[6-(*N*-*t*-BOC-amino)hexanoyl]oxy]methyl]-1(2*H*)-naphthalenyl]methyl]-1,4-cyclohexadiene-1,4-dione (16).** $Pd(PPh)_3$ (7.9 mg, 6.9 μmol) was placed in a flask with THF (0.6 mL) and $H_2O$ (0.6 mL). Chloroquinone **15e**

(16.7 mg, 0.03 mmol) in THF (0.6 mL) and $NaHCO_3$ (1 M, 61 μL) were added dropwise to the flask. After completion of the addition, the reaction mixture was heated to 80 °C for 10 min; then the reaction was quenched with HCl (5%). The aqueous layer was extracted with $Et_2O$ (3×), and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The crude product was purified by silica gel chromatography (1:1:0.001 hexanes:$Et_2O$:AcOH) to yield quinone **16** (1.2 mg, 7%) as a yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz)-$\delta$ 5.87 (1H, s), 4.71 (2H, d, $J$ = 10.5 Hz), 4.56 (1H, br s), 4.51 (1H, s), 4.49 (1H, s), 4.33 (1H, t, $J$ = 11.2 Hz), 3.87 (3H, s), 3.13 (2H, dt, $J$ = 6.5, 6.0 Hz), 2.76 (1H, d, $J$ = 13.0 Hz), 2.27 (2H, t, $J$ = 8.1 Hz), 2.26 (1H, d, $J$ = 13.2 Hz), 2.08 (2H, br s), 1.86−1.52 (10H, m), 1.48 (9H, s), 1.35−1.20 (6H, m), 1.12 (3H, s), 0.94 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 180.9, 179.5, 174.4, 159.8, 156.6, 145.0, 144.3, 110.2, 107.4, 103.9, 79.7, 64.9, 57.4, 49.2, 44.2, 41.6, 41.4, 36.8, 35.0, 33.4, 33.1, 30.7, 30.4, 29.4, 28.8, 27.0, 24.8, 22.8, 22.1, 21.8, 21.0; IR (thin film, NaCl)-3423, 2963, 2931, 1762, 1684, 1643, 1629, 1589, 1465, 1441, 1230 cm$^{-1}$; [α]$^{25}_D$ = +10 (*c* 0.3, $CHCl_3$).

**(−)-2-Methoxy-5-hydroxy-6-[[*trans*-octahydro-5*β*,8a*β*-dimethyl-6*β*-[[[6-(*N*-*t*-BOC-amino)hexanoyl]oxy]methyl]-1(2*H*)-naphthalenyl]methyl]-1,4-cyclohexadiene-1,4-dione (19):** see quinone **16** for similar experimental; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 5.87 (1H, s), 4.58 (1H, br s), 4.51 (1H, d, $J$ = 10.1 Hz), 4.50 (1H, s), 4.47 (1H, s), 4.22 (1H, t, $J$ = 5.9 Hz), 3.86 (3H, s), 3.13 (2H, dt, $J$ = 6.7, 5.2 Hz), 2.65 (1H, d, $J$ = 14.1 Hz), 2.45 (1H, d, $J$ = 13.8 Hz), 2.32 (2H, t, $J$ = 7.3 Hz), 2.16 (3H, m), 1.77−1.58 (4H, m), 1.44 (9H, s), 1.41−1.20 (8H, m), 1.07 (3H, s), 0.90 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 181.7, 179.8, 174.2, 159.8, 156.8, 145.8, 145.6, 107.8, 105.7, 100.9, 66.6, 64.1, 57.8, 51.8, 44.2, 44.0, 41.8, 41.4, 40.0, 39.8, 38.0, 36.2, 30.1, 28.4, 27.1, 26.8, 25.8, 24.1, 23.8, 22.0; IR (thin film, NaCl) 3417, 2925, 2866, 1734, 1613, 1353, 1254, 1184, 1120 cm$^{-1}$; [α]$^{25}_D$ = −10 (*c* 0.1, $CHCl_3$).

**(−)-*trans*-Octahydro-5α-[(2-chloro-3,5-dimethoxyphenyl)methyl]-5*β*,6*β*,8a*β*-trimethyl-1*β*-(hydroxymethyl)-1(2*H*)-naphthalene (20).** Olefin **13** (77 mg, 0.20 mmol) dissolved in THF (1 mL) was cooled to 0 °C. $BH_3$·$SMe_2$ (10 M, 0.031 mL, 0.31 mmol) was added dropwise to the cooled solution over 30 min. After completion of addition the reaction mixture was allowed to stir at 25 °C for 3 h; then NaOH (0.2 mL, 6 M) and EtOH (1 mL) were added. Reaction mixture was cooled again to 0 °C, and 30% $H_2O_2$ (0.2 mL) was added. After completion of addition the mixture was heated to reflux for 1 h. The reaction was then quenched with water and ice, and the aqueous portion was extracted with $Et_2O$ (3×). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The crude oil was purified using silica gel chromatography (3:1 hexanes:EtOAc) to yield alcohol **20** (74 mg, 92%) as a clear oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.40 (1H, d, $J$ = 2.7 Hz), 6.37 (1H, d, $J$ = 2.8 Hz), 3.86 (3H, s), 3.78 (3H, s), 3.44 (1H, dd, $J$ = 10.6, 8.1 Hz), 3.20 (1H, dd, $J$ = 10.4, 8.4 Hz), 2.79 (1H, d, $J$ = 14.1 Hz), 2.72 (1H, d, $J$ = 14.1 Hz), 1.77 (4H, m), 1.61 (2H, m), 1.41−1.19 (8H, m), 0.98 (3H, s), 0.92 (3H, d, $J$ = 6.4 Hz), 0.81 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 158.3, 156.3, 140.1, 109.7, 98.2, 64.3, 56.8, 56.2, 54.4, 50.6, 39.0, 37.92, 37.87, 28.4, 28.3, 27.1, 26.1, 24.2, 24.1, 23.9, 19.2, 18.2, 15.8; IR (thin film, NaCl) 3383, 2936, 2872, 1587, 1454, 1324, 1201, 1161, 1087, 1039, 756 cm$^{-1}$; HRMS calcd for $C_{23}H_{35}O_3Cl$ 394.2275, found 394.2279; MS (70 eV) *m*/*z* (rel int) 396($M^{2+}$, 5), 394($M^+$, 13), 209(27), 186(100), 151(12), 135(35), 121(20), 95(28), 67(16); [α]$^{25}_D$ = −15 (*c* 7.0, $CHCl_3$).

**(−)-*trans*-Octahydro-5α-[(2-chloro-3,5-dimethoxyphenyl)methyl]-5*β*,6*β*,8a*β*-trimethyl-1*β*-(hydroxymethyl)-naphthyl 6-(*N*-*t*-BOC-amino)hexanoate (21).** Alcohol **20** (51 mg, 0.13 mmol), 6-(*N*-*t*-BOC-amino)hexanoic acid (30.0 mg, 0.13 mmol), and DMAP (24 mg, 0.20 mmol) were placed in a flask and cooled to 0 °C. EDCI (37.0 mg, 0.20 mmol) dissolved in $CH_2Cl_2$ (1.5 mL) was added dropwise. The mixture was stirred at 0 °C for 2 h and then allowed to warm to 25 °C. After 12 h the reaction was quenched with saturated $NH_4Cl$. The aqueous layer was extracted with $CH_2Cl_2$ (2×). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The crude product was purified by silica gel chromatography (7:3 hexanes:EtOAc) to yield ester **21** (74 mg, 94%) as a clear yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.41 (1H, d, $J$ = 2.6 Hz), 6.37 (1H, d, $J$ = 2.6 Hz), 4.51 (1H, br s), 4.18 (1H, d, $J$ = 5.5 Hz), 4.15 (1H, dd, $J$ = 11.3, 5.1 Hz), 3.97 (2H, dd, $J$ = 10.7, 8.6 Hz), 3.87 (3H, s), 3.80 (3H, s), 3.10 (2H, dt, $J$ = 6.8, 6.6 Hz), 2.79 (1H, d, $J$ = 13.9 Hz), 2.73 (1H, d, $J$ = 14.5 Hz), 2.25 (2H, t, $J$ = 7.3 Hz), 1.79 (1H, br d, $J$ = 7.2 Hz), 1.76−1.59 (7H, m), 1.43 (9H, s), 1.40−1.30 (9H, m), 1.08 (3H, s), 0.92 (3H, d, $J$ = 6.0 Hz), 0.83 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 174.6, 158.3, 156.3, 140.1, 116.8, 109.7, 98.2, 80.0, 66.2, 56.9, 56.2, 50.6, 50.4, 43.2, 42.4, 41.1, 38.9, 37.9, 37.3, 35.0, 30.5, 29.1, 28.2, 27.03, 26.97, 26.3, 25.3, 23.8, 20.3, 19.1, 18.2, 15.7; IR (thin film, NaCl) 3371, 2917, 2855, 1730, 1712, 1688, 1590, 1537, 1503, 1453 cm$^{-1}$; HRMS calcd for $C_{34}H_{54}NO_6Cl$ 607.3639, found 607.3634; MS (70 eV) *m*/*z* (rel int) 609(<1, $M^{2+}$), 607(<1, $M^+$), 515(1), 446(<1), 365(4), 321(50), 190(78), 151(28), 121(35), 95(34); [α]$^{25}_D$ = −30 (*c* 3.0, $CHCl_3$).

**(+)-2-Methoxy-5-chloro-6-[[*trans*-octahydro-5*β*,6*β*,8a*β*-trimethyl-1*β*-[[[6-(*N*-*t*-BOC-6-amino)hexanoyl]oxy]methyl]-5α-naphthyl]methyl]-1,4-cyclohexadiene-1,4-dione (21e).** Arene **21** (95 mg, 0.16 mmol) was dissolved in $CH_3CN$ (7.5 mL). CAN (683 mg, 1.25 mmol) dissolved in water (1.25 mL) was added dropwise to the stirring $CH_3CN$ solution over 1.25 h. After 2 h the reaction mixture was diluted with $Et_2O$ and extracted (5×). The organic solution was washed with brine, dried over $Na_2SO_4$, and concentrated. The crude product was purified by silica gel chromatography (1:1 hexanes:$Et_2O$) to yield chloroquinone **21e** (85 mg, 92%) as a yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.04 (1H, s), 4.51 (1H, br s), 4.21 (1H, dd, $J$ = 10.4, 3.3 Hz), 3.86 (3H, s), 3.69 (2H, dd, $J$ = 10.6, 3.7 Hz), 3.10 (2H, dt, $J$ = 7.3, 6.0, Hz), 2.79 (1H, d, $J$ = 12.8 Hz), 2.72 (1H, d, $J$ = 12.8 Hz), 2.27 (2H, t, $J$ = 7.3 Hz), 1.80 (2H, br d, $J$ = 10.8 Hz), 1.69−1.53 (8H, m), 1.43 (9H, s), 1.34−1.08 (8H, m), 0.85 (3H, s), 0.83 (3H, s), 0.81 (3H, d, $J$ = 6.4 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 180.8, 179.6, 174.5, 160.1, 156.3, 145.6, 140.1, 107.3, 66.1, 57.4, 54.7, 50.5, 45.9, 41.1, 40.2, 40.1, 39.1, 38.3, 35.0, 30.4, 29.1, 28.4, 27.2, 27.0, 26.3, 25.3, 24.4, 19.5, 17.2, 15.6; IR (thin film, NaCl) 3402, 2930, 2867, 1731, 1713, 1678, 1632, 1456, 1366, 1226, 1168 cm$^{-1}$; HRMS calcd for $C_{33}H_{50}ClNO_7$ 607.3275, found 607.3278; MS (70 eV) *m*/*z* (rel int) 609(1, $M^{2+}$), 607(2, $M^+$), 551(3), 515(4), 507(18), 497(4), 471(36), 377(5), 366(18), 358(3), 342(76), 322(100), 299(10), 191(40), 175(8), 135(9), 121(11), 109(13), 95(20), 81(8), 69(12), 57(23), 43(14); [α]$^{25}_D$ = +7 (*c* 5.0, $CHCl_3$); UV−vis (MeOH) 203 (4.62), 288 (4.16) nm.

**(+)-2-Methoxy-5-hydroxy-6-[[*trans*-octahydro-5*β*,6*β*,-8a*β*-trimethyl-1*β*-[[[6-(*N*-*t*-BOC-amino)hexanoyl]oxy]-methyl]-5α-naphthyl]methyl]-1,4-cyclohexadiene-1,4-dione (22).** $Pd(Ph_3P)_4$ (20.7 mg, 0.018 mmol) was placed in a flask with THF (2.5 mL) and $H_2O$ (2.5 mL). Chloroquinone **21e** (43.6 mg, 0.072 mmol) in THF (2.5 mL) and $NaHCO_3$ (1 M, 0.16 mL) were added dropwise to the flask. After completion of the addition the reaction mixture was heated to 80 °C for 10 min; then the reaction quenched with HCl (5%). The aqueous layer was extracted with $Et_2O$ (3×), and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The crude product was purified by silica gel chromatography (1:1:0.001 hexanes:$Et_2O$:AcOH) to yield quinone **22** (5.2 mg, 16%, 75% conversion) as a yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.56 (1H, br s), 5.88 (1H, s), 4.51 (1H, br s), 4.22 (1H, d, $J$ = 10.2 Hz), 3.88 (3H, s), 3.64 (2H, dd, $J$ = 10.5, 8.2 Hz), 3.10 (2H, dt, $J$ = 6.7, 6.6 Hz), 2.55 (1H, d, $J$ = 13.7 Hz), 2.45 (1H, d, $J$ = 13.5 Hz), 2.25 (2H, t, $J$ = 7.1 Hz), 2.00 (2H, d, $J$ = 11.0 Hz), 1.80 (2H, br d, $J$ = 11.7 Hz), 1.60 (4H, m), 1.43 (9H, s), 1.34−1.16 (10H, m), 0.95 (3H, d, $J$ = 6.2 Hz), 0.84 (3H, s), 0.80 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 180.6, 179.8, 173.2, 159.7, 156.4, 146.6, 139.1, 107.3, 65.3, 58.1, 54.6, 51.1, 48.1, 44.0, 42.1, 40.2, 39.7, 38.0, 35.7, 30.4, 28.8, 26.2, 26.4, 24.5, 23.8, 23.2, 22.2, 19.1, 18.2, 17.5; IR (thin film, NaCl) 3348, 2931, 2862, 1731, 1714, 1694, 1660, 1608, 1453, 1367, 1238, 1170 cm$^{-1}$; [α]$^{25}_D$ = +10 (*c* 0.2, $CHCl_3$); UV−vis (MeOH) 212 (4.24), 287 (3.98) nm (ilimaquinone: 210 (4.35), 288 (4.06) nm).[3a] Anal. Calcd for $C_{33}H_{51}NO_8$: C, 67.21; H, 8.72; N, 2.37. Found: C, 67.10; H, 8.69; N, 2.38.

**(−)-*trans*-Octahydro-5α-[(2,5-dimethoxyphenyl)methyl]-5*β*,6*β*,8a*β*-trimethyl-1-methylenenaphthalene (24).** Ke-

tone **23** (356 mg, 1.0 mmol) in DMSO (5 mL) was added dropwise to a stirring solution of $Ph_3PCH_2$ (22.5 mL, 0.4 M, 9 mmol) in a 100 mL round bottom flask. The reaction mixture was heated to 75 °C for 5 h and cooled to 25 °C, the reaction quenched with $H_2O$, and the mixture extracted with $Et_2O$ (3×). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The resulting oil was purified by silica gel chromatography (99:1 hexanes:$Et_2O$) to afford **24** (310 mg, 90%) as a white solid: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.70 (1H, d, $J$ = 3.0 Hz), 6.67 (1H, s), 6.64 (1H, d, $J$ = 2.9 Hz), 4.40 (1H, t, $J$ = 2.4 Hz), 4.36 (1H, t, $J$ = 2.1 Hz), 3.75 (3H, s), 3.71 (3H, s), 2.65 (1H, d, $J$ = 14.1 Hz), 2.58 (1H, d, $J$ = 13.9 Hz), 2.32 (1H, td, $J$ = 14.0, 5.2 Hz), 2.08 (2H, d, $J$ = 16.0 Hz), 1.89 (1H, m), 1.49−1.12 (8H, m), 1.05 (3H, s), 1.00 (3H, d, $J$ = 6.4 Hz), 0.84 (3H, s); $^{13}$C NMR ($CDCl_3$, 400 MHz) $\delta$ 160.9, 153.5, 153.3, 129.3, 119.4, 111.9, 111.4, 103.3, 55.3, 55.1, 48.7, 42.8, 40.9, 37.8, 37.2, 36.9, 33.8, 29.0, 28.4, 23.8, 21.3, 18.4, 18.2; IR (thin film, NaCl) 2924, 1495, 1457, 1218, 1048, 885, 803, 797, 715 cm$^{-1}$; mp 74−75 °C; $[\alpha]^{25}_D = -50$ ($c$ 2.4, EtOAc). Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.00. Found: C, 80.29; H, 10.16.

**Isoavarone (25).** CAN (35.5 mg, 0.648 mmol), dissolved in $H_2O$ (500 $\mu$L), was added dropwise to compound **24** (8.0 mg, 0.024 mmol) in $CH_3CN$ (500 $\mu$L). The reaction was monitored hourly by TLC (95:5 hexanes:$Et_2O$), and after 5 h, the reaction mixture was diluted with $H_2O$ (2 mL) and $Et_2O$ (2 mL). The reaction mixture was extracted with $Et_2O$ (2 mL, 3×), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (98:2 hexanes:$Et_2O$) yielded compound **25** as a red oil (2.8 mg, 57%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.76 (1H, s), 6.68 (1H, s), 6.55 (1H, s), 4.45 (2H, br s), 2.58 (1H, d, $J$ = 13.8 Hz), 2.42 (1H, d, $J$ = 1.4 Hz), 2.31 (2H, t, $J$ = 13.0 Hz), 2.08 (2H, d, $J$ = 12.6 Hz), 1.89 (2H, d, $J$ = 11.2 Hz), 1.77 (2H, m), 1.25 (3H, s), 0.94 (3H, d, $J$ = 13.9 Hz), 0.86 (3H, br s); $^{13}$C NMR ($CDCl_3$, 400 MHz) $\delta$ 160.3, 148.1, 137.8, 137.2, 128.9, 124.5, 110.6, 104.0, 99.3, 49.6, 37.3, 35.9, 33.5, 30.4, 28.7, 28.1, 23.3, 21.3, 17.6 (partial carbon); IR (thin film, NaCl) 2930, 2867, 1665, 1652, 1476, 1382, 1255, 1092, 890 cm$^{-1}$; HRMS calcd for $C_{21}H_{28}O_2$ 312.2089, found 312.2076; MS (70 eV) $m/z$ (rel int) 191(51), 149(35), 109(31), 95(100), 69(41), 59(51), 57(56).

**Avarone (2).** The olefin **24** (13 mg, 0.038 mmol) was dissolved in ethanol (0.1 mL, 95%) and chloroform (0.1 mL). $RhCl_3 \cdot H_2O$ (1 mg, 0.004 mmol) was added to the stirring solution. After the addition the reaction mixture was heated at reflux under $N_2$ for 2 days. The reaction mixture was cooled to 25 °C, diluted with $Et_2O$, and filtered through silica gel (2 cm). The filtrate was concentrated to yield avarol dimethyl ether as a clear oil (11 mg, 85%).

$CrO_3$ (257 mg, 0.47 mmol) in $H_2O$ (1.7 mL) was added dropwise to avarol dimethyl ether (14.4 mg, 0.042 mmol) in THF (1.7 mL) at rt. The reaction was monitored by TLC (95:5 hexanes:EtOAc), and after 1 h $H_2O$ (0 °C) was added. The reaction mixture was extracted with $Et_2O$ (3×), washed with (saturated) $NH_4Cl$, dried over $MgSO_4$, filtered, and concentrated. Purification with Ag-impregnated silica gel (20%, w/w) chromatography (95:5 hexanes:EtOAc) afforded avarone (**2**) (7.5 mg, 57%) that was identical in all aspects to the natural product:[23] $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.77 (2H, m), 6.51 (1H, br s), 5.14 (2H, br s), 2.64 (1H, d, $J$ = 13.4 Hz), 2.43 (1H, d, $J$ = 13.6 Hz), 2.02 (1H, m), 1.84 (3H, q, $J$ = 9.7 Hz), 1.66 (1H, t, $J$ = 3.3 Hz), 1.62 (1H, t, $J$ = 3.3 Hz), 1.53 (3H, s), 1.38 (2H, dt, $J$ = 9.9, 3.3 Hz), 1.00 (3H, s), 0.93 (3H, d, $J$ = 7.1 Hz), 0.85 (3H, s); IR (thin film, NaCl) 2911, 1651, 1654 cm$^{-1}$.

(23) Minale, L.; Riccio, R.; Sodano, G. *Tetrahedron Lett.* **1974**, *38*, 3401.

**Secretion Assay.** All plasticware and glassware were presterilized or purchased sterile. Cell culture media was filtered through Nalgene sterile filters with 0.2 $\mu$m nylon membrane filters before use. The plasmid encoding for secreted AP was obtained from the Schreiber laboratory at Harvard University and used with permission. Incubation refers to storing cells in tissue culture flasks with canted necks and vent caps in a $CO_2$ incubator at 37 °C, 5.0% $CO_2$, and 100% humidity. Centrifugation, pelleting, or spinning down refers to using a swinging bucket centrifuge at room temperature at 1000 rpm for 10 min and then aspirating the spent media. Cell counts were obtained using a hemacytometer with cells stained with trypan blue (0.4%); counts were done in duplicate and averaged. Cell morphology was monitored using a phase-contrast cell culture light microscope at 40×.

Jurkat cells were incubated in RPMI 1640 media (without phenol red), 10% fetal bovine serum (FBS), and 5% penicillin/streptomycin. For normal cell maintenance, cells were grown until saturation (1.5−2.5 × 10$^6$ cells/mL) and then diluted 10-fold with fresh media. To run the assay, 1 × 10$^7$ cells were pelleted (amount required for two compounds assayed in duplicate). Cells were rinsed with RPMI 1640 media and resuspended in 500 $\mu$L of RPMI 1640 media. The cells were pipetted into a 4 mm cuvette containing plasmid (10 $\mu$g). Equilibration (20 min, rt) was then followed by electroporation (960 $\mu$F, 300 V, rt). The cells were reequilibrated (20 min, rt), then diluted with unselected media (10.0 mL, RPMI 1640, 10% FBS), and incubated for 48 h. Under these conditions, a 50% viability of cells was obtained. The cells were then pelleted and resuspended in fresh media (4 mL, RPMI 1640, 10% FBS, 5% penicillin/streptomycin).

A range of compound concentrations was introduced into 96-well plates. Unactivated cells (100 $\mu$L, 1.2 × 10$^6$ cells/mL) were pipetted into the wells. To activate the cells, ionomycin and PMA (2 $\mu$M and 100 ng/mL concentrations, respectively) were added. The total volume in each well was diluted to 200 $\mu$L with fresh media. The plate was incubated overnight (37 °C, 5% $CO_2$, 100% humidity) and then heated (68 °C, 1.5 h) to denature sensitive phosphatases. A *p*-nitrophenyl phosphate solution (100 $\mu$L, 1 mg/mL of *p*-nitrophenyl phosphate in 2 M diethanolamine bicarbonate, pH 10.0) was added to the wells of a new plate. The lyzed cells (100 $\mu$L) were added to the corresponding *p*-nitrophenyl phosphate-containing wells and incubated for 12−24 h. The absorption (410 nm) of each well was measured using a microplate spectrophotometer.

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**Supporting Information Available:** $^1$H NMR spectra for all new compounds (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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