Synthesis and Cytotoxic Evaluation of Some Cribrostatin–Ecteinascidin Analogues[⊥]

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Analogues of cribrostatin IV (**1**) and the potent antineoplastic agent ecteinascidin 743 (**2**) have been synthesized. The cytotoxic activity of these compounds (**5**, **14**, **20**) has been determined, and the cyanoamine−cribrostatin analogue (**14**) exhibits a 20-fold improvement with regard to the natural product **1**.

Since the isolation of naphthyridinomycin in 1974, the tetrahydroisoquinoline antitumor antibiotics have elicited significant excitement both for their complex, intriguing structural features and for their highly potent cytotoxic properties.[1] Most notably, syntheses[2–5] and pharmaceutical evaluation[6–9] of ecteinascidin 743 (Et 743, **2**) have confirmed the low nanomolar cytotoxic activity of this benchmark compound (also called Yondelis) and have propelled it to the brink of FDA approval for the treatment of ovarian and other forms of cancer.

In 2000, George R. Pettit and co-workers first reported in this journal the isolation and structure of a new member of this family, which they termed cribrostatin IV (**1**, Figure 1).[10] Subsequently, Kubo and colleagues reported a reassignment of the previously reported structure of renieramycin H as also corresponding to **1**.[11]

Our interest in **1** stemmed from its highly functionalized pentacyclic core, in which every skeletal carbon appears in an oxidized form. Additionally, the low-micromolar cytotoxicity of cribrostatin IV in the *absence* of the characteristic N-2/C-21 cyanomethinyl or hydroxymethinyl (preiminium ion) functionalities in Et 770 and 743 suggests that the highly oxygenated core of cribrostatin IV and/or the idiosyncratic C-3/C-4 olefin allows it to overcome this ostensible prerequisite for activity.[1]

Hypothetically, the replacement of the C-21 lactam of **1** with a labile, preiminium functionality should yield a more active congener. In our longstanding synthesis efforts toward Et 743,[12] and upon completion of the cribrostatin IV odyssey,[13] our laboratory has established access to a wide range of functionalized pentacyclic scaffolds, many of which include the intriguing C-3/C-4 double bond of cribrostatin. This report serves to detail the synthesis of several analogues of this type and to reveal the preliminary connections we have observed between structure and cytotoxic activity.

Results and Discussion

Chemistry. Arguably, the most intriguing general scaffold for the purpose of this study is one in which the C-3/C-4 double bond exists alongside a C-21 preiminium species (*vide infra*). Beyond that, we were also eager to compare some of the other features of the Et 743 manifold in this context, especially the A/E-ring aromatic portions, which differ significantly from those found in **1** and which also have been previously deemed important for potent biological activity.[6] With these two parameters in mind, our initial analogue goals became those shown in Figure 2.

With regard to C-21, we hoped to use the reductive-cyanation conditions optimized in our formal Et 743 synthesis.[12] To this end,

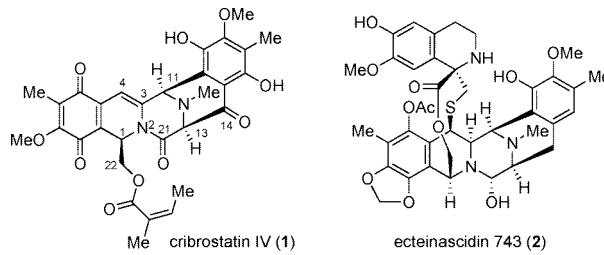

Figure 1. Structures of cribrostatin IV (**1**) and ecteinascidin 743 (**2**).

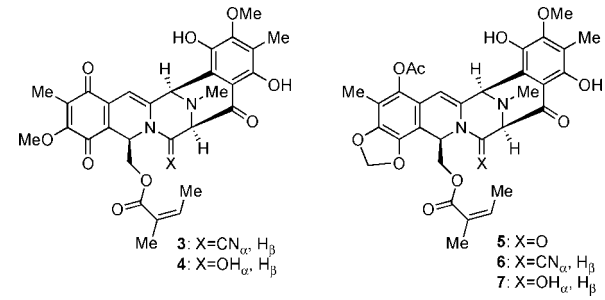

Figure 2. Originally proposed targets for derivatization of the natural products.

our studies commenced with hydrogenolysis of the known enepentacycle **8**[13] to afford diol **9**, which upon sequential treatment with the ate complex[14] derived from a 1:1 admixture of DIBAL-H and *n*-BuLi followed by KCN yielded C-21 cyanoamine **10**, but in low yield (<15%). The major product was the over-reduced, undesired amine **11** (Scheme 1). Unfortunately, attempted optimization of this sequence utilizing a variety of reducing agents (borane complexes, Red-Al, DIBAL-H, or LAH) and cyanation agents (KCN or TMSCN) uniformly led to this same dead end in the form of **11**.

These results are attributed to the presence of the C-3/C-4 double bond, which reduces a degree of torsional freedom in the B-ring. As such, upon half-reduction of the C-21 lactam, the lack of flexibility in the B-ring hinders the formation of an oxazolidine intermediate, leaving a highly reactive carbinolamine functionality easily reduced to the undesired amine, **11**. In addition, the conjugation between the electron rich A-ring and N-2 also may contribute to the relative ease of reduction observed in this system by stabilizing a transient iminium cation.

Indeed, the only successful cyanoamine syntheses of this type in the literature are reported on pre-pentacyclic intermediates or on substrates saturated at C-3.[1] Taking these data into account, the key to our eventual success was found in combining the highly efficient reductive-cyanation sequence reported in 2005 by Williams and co-workers[15] with a C-3-saturated variant of our own (Scheme

[⊥] Dedicated to Dr. G. Robert Pettit of Arizona State University for his pioneering work on bioactive natural products.

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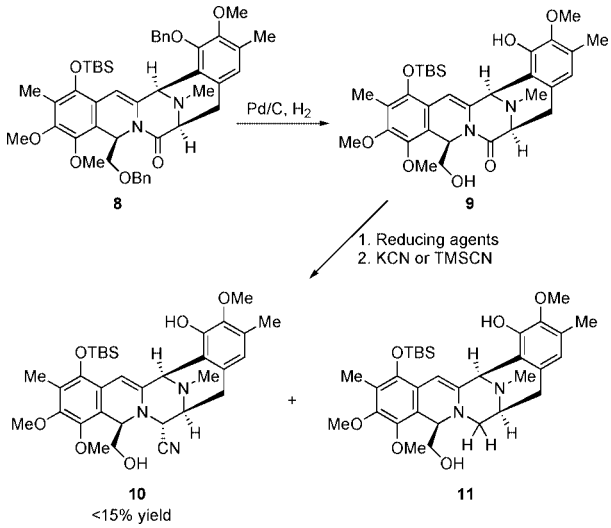
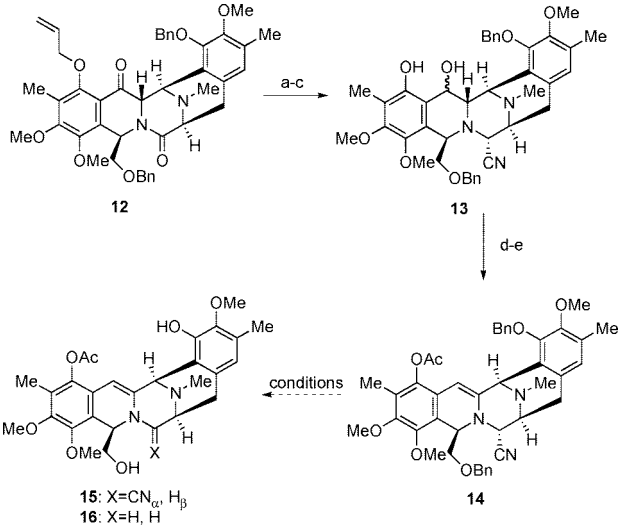
Scheme 1. Failed Reductive Cyanation of Unsaturated Pentacyclic Diol



Scheme 2. Synthetic Route toward Cyano-cribrostatin IV Analogue **14**[a]



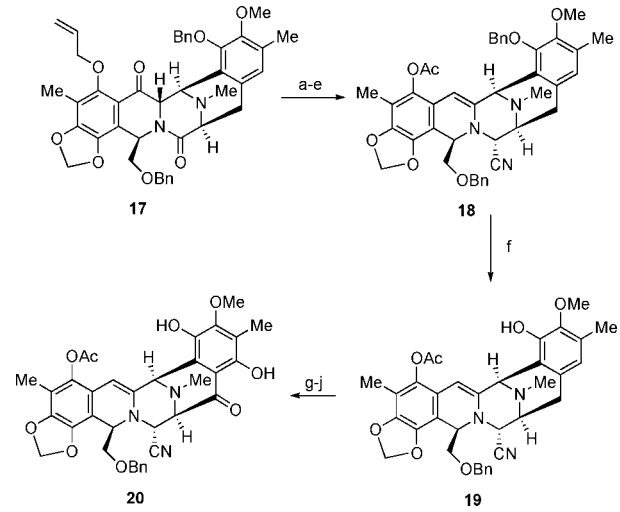
[a] Key: (a) LAH, THF; (b) KCN, AcOH, H_2O; (c) $(Ph_3P)_2PdCl_2$, Bu_3SnH, AcOH, CH_2Cl_2, 69% (over three steps); (d) *p*-TsOH, $MgSO_4$, benzene; (e) Ac_2O, TEA, CH_2Cl_2, 90% (over two steps).

2). In the event, treatment of known keto-pentacycle **12**[13] under the Williams protocol installed the desired C-21 cyanoamine function. The stereochemistry at C-4 was not rigorously assigned since installation of the double bond would follow. Accordingly, removal of the phenolic allyl ether, dehydration of the C-4 benzylic alcohol under acidic conditions, and protection of the A-ring phenol led to desired cyano-ene pentacyclic analogue **14** (Scheme 2). It should be noted that attempted dehydration prior to phenol deprotection failed in this case.

In the forward progression, what remained was introduction of the C-22 angelate ester and oxidation state adjustments of the A-, D-, and E-rings. To that end, a screening of various hydrogenolysis (palladium, platinum, Raney nickel catalysts), Lewis acidic (BCl_3, BBr_3), and nucleophilic (TMSI, thiolates) conditions typically employed for deprotection of benzyl ethers[16] led to either recovered starting material, decomposition, or the undesired amine **16**.

The difficulties accompanied with installing the C-21 cyanoamine coupled with our inability to find debenzylation conditions had significantly depleted the supply of advanced material. It soon became apparent that reaching the C-21 cyano-cribrostatin IV analogue (**3**) through our current route was not an achievable goal

Scheme 3. Synthetic Route toward Hybrid Analogue **20**[a]



[a] Key: (a) LAH, THF; (b) KCN, AcOH, H_2O; (c) $(Ph_3P)_2PdCl_2$, Bu_3SnH, AcOH, CH_2Cl_2, 62% (over three steps); (d) *p*-TsOH, $MgSO_4$, benzene; (e) Ac_2O, TEA, CH_2Cl_2, 90% (over two steps), (f) 10% Pd/C, H_2 (1 atm), MeOH, 33%; (g) salcomine, O_2 (5 bar), THF, 82%; (h) SeO_2, 1,4-dioxane; (i) DMP, CH_2Cl_2; (j) Zn, AcOH, 82% (over three steps).

in the short term. However, we believed intermediate **14** could be an initial analogue to work from, as it had two key structural features: a C-3/C-4 double bond and a cyanoamine functionality at C-21. At this time, the focus shifted to the synthesis of cyano- and hydroxy-hybrid analogues (cf. **6** and **7**).

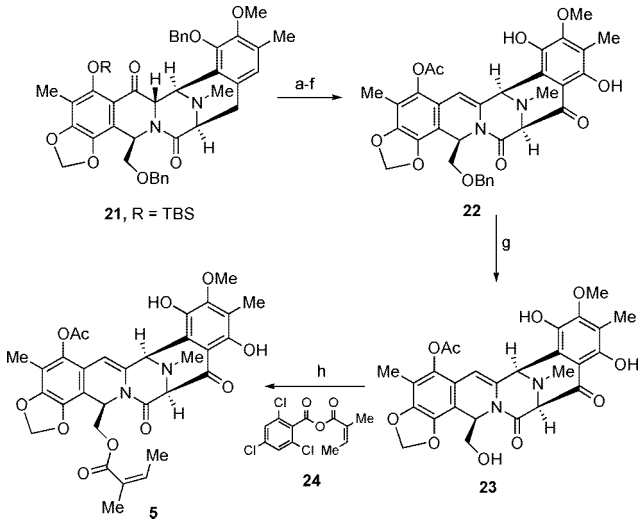
Thus, known keto-pentacycle **17** of the Et 743 series[12] was treated in the same fashion as previously described for the conversion of **12** into **14**. These results are depicted in Scheme 3.

Having achieved intermediate **18** without issue, the difficult task of deprotecting the benzyl groups in the presence of the sensitive C-21 cyanoamine function (cf. **14** to **15**) was again at hand. In the event, treatment of **18** under catalytic hydrogenation conditions did afford the partially debenzylated compound **19**, albeit in low yield (33%), along with the undesired amine saturated at C-21 (not shown). The limited amount of material that was obtained was thus advanced through a series of efficient oxidation state adjustments. Oxidation of the phenol gave the E-ring benzoquinone,[13,17] allylic oxidation of the quinone yielded the C-14 alcohol,[18] Dess–Martin periodinane[19] oxidation afforded the corresponding keto-quinone intermediate, and, finally, quinone reduction with zinc gave the desired keto-hydroquinone **20**.[20,21] Not surprisingly, an extensive search for conditions to debenzylate the C-22 benzyloxy function led to undesired reduction of the C-21 cyanoamine.[16] Despite our unsuccessful attempts to install the C-22 angelate ester in either reduced-lactam series, keto-hydroquinone **20** could—like **14**—be used as an initial hybrid-analogue for biological testing, as it had several key structural features worth examining.

In addition to our work toward the cyanoamine-type cribrostatin IV analogues, we also synthesized a lactam variant (**5**) containing all of the features held in the natural B−E-ring scaffold of cribrostatin IV, but substituting the A-ring of the more potent Et 743. This synthesis followed a modified, though analogous, route to that which we reported for the natural product (Scheme 4).[13]

In summary, attempts to synthesize cyano- and hydroxy-cribrostatin IV analogues **3** and **4** and cyano- and hydroxy-hybrid analogues **6** and **7** were interrupted due to difficulties in benzyl ether deprotection in the presence of the C-21 cyanoamine. Nevertheless, a simplified cyano-cribrostatin IV analogue (**14**) has been synthesized, which will allow us to evaluate the significance of both the C-3/C-4 double bond and the key C-21 cyanoamine function in the context of the cribrostatin IV scaffold. In addition, *des*-angelate-cyano-hybrid analogue **20** was synthesized. Important structural features of this analogue include (1) the Et 743 methyl-

Scheme 4. Successful Synthesis of Et 743–Cribrostatin IV Hybrid Analogue **5**[a]



[a] Key: (a) TBAF, then Ac_2O, CH_2Cl_2, 0 °C, quant; (b) 10% Pd/C, H_2, EtOAc, 2 h, 85%; (c) $Co(salen)_2$, 5 atm O_2, THF, 76%; (d) SeO_2, 1,4-dioxane, 100°C, quant; (e) DMP, CH_2Cl_2, rt, 2 h; (f) Zn, HOAc, 83%, 2 steps; (g) 10% Pd/C, H_2, EtOAc, 54% (28% of C_{14} alcohol); (h) **24**, toluene, 70 °C, 2–3 days, 55%.[22]

Table 1.[a]

synthetic compound	cell line	GI_{50}	TGI	LC_{50}
cribrostatin IV (**1**)	breast	4.49	nd	nd
	lung	7.09	11.60	nd
	colon	6.74	7.43	nd
hybrid (**5**)	breast	14.00	nd	nd
	lung	7.73	nd	nd
	colon	11.10	nd	nd
cyano-cribrostatin (**14**)	breast	0.26	0.35	0.48
	lung	0.24	0.30	0.41
	colon	0.20	0.26	0.36
cyano-hybrid (**20**)	breast	5.63	nd	nd
	lung	6.57	nd	nd
	colon	4.06	6.72	14.50

[a] Cytotoxicities reported in μM (nd = not determined).

enedioxybenzene A-ring, (2) the C-3/C-4 double bond, D- and E-rings of cribrostatin IV (**1**), and (3) the C-21 cyanoamine function. Lastly, a formal Et 743-cribrostatin IV hybrid was also synthesized for the purpose of analyzing the effect of substituting both oxidation state and substitution pattern on the A-ring, while otherwise maintaining the entirety of the cribrostatin IV framework. These analogues (**14**, **20**, and **5**) along with synthetic cribrostatin IV (**1**) were submitted to our collaborators at PharmaMar for biological testing, the results and preliminary analyses of which are described below.

Biology. In collaboration with PharmaMar, a biopharmaceutical company based in Spain, the cytotoxicities of synthetic cribrostatin IV (**1**) as well as cribrostatin IV analogues were studied. The methods used by PharmaMar are described in the Experimental Section.

Synthetic cribrostatin IV (**1**), cyano-cribrostatin IV analogue **14**, cyano-hybrid analogue **20**, and total hybrid analogue **5** were tested for cytotoxicity against representative human tumor cell lines, including breast (MDA-MB-231), lung (A-549), and colon (HT-29) in the dosing range of 10 to 0.0026 μg/mL. Dose–response curves for each of the test compounds were generated using the National Cancer Institute (NCI) algorithm.[23] From the generated curves, values of GI_{50}, TGI, and LC_{50} were interpolated, as summarized in Table 1.

The results suggest that synthetic cribrostatin IV (**1**) and the cyano-hybrid analog (**20**) behave in a similar manner, acting as cytostatic compounds, reaching a total growth inhibition (TGI) at the highest dose, without net cell killing. The assay performed with synthetic cribrostatin IV (**1**) corroborated the results obtained by Pettit and co-workers, which indicated **1** to exhibit low micromolar cytotoxicity ($GI_{50} \sim 5$ μM).[10] It should be noted that the cyano-hybrid analogue (**20**) presented some cytotoxic activity in HT-29 colon cells ($LC_{50} \sim 14.5$ μ M). The total hybrid analogue (**5**) is the least active in terms of potency, showing only minor cytostatic activity at the highest concentration used. Excitingly, the cyano-cribrostatin IV analogue (**14**) exhibits concentration-dependent cytotoxic activity in all three cell lines studied, with LC_{50} values in the high nanomolar range (~400 nM).

Lending further support to the well-documented mechanism of action for this family of alkaloids, the overarching trend observed in this study is that the ability for C_{21} to accept a nucleophile is paramount when predicting cytotoxicity.[7] Indeed, the cyano-cribrostatin IV analogue (**14**) ($GI_{50} \sim 250$ nM) displayed a 20-fold increase in cytotoxicity as compared to isolated cribrostatin IV (**1**), despite its relative structural simplicity. Unfortunately, from this preliminary study the actual effect of the C-3/C-4 double bond is inconclusive. In addition, the oxidation states of the A-, D-, and E-rings showed no definitive influence on cytotoxicity in the case of cyano-analogues.[15] However, the positive effect on cytotoxicity of the vinylogous imide[13] framework resulting from the quinone in natural cribrostatin IV is supported by the lack of activity observed in hybrid **5**. Armed with these preliminary observations and with confirmation that a simpler structural analogue bearing the cyanoamine (e.g., **14**) can exhibit significant improvements in potency, we have embarked on a more general SAR study to gain a finer understanding of this intriguing system, the results of which will appear in a later publication.

Experimental Section

General Experimental Procedures. All nonaqueous reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. All reagents were commercially available and used without further purification from Sigma-Aldrich and TCI America, unless indicated otherwise. Solvents were reagent grade and purified by standard techniques: THF was distilled from Na-benzophenone or filtered through a dry-solvent system; CH_2Cl_2 was distilled from CaH_2 or filtered through a dry-solvent system; all other solvents were Aldrich "anhydrous" grade solvents, unless indicated otherwise. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) on Merck silica gel 60-F254 coated 0.25 mm plates. Compounds were visualized by dipping the plates in a cerium sulfate–molybdate solution followed by heating. Concentrations were performed under reduced pressure using a Büchi rotary evaporator. Flash chromatography was performed using Silicycle silica gel (0.040–0.063 mesh) unless otherwise indicated. Preparative thin-layer chromatography (pTLC) was performed with Merck silica gel 60-F254 coated 0.50 mm plates. Yields reported are for isolated, spectroscopically pure compounds. Melting points are uncorrected. $CDCl_3$ was allowed to stand over K_2CO_3 and 4 Å molecular sieves to neutralize and dry prior to NMR sample preparation. ^1H and ^{13}C NMR spectra were measured at 300, 400, or 500 and 75, 100, or 125 MHz, respectively, with either a Bruker AMX-300, AMX-400, or DRX-500 FT NMR spectrometer. Chemical shifts are reported as δ values in ppm referenced to $CDCl_3$ (^1H NMR = δ 7.26 and ^{13}C NMR = δ 77.16). Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); m (multiplet); bs (broad singlet). Infrared spectra (IR) were obtained as thin films on a Perkin–Elmer Paragon 1000 FTIR spectrometer and are reported in wavenumbers (cm^{-1}). Mass spectra and high-resolution mass spectra (HRMS) were obtained on a JEOL JMS-DMX-303 and a NERMAG R10-10 spectrometer. Optical rotations were measured on a JASCO DIP-1000 spectrometer.

The cytotoxicity assay performed by PharmaMar consisted of three representative human tumor cell lines: non-small cell lung cancer (A-549), colon cancer (HT-29), and breast cancer (MDA-MB-231). These cells were plated in 96-well microtiter plates and incubated 24 h before treatment with vehicle alone (control) or varying concentrations of synthetic cribrostatin IV (**1**), cyano-cribrostatin IV analogue (**14**), cyano-

hybrid analogue (**20**), and total hybrid analogue (**5**) ranging from 10 to 0.0026 μg/mL (10 dilutions). The sulforhodamine B (SRB) method was used to measure the cellular protein content of adherent and suspension cell cultures. This method consists of the following steps: (1) the cells in the 96-well microtiter plates were washed twice with a phosphate buffer solution (PBS), then (2) fixed for 15 min with a 1% glutaraldehyde solution, then (3) rinsed twice more with PBS, (4) then stained with 0.4% (wt/vol) SRB dissolved in 1% acetic acid for 30 min at room temperature, (5) the cells were then rinsed several times in 1% acetic acid solution and air-dried, (6) the protein-bound SRB dye was then extracted with 10 mM unbuffered tris(hydroxymethyl)aminomethane (Tris) base solution, and finally (7) the absorbance of this solution was determined at 490 nm. Data points were collected in the following way: (1) before treatment, one plate from each of the three cell lines was analyzed using the SRB method and used for the time zero (Tz) point references, (2) treated cells were further incubated for 72 h and analyzed with the SRB method. With these data points dose–response curves were generated using the National Cancer Institute (NCI) algorithm.

Synthesis of Dimethoxybenzene-cyanoamine (13). To a solution of keto-pentacycle **12** (67.0 mg, 0.0933 mmol) in 15 mL of THF, at –78 °C, was added, dropwise, a 1.0 M THF solution of $LiAlH_4$ (2.80 mL, 2.80 mmol, 30 equiv). The solution was aged for 12 h to room temperature. The reaction was then cooled to –78 °C, which was followed by careful addition of KCN (69.0 mg, 1.41 mmol, 15 equiv) in 3.0 mL of H_2O. The cooling bath was removed, followed by addition of AcOH (0.11 mL, 1.77 mmol, 20 equiv) and 1.5 mL of THF. The resultant slurry was aged for 12 h to room temperature. The reaction was then quenched by a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The organic layers were combined, dried with $MgSO_4$, and concentrated by rotary evaporation. The crude foam was dissolved in 5 mL of CH_2Cl_2. To this solution, at room temperature, was added Bu_3SnH (38 μL, 0.121 mmol, 1.5 equiv), AcOH (53 μL, 0.936 mmol, 10 equiv), and $(Ph3P)_2PdCl_2$ (13.0 mg, 0.185 mmol, 0.2 equiv). The solution was aged 15 min and then the reaction concentrated by rotary evaporation. The residue was purified by column chromatography with 35% EtOAc/hexanes to provide 44.0 mg (69%) of an off-white foam: $[\alpha]^{17}_D$ +11.21 (*c* 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (1H, s), 7.43–7.32 (5H, m), 7.26 (3H, m), 6.98 (2H, m), 6.58 (1H, s), 5.58 (1H, t, *J* = 9.77 Hz), 5.09 (1H, d, *J* = 11.02 Hz), 5.05 (1H, d, *J* = 11.02 Hz), 4.15 (1H, s), 3.99 (1H, dd, *J* = 2.54 Hz, 8.50 Hz), 3.85 (3H, m), 3.77 (3H, s), 3.76 (3H, s), 3.62 (1H, dd, *J* = 2.76 Hz, 11.25 Hz), 3.31–3.05 (4H, m), 2.54 (1H, d, *J* = 17.92 Hz), 2.27 (3H, s), 2.14 (3H, s), 2.13 (3H, s), 1.44 (1H, d, *J* = 10.00 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.1, 148.8, 148.2, 142.1, 138.5, 137.1, 130.5, 129.6, 128.7, 128.6, 128.4, 128.0, 127.1, 126.9, 125.9, 124.8, 123.6, 119.9, 118.6, 117.2, 75.1, 73.7, 71.6, 63.1, 61.4, 60.5, 60.1, 60.0, 58.8, 58.2, 55.8, 41.8, 25.3, 15.9, 8.9; IR (NaCl) 3373, 2931, 2360, 1455, 1414, 1121, 1066, 1013 cm^{-1}; HRMS (FAB) calcd for $C_{41}H_{45}N_3O_7$ [M + H] 691.33; found 692.3310.

Synthesis of Dimethoxybenzene-cyanoamine Analogue (14). To a solution of cyanoamine **13** (15.0 mg, 0.0217 mmol) and $MgSO_4$ (11.0 mg, 0.0868 mmol, 4 equiv) in 1.5 mL of benzene, at 25 °C, was added *p*-TsOH (61.8 mg, 0.325 mmol, 15 equiv). The solution was aged for 4 h at room temperature. The reaction was then diluted with H_2O and extracted with CH_2Cl_2 (3×). The organic layers were combined, dried with $MgSO_4$, and concentrated by rotary evaporation. The crude film was dissolved in 1.5 mL of CH_2Cl_2. To this solution, at room temperature, was added Ac_2O (20 μL, 0.217 mmol, 10 equiv) and TEA (30 μL, 0.217 mmol, 10 equiv). The solution was aged 5 h at room temperature. The reaction was then quenched with an aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The residue was purified by pTLC with 35% EtOAc/hexanes to provide 13.8 mg (90%) of a yellowish foam: $[\alpha]^{17}_D$ +95.92 (*c* 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (2H, d, *J* = 7.51 Hz), 7.42 (2H, t, *J* = 7.37 Hz), 7.37-7.26 (4H, m), 7.13 (2H, d, *J* = 7.33 Hz), 6.43 (1H, s), 5.62 (1H, s), 5.11 (1H, d, *J* = 11.27 Hz), 5.05 (1H, d, *J* = 11.27 Hz), 4.73 (1H, d, *J* = 7.47 Hz), 4.56 (1H, s), 4.21 (1H, s), 3.98 (2H, dd, *J* = 12.18 Hz, 15.65 Hz), 3.83 (3H, s), 3.79 (3H, s), 3.74 (3H, s), 3.45 (1H, d, *J* = 7.75 Hz), 3.25–2.95 (3H, m), 2.66 (1H, d, *J* = 17.80 Hz), 2.40 (3H, s), 2.20 (3H, s), 1.98 (3H, s), 1.95 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4, 148.9, 148.5, 146.2, 139.0, 138.2, 137.9, 130.5, 128.4, 128.1, 127.7, 127.6, 127.5, 127.2, 126.7, 125.0, 124.5, 121.1, 119.1, 117.1, 96.1, 74.1, 73.0, 72.7, 60.7, 60.5, 60.2, 57.6, 57.2, 56.6, 56.0, 41.6, 29.8, 27.6, 20.2, 16.0, 9.9; IR (NaCl) 2929, 2852, 2360, 1762, 1685, 1453, 1350, 1205, 1064, 1007 cm^{-1}; HRMS (FAB) calcd for $C_{43}H_{45}N_3O_7$ [M + H] 715.33; found 716.3328.

Synthesis of Hybrid Cyanoamine Acetate (18). To a solution of keto-pentacycle **17** (84.0 mg, 0.119 mmol) in 12 mL of THF, at –78 °C, was added, dropwise, a 1.0 M THF solution of $LiAlH_4$ (3.00 mL, 2.99 mmol, 25 equiv). The solution was aged for 12 h to room temperature. The reaction was then cooled to –78 °C followed by careful addition of KCN (87.0 mg, 1.78 mmol, 15 equiv) in 3.8 mL of H_2O. The cooling bath was removed, followed by addition of AcOH (0.13 mL, 2.38 mmol, 20 equiv) and 3 mL of THF. The resultant slurry was aged for 12 h to room temperature. The reaction was then quenched by a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The organic layers were combined, dried with $MgSO_4$, and concentrated by rotary evaporation. The crude foam was dissolved in 5 mL of CH_2Cl_2. To this solution, at room temperature, was added Bu_3SnH (48 μL, 0.179 mmol, 1.5 equiv), AcOH (67 μL, 1.19 mmol, 10 equiv), and $(Ph_3P)_2PdCl_2$ (16.7 mg, 0.0238 mmol, 0.2 equiv). The solution was aged 15 min and then the reaction concentrated by rotary evaporation. The residue was purified by column chromatography with 35% EtOAc/hexanes to provide 50.0 mg (62%) of hybrid cyanoamine alcohol as an off-white foam: $[\alpha]^{17}_D$ +4.37 (*c* 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (1H, s), 7.41–7.30 (5H, m), 7.26 (3H, m), 6.96 (2H, m), 6.57 (1H, s), 5.83 (2H, d, *J* = 1.98 Hz), 5.58 (1H, t, *J* = 10.10 Hz), 5.09 (1H, d, *J* = 10.92 Hz), 5.02 (1H, d, *J* = 10.92 Hz), 4.28 (1H, s), 3.92 (1H, d, *J* = 12.10 Hz), 3.88 (1H, d, *J* = 2.48 Hz), 3.82 (1H, d, *J* = 12.07 Hz), 3.79 (1H, d, *J* = 1.57 Hz), 3.77 (3H, s), 3.62 (1H, dd, *J* = 2.83 Hz, 11.25 Hz), 3.30–3.08 (3H, m), 2.93 (1H, d, *J* = 9.96 Hz), 2.50 (1H, d, *J* = 17.86 Hz), 2.27 (3H, s), 2.16 (3H, s), 2.09 (3H, s), 1.39 (1H, d, *J* = 10.35 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.2, 148.7, 148.3, 145.5, 138.3, 137.1, 135.8, 130.5, 129.6, 128.8, 128.6, 128.4, 127.9, 127.1, 126.7, 125.8, 124.7, 120.1, 113.3, 111.1, 107.4, 100.0, 75.1, 73.7, 70.4, 62.9, 60.7, 60.1, 59.3, 58.2, 55.7, 51.0, 41.9, 25.3, 15.9, 8.80; IR (NaCl) 3436, 2918, 2357, 1455, 1385, 1325, 1237, 1109, 1072 cm^{-1}; HRMS (FAB) calcd for $C_{40}H_{41}N_3O_7$ [M + H] 675.29; found 675.2941.

To a solution of hybrid cyanoamine alcohol (14.0 mg, 0.0207 mmol) and $MgSO_4$ (10.0 mg, 0.0839 mmol, 4 equiv) in 1.5 mL of benzene, at 25 °C, was added *p*-TsOH (59.0 mg, 0.311 mmol, 15 equiv). The solution was aged for 1 h at room temperature. The reaction was then diluted with H_2O and extracted with CH_2Cl_2 (3×). The organic layers were combined, dried with $MgSO_4$, and concentrated by rotary evaporation. The crude ene-pentacyclic film was dissolved in 1.5 mL of CH_2Cl_2. To this solution, at room temperature, were added Ac_2O (19.6 μL, 0.207 mmol, 10 equiv) and TEA (28.9 μL, 0.207 mmol, 10 equiv). The solution was aged 5 h at room temperature. The reaction was then quenched with an aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The residue was purified by pTLC with 35% EtOAc/hexanes to provide 13.0 mg (90%) of acetate as a yellowish foam: $[\alpha]^{17}_D$ +80.21 (*c* 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (2H, d, *J* = 7.24 Hz), 7.43 (2H, t, *J* = 7.28 Hz), 7.37- 7.26 (4H, m), 7.14 (2H, d, *J* = 7.04 Hz), 6.46 (1H, s), 5.92 (1H, s), 5.88 (1H, s), 5.65 (1H, s), 5.12 (1H, d, *J* = 11.24 Hz), 5.03 (1H, d, *J* = 11.24 Hz), 4.61 (1H, dd, *J* = 2.52 Hz, 9.76 Hz), 4.54 (1H, s), 4.19 (1H, s), 4.02 (1H, d, *J* = 11.96 Hz), 3.99 (1H, d, *J* = 11.96 Hz), 3.80 (3H, s), 3.41 (1H, d, *J* = 7.08 Hz), 3.18 (1H, dd, *J* = 2.68 Hz, 9.36 Hz), 3.11–2.98 (2H, m), 2.62 (1H, d, *J* = 17.84 Hz), 2.35 (3H, s), 2.21 (3H, s), 1.97 (3H, s), 1.92 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7, 148.9, 148.6, 140.1, 138.1, 137.8, 130.4, 128.4, 128.0, 127.6, 127.3, 126.7, 126.4, 124.8, 118.9, 118.0, 112.3, 105.6, 101.2, 96.7, 74.1, 73.2, 72.8, 60.4, 58.3, 56.8, 56.6, 56.3, 41.7, 26.6, 20.1, 16.0, 9.8; IR (NaCl) 2929, 1762, 1455, 1368, 1317, 1202, 1120, 1074, 1028 cm^{-1}; HRMS (FAB) calcd for $C_{42}H_{41}N_3O_7$ [M + H] 699.29; found 700.3031.

Synthesis of Hybrid Phenol (19). To solution of acetate **18** (28.0 mg, 0.0400 mmol) in 3 mL of MeOH, at 25 °C, was added 30% Pd/C (5.6 mg, 20% w/w), and the mixture was purged and pressurized under 1 atm of H_2. The solution was aged for 6 h at room temperature. The reaction was then filtered through cotton and concentrated. The residue was purified by pTLC with 50% EtOAc/hexanes to provide 8 mg (32.8%) of a yellow film: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (3H, m), 7.15 (2H, d, *J* = 7.60 Hz), 6.23 (1H, s), 5.93 (1H, s), 5.87 (1H, s), 5.72 (1H, s), 5.68, (1H, s), 4.63 (1H, dd, *J* = 2.40 Hz, 9.60 Hz), 4.50 (1H, s), 4.25 (1H, s), 4.11 (1H, d, *J* = 12.00 Hz), 3.98 (1H, d, *J* = 12.00 Hz), 3.78 (3H, s), 3.43 (1H, d, *J* = 7.60 Hz), 3.18 (1H, dd, *J* = 2.80 Hz, 9.20 Hz), 3.11–2.98 (2H, m), 2.59 (1H, d, *J* = 17.60 Hz), 2.48 (3H, s), 2.38 (3H, s), 2.21 (3H, s), 1.97 (3H, s); ^{13}C NMR ($CDCl_3$,

100 MHz) δ 169.3, 145.8, 144.5, 143.1, 140.4, 138.3, 137.8, 136.1, 128.4, 128.1, 127.4, 127.0, 121.0, 119.5, 119.3, 118.4, 112.3, 105.8, 101.3, 95.8, 73.1, 73.0, 60.8, 57.5, 56.6, 55.8, 41.5, 29.7, 26.9, 20.4, 15.8, 9.5; IR (NaCl) 3441, 2918, 2363, 1769, 1638, 1462, 1434, 1374, 1198, 1121, 1083 cm^{-1}; HRMS (FAB) calcd for $C_{35}H_{35}N_3O_7$ [M + H] 609.25; found 610.2531; $[\alpha]^{17}_D$ +69.28 (*c* 1.0 $CHCl_3$).

Synthesis of Hybrid-Cyanoamine Analogue (20). To solution of phenol **19** (11.2 mg, 0.0184 mmol) in 3 mL of THF, at 25 °C, was added salcomine (1 mg, 0.00308 mmol, 0.17 equiv), and the mixture was purged and pressurized under 5 bar of O_2. The solution was aged for 12 h at room temperature. The reaction was then filtered through cotton and concentrated. The residue was purified by pTLC with 50% EtOAc/hexanes to provide 9.4 mg (82.2%) of quinone as a purple film: $[\alpha]^{17}_D$ −70.20 (*c* 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (3H, m), 7.18 (2H, d, *J* = 6.96 Hz), 5.93 (1H, s), 5.87 (1H, s), 5.54, (1H, s), 4.63 (1H, dd, *J* = 2.61 Hz, 9.46 Hz), 4.42 (1H, s), 4.29 (1H, d, *J* = 11.64 Hz), 4.19 (1H, d, *J* = 11.64 Hz), 4.16 (1H, s), 4.00 (3H, s), 3.42 (1H, d, *J* = 7.33 Hz), 3.30 (2H, m), 2.79 (1H, d, *J* = 7.53 Hz), 2.48 (1H, m), 2.42 (3H, s), 2.37 (3H, s), 1.97 (3H, s), 1.96 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 186.9, 181.5, 179.1, 155.5, 137.4, 137.1, 136.4, 132.6, 128.5, 127.9, 127.8, 118.6, 117.7, 112.7, 105.6, 101.5, 98.9, 73.6, 72.9, 61.0, 57.3, 56.4, 55.6, 53.8, 41.3, 21.8, 20.4, 9.5, 8.7; IR (NaCl) 2926, 2852, 1762, 1654, 1457, 1198, 1075 cm^{-1}; HRMS (FAB) calcd for $C_{35}H_{33}N_3O_8$ [M + H] 623.23; found 624.2360.

To a solution of cyanohybrid quinone (13.0 mg, 0.0181 mmol) in 3 mL of dioxane was added selenium(IV) oxide (1 mg, 0.00308 mmol, 0.17 equiv). The solution was aged for 12 h at 100 °C in an oil bath. The reaction was quenched with $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The organic layers were combined, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified taken up in 2 mL of CH_2Cl_2, and DMP was added at room temperature. The mixture was aged for hours. The reaction was quenched with 10% NaS_2O_3 in saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The residue was then dissolved in 1 mL of AcOH, and zinc was added at room temperature. The reaction was aged for 15 min with vigorous stirring and then filtered through cotton, quenched with $NaHCO_3$, and extracted with CH_2Cl_2 (3×). The residue was purified by pTLC with 50% EtOAc/hexanes to provide 9.4 mg (82.2%) of ketohydroquinone as a purple film: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (2H, d, *J* = 8.00 Hz), 7.83 (2H, m), 7.29 (2H, m), 7.08 (2H, m), 5.93 (1H, s), 5.87 (1H, s), 5.75 (1H, s), 4.63 (1H, dd, *J* = 2.61 Hz, 9.46 Hz), 4.60 (1H, s), 4.25 (1H, d, *J* = 11.64 Hz), 3.90 (3H, s), 3.88 (1H, d, *J* = 11.64 Hz), 3.56 (1H, s), 3.11 (2H, d, *J* = 7.53 Hz), 2.90 (1H, m), 2.60 (3H, s), 2.37 (3H, s), 2.21 (3H, s), 1.96 (3H, s); HRMS (FAB) calcd for $C_{35}H_{33}N_3O_9$ [M + H] 639.22; found 640.2325.

Synthesis of Acetate 22. To a solution of known ene-pentacycle **21** (34 mg, 44.8 μmol) in 2 mL of CH_2Cl_2, at 0 °C, was added TBAF (67μL, 1 M in THF, 1.5 equiv). TLC indicated complete conversion to phenol in 5 min, at which time acetic anhydride (67 μL, 1 M in CH_2Cl_2, 1.5 equiv) was added. After 5 min, TLC indicated a complete reaction. The reaction mixture was poured into brine and extracted with CH_2Cl_2 (3 × 5 mL), dried with $MgSO_4$, and filtered (cotton). pTLC with 50% EtOAc/hexanes gave 31 mg (quantitative) of the acetate as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48–7.37 (5H, m), 7.26–7.19 (3H, m), 6.96 (2H, d, *J* = 6.40 Hz), 6.51 (1H, s), 6.14–6.11 (1H, m), 5.92 (1H, s), 5.88 (1H, s), 5.73 (1H, s), 5.06 (2H, dd, *J* = 10.40, 64.00 Hz), 4.56 (1H, s), 3.94 (2H, dd, *J* = 12.0, 36.0 Hz), 3.74 (3H, s), 3.63 (1H, d, *J* = 4.00 Hz), 3.27–3.23 (2H, m), 3.15–3.01 (1H, m), 3.99 (1H, d, *J* = 4.00 Hz), 2.46 (3H, s), 2.14 (3H, s), 2.04 (3H, s), 1.98 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 168.2, 149.5, 148.6, 145.7, 141.2, 139.0, 138.4, 138.2, 133.2, 131.8, 128.7, 128.2, 127.8, 127.6, 127.2, 126.9, 126.7, 126.3, 116.7, 114.5, 108.9, 102.0, 101.9, 73.9, 72.7, 70.2, 60.9, 60.5, 56.9, 46.6, 41.7, 33.2, 20.3, 15.9, 9.6; HRMS (FAB) calcd for $C_{41}H_{40}N_2O_8$ [M + H] 688.3; found 689.2863.

To a solution of the acetate (60 mg, 87.1 μmol) in 24 mL of EtOAc, at 25 °C, was added 10% Pd/C (20 mg, 33% w/w), and the mixture was purged and pressurized under 1 atm of H_2. The suspension was stirred for 2 h at room temperature and monitored by LCMS, which showed product and starting material. Additional 10% Pd/C (25 mg, 42% w/w) was added, and after stirring for 2 h more the reaction was filtered through cotton and concentrated. The residue was purified by pTLC with 60% EtOAc/hexanes to provide 45 mg (85%) of clean phenol: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.18 (3H, m), 6.99 (2H, d, *J* = 6.84 Hz), 6.24 (1H, s), 6.16–6.09 (1H, m), 5.91 (2H, s), 5.88 (1H, s), 5.81 (1H, s), 4.55 (1H, s), 3.86 (2H, dd, *J* = 12.16, 32.4 Hz), 3.66–3.62 (4H, m), 3.47 (1H, s), 3.30–3.06 (3H, m), 2.96 (2H, d, *J* = 16.44 Hz), 2.53 (3H, s), 2.41 (3H, s), 2.10 (3H, s), 2.00 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 168.5, 145.7, 143.7, 138.9, 132.7, 129.7, 128.7, 128.4, 127.4, 127.1, 122.5, 119.6, 112.7, 119.1, 102.1, 102.0, 72.9, 70.4, 61.3, 56.9, 46.9, 42.0, 33.4, 21.0, 16.1, 9.9; HRMS (FAB) calcd for $C_{34}H_{34}N_2O_8$ [M + H] 598.23; found 599.2393.

To a solution of ene-pentacyclic phenol (14 mg, 30.1 μmol) in 2 mL of THF, in a Parr-type bomb apparatus, at 25 °C, was added *N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II) (salcomine, 4 mg, 40 mol %). The reaction was purged and pressurized under 5–10 atm of O_2. The suspension was stirred for 12 h at room temperature. Upon completion (TLC), the red reaction mixture was concentrated and purified (pTLC, 65% EtOAc/hexane) to provide 14 mg (76%) of quinone as a red residue: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.21 (3H, m), 7.01–7.00 (2H, m), 6.12 (1H, t, *J* = 6 Hz), 5.94 (1H, s), 5.92 (1H, s), 5.9 (1H, s), 4.42 (1H, s), 4.27 (2H, dd, *J* = 12.0, 62.6 Hz), 3.86 (3H, s), 3.67–3.6 (1H, m), 3.3309 (2H, d, *J* = 5.92 Hz), 2.88–2.86 (2H, m), 2.49 (1H, s), 2.43 (1H, s), 2 (1H, s), 1.8 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.8, 181.0, 169.2, 167.0, 155.5, 146.1, 141.0, 139.8, 139.4, 137.9, 137.1, 129.9, 129.1, 128.4, 127.5, 127.0, 116.6, 112.7, 108.8, 104.3, 102.0, 72.9, 69.7, 61.1, 59.8, 54.9, 46.3, 41.3, 29.8, 29.4, 20.7, 9.6, 8.8; HRMS (FAB) calcd for $C_{34}H_{32}N_2O_9$ [M + H] 612.21; found 613.2186.

To a solution of ene-pentacyclic quinone (14 mg, 22.9 μmol) in 2 mL of 1,4-dioxane, at 25 °C, was added selenium(IV) oxide (7.6 mg, 3 equiv). The reaction was stirred at 100 °C in a sealed vial for 7 h and monitored by TLC. When complete, the reaction was cooled to rt, concentrated, and purified (pTLC, 70% EtOAc/hexane) to provide 15 mg (quant) of quinone alcohol as a red residue: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.19 (3H, m), 7.01–6.95 (2H, m), 6.01–6.05 (1H, m), 5.98 (1H, s), 5.92 (1H, s), 5.91 (1H, s), 4.84 (1H, s), 4.43 (1H, s), 4.24 (2H, dd, *J* = 11.92, 69.82 Hz), 3.86 (3H, s), 3.66 (1H, s), 3.48 (1H, s), 3.35–3.25 (2H, m), 2.89 (1H, s, br), 2.55 (3H, s), 2.44 (3H, s), 2.01 (3H, s), 1.81 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.7, 181.5, 169.2, 163.7, 155.6, 146.3, 141.0, 139.6, 138.3, 137.8, 129.4, 128.4, 127.7, 127.6, 127.1, 116.4, 112.8, 108.9, 105.4, 102.1, 72.9, 69.5, 67.2, 65.2, 61.1, 55.3, 46.3, 41.6, 29.8, 20.7, 9.6, 8.7; HRMS (FAB) calcd for $C_{34}H_{32}N_2O_{10}$ [M + H] 628.21; found 629.2132.

To a solution of quinone alcohol (15 mg, 23.9 μmol) in 2 mL of CH_2Cl_2, at 25 °C, was added DMP (15 mg, 1.5 equiv). The reaction was stirred 1–2 h, monitored by TLC before being quenched with aqueous 10% $Na_2S_2O_3$ in saturated $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried over $MgSO_4$, filtered (cotton), concentrated, and taken forward as is. To the crude keto-quinone were added AcOH (0.5 mL) and a small scoop of zinc dust at rt. Within 5 min, the reaction mixture changed from blue to yellow, and TLC indicated a complete conversion. The AcOH was removed under reduced pressure and the residue purified by pTLC to give 12.5 mg (83%, 2 steps, 19.9 μmol) of yellow, hydroquinone residue. Keto-quinone: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21–7.18 (3H, m), 6.95–6.90 (2H, m), 6.15–6.09 (1H, m), 6.02 (1H, s), 5.91 (2H, s), 4.68 (1H, s), 4.19 (2H, dd, *J* = 12.12, 58.78 Hz), 3.98 (1H, s), 3.85 (3H, s), 3.45–3.35 (1H, m), 3.35–3.26 (1H, m), 2.55 (3H, s), 2.45 (3H, s), 2.01 (3H, s), 1.8 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.7, 183.7, 182.3, 169.2, 159.7, 155.2, 146.9, 141.0, 139.9, 137.6, 130.3, 129.1, 128.3, 127.7, 126.9, 126.6, 125.1, 116.1, 112.9, 109.0, 107.1, 106.0, 102.2, 73.9, 72.7, 71.7, 69.6, 57.0, 55.9, 47.8, 47.3, 46.8, 41.5, 29.8, 20.7, 9.4, 8.9; HRMS (FAB) calcd for $C_{34}H_{30}N_2O_{10}$ [M + H] 626.19; found 629.2153. Keto-hydroquinone (**22**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.33 (1H, s), 7.26–7.15 (3H, m), 6.90225 (2H, d, *J* = 6.68 Hz), 6.19–6.10 (1H, m), 5.99 (1H, s), 5.93 (1H, s), 5.9 (1H, s), 5.61 (1H, s, br), 4.75 (1H, s), 4.07 (1H, s), 3.96 (2H, s), 3.74 (3H, s), 3.29–3.15 (2H, m), 2.57 (3H, s), 2.42 (3H, s), 2.09 (3H, s), 2.01 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.9, 169.3, 160.9, 156.3, 153.1, 146.1, 141.2, 139.4, 138.0, 137.9, 129.8, 128.3, 127.3, 126.9, 122.2, 118.5, 116.4, 112.7, 109.1, 108.7, 102.8, 102.0, 72.8, 72.7, 70.1, 61.2, 56.9, 47.3, 41.4, 20.7, 9.6, 9.0; HRMS (FAB) calcd for $C_{34}H_{32}N_2O_{10}$ [M + H] 628.21; found 629.2157.

Synthesis of Homobenzylic Alcohol (23). To solution of **22** (12.5 mg, 19.9 μmol) in 7 mL of EtOAc, at 25 °C, was added 10% Pd/C (7 mg, 56% w/w), and the mixture was purged and pressurized under 1 atm of H_2. The suspension was stirred for 24 h at room temperature and monitored by TLC and LCMS. Upon complete consumption of **21**, the mixture was filtered (cotton), concentrated, and purified (pTLC, 70% EtOAc/hexanes) to provide 5.8 mg (54%) of desired product along with 3 mg of keto-

reduced product (28%, shown in box above): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.39 (1H, s), 6.02–5.97 (3H, m), 5.93 (1H, s), 5.68 (1H, s, br), 4.75 (1H, s), 4.07 (1H, s), 3.85 (3H, s), 3.49–3.40 (1H, m), 3.35–3.25 (1H, m), 2.56 (3H, s), 2.42 (3H, s), 2.19 (3H, s), 2.01 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.9, 169.3, 162.0, 156.3, 153.2, 146.2, 141.4, 139.5, 137.9, 129.8, 121.7, 118.9, 116.0, 113.0, 108.9, 108.1, 102.7, 102.1, 72.6, 64.4, 61.4, 56.8, 49.9, 41.4, 20.7, 9.6, 9.1; HRMS (FAB) calcd for $C_{27}H_{27}N_2O_{10}$ [M + H] 538.16; found 539.1658.

Synthesis of Hybrid Analogue 5. A 0.25 M solution of mixed anhydride **24** was prepared by dissolving angelic acid (5 mg, 50 μmol) in toluene (0.2 mL) and adding TEA (7μL) and 2,4,6-trichlorobenzoyl chloride (8 μL). To a solution of **23** (3 mg, 5.6 μmol) in 150 μL of toluene, at 25 °C, was added 0.25 M **24** solution (33 μL, 1.5 equiv). The reaction mixture was then stirred in a sealed vial at 70 °C for 72 h before solvent removal and purification (pTLC, 50% EtOAc/hexanes) gave 1.9 mg (55%) of a yellow residue: $[\alpha]^{17}_D$ +173.82 (*c* 0.20 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.36 (1H, s), 6.25 (1H, m), 6.03 (1H, s), 5.98 (1H, s), 5.95–5.90 (2H, m); 5.54 (1H, s), 4.72 (1H, s), 4.04 (1H, s), 3.93–3.85 (5H, m), 2.55 (3H, s), 2.41 (3H, s), 2.15 (3H, s), 2.02 (3H, s), 1.77 (3H, d, J = 6 Hz), 1.51 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.7, 169.2, 167.0, 160.9, 156.2, 153.1, 146.2, 141.2, 139.5, 139.1, 138.0, 129.5, 127.0, 121.6, 118.6, 116.2, 113.1, 109.0, 107.5, 102.8, 102.3, 76.7, 72.7, 62.7, 61.4, 56.9, 46.5, 41.4, 29.8, 20.6, 20.0, 15.7, 9.7, 9.1; HRMS (FAB) calcd for $C_{32}H_{32}N_2O_{11}$ [M + H] 620.20; found 621.2071.

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