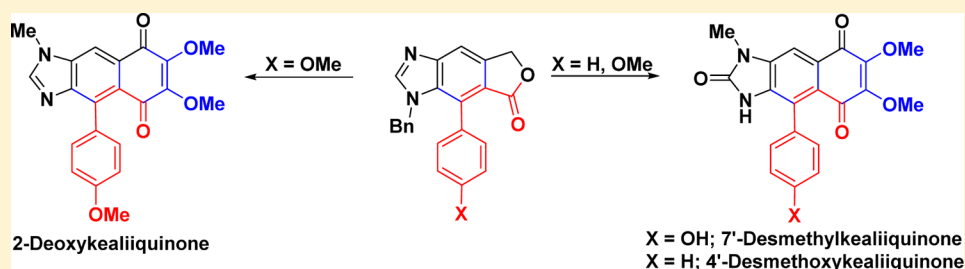# Total Synthesis of 7′-Desmethylkealiiquinone, 4′-Desmethoxykealiiquinone, and 2-Deoxykealiiquinone

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S *Supporting Information*

ABSTRACT: Synthetic approaches to the imidazonaphthoquinone core of kealiiquinone and related *Leucetta*-derived alkaloids are described. The polysubstituted benzimidazole framework can be constructed through intramolecular Diels−Alder reactions of propiolate-derived enynes followed by oxidation. Adjustment of the oxidation state of the thus formed lactone allows introduction of the 2,3-dihydroxybenzoquinone moiety through a presumed benzoin-like condensation between a phthaldehyde derivative and a masked glyoxal equivalent catalyzed by a cyanide ion. Oxidation of the C2-position can be accomplished through application of an operationally simple treatment of an imidazolium salt with bleach, thus producing the corresponding 2-imidazolone. Debenzylation of a late stage intermediate en route to kealiiquinone was compromised by concomitant *O*-demethylation upon treatment with triflic acid resulting in the formation of non-natural 7′-desmethylkealiiquinone. Other endgame strategies were evaluated; however, these efforts did not lead to completion of a synthesis of kealiiquinone but did provide access to other closely related analogues.

■ INTRODUCTION

Marine sponges have emerged as excellent sources of structurally diverse natural products[1,2] that possess activities against a number of important disease targets and as such serve as leads in medicinal chemistry programs.[3] Our laboratories have developed interests in the imidazole-containing alkaloids[4] belonging to the oroidin or the *Leucetta* families[5,6] of natural products. These synthetic programs have largely centered on the discovery and development of new methods and strategies for the elaboration of simple imidazole derivatives rather than the *de novo* construction of the imidazole ring.[7,8] In this manuscript, we describe the application of two such methods to the syntheses of three analogs of the imidazonaphthoquinone alkaloids kealiiquinone (1)[9] and 2-deoxy-2-aminokealiiquinone (2) (Figure 1).[10] Specifically the use of an intramolecular Diels−Alder reaction to construct a polysubstituted dihydrobenzimidazole[11] and oxidation of the imidazole C2-position via the intermediacy of imidazolium salts.[12]

Kealiiquinone (1) was isolated from a *Leucetta sp.* found off the islands of Guam and Saipan by the Scheuer lab and characterized by a combination of spectroscopic methods and X-ray crystallography.[9] More recently Schmitz and co-workers reported the isolation and characterization of the 2-amino congener 2 from *Leucetta chagosensis* collected in Chuuk State (part of the Federated States of Micronesia).[10] In both cases, biological activity was not reported by the isolation groups,

although the presence of the quinone would suggest that they might be good bio-Michael acceptors. The biosynthetic details of the *Leucetta* alkaloids are unknown, although it has been speculated that kealiiquinone (1) may be derived from the kealiinines (3−5)[13−15] through oxidation of the C-ring.[16] An alternative hypothesis has been posited involving the intermediacy and subsequent cyclization of the quinone-containing naamidine F (6).[17] Prior to our efforts,[18] only one report of a total synthesis of kealiiquinone has appeared from the Ohta lab resulting in the synthesis of the 2-keto tautomer of the natural product.[19,20] A second total synthesis of kealiiquinone (1) and the first of 2-deoxy-2-aminokealiiquinone (2) have been completed by our lab using a complementary bioinspired Friedel−Crafts-like strategy to the approach described by Ohta and co-workers. The synthetic version and a regioisomer were evaluated in a panel of cancer cell lines and shown to possess modest activity,[21] but the activity profile suggested a possible unique mechanism of action. However, this facet does not appear to have been pursued further by the Ohta group or anyone else. Very recently, syntheses of the less oxidized kealiinines have been reported independently by two groups,[14] including ours.[15] The cytotoxicity of the kealiinines (3−5), the kealiiquinones (1 and 2), and several intermediates
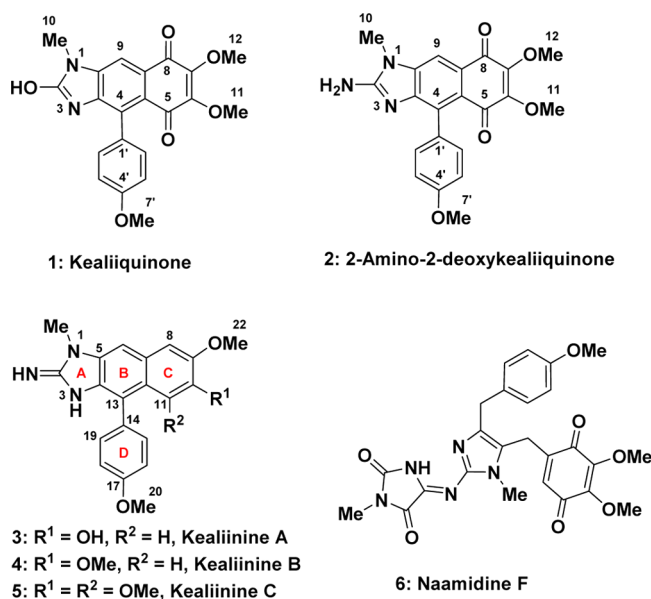
Figure 1. Naphthimidazole natural products isolated from *Leucetta* sponges.

have been investigated and shown for the most part to possess modest activity (IC_{50} = 20−95 μM in MTT growth assay with MCF7 breast cancer cell lines).[14,16]

■ RESULTS AND DISCUSSION

Synthetic Strategy. We were intrigued by the opportunity offered by kealiiquinone (**1**) to demonstrate the utility of several aspects of imidazole chemistry that we have developed,[7] as well as providing a platform to develop novel chemistry along the way.[12] Accordingly, our retrosynthetic analysis of the target is shown in Figure 2. Our experience with Diels−Alder
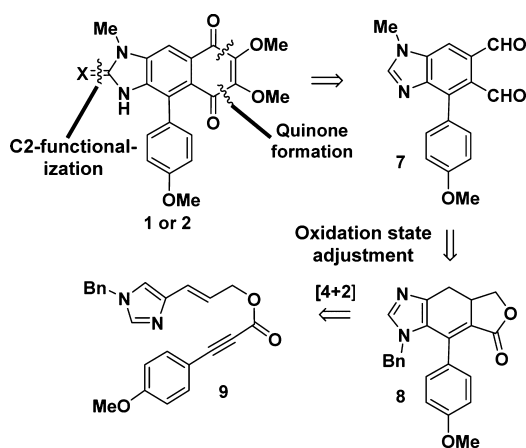

Figure 2. Overview of the synthetic strategy toward kealiiquinone.

reactions of 4-vinylimidazoles suggested that an intramolecular variant of this chemistry would provide rapid and controlled access to polysubstituted benzimidazole (**8**→**9**, Figure 2).[11,22−32] In our hands we have found the 4-isomers to be superior in the cycloaddition chemistry and thus the choice of a benzyl protecting group in enyne **9** would permit the position-selective incorporation of the methyl substituent later in the synthetic sequence. Whereas the cycloaddition chemistry would properly position substituents around the core framework, a

method was needed for the installation of the 2,3-dimethoxy-quinone moiety. While there were limited options for this transformation, chemistry reported by Venuti,[33] using a cyanide-catalyzed, benzoin-like condensation via the dialdehyde **7** offered a potential solution (Figure 2). Elaboration at the C2-position of the imidazole via metalation and electrophilic quench would then deliver either of the two kealiiquinone natural products **1** and **2** from a common late-stage intermediate (Figure 2).[34,35]

Initial Experiments. As part of our exploratory efforts on the intramolecular Diels−Alder and as a prelude to an approach to kealiiquinone we had prepared dihydrobenzimidazole **14** from *N*-benzyl protected enyne **13** in 83% yield.[11] Initial experiments directed toward aromatization of the cycloadduct were performed with 10% Pd−C and air, and while these conditions provided the required product **15** (Scheme 1), it

Scheme 1. Assembly of the Benzimidazole Core
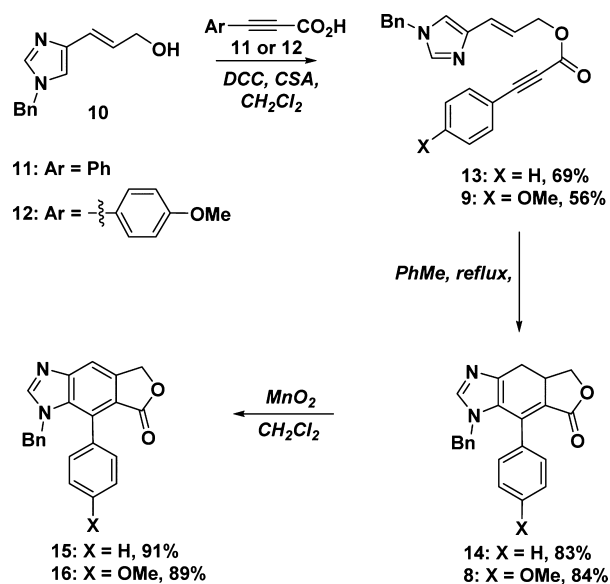
gave inconsistent yields and required extended reaction times for good conversions. Subsequently, we found that the aromatization could be effected efficiently and reproducibly in the presence of MnO_2, delivering **15** in 91% yield.[36]

Since these preliminary experiments were successful, we decided to construct the full substrate which required the preparation of the anisyl substituted propiolic acid **12**. This was prepared through a Sonogashira cross-coupling between *p*-iodoanisole and propargyl alcohol (85%).[37] Oxidation of the product with MnO_2 provided the aldehyde (85%)[38] and a subsequent Pinnick oxidation produced the corresponding propiolic acid **12** (60%).[39,40] The acid **12** was coupled with the benzyl protected vinylimidazole **10** through a DCC-mediated condensation delivering enyne **9** (Scheme 1). Subjection of the thus obtained enyne **9** to heating in toluene at reflux for 48 h resulted in the formation of the dihydrobenzimidazole **8** in excellent yield. Oxidation with MnO_2 affords the aromatized benzimidazole **16** in good yield (Scheme 1). The structure of **16** was confirmed through X-ray crystallography (see SI) which nicely illustrated the relative location of the two aromatic substituents.[18] Of note is the slight pyramidalization of the imidazole N1 ($\Sigma\angle$ = 353.89°) and the deviation from orthogonality around the C3−C10 bond (crystallographic

Scheme 2. Initial Approach to Elaboration of Benzimidazole Core
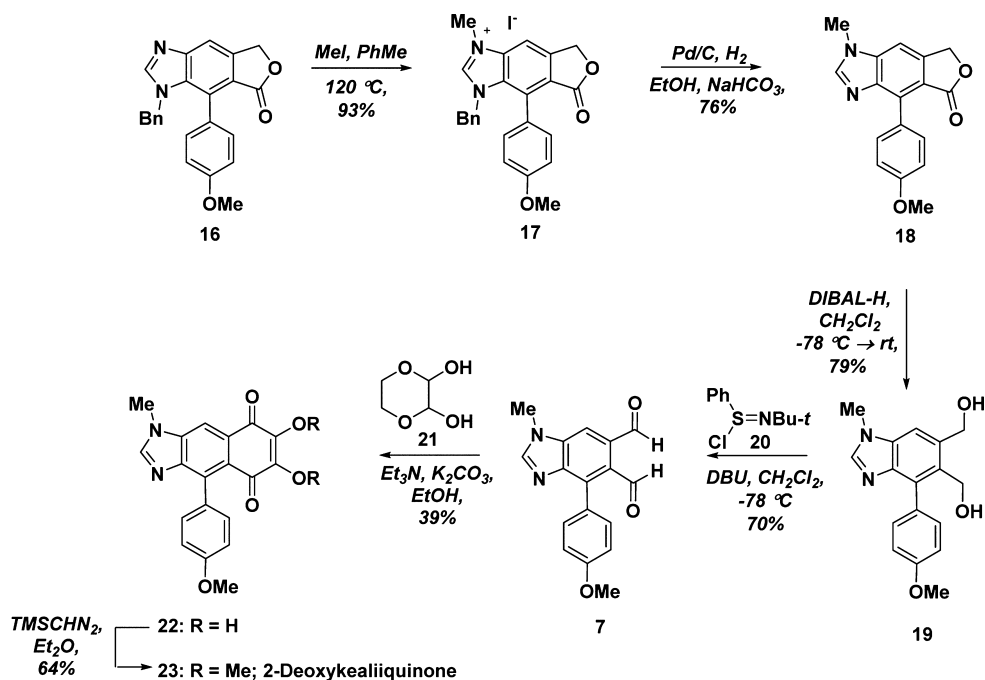
Scheme 3. Early Introduction of 2-Oxo Group

29: 7'-Desmethylkealiiquinone

X-ray structure of compound **25**
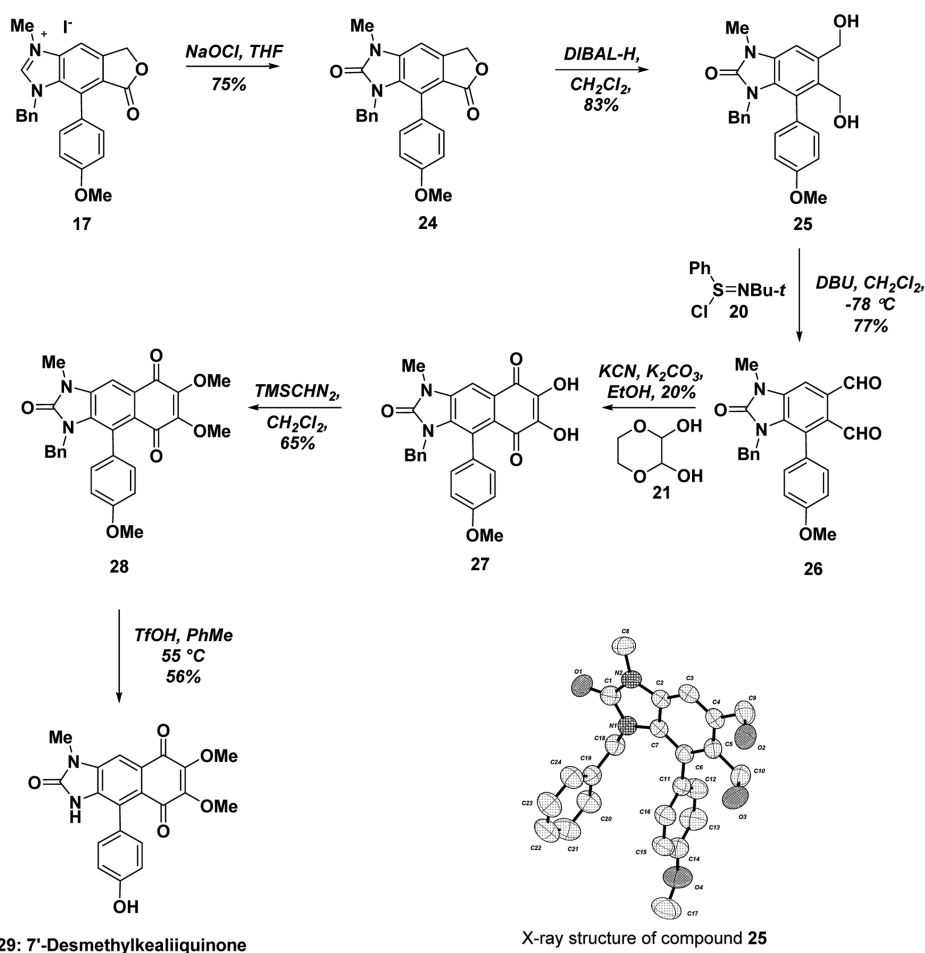
numbering). Presumably both structural effects minimize nonbonded interactions between the *N*-benzyl and anisyl moieties. At this stage, both the unsubstituted and *p*-methoxy systems **15** and **16** were taken through the same set of reactions

**Scheme 4. Late Stage Introduction of the 2-Oxo Group**
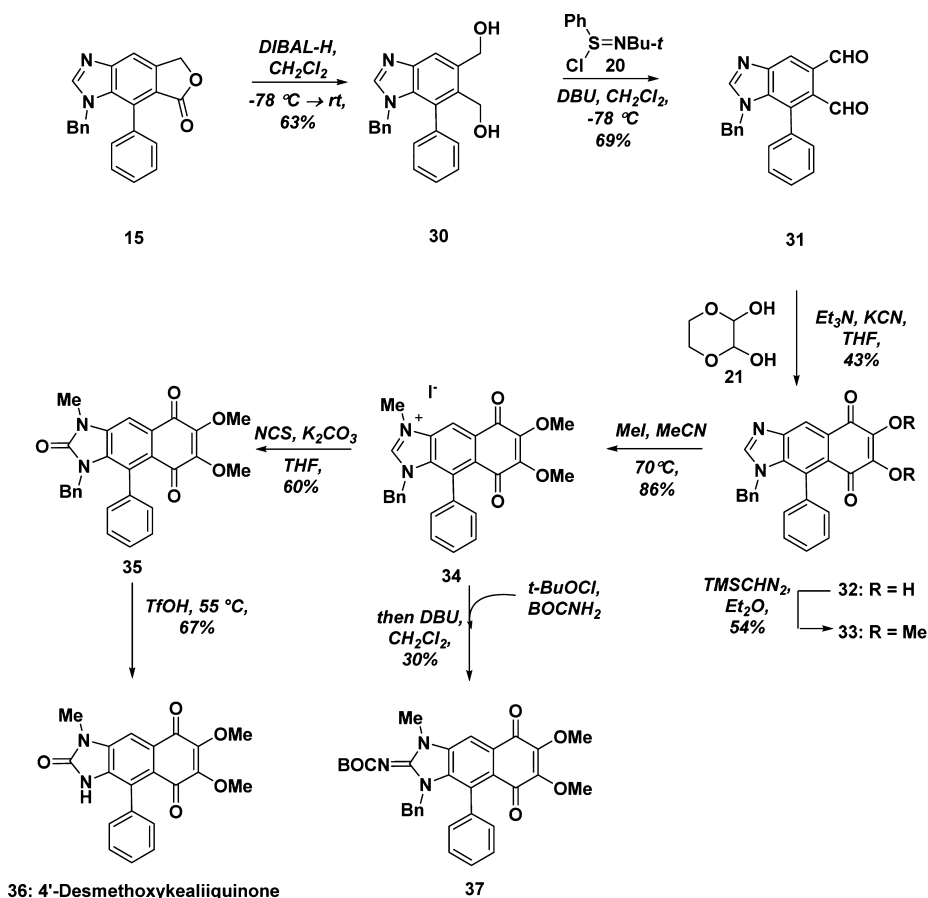
to construct the imidazonaphthoquinone framework but in slightly different sequences as described in Schemes 2, 3, and 4.

First Generation Approach. Initially, it was decided to introduce the N-methyl group on the p-anisyl-containing substrate **16**, as this can be accomplished via the intermediacy of the imidazolium salt by hydrogenolysis of the benzyl group (Scheme 2). Conversion of **16** to the imidazolium salt **17** was accomplished uneventfully by treatment with methyl iodide, and subsequent catalytic hydrogenation of **17** delivered the corresponding debenzylated N-methyl benzimidazole derivative **18**. In our preliminary experiments we noted some variability in the yield of this reaction. Ultimately however it was recognized that hydrolysis of the lactone occurred; treatment of the crude hydrogenation product with aqueous acid recycled the γ-hydroxy acid thus providing improved yields and reproducibility. This strategy for introduction of the methyl group has the advantage of avoiding potential selectivity issues in comparison to an approach involving direct methylation of the parent benzimidazole.[41] Reduction of the lactone to the corresponding diol **19** was accomplished effectively with DIBAL, setting the stage for the installation of the final ring. In order to accomplish this critical transformation, the corresponding dialdehyde **7** was required. Initial attempts to convert diol **19** to the phthaldehyde derivative **7** with common oxidants were thwarted by the formation of the lactone; only Swern conditions were partially successful. In this latter case there was some batch to batch inconsistency, the cause of which we were unable to track down. Fortunately, this led us to investigate reagents that behaved mechanistically similarly to Swern reagents; among these, the best system we identified was

reported by Mukaiyama and co-workers involving sulfinimidoyl chlorides, e.g., **20** in the presence of DBU.[42] This reagent combination reproducibly resulted in the formation of the phthaldehyde **7** in yields between 65% and 75%. With the aldehyde in hand we were in position to evaluate Venuti's method for its conversion into the corresponding dihydroxy benzoquinone **22**.[33] Gratifyingly, we found that the 2,3-dihydroxybenzoquinone **22** was produced reproducibly, albeit, in a modest yield of approximately 40%. At this stage, all that remained to be done to complete the total synthesis of kealiiquinone (**1**) was the conversion of the hydroxyl groups to methyl ethers and oxidation at C2. The first task was accomplished by taking advantage of the fact that the OH groups are part of a vinylogous acid and as such reacted efficiently with TMS-diazomethane, delivering dimethoxyquinone **23**. However, the introduction of functionality at C2 was significantly more difficult. We and others have routinely used metalation by deprotonation at C2 with a strong base (BuLi or LDA) and followed that by trapping with a suitable electrophile:[15,16] in this context either (TMSO)$_2$ for kealiiquinone (**1**)[35] or TsN$_3$ for the amino congener **2**.[34] Multiple attempts to perform this chemistry with **23** as a substrate simply failed to produce the anticipated products; indeed these reactions did not produce any products that we were able to characterize. Experiments to trap out any metalated intermediates with D$_2$O or methanol-D$_4$ were similarly unsuccessful. Although we have no experimental evidence to support our hypothesis, we suspect that electron transfer processes are intervening. As a means to circumvent these issues, we briefly attempted to introduce functionality at

Scheme 5. Attempted Use of a Temporary Activating Group
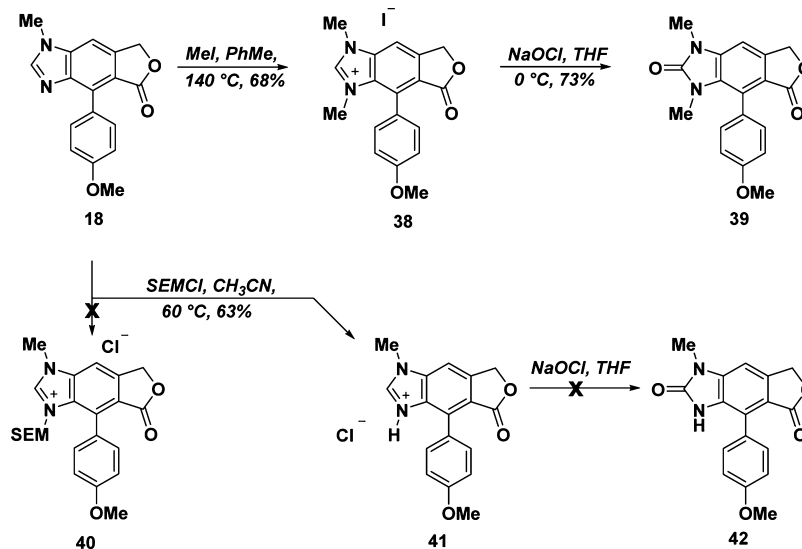
C2 earlier in the sequence by metallating with *n*-BuLi on lactones **16** or **18**; however issues with solubility or deprotonation occurring on the *N*-benzyl or the lactone methylene compromised this strategy. Alternative timings for introducing the C2-functionality were rejected as these options invariably increased the step count unacceptably.

Second Generation Approach. Given this late stage failure to functionalize at C2 of the naphthimidazole, we began to contemplate our options for moving the synthesis forward, and it occurred to us that the imidazolium salts that were prepared as a means to selectively methylate the benzimidazoles may be easier to functionalize given the increased acidity of the proton at C2 in these systems.[43] Based on this hypothesis, we have developed an extremely mild method for introducing oxygen at C2 through exposure of the imidazolium ion to bleach or alternatively nitrogen can be introduced through exposure to *N*-chlorosulfonamides or *N*-chlorocarbamates; this chemistry has been described in more detail elsewhere.[12] With this method in hand we subjected the lactone imidazolium species **17** to bleach and found that it too underwent the oxidation to provide the 2-benzimidazolone **24** in good yield (Scheme 3). An X-ray structure determination on the DIBAL-reduction product **25** unequivocally demonstrates the introduction of the 2-oxo moiety and served to confirm the relative location of the methyl and aryl groups.[18] At this point we elaborated the benzimidazolone **25** in a largely analogous fashion to the corresponding phthaldehyde **26**. Although the efficiency was lower, dialdehyde **26** was converted into the dihydroxyquinone **27** and subsequently the hydroxyl groups were converted into methoxy groups by treatment with TMS-diazomethane (**27** → **28**, Scheme 3). All that remained to complete the revised synthesis of kealiiquinone (**1**) was removal of the *N*-benzyl protecting group; unfortunately this proved to be exceedingly difficult. While *N*-benzyl groups can be removed quite readily from amines under a variety of conditions, amides on the other hand tend to be much more challenging substrates. Indeed it was found that standard reductive or oxidative conditions failed to remove the *N*-benzyl moiety.[44] Ultimately, we determined that heating the substrates in neat triflic acid resulted in debenzylation with reasonable efficiencies.[45] Unfortunately, in the case of the precursor to kealiiquinone, these reaction conditions led to the selective

demethylation of the 7'-methyl and thus the formation of 7'-desmethylkealiiquinone (**29**). In an effort to access the natural product, various attempts were made to remethylate the phenolic hydroxyl group. In our hands this resulted in overmethylation (methylation of the imidazole nitrogen and the hydroxyl group) or *N*-methylation under a variety of different conditions and with different methyl sources.

Late Stage Functionalization. An alternative strategy was explored concurrently with the one described above in which the introduction of the C2-substituent was delayed until the end of the synthesis. In part this was undertaken in order to not only evaluate the strategy in general but also establish whether the highly functionalized quinones were viable substrates in our oxidative chemistry. Thus lactone **15** was reduced to the corresponding diol **30** and then converted to the phthaldehyde **31** upon treatment with **20** (Scheme 4). Conversion to the 2,3-dihydroxyquinone **32** was accomplished with glyoxal **21**, followed by methylation with TMS-diazomethane. Methylation of the imidazole nitrogen to prepare the imidazolium salt **34** was then carried out by exposure of **33** to methyl iodide in acetonitrile at reflux. Initial oxidation experiments of **34** with bleach resulted in the formation of the imidazolone **35**, but the yields were rather low, *ca.* 20%. Fortunately, we had established previously that other chloronium sources effect this chemistry, and so exposure of **34** to NCS and aqueous potassium carbonate delivered the imidazolone **35** in 60% yield.[12] Reaction of the imidazolone with TfOH at 55 °C resulted in debenzylation and the formation of 4'-desmethoxykealiiquinone (**36**). With the imidazolium salt in hand, we also took the opportunity to evaluate the introduction of an imino group through exposure to an *N*-chlorocarbamate (Scheme 4); to date only simple benzimidazolium and imidazolium salts had been investigated in this chemistry.[12] While the yield turned out to be quite modest, the reaction of **34** with *N*-chloro *tert*-butylcarbamate (produced *in situ* from *tert*-butyl carbamate and *t*-BuOCl) did produce the expected product **37** (Scheme 4). A preliminary attempt to remove the Bn- and BOC-protecting groups by sequential treatment with TfOH and then TFA was not successful.

One further strategy was evaluated to prepare the imidazolium salt near the end of the synthesis with a more easily removable *N*-substituent, but one that was capable of

activating the oxidation (Scheme 5). To test the feasibility of such an approach given that the N3-position is relatively hindered, lactone **18** was used as a model and converted to the corresponding dimethyl imidazolium salt **38**. Gratifyingly, treatment of the salt with bleach resulted in C2-oxidation to deliver imidazolone **39** in good yield suggesting that late stage functionalization through application of our chemistry was achievable. Frustratingly however, extension of this chemistry with removable substituents on N3 was unsuccessful. Specifically, attempted introduction of a MOM group was unsuccessful, whereas the attempted incorporation of a SEM group[35] resulted in the net protonation of the imidazole and production of the imidazolium salt **41**.[46] The significant downfield shift of the C2-proton absorbance in the ^{1}H NMR spectrum of the product is characteristic of the formation of an imidazolium species. This was further confirmed when an X-ray crystal structure of this product was obtained, which clearly indicates the protonation of the nitrogen along with chloride as the counterion (see Supporting Information). Our assumption here is that the proximity of the aryl group to the nitrogen atom renders it sterically hindered and only small electrophiles can access it. Attempts to oxidize the protonated imidazolium salt **41** with bleach to the corresponding imidazolone **42** were not successful. Presumably, the basic nature of the reaction conditions simply results in deprotonation and inactivation of the imidazole.

■ **CONCLUSION**

Efficient routes have been developed to the heterocyclic framework of kealiiquinone through application of an intra-molecular Diels−Alder reaction of an enyne, C2-functionalization through a novel oxidation of imidazolium salts, and application of an underutilized method for the formation of dihydroxy quinones from phthaldehydes. Indeed, this work constitutes the first application of Venuti's method for the *de novo* construction of a 2,3-dimethoxyquinone. Unfortunately deprotection of an *N*-benzyl moiety from the penultimate intermediate resulted in concomitant demethylation delivering 7′-desmethylkealiiquinone rather than the natural product. Similar chemistry has been used to obtain related materials lacking the 4′-methoxy group and the 2-oxo group which will enable the SAR investigations of this unique family of natural products.

■ **EXPERIMENTAL SECTION**

Chemicals were used as received unless indicated otherwise. NMR spectra were obtained at either 500 or 300 MHz (for ^{1}H NMR spectra) or 125 or 75 MHz (for ^{13}C NMR) in CDCl$_3$ unless indicated otherwise. ^{1}H NMR spectra were referenced to residual protiosolvent unless indicated otherwise (CHCl$_3$ δ = 7.26 ppm). For spectra recorded in other solvents, residual MeOH (δ = 3.31 ppm) or DMSO (δ = 2.50 ppm) were used as internal references. ^{13}C NMR spectra were recorded in CDCl$_3$ (unless otherwise indicated) using residual CHCl$_3$ (δ = 77.2 ppm) as an internal reference. For spectra recorded in other solvents, residual MeOH (δ = 39.5 ppm) and DMSO (δ = 49.0 ppm) were used as internal references. Infrared (IR) spectra were obtained on neat samples (ATR spectroscopy) or using either KBr pellets for solids or neat films on NaCl plates for liquids (transmission). Analytical thin-layer chromatography (TLC) was performed on silica gel plates, 200 mesh with F254 indicator. Visualization was accomplished by UV light (254 nm) and/or a 10% ethanol solution of KMnO$_4$. Flash column chromatography was performed with 230−400 silica. High resolution mass spectra (HRMS)

were recorded by electrospray ionization (ESI-TOF) or atmospheric-pressure chemical ionization (APCI-TOF) unless otherwise indicated.

(2E)-3-(1-Benzyl-1H-imidazol-4-yl)prop-2-enyl 3-(4-methoxyphenyl)propynoate (9). Propiolic acid **12** (2.00 g, 11.4 mmol), alcohol **10** (2.94 g, 13.7 mmol), DMAP (0.14 g, 1.2 mmol), and camphorsulfonic acid (0.16 g, 0.70 mmol) were dissolved in CH$_2$Cl$_2$ (50 mL) and cooled to −78 °C under N$_2$. DCC (3.50 g, 17.1 mmol) dissolved in CH$_2$Cl$_2$ (20 mL) was added dropwise. The mixture was allowed to come to rt and stir for 2 h. The solids were filtered through Celite and washed with CH$_2$Cl$_2$. The filtrate was reduced, and the resulting brown residue was purified by column chromatography (8:2 EtOAc/Hexane) to afford **9** as an off-white solid (2.53 g, 56%). Mp: 65−67 °C; ^{1}H NMR: δ = 7.52 (s, 1H), 7.49 (d, *J* = 2.1 Hz, 2H), 7.36−7.31 (m, 3H), 7.15−7.13 (m, 2H), 6.86 (m, 3H), 6.58 (d, *J* = 15.6 Hz, 1H), 6.47−6.38 (dt, *J* = 15.5, *J* = 6.2 Hz, 1H), 5.06 (s, 2H), 4.82 (d, *J* = 6.6 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR: δ = 161.6, 154.2, 139.8, 137.9, 135.9, 135.0, 129.1, 128.5, 127.4, 127.0, 120.6, 117.9, 114.4, 111.5, 87.3, 80.1, 66.5, 55.5, 51.0; IR (KBr, cm^{-1}): 3105, 2195, 1899, 1697, 1602, 1567, 1541; HR-ESIMS (*m/z*): calcd for [M + H]$^+$ C$_{23}$H$_{21}$N$_2$O$_3$ is 373.1547, found 373.1564.

3-Benzyl-4-(4-methoxyphenyl)-3,7,7a,8-tetrahydro-5H-furo-[3,4-f]benzimidazol-5-one (8). Enyne **9** (2.54 g, 6.84 mmol) was dissolved in toluene (200 mL) and purged with N$_2$ for 15 min. The solution was then heated at 130 °C in a sealed tube for 48 h. The solvent was removed, and the resulting solids were washed with diethyl ether to afford **8** as an off-white solid (2.14 g, 84%). Mp: 199−201 °C; ^{1}H NMR: δ = 7.44 (s, 1H), 7.24−7.10 (m, 5H), 6.85 (dd, *J* = 5.7, 1.8 Hz, 2H), 6.64 (dd, *J* = 5.1, 1.5 Hz, 2H), 4.68 (dd, *J* = 16.5, 7.5 Hz, 2H), 4.43 (d, *J* = 15.6 Hz, 1H), 4.01 (t, *J* = 8.7 Hz, 1H), 3.83 (s, 3H), 3.67−3.58 (m, 1H), 3.06 (dd, *J* = 15.0, 8.7 Hz, 1H), 2.73 (dd, *J* = 17.1, 15.9 Hz, 1H); ^{13}C NMR: δ = 168.1, 160.3, 144.4, 141.2, 139.4, 135.8, 128.7, 128.4, 128.1, 126.6, 123.9, 117.2, 70.6, 55.4, 50.3, 38.1, 28.0; IR (KBr, cm^{-1}): 3465, 2946, 1737, 1621, 1512, 1252; HR-ESIMS (*m/z*): calcd for [M + H]$^+$ C$_{23}$H$_{21}$N$_2$O$_3$ 373.1547, found 373.1571.

3-Benzyl-4-phenyl-3,7-dihydro-5H-furo[3,4-f]benzimidazol-5-one (15). To **14**[11] (5.5 g, 16 mmol) in CH$_2$Cl$_2$ (250 mL) was added MnO$_2$ (∼85% act.) (15 g) followed by heating at 40 °C for 48 h. The solids were filtered through Celite and washed with CH$_2$Cl$_2$. The filtrate was reduced to give the product as a white solid (5.0 g, 91%). Mp: 185−186 °C; ^{1}H NMR: δ = 8.02 (s, 1H), 7.85 (s, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.18−7.13 (m, 4H), 6.54 (d, *J* = 7.5 Hz, 2H), 5.37 (s, 2H), 4.93 (s, 2H); ^{13}C NMR: δ = 169.8, 148.9, 140.5, 135.7, 132.3, 129.8, 128.8, 128.6, 128.1, 127.9, 127.6, 126.2, 118.4, 112.6, 68.1, 50.3; IR (cm^{-1}): 3005, 2923, 1752, 1497, 1363, 1251, 1130, 1018; HR-ESIMS (*m/z*): calcd for [M + Na]$^+$ C$_{22}$H$_{16}$N$_2$O$_2$Na 363.1104, found 363.1114.

3-Benzyl-4-(4-methoxyphenyl)-3,7-dihydro-5H-furo[3,4-f]-benzimidazole-5-one (16). **8** (7.0 g, 19 mmol) was dissolved in CH$_2$Cl$_2$ (500 mL), and MnO$_2$ (18.0 g, 188 mmol) was added. Then the mixture was stirred at rt for 24 h. The solids were filtered and washed with CH$_2$Cl$_2$ followed by MeOH. The filtrate was concentrated to give **16** as an off-white solid (6.24 g, 89%). Mp: 176−178 °C; ^{1}H NMR: δ = 8.01 (s, 1H), 7.82 (s, 1H), 7.21−7.16 (m, 3H), 7.06 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 7.5 Hz, 2H), 5.35 (s, 2H), 4.97 (s, 2H), 3.84 (s, 3H); ^{13}C NMR: δ = 170.0, 159.8, 149.4, 148.9, 140.5, 135.8, 132.7, 131.0, 128.7, 128.0, 127.6, 126.2, 124.2, 118.5, 113.3, 112.4, 68.0, 55.3, 50.3; IR (KBr, cm^{-1}): 2947, 1739, 1614, 1500, 1347, 1253; HR-ESIMS (*m/z*): calcd for [M + Na]$^+$ C$_{23}$H$_{18}$N$_2$O$_3$Na 393.1210, found 393.1210.

3-Benzyl-4-(4-methoxyphenyl)-1-methyl-5-oxo-5,7-dihydro-3H-furo[3,4-f]benzimidazol-1-ium Iodide (17). **16** (0.37 g, 1.0 mmol) was dissolved in toluene (20 mL), and MeI (0.20 mL, 3.2 mmol) was added. The mixture was heated at 120 °C for 24 h during which additional aliquots of methyl iodide (0.5 equiv) were added until no starting material could be detected by TLC. The solids were filtered and washed with EtOAc to afford **17** as a pale yellow solid (0.48 g, 93%). Mp: 198−200 °C; ^{1}H NMR: δ = 10.50 (s, 1H), 8.03 (s, 1H), 7.25−7.12 (m, 5H), 6.94−6.87 (m, 4H), 5.43 (s, 2H), 5.27 (s, 2H), 4.32 (s, 3H), 3.86 (s, 3H); ^{13}C NMR: δ = 167.7, 160.8, 146.4, 144.8, 136.8, 132.2, 131.4, 131.1, 130.1, 129.2, 127.7, 122.8, 121.0,

113.9, 106.7, 68.0, 55.5, 53.2, 35.4; IR (cm^{-1}): 2939, 1775, 1612, 1575, 1501, 1451, 1378, 1337; HR-ESIMS (m/z): calcd for [M + H]$^+$ C$_{24}$H$_{21}$N$_2$O$_3$ 385.1547, found 385.1548.

4-(4-Methoxyphenyl)-1-methyl-1,7-dihydrofuro[3,4-f]-benzimidazol-5-one (18). To imidazolium salt **17** (0.44 g, 0.86 mmol) was added EtOH (50 mL) and sat. NaHCO$_3$ (5 mL), followed by 10% Pd/C (0.10 g). The reaction mixture was heated at 80 °C under H$_2$ (1 atm) for 24 h. The solids were filtered and washed with CH$_2$Cl$_2$/MeOH followed by water. The aqueous solution was then acidified to pH = 5 with 3 M HCl and stirred for 2 h. The resulting aqueous solution was extracted multiple times with CH$_2$Cl$_2$. The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated. The resulting solid was recrystallized from MeOH to afford **18** as a white solid (0.19 g, 76%). Mp: >250 °C; ^{1}H NMR (DMSO-d$_6$): δ = 8.32 (s, 1H), 7.69 (s, 1H), 7.55 (d, J = 9.2 Hz, 2H), 6.98 (d, J = 9.2 Hz, 2H), 5.39 (s, 2H), 3.89 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (DMSO-d$_6$): δ = 170.5, 159.7, 147.9, 143.1, 142.6, 139.8, 133.4, 133.2, 125.4, 114.6, 113.2, 102.9, 68.4, 55.7, 31.6; IR (KBr, cm^{-1}): 3044, 2957, 2835, 1739, 1603, 1501, 1453; HR-ESIMS (m/z): calcd for [M + H]$^+$ C$_{17}$H$_{15}$N$_2$O$_3$ 295.1077, found 295.1092.

[4-(4-Methoxyphenyl)-1-methyl-1H-benzimidazole-5,6-diyl]-dimethanol (19). Benzimidazole **18** (0.19 g, 0.65 mmol) was dissolved in CH$_2$Cl$_2$ (5 mL) and cooled to −78 °C under N$_2$. DIBAL-H (1 M in Hexane) (1.5 mL, 1.5 mmol) was added dropwise, and the reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction mixture was cooled to 0 °C, and water was added slowly followed by MeOH. The solids were filtered and washed with CH$_2$Cl$_2$ and MeOH. The organic extract was separated, and the residual aqueous solution was extracted multiple times with CH$_2$Cl$_2$. The combined organic extracts were dried (anhyd. Na$_2$SO$_4$) and concentrated. The resulting white solid was triturated with Et$_2$O to afford **19** as a white solid (0.15 g, 79%). Mp: 245−247 °C; ^{1}H NMR (DMSO-d$_6$): δ = 8.02 (s, 1H), 7.58 (s, 1H), 7.43 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 5.25 (t, J = 5.5 Hz, 1H), 4.83 (d, J = 5.2 Hz, 2H), 4.79 (t, J = 4.8 Hz, 1H), 4.43 (d, J = 4.5 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (DMSO-d$_6$): δ = 158.8, 144.7, 141.6, 137.6, 134.2, 133.3, 132.5, 129.9, 129.8, 113.5, 108.4, 62.4, 58.5, 55.6, 31.2; IR (cm^{-1}): 3074, 2889, 1608, 1574, 1340, 1237, 1174, 1015; HR-ESIMS (m/z): calcd for [M + H]$^+$ C$_{17}$H$_{19}$N$_2$O$_3$ 299.1390, found 299.1411.

4-(4-Methoxyphenyl)-1-methyl-1H-benzimidazole-5,6-dicarbaldehyde (7). Diol **19** (0.10 g, 0.34 mmol) was dissolved in CH$_2$Cl$_2$, and DBU (0.2 mL, 1.34 mmol) was added. The solution was cooled to −78 °C under N$_2$, and N-tert-butylbenzenesulfinimidoyl chloride (**20**) (0.22 g, 1.02 mmol) dissolved in CH$_2$Cl$_2$ (5 mL) was added dropwise. The mixture was stirred at −78 °C for 30 min. The reaction mixture was quenched with sat. NaHCO$_3$, and the organic layer was separated. The remaining aqueous solution was extracted with CH$_2$Cl$_2$ (2×). The combined organic extracts were dried (anhyd. Na$_2$SO$_4$) and concentrated. The resulting residue was purified by column chromatography (the silica gel was neutralized with 5% Et$_3$N prior to purification) (EtOAc to 2% MeOH in EtOAc) to afford **7** as an off-white solid (0.069 g, 70%). ^{1}H NMR: δ = 10.61 (s, 1H), 10.16 (s, 1H), 8.09 (s, 1H), 8.05 (s, 1H), 7.49 (d, 2H, J = 8.4 Hz), 7.08 (d, 2H, J = 8.4 Hz), 3.97 (s, 3H), 3.89 (s, 3H); ^{13}C NMR: δ = 193.5, 192.9, 160.2, 147.7, 145.3, 139.8, 136.7, 133.1, 132.7, 129.5, 125.1, 114.1, 109.7, 55.5, 31.7; IR (KBr, cm^{-1}): 3105, 2928, 2881, 1777, 1751, 1682, 1663, 1566; HR-ESIMS (m/z): calcd for [M + H]$^+$ C$_{17}$H$_{15}$N$_2$O$_3$ 295.1077, found 295.1110.

6,7-Dihydroxy-4-(4-methoxyphenyl)-1-methyl-1H-naphtho-[2,3-d]imidazole-5,8-dione (22). To phthaldehyde **7** (74 mg, 0.27 mmol) in EtOH (1.5 mL) was added **21** (50 mg, 0.81 mmol) followed by the simultaneous addition of KCN (0.021 g, 0.33 mmol) in H$_2$O (0.5 mL) and Et$_3$N (0.040 mL, 0.27 mmol). The reaction was stirred at rt for 15 min and then quenched with 10% HCl until a pH = 5 was attained. The aqueous layer was extracted with CH$_2$Cl$_2$ (3×) and discarded. The aqueous layer was reduced, and the resulting solids were filtered and washed with acetone to give **22** as a red-orange solid (35 mg, 39%). ^{1}H NMR (DMSO-d$_6$): δ = 9.73 (brs, 2H), 8.34 (s, 1H), 8.18 (s, 1H), 7.16 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 3.93 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (DMSO-d$_6$): δ = 181.8, 181.3, 158.9,

148.8, 146.8, 141.9, 139.4, 137.1, 135.8, 131.1, 129.9, 127.5, 121.5, 113.4, 109.6, 55.6, 31.9; IR (cm^{-1}): 2981, 1642, 1627, 1608, 1337, 1243, 1211, 1021; HR-ESIMS (negative mode) (m/z): calcd for [M−H]$^-$ C$_{19}$H$_{13}$N$_2$O$_5$ 349.0830, found 349.0832.

6,7-Dimethoxy-4-(4-methoxyphenyl)-1-methyl-1H-naphtho-[2,3-d]imidazole-5,8-dione/2-Deoxykealiiquinone (23). To dihydroxyquinone **22** (23 mg, 0.066 mmol) in THF (3 mL) were added MeOH (1 mL) and TMSCHN$_2$ (2.0 M in Et$_2$O) (0.080 mL, 0.16 mmol) with subsequent stirring at rt for 1 h. The reaction mixture was diluted with CH$_2$Cl$_2$ and washed with sat. NaHCO$_3$, dried (anhyd. Na$_2$SO$_4$), and concentrated. The resulting residue was purified by column chromatography (2:8 acetone/hexane to 1:1 acetone/hexane) to give **23** as an orange residue (16 mg, 64%). ^{1}H NMR: δ = 8.24 (s, 1H), 8.00 (s, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 4.10 (s, 3H), 4.01 (s, 3H), 3.95 (s, 3H), 3.86 (s, 3H); ^{13}C NMR: δ = 182.3, 182.0, 159.1, 148.9, 147.4, 146.5, 136.8, 130.6, 130.2, 128.8, 128.3, 122.8, 114.5, 113.8, 108.8, 61.4, 61.3, 55.3, 31.7; IR (cm^{-1}): 2924, 2852, 1658, 1618, 1515, 1456, 1341, 1307, 1245, 1215, 1054; HR-APCIMS (m/z): calcd for [M + H]$^+$ C$_{21}$H$_{18}$N$_2$O$_5$ 379.1288, found 379.1296.

3-Benzyl-4-(4-methoxyphenyl)-1-methyl-3,7-dihydro-1H-furo[3,4-f]benzimidazole-2,5-dione (24). Imidazolium salt **17** (1.0 g, 1.9 mmol) in THF (40 mL) was cooled to 0 °C, and 5% NaOCl (30 mL) was added dropwise. The reaction was allowed to come to rt and stirred for 30 min. The reaction was diluted with EtOAc, and the aqueous layer was extracted with EtOAc (2×). The combined organic extracts were washed with H$_2$O and then brine, dried (anhyd. Na$_2$SO$_4$), and concentrated. The resulting residue was purified by column chromatography (7:3 EtOAc/Hexane) to give **24** as an off-white solid (0.58 g, 75%). Mp: 185−187 °C; ^{1}H NMR: δ = 7.12−7.09 (m, 3H), 7.03 (s, 1H), 6.94 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.9 Hz, 2H), 6.58−6.56 (m, 2H), 5.23 (s, 2H), 4.79 (s, 2H), 3.83 (s, 3H), 3.57 (s, 3H); ^{13}C NMR: δ = 169.8, 159.7, 155.6, 141.8, 136.4, 136.2, 131.3, 128.2, 127.8, 127.2, 126.0, 124.0, 123.6, 117.1, 113.1, 99.5, 67.7, 55.3, 45.8, 27.8; IR (cm^{-1}): 1748, 1705, 1609, 1517, 1496, 1352, 1244, 1028; HR-ESIMS (m/z): calcd for [M + Na]$^+$ C$_{24}$H$_{20}$N$_2$O$_4$Na 423.1315, found 423.1316.

[3-Benzyl-4-(4-methoxyphenyl)-1-methyl-1H-benzimidazole-5,6-diyl]dimethanol-2-one (25). Imidazolone **24** (1.4 g, 3.5 mmol) was dissolved in CH$_2$Cl$_2$ (25 mL) and cooled to −78 °C under N$_2$. DIBAL-H (1 M in hexanes) (9.8 mL, 9.8 mmol) was added dropwise, then allowed to come to rt, and stirred for 4 h. The reaction mixture was cooled to 0 °C, and water was added slowly followed by MeOH. The solids were filtered through Celite and washed with CH$_2$Cl$_2$. Water was added to the filtrate, and the organic layer was separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2×). The combined organic extracts were dried (anhyd. Na$_2$SO$_4$) and concentrated. The resulting solids were washed with hexane and then Et$_2$O to give **25** as an off-white solid (1.17 g, 83%). Mp: 205−206 °C; ^{1}H NMR: δ = 7.11−7.09 (m, 3H), 7.03 (s, 1H), 6.87 (d, J = 8.6 Hz, 2H), 6.70 (d, J = 8.6 Hz, 2H), 6.59−6.57 (m, 2H), 4.81 (s, 2H), 4.64 (s, 2H), 4.38 (s, 2H), 3.82 (s, 3H), 3.46 (s, 3H); ^{13}C NMR: δ = 159.4, 155.5, 137.1, 134.0, 132.5, 131.5, 130.1, 128.1, 127.2, 126.9, 125.8, 125.6, 113.4, 108.5, 65.1, 59.5, 55.4, 45.4, 27.4; IR (cm^{-1}): 3313, 2930, 1669, 1611, 1515, 1398, 1244, 1181; HR-APCIMS (m/z): calcd for [M + H]$^+$ C$_{24}$H$_{25}$N$_2$O$_4$ 405.1809, found 405.1826.

3-Benzyl-4-(4-methoxyphenyl)-1-methyl-1H-benzimidazole-5,6-dicarbaldehyde-2-one (26). Diol **25** (0.22 g, 0.54 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL) and cooled to −78 °C under N$_2$. DBU (0.32 mL, 2.2 mmol) was added followed by **20** (0.38 g, 1.7 mmol) in CH$_2$Cl$_2$ (1 mL), and the reaction was stirred at −78 °C for 30 min. Sat. NaHCO$_3$ was added, and the solution was allowed to come to rt. The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2×). The combined organic extracts were dried (anhyd. Na$_2$SO$_4$) and concentrated. The resulting residue was purified by column chromatography (the silica gel was neutralized with Et$_3$N prior to purification) (4:6 EtOAc/hexane) to give **26** as an off-white solid (0.17 g, 77%). Mp: 152−155 °C ; ^{1}H NMR: δ = 10.40 (s, 1H), 9.67 (s, 1H), 7.68 (s, 1H), 7.14−7.08 (m, 3H), 6.92 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.6 Hz, 2H), 6.54 (d, J = 6.8 Hz, 2H), 4.74 (s, 2H), 3.84 (s,

3H), 3.59 (s, 3H); ^{13}C NMR: δ = 192.6, 192.0, 160.1, 155.6, 136.1, 133.7, 132.2, 131.9, 131.8, 130.2, 128.3, 128.0, 127.3, 125.6, 123.6, 113.7, 106.5, 55.5, 45.8, 27.9; IR (cm^{-1}): 2934, 1701, 1675, 1606, 1513, 1357, 1243, 1076; HR-ESIMS (m/z): calcd for [M + Na]$^+$ $C_{24}H_{20}N_2O_4Na$ 423.1315, found 423.1309.

3-Benzyl-6,7-dihydroxy-4-(4-methoxyphenyl)-1-methyl-1H-naphtho[2,3-d]imidazole-2,5,8-trione (27). To phthaldehyde **26** (0.10 g, 0.25 mmol) in THF (3 mL) was added **21** (42 mg, 0.75 mmol) followed by the addition of KCN (0.029 g, 0.44 mmol) and K_2CO_3 (0.17 g, 1.3 mmol) in H_2O (1 mL). The reaction was stirred at rt for 5 min, then quenched with 6 M HCl, and diluted with H_2O (5 mL). The aqueous layer was extracted with EtOAc (2×). The combined organic extracts were washed with H_2O and then brine, dried (anhyd. Na_2SO_4), and concentrated. An orange-red residue was recovered, and cold MeOH was added. The resulting solids were filtered to give the dihydroxyquinone **27** as an orange solid (22 mg, 20%). Mp: 204−206 °C; ^{1}H NMR (DMSO-d_6): δ = 9.65 (s, 1H), 9.60 (s,1H), 7.80 (s, 1H), 7.13−7.11 (m, 3H), 6.79 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 8.6 Hz, 2H), 6.56−6.54 (m, 2H), 4.44 (s, 2H), 3.71 (s, 3H), 3.50 (s, 3H); ^{13}C NMR (DMSO-d_6): δ = 181.6, 181.1, 159.1, 155.1, 141.0, 138.4, 137.3, 134.0, 131.2, 130.5, 128.5, 127.7, 127.3, 127.0, 125.7, 125.0, 122.6, 113.5, 106.0, 55.6, 45.5, 28.1; IR (cm^{-1}): 3240, 1697, 1654, 1597, 1514, 1400, 1283, 1243. HRMS-ESI (negative mode) (m/z): Calcd for $C_{26}H_{19}N_2O_6$ [M − H]$^-$ 455.1249, found 455.1243.

3-Benzyl-6,7-dimethoxy-4-(4-methoxyphenyl)-1-methyl-1H-naphtho[2,3-d]imidazole-2,5,8-trione (28). The dihydroxyquinone **27** prepared above (22 mg, 0.048 mmol) was dissolved in THF (3 mL), and MeOH (0.5 mL) was added followed by TMSCHN$_2$ (2.0 M in Et$_2$O) (0.07 mL, 0.15 mmol) with subsequent stirring at rt for 30 min. The reaction was diluted with EtOAc and washed with 2 M Na_2CO_3 (2×) and then brine. The organic extracts were dried (anhyd. Na_2SO_4) and concentrated. The resulting residue was purified by column chromatography (1:1 EtOAc/Hexane) to give **28** as an orange solid (15 mg, 65%). Mp: 176−178 °C; ^{1}H NMR: δ = 7.82 (s, 1H), 7.13−7.11 (m, 3H), 6.79 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 6.58−6.56 (m, 2H), 4.60 (s, 2H), 4.03 (s, 3H), 3.92 (s, 3H), 3.81 (s, 3H), 3.60 (s, 3H); ^{13}C NMR: δ = 182.0, 181.5, 159.2, 155.4, 148.1, 145.2, 136.6, 134.0, 130.1, 128.2, 127.1, 127.0, 125.5, 124.0, 113.5, 105.4, 61.4, 61.3, 55.3, 45.8, 27.9; IR (cm^{-1}): 2950, 1716, 1651, 1619, 1601, 1455, 1241, 1211; HR-ESIMS (m/z): calcd for [M + Na]$^+$ $C_{28}H_{24}N_2O_6Na$ 507.1527, found 507.1533.

4-(4-Hydroxyphenyl)-6,7-dimethoxy-1-methyl-1H-naphtho-[2,3-d]imidazole-2,5,8-trione/7′-Desmethylkealiiquinone (29). To **28** (30 mg, 0.062 mmol) was added TfOH (2.5 mL), and the mixture was heated at 55 °C in a vial for 4 h. The reaction was allowed to cool to rt and poured into EtOAc. Water was added, and the solution was neutralized with sat. NaHCO$_3$. The aqueous layer was extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (anhyd. Na_2SO_4). and concentrated. The resulting residue was purified by column chromatography (8:2 EtOAc/Hexane) to give **29** as an orange solid (10 mg, 56%). Mp: >290 °C; ^{1}H NMR (DMSO-d_6): δ = 10.95 (s, 1H), 9.41 (s, 1H), 7.63 (s, 1H), 6.96 (d, J = 8.6 Hz, 2H), 6.75 (d, J = 8.6 Hz, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (DMSO-d_6): δ = 181.9, 181.7, 157.2, 155.3, 148.4, 145.6, 134.4, 133.1, 130.3, 127.0, 126.4, 124.5, 123.2, 115.8, 104.9, 61.2 (2C), 27.3; IR (cm^{-1}) = 3200, 2921, 2851, 1702, 1656, 1609, 1515, 1105, 1059, 1033; HR-ESIMS (m/z): calcd for [M + Na]$^+$ $C_{20}H_{16}N_2O_6Na$ 403.0901, found 403.0911.

[3-Benzyl-4-phenyl-1H-benzimidazole-5,6-diyl]dimethanol (30). Benzimidazole **15** (5.0 g, 15 mmol) was dissolved in CH$_2$Cl$_2$ (100 mL) and cooled to −78 °C under N$_2$. DIBAL-H (1 M in hexanes) (41 mL, 41 mmol) was added dropwise, and the mixture was allowed to come to rt and stirred overnight. The reaction mixture was then cooled to 0 °C, and water was added slowly followed by MeOH. The solids were filtered through Celite and washed with CH$_2$Cl$_2$. Water was added to the filtrate, and the organic layer was separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2×). The combined organic extracts were dried (anhyd. Na$_2$SO$_4$) and concentrated. The resulting solids were washed with Et$_2$O to give **30** as a white solid (3.2

g, 63%). Mp: 191−193 °C; ^{1}H NMR: δ = 7.81 (s, 1H), 7.79 (s, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 7.4 Hz, 2H), 7.18−7.12 (m, 3H), 7.08 (d, J = 6.9 Hz, 2H), 6.50 (d, J = 6.9 Hz, 2H), 4.91 (s, 2H), 4.74 (s, 2H), 4.49 (s, 2H); ^{13}C NMR: δ = 146.0, 143.4, 136.5, 135.9, 135.1, 134.1, 131.5, 130.4, 128.6, 128.1, 128.0, 127.7, 127.7, 126.0, 121.2, 65.4, 59.6, 49.6; IR (cm^{-1}): 3056, 2856, 1504, 1441, 1311, 1175, 1018, 1000; HR-ESIMS (m/z): calcd for [M + H]$^+$ $C_{22}H_{21}N_2O_2$ 345.1598, found 345.1604.

3-Benzyl-4-phenyl-1H-benzimidazole-5,6-dicarbaldehyde (31). Diol **30** (3.0 g, 8.7 mmol) was dissolved in CH$_2$Cl$_2$ (75 mL) and cooled to −78 °C under N$_2$. DBU (4.8 mL, 35 mmol) was added followed by **20** (4.7 g, 22 mmol) in CH$_2$Cl$_2$ (3 mL), and the reaction was stirred at −78 °C for 30 min. Sat. NaHCO$_3$ was added, and the solution was allowed to come to rt. The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2×). The combined organic extracts were dried (anhyd. Na$_2$SO$_4$) and concentrated. The resulting residue was purified by column chromatography (the silica gel was neutralized with Et$_3$N prior to purification) (6:4 EtOAc/Hexane) to give **31** as a white solid (2.0 g, 68%). Mp: 167−169 °C; ^{1}H NMR: δ = 10.49 (s, 1H), 9.88 (s, 1H), 8.43 (s,1H), 8.06 (s, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 8.0 Hz, 2H), 7.23 (d, J = 7.5 Hz, 1H), 7.21−7.14 (m, 4H), 6.51 (d, J = 7.5 Hz, 2H), 4.86 (s, 2H); ^{13}C NMR: δ = 192.8, 192.4, 149.7, 146.8, 135.4, 134.0, 132.9, 132.4, 132.0, 131.4, 130.5, 129.2, 128.9, 128.4, 128.2, 125.9, 121.8, 50.2; IR (cm^{-1}): 3070, 2871, 1756, 1678, 1595, 1488, 1455, 1303, 1213; HR-ESIMS (m/z): calcd for [M + Na]$^+$ $C_{22}H_{16}N_2O_2Na$ 363.1104, found 363.1108.

3-Benzyl-6,7-dihydroxy-4-phenyl-1H-naphtho[2,3-d]imidazole-5,8-dione (32). To phthaldehyde **31** (150 mg, 0.44 mmol) in THF was added **21** (0.037 g, 0.66 mmol) followed by the simultaneous addition of KCN (29 mg, 0.44 mmol) in H$_2$O (1 mL) and Et$_3$N (0.06 mL, 0.44 mmol). The reaction was stirred at rt for 15 min and then quenched with H$_2$O (5 mL). 1 M HCl was added until pH = 5 was reached, and the aqueous layer was extracted with EtOAc (2×). The combined organic extracts were dried (anhyd. Na$_2$SO$_4$) and concentrated. An orange-red residue was recovered and recrystallized from MeOH to give **32** as an orange-red solid (74 mg, 43%). Mp: 280 °C (decomp.); ^{1}H NMR (DMSO-d_6): δ = 9.71 (brs, 2H), 8.46 (s, 1H), 8.30 (s, 1H), 7.32−7.29 (m, 1H), 7.19−7.16 (m, 5H), 7.01−7.00 (m, 2H), 6.45 (d, J = 4.6 Hz, 2H), 4.75 (s, 2H); ^{13}C NMR (DMSO-d_6): δ = 181.6, 181.1, 151.2, 146.6, 141.8, 139.6, 137.6, 136.5, 135.5, 129.3, 129.1, 128.8, 128.2, 127.8, 127.8, 127.1, 125.9, 122.9, 118.7, 49.3; IR (cm^{-1}): 2831, 1662, 1615, 1595, 1569, 1343, 1315, 1206, 1189, 905; HR-APCIMS (m/z): calcd for [M + H]$^+$ $C_{24}H_{17}N_2O_4$ 397.1183, found 397.1196.

3-Benzyl-6,7-dimethoxy-4-phenyl-1H-naphtho[2,3-d]-imidazole-5,8-dione (33). Dihydroxyquinone **32** (84 mg, 0.21 mmol) was suspended in THF (5 mL), and MeOH (2.0 mL) was added followed by TMSCHN$_2$ (2.0 M in Et$_2$O) (0.37 mL, 0.74 mmol) with subsequent stirring at rt for 4 h. The reaction was diluted with EtOAc and washed with sat. NaHCO$_3$ (2×), dried (anhyd. Na$_2$SO$_4$), and concentrated. The resulting residue was purified by column chromatography (1:1 EtOAc/Hexane) to give **33** as a yellow solid (45 mg, 54%). Mp: 189−191 °C; ^{1}H NMR: δ = 8.65 (s, 1H), 7.92 (s, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.23−7.18 (m, 3H), 7.04 (d, J = 7.5 Hz, 2H), 6.57 (d, J = 8.0 Hz, 2H), 4.65 (s, 2H), 4.07 (s, 3H), 3.94 (s, 3H); ^{13}C NMR: δ = 182.1, 181.9, 149.5, 148.7, 147.0, 146.4, 136.1, 135.9, 135.8, 129.2, 128.8, 128.5, 128.3, 128.1, 127.9, 127.8, 126.1, 124.0, 120.2, 61.4, 61.3, 50.0; IR (cm^{-1}): 3009, 2940, 1649, 1596, 1441, 1348, 1291, 1027; HR-ESIMS (m/z): calcd for [M + H]$^+$ $C_{26}H_{21}N_2O_4$ 425.1496, found 425.1490.

3-Benzyl-6,7-dimethoxy-1-methyl-4-phenyl-1H-naphtho-[2,3-d]imidazolium-5,8-dione Iodide (34). To quinone **33** (45 mg, 0.11 mmol) in CH$_3$CN (8 mL) was added MeI (0.20 mL) followed by heating at 70 °C for 15 h. The reaction mixture was concentrated, and the resulting residue was triturated with Et$_2$O to give **34** as a red-orange solid (52 mg, 86%). Mp: 184−188 °C; ^{1}H NMR: δ = 10.33 (s, 1H), 8.49 (s, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.29−7.27 (m, 3H), 7.18 (d, J = 7.5 Hz, 2H), 6.96 (d, J = 7.5 Hz, 2H), 4.93 (s, 2H), 4.26 (s,3H), 4.10 (s, 3H), 3.98 (s, 3H); ^{13}C NMR: δ = 180.2, 180.0, 149.3, 147.7, 146.4, 134.9, 132.9, 132.9, 132.3, 132.2,

131.1, 129.4, 129.3, 128.9, 128.6, 128.0, 127.0, 111.8, 61.6 (2C), 53.0, 34.9; IR (cm^{-1}): 3031, 2945, 1718, 1660, 1609, 1452, 1314, 1209, 1052, 916; HR-ESIMS (m/z): calcd for [M]$^+$ C$_{27}$H$_{23}$N$_2$O$_4$ 439.1652, found 439.1634.

3-Benzyl-6,7-dimethoxy-1-methyl-4-phenyl-1H-naphtho-[2,3-d]imidazole-2,5,8-trione (35). To imidazolium salt **34** (31 mg, 0.055 mmol) in THF (1 mL) was added 1 M K$_2$CO$_3$ (0.27 mL) and NCS (8 mg, 0.06 mmol), followed by stirring at rt for 30 min. The reaction was diluted with water (4 mL) and extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine, dried, and concentrated. The resulting residue was purified by column chromatography (1:1 EtOAc/Hexane) to give **35** as a yellow solid (15 mg, 60%). Mp: 160−162 °C; ^{1}H NMR: δ = 7.84 (s, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.17 (t, J = 7.5 Hz, 2H), 7.13−7.09 (m, 3H), 6.89 (d, J = 6.9 Hz, 2H), 6.53 (d, J = 6.3 Hz, 2H), 4.52 (s, 2H), 4.03 (s, 3H), 3.91 (s, 3H), 3.60 (s, 3H); ^{13}C NMR: δ = 181.9, 181.4, 155.4, 148.1, 145.3, 136.5, 135.2, 134.0, 131.4, 129.0, 128.2, 128.1, 127.9, 127.5, 127.1, 125.6, 125.5, 123.7, 105.5, 61.4, 61.3, 45.7, 27.9; IR (cm^{-1}): 2927, 1709, 1651, 1620, 1601, 1452, 1344, 1209, 1059; HR-ESIMS (m/z): calcd for [M + Na]$^+$ C$_{27}$H$_{22}$N$_2$O$_5$Na 477.1421, found 477.1438.

6,7-Dimethoxy-1-methyl-4-phenyl-1H-naphtho[2,3-d]-imidazole-2,5,8-trione/4′-Desmethoxykealiiquinone (36). To imidazolone **35** (25 mg, 0.055 mmol) was added TfOH (2 mL) followed by heating at 55 °C for 4 h. The reaction was quenched with water and neutralized with sat. NaHCO$_3$. The aqueous layer was extracted with EtOAc (2×), and the combined organic extracts were washed with brine, dried, and concentrated. The resulting residue was purified by column chromatography (6:4 EtOAc/Hexane) to give **36** as a yellow waxy solid (10 mg, 67%). ^{1}H NMR: δ = 8.11 (brs, 1H), 7.74 (s, 1H), 7.49−7.43 (m, 3H), 7.22−7.21 (m, 2H), 4.07 (s, 3H), 3.97 (s, 3H), 3.47 (s, 3H); ^{13}C NMR: δ = 181.9, 181.5, 154.2, 147.6, 146.0, 135.3, 134.1, 131.6, 129.1, 128.3, 128.1, 127.8, 124.3, 123.0, 105.5, 61.5, 61.4, 27.4; IR (cm^{-1}): 2919, 1708, 1648, 1623, 1443, 1332, 1245, 1194, 1056, 1026; HR-APCIMS (m/z): calcd for [M + H]$^+$ C$_{20}$H$_{17}$N$_2$O$_5$ 365.1132, found 365.1144.

3-Benzyl-2-$tert$-butylcarbonylimino-6,7-dimethoxy-1-methyl-4-phenyl-1H-naphtho[2,3-d]imidazole-2,5,8-trione (37). To $tert$-butyl carbamate (19 mg, 0.16 mmol) in CH$_2$Cl$_2$ (2 mL) was added t-BuOCl (0.02 mL, 0.17 mmol), followed by stirring at rt for 20 min. The reaction mixture was cooled to 0 °C, and DBU (0.033 mL, 0.22 mmol) was added followed by **34** in CH$_2$Cl$_2$ (3 mL). The reaction was stirred at rt for 30 min and then diluted with water. The aqueous layer was extracted with CH$_2$Cl$_2$ (2×), and the combined organic extracts were washed with brine, dried (anhyd. Na$_2$SO$_4$), and concentrated. The crude residue was purified by column chromatography (1:1 EtOAc/Hexane) to give **37** as a yellow-orange residue (10 mg, 30%). ^{1}H NMR: δ = 7.98 (s, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 2H), 7.12−7.07 (m, 3H), 6.84 (d, J = 6.9 Hz, 2H), 6.44 (d, J = 6.9 Hz, 2H), 4.70 (s, 2H), 4.03 (s, 3H), 3.90 (s,3H), 3.68 (s,3H), 1.46 (s,9H); ^{13}C NMR: δ = 181.6, 181.1, 158.3, 153.9, 148.3, 145.5, 135.8, 135.4, 134.6, 132.3, 128.9, 128.2, 128.2, 128.1, 128.0, 127.1, 127.1, 125.4, 124.5, 106.6, 78.9, 61.4, 61.3, 47.3, 31.8, 28.3; IR (cm^{-1}): 2929, 1655, 1581, 1443, 1308, 1207, 1147, 1047, 1026; HR-ESIMS (m/z): calcd for [M + H]$^+$ C$_{32}$H$_{32}$N$_3$O$_6$ is 554.2286, found 554.2290.

4-(4-Methoxyphenyl)-1,3-dimethyl-5-oxo-5,7-dihydro-3H-furo[3,4-f]benzimidazol-1-ium Iodide (38). To benzimidazole **18** (25 mg, 0.085 mmol) in toluene (10 mL) was added MeI (0.030 mL, 0.42 mmol), followed by heating to 140 °C for 20 h. The solvent was reduced to give **38** (25 mg, 68%) as an off-white solid. Mp: 253−256 °C; ^{1}H NMR (CD$_3$OD): δ = 8.13 (s, 1H), 7.37 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 5.51 (s, 2H), 4.18 (s, 3H), 3.88 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (CD$_3$OD): δ = 168.9, 160.9, 145.2, 136.7, 131.1, 130.8, 130.5, 121.8, 113.3, 106.3, 68.4, 54.6, 36.2, 32.9; IR (cm^{-1}): 2960, 1772, 1612, 1577, 1378, 1241, 1065, 1018, 823; HR-ESIMS (m/z): calcd for [M]$^+$ C$_{18}$H$_{17}$N$_2$O$_3$ 309.1234, found 309.1229.

4-(4-Methoxyphenyl)-1,3-dimethyl-3,7-dihydro-1H-furo[3,4-f]benzimidazole-2,5-dione (39). Imidazolium salt **38** (10 mg, 0.023 mmol) in THF was cooled to 0 °C, and 5% NaOCl (0.3 mL) was added followed by stirring for 10 min. The reaction was diluted with water and extracted with EtOAc (2×). The combined organic

extracts were dried (anhyd. Na$_2$SO$_4$) and concentrated. The resulting solids were purified by PTLC (EtOAc) to give **39** as a white solid (6 mg, 73%). Mp: 239−240 °C; ^{1}H NMR: δ = 7.26 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 6.98 (s, 1H), 5.25 (s, 2H), 3.87 (s, 3H), 3.49 (s, 3H), 2.92 (s, 3H); ^{13}C NMR: δ = 170.0, 159.9, 155.4, 141.5, 135.8, 131.3, 128.9, 124.1, 123.4, 116.8, 113.3, 99.3, 67.9, 55.3, 30.3, 27.7; IR (cm^{-1}): 2930, 2838, 1761, 1700, 1609, 1520, 1482, 1357, 1287, 1248, 1196, 1179, 1139, 1078; HR-APCIMS (m/z): calcd for [M + H]$^+$ C$_{18}$H$_{17}$N$_2$O$_4$ 325.1183, found 325.1191.

4-(4-Methoxyphenyl)-1-methyl-5-oxo-5,7-dihydro-1H-furo-[3,4f][3,1]benzimidazol-3-ium Chloride (41). To **18** (72 mg, 0.24 mmol) in acetonitrile (10 mL) was added SEMCl (50 mg, 0.30 mmol) followed by stirring at 60 °C for 1 h. The reaction mixture was cooled to 0 °C, and the precipitated solids were filtered and washed with Et$_2$O to give **41** as a white solid (51 mg, 63%). Mp: 255−258 °C; ^{1}H NMR (CD$_3$OD): δ = 9.56 (d, J = 4.6 Hz, 1H), 8.06 (s, 1H), 7.51 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 5.52 (s, 2H), 4.19 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (CD$_3$OD): δ = 169.3, 161.1, 145.7, 145.1, 136.4, 131.3, 130.5, 122.0, 119.9, 113.8, 105.2, 68.5, 54.6, 32.7; IR (cm^{-1}): 3155, 2942, 1728, 1623, 1506, 1392, 1243, 1142, 1110, 1012; HR-ESIMS (m/z): calcd for [M + Na]$^+$ C$_{17}$H$_{14}$N$_2$O$_3$Na 317.0897, found 317.0903.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds are provided. Additional and enlarged figures of the X-ray crystal structures of compounds **16**, **25**, and **41**. CIF data are provided for compound **41**. These materials are available free of charge on the Internet via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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