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

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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. Debenzylolation of a late stage intermediate en route to kealiiquinone was compromised by concomitant O-demethylation upon treatment with tritic 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 alkaloids4 as leads in medicinal chemistry programs.3 Our laboratories are described by Ohta and co-workers. The synthetic version and introduction of the 2-keto tautomer of the natural product.19,20 A second 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 (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,16 only one report of a total synthesis of kealiiquinone has appeared from the Ohta lab resulting in the synthetic 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 (3–5)13–15 and the kealiiquinones (1 and 2), and several intermediates...
have been investigated and shown for the most part to possess modest activity (IC50 = 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 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).11,23–32 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 metatation 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 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 MnO2, 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 MnO2 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 MnO2 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 (Σ= 353.89°) and the deviation from orthogonality around the C3–C10 bond (crystallographic...
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.
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 recyclized 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. 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 sulfinimidoxydichloride, e.g., 20 in the presence of DBU. 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 dihydroxybenzoquinone 22. 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: in this context either (TMSO)2 for kealiiquinone (1) or TsN3 for the amino congener 2. 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 D2O or methanol-D4 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 4. Late Stage Introduction of the 2-Oxo Group](image-url)
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 methylene the benzimidazoles may be easier to functionalize given the increased acidity of the proton at C2 in these systems. 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-chlorosulfonylamides or N-chlorocarbamates; this chemistry has been described in more detail elsewhere. With this method in hand we subjected the lactone imidazolone 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-species unequivocally demonstrates the introduction of the 2-oxo moiety and served to confirm the relative location of the methyl and aryl groups. 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, amidine 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.

Ultimately, we determined that heating the substrates in neat triflic acid resulted in debenzylation with reasonable efficiencies. 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. Reaction of the imidazolone with TiOH 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. 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 TiOH 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 resulted in the net protonation of the imidazole and production of the imidazolium salt 41. The significant downfield shift of the C2-proton absorbance in the 1H 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 constitutes the first application of Venuti’s method for the formation of functionalized through application of an underutilized method for the formation of an imidazolone such an approach given that the N3-position is relatively 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 resulted in the net protonation of the imidazole and production of the imidazolium salt 41. The significant downfield shift of the C2-proton absorbance in the 1H 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 constitutes the first application of Venuti’s method for the formation of functionalized through application of an underutilized method for the formation of an imidazolone such an approach given that the N3-position is relatively activating the oxidation (Scheme 5).
1H NMR (DMSO-d6): 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); 13C NMR (DMSO-d6): 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, 2975, 2835, 1739, 1603, 1501, 1453; HR-ESIMS (m/z): calcd for [M + H]+ C17H15N2O3 295.1077, found 295.1072.

[4-(4-Methoxyphenyl)-1-methyl-1H-benzimidazole-5,6-diyldimethanone] (19). Benzimidazole 18 (0.19 g, 0.65 mmol) was dissolved in CHCl₃ (5 mL) and cooled to −78 °C under N₂. 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 then cooled to 0 °C and was added with EtOH and MeOH. The solids were filtered and washed with CHCl₃ and MeOH. The organic extract was separated, and the residual aqueous solution was extracted multiple times with CHCl₃. The combined organic extracts were dried (anhyd. Na₂SO₄) and concentrated. The resulting white solid was triturated with EtO₂ to afford 19 as a white solid (0.15 g, 79%). Mp: 245–247 °C; 1H NMR (DMSO-d6): δ = 8.02 (s, 1H), 7.38 (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); 13C NMR (DMSO-d6): δ = 158.8, 144.7, 141.6, 137.6, 134.2, 133.3, 125.9, 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]+ C₂₁H₁₆N₅O₂ 331.1300, found 329.1301.
3-Benzyl-6,7-dihydroxy-4-phenyl-1-hexahydroimidazole-2,3-dione (31). Diol 30 (30 g, 8.7 mmol) was dissolved in CHCl₃ (75 mL) and cooled to −78 °C under N₂. DBU (4.8 mL, 35 mmol) was added followed by 20 (4.7 g, 22 mmol) in CHCl₃ (3 mL), and the reaction was stirred at −78 °C for 30 min. Sat. NaHCO₃ was added, and the solution was allowed to come to rt. The organic layer was separated, and the aqueous layer was extracted with CH₃Cl (2x). The combined organic extracts were dried (anhyd. Na₂SO₄) and concentrated. The resulting residue was purified by column chromatography (the silica gel was neutralized with Et₃N prior to purification) (6:4 EtOAc/Hexane) to give 31 as a white solid (2.0 g, 68%). Mp: 167−169 °C; ¹H 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). ¹³C 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, 1765, 1678, 1595, 1488, 1455, 1303, 1213; HR-ESIMS (m/z): calcd for [M + Na⁺]C₂₁H₁₆N₂O₆Na⁺ 363.1104, found 363.1102.

3-Benzyl-6,7-dihydroxy-4 phenyl-1 phenothiazine (32). To phthalide 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 H₂O (1 mL) and EtN (0.06 mL, 0.44 mmol). The reaction was stirred at rt for 15 min and then quenched with H₂O (5 mL). 1 M HCl was added until pH = 5 was reached, and the aqueous layer was extracted with EtOAc (2x). The combined organic extracts were dried (anhyd. Na₂SO₄) and concentrated. The resulting residue was purified by column chromatography (1:1 EtOAc/Hexane) to give 32 as an orange oil (74% yield). Mp: 280 °C (decomp.). ¹H NMR (DMSO-d₆): 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); ¹³C NMR (DMSO-d₆): δ = 181.6, 181.1, 151.2, 146.6, 141.6, 139.6, 137.6, 136.3, 135.9, 135.8, 135.7, 135.6, 135.5, 135.3, 135.2, 129.3, 129.1, 128.8, 128.2, 127.8, 127.8, 125.9, 122.9, 118.7, 49.3; IR (cm⁻¹): 2831, 1662, 1615, 1595, 1569, 1343, 1315, 1206, 1189, 905; HR-APICMS (m/z): calcd for [M + H⁺]C₂₁H₁₆N₄O₆ 397.1183, found 397.1196.

3-Benzyl-6,7-dihydroxy-4 phenyl-1 phenothiazine 32. Dihydroxyquinone 32 (84 mg, 0.21 mmol) was suspended in THF (5 mL), and MeOH (0.2 mL) was added followed by TMSCHN₂ (2.0 M in Et₂O) (0.07 mL, 0.15 mmol) with subsequent stirring at rt for 4 h. The reaction was diluted with EtOAc and washed with sat. NaHCO₃ (2x), dried (anhyd. Na₂SO₄), 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; ¹H NMR: δ = 8.65 (s, 1H), 7.92 (s, 1H), 7.57 (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); ¹³C 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, 61.4, 61.3, 50.0; IR (cm⁻¹): 3009, 2940, 1694, 1546, 1438, 1291, 1027; HR-ESIMS (m/z): calcd for [M + H⁺]C₂₁H₁₆N₄O₆ 425.1496, found 425.1490.

3-Benzyl-6,7-dihydroxy-1 methyl-4 phenyl-1 phenothiazine 32. To quinone 33 (45 mg, 0.11 mmol) in CH₂CN (8 mL) was added Mel (0.20 mL) followed by heating at 70 °C for 15 h. The reaction mixture was concentrated, and the resulting residue was triturated with EtOAc to give 34 as a red-orange solid (52 mg, 86%). Mp: 184−188 °C; ¹H 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); ¹³C NMR: δ = 180.2, 180.0, 149.3, 147.7, 146.4, 134.9, 132.9, 132.9, 132.2, 132.2.
4-(4-Methoxyphenyl)-1-methyl-5-oxo-5,7-dihydro-1H-furo[3,4-f][1]benzimidazol-3-ium Chloride (41). To 18 (72 mg, 0.24 mmol) in acetonitrile (10 mL) was added SEMCI (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 EtOAc to give 41 as a white solid (51 mg, 63%). Mp: 255–258 °C; [M + H]⁺ NMR (CD2Cl2): δ = 9.56 (d, J = 6.4 Hz, 1H), 8.06 (s, 1H), 7.51 (d, J = 6.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 5.52 (s, 3H), 3.89 (s, 3H); 13C NMR (CD2Cl2): δ = 169.3, 161.1, 145.7, 145.1, 136.4, 131.3, 130.5, 122.0, 119.9, 131.8, 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): calcld for [M + Na⁺] C25H19N3O4Na 371.0897, found 371.0903.

ASSOCIATED CONTENT

S Supporting Information
Copies of ¹H and ¹³C 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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REFERENCES

(1) Morris, J. C. Nat. Prod. Rep. 2013, 30, 783.
(2) Blunt, J. W.; Coppel, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsen, M. R. Nat. Prod. Rep. 2013, 30, 237.
(3) R., M. H.; L. Future Med. Chem. 2011, 3, 1475.
(4) Zhong, J. Nat. Prod. Rep. 2013, 30, 869.
(5) Koswatta, P. B.; Lovely, C. J. Nat. Prod. Rep. 2011, 28, 511.
(6) Sullivan, J. D.; Giles, R. L.; Looper, R. E. Curr. Bioact. Compd. 2009, 5, 39.
(7) Du, H.; He, Y.; Rasapalli, S.; Lovely, C. J. Synlett 2006, 965.
(8) Lovely, C. J. Strategies and Tactics in Organic Synthesis; Harmata, M. Ed; Academic Press: 2012; Vol. 8, Chapter 8.
(9) Ake, R. K.; Carroll, T. R.; Yoshida, W. Y.; Scheuer, P. J.; Stout, T. J.; Clardy, J. J. Org. Chem. 1990, 55, 44.
(10) Fu, X.; Barnes, J. R.; Do, T.; Schmitz, F. J. J. Nat. Prod. 1997, 60, 497.
(11) He, Y.; Krishnamoorthy, P.; Lima, H. M.; Chen, Y.; Wu, H.; Sivappa, R.; Dias, H. V. R.; Lovely, C. J. Org. Biomol. Chem. 2011, 9, 2685.
(12) Lima, H. M.; Lovely, C. J. Org. Lett. 2011, 13, 5736.
(13) Hassan, W.; Edrada, R.; Ebel, R.; Wray, V.; Berg, A.; Van Soest, R.; Wiryowidagdo, S.; Proksch, P. J. Nat. Prod. 2004, 67, 817.
(14) Gibbons, J. B.; Gilgorsch, K. M.; Welm, B. E.; Leoper, R. E. Org. Lett. 2012, 14, 4734.
(15) Das, J.; Koswatta, P. B.; Yousufuddin, M.; Jones, J. D.; Lovely, C. J. Org. Lett. 2012, 14, 6210.
(16) Das, J.; Bhan, A.; Mandal, S.; Lovely, C. J. Bioorg. Med. Chem. Lett. 2013, 23, 6183.
(17) Carroll, A. R.; Bowden, B. F.; Coll, J. C. Aus. J. Chem. 1993, 46, 1229.
(18) For a preliminary report of this work see: Lima, H. M.; Sivappa, R.; Yousufuddin, M.; Lovely, C. J. Org. Lett. 2012, 14, 2274.
(19) Kawasaki, I.; Taguchi, N.; Yamashita, M.; Ohta, S. Chem. Pharm. Bull. 1997, 45, 1393.
(20) Kawasaki, I.; Taguchi, N.; Yamamoto, T.; Yamashita, M.; Ohta, S. Tetrahedron Lett. 1995, 36, 8251.
(21) Nakamura, S.; Tsuno, N.; Yamashita, M.; Kawasaki, I.; Ohta, S.; Ohishi, Y. J. Chem. Soc., Perkin Trans. 1 2001, 429.
(22) Lovely, C. J.; Du, H.; Dias, H. V. R. Heterocycles 2003, 60, 1.
(23) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. Org. Lett. 2003, 5, 3623.
(24) Lovely, C. J.; Du, H.; Dias, H. V. R. Org. Lett. 2001, 3, 1319.
(25) Lovely, C. J.; Du, H.; Sivappa, R.; Bhandari, M. R.; He, Y.; Dias, H. V. R. J. Org. Chem. 2007, 72, 3741.
(26) Sivappa, R.; Makkerjee, S.; Dias, H. V. R.; Lovely, C. J. Org. Biomol. Chem. 2009, 7, 3215.
(27) Sivappa, R.; Hernandez, N. M.; He, Y.; Lovely, C. J. Org. Lett. 2007, 9, 3861.
(28) Walters, M. A.; Lee, M. D. Tetrahedron Lett. 1994, 35, 8307.
(29) Deghati, P. Y. F.; Wanner, M. J.; Koomen, G.-J. Tetrahedron Lett. 1998, 39, 4561.
(30) Watson, L. J.; Harrington, R. W.; Clegg, W.; Hall, M. J. Org. Biomol. Chem. 2010, 12, 6649.
(31) Cotterill, L. J.; Harrington, R. W.; Clegg, W.; Hall, M. J. Org. Chem. 2010, 75, 4604.
(32) Pöverlein, C.; Breckle, G.; Lindel, T. Org. Lett. 2006, 8, 819.
(33) Venuti, M. C. Synthesis 1982, 61.
(34) Lindel, T.; Hochgürtel, M. Tetrahedron Lett. 1998, 39, 2541.
(35) Lipshutz, B. H.; Huff, B.; Hagen, W. Tetrahedron Lett. 1988, 29, 3411.
(36) Fatiadi, A. J. Synthesis 1976, 133.
(37) Franks, M. A.; Schrader, E. A.; Pietsch, E. C.; Pennella, D. R.; Torti, S. V.; Welker, M. E. Bioorg. Med. Chem. 2005, 13, 2221.
(38) Auffrant, A.; Jaun, B.; Jarowski, P. D.; Houk, K. N.; Diederich, F. Chem.—Eur. J. 2004, 10, 2906.
(39) Lindgren, B. O.; Nilsson, T. Acta Chem. Scand. 1973, 27, 888.
(40) Bal, B. S.; Chulders, W. E., Jr.; Pinnick, H. W. Tetrahedron 1981, 37, 2091.
(41) He, Y.; Chen, Y.; Du, H.; Schmid, L. A.; Lovely, C. J. Tetrahedron Lett. 2004, 45, 5529.
(42) Matsuo, J.-i.; Iida, D.; Tatani, K.; Mukaiyama, T. Bull. Chem. Soc. Jpn. 2002, 75, 225.
(43) Tskhovrebov, A. G.; Vuichoud, B.; Solari, E.; Scopelliti, R.; Severin, K. J. Am. Chem. Soc. 2013, 135, 9486.
(44) We investigated a number of standard conditions, including PCC, PDC, IBX, and MnO₂, but these oxidants resulted in the formation of the corresponding lactone.
(45) Rombouts, F.; Franken, D.; Martínez-Lamenca, C.; Braeken, M.; Zavattaro, C.; Chen, J.; Trabanco, A. A. Tetrahedron Lett. 2010, 51, 4815.
(46) We briefly explored the possibility of carrying the SEM group from the beginning of the sequence, and we had no difficulty in producing the benzimidazole derivative related to 16. However, an attempted methylation resulted in the formation of the methylated benzimidazole 18, and so this approach was not pursued any further.