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Total Synthesis of 7′-Desmethylkealiiquinone

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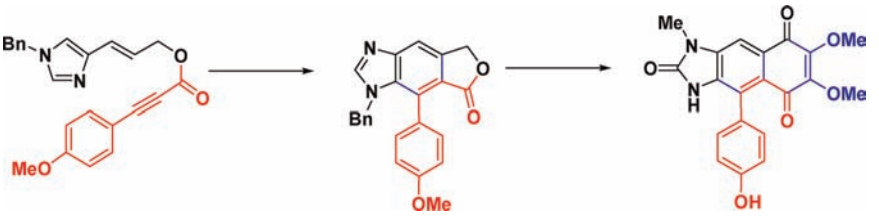
ABSTRACT



The total synthesis of an analogue of the marine alkaloid kealiiquinone has been completed through application of an intramolecular Diels–Alder reaction of an imidazole-containing enyne. Oxidative aromatization of the lactone adduct and *N*-methylation facilitates C2-oxidation via the imidazolium salt. Conversion of the lactone to the phthalaldehyde derivative and then to the dihydroxybenzoquinone was achieved via a reaction with glyoxal in the presence of KCN. Esterification of the vinylogous diacid and deprotection provided 7′-desmethylkealiiquinone.

Marine sponges have produced and continue to provide a large number of architecturally unique and biologically active natural products.[1,2] These natural products have provided a fertile testing ground for the development and refinement of new synthetic methods and strategies.[1] Our group has been particularly interested in the development of synthetic approaches to the growing number of imidazole-containing natural products from marine sponges.[3,4] Sponges of the *Leucetta* and *Clathrina* genus produce a remarkable number of diverse secondary metabolites in which an imidazole is a characteristic structural motif.[5] Recently, our attention has been directed to two structurally related imidazonaphthoquinone natural products, kealiiquinone (**1**)[6] and its 2-amino congener (2-amino-2-deoxykealiiquinone (**2**)),[7] which were isolated by the Clardy and Schmitz groups, respectively, from two *Leucetta* sponges (Figure 1). Although these compounds were not reported to possess exceptional biological activity, they are cytotoxic. An isomer of **1**[8] has been shown to exhibit fairly potent anticancer activity which based on its profile is thought to be mediated through a novel mode of action. More recently, several naturally occurring analogues of kealiiquinone, kealiinines A–C (**3**–**5**), have been reported and have been suggested as possible biosynthetic precursors to **1** and **2**.[9]

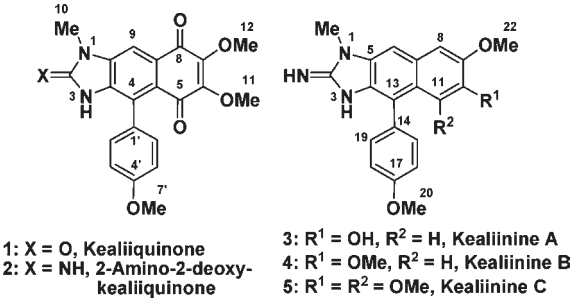


Figure 1. Structures of the kealiinine family of alkaloids.

(1) Morris, J. C.; Phillips, A. J. *Nat. Prod. Rep.* **2011**, *28*, 269.
(2) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2011**, *28*, 196.
(3) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143.
(4) For a summary of some of our efforts, see:Du, H.; He, Y.; Sivappa, R.; Lovely, C. J. *Synlett* **2006**, 965.
(5) Koswatta, P. B.; Lovely, C. J. *Nat. Prod. Rep.* **2011**, *28*, 511.
(6) Akee, R.; Carroll, T. R.; Yoshida, W. Y.; Scheuer, P. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1990**, *55*, 1944.
(7) Fu, X.; Schmitz, F. J.; Tanner, R. S.; Kelly-Borges, M. *J. Nat. Prod.* **1998**, *61*, 384.
(8) Nakamura, S.; Tsuno, N.; Yamashita, M.; Kawasaki, I.; Ohta, S.; Ohishi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 429.
(9) Hassan, W.; Edrada, R. A.; Ebel, R.; Wray, V.; Berg, A.; van Soest, R. W. M.; Wiryowidagdo, S.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 817.
(10) (a) Kawasaki, I.; Taguchi, N.; Yamamoto, T.; Yamashita, M.; Ohta, S. *Tetrahedron Lett.* **1995**, *36*, 8251. (b) Kawasaki, I.; Taguchi, N.; Yamashita, M.; Ohta, S. *Chem. Pharm. Bull.* **1997**, *45*, 1393.

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To date, one synthesis of kealiiquinone (**1**) has been described in the literature by Ohta and co-workers[10] and involves the sequential metalation and electrophilic trapping of a 2-thio-substituted imidazole. Subsequent Friedel–Crafts alkylation and adjustment of the oxidation state around the oxygenated benzimidazole provides **1**. Our approach to this system involves a different and complementary strategy centered on de novo quinone assembly and intramolecular Diels–Alder reaction of a 4-vinylimidazole derivative, chemistry which we have extensively investigated in our laboratories.[11,12]

This strategy, which is depicted retrosynthetically in Figure 2, involves the late-stage introduction of the C2 imidazole functionality, thereby potentially allowing access to both **1** and **2** from an advanced and common intermediate. The precursor imidazonaphthoquinone would be obtained by an interesting and rarely used annulation reaction for incorporation of the dihydroxyquinone moiety involving a masked glyoxal equivalent.[13] The requisite phthalaldehyde precursor **6** would be obtained from lactone **7**, which in turn would be constructed through the Diels–Alder oxidation sequence involving the enyne **8**.

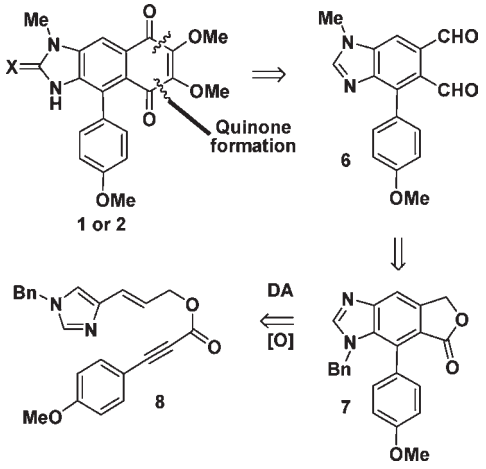
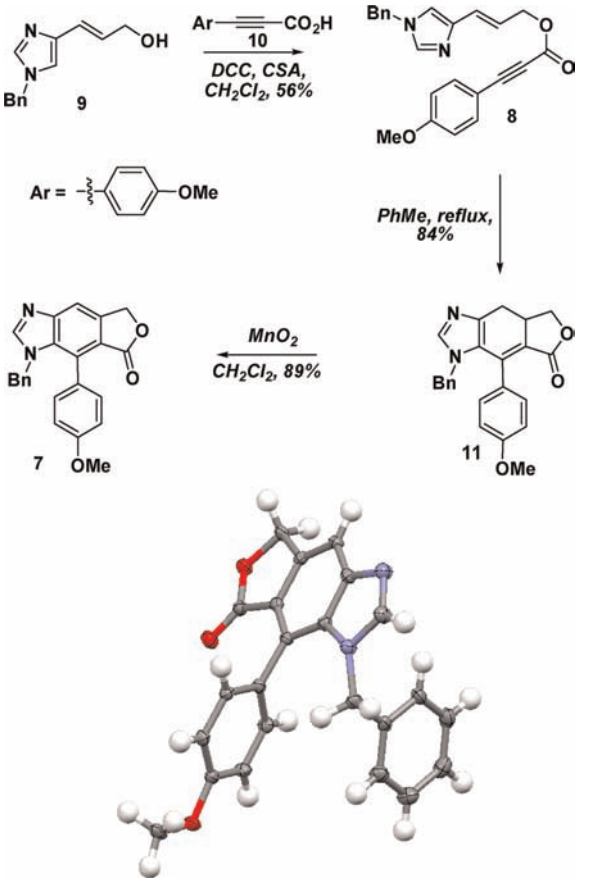


Figure 2. Retrosynthetic analysis of kealiiquinones **1** and **2**.

In a forward sense, our synthesis began with the construction of the enyne **8** which was obtained from the DCC-mediated esterification of the 4-vinylimidazole **9** and the arylpropiolic acid derivative **10** (Scheme 1). The vinylimidazole can be obtained in three steps from urocanic acid by methods previously described by us in excellent yield.[11] The enyne undergoes a smooth Diels–Alder reaction leading to the formation of the dihydrobenzimidazole **11** in 89% yield. Subjection of the cycloadduct to oxidation by treatment with MnO_2 provided the benzimidazole **7** in 95% yield.[14] Benzimidazole **7** was nicely crystalline, and so the structure of the oxidized cycloadduct was confirmed through an X-ray structure determination (Scheme 1).

Scheme 1. Assembly of the Benzimidazole Framework and X-ray Structure of Compound **7**



Our choice of the benzyl-protected 4-vinylimidazole was guided by experience with vinylimidazoles which indicated that the 4-isomers are better substrates in Diels–Alder reactions, and we have developed a number of efficient methods for construction of such derivatives.[11] As a result, our approach required an "isomerization" step in order to properly position the *N*1-methyl group. It proved quite convenient to accomplish this tactic with **7**. Specifically, it was found that treatment of **7** with methyl iodide provided the imidazolium salt **12**. Catalytic hydrogenation led to efficient debenzylation, leaving the methyl group in the

(11) (a) 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. (b) Sivappa, R.; Mukherjee, S.; Lovely, C. J. *Org. Biomol. Chem.* **2009**, *7*, 3215. (c) Sivappa, R.; Hernandez, N. M.; He, Y.; Lovely, C. J. *Org. Lett.* **2007**, *9*, 3861. (d) Lovely, C. J.; Du, H.; Sivappa, R.; Bhandari, M. K.; He, Y.; Dias, H. V. R. *J. Org. Chem.* **2007**, *72*, 3741. (e) Lovely, C. J.; Du, H.; He, Y.; Dias, H. V. R. *Org. Lett.* **2004**, *6*, 735. (f) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett.* **2003**, *5*, 3623. (g) Lovely, C. J.; Du, H.; Dias, H. V. R. *Heterocycles* **2003**, *60*, 1. (h) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.* **2001**, *3*, 1319.

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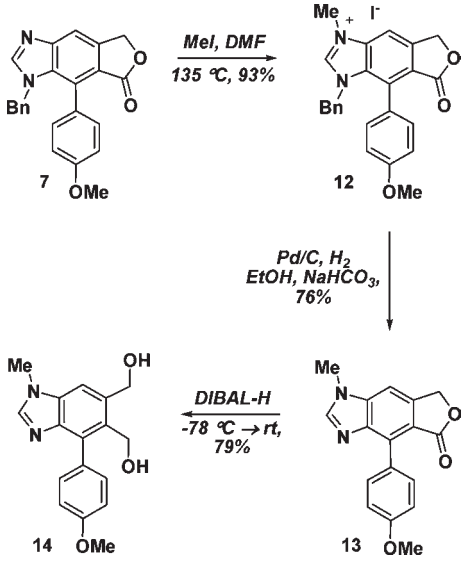
(13) Venuti, M. C. *Synthesis* **1982**, 61.

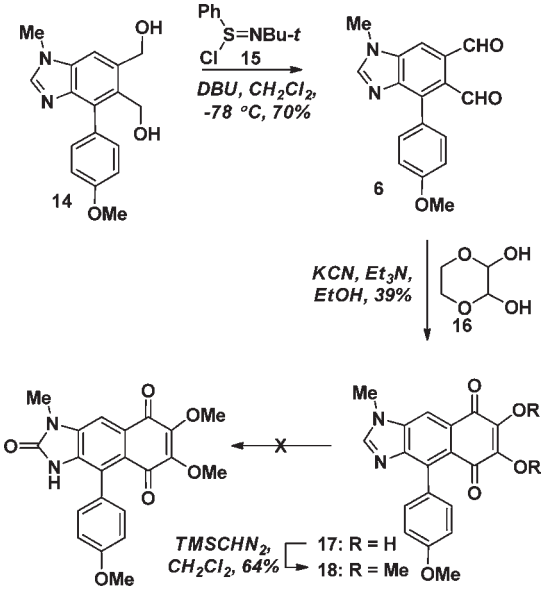
(14) Fatiadi, A. J. *Synthesis* **1976**, 133.

correct position affording **13** (Scheme 2). However, the presence of aqueous base resulted in variable levels of

Scheme 2. Site-Selective Methylation and Oxidation-State Adjustment



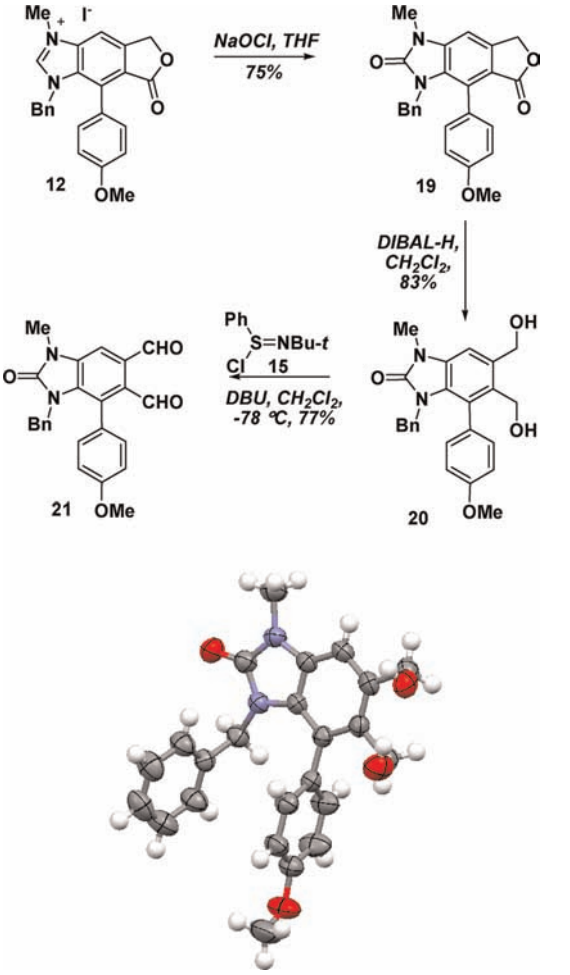
Scheme 3. Installation of Quinone and Attempted Elaboration of C2



lactone hydrolysis during this reaction; thus, treatment of the reduction product with acid prior to purification was necessary to reproducibly provide **13** in good yields. The lactone was then reduced to the corresponding diol **14** on treatment with DIBAL-H.

With diol **14** in hand, we were in a position to introduce the final ring, and to accomplish this, the diol required oxidation to the dialdehyde. However, this transformation

Scheme 4. Successful C2-Oxidation and X-ray Crystal Structure of Compound **20**



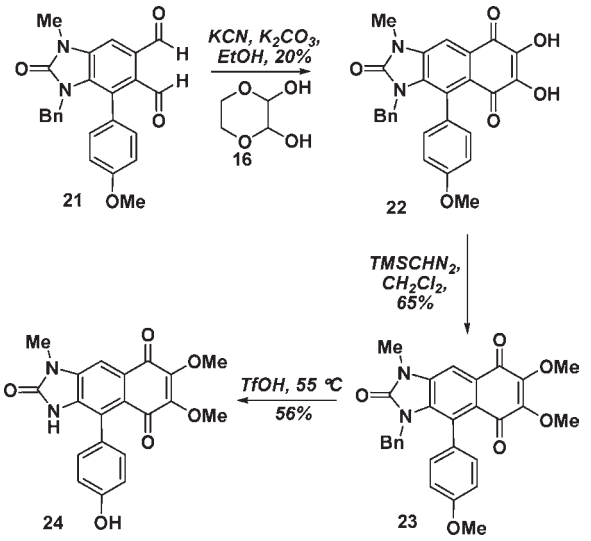
proved to be a more challenging undertaking than anticipated. Out of the initial set of common oxidants that we evaluated, Swern conditions were found to be most encouraging, but there were some reproducibility issues. Therefore, we searched for Swern-like oxidations with improved reliability. In the process of this search, we came across the use of *S*-chlorosufinimines reported by Mukaiyama and co-workers and found this procedure to be the most reproducible, providing the dialdehyde **6** in ~70% yield (Scheme 3).[15] The phthalaldehyde **6** was then reacted with the masked glyoxal derivative **16** to arrive at the 2,3-dihydroxyquinone **17** in moderate but reproducible yield.[13] Treatment of **17** (effectively a vinylogous diacid)

(15) Matsuo, J.-i.; Iida, D.; Tatani, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 223.

(16) We have used this strategy extensively in various total syntheses; see, for example: (a) Lima, H. M.; Garcia-Barboza, B. J.; Khatibi, N. N.; Lovely, C. J. *Tetrahedron Lett.* **2011**, *52*, 5725. (b) Koswatta, P.; Lovely, C. J. *Chem. Commun.* **2010**, *46*, 2148. (c) Koswatta, P.; Lovely, C. J. *Tetrahedron Lett.* **2010**, *51*, 164. (d) Koswatta, P. B.; Lovely, C. J. *Tetrahedron Lett.* **2009**, *50*, 4998. (e) Koswatta, P.; Sivappa, R.; Dias, H. V. R.; Lovely, C. J. *Synthesis* **2009**, 2970. (f) Bhandari, M. R.; Sivappa, R.; Lovely, C. J. *Org. Lett.* **2009**, *11*, 1535. (g) Koswatta, P. B.; Sivappa, R.; Dias, H. V. R.; Lovely, C. J. *Org. Lett.* **2008**, *10*, 5055.

(17) Lima, H. M.; Lovely, C. J. *Org. Lett.* **2011**, *13*, 5736.

Scheme 5



with TMS-diazomethane led to esterification and formation of the dimethyl derivative **18**. We have routinely functionalized imidazoles and benzimidazoles via lithiation and electrophilic trapping to incorporate either the 2-oxo or 2-amino group. Unfortunately, C2-metalation of **18** with LDA and trapping with an appropriate electrophile (e.g., $(PhCO_2)_2$ or TsN_3) was not successful.[16] Although we do not know the precise fate of the imidazole-containing species, a brightly colored and water-soluble material was produced, suggesting some sort of electron-transfer process. Clearly, in order to move this project forward we had to overcome this roadblock. A general solution to functionalizing at the C2-position of imidazoles has been reported recently by our laboratory through the use of hypochlorite or *N*-chloroamides with imidazolium salts. This leads to the direct formation of 2-imidazolones and 2-iminoimidazoles, respectively.[17]

Specifically, we found that treating a THF solution of **12** with commercial bleach solutions provided the 2-benzimidazolone **19** in an excellent 75% yield (Scheme 4).[17] Lactone reduction to the diol was accomplished with DIBAL (confirmed by X-ray crystallography), and oxidation to the dialdehyde **21** was performed as above with the thioimidoyl chloride.[15] Subsequent treatment of the phthaladehyde **21** with the glyoxal derivative **16** and KCN provided the dihydroxy quinone **22**[13] which upon treatment with TMS-diazomethane provided 3-benzyl kealiiquinone **23** (Scheme 5). It is well recognized that the removal of benzyl groups from amides can be a challenging proposition with many of the standard debenzylation techniques failing to result in cleavage. We also found this to be the case with imidazolone **23**. We subsequently determined that the benzyl moiety could be removed upon treatment with TfOH and heating (55 °C), but this also resulted in the loss of the methyl group on the *p*-anisyl moiety.[18] A number of attempts have been made to remethylate the phenolic OH, but these have not been successful due to either bismethylation or selective *N*-methylation.

In summary, we have developed a convenient 10-step synthesis of a close analogue of the *Leucetta*-derived alkaloid kealiiquinone via an intramolecular Diels–Alder reaction from the known vinylimidazole **9**. Introduction of the C2-oxo moiety was accomplished through a novel hypochlorite-mediated oxidation. Incorporation of the quinone fragment was accomplished through the use of a masked glyoxal system. Efforts to improve the efficiency of the quinone forming step and to obtain the 2-deoxy-2-amino congener **2** are underway.

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Supporting Information Available. Detailed experimental procedures and copies of ^1H and ^{13}C NMR spectra for all new compounds. X-ray data for compounds **7** and **20** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org. The authors declare no competing financial interest.

(18) Rombouts, F.; Franken, D.; Martínez-Lamenca, C.; Braeken, M.; Zavattaro, C.; Chen, J.; Trabanco, A. A. *Tetrahedron Lett.* **2010**, *51*, 4815.

The authors declare no competing financial interest.