Total Synthesis of Diplamine, a Cytotoxic Pyridoacridine Alkaloid from a Pacific Tunicate

Bruce G. Szczepankiewicz and Clayton H. Heathcock*

Department of Chemistry, University of California, Berkeley, California 94720

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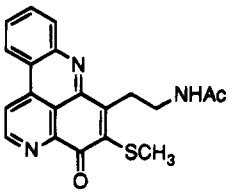
Summary: The total synthesis of diplamine (**1**) has been accomplished in 21 steps from commercially available materials.

Diplamine (**1**), a cytotoxic marine alkaloid isolated from the Pacific tunicate *Diplosoma sp.*,[1] is among the most biologically active of all the known pyrido[2,3,4-*kl*]acridine alkaloids.[2] As part of a general program of synthesis of quinonimine alkaloids, we have carried out the first total synthesis of this interesting natural product.



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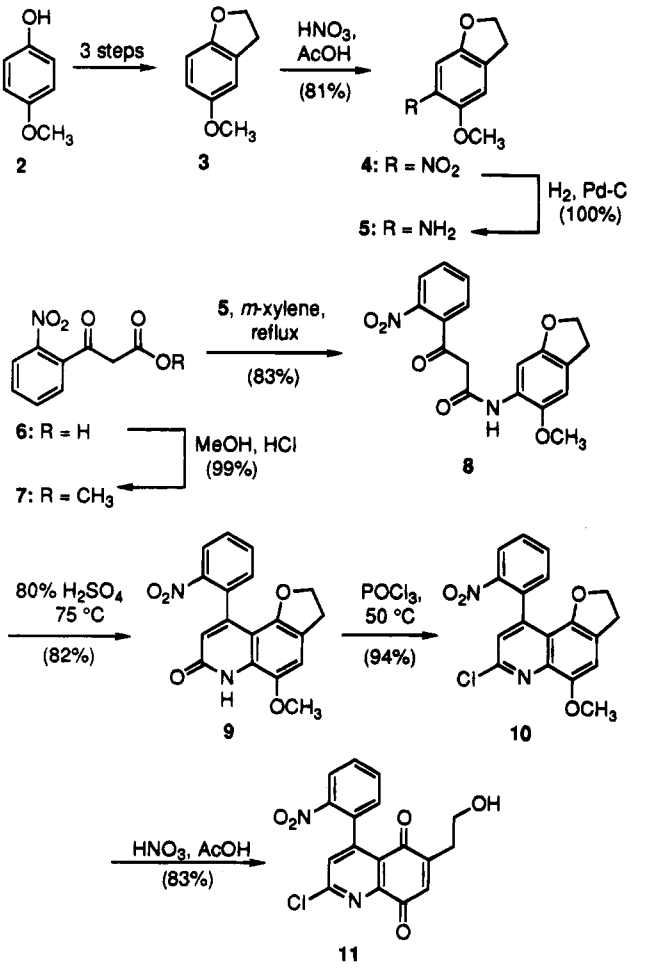
The quinoline portion of diplamine was prepared from a suitably substituted β-keto amide by way of the Knorr quinolone synthesis[3] (Scheme 1). Two-carbon annulation of 4-methoxyphenol (**2**) provided 4-methoxy-2,3-dihydrobenzo[*b*]furan (**3**) according to the published three-step procedure.[4] Nitration proceeded with high regioselectivity to provide the 6-nitro isomer **4**, which was hydrogenated to aniline **5**. The known β-keto acid **6**, prepared in two steps from 2-nitrobenzoyl chloride,[5] was esterified to obtain methyl ester **7**. β-Keto amide **8** was produced by heating a solution of aniline **5** and ester **7** in *m*-xylene at reflux. Treatment of β-keto amide **8** with hot, 80% sulfuric acid solution effected smooth conversion to quinolone **9**, which was converted into chloroquinoline **10** by reaction with warm $POCl_3$.[6] Oxidation of a suspension of this *p*-dialkoxyquinoline in acetic acid with concentrated nitric acid gave the (2-hydroxyethyl)quinone **11**. This compound exists as the (hydroxyethyl)quinone, and not the hemiacetal, as indicated by its ^1H and ^{13}C NMR spectra. For example, of the 17 ^{13}C NMR spectral resonances observed, two with chemical shifts of 181.48 and 184.54 ppm result from the two carbonyl groups of a quinone. Furthermore, the ^1H NMR signal (3.78 ppm, 400 MHz, $CDCl_3$) assigned to the carbinol appears as an ordinary triplet in **11**, whereas these protons appear as two overlapping doublets of triplets centered at 4.28 and 4.35 ppm in the precursor dihydrofuran **10**.[7]

Scheme 1



Although the synthesis outlined in Scheme 1 provided the (hydroxyethyl)quinone on a convenient scale in good overall yield, we encountered significant problems in activating the hydroxy group for displacement by nitrogen nucleophiles. These difficulties were finally understood upon an attempted preparation of (chloroethyl)quinone **12** (Scheme 2). When alcohol **11** was treated with $POCl_3$, dihydrofuranoquinoline **13** was isolated in high yield. We believe that, after activation of the alcohol, intramolecular attack by the proximal carbonyl oxygen occurs. The resulting oxonium intermediate is then quenched in a Michael sense by a nucleophile, in the case at hand, chloride ion. Although this reaction complicated several of our initial attempts to install the nitrogen in the side chain, in this case we realized that the presence of the nuclear chlorine would facilitate later introduction of the methylthio group.

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(1) Charyulu, G. A.; McKee, T. C.; Ireland, C. M. *Tetrahedron Lett.* **1989**, *30*, 4201.

(2) For recent reviews of these alkaloids, see: (a) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771; (b) Molinski, T. F. *Chem. Rev.* **1993**, *93*, 1825.

(3) Jones, G. In *The Chemistry of Heterocyclic Compounds,* Jones, G., Ed.; Wiley: New York, 1977; Vol. 32, pp 151–158.

(4) Alabaster, R. J.; Cottrell, I. F.; Marley, H.; Wright, S. H. B. *Synthesis* **1988**, 950.

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(6) Chloroquinoline **10** is only sparingly soluble in most common solvents, with the exception of pyridine. Fortunately, the product is obtained nearly free of impurities simply by collecting the precipitate obtained after pouring the reaction mixture into ice-water.

(7) Other dihydrofuranoquinolines (e.g., **9** and **13**) showed similar ^1H NMR signals for the corresponding protons.

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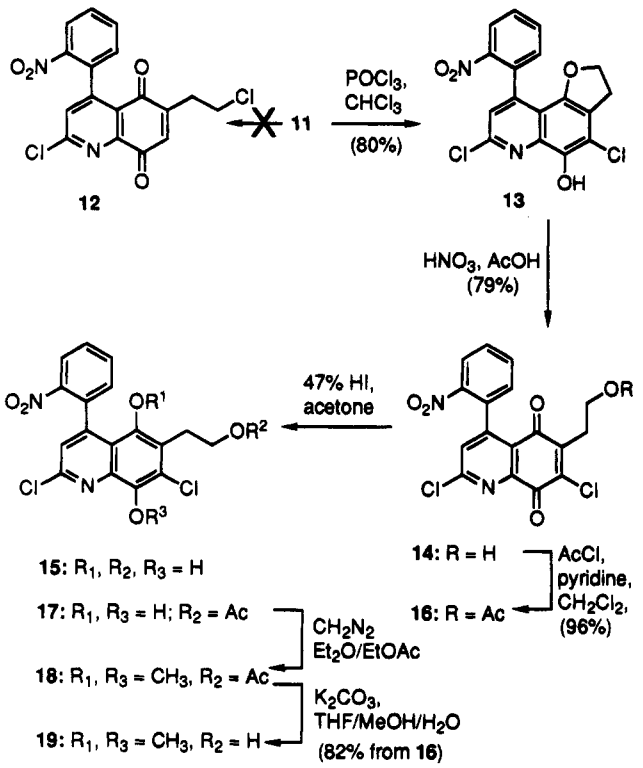
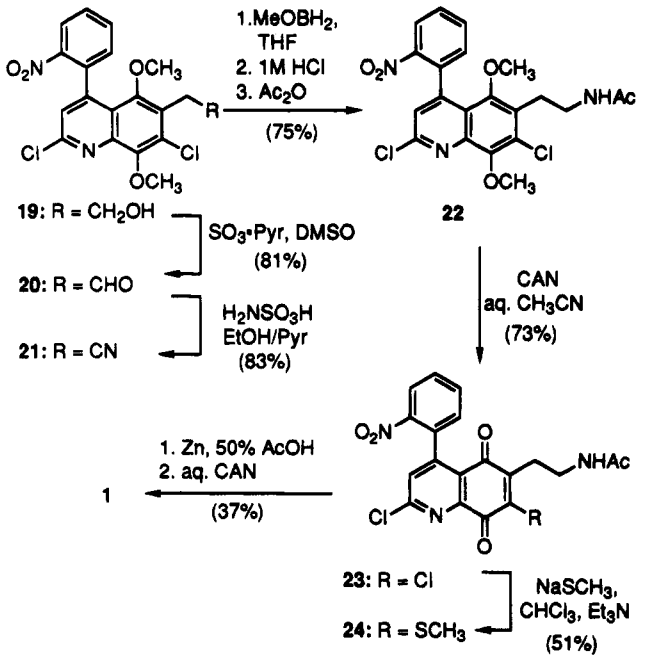
Scheme 2



The hydroxyethyl side chain was regenerated by oxidation of dichloroquinoline **13** with nitric acid; chloroquinone **14** was thereby obtained in good yield. However, because the chloroquinone is rather electrophilic, it was necessary to protect this nucleus before installation of the requisite aliphatic amine. To this end, compound **14** was reduced with complete chemoselectivity to hydroquinone **15** by aqueous hydriodic acid.[8] Selective methylation of the phenolic oxygens was accomplished with potassium carbonate and methyl iodide or dimethyl sulfate, but yields were unacceptably low. Although higher methylation yields were realized on treatment of the hydroquinone with diazomethane, trimethylation was a serious side reaction. This problem was therefore avoided by acylation of alcohol **14** to give acetoxy quinone **16**. Reduction of this quinone to the corresponding hydroquinone **17** was then followed by dimethylation with diazomethane to obtain dimethoxyquinoline **18**. Finally, deacylation was accomplished with potassium carbonate in a mixture of THF, methanol, and water to provide the desired alcohol **19**. The overall yield for this three-step sequence was 82%.

With alcohol **19** in hand, we then attempted to displace activated alcohol derivatives with appropriate nitrogen nucleophiles. Although some of these attempts were partially successful, none of these transformations was found to give suitable yields. Ultimately, we settled on a modified reductive amination to install the nitrogen functionality (Scheme 3). Thus, alcohol **19** was oxidized to the corresponding aldehyde **20**, which was subsequently converted to the nitrile **21** in one pot by condensation with hydroxylamine-*O*-sulfonic acid, followed by *in situ* elimination of sulfuric acid.[9] The chemoselective reduction of the nitrile to the primary amine could be effected with

Scheme 3



borane,[10] but before hydrolysis of the intermediate borazine with 6 M or 12 M HCl was complete, partial hydrolysis of the chloroquinoline was observed. Acylation of the resulting amine during the workup gave amide **22** in only 59% yield. Interestingly, treatment of the borane with 1 equiv of methanol prior to nitrile reduction allowed for workup by stirring with 1 M HCl at room temperature for 72 h. These significantly milder conditions left the chloroquinoline intact.[11] Acylation of the amine during the workup then afforded amide **22** in satisfactory yield.

With amide **22** in hand, the synthesis of diplamine was rapidly completed. Oxidative demethylation of dimethoxyquinoline **22** with ceric ammonium nitrate[12] gave quinone **23**,[13] which was treated with sodium methanethiolate and a small amount of triethylamine[13] to afford **24**. Zinc–acetic acid reduction of this material, followed by oxidative workup, provided synthetic diplamine (**1**), which proved to be identical in all respects (^{1}H NMR, ^{13}C NMR, IR, UV, TLC mobility) to an authentic sample of the natural material.

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Supplementary Material Available: Experimental procedures and spectral data for all compounds, as well as reproductions of selected spectra from this manuscript (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(11) To our knowledge, this is the first reported use of methoxyborane as a reducing agent.

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(13) For a similar example, see: Adams, R.; Reifschneider, W. *Bull. Soc. Chim. Fr.* **1958**, 23.