Tetrahedron Letters,Vol.28,No.42,pp 4969-4972,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

STUDIES ON A BIOMIMETIC APPROACH TO AEROTHIONIN AND PSAMMAPLYSIN-A

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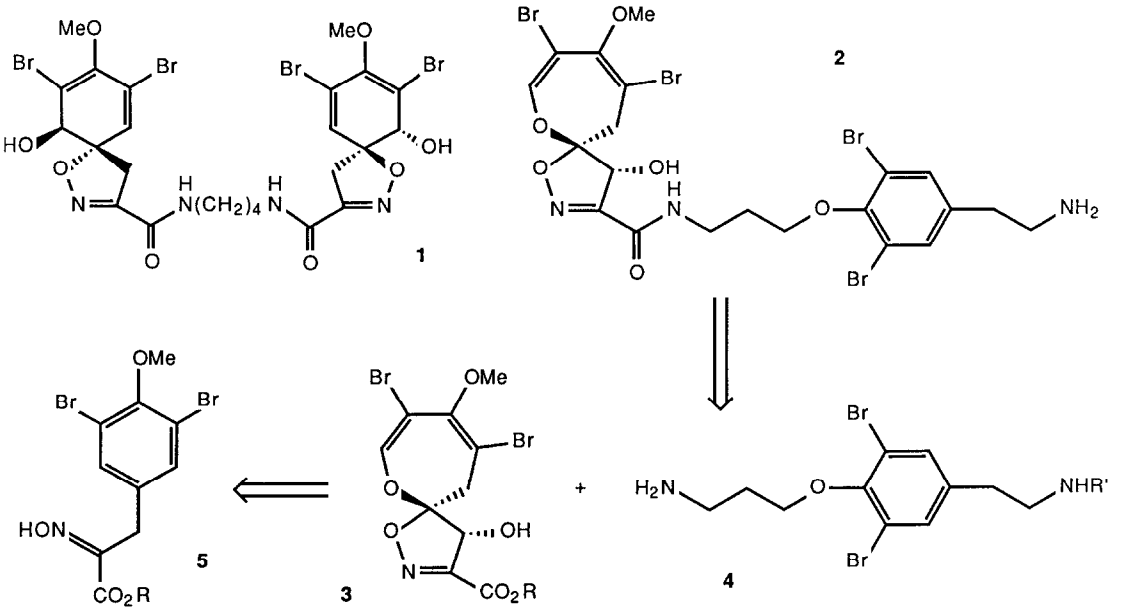
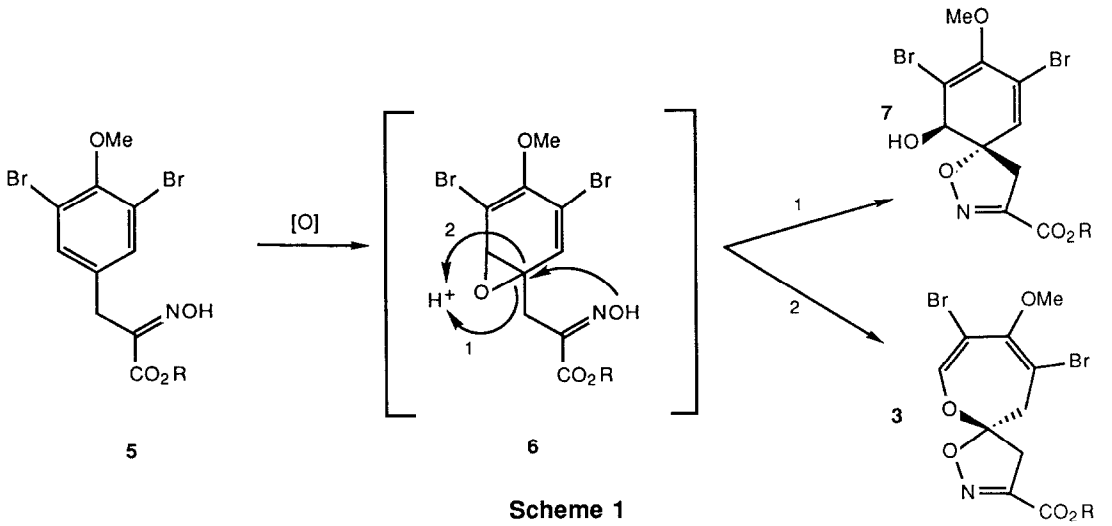
Summary: Oxidation of a plausible biological precursor for the spirocyclic systems of aerothionin (**1**) and psammaplysin-A (**2**) is described.

In the last two decades, a number of natural products have been isolated from sponges of the order Verongida. Most of them can be formulated as products generated by the aromatic oxidation of dibromotyrosine. Aerophobin-1,[1] aerothionin (**1**),[2] and psammaplysin-A (**2**)[3] are pertinent examples. While the natural role of these compounds is unknown, they all have some biological activity in antibacterial testing. A recent report on the related compound purealin showed inhibition of Na/K ATPase and myosin Ca ATPase and activation of myosin K/EDTA ATPase.[4]





5 6

Scheme 1

The most interesting structural aspect of these molecules is the spirocyclic isoxazoline ring system. Compounds with this spirocyclic system have been isolated only from the sponges of order Verongida. The purported precursor is the oxime **5**, a derivative of dibromotyrosine. Were **5** oxidized to arene oxide **6**, the final spirocycles could be formed by nucleophilic attack of the oxime hydroxyl on the epoxide (Scheme 1). The epoxide can open by breaking a carbon-oxygen bond to give the [5,3] spirocyclic alcohol in a reaction analogous to the NIH shift[5] or by breaking the carbon-carbon bond to yield the [6,3] spirocyclic ketal in a mechanism similar to the arene oxide-oxepin tautomerism.[6]

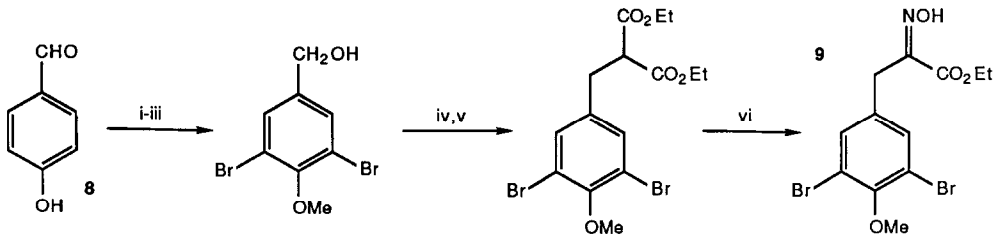
A synthetic approach incorporating this proposed scheme was explored. Compound **2** was retrosynthetically disconnected at the carbon-nitrogen amide bond into two pieces. The mono-N-acetyl protected amine **4** (R'=Ac) was synthesized from tyramine hydrochloride in five steps with an overall yield of 17%. The carboxyl portion retrosynthetically was envisioned as arising from the oxime **5**. Ethyl ester **9** was synthesized from p-hydroxybenzaldehyde (**8**) in six steps with an overall yield of 25%.

Four methods were used to oxidize compound **9**:

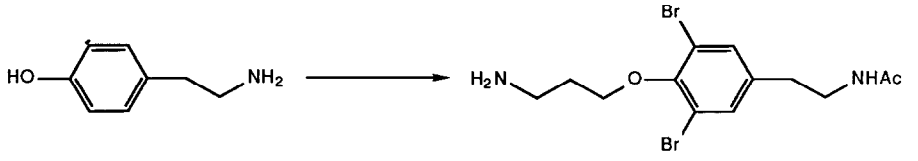
i. The porphyrin oxidation of the oxime was performed using conditions conducive to aromatic hydroxylation worked out by Tabushi and Morimitsu.[7] In a typical experiment,10.0 μL colloidal platinum in polyvinylpyrollidine (Pt·PVP, 6.6 μM, 4.1 x 10^{-7} eq),[8] 3.80 mg benzoic anhydride (0.12 eq), 2.5 μL N-methyl imidazole (0.22 eq), 1.80 mg TPP·MnCl (0.018 eq), and 55.0 mg **9** (1.00 eq)

were stirred in 1.5 mL dry ethanol under a 1:1 hydrogen:oxygen atmosphere for several days. Only a trace of non-starting material was obtained after HPLC purification, but no identification was possible.

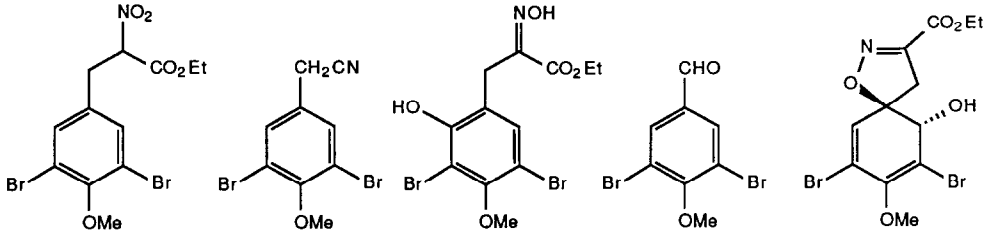
ii. Oxime **9** was also oxidized using a system of t-butyl hydroperoxide and molybdenum dodecacarbonyl heated to 93° in a sealed tube[9] for times ranging from 14 hours to 37 days. With ethanol as a solvent, the oxidation proceeded extremely slowly. Over 50% of starting material was recovered after several days. Numerous oxidation products were isolated and four compounds were identified. Two products were the nitro compound **10** and the benzyl cyanide **11**. The third product **12** was the result of aromatic hydroxylation and the last was the benzaldehyde **13**. Although aldehyde **13** was an intermediate on the pathway to oxime **5**; HPLC purification of **5** prior to oxidation showed that **13** was not a contaminant.



i) NBS, 90% ii) MeI, K_2CO_3, 90% iii) $NaBH_4$,85% iv) NaI, $BF_3{\cdot}Et_2O$, 75%
v) NaH, $CH_2(COOEt)_2$, 75% vi) BuONO, NaOEt, 70%



i) Ac_2O, NaOAc, 75% ii) Br_2, 60% iii) $Br(CH_2)_3Br$, NaH, 60% iv) K^+Pth^-,60% v) H_2NNH_2, 60%



iii. Oxidation of **9** proceeded much faster in benzene using the oxidizing conditions of method **ii**. Recovery of starting material was negligible after 24 hours and the same four major oxidation products were isolated and identified. Furthermore, the spirocycle **14** was also isolated as an minor oxidation product in 3-4% yield. Compound **14** was identified using ^{1}H NMR and chemical ionization MS;[10] the NMR spectrum was similar to that reported for the methyl ester.[11]

iv. The last method of oxidation employed trifluoroperacetic acid in a biphasic system as reported by Jerina and Daly.[12,13] Oxidations using this system proceeded cleanly and gave relatively few products. Recovered starting material decreased with longer reaction times; after 37 days, virtually no oxime was isolated. The identified products were the same four reported isolated from the reaction in ethanol. Efforts to find the spirocycle **14** were not successful. Furthermore, throughout the experiments no isolated compound could be conclusively identified as the spirocyclic system **3** (R=Et) of psammaplysin-A (**2**).

Typically, aromatic oxidations are performed on simple systems--benzene and anisole--and are run for only a few minutes to prevent secondary reactions. Yields of products are ususally ten percent or less.[12,13] The isolation and identification of **14** from the peroxide oxidation supports the proposed bio-oxidation of **9** to the spirocyclic systems seen in natural products from the Verongida sponges. Synthesis of the methyl ester analogue of **14** would complete a formal, albeit low-yield, biomimetic synthesis of aerothionin (**1**).[11] Further oxidation studies may reveal better methods for generating the necessary arene oxide and subsequently the desired spirocycles.

Acknowledgments: This work was supported by the National Institutes of Health (CA24487).

REFERENCES

1. P.D. Bartlett and T.G. Traylor. *J. Am. Chem. Soc.* **83**, 856 (1961).
2. J.A. McMillan, I.C. Paul, Y.M. Goo, and K.L. Rinehart, Jr. *Tetrahedron Lett.*, **22**, 39-42(1981) and references therein.
3. D.M. Roll, C.W.J. Chang, P.J. Scheuer, G.A. Gray, J.N. Shoolery, G.K. Matsumoto, G.D. VanDuyne, and J. Clardy. *J. Am. Chem. Soc.* **107**, 2916-20(1985) and references therein.
4. H. Nakamura, H. Wu, J. Kobayashi, Y. Nakamura, and Y. Ohizumi. *Tetrahedron Lett.* **26**, 4517-20(1985).
5. D.M. Jerina and J.W. Daly. *Science.* **185**, 573-82(1974) and references therein.
6. E. Vogel and H. Günther. *Angew. Chemie Int. Ed.* **6**, 385-401(1967).
7. I. Tabushi and K. Morimitsu. *Tetrahderon Lett.* **27**, 51-4(1986).
8. H. Hirai, Y. Nakao, and N. Toshima. *J. Macromol. Sci.-Chem.* **A13**, 727-50(1979).
9. M.N. Sheng and J.G. Zajacek. *Advan. Chem. Series.* **1968**, 418-32.
10. Spectral data for **14**: CIMS, m/z= 412(M^++3, trace); ^{1}H NMR($CDCl_3$, 400 MHz) δ 6.47 (1H, s), 5.24 (1H, d, J=5.9 Hz), 4.30 (1H, d, J=6.0), 3.94 (1H, d, J=7.7), 3.10 (1H, d, J=7.8), 4.17 (2H, q, 8.2), 1.22, (3H, t, 8.2), and 3.81 (3H, s) ppm.
11. S. Nishiyama and S. Yamamura. *Bull. Chem. Soc. Jpn.* **58**, 3453-6(1985).
12. D.M. Jerina, J.W. Daly, and B. Witkop. *Biochemistry.* **10**, 366-72(1971).
13. D. Jerina, G. Guroff, and J. Daly. *Arch. Biochem. Biophys.* **124**, 612-15(1968).

(Received in USA 16 June 1987)