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TOTAL SYNTHESES OF (±)-AEROTHIONIN AND (±)-HOMOAEROTHIONIN

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Summary: Both aerothionin and homoaerothionin, the novel metabolites of the sponges *Aplysina aerophoba*, *A. fistularis* and *Verongia thiona*, have been synthesized in racemic form.

Both aerothionin (1) and homoaerothionin (2), the novel structures of which have a spiroisoxazoline moiety and are quite attractive to us, have been isolated from the sponges *Aplysina aerophoba*, *A. fistularis* and *Verongia thiona*.[1,2] Recently, the absolute stereostructure of aerothionin was unambiguously determined to be 1 by means of an X-ray crystallographic analysis together with the circular dichroism of 1.[2] In the present paper, we wish to describe the total syntheses of (±)-aerothionin and (±)-homoaerothionin.

The known azlactone[1] derived from 2-benzyloxy-3,5-dibromo-4-methoxybenzaldehyde was readily converted into a benzyl ester (3)[3] in three steps [1) 10% KOH in H_2O - dioxane (1 : 1) (100 °C, 9h); 2) $NH_2OH \cdot HCl$ - 10% KOH in H_2O - dioxane (1 : 1) (room temp., overnight); 3) benzyl chloride - K_2CO_3 in DMF (room temp., overnight); 35% overall yield]. This ester was further treated with K_2CO_3 in MeOH - dioxane (1 : 1) (room temp., 40 min) followed by hydrogenolysis using Pd black in dioxane - AcOH (1 : 1) (room temp., overnight) to afford the corresponding methyl ester (4),[4] in 74% overall yield. On treatment with thallium (III) trifluoroacetate (2.4 eq) in CF_3COOH (room temp., 4 h),[5] 4 (1.1 eq) was converted into a desirable dienone (5)[6] in 27% yield.

As reported by Forrester *et al.*,[7] $NaBH_4$ reduction of tetradehydroaerothionin in dioxane afforded only unnatural cis-cis-aerothionin. However, reduction of 5 was successfully carried out using excess $Zn(BH_4)_2$ in CH_2Cl_2 - Et_2O (3 : 2) (room temp., 7 min) to give the corresponding trans and cis isomers (6 and 7)[8] in 29 and 40% yields, respectively.[9] A mixture of 6 (2.5 eq) and 1,4-diaminobutane (1 eq) was allowed to stand at room temperature overnight to give the corresponding diamide,[10] in 18% yield,[11] whose mass (FD), IR and ^1H NMR spectra were completely identical with those of natural aerothionin (1).[1] In addition, the synthetic and natural compounds both have the same retention time and Rf value in their HPLC [Develosil 6 (4.6 mm x 250 mm); hexane - acetone (5 : 1); flow rate: 1 ml/min; pressure: 80 Kg/cm^2] and TLC [Kieselgel PF_{254}; benzene - acetone (5 : 1)], respectively.[12]

Similarly, the synthetic diamide, which was readily obtained on amidation of 6 (2 eq) with 1,5-diaminopentane (1 eq) under the same condition as described in the case of aerothionin (1), was completely identical with natural homoaerothionin (2) [mass (FD), IR, ^1H NMR, HPLC and TLC].[13]

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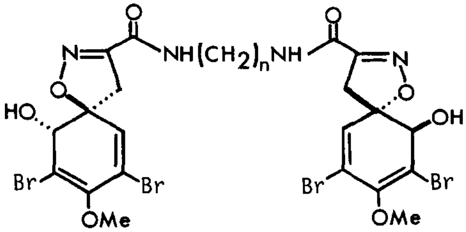
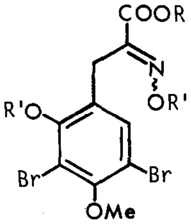
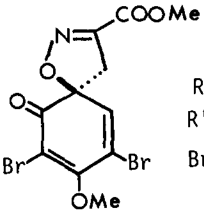


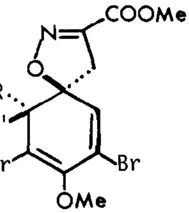
1 (n = 4)
2 (n = 5)



3 R = R'= Bn
4 R = Me, R'= H



5



6 R = OH, R'= H
7 R = H, R'= OH

providing us with the authentic samples of aerothionin, homoaerothionin, and cis-cis-aerothionin. This research has been supported in part by grants from the Takeda Science Foundation, to which grateful acknowledgment is made.

References and Notes

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2. J. A. McMillan, I. C. Paul, Y. M. Goo, K. L. Rinehart, Jr., W. C. Krueger, and L. M. Pschigoda, Tetrahedron Lett., 22, 39 (1981).
3. 3: mp 83 - 85 °C (hexane - AcOEt); $C_{31}H_{27}NO_5{}^{79}Br_2$ [m/e 651.0244(M^+)]; IR (film) 1720, 1600, 1580 cm^{-1}; ^1H NMR ($CDCl_3$): δ3.85(3H, s), 3.88(2H, s), 4.88(2H, s), 5.12(2H, s), 5.22(2H, s), 7.2 - 7.5(16H, complex).
4. 4: mp 148 - 149 °C (hexane - AcOEt); $C_{11}H_{11}NO_5{}^{79}Br^{81}Br$ [m/e 396.8984(M^+)]; IR (film) 3300, 1730, 1700sh., 1650, 1590, 1550 cm^{-1}; ^1H NMR ($CDCl_3$): δ3.85(3H, s), 3.88(3H, s), 3.92(2H, s), 7.42(1H, s).
5. Other oxidizing agents, including Br_2, 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one and others, were not effective in this case.
6. 5 as a syrup: $C_{11}H_9NO_5{}^{79}Br^{81}Br$ [m/e 394.8809(M^+)]; IR (film) 1710, 1670, 1585, 1530 cm^{-1}; ^1H NMR ($CDCl_3$): δ3.27(1H, d, J= 18Hz), 3.65(1H, d, J= 18Hz), 3.93(3H, s), 4.20 (3H, s), 6.78(1H, s).
7. A. R. Forrester, R. H. Thomson, and Soo-On Woo, Liebigs Ann. Chem., 1978, 66.
8. 6 as a syrup: $C_{11}H_{11}NO_5{}^{79}Br^{81}Br$ [m/e 396.8979(M^+)]; IR (film) 3400, 1725, 1630, 1590, 1580 cm^{-1}; ^1H NMR (acetone-d_6): δ3.17(1H, d, J= 18Hz), 3.73(3H, s), 3.83(3H, s), 3.85 (1H, d, J= 18Hz), 4.22(1H, d, J= 7.5Hz), 5.38(1H, d, J= 7.5Hz), 6.52(1H, s).
   7 as a syrup: $C_{11}H_{11}NO_5{}^{79}Br_2$ [m/e 394.8987(M^+)]; IR (film) 3470, 1730, 1620, 1595, 1575 cm^{-1}; ^1H NMR (acetone-d_6): δ3.42(2H, s), 3.68(3H, s), 3.70(3H, s), 4.53(1H, d, J= 7.5Hz), 4.98(1H, d, J= 7.5Hz), 6.58(1H, s).
9. Further study on the cis and trans selectivities is in progress.
10. On addition of the amine, the cis isomer (7) was simultaneously decomposed.
11. The starting material (6) was recovered in 38% yield.
12. A possibility, in which the synthetic sample contains both aerothionin and its diasteroisomer, is not necessarily ruled out.
13. As pointed out in the case of aerothionin (1), the synthetic sample may also contain both homoaerothionin (2) and its diastereoisomer. At present, however, we have no evidence for that.

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