

Synthetic Studies on Bioactive Marine Natural Products, Synthesis of the Spiroisoxazoline Derivatives, Employing Electrochemical Methodology

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In recent years, several bromophenylpyruvic acid derivatives have been isolated from marine origin as secondary metabolites. These alkaloids containing bromine atoms possess the spirocyclic isoxazoline structures and their diverse biological activities prompted many synthetic groups to achieve their total synthesis. Among such investigations, we accomplished the first total synthesis of aerothionin, homoaerothionin, aerophobin: the spiroisoxazoline structure **1**, which is a fundamental framework of these natural products, was constructed by the TFA (thallium trifluoroacetate) oxidation of phenol **2**, followed by $Zn(BH_4)_2$ reduction of spirodienone **3** (ref. 1). However, the methodology of the thallium oxidation has several problems: (1) this reaction produced a considerable amount of by-products such as dimers and benzofurans, and (2) excess amounts of the toxic thallium oxidant was required to acquire good yields. Based on such background, we elaborated an improved synthetic methodology of the spiroisoxazolines **1** by employing anodic oxidation of the corresponding phenol derivative **2** (ref. 2).

Anodic oxidation of **2** was attempted as the following procedure. *Procedure:* the oxidation was performed under CCE or CPE conditions employing a glassy carbon beaker as an anode, a platinum wire as a cathode, and appropriate supporting salts (ca. 0.2 mol / L). The MeOH – $LiClO_4$ combinations provided spiroisoxazoline compound **3** and by-products (**4**, **5**). In contrast, the best condition gave **3** in 68% yield, when **2** (1 mmol / L) was oxidized under CPE conditions MeCN – nBu_4NClO_4 . Successive reduction of **3** with $Zn(BH_4)_2$ or $NaBH_4 / CeCl_3$ afforded a corresponding spiroisoxazoline **1**.

Aerophysinin-1 **6**, isolated from the marine sponge *Verongia aerophoba*, also has the characteristic 1,2-dihydroarene-1,2-diol containing a nitrile group. To accomplish the efficient synthesis of **6** from spiroisoxazoline **1**, a new ring-opening reaction of the isoxazoline moiety **I** to the corresponding nitrile **II** was found (ref. 3).

Zamamistatin **7**, isolated from the Okinawan sponge *Pseudoceratina purpurea*, possesses the unprecedented bis-spiroisoxazole-structure. Details of our research progress to zamamistatin **7** and related natural products will be also discussed.

References

1. Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1983**, *24*, 3351-3352; Nishiyama, S.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1986**, *58*, 3453-3457; Yamamura, S.; Nishiyama, S. *Synlett* **2002**, 533-543.
2. Ogamino, T.; Ishikawa, Y.; Nishiyama, S.

Heterocycles **2003**, *61*, 73-79.

3. Ogamino, T.; Nishiyama, S. *Tetrahedron* **2003**, *59*, 9419-9423.

