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ELECTROCHEMICAL SYNTHESIS OF SPIROISOXAZOLE DERIVATIVES AND ITS APPLICATION TO NATURAL PRODUCTS

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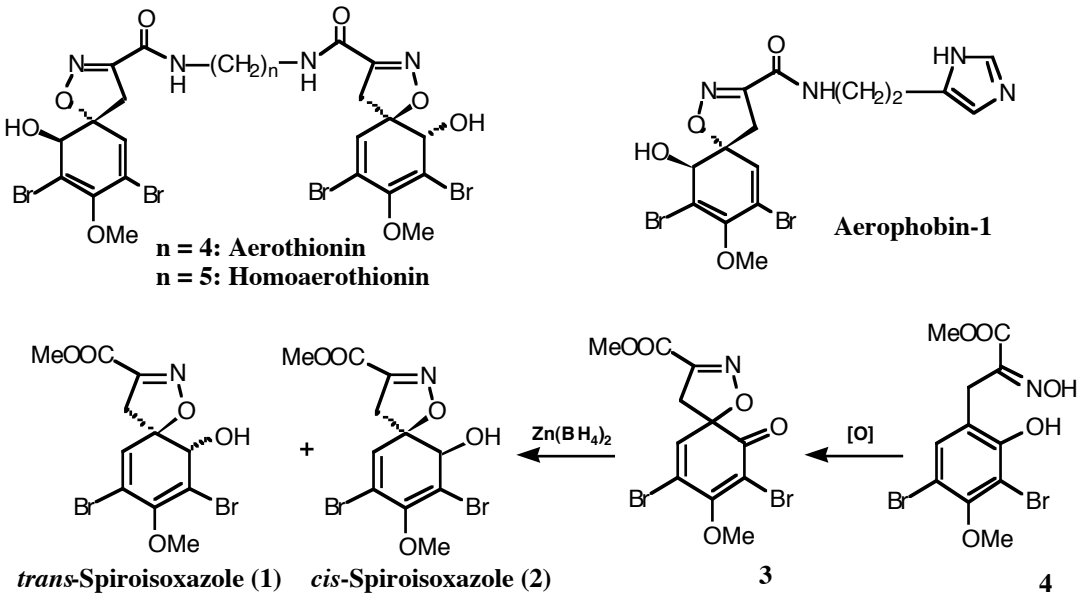
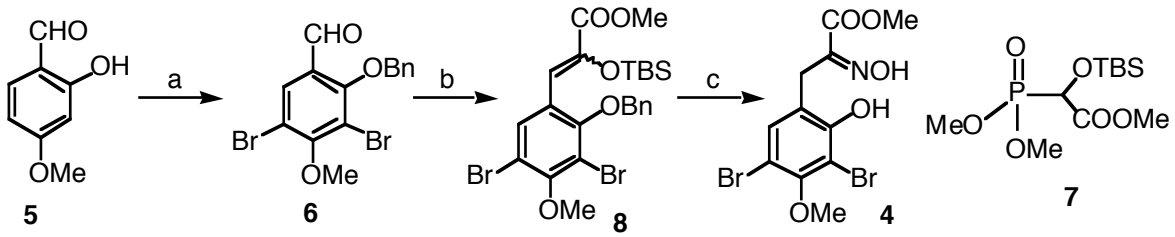
Abstract – Efficient synthesis of the *trans*-spiroisoxazole (**1**) and its unnatural *cis*-isomer (**2**) was accomplished by employing anodic oxidation of **4**, followed by $Zn(BH_4)_2$ reduction. This method was applied to an assembly of the carbon framework of zamamistatin (**12**).

A family of marine natural products, carrying a dibromophenylpyruvic acid oxime moiety,[1] is of interest, because of their diverse biological activities, as well as a typical spiroisoxazole framework (**1**), biogenesis of which might involve epoxidation of an aromatic ring, followed by intramolecular nucleophilic attack of an oxime.[2] In this context, we accomplished the first total synthesis of aerothionins and aerophobin-1[3] by the TTFA (thallium (III) trifluoroacetate) oxidation of phenol (**4**),[4] followed by $Zn(BH_4)_2$ reduction of spirodienone (**3**). In particular, reduction of the ketone usually provided unnatural *cis*-form (**2**).[5] Although the thallium oxidation was a reliable method to give the expected spirodienones, the reaction produced a considerable amount of by-products such as dimers or benzofurans; furthermore, excess amounts of the oxidant were required to complete the reaction. This reaction feature should be reconsidered from the viewpoint of recent environmental concerns. Against such background, an improved synthetic methodology of the spiroisoxazoles (type-**3**) was elaborated by employing anodic oxidation of the corresponding phenol derivatives. We disclose herein our research progress involving synthetic attempts toward zamamistatin (**12**).[6]



The phenol (**4**) for the oxidation was synthesized through the Horner-Wadsworth-Emmons reaction (Scheme 1), while our previous investigation included hydrolysis of the azulactone.[3a,b]

Thus, bromination of **5**, followed by benzylation afforded **6**, which on coupling with an anion of **7** gave enol ether (**8**) in a good overall yield. On exposure to hydroxylamine hydrochloride, **8** underwent simultaneous deprotection and oximation. Finally, selective hydrogenolysis produced the expected substrate (**4**) for electrolysis.



Scheme 1. *Reagents*: a. i) pyridinium bromide perbromide / Py, 88%; ii) BnBr, K_2CO_3 / DMF, 90%. b. LHMDS, **7**, 96%. c. i) $NH_2OH \bullet HCl$ / MeOH, 91%; ii) H_2, 10% Pd-C / AcOH – dioxane, 85%.

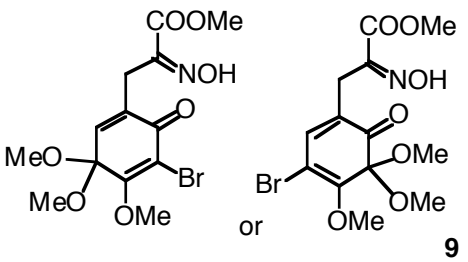
Anodic oxidation of **4** was attempted at the following procedure. *Procedure*: the oxidation was performed under CCE (constant current electrolysis) or CPE (constant potential electrolysis) conditions employing a glassy carbon beaker (200 or 50 mL) as an anode, a platinum wire as a cathode, and

appropriate supporting salts (*ca*. 0.2 mol / L). As can be seen in Table 1, the MeOH - $LiClO_4$ combinations (entries 1 - 3) provided by-products (**9**, **10**). Formation of dimer (**10**) implied that insufficient potential caused one-electron oxidation to give diaryl ether through a radical intermediate (**11**). Upon using a constant potential at 1.3 V *vs*. SCE, current was used for other oxidation, resulting in recovery of unreacted **4**. The acidic dioxane and acetone were obviously unfit solvents (entries 4, 5), although they contributed to production of oxa-spiro derivatives.[7] Eventually, the best condition was obtained when **4** (1 mmol / L) was oxidized under CPE conditions in MeCN - nBu$_4$NClO$_4$ (entry 7). Successive reduction of **4** with $Zn(BH_4)_2$ involving a work-up procedure with $MgSO_4$, afforded corresponding *tans* and *cis* alcohols (**1**, **2**) in 41 and 39% yields, respectively, which were twice higher than those reported previously.[3] In addition, exposure of unnecessary **2** to Et_2NH effected -elimination to give **4**, which could be repeatedly submitted to the oxidation.

Table 1. Anodic Oxidation of Dibromophenylpyruvic Acid Oxime (**4**)

entry	solvent	supporting salt	potential (V *vs*. SCE)	current (mA)[b]	conc. of **4** (mmol/L)	yields (%)			
						3	**9**	**10**	**4**
1	MeOH	$LiClO_4$	0.9-1.3	10	3	11	8	41	-
2	MeOH	$LiClO_4$	0.9-1.3	10	1	18	12	14	-
3	MeOH	$LiClO_4$	1.3	80-5	3	19	17	14	20
4	a	$LiClO_4$	1.5-1.7	50	3		no reaction		
5	acetone	nBu$_4$NClO$_4$	1.6	50-9	3		multi spots		
6	MeCN	nBu$_4$NClO$_4$	1.6	50-5	3	49	-	-	7
7	MeCN	nBu$_4$NClO$_4$	1.6	20-5	1	68	-	-	-

a. 10%$HClO_4$ / dioxane. b. Equivalent of current: 2 F / mol.



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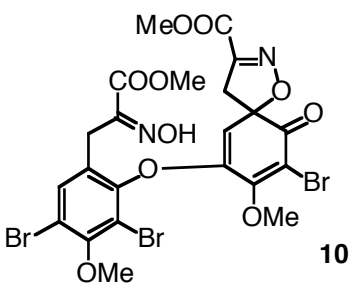

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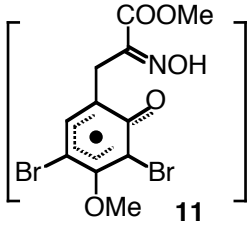

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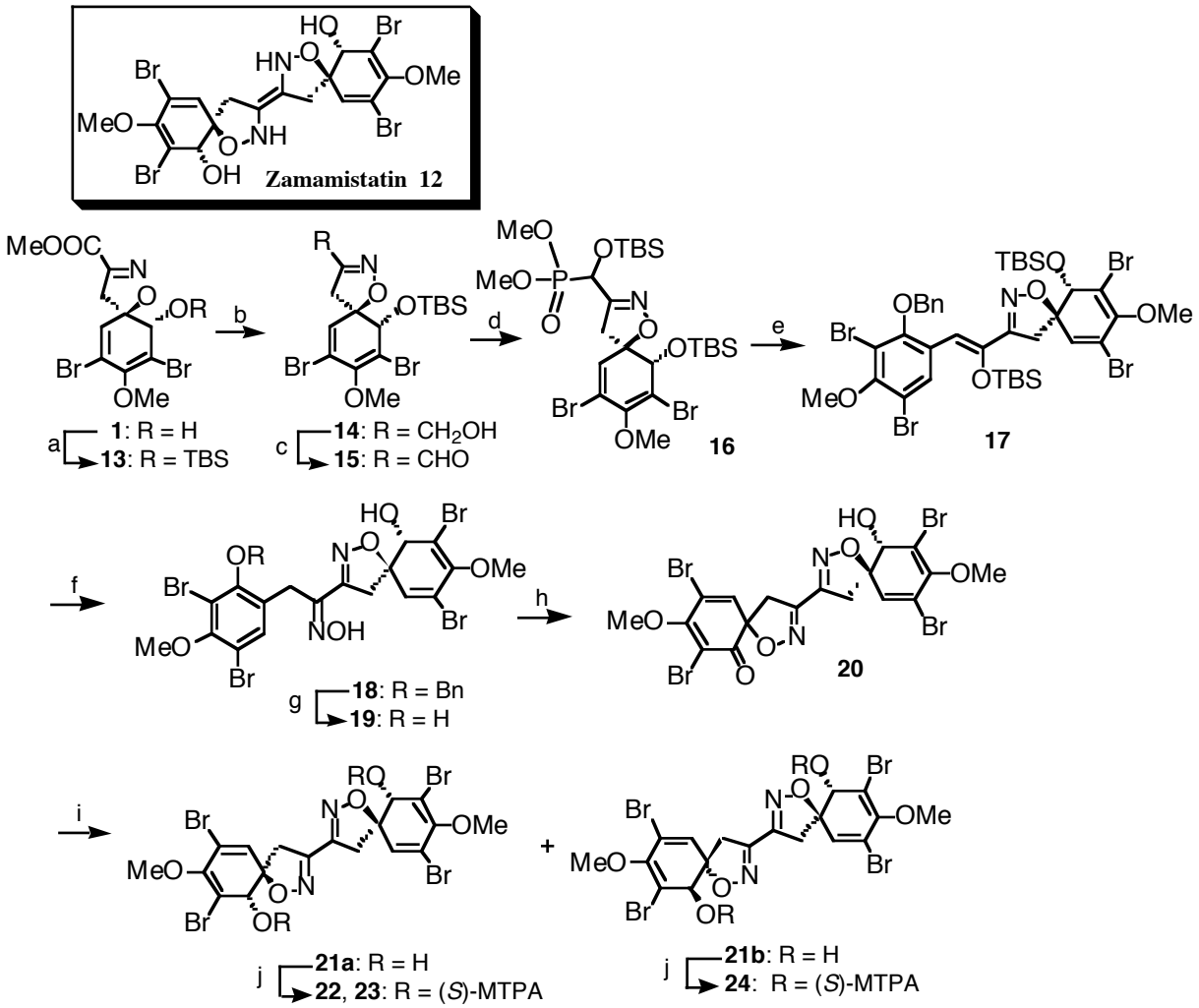
In the next stage, our attention turned to application of this electrochemical methodology to synthesis of natural products. A literature survey of dibromophenylpyruvic acid derivatives of marine origin indicated zamamistatin (**12**), isolated from the Okinawan sponge *Pseudoceratina purpurea*.[6] The unprecedented bisspiroisoxazole-structure possessed antibacterial activity against *Rhodospirillum salexigens* SCRC 113, which implied **12** would be a candidate of an inhibitor of biofouling.



Scheme 2. *Reagents*: a. TBSOTf, 2,6-lutidine. b. $LiBH_4$, 78% in two steps. c. DMSO, SO_3•Py, Et_3N, 90%. d. i) dimethyl phosphite, Et_3N; ii) TBSCl, Imd., 89%. e. LHMDS / THF, then **6**, 47%. f. i) TBAF; ii) NH_2OH•HCl, 98% in two steps. g. H_2, Pd black / AcOH - dioxane, 54%. h. CPE, 1.6 V vs SCE, 2 F / mol, $n$$Bu_4NClO_4$ / MeCN, 35%. i. $Zn(BH_4)_2$ / CH_2Cl_2, **21a**: 26%, **21b**: 23%. j. (*S*)-MTPACl, DMAP, Py, **22**: 45%, **23**: 43%, **24**: 78%.

After protection of an allyl alcohol of **1** as a siloxy ether (**13**), $LiBH_4$ reduction provided alcohol (**14**) in 78% yield from **1** (Scheme 2). Compound (**14**) was oxidized to give aldehyde (**15**), which was coupled with dimethyl phosphite under basic conditions, followed by protection of an alcohol generated, leading to the Horner-Wadsworth-Emmons reagent (**16**). Coupling of an anion of **16** with **6** provided **17** in 47% yield. Successively, **17** was converted through **18**[8] into oxime-phenol (**19**), which on anodic oxidation provided the bisspiroisoxazoline derivative (**20**), as a diastereomeric mixture. $Zn(BH_4)_2$ reduction of **20** gave **21a**[9] and **21b**[9] in 26 and 23% yields, respectively. The stereochemistry of **21a** and **21b** could be distinguished by conversion into their (*S*)-MTPA esters: **21a** gave a separable mixture of **22** and **23**, whereas **21b** provided **24** as the sole product. Since zamamistatin (**12**) has a C_2 symmetry, introduction of an optically active MTPA residue to racemic **21a**, would produce a mixture of diastereomers, while *meso*-compound (**21b**) gave *meso*-product (**24**). Accordingly, **21a** should possess the same stereochemistry of the two spiro-centers as zamamistatin (**12**).[10]

In conclusion, we have accomplished an improved synthetic method of the spiroisoxazole derivatives (**1**, **2**) by using anodic oxidation. This method provided access to the assembly of the zamamistatin-framework. Further investigation towards the natural zamamistatin molecule and related natural products carrying dibromophenylpyruvic acid oxime is in progress.

ACKNOWLEDGMENTS

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8. The TBAF treatment effected a high-yield conversion of the TBS-enol ether into the oxime. Upon a direct use of NH_2OH•HCl as in the case of **8**, **18** was obtained in 39% yield.
9. **21a**: IR (film) 3434 cm^{-1}; NMR δ_H ($CDCl_3$) 2.29 (2H, d, *J*= 8.3 Hz), 3.03 (2H, d, *J*= 17.6 Hz), 3.76 (6H, s), 4.00 (2H, d, *J*= 17.6 Hz), 4.44 (2H, d, *J*= 8.3 Hz), 6.33 (2H, s); δ_C ($CDCl_3$) 38.6, 60.2, 73.9, 91.0, 112.3, 121.1, 131.0, 148.0, 150.9. HRMS *m/z* (M^+-OH) Calcd for $C_{18}H_{15}N_2O_5{}^{79}Br_4$, 654.7715. Found: 654.7755. **21b**: IR (film) 3436 cm^{-1}; NMR δ_H (acetone-d_6) 3.23 (2H, d, *J*= 17.6 Hz), 3.72 (6H, s), 3.87 (2H, d, *J*= 17.6 Hz), 4.15 (2H, d, *J*= 8.3 Hz), 5.44 (2H, d, *J*= 8.3Hz), 6.51 (2H, s); δ_C (acetone-d_6) 39.7, 60.2, 75.1, 91.3, 113.7, 122.1, 132.0, 148.6, 151.9. HRMS *m/z* (M^+) Calcd for $C_{18}H_{16}N_2O_6{}^{79}Br_4$, 671.7682. Found: 671.7712.
10. Unfortunately, efforts to convert into natural product (**12**) have been unsuccessful up to now, and continuous attempts are still in progress.