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A new ring-opening access to aeroplysinin-1, a secondary metabolite of *Verongia aerophoba*

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Abstract—An improved synthetic methodology of spiroisoxazolines by employing anodic oxidation of the corresponding phenol derivative has been established. An alternative efficient synthesis of aeroplysinin-1 **1** has been achieved by employing the ring-opening reaction of spiroisoxazolines **10b**, **10c** as a key step.

1. Introduction

In recent years, several bromophenylpyruvic acid derivatives of marine origin have been isolated as secondary metabolites.[1] These alkaloids containing bromine atoms possess spirocyclic isoxazoline structures such as aerothionin **2**, homoaerothionin **3**, aerophobin-1 **4**, and zamamistatin **5** or phenolic oxime-structures such as bastadin-6 **6** (Fig. 1).

Their diverse biological activities prompted many synthetic groups to achieve their total synthesis. Among such investigations, we accomplished the first total synthesis of **2**, **3**, and **4**:[2] the spiroisoxazoline structure **9**, which is a fundamental framework of these natural products, was constructed by the TTFA (thallium trifluoroacetate) oxidation of phenol **7**, followed by $Zn(BH_4)_2$ reduction of spirodienone **8** (Scheme 1). However, the methodology of the thallium oxidation incurs problems: (1) this reaction

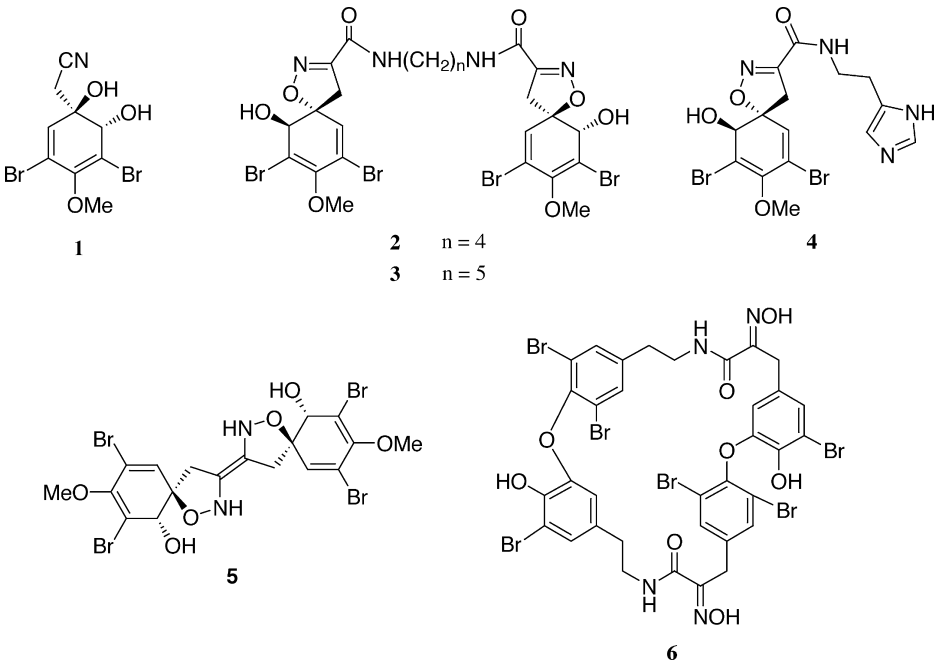

Figure 1. Structures of bromophenylpyruvic acid derivatives.

Keywords: anodic oxidation; ring-opening reaction; aeroplysinin; *Verongia aerophoba*.
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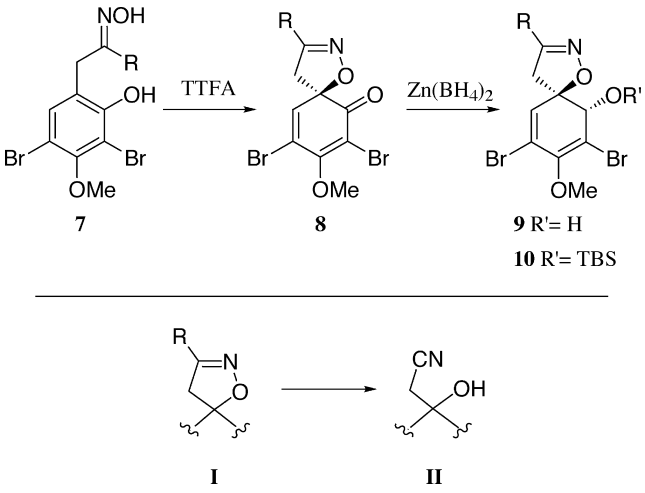


Scheme 1.

produced a considerable amount of by-products such as dimers and benzofurans, and (2) excess amount of the toxic thallium oxidant was required to acquire good yields. Therefore, an efficient methodology fitted to recent environmental concerns, should be developed for construction of the spiroisoxazoline moiety. Based on such background, we elaborated an improved synthetic methodology of spiroisoxazolines **8** by employing anodic oxidation of the corresponding phenol derivative **7**.[3] During manipulation of spiroisoxazoline derivative **10** toward such relevant natural products as zamamistatin **5**, we found a new ring-opening of the isoxazoline moiety **I** to the corresponding nitrile **II**. This reaction would be a useful method for synthesis of aeroplysinin-1 **1**. Aeroplysinin-1 **1**, isolated from the marine sponge *Verongia aerophoba*, also has a characteristic structure, 1,2-dihydroarene-1,2-diol containing a nitrile.[4] This bromophenylpyruvic acid derivative **1** has been of interest, because **1** has a significant antifouling bioactivity,[5] and was employed as a model molecule toward designed analogue molecules of an inhibitor of tyrosine-kinase.[6] Faulkner et al. reported a synthesis of **1** by phenolic oxidation using $Pb(OAc)_4$.[7]

We describe herein the construction of spiroisoxazolines **8** by employing anodic oxidation of the corresponding phenol derivative **7**, and a new efficient synthesis of **1**.

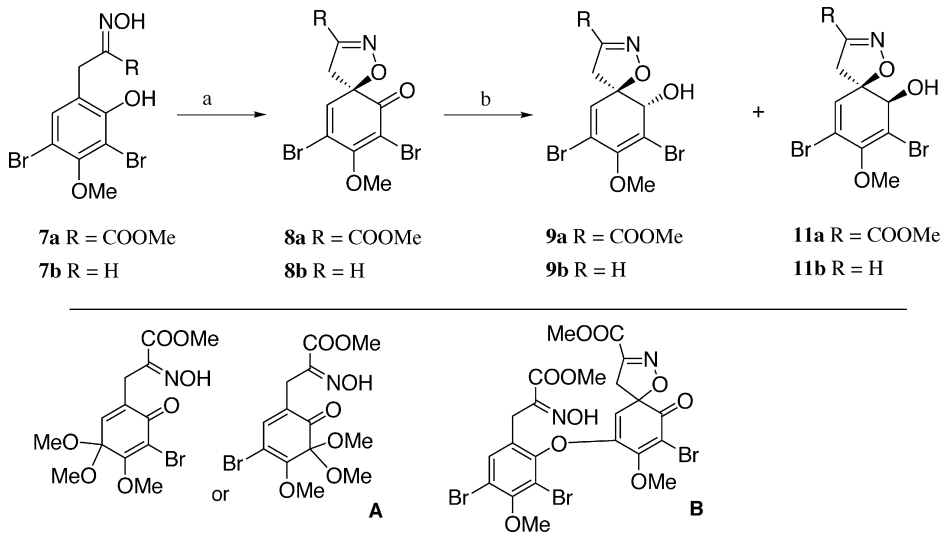
2. Results and discussion

2.1. Construction of spiroisoxazoline by electrochemical reaction

An improved synthetic methodology of spiroisoxazolines **8** was elaborated by employing anodic oxidation of the phenol derivative **7a**, which was used in our thallium oxidation.[2] Upon using our standard constant current electrolysis (CCE) conditions ($LiClO_4$ as a supporting salt in MeOH), desired **8a** was produced below 20% yield, along with a considerable amount of dimethyl acetals (**A**) or dimer (**B**). In addition to the by-products, unreacted **7a** was recovered under constant potential electrolysis (CPE) at 1.3 V vs SCE conditions employing the same additive and solvent as mentioned above. Acidic conditions, which are preferably used for two-electron oxidation, provided no successful results. Consequently, the optimized condition to give **8a** in 68% yield was attained when **7a** was oxidized under CPE conditions in the presence of nBu$_4$NClO$_4$ in MeCN.[3] Under the same conditions, aldehyde-oxime **7b** was oxidized to give **8b** in 28% yield.[8] By using an improved work-up procedure using $MgSO_4$ instead of usual extraction, $Zn(BH_4)_2$ reduction of **8a** afforded the corresponding *trans* and *cis*-alcohols **9a**, **11a** in 41 and 39% yields, which were two-times higher than the yield previously reported.[2] In the same way, reduction of **8b** provided *trans*-alcohol **9b** (28%) and *cis*-alcohol **11b** (4%) (Scheme 2).[8]

2.2. Ring-opening reaction to β-hydroxynitrile

A new ring-opening reaction of spiroisoxazoline **10b** under EtMgBr conditions produced β-hydroxynitrile **12** in 55% yield (Table 1, entry 1). To understand the scope and limitation of this reaction, spiroisoxazoline derivatives were synthesized: protection of these spiroisoxazolines **9a**, **9b**



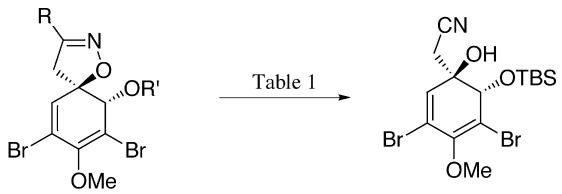
Scheme 2. *Reagents and conditions*: (a) CPE: +1600 mV vs SCE, 2.0 F/mol, MeCN, nBu$_4$NClO$_4$ (supporting salt), platinum wire (cathode)–glassy carbon beaker (anode), (**8a**, 68%; **8b**, 28%); (b) $Zn(BH_4)_2$, CH_2Cl_2 (**9a**, 41% and **11a**, 39%; **9b**, 28% and **11b**, 4%).

Table 1. The ring-opening reactions of spiroisoxazolines to β-hydroxynitrile

Entry	Substrate	Condition[a]	Product (yield, %)
1	**10b**	EtMgBr, THF, −78°C	**12** (55)
2	**10b**	Et_3N, MeOH, reflux	**12** (97)
3	**9b**	Et_3N, MeOH, reflux	Decomposition[b]
4	**10c**	DMF, 60°C	**12** (93)
5	**10a**	NaCl, DMSO, 100°C	Decomposition

[a] See Section 3.
[b] On monitoring the reaction by TLC (EtOAc), no moving spot was observed.

gave siloxy ethers **10a**, **10b**. Ester **10a** was converted into carboxylic acid **10c** by hydrolysis. The ring-opening reaction of spiroisoxazolines **9b**, **10b** possessing a hydrogen atom on the imine-carbon was attempted under Et_3N conditions.[9] Thus, the ring-opening reaction of **10b** yielded **12** in 97% yield (entry 2). The reactions might proceed through removal of the imine-proton by a base (Grignard reagent or Et_3N), followed by the N–O bond cleavage to deliver the nitrile **12**. However, under the same Et_3N conditions, the ring-opening of **9b** gave rise to decomposition (entry 3). On the other hand, the reaction of carboxyisoxazoline **10b** under thermal decarboxylation conditions, gave the β-hydroxynitrile **12** in high yield, through decarboxylation followed by heterolysis of the N–O bond (entry 4). In contrast to entry 4, the reaction of **10a** under NaCl/DMSO conditions gave no reaction at room temperature, while tar was obtained at 100°C (entry 5). In contrast to a carboxylic acid case **10c**, direct conversion of ester **10a** was unsuccessful, probably owing to thermal instability of the spiroisoxazoline moiety (Scheme 3).



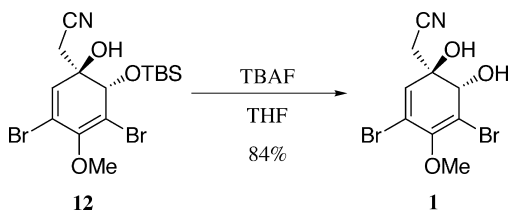
9b R= H, R'= H
10a R= COOMe, R'= TBS
10b R= H, R'= TBS
10c R= COOH, R'= TBS

12

Scheme 3.

2.3. A new efficient synthesis of aeroplysinin-1 1

The TBS group of **12** was removed with TBAF in THF to give aeroplysinin-1 **1** in 84% yield (Scheme 4). Synthetic aeloplysinin-1 **1** was identified with natural **1** by comparison of their ^1H and ^{13}C NMR spectra.



12 **1**

Scheme 4.

In conclusion, the anodic oxidation of phenol **7**, followed by $Zn(BH_4)_2$ reduction provided an improved synthesis of spiroisoxazoline **8**, an important synthetic intermediate of the marine natural product carrying phenylpyruvic acid oxime. An alternative access to **1** has been accomplished by the ring-opening of the corresponding isoxazoline ring as a key step.

3. Experimental

IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were obtained on JEOL JNM EX-270 and JEOL JNM GX-400 spectrometers in deuteration solvent using tetramethylsilane as an internal standard. High-resolution mass spectra were obtained on a Hitachi M-80 B GC–MS spectrometer operating at the ionization energy of 70 eV. Preparative and analytical TLC were carried out on silica gel plates (Kieselgel 60 F254, E. Merck AG, Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Kanto Chemical silica 60N (spherical, neutral, 63–210 μm) was used for column chromatography.

3.1. General procedure for anodic oxidation of phenolic oximes

A solution of a phenol derivative in a solvent containing an electrolyte was electrolyzed, using a glassy carbon beaker as an anode and a platinum wire as a cathode. The reaction mixture was partitioned between an organic layer and H_2O. The organic layer was dried over Na_2SO_4, and evaporated to give a crude product, which was purified by preparative TLC.

3.1.1. Methyl 7,9-dibromo-8-methoxy-6-oxo-4-oxa-3-azaspiro[4.5]deca-2,7,9-triene-2-carboxylate (8a). Electrolysis of **7a** (10 mg, 0.025 mmol) in MeCN (25 mL) containing nBu_4NClO_4 (1.5 g) [CPE: +1600 mV vs SCE] provided **8a** (6.7 mg, 68%).[10]

3.1.2. 7.9-Dibromo-8-methoxy-1-oxa-2-azaspiro[4.5]-deca-2,7,9-trien-6-one (8b). Electrolysis of **7b** (10 mg, 0.022 mmol) in MeCN (25 mL) containing nBu_4NClO_4 (1.5 g) [CPE: +1600 mV vs. SCE] provided **8b** (2.7 mg, 28%) as a colorless oil; IR (film) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10 (1H, dd, J=1.8, 17.6 Hz), 3.43 (1H, dd, J=1.8, 17.6 Hz), 4.16 (3H, s), 6.75 (1H, s), 7.18 (1H, t, J=1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 46.8, 62.0, 82.8, 107.1, 119.6, 137.4, 144.4, 163.2, 190.0. Found: m/z 334.8827. Calcd for $C_9H_7{}^{79}Br_2NO_3$: M, 334.8797.

3.1.3. Methyl (6*S* *,5*R* *)-7,9-dibromo-6-hydroxy-8-methoxy-4-oxa-3-azaspiro[4.5]deca-2,7,9-triene-2-carboxylate (9a). To a solution of **8a** (900 mg, 2.3 mmol) in CH_2Cl_2 (5 mL) was added $Zn(BH_4)_2$ (ethereal solution, 4 mL)[11] at room temperature under an argon atmosphere; the mixture was stirred for 10 min. After the addition of water (0.4 mL), the mixture was stirred for another 20 min, then $MgSO_4$ was added. The resulting mixture was filtered, and the filtrate was evaporated. The residue was purified by silica-gel column chromatography (hexane/EtOAc 5/1→3/1) to give **9a** (367 mg, 41%) and **11a** (354 mg, 39%).[10]

3.1.4. (6*S* *,5*R* *)-7,9-Dibromo-8-methoxy-1-oxa-2-azaspiro[4.5]deca-2,7,9-trien-6-ol (9b). To a solution of **8b** (320 mg, 0.96 mmol) in CH_2Cl_2 (5 mL) was added $Zn(BH_4)_2$ (ethereal solution, 2 mL)[11] at room temperature under an argon atmosphere. The reaction mixture was treated with essentially the same procedure as in the case of **8a** to give *trans*-alcohol **9b** (89 mg, 28%) and *cis*-alcohol **11b** (10 mg, 4%) as colorless oils.

Compound **9b**. IR (film) 3357, 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78 (1H, dd, J=1.6, 18.1 Hz), 3.73 (1H, dd, J=1.6, 18.1 Hz), 3.76 (3H, s), 4.39 (1H, s), 6.31 (1H, s), 7.17 (1H, t, J=1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 40.7, 60.1, 74.1, 88.5, 112.1, 120.5, 132.0, 146.4, 146.5. Found: m/z 336.8934. Calcd for $C_9H_9{}^{79}Br_2NO_3$: M, 336.8949.

Compound **11b**. IR (film) 3398, 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.07 (1H, dd, J=1.8, 18.3 Hz), 3.28 (1H, dd, J=1.8, 18.3 Hz), 3.76 (3H, s), 4.33 (1H, s) 6.34 (1H, s), 7.21 (1H, t, J=1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 44.9, 60.1, 74.9, 85.2, 112.4, 121.1, 131.2, 146.6, 148.2. Found: m/z 338.8967. Calcd for $C_9H_9{}^{79}Br^{81}BrNO_3$: M, 338.8930.

3.1.5. Methyl (10*S* *,5*R* *)-7,9-dibromo-8-methoxy-10-(1,1,2,2,-tetramethyl-1-silapropoxy)-4-oxa-3-azaspiro-[4.5]deca-2,6,8-triene-2-carboxylate (10a). To a solution of alcohol **9a** (350 mg, 0.88 mmol) in CH_2Cl_2 (5 mL) were added 2,6-lutidine (1.0 mL, 8.8 mmol), and TBSOTf (1.0 mL, 4.4 mmol) at 0°C under an argon atmosphere; the reaction mixture was stirred overnight. The reaction mixture was diluted with water, and extracted with $CHCl_3$ (3 times). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica-gel column chromatography (hexane/EtOAc 10/1) to give **10a** (585 mg, quant.) as a colorless oil: IR (film) 2954, 1728, 1597, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (3H, s), 0.16 (3H, s), 0.86 (9H, s), 2.85 (1H, d, J=18.1 Hz), 3.69 (3H, s), 3.85 (3H, s), 3.87 (1H, d, J=18.1 Hz), 4.77 (1H, s), 6.41 (1H, s); ^{13}C NMR ($CDCl_3$) δ −4.3, −3.9, 18.3, 25.9, 37.7, 52.9, 59.8, 73.4, 94.1, 115.3, 118.6, 133.1, 147.5, 151.3, 160.3. Found: m/z 430.0626. Calcd for $C_{17}H_{25}{}^{79}BrNO_5Si$: M−Br, 430.0684.

3.1.6. (10*S* *,5*R* *)-7,9-Dibromo-8-methoxy-10-(1,1,2,2-tetremethyl-1-silapropoxy)-1-oxa-2-azaspiro[4.5]deca-2,6,8-triene (10b). To a solution of alcohol **9b** (89 mg, 0.26 mmol) in CH_2Cl_2 (5 mL) was added 2,6-lutidine (0.24 mL, 2.0 mmol), and TBSOTf (0.24 mL, 1.0 mmol) at 0°C under an argon atmosphere. Essentially the same procedure as in the case of **9a** provided **10b** (84 mg, 90%) as a colorless oil: IR (film) 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (3H, s), 0.18 (3H, s), 0.90 (9H, s), 2.68 (1H, dd, J=1.5, 17.8 Hz), 3.68 (1H, dd, J=1.8, 17.8 Hz), 3.71 (3H, s), 4.72 (1H, s), 6.38 (1H, s), 7.09 (1H, dd, J=1.5, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ −4.3, −3.9, 18.3, 26.0, 40.0, 59.7, 73.6, 88.7, 115.1, 118.0, 134.4, 146.0, 147.5. Found: m/z 372.0625. Calcd for $C_{15}H_{23}{}^{79}BrNO_3Si$: M−Br, 372.0629.

3.1.7. (10*S* *,5*R* *)-7,9-Dibromo-8-methoxy-10-(1,1,2,2,-tetramethyl-1-silapropoxy)-4-oxa-3-azaspiro[4.5]deca-2,6,8-triene-2-carboxylic acid (10c). To a solution of **10a** (20 mg, 0.038 mmol) in MeOH (0.5 mL) was added 6N aqueous NaOH (3 drops) at room temperature: the reaction mixture was stirred for 30 min. The mixture was neutralized with 1N aqueous HCl, then extracted with EtOAc (3 times). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give **10c** (20 mg, quant.) as a colorless oil: IR (film) 3440, 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12 (3H, s), 0.19 (3H, s), 0.90 (9H, s), 2.89 (1H, d, J=18.5 Hz), 3.71 (3H, s), 3.90 (1H, d, J=18.5 Hz), 4.81 (1H, s), 6.44 (1H, s); ^{13}C NMR ($CDCl_3$) δ −4.3, −3.9, 18.3, 25.9, 37.1, 59.8, 73.4, 95.1, 115.2, 118.9, 132.7, 147.6, 151.2, 162.4. Found: m/z 496.9689. Calcd for $C_{16}H_{23}{}^{79}Br^{81}BrNO_5Si$: M, 496.9691.

3.1.8. 2-[(6*S* *,1*R* *)-3,5-Dibromo-1-hydroxy-4-methoxy-6-(1,1,2,2-tetramethyl-1-silapropoxy)cyclohexa-2,4-dienyl]ethanenitrile (12). *Method A*. To a solution of isoxazoline **10b** (16.6 mg, 0.037 mmol) in THF (1 mL) was added EtMgBr (0.1 mL, 1.0 M THF solution) at −78°C under an argon atmosphere; the reaction mixture was stirred for 4 h. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted 3 times with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by preparative TLC (hexane/EtOAc 2/1) to give **12** (8.4 mg, 55%) as a colorless oil.

Method B. A solution of isoxazoline **10b** (7.7 mg, 0.017 mmol) in Et_3N (0.3 mL)–MeOH (0.3 mL) was stirred at refluxing temperature for 1 h. The reaction mixture was diluted with water, and extracted 3 times with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by preparative TLC (hexane/EtOAc 2/1) to give **12** (7.4 mg, 97%) as a colorless oil.

Method C. A solution of carboxyisoxazoline **10c** (2.7 mg, 5.4 μmol) in DMF (0.5 mL) was heated at 60°C under an argon atmosphere for 2 h. The reaction mixture was cooled to room temperature, then evaporated to give **12** (2.3 mg, 93%) as a colorless oil: IR (film) 3433, 2260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.21 (3H, s), 0.23 (3H, s), 0.92 (9H, s), 2.75 (2H, s), 3.75 (3H, s), 4.45 (1H, s), 6.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −4.3, −3.7, 18.4, 25.2, 26.0, 59.8, 75.2, 78.0, 113.5, 116.6, 120.6, 132.3, 148.1. Found: m/z 372.0648. Calcd for $C_{15}H_{23}{}^{79}BrNO_3Si$: M−Br, 372.0629.

3.1.9. (±)-Aeroplysinin-1 (1). To a solution of **12** (5.0 mg, 0.011 mmol) in THF (0.3 mL) was added TBAF (0.1 mL, 1.0 M THF solution) at 0°C under an argon atmosphere; the reaction mixture was stirred for 1 h. The mixture was diluted with water, and extracted 3 times with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by preparative TLC (hexane/EtOAc 1/1) to give aeroplysinin-1 **1** (4.2 mg, 84%) as a colorless oil: IR (film) 3390, 2260 cm^{-1}; ^1H NMR (CD_3CN) δ 2.71 (2H, s), 3.65 (3H, s), 4.03 (1H, d, J= 7.8 Hz), 4.22 (1H, d, J=7.8 Hz), 4.29 (1H, s), 6.29 (1H, s); ^{13}C NMR (CD_3CN) δ 26.6, 60.4, 74.4, 78.3, 113.5, 118.2, 120.9, 133.3, 148.4. Found: m/z 336.8938. Calcd for $C_9H_9{}^{79}Br_2NO_3$: M, 336.8949.

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