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Asymmetric synthesis of aerothionin, a marine dimeric spiroisoxazoline natural product, employing optically active spiroisoxazoline derivative

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Abstract—Successful first synthesis of optically pure (+)- and (−)-aerothionins (**1**) from the racemic spiroisoxazoline derivative **8** has been accomplished. The absolute configuration of natural (+)-**1** was determined by comparison of (+)- and (−)-**8** with related derivatives.

Up to now, several spiroisoxazoline natural products have been isolated from marine origins (Fig. 1).[1] Among them, dimeric natural products carrying two spiroisoxazoline units, such as aerothionin (**1**),[2] homoaerothionin (**2**), caissarin B (**3**),[3] fisturalin 3 (**4**),[4] calafianin (**5**),[5] and their congeners,[6] were reported to show significant bioactivity, mainly antimicrobial and cytotoxic activities. In addition, antihistamine activity of archerine (**6**)[7] and K, Na-ATPase inhibitory activity of ianthesin C (**7**)[8] were reported.

Synthetic studies on these natural products have been carried out by several groups.[9] The first total synthesis of aerothionin (**1**), produced by the amidation of (±)-**8** with the corresponding diamine, was reported by our group,[10] although diastereomeric separation of natural **1** and its diastereoisomer was unsuccessful. Asymmetric synthesis of the spiroisoxazoline unit **8** (70–80% ee) was reported by Hoshino et al.,[11] although separation of diastereomers derived from **8** carrying insufficient optical purity was unsuccessful. From the viewpoint of biological investigation, acquisition of completely pure dimeric spiroisoxazoline compounds without contamination of their diastereoisomer is essential for evaluation of enantiomerical difference. We describe herein the synthesis of optically active spiroisoxazoline **8** and its synthetic access to optically pure (+)- and (−)-**1**.

As reported previously, synthesis of the racemic spiroisoxazoline compound (±)-**8** was efficiently achieved by electrochemical oxidation of **9**, followed by $Zn(BH_4)_2$ reduction of **10** (Scheme 1).[12]

The coupling reaction of (±)-**8** with several chiral reagents was attempted to produce a chromatographically separable diastereomeric mixture. After repeated inspection, it was observed that camphanic acid esters **11** and **12**, produced by esterification with (−)-camphanic chloride, were easily separable by silica gel chromatography (Scheme 2).[13]

The optically active spiroisoxazoline compounds (+)- and (−)-**8** were successfully obtained by solvolysis of **11** and **12** under basic conditions (Scheme 3). Their optical purity was confirmed by chiral HPLC analysis (Daicel CHIRALPAK AD-H: 100% EtOH) of (+)- and (−)-**10**, which were produced by the Dess–Martin oxidation of (+)- and (−)-**8** (Scheme 4). No observation of the corresponding enantiomeric isomers on the HPLC chart indicated that both enantiomers possess complete optical purity.[14] To determine their absolute stereochemisty, (+)- and (−)-**8** were submitted to acid hydrolysis, followed by cyclization to yield (+)- and (−)-**13**, optical rotations {$[\alpha]_D^{23}$ +322.8 (*c* 1.0, $CHCl_3$)

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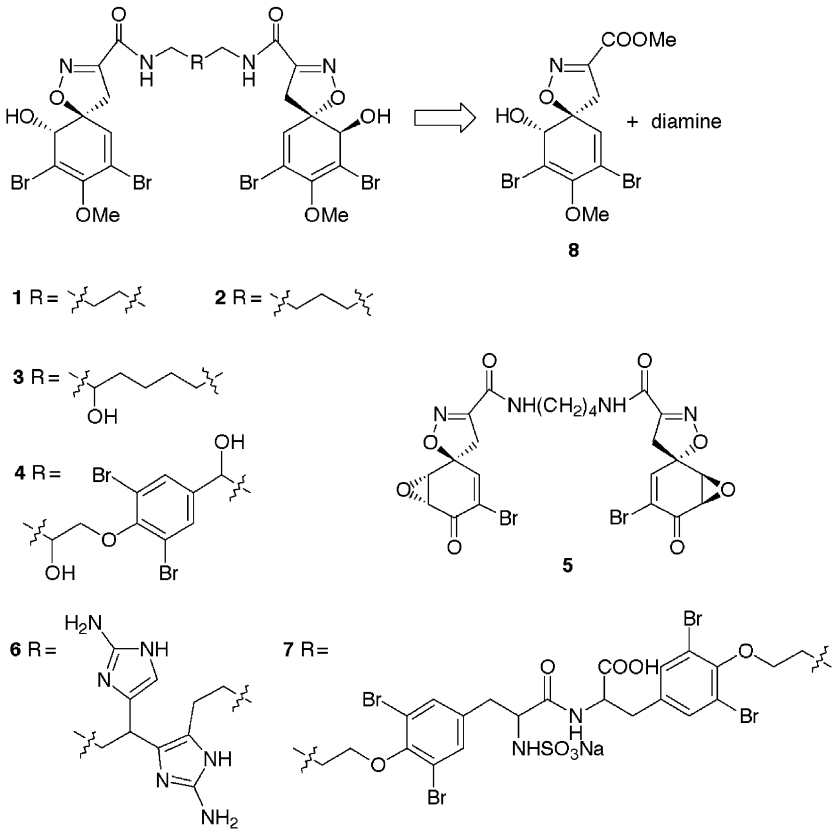
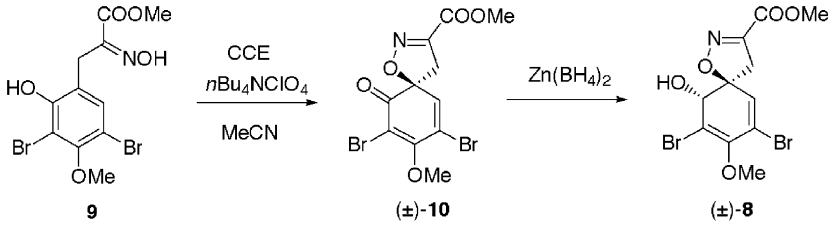
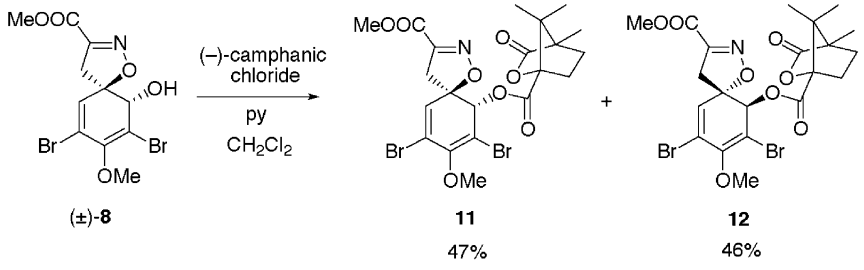


Figure 1. Structures of dimeric spiroisoxazoline natural products.



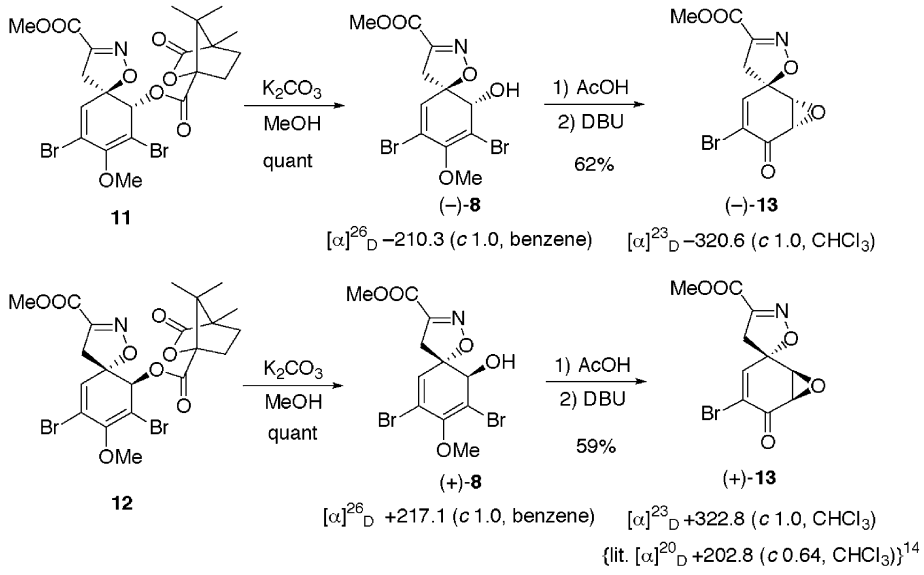
Scheme 1. Synthesis of spiroisoxazoline (±)-**8**.



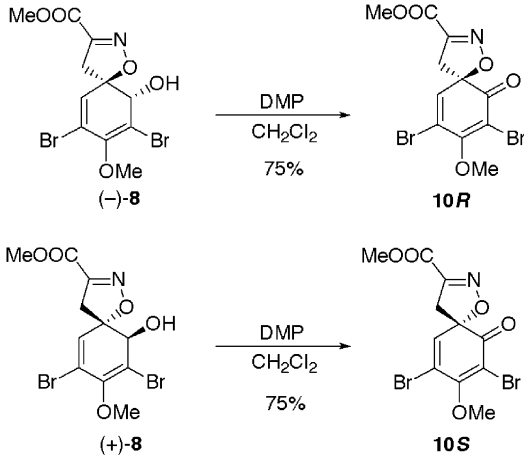
Scheme 2. Esterification of (±)-**8** by (−)-camphanic chloride.

and $[\alpha]_D^{23}$ −320.6 (*c* 1.0, $CHCl_3$)} of which were compared with the reported data {$[\alpha]_D^{20}$ +202.8 (*c* 0.64, $CHCl_3$)}[15] (Scheme 3).[16,17] Although the reported absolute value of optical rotation was different from our data, the plus sign of the reported **13** indicated that the absolute configuration of (+)- and (−)-**13** might be as depicted in Scheme 3.

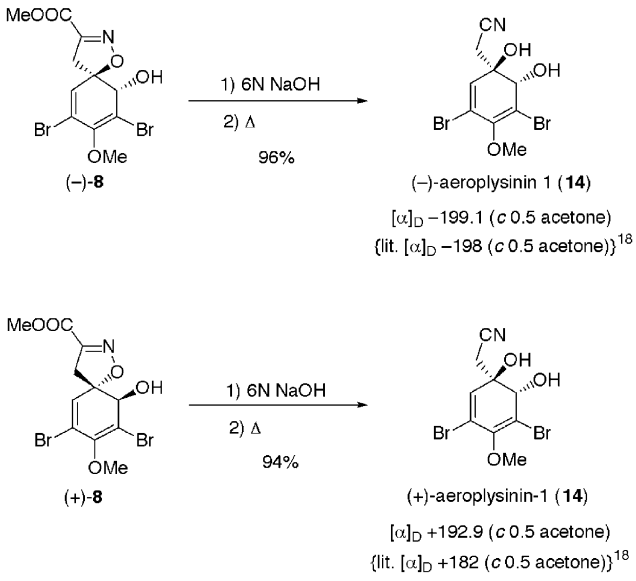
To obtain further structure proof, a synthesis of aeroplysinin-1 (**14**), the absolute configuration of which was



Scheme 3. Synthesis of optically active spiroisoxazoline **8**.



Scheme 4. Derivation of **8**–**10** for optically purity analysis.

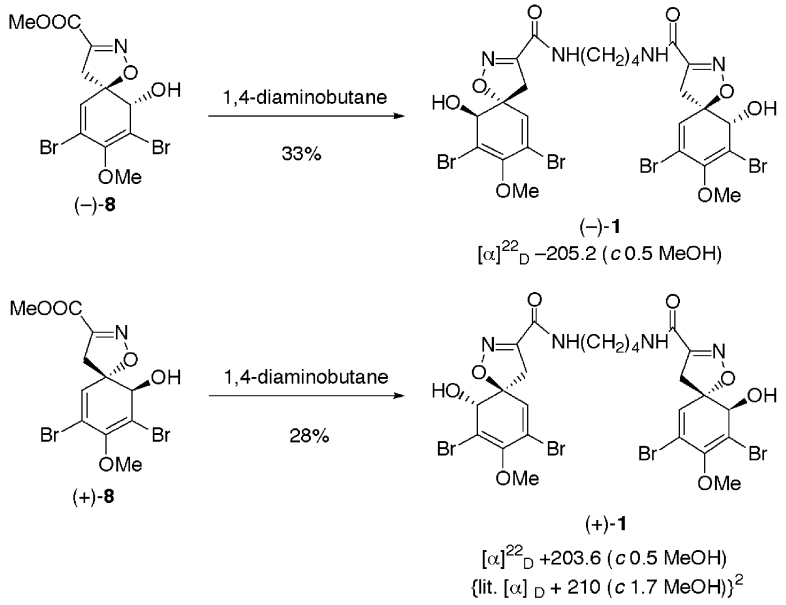


Scheme 5. Synthesis of optically active aeroplysinin-1 (**14**).

determined by X-ray crystallographic analysis, was performed by using (+)- and (−)-**8**, according to the same procedure as described previously (Scheme 5).[12b] Consequently, their optical rotations {(−)-**14**: $[\alpha]_D^{23}$ −199.1 (*c* 0.5 acetone); (+)-**14**: $[\alpha]_D^{23}$ +192.9 (*c* 0.5 acetone)} were identical with the reported data {(−)-**14**: $[\alpha]_D$ −198 (*c* 0.5 acetone); (+)-**14**: $[\alpha]_D$ +182 (*c* 0.5 acetone)}.[18]

Finally, optically pure (+)- and (−)-**1** were successfully synthesized by condensation of (+)- and (−)-**8** with 1,4-diaminobutane[10] (Scheme 6). The ^{1}H NMR data of the synthetic **1** was superimposable to the reported data.[2] Previously, Rinehart reported the absolute configuration of natural **1** {$[\alpha]_D$ +210 (*c* 1.7, MeOH)}[2c] by means of an X-ray crystallographic analysis, together with its circular dichroism.[19] Our synthetic samples exhibited the optical rotations {$[\alpha]_D^{22}$ −205.2 (*c* 0.5, MeOH) and $[\alpha]_D^{22}$ +203.8 (*c* 0.5, MeOH)} and the absolute configuration of **1** should be as described in Scheme 6, which definitely supported the report by Rinehart.

In conclusion, the optically active spiroisoxazoline units (+)- and (−)-**8** were produced, and the synthesis of (+)- and (−)-**1** without contamination of its diastereomer was unambiguously achieved. By this investigation, the absolute configuration of **1** was synthetically determined. This investigation will open up a synthetic access to other dimeric spiroisoxazoline natural products, and their biological profiles.



Scheme 6. Synthesis of optically active aerothionin (**1**).

Acknowledgments

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13. Compound **11**: IR (film) 1795, 1749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, s), 1.09 (3H, s), 1.11 (3H, s), 1.71 (1H, m), 1.93 (1H, m), 2.11 (1H, m), 2.38 (1H, m), 3.03 (1H, d, $J = 18.0$ Hz), 3.67 (1H, d, $J = 18.0$ Hz), 3.78 (3H, s), 3.91 (3H, s), 6.12 (1H, s), 6.42 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.7, 16.6, 16.8, 29.0, 31.3, 39.2, 53.2, 54.5, 54.8, 60.2, 60.3, 74.3, 90.9, 107.2, 120.7, 130.8, 149.8, 151.5, 159.8, 166.3, 177.5. HRMS found *m/z* 574.9778, calcd for $C_{21}H_{23}Br_2NO_8$: M^+, 574.9790. Compound **12**: IR (film) 1792, 1747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.05 (3H, s), 1.12 (3H, s), 1.68 (1H, m), 1.93 (1H, m), 2.06 (1H, m), 2.45 (1H, m), 3.06 (1H, d, $J = 18.5$ Hz), 3.60 (1H, d, $J = 18.5$ Hz), 3.78 (3H, s), 3.91 (3H, s), 6.07 (1H, s), 6.40 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.7, 16.6, 16.9, 29.0, 31.0, 39.5, 53.1, 54.6, 55.0, 60.2, 60.3, 74.7, 90.8, 106.8, 121.2, 130.6, 150.1, 151.6, 160.0, 166.5, 177.8. HRMS found *m/z* 574.9780, calcd for $C_{21}H_{23}Br_2NO_8$: M^+, 574.9790.
14. Optical purity analysis of **10** by chiral HPLC showed large difference in the retention times (**10*R***: 18 min, **10*S***: 26 min), although the enantiomers of **8** were not separated.

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17. (+)- and (−)-Calafianins (**5**) {$[\alpha]_D^{22}$ −253.2 (*c* 0.2, acetone) and $[\alpha]_D^{22}$ +249.4 (*c* 0.2, acetone)} were synthesized by utilizing (+)- and (−)-**13** as previously reported.[16] Unfortunately, clear optical rotation of the natural products was not available, but only a positive sign was reported.[5] In addition, comparison with the wave length of the CD spectra reported indicated the absolute structure of calafianin (**5**) might be as depicted in Figure 1.
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19. Rinehart mentioned that data of the X-ray crystallographic analysis was still ambiguous.[2c]