Isolation, Synthesis, and Radical-Scavenging Activity of Rhodomelin A, a Ureidobromophenol from the Marine Red Alga Rhodomela confervoides

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Supporting Information

ABSTRACT: A novel ureidobromophenol, rhodomelin A (1), was characterized from Rhodomela confervoides. Its structure was elucidated by spectroscopic analysis. Both enantiomers of 1 were synthesized using a convergent strategy starting from D/L-pyroglutamic acids, respectively, allowing assignment of the R-configuration for the naturally occurring isomer by chiral HPLC analysis. Rhodomelin A represents the first example of a naturally occurring ureidopyrrolidone alkaloid incorporating a γ-aminobutyric acid unit. The scavenging activity of 1 toward DPPH (1,1-diphenyl-2-picrylhydrazyl) and ABTS (2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate)) radicals was assayed.

The marine red algal species of the genus Rhodomela (family Rhodomelaceae, order Ceramiales) have previously reported several bromophenols from ureidobromophenol, namely, rhodomelin A (1, Figure 1), which represents the first example of a ureidopyrrolidone alkaloid incorporating a γ-aminobutyric acid and 2,3-dibromo-4,5-dihydroxybenzyl units. Compound 1 has a chiral center at C-1 which is far from the 2,3-dibromo-4,5-dihydroxybenzyl chromophore, thus precluding assignment of its absolute configuration with confidence by ECD methods. Attempts to obtain quality crystals of 1 for X-ray crystallographic analysis were not successful.

We report herein the isolation and structure elucidation of 1, the synthesis of both possible enantiomers, and subsequent chiral HPLC analysis to determine the absolute configuration of 1. The ability to scavenge DPPH and ABTS radicals was assayed as well.

Figure 1. Chemical structure of rhodomelin A (1).

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aliphatic and one aromatic methine, six aliphatic methylenes, and eight nonprotonated (five aromatic and three carbonyl) carbon atoms (Table 1). COSY data disclosed two spin systems corresponding to −NHCH(NH)CH₂− and −CH₂CH₂CH₂− substructures (Figure 2). Through iterative analyses of the battery of 1D and 2D NMR spectroscopic data, compound 1 was deduced to have four substructures including a 2,3-dibromo-4,5-dihydroxybenzyl unit, 2 a substituted butanoic acid moiety, a ureido group,1b and a pyrrolidone residue. These fragments accounted for all components of the molecular formula and unsaturations. The linkage of one nitrogen atom (N-1) in the ureido unit to C-4 of the butanoic acid moiety and to C-7′ of the 2,3-dibromo-4,5-dihydroxybenzyl unit was supported by HMBC correlations from H-4 to C-5 and from H₂-7′ to C-2′, C-6′, and C-5, respectively, whereas the linkage of another nitrogen atom in the ureido unit (N-2) to the pyrrolidone residue was evidenced by a COSY interaction from NH-2 to H-1″ and by an HMBC correlation from NH-2 to C-2″ (Figure 2). These key correlations enabled assignment of the planar structure of 1 as N-(2,3-dibromo-4,5-dihydroxybenzyl)-N′-(5-oxopyrrolidin-2-yl)-γ-ureidobutyric acid, which was named rhodomelin A. A hypothetical biosynthetic pathway for 1 is proposed in Scheme S1 (Supporting Information).

Compound 1 has one chiral center at C-1″ and assignment of its absolute configuration was challenging. This chiral center is far from the 2,3-dibromo-4,5-dihydroxybenzyl chromophore and thus ECD calculation was not useful in determining its absolute configuration. Attempts to get quality crystals for X-ray analysis were not successful. We therefore concentrated our efforts toward a total synthesis of both enantiomers of 1.

Rhodomelin A (1) contains an acid/base-sensitive 5-ureidopyrrolidone unit and a dibromo-substituted phenolic moiety. Retrosynthetically speaking, compound 1 could be disconnected to amino ester 2 and pyroglutamic isocyanate 3 through a nucleophilic 1,2-addition. The former (2) could further be derived from lanosolaldehyde (4), which could be synthesized from vanillin in two steps, while the latter (3) could be generated through Curtius rearrangement4 from commercially available chiral pyroglutamic acid in a one-pot transformation. This convergent strategy would allow both enantiomers of 1 be accessed through one unified route starting with D/L-pyroglutamic acids (Scheme 1).

Our synthesis started with regioselective protection of the known compound lanosolaldehyde 4, followed by a reductive amination with amino ester salt 6 in 72% yield. The multisubstituted phenolic fragment 2 was obtained readily upon quantitative removal of Boc protecting group (Scheme 2).

The second required fragment, L-pyroglutamic isocyanate (3), was formed diastereoselectively in situ through a modified one-pot Curtius rearrangement and was then coupled with fragment 2 to provide a protected version of the conserved chiral fragment 3 in good yield (75%). The Bn- and Cbz-protecting groups were then removed in one step under

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**Table 1. ¹H and ¹³C NMR Data for Rhodomelin A (1)\(^a\)**

| no. | δ\(_\text{H}\) mult (J, Hz) | δ\(_\text{C}\) |
|-----|----------------|---------|
| 1   | 174.5, C        |         |
| 2   | 2.20, t (7.3)   | 30.8, CH₂ |
| 3   | 1.68, m         | 23.2, CH₂ |
| 4   | 3.13, m         | 45.3, CH₂ |
| 5   |                | 156.5, C  |
| 1′  |                | 129.2, C  |
| 2′  |                | 113.5, C  |
| 3′  |                | 112.8, C  |
| 4′  |                | 143.5, C  |
| 5′  |                | 145.4, C  |
| 6′  | 6.63, s         | 113.3, CH |
| 7′  | 4.39, d (16.7)  | 50.4, CH₂ |
|     | 4.32, d (16.7)  |         |
| 1″  | 5.37, m         | 62.0, CH  |
| 2″  | 2.29, m         | 27.5, CH₂ |
|     | 1.84, m         |         |
| 3″  | 2.30, m         | 29.1, CH₂ |
|     | 2.05, m         |         |
| NH-2| 6.98, d (8.1)   |         |
| NH-3| 7.88, br s      |         |

\(^a\)Recorded in DMSO-\(d_6\) at 500 MHz for \(^1\)H and 125 MHz for \(^13\)C.

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**Figure 2.** Key HMBC (red arrows) and COSY (blue bold lines) correlations for rhodomelin A (1).
hydrogenation, and an additional LiOH-mediated hydrolysis yielded (R)-configured rhodomelin A (Scheme 3).

Scheme 3. Synthesis of (R)-Rhodomelin A

The same synthetic sequence was followed starting from d-pyroglutamic acid and yielded (S)-rhodomelin A (Scheme 4).

Scheme 4. Synthesis of (S)-Rhodomelin A

The NMR data, optical rotations, and chiral HPLC profiles of the natural rhodomelin A (1) were compared with those of synthesized (R)- and (S)-1. As shown in Table S1 (Supporting Information), the 1H and 13C NMR data for natural 1 were essentially identical to those of synthesized (R)-1 and (S)-1. As for specific optical rotation, the value of rhodomelin A ([α]25D +18.5 (c 0.09, MeOH)) was in good agreement with that of the synthesized (R)-1 ([α]25D +21.1 (c 0.19, MeOH)) and opposite to that of the synthesized (S)-1 ([α]25D −17.9 (c 0.28, MeOH)), indicating that the absolute configuration at C-1α of natural rhodomelin A (R) was R.

The results from chiral HPLC analysis showed that natural 1 had the same retention time and identical UV spectrum as that of synthesized (R)-1. As expected, natural 1 and synthesized (S)-1 had the same UV profile, but different retention times (Figure 3), further confirming that the absolute configuration at C-1α of natural 1 is R.

The radical-scavenging activities of natural 1 were evaluated using DPPH+ and TEAC+ assays following previously reported methods. Compound 1 displayed significant scavenging activity against DPPH with IC50 value of 3.82 μM, which is 21.5-fold more potent than that of the positive control BHT (IC50 = 82.13 μM). In addition, this compound also exhibited moderate scavenging activity against ABTS radicals with a TEAC value of 4.37 mM (Table 2). The synthetic (R)- and (S)-1 were also tested for the activity against DPPH radicals, with the (R)-isomer having stronger activity (IC50 = 4.60 μM) than that of the (S)-isomer (IC50 = 8.90 μM).

In conclusion, a novel ureidobromophenol (rhodomelin A, 1) was isolated and identified from the marine red alga Rhodomela confervoides. Its planar structure was determined by analysis of spectroscopic data, and the absolute configuration was unambiguously assigned by total synthesis and chiral HPLC analysis. Rhodomelin A (1) represents the first example of a naturally occurring ureidopyrrolidone alkaloid incorporating a γ-aminoxybutyric unit and showed potent scavenging activity against DPPH and ABTS radicals.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orlett.7b03716.

 Experimental details and spectra for natural and synthesized 1 (PDF)

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Notes
The authors declare no competing financial interest.

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