Total Synthesis of Sarcophytonolide H and Isosarcophytonolide D: Structural Revision of Isosarcophytonolide D and Structure–Antifouling Activity Relationship of Sarcophytonolide H

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Supporting Information Placeholder

ABSTRACT: The first total syntheses of sarcophytonolide H and the originally proposed and correct structures of isosarcophytonolide D have been achieved via transannular ring-closing metathesis (RCM). These total syntheses culminated in the stereostructural confirmation of sarcophytonolide H and the reassignment of isosarcophytonolide D, respectively. The antifouling activity of the synthetic sarcophytonolide H and its analogues was also evaluated.

Corals have been recognized as a rich source of secondary metabolites with a variety of skeletons and biological activities.1 Cembranolide diterpenes,2 isolated from octocorals and soft corals, display a diverse range of biological activities such as antifouling,3 antifungal,4 antiviral,5 cytotoxic,6 and ichthyotoxic activities.7 Ecologically, it has been suggested that these natural products play significant roles in the survival of corals as defensive, competitive, and reproductive substances.8a,8b Sarcophytonolides are cembranolides isolated from the soft corals of genus Sarcophyton by Guo’s research group since 2005.9 As depicted in Figure 1, they have a 14-membered macrocycle and a butenolide unit as common structures. We previously established the absolute configuration of (+)-sarcophytonolide C (1) by the total synthesis of its two possible stereoisomers at the C8 position.10,11 The absolute stereochemistry of sarcophytonolide H (3), which possesses a β-oriented acetoxy group at the C14 position, was determined by analysis of its 2D NMR spectra and the modified Mosher method.12 The relative configuration of sarcophytonolide D (2) bearing an α-positioned acetoxy moiety (C14) was elucidated by NOE observations.13 The relative stereochemistries at the C1, C2, and C14 positions of sarcophytonolides I (4), J (5), and isosarcophytonolide D (6) were determined by the similarity of their NMR data to those of sarcophytonolide D (2).9c,9d Qian and co-workers have reported that sarcophytonolides H (3) and J (5) show antifouling activity against the larval settlement of barnacle Balanus (Amphibalanus) amphitrite with EC50 values of 5.98 μg/mL and 7.50 μg/mL, respectively.12 Herein, we describe the first total synthesis of sarcophytonolide H (3) and the originally proposed and correct structures of isosarcophytonolide D, which resulted in the stereostructural revision of isosarcophytonolide D. Furthermore, we also report the structure–antifouling activity relationship of 3.

Figure 1. Structures of sarcophytonolides 1–6.

Retrosynthetic analysis of sarcophytonolide H (3) and the proposed structure 6 of isosarcophytonolide D, wherein the structural differences are the oxidation degree at the C6 position and the stereochemistry at the C14 position, is depicted in Scheme 1. The common structures, namely, the 14-membered macrocycle and butenolide moiety, could potentially be constructed by macrolactonization13 and subsequent transannular ring-closing metathesis (RCM)4 of hydroxycarboxylic acids 7 and 8, respectively. Macrolactonization precursors 7 and 8 could possibly be prepared by the addition reaction of 2-alkoxycarbonyl allylic
metal 9 to aldehydes 10 and 11. The aldehydes 10 and 11 were broken down into allylic bromide 12 and aldehyde 13.

Scheme 1. Retrosynthetic Analysis of Sarcophytonolide H (3) and the Proposed Structure 6 of Isosarcophytonolide D

Our synthesis of the C14-stereoisomers 18 and 19 is described in Scheme 2. Selective acetylation of diol 1410 and subsequent protection of the remaining secondary hydroxy group with TBSOTf afforded the corresponding silyl ether. Reductive removal of the acetyl group with DIBAL-H followed by oxidation of alcohol 15 with TEMPO/Phl(OAc)315 provided aldehyde 16. Treatment of 16 with allylic bromide 1716 (1.2 equiv) in the presence of SmI217,18 produced the desired α-adducts 18 and 19 in 53% and 40% yields, respectively. Formation of the corresponding γ-adduct was not observed at all in this reaction.19 The C11/C12 alkene geometries of 18 and 19 were confirmed by the observed NOEs of H-11/H-13 (3% in 18 and 2% in 19). The resulting stereochemistry at the C14 position of 18 was determined by the modified Mosher method.20,21

Scheme 2. Synthesis of Alcohols 18 and 19

We next examined the transformation of 18 to sarcophytonolide H (3) possessing the 14S configuration. Thus, protection of the secondary alcohol 18 as the MOM ether followed by selective removal of the primary TBS group gave alcohol 20 (Scheme 3). TEMPO oxidation15 of 20 and subsequent Wittig reaction afforded alkene 21. The pivalate 21 was deprotected with DIBAL-H to yield alcohol 22, which was oxidized to the corresponding aldehyde. The asymmetric alkoxy carbonylation of the resulting aldehyde was carried out by using the chiral allylic boronate 23 according to Chataigner’s protocol22 to provide the desired product 24 in 88% yield over two steps with a 13:1 diastereoselectivity23. Protection of the resulting hydroxy moiety in 24 as the PMB ether, removal of the TBS protective group, and hydrolysis of the ester portion produced hydroxy carboxylic acid 25. Macrolactonization of 25 was performed with 2-methyl-6-nitrobenzoic anhydride (MNBA)/DMAP24 to give the 15-membered lactone 26. The tetractene 26 was treated with second-generation Hoveyda-Grubbs catalyst (27)25 to afford the desired product, whose C7/C8 and C11/C12 alkene portions were inert to the reaction conditions.26 The obtained butenolide underwent removal of the MOM group with HCl in i-ProOH27 to provide alcohol 28 in 52% yield over two steps. The resulting hydroxy moiety in 28 was acetylated and the PMB ether was deprotected with DDQ to produce sarcophytonolide H (3). The synthetic sarcophytonolide H (3) displayed 1H and 13C NMR data21 and specific rotation28 which were in full agreement with those of the natural product.9b,29 Thus, the absolute configuration of sarcophytonolide H was unambiguously confirmed.

Scheme 3. Synthesis of Sarcophytonolide H (3)
We next tried to synthesize the proposed structure 6 of isosarcophytonolide D with the 14R configuration. Thus, the alcohol 19 was transformed to 6 over 15 steps by the similar sequence to that used for sarcophytonolide H (3) (Scheme 4).21

**Scheme 4. Synthesis of the Proposed Structure 6 of Isosarcophytonolide D**

With the proposed structure 6 of isosarcophytonolide D in hand, we next carefully analyzed the 1H–1H COSY, HMQC, and HMBC spectra of 6 and compared the NMR data between the synthetic product 6 and the natural product. The 1H and 13C NMR data of the synthesized 6 were clearly different from the reported data of natural isosarcophytonolide D, 9d respectively.21 Especially, as shown in Table 1, the chemical shift deviations were found to be critical around the C14 position in both 1H and 13C NMR spectra. Therefore, we predicted the correct structure of isosarcophytonolide D to be that drawn as 37, which is the C14-epimer of 6 (Scheme 5).

**Scheme 5. Synthesis of the Predicted Structure 37 of Isosarcophytonolide D**

We next evaluated the antifouling activity32 and toxicity of the synthetic sarcophytonolide H (3) and its analogues 38, 39,31 25, and 22 against the cypris larvae of barnacle *Balanus (Amphibalanus) amphitrite*. Our results described in Table 2 suggest that the tetraene 39, which was the most antifouling active and non-toxic, is a good candidate for further pursuing the environmentally-benign antifouling compound.21

**Table 1. Chemical Shift Deviations (δN–S) between Natural Isosarcophytonolide D and the Synthetic 6 in the 1H and 13C NMR**

<table>
<thead>
<tr>
<th>position</th>
<th>1H NMR</th>
<th>13C NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–0.24</td>
<td>+3.3</td>
</tr>
<tr>
<td>2</td>
<td>–0.12</td>
<td>+0.9</td>
</tr>
<tr>
<td>13</td>
<td>–0.24</td>
<td>–1.6</td>
</tr>
<tr>
<td>14</td>
<td>–0.37</td>
<td>+4.0</td>
</tr>
<tr>
<td>15</td>
<td>–0.10</td>
<td>–2.6</td>
</tr>
</tbody>
</table>

αδN and δS are chemical shifts of the natural product and the synthetic product. Chemical shifts are recorded in ppm with reference to the internal residual solvent signal (CDCl3, 7.26 ppm in 1H NMR and 77.0 ppm in 13C NMR).

**Table 2. Antifouling Activity (EC50) and Toxicity (LC50) of the Synthetic Sarcophytonolide H (3) and Its Analogues**

<table>
<thead>
<tr>
<th>compound</th>
<th>EC50</th>
<th>LC50</th>
</tr>
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<tbody>
<tr>
<td>3</td>
<td>3.36</td>
<td>&gt;50</td>
</tr>
<tr>
<td>38</td>
<td>3.08</td>
<td>&gt;50</td>
</tr>
<tr>
<td>39</td>
<td>1.61</td>
<td>&gt;50</td>
</tr>
<tr>
<td>25</td>
<td>3.27</td>
<td>19.4</td>
</tr>
<tr>
<td>22</td>
<td>&gt;50</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

*Against the cypris larvae of barnacle *Balanus (Amphibalanus) amphitrite*. EC50 and LC50 values in μg/mL.

In conclusion, we have accomplished the first total synthesis of sarcophytonolide H (3) and the originally proposed and correct structures of isosarcophytonolide D, 6 and 37, by using...
transannular RCM as a key step. The structural revision of isosarcophytonolides D suggests that the C14 stereochiristries of sarcophytonolides D (2), I (4), and J (5) also need to be reconsidered. We also evaluated the antifouling activity and the toxicity of the synthetic sarcophytonolide H and its analogues, which denotes that the tetraene 39 is a good candidate for the creation of the antifouling agent without toxicity. Further synthetic and biological study of sarcophytonolides is currently underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data of all new compounds, evaluation procedures of antifouling activity and toxicity, and NMR spectra of all new compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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