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SHORT COMMUNICATION

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A Biomimetic Approach to the Synthesis of the Core Structure of the Marine Sponge Terpene Halichonadin G

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Dedicated to Professor Sir Jack Baldwin

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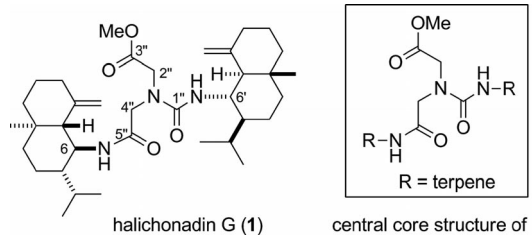
A pathway for the biosynthesis of halichonadin G involving the unique action of ugiase and isocyanide oxidase is proposed. This hypothesis was tested in a biomimetic approach to the synthesis of the core structural unit of this marine sponge terpene, which relies on a key Ugi coupling reaction and an isocyanide-to-isocyanate oxidative transformation. The results of this effort demonstrate that the biomimetic strategy can be employed to construct the core structure of halichonadin G in an efficient manner.

Introduction

Over the past several decades, we have focused our research efforts on the synthesis of terpene isocyanides isolated from marine organisms.[1] During this research endeavor, we proposed a strategy for the synthesis of novel, marine organism derived terpenes, such as boneratamides and exigurin,[2] which relies on the use of in vivo Ugi coupling reactions[3] of terpene isocyanides. The boneratamides were isolated from the marine sponge *Axinyssa aplysinoides*, collected in Indonesia, and characterized by Andersen and co-workers in 2004.[4] Exigurin is a terpene isolated from the marine sponge *Geodia exigna* collected off Oshima island, Kagoshima Prefecture, Japan, and its structure was elucidated by the Ikegami group in 2003.[5]

In 2010, Rodriguez and Aviles isolated the diterpenoid β-lactam monamphilectine A from a Puerto Rican marine sponge *Hymeniacidon* sp. and carried out a semisynthesis of this substance, which employed a multicomponent Ugi reaction starting with (–)-8,15-dicyano-11(20)-amphilectene.[6] In 2012, halichonadins K and L were isolated and characterized by Kobayashi and co-workers.[7] This group also suggested that the routes for biosynthesis of these halichonadins involve a reaction of an iminium cation with a terpene isocyanide.[7] Quickly following Kobayashi's proposal, Poupon described a biomimetic, three-component assembly to construct the central core structure of halichonadins K and L.[8] The intensity of these recent reports prompted us to describe the results of our recent investigations aimed at exploring a biomimetic synthesis of halichonadin G.

Halichonadin G is a marine natural product isolated in 2011 by Kobayashi and his co-workers from the sponge *Halichondria* sp. collected at Unten Port on Okinawa Island.[9] The structure of halichonadin G (**1**), an optically active amorphous solid, was elucidated by extensive spectroscopic analyses as shown in Figure 1.[9] The central core structure of **1** is iminodiacetic acid (IDA) methyl ester, to which two common eudesmane sesquiterpenoid units are appended through amide and urea functionalities.



halichonadin G (**1**) central core structure of **1**

Figure 1. Structures of halichonadin G and its central core structure.

Results and Discussion

In considering the biosynthetic origin of halichonadin G (**1**), it is important to recognize that in 2005 Kobayashi described the isolation of the terpene isocyanide halichonadin C (**2**) from the same marine sponge found at Unten Port

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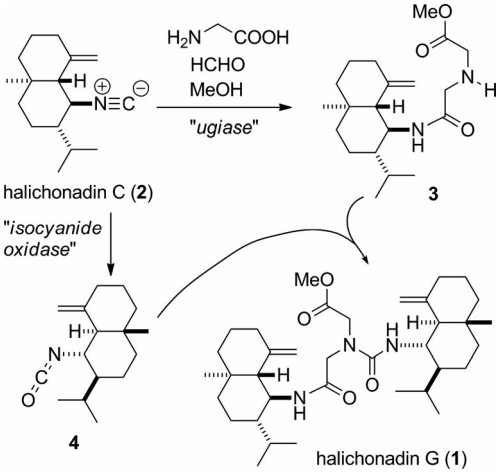
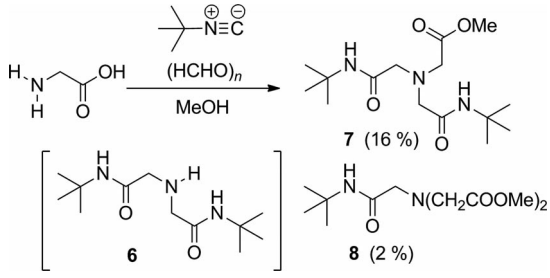
(Scheme 1).[10] This finding along with chemical intuition suggests that halichonadin C (**2**) is a likely biogenetic precursor of halichonadin G (**1**). In a route based on this proposal, a hypothetical ugiase might promote a Ugi reaction of **2** with glycine, formaldehyde, and methanol to generate terpene–IDA conjugate **3**, in which the IDA core is linked to the terpene unit through an amide bond. In turn, the action of an isocyanide oxidase on isocyanide **2** would produce isocyanate **4**, which through reaction with conjugate **3** would generate the urea bond in halichonadin G (**1**). To explore the chemical foundation of this proposed biosynthetic pathway, we embarked on a study aimed at the synthesis of an analogue of halichonadin G.



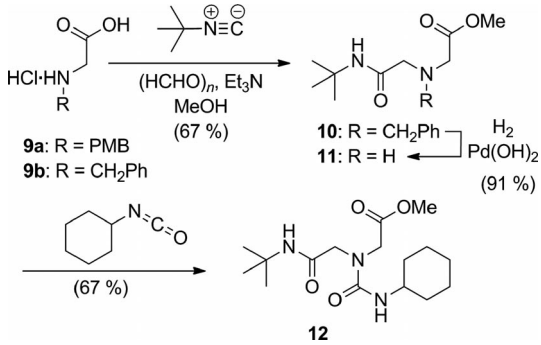
Scheme 1. Plausible biosynthetic pathway of halichonadin G illustrating its origin from terpene isocyanide halichonadin C.

Preliminary studies focused on the Ugi five-center four-component reaction (U-5C-4CR)[11] of *tert*-butyl isocyanide, glycine, formaldehyde, and methanol (Scheme 2). Disappointingly, we did not observe the formation of desired Ugi coupling product **6**, and unwanted products **7** and **8** were isolated in 16 and 2% yield, respectively. Major product **7** most likely arises from **6** through an over-Ugi reaction.



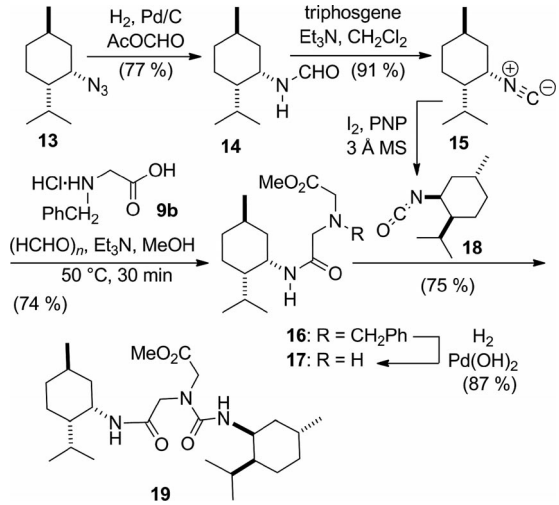
Scheme 2. Unsuccessful model experiments to mimic the proposed biosynthesis of halichonadin G.

To circumvent the problem associated with the higher reactivity of the amine group in **6** than that in glycine, we carried out the Ugi reaction by employing nitrogen *p*-methoxybenzyl (PMB) protected glycine derivative **9a** (Scheme 3). Unfortunately, this process generated desired Ugi product **10** (R = PMB) in a very low yield (<12%). However, by switching the protecting group to the more robust benzyl group, product **10** (R = CH_2Ph) was isolated in an improved 67% yield. Removal of the benzyl group in **10** by using 2,2,2-trichloroethyl chloroformate formed the corresponding 2,2,2-trichloroethoxycarbonyl (Troc) derivative, albeit in low to variable yields (13–44%). Although catalytic hydrogenolytic cleavage of benzyl protecting groups is usually sluggish and often requires elevated hydrogen pressures,[12] hydrogenolysis of **10** by using Pearlman's catalyst proceeded smoothly at atmospheric pressure to furnish amine **11** in 91% yield. Treatment of **11** with commercially available cyclohexyl isocyanate then afforded IDA methyl ester **12** (67%), which contains the *N*-*tert*-butyl and *N*-cyclohexyl groups linked through an amide and urea bond, respectively.



Scheme 3. Synthesis of the core structure in halichonadin G.

We next turned our attention to the synthesis of the central core of halichonadin G, which is linked to the two terpene units (Scheme 4). Starting with known azide **13**, prepared from (–)-menthol,[13] menthyl isocyanide **15** was synthesized in 70% overall yield by a sequence involving (1) hydrogenation of azide **13** followed by formylation with acetic formic anhydride and (2) dehydration of resulting formamide **14** with triphosgene and triethylamine. Biomimetic U-5C-4CR of isocyanide **15** with *N*-benzylglycine **9b** and paraformaldehyde in methanol proceeded smoothly at

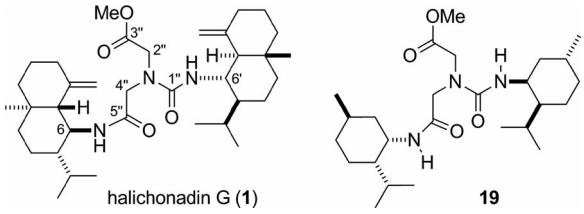


Scheme 4. Synthesis of a menthyl analogue of halichonadin G.

50 °C over 30 min to produce coupling product **16** in 74% yield. Hydrogenolysis of the benzyl group in **16** proceeded uneventfully to furnish secondary amine **17** in 87% yield. In a parallel route, isocyanate **18** was prepared by oxidation of isocyanide **15** with pyridine *N*-oxide (PNP) and a catalytic amount of iodine in the presence of 3 Å molecular sieves (MS).[14] Finally, reaction of isocyanate **18** with **17** gave rise to **19**, the menthyl analogue of halichonadin G, in 75% yield after chromatographic purification.

A comparison of the ^{1}H NMR spectroscopic data in the IDA moieties of natural halichonadin G (**1**) and menthyl analog **19** is shown in Table 1. The ^{1}H NMR chemical shift and coupling properties of the methylene hydrogen atoms (2′′-H and 4′′-H by using halichonadin G numbering) in the IDA unit of **19** are quite similar to those of **1**. The chemical shifts of the 6-NH and 6′-NH amide hydrogen atoms in halichonadin G (δ = 4.04 and 7.12 ppm) reside upfield relative to those in menthyl analogue **19** (δ = 5.22 and 7.89 ppm). This phenomenon is presumably a consequence of the shielding effect of the adjacent alkene moiety in halichonadin G. Moreover, all ^{13}C NMR chemical shifts for the carbon atoms in the IDA moieties of menthyl analog **19** and halichonadin G (**1**) are quite similar (Table 2).

Table 1. Comparison of selected ^{1}H NMR spectroscopic data[a] for halichonadin G (**1**) and model compound **19**.



Position	1		19	
	δ_H [ppm]	M[b] (J [Hz])	δ_H [ppm]	M[b] (J [Hz])
2′′	4.12	d (17.3)	4.34[c]	d (17.9)
2′′	3.59	d (17.3)	3.94	d (17.9)
4′′	3.92	d (18.1)	3.89[c]	d (16.4)
4′′	3.56	d (18.1)	3.73	d (16.4)
6-NH[d]	7.12	br. d (9.2)	7.89	br. d (8.6)
6′-NH[d]	4.04	br. d (8.9)	5.22	br. d (8.6)
OMe	3.73	s	3.76	s

[a] Measured in $CDCl_3$. [b] M = multiplicity. [c] Assignments determined by HMBC experiments. [d] Assignment of these signals may be interchangeable.

Table 2. Comparison of selected ^{13}C NMR spectroscopic data[a] for halichonadin G (**1**) and model compound **19** and their differences ($\Delta\delta$).

Position	δ_C [ppm]		$\Delta\delta$[b] [ppm]
	1	19	
1′′	157.7	157.6	0.1
2′′	51.2	50.8	0.4
3′′	171.8	172.2	–0.4
4′′	53.8	54.7	–1.1
5′′	168.8	168.8	0

[a] Measured in $CDCl_3$. [b] $\Delta\delta = \delta_1 - \delta_{19}$.

Conclusions

In the study described above, we successfully tested the chemical features of our proposed biosynthesis of terpenes related to halichonadin G. In the biomimetic pathway targeted at menthyl analog **19**, the core structure of halichonadin G was constructed by utilizing a Ugi five-center four-component reaction and an isocyanide oxidation as the two key steps. The results of this effort serve to support the proposal that Nature utilizes Ugi-type reactions in biosynthetic pathways to create molecular diversity in natural products. Studies targeted at the synthesis of halichonadin G are now underway in our laboratory.

Supporting Information (see footnote on the first page of this article): Experimental details and copies of the ^{1}H NMR and ^{13}C NMR spectra of all relevant compounds.

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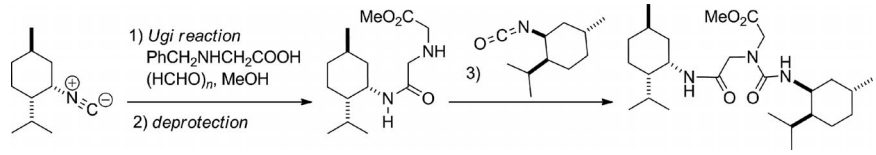
Biomimetic Synthesis



A unique pathway for the biosynthesis of the marine sponge terpene halichonadin G is proposed. On the basis of this proposal, a biomimetic approach involving a Ugi coupling reaction is designed and applied to the efficient construction of the core structure of halichonadin G.

Keywords: Biomimetic synthesis / Multicomponent reactions / Natural products / Terpenoids

