A Biomimetic Approach to Terpenes Isolated from Marine Sponges: a Ugi Coupling Reaction in a Hypothetical Biosynthesis

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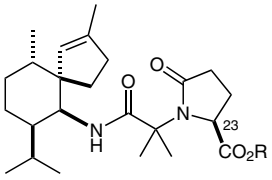
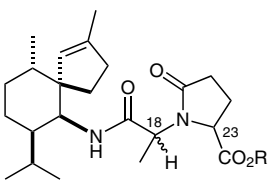
Abstract: A unique pathway for the biosynthesis of marine sponge terpenes is proposed. Based on this proposal, a biomimetic approach using a Ugi coupling reaction has been designed and applied to the efficient construction of the right-side, peptide-like portions of boneratamides and exigurin.

Key words: Ugi reaction, biomimetic synthesis, terpenes, marine sponges, ugiase

Over the past several decades, our research has focused on the development of the synthesis of terpene isocyanides found in marine organisms.[1] In recent research endeavors in this area, our attention has been drawn to the structurally unique group of terpenes, boneratamides A–C (Figure 1).[2] Boneratamides A–C were isolated from the marine sponge *Axinyssa aplysinoides* by Andersen and co-workers in 2004 and the relative stereochemistry of boneratamide A (**1**) was determined by X-ray crystallographic analysis of the corresponding methyl ester **2** (only one enantiomer with a C-23*S* absolute configuration is shown). The structures of boneratamides B (**3**) and C (**4**) were elucidated by extensive NMR spectroscopic studies on the corresponding methyl esters **5** and **6**, which established that boneratamides B (**3**) and C (**4**) are stereoisomers differing in the relative configuration at either one or both of the C18 and C23 stereogenic centers.



boneratamide A (**1**): R = H
methyl ester of boneratamide A (**2**): R = Me



boneratamide B (**3**) and C (**4**): R = H
methyl ester of boneratamide B (**5**) and C (**6**): R = Me

Figure 1 Structures of boneratamides A–C and their methyl esters

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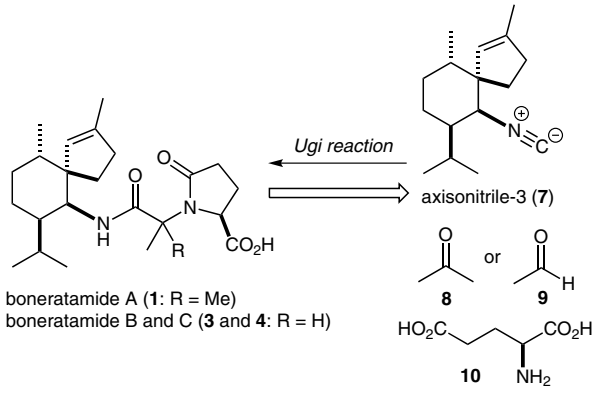
Apparently, boneratamides have no isocyano functionality and they are comprised of a terpene unit (left side) linking via an amide bond to a peptide-like moiety (right-side). The unique structure of the right-side portion of boneratamides inspired us, because we surmised that these terpenes might be derived from the terpene isocyanide, axisonitrile-3[3] by a hitherto unrecognized biosynthetic pathway. Our hypothetical biosynthetic pathway of the right-side portions of boneratamides A–C is presented retrosynthetically in Scheme 1, which reveals their origin as a terpene isocyanide and simple precursors. The key step in the proposed route is a Ugi coupling reaction,[4] which shows that boneratamides A–C might be traced back to three building blocks, including axisonitrile-3 (**7**), a carbonyl component, either acetone (**8**) or acetaldehyde (**9**), and glutamic acid (**10**). In order to explore the plausibility of this biosynthetic hypothesis, we conducted an investigation of the synthesis of boneratamides A–C using a biomimetic strategy that is based on the putative Ugi coupling reaction.



Scheme 1 Retrobiosynthetic analysis of boneratamides illustrating their terpene isocyanide origin

During the course of our research efforts in this area, halichonadins K and L were isolated from marine sponges by Kobayashi and his co-workers.[5] These workers suggested the possibility that the biogenetic origin of halichonadins K and L involved reaction of an intermediate iminium cation with a terpene isocyanide. This publication has prompted us to disclose our own independently derived proposal for the biosynthesis of terpenes from marine sponges and to disclose preliminary synthetic studies, the first in vitro chemical evidence for the proposed biosynthetic pathway.

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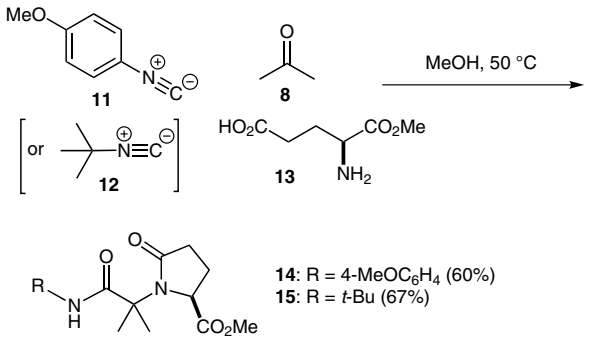
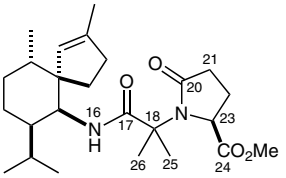
A Ugi one-pot multicomponent reaction (MCR) of *p*-methoxyphenyl isocyanide (**11**),[6] acetone (**8**) and the glutamic acid derivative **13** was explored as a model for the key process involved in the proposed boneratamide terpene biosynthesis pathway (Scheme 2). It is well known that the use of β-amino acids as a bifunctional coupling component in the Ugi four-center three-component reaction (U-4C-3CR) results in β-lactam ring formation.[7] Consequently, we elected to employ γ-amino acid **13** as a substrate, with the expectation that the U-4C-3CR would lead to the construction of a γ-lactam structure corresponding to the right-side portion of boneratamide A.[8] After some experiments, we were delighted to find that the Ugi coupling process did indeed generate the right-side portion of boneratamide A. In fact, reaction of isocyanide **11**, acetone (**8**; 10 equiv) and L-glutamic acid 1-methyl ester (**13**; 1.5 equiv) in methanol at 50 °C, followed by chromatographic purification, furnished γ-lactam **14** in 60% yield. Furthermore, the sterically hindered *tert*-butyl isocyanide (**12**), serving as a model of axisonitrile-3 (**7**), also participated in this Ugi reaction producing γ-lactam **15** in 67% yield.[9] Inspection of the ^{1}H NMR and ^{13}C NMR data for boneratamide A methyl ester (**2**) and γ-lactam **15** summarized in Table 1 shows that the NMR data of **15** are in good accord with those reported for **2**. These observations demonstrate that a simple and remarkably efficient biomimetic one-pot process led to the formation of the right-side portion of boneratamide A (**1**).

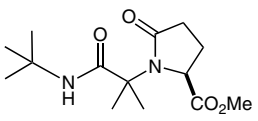


Scheme 2 One-pot synthesis of the right-side portion of boneratamide A by a Ugi reaction

Table 1 Comparison of NMR Data (C_6D_6, 500 MHz) for the Methyl Ester of Boneratamide A (**2**) with γ-Lactam **15**



methyl ester of boneratamide A (**2**)



γ-lactam **15**

Position	^{1}H NMR		^{13}C NMR	
on **2**	**2**[a]	**15**	**2**[a]	**15**
16	7.49 (d, *J* = 10.4 Hz)	7.29 (1 H, br s)		
17			172.7	172.4
18			60.9	60.6
20			174.0	173.9
21	1.79 (ddd, *J* = 16.4, 9.5, 1.9 Hz)	1.75 (1 H, ddd, *J* = 16.6, 9.2, 1.7 Hz)	30.0	29.9
21	2.14 (m)	2.04 (1 H, ddd, *J* = 16.6, 11.4, 9.2 Hz)		
22	1.30 (m)	1.25 (1 H, m)	24.5	24.6
22	1.42–1.50	1.37–1.44 (1 H, m)		
23	3.78 (dd, *J* = 9.8, 1.5 Hz)	3.72 (1 H, dd, *J* = 9.7, 1.1 Hz)	57.8	57.8
24			175.5	175.8
25	1.66 (s)	1.56 (3 H, s)	23.8	23.4
26	1.25 (s)	1.12 (3 H, s)	25.6	25.3
OMe	3.17 (s)	3.11 (3H, s)	52.5	52.4

[a] NMR data of **2** are reproduced from the isolation paper; see ref. 2.

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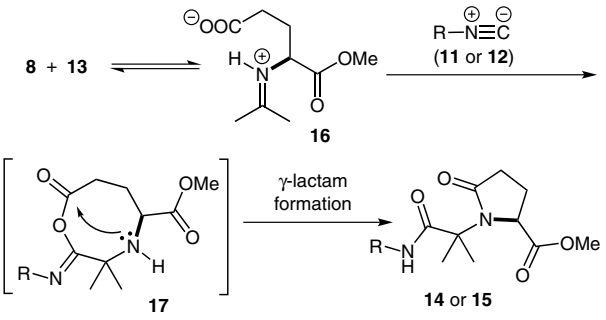
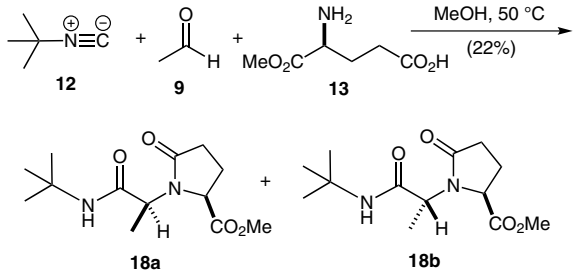
A plausible reaction mechanism for the U-4C-3CR forming **14** and **15** is shown in Scheme 3. In this pathway, reaction of acetone (**8**) with amino acid **13** affords the protonated Schiff base **16**, which reacts with the isocyanide (**11** or **12**) to produce *O*-acylimidate intermediate **17**. Finally, O-to-N acyl migration of **17** gives rise to the final γ-lactam core in **14** or **15**.[10]



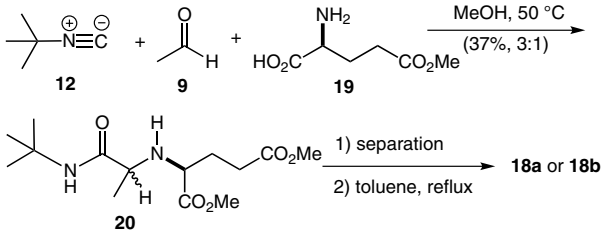
Scheme 3 A plausible mechanism for the Ugi reaction

Encouraged by these results, we examined a closely related process that serves as a model for generating the right-side portion of boneratamide B (**3**) and boneratamide C (**4**) (Scheme 4). Disappointingly, we observed that Ugi coupling reaction of *tert*-butyl isocyanide **12**, acetaldehyde (**9**) and γ-amino acid **13** produced an inseparable 1:1 mixture of the γ-lactams **18a** and **18b** in a low yield (22%).



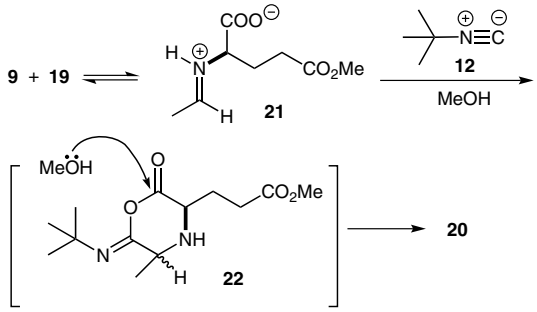
Scheme 4 Model for the synthesis of the right-side portion of boneratamide B and boneratamide C

In order to find a more efficient method to produce **18a** and **18b** in pure forms, our attention turned to a stepwise synthetic route (Scheme 5) involving a Ugi five-center-four-component reaction (U-5C–4CR),[11] in which α-amino acid **19** serves as a bifunctional starting material. Treatment of *tert*-butyl isocyanide **12** with acetaldehyde (**9**) and L-glutamic acid 5-methyl ester (**19**) afforded a 3:1 mixture of the diastereomeric amides **20** in 37% yield. To our delight, a mixture of **20** could be separated and each isomer was individually subjected to heating in toluene, furnishing the respective γ-lactams **18a** and **18b** in pure form. Although the relative stereochemistries of the diastereomers of **18** and **20** could not be assigned, the NMR spectroscopic properties of these substances support their structural assignments and, importantly, they show that the isomers of **18** have structures, which are identical to the right-side portions of each boneratamide B and C.[12]



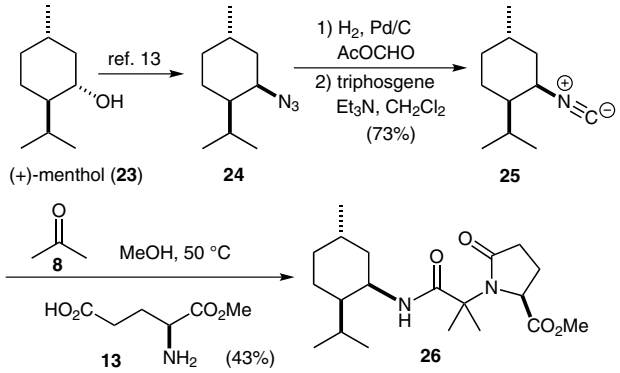
Scheme 5 Improved synthesis of **18** using U-5C-4CR

Formation of **20** in the U-5C–4CR appears to be governed by the reactivity of the cyclic *O*-acylimidate intermediate **22** (Scheme 6). Schiff base **21**, formed by the reaction of acetaldehyde (**9**) with α-amino acid **19**, would react with isocyanide **12** to afford intermediate **22**. Since O-to-N acyl migration of **22** would produce a highly strained α-lactam, methanol intercepts the *O*-acylimidate **22** to form **20**.



Scheme 6 Mechanism for U-5C-4CR forming **20**

Synthesis of the despirocyclic boneratamide A analogue **26** was explored (Scheme 7). The known azide **24**,[13] prepared from (+)-menthol (**23**), was transformed to the terpene isocyanide **25** in 73% overall yield by employing a sequence involving: (1) hydrogenation of the azide **24**, (2) reaction of the resulting amine with acetic formic anhydride, and (3) dehydration of the formed formamide with triphosgene and triethylamine. Ugi reaction of isocyanide



Scheme 7 Synthesis of **26**, a despirocyclic boneratamide A analogue

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25, using conditions similar to those described in Scheme 2, delivered **26** in 43% yield.

Parallel to our synthetic studies of boneratamides, we have surveyed the literatures in order to uncover more examples of marine natural products that might be biosynthesized via pathways involving Ugi coupling reaction. This literature browsing found two buried examples, exigurin (**27**) and halichonadin G (**28**; Figure 2). Exigurin (**27**) was isolated by Ikegami group in 2003 from the marine sponge *Geodia exigna*.[14] In 2011, Kobayashi and his coworkers isolated halichonadin G (**28**) from the sponge *Halichondria sp*.[15] These terpenes share the interesting amide structural unit **29**. We envisioned that the common structural unit **29** could be synthesized with a similar scenario using U-5C-4CR, which employs a terpene isocyanide and a glycine derivative along with formaldehyde.

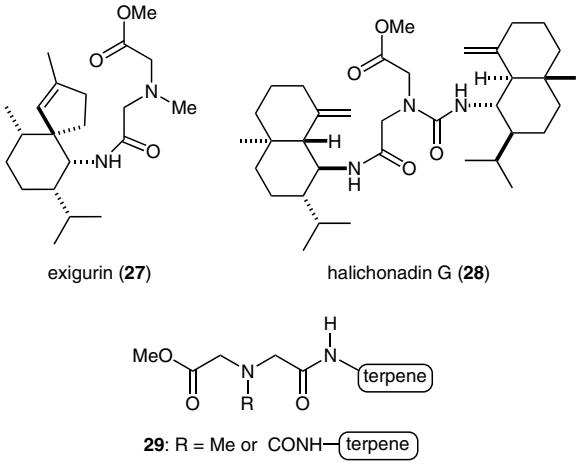
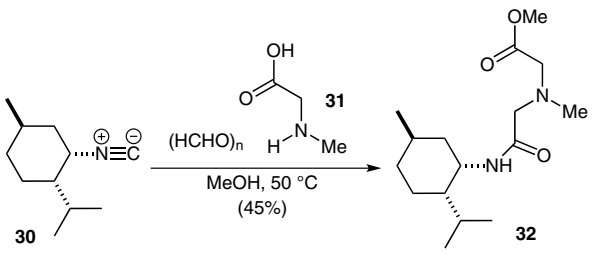


Figure 2 Exigurin, halichonadin G and their common amide structural unit **29**

We examined the synthesis of the common structural unit **29** in exigurin (Scheme 8). The model isocyanide **30** was prepared from (–)-menthol by utilizing a procedure similar to that described for the preparation of its enantiomer **25** in Scheme 7. One-pot multicomponent Ugi reaction of isocyanide **30**, paraformaldehyde and sarcosine (**31**) in methanol led to the formation of the terpene amide **32** in 45% yield. Although low yielding, this potentially biomimetic one-step U-5C-4CR approach to construction of the structural unit **29** found in the marine natural product exigurin is impressive.



Scheme 8 Synthesis of an exigurin analogue

In the study described above, we have demonstrated that approaches that mimic the newly proposed biosynthetic pathways can be employed to generate the peptide-type units in the boneratamides A–C and exigurin. Although the yields of Ugi reaction in our preliminary results are only moderate, the concise nature of the multicomponent, one-pot procedures makes the routes particularly attractive. In addition, our studies shed some light on the potentially important role played by Ugi reactions in the biosynthesis of natural products found in marine organisms, which suggests possible involvement of a putative 'ugiase' enzyme. The Ugi reaction has been exploited extensively for combinatorial diversity-oriented synthesis in the filed of medicinal chemistry, and it is quite surprising for us to recognize that Nature also employs the Ugi reaction to build up molecular diversity in natural product biosynthesis. Further studies on the synthesis of boneratamides are now under investigation in our laboratory.

Acknowledgment

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(9) A solution of L-glutamic acid 1-methyl ester (**13**; 430 mg, 2.67 mmol) and acetone (**8**; 1.30 mL, 17.8 mmol) in MeOH (25.0 mL) was treated with *tert*-butyl isocyanide (**12**; 0.20 mL, 1.78 mmol). After stirring at r.t. for 1.5 h, the solution

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was heated at 50 °C for 24 h, followed by refluxing for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in EtOAc and H_2O. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated to afford the residue, which was purified by silica gel chromatography to furnish γ-lactam **15** (337 mg, 67%).

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