HETEROCYCLES, Vol. 92, No. 6, 2016, pp. 1040 - 1053. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 22nd February, 2016, Accepted, 24th March, 2016, Published online, 18th April, 2016
DOI: 10.3987/COM-16-13442

A BIOMIMETIC APPROACH TO THE SYNTHESIS OF TERPENE-AMINO ACID CONJUGATES. THE UGI REACTION IN THE HYPOTHETICAL BIOSYNTHESIS OF MARINE NATURAL PRODUCTS

Yoshiyasu Ichikawa,*[a] Kenta Saito,[a] Rika Mimura,[a] Ayumi Kitamori,[a] Akihito Matsukawa,[a] Akifumi Ikeda,[a] Toshiya Masuda,[b] Hiyoshizo Kotsuki,[a] and Keiji Nakano[a]

[a]Faculty of Science, Kochi University, Akebono-cho Kochi 780-8520, Japan; E-mail: ichikawa@kochi-u.ac.jp. [b]Graduate School of Human Life Science, Osaka City University

Abstract – A unique pathway for the biosynthesis of the marine sponge terpenes, exigurin and boneratamides A–C, is proposed. Based on this proposal, a biomimetic strategy on key Ugi coupling reactions between terpene isocyanides and amino acids was developed for construction of the core structures of exigurin and boneratamides A–C.

INTRODUCTION

In 2003, Ohta and Ikegami at Hiroshima University reported the isolation and structural elucidation of exigurin (**1**) along with (–)-10-*epi*-axisonitrile-3 (**2**) from the marine sponge *Geodia exigua* collected in the Oshima Island in the Kagoshima Prefecture of Japan (Figure 1).[1] While (–)-10-*epi*-axisonitrile-3 (**2**) is a typical marine terpene isocyanide, previously isolated from the nudibranch *Phylliella pustulosa*,[2] exigurin (**1**) has an unprecedented structure in which a terpene unit and sarcosine (*N*-methylglycine) are joined through an amide linkage. Although Garson and Simpson suggested that (–)-10-*epi*-axisonitrile-3 (**2**) plays a possible precursor role in the biosynthesis of exigurin, questions have arisen about the metabolic origin of this marine sponge terpene-amino acid conjugate.[3]

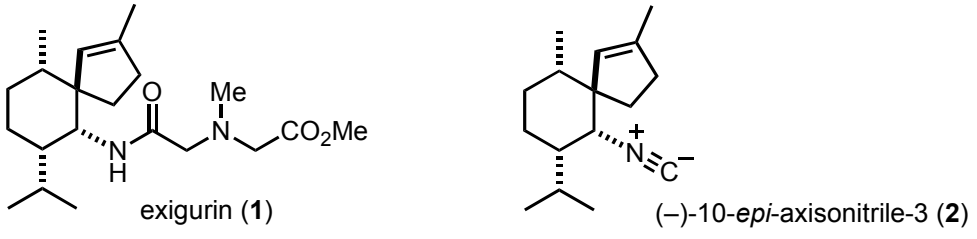
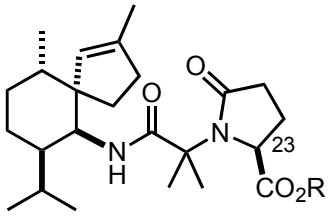
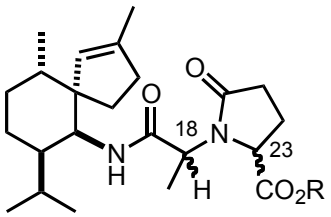


Figure 1. Structures of exigurin (**1**) and (–)-10-*epi*-axisonitrile-3 (**2**)

In 2004, Andersen and co-workers at the University of British Columbia reported the isolation of boneratamides A–C from the marine sponge *Axinyssa aplysinoides* collected in Indonesia.[4] X-Ray crystallographic analysis of the methyl ester of boneratamide A (**4**) established the relative stereochemistry of boneratamide A (**3**) as represented in Figure 2 (only one enantiomer with C-23*S* absolute configuration is shown). Boneratamide A is a terpene-amino acid conjugate in which the terpene unit and pyroglutamic acid are connected through a 2-aminoisobutyramide moiety. The structures of boneratamides B and C (**5**) were elucidated by extensive NMR spectroscopic analysis on the corresponding methyl esters **6**, which revealed that boneratamides B and C are stereoisomers differing in the relative configuration at either one or both of the C18 and C23 stereogenic centers. Like boneratamide A (**3**), boneratamides B and C (**5**) are conjugates of a terpene unit and pyroglutamic acid.



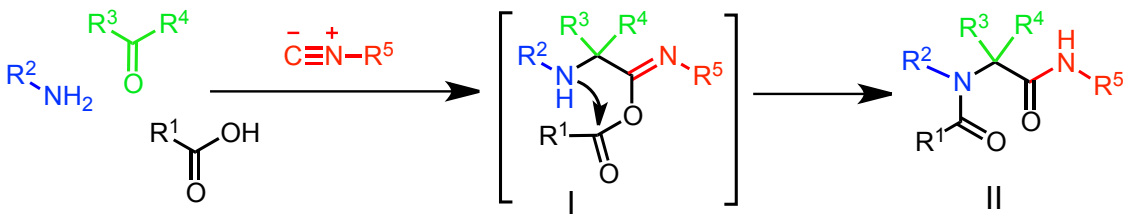
boneratamide A (**3**): R = H
metyl ester (**4**): R = Me



boneratamides B and C (**5**): R = H
metyl esters (**6**): R = Me

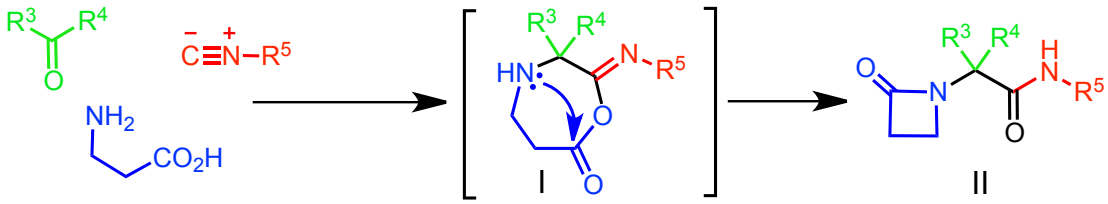
Figure 2. Structures of boneratamides A–C and their methyl esters

We previously put forth the hypothesis that exigurin and boneratamides A–C might be generated in marine organisms through a hitherto unrecognized biosynthetic pathway that involves key Ugi reactions.[5] The Ugi reaction is a multicomponent reaction which combines four components including an amine, aldehyde or ketone, carboxylic acid and isocyanide, in a one-pot manner to produce an α-acylaminoamide **II** (Scheme 1). This process, known as the Ugi four-component reaction (U-4CR), has found widespread use in both diversity and target oriented organic syntheses.[6] The currently accepted mechanism of the U-4CR starts with condensation of the amine with carbonyl compound to form a Schiff's base, which then reacts with the isocyanide to generate the transient O-acyl imido intermediate **I**. Spontaneous O-to-N acyl migration of **I** results in the formation of the stable α-acylaminoamide product **II**.



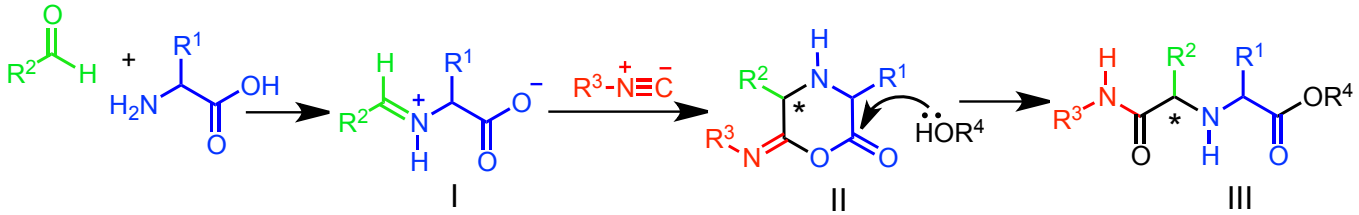
Scheme 1. The Ugi four component reaction (U-4CR)

In an extension of the U-4CR, bifunctional reagents in which the participating functional groups are present in a single component, have been used to construct unique structures such as β-lactams and iminodicarboxylic acids. In the route for β-lactam synthesis, β-amino acids serve as bifunctional starting materials instead of the amine and carboxylic acid components (Scheme 2).[7] A plausible reaction mechanism involves initial condensation of the β-amino acid with the carbonyl component to form a Schiff's base, which then reacts with the isocyanide to form a seven-membered ring intermediate **I**. Intramolecular O-to-N-acyl migration of **I** results in the formation of the β-lactam **II**. This type of the process for β-lactam synthesis is referred to as the Ugi-four-center three-component reaction (U-4C-3CR).[8]



Scheme 2. The Ugi-four-center three-component reaction (U-4C-3CR) for the synthesis of β-lactams

A modification of the U-4CR using amino acids as bifunctional starting materials is classified as the Ugi five-center four-component reaction (U-5C-4CR) (Scheme 3).[9] The proposed reaction mechanism of the U-5C-4CR begins with condensation of the amino acid with the aldehyde to form the corresponding protonated Schiff's base **I**. Addition of the isocyanide then produces the cyclic O-acyl-imide **II**. High strain energy associated with the formation of α-lactam ring prevents **II** from undergoing intramolecular O-to-N-acyl migration. As a result, nucleophilic attack of the fourth component, such as methanol used as the solvent, occurs at the carboxylic carbon (the fifth reacting center). Subsequent six-membered ring opening leads to the formation of the iminodicarboxylic acid derivative **III**. It should be noted that this process creates a stereogenic center in the product **III**.

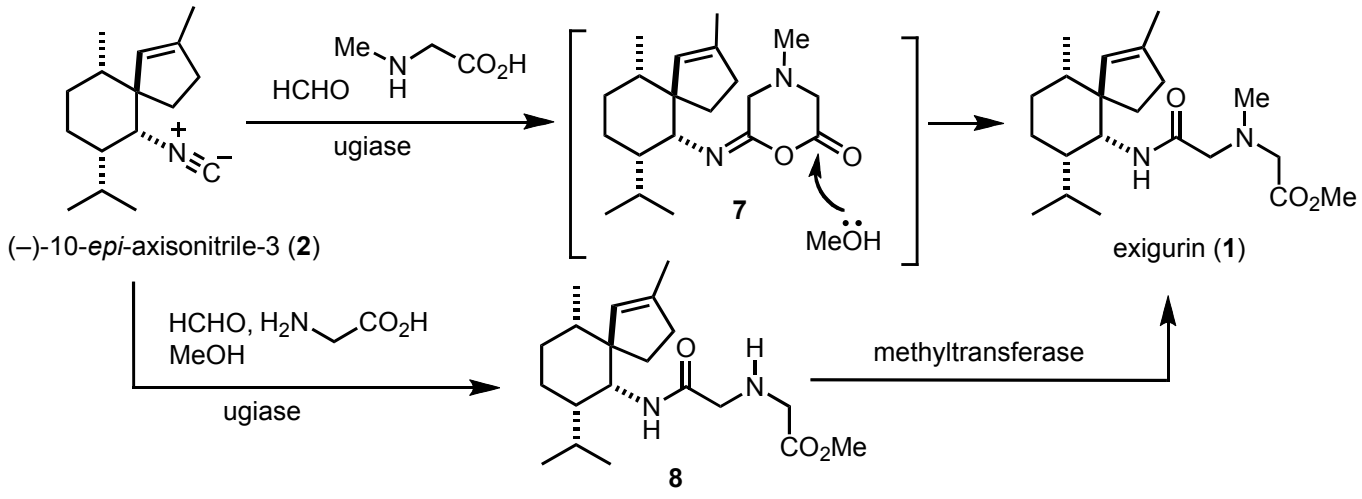


Scheme 3. The Ugi five-center four-component reaction (U-5C-4CR) forming iminodicarboxylic acid derivatives

Taking U-4CR, U-4C-3CR and U-5C-4CR processes into consideration, analysis of the structures of exigurin (**1**), boneratamide A (**3**), boneratamides B and C (**5**) led us to recognize the structural resemblance among these terpene-amino acid conjugates. Specifically, these linked terpene-amino acid conjugates possess a common structural motif of iminodicarboxylic acid moiety, which connects the terpene and amino acid residues. This type of structural motif has been known as a product of the Ugi reaction in the field of organic syntheses. Although the Ugi reaction has been used extensively in combinatorial, diverse oriented synthesis,[10] it is quite surprising for us to imagine that Nature employs a similar approach to build up a diversity of secondary metabolites in biosynthesis. We now report a further development and observations of our studies aiming at a biomimetic approach to the synthesis of terpene-amino acid conjugates exigurin and boneratamides A–C.

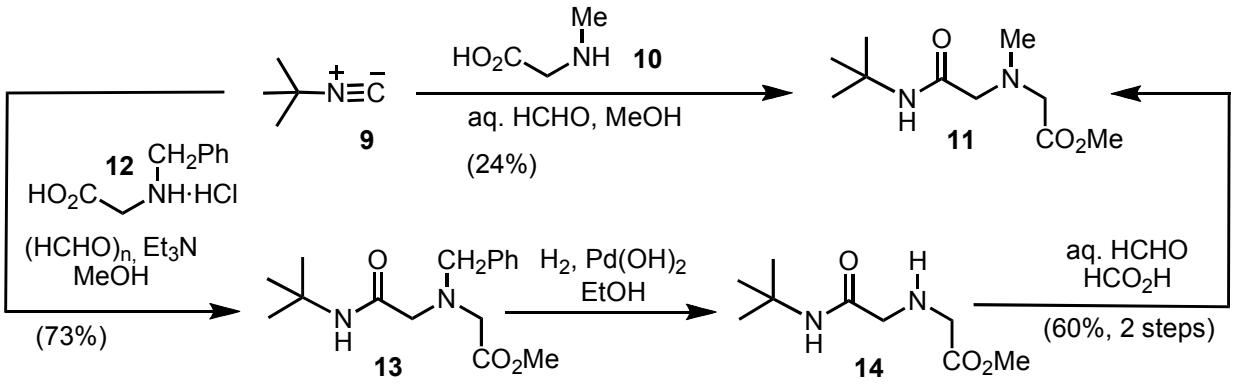
RESULTS AND DISCUSSION

Two hypothetical biosynthetic pathways for construction of the right hand, amide portion of exigurin are presented in Scheme 4. The key step in each route, involving a ugiase catalyzed U-5C-4CR, suggests that exigurin may be traced back to three building blocks consisting of (–)-10-*epi*-axisonitrile-3 (**2**) and two other simple precursors such as formaldehyde and either sarcosine or glycine. The Ugi reaction is known to be promoted by an enzyme,[11] and this precedent led us to propose a putative ugiase enzyme that catalyzes the Ugi process in a manner reminiscent of the Ugi reaction in organic synthesis. In the clockwise hypothetical pathway, the U-5C-4CR of (–)-10-*epi*-axisonitrile-3 (**2**) with the iminium ion formed from formaldehyde and sarcosine generates the cyclic O-acyl imidate **7**, which reacts with methanol to furnish exigurin (**1**). In the other route, the U-5C-4CR of formaldehyde and glycine with the isocyanide **2** produces **8**, which is transformed to exigurin (**1**) by the action of methyltransferase.



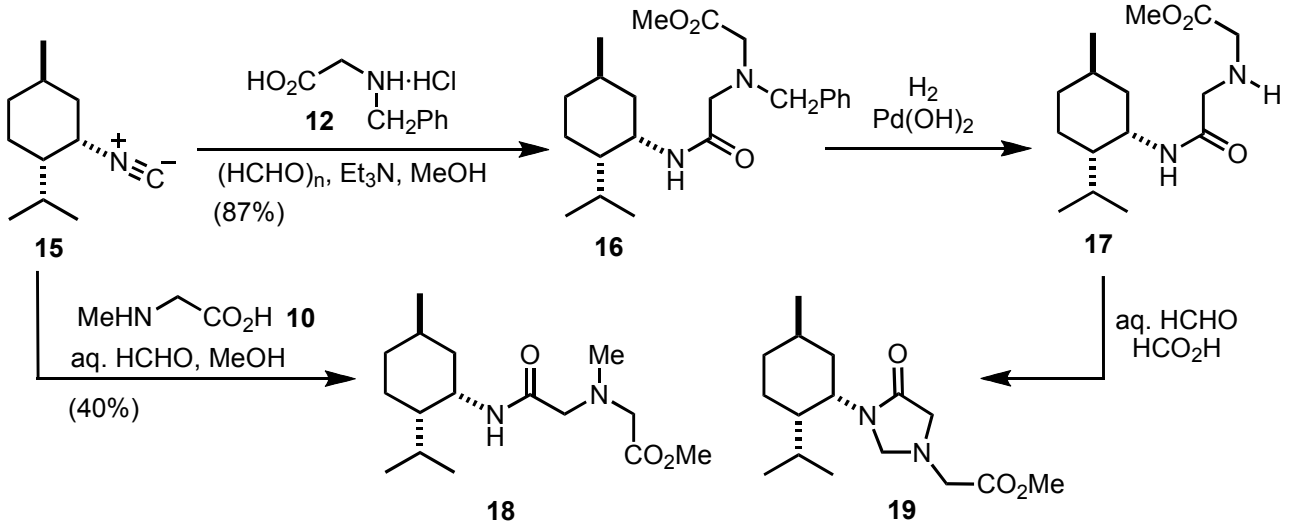
Scheme 4. Two plausible biosynthetic pathways of exigurin (**1**) through the U-5C-4CR

Reaction of *t*-butyl isocyanide (**9**) with sarcosine (**10**) and aqueous formaldehyde was selected to evaluate the feasibility of the Ugi processes that take place in the hypothetical biosynthetic pathway (Scheme 5). The U-5C-4CR of these substances in methanol took place smoothly at room temperature to form **11** albeit in low yield (24%). After unsuccessful attempts to improve the yields of this process, the alternative hypothetical biosynthesis scenario shown in Scheme 4 was explored. Since the use of glycine as a substrate of the Ugi reaction leads to over-Ugi products,[12] *N*-protected glycine was utilized as the amino acid substrate. To our delight, the U-5C-4CR using *t*-butyl isocyanide (**9**), *N*-benzylglycine (**12**) and paraformaldehyde generated amide **13** in 73% yield. Removal of the benzyl group in **13** followed by the reductive amination of **14** under the Eschweiler-Clarke reaction conditions furnished **11** in 60% yield in two steps.



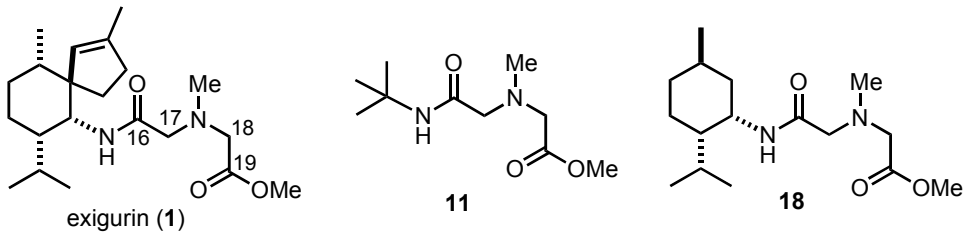
Scheme 5. Model synthesis of the right part of exigurin

We next turned our attention to synthesize a terpene-amino acid conjugate, which possesses the structural motif corresponding to the right part of exigurin (Scheme 6). The terpene isocyanide **15**, prepared from (–)-menthol by a method we previously developed,[12a] was treated with *N*-benzyl glycine **12** and paraformaldehyde in methanol under similar conditions to those depicted in Scheme 5. This U-5C-4CR proceeded uneventfully to afford **16** in 87% yield. Hydrogenolysis of the benzylamine in **16** produced **17**, which was subjected to the Eschweiler-Clarke reaction conditions. To our surprise, we observed a considerable amount of a byproduct, the structure of which was tentatively assigned as cyclic amide **19**. Separation of **19** was difficult due to its similar TLC behavior with **18**. In contrast to the low-yield observed for reaction of *t*-butyl isocyanide (**9**), the U-5C-4CR of the terpene isocyanide **15** with sarcosine (**10**) and aqueous formaldehyde produced **18** in 40% yield. ^{1}H and ^{13}C NMR data for exigurin (**1**), model compound **11** and despiro-exigurin **18** are summarized in Table 1, which shows that the NMR data of both **11** and **18** are in good accord with those reported for exigurin (**1**). Thus, although the yield is modest, synthesis of despiro-exigurin **18** having the right structure found in exigurin was achieved through operationally simple one-pot U-5C-4CR process.



Scheme 6. Synthesis of despiro-exigurin **18**.

Table 1. ^{1}H and ^{13}C NMR data for exigurin (**1**), model compounds **11** and **18**



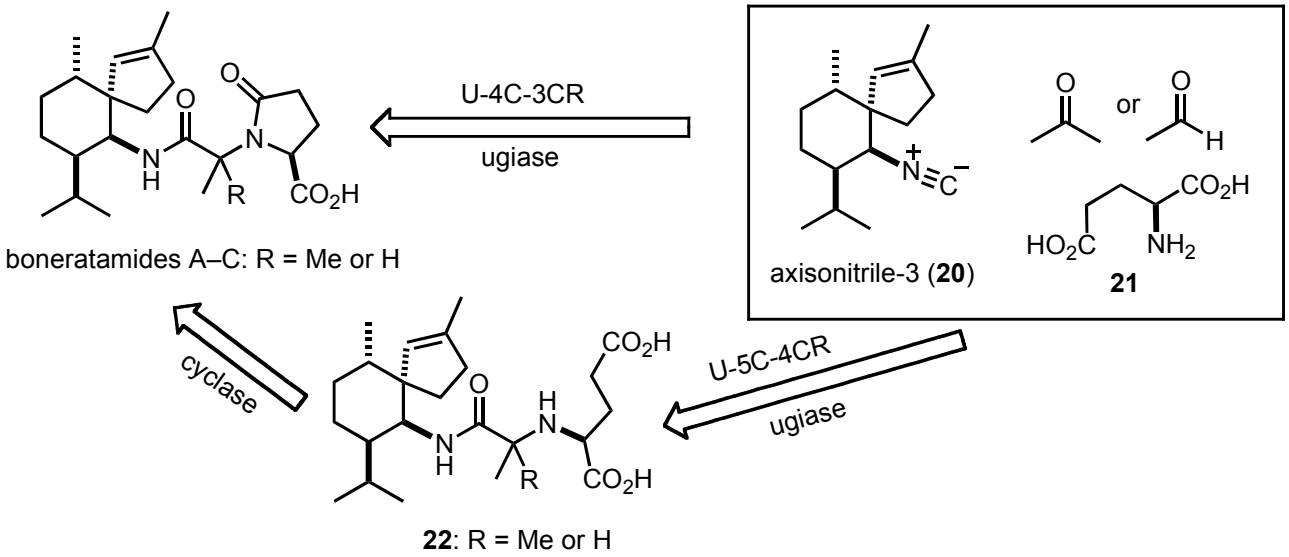
	^{1}**H NMR** (C_6D_6, 500 MHz)		
	1*	**11**	**18**
17	3.05 (2H, s)	2.92 (2H, s)	2.98 (2H, s)
17-NMe	2.09 (3H, s)	2.02 (3H, s)	2.03 (3H, s)
18	2.85 (2H, s)	2.84 (2H, s)	2.75–2.86 (2H, s)
19-OMe	3.28 (3H, s)	3.26 (3H, s)	3.23 (3H, s)

	^{13}**C NMR** (C_6D_6, 125 MHz)		
	1*	**11**	**18**
16	168.98	169.1	168.5
17	61.55	61.9	61.5
17-NMe	43.19	42.7	43.0
18	58.41	58.2	58.3
19	170.64	171.0	170.9
19-OMe	51.03	51.1	51.2

* NMR data of **1** are reproduced from the ref. 1a.

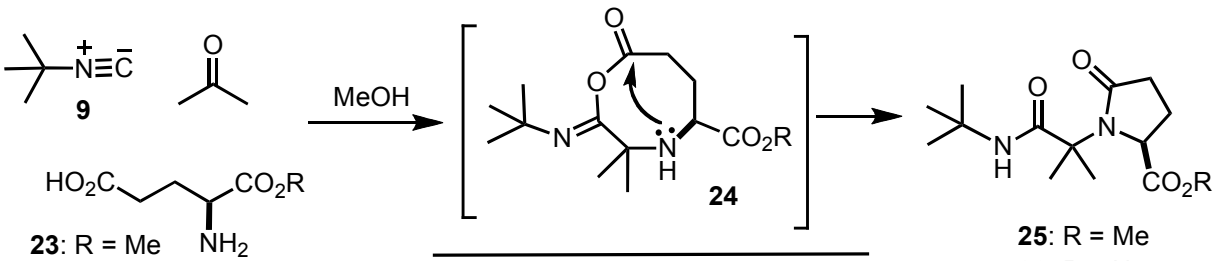
Two retrosynthetic scenarios, based on the hypothetical biosynthesis pathway, can be envisaged for the synthesis of boneratamides A–C (Scheme 7). A plausible intermediate in the biosynthetic route to boneratamides A–C is axisonitrile-3 (**20**), a terpene isocyanide previously isolated from the marine sponge *Axinella cannabina*.[13] Based on this proposal, boneratamides A–C can be envisioned to arise from three building blocks including axisonitrile-3 (**20**), either acetone or acetaldehyde, and glutamic acid (**21**). Moreover, because U-4C-3CR of β-amino acids leads to β-lactams (Scheme 2), we surmised that

corresponding reactions of γ-amino acids such as glutamic acid would produce γ-lactam ring systems present in boneratamides A–C. Another possible retrosynthetic scenario for the preparation of boneratamides A–C follows a stepwise sequence starting with U-5C-4CR of glutamic acid (**21**) as a bifunctional reagent and water as the fourth component to form **22**, which subsequently cyclizes to form γ-lactam core structure in boneratamides A–C.



Scheme 7. Two possible retro-synthetic scenarios for biosynthesis of boneratamides A–C

Initial studies probing these scenarios focused on the synthesis of the right part of boneratamide A employing *t*-butyl isocyanide (**9**) as a model substrate (Scheme 8). We observed that U-4C-3CR of **9**, acetone (10 equiv) and α-methyl L-glutamate (**23**) (1.0 equiv) in methanol proceeds smoothly at 50 °C to produce the γ-lactam **25** (69%) that possesses the structural motif found in boneratamide A methyl ester (**4**) (Scheme 8, entry A). A plausible mechanism for formation of **25** involves generation of the oxazepinone

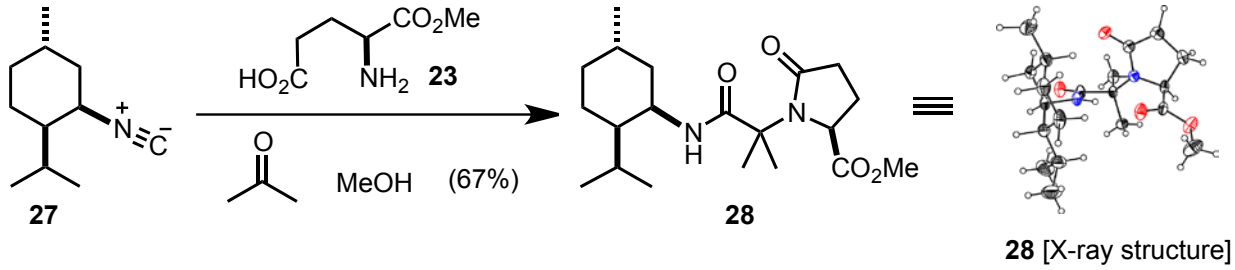


entry	product	yield (%)
A	**25**	69
B	**25** and **26**	19 and 10

Scheme 8. One-pot synthesis of the right-hand amide portion of boneratamide A

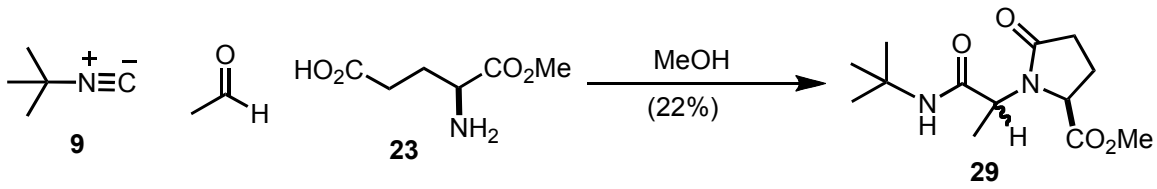
intermediate **24**, which then undergoes intramolecular O-to-N-acyl migration. In the case of the U-4C-3CR using glutamic acid **21** as the substrate, a mixture of methyl ester **25** and carboxylic acid **26** was isolated in 19% and 10% yield, respectively (entry B). Note that the structure of free carboxylic acid in **26** corresponds to the right hand structure of boneratamide A.

We next explored the synthesis of the despiro analogue of boneratamide A employing a terpene isocyanide **27**,[14] which was prepared from (+)-menthol (Scheme 9). The U-4C-3CR of terpene isocyanide **27** using reaction conditions similar to those described in Scheme 8 furnished the desired despiro-boneratamide A **28** in 67% yield. It should be noted that in this highly efficient one-pot process, conjugation of terpene with amino acid took place along with γ-lactam ring formation. ^{1}H and ^{13}C NMR analysis of **28** shows an approximately 1:1 mixture of amide rotamers. Fortunately, we obtained a nice crystalline **28**, and X-ray crystallographic analysis of **28** leads to an unambiguous assignment of its structure.



Scheme 9. Synthesis of despiro-boneratamide A **28**

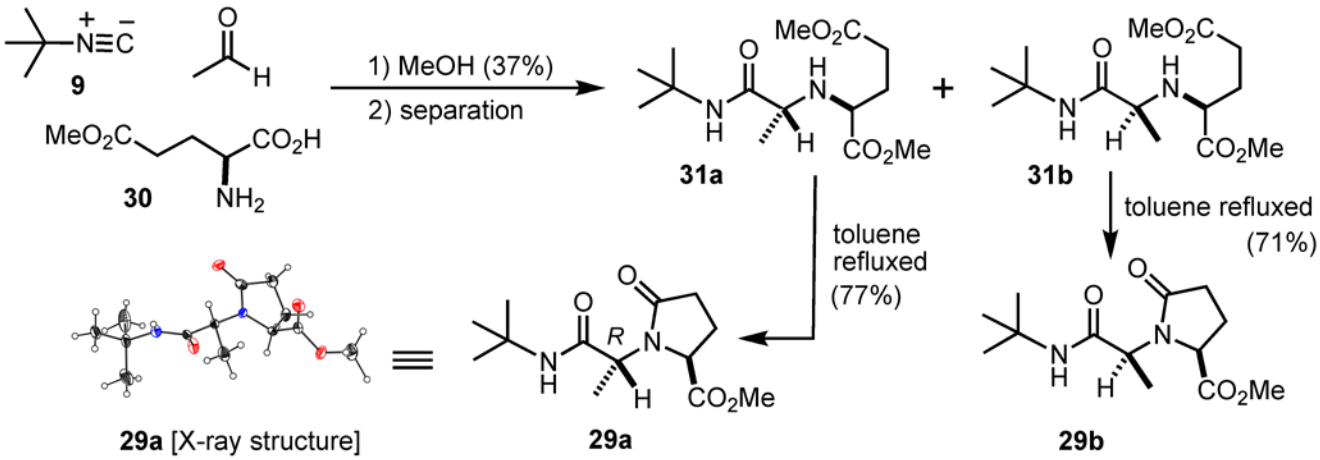
Synthesis of the right-hand portion of boneratamides B and C was explored using the reaction conditions established during the model synthesis of boneratamide A (Scheme 10). Disappointingly, the U-4C-3CR employing *t*-butyl isocyanide (**9**), acetaldehyde and α-methyl L-glutamate **23** produced a 1:1 mixture of products **29** in low yields. Moreover, the diastereomers display similar TLC behavior, which hampered separation and identification.



Scheme 10. Attempted synthesis of the right-hand portion of boneratamides B and C

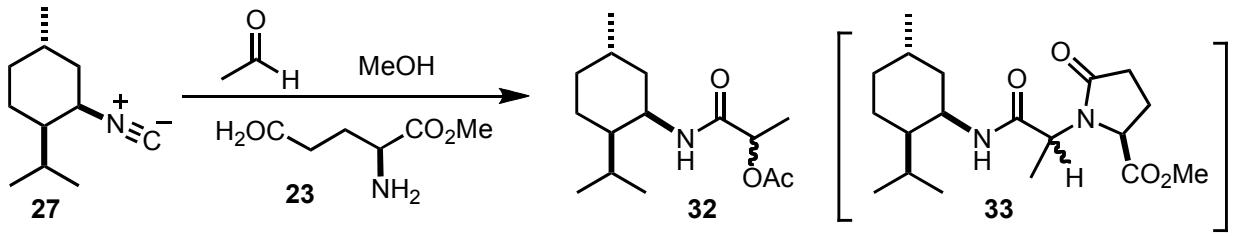
In order to improve yields and to obtain each stereoisomer **29** in pure form, we turned our attention to an alternative stepwise approach, which corresponds to the second hypothetical biosynthetic route depicted

in Scheme 7. In this way, the U-5C-4CR of *t*-butyl isocyanide (**9**), acetaldehyde and γ-methyl L-glutamate (**30**) provided a 3:1 mixture of products **31a** and **31b** in 37% yield (Scheme 11). To our delight, this mixture could be separated and each respective isomer was cyclized by heating in toluene to furnish **29a** and **29b** in 77% and 71% respective yields. Fortunately, the major stereoisomer **29a** is crystalline and the newly formed stereogenic center in **29a** was firmly secured by X-ray crystallographic analysis to assign the *R* absolute configuration.



Scheme 11. Model synthesis of the right portions of boneratimides B and C via a stepwise approach

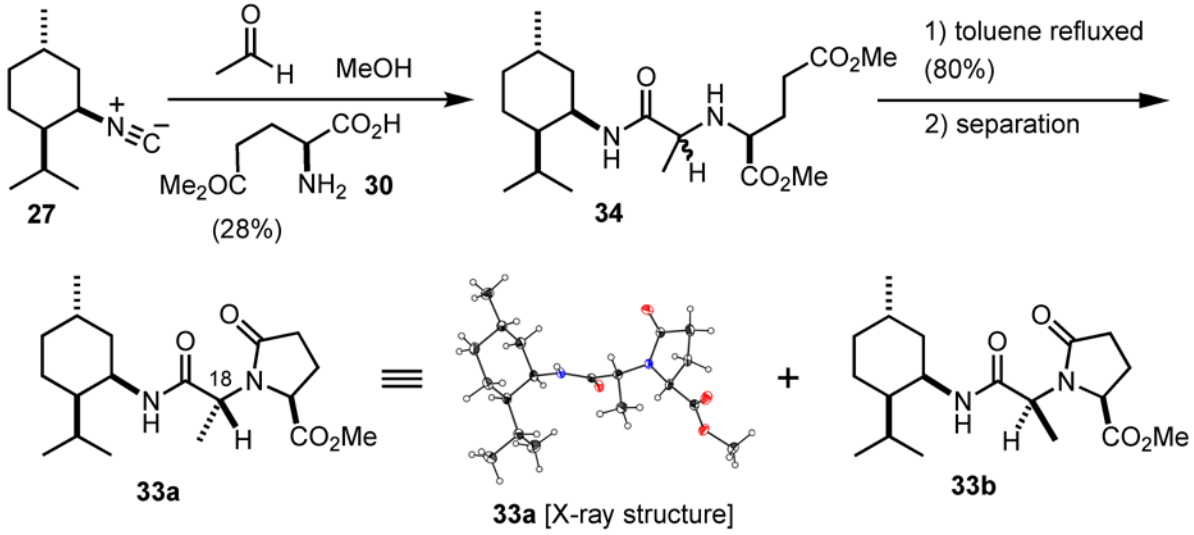
We next investigated to synthesize despiro analogues of boneratamides B and C using U-4C-3CR (Scheme 12). Unfortunately, the U-4C-3CR of terpene isocyanide **27**, acetaldehyde and α-methyl L -glutamate **23** produced an intractable tarry reaction products and none of the desired **33** was detected by ^{1}H NMR and TLC analysis of the crude products. One of the isolable and identified by-products was **32**, which presumably arose via the Passerini reaction of isocyanide **27** with acetaldehyde followed by the Cannizzaro reaction.



Scheme 12. Unsuccessful U-4C-3CR for the synthesis of despiro analogues of boneratamides B and C

The stepwise U-5C-4CR approach was then employed to synthesize despiro analogues of boneratamides B and C **33** (Scheme 13). In this route, reaction of the terpene isocyanide **27** using conditions similar to

those described in Scheme 11 afforded an inseparable mixture of the products **34** in 28% yield. Heating a solution of this mixture **34** in refluxing toluene facilitated cyclization to form a 3:2 mixture of γ-lactams **33a** and **33b** in 80% yield. Repeated chromatographic separations gave isomer **33a** as a crystalline substance. X-Ray crystallographic analysis confirmed the structure of **33a** and the newly formed stereocenter corresponding to the C18 positions of boneratamides B and C was assigned to be *R* configuration.



Scheme 13. Synthesis of despiro analogues of boneratamides B and C

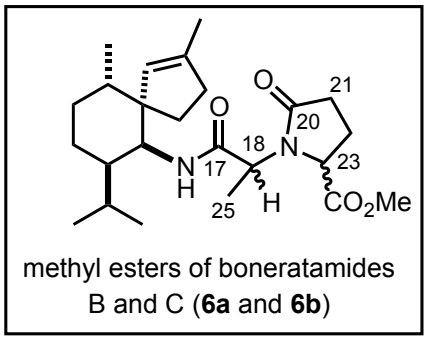
The comparison of the NMR data of **33a** and **33b** with those of natural boneratamide B and C methyl esters is summarized in Table 2. The ^{1}H and ^{13}C NMR data for the methyl esters of boneratamides B and C were found to compare favourably with those of the despiro analogues **33a** and **33b**. However, characteristic resonances that would enable differentiation of boneratamides B and C as well as **33a** and **33b** were not present in the spectra. Although the assignment of the configurations to the C18 stereocenters in natural boneratamides B and C remains unclear, X-ray analysis of **33a** coupled with comparison of NMR data in Table 2 confirms the proposed structures of natural boneratamides B and C.

CONCLUSIONS

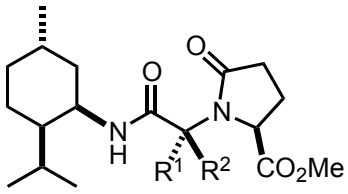
Motivated by the belief that 'molecules in nature obey the rules of organic chemistry and follow nonenzymatic mechanism',[15] the Ugi chemistry presumably carried out by marine organisms was explored on the bench in the laboratory. Our research endeavour along this line led to the synthesis of terpene-amino acid conjugates that have identical structural motifs found in exigurin and boneratamides A–C in a manner pertinent to our proposed biogenetic pathway. In particular, the synthesis of despiro

analogue of boneratamide A **28** showed remarkable efficiency to assemble multiple components in a one-pot process. The results of the current study shed light on a long-standing mystery relating to the biosynthetic origin of exigurin and boneratamides. The Ugi type reaction is not confined to the realm of organic synthesis, and it is now apparent that conjugation of terpenes with amino acids by the Ugi reaction is one of the Nature's strategies to expand the diversity of natural products.

Table 2. Selected ^{1}H and ^{13}C NMR data for boneratamide B and C methyl esters (**6a** and **6b**) and despiro analogues **33a** and **33b**



methyl esters of boneratamides B and C (**6a** and **6b**)



33a: R^1 = Me, R^2 = H
33b: R^1 = H, R^2 = Me

	^{13}C NMR (C_6D_6,125 MHz)			
	6a*	**6b***	**33a**	**33b**
17	170.2	170.0	170.5	169.6
18	53.3	53.5	52.2	52.6
20	175.6	175.9	175.7	176.0
23	58.8	58.1	59.2	58.0
24	173.4	172.4	174.0	172.4
25	14.1	14.4	15.3	14.2
OMe	51.9	52.0	52.2	52.1

	^{1}H NMR (C_6D_6, 500 MHz)			
	6a*	**6b***	**33a**	**33b**
NH	6.91 d, *J* = 10.8 Hz	7.20 d, *J* = 10.9 Hz	7.16 overlapped with C_6H_6	7.29 d, *J* = 10.9 Hz
18	4.46 q, *J* = 7.2 Hz	4.52 q, *J* = 7.3 Hz	4.61 q, *J* = 7.0 Hz	4.60 q, *J* =7.0 Hz
21	1.87 ddd, *J* = 16.6, 9.6, 2.4 Hz	1.84 ddd, *J* = 16.8, 9.6, 3.4 Hz	1.85 brdd, *J* = 16.5, 10.0 Hz	1.86 ddd, *J* = 16.5, 9.5, 3.5 Hz
21	2.26 m	2.27 m	2.24 dt, *J* = 16.5, 10.0 Hz	2.27 dq, *J* = 16.5, 9.5 Hz
23	4.11 dd, *J* = 9.5, 1.8 Hz	3.86 dd, *J* = 8.8, 2.8 Hz	4.37 brd, *J* = 10.0 Hz	4.49 dd, *J* = 8.0, 3.5 Hz
25	1.37 d, *J* = 7.2 Hz	1.34 d, *J* = 7.2 Hz	1.42 d, *J* = 7.0 Hz	1.26 d, *J* = 7.0 Hz
OMe	3.22 s	3.34 s	3.25 s	3.38 s

* NMR data of methyl esters of boneratamide B and C (**6a** and **6b**) are reproduced from the ref. 4.

EXPERIMENTAL

U-5C-4-CR for the synthesis of despiro-exigurin 18. To a solution of sarcosine (**10**) (135 mg, 1.51 mmol) in MeOH (20.0 mL) at room temperature was added aqueous formaldehyde (37%, 0.10 mL, 1.33 mmol). After stirring at 50 °C for 20 min, terpene isocyanide **15** (100 mg, 0.61 mmol) was added. The solution was stirred at 50 °C for 20 min, and concentrated under reduced pressure. The resulting residue was treated with water, and the aqueous layers were extracted with AcOEt (× 3). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue (131 mg) was subjected to silica gel chromatography (AcOEt/hexane 1:1, containing 1% isopropylamine) to afford methyl ester **18** (72 mg, 40%) as a colorless oil: $[\alpha]^{D}_{26}$ +22.3 (*c* 1.00, $CHCl_3$); IR (NaCl) ν_{max} 3473, 3352, 2950, 2922, 1747, 1679, 1517, 1457, 1199 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.86 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.91–1.16 (m, 6H), 1.22–1.35 (m, 1H), 1.38–1.52 (m, 1H), 1.75 (dt, *J* = 13.0, 3.0 Hz, 1H), 1.82–1.88 (m, 2H), 2.42 (s, 3H), 3.16 (s, 2H), 3.32 (s, 2H), 3.71 (s, 3H), 4.32 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.56 (brd, *J* = 9.0 Hz, 1H); ^1H NMR (C_6D_6, 500 MHz) δ 0.72–0.92 (m, 2H), 0.98 (dt, *J* = 13.0, 3.0 Hz, 1H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.18 (ddt, *J* = 17.0, 8.0, 3.0 Hz, 1H), 1.40–1.52 (m, 1H), 1.53–1.68 (m, 2H), 1.72 (brd, *J* = 13.0 Hz, 1H), 1.98–2.09 (m, 4H), 2.80 (d, *J* = 17.0 Hz, 1H), 2.82 (d, *J* = 17.0 Hz, 1H), 2.98 (d, *J* = 17.0 Hz, 1H), 3.01 (d, *J* = 14.0 Hz, 1H), 3.23 (s, 3H), 4.65 (dq, *J* = 13.0, 7.0 Hz, 1H), 7.59 (brd, *J* = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.6, 20.9, 22.2, 25.2, 26.7, 29.5, 34.7, 40.1, 43.1, 45.4, 46.2, 51.5, 58.4, 60.9, 169.1, 170.8; ^{13}C NMR (C_6D_6, 125 MHz) δ 21.0, 21.3, 22.6, 25.7, 27.1, 30.0, 35.3, 40.9, 43.0, 45.6, 46.8, 51.2, 58.3, 61.5, 168.5, 170.9. HRMS(ESI): *m/z* calcd for $C_{16}H_{30}N_2O_3Na$ $[M+Na]^+$ 321.2154, found 321.2155.

U-4C-3CR for the synthesis of despiro-boneratamide A 28. To a solution of L-glutamic acid 1-methyl ester (**23**) (219 mg, 1.36 mmol) and acetone (0.70 mL, 9.1 mmol) in MeOH (15.0 mL) was added isocyanide **27** (150 mg, 0.91 mmol). After stirring at room temperature for 1.5 h, the solution was heated at 50 °C for 3 days, followed by refluxing for 2 days. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in AcOEt and water. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic extracts were dried (Na_2SO_4) and concentrated to afford a residue, which was subjected to silica gel chromatography (AcOEt/hexane 1:1 to 4:1) to furnish γ-lactam **28** (222 mg, 67%): mp 139–140 °C (recrystallized from hexane); $[\alpha]_D^{25}$ –24.9 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max} 3370, 2950, 1731, 1664, 1528, 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.82–1.90 (m, 26H), 2.09 (m, 1H), 2.20 (dq, *J* = 13.2, 2.9 Hz, 1H), {2.37 (m)}, 3.15 (d, *J* = 13.2 Hz, 3H), 3.74 (ddd, *J* = 20.0, 9.7, 1.7 Hz, 1H), 4.71 (m, 1H), 7.50 (d, *J* = 9.2 Hz, 1H), {7.60 (d, *J* = 8.0 Hz)}; ^{13}C NMR (C_6D_6, 125 MHz) δ 21.1, (21.4), 21.6, (21.7), 22.9, (22.9), 23.4, (23.6), (24.4), 24.6, 25.3, (25.5), (25.8), 25.9, (27.1), 27.3, 29.8, (29.8), (30.0), 30.2, 35.6, (35.6), 40.5, (40.6), 46.4,

(46.6), 46.8, (47.0), (52.36), 52.45, 57.4, (57.8), 60.3, (60.5), (172.2), 172.4, 173.7, (174.2), (175.6), 176.1. HRMS(ESI): *m/z* calcd for $C_{20}H_{34}N_2O_4Na$ $[M+Na]^+$ 389.2416, found 389.2401; HRMS(ESI): m/z calcd for $C_{20}H_{34}N_2O_4K$ $[M+K]^+$ 405.2156, found 405.2155.

REFERENCES AND NOTES

1. To the best of our knowledge, exigurin is the first literature−emerged example of secondary metabolites produced through the Ugi reaction. a) M. M. Uy, S. Ohta, M. Yanai, E. Ohta, T. Hirata, and S. Ikegami, *Tetrahedron*, 2003, **59**, 731. For other natural products presumably derived from the Ugi reaction, see the references; b) E. Avilés and A. D. Rodríguez, *Org. Lett.,* 2010, **12**, 5290; c) S. Suto, N. Tanaka, J. Fromont, and J. Kobayashi, *Tetrahedron Lett*., 2011, **52**, 3470; d) N. Tanaka, S. Suto, H. Ishiyama, T. Kubota, A. Yamano, M. Shiro, J. Fromont, and J. Kobayashi, *Org. Lett*., 2012, **14**, 3498; e) N. Tanaka, S. Suto, M. Asai, T. Kusama, A. Takahashi-Nakaguchi, T. Gonoi, J. Fromont, and J. Kobayashi, *Heterocycles*, 2015, **90**, 173.
2. T. Okino, E. Yoshimura, H. Hirota, and N. Fusetani, *Tetrahedron*, 1996, **52**, 9447.
3. M. J. Garson and J. S. Simpson, *Nat. Prod. Rep*., 2004, **21**, 164.
4. D. E. Williams, B. O. Patrick, A. Tahir, R. Van Soest, M. Roberge, and R. J. Andersen, *J. Nat. Prod*., 2004, **67**, 1752.
5. This work has been communicated in preliminary form. See the reference, K. Saito, A. Nishimori, H. Kotsuki, K. Nakano, and Y. Ichikawa, *Synlett*, 2013, **24**, 757.
6. a) I. Ugi, *Angew. Chem., Int. Ed. Engl*., 1962, **1**, 8; b) I. Ugi, *Angew. Chem., Int. Ed. Engl*., 1982, **21**, 810.
7. I. Ugi and C. Steinbrückner, *Chem. Ber*., 1961, **94**, 2802.
8. C. Hulme and J. Dietrich, *Mol. Divers*., 2009, **13**, 195.
9. a) A. Demharter, W. Hörl, E. Herdtweck, and I. Ugi, *Angew. Chem., Int. Ed. Engl*., 1996, **35**, 173; b) I. Ugi, A. Demharter, W. Hörl, and T. Schmid, *Tetrahedron*, 1996, **52**, 11657.
10. a) A. Dömling and I. Ugi, *Angew. Chem. Int. Ed*., 2000, **39**, 3168; b) A. Dömling, *Chem. Rev*., 2006, **106**, 17.
11. S. Kłossowski, B. Wiraszka, S. Berłożecki, and R. Ostaszewski, *Org. Lett*., 2013, **15**, 566.
12. a) K. Saito, A. Nishimori, R. Mimura, K. Nakano, H. Kotsuki, T. Masuda, and Y. Ichikawa, *Eur. J. Org. Chem*., 2013, **2013**, 7041; b) R. Mimura, A. Kitamori, A. Ikeda, T. Masuda, K. Nakano, H. Kotsuki, and Y. Ichikawa, *Synthesis*, 2015, **47**, 3043.
13. B. Di Blasio, E. Fattorusso, S. Magno, L. Mayol, C. Pedone, C. Santacroce, and D. Sica, *Tetrahedron*, 1976, **32**, 473.
14. This terpene isocyanide **27** is an enantiomer of **15**. For the synthesis of **27**, see the SI.

15. This dogma is taken from the reference; B. Lowry, C. T. Walsh, and C. Khosla, *Synlett*, 2015, **26**, 1008.