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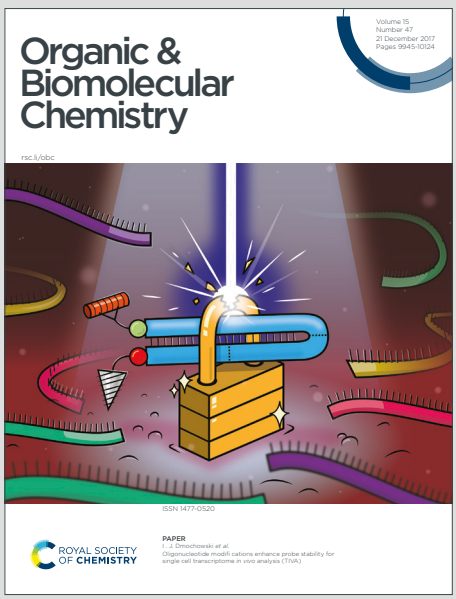

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ARTICLE

Total Synthesis of Exigurin: Ugi Reaction in a Hypothetical Biosynthesis of Natural Products

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Seijiro Hosokawa,*[a] Keisuke Nakanishi,[a] Yutaro Udagawa,[a] Mitsutoshi Maeda,[b] Seiya Sato,[b] Keiji Nakano,[b] Toshiya Masuda[c] and Yoshiyasu Ichikawa*[b]

The first total synthesis of a marine natural product exigurin has been accomplished in 13 steps starting from (+)-menthone. The key intermediate (–)-10-*epi*-axisonitrile-3 was prepared using stereoselective intramolecular cyclopropanation followed by cyclopropane ring opening reaction by azide anion. A bioinspired Ugi reaction of (–)-10-*epi*-axisonitrile-3, formaldehyde, sarcosine and methanol successfully constructed the target exigurin in which its terpene and amino acid units are linked through an amide bond.

Introduction

The marine world is characterized by countless numbers of unique organisms that produce an extraordinary abundance of structurally and functionally diverse secondary metabolites.[1] Consequently, marine organisms have continued to serve as sources for a wide variety of biologically active natural products, which are generated by unique biosynthetic pathways that are not present in land organisms.[2] With this ocean's blessing in mind, we have focused on two marine natural products, exigurin (**1**) and boneratamide A (**2**) (Fig. 1). Exigurin (**1**) was isolated in 2003 by Ohta and Ikegami from the marine sponge *Geodia exigua* collected in Oshima island.[3] In the following year, Anderson and co-workers isolated boneratamide A (**2**) from the marine sponge *Axinyssa aplysinoides* collected in Indonesia.[4]

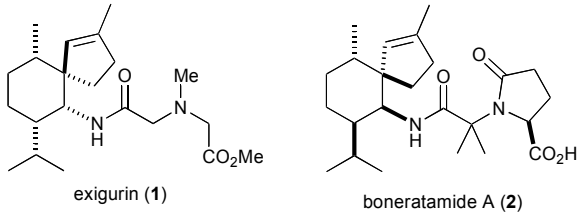

Figure 1 Structures of exigurin and boneratamide A

We were captivated by the unusual structures of exigurin (**1**) and boneratamide A (**2**), both of which contain terpene and amino acid units connected through an amide linkage. Of particularly interest is the fact that these terpene-amino acid conjugates possess a common imino-diacetic acid structural motif. This type of structural motif is found in products of the Ugi reaction,[5] which has found widespread use in both diversity and target-oriented organic synthesis.[6] This relationship led us to propose that exigurin and boneratamide A might be constructed in the marine sponges through hitherto unrecognized biosynthetic pathway that utilizes Ugi reactions (Scheme 1).[7] Specifically, exigurin (**1**) might originate from four building blocks including (–)-10-*epi*-axisonitrile-3 (**3**),[8] and the simple substances formaldehyde, sarcosine and methanol. Similarly, Ugi reaction between axisonitrile-3 (**4**),[9] acetone and glutamic acid could be the key step in the biosynthesis of boneratamide A (**2**). Although Rodriguez used the Ugi reaction to transform 8,15-diisocyano-11(20)-amphilectene to monamphilectine A,[10] the possibility that a Ugi type pathway is involved in the biosynthesis of exigurin and boneratamide A has been overlooked by the scientific community.[11]

[a] *Department of Applied Chemistry, Faculty of Advanced Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan, E-mail: seijiro@waseda.jp*
[b] *Faculty of Science, Kochi University, Akebono-cho, Kochi 780-8520, Japan, E-mail: ichikawa@kochi-u.ac.jp*
[c] *Graduate School of Human Life Science, Osaka City University, Osaka 558−8585, Japan.*

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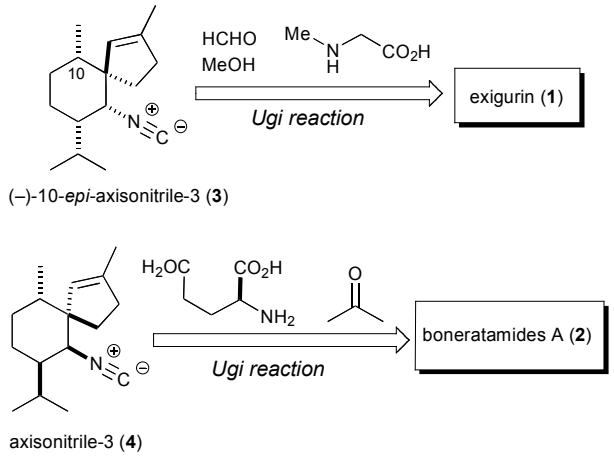
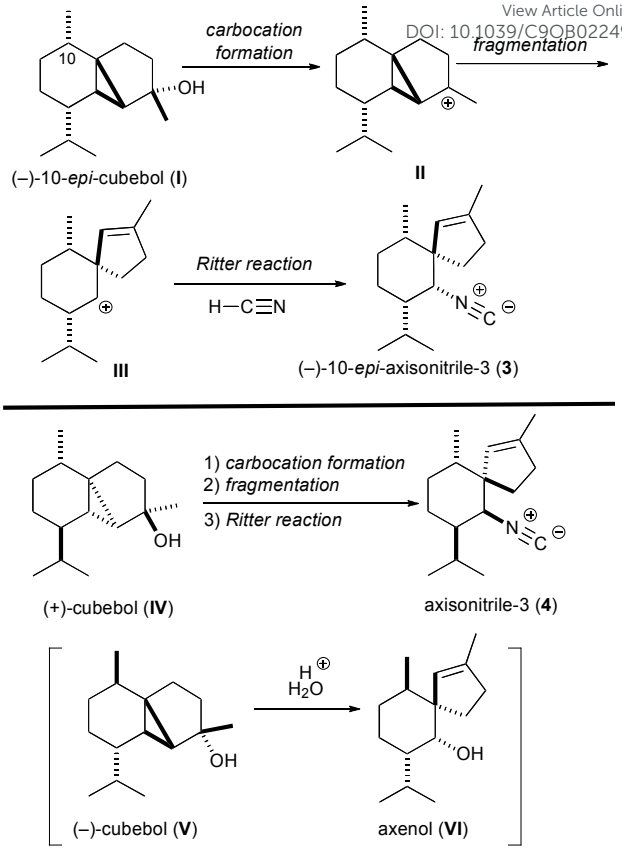


Scheme 1 Presumed biosyntheses of exigurin and boneratamide A from marine terpene isocyanides



Scheme 2 Hypothetical biosynthesis of (–)-10-*epi*-axisonitrile-3 and axisonitrile-3

In order to assess the feasibility of the hypothesis described above and to generate sufficient quantities for biological studies, we designed a research project aimed at the total synthesis of exigurin (**1**) and boneratamide A (**2**). The initial stage of this project focused on the synthesis of (–)-10-*epi*-axisonitrile-3 (**3**) and axisonitrile-3 (**4**), which would serve as substrates in the hypothetical Ugi reactions. The recent report on the synthesis of exiguamide, a precursor of (–)-10-*epi*-axisonitrile-3 (**3**), by Watanabe and Takikawa[12] prompted us to present the results of the preliminary phase of our investigation, which resulted in the synthesis of (–)-10-*epi*-axisonitrile-3 (**3**), a key intermediate for axisonitrile-3 (**4**) and total synthesis of exigurin (**1**).

Results and discussion

Our plan for the synthesis of (–)-10-*epi*-axisonitrile-3 (**3**) and axisonitrile-3 (**4**) was guided by a consideration of the hypothetical biosynthetic routes depicted in Scheme 2. In the case of (–)-10-*epi*-axisonitrile-3 (**3**), ionization of (–)-10-*epi*-cubebol (**I**) would form the cyclopropylcarbinyl cation **II**, which upon cyclopropane ring opening would produce homoallylic carbocation **III**. Cyanide promoted Ritter reaction of **III** would then generate the (–)-10-*epi*-axisonitrile-3 (**3**).[13a,b] A similar reaction sequence applied to (+)-cubebol (**IV**) would generate axisonitrile-3 (**4**). These hypothetical biosynthetic pathways are supported by the report of De Rosa and his co-workers, who isolated (–)-cubebol (**V**) and axenol (**VI**) from the marine alga T*aonia atomaria* and proposed that they are biosynthetically related via solvolytic conversion of **V** to **VI**.[13c]

Guided by the hypothetical biosynthesis shown in Scheme 2, we formulated a retrosynthetic analysis of (–)-10-*epi*-axisonitrile-3 (**3**) and axisonitrile-3 (**4**) (Scheme 3). When we could take advantage for introducing a nitrogen substituent using the Ritter reaction for the synthesis of (–)-10-*epi*-axisonitrile-3 (**3**), we could utilize cyclopropyl ketone **I** as a precursor to generate carbocation for the Ritter reaction. Moreover, cyclopropyl ketone **I** would be derived by intramolecular cyclopropanation of α-diazoketone **II**, which would be produced from a simple terpene building block (+)-menthone (**5**). Similarly, retrosynthetic analysis of axisonitrile-3 (**4**) may lead to cyclopropyl ketone **III** and α-diazoketone **IV** which would be derived from a common starting material, (+)-menthone (**5**).

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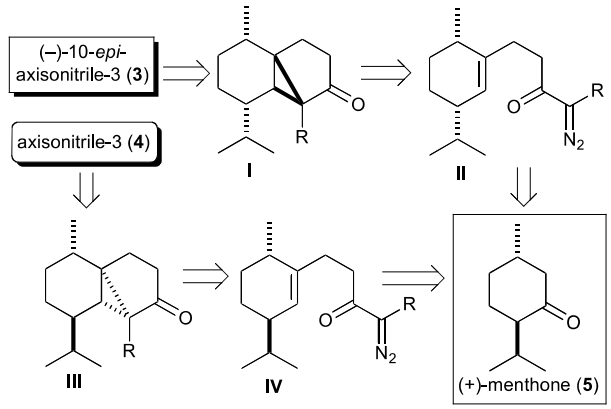
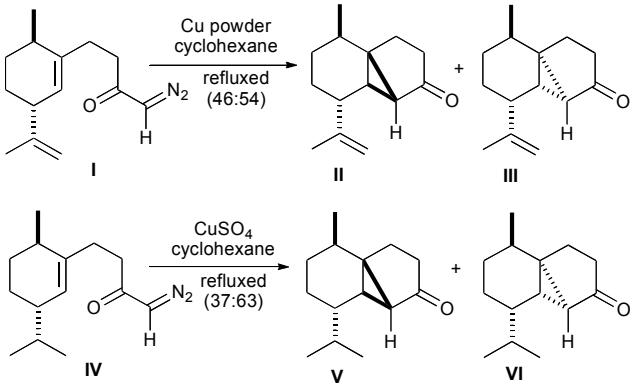


Scheme 3 Retrosynthetic analysis of (–)-10-*epi*-axisonitrile-3 and axisonitrile-3

Given the retrosynthesis outlined in Scheme 3, one challenging aspect of an approach to the synthesis of (–)-10-*epi*-axisonitrile-3 (**3**) and axisonitrile-3 (**4**) is stereocontrol in the intramolecular cyclopropanation reactions of α-diazoketones **II** and **IV** (Scheme 3).[14] A literature survey revealed that a similar intramolecular cyclopropanation used by Yoshikoshi in the synthesis of (–)-cubebol (**I** → **II** and **III**, Scheme 4)[15] produced an approximately 1:1 mixture of cyclopropanation products. Likewise, Piers reported cyclopropanation of α-diazoketone **IV** in the synthesis of β-cubebene.[16] In this case, the diastereo-facial selectivity in cyclopropanation was poor in favour of undesired diastereomer **VI**. In analysing these previous observations, we reasoned that the observed low degrees of stereoselectivity might be a consequence of the fact that α-diazoketones **I** and **IV** both possess sterically small hydrogen atoms at their α-positions. We surmised that introduction of a more sterically bulky substituent at the diazoketone α-position could increase steric repulsive interactions between diazoketone moiety and isopropyl group in the transition state of cyclopropanation, leading to improved facial selectivity.



Scheme 4 Previous works of related intramolecular cyclopropanation

The analysis of the previous works led us to select the β-keto sulfones **6** and **7** as key intermediates for the synthesis of (–)-10-*epi*-axisonitrile-3 and axisonitrile-3 (Figure 2). We expected that bulky phenyl sulfonyl group would be placed on the cyclohexene ring in a transition state of cyclopropanation, which would cause enhanced steric interaction between phenyl sulfonyl group and isopropyl group. As a result, the intramolecular cyclopropanation reaction would occur on the more sterically accessible cyclohexene face anti to the isopropyl group. Furthermore, a higher selectivity of **6** for cyclopropanation than that of **7** would be expected, because the phenyl sulfonyl group in **6** would be strongly influenced by the pseudo-axial methyl group on C(10) in the transition state for cyclopropanation. In addition to introducing steric bulk, we expected that the phenyl sulfonyl group would facilitate diazo group transfer to the α-methylene positions of **6** and **7**. With these analyses in mind, we focused attention on the synthesis of β-keto sulfones **6** and **7** and their diazo transfer-intramolecular cyclopropanation sequences.

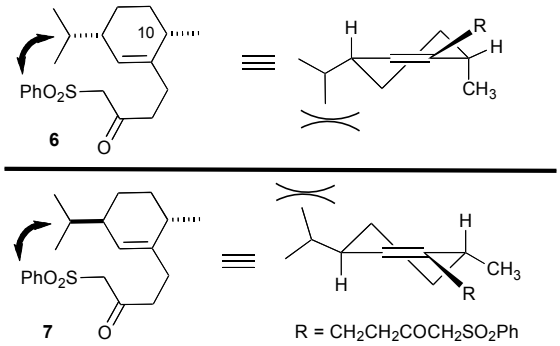
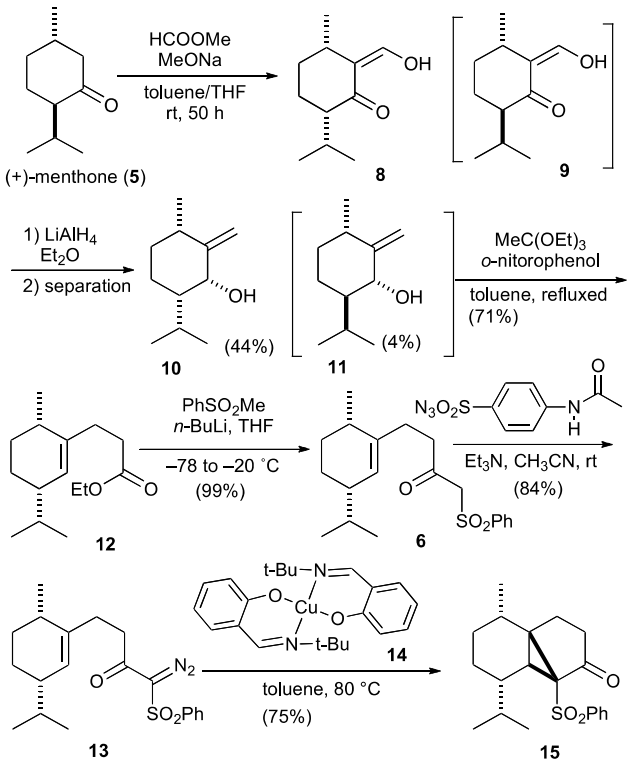


Figure 2 Candidates for intramolecular cyclopropanation precursors

The synthesis of β-keto sulfone **6** and its intramolecular cyclopropanation for the synthesis of (–)-10-*epi*-axisonitrile-3 are outlined in Scheme 5. Following the procedure reported by Hodgson,[17] allyl alcohol **10** was prepared from (+)-menthone (**5**). Accordingly, formylation of **5** with methyl formate and sodium methoxide, accompanied by epimerization of the isopropyl group-substituted stereogenic center, produced an inseparable 93:7 mixture of hydroxymethylene ketones **8** and **9**. Reduction of this mixture with lithium aluminum hydride (LAH) in ether followed by chromatographic separation afforded allyl alcohols **10** and **11** in respective 44% and 4% yields from (+)-menthone (**5**). This LAH reduction presumably occurred via a sequence involving (i) hydride addition to deprotonated exocyclic olefin, (ii) β-

elimination of aluminum-complexed oxygen from the formed ketone enolate, and (iii) reduction of the resulting enone.[18] Johnson-Claisen rearrangement of **10** was effected by heating with triethyl orthoacetate in toluene in the presence of *o*-nitrophenol to furnish γ,δ-unsaturated ester **12** in 71% yield.[19] Treatment of methyl phenyl sulfone with *n*-butyllithium generated (phenylsulfonyl)methyl lithium, which reacted with ester **12** to afford β-keto sulfone **6** in excellent yield.[20] Subsequent diazo transfer was accomplished by treatment of **6** with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and triethylamine to provide the cyclopropanation substrate **13** in 84% yield.[21] Pleasingly, heating a toluene solution of α-diazo-β-keto sulfone **13** in the presence of copper (II) *N*-(*tert*-butyl)salicylaldimine (**14**)[22] at 80 °C resulted in formation of cyclopropyl ketone **15** as a single diastereomer in 75% yield.



Scheme 5 Preparation of cyclopropyl ketone intermediate in the synthesis of (–)-10-*epi*-axisonitrile-3

The structure of cyclopropyl ketone **15** was established by using X-ray crystallographic method (Figure 3). Analysis of the crystal structure shows that the right-hand cyclohexane ring in **15** exists in a boat conformation, which avoids an unfavorable axial orientation of C(10) methyl group in a chair conformation.

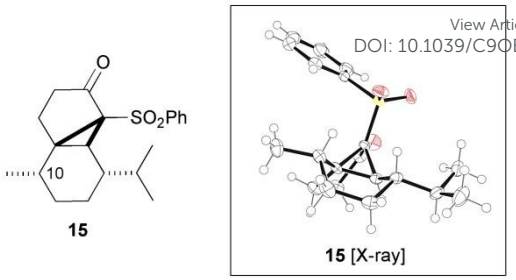


Figure 3 X-ray crystallographic analysis of **15**

Preparation of the cyclopropyl ketone intermediate required for the synthesis of axisonitrile-3 started with kinetic formylation of (+)-menthone (**5**) previously reported by Hodgson[17a,23] (Scheme 6). Deprotonation of **5** with lithium diisopropyl amide (LDA) in THF at –78 °C, followed by treatment with 2,2,2-trifluoroethyl formate produced hydroxymethylene ketone **9**, which was then reduced with LAH to afford allyl alcohol **11**. Although the yield of this two step sequence was low especially when performed on a large-scale (15%), the process produced **11** without altering the configuration of the isopropyl group-substituted stereogenic center. Following the same sequence of reactions depicted in Scheme 5, allyl alcohol **11** was transformed into α-diazo-β-ketosulfone **17**. Intramolecular cyclopropanation of **17** using catalyst **14** was carried out under conditions similar to those employed to convert **13** into **15**. Disappointingly, this cyclopropanation produced a mixture of multiple substances from which the desired product **19** was obtained in only 17% yield. In an effort to improve yields of cyclopropanation process, we attempted to optimize the copper catalyst by replacement of alkyl groups on the imines and introduction of substituents on the *para*-position in benzene rings.[24] After considerable experimentation, we found that the catalyst **18** (R^1 = CH_3, R^2 = F) gave the most promising results. In the event, cyclopropanation of **17** using the catalyst **18** afforded cyclopropyl ketone **19** in 47% yield. The structure of **19** was unambiguously determined by X-ray crystallographic analysis. Pleasingly, the intramolecular cyclopropanation of **17** occurred from the opposite side to the isopropyl group to install the desired stereochemistry.

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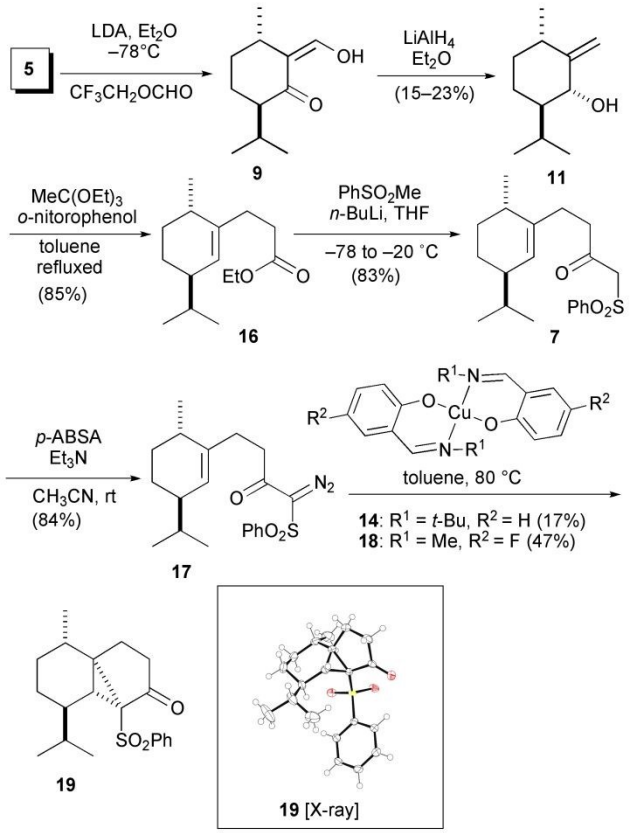
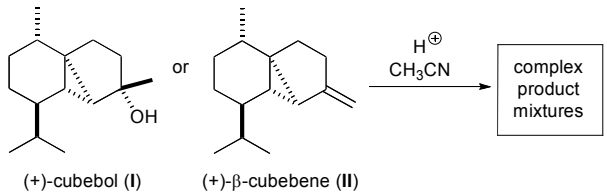


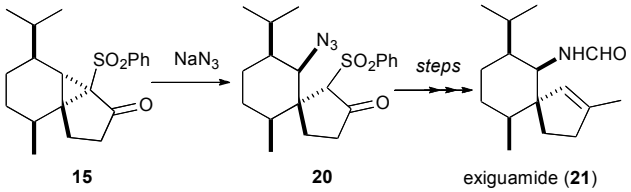
Scheme 6 Preparation of cyclopropyl ketone intermediate for the synthesis of axisonitrile-3

In a study that paralleled the synthesis of cyclopropyl ketone intermediates **15** and **19**, we investigated the feasibility of the key Ritter reaction in the hypothetical biosynthetic routes depicted in Scheme 2. For this purpose, we chose (+)-cubebol (**I**) and (+)-β-cubebene (**II**) as substrates (Scheme 7), because they are ideal for testing the hypothesis of De Rosa. Moreover, (+)-cubebol (**I**) and (+)-β-cubebene (**II**) can be readily prepared from D-carvone using routes reported by Fehr[25] and Fürstner.[26] Disappointingly, we observed that Ritter reactions of both (+)-cubebol (**I**) and (+)-β-cubebene (**II**) with acetonitrile produced complex product mixtures,[27] and not even trace amounts of the Ritter reaction products.



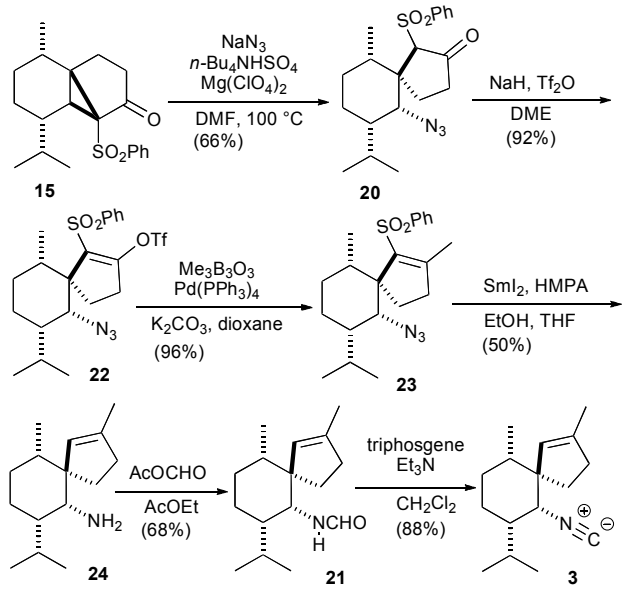
Scheme 7 Unsuccessful Ritter reaction

During our studies of the Ritter reaction, a preliminary report of the synthesis of exiguamide (**21**) was reported by Watanabe and his coworkers (Scheme 8).[28] To our surprise, Watanabe's group used cyclopropyl ketone **15** as an intermediate in their synthetic route. Moreover, Watanabe's initial plan for the synthesis of exiguamide was based on cyclopropane ring opening process using Ritter reaction. As in our approach, this process proved to be unsuccessful. This led Watanabe to implement a revised synthetic plan employing azide anion promoted cyclopropane ring opening.[29] Owing to our observations and the lack of success encountered by Watanabe, we decided to abandon the Ritter reaction approach and to use cyclopropane ring opening reaction of **15** with azide anion.



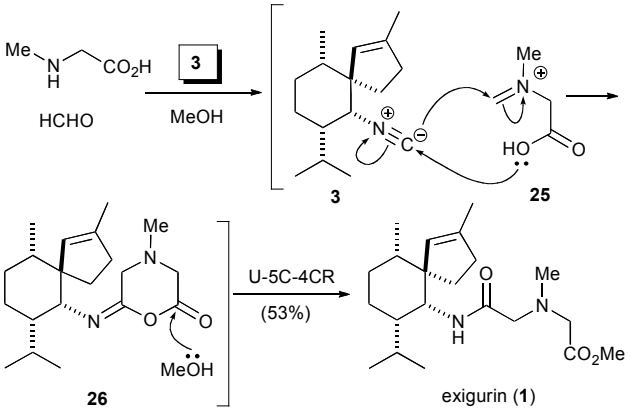
Scheme 8 A preliminary report for the synthesis of exiguamide by Watanabe group

The route for our synthesis of (–)-10-epi-axisonitrile-3 (**3**) via exiguamide (**21**) starting from cyclopropyl ketone **15** is given in Scheme 9. Initial attempts of the doubly activated cyclopropane ring opening reaction of **15** with azide anion (NaN_3) in a variety of solvents (HMPA, DMPU or DMF) under thermal conditions (around 100 °C) gave none of the desired product.[30] However, we found that when conditions described by Melnikov (NaN_3, $Et_3N \cdot HCl$, DMF, 100 °C) were utilized, **15** was transformed to ring opened adduct **20** albeit in only 30% yield.[31] Encouraged by this result, we screened Lewis acid additives and found that reaction of **15** in the presence of magnesium perchlorate in DMF at 100 °C produced **20** in 28% yield.[32] Further improvement using a combination of magnesium perchlorate and phase transfer catalyst (n-$Bu_4N \cdot HSO_4$) in DMF at 100 °C increased the yield of **20** up to 66%. Introduction of the methyl group and double bond to **20** was achieved in two steps involving triflation of ketosulfone **20** with triflic anhydride and sodium hydride, followed by palladium-catalyzed Suzuki-Miyaura coupling of the resulting vinyl triflate **22** employing trimethylboroxine.[33] These processes formed **23** in 88% yield over two steps. Treatment of **23** with samarium diiodide in the presence of HMPA and ethanol caused removal of sulfonyl group and concurrent azide reduction to afford amine **24**.[34] Formylation of amine **24** with acetic formic anhydride provided exiguamide (**21**) in 34% yield over two steps. Finally, dehydration of **21** with triphosgene in the presence of triethylamine gave rise to (–)-10-*epi*-axisonitrile-3 (**3**) in 88% yield.[35]



Scheme 9 Synthesis of exiguamide and (–)-10-*epi*-axisonitrile-3

With (–)-10-*epi*-axisonitrile-3 (**3**) in hand, the stage was now set to carry out bioinspired Ugi five-centre four-component reaction (U-5C-4CR) leading to exigurin (**1**) (Scheme 10).[36] In the event, a solution of sarcosine and formaldehyde in methanol at 50 °C was treated with (–)-10-*epi*-axisonitrile-3 (**3**). After stirring the reaction mixture at 50 °C for 20 minutes, exigurin (**1**) was isolated in 53% yield after chromatographic purification. The probable reaction mechanism of the U-5C-4CR started with condensation of sarcosine with formaldehyde to form the corresponding iminium ion **25**. After addition of (–)-10-*epi*-axisonitrile-3 (**3**) to **25**, cyclic *O*-acyl-imide **26** would form. Nucleophilic attack of methanol (fourth component) occurs at the carboxylic carbon (fifth reacting centre) in **26**. Subsequent six-membered ring opening reaction would lead to the formation of exigurin (**1**). Although the yield was modest, the multiple step sequence of U-5C-4CR took place in one-pot under mild reaction conditions to furnish exigurin (**1**).



Scheme 10 Total synthesis of exigurin through the U-5C-4CR

The ^{1}H and ^{13}C NMR spectra recorded on synthetic exigurin (**1**) were in full agreement with those reported for the natural product.[35] However, the specific rotation of the synthetic material ($[\alpha]_D^{25}$ = +24.3, *c* = 0.69, $CHCl_3$) differed in sign from that of natural exigurin ($[\alpha]_D^{24}$ = −32, *c* = 0.03, $CHCl_3$). Ohta and Ikegami reported that (–)-10-*epi*-axisonitrile-3 and exigurin were isolated from the same sponge and that natural (–)-10-*epi*-axisonitrile-3 has a negative specific rotation ($[\alpha]_D^{25}$ = −43.5, *c* = 0.64, $CHCl_3$), which is identical to that observed for our synthetic substance ($[\alpha]_D^{23}$ = −37.8, *c* = 0.75, $CHCl_3$). Considering the plausible biosynthesis of exigurin, the absolute configuration of natural and synthetic (–)-*10*-epi-axisonitrile-3 should be the same with that of natural exigurin. In addition, the reported characterization of natural exigurin was carried out using only microgram quantities (400 μg of exigurin from wet sponge in 0.0003% isolated yield). Thus, we speculate that the discrepancy between the specific rotation of synthetic and natural exigurin is a consequence of inaccuracies in measuring specific rotations with exceptionally small sample quantities.

Conclusions

In summary, we developed stereoselective intramolecular cyclopropanation for the preparation of key cyclopropyl ketone intermediates **15** and **19** for the synthesis of (–)-10-*epi*-axisonitrile-3 (**3**) and axisonitrile-3 (**4**) starting with a common starting material (+)-menthone (**5**). Further manipulation of cyclopropyl ketone intermediate **15** led to the successful synthesis of (–)-10-*epi*-axisonitrile-3 (**3**). Bioinspired U-5C-4CR employing (–)-10-*epi*-axisonitrile-3 (**3**), formaldehyde and sarcosine in methanol showed remarkable efficiency to assemble multicomponents in a one-pot process to establish the first total synthesis of exigurin (**1**) in 13 steps from (+)-menthone (**5**). The results of the current study shed light on a long-standing mystery relating to the biosynthetic origin of exigurin.[37] It is now apparent that the Ugi type reaction is not confined to the realm of organic synthesis and 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. Further studies on the synthesis of boneratamide A are under way in our laboratory.

Experimental

For full experimental procedures, spectroscopic and analytical data for all new compounds including copies of NMR spectra, see the ESI.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are most grateful to Professor Shinji Ohta (Hiroshima University) for kindly providing us with NMR spectra data of exiguamide (**21**), (–)-10-*epi*-axisonitrile-3 (**3**) and exigurin (**1**). The Materials Characterization Central Laboratory at Waseda University is gratefully acknowledged for X-ray analysis. We acknowledge the financial support provided by a Grant-in-Aid for Scientific Research (C) (16K01916) from MEXT.

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