Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Studies on Aculeines: Synthetic Strategy to the Fully Protected Protoaculeine B, the *N*-Terminal Amino Acid of Aculeine B

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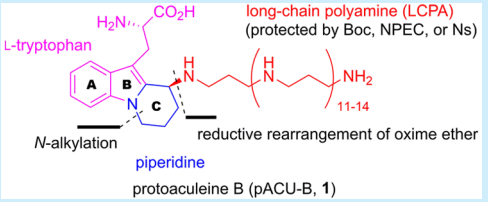
Supporting Information

ABSTRACT: A synthetic strategy for accessing protoaculeine B (**1**), the *N*-terminal amino acid of the highly modified peptide toxin aculeine, was developed via the synthesis of the fully protected natural homologue of **1** with a 12-mer poly(propanediamine). The synthesis of mono(propanediamine) analog **2**, as well as core amino acid **3**, was demonstrated by this strategy. New amino acid **3** induced convulsions in mice; however, compound **2** showed no such activity.



Aculeines (ACUs, Figure 1) are modified peptide toxins isolated from the marine sponge *Axinyssa aculeata*

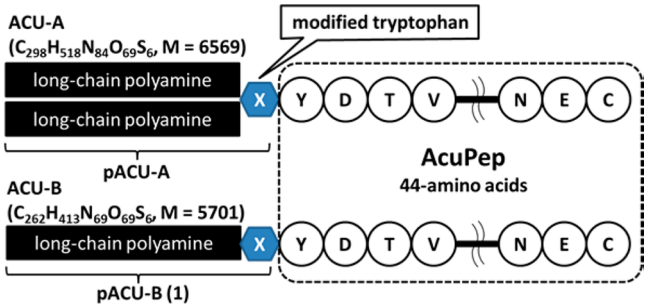
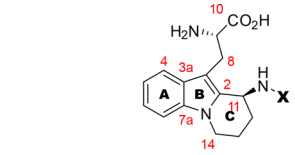


Figure 1. Schematic structures of ACU-A, ACU-B, and the *N*-terminal residues pACU-A and pACU-B (**1**).[1,2]

collected in Iriomote, Japan.[1] To date, three ACUs (A−C) have been isolated as the principle toxic compounds in the sponge.[1] ACU-A and ACU-B are comprised of a common 44-amino acid ribosomal peptide, AcuPep, conjugated with highly modified protoaculeine residues on their *N*-termini.

Protoaculeine B (pACU-B, **1**, Figures 1 and 2) was isolated from the same sponge in its free form and was readily identified as an *N*-terminal amino acid derivative of ACU-B.[2] Structurally, **1** is composed of a tryptophan-derived heterotricycle and a long-chain polyamine (LCPA) that is a linearly extended 14-mer of 1,3-propanediamine. ACUs are the first example of peptides that are post-translationally modified by polyamine; the exception to this is silaffin,[3] which is a silica-depositing protein bearing LCPA-modified lysine residues that was found in the silica skeleton of a diatom.

ACUs are toxic to various mammalian cells and show pro-convulsant activity in mice. Interestingly, the mechanism of these discrete actions stems from their ability to disrupt cell



	X
protoaculeine B (pACU-B, **1**)	11-14 long-chain polyamine (LCPA) (14-mer as the major component)
mono(propanediamine) analog **2**	NH_2
desLCPA analog **3**	H

Figure 2. Protoaculeine B (**1**) and the artificial partial structures **2** and **3**.

membranes[1] through the unique interaction between ACUs and the plasma membrane; for example, ACU-A lysed erythrocytes with greater potency than sodium dodecyl sulfate (SDS), but its efficacy was less than 80% of that of the detergent.[1] This "partial" action of ACU-A suggested that the membrane disruption by ACU-A was partly reversible; yet, its detailed mechanism of action is yet to be determined.

Recently, independent of this study, LCPA was reported to interact with lipid bilayers to form three-dimensional stacks on the surface of artificial lipid membranes, but the stack formation depended on the number of polyamine units in the LCPA.[4] This observation suggests the possibility that the LCPA moiety

Received: April 27, 2018

DOI: 10.1021/acs.orglett.8b01331
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in the ACUs also plays a significant role in the unique interactions between ACUs and cell membranes. Natural ACUs, however, were obtained as an inseparable mixture of homologues with different LCPA lengths.[1] Thus, it has been difficult to examine the above hypothesis using pure, structurally defined compounds. Toward our ultimate goal of a chemical synthesis of ACUs, various analogues, and model compounds, herein, we developed a synthetic strategy for accessing pACUs via the preparation of the fully protected minor homologue of **1**. We also discuss the bioactivity of the unprotected core amino acid with mono(propanediamine) **2** and desLCPA analog **3**.

Retrosynthetically, **1** can be prepared from two fragments, heterotricyclic *N*-Ns amine fragment **A** and hydroxylated LCPA fragment **B**, which were expected to be assembled by a Mitsunobu reaction (Figure 3). First, we synthesized mono-

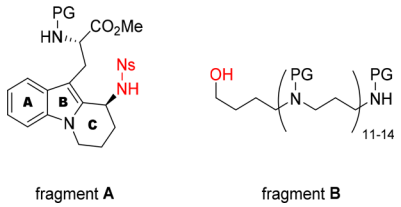
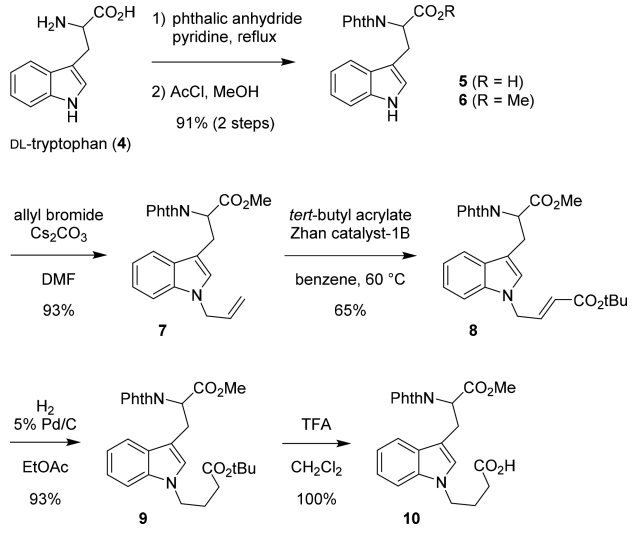


Figure 3. Key fragments for our synthesis of pACU-B (**1**). PG = protecting group.

(propanediamine) analog **2** in racemic form via fragment **A**, featuring the stereoselective introduction of the C11-amino group via an oxime. Then, we conducted an iterative synthesis of poly(propanediamine) toward fragment **B** employing our new strategy of using a photoremovable 1-(2-nitrophenyl)-ethoxycarbonyl (NPEC) group for the temporary protection of the amines. From fragments **A** and **B**, fully protected pACU-B **31** with the 12-mer polyamine was finally synthesized, and the utility of our strategy for incorporating various polyamine side chains into the desired amino acid is demonstrated, as follows.

First, we prepared phthalimide (Phth)-protected tryptophan derivative **5**, which was esterified to provide **6** in 91% yield (Scheme 1).[5] *N*-Allylation of **6** with allyl bromide and Cs_2CO_3 afforded **7** in 93% yield.[6] It should be noted that complete

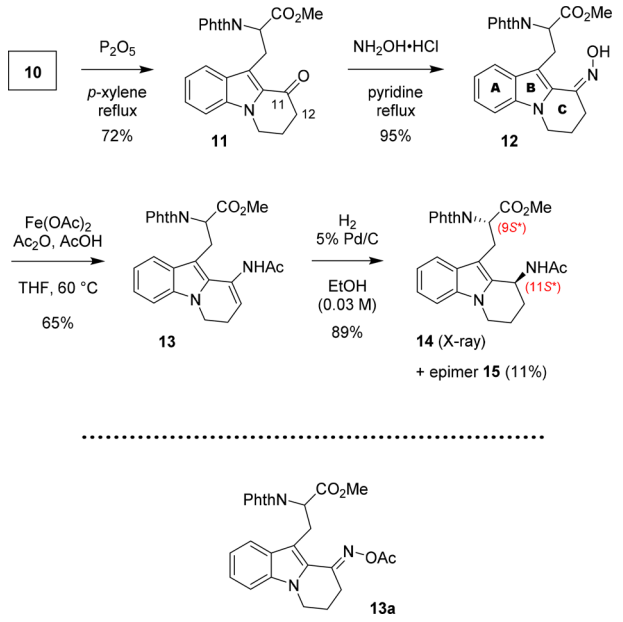
Scheme 1. Homologation of the C-Ring Carbon Chain



racemization was observed here, when the synthesis started with L-tryptophan. However, an enantioselective synthesis using this route would be possible starting from L-tryptophanol, and this is currently underway.[7] Homologation of the C-ring carbon chain by cross metathesis of **7** with *tert*-butyl acrylate mediated by Zhan catalyst-1B[8] gave α,β-unsaturated ester **8** in 65% yield. Regioselective hydrogenation of **8** (H_2, 5% Pd/C) afforded **9**, which was then treated with TFA to quantitatively form carboxylic acid **10**.

With carboxylic acid **10** in hand, a Friedel–Crafts-type cyclization was attempted for the construction of the C-ring (Scheme 2). Because *O*-acylphosphoric acid is known to be a

Scheme 2. Formation of the C-Ring and Stereoselective Elaboration of the (11*S)-Amino Group**



suitable intermediate when an indole derivative is used as the substrate,[9] we first used polyphosphoric acid, which gave ketone **11** in 25% yield at 90 °C; however, the yield was dramatically improved to 72% when P_2O_5 was employed in *p*-xylene at reflux.[10] The structure of **11** was confirmed using NMR spectroscopy. To introduce a nitrogen-containing functional group at the C11 position on the C-ring, we first examined an Ir-catalyzed reductive amination;[11] however, this strategy only induced elimination across C11–C12 of **11**. After several trials, a multistep sequence via an oxime was found to be the most practical strategy. Thus, ketone **11** was reacted with $NH_2OH{\cdot}HCl$ in pyridine to provide oxime **12** in excellent yield (95%), which was then converted to *N*-Ac enamide **13**. In this transformation, following the report by Tang,[12] $Fe(OAc)_2$ and Ac_2O gave desired acetamide **13** in a satisfactory yield (65%) accompanied by oxime *O*-acetate **13a** (14%, see Scheme 2) and ketone **11** (5%). Since enamide **13** was unstable even in $CDCl_3$, ketone **11** would have been generated by acidic hydrolysis of **13**. It was also found that oxime *O*-acetate **13a** is an intermediate, since it was converted to *N*-Ac enamide **13** in 53% yield upon exposure to the same reaction conditions used for the conversion of **12** to **13** ($Fe(OAc)_2$, Ac_2O, AcOH, THF, 60 °C). A related observation has been reported by Bonderoff et al.[13]

DOI: 10.1021/acs.orglett.8b01331
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Next, we attempted the regio- and stereoselective hydrogenation of enamide **13** (Scheme 2). Due to the poor solubility of **13** in EtOH, the reaction was conducted under dilute conditions (0.03 M), and gratifyingly, the desired (9*S**,11*S**) isomer of **14** was obtained as the major product (89% yield) along with the (9*S**,11*R**) diastereomer of **15** (11%). The stereochemistry of **14** was determined by single-crystal X-ray analysis (Figure 4). The stereoselectivity is apparently

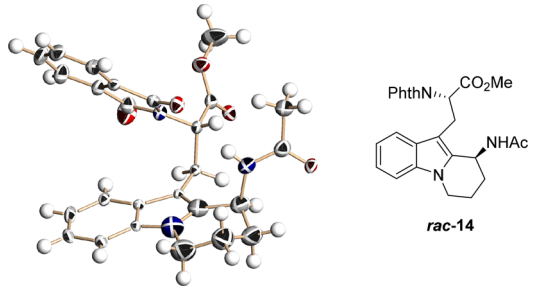


Figure 4. ORTEP drawing of conformer **A** of *rac*-**14** with the ellipsoids obtained from single-crystal X-ray diffraction measurements at 183 K drawn at the 50% probability level.

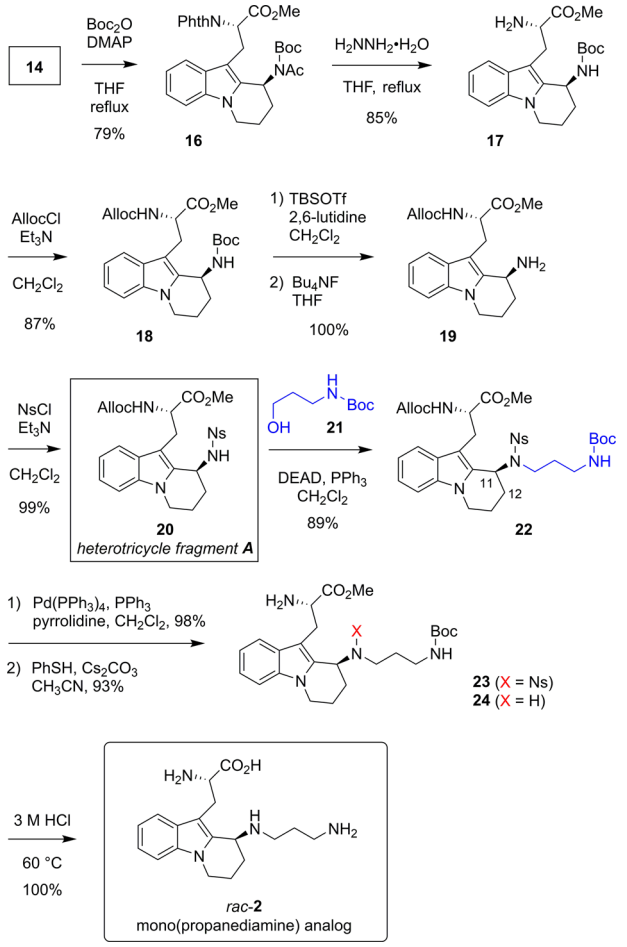
controlled by the chiral center in the amino acid side chain through remote asymmetric induction. In fact, the crystal structure of product **14** (Figure 4) shows that the upper face is sterically shielded by the Phth group. Thus, the hydrogen atoms on the catalyst surface might only have approached from the α-face of **13** during the hydrogenation.

With fully functionalized heterotricycle **14** in hand, some protecting group manipulations were carried out in a stepwise manner to prepare *N*-Ns amine **20** (Scheme 3), key heterotricyclic fragment **A**. First, a Boc group was introduced onto the acetamide (Boc_2O, DMAP, THF, reflux) to give imide **16** in 79% yield, which was then treated with $H_2NNH_2{\cdot}H_2O$ in refluxing THF to induce simultaneous removal of the Phth[14] and Ac[15] groups, furnishing amine **17** in 85% yield. Then, amine **17** was transformed into *N*-Ns amine **20**. Thus, after protection of amine **17** with an Alloc group (AllocCl, Et_3N), the Boc group was removed by Ohfune's two-step procedure[16] to give amine **19** (100% over two steps), and **19** was immediately reprotected with NsCl to furnish desired *N*-Ns amine **20** in 99% yield.

As we planned to employ a Mitsunobu reaction for the coupling of the key fragments (Figure 3),[17] the applicability of this strategy was tested by synthesizing mono(propanediamine) analog **2** from *N*-Ns amine **20** and alcohol **21**[18] (Scheme 3). Although we expected the coupling at such a sterically crowded *N*-Ns amine to be difficult, the reaction proceeded quite smoothly by using DEAD and PPh_3 in CH_2Cl_2, and **22** was generated in 89% yield in 1 h. Coupling product **22** was found to be stable, and no competing side reactions such as elimination across the C11−C12 bond were observed. Finally, fully protected pACU-B analog **22** with a mono(propanediamine) chain was subjected to sequential deprotection of the Alloc group by Pd(0),[19] Ns group by thiophenoxide,[17b] and Boc group and methyl ester by acidic hydrolysis to furnish *rac*-**2** in 91% yield over three steps. The overall yield was 9.5% for 20 total steps. desLCPA analog *rac*-**3** was also synthesized from **17** by acidic hydrolysis (see Figure 2 and the Supporting Information (SI)).

Then, we turned our attention to LCPA fragment **B** (see Figure 3),[20] and we began our synthesis with the preparation of

Scheme 3. Synthesis of the Mono(propanediamine) Analog 2



the 12-mer polyamine with 11 Ns groups by the Ns strategy.[17b,21] Unfortunately, the protected polyamine was found to be insoluble in most generally used organic solvents except for DMF and pyridine.[22] We thus sought to reduce the number of the Ns groups to improve the solubility. The synthesis of the 12-mer polyamine **29** with four Ns groups by our new strategy,[23] which utilizes two persistent (Boc, Ns) and one temporary (NPEC)[24] protecting groups on the amines, is shown in Scheme 4. Here, 3-mer polyamine **25** was designed as the key building block for the iterative synthesis of 12-mer polyamine **29**, and **25** was prepared from 1,3-propanediamine over five steps (see the SI). Photoirradiation of *N*-NPEC-*N*-Ns amine **25** by a high-pressure Hg lamp (MeOH, 0 °C, 10 min) provided *N*-Ns amine **26** in 94% yield without decomposition of the Ns group. On the other hand, **25** was also converted to alcohol **27** in 88% yield by the selective deprotection of the Tr group by exposure to 2,2,2-trifluoroethanol (TFE) at reflux. Mitsunobu coupling (DEAD, PPh_3, PhH) of *N*-Ns amine **26** and as-prepared alcohol **27** gave 6-mer polyamine **28** in 82% yield. 12-Mer polyamine **29** was synthesized similarly by the coupling of two 6-mers derived from **28** by repetition of the three-step sequence (split, deprotection, and coupling, see Scheme 4). As expected, as-prepared 12-mer polyamine **29** showed satisfactory solubility in organic solvents such as PhH, $CHCl_3$, and EtOAc. The overall yield for **29** was 2.3% over nine steps from 1,3-propanediamine.

DOI: 10.1021/acs.orglett.8b01331
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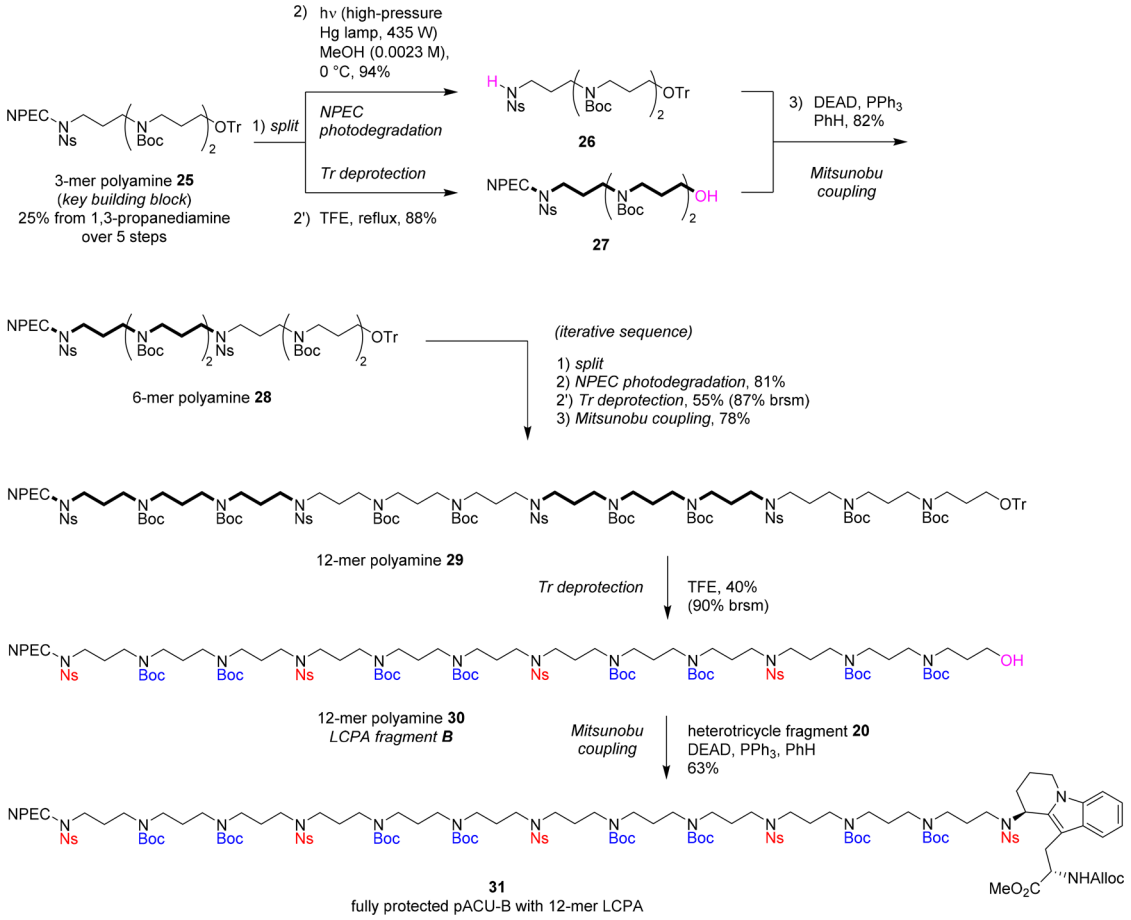
Scheme 4. Synthesis of Fully Protected pACU-B 31 with 12-mer LCPA



Finally, the coupling between heterotricyclic part **A** and long-chain portion **B** was conducted, as follows (Scheme 4). First, the Tr ether of **29** was cleaved with TFE to give alcohol **30** (90% brsm), which was then subjected to Mitsunobu coupling with *N*-Ns amine **20**. In the presence of excess DEAD (3 equiv), the reaction was complete in 3 h and furnished **31** in 63% yield as the fully protected conjugate of the modified tryptophan and 12-mer LCPA. Although pACU-B (**1**) was reported to bear 14-mer LCPA,[2] minor homologues with LCPA structures ranging from 12- to 15-mers were also observed (see the SI). Thus, 12-mer **31** synthesized herein can be regarded as the precursor to the natural form. Attempts toward the final deprotection in a stepwise manner are currently underway.

With unique amino acids **2** and **3** in their unprotected forms in hand, we tested their biological activities. Since ACUs exhibit potent convulsant activity in mice upon intracerebroventricular (i.c.v.) injection, **2** and **3** were administered (i.c.v.) at 50 μg/mouse. Interestingly, desLCPA analog **3** induced convulsions including myoclonic convulsions, while mono(propanediamine) analog **2** did not cause noticeable behavioral changes in the mice. Neither **2** nor **3** showed cytotoxicity or cell lysis activity in cultured tumor cells (HeLa cells) at 100 μg/mL, which suggests the importance of LCPA and/or AcuPep in interacting with the cell membrane. Introducing even a short polyamine unit onto desLCPA analog **3** can reduce the activity of **3**, which is consistent with our previous observation that **1** did not cause behavioral effects in mice. Since the behavioral activity observed in **3** has obviously no relation to the inherent cytotoxicity or the cell lysis activity of ACUs, detailed evaluation of the activity of **3** against neuronal receptors is in progress, and the results will be reported in due course.

In conclusion, we have developed pathways to synthesize fully protected pACU-B **31**, which is expected to pave the way for the large-scale synthesis of **1** in a structurally defined manner. The rapid synthesis of related compounds would be possible on a polymer support if an NPEC group is employed as a photocleavable linker.[25] The putative neuronal activity observed in *rac*-**3** may suggest its potential interaction with synaptic receptors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01331.

Detailed experimental procedures and analytical data for all new compounds (PDF)

Accession Codes

CCDC 1833350 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

DOI: 10.1021/acs.orglett.8b01331
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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was financially supported by a Grant-in-Aid for Scientific Research (15H04546 to R.S.) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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DOI: 10.1021/acs.orglett.8b01331
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