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Divergent total syntheses of kavaratamide A, B, and C

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The stereoselective total synthesis of kavaratamide A, a linear lipopeptide isolated from *Moorena bouillonii*, a marine cyanobacterium from Kavaratti, India, was successfully achieved using a simple and efficient method. The synthesis strategy uses a Reformatsky reaction to stereoselectively construct the (3*S*)-3-hydroxydecanoic acid (HDA) fragment, which is a key lipid component of the molecule. The peptide backbone was constructed *via* sequential Steglich esterification and amidation reactions to ensure high efficiency and selectivity. Furthermore, the total syntheses of kavaratamide B and C were also accomplished using a divergent total synthesis strategy, thereby demonstrating the versatility of this approach. The developed synthetic route provides access to these bioactive natural products in good yields and offers a platform for further medicinal chemistry investigations.

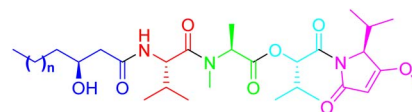
Introduction

Lipopeptides^{1,2} are unique natural products that comprise lipid and peptide moieties. They exhibit diverse biological properties, including antibacterial, antifungal, antiviral, anti-cancer, and immunomodulatory activities. Lipopeptides are synthesized by bacteria, fungi, and cyanobacteria *via* non-ribosomal peptide synthetase (NRPS) pathways.³ Their amphiphilic natures, which arise from their hydrophobic lipid tails and hydrophilic peptide backbones, enable them to interact with biological membranes; consequently, they are valuable drug-development candidates.

Marine-derived lipopeptides, especially those isolated from cyanobacteria, have gained significant attention owing to their complex structures and biologically active secondary metabolites.⁴ These compounds exhibit a diverse range of pharmacological properties, including potent cytotoxicities, as demonstrated by the activities of apratoxin A⁵ and the lyngbyabellins,⁶ columbamides,⁷ and ulongamides.⁸ Kavaratamide A is a linear lipopeptide isolated from *Moorena bouillonii*, a marine cyanobacterium collected from Kavaratti, India,⁹ and was discovered through global natural product social (GNPS) molecular networking combined with manual inspections of liquid chromatography-mass spectrometry (LC-MS) and liquid chromatography-diode array detector (LC-DAD) traces (Fig. 1). Kavaratamide A contains a rare isopropyl *O*-methylpyrrolinone (tetramic acid) moiety;¹⁰ to the best of our knowledge, this structural motif has only been previously reported in a few natural products, including the mirabimides from the

*Scytonema mirabile*¹¹ cyanobacterium, malyngamide X from the *Bursatella leachii*¹² sea hare, and iheyamide A from *Dapis* sp.¹³ cyanobacteria. Many marine-derived natural products that contain the tetramic acid scaffold have demonstrated significant pharmacological potential, including staphtotetrin (antibacterial), reutericyclin (antimicrobial), tenuazonic acid (anticancer and antiviral). In addition, the mirabimides, malyngamide X, and iheyamide A have been linked to cytotoxic and anti-parasitic activities. The structural and electronic properties of tetramic acid play significant roles in metal chelation, redox activity, and membrane permeability;¹⁴ consequently, it is a promising drug-discovery scaffold. Notably, the antitrypanosomal activities of the iheyamides A–C against *Trypanosoma brucei* (TB) *rhodesiense* suggest that the tetramic acid unit may function as a potential pharmacophore along with the peptide chain.¹⁵ Moreover, kavaratamide A is moderately cytotoxic toward human medulloblastoma D283-MED cells, with a CC₅₀ value of 7.1 ± 0.3 μM, indicative of promising bioactivity against cancer cells.⁹

In addition to kavaratamide A, two minor analogs, namely kavaratamide B and C, were identified by comprehensively analyzing their MS/MS fragmentation patterns and biosynthetic pathways. These analogs feature core structures that are similar



Kavaratamide A (n = 5) (1a)
Kavaratamide B (n = 3) (1b)
Kavaratamide C (n = 7) (1c)

Fig. 1 Structures of kavaratamide A, B, and C.

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to that of kavaratamide A but differ in their lipid fragments; kavaratamide B contains a 3-hydroxyoctanoic acid moiety,⁹ while kavaratamide C contains a 3-hydroxydodecanoic acid unit, which serve as excellent examples of targets than can be synthesized using a common late-stage intermediate. Furthermore, structurally elucidating and synthesizing these lipopeptides provide valuable insight into their biosynthetic origins and potential bioactivities.

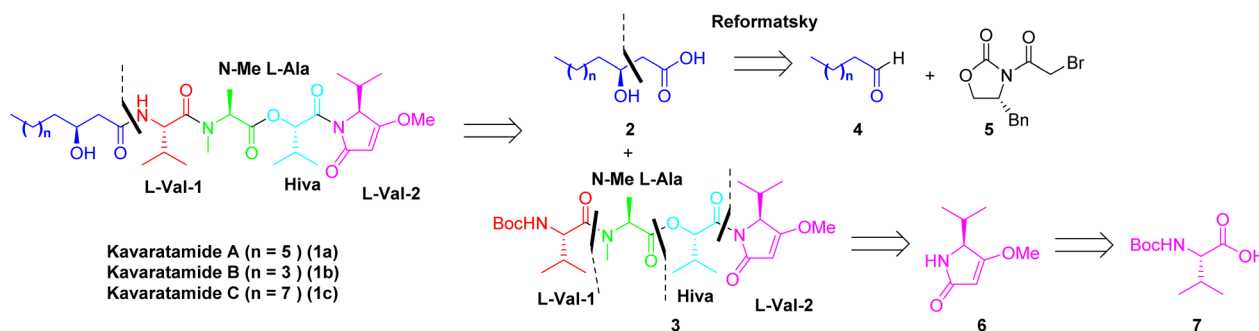
Owing to their unique structures and biological significance, the total syntheses of kavaratamide A, B, and C are crucial for further studies into their bioactivities and potential medicinal uses.

Several strategies have been developed for the synthesis of non-proteinogenic amino acids,¹⁶ which serve as essential building blocks for complex natural products. Key methods for synthesizing their side-chains include cross-metathesis, palladium-catalyzed alkene hydrogenation,¹⁷ asymmetric hydrogenation using chiral Ru(II) catalysts,^{18–20} oxirane ring opening,²¹ Sharpless asymmetric dihydroxylation,^{22,23} chiral quaternary ring opening,^{24,25} and acid–amine condensation. These approaches efficiently provide stereoselective access to diverse amino-acid scaffolds and facilitate the syntheses of structurally complex bioactive compounds. Several groups have recently reported the total synthesis of kavaratamide A. Chen and co-workers achieved the synthesis through Evans aldol and Steglich esterification sequence,²⁶ while Kontham and co-workers²⁷ utilized a convergent Keck asymmetric allylation approach. Lindsley's group developed a modular total synthesis that also enabled analog preparation.²⁸ Herein, we report the total syntheses of kavaratamides A, B, and C *via* a divergent total synthesis strategy. This work demonstrates a flexible and convergent approach for accessing structurally diverse lipopeptides and is consistent with our research focus on the synthesis of bioactive natural products. The key step involves using Reformatsky chemistry²⁹ to stereoselectively construct acid fragments that serve as the crucial lipid components of these lipopeptides. The peptide backbone was assembled *via* sequential Steglich esterification and amidation reactions to ensure high efficiency and precise stereochemical control.^{30,31} In addition, kavaratamide B and C were successfully synthesized using a similar strategy, thereby highlighting the robustness and versatility of the developed synthetic approach.

Results and discussion

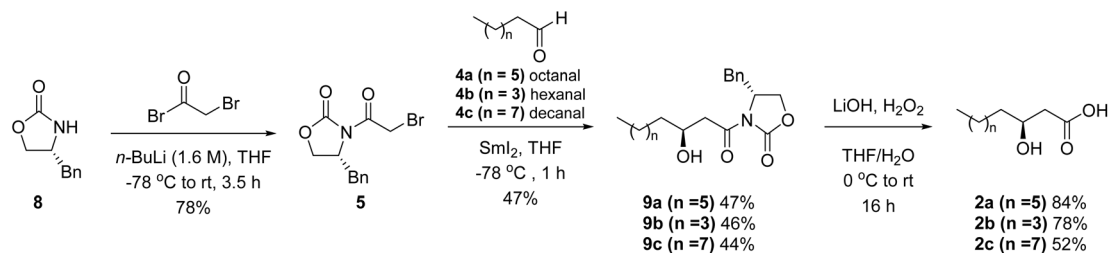
Retrosynthetic analysis (Scheme 1) reveals that kavaratamide A, B, and C could be synthesized by treating a β -hydroxycarboxylic acid (BHA) **2** with a tetrapeptide **3** *via* amide coupling. The BHA **2** was obtained *via* a two-step Reformatsky reaction²⁹ involving an aldehyde **4** and (*R*)-4-benzyl-3-(2-bromoacetyl)oxazolidin-2-one **5** (Scheme 2). Tetrapeptide **3** was synthesized through a series of coupling reactions involving a tetramic acid **6**, which can be prepared from commercially available Boc-*N*-L-valine **7**.³²

Our synthesis began by preparing the key BHA intermediates using a SmI₂-mediated Reformatsky reaction. The (*R*)-4-benzyl-3-(2-bromoacetyl)oxazolidin-2-one (**5**) was synthesized in 78% yield by treating (*R*)-4-benzyl-oxazolidin-2-one chiral auxiliary (**8**) with *n*-BuLi, followed by bromoacetyl bromide. We prepared the key (*R*)-4-benzyl-3-((*S*)-3-hydroxydecanoyl)-oxazolidin-2-one intermediate (**9a**) by condensing (*R*)-4-benzyl-3-(2-bromoacetyl)oxazolidin-2-one (**5**) with octanal (**4a**) at -78°C mediated by SmI₂. SmI₂ enables a unique and chemoselective transformation that was not attainable using other conventional reagents. Here, we first slowly added a mixture of **5** and **4a** in THF to a 0.1 M solution of SmI₂ in THF at -78°C , with the resulting mixture stirred for 1 h, which afforded **9a** in 47% yield (*dr* = 8.8 : 1.2, determined by isolated yield). The moderate yield can be ascribed to partial conversion of the starting material, indicating that the reaction did not proceed to completion even upon treatment with 3.0 equivalents of SmI₂. This may be due to steric hindrance around the reactive site or limited accessibility of SmI₂ to the substrate under the applied conditions. Despite the modest yield, this step proceeds with excellent selectivity and functional group tolerance. Subsequent hydrolysis of **9a** with hydrogen peroxide and LiOH furnished the desired β -hydroxydecanoic acid (**2a**) in 84% yield. Intermediates **2b** and **2c**, which are required for the preparation of kavaratamide B and C, respectively, were synthesized using the same strategy. The corresponding oxazolidinone intermediates **9b** (*dr* = 9.1 : 0.9) and **9c** (*dr* = 8.1 : 1.9, determined by isolated yield) were obtained by the SmI₂-mediated condensation of **5** with hexanal (**4b**) and decanal (**4c**), respectively, at -78°C . Amides **9b** and **9c** were hydrolyzed under the same conditions as those used for **9a**, which resulted in the formation of BHAs **2b** and **2c** in good yields.



Scheme 1 Retrosynthetic analysis of kavaratamide A, B, and C.



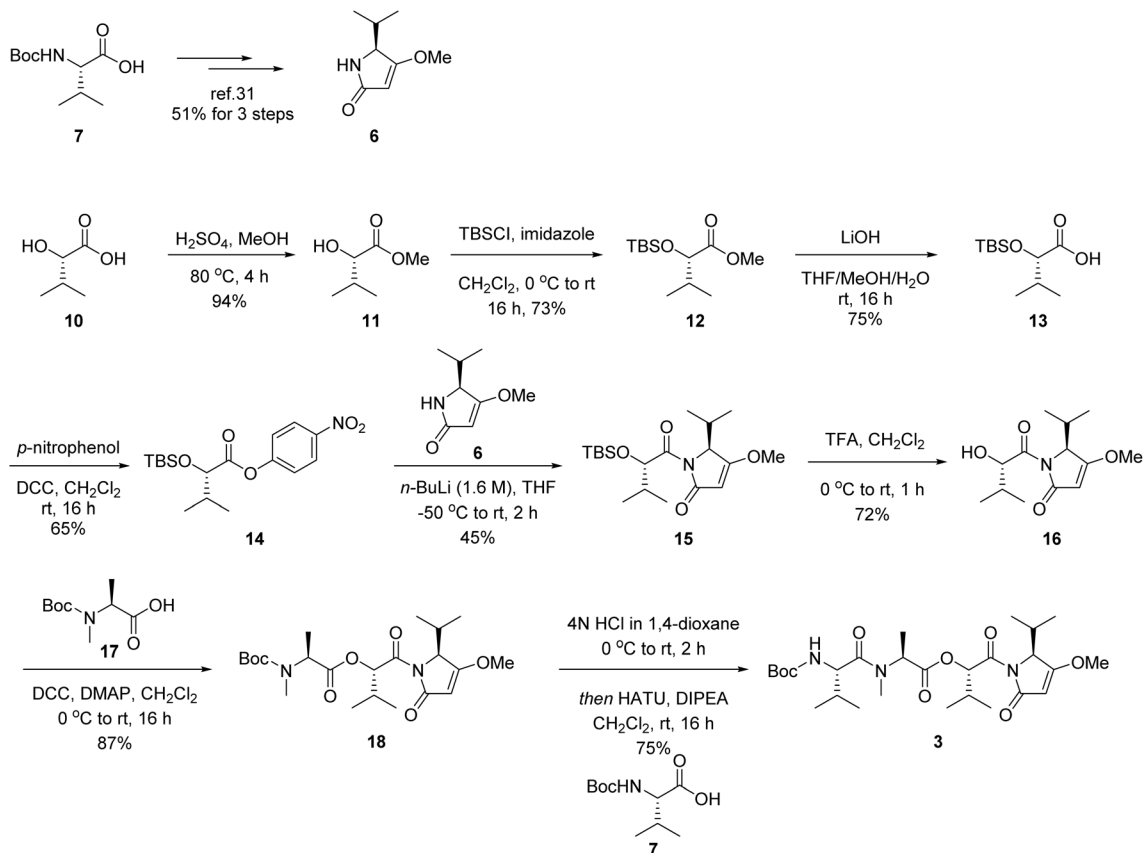
Scheme 2 β -Hydroxycarboxylic acid synthesis.

We prepared tetramic acid **6** as part of our synthetic studies toward key tetradepsipeptide intermediate **3** (Scheme 3). The synthesis began by coupling Boc-*N*-1-valine (**7**) with Meldrum's acid using DCC and DMAP as coupling agents. The resulting intermediate was refluxed in methanol to produce vinylogous carbamic acid, which was used in subsequent steps without further purification. Vinylogous carbamic acid was reacted with methanol under Mitsunobu conditions with triphenylphosphine (PPh_3) and diisopropyl azodicarboxylate (DIAD) to afford Boc-protected tetramic acid in 60% overall yield over two steps. Finally, *N*-Boc-deprotected using trifluoroacetic acid (TFA) in CH_2Cl_2 , to give tetramic acid **6** in 85% yield.³²

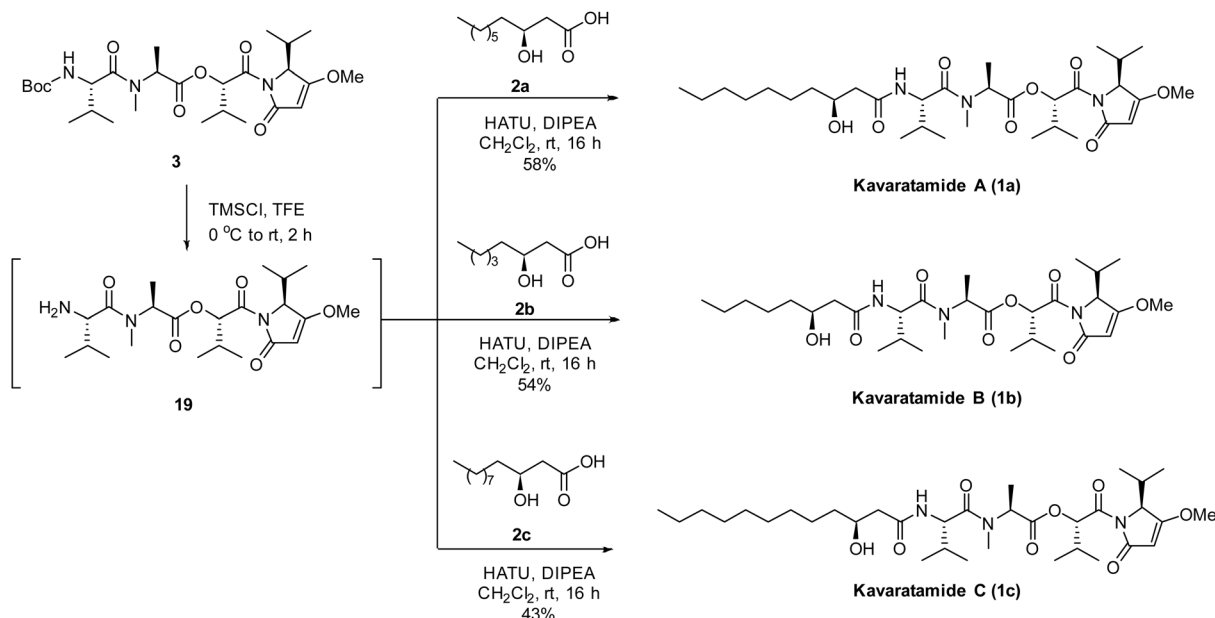
We next synthesized the TBS-protected methyl ester of (*S*)-hydroxyisovaleric acid [(*S*)-Hiva] (**12**). Accordingly, (*S*)-Hiva was refluxed in methanol with a catalytic amount of H_2SO_4 to afford methyl (*S*)-hydroxyisovalerate (**11**) in 94% yield; **11** was then TBS-

protected using TBSCl and imidazole in CH_2Cl_2 to give TBS-protected methyl ester **12** in 73% yield. Hydrolysis of **12** with LiOH produced the corresponding acid intermediate **13** in 75% yield.

With intermediates **6** and **13** in hand, we next examined coupling them to give TBS-protected didepsipeptide **15**. However, our attempts to directly couple **6** with **13** using the HATU, DIPEA coupling and Grignard chemistry in THF proved unsuccessful; not surprisingly, there are limited literature precedents for such a transformation. To overcome this challenge, we activated compound **13** through Steglich esterification with *p*-nitrophenol and DCC, which provided intermediate **14** in 65% yield. Compounds **14** and **6** were then successfully coupled by using *n*-BuLi as base to afford TBS-protected didepsipeptide **15** in 45% yield.



Scheme 3 Synthesis of a key intermediate toward kavaratamide A, B, and C.



Scheme 4 Completing the syntheses of kavaratamide A, B, and C.

With the aim of synthesizing tetradepsipeptide intermediate **3**, we initially attempted to deprotect dipeptide **15** with tetrabutylammonium fluoride (TBAF); however, this method gave **16** in low yield owing to the formation of undesired byproducts (multiple spots on TLC), which ultimately reduced the reaction efficiency and yield. Consequently, we switched basic condition to acidic condition with trifluoroacetic acid (TFA) as the deprotecting agent, which successfully yielded dipeptide **16** in 72% yield, which was then esterified with Boc-*N*-Me-L-alanine (**17**), itself prepared from *N*-Me-L-alanine and Boc₂O,³³ under Steglich conditions, to afford tripeptide **18**. Esterification facilitated by DCC and DMAP provided intermediate **18** in an impressive yield of 87%. Subsequent *N*-Boc deprotection under acidic conditions using 4 N HCl in dioxane and HATU-mediated coupling with Boc-*N*-L-valine (**7**) furnished tetradepsipeptide **3**, a key intermediate in our divergent total synthesis.

With the advanced intermediates in hand, we next focused on synthesizing the natural products, as shown in Scheme 4. First, tetradepsipeptide **3** was *N*-Boc-deprotected using TMSCl in 2,2,2-trifluoroethanol (TFE) at room temperature for 2 h to afford the corresponding free amine **19**, which was subsequently coupled with β-hydroxydecanoic acid (**2a**) under HATU-mediated amide-coupling conditions to produce kavaratamide A (**1a**). We also examined an alternative *N*-Boc deprotection approach using 4 N HCl in dioxane at 0 °C for 2 h; however, these conditions led to the cleavage of the ester bond, which resulted in the formation of **16** alongside the desired intermediate.³⁴ The overall strategy prioritizes robustness, scalability, and chemoselectivity, which outweigh the drawback of a longer sequence.

Kavaratamide B and C were synthesized in a similar manner (Scheme 4). Tetradepsipeptide **3** was first deprotected using the

same condition and subsequently directly coupled with β-hydroxyoctanoic acid (**2b**) or β-hydroxydodecanoic acid **2c** under HATU-mediated conditions to give kavaratamide B (**1b**) (54%) or kavaratamide C (**1c**) (43%), respectively. These syntheses provide a foundation for divergent methods for preparing other kavaratamide analogs and for further biologically evaluating kavaratamide A, B, and C.

The structures of synthetic kavaratamides A–C were confirmed by comprehensive spectroscopic and analytical data. The ¹H and ¹³C NMR spectra of the synthetic compounds were in excellent agreement with those reported for the natural products (comparison table in SI), showing identical chemical shifts and coupling patterns. The HRMS data showed molecular ion peaks consistent with the calculated molecular masses, confirming the correct molecular compositions. Furthermore, the measured optical rotation values for kavaratamides A, B and C validating the absolute configurations of the synthetic products. These results unambiguously confirm that our synthetic kavaratamides are structurally and stereochemically identical to the natural isolates.

Conclusions

We successfully developed a synthetic route toward kavaratamide A, B, and C that uses a stepwise approach involving key intermediates, such as a β-hydroxycarboxylic acid, a tetramic acid, and a tetradepsipeptide. The synthesis commenced with the preparation of the β-hydroxycarboxylic acid intermediates using SmI₂-mediated Reformatsky chemistry, which was followed by the preparation of the tetramic acid and depsipeptide fragments *via* Steglich esterification and HATU-mediated coupling reactions. The final assembly of kavaratamide A, B, or C was achieved through *N*-Boc deprotection of the tetradepsipeptide intermediate, followed by selective amide



coupling with the corresponding β -hydroxycarboxylic acid. This study not only provides an efficient strategy for the synthesis of the kavaratamides, but also offers insight into the challenges associated with constructing and optimizing complex lipopeptide structures. The developed methodology is expected to provide a foundation for the synthesis of related natural products and their analogs, as well as further biological evaluations.

Author contributions

S.·H.·K. conceived this project and S.·H.·K. & J. L. funded and provided direction for this project. D. R. conducted experiments, analyzed the data. B. H. H. N and Y. W. conducted experiments and analyzed the data. D. R., S.·H.·K and J. L. prepared this manuscript including SI.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental procedure, ^1H -NMR, ^{13}C -NMR, HRMS and optical rotation. See DOI: <https://doi.org/10.1039/d5ra07822a>.

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