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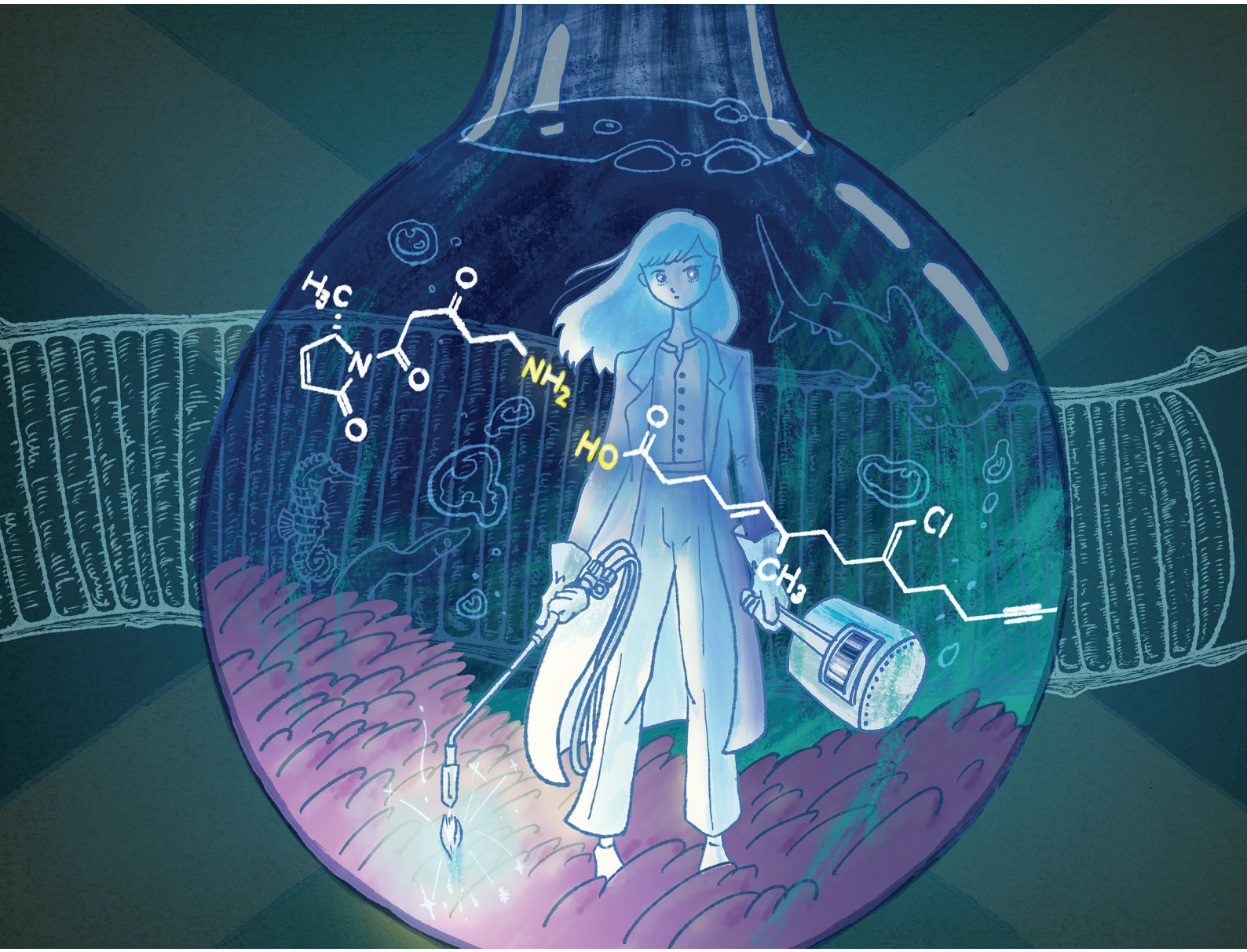

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Total synthesis of jamaicamide B†

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Jamaicamide B was isolated from the cyanobacterium *Moorea producens* in Jamaica and shows neurotoxicity. This unique mixed peptide–polyketide structure contains a pyrrolinone ring, a β-methoxy enone, an (*E*)-olefin, an undetermined stereocenter at C9, an (*E*)-chloroolefin, and a terminal alkyne. We report herein the first total synthesis and structural confirmation of the marine natural product (9*R*)-jamaicamide B.

Natural products are considered to be important resources for drug discovery and development.[1] Jamaicamides A, B (**1**), and C (Fig. 1) are highly functionalized lipopeptides and were isolated by Gerwick and co-workers in 2004 from a dark green strain of the cyanobacterium *Moorea producens* found in Hector's Bay, Jamaica.[2] These amide-type marine natural products have a unique peptide–polyketide mixed structure containing a pyrrolinone ring (C20–C23), a β-methoxy enone (C17–C19), an (*E*)-olefin (C10–C11), an (*E*)-chloroolefin (C6–C27), an undetermined stereocenter (C9), and an unusual terminal alkynyl bromide (C1–C2; only in jamaicamide A).

Due to their intriguing structural features, biosynthesis of jamaicamides has been studied since their discovery.[2–4] Recently, enzymatic halogenation of terminal alkynes has been found in JamD,[4] which is one of the mixed peptide/polyketide synthetase. Moreover, the jamaicamide family exhibits multiple biological activities, including sodium channel-blocking activity and cytotoxicity against both H-460 human lung and Neuro-2a mouse neuroblastoma cell lines.[2] It was also reported that jamaicamide B **1** shows anti-malarial activity and cytotoxicity to Vero cells.[5]

In synthetic studies of jamaicamides, the polyketide fragment of (*S*)-jamaicamide C was stereoselectively synthesized by Paige and co-workers employing Negishi cross-coupling and Johnson–Claisen rearrangement as the key steps.[6] In contrast, we synthesized the *N*-di-*tert*-butoxycarbonyl [(Boc)$_2$]-protected peptide moiety of the jamaicamides starting from chiral natural amino acids.[7] We also reported the stereo- and regioselective synthesis of the polyketide unit, including construction of the (*E*)-chloroolefin moiety *via* Wittig reaction followed by separation of the (*E*) and (*Z*)-isomers, the chiral methyl stereocenter at C9 *via* Evans' strategy, and the (*E*)-olefin *via* Julia–Kocienski coupling.[8,9] However, the total synthesis of jamaicamides has to date not been accomplished, probably due to the unusual skeleton and the expected labile moieties such as the β-methoxy enone, pyrrolinone ring, and terminal alkynes. The related natural products biakamides A–D are chloro-olefines isolated from an Indonesian marine sponge and their total synthesis has been reported.[10]

Given their interesting chemical structures, attractive biological activities and unique biosynthesis as secondary metabolites, we embarked on and herein report the first total synthesis of jamaicamide B **1**. Our approach starts with the condensation of peptide and polyketide moieties, followed by determination of the stereochemistry at C9 by comparison of the optical rotation values of synthetic (9*S*)- and (9*R*)-isomers with the natural product.

As illustrated in the retrosynthetic analysis shown in Scheme 1, **1** can be divided into two fragments: a pyrrolinone-containing peptide moiety and a polyketide moiety. Stereoselective synthesis of the *N*-[(Boc)$_2$]-protected peptide moiety starting from L-alanine and *N*-Boc-β-alanine using

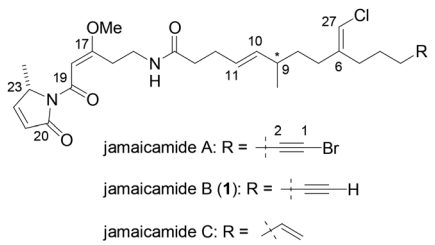

Fig. 1 Structures of jamaicamides.[2]

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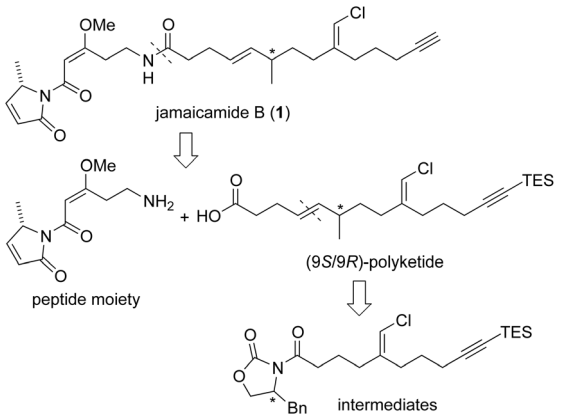


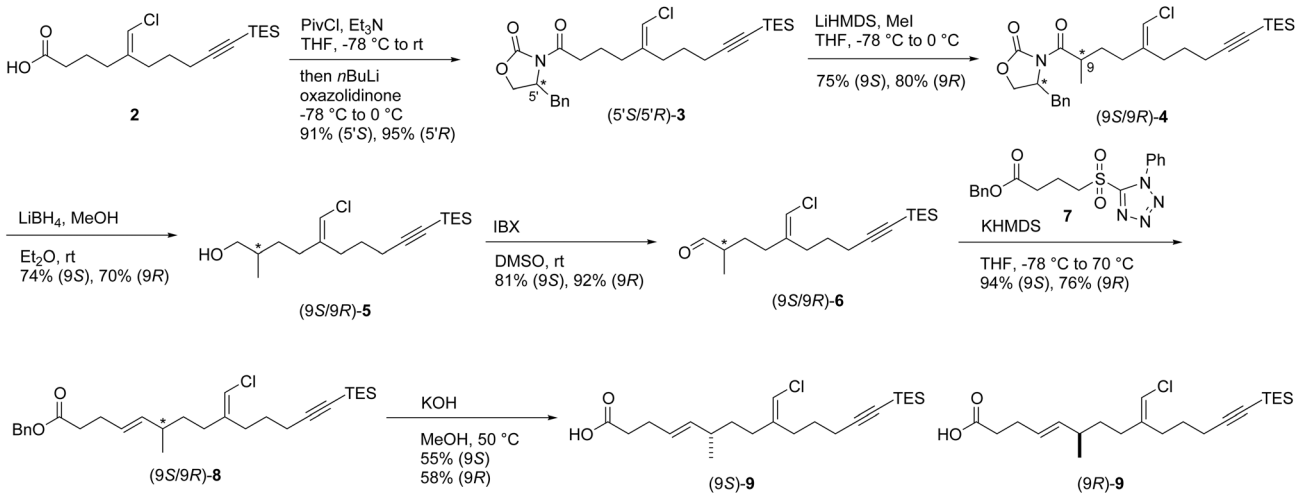
Scheme 1 Retrosynthetic analysis of 1.

Meldrum's acid has been reported,[7] as has the stereo- and regioselective synthesis of the polyketide moiety.[8,9] The 13-step synthesis of the latter moiety started from pentane-1,5-diol *via* Wittig reaction, followed by separation of the (*E*) and (*Z*) isomers for the (*E*)-chloroolefin, and Julia–Kocienski coupling to form the (*E*)-olefin with (9*S*) configuration by Evans' chiral auxiliary. To determine the configuration of **1**, a stereocenter at C9 would be installed by means of Evans' oxazolidinone methodology to prepare both the (9*S*) and (9*R*)-polyketide intermediates.[9]

The synthesis commenced with the previously reported carboxylic acid **2** from pentane-1,5-diol in nine steps in 9% yield (Scheme 2).[9] Acylation of **2** with pivaloyl chloride (PivCl) gave the ester intermediate, followed by conversion to the oxazolidinone-based chiral auxiliary using (5′*S*/5′*R*)-4-benzyl-2-oxazolidinone and *n*-butyllithium (*n*BuLi) to give (5′*S*)-**3** and (5′*R*)-**3** at −78 °C to room temperature in 91% and 94% yields in two steps, respectively. In our previous study, oxazolidinone was inserted at −78 °C to −40 °C to afford (5′*S*)-**3** in 65% yield.[9] The enolate of oxazolidinone **3** was then generated by treatment with lithium hexamethyldisilazide (LiHMDS), followed by the addition of iodomethane (MeI) to provide (9*S*)-**4** in 75% yield and (9*R*)-**4** in 80% yield, respectively.[11,12] Removal of the oxazolidinone in **4** using lithium borohydride ($LiBH_4$) led to the alcohol (9*S*)-**5** in 74% yield and (9*R*)-**5** in 70% yield, respectively. Next, **5** was oxidized with 2-iodoxybenzoic acid (IBX) to afford aldehyde (9*S*)-**6** in 81% yield and (9*R*)-**6** in 92% yield, respectively, whereas the previous conditions (TPAP/NMO) gave (9*S*)-**6** in 74% yield.[9] Transformation of the aldehyde **6** into the desired (*E*)-olefin was accomplished *via* a Julia–Kocienski coupling reaction.[13,14] The prepared sulfone **7**[8,9] was treated with potassium hexamethyldisilazide (KHMDS) to produce the corresponding anion, which was then reacted with **6** to give the desired olefin (9*S*)-**8** and (9*R*)-**8** in 94% and 76% yields, respectively. When NaHMDS was reacted with (9*S*)-**6**, the product (9*S*)-**8** was obtained in 46% yield.[9] The benzyl ester in **8** was converted to a carboxylic acid under basic hydrolysis conditions to afford carboxylic acid (9*S*)-**9** (55%; *E*/*Z* = 92 : 8) and (9*R*)-**9** (58%; *E*/*Z* = 97 : 3), respectively, and the *E*/*Z* ratios were determined by ^{1}H NMR analysis.[15] The moderate yield of the saponification is probably due to the partial cleavage of the TES group.

The synthesis of peptide fragment **11a** was first investigated by deprotection of the Boc group in *N*-[$(Boc)_2$]-protected peptide moiety **10**,[7] which was synthesized previously (Table 1). Treatment of **10** with trifluoroacetic acid (TFA) in dichloromethane (CH_2Cl_2) solely gave the undesired product **11b** in 93% yield upon removal of the β-methoxy enone moiety (entry 1). The same tendency was observed when 4 M hydrochloric acid solution in 1,4-dioxane was used, suggesting that acidic conditions promoted undesired demethylation (entry 2). Application of a 2 : 1 mixture of trifluoromethanesulfonate (TMSOTf)/2,6-lutidine gave a complex mixture (entry 3). These results suggested that the β-methoxy enone moiety in **10**, attached to the electron-withdrawing pyrrolinone, is labile under acidic conditions.

Our next target molecule was the peptide moiety **20′** (Scheme 3) bearing a 2-(trimethylsilyl)ethoxycarbonyl (Teoc)



Scheme 2 Synthesis of polyketide 9.

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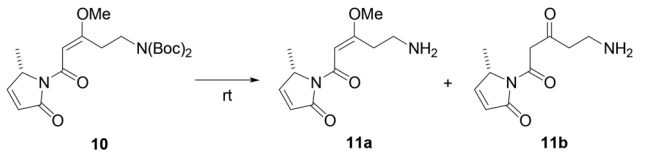
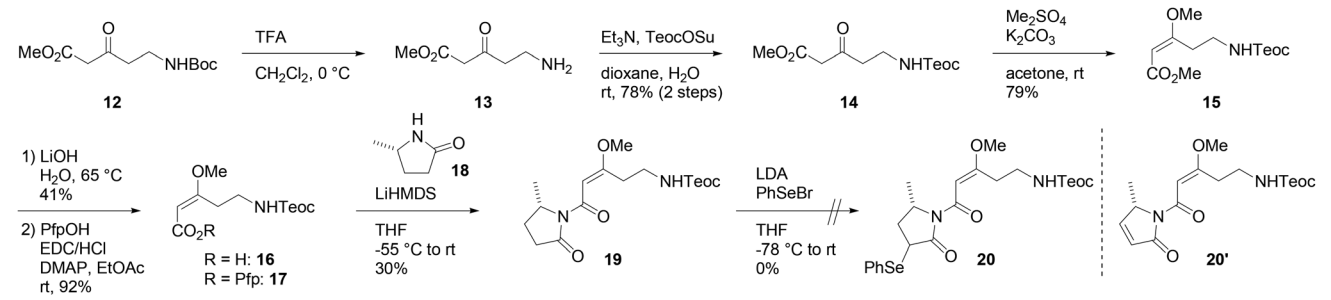
Table 1 Removal of the Boc group of **10**



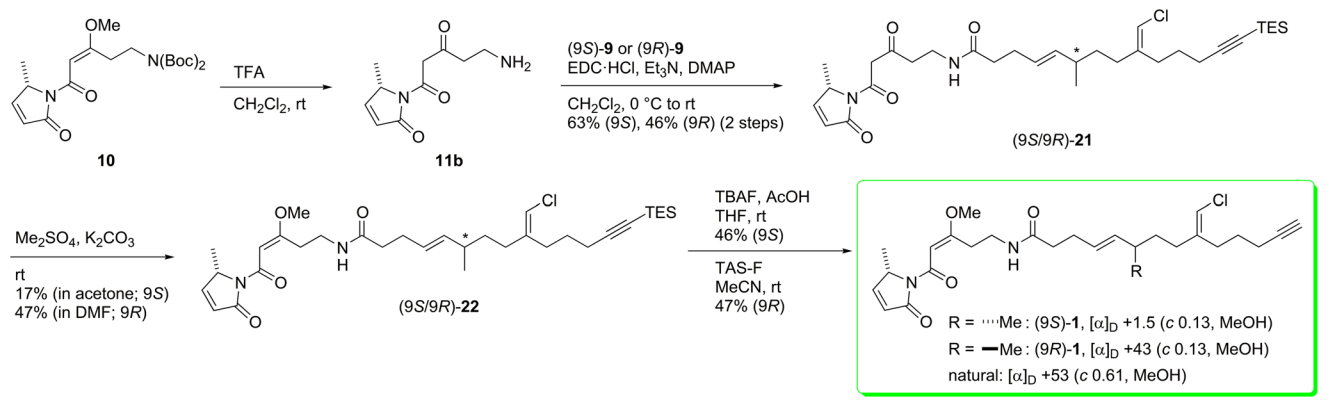
Entry	Conditions	Time	Yield (**11a**)	Yield (**11b**)
1	TFA in CH_2Cl_2	20 min	0%	93%
2	HCl in dioxane	30 min	0%	92%
3	TMSOTf/2,6-lutidine (2 : 1)	30 min	Complex mixture	

protecting group, since Teoc can be selectively removed using a fluorine anion such as tetrabutylammonium fluoride (TBAF). Starting from β-keto ester **12**, synthesized from Boc-β-alanine in two steps,[7] the removal of Boc using TFA followed by protection with Teoc *via* **13** gave compound **14** in 78% yield in two steps. β-Methoxy enone **15** was then formed using dimethyl sulfone in 79% yield. The hydrolysis of **15** using LiOH gave **16** in 41% yield, followed by generation of the pentafluorophenol (Pfp) ester **17** in 92% yield. Condensation with six equivalents of pyrrolidone **18**, obtained from L-alanine in five steps,[7] afforded compound **19** in 30% yield using LiHMDS. However, treatment with lithium diisopropylamide (LDA) and PhSeBr failed to provide the desired **20**, but rather gave a complex mixture. We therefore ruled out this synthetic route.

Thus, we turned our attention to taking advantage of the above obtained undesired β-ketoamide **11b**. As shown in Scheme 4, *N*-[(Boc)$_2$]-protected peptide moiety **10**[7] was treated with TFA to give β-ketoamide **11b**, which was further reacted with carboxylic acid **9** and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC·HCl) *in situ*, successfully giving (9*S*)-**21** in 63% yield and (9*R*)-**21** in 46% yield, respectively. The ketone moiety of (9*S*)-**21** was then methylated with Me_2SO_4 in acetone to give (9*S*)-**22** in 17% yield. Removal of the triethysilyl (TES) group using TBAF in the presence of acetic acid (AcOH) produced (9*S*)-**1** in 46% yield. The NMR spectrum of (9*S*)-**1** showed excellent agreement with that of the natural product including the newly formed olefin geometry, but its optical rotation value was different {$[\alpha]_D$ = +1.5 (synthetic) *vs.* +53 (natural)[2]}. Methylation of the ketone of (9*R*)-**21** in *N*,*N*-dimethylformaldehyde (DMF) gave (9*R*)-**22** in 47% yield, followed by removal of the terminal TES group using tris(dimethylamino)sulfonium difluorotrimethylsilicatetetrabutylammonium fluoride (TAS-F)[16] in acetonitrile (AcCN) to afford (9*R*)-**1** in 47% yield. The ^{1}H and ^{13}C NMR spectra and optical rotation of (9*R*)-**1** were in excellent agreement with those of the natural product {$[\alpha]_D$ = +43 (synthetic) *vs.* +53 (natural)[2]}, suggesting that the stereochemistry at C9 in jamaicamide B **1** is the (*R*)-configuration.



Scheme 3 Attempt to synthesize **20**.



Scheme 4 Total synthesis of jamaicamide B **1**.

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In summary, the total synthesis of jamaicamide B **1** was achieved for the first time in 18 steps in 0.2% overall yield starting from pentane-1,4-diol. The synthesis involved Evans' asymmetric methylation and a Julia–Kocienski coupling reaction. The unknown stereochemistry at C9[2] was determined to be the (*R*)-configuration by comparing the optical rotation values of both stereoisomers. This synthetic methodology will enable the synthesis of analogues of **1**, such as jamaicamides A and C, facilitate their structure–activity relationship (SAR) studies, and shed light on the unexplored biological functions of these unique molecules.

Conflicts of interest

There are no conflicts to declare.

Note added after first publication

This article replaces the version published on 8th May 2024 which contained errors in the stereochemical descriptors Scheme 1, Scheme 2 and Scheme 4.

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