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Synthesis of the cyclic heptapeptide core of callipeltin A†

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Macrolactonisation of a novel heptapeptide precursor with PyAOP proved to be an excellent method for preparation of the cyclic depsipeptide core of callipeltin A. The individual building blocks were obtained in high yield and selectivity and successive coupling allowed for the straightforward preparation of the linear heptapeptide from tyrosine **6** in 27% over 12 steps.

Introduction

Callipeltin A (Fig. 1), first isolated in 1996 by Zampella *et al.* from the marine sponge *Callipelta* sp. near the east coast of New Caledonia in the Pacific Ocean, is a novel decapeptide that consists of a cyclic heptapeptide core and a highly functionalised sidechain R.[1] The side chain contains several complex nonproteinogenic amino acids along with a rare terminal β-hydroxy acid. The natural product has undergone several structural revisions, including the reconfiguration of the β-hydroxy acid,[2a] determination of the configuration of the β-methoxy tyrosine residue,[2b] and reassignment of both threonine moieties to D-allo-threonine.[2c] To date, the callipeltin family includes 17 representatives up to callipeltin Q.[2a,3]

The callipeltins belong to a class of structurally related marine natural products, such as mirabamides,[4] papuamides[5] and neamphamides.[6] While callipeltin A displays some notable antiviral, antifungal and cytotoxic activity,[1,3a,7] the structural complexity of the natural product, in particular, has raised the interest of synthetic chemists. Several research groups reported asymmetric routes toward the amino acid building blocks (2*R*,3*R*)-β-methoxy tyrosine,[8] (3*S*,4*R*)-dimethyl-L-glutamine (diMeGln)[9] and (2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxy-heptanoic acid (AGDHE).[10] Additionally, the synthesis of hydroxy acid (2*R*,3*R*,4*R*) 3-hydroxy-2,4,6-trimethyl-heptanoic acid (TMEHA) was described.[11] In 2005 and 2006, Lipton *et al.* achieved the first synthesis of the callipeltins D, E and B *via* solid-phase peptide synthesis.[12a–c] More recently, Konno *et al.* reported a similar route toward callipeltin E along with the synthesis of callipeltin B and M.[12d,e] While both research teams could synthesise the simplified representative callipeltin B, containing a dimethyl pyroglutamic acid instead of the complex side chain, no successful synthesis of the parent structure of callipeltin A has been reported to date.

To enable the synthesis of callipeltin A and derivatives thereof for structure–activity relationship (SAR) studies, the development of a flexible and robust synthetic route is highly desirable.

Results and discussion

Herein, we report the straightforward access of the cyclic heptapeptide core of callipeltin A, the parent structure of this class of natural products.

To begin our synthesis of the peptide core, we prepared the nonproteinogenic amino acid building blocks, β-methoxy tyrosine and D-*allo*-threonine. The synthesis of the tyrosine moiety was based on an asymmetric Sharpless dihydroxylation, which provided diol **2** in a highly enantio-selective fashion (Scheme 1).[13] We achieved the selective nosylation of the α-hydroxy group with nosyl-chloride treatment. Furthermore, the immediate substitution with sodium azide afforded azido ester **3** in good yield. The second hydroxy group was converted

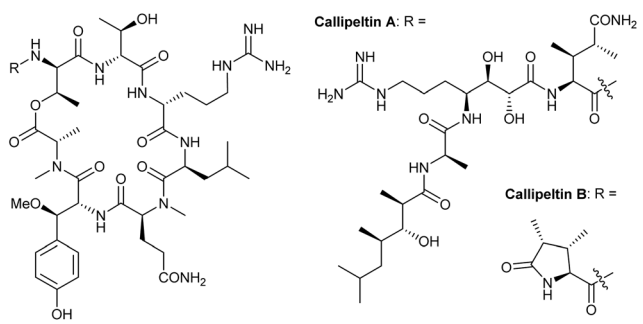

Fig. 1 Structure of callipeltin A and B.

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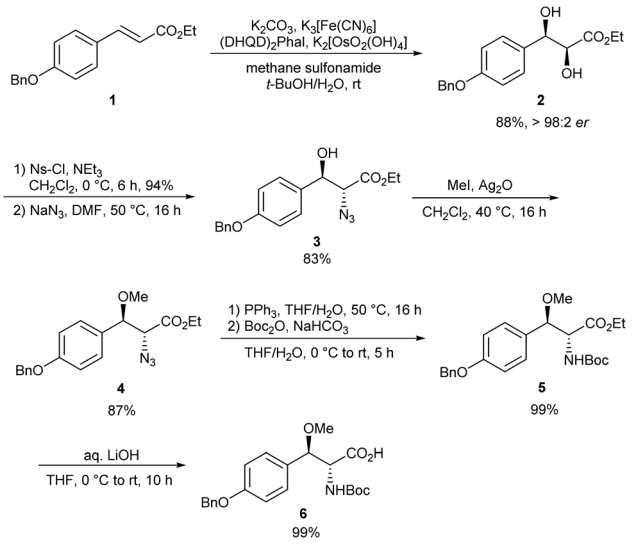
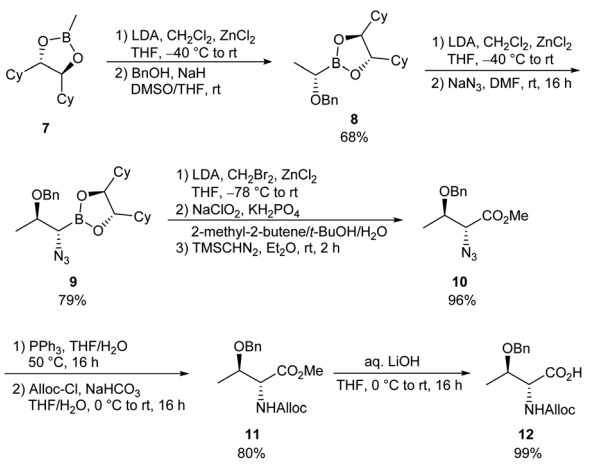


Scheme 1 Preparation of protected tyrosine **6**.

into the corresponding methyl ether using a protocol of Cuevas with methyl iodide in the presence of silver oxide.[13] Azide **4** was reduced by the Staudinger reaction, and the resulting amine was Boc-protected (**5**). Finally, the saponification of the methyl ester provided protected tyrosine **6** in almost quantitative yield.

The synthesis of the protected D-*allo*-threonine building block was attempted *via* three successive Matteson homologations[14] from known methyl boronic ester **7**.[15] The first homologation introduced the benzyl-protected hydroxy functionality by treatment of the intermediary α-chloro boronic ester with sodium benzylate in the presence of zinc chloride (Scheme 2). A second homologation followed by substitution with sodium azide afforded α-azido boronic ester **9** as a single stereoisomer. The ensuing homologation of boronic ester **9** to the corresponding carboxylic acid under typical conditions initially suffered from low conversion rates and the formation of several side products. These issues could be avoided when the reaction was carried out with dibromomethane instead of dichloromethane to yield the corresponding α-bromo boronic ester.[16] The oxidation of the intermediary α-bromo boronic ester under Pinnick-type conditions followed by treatment with TMS-diazomethane afforded azido ester **10**. In addition, azide reduction was achieved *via* Staudinger reaction, and the resulting amine was protected as its Alloc carbamate **11**. The saponification of the methyl ester with lithium hydroxide gave rise to protected D-*allo*-threonine **12** in a quantitative fashion.



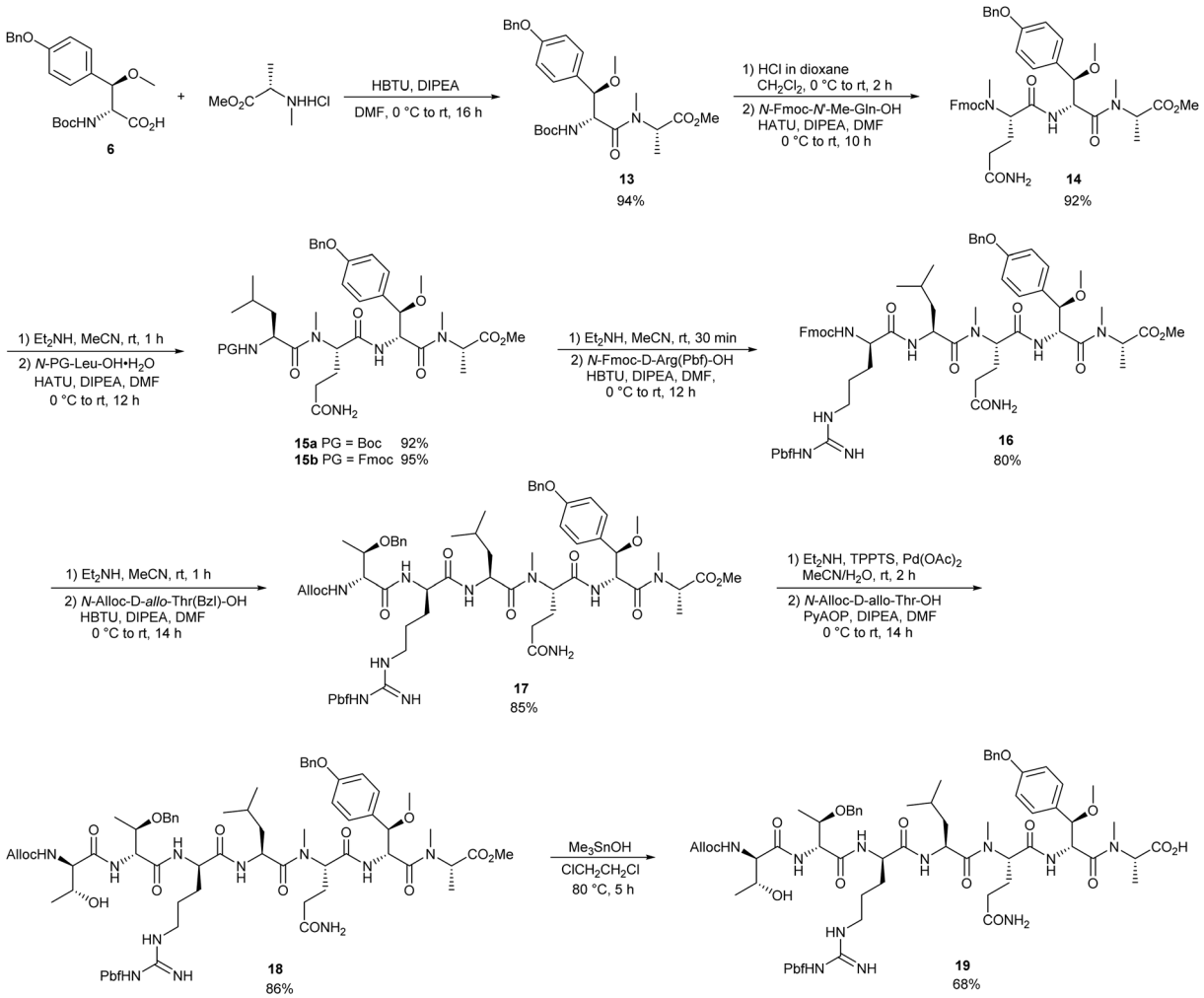
Scheme 2 Matteson homologation toward D-*allo*-threonine **12**.

The peptide chain assembly started with tyrosine **6**, which was coupled with *N*-Me-Ala-OH (Scheme 3). Best results were obtained with the uronium coupling reagent HBTU, which minimised the elimination of methanol from the β-methoxy tyrosine upon activation, thus affording dipeptide **13** in acceptable yield. We prepared the required *N*-methyl glutamine for the ensuing coupling step from commercially available Fmoc-Gln(Trt)-OH by hemiaminal formation and ionic hydrogenation to install the *N*-methyl group (see ESI† for more details).[17]

The *N*-terminal deprotection of dipeptide **13** with hydrochloric acid and subsequent coupling of the resulting hydrochloride with *N*-Fmoc-*N*′-Me-Gln-OH in the presence of HATU and DIPEA gave rise to tripeptide **14**. After the treatment of **14** with excess diethylamine to achieve Fmoc deprotection, the free amine was reacted with Boc- and Fmoc-Leu-OH by activation with HATU to obtain tetrapeptide **15a** and **15b**, respectively. However, the removal of the Boc group was impossible under various conditions because of the decomposition of the peptide under Lewis and Brønsted acidic conditions. In contrast, the treatment of Fmoc-tetrapeptide **15b** with excess diethylamine led to the clean deprotection of the N-terminus. Furthermore, subsequent coupling with commercially available *N*-Fmoc-D-Arg(Pbf)-OH in the presence of HBTU gave pentapeptide **16** in good yield.

After N-terminal Fmoc deprotection was carried out under identical conditions once more, the resulting amine was reacted with D-*allo*-threonine **17** *via* HBTU activation. The final Alloc-deprotection was achieved by palladium catalysed allylic alkylation with water-soluble phosphine ligand TPPTS (3,3′,3″-phosphanetriyltris-(benzenesulfonic acid) trisodium salt).[18] The ensuing coupling initially suffered from low conversion when typical coupling reagents such as HBTU, EDC, HATU or COMU were used. However, PyAOP,[19] the nitrogen analogue of PyBOP known to be an exceptional reagent for coupling and cyclisation of sensitive substrates, worked excellently. As a result, heptapeptide **18** could be obtained in 86% yield.

While methyl ester **18** underwent saponification rapidly, a loss in the molecular mass of 58 was detected, corresponding to the loss of an allyl alcohol fragment. NMR analysis verified the assumption of N-terminal oxazolidinone formation *via* base-induced intramolecular cyclisation. Attempts to suppress the oxazolidinone formation using different metal hydroxides or performing the reaction at a lower temperature gave similar results. Fortunately, the use of the mild and significantly less basic saponification reagent Me_3SnOH, initially described by



Scheme 3 Synthesis of linear peptide **19**.

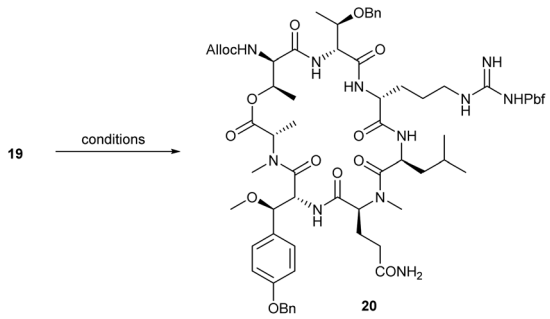
Nicolaou *et al.*,[20] selectively afforded the desired carboxylic acid **19** in good yield.

With the hydroxy acid **19** in hand, we then examined the macrocyclisation *via* a protocol described by Konno *et al.*, who achieved cyclisation of a similar linear peptide in 44% yield. They used an excess of DIC and DMAP at 45 °C during their synthesis of callipeltin B.[12e] In the case of linear heptapeptide **19**, macrolactone **20** was obtained in only 32% along with 64% of *N*-acylurea resulting from acyl migration of the intermediary *O*-acylisourea (Table 1, entry 1). While such yields are common for the cyclisation of complex peptides and depsipeptides, we made additional attempts to increase the yield.

First, the reaction was carried out under Yamaguchi conditions.[21] However, all experiments using this protocol showed no product formation (entry 2); thus, the initial reaction conditions were re-examined. The reaction was carried out with excesses of DIC and DMAP at various temperatures and concentrations, but the yield could only be improved slightly at 70 °C (entry 3).

In subsequent attempts, the use of PyAOP, known to be an excellent reagent for macrolactamisation, providing exceptional results in earlier peptide couplings, was studied (entries 4 and 5). As expected, without the addition of DMAP, the use of PyAOP at room temperature resulted in no conversion, owing to the lower nucleophilicity of the alcohol compared to amine couplings. When an excess of DMAP was added, however, and the reaction was conducted at elevated temperatures, macrolactone **20** was obtained in 59% yield. Increasing the temperature to 70 °C resulted in the formation of macrolactone in exceptional yield, surprisingly, without significant erosion of the adjacent stereocentre of the activated *N*-methyl alanine. Trace amounts of the epimer (1–2%) were readily removed during purification *via* preparative HPLC. The obtained macrolactone **20** represents a protected derivative of the peptide core of callipeltin A. After the cleavage of the *N*-terminal Alloc protection group, this cyclic peptide should allow for coupling with the sidechain to access the natural product quickly.

Table 1 Attempts of macrolactonisation



Entry	Conditions	Solvent	*c* [mM]	*Y* [%]
1	DIC (5 eq.), DMAP (20 eq.), 45 °C, 72 h	DMF	7.5	32%
2	Yamaguchi reagent (1.5 eq.), DMAP (1–20 eq.), NEt_3 (5.0 eq.) 20 °C, 24 h	Toluene	1.0	—
3	DIC (5 eq.), DMAP (20 eq.), 70 °C, 72 h	DMF	7.5	39%
4	PyAOP (1.2 eq.), DMAP (20 eq.), 45 °C, 72 h	DMF	7.5	59%
5	PyAOP (1.2 eq.), DMAP (20 eq.), 70 °C, 72 h	DMF	7.5	83%

Conclusions

In conclusion, we developed a straightforward approach to obtaining the protected cyclic depsipeptide core of callipeltin A. This route includes the preparation of the nonproteinogenic amino acid building blocks in a highly stereoselective fashion and the subsequent assembly of the peptide chain *via* successive deprotection and peptide coupling steps. The homologation of chiral boronic esters using Matteson's protocol was an effective tool for preparing protected D-allo-threonine **12**. Further application of this method in the synthesis of amino acids is ongoing. Furthermore, we achieved the cyclisation of linear peptide **19** with PyAOP in excellent yield without significant erosion of the adjacent stereocentre of the activated amino acid. After Alloc deprotection, the resulting amine should readily be coupled with the side chain of callipeltin A to afford the natural product in a few additional steps. The synthesis of the sidechain and the coupling of both parts of callipeltin A are underway and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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