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Total synthesis of apratoxin A and B using Matteson's homologation approach†

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Apratoxin A and B, two members of an interesting class of marine cyclodepsipeptides are synthesized in a straightforward manner *via* Matteson homologation. Starting from a chiral boronic ester, the polyketide fragment of the apratoxins was obtained *via* five successive homologation steps in an overall yield of 27% and very good diastereoselectivity. This approach is highly flexible and should allow modification also of this part of the natural products, while previous modifications have been carried out mainly in the peptide fragment.

Introduction

The apratoxins are a class of cyclodepsipeptides produced by cyanobacteria.[1] The first described member of this group, apratoxin A, was isolated by Moore and Paul *et al.* from the marine cyanobacterium *Lyngbya majuscula* in 2001.[2] It showed potent cytotoxicity towards a range of tumor cell lines in the sub nanomolar range,[3] acting as a broad-spectrum Sec61 inhibitor[4] targeting HER/ErbB family proteins.[5] Over the following years, a wide range of further apratoxins have been isolated.[6] Some of these structures are shown in Fig. 1.

The apratoxins form a 25-membered ring consisting of a pentapeptide and a rather unusual polyketide fragment, containing, in most cases, a terminal *t*-butyl group. The apratoxins differ mainly in their methylation pattern (apratoxins A–D) or in the composition of the peptide fragment. While most apratoxins embody an unusual unsaturated prolonged cysteine unit, in some of the members of the apratoxin S family, artificial derivatives obtained by a medicinal chemistry campaign, this unit is (structurally) reduced.[7] The unusual polyketide fragment is common to most family members. In case of apratoxin D, its carbon chain is even one carbon longer. Detailed studies indicate that an iron-dependent methyltransferase directs the *tert*-butyl group formation by initiating the assembly of the apratoxin A polyketide starter unit.[8]

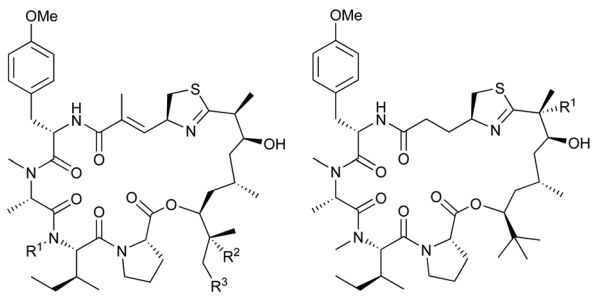

Fig. 1 Selected apratoxins.

Not surprisingly, the excellent cytotoxicities in the low nanomolar range, and the interesting mode of action initiated synthetic investigations for the synthesis of the polyketide fragment of the apratoxins,[9] the apratoxins themselves[10] as well as derivatives for SAR studies.[11] Common to all syntheses of apratoxin A is the late-stage assembly of the thiazoline moiety, which is oxidatively sensitive and potentially prone to unwanted side reactions, *e.g.* epimerization of the adjacent stereogenic centre. To synthesise the polyketide fragment, asymmetric cuprate additions or allyl isomerisations are used to introduce the internal methyl group, while the two stereogenic centres adjacent to the thiazoline ring are generated *via* different versions of aldol reactions.

Results and discussion

Since a couple of years our group is involved in the synthesis of natural products,[12] especially cyclic peptides with interest-

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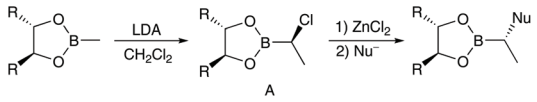
ing biological activities.[13] Recently, we have become interested in the synthesis of peptide/polyketide hybrids[14] such as the apratoxins, with a focus on aldol-free polyketide synthesis. The aldol reaction,[15] or alternatively an allylation/ozonolysis sequence,[16] is perfectly suited to generating the 3, 5, 7, ...-polyhydroxylated carboxylic acids found in many natural products, with methyl groups between the hydroxy functionalities, but these reactions are more or less restricted to this substitution pattern. With the synthesis of lagunamide A,[17] we could show that also other approaches, such as Matteson homologations,[18] which are more flexible, are well suited to the synthesis of complex polyketides. This elegant stereoselective prolongation of chiral boronic esters was introduced by Donald Matteson 40 years ago (Scheme 1).[19]

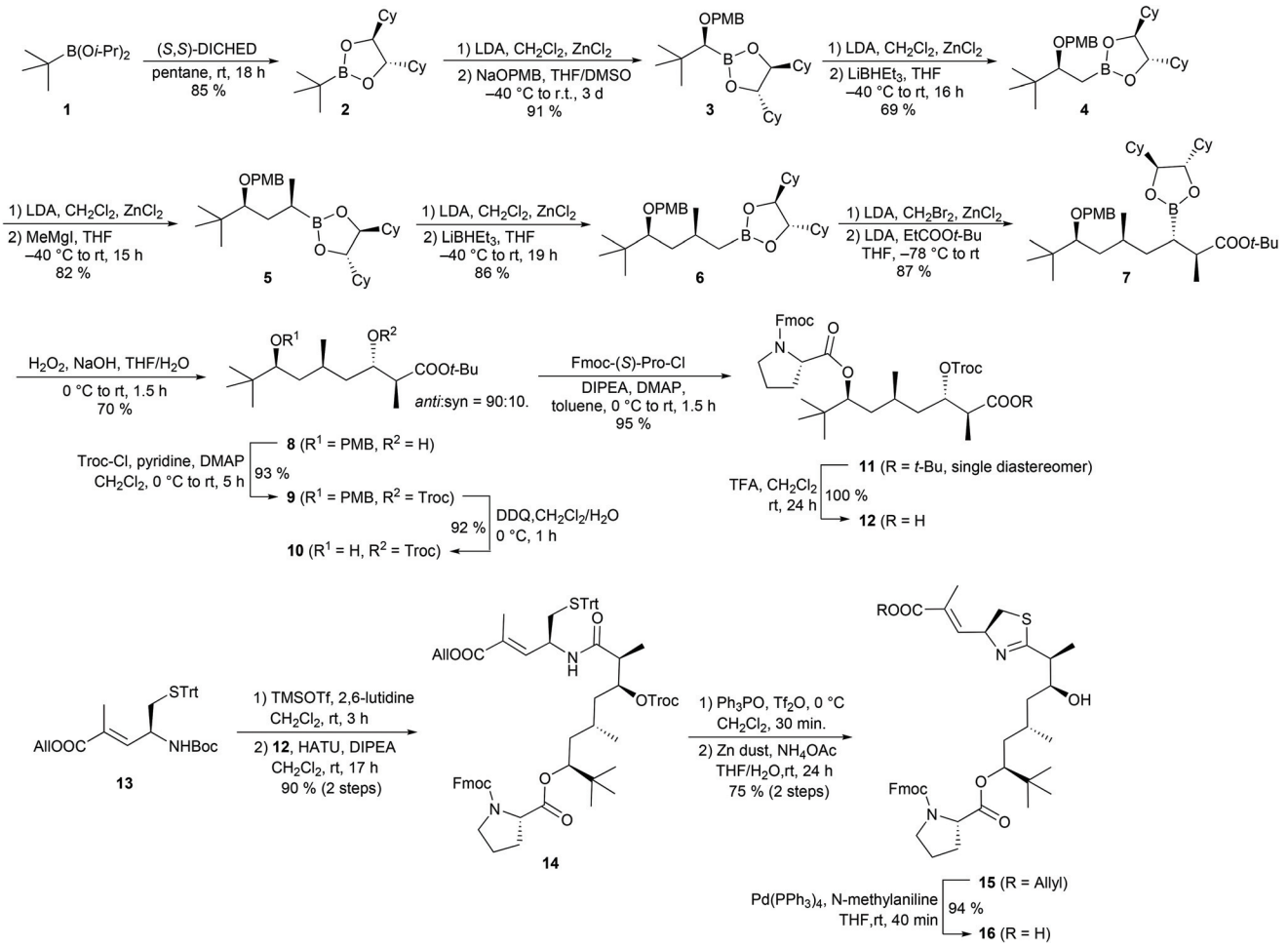
A key step of this protocol is the highly stereoselective formation of an α-chloro boronic ester **A**, which can be subjected to nucleophilic substitution under S_N2-conditions with a wide range of nucleophiles such as Grignard reagents, alkoxides or certain enolates.[20] Continual application of this procedure allows the stepwise stereoselective incorporation of a wide range of substituents and functionalities into a growing carbon chain.

We attempted to prepare the polyketide fragment of apratoxin A and B using the above-mentioned Matteson homologation approach. Starting from diisopropyl *tert*-butylboronate **1**[21] transesterification with (*S*,*S*)-DICHED (dicyclohexylethane-1,2-diol)[22] gave the chiral boronic ester **2** (Scheme 2). While homologation of sterically demanding **2** to the α-chloroboronic ester proceeded smoothly under the usual conditions, the subsequent substitution to the alkoxyboronic ester **3** was sluggish and incomplete when we used only a slight excess (1.3 eq.) of NaOPMB. In contrast, with a larger excess (3.0 eq.) of alkoxide, we observed full conversion and could isolate **3** in excellent yield.

In the following step, we introduced a CH_2 group by treating the intermediate α-chloroboronic ester with $LiBHEt_3$. Next, we used a methyl Grignard reagent as a nucleophile, which cleanly yielded **5**. Introduction of a second CH_2 unit gave the



Scheme 1 Matteson homologation.

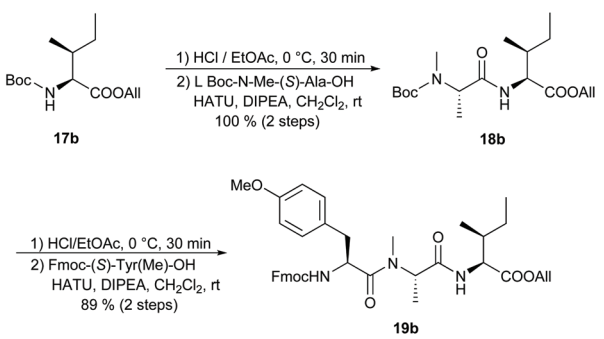


Scheme 2 Synthesis of the apratoxin polyketide fragment.

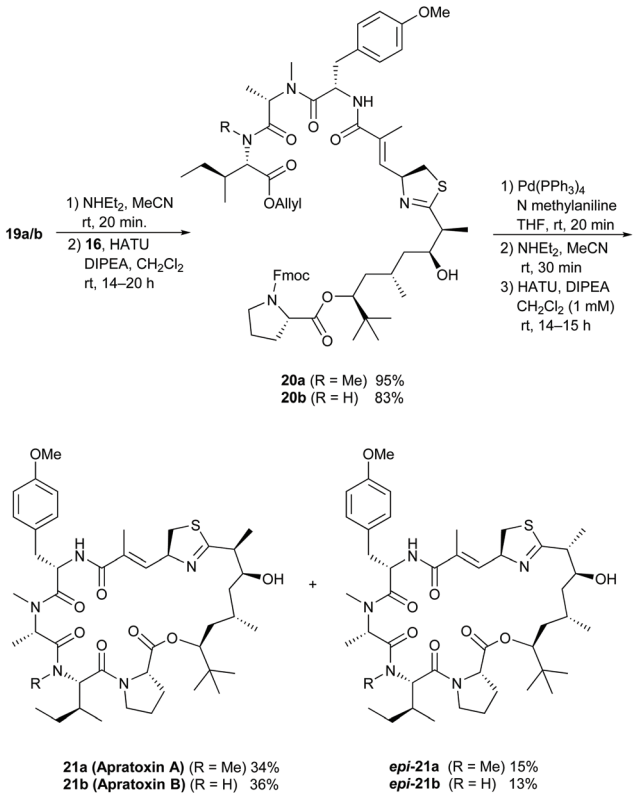
prolonged boronic ester **6** in good yield. In the following homologation step, we applied the lithium enolate of *tert*-butyl propionate as a nucleophile. Similar reactions of simple α-haloboronic esters with enolates have already been described by Matteson *et al.*[20a,b] but, surprisingly, this method has not been applied to the synthesis of more complex natural products so far. A reason for this may be that this reaction requires the use of α-bromoboronic esters which are more reactive, but also more prone to epimerization than their chloro-analogues.[23] Fortunately, we could completely suppress epimerization by quenching the formation of the α-bromoboronic ester at low temperature (−55 °C) and immediately treated the crude product with the enolate. While the homologations from **2** to **6** provided the products as single diastereomers, we obtained **8** as a mixture of *syn* and *anti* isomers, but with good *anti* selectivity (d.r. = 9 : 1 after oxidation of the boronic ester to alcohol **8**). *O*-Troc protection of **8** followed by oxidative cleavage of the PMB ether provided alcohol **10**, which we reacted with Fmoc-(*S*)-Pro-Cl[24] to ester **11** in almost quantitative yield and without epimerization of the α-stereogenic centre of proline. Acidic cleavage of the *tert*-butyl ester gave access to crude carboxylic acid **12**. *N*-Boc deprotection of the modified cysteine building block **13**, followed by coupling with acid **12**, yielded amide **14**, which is a known intermediate of the apratoxin A synthesis reported by Doi *et al.*[10c,11c] To convert **14** into a thiazoline, we applied Kelly's method using Tf_2O and Ph_3PO.[25] For the subsequent cleavage of the Troc carbamate, we examined several conditions, *e.g.* with a Zn/Cu couple or Me_3SnOH[26] as a deprotection reagent, but Doi's protocol using zinc dust and aqueous NH_4OAc[10c,11c] gave **15** in the best yield. Pd-catalysed cleavage of the allyl ester provided carboxylic acid **16**.

We were also interested in preparing apratoxin B[27] for which, to our knowledge, there has not yet been a total synthesis reported. Starting from Boc-(*S*)-Ile-OAllyl (**17b**),[28] we synthesised the tripeptide building block **19b** in two HATU-mediated peptide couplings, achieving excellent overall yield (Scheme 3). The corresponding apratoxin A tripeptide **19a**, in which (*S*)-Ile is replaced by *N*-Me-(*S*)-Ile, was prepared according to known procedures.[10c,11c]

Coupling of the polyketide fragment **16** with Fmoc-deprotected **19a** or **19b** yielded the linear precursors **20a** and **20b**,



Scheme 3 Synthesis of the apratoxin B tripeptide.



Scheme 4 Synthesis of apratoxin A and B.

which we cyclised to the natural products after cleavage of the allyl and Fmoc protecting groups (Scheme 4). As reported in previous syntheses,[10c,d,11c,d] we observed partial epimerization of the stereogenic center adjacent to the thiazoline moiety during the steps from **15** to **21**, and we obtained the cyclisation products as mixtures of two diastereomers **21a/b** and ***epi*-21a/b**. Interestingly, no water elimination to the α,β-unsaturated thiazoline occurred under these conditions. In both cases, we were able to separate the isomers *via* preparative HPLC to isolate the diastereomerically pure natural products.

Conclusions

In conclusion: we have shown that the Matteson homologation is perfectly suited to generating the unusual polyketide fragment of the apratoxins. Starting from a chiral boronic ester (**2**), we were able to prepare the desired building block **8** of apratoxin A and B *via* five successive Matteson homologations and subsequent oxidation, achieving an overall yield of 27% and very good diastereoselectivity. Obviously, even a sterically demanding *tert*-butyl group is well accepted in the boronic ester and, therefore, this protocol should also be perfectly suited for the synthesis of libraries of derivatives for SAR studies, simply by changing the nucleophilic coupling partners in the homologation steps. Further applications are currently under investigation.

Conflicts of interest

There are no conflicts to declare.

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