Stereoselective Synthesis of a Protected Side Chain of Meliponamycin A

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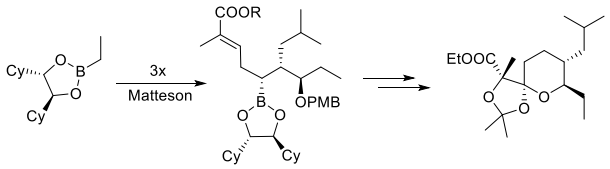
Supporting Information Placeholder

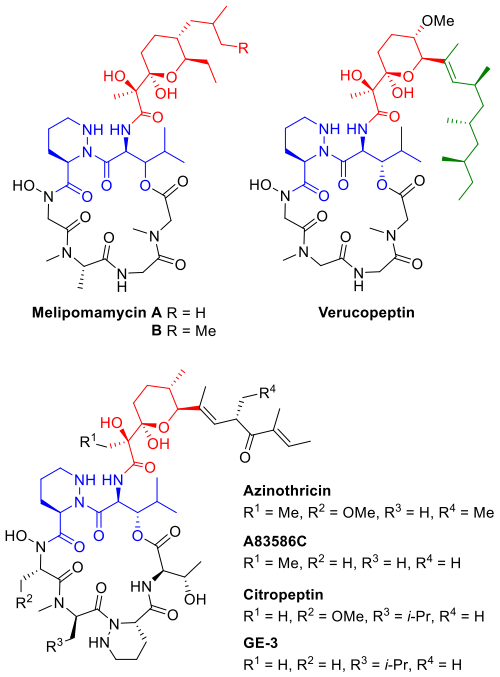


ABSTRACT: The Matteson homologation was found to be a versatile tool for the construction of the linear polyketide side chain of Meliponamycin, and related compounds, in only four steps. The ester dienolate version of this reaction allowed the introduction of the unsaturated ester moiety in a highly stereoselective fashion. Boronate oxidation/desoxygenation and Sharpless dihydroxylation are additional key steps in the stereoselective construction of this highly functionalized tetrahydropyran ring system, which is characteristic of this substance class.

Pupo et al. recently described the isolation of the meliponamycins, new cyclohexadepsipeptides isolated from *Streptomyces* sp. ICBG1318, which is associated with *M. scutellaris* nurse bees (Figure 1).[1] Both compounds show strong activity against human pathogens, such as *Staphylococcus aureus* and *Leishmania infantum*. The most interesting structural feature is a cyclized polyketide fragment containing a tetrahydropyranyl (THP) ring system (red) connected to the piperazic acid β-hydroxyleucine dipeptide fragment (blue) of the depsipeptide ring. This structural motif is found in a range of other cyclodepsipeptides such as the oleamycins,[2] variapeptin[3] and polyoxypeptin.[4] The different natural products vary mainly in the "southern" peptide part (black), which contain additional piperazic acid or hydroxylated building blocks. Most of them feature rather simple alkyl substituents attached to the THP ring. A more elaborated example is verucopeptin (Figure 1), containing a methoxy substituent and a more complex polyketide side chain (green).[5] Comparable side chains are also found in azinothricin[6] and related derivatives such as A83586C,[7] citropeptin[8] or GE-3.[9]

Almost all of these natural products show potent antibiotic and/or anti-cancer activities. Therefore, it is not surprising that several routes have been developed towards their syntheses, along with derivatives, for structure–activity relationship (SAR) studies. Several syntheses exist for the unusual piperazic acid,[10] as well as for the cyclic peptides.[11-13] For around twenty years, the Hale group investigated the syntheses of azinothricin A, A83586C and related compounds. Their ideas and efforts are described in detail in a review article published in 2020.[14]

Figure 1. Natural depsipeptides containing tetrahydropyranyl side chains

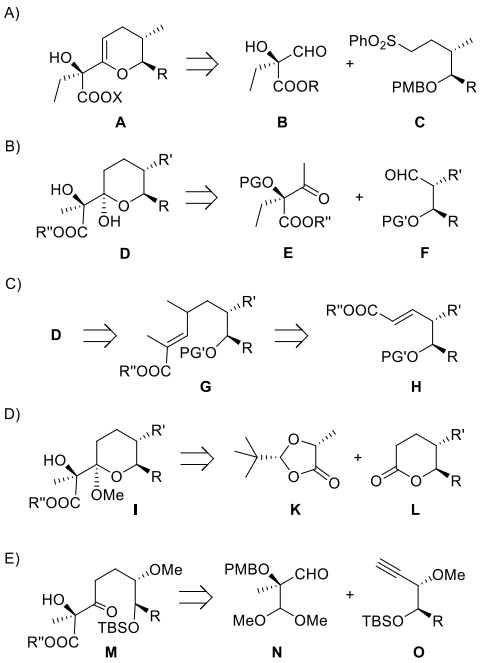


Although the unsaturated side chains of the meliponamycins are less complex than other natural products of the same class, the stereoselective construction of the tetrahydropyran ring is still far from trivial.[15-18] It took several attempts until an activated dihydropyran derivative **A**, suitable for coupling, could be obtained via a Julia-Lythgoe-type addition of deprotonated sulfone **C** onto chiral aldehyde **B**, followed by oxidation, desulfonation, deprotection (PMB cleavage) and water elimination (Scheme 1A). The stereogenic centers of the starting materials **B** and **C** were introduced via Sharpless dihydroxylation and Sharpless epoxidation/epoxide opening, respectively.[19] Hamada et al. used an aldol condensation between the enolate of chiral β-ketoester **E** and chiral aldehyde **F** to generate ester **D**, after hydrogenation and *O*-deprotection (Scheme 1B).[20] **E** was obtained via asymmetric dihydroxylation, while **F** was obtained via an asymmetric aldol addition. **D** was also be obtained via an asymmetric dihydroxylation/oxidation/*O*-deprotection sequence from **G** (Scheme 1C), easily accessible by standard operations from chiral ester **H**.[21,22]

In an alternative approach, Caldwell et al. reported that an asymmetric aldol reaction between an enolate of Seebach ester **K**[23] and a chiral lactone **L** can be used as the key step for controlling the stereochemistry of two newly formed stereogenic centers (Scheme 1D).[24] A subsequent methylation of the hemiketal formed, followed by transesterification provided the required compound **I**. This approach was also used by Lorca and Kurosa as well as Qin and Yao, during their syntheses of polyoxypeptin.[25,26] Their protocols mainly differ in the preparation of the chiral lactone. During the synthesis of verucopeptin, Kateya et al. recently synthesized methoxy-substituted tetrahydropyran-precursor **M** via a nucleophilic attack of alkyne **O** onto chiral aldehyde **N** (Scheme 1E).[27] Both building blocks were obtained following multistep syntheses. The two stereogenic centers adjacent to the alkyne in **N** were introduced via asymmetric aldol addition. The stereogenic centers at the methyl groups of the polyketide chain were the result of several stereoselective transformations.[27,28]

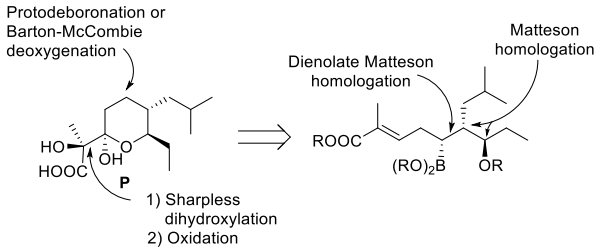
In principle, this part of the molecule should also be accessible via Matteson homologation, an approach which would be expected to generate the required substitution pattern in a highly stereoselective fashion,[29-31] and which was used in several natural product syntheses by the Aggarwal group.[32-34] In contrast to other standard methods in polyketide syntheses, e.g. aldol reactions, this one-carbon homologation allows the introduction of a wide range of substituents (*C*-, *N*-, *O*-nucleophiles) at almost any position of the polyketide chain. We recently used this protocol in the total synthesis of several natural products, such as apratoxin[35], doliculides[36] and lagunamides.[37] Since the synthesis of linear functionalized alkyl chains is a well evaluated protocol, we were interested to see if it might also be suitable for the stereoselective synthesis of heterocycles, such as the tetrahydropyran moiety of the natural products discussed. As an example, we chose the side chain of meliponamycin A as a target structure to develop a straightforward Matteson homologation-based synthetic route. Our retrosynthetic plan is shown in Scheme 2.

Scheme 1. Synthetic approaches toward the tetrahydropyranyl ring system



The idea was to introduce the two stereogenic centers on the righthand side of lactol **P** via classical Matteson homologation and the unsaturated ester substituent by a recently developed ester dienolate homologation.[38] Finally, the boron atom should be removed either by protodeboronation or via oxidation/Barton-McCombie reduction. In principle, hydroxy- or other heteroatom functionalities can also be introduced at this position.

Scheme 2. Our approach

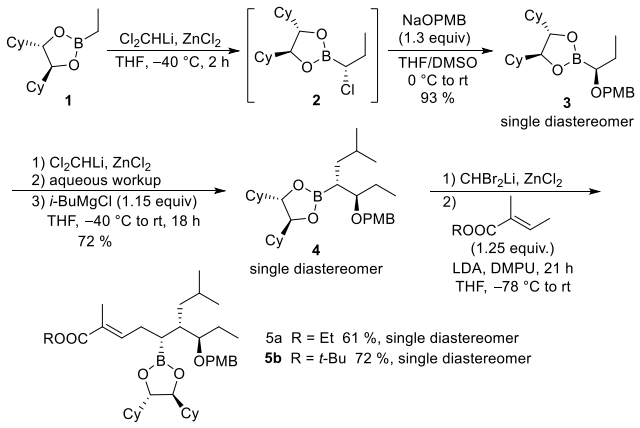


Our synthesis began with ethylboronic ester **1**, containing (*S*,*S*)-1,2-dicyclohexyl-1,2-ethanediol (DICHED) as a chiral auxiliary. Treating of **1** with lithiated dichloromethane in the presence of $ZnCl_2$ generated chiral α-chloroboronic ester **2**, which was directly treated with deprotonated *p*-methoxybenzylalcohol to provide an α-oxygenated boronic ester **3** in excellent yield and as a single diastereomer. The best results were obtained in a mixture of THF and DMSO. The next step was the introduction of the *i*-butyl side chain, which was found to be less trivial than expected. If the reaction was run as a one pot reaction with an excess of Grignard reagent (2.5 equiv), as in the first case, no reaction was observed, even after 5 days. The same is true if the initially formed α-chloroboronic ester was

isolated and then treated separately with *i*-BuMgCl/$ZnCl_2$. $ZnCl_2$ is sometimes used to support the substitution of chloride via chelate complex formation, but in this case product **4** was only observed in the absence of $ZnCl_2$, and the best yields were obtained if the Grignard reagent was used only in slight excess. *i*-Butylboronic ester was formed as a side product, which could be separated by chromatography.

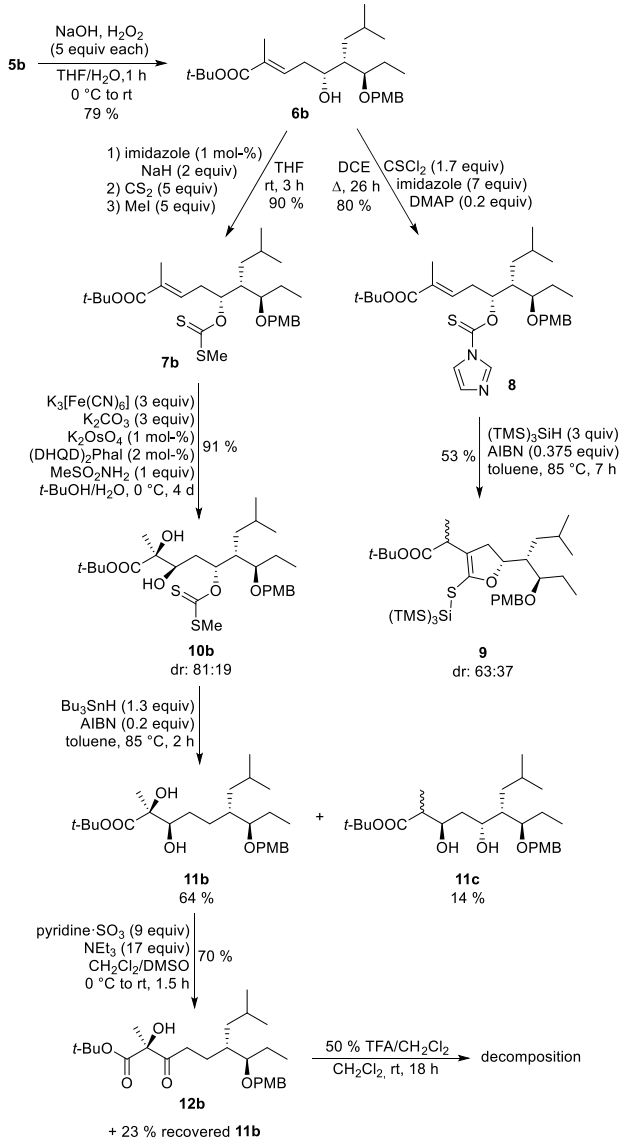
In principle, a CH_2 group could be introduced into **4** via Matteson homologation by either reducing the initially formed α-halogenboronic ester[35] or by directly employing deprotonated bromomethane.[39] After an additional homologation with (dichloromethyl)lithium, the resulting α-chloroboronic ester could be oxidized to an aldehyde and subjected to an olefination reaction.[37] However, we decided to introduce the whole substituent directly in a single step and then remove the boron substituent later in the synthesis. Therefore, dienolates of tiglic esters were employed. Boronic ester **4** was first reacted with lithiated dibromomethane, which acted as a nucleophile to generate the more reactive α-bromoboronic ester, which was directly reacted with the dienolates. The desired unsaturated esters **5a** and **5b** were obtained in synthetically useful yields as single stereoisomers (Scheme 3).

Scheme 3. Synthesis of the side chain carbon skeleton via Matteson homologation



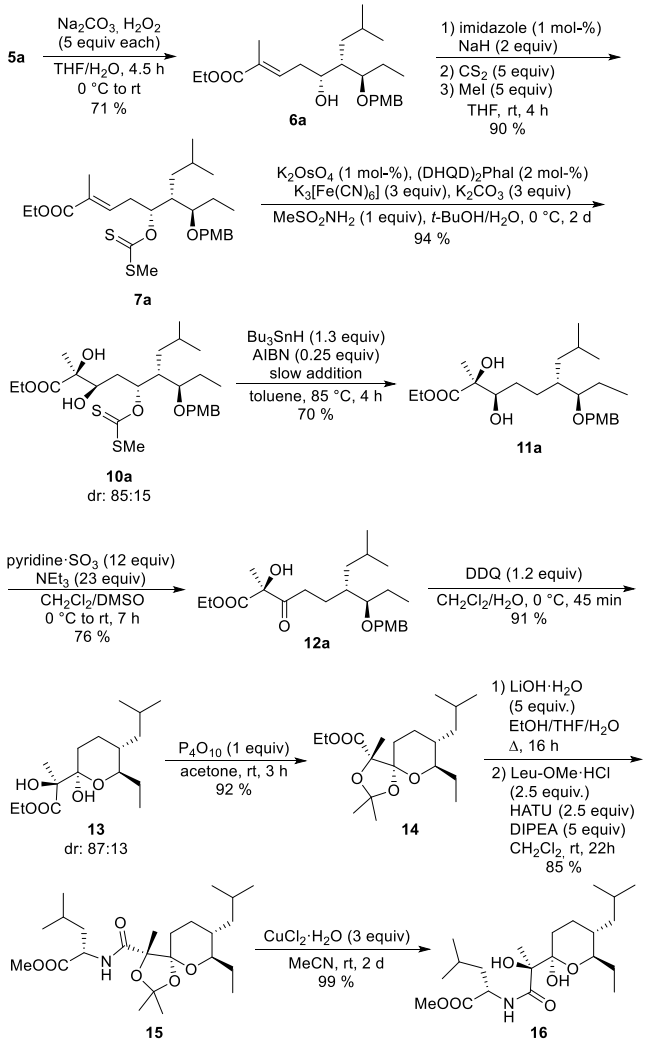
The most straightforward way to **P** would be a removal of the boron substituent by protodeboronation. Although several examples for this kind of reaction have been reported in the literature,[40-42] none of these protocols provided the desired product in our case. Therefore, we decided to oxidize **5b** to the corresponding alcohol **6b** and then use a Barton-McCombie reduction to eliminate the oxygen (Scheme 4). Oxidation of **5b** proceeded uneventfully and without affecting the unsaturated ester. Alcohol **6b** could easily be converted into xanthate **7b** and imidazolide **8**, which were subjected to radical reduction conductions. Unfortunately, the reaction of **8** did not afford the desired reduction, instead delivering dihydrofuran derivative **9**, presumably by addition of the primarily formed radical onto the double bond. In the case of xanthate **7b**, only decomposition of the starting material was observed. As it was clear that the electron-poor double bond was the issue, we decided to perform the radical reduction after the asymmetric dihydroxylation of the double bond. Using commercially available AD-mix β (0.4 mol-% Os), the reaction was very slow and complete conversion was not observed, even after 4 days. Switching to 1 mol-% K_2OsO_4 allowed the desired product **10b** to be obtained in high yield, but with only moderate diastereoselectivity. Interestingly, no reaction was observed with imidazolide **8** under the same reaction conditions. With **10b** in hand, we investigated several reduction conditions, but only a combination of Bu_3SnH/ AIBN provided the desired product **11b** in satisfying yield. Surprisingly, diol **11c** was formed as a side product under these conditions, probably via intramolecular xanthate migration. This side product could easily be removed by chromatography. After the oxidation of alcohol **11b** to ketone **12b**, we attempted the simultaneous cleavage of the PMB ether and the *t*-butyl ester, which would have provided the desired side chain. However, only decomposition of **12b** was observed.

Scheme 4. First attempt to generate the tetrahydropyran ring



This prompted us to also investigate the final steps with unsaturated ethyl ester **5a**, which might be saponified at the end of the sequence (Scheme 5). In the oxidation step of **5a** to **6a**, NaOH was replaced by Na_2CO_3 to avoid premature saponification of the ester. The subsequent xanthate formation to form **7a**, and then dihydroxylation to form **10a**, provided better yields and selectivities than the corresponding reactions to deliver **7b** and **10b** in the previously employed route. To suppress the formation of the side product in the radical reduction step, a procedure where **10a** and AIBN were added slowly to Bu_3SnH was employed. Under these conditions no xanthate migration was observed and **11a** could be obtained in good yield. The subsequent oxidation of **11a** to **12a** was slow and required a large excess of oxidizing reagent, but nonetheless afforded the desired product in good yield. Oxidative cleavage of the PMB ether **12a** resulted in direct cyclization to the derived product **13**, which could be obtained in diastereomerically pure form either by using preparative HPLC or crystallization. All attempts to saponify **13** to the free carboxylic acid failed under all of the conditions used. Instead, deprotonation of the hemiacetal initiated a retro Claisen condensation and the corresponding lactone was isolated as the sole product. To suppress this side reaction, we converted **13** into the acetonide **14**.

Scheme 5. Synthesis of the tetrahydropyran ring system



Its saponification with LiOH proceeded smoothly and the corresponding lithium salt obtained could be directly coupled to an amino acid derivative with high overall yield. Finally, the acetonide was cleaved in high yield using $CuCl_2 \cdot 2\ H_2O$.

In conclusion, we have shown that employing ester dienolates as nucleophiles in Matteson homologation reactions significantly increases the synthetic potential of this protocol and allows the synthesis of polyketide fragments in a highly stereoselective fashion. All stereogenic centers, including the double bond, are obtained as single stereoisomers. Further modifications and applications to natural product syntheses are currently under investigation.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and copies of ^1H and ^{13}C NMR spectra and HPLC chromatograms. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial support from Saarland University and the DFG (Grants: Ka 880/13-1; Bruker Neo 500 - 447298507) is gratefully acknowledged. Thanks to Christine Walt from Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) for support on mass spectrometry.

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