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Stereoselective synthesis of five- and six-membered carbocycles *via* Matteson homologation/ring closing metathesis†

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The Matteson homologation is found to be a versatile tool for the stereoselective synthesis of polyunsaturated alkyl boronic esters, which are excellent precursors for the construction of five- and six-membered carbocycles *via* ring-closing metathesis. The high diversity of the Matteson reaction allows for the preparation of highly substituted cyclic boronic esters, which are also suitable for further homologations.

Introduction

Highly substituted and functionalised carbocycles are widespread in a broad range of natural products, *e.g.* terpenoids, with interesting biological properties. Common structural motifs are substituted saturated or unsaturated cyclopentanes and -hexanes, as well as combinations of both (Fig. 1).[1] Therefore, straightforward and extremely flexible strategies for synthesising these challenging structures are highly desirable. The ring-closing metathesis of functionalised and substituted dienes has been developed as a suitable approach, and many examples have been reported over the last few decades.[2]

We recently reported the synthesis of allyl boronic esters[3] *via* Matteson homologation,[4] which could provide suitable candidates for ring-closing metathesis as long as a second double bond could be incorporated during further homologation steps.[5] Donald Matteson described this interesting reaction initially in the early 1960s[6] and developed it in the 1980s[7] as a valuable tool in organic synthesis.[8]

Typically, a chiral alkyl boronic ester **A** is reacted with deprotonated dichloromethane in the presence of zinc chloride, generating an α-chloroboronic ester **B** in a highly stereoselective fashion (Scheme 1A). The addition of a suitable nucleophile onto the boron atom generates a boronate complex, which undergoes a 1,2-shift of the nucleophile to the α-position, replacing the chlorine in a S_N2-fashion.[5] Ongoing homologation allows the highly stereoselective synthesis of substituted and functionalised carbon chains. Common nucleophiles are alkoxides[9] or organometallic compounds, such as alkyl-lithium or -magnesium reagents.[10] In addition, allyl zinc reagents are well-suited to introduce unsaturated substituents,[11] as well as vinyl organometallics.[3,12]

In contrast to alkyl nucleophiles, which are generally not problematic, vinyl nucleophiles tend to undergo various side reactions, such as vinylboronic ester (**C**) formations (Scheme 1B).[13] However, under optimised conditions, where the vinyl Grignard reagent is added in the presence of $ZnCl_2$, these side reactions can be suppressed almost completely, and allyl boronic ester **D** is obtained in high yields (Scheme 1C).[3]

We are now interested in such allylboronic esters being further homologated and, in particular, if they allow the introduction of a second double bond, generating suitable substrates for ring-closing metatheses. Hoffmann and others[14] have used chiral allyl boronic esters intensively in carbonyl allylations for polyketide syntheses. However, to our knowledge, few examples of Matteson homologations of allyl boronic esters have been reported, probably because of several issues.[13,15] For example, Brown *et al.* reported side reactions, such as allyl migration,[16] and Hirschhäuser *et al.* obtained lowdiastereoselectivity.[17]

Results and discussion

In recent years, we have applied the Matteson homologation successfully in several syntheses of natural products, in par-

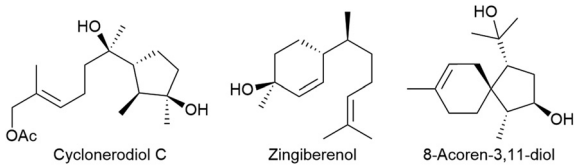

Fig. 1 Selected terpenoid marine natural products.

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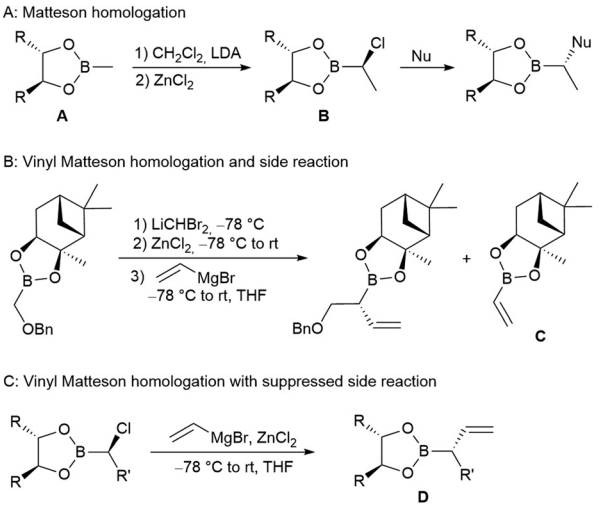
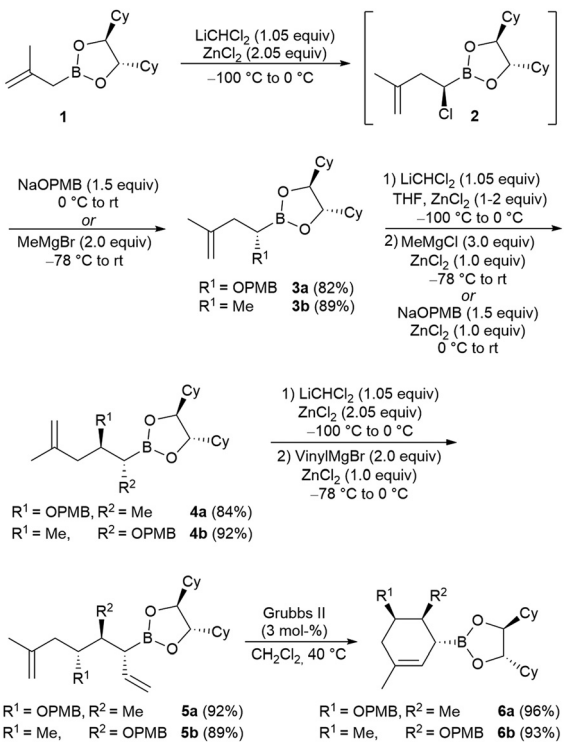


Scheme 1 Matteson homologations.

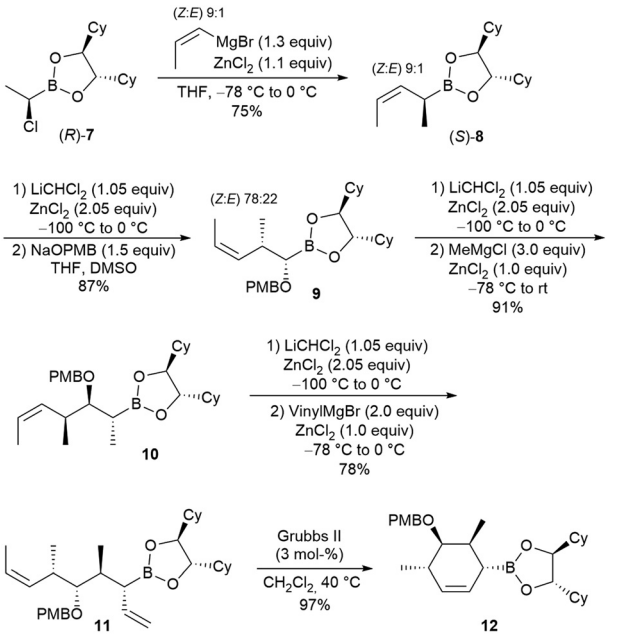
ticular, peptides[18] and peptide/polyketides conjugates.[19] Because of our additional interest in the class of terpenoids, we also investigated methylallylboronic ester **1**, which was converted into the corresponding α-chloro boronic ester **2** under our previously optimised conditions (Scheme 2). To this end, dichloromethane was deprotonated with BuLi at −100 °C, and the addition of **1**, as well as two equivalents of $ZnCl_2$, resulted in the formation of **2**, which was not isolated. The nucleophile, either deprotonated *p*-methoxybenzylalcohol (at 0 °C) or methyl Grignard reagent (at −78 °C), was added, and the mixture was warmed to room temperature over 24 h. Under these conditions, both desired products **3a** and **3b** could be obtained in high yields without forming side products.

The next homologation step proceeded without any problems, and we could obtain the two products **4a** and **4b** with an inverted substitution pattern. For the introduction of the second double bond, we used vinyl magnesium bromide in the third homologation step.[3] In this case, the corresponding α-chloroboronic ester of the first step was isolated and reacted in the presence of exactly one equiv. $ZnCl_2$ with vinyl magnesium bromide. Even with an excess of Grignard reagent, excellent yields of the desired allyl boronic esters **5a** and **5b** were obtained without the formation of vinylboronic ester as the commonly observed side product. Ring-closing metathesis was performed at 40 °C using second-generation Grubbs catalyst[20] generating cyclohexene derivatives **6** containing three stereogenic centres and a threefold substituted double bond. Clearly, the substitution pattern of the linear precursor had no significant influence on the homologation or the cyclisation step.

To also acquire access to fourfold substituted cyclohexenes, we started with the known α-chloroboronic ester **7**,[3,11] which was reacted with (*Z*)-1-propenyl magnesium bromide (Scheme 3). The Grignard reagent was freshly prepared from pure (*Z*)-1-bromopropene, but the desired boronic ester **8** was obtained as a 9 : 1 (*Z*/*E*) mixture. During the formation of the Grignard reagent, partial (*Z*/*E*)-isomerisation occurred. However, in our case, this phenomenon was completely irrelevant because the methyl substituent would be finally removed in the metathesis step. For this reason, the commercially available *E*/*Z* mixture of 1-bromopropene can also be used as an alternative to pure (*Z*)-1-bromopropene.



Scheme 2 Synthesis of threefold substituted cyclohexenes **6**.



Scheme 3 Synthesis of tetrafold substituted cyclohexene **12**.

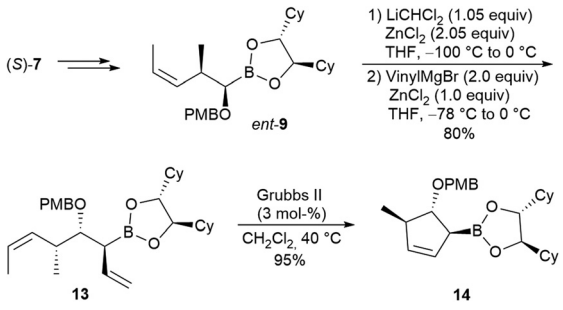
The prolongation of the alkyl chain was performed as described, but interestingly, the (*Z*/*E*)-ratio changed slightly in the subsequent homologation step. This result was rather surprising since the reaction conditions should not cause an isomerisation of the double bond.

One explanation might be that the homologation of allylboronic ester **8** does not proceed in a S_N2- but a $S_{N'}$-fashion, at least in part. While $S_{N'}$ substitution did not change the substitution pattern in this case, it can influence the double-bond geometry *via* allyl migration. Since the double bond configuration did not matter in our case, we proceeded with the following two homologation steps to boronic ester **11**. Its ring-closing metathesis provided the highly substituted cyclohexene **12** as a single stereoisomer in almost quantitative yield.

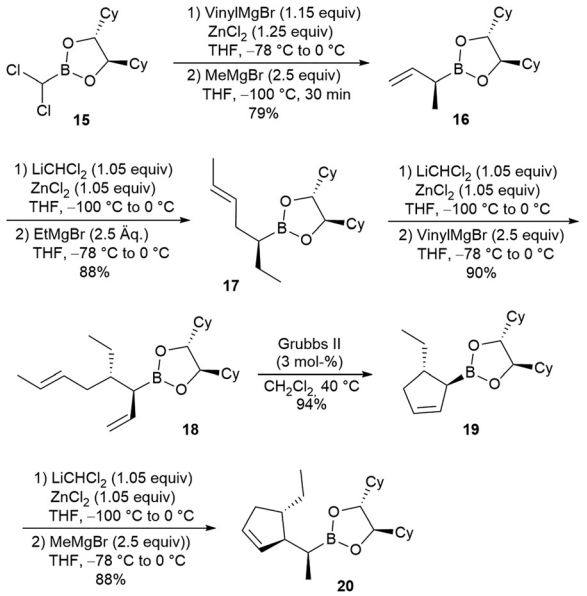
The corresponding five-membered ring systems also became available by simply reducing the number of homologation steps (Scheme 4). The enantiomer of **9** (*ent*-**9**), obtained from the boronic ester (*S*)-**7** containing the enantiomeric chiral ligand, was directly converted into the allylboronic ester **13**, which was cyclised to cyclopentene **14** in comparable yield.

Finally, we looked more closely at the isomerisation of the double bond in the homologation of allylboronic ester **8**. We assumed that at least a partial $S_{N'}$ might occur during homologation. In principle, this might also happen with boronic ester **1** but, in this case, does not influence product formation.

To investigate this option, we synthesised α-methylated boronic ester **16** starting form known dichloroboronic ester **15** (Scheme 5).[14] This smart approach allowed the synthesis of both diastereomeric boronic esters simply by changing the order of nucleophile introduction. We used vinylmagnesium bromide in the first step and methylmagnesium bromide in the second. Therefore, the configuration at the α-position was the opposite of that in the previous example (**8**), where the methyl group was incorporated first. However, unexpectedly, in the next homologation step, the expected homologation product was not formed at all, but the derivative with a linear side chain and a terminal methyl group at the double bond developed instead. In this case, the homologation proceeded exclusively in a $S_{N'}$ mode, giving rise to the *trans*-configured product **17** exclusively. This $S_{N'}$ reaction was already observed for the formation of the corresponding α-chloroboronic ester intermediate, whereas the second step (nucleophile addition) proceeded in the expected way. Further homologation and ring-closing metathesis provided the double-substituted cyclopentene **19**, again in excellent yield.



Scheme 4 Synthesis of threefold substituted cyclopentene **14**.



Scheme 5 Synthesis of threefold substituted cyclopentene **19**.

In all examples investigated, the resulting metathesis products were also allylboronic esters. Therefore, we exemplarily undertook a subsequent homologation step with **19** to ensure the cyclic alkenes could be prolonged predictably. Furthermore, the accustomed high yield could be obtained, indicating that this protocol is well suited for synthesising complex carbocyclic structures. More detailed investigations concerning the allyl migration during the homologation of allylboronic esters are currently underway.

Conclusions

In conclusion, we showed that the high diversity of the Matteson homologation along with the functional group tolerance of the ring-closing metathesis generates an effective tool for the stereoselective synthesis of complex natural products and related structures. No stereoisomers formed in any reaction step, except during allyl migration. However, this isomerisation is not reflected in the final products.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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