RESEARCH ARTICLE

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Synthesis of oxylipids *via* a boronic ester cycloetherification approach†

Markus Tost [iD] and Uli Kazmaier [iD] *

Deprotonated trimethylsilylethanol can be used as a nucleophile in Matteson homologations. This *O*-protection group is stable under the usual reaction conditions of the Matteson reaction, but after two further homologation steps it is automatically cleaved off and cycloetherification can take place, giving rise to substituted tetrahydrofurans in a highly stereoselective fashion. This elegant protocol was used in the synthesis of various oxylipids.

Introduction

Substituted tetrahydrofurans (THFs) are frequently occurring secondary metabolites of terrestrial[1] as well as marine organisms.[2] For example, the large group of amphidinolides[3] are rather complex macrolides, many of which show antitumor activities, often in the nanomolar range. In addition to 2,5-disubstituted THF structures, 2,3,5-trisubstituted THFs are also often found in bioactive natural products, that's why new synthesis strategies for their total synthesis are of great interest.[4] In addition to methyl groups, the substituents are usually hydroxy groups (acylated and alkylated) (Fig. 1). For example, *trans*-Kumausin is isolated from the red algae *Laurencia nipponica*,[5] while the lipid diols *trans*-oxylipid and *cis*-oxylipid are produced by brown algae on the south coast of Australia.[6,7] Both oxylipids show antihelmintic activity *in vitro*, which prevents larval development in parasitic nematodes.

The pharmacologically interesting properties of these natural products initiated the development of a large number of syntheses towards these unusual structures. A recent review article by Fernandes *et al.* very nicely compiles the different synthesis routes reported so far.[4a] For example, intramolecular epoxy openings[8] lead to α-oxygenated THF motifs, as in oxylipids.[9] Oxa-Michael additions succeed in the formation of cyclic β-oxygenated ketones and carboxylic acid derivatives,[10] as they are found in amphidinolides,[11] to name just a few methods. In nature, too, these THF motifs are often built up from linear polyketides *via* cyclization reactions.[2a]

The highly diastereoselective Matteson homologation (Scheme 1) should also be suitable for the synthesis of substituted tetrahydrofurans, as it allows the formation of arbitrarily substituted and functionalized carbon chains. The reaction of deprotonated dichloromethane with chiral boronic acid esters **A** yields α-chloroboronic acid ester **B** in a highly stereoselective fashion, which can then be further reacted with nucleophiles (Nu⁻), such as Grignard reagents, alkoxides or enolates to yield homologated boronic ester **C** (Scheme 1a).[12] In general, the products are formed as single stereoisomers, based on the double diastereo-differentiating reaction mechanism.[13] The repetition of this reaction sequence enables the stereoselective synthesis of highly substituted carbon chains with adjacent stereocenters. As a rule, the carbon chain can be extended without problems, only in case of alkoxy-substituted boronic esters there are sometimes long reaction times and moderate yields. This effect is particularly pronounced for δ-alkoxy-substituted boronic esters, in which the Lewis-basic oxygen very likely coordinates to the Lewis-acid boron atom and thus prevents the addition of another nucleophiles.[14] On the other hand, such an interaction should also activate the oxygen as a leaving group, so that the *O*-substituent can be split off more easily. During studies on the synthesis of leuconolides,
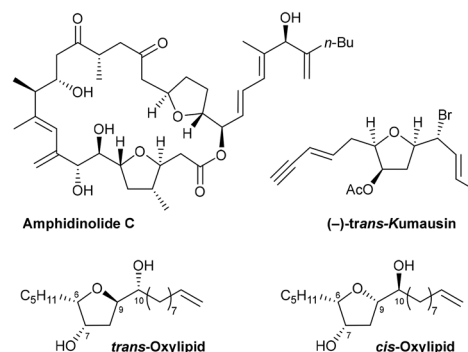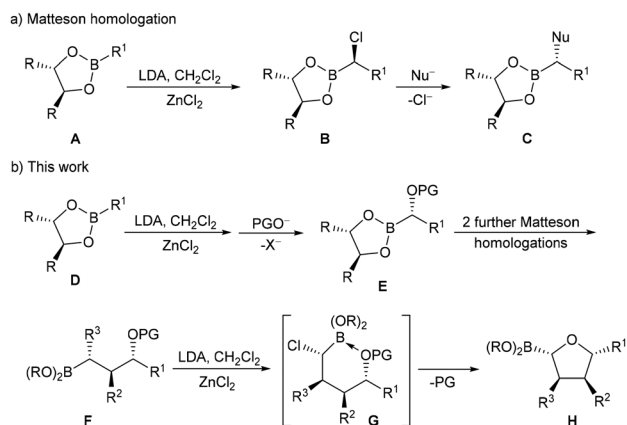
Organic Chemistry, Saarland University, P.O. Box 151150, 66041 Saarbrücken, Germany. E-mail: u.kazmaier@mx.uni-saarland.de

Fig. 1 Structures of selected THF-containing natural products.

Amphidinolide C

(–)-*trans*-Kumausin

trans-Oxylipid

cis-Oxylipid

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Scheme 1   Matteson homologation and new application.

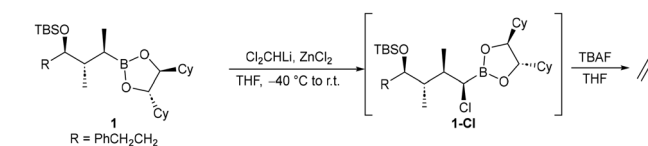Scheme 2   First attempts of boronic ester cycloetherification.

Matteson *et al*. observed the partial cleavage of a benzyl ether, which indicates exactly such an activation.[14]

Results and discussion

Our research group has been working for years on the synthesis of natural products, in particular peptides[15] and peptide–polyketide conjugates.[16] The Matteson homologation is increasingly[17] being used, and we were interested to see if this very useful reaction can also be used to generate polyketides and polypropionates with such furan substructures.

Therefore, our goal was to build up substituted THF motifs, as in oxylipids, by boronic ester cycloetherification (Scheme 1b). Starting from boronic acid ester **D**, the α-chloroboronic acid esters **G** should be accessible *via* four iterative Matteson homologation steps. Subsequent deprotection of the alcohol and cyclization should lead to THF-derivative **H**. The method should take advantage of the fact that a 6-ring chelate of **G** can be formed with a suitable protecting group (PG) who's cleavage is activated by the Lewis acid boron.[14] Therefore, it was necessary to find a suitable protecting group, which can be introduced directly *via* the Matteson reaction, which is stable under the usual reaction conditions, and which can also be split off again, if necessary, under conditions compatible with the boronic acid ester.

In search of a suitable *O*-protecting group, we turned to the *tert*-butyldimethylsilyl (TBS) protecting group, which can be split off with fluoride or under acidic conditions. The corresponding TBS-protected boronic ester **1** could be obtained simply by a protecting group switch from the corresponding benzylether. Homologation to the α-chloroboronic ester **1-Cl** proceeded without any problems, but the TBS protection group could not be split off with TBAF, even using several equivalents and long reaction times (Scheme 2). Attempts using acidic conditions were also unsuccessful and the use of HF or Py–HF led to the decomposition of the boronic acid ester.
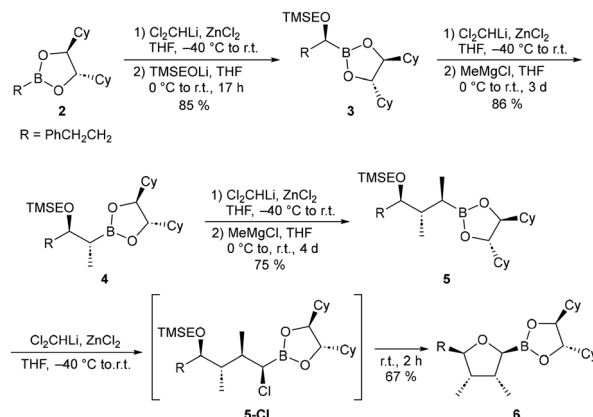
Since we suspected that the steric demand of the TBS group could prevent coordination towards the boron, we decided to switch to the smaller trimethylsilylethyl (TMSE) protecting group. This functionality can also be split off with fluoride,[18] whereby the corresponding alcoholate is formed under fragmentation and ethylene cleavage. In this case, a possible attack of the fluoride takes place further away from the coordinated *O*-atom and we hoped that steric aspects would not play a role in this case.

As a first example, boronic ester **2** was reacted with deprotonated dichloromethane and subsequently with trimethylsilyl ethanolate, providing the desired boronic ester **3** in good yield (Scheme 3). The two subsequent homologation steps under standard conditions also proceeded without any problems giving rise to boronic ester **5**, which we needed for our cyclization experiments. During the further homologation of **5**, the corresponding α-chloroboronic ester **5-Cl** could be detected in the reaction mixture by NMR spectroscopy, but it underwent the desired cycloetherification to **6** directly within 2 h. Obviously, the chloride present in the reaction mixture is already sufficient to split off TMSCl and ethylene from the oxygen, activated by coordination, whereby the boron alcoholate formed in this process undergoes an S_N2-like 1,2-shift to THF derivative **6**.

With this successful cycloetherification in our hands, we turned to the application of this method for the synthesis of natural products and comparable structures. We focused on the class of oxylipids, whereby the *cis* and the *trans* form differ primarily in the position of the substituents at the 2,5-position of the tetrahydrofuran ring (C-6, C-9) and in the position of the OH group at C-10 (Fig. 1).
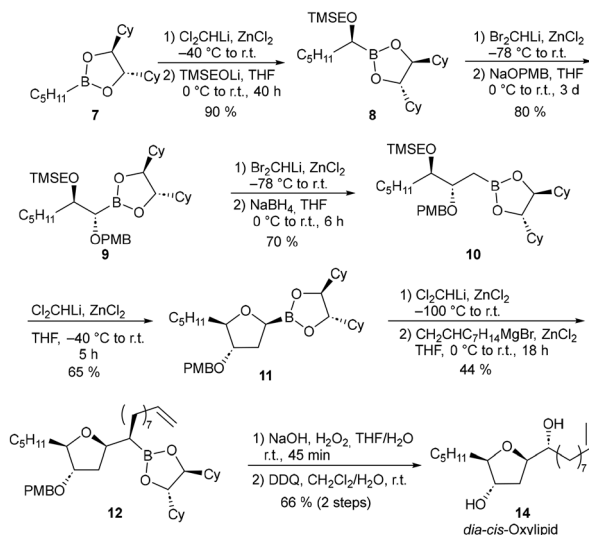

Scheme 3   Successful cycloetherification using cleavable TMSE ethers.

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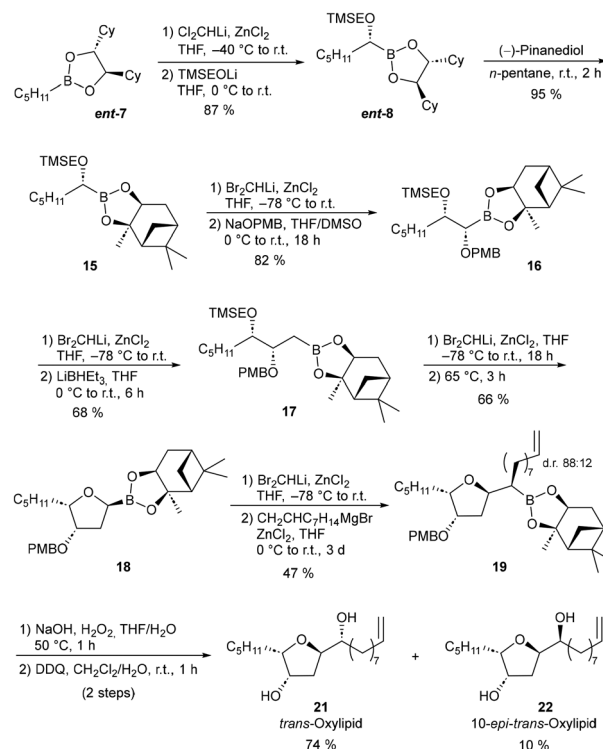*Org. Chem. Front.*, 2025, **12**, 3288–3292 | **3289**

To test the reaction sequence on a simple example first, we decided to start with the synthesis of a *dia-cis*-oxylipid (Scheme 4). In Matteson homologations, neighboring stereogenic centers are always introduced in a 1,2-*anti*-configuration, which in the case of oxylipids should lead to the *dia-cis*-oxylipid **14**. Although we were recently able to show that the configuration of methyl groups can be reversed in growing chains,[19] this is not so easy to do with hydroxyl groups and requires additional steps.

In our case, the *n*-pentyl boronic ester **7** was first homologated with Cl₂CHLi and then converted to boronic ester **8** with lithium trimetyhlsilylethanolate under the previously optimized conditions (Scheme 4). Subsequent homologation with deprotonated dibromomethane yielded the α-bromoboronic ester, which was not isolated but directly reacted with NaOPMB to form boronic ester **9**. Further homologation with deprotonated dibromomethane and reduction of the α-bromoboronic ester formed allowed the introduction of a methylene group in boronic ester **10**,[20] which was then subjected to cycloetherification under the previously optimized conditions to the THF derivative **11**. The yield achieved was comparable to that of our model reaction (Scheme 3). To complete the synthesis, **11** was reacted with Cl₂CHLi at −100 °C and the corresponding α-chloroboronic ester was reacted with freshly produced 8-nonen-1-ylmagnesium bromide in the presence of ZnCl₂ to form boronic acid ester **12**. Its oxidation to the protected alcohol (**13**) and subsequent DDQ-mediated cleavage of the PMB ether led to the desired 7-*epi-cis*-oxylipid **14** as a single diastereomer. By using the enantiomeric boronic ester ***ent*-7**, the enantiomeric 7-*epi-cis*-oxylipid could also be obtained.

The enantiomeric *n*-pentyl boronic ester ***ent*-7** was also used to obtain *trans*-oxylipid (**21**) (Scheme 5). As already indicated, alkyl groups can be inverted quite easily, but a reversal of the configuration of alkoxy residues is not a trivial issue.[21]

Scheme 5 Boronic ester cycloetherification in the synthesis of *trans*-oxylipids.

Unfortunately, some approaches described in the literature[22] could not be transferred to the C₂-symmetric boronic acid DICHED esters. An alternative approach, however, is the transesterification of a boronic ester with the inversely directing auxiliary, which of course requires additional efforts.[23] In the case of DICHED-boronic ester, a transesterification to the inversely directing pinanediol-boronic ester is reported[24] as comparably effortless due to the higher thermodynamic stability, which is why we chose this approach (Scheme 5).[25] ***Ent*-7** was homologated as described before with Cl₂CHLi and then converted to ***ent*-8** with TMSEOLi. For transesterification, this boronic ester was dissolved in ether and reacted with 1.1 eq. (−)-Pinanediol, according to a protocol described by Hirschhäuser *et al.*[26] Free (*R*,*R*)-DICHED gradually dropped out of the solution, with an equilibrium after 4 d with a conversion rate of 93%. However, if the reaction was not carried out in ether but in pentane, the thermodynamically more stable pinandiol boronic acid ester **15** was quantitatively formed in 2 h, since shortly after the addition of the pinanediol, (*R*,*R*)-DICHED precipitated out of the solution and was thus removed from equilibrium. **15** could thus be obtained in a very good yield, easily separated from excess pinanediol and DICHED. In a subsequent homologation with Br₂CHLi and substitution with NaOPMB, the 1,2-*syn* substituted boronic acid ester **16** was obtained in good yield. In the subsequent homologation step Br₂CHLi was also chosen in analogy to the last step, as with Cl₂CHLi β-elimination was observed as a side reaction. Subsequent substitution with LiBHEt₃ resulted in

Scheme 4 Synthesis of 7-*epi-cis*-oxylipid **14** *via* cycloetherification.

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boronic acid ester **17**. The subsequent cycloetherification was successful with both the corresponding α-chloroboronic ester and the α-bromoboronic ester, but the ring closure to **18** only took place at an elevated temperature. Interestingly, the subsequent homologation with Cl_2CHLi and substitution with the Grignard reagent yielded a significantly worse yield (27%) and poorer selectivity (dr 68 : 32) than the reaction *via* the corresponding α-bromoboronic ester (dr 88 : 12). After oxidation to the alcohols (**20**) and DDQ-mediated cleavage of the PMB protection group, *trans*-oxylipid **21** as well as the corresponding diastereomer 10-*epi-trans*-oxylipid **22** were obtained and chromatographically separated.

Conclusions

In summary, Matteson homologation is not only suitable for the synthesis of substituted linear carbon chains in a highly stereoselective manner, but also cyclic tetrahydrofuran motifs. For example, deprotonated trimethylsilylethanol can be used as a nucleophile without any problems, the trimethylsilylethyl protection group is stable under the usual reaction conditions, but after two further homologation steps it is automatically cleaved off and cycloetherification takes place. This elegant protocol was used in the synthesis of various oxylipids.

Data availability

Electronic Supplementary Information (ESI) available: Copies of ^1H and ^{13}C NMR spectra and experimental details. See **https://doi.org/10.1039/D5QO00213C**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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