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Stereoselective Syntheses of Highly Substituted Tetrahydrofurans based on Matteson Homologations

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Deprotonated trimethylsilylethanol is an excellent nucleophile for Matteson homologations. It can be introduced in high yields and the products are stable under the usual basic reaction conditions. After two further homologation steps, the protective group is automatically cleaved off via a six-membered ring *O-B* coordination, providing highly substituted tetrahydrofurans.

Substituted tetrahydrofurans are widespread structural motifs in a variety of natural products of terrestrial[1] and marine organisms.[2] For example, uvaricin, which was first isolated in 1982 from plants of the *Annonaceae* family, belongs to the large substance class (>500 members) of acetogenins, many of which have cytotoxic, antiparasitic or neurotoxic effects (Figure 1).[3] All of them contain multiple, differently substituted tetrahydrofurans. Nonactin, isolated from *Streptomyces griseus subsp. griseus* ETH A7796,[4] belongs to the large family of naturally occurring cyclic ionophores, also known as macrotetrolide antibiotics.[5] Macrolidic Amphidinolides from marine dinoflagellates, containing a wide range of substitution patterns.[6] Many of them contain more or less highly substituted tetrahydrofuran rings and often show antimicrobial or antifungal as well as cytotoxic properties.[7] In addition to the widely distributed 2,5-disubstituted tetrahydrofurans, the 2,3,5-trisubstituted or α-methylated THF derivatives are also ubiquitous in bioactive natural products, such as in amphidinolide Y. Due to the diverse and interesting biological activities of these compounds, it is not surprising that a large number of synthetic routes have been developed to build up these differently substituted tetrahydrofurans.[8] For example, intramolecular epoxy opening[9] leads to α-oxygenated THF motifs, such as in uvaricin.[10] Oxa-Michael additions succeed in the formation of cyclic β-oxygenated carboxylic acid derivatives,[11] as they are found in nonactins, to name just a few methods.

Our research group has been working for years on the synthesis of natural products, in particular peptides[12] and peptide-polyketide conjugates.[13] The Matteson homologation[14] is increasingly being used for this purpose, and we wanted to see if this very useful reaction could also be used to build polyketides and polypropionates with such furan substructures.

The Matteson homologation is a stereoselective extension reaction of boronic acid esters (Scheme 1a). The reactions of deprotonated dichloro- or dibromomethane with chiral boronic acid esters **A** provide highly stereoselective α-haloboronic acid esters **B**, which can be further reacted with various nucleophiles (Nu), such as Grignard reagents, alkoxides or enolates (Scheme 1a).[15] In general, the products are formed as single stereoisomers, based on the double diastereo-differentiating reaction mechanism.[16] In this respect the classical auxiliary-based Matteson reaction is superior to other versions, such as Aggarwal's lithiation–borylation protocol[17] or the recently described catalytic enantioselective homologations by Jacobsen *et al.*,[18] although these methods also can provide excellent *ee*-values.

The repetition of the reaction sequence enables the stereoselective synthesis of highly substituted carbon chains with 1,2-*anti*-configured adjacent stereocenters. While the addition of Grignard reagents usually proceeds without problems and in high yields, the addition of alkoxides can occasionally cause problems, especially in further extensions of alkoxy-substituted boronic acid esters.[19] These problems are particularly pronounced in δ-alkoxy-substituted boronic esters, in which the Lewis-based oxygen very likely coordinates to the Lewis-acid boron atom and thus prevents the addition of nucleophiles.[20] On the other hand, such an interaction should also activate oxygen as a leaving group, so that the *O* substituent can be

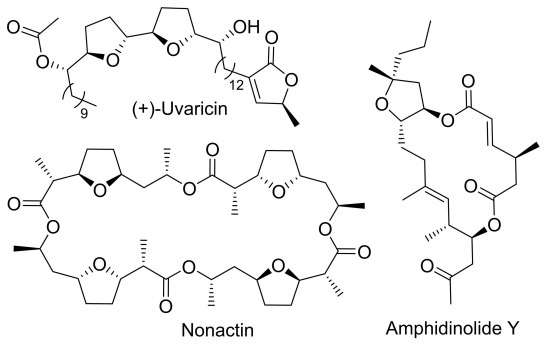

Figure 1. Natural products containing substituted tetrahydrofurans.

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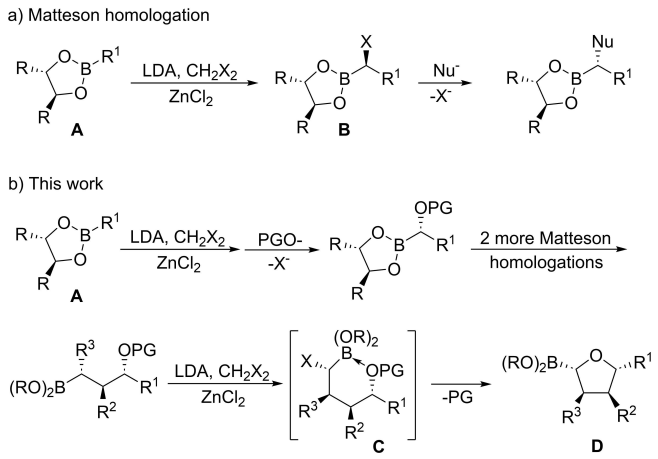
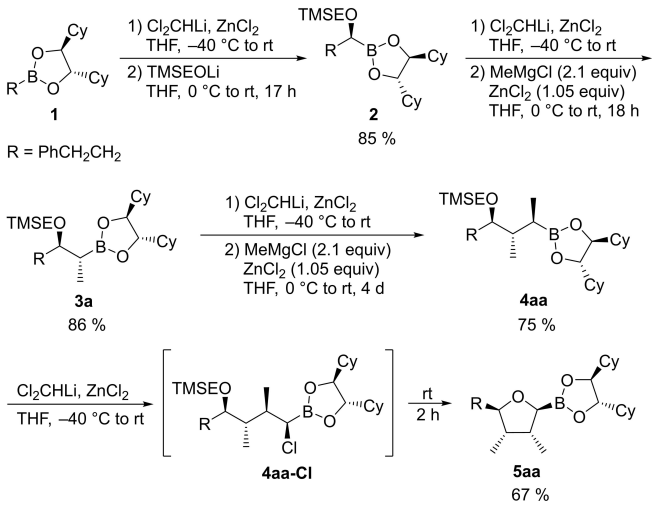


Scheme 1. The Matteson homologation.



Scheme 2. Synthesis of highly substituted tetrahydrofuran **5aa** via Matteson homologation.

split off more easily. During studies on the synthesis of leuconolides, Matteson et al. observed the partial cleavage of a benzyl ether, which indicates exactly such an activation.[20]

Therefore, we were interested to see if such a coordination/protecting group cleavage effect could also be utilized to build up highly substituted furans (Scheme 1b). The aim was to find a protection group (PG) that can be easily introduced, which is completely stable under the usual conditions of Matteson homologation, but which can be split off in the event of a coordination to the boron atom (**C**), preferably also under the reaction conditions. The resulting alkoxide already coordinates to the boron atom and should replace the halogen atom in an intramolecular S_N2 reaction to form the desired tetrahydrofuran **D** (Scheme 1b).

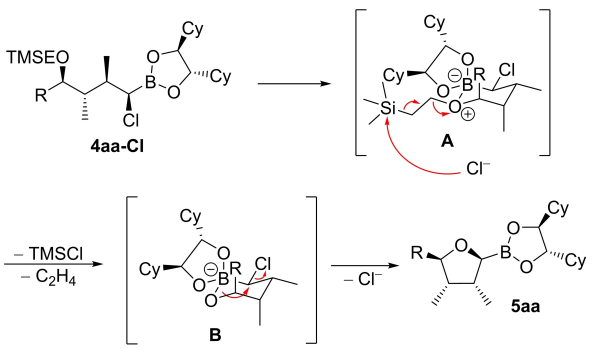
The decisive question was which protecting group is suitable for such a reaction sequence. In a first attempt, TBS protection group was used, but cleavage of this protecting group under acidic conditions or with fluoride agents could not be achieved, probably due to the high affinity of boron to fluorine. We therefore chose the trimethylsilylethyl protection group (TMSE), which is also cleaved off with fluoride,[21] whereby the corresponding alcoholate is formed via fragmentation and ethylene release.[22] While the use of fluoride proved critical before, we had the hope that a cleavage of this PG could be achieved with other halides present under the usual reaction conditions of Matteson homologations.

Accordingly, the boronic acid ester **1** was homologated to the corresponding α–chloroboronic ester and then reacted with lithium trimethylsilylethanolate as a nucleophile (Scheme 2), providing the desired product **2** in high yield as a single stereoisomer. In the subsequent homologation and reaction with MeMgCl the boronic ester **3a** was also obtained in good yield (80%). However, if the reaction was conducted as a one-pot reaction, the reaction was very slow and took almost three days for completion. The reduced reactivity in reactions with Grignard nucleophiles caused by an alkoxy residue in proximity to the leaving group is not uncommon and has already been observed by Matteson and Peterson.[19]

We could solve this problem by isolation of the α-chloroboronic ester and its reaction with the Grignard reagent and $ZnCl_2$ in a ratio of 2:1. This diminished the reaction time to 18 hours. Unfortunately, similar conditions in the following homologation step to compound **4aa** didn't lead to comparable reduced reaction times and the formation of about 3% of methylboronic ester **1a**. This might be caused by the reaction of the desired product **4aa** with the Grignard reagent used in excess.[23] Probably, a boronate complex is formed, which leads to the formation of the alkyl boronic ester during hydrolysis. Unfortunately, the excess of the Grignard reagent is necessary for full conversion, since the α-chloroboronic ester cannot be separated from boronic ester **3a**.

During the further homologation of compound **4aa**, the corresponding α-chloroboronic ester **4aa-Cl** could be determined by NMR, but within 2 h the desired cycloetherification product **5aa** was received directly.

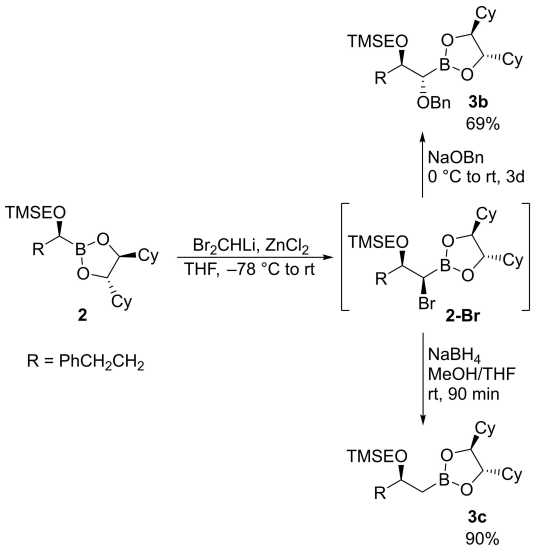
A possible cyclization scenario is shown in Scheme 3. The intermediate α-chloroboronic ester **4aa-Cl** probably forms the desired *O*–*B*–6–ring chelate complex **A**. Due to the positive (formal) charge on the oxygen atom, a cleavage of the TMSE protection group is favored, and chloride from the reaction mixture is already sufficient to eliminate TMSCl and ethylene,



Scheme 3. Proposed mechanism for cycloetherification.

whereby the boron alcoholate formed in this process undergoes an S_N2-like 1,2-rearrangement to the THF derivative **5 aa**.

The Matteson reaction allows for the use of a large number of different nucleophiles in the substitution step. In addition to methyl groups, naturally occurring THF motives also have unsubstituted CH_2 and hydroxyl groups as functionalities. Compound **2** was therefore subjected to two further homologations and was converted on one hand with benzyl alcoholate to **3 b** (Scheme 4). In this case, homologation was carried out with Br_2CHLi to the more reactive α-bromoboronic ester in order to facilitate the introduction of the alcoholate in the vicinity of an alkoxy residue.[19] Compared to the analogue α-chloroboronic ester, the yield could be increased from 46% to 69% and no epimerization at the α-*C* atom was detected. To extend by a CH_2 unit, the corresponding α-bromoboronic ester was reduced to **3 c** with $NaBH_4$.



Scheme 4. Synthesis of boronic esters **3 b** and **3 c**.

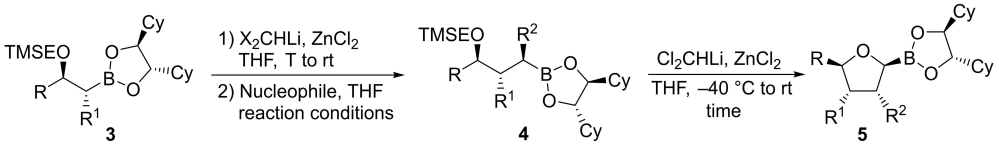
To expand the substrate scope for the cycloetherification, the compounds **3 a–c** were homologated again and substituted with different nucleophiles (Table 1). Starting from **3 a**, the two derivatives **4 ab** and **4 ac** were obtained in good yields. Compound **3 b** was transferred to the α–bromoboronic ester, then isolated and converted to **4 ba** with MeMgCl. The corresponding α–chloroboronic ester led to poorer yields and the formation of byproducts during the substitution step, especially in the presence of Zn salts.

For the introduction of benzyl alcoholate, the α-bromoboronic ester could be converted in a one pot reaction to **4 bb**. By reduction with $NaBH_4$, **4 bc** could be successfully obtained. **3 c** could be converted into the corresponding α-chloroboronic ester which was reacted directly with MeMgCl to **4 ca**. Compared to compound **4 aa**, the reaction time was significantly shortened due to the lower steric hindrance and no methylboronic ester **1 a** could be detected as byproduct. The introduction of the alcoholate to compound **4 cb** was just as easy as the reduction of the analogue α-bromoboronic ester with $NaBH_4$ to **4 cc**.

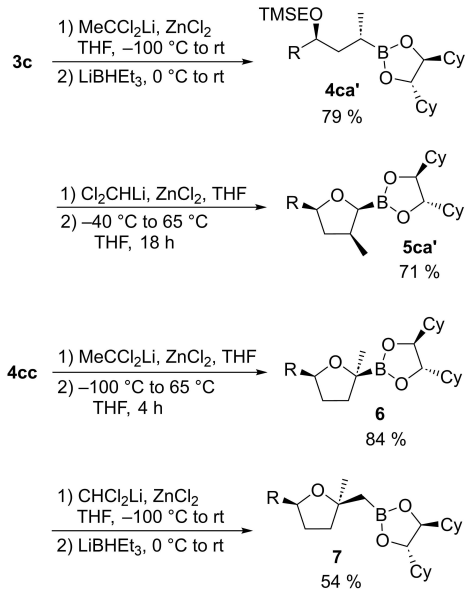
The new compounds **4** were then homologated with Cl_2CHLi to check whether the cycloetherification takes place on these substrates as spontaneously as in the first example (Scheme 2). The benzyl ether **4 ab** was tolerated in cycloetherification, which was also completed after 2 hours. Interestingly, for **4 ac**, the reaction was found to be much slower. Overall, cyclizations were successfully carried out on all substrates with yields of 50–79%, with the higher substituted substrates in particular cyclizing within a few hours. The less substituted substrates required a significantly longer reaction time, especially for **4 cc**, which can be explained by the lack of the Thorpe-Ingold effect.[24]

The classical Matteson homologation always yields 1,2-*anti*-substituted products in a highly stereoselective manner. In order to obtain the corresponding diastereomeric products, homologation with CH_3CCl_2Li and subsequent reduction is recommended (Scheme 5).[25] Via this protocol, the diastereo-

Table 1. Cycloetherifications.



3	R^1	X	T [°C]	Reaction Conditions	R^2	4	Yield [%]	Time	5	Yield [%]
3 a	Me	Cl	−40	BnONa, THF, 0 °C to rt, 3 d	OBn	**4 ab**	86	2 h	**5 ab**	67
3 a	Me	Br	−78	$NaBH_4$, MeOH/THF, rt, 2 h	H	**4 ac**	77	5 h	**5 ac**	79
3 b	OBn	Br	−78	MeMgBr, THF, −0 °C to rt, 14 h	Me	**4 ba**	66	3 h	**5 ba**	50
3 b	OBn	Br	−78	BnONa, THF, 0 °C to rt, 20 h	OBn	**4 bb**	57	16 h	**5 bb**	53
3 b	OBn	Br	−78	$NaBH_4$, MeOH/THF, rt, 3 h	H	**4 bc**	71	6 h	**5 bc**	78
3 c	H	Cl	−40	MeMgBr, THF, 0 °C to rt, 24 h	Me	**4 ca**	79	16 h	**5 ca**	72
3 c	H	Cl	−40	BnONa, THF, 0 °C to rt, 18 h	OBn	**4 cb**	56	24 h	**5 cb**	64
3 c	H	Br	−78	$NaBH_4$, MeOH/THF, rt, 3 h	H	**4 cc**	81	3 d	**5 cc**	72



Scheme 5. Application of methylated carbenoids.

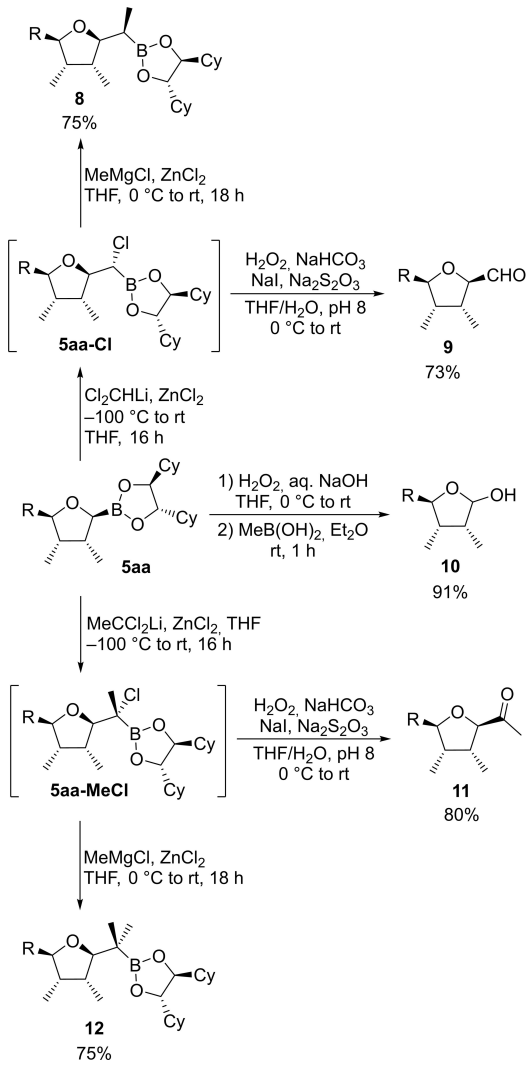
meric products **4ca'** and **5ca'** could also be obtained stereoselectively from **3c**. If the methylated carbenoid was reacted with **4cc**, α-methylated furan derivative **6** became accessible, a motif which is also very often found in natural products, such as amphidinolide Y. Even such highly substituted boronic esters could be easily subjected to further homologations, e.g. to **7**.

In order to determine the synthetic potential of this method, **5aa** was converted into a number of other derivatives (Scheme 6). Homologation of **5aa** with Cl_2CHLi at –100 °C led to the corresponding α–chloroboronic ester **5aa-Cl**, which was subsequently converted to **8** with MeMgCl and $ZnCl_2$, while oxidation yielded the corresponding aldehyde **9** without epimerization at the α–*C* atom.[26]

Oxidation of **5aa** without prior homologation led to hemiacetal **10**, whereby for chromatographic purification it was necessary to stir with methylboronic acid to remove (*S*,*S*)–DICHED as methylboronic ester **1a**, which can be used again in Matteson reactions.[27]

Boronic ester **5aa** could also be converted into α–chloroboronic ester **5aa-MeCl** with CH_3CHCl_2Li, but in this case only in moderate selectivity (80:20), which is not an issue if **5aa-MeCl** is oxidized to the corresponding ketone **11**.[26] Reaction with MeMgCl leads to the formation of the geminal dimethylated product **12**.[25b] The formation of **5aa-MeCl** was the only reaction where a second stereoisomer could be detected.

In conclusion, we could show that deprotonated trimethylsilylethanol is an excellent nucleophile for Matteson homologations. It can be introduced in high yields and is stable under the usual reaction conditions. After two further homologation steps, the protective group is automatically cleaved off under the performed reaction conditions to form highly substituted tetrahydrofurans via a six-membered ring *O-B* coordination. Many substitution pattern of naturally occurring tetrahydrofurans can be achieved by this protocol.



Scheme 6. Further modifications of boron-substituted tetrahydrofurans.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Cycloetherifications · Matteson homologations · Natural products · Polyketides · Tetrahydrofurans

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