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Very Important Paper

Combining Matteson Homologations and Claisen Rearrangements – An Efficient Protocol for Amino Acid Synthesis

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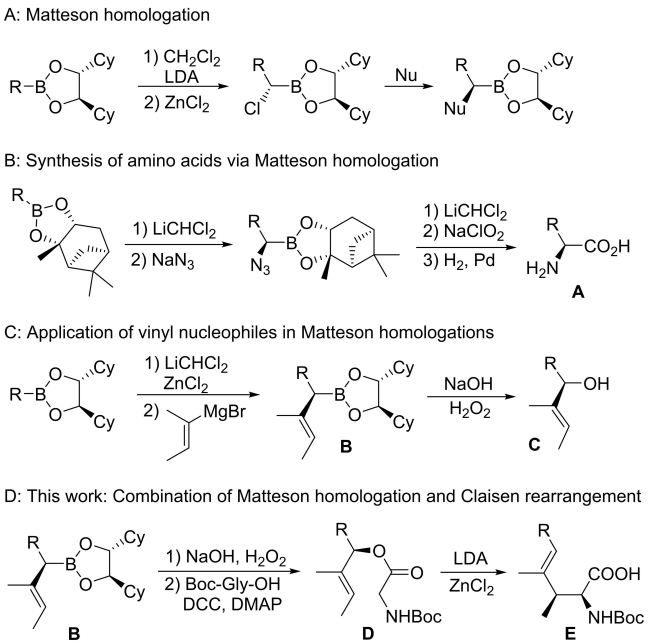
The Matteson homologation with vinyl nucleophiles was found to be an efficient and versatile protocol for the synthesis of substituted chiral allyl alcohols in a highly stereoselective fashion. These alcohols can be coupled with *N*-protected glycine and subsequently subjected to zinc-chelated ester-enolate Claisen rearrangements to yield highly substituted unsaturated amino acids. By varying the nucleophiles used in the Matteson homologations, the method allows control over not only the stereogenic centers but also the side-chain substitution pattern in the newly formed γ,δ-unsaturated amino acids.

Introduction

α-Amino acids are not only one of the most fundamental building blocks of life[1] but also highly useful chiral building blocks for chemical synthesis.[2] In addition to the 20 proteinogenic amino acids, non-proteinogenic amino acids, with their unusual side chains, have drawn significant interest from a synthetic and pharmaceutical perspective.[3] Many of them are formed as secondary metabolites in bacteria, plants, fungi, or marine organisms and are incorporated into complex natural products with highly attractive properties.[4] They are often biosynthesized by nonribosomal peptide synthetases (NRPSs), enzyme complexes with the ability to process non-proteinogenic amino acids and incorporate them into complex structures.[5] Not surprisingly, a wide range of methods have been developed for the synthesis of such unusual amino acids.[6]

An appealing alternative to the classical approaches is the Matteson homologation,[7] a synthetic protocol we recently used in the total synthesis of several polyketide-type natural products.[8] The Matteson reaction is a highly stereoselective chain extension of chiral boronic esters, producing one-carbon homologated

α-chloroboronic esters in a highly diastereoselective fashion (Scheme 1A).[9] These intermediates can be reacted with a wide range of nucleophiles to obtain α-chiral substituted alkylboronic esters, which are suitable for further homologation reactions. Lithium or magnesium reagents are well suited in this regard and result in excellent yields, though other nucleophiles, such as alkoxides or enolates, can also be applied.[7] Recently, we showed that allylzinc reagents and ester dienolates are versatile nucleophiles in this protocol as well.[10] The use of certain types of nitrogen nucleophiles, such as azides, allows for the synthesis of amines (**A**, Scheme 1B).[11] Although this method offers great potential and several syntheses of α-amino/amido boronates or boronic acids have been reported in the literature, it is rarely used to obtain amino acids.[12]



Scheme 1. Applications of Matteson reactions.

Our group's recent involvement in the synthesis of peptide natural products[13] sparked the interest in using the Matteson protocol for the synthesis of highly functionalized and substituted amino acids.[14] Our studies of the Matteson homologation using vinyl nucleophiles (Scheme 1C)[15] motivated us to pursue a different route to form complex amino acid deriva-

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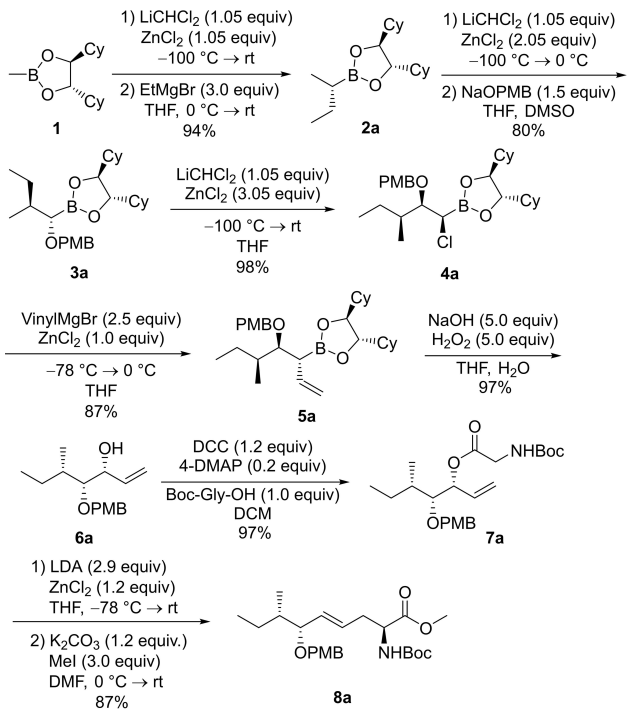
tives. Vinyl Grignard reagents are well suited to the formation of allylboronic esters (**B**), which can be converted to chiral allyl alcohols (**C**). Ester-enolate Claisen rearrangements[16] of the corresponding glycine esters **D** should make it possible to obtain unusual amino acids **E** in very few steps (Scheme 1D). The stereochemical information of the allyl alcohol should be transferred to the chiral center of the α-amino acid via a chair-like transition state.[17]

Results and Discussion

To evaluate our proposed synthetic route, we started the synthesis with the known methylboronic ester **1** using (*S*,*S*)-DICHED as a chiral auxiliary (Scheme 2).[15,18] Multiple consecutive Matteson homologations following standard conditions resulted in the chiral boronic ester **3a**, which was converted into the allylboronic ester **5a** under our previously optimized conditions.[15] Ultimately, the most important process in this reaction was the isolation of the α-chloroboronic ester **4a** and its conversion under well-defined conditions. Through the addition of zinc chloride and the reaction with a vinyl Grignard reagent at a low temperature, we obtained **5a** in good yield without the formation of any side products. Notably, the formation of the corresponding vinylboronic ester, a very common side product in such reactions,[19] was completely suppressed. The oxidation of **5a** to the allyl alcohol **6a** and the esterification with Boc-protected glycine under Steglich esterification reaction conditions[20] yielded the allyl glycine ester **7a** in excellent yield, which could then be directly subjected to our previously developed chelate-enolate Claisen rearrangement.[16]

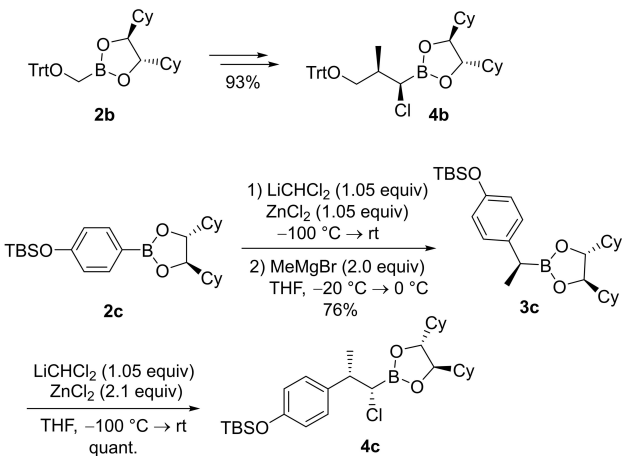


Scheme 2. Synthesis of unusual amino acid derivative **8a**.

For analytical purposes, the resulting carboxylic acid was directly converted into the methyl ester **8a**, which was obtained as a single stereoisomer. Two of the three stereogenic centers of the molecule were introduced through the Matteson reactions, while the (*S*)-configuration at the α-carbon was transferred from the allyl ester through rearrangement with perfect chirality transfer.[16] The (*E*)-double bond was formed exclusively, allowing further stereoselective modifications at this position.

After achieving success in the first synthesis, we embarked on evaluating the substrate scope. Using differently substituted vinyl nucleophiles in the Matteson homologations should provide a simple way to modify the substitution pattern at the β-position and the double bond of the amino acid side chain. To examine this in more detail, we exemplarily synthesized two additional α-chloroboronic esters **4b** and **4c** (Scheme 3). The boronic ester **2b**,[15,21] was converted into the α-chloroboronic ester **4b** under standard conditions. With the primary alcohol moiety, it should be possible to obtain terminal functionalized amino acids. The second α-chloroboronic ester **4c** was obtained from the aryl boronate **2c**[22] and was selected to cover the scope of aromatic amino acids. Since the Matteson homologation of aromatic boronic esters is known to be problematic due to the increased epimerization rate of the resulting benzylic α-chloroboronic esters,[23] we had to optimize this step to obtain enantiomerically pure amino acids. Notably, the generation of $LiCHCl_2$ (from CH_2Cl_2 and *n*-BuLi at −100 °C) and the one-pot procedure without isolation of the benzylic αchloroboronic ester proved to be critical for the synthesis of **3c**.[22] In contrast to the case for the previous boronic esters **4a** and **4b**, we used the enantiomeric chiral auxiliary (*R*,*R*)-DICHED for this substrate to also gain access to (*R*)-configured α-amino acids.

In the subsequent step, we used the three α-chloroboronic esters **4a**–**c** to introduce differently substituted vinyl nucleophiles (Scheme 4). Since the olefin geometry should directly influence the configuration of the β-substituent after the Claisen rearrangement, we used (*Z*)-propenylmagnesium bromide in combination with compound **4b** to obtain the (*Z*)-configured allyl boronate **5b**. The Grignard reagent had to be



Scheme 3. Synthesis of α-chloroboronic esters **4b** and **4c**.

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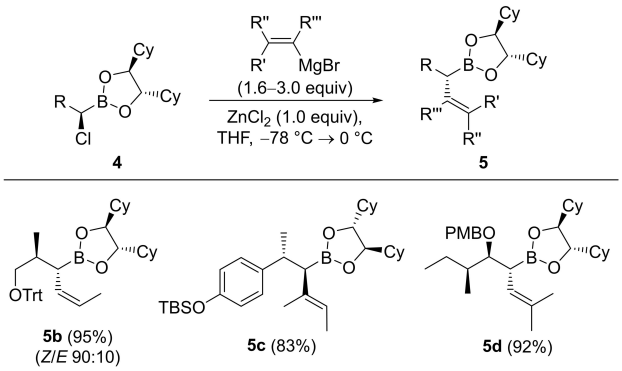
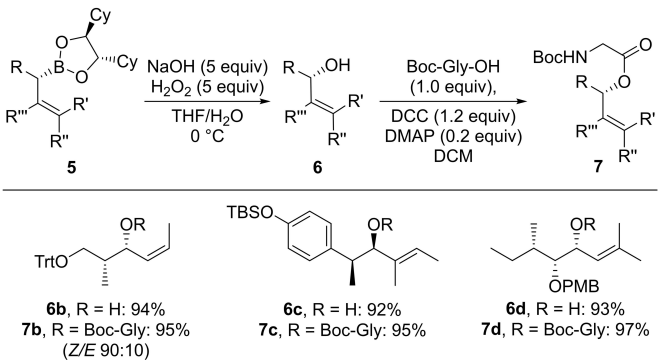
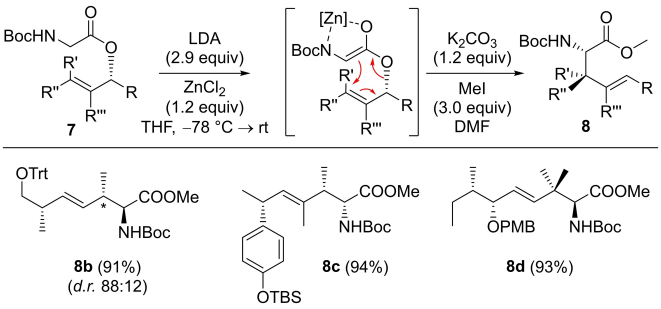


Scheme 4. Matteson reaction using vinyl nucleophiles.

freshly prepared from (*Z*)-propenyl bromide and magnesium, presumably resulting in slight *E*/*Z* isomerization,[15] which was transferred to the boronate **5b** (*Z*/*E* 90:10). Although these isomers were inseparable, this mixture provided a significant opportunity to directly examine the chirality transfer in the Claisen rearrangement. The Grignard reagent 1-methyl-1-propenylmagnesium bromide, which was used with compound **4c**, resulted in the formation of the boronate **5c**, exclusively obtained as the thermodynamically more stable *E*-isomer. Finally, compound **4a**, which we had already reacted with a simple vinyl nucleophile in Scheme 2, was also successfully reacted with 2-methyl-1-propenylmagensium bromide to yield the allyl boronate **5d** in excellent yield.



Scheme 5. Synthesis of allyl alcohols and allyl esters.



Scheme 6. Zinc-chelated ester-enolate Claisen rearrangements.

Using the established protocol of boronate oxidation with $NaOH/H_2O_2$, we converted the allyl boronates **5** to the corresponding allyl alcohols **6** (Scheme 5). No side reactions of the electron-rich double bonds with the peroxide were observed, and the cleaved DICHED auxiliaries can be recovered in this step if desired. Esterification under standard Steglich esterification conditions[20] allowed for the synthesis of esters **7** in almost quantitative yields.

Finally, we subjected the allyl esters **7** to zinc-chelated ester-enolate Claisen rearrangements (Scheme 6). For analytical purposes, the resulting amino acids were again converted into the corresponding methyl esters. The rearrangement of allyl ester **7b** resulted in the formation of the β-branched αamino acid derivative **8b**. The product was obtained as a mixture of two diastereomers (*d.r.* 88:12), reflecting the (*Z*)/(*E*) ratio of **7b** and indicating an almost perfect chirality transfer in the Claisen rearrangement. In the case of compound **8c**, the precursor **7c** was used as the single *E*-isomer and resulted in a single diastereomer in 94% yield. In addition, the trisubstituted double bond in **7c** resulted in a substituted olefin side chain in **8c**. The allyl ester **7d**, with two geminal methyl groups attached to the olefin, led to the expected product **8d**, also in excellent yield, allowing the introduction of a quaternary center at the β-position.

Conclusion

In conclusion, we synthesized four unusual amino acid derivatives with functionalized γ,δ-unsaturated side chains using a combination of Matteson homologations and zinc-chelated ester-enolate Claisen rearrangements. The method provides high flexibility regarding the substitution pattern, resulting from the large variety of nucleophiles applicable in the Matteson homologation. Notably, the olefin substitution pattern and the configuration of the β-substituent in the side chain can be easily modified by varying the type of vinyl nucleophile used. The synthesis of both (*R*)- and (*S*)-isomers is possible depending on the chiral auxiliary used, revealing the significant potential of this protocol for the synthesis of complex molecules.

Experimental Section

General information: All air and moisture sensitive reactions were carried out in dried glassware (>100 °C) under nitrogen atmosphere. Anhydrous solvents were purchased from Acros Organics or dried before use (THF was distilled over sodium/benzophenone) and stored under nitrogen atmosphere. The products were purified by column chromatography on silica gel columns (Machery-Nagel 60, 0.063–0.2 mm). Mixtures of diethyl ether (Et_2O) and pentane (distilled prior to use) were generally used as eluents. For reverse-phase chromatography (indicated by C-18-SiO_2), a Büchi *Reverleris PREP Chromatography* system was used with *Telos Flash C18* columns and MeCN/H_2O solvents. Analytical TLC was performed on pre-coated silica gel plates (Machery-Nagel, Polygram Sil G/UV_{254}). Detection was accomplished with UV light (254 nm), $KMnO_4$ solution or cerium(IV)/ ammonium molybdate solution. Melting

points were determined with a MEL-TEMP II (Laboratory devices) apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance II 400 MHz spectrometer [^{1}H 400 MHz and ^{13}C 100 MHz], a Bruker Advance I 500 MHz spectrometer [^{1}H 500 MHz and ^{13}C 125 MHz] or a Bruker AV 500 Neo spectrometer [^{1}H 500 MHz and ^{13}C 125 MHz]. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS or internal solvent signal. Peaks were assigned using (^{1}H,^{1}H)-cosy, (^{1}H,^{13}C)-hsqc and (^{1}H,^{13}C)-hmbc spectra. Mass spectra were recorded with a Finnigan MAT 95 spectrometer (quadrupole) using the CI technique. Optical rotations were measured with a Jasco P-2000 polarimeter in a thermostated (20 °C ± 1 °C) cuvette, using a sodium vapor lamp (λ = 589 nm) as radiation source. $[\alpha]_D^{20}$ values are given in 10^{-1} deg cm^2 g^{-1}. Compounds **1**, **2b** and (*R*,*R*)- or (*S*,*S*)-DICHED were prepared according to known literature protocols.

General procedures (GP):

GP-1: Matteson homologation: In a flame-dried Schlenk flask, anhydrous CH_2Cl_2 (1.7 equiv) was dissolved in anhydrous THF (2.0 mL/mmol) and cooled to a temperature between −110 °C to −100 °C using an ethanol/liquid nitrogen bath. To the cooled solution, *n*-BuLi (1.05 equiv, 2.5 M in hexanes) was slowly added by dropwise addition. For larger quantities, the *n*-BuLi solution was diluted with 1–2 mL anhydrous THF, pre-cooled to −78 °C and added by cannulation. The mixture was stirred for 30 min at −100 °C before adding a solution of the boronate (1.0 equiv) in anhydrous THF (1.5 mL/mmol). After another 30 min of stirring, a solution of $ZnCl_2$ (1.05–3.05 equiv, flame-dried *in vacuo*) in anhydrous THF (0.8 mL/mmol $ZnCl_2$) was added. The mixture was allowed to warm to room temperature and stirred for 6–24 h before continuing with either variant A) or variant B). **Variant A) Isolation of α-chloroboronic ester**: To obtain the α-chloroboronic ester, the reaction mixture was added to a separating funnel with saturated NH_4Cl solution and pentane. The phases were separated, the aqueous phase was extracted with pentane and the combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was dried in vacuo. The obtained α-chloroboronic ester was used in the next reactions without further purification. **Variant B) Conversion of the α-chloroboronic ester**: To obtain the homologated, substituted boronic ester, the reaction mixture was again cooled to the specified temperature (−78 °C to 0 °C) and the nucleophile solution was slowly added. The reaction was allowed to warm to the specified temperature (0 °C or room temperature) and stirred for 16–48 h. Upon completion (checked by ^{1}H NMR or TLC analysis), the reaction mixture was added to a separating funnel with saturated NH_4Cl solution and pentane. The phases were separated, the aqueous phase was extracted with pentane and the combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography.

GP-2: Reaction of α-chloroboronic esters: The α-chloroboronic ester (1.0 equiv) was dissolved in anhydrous THF (10 mL/mmol), $ZnCl_2$ (1.0 equiv, flame-dried *in vacuo*) was added at room temperature and the solution was stirred for 5 min before cooling to the specified temperature (−100 °C to 0 °C). Afterwards, the nucleophile solution (1.0–3.0 equiv) was slowly added and the solution was allowed to warm to room temperature and stirred for 1–3 days. Upon completion (checked by ^{1}H NMR or TLC analysis), the reaction mixture was added to a separating funnel with saturated NH_4Cl solution and pentane. The phases were separated, the aqueous phase was extracted with pentane and the combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography.

GP-3: Oxidation of boronic esters: The boronic ester (1.0 equiv) was dissolved in THF (3 mL/mmol) and NaOH (5.0 equiv) in H_2O (3 mL/mmol boronic ester) and H_2O_2 (5.0 equiv, 33 % in H_2O) were added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was diluted with sat. NaCl solution, extracted with Et_2O (2x) and the organic phase was dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography.

GP-4: Steglich esterification: The alcohol (1.0 equiv) and *N*-Boc-glycine (1.00–1.05 equiv) were dissolved in anhydrous CH_2Cl_2 (10 mL/mmol) and 4DMAP (0.2 equiv) and DCC (1.2 equiv) were added at 0 °C. The mixture was stirred overnight at room temperature, filtered through a pad of Celite (rinsed with CH_2Cl_2) and concentrated *in vacuo*. The crude product was purified by column chromatography.

GP-5: Zinc-chelated ester-enolate Claisen rearrangement and methyl ester formation: To a solution of freshly distilled DIPA (3.0 equiv) in anhydrous THF (0.6 mL/mmol) was added *n*-BuLi (2.9 equiv, 2.5 M in hexanes) at −20 °C. The mixture was stirred at room temperature and cooled to −78 °C afterwards. In a second flask, the *N*-protected glycine allylester (1.0 equiv) was dissolved in anhydrous THF (3.0 mL/mmol) and a solution of $ZnCl_2$ (1.2 equiv, flame-dried *in vacuo*) in anhydrous THF (1.0 mL/mmol) was added. The solution was cooled to −78 °C and the LDA solution was added by cannulation. Upon complete addition, the remaining dry ice was removed from the cooling bath and the mixture was warmed to room temperature overnight. The mixture was acidified to pH 2 by addition of 1 M $KHSO_4$ solution, extracted with CH_2Cl_2 (3×) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was dissolved in anhydrous DMF (2.5 mL/mmol). Iodomethane (3.0 equiv) and K_2CO_3 (1.2 equiv) were added at 0 °C and stirred overnight at room temperature. The mixture was diluted with Et_2O, washed with H_2O, sat. Na_2SO_3 and sat. NaCl solution and dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: claisen rearrangement · matteson homologation · stereoselective synthesis · unsaturated amino acids · vinyl nucleophiles

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