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Stereoselective Synthesis of Complex α-Amino Acid Derivatives Using Boron and Palladium Chemistry

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Dedicated to Professor Franc Meyer and Christian Limberg on the Occasion of their 120th Birthday

Matteson homologation of boronic acid esters allows the highly stereoselective synthesis of complex allyl alcohols, which are valuable substrates for palladium-catalyzed allylic alkylations. With highly reactive amino acid zinc enolates, *trans*-configured γ,δ-unsaturated amino acid derivatives are obtained as single regioisomer. Excellent 1,4-chirality transfer from the allylic substrate into the stereogenic α-center of the amino acid is observed in all cases.

1. Introduction

Many pharmaceuticals are based on natural products,[1] often isolated from plants, fungi, and microorganisms.[2] The structures of the isolated compounds are as diverse as their producers. Many contain modified amino acids, which usually increase their proteolytic stability and impede enzymatic degradation. **Figure 1** shows two examples: Leucinostatin Y is an antimicrobial and antitumor antibiotic showing good activity against the murine leukemic cell line L 1210.[3] Persephacin shows a strong antifungal effect against a large number of pathogenic yeasts as well as filamentous fungi such as *Aspergillus fumigatus*.[4] This natural product is therefore a promising candidate for the development of a broad-spectrum antifungal agent.

Typical modifications that contribute to the metabolic stabilization of natural products are *N*-methylations (blue), *C*-methylations (green), and hydroxylations (brown) of proteinogenic amino acids, as well as the incorporation of completely unusual amino acids (red) that cannot be derived directly from proteinogenic amino acids.[5] These have to be synthesized by the microorganisms themselves using important resources,[6] which is why these building blocks are usually involved in the biological activity of the natural products.[7] In order to further develop such natural products as active ingredients, efficient stereoselective synthetic methods are required to get access to such unusual amino acids, whereby classical amino acid syntheses, which focus primarily on the stereoselective generation of the α- (and/or) β-stereogenic center, are of little help.[8] In principle, synthetic strategies are required that allow the stereoselective introduction of different substituents at almost any position to obtain derivatives for studies of structure–activity relationships (SAR studies).[9]

Boron chemistry is especially predestined to generate such unusual amino acids. As early as 1963, Matteson et al. reported that α-haloboronic acid esters can be reacted easily with nucleophiles, as the boron atom exerts a significant neighboring group effect.[10] The nucleophile first coordinates to the boron atom to form a borate complex, from which it replaces the halogen atom in an S_N2 reaction via 1,2 migration.[11] Since the synthesis of α-haloboronic acid esters was not a trivial issue, this beautiful method was not used for some time, until Matteson was able to show that α-chloroboronic acid esters can be obtained by reacting arbitrary alkylboronic acid esters with (dichloromethyl) lithium,[12] whereby this process also succeeds stereoselectively if chiral dioles are used as auxiliaries (**Scheme 1**).[13] Reaction of the chiral α-chloroboronic acid esters with different nucleophiles therefore generates α-substituted boronic acid esters in a highly stereoselective fashion. Since this synthetic sequence can be repeated several times, carbon chains with different substituents can be obtained in a highly stereoselective manner, whereby the newly formed stereocenters are almost exclusively controlled by the chiral auxiliary in the boronic acid ester. Therefore, the chiral auxiliary is not used to build up only one stereogenic center, as in most asymmetric syntheses, but to a whole series of neighboring stereogenic centers, which are usually 1,2-*anti*- or 1,3-*syn*-configured.[11]

Therefore, the Matteson homologation is ideally suited for the construction of polyketides that contain precisely these structural elements.[14] We have also used this reaction in a number of natural product syntheses.[15] If azides are used as nucleophiles in the Matteson reaction, aminoboronic acids[16] or amino acids are also obtained in an elegant fashion.[17]

2. Results and Discussion

Here we want to illustrate that the chiral information generated during the Matteson homologation can also be transferred to the

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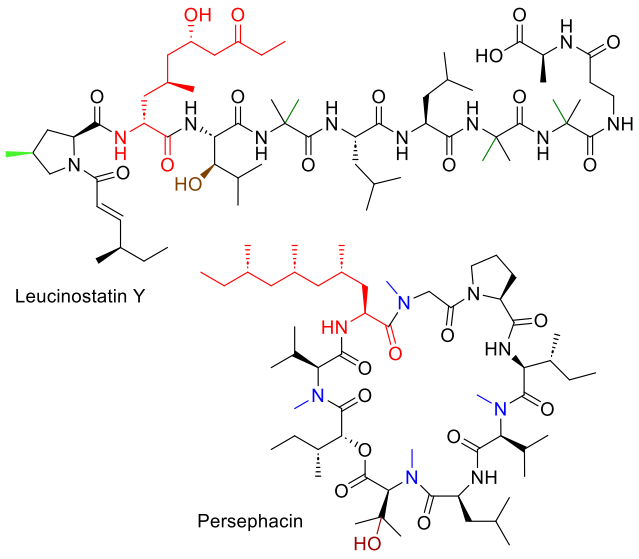
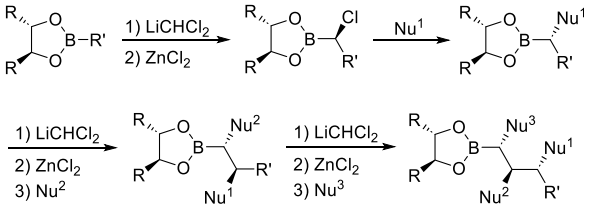


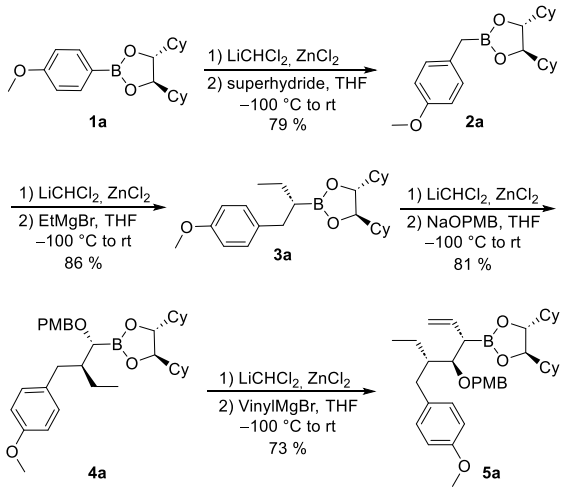
Figure 1. Natural products containing unusual amino acids.



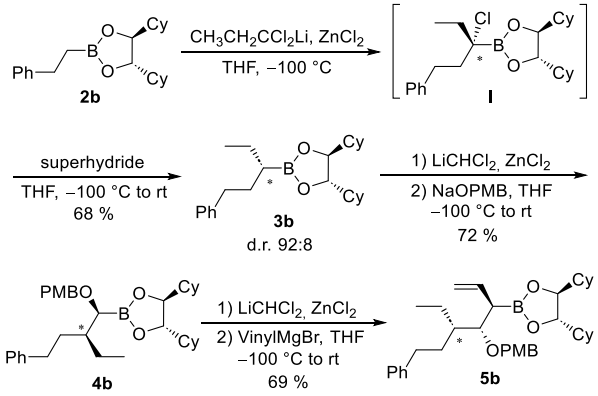
Scheme 1. Matteson homologation.

α-chiral center of amino acids via another important reaction, the Pd-catalyzed allylic alkylation.[18] In the last 50 years, Pd-catalyzed allylic alkylation has become one of the most important catalytic reactions, along with some other cross-coupling reactions.[19] Originally, the reaction was only applicable to stabilized carbanions as nucleophiles, such as malonates, which was a significant limitation. In 1999, we were able to show that chelated amino acid ester enolates can also be used as nucleophiles.[20] By forming a stable chelate complex, metal salts such as Zn^{2+} prevent the amino acid ester enolates from coordinating to the Pd, which would lead to its deactivation. At the same time, they retain the high reactivity of a classical metal enolates, which is why these chelate enolates often react with Pd-allyl-complexes at −78 °C.[21] Under these conditions, typical side reactions of the π-ally-palladium complexes, such as π-σ-π isomerization,[22] can be suppressed almost completely. As our earlier work has shown, this isomerization already starts at around −60 to −50 °C. In the case of 1,3-disubstituted allyl complexes, this leads to a double bond isomerization of *cis*-allyl substrates, and in the case of terminal chiral allyl acetates and carbonates, to the loss of chiral information if less reactive nucleophiles are used.[23]

We now wanted to figure out whether arbitrarily complex allyl substrates could be converted into enantiomerically pure amino acids. How such complex allyl substrates can be obtained is illustrated by the synthesis of two branched alkylboronic acid esters (**Scheme 2** and **3**).



Scheme 2. Synthesis of boronic ester **5a**.



Scheme 3. Synthesis of boronic ester **5b**.

Thus, starting from arylboronic acid ester **1a**, reaction with (dichloromethyl)lithium yields the corresponding α-chloroboronic acid ester,[24] which can be reduced to **2a** with superhydride (Scheme 2). This protocol allows the generation of methylene groups during the Matteson homologation. In a second homologation step, the corresponding α-chloroboronic acid ester was reacted with ethylmagnesium bromide, which leads to the stereoselective incorporation of an alkyl group obtaining boronic acid ester **3a** as a single stereoisomer. If alkoxides are used as nucleophiles, protected OH groups can be stereoselectively introduced into the growing carbon chain,[25] as demonstrated by the example of boronester **4a**. By using vinyl magnesium bromide in the fourth homologation step, allylboronic ester **5a** is obtained also as single stereoisomer.[26] The configuration of the 1,2-*anti*- and 1,3-*syn*-oriented substituents is controlled exclusively by the chiral diol used as an auxiliary.

To get access to 1,2-*syn*-configured products, the protocol can easily be modified, for example by introducing the alkyl residue not as a Grignard reagent, but as a chlorocarbenoid in the first step (Scheme 3).[27] The dialkylated α-chloroboronic acid ester **I**, obtained by such a process, can then be reduced with superhydride. By using the enantiomeric chiral diol as an auxiliary, the

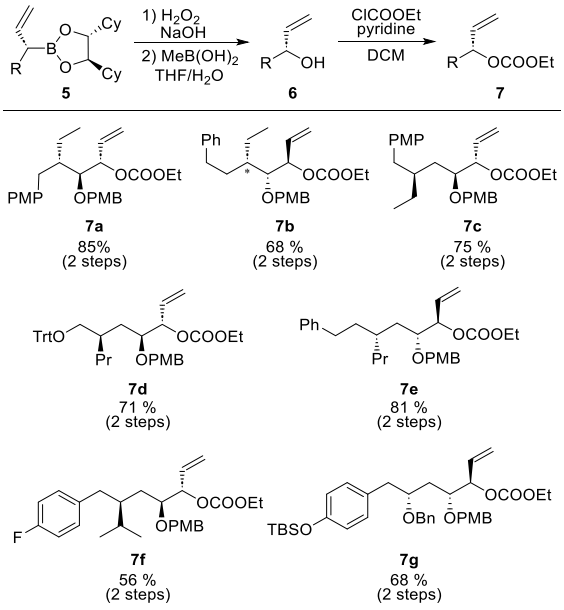
enantiomeric series of boron esters are obtained. For example, starting from boronic acid ester **2b,** the α-alkylated boronic ester **3b** is obtained via **I**. However, the introduction of the "inverted alkyl residue" is not quite as stereoselective as the classical Matteson homologation, but the wrong diastereomer has no influence on the introduction of further stereocenters and can in most cases be removed at a later stage. As before, the introduction of the other substituents was highly stereoselective providing finally boronic acid ester **5b**.

According to this synthetic protocol five further allylboronic acid esters **5c**-**5g** were obtained from different boronic acid esters, which were oxidized to the alcohols and converted into the corresponding allyl carbonates (**Scheme 4**).

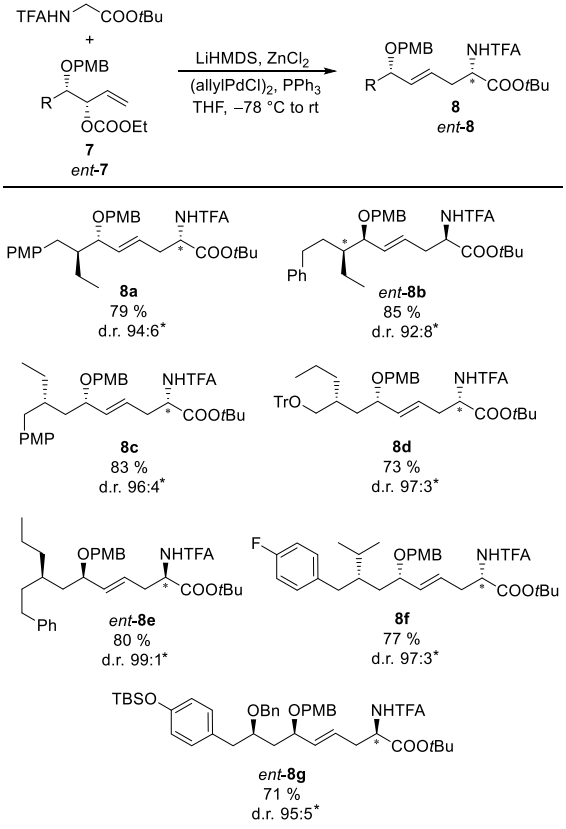
The synthesized allyl carbonates **7** were following subjected to palladium-catalyzed allylic alkylation of a zinc-chelated glycine ester enolate (**II**, Scheme 6) to provide complex, unnatural amino acids (**Scheme 5**).[28] Good yields and very good diastereoselectivities with ratios of up to 99:1 were achieved for all seven compounds. With the 1,2-*anti*-configured substrate **7a**, the lowest selectivity was observed with a diastereomer ratio of 94:6, all other derivatives provided better selectivities.

Although 8% of a second stereoisomer were observed with the comparable 1,2-*syn*-configured substrate **7b**, this did not result from the allylic alkylation as such, but from the less selective introduction of the "inverted" ethyl group in the first step of the Matteson homologation. The allylic alkylation was completely stereoselective in this case (d.r. >99:1). With increasing distance of the second *syn* substituent from the allyl complex (**7c**–**7g**), the selectivity of the allylation decreased slightly, but was consistently in the range of ≥95:5. In all examples, only the *trans*-configured double bond was obtained.

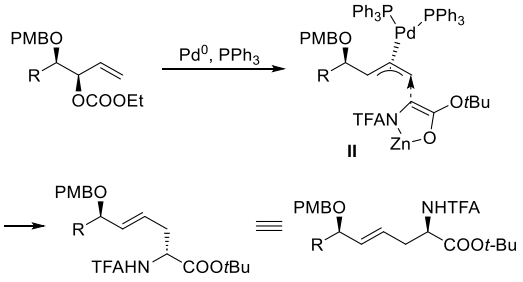
The excellent 1,4-chirality transfer can be attributed to the very mild reaction conditions.[29] The formation of the π-allyl–palladium complex already takes place at −78 °C, a temperature



Scheme 4. Synthesis of allylcarbonates **7**.

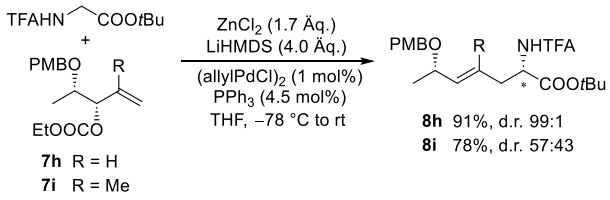


Scheme 5. Synthesis of complex α-amino acid derivatives **8**.

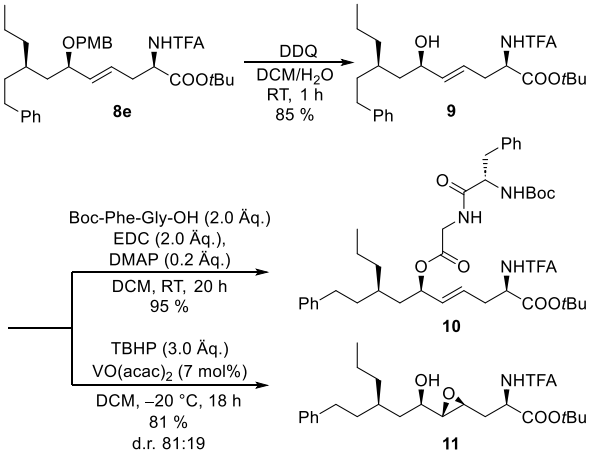


Scheme 6. Mechanistic explanation of stereoselectivity.

at which no π-σ-π isomerization takes place even in terminal π-allyl complexes (**Scheme 6**). Nucleophilic attack of palladium occurs *trans* to the leaving group, causing the palladium to be oriented on the opposite side to the neighboring alkoxy substitute. This corresponds to the thermodynamically most favorable complex, as calculations by Szabó et al. show.[30] These indicate that electron-withdrawing alkoxy substituents in the vicinity of the π-allyl–palladium complex are more or less antiperiplanar oriented to palladium, and that the nucleophilic attack occurs at the allylic position away from the heteroatom. This also explains the excellent regioselectivity of the attack of the chelated enolate and the exclusive formation of the linear amino acid.[31] The attack of the enolate is in turn *trans* to the palladium, so that steric interactions are minimized.



Scheme 7. Control experiment with the simplified allyl carbonates **7h** and **7i**.



Scheme 8. Synthetic transformations of 8e.

To verify this assumption, a control experiment was carried out with a simplified allyl carbonate **7h** (**Scheme 7**),which, as expected, delivered the desired product **8h** as the only regio- and stereoisomer. In comparison, the methylated allyl substrate **7i** also delivered the expected product **8i** in a good yield, but unselectively. For steric reasons, both the ionization and the formation of the π-allyl complex as well as the nucleophilic attack of the enolate do not occur at −78 °C but only at a higher temperature, so that the isomerization of the terminal π-allyl complex is noticeable here.

The *p*-methoxybenzyl (PMB) protection group was chosen to control the regioselectivity of the nucleophilic attack onto the allyl complex on the one hand and to introduce a protective group that can be easily cleaved afterward without affecting other functionalities of the amino acid (**Scheme 8**). In the case of PMB, this is achieved under oxidative conditions.[32] The allyl alcohol **9** formed in this process can be easily linked to amino acids and peptides, which allows the incorporation of the newly formed amino acid into larger peptides (**10**). Also, the free OH functionality can be used as a directing group for transition metal-catalyzed reactions, as illustrated by the example of Sharpless epoxidation (**11**).[33]

3. Conclusion

In conclusion, we could show that the Matteson homologation of boronic acid esters is predestined for the stereoselective synthesis of complex allyl alcohols, which in turn represent valuable substrates for palladium-catalyzed allylic alkylation. With highly reactive amino acid zinc enolates, isomerization-free conversions to linear amino acids with perfect regioselectivity and excellent 1,4-chirality transfer are achieved.

4. Experimental Section

General Information: All air- and moisture-sensitive reactions were performed in dried glassware (>100 °C) under a nitrogen atmosphere. THF was dried by distillation over sodium/benzophenone and stored under a nitrogen atmosphere before use. All other anhydrous solvents were purchased from *Acros Organics*. The solvents pentane, diethyl ether, and ethyl acetate were distilled prior to use. The crude products were purified by column chromatography on silica gel (*Machery-Nagel 60*, 0.04–0.063 or 0.063–0.2 mm). In some cases, the purification was carried out by reversed-phase flash chromatography using the *Büchi Reveleris Prep Chromatography* system with *Büchi FlashPure Select C18* (30 µm spherical) columns. Analytical TLC was performed on precoated silica gel plates (*Machery-Nagel*, Polygram Sil G/UV_{254}), using UV light (254 nm) or a cerium(IV)/ ammonium molybdate solution for detection. ^{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). $CDCl_3$ was mixed with the internal standard TMS and used as NMR-solvent. The spectra were analyzed with the *ACD/NMR* Software Processor *Academic Edition* (Version: 12.0) and the chemical shifts δ are reported in ppm relative to the internal solvent signal or TMS. The assignment of the peaks was carried out using (^{1}H,^{1}H)-cosy, (^{1}H,^{13}C)-hsqc and (^{1}H,^{13}C)-hmbc spectra. The α-carbon atoms of the boronic esters could not be observed in the ^{13}C-NMR spectra. HPLC was performed with the system *LaChrom D-7000* from *Merck Hitachi* using the chiral column *Chiracel OD-H* (4.6 x 250 mm, particle size 5 µm). The signals were detected with a diode array detector (*LaChrom L-7455*) and the analysis was carried out with the MultiHSM-manager from *Merck Hitachi*. Optical rotations were measured on a *A. Krüss Optronic GmbH P8000-T* polarimeter with a sodium vapor lamp (589 nm) at 20 °C. The measured values are given in 10^{-1} deg cm^2 g^{-1}. High resolution mass spectra were recorded with a Finnigan MAT 95 spectrometer (quadrupole) using the CI technique.

General Procedures (GP): GP-1: Matteson Homologation

Preparation of the Carbenoid: In a flame-dried Schlenk flask, anhydrous dichloromethane or 1,1-dichloropropane (2.5 eq. or 1.5 eq.) was dissolved in anhydrous THF (2.0 mL mmol^{-1}) and cooled to −110 °C. To this solution, *n*BuLi (1.5 eq., 2.5 M in THF) was added dropwise and the reaction mixture was stirred at −100 °C for 30 min.

Homologation: A solution of the boronic ester (1.0 eq.) in anhydrous THF (1.5 mL mmol^{-1}) was cooled to −78 °C and slowly added to the carbenoid solution at −100 °C. After stirring at this temperature for 30 min, $ZnCl_2$ (1.1–3.1 eq., flame-dried in vacuo) dissolved in anhydrous THF (0.8 mL mmol^{-1} $ZnCl_2$) was added and the reaction mixture was slowly warmed to room temperature over night to obtain the αchloroboronic ester.

Reaction with the Nucleophile: The α-chloroboronic ester solution was cooled to 0 °C and the nucleophile (1.2–3.5 eq.) was added dropwise. After stirring at room temperature for 5 h to 3 days, the mixture was diluted with pentane and transferred to a separatory funnel containing saturated NH_4Cl solution and pentane. The phases were separated and the aqueous phase was extracted three times with pentane. After drying the combined organic layers over $MgSO_4$, the solvent was removed in vacuo and the crude product was purified by column chromatography.

If a vinyl nucleophile was used, the α-chloroboronic ester was isolated after the homologation step by working-up the reaction mixture as described before. For the further reaction with the vinyl nucleophile, the isolated α-chloroboronic ester was added to a solution of $ZnCl_2$ (1.1 eq., flame-dried in vacuo) in anhydrous THF (3.5 mL mmol^{-1}) and cooled to −78 °C. The nucleophile (2.0 eq.) was added dropwise and the reaction mixture was slowly warmed to room temperature. After stirring for 1 day, the work-up and the purification were carried out as described before.

For the synthesis of the α-PMB boronic ester, the nucleophile solution was prepared as follows: In a flame-dried Schlenk tube, NaH (1.5 eq., 60% in mineral oil) was suspended in anhydrous THF (0.5 mL mmol^{-1}) and anhydrous DMSO (1.4 mL mmol^{-1}). 4-Methoxybenzylalcohol (1.6 eq.) was added dropwise and the suspension was stirred at room temperature for 4 h.

GP-2: Oxidation of the Boronic Esters

Oxidation: To a solution of the boronic ester (1.0 eq.) in THF (2.0 mL mmol^{-1}) was added H_2O_2 (5.0 eq., 33% in H_2O) and NaOH (5.0 eq.) dissolved in H_2O (2.0 mL mmol^{-1}) at 0 °C. After stirring at 0 °C for 20 min, the reaction mixture was diluted with saturated NaCl solution and ethyl acetate. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure.

Separation of DICHED: The residue was dissolved in Et_2O (5.0 mL mmol^{-1}) at room temperature and methylboronic acid (1.3 eq.) was added. After stirring for 30 min, the solvent was removed in vacuo and the crude product was purified by column chromatography.

GP-3: Synthesis of Ethyl Carbonates

The alcohol (1.0 eq.) was dissolved in anhydrous DCM (1.5 mL mmol^{-1}) and pyridine (1.5 eq.) was added. After cooling to 0 °C, ethyl chloroformate (1.3 eq.) was added dropwise and the solution was stirred for 4 h at room temperature. The reaction mixture was diluted with ethyl acetate and washed with 1 N HCl solution and saturated NaCl solution. The solvent was removed in vacuo and the crude product was purified by column chromatography.

GP-4: Pd-Catalyzed Allylic Alkylation with Zn-Chelated Glycine Ester Enolates

Preparation of the Zinc-Chelated Glycine Ester Enolate: In a flame-dried Schlenk tube, a solution of TFAGly-O*t*Bu in anhydrous THF (4 mL mmol^{-1}) was cooled to −78 °C and LiHMDS (1.0 M in THF, 2.7 mL mmol^{-1}) was added dropwise. After stirring at this temperature for 30 min, a solution of $ZnCl_2$ (1.7 eq., flame-dried in vacuo) in anhydrous THF (4.5 mL mmol^{-1}) was added and the resulting solution was stirred for another 30 min at −78 °C.

Preparation of the π-Allyl-Pd-Complex: For the preparation of the catalyst solution, $(allylPdCl)_2$ (1.0 mol%) and PPh_3 (4.5 mol%) were dissolved in anhydrous THF (2.0 mL mmol^{-1}) at room temperature. The mixture was stirred for 10 min, the allyl carbonate (1.0 eq.) was added, and it was stirred for another 5 min at room temperature.

Allylic Alkylation: The π-allyl-Pd-complex-solution was added dropwise to the ester enolate solution at −78 °C and the reaction mixture was stirred for 1 day while warming to room temperature. The reaction mixture was treated with ethyl acetate und 1 M $KHSO_4$ solution, the phases were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic phases were dried over $MgSO_4$ und the solvent was evaporated. The crude product was purified by column chromatography.

(4*R*,5*R*)-4,5-Dicyclohexyl-2-((*S*)-1-(4-methoxyphenyl)butan-2-yl)-1,3,2-dioxaborolane (3a): According to **GP-1**, the boronic ester **2a** (2.02 g, 5.67 mmol) was reacted with *n*BuLi (2.38 mL, 5.95 mmol, 2.5 M in hexanes), anhydrous dichloromethane (912 µL, 1.20 g, 14.2 mmol), $ZnCl_2$ (1.62 g, 11.9 mmol) and EtMgBr (4.82 mL, 11.3 mmol, 2.35 M in diethyl ether) for 1 day. After purification by column chromatography (silica, pentane/diethyl ether 99:1), the product **3a** (1.94 g, 4.87 mmol, 86%) was obtained as a colorless oil. R_f(**3a**) = 0.31 (pentane/diethyl ether 99:1). $[\alpha]_D^{20} = +51.3$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12–7.10 (m, 2 H), 6.80–6.77 (m, 2 H), 3.77 (s, 3 H), 3.78–3.75 (m, 2 H), 2.72–2.59 (m, 2 H), 1.73–1.65 (m, 8 H), 1.52–1.49 (m, 2 H), 1.45 (quint, J = 7.2 Hz, 2 H), 1.38–1.31 (m, 1 H), 1.26–1.10 (m, 8 H), 0.94 (t, J = 7.3 Hz, 3 H), 1.010.80 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 134.6, 129.6, 113.4, 83.3, 55.2, 43.0, 35.9, 28.3, 27.4, 26.4, 26.0, 25.9, 23.9, 13.5 ppm. HRMS (CI): m/z calcd for $C_{25}H_{39}BO_3$ $[M]^+$: 398.2992, found: 398.3002.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-((*S*)-1-phenylpentan-3-yl)-1,3,2-dioxaborolane (3b): According to **GP-1**, the phenylethylboronic ester **2b** (2.00 g, 5.88 mmol) was treated with *n*BuLi (2.82 mL, 7.05 mmol, 2.5 M in hexanes), 1,1-dichloropropane (881 µL, 996 mg, 8.82 mmol), $ZnCl_2$ (881 mg, 6.46 mmol), and superhydride (7.05 mL, 7.05 mmol, 1 M in THF) for 5 h. The crude product was purified by column chromatography (silica, pentane/diethyl ether 99:1) to get the boronic ester **3b** (1.52 g, 3.97 mmol, 68%, d.r. 92:8) as a colorless oil. The diastereomeric ratio was determined on the carbonate **7b** due to better signal separation in the NMR spectrum. R_f(**3b**) = 0.65 (pentane/diethyl ether 99:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.23 (m, 2 H), 7.20–7.15 (m, 3 H), 3.87–3.82 (m, 2 H), 2.69–2.54 (m, 2 H), 1.83–1.74 (m, 6 H), 1.71–1.60 (m, 6 H), 1.55–1.42 (m, 2 H), 1.35–1.28 (m, 2 H), 1.27–1.17 (m, 5 H), 1.14–0.97 (m, 6 H), 0.93 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 128.4, 128.2, 125.5, 83.3, 43.2, 35.4, 33.1, 28.5, 27.6, 26.5, 26.0, 25.9, 24.0, 13.6 ppm. HRMS (CI): m/z calcd for $C_{25}H_{40}BO_2$ $[M+H]^+$: 383.3116, found: 383.3127.

(4*R*,5*R*)-4,5-Dicyclohexyl-2-((1*R*,2*S*)-2-(4-methoxybenzyl)-1-((4-methoxybenzyl)oxy)butyl)-1,3,2-dioxaborolane (4a): According to **GP-1**, the boronic ester **3a** (1.50 g, 3.77 mmol) was reacted with *n*BuLi (1.58 mL, 3.95 mmol, 2.5 M in hexanes), anhydrous dichloromethane (606 µL, 799 mg, 9.41 mmol), $ZnCl_2$ (1.08 g, 7.91 mmol), and freshly prepared NaOPMB solution (10.7 mL, 5.66 mmol, 0.53 M in THF/DMSO) for 1 day. After purification by column chromatography (silica, pentane/diethyl ether 9:1), the product **4a** (1.67 g, 3.05 mmol, 81%) was obtained as a colorless oil. R_f(**4a**) = 0.38 (pentane/diethyl ether 9:1). $[\alpha]_D^{20} = +36.0$ 0 ($c = 1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.19 (m, 2 H), 7.09–7.07 (m, 2 H), 6.83–6.81 (m, 2 H), 6.80–6.78 (m, 2 H), 4.484.31 (m, 2 H), 3.92–3.89 (m, 2 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.27 (d, J = 4.9 Hz, 1 H), 2.71–2.66 (m, 1 H), 2.61–2.56 (m, 1 H), 1.88–1.75 (m, 7 H), 1.70–1.67 (m, 2 H), 1.63–1.57 (m, 3 H), 1.55–1.48 (m, 1 H), 1.35–1.30 (m, 2 H), 1.26–1.10 (m, 6 H), 1.12–0.98 (m, 4 H), 0.84 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 157.5, 133.7, 131.4, 130.2, 129.4, 113.5, 113.4, 83.7, 72.0, 52.2, 44.4, 43.0, 36.1, 28.5, 27.6, 26.4, 26.0, 25.9, 23.4, 12.0 ppm. HRMS (CI): m/z calcd for $C_{34}H_{48}BO_5$ $[M-H]^+$: 547.3595, found: 547.3626.

(4*R*,5*R*)-4,5-Dicyclohexyl-2-((3*S*,4*R*,5*S*)-5-(4-methoxybenzyl)-4-((4-methoxybenzyl)oxy)hept-1-en-3-yl)-1,3,2-dioxaborolane (5a): According to **GP-1**, the boronic ester **4a** (770 mg, 1.40 mmol) was reacted with *n*BuLi (590 µL, 1.47 mmol, 2.5 M in hexanes), anhydrous dichloromethane (226 µL, 298 mg, 3.51 mmol), and $ZnCl_2$ (593 mg, 4.35 mmol) over night to get the α-chloroboronic ester. After isolation, the α-chloroboronic ester was treated with $ZnCl_2$ (201 mg, 1.47 mmol) and vinylMgBr (2.81 mL, 2.81 mmol, 1 M in THF) for 1 day. Column chromatography (silica, pentane/diethyl ether 95:5) provided the allylboronic ester **5a** (605 mg, 1.03 mmol, 73%) as a colorless oil. R_f(**5a**) = 0.50 (pentane/diethyl ether 9:1). $[\alpha]_D^{20} = +19.3$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.23 (m, 2 H), 7.06–7.04 (m, 2 H), 6.86–6.84 (m, 2 H), 6.80–6.78 (m, 2 H), 5.84 (dt, J = 17.0, 10.1, 1 H), 5.10 (dd, J = 17.1, 1.3 Hz, 1 H), 5.01 (dd, J = 10.1, 1.9 Hz, 1 H), 4.60–4.47 (m, 2 H), 3.81–3.80 (m, 2 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.74 (dd, J = 8.4, 2.9 Hz, 1 H), 2.85 (dd, J = 14.1, 4.8 Hz, 1 H), 2.53 (t, J = 9.2 Hz, 1 H), 2.36 (dd, J = 14.0,

9.4 Hz, 1 H), 1.80–1.77 (m, 3 H), 1.72–1.69 (m, 4 H), 1.64–1.61 (m, 2 H), 1.56–1.53 (m, 2 H), 1.46–1.28 (m, 2 H), 1.28–1.21 (m, 2 H), 1.13–1.09 (m, 6 H), 1.02–0.91 (m, 4 H), 0.82 (t, $J = 7.5$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 157.5, 137.3, 134.2, 131.6, 130.0, 128.2, 115.2, 113.5, 113.4, 83.6, 81.0, 72.2, 55.2, 45.4, 43.0, 34.3, 28.4, 27.8, 26.4, 26.0, 25.8, 22.8, 12.0 ppm. HRMS (CI): m/z calcd for $C_{37}H_{52}BO_5$ $[M\text{-}H]^+$: 587.3908, found: 587.3896.

(3*S*,4*S*,5*S*)-5-(4-Methoxybenzyl)-4-((4-methoxybenzyl)oxy)hept-1-en-3-ol (6a): According to **GP-2**, the allylboronic ester **5a** (301 mg, 511 μmol) was reacted with NaOH (102 mg, 2.56 mmol), H_2O_2 (237 μL, 264 mg, 2.56 mmol, 33% in H_2O), and methylboronic acid (36.7 mg, 614 μmol) for 20 min. The crude product was purified by column chromatography (silica, pentane/ethyl acetate 9:1) to get the alcohol **6a** (179 mg, 483 μmol, 94%) as a colorless oil. R_f(**6a**) = 0.26 (pentane/ethyl acetate 85:15). $[\alpha]_D^{20} = +7.2$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.23 (m, 2 H), 7.067.04 (m, 2 H), 6.90–6.87 (m, 2 H), 6.83–6.80 (m, 2 H), 5.86 (ddd, $J = 17.1$, 10.5, 6.5 Hz, 1 H), 5.34 (dd, $J = 17.1$, 1.4, 1 H), 5.23 (dd, $J = 10.4$, 1.2, 1 H), 4.60–4.51 (m, 2 H), 4.18 (t, $J = 6.2$ Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.39 (dd, $J = 5.9$, 3.5 Hz, 1 H), 2.78 (dd, $J = 14.1$, 5.9 Hz, 1 H), 2.50 (dd, $J = 14.0$, 8.7 Hz, 1 H), 2.54 (bs, 1 H), 1.86–1.78 (m, 1 H), 1.54–1.33 (m, 2 H), 0.88 (t, $J = 7.4$, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 157.7, 138.5, 133.3, 130.5, 130.0, 129.5, 116.8, 113.8, 113.7, 82.6, 74.2, 73.3, 55.3, 55.2, 43.9, 34.8, 23.0, 11.8 ppm. HRMS (CI): m/z calcd for $C_{23}H_{30}O_4$ $[M]^+$: 370.2144, found: 370.2177.

Ethyl-((3*S*,4*S*,5*S*)-5-(4-methoxybenzyl)-4-((4-methoxybenzyl)oxy) hept-1-en-3-yl)carbonate (7a): According to **GP-3**, the alcohol **6a** (144 mg, 389 μmol) was treated with pyridine (47.2 μL, 46.1 mg, 583 μmol) and ethyl chloroformate (48.5 μL, 54.8 mg, 505 μmol) for 4 h. After purification by column chromatography (silica, pentane/ethyl acetate 9:1), the carbonate **7a** (154 mg, 348 μmol, 90%) was obtained as a colorless oil. R_f(**7a**) = 0.36 (pentane/ethyl acetate 9:1). $[\alpha]_D^{20} = -4.5$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.26 (m, 2 H), 7.047.02 (m, 2 H), 6.89–6.85 (m, 2 H), 6.82–6.79 (m, 2 H), 5.83 (ddd, $J = 17.4$, 10.3, 7.6 Hz, 1 H), 5.41 (d, $J = 17.2$ Hz, 1 H), 4.36 (t, $J = 7.0$ Hz, 1 H), 5.33 (d, $J = 10.4$ Hz, 1 H), 4.74–4.52 (m, 2 H), 4.18 (q, $J = 7.1$, 2 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.63 (dd, $J = 7.6$, 2.6 Hz, 1 H), 2.83 (dd, $J = 14.1$, 4.3 Hz, 1 H), 2.42 (dd, $J = 14.1$, 9.8 Hz, 1 H), 1.72–1.64 (m, 1 H), 1.29 (t, $J = 7.1$ Hz, 3 H), 1.39–1.26 (m, 2 H), 0.78 (t, $J = 7.5$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 157.7, 154.6, 133.3, 131.0, 130.0, 129.3, 119.7, 113.6, 81.1, 80.3, 74.6, 63.9, 55.3, 55.2, 43.5, 34.0, 22.6, 14.3, 11.7 ppm. HRMS (CI): m/z calcd for $C_{26}H_{33}O_6$ $[M-H]^+$: 441.2277, found: 441.2258.

Tert-butyl-(2*S*, 6*S*,7*S*, *E*)-7-(4-methoxybenzyl)-6-((4-methoxybenzyl)oxy)-2-(2,2,2-trifluoracetamido)non-4-enoate (8a): According to **GP-4**, the carbonate **7a** (62.0 mg, 140 μmol) was reacted with TFAGly-O*t*Bu (47.7 mg, 210 μmol), LiHMDS (560 μL, 560 μmol, 1.0 M in THF), $ZnCl_2$ (32.5 mg, 238 μmol), $(allylPdCl)_2$ (1.03 mg, 2.80 μmol), and PPh_3 (2.02 mg, 7.71 μmol) for 1 day. Column chromatography (silica, pentane/ethyl acetate 9:1) and reversed-phase flash chromatography (H_2O/MeCN 9:1 → MeCN) provided the amino acid **8a** (64.3 mg, 111 μmol, 79%, NMR and HPLC: d.r. 94:6) as a colorless oil. R_f(**8a**) = 0.32 (pentane/ethyl acetate 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.19 (m, 2 H), 7.04–7.02 (m, 2 H), 6.91 (d, $J = 7.1$ Hz, 1 H), 6.85–6.83 (m, 2 H), 6.80–6.78 (m, 2 H), 5.54 (dd, $J = 15.4$, 7.6 Hz, 1 H), 5.43 (dt, $J = 15.4$, 7.2 Hz, 1 H), 4.59–4.55 (m, 1 H), 4.44–4.15 (m, 2 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.60 (dd, $J = 7.5$, 5.6 Hz, 1 H), 2.81–2.74 (m, 1 H), 2.65–2.58 (m, 2 H), 2.56–2.51 (m, 1 H), 1.78–1.71 (m, 1 H), 1.50 (s, 9 H), 1.47–1.40 (m, 1 H), 1.18–1.07 (m, 1 H), 0.82 (t, $J = 7.4$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 159.0, 157.6, 156.5 (q, $^2J_{C,F} = 37.4$ Hz, C-21), 134.8, 133.0, 130.7, 130.0, 129.1, 126.1, 115.6 (q, $^1J_{C,F} = 287.6$ Hz), 113.6, 113.5, 83.6, 80.3, 69.8, 55.2, 52.7, 46.2, 34.5, 34.3, 28.0, 21.6, 11.3 ppm. HRMS (CI): m/z calcd for $C_{31}H_{40}F_3NO_6$ $[M]^+$: 579.2808, found: 579.2780.

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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.

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