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Stereoselective Synthesis of α-Azido Esters and α-Amino Acid Derivatives via Matteson Homologation of Boronic Esters

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Dedicated to Professor Michael Veith on the Occasion of his 80th Birthday

Matteson homologation with sodium azide in DMF proved to be an excellent highly stereoselective tool for the synthesis of complex α-azido and α-amino acids. Both enantiomers are easily accessible via the choice of the chiral boronic ester auxiliary.

Introduction

Peptide natural products often contain rather unusual amino acids and exhibit interesting biological activities. For example, the anti-HIV homophymine cyclodepsipeptides, containing highly methylated glutamine and β-hydroxy acid (Figure 1, marked in red), show strong cytotoxicity against a panel of human cancer cell lines, notably the human prostate and ovarian adenocarcinoma cell lines.[1] Bottromycin is another example containing a series of methylated amino acids, such as 4-methylproline, 3-methylphenylalanine, and *tert*-leucine (3-methylvaline). Bottromycins are effective against problematic human pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE).[2] In many cases, these unusual building blocks are essentially responsible for biological activity. Therefore, there is significant interest in the efficient and straightforward synthesis of these amino acids.[3]

For several years, our research group has been working on the stereoselective synthesis of unusual amino acids based on the reactions of chelated glycine ester enolates. For example, transition metal-catalyzed allylic alkylations[4] or Claisen rearrangements[5] give rise to γ,δ-unsaturated amino acids, which can be further functionalized. Furthermore, rather complex side chains can be constructed if these reactions are combined with Matteson homologations.[6] This iterative elongation of boronic esters has become an increasingly powerful tool for natural product synthesis.[7]

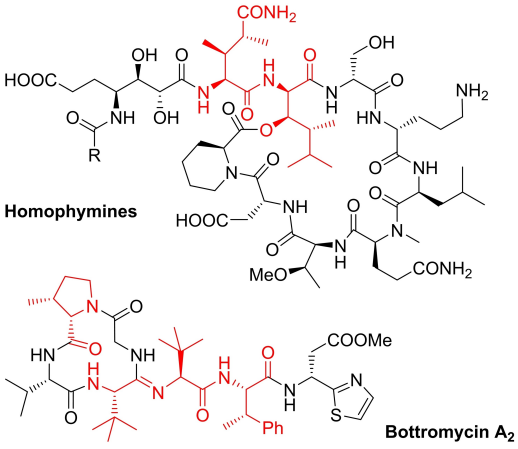
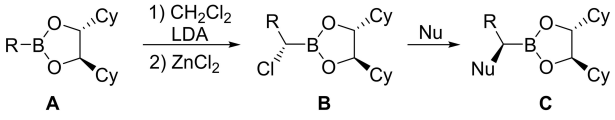


Figure 1. Natural products containing unusual amino acids.

The treatment of chiral boronic esters **A** with carbenoids bearing two leaving groups, such as dichloromethyllithium ($LiCHCl_2$), generates boronate complexes, which, upon 1,2-migration of the boron substituent, afford α-chloro boronic esters **B** in a highly diastereoselective fashion (Scheme 1).[8] These intermediates can be reacted with a wide range of nucleophiles to yield α-chiral substituted alkylboronic esters **C**, which are suitable for further homologation reactions. Typically, the nucleophiles used are organometallics, alkoxides, and metal hydrides.



Scheme 1. Matteson homologation.

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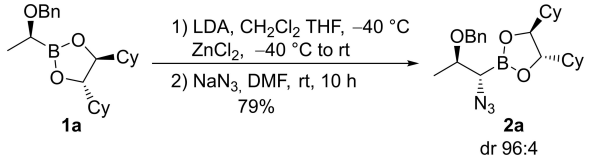
The introduction of nitrogen nucleophiles has proven rather challenging, and only scattered reports have been published since the discovery of the reaction.[6c] Matteson described the use of $LiN(TMS)_2$ as a masked amine,[9] but subsequent homologations were proven impossible due to the instability of the silylamine formed. Alternatively, sodium azide can be used as a nucleophile under phase transfer conditions.[10] Nitromethane or ethyl acetate should be used as the organic phase rather than the commonly used dichloromethane to avoid the formation of diazidomethane.[11] Recently, Dong and Xie described the insertion of carbenoids into the N–B bonds of aminoboranes;[12] this allowed for the terminal installment of amines, though the introduction of amino groups into an existing carbon chain was not possible.

In recent years, we have directed our attention to applying the Matteson reaction to the total synthesis of polyketide natural products,[13] extending the spectrum of nucleophiles that could be used.[14] Based on these results and our interest in the preparation of nonproteinogenic amino acids, we have also envisioned the synthesis of complex amino acids via the iterative homologation of boronic esters.[15]

Results and Discussion

As mentioned earlier, the major issue with this approach entails the introduction of the amine moiety as well as its homologation. The introduction of metal azides under Matteson's phase transfer conditions is, however, frequently accompanied by the partial epimerization of the α-stereogenic center. Matteson ascribed this problem to the similar nucleophilicities of the chloride leaving group and the azide as well as prolonged reaction times of up to 10 days. We identified DMF as an optimal solvent for the nucleophilic displacement of α-chloro boronic esters such as **1a** with sodium azide, giving rise to α-azido boronic ester **2a** in high yield and diastereoselectivity (Scheme 2). The reaction proceeded significantly faster than the case under phase transfer conditions and reached completion after 8–10 hours.



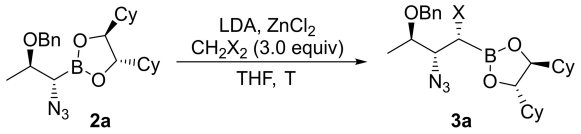
Scheme 2. Synthesis of α-azido boronic ester **2a**.

However, further homologation of boronic ester **2a** under the same conditions as before proceeded with incomplete conversion, further necessitating optimization studies (0.2 mmol scale), as presented in Table 1. In addition to the incomplete conversion, homologation to the α-chloro boronic ester **3aCl** (entry 1) was consistently accompanied by the formation of several unidentified side products. Therefore, homologations with $LiCHBr_2$ to the more reactive α-bromo boronic ester **3aBr** were also investigated. Initial attempts under the usual conditions (entry 2) provided a clean reaction though also led to incomplete conversion. The variation of several reaction conditions, such as reducing the amount of zinc chloride (entry 3) or increasing the amount of LDA (entry 4), had no significant effect.

However, conducting the reaction on a larger (10 mmol) scale led to almost quantitative conversion, and **3aBr** was obtained in 96% yield (entry 5), contaminated with only 4% of unreacted **2a**.

With this protocol in hand, a variety of azido boronic esters **2** were prepared via (consecutive) Matteson homologations. In these cases an alternative approach was used to generate the lithium carbenoids, using *n*-BuLi as a base at −100 °C. Under these conditions the α-azido boronic esters **2** were obtained as single stereoisomers.[8a] These compounds were then readily transformed into the α-azido acids[16] or esters **4** via a final Matteson homologation and subsequent Pinnick oxidation of the resulting α-halo boronic esters **3**. Methylboronic acid was added after an acidic workup to remove (and recover) the chiral auxiliary as methylboronic ester.[13a] Some α-azido acids were esterified with either TMS-diazomethane or *t*-butyl bromide/K_2CO_3.[17] This protocol allowed for the synthesis of a wide range of substituted α-amino acid derivatives **4** (Table 2). The lower yields obtained for the α-azido esters ***ent*–4h** to ***ent*–4j** mainly resulted from an unsatisfactory esterification step. The use of the enantiomeric

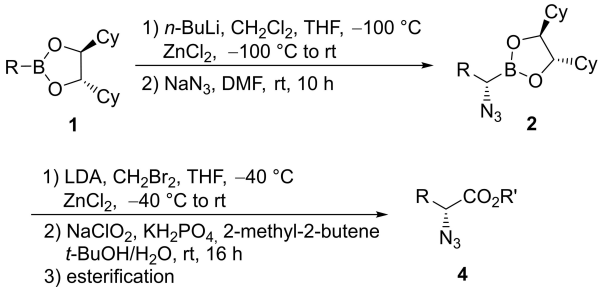
Table 1. Homologation of α-azido boronic ester **2a**.

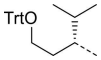
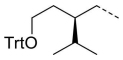


Entry	LDA [equiv]	$ZnCl_2$ [equiv]	T	X	**3a**	conv.[a] [%]
1	1.25	3.0	−40 °C to rt	Cl	**3aCl**	84
2	1.25	3.0	−78 °C to rt	Br	**3aBr**	85
3	1.25	2.0	−78 °C to rt	Br	**3aBr**	87
4	2.00	3.0	−78 °C to rt	Br	**3aBr**	89
5[b]	2.00	3.0	−78 °C to rt	Br	**3aBr**	96

[a] Determined via ^{1}H NMR spectroscopy; [b] Reaction performed on a 10 mmol scale.

Table 2. Preparation of α-azido esters **4** via Matteson homologation.

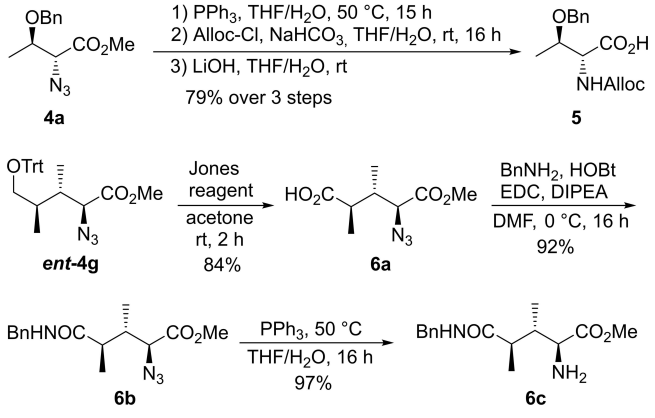


1	R	2	Yield [%]	4	R′	Yield [%]
1a[18]		**2a**	79[a]	**4a**	Me	96 (3 steps)
1b[19]		**2b**	99	**4b**	Me	93 (3 steps)
***ent*–1c**[18]		***ent*–2c**	92	***ent*–4c**	H	60 (2 steps)
***ent*–1d**[20]		***ent*–2d**	93	***ent*–4d**	H	83 (2 steps)
***ent*–1e**[20]		***ent*–2e**	95	***ent*–4e**	H	84 (2 steps)
1f[18]		**2f**	99	**4f**	Me	96 (3 steps)
***ent*--1g**[21]		***ent*–2g**	85[a]	***ent*–4g**	Me	83[b] (3 steps)
***ent*–1h**		***ent*–2h**	99	***ent*–4h**	*t*-Bu	68 (3 steps)
***ent*–1i**		***ent*–2i**	98	***ent*–4i**	*t*-Bu	53 (3 steps)
***ent*–1j**		***ent*–2j**	95	***ent*–4j**	*t*-Bu	38 (3 steps)

[a] LDA was used to deprotonate CH_2Cl_2; [b] Homologation of the azido boronic ester was performed with CH_2Cl_2 rather than CH_2Br_2.

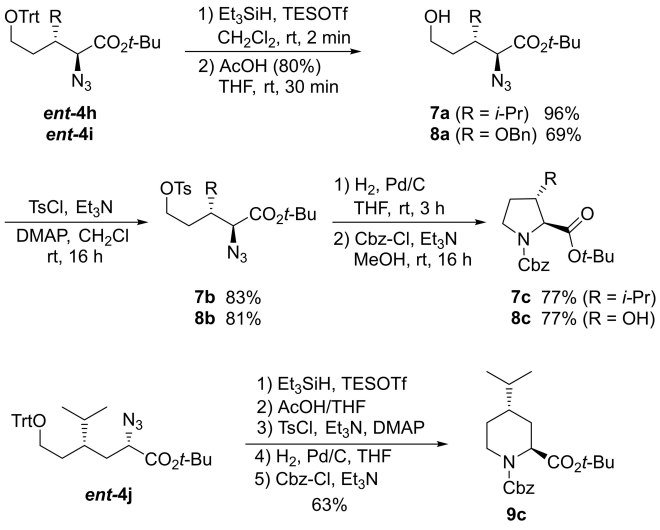
auxiliary gave rise to the enantiomeric products ***ent*–2** and ***ent*–4**.

The obtained azido acids and esters were readily transformed into the corresponding amino acids and peptides via well-known procedures (Scheme 3). For example, azide **4a** was reduced via the Staudinger reaction followed by the Alloc protection of the resulting amine and saponification of the methyl ester to the protected D-*allo*-threonine **5**, a common building block in many natural products. α-Azido ester ***ent*–4g** was converted into the proprietary glutamic acid derivative **6c**. The corresponding amino acid is a component of homophymines as well as several other related natural products. The reaction of ***ent*–4g** with an excess of Jones reagent led to the cleavage of the trityl (Trt) ether, and the direct oxidation of the primary alcohol led to the formation of carboxylic acid **6a**. The free amine **6c** was obtained via the coupling with benzylamine and the subsequent Staudinger reduction of the azide.



Scheme 3. Synthesis of linear protected amino acid derivatives.

Trt-protected azido esters, such as ***ent*–4g** to ***ent*–4j**, are also good candidates for the synthesis of cyclic amino acids, such as substituted prolines and pipecolic acids (Scheme 4). α-Azido esters ***ent*–4h/i** were selectively Trt-deprotected to the corresponding alcohols **7a** and **8a**,[22] and the subsequent reaction with tosyl chloride yielded the tosylates **7b** and **8b**. Heterogenous catalytic hydrogenation of the azido group and treatment with Cbz–Cl resulted in the protected proline *tert*-butyl esters **7c** and **8c**. Applying the same synthetic protocol to



Scheme 4. Synthesis of cyclic protected amino acid derivatives.

the elongated derivative ***ent*–4 j** produced the pipecolic acid derivative **9 c** in good yield.

Conclusions

In conclusion, we developed a straightforward protocol of iterative/successive Matteson homologation and terminal oxidation to access a variety of α-azido and α-amino acid derivatives in a highly stereoselective fashion. Due to the significant flexibility of Matteson homologation, aryl and alkyl groups as well as protected hydroxy groups can be introduced at almost any position. The protocol is equally suitable for linear amino acids and cyclic derivatives of variable ring size. Since such unusual amino acids are important building blocks of many natural products with notable biological activities, this synthetic route is well suited to the generation of small libraries of natural products for structure–activity relationship (SAR) studies.

Experimental Section

(**4*S*,5*S***)-**2**-((**1*S*,2*R***)-**1-Azido-2-(benzyloxy) propyl**)-**4,5-dicyclohexyl-1,3,2-dioxaborolane** (**2 a**): A Schlenk tube was flame dried and DIPA (1.97 mL, 13.9 mmol) was dissolved in dry THF (3 mL). The tube was cooled to −20 °C and *n*-BuLi (5.13 mL, 12.8 mmol, 2.5 M in hexane) was added dropwise. After complete addition, the mixture was stirred for 20 minutes at room temperature. In a second Schlenk tube $ZnCl_2$ (4.20 g, 30.8 mmol) was dried under high vacuum with a heat gun and after cooling to room temperature dissolved in THF (15 mL). The third Schlenk tube was flame dried and boronic ester **1 a**[14] (3.80 g, 10.2 mmol), CH_2Cl_2 (1.98 mL, 30.8 mmol) and THF (15 mL) were added. After cooling to −40 °C, the freshly prepared LDA solution was slowly added, and the mixture was stirred for 10–15 minutes at this temperature. The $ZnCl_2$ solution was rapidly added, and the reaction was warmed up and stirred for 16 hours at room temperature. After aqueous work up and removal of the solvent, the chloro boronic ester was dissolved in DMF (100 mL). Sodium azide (6.67 g, 103 mmol) was added and the mixture was stirred at room temperature for 10 hours. Aqueous work up and flash chromatography (silica, pentane/diethyl ether 95:5) afforded azide **2 a** (3.43 g, 8.02 mmol, 79%, 96:4 *dr*) as a colorless oil. R_f (**2 a**) = 0.49 (pentane/diethyl ether 9:1). $[\alpha]_D^{20} = -41.6$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (m, 10 H), 1.31 (d, *J* = 6.4 Hz, 3 H), 1.33 (m, 2 H), 1.59 (m, 2 H), 1.66 (m, 2 H), 1.74 (m, 6 H), 3.30 (d, *J* = 3.1 Hz, 1 H), 3.91 (qd, *J* = 6.4 Hz, *J* = 3.2 Hz, 1 H), 3.94 (m, 2 H), 4.58 (s, 2 H), 7.25 (m, 1 H), 7.33 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 25.8, 25.9, 26.3, 27.3, 28.3, 42.8, 53.2, 70.7, 77.0, 84.2, 127.4, 127.4, 128.3, 138.4 ppm. HRMS (CI): The compound decomposes during the measurements.

Methyl (**2*R*,3*R***)-**2-azido-3-(benzyloxy) butanoate** (**4 a**): According to the preparation of **2 a**, azide **2 a** (2.00 g, 4.70 mmol) was treated with CH_2Br_2 (985 μL, 14.1 mmol), DIPA (905 μL, 6.35 mmol), *n*-BuLi (2.35 mL, 5.88 mmol, 2.5 M in hexane) and $ZnCl_2$ (1.92 g, 14.1 mmol) at −78 °C. After warming to room temperature, stirring continued for 12 hours. After aqueous work up, the bromo boronic ester was suspended in *t*-BuOH/H_2O (135 mL, 2:1) before 2-methyl-2-butene (19.9 mL, 188 mmol), sodium chlorite (5.31 g, 47.0 mmol) and KH_2PO_4 (6.40 g, 47.0 mmol) were added. The mixture was stirred at room temperature overnight, acidified with 10% citric acid (pH 4) and extracted three times with diethyl ether. Washing of the combined organic layer with sat. $Na_2S_2O_3$ and drying over Na_2SO_4 was followed by esterification of the cleaved diol with methylboronic acid (338 mg, 5.64 mmol) in diethyl ether (40 mL) in the presence of $MgSO_4$ (1.13 g, 9.40 mmol). After filtration of the reaction mixture and evaporation of the solvent, the residue was dissolved in toluene/MeOH (94 mL, 5:1) and TMS-diazomethane (3.53 mL, 7.05 mmol) was added. After complete consumption of the starting material (TLC), the reaction was diluted with diethyl ether and quenched by addition of 10% acetic acid. The layers were separated, the aqueous layer extracted once with diethyl ether and the combined organic layer was washed with sat. $NaHCO_3$ solution and brine. Drying over Na_2SO_4 and purification via flash chromatography (silica, pentane/diethyl ether 92:8) afforded methyl ester **4 a** (1.13 g, 4.53 mmol, 96%) as a colorless oil. R_f (**4 a**) = 0.41 (pentane/diethyl ether 4:1). $[\alpha]_D^{20} = -23.9$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.2 Hz, 3 H), 3.78 (s, 3 H), 3.98 (qd, *J* = 6.2 Hz, *J* = 5.3 Hz, 1 H), 4.06 (d, *J* = 5.0 Hz, 1 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 7.32 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 52.6, 65.5, 71.3, 75.3, 127.6, 127.8, 128.4, 137.6, 169.0 ppm. HRMS (CI): m/z calcd for $C_{12}H_{15}NO_3$ $[M\text{-}N_2]^+$: 221.1046, found: 221.1057.

(**2*R*,3*R***)-**2-(Allyloxy) carbonylamino-3-(benzyloxy) butanoic acid** (**5**): To a solution of azide **4 a** (900 mg, 3.61 mmol) in THF/H_2O (36 mL, 25:1) PPh_3 (2.84 g, 10.8 mmol) was added and the mixture was heated to 50 °C for 15 hours. After cooling to room temperature, H_2O (10 mL) and $NaHCO_3$ (607 mg, 7.22 mmol) were added. The mixture was cooled to 0 °C, allyl chloroformate (578 μL, 5.42 mmol) was added dropwise and the reaction was stirred overnight. The reaction was quenched with 1 M HCl, the mixture extracted three times with CH_2Cl_2, and the combined organic layers were washed with brine. After drying (Na_2SO_4), evaporation of the solvent in vacuo and flash chromatography (silica, pentane/diethyl ether 3:1→2:1) the Alloc-protected amino acid methyl ester (891 mg, 2.90 mmol, 80%) was obtained as a colorless oil. R_f = 0.15 (pentane/diethyl ether 3:1). $[\alpha]_D^{20} = -12.7$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.5 Hz, 3 H), 3.75 (s, 3 H), 3.87 (m, 1 H), 4.56 (m, 5 H), 5.21 (d, *J* = 10.4 Hz, 1 H), 5.30 (d, *J* = 17.1 Hz, 1 H), 5.39 (d, *J* = 8.3 Hz, 1 H), 5.91 (ddt, *J* = 16.8 Hz, *J* = 10.9 Hz, *J* = 5.5 Hz, 1 H), 7.30 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 52.3, 57.2, 65.8, 70.9, 74.9, 117.8, 127.6, 127.7, 128.3, 132.5, 137.8, 155.8, 170.7 ppm. HRMS (CI): m/z calcd for $C_{16}H_{22}NO_5$ $[M+H]^+$: 308.1492, found: 308.1486.

The methyl ester (400 mg, 1.30 mmol) was dissolved in THF (13 mL) and LiOH (1.43 mL, 1.43 mmol, 1.0 M, 1.0 equiv) was added at 0 °C. After stirring at room temperature until complete conversion was observed (TLC), the reaction was acidified (pH 2) with 1 M HCl and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed *in vacuo* to afford carboxylic acid **5** (377 mg, 1.28 mmol, 99%) as a colorless oil. R_f(**5**) = 0.06 (pentane/diethyl ether 7:3). $[\alpha]_D^{20} = -17.4$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.4 Hz, 3 H), 3.93 (m, 1 H), 4.58 (m, 5 H), 5.21 (d, *J* = 10.6 Hz, 1 H), 5.31 (d, *J* = 17.2 Hz, 1 H), 5.49 (d, *J* = 8.1 Hz, 1 H), 5.91 (ddt, *J* = 16.8 Hz, *J* = 10.9 Hz, *J* = 5.4 Hz, 1 H), 7.31 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 56.9, 65.9, 71.0, 74.9, 117.8, 127.8, 127.8, 128.4, 132.6, 137.8, 156.0, 172.8 ppm. HRMS (CI): m/z calcd for $C_{15}H_{20}NO_5$ $[M+H]^+$: 294.1336, found: 294.1355.

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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: Amino acids · Azides · Matteson homologation · Natural products · Stereoselective synthesis

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