Research Article

(R)-α-Aminoadipic Acid: A Versatile Precursor for the Synthesis of D-Amino Acids

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The ready accessibility of (R)-α-aminoadipic acid by enzymatic cleavage of cephalosporin C (CephC) in the production of 7-aminocephalosporanic acid (7-ACA) on a large scale makes it a favorable chiral pool building block for the synthesis of unusual amino acids. A route for the synthesis of C-5-alkenyl and C-6-alkylidene derivatives of (R)-pipecolic acid is described which utilizes (R)-α-aminoadipic acid as the enantiomerically pure starting material. Moreover, the synthesis of azido and triazolyl derivatives of (R)-α-aminoadipic acid is reported.

1. Introduction

α-Amino acids, one of the important classes of natural products, play fundamental roles in chemistry and biology. In addition to their vital roles as building block of proteins and as intermediates in metabolism, they also constitute a broad array of chiral pool building blocks and organocatalysts [1–3]. Their ready availability, low cost, and high enantiomeric purity make them valuable starting materials for the synthesis of unusual amino acids. D-Amino acids are far less abundant in nature in contrast to L-configured counterparts. In addition, D-amino acids display interesting conformational features; for example, they stabilize turn conformations in peptides [4].

α-Aminoadipic acid is a six-carbon analog of aspartic and glutamic acid which is found in plants and microorganisms. It is a metabolite in the principal biochemical pathway of lysine [5]. During the past decades, α-aminoadipic acid has received attention from chemists active in the areas of peptide chemistry, organic synthesis, biosynthesis, and neuroscience. (R)-α-Aminoadipic acid exhibits a selective antagonistic activity at the N-methyl-D-aspartate subtype of glutamate receptors [6, 7]. It has also been used in the synthesis of carbocyclic nucleoside precursors [8]. (R)-α-Aminoadipic acid 1 is a constituent of cephalosporin C and penicillin N. In the pharmaceutical semisynthesis of cephalosporin derivatives, the central intermediate 7-aminocephalosporanic acid (7-ACA) is obtained by enzymatic cleavage of the fermentation product cephalosporin C (CephC) [9]. As the enantiomerically pure (R)-α-aminoadipic acid is available from this process on a large scale, we embarked on a project to explore the application of this chiral pool building block for the synthesis of (R)-pipecolic acid and its derivatives [10, 11].

Pipecolic acid, also known as homoproline or piperidine-2-carboxylic acid, a six-carbon natural nonproteinogenic α-amino acid, is an intermediate of lysine metabolism in various organisms including bacteria, yeast, fungi, and mammals. (S)-Pipecolic acid is an important precursor of several bioactive compounds such as synthetic peptides [12], local anesthetics [13], and potential enzyme inhibitors [14, 15] and is a component of biologically important natural products such as the immunomodulators rapamycin [16], the immunosuppressant FK506 [17], the antitumor antibiotic sandramycin [18], and the anticancer agent VX710 [19]. It also occurs in the efrapeptins and neoefrapeptins, ATPase inhibiting peptide families [20]. (R)-Pipecolic acid is present in the histone deacetylase inhibitors trapoxin A and apicidin [21]. These applications of pipecolic acid stimulated us to synthesize further derivatives of pipecolic acid which could be further employed in peptide modifications.
2. Material and Methods

All reactions were carried out in oven-dried glassware with magnetic stirrers under an argon atmosphere. THF was dried over Na/benzophenone and DCM was dried over CaH₂. Commercially available chemicals were purchased from Sigma-Aldrich and Alfa Aesar. EtOAc and n-pentane were distilled before use. Flash chromatography was carried out using silica gel, particle size 0.035–0.070 mm. Specific rotation of synthesized compounds was recorded on a Jasco DIC-366 digital polarimeter. ¹H NMR spectra were recorded on a 500 MHz Bruker DRX spectrometer in CDCl₃ (unless otherwise stated) referenced relative to residual CHCl₃ (δ = 7.26 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. ¹³C NMR spectra were recorded on a 125.7 MHz spectrometer with proton decoupling. TMS as an internal standard was used for all ¹H and ¹³C NMR measurements. ¹H NMR spectra were recorded on a 500 MHz Bruker DRX spectrometer in CDCl₃ and CD₂Cl₂ using TMS as an internal standard. H atoms were referenced relative to residual CHCl₃ in ppm. In the case of other solvents, H atoms were referenced relative to residual solvent. The 125.7 MHz Bruker DRX is equipped with an Autospec X magnetic sector mass spectrometer with EBE geometry (Vacuum Generators, Manchester, UK) equipped with a standard EI or CI source. Samples were introduced by push rod in aluminium crucibles if not otherwise noted. Ions were accelerated by 8 kV in EI mode and 6 kV in CI mode. Accurate mass measurement experiments with ESI or MALDI were performed using a Fourier transform ion cyclotron resonance mass spectrometer APEX III (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 70 T, 160 mm bore superconducting magnet (Bruker Analytik GmbH—Magnetics, Karlsruhe, Germany), infinity cell, and interfaced with an external (nano)ESI or MALDI ion source. Nitrogen served both as the nebulizer gas and the dry gas for ESI. Nitrogen was generated by a Bruker nitrogen generator NGM II. Argon served as a cooling gas in the infinity cell and a collision gas for MS² experiments.

Benzyll (R)-2-(Benzyloxycarbonylamino)-6-(methylsulfonyloxyl)hexanoate (7). Et₃N (1.68 mmol, 2.5 eq., 0.23 mL) and methanesulfonyl chloride (0.81 mmol, 1.2 eq., 0.06 mL) were added to a solution of 4 (0.673 mmol, 1 eq., 250 mg) in dry CH₂Cl₂ (8 mL) at 0°C, and the mixture was stirred at the same temperature. The progress of the reaction was monitored by TLC. After the reaction was complete (~45 min), it was quenched by addition of water (10 mL). The mixture was then extracted with CH₂Cl₂ (3 × 15 mL), and the combined organic phase was washed with brine (15 mL) and dried over anhydrous Na₂SO₄. Evaporation of solvent and silica gel column chromatography of the resulting residue (n-pentane/EtOAc 6:4) gave the corresponding mesylate 7 (270 mg, 92%) as a colorless oil.

[α]D²³ = +23.0 (c = 1.5, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 7.40–7.33 (m, 10H, Ar-H), 5.27–5.03 (m, 4H, CH₂), 2.95 (s, 3H, CH₃), 1.87 (m, 6H, CH₂), 1.83–1.66 (m, 3H, CH₃), 1.51–1.35 (m, 2H, CH₂). ¹³C NMR (125.7 MHz, CDCl₃): δ = 172.0 (COO), 155.9 (N(COO)), 136.5 (Ar-C), 135.2 (Ar-C), 128.7 (10 Ar-C), 69.4 (OCH₃), 67.2 (Bn-CH₃), 67.0 (Bn-CH₃), 53.6 (CH), 37.2 (CH₂), 31.9 (CH₂), 28.5 (CH₂), 21.2 (CH₂). C₂₂H₂₇NO₃S (449.16). HRMS (ESI-FT-ICR): m/z = 472.14057; calcd. for [C₂₂H₂₇NO₃SNa]+: m/z = 472.1404.

Benzyl (R)-6-Azido-2-(benzyloxycarbonylaminohexanooate (8). NaN₃ (1.00 mmol, 1.5 eq, 70 mg) was added to a solution of mesylate 7 (0.68 mmol, 1 eq., 300 mg) in dry DMF (8 mL). The reaction mixture was stirred at room temperature for 18 h. It was then poured into water (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phase was washed with brine (20 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue thus obtained was purified by silica gel column chromatography (ether/EtOAc 7:3) to give 8 (202 mg, 76%) as a colorless oil.

[α]D²³ = +30.1 (c = 1.5, CHCl₃). ¹H NMR (500 MHz, Me₂OD): δ = 7.39–7.28 (m, 10H, Ar-H), 5.22–5.13 (m, 2H, Bn-CH₂), 5.10 (s, 2H, Bn-CH₂), 4.15 (m, 1H, CH), 3.24 (t, J = 6.7 Hz, 2H, CH₂), 1.82 (m, 1H, CH₂), 1.67 (m, 1H, CH₂), 1.60–1.50 (m, 2H, CH₂), 1.49–1.40 (m, 2H, CH₂). ¹³C NMR (125.7 MHz, CDCl₃): δ = 174.9 (COO), 159.7 (N(COO)), 139.3 (Ar-C), 138.3 (Ar-C), 128.6 (10 Ar-C), 68.9 (CH₂), 68.7 (CH₂), 56.5 (CH₃), 53.2 (CH₂), 33.2 (CH₂), 30.4 (CH₂), 25.1 (CH₂). C₂₁H₂₃N₃O₄ (396.18). HRMS (ESI-FT-ICR): m/z = 397.18724; calcd. for [C₂₁H₂₃N₃O₄H]+: m/z = 397.18703.

2.1. General Procedure for Copper Catalyzed Azide-Alkyne Cycloaddition (CuAAC). Substituted alkyne (0.352 mmol, 1 eq.) was added to a solution of azide 8 (0.352 mmol, 1 eq.) in a 1:9 mixture of DMSO (0.5 mL) and H₂O (4.5 mL). CuSO₄·5H₂O (0.088 mmol, 0.25 eq.) was added to the mixture, followed by the addition of sodium ascorbate (0.160 mmol, 0.5 eq.). The reaction mixture was vigorously stirred overnight at room temperature. After completion (monitored by TLC) the reaction was quenched by addition of water and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic phase was washed with water and brine and concentrated in vacuo. The residue was purified by flash column chromatography (n-pentane/EtOAc 1:1) to give the product as colorless oil.

2.1.1. Benzyl (R)-2-(Benzyloxycarbonylaminol)-6-(4-phenyl-1H-1,2,3-triazol-1-yl)hexanoate (II). Colorless oil, yield 100 mg (57%). [α]D²³ = +27.3 (c = 1.5, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 7.82–7.76 (m, 2H, Ar-H), 7.69 (s, 1H, Ar-H), 7.42–7.40 (m, 2H, Ar-H), 7.35–7.30 (m, 1H, Ar-H), 5.34 (d, J = 8.2 Hz, 2H, NH), 5.19–5.04 (m, 4H, Bn-CH₂), 4.43 (m, 1H, CH₂), 4.31 (t, J = 7.1 Hz, 2H, CH₂), 1.96–1.87 (m, 2H, CH₂) 1.75–1.68 (m, 2H, CH₂), 1.35 (m, 1H, CH₂), 1.28 (m, 1H, CH₂). ¹³C NMR (125.7 MHz, CDCl₃): δ = 171.9 (COO), 155.8 (N(COO)), 147.7 (C), 136.1 (Ar-C), 135.1 (Ar-C), 130.6 (3 Ar-C), 128.8 (12 Ar-C), 125.7 (Ar-C), 119.4 (CH), 67.3 (Bn-CH₃), 67.0 (Bn-CH₃), 53.4 (CH), 49.9 (CH₂), 32.0 (CH₂), 29.6 (CH₂), 22.0 (CH₂). C₂₃H₂₅N₄O₄ (498.18). HRMS (ESI-FT-ICR): m/z = 521.21663; calcd. for [C₂₃H₂₅N₄O₄Na]+: m/z = 521.21593.

2.1.2. Benzyl (R)-2-(Benzyloxycarbonylaminol)-6-(4-ethoxycarbonyl-1H-1,2,3-triazol-1-yl)hexanoate (IIB). Colorless oil, yield 75 mg (60%). [α]D²³ = +21.4 (c = 1.5, CHCl₃).
2.2. General Procedure for Ruthenium Catalyzed Azide-Alkyne Cycloaddition (RuAAC). A mixture of azide 8 (0.252 mmol, 1 eq., 100 mg), alkyne (0.504 mmol, 2 eq.), and CpRuCl(PPh\(_3\))\(_2\) (0.005 mmol, 0.02 eq.) in benzene (7 mL) was stirred under reflux for 24 h. The progress of the reaction was monitored by TLC. After completion of reaction, the solvent was evaporated under vacuum, and the product was purified by silica gel chromatography (n-pentane/EtOAc 1:1) to give the product as colorless oil.

2.2.1. (R)-Benzyl 2-((Benzoxycarbonyl)amino)-6-(5-phenyl-1H-1,2,3-triazol-1-yl)hexanoate (9). Colorless oil, yield 80 mg (64%). [\(\alpha\]\(_D\)\(^{25}\) = +27.8 (c = 1.5, CHCl\(_3\)). H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.79\) (s, 1H, Ar-H), 7.52–7.48 (m, 3H, Ar-H), 7.39–7.30 (m, 2H, Ar-H), 5.32 (d, \(J = 8.3\) Hz, 1H, NH), 5.20–5.13 (m, 2H, CH\(_2\)), 5.11 (s, 2H, Bn-CH\(_2\)), 4.37 (m, 1H, CH), 4.28 (t, \(J = 7.3\) Hz, 2H, CH\(_2\)), 1.88–1.78 (m, 3H, CH\(_3\)), 1.60 (m, 1H, CH\(_2\)), and 1.35–1.20 (m, 2H, CH\(_2\)). C\(_{26}\)H\(_{30}\)N\(_2\)O\(_6\) (494.23). HRMS (ESI-FT-ICR): m/z = 521.21667; calcd. for [C\(_{26}\)H\(_{30}\)N\(_2\)O\(_4\)]\(^+\): m/z = 521.21593.

2.2.2. Benzyl (R)-2-((Benzoxycarbonyl)amino)-6-(5-ethoxy-carbonyl-1H-1,2,3-triazol-1-yl)hexanoate (10). Colorless oil, yield 65 mg (52%). [\(\alpha\]\(_D\)\(^{23}\) = +22.0 (c = 1.5, CHCl\(_3\)). H NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.04\) (s, 1H, Ar-H), 7.39–7.33 (m, 10H, Ar-H), 5.39 (br d, \(J = 8.3\) Hz, NH), 5.22–5.14 (m, 2H, Bn-CH\(_2\)), 5.11 (s, 2H, Bn-CH\(_2\)), 4.45–4.30 (m, 3H, CH\(_3\)), 4.32 (t, \(J = 7.3\) Hz, 2H, CH\(_2\)), 1.96–1.86 (m, 3H, CH\(_2\)), 1.73 (m, 1H, CH\(_3\)) 1.39 (t, \(J = 7.1\) Hz, 3H, CH\(_2\)), 1.37–1.27 (m, 2H, CH\(_2\)). C\(_{28}\)H\(_{32}\)O\(_4\)N\(_2\) (574.21). HRMS (ESI-FT-ICR): m/z = 517.20527; calcd. for [C\(_{28}\)H\(_{32}\)O\(_4\)N\(_2\)]\(^+\): m/z = 517.20567.

2.3. General Procedure for Wittig Reaction with Nonstabilized Ylids. n-Butyl lithium (0.1 mL, 1.6 M in hexane, 0.08 mmol) was added to a stirred solution of triphenylalkylphosphonium bromide (0.08 mmol, 1 eq.) in THF (5 mL), and the resulting mixture was stirred at room temperature for 30 min. The solution of aldehyde 3 (25 mg, 0.07 mmol) in THF (3 mL) was added dropwise to the mixture. The reaction mixture was stirred at room temperature for 1.3 h. After completion of the reaction monitored by TLC (hexane/EE, 7:3), it was quenched by addition of water and extracted with ether. The combined ether layers were dried and concentrated. The crude product was purified by flash chromatography on silica gel (n-hexane/EtOAc 7:3).

2.3.1. Dibenzyl (R)-5-Vinyl-3,4-dihydropyridine-1,2(2H)-dicarboxylate (13a). Colorless oil, yield 45.5 mg (60%) [10, II].

2.3.2. Dibenzy (R)-5-(2-Methyl-1-propanyl)-3,4-dihydropyridine-1,2(2H)-dicarboxylate (13b). Colorless oil, yield 105 mg (65%). [\(\alpha\]\(_D\)\(^{23}\) = +33.2 (c = 1.5, CHCl\(_3\)). H NMR (500 MHz, CDCl\(_3\), conformer mixture): \(\delta = 7.49–7.29\) (m, 10H, Ar-H), 6.94/6.82 (s, 1H, CH), 5.75/5.74 (s, 1H, CH), 5.30–5.11 (m, 4H, Bn-CH\(_2\)), 4.89 (m, 1H, CH), 2.45 (m, 1H, CH\(_2\)), 2.12 (m, 1H, CH\(_2\)), 2.03 (m, 1H, CH\(_2\)), 1.95 (m, 1H, CH\(_2\)), 1.80 (s, 3H, CH\(_3\)), 1.77/1.88 (d, \(J = 5\) Hz, 3H, CH\(_3\)). C\(_{30}\)H\(_{34}\)O\(_4\)N\(_2\) (497.21). HRMS (EI): m/z = 405.19370; calcd. for [C\(_{30}\)H\(_{34}\)O\(_4\)N\(_2\)]\(^+\): m/z = 405.19401.

2.3.3. (R,E)-Dibenzy 5-(1-Butenyl)-3,4-dihydropyridine-1,2(2H)-dicarboxylate and (R,Z)-Dibenzy 5-(1-Butenyl)-3,4-dihydropyridine-1,2(2H)-dicarboxylate (13c). Colorless oil, yield 110 mg (68%). [\(\alpha\]\(_D\)\(^{23}\) = +31.1 (c = 1.5, CHCl\(_3\)). H NMR (500 MHz, CDCl\(_3\), E/Z and conformer mixture): \(\delta = 7.42–7.27\) (m, 10H, Ar-H), 7.06/6.91 (s, 1H, CH), 6.07/5.95, 5.72/5.67, 5.22 (d, \(I_{trans} = 15.7\) Hz and 2d, \(I_{cis} = 11.6\) Hz, 1H, CH), 5.54–5.11 (m, 1H, Bn-CH\(_2\)), 4.97 (m, 1H, CH), 2.45 (m, 1H, CH\(_2\)), 2.31–2.03 (m, 4H, CH\(_2\)), 1.96 (m, 1H, CH\(_2\)), 1.05–0.95 (m, 3H, CH\(_3\)). C\(_{29}\)H\(_{34}\)O\(_4\)N\(_2\) (498.21). HRMS (EI): m/z = 405.19420; calcd. for [C\(_{29}\)H\(_{34}\)O\(_4\)N\(_2\)]\(^+\): m/z = 405.19401.

2.3.4. (R,E)-Dibenzy 5-(1-Propenyl)-3,4-dihydropyridine-1,2(2H)-dicarboxylate and (R,Z)-Dibenzy 5-(1-Propenyl)-3,4-dihydropyridine-1,2(2H)-dicarboxylate (13d). Colorless oil, yield 94 mg (61%). [\(\alpha\]\(_D\)\(^{23}\) = +30.7 (c = 1.5, CHCl\(_3\)). H NMR (500 MHz, CDCl\(_3\), conformer mixture, signals of both E and Z isomer): \(\delta = 7.31–7.16\) (m, 10H, Ar-H),
2.4. General Procedure for Wittig Reaction with Stable Ylids.

The corresponding 2-(triphenylphosphoranylidene)acetate (0.067 mmol, 1 eq.) was added to the solution of protected aldehyde 6 (0.037 mmol, 1 eq., 100 mg) in dry toluene (7 ml), and the reaction mixture was refluxed for 18 h. The progress of the reaction was monitored by TLC till the aldehyde was consumed. After completion, the reaction mixture was concentrated and the product was purified chromatographically (pet. Ether/EtOAc 7:3) to afford the desired product.

2.4.1. Dibenzyl (R,E)-5-(3-Ethoxy-3-oxo-1-propenyl)-3,4-dihydropyridine-1,2(2H)-dicarboxylate (14a).

Palladium-black (10%), 0.391 mmol, 2M LiCl, 4 ml of DMF, 15% of CH3CN, and the solution was stirred at 25 °C for 2 h. After completion of the reaction, the mixture was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (n-pentane/EtOAc 4:1) to give the enaminocarbonyl ester as pale-yellow oil.

2.4.2. Dibenzyl (R,E)-5-(3-Methoxy-3-oxo-1-propenyl)-3,4-dihydropyridine-1,2(2H)-dicarboxylate (14b).

Palladium-black (10%), 0.391 mmol, 2M LiCl, 4 ml of DMF, 15% of CH3CN, and the solution was stirred at 25 °C for 2 h. After completion of the reaction, the mixture was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (n-pentane/EtOAc 4:1) to give the enaminocarbonyl ester as pale-yellow oil.

2.4.3. Dibenzyl (R,E)-5-(3-Benzoxy-3-oxo-1-propenyl)-3,4-dihydropyridine-1,2(2H)-dicarboxylate (14c).

Colorless oil, yield 83 mg (62%). [α]D23 = +14.9 (c = 1.5, CHCl3); 1H NMR (500 MHz, CDCl3, conformer mixture): δ = 7.49–7.27 (m, 17H, Ar-H, CH), 5.75/5.76 (d, J = 14.6 Hz, 1H, CH), 5.77–5.12 (m, 6H, Bn-CH2), 4.98 (m, 1H, CH), 2.51 (m, 1H, CH2), 2.22 (m, 1H, CH2), 2.00–1.88 (m, 2H, CH2), 1H NMR (125.7 MHz, CDCl3, conformer mixture): δ = 170.0/169.9 (COO), 167.2/167.1 (C=O), 145.1/145.0 (CH=CHCO), 135.3/135.2 (2 Ar-C), 132.0/131.6 (CH=C), 128.7 (10 Ar-CH), 115.5/115.0 (C-CH), 113.6/113.5 (CHCOO), 68.7/68.5 (Bn-CH2), 67.3/67.2 (Bn-CH3), 60.0/59.9 (CH3), 54.3/53.9 (CH2), 23.0/22.7 (CH3), 18.0/17.8 (CH2), 14.3/14.2 (CH3). C25H25N2O4 (449.18). HRMS (EI): m/z = 449.18190; calcld. for C25H25N2O4: m/z = 449.1834.

2.5. General Procedure for the Preparation of Enamino Esters.

A solution of lithium diisopropylamide (0.391 mmol, 2 M in heptanes) in THF (5 ml) was cooled to –78 °C. Substituted acetate (0.778 mmol, 1 eq.) in THF (1 ml) was added dropwise over 30 min, and the solution was allowed to stir for a further 30 min. Protected lactam 16 (0.778 mmol, 1 eq.) in THF (2 ml) was added over 30 min at –78 °C. Then the solution was allowed to warm up to RT and stirred for 18 h. Satd. aq. NH4Cl solution (10 ml) was added and the mixture was extracted with CH2Cl2 (3 × 100 ml). The combined organic phase was washed with brine (2 × 150 ml) and dried over MgSO4, and the solvent was removed in vacuo. TFA (2.1 ml, 28 mmol) was added to the crude residue, and the resulting mixture was stirred for 3 h at 25 °C. Excess TFA was removed in vacuo and the resulting oil was dissolved in CH2Cl2 (5 ml). Sat. aq. Na2CO3 was added to neutralize the solution, and the organic components were extracted with CH2Cl2 (3 × 15 ml). The combined organic phase was dried over MgSO4, and the solvent was evaporated in vacuo. The resulting yellow oil was purified by flash column chromatography (pet. Ether/EtOAc 4:1) to give the enaminocarbonyl ester as pale-yellow oil.
We previously disclosed the syntheses of alcohol 4, enamine 5, and aldehyde 6 from (R)-α-aminoadipic acid (Scheme 1) \[10,11\].

### Scheme 1: Synthesis of starting materials (alcohol 4, enamine 5, and aldehyde 6) \[10,11\].

### Scheme 2: Synthesis of azide and triazole derivatives of (R)-α-aminoadipic acid.

2.5.3. **Methyl (R,Z)-6-(2-tert-Butoxy-2-oxoethylidene)piperidine-2-carboxylate** (17c). Yellow oil, yield 65 mg (66%). $[\alpha]_D^{23} = +12.9$ (c = 1.5, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$, conformer mixture): $\delta = 8.92$ (br s, 1H, NH), 4.43 (br s, 1H, C=CH), 4.05 (m, 1H, CH), 3.79 (s, 3H, COOCH$_3$), 2.36–2.32 (m, 2H, CH$_2$), 2.12 (m, 1H, CH$_2$), 1.87 (m, 1H, CH$_2$), 1.73 (m, 1H, CH$_2$), 1.65 (m, 1H, CH$_2$), 1.48 (s, 9H, C(CH$_3$)$_3$). $^13$C NMR (125 MHz, CDCl$_3$): $\delta = 172.5$ (COO), 170.3 (COO), 159.8 (CO=CH), 84.7 (C=CH), 78.1 (C(CH$_3$)$_3$), 53.7 (CH$_3$), 52.5 (CH$_2$), 28.8 (CH$_2$), 28.6 (3 C(CH$_3$)$_3$), 26.1 (CH$_2$), and 18.9 (CH$_3$). C$_{11}$H$_{17}$NO$_3$ (255.15). HRMS (EI) $m/z = 255.14763$; calcd. for [C$_{11}$H$_{17}$NO$_3$]$^+$: $m/z = 255.14651$.

2.5.5. **Ethyl (R,Z)-6-(2-Ethoxy-2-oxoethylidene)piperidine-2-carboxylate** (17e). Yellow oil, yield 47 mg (53%). $[\alpha]_D^{23} = +19.6$ (c = 1.5, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$, conformer mixture): $\delta = 9.01$ (br s, 1H, NH), 4.48 (br s, 1H, C=CH), 4.24 (q, $J = 7.1$ Hz, 2H, CH$_2$), 4.12 (q, $J = 7.1$ Hz, 2H, CH$_2$), 4.03 (dd, $J = 8.0$ Hz, 5.4 Hz, 1H, CH), 2.36–2.32 (m, 2H, CH$_2$), 2.15 (m, 1H, CH$_2$), 1.84 (m, 1H, CH$_2$), 1.75 (m, 1H, CH$_2$), 1.67 (m, 1H, CH$_2$), 1.30 (t, $J = 7.1$ Hz, 3H, CH$_2$), 1.26 (t, $J = 7.1$ Hz, 3H, CH$_2$). $^13$C NMR (125 MHz, CDCl$_3$): $\delta = 170.8$ (COO), 170.3 (COO), 160.7 (C=CH), 82.7 (C=CH), 61.5 (CH$_2$), 58.4 (CH), 53.7 (CH$_2$), 28.8 (CH$_2$), 26.0 (CH$_2$), 18.8 (CH$_3$), 14.6 (CH$_3$), 14.1 (CH$_3$). HRMS (EI) $m/z = 241.13120$; calcd. for [C$_{11}$H$_{19}$NO$_3$]$^+$: $m/z = 241.13141$.

### 3. Results and Discussion

We previously disclosed the syntheses of alcohol 4, enamine 5, and aldehyde 6 from (R)-α-aminoadipic acid (Scheme 1) \[10,11\].
Amino acids with azido functions in the side chain are appreciated in organic synthesis for its ease of introduction into complex structures, convenient conversion to a primary amine [22], and participation in dipolar cycloaddition reactions [23], especially with respect to bioorthogonal reactions [24]. For the synthesis of the azide 8, alcohol 4 was first converted into the methane sulfonate 7 using methanesulfonyl chloride and triethylamine. It was then converted into azide 8 by treatment with sodium azide in DMF at room temperature.

Keeping in view the importance of triazole system [25] and with this azide intermediate in our hands, we performed click reactions using CuSO₄/ascorbate and Cp′Ru(PPh₃)₂Cl₂ as catalysts for the synthesis of 1,4- and 1,5-disubstituted triazole amino acid derivatives. Treatment of azide 8 with alkynes proceeded smoothly in the presence of a catalytic amount of CuSO₄ and sodium ascorbate in a 10% solution of DMSO in water to produce 1,4-disubstituted-1,2,3-triazole derivatives 11 and 12 in good yields, respectively. The synthesis of 1,5-disubstituted triazole regioisomers was carried out successfully under ruthenium catalysis in good yields by refluxing azide 8 and catalyst and alkyne in benzene (Scheme 2).

Aldehyde moieties present in amino acids constitute a class of chiral synthons, valuable for the synthesis of optically active compounds and, in particular, for the synthesis of unusual amino acids. Thus, for the synthesis of C-5-alkenyl derivatives of (R)-piperolic acid, formylation of enamine 5 by Vilsmeier-Haack reaction under reflux conditions was performed to provide protected aldehyde 6 (Scheme 1). One example of a Wittig reaction of aldehyde 6 giving a vinyl derivative of piperolic acid has already been described by us [12]. In order to explore the scope of the reaction, aldehyde 6 was treated with a range of Wittig reagents to afford C-5-alkenyl derivatives of (R)-piperolic acid. The reaction was carried out with nonstabilized ylids generated in situ from alkyl triphenylphosphonium bromides with n-ButLi at −78°C to afford the alkenyl substituted products in good yield. Compounds 13c and 13d were obtained as a mixture of E/Z isomers (Scheme 3; 13a–d).

Wittig reaction of aldehyde 6 was also investigated with an array of stabilized ylids that are preformed and added to suitable carbonyl compounds. This reaction was performed in toluene as a solvent under refluxing conditions for 18 hours and provided exclusively E-configured α,β-unsaturated ester derivatives of piperolic acid 14 (Scheme 3, 14a–c).

Strongly acidic or basic reaction conditions often lead to epimerization or racemization in susceptible chiral compounds. Therefore, the enantiomeric purity of the reaction products 6 and 13a was determined by chiral HPLC (Chiralpak-AD).

For comparison the S-configured enantiomers ent-6 and ent-13a were synthesized starting from (S)-α-aminoacidic acid and analyzed as well. No epimerization could be detected for the two compounds investigated (Figure 1).

(R)-6-Oxopiperolic acid derivatives 15 can be easily prepared from (R)-α-aminoacidic acid in consecutive steps of esterification and cyclization during Kugelrohr distillation according to previously reported procedures [12, 26]. The amide group of 15 was Boc-protected with Boc anhydride and DMAP in acetonitrile at room temperature. For synthesis of C6-exocyclic enamine esters of piperolic acid, compound 16 was reacted with a variety of substituted alkyl acetates in presence of LDA followed by treatment with TFA for 2h at room temperature to give the desired compounds...
(Scheme 4). The Z configuration of the synthesized compounds was established on the basis of chemical shift values of the alkenyl and the NH protons. The chemical shift values for these protons are significantly deshielded which indicates the Z configuration, and this is in good agreement with the data reported for 5-membered cyclic analogs of these compounds [27].

In summary, efficient and simple syntheses of C-5 alkenyl and C-6 enamo ester derivatives of piperidic acid are presented from enantiopure (R)-α-aminoadipic acid. Furthermore, the 6-azido and regiosomeric 6-triazolyl derivatives of amino (R)-α-aminohexanoic acid were prepared starting from (R)-α-aminoadipic acid by CuAAC or RuAAC.

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