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## Synthesis of enantiomerically enriched $\beta$ -*N*-amino (*S*)- $\alpha$ -alanine analogs *via* sequential reactions on a chiral Ni(II) complex

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A concise synthetic route to enantiomerically enriched  $\beta$ -*N*-substituted (*S*)- $\alpha$ -diaminopropanoic acids is reported. An acetylene group was introduced into the alanine side chain by nucleophilic Michael addition of substituted propargylamines to the dehydroalanine moiety in a chiral Ni(II) complex, which afforded  $\beta$ -*N*-propargylamino derivatives in high ee ( $\approx 90\%$ ). Subsequent Glaser, Sonogashira, and [3 + 2]-cycloaddition reactions delivered structurally diverse products with ee up to 99%. The isolated auxiliary (*S*)-BPB can be recovered and reused without any loss of enantiointegrity. Biological screening of the products identified (*S*)-3-(*N*-(1-phenylethyl)-*N*-(prop-2-ynyl)amino)-2-aminopropanoic acid as a moderate bacterial collagenase inhibitor ( $IC_{50} = 0.69$  mM), demonstrating the potential of this platform for enzyme inhibitor development.

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## Introduction

$\alpha,\beta$ -Diamino acids represent a rare but highly significant class of non-proteinogenic amino acids that have attracted growing attention due to their unique structural and functional properties.<sup>1,2</sup> For example, *L*-tambroline, an  $\alpha,\beta$ -diamino acid incorporated into the non-ribosomal peptide tambromycin, plays a key structural role in the compound's antiproliferative properties.<sup>3</sup> Among  $\alpha,\beta$ -diamino acids, the most studied examples are *L*-quisqualic acid, *L*-lupinic acid, and *L*-willardine (Fig. 1). *L*-Quisqualic acid is a potent AMPA and mGlu receptor agonist used to investigate excitatory neurotransmission and excitotoxicity. *L*-Lupinic acid, a non-proteinogenic amino acid from *Lupinus* species, serves as a probe of nitrogen metabolism and polyamine biosynthesis. *L*-Willardine, a pyrimidine-containing AMPA agonist, is applied in studies of glutamatergic signaling and receptor structure–activity relationships.<sup>2</sup>

The presence of  $\alpha,\beta$ -diamino acid fragments in bioactive natural products such as streptothricins, viomycin, and

capreomycin highlights their value as pharmacophores in antimicrobial and anticancer drug discovery.

Notably, incorporating these motifs into drug structures can prolong pharmacological action, supporting molecular design strategies that improve metabolic stability and biological activity.<sup>4,5</sup> Likewise, the introduction of unnatural  $\alpha$ -amino acids into peptide frameworks enables fine control over pharmacokinetic and pharmacodynamic properties—enhancing membrane permeability, enzymatic stability, and receptor selectivity—while improving antibacterial potency and reducing toxicity. Together, these features address key limitations of canonical peptides and offer promising avenues for combating antibiotic-resistant pathogens.<sup>6–8</sup> Among unnatural  $\alpha,\beta$ -diamino acids, derivatives featuring functionally substituted aliphatic, aromatic, or heterocyclic groups in the side chain attracted particular interest. Specifically,  $\beta$ -*N*-substituted alanine analogs are key structural components of several clinically relevant antibiotics, including *Tuberactinomycins*, *Bleomycins*, *Edeines*, and *Capreomycins*.<sup>9</sup>

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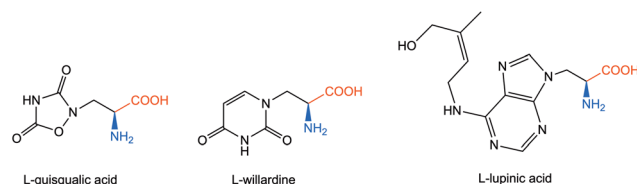
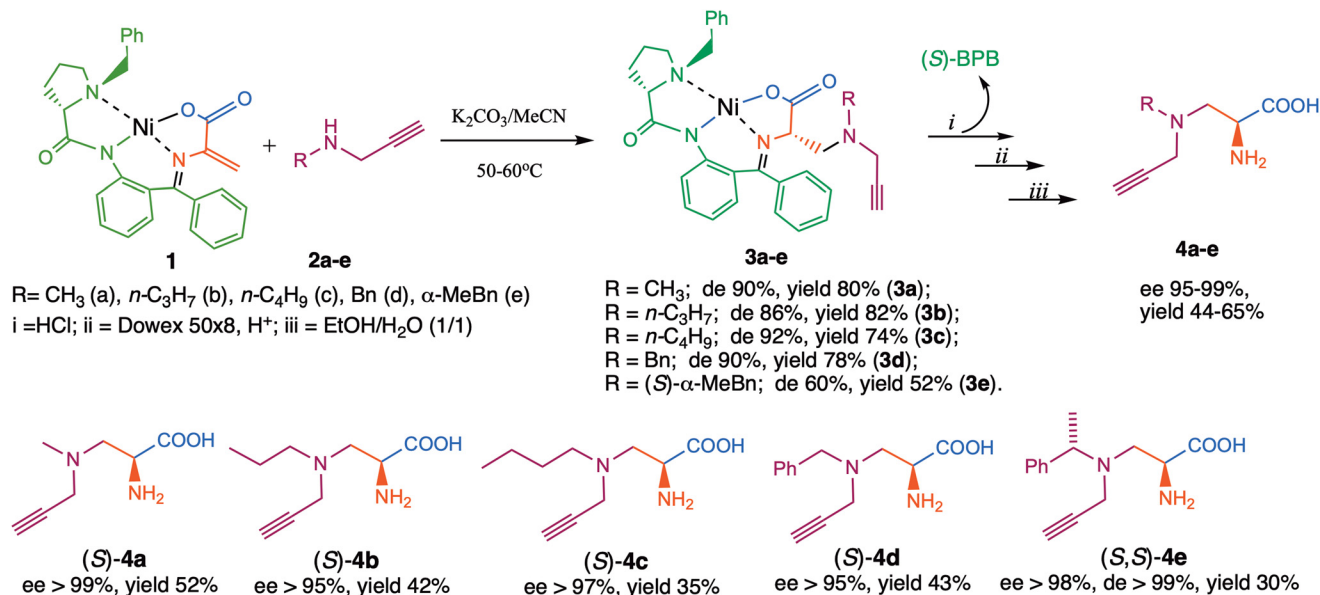


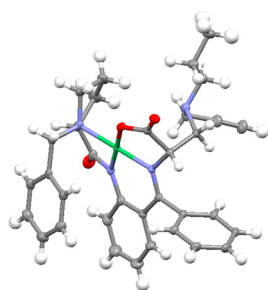
Fig. 1 Selected bioactive natural  $\alpha,\beta$ -diamino acids.







**Scheme 1** The addition of the propargylamines **2a–e** to the C=C bond of **1**.



**Fig. 2** X-Ray structure of complex **3b**.

mineralization and crystallization from aqueous ethanol. The initial chiral auxiliary (*S*)-BPB was regenerated in a nearly quantitative yield (>96%) without loss of enantiomeric purity and was reused without any loss of chiral integrity.

Using this method, amino acids **4a–e** were obtained in pure crystalline form, with high enantiomeric purities (ee 95–99%), as confirmed by chiral HPLC analysis, and in 30–52% chemical yield. The reported yields refer to the isolated recrystallized products; they could likely be improved through further optimization of the recrystallization procedure. At an industrial scale, additional material can be recovered from the mother liquor, thereby increasing the overall yield. These results indicate that the method is readily applicable for preparing other enantiomerically enriched amino acids bearing a propargylamino moiety.

The terminal alkyne groups in the side chain of the synthesized complexes can serve as valuable handles for further synthetic modification. In this study, complexes **3b** and **3d** were subjected to Sonogashira and Glaser cross-coupling reactions, a complex **3b** was additionally employed in a [3 + 2] cycloaddition (Scheme 2).

Arylation of the terminal acetylene group in complexes **3b** and **3d** by Sonogashira coupling (Scheme 2, route A) gave rise to complexes **5b** and **5d** with good yield. During the reaction, a side product was formed, which was identified as a dimerization product. This observation prompted us to optimize a Glaser homocoupling reaction (route B), enabling the efficient synthesis of dimeric complex **6b** and **6d** in good yield. In a [3 + 2]-cycloaddition, 4-nitrophenylazide was reacted with the terminal alkyne group of complex **3b** to furnish complex **7b** in a good yield, which was converted to the respective amino acid **9b** featuring a 1,2,3-triazole moiety in the side chain (route C).

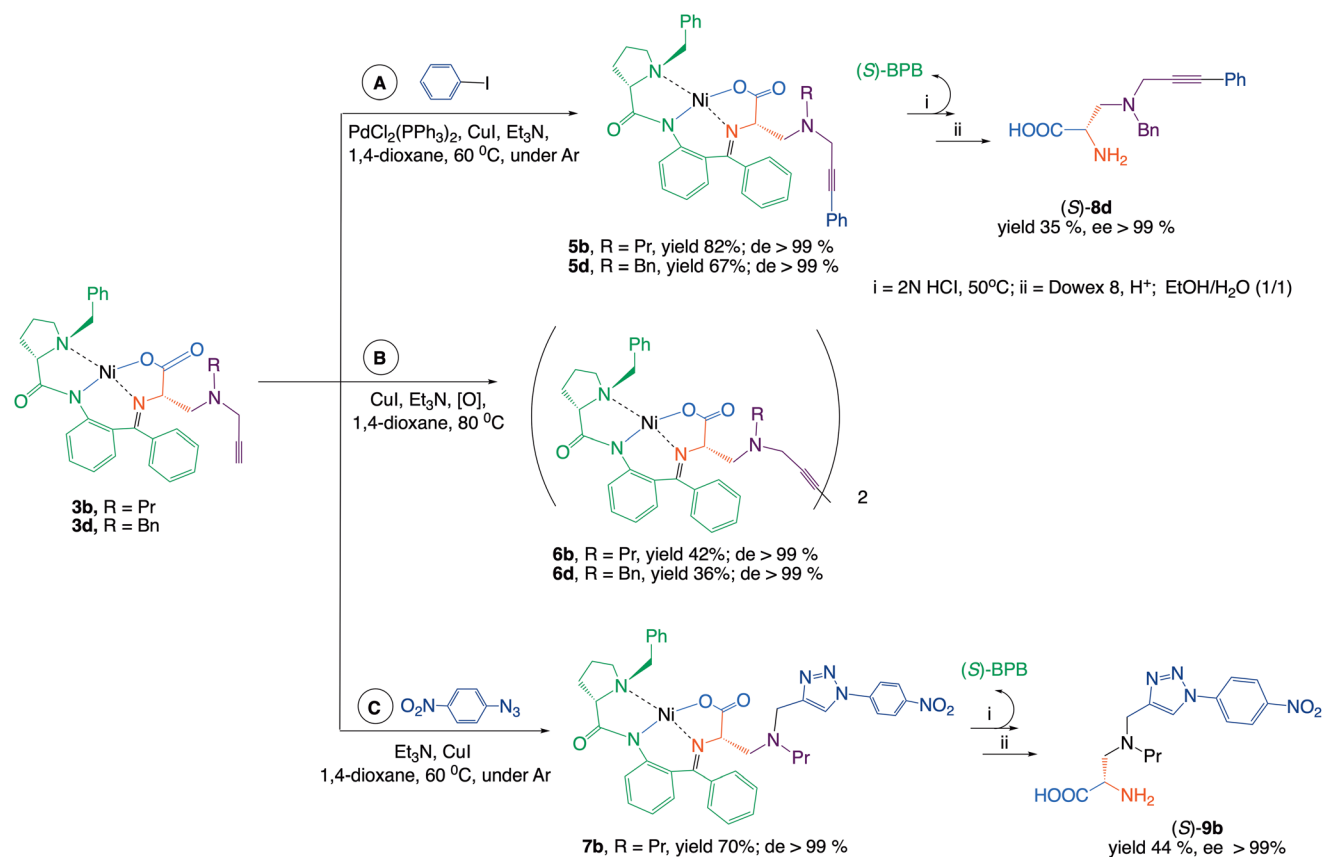
In the cross-coupling and [3 + 2]-cycloaddition reactions, the initial **3b** complex was used as pure (*S,S*)-diastereoisomer (Scheme 2). It is worth noting that the chiral  $\alpha$ -carbon of these amino acid fragments does not directly participate in the formation of new carbon–carbon bond reactions.

However, weak basis conditions of the reaction may cause partial epimerization of this stereogenic center. Therefore, the chiroptical data of the intermediate complexes and the isolated final amino acids were checked. The NMR analysis of **5b–7b** revealed that in the cross-coupling and [3 + 2]-cycloaddition reactions, the stereochemical integrity remained intact. This was additionally confirmed by the circular dichroism (CD) method (see the SI). The target amino acids were isolated from the diastereomeric mixture of complexes **5b–7b** using standard procedures.<sup>3</sup> The structure and enantiomeric purity of crystallized amino acids **8d** and **9b** were confirmed by analytical techniques.

## Biological activity and docking

Molecular docking analysis revealed that all examined (*S*)-configured  $\alpha$ -amino acid derivatives (**4a–e**) are capable of interact-





**Scheme 2** Cross-coupling and [3 + 2]-cycloaddition reactions of complexes **3b** and **3d**.

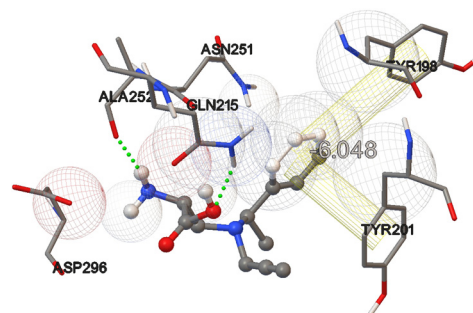
ing with bacterial collagenase, as reflected by their calculated Gibbs free energy ( $\Delta G$ ) values (Table 1). Among the tested compounds, acid **4e**, featuring a 1-phenylethyl substituent on the nitrogen atom, exhibited the strongest binding affinity with a  $\Delta G$  of  $-6.048$  kcal mol<sup>-1</sup>.

The docking results indicate that binding affinity correlates with the nature of the substituent on nitrogen. Compounds with bulkier or aromatic groups, as in **4d** and **4e**, exhibited stronger binding, likely due to enhanced van der Waals forces

or  $\pi$ - $\pi$  interactions within the enzyme's active site. In contrast, compound **4b**, featuring a linear propyl chain, showed the weakest interaction ( $\Delta G = -3.989$  kcal mol<sup>-1</sup>), suggesting that smaller or less conjugated side chains may not engage in sufficient stabilizing interactions. For compound **4e**, detailed interaction analysis (Fig. 3) showed that (*S*)-3-(*N*-(1-phenylethyl)-*N*-(prop-2-ynyl)amino)-2-aminopropanoic acid (**4e**) interacts with bacterial collagenase ( $\Delta G = -6.048$  kcal mol<sup>-1</sup>) through two hydrogen bonds and 2  $\pi$ - $\pi$  interactions. The carboxyl group forms a hydrogen bond with the free amino group

**Table 1** Binding affinity ( $\Delta G$ ) of compounds **4a–e** with collagenase predicted by molecular docking

Obtained $\alpha$ -amino acids	$\Delta G$
( <i>S</i> )-3-( <i>N</i> -Methyl- <i>N</i> -(prop-2-ynyl)amino)-2-aminopropanoic acid ( <b>4a</b> )	-4.331
( <i>S</i> )-3-( <i>N</i> -(Prop-2-ynyl)- <i>N</i> -propylamino)-2-aminopropanoic acid-4-ynoic acid ( <b>4b</b> )	-3.989
( <i>S</i> )-3-( <i>N</i> -Butyl- <i>N</i> -(prop-2-ynyl)amino)-2-aminopropanoic acid ( <b>4c</b> )	-4.324
( <i>S</i> )-3-( <i>N</i> -Benzyl- <i>N</i> -(prop-2-ynyl)amino)-2-aminopropanoic acid ( <b>4d</b> )	-4.611
( <i>S</i> )-3-( <i>N</i> -(( <i>S</i> )-1-Phenylethyl)- <i>N</i> -(prop-2-ynyl)amino)-2-aminopropanoic acid ( <b>4e</b> )	-6.048
( <i>S</i> )-2-Amino-3-(benzyl(3-phenylprop-2-yn-1-yl)amino)propanoic acid ( <b>8d</b> )	-6.821
( <i>S</i> )-2-Amino-3-(((1-(4-nitrophenyl)-1 <i>H</i> -1,2,3-triazol-4-yl)methyl)(propyl)amino)propanoic acid ( <b>9b</b> )	-6.469



**Fig. 3** Molecular docking analysis of the interaction between collagenase and (*S,S*)-3-(*N*-(1-phenylethyl)-*N*-(prop-2-ynyl)amino)-2-aminopropanoic acid (**4e**).



of Gln215 (2.121 Å) while the amino group forms an additional hydrogen bond with the carboxyl group of Ala252 (2.145 Å). Aromatic  $\pi$ - $\pi$  interactions occur with Tyr201 (4.541 Å) and Tyr198 (6.854 Å). Notably, this binding site lies within the activator domain, which is responsible for full enzymatic activity on collagen.<sup>39</sup>

## Determination of collagenase activity of compound 4e

Molecular docking analysis identified (*S*)-3-(*N*-(1-phenylethyl)-*N*-(prop-2-ynyl)amino)-2-aminopropanoic acid (**4e**) as a candidate for experimental evaluation of its effect on collagenase activity. Enzymatic assays were performed with **4e** at concentrations ranging from 0.2 to 2 mM. The compound effectively inhibited collagenase activity, consistent with the predicted strong binding affinity, with an IC<sub>50</sub> of 0.69 ± 0.014 mM, indicating moderate inhibitory potency. These findings suggest that compound **4e** may serve as a promising lead compound for the development of collagenase inhibitors.

## Experimental

### Materials

All starting reagents were obtained from commercial sources and used without further purification. The initial complexes **1** and substituted propargyl amines were prepared following literature protocols.<sup>40</sup> TLC analyses were performed on glass plates coated with silica gel 60 F<sub>254</sub>. Column chromatography was performed on silica (60 × 120 mesh) using glass columns. Melting points (mp) were determined using an Electrothermal apparatus. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Mercury-300 spectrometer (300 MHz and 75 MHz, respectively) using TMS as an internal standard (0.0 ppm). Elemental analyses were performed using a EURO EA 3000 instrument.

The enantiomeric purity of the amino acids was determined by HPLC using a Waters Alliance 2695 HPLC System equipped with chiral phase column Nautilus-E, 5 μm, 4.6 mm × 250 mm (BioChemMak ST); and a mixture of 20% MeOH and 80% 88 mM aqueous solution of KH<sub>2</sub>PO<sub>4</sub> was used as an eluent. The optical rotation was measured on a PerkinElmer Elmer-341 polarimeter. LCMS analysis was performed on Shimadzu LCMS 2020 with Prominence-I LC-2030C 3D. The CD analyses were carried out using Chirascan™ V100. The unit cells parameters of crystals were measured on an Enraf-Nonius automated diffractometer CAD-4 at room temperature using the diffraction angles of 24 reflections. Crystallographic data have been deposited at the CCDC under 2486969.

### General procedure for nucleophilic Michael addition to complex 1

1.5 g (2.85 mmol) of complex **1**, 1.97 g (14.25 mmol) of K<sub>2</sub>CO<sub>3</sub>, and 8.55 mmol of nucleophile were dissolved in 20 mL of acetonitrile. The reaction mixture was stirred at 50–60 °C. The

progress of the reaction was monitored by TLC on silica, using a 3 : 1 mixture of ethyl acetate and chloroform. Upon completion of the reaction, as confirmed by TLC monitoring (disappearance of the starting complex and appearance of the product), the reaction mixture was filtered to remove potassium carbonate and the filtrate was concentrated under reduced pressure to remove acetonitrile. The resulting residue was extracted with chloroform–water (3 × 30 mL). The extraction was continued until the aqueous phase reached a neutral pH. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness under reduced pressure. The crude products were purified by column chromatography on silica gel, eluting with a 2 : 1 mixture of acetone and chloroform, to afford complexes **3a,b** and **3d,e**. Complex **3c** was recrystallized from acetone.

### General procedure for Sonogashira reaction

Iodobenzene (2.5 mL, 12.2 mmol) and 5 mL of triethylamine were placed in a pressure tube under an argon atmosphere, followed by the addition of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.1 g, 0.15 mmol) and copper iodide (0.058 g, 0.3 mmol) under argon. Then, 1,4-dioxane (5 mL) and complexes **3b** (1.85 g, 3.05 mmol) or **3d** (2.0 g, 3.05 mmol) were added to the reaction vessel. The reaction mixture was stirred at 60 °C and was monitored by thin-layer chromatography (TLC) on silica gel using ethyl acetate/chloroform (3 : 1, v/v) as the eluent. Upon completion of the reaction, as indicated by TLC monitoring (disappearance of the starting complex and appearance of the product), the mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The organic layer was separated and washed successively with water (3 × 20 mL) and brine (20 mL). The combined organic extracts were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford the crude product. A small portion of the products was purified by column chromatography for the characterization of complexes **5b** and **5d**.

### General procedure for Glaser reaction

Complex **3b** (1.85 g, 3.05 mmol) or **3d** (2.00 g, 3.05 mmol) and copper(i) iodide (0.58 g, 3.05 mmol) were added to a mixture of 1,4-dioxane (5 mL) and triethylamine (5 mL). The reaction mixture was stirred at 80 °C, and the progress of the reaction was monitored by thin-layer chromatography (TLC) on silica gel using ethyl acetate/chloroform (3 : 1, v/v) as the eluent. Upon completion of the reaction, as indicated by TLC monitoring (disappearance of the starting complex and appearance of the product), the mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The organic layer was separated and washed successively with water (3 × 20 mL) and brine (20 mL). The combined organic extracts were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford the crude product. A small portion of the crude residue was purified by column chromatography on silica gel (ethyl acetate/chloroform, 3 : 1, v/v) to yield the analytically pure compounds **6b** and **6d** for characterization.



### General procedure for [2 + 3]-cycloaddition reaction

1-Azido-4-nitrobenzene (1.08 g, 6.5 mmol) was dissolved in 5 mL of 1,4-dioxane in a round-bottom flask under an argon atmosphere at room temperature. Copper iodide (0.062 g, 0.3 mmol) was added to the solution, and the mixture was stirred for 5 minutes. Then triethylamine (1.14 mL, 8.2 mmol) was added, and stirring was continued for 30 minutes. After that, complex **3b** (2.0 g, 3.3 mmol) was added, and the reaction mixture was stirred at 60 °C and was monitored by TLC gel using ethyl acetate/chloroform (3:1, v/v) as the eluent. Upon completion of the reaction, as indicated by TLC monitoring (disappearance of the starting complex and appearance of the product), the mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The organic layer was separated and washed successively with water (3 × 20 mL) and brine (20 mL). The combined organic extracts were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford the crude product. The filtrate was concentrated to dryness under reduced pressure, and the residue was recrystallized from acetone to yield a pure product. A small portion (0.1 g) was used for the characterization of complex **7b**.

### General procedure for isolation of amino acids

Diastereomeric mixtures of complexes **3a–e**, **5b**, **5d**, **6b**, **6d**, and **7b** (before chromatography) were suspended in CH<sub>3</sub>OH and then were added slowly to a vigorously stirred 4 M aqueous HCl at 50–60 °C.

After decomposition of the complexes (*ca.* 20 min), the target amino acids were demineralized using cation-exchange resin Dowex 50-8 (H<sup>+</sup>) and then recrystallized from an aqueous ethanol. The structure, chemical, and optical purities of the target amino acids **4a–e**, **8d**, and **9b** were established by physicochemical methods – NMR, HPLC, CD, [ $\alpha$ ]<sub>D</sub>.

### Molecular docking

The 3D structures of the compounds were built using ChemBioOffice 2010 (ChemBio3D Ultra 12.0). Minimization of the ligand free energy was performed using the MM2 force field and the truncated Newton–Raphson method. The crystallographic structure of collagenase G (PDB ID: 2Y50) was used in the analysis. Water molecules were removed, and polar hydrogens were added according to the software producer's suggested protocol for macromolecule preparation.

Docking of ligands to the enzymes was performed using AutoGrid 4 and AutoDock Vina 1.2.3 software.<sup>41</sup> Ligands were ranked based on an energy-dependent score function, and protein–ligand interactions were modelled on a grid to speed up calculations.

Interaction modes were identified; bond types and lengths were also determined.

### Determination of collagenase activity

Collagenase activity was determined by a method based on the measurement of free amino groups that are released during substrate hydrolysis.<sup>42</sup> The reaction mixture consisted of 0.05

M HEPES buffer (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) with pH 7.2, 10 mg mL<sup>-1</sup> gelatin and 0.025 mg mL<sup>-1</sup> collagenase; the reaction was carried out at 37 °C. To determine the concentration of amino groups, the *ortho*-phthalaldehyde (OPA) reagent was used, consisting of 0.2 M borate buffer with pH 9.7, 0.1667 mg mL<sup>-1</sup> OPA and 1.18 mM mercaptoethanol. Aliquots of 50  $\mu$ L were taken every 30 minutes, and the reaction was stopped by adding 10  $\mu$ L of 30% trichloroacetic acid. Then 1.5 mL of OPA reagent and 1.5 mL of water were added to the resulting sample, and the A340 value was recorded after 5 minute incubation at 27 °C.

## Conclusions

A highly selective asymmetric synthesis of a series of  $\beta$ -*N*-propargylamino substituted (*S*)- $\alpha$ -aminopropanoic acids has been developed *via* nucleophilic Michael addition of substituted propargyl amines to the C=C bond of dehydroalanine in a square-planar Ni<sup>II</sup> complex of its Schiff base with chiral auxiliary (*S*)-BPPB. This approach afforded enantiomerically enriched (*S*)- $\beta$ -(*N*-propargylamino)alanines featuring diverse alkyl side chains, all obtained with high diastereomeric excess (*de* ~90%). The terminal alkyne group of some intermediates was further functionalized through Sonogashira cross-coupling with iodobenzene, Glaser dimerization, and [3 + 2]-cycloaddition with 4-nitrophenylazide. The latter reaction yielded (*S*)- $\beta$ -(*N*-aminosubstituted)- $\alpha$ -alanine derivatives containing a 1,2,3-triazole ring linked to a *p*-nitrophenyl moiety. The final amino acids were obtained with high enantiomeric purity (*ee* > 98%).

Importantly, molecular docking and *in vitro* enzymatic assays revealed that one of the synthesized compounds, (*S*)-3-(*N*-(1-phenylethyl)-*N*-(prop-2-ynyl)amino)-2-aminopropanoic acid (**4e**), acts as a moderate inhibitor of bacterial collagenase, with an IC<sub>50</sub> value of 0.69 ± 0.014 mM. These findings highlight the potential of  $\beta$ -*N*-aminosubstituted (*S*)- $\alpha$ -alanines as versatile scaffolds for the development of biologically active molecules, particularly enzyme inhibitors.

## Author contributions

Emma A. Khachatryan (EAK) data curation, investigation, methodology, formal analysis; Lala A. Stepanyan (LAS) data curation, validation, visualization; Hasmik R. Gevorgyan (HRG) data curation, validation, writing – review & editing; Armen S. Sargsyan (ASSa) investigation, methodology, validation; Anahit M. Hovhannisyan (AMH) data curation, formal analysis, visualization; Anna F. Mkrtchyan (AFM) conceptualization, formal analysis, writing – original draft, writing – review & editing, resources, supervision, project administration; Andrei V. Malkov (AVM) formal analysis, methodology, visualization, writing – original draft, writing – review & editing; Ashot S. Saghyan (ASS) funding acquisition, methodology, project administration, supervision, writing – original draft, writing – review & editing.



## Conflicts of interest

There are no conflicts to declare.

## Data availability

Additional data related to the molecular docking studies are available from the corresponding author upon reasonable request. All experimental data supporting the findings of this study—including synthetic procedures, characterization data (NMR, HPLC, X-ray crystallography), and biological assay results—are provided in the Supplementary Information. The Supplementary Information also contains detailed experimental procedures, instrumentation details, NMR and MS spectra, HPLC analyses, X-ray crystallographic data, and molecular docking results. See DOI: <https://doi.org/10.1039/d5ob01593f>.

CCDC 2486969 (3b) contains the supplementary crystallographic data for this paper.<sup>43</sup>

## Acknowledgements

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