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Synthesis of enantiomerically enriched β -*N*-amino (*S*)- α -alanine analogs *via* sequential reactions on a chiral Ni(II) complex

Emma A. Khachatryan,^a Lala A. Stepanyan,^b Hasmik R. Gevorgyan,^{b,c} Armen S. Sargsyan,^b Anahit M. Hovhannisyan,^a Anna F. Mkrtychyan,^a Andrei V. Malkov^d and Ashot S. Saghyan^{*a,b}

A concise synthetic route to enantiomerically enriched β -*N*-substituted (*S*)- α -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 β -*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

α,β -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.^{1,2} For example, *L*-tambroline, an α,β -diamino acid incorporated into the non-ribosomal peptide tambromycin, plays a key structural role in the compound's antiproliferative properties.³ Among α,β -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.²

The presence of α,β -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.^{4,5} Likewise, the introduction of unnatural α -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.^{6–8} Among unnatural α,β -diamino acids, derivatives featuring functionally substituted aliphatic, aromatic, or heterocyclic groups in the side chain attracted particular interest. Specifically, β -*N*-substituted alanine analogs are key structural components of several clinically relevant antibiotics, including *Tuberactinomycins*, *Bleomycins*, *Edeines*, and *Capreomycins*.⁹

^aInstitute of Pharmacy, Yerevan State University, 1 Alex Manoogian Str., 0025 Yerevan, Armenia. E-mail: anna_mkrtychyan@ysu.am; Fax: +374 60 710 410; Tel: +37460 710 427

^bScientific and Production Center “Armbiotechnology” of NAS RA, 14 Gyurjyan Str., 0056 Yerevan, Armenia

^cScientific and Technological Center of Organic and Pharmaceutical Chemistry of NAS RA, 26 Azatutyan Ave., 0014 Yerevan, Armenia

^dDepartment of Chemistry, Loughborough University, University Road, Loughborough, LE11 3TU, UK

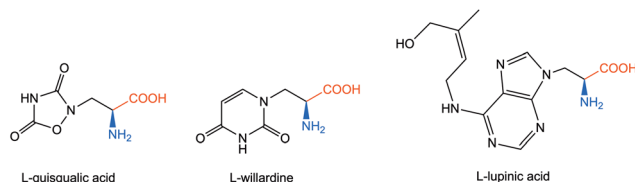


Fig. 1 Selected bioactive natural α,β -diamino acids.



Propargylamine motifs are also well-established in pharmaceutical chemistry.^{10–12} Notably, compounds such as pargyline, rasagiline, selegiline, and clorgiline containing an *N*-propargyl group, are potent inhibitors of monoamine oxidases A and B and have found direct clinical application in the treatment of neurodegenerative disorders, including Parkinson's disease¹³ and Alzheimer's disease.^{14–16} Derivatives of propargylamines are widely employed as synthetic building blocks.^{17–19} The broad utility of propargylamines stems from their unique structure, which combines a nucleophilic β -amino group with a reactive alkyne moiety, thereby enabling diverse chemical transformations. Their incorporation into peptides facilitates the formation of cyclic structures *via* click chemistry, allowing access to novel amino acids and peptidomimetics. C-Terminal propargyl amides also act as irreversible cysteine protease inhibitors through Michael-type addition, highlighting their pharmacological potential and suitability for further functionalization *via* alkyne coupling.^{20–22}

The synthetic accessibility of α,β -diamino acids has historically posed a formidable challenge, primarily due to the inherent reactivity of vicinal amino groups and the difficulty of achieving stereocontrolled functionalization. Several strategies have been developed for the stereoselective synthesis of α,β -diamino acids. Early approaches, which date back to the mid-20th century, were largely limited to multistep sequences with poor stereoselectivity and low yields, confining their use to specialized applications.^{1,2}

More recently, an efficient enzymatic Mannich-type protocol for accessing α,β -diamino acids has been reported, broadening the available biocatalytic repertoire.^{23,24} Among chemical methods, one of the most widely applied approaches is the asymmetric Mannich reaction, in which glycine Schiff bases or glycine equivalents undergo chiral-catalyst-controlled addition to imines, affording α,β -diamino acid derivatives with high *enantio*- and *diastereoselectivity*.^{25,26}

Complementary routes to α,β -diamino acids employ haloalkanoate-based methodologies, particularly the nucleophilic substitution in α,β -dibromo esters, which delivers diamino succinates, piperazines, and aziridines as synthetically versatile intermediates.²⁷ Enantioselective approaches based on alkenoates have also been developed, including osmium-mediated deamination,^{28,29} and electrophilic diamination with dichloro-sulfonamides.^{30,31} Further, Michael additions to dehydroalanine complexes^{32,33} and electrophilic amination of enolates provide highly modular routes to structurally diverse, enantiopure α,β -diamino acid frameworks.

The asymmetric synthesis of β -*N*-substituted analogues of (*S*)- α -alanine *via* nucleophilic addition of nitrogen nucleophiles to the C=C bond of the dehydroalanine moiety of the complexes was developed in our group,^{34–36} albeit with limited scope.

Our interest in alkyne-substituted amino acids and in exploring the synthetic potential of alkyne functionalities was highlighted using *O*-propargyl derivatives of β -hydroxy- α -amino acids such as serine and threonine.^{37,38} These derivatives were obtained with the aid of square-planar Ni(II) complexes of

Schiff bases derived from dehydroamino acids (dehydroalanine and dehydroaminobutyric acid) and the chiral auxiliary (*S*)-2-*N*-(*N*-benzylpropyl)aminobenzophenone (BPB).

In the present study, a similar strategy was employed to introduce a propargylamine moiety into the amino acid side chain and to enable subsequent elaboration of the alkyne functionality through various cross-coupling reactions.

Results and discussion

The square-planar Ni(II) complex of the Schiff base derived from dehydroalanine and the chiral auxiliary (*S*)-BPB (**1**) was used as a template. This complex was synthesized according to a previously established procedure.³⁴ The nucleophilic addition of amines **2a–e** to the C=C bond in **1** was carried out under basic catalysis conditions (Scheme 1).

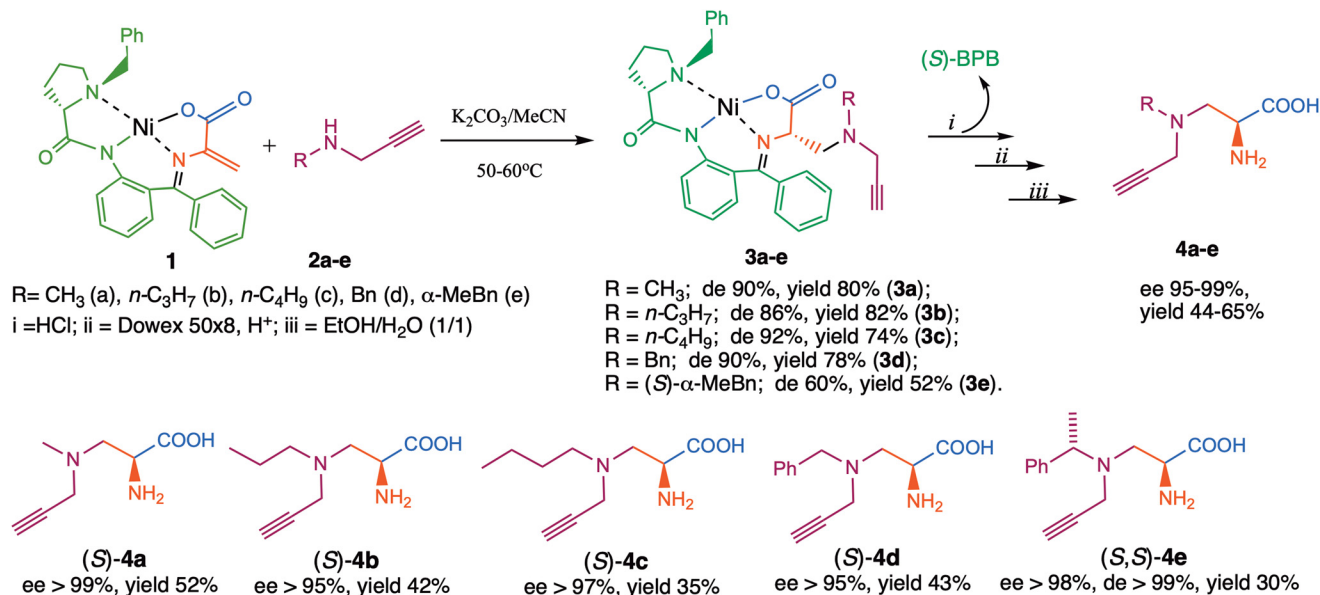
The progress of the reaction was monitored by TLC by the disappearance of initial complex **1**. The process is thermodynamically controlled, providing a high diastereomeric excess of the main (*S,S*)-diastereomer of the addition product. The structure and absolute configuration of the main diastereomeric complexes were rigorously established by physicochemical methods after chromatographic purification of the product.^{34–38} The (*S*)-absolute configuration of the α -carbon atom of the amino acid moiety was assigned using the positive sign of $[\alpha]_D$ in analogy with previously reported, similar Ni(II) complexes of other amino acids.^{34–38}

Additional verification was obtained by the circular dichroism (CD) spectra: positive Cotton effects of the main diastereomers **3a–e** in the 500–580 nm region indicated (*S*)-absolute configuration of the α -carbon atom of the amino acid moiety (see experimental part). For comparison, the CD spectra of (*S,S*)- and (*S,R*)-diastereomers of the similar alanine complexes with the absolute configuration established by X-ray crystallography are also given. In addition to the points mentioned above, we also obtained the X-ray structure of the **3b** complex, which further confirmed our previous description (Fig. 2).

The ratio of diastereomers of the addition products was determined from the ¹H NMR spectra by integrating the methylene protons signals of the *N*-benzylproline group. This was also verified by chiral HPLC analysis of the corresponding amino acids (**4a–e**), obtained by acid hydrolysis of a mixture of diastereomeric complexes followed by ion-exchange demineralization of the hydrolysate before chromatographic purification. (*S,S*)-Diastereomers of **3a–e** were formed with high diastereomeric excess (86–92%) (Scheme 1). To confirm the stereocontrolling ability of (*S*)-BPB, the corresponding complexes were prepared using (*R*)-BPB, leading to the isolation of amino acids with the expected (*R*)-absolute configuration ((*R*)-**4b** and (*R*)-**4d**). These results demonstrate that the ligand exerts identical stereocontrol in the opposite enantiomeric series.

The pure target amino acids were isolated using a standard protocol: the diastereomeric mixture of complexes **3a–e** was subjected to acid hydrolysis, followed by ion-exchange de-





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

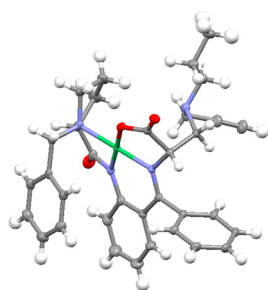


Fig. 2 X-Ray structure of complex 3b.

mineralization and crystallization from aqueous ethanol. The initial chiral auxiliary (*S*)-BPPB 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).

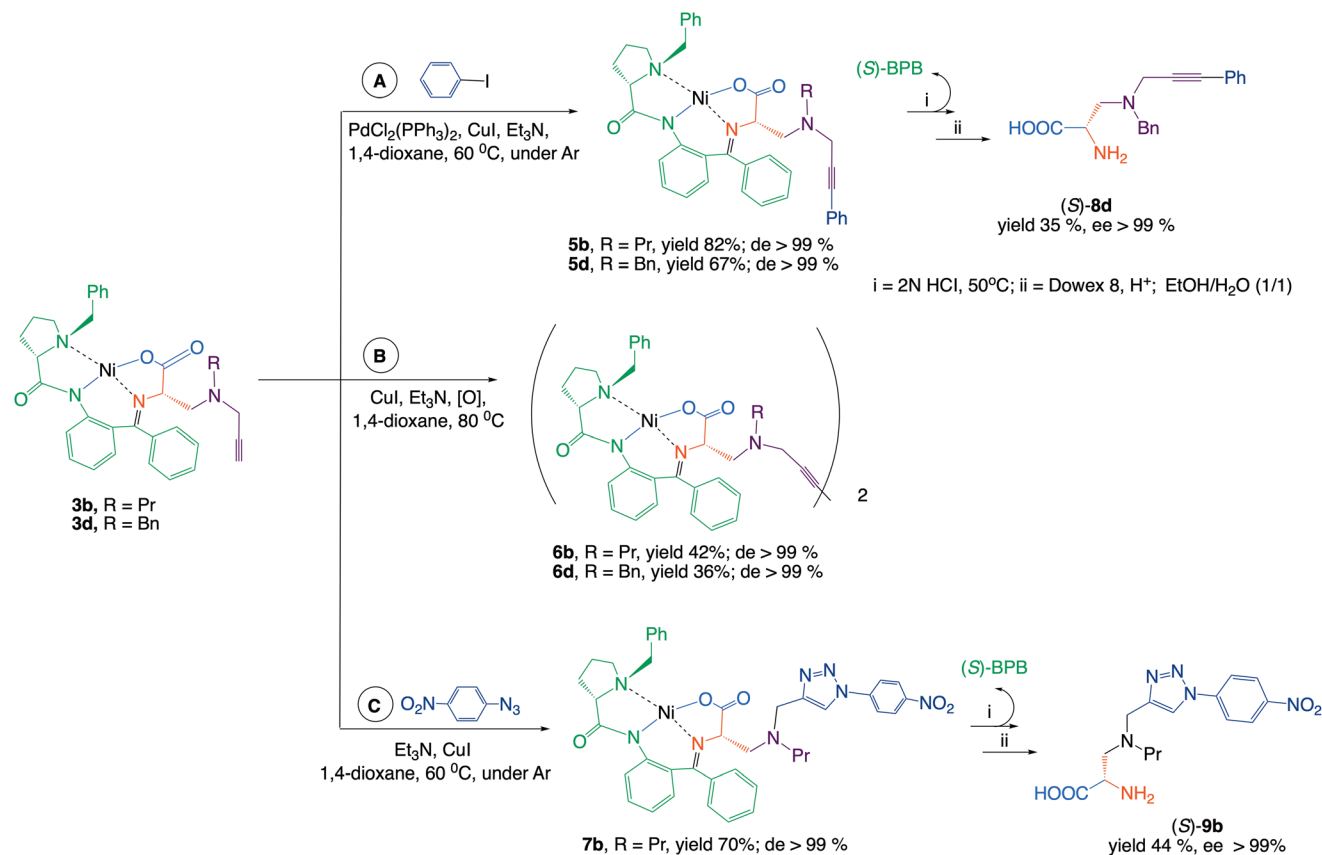
In the cross-coupling and [3 + 2]-cycloaddition reactions, the initial **3b** complex was used as pure (*S,S*)-diastereoisomer (Scheme 2). It is worth noting that the chiral α -carbon of these amino acid fragments does not directly participate in the formation of new carbon–carbon bond reactions.

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.³ 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 α -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 (ΔG) 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 ΔG of -6.048 kcal mol⁻¹.

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 π - π 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⁻¹), 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⁻¹) through two hydrogen bonds and 2 π - π interactions. The carboxyl group forms a hydrogen bond with the free amino group

Table 1 Binding affinity (ΔG) of compounds **4a–e** with collagenase predicted by molecular docking

Obtained α -amino acids	ΔG
(<i>S</i>)-3-(<i>N</i> -Methyl- <i>N</i> -(prop-2-ynyl)amino)-2-aminopropanoic acid (4a)	-4.331
(<i>S</i>)-3-(<i>N</i> -(Prop-2-ynyl)- <i>N</i> -propylamino)-2-aminopropanoic acid-4-ynoic acid (4b)	-3.989
(<i>S</i>)-3-(<i>N</i> -Butyl- <i>N</i> -(prop-2-ynyl)amino)-2-aminopropanoic acid (4c)	-4.324
(<i>S</i>)-3-(<i>N</i> -Benzyl- <i>N</i> -(prop-2-ynyl)amino)-2-aminopropanoic acid (4d)	-4.611
(<i>S</i>)-3-(<i>N</i> -((<i>S</i>)-1-Phenylethyl)- <i>N</i> -(prop-2-ynyl)amino)-2-aminopropanoic acid (4e)	-6.048
(<i>S</i>)-2-Amino-3-(benzyl(3-phenylprop-2-yn-1-yl)amino)propanoic acid (8d)	-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 (9b)	-6.469

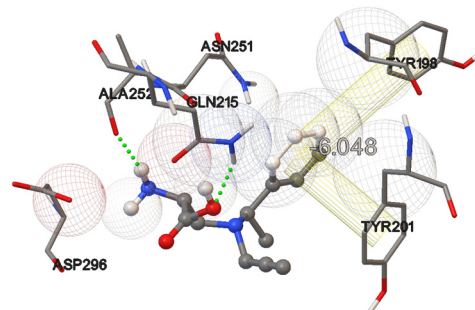


Fig. 3 Molecular docking analysis of the interaction between collagenase and (*S,S*)-3-(*N*-(1-phenylethyl)-*N*-(prop-2-ynyl)amino)-2-aminopropanoic acid (**4e**).



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 MgSO₄, 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 CH₃OH 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⁺) 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, [α]_D.

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.⁴¹ 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.⁴² The reaction mixture consisted of 0.05

M HEPES buffer (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) with pH 7.2, 10 mg mL⁻¹ gelatin and 0.025 mg mL⁻¹ 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⁻¹ OPA and 1.18 mM mercaptoethanol. Aliquots of 50 μ L were taken every 30 minutes, and the reaction was stopped by adding 10 μ 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 β -*N*-propargylamino substituted (*S*)- α -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^{II} complex of its Schiff base with chiral auxiliary (*S*)-BPPB. This approach afforded enantiomerically enriched (*S*)- β -(*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*)- β -(*N*-aminosubstituted)- α -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 IC₅₀ value of 0.69 ± 0.014 mM. These findings highlight the potential of β -*N*-aminosubstituted (*S*)- α -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. Hovhannisyanyan (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. Saghyanyan (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.⁴³

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