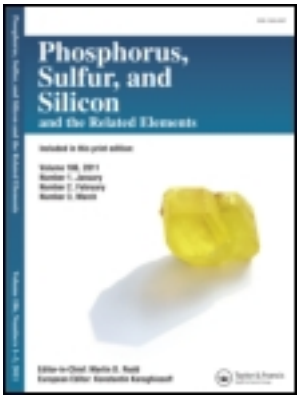

Phosphorus, Sulfur, and Silicon and the Related Elements

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Stereoselective Synthesis of β^3-Amino Acids and β-Oligopeptides Promoted by Organoselenium Intermediates

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STEREOSELECTIVE SYNTHESIS OF β^3-AMINO ACIDS AND β-OLIGOPEPTIDES PROMOTED BY ORGANOSELENIUM INTERMEDIATES

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Abstract *Propargylic amines can be valid precursors for the synthesis of β^3-amino acids. This can be effected by a selenium-mediated conversion of the carbon–carbon triple bond to a, Se-phenyl selenocarboxylate intermediate. The reactive Se-phenyl selenocarboxylate intermediates can be trapped with water, alcohols, or the amine of an amino acid derivative to give β^3-amino acids, β^3-amino esters, or mixed peptides, respectively.*

Keywords α-Amino acids; β-amino acids; propargylic amines; selenium

INTRODUCTION

The synthesis of optically active β^3-amino acids and their derivatives has received considerable interest over the past decades because these one-carbon homologues of α-amino acids are fundamental building blocks for the preparation of pharmaceutically important compounds,[1] natural products,[2] and β-peptides.[3] Pioneering works by Seebach et al. and Gellman et al. revealed that incorporating β^3-amino acids into peptide chains induces new secondary and tertiary structures and, in selected cases, leads to biological activity.[3] Furthermore, the enzymes in the body do not act on β-peptide bonds. All of these features confer to β-peptides valuable characteristics as promising candidates in pharmaceutical applications as peptidomimetics[4] as well as powerful new tools for basic research. Due to their importance, different approaches have been developed for the synthesis of β^3-amino acids in optically active form.[5] We describe here a new and mild process for the stereospecific conversion of optically active propargylic amines **1** (Scheme 1) into *N*-phthaloyl β^3-amino acids. We also report on the further use of the *Se*-phenyl selenocarboxylate intermediates **4** for a clean phase-solution synthesis of oligopeptides.

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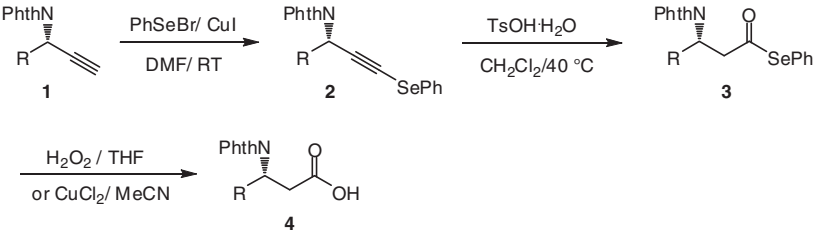
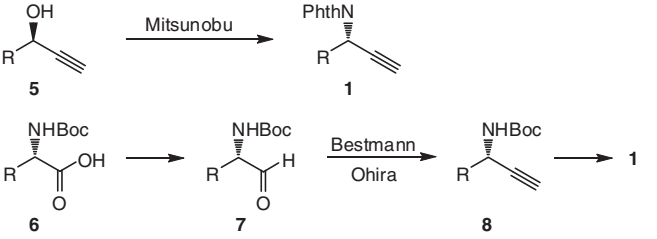


Scheme 1 Multistep synthesis of *N*-phthaloyl-β^3-amino acids **4** from *N*-phthaloyl propargylic amines **1**.

RESULTS AND DISCUSSION

The *N*-phthaloyl propargylic amines **1** were reacted (Scheme 1) with phenylselenenyl bromide in dimethylformamide (DMF) and in the presence of cuprous iodide to give the corresponding alkynyl phenyl selenides **2**, which, in the presence of toluenesulfonic acid, gave the selenol esters **3** in excellent yields as previously reported by us.[6] Finally, the simple hydrolysis of compounds **3** promoted by copper chloride (Method A) or through oxidation of the selenium atom (Method B) let us to obtain the *N*-phtaloyl β^3-amino acids **4**.

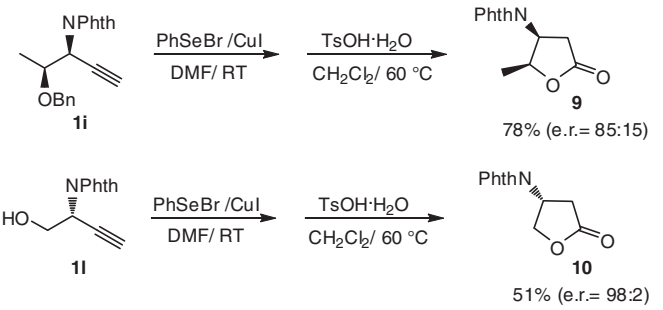
The *N*-phthaloyl propargylic amines **1** necessary for this synthesis were easily obtained from different chiral nonracemic propargylic alcohols **5** by a Mitsunobu reaction (Scheme 2) with complete inversion of configuration at the stereogenic carbon atom as confirmed by their high-performance liquid chromatography (HPLC) analysis on the chiral stationary phase.[7] Optically active *N*-phthaloyl propargylic amines **1** were also prepared by a multistep procedure from commercially available *N*-Boc α-amino acids **6** by the Bestmann-Ohira homologation of the corresponding aldehyde intermediates **7** (Scheme 2). Because of the chemical instability of the Boc-protecting group in the following reaction, compounds **8** were converted into the corresponding *N*-phthaloyl derivatives **1** in good global yields.[8]



Scheme 2 Preparation of *N*-phthaloyl propargylic amines **1**.

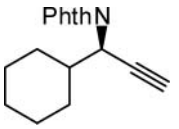
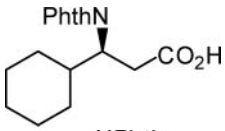
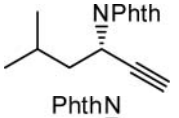
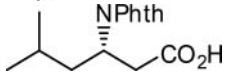
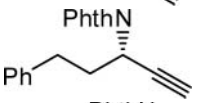
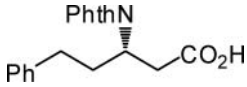
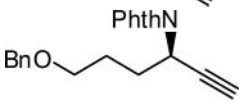
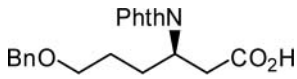
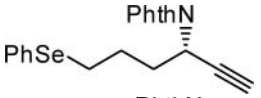
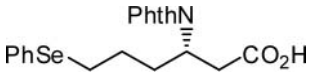
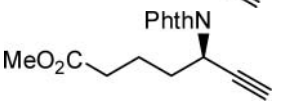
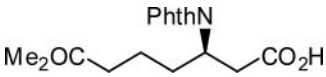
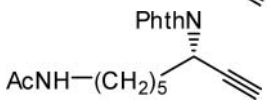
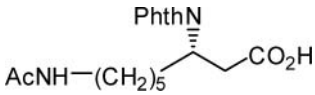
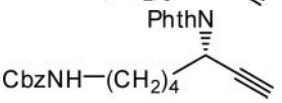
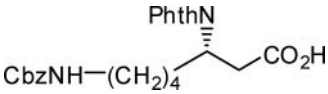
In Table 1 some of the enantioenriched *N*-phthaloyl β^3-amino acids **4** obtained in good overall yields from **1** by a multistep procedure without purification of the alkynyl phenyl selenides **2** and the selenol esters **3** intermediates are reported. Interestingly, the leaving phenylselenol group was oxidized by copper(II) to diphenyl diselenide (Method A), which was almost quantitatively recovered at the end of the reactions.

When the *N*-phthaloyl propargylic amines **1i** and **1l** were subjected to the same procedure, the reaction of the alkynyl phenyl selenide intermediates with toluenesulfonic acid gave the lactones **9** and **10** (Scheme 3) in good yields. This was in agreement with



Scheme 3 Formation of lactones **9** from **1i** and lactone **10** from **1l**.

Table 1 Multistep preparation of enantiomerically enriched *N*-phthaloyl β^3-amino acids **4** from *N*-phthaloyl propargylic amines **1**

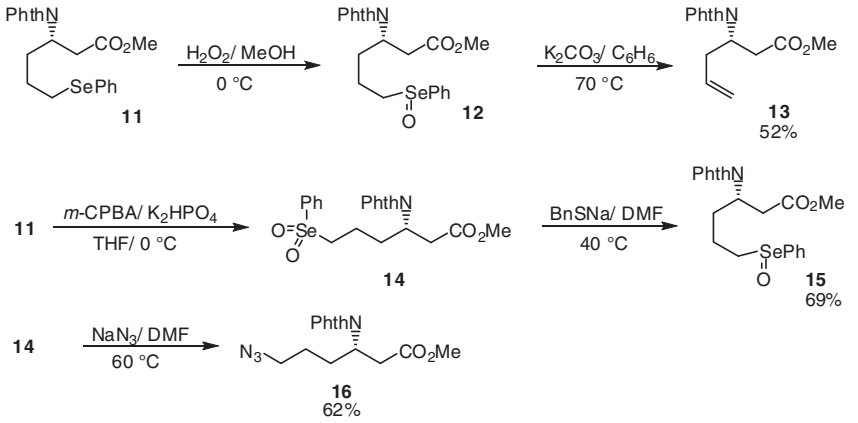
	N-Phthaloyl propargylic amines		*N*-Phthaloyl β^3-amino acids	Yield[a] (%)	e.r.[b]
1a		**4a**		62	94:6
1b		**4b**		68	99:1
1c		**4c**		76[c]	77:23
1d		**4d**		50	92:8
1e		**4e**		46	97:3
1f		**4f**		52	93:7
1g		**4g**		67c	96:4
1h		**4h**		50[c]	88:12

[a]Total yield calculated from **1**.
[b]Determined by chiral HPLC.
[c]The acid was obtained by oxidation with hydrogen peroxide.

previous results from our laboratory[9] where alkynyl phenyl selenides possessing an oxygen atom in a suitable position reacted with toluene sulfonic acid to give rise to a proton-induced ring-closure reaction affording γ-lactones.

Furthermore, the mild experimental conditions employed are compatible with different functionalities present in the substrates as alkenyl, aryl, and ether groups as well as esters, amides, benzyloxycarbonyl, and phenylseleno groups. However, HPLC analysis of the methyl ester derivatives of acids **4c** and **4h** revealed that partial racemization of the starting α-amino acids occurred during the homologation step, probably because of the configurational instability of the aldehyde intermediates **7**.[10] The *N*-phthaloyl β^3-amino acids **4** can be easily deprotected by reaction with hydrazine hydrated to give the corresponding β^3-amino acids hydrochloride as demonstrated in our previous works for the synthesis of the biologically active *D*-BAOA[11] and iturinic acid.[12]

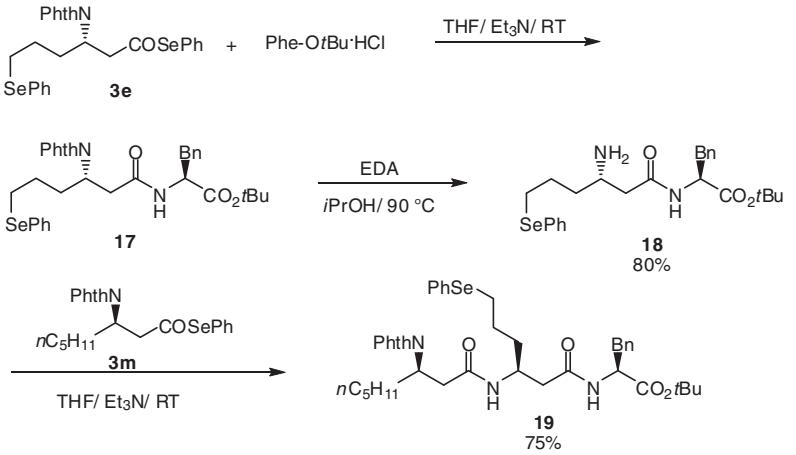
The importance of the organoselenium compounds is related to the numerous chemical manipulations in which they can be involved. Thus, the oxidation of the β-amino ester derivative **11** with hydrogen peroxide gave the corresponding selenoxide **12**, which easily eliminated a molecule of phenylselenenic acid to give the unsaturated β-amino ester **13** in 52% total yield (Scheme 4). Then, reaction of **11** with an excess of chloroperoxybenzoic acid in tetrahydrofuran and in the presence of potassium hydrogen phosphate gave the corresponding selenone **14**. The intermolecular nucleophilic substitution of the selenonyl group with thiolate or azide ions gave the functionalized β-amino ester derivatives **15** and **16**, respectively, and in good overall yields. These amino acid derivatives **13**, **15**, and **16** represent important building blocks in the synthesis of peptidomimetics due the particular reactivity of the alkenyl, thiol, and azido groups.



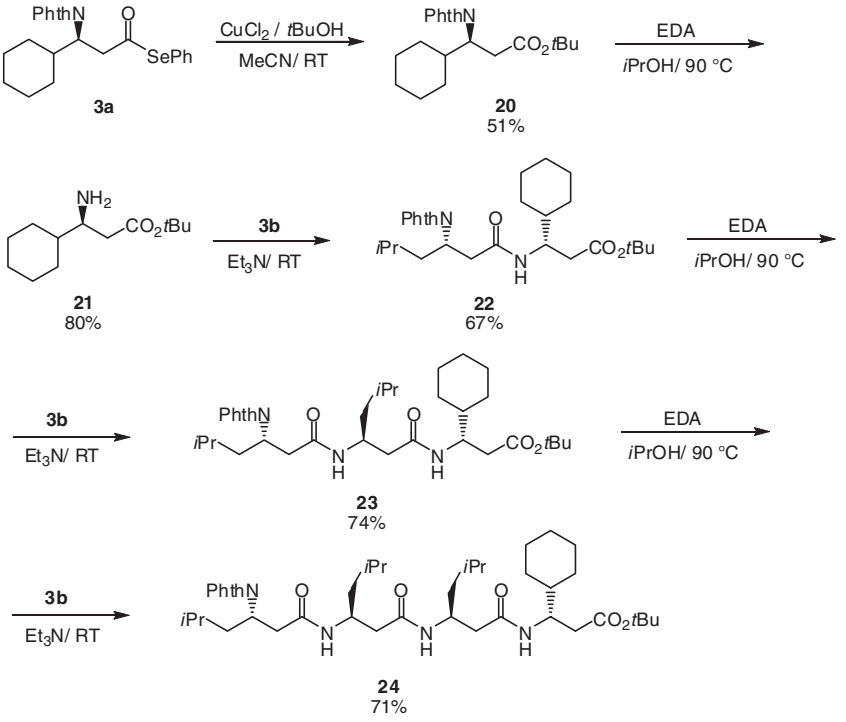
Scheme 4 Synthesis of substituted β-amino acid derivatives **13**, **15**, and **16** from selenium-containing β-amino ester **11**.

Another important aspect of the illustrated procedure is that the selenol ester intermediates **3** are selective acyl transfer agents. They are more reactive than the corresponding thio or oxo esters and they do not need a catalyst to react with the amino group. We employed these intermediates for a clean synthesis of β- or α/β-oligopeptides by simple reaction of a selenol ester with β- or α-amino acids, respectively.[7] Thus, the selenol ester intermediates **3e** were reacted with phenylalanine ester in tetrahydrofuran (THF), at room temperature, under air and in the presence of triethyl amine to give the corresponding α/β-dipeptide **17** in good global yield (Scheme 5). In addition, almost all of the phenylseleno group was recovered as diphenyl diselenide at the end of the process. Then the selective

N-terminus deprotection of dipeptide **17** by reaction with ethylene diamine in isopropanol[7] at 90°C gave the amino-free dipeptide **18** in 80% yield. This compound was employed for the solution-phase synthesis of the mixed α/β-tripeptide **19**, which was easily obtained in 75% yield by simple reaction of **18** with crude selenol ester **3m**.



Scheme 5 Multistep liquid-phase synthesis of the α/β-tripeptide **19**. EDA = Ethylenediamine.



Scheme 6 Multistep liquid-phase synthesis of the β-tetrapeptide **24**. EDA = Ethylenediamine.

It is noteworthy that these selenium-mediated oligopeptides syntheses occur without the use of coupling reagents and activating agents. Finally, the amino ester **21** easily prepared from selenol ester **3a** reacted with crude selenol ester **3b** as described above to give the β-dipeptide **22** in 67% yield (Scheme 6). The N-deprotection of this dipeptide, followed by coupling with selenol ester **3b**, gave the β-tripeptide **23** in 74% yield. The final N-deprotection of **23** gave the corresponding amino-free β-tripeptide intermediate, which after reaction with selenol ester **3b** gave the β-tetrapeptide **24** in 71% combined yield.

Due to the nature of the transformations involved, no racemization occurred during the formation of the dipeptide, tripeptide, and tetrapeptide as confirmed by their diastereoisomeric composition determined through proton nuclear magnetic resonance.[7]

CONCLUSION

In summary, the methodology proposed provides a new procedure for the stereospecific synthesis of β-amino acids from propargylic amines. Moreover, the *Se*-phenyl selenocarboxylate intermediates can be employed in the solution-phase synthesis of oligopeptides because the phtaloyl group represents a practicable β-amino acids protecting group. This methodology seems to be of general application because different functionalities are tolerated under the reaction conditions employed; thus, it favorably compares with other previously described methods for the synthesis of β-amino acids.

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