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Synthesis of an enantiopure isoxazolidine monomer for β^3-aspartic acid in chemoselective β-oligopeptide synthesis

Hiroshi Ishida, Nancy Carrillo, Jeffrey W. Bode *

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104, United States

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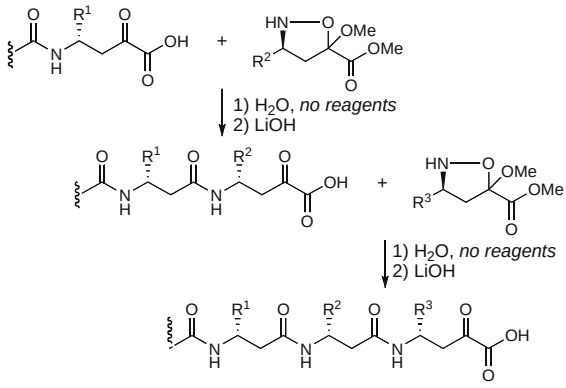
ABSTRACT

The synthesis of an enantiopure isoxazolidine monomer for the incorporation of β^3-aspartic acid residues into β^3-oligopeptides via chemoselective α-ketoacid–hydroxylamine amide formation is disclosed. This route involves nitrone cycloaddition of 3-thiophenylpropanal and circumvents limitations of other potential starting materials.

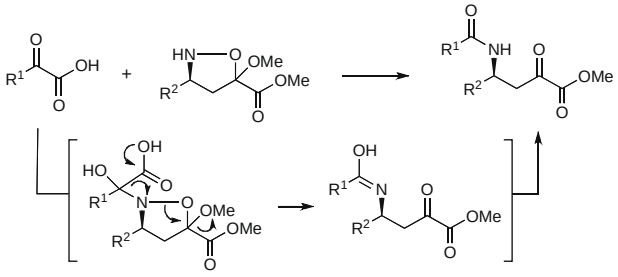
We have recently reported a highly chemoselective amide-bond forming reaction between α-ketoacids and hydroxylamines.[1] In addition to its potential for the fragment coupling of unprotected α-peptide fragments, we have explored its application to the iterative, aqueous synthesis of oligo-β^3-peptides,[2] an exciting class of peptidomimetics of contemporary interest in medicinal and bioorganic chemistry.[3]

Our novel approach to the synthesis of these oligopeptides takes advantage of the chemoselective coupling of a growing β-peptide chain with chiral isoxazolidines. The amide formation results in N–O bond cleavage and the formation of an α-ketoester. Following hydrolysis, the chain is poised for iterative elongation (Scheme 1). The key amide forming reaction requires no reagents, produces only carbon dioxide and methanol as byproducts (Scheme 2), and operates in the presence of unprotected functional groups including amines and carboxylic acids. As such, it offers great potential as an alternative route to the preparation of β-oligopeptides that circumvents challenges of the established methods including difficult couplings and deprotections in longer β-peptide chains and improved access to the requisite β-peptide monomers.

The major challenge to the widespread adoption of this method for β^3-peptide synthesis is the need to prepare the isoxazolidine monomers as single enantiomers. We have reported the use of Vasella's mannose-derived nitrones[4] as chiral auxiliaries for their asymmetric synthesis via 1,3-dipolar cycloaddition with 2-methoxymethacrylate (Scheme 3). Following purification of the cycloadducts and removal of the auxiliary, the desired isoxazolidine monomers are obtained, in most cases, in enantiomerically pure form. This approach has proven successful for the synthesis of isoxazolidine monomers bearing most of the common amino acid sidechains, including those found in leucine, valine, phenylalanine, lysine, glutamic acid, glycine, and numerous others. Unfortunately, this procedure fails for the most logical synthetic approaches to the monomer containing the side chain found in aspartic acid. This is particularly disappointing as some of the most exciting advances in the properties of longer β^3-oligopeptides are with sequences rich in this amino acid residue.[5]



Scheme 1. Synthesis of β^3-oligopeptides by iterative, aqueous synthesis via α-ketoacid–isoxazolidine couplings.



Scheme 2. Reaction pathway for chemoselective amide formation.

* Corresponding author. Tel./fax: +1 215 573 1953.
E-mail address: bode@sas.upenn.edu (J.W. Bode).

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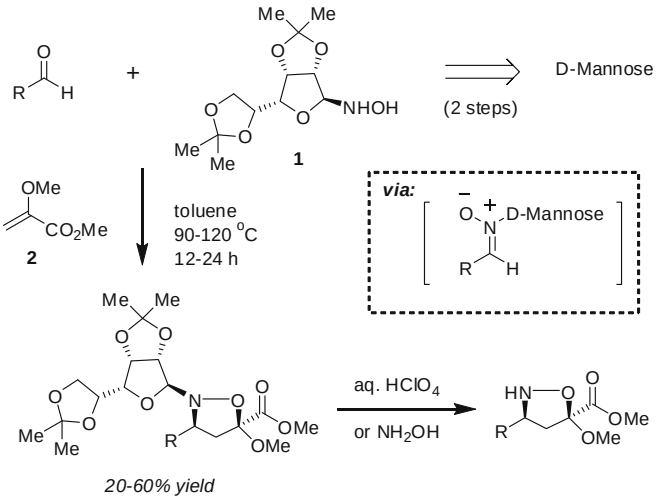
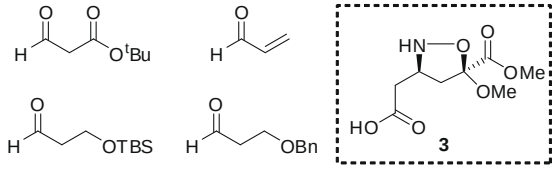


Scheme 3. General approach to the synthesis of enantiopure isoxazolidine monomers via nitrone cycloaddition.



Scheme 4. Target aspartic acid monomer **3** and aldehyde starting materials deemed unsuitable for its preparation via nitrone cycloaddition.

In this Letter, we document a versatile workaround to the synthesis of an enantiopure isoxazolidine monomer **3** containing the aspartic acid side chain. This approach is high yielding, readily executed on a preparative scale, and offers an entry into isoxazolidine monomers bearing functionality poised for further elaboration.

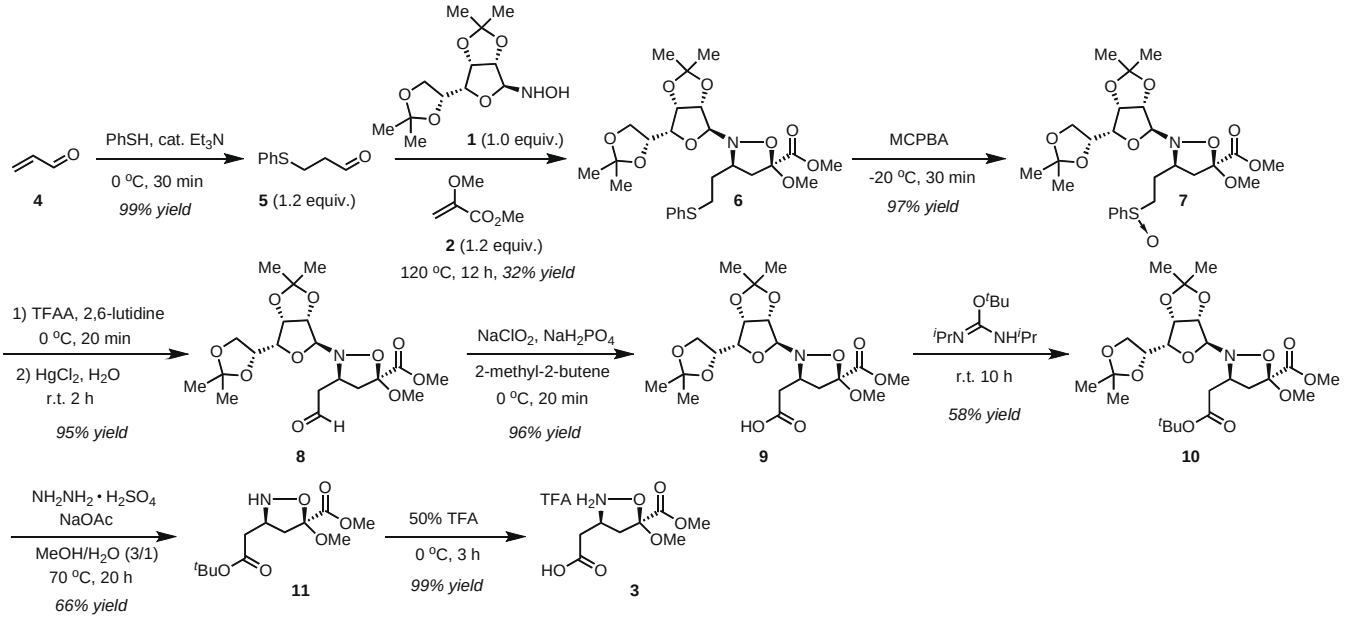
Our studies began by considering the most direct methods to access the aspartic acid-derived monomer **3**. In our previous synthesis of the glutamic acid side chain, which is a one carbon homologue of our target, we successfully employed an omega-*tert*-butylester aldehyde in the nitrone cycloaddition. In the case of aspartic acid, however, the necessary aldehyde was difficult to prepare and employ due to its propensity to adopt the enol form (Scheme 4). The obvious alternatives, protected-β-hydroxyaldehydes, could be prepared but underwent elimination or other unproductive pathways during the attempted cycloaddition step. Brief attempts to employ acrolein as a starting aldehyde were not initially successful.

In contrast to the β-oxo-substituted counterparts, we were pleased to find that β-mercaptoaldehydes were easily prepared[6] and suitable for use in the chiral auxiliary-directed cycloaddition (Scheme 5). Importantly, cycloadduct **6** could be obtained as a single enantiomer following purification by column chromatography and recrystallization. Although the overall yield for the cycloaddition and subsequent removal of the minor diastereomer were modest, the two-step sequence from acrolein could be easily executed on a preparative scale.

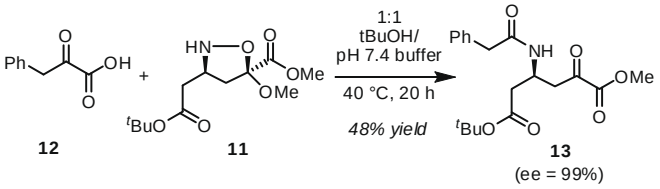
In order to convert the sulfide of **6** to the desired carboxylic acid, we effected a Pummerer oxidation by oxidation of the sulfide to the sulfoxide followed by treatment with trifluoroacetic anhydride and workup in the presence of mercury chloride to afford aldehyde **8** in 95% overall yield.[7] This aldehyde is, in itself, a valuable scaffold for the preparation of unnatural β-amino acid side chains. It can also be readily oxidized to carboxylic acid **9** under standard conditions and in excellent yield.[8]

Deprotection of the sugar can be pursued at this stage of the synthesis, but we found it advantageous in terms of handling and purity of the final product to first protect the carboxylic acid side chain. A number of standard protocols for *tert*-butyl ester formation failed, but we found success with *tert*-butyl *N,N′*-diisopropylisourea.[9] Removal of the chiral auxiliary was best effected with aqueous hydrazine to afford **11**.

Although **11** serves as a suitable monomer for β^3-oligopeptide synthesis, we have often found it advantageous to employ the side chain-unprotected monomers for our ongoing studies on the application of these reagents for aqueous peptide synthesis. The *tert*-butyl group of **11** can be easily removed by treatment with trifluoroacetic acid, providing TFA salt **3**, which can be used directly in the amide forming reaction with α-ketoacids .



Scheme 5. Syntheis of aspartic acid side chain isoxazoline monomer **3**.



Scheme 6. Amide-forming ligation of **11** and confirmation of enantiopurity. A small amount of ***ent*-11** was prepared using a different chiral auxiliary in order to analyze the enantiopurity by HPLC on chiral columns.

^{1}H and ^{13}C NMR analyses of intermediates **6** and **10** showed only a single diastereomer, suggesting that the final isoxazolidine would be obtained as a single enantiomer. To confirm and better quantify the enantiopurity, we first subjected **11** to amide formation with phenylpyruvic acid in 1:1 ^{t}BuOH/pH 7.4 buffer to afford α-ketoester **13** (Scheme 6). Analysis of this material by HPLC on a chiral column established that **11** and by analogy **10** and **3** were obtained in >99% ee.

In summary, we have disclosed an effective synthetic route to isoxazolidine monomer **3**, which allows incorporation of a β^3-aspartic acid residue into a growing peptide chain via the keto-acid–hydroxylamine amide ligation. In addition to providing access to an important monomer, this route will allow access to other important monomers including asparagine, methionine, and unnatural side chains derived from **3** or its synthetic intermediates.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.045.

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