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Organoselenium-Based Entry into Versatile, α -(2-Tributylstannyl)vinyl Amino Acids in Scalemic Form: A New Route to Vinyl Stannanes

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Described herein is a synthetically malleable class of quaternary, α -(2-trialkylstannyl)vinyl amino acid (AA) building blocks with potential applications in *de novo* peptide design and engineering. The stereocontrolled route to these AA's highlights the versatility of the phenylseleno group, acting to (i) mask a double bond, (ii) direct a low-temperature alkylation reaction, (iii) facilitate an alkene unmasking step and (iv) mediate the introduction of a stannylvinyl group through a new substitution reaction that it is expected to prove useful in other synthetic contexts.

In recent years, there has been heightened interest in α -branched AA's, in general. As the free monomers, quaternary AA's bearing β,γ -unsaturation are potential suicide inactivators for AA-processing enzymes.¹ When incorporated into peptides, quaternary AA's can be used to promote α -helical,² 3_{10} -helical³ or β -turn⁴ secondary structures. They may also be site-specifically engineered into proteins.⁵ They are useful building blocks for natural products⁶ or combinatorial libraries,⁷ and generally enhance the proteolytic stability of their derivative peptides.⁸ For all such applications, scalemic α -branched AA's are desirable.^{9,10,11} The stereodivergent route detailed below allows one to access the D- or L-enantiomer at will, and adds a dimension of synthetic flexibility inherent in the stannylvinyl α -branch.

Our approach emanates from N-benzoyl-protected L-vinylglycine¹² and involves the installation of a directing β -stereocenter in an episelenonium ion-mediated 5-exo-trig cyclization (Scheme 1). Readily separable by SiO₂ chromatography, diastereomeric oxazolines **2** and **3**,¹³ serve as precursors to enantiomeric enolates, each of which undergoes α -alkylation with essentially absolute 1,2-stereoinduction (Table 1). Thus, **2** and **3** may be regarded as synthons for L- and D-higher vinyl AA's, respectively.

Interestingly, intermolecular α -alkylation effectively competes with intramolecular expulsion of the β -amidate leaving group, presumably for stereoelectronic reasons. That the alkyl halide approaches the enolate exclusively anti to the β -(phenylseleno)methyl directing group was verified by independent synthesis of the both the anti (**4a**) and (hypothetical) syn (**7a**) BnBr-alkylation products (Scheme 2). The alkylation reactions of **2** and **3** with BnBr

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Supporting Information Available. Complete experimental procedures, spectral product characterization and chiral HPLC traces (enantiomeric purity). This material is available free of charge via the Internet at <http://pubs.acs.org>.

produce cleanly the anti-alkylation products, *L*-**4a** and *D*-**4a**, respectively. The syn alkylation product (**7a**) is absent (chiral HPLC).

Following installation of the AA side chain in a *D*- or *L*-fashion, the original β,γ -unsaturation is unmasked via base-mediated oxazoline ring-opening (Table 1). The β -phenylseleno group presumably promotes this reaction by increasing the acidity of the β -protons. The reaction is stereoselective, producing only the *E*-vinyl selenides here.

Upon heating with HSnBu_3 and AIBN in toluene, the α -(2-phenylseleno)vinyl branch is smoothly converted to an α -(2-tributylstannyl)vinyl branch (Table 2). While substitution reactions of vinyl sulfides¹⁴ and sulfones¹⁵ with trialkyltin hydrides have been described; for vinyl selenides, to our knowledge, only instances of reduction¹⁶ or reductive cyclization¹⁷ reactions have been reported heretofore. Seeing as **8a–e** are obtained exclusively as the *E*-isomers, this new substitution reaction appears to be highly stereoselective.^{18,19}

Scheme 3 illustrates the results of an initial survey of the versatility of this α -stannylvinyl branch. These quaternary AA's effectively serve as either vinyl stannane or vinyl halide Stille coupling partners,²⁰ allowing for diene installation and Diels-Alder chemistry along the α -branch. Alternatively, protodestannylation provides the free, *L*- or *D*-vinyl AA's (Table 2; includes vinyl-*m*-Tyr, a potent suicide substrate for DOPA DC)¹ with stereospecific deuterium incorporation also available, if desired. Investigations into the range/efficiency of synthetic elaboration possible with these quaternary, α -stannylvinyl AA's, and into the scope and mechanism of this new deselenative route to vinyl stannanes are underway and will be described in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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19. It is possible that this new transformation (5→8) is stereospecific, proceeding with retention of alkene configuration. However, in the absence of data for the corresponding *Z*-vinyl selenides (not available here), one cannot yet evaluate this. Indeed, the situation in an apparently related reaction is complex. Namely, McCarthy^{15a} reports that whereas the conversion of β,β -*d*-substituted- α -fluorovinyl sulfones to the corresponding α -fluorinated vinyl stannanes is stereospecific (retention), for β -*mono*substituted- α -fluorovinyl sulfones the transformation is not stereospecific. Hence, a definitive conclusion must await the results of a thorough investigation of this new transformation across a spectrum of alkene substitution patterns and geometric isomers.
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Scheme 1.

Scheme 2.

Scheme 3a.

^aKey: (i) Pd₂dba₃, p-I-C₆H₄-NO₂, THF (85%); (ii) DCl, D₂O, , then Dowex-50 (75%); (iii) I₂, CCl₄ (92%); (iv) H₂C=CHSnBu₃, Pd₂dba₃, Pfur₃, NMP (65%) (v) DMAD, then Br₂, CCl₄/KOtBu, DMF.

Table 1

Stereocontrolled Side Chain Introduction/Alkene Unmasking

starting oxazoline	alkyl halide	AA analogue	%ee ^a	alkyl. yield ^b	unmask yield ^b
2	BnBr	Phe(<i>L-4/5 a</i>)	99	90%	76%
3	BnBr	Phe(<i>D-4 a</i>)	>99	80%	---
2	CH ₃ I	Ala(<i>L-4/5 b</i>)	99	82%	77%
3	CH ₃ I	Ala(<i>D-4/5 b</i>)	>99	79%	71%
2	BnOCH ₂ Br	Ser(<i>L-4/5 c</i>)	99	80%	80%
2	EtO ₂ CCH ₂ Br	Asp(<i>L-4/5 d</i>)	99	86%	74%
2	ICH ₂ C ₆ H ₄ - <i>m</i> -OTBS	<i>m</i> -Tyr (<i>L-4/5 e</i>)	98	90%	75%
2	E-PhCH=CHCH ₂ Br	Cinn-Gly(<i>L-4 f</i>)	>99	78%	---

^a ee's are determined by chiral HPLC (Chiracel OD) vs. racemic standard for **4a-f**.^b Yields are of isolated, purified compounds.

Table 2

A New Transformation: Deselenative Stannylation

(2-seleno)-vinyl AA	R	AA analogue	Yield 8 ^a	Yield 9 ^a
<i>L</i> -5 a	Bn	Phe	84%	85%
<i>L</i> -5b	Me	L-Ala	87%	83%
<i>D</i> -5 b	Me	D-Ala	85%	90%
<i>L</i> -5 c	CH_2OBn	Ser	85%	98%
<i>L</i> -5d	$\text{CH}_2\text{CO}_2\text{Me}$	Asp	85%	82%
<i>L</i> -5e	$\text{CH}_2\text{C}_6\text{H}_4\text{-}m\text{-OTBS}$	<i>m</i> -Tyr	83%	91% ^b

^aYields are of isolated, purified compounds.^bIsolated as the HCl salt.