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

David B. Berkowitz,* Jill M. McFadden, Esmort Chisowa, and Craig L. Semerad

Department of Chemistry, University of Nebraska Lincoln, Nebraska 68588-0304

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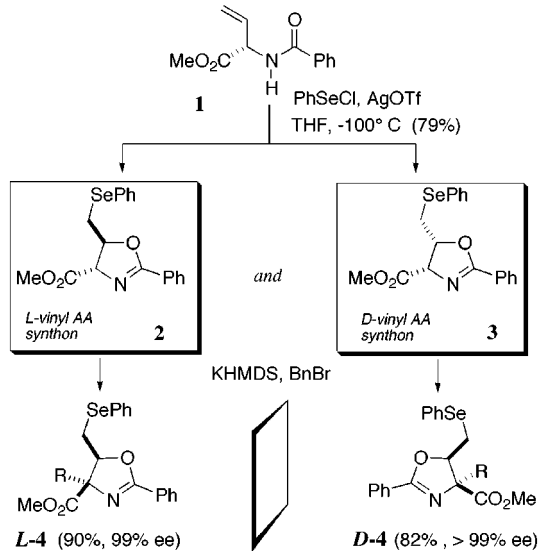
Described herein is a synthetically malleable class of quaternary, α-(2-trialkylstannyl)vinyl amino acid (AA) building blocks with potential applications in *de novo* peptide design and engineering. The stereocontrolled route to these AAs highlights the versatility of the phenylseleno group, acting to (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 is expected to prove useful in other synthetic contexts.

In recent years, there has been heightened interest in α-branched AAs, in general. As the free monomers, quaternary AAs bearing β,γ-unsaturation are potential suicide inactivators for AA-processing enzymes.[1] When incorporated into peptides, quaternary AAs can be used to promote α-helical,[2] 3_{10}-helical,[3] or β-turn[4] secondary structures. They may also be site-specifically engineered into proteins.[5] They are useful building blocks for natural products[6] or combinatorial libraries,[7] and generally enhance the proteolytic stability of their derivative peptides.[8] For all such applications, scalemic α-branched AAs are desirable.[9−11] 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.

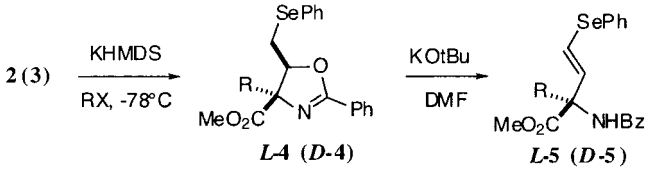
Scheme 1



Our approach emanates from *N*-benzoyl-protected L-vinylglycine[12] and involves the installation of a directing β-stereocenter in an episelenonium ion-mediated 5-exo-trig cyclization (Scheme 1). Readily separable by SiO_2 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 AAs, 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 both the anti (**4a**) and (hypothetical) syn (**7a**) BnBr-alkylation products (Scheme 2). The alkylation reactions of **2** and **3** with BnBr produce cleanly the anti alkylation products, L-**4a** and D-**4a**, respectively. The syn alkylation product (**7a**) is absent (chiral HPLC).

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(L-**4**/**5a**)	99	90	76
3	BnBr	Phe(D-**4a**)	>99	80	---
2	CH_3I	Ala(L-**4**/**5b**)	99	82	77
3	CH_3I	Ala(D-**4**/**5b**)	>99	79	71
2	$BnOCH_2Br$	Ser(L-**4**/**5c**)	99	80	80
2	EtO_2CCH_2Br	Asp(L-**4**/**5d**)	99	86	74
2	$ICH_2C_6H_4$-*m*-OTBS	m-Tyr(L-**4**/**5e**)	98	90	75
2	*E*-PhCH=$CHCH_2Br$	Cinn-Gly(L-**4f**)	>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.

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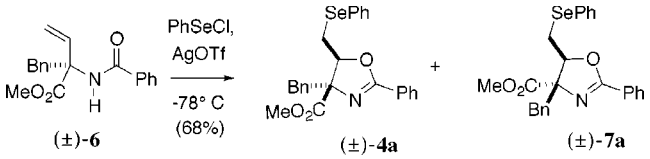
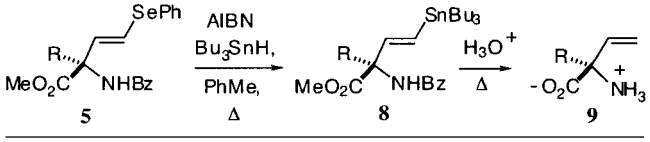
Scheme 2



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.

Table 2. A New Transformation: Deselenative Stannylation

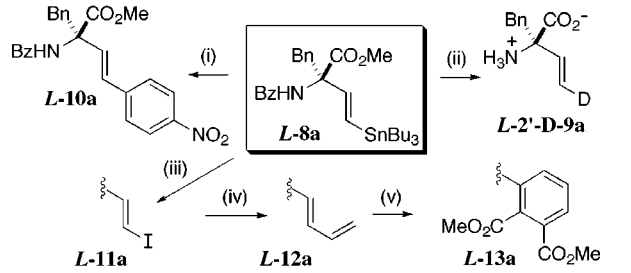


(2-seleno)-vinyl AA	R	AA analogue	yield 8[a] (%)	yield 9[a] (%)
L-**5a**	Bn	Phe	84	85
L-**5b**	Me	L-Ala	87	83
D-**5b**	Me	D-Ala	85	90
L-**5c**	CH_2OBn	Ser	85	98
L-**5d**	CH_2CO_2Me	Asp	85	82
L-**5e**	$CH_2C_6H_4$-*m*-OTBS	m-Tyr	83	91[b]

[a] Yields are of isolated, purified compounds. [b] Isolated as the HCl salt.

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 sulfides[14] and sulfones[15] with trialkyltin hydrides have been described; for vinyl selenides, to our knowledge, only instances of reduction[16] or reductive cyclization[17] 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[a]



[a] Key: (i) Pd_2dba_3, p−I−C_6H_4−NO_2, THF (85%); (ii) DCl, D_2O, Δ, then Dowex-50 (75%); (iii) I_2, CCl_4 (92%); (iv) H_2C=$CHSnBu_3$, Pd_2dba_3, $Pfur_3$, NMP (65%) (v) DMAD, Δ then Br_2, CCl_4/KOtBu, DMF.

Scheme 3 illustrates the results of an initial survey of the versatility of this α-stannylvinyl branch. These quaternary AAs 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 AAs (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 AAs, and into the scope and mechanism of this new deselenative route to vinyl stannanes are underway and will be described in due course.

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

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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-*di*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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