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

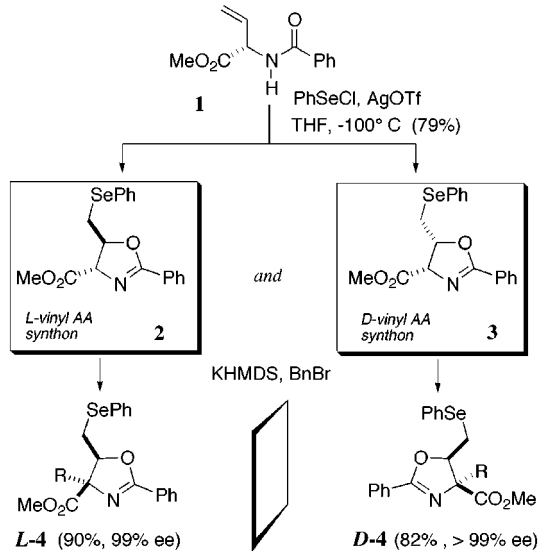
Department of Chemistry, University of Nebraska Lincoln, Nebraska 68588-0304

Received August 4, 2000

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.

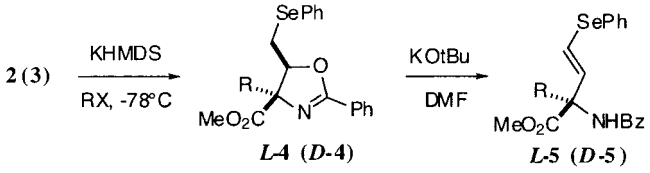
Scheme 1



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.

(1) Berkowitz, D. B.; Jahng, W.-J.; Pedersen, M. L. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2151−2156; Elegant mechanistic work: Nanavati, S. M.; Silverman, R. B. *J. Am. Chem. Soc.* **1991**, *113*, 9341−9349.

(2) (a) Schafmeister, C. E.; Po, J.; Verdine, G. L. *J. Am. Chem. Soc.* **2000**, *122*, 5891−5892. (b) Yokum, T. S.; Gauthier, T. J.; Hammer, R. P.; McLaughlin, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1167−1168. (c) Altmann, K.-H.; Altmann, E.; Mutter, M. *Helv. Chim. Acta* **1992**, *75*, 1198−1210. (d) Karle, I.; Balaram, P. *Biochemistry* **1990**, *29*, 6747−6756.

(3) (a) Jaun, B.; Tanaka, M.; Seiler, P.; Kühnle, F. N. M.; Braun, C.; Seebach, D. *Liebigs Ann./Recueil* **1997**, 1697−1710. (b) Aubry, A.; Bayeul, D.; Précigoux, G.; Pantano, M.; Formaggio, F.; Crisma, M.; Toniolo, C.; Boesten, W. H. J.; Schoemaker, H. E.; Kamphuis, J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 525−529.

(4) (a) Obrecht, D.; Altorfer, M.; Lehmann, C.; Schonholzer, Muller, K. *J. Org. Chem.* **1996**, *61*, 4080−4086. (b) Wipf, P.; Hemgartner, H. *Helv. Chim. Acta* **1988**, *71*, 258−267.

(5) (a) Mendel, D.; Ellman, J.; Schultz, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 4359−4360. (b) See also: van Hest, J. C. M.; Kiick, K. L.; Tirrell, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 1282−1288.

(6) (a) Murray, W. V.; Sun, S.; Turchi, I. J.; Brown, F. K.; Gauthier, A. D. *J. Org. Chem.* **1999**, *64*, 5930−5940. (b) Campbell, A. D.; Raynam, T. M.; Taylor, R. J. K. *Tetrahedron Lett.* **1999**, *40*, 5263−5266. (c) Trost, B. M.; Lemoine, R. C. *ibid.* **1996**, *37*, 9161−9164. (d) Huwe, C. M.; Blechert, S. *Ibid.* **1995**, *36*, 1621−1624. (e) Krol, W. J.; Mao, S.; Steele, D. L.; Townsend, C. A. *J. Org. Chem.* **1991**, *56*, 728−731. (f) Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515−4523.

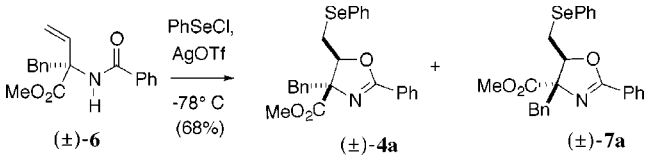
(7) (a) Fornicola, R. S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528−3529. (b) Scott, W. L.; Zhou, C.; Fang, Z.; O'Donnell, M. J. *Tetrahedron Lett.* **1997**, *38*, 3695−3698. (c) O'Donnell, M. J.; Zhou, C.; Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070−6071. (d) Wenschuh, H.; Beyermann, M.; Krause, E.; Brudel, M.; Winter, R.; Schümann, M., Carpino, L. A.; Bienert, M. *J. Org. Chem.* **1994**, *59*, 3275−3280.

(8) (a) Sall, D. J.; Shuman, R. T.; Smith, G. F.; Wiley: M. R. U.S. Patent No. 5,484,772, July 16, 1996; (b) Frauer, A.; Mehlführer, M.; Thirring, K.; Berner, H.; *J. Org. Chem.* **1994**, *59*, 4215−4222. (c) Veber, D. F.; Freidinger, R. M. *Trends Neurosci.* **1985**, *8*, 392−396. (d) Khosla, A.; Stachowiak, K.; Smeby, R. R.; Bumpus, F. M.; Piriou, F.; Lintner, K.; Fermandjian, S. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 757−760.

(9) Reviews: (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599. (b) Davis. F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13−18. (c) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225−227. (d) Goodman, M.; Zhang, J. *Chemtracts: Org. Chem.* **1997**, 10, 629−645. (e) Seebach, D.; Sting, A. R.; Hoffman, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2748. (f) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383−389. (g) Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon Press: Oxford, 1989.

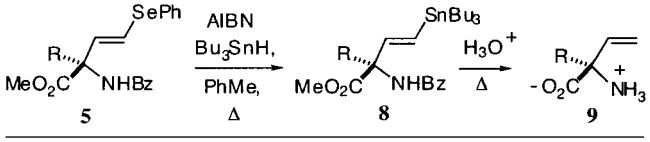
10.1021/ja0055110 CCC: $19.00
Published on Web 10/21/2000

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

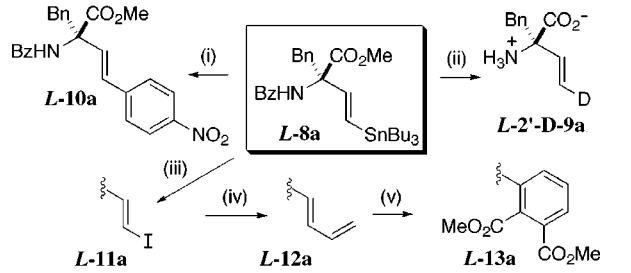


(2-seleno)-vinyl AA	R	AA analogue	yield 8[a] (%)	yield 9[a] (%)
L-**5a**	Bn	Phe	84	85
L-**5b**	Me	L-Ala	87	83
D-**5b**	Me	D-Ala	85	90
L-**5c**	CH_2OBn	Ser	85	98
L-**5d**	CH_2CO_2Me	Asp	85	82
L-**5e**	$CH_2C_6H_4$-*m*-OTBS	m-Tyr	83	91[b]

[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.

Acknowledgment. Financial support from the National Institutes of Health (CA 62034) is gratefully acknowledged. D.B.B. is an Alfred P. Sloan Fellow (1997−2001). C.L.S. was a participant in the UNL Summer Undergraduate Research Program. We thank R. K. Shoemaker and R. L. Cerny for 2D NMR and MS support, respectively. This research was facilitated by grants for NMR and GC/MS instrumentation from the NIH (SIG 1-S10-RR06301) and the NSF (CHE-93000831), respectively.

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.

JA0055110

(10) Recent advances: (a) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228−5229. (b) Davis, F. A.; Zhou, P.; Fang, T.; Reddy, G. V.; Zhang, Y. *J. Org. Chem.* **1999**, *64*, 7559−7567. (c) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727-10737. (d) Wenglowsky, S.; Hegedus, L. S. *J. Am. Chem. Soc*. **1998**, *120*, 12468-12473. (e) Seebach, D.; Hoffmann, M. *Eur. J. Org. Chem.* **1998**, *1337*, 7−1351. (f) Meyer, L.; Poirier, J. M.; Duhamel, P. Duhamel, L. *J. Org. Chem.* **1998**, *63*, 8094−8095. (g) Charette, A. B.; Mellon, C. *Tetrahedron*, **1998**, *54*, 10525-10535. (h) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445−446.

(11) For enantiocontrolled syntheses of higher (R ≠ H) α-vinyl AAs, see: (a) Berkowitz, D. B.; McFadden, J. M.; Sloss, M. K. *J. Org. Chem.* **2000**, *65*, 2907−2918. (b) Frutos, R. P.; Spero, D. M. *Tetrahedron Lett.* **1998**, *39*, 2475−2478. (c) Colson, P.-J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918−5924. (d) Seebach, D.; Bürger, H. M.; Schickli, C. P. *Liebigs Ann. Chim.* **1991**, 669−684. (e) Weber, T.; Aeschimann, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1365−1377.

(12) Berkowitz, D. B.; Smith, M. K. *Synthesis* **1996**, 39−41 and references therein.

(13) Oxazolines **2** and **3** (1:1-1.3:1) are obtained with an ee that reflects the enantiomeric purity of the starting vinylglycine derivative, provided that this cyclization is performed at low temperature. We note that even in cases where this is 96% ee, say, either **2** or **3** may be obtained in >99%ee with a single recrystallization from hexane.

(14) (a) Hollingsworth, G. J.; Perkins, G.; Sweeney, J. *J. Chem. Soc., Perkin Trans. I* **1996**, 1913−1919. (b) Williams, J. P. Ph.D. Thesis, University of Michigan, 1991. (c) White, J. D.; Pallenberg, A. J. *Tetrahedron Lett*. **1986**, *27*, 5591−5594. (d) Tanaka, H.; Hayakawa, H.; Obi, Kikoh; Miyasaka, T. *Tetrahedron* **1986**, *42*, 4187−4195. (e) Schmidt, R. R.; Betz, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 430−431.

(15) (a) McCarthy, J. R.; Huber, E. W.; Le, T.-H.; Laskovics; F. M.; Matthews, D. P. *Tetrahedron* **1996**, *52*, 45−58. (b)Wnuk, S. F.; Robins, M. J. *Can. J. Chem.* **1993**, *71*, 192−198. (c) McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439−7440. (d) Dubois, E.; Beau, J.-M. *Tetrahedron Lett.* **1990**; *31*, 5165−5168. (e) Watanabe, Y.; Ueno. Y.; Araki, T.; Endo, T.; Okawara, M. *Tetrahedron Lett.* **1986**, *27*, 215−218.

(16) (a) Saluzzo, C.; Alvernhe, G.; Anker, D.; Haufe, G. *Tetrahedron Lett.* **1990**, *31*, 2127−2130. (b) Denis, J. N.; Krief, A. *Tetrahedron Lett.* **1982**, *23*, 3411−3414.

(17) Batty, D.; Crich, D. *J. Chem. Soc., Perkin Trans. I* **1991**, 2894−2895.

(18) We note that one must always be concerned about the possible isomerization of vinyl stannanes in the presence of $HSnBu_3$ and Δ: (a) Leusink, A. J.; Budding, H. A. *J. Organomet. Chem.* **1968**, *11*, 541−547. However, in no cases were the *Z*-isomers of vinyl stannanes **8a**−**e** observed here, even where reactions of vinyl selenides **5** were stopped prior to complete conversion and analyzed by ^1H NMR.

(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.

(20) For Stille couplings with α-unbranched AAs, see: (a) Reginato, G.; Mordini, A.; Caracciolo, M. *J. Org. Chem.* **1997**, *62*, 6187−6192. (b) Crisp, G. T.; Gebauer, M. G. *Tetrahedron Lett.* **1995**, *36*, 3389−3392.