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Diastereoselective Allylstannane Additions to (*S*)-5,6-Dihydro-2*H*-5-phenyloxazin-2-one. A Concise Synthesis of (*S*)-*β*-Methylisoleucine

Julie A. Pigza[§,‡] and Tadeusz F. Molinski*[,§,†]

Department of Chemistry and Biochemistry, and Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, 9500 Gilman Drive MC0358, La Jolla, California 92093

tmolinski@ucsd.edu

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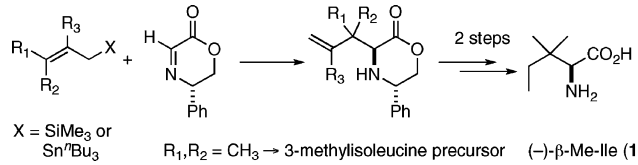
ABSTRACT



The addition of allyl stannanes to (*S*)-4,5-dihydro-5-phenyl-2*H*-oxazinone (3) was achieved under Brønsted acid catalysis to give 2-allylmorpholinones with high diastereoselectivity (up to dr 14.2:1). The product of dimethylallyltributylstannane addition to 3 was converted to L-*β*-methylisoleucine, an α-amino acid residue found in the complex, biologically active marine-derived peptides polytheonamides A and B, and polydiscamides A−C.

Marine peptides often contain highly modified amino acids, including chlorinated amino acids,[1] *β*-amino acids,[2] and highly substituted *β*,*β*-dimethyl-α-amino acids.[3] L-*tert*-Leucine (**1a**) and L-*tert*-amylglycine (*β*-methylisoleucine, **1b**) occur in the 48-mers polytheonamides A and B (two highly cytotoxic *β*-helix, membrane-pore forming peptides from the marine sponge, *Theonella swinhoei*).[4] The peptides polydiscamide A from *Discodermia*[5a] (**2**, Figure 1) and the polydiscamides B−C from the sponge *Ircinia*,[5b] which are the first nonendogenous inhibitors of sensory neuron-specific G-protein coupled receptors (SNSRs), also contain **1a** and **1b**.[6] The amino acid *γ*-hydroxy-*tert*-leucine (L-pantonine, **1c**) was proposed as an intermediate in the biosynthesis of pantoic acid.[7] With an eye to the synthesis of highly biologically active, cyclic peptides, we sought to fulfill a need for a general synthesis of highly *β*-branched α-amino acids.

[§] Department of Chemistry and Biochemistry.
[†] Skaggs School of Pharmacy and Pharmaceutical Sciences.
[‡] Present address: Queensborough Community College 222-05 56th Avenue, Bayside, NY 11364.

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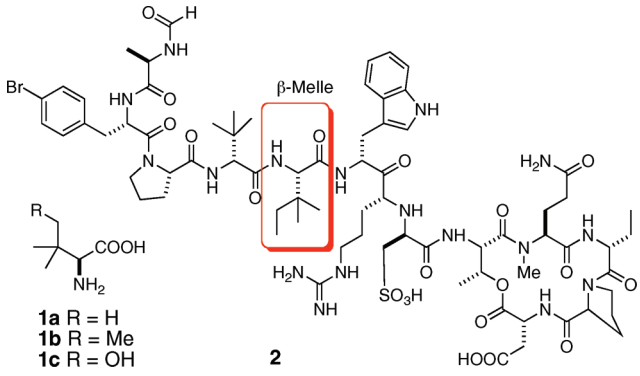

Figure 1. Structures of L-*tert*-leucine (**1a**), L-*β*-methylisoleucine (*tert*-amylglycine, **1b**), pantonine (**1c**), and polydiscamide A (**2**), a marine-derived peptide containing *β*,*β*-dimethyl-substituted α-amino acids.

Racemic syntheses of *tert*-alkyl-α-amino acids have been reported.[8] Asymmetric preparation of L-**1a** and L-**1b** was achieved by tandem-enzyme coupled reductive amination of the corresponding α-ketoacids.[9] However, this biotechnology is not amenable to preparation of the D-antipode due to the enantiospecificity of the enzymes. In this report, we demonstrate a concise *asymmetric* synthesis of L-**1b** that exploits an efficient allylstannane addition to highly electrophilic 2*H*-oxazinone, **3**, a chiral glycine equivalent, and is amenable to preparation of D-**1** or other highly branched amino acids.

SeO_2-promoted oxidative rearrangement of 2-substituted oxazolines **ii** (Figure 2) to 5,6-dihydro-2*H*-1,4-oxazin-2-ones

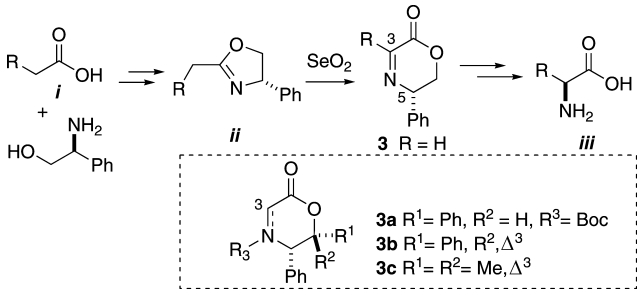

Figure 2. Oxazoline−oxazinone oxidative rearrangement.

(e.g., **3**, hereafter, referred to as 'oxazinones'),[10] followed by hydrogenation-hydrogenolysis,[11] allows convenient access to a wide variety of α-amino acids, **iii**.[12] Thus, the conversion of carboxylic acid **i** to **iii** constitutes a highly useful transformation: formal preparation of amino acids by oxidative insertion of NH_2 to the α-carbon of a carboxylic acid of either configuration by choice of an appropriate chiral auxiliary,[13] *R*- or *S*-phenylglycinol, obtained readily from the corresponding commercially available phenylglycines.

The highly electrophilic 3-*unsubstituted* oxazinone **3**[14] is particularly attractive as a chiral glycine equivalent that can add a variety of carbon-centered nucleophiles at the C=N bond to give morpholinone amino acid precursors; however, the diastereoselectivity and yield of these additions can be variable. For example, addition of MeMgBr or *t*-BuMgBr to **3** in the presence of BF_3•Et_2O gave one detectable diastereomer in poor yield (34% and 33%, respectively).[15] We now describe the synthesis of 3-allylmorpholinones by highly diastereoselective allyl stannane additions to **3** promoted by Brønsted acid to give **4**, and subsequent conversion to *β*-methylisoleucine (**1b**).

Oxazoline (**ii**, R = H, Figure 2) was prepared in two steps from *S*-phenylglycinol[16,17] in 80% yield.[10,18] The original procedure for SeO_2-promoted rearrangement of the oxazoline to (*S*)-oxazinone **3**[10] required refluxing 1,4-dioxane for 2 h. Instead, short exposure of the substrate (∼1 mmol scale) to SeO_2 in a microwave reactor (10 min, 300 W, 110 °C), adapted from Snider's procedure for SeO_2-promoted allylic oxidations,[19] improved the yield of **3** (74%) and reduced byproducts.

As reported earlier,[20] BF_3•Et_2O-promoted additions of allyltrimethylsilane, methallyltrimethylsilane, and dimethylallyltrimethylsilane to (*S*)-**3** (entries 1−3, Table 1) gave only modest diastereoselectivity and/or low yields of **4**. The diastereoselectivity of BF_3•Et_2O-promoted allyltrimethylsilane addition to **3** was 8:1 to give **4a** (entry 1, 73% yield), but with the more hindered nucleophiles, dimethylallyltrimethylsilane and methallyltrimethylsilane, the diastereoselectivity diminished to 5:1 (entry 2, 25% yield) and 2:1 (entry 3, 60%), respectively.[21] Addition of allyltributylstannane in the pres-

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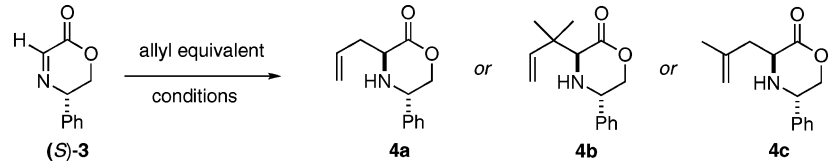
Table 1. Acid-Promoted Allylsilane and Allylstannane Additions to Oxazinone (*S*)-**3**



(*S*)-**3** **4a** **4b** **4c**

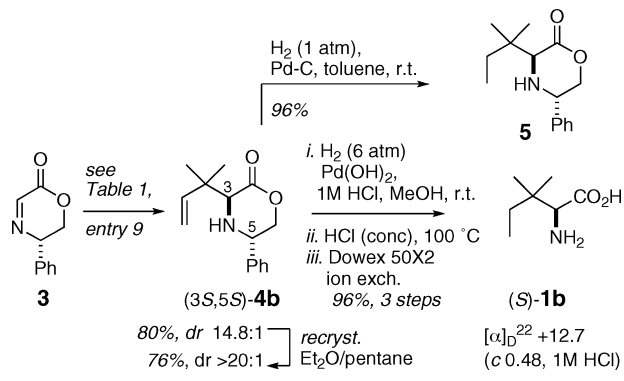
entry	allyl equivalent	product	Brønsted or Lewis acid	solvent	temp, time	yield (%)[a]	*dr*[b]	ref.
1	$SiMe_3$	**4a**	$BF_3{\bullet}Et_2O$	CH_2Cl_2	−78 °C, 0.5 h	73[c]	8:1	20
2	$SiMe_3$	**4b**	$BF_3{\bullet}Et_2O$	CH_2Cl_2	−78 °C, 0.5 h	25[c,d,e]	5:1	20
3	$SiMe_3$	**4c**	$BF_3{\bullet}Et_2O$	CH_2Cl_2	−78 °C, 1 h	60[c]	2:1	20
4	$SiMe_3$	**4c**	TFA	CH_2Cl_2	−78 °C, 1 h	54[c]	2.6:1	*g*
5	Sn^nBu_3	**4a**	$BF_3{\bullet}Et_2O$	CH_2Cl_2	−78 °C, 1 h	35[c,e]	3.2:1	*g*
6	Sn^nBu_3	**4a**	TFA	CH_2Cl_2	−78 °C, 1 h	60[c]	5:1	*g*
7	Sn^nBu_3	**4b**	$BF_3{\bullet}Et_2O$	CH_2Cl_2	−78 °C, 0.5 h	64(75)[f]	7.1:1	*g*
8	Sn^nBu_3	**4b**	TFA	CH_2Cl_2	−20 °C, 1 h	68[f]	6.2:1	*g*
9	Sn^nBu_3	**4b**	TFA	CH_2Cl_2	−78 °C, 1 h	**80**[f]	**14.8:1**	*g*
10	Sn^nBu_3	**4b**	TFA	CH_3CN	−30 °C, 2 h	62[f]	12.5:1	*g*
11	Sn^nBu_3	**4c**	TFA	CH_2Cl_2	−78 °C, 1 h	37[c,e]	1.4:1	*g*

[a] Isolated yield after SiO_2 column chromatography (yields in parentheses are based on recovered starting material). [b] dr, from ^1H NMR integration. [c] Diastereomers not separated. [d] Unoptimized. [e] In addition to an unidentified byproduct (see refs 20 and 22). [f] Major diastereomer separated by crystallization. [g] Reference = this work.

ence of either $BF_3{\bullet}Et_2O$ or TFA also gave **4a** with low diastereoselectivities (dr 3.2:1 and 5:1, respectively, entries 5 and 6),[22] as did use of methallyltributylstannane[23] to give **4c** (37%, dr 1.4:1, entry 11). Gratifyingly, addition of dimethylallyltributylstannane to **3** *in the presence of TFA* (−78 °C, CH_2Cl_2, 1 h, entry 9) gave a *dramatic increase* in both the yield and diastereoselectivity for **4b** (dr 14.8:1, 80% yield). The major diastereomer (3*S*,5*S*)-**4b** was purified from the diastereomeric mixture by selective recrystallization from Et_2O/pentane (dr >20:1 Scheme 1).[24] A similar outcome was observed when the addition was carried out in acetonitrile at −30 °C (dr 12.5:1, 62% yield, entry 10), but diastereoselectivity eroded when the reaction was conducted with TFA in CH_2Cl_2 at higher temperatures (−20 °C, dr 6.2:1, 68% yield, entry 8) or when using $BF_3{\bullet}Et_2O$ instead of TFA (−78 °C, dr 7.1:1, 64%, entry 7).

The surprising difference in the outcome of additions of the two dimethylallyltrialkylsilane (entry 2) and stannanes (entries 9 and 10) to oxazinone **3** deserves some comment. The role of the Brønsted or Lewis acid is activation of the imine to an iminium ion (Figure 3). For electronic reasons,

Scheme 1. Conversion of Morpholinone (3*S*,5*S*)-**4b** to L-β-Methylisoleucine **1b**



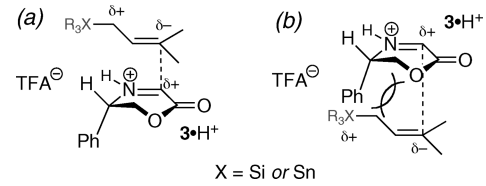


Figure 3. Possible transition states for the reaction of **3**•H^+ with dimethylallylsilane or dimethylallylstannane.

both dimethylallyltrialkylsilane and the corresponding stannane add at their more substituted sp^2 olefinic carbon. Consequently, the higher diastereoselectivity in the formation of (3*S*,5*S*)-**4b** from the stannane in the presence of TFA may be due to relaxed steric congestion with the ion pair

3·H^+ TFA^- compared to the corresponding bulkier **3**·BF_3 complex. Under these conditions, tighter association of the vinyl bond to the C=N bond is allowed, serving to amplify differences in energies between top and bottom facial additions (Figure 3, parts a and b, respectively) in the respective transition states and favoring approach of the nucleophilic allyl equivalent from the side opposite the Ph group.

The synthesis of (−)-*β*-methylisoleucine (**1b**) was accomplished by conversion of the dimethylallylated morpholinone (3*S*,5*S*)-**4b** as follows (Scheme 1). Hydrogenation of (3*S*,5*S*)-**4b** under acidic conditions (6 atm, $Pd(OH)_2$, MeOH, 1 M HCl) followed by exhaustive acid hydrolysis (refluxing HCl) provided the optically pure amino acid salt (L-**1b**·HCl, Scheme 1), which was converted to the free amino acid by ion-exchange chromatography (elution with 2 M NH_4OH) to neutral L-**1b** (96% yield, two steps). The optical rotation of L-**1b** $([\alpha]^{22}_D$ +12.7 (*c* 0.48, 1 M HCl), lit.[9] +9.9 (*c* 1 M, 1 M HCl)) and ^1H and ^{13}C NMR data[6,25] matched the literature values. Thus, L-**1b** was obtained in three steps from the chiral glycine equivalent (*S*)-**3** in an overall yield of 58%.

Additions of dimethylallyl anion equivalent to **3** should find wider applicability in the synthesis of other *β*,*β*-dimethyl-substituted amino acids. The versatile vinyl "handle" in intermediate (3*S*,5*S*)-**4b** may find uses for the preparation of amino acid derivatives related to **1b**. For example, selective hydrogenation of the terminal vinyl group of (3*S*,5*S*)-**4b** (Scheme 1, H_2, Pd−C, 96%) to give **5** models a potential route to the preparation of specifically labeled [^{2}H]- and [^{3}H]-(*S*)-**1b**. Oxidative or reductive modifications of the terminal vinyl group or olefin metathesis should provide access to other highly modified natural and non-natural amino acids, including the *γ*-methysulfinyl-*tert*-leucine residue found in polytheonamide A.[4]

In summary, the versatility of chiral glycine synthon **3** for α-amino acid synthesis has been extended to highly diastereoselective additions of dimethylallylstannane and a concise conversion of the product (3*S*,5*S*)-**4b** to the highly branched amino acid (−)-*β*-methylisoleucine (L-**1b**). The configurations of amino acids derived through allylstannane additions to **3** complement those from hydrogenation of oxazinones[11,12] (Figure 2, **3** R = alkyl). Consequently, antipodal amino acids can be obtained in high yield from oxazinones derived from a common phenylglycinol chiral auxiliary.

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Note Added after ASAP Publication. Figure 2 contained errors in the version published ASAP February 17, 2010; the corrected version posted on the web February 19, 2010.

Supporting Information Available: Experimental procedures, full spectroscopic data, and ^1H, ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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