Total Synthesis of (−)-Muscoride A

Peter Wipf*,[1] and Srikanth Venkatraman

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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The recently isolated cyanobacterium metabolite muscoride A was synthesized in 15 steps and in 4.3% overall yield. Novel structural features of this peptide antibiotic include the presence of a threonine-derived bioxazole core and an *N*-(1,1-dimethyl)allyl ("reverse prenyl") valine residue. In the context of our synthesis, efficient new strategies for the preparation of these segments were developed. The synthesis of two epimers of muscoride A allowed the unambiguous assignment of the relative and absolute configuration of the natural product by NMR and optical rotation analyses.

Terrestrial freshwater as well as marine organisms have been the source of a great variety of natural products with novel architecture and functionalities.[2] The ubiquitous incorporation of oxazole moieties in these secondary metabolites is exemplified by the phosphatase inhibitor calyculin A,[3] the cytotoxic macrolide phorboxazole A,[4] and the polyazole tantazole[5] (Figure 1).

In contrast to the large number of natural products that contain isolated oxazole rings, significantly fewer compounds with contiguously linked polyoxazoles are known: halichondramides,[6] ulapualides,[7] and mycalolides[8] incorporate teroxazole segments and hennoxazole A[9] and diazonamides[10] contain a bioxazole core (Figure 2).

More recently, the isolation of a new bioxazole peptide alkaloid from the freshwater cyanobacterium *Nostoc muscorum* was reported by Sakakibara and co-workers (Figure 3).[11] Muscoride A (**1**) showed antibacterial activity and raised our interest because of its novel structural features invoking a distant relationship to the potent DNA gyrase inhibitor microcin B17.[12] The bioxazole core of muscoride A is formally derived from two threonine residues, which is rather remarkable since even isolated oxazoles derived from threonine are rare.[13] Muscoride A also appears to be the first natural product with a reverse prenyl function at the α-nitrogen of an amino acid residue, in this case valine.[14]

For our recently described total syntheses of thiangazole and hennoxazole A,[15,16] we had developed a method for the introduction of bi-azole segments in polyfunctionalized compounds.[17] We were quite confident that this method was applicable for the preparation of the threonine-derived bioxazole core of muscoride A, but this remained to be proven. In addition, we were interested in establishing a straightforward general protocol for the preparation of *N*-reverse-prenylated amino acids because we envision these to become an attractive new motif in peptide chemistry for manipulation of secondary structure and inhibition of enzymatic degradation.

To achieve a reasonable level of convergence in our synthesis, our retrosynthetic plan disconnected muscoride A between the valine and proline residues (Figure 4). The tripeptide ester **4** could easily be prepared by standard peptide coupling techniques and would serve as the precursor for the bioxazole moiety **2**. Acylation of this segment with an active ester derivative of *N*-reverse-prenylated valine **3** should directly lead to the natural product. To avoid the potential problems in the separation of regioisomers that would likely be formed in the dimethylallylation of valine, we chose propargylated valine derivative **5** as a precursor to **3**. We arbitrarily selected the more readily available L-amino acids as starting materials. Our total synthesis of (−)-muscoride A ultimately established the stereochemistry at C(8) and C(13) as shown in Figure 3, but the configuration at these stereocenters had remained unresolved in the NMR-based structure elucidation by Sakakibara et al.[11]

Synthesis of the Bioxazole Segment of Muscoride A. Dipeptide **7** was readily obtained from the condensation of Boc-protected L-proline with threonine methyl ester hydrochloride in the presence of isobutyl chloroformate (IBCF, Scheme 1).[18] Oxidative cyclodehydration[17] of the threonine residue by side-chain oxidation with Dess−Martin Periodinane[19] followed by exposure to

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(9) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3173.

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(13) Cyclodehydrated threonines are, however, frequently encountered at the oxazoline oxidation level.[2]

(14) Natural products incorporating reverse prenyl groups at various indole ring positions are quite common. For example, see: (a) (Asterriquinone) Yamamoto, Y.; Nishimura, K; Kiriyama, N. *Chem. Pharm. Bull.* **1976**, *24*, 1853. (b) (Okaramine A) Hayashi, H.; Takiuchi, K.; Murao, S.; Arai, M. *Agric. Biol. Chem.* **1989**, *53*, 461. (c) (Amauromine) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143. (d) (Gypsetin) Schkeryantz, J. M.; Woo, J. C. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 7025.

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S0022-3263(96)00891-2 CCC: $12.00

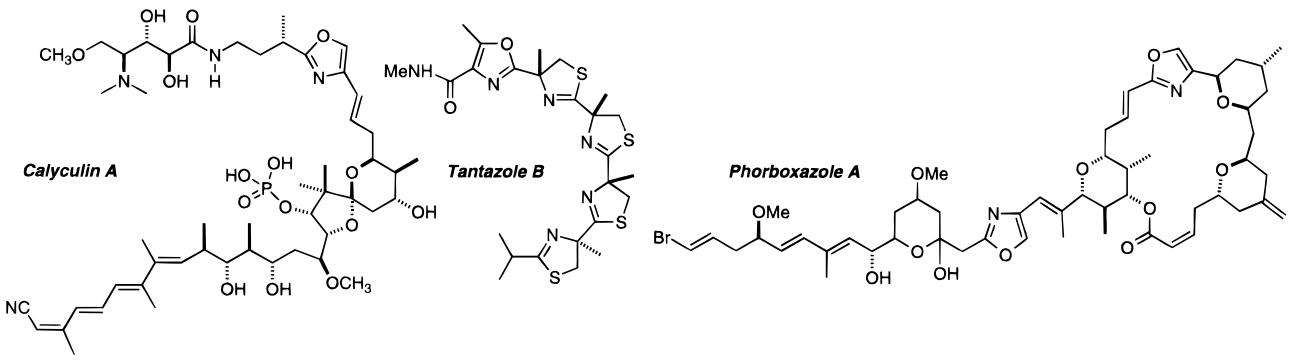

Figure 1. Some oxazole-containing secondary metabolites.

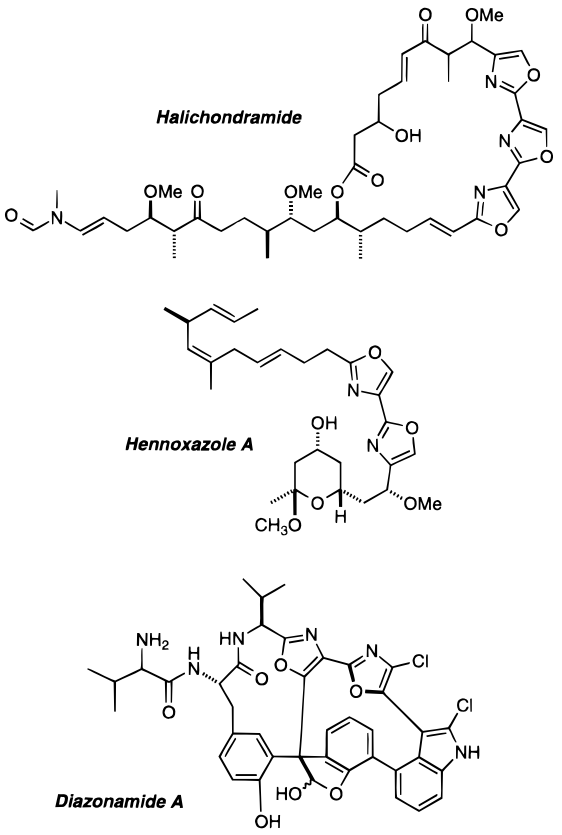

Figure 2. Natural products with ter- and bioxazole moieties.

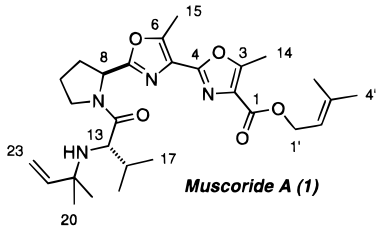

Figure 3. Muscoride A, a bioxazole peptide alkaloid from a freshwater cyanobacterium.

electrophilic phosphorus reagent assembled the first heterocycle in 68% yield.

Oxazole **8** was homologated by hydrolysis of the methyl ester and coupling with L-threonine. The subsequent oxidative cyclodehydration[17] of tripeptide **9** closed the second oxazole ring in 65% yield. This iterative formation of the bioxazole core of muscoride A was superior to the alternative tandem oxidative cyclodehydration of the prolylthreonylthreonine intermediate **4**, since the manipulation of this polar tripeptide in common organic solvents was difficult.

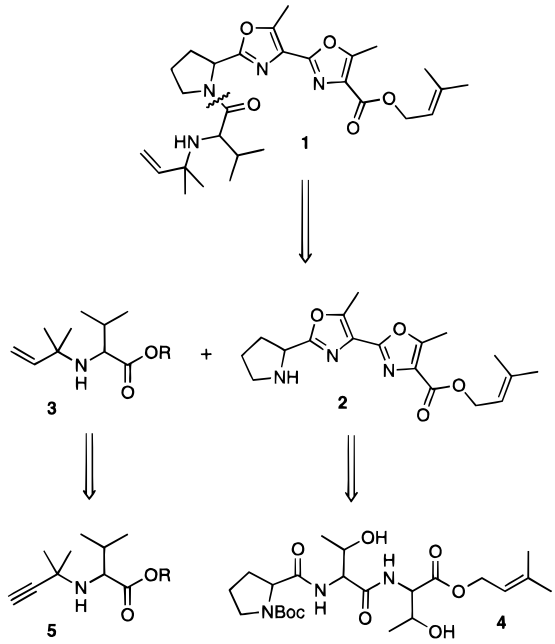

Figure 4. Retrosynthetic analysis.

To complete the synthesis of the *C*-terminal segment of muscoride A, the methyl ester **10** was converted to the 3,3-dimethylallyl ester **11** by saponification followed by prenylation in the presence of BOP Reagent.[20] The overall yield for the preparation of segment **11** from proline **6** was 19.3%, and this synthesis was readily scaled up to gram quantities.

Synthesis of the Reverse-Prenylated Valine Residue of Muscoride A. After the efficient preparation of the heterocyclic segment **11** by the use of our recently developed variant of the Robinson−Gabriel oxazole synthesis, we required an equally efficient route to the *N*-terminal amino acid residue carrying the unique reverse-prenylation signature. As expected, our first attempt to directly introduce this five-carbon appendage by treatment of L-valine methyl ester with dimethylallyl chloride required vigorous heating and led to very low yields of the desired compound in addition to many other side products. Fortunately, the analogous propargylation of ester **12** was accomplished very cleanly under the

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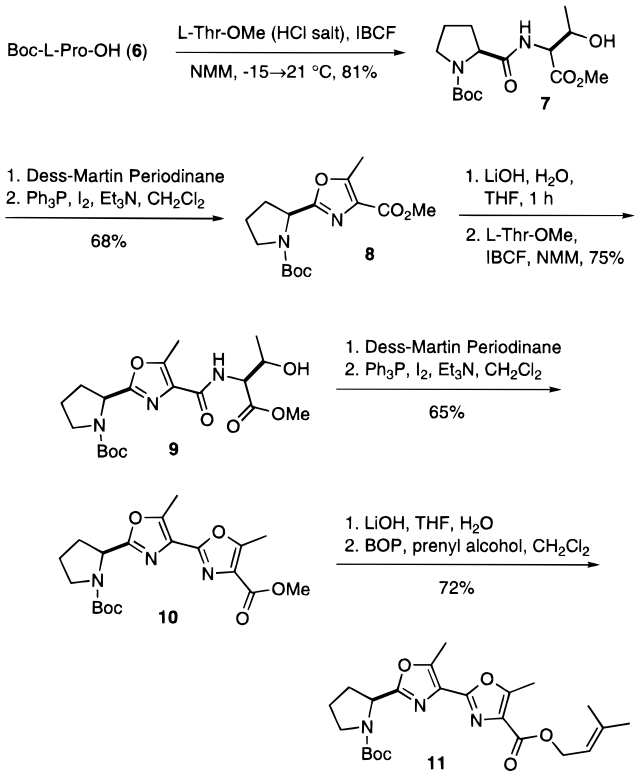
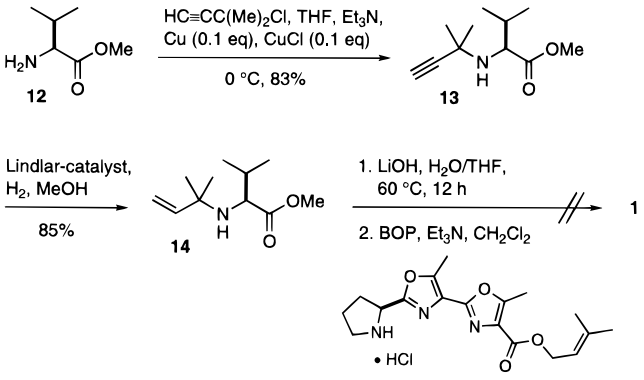
Scheme 1



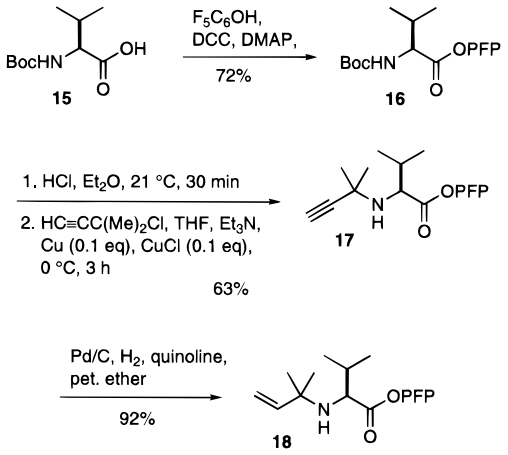
Scheme 2



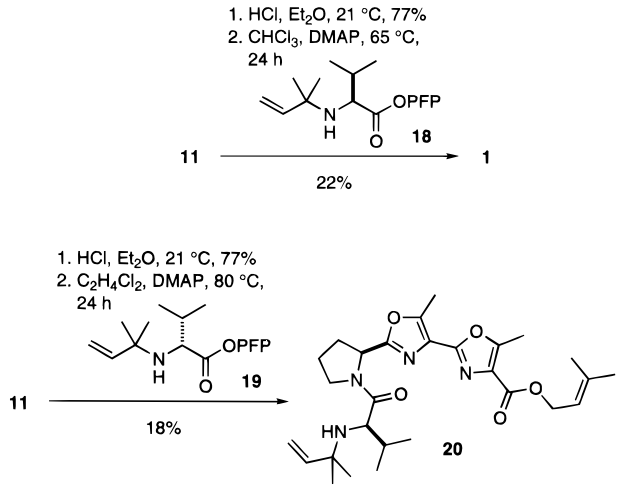
conditions of Hennion and Hanzel[21] with dimethylpropargyl chloride in the presence of catalytic copper and cuprous chloride (Scheme 2). This mechanistically interesting protocol provided *N*-(1,1-dimethyl)propargylated valine **13** at 0 °C in 83% yield. The terminal alkyne was partially hydrogenated using Lindlar catalyst to form alkene **14**. Attempts to hydrolyze the methyl ester of **14** at 25 °C were sluggish, but at 60 °C the saponification was complete after 12 h. However, all attempts to couple the resulting lithium salt with the amine hydrochloride derived from **11** met with failure. We therefore decided to activate the valine residue before the propargylation−reduction sequence (Scheme 3).

Condensation of Boc-L-valine with pentafluorophenol in the presence of DCC provided the activated PFP ester **16**.[22] The subsequent copper-catalyzed alkylation of **16** with 3-chloro-3-methyl-1-butyne proceeded cleanly at 0

Scheme 3



Scheme 4



°C in 63% yield to give ester **17**. An increase in either reaction temperature or reaction time resulted not only in a yield improvement but also in the formation of a mixture of inseparable products arising from Glaser coupling.[23] Similarly, the reduction of alkyne **17** under standard Lindlar conditions resulted in over-reduction and decomposition. Fortunately, however, we were able to optimize this step by the use of Pd/C in petroleum ether in the presence of quinoline to give 92% of building block **18**.

Segment Condensation. The total synthesis of (6*S*,-14*S*)-muscoride A was accomplished by simply heating the active ester **18** and the hydrochloride salt derived from **11** in chloroform in the presence of DMAP (Scheme 4). Due to the severe level of steric hindrance in both the carboxyl and the amine component in this reaction, the yield of coupling product generally did not exceed 22%. We also noticed that the amine was not stable under the reaction conditions and slowly decomposed to unidentified side products. Variations in solvent and temperature provided only marginal improvements in the efficiency of the final segment condensation. Nonetheless, >100 mg quantities of the natural product were routinely accessible via this route. Synthetic (6*S*,14*S*)-muscoride A was found to have physical data identical to those reported[11] for the natural product. To further support the structural assignment of muscoride A, we

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prepared the (6*R*,14*S*)-diastereomer **20** by condensation of D-valine-derived **19** with tripeptide ester **11**. The two epimers **1** and **20** had distinctively different spectroscopic and chiroptical properties. For **1**, an $[\alpha]_D$ −93° (*c* 0.5, MeOH, 25 °C) compared closely with the reported −89° (*c* 0.7, MeOH, 25 °C), whereas the $[\alpha]_D$ −54° (*c* 0.54, MeOH, 25 °C) for the (6*R*,14*S*)-diastereomer **20** was considerably lower. The ^{1}H NMR of **1** was identical to the natural product, and epimer **20** displayed several clearly different splitting patterns and chemical shifts.[24]

Conclusion. We have developed a straightforward convergent strategy for the preparation of the structurally novel peptide alkaloid muscoride A. The heterocyclic bioxazole core was efficiently prepared by consecutive oxidative cyclodehydrations of threonine residues. This application underscores the broad scope of our recently developed protocols for oxazole synthesis.[15−17] The copper-catalyzed *N*-propargylation of a valine active ester via the Hennion−Hanzel protocol followed by modified Lindlar reduction allowed a direct access to the *C*-terminal activated reverse-prenylated amino acid segment. We believe that this is a general protocol for the preparation of novel reverse-prenylated amino acid building blocks that have potentially attractive applications as conformationally rigidified peptide analogs.[25]

Due to the steric hindrance of the coupling components **11** and **18**, the final segment condensation proceeded in low yield. Nonetheless, muscoride A and its epimer **20** were readily obtained in an overall yield of 4.3% from L-proline **6**. Spectral comparisons between synthetic and natural **1** and epimer **20** allowed the unambiguous assignment of the relative and absolute stereochemistry of the natural product. We are currently evaluating the spectrum of biological activities and metal-binding properties[26] of this cyanobacterium metabolite.

Experimental Section

General Methods. All glassware was dried in an oven at 150 °C prior to use. THF and dioxane were dried by distillation over Na/benzophenone under a nitrogen atmosphere. Dry CH_2Cl_2, DMF, and CH_3CN were obtained by distillation from CaH_2. Other solvents or reagents were used as acquired except when otherwise noted. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F-254 plates available from Merck. Column chromatography was performed using silica gel 60 (particle size 0.040−0.055 mm, 230−400 mesh). Visualization was accomplished with UV light or by staining with a basic $KMnO_4$ solution or Vaughn's reagent. NMR spectra were recorded in $CDCl_3$ unless otherwise noted at either 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR).

2(*S*)-(2′(*R*)-Hydroxy-1′(*S*)-(methoxycarbonyl)propylcarbamoyl)-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (7). A solution of 7.0 g (33.0 mmol) of Boc-L-proline **6** in 50 mL of dry CH_2Cl_2 at −15 °C was treated with 4 mL (36.0 mmol) of *N*-methylmorpholine (NMM) and 4.9 mL (38.0 mmol) of isobutyl chloroformate (IBCF). The reaction mixture was stirred for 10 min, and the temperature slowly rose to −5 °C. After a solution of 6.1 g (36.0 mmol) of threonine methyl ester hydrochloride and 4 mL (36.0 mmol) of NMM in 20 mL of dry DMF was added, the reaction mixture was stirred at 25 °C for 0.5 h, diluted with 100 mL of H_2O, and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with H_2O (50 mL), 2 M HCl (50 mL), and brine (50 mL), dried ($MgSO_4$), concentrated in vacuo, and chromatographed on SiO_2 (EtOAc/hexanes 4:1) to yield 8.8 g (81%) of **7** as a viscous oil: R_f 0.65 (EtOAc/hexanes 19:1); $[\alpha]_D$ +60° (*c* 1.1, $CHCl_3$, 25 °C); IR (neat) 3431, 3297, 1750, 1683, 1257, 1165, 1122 cm^{-1}; ^{1}H NMR (365 K, DMSO) δ 7.32 (d, 1 H, J = 7.2 Hz), 4.8−4.3 (b, 1 H), 4.32−4.24 (m, 2 H), 4.14−4.10 (m, 1 H), 3.65 (s, 3 H), 3.36 (m, 2 H), 2.14−2.05 (m, 1 H), 1.96−1.89 (m, 1 H), 1.86−1.76 (m, 2 H), 1.40 (s, 9 H), 1.10 (d, 3 H, J = 6.2 Hz); ^{13}C NMR δ 173.3, 172.6, 171.1, 155.2, 154.6, 80.4, 68.2, 67.5, 60.9, 59.9, 57.4, 52.3, 46.9, 31.0, 28.8, 28.2, 24.5, 23.6, 19.9; MS (EI) *m*/*z* (rel intensity) 330 (M^+, 10); HRMS *m*/*z* calcd for $C_{15}H_{26}N_2O_6$ 330.1790, found 330.1801.

2-[1′-(*tert*-Butoxycarbonyl)pyrrolidin-2′(*S*)-yl]-5-methyloxazolyl-4-carboxylic Acid Methyl Ester (8). A solution of 4.6 g (14.0 mmol) of dipeptide **7** in 50 mL of dry CH_2Cl_2 was treated with 7.0 g (16.5 mmol) of the Dess−Martin reagent and stirred at 25 °C for 2 h. The reaction mixture was concentrated in vacuo and chromatographed on SiO_2 (EtOAc/hexanes 7:3) to yield 3.9 (81%) of the methyl ketone which was immediately used without further purification.

A solution of the methyl ketone in 10 mL of dry THF was added dropwise to a solution of 6.5 g (25.0 mmol) of Ph_3P, 5.8 g (22.5 mmol) of I_2, and 6 mL (41.0 mmol) of Et_3N in 35 mL of THF at −78 °C. The reaction mixture was stirred at −78 °C for 3 h and diluted with 100 mL of H_2O. The solution was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with H_2O (50 mL), $Na_2S_2O_3$ (50 mL), 2 M HCl (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo, and chromatographed on SiO_2 (EtOAc/hexanes 1:1) to yield 3.1 g (68%) of **8** as a viscous oil: R_f 0.5 (EtOAc/hexanes 1:1); $[\alpha]_D$ −60.8° (*c* 1.1, $CHCl_3$, 25 °C); IR (neat) 1700, 1621, 1162, 1101 cm^{-1}; ^{1}H NMR (383 K, DMSO) δ 4.81 (dd, 1 H, J = 8.1, 3.5 Hz), 3.80 (s, 3 H), 3.46−3.40 (m, 2 H), 2.53 (s, 3 H), 2.41−2.24 (m, 1 H), 2.02−1.89 (m, 3 H), 1.31 (s, 9 H); ^{13}C NMR δ 163.1, 162.7, 156.1, 155.8, 154.3, 153.7, 127.3, 127.1, 79.9, 54.7, 54.4, 51.9, 46.7, 46.4, 32.5, 31.5, 28.3, 28.1, 24.3, 23.7, 11.9; k MS (EI) *m*/*z* (rel intensity) 310 (M^+, 5); HRMS *m*/*z* calcd for $C_{15}H_{22}N_2O_5$ 310.1528, found 310.1524.

2′(*S*)-[4-(2(*R*)-Hydroxy-1(*S*)-(methoxycarbonyl)propylcarbamoyl)-5-methyloxazol-2-yl]-pyrrolidine-1′-carboxylic Acid *tert*-Butyl Ester (9). A solution of 3.1 g (10.0 mmol) of oxazole **8** in 30 mL of THF/H_2O (1:1) was treated with 0.4 g (10 mmol) of LiOH·H_2O and stirred at 25 °C for 1 h. The reaction mixture was acidified to pH 2 with concentrated HCl and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered, concentrated in vacuo, and used without further purification.

A solution of the crude acid in 15 mL of CH_2Cl_2 under Ar was cooled to −15 °C and treated with 1.2 g (12.0 mmol, 1.3 mL) of NMM and 1.6 g (12.0 mmol, 1.6 mL) of IBCF. The reaction mixture was stirred for 10 min, and the temperature rose to −5 °C. After a solution of 2.5 g (15.0 mmol) of Thr-OMe and 1.7 mL (15.0 mmol) of NMM in 10 mL of dry DMF was added, the reaction mixture was stirred at 25 °C for 50 min, diluted with H_2O (50 mL), and washed with CH_2Cl_2 (3 × 30 mL). The combined organic layers were extracted with 2 M HCl (30 mL), H_2O (30 mL), and brine (30 mL), dried ($MgSO_4$), and chromatographed on SiO_2 (EtOAc/hexanes 4:1) to yield 3.0 g (75%) of **9** as a viscous liquid: R_f 0.4 (EtOAc/hexanes 4:1); $[\alpha]_D$ −44.4° (*c* 1.0, $CHCl_3$, 25 °C); IR (neat) 3416, 1750, 1674, 1635, 1160, 1121 cm^{-1}; ^{1}H NMR (373 K, DMSO) δ 7.46 (d, 1 H, J = 8.3 Hz), 4.84−4.80 (m, 1 H), 4.44−4.40 (m, 1 H), 4.23−4.17 (m, 1 H), 3.66 (s, 3 H), 3.49−3.38 (m, 2 H), 2.53 (s, 3 H), 2.33−2.26 (m, 1 H), 2.04−1.87 (m, 3 H), 1.30 (s, 9 H), 1.11 (d, 3 H, J = 6.3 Hz); ^{13}C NMR δ 171.3, 162.4, 162.1, 154.4, 153.9, 153.3, 153.0, 128.5, 80.0, 67.9, 67.6, 56.9, 54.6, 54.4, 52.5, 46.7, 46.3, 32.2, 31.3, 28.3, 28.1, 24.2, 23.6, 19.8, 11.7; MS (EI)-*m*/*z* (rel intensity) 411 (M^+, 5); HRMS *m*/*z* calcd for $C_{19}H_{29}N_3O_7$ 411.2005, found 411.2008.

(24) ^{1}H and ^{13}C NMR of **1** and **20** are shown in the supporting information.

(25) The reverse-prenylated valine residue has a strong preference for fully extended conformations ($\phi = -110 \pm 20°$, $\psi = -170 \pm 20°$), in contrast to just *N*-methylated amino acid. Ramachandran plots of $H_2C{=}CHC(Me)_2$-Val-NHMe and Me-Val-NHMe are shown in the supporting information.

(26) For a study of the metal-complexation properties of teroxazole segments of halichondramides, see: James, D. M.; Wintner, E.; Faulkner, D. J.; Siegel, J. S. *Heterocycles* **1993**, *35*, 675.

2′-(1-(*tert*-Butoxycarbonyl)pyrrolidin-2(*S*)-yl)-5,5′-dimethyl-2,4′-bioxazolyl-4-carboxylic Acid Methyl Ester (10). A solution of 3.0 g (7.3 mmol) of ester **9** in 15 mL of dry CH_2Cl_2 was treated with 3.2 g (7.5 mmol) of Dess−Martin reagent and stirred at 25 °C for 3 h. The reaction mixture was concentrated in vacuo and chromatographed on SiO_2 (EtOAc/hexanes 7:3) to yield the methyl ketone which was immediately used for the next reaction.

A solution of the methyl ketone in 15 mL of THF was added dropwise to a solution of 4.7 g (18 mmol) of Ph_3P, 4.2 g (14.6 mmol) of I_2, and 4.2 mL (29 mmol) of Et_3N in 30 mL of dry THF at −78 °C. The reaction mixture was stirred at −78 °C for 3 h and diluted with 30 mL of H_2O. The solution was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with a 10% solution of $Na_2S_2O_3$ (30 mL), 2 M HCl (30 mL), H_2O (30 mL), and brine (30 mL) and dried (Na_2SO_4). The organic layer was filtered, concentrated in vacuo, and chromatographed on SiO_2 (EtOAc/hexanes 2:3) to yield 2.0 g (65%) of **10** as a pale yellow oil: R_f 0.65 (EtOAc/hexanes 3:2); $[\alpha]_D$ −53° (*c* 1.1, $CHCl_3$, 25 °C); IR (neat) 3591, 1699, 1197, 1057 cm^{-1}; ^1H NMR (373 K, DMSO) δ 4.86−4.82 (m, 1 H), 3.62 (s, 3 H), 3.47−3.40 (m, 2 H), 2.60 (s, 3 H), 2.58 (s, 3 H), 2.28−2.24 (m, 1 H), 2.03−1.87 (m, 3 H), 1.30 (s, 9 H); ^{13}C NMR δ 164.2, 162.7, 156.0, 154.1, 153.8, 149.9, 128.3, 124.5, 80.0, 54.8, 54.5, 52.0, 46.5, 32.6, 28.4, 28.2, 24.4, 23.8, 12.1, 11.8; MS (EI) *m*/*z* (rel intensity) 391 (M^+, 25); HRMS *m*/*z* calcd for $C_{19}H_{25}N_3O_6$ 391.1743, found 391.1741.

2′-(1-(*tert*-Butoxycarbonyl)pyrrolidin-2(*S*)-yl)-5,5′-dimethyl-2,4′-bioxazolyl-4-carboxylic Acid 3-Methyl-but-2-enyl Ester (11). A solution of 1.9 g (4.9 mmol) of bioxazole **10** in 10 mL of THF/H_2O (1:1) was treated with 400 mg (10 mmol) of $LiOH\cdot H_2O$ and stirred at 25 °C for 2 h. The reaction was quenched by addition of concentrated HCl, and the pH was adjusted to 1. The solution was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude acid was used without further purification.

A solution of the acid in 5 mL of CH_2Cl_2 was treated with 870 mg (10.0 mmol) of prenyl alcohol, 1.8 mL (15.0 mmol) of Et_3N, and 3.3 g (7.5 mmol) of BOP Reagent and stirred at 25 °C for 12 h. The reaction was quenched by the addition of H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with H_2O (30 mL) and 2 M HCl (30 mL), dried (Na_2SO_4), filtered, concentrated in vacuo, and chromatographed on SiO_2 (EtOAc/hexanes 2:3) to yield 1.4 g (72%) of **11** as a colorless oil: R_f 0.45 (EtOAc/hexanes 2:3); $[\alpha]_D$ −53° (*c* 1.5, $CHCl_3$, 25 °C); IR (neat) 1734, 1703, 1202, 1163, 1098 cm^{-1}; ^1H NMR (373 K, DMSO) δ 5.49−5.40 (m, 1 H), 4.88−4.84 (m, 1 H), 4.78 (d, 2 H, *J* = 7.0 Hz), 3.49−3.43 (m, 2 H), 2.62 (s, 3 H), 2.60 (s, 3 H), 2.32−2.25 (m, 1 H), 2.05−1.91 (m, 3 H), 1.77 (bs, 3 H), 1.75 (bs, 3 H), 1.32 (s, 9 H); ^{13}C NMR δ 164.0, 163.6, 162.4, 155.7, 154.0, 150.3, 149.9, 139.2, 128.6, 124.5, 118.5, 80.0, 61.9, 54.8, 54.5, 46.5, 32.6, 28.2, 25.8, 23.8, 18.1, 12.2, 11.8; MS (EI) *m*/*z* (rel intensity) 445 (M^+, 25); HRMS *m*/*z* calcd for $C_{23}H_{31}N_3O_6$ 445.2212, found 445.2234.

2(*S*)-((*tert*-Butoxycarbonyl)amino)-3-methyl-butyric Acid 2,3,4,5,6-Pentafluorophenyl Ester (16). A solution of 4.15 g (20.0 mmol) of acid **15** in 20 mL of dry CH_2Cl_2 was treated with 3.6 g (19.5 mmol) of pentafluorophenol, 4.12 g (20.0 mmol) of DCC, and 516 mg (4.2 mmol) of DMAP. The reaction mixture was stirred at 25 °C for 12 h, concentrated in vacuo, and chromatographed on SiO_2 (EtOAc/hexanes 1:19) to yield 5.5 g (72%) of **16** as an amorphous solid: R_f 0.25 (EtOAc/hexanes 1:19); mp 63−64 °C; $[\alpha]_D$ −17.6° (*c* 1.0, $CHCl_3$, 25 °C); IR (neat) 1782, 1707, 1246, 1167 cm^{-1}; ^1H NMR δ 5.01 (d, 1 H, *J* = 8.8 Hz), 4.57 (dd, 2 H, *J* = 8.7, 4.5 Hz), 2.38−2.30 (m, 1 H), 1.47 (s, 9 H), 1.09 (d, 3 H, *J* = 6.7 Hz), 1.03 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 168.8, 155.5, 141.2, 139.7, 137.9, 80.5, 58.7, 31.2, 28.3, 19.0, 17.5; MS (CI, isobutane) *m*/*z* (rel intensity) 384 ($[M + 1]^+$, 10).

2(*S*)-(1′,1′-Dimethylallylamino)-3-methylbutyric Acid 2,3,4,5,6-Pentafluorophenyl Ester (18). A solution of 6.0 g (15.6 mmol) of ester **16** was treated for 30 min with 60 mL of a solution of saturated HCl in ether. The reaction mixture was concentrated in vacuo to yield 4.1 g of L-valine pentafluorophenyl ester hydrochloride that was immediately used without further purification.

A suspension of 2.0 g (6.5 mmol) of L-valine pentafluorophenyl ester hydrochloride in 10 mL of dry THF was treated with 65 mg (0.65 mmol) of CuCl, 45 mg (0.65 mmol) of Cu powder, and 2.1 mL (14.3 mmol) of Et_3N. The reaction mixture was cooled to 0 °C, treated dropwise with a solution of 0.75 g (7.5 mmol) of 3-chloro-3-methyl-1-butyne in 5 mL of THF, stirred at 0 °C for 3 h, diluted with 50 mL of ether, and filtered through a plug of Celite. The filtrate was concentrated in vacuo and chromatographed on SiO_2 (EtOAc/hexanes 1:19) to yield 1.4 g (63%) of alkyne **17** which was used directly for the next step.

A solution of 200 mg (0.57 mmol) of **17** in 7 mL of petroleum ether was treated with 30 mg of 10% Pd/C and 150 μL of quinoline, and H_2 gas was bubbled through the solution for 45−60 min. The reaction mixture was filtered through a plug of Celite, concentrated in vacuo, and chromatographed on SiO_2 (EtOAc/hexanes 1:19) to yield 184 mg (92%) of **18** as a colorless liquid: R_f 0.4 (EtOAc/hexanes 1:19); $[\alpha]_D$ −53.7° (*c* 1.5, $CHCl_3$, 25 °C); IR (neat) 1783, 1090, 1059 cm^{-1}; ^1H NMR δ 5.73 (dd, 1 H, *J* = 17.6, 10.8 Hz), 5.11−5.04 (m, 2 H), 3.35 (d, 1 H, *J* = 4.9 Hz), 2.08−2.02 (m, 1 H), 1.66 (s, 1 H), 1.19 (s, 3 H), 1.18 (s, 3 H), 1.07 (d, 3 H, *J* = 6.9 Hz), 0.97 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 173.3, 145.5, 141.2, 139.7, 137.9, 113.0, 60.7, 54.5, 32.7, 27.1, 26.8, 19.3, 17.6; MS (CI, isobutane) *m*/*z* (rel intensity) 352 ($[M + 1]^+$, 100).

2(*R*)-(1′,1′-Dimethylallylamino)-3-methylbutyric Acid 2,3,4,5,6-Pentafluorophenyl Ester (19). According to the procedures for the synthesis of **18** from **16**, 5.5 g (14.3 mmol) of Boc-D-valine pentafluorophenyl ester were converted to 900 mg (18%) of **19**: $[\alpha]_D$ +52.1° (*c* 1.45, $CHCl_3$, 25 °C).

2′(*S*)-{1-[1,1-Dimethylallylamino)-3-methylbutyryl]pyrrolidin-2(*S*)-yl}-5,5′-dimethyl-2,4′-bioxazolyl-4-carboxylic Acid 3-Methyl-but-2-enyl Ester (Muscoride A, 1). A solution of 1.4 g (3.14 mmol) of bioxazole **11** in 35 mL of Et_2O saturated with HCl gas was stirred at 21 °C for 30 min. The reaction mixture was concentrated in vacuo to yield 920 mg (77%) of crude hydrochloride that was used without further purification.

A solution of 400 mg (1.05 mmol) of activated L-valine **18** in 2 mL of $CHCl_3$ was treated with 600 mg (1.50 mmol) of the amine hydrochloride derived from **11**, 322 μL (2.25 mmol) of Hünig's base, and 130 mg (1 mmol) of DMAP. The reaction mixture was heated at reflux for 24 h, concentrated in vacuo, and chromatographed on SiO_2 (EtOAc/hexanes 1:1) to yield 119 mg (22%) of **1** as a viscous oil: R_f 0.6 (EtOAc/hexanes 1:1); $[\alpha]_D$ −92.8° (*c* 0.5, MeOH, 25 °C); IR (neat) 1733, 1713, 1651, 1202, 1174, 1057 cm^{-1}; ^1H NMR (500 MHz) δ 5.75 (dd, 1 H, *J* = 17.6, 10.8 Hz), 5.47−5.45 (m, 1 H), 5.20−5.18 (m, 1 H), 4.96 (d, 1 H, *J* = 17.5 Hz), 4.91 (d, 1 H, *J* = 10.6 Hz), 4.82 (d, 2 H, *J* = 7.3 Hz), 3.67−3.61 (m, 2 H), 2.95 (d, 1 H, *J* = 5.1 Hz), 2.66 (s, 3 H), 2.63 (s, 3 H), 2.24−2.14 (m, 3 H), 2.02−1.99 (m, 1 H), 1.9−1.7 (b, 1 H), 1.78 (s, 3 H), 1.76 (s, 3 H), 1.8−1.6 (m, 1 H), 1.12 (s, 3 H), 1.10 (s, 3 H), 0.98 (d, 3 H, *J* = 6.6 Hz), 0.84 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz) δ 176.1, 163.2, 162.5, 155.8, 154.1, 150.1, 148.0, 139.2, 128.6, 124.7, 118.6, 111.1, 61.9, 59.2, 54.6, 54.3, 46.8, 32.0, 30.7, 28.1, 26.2, 25.9, 25.1, 19.8, 18.2, 17.6, 12.3, 11.9; MS (EI) *m*/*z* (rel intensity) 512 (M^+, 22); HRMS *m*/*z* calcd for $C_{28}H_{40}N_4O_5$ 512.2998, found 512.2985.

2′(*R*)-{1-[1,1-Dimethylallylamino)-3-methylbutyryl]pyrrolidin-2(*S*)-yl}-5,5′-dimethyl-2,4′-bioxazolyl-4-carboxylic Acid 3-Methyl-but-2-enyl Ester (20). A solution of 200 mg (0.56 mmol) of activated D-valine **19** in 2 mL of 1,2-dichloroethane was treated with 100 mg (0.25 mmol) of the amine hydrochloride derived from **11** and 130 mg (1.1 mmol) of DMAP. The reaction mixture was heated at reflux for 24 h, concentrated in vacuo, and chromatographed on SiO_2 (EtOAc/hexanes 1:1) to yield 25 mg (18%) of **20** as a viscous oil: R_f 0.6 (EtOAc/hexanes 1:1); $[\alpha]_D$ −54° (*c* 0.58, MeOH, 25 °C); IR (neat) 1712, 1646, 1169, 1097, 1055 cm^{-1}; ^1H NMR (500 MHz, major rotamer) δ 5.70 (dd, 1 H, *J* = 9.0, 5.0 Hz), 5.48−5.44 (m, 1 H), 5.17−5.14 (m, 1 H), 5.01 (dd, 1 H, *J* = 18.0, 1.0 Hz), 4.99 (dd, 1 H, *J* = 10.6, 1.0 Hz), 4.82 (d, 2 H, *J* = 7.1 Hz),

3.73−3.68 (m, 1 H), 3.58−3.53 (m, 1 H), 2.94 (d, 1 H, J = 5.0 Hz), 2.67 and 2.66 (2s, 6 H), 2.27−2.14 (m, 3 H), 2.05−2.0 (m, 2 H), 1.77 (s, 3 H), 1.76 (s, 3 H), 1.7−1.6 (m, 1 H), 1.09 (s, 3 H), 1.04 (s, 3 H), 0.93 (d, 3 H, J = 6.7 Hz), 0.89 (d, 3 H, J = 6.7 Hz); ^{13}C NMR (125 MHz, major rotamer) δ 175.6, 163.3, 162.5, 155.6, 154.2, 149.9, 147.8, 139.2, 128.6, 124.7, 118.6, 111.7, 61.9, 59.3, 54.5, 54.3, 46.6, 32.0, 30.8, 27.5, 27.1, 25.9, 24.6, 20.0, 18.2, 17.6, 12.2, 11.8; MS (EI) m/z (rel intensity) 512 (M^+, 10); HRMS m/z calcd for $C_{28}H_{40}N_4O_5$ 512.2998, found 512.3015.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for muscoride A, **20**, and synthetic intermediates; Ramachandran plots for *N*-reverse-prenylated valine methyl amide and *N*-methyl valine methyl amide (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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