Synthesis of Microcolin B, a Potent New Immunosuppressant Using an Efficient Mixed Imide Formation Reaction

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Microcolin B, a potent new immunosuppressant isolated from blue-green alga *Lyngbya majuscula* off the Venezuelan coast, has been made using a methyl-directed asymmetric hydrogenation reaction with rhodium on alumina catalyst on lactone **4** for the synthesis of the key (*R*,*R*)-2,4-dimethyloctanoic acid fragment **1**. A new, direct mixed imide formation reaction was also developed for the production of the unusual prolylpyrrolen-2-one **2** portion of microcolin. The pentafluorophenyl ester of CBZ-proline **5** was reacted with the lithium imidate of lactam **6**, providing the mixed imide in 80% yield. Coupling of acid **1** with the N-terminus of the tripeptide, followed by coupling with pyrrolylproline **2**, gave microcolin B. The new mixed-imide forming reaction was also applied to a formal total synthesis of microcolin A. The pentafluorophenyl ester of TBS-protected *cis*-hydroxyproline was coupled with lactam **6**, and the resultant imide was converted to the key pyrrolylproline made previously for microcolin A.

The discovery of potent immunosuppressive agents has led to dramatic clinical successes in the treatment of organ rejection following transplantation.[1] These drugs, in particular, FK506 and cyclosporin A, have also proven to be excellent probes of the mechanism of cytosolic T-cell signaling. Recently a variety of new immunosuppressive agents have been discovered that appear to have distinct modes of activity holding promise for the development of new agents that may be specific to T-cells and have lower toxicities relative to FK506 and cyclosporin.[2] In particular, Koehn reported the isolation of two new extremely potent unusual acylpeptide, proline-containing immunosuppressants, microcolins A and B.[3] The EC_{50} values for the human two-way mixed lymphocyte response (MLR) were 0.02 and 4.1 nM, respectively. In comparison, in the same assay the EC_{50} for FK506 is 20 nM and cyclosporin 23 nM. While the mode of action of these new compounds is unclear at this time, the unsaturated pyrrolylproline C-terminus seems to suggest the likelihood of a covalent adduct in that the saturated compound is far less potent (EC_{50} 680 nM).[4]

The potent activity and unique structural features of microcolin prompted our efforts to develop a general and efficient synthetic route with particular attention to the 2,4-"skip" dimethyloctanoic acid *N*-terminal group, a feature common to other natural products, in particular, zaragozic acid,[5] and the unusual pyrrolylproline mixed imide.[6] Very recently, Decicco has reported a route to microcolin A involving two Evans alkylations requiring 25 equiv of chiral triflate for the dimethyloctanoic acid fragment.[7] A known Meldrum's acid-based route was used to form the mixed imide portion. Each of the four possible diastereomers was made for the dimethyloctanoic acid fragment, establishing the absolute stereochemistry as *R*,*R*. Our new route, the first total synthesis of microcolin B, includes a substrate-controlled route to acid **1** using an efficient methyl-directed lactone hydrogenation. In addition, we have developed a general new mixed imide-forming reaction that employs addition of the imidate formed by deprotonation of lactam **6** to the pentafluorophenyl ester of protected proline **5**. This new method tolerates a variety of protecting groups and does not rely on the use of a labile acid chloride as required by known methods for acyclic imide synthesis (Figure 1).

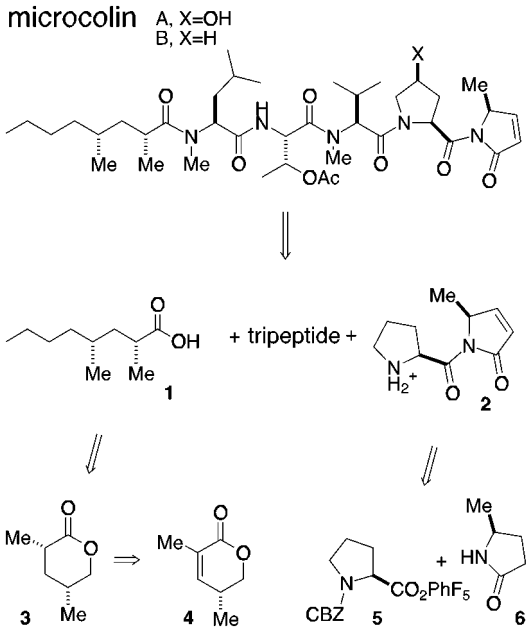

Figure 1.

Results and Discussion

Synthesis of acid **1** started with commercially available *S*-methyl ester **7** (Scheme 1). Protection as the THP

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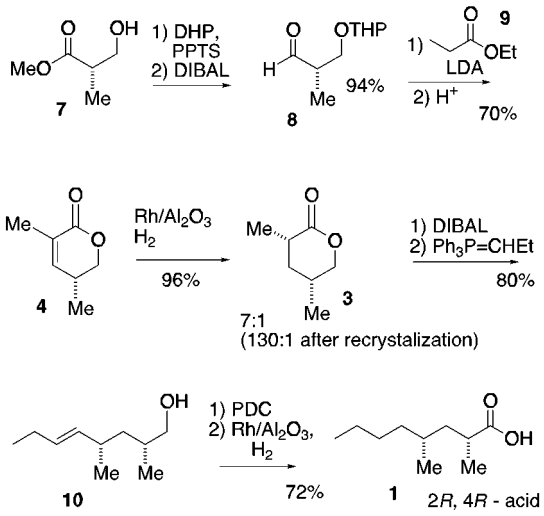
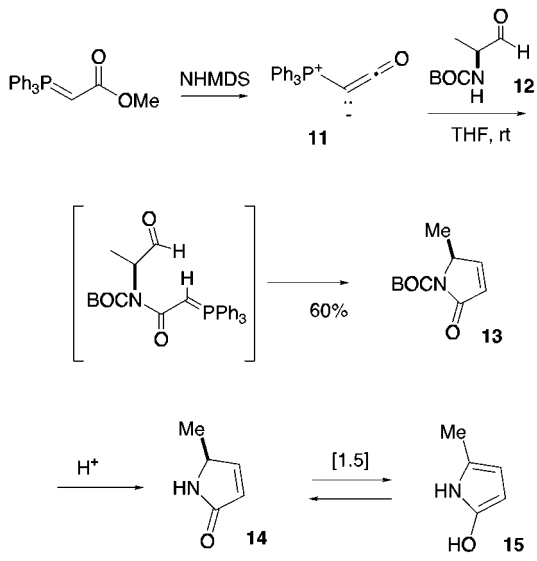
Scheme 1



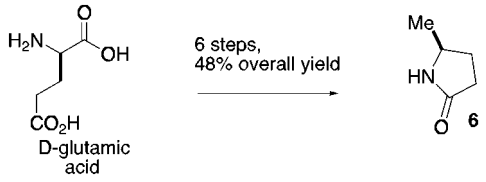
ether and reduction with DIBAL gave aldehyde **8** in 94% yield. Treatment with the lithium enolate of ethyl propionate **9** gave the aldol adduct that was treated with *p*-toluenesulfonic acid to provide the unsaturated lactone **4** according to the conditions of Still.[8] Reduction using rhodium on alumina catalyst at −10 °C in ether then gave lactone **3** in 96% yield.[9] Two recrystallizations of **3** from ether−pentane increased the initial 7:1 selectivity, which was also reported by Still, to now a selectivity greater than 130:1 (NMR). Use of palladium on carbon (10%) as the hydrogenation catalyst gave **3** in lower yield (68%) and selectivity (6:1). Reduction with DIBAL to the lactol followed by a Wittig reaction gave alcohol **10** (8:1 *Z*:*E*) in 81% overall yield.[10] Oxidation using pyridinium dichromate (PDC) in DMF gave the acid,[11] which was then hydrogenated using rhodium on alumina to give the key intermediate *R*,*R*-acid **1**. During this hydrogenation step, the isomeric composition was eroded to 14:1 for the product acid **1**. Interestingly, when an analogous, homochiral *R*,*R*-substrate bearing a more simple terminal olefin was hydrogenated under these conditions a 1:1 mixture resulted.

Initially, it was envisioned that the pyrrolylproline fragment **2** would arise from a suitably protected pyrrolen-2-one intermediate such as **13** (Scheme 2). However, racemization of 5-substituted pyrrolenone **14** readily occurs upon deprotection through the aromatic pyrrole **15** that is produced due to the lability of the hydrogen at C5. The acidity is increased by the charge-separated resonance form of the free amide leading to rapid equilibration.[12] Even though a protected pyrrolenone **13** could not be used directly in the microcolin synthesis, a new route to this class of useful compounds was developed by using Bestmann's ketenylidene triphenylphosphorane **11**.[13] This stable ylide is readily obtained as a

Scheme 2



Scheme 3



crystalline solid from (carbomethoxymethylidene)triphenylphosphorane reacted with sodium hexamethylsilazide. The BOC-protected amino aldehyde **12**[14] was added to the Bestmann reagent in THF at 1:1 stoichiometry to give pyrrolenone **13** in 60% yield.

The racemization problem of **13** prompted the decision to use a saturated intermediate **6** for coupling to proline and defer introduction of the double bond to a later step. While **6** could be made from **13** using first hydrogenation followed by protecting group removal, the procedure of Amstutz was found to be most convenient to access **6** from D-glutamic acid (Scheme 3).[15]

Imide formation is commonly performed using an acid chloride reacted with an amide under basic conditions.[16] The key problem to be overcome in this case is the reduced nucleophilicity of the amide nitrogen due to carbonyl delocalization. The solution then is to use a more reactive acylating reagent or increase the nucleophilicity of the amide. With acid-sensitive functionality in the prolyl acylating reagent, we chose to focus on the amide reactivity. The formation of an acid chloride using thionyl chloride becomes problematic when acid-sensitive functionality are present. In the case of proline, protecting group removal and epimerization were observed upon attempted formation of the acid chloride under these known conditions. The coupling of prolyl chloride with lactam **6** under the most promising known conditions with dimethylaniline as solvent proved to be very low

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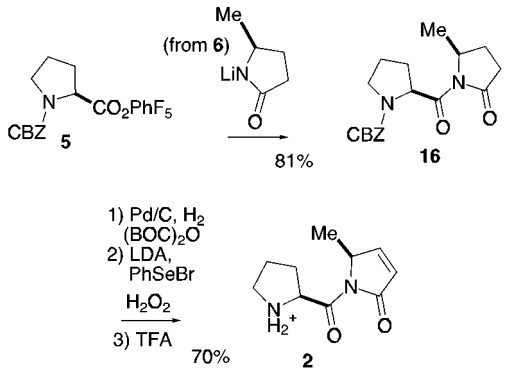
Scheme 4

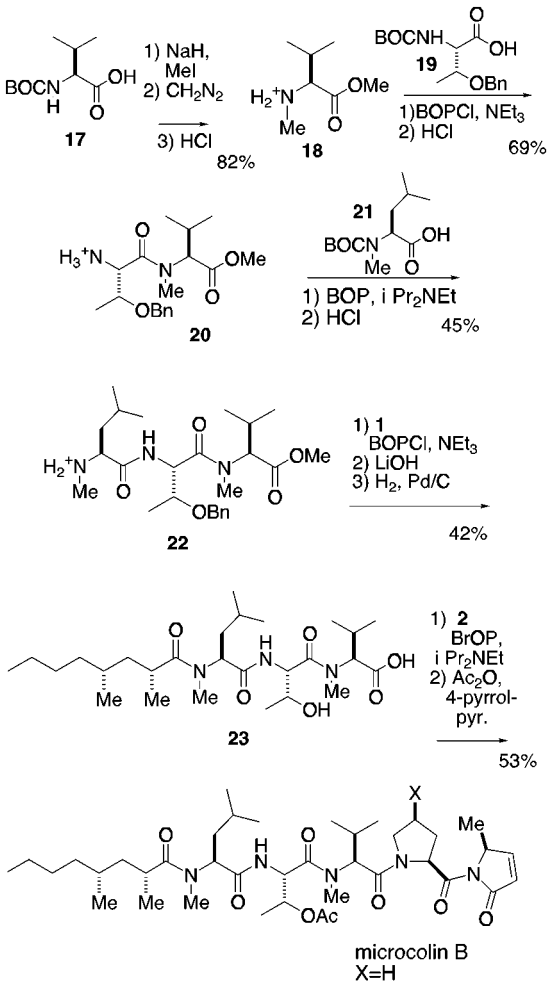


yielding (<15%).[16a] The use of phenyl esters and mixed anhydrides for problematic amide bond-forming reactions[17] prompted our decision to investigate the use of the stable, easily accessible pentafluorophenyl esters for this critical mixed imide formation step. CBZ-protected proline was reacted with pentafluorophenol under standard DCC coupling conditions to give **5** in 91% isolated yield (Scheme 4). Lactam **6** was treated with butyllithium in THF at −78 °C to give the imidate that was then treated with a THF solution of ester **5**. The product **16** was obtained in 81% yield after chromatography as a mixture of CBZ rotamers. The unsaturation was then introduced in the usual fashion using LDA, phenylselenium bromide, and peroxide.[18] Trifluoroacetic acid treatment then gave the known salt **2** as a single isomer in 70% overall yield.[19]

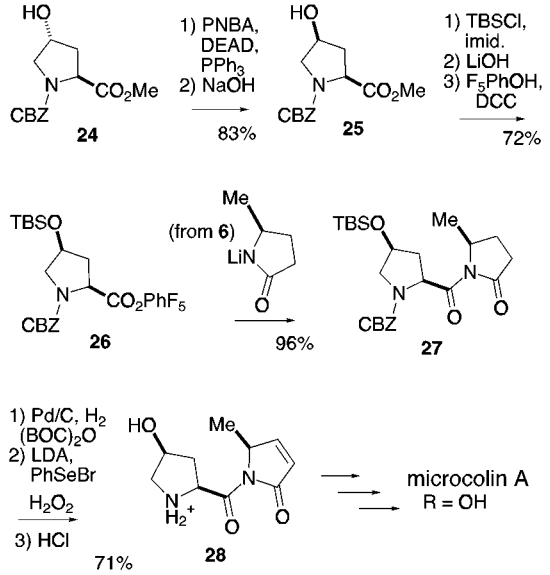
Completion of the synthesis of microcolin B involved formation of the tripeptide **22** following standard procedures (Scheme 5). The *N*-methylations were performed according to the conditions of Benoiton to make compounds **18** and **21**.[20] Coupling of acid **1** with peptide **22** was achieved using BOP-Cl.[21] Methyl ester hydrolysis and hydrogenation gave acylpeptide **23** in 42% overall yield. Coupling with **2** was conducted using BROP (bromotris(dimethylamino)phosphonium hexafluorophosphate) in the presence of diisopropylethylamine.[22] Attachment of the acetate on the threonine side chain was performed using acetic anhydride with added 4-pyrrolidinopyridine in 53% overall yield to give microcolin B that was identical in all respects to the natural material (^{1}H and ^{13}C NMR, IR, MS, and optical rotation).

The new mixed imide reaction was also extended to microcolin A (X = OH) beginning with *trans*-4-hydroxyproline (Scheme 6). After Mitsunobu inversion[23] and hydrolysis, the CBZ-protected methyl ester was converted to silyl ether **26** and reacted with the imidate of **6** as before. The mixed imide product **27** in this case was obtained in 96% yield after purification. This material was then converted to the amine salt **28** used previously for the synthesis of microcolin A[7] for comparison, completing the formal synthesis.

Scheme 5



Scheme 6



In conclusion, we have developed a new direct route to the microcolins A and B using an efficient substrate-directed hydrogenation reaction for the synthesis of acid **1**, providing a new route to chiral 2,4-dimethyl carboxylic acids. The stable pentafluorophenyl ester-based method for imide formation is a general route that should prove applicable to other targets. The route involves nine steps to **1** in 19% overall yield with no chiral auxiliaries compared to the previous route of 29% requiring 25 equiv

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of a key chiral triflate and two chiral auxiliaries. The route to **28**, the key hydroxyprolylpyrrolenone, was made in nine steps counting from *trans*-hydroxyproline, in 41% overall yield compared to the previous nine-step route, that began with *cis*-proline.

Experimental Section

General Methods. All moisture-sensitive reactions were carried out under argon in oven-dried glassware, and solvents were appropriately dried before use. NMR spectra were recorded in chloroform-*d* (unless otherwise indicated) with chemical shifts reported in ppm referenced to residue chloroform (7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C). IR spectra were recorded as thin films on NaCl plates unless otherwise stated. Optical rotations were obtained at 589 nm. Concentrations for optical rotations are reported in g/mL. LR or HR mass spectra were recorded at 70 eV or using FAB. Melting points are uncorrected.

(*S*)-2-Methyl-3-(tetrahydropyranyloxy)propanal (8). A solution of methyl 3-hydroxy-(*S*)-2-methylpropionate (5 g, 42.4 mmol), 3,4-dihydro-2*H*-pyran (DHP, 5.35 g, 63.6 mmol), and pyridinium *p*-toluenesulfonate (PPTS, 1.60 g, 6.36 mmol) in CH_2Cl_2 (150 mL) was stirred at rt for 2 h. It was diluted with Et_2O (150 mL) and washed with half-saturated brine (50 mL) to remove the catalyst. The organic layer was separated and washed with saturated $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated. The essentially pure material was subjected to short-path distillation to give THP ether as a colorless liquid (8.4 g, 98%): bp 90 °C (0.6 mmHg); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.58 (m, 1H), 3.80 (m, 2H), 3.66 (s, 3H), 3.48 (m, 2H), 2.72 (m, 1H), 1.70 (m, 2H), 1.48 (m, 4H), 1.15 (d, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two diastereomers at THP's C-2′ in a ratio of ca. 1:1 δ 175.83, 175.75, 99.5, 98.8, 69.8, 69.5, 62.6, 62.2, 52.1, 40.7, 40.5, 30.94, 30.87, 25.9, 25.8, 19.8, 19.6, 14.5; MS (CI) m/e 203 (M + H)$^+$.

To a stirring solution of the above THP ether (7.90 g, 39.1 mmol) in CH_2Cl_2 (370 mL) at −90 °C was added DIBAL in toluene (1.5 M, 27.4 mL, 41.0 mmol) *via* syringe pump over 40 min. The tip of the needle touched the inner wall of the flask to precool the DIBAL solution before entering the ether solution. After being stirred for 1 h, the reaction was quenched by slowly adding MeOH (32 mL) at −90 °C followed by saturated Rochelle salts solution (Na^+/K^+ tartrate) (230 mL) and allowing the mixture to warm to rt. After vigorous stirring for 3 h, the CH_2Cl_2 layer was collected, and the aqueous phase was washed with CH_2Cl_2 (2 × 110 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The crude was purified by flash chromatography, eluting first with straight hexanes and then with EtOAc: hexanes (1:4) to give 6.46 g (96%) of pure **8**: ^{1}H NMR (200 MHz, $CDCl_3$) mixture of two diastereomers at THP's C-2′ in a ratio of ca. 1:1 δ 9.72 (s, 1H), 4.58 (m, 1H), 3.95 (m, 1H), 3.80 (m, 1H), 3.56 (m, 1H), 3.48 (m, 1H), 2.63 (m, 1H), 1.72 (m, 2H), 1.54 (m, 4H), 1.11 (d, J = 7.0 Hz, 3H, one diastereomer), 1.09 (d, J = 7.0 Hz, 3H, other diastereomer); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two diastereomers δ 204.4, 204.3, 99.6, 99.1, 68.0, 67.7, 62.6, 62.4, 47.2, 47.1, 30.8, 25.8, 19.7, 19.6, 11.2, 11.1s; MS (CI) m/e 173 (M + H)$^+$; FTIR ($CDCl_3$) 2726 cm^{-1}.

(*R*)-3,5-Dimethyl-6-hydro-2*H*-pyran-2-one (4). To a stirring solution of diisopropylamine (DIPA, 5.7 mL, 40.9 mmol) in THF (40 mL) at −15 °C was added dropwise *n*-BuLi in hexane (2.5 M, 16.4 mL, 40.9 mmol) *via* syringe pump over 20 min. After the addition was complete, the reaction mixture was stirred for 15 min and then cooled to −78 °C. To this solution was slowly added ethyl propionate (4.68 mL, 40.9 mmol) *via* syringe over 15 min. The resulting solution was stirred for 1 h at −78 °C. Then, aldehyde **8** (6.40 g, 37.2 mmol) was added dropwise to the vigorously stirring solution at −78 °C over 15 min. After the solution was stirred for 15 min, saturated NH_4Cl (15 mL) was added, and the mixture was allowed to warm to rt. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with H_2O (60 mL) and brine (60 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash chromatography eluting with EtOAc: hexanes (15:85) to give 7.62 g (74.8%) of pure aldol adduct: MS (CI) m/e 275 (M + H)$^+$; FTIR ($CDCl_3$) 3504, 2942, 1732, 1458, 1376, 1260, 1184, 1120, 1032, 904 cm^{-1}.

A mixture of the above aldol adduct (7.5 g, 27.4 mmol) and *p*-toluenesulfonic acid (6.52 g, 32.88 mmol) in benzene (250 mL) was refluxed for 12 h. The water generated was trapped by means of a Dean−Stark apparatus. The reaction mixture was allowed to cool to rt, washed with 10% $NaHCO_3$ (80 mL) and water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. The crude was subjected to vacuum distillation to give 3.27 g (94.7%) of pure **4** as a colorless liquid: $[\alpha]^{25}_D$ −34.7° (*c* 0.1, $CDCl_3$); bp 62 °C (0.6 mmHg); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.47 (dd, J = 3.2, 1.4 Hz, 1H), 4.33 (ddd, J = 10.8, 5.0, 1.0 Hz, 1H), 3.98 (dd, J = 10.8, 8.4 Hz, 1H), 2.63 (m, 1H), 1.88 (t, J = 1.7 Hz, 3H), 1.08 (d, J = 8.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.9, 146.2, 127.7, 72.7, 29.7, 17.6, 16.2; MS (CI) m/e 127 (M + H)$^+$; FTIR ($CDCl_3$) 1718 cm^{-1}.

(3*S*,5*R*)-3,5-Dimethyltetrahydropyran-2-one (3). A mixture of **4** (1.89 g, 15 mmol) and 5% Rh/Al_2O_3 (1.54 g, 0.75 mmol) in Et_2O (150 mL) was stirred under an atmosphere of H_2 (balloon) at −10 °C for 10 h. The reaction was passed through a short plug of silica gel and concentrated to give a mixture of *cis* and *trans* products (7:1, 1.85 g, 96.4%). The diastereomerically pure *cis* product was obtained by recrystallizing the above mixture twice at 4 °C using Et_2O:pentane (*cis*:*trans* 130:1, 41% overall recovery): mp 45−46 °C (lit.[9] mp 41−46 °C); $[\alpha]^{27}_D$ 41.6° (*c* 0.1, $CHCl_3$), (lit.[9] $[\alpha]^{20}_D$ 41.9° (*c* 0.05, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.32 (ddd, J = 11.0, 4.6, 2.2 Hz, 1H), 3.88 (dd, J = 11.0, 9.2 Hz, 1H), 2.56 (m, 1H), 2.11 (m, 2H), 1.27 (m, 1H), 1.26 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.0, 75.3, 37.2, 35.8, 29.0, 17.8, 17.4; MS (CI) m/e 129 (M + H)$^+$; FTIR ($CDCl_3$) 1734 cm^{-1}.

(2*R*,4*S*)-2,4-Dimethyl-5-octen-1-ol (10). To a stirring solution of lactone **3** (0.37 g, 2.89 mmol) in toluene (12 mL) at −60 °C was slowly added DIBAL in toluene (1.5 M, 2.02 mL, 3.03 mmol). The reaction mixture was stirred for 1 h, quenched by slowly adding methanol (2.5 mL) followed by saturated Rochelle salts (Na^+/K^+ tartrate) (15 mL), and warmed to rt. After the mixture was vigorously stirred for 3 h, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. The crude was purified by flash chromatography eluting first with straight hexanes to remove the remaining toluene followed by EtOAc:hexanes (1:4) to give 0.362 g (96%) of intermediate lactol as a colorless oil: MS (CI) m/e 131 (M + H)$^+$; FTIR (neat) 3394, 2954, 2928, 1460, 1378, 1272, 1184, 1130, 1078, 1044, 1022, 990 cm^{-1}.

To a stirring suspension of propyltriphenylphosphonium bromide (2.36 g, 6.13 mmol) in THF (6 mL) was added *n*-BuLi in hexane (2.5 M, 2.4 mL, 6.0 mmol) at 0 °C over 10 min. The mixture was stirred for 45 min at rt and then cooled to 0 °C. To this mixture was cannulated the above lactol (0.362 g, 2.78 mmol) in THF (6 mL). The reaction was then refluxed for 3 h. It was then cooled to rt and quenched with ice−water. Saturated NaCl solution (10 mL) was added, and the mixture was extracted with Et_2O:petroleum ether (40−60 °C) (1:1) (3 × 100 mL). The organic layers were combined and washed with brine, dried ($MgSO_4$) and concentrated. The crude was purified by flash chromatography eluting with EtOAc:hexanes (1:9) to give 0.36 g (83.4%) of pure **10** as a colorless oil (*Z*:*E* 8:1): ^{1}H NMR (200 MHz, $CDCl_3$) *Z* isomer δ 5.29 (dt, J = 11.2, 7.6 Hz, 1H), 5.01 (dd, J = 11.0, 9.8 Hz, 1H), 3.42 (dd, J = 10.4, 6.0 Hz, 1H), 3.35 (dd, J = 10.4, 6.4 Hz, 1H), 2.53 (m, 1H), 1.99 (m, 3H), 1.57 (m, 1H), 1.27 (m, 2H), 0.96 (d, J = 7.2 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) *Z* isomer δ 184.0, 134.6, 131.8, 41.3, 37.9, 29.9, 22.1, 21.3, 17.1, 15.0; MS (CI) m/e 157 (M + H)$^+$.

(2*R*,4*R*)-2,4-Dimethyloctanoic Acid (1). A solution of **10** (0.362 g, 2.32 mmol) and pyridinium dichromate (PDC, 4.36 g, 11.6 mmol) in DMF (8.5 mL) was stirred at rt for 10 h. It was then poured into 40 mL of H_2O and extracted with Et_2O (3 × 80 mL). The ether layers were combined and washed

with brine, dried ($MgSO_4$), and concentrated. The crude was purified by column chromatography eluting with EtOAc:hexanes (5:95) to give 0.294 g (75%) of unsaturated acid (*Z*:*E* 8:1) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) *Z* isomer δ 10.6 (bs, 1H), 5.34 (dt, J = 10.5, 7.5 Hz, 1H), 5.06 (dd, J = 10.5, 8.8 Hz, 1H), 2.53 (m, 1H), 2.46 (m, 1H), 2.04 (m, 2H), 1.66 (ddd, J = 13.5, 9.5, 5.8 Hz, 1H), 1.38 (ddd, J = 13.5, 8.3, 5.3 Hz, 1H), 1.15 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) *Z* isomer δ 184.3, 134.6, 131.8, 41.3, 29.9, 22.0, 21.3, 17.0, 15.0; MS (CI) *m*/*e* 171 (M + H)$^+$; FTIR ($CDCl_3$) 2964, 2936, 2874, 1708, 1464, 1416, 1378, 1278, 1236, 1208, 1132, 1070, 954, 808, 744 cm^{-1}.

A mixture of the above unsaturated acid (88 mg, 0.52 mmol) and 5% Rh/Al_2O_3 (106 mg, 0.052 mmol) in MeOH (7 mL) was stirred under an H_2 atmosphere (balloon) at 4 °C for 4 h. The reaction mixture was then filtered through a pad of silica gel to remove the catalyst. The filtrate was concentrated to give 86 mg (96.5%) of pure **1** (*syn*:*anti* 14:1): $[\alpha]^{22}_D$ −7.9° (*c* 0.015, MeOH) (lit.[7] $[\alpha]^{25}_D$ −8.4° (*c* 0.09, MeOH)); ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.0 (bs, 1H), 2.57 (m, 1H), 1.73 (ddd, J = 5.6, 8.4, 14.0 Hz, 1H), 1.47 (m, 1H) 1.26 (m, 7H), 1.18 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 6.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 184.4, 41.7, 37.8, 37.2, 31.2, 29.5, 23.4, 20.0, 18.3, 14.6; MS (CI) *m*/*e* 173 (M + H)$^+$; FTIR ($CDCl_3$) 1708 cm^{-1}.

Ketenylidenetriphenylphosphorane (11). To a stirring solution of methyl (triphenylphosphoranylidene)acetate (5 g, 15.0 mmol) in benzene (100 mL) at 0 °C was added dropwise a solution of sodium bis(trimethylsilyl)amide (NHMDS, 1 M, 16.5 mL, 16.5 mmol). Once the addition was complete, the reaction was heated at 60 °C for 20 h. The reaction was then allowed to cool to rt and concentrated to give a white residue. The residue was recrystallized from toluene to give 3.14 g (87%) of pure **11** as white needles: FTIR (KBr) 2099 cm^{-1}.

1-Boc-(*S*)-5-methyl-2-pyrrolinone (13). To a stirring solution of **11** (0.18 g, 0.58 mmol) in THF (1.2 mL) was added dropwise a solution of aldehyde **12** (0.1 g, 0.58 mmol) in THF (1.2 mL). The reaction mixture was stirred at rt for 20 h and then concentrated to give an orange oil. The crude was purified by flash chromatography eluting with EtOAc:hexanes (1:1) to give 68.4 mg (60%) of pure **13**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.10 (dd, J = 6.1, 2.1 Hz, 1H), 6.07 (dd, J = 6.1, 1.6 Hz, 1H), 4.62 (m, 1H), 1.57 (s, 9H), 1.44 (d, J = 6.8 Hz, 3H); FTIR ($CDCl_3$) 1774, 1716 cm^{-1}.

Pentafluorophenyl (*S*)-*N*-Cbz-prolinate (5). To a stirring solution of *N*-Cbz-L-proline (2.00 g, 8.02 mmol) and pentafluorophenol (1.63 g, 8.82 mmol) in anhydrous EtOAc (20 mL) at 0 °C was added dicyclohexylcarbodiimide (DCC, 1.82 g, 8.82 mmol). The reaction mixture was warmed to rt and stirred for 2.5 h. The reaction then was diluted with hexanes (150 mL), and the resulting white precipitate was removed by vacuum filtration. The precipitate was washed with cold EtOAc (250 mL). The filtrate and wash were combined and concentrated. The crude was purified by flash chromatography eluting with EtOAc:hexanes (3:7) to give 3.2 g (96%) of pure **5** as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 1:1 δ 7.34 (m, 5H), 5.26 (d, J = 12.4 Hz, 1H, one rotamer), 5.24 (d, J = 12.4 Hz, 1H, other rotamer), 5.21 (d, J = 12.4 Hz, 1H, one rotamer), 5.09 (d, J = 12.4 Hz, 1H, other rotamer), 4.74 (dd, J = 9.2, 3.8 Hz, 1H, one rotamer), 4.70 (dd, J = 9.2, 3.6 Hz, 1H, other rotamer), 3.64 (m, 2H), 2.40 (m, 1H), 2.28 (m, 1H), 2.04 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two rotamers δ 169.5, 169.3, 155.3, 154.6, 136.9, 136.6, 128.9, 128.8, 128.4, 68.0, 67.8, 59.4, 58.9, 47.5, 47.0, 31.7, 30.6, 24.9, 24.0; MS (CI) *m*/*e* 416 (M + H)$^+$.

(*S*)-1-[(*S*)-*N*-Cbz-prolyl]-5-methyl-2-pyrrolidinone (16). To a stirring solution of **6** (0.55 g, 5.60 mmol) in THF (10 mL) at −78 °C was slowly added *n*-BuLi (2.5 M, 2.24 mL, 5.60 mmol) in hexane. After the solution was stirred at −78 °C for 15 min, a solution of pentafluorophenyl ester **5** (2.33 g, 5.60 mmol) in THF (10 mL) cooled to −78 °C was cannulated to the reaction, and the mixture was stirred at −78 °C for 4 h. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and allowed to warm to rt. The reaction mixture was extracted with EtOAc (3 × 100 mL), and extracts were washed with H_2O (60 mL) and brine (60 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash chromatography eluting with EtOAc:hexanes (2:3) to give 1.50 g (81%) of pure **16** as a colorless oil: $[\alpha]^{22}_D$ −46° (*c* 0.092, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 1:1 δ 7.31 (m, 5H), 5.39 (dd, J = 9.5, 3.0 Hz, 1H, one rotamer), 5.34 (dd, J = 9.0, 3.5 Hz, 1H, other rotamer), 5.19 (d, J = 13.0 Hz, 1H, one rotamer), 5.10 (d, J = 13.0 Hz, 1H, other rotamer), 5.06 (d, J = 12.5 Hz, 1H, one rotamer), 5.03 (d, J = 12.5 Hz, 1H, other rotamer), 4.48 (m, 1H, one rotamer), 4.37 (m, 1H, other rotamer), 3.65 (m, 2H), 3.58 (dt, J = 10.0, 7.5 Hz, 1H, one rotamer), 3.52 (dt, J = 10.5 Hz, 7.5 Hz, 1H, other rotamer), 2.78 (ddd, J = 18.0, 12.4, 9.0 Hz, 1H, one rotamer), 2.62 (ddd, J = 18.0, 11.5, 9.5 Hz, 1H, other rotamer), 2.46 (m, 2H), 2.18 (m, 1H), 1.90 (m, 1H), 1.75 (dt, J = 9.5, 1.5 Hz, 1H, one rotamer), 1.62 (dt, J = 9.5, 1.5 Hz, 1H, other rotamer), 1.36 (d J = 6.5 Hz, 3H, one rotamer), 0.95 (d J = 6.0 Hz, 3H, other rotamer); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two rotamers δ 175.8, 173.9, 155.2, 154.7, 173.3, 137.2, 128.9, 128.8, 128.3, 128.2, 128.1, 127.8, 67.3, 61.4, 60.6, 53.8, 53.7, 47.9, 47.4, 32.4, 31.3, 30.4, 25.9, 25.7, 24.4, 23.5, 19.8, 19.2; MS (CI) *m*/*e* 331 (M + H)$^+$.

(*S*)-1-[(*S*)-Prolyl]-5-methyl-2-pyrrolenone Trifluoroacetate (2). A mixture of **16** (1.46 g, 4.42 mmol), di-*tert*-butyl dicarbonate (1.24 g, 5.66 mmol), and 10% Pd/C (0.235 g, 0.22 mmol) in MeOH (65 mL) was stirred under an atmosphere of hydrogen (balloon) at rt for 1 h. The catalyst was filtered off, and the filtrate was concentrated. The crude was purified by flash chromatography eluting with EtOAc:hexanes (1:1) to give 1.31 g (100%) of the Boc-protected product as a white solid: $[\alpha]^{22}_D$ −40.1° (*c* 0.057, $CHCl_3$); mp 46 °C; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 1:1 δ 5.28 (t, J = 10.8 Hz, 1H), 4.46 (m, 1H), 3.60 (m, 1H, one rotamer), 3.55 (m, 1H, other rotamer), 3.48 (m, 1H, one rotamer), 3.40 (m, 1H, other rotamer), 2.74 (m, 1H), 2.50 (dd, J = 17.5, 9.0 Hz, 1H, one rotamer), 2.45 (dd, J = 18.0, 9.5 Hz, 1H, other rotamer), 2.33 (m, 1H), 2.19 (m, 1H), 1.86 (m, 3H), 1.74 (m, 1H), 1.44 (s, 9H, one rotamer), 1.38 (s, 9H, other rotamer), 1.34 (d, J = 5.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two rotamers δ 174.8, 173.6, 173.3, 153.8, 153.4, 78.9, 59.9, 59.8, 52.9, 52.8, 46.6, 46.3, 31.5, 30.3, 29.4, 28.1, 28.0, 27.9, 24.9, 24.8, 23.5, 22.5, 19.1, 19.0; MS (CI) *m*/*e* 297 (M + H)$^+$.

A 0.5 M solution of LDA was prepared by dissolving freshly distilled diisopropylamine (DIPA, 0.70 mL, 5.0 mmol) in THF (7.3 mL) and cooling it to −78 °C. To this solution was added a solution of *n*-BuLi in hexane (2 mL, 5.0 mmol). The solution was stirred at −78 °C for 30 min before LDA was ready for use. To a stirring solution of the above Boc-protected compound (0.5 g, 1.69 mmol) in THF (6 mL) at −78 °C was added dropwise the LDA solution (3.72 mL, 1.86 mmol). After the solution was stirred for 10 min, a solution of phenylselenyl bromide (0.439 g, 1.86 mmol) in THF (3 mL) was added rapidly dropwise. The reaction mixture was warmed to 0 °C and then distilled H_2O (0.7 mL), and acetic acid (0.2 mL) and 30% hydrogen peroxide (0.93 mL) were added. After the solution was stirred for 30 min, saturated $NaHCO_3$ (18 mL) and H_2O (18 mL) were added to the reaction mixture, and the resulting solution was extracted with EtOAc (3 × 30 mL). The extracts were washed with H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated. The crude was purified by flash chromatography eluting with EtOAc:hexanes (3:7) to give 0.35 g (70.4%) of the pure corresponding pyrrolenone as a colorless oil: $[\alpha]^{22}_D$ −85° (*c* 0.011, $CHCl_3$) (lit.[19] $[\alpha]^{22}_D$ −92° (*c* 0.011, $CHCl_3$)); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 2:1 δ 7.26 (dd, J = 6.0, 2 Hz, 1H, major rotamer), 7.22 (dd, J = 6.0, 1.5 Hz, 1H, minor rotamer), 6.09 (dd, J = 6.0, 1.0 Hz, 1H, major rotamer), 6.05 (dd, J = 6.0, 1.0 Hz, 1H, minor rotamer), 5.34 (dd, J = 9.0, 3.0 Hz, 1H), 4.76 (dq, J = 6.5, 2.0 Hz, 1H), 3.64 (m, 1H, major rotamer), 3.58 (m, 1H, minor rotamer), 3.51 (m, 1H, major rotamer), 3.46 (m, 1H, minor rotamer), 2.37 (m, 1H), 1.89 (m, 2H), 1.63 (m, 1H), 1.49 (d, J =7.0 Hz, 3H, major rotamer), 1.47 (d, J = 7.0 Hz, 3H, minor rotamer), 1.45 (s, 9H, minor rotamer), 1.38 (s, 9H, major rotamer); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two rotamers δ 173.1, 173.0, 169.9, 169.8, 154.0, 153.8, 125.5, 125.4, 79.5, 59.8, 58.0, 47.1, 46.8, 30.6, 29.6, 28.3, 23.9, 22.9, 17.8, 17.1; MS (CI) *m*/*e* 295 (M + H)$^+$.

The above pyrrolenone (78 mg, 0.27 mmol) was dissolved in a 1:1 mixture of trifluoroacetic acid/dichloromethane (0.36 mL, 1:1, v/v). After being stirred at rt for 30 min, the reaction was concentrated. The remaining trifluoroacetic acid was azeotroped with hexanes five times to give 91 mg (100%) of trifluoro acetate **2** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, J = 6.0, 2.0 Hz, 1H), 6.12 (dd, J = 6.0, 1.3 Hz, 1H), 5.30 (t, J = 7.3 Hz, 1H), 4.78 (q, J = 6.5 Hz, 1H), 3.53 (t, J = 6.5 Hz, 1H), 2.68 (m, 1H), 2.17 (m, 1H), 2.02 (m, 2H), 1.50 (d, J = 6.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1, 168.4, 155.8, 125.3, 61.2, 59.0, 29.5, 26.7, 24.2, 17.7; MS (CI) m/e 195 $(M + H)^+$; HRMS calcd for $C_{10}H_{15}N_2O_2$ 195.1134, found 195.1130; FTIR ($CDCl_3$) 1734, 1698 cm^{-1}.

***N*-Me-Val-OMe·HCl (18).** To a stirring solution of *N*-Boc-Val (2.0 g, 9.2 mmol) and methyl iodide (5.73 mL, 92 mmol) in THF (34 mL) was added a 60% mineral oil dispersion of sodium hydride (1.10 g, 92 mmol) in several portions. After being stirred for 24 h at rt, the reaction was quenched by adding EtOAc (5 mL) and H_2O (5 mL). The mixture was concentrated, and the residue was partitioned between Et_2O (50 mL) and H_2O (100 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL). The Et_2O extracts were washed with saturated $NaHCO_3$ (1 × 50 mL). The aqueous layers were combined and acidified with 5% citric acid to pH 3. This solution was then extracted with EtOAc (3 × 200 mL). The combined extracts were washed with H_2O (1 × 100 mL), 5% $Na_2S_2O_4$ (1 × 100 mL), and brine (1 × 100 mL), dried ($MgSO_4$), and concentrated to give 1.93 g (91.0%) of pure *N*-Boc-*N*-Me-Val: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.93 (d, J = 10.6 Hz, 1H), 2.89 (s, 3H), 2.35 (m, 1H), 1.48 (s, 9H), 1.04 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 1H); MS (CI) m/e 232 $(M + H)^+$.

The above acid was converted to the corresponding methyl ester using the following procedure: potassium hydroxide (2.15 g, 38.3 mmol) was dissolved in an EtOH/Et_2O mixture (60 mL, 2:1). This solution was treated with DIAZALD (1.64 g, 7.65 mmol). The diazomethane generated at rt was blown *via* a stream of nitrogen into a flask containing *N*-Boc-*N*-Me-Val (1.18 g, 5.1 mmol) in Et_2O at 0 °C. Nitrogen was continued to be blown into the flask until the yellow color in both flasks disappeared. The ether solution was concentrated to give 1.22 g (98%) of pure methyl ester as a colorless oil: $[\alpha]^{25}_D$ −87.3° (c 0.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.27 (d, J = 10.4 Hz, 1H), 3.70 (s, 3H), 2.81 (s, 3H), 2.15 (m, 1H), 1.45 (s, 9H), 0.98 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 1H); MS (CI) m/e 246 $(M + H)^+$; FTIR ($CDCl_3$) 1742, 1700 cm^{-1}.

The above ester (1.2 g, 4.9 mmol) was dissolved in a 4 N HCl−dioxane solution (100 mL, 400 mmol) and stirred at rt for 1.5 h. The reaction was concentrated to give 0.816 g (92%) of **18**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.35 (bs, 1H), 9.61 (bs, 1H), 3.86 (s, 3H), 3.60 (m, 1H), 2.77 (s, 3H), 2.61 (m, 1H), 1.18 (d, J = 7.4 Hz, 3H), 1.14 (d, J = 7.4 Hz, 3H); MS (CI) m/e 146 $(M + H)^+$; FTIR ($CDCl_3$) 3752, 1746, 1012 cm^{-1}.

OBn-Thr-*N*-Me-Val-OMe·HCl (20). *N*-Boc-OBn-Thr (2.07 g, 6.69 mmol) and **18** (0.81 g, 4.46 mmol) were dissolved in CH_2Cl_2 (15 mL). This solution was treated with BOP-Cl (1.70 g, 6.69 mmol) and triethylamine (2.05 mL, 14.7 mmol). After being stirred at rt for 1.5 h, the reaction was quenched with 10% citric acid (1 × 80 mL) and extracted with EtOAc (3 × 80 mL). The extracts were washed with 10% citric acid (40 mL), saturated $NaHCO_3$ (1 × 100 mL), and brine (1 × 100 mL), dried ($MgSO_4$) and concentrated. The crude was purified by flash chromatography eluting with EtOAc:hexanes (3:7) to give 1.40 g (72.2%) of dipeptide as a colorless oil: $[\alpha]^{25}_D$ −51.6° (c 0.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.49 (d, J = 8.4 Hz, 1H), 4.94 (d, J = 10.6 Hz, 1H), 4.72 (dd, J = 4.0, 2.4 Hz, 1H), 4.56 (dd, J = 11.5, 4.4 Hz, 1H), 4.51 (dd, J = 11.5, 5.0 Hz, 1H), 3.81 (m, 1H), 3.63 (s, 1H), 3.07 (s, 1H), 2.20 (m, 1H), 1.42 (s, 9H), 1.20 (d, J = 6.2 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0, 157.5, 138.8, 130.1, 128.8, 128.3, 128.1, 80.1, 76.2, 71.9, 62.3, 55.0, 52.2, 32.0, 28.8, 27.5, 20.3, 19.2, 16.8; MS (CI) m/e 437 $(M + H)^+$; FTIR ($CDCl_3$) 3334, 1740, 1712, 1648, 740, 698 cm^{-1}.

The above dipeptide (1.15 g, 2.64 mmol) was dissolved in a 4 N HCl−dioxane solution (53 mL, 80 mmol) and stirred at rt for 1.5 h. The reaction was concentrated to give 0.95 g (96%) of crude **20**. MS (CI) m/e 337 $(M + H)^+$.

***N*-Me-Leu-OBn-Thr-*N*-Me-Val-OMe·HCl (22).** The dipeptide HCl salt **20** (0.926 g, 2.49 mmol) and *N*-Boc-*N*-Me-Leu (0.671 g, 2.74 mmol) were dissolved in CH_3CN (7 mL). This solution was treated with BOP (1.21 g, 2.74 mmol) and diisopropylethylamine (DIEA, 1.12 mL, 6.23 mmol). After being stirred at rt for 3 h, the reaction was concentrated, and the residue was partitioned between 3 N HCl (50 mL) and EtOAc (70 mL). The layers were separated, and the aqueous was extracted with EtOAc (2 × 70 mL). The organic layers were combined and washed with saturated $NaHCO_3$ (70 mL) and brine (70 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash chromatography eluting with EtOAc:hexanes (2:3) to give 0.63 g (45%) of pure tripeptide as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (m, 5H), 6.90 (bs, 1H), 4.96 (dd, J = 8.4, 4.2 Hz, 1H), 4.91 (d, J =10.2 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.42 (dd, J = 8.4, 4.6 Hz, 1H), 3.82 (m, 1H), 3.60 (s, 3H), 3.03 (s, 3H), 2.70 (s, 3H), 2.18 (m, 1H), 1.65 (m, 2H), 1.48 (m, 1H), 1.40 (s, 9H), 1.14 (d, J= 6.6 Hz, 3H), 0.98 (d, J = 6.2 Hz, 3H), 0.90 (d, J = 6.0 Hz, 3H), 0.87 (d, J = 6.2 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H); MS (CI) m/e 564 $(M + H)^+$; FTIR ($CDCl_3$) 3328, 1742, 1684 cm^{-1}.

The above tripeptide (0.423 g, 0.751 mmol) was dissolved in a 4 N HCl−dioxane solution (15 mL, 60 mmol) and stirred at rt for 1.5 h. The reaction mixture was concentrated to give crude **22** (0.37 g, 99%): MS (CI) m/e 464 $(M + H)^+$.

((2*R*,4*R*)-2,4-Dimethyloctanoyl)-*N*-Me-Leu-OBn-Thr-*N*-Me-Val (23). Tripeptide HCl salt **22** (87 mg, 0.174 mmol) and (2*R*,4*R*)-2,4-dimethyloctanoic acid (**1**) (30 mg, 0.174 mmol) were dissolved in CH_2Cl_2 (2 mL). This solution was treated with BOP-Cl (44 mg, 0.174 mmol) and triethylamine (48 μL, 0.349 mmol). After being stirred at rt for 1.5 h, the reaction was quenched with 10% citric acid (2.5 mL) and extracted with EtOAc (3 × 10 mL). The extracts were washed with 10% citric acid (2.5 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash chromatography eluting with EtOAc:hexanes (2:3) to give 52 mg (49%) of pure ((2*R*,4*R*)-2,4-dimethyloctanoyl-*N*-Me-Leu-OBn-Thr-*N*-Me-Val-OMe as a colorless oil: $[\alpha]^{23}_D$ −120.4° (c 0.0026, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.98 (d, J = 7.5 Hz, 1H), 5.28 (dd, J = 10.0, 5.5 Hz, 1H), 4.95 (dd, J = 7.5, 5.0 Hz, 1H), 4.92 (d, J = 10.5 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 11.5 Hz, 1H), 3.82 (m, 1H), 3.63 (s, 3H), 3.06 (s, 3H), 2.87 (s, 3H), 2.73 (m, 1H), 2.21 (m, 1H), 1.70 (m, 3H), 1.38 (m, 1H), 1.25 (m, 6H), 1.18 (d, J = 6.5 Hz, 3H), 1.13 (d, J = 6.0 Hz, 3H), 1.07 (m, 1H), 1.04 (m, 1H), 0.99 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H); MS (CI) m/e 618 $(M + H)^+$.

To a stirring and cooled (0 °C) solution of the above tripeptide (42 mg, 0.068 mmol) in THF/MeOH/H_2O (3:1:1, 4.5 mL) was added LiOH·H_2O (9 mg, 0.2 mmol). After being stirred for 12 h, the reaction was quenched with aqueous NH_4Cl (2 mL) and extracted with EtOAc (3 × 25 mL). The extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to give 36.8 mg of acid (90%): $[\alpha]^{22}_D$ −74° (c 0.012, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 5H), 7.15 (bs, 1H), 5.29 (dd, J = 10.0, 6.5 Hz, 1H), 5.01 (t, J =6.5 Hz, 1H), 4.61 (bs, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 3.86 (m, 1H), 3.14 (s, 3H), 2.90 (s, 3H), 2.73 (m, 1H), 2.34 (m, 1H), 1.70 (m, 3H), 1.38 (m, 1H), 1.25 (m, 6H), 1.16 (d, J = 7.0 Hz, 3H), 1.12 (d, J = 6.5 Hz, 3H), 1.08 (m, 1H), 1.03 (d, J = 6.0 Hz, 3H), 1.00 (m, 1H), 0.98 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.88 (t, J = 6.5 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 6.0 Hz, 3H); MS (CI) m/e 618 $(M + H)^+$.

A mixture of the above acid (36 mg, 0.060 mmol) and 10% Pd/C (6.3 mg, 0.006 mmol) in EtOH (1.5 mL) was stirred under an atmosphere of hydrogen (balloon) at rt for 6 h. The catalyst was filtered off, and the filtrate was concentrated to give 29.5 mg (96%) of **23** as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 1:1 δ 7.37 (d, J = 8.6 Hz, 1H, one rotamer), 7.25 (d, J = 8.4 Hz, 1H, other rotamer), 5.32 (dd, J = 10.6, 4.7 Hz, 1H, one rotamer), 5.28 (dd, J =

10.6, 5.0 Hz, 1H, other rotamer), 4.80 (t, J =9.4 Hz, 1H, one rotamer), 4.78 (t, J =9.4 Hz, 1H, other rotamer), 4.26 (d, J = 11.1 Hz, 1H, one rotamer), 4.19 (d, J = 11.1 Hz, 1H, other rotamer), 3.67 (m, 1H), 3.12 (s, 3H, one rotamer), 3.00 (s, 3H, one rotamer), 2.97 (s, 3H, other rotamer), 2.88 (s, 3H, other rotamer), 2.80 (m, 1H), 2.26 (m, 1H), 1.70 (m, 3H), 1.39 (m, 1H), 1.25 (m, 6H), 1.15 (d, J = 7.0 Hz, 3H), 1.12 (d, J = 6.5 Hz, 3H), 1.08 (m, 1H), 1.05 (d, J = 6.2 Hz, 3H), 1.00 (m, 1H), 0.94 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.88 (t, J= 6.5 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.0 Hz, 3H); MS (CI) m/e 514 $(M + H)^+$.

Desacetylmicrocolin B. 23 (10.8 mg, 0.0195 mmol) and imide **2** were dissolved in CH_2Cl_2 (0.5 mL). This solution was treated with BROP (Aldrich, 7.6 mg, 0.0195 mmol) and diisopropylethylamine (DIEA, 10 μL, 0.058 mmol). After being stirred at rt for 12 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with saturated NH_4Cl (5 mL), saturated $NaHCO_3$ (5 mL), and brine (5 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash chromatography eluting with EtOAc:hexanes (7:3) to give 7.43 mg (55%) of pure desacetylmicrocolin B as a colorless oil: $[\alpha]^{23}_D$ −156° (c 0.001, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (dd, J = 6.5, 2.0 Hz, 1H), 6.96 (d, J = 9.5 Hz, 1H), 6.06 (dd, J = 6.0, 1.5 Hz, 1H), 5.46 (dd, J = 8.5, 5.0 Hz, 1H), 5.22 (dd, J = 8.5, 7.0 Hz, 1H), 5.02 (d, J = 11.5 Hz, 1H), 4.77 (q, J = 7.0 Hz, 1H), 4.76 (d, J = 8.0 Hz, 1H), 4.09 (dq, J = 6.0, 1.5 Hz, 1H), 3.80 (m, 2H), 3.09 (s, 3H), 2.97 (s, 3H), 2.83 (m, 1H), 2.38 (ddd, J = 15.0, 12.5, 7.0 Hz, 1H), 2.28 (m, 1H), 2.04 (m, 1H), 1.95 (m, 1H), 1.88 (m, 1H), 1.85 (m, 1H), 1.73 (ddd, J = 14.5, 10.5, 4.5 Hz, 1H), 1.57 (ddd, J = 14.5, 10.0, 5.0 Hz, 1H), 1.46 (d, J = 6.5 Hz, 3H), 1.41 (m, 2H), 1.25 (m, 6H), 1.12 (d, J = 6.5 Hz, 3H), 1.09 (m, 1H), 1.06 (d, J = 6.0 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.87 (t, J = 6.5 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H); FABMS 690.5 $(M + H)^+$, HR-FABMS calcd for $C_{37}H_{64}N_5O_7$ 690.4806, found 690.4791.

Microcolin B. Desacetylmicrocolin B (6.1 mg, 0.0085 mmol) was dissolved in CH_2Cl_2 (0.5 mL). This solution was treated with 4-pyrrolidinopyridine (2.7 mg, 0.0257 mmol) followed by acetic anhydride (2.5 μL, 0.0266 mmol). After being stirred at rt for 6 h, the reaction mixture was concentrated, and the residue was purified by flash chromatography eluting with EtOAc:hexanes (7:3) to give 6.1 mg (96%) of pure microcolin B as a clear glass: $[\alpha]^{25}_D$ −168.3° (c 0.001, EtOH) (lit.[3] $[\alpha]^{25}_D$ −174° (c 0.005, EtOH)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (dd, J = 6.0, 1.5 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 6.06 (dd, J = 6.0, 1.5 Hz, 1H), 5.46 (dd, J = 8.5, 5.0 Hz, 1H), 5.28 (dd, J = 10.5, 5.5 Hz, 1H), 5.26 (q, J = 6.5 Hz, 1H), 5.05 (d, J = 11.0 Hz, 1H), 4.97 (dd, J = 9.0, 3.5 Hz, 1H), 4.76 (q, J = 6.5 Hz, 1H), 3.79 (ddd, J = 16.5, 10.0, 6.5 Hz, 1H), 3.71 (ddd, J = 16.5, 10.0, 6.5 Hz, 1H), 3.12 (s, 3H), 2.96 (s, 3H), 2.84 (m, 1H), 2.42 (m, 1H), 2.26 (m, 1H), 2.01 (m, 2H), 2.00 (s, 3H), 1.87 (m, 1H), 1.85 (m, 1H), 1.73 (ddd, J = 14.5, 10.5, 4.5 Hz, 1H), 1.57 (ddd, J = 15.0, 9.5, 5.5 Hz, 1H), 1.46 (d, J = 6.5 Hz, 3H), 1.41 (m, 1H), 1.27 (m, 1H), 1.26 (m, 1H), 1.25 (m, 4H), 1.18 (m, 1H), 1.16 (d, J = 6.5 Hz, 3H), 1.13 (d, J = 6.5 Hz, 3H), 1.09 (m, 1H), 1.00 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 6.5 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H), 0.80 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 172.1, 171.3, 169.9, 169.84, 169.79, 168.4, 153.8, 125.6, 68.8, 60.1, 59.4, 58.2, 53.9, 52.1, 48.1, 42.0, 37.2, 36.0, 33.9, 30.9, 30.6, 30.5, 29.2, 29.0, 27.4, 24.9, 24.7, 23.5, 23.0, 21.7, 21.1, 19.7, 18.9, 18.5, 18.3, 17.3 (2), 14.2; FABMS 732.5 $(M + H)^+$; HR-FABMS calcd for $C_{39}H_{66}N_5O_8$ 732.4911, found 732.4896.

Methyl (2*S*,4*R*)-*N*-Cbz-4-hydroxyprolinate (24). Using the DIAZALD procedure outlined for **18**, (2*S*,4*R*)-*N*-Cbz-4-hydroxyproline (5.0 g, 18.9 mmol) was converted to its corresponding methyl ester **24** to yield 5.26 g (100%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 3:2 δ 7.32 (m, 5H), 5.11 (m, 2H), 4.46 (m, 2H), 3.73 (s, 3H, minor rotamer), 3.62 (m, 2H), 3.53 (s, 3H, major rotamer), 2.86 (bs, 1H), 2.30 (m, 1H), 2.03 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two rotamers δ 173.1, 173.0, 155.0, 154.5, 136.2, 136.0, 128.3,128.2, 127.9, 127.7, 127.6, 69.8, 69.1, 67.1, 57.8, 57.6, 55.1, 54.5, 52.3, 52.0, 38.0, 38.2; MS (CI) m/e 280 $(M + H)^+$.

Methyl (2*S*,4*S*)-*N*-Cbz-4-hydroxyprolinate (25). To a stirring solution of the ester **24** (5.26 g, 18.9 mmol) in THF (150 mL) was added *p*-nitrobenzoic acid (PNBA, 12.6 g, 75.8 mmol) followed by Ph_3P (19.8 g, 75.4 mmol). The solution was then cooled to 0 °C, and diethyl azodicarboxylate (DEAD, 13.2 g, 75.6 mmol) was added dropwise over ca. 10 min. After being stirred at rt for 18 h, the reaction mixture was concentrated to give a thick yellow oil. Et_2O and a small amount of hexane was added, and the reaction mixture was stirred until a precipitate formed. The precipitate was removed by vacuum filtration, and the filter cake was washed with Et_2O/hexane (1:1). The filtrates were concentrated to give crude PNBA ester. Flash chromatography eluting with a gradient between EtOAc:hexanes (1:9) and EtOAc:hexanes (1:1) gave 7.13 g (88%) of pure PNBA ester as a white solid: mp 112 °C; $[\alpha]^{25}_D$ −19.5° (c 0.062, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 1:1 δ 8.30 (d, J = 8.5 Hz, 2H), 8.15 (d, J = 8.5 Hz, 2H), 7.36 (m, 5H), 5.61 (m, 1H), 5.21 (m, 2H), 4.64 (m, 1H), 3.89 (m, 2H), 3.72 (s, 3H, one rotamer), 3.58 (s, 3H, other rotamer), 2.55 (m, 2H).

The above PNBA ester (2.5 g, 5.84 mmol) was treated with 1 N NaOH (5.2 mL) in MeOH (30 mL) at 0 °C for 15 min. Saturated $NaHSO_4$ (25 mL) was added, and the mixture was extracted with EtOAc (3 × 40 mL). The combined extracts were washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash chromatography eluting with a gradient between EtOAc: hexanes (1:9) and EtOAc/hexanes (1:1) to give 1.54 g (94.4%) of pure **25** as a colorless oil: $[\alpha]^{25}_D$ −22° (c 0.035, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 1:1 δ 7.34 (m, 5H), 5.13 (m, 2H), 4.40 (m, 2H), 3.80 (s, 3H, one rotamer), 3.68 (m, 2H), 3.61 (s, 3H, other rotamer), 2.86 (bs, 1H), 2.32 (m, 1H), 2.13 (d, J = 13.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two rotamers δ 175.6, 175.4, 155.5, 154.7, 136.8, 136.7, 129.0, 128.7, 128.6, 128.5, 128.3, 71.6, 70.6, 67.8, 58.6, 58.2, 56.5, 56.2, 53.4, 53.1, 39.2, 38.3; MS (CI) m/e 280 $(M + H)^+$.

Pentafluorophenyl (2*S*,4*S*)-*N*-Cbz-4-[(*tert*-butyldimethylsilyl)oxy]prolinate (26). A solution of the hydroxyproline **25** (1.5 g, 5.37 mmol), imidazole (0.768 g, 11.28 mmol), and *tert*-butyldimethylsilyl chloride (0.89 g, 5.91 mmol) in DMF (14 mL) was stirred at room temperature for 36 h. The reaction then was quenched by adding 25 mL of water. This solution was extracted with EtOAc (3 × 50 mL). The combined extracts were washed with H_2O (5 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), and concentrated to give 2.00 g (95%) of TBS protected product, which was used directly in the next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 1:1 δ 7.34 (m, 5H), 5.22 (d, J = 12.2 Hz, 1H, one rotamer), 5.21 (d, J = 12.2 Hz, 1H, one rotamer), 5.12 (d, J = 12.2 Hz, 1H, other rotamer), 5.08 (d, J = 12.2 Hz, 1H, other rotamer), 4.43 (m, 2H), 3.73 (s, 3H, one rotamer), 3.66 (m, 1H), 3.61 (s, 3H, other rotamer), 3.43 (m, 1H), 2.22 (m, 2H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two rotamers δ 172.9, 172.5, 155.4, 155.0, 137.2, 137.1, 128.9, 128.4, 128.3, 71.1, 70.3, 67.6, 67.5, 58.4, 58.2, 55.6, 55.3, 52.6, 52.5, 39.3, 26.1, 18.4, −4.48, −4.57; MS (CI) m/e 394 $(M + H)^+$; FTIR ($CDCl_3$) 1760, 1716 cm^{-1}.

A solution of the above TBS-protected compound (1.5 g, 3.81 mmol) and $LiOH·H_2O$ (0.48 g, 11.43 mmol) in THF/MeOH/H2O (150 mL, 3:1:1) was stirred at 0 °C for 24 h. Then saturated citric acid (90 mL) was added, and the reaction mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with H_2O (1 × 100 mL) and brine (1 × 100 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash chromatography eluting with EtOAc:hexanes (2:3) to give 1.20 g (83%) of TBS-protected *cis*-hydroxyproline: ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.78 (s, 1H), 7.30 (m, 5H), 5.14 (m, 2H), 4.40 (m, 2H), 3.64 (m, 1H), 3.42 (m, 1H), 2.21 (m, 2H), 0.84 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two rotamers δ 177.3, 176.8, 155.7, 155.2, 136.9, 128.9, 128.7, 128.4, 128.2, 71.0, 70.3, 67.7, 58.3, 58.0, 55.6, 55.2, 40.0, 39.0, 26.1, 18.3, −4.4; MS (CI) m/e 380 $(M + H)^+$.

To a stirring solution of the above TBS-protected hydroxyproline (0.30 g, 0.79 mmol) and pentafluorophenol (0.160 g, 0.87 mmol) in EtOAc (3 mL) at 0 °C was added dicyclohexylcarbodiimide (DCC, 0.18 g, 0.87 mmol). The reaction mixture was then stirred at rt for 2.5 h. The reaction mixture was diluted with hexanes (25 mL), and the resulting white precipitate was removed by vacuum filtration. The precipitate was washed with cold EtOAc (100 mL). The filtrate and wash were combined and concentrated. The crude was purified by flash chromatography eluting with EtOAc:hexanes (1:4) to give 0.390 g (91%) of pure **28** as a white solid: mp 71 °C; ^{1}H NMR (200 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 1:1 δ 7.35 (m, 5H), 5.25 (d, J = 12.2 Hz, 1H, one rotamer), 5.20 (d, J = 12.2 Hz, 1H, one rotamer), 5.14 (d, J = 12.2 Hz, 1H, other rotamer), 5.13 (d, J = 12.2 Hz, 1H, other rotamer), 4.81 (dd, J = 9.0, 3.8 Hz, 1H, one rotamer), 4.76 (dd, J = 9.2, 3.4 Hz, 1H, other rotamer), 4.48 (m, 1H), 3.73 (m, 1H), 3.51 (m, 1H), 2.42 (m, 2H), 0.84 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two rotamers δ 168.1, 167.9, 155.3, 154.7, 136.9, 136.6, 129.0, 128.9, 128.5, 71.2, 70.3, 68.1, 67.9, 58.1, 57.7, 55.9, 55.4, 40.2, 39.2, 26.0, 18.5, −4.5; MS (CI) m/e 546 $(M + H)^+$.

(*S*)-1-[(2′*S*,4′*S*)-*N*-Cbz-4′-[(*tert*-butyldimethylsilyl)-oxy]prolyl]-5-methyl-2-pyrrolidinone (27). Using the procedure outlined for **16**, pentafluoro ester **26** (0.35 g, 0.64 mmol) and **6** (76 mg, 0.77 mmol) were coupled to give 0.284 g (96%) of pure **27** as a colorless oil after flash chromatography eluting with EtOAc:hexanes (2:3): $[\alpha]^{22}_D$ −18.8° (c 0.028, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 1:1 δ 7.30 (m, 5H), 5.26 (ddd, J = 8.5, 5.5, 2.5 Hz, 1H), 5.19 (d, J = 12.5 Hz, 1H, one rotamer), 5.11 (d, J = 12.5 Hz, 1H, one rotamer), 5.07 (d, J = 12.5 Hz, 1H, other rotamer), 5.03 (d, J = 12.5 Hz, 1H, other rotamer), 4.44 (m, 1H, one rotamer), 4.36 (m, 1H, other rotamer), 4.35 (m, 1H), 3.84 (dd, J = 5.8, 13.6 Hz, 1H, one rotamer), 3.78 (dd, J = 5.8, 13.2 Hz, 1H, other rotamer), 3.44 (dd, J = 7.9, 4.5 Hz, 1H, one rotamer), 3.39 (dd, J = 7.7, 4.9 Hz, 1H, other rotamer), 2.59 (m, 3H), 2.14 (m, 1H), 1.80 (m, 2H), 1.36 (d J = 6.5 Hz, 3H, one rotamer), 1.06 (d J = 6.0 Hz, 3H, other rotamer), 0.84 (s, 9H), 0.04 (s, 3H, one rotamer), 0.03 (s, 3H, one rotamer), 0.02 (s, 3H, other rotamer), 0.01 (s, 3H, other rotamer); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two rotamers δ 176.0, 175.9, 172.3, 155.5, 155.0, 136.9, 136.8, 128.9, 128.8, 128.5, 128.4, 128.1, 70.7, 70.0, 67.8, 67.6, 60.7, 60.3, 55.5, 55.3, 54.3, 54.1, 40.4, 39.6, 32.2, 26.0, 25.8, 19.3, 19.1, 18.2, −4.48, −4.61; MS (CI) m/e 461 $(M + H)^+$; FTIR ($CDCl_3$) 1718, 1520 cm^{-1}.

(*S*)-1-[(2′*S*,4′*S*)-4′-hydroxyprolyl]-5-methyl-2-pyrrolenone·HCl (28). Using the procedure outlined for **2**, **27** (0.142 g, 0.31 mmol) was converted to Boc-pyrrolidinone as a colorless oil in a yield of 120 mg (92%) after flash chromatography eluting with EtOAc:hexanes (1:9): $[\alpha]^{20}_D$ −27.2° (c 0.0204, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 1:1 δ 5.15 (m, 1H), 4.43 (m, 1H), 4.30 (m, 1H), 3.74 (dd, J = 10.8, 5.9 Hz, 1H, one rotamer), 3.67 (dd, J = 10.6, 6.2 Hz, 1H, other rotamer), 3.30 (dd, J = 5.1, 10.5 Hz, 1H, one rotamer), 3.25 (dd, J = 5.5, 10.5 Hz, 1H, other rotamer), 2.57 (m, 3H), 2.14 (m, 1H), 1.72 (m, 2H), 1.42 (s, 9H, one rotamer), 1.35 (s, 9H, other rotamer), 1.31 (d, J = 6.4 Hz, 3H), 0.82 (s, 9H, one rotamer), 0.80 (s, 9H, other rotamer), 0.00 (s, 6H, one rotamer), −0.02 (s, 6H, other rotamer); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two rotamers δ 175.6, 173.0, 172.5, 154.7, 154.3, 80.2, 80.1, 70.6, 69.9, 60.2, 59.8, 55.0, 54.7, 54.0, 53.9, 40.1, 39.2, 32.4, 28.8, 28.7, 26.1, 26.0, 25.8, 25.7, 19.8, 19.6, −4.4, −4.6; MS (CI) m/e 427 $(M + H)^+$; HRMS calcd for $C_{21}H_{39}N_2O_5Si$ 427.2628, found 427.2645; FTIR (CDCl3) 1700, 1534, 1518 cm^{-1}.

According to the procedure outlined for **2** using LDA, phenylselenium bromide, and hydrogen peroxide, the above pyrrolidinone (0.116 g, 0.27 mmol) was converted to the corresponding pyrrolenone in a yield of 94 mg (81%) after radial chromatography eluting with EtOAc:hexanes (1:9): $[\alpha]^{20}_D$ −26.5° (c 0.018, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two rotamers in a ratio of ca. 3:2 δ 7.26 (dd, J = 6.0, 2.0 Hz, 1H, major rotamer), 7.22 (dd, J = 6.0, 2.0 Hz, 1H, minor rotamer), 6.07 (dd, J = 6.0, 1.5 Hz, 1H, major rotamer), 6.03 (dd, J = 6.0, 1.5 Hz, 1H, minor rotamer), 5.20 (m, 1H, major rotamer), 5.24 (dd, J = 8.5, 6.5 Hz, 1H, minor rotamer), 5.22 (dd, J = 8.5, 6.5 Hz, 1H, major rotamer), 4.76 (dq, J = 6.5, 2.0 Hz, 1H), 4.34 (m, 1H), 3.82 (dd, J = 10.5, 6.0 Hz, 1H, major rotamer), 3.72 (dd, J = 10.5, 6.5 Hz, 1H, minor rotamer), 3.32 (dd, J = 10.5, 6.0 Hz, 1H, major rotamer), 3.27 (dd, J = 10.5, 6.0 Hz, 1H, minor rotamer), 2.67 (m, 1H), 1.76 (m, 1H), 1.49 (d, J = 6.5 Hz, 1H, major rotamer), 1.47 (d, J = 6.5 Hz, 1H, minor rotamer), 1.44 (s, 9H, minor rotamer), 1.37 (s, 9H, major rotamer), 0.84 (s, 9H, minor rotamer), 0.82 (s, 9H, major rotamer), 0.04 (s, 3H, minor rotamer), 0.03 (s, 3H, major rotamer), 0.02 (s, 3H, minor rotamer), 0.00 (s, 3H, major rotamer); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of two rotamers δ 172.6, 172.2, 170.3, 154.6, 154.4, 154.1, 126.0, 125.9, 80.2, 80.0, 70.9, 69.9, 60.1, 59.3, 58.9, 58.7, 54.5, 54.0, 39.6, 38.6, 28.9, 28.8, 26.1, 19.8, 18.6, 18.4, −4.4, −4.5; MS (CI) m/e 425 $(M + H)^+$; HRMS calcd for $C_{21}H_{37}N_2O_5Si$ 425.2472, found 425.2467.

The above protected pyrrolenone (64 mg, 0.15 mmol) was treated with 4 N HCl in dioxane (1.5 mL, 6 mmol) at 0 °C. After being stirred at 0 °C for 2 h, the reaction mixture was concentrated to give 35 mg (95%) of crude **28** as a white solid: $[\alpha]^{20}_D$ +43.7° (c 0.007, MeOH) (lit.[7] $[\alpha]^{25}_D$ +33.9° (c 0.06, MeOH)); ^{1}H NMR (200 MHz, $CDCl_3$ + MeOH-d_4) δ 7.51 (dd, J = 6.2, 1.8 Hz, 1H), 6.13 (dd, J = 6.2, 1.4 Hz, 1H), 5.20 (dd, J = 10.7, 3.6 Hz, 1H), 4.83 (q, J = 6.4 Hz, 1H), 4.53 (bs, 1H), 3.46 (m, 1H), 3.32 (m, 1H), 2.77 (ddd, J = 14.8, 10.4, 4.4 Hz, 1H), 2.05 (d, J = 14.8 Hz, 1H), 1.52 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$ + MeOH-d_4) δ 174.6, 171.7, 160.8, 128.7, 73.1, 64.6, 63.3, 58.2, 42.5, 21.5; MS (CI) m/e 211 $(M + H)^+$.

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Supporting Information Available: NMR spectra of key intermediates (20 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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