Total Asymmetric Synthesis of the Potent Immunosuppressive Marine Natural Product Microcolin A

Carl P. Decicco* and Paul Grover

Chemical and Physical Sciences, Dupont Merck Pharmaceutical Company, Experimental Station, Wilmington, Delaware 19880-0353

Received November 30, 1995[⊗]

The total asymmetric synthesis of the potent immunosuppressive compound microcolin A is reported. The synthesis establishes the absolute stereochemistry of microcolin A as C-36*R*, C-38*R*, and C-4*S* on the basis of the diastereoselective preparation of all four possible diastereomers of the lipid region (fragment A) and diastereoselective synthesis of fragment C starting from natural L-(*S*)-alanine. The strategy involves a convergent assemblage of three optically pure fragments and is amenable to chemical modifications to examine structural analogs for biological study.

Introduction

The search for new immunosuppressive agents from natural sources has led to the discovery of structurally diverse and biologically operative compounds. Cyclosporin[1] and FK506[2] are two examples of natural products that have shown particular promise in the treatment of organ transplantation rejection through suppression of the immune response. Studies on the mechanism of action[3] of these and the related agent rapamycin[4] have led to an enhanced understanding of intracellular events involved in the signal transduction pathway leading to immune suppression. Recently discovered immunosuppressants such as tetranactin,[5] didemnin B,[6] and discodermolide[7] all seem to have related but unique modes of action, suggesting that these compounds have discrete intracellular target mechanisms.[8] In addition, these compounds may eventually lead to the discovery of novel intracellular targets for immunosuppression and new therapeutics devoid of the toxic side effects associated with our current drugs.[9]

The marine environment continues to be a rich source of structurally diverse and biologically active molecules for study. Koehn and co-workers have recently reported the isolation of microcolins A and B, two very potent immunosuppressive agents from the Venezuelan blue-green algae *Lyngbya majuscula*.[10] The microcolins are related in structure to majusculamide D and deoxymajusculamide D,[11] two cytotoxins isolated from the same species. Microcolins A and B were found to be potent inhibitors of the human two-way mixed lymphocyte response (MLR) with EC_{50} values of 0.02 and 4.1 nM for A and B, respectively. In comparison to cyclosporin A, microcolin A is approximately 10^3 times more potent in human MLR. Recent data on microcolin A indicate that it may be selectively targeting B-cell populations *in vivo* while sparing T-cell numbers and function.[12] The mode of action of these compounds is, however, currently unknown. The potency and novelty of these natural products make them important targets for total synthesis, to produce quantities of materials for further biological study. Our synthetic strategy matured from our desire to have an approach amenable to the synthesis of chemical analogs suitable for biological study and the versatility to make all of the possible diastereomers of the microcolins, as the absolute stereochemistry of three of the asymmetric centers in the molecule were not assigned in the original isolation work.

The complete structure elucidation for both microcolins A and B[10] (microcolin A being C-10*S* hydroxy microcolin B) along with semisynthetic degradation work[13] has been published. In this paper, we report the first total synthesis of Microcolin A, the absolute stereochemistry of C-4, C-36, and C-38, and confirmation of the of C-10*S* stereochemistry, based on a comparison of the spectral data of the natural material with our synthetically derived compounds. The methodology we used for the synthesis of the chiral α,γ-dimethyl-substituted alkyl chain employs a modification of the iterative process first suggested by Evans in his ionomycin synthesis[14] and is based on the use of chiral imide oxazolidinone substrates and alkyl triflates as electrophiles.[15] Using triflates as alkylating agents (a more reactive electrophile),[16] we have been able to make all four diastereomers of fragment A

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1996.

(1) For a comprehensive review, see: Ishizaka, K.; Lachmann, P. J.; Kallos, P.; Waksman, B. H. In *Progress in Allergy*; Borel, J. F., Ed.; Karger: Basel, Switzerland, 1986; Vol. 38.

(2) Kino, T.; Hatanake, H.; Miyata, S.; Inamura, N.; Nishiyama, M.; Yajima, T.; Gotto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Ochai, T. *J. Antibiot.* **1987**, *40*, 1356.

(3) Schreiber, S. L.; Crabtree, G. R. *Immunol. Today* **1992**, *13*, 136.

(4) Seghal, S. N.; Baker, H. Vezina; C. *J. Antibiot.* **1975**, *31*, 727. Martel, R. R.; Klicius, J.; Galat, S. *Can. J. Physiol. Pharmacol.* **1977**, *55*, 48.

(5) Tanouchi, Y.; Shichi, H. *Immunology* **1988**, *63*, 471. Callewaert, D. M.; Radcliff, G.;Tanouchi, Y.; Sichi, H. *Immunopharmacology* **1988**, *16*, 25.

(6) Montgomery, D. W.; Celniker, A.; Zukoski, C. F. *Transplantation* **1987**, *43*, 133; Montgomery, D. W.; Zukoski, C. F. *Transplantation* **1985**, *40*, 49.

(7) Longley, R. E.; Caddigan, D.; Harmody, D.; Gunasekera, M.; Gunasekera, S. P. *Transplantation* **1991**, *52*, 650; 656.

(8) Teunissen, M. B. M.; Pistoor, F. H. M.; Rongen, H. A. H.; Kapsenberg, M. L.; Bos, J. D. *Transplantation* **1992**, *53*, 875.

(9) Strom, T. B.; Loertscher, R. *N. Eng. J. Med.* **1984**, *311*, 728.

(10) Koehn, F. E.; Longley, R. E.; Reed, J. K. *J. Nat. Prod.* **1992**, *55*, 613.

(11) Moore, R. E.; Entzeroth, M. *Phytochemistry* **1988**, *27*, 3101.

(12) Longley, R. E.; Koehn, B.; Reilly, B.; Ward, J. Abstract, Joint Meeting of the American Association of Immunologists and the Clinical Immunology Society, May 1993; Paper 1594.

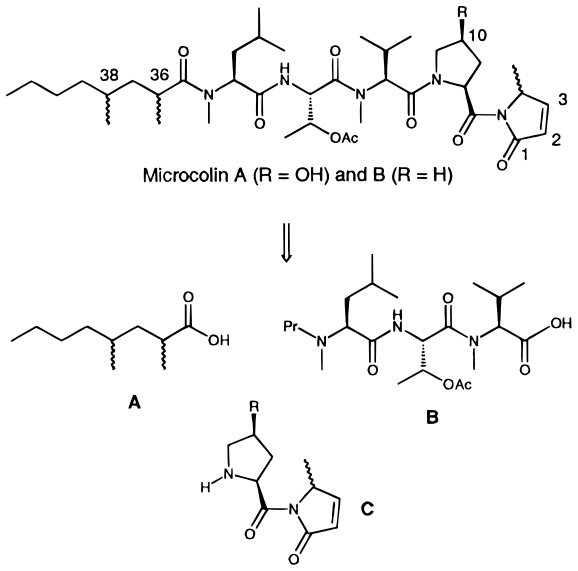
(13) Koehn, B.; McConnel, O. J.; Longley, R. E.; Sennett, S. H.; Reed, J. K. *J. Med. Chem.* **1994**, *37*, 3181.

(14) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.

(15) Decicco, C. P.; Nelson, D. J.; Corbett, R. L.; Dreabit, J. C. *J. Org. Chem.* **1995**, *60*, 4782. Canan Koch, S. S.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725. Hoffman, R. V.; Kim, H.-O. *Tetrahedron Lett.* **1993**, *34*, 2051. Bates, R. B.; Taylor, S. R. *J. Org. Chem.* **1994**, *59*, 245. Bates, R. B.; Taylor, S. R. *J. Org. Chem.* **1993**, *58*, 4469. Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195. Williams, D. R.; McGill, J. M. *J. Org. Chem.* **1990**, *55*, 3457.

S0022-3263(95)02123-2 CCC: $12.00

Scheme 1



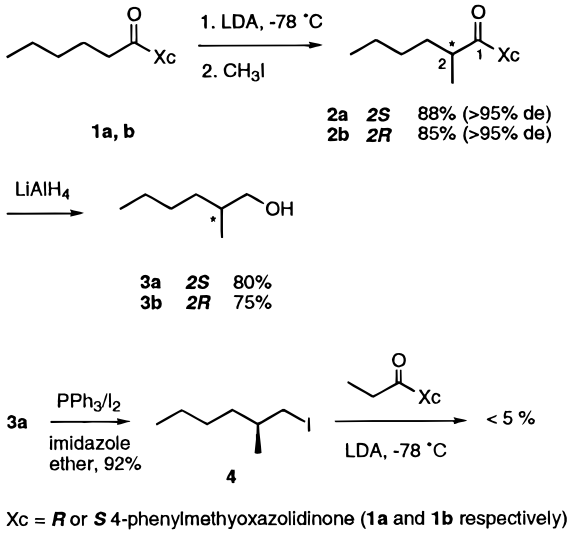
in a highly efficient and synthetically economical way that should be amenable to other molecules containing this common repeating fragment of chiral α,γ-dimethyls.

Results

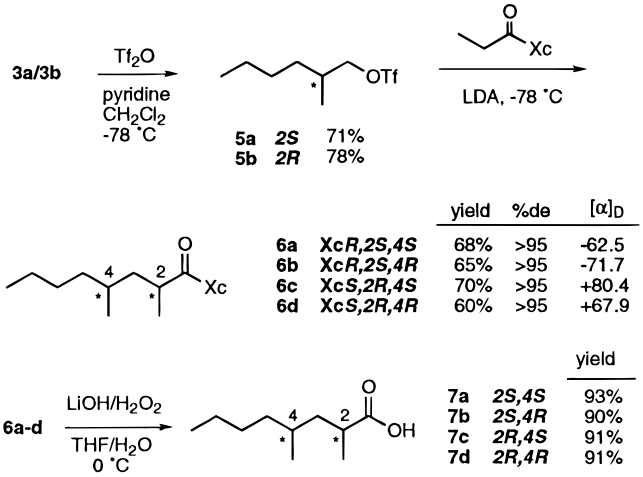
Synthetic Strategy. Microcolin A is a linear lipopeptide containing a dimethyl-substituted octanoyl chain linked to a peptidic region. Retrosynthetically, our strategy invokes two disconnections to provide three target fragments which were assembled in a convergent manner (Scheme 1). The central linear tripeptide region (fragment B) consisting of *N*-Me-Leu-OAc-Thr-*N*-Me-Val was assembled using peptide coupling chemistry, with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) found to be the reagent of choice for effecting the coupling of these hindered amino acids. Fragment C, containing an unnatural *cis-allo*-hydroxyproline (*cis-allo*-HyPro) in microcolin A (proline in microcolin B) and an interesting 4-methylpyrrolidinone of undefined stereochemistry, required a diastereoselective synthesis to determine unambiguously the stereochemistry at C-4. From the natural product determination study, the unsaturation in the pyrrolidinone ring has been shown to be critical for immunosuppressive activity as determined in the MLR analysis,[13] as well as a challenging and unusual functional group we had to assemble. As mentioned above, an asymmetric synthesis of the α,γ-dimethyloctanoyl chain (fragment A) targeting all four possible diastereomers was also required. We desired a direct and general method of assembling this fragment, preferably not requiring deoxygenation from an asymmetric aldol coupling. Our diastereoselective synthesis of fragment A was based on findings from previous work that triflates are superior alkylating agents and reactive electrophiles for addition to Evans chiral imide enolates.[16]

Fragment A. The asymmetric synthesis of the diastereomers of the 1,3-dimethyloctanoyl chain (fragment A) was achieved as depicted in Schemes 2 and 3. *R* and *S* **1** were prepared from hexanoyl chloride and the lithium anion of *R* and/or *S* 4-(phenylmethyl)oxazolidinone using standard conditions.[17] Deprotonation with LDA followed by alkylation with methyl iodide to give **2** proceeded with the expected excellent diastereocontrol (>95% de). Reduction of **2** with $LiAlH_4$ to give **3** and conversion to iodide **4** was then carried out. We first attempted the asymmetric alkylation of the chiral propionimide with the corresponding iodide **4** and obtained <5% yield of the desired alkylation product. However, with the use of the more reactive triflate leaving group, we observed efficient asymmetric conversion to the desired addition product(s) **6** (Scheme 3). Transformation of the alcohol **3** to triflate **5** and subsequent reaction with 3-propanoyl-4-(phenylmethyl)oxazolidinone, as mentioned above, gave **6a**−**d** with excellent diastereochemical control, irrespective of the absolute stereochemistry at the γ-carbon (C-4 in **6**), and in good overall chemical yield (Scheme 3).

Scheme 2



Scheme 3

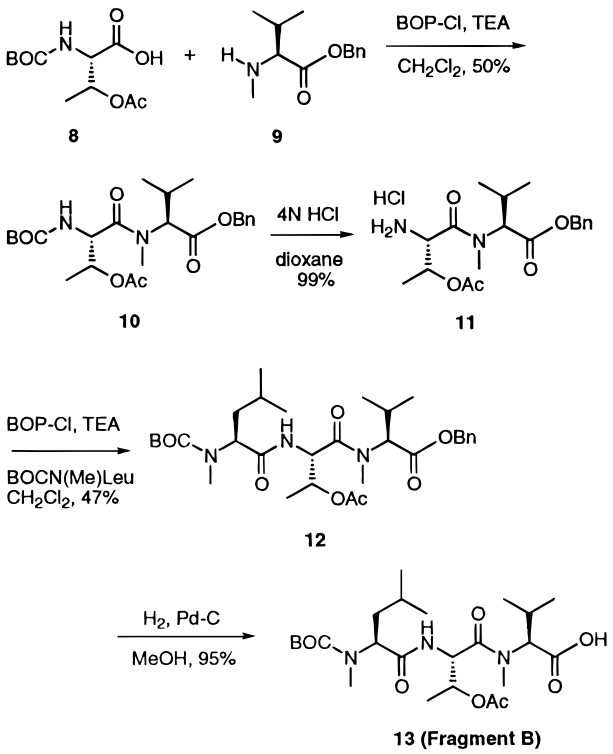


Employing this triflate alkylation methodology, we made all four diastereomers of this fragment. This three step method of assembling chiral 1,3-dialkyl fragments, as first suggested by Evans, offers advantages over related approaches that utilize aldol couplings. While the latter efficiently provides the desired products with high diastereoselectivity, an undesirable deoxygenation step is required after the coupling. In principle, this

(16) Evans and co-workers solved this problem by substituting a more reactive chiral enolate nucleophile derived from L-prolinol *N*-propionamide (see ref 14).

(17) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

Scheme 4



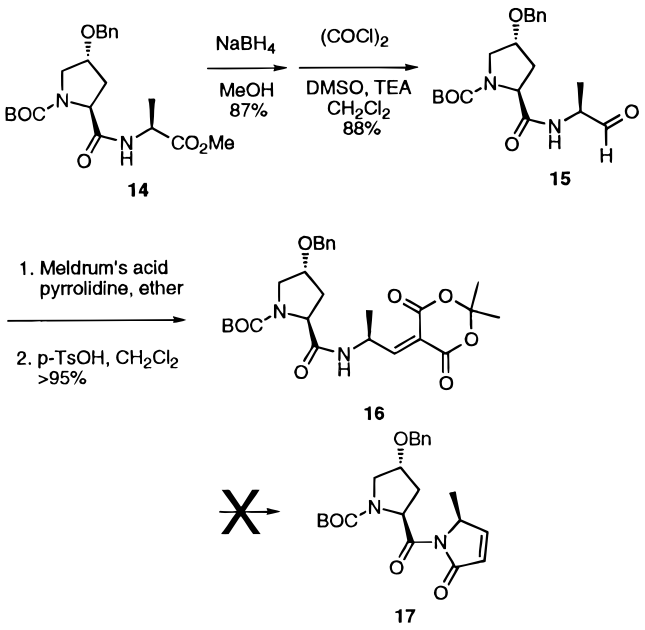
iterative approach can be used to assemble long chains of chiral 1,3-dimethyl-substituted fragments, with essentially the same starting chiral propionimide (or its corresponding antipode) enolate in each case, and, if desired, regenerate the chiral auxiliary through hydrolysis.

Removal of the chiral auxiliary using standard conditions yielded fragments **7a**−**d** (fragment A) in good yield and suitably functionalized for coupling to the N-Me-Leu of fragment B.

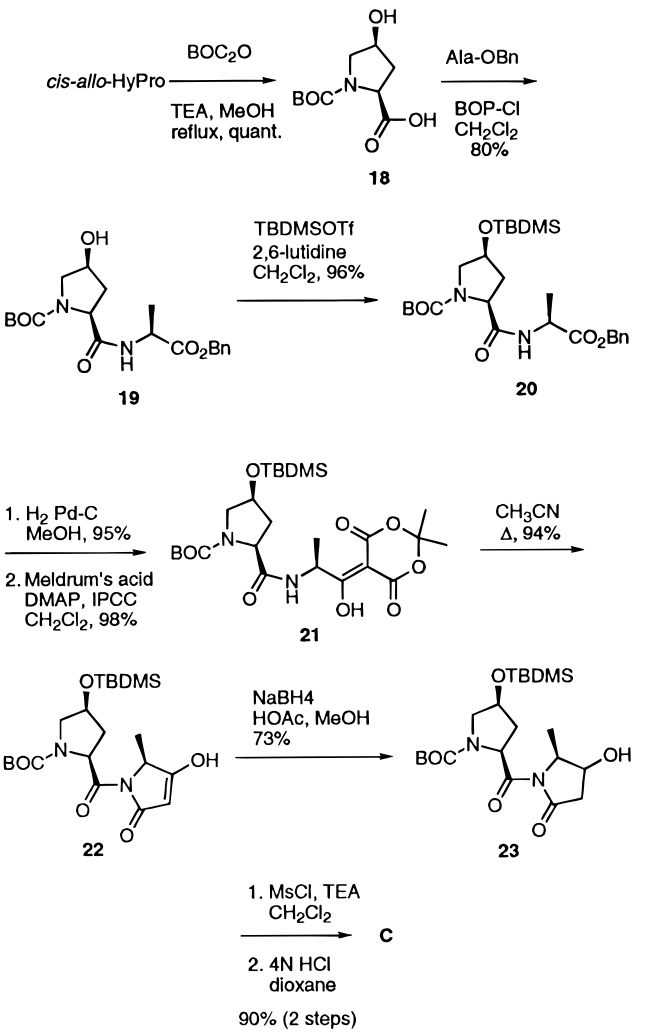
Fragment B. The central tripeptide fragment B was assembled by coupling suitably protected amino acids as detailed in Scheme 4. In the case of these highly hindered peptide couplings, we found BOP-Cl[18] to be the reagent of choice, with superior turnover efficiency and time to completion to product, over 1-hydroxy-7-azabenzotriazole[19] and acid fluoride couplings.[20] Optimization of these coupling steps has provided us with quantities of this intermediate, in relatively good chemical yield, suitably protected for connection to the other two fragments and for future incorporation into chemical analogs for biological study.

Fragment C. A direct approach to fragment C, based on a modification of a procedure by Roux et. al.,[21] was first modeled starting with *N* Boc-*O*-benzylhydroxyproline[22] (natural) and coupling to L-Ala methyl ester to give **14** (Scheme 5). A two-step conversion gave aldehyde **15** followed by reaction with Meldrum's acid to give intermediate **16**. We had attempted to form the pyrrolidinone directly at this stage; however, all attempts through

Scheme 5



Scheme 6

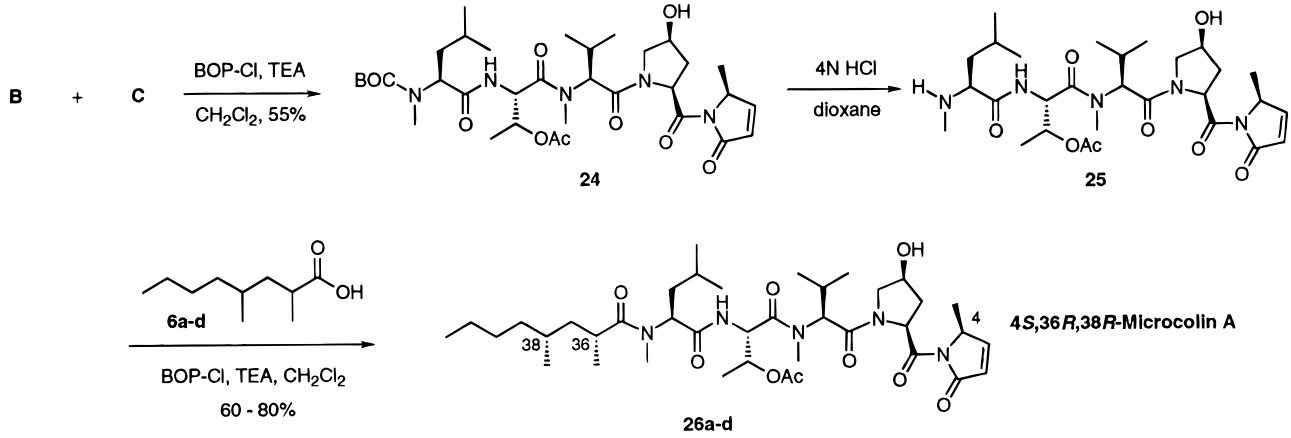


heating to effect the cyclization−decarboxylation of **16** to **17** failed.

Fragment C was successfully assembled through the synthetic steps depicted in Scheme 6. The nitrogen of *cis-allo*-HyPro was first protected as a Boc (**18**), followed

(18) Tung, R. D.; Rich, D. H. *J. Am. Chem. Soc.* **1985**, *107*, 4342.
(19) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.
(20) Carpino, L. A.; Mansour, M. E.; Sadat-Aalsee, D. *J. Org. Chem.* **1991**, *56*, 2611.
(21) Roux, F.; Galeotti, N.; Poncet, J.; Jouin, P.; Cros, S.; Zenke, G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1947.
(22) Boc-HyPro(OBn)OH was chosen for the model study because it is much less expensive than the *cis-allo*-HyPro found in microcolin A.

Scheme 7



by coupling with Ala-OBn to give **19**. Protection of the secondary alcohol as a TBDMS ether gave compound **20**. Removal of the benzyl ester protecting group followed by treatment with Meldrum's acid gave **21**, which in this case underwent efficient thermal cyclization to yield the vinyl hydroxy pyrrolidinone **22**. The net deoxygenation of the hydroxyl group of **22** was accomplished in two steps by first reducing the double bond and then converting the hydroxyl to the mesylate as shown in the scheme, which spontaneously eliminated in the presence of TEA. Acid hydrolysis of the TBDMS protecting group yielded fragment C. Comparison of the spectral data for this fragment to that of natural microcolin, as well as to that of majusculamide (in which this fragment is also present), established the absolute stereochemistry of C-4 as *S*. We also note that, through analogous steps, starting with D-Ala-OBn (not shown), we made the corresponding fragment with C-4*R* stereochemistry. It was clear from the spectral analysis of epi-fragment C when compared to the C-4*S* fragment that microcolin does have the *S* stereochemistry at C-4. This was supported by spectral comparison to reported spectral data from studies by Moore[11] on the oxidative degradation of majusculamide D, in which it was shown that the pyrrolinone ring was derived from L-alanine, thus establishing the stereochemistry of C-4 as *S* in that related natural product. The stereochemistry was unambiguously confirmed spectroscopically by comparing the synthetic material derived from fragment C with authentic, natural microcolin A (*vide infra*).

Convergent Assemblage of Fragments A, B, and C. Assemblage of the three fragments was then carried out as depicted in Scheme 7. B and C were coupled using BOP-Cl in 55% yield to give **24** followed by deprotection of the Boc group yielding the free amine B−C fragment **25**. Each of the diastereomerically pure chiral acids **7a**−**d** was then coupled with **25** to give microcolin A along with the C-36, C-38 diastereomers of the natural products **26a**−**d**. Spectroscopic data for the three diastereomers of microcolin A prepared via this route are provided for comparison in the Experimental Section. However, from a direct comparison of the chemical shift data for C-4, C-36, and C-38 and the couplings observed for these resonances, it was not possible to unambiguously assign the absolute stereochemistry of the natural material (see Experimental Section). In addition, a concentration effect on the chemical shift values was observed which made a comparative assignment to literature values impossible. We assigned the C-36, C-38 stereochemistry from a spectroscopic comparison to authentic microcolin A (graciously provided for comparison by Dr. Ross Longley of the Harbor Branch Oceanographic Institute). The correct stereochemical assignments were made on the basis of examining the ^{1}H resonances of each of the isomers **26a**−**d** with spiked concentrations of the authentic material. Thus the correct absolute configuration of natural microcolin A as determined by this unambiguous method is C-4*S*, C36*R*, and C-38*R*.

Discussion

Microcolin A was prepared in 21 steps and 1.7% overall yield as a single diastereomer from readily available starting materials. This approach provides versatility which allows for the simple preparation of chemical analogs of the natural material. Spectroscopic data for natural microcolin A compared favorably with the synthetically derived material, and data for the C-36, C-38 diastereomers of microcolin are reported in the Experimental Section. We are currently evaluating this material in biological assays to delineate the mechanism of action of this interesting natural product and are examining chemical analogs and isomers of the natural material for biological activities. Further synthetic and biological studies on the microcolins are ongoing and will be published in due course.

Experimental Section

General Methods. All reactions were carried out under nitrogen by standard reaction techniques, unless noted otherwise. Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen. Nuclear magnetic resonance spectra were obtained on a Varian 300 spectrometer. Optical rotations were measured at 25 °C. Analytical thin layer chromatography was carried out with Merck silica gel (70−230 mesh, ASTM). Preparative chromatography was performed with Merck silica gel (35−70 μm, 60 Å). Elemental analyses were conducted by Quantitative Technologies, Inc.

(4*S*)-3-Hexanoyl-4-benzyl-2-oxazolidinone (1a). To a cooled (−78 °C) solution of (*S*)-(−)-4-benzyl-2-oxazolidinone (5.0 g, 28.2 mmol) in THF (100 mL) was added *n*-BuLi (11.28 mL, 2.5 M, 28.2 mmol) dropwise over a 15 min period. The resulting solution was allowed to stir at −78 °C for 15 min and then treated with hexanoyl chloride (4.32 mL, 30.9 mmol). After an additional 15 min of stirring, the resulting cold (−78 °C) solution was allowed to warm to 25 °C and then quenched with aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with three 50 mL portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed (SiO_2, 20−25% gradient, EtOAc−hexane) to provide 7.40 g (95%) of pure **1a**:

$[\alpha]^{25}_D$ +99.4° (*c* 0.34, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.68 (m, 1H), 4.20 (m, 2H), 3.29 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.93 (m, 2H), 2.77 (dd, *J* = 12.7, 9.5 Hz, 1H), 1.70 (t, *J* = 7.0 Hz, 2H), 1.37 (m, 4H), 0.92 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.3, 153.3, 135.3, 129.3, 128.8, 127.1, 66.0, 55.0, 37.8, 35.4, 31.2, 23.8, 22.3, 13.8; MS (CI) *m/e* 276 $(M + H)^+$; IR (neat) 2956, 2930, 2870, 1784, 1700, 1388, 1212, 702 cm^{-1}.

[3(2*S*)4*S*]-3-(2-Methylhexanoyl)-4-benzyl-2-oxazolidinone (2a). To a cooled (−78 °C) suspension of the imide **1a** (7.3 g, 26.5 mmol) in THF (90 mL) was added $NaN(TMS)_2$ (29.2 mL, 29.1 mmol, 1 M) dropwise over a 30 min period. After 15 min of stirring, the resulting cold (−78 °C) solution was treated with methyl iodide (11.3 mL, 79.5 mmol) and allowed to stir at −78 °C for 3 h before being warm to 25 °C overnight. The reaction was quenched with water (100 mL), and the aqueous layer was extracted with three 50 mL portions of EtOAc. The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed (SiO_2, 15−25% gradient, EtOAc−hexane) to provide 5.1 g (88%) of pure **2a**: $[\alpha]^{25}_D$ +104.4° (*c* 0.47, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.68 (m, 1H), 4.20 (m, 2H), 3.70 (q, 1H), 3.26 (dd, *J* = 13.2, 2.9 Hz, 1H), 2.77 (dd, *J* = 13.2, 9.5 Hz, 1H), 1.74 (m, 1H), 1.43 (m, 1H), 1.29 (m, 4H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 177.2, 152.9, 135.3, 129.3, 128.8, 127.2, 65.9, 55.2, 37.8, 37.5, 33.0, 29.3, 22.6, 17.2, 13.8; MS (CI) *m/e* 290 $(M + H)^+$; IR (neat) 2958, 2932, 2860, 1782, 1698, 1386, 1238, 1208, 702 cm^{-1}.

(*S*)-2-Methylhexan-1-ol (3a). To a cooled (0 °C) suspension of the imide **2a** (5.1 g, 17.6 mmol) in THF (56 mL) was added $LiAlH_4$ in small portions over a 15 min period. After an additional 30 min of stirring, the cold (0 °C) reaction was slowly quenched with brine (25 mL). EtOAc (75 mL) was added to precipitate the aluminum salts, which were then filtered and dried ($MgSO_4$), and the solution was concentrated *in vacuo*. The crude product was then chromatographed (SiO_2, 15% EtOAc−hexane) to provide 1.57 g (80%) of pure alcohol **3a**: $[\alpha]^{25}_D$ −14.2° (*c* 0.31, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (m, 1H), 3.41 (m, 1H), 1.59 (m, 1H), 1.31 (m, 6H), 1.11 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.90 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 68.3, 35.6, 32.7, 29.1, 22.8, 16.4, 13.9; MS (DCI) m/e 134 $(M + NH_4)^+$; IR (neat) 3342, 2956, 2926, 2872, 1466, 1378, 1040 cm^{-1}.

(*S*)-2-Methylhexyl Trifluoromethanesulfonate (5a). To a cooled (−78 °C) suspension of the alcohol **3a** (200 mg, 1.72 mmol) in CH_2Cl_2 (15 mL) was added pyridine (0.16 mL, 2.0 mmol). After the solution was stirred an additional 30 min at −78 °C, triflic anhydride (0.29 mL, 1.72 mmol) was added dropwise over a 20 min period, after which the reaction mixture was slowly warmed to −20 °C for an additional 30 min period. The reaction was then quenched with brine (30 mL), and the aqueous layer was extracted with three 30 mL portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed (SiO_2, 10% EtOAc−hexane) to provide 0.30 g (71%) of pure **5a**: $[\alpha]^{25}_D$ −1.9° (*c* 0.27, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (m, 2H), 1.94 (m, 1H), 1.30 (m, 6H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 120.7, 81.8, 33.1, 31.9, 28.5, 22.5, 15.9, 13.7; IR (neat) 2964, 2934, 2864, 1468, 1414, 1246, 1206, 1148, 942, 618 cm^{-1}.

Representative Procedure for Preparation of 3-(2,4-Dimethyloctanoyl)-4-benzyl-2-oxazolidinones 6a−d. Synthesis of [3(2*R*,4*R*)4*S*]-3-(2,4-Dimethyloctanoyl)-4-benzyl-2-oxazolidinone (6d). To a cooled (−78 °C) suspension of lithium diisopropylamide (3.21 mmol) in THF (10.0 mL) was added (4S)-3-propanoyl-4-benzyl-2-oxazolidinone (748 mg, 3.21 mmol). After 45 min of stirring, the resulting cold (−78 °C) solution was treated with the triflate **5** (11.3 mL, 79.5 mmol) and allowed to stir at −78 °C for 3 h before being warmed to warm to 25 °C overnight. The reaction was quenched with water (50 mL), and the aqueous layer was extracted with three 50 mL portions of EtOAc. The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed (SiO_2, 10−15% gradient, EtOAc−hexane) to provide 730 mg (60%) of pure **6d**: $[\alpha]^{25}_D$ +67.9° (*c* 0.33, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 5H), 4.69 (m, 1H), 4.16 (m, 2H), 3.93 (m, 1H), 3.29 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.72 (dd, *J* = 13.2, 9.5 Hz, 1H), 1.87 (ddd, *J* = 13.5, 8.4, 5.9 Hz, 1H), 1.29 (m, 8H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 177.6, 153.0, 135.3, 129.3, 128.8, 127.2, 65.8, 55.2, 41.3, 37.9, 36.4, 35.1, 30.7, 29.0, 22.8, 19.8, 17.9, 14.0; MS (CI) *m/e* 332 $(M + H)^+$; IR (neat) 2958, 2928, 2872, 1782, 1698, 1386, 1350, 1212, 702 cm^{-1}. Anal. Calcd for $C_{20}H_{29}O_3N$: C, 72.47; H, 8.83; N, 4.23. Found: C, 72.82; H, 9.04; N, 4.00.

Data for [3(2*S*,4*S*)4*R*]-3-(2,4-dimethyloctanoyl)-4-benzyl-2-oxazolidinone (6a) prepared from 5a and (4*R*)-3-propanoyl-4-benzyl-2-oxazolidinone: yield 68%; $[\alpha]^{25}_D$ −62.3° (*c* 0.24, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 5H), 4.69 (m, 1H), 4.16 (m, 2H), 3.93 (m, 1H), 3.29 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.72 (dd, *J* = 13.2, 9.5 Hz, 1H), 1.87 (ddd, *J* = 13.5, 8.4, 5.9 Hz, 1H), 1.29 (m, 8H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 177.6, 153.0, 135.3, 129.3, 128.8, 127.2, 65.8, 55.2, 41.3, 37.9, 36.4, 35.1, 30.7, 29.0, 22.8, 19.8, 17.9, 14.0; MS (CI) *m/e* 332 $(M + H)^+$; IR (neat) 2958, 2928, 2872, 1782, 1698, 1386, 1350, 1212, 702 cm^{-1}.

Data for [3(2*S*,4*R*)4*R*]-3-(2,4-dimethyloctanoyl)-4-benzyl-2-oxazolidinone (6b) prepared from 5b and (4*R*)-3-propanoyl-4-benzyl-2-oxazolidinone: yield 65%; $[\alpha]^{25}_D$ −71.7° (*c* 0.24, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.70 (m, 1H), 4.16 (m, 2H), 3.87 (m, 1H), 3.30 (dd, *J* = 13.5, 3.3 Hz, 1H), 2.72 (dd, *J* = 13.2, 9.9 Hz, 1H), 1.55 (m, 1H), 1.44 (m, 1H), 1.29 (bs, 7H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.90 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 177.7, 135.3, 129.3, 129.0, 128.0, 65.8, 55.2, 40.7, 37.9, 37.0, 35.2, 30.3, 29.1, 22.8, 19.0, 16.6, 14.0; MS (CI) *m/e* 332 $(M + H)^+$; IR (neat) 2958, 2926, 1782, 1698, 1454, 1386, 1210 cm^{-1}.

Data for [3(2*R*,4*S*)4*S*]-3-(2,4-dimethyloctanoyl)-4-benzyl-2-oxazolidinone (6c) prepared from 5a and (4*S*)-3-propanoyl-4-benzyl-2-oxazolidinone: yield 70%; $[\alpha]^{25}_D$ +80.4° (*c* 0.27, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.70 (m, 1H), 4.16 (m, 2H), 3.87 (m, 1H), 3.30 (dd, *J* = 13.5, 3.3 Hz, 1H), 2.72 (dd, *J* = 13.2, 9.9 Hz, 1H), 1.55 (m, 1H), 1.44 (m, 1H), 1.29 (bs, 7H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.90 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 177.8, 152.9, 135.3, 129.3, 128.8, 127.2, 65.8, 55.2, 40.7, 37.9, 37.0, 35.2, 30.3, 29.1, 22.8, 19.0, 16.6, 14.0; MS (CI) *m/e* 332 $(M + H)^+$; IR (neat) 2958, 2926, 1782, 1698, 1454, 1386, 1210 cm^{-1}.

Representative Procedure for Preparation of 2,4-Dimethyloctanoic Acids 7a−d. Synthesis of (2*R*,4*R*)-2,4-Dimethyloctanoic Acid (7d). To a cooled (0 °C) suspension of imide **6d** (110 mg, 0.32 mmol) in a THF/H_2O (2.0/0.5 mL) solvent system was added 30% H_2O_2 (0.27 mL, 2.65 mmol), followed by 4.0 M LiOH/H_2O (0.33 mL, 1.32 mmol) at 0 °C. After 1.5 h of stirring, the solvent was removed *in vacuo*, and the residue was diluted with H_2O (5.0 mL). The mixture was treated with 1 N HCl until pH 2 and then extracted with EtOAc (4 × 30 mL). The EtOAc layers were combined, dried ($MgSO_4$), and then concentrated *in vacuo*. The resulting residue was chromatographed (SiO_2, 30% EtOAc−hexane) to provide 52.0 mg (91%) of pure **7d**: $[\alpha]^{25}_D$ −8.4° (*c* 0.09, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (m, 1H), 1.73 (ddd, *J* = 13.9, 8.8, 5.1 Hz, 1H), 1.47 (m, 1H), 1.27 (m, 7H), 1.18 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 5.5 Hz, 3H); MS (CI) *m/e* 173 $(M + H)^+$; IR (neat) 2958, 2928, 2874, 1708, 1466, 1224 cm^{-1}.

Data for (2*S*,4*S*)-2,4-dimethyloctanoic acid (7a) prepared from 6a: yield 93%; $[\alpha]^{25}_D$ +8.4° (*c* 0.09, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (m, 1H), 1.73 (ddd, *J* = 13.9, 8.8, 5.1 Hz, 1H), 1.47 (m, 1H), 1.27 (m, 7H), 1.18 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 5.5 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 183.6, 41.12, 37.2, 36.5, 30.6, 28.8, 22.8, 19.4, 17.6, 13.9; MS (CI) *m/e* 173 $(M + H)^+$; IR (neat) 2958, 2928, 2874, 1708, 1466, 1224 cm^{-1}.

Data for (2*S*,4*R*)-2,4-dimethyloctanoic acid (7b) prepared from 6b: yield 90%; $[\alpha]^{25}_D$ +6.5° (*c* 0.05 , MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (m, 1H), 1.50 (m, 1H), 1.29 (m, 8H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 4.8 Hz, 3H), 0.86 (d,

J = 6.0 Hz, 3H); MS (CI) *m/e* 173 $(M + H)^+$; IR (neat) 2958, 2928, 2874, 1706, 1466, 1224, 946 cm^{-1}.

Data for (2*R*,4*S*)-2,4-dimethyloctanoic acid (7c) prepared from 6c: yield 91%; $[\alpha]^{25}_D$ −6.4° (*c* 0.09, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (m, 1H), 1.50 (m, 1H), 1.29 (m, 8H), 1.15 (d, J = 7.0 Hz, 3H), 0.99 (t, J = 4.8 Hz, 3H), 0.86 (d, J = 6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 183.7, 40.7, 37.05, 36.6, 30.3, 28.9, 22.8, 19.2, 16.7, 13.9; MS (CI) *m/e* 173 $(M + H)^+$; IR (neat) 2958, 2928, 2874, 1706, 1466, 1224, 946 cm^{-1}.

***N*-Boc-OAc-Thr-*N*-Me-Val-OBn (10).** *N*-Boc-OAc-Thr (**8**) (3.9 g, 14.8 mmol) was dissolved in dry CH_2Cl_2 (100 mL) and was treated with *N*-Me-Val-OBn·*p*-Ts, **9** (3.9 g, 14.8 mmol). To this were added BOP-Cl (3.76 g, 14.8 mmol) and triethylamine (4.53 mL, 32.6 mmol). After bein stirred overnight at 25 °C, the reaction mixture was washed with 75 mL each of aqueous NH_4Cl, aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and then concentrated *in vacuo* and chromatographed (SiO_2, 20−25% gradient, EtOAc−hexane) to provide 3.30 g (50%) of pure **10**: $[\alpha]^{25}_D$ −55.7 ° (*c* 0.26, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.37 (d, J = 9.5 Hz, 1H), 5.20 (t, J = 5.5 Hz, 1H), 5.15 (s, 2H), 4.91 (d, J = 10.6 Hz, 1H), 4.67 (dd, J = 9.2, 5.5 Hz, 1H), 3.05 (s, 3H), 1.96 (s, 3H), 1.42 (s, 9H), 1.15 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); MS (CI) *m/e* 453 $(M + H)^+$; IR (neat) 3334, 2976, 2936, 1740, 1712, 1652, 1498, 1368, 1238, 1172 cm^{-1}.

OAc-Thr-*N*-Me-Val-OBn·HCl (11). The dipeptide **10** (2.06 g, 4.5 mmol) was treated with 4 N HCl in dioxane (62 mL) and was allowed to stir for 4 h at 0 °C. The solvent was then removed *in vacuo* to provide 1.81 g of crude **11** (99%) as a white solid: $[\alpha]^{25}_D$ −39.0° (*c* 0.26, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.32 (m, 1H), 5.14 (s, 2H), 4.88 (d, J = 10.6 Hz, 1H), 4.72 (m, 1H), 3.77 (m, 1H), 3.67 (m, 1H), 3.09 (s, 3H), 2.20 (m, 1H), 2.00 (s, 3H), 1.34 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.2 Hz, 3H), 0.91 (d, J = 6.2 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.8, 167.1, 128.4, 128.3, 67.4, 66.8, 62.3, 53.7, 31.4, 28.1, 27.2, 20.9, 19.5, 19.0, 16.8; MS (CI) m/e 365 $(M + H)^+$; IR (neat) 2970, 1742, 1666, 1374, 1202, 1038 cm^{-1}.

***N*-Boc-*N*-Me-Leu-OAc-Thr-*N*-Me-Val-OBn (12).** The amine hydrochloride **11** (0.50 g, 1.25 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and was treated with Boc-*N*-Me-Leu (0.31 g, 1.25 mmol). To this solution were added BOP-Cl (0.35 g, 1.37 mmol) and triethylamine (0.39 mL, 2.75 mmol). After being stirred overnight at 25 °C, the reaction mixture was washed with 20 mL each of aqueous NH_4Cl, aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed (SiO_2, 25−35% gradient, EtOAc−hexane) to provide 0.35 g (47%) of pure **12**: $[\alpha]^{25}_D$ −2.9° (*c* 0.74, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.8 (bs, 1H), 5.24 (m, 1H), 5.15 (s, 2H), 4.98 (dd, J = 8.8, 4.8 Hz, 1H), 4.91 (d, J = 11.1 Hz, 1H), 4.60 (m, 1H), 3.06 (s, 3H), 2.76 (s, 3H), 2.20 (m, 1H), 1.93 (s, 3H), 1.70 (m, 2H), 1.49 (bs, 9H), 1.12 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H); MS (CI) *m/e* 592 $(M + H)^+$; IR (neat) 3330, 2962, 1740, 1688, 1654, 1368, 1236, 1154 cm^{-1}. Anal. Calcd for $C_{31}H_{49}N_3O_8$: C, 62.92; H, 8.35. Found: C, 63.11; H, 8.21.

***N*-Boc-*N*-Me-Leu-OAc-Thr-*N*-Me-Val (13, Fragment C).** The benzyl ester **12** was dissolved in MeOH (5 mL), and to this solution was added 10% Pd/C (40 mg). The mixture was stirred under an atmosphere of H_2 (balloon) for 2 h, followed by filtration and concentration *in vacuo*, to provide 0.25 g (85%) of **13**. $[\alpha]^{25}_D$ −84.1° (*c* 0.25, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (bs, 1H), 6.87 (bs, 1H), 5.30 (bs, 1H), 5.07 (dd, J = 8.4, 4.0 Hz, 1H), 4.77 (bs, 1H), 4.63 (bs, 1H), 4.11 (m, 1H), 3.75 (m, 1H), 3.64 (m, 1H), 3.11 (s, 3H), 2.78 (s, 3H), 2.23 (m, 1H), 2.00 (s, 3H), 1.91 (m, 1H), 1.77 (m, 1H), 1.64 (m, 1H), 1.49 (s, 9H), 1.22 (bs, 3H), 1.06−0.98 (m, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.5, 171.6, 170.5, 169.9, 69.2, 62.2, 56.1, 52.2, 36.5, 31.6, 29.8, 29.2, 28.2, 26.7, 24.5, 23.0, 21.3, 20.7, 19.7, 18.5, 16.6; MS (CI) *m/e* 502 $(M + H)^+$; IR (CH_2Cl_2) 3306, 2964, 2874, 1742, 1688, 1650, 1390, 1368, 1236, 1154, 736 cm^{-1}. Anal. Calcd for $C_{24}H_{43}O_8N_3$: C, 57.47; H, 8.64. Found: C, 57.03; H, 8.22.

***N*-Boc-*cis*-4-hydroxyproline (18).** To a solution of *cis-allo*-hydroxyproline (2.0 g, 15.2 mmol) in 10% triethylamine/methanol (25 mL) was added di-*tert*-butyl dicarbonate (6.63 g, 30.4 mmol). After being refluxed for 45 min, the reaction was allowed to cool and the solvent removed *in vacuo*. To the crude product was added NaH_2PO_4 (200 mg), and the solution was acidified to pH 2 with 1 N HCl. The solution was extracted with EtOAc (4 × 75 mL), and the combined organic fractions were collected and dried ($MgSO_4$), and the solvent was removed *in vacuo* to provide 5.59 g of crude product **18** (100%): $[\alpha]^{25}_D$ −38.1° (*c* 0.31, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (bs, 1H), 4.43 (m, 1H), 4.35 (m, 1H), 3.65 (m, 1H), 3.52 (m, 1H), 2.30 (m, 2H), 1.45 (s, 9H). MS (CI) *m/e* 232 $(M + H)^+$; IR (neat) 3440, 2976, 2924, 2878, 1736, 1706, 1672, 1408, 1372, 1256, 1090 cm^{-1}.

***N*-Boc-cis-4-HyPro-Ala-OBn (19).** L-Alanine benzyl ester (3.70 g, 17.2 mmol) was dissolved in dry CH_2Cl_2 (150 mL) and was treated with Boc-*cis*-HyPro (**18**, 3.51 g, 15.20 mmol). To this solution were added BOP-Cl (4.40 g, 17.2 mmol) and triethylamine (4.65 mL, 33.4 mmol). After being stirred overnight at 25 °C, the reaction mixture was washed with 50 mL each of aqueous NH_4Cl, aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed (SiO_2, 70−90% gradient, EtOAc−hexane) to provide 4.77 g (80%) of pure **19**: $[\alpha]^{25}_D$ −41.6° (*c* 0.15, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (bs, 1H), 7.35 (m, 5H), 6.81 (bs, 1H), 5.18 (s, 2H), 5.11 (d, J = 9.5 Hz, 1H), 4.60 (m, 1H), 4.35 (m, 1H), 3.50 (m, 2H), 2.23 (m, 2H), 1.45 (bs, 12H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.2, 172.0, 167.8, 128.5, 128.3, 128.0, 70.6, 67.0, 59.3, 56.8, 48.5, 36.0, 28.2, 17.5; MS (CI) *m/e* 393 $(M + H)^+$; IR (KBr) 3304, 2978, 1746, 1700, 1666, 1550, 1456, 1394, 1160, 752 cm^{-1}.

***N*-Boc-*cis*-4-(*tert*-butyldimethylsilyl)HyPro-Ala (20).** To a solution of alcohol **19** (4.27 g, 13.5 mmol) in CH_2Cl_2 (13 mL) was added 2,6-lutidine (3.15 mL, 27.0 mmol), followed by *tert*-butyldimethylsilyl triflate (4.65 mL, 20.2 mmol) at 0 °C. After stirring at 0 °C for 15 min, the reaction was allowed to warm to 25 °C and stir for 15 additional min. The reaction mixture was washed with water (50 mL), followed by extraction with CH_2Cl_2. The CH_2Cl_2 fractions were combined and dried ($MgSO_4$), the solvent was removed *in vacuo*, and the residue was chromatographed (SiO_2, 25−30% gradient, EtOAc−hexane) to provide 5.63g (97%) of the pure ether **20**: $[\alpha]^{25}_D$ −46.3° (*c* 0.19, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (bs, 5H), 6.90 (d, J = 7.7 Hz, 1H), 5.12 (s, 2H), 4.51 (m, 1H), 4.26 (m, 2H), 3.54 (m, 1H), 3.38 (m, 1H), 2.21 (m, 2H), 1.39 (s, 9H), 1.35 (d, J = 7.0 Hz, 3H), 0.80 (s, 9H), 0.00 (s, 6H). MS (CI) *m/e* 507 $(M + H)^+$; IR (neat) 3302, 2954, 2930, 2884, 2858, 1746, 1704, 1668, 1544, 1390, 1158, 838 cm^{-1}. Anal. Calcd for $C_{26}H_{42}O_6Si_1N_2$: C, 61.32; H, 8.35; N, 5.53. Found C, 61.51; H, 8.33; N, 5.50.

[*N*-Boc-*cis*-4-(*tert*-butyldimethylsilyl)HyPro-Ala]-2,2-dimethyl-1,3-dioxane-4,6-dione (21). The benzyl ester was dissolved in MeOH (50 mL), and to this solution was added 10% Pd/C (400 mg). The mixture was stirred under an atmosphere of H_2 (balloon) for 2 h, after which it was filtered. The filtrate was concentrated *in vacuo* to provide 2.62 g (90%) of **20** which was used crude in the next step: $[\alpha]^{25}_D$ −38.2° (*c* 0.10, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (bs, 1H), 6.88 (bs, 1H), 4.40 (m, 1H), 4.38 (bs, 1H), 4.30 (m, 1H), 3.55 (m, 1H), 3.31 (m, 1H), 2.22 (m, 1H), 2.18 (m, 1H), 1.38 (bs, 12H), 0.80 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.25, 172.51, 155.63, 81.10, 70.35, 60.06, 55.66, 53.41, 48.43, 28.07, 25.64, 17.98; MS (CI) *m/e* 417 $(M + H)^+$; IR (KBr) 3390, 2956, 2930, 2856, 1704, 1624, 1384, 1012, 780 cm^{-1}.

To a cooled (−5 °C) solution of **20** (2.50 g, 6.0 mmol), Meldrum's acid (1.29 g, 9.0 mmol), and DMAP (1.83 g, 15.0 mmol) in CH_2Cl_2 (22 mL) was added dropwise (0.5 h) a solution of isopropenyl chloroformate (0.72 mL, 6.6 mmol) in CH_2Cl_2 (6 mL). After stirring for 2 h at −5 °C, the reaction mixture was washed with 5% $KHSO_4$ (2 × 40 mL), dried ($MgSO_4$), and concentrated *in vacuo* to provide 3.21 g (98%) of **21**: $[\alpha]^{25}_D$ −24.3° (*c* 0.29, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 9.0 Hz, 1H), 7.60 (bs, 1H), 6.67 (d, J = 9.0 Hz, 1H), 5.61 (m, 1H), 4.32 (m, 2H), 3.19 (m, 2H), 2.35 (m, 1H), 1.68 (s, 6H), 1.41 (bs, 12H), 0.80 (bs, 9H), 0.00 (s, 6H); MS (CI) *m/e* 543 $(M + H)^+$; IR (KBr) 2954, 2932, 1756, 1726, 1694, 1472, 1394, 1258, 1164, 838 cm^{-1}.

(5*S*)-1-[*N*-Boc-*cis*-4-(*tert*-butyldimethylsilyl)HyPro-Ala]-4-hydroxy-5-methylpyrrol-2(5*H*)-one (22). Crude **21** (3.06 g, 5,64 mmol) was dissolved in CH_3CN (20 mL) and refluxed for 2.5 h. The solvent was removed under reduced pressure to provide 2.41 g (97%) crude pyrrolidine **22**: $[\alpha]^{25}_D$ −21.2° (*c* 0.38, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17 (m, 1H), 4.92 (m, 1H), 4.40 (m, 1H), 4.23 (m, 1H), 3.61 (m, 1H), 3.31 (s, 1H), 3.20 (m, 1H), 2.53 (m, 1H), 1.43 (m, 1H), 1.35 (s, 12H), 0.81 (s, 9H), −0.06 (s, 6H); MS (CI) *m/e* 441 $(M + H)^+$; IR (CH_2Cl_2) 2932, 1756, 1702, 1620, 1394, 1258, 1166, 776 cm^{-1}.

(5*S*)-1-[*N*-Boc-*cis*-4-(*tert*-butyldimethylsilyl)HyPro-Ala]-4-hydroxy-5-methylpyrrolidin-2-one (23). A solution of the crude pyrrol-2(5*H*)-one **22** (2.40 g, 5.44 mmol) was dissolved in a 10% mixture of HOAc/CH_2Cl_2 (30 mL), cooled in an ice bath, and stirred vigorously while being treated portionwise with $NaBH_4$ (0.38g, 10.1 mmol) over 0.5 h. The mixture was maintained for an additional 4 h at the same temperature. It was then poured into ice-cold water and the organic layer was washed with water and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude oil obtained was chromatographed (SiO_2, 42−50% gradient, EtOAc−hexane) to provide 1.63 g (73%) of pure **23**: $[\alpha]^{25}_D$ −10.6° (*c* 0.10, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (m, 1H), 4.41 (m, 2H), 4.28 (m, 1H), 3.68 (m, 1H), 3.25 (m, 2H), 2.68 (m, 2H), 2.51 (m, 1H), 1.72 (m, 1H), 1.36 (s, 9H), 1.29 (m, 3H), 0.79 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.8, 172.0, 153.9, 79.8, 69.4, 65.2, 60.0, 56.7, 54.2, 39.5, 38.5, 28.2, 25.5, 17.7; MS (CI) *m/e* 443 $(M + H)^+$; IR (CH_2Cl_2) 3444, 2954, 2932, 1744, 1708, 1676, 1408, 1366, 1254, 1202, 1098, 838 cm^{-1}.

(5*S*)-1-[*N*-HCl-*cis*-4-HyPro-Ala]-5-methylpyrrol-2(5*H*)-one (C). Alcohol **23** (220 mg, 0.49 mmol) was dissolved in CH_2Cl_2 (4 mL) and treated with methanesulfonyl chloride (0.097 mL, 0.845 mmol) followed by triethylamine (0.21 mL, 1.49 mmol) at 25 °C. After 1 h, the reaction mixture was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.111 mL, 0.74 mmol), and this solution was allowed to stir for an additional 20 min. The solvent was removed *in vacuo* and chromatographed (SiO_2, 42−50% gradient, EtOAc−hexane) to provide 190 mg (90%) of the pure unsaturated product: $[\alpha]^{25}_D$ −3.3° (*c* 0.15, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 6.2, 2.2 Hz, 1H), 6.03 (dd, *J* = 5.9, 1.5 Hz, 1H), 5.19 (dd, *J* = 8.8, 6.2 Hz, 1H), 4.72 (dq, *J* = 6.6, 1.8 Hz, 1H), 4.31 (m, 1H), 3.79 (dd, *J* = 10.6, 6.6 Hz, 1H), 3.26 (d, *J* = 4.8 Hz, 1H), 2.62 (m, 1H), 1.74 (m, 1H), 1.45 (d, *J* = 6.9 Hz, 3H), 1.33 (s, 9H), 0.79 (s, 9H), 0.00 (s, 6H); MS (CI) *m/e* 425 $(M + H)^+$; IR (CH_2Cl_2) 2954, 2932, 2858, 1708, 1474, 1402, 1366, 1254, 1098, 838 cm^{-1}. Anal. Calcd for $C_{21}H_{36}O_5SiN_2$: C, 59.40; H, 8.55. Found: C, 59.32; H, 8.55.

The protected substrate (160 mg, 0.37 mmol) was treated with 4 N HCl in dioxane (4 mL) and was allowed to stir for 2 h at 0 °C. After 2 h, the solvent was removed *in vacuo* to provide 90.5 mg of crude **C** (97%) as a white solid: $[\alpha]^{25}_D$ +33.9° (*c* 0.06, MeOH); ^{1}H NMR (300 MHz, D_2O + MeOH-d_4) δ 7.61 (d, *J* = 5.1 Hz, 1H), 6.18 (d, *J* = 5.1 Hz, 1H), 5.24 (m, 1H), 4.83 (m, 1H), 4.55 (bs, 1H), 3.52 (bs, 1H), 3.47 (bs, 1H), 2.79 (m, 1H), 2.07 (m, 1H), 1.52 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.2, 171.3, 160.6, 127.7, 72.6, 64.1, 62.7, 57.4, 41.7, 20.3; MS (CI) *m/e* 211 $(M + H)^+$; IR (KBr) 3342, 3010, 2868, 2724, 1730, 1680, 1574, 1336, 1298, 818 cm^{-1}.

***N*-Boc-*N*-Me-Leu-OAc-Thr-*N*-Me-Val-[(5*S*)-1-[*N*-HCl-*cis*-4-HyPro-Ala]-5-methylpyrrol-2(5*H*)-one] (24).** The acid **7** (77.0 mg, 0.15 mmol) was dissolved in dry CH_2Cl_2 (2.0 mL), and was treated with the amine hydrochloride **C** (38 mg, 0.15 mmol). To this were added Bop-Cl (59.0 mg, 0.23 mmol) and triethylamine (0.047 mL, 0.34 mmol). After being stirred overnight at 25 °C, the reaction mixture was washed with 5 mL each of aqueous NH_4Cl, aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed (SiO_2, 80−100% gradient, EtOAc−hexane) to provide 52.8 mg (50%) of pure **24**: $[\alpha]^{25}_D$ −112.9° (*c* 0.12, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 6.2, 1.8 Hz, 1H), 6.88 (bs, 1H), 6.73 (bs, 1H), 6.09 (dd, *J* = 6.2, 1.5 Hz, 1H), 5.66 (dd, *J* = 9.5, 1.8 Hz, 1H), 5.28 (m, 1H), 5.02 (d, *J* = 11.3 Hz, 1H), 5.00 (dd, *J* = 8.8, 3.3 Hz, 1H), 4.81 (qt, *J* = 6.6, 1.8 Hz, 1H), 4.61 (m, 2H), 4.38 (bm, 1H), 3.83 (m, 2H), 3.11 (s, 3H), 2.78 (s, 3H), 2.49 (ddd, *J* = 14.6, 10.2, 5.1 Hz, 1H), 2.26 (m, 1H), 2.05 (s, 3H), 2.03 (m, 1H), 1.65 (m, 1H), 1.50 (bs, 13H), 1.19 (d, *J* = 6.2 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.2 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H); MS (CI) *m/e* 694 $(M + H)^+$; IR (neat) 3424, 2962, 2936, 2872, 1732, 1688, 1642, 1388, 1236 cm^{-1}.

***N*-HCl-*N*-Me-Leu-OAc-Thr-*N*-Me-Val-[(5*S*)-1-[*N*-HCl-*cis*-4-HyPro-Ala]-5-methylpyrrol-2(5*H*)-one] (25).** The substrate **24** (70 mg, 0.100 mmol) was treated with 4 N HCl in dioxane (3 mL) and was allowed to stir for 4 h at 0 °C. After 4 h, the solvent was removed *in vacuo* to provide 62.1 mg of crude **25** (98%): $[\alpha]^{25}_D$ −82.1° (*c* 0.14, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.8 Hz, 1H), 7.28 (dd, *J* = 6.2, 2.2 Hz, 1H), 6.10 (dd, *J* = 6.2, 1.4 Hz, 1H), 5.88 (bs, 1H), 5.65 (dd, *J* = 9.9, 2.5 Hz, 1H), 5.28 (m, 2H), 5.07 (dd, *J* = 8.4, 4.4 Hz, 1H), 5.04 (d, *J* = 11.0 Hz, 1H), 4.81 (qt, *J* = 7.0, 1.8 Hz, 1H), 4.39 (bm, 1H), 3.86 (d, *J* = 11.7 Hz, 1H), 3.77 (dd, *J* = 11.4, 4.4 Hz, 1H), 3.55 (t, *J* = 6.2 Hz, 1H), 3.14 (s, 3H), 2.55 (s, 3H), 2.51 (m, 1H), 2.29 (m, 1H), 2.03 (s, 3H), 2.00 (m, 1H), 1.66 (m, 3H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 5.8 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.7, 174.3, 171.5, 170.0, 170.0, 169.8, 168.5, 154.1, 125.2, 71.6, 68.6, 62.1, 59.2, 58.5, 58.0, 56.6, 52.2, 40.9, 36.4, 33.1, 30.5, 27.0, 24.8, 22.4, 22.2, 20.9, 18.7, 18.0, 17.3, 16.8; MS (CI) *m/e* 594.6 $(M + H)^+$; IR (CH_2Cl_2) 3326, 2962, 2874, 1730, 1642, 1460, 1408, 1374, 1238, 1062 cm^{-1}.

Microcolin A (26d). Amine hydrochloride **25** (14.0 mg, 0.022 mmol) was dissolved in dry CH_2Cl_2 (0.5 mL) and was treated with acid **7d** (4.9 mg, 0.029 mmol). To this solution were added BOP-Cl (7.5 mg, 0.029 mmol) and triethylamine (6.8 mL, 0.029 mmol). After being stirred overnight at 25 °C, the reaction mixture was washed with 5 mL each of aqueous NH_4Cl, aqueous $NaHCO_3$, and brine, concentrated *in vacuo*, and chromatographed (SiO_2, 80−100% gradient, EtOAc−hexane) to provide 9.3 mg (56%) of pure microcolin A: $[\alpha]^{25}_D$ −132° (*c* 0.02, EtOH); Lit.[10] $[\alpha]^{25}_D$ −145.3°(*c* 0.0026, EtOH): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 6.0, 2.0 Hz, 1H, H-3), 7.02 (d, *J* = 8.9 Hz, 1H, H-22), 6.09 (dd, *J* = 6.0, 1.6 Hz, 1H, H-2), 5.66 (dd, *J* = 10.0, 2.4 Hz, 1H, H-8), 5.28 (dd, *J* =10.3, 5.6 Hz, 1H, H-28), 5.25 (m, 1H, H-23), 5.02 (d, *J* = 11.1 Hz, 1H, H-14), 4.96 (dd, *J* = 8.9, 3.0 Hz, 1H, H-21), 4.81 (qt, *J* = 6.8, 1.9 Hz, 1H, H-4), 4.38 (m, 1H, H-10), 3.84 (m, 2H, H-11), 3.09 (s, 3H, H-19), 2.96 (s, 3H, H-34), 2.85 (m, 1H, H-36), 2.49 (ddd, *J* = 14.3, 10.0, 4.8 Hz, 1H, H-9), 2.26 (m, 1H, H-16), 2.02 (m, 1H, H-9), 2.01 (s, 3H, H-26), 1.88 (ddd, *J* = 13.3, 9.5, 4.5 Hz, 1H, H-37), 1.73 (ddd, *J* = 14.0, 10.5, 4.9 Hz, 1H, H-30), 1.58 (ddd, *J* = 14.0, 9.5, 5.7 Hz, 1H, H-30), 1.47 (d, *J* = 6.8 Hz, 3H, H-6), 1.44 (m, 1H, H-31), 1.34 (m, 1H, H-38), 1.28 (m, 1H, H-39), 1.28 (m, 2H, H-40), 1.28 (m, 2H, H-41), 1.17 (d, *J* = 6.5 Hz, 3H, H-24), 1.13 (d, *J* = 6.8 Hz, 3H, H-43), 1.12 (m, 1H, H-37), 1.11 (m, 1H, H-39), 0.99 (d, *J* = 6.5 Hz, 3H, H-18), 0.95 (d, *J* = 6.6 Hz, 3H, H-33), 0.89 (t, *J* = 6.6 Hz, 3H, H-42), 0.87 (d, *J* = 6.5 Hz, 3H, H-32), 0.85 (d, *J* = 6.5 Hz, 3H, H-44), 0.82 (d, *J* = 6.7 Hz, 3H, H-17); ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.9 (C-35), 174.5 (C-7), 171.3 (C-27), 169.8 (C-1), 169.8 (C-20), 169.8 (C-25), 168.9 (C-13), 154.1 (C-3), 125.3 (C-2), 71.7 (C-10), 68.4 (C-23), 59.2 (C-14), 58.6 (C-8), 58.1 (C-4), 56.9 (C-11), 53.8 (C-28), 51.8 (C-21), 41.8 (C-37), 37.0 (C-39), 36.6 (C-9), 35.8 (C-30), 33.7 (C-36), 30.7 (C-38), 30.3 (C-19), 30.3 (C-34), 29.1 (C-40), 27.1 (C-16), 24.8 (C-31), 23.3 (C-33), 22.8 (C-41), 21.5 (C-32), 21.0 (C-26), 19.5 (C-44), 18.8 (C-18), 18.4 (C-17), 18.2 (C-43), 17.3 (C-24), 16.9 (C-6), 14.0 (C-42); MS (CI) *m/e* 748.8 $(M + H)^+$. Anal. Calcd for $C_{39}H_{66}O_9N_5$: C, 62.54; H, 8.88. Found C, 62.11; H, 8.77.

Data for C-36*S*, C-38*S* *epi*-microcolin (26a): $[\alpha]^{25}_D$ −150° (*c* 0.02, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 6.1, 2.1 Hz, 1H, H-3), 6.81 (d, *J* = 8.9 Hz, 1H, H-22), 6.09 (dd, *J* = 6.1, 1.7 Hz, 1H, H-2), 5.67 (dd, *J* = 10.0, 2.1 Hz, 1H, H-8), 5.26 (m, 1H, H-23), 5.24 (m, 1H, H-28), 5.02 (d, *J* = 11.1 Hz, 1H, H-14), 4.96 (dd, *J* = 8.8, 2.8 Hz, 1H, H-21), 4.81 (qdd, *J* = 6.8, 2.1, 1.7 Hz, 1H, H-4), 4.38 (m, 1H, H-10), 3.87 (dd, *J* = 11.8, 1.6 Hz, 1H, H-11), 3.80 (dd, *J* = 11.8, 4.4 Hz, 1H, H-11), 3.10 (s, 3H, H-19), 2.98 (s, 3H, H-34), 2.86 (m, 1H, H-36), 2.48 (ddd, *J* = 14.3, 10.7, 5.2 Hz, 1H, H-9), 2.26 (m, 1H, H-16), 2.00 (m, 1H, H-9), 2.00 (s, 3H, H-26), 1.80 (ddd, *J* = 13.6, 8.1, 5.9 Hz, 1H, H-37), 1.67 (m, 2H, H-30), 1.47 (d, *J* = 6.8 Hz, 3H,

H-6), 1.46 (m, 1H, H-38), 1.44 (m, 1H, H-31), 1.31 (m, 1H, H-39), 1.28 (m, 2H, H-41), 1.26 (m, 2H, H-40), 1.17 (d, J = 6.5 Hz, 3H, H-24), 1.12 (d, J = 6.8 Hz, 3H, H-43), 1.10 (m, 1H, H-37), 1.09 (m, 1H, H-39), 0.99 (d, J = 6.5 Hz, 3H, H-18), 0.94 (d, J = 6.6 Hz, 3H, H-33), 0.88 (t, J = 6.6 Hz, 3H, H-42), 0.88 (d, J = 6.5 Hz, 3H, H-32), 0.86 (d, J = 6.6 Hz, 3H, H-44), 0.81 (d, J = 6.7 Hz, 3H, H-17); ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.7 (C-35), 174.7 (C-7), 171.3 (C-27), 169.8 (C-1), 169.8 (C-20), 169.7 (C-25), 168.9 (C-13), 154.1 (C-3), 125.4 (C-2), 71.9 (C-10), 68.4 (C-23), 59.2 (C-14), 58.6 (C-8), 58.1 (C-4), 57.0 (C-11), 54.4 (C-28), 51.8 (C-21), 41.4 (C-37), 36.8 (C-39), 36.6 (C-9), 36.6 (C-30), 33.7 (C-36), 30.7 (C-34), 30.5 (C-38), 30.4 (C-19), 29.7 (C-40), 27.1 (C-16), 25.0 (C-31), 23.2 (C-33), 23.1 (C-41), 21.8 (C-32), 21.0 (C-26), 20.0 (C-44), 18.9 (C-18), 18.4 (C-17), 18.1 (C-43), 17.4 (C-24), 16.9 (C-6), 14.1 (C-42); MS (CI) *m/e* 748.8 $(M + H)^+$.

Data for C-36*S*, C-38*R* *epi*-microcolin (26b): $[\alpha]^{25}_D$ −121.6° (*c* 0.088, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 6.0, 2.0 Hz, 1H, H-3), 6.83 (d, J = 8.9 Hz, 1H, H-22), 6.06 (dd, J = 6.0, 1.6 Hz, 1H, H-2), 5.64 (dd, J = 10.0, 2.2 Hz, 1H, H-8), 5.23 (m, 1H, H-23), 5.18 (dd, J = 8.5, 7.3 Hz, 1H, H-28), 4.99 (d, J = 11.1 Hz, 1H, H-14), 4.93 (dd, J = 8.9, 2.9 Hz, 1H, H-21), 4.78 (qt, J = 6.8, 1.9 Hz, 1H, H-4), 4.35 (m, 1H, H-10), 3.83 (dt, J = 11.6, 1.4 Hz, 1H, H-11), 3.78 (dd, J = 11.6, 4.3 Hz, 1H, H-11), 3.07 (s, 3H, H-19), 2.94 (s, 3H, H-34), 2.77 (m, 1H, H-36), 2.45 (ddd, J = 14.2, 10.1, 4.8 Hz, 1H, H-9), 2.23 (m, 1H, H-16), 1.98 (s, 3H, H-26), 1.64 (m, 2H, H-30), 1.45 (m, 1H, H-38), 1.44 (d, J = 6.8 Hz, 3H, H-6), 1.43 (m, 1H, H-31), 1.42 (m, 2H, H-37), 1.26 (m, 2H, H-41), 1.25 (m, 1H, H-39), 1.25 (m, 1H, H-39), 1.25 (m, 2H, H-40), 1.14 (d, J = 6.5 Hz, 3H, H-24), 1.13 (m, 1H, H-37), 1.08 (d, J = 6.7 Hz, 3H, H-43), 0.96 (d, J = 6.5 Hz, 3H, H-18), 0.91 (d, J = 6.7 Hz, 3H, H-33), 0.85 (t, J = 6.8 Hz, 3H, H-42), 0.85 (d, J = 6.6 Hz, 3H, H-32), 0.84 (d, J = 6.5 Hz, 3H, H-44), 0.78 (d, J = 6.7 Hz, 3H, H-17); ^{13}C NMR (400 MHz, $CDCl_3$) δ 178.0 (C-35), 174.6 (C-7), 171.1 (C-27), 169.8 (C-1), 169.8 (C-20), 169.8 (C-25), 168.9 (C-13), 154.1 (C-3), 125.3 (C-2), 71.8 (C-10), 68.4 (C-23), 59.2 (C-14), 58.6 (C-8), 58.1 (C-4), 56.9 (C-11), 54.6 (C-28), 51.9 (C-21), 41.8 (C-37), 37.3 (C-39), 36.1 (C-9), 35.4 (C-30), 33.8 (C-36), 30.4 (C-38), 30.4 (C-19), 30.6 (C-34), 29.0 (C-40), 27.1 (C-16), 24.9 (C-31), 23.1 (C-33), 22.9 (C-41), 21.8 (C-32), 21.0 (C-26), 19.4 (C-44), 18.8 (C-18), 18.3 (C-17), 17.4 (C-24), 17.0 (C-43), 16.9 (C-6), 14.1 (C-42); MS (CI) *m/e* 748.8 $(M + H)^+$.

Data for C-36*R*, C-36*S* *epi*-microcolin (26c): $[\alpha]^{25}_D$ −148.6° (*c* 0.074, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, J = 6.1, 2.1 Hz, 1H, H-3), 7.03 (d, J = 8.9 Hz, 1H, H-22), 6.09 (dd, J = 6.1, 1.6 Hz, 1H, H-2), 5.66 (dd, J = 9.9, 2.3 Hz, 1H, H-8), 5.26 (m, 1H, H-28), 5.25 (m, 1H, H-23), 5.02 (d, J = 11.1 Hz, 1H, H-14), 4.96 (dd, J = 8.9, 3.1 Hz, 1H, H-21), 4.81 (m, 1H, H-4), 4.38 (m, 1H, H-10), 3.84 (m, 2H, H-11), 3.10 (s, 3H, H-19), 2.96 (s, 3H, H-34), 2.82 (dd, J = 6.7, 6.7 Hz, 1H, H-36), 2.49 (m, 1H, H-9), 2.27 (m, 1H, H-16), 2.02 (m, 1H, H-9), 2.00 (s, 3H, H-26), 1.67 (m, 2H, H-30), 1.61 (m, 1H, H-37), 1.46 (d, J = 6.8 Hz, 3H, H-6), 1.40 (m, 1H, H-38), 1.43 (m, 1H, H-31), 1.35 (m, 1H, H-37), 1.30 (m, 1H, H-39), 1.28 (m, 2H, H-41), 1.29 (m, 2H, H-40), 1.16 (d, J = 6.5 Hz, 3H, H-24), 1.12 (d, J = 6.7 Hz, 3H, H-43), 1.09 (m, 1H, H-39), 0.99 (d, J = 6.5 Hz, 3H, H-18), 0.94 (d, J = 6.7 Hz, 3H, H-33), 0.89 (m, 3H, H-42), 0.87 (d, J = 6.6 Hz, 3H, H-32), 0.86 (m, 3H, H-44), 0.82 (d, J = 6.7 Hz, 3H, H-17); ^{13}C NMR (400 MHz, $CDCl_3$) δ 178.0 (C-35), 174.5 (C-7), 171.3 (C-27), 169.8 (C-1), 169.8 (C-20), 169.8 (C-25), 168.9 (C-13), 154.1 (C-3), 125.3 (C-2), 71.8 (C-10), 68.4 (C-23), 59.2 (C-14), 58.6 (C-8), 58.1 (C-4), 56.9 (C-11), 53.9 (C-28), 51.9 (C-21), 41.5 (C-37), 36.6 (C-39), 36.5 (C-9), 36.0 (C-30), 33.8 (C-36), 30.7 (C-38), 30.4 (C-34), 30.3 (C-19), 29.2 (C-40), 27.1 (C-16), 24.8 (C-31), 23.2 (C-33), 23.0 (C-41), 21.7 (C-32), 21.0 (C-26), 19.7 (C-44), 18.8 (C-18), 18.4 (C-17), 17.5 (C-43), 17.4 (C-24), 16.9 (C-6), 14.1 (C-42); MS (CI) *m/e* 748.8 $(M + H)^+$.

Acknowledgment. The authors gratefully thank Dr. Gregory Nemeth and Ernie Schubert for their analytical contribution and NMR spectral interpretation. P.G. acknowledges DMPC for their financial support in the form of an industrial postdoctoral fellowship.

Supporting Information Available: Copies of NMR spectra (22 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.

JO952123L