Total Synthesis of the Thiopeptide Promothiocin A

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Abstract: The thiopeptide (or thiostrepton) antibiotics are a class of sulfur-containing highly modified cyclic peptides with interesting biological activity. Described herein is the total synthesis of the thiopeptide antibiotic promothiocin A, which utilizes a modified Bohlmann−Rahtz pyridine synthesis to establish the oxazolyl−thiazole−pyridine heterocyclic centerpiece of the antibiotic. The oxazole building blocks were obtained by a dirhodium(II)-catalyzed chemoselective carbenoid N−H insertion reaction followed by cyclodehydration, and the thiazoles by the Hantzsch reaction. Two different strategies for macrocyclization were successfully employed, with the dehydroalanine side chain of the natural product being introduced in the last steps of the synthesis.

Introduction

The thiopeptide (or thiostrepton) antibiotics are a class of sulfur-containing highly modified cyclic peptides characterized by several common structural features: the presence of thiazole and, in some cases, oxazole rings, unusual and dehydro amino acids, and a heterocyclic centerpiece of a tri- or tetrasubstituted pyridine all in a macrocyclic array. Many of the compounds such as thiostrepton itself,[1] nosiheptide,[2] and the micrococcins[3,4] (Figure 1) have been known for some time; others such as the amythiamycins,[5−7] and the promothiocins[8] (Figure 2), have been isolated more recently.

Most of the thiopeptide antibiotics inhibit protein synthesis in bacteria, and share a common mode of action. They act by binding to the complex of 23SrRNA with ribosomal protein L11, inhibiting the action of GTP-dependent elongation factors,[9,10] although this has only been studied in detail for thiostrepton. The role of thiopeptides in gene regulation has also been studied, and recently attempts have been made to delineate some basic structure activity relationships, for example, the importance of the dehydroalanine side chains, within the series of natural products.[11] In addition, thiopeptides have some potential as antimalarials,[12,13] micrococcin being a potent growth inhibitor of the human malaria parasite *Plasmodium falciparum.*[14]

Despite the fascinating biological activity of the thiopeptide antibiotics, little synthetic work has been carried out to date, and the only reported total synthesis is that of micrococcin.[15−17] However, the syntheses of various fragments of nosiheptide,[18−24] and of the pyridine fragments of berninamycin,[25] the micrococcins,[26,27] the sulfomycins,[28,29] A10255,[30] and GE 2270 A[31] have been reported. We now describe the details of the first

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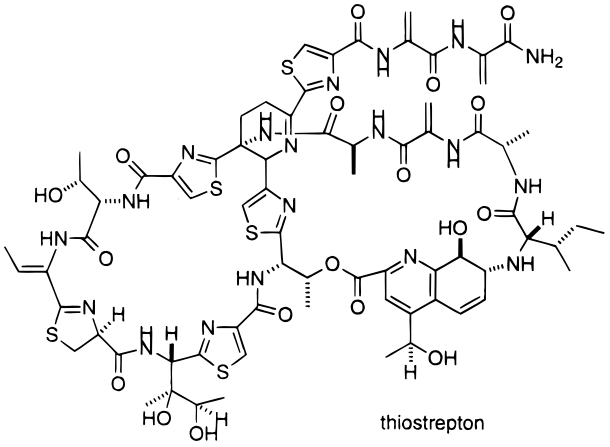
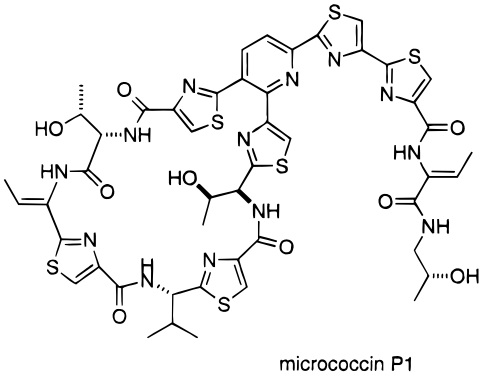




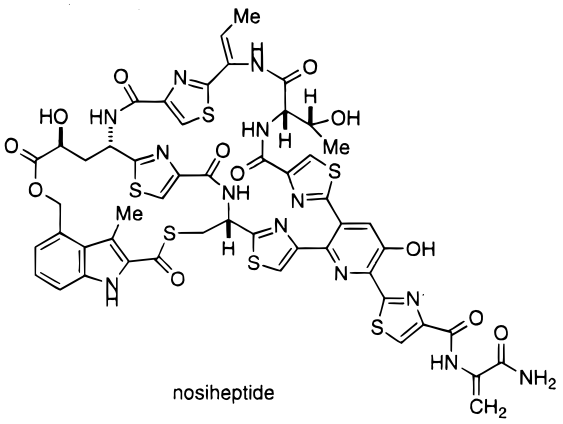
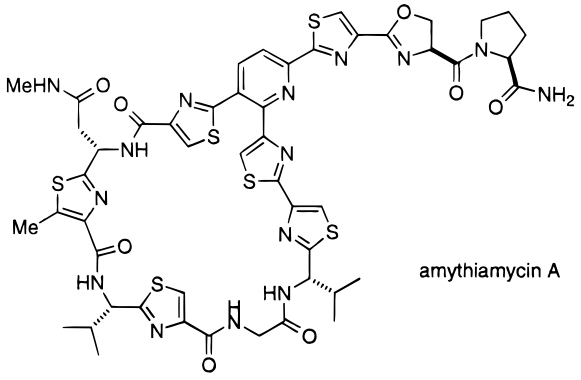


Figure 1. Structures for thiostrepton, micrococcin P1, and nosiheptide.



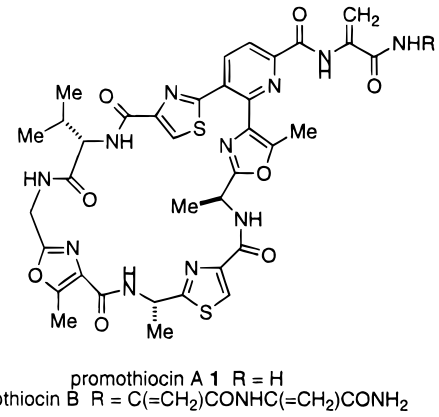


Figure 2. Structures for amythiamycin A and promothiocin A.

total synthesis of promothiocin A (**1**),[32] a thiopeptide antibiotic isolated from *Streptomyces* sp. SF2741.[8]

Results and Discussion

The structure of promothiocin A (**1**) was established by NMR spectroscopy, although the stereochemistry of the natural product was not reported.[8] Therefore we have assumed that the three stereocenters result from natural amino acids as indicated in Figure 2, and could be incorporated from suitable derivatives of (*S*)-alanine and (*S*)-valine. The overall plan, indicated by the arrows in Scheme 1 was to form the macrocycle by two peptide-coupling reactions followed by introduction of the dehydroalanine (Dha) side chain (3) as the last step. Two bonds, labeled as (1) and (2) in Scheme 1, were selected as possible sites for the key macrocyclization reaction. Both strategies required an oxazole−thiazole−pyridine fragment **2** and the peptide fragments **3** or **4** which would appear to be readily easily synthesized from valine and the oxazole and thiazole amino acid derivatives **6a** and **7** (Scheme 1). Further analysis of the pyridine **2** reveals a slightly simpler trisubstituted pyridine **5**, with the thiazole ring being built up from the ester via the corresponding thioamide in a conventional Hantzsch synthesis.

In view of the difficulties associated with the synthesis of polysubstituted pyridines, we decided at the outset that we would construct the pyridine fragment by a ring synthesis rather than by an approach involving sequential modification and substitution of an existing ring. At the time (1996), all published approaches to related pyridines (see above) relied on this stepwise modification of a preformed pyridine, although during the course of our work, Ciufolini published an elegant synthesis of the heterocyclic core of the micrococcins, in which the pyridine ring was assembled from two fragments which were combined to give a 1,5-diketone precursor for subsequent reaction with ammonia and final dehydrogenation to aromatize the ring.[33] Our plan (Scheme 2) was to construct the pyridine **5** by the reaction of an enamine with an ynone.

This method of pyridine formation (enamine plus ynone), first reported by Bohlmann and Rahtz 40 years ago (Scheme 3),[34] has found little use to date, and although it is related to the corresponding reaction of enamines with enones and hence to the well-known Hantzsch dihydropyridine synthesis, the use of ynones leads to an aromatic product directly thus obviating the need for a final aromatizing oxidative step.

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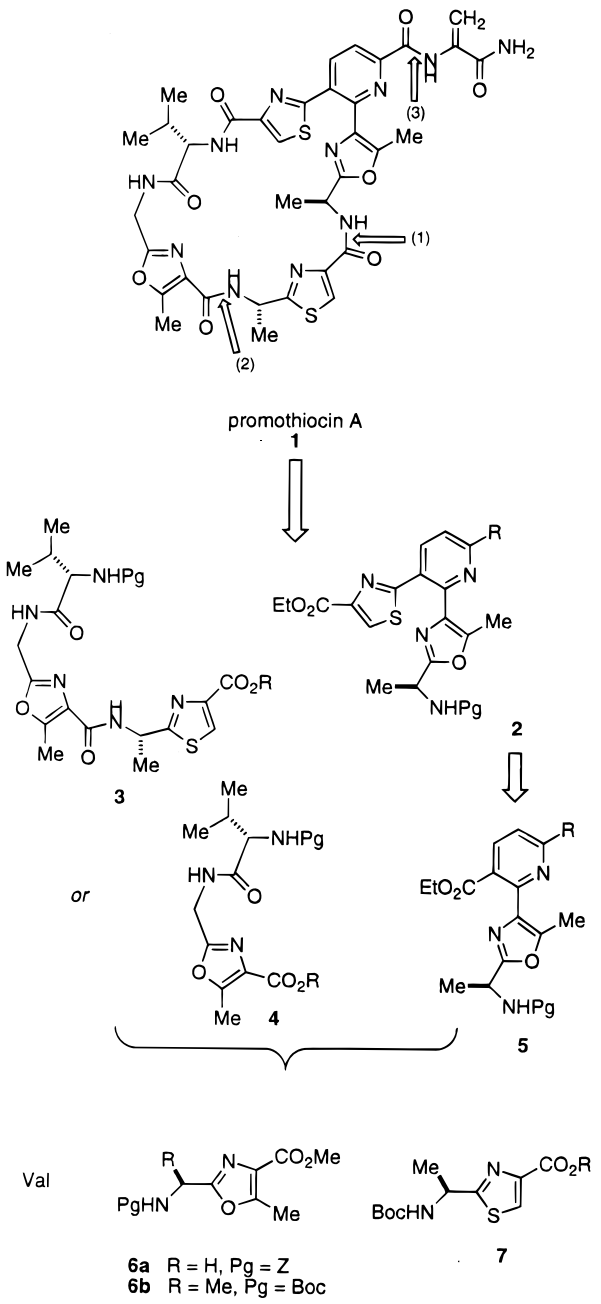
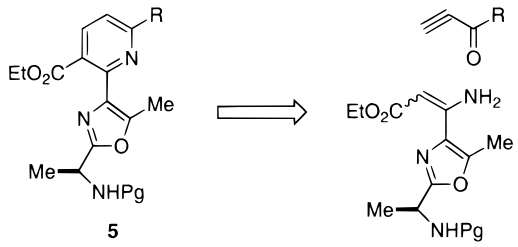
Scheme 1[a]



[a] Pg = protecting group; (1), (2) = alternative sites for macrocyclization; (3) = attachment of Dha side chain.

Scheme 2



In their original paper,[34] Bohlmann and Rahtz reported the synthesis of a number of simple alkyl- and aryl-substituted pyridine-3-esters or -nitriles, for example, as shown in Scheme 3. If the method is to be extended to the synthesis of pyridines suitable for incorporation into thiopeptides, then the inclusion of heteroaromatic groups at C-2 and C-6 (pyridine numbering) is required. Therefore we have carried out a brief investigation of the scope of the Bohlmann−Rahtz reaction. Enamino esters **8**−**10** and alkynones **11**−**13** were prepared by standard methodology (see Experimental Section), and using these substrates we have developed a standard set of conditions for the pyridine-forming reaction. Thus the enamino ester and acetylenic ketone were stirred together in ethanol at ca. 50 °C overnight to effect the initial conjugate addition reaction, followed by removal of the solvent and heating of the residue at 125−140 °C for 1 h to effect the cyclization.

Scheme 3

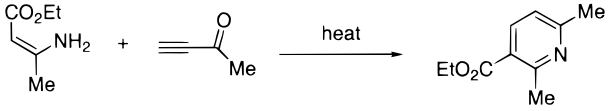
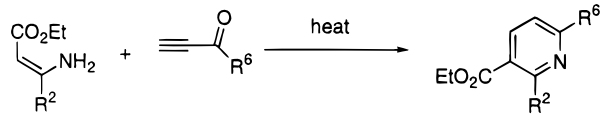


Table 1. Reaction of Enamino Esters with Alkynones



8 - 10 **11 - 13** **14 - 18**

enamino ester	R^2	alkynone	R^6	pyridine	yield/%
9	Ph	**11**	Me	**14**	89
10	2-thienyl	**11**	Me	**15**	81
8	Me	**12**	4-tolyl	**16**	100
8	Me	**13**	2-thiazolyl	**17**	97
10	2-thienyl	**13**	2-thiazolyl	**18**	70

In this manner the pyridines **14**−**18** were formed in good yield (Table 1). Heteroaromatic substituents are clearly tolerated at C-2 and C-6, although the need to use a 5-fold excess of the alkynone to obtain good yields somewhat detracts from using the method to access pyridines that contain such a substituent at C-6, such as the core heterocyclic structures of the micrococcins and amythiamycins. Nevertheless, it appeared that our projected synthesis of the pyridine core **5** of promothiocin A (Scheme 2) was viable.

The synthesis itself began with *N*-Boc-alaninamide,[35] which was converted into the chiral oxazole **6b** using a route based on our previously developed rhodium carbenoid N−H insertion methodology.[36] Dirhodium(II) acetate catalyzed reaction of the alaninamide with methyl diazoacetoacetate resulted in regioselective insertion of the presumed metallocarbenoid intermediate into the amide N−H bond to give the ketoamide **19** in 80% yield. Cyclodehydration using the Wipf protocol (Ph_3P, I_2, Et_3N)[37] gave the required oxazole **6b** in good yield, and without racemization as judged by HPLC on a chiral stationary phase. Subsequent hydrolysis gave the corresponding carboxylic acid **20** ready for homologation to the β-ketoester **21**, the precursor to the required enamino ester **22.** The homologation of the acid **20** was carried out by mixed anhydride formation followed by reaction with magnesium ethyl malonate,[38] and gave the β-ketoester **21**. More recent methods of homologation involving imidazolides[39] or acid chlorides[40,41] were all less satisfactory

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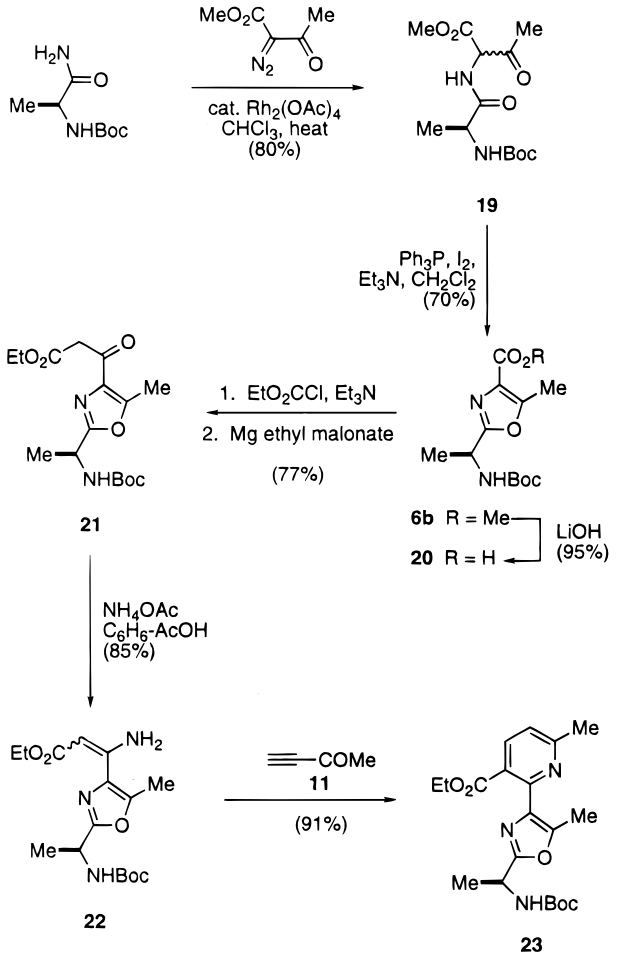
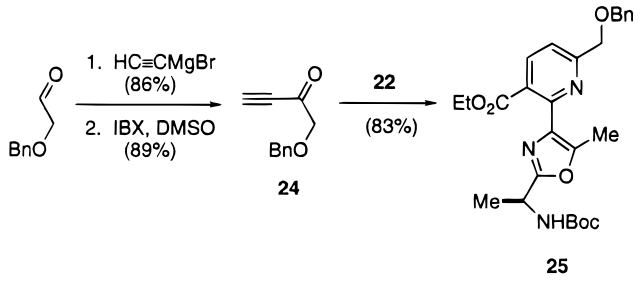
Scheme 4



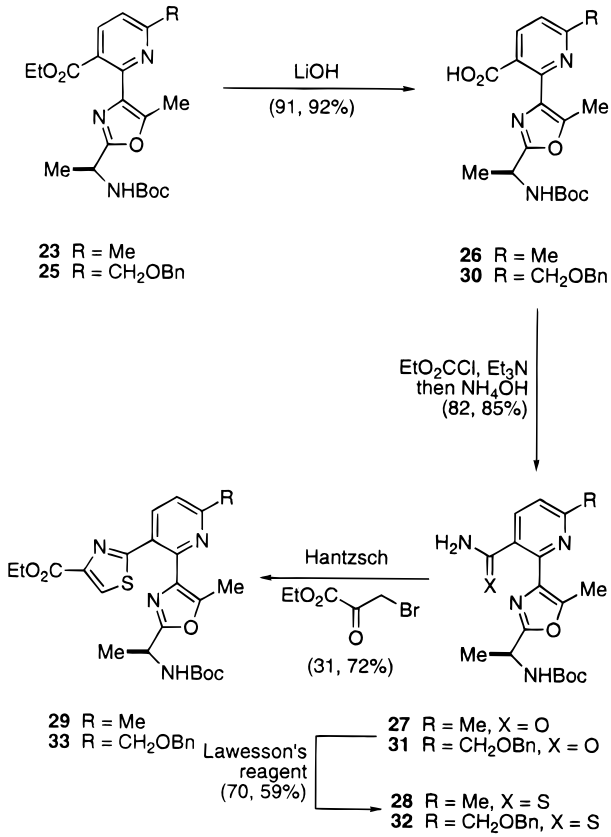
than the mixed anhydride method. The required enamine **22** was formed by reaction of β-ketoester **21** with ammonium acetate in benzene−acetic acid, although an increase in the amount of ammonium acetate and acetic acid over and above those specified in the literature procedure[42] was necessary for complete conversion. The enamino ester **22** was isolated as a single geometric isomer, presumed to be the *Z*-isomer. The key pyridine-forming step was initially carried out using commercially available 3-butyn-2-one (**11**) as the acetylenic ketone component, and proceeded under our standard conditions to give the 2,3,6-trisubstituted pyridine **23** in excellent yield (Scheme 4).

Although, in principle, the 6-methyl group in the pyridine **23** could be used as a precursor to the carboxylic acid that is eventually required at that position for coupling to a dehydroalanine fragment, it was decided to incorporate a more highly functionalized carbon at C-6. A protected primary alcohol group was chosen rather than carry through another ester group, the deprotection of which would require a method that was orthogonal to the other ester groups present (q.v.). The required aldehyde **24** was prepared from benzyloxyacetaldehyde by addition of ethynylmagnesium bromide followed by oxidation of the resulting propargylic alcohol with *o*-iodoxybenzoic acid (IBX) in DMSO.[43,44] Simply heating alkynone **24** with enamine

Scheme 5



Scheme 6



22 gave the required 2,3,6-trisubstituted pyridine **25** in good yield (Scheme 5), establishing that the Bohlmann−Rahtz method can be used for the synthesis of relatively complex pyridines.

With a route to the key pyridine (structure **5**, Scheme 1) established, the next step was to elaborate the thiazole ring at the 3-position to complete the synthesis of the heterocyclic core of the promothiocins. The reaction was initially carried out on the 6-methylpyridine **23**, and although the early steps [ester hydrolysis (91%), conversion to the corresponding amide **27** (82%) and hence thioamide **28** (70%)] proceeded without incident and in good yield (Scheme 6), the reaction of thioamide **28** with ethyl bromopyruvate under standard Hantzsch reaction conditions proceeded in poor yield (31%). Therefore, in the case of the 6-(benzyloxymethyl)pyridine-3-thiocarboxamide **32**, obtained from the ester **25** via the acid **30** and amide **31** (Scheme 6), the modified Hantzsch procedure was employed. This method, which was originally developed for the synthesis of thiazoles from thioamides containing a chiral center obtained from α-amino acids (see below),[45−49] involved reaction of the

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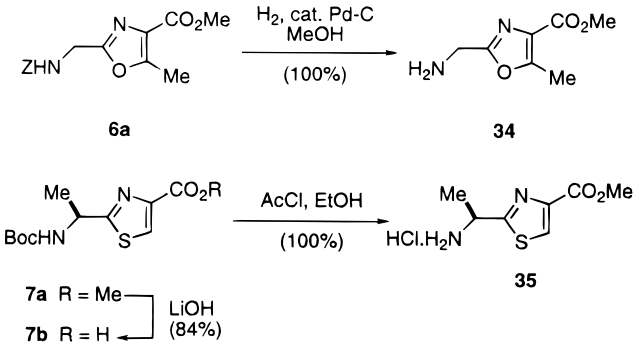
Scheme 7



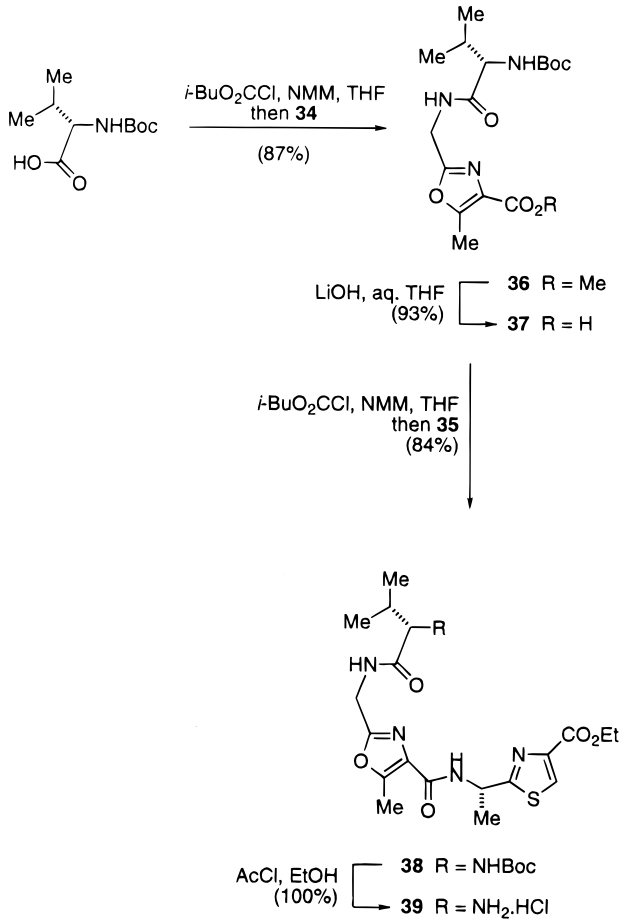
thioamide **32** with ethyl bromopyruvate in the presence of potassium hydrogen carbonate below 0 °C followed by dehydration of the intermediate thiazoline using trifluoroacetic anhydride and 2,6-lutidine and gave the required 2-oxazolyl-3-thiazolylpyridine **33** in good yield (72%) (Scheme 6).

With the heterocyclic core of the promothiocins now in hand, attention was turned to the assembly of a suitable tripeptide **3** for coupling to the pyridine fragment in macrocyclization strategy (1) (Scheme 1). This required the deprotection of the amino groups in the oxazole **6a** and thiazole **7a**. Thus the oxazole **6a**, prepared as previously described,[36] was deprotected by hydrogenolysis of the benzyloxycarbonyl group over palladium-on-charcoal to give the aminomethyloxazole **34** in quantitative yield (Scheme 7). Similarly, the known *N*-protected aminoethylthiazole **7a**, obtained with an ee of >99.5% using the modified Hantzsch procedure,[48] was deprotected using ethanolic HCl to give the amine hydrochloride **35** and, separately, hydrolyzed to the known acid **7b** (Scheme 7).[50]

The assembly of the tripeptide fragment started with *N*-Boc-valine which was coupled to the aminomethyloxazole **34** in high yield by mixed anhydride methodology using isobutyl chloroformate and *N*-methylmorpholine (NMM) as base. This gave the protected valine−oxazole dipeptide **36**, hydrolysis of which gave the carboxylic acid **37**. Mixed anhydride activation of the acid **37** followed by coupling with aminoethylthiazole **35** gave the valine−oxazole−thiazole tripeptide **38** in high yield (Scheme 8). Finally, deprotection of the *N*-terminal Boc group with ethanolic HCl gave the amine hydrochloride **39** for subsequent coupling to the pyridine fragment.

The coupling of the upper and lower fragments of the promothiocin macrocycle was also achieved using mixed anhydride methodology. Thus hydrolysis of the ethyl ester in the oxazolyl−thiazolyl−pyridine **33** gave the corresponding acid **40**. This was followed by activation with isobutyl chloroformate/NMM and coupling to the amine **39**, and resulted in the formation of the terminally protected linear "peptide" **41** in 69% yield (Scheme 9). Although there are several methods available for the synthesis of macrocyclic lactams by formation of the amide bond, we favor the Schmidt pentafluorophenyl ester protocol[51−55] used in our recent synthesis of nostocyclamide.[56]

Scheme 8



Hence the *C*-terminal ester group in **41** was hydrolyzed and the resulting acid **42** converted into the corresponding pentafluorophenyl ester by coupling with pentafluorophenol in the presence of the water-soluble carbodiimide reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI). The active ester was not purified but was treated with a solution of HCl in dioxane to effect deprotection of the *N*-terminal Boc group. Workup with aqueous potasium hydrogen carbonate and subsequent treatment with triethylamine then effected the desired lactamization reaction to give the promothiocin macrocycle **43** (Scheme 9).

With the successful cyclization of the peptide **42** to give the promothiocin macrocycle **43**, attention was turned to the alternative lactamization protocol (strategy 2, Scheme 1). Thiazole carboxylic acid **40** was activated using the mixed anhydride method and reacted with the amine hydrochloride **44**, obtained by deprotection of the valine−oxazole dipeptide **36**, to give the coupled product **45** in modest yield (Scheme 10). The pyridine peptide **45** was deprotected at its *N*-terminus and coupled with the thiazole carboxylic acid **7b**, again using the proven mixed anhydride methodology to give the protected cyclization precursor **46** in 77% yield. Macrolactamization was then effected using the protocol developed for the first route. Thus the *C*-terminal methyl ester in **46** was hydrolyzed (92%)

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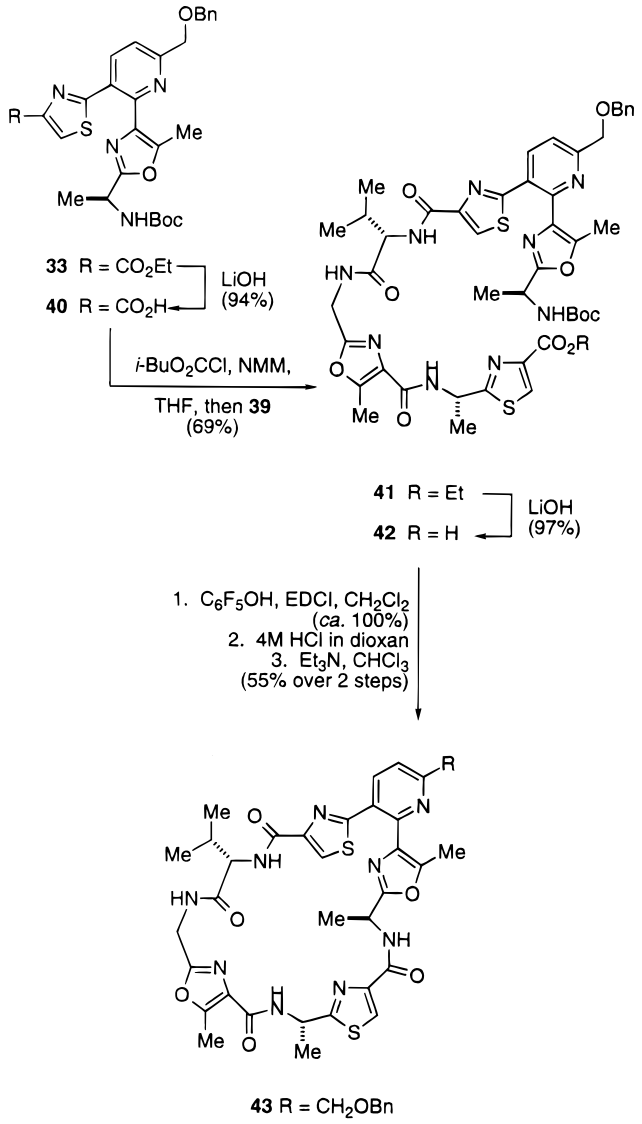
(55) Schmidt, U.; Weinbrenner, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1003−1004.
(56) Moody, C. J.; Bagley, M. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 601−607.

Scheme 9

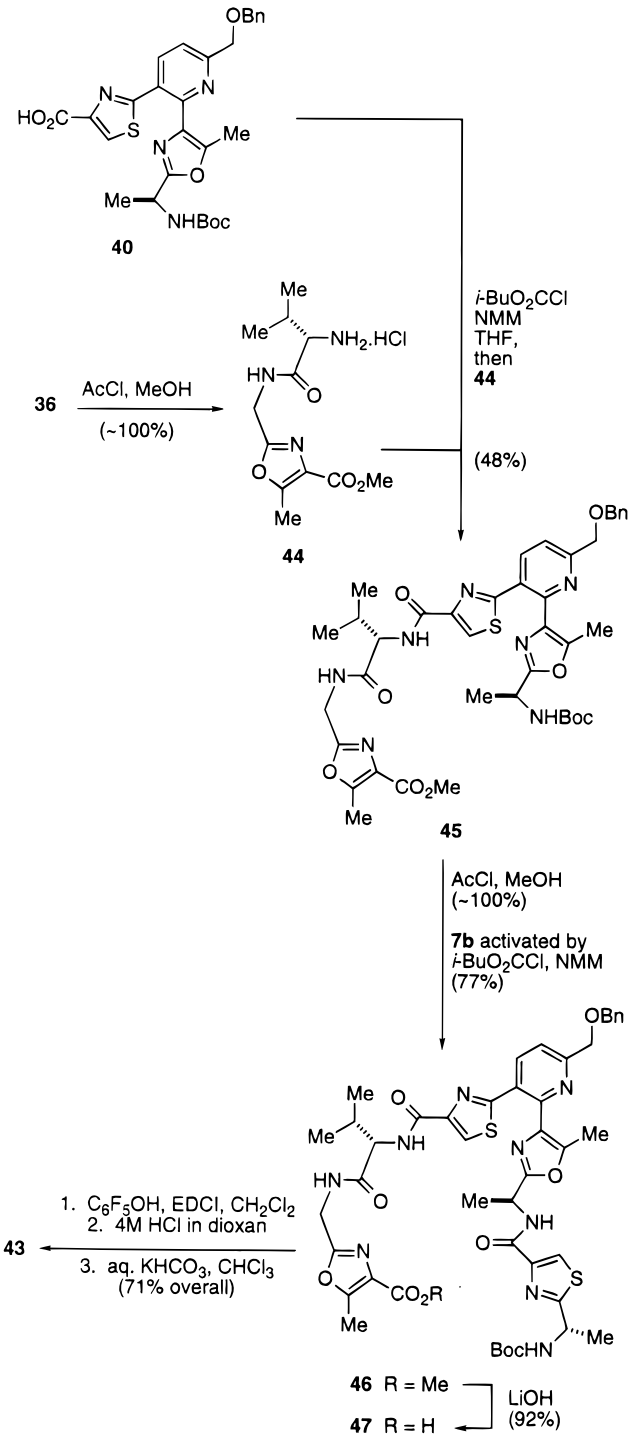


and the resulting acid **47** converted into the corresponding pentafluorophenyl ester. The active ester was not purified but was treated with HCl/dioxane to remove the *N*-terminal Boc group. Workup with aqueous potassium hydrogen carbonate solution then effected slow macrocyclization to give the promothiocin macrocycle **43** (Scheme 10), identical with the sample prepared by the previous cyclization strategy.

With two successful macrocyclization strategies established, it remained to convert the 6-(benzyloxymethyl)pyridine into the corresponding carboxylic acid, and then attach the dehydroalanine amide side chain to complete the synthesis. However, these final steps proved far from trivial. Attempted cleavage of the benzyl ether by catalytic hydrogenolysis under a variety of conditions failed. Under a variety of conditions (e.g. H_2, 10% Pd−C or $HCONH_4$, 10% Pd−C) there was no reaction, and under forcing conditions (higher pressure of H_2 or higher temperature) there was apparently competing reduction of the heterocyclic core. Therefore a Lewis acid based cleavage was used, and treatment of the benzyl ether **43** with boron trichloride dimethyl sulfide complex[57] gave the required pyridine-2-methanol derivative **48**, albeit in modest yield (39%). All attempts to oxidize the primary alcohol **48** to the carboxylic

(57) Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward, S. E. *Synlett* **1993**, 663−664.

Scheme 10

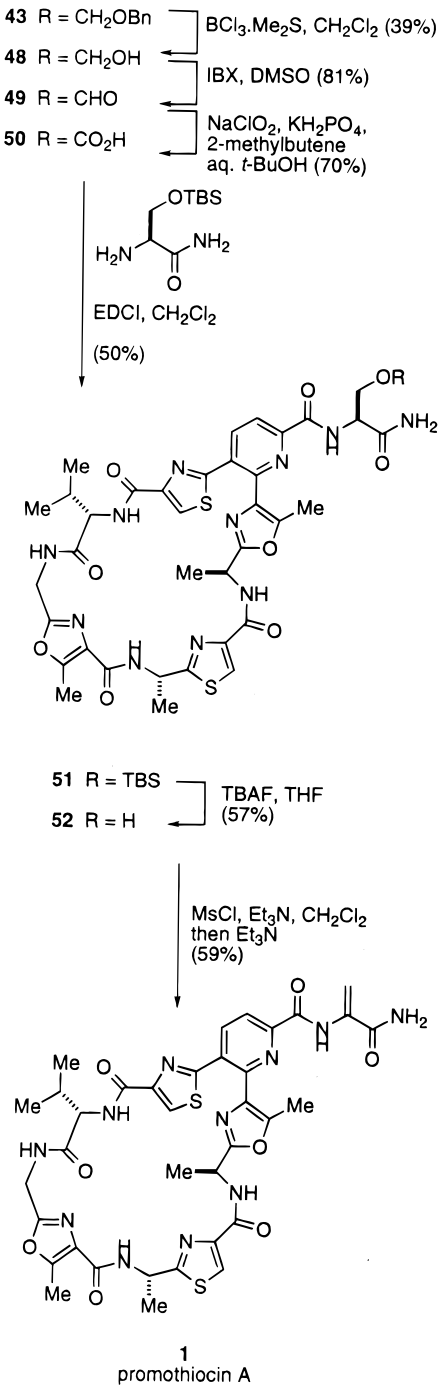


acid **50** directly using nitric acid, potassium permanganate, or platinum/oxygen proved fruitless, and therefore a two-step procedure was adopted. Oxidation to the pyridine-2-carboxaldehyde **49** was effected using IBX in DMSO; further oxidation with sodium chlorite[58] finally gave the desired acid **50** (Scheme 11).

The attachment of the dehydroalanine side chain to the promothiocin macrocycle was relatively straightforward using a serine-based precursor to the dehydroamino acid.[50] Commercially available serinamide hydrochloride was *O*-protected as its *tert*-butyldimethylsilyl (TBS) ether, and coupled with the acid **50** using EDCI to give the amide **51**. This was deprotected

(58) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175−1176.

Scheme 11



with TBAF and the resulting serine derivative **52** dehydrated (MsCl, Et_3N) to install the dehydroalanine side chain, and hence complete the synthesis of promothiocin A **1** (Scheme 11). The synthetic material had 400 MHz ^1H and 100 MHz ^{13}C NMR spectra identical with those reported for the natural product, together with a similar specific rotation. Thus we have completed the first total synthesis of the thiopeptide promothiocin A **1**.

Experimental Section

For general experimental details, see ref 36. Coupling constants are reported in hertz. Compounds characterized by high-resolution mass spectrometry were chromatographically homogeneous.

Investigation of the Bohlmann−Rahtz Pyridine Synthesis. Details for 3-aminopropenoates and alkynones are given in the Supporting Information.

General Method for Pyridine Synthesis. To a stirred solution of the enamino ester (2 mmol) in ethanol (5 mL) was added the alkynone (10 mmol). The mixture was stirred at ca. 50 °C overnight, the ethanol was removed in vacuo, and the reaction mixture was heated to 125 °C for 1 h and purified by flash chromatography on silica eluting with ethyl acetate−light petroleum (1:6) to give pyridines **14**−**18** (data in Supporting Information).

Synthesis of Oxazoles and Thiazoles. (a) (S)-Methyl 2-[1-(tert-Butoxycarbonyl)aminoethyl]-5-methyloxazole-4-carboxylate (6b). A solution of methyl diazoacetoacetate (6.6 g, 47.0 mmol) in dry chloroform (50 mL) was added dropwise over 6 h to a solution of *N*-(*tert*-butoxycarbonyl)-*S*-alaninamide[35] (7.3 g, 39.0 mmol) and dirhodium(II) acetate (0.34 g, 0.77 mmol) in dry chloroform (600 mL) heated under reflux. The reaction mixture was heated under reflux overnight, allowed to cool, and evaporated in vacuo to give a pink solid. Purification by flash chromatography on silica, eluting with ethyl acetate−light petroleum (2:3), followed by recrystallization yielded *N*-(*tert*-butoxycarbonyl)-*N*′-[2-(1-methoxycarbonyl-3-oxobutyl)]-*S*-alaninamide (**19**) (9.3 g, 80%) as colorless crystals, mp 108−109 °C (from chloroform−light petroleum) as a mixture of diastereomers. IR (KBr) 3394, 3300, 1752, 1717, 1658, 1522, 1503, 1367, 1291, 1250, 1214, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (1 H, br s, exch D_2O, NH), 5.25 (1 H, d, $J = 6.7$, C*H*CO_2Me), 5.08 (1 H, d, $J = 6.6$, exch D_2O, N*H*Boc), 4.27 (1 H, m, C*H*Me), 3.82 (3 H, s, OMe), 2.37 (3 H, s, Me), 1.46 (9 H, s, CMe_3), 1.38 (3 H, d, $J = 7.2$, CH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1 (C), 172.6 (C), 166.4 (C), 155.4 (C), 80.3 (C), 62.9 (CH), 53.3 (Me), 50.0 (CH), 28.2 (Me), 27.8 (Me), 18.1 (Me); MS (EI) *m*/*z* (relative intensity) 246 (4%), 229 (8), 215 (3), 204 (22), 182 (28), 157 (40), 129 (38), 102 (100), 96 (56), 88 (73), 81 (36), 70 (63); HRMS calcd for $C_{13}H_{22}N_2O_6$ (M) 302.1478, found 302.1469. Anal. Calcd for $C_{13}H_{22}N_2O_6$: C, 51.6; H, 7.3; N, 9.3. Found: C, 51.5; H, 7.3; N, 9.0.

Triethylamine (16 mL, 115 mmol) and a solution of *N*-(*tert*-butoxycarbonyl)-*N*′-[2-(1-methoxycarbonyl-3-oxobutyl)]-S-alaninamide (**19**) (8.4 g, 28.0 mmol) in dry dichloromethane (40 mL) were added sequentially to a stirred solution of triphenylphosphine (14.7 g, 56.0 mmol) and iodine (14.2 g, 56.0 mmol) in dry dichloromethane (150 mL) at room temperature. The mixture was stirred overnight, evaporated in vacuo, purified by flash chromatography on silica eluting with ethyl acetate−light petroleum (1:3), and recrystallized to give the *title compound* (5.6 g, 70%) as a colorless solid, mp 94−95 °C (from ether−light petroleum). $[\alpha]_D^{22}$ −44.0 (*c* 1.0, $CHCl_3$); IR (KBr) 3357, 3018, 2995, 2984, 2955, 2938, 1719, 1689, 1622, 1526, 1443, 1392, 1368, 1349, 1329, 1250, 1206, 1175, 1101, 1064, 982, 865, 823, 785, 640 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 5.18 (1 H, br s, exch D_2O, NH), 4.92 (1 H, m, CH), 3.89 (3 H, s, OMe), 2.59 (3 H, s, Me), 1.51 (3 H, d, $J = 7.0$, CH*Me*), 1.42 (9 H, s, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (C), 162.6 (C), 156.5 (C), 154.8 (C), 127.3 (C), 80.0 (C), 51.9 (Me), 44.6 (CH), 28.3 (Me), 20.2 (Me), 11.9 (Me); MS (EI) *m*/*z* (relative intensity) 284 (M^+, 3%), 243 (6), 228 (45), 211 (10), 198 (34), 155 (23), 127 (54), 121 (82), 105 (20), 84 (41), 57 (100); HRMS calcd for $C_{13}H_{20}N_2O_5$ (M) 284.1372, found 284.1369. Anal. Calcd for $C_{13}H_{20}N_2O_5$: C, 54.9; H, 7.1; N, 9.9. Found: C, 54.8; H, 7.1; N, 10.0.

HPLC: ee >99%; ChiralPak AD, hexane−2-propanol (90:10), 1.0 mL min^{-1}, $R_T = 8.0$ min (*R*-isomer has $R_T = 6.0$ min)

(b) (*S*)-2-[1-(*tert*-Butoxycarbonyl)aminoethyl]-5-methyloxazole-4-carboxylic Acid (20). Lithium hydroxide monohydrate (3.6 g, 86.0 mmol) was added in one portion to a stirred solution of (*S*)-methyl 2-[1-(*tert*-butoxycarbonyl)aminoethyl]oxazole-4-carboxylate (**6b**) (4.9 g, 17.0 mmol) in methanol−water (5:1) (90 mL) at room temperature. The solution was stirred for 5 h, the methanol was evaporated in vacuo, and the mixture was partitioned between ether (50 mL) and water (50 mL). The ethereal layer was further extracted with water (35 mL) and the aqueous layers were combined, acidified to pH 3 with aqueous citric acid (10%), and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (75 mL), dried (Na_2SO_4), and evaporated in vacuo to give the title compound (4.4 g, 95%) as a *colorless solid*, mp 119−120 °C (from ethyl acetate-light petroleum). $[\alpha]_D^{22}$ −63.8 (*c* 1.0, $CHCl_3$); IR (KBr) 3429, 3365, 2983, 2939, 1693, 1617, 1518, 1450, 1392, 1367, 1331, 1304, 1250, 1175, 1102, 1063, 979, 936, 869, 794, 772 cm^{-1};^1H NMR (400 MHz, $CDCl_3$)

δ 8.06 (1 H, br s, exch D_2O, CO_2H), 6.09 (1 H, m, exch D_2O, NH), 4.98 (1 H, m, CH), 2.63 (3 H, s, Me), 1.54 (3 H, d, J = 7.1, CH*Me*), 1.40 (9 H, s, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9 (C), 164.2 (C), 157.2 (C), 155.3 (C), 127.0 (C), 79.9 (C), 44.6 (CH), 28.3 (Me), 20.1 (Me), 11.9 (Me); MS (EI) *m*/*z* (relative intensity) 270 (M^+, 0.5%), 214 (86), 197 (28), 169 (16), 154 (38), 144 (17), 124 (53), 110 (15), 88 (29), 70 (39), 57 (100); HRMS calcd for $C_{12}H_{18}N_2O_5$ (M) 270.1216, found 270.1211. Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.3; H, 6.7; N, 10.4. Found: C, 53.2; H, 6.8; N, 10.5.

(c) Methyl 2-(Aminomethyl)-5-methyloxazole-4-carboxylate (34). A suspension of 10% palladium on charcoal (260 mg) in a solution of methyl 2-[(benzyloxycarbonylamino)methyl]-5-methyloxazole-4-carboxylate (**6a**)[36] (1.30 g, 4.4 mmol) in methanol (50 mL) was stirred under H_2 (1 atm) at room temperature for 4 h. The reaction was filtered through a plug of Celite, the plug was washed with ethyl acetate (50 mL), and the filtrates were combined and evaporated in vacuo to give the *title compound* (0.74 g, 100%) as a colorless oil. IR (film) 3381, 3054, 2989, 2954, 2925, 2854, 1718, 1620, 1436, 1352, 1193, 1103, 757, 721, 696 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (2 H, s, CH_2), 3.91 (3 H, s, OMe), 2.61 (3 H, s, Me), 1.64 (2 H, br s, exch D_2O, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (C), 163.0 (C), 156.8 (C), 127.6 (C), 52.2 (Me), 39.7 (CH_2), 12.2 (Me); MS (EI) *m*/*z* (relative intensity) 170 (M^+, 100%), 142 (35), 138 (39), 127 (33), 110 (40); HRMS calcd for $C_7H_{10}N_2O_3$ (M) 170.0691, found 170.0689.

(d) (*S*)-Ethyl 2-[1-(*tert*-Butoxycarbonylamino)ethyl]thiazole-4-carboxylate (7a). A stirred solution of (S)-*N*-*tert*-butoxycarbonylthioalaninamide[46] (1.57 g, 7.7 mmol) in DME (25 mL) was cooled to −30 °C under nitrogen. Potassium hydrogen carbonate (3.12 g, 31.2 mmol) and ethyl bromopyruvate (5.59 g, 28.7 mmol) were added and the mixture warmed to ca. −10 °C and stirred overnight at this temperature. The mixture was filtered and recooled to −30 °C. Trifluoroacetic anhydride (5.05 g, 24.1 mmol) and 2,6-lutidine (5.15 g, 48.1 mmol) were added, and the mixture was allowed to stir at ca. −20 °C for 30 min. Water (4 mL) was added, and the mixture was concentrated and partitioned between water and chloroform. The organic extracts were dried and evaporated and the residue purified by flash chromatography on silica eluting with light petroleum−ethyl acetate (4:1.5) to give a solid that was recrystallized from ethyl acetate−light petroleum to give the title compound as colorless needles (2.07 g, 90%), mp 88−89 °C (lit.[46] mp 89.5 °C). $[\alpha]_D^{24}$ −39.7 (*c* 1.0, $CHCl_3$) (lit.[48] $[\alpha]_D^{24}$ −40.0 (*c* 1.15, $CHCl_3$)); IR (KBr) 3371, 3117, 2991, 2941, 1720, 1687, 1515, 1499, 1370, 1296, 1232, 1167, 1088, 1060, 1019, 991, 767 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (1 H, s, CH), 5.26 (1 H, br s, exch. D_2O, NH), 5.07 (1 H, m, C*H*NH), 4.37 (2 H, q, J = 7.1, OC*H*$_2$Me), 1.59 (3 H, d, J = 7.0, CH*Me*), 1.41 (9H, s, *t*-Bu), 1.36 (3 H, t, J = 7.1, CH_2*Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (C), 161.3 (C), 154.9 (C), 147.2 (C), 127.1 (CH), 80.2 (C), 61.3 (CH_2), 48.9 (CH), 28.3 (Me), 21.7 (Me), 14.3 (Me); MS (EI) *m*/*z* (relative intensity) 300 (M^+, 2%), 255 (7), 244 (80), 227 (20), 211 (4), 199 (27), 185 (26), 174 (17), 153 (12), 139 (22), 138 (22), 126 (35), 112 (17), 84 (12), 70 (11), 57 (100); HRMS calcd for $C_{13}H_{20}N_2O_4S$ (M) 300.1160, found 300.1145. Anal. Calcd for $C_{13}H_{20}N_2O_4S$: C, 52.0; H, 6.7; N, 9.3. Found: C, 51.8; H, 6.8; N, 9.3.

HPLC: ee >99.5%; Chiralcel OD, hexane−2-propanol (90:10), 1.0 mL min^{-1}, R_T = 6.1 min (*R*-isomer has R_T = 7.3 min)

(e) (*S*)-Ethyl 2-[1-(Aminoethyl)]thiazole-4-carboxylate Hydrochloride Salt (35). Acetyl chloride (2.5 mL, 35.0 mmol) was added portionwise to a stirred solution of (*S*)-ethyl 2-[1-(*tert*-butoxycarbonylamino)ethyl]thiazole-4-carboxylate (**7a**) (0.52 g, 1.7 mmol) in dry ethanol (60 mL) at 0 °C. The mixture was warmed rapidly to room temperature, stirred overnight, and evaporated in vacuo to give the title compound (0.46 g, 1.75 mmol) as a colorless foam that was used without further purification.

(f) (*S*)-Ethyl 3-{2-[1-(*tert*-Butoxycarbonyl)aminoethyl]-5-methyloxazol-4-yl}-3-oxopropanoate (21). (i) Formation of magnesium enolate of ethyl hydrogen malonate. A solution of methylmagnesium bromide in THF (3 M; 11 mL, 33.0 mmol) was added to a stirred suspension of potassium ethyl malonate (5.6 g, 33.0 mmol) in dry THF (35 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, warmed rapidly to room temperature, and stirred for 1.5 h.

(ii) Formation of ethyl 3-oxazolyl-3-oxopropanoate: To a stirred solution of (*S*)-2-[1-(*tert*-butoxycarbonyl)aminoethyl]oxazole-4-carboxylic acid (**20**) (4.4 g, 16.0 mmol) and triethylamine (2.4 mL, 17.0 mmol) in dry THF (50 mL) was added ethyl chloroformate (1.6 mL, 17.0 mmol) dropwise over 5 min at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, the above solution of ethyl malonate magnesium enolate in THF was added, and the mixture was warmed to room temperature overnight. Saturated aqueous ammonium chloride solution (50 mL) was added, and the mixure was evaporated in vacuo and partitioned between chloroform (100 mL) and water (75 mL). The aqueous layer was further extracted with chloroform (75 mL) and the organic extracts were combined, washed sequentially with aqueous acetic acid (5%; 125 mL), saturated aqueous sodium hydrogen carbonate solution (125 mL), and brine (125 mL), dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography on silica eluting with ethyl acetate−light petroleum (1:4) to give the *title compound* (4.3 g, 77%) as a pale yellow oil. $[\alpha]_D^{22}$ −44.8 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3443, 2984, 2936, 2908, 2875, 1734, 1715, 1691, 1607, 1501, 1369, 1167, 1054, 1032, 909 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (1 H, br s, exch D_2O, NH), 4.89 (1 H, m, CH), 4.19 (2 H, q, J = 7.1, OC*H*$_2$Me), 3.91 (2 H, s, CH_2), 2.60 (3 H, s, Me), 1.50 (3 H, d, J = 7.0, CH*Me*), 1.45 (9 H, s, CMe_3), 1.26 (3 H, t, J = 7.1, CH_2*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C), 167.7 (C), 161.9 (C), 155.7 (C), 154.8 (C), 133.6 (C), 80.2 (C), 61.1 (CH_2), 46.6 (CH_2), 44.6 (CH), 28.3 (Me), 20.0 (Me), 14.1 (Me), 12.2 (Me); MS (EI) *m*/*z* (relative intensity) 340 (M^+, 0.3%), 284 (20), 240 (15), 166 (24), 110 (11), 86 (79), 84 (100), 57 (45), 51 (52); HRMS calcd for $C_{16}H_{24}N_2O_6$ (M) 340.1634, found 340.1636.

(g) (*S*)-Ethyl 3-Amino-3-{2-[1-(*tert*-butoxycarbonyl)aminoethyl]-5-methyloxazol-4-yl}propenoate (22). A mixture of the β-ketoester **21** (4.2 g, 12.3 mmol) and ammonium acetate (9.5 g, 123.0 mmol) in benzene−acetic acid (5:1) (150 mL) was heated under reflux for 24 h using a Dean and Stark trap. The mixture was allowed to cool and partitioned between ether (200 mL) and saturated aqueous sodium hydrogen carbonate solution (200 mL), and the organic layer was dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography on silica eluting with ethyl acetate−light petroleum (1:3) to give the *title compound* (3.5 g, 85%) as colorless needles, mp 103−104 °C (from ether−light petroleum). $[\alpha]_D^{22}$ −60.5 (*c* 1.1, $CHCl_3$); IR (KBr) 3455, 3351, 2986, 2939, 2903, 1681, 1669, 1606, 1515, 1368, 1335, 1269, 1254, 1210, 1153, 1058, 783 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (2 H, br s, exch D_2O, NH_2), 5.09 (1 H, br s, exch D_2O, NH), 4.89 (1 H, m, C*H*Me), 4.83 (1 H, m, =CH), 4.16 (2 H, q, J = 7.1, OC*H*$_2$Me), 2.49 (3 H, s, Me), 1.51 (3 H, d, J = 7.0, CH*Me*), 1.45 (9 H, s, CMe_3), 1.29 (3 H, t, J = 7.1, CH_2*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C), 162.2 (C), 154.9 (C), 151.4 (C), 147.8 (C), 130.8 (C), 82.2 (CH), 80.1 (C), 58.8 (CH_2), 44.7 (CH), 28.3 (Me), 20.1 (Me), 14.6 (Me), 12.5 (Me); MS (EI) *m*/*z* (relative intensity) 339 (M^+, 27%), 283 (47), 266 (10), 237 (16), 220 (22), 211 (24), 195 (55), 167 (24), 150 (32), 84 (33), 70 (22), 57 (100); HRMS calcd for $C_{16}H_{25}N_3O_5$ (M) 339.1794, found 339.1785. Anal. Calcd for $C_{16}H_{25}N_3O_5$: C, 56.6; H, 7.4; N, 12.4. Found: C, 56.8; H, 7.4; N, 12.4.

Synthesis of 2-Oxazolyl−3-Thiazolyl−Pyridines. (a) 1-Benzyloxy-3-butyn-2-one (24). A solution of ethynylmagnesium bromide in THF (0.5 M; 38 mL, 19.0 mmol) was added to a stirred solution of benzyloxyacetaldehyde (2.4 g, 16.0 mmol) in dry THF (40 mL) at 0 °C. The solution was stirred at 0 °C for 2 h, saturated aqueous ammonium chloride solution (5 mL) was added, and the mixture was evaporated in vacuo and partitioned between ether (75 mL) and saturated aqueous ammonium chloride solution (75 mL). The ethereal layer was washed with brine (75 mL), dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography on silica eluting with ether−light petroleum (1:2) to give 1-benzyloxy-3-butyn-2-ol (2.4 g, 86%) as a colorless oil. IR ($CHCl_3$) 3308, 3090, 3070, 2926, 2869, 1496, 1454, 1360, 1311, 1114, 1088, 1028 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.28 (5 H, m, PhH), 4.64 (1 H, d, J = 12.0, PhC*H*H), 4.60 (1 H, d, J = 12.0, PhCH*H*), 4.56 (1 H, ddd, J = 7.0, 3.8, 2.3, C*H*CH$_2$), 3.66 (1 H, dd, J = 9.8, 3.8, CHC*H*H), 3.59 (1 H, dd, J = 9.8, 7.0, CHCH*H*), 2.85 (1 H, br s, exch D_2O, OH), 2.46 (1 H, d, J = 2.3, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5 (C), 128.5 (CH), 127.9 (CH), 127.8 (CH), 81.8 (C), 73.7 (CH), 73.49 (CH_2), 73.46 (CH_2), 61.5

(CH); MS (EI) *m*/*z* (relative intensity) 176 (M^+, 2%), 146 (11), 117 (11), 91 (100), 70 (8), 65 (12); HRMS calcd for $C_{11}H_{12}O_2$ (M) 176.0837, found 176.0837.

A solution of IBX (15.3 g, 54.5 mmol) in DMSO (400 mL) was stirred for 15 min at room temperature until homogeneous. A solution of 1-benzyloxybut-3-yn-2-ol (2.0 g, 11.5 mmol) in DMSO (5 mL) was added, then the mixture was stirred for 4 h at room temperature, warmed to 35 °C, and stirred overnight. Water (50 mL) was added and the mixture was stirred at room temperature for 10 min and cooled in ice. The white precipitate was filtered and the filtrate was partitioned between ether (200 mL) and water (300 mL). The aqueous layer was further extracted with ether (150 mL) and the ethereal extracts were combined, washed sequentially with water (3 × 150 mL), saturated aqueous sodium hydrogen carbonate solution (200 mL), and brine (200 mL), dried (Na_2SO_4), and evaporated in vacuo to give the *title compound* (1.8 g, 89%) as an orange oil used without further purification. IR (film) 3262, 3091, 3067, 3033, 2927, 2870, 2094, 1702, 1499, 1457, 1070, 748, 701 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.29 (5 H, m, PhH), 4.65 (2 H, s, PhCH_2), 4.25 (2 H, s, CH_2), 3.33 (1 H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4 (C), 136.8 (C), 128.6 (CH), 128.2 (CH), 128.0 (CH), 81.4 (CH), 79.4 (C), 75.7 (CH_2), 73.5 (CH_2); MS (EI) *m*/*z* (relative intensity) 174 (M^+, 0.4%), 143 (6), 116 (66), 107 (96), 91 (98), 77 (63), 65 (98), 53 (100); HRMS calcd for $C_{11}H_{10}O_2$ (M) 174.0681, found 174.0685.

(b) (*S*)-Ethyl 6-(Benzyloxy)methyl-2-{2-[1-(*tert*-butoxycarbonyl)-aminoethyl]-5-methyloxazol-4-yl}pyridine-3-carboxylate (25). A solution of the enaminone **22** (1.40 g, 4.0 mmol) and 1-benzyloxy-3-butyn-2-one (**24**) (0.95 g, 5.5 mmol) in ethanol (100 mL) was stirred overnight at 50 °C. The mixture was evaporated in vacuo, heated to 140 °C in vacuo for 30 min, allowed to cool, and purified by flash chromatography on silica eluting with ether−light petroleum (2:3) to give the *title compound* (1.70 g, 83%) as a pale yellow foam. $[\alpha]_D^{22}$ −21.4 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) 3442, 2985, 2934, 2869, 1715, 1508, 1369, 1286, 1166, 1107, 1056 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (1 H, d, J = 8.0, 4-H), 7.48 (1 H, d, J = 8.0, 5-H), 7.41−7.27 (5 H, m, PhH), 5.23 (1 H, d, J = 7.2, exch D_2O, NH), 4.94 (1 H, m, CH), 4.72 (2 H, s, PyCH_2), 4.66 (2 H, s, PhCH_2), 4.31 (2 H, q, J = 7.1, OCH_2Me), 2.56 (3 H, s, Me), 1.52 (3 H, d, J = 6.9, CH*Me*), 1.45 (9 H, s, CMe_3), 1.28 (3 H, t, J = 7.1, CH_2*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1 (C), 161.7 (C), 160.1 (C), 154.9 (C), 149.2 (C), 148.5 (C), 137.8 (C), 137.7 (CH), 133.3 (C), 128.5 (CH), 127.8 (CH), 127.7 (CH), 126.6 (C), 118.9 (CH), 79.8 (C), 73.0 (CH_2), 72.7 (CH_2), 61.5 (CH_2), 44.7 (CH), 28.4 (Me), 20.4 (Me), 14.1 (Me), 11.8 (Me); MS (EI) *m*/*z* (relative intensity) 495 (M^+, 3%), 439 (9), 422 (5), 395 (6), 333 (21), 315 (53), 269 (50), 248 (49), 231 (27), 200 (21), 172 (15), 105 (33), 91 (100), 77 (30), 57 (18); HRMS calcd for $C_{27}H_{33}N_3O_6$ (M) 495.2369, found 495.2369.

(c) (*S*)-6-(Benzyloxy)methyl-2-{2-[1-(*tert*-butoxycarbonyl)aminoethyl]-5-methyloxazol-4-yl}pyridine-3-carboxylic Acid (30). Lithium hydroxide monohydrate (1.4 g, 34.4 mmol) was added in one portion to a stirred solution of the ester **25** (1.7 g, 3.4 mmol) in THF−water (5:1) (120 mL) at room temperature. The solution was stirred for 2 days, warmed to 45 °C, and stirred overnight. The THF was evaporated in vacuo and the mixture was partitioned between ether (50 mL) and water (150 mL). The aqueous layer was acidified to pH 3 with aqueous citric acid (10%) and extracted with ethyl acetate (2 × 75 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and evaporated in vacuo to give the *title compound* (1.5 g, 92%) as a colorless foam. $[\alpha]_D^{24}$ −68.3 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3446, 3310, 2984, 2931, 2869, 1711, 1581, 1499, 1457, 1425, 1369, 1163, 1112, 1073, 1041 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 12.51 (1 H, br s, exch D_2O, CO_2H), 8.33 (1 H, d, J = 8.1, 4-H), 7.51 (1 H, d, J = 8.1, 5-H), 7.40−7.25 (5 H, m, PhH), 6.05 (1 H, d, J = 6.6, exch D_2O, NH), 5.01 (1 H, m, CH), 4.73 (1 H, d, J = 14.2, PyC*H*H), 4.69 (1 H, d, J = 14.2, PyCH*H*), 4.66 (2 H, s, PhCH_2), 2.58 (3 H, s, Me), 1.53 (3 H, d, J = 7.0, CH*Me*), 1.38 (9 H, s, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3 (C), 163.1 (C), 160.8 (C), 155.2 (C), 149.8 (C), 148.6 (C), 140.5 (CH), 137.7 (C), 132.4 (C), 128.5 (CH), 127.9 (CH), 127.8 (CH), 126.1 (C), 119.6 (CH), 79.8 (C), 73.1 (CH_2), 72.5 (CH_2), 44.7 (CH), 28.3 (Me), 19.9 (Me), 12.1 (Me); MS (EI) *m*/*z* (relative intensity) 467 (M^+, 0.3%), 439 (1), 422 (0.5), 411 (2), 333 (4), 305 (12), 287 (35), 269 (34), 243 (14), 200 (26), 172 (21), 145 (24), 117 (39), 107 (51), 105 (56), 91 (100); HRMS calcd for $C_{25}H_{29}N_3O_6$ (M) 467.2056, found 467.2070.

(d) (*S*)-6-(Benzyloxy)methyl-2-{2-[1-(*tert*-butoxycarbonyl)aminoethyl]-5-methyloxazol-4-yl}pyridine-3-carboxamide (31). To a stirred solution of the pyridine-3-carboxylic acid **30** (1.50 g, 3.1 mmol) and triethylamine (0.60 mL, 4.3 mmol) in dry THF (70 mL) was added ethyl chloroformate (0.35 mL, 3.7 mmol) dropwise over 3 min at −10 °C. The reaction mixture was stirred at −10 °C for 50 min and a solution of aqueous ammonia (32%; 3.5 mL) was added. The mixture was stirred at −10 °C for 45 min and warmed rapidly to room temperature. Saturated aqueous ammonium chloride solution (50 mL) was added and the mixture was concentrated in vacuo and extracted with dichloromethane (3 × 100 mL). The organic extracts were combined, dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography on silica eluting with ethyl acetate−dichloromethane−triethylamine (20:10:1) to give the *title compound* (1.20 g, 85%) as a colorless solid, mp 122−123 °C (from isopropyl alcohol−ether). $[\alpha]_D^{22}$ −45.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3524, 3448, 3405, 2984, 2934, 2869, 1713, 1673, 1588, 1502, 1368, 1163 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (1 H, d, J = 8.1, 4-H), 7.54 (1 H, d, J = 8.1, 5-H), 7.41−7.28 (5 H, m, PhH), 7.25 (1 H, br s, exch D_2O, N*H*H), 5.92 (1 H, br s, exch D_2O, NH*H*), 5.17 (1 H, d, J = 7.8, exch D_2O, N*H*Boc), 4.92 (1 H, m, CH), 4.71 (2 H, s, PyCH_2), 4.66 (2 H, s, PhCH_2), 2.46 (3 H, s, Me), 1.52 (3 H, d, J = 7.0, CH*Me*), 1.45 (9 H, s, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (C), 162.1 (C), 160.1 (C), 155.0 (C), 149.4 (C), 147.4 (C), 139.0 (CH), 137.7 (C), 133.2 (C), 129.8 (C), 128.5 (CH), 127.9 (CH), 127.8 (CH), 119.9 (CH), 80.1 (C), 73.0 (CH_2), 72.7 (CH_2), 44.8 (CH), 28.3 (Me), 19.9 (Me), 11.6 (Me); MS (EI) *m*/*z* (relative intensity) 466 (M^+, 1%), 410 (10), 366 (4), 349 (11), 304 (11), 287 (25), 286 (33), 269 (98), 260 (14), 243 (12), 200 (33), 172 (12), 91 (100); HRMS calcd for $C_{25}H_{30}N_4O_5$ (M) 466.2216, found 466.2232. Anal. Calcd for $C_{25}H_{30}N_4O_5$: C, 64.4; H, 6.5; N, 12.0. Found: C, 64.4; H, 6.4; N, 11.7.

(e) (*S*)-6-(Benzyloxy)methyl-2-{2-[1-(*tert*-butoxycarbonyl)aminoethyl]-5-methyloxazol-4-yl}pyridine-3-thiocarboxamide (32). A solution of the carboxamide **31** (215 mg, 0.46 mmol) and Lawesson's reagent (108 mg, 0.27 mmol) in benzene (50 mL) was heated under reflux for 5 h. The mixture was allowed to cool, evaporated in vacuo, and purified by flash chromatography on silica eluting with ethyl acetate−dichloromethane−triethylamine (10:20:1) to give the *title compound* (130 mg, 59%) as a yellow oil. $[\alpha]_D^{25}$ −57.7 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3445, 3372, 3290, 2987, 2934, 2867, 1712, 1506, 1166 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (1 H, br s, exch D_2O, N*H*H), 8.22 (1 H, d, J = 8.0, 4-H), 8.11 (1 H, br s, exch D_2O, NH*H*), 7.49 (1 H, d, J = 8.0, 5-H), 7.40−7.26 (5 H, m, PhH), 5.22 (1 H, br s, N*H*Boc), 4.88 (1 H, m, CH), 4.68 (2 H, s, PyCH_2), 4.64 (2 H, s, PhCH_2), 2.40 (3 H, s, Me), 1.49 (3 H, d, J = 7.0, CH*Me*), 1.43 (9 H, s, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0 (C), 162.1 (C), 159.9 (C), 155.0 (C), 149.0 (C), 144.6 (C), 139.7 (CH), 137.7 (C), 136.1 (C), 123.0 (C), 128.5 (CH), 127.9 (CH), 127.8 (CH), 119.9 (CH), 80.2 (C), 73.0 (CH_2), 72.5 (CH_2), 44.7 (CH), 28.4 (Me), 19.8 (Me), 11.4 (Me); MS (EI) *m*/*z* (relative intensity) 392 (3%), 338 (7), 333 (7), 305 (7), 286 (18), 242 (26), 240 (23), 225 (52), 210 (19), 91 (100), 56 (51); HRMS calcd for $C_{25}H_{31}N_4O_4S$ (M) 483.2066, found 483.2053.

(f) (*S*)-6-(Benzyloxy)methyl-2-{2-[1-(*tert*-butoxycarbonyl)aminoethyl]-5-methyloxazol-4-yl}-3-(4-ethoxycarbonylthiazol-2-yl)pyridine (33). Potassium hydrogen carbonate (109 mg, 1.10 mmol) and ethyl bromopyruvate (0.11 mL, 0.88 mmol) were added sequentially to a stirred solution of the thioamide **32** (131 mg, 0.27 mmol) in dry THF (4 mL) at −3 °C. The mixture was stirred for 16 h and filtered, washing with ether (10 mL). The combined filtrates were evaporated in vacuo and the residue was dissolved in dry THF (3 mL) and cooled to 0 °C and a solution of trifluoroacetic anhydride (0.15 mL, 1.1 mmol) and 2,6-lutidine (0.25 mL, 2.1 mmol) in dry THF (3 mL) at 0 °C was added. The solution was stirred for 3 h and an aqueous solution of citric acid (10%; 5 mL) was added. The mixture was concentrated in vacuo and partitioned between chloroform (20 mL) and aqueous citric acid solution (10%; 10 mL). The aqueous layer was extracted with chloroform (2 × 20 mL) and the organic extracts were combined, dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography

on silica, eluting with ethyl acetate−light petroleum (1:2), to give the *title compound* (110 mg, 72%) as a pale yellow oil. $[\alpha]_D^{23}$ −26.8 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 3437, 2985, 2929, 2857, 1715, 1500, 1455, 1370, 1163, 1097 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (1 H, d, J = 8.1, 4-H), 8.17 (1 H, s, SCH), 7.61 (1 H, d, J = 8.1, 5-H), 7.41−7.26 (5 H, m, PhH), 5.09 (1 H, br s, exch D_2O, NH), 4.89 (1 H, m, CH), 4.76 (2 H, s, PyCH_2), 4.67 (2 H, s, PhCH_2), 4.42 (2 H, q, J = 7.2, OCH_2Me), 2.26 (3 H, s, Me), 1.46 (3 H, d, J = 6.8, CH*Me*), 1.43 (9 H, s, CMe_3), 1.40 (3 H, t, J = 7.2, CH_2*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C), 162.9 (C), 161.3 (C), 160.2 (C), 154.9 (C), 154.8 (C), 148.6 (C), 147.1 (C), 138.9 (CH), 137.7 (C), 132.6 (C), 128.9 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.6 (C), 120.2 (CH), 79.8 (C), 73.1 (CH_2), 72.7 (CH_2), 61.5 (CH_2), 44.7 (CH), 28.3 (Me), 20.3 (Me), 14.3 (Me), 11.1 (Me); MS (EI) *m*/*z* (relative intensity) 578 (M^+, 17%), 522 (24), 478 (27), 434 (18), 416 (18), 398 (33), 370 (32), 355 (20), 328 (18), 273 (18), 210 (12), 91 (100), 77 (32), 57 (63); HRMS calcd for $C_{30}H_{34}N_4O_6S$ (M) 578.2216, found 578.2201.

Coupling Reactions. (a) *N*-Boc-Valine−Oxazole Dipeptide Methyl Ester 36. *N*-Methylmorpholine (0.50 mL, 4.6 mmol) and isobutyl chloroformate (0.46 mL, 3.6 mmol) were added sequentially to a stirred solution of *N*-*tert*-butoxycarbonyl-L-valine (0.70 g, 3.2 mmol) in dry THF (15 mL) at −10 °C. The mixture was stirred for 20 min at −10 °C, a solution of ethyl 2-(aminomethyl)oxazole-4-carboxylate (**34**) (0.74 g, 4.4 mmol) in dry THF (10 mL) was added, and the reaction mixture was warmed to 0 °C, stirred for 1 h, and partitioned between ethyl acetate (50 mL) and water (100 mL). The aqueous layer was further extracted with ethyl acetate (50 mL) and the organic extracts were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate solution (75 mL) and brine (75 mL), dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (2:1) to give the *title compound* (1.00 g, 87%) as colorless crystals, mp 130−131 °C (from ethyl acetate−light petroleum). $[\alpha]_D^{22}$ −9.6 (*c* 1.67, $CHCl_3$); IR (KBr) 3325, 3080, 2967, 2873, 1719, 1684, 1659, 1627, 1527, 1443, 1388, 1368, 1344, 1250, 1214, 1172, 1104, 826, 787 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (1 H, m, CH_2N*H*), 5.06 (1 H, br s, N*H*Boc), 4.55 (2 H, d, J = 5.5, CH_2NH), 4.00 (1 H, m, C*H*NH), 3.88 (3 H, s, OMe), 2.58 (3 H, s, Me), 2.17 (1 H, m, Me_2C*H*), 1.42 (9 H, s, CMe_3), 0.96 (3 H, d, J = 6.8, *Me*CHMe), 0.90 (3 H, d, J = 6.8, MeCH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (C), 162.4 (C), 158.5 (C), 156.8 (C), 155.9 (C), 127.5 (C), 80.0 (C), 59.8 (CH), 51.9 (Me), 36.4 (CH_2), 30.8 (CH), 28.3 (Me), 19.2 (Me), 17.5 (Me), 11.9 (Me); MS (EI) *m*/*z* (relative intensity) 370 (MH^+, 4%), 314 (5), 296 (6), 270 (5), 172 (23), 155 (32), 116 (56), 72 (100), 57 (83), 41 (32); HRMS calcd for $C_{17}H_{27}N_3O_6$ (M) 369.1900, found 369.1887. Anal. Calcd for $C_{17}H_{27}N_3O_6$: C, 55.3; H, 7.4; N, 11.4. Found: C, 55.0; H, 7.3; N, 11.3.

(b) *N*-Boc-Valine−Oxazole Dipeptide Carboxylic Acid 37. Lithium hydroxide monohydrate (0.53 g, 13.0 mmol) was added to a solution of the ester **36** (0.94 g, 2.5 mmol) in THF−water (5:1) (70 mL) at room temperature. The reaction mixture was stirred overnight, concentrated in vacuo, and partitioned between water (50 mL) and ether (75 mL). The aqueous layer was separated, acidified to pH 3 with aqueous citric acid solution (10%), and extracted with ethyl acetate (3 × 60 mL). The organic layers were combined, washed with brine (100 mL), dried (Na_2SO_4), and evaporated in vacuo to give the *title compound* (0.84 g, 93%) as colorless prisms, mp 187−188 °C dec (from 2-propanol−ether). $[\alpha]_D^{25}$ +3.3 (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 3438, 3311, 2972, 2933, 2875, 1706, 1681, 1630, 1503, 1164, 1103 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$, 55 °C) δ 10.08 (1 H, br s, CO_2H), 7.69 (1 H, br s, CH_2N*H*), 5.46 (1 H, br s, N*H*Boc), 4.54 (2 H, m, CH_2NH), 4.03 (1 H, m, C*H*NH), 2.54 (3 H, s, Me), 2.07 (1 H, m, Me_2C*H*), 1.35 (9 H, s, CMe_3), 0.89 (3 H, d, J = 6.8, *Me*CHMe), 0.86 (3 H, d, J = 6.8, MeCH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 (C), 164.2 (C), 159.3 (C), 157.2 (C), 156.0 (C), 127.3 (C), 79.8 (C), 59.6 (CH), 36.0 (CH_2), 31.2 (CH), 28.2 (Me), 19.1 (Me), 17.8 (Me), 11.8 (Me); MS (EI) *m*/*z* (relative intensity) 356 (MH^+, 1%), 300 (4), 282 (23), 264 (7), 228 (27), 182 (31), 172 (58), 155 (37), 149 (36), 141 (59), 123 (46), 116 (79), 98 (41), 72 (100); HRMS calcd for $C_{16}H_{25}N_3O_6$ (M) 355.1743, found 355.1741.

(c) *N*-Boc-Valine−Oxazole−Thiazole Tripeptide Ethyl Ester 38. *N*-Methylmorpholine (0.50 mL, 4.6 mmol) and isobutyl chloroformate (0.23 mL, 1.8 mmol) were added sequentially to a stirred solution of dipeptide carboxylic acid **37** (0.68 g, 1.8 mmol) in dry THF (20 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C, a solution of (*S*)-ethyl 2-[1-(aminoethyl)]thiazole-4-carboxylate hydrochloride salt (**35**) (0.41 g, 1.8 mmol) in dry THF (10 mL) was added, and the reaction was stirred for 1 h and partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was further extracted with ethyl acetate (2 × 50 mL) and the organic extracts were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate solution (75 mL) and brine (75 mL), dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (3:2) to give the *title compound* (0.83 g, 84%) as a colorless foam. $[\alpha]_D^{24}$ −23.8 (*c* 0.94, $CHCl_3$); IR (film) 3358, 3317, 3119, 3056, 2979, 2931, 2874, 1725, 1684, 1652, 1514, 1368, 1338, 1211, 1163, 1104, 1067, 1020, 856, 737 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (1 H, s, SCH), 7.55 (1 H, d, J = 7.3, MeCHN*H*), 6.70 (1 H, m, CH_2N*H*), 5.54 (1 H, dq, J = 7.3, 7.0, C*H*Me), 5.16 (1 H, br s, N*H*Boc), 4.54 (1 H, dd, J = 17, 6, C*H*HNH), 4.49 (1 H, dd, J = 17, 6, CH*H*NH), 4.41 (2 H, q, J = 7.0, OCH_2Me), 4.02 (1 H, dd, J = 9.0, 7.0, CHC*H*NH), 2.60 (3 H, s, Me), 2.21 (1 H, m, Me_2C*H*), 1.75 (3 H, d, J = 7.0, CH*Me*), 1.42 (9 H, s, CMe_3), 1.40 (3 H, t, J = 7.0, CH_2*Me*), 1.00 (3 H, d, J = 6.8, *Me*CHMe), 0.96 (3 H, d, J = 6.8, MeCH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7 (C), 172.5 (C), 161.3 (C), 161.2 (C), 157.4 (C), 156.2 (C), 153.9 (C), 147.1 (C), 128.9 (C), 127.1 (CH), 79.7 (C), 61.3 (CH_2), 59.8 (CH), 46.8 (CH), 36.6 (CH_2), 31.1 (CH), 28.2 (Me), 21.1 (Me), 19.2 (Me), 18.0 (Me), 14.3 (Me), 11.6 (Me); MS (EI) *m*/*z* (relative intensity) 538 (MH^+, 10%), 482 (9), 464 (56), 438 (58), 394 (13), 366 (22), 323 (86), 264 (44), 221 (18), 199 (74), 138 (69), 116 (56), 98 (35), 85 (39), 72 (78), 57 (100); HRMS calcd for $C_{24}H_{35}N_5O_7S$ (M) 537.2257, found 537.2268.

(d) Valine−Oxazole−Thiazole Tripeptide Ethyl Ester Hydrochloride 39. Acetyl chloride (0.60 mL, 8.4 mmol) was added portionwise to a stirred solution of *N*-(*tert*-butoxycarbonyl)-protected tripeptide **38** (228 mg, 0.42 mmol) in dry ethanol (15 mL) at room temperature. The mixture was stirred overnight and evaporated in vacuo to give the title compound (201 mg, 0.42 mmol) as a colorless foam that was used without further purification.

(e) Oxazole−Pyridine−Thiazole Carboxylic Acid 40. Lithium hydroxide monohydrate (110 mg, 2.50 mmol) was added to a solution of oxazole−pyridine−thiazole ethyl ester **33** (244 mg, 0.42 mmol) in THF−water (5:1) (25 mL) at room temperature. The reaction mixture was stirred overnight, evaporated in vacuo, and partitioned between water (50 mL) and ether (50 mL). The aqueous layer was separated, acidified to pH 3 with aqueous citric acid solution (10%), and extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, washed with brine (40 mL), dried (Na_2SO_4), and evaporated in vacuo to give the *title compound* (218 mg, 94%) as a pale yellow foam. $[\alpha]_D^{20}$ −39.8 (*c* 1.57, $CHCl_3$); IR ($CHCl_3$) 3443, 2984, 2935, 2869, 1712, 1508, 1456, 1371, 1342, 1096, 1056, 994 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (1 H, br s, exch D_2O, CO_2H), 8.38 (1 H, d, J = 8.0, Py-4-H), 8.21 (1 H, s, SCH), 7.62 (1 H, d, J = 8.0, Py-5-H), 7.42−7.26 (5 H, m, PhH), 6.30 (0.15 H, m, exch D_2O, N*H*Boc), 5.47 (0.85 H, m, exch D_2O, N*H*Boc), 4.94 (1 H, m, C*H*Me), 4.76 (2 H, s, PyCH_2), 4.66 (2 H, s, PhCH_2), 2.33 (3 H, s, Me), 1.49 (3 H, d, J = 7.0, CH*Me*), 1.40 (9 H, s, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (C), 163.6 (C), 163.4 (C), 160.2 (C), 155.1 (C), 148.8 (C), 148.1 (C), 146.7 (C), 139.0 (CH), 137.7 (C), 132.3 (C), 130.0 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.6 (C), 120.6 (CH), 79.9 (C), 73.1 (CH_2), 72.6 (CH_2), 44.7 (CH), 28.3 (Me), 20.1 (Me), 11.1 (Me); MS (CI) *m*/*z* (relative intensity) 551 (MH^+, 9%), 445 (2), 217 (3), 189 (5), 161 (20), 144 (18), 126 (19), 110 (26), 108 (61), 106 (46), 91 (35), 74 (40), 61 (49), 58 (100); HRMS calcd for $C_{28}H_{31}N_4O_6S$ (MH) 551.1964, found 551.2002.

(f) *N*-(*tert*-Butoxycarbonyl)-Protected Linear Peptide Ethyl Ester 41. *N*-Methylmorpholine (120 μL, 1.10 mmol) and isobutyl chloroformate (55 μL, 0.42 mmol) were added sequentially to a stirred solution of oxazole−pyridine−thiazole carboxylic acid **40** (218 mg, 0.40 mmol) in dry THF (6 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C, a solution of amine hydrochloride salt **39** (201 mg, 0.42 mmol) in dry THF (6 mL) was added, and the reaction was stirred for 1 h and partitioned between ethyl acetate (20 mL) and water (30 mL). The

aqueous layer was further extracted with ethyl acetate (20 mL) and the organic extracts were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate solution (25 mL) and brine (25 mL), dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum−triethylamine (30:10:1) to give the *title compound* (263 mg, 69%) as a colorless solid, mp 88−90 °C. $[\alpha]_D^{23}$ −14.4 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3442, 3404, 3126, 2985, 2936, 2877, 1716, 1770, 1506, 1369, 1163, 1101, 1055 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (1 H, d, J = 8.2, Py-4-H), 8.07 (1 H, s, SCH), 8.05 (1 H, s, SCH), 7.86 (1 H, d, J = 9.0, CHCHN*H*), 7.64 (1 H, d, J = 8.2, Py-5-H), 7.55 (1 H, d, J = 8.0, MeCHN*H*), 7.41−7.26 (6 H, m, PhH and CH_2N*H*), 5.52 (1 H, dq, J = 8.0, 7.0, C*H*Me), 5.27 (1 H, m, N*H*Boc), 4.90 (1 H, m, C*H*Me), 4.76 (2 H, s, PyCH_2), 4.67 (2 H, s, PhCH_2), 4.58 (1 H, dd, J = 16.8, 5.8, C*H*HNH), 4.54 (1 H, dd, J = 9.0, 7.0, CHC*H*NH), 4.40 (1 H, dd, J = 16.8, 5.4, CH*H*NH), 4.37 (2 H, q, J = 7.2, OCH_2Me), 2.55 (3 H, s, Me), 2.29 (1 H, m, Me_2C*H*), 2.24 (3 H, s, Me), 1.71 (3 H, d, J = 7.0, CH*Me*), 1.47 (3 H, d, J = 6.9, CH*Me*), 1.40 (9 H, s, CMe_3), 1.36 (3 H, t, J = 7.2, CH_2*Me*), 1.02 (3 H, d, J = 7.0, *Me*CHMe), 1.00 (3 H, d, J = 7.0, MeCH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6 (C), 171.3 (C), 164.9 (C), 163.2 (C), 161.2 (C), 161.13 (C), 161.07 (C), 160.4 (C), 157.5 (C), 154.9 (C), 154.2 (C), 149.3 (C), 148.5 (C), 148.2 (C), 147.1 (C), 138.5 (CH), 137.7 (C), 132.7 (C), 128.7 (C), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.5 (C), 127.3 (CH), 125.3 (CH), 120.5 (CH), 79.8 (C), 73.1 (CH_2), 72.7 (CH_2), 61.4 (CH_2), 58.5 (CH), 46.9 (CH), 44.7 (CH), 36.6 (CH_2), 31.2 (CH), 28.3 (Me), 21.2 (Me), 20.2 (Me), 19.4 (Me), 18.1 (Me), 14.3 (Me), 11.6 (Me), 11.0 (Me); *m*/*z* (electrospray) 970 (MH^+, 65%), 870 (12), 793 (8), 631 (18), 509 (11), 508 (10), 463 (40), 458 (29), 455 (15), 149 (54), 91 (30); HRMS calcd for $C_{47}H_{56}N_9O_{10}S_2$ (MH) 970.3592, found 970.3564.

(g) *N*-(*tert*-Butoxycarbonyl)-Protected Linear Peptide Carboxylic Acid 42. Lithium hydroxide monohydrate (54 mg, 1.30 mmol) was added to a solution of *N*-(*tert*-butoxycarbonyl)-protected linear peptide ethyl ester **41** (208 mg, 0.22 mmol) in THF−water (5:1) (20 mL) at room temperature. The reaction was stirred overnight, evaporated in vacuo, and partitioned between water (30 mL) and ether (30 mL). The aqueous layer was separated, acidified to pH 2.5 with aqueous citric acid solution (10%), and extracted with ethyl acetate (3 × 25 mL). The organic layers were combined, washed, with brine (25 mL), dried (Na_2SO_4), and evaporated in vacuo to give the *title compound* (214 mg, 94%) as a colorless solid, mp 122−123 °C. $[\alpha]_D^{25}$ −14.0 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3439, 3401, 3125, 2984, 2932, 2875, 1730, 1715, 1667, 1637, 1510, 1455, 1377, 1165, 1099, 1045 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (1 H, d, J = 8.2, Py-4-H), 8.12 (1 H, s, SCH), 8.10 (1 H, s, SCH), 7.97 (1 H, d, J = 8.9, CHCHN*H*), 7.73 (1 H, d, J = 7.0, MeCHN*H*), 7.65 (1 H, m, CH_2N*H*), 7.64 (1 H, d, J = 8.2, Py-5-H), 7.41−7.27 (5 H, m, PhH), 5.82 (1 H, br s, CO_2H), 5.51 (1 H, m, C*H*Me), 5.41 (1 H, br s, N*H*Boc), 4.93 (1 H, m, C*H*Me), 4.76 (2 H, s, PyCH_2), 4.68 (2 H, s, PhCH_2), 4.57 (1 H, m, CHC*H*NH), 4.55 (1 H, dd, J = 16.8, 5.3, C*H*HNH), 4.47 (1 H, dd, J = 16.8, 5.3, CH*H*NH), 2.54 (3 H, s, Me), 2.29 (1 H, m, Me_2C*H*), 2.24 (3 H, s, Me), 1.68 (3 H, d, J = 6.9, CH*Me*), 1.48 (3 H, d, J = 6.9, CH*Me*), 1.39 (9 H, s, CMe_3), 1.01 (3 H, d, J = 6.4, *Me*CHMe), 1.00 (3 H, d, J = 6.4, MeCH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 (C), 171.5 (C), 164.8 (C), 163.5 (C), 162.7 (C), 161.3 (C), 161.1 (C), 160.3 (C), 157.9 (C), 155.1 (C), 154.2 (C), 149.0 (C), 148.3 (C), 146.7 (C), 138.5 (CH), 137.7 (C), 132.6 (C), 128.6 (C), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.6 (C), 125.8 (CH), 120.6 (CH), 79.9 (C), 73.1 (CH_2), 72.6 (CH_2), 58.6 (CH), 46.8 (CH), 44.7 (CH), 36.5 (CH_2), 31.1 (CH), 28.3 (Me), 21.3 (Me), 20.1 (Me), 19.3 (Me), 18.2 (Me), 11.6 (Me), 11.0 (Me), one C unobserved; MS (FAB) *m*/*z* (relative intensity) 941 (M^+, 41%), 841 (30), 765 (6), 603 (28), 481 (18), 391 (48), 311 (11), 149 (100); HRMS calcd for $C_{45}H_{51}N_9O_{10}S_2$ (M) 941.3200, found 941.3251.

(h) Macrocyclic peptide 43. 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (46 mg, 240 μmol) was added to a stirred solution of *N*-(*tert*-butoxycarbonyl)-protected linear peptide carboxylic acid **42** (196 mg, 208 μmol) and pentafluorophenol (46 mg, 250 μmol) in dry dichloromethane (5 mL) at 0 °C. The reaction mixture was warmed slowly to room temperature over 16 h, evaporated in vacuo, and partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous layer was further extracted with ethyl acetate (20 mL) and the organic extracts were combined, washed with brine (20 mL), dried (Na_2SO_4), and evaporated in vacuo to afford the crude pentafluorophenyl ester (240 mg, quant) that was used without further purification. A solution of hydrogen chloride in dioxane (4.0 M; 8 mL) was added to a stirred solution of the pentafluorophenyl ester (240 mg, 208 μmol) in dry dioxane (15 mL) at room temperature. The mixture was stirred for 3.5 h and dissolved in chloroform (150 mL). Aqueous potassium hydrogen carbonate solution (1.0 M; 250 mL) was added and the mixture was shaken vigorously for 5 min and then separated. The aqueous layer was further extracted with chloroform (2 × 50 mL) and the organic extracts were combined and dried (Na_2SO_4). Triethylamine (0.60 mL, 4.2 mmol) was added and the solution was stirred at room temperature for 4 days, evaporated in vacuo, and purified by flash chromatography on silica, eluting with ethyl acetate−chloroform−triethylamine (40:10:1), to give the *title compound* (94 mg, 55%) as a colorless solid, mp 110−111 °C. $[\alpha]_D^{25}$ +7.0 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3401, 3123, 2970, 2934, 2875, 1666, 1538, 1374, 1102, 1048, 998 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (1 H, d, J = 8.2, Py-4-H), 8.10 (1 H, s, SCH), 7.85 (1 H, s, SCH), 7.76 (1 H, d, J = 8.5, MeCHN*H*), 7.75 (1 H, d, J = 8.5, CHCHN*H*), 7.67 (1 H, d, J = 8.2, Py-5-H), 7.44−7.29 (6 H, m, PhH and MeCHN*H*), 6.88 (1 H, t, J = 5.6, CH_2N*H*), 5.43 (2 H, m, 2 C*H*Me), 4.81 (1 H, d, J = 14.2, PyC*H*H), 4.75 (1 H, d, J = 14.2, PyCH*H*), 4.70 (2 H, s, PhCH_2), 4.55 (1 H, dd, J = 16.8, 5.6, C*H*HNH), 4.49 (1 H, dd, J = 16.8, 5.6, CH*H*NH), 4.45 (1 H, dd, J = 8.5, 5.8, CHC*H*NH), 2.59 (3 H, s, Me), 2.53 (1 H, m, Me_2C*H*), 2.46 (3 H, s, Me), 1.67 (3 H, d, J = 6.9, CH*Me*), 1.60 (3 H, d, J = 7.0, CH*Me*), 1.08 (3 H, d, J = 6.9, *Me*CHMe), 1.07 (3 H, d, J = 6.7, MeCH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (C), 171.2 (C), 164.4 (C), 163.1 (C), 161.6 (C), 160.9 (C), 160.4 (C), 160.1 (C), 157.6 (C), 153.8 (C), 148.69 (C), 148.67 (C), 148.6 (C), 148.4 (C), 138.4 (CH), 137.7 (C), 132.9 (C), 128.8 (C), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.5 (C), 125.4 (CH), 124.7 (CH), 120.6 (CH), 73.2 (CH_2), 72.7 (CH_2), 59.0 (CH), 46.0 (CH), 43.2 (CH), 36.3 (CH_2), 29.9 (CH), 20.2 (Me), 19.7 (Me), 19.5 (Me), 17.8 (Me), 11.6 (Me), 11.2 (Me); MS (EI) *m*/*z* (relative intensity) 823 (M^+, 20%), 731 (6), 717 (12), 362 (3), 256 (7), 138 (17), 105 (63), 91 (100), 77 (51); HRMS calcd for $C_{40}H_{41}N_9O_7S_2$ (M) 823.2570, found 823.2593.

Alternative Macrocyclization Strategy. (a) Valine−Oxazole Dipeptide Methyl Ester Hydrochloride 44. Acetyl chloride (0.49 mL, 6.90 mmol) was added dropwise to a stirred solution of the *N*-(*tert*-butoxycarbonyl)-protected dipeptide **36** (127 mg, 0.35 mmol) in dry methanol (10 mL) at room temperature. The mixture was stirred overnight and evaporated in vacuo to give the title compound (ca. 100%) as a pale yellow foam used directly in the next step.

(b) Pyridine 45. The oxazole−pyridine−thiazole carboxylic acid **40** (158 mg, 0.29 mmol) was dissolved in dry THF (5 mL) at 0 °C, and treated successively with *N*-methylmorpholine (80 μL, 0.73 mmol) and isobutyl chloroformate (4l μL, 0.32 mmol). The mixture was stirred at 0 °C for 30 min, a solution of the amine hydrochloride salt **44** (ca. 0.35 mmol) in dry THF (2 mL) was added, and the mixture was stirred for 1 h. Workup as above (for compound **41**) and flash chromatography on silica, eluting with ethyl acetate−light petroleum−triethylamine (30:10:1), gave the *title compound* (110 mg, 48%) as a colorless oil. $[\alpha]_D^{25}$ −11.0 (*c* 1.06, $CHCl_3$); IR (CH_2Cl_2) 3483, 3395, 3124, 2987, 2934, 2877, 1720, 1664, 1538, 1497, 1369, 1102 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (1 H, d, J = 8.2, Py-4-H), 8.14 (1 H, s, SCH), 7.85 (1 H, d, J = 8.5, MeCHN*H*), 7.72 (1 H, t, J = 5.6, CH_2N*H*), 7.63 (1 H, d, J = 8.2, Py-5-H), 7.36−7.26 (6 H, m, PhH and CHN*H*), 5.36 (1 H, br, C*H*NH), 4.90 (1 H, br, C*H*NH), 4.68 (2 H, s, PyCH_2), 4.64 (3 H, s + m, PhCH_2 and CH*H*NH), 4.48 (1 H, dd, J = 16.8, 5.6, C*H*HNH), 3.82 (3 H, s, OMe), 2.52 (3 H, s, Me), 2.22 (1 H, m, Me_2C*H*), 2.19 (3 H, s, Me), 1.46 (3 H, d, J = 7.0, CH*Me*), 1.40 (9 H, s, CMe_3), 0.99 (3 H, d, J = 7.0, *Me*CHMe), 0.97 (3 H, d, J = 7.0, MeCH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (C), 164.8 (C), 163.2 (C), 162.4 (C), 160.9 (C), 160.3 (C), 158.7 (C), 156.8 (C), 154.9 (C), 149.2 (C), 148.5 (C), 148.1 (C), 138.5 (C), 137.7 (CH), 132.7 (C), 128.6 (CH), 127.9 (CH), 127.8 (CH), 127.5 (C), 127.4 (CH), 125.6 (C), 120.4 (CH), 79.7 (C), 73.1 (CH_2), 72.6 (CH_2), 58.1 (CH), 51.1 (Me), 44.7 (CH), 36.3 (CH_2), 31.6 (CH), 28.3 (Me), 20.1 (Me), 19.3 (Me), 18.1 (Me), 11.9 (Me), 10.9 (Me); MS (FAB) *m*/*z* (relative intensity) 824 (M + Na^+, 100%),

802 (MH^+, 41), 724 (19), 702 (56), 685 (10), 487 (22), 256 (5), 149 (15); HRMS calcd for $C_{40}H_{48}N_7O_9S$ (MH) 802.3234, found 802.3205.

(c) Cyclization Precursor 46. Acetyl chloride (0.22 mL, 3.11 mmol) was added dropwise to a solution of the *N*-(*tert*-butoxycarbonyl)-protected pyridyl oxazole **45** (100 mg, 0.12 mmol) (prepared by hydrolysis of ester **7a** as described in the literature[50]) in dry methanol (10 mL) at 0 °C. The mixture was stirred overnight at room temperature and evaporated in vacuo to give the amine hydrochloride (ca. 0.12 mmol) used directly in the next step.

The thiazole carboxylic acid **7b** (51 mg, 0.19 mmol) was dissolved in dry THF (5 mL) at 0 °C and treated successively with *N*-methylmorpholine (55 μL, 0.50 mmol) and isobutyl chloroformate (24 μL, 0.19 mmol). The mixture was stirred at 0 °C for 45 min, the above amine hydrochloride salt added in dry THF (5 mL), and the mixture stirred for 1 h. Workup as above (for compound **41**) and flash chromatography on silica, eluting with ethyl acetate−light petroleum−triethylamine (40:10:1), gave the *title compound* (92 mg, 77%) as a colorless foam. $[\alpha]_D^{27}$ +2.0 (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 3439, 3018, 2934, 1717, 1655, 1540, 1497 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (1 H, d, J = 7.4, Py-4-H), 8.01 (1 H, s, SCH), 7.98 (1 H, s, SCH), 7.86 (1 H, d, J = 8.6, MeCHN*H*), 7.61 (2 H, br d, J = 7.4, Py-5-H and CHN*H*), 7.38−7.26 (6 H, m, PhH and NH), 5.55 (1 H, br, N*H*Boc), 5.37 (1 H, m, C*H*NH), 5.00 (1 H, br, C*H*NH), 4.74 (2 H, s, PyCH_2), 4.66 (2 H, s, PhCH_2), 4.60 (1 H, dd, J = 16.3, 5.8, C*H*HNH), 4.54 (1 H, br, C*H*NH), 4.48 (1 H, dd, J = 16.3, 5.4, CH*H*NH), 3.81 (3 H, s, OMe), 2.51 (3 H, s, Me), 2.30 (3 H, s, Me), 2.25 (1 H, m, Me_2C*H*), 1.56 (3 H, d, J = 7.0, CH*Me*), 1.53 (3 H, d, J = 6.9, CH*Me*), 1.40 (9 H, s, CMe_3), 0.98 (3 H, d, J = 6.6, *Me*CHMe), 0.96 (3 H, d, J = 6.6, MeCH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5 (C), 171.2 (C), 164.7 (C), 162.5 (C), 162.4 (C), 161.0 (C), 160.2 (C), 160.1 (C), 158.7 (C), 156.7 (C), 155.0 (C), 149.1 (C), 149.0 (C), 148.6 (C), 138.7 (CH), 137.7 (C), 132.4 (C), 128.5 (CH), 127.8 (CH), 127.7 (CH), 127.5 (C), 127.4 (C), 125.5 (CH), 123.7 (CH), 120.3 (CH), 80.2 (C), 73.0 (CH_2), 72.6 (CH_2), 58.3 (CH), 51.8 (Me), 48.7 (CH), 42.9 (CH), 36.3 (CH_2), 31.4 (CH), 28.3 (Me), 21.1 (Me), 19.5 (Me), 19.3 (Me), 18.0 (Me), 11.9 (Me), 11.1 (Me), one C unobserved; MS (FAB) *m*/*z* (relative intensity) 978 (M + Na^+, 100%), 956 (MH^+, 30), 878 (13), 856 (24), 686 (6), 658 (5), 487 (4), 199 (8); HRMS calcd for $C_{46}H_{54}N_9O_{10}S_2$ (MH) 956.1080, found 956.3409.

(d) Oxazole Carboxylic Acid 47. The above ester **46** (74 mg, 0.077 mmol) was dissolved in THF−water (5:1) (5 mL); lithium hydroxide monohydrate (18 mg, 0.430 mmol) was added, and the mixture was stirred overnight at room temperature. Workup as above (for compound **22**) gave the *title compound* (67 mg, 92%) as a colorless foam. $[\alpha]_D^{25}$ +31.5 (*c* 1.33, $CHCl_3$); IR ($CHCl_3$) 3441, 3397, 3300, 2979, 2935, 1712, 1651, 1495, 1369, 1169, 1097, 1057, 929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (1 H, d, J = 8.1, Py-4-H), 8.35 (1 H, br s, CH_2N*H*), 8.28 (1 H, s, SCH), 8.22 (1 H, s, SCH), 8.03 (1 H, d, J = 8.8, CHN*H*), 7.88 (1 H, d, J = 7.9, CHN*H*), 7.65 (1 H, d, J = 8.1, Py-5-H), 7.39−7.26 (6 H, m, PhH and NH), 5.42 (2 H, br m, CO_2H and C*H*NH), 4.98(1 H, br, C*H*NH), 4.76 (2 H, s, PyCH_2), 4.72 (2 H, m, CH_2NH), 4.67 (2 H, s, PhCH_2), 4.51 (1 H, br, C*H*NH), 2.53 (3 H, s, Me), 2.23 (4 H, s + m, Me and Me_2C*H*), 1.66 (3 H, d, J = 6.7, CH*Me*), 1.52 (3 H, d, J = 6.9, CH*Me*), 1.43 (9 H, s, CMe_3), 1.01 (6 H, d, J = 5.7, *Me*$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7 (C), 171.5 (C), 164.2 (C), 163.7 (C), 163.0 (C), 161.1 (C), 160.1 (C), 158.7 (C), 157.2 (C), 155.1 (C), 148.7 (C), 148.6 (C), 148.3 (C), 148.1 (C), 138.5 (CH), 137.7 (CH), 132.7 (C), 128.5 (CH), 128.0 (C), 127.9 (CH), 127.8 (CH), 127.6 (C), 126.9 (C), 124.7 (CH), 120.8 (CH), 80.3 (C), 73.1 (CH_2), 72.6 (CH_2), 58.4 (CH), 48.7 (CH), 43.6 (CH), 36.0 (CH_2), 31.7 (Me), 29.6 (CH), 28.3 (Me), 21.1 (Me), 19.3 (Me), 18.5 (Me), 11.9 (Me), 10.9 (Me), one C unobserved; MS (FAB) *m*/*z* (relative intensity) 964 (M + Na^+, 100%), 942 (MH^+, 23), 941 (M^+, 6), 864 (13), 842 (17), 680 (11), 242 (11), 199 (21), 152 (23); HRMS calcd for $C_{45}H_{51}N_9O_{10}S_2$ (M) 941.3200, found 941.3200.

(e) Macrocyclic Peptide 43. 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (13.4 mg, 70 μmol) was added to a stirred solution of *N*-(*tert*-butoxycarbonyl)-protected linear peptide carboxylic acid **47** (57 mg, 61 μmol) and pentafluorophenol (13 mg, 73 μmol) in dry dichloromethane (3 mL) at 0 °C. The reaction was warmed slowly to room temperature over 16 h, evaporated in vacuo, and partitioned between ethyl acetate (10 mL) and brine (10 mL). The aqueous layer was further extracted with ethyl acetate (10 mL) and the organic extracts were combined, dried (Na_2SO_4), and evaporated in vacuo to afford the crude pentafluorophenyl ester that was used without further purification. A solution of hydrogen chloride in dioxane (4.0 M; 2.3 mL) was added to a stirred solution of the pentafluorophenyl ester in dry dioxane (3 mL) at room temperature. The mixture was stirred for 16 h and dissolved in chloroform (100 mL). Aqueous potassium hydrogen carbonate solution (1.0 M; 100 mL) was added and the mixture was shaken vigorously for 5 min and then separated. The aqueous layer was further extracted with chloroform (2 × 50 mL) and the organic extracts were combined and stirred over Na_2SO_4 for 2 days. The mixture was evaporated in vacuo and the residue purified by flash chromatography on silica, eluting with ethyl acetate−methanol−triethylamine (50:1:1). A second column (silica, ethyl acetate−chloroform−triethylamine (40:10:1)) was required to obtain the *title compound* (36 mg, 71%) as a colorless solid, identical with the previous sample.

Elaboration of Dehydroalanine Side Chain. (a) Pyridine-2-methanol (48). A solution of boron trichloride−methyl sulfide complex (2.0 M in dichloromethane; 1.2 mL, 2.30 mmol) was added to a stirred solution of benzyl ether **43** (94 mg, 0.11 mmol) in dry dichloromethane (10 mL) at 0 °C. The mixture was stirred for 5 min, warmed to room temperature, stirred overnight, and partitioned between a solution of aqueous citric acid (10%; 20 mL) and chloroform (30 mL). The aqueous layer was further extracted with chloroform (2 × 20 mL) and the organic extracts were dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography on silica, eluting with ethyl acetate−methanol−triethylamine (75:5:1) to give the *title compound* (33 mg, 39%) as a colorless solid, mp 163−164 °C. $[\alpha]_D^{21}$ +4.2 (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 3400, 3122, 3009, 2972, 2935, 2875, 1667, 1539, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (1 H, d, J = 8.2, Py-4-H), 8.11 (1 H, s, SCH), 7.87 (1 H, s, SCH), 7.74 (2 H, d, J = 8.5, MeCHN*H* and CHCHN*H*), 7.42 (1 H, d, J = 8.2, Py-5-H), 7.37 (1 H, d, J = 8.6, MeCHN*H*), 6.76 (1 H, t, J = 5.7, CH_2N*H*), 5.43 (2 H, m, 2 C*H*Me), 4.87 (2 H, s, CH_2OH), 4.56 (1 H, dd, J = 17.0, 6.0, C*H*HNH), 4.50 (1 H, dd, J = 17.0, 6.0, CH*H*NH), 4.44 (1 H, dd, J = 8.5, 6.0, CHC*H*NH), 3.49 (1 H, br s, OH), 2.60 (3 H, s, Me), 2.53 (1 H, m, Me_2C*H*), 2.50 (3 H, s, Me), 1.69 (3 H, d, J = 6.8, CH*Me*), 1.63 (3 H, d, J = 7.2, CH*Me*), 1.08 (3 H, d, J = 6.7, *Me*CHMe), 1.07 (3 H, d, J = 7.1, MeCH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.31 (C), 171.26 (C), 164.4 (C), 162.9 (C), 161.4 (C), 160.9 (C), 160.8 (C), 160.4 (C), 157.7 (C), 153.8 (C), 148.78 (C), 148.75 (C), 148.69 (C), 148.1 (C), 138.6 (CH), 132.9 (C), 128.8 (C), 127.3 (C), 125.4 (CH), 124.8 (CH), 119.7 (CH), 64.3 (CH_2), 58.9 (CH), 45.9 (CH), 43.2 (CH), 36.3 (CH_2), 30.3 (CH), 20.0 (Me), 19.7 (Me), 19.6 (Me), 18.0 (Me), 11.6 (Me), 11.3 (Me); MS (EI) *m*/*z* (relative intensity) 733 (M^+, 40%), 717 (58), 675 (6), 396 (8), 299 (18), 228 (17), 207 (27), 138 (45), 55 (100); HRMS calcd for $C_{33}H_{35}N_9O_7S_2$ (M) 733.2101, found 733.2077.

(b) Pyridine-2-carboxaldehyde (49). A solution of *o*-iodoxybenzoic acid (64 mg, 229 μmol) in DMSO (2 mL) was stirred at room temperature for 30 min until homogeneous. A solution of pyridine-2-methanol (**44**) (33 mg, 44 μmol) in DMSO (2 mL) was added, the mixture was stirred for 4 h, and water (3 mL) was added. After a further 10 min, the mixture was partitioned between ethyl acetate (15 mL) and water (10 mL). The aqueous layer was further extracted with ethyl acetate (2 × 15 mL) and the organic extracts were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate solution (25 mL), water (25 mL), and brine (25 mL), dried (Na_2SO_4), and evaporated in vacuo to give *aldehyde* (26 mg, 81%) as a colorless solid, mp 162−163 °C. $[\alpha]_D^{24}$ +21.6 (*c* 0.81, $CHCl_3$); IR ($CHCl_3$) 3401, 3122, 2957, 2918, 2851, 1730, 1668, 1539, 1375, 1248, 1045, 591 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.11 (1 H, s, CHO), 8.55 (1 H, d, J = 8.1, Py-4-H), 8.10 (1 H, s, SCH), 8.01 (1 H, d, J = 8.1, Py-5-H), 7.94 (1 H, s, SCH), 7.76 (1 H, d, J = 8.6, CHCHN*H*), 7.72 (1 H, d, J = 8.4, CHN*H*), 7.36 (1 H, d, J = 8.7, CHN*H*), 7.04 (1 H, t, J = 6.0, CH_2N*H*), 5.41 (2 H, m, 2 C*H*Me), 4.59 (1 H, dd, J = 17.0, 6.0, C*H*HNH), 4.48−4.37 (2 H, m, CH*H*NH and CHC*H*NH), 2.56 (6 H, s, 2 Me), 2.46 (1 H, m, Me_2C*H*), 1.65 (3 H, d, J = 6.8, CH*Me*), 1.60 (3 H, d, J = 7.1, CH*Me*), 1.07 (3 H, d, J = 6.8, *Me*CHMe), 1.06 (3 H, d, J = 6.8, MeCH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3 (CH), 171.3 (C), 171.2 (C), 163.2 (C), 163.1 (C), 161.1 (C), 160.8 (C), 160.5 (C),

157.7 (C), 153.8 (C), 152.3 (C), 149.8 (C), 149.6 (C), 149.1 (C), 148.6 (C), 139.1 (CH), 132.3 (C), 132.1 (C), 128.9 (C), 126.4 (CH), 124.9 (CH), 120.2 (CH), 58.9 (CH), 46.0 (CH), 43.3 (CH), 36.2 (CH_2), 30.4 (CH), 19.9 (Me), 19.6 (Me), 19.6 (Me), 18.1 (Me), 11.5 (Me), 11.4 (Me); MS (EI) *m*/*z* (relative intensity) 731 (M^+, 19%), 663 (6), 462 (40), 419 (8), 348 (29), 320 (26), 242 (15), 165 (18), 138 (38), 121 (100); HRMS calcd for $C_{33}H_{33}N_9O_7S_2$ (M) 731.1944, found 731.1958.

(c) (*S*)-*O*-*tert*-Butyldimethylsilylserinamide. *tert*-Butyldimethylsilyl chloride (215 mg, 1.4 mmol) was added to a stirred solution of L-serinamide hydrochloride (200 mg, 1.4 mmol), triethylamine (0.62 mL, 4.5 mmol), and 4-(dimethylamino)pyridine (9 mg, 0.07 mmol) in dry acetonitrile (5 mL) at room temperature. The mixture was stirred overnight and partitioned between dichloromethane (50 mL) and water (50 mL). The aqueous layer was further extracted with dichloromethane (2 × 50 mL) and the organic extracts were combined, dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography on silica, eluting with ethyl acetate−methanol (12:1) to give the *title compound* (170 mg, 55%) as a colorless solid, mp 38−40 °C. $[\alpha]_D^{24}$ −24.6 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3506, 3377, 2956, 2931, 1682, 1556, 1473, 1464, 1258, 1100, 1005, 940, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (1 H, s, exch D_2O, OCN*H*H), 6.45 (1 H, s, exch D_2O, OCNH*H*), 3.74 (1 H, dd, *J* = 9.8, 5.1, C*H*H), 3.71 (1 H, dd, *J* = 9.8, 6.0, CH*H*), 3.38 (1 H, m, CH), 1.83 (2 H, s, exch D_2O, NH_2), 0.83 (9 H, s, CMe_3), 0.01 (6 H, s, $SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (C), 65.3 (CH_2), 56.6 (CH), 25.8 (Me), 18.1 (C), −5.49 (Me), −5.53 (Me); MS (EI) *m*/*z* (relative intensity) 219 (MH^+, 25%), 203 (13), 188 (26), 174 (67), 161 (90), 144 (79), 130 (15), 116 (100), 102 (33), 89 (44), 86 (46), 75 (68), 73 (83), 59 (37); HRMS calcd for $C_9H_{23}N_2O_2Si$ (MH) 219.1529, found 219.1529.

(d) (+)-Promothiocin A (1). Sodium chlorite (4 mg, 40 μmol) was added to a stirred solution of aldehyde **49** (26 mg, 36 μmol), potassium dihydrogen orthophosphate (17 mg, 126 μmol), and 2-methyl-2-butene (100 μL) in *tert*-butanol−water (1:1) (4 mL) at room temperature. The mixture was stirred for 5 h and partitioned between chloroform (15 mL) and water (10 mL). The aqueous layer was acidified to pH 4 with aqueous citric acid (10%) and further extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried (Na_2SO_4), and evaporated in vacuo to give crude acid **50** (19 mg, 70%) as a colorless solid that was used without further purification.

1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (6 mg, 28 μmol) was added to a stirred solution of (*S*)-*O*-*tert*-butyldimethylsilylserinamide (7 mg, 33 μmol) and the acid **50** (19 mg, 25 μmol) in dry dichloromethane (3 mL) at room temperature. The mixture was stirred overnight and partitioned between dichloromethane (10 mL) and water (10 mL). The aqueous layer was further extracted with chloroform (3 × 10 mL) and the organic extracts were combined, washed with brine (10 mL), dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography on silica, eluting with ethyl acetate−methanol (15:1) to give the amide **51** (12 mg, 50%) as a colorless solid that was used without further purification.

Tetrabutylammonium fluoride (1.0 M; 24 μL) was added to a stirred solution of the amide **51** (8 mg, 8 μmol) in dry THF (3 mL) at room temperature. The mixture was stirred for 1.5 h and saturated aqueous ammonium chloride solution (1 mL) was added. The solution was concentrated in vacuo and partitioned between chloroform (7 mL) and water (7 mL). The aqueous layer was further extracted with chloroform (2 × 7 mL) and the organic extracts were combined, dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography on silica, eluting with ethyl acetate−methanol (15:1) to give amide **52** (4 mg, 57%) as a colorless solid that was used without further purification.

Methanesulfonyl chloride (10 μL) was added to a stirred solution of amide **52** (4 mg, 5 μmol) and triethylamine (100 μL) in dry dichloromethane (3 mL) at room temperature. The mixture was stirred for 1 h and partitioned between chloroform (7 mL) and water (7 mL). The aqueous layer was further extracted with chloroform (2 × 7 mL) and the organic extracts were combined, dried (Na_2SO_4), and evaporated in vacuo. The solid residue was dissolved in dichloromethane (3 mL) and triethylamine (100 μL) was added. The mixture was stirred overnight at room temperature, evaporated in vacuo, and purified by flash chromatography on silica, eluting with chloroform−acetone (3:2) to give the title compound (2.2 mg, 59%) as a colorless solid, mp 268−272 °C dec (lit.[8] mp 268−272 °C). $[\alpha]_D^{23}$ +87.3 (*c* 0.34, $CHCl_3$-MeOH, 1:1) (lit.[8] $[\alpha]_D^{21}$ +79.2 (*c* 0.69, $CHCl_3$-MeOH, 1:1)); IR ($CHCl_3$) 3412, 3334, 3121, 2964, 2931, 2873, 1670, 1521, 1040, 998, 920, 889, 864 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 10.67 (1 H, s, CH_2CHNH), 8.85 (1 H, dd, *J* = 7.4, 4.4, CH_2NH), 8.52 (1 H, d, *J* = 8.0, Py-4-H), 8.37 (1 H, s, SCH), 8.24 (1 H, s, SCH), 8.22 (1 H, d, *J* = 7.9, CHN*H*), 8.18 (1 H, d, *J* = 8.0, Py-5-H), 8.13 (1 H, s, N*H*H), 8.12 (1 H, d, *J* = 8.6, CHN*H*), 8.02 (1 H, d, *J* = 8.9, CHCHN*H*), 7.65 (1 H, s, NH*H*), 6.57 (1 H, s, CC*H*H), 5.80 (1 H, s, CCH*H*), 5.42 (1 H, m, C*H*Me), 5.01 (1 H, m, C*H*Me), 4.56 (1 H, dd, *J* = 16.1, 7.4, C*H*HNH), 4.38 (1 H, dd, *J* = 8.9, 6.4, NHC*H*CH), 4.19 (1 H, dd, *J* = 16.1, 4.4, CH*H*NH), 2.66 (3 H, s, Me), 2.53 (3 H, s, Me), 2.17 (1 H, m, Me_2CH), 1.60 (3 H, d, *J* = 6.7, CH*Me*), 1.48 (3 H, d, *J* = 7.0, CH*Me*), 0.95 (6 H, d, *J* = 6.4, $CHMe_2$); ^{13}C NMR (100 MHz, d_6-DMSO) δ 171.8 (C), 170.7 (C), 164.9 (C), 163.7 (C), 161.8 (C), 161.2 (C), 160.1 (C), 159.9 (C), 159.7 (C), 158.5 (C), 152.6 (C), 149.2 (C), 149.0 (C), 149.0 (C), 148.5 (C), 148.0 (C), 141.2 (CH), 133.6 (C), 132.4 (C), 130.3 (C), 128.5 (C), 126.8 (CH), 125.0 (CH), 120.6 (CH), 102.4 (CH_2), 57.5 (CH), 45.2 (CH), 43.1 (CH), 35.2 (CH_2), 31.2 (CH), 19.8 (Me), 19.4 (Me), 18.2 (Me), 18.1 (Me), 11.5 (Me), 11.2 (Me); MS (EI) *m*/*z* (relative intensity) 816 (MH^+, 0.2%), 747 (12), 729 (5), 369 (4), 207 (15), 83 (100).

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Supporting Information Available: Experimental details for compounds **6a**, **7b**, **8**−**18**, **23**, and **26**−**29** and ^1H and ^{13}C NMR spectra of compounds **6b**, **7a**, **10**, **14**−**23**, 1-benzyloxy-3-butyn-2-ol, **24**−**34**, **36**−**38**, **40**−**43**, **45**−**49**, (*S*)-*O*-*tert*-butyldimethylsilylserinamide, and (synthetic) promothiocin A **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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