Total Synthesis of (−)-Thiangazole and Structurally Related Polyazoles

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Thiangazole was reported to be an extremely potent, nontoxic inhibitor of HIV-1 in MT4 cell assays. By employing a strategy of selective oxazoline–thiazoline interconversions, we have accomplished a total synthesis of the natural product in 16 steps and 1.1% overall yield from (*S*)-α-methylserine. This new methodology is especially useful for the preparation of analogs of thiangazole and structure–activity studies. Our preliminary biological testing of (−)-thiangazole revealed a high level of cytotoxicity that was considerably reduced in the oxazoline-containing analogs.

The polythiazoline thiangazole (**1**) was isolated in 1992 from a myxobacterium *Polyangium* sp. strain.[2] Reports of its antihelmintic[3] and, especially, its extremely high potency in HIV-1 inhibition[2,4] have triggered several synthetic,[5] structural,[6] and biological[7] investigations. Thiangazole was also reported to exhibit no cell toxicity even at millimolar levels.[2] The lack of cytotoxicity for this compound appeared surprising considering the moderate to high levels of cytotoxicity observed with the structurally closely related mirabazoles and tantazoles (Figure 1).[8]

In this paper, we present a concise total synthesis of the natural product that employs the trisoxazoline **9** as an intermediate and uses new methodology for an efficient triple oxazoline → thiazoline conversion (Figure 2). This approach is especially attractive for the preparation of analogs of the natural product for SAR studies. Specifically, oxazoline analogs **2** and **14** and thiazoline **17** were prepared from readily accessible intermediates of the total synthesis. Surprisingly, our own structure–activity studies for thiangazole and a series of closely related compounds have failed to confirm significant antiviral activities and, in contrast, established consistently high levels of cytotoxicity for the thiazoline-containing isomers.

Total Synthesis of (−)-Thiangazole. Acylation of D-threonine methyl ester with *N*-[(trimethylsilyl)ethyl]-sulfonyl-protected (*S*)-α-methylserine **3**[9] in the presence of the coupling reagent PyBroP[10] and DMAP gave the dipeptide **4** in 82% yield (Scheme 1). Since the threonine α- and β-stereocenters are destroyed in the subsequent conversion of **4** to the oxazole **5**, alternatively both L- and D,L-threonine can be employed in this coupling. However, the use of L-threonine methyl ester led to considerably reduced coupling yields (and rates) with (*S*)-**3**, probably due to unfavorable steric interactions in the transition state for the acylation with the highly hindered acid **3**. Accordingly, acylation with the readily available unnatural D-isomer of threonine occurs via a diastereomeric transition state of lower energy. Oxazole synthesis[11] via

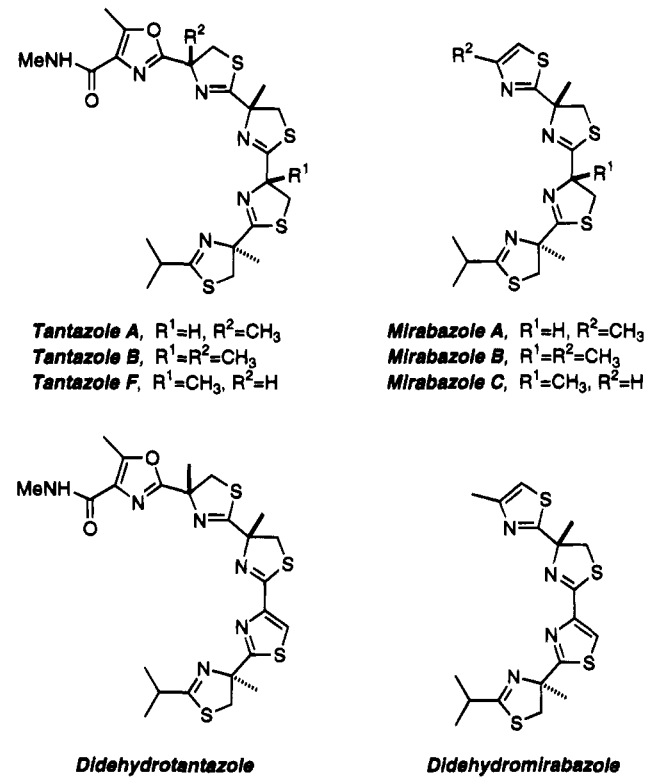

Figure 1. Cytotoxic metabolites from the blue-green alga *Scytonema mirabile*.

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(1) Eli Lilly Grantee, 1993–1995; Alfred P. Sloan Research Fellow, 1994–1996; NSF Presidential Faculty Fellow, 1994–1999; Camille Dreyfus Teacher–Scholar, 1995–1997.

(2) Jansen, R.; Kunze, B.; Reichenbach, H.; Jurkiewicz, E.; Hunsmann, G.; Höfle, G. *Liebigs Ann. Chem.* **1992**, 357.

(3) Höfle, G.; Bedorf, N.; Forche, E.; Gerth, K.; Irschik, H.; Jansen, R.; Kunze, B.; Reichenbach, H.; Sasse, F. *PCT Int. Appl. WO* 92 11,258; *Chem. Abstr.* **1992**, *117*, 226295w.

(4) (a) Hunsmann, G.; Jurkiewicz, E.; Reichenbach, H.; Forche, E.; Gerth, K.; Irschik, H.; Kunze, B.; Sasse, F.; Höfle, G. *PCT Int. Appl. WO* 92 11,008; *Chem. Abstr.* **1993**, *118*, 52420m. (b) Jurkiewicz, E.; Jansen, R.; Kunze, B.; Trowitzsch-Kienast, W.; Forche, E.; Reichenbach, H.; Höfle, G.; Hunsmann, G. *Antiviral Chem. Chemother.* **1992**, *3*, 189.

(5) For previous total syntheses of thiangazole, see: (a) Boyce, R. J.; Mulqueen, G. C.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 5705. (b) Ehrler, J.; Farooq, S. *Synlett* **1994**, *9*, 702. (c) Parsons, R. L.; Heathcock, C. H. *J. Org. Chem.* **1994**, *59*, 4733.

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(8) (a) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 8195. (b) Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1991**, *32*, 2593. (c) Carmeli, S.; Paik, S.; Moore, R. E.; Patterson, G.; Yoshida, W. Y. *Tetrahedron Lett.* **1993**, *34*, 6681. For the total synthesis and stereochemical assignment of tantazoles, see: (d) Fukuyama, T.; Xu, L. H. *J. Am. Chem. Soc.* **1993**, *115*, 8449.

(9) Prepared in multigram quantities from (*S*)-2-methylglycidol: Wipf, P.; Venkatraman, S.; Miller, C. P. *Tetrahedron Lett.* **1995**, *36*, 3639.

(10) PyBroP = Bromotripyrrolidinophosphonium hexafluorophosphate: Coste, J.; Frerot, E.; Jouin, P. *J. Org. Chem.* **1994**, *59*, 2437.

(11) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.

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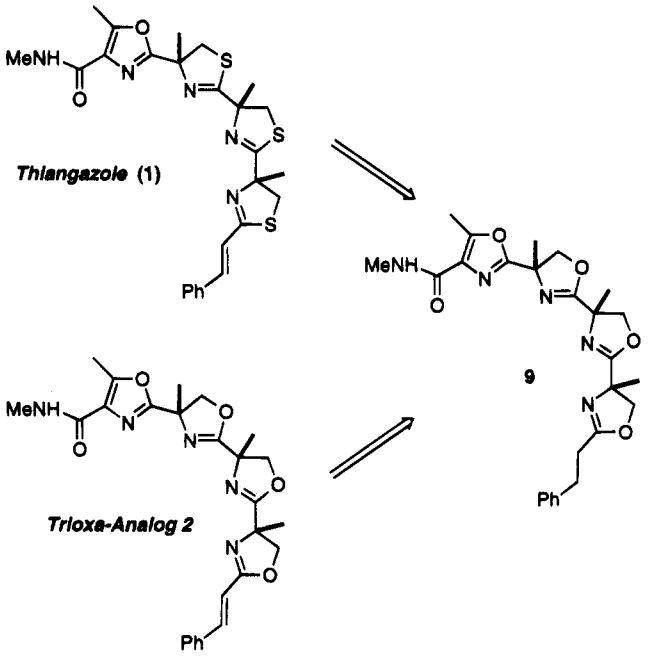
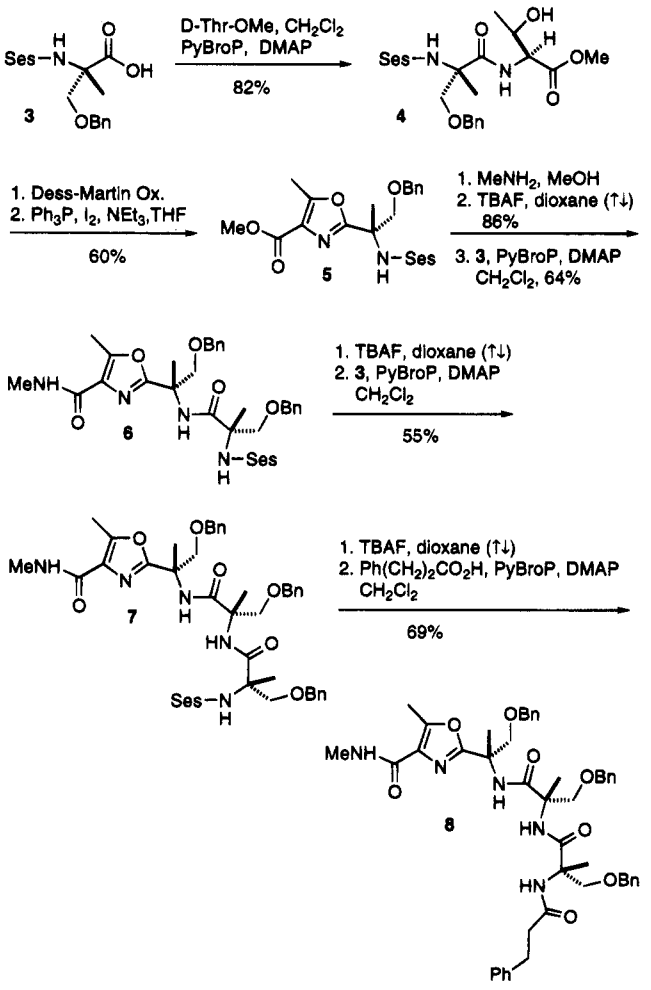


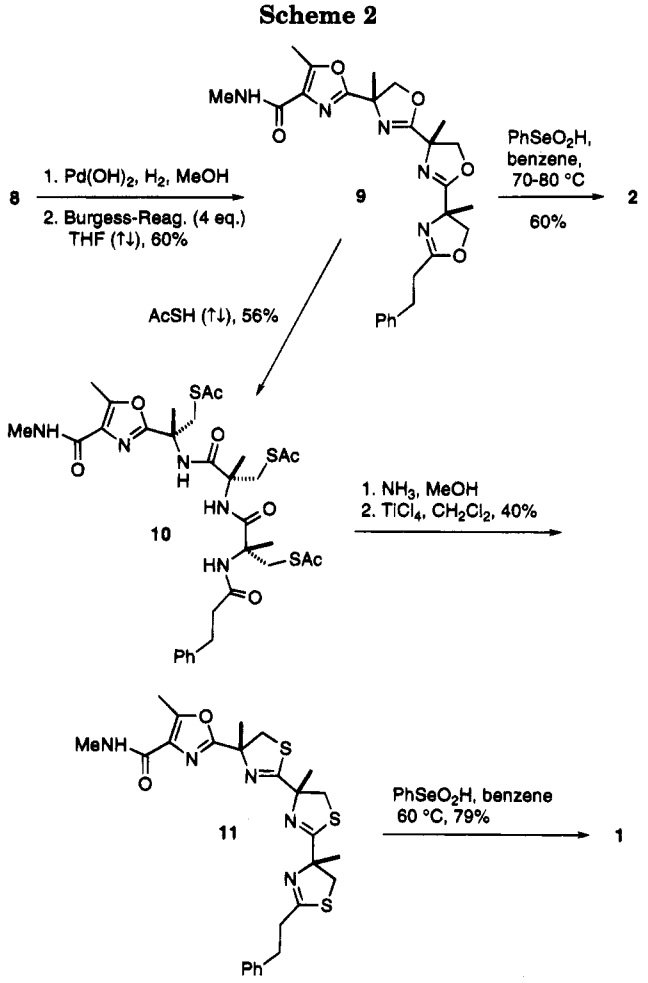
Figure 2. Retrosynthetic approach.

Scheme 1



side-chain Dess–Martin oxidation and cyclodehydration of dipeptide **4** with triphenylphosphine/iodine provided the highly functionalized oxazole **5** in 60% yield. After aminolysis of the C-terminal methyl ester, the N-terminus of **5** was readily extended to the *N*-dihydrocinnamoyl tetrapeptide **8** by an iterative sequence of deprotections with TBAF and couplings with **3** and dihydrocinnamic acid. Oxazole **8** was isolated in 21% overall yield from dipeptide **5**.

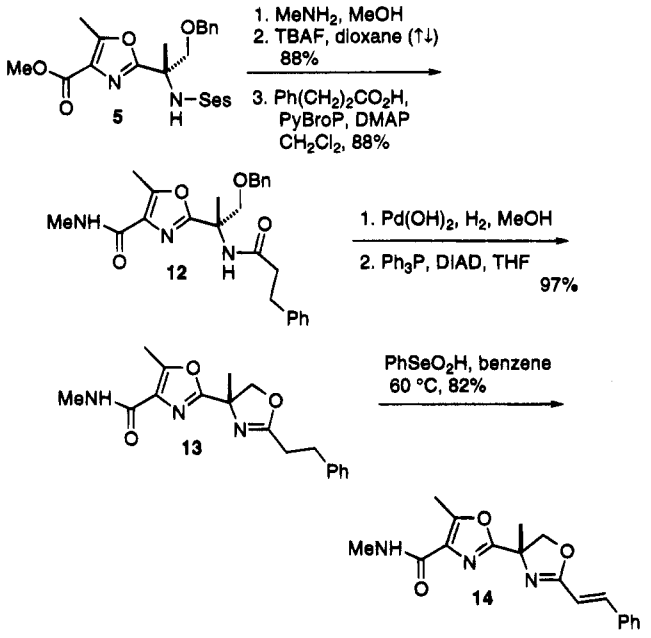
Scheme 2



The use of α-methylserine rather than α-methylcysteine amino acid building blocks considerably facilitated the preparation of the multiple-linked heterocycles found in thiangazole and provided maximum flexibility for analog syntheses. Catalytic hydrogenation of **8** with $Pd(OH)_2$ in methanol, followed by a triple cyclization reaction with excess Burgess reagent[12] gave trisoxazoline **9** in a highly satisfactory 60% yield (Scheme 2). Dehydrogenation with benzeneseleninic acid according to Barton's protocol[13] provided the desired analog **2**. Alternatively, a facile oxazoline → thiazoline conversion was achieved by conversion of the trisoxazoline to the α-methylcysteine derivative **10** in the presence of thioacetic acid.[14] Aminolysis and Lewis acid-induced simultaneous cyclodehydration of the three *S*-deprotected cysteine residues with titanium tetrachloride according to Heathcock's procedure[15] led to **11**, the tristhiazoline isomer of **9**. Finally, oxidation of **11** with $PhSeO_2H$ completed the total synthesis of thiangazole (**1**) in an overall yield of 18% from the common intermediate **9**. Synthetic **1** was

(12) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907.
(13) Barton, D. H. R.; Motherwell, W. B.; Wozniak, J.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1865.
(14) For a related reaction, see: Fry, E. M. *J. Org. Chem.* **1950**, *15*, 438.
(15) Walker, M. A.; Heathcock, C. H. *Tetrahedron Lett.* **1994**, *35*, 1379.

Scheme 3

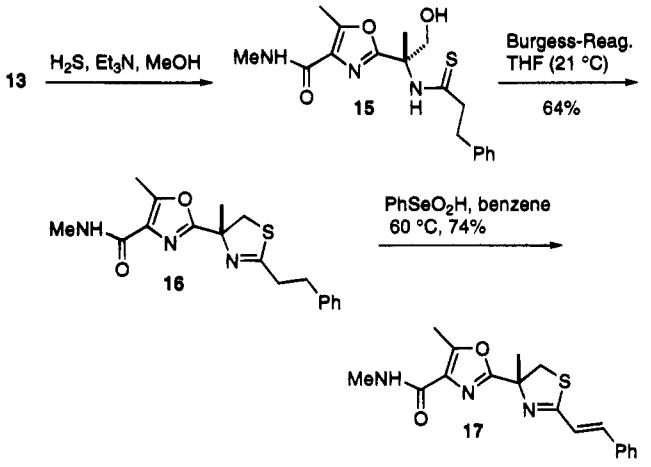


spectroscopically and chromatographically indentical to a sample of the natural compound provided by Jansen et al.

Preparation of Analogs. Oxazolines are isoelectronic substitutes for thiazolines, and comparison of the pharmacological profile of these five-membered heterocycles can contribute valuable data to structure–activity studies of biologically active compounds. The most complete series of thiazoline–oxazoline replacements in natural products can be found within the *Lissoclinum* family of marine cyclopeptides, where the presence of thiazoline rings often appears to mediate higher levels of cytotoxicity.[16] Our retrosynthetic approach to thiangazole had been designed with the intent to expedite SAR studies with oxazoline-containing analogs of the natural product by using them as actual intermediates of the synthetic pathway. This has already been demonstrated in Scheme 2 for the preparation of **9** and **2**. Additional oxazoline–thiazoline pairs such as **14** and **17** are readily prepared with this strategy (Scheme 3).

Aminolysis of oxazole **5** with methylamine in methanol followed by removal of the [(trimethylsilyl)ethyl]sulfonyl protective group and *N*-acylation with dihydrocinnamic acid gave oxazole **12** in 77% yield. Hydrogenolysis of the benzyl ether and formation of the oxazoline under Mitsunobu conditions[17] provided **13** in 97% yield, and subsequent Barton dehydrogenation with benzeneseleninic acid led to the bis-azole **14**. The thiazoline analogs of **13** and **14** were readily obtained by thiolysis[18] of oxazoline **13** (Scheme 4). In contrast to the selective opening at C(5) of the oxazoline with thioacetic acid (Scheme 2), the neutral to slightly basic reaction conditions of thiolysis with H_2S and triethylamine in methanol led to regioselective attack at C(2) of the oxazoline **13** and provided thioamide **15** after ring opening.[18] Cyclodehydration[19] of **15** with Burgess reagent and side-chain oxidation completed the synthesis of the thiangazole analog **17**.

Scheme 4



Conclusion. A novel strategy based on selective oxazoline → thiazoline conversions via cysteines or thioamide intermediates has successfully been applied toward the total syntheses of the natural polyazole thiangazole and analog structures. This strategy is distinctively different from earlier approaches[5] and minimizes synthetic manipulations of intermediates containing sensitive sulfur moieties. Beyond applications for natural products total synthesis, the interconversion of oxazolines and thiazolines is of general value in medicinal chemistry since both heterocycles are often used pharmacophores in biologically active compounds and exhibit different levels of cytotoxicity and bioavailability. Contrary to the published results,[2,4] our own preliminary analyses of thiangazole did not show any selective anti-HIV-1 activity in CEM-T_4 and H9 cell assays, but found the natural product to be highly cytotoxic with a TD_{50} of 0.003 μM. The level of cytotoxity for the oxazoline analogs was lower by at least a factor of 10^4. Further details of the biological evaluation of polyazoles will be reported in due course.

Experimental Section

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

(2*R*,3*S*)-2-[[(2*S*)-3-(Benzyloxy)-2-methyl-2-[[[2-(trimethylsilyl)ethyl]sulfonyl]amino]propionyl]amino]-3-hydroxybutyric Acid Methyl Ester (4). A solution of 500 mg (1.4 mmol) of **3**, 1.0 g (2.1 mmol) of PyBrOP, 360 mg (2.1 mmol) of D-threonine methyl ester, and 1.2 mL (6.5 mmol) of Hünig's base in 4 mL of CH_2Cl_2 was stirred at 21 °C for 12 h. The reaction mixture was concentrated and chromatographed on SiO_2 (EtOAc/hexanes, 1:1) to yield 505 mg (82%) of **4** as a viscous oil: R_f 0.6 (EtOAc/hexanes, 1:1); $[\alpha]_D$ −6.2° (*c* 0.70, $CHCl_3$, 25 °C); IR (neat) 3349, 2952, 1744, 1669, 1520, 1455, 1435, 1321, 1252, 1210, 1169, 1140, 1021, 897, 858 cm^{-1}; ^{1}H NMR δ 7.54 (d, 1 H J = 8.7 Hz), 7.31 (s, 5 H), 5.59 (s, 1 H), 4.60, 4.51 (AB, 2 H, J = 10.4 Hz), 4.52–4.59 (m, 1 H), 4.33–4.28 (m, 1 H), 3.85, 3.64 (AB, 2 H, J = 9.4 Hz), 3.70 (s, 3 H), 3.03–2.97 (m, 2 H), 1.58 (s, 3 H), 1.24 (b, 1 H), 1.19 (d, 3 H, J

(16) (a) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771. (b) Wipf, P. *Chem. Rev.*, **1995**, *95*, 2115 and references therein.
(17) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267.
(18) Wipf, P.; Venkatraman, S.; Fritch, P. C.; Miller, C. P. *Tetrahedron Lett.* **1995**, *51*, 6395.
(19) Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397.

= 6.3 Hz), 1.04−0.97 (m, 2 H), 0.00 (s, 9 H); ^{13}C NMR δ 172.8, 171.0, 137.0, 128.5, 128.0, 127.9, 74.3, 73.6, 68.2, 62.4, 57.8, 52.5, 52.3, 20.4, 20.0, 10.6, −2.1; MS (CI, isobutane) *m/z* (relative intensity) 489 ([M + 1]$^+$, 100), 471 (20), 445 (20) 425 (12), 397 (20), 381 (10), 353 (20), 328 (10), 307 (8), 279 (4), 236 (9), 215 (2).

(2*R*)-2-[2(*S*)-3-(Benzyloxy)-2-methyl-2-[[[2-(trimethylsilyl)ethyl]sulfonyl]amino]propionyl]amino]-3-oxobutyric Acid Methyl Ester (4a). A solution of 1.9 g (3.9 mmol) of **4** in 7 mL of CH_2Cl_2 was treated with 2.0 g (4.7 mmol) of Dess-Martin periodinane and stirred at 21 °C for 20 min. The reaction mixture was filtered through a plug of basic Al_2O_3, concentrated, and chromatographed on SiO_2 (EtOAc/hexanes, 1:1) to yield 1.8 g (90%) of **4a** as a viscous oil: R_f 0.45 (EtOAc/hexanes, 1:2); $[\alpha]_D$ −6.17° (*c* 0.7, $CHCl_3$, 23 °C); IR (neat) 2953, 1755, 1728, 1676, 1507, 1437, 1362, 1325, 1252, 1211, 1169, 1142, 1021, 843, 739 cm^{-1}; ^{1}H NMR δ 8.08 (b, 1 H), 7.23−7.33 (bs, 5 H), 5.45 (s, 1 H), 5.19 (d, 1 H, *J* = 6.0 Hz), 4.61 (s, 2 H), 3.87−3.82 (m, 1 H), 3.78 (s, 3 H), 3.68−3.64 (m, 1 H), 3.04−2.98 (m, 2 H), 2.34 (s, 3 H), 1.61 (s, 3 H), 1.07−1.00 (m, 2 H), 0.16 (s, 9 H); ^{13}C NMR δ 197.9, 172.5, 166.1, 136.8, 128.5, 128.0, 127.9, 73.7, 63.4, 61.8, 53.3, 52.3, 27.9, 20.7, 10.6, −2.1; MS (EI) *m/z* (relative intensity) 365 (M − $PhCH_2OCH_2$]$^+$, 4), 328 (12), 319 (25), 305 (6), 291 (8), 273(6), 264 (15), 231 (50), 203 (10), 164 (20), 149 (20), 132 (10), 101 (8), 91 (80), 73 (100) 65 (10), 57 (20); HRMS *m/z* calcd for $C_{15}H_{26}NO_3SSi$ [M-$C_6H_8NO_4$] 328.1402; found 328.1401.

2-[(1*S*)-2-(Benzyloxy)-1-methyl-1-[[[2-(trimethylsilyl)ethyl]sulfonyl]amino]ethyl]-5-methyloxazole-4-carboxylic Acid Methyl Ester (5). A solution of 1.8 g (3.5 mmol) of ketone **4a** in 7 mL of THF was added dropwise at −60 °C to a solution of 2.8 g (10.7 mmol) of triphenylphosphine, 2.4 g (9.3 mmol) of iodine, and 1.8 g (18 mmol) of Et_3N in 30 mL of THF. The reaction mixture was stirred at −60 °C for 20 min and 0 °C for 2 h, diluted with 30 mL of H_2O, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo and chromatographed on SiO_2 (EtOAc/hexanes, 2:5) to yield 1.2 g (66%) of **5** as a viscous oil: R_f 0.76 (EtOAc/hexanes, 2:3); $[\alpha]_D$ −14.3° (*c* 3.6, $CHCl_3$, 23 °C); IR (neat) 2952, 1719, 1619, 1441, 1387, 1352, 1329, 1252, 1229, 1202, 1171, 1092, 843, 743, 698 cm^{-1}; ^{1}H NMR δ 7.32−7.28 (m, 3 H), 7.23−7.21 (m, 2 H), 5.29 (s, 1 H), 4.51 (s, 2 H), 3.88 (s, 3 H), 3.80, 3.71 (AB, 2 H, *J* = 9.2 Hz), 3.01−2.94 (m, 2 H), 2.61 (s, 3H), 1.80 (s, 3 H), 1.06−1.00 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR δ 162.6, 162.2, 156.8, 137.1, 128.5, 128.0, 127.6, 75.4, 73.3, 58.4, 52.3, 52.0, 22.1, 12.1, 10.4, −2.0; MS (CI, isobutane) *m/z* (relative intensity) 469 ([M + 1]$^+$, 100), 471 (20), 453 (3), 393 (25), 303 (25), 288 (10), 273 (10), 255 (10), 232 (10), 197 (5), 183 (10), 166 (5), 142 (5), 91 (10), 73 (20); HRMS *m/z* calcd for $C_{13}H_{23}N_2O_5SSi$ [M − $PhCH_2OCH_2$]$^+$ 347.1096; found 347.1069.

2-[(1*S*)-2-(Benzyloxy)-1-methyl-1-[[[2-(trimethylsilyl)ethyl]sulfonyl]amino]ethyl]-5-methyloxazole-4-carboxylic Acid Methylamide (5a). A solution of 60 mg (0.12 mmol) of **5** in 3 mL of MeOH was saturated at 0 °C with CH_3NH_2 (gas). The reaction mixture was stirred at 21 °C for 12 h and concentrated in vacuo to yield 60 mg (100%) of **5a** as a viscous oil: R_f 0.6 (EtOAc/hexanes, 4:1); $[\alpha]_D$ −18° (*c* 1.2, $CHCl_3$, 25 °C); IR (neat) 2946, 1659, 1649, 1632, 1530, 1453, 1414, 1327, 1250, 1140, 1107, 1001, 841, 737, 698 cm^{-1}; ^{1}H NMR δ 7.33−7.26 (m, 3 H), 7.22−7.18 (m, 2 H), 6.86 (d, 1 H, *J*= 4.8 H), 5.26 (s, 1 H), 4.54, 4.50 (AB, 2 H, *J* = 9.2 Hz), 3.74, 3.70, (AB, 2 H, *J* = 9.2 Hz), 2.96−2.90 (m, 2 H), 2.93 (d, 3 H, *J* = 5.0 Hz), 2.62 (s, 3 H), 1.76 (s, 3 H), 1.05−0.99 (m, 2 H), 0.09 (s, 9 H); ^{13}C NMR δ 162.3, 161.0, 153.2, 137.2, 129.3, 128.6, 128.1, 127.7, 75.1, 73.4, 58.4, 52.3, 25.6, 22.0, 11.8, 10.5, −2.0 ; MS (EI) *m/z* (relative intensity) 452 ([M − CH_3]$^+$, 5), 426 (4), 394 (4), 360 (4), 346 (30), 302 (100), 287 (15), 272 (50), 254 (60), 229 (10), 213 (30), 194 (10), 182 (10), 164 (10), 151 (10), 114 (10), 101 (10), 91 (50), 73 (55); HRMS *m/z* calcd for $C_{13}H_{24}N_3O_4SSi$ M − $PhCH_2OCH_2$] 346.1256; found 346.1297.

2-[(1*S*)-2-(Benzyloxy)-1-[[(2*S*)-3-(benzyloxy)-2-methyl-2-[[[2-(trimethylsilyl)ethyl]sulfonyl]amino]propionyl]amino]-1-methylethyl]-5-methyloxazole-4-carboxylic Acid Methylamide (6). A solution of 140 mg (0.30 mmol) of **5a** in 0.5 mL of dry dioxane was heated at reflux for 12 h with 235 mg (0.9 mmol) of TBAF. The reaction mixture was concentrated and chromatographed on SiO_2 (acetone/hexanes 2:1) to yield 92 mg (86%) of amine. A solution of this amine in 0.4 mL of CH_2Cl_2 was treated with 123 mg (0.33 mmol) of **3** and 98 mg (0.75 mmol) of Hünig's base. The reaction mixure was cooled to 0 °C and treated with 150 mg (0.30 mmol) of PyBrOP and 26 mg (0.22 mmol) of DMAP, stirred overnight at 21 °C, concentrated in vacuo and chromatographed on SiO_2 (EtOAc/hexanes, 3:2) to yield 100 mg (64%) of **6** as a thick oil: R_f 0.4 (EtOAc/hexanes, 2:1); $[\alpha]_D$ −2.7° (*c* 2.8, $CHCl_3$, 25 °C); IR (neat) 2946, 1667, 1532, 1455, 1412, 1372, 1325, 1250, 1200, 1140, 1100, 1028, 841, 739, 698 cm^{-1}; ^{1}H NMR δ 8.25 (s, 1 H), 7.34−7.27 (m, 8 H), 7.19−7.17 (m, 2 H), 7.10 (q, 1 H, *J* = 5.0 Hz), 5.44 (s, 1 H), 4.59, 4.50 (AB, 2 H, *J* = 11.9 Hz), 4.47, 4.42 (AB, 2 H, *J* = 12.4 Hz), 3.92, 3.77 (AB, 2 H, *J* = 9.3 Hz), 3.90, 3.58 (AB, 2 H, *J* = 9.3 Hz), 3.04−2.96 (m, 2 H), 2.90 (d, 3 H, *J* = 5 Hz), 2.59 (s, 3 H), 1.72 (s, 3 H), 1.61 (s, 3 H), 1.07−0.98 (m, 2 H), 0.03 (s, 9 H); ^{13}C NMR δ 171.9, 162.4, 161.5, 153.0, 137.8, 137.6, 128.6, 128.4, 128.1, 127.8, 127.6, 74.4, 73.6, 73.2, 72.8, 62.5, 56.7, 52.5, 25.6, 20.9, 19.9, 11.7, 10.8, −2.0; MS (EI) *m/z* (relative intensity) 658 (M$^+$, 2), 550 (5), 537 (12), 328 (5), 288 (20), 264 (10), 236 (10), 180 (30), 164 (10), 132 (20), 101 (10), 91 (100), 73 (60); HRMS *m/z* calcd for $C_{24}H_{37}N_4O_6SSi$ (M − $BnOCH_2$) 537.2203; found 537.2196.

2-[(1*S*)-2-(Benzyloxy)-1-[[(2*S*)-3-(benzyloxy)-2-[[(3*S*)-3-(benzyloxy)-2-methyl-2-[[[2-(trimethylsilyl)ethyl]sulfonyl]amino]propionyl]amino]-2-methyl-propionyl]amino]-1-methylethyl]-5-methyloxazole-4-carboxylic Acid Methylamide (7). A solution of 90 mg (0.14 mmol) of **6** and 221 mg (0.84 mmol) of TBAF in 0.5 m L of dry dioxane was heated at reflux for 12 h. The reaction mixture was concentrated in vacuo and chromatographed on SiO_2 (acetone/hexanes, 3:2) to yield 59 mg (86%) of amine. A solution of this amine in 0.4 mL of CH_2Cl_2 was treated with 63 mg (0.17 mmol) of **3**, cooled to 0 °C and treated with 62 mg (0.48 mmol) of Hünig's base and 85 mg (0.17 mmol) of PyBrOP. After 10 min, 30 mg (0.24 mmol) of DMAP was added and the mixture was stirred for 12 h. The reaction mixture was concentrated in vacuo and chromatographed on SiO_2 (EtOAc/hexanes, 7:3) to yield 55 mg (64%) of **7** as a viscous oil: R_f 0.35 (EtOAc/Hexanes 8:2); $[\alpha]_D$ −5.3° (*c* 2.3, $CHCl_3$, 25 °C); IR (neat) 3360, 2926, 1667, 1651, 1532, 1455, 1412, 1371, 1323, 1252, 1202, 1102, 1028, 843, 739 cm^{-1}; ^{1}H NMR δ 7.75 (s, 1 H), 7.64 (s, 1 H), 7.34−7.23 (m, 13 H), 7.21−7.19 (m, 2 H), 6.98 (q, 1 H, *J* = 5 Hz), 5.31 (s, 1 H), 4.60−4.44 (m, 6 H), 3.93, 3.88 (AB, 2 H, *J* = 9.3 Hz), 3.84, 3.57 (AB, 2 H, *J* = 9.2 Hz), 3.77, 3.54 (AB, 2 H, *J* = 9.1 Hz), 3.01−2.94 (m, 2 H), 2.86 (d, 3 H, *J* = 7 Hz), 2.56 (s, 3 H), 1.69 (s, 3 H), 1.58 (s, 3 H), 1.52 (s, 3 H), 1.07−0.9 (m, 2 H), 0.02 (s, 9 H); ^{13}C NMR δ 171.9, 171.8, 162.7, 161.8, 152.5, 138.0, 137.5, 137.0, 129.0, 128.9, 128.6, 128.5, 128.3, 128.2, 127.8, 127.6, 127.5, 77.3, 74.4, 73.6, 73.2, 73.1, 62.6, 60.2, 56.3, 52.4, 25.6, 21.2, 20.2, 19.7, 11.7, 10.7, −2.0; MS (FAB, CH_2Cl_2/MNBA) 850 ([M + 1]$^+$, 100).

2-[(1*S*)-2-(Benzyloxy)-1-[[(2*S*)-3-(benzyloxy)-2-[[(3*S*)-3-(benzyloxy)-2-methyl-2-[(3-phenylpropionyl)amino]propionyl]amino]-2-methylpropionyl]amino]-1-methylethyl]-5-methyloxazole-4-carboxylic Acid Methylamide (8). A solution of 50 mg (0.06 mmol) of **7** and 94 mg (0.36 mmol) of TBAF in 0.4 mL of dioxane was heated at reflux for 12 h. The reaction mixture was concentrated in vacuo and chromatographed on SiO_2 (acetone/hexanes, 1:1) to yield 32 mg (80%) of amine. A solution of this amine in 0.4 mL of CH_2Cl_2 was treated with 27 mg (0.18 mmol) of dihydrocinnamic acid, cooled to 0 °C and treated with 59 mg (0.45 mmol) of Hünig's base and 63 mg (0.12 mmol) of PyBrOP. The reaction mixture was stirred at 21 °C overnight, concentrated in vacuo and chromatographed on SiO_2 (acetone/hexanes, 2:3) to yield 34 mg (85%) of **8** as viscous oil: R_f 0.63 (acetone/hexanes, 1:1); $[\alpha]_D$ −3.1° (*c* 1.7, $CHCl_3$, 25 °C); IR (neat), 3308, 2928, 2863, 2363, 2342, 1653, 1534, 1497, 1474, 1455, 1370, 1202, 1100, 843, 739 cm^{-1}; ^{1}H NMR δ 7.75 (s, 1 H), 7.35−7.18 (m, 18 H), 7.13−7.11 (m, 4 H), 6.27 (s, 1H), 4.55−4.40 (m, 6 H), 4.01, 3.87 (AB, 2 H, *J* = 9.3 Hz), 3.87, 3.52 (AB, 2 H, *J* = 9.2 Hz), 3.79, 3.51 (AB, 2 H, *J* = 9.2 Hz), 2.95−2.77 (m, 2 H), 2.84 (d, 3 H, *J* = 5.1 Hz), 2.56 (s, 3 H), 2.38 (t, 2 H, *J* = 7.7 Hz), 1.76 (s, 3 H), 1.56 (s, 3 H), 1.49 (s, 3 H); ^{13}C NMR δ 172.3, 172.1, 171.7, 162.7,

162.0, 152.3, 140.4, 138.1, 137.6, 137.3, 129.0, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 126.3, 73.7, 73.5, 73.2, 73.1, 60.4, 60.1, 56.3, 38.5, 31.4, 25.4, 21.4, 19.9, 11.8; MS (FAB, CH_2Cl_2/MNBA) 818 ([M + 1]$^+$, 100).

(4′*S*,4″*S*,4‴*S*)-5,4′,4″,4‴-Tetramethyl-2‴-phenethyl-4′,5′,4″,5″,4‴4′,5‴-hexahydro[2,4′:2′,4″:2″,4‴]quateroxazole-4-carboxylic Acid Methylamide (9). A solution of 400 mg (0.48 mmol) of **8** in 4 mL of MeOH was treated with 40 mg of 20% $Pd(OH)_2$/C and H_2 was bubbled through the reaction mixture for 1 h. The suspension was filtered through a plug of celite and concentrated in vacuo to yield 168 mg (100%) of crude triol.

A solution of 20 mg (36.0 μmol) of this triol in 1 mL of dry THF was treated with 42 mg (162.0 μmol) of Burgess reagent and stirred at 21 °C for 25 min. Subsequently, the reaction mixture was heated at 70 °C for 2 h, concentrated in vacuo and chromatographed on SiO_2 (acetone/hexanes, 1:1) to yield 12 mg (60%) of **9**: R_f 0.67 (acetone/hexanes, 7:3); 0.4 (MeOH/EtOAc, 1:19); $[\alpha]_D$ 129.8° (*c* 2.4, $CHCl_3$, 25 °C); IR (neat) 2342, 1686, 1653, 1638, 1626, 1607, 1545, 1526, 1509, 1497, 1464, 1447, 1352, 1192, 1102, 986, 941, 729, 662, 471 cm^{-1}; ^{1}H NMR δ 7.31−7.20 (m, 5 H), 6.92 (bs, 1 H), 4.84 (d, 1 H, *J* = 8.7 Hz), 4.74 (d, 1 H, *J* = 8.6 Hz), 4.68 (d, 1 H, *J* = 8.5 Hz), 4.23 (d, 1 H, *J* = 8.7 Hz), 4.14 (d, 1 H, *J* = 8.6 Hz), 4.05 (d, 1 H, *J* = 8.5 Hz), 2.97 (t, 2 H, *J* = 7.7 Hz), 2.94 (d, 3 H, *J* = 5 Hz), 2.64 (t, 2 H, *J* = 7.0 Hz), 2.64 (s, 3 H), 1.67 (s, 3 H), 1.54 (s, 3 H), 1.49 (s, 3 H); ^{13}C NMR δ 170.0, 169.7, 168.3, 162.5, 161.9, 153.6, 140.4, 129.2, 128.5, 128.4, 126.3, 76.4, 69.5, 69.4, 32.1, 29.9, 25.7, 25.6, 11.8; MS (EI) *m*/*z* (relative intensity) 493 (M$^+$, 87), 463 (10), 449 (10), 372 (5), 346 (100), 331(5), 314 (30), 302 (15), 272 (10), 264 (50), 236 (5), 207 (5), 197 (25), 188 (55), 166 (30), 150 (20), 140 (40), 132 (10), 124 (70), 113 (15); HRMS *m*/*z* calcd for $C_{26}H_{31}N_5O_5$ 493.2325; found 493.2318.

(4′*S*,4″*S*,4‴*S*)-5,4′,4″,4‴-Tetramethyl-2‴-styryl-4′,5′,4″,5″,4‴,5‴-hexahydro[2,4′:2′,4″:2″,4‴]quateroxazole-4-carboxylic Acid Methylamide (2). A solution of 8 mg (16.0 μmol) of **9** in 1 mL of benzene was heated at 70−80 °C for 1 h with 5 mg (26.0 μmol) of benzeneseleninic acid. The reaction mixture was directly chromatographed on SiO_2 containing a layer of basic alumia on the top of the column (acetone/hexanes, 3:2) to yield 5.3 mg (60%) of **2** as a viscous liquid: R_f 0.67 (acetone/hexanes, 7:3); $[\alpha]_D$ 83.7 (*c* 0.1, $CHCl_3$, 23 °C); IR (neat) 2917, 1647, 1642, 1605, 1570, 1565, 1553, 1547, 1536, 1528, 1518, 1511, 1485, 1441, 1352, 1275, 1194, 1103, 978, 941 cm^{-1}; ^{1}H NMR δ 7.49−7.46 (m, 2 H), 7.42 (d, 1 H, *J* = 16.4 Hz), 7.39−7.35 (m, 3 H), 6.92 (bs, 1 H), 6.66 (d, 1 H, *J* = 16.1 Hz), 4.85 (d, 1 H, *J* = 8.7 Hz), 4.81 (d, 1 H, *J* = 9.0 Hz), 4.77 (d, 1 H, *J* = 9.0 Hz), 4.23 (d, 1 H, *J* = 8.7 Hz), 4.20 (d, 1 H, *J* = 9.0 Hz), 4.18 (d, 1 H, *J* = 9.0 Hz), 2.94 (d, 3 H, *J* = 5 Hz), 2.64 (s, 3 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.54 (s, 3 H); ^{13}C NMR δ 170.0, 169.7, 164.4, 162.5, 161.9, 153.6, 141.2, 135.0, 129.8, 129.2, 129.0, 128.4, 127.6, 114.8, 77.5, 76.2, 69.7, 69.6, 69.4, 25.7, 25.6, 11.8; MS (EI) *m*/*z* (relative intensity) 491 (M$^+$, 100), 460 (15), 447 (25), 433 (10), 400 (10), 347 (32), 314 (10), 264 (20), 253 (10), 239 (5), 207 (10), 197 (20), 186 (85), 166 (25), 150 (20), 140 (35), 124 (55), 91 (35), 68 (30), 57 (40); HRMS *m*/*z* calcd for $C_{26}H_{29}N_5O_5$ 491.2168; found 491.2216.

(4*R*,4′*S*,4″*S*)-5-Methyl-2-[4,4′,4″-trimethyl-2″-phenethyl-4,5,4′,5′,4″,5″-hexahydro-[2,4′:2′4″]terthiazol-4-yl]oxazole-4-carboxylic Acid Methylamide (11). A solution of 60 mg (0.12 mmol) of **9** in 1 mL of thiolacetic acid was heated at reflux for 1 h under an N_2 atmosphere. The reaction mixture was concentrated in vacuo and chromatographed on SiO_2 (acetone/CH_2Cl_2, 1:5) to yield 44 mg (56%) of **10** which was directly used for the next step: R_f 0.6 (acetone/CH_2Cl_2 1:3).

A solution of 30 mg (0.04 mmol) of **10** in 1 mL of saturated methanolic ammonia was stirred at 21 °C for 1 h, concentrated in vacuo, and treated with 2 mL of a 1:1 mixture of CH_2Cl_2 and $TiCl_4$. The reaction mixture was stirred at 21 °C for 24 h and poured into a solution of saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and chromatographed on SiO_2 (acetone/hexanes, 3:7) to yield 9 mg (40%) of tristhiazoline **11** as a glassy solid: R_f 0.6 (acetone/hexanes, 2:3); $[\alpha]_D$ −187° (*c* 0.4, $CHCl_3$, 25 °C); IR (neat) 3373, 2976, 2862, 1670, 1653, 1540, 1437, 1369, 1197, 1097, 1013, 901 cm^{-1}; ^{1}H NMR δ 7.31−7.19 (m, 5 H), 6.91 (bs, 1 H), 3.85 (d, 1 H, *J* = 11.4 Hz), 3.77 (d, 1 H, *J* = 11.4 Hz), 3.73 (d, 1 H, *J* = 11.4 Hz), 3.30 (d, 1 H, *J* = 11.4 Hz), 3.25 (d, 1 H, *J* = 11.4 Hz), 3.20 (d, 1 H, *J* = 11.4 Hz), 3.04−2.98 (m, 2 H), 2.94 (d, 3 H, *J* = 5.0 Hz), 2.83 (t, 2 H, *J* = 7.0 Hz), 2.65 (s, 3 H), 1.67 (s, 3 H), 1.60 (s, 3 H), 1.57 (s, 3 H); ^{13}C NMR δ 178.4, 178.2, 171.7, 162.6, 162.4, 153.4, 140.4, 129.2, 128.5, 126.3, 83.7, 79.5, 76.7, 43.8, 43.1, 42.0, 36.0, 33.6, 26.2, 25.8, 25.6, 24.4, 11.8; MS (EI) *m*/*z* (relative intensity) 541 (M$^+$, 15), 526 (50), 508 (10), 404 (10), 379 (15), 337 (60), 303 (65), 280 (100), 262 (60), 245 (10), 214 (5), 204 (95), 192 (15), 182 (35), 172 (60), 150 (20), 140 (20), 112 (10), 91(75), 73 (50); HRMS *m*/*z* calcd for $C_{26}H_{31}N_5O_2S_3$ 541.1639; found 541.1601.

(4*R*,4′*S*,4″*S*)-5-Methyl-2-[4,4′,4″-trimethyl-2″-styryl-4,5,4′,5′,4″,5″-hexahydro[2,4′2′,4″]terthiazol-4-yl]oxazole-4-carboxylic Acid Methylamide (Thiangazole, 1). A solution of 9 mg (0.02 mmol) of **11** in 0.4 mL of dry benzene was treated with 7 mg (0.04 mmol) of benzeneseleninic acid and heated at 60 °C for 45 min. The reaction mixture was chromatographed on SiO_2 with a band of basic Al_2O_3 on the top of the column (acetone/hexanes, 1:4) to yield 7.0 mg (79%) of thiangazole (**1**) as a glassy solid: R_f 0.6 (acetone/hexanes, 2:3); $[\alpha]_D$ −245° (*c* 0.09, MeOH, 25 °C); IR (neat) 3420, 2977, 2929, 2855, 1668, 1633, 1449, 1157, 1013, 754; ^{1}H NMR δ 7.51−7.49 (m, 2 H), 7.39−7.34 (m, 3 H), 7.15, 7.06 (AB, 2 H, *J* =16.3 Hz), 6.93 (bs, 1 H), 3.86 (d, 1 H, *J* = 11.1 Hz), 3.84 (d, 1 H, *J* = 11.3 Hz), 3.76 (d, 1 H, *J* = 11.3 Hz), 3.38 (d, 1 H, *J* = 11.1 Hz), 3.29 (d, 1 H, *J* = 11.5 Hz), 3.22 (d, 1 H, *J* = 11.3 Hz), 2.94 (d, 3 H, *J* = 5 Hz), 2.65 (s, 3 H), 1.69 (s, 3 H), 1.68 (s, 3 H), 1.56 (s, 3 H); ^{13}C NMR (125 MHz) δ 178.2, 168.1, 162.6, 162.4, 153.5, 142.1, 135.1, 129.8, 129.2, 129.0, 127.7, 122.5, 83.7, 83.5, 79.4, 43.2, 42.5, 42.0, 26.2, 25.7, 25.6, 24.4, 11.8; MS (EI) *m*/*z* (relative intensity) 539 (M$^+$, 25), 439 (30), 379 (10), 337 (45), 301 (90), 280 (40), 260 (90), 243 (15), 213 (50), 202 (100), 182 (20), 172 (45), 150 (15), 140 (20), 130 (15), 115 (15), 100 (10), 85 (15), 73 (80), 59 (10); HRMS *m*/*z* calcd for $C_{26}H_{29}N_5O_2S_3$ 539.1483; found 539.1444.

2-[(1*S*)-2-(Benzyloxy)-1-methyl-1-[(3-phenyl-propionyl)amino]ethyl]-5-methyloxazole-4-carboxylic Acid Methylamide (12). A solution of 345 mg (0.75 mmol) of **5a** and 1.0 g (3.8 mmol) of TBAF·$3H_2O$ in 2 mL of dry dioxane was heated at reflux for 12 h. The reaction mixture was concentrated and chromatographed on SiO_2 (acetone/hexanes, 7:3) to yield 250 mg (88%) of amine that was used without further purification: R_f 0.58 (acetone).

To a solution of 200 mg (0.64 mmol) of this amine and 192 mg (1.28 mmol) of dihydrocinnamic acid in 2 mL of CH_2Cl_2 were added 700 mg (1.4 mmol) of PyBrOP and 0.35 mL (1.9 mmol) of Hünig's base. The reaction mixture was stirred for 12 h, concentrated in vacuo and chromatographed on SiO_2 (EtOAc/hexanes, 8:1) to yield 250 mg (88%) of **12** as a crystalline solid: mp 102−104 °C; R_f 0.6 (EtOAc); $[\alpha]_D$ −8.9° (*c* 0.56, MeOH, 25 °C); IR (neat) 3029, 2930, 2869, 2361, 2344, 1653, 1576, 1559, 1539, 1476, 1455, 1408, 1204, 1098, 843 cm^{-1}; ^{1}H NMR δ 7.32−7.16 (m, 10 H), 6.85 (bd, 1 H, *J* = 5 Hz), 6.36 (s, 1 H), 4.49, 4.44 (AB, 2 H, *J* = 12.1 Hz), 3.81, 3.72 (AB, 2 H, *J* = 9.2 Hz), 2.94 (t, 2 H, *J* = 7.7 Hz), 2.90 (d, 3 H, *J* = 5 Hz), 2.58 (s, 3 H), 2.52 (t, 2 H, *J* = 7.1 Hz), 1.69 (s, 3 H); ^{13}C NMR δ 171.6, 162.4, 161.6, 152.7, 140.8, 137.4, 129.0, 128.4, 127.9, 127.6, 126.2, 73.3, 73.2, 56.1, 38.4, 31.3, 25.4, 21.1, 11.6; MS (EI) *m*/*z* (relative intensity) 435 ([M]$^+$, 10), 404 (6), 377 (10), 344 (4), 314 (20), 286 (8), 270 (7), 229 (10), 182 (100), 166 (10), 151(10), 110 (10), ,91 (60), 65 (10); HRMS *m*/*z* calcd for $C_{25}H_{29}N_3O_4$ 435.2158; found 435.2176.

(4′*S*)-5,4′-Dimethyl-2′-phenethyl-4′5′-dihydro-2,4′-bioxazolyl-4-carboxylic Acid Methylamide (13). Hydrogen gas was bubbled through a solution of 250 mg (0.55 mmol) of **12** in 5 mL of MeOH in the presence of 50 mg of 20% $Pd(OH)_2$/C. After 45 min, the solution was filtered through a plug of celite, concentrated in vacuo and dried in vacuo for 2 h to give crude alcohol that was used without further purification: R_f 0.1 (EtOAc).

A solution of 100 mg (0.28 mmol) of crude alcohol in 1 mL of dry THF was treated at 0 °C with 88 mg (0.33 mmol) of Ph_3P and 70 mg (0.33 mmol) of DIAD. The reaction mixture was stirred at 0 °C for 10 min and at 21 °C for 0.5 h. The

reaction mixture was concentrated in vacuo and chromatographed on SiO_2 (acetone/ether, 1:40) to yield 92 mg (97%) of oxazoline **13** as a viscous liquid: R_f 0.55 (EtOAc); $[\alpha]_D$ −86° (*c* 0.58, MeOH, 25 °C); IR (neat) 2928, 1732, 1657, 1636, 1539, 1455, 1196, 1109, 997, 845 cm^{-1}; ^1H NMR δ 7.29−7.16 (m, 5 H), 6.91 (b, 1 H), 4.76, 4.11 (AB, 2 H, J = 8.9 Hz), 2.97 (t, 2 H, J = 7.5 Hz), 2.93 (d, 3 H, J = 5.1 Hz), 2.67−2.61 (m, 2 H), 2.61 (s, 3 H), 1.61 (s, 3 H); ^{13}C NMR δ 168.3, 162.5, 162.3, 153.4, 140.2, 129.0, 128.5, 128.4, 126.3, 76.5, 69.3, 32.0, 29.8, 25.9, 25.5, 11.7; MS (CI, isobutane) *m*/*z* (relative intensity) 328 ([M + 1]$^+$, 100), 327 (10), 311 (5),231 (3), 197 (4), 180 (4), 147 (2), 91 (2).

(4′*S*)-5,4′-Dimethyl-2′-styryl-4′5′-dihydro-2,4′-bioxazolyl-4-carboxylic Acid Methylamide (14). A solution of 40 mg (0.12 mmol) of **13** in 3 mL of dry benzene was treated with 25 mg (0.13 mmol) of benzeneseleninic acid and heated at 70° C for 1.5 h. The reaction mixture was directly adsorbed onto SiO_2 and chromatographed (EtOAc/hexanes, 3:2) to yield 33 mg (82%) of **14** as a viscous oil: R_f 0.55 (EtOAc); $[\alpha]_D$ 116° (*c* 0.57, $CHCl_3$, 25 °C); IR (neat) 1657, 1651, 1634, 1605, 1574, 1538, 1449, 1360, 1283, 1196, 1109, 1005, 974, 760, 698 cm^{-1}; ^1H NMR δ 7.51−7.37 (m, 5 H), 7.45 (d, 1 H, J = 16.5 Hz), 6.94, (bs, 1 H), 6.65 (d, 1 H, J = 16.2 Hz), 4.90 (d, 1 H, J = 8.5 Hz), 4.27 (d, 1 H, J = 8.5 Hz), 2.94 (d, 3 H, J = 5 Hz), 2.65 (s, 3 H), 1.75 (s, 3 H); ^{13}C NMR δ 164.5, 162.5, 153.6, 141.5, 134.9, 129.9, 129.0, 128.7, 127.7, 114.5, 76.4, 69.6, 26.0, 25.6, 11.8; MS (EI) *m*/*z* (relative intensity) 325 (M$^+$, 55), 310 (55), 295 (20), 277 (100), 236 (5), 203 (55), 186 (50), 163 (40), 149 (25), 131 (40), 112 (80), 103 (40), 97 (20), 91 (50), 83 (25), 77 (50); HRMS *m*/*z* calcd for $C_{18}H_{19}N_3O_3$ 325.1426; found 325.1446.

5-Methyl-2-[(4*R*)-4-methyl-2-phenethyl-4,5-dihydrothiazol-4-yl]oxazole-4-carboxylic Acid Methylamide (16). A solution of 80 mg (0.24 mmol) of **13** in 2.00 mL of MeOH/Et_3N (2:1) was saturated with H_2S gas and stirred at 21 °C for 3 days. Excess H_2S, MeOH, and Et_3N were removed by evaporation in vacuo through a solution of bleach, and the residue was chromatographed on SiO_2 (EtOAc/hexanes, 4:1) to yield 73 mg of 2-[(1*S*)-2-hydroxy-1-methyl-1-[[3-(phenylthio)propionyl]amino]ethyl]-5-methyloxazole-4-carboxylic acid methylamide (**15**) that was directly used for the next step: R_f 0.4 (EtOAc).

A solution of 83 mg (0.22 mmol) of thioamide **15** in 2.0 mL of THF was treated with 170 mg (0.67 mmol) of Burgess reagent and stirred at room temperature for 3.5 h. The reaction mixture was quenched with 0.5 mL of MeOH, concentrated in vacuo, and chromatographed on SiO_2 (EtOAc/hexanes, 3:2) to yield 55 mg (64%) of **16** as a viscous oil: R_f 0.5 (EtOAc); $[\alpha]_D$ 40.2° (*c* 0.73, $CHCl_3$, 25 °C); IR (neat) 1653, 1619, 1561, 1549, 1518, 1489, 1441, 1401, 1368, 1327, 1186, 1142, 1102, 994, 741 cm^{-1}; ^1H NMR δ 7.37−7.20 (m, 5 H), 6.94 (bs, 1 H), 3.95 (d, 1 H, J = 11.2 Hz), 3.26 (d, 1 H, J = 11.2 Hz), 3.02−2.94 (m, 2 H), 2.94 (s, 3 H), 2.89−2.83 (m, 2 H), 2.65 (s, 3 H), 1.64 (s, 3 H); ^{13}C NMR δ 171.3, 162.5, 162.4, 153.4, 140.1, 129.1, 128.5, 128.4, 126.4, 79.5, 42.7, 36.0, 33.7, 25.6, 24.7, 11.8; MS (EI) *m*/*z* (relative intensity) 343 (M$^+$, 100), 328 (10), 310 (15), 297 (7), 212 (43), 179 (70), 162 (10), 153 (25), 137 (10), 123 (10), 112 (8), 105 (10), 98 (20), 91(75), 69 (25), 57 (75); HRMS *m*/*z* calcd for $C_{18}H_{21}N_3O_2S$ 343.1354; found 343.1322.

5-Methyl-2-[(4*R*)-4-methyl-2-styryl-4,5-dihydrothiazol-4-yl]-oxazole-4-carboxylic Acid Methylamide (17). A solution of 36 mg (0.11 mmol) of **16** in 1 mL of benzene was heated at 60 °C for 0.5 h with 25 mg (0.13 mmol) of benzeneseleninic acid. The reaction mixture was chromatographed on SiO_2 (EtOAc/hexanes, 1:1) to yield 27 mg (74%) of **17** as an oil: R_f 0.8 (EtOAc); $[\alpha]_D$ 52° (*c* 0.57, $CHCl_3$, 25 °C); IR (neat) 2326, 2301, 1651, 1634, 1619, 1558, 1540, 1522, 1507, 1491, 1440, 1184, 1091, 955, 748 cm^{-1}; ^1H NMR δ 7.51−7.48 (m, 2 H), 7.42−7.36 (m, 3 H), 7.17, 7.07 (AB, 2 H, J = 16.2 Hz), 6.97 (bs, 1 H), 4.00 (d, 1 H, J = 11.1 Hz), 3.38 (d, 1 H, J = 11.1 Hz), 2.94 (d, 3 H, J = 5.0 Hz), 2.67 (s, 3 H), 1.76 (s, 3 H); ^{13}C NMR δ 167.7, 162.5, 162.4, 153.5, 142.2, 135.0, 129.9, 129.2, 129.0, 127.6, 122.3, 79.3, 41.7, 25.6, 24.7, 11.8; MS (EI) *m*/*z* (relative intensity) 341 (M$^+$, 80), 326 (25), 308 (25), 295 (25), 237 (5), 212 (100), 202 (15), 179 (85), 168 (10), 155 (30), 130 (15), 130 (15), 115 (10), 98 (15), 85 (20), 73 (30), 66 (20), 58 (15); HRMS *m*/*z* calcd for $C_{18}H_{19}N_3O_2S$ 341.1197; found 341.1263.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **1**, **2**, and **4**-**17** (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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