Total Synthesis of Cystothiazoles A and C

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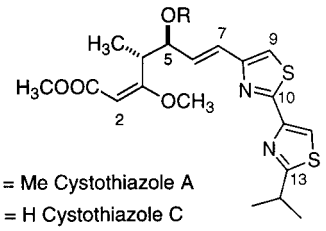
An efficient pathway culminating in the enantiocontrolled preparation of cystothiazoles A and C has been described. The cystothiazoles demonstrate potent antifungal activity and function as novel inhibitors of mitochondrial oxidation at a specific site on the cytochrome bc_1 complex. These studies outline a general and flexible plan that can be readily adapted for the synthesis of a variety of related five-membered heterocyclic systems and for biological investigations of structure−activity relationships. The core [2,4′]bisthiazole component **8** was prepared in six steps, and the use of the Horner−Emmons olefination to yield the α,β-unsaturated ester **10** set the stage for an asymmetric Evans aldol process, which established the required C_4/C_5 stereochemistry. Finally the cystothiazoles A and C were prepared via a stereocontrolled O-alkylation of the precursor β-keto esters **22a** and **22b**.

Introduction

In 1998, Sakagami and co-workers reported the isolation of six secondary metabolites, designated cystothiazoles A−F, as a series of new antibiotics from the myxobacterium culture broth of *Cystobacter fuscus*.[1,2] This family of bis-thiazoles has demonstrated potent antifungal activity against the phytopathogenic fungus *Phytophthora capsici* (0.05−5 μg/disk) and has shown activity against a broad range of additional fungi with no effect on bacterial growth. Structural elucidations were carried out by a series of proton and carbon NMR, HMBC, and HETCOR experiments, coupled with analyses of FABMS data.[1,2] The cystothiazoles are structurally related to the myxothiazoles[3a,b] and melithiazoles,[3c] all of which can be included under the more expansive category of β-methoxyacrylic acid natural products, such as the strobilurins[3d] and oudemansins[3d] isolated from myxobacteria. Studies of in vitro cytotoxicity using human colon carcinoma HCT-116 and human leukemia K562 showed greater IC_{50} values for cystothiazole A compared to those of myxothiazole A. On the other hand, cystothiazole A generally exhibited greater antifungal potency than myxothiazole A. Structural comparisons are particularly significant in view of a unified proposal for a novel mode of action via the inhibition of NADH oxidase by binding at a specific sub-mitochondrial membrane site on the cytochrome bc_1 complex.[3d] While related substances have been developed as commercial fungicides,[4] cytotoxicity is not associated with the β-methoxyacrylate moiety.[3c,5a,b]



1 R = Me Cystothiazole A
2 R = H Cystothiazole C

Pattenden and co-workers reported a synthesis of myxothiazole A,[6] and several approaches toward the preparation of these antibiotics have been described.[3d,7] Transformations providing melithiazoles B[8a] and C,[9] as well as myxothiazole Z,[8b] have been demonstrated via semisynthesis pathways from degradation intermediates. Very recently, Kobayashi and co-workers have published an asymmetric total synthesis of methoxystrobilurin K.[10a,b] Herein, we report a general route for the enantiocontrolled syntheses of cystothiazoles A (**1**) and C (**2**) that is broadly applicable for the formation of analogues and derivatives for biological investigations.

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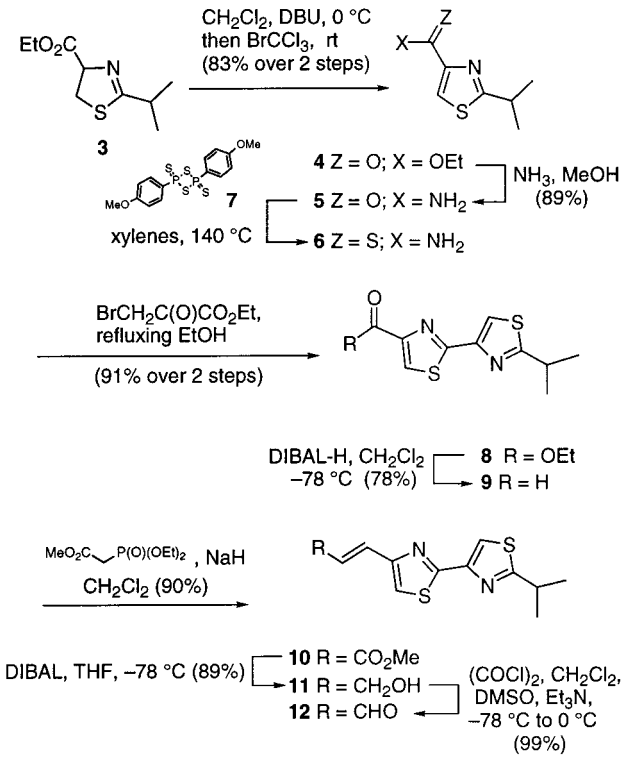
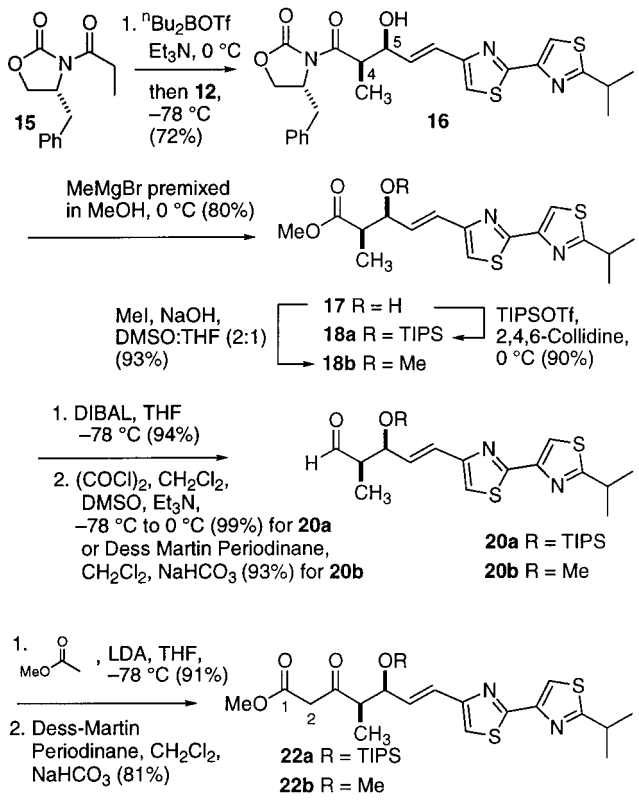
Scheme 1



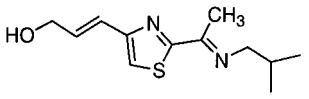
Scheme 2



Results and Discussion

Our enantiocontrolled synthesis describes a flexible plan that prepares a bis-thiazole core for the application of the asymmetric Evans aldol methodology for the development of the C_4/C_5 vicinal stereochemistry. The starting thiazoline ethyl ester **3** was readily prepared via the condensation of cysteine ethyl ester hydrochloride with the substituted imidate formed upon treatment of a solution of isobutyronitrile and ethanol in chloroform with hydrogen chloride.[11] As illustrated in Scheme 1, oxidation of crude thiazoline **3** with DBU and bromotrichloromethane gave the thiazole **4** in 83% overall yield for the two steps.[12] Subsequent ammonolysis of ester **4** led to the thioamide **6** via a high-yielding conversion from the primary amide **5** with the Lawesson's reagent **7**.[13] Direct condensation with ethyl bromopyruvate, following the general protocol as described by Ciufolini and Shen,[14] provided the desired bis-thiazole ethyl ester **8** in 91% yield from the amide **5**. Finally, a series of standard hydride reductions and a carbon chain elongation via the Horner–Emmons olefination with trimethyl phosphonoacetate led to the heterocyclic core component **12**.

Lewis acid complexation is particularly effective in [2,4′]bisthiazoles, [2,4′]bisoxazoles, and related systems. These properties have been discussed in light of site-directed ring metalation in [2,4′]bisoxazoles.[15] Our observations regarding the DIBAL reductions in **8** and **10** are consistent with these views, as solvent effects played an important role in these transformations. In the efficient direct conversion to aldehyde **9**, the use of methylene chloride facilitated internal coordination of a stabilized tetrahedral intermediate upon hydride delivery to ester **8**. However, our deployment of DIBAL in CH_2Cl_2 for the reduction of **10** led to substantial amounts of methyl ketone **14** derived from hydrolysis of **13**. Höfle and co-workers have recently reported similar findings and have proposed a mechanism to account for the reductive cleavage via nitrogen complexation for activation and internal hydride delivery.[9] This ring-cleavage reaction was minimized by the use of THF as a Lewis basic solvent to moderate DIBAL reactivity and competitively diminish thiazole coordination.



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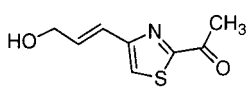

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Enantiocontrol was achieved with selective formation of the vicinal 4*R*,5*S* stereochemistry in **16** via utilization of the Evans aldol methodology[16] for condensation of the (*Z*)-O-boron enolate derived from the substituted oxazolidinone **15** (Scheme 2) with the α,β-unsaturated aldehyde **12**. This asymmetric aldol reaction provided pure adduct **16** in 72% yield with complete diastereoselectivity following flash silica gel chromatography. Assumption of the 4*R*,5*S* syn stereochemistry in **16** was based on the substantial literature precedence for the Evans aldol process, which was ultimately confirmed upon conversion to the natural products.

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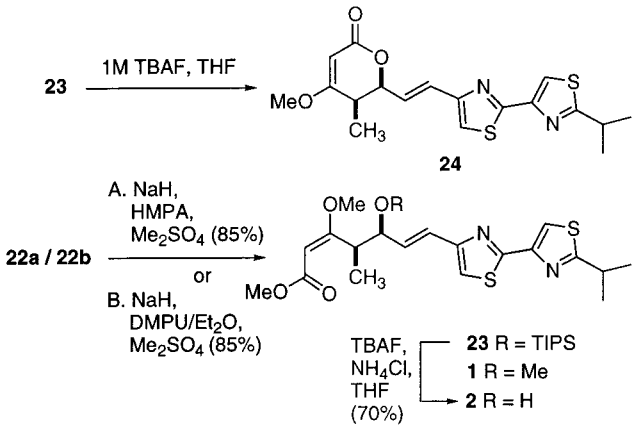
Removal of the chiral auxiliary by methanolysis[17] led to the desired esters **18a** and **18b**, respectively, following the silyl ether protection or methylation of **17**. While O-alkylation with methyl iodide proceeded smoothly under basic conditions, methylation of the C_5 alcohol in **16** or **17** failed with more reactive species such as trimethyloxonium tetrafluoroborate. The remaining two-carbon segment (C_1-C_2) of cystothiazoles A and C was most conveniently incorporated by initial reduction of the individual esters **18a** and **18b** to their respective alcohols **19a**,**b** (not shown). Transformation to the corresponding aldehyde **20a** was accomplished in nearly quantitative yield using the Swern oxidation.[18] However, this procedure facilitated the elimination of methanol in the case of **18b**, affording the fully conjugated aldehyde as the major product. This problem was completely avoided by application of the Dess−Martin periodinane oxidation,[19] providing **20b** in 93% yield. Each of these aldehydes **20a** and **20b** underwent successful low-temperature condensation with the enolate derived from methyl acetate.[20] The resulting mixture of diastereomeric alcohols **21a** and **21b** were immediately submitted for oxidation to the β-keto esters **22a** and **22b** with the Dess−Martin periodinane.[19]

Crucial generation of the (*E*)-β-methoxyacrylate functionality demanded a stereocontrolled O-alkylation of ketone **22**. Solvent effects are known to play an important role in accelerating the overall rate of such reactions and in facilitating O- versus C-alkylation. Aspects of stereocontrol in the O-alkylations of these enolate systems are also solvent dependent, since factors that negate internal metal cation coordination or lead to dipole minimization are paramount. As expected, cystothiazole A was conveniently prepared from **22b**, as shown below, via deprotonation in hexamethylphosphoric triamide (HMPA) as solvent and methylation using freshly distilled dimethyl sulfate.[21] The examination of the crude product by high field proton NMR indicated at least a 16.5:1 ratio of *E*/*Z* isomers, and pure cystothiazole A (**1**) was obtained after careful separation via silica gel chromatography [[α]$^{20}_D$ +104 (*c* 0.07, $CHCl_3$) (lit.[1] [α]$^{23}_D$ +109 (*c* 0.24, $CHCl_3$))].



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The nature of the C_5 hydroxyl group of cystothiazole C (**2**) posed additional problems. The corresponding O-alkylation of **22a** was less effective in HMPA. However, a slow methylation proceeded in a solvent mixture of *N*,*N*′-dimethylpropyleneurea (DMPU) and diethyl ether (1:1 by volume), giving an 85% yield of *E*/*Z*-methyl ethers (8:1 ratio, respectively). The desired (*E*)-β-methoxy **23** was separated by flash silica gel chromatography for subsequent fluoride-induced silyl ether cleavage. Unfortunately, the use of commercial reagent tetra-*n*-butylammonium fluoride (1 M TBAF in THF) led to the formation of the six-membered lactone **24** as the principal product. Lactone **24** has been previously described in the efforts toward isolation of the cystothiazoles.[2] After the examination of several alternatives, optimum conditions for desilylation were achieved with TBAF (1 M in THF) buffered by the addition of solid ammonium chloride to give **2** [[α]$^{30}_D$ +143 (*c* 1.03, $CHCl_3$) (lit.[2] [α]$^{23}_D$ +145 (*c* 0.2, $CHCl_3$))] in 70% isolated yield as a stable white powder. Individual comparisons of synthetic **1** and **2** with the detailed spectral data reported for the cystothiazoles A and C, respectively, proved identical in all respects.[1,2]

In summary, our results have described a simple sequence for the enantiocontrolled preparation of cystothiazoles A and C, which is readily adaptable for the synthesis of related analogues and derivatives.

Experimental Section

General Methods. Infrared (FT-IR) spectra were recorded on a Galaxy 4020 FT-IR or Nicolet Avator 360 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian VXR-400 (400 MHz) spectrometer with $CDCl_3$ as the solvent. Chemical shifts are reported in ppm on the δ scale using the residual chloroform ($CHCl_3$) as a reference: δ 7.26 ppm for ^{1}H NMR; 77.0 ppm for ^{13}C NMR. Mass spectral data (MS and HRMS) were recorded on a Kratos MS 80 RFAQQ mass spectrometer by use of chemical ionization (CI). Optical rotations were obtained on a PerkinElmer 241 polarimeter at 589 nm (sodium D line). Analytical thin-layer chromatography (TLC) was performed on precoated (0.25 mm thick) glass-backed silica gel (60F-254) plates from E. Merck. Spots were visualized under UV light and/or staining with ethanolic *p*-anisaldehyde or ceric ammonium molybdate. Flash chromatography was performed using silica gel 30−63 micron (230−400 mesh) from Scientific Absorbents. Elemental analysis data were obtained from Atlantis Microlab, Inc., Norcross, GA. All reagents and solvents were used as received unless noted otherwise. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled under nitrogen from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2), toluene, and triethylamine were distilled from calcium hydride prior to use under dry air. Dimethyl sulfoxide, *N*,*N*-dimethyformamide (DMF), hexamethylphosphoramide (HMPA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and *N*,*N*′-dimethylpropyleneurea (DMPU) were distilled from calcium hydride and stored over 4 Å molecular sieves. All reactions were conducted in flame- or oven-dried glassware under an atmosphere of argon unless otherwise noted.

2-Isopropylthiazole-4-carboxylic Acid Ethyl Ester (4). To a solution of the hydrochloride salt of isobutyrimidic acid ethyl ester (8.30 g, 54.9 mmol) and cysteine ethyl ester hydrochloride (10.3 g, 54.9 mmol) in CH_2Cl_2 (100 mL) was added triethylamine (7.70 mL, 54.9 mmol) dropwise. The white suspension was stirred at room temperature for 16 h. The mixture was diluted with ether (300 mL) and filtered. The filtrate was concentrated in vacuo and dried under high vacuum (<2 mm Hg) to afford 9.90 g (90%) of the known thiazoline **3**.[9] The crude residue was used without purification in the next step following partial characterization: $R_f = 0.22$ in 20% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (dd,

J = 9.6, 8.6 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 3.52 (dd, J = 8.6, 11.2 Hz, 1H), 3.46 (dd, J = 9.6, 11.2 Hz, 1H), 2.89 (qq, J = 6.8, 7.2 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.24 (d, J = 7.2 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H).

To a solution of thiazoline **3** (8.3 g, 55 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (16.5 mL, 110 mmol). After the mixture was stirred at 0 °C for 10 min, bromotrichloromethane (5.4 mL, 55 mmol) was added to the mixture. The reaction was warmed to room temperature and stirred for 16 h. The mixture was diluted with CH_2Cl_2 (200 mL) and washed with aqueous saturated $NaHCO_3$ (2 × 150 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (20% EtOAc/hexanes) to afford 9.1 g (83% over two steps) of thiazole **4** as a colorless oil: R_f = 0.28 in 20% EtOAc/hexanes; IR (neat) 3117, 2972, 1730, 1208 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.33 (sept, J = 6.8 Hz, 1H), 1.32 (d, J = 6.8 Hz, 6H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 161.4, 146.5, 126.2, 61.1, 33.4, 23.1, 14.3; HRMS *m/e* calcd for $C_9H_{13}NO_2S$ (M^+) 199.0667, found 199.0665.

2-Isopropylthiazole-4-carboxylic Acid Amide (5). Ammonia gas was bubbled through a solution of thiazole **4** (7.80 g, 39.2 mmol) in MeOH (150 mL) for 15 min. The reaction mixture was sealed and stirred at room temperature for 15 h. The mixture was concentrated in vacuo, and the crude residue was purified by flash silica gel chromatography (50% EtOAc/hexanes) to afford 5.80 g (87%) of amide **5** as a white solid: R_f = 0.22 in 50% EtOAc/hexanes; IR (neat) 3355, 3229, 3094, 1684, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.20 (br s, 1H), 6.02 (br s, 1H), 3.29 (sept, J = 7.2 Hz, 1H), 1.41 (d, J = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0, 163.2, 148.8, 123.1, 33.2, 22.9; HRMS *m/e* calcd for $C_7H_{10}N_2OS$ (M^+) 170.0514, found 170.0508.

2′-Isopropyl[2,4′]bithiazolyl-4-carboxylic Acid Ethyl Ester (8). To a suspension of thiazole **5** (2.70 g, 15.7 mmol) in xylenes (30 mL) was added Lawesson's reagent (3.2 g, 7.9 mmol). The solution was refluxed for 2 h and then was cooled to room temperature and concentrated in vacuo. The residue was diluted with ethanol (35 mL), and freshly distilled ethylbromopyruvate (2.00 mL, 15.8 mmol) was added. The mixture was heated to reflux for 45 min, and solid K_2CO_3 was added portionwise carefully until gas evolution ceased. After being cooled to room temperature, the mixture was filtered and concentrated in vacuo. The residue was diluted with CH_2Cl_2 (150 mL) and washed with aqueous saturated Na_2CO_3 (2 × 75 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (20% EtOAc/hexanes) to afford 4.03 g (91% over two steps) of bis-thiazole **8**: R_f = 0.74 in 50% EtOAc/hexanes; IR (neat) 3117, 2970, 1728, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.02 (s, 1H), 4.44 (q, J = 7.2 Hz, 2H), 3.36 (sept, J = 7.2 Hz, 1H), 1.44 (d, J = 7.2 Hz, 6H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 163.6, 161.3, 147.8, 147.7, 127.4, 116.0, 61.3, 33.2, 22.9, 14.3; HRMS *m/e* calcd for $C_{12}H_{14}N_2O_2S_2$ (M^+) 282.0497, found 282.0511. Anal. Calcd for $C_{12}H_{14}N_2O_2S_2$: C, 51.04; H, 5.00; N, 9.92; S, 22.71. Found: C, 51.01; H, 4.92; N, 9.84; S, 22.85.

2′-Isopropyl[2,4′]bithiazolyl-4-carbaldehyde (9). To a solution of ester **8** (4.60 g, 16.3 mmol) in CH_2Cl_2 (80 mL) at −78 °C was added diisobutylaluminum hydride (41 mL of a 1.0 M solution in hexanes, 41 mmol). The mixture was stirred for 40 min at −78 °C and then was quenched with the dropwise addition of acetone (10 mL) and warmed to room temperature. After dilution with CH_2Cl_2 (200 mL) and aqueous 20% sodium potassium tartrate (400 mL), the biphasic solution was stirred vigorously for 16 h. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (25% EtOAc/hexanes) to afford 3.30 g (78%) of aldehyde **9** as a white solid: R_f = 0.77 in 50% EtOAc/hexanes; IR (neat) 3096, 2969, 2826, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.18 (s, 1H), 7.98 (s, 1H), 3.38 (sept, J = 6.8 Hz, 1H), 1.46 (d, J = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.6, 178.9, 164.3, 155.5, 147.6, 127.9, 116.2, 33.2, 22.9; HRMS *m/e* calcd for $C_{10}H_{10}N_2OS_2$ (M^+) 238.0235, found 238.0239. Anal. Calcd for $C_{10}H_{10}N_2OS_2$: C, 50.39; H, 4.23; N, 11.75; S, 26.91. Found: C, 50.54; H, 4.28; N, 11.63; S, 26.99.

(*E*)-3-(2′-Isopropyl[2,4′]bithiazolyl-4-yl)acrylic Acid Methyl Ester (10). To a room-temperature solution of trimethyl phosphonoacetate (813 μL, 5.02 mmol) in THF (25 mL) was added NaH (60% dispersion in mineral oil, 201 mg, 5.02 mmol). The mixture was stirred until gas evolution ceased, and then a solution of aldehyde **9** (997 mg, 4.18 mmol) in THF (5.2 mL) was added via cannula. The resultant mixture was stirred for 30 min, diluted with CH_2Cl_2 (25 mL), and washed with brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash silica gel chromatography (15% EtOAc/hexanes) to afford 1.11 g (90%) of **10** as a white solid: R_f = 0.91 in 25% EtOAc/hexanes; IR (neat) 3127, 3086, 1715, 1648, 1273, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.63 (d, J = 15.6 Hz, 1H), 7.43 (s, 1H), 6.93 (d, J = 15.6 Hz, 1H), 3.82 (s, 3H). 3.38 (sept, J = 6.8 Hz, 1H), 1.45 (d, J = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 167.7, 163.7, 152.4, 148.3, 136.6, 122.1, 120.3, 115.7, 51.8, 33.4, 23.2; HRMS *m/e* calcd for $C_{13}H_{14}N_2O_2S_2$ (M^+) 294.0497, found 294.0499. Anal. Calcd for $C_{13}H_{14}N_2O_2S_2$: C, 53.04; H, 4.79; N, 9.52; S, 21.78. Found: C, 53.05; H, 4.76; N, 9.48; S, 21.87.

(*E*)-3-(2′-Isopropyl[2,4′]bithiazolyl-4-yl)-2-propen-1-ol (11). To a solution of α,β-unsaturated ester **10** (1.09 g, 3.70 mmol) in THF (19 mL) at −78 °C was added diisobutylaluminum hydride (11.1 mL of a 1.0 M solution in hexanes, 11.1 mmol) dropwise. The mixture was stirred at −78 °C for 1 h and then was quenched with the dropwise addition of acetone (2 mL) and warmed to room temperature. After dilution with CH_2Cl_2 (100 mL) and aqueous 20% sodium potassium tartrate (110 mL), the biphasic solution was stirred vigorously for 16 h. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (20% EtOAc/CH_2Cl_2) to afford 880 mg (89%) of alcohol **11** as a white solid: R_f = 0.16 in 25% EtOAc/hexanes; IR (neat) 3261, 3113, 2992, 2920, 2859 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.04 (s, 1H), 6.74 (dt, J = 5.2, 15.6 Hz, 1H), 6.62 (d, J = 15.6 Hz, 1H), 4.32 (d, J = 5.2 Hz, 2H), 3.35 (sept, J = 6.8 Hz, 1H), 2.85 (br s, 1H), 1.42 (d, J = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 162.9, 154.2, 148.5, 132.0, 123.3, 115.3, 114.9, 62.9, 33.3, 23.0; HRMS *m/e* calcd for $C_{12}H_{14}N_2OS_2$ (M^+) 266.0548, found 266.0536. Anal. Calcd for $C_{12}H_{14}N_2OS_2$: C, 54.11; H, 5.30; N, 10.52; S, 24.07. Found: C, 54.22; H, 5.21; N, 10.44; S, 24.03.

(*E*)-3-(2′-Isopropyl[2,4′]bithiazolyl-4-yl)propen-1-al (12). To a solution of oxalyl chloride (576 μL, 6.60 mmol) in CH_2Cl_2 (66 mL) at −78 °C was added dimethyl sulfoxide (1.21 mL, 13.2 mmol). After the mixture was stirred for 10 min at −78 °C, a solution of alcohol **11** (879 mg, 3.30 mmol) in CH_2Cl_2 (5.2 mL) was added via cannula. The mixture was stirred for 10 min, and then triethylamine (2.12 mL, 19.8 mmol) was added. After being stirred for 15 min, the mixture was warmed to 0 °C and stirred at 0 °C for 1 h. Sodium bicarbonate (50 mL, aqueous saturated) was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (15% EtOAc/hexanes) to afford 869 mg (99%) of aldehyde **12** as a yellow solid: R_f = 0.47 (25% EtOAc/hexanes); IR (neat) 3114, 3099, 2965, 2927, 2808, 2721, 1674, 1625, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.58 (s, 1H), 7.45 (d, J = 15.3 Hz, 1H), 7.04 (dd, J = 8.0, 15.3 Hz, 1H), 3.38 (sept, J = 6.9 Hz, 1H), 1.45 (d, J = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 178.9, 163.9, 152.2, 148.0, 143.5, 130.5, 123.4, 115.9, 33.3, 23.0; HRMS *m/e* calcd for $C_{12}H_{12}N_2OS_2$ (M^+) 264.0391, found 264.0396. Anal. Calcd for $C_{12}H_{12}N_2OS_2$: C, 54.52; H, 4.58; N, 10.60; S, 24.26. Found: C, 54.64; H, 4.71; N, 10.21; S, 23.66.

(*R*)-4-Benzyl-3-[(2*R*,3*S*)-(*E*)-3-hydroxy-5-(2′-isopropyl-[2,4′]bithiazolyl-4-yl)-2-methylpent-4-enoyl]oxazolidin-2-one (16). To a solution of (*R*)-4-phenyl-2-oxazolidinone **15** (343 mg, 1.47 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added freshly distilled dibutylboron triflate (513 μL, 1.71 mmol). After the solution was stirred for 5 min at 0 °C, triethylamine (307 μL, 2.20 mmol) was added carefully to the mixture, maintaining the internal temperature below 3 °C. After being stirred for 5 min at 0 °C, the solution was cooled to −78 °C, and aldehyde **12** (323 mg, 1.22 mmol) in CH_2Cl_2 (1.2 mL) was added via cannula. The mixture was stirred at −78 °C for 30 min, slowly warmed to 0 °C, and stirred for an additional 2 h. The reaction was then quenched by addition of 2:1 MeOH/aqueous pH 7 phosphate buffer (6 mL), followed by careful addition of 2:1 MeOH/30% aqueous H_2O_2 (6 mL). The mixture was stirred at 0 °C for 1 h, and the volatiles were removed in vacuo. The resultant slurry was diluted with EtOAc (10 mL) and washed with aqueous saturated $NaHCO_3$ (15 mL) solution. The aqueous layer was re-extracted with EtOAc (2 × 15 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (15% EtOAc/CH_2Cl_2) to afford 526 mg (72%) of aldol product **16** as a light yellow foam: $R_f = 0.42$ in 50% EtOAc/hexanes; $[\alpha]^{28}_D$ −33.3 (*c* 0.35, $CHCl_3$); IR (neat) 3450, 3105, 2967, 2925, 1778, 1697, 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.35−7.20 (m, 5H), 7.10 (s, 1H), 6.73 (dd, *J* = 1.2, 15.6 Hz, 1H), 6.64 (dd, *J* = 5.2, 15.6 Hz, 1H), 4.72 (m, 2H), 4.25−4.17 (m, 2H), 4.02 (dq, *J* = 4.0, 7.2 Hz), 3.34 (sept, *J* = 6.8 Hz, 1H), 3.26 (dd, *J* = 3.0, 13.6 Hz), 3.11 (br s, 1H), 2.81 (dd, *J* = 9.6, 13.6 Hz), 1.44 (d, *J* = 6.8 Hz, 6H), 1.33 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 176.6, 162.8, 154.2, 153.1, 148.7, 135.1, 131.8, 129.4, 129.0, 127.2, 115.8, 115.0, 72.1, 66.2, 55.2, 42.9, 37.8, 33.3, 23.1, 11.3; HRMS *m/e* calcd for $C_{25}H_{27}N_3O_4S_2$ (M^+) 497.1443, found 497.1419.

(*E*)-(2*R*,3*S*)-3-Hydroxy-5-(2′-isopropyl[2,4′]bithiazolyl-4-yl)-2-methyl-4-pentenoic Acid Methyl Ester (17). Methylmagnesium bromide (1.38 mL of a 3.0 M solution in Et_2O, 4.14 mmol) was added to methanol (7 mL) at 0 °C. After the suspension was stirred for 5 min at 0 °C, oxazolidinone **16** (515 mg, 1.04 mmol) in methanol (2.2 mL) was added. The reaction was stirred at 0 °C for 3 h before quenching with aqueous saturated NH_4Cl (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (25% EtOAc/hexanes) to afford 292 mg (80%) of methyl ester **17** as a light yellow viscous oil: $R_f = 0.50$ in 50% EtOAc/hexanes; $[\alpha]^{28}_D$ +13.2 (*c* 0.5, $CHCl_3$); IR (neat) 3445, 3113, 2969, 1732, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.09 (s, 1H), 6.72 (dd, *J* = 1.2, 15.6 Hz, 1H), 6.61 (dd, *J* = 5.0, 15.6 Hz, 1H), 4.69 (m, 1H), 3.74 (s, 3H), 3.38 (sept, *J* = 6.8 Hz, 1H), 2.81 (br s, 1H), 2.77 (dq, *J* = 4.0, 7.2 Hz), 1.44 (d, *J* = 6.8 Hz, 6H), 1.25 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 175.8, 162.8, 154.1, 148.6, 131.7, 124.2, 115.8, 115.0, 72.3, 51.9, 44.6, 33.3, 23.1, 11.1; HRMS *m/e* calcd for $C_{16}H_{20}N_2O_3S_2$ (M^+) 352.0915, found 352.0911.

(*E*)-(2*R*,3*S*)-5-(2′-Isopropyl[2,4′]bithiazolyl-4-yl)-3-methoxy-2-methyl-4-pentenoic Acid Methyl Ester (18b). To a solution of alcohol **17** (120 mg, 0.34 mmol) in DMSO/THF (2:1) (3.5 mL) with a trace amount of water (2 μL) was added methyl iodide (7 mL). The mixture was cooled to 0 °C, and sodium hydroxide (450 mg, powdered by mortar and pestle) was added in small portions. After being stirred at 0 °C for 30 min, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and pH 3 phosphate buffer (15 mL) was added. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 7 mL). The combined organic phases were washed with aqueous saturated NaCl (15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (15% EtOAc/hexanes) to afford 116 mg (93%) of **18b**: $R_f = 0.42$ in 25% EtOAc/hexanes; $[\alpha]^{25}_D$ +9.7 (*c* 2.25, $CHCl_3$); IR (neat) 3101, 2967, 2931, 2823, 1738, 1181, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.11 (s, 1H), 6.62 (d, *J* = 15.6 Hz, 1H), 6.49 (dd, *J* = 7.4, 15.6 Hz, 1H), 4.03 (dd, *J* = 6.4, 7.4 Hz, 1H), 3.67 (s, 3H), 3.36 (sept, *J* = 6.8 Hz, 1H), 3.33 (s, 3H), 2.71 (dq, *J* = 6.8, 6.8 Hz, 1H), 1.42 (d, *J* = 6.8 Hz, 6H), 1.24 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 174.5, 162.8, 153.8, 148.5, 130.1, 126.2, 115.9, 115.0, 82.8, 57.1, 51.7, 45.0, 33.3, 23.1, 12.1; HRMS *m/e* calcd for $C_{17}H_{22}N_2O_3S_2$ (M^+) 366.1072, found 366.1074.

(*E*)-(2*R*,3*S*)-5-(2′-Isopropyl[2,4′]bithiazolyl-4-yl)-2-methyl-3-triisopropylsilanyloxy-4-pentenoic Acid Methyl Ester (18a). To a solution of alcohol **17** (275 mg, 0.780 mmol) in CH_2Cl_2 (4 mL) was added 2,4,6-collidine (476 μL, 3.59 mmol). The mixture was cooled to 0 °C, and triisopropylsilyl trifluoromethanesulfonate (344 μL, 1.28 mmol) was added dropwise. After the mixture was stirred for 45 min, it was diluted with CH_2Cl_2 (5 mL) and quenched with aqueous saturated NH_4Cl (10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (2.5% EtOAc/hexanes) to afford 357 mg (90%) of **18a** as a colorless oil: $R_f = 0.67$ in 25% EtOAc/hexanes; $[\alpha]^{28}_D$ +40.7 (*c* 1.46, $CHCl_3$); IR (neat) 2944, 2866, 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.09 (s, 1H), 6.63 (dd, *J* = 6.8, 15.6 Hz, 1H), 6.56 (d, *J* = 15.6 Hz, 1H), 4.76 (dd, *J* = 4.8, 6.8 Hz, 1H), 3.66 (s, 3H), 3.38 (sept, *J* = 7.2 Hz, 1H), 2.70 (dq, *J* = 4.8, 6.8 Hz, 1H), 1.44 (d, *J* = 7.2 Hz, 6H), 1.24 (d, *J* = 6.8 Hz, 3H), 1.06−1.05 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 174.7, 162.7, 154.3, 148.8, 133.8, 124.0, 115.9, 115.4, 75.2, 51.5, 47.2, 33.4, 23.2, 18.1, 13.0, 12.6, 11.6; HRMS *m/e* calcd for $C_{25}H_{40}N_2O_3S_2Si$ (M^+) 508.2250, found 508.2225. Anal. Calcd for $C_{25}H_{40}N_2O_3S_2Si$: C, 59.01; H, 7.92; N, 5.51; S, 12.60. Found: C, 59.19; H, 8.01; N, 5.30; S, 12.23.

(*E*)-(2*S*,3*S*)-5-(2′-Isopropyl[2,4′]bithiazolyl-4-yl)-3-methoxy-2-methyl-4-penten-1-ol (19b). To a solution of ester **18b** (0.11 g, 0.30 mmol) in THF (3.0 mL) at −78 °C was added diisobutylaluminum hydride (1.0 mL of a 1.0 M in hexanes, 1.0 mmol) dropwise. The mixture was stirred at −78 °C for 1 h. The reaction was quenched with careful addition of acetone (2 mL) and warmed to room temperature. After dilution with CH_2Cl_2 (50 mL) and aqueous 20% sodium potassium tartrate (50 mL), the biphasic solution was stirred vigorously for 16 h. The phases were separated, and the aqueous phase was re-extracted with EtOAc (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (25% EtOAc/CH_2Cl_2) to afford 100 mg (98%) of alcohol **19b**: $R_f = 0.10$ in 25% EtOAc/hexanes; $[\alpha]^{25}_D$ +42.4 (*c* 1.25, $CHCl_3$); IR (neat) 3414, 3101, 2966, 2929, 1182, 1081, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.11 (s, 1H), 6.71 (d, *J* = 15.6 Hz, 1H), 6.54 (dd, *J* = 6.8, 15.6 Hz, 1H), 3.91 (dd, *J* = 4.0, 6.8 Hz, 1H), 3.73 (dd, *J* = 7.6, 10.6 Hz, 1H), 3.59 (dd, *J* = 4.4, 10.6 Hz, 1H), 3.36 (sept, *J* = 6.8 Hz, 1H), 3.34 (s, 3H), 2.77 (br s, 1H), 2.09 (m, 1H), 1.43 (d, *J* = 6.8 Hz, 6H), 0.94 (d, *J* = 6.8 Hz, 3H): ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 162.9, 153.9, 148.5, 129.8, 126.2, 115.7, 115.1, 85.5, 65.9, 57.0, 39.8, 33.3, 23.1, 12.2; HRMS *m/e* calcd for $C_{16}H_{22}N_2O_2S_2$ (M^+) 338.1123, found 338.1123.

(*E*)-(2*S*,3*S*)-5-(2′-Isopropyl[2,4′]bithiazolyl-4-yl)-2-methyl-3 triisopropylsilanyloxy-4-penten-1-ol (19a). To a solution of ester **18a** (333 mg, 0.654 mmol) in THF (3.5 mL) at −78 °C was added diisobutylaluminum hydride (1.96 mL of a 1.0 M in hexanes, 1.96 mmol) dropwise. The mixture was stirred at −78 °C for 1.5 h. The reaction was quenched with acetone (2 mL) and warmed to room temperature. After dilution with CH_2Cl_2 (100 mL) and aqueous 20% sodium potassium tartrate (100 mL), the biphasic solution was stirred vigorously for 16 h. The phases were separated, and the aqueous phase was re-extracted with CH_2Cl_2 (2 × 75 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (10% EtOAc/CH_2Cl_2) to afford 294 mg (94%) of alcohol **19a** as a viscous light yellow oil: $R_f = 0.46$ in 25% EtOAc/hexanes; IR (neat) 3414, 2961, 2942, 2864, 1086, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.09 (s, 1H), 6.71 (dd, *J* = 6.4, 15.6 Hz, 1H), 6.61 (d, *J* = 15.6 Hz, 1H), 4.57 (dd, *J* = 4.0, 6.4 Hz, 1H), 3.80 (m 1H), 3.54 (m, 1H), 3.38

(sept, J = 6.8 Hz, 1H), 3.20 (br s, 1H), 2.27 (m, 1H), 1.44 (d, J = 6.8 Hz, 6H); 1.12−1.08 (m, 21H), 0.88 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 162.7, 154.2, 148.7, 131.5, 124.4, 115.3, 114.9, 78.0, 65.7, 41.4, 33.3, 23.1, 18.0, 13.1, 12.2; HRMS *m/e* calcd for $C_{24}H_{40}N_2O_2S_2Si$ (M^+) 480.2300, found 480.2307.

(*E*)-(4*R*,5*S*)-7-(2′-Isopropyl[2,4′]bithiazolyl-4-yl)-5-methoxy-4-methyl-3-oxo-6-heptenoic Acid Methyl Ester (22b). To a solution of alcohol **19b** (92 mg, 0.27 mmol) in CH_2Cl_2 (2.7 mL) at room temperature were added solid $NaHCO_3$ (230 mg, 2.73 mmol) and the Dess−Martin periodinane[18] (140 mg, 0.330 mmol). After the mixture was stirred for 20 min at room temperature, the reaction was quenched by slow addition of aqueous saturated $Na_2S_2O_3$ (5 mL) and stirred for 15 min until gas evolution ceased. The mixture was then diluted with EtOAc (10 mL), the layers were separated, and the organic layer was washed with saturated aqueous NH_4Cl (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was immediately purified by flash silica gel chromatography (10% EtOAc/hexanes) to afford 85 mg (93%) of **20b**, which was immediately submitted to the next reaction after partial characterization: R_f = 0.39 in 25% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, J = 0.8 Hz, 1H), 7.86 (s, 1H), 7.13 (s, 1H), 6.66 (d, J = 15.6 Hz, 1H), 6.52 (dd, J = 15.6, 7.6 Hz, 1H), 4.19 (dd, J = 7.2, 4.8 Hz, 2H), 3.37 (sept, J = 6.8 Hz, 1H), 3.35 (s, 3H), 2.63 (m, 1H), 1.44 (d, J = 6.8 Hz, 6H), 1.18 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 178.7, 163.0, 153.6, 148.5, 129.3, 126.5, 116.2, 115.1, 81.5, 57.0, 51.1, 33.3, 23.1, 8.7.

To a solution of diisopropylamine (93 μL, 0.72 mmol) in THF (2.2 mL) at 0 °C was added *n*-butyllithium (420 μL of a 2.5 M solution in hexanes, 1.09 mmol). The solution was stirred for 10 min at 0 °C and then cooled to −78 °C, and methyl acetate (0.5 M in THF, 1.8 mL, 0.90 mmol) was added dropwise. The mixture was stirred for 15 min at −78 °C followed by the addition of aldehyde **20b** (91 mg, 0.27 mmol) in THF (1.2 mL) via cannula. After being stirred for 1 h at −78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL). The organic phase was separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (20% EtOAc/hexanes) to afford 70 mg (63%) of **21b** as a (∼1.5:1 ratio) mixture of diastereomers: R_f = 0.57, 0.61 in 50% EtOAc/hexanes; IR (neat) 3476, 3101, 2970, 2932, 1735, 1179, 1080 cm^{-1}; HRMS *m/e* calcd for $C_{19}H_{26}N_2O_4S_2$ (M^+) 410.1334, found 410.1333.

To a solution of alcohol **21b** (70 mg, 0.17 mmol) in CH_2Cl_2 (3 mL) at room temperature were added solid $NaHCO_3$ (143 mg, 87.0 mmol) and the Dess−Martin periodinane[18] (87 mg, 0.20 mmol). After the mixture was stirred for 15 min, the reaction was quenched by slow addition of aqueous saturated $Na_2S_2O_3$ (5 mL) and stirred until gas evolution ceased. The quenched reaction mixture was then diluted with EtOAc (10 mL), the layers were separated, and the organic layer was washed with saturated aqueous NH_4Cl (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (20% EtOAc/hexanes) to afford 68 mg (98%) of β-keto ester **22b**: R_f = 0.38 in 33% EtOAc/hexanes; $[\alpha]^{30}_D$ +3.8 (*c* 0.71, $CHCl_3$); IR (neat) 3105, 2970, 2934, 1748, 1714, 1313, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.12 (s, 1H), 6.60 (d, J = 15.6 Hz, 1H), 6.41 (d, J = 7.4, 15.6 Hz, 1H), 4.00 (dd, J = 6.4, 6.4 Hz, 1H), 3.70 (s, 3H), 3.64 (A of AB, J_{AB} = 16.0 Hz, 1H), 3.55 (B of AB, J_{AB} = 16.0 Hz, 1H), 3.37 (sept, J = 7.2 Hz, 1H), 3.33 (s, 3H), 2.98 (dq, J = 6.4, 6.4 Hz, 1H), 1.43 (d, J = 6.8 Hz, 6H), 1.18 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.8, 179.0, 168.1, 163.1, 153.9, 148.8, 129.5, 127.1, 116.4, 116.0, 115.3, 83.0, 57.2, 51.4, 49.4, 33.6, 23.4, 12.0; HRMS *m/e* calcd for $C_{19}H_{24}N_2O_4S_2$ (M^+) 408.1177, found 408.1173.

(*E*)-(4*R*,5*S*)-7-(2′-Isopropyl[2,4′]bithiazolyl-4-yl)-4-methyl-3-oxo-5-triisopropylsilanyloxy-6-heptenoic Acid Methyl Ester (22a). To a solution of oxalyl chloride (142 μL, 1.62 mmol) in CH_2Cl_2 (17 mL) at −78 °C was added dimethyl sulfoxide (297 μL, 3.24 mmol). After the mixture was stirred at −78 °C for 10 min, a solution of alcohol **19a** (260 mg, 0.540 mmol) in CH_2Cl_2 (1.2 mL) was added via cannula. The mixture was stirred for 10 min, triethylamine (522 μL, 4.87 mmol) was added, and the reaction mixture stirred for an additional 15 min. After the mixture was stirred for 1 h at 0 °C, aqueous saturated $NaHCO_3$ (20 mL) was added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (5% EtOAc/hexanes) to afford 258 mg (quantitative) of aldehyde **20a** as a yellow oil: R_f = 0.65 in 25% EtOAc/hexanes; $[\alpha]^{28}_D$ +28.4 (*c* 1.36, $CHCl_3$); IR (neat) 2942, 2861, 1726, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.85 (s, 1H), 7.08 (s, 1H), 6.64−6.63 (m, 2H), 4.82 (m, 1H), 3.37 (sept, J = 7.2 Hz, 1H), 2.68 (m, 1H), 1.44 (d, J = 7.2 Hz, 6H), 1.14 (d, J = 7.2 Hz, 3H), 1.09−1.07 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.7, 178.6, 162.8, 154.0, 148.7, 132.2, 124.4, 115.7, 114.9, 74.3, 53.2, 33.3, 23.1, 18.1, 12.5, 9.1; HRMS *m/e* calcd for $C_{21}H_{31}N_2O_2S_2Si$ (M^+) 435.1596, found 435.1569. Anal. Calcd for $C_{24}H_{38}N_2O_2S_2Si$: C, 60.21; H, 8.00; N, 5.85; S, 13.39. Found: C, 60.06; H, 7.82; N, 5.81; S, 13.11.

To a solution of diisopropylamine (181 μL, 1.29 mmol) in THF (4.3 mL) at 0 °C was added *n*-butyllithium (848 μL of a 2.5 M solution in hexanes, 2.12 mmol). The solution was stirred for 10 min at 0 °C and then cooled to −78 °C. Methyl acetate (0.5 M in THF, 3.50 mL, 1.75 mmol) was added dropwise at −78 °C. The mixture was stirred for 15 min followed by the addition of aldehyde **20a** (255 mg, 0.53 mmol) in THF (1.2 mL) via cannula. After the mixture was stirred for 1 h at −78 °C, the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The organic phase was separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (15% EtOAc/hexanes) to afford 267 mg (91%) of **21a** as a (∼1:1 ratio) mixture of diastereomers: R_f = 0.41, 0.44 in 25% EtOAc/hexanes; IR (neat) 3484, 2942, 2856, 1732, 1086 cm^{-1}; HRMS *m/e* calcd for $C_{27}H_{44}N_2O_4S_2Si$ (M^+) 552.2512, found 552.2516. Anal. Calcd for $C_{27}H_{44}N_2O_4S_2Si$: C, 58.66; H, 8.02; N, 5.07; S, 11.60. Found: C, 58.59; H, 7.85; N, 5.05; S, 11.32.

To a solution of alcohol **21a** (256 mg, 0.460 mmol) in CH_2Cl_2 (3 mL) were added $NaHCO_3$ (390 mg, 4.64 mmol) and the Dess−Martin periodinane[18] (236 mg, 0.560 mmol) at room temperature. After the mixture was stirred for 5 min, the reaction was quenched by slow addition of aqueous saturated $Na_2S_2O_3$ (5 mL) and stirred for 20 min until gas evolution ceased. After dilution with EtOAc (10 mL), the layers were separated, and the organic layer was washed with saturated aqueous NH_4Cl (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (10% EtOAc/hexanes) to afford 205 mg (81%) of β-keto ester **22a** as a light yellow oil: R_f = 0.64 in 25% EtOAc/hexanes; $[\alpha]^{30}_D$ +26.0 (*c* 1.15, $CHCl_3$); IR (neat) 3453, 2944, 2866, 1748, 1717, 1653, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.09 (s, 1H), 6.57 (d, J = 15.6 Hz, 1H), 6.49 (dd, J = 6.0, 15.6 Hz, 1H), 4.57 (dd, J = 5.2, 6.4 Hz, 1H), 3.71 − 3.67 (m, 5H), 3.37 (sept, J = 7.2 Hz, 1H), 3.08 (m, 1H), 1.44 (d, J = 7.2 Hz, 6H), 1.16 (d, J = 7.2 Hz, 3H), 1.10−1.05 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5, 178.5, 167.8, 162.6, 154.0, 148.8, 131.9, 124.7, 115.6, 114.9, 75.8, 53.4, 52.0, 50.0, 33.3, 23.1, 18.1, 12.6, 12.5; HRMS *m/e* calcd for $C_{24}H_{35}N_2O_4S_2Si$ ($M^+ - C_3H_7$) 507.1807, found 507.1787. Anal. Calcd for $C_{27}H_{42}N_2O_4S_2Si$: C, 58.87; H, 7.69; N, 5.09; S, 11.64. Found: C, 58.99; H, 7.57; N, 5.10; S, 11.37.

(*E*)-(*R*)-4-[(*S*)-(*E*)-3-(2′-Isopropyl[2,4′]bithiazolyl-4-yl)-1-triisopropylsilanyloxyallyl)-3-methoxy-2-pentenoic Acid Methyl Ester (23). To a suspension of NaH (60% dispersion in mineral oil, 4 mg, 0.1 mmol) in DMPU (0.5 mL) at 0 °C was added a solution of β-keto ester **22a** (49 mg, 89 μmol) in DMPU (0.6 mL) via cannula. The mixture was stirred until gas evolution ceased. Dimethyl sulfate (17 μL, 0.18 mmol) was added and the reaction stirred for 24 h at room temperature. After dilution with Et_2O (1 mL), the reaction was stirred with periodic addition of small amounts of NaH (0.5−1 mg) every

3 h until completion as observed by TLC (total reaction time ~50 h). The mixture was diluted with Et_2O (5 mL) and quenched by addition of dimethylamine (2 N in H_2O, 2 mL) and H_2O (2 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was estimated to be comprised of an 8:1 ratio of *E*/*Z* olefin isomers by ^{1}H NMR signal interpretation and was purified by flash silica gel chromatography (2.5% EtOAc/hexanes) to afford 37 mg (73%) of β-keto ester **23** as a colorless oil: $R_f = 0.71$ in 25% EtOAc/hexanes, $[\alpha]^{30}_D$ +108.2 (*c* 1.42, $CHCl_3$); IR (neat) 2942, 2866, 1709, 1622, 1144, 1103 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.06 (s, 1H), 6.54−6.40 (m, 2H), 4.93 (s, 1H), 4.50 (dd, J = 6.0, 6.8 Hz), 4.12 (dq, J = 7.2, 7.2 Hz, 1H), 3.65 (s, 3H), 3.58 (s, 3H), 3.37 (sept, J = 6.8 Hz, 1H), 1.43 (d, J = 6.8 Hz, 6H), 1.22 (d, J = 7.2 Hz, 3H), 1.05 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 177.5, 167.8, 162.3, 154.8, 148.8, 135.1, 123.2, 114.7, 114.3, 90.8, 76.4, 55.3, 50.7, 42.1, 33.3, 23.2, 18.2, 18.1, 13.8, 12.6; HRMS *m*/*e* calcd for $C_{28}H_{44}N_2O_4S_2Si$ (M^+) 564.2512, found 564.2500.

The minor *Z* isomer was partially characterized as follows: $R_f = 0.75$ in 25% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.07 (s, 1H), 6.56−6.50 (m, 2H), 5.07 (s, 1H), 4.47 (dd, J = 6.0, 6.0 Hz), 3.90 (s, 3H), 3.64 (s, 3H), 3.38 (sept, J = 6.8 Hz, 1H), 2.52 (dq, J = 6.8, 12.4 Hz, 1H), 1.44 (d, J = 6.8 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H), 1.07 (m, 21H).

Cystothiazole A (1). To a suspension of NaH (60% dispersion in mineral oil, 4 mg, 0.1 mmol) in HMPA (0.2 mL) at 0 °C was added a solution of β-keto ester **22b** (21 mg, 51 μmol) in HMPA (0.2 mL) via cannula. The mixture was stirred until gas evolution ceased. Dimethyl sulfate (10 μL, 0.11 mmol) was added and the reaction stirred for 8 h at room temperature. After dilution with Et_2O (2 mL), the mixture was washed by addition of dimethylamine (2 N in H_2O, 1 mL) and H_2O (2 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (10% EtOAc/hexanes) to afford a 16.5:1 ratio mixture of cystothiazole A **1** (17 mg) and its olefin isomer (distinguished by distinct ^{1}H NMR signals: δ 5.11 (s, 1H), 3.66 (s, 3H), 2.51 (dq, J = 6.8, 6.8 Hz)) as a white solid (73%). Further purification was achieved via preparative thin layer silica gel chromatography (multiple elusions using 5% EtOAc/hexanes) to afford pure cystothiazole A (>20:1 in favor of **1** by ^{1}H NMR): $R_f = 0.26$ in 20% EtOAc/hexanes, $[\alpha]^{22}_D$ +104.0 (*c* 0.07, $CHCl_3$); IR (neat) 3103, 2966, 2926, 1710, 1623, 1145, 1094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.09 (s, 1H), 6.57 (d, J = 15.6 Hz, 1H), 6.41 (dd, J = 7.6, 15.6 Hz, 1H), 4.96 (s, 1H), 4.17 (dq, J = 7.2, 7.2 Hz, 1H), 3.81 (dd, J = 7.2, 7.2 Hz), 3.66 (s, 3H), 3.60 (s, 3H), 3.37 (sept, J = 6.8 Hz, 1H), 3.33 (s, 3H), 1.44 (d, J = 6.8 Hz, 6H), 1.22 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 176.7, 167.7, 162.6, 154.4, 148.7, 131.6, 125.6, 115.0, 114.8, 91.0, 84.4, 57.0, 55.5, 50.8, 39.8, 33.3, 23.2, 14.1; HRMS *m*/*e* calcd for $C_{20}H_{26}N_2O_4S_2$ (M^+) 422.1334, found 422.1351.

Cystothiazole C (2). To a solution of **23** (42 mg, 74 μmol) in THF (1 mL) were added NH_4Cl (8.0 mg. 0.15 mmol) and tetrabutylammonium fluoride (149 μL of a 1 M solution in THF, 0.149 mmol). The mixture was stirred for 30 min, and additional amounts of tetrabutylammonium fluoride (1 M in THF, 149 μL, 149 μmol) were added with stirring for 45 min. After dilution with CH_2Cl_2 (5 mL), saturated aqueous NH_4Cl (5 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (25% EtOAc/hexanes) affording 21 mg (70%) of cystothiazole C **2** as a white powder: $R_f = 0.57$ (50% EtOAc/hexanes); $[\alpha]^{30}_D$ +142.7 (*c* 1.03, $CHCl_3$); IR (neat) 3449, 3075, 2966, 1708, 1618, 1146 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.06 (s, 1H), 6.68 (d, J = 15.6 Hz, 1H), 6.61 (dd, J = 4.8, 15.6 Hz), 5.09 (s, 1H), 4.52 (dd, J = 4.8, 4.8 Hz), 4.17 (dq, J = 4.8, 7.2 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 3.38 (sept, J = 7.2 Hz, 1H), 2.93 (br s, 1H), 1.44 (d, J = 7.2 Hz, 6H), 1.18 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 176.9, 168.6, 162.5, 154.6, 148.8, 132.7, 123.5, 115.1, 114.7, 91.5, 74.8, 55.7, 51.1, 40.4, 33.3, 23.1, 12.4; HRMS *m*/*e* calcd for $C_{19}H_{24}N_2O_4S_2$ (M^+) 408.1177, found 408.1178.

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