Concise Syntheses of Cystothiazoles A, C, D, and Melithiazol B

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A convergent synthesis of cystothiazoles C 1 and D 3 was achieved based on Julia coupling between the functionalized aldehyde 5b, corresponding to left half of the final molecule, and aryl sulfone 6 or 7, bearing a bithiazole moiety, corresponding to right half. Methylation of 1 and 3 gave cystothiazole A 2 and melithiazol B 4, respectively. The overall yield (5 steps from (2*R*,3*S*)-3-methylpent-4-yne-1,2-diol 10; 57%) of 5b *via* the present route was improved in comparison to that of the previously reported functionalized aldehyde 5a (7 steps from 10; 13%). By applying the modified Julia coupling method, selectivity (6*E*/6*Z*=20 : 1—26 : 1) toward the (6*E*)-form of the coupled products (15 or 19) against the corresponding (6*Z*)-form was improved in comparison to the Wittig method (6*E*/6*Z*=4 : 1—6.9 : 1).

Key words cystothiazole; melithiazol; antibiotic; total synthesis; asymmetric synthesis; Julia coupling

Several antifungal substances, cystothiazoles A (**2**), C (**1**), D (**3**),[1,2] and melithiazol B (**4**)[3] were isolated from different strains of the myxobacterium *Cystobacter fuscus* and *Archangium gephyra*, respectively. These antifungal substances possessing a bithiazole skeleton as well as a β-methoxyacrylate moiety, and **2** have shown potent antifungal activity against the phytopathogenic fungus *Phytophthora capsici* (2 μg/disk), and have also shown activity against a broad range of additional fungi with no effect on bacterial growth.[1] Furthermore, when **2** was examined for *in vitro* cytotoxicity using human colon carcinoma HCT-116 and human leukemia K562 cells, the resulting IC_{50} values were 110—130 ng/ml, which were significantly higher than those of myxothiazol A.[4—6] The fungicidal activity of these β-methoxyacrylate (MOA) inhibitors has been shown to be due to their ability to inhibit mitochondrial respiration by blocking electron transfer between cytochrome b and cytochrome c.[7] The absolute structure of **2** was established by a combination of spectroscopic analysis and chemical degradation of the natural product.[1] The left-side structure of **2** has been reported to be responsible for its antifungal activity.[8] For the purpose of studying the structure–biological activity relationships of cystothiazole A congeners, efficient synthesis of the left-side aldehyde **5a** is considered to be highly important.

The first enantiocontrolled synthesis of **2** was achieved based on the preparation of a bis-thiazole core and application of an asymmetric Evans aldol methodology for development of the C(4)/C(5) vicinal stereochemistry.[9] After our syntheses of cystothiazoles A (**2**)[10,11] and B[12] were reported, further syntheses of cystothiazoles A **2**,[8,13—16] and B,[16] as well as syntheses of the C[9,14] and E[17,18] types, were reported. In this paper, we describe a concise chiral synthesis of cystothiazoles A (**2**) and C (**1**) and melithiazol B (**4**) for the purpose of improving the overall yield and the (*E*)-selectivity at the C(6)/C(7) double bond. Moreover, the first chiral synthesis of cystothiazole D (**3**) is described. Our retrosynthetic strategy for these natural products is illustrated in Chart 1. It can be seen that these compounds can be synthesized by modified Julia coupling[19] between the left-side aldehyde **5b** and the right-side sulfone **6** or **7**. The synthesis of the left-side aldehyde **5b** is shown in Chart 2.

The starting (2*R*,3*S*)-diol **10** was obtained from (2*R*,3*S*)-epoxy butanoate **8**[20—23] *via* (2*R*,3*S*)-2-hydroxy ester **9** using a previously reported procedure.[11] Bis-silylation (**11**, quantitative yield) of **10** followed by consecutive treatment with *n*-BuLi and methyl chloroformate gave acetylenecarboxylate **12** in 93% overall yield. It was previously reported that conjugate addition of MeOH to a 3-substituted prop-2-ynoate congener in the presence of Bu_3P selectively gave a (2*E*)-3-methoxy-acrylate congener.[24] Applying this procedure, conjugate addition of MeOH to acetylenecarboxylate **12** in the presence of a catalytic amount of Bu_3P afforded a single isomer, (*E*)-β-methoxy-α,β-unsaturated ester **13**, in 90% yield. Determination of the (*E*)-geometry of **13** seemed to be difficult at this stage, but the geometry of **13** was confirmed by the fact that it was converted to the natural product cystothia-

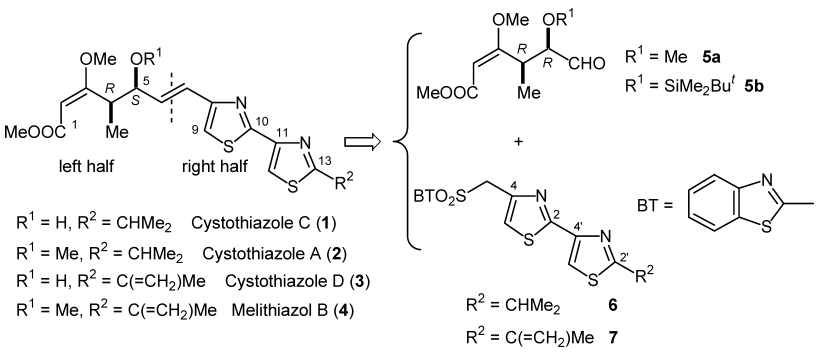

Chart 1

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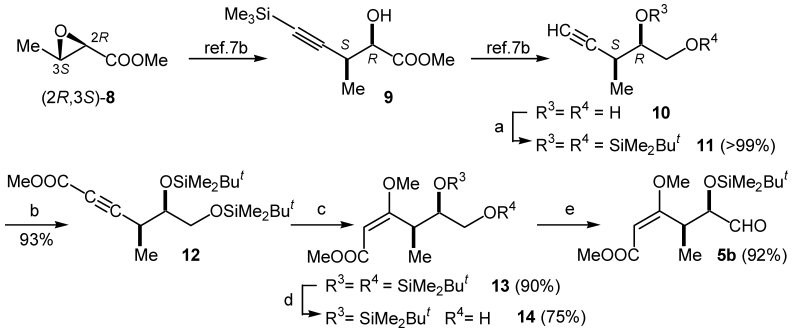
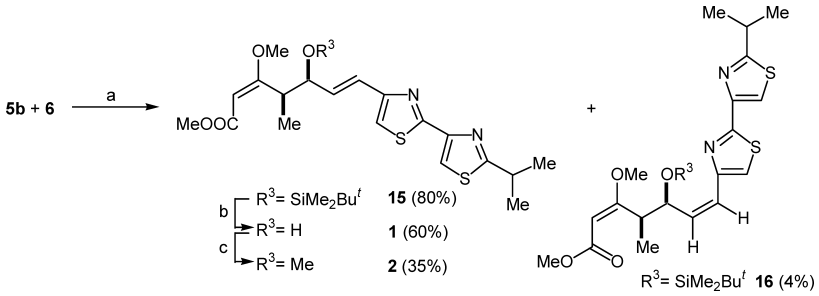


Reagent and conditions: (a) ^{t}BuMe$_2$SiCl/imidazole/CH_2Cl_2, (b) *n*-BuLi/ClCOOMe/THF, (c) Bu_3P/MeOH/CH_2Cl_2, (d) HF·pyridine/THF, (e) Dess–Martin periodinane/CH_2Cl_2.

Chart 2



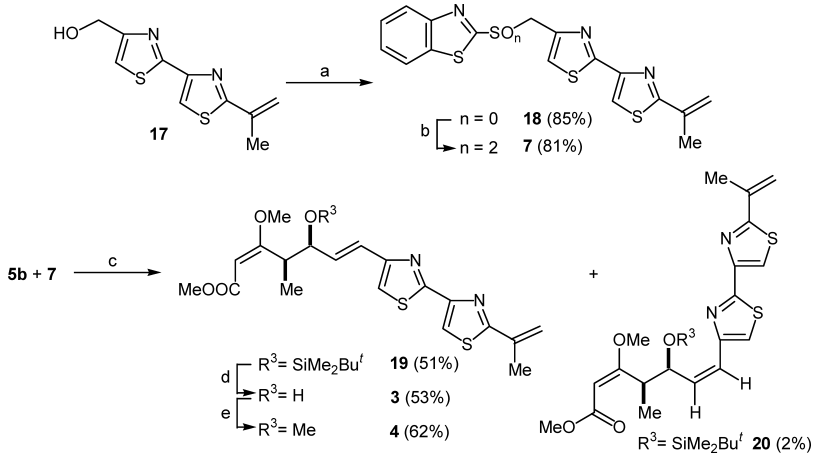
Reagents and conditions: (a) LiN(SiMe$_3$)$_2$/THF, (b) $Bu_4F^+F^-$/THF, (c) $Me_3O^+BF_4^-$/proton sponge/CH_2Cl_2.

Chart 3

zole C (**1**). Selective deprotection of the silyl groups in bis-silyl ether **13** was achieved using HF·pyridine in THF to provide **14** in 75% yield. Dess–Martin oxidation of **14** afforded the corresponding aldehyde **5b** (92% yield), which was used for the subsequent reaction without further purification. Next, modified Julia coupling of aldehyde **5b** with the previously reported sulfone **6**[13] was carried out (Chart 3). The reaction of **5b** and **6** in the presence of lithium bis(trimethylsilyl)amide in THF gave a mixture (*E*/*Z*=20/1) of coupled products, which were separated to give (*E*)-**15** (80%) and (*Z*)-**16** (4%). Deprotection of (*E*)-**15** with tetrabutylammonium fluoride gave cystothiazole C **1** ($[\alpha]_D$ +142.7° (*c*=1.25, $CHCl_3$)) in 60% yield. The spectral data (^{1}H- and ^{13}C-NMR) of synthetic **1** were identical to those of the natural product,[2] including the sign of specific rotation ($[\alpha]_D^{23}$ +145° (*c*=0.2, $CHCl_3$)). Methylation of synthetic **1** using Meerwein's reagent ($Me_3O^+BF_4^-$) in the presence of proton sponge provided cystothiazole A **2** ($[\alpha]_D$ +105.2° (*c*=0.34, $CHCl_3$)) in 35% yield along with the starting material **1** (37% recovery). The spectral data (^{1}H- and ^{13}C-NMR) of synthetic **2** were identical to those of the natural product,[1] including the sign of specific rotation ($[\alpha]_D$ +109° (*c*=0.24, $CHCl_3$)).

Next the syntheses of cystothiazole D (**3**) and melithiazol B (**4**) were carried out (Chart 4). Treatment of the previously reported primary alcohol **17**,[25] bearing a bithiazole skeleton, with 2-mercaptobenzothiazole (BTSH) in the presence of Ph_3P and diethylazodicarboxylate (DEAD) provided the sulfide **18** in 85% yield. This was then subjected to oxidation with 30% H_2O_2 in the presence of $Mo_7O_{24}(NH_4)_6\cdot 4H_2O$ to give the corresponding sulfone **7** in 81% yield. The reaction of **5b** and **7** in the presence of lithium bis(trimethylsilyl)-amide in THF gave a mixture (*E*/*Z*=26/1) of coupled products, which were separated to give (*E*)-**19** (51%) and (*Z*)-**20** (2%). Deprotection of (*E*)-**19** with tetrabutylammonium fluoride gave **3** ($[\alpha]_D$ +136.4° (*c*=0.84, $CHCl_3$)) in 53% yield. The spectral data (^{1}H- and ^{13}C-NMR) of synthetic **3** were identical to those of the natural product,[2] including the sign of specific rotation ($[\alpha]_D$ +134° (*c*=0.05, $CHCl_3$)). Thus, the absolute structure of natural cystothiazole D (**3**) was confirmed by its first synthesis of **3**. Methylation of synthetic **3** using Meerwein's reagent ($Me_3O^+BF_4^-$) in the presence of proton sponge provided melithiazol B (**4**) ($[\alpha]_D$ +94.0° (*c*=0.72, $CHCl_3$)) in 62% yield. The spectral data (^{1}H- and ^{13}C-NMR) of synthetic **4** were identical to those previously reported,[25] including the sign of specific rotation ($[\alpha]_D^{23}$ +83.6° (*c*=0.99, $CHCl_3$)).

In conclusion, convergent syntheses of cystothiazoles C **1** and D **3** were achieved based on Julia coupling between the functionalized aldehyde **5b**, corresponding to left-side of the final molecule, and aryl sulfone **6** or **7**, bearing a bithiazole moiety corresponding to right-side. Methylation of **1** and **3** gave cystothiazole A (**2**) and melithiazol B (**4**), respectively. Bis-silylation of (2*R*,3*S*)-3-methyl-pent-4-yne-1,2-diol **10**, followed by introduction of a methoxycarbonyl group to the terminal acetylenic carbon, gave acetylenecarboxylate **12** (93% overall yield), which was treated with MeOH in the presence of Bu_3P to selectively afford (*E*)-*β*-methoxyacrylate congener **13** in 90% yield. Selective desilylation of **13** gave primary alcohol **14** (75%), which was subjected to Dess–Martin oxidation to afford the left-side aldehyde **5b** (92%). The overall yield (5 steps from **10**; 57%) of **5b** *via* the present route was improved in comparison to that of **5a** (7 steps from **10**; 13%) by way of the previously reported



Reagents and conditions: (a) 2-mercaptobenzothiazole (BTSH)/DEAD/Ph_3P/THF, (b) $H_2O_2/Mo_7O_{24}(NH_4)_6 \cdot 4H_2O$/EtOH, (c) $LiN(SiMe_3)_2$/THF, (d) $Bu_4N^+F^-$/THF, (e) $Me_3O^+BF_4^-$/proton sponge/CH_2Cl_2.

Chart 4

route.[10,11] By applying this modified Julia coupling method, selectivity (6*E*/6*Z*=20 : 1—26 : 1) toward the (6*E*)-form (**15** or **19**) against the corresponding (6*Z*)-form was improved in comparison to the Wittig method (6*E*/6*Z*=4 : 1[11]—6.9 : 1[15]).

Experimental

General All melting points were measured on a Büchi 535 melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker AV400M digital NMR spectrometer in $CDCl_3$. High-resolution mass spectra (HR-MS) and the fast atom bombardment mass spectra (FAB-MS) were obtained with a JEOL JMS 600H spectrometer and JEOL GC-Mate spectrometer (matrix; *m*-nitrobenzylalcohol). IR spectra were recorded with a JASCO FT/IR-4100 spectrometer. Optical rotations were measured with a JASCO P-1020 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (KANTO silica-gel 60N, spherical, neutral, 40—50 μM) was employed.

(−)-(3*S*,4*R*)-4,5-Bis-(*tert*-butyldimethylsilyloxy)-3-methylpent-1-yne (11) To a solution of (2*R*,3*S*)-3-methylpent-4-yne-1,2-diol (1.4 g, 12.3 mmol) in CH_2Cl_2 (20 ml), imidazole (2.09 g, 30.7 mmol) and *tert*-butyldimethylsilyl chloride (4.62 g, 30.7 mmol) were added. The mixture was stirred at room temperature for 4 h, and additional amounts of imidazole (1 g, 14.7 mmol) and *tert*-butyldimethylsilyl chloride (2 g, 13.3 mmol) were added with stirring for 2 h at 40 °C. The mixture was diluted with CH_2Cl_2, and washed with H_2O and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (70 g, *n*-hexane/EtOAc=9/1) to afford **11** (4.2 g, quantitative yield) as a colorless oil. **11**; $[\alpha]_D^{22}$ −0.592° (*c*=1.08, $CHCl_3$), IR (neat): 3313, 2116, 1094 cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.08 (6H, s), 0.10 (6H, s), 0.89 (18H, s), 1.16 (3H, d, *J*=7.1 Hz), 2.02 (1H, d, *J*=2.5 Hz), 2.65—2.73 (1H, m), 3.57—3.63 (2H, m), 3.69 (1H, dd, *J*=10.6, 5.3 Hz). ^{13}C-NMR (101 MHz, $CDCl_3$): δ −5.40, −5.37, −4.66, −4.22, 15.35, 18.20, 18.36, 25.91 (3C), 25.96 (3C), 28.72, 65.20, 69.00, 75.79, 87.72. HR-MS (*m*/*z*): Calcd for $C_{18}H_{38}O_2Si_2$: 285.1706 (M−*t*Bu)$^+$. Found: 285.1705.

(4*S*,5*R*)-5,6-Bis-(*tert*-butyldimethylsilyloxy)-4-methylhex-2-ynoic Acid Methyl Ester (12) To a solution of **11** (3.9 g, 11.4 mmol) in THF (40 ml) at −78 °C, 1.59 M solution of *n*-butyllithium in *n*-hexane (8.6 ml, 13.6 mmol) was added. The mixture was stirred at −78 °C for 0.5 h and then methyl chloroformate (1.06 ml, 13.7 mmol) was added. After being warmed to room temperature and stirred for 1 h, the reaction was quenched with aqueous saturated NH_4Cl at −78 °C. The mixture was diluted with EtOAc, the separated organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (80 g, *n*-hexane/EtOAc=9/1) to afford **12** (4.24 g, 93%) as a colorless oil. **12**: $[\alpha]_D^{24}$ −1.28° (*c*=1.14, $CHCl_3$), IR (neat): 2237, 1720, 1254 cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.05 (6H, s), 0.08 (3H, s), 0.11 (3H, s), 0.89 (18H, s), 1.19 (3H, d, *J*=7.0 Hz), 2.88 (1H, dq, *J*=7.0, 4.5 Hz), 3.52 (1H, dd, *J*=10.3, 6.5 Hz), 3.58 (1H, dd, *J*=10.3, 5.0 Hz), 3.75 (3H, s), 3.76—3.80 (1H, m). ^{13}C-NMR (101 MHz, $CDCl_3$): δ −5.44, −5.38, −4.78, −4.29, 13.64, 18.17, 18.33, 25.86 (3C), 25.94 (3C), 28.80, 52.51, 64.65, 73.52, 73.52, 74.68, 92.76, 154.30. *Anal.* Calcd for $C_{20}H_{40}O_4Si_2 \cdot 1.5H_2O$: C, 58.63; H, 10.09. Found: C, 59.00; H, 10.11. HR-MS (*m*/*z*): Calcd for $C_{20}H_{40}O_4Si_2$: 343.1761 (M−*t*Bu)$^+$. Found: 343.1763.

(4*R*,5*R*)-5,6-Bis-(*tert*-butyldimethylsilyloxy)-3-methoxy-4-methylhex-(2*E*)-enoic Acid Methyl Ester (13) To a solution of **12** (0.95 g, 2.37 mmol) in CH_2Cl_2 (5 ml) were added MeOH (0.48 ml) and tributylphosphine (0.059 ml, 0.24 mmol). The mixture was stirred at room temperature for 0.5 h, and then concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (30 g, *n*-hexane/EtOAc=9/1) to afford **13** (0.93 g, 90%) as colorless oil. **13**: $[\alpha]_D^{23}$ −16.6° (*c*=2.03, $CHCl_3$), IR (neat): 1718, 1631 cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.0099 (3H, s), 0.031 (3H, s), 0.049 (3H, s), 0.052 (3H, s), 0.87 (9H, s), 0.89 (9H, s), 1.03 (3H, d, *J*=6.8 Hz), 2.75 (1H, dq, *J*=6.8, 3.8 Hz), 3.45 (1H, dd, *J*=7.3, 10.1 Hz), 3.52 (1H, dd, *J*=5.0, 10.1 Hz), 3.66 (3H, s), 3.78—3.82 (1H, m), 3.88 (3H, s), 5.02 (1H, s). ^{13}C-NMR (101 MHz, $CDCl_3$): δ −5.46, −5.39, −4.94, −4.32, 11.64, 18.12, 18.28, 25.86 (3C), 25.92 (3C), 39.86, 50.79, 59.21, 64.89, 73.43, 96.37, 165.93, 174.62. *Anal.* Calcd for $C_{21}H_{44}O_5Si_2$: C, 58.29; H, 10.25. Found: C, 57.82; H, 10.30. HR-MS (*m*/*z*): Calcd for $C_{21}H_{44}O_5Si_2$: 375.2023 (M−*t*Bu)$^+$. Found: 375.2033.

(4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-6-hydroxy-3-methoxy-4-methylhex-(2*E*)-enoic Acid Methyl Ester (14) To a solution of **13** (0.152 g, 0.351 mmol) in THF (1 ml) was added HF·Py (0.04 ml) at 0 °C. The mixture was gradually warmed to room temperature, and then stirred for 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The mixture was diluted with EtOAc and the separated organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash silica gel column chromatography (2 g, *n*-hexane/EtOAc=7/1) to afford **14** (0.084 g, 75%) as a colorless oil. **14**: $[\alpha]_D^{23}$ +10.8° (*c*=2.17, $CHCl_3$), IR (neat): 3480, 1716, 1629 cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.09 (6H, s), 0.91 (9H, s), 1.13 (3H, d, *J*=7.3 Hz), 1.81 (1H, br. dd *J*=6.08, 6.08 Hz), 2.59 (1H, dq, *J*=7.3, 7.08 Hz), 3.54—3.58 (2H, m), 3.66 (3H, s), 3.74 (1H, ddd, *J*=7.3, 3.8, 3.8 Hz), 3.94 (3H, s), 5.05 (1H, s). ^{13}C-NMR (101 MHz, $CDCl_3$): δ −4.58, −4.29, 15.22, 18.17, 25.91 (3C), 42.90, 51.02, 60.77, 64.75, 74.65, 95.91, 165.84, 173.83. HR-MS (*m*/*z*): Calcd for $C_{15}H_{30}O_5Si$: 261.1158 (M−*t*Bu)$^+$. Found: 261.1156.

(4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-methoxy-4-methyl-6-oxohex-(2*E*)-enoic Acid Methyl Ester (5b) To a solution of **14** (0.210 g, 0.659 mmol) in CH_2Cl_2 (2 ml) was added Dess–Martin periodinane (0.308 g, 0.726 mmol) at 0 °C. After being stirred at room temperature for 0.5 h, saturated aqueous $NaHCO_3$ was added at 0 °C. The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was passed through short silica gel pad to afford **5b** (0.192 g, 92%) as colorless oil. This product was used for the next reaction without further purification. Because this product was not stable, so it was promptly used to the next reaction. **5b**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.05 (6H, d, *J*=5.8 Hz), 1.11 (3H, d, *J*=7.1 Hz), 2.70 (1H, dq, *J*=7.1, 4.8 Hz), 3.67 (3H, s), 3.92 (3H, s), 4.05 (1H, dd, *J*=4.8, 1.5 Hz), 5.06 (1H, s), 9.59 (1H, d, *J*=1.5 Hz).

(2*E*,6*E*)-(4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(2′-isopropyl-[2,4′]bithiazolyl-4-yl)-3-methoxy-4-methylhepta-2,6-dienoic Acid Methyl

Ester (15) and (2*E*,6*Z*)-(4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(2′-isopropyl-[2,4′]bithiazolyl-4-yl)-3-methoxy-4-methylhepta-2,6-dienoic Acid Methyl Ester (16) To a solution of the reported aryl sulfone **6** (0.281 g, 0.60 mmol) in THF (2 ml) was added 1.06 M solution of lithium bis(trimethylsilylamide) in THF (0.57 ml, 0.61 mmol) at −50 °C. After being stirred at −50 °C for 0.5 h, **5b** (0.192 g, 0.607 mmol) in THF (1 ml) was slowly added. The mixture was gradually warmed to room temperature and stirred for 0.5 h. The reaction was quenched with saturated aqueous NH_4Cl at 0 °C. The mixture was extracted with EtOAc and washed with brine. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (10 g, *n*-hexane/EtOAc=8/1) to afford (6*Z*)-**16** (0.014 g, 4%) and (6*E*)-**15** (0.253 g, 80%) as colorless oil in elution order. (6*E*)-**15**: $[\alpha]_D^{23}$ +79.1° (*c*=1.37, $CHCl_3$), IR (neat): 3113, 1711, 1622 cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.013 (3H, s), 0.034 (3H, s), 0.91 (9H, s), 1.16 (3H, d, *J*=7.08 Hz), 1.43 (3H, s), 1.44 (3H, s), 3.34—3.41 (1H, m), 3.60 (3H, s), 3.65 (3H, s), 4.03—4.09 (1H, m), 4.39—4.42 (1H, m), 4.95 (1H, s), 6.49—6.58 (2H, m), 7.04 (1H, s), 7.84 (1H, s).^{13}C-NMR (101 MHz, $CDCl_3$): δ −4.96, −4.07, 13.17, 18.19, 23.16 (2C), 25.86 (3C), 33.35, 41.68, 50.73, 55.37, 75.59, 90.61, 114.46, 114.71, 122.97, 134.88, 148.85, 154.86, 162.39, 167.84, 177.70, 178.54, FAB-HR-MS (*m*/*z*): Calcd for $C_{25}H_{39}N_2O_4S_2Si$: 523.2121 $(M+H)^+$. Found: 523.2121. (6*Z*)-**16**: $[\alpha]_D^{22}$ +15.6° (*c*=1.10, $CHCl_3$). IR (neat) 3109, 1714, 1631 cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.032 (3H, s), 0.062 (3H, s), 0.93 (9H, s), 1.14 (3H, d, *J*=7.06 Hz), 1.43 (3H, s), 1.45 (3H, s), 2.45—2.52 (1H, m), 3.33—3.42 (1H, sept, *J*=7.06 Hz), 3.65 (3H, s), 3.91 (3H, s), 4.39—4.4 (1H, m), 5.06 (1H, s), 6.53—6.62 (2H, m), 7.06 (1H, s), 7.85 (1H, s). ^{13}C-NMR (101 MHz, $CDCl_3$): δ −4.95, −4.15, 13.61, 18.26, 23.15, 23.17, 25.92 (3C), 33.37, 46.83, 50.89, 60.51, 74.43, 96.18, 114.89, 115.13, 123.28, 134.34, 148.76, 154.43, 162.71, 165.87, 173.72, 178.63. FAB-HR-MS (*m*/*z*): Calcd for $C_{25}H_{39}N_2O_4S_2Si$: 523.2121 $(M+H)^+$. Found: 523.2121.

Cystothiazole C (1) To a solution of **15** (64 mg, 0.122 mmol) in THF (1.5 ml) was added 1.0 M solution of tetrabutylammonium fluoride in THF (0.61 mmol) at 0 °C. After being stirred for 3 h, H_2O was added. The mixture was diluted and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (1 g, *n*-hexane/EtOAc=2/1) to afford cyctothiazole C (**1**, 30 mg, 60%) as a colorless oil. **1**: $[\alpha]_D^{21}$ +142.7° (*c*=1.25, $CHCl_3$), IR (neat): 3423, 3109, 1708, 1620, 1147 cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.18 (3H, d, *J*=7.0 Hz), 1.44 (6H, d, *J*=6.6 Hz), 2.93 (1H, br. s), 3.37 (1H, sept, *J*=6.6 Hz), 3.65 (3H, s), 3.70 (3H, s), 4.17 (1H, dq, *J*=7.0, 4.5 Hz), 4.52 (1H, dd, *J*=4.5, 4.5 Hz), 5.09 (1H, s), 6.61 (1H, dd, *J*=15.9, 5.0 Hz), 6.68 (1H, d, *J*=15.9 Hz), 7.06 (1H, s), 7.85 (1H, s). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 12.48, 23.15 (2C), 33.35, 40.47, 51.13, 55.68, 74.79, 91.54, 114.77, 115.15, 123.52, 132.71, 148.82, 154.63, 162.55, 168.67, 176.90, 178.57. FAB-HR-MS (*m*/*z*): Calcd for $C_{19}H_{25}N_2O_4S_2$: 409.1256 $(M+H)^+$. Found: 409.1258.

Cystothiazole A (2) To a solution of cystothiazole C (**1**, 9.3 mg, 0.023 mmol) in CH_2Cl_2 (0.5 ml) were added $Me_3O^+BF_4^-$ (10 mg, 0.067 mmol) and protone-sponge (14 mg, 0.065 mmol) at 0 °C. After stirring for 1.5 h at 0 °C, additional $Me_3O^+BF_4^-$ (10 mg, 0.067 mmol) and protone sponge (14 mg, 0.0653 mmol) was added. The mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with H_2O. The separated organic layer was washed with brine, dried and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography (1 g, *n*-hexane/EtOAc=5/1) to afford the starting material (**1**, 3.4 mg, 37% recovery) and cystothiazole A (**2**, 4 mg, 35 %) as a colorless oil. **2**: $[\alpha]_D^{23}$ +105.2° (*c*=0.34, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, d, *J*=7.0 Hz), 1.44 (6H, d, *J*=6.8 Hz), 3.33 (3H, s), 3.37 (1H, sept, *J*=6.8 Hz), 3.60 (3H, s), 3.66 (3H, s), 3.81 (1H, dd, *J*=7.0, 7.0 Hz), 4.14—4.21 (1H, m), 4.97 (1H, s), 6.41 (1H, dd, *J*=15.8, 7.5 Hz), 6.57 (1H, d, *J*=15.8 Hz), 7.09 (1H, s), 7.84 (1H, s). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 14.11, 23.17 (2C), 33.37, 39.86, 50.81, 55.53, 57.01, 84.41, 91.12, 114.82, 114.99, 125.61, 131.63, 148.76, 154.47, 162.58, 167.73, 176.75, 178.63. FAB-HR-MS (*m*/*z*): Calcd for $C_{20}H_{27}N_2O_4S_2$: 423.1412 $(M+H)^+$. Found: 423.1413.

2-(2′-Isopropenyl[2,4′]bithiazolyl-4-methylenethio)benzothiazole (18) To a solution of the reported primary alcohol **17**[25] (0.29 g, 1.22 mmol) and 2-mercaptobenzothiazole (0.24 g, 1.43 mmol) in THF (6 ml) were added triphenylphosphine (0.45 g, 1.72 mmol) and 40% solution of diethylazodicarboxylate in toluene (0.57 ml) at room temperature. After being stirred for 10 min, the mixture was concentrated *in vacuo* and purified by flash silica gel column chromatography (20 g, *n*-hexane/EtOAc=4/1) to afford **18** (0.40 g, 85%) as colorless needles. **18**: mp 104—107 °C, IR (KBr): 1425, 992, 746 cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.27 (3H, s), 4.77 (1H, s), 4.77 (1H, s), 5.36 (1H, br. s), 5.90 (1H, s), 7.28—7.32 (1H, m), 7.35 (1H, s), 7.40—7.45 (1H, m), 7.74—7.76 (1H, m), 7.86 (1H, s), 7.90—7.92 (1H, m). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 20.42, 33.10, 115.69, 117.41, 117.73, 121.04, 121.60, 124.34, 126.06, 135.46, 137.77, 149.35, 152.25, 153.14, 163.06, 165.95, 169.89. *Anal.* Calcd for $C_{17}H_{13}N_3S_4$: C, 52.68; H, 3.38; N, 10.84. Found: C, 52.76; H, 3.65; N, 10.66.

2-(2′-Isopropenyl[2,4′]bithiazolyl-4-methylenesulfonyl)benzothiazole (7) To a solution of **17** (0.493 g, 1.27 mmol) in EtOH (10 ml) were added $Mo_7O_{24}(NH_4)_6\cdot 4H_2O$ (0.157 g, 0.127 mmol) and 30% H_2O_2 (2 ml). After being stirred for 2 h, additional $Mo_7O_{24}(NH_4)_6\cdot 4H_2O$ (0.1 g, 0.091 mmol) and 30% H_2O_2 (1 ml) were added. The mixture was stirred for additional 1 h, and diluted with H_2O and EtOAc. The organic layer was washed with 10% aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash silica gel column chromatography (30 g, *n*-hexane/EtOAc=2/1) to afford **7** (0.431 g, 81%) as colorless needles. **7**: mp 157—160 °C, IR (KBr): 1338, 1148 cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.22—2.23 (3H, m), 4.99 (2H, s), 5.34 (1H, br. s), 5.86 (1H, s), 7.19 (1H, s), 7.37 (1H, s), 7.57—7.60 (1H, m), 7.63—7.67 (1H, m), 7.92—7.94 (1H, m), 8.28—8.30 (1H, m). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 20.34, 57.10, 115.68, 117.50, 121.64, 122.27, 125.66, 127.60, 127.98, 137.37, 137.63, 142.79, 148.73, 152.72, 163.23, 165.16, 169.91. *Anal.* Calcd for $C_{17}H_{13}N_3O_2S_4$: C, 48.67; H, 3.12; N, 10.02. Found: C, 49.05; H, 3.39; N, 9.45. FAB-MS (*m*/*z*): 420 (M^++H).

(2*E*,6*E*)-(4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(2′-isopropenyl-[2,4′]bithiazolyl-4-yl)-3-methoxy-4-methylhepta-2,6-dienoic Acid Methyl Ester (19) and (2*E*,6*Z*)-(4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(2′-isopropenyl-[2,4′]bithiazolyl-4-yl)-3-methoxy-4-methylhepta-2,6-dienoic Acid Methyl Ester (20) To a solution of **7** (0.172 g, 0.410 mmol) in THF (1.5 ml) was added 1.06 M solution of lithium bis(trimethylsilylamide) in THF (0.37 ml, 0.39 mmol) at −60 °C. After being stirred at −60 °C for 0.5 h, **5b** (0.118 g, 0.373 mmol) in THF (1 ml) was slowly added. The mixture was gradually warmed to −20 °C and stirred for 0.5 h. The reaction was quenched with saturated aqueous NH_4Cl at 0 °C and warmed to room temperature. The mixture was extracted with EtOAc and washed with brine. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (10 g, *n*-hexane/EtOAc=8/1) to afford (6*Z*)-**20** (4 mg, 2%) and (6*E*)-**19** (98 mg, 51%) as colorless oil. (6*E*)-**19**: $[\alpha]_D^{23}$ +78.4° (*c*=1.845, $CHCl_3$), IR (neat): 3115, 1710, 1621 cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.018 (3H, s), 0.037 (3H, s), 0.92 (9H, s), 1.16 (3H, d, *J*=6.7 Hz), 2.28 (3H, s), 3.60 (3H, s), 3.65 (3H, s), 4.06 (1H, m), 4.41 (1H, dd, *J*=6.7, 4.8 Hz), 4.96 (1H, s), 5.35 (1H, bs), 5.91 (1H, s), 6.50—6.59 (2H, m), 7.06 (1H, s), 7.89 (1H, s). ^{13}C-NMR (101 MHz, $CDCl_3$): δ −4.97, −4.08, 13.10, 18.18, 20.44, 25.86 (3C), 41.67, 50.72, 55.37, 75.55, 90.60, 114.72, 115.48, 117.22, 122.89, 134.95, 137.84, 149.76, 154.89, 162.25, 167.83, 169.70, 177.70. FAB-HR-MS (*m*/*z*): Calcd for $C_{25}H_{37}N_2O_4S_2Si$: 521.1964 $(M+H)^+$. Found: 521.1965. (6*Z*)-**20**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.034 (3H, s), 0.063 (3H, s), 0.93 (9H, s), 1.15 (3H, d, *J*=7.0 Hz), 2.28 (3H, s), 2.46—2.52 (1H, m), 3.65 (3H, s), 3.92 (3H, s), 4.41 (1H, dd, *J*=4.5, 4.5 Hz), 5.06 (1H, s), 5.36 (1H, s), 5.91 (1H, s), 6.54—6.62 (2H, m), 7.07 (1H, s), 7.90 (1H, s). ^{13}C-NMR (101 MHz, $CDCl_3$): δ −4.95, −4.07, 13.12, 18.20, 20.45, 25.87 (3C), 41.68, 50.74, 55.38, 75.56, 90.61, 114.74, 115.50, 117.24, 122.91, 134.96, 137.85, 149.78, 154.91, 162.26, 167.85, 169.72, 177.72. FAB-HR-MS (*m*/*z*): Calcd for $C_{25}H_{37}N_2O_4S_2Si$: 521.1964 $(M+H)^+$. Found: 521.1965.

Cystothiazole D (3) To a solution of **19** (15 mg, 0.0288 mmol) in THF (1 ml) was added 1.0 M solution of tetrabutylammonium fluoride in THF (0.086 ml, 0.086 mmol) at 0 °C. After being stirred for 3 h, H_2O was added. The mixture was diluted and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (1 g, *n*-hexane/EtOAc=2/1) to afford **3** (6.2 mg, 53%) as a colorless oil. **3**: $[\alpha]_D^{24}$ +136.4° (*c*=0.84, $CHCl_3$), IR (neat): 3424, 3110, 1708, 1621, 1147 cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.18 (3H, d, *J*=7.1 Hz), 2.28 (3H, s), 2.91 (1H, d, *J*=2.8 Hz), 3.66 (3H, s), 3.70 (3H, s), 4.18(1H, dq, *J*=7.1, 4.5 Hz), 4.50—4.54 (1H, m), 5.09 (1H, s), 5.36 (1H, d, *J*=1.0 Hz), 5.91 (1H, s), 6.62 (1H, dd, *J*=15.9, 5.0 Hz), 6.68 (1H, d, *J*=15.9 Hz), 7.07 (1H, s), 7.90 (1H, s). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 12.46, 20.45, 40.47, 51.13, 55.69, 74.79, 91.56, 115.42, 115.56, 117.28, 123.48, 132.77, 137.84, 149.74, 154.67, 162.42, 168.68, 169.78, 176.91. FAB-HR-MS (*m*/*z*): Calcd for $C_{19}H_{23}N_2O_4S_2$: 407.1099 $(M+H)^+$. Found: 407.1099.

Melithiazol B (4) To a solution of **3** (11.3 mg, 0.027 mmol) in CH_2Cl_2 (0.7 ml) were added $Me_3O^+BF_4^-$ (12.3 mg, 0.083 mmol) and protone sponge

(17.9 mg, 0.083 mmol) at 0 °C. After stirring for 3 h, H_2O was added. The separated organic layer was extracted with EtOAc, washed with brine, dried and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography (1 g, *n*-hexane/EtOAc=4/1) to afford **4** (7.2 mg, 62%) and the starting material **3** (1.4 mg, 12% recovery) as a colorless oil. **4**: $[\alpha]_D^{24}$ +94.0° (*c*=0.72, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, d, *J*=7.1 Hz), 2.28 (3H, s), 3.34 (3H, s), 3.61 (3H, s), 3.67 (3H, s), 3.82 (1H, dd, *J*=7.8, 7.8 Hz), 4.14—4.21 (1H, m), 4.97 (1H, s), 5.37 (1H, s), 5.91 (1H, s), 6.42 (1H, dd, *J*=15.9, 7.6 Hz), 6.58 (1H, d, *J*=15.9 Hz), 7.10 (1H, s), 7.89 (1H, s). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 14.09, 20.44, 39.86, 50.81, 55.53, 57.02, 84.39, 91.11, 115.26, 115.59, 117.31, 125.53, 131.82, 137.82, 149.65, 154.48, 162.44, 167.73, 169.80, 176.75. FAB-HR-MS (*m*/*z*): Calcd for $C_{20}H_{25}N_2O_4S_2$: 421.1256 $(M+H)^+$. Found: 421.1257.

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References and Notes

1) Ojika M., Suzuki Y., Tsukamoto A., Sakagami Y., Fudou R., Yoshimura T., Yamanaka S., *J. Antibiot.*, **51**, 275—281 (1998).
2) Suzuki Y., Ojika M., Sakagami Y., Fudou R., Yamanaka S., *Tetrahedron*, **54**, 11399—11404 (1998).
3) Böhlendrof B., Herrmann M., Hecht H.-J., Sasse F., Forche E., Kunze B., Reichenbach H., Höfle G., *Eur. J. Org. Chem.*, **1999**, 2601—2608 (1999).
4) Gerth K., Irschik H., Reichenbach H., Trowitzsch W., *J. Antibiot.*, **33**, 1474—1479 (1980).
5) Trowitzsch W., Reifenstahl G., Wray V., Gerth K., *J. Antibiot.*, **33**, 1480—1490 (1980).
6) Trowitzsch W., Höfle G., Sheldrick W. S., *Tetrahedron Lett.*, **22**, 3829—3832 (1981).
7) Thierbach G., Reichenbach H., *Biochim. Biophys. Acta*, **638**, 282—289 (1981).
8) Ojika M., Watanabe T., Qi J., Tanino T., Sakagami Y., *Tetrahedron*, **60**, 187—194 (2004).
9) Williams D. R., Patnaik S., Clark M. C., *J. Org. Chem.*, **66**, 8463—8469 (2001).
10) Kato K., Nishimura A., Yamamoto Y., Akita H., *Tetrahedron Lett.*, **43**, 643—645 (2002).
11) Kato K., Sasaki T., Takayama H., Akita H., *Tetrahedron*, **59**, 2679—2685 (2003).
12) Sasaki T., Kato K., Akita H., *Chem. Pharm. Bull.*, **52**, 770—771 (2004).
13) Akita H., Sutou N., Sasaki T., Kato K., *Tetrahedron*, **62**, 11592—11598 (2006).
14) Bach T., Heuser S., *Chem. Eur. J.*, **8**, 5585—5592 (2002).
15) DeRoy P. L., Charette A. B., *Org. Lett.*, **5**, 4163—4165 (2003).
16) Shao J., Panek J. S., *Org. Lett.*, **6**, 3083—3085 (2004).
17) Bach T., Heuser S., *Angew. Chem. Int. Ed.*, **40**, 3184—3185 (2001).
18) Takayama H., Kato K., Kimura M., Akita H., *Heterocycles*, **71**, 75—85 (2007).
19) Blakemore P. R., *J. Chem. Soc., Perkin Trans. I*, **2002**, 2563—2585 (2002).
20) Akita H., Kawaguchi T., Enoki Y., Oishi T., *Chem. Pharm. Bull.*, **38**, 323—328 (1990).
21) Akita H., Todoroki R., Endo H., Ikari Y., Oishi T., *Synthesis*, **1993**, 513—516 (1993).
22) Kato K., Ono M., Akita H., *Tetrahedron Asymmetry*, **8**, 2295—2298 (1997).
23) Osaka Yuki Kagaku Kogyo Co., Ltd. (Japan), Japan Kokai Tokkyo Koho JP 5-276966 (1993).
24) Inanaga J., Baba Y., Hanamoto T., *Chem. Lett.*, **1993**, 241—244 (1993).
25) Akita H., Sasaki T., Takayama H., Kato K., *Heterocycles*, **66**, 219—228 (2005).