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Total synthesis of (+)-myxothiazols A and Z ☆

Yuki Iwaki [a,b], Masahiro Kaneko [a], Hiroyuki Akita [a,*]

[a] *Faculty of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274-8510, Japan*
[b] *Research Institute, Novartis Pharma K.K.;8 Ohkubo, Tsukuba, Ibaraki 300-2611, Japan*

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ABSTRACT

The first synthesis of (+)-myxothiazol A **1** was achieved based on a modified Julia olefination between (3,5*R*)-dimethoxy-(4*R*)-methyl-6-oxo-(2*E*)-hexenamide **3**, corresponding to the left side of the final molecule, and 4-(2″-benzothiazolyl)sulfonylmethyl-2′-[(1‴*R*),6‴-dimethylhepta-(2‴*E*),(4‴*E*)-dienyl]-2,4′-bithiazole **6,** corresponding to the right side. The synthesis of (+)-myxothiazol Z **2** was also achieved based on modified Julia olefination between (3,5*R*)-dimethoxy-(4*R*)-methyl-6-oxo-(2*E*)-hexenoate **4**, corresponding to left side of the final molecule, and (*S*)-sulfone **6**.

1. Introduction

Myxothiazols A **1** and Z **2** possessing a bithiazole skeleton as well as a β-methoxyacrylate moiety were isolated from the myxobacterium *Myxococcus fulvus* strain Mxf16[1] and *M. fulvus*, respectively. Feeding experiments with labeled precursors established biosynthesis of **2** from **1**.[2] Myxothiazol A **1** is active against many filamentous fungi, and completely inhibits growth of *Mucor hiemalis* at a concentration of 2 μg/mL.[1] The fungicidal activity of the 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*.[3] Myxothiazol Z **2** was reported to exhibit potent cytotoxicity against human tumor cell.[4] The structure of myxothiazol A **1** was established by a combination of chemical degradation and NMR study, and its absolute configuration at C(14)-carbon was determined by X-ray analysis of its degradation product.[5] The synthesis of a diastereomeric mixture of **1** was achieved based on a Wittig coupling between racemic aldehyde (±)-**3** corresponding to the left half and chiral phosphonium salt (*S*)-**5** corresponding to the right half.[6] Meanwhile, the synthesis of (+)-**2** was reported by a Wittig coupling between chiral aldehyde (4*R*,5*R*)-**4** and (*S*)-**5**.[6] (Scheme 1) The chiral synthesis of **1** has not been achieved to date, and we now report the first synthesis of (+)-**1** based on modified Julia olefination between the chiral aldehyde (4*R*,5*R*)-**3** and the chiral benzothiazole sulfone (*S*)-**6**. Furthermore, we describe the synthesis of (+)-**2** based on modified Julia olefination between a (4*R*,5*R*)-**4** and a (*S*)-**6**.

2. Results and discussion

2.1. Synthesis of left half (4*R*,5*R*)-3 and (4*R*,5*R*)-4

The synthesis of (±)-**3** was achieved in 1% overall yield (9 steps) based on a condensation reaction between cinnamaldehyde and the dianion derived from methyl 3-oxopentanoate followed by several synthetic steps.[6] In this case, the preparation of a chiral form of **3** could be possible due to the resolution of an intermediate. On the other hand, the synthesis of (4*R*,5*R*)-**4** was reported based on an Evans asymmetric aldol condensation procedure.[6b] The preparation of (4*R*,5*R*)-**3** and (4*R*,5*R*)-**4** was achieved by the following synthetic route as shown in Scheme 2.

By applying the previously reported procedure,[7] the reaction of (2*R*,3*S*)-epoxy butanoate **7**[8] and lithium silyl-acetylide in the presence of Et_2AlCl gave the diastereomerically pure compound **8** {$[\alpha]_D^{24} = -7.6$ (*c* 1.09, $CHCl_3$)} in 72% yield. Methylation of **8** followed by consecutive desilylation and reduction afforded **10** {$[\alpha]_D^{27} = -27.6$ (*c* 1.05, $CHCl_3$)} in 59% overall yield. Silylation of **10** afforded the silyl ether **11** {93%, $[\alpha]_D^{25} = -4.7$ (*c* 1.06, $CHCl_3$)}, which was treated with *n*-BuLi and methyl chloroformate to give an acetylenecarboxylate **12** {$[\alpha]_D^{24} = -15.1$ (*c* 0.86, $CHCl_3$)} in 88% yield. By applying the reported procedure,[9] conjugate addition of MeOH to acetylenecarboxylate **12** in the presence of a catalytic amount of Bu_3P afforded a single isomer, (*Z*)-β-methoxy-α,β-unsaturated ester **13** {$[\alpha]_D^{25} = -15.6$ (*c* 0.96, $CHCl_3$)} in 86% yield. The (*Z*)-geometry of **13** was confirmed by the NOE enhancement for the olefinic proton and the methine proton (8.6%). The formation of (*Z*)-**13** from **12** could be explained as shown in Scheme 3. Addition of tributyl phosphine to **12** followed by MeOH attack would give intermediates **TS-A** and **TS-B**. Intermediate **TS-B** could lead to (*Z*)-form **13** because **TS-B** is more stable than **TS-A** due to stereochemical repulsion in **TS-A**.

☆ A part of this work was already reported as a preliminary communication (see Ref. 12).

* Corresponding author. Tel.: +81 047 472 1805; fax: +81 047 472 1825.
E-mail address: akita@phar.toho-u.ac.jp (H. Akita).

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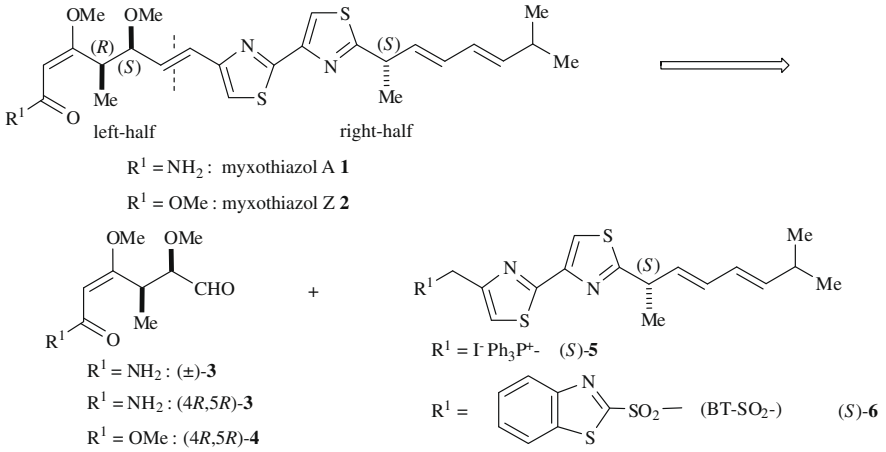
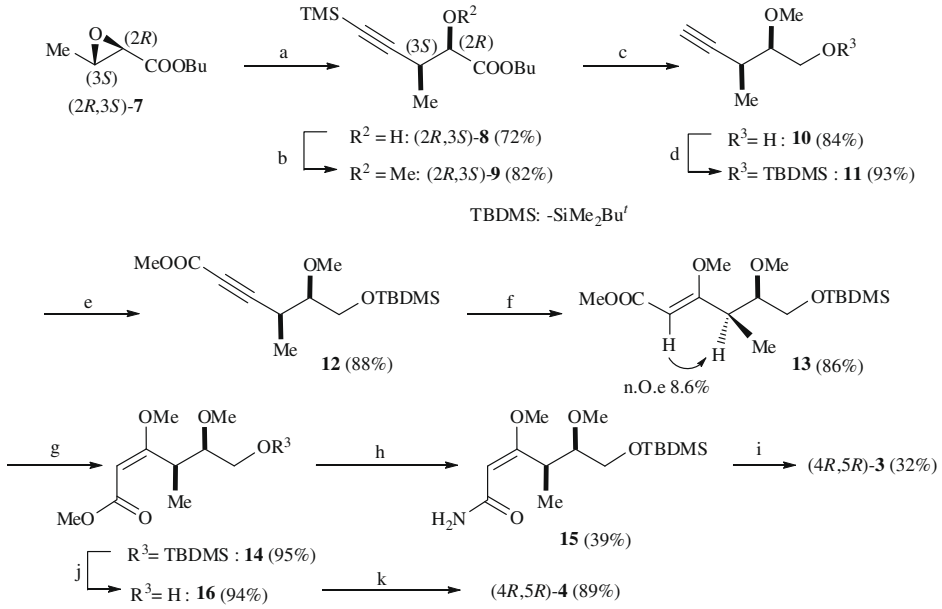


Scheme 1.



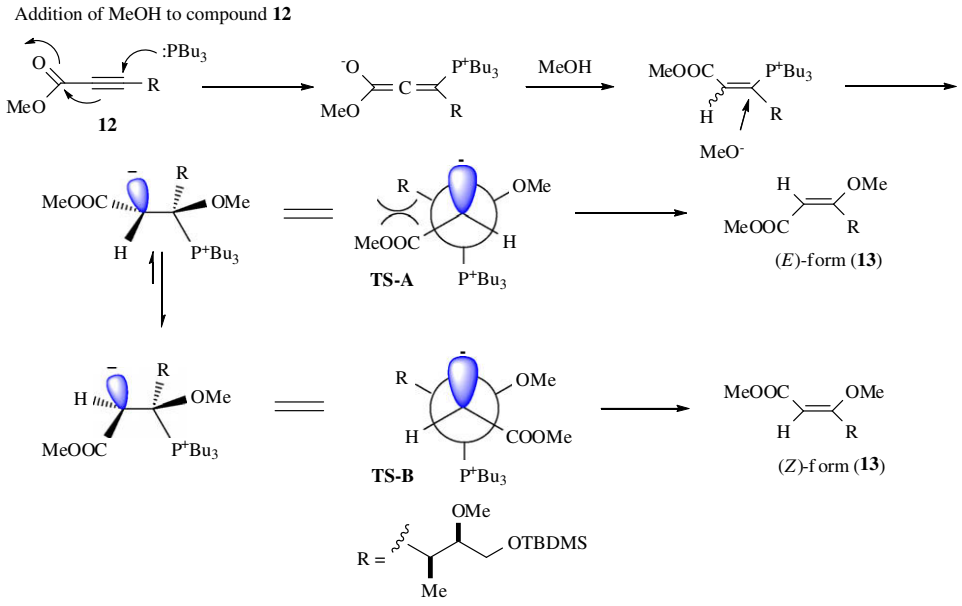
Scheme 2. Reagents: (a) trimethylsilylacetylene/*n*-BuLi/Et_2AlCl/THF; (b) MeI/Ag_2O/DMF; (c) (1) *n*-$Bu_4N^+F^-$/THF (2) $LiBH_4$; (d) TBDMSCl/imidazole/DMF; (e) *n*-BuLi/ClCOOMe; (f) Bu_3P/MeOH; (g) $CDCl_3$ or 4 M−HCl in dioxane/$CHCl_3$; (h) (1) $Ba(OH)_2{\cdot}8H_2O$/MeOH, 70 °C (2) 0.5 M HCl (3) WSCD·HCl/HOAt/Et_3N/DMF; (4) 28% aqueous NH_3; (i) (1) HF–pyridine (2) TPAP/NMO/MS-4A/CH_2Cl_2; (j) $Et_3N(HF)_3/CH_2Cl_2$; (k) Dess–Martin periodinane.

Isomerization of (*Z*)-**13** to (*E*)-**14** was carried out by the following procedure. When a solution of (*Z*)-**13** in aged $CDCl_3$ (see Section 4) was stood for 3 d at room temperature, (*E*)-**14** was obtained exclusively in 95% yield. ^{1}H NMR spectra of (*E*)-**14** were identical with those of the previously reported (*E*)-**14**.[10] Meanwhile, a solution of (*Z*)-**13** in $CHCl_3$ containing EtOH as stabilizer was treated with a small amount of 4 M HCl in dioxane to give a mixture of (*E*)-**14** and a trace amount of (4*R*,5*R*)-6-*tert*-butyldimethylsiloxy-3-ethoxy-5-methoxy-4-methyl-2(*E*)-hexenoate. This experiment indicated that proton (H^+)-assisted isomerization of (*Z*)-**13** to (*E*)-**14** to seek the thermodynamically more stable (*E*)-**14** from (*Z*)-**13** had occurred as shown in Scheme 4.

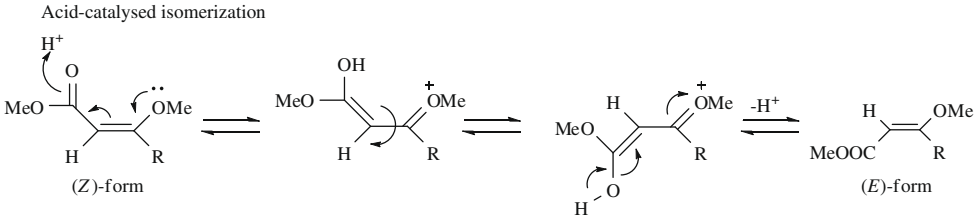
Conversion of the ester group to an amide was carried out by the following procedure. Alkaline hydrolysis of the crude (*E*)-**14** followed by acid treatment gave a carboxylic acid. Treatment of this acid with water-soluble carbodiimide hydrochloric acid salt (WSCD·HCl) in the presence of 1-hydroxy-7-aza-benzotriazole (HOAt) followed by addition of aqueous NH_3 gave the desired amide **15** {$[\alpha]_D^{27} = +35.7$ (*c* 0.84, $CHCl_3$)} in 39% overall yield from (*E*)-**14**. Desilylation of **15** with HF·pyridine followed by oxidation with tetrapropylammonium perruthenate (TPAP) in the presence of 4-methylmorpholine N-oxide (NMO) and MS-4A afforded the desired aldehyde (4*R*,5*R*)-**3** in 32% overall yield. ^{1}H NMR data of the synthetic (4*R*,5*R*)-**3** were consistent with those of the reported (±)-**3**.[6b] This aldehyde **3** was used in the next reaction without further purification after passing through silica gel pad to remove the reagents. Desilylation of **14** with $Et_3N{\cdot}(HF)_3$ followed by oxidation with Dess–Martin reagent gave the desired aldehyde (4*R*,5*R*)-**4** in 84% yield from **14**.

2.2. Synthesis of right half (*S*)-6, myxothiazols A 1 and Z 2

The starting chiral alcohol (*S*)-**17** was previously obtained based on lipase-assisted asymmetric hydrolysis of racemic acetate of **17**.[11] Treatment of (*S*)-**17** with 2-mercaptobenzothiazole (BTSH) in the presence of Ph_3P and diethyl azodicarboxylate (DEAD) gave the corresponding sulfide (*S*)-**18** {$[\alpha]_D^{26} = -92.9$ (*c* 1.48, $CHCl_3$)} in 93% yield. Then, $LiBH_4$ reduction of (*S*)-**18** followed by oxidation with 35% H_2O_2 in the presence of $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ provided the corresponding sulfone-alcohol, which was again treated with 2-mercaptobenzothiazole (BTSH) in the presence of Ph_3P and DEAD to afford the corresponding sulfide (*S*)-**19** {$[\alpha]_D^{26} = -74.4$

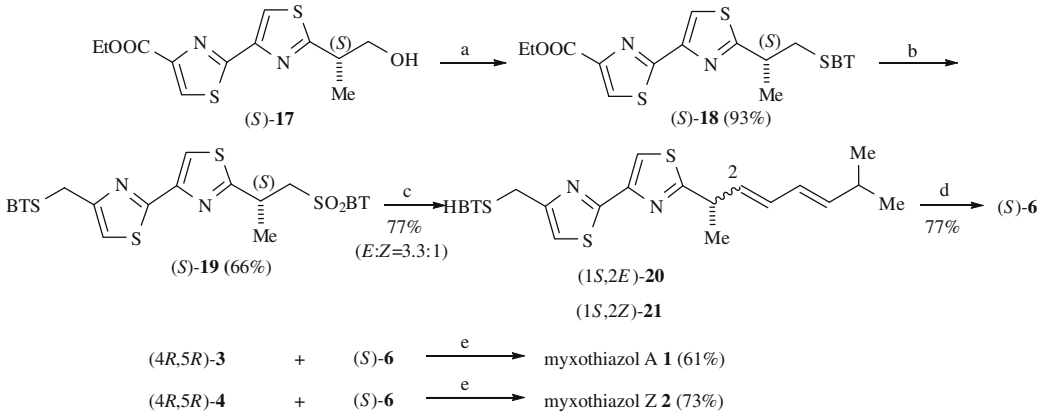


Scheme 3.



Scheme 4.

(c 0.77, $CHCl_3$)} in 66% overall yield. The reaction of (S)-**19** and (2E)-4-methylpentenal in the presence of lithium bis(trimethylsilyl)amide (LHMDS) in THF gave a mixture (E/Z = 3.3/1) of coupled products, which were separated chromatographically to give (E)-**20** {$[\alpha]_D^{27} = +7.8$ (c 0.525, $CHCl_3$)} (59%) and (Z)-**21** {$[\alpha]_D^{27} = -82.3$ (c 0.81, $CHCl_3$)} (18%). Oxidation of (E)-**20** under the same condition as preparation of (S)-**19** provided the desired (S)-**6** ($[\alpha]_D^{25} = -3.6$ (c 0.6, $CHCl_3$)) in 77% yield. The overall yield of (S)-**6** from the reported (S)-**17** was 28% (4 steps). In contrast, the overall yield of (S)-**5** from the commercially available (2R)-3-hydroxy-2-methylpropanoate was 1% (19 steps).[6] Finally, modified Julia coupling between the chiral aldehyde (4R,5R)-**3** and the chiral benzothiazole sulfone (S)-**6** in the presence of LHMDS afforded (+)-myxothiazol A (**1**) {$[\alpha]_D^{27} = +33.5$ (c 0.70, MeOH)} in 61% yield. The spectral data of the synthetic **1** were identical with those of natural (+)-myxothiazol A **1** {$[\alpha]_D^{25} = +43.4$ (c 6.0, MeOH)}[1] including the sign of a specific rotation, although the concentration of both samples was different. Julia coupling between a chiral aldehyde (4R,5R)-**4** and a chiral benzothiazole sulfone (S)-**6** in the presence of LHMDS afforded (+)-myxothiazol Z (**2**) {$[\alpha]_D^{27} = +85.7$ (c 1.66, MeOH)} in 73% yield. The spectral data of the synthetic **2** were identical with those of natural (+)-myxothiazol Z **2** {$[\alpha]_D^{22} = +79.2$ (c 1.4, MeOH)}[2] including the sign of a specific rotation (Scheme 5).



Scheme 5. Reagents: (a) 2-mercaptobenzothiazol (BTSH)/DEAD/Ph_3P/THF; (b) (1)$LiBH_4$/THF (2)H_2O_2/$Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$/EtOH (3)BTSH/DEAD/$Ph_3P$/THF; (c) LHMDS/(2$E$)-4-methylpentenal/THF; (d) H_2O_2/$Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$/EtOH; (e) LHMDS/THF.

3. Conclusion

In conclusion, first synthesis of (+)-myxothiazol A **1** was achieved based on a modified Julia olefination between the functionalized aldehydes (4*R*,5*R*)-**3,** corresponding to the left side of the final molecule, and chiral benzothiazole sulfone (*S*)-**6**, bearing a bithiazole moiety corresponding to right side. (+)-Myxothiazol Z **2** was also synthesized based on a modified Julia coupling between the functionalized aldehyde (4*R*,5*R*)-**4** and (*S*)-**6**. The desired aldehyde (4*R*,5*R*)-**3** was obtained from the starting epoxy ester (2*R*,3*S*)-**7** in 4% total overall yield (9 steps). Furthermore, the desired aldehyde (4*R*,5*R*)-**4** was obtained from the starting epoxy ester (2*R*,3*S*)-**7** in 27% total overall yield (9 steps). Meanwhile, chiral benzothiazole sulfone (*S*)-**4** was obtained from (*S*)-4-ethoxycarbonyl-2′-(1-hydroxymethylethyl)-2,4′-bithiazole **14** in 28% overall yield (4 steps). Finally, a modified Julia olefination between (4*R*,5*R*)-**3** and (*S*)-**6** afforded (+)-myxothiazol A **1** in 61% yield, and coupling of (4*R*,5*R*)-**4** and (*S*)-**6** provided (+)-myxothiazol Z **2** in 73% yield The present coupling yield (61%) was better in comparison to the reported Wittig procedure (22% yield for (+)-**1**).[6b]

4. Experimental

4.1. 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 AV400 M digital NMR spectrometer in $CDCl_3$. Electrosprey ionization-mass spectrometry (ESI-MS) and fast atom bombardment mass spectra (FAB-MS) were performed with JEOL JMS-T100LP or JEOL JMS SX-102A (matrix; m-nitrobenzyl alcohol) mass spectrometers. 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 60 N, spherical, neutral, 40–50) was employed.

4.2. *n*-Butyl (2*R*,3*S*)-2-hydroxy-3-methyl-5-trimethylsilyl-4-pentynoate 8

To a solution of trimethylsilylacetylene (9.82 g, 99.7 mmol) in toluene (100 mL) at −40 °C under argon atmosphere was added 2.6 M solution of *n*-BuLi in *n*-hexane (38.5 mL, 99.7 mmol), and the reaction mixture was stirred for 10 min. To the above reaction mixture was added 1 M solution of Et_2AlCl in *n*-hexane (62.5 mL, 99.7 mmol), and the reaction mixture was stirred for 1 h at 0 °C. To the above reaction mixture was added (2*R*,3*S*)-**7** (12.64 g, 80 mmol) at 0 °C, and the reaction mixture was stirred for 1 h. After addition of H_2O (100 mL) to the reaction mixture, the reaction mixture was filtered off with the aid of Celite to give a filtrate. The filtrate was dried over $MgSO_4$ and evaporated to afford a crude oil, which was purified by chromatography on silica gel (310 g, *n*-hexane/EtOAc = 40:1) to provide (2*R*,3*S*)-**8** (14.8 g 72%) as a colorless oil. (2*R*,3*S*)-**8**: $[\alpha]_D^{24} = -7.6$ (*c* 1.09, $CHCl_3$); IR (neat): 3487, 2168, 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.14 (9H, s), 0.95 (3H, t, *J* = 7.6 Hz), 1.21 (3H, d, *J* = 7.2 Hz), 1.36–1.45 (2H, m), 1.63–1.70 (2H, m), 2.94 (1H, dq, *J* = 3.2, 7.2 Hz), 4.15–4.26 (3H, m). ^{13}C NMR (101 MHz, $CDCl_3$): δ −0.06 (3C), 13.6, 15.8, 19.1, 30.6, 32.3, 65.7, 73.4, 86.7, 106.4, 172.9. HRMS (FAB) (*m*/*z*): calcd for $C_{13}H_{25}O_3Si$ (M+H)$^+$: 257.1573, found: 257.1539.

4.3. *n*-Butyl (2*R*,3*S*)-3-methyl-2-methoxy-5-trimethylsilyl-4-pentynoate 9

A mixture of **8** (2.105 g, 9.8 mmol), methyl iodide (18 g, 127 mmol), and Ag_2O (3.2 g, 13.8 mmol) in DMF (6 mL) was stirred for 48 h at room temperature. The reaction mixture was diluted with EtOAc (30 mL) and filtered off with the aid of Celite. The filtrate was diluted with H_2O and extracted with *n*-hexane. The organic layer was dried over $MgSO_4$. Concentration of the organic layer gave a crude residue, which was chromatographed on silica gel (50 g, *n*-hexane/EtOAc = 60:1) to provide (2*R*,3*S*)-**9** (1.819 g, 82% yield) as a colorless oil. (2*R*,3*S*)-**9**: $[\alpha]_D^{24} = +0.8$ (*c* 1.54, $CHCl_3$); IR (neat): 2175, 1748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.13 (9H, s), 0.95 (3H, t, *J* = 7.2 Hz), 1.23 (3H, d, *J* = 6.8 Hz), 1.36–1.46 (2H, m), 1.63–1.70 (2H, m), 2.91 (1H, dq, *J* = 6.8, 6.8 Hz), 3.44 (3H, s), 3.68 (1H, d, *J* = 6.8 Hz), 4.18 (2H, t, *J* = 11.2 Hz), 4.18 (1H, dq, *J* = 6.8, 6.8 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 0.3 (3C), 13.6, 16.4, 19.1, 30.5, 30.6, 58.8, 64.8, 84.0, 86.4, 106.6, 170.9. HRMS (FAB) (*m*/*z*): calcd for $C_{14}H_{27}O_3Si$ (M+H)$^+$: 271.1729, found: 271.1730.

4.4. (2*R*,3*S*)-3-Methyl-2-methoxy-5-trimethylsilyl-4-pentyn-1-ol 10

To a solution of (2*R*,3*S*)-**9** (1.66 g, 7.3 mmol) in THF (20 mL) was added 1 M tetrabutylammonium fluoride (TBAF) in THF solution (3.7 mL, 3.7 mmol) at 0 °C, and the whole mixture was stirred for 10 min at 0 °C. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was used for the next reaction without further purification. To a solution of the above 2-methoxy ester in THF (20 mL) was added $LiBH_4$ (0.641 g, 29.4 mmol) at 0 °C, and the whole mixture was stirred for 60 min at room temperature. The reaction mixture was diluted with MeOH (2 mL), H_2O (100 mL) and Et_2O (100 mL), and the whole mixture was stirred for 12 h at the same temperature. The generated precipitate was filtered off with the aid of Celite to afford the filtrate. The filtrate was extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the filtrate gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane/EtOAc = 5:1) to provide a colorless oil (−)-**10** (0.66 g, 84%). Compound (−)-**10**: $[\alpha]_D^{27} = -27.6$ (*c* 1.05, $CHCl_3$); IR (neat): 3429, 3296, 2113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, d, *J* = 6.8 Hz), 2.11 (1H, d, *J* = 2.4 Hz), 2.38 (1H, br s), 2.76 (1H, ddq, *J* = 2.4, 6.8, 6.8 Hz), 3.16 (1H, ddd, *J* = 3.2, 5.6, 6.8 Hz), 3.80 (2H, dq, *J* = 12, 5.6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 17.1, 27.3, 58.4, 61.9, 70.3, 84.5, 85.5. HRMS (FAB) (*m*/*z*): calcd for $C_7H_{13}O_2$ (M+H)$^+$: 129.0916, found 129.0919.

4.5. (2*R*,3*S*)-1-*tert*-Butyldimethylsiloxy-3-methyl-2-methoxy-4-pentyn 11

A solution of (−)-**10** (0.452 g, 3.5 mmol), imidazole (0.492 g, 7.1 mmol), and ^{t}butyldimethylsilyl chloride (TBDMSCl, 0.797 g, 5.3 mmol) in DMF (2 mL) was stirred for 1 h at room temperature. The reaction mixture was diluted with brine and extracted with EtOAc/*n*-hexane (1:1). The organic layer was dried over $MgSO_4$ and evaporated to give a crude **11**, which was chromatographed on silica gel (30 g, *n*-hexane/EtOAc = 30:1) to afford **11** (0.801 g, 93%) as a colorless oil. Compound (−)-**11**: $[\alpha]_D^{25} = -4.7$ (*c* 1.06, $CHCl_3$); IR (neat): 2115 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (6H, s), 0.89 (9H, s), 1.21 (3H, d, *J* = 7.2 Hz), 2.05 (1H, d, *J* = 2.4 Hz), 2.68 (1H, ddq, *J* = 2.4, 7.2, 6.4 Hz), 3.16 (1H, ddq, *J* = 4.4, 5.6, 6.4 Hz), 3.71 (1H, dd, *J* = 5.6, 10.8 Hz), 3.82 (1H, dd, *J* = 4.4, 10.8 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ −5.46, −5.41, 16.4, 18.3, 25.9(3C), 27.4, 59.0, 63.3, 69.4, 84.6, 86.5. HRMS (FAB) (*m*/*z*): calcd for $C_{13}H_{27}O_2Si$ (M+H)$^+$: 243.1781, found: 243.1785.

4.6. Methyl (4*S*,5*R*)-6-*tert*-butyldimethylsiloxy-4-methyl-5-methoxy-2-hexynoate 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, 88%) as a colorless oil. Compound **12**: $[\alpha]_D^{24} = -15.1$ (*c* 0.86, $CHCl_3$); IR (neat): 2236, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.06 (6H, s), 0.89 (9H, s), 1.25 (3H, d, *J* = 7.2 Hz), 2.86 (1H, dq, *J* = 7.2, 6.8 Hz), 3.23–3.27 (1H, m), 3.47 (3H, s), 3.68–3.77 (2H, m), 3.74 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ −5.52, −5.47, 15.0, 18.2, 25.8 (3C), 27.5, 52.5, 59.0, 62.7, 73.7, 83.6, 91.3, 154.1. HRMS (FAB) (*m/z*): calcd for $C_{15}H_{29}O_4Si$: 301.1836 $(M+H)^+$ Found: 301.1837.

4.7. Methyl (4*R*,5*R*)-6-*tert*-butyldimethylsiloxy-3,5-dimethoxy-4-methyl-2(*Z*)-hexenoate 13

A mixture of (−)-**12** (1.25 g, 4.2 mmol), $(n\text{-Bu})_3P$ (0.254 g, 1.25 mmol), and MeOH (0.335 g, 10.5 mmol) in CH_2Cl_2 (25 mL) was stirred for 4 h at room temperature. The reaction mixture was evaporated to give a crude residue, which was chromatographed on silica gel (30 g, *n*-hexane/EtOAc = 50:1) to afford (−)-**13** (1.19 g, 86%) as a colorless oil. Compound (−)-**13**: $[\alpha]_D^{24} = -15.6$ (*c* 0.96, $CHCl_3$); IR (neat): 1717, 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ0.05 (6H, s), 0.89 (9H, s), 1.11 (3H, d, *J* = 7.2 Hz), 2.59 (1H, dq, *J* = 6.8, 6.8 Hz), 3.30 (1H, dd, *J* = 5.6, 6.8 Hz), 3.41 (3H, s), 3.61 (2H, d, *J* = 5.6 Hz), 3.66 (3H, s), 3.91 (3H, s), 5.07 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ −5.45, −5.38, 13.4, 18.3, 25.9(3C), 40.5, 50.9, 59.3, 60.2, 62.9, 83.1, 95.8, 165.9, 174.7. HRMS (FAB) (*m/z*): calcd for $C_{16}H_{33}O_5Si$ $(M+H)^+$: 333.2097, found: 332.2120.

4.8. Methyl (4*R*,5*R*)-6-*tert*-butyldimethylsiloxy-3,5-dimethoxy-4-methyl-2(*E*)-hexenoate 14

(1) A solution of (−)-**13** (0.103 g, 0.45 mmol) in $CDCl_3$ (2 mL; D, 99.8% including 1% V/V TMS, silver foil, available from Cambridge Isotope Laboratories Inc.) was stood for 2 weeks at room temperature. Evaporation of the solvent gave **14** as a colorless oil (0.098 g, 95%), which was used for the next reaction without further purification. Compound **14**: ^1H NMR (400 MHz, $CDCl_3$): δ 0.03 (6H, s), 0.87 (9H, s), 1.15 (3H, d, *J* = 7.2 Hz), 3.33 (1H, dq, *J* = 3.0, 7.2 Hz), 3.46 (3H, s), 3.54 (1H, dd, *J* = 7.2, 11.2 Hz), 3.61 (3H, s), 3.61–3.65 (1H, m), 3.65 (3H, s), 3.97–4.04 (1H, m), 4.96 (1H, s). (2) To a solution of (−)-**13** (0.205 g, 0.617 mmol) in $CHCl_3$ (5 mL) was added one drop of 4 N HCl in dioxane. After stirring for 3 min, saturated aqueous $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography to give **14** (0.166 g, 81%) as a colorless oil.

4.9. Methyl (4*R*,5*R*)-6-*tert*-butyldimethylsiloxy-3,5-dimethoxy-4-methyl-2(*E*)-hexenamide 15

A solution of **14** (0.50 g, 1.50 mmol) in MeOH (8 mL) was heated with $Ba(OH)_2{\cdot}8H_2O$ (1.90 g, 6.01 mmol) at 70 °C. After 4 h, the reaction mixture was filtered to remove precipitate. The filtrate was diluted with EtOAc and washed with 0.5 N HCl and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in DMF (5 mL) and treated with WSCD·HCl (water-soluble carbodiimide hydrochloric acid salt) (0.432 g, 2.26 mmol), HOAt (1-hydroxy-7-aza-benzotriazole) (0.246 g, 1.80 mmol), and Et_3 N (0.315 mL, 2.26 mmol). The mixture was stirred at 50 °C for 0.5 h, and then 28% aqueous NH_3 (0.5 mL) was then added. After stirring at 50 °C for 0.5 h, additional WSCD·HCl (0.202 g, 1.05 mmol), HOAt (0.123 g, 0.90 mmol), Et_3N (0.147 mL, 1.05 mmol), and 28% aqueous NH_3 (0.5 mL) were added and then stirred for further 0.5 h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated, and purified with silica gel column chromatography (silica gel 40 g, EtOAc/*n*-hexane = 1:2→1:0) to give **15** as a white wax (0.187 g, 39% for 2 steps). Compound **15**: $[\alpha]_D^{27} = +35.7$ (*c* 0.84, $CHCl_3$); IR (KBr): 2930, 1672, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.056 (3H, s), 0.069 (3H, s), 0.90 (9H, s), 1.16 (3H, d, *J* = 6.8 Hz), 3.27–3.32 (1H, m), 3.46 (3H, s), 3.54–3.60 (1H, m), 3.58 (3H, s), 3.76 (1H, dd, *J* = 11.4, 2.8 Hz), 3.85–3.92 (1H, m), 4.93 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ −5.43, −5.27, 15.08, 18.47, 25.97 (3C), 36.79, 55.04, 59.09, 64.16, 84.62, 94.22, 169.05, 171.59. HRMS (FAB) (*m/z*): calcd for $C_{15}H_{32}NO_4S_i$: 318.2101 $(M+H)^+$, found: 318.2135.

4.10. (3,5*R*)-Dimethoxy-(4*R*)-methyl-6-oxo-(2*E*)-hexenamide 3

To a solution of **15** (0.040 g, 0.126 mmol) in THF (1.5 mL) was treated HF·Py (0.1 mL) at 0 °C. After stirring at room temperature for 0.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in CH_2Cl_2 (1.5 mL) and treated with TPAP (tetrapropylammonium perruthenate) (0.004 g, 0.0114 mmol), NMO (0.030 g, 0.256 mmol), and MS-4 Å (0.020 g) at 0 °C. After stirring for 5 min, additional NMO (0.020 g, 0.171 mmol) and MS-4 Å (0.020 g) were added and stirred for further 5 min. Completion of the reaction was confirmed by TLC, the reaction mixture was passed through silica gel pad to remove the reagents (silica gel 2 g, EtOAc). The filtrate was concentrated to give (4*R*,5*R*)-**3** (0.008 g containing slight impurities, 32% for 2 steps), which was used for the next reaction quickly without further purification. (4*R*,5*R*)-**3**: IR (neat): 2940, 1731, 1662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (3H, d, *J* = 7.3 Hz), 3.44 (3H, s), 3.55 (1H, dd, *J* = 6.7, 2.7 Hz), 3.60 (3H, s), 3.54 (1H, dq, *J* = 7.3, 6.7 Hz), 5.00 (1H, s), 5.45 (2H, br s × 2), 9.59 (1H, d, *J* = 2.7 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.9, 36.4, 55.3, 58.5, 87.6, 93.9, 168.5, 171.1, 202.1. HRMS (FAB) (*m/z*): calcd for $C_9H_{16}NO_4$: 202.1079 $(M+H)^+$, found: 202.1098.

4.11. Methyl (3,5*R*)-dimethoxy-(4*R*)-methyl-6-oxo-(2*E*)-hexenoate 4

A mixture of **14** (0.253 g, 0.76 mmol) and $Et_3N{\cdot}(HF)_3$ (1.3 g, 7.6 mmol) in CH_2Cl_2 (4 mL) was stirred for 12 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with 7% aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude residue, which was chromatographed on silica gel (5 g, *n*-hexane/EtOAc = 3:1) to afford (+)-**16** (0.156 g, 94%) as a colorless oil. Compound (+)-**16**: $[\alpha]_D^{27} = +91.4$ (*c* 0.64, $CHCl_3$); IR (KBr): 3450, 1711, 1623, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (3H, d, *J* = 6.8 Hz), 3.24–3.32 (1H, m), 3.44–3.48 (1H, m), 3.45 (3H, s), 3.63 (3H, s),3.67–3.73 (1H, m), 3.69 (3H, s), 4.07–4.15 (1H, m), 5.05 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ14.5, 36.0, 51.2, 55.6, 58.1, 61.4, 83.6, 91.4, 168.6, 176.6. HRMS (FAB) calcd for $C_{10}H_{19}O_5$ $(M+H)^+$: 219.1232, found: 219.1191. A mixture of (+)-**16** (0.142 g, 0.65 mmol) and Dess–Martin reagent (0.708 g, 1.67 mmol) in CH_2Cl_2 (6 mL) was stirred for 2 h at room temperature. The reaction mixture was diluted with ether. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude residue, which was chromatographed on silica gel (5 g, *n*-hexane/EtOAc = 9:1) to provide a colorless oil (+)-**4** (0.125 g, 89%). Compound (+)-**4**: $[\alpha]_D^{27} = +104.7$ (*c* 0.55,

$CHCl_3$); IR (KBr): 1712, 1628, 1441, 1149, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, d, J = 7.2 Hz), 3.43 (3H, s), 3.56 (1H, dd, J = 2.4, 6.8 Hz), 3.64 (3H, s), 3.68 (3H, s), 4.48 (1H, dq, J = 6.8, 7.2 Hz), 5.07 (1H, s), 9.59 (1H, q, J = 2.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.9, 36.5, 51.0, 55.7, 58.6, 87.4, 91.9, 167.6, 174.4, 202.1. HRMS (FAB) (m/z): calcd for $C_{10}H_{17}O_5$ $(M+H)^+$: 217.1076, found: 217.1079.

4.12. (*S*)-4-Ethoxycarbonyl-2′-(1-benzothiazolylsulfanylmethylethyl)-2,4′-bithiazole 18

To a solution of (*S*)-**17** (0.540 g, 1.81 mmol), 2-mercaptobenzothiazole (0.363 g, 2.17 mmol) and triphenylphosphine (0.665 g, 2.53 mmol) in THF (10 mL) was added DEAD (40% toluene solution, 0.86 mL). After stirring for 0.5 h, the reaction mixture was concentrated and purified by silica gel column chromatography (silica gel 50 g, EtOAc/*n*-hexane = 1:95→1:1) to afford (*S*)-**18** (0.754 g, 93%) as a colorless oil. Compound (*S*)-**18**: $[\alpha]_D^{26} = -92.9$ (*c* 1.48, $CHCl_3$); IR (KBr): 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (3H, t, J = 7.2 Hz), 1.61 (3H, d, J = 6.8 Hz), 3.71–3.80 (2H, m), 3.85–3.94 (1H, m), 4.44 (2H, q, J = 7.2 Hz), 7.27 (1H, ddd, J = 8.4, 7.2, 1.2 Hz), 7.40 (1H, ddd, J = 8.4, 7.2, 1.2 Hz), 7.72 (1H, ddd, J = 8.0, 1.2, 0.4 Hz), 7.86 (1H, ddd, J = 8.0, 1.2, 0.4 Hz), 8.05 (1H, s), 8.16 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.3, 20.3, 38.3, 39.2, 61.4, 116.7, 120.9, 121.4, 124.2, 125.9, 127.6, 135.2, 147.8, 147.9, 153.0, 161.3, 163.3, 166.1, 174.1. HRMS (FAB) (m/z): calcd for $C_{19}H_{18}N_3O_2S_4$: 448.0282 $(M+H)^+$, found: 448.0273.

4.13. (*S*)-4-Benzothiazolylsulfanylmethyl-2′-(1-benzothiazolylsulfonylmethylethyl)-2,4′-bithiazole 19

To a solution of (*S*)-**18** (0.754 g, 1.69 mmol) in THF (10 mL) was added $LiBH_4$ (0.048 g, 2.19 mmol). After stirring for 2 h, the reaction was quenched with H_2O. The mixture was extracted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in EtOH (10 mL) and treated with 35% H_2O_2 (3 mL) and $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (0.208 g, 0.168 mmol). After stirring for 3 h, the mixture was diluted with EtOAc and washed with H_2O, 10% aqueous $Na_2S_2O_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was passed through silica gel pad (eluent; EtOAc) and again concentrated. The solution of the residue, 2-mercaptobenzothiazole (0.318 g, 1.90 mmol), and triphenylphosphine (0.569 g, 2.17 mmol) in THF (10 mL) was treated with DEAD (40% toluene solution, 0.855 mL). After stirring for 0.5 h, the mixture was concentrated and purified by silica gel column chromatography (silica gel 40 g, EtOAc/*n*-hexane = 5:95→8:92) to afford (*S*)-**19** (0.650 g, 66% for 3 steps) as a colorless amorphous solid. Compound (*S*)-**19**: $[\alpha]_D^{27} = -74.4$ (*c* 0.77, $CHCl_3$); IR (KBr): 3102, 2971, 2915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.62 (3H, d, J = 7.1 Hz), 3.77 (1H, dd, J = 14.7, 6.1 Hz), 3.98–4.06 (1H, m), 4.49 (1H, dd, J = 14.7, 7.1 Hz), 4.70 (1H, s), 7.26 (1H, s), 7.30–7.34 (1H, m), 7.39–7.51 (3H, m), 7.68 (1H, s), 7.75–7.81 (2H, m), 7.91–7.95 (1H, m), 8.03–8.08 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$): δ 22.1, 33.0, 33.7, 60.1,115.7, 117.8, 121.1, 121.6, 122.1, 124.4, 125.5, 126.1, 127.4, 128.0, 135.4, 136.9, 148.6, 152.1, 152.5, 153.1, 162.1, 165.6, 165.9, 171.9. HRMS (ESI) (m/z): calcd for $C_{24}H_{18}N_4O_2S_6$: 585.9754 $(M)^+$, found: 585.9769.

4.14. 4-(2″-Benzothiazolyl)sulfanylmethyl-2′-[(1‴*S*),6‴-dimethylhepta-(2‴*E*),(4‴*E*)-dienyl]-2,4′-bithiazole 20

To a solution of (*S*)-**19** (0.198 g, 0.337 mmol) and (2*E*)-4-methylpentenal (0.066 g, 0.675 mmol) in THF (2 mL) was added LHMDS (1.06 M THF solution, 0.65 mL) at −78 °C. After 5 min, additional LHMDS (0.05 mL) was added, and the mixture was stirred for further 10 min. The reaction was quenched with saturated aqueous NH_4Cl and warmed to room temperature. The mixture was extracted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (silica gel 20 g, EtOAc/*n*-hexane = 1:4) to afford a mixture of **20** and **21** (3.3:1 mixture of *E*:*Z* by ^1H NMR, 0.122 g, 77%) as a colorless amorphous. The (*Z*)-isomer **21** was removed by careful silica gel chromatography before the next step. (*E*)-isomer **20**: $[\alpha]_D^{27} = +7.8$ (*c* 0.525, $CHCl_3$); IR (KBr): 2959, 1459, 1426 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (6H, d, J = 6.8 Hz), 1.53 (3H, d, J = 6.8 Hz), 2.29–2.38 (1H, m), 3.90–3.97 (1H, m), 4.76 (2H, s), 5.67 (1H, dd, J = 15.2, 6.8 Hz), 5.78 (1H, dd, J = 15.2, 7.6 Hz), 6.01 (1H, ddd, J = 15.6, 10.4, 0.8 Hz), 6.17 (1H, dd, J = 15.6, 10.4 Hz), 7.24–7.30 (1H, m), 7.34 (1H, s), 7.40–7.46 (1H, m), 7.73–7.76 (1H, m), 7.83 (1H, s), 7.89–7.91 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.8, 22.2, 22.2, 31.0, 33.0, 41.2, 112.2, 117.6, 121.0, 121.3, 121.5, 124.3, 124.6, 126.0, 126.5, 127.1, 131.9, 132.4, 135.4, 142.4, 153.0, 176.4, 190.8. HRMS (ESI) (m/z): calcd for $C_{23}H_{23}N_3S_4$: 469.0775 $(M)^+$, found: 469.0775 (*Z*)-isomer **21**: $[\alpha]_D^{27} = -82.3$ (*c* 0.81, $CHCl_3$); IR (neat): 2959, 1457, 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (6H, dd, J = 6.8, 2.0 Hz), 1.51 (3H, d, J = 7.0 Hz), 2.31–2.42 (1H, m), 4.29–4.38 (1H, d-sep, J = 6.8, 1.0 Hz), 4.76 (2H, s), 5.47 (1H, dd, J = 10.1, 10.1 Hz), 5.77 (1H, dd, J = 15.1, 6.5 Hz), 6.10 (1H, dd, J = 11.0 Hz), 6.33 (1H, dd, J = 15.1, 11.0 Hz), 7.28–7.32 (1H, m), 7.33 (1H, s), 7.40–7.44 (1H, m), 7.74 (1H, d, J = 8.1 Hz), 7.82 (1H, s), 7.90 (1H, d, J = 8.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.7, 22.2, 22.3, 31.4, 33.1, 36.9, 115.6, 117.5, 121.0, 121.6, 121.9, 124.3, 126.1, 130.4, 130.7, 135.5, 144.6, 148.7, 152.2, 153.1, 163.2, 166.0, 176.3. HRMS (ESI) (m/z): calcd for $C_{23}H_{23}N_3S_4$: 469.0775 $(M)^+$, found: 469.0746.

4.15. 4-(2″-Benzothiazolyl)sulfonylmethyl-2′-[(1‴*S*),6‴-dimethylhepta-(2‴*E*),(4‴*E*)-dienyl]-2,4′-bithiazole 6

A solution of **20** (0.062 g, 0.132 mmol) in EtOH (3 mL) was treated with 35% H_2O_2 (1 mL) and $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (0.033 g, 0.0264 mmol). The reaction mixture was stirred for 10 h and then diluted with H_2O. The mixture was extracted with EtOAc and washed with 10% aqueous $Na_2S_2O_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (silica gel 15 g, EtOAc/*n*-hexane = 10:90→80:20) to afford (*S*)-**6** (0.051 g, 77%) as colorless amorphous. Compound (*S*)-**6**: $[\alpha]_D^{25} = -3.6$ (*c* 0.60, $CHCl_3$); IR (CCl_4): 1338, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (6H, d, J = 6.8 Hz), 1.50 (3H, d, J = 7.2 Hz), 2.29–2.38 (1H, m), 3.83–3.90 (1H, m), 4.98 (2H, s), 5.68 (1H, dd, J = 15.6, 7.2 Hz), 5.74 (1H, dd, J = 15.6, 7.6 Hz), 6.00 (1H, dd, J = 15.6, 9.2 Hz), 6.15 (1H, dd, J = 15.6, 10.4 Hz), 7.18 (1H, s), 7.35 (1H, s), 7.54–7.58 (1H, m), 7.62–7.66 (1H, m), 7.91–7.93 (1H, m), 8.26–8.28 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.7, 22.2, 22.4, 31.1, 41.1, 57.0, 115.7, 121.4, 122.2, 123.1, 125.6, 126.4, 127.6, 127.9, 131.9, 132.3, 137.3, 142.4, 142.7, 152.7, 163.3, 171.8, 176.3. HRMS (ESI) (m/z): calcd for $C_{23}H_{23}N_3O_2S_4$: 501.0670 $(M)^+$, found: 501.0673.

4.16. Myxothiazol A 1

To a solution of (*S*)-**6** (0.047 g, 0.0929 mmol) in THF (1 mL) was added LHMDS (1.06 M THF solution, 0.092 mL) at −78 °C under a N_2 atmosphere. The mixture was gradually warmed to −30 °C over 30 min, then cooled to −78 °C and (4*R*,5*R*)-**3** (0.017 g, 0.0845 mmol) in THF (0.5 mL) was added. The reaction mixture was gradually warmed to −40 °C, and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (silica gel

10 g, EtOAc/*n*-hexane = 1:1→1:0) to give myxothiazol A **1** (0.025 g, 61% from (4*R*,5*R*)-**3**) as colorless oil. myxothiazol A **1**: $[\alpha]_D^{26} = +33.5$ (*c* 0.70, MeOH); IR (neat): 2963, 1667, 1598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (6H, d, *J* = 6.8 Hz), 1.17 (3H, d, *J* = 6.8 Hz), 1.55 (3H, d, *J* = 6.8 Hz), 2.30–2.39 (1H, m), 3.34 (3H, s), 3.58 (3H, s), 3.79–3.83 (1H, m), 3.94 (1H, dq, *J* = 6.8, 6.8 Hz), 4.10 (1H, dq, *J* = 6.8, 6.8 Hz), 4.94 (1H, s), 5.69 (1H, dd, *J* = 15.1, 6.8 Hz), 5.80 (1H, dd, *J* = 15.1, 7.4 Hz), 6.02 (1H, dd, *J* = 15.1, 10.4 Hz), 6.19 (1H, dd, *J* = 15.1, 10.4 Hz), 6.42 (1H, dd, *J* = 15.6, 8.1 Hz), 6.57 (1H, d, *J* = 15.6 Hz), 7.12 (1H, s), 7.86 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.3, 20.9, 22.3, 31.1, 39.7, 41.3, 55.1, 56.8, 85.2, 94.3, 115.2, 115.6, 126.0, 126.6, 131.3, 131.9, 132.6, 142.4, 149.0, 154.4, 162.6, 169.1, 171.7, 176.3. HRMS (ESI) (*m*/*z*): calcd for $C_{25}H_{33}N_3O_3S_2$: 487.1963 $(M)^+$, found: 487.1986.

4.17. Myxothiazol Z 2

To a solution of (*S*)-**6** (0.096 g, 0.191 mmol) in THF (1.5 mL) was added LHMDS (1.06 M THF solution, 0.19 mL) at −78 °C under N_2 atmosphere. The reaction mixture was gradually warmed up to −20 °C over 30 min and then cooled to −60 °C. To this mixture was added (4*R*,5*R*)-**4** (0.050 g, 0.230 mmol) in THF (0.5 mL). After stirring at −60 °C for 10 min, the reaction was quenched with saturated aqueous NH_4Cl at −15 °C. The mixture was extracted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (silica gel 15 g, EtOAc/*n*-hexane = 17:83→25:75) to afford myxothiazol Z **2** (9:1 of *E*:*Z* mixture by ^1H NMR, 0.070 g, 73%). The (6*Z*) isomer was carefully removed by preparative TLC (EtOAc/toluene). myxothiazol Z (**2**): $[\alpha]_D^{27} = +85.7$ (*c* 1.66, MeOH); IR (neat): 2963, 1711, 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (6H, d, *J* = 6.5 Hz), 1.22 (3H, d, *J* = 7.0 Hz), 1.55 (3H, d, *J* = 7.0 Hz), 2.31–2.41 (1H, m), 3.33 (3H, s), 3.60 (3H, s), 3.66 (3H, s), 3.81 (1H, dd, *J* = 8.1, 8.1 Hz), 3.91–3.98 (1H, m), 4.14–4.21 (1H, m), 4.96 (1H, s), 5.68 (1H, dd, *J* = 15.1, 6.5 Hz), 5.80 (1H, dd, *J* = 15.1, 7.0 Hz), 6.02 (1H, dd, *J* = 14.6, 10.2 Hz), 6.18 (1H, dd, *J* = 15.1, 10.2 Hz), 6.40 (1H, dd, *J* = 15.6, 7.6 Hz), 6.57 (1H, d, *J* = 15.6 Hz), 7.09 (1H, s), 7.85 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1, 20.9, 22.3 (2C), 31.1, 39.9, 41.3, 50.8, 55.5, 57.0, 84.4, 91.1, 115.0, 115.5, 125.6, 126.6, 131.7, 131.9, 132.6, 142.4, 149.0, 154.5, 162.5, 167.7, 176.2, 176.7. HRMS (ESI) (*m*/*z*): calcd for $C_{26}H_{34}N_2O_4S_2$: 502.1960 $(M)^+$, found: 502.1966.

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