Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 6579–6593

TETRAHEDRON

Total synthesis of mycothiazole, a polyketide heterocycle from marine sponges

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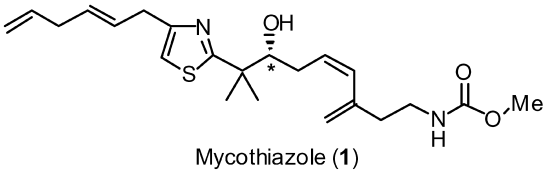
Received 18 April 2003; revised 29 May 2003; accepted 26 June 2003

Abstract—Mycothiazole isolated from marine sponges has been efficiently synthesized in a convergent manner. The key reactions involve the thiazole synthesis by dehydrogenation of the thiazolidine with chemical manganese dioxide (CMD), the Stille coupling, and the Nagao asymmetric acetate aldol reaction using the chiral 1,3-thiazolidine-2-thione. This synthesis clearly established the absolute configuration of natural mycothiazole to be (*R*).

1. Introduction

Mycothiazole was isolated from a marine sponge *Spongia mycofijiensis* collected from Vanuatu by Crews and co-workers[1] in 1988. The same compound was isolated from a marine sponge of the genus *Dactylospongia* collected off the coast of the Vanuatu islands[2] in 2001. Mycothiazole exhibited anthelminthic activity in vitro while high toxicity was observed in mice.[1] National Cancer Institute (NCI) in the United States reported that mycothiazole had selective toxicity toward lung cancer cells.[3] The unique structure of mycothiazole is featured by an unusual thiazole ring, derived from cysteine, which is imbedded between two acyclic polyketide chains. Mycothiazole has only one stereogenic center, but its absolute configuration had remained to be determined. Our continuing interests on the synthesis of structurally unique and biologically interesting marine natural products[4,5] led us to synthesize mycothiazole. We now describe an efficient total synthesis of both of (*R*) and (*S*)-mycothiazoles, which culminated in the determination of the absolute configuration of natural mycothiazole to be (*R*), as shown in the structure **1** (Fig. 1).[6,7] The key reactions utilized are the dehydrogenation of the thiazolidine with chemical manganese dioxide (CMD),[8] the Stille coupling,[9] and the Nagao asymmetric acetate aldol reaction using the chiral 1,3-thiazolidine-2-thione.[10]



Mycothiazole (**1**)

Figure 1. Structure of mycothiazole.

2. Synthetic strategy

Our synthetic strategy for mycothiazole involved the dehydrogenation of the thiazolidine **4**, prepared from methyl pivalate (**2**) and L-cysteine methyl ester (**3**), to the corresponding thiazole utilizing CMD. The successive Stille coupling of the bromide **5** with the stannanes **6** and then **7** would give the isolated diene **8**. The Nagao acetate aldol reaction of **8** with the (*S*) or (*R*)-thiazolidinethione **9** would give the corresponding aldol with (*R*) or (*S*)-configuration, respectively. Construction of the whole carbon skeleton could be achieved by the Stille coupling between the (*R*) or (*S*)-vinyl iodide **10** and the stannane **11**, and the target mycothiazole ((*R*)-**1** or (*S*)-**1**) would be obtained after deprotection (Scheme 1).

3. Synthesis of the thiazole fragment

Total synthesis of mycothiazole commenced with the construction of the requisite thiazole skeleton, which was carried out by use of the CMD method developed by our group,[8a] shown in Scheme 2. The CMD method has an advantage of shorter steps with simplicity and little racemization occurs compared to the well-known Hantzsch method.[11] Thus, methyl hydroxypivalate (**2**) was silylated

Keywords: chemical manganese dioxide; Stille coupling; aldol reaction; marine natural product; absolute configuration.
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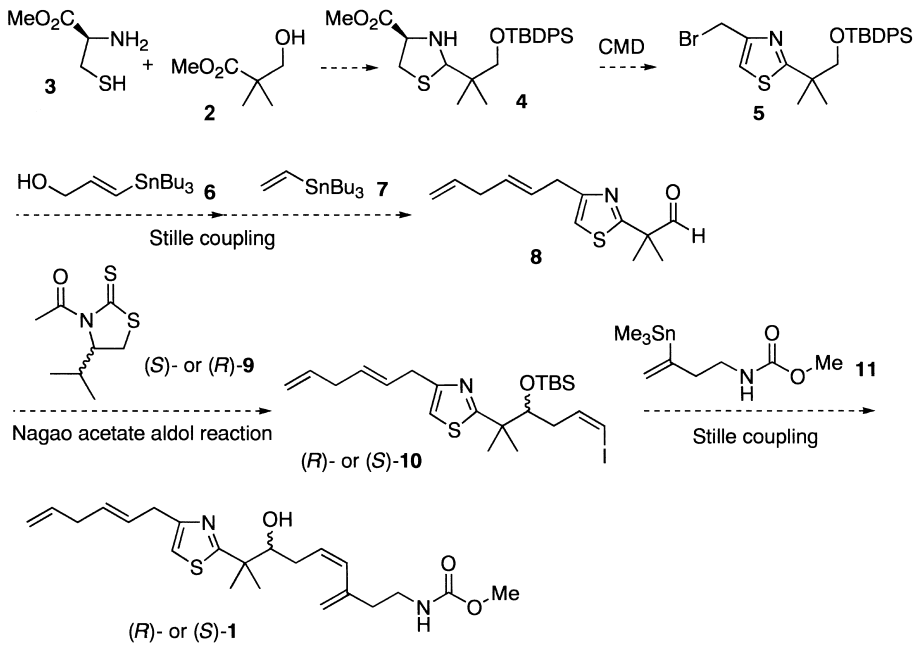
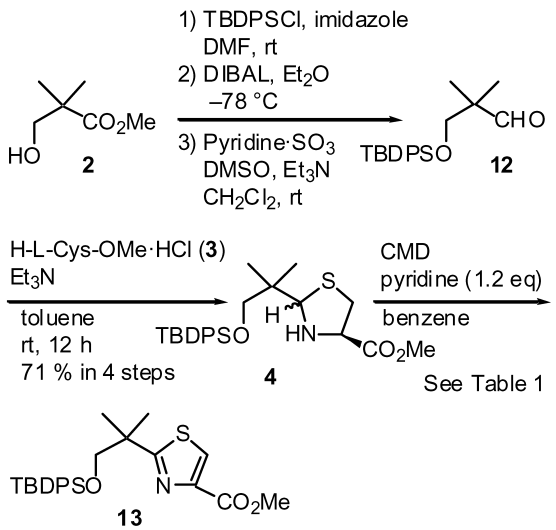
doi:10.1016/S0040-4020(03)01020-2



Scheme 1. Synthetic strategy for mycothiazole.



Scheme 2. Preparation of the thiazole **13** by CMD dehydrogenation.

with *tert*-butyldiphenylsilyl chloride (TBDPSCl) followed by reduction with diisobutylaluminum hydride (DIBAL) and then DMSO oxidation using sulfur trioxide–pyridine (the Parikh–Doering method), giving the O-protected aldehyde **12**. Condensation with L-cysteine methyl ester (**3**) afforded the thiazolidine **4** in 71% yield from **2**. Dehydrogenation of **4** with commercially available CMD[12] sluggishly proceeded under the standard conditions[8a] to give the thiazole **13** in miserable yield with recovery of the aldehyde **12** (entry 1 in Table 1). Use of manganese dioxide prepared by the Goldman's procedure[13] afforded the thiazole **13** in better yield, but it lacked reproducibility (entries 3 and 4). We reasoned that low activity of commercially available CMD would be due to a little quantity of moisture that CMD absorbed during storage. Thus CMD was activated by azeotropic removal of water before the reaction and used for dehydrogenation. As shown in Table 1 (entries 5–7), the dehydrogenation proceeded to a better extent with good reproducibility even on a larger scale (entry 7). In this particular case, the thiazole synthesis using the Hantzch method did not proceed at all.[14]

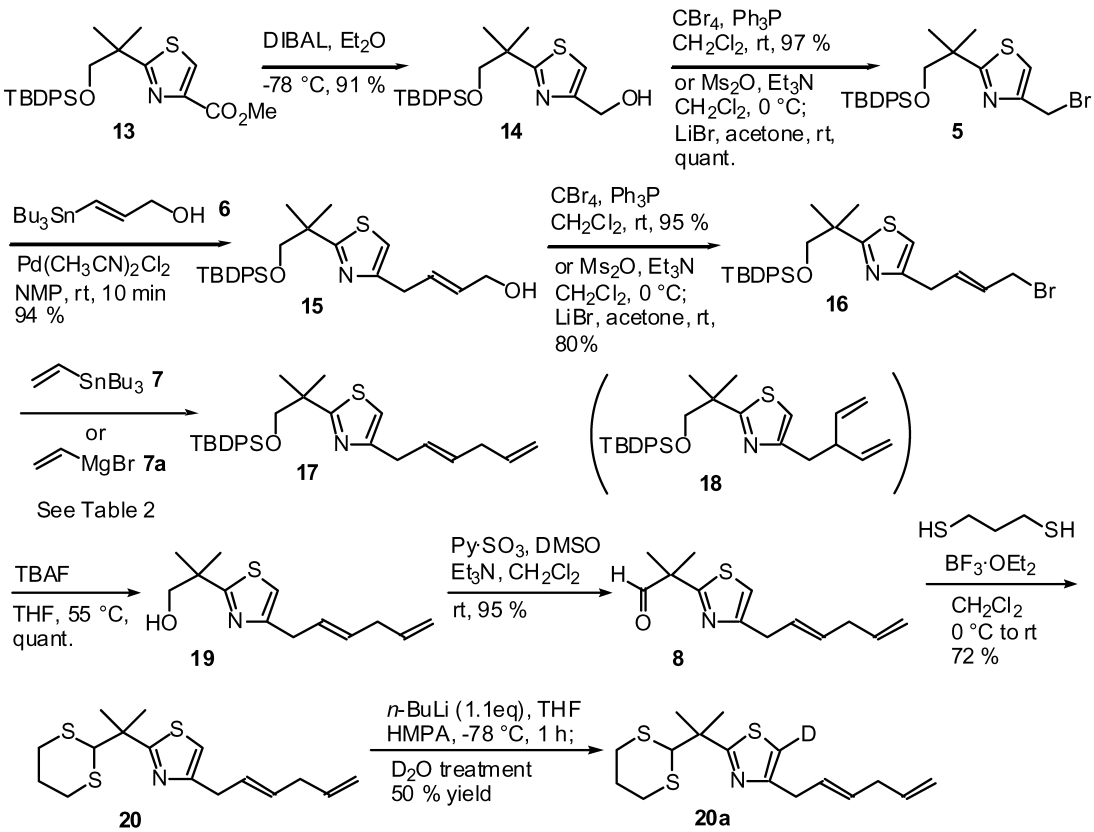
Table 1. Conversion of the thiazolidine **4** to the thiazole **13** with CMD

Entry	Thiazolidine **4** (mmol)	MnO_2 (equiv.)	Reaction conditions	Yield (%) of thiazole **13**
1	0.25	100	55°C, 12 h	Trace[a]
2	0.25	100	Reflux, 6 h	15
3	0.25	25[b]	55°C, 2 h	61
4	6.6	50[b]	55°C, 48 h	20
5	0.25	60[c]	Reflux, 12 h	62
6	2.3	50[c]	Reflux, 15 h	55
7	32.0	50[c]	Reflux, 2 h	50

[a] Aldehyde **12** was recovered in 65%.
[b] Activated MnO_2 was prepared by the Goldman method.
[c] CMD purchased from Wako Pure Chemical Industries, Ltd was activated by azeotropic removal of H_2O before the reaction.

4. Synthesis of the left fragment

The left fragment **8** was synthesized from the thiazole **13** utilizing the Stille coupling, shown in Scheme 3. The thiazole **13** was first reduced with DIBAL to give the alcohol **14**, which was converted to the bromide **5** in two ways. The first method using carbon tetrabromide and triphenylphosphine afforded the bromide **5** in excellent yield, but the yield decreased on a large scale probably due to the formation of the corresponding phosphonium salt because of higher reactivity of the bromide **5**. The second method by mesylation and then treating with lithium bromide[15] gave the bromide **5** in almost quantitative yield with good reproducibility. The Stille coupling of the



Scheme 3. Preparation of the left fragment **8**.

bromide **5** with the vinylstannane **6**[16] prepared by hydrostannylation of propargyl alcohol smoothly proceeded to give the alcohol **15** in excellent yield. Conversion of the alcohol **15** to the corresponding bromide **16** was carried out by the two methods as above in good yields.

The first attempt of the Stille coupling between the bromide **16** and the vinyltributylstannane **7** afforded the desired the S_N2 type coupling product **17** together with a small amount of the S_N2' type coupling product **18**. Thus the reaction conditions of this Stille coupling was investigated as shown in Table 2. Although the formation of the S_N2' type coupling product **18** could not be suppressed completely, the best result was obtained by use of $Pd(CH_3CN)_2Cl_2$ in *N*-methyl-2-pyrrolidone (NMP) (entry 1). Interestingly, addition of ligands retarded the reaction velocity and lowered the yield (entries 7 and 8). The use of the Grignard reagent **7a** in place of the stannane **7** afforded the S_N2' type product **18** as the major product (entry 9) while addition of the copper salt mainly afforded the S_N2 type product **17** (entries 10 and 11).

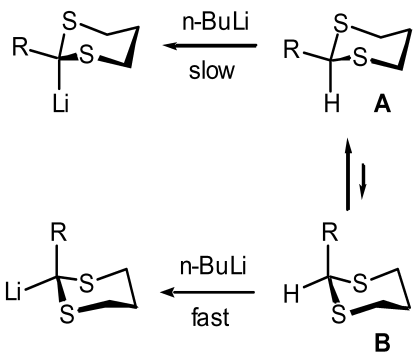
Deprotection of the TBDPS group from **17** required heating with tetrabutylammonium fluoride (TBAF) to give the alcohol **19**, which was oxidized with the Parikh–Doering method to give the aldehyde **8**.

In addition, the aldehyde **8** was converted to the 1,3-dithiane **20** by treatment with 1,3-propanedithiol. Although the C_2-position of the dithiane ring of **20** is sterically hindered, we thought that the alkylation at the C_2-position might occur if the anion could be formed. As a preliminary experiment for this dithiane-coupling route, the formation of the anion at

Table 2. Preparation of the isolated diene **17** by the Stille coupling

Entry	Electrophile	Catalyst (10 mol%)	Ligand (20 mol%)	Solvent	Reaction conditions	Yield (%) of **17**[a]
1	**7**	$Pd(CH_3CN)_2Cl_2$	–	NMP	rt, 40 min	85[b]
2	**7**	$Pd(CH_3CN)_2Cl_2$	–	DMF	rt, 20 min	61[b]
3	**7**	$Pd(CH_3CN)_2Cl_2$	–	THF	rt, 3 h; 50°, 4 h	38[b]
4	**7**	$Pd(Ph_3P)_4$	–	Toluene	80°C, 12 h	0
5	**7**	$Pd(Ph_3P)_2Cl_2$	–	NMP	rt, 12 h; 80°C, 3 h	36[b]
6	**7**	$Pd(dba)_2$	–	NMP	rt, 1 h	48[b]
7	**7**	$Pd(dba)_2$	Ph_3As	NMP	rt, 12 h	20[b]
8	**7**	$Pd(dba)_2$	BINAP	NMP	rt, 12 h; 60°C, 5 h	62[b]
9	**7a**	–	–	THF	50°C, 1 day	17 (60)
10	**7a**	CuI	–	THF	−78°C, 30 min	67 (27)
11	**7a**	Li_2CuCl_4	–	THF	−78°C, 30 min	66[b]

[a] The yields in the parentheses are the S_N2' product **18**.
[b] A trace amount (less than 10%) of **18** was also obtained.



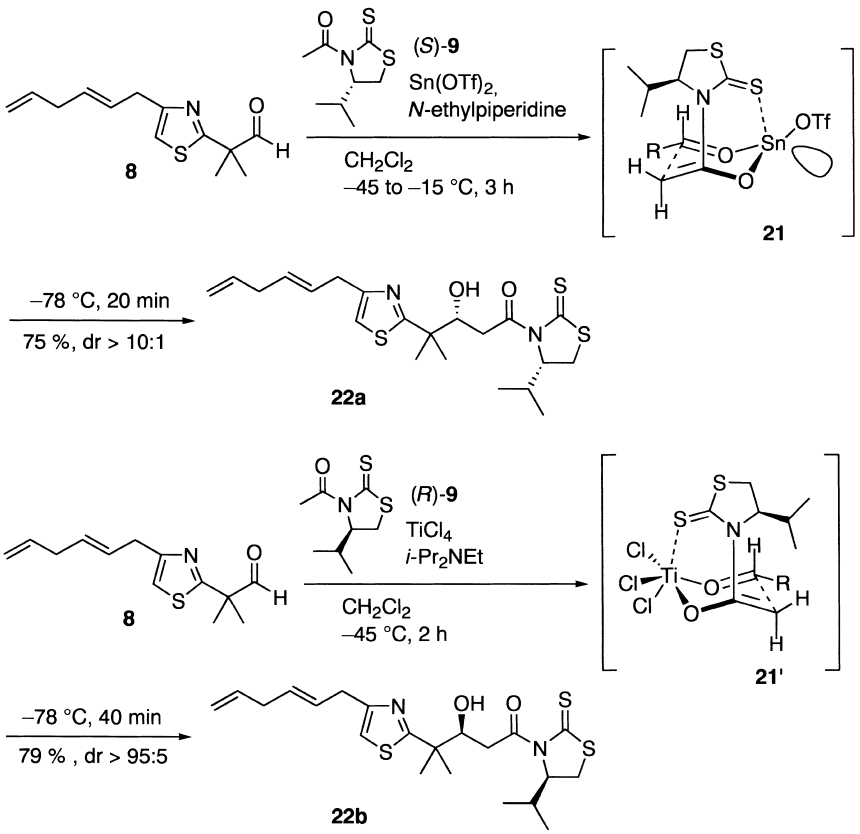
Scheme 4. Conformation of the lithiated dithiane.

the C_2-position was investigated by treating **20** with BuLi–HMPA and then D_2O. Investigation of the product **20a** by ^1H NMR spectra revealed that the deuteration occurred at the C_5-position of the thiazole ring, over 85%, but not at the C_2-position of the dithiane ring. In general, the equatorial anion of the dithiane is preferred to the axial one.[17] However, the reactant containing the bulky substituents at the C_2-position of the dithiane such as **20** tends to hold its bulky substituents to be equatorial as a preferred conformation (**A**, Scheme 4). Thus, the anion is not easily generated because the abstraction of equatorial proton requires the ring inversion (**B**, Scheme 4) or the direct abstraction of the axial proton. The acidity of the methine of the dithiane is not so high (pK_a ca. 31) and the dithiane **20** will not easily undergo the ring inversion to hold the bulky thiazole substituent axial. Thus, the proton abstraction occurred at the C_5 position of the thiazole.[18] In addition, the low recovery (50%) of the reactant in the deuteration suggested that the left fragment was labile under strongly alkaline conditions. Since preliminary experiments of the alkylation also failed, the dithiane-coupling route was abandoned.

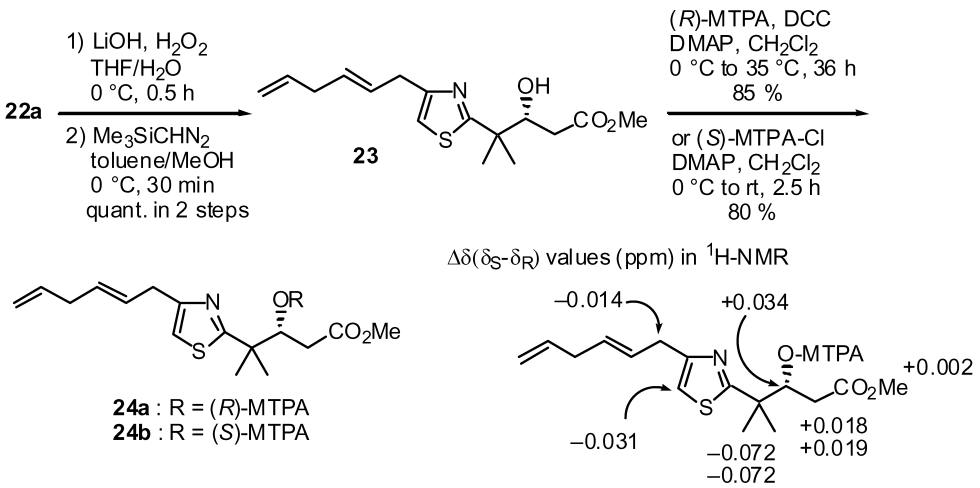
5. The Nagao asymmetric acetate aldol reaction

The stereoselective construction of the stereogenic center of mycothiazole was accomplished by the use of Nagao asymmetric acetate aldol reaction, shown in Scheme 5. Although the absolute configuration of **1** was not known, we first aimed to construct (*R*)-mycothiazole ((*R*)-**1**) by use of the (*S*)-thiazolidinethione ((*S*)-**9**). The aldehyde **8** smoothly underwent the aldol reaction with the (*S*)-**9**, obtained from (*S*)-valine,[19,20] using stannous triflate ($Sn(OTf)_2$) and *N*-ethylpiperidine[10] to give **22a** with good diastereoselectivity (>10:1). The good stereoselectivity is explained by the formation of the tin enolate **21**. Incidentally, the enantiomer of **22a** (**22b**) was obtained with excellent diastereoselectivity (>95:5) by use of (*R*)-thiazolidinethione ((*R*)-**9**) together with titanium tetrachloride and diisopropylethylamine via the titanium enolate **21′**.[21]

The absolute configuration of the newly created stereogenic center derived from the tin enolate **21** was expected to be (*R*) and unambiguously determined by use of the modified Mosher method,[22] as shown in Scheme 6. Removal of the chiral auxiliary from **22a** under alkaline conditions[23] followed by methyl esterification with trimethylsilyldiazomethane[24] afforded the hydroxy ester **23**, which was



Scheme 5. The Nagao acetate aldol reaction.



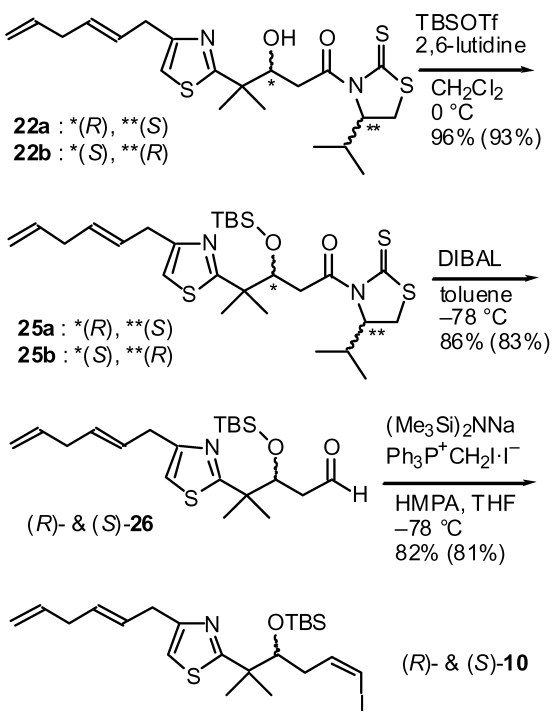
Scheme 6. Confirmation of the absolute configuration of the aldol **22a**.

converted to (*R*) and (*S*)-MTPA esters (**24**). Determination of the absolute configuration of **24** was carried out by comparison of ^{1}H NMR spectra, shown in Scheme 6.

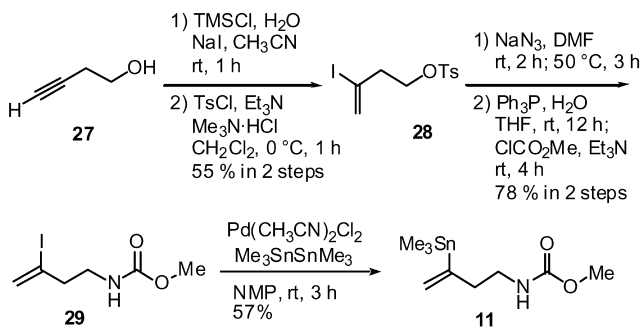
The hydroxy group of the aldol product **22a** was protected as the *tert*-butyldimethylsilyl (TBS) group. The TBS derivative **25a** was reduced with DIBAL to give the aldehyde (*R*)-**26**,[25] which underwent the Wittig reaction under salt-free conditions[26] to give the (*Z*)-vinyl iodide (*R*)-**10** as a single isomer (Scheme 7). The enantiomer of **10** ((*S*)-**10**) was anaologously prepared from **22b**.

6. Synthesis of the right fragment

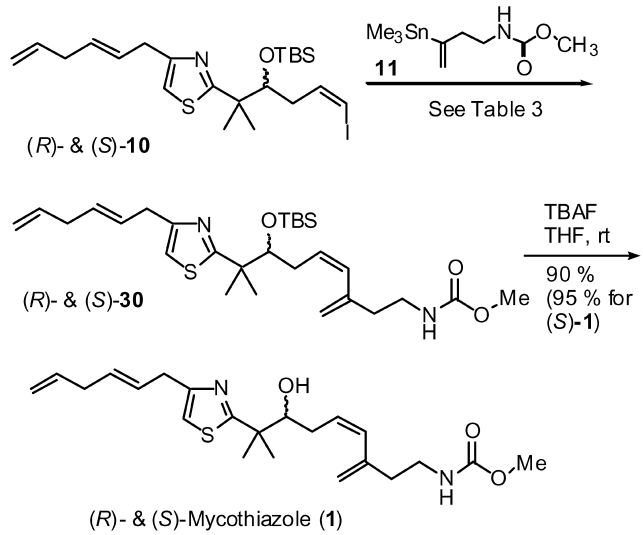
The required right fragment **11** was prepared starting from 3-butyn-1-ol (**27**), which underwent the Markovnikov addition of hydrogen iodide[27] and then tosylation[28] to give the tosylate **28**, shown in Scheme 8. Replacement of the tosyl function with the azide one, reduction with triphenylphosphine, followed by treatment with methyl chlorocarbonate in a single pot furnished the vinyl iodide **29**, which was converted to the required stannane derivative **11** by use of hexamethylditin and $Pd(CH_3CN)_2Cl_2$.[29]



Scheme 7. Preparation of the vinyl iodides (*R*)- and (*S*)-**10**. Yields in parentheses correspond to those of **25b**, (*S*)-**26**, and (*S*)-**10**.



Scheme 8. Preparation of the right fragment **11**.



Scheme 9. Total synthesis of mycothiazole.

Table 3. The Stille coupling of (*R*)- and (*S*)-**10** with **11**

Entry	Reagents	Conditions	Yield (%)
1	$Pd(CH_3CN)_2Cl_2$ (20 mol%) NMP	rt to 50°C	0
2	$Pd(dba)_2$ (40 mol%) $CdCl_2$ (1.0 equiv.) *i*-Pr_2NEt (30 mol%) NMP	rt, 7 h	25
3	$Pd(Ph_3P)_4$ (40 mol%) CuCl (5.0 equiv.) LiCl (6.0 equiv.), DMSO	rt, 15 h	63 (38)[a]

[a] (*S*)-**10** was used.

7. Total synthesis of mycothiazole

With the requisite left and right fragments in hand, the construction of the full carbon skeleton was carried out (Scheme 9). The first attempt to couple (*R*)-**10** with **11** using $Pd(CH_3CN)_2Cl_2$ completely failed to give the diene **30**, as shown in Table 3. Addition of $CdCl_2$[30] to accelerate the trans-metalation gave the diene **30** in low yield. The most favorable result was obtained by use of Corey's conditions,[31] and the desired coupling product (*R*)-**30** was formed in 63% yield. Finally, treatment of (*R*)-**30** with TBAF afforded (*R*)-mycothiazole (**1**) in good yield. The synthetic mycothiazole was identified with the natural one by ^1H- and ^{13}C NMR, IR, and HRMS spectral data. However, the specific rotation of the synthetic mycothiazole was different from each other though the sign was the same: $[\alpha]_D^{23}=-26.0$ (*c* 0.6, $CHCl_3$) for synthetic one; $[\alpha]_D^{20}=-3.8$ (*c* 2.9, $CHCl_3$) for natural one. The reason for this discrepancy is not clear, but might be due to the labile nature of mycothiazole,[32] contamination of artifacts from mycothiazole, or the difference of the concentration on the measurement of the specific rotation. Furthermore, (*S*)-mycothiazole was similarly prepared from (*S*)-**10** and **11** in 2 steps. The specific rotation of (*S*)-**1** was found to be $[\alpha]_D^{23}=+22.0$ (*c* 0.6, $CHCl_3$), which clearly indicated natural mycothiazole to have negative specific rotation in $CHCl_3$.

In summary, we have accomplished the first total synthesis of mycothiazole in both (*R*) and (*S*)-forms and established the absolute configuration of natural mycothiazole to be (*R*). The synthesis demonstrates the utilities of the Nagao acetate aldol reaction and cuprous chloride accelerated Stille coupling with a 1-substituted vinylstannane and a (*Z*)-vinyl iodide. Furthermore, the azeotropic activation of commercially available CMD was found to be effective in the CMD-mediated thiazole synthesis of reproducibility even on a large scale.

8. Experimental

8.1. General

Melting points were determined on a YANAGIMOTO micro melting point apparatus (hot plate) and are uncorrected. Infrared (IR) spectra were measured on a NaCl plate with a SHIMADZU FTIR-8100 spectrometer. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter with sodium lamp (λ=589 nm, D line) and were recorded as follows: $[\alpha]_D^T$ (*c* g/100 mL, solvent). ^1H and ^{13}C NMR spectra were recorded on a JEOL EX-270 spectrometer at 270 and 67.8 MHz, respectively, and were obtained at the indicated field as solution in deuterochloroform ($CDCl_3$) unless otherwise indicated. Chemical shifts were reported in parts per million (ppm, δ) from tetramethylsilane or $CHCl_3$ as internal standard. Spectra splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. Mass spectra were obtained on a JEOL JMS-SX 102A (EI) and JMS-AX 505HA (FAB) spectrometer. Column chromatography was performed with silica gel BW-820 MH or BW-200 (Fuji Davison Co.). Flash column chromatography was performed with silica gel 60 particle size 40–63 μm (Cica-MERCK). HPLC was carried out with a JASCO UV-970 (detector) and PU-980 (pump) high pressure liquid chromatography.

Solvents for extraction and chromatography were reagent grade and distilled from the indicated drying agents: tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone ketyl. Diethyl ether (Et_2O) was distilled from lithium aluminum hydride. Dichloromethane (CH_2Cl_2), toluene, acetone, and acetonitrile (CH_3CN) were dried by distillation from calcium hydride. Hexamethylphosphoramide (HMPA), *N*-methyl-2-pyrrolidone (NMP), dimethyl sulfoxide (DMSO), and methanol (MeOH) were distilled from calcium hydride and stored over 4 Å molecular sieves. *N*-Ethylpiperidine was distilled from calcium hydride and stored over sodium hydroxide. Triethylamine (Et_3N) was dried over sodium hydroxide. All other commercially available reagents were used as received.

8.1.1. 3-*tert*-Butyldiphenylsilyloxy-2,2-dimethylpropanal (12). To a stirred solution of methyl hydroxypivalate (**2**) (20 g, 0.151 mol) in DMF (300 mL) was added TBDPSCl (41.2 mL, 0.155 mol) and imidazole (24.7 g, 0.363 mol) at 0°C. After stirring for 14 h at room temperature, 1 M aqueous $KHSO_4$ (300 mL) was added, and the mixture was extracted with EtOAc (500 mL). The organic layer was washed with 1 M $KHSO_4$ (2×100 mL), H_2O (100 mL), and saturated brine (100 mL), and dried over $MgSO_4$. Filtration and concentration in vacuo gave the crude TBDPS ether of **2** (67 g, quant.) as a colorless oil, which was used in the next reaction without further purification. An analytical sample was obtained by column chromatography (silica gel BW-820 MH, hexane/ether=8:1): IR ν_{max} (neat) cm^{-1} 1736, 1473, 1429, 1238, 1192, 1153, 1113, 702; ^1H NMR ($CDCl_3$) δ 1.03 (9H, s, Bu^t), 1.19 (6H, s, CH_3×2), 3.64 (2H, s, TBDPSOCH_2), 3.67 (3H, s, CO_2CH_3), 7.34–7.49 (m, 6H, Ph), 7.64–7.70 (m, 4H, Ph). Anal. calcd for $C_{22}H_{30}O_3Si$: C, 71.31; H, 8.16. Found: C, 71.41; H, 8.19.

To a stirred solution of the above crude TBDPS ether of **2** (19.2 g, 51.8 mmol) in ether (100 mL) was added dropwise DIBAL (0.94 M in hexane, 138 mL, 129.6 mmol) at −78°C under argon. After stirring for 30 min at −78°C, the mixture

was treated with 1 M aqueous $KHSO_4$ (100 mL) and warmed to room temperature. After stirring for 1 h, the mixture was extracted with EtOAc (3×100 mL). The combined extracts were washed with 1 M aqueous $KHSO_4$ (3×50 mL), H_2O (50 mL), and saturated brine (50 mL), and dried over Na_2SO_4. Filtration and concentration in vacuo gave the crude alcohol as a colorless oil (18.5 g), which was used in the next reaction without further purification. An analytical sample was obtained by column chromatography (silica gel BW-820 MH, hexane/ether=5:1): IR ν_{max} (neat) cm^{-1} 3431, 1473, 1427, 1113, 825, 702; ^1H NMR ($CDCl_3$) δ 0.89 (6H, s, C*H*$_3$×2), 1.07 (9H, s, *Bu*^{t}), 2.38 (1H, t, *J*=5.9 Hz, disappeared with D_2O, O*H*), 3.48, (2H, s, TBDPSOC*H*$_2$), 3.51 (2H, d, *J*=5.6 Hz, C*H*$_2$OH), 7.34–7.49 (6H, m, Ph), 7.64–7.70 (4H, m, Ph). Anal. calcd for $C_{21}H_{30}O_2Si$: C, 73.63; H, 8.83. Found: C, 73.34; H, 8.64.

To a stirred solution of the above crude alcohol (18.5 g) and Et_3N (21.7 mL, 155 mmol) in CH_2Cl_2 (150 mL) at 0°C was added a solution of pyridine·SO_3 (24.7 g, 155 mmol) in DMSO (150 mL). The resulting solution was stirred at room temperature for 20 min and then quenched with saturated aqueous $NaHCO_3$ (150 mL). After CH_2Cl_2 was removed in vacuo, the residue was extracted with ether (3×100 mL). The combined extracts were washed with 1 M aqueous $KHSO_4$ (2×50 mL) and saturated brine (50 mL), and dried over $MgSO_4$. Filtration and concentration in vacuo gave the crude aldehyde **12** (13.5 g) as a pale yellow oil. This material was used in the next reaction without further purification. An analytical sample, a colorless oil, was obtained by column chromatography (silica gel BW-820 MH, hexane/ether=5:1): IR ν_{max} (neat) cm^{-1} 1730, 1474, 1429, 1113, 908, 735; ^1H NMR ($CDCl_3$) δ 1.03 (9H, s, *Bu*^{t}), 1.06 (6H, s, C*H*$_3$×2), 3.64 (2H, s, TBDPSOC*H*$_2$), 7.34–7.49 (6H, m, Ph), 7.60–7.69 (4H, m, Ph), 9.60 (1H, s, C*H*O); ^{13}C NMR ($CDCl_3$) δ 18.58 (CH_3×2), 19.28 (4°), 26.74 (CH_3×3), 48.36 (4°), 68.86 (CH_2), 127.71 (CH, Ph), 129.76 (CH, Ph), 133.08 (4°, Ph), 135.62 (CH, Ph), 205.71 (4°, C=O); HRMS (EI) calcd for $C_{17}H_{19}O_2Si$ (M^+-Bu^t): 283.1154. Found: 283.1152.

8.1.2. Methyl 2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl] thiazolidine-4-carboxylate (4). To a stirred solution of the crude aldehyde **12** (13.5 g, 40 mmol) in toluene (100 mL) was added H-L-Cys-OMe·HCl (**3**) (7.6 g, 44 mmol) and Et_3N (6.4 mL, 46 mmol) successively at 0°C. After being stirred at room temperature for 12 h, the mixture was filtered and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 250 g, hexane/ether=8:1 to 4:1) to give the thiazolidine **4** as a colorless oil (16.8 g, 71% from methyl hydroxypivalate, ca. 2:1 diastereomixture by ^1H NMR), which formed a solid foam under high vacuum: IR ν_{max} ($CHCl_3$) cm^{-1} 3310, 1746, 1472, 1482, 1361, 1198, 1173, 1152, 1113, 826, 702; HRMS (EI) calcd for $C_{25}H_{35}NO_3SSi$: 457.2107. Found: 457.2109.

8.1.3. Methyl 2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazole-4-carboxylate (13). A suspension of CMD (1.3 g, 15 mmol) in benzene (5 mL) was refluxed with stirring for 3 h using a Dean–Stark apparatus (molecular sieves type 4A). To the resulting suspension was added pyridine (51 μL) followed by a solution of the thiazolidine **4** (115 mg, 0.25 mmol) in benzene (1 mL), and then the mixture was refluxed for 12 h. The resulting mixture was filtered through the pad of celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-200, 9 g, hexane/ether=9:1) to give the thiazole **13** (70 mg, 62%) as a colorless oil: IR ν_{max} (neat) cm^{-1} 1736, 1724, 1485, 1429, 1244, 1221, 1118, 1105, 910, 735; ^1H NMR ($CDCl_3$) δ 1.00 (9H, s, *Bu*^{t}), 1.48 (6H, s, C*H*$_3$×2), 3.76 (2H, s, TBDPSOC*H*$_2$), 3.94 (3H, s, CO_2CH_3), 7.34–7.44 (6H, m, Ph), 7.55–7.60 (4H, m, Ph), 8.09 (1H, s, thiazole-5-H); ^{13}C NMR ($CDCl_3$) δ 19.23 (4°), 25.32 (CH_3×2), 26.79 (CH_3×3), 43.33 (4°), 52.22 (CH_3), 72.29 (CH_2), 127.12 (CH, thiazole-5), 127.58 (CH, Ph), 129.60 (CH, Ph), 133.08 (4°, Ph), 135.54 (CH, Ph), 146.02 (4°, C=O), 162.12 (4°, thiazole-4), 178.63 (4°, thiazole-2). Anal. calcd for $C_{25}H_{31}NO_3SSi$: C, 66.18; H, 6.89; N, 3.10. Found: C, 66.65; H, 7.17; N, 2.99.

8.1.4. 4-Hydroxymethyl-2-[2-(*tert*-butyldimethylsilyloxy)-1,1-dimethylethyl]thiazole (14). To a stirred solution of the thiazole **13** (1.82 g, 4.01 mmol) in ether (20 mL) was added dropwise DIBAL (0.94 M in hexane, 8.75 mL, 8.22 mmol) at −78°C under argon. After stirring for 30 min, the reaction was quenched with 1 M aqueous $KHSO_4$, and the mixture was warmed to room temperature. The mixture was stirred for 1 h and extracted with ether (50 mL). The extract was washed with 1 M aqueous $KHSO_4$ (3×10 mL), H_2O (10 mL), and saturated brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 70 g, hexane/ether=4:1 to 2:1) to give the alcohol **14** (1.54 g, 91%) as a colorless solid: mp 107–108°C (hexane–ether): IR ν_{max} ($CHCl_3$) cm^{-1} 3370, 1427, 1390, 1361, 1113, 1059, 908, 735; ^1H NMR ($CDCl_3$) δ 1.00 (9H, s, *Bu*^{t}), 1.44 (6H, s, C*H*$_3$×2), 2.67 (1H, brs, disappeared with D_2O, O*H*), 3.73 (2H, s, TBDPSOC*H*$_2$), 4.72 (2H, s, C*H*$_2$OH), 7.03 (1H, s, thiazole-5-*H*), 7.30–7.44 (6H, m, Ph), 7.56–7.62 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.28 (4°), 25.36 (CH_3×2), 26.74 (CH_3×3), 43.07 (4°), 60.92 (CH_2OH), 72.58 (CH_2), 113.55 (CH, thiazole-5), 127.58 (CH, Ph), 129.58 (CH, PH), 133.35 (4°, Ph), 135.60 (CH, Ph), 155.38 (4°, thiazole-4), 178.63 (4°, thiazole-2). Anal. calcd for $C_{24}H_{31}NO_2SSi$: C, 67.72; H, 7.34; N, 3.29. Found: C, 67.56; H, 7.20; N, 3.16.

8.1.5. 4-Bromomethyl-2-[2-(*tert*-butyldimethylsilyloxy)-1,1-dimethylethyl]thiazole (5). (i) *With Ms_2O–LiBr.* To a stirred solution of the alcohol **14** (300 mg, 0.705 mmol) in CH_2Cl_2 (2.3 mL) at 0°C under argon was added Et_3N (150 μL, 10.6 mmol) followed by Ms_2O (160 mg, 0.92 mmol). The mixture was stirred at 0°C 20 min, and acetone (2.3 mL) was added, followed by LiBr (367 mg, 4.23 mmol). After at room temperature for 1 h, saturated aqueous NH_4Cl (5 mL) was added, and the mixture was extracted with ether (3×10 mL). The combined extracts were washed with saturated aqueous NH_4Cl (5 mL) and saturated brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 20 g, hexane/ether=20:1 to 10:1) to give the bromide **5** (344 mg, quant.) as a colorless oil: IR ν_{max} (neat) cm^{-1} 1471, 1428, 1251, 1113, 1059, 909, 737, 702; ^1H NMR ($CDCl_3$) δ 0.99 (9H, s, *Bu*^{t}), 1.45 (6H, s, C*H*$_3$×2), 3.73 (2H, s, TBDPSOC*H*$_2$), 4.57

(2H, s, CH_2Br), 7.18 (1H, s, thiazole-5-*H*), 7.35–7.43 (6H, m, Ph), 7.55–7.58 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.25 (4°), 25.29 (CH_3×2), 26.70 (CH_3×3), 27.53 (CH_2Br), 43.13 (4°), 72.53 (CH_2), 116.86 (CH, thiazole-5), 127.57 (CH, Ph), 129.54 (CH, PH), 133.24 (4°, Ph), 135.56 (CH, Ph), 151.27 (4°, thiazole-4), 178.47 (4°, thiazole-2). Anal. calcd for $C_{24}H_{30}BrNOSSi$: C, 59.00; H, 6.19; N, 2.87. Found: C, 59.21; H, 6.37; N, 2.76.

(ii) *With CBr_4–Ph_3P*. To a stirred solution of **14** (25.7 mg, 0.06 mmol) in CH_2Cl_2 (1.0 mL) were added CBr_4 (21.4 mg, 0.12 mmol) and Ph_3P (25.7 mg, 0.12 mmol) at 0°C. After stirring at room temperature for 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and then the mixture was extracted with ether (30 mL). The organic layer was washed with H_2O (5 mL) and saturated brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 10 g, hexane/ether=100:1 to 10:1) to give the bromide **5** (28.3 mg, 97%) as a colorless oil.

8.1.6. (2*E*)-4-{2-[2-(*tert*-Butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazol-4-yl}but-2-ene-1-ol (15). To a stirred solution of the bromide **5** (250 mg, 0.512 mmol) and the vinylstannane **6**[16] (195.4 mg, 0.563 mmol) in previously degassed NMP (2.5 mL) was added $Pd(CH_3CN)_2Cl_2$ (13.3 mg, 10 mol%) under argon. After stirring at room temperature for 10 min, 28% aqueous NH_3 (3 mL) was added. The mixture was stirred at room temperature for 30 min, diluted with EtOAc (40 mL), washed with H_2O (10 mL), 1 M aqueous $KHSO_4$ (10 mL), and saturated brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 25 g, hexane/EtOAc=3:1 to 2:1) to give **15** (225 mg, 94%) as a colorless oil: IR ν_{max} (neat) cm^{-1} 3346, 1471, 1427, 1113, 1061, 824, 737, 702; ^{1}H NMR ($CDCl_3$) δ 0.99 (9H, s, *Bu^t*), 1.44 (6H, s, CH_3×2), 1.67 (1H, brs, disappeared with D_2O, O*H*), 3.54 (2H, d, *J*=6.6 Hz, CH_2), 3.73 (2H, s, TBDPSOCH_2), 4.12 (2H, t, *J*=5.6 Hz, CH_2OH), 5.70–5.79 (1H, m, CH=C*H*CH$_2$OH), 5.85–5.99 (1H, m, C*H*=CHCH$_2$OH), 6.78 (1H, s, thiazole-5-*H*), 7.32–7.42 (6H, m, Ph), 7.54–7.56 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.27 (4°), 25.34 (CH_3×2), 26.70 (CH_3×3), 34.41 (CH2), 42.93 (4°), 63.16 (CH_2OH), 72.65 (CH_2), 112.51 (CH, thiazole-5), 127.53 (CH, Ph), 129.11 (CH, vinyl), 129.51 (CH, PH), 131.11 (CH, vinyl), 133.41 (4°, Ph), 135.54 (CH, Ph), 154.45 (4°, thiazole-4), 177.70 (4°, thiazole-2). Anal. calcd for $C_{27}H_{35}NO_2SSi$: C, 69.63; H, 7.57; N, 3.01. Found: C, 69.39; H, 7.67; N, 3.07.

8.1.7. 4-((2*E*)-4-Bromobut-2-enyl)-2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazole (16). To a stirred solution of **15** (16.0 mg, 0.0344 mmol) in CH_2Cl_2 (0.6 mL) was added CBr_4 (22.8 mg, 0.0688 mmol) and Ph_3P (27.1 mg, 0.103 mmol) at 0°C. After stirring at room temperature for 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and then the mixture was extracted with ether (30 mL). The organic layer was washed with H_2O (5 mL) and saturated brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 9 g, hexane/ether=30:1) to give the bromide **16** (26.0 mg, 95%) as a pale yellow oil: IR ν_{max} (neat) cm^{-1} 1472, 1427, 1206, 1113, 1059, 738, 702; ^{1}H NMR ($CDCl_3$) δ 0.99 (9H, s, *Bu^t*), 1.44 (6H, s, CH_3×2), 3.55 (2H, d, *J*=6.6 Hz, CH_2), 3.73 (2H, s, TBDPSOCH_2), 3.96 (2H, d, *J*=7.3 Hz, CH_2Br), 5.74–5.85 (1H, m, CH=C*H*CH$_2$Br), 5.96–6.08 (1H, m, C*H*=CHCH$_2$Br), 6.78 (1H, s, thiazole-5-*H*), 7.33–7.42 (6H, m, Ph), 7.56–7.60 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.32 (4°), 25.34 (CH_3×2), 26.69 (CH_3×3), 32.85 (CH_2), 34.25 (CH_2), 43.02 (4°), 72.69 (CH_2), 112.83 (CH, thiazole-5), 127.56 (CH, Ph), 128.23 (CH, vinyl), 129.56 (CH, Ph), 132.83 (CH, vinyl), 133.46 (4°, Ph), 135.62 (CH, Ph), 153.67 (4°, thiazole-4), 177.86 (4°, thiazole-2). Anal. calcd for $C_{27}H_{34}BrNOSSi$: C, 61.35; H, 6.48; N, 2.65. Found: C, 61.44; H, 6.65; N, 2.59.

8.1.8. 2-[2-(*tert*-Butyldiphenylsilyloxy)-1,1-dimethylethyl]-4-(2*E*)-hexa-2,5-dienylthiazole (17). To a stirred solution of the bromide **16** (165 mg, 0.312 mmol) and tri-*n*-butylvinylstannane (148 mg, 0.468 mmol) in previously degassed NMP (3 mL) at room temperature under argon was added $Pd(CH_3CN)_2Cl_2$ (8.0 mg, 10 mol%). After the mixture was stirred for 40 min, 1N aqueous NaOH (5 mL) and ether (10 mL) were added.[33] The mixture was stirred for 1 h and filtered. The filtrate was washed with 1N aqueous NaOH (5 mL), H_2O (5 mL), and saturated brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-200, 20 g, hexane/ether=50:1 to 30:1) to give the skipped diene **17** (127 mg, 85%) as a colorless oil: IR ν_{max} (neat) cm^{-1} 1472, 1427, 1206, 1113, 1059, 738, 702; ^{1}H NMR ($CDCl_3$) δ 0.99 (9H, s, *Bu^t*), 1.44 (6H, s, CH_3×2), 2.80 (2H, m, CH_2), 3.50 (2H, d, *J*=6.3 Hz, CH_2), 3.73 (2H, s, TBDPSOCH_2), 4.95–5.11 (2H, m, CH=CH_2), 5.50–5.92 (3H, m, vinyl-*H*×3), 6.76 (1H, s, thiazole-5-*H*), 7.32–7.42 (6H, m, Ph), 7.57–7.62 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.32 (4°), 25.39 (CH_3×2), 26.74 (CH_3×3), 34.90 (CH_2), 36.62 (CH_2), 42.95 (4°), 72.72 (CH_2), 112.20 (CH, thiazole-5), 115.11 (CH_2, vinyl), 127.57 (CH, Ph), 128.10 (CH, vinyl), 129.52 (CH, Ph), 130.01 (CH, vinyl), 133.50 (4°, Ph), 135.63 (CH, Ph), 136.95 (CH, vinyl), 155.33 (4°, thiazole-4), 177.47 (4°, thiazole-2). Anal. calcd for $C_{29}H_{37}NOSSi$: C, 73.21; H, 7.84; N, 2.94. Found: C, 72.93; H, 7.72; N, 2.84.

8.1.9. 2-((2*E*)-4-Hexa-2,5-dienylthiazol-2-yl)-2-methylpropanol (19). To a stirred solution of **17** (404 mg, 0.849 mmol) in THF (3.0 mL) was added TBAF·*x*H_2O (555 mg) at room temperature. After stirring for 2 h at 55°C, H_2O (3.0 mL) was added, and the mixture was extracted with EtOAc (30 mL). The extract was washed with H_2O (5 mL) and saturated brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820MH, 30 g, hexane/ether=10:1 to 8:1) to give the free alcohol **19** (203 mg, quant.) as a colorless oil: IR ν_{max} (neat) cm^{-1} 3389, 1522, 1464, 1427, 1206, 1113, 1059, 738, 702; ^{1}H NMR ($CDCl_3$) δ 1.39 (6H, s, CH_3×2), 2.81 (2H, t, *J*=6.3 Hz, CH_2), 3.46 (2H, d, *J*=6.3 Hz, CH_2), 3.69 (2H, s, HOCH_2), 4.29 (1H, brs, disappeared with D_2O, O*H*), 4.97–5.09 (2H, m, CH=CH_2), 5.50–5.95 (3H, m, vinyl-*H*×3), 6.77 (1H, s, thiazole-5-*H*); ^{13}C NMR ($CDCl_3$) δ 25.39 (CH_3×2), 34.90 (CH_2), 36.62 (CH_2), 42.95 (4°), 72.72 (CH_2), 112.20 (CH, thiazole-5), 115.11 (CH_2, vinyl), 127.57 (CH, Ph), 128.10 (CH, vinyl), 129.52 (CH, Ph), 130.01 (CH,

vinyl), 133.50 (4°, Ph), 135.63 (CH, Ph), 136.95 (CH, vinyl), 155.33 (4°, thiazole-4), 177.47 (4°, thiazole-2); HRMS (EI) calcd for $C_{13}H_{19}NOS$: 237.1187. Found: 237.1189.

8.1.10. 2-((2*E*)-4-Hexa-2,5-dienylthiazol-2-yl)-2-methylpropionaldehyde (8). To a stirred solution of the alcohol **19** (356 mg, 1.50 mmol) and Et_3N (627 μL, 4.50 mmol) in CH_2Cl_2 (5.0 mL) at 0°C was added a solution of pyridine·SO_3 (717 mg, 4.50 mmol) in DMSO (5.0 mL). The resulting solution was stirred at room temperature for 20 min and the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). After CH_2Cl_2 was removed in vacuo, the residue was extracted with ether (3×15 mL). The combined organic layer was washed with 1 M aqueous $KHSO_4$ (2×10 mL) and saturated brine (10 mL), and dried over $MgSO_4$. Filtration, concentration in vacuo, and purification by column chromatography (silica gel BW-820 MH, 20 g, hexane/ether=10:1 to 8:1) gave the aldehyde **8** (335 mg, 95%) as a colorless oil: IR ν_{max} (neat) cm^{-1} 1736, 1516, 1462, 1064, 972, 910; ^1H NMR ($CDCl_3$) δ 1.57 (6H, s, C*H*$_3$×2), 2.81 (2H, t, *J*=6.3 Hz, C*H*$_2$), 3.52 (2H, d, *J*=5.3 Hz C*H*$_2$), 4.96–5.10 (2H, m, CH=C*H*$_2$), 5.50–5.92 (3H, m, vinyl-*H*×3), 6.86 (1H, s, thiazole-5-*H*), 9.69 (1H, s, C*H*O); ^{13}C NMR ($CDCl_3$) δ 22.86 (CH_3×2), 34.74 (CH_2), 36.53 (CH_2), 51.74 (4°), 113.39 (CH, thiazole-5), 115.18 (CH_2, vinyl), 127.58 (CH, vinyl), 130.38 (CH, vinyl), 136.78 (CH, vinyl), 156.73 (4°, thiazole-4), 171.46 (4°, thiazole-2), 200.04 (4°, C=O); HRMS (EI) calcd for $C_{13}H_{17}NOS$: 235.1031. Found: 235.1035.

8.1.11. 2-(1-[1,3]-Dithian-2-yl-1-methylethyl)-4-((2*E*)-hexa-2,5-dienyl)thiazole (20). To a stirred solution of **8** (20.0 mg, 0.085 mmol) in CH_2Cl_2 (1.0 mL) were added 1,3-propanedithiol (13 μL, 0.127 mmol) and BF_3·OEt_2 (26 μL, 0.213 mmol) at 0°C under argon. The mixture was stirred at 0°C for 1 h and at room temperature for 4 h, before the addition of 1N aqueous NaOH. The mixture was extracted with EtOAc, and the extract was washed with 1N aqueous NaOH (×2) and saturated brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820MH, 30 g, hexane/EtOAc=20:1) to give the dthiane **20** (20 mg, 72%) as a white solid: mp 69–71°C: IR ν_{max} ($CHCl_3$) cm^{-1} 1518, 1456, 1422, 1057; ^1H NMR ($CDCl_3$) δ 1.61 (6H, s, C*H*$_3$×2), 1.75–1.90 (1H, m, dithiane-5-C*H*$_2$), 2.00–2.18 (1H, m, dithiane-4-C*H*$_2$), 2.76–2.98 (6H, m, dithiane-3,6-C*H*$_2$, C*H*$_2$), 3.52 (2H, d, *J*=6.3 Hz, C*H*$_2$), 4.64 (1H, s, dithiane-2-C*H*), 4.96–5.10 (2H, m, CH=C*H*$_2$), 5.50–5.92 (3H, m, vinyl-*H*×3), 6.78 (1H, s, thiazole-5-*H*); ^{13}C NMR ($CDCl_3$) δ 26.00 (CH_2), 26.09 (CH_3×2), 31.30 (CH_2×2), 34.85 (CH_2), 36.72 (CH_2), 60.34 (4°), 112.44 (CH, thiazole-5), 115.04 (CH_2, vinyl), 127.72 (CH, vinyl), 130.14 (CH, vinyl), 136.81 (CH, vinyl), 155.72 (4°, thiazole-4), 176.71 (4°, thiazole-2). Anal. calcd for $C_{16}H_{23}NS_3$·1/10*n*-hexane: C, 59.66; H, 7.36; N, 4.19. Found: C, 59.82; H, 7.48; N, 4.45.

8.1.12. (3*R*)-4-((2*E*)-4-Hexa-2,5-dienylthiazol-2-yl)-3-hydroxy-1-((4*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)-4-methylpentan-1-one (22a). To a cooled (−45°C) suspension of $Sn(OTf)_2$ (163 mg, 0.39 mmol) in CH_2Cl_2 (1.0 mL) under argon were added *N*-ethylpiperidine (57 μL, 0.416 mmol) and a solution of the thiazolidinethione (*S*)-**9**[10b] (52.9 mg, 0.260 mmol) in CH_2Cl_2 (1.0 mL). The solution was stirred at −45°C for 1 h and then at −15°C for 2 h. After the mixture was cooled to −78°C, a solution of the aldehyde **8** (47.0 mg, 0.200 mmol) in CH_2Cl_2 (1.0 mL) was added and the mixture was stirred for 20 min. The reaction was quenched with pH 7 phosphate buffer, diluted with EtOAc, and the mixture was warmed to room temperature. The solid was filtered through the pad of celite, and extracted with EtOAc. The organic layer was washed with H_2O and saturated brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography (silica gel 60 particle size 40–63 μm; Cica-MERCK, 9+1 g, hexane/EtOAc=10:1 to 3:1) gave the aldol **22a** (65.7 mg, 75%) as a yellow oil: $[\alpha]_D^{24}$=+233.3 (*c* 0.77, $CHCl_3$): IR ν_{max} (neat) cm^{-1} 3383, 1700, 1468, 1368, 1306, 1261, 1167, 1042, 912, 733; ^1H NMR ($CDCl_3$) δ 0.98 (3H, d, *J*=7.2 Hz, isopropyl C*H*$_3$), 1.05 (3H, d, *J*=7.0 Hz, isopropyl C*H*$_3$), 1.43 (3H, s, C*H*$_3$), 1.47 (3H, s, C*H*$_3$), 2.39 (1H, m, isopropyl C*H*), 2.81 (2H, brt, C*H*$_2$), 3.02 (1H, dd, *J*=1.0, 11.6 Hz, thiazolidine-4-*H*), 3.37 (2H, d, *J*=5.6 Hz, α-C*H*$_2$), 3.48 (3H, m, C*H*$_2$, thiazolidine-4-*H*), 4.34 (1H, brt, C*H*OH), 4.75 (1H, brs, disappeared with D_2O, O*H*), 4.98–5.17 (3H, m, CH=C*H*$_2$, thiazolidine-3-*H*), 5.52–5.92 (3H, m, vinyl-*H*×3), 6.78 (1H, s, thiazole-5-*H*); ^{13}C NMR ($CDCl_3$) δ 17.65 (CH_3), 19.07 (CH_3), 24.51 (CH_3), 26.60 (CH_3), 30.55 (CH_2, thiazolidine-5), 30.78 (CH, isopropyl), 34.65 (CH_2), 36.55 (CH_2), 40.79 (CH_2), 44.17 (4°), 71.81 (CH, thiazolidine-4), 75.04 (CH, β), 112.13 (CH, thiazole-5), 115.11 (CH_2, vinyl), 127.64 (CH, vinyl), 130.30 (CH, vinyl), 136.86 (CH, vinyl), 155.47 (4°, thiazole-4), 172.54 (4°, thiazole-2), 177.84 (4°, C=O), 203.07 (4°, C=S); HRMS (EI) calcd for $C_{21}H_{30}N_2O_2S_3$: 438.1469. Found: 438.1470. Diastereomer ratio was determined by the integration of C*H*OH proton (4.25:4.34>1:10) in ^1H NMR of the crude product.

8.1.13. (3*S*)-4-((2*E*)-4-Hexa-2,5-dienylthiazol-2-yl)-3-hydroxy-1-((4*R*)-4-isopropyl-2-thioxothiazolidin-3-yl)-4-methylpentan-1-one (22b). To a stirred solution of (*R*)-**9** (185 mg, 0,911 mmol) in CH_2Cl_2 (4.5 mL) were added $TiCl_4$ (100 μL, 0.911 mmol) and *i*-Pr_2NEt (159 μL, 0.911 mmol) successively at −45°C under N_2, and then the mixture was stirred for 2 h. The mixture was cooled to −78°C, and a solution of **8** (143 mg, 0.608 mmol) in CH_2Cl_2 (3.0 mL plus 0.5×2 mL of rinse) was added via cannula. The mixture was stirred for 40 min, and then the reaction was quenched with saturated NH_4Cl. The mixture was extracted with EtOAc, and the organic layer was washed with H_2O and saturated brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (silica gel BW-200, 25 g, hexane/EtOAc=7:1 to 4:1) gave the aldol **22b** (210 mg, 79%) as a yellow oil: $[\alpha]_D^{22}$=−237.3 (*c* 0.84, $CHCl_3$): IR ν_{max} (neat) cm^{-1} 3378, 1700, 1468, 1370, 1306, 1262, 1167, 1042, 731; ^1H NMR ($CDCl_3$) δ 0.97 (3H, d, *J*=6.9 Hz, isopropyl C*H*$_3$), 1.05 (3H, d, *J*=6.8 Hz, isopropyl C*H*$_3$), 1.43 (3H, s, C*H*$_3$), 1.47 (3H, s, C*H*$_3$), 2.32–2.45 (1H, m, isopropyl CH), 2.80 (2H, t, *J*=5.8 Hz, CH_2), 3.01 (1H, d, *J*=11.5 Hz, thiazolidine-4-H), 3.37 (2H, d, *J*=5.9 Hz, α-CH_2), 3.42–3.55 (3H, m, CH_2, thiazolidine-4-H), 4.34 (1H, brt, CHOH), 4.75 (1H, brs, disappeared with D_2O, OH), 4.98–5.17 (3H, m, CH=CH_2, thiazolidine-3-H),

5.52–5.92 (3H, m, vinyl-H×3), 6.77 (1H, s, thiazole-5-H); ^{13}C NMR ($CDCl_3$) δ 17.78 (CH_3), 19.20 (CH_3), 24.63 (CH_3), 26.75 (CH_3), 30.65 (CH_2, thiazolidine-5), 30.90 (CH, isopropyl), 34.75 (CH_2), 36.66 (CH_2), 40.88 (CH_2), 44.25 (4°), 71.85 (CH, thiazolidine-4), 75.08 (CH, β), 112.10 (CH, thiazole-5), 115.07 (CH_2, vinyl), 127.57 (CH, vinyl), 130.24 (CH, vinyl), 136.79 (CH, vinyl), 155.37 (4°, thiazole-4), 172.41 (4°, thiazole-2), 177.72 (4°, C=O), 202.90 (4°, C=S); HRMS (EI) calcd for $C_{21}H_{30}N_2O_2S_3$: 438.1469. Found: 438.1454. Diastereoselectivity was >95:5 as determined by the ^{1}H NMR of the crude product.

8.1.14. Methyl (3*R*)-4-((2*E*)-4-hexa-2,5-dienylthiazol-2-yl)-3-hydroxypentanoate (23). To a stirred solution of the aldol **22a** (31.1 mg, 0.071 mmol) in THF (1.5 mL)–H_2O (0.5 mL) were added 30% aqueous H_2O_2 (48 μL, 0.426 mmol) and then 0.5N LiOH (284 μL, 0.142 mmol), and the mixture was stirred at 0°C for 0.5 h. After quenching with 1.5N aqueous Na_2SO_3 (1 mL), 1 M aqueous $KHSO_4$ (1 mL) was added and the mixture was extracted with EtOAc (×3). The extracts were dried over Na_2SO_4, and concentrated in vacuo to give a yellow oil (35 mg). This oil was dissolved in toluene (1.2 mL)–MeOH (0.4 mL), and $TMSCHN_2$ (2 M in hexane, 71 μL, 0.142 mmol) was dropwise added. After the mixture was stirred at 0°C for 0.5 h, the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2 BW820MH, 10 g, hexane/EtOAc=6:1→5:1) to give the hydroxy ester **23** (22.7 mg, quant.) as a colorless oil, $[\alpha]_D^{25}$=+14.3 (*c* 1.1, $CHCl_3$): IR ν_{max} ($CDCl_3$) cm^{-1} 3402, 1740, 1437, 1298, 1172, 1055, 993, 972, 914; ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, s, Me), 1.46 (3H, s, Me), 2.31 (1H, dd, *J*=15.2, 1.2 Hz), 2.50 (1H, dd, *J*=14.8, 2.6 Hz), 2.80 (2H, t, *J*=5.9 Hz), 3.47 (2H, d, *J*=5.9 Hz), 3.70 (3H, s, OMe), 4.21 (1H, dd, *J*=10.2, 2.3 Hz), 4.80 (1H, brs), 4.99–5.08 (2H, m), 5.54–5.89 (3H, m), 6.78 (1H, s); ^{13}C NMR ($CDCl_3$) δ 24.51 (CH_3), 26.65 (CH_3), 34.66 (CH_2), 36.59 (CH_2), 37.61 (CH_2), 44.08 (4°), 51.82 (CH_3), 75.24 (CH), 112.15 (CH, thiazole-5), 115.22 (CH_2), 127.56 (CH), 130.49 (CH), 136–84 (CH), 155.58 (4°, thiazole-4), 172.86 (4°, C=O), 177.80 (4°, thiazole-2).

8.1.15. (*R*)-MTPA ester (24a). To a stirred solution of the hydroxy ester **23** (15.4 mg, 0.050 mmol) in CH_2Cl_2 (1 mL) were added (*R*)-MTPA (15.2 mg, 0.065 mmol), DCC (13.4 mg, 0.065 mmol), and DMAP (2 mg) with ice-cooling. After the mixture was stirred at room temperature for 12 h, (*R*)-MTPA (15.2 mg, 0.06 5 mmol), DCC (13.4 mg, 0.065 mmol), and DMAP (2 mg) were again added. The mixture was stirred at room temperature for 4 h and at 35°C for 20 h. After dilution with EtOAc, the mixture was washed with saturated aqueous $NaHCO_3$ and saturated brine, and dried over Na_2SO_4. Concentration followed by column chromatography (SiO_2 BW-820MH, 9 g, hexane/EtOAc=12:1→8:1) afforded the (*R*)-MTPA ester (22.4 mg, 85%) as a colorless oil: $[\alpha]_D^{25}$=+12.1 (*c* 1.1, $CHCl_3$): IR ν_{max} ($CDCl_3$) cm^{-1} 1735, 1437, 1298, 1250, 1171, 1123, 1015; ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, s), 1.45 (3H, s), 2.50 (1H, dd, *J*=16.5, 9.21 Hz), 2.71 (1H, dd, *J*=16.2, 3.0 Hz), 2.79 (2H, brt, *J*=6.3 Hz), 3.45 (3H, d, *J*=2.0 Hz), 3.47 (2H, d, *J*=6.6 Hz), 3.59 (3H, s), 5.05 (2H, m), 5.51–5.88 (3H, m), 5.90 (1H, dd, *J*=9.2, 2.9 Hz), 6.79 (1H, s), 7.35–7.39 (3H, m), 7.42–7.49 (2H, m); HRMS(EI) calcd for $C_{26}H_{30}F_3NO_5S$; 525, 1797. Found: 525.1804.

8.1.16. (*S*)-MTPA ester (24b). To a stirred solution of (*S*)-MTPA (17 mg, 0.071 mmol) in hexane (1 mL) were added DMF (55 μL, 0.071 mmol) and oxalyl chloride (31 μL, 0.356 mmol) under argon. The mixture was stirred at room temperature for 1 h, filtered over celite, and concentrated to give (*S*)-MTPA-Cl which was directly used for the next step.

To a stirred solution of the hydroxy ester **23** (11 mg, 0.0356 mmol) in CH_2Cl_2 (1 mL) were added Et_3N (15 μL, 0.107 mmol), (*S*)-MTPA–Cl in hexane (1 mL), and DMAP (2 mg) with ice-cooing. The mixture was stirred at 0°C to room temperature for 2.5 h. After addition of saturated aqueous $NaHCO_3$, the mixture was extracted with EtOAc. The extracts were washed with water and saturated brine, and dried over Na_2SO_4. Concentration in vacuo followed by chromatography (SiO_2 BW-820MH, 9 g, hexane/EtOAc=10:1→8:1) of the concentrated residue afforded the (*S*)-MTPA ester (15.1 mg, 81%) as a colorless oil: $[\alpha]_D^{25}$=−15.5 (*c* 0.7, $CHCl_3$): IR ν_{max} ($CDCl_3$) cm^{-1} 1755, 1437, 1298, 1260, 1171, 1122, 1017; ^{1}H NMR ($CDCl_3$) δ 1.34 (3H, s), 1.38 (3H, s), 2.52 (1H, dd, *J*=16.2, 9.2 Hz), 2.73 (1H, dd, *J*=16.2, 2.6 Hz), 2.80 (2H, brt, *J*=5.6 Hz), 3.46 (2H, d, *J*=6.3 Hz), 3.51 (3H, s), 3.59 (3H, s), 4.98–5.08 (2H, m), 5.53–5.91 (3H, m), 5.86 (1H, dd, *J*=9.6, 2.6 Hz), 6.76 (1H, s), 7.34–7.39 (3H, m), 7.52–7.55 (2H, m); HRMS(EI) calcd for $C_{26}H_{30}F_3NO_5S$: 525.1797. Found, 525.1805.

8.1.17. (4*R*)-3-[(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-((2*E*)-4-hexa-2,5-dienylthiazol-2-yl)-4-methylpentanoyl]-4-isopropylthiazolidin-2-one (25a). To a stirred solution of **22a** (71.9 mg, 0.130 mmol) in CH_2Cl_2 (1.3 mL) at 0°C under argon were added 2,6-lutidine (25.7 μL, 0.221 mmol) and TBSOTf (43.9 μL, 0.191 mmol). After stirring for 30 min, 1 M aqueous $KHSO_4$ (3 mL) was added, and the mixture was extracted with ether (30 mL). The organic layer was washed with 1 M aqueous $KHSO_4$ (2×4 mL), H_2O (4 mL), and saturated brine (4 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 10 g, hexane/ether=8:1) to give the TBS ether **25a** (77.7 mg, 96%) as a yellow oil: $[\alpha]_D^{23}$=+240.4 (*c* 1.3, $CHCl_3$): IR ν_{max} (neat) cm^{-1} 1699, 1471, 1368, 1296, 1258, 1169, 1090, 1042, 912, 837, 777, 735; ^{1}H NMR ($CDCl_3$) δ −0.05 (3H, s, C*H*$_3$), −0.03 (3H, s, C*H*$_3$), 0.80 (9H, s, *Bu*^{t}), 0.94 (3H, d, *J*=6.9 Hz, isopropyl C*H*$_3$), 1.04 (3H, d, *J*=6.9 Hz, isopropyl C*H*$_3$), 1.36 (3H, s, C*H*$_3$), 1.44 (3H, s, C*H*$_3$), 2.24–2.38 (1H, m, isopropyl C*H*), 2.80 (2H, brt, C*H*$_2$), 2.99 (1H, d, *J*=11.6 Hz, thiazolidine-4-*H*), 3.35 (2H, d, *J*=4.9 Hz, α-C*H*$_2$), 3.38–3.50 (3H, m, C*H*$_2$, thiazolidine-4-*H*), 4.74 (1H, brt, C*H*OTBS), 4.98–5.10 (3H, m, CH=C*H*$_2$, thiazolidine-3-*H*), 5.54–5.89 (3H, m, vinyl-*H*×3), 6.78 (1H, d, *J*=1.0 Hz, thiazole-5-*H*); ^{13}C NMR ($CDCl_3$) δ −5.14 (CH_3), −4.56 (CH_3), 17.97 (CH_3), 18.22 (4°, Bu^t), 19.07 (CH_3), 24.94 (CH_3), 25.29 (CH_3), 25.93 (CH_3×3, Bu^t), 30.66 (CH_2, thiazolidine-5), 30.87 (CH, isopropyl), 34.87 (CH_2), 36.62 (CH_2), 43.34 (α-CH_2), 45.86 (4°), 71.48 (CH, thiazolidine-4), 75.04 (β-CH,), 112.40 (CH, thiazole-5), 115.06 (CH_2, vinyl), 128.10 (CH, vinyl),

129.92 (CH, vinyl), 136.96 (CH, vinyl), 155.24 (4°, thiazole-4), 172.04 (4°, thiazole-2), 177.02 (4°, C═O), 202.57 (4°, C═S); HRMS (EI) calcd for $C_{27}H_{44}N_2O_2S_3Si$: 552.2334. Found: 552.2336.

8.1.18. (4*S*)-3-[(3*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-((2*E*)-4-hexa-2,5-dienylthiazol-2-yl)-4-methylpentanoyl]-4-isopropylthiazolidin-2-one (25b). To a stirred solution of **22b** (210 mg, 0.479 mmol) in CH_2Cl_2 (3.0 mL) at 0°C under argon were added 2,6-lutidine (112 μL, 0.958 mmol) and TBSOTf (165 μL, 0.718 mmol). After stirring for 30 min, 1 M aqueous $KHSO_4$ (3 mL) was added, and the mixture was extracted with ether (30 mL). The organic layer was washed with 1 M aqueous $KHSO_4$ (2×4 mL), H_2O (4 mL), and saturated brine (4 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-200, 20 g, hexane/ether=12:1) to give the TBS ether **25b** (245 mg, 93%) as a yellow oil: $[\alpha]_D^{23}=-228.3$ (*c* 1.2, $CHCl_3$): IR ν_{max} (neat) cm^{-1} 1700, 1471, 1370, 1296, 1258, 1169, 1090, 1042, 918, 837, 777, 735; ^1H NMR ($CDCl_3$) δ −0.04 (3H, s, C*H*$_3$), −0.03 (3H, s, CH3), 0.80 (9H, s, But), 0.94 (3H, d, *J*=6.9 Hz, isopropyl CH3), 1.04 (3H, d, *J*=6.8 Hz, isopropyl CH3), 1.37 (3H, s, CH3), 1.44 (3H, s, CH3), 2.27–2.37 (1H, m, isopropyl CH), 2.80 (2H, brt, CH2), 2.99 (1H, d, *J*=11.5 Hz, thiazolidine-4-H), 3.35 (2H, d, *J*=4.6 Hz, α-CH2), 3.40–3.50 (3H, m, CH2, thiazolidine-4-H), 4.74 (1H, brt, CHOTBS), 4.98–5.10 (3H, m, CH═CH2, thiazolidine-3-H), 5.51–5.92 (3H, m, vinyl-H×3), 6.73 (1H, s, thiazole-5-H); ^{13}C NMR (CDCl3) δ −4.96 (CH3), −4.40 (CH3), 18.09 (CH3), 18.35 (4°, But), 19.20 (CH3), 25.07 (CH3), 25.40 (CH3), 26.03 (CH3×3, But), 30.76 (CH2, thiazolidine-5), 30.98 (CH, isopropyl), 34.99 (CH_2), 36.72 (CH_2), 43.42 (α-CH_2), 45.94 (4°), 71.52 (CH, thiazolidine-4), 75.26 (β-CH), 112.36 (CH, thiazole-5), 115.01 (CH_2, vinyl), 128.02 (CH, vinyl), 129.85 (CH, vinyl), 136.89 (CH, vinyl), 155.11 (4°, thiazole-4), 171.90 (4°, thiazole-2), 176.88 (4°, C═O), 202.38 (4°, C═S); HRMS (EI) calcd for $C_{27}H_{44}N_2O_2S_3Si$: 552.2334. Found: 552.2333.

8.1.19. (3*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-((2*E*)-4-hexa-2,5-dienylthiazol-2-yl)-4-methylpentanal ((*R*)-26). To a stirred cooled (−78°C) solution of the TBS ether **25a** (71.9 mg, 0.130 mmol) in toluene (1.3 mL) under argon was added DIBAL (0.95 M in hexane, 342 μL, 0.325 mmol). After stirring for 1 h, 1 M aqueous $KHSO_4$ (2 mL) was added, and the resulting mixture was stirred at room temperature for 1 h. After the reaction mixture was extracted with ether (30 mL), the organic layer was washed with 1 M aqueous $KHSO_4$ (3×4 mL) and saturated brine (4 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 10 g, hexane/ether=10:1) to give (*R*)-**26** (43.8 mg, 86%) as a colorless oil: $[\alpha]_D^{23}=-13.1$ (*c* 2.0, $CHCl_3$): IR ν_{max} (neat) cm^{-1} 1728, 1471, 1255, 1049, 1042, 837, 777; ^1H NMR ($CDCl_3$) δ −0.01 (3H, s, C*H*$_3$), 0.03 (3H, s, C*H*$_3$), 0.86 (9H, s, *Bu*^{t}), 1.38 (3H, s, C*H*$_3$), 1.42 (3H, s, C*H*$_3$), 2.39–2.67 (2H, m, α-C*H*$_2$), 2.80 (2H, brt, C*H*$_2$), 3.47 (2H, m, C*H*$_2$), 4.56 (1H, brt, C*H*OTBS), 4.97–5.09 (2H, m, CH═C*H*$_2$), 5.53–5.90 (3H, m, vinyl-*H*×3), 6.75 (1H, d, *J*=1.0 Hz, thiazole-5-*H*), 9.56 (1H, t, *J*=1.8 Hz, CHO); ^{13}C NMR ($CDCl_3$) δ −4.56 (CH_3), −3.92 (CH_3), 18.39 (4°), 24.48 (CH_3), 26.09 (CH_3), 26.15 (CH_3×3, Bu^t), 35.11 (CH_2), 36.91 (CH_2), 46.06 (α-CH_2), 48.86 (4°), 74.20 (β-CH,), 113.06 (CH, thiazole-5), 115.44 (CH_2, vinyl), 128.25 (CH, vinyl), 130.44 (CH, vinyl), 137.22 (CH, vinyl), 155.80 (4°, thiazole-4), 176.94 (4°, thiazole-2), 201.20 (4°, C═O); HRMS (EI) calcd for $C_{21}H_{35}NO_2SSi$: 393.2158. Found: 393.2115.

8.1.20. (3*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-((2*E*)-4-hexa-2,5-dienylthiazol-2-yl)-4-methylpentanal ((*S*)-26). To a stirred cooled (−78°C) solution of the TBS ether **25b** (245 mg, 0.443 mmol) in toluene (2.5 mL) under argon was added DIBAL (1.01 M in toluene, 877 μL, 0.886 mmol). After stirring for 10 min, 1 M aqueous $KHSO_4$ (2 mL) was added, and the resulting mixture was stirred at room temperature for 1 h. After the reaction mixture was extracted with ether (30 mL), the organic layer was washed with 1 M aqueous $KHSO_4$ (3×4 mL) and saturated brine (4 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-200, 20 g, hexane/ether=12:1–10:1) to give (*S*)-**26** (145 mg, 83%) as a colorless oil: $[\alpha]_D^{22}=+15.0$ (*c* 1.0, $CHCl_3$): IR ν_{max} (neat) cm^{-1} 1728, 1471, 1254, 1049, 1042, 837, 777; ^1H NMR ($CDCl_3$) δ −0.01 (3H, s, C*H*$_3$), 0.03 (3H, s, C*H*$_3$), 0.87 (9H, s, *Bu*^{t}), 1.38 (3H, s, C*H*$_3$), 1.42 (3H, s, C*H*$_3$), 2.40–2.67 (2H, m, α-C*H*$_2$), 2.80 (2H, brt, C*H*$_2$), 3.47 (2H, d, *J*=6.4 Hz, C*H*$_2$), 4.56 (1H, brt, C*H*OTBS), 4.98–5.08 (2H, m, CH═C*H*$_2$), 5.51–5.92 (3H, m, vinyl-*H*×3), 6.76 (1H, s, thiazole-5-*H*), 9.56 (1H, t, *J*=1.8 Hz, CHO); ^{13}C NMR ($CDCl_3$) δ −4.73 (CH_3), −4.08 (CH_3), 18.19 (4°), 24.26 (CH_3), 25.88 (CH_3), 25.94 (CH_3×3, Bu^t), 34.88 (CH_2), 36.68 (CH_2), 45.80 (α-CH_2), 48.59 (4°), 73.90 (β-CH,), 112.68 (CH, thiazole-5), 115.06 (CH_2, vinyl), 127.83 (CH, vinyl), 130.04 (CH, vinyl), 136.81 (CH, vinyl), 155.34 (4°, thiazole-4), 176.46 (4°, thiazole-2), 200.70 (4°, C═O); HRMS (EI) calcd for $C_{21}H_{35}NO_2SSi$: 393.2158. Found: 393.2164.

8.1.21. 2-[(2*R*,4*E*)-2-(*tert*-Butyldimethylsilyloxy)-5-iodo-1,1-dimethylpent-4-enyl]-(2*E*)-4-hexa-2,5-dienylthiazole ((*R*)-10). To a suspension of $Ph_3P^+CH_2I\cdot I^-$[25] (237 mg, 0.516 mmol) in THF (1.5 mL) at room temperature under argon was added 1.0 M solution of NaHMDS (516 μL, 0.516 mmol) in THF. The mixture was stirred for 5 min, and cooled to −78°C and then HMPA (179 μL, 1.030 mmol) was added. After stirring for 5 min, a solution of (*R*)-aldehyde **26** (40.6 mg, 0.103 mmol) in THF (1.0 mL) was added, and the mixture was stirred for 20 min. H_2O (2.0 mL) was added, and the mixture was warmed to room temperature. The resulting mixture was filtered and the filtrate was extracted with ether (30 mL). The organic layer was washed with H_2O (5.0 mL) and saturated brine (5.0 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 9+1 g, hexane/ether=80:1 to 60:1) to give (*R*)-**10** (43.8 mg, 82%) as a colorless oil: $[\alpha]_D^{23}=-17.1$ (*c* 0.76, $CHCl_3$): IR ν_{max} (neat) cm^{-1} 1471, 1255, 1094, 1048, 970, 912, 837, 776; ^1H NMR ($CDCl_3$) δ −0.01 (3H, s, C*H*$_3$), 0.05 (3H, s, C*H*$_3$), 0.87 (9H, s, *Bu*^{t}), 1.38 (3H, s, C*H*$_3$), 1.44 (3H, s, C*H*$_3$), 2.80 (2H, brt, *J*=5.6 Hz, C*H*$_2$), 3.49 (2H, d, *J*=6.2 Hz, C*H*$_2$), 4.19 (1H, t, *J*=5.3 Hz, C*H*OTBS), 4.97–5.09 (2H, m, CH═C*H*$_2$),

5.53–5.90 (3H, m, vinyl-*H*×3), 6.06–6.16 (2H, m, C*H*═C*H*I), 6.73 (1H, s, thiazole-5-*H*); ^{13}C NMR ($CDCl_3$) δ −4.74 (CH_3), −3.81 (CH_3), 18.17 (4°), 24.49 (CH_3), 25.72 (CH_3), 25.99 (CH_3×3, Bu^t), 34.92 (CH_2), 36.64 (CH_2), 39.39 (CH_2), 46.08 (4°), 77.83 (CHOTBS), 82.70 (CHI), 112.31 (CH, thiazole-5), 115.15 (CH_2, vinyl), 128.16 (CH, vinyl), 129.96 (CH, vinyl), 136.96 (CH, vinyl), 138.74 (CH, *Z*-vinyl), 155.38 (4°, thiazole-4), 177.81 (4°, thiazole-2); HRMS (EI) calcd for $C_{22}H_{36}INOSSi$: 517.1332. Found: 517.1336.

8.1.22. 2-[(2*S*,4*Z*)-2-(*tert*-Butyldimethylsilyloxy)-5-iodo-1,1-dimethylpent-4-enyl]-(2*E*)-4-hexa-2,5-dienylthiazole ((*S*)-10). To a suspension of $Ph_3P^+CH_2I\cdot I^-$[25] (100 mg, 0.189 mmol) in THF (0.6 mL) at room temperature under argon was added 1.0 M solution of NaHMDS (183 μL, 0.183 mmol) in THF. After stirring for 5 min, the solution was cooled to −78°C and HMPA (65.8 μL, 0.378 mmol) was added and the mixture was stirred for 5 min. A solution of the aldehyde (*S*)-**26** (24.8 mg, 0.063 mmol) in THF (0.5 mL) was added. After stirring for 30 min, H_2O (2.0 mL) was added, and the mixture was warmed to room temperature. The resulting mixture was filtered and the filtrate was extracted with ether (30 mL). The organic layer was washed with H_2O (5.0 mL) and saturated brine (5.0 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 7+1 g, hexane/ether=100:1) to give (*S*)-**10** (26.5 mg, 81%) as a colorless oil: $[\alpha]_D^{22}$=+16.8 (*c* 1.1, $CHCl_3$): IR ν_{max} (neat) cm^{-1} 1472, 1256, 1094, 1048, 970, 912, 837, 776; ^{1}H NMR ($CDCl_3$) δ −0.10 (3H, s, CH_3), 0.05 (3H, s, CH_3), 0.87 (9H, s, *Bu*^{t}), 1.38 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.80 (2H, brt, *J*=5.6 Hz, CH_2), 3.49 (2H, d, *J*=6.3 Hz, CH_2), 4.19 (1H, t, *J*=5.3 Hz, C*H*OTBS), 4.98–5.08 (2H, m, CH═CH_2), 5.51–5.92 (3H, m, vinyl-*H*×3), 6.06–6.16 (2H, m, C*H*═C*H*I), 6.73 (1H, s, thiazole-5-*H*); ^{13}C NMR ($CDCl_3$) δ −4.61 (CH_3), −3.66 (CH_3), 18.26 (4°), 24.58 (CH_3), 25.81 (CH_3), 26.06 (CH_3×3, Bu^t), 34.98 (CH_2), 36.71 (CH_2), 39.45 (CH_2), 46.12 (4°), 77.82 (CHOTBS), 82.69 (CHI), 112.25 (CH, thiazole-5), 115.06 (CH_2, vinyl), 128.05 (CH, vinyl), 129.86 (CH, vinyl), 136.85 (CH, vinyl), 138.63 (CH, *Z*-vinyl), 155.22 (4°, thiazole-4), 177.62 (4°, thiazole-2); HRMS (EI) calcd for $C_{22}H_{36}INOSSi$: 517.1332. Found: 517.1334.

8.1.23. 3-Iodobut-3-enyl toluene-4-sulfonate (28). NaI (6.0 g, 40 mmol) was dissolved in CH_3CN (30 mL) at room temperature and then to the mixture was added TMSCl (5.08 mL, 40 mmol) followed by H_2O (360 μL, 20 mmol). After 10 min, a solution of 3-butyn-1-ol (**27**) (1.4 g, 20 mmol) in CH_3CN (5.0 mL) was added to the mixture and the resulting mixture was allowed to react for 1 h at room temperature. The reaction was quenched with H_2O (60 mL) and the mixture was extracted with ether (3×50 mL). Drying over $MgSO_4$, filtration, and evaporating ether gave crude the iodo alcohol (3.8 g) as a reddish brown oil.

This crude iodo alcohol (3.8 g) was dissolved in CH_2Cl_2 (25 mL), and cooled to 0°C. To the stirred solution were added TsCl (5.72 g, 35 mmol), Et_3N (5.58 mL, 40 mmol), and $Me_3N\cdot HCl$ (190 mg, 2 mmol). After the mixture was stirred at 0°C for 1 h, the reaction was quenched with H_2O (50 mL) and the mixture was extracted with ether (3×60 mL). The combined extracts were successively washed with 1 M aqueous $KHSO_4$ (50 mL), saturated aqueous $Na_2S_2O_3$ (30 mL), H_2O (40 mL), and saturated brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 250 g, hexane/ether=6:1 to 4:1) to give the tosylate **28** (3.90 g, 55% for 2 steps) as a pale brown oil: IR ν_{max} (neat) cm^{-1} 1360, 1190, 1176, 978, 909, 816, 774, 664; ^{1}H NMR ($CDCl_3$) δ 2.45 (3H, s, CH_3–Ar), 2.72 (2H, dt, *J*=0.7, 6.3 Hz, CH_2, allyl), 4.13 (2H, t, *J*=6.3 Hz, CH_2OTs), 5.78 (1H, d, *J*=1.6 Hz, vinyl), 6.11 (1H, dd, *J*=1.6, 3.0 Hz, vinyl), 7.35 (2H, d, *J*=7.9 Hz, Ar), 7.80 (2H, dd, *J*=4.6, 6.6 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 21.6 (CH_3), 44.28 (CH_2, allyl), 68.03 (CH_2), 103.58 (4°), 127.94 (CH, *p*-tol-*o*), 129.15 (CH_2, vinyl), 129.85 (CH, *p*-tol-*m*), 132.72 (4°, *p*-tol), 144.89 (4°, *p*-tol-*p*); HRMS (EI) calcd for $C_{11}H_{13}O_3S$ (M^+−I): 225.0585. Found: 225.0586.

8.1.24. Methyl (3-iodobut-3-enyl)carbamate (29). To a stirred solution of the tosylate **28** (5.42 g, 15.38 mmol) in DMF (40 mL) at 0°C was added NaN_3 (3.0 g, 46.14 mmol). After being stirred at room temperature for 2 h, the mixture was heated to 50°C for 3 h. The reaction was quenched with H_2O (80 mL), and the mixture was extracted with ether (3×50 mL). The combined organic layer was successively washed with 1 M aqueous $KHSO_4$ (40 mL), H_2O (40 mL), and saturated brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude azide (3.33 g) as a yellow oil, which was used for the next step without further purification.

This crude azide (3.33 g) was dissolved in THF (50 mL) and cooled to 0°C. The solution was treated with Ph_3P (5.9 g, 22.5 mmol) and H_2O (405 μL, 22.5 mmol), and stirred at room temperature for 12 h. To the resulting mixture were added $ClCO_2Me$ (2.32 mL, 30.0 mmol) and Et_3N (4.18 mL, 30 mmol) at 0°C. After stirring at room temperature for 4 h, H_2O (80 mL) was added, and the mixture was extracted with ether (3×60 mL). The combined extracts were washed with 1 M aqueous $KHSO_4$ (40 mL), H_2O (40 mL), and saturated brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 250 g, hexane/ether=7:1 to 3:1) to give the methylcarbamate **29** (3.05 g, 78% from **28**) as a pale yellow oil: IR ν_{max} (neat) cm^{-1} 3339, 1701, 1536, 1260, 1217, 1130, 1049, 901, 779, 733; ^{1}H NMR ($CDCl_3$) δ 2.58 (2H, t, *J*=6.4 Hz, CH_2, allyl), 3.32–3.40 (2H, m, CH_2NH), 3.67 (3H, s, CH_3CO_2NH), 4.76 (1H, brs, CH_3CO_2N*H*), 5.80 (1H, d, *J*=1.3 Hz, vinyl), 6.11 (1H, d, *J*=1.3 Hz, vinyl); ^{13}C NMR ($CDCl_3$) δ 39.84 (CH_2, allyl), 45.01 (CH_2), 52.11 (CH_3), 107.75 (4°), 128.12 (CH_2, vinyl), 156.84 (4°, C═O); HRMS (EI) calcd for $C_6H_{10}NO_2$ (M^+−I): 128.0712. Found: 128.0723.

8.1.25. Methyl [3-(trimethylstannanyl)but-3-enyl]carbamate (11). To a stirred solution of **29** (51.0 mg, 0.20 mmol) and $Me_3SnSnMe_3$ (131 mg, 0.40 mmol) in previously degassed NMP (1 mL) at room temperature under argon was added $Pd(CH_3CN)_2Cl_2$ (5.2 mg, 10 mol%). After stirring for 3 h, H_2O (2 mL) was added, and the mixture was extracted with ether (30 mL). The organic layer was washed with 1 M aqueous $KHSO_4$ (5 mL), H_2O (5 mL), and

saturated brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 10 g, hexane/ether=8:1 to 7:1) to give **11** (33.0 mg, 57%) as a colorless oil: IR ν_{max} (neat) cm^{-1} 3346, 1709, 1538, 1258, 1192, 920, 774; ^1H NMR ($CDCl_3$) δ 0.14 (9H, s, CH_3×3), 2.44 (2H, t, J=6.6 Hz, CH_2, allyl), 3.18–3.28 (2H, m, CH_2NH), 3.64 (3H, s, CH_3CO_2NH), 4.68 (1H, brs, CH_3CO_2NH), 5.22–5.28 (1H, m, vinyl), 5.68–5.74 (1H, m, vinyl); ^{13}C NMR ($CDCl_3$) δ −9.63 (CH_3×3), 40.13 (CH_2, allyl), 40.49 (CH_2), 51.84 (CH_3), 127.20 (CH_2, vinyl), 152.17 (4°), 156.84 (4°, C=O); HRMS (EI) calcd for $C_8H_{16}NO_2Sn$ (M^+-CH_3): 278.0203. Found: 278.0203.

8.1.26. Methyl [(7*R*,4*E*)-7-(*tert*-butyldimethylsilyloxy)-8-(4-(2*E*)-hexa-2,5-dienylthiazol-2-yl)-8-methyl-3-methyl-enenon-4-enyl]carbamate ((*R*)-30). A dry round bottom flask was charged with LiCl (12.7 mg, 0.30 mmol) and dried with flame under high vacuum. Upon cooling, $Pd(Ph_3P)_4$ (11.6 mg, 20 mol%) and CuCl (24.8 mg, 0.25 mmol) were added under argon, and a solution of the vinyl iodide (*R*)-**10** (25.9 mg, 0.05 mmol) and the trimethylstannane **11** (21.9 mg, 0.075 mmol) in previously degassed DMSO (1.0 mL) was added. After the mixture was stirred at room temperature for 12 h, $Pd(Ph_3P)_4$ (11.6 mg, 20 mol%) was added since TLC indicated that the reaction had not gone to completion. After stirring for 3 h, 1N aqueous NaOH (2 mL) and ether (5 mL) was added, and the resulting mixture was filtered through the pad of celite and extracted with ether (30 mL). The extract was washed with 1N aqueous NaOH (5 mL), H_2O (5 mL), 1 M aqueous $KHSO_4$ (5 mL), and saturated brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-200, 10 g, hexane/EtOAc=15:1 to 11:1) to give (*R*)-**30** (16.3 mg, 63%) as a pale yellow oil: $[\alpha]_D^{24}=-0.15$ (*c* 0.91, $CHCl_3$): IR ν_{max} (neat) cm^{-1} 3340, 1728, 1520, 1471, 1256, 1096, 1049, 837, 776; ^1H NMR ($CDCl_3$) δ −0.08 (3H, s, CH_3), 0.04 (3H, s, CH_3), 0.87 (9H, s, Bu^t), 1.34 (3H, s, CH_3), 1.40 (3H, s, CH_3), 2.23 (2H, t, J=6.6 Hz, CH_2=$CHCH_2$), 2.32–2.39 (2H, m, allyl CH_2), 2.80 (2H, brt, J=6.3 Hz, allyl CH_2), 3.16–3.27 (2H, brm, CH_2NH), 3.47 (2H, d, J=6.3 Hz, CH_2), 3.65 (3H, s, $NHCO_2CH_3$), 4.06 (1H, t, J=5.0 Hz, CHOTBS), 4.84–5.08 (5H, m, CH=CH_2×2, $NHCO_2CH_3$), 5.49–5.92 (5H, m, vinyl-H×5), 6.73 (1H, d, J=1.0 Hz, thiazole-5-H); ^{13}C NMR ($CDCl_3$) δ −4.65 (CH_3), −3.59 (CH_3), 18.22 (4°), 24.57 (CH_3), 25.90 (CH_3), 26.02 (CH_3×3, Bu^t), 33.10 (CH_2), 34.84 (CH_2), 36.62 (CH_2), 37.32 (CH_2), 39.34 (CH_2), 46.22 (4°), 51.95 (CH_3), 79.35 (CHOTBS), 112.29 (CH, thiazole-5), 115.13 (CH_2, vinyl), 115.83 (CH_2, vinyl), 128.07 (CH, vinyl), 129.02 (CH, vinyl), 130.03 (CH, vinyl), 130.78 (CH, vinyl), 136.93 (CH, vinyl), 141.89 (4°, vinyl), 155.27 (4°, thiazole-4), 156.93 (4°, C=O), 178.06 (4°, thiazole-2); HRMS (EI) calcd for $C_{28}H_{46}N_2O_3SSi$: 518.2998. Found: 518.2974.

8.1.27. Methyl [(7*S*,4*Z*)-7-(*tert*-butyldimethylsilyloxy)-8-(4-(2*E*)-hexa-2,5-dienylthiazol-2-yl)-8-methyl-3-methyl-enenon-4-enyl]carbamate ((*S*)-30). A dry round bottom flask was charged LiCl (12.3 mg, 0.289 mmol) and dried with flame under high vacuum. Upon cooling, $Pd(Ph_3P)_4$ (11.2 mg, 20 mol%) and CuCl (23.9 mg, 0.242 mmol) were added under argon, and the a solution of vinyl iodide (*S*)-**10** (25.0 mg, 0.0483 mmol) and vinyl stannane **11** (21.2 mg, 0.0725 mmol) in previously degassed DMSO (1.0 mL) was added. After the mixture was stirred at room temperature for 6 h, $Pd(Ph_3P)_4$ (11.2 mg, 20 mol%) was added since TLC indicated that the reaction had not gone to completion. After stirring for 17 h, 1N aqueous NaOH (2 mL) and ether (5 mL) was added, and the resulting mixture was filtered through the pad of celite and extracted with ether (30 mL). The extract was washed with 1N aqueous NaOH (5 mL), H_2O (5 mL), 1 M aqueous $KHSO_4$ (5 mL), and saturated brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-200, 10 g, hexane/EtOAc=10:1) to give (*S*)-**30** (9.5 mg, 38%) as a colorless oil: $[\alpha]_D^{25}=+0.47$ (*c* 0.90, $CHCl_3$): IR ν_{max} (neat) cm^{-1} 3347, 1728, 1520, 1471, 1256, 1096, 1049, 837, 776; ^1H NMR ($CDCl_3$) δ −0.08 (3H, s, CH_3), 0.05 (3H, s, CH_3), 0.88 (9H, s, Bu^t), 1.34 (3H, s, CH_3), 1.40 (3H, s, CH_3), 2.23 (2H, t, J=6.6 Hz, CH_2=$CHCH_2$), 2.33–2.39 (2H, m, allyl CH_2), 2.80 (2H, brt, J=6.3 Hz, allyl CH_2), 3.20–3.22 (2H, brm, CH_2NH), 3.48 (2H, d, J=6.4 Hz, CH_2), 3.65 (3H, s, $NHCO_2CH_3$), 4.06 (1H, t, J=5.0 Hz, CHOTBS), 4.85–5.09 (5H, m, CH=CH_2×2, $NHCO_2CH_3$), 5.49–5.92 (5H, m, vinyl-H×5), 6.73 (1H, s, thiazole-5-H); ^{13}C NMR ($CDCl_3$) δ −4.50 (CH_3), −3.46 (CH_3), 18.33 (4°), 24.65 (CH_3), 25.98 (CH_3), 26.10 (CH_3×3, Bu^t), 33.17 (CH_2), 34.91 (CH_2), 36.69 (CH_2), 37.39 (CH_2), 39.41 (CH_2), 46.27 (4°), 52.00 (CH_3), 79.35 (CHOTBS), 112.21 (CH, thiazole-5), 115.06 (CH_2, vinyl), 115.75 (CH_2, vinyl), 127.96 (CH, vinyl), 128.92 (CH, vinyl), 129.93 (CH, vinyl), 130.67 (CH, vinyl), 136.82 (CH, vinyl), 141.75 (4°, vinyl), 155.11 (4°, thiazole-4), 156.78 (4°, C=O), 177.87 (4°, thiazole-2); HRMS (EI) calcd for $C_{28}H_{46}N_2O_3SSi$: 518.2998. Found: 518.2998.

8.1.28. (*R*)-Mycothiazole ((*R*)-1). To a stirred solution of (*R*)-**30** (18.1 mg, 0.035 mmol) in THF (1.0 mL) at 0°C was added TBAF·xH_2O (60 mg). After stirring at room temperature for 2 h, H_2O (2 mL) was added, and the mixture was extracted with EtOAc (3×10 mL). The combined extracts were washed with saturated brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820 MH, 10 g, hexane/EtOAc=6:1 to 2:1) to give (*R*)-**1** (12.7 mg, 90%) as a colorless viscous oil: $[\alpha]_D^{23}=-26.0$ (*c* 0.64, $CHCl_3$); lit.[1] $[\alpha]_D^{20}=-3.8$ (*c* 2.9, $CHCl_3$): IR ν_{max} (neat) cm^{-1} 3328, 1705, 1522, 1466, 1271, 1055, 972, 908; ^1H NMR ($CDCl_3$) δ 1.39 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.18–2.43 (4H, m, allyl CH_2×2), 2.80 (2H, t, J=6.0 Hz, allyl CH_2), 3.16–3.33 (2H, m, CH_2NH) 3.46 (2H, d, J=5.6 Hz, CH_2), 3.63 (3H, s, $NHCO_2CH_3$), 3.78 (1H, dd, J=3.0, 9.6 Hz, CHOH), 4.88–5.09 (5H, m, decrease 1H with D_2O, CH=CH_2×2, OH), 5.43 (1H, brs, NH), 5.52–5.91 (5H, m, vinyl-H×5), 6.77 (1H, s, thiazole-5-H); ^{13}C NMR ($CDCl_3$) δ 23.85 (CH_3), 26.67 (CH_3), 30.59 (CH_2), 34.65 (CH_2), 36.57 (CH_2), 37.14 (CH_2), 39.37 (CH_2), 44.55 (4°), 51.83 (CH_3), 78.11 (CHOH), 111.95 (CH, thiazole-5), 115.22 (CH_2, vinyl), 115.85 (CH_2, vinyl), 127.57 (CH, vinyl), 130.44 (CH, vinyl), 130.60 (CH, vinyl), 130.85 (CH, vinyl), 136.80 (CH, vinyl), 142.48 (4°, vinyl), 155.35 (4°,thiazole-4), 157.12 (4°, C=O), 179.37 (4°, thiazole-2); HRMS (EI) calcd for $C_{22}H_{32}N_2O_3S$: 404.2134. Found: 404.2134.

8.1.29. (*S*)-Mycothiazole ((*S*)-1). To a stirred solution of (*S*)-**30** (18.2 mg, 0.0351 mmol) in THF (1.0 mL) at 0°C was added TBAF·xH$_2$O (1 M in THF, 70.2 μL, 0.0702 mmol). After stirring at room temperature for 30 min, TBAF·xH$_2$O (1 M in THF, 100 μL, 0.100 mmol) was added. After stirring at room temperature for 1 h, H$_2$O (2 mL) was added, and the mixture was extracted with EtOAc (3×10 mL). The combined extracts were washed with saturated brine (5 mL), dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-200, 10 g, hexane/EtOAc=6:1 to 4:1) to give (*S*)-**1** (13.5 mg, 95%) as a colorless viscous oil: $[\alpha]_D^{25}$=+22.3 (*c* 0.53, CHCl$_3$): IR ν_{max} (neat) cm^{-1} 3332, 1705, 1522, 1466, 1271, 1053, 972, 911; ^{1}H NMR (CDCl$_3$) δ 1.39 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.20–2.45 (4H, m, allyl CH_2×2), 2.80 (2H, dt, *J*=5.2, 1.2 Hz, allyl CH_2), 3.15–3.22 (1H, m, CH_2NH), 3.26–3.33 (1H, m, CH_2NH), 3.46 (2H, dt, *J*=6.7, 0.9 Hz, CH_2), 3.63 (3H, s, NHCO$_2$CH_3), 3.79 (1H, dd, *J*=10.4, 2.1 Hz, C*H*OH), 4.88 (1H, brs, CH=CH_2), 4.92 (1H, brs, O*H*), 4.99–5.07 (3H, m, CH=CH_2×2), 5.44 (1H, brs, N*H*), 5.54–5.71 (3H, m, vinyl-*H*×3), 5.79–5.89 (2H, m, vinyl-*H*×2), 6.77 (1H, d, *J*=0.9 Hz, thiazole-5-*H*); ^{13}C NMR (CDCl$_3$) δ 23.83 (CH$_3$), 26.66 (CH$_3$), 30.59 (CH$_2$), 34.65 (CH$_2$), 36.56 (CH$_2$), 37.13 (CH$_2$), 39.36 (CH$_2$), 44.56 (4°), 51.83 (CH$_3$), 78.12 (CHOH), 111.95 (CH, thiazole-5), 115.21 (CH$_2$, vinyl), 115.84 (CH$_2$, vinyl), 127.55 (CH, vinyl), 130.44 (CH, vinyl), 130.58 (CH, vinyl), 130.86 (CH, vinyl), 136.81 (CH, vinyl), 142.48 (4°, vinyl), 155.34 (4°,thiazole-4), 157.13 (4°, C=O), 179.36 (4°, thiazole-2); HRMS (EI) calcd for $C_{22}H_{32}N_2O_3S$: 404.2134. Found: 404.2132.

Acknowledgements

We are grateful to Professor P. Crews, University of California, Santa Cruz, for sending us the natural mycothiazole and a copy of its ^{1}H NMR spectrum. This work was financially supported in part by Grant-in-Aids from the Ministry of Education, Culture, Sports, Science and Technology, Japan. One of the authors (H. S.) thanks the Research Fellowship of Japan Society for the Promotion of Science for Young Scientists.

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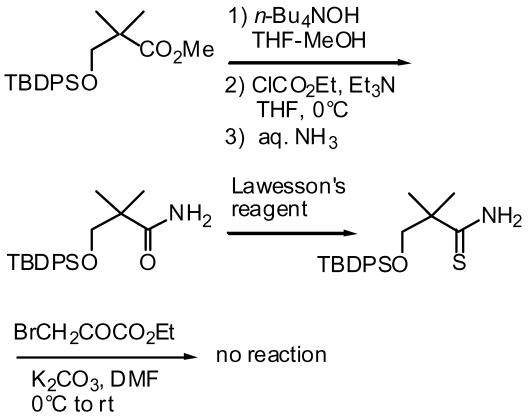

Scheme 10. The Hantzch method.

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