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Asymmetric Total Synthesis of (−)-Mycothiazole

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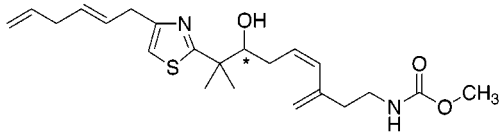
ABSTRACT



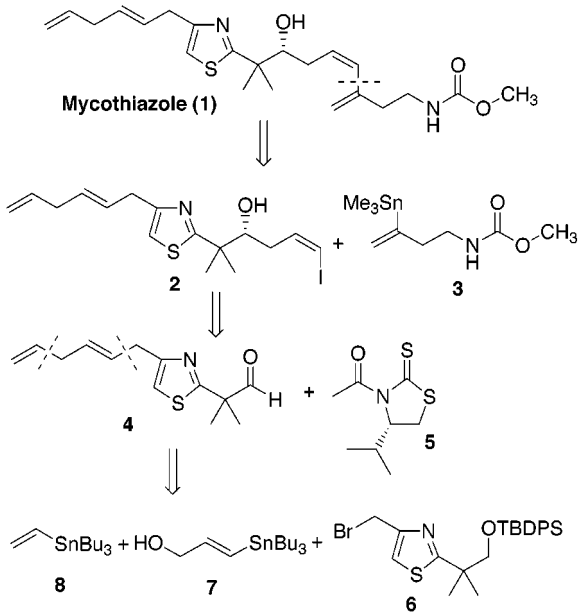
Mycothiazole (1)

In this Letter we describe the first total synthesis of mycothiazole, a polyketide thiazole from a marine sponge. Key steps include our CMD oxidation for the conversion of thiazolidine 11 to thiazole 12 and the Nagao acetate aldol reaction of 5 with aldehyde 4 to construct the chiral secondary alcohol. The skipped diene was constructed by the standard Stille coupling, and the conjugated diene was synthesized by lithium-(I)- and copper(I)-mediated Stille coupling.

Mycothiazole (**1**) was isolated from *Spongia mycofijiensis* collected in Vanuatu by Crews et al.,[1] and it exhibited anthelmintic activity (in vitro) while high toxicity was observed in mice. The most unique feature of its structure is a thiazole ring which is imbedded between two acyclic polyketide chains. While mycothiazole (**1**) was the first example of the 2,4-disubstituted thiazole to be reported, a few examples such as patellazoles A−C[2] and pateamine[3] have also been reported. Furthermore, the side chains of **1** contain skipped diene and conjugated diene systems which consist of exo- and *Z*-configured olefins. Although **1** has only one stereogenic center at the secondary alcohol, its configuration had not been determined. For the purpose of elucidation of the absolute configuration and further biological activity, we have embarked on the total synthesis of mycothiazole (**1**).

Our retrosynthetic approach is shown in Scheme 1. We disconnected the unstable conjugated diene of **1** to *Z*-iodide **2** and 1-substituted vinylstannane **3** which could be combined by Stille coupling.[4] The secondary alcohol of **2** could be constructed by the Nagao acetate aldol reaction using chiral 1,3-thiazolidine-2-thione **5**[5] with aldehyde **4**. The nonconjugated diene could be synthesized by iterative Stille coupling using vinylstannanes **7** and **8**.

Scheme 1



(1) Crews, P.; Kakou, Y.; Quiñoà, E. *J. Am. Chem. Soc.* **1988**, *110*, 4365−4368.
(2) Zabriskie, T. M.; Mayne, C. L.; Ireland, C. M. *J. Am. Chem. Soc.* **1988**, *110*, 7919−7920.
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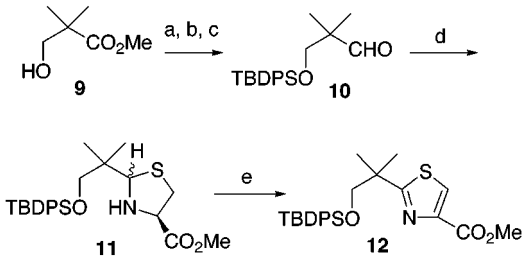
By following this synthetic strategy, we began to synthesize thiazole moiety **12**.[6] We had already developed the synthesis of thiazolidines from *N*-protected α-amino aldehydes and the cysteine methyl ester which were subsequently dehydrogenated to thiazoles using chemical manganese dioxide (CMD);[7] these were produced for dry battery manufacture. Therefore, we applied this methodology to the synthesis of the core part of **1**.

As shown in Scheme 2, protection of the hydroxy function of methyl hydroxypivalate with *tert*-butyl diphenylsilyl chloride (TBDPSCl), followed by reduction of the ester group and oxidation of the resulting alcohol, gave aldehyde **10**, which was condensed with L-cysteine methyl ester to give thiazolidine **11** as a diastereomeric mixture (71% yield in four steps). The initial attempt of CMD oxidation of **11** did not proceed, and the thiazolidine was slowly hydrolyzed to aldehyde **10**, probably because of the moisture contained in commercially available CMD.[8] Therefore, we activated CMD by azeotropic removal of H_2O with benzene, which oxidized **11** to thiazole **12** in 62% yield. Remarkably, this modified procedure gave a reproducible yield and was also tolerant even on a large scale.[9]

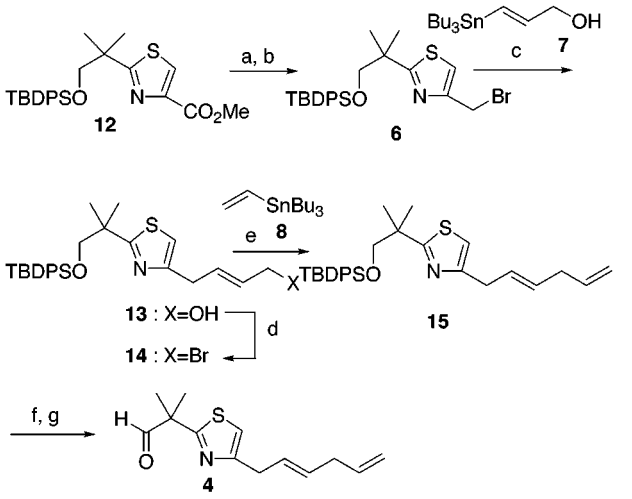
Scheme 2[a]



[a] (a)TBDPSCl, imidazole, DMF, rt, 14 h; (b) DIBAL, Et_2O, −78 °C, 30 min; (c) pyridine·SO_3, DMSO, Et_3N, CH_2Cl_2, rt, 20 min; (d) H-L-Cys-OMe·HCl, Et_3N, toluene, rt, 12 h, 71% in four steps; (e) CMD, pyridine, benzene, reflux, 12 h, 62%.

The following synthesis of aldehyde **4** is summarized in Scheme 3. After reduction of the ester (91% yield), treatment of the resulting alcohol with Ms_2O and then LiBr quantitatively provided bromide **6**. The Stille coupling of **6** with vinylstannane **7**,[10] obtained from propargyl alcohol in a single step, using $Pd(CH_3CN)_2Cl_2$ as a catalyst in the absence of phosphine ligand rapidly proceeded to give coupling product **13** in 94% yield. Conversion of **13** to the corresponding allyl bromide **14** (95% yield) followed by coupling with tri-*n*-butylvinylstannane **8** afforded skipped diene **15**[11] in 85% yield. After deprotection of the TBDPS ether with TBAF, oxidation of the resulting alcohol gave aldehyde **4** in excellent yield.

Scheme 3[a]



[a] (a) DIBAL, Et_2O, −78 °C, 30 min, 91%; (b) Ms_2O, Et_3N, CH_2Cl_2, 0 °C, 20 min; LiBr, acetone, rt, 1 h, quantitative; (c) **7**, $Pd(CH_3CN)_2Cl_2$ (10 mol %), NMP, rt, 10 min, 94%; (d) CBr_4, Ph_3P, CH_2Cl_2, rt, 10 min, 95%; (e) **8**, $Pd(CH_3CN)_2Cl_2$(10 mol %), NMP, rt, 40 min, 85%; (f) TBAF, THF, 55 °C, 2 h, quantitative; (g) pyridine·SO_3, DMSO, Et_3N, CH_2Cl_2, rt, 20 min, 95%.

The introduction of the C_2-unit accompanied by the stereoselective construction of the chiral center was performed by the Nagao acetate aldol reaction of aldehyde **4** with *N*-acetylthiazolidinethione **5**,[5] which proceeded smoothly to give (*R*)-aldol adduct **17** in a highly diastereoselective fashion (>10:1 dr by ^1H NMR spectrum of the crude product). The transition state of the reaction is probably **16**, shown in Scheme 4. Major diastereoisomer **17** could be isolated in a pure state in 75% yield by SiO_2 column chromatography. Confirmation of the stereoconfiguration was achieved by using a modified Mosher method.[12] The removal of the chiral auxiliary with LiOH and H_2O_2[13] followed by

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(6) Other synthetic methods for the thiazole moiety of mycothiazole (**1**) have been reported. Serra, G.; Mahler, G.; Mante, E. *Heterocycles* **1998**, *48*, 2035−2048.

(7) (a) Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252−1255. (b) Aoyama, T.; Sonoda, N.; Yamauchi, M.; Toriyama, K.; Anzai, A.; Ando, A.; Shioiri, T. *Synlett* **1998**, 35−36.

(8) CMD was purchased from Wako Pure Chemical Industries, Ltd.

(9) We obtained **12** in 50% yield on a 30 mmol scale.

(10) (a) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851−3854. (b) Oddon, G.; Uguen, D. *Tetrahedoron Lett.* **1988**, *39*, 1153−1156.

(11) This reaction also gave a trace amount of S_N2'-type product which was the major product in copper-mediated coupling of **14** with vinylmagnesium bromide.

(12) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(13) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141−6144.

(14) (a) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475−1478. (b) Shioiri, T.; Aoyama, T. *Encyclopedia of Reagents for Organic Synthesis*, Vol. 7; Paquette, L. A., Ed.; John. Wiley & Sons: Chichester, 1985; p 5248

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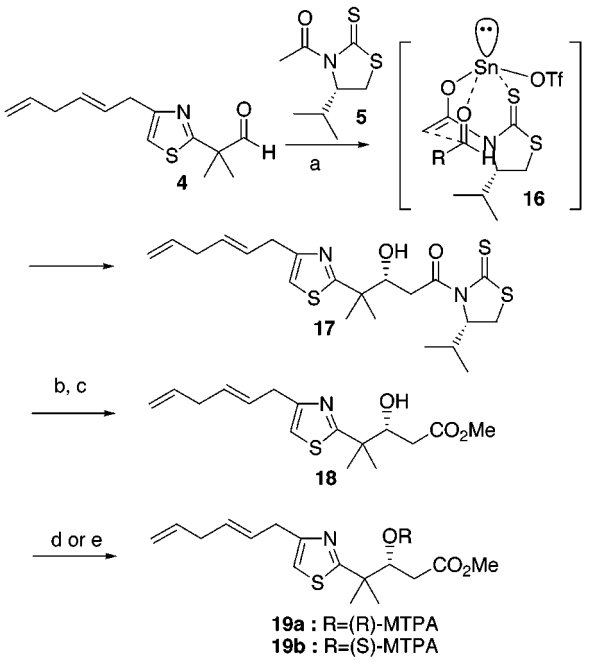
(16) Kamiyama, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675−676.

(17) Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahedron* **1999**, *55*, 2183-2192.

Scheme 4[a]



[a] (a) **5**, $Sn(OTf)_2$, *N*-ethylpiperidine, CH_2Cl_2, −45 to −15 °C, 3 h; **4**, −78 °C, 20 min, 75%; (b) LiOH, H_2O_2, THF/H_2O, 0 °C, 15 min; (c) $TMSCHN_2$, MeOH/toluene (3:1), rt, 30 min quantitative in two steps; (d) (*R*)-MTPA, DCC, DMAP, CH_2Cl_2, rt, 16 h, then 35 °C, 20 h, 85%; (e) (*S*)-MTPA-Cl, DMAP, CH_2Cl_2, 0 °C to rt, 2.5 h, 81%.

esterification using $TMSCHN_2$[14] quantitatively afforded *β*-hydroxy ester **18**. Alcohol **18** was treated with (*R*)-MTPA, DCC, and DMAP or (*S*)-MTPA-Cl[15] and DMAP to give the corresponding MTPA esters **19a** and **19b**, respectively, in high yield. As predicted, the configuration of the secondary alcohol was determined to be (*R*) by analysis of ^{1}H NMR spectra.

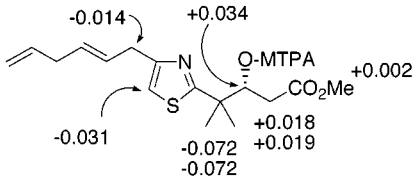
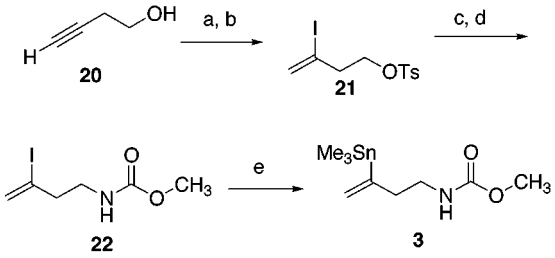


Figure 1. $\Delta\delta$ ($\delta S - \delta R$) values (ppm) for ^{1}H NMR.

The other required fragment, 1-substituted vinylstannane **3**, was synthesized as shown in Scheme 5. Thus, regioselective addition of HI to 3-butyn-1-ol **20** under Ishii conditions[16] followed by Me_3N-catalyzed tosylation[17] gave vinyl iodide **21** in 55% yield (two steps). After conversion of tosylate to the azide with NaN_3, reduction with Ph_3P followed by protection with methoxycarbonyl chloride furnished compound **22** in 78% yield for two steps. Finally,

Scheme 5[a]



[a] (a) TMSCl, NaI, H_2O, CH_3CN, rt, 1 h; (b) TsCl, Et_3N, Me_3N·HCl, CH_2Cl_2, 0 °C, 1 h, 55% in two steps; (c) NaN_3, DMF, rt, 2 h, then, 50 °C, 3 h; (d) Ph_3P, H_2O, THF, rt, 12 h; $ClCO_2Me$, Et_3N, rt, 4 h, 78% in two steps; (e) $Me_3SnSnMe_3$, $Pd(CH_3CN)_2Cl_2$ (10 mol %), NMP, rt, 4 h, 57%.

conversion of iodide **22** to trimethyltin analogue **3** was achieved with $Me_3SnSnMe_3$[18] in 56% yield.

The construction of mycothiazole is summarized in Scheme 6. After protection of the secondary alcohol of **17** with TBSOTf, removal of the chiral auxiliary with DIBAL[19] gave the aldehyde **23** in 86% yield. Homologation of **23** to (*Z*)-vinyl iodide **2** was effected in a completely stereoselective manner in 82% yield by treatment with $Ph_3P^+CH_2I \cdot I^-$ under "salt-free" condition developed by Stork.[20]

The first attempt to accomplish the final cross-coupling of **2** to **3** with $Pd(CH_3CN)_2Cl_2$ was ineffective, and no desired product was obtained. Instead, **3** was decomposed when the temperature was raised. Alternatively, addition of $CdCl_2$[21] to accelerate the rate of transmetalation gave the coupling product **24** in only 25% yield. However, CuCl- and LiCl-mediated Stille coupling modified by Corey[22] afforded **24** in 63% yield without the *cine* (Heck-type) product.[23] Finally, deprotection of the TBS group using TBAF provided (−)-mycothiazole in 90% yield. Although this material proved to be identical in all respects (^{1}H and ^{13}C NMR, IR, HRMS) with natural mycothiazole, there are differences in the $[\alpha]_D$ values between the synthetic and natural products (synthetic, $[\alpha]^{23}_D$ −26.0 (*c* 0.6, $CHCl_3$); natural, $[\alpha]^{23}_D$ −3.8 (*c* 2.9, $CHCl_3$)). It is possible that contamination with artifacts exists in natural mycothiazole.[24] Using the modified Mosher analysis, the absolute stereochemistry of the synthetic product

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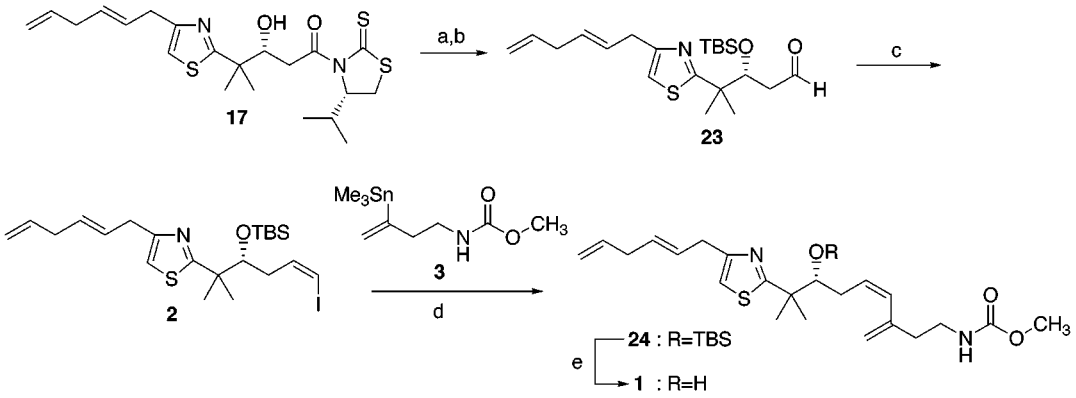
(22) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605.
(23) (a) Farina, V.; Hossain, M. A. *Tetrahedron Lett.* **1996**, *37*, 6997−7000. (b) Crisp, G. T.; Glink, P. T. *Tetrahedron.* **1994**, *50*, 3213−3234. See also ref 22.
(24) The (*R*)-mycothiazole we synthesized was found to be rather labile. In fact, when we received the natural mycothiazole from P. Crews' laboratory (we thank Prof. Crews for sending the natural sample and ^{1}H NMR spectrum), it was decomposed, and we could not measure its optical rotation. Thus, the natural sample may have contaminated with decomposed products such as dehydration products, further oxidation products, or isomerization products when its optical rotation was measured.

Scheme 6[a]



[a] (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 96%; (b) DIBAL, toluene, −78 °C, 1 h, 86%; (c) $Ph_3P^+CH_2I\cdot I^-$, NaHMDS, HMPA, THF, −78 °C, 1 h, 82%; (d) $Pd(Ph_3P)_4$ (40 mol %), CuCl (5.0 equiv), LiCl (6.0 equiv), DMSO, rt, 15 h, 63%; (e) TBAF, THF, rt, 2 h, 90%.

can be determined, and (−)-mycothiazole is assigned as (*R*). However, due to the disparity in $[\alpha]_D$ values, we cannot make a definitive assignment of the mycothiazole at the present time.

In summary, we have accomplished the first asymmetric total synthesis of (−)-mycothiazole. During the course of the synthesis, we have demonstrated the utilities of the Nagao acetate aldol reaction and cuprous chloride accelerated Stille coupling with a 1-substituted vinylstannane and a (*Z*)-vinyl iodide. In addition, we have found that azeotropic activation of CMD allowed the CMD-mediated thiazole synthesis to be reproducible even on a large scale. Further application of this CMD methodology to the thiazole-containing natural products is underway in our laboratory and will be reported in due course.[25]

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Supporting Information Available: Experimental procedures for the preparation of compound **17** and all compounds reported in Scheme 2, 3, 5, and 6. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Our preliminary work has recently been reported, see: Fujiwara, H.; Tojiki, K.; Yokokawa, F.; Shioiri, T. *Peptide Science 1999*; Fujii, N., Ed.; The Japanese Peptide Society: Minoh, 2000, pp 9−12.