

Asymmetric Total Synthesis of
(–)-Mycothiazole

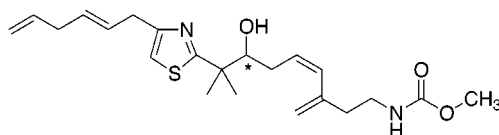
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Received May 15, 2000

ABSTRACT

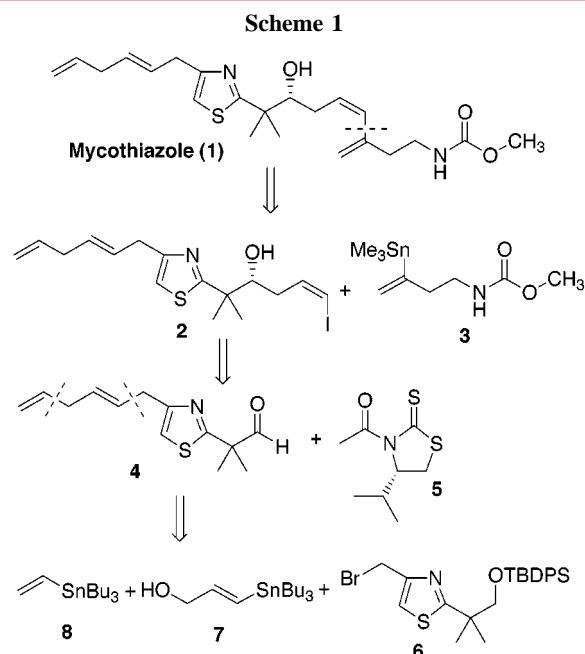


Mycothiazole (1)

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–C² and pateamine³ 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**.

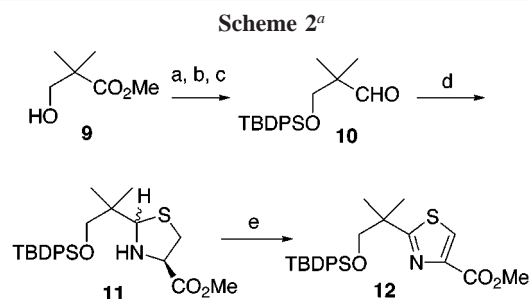
(1) Crews, P.; Kakou, Y.; Quiñoà, E. *J. Am. Chem. Soc.* **1988**, *110*, 4365–4368.

(2) Zabriskie, T. M.; Mayne, C. L.; Ireland, C. M. *J. Am. Chem. Soc.* **1988**, *110*, 7919–7920.

(3) Northcote, P. T.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron. Lett.* **1991**, *32*, 6411–6414.

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



^a (a) TBDPSCl, imidazole, DMF, rt, 14 h; (b) DIBAL, Et₂O, -78 °C, 30 min; (c) pyridine·SO₃, DMSO, Et₃N, CH₂Cl₂, rt, 20 min; (d) H-L-Cys-OMe·HCl, Et₃N, toluene, rt, 12 h, 71% in four steps; (e) CMD, pyridine, benzene, reflux, 12 h, 62%.

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 H₂O 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

(4) Reviews: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 508–524. (b) Mitchell, T. N. *Synthesis* **1992**, 803–815. (c) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, 50, 1–652. (d) Duncton, M. A. J.; Pattenden, G. J. *Chem. Soc., Perkin Trans. 1* **1999**, 1235–1246.

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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.

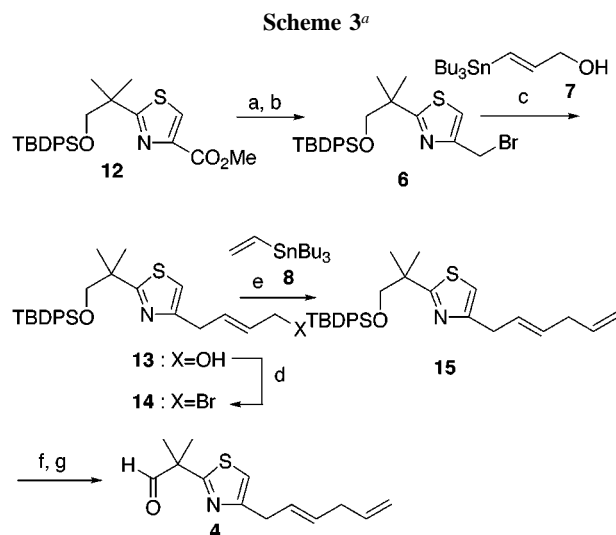
(10) (a) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, 23, 3851–3854. (b) Odon, G.; Uguen, D. *Tetrahedron Lett.* **1988**, 39, 1153–1156.

(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.

The following synthesis of aldehyde **4** is summarized in Scheme 3. After reduction of the ester (91% yield), treatment



^a (a) DIBAL, Et₂O, -78 °C, 30 min, 91%; (b) Ms₂O, Et₃N, CH₂Cl₂, 0 °C, 20 min; LiBr, acetone, rt, 1 h, quantitative; (c) **7**, Pd(CH₃CN)₂Cl₂ (10 mol %), NMP, rt, 10 min, 94%; (d) CBr₄, Ph₃P, CH₂Cl₂, rt, 10 min, 95%; (e) **8**, Pd(CH₃CN)₂Cl₂ (10 mol %), NMP, rt, 40 min, 85%; (f) TBAF, THF, 55 °C, 2 h, quantitative; (g) pyridine·SO₃, DMSO, Et₃N, CH₂Cl₂, rt, 20 min, 95%.

of the resulting alcohol with Ms₂O 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(CH₃CN)₂Cl₂ 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.

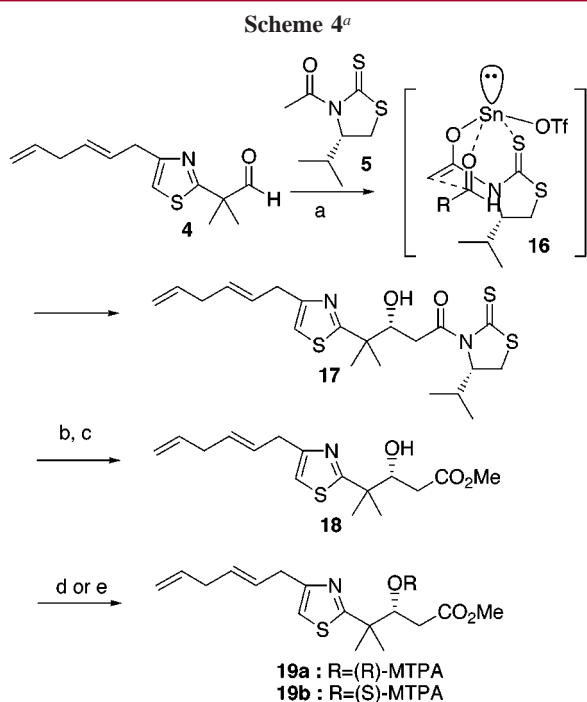
The introduction of the C₂-unit accompanied by the stereoselective construction of the chiral center was performed by the Nagao acetate aldol reaction of aldehyde **4** with *N*-acetylthiazolidinethione **5**,⁵ which proceeded smoothly to give (*R*)-aldol adduct **17** in a highly diastereoselective 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 SiO₂ column chromatography. Confirmation of the stereoconfiguration was achieved by using a modified Mosher method.¹² The removal of the chiral auxiliary with LiOH and H₂O₂¹³ followed by

(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.

(15) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, 32, 7165–7166.

(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.



^a (a) **5**, Sn(OTf)₂, *N*-ethylpiperidine, CH₂Cl₂, -45 to -15 °C, 3 h; **4**, -78 °C, 20 min, 75%; (b) LiOH, H₂O₂, THF/H₂O, 0 °C, 15 min; (c) TMSCHN₂, MeOH/toluene (3:1), rt, 30 min quantitative in two steps; (d) (*R*)-MTPA, DCC, DMAP, CH₂Cl₂, rt, 16 h, then 35 °C, 20 h, 85%; (e) (*S*)-MTPA-Cl, DMAP, CH₂Cl₂, 0 °C to rt, 2.5 h, 81%.

esterification using TMSCHN₂¹⁴ quantitatively afforded β -hydroxy ester **18**. Alcohol **18** was treated with (*R*)-MTPA, DCC, and DMAP or (*S*)-MTPA-Cl¹⁵ 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 ¹H NMR spectra.

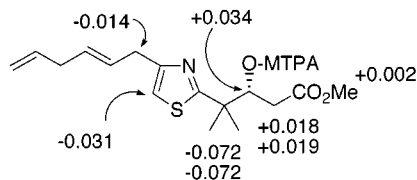
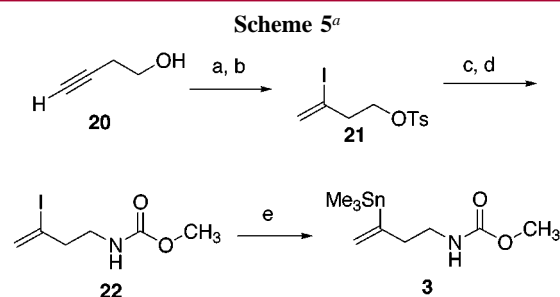


Figure 1. $\Delta\delta$ ($\delta_S - \delta_R$) values (ppm) for ¹H NMR.

The other required fragment, 1-substituted vinylstannane **3**, was synthesized as shown in Scheme 5. Thus, regioselective addition of HI to 3-butyne-1-ol **20** under Ishii conditions¹⁶ followed by Me₃N-catalyzed tosylation¹⁷ gave vinyl iodide **21** in 55% yield (two steps). After conversion of tosylate to the azide with NaN₃, reduction with Ph₃P followed by protection with methoxycarbonyl chloride furnished compound **22** in 78% yield for two steps. Finally,



^a (a) TMSCl, NaI, H₂O, CH₃CN, rt, 1 h; (b) TsCl, Et₃N, Me₃N·HCl, CH₂Cl₂, 0 °C, 1 h, 55% in two steps; (c) NaN₃, DMF, rt, 2 h, then, 50 °C, 3 h; (d) Ph₃P, H₂O, THF, rt, 12 h; ClCO₂Me, Et₃N, rt, 4 h, 78% in two steps; (e) Me₃SnSnMe₃, Pd(CH₃CN)₂Cl₂ (10 mol %), NMP, rt, 4 h, 57%.

conversion of iodide **22** to trimethyltin analogue **3** was achieved with Me₃SnSnMe₃¹⁸ 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 DIBAL¹⁹ 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 Ph₃P⁺CH₂I⁻ under “salt-free” condition developed by Stork.²⁰

The first attempt to accomplish the final cross-coupling of **2** to **3** with Pd(CH₃CN)₂Cl₂ was ineffective, and no desired product was obtained. Instead, **3** was decomposed when the temperature was raised. Alternatively, addition of CdCl₂²¹ to accelerate the rate of transmetalation gave the coupling product **24** in only 25% yield. However, CuCl- and LiCl-mediated Stille coupling modified by Corey²² 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 (¹H and ¹³C NMR, IR, HRMS) with natural mycothiazole, there are differences in the [α]_D values between the synthetic and natural products (synthetic, [α]_D²³ –26.0 (*c* 0.6, CHCl₃); natural, [α]_D²³ –3.8 (*c* 2.9, CHCl₃)). 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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(19) Izawa, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1979**, 52, 555–558.

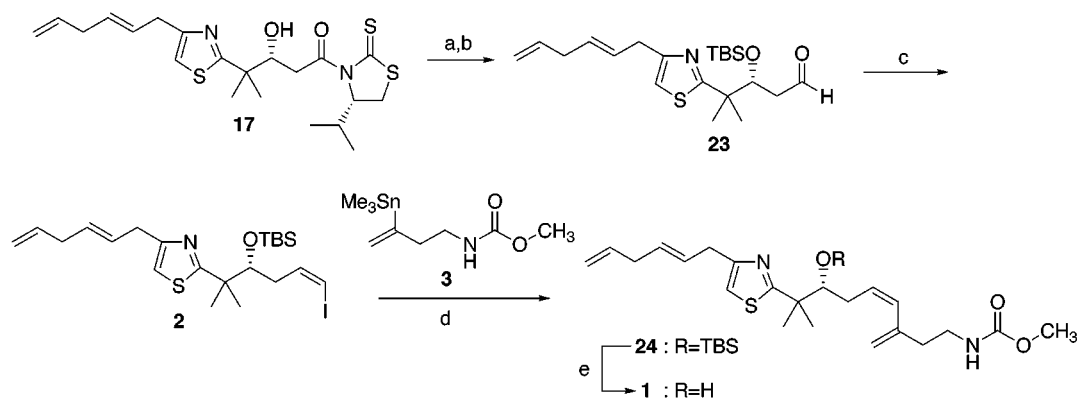
(20) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, 30, 2173–2174.

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(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 ¹H 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, CH₂Cl₂, 0 °C, 30 min, 96%; (b) DIBAL, toluene, −78 °C, 1 h, 86%; (c) Ph₃P⁺CH₂I[−], NaHMDS, HMPA, THF, −78 °C, 1 h, 82%; (d) Pd(Ph₃P)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 [α]_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

Acknowledgment. This work was financially supported in part by Grant-in-Aids from the Ministry of Education, Science, Sports and Culture, Japan.

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.