

Total Synthesis of Cystothiazoles  
A and B

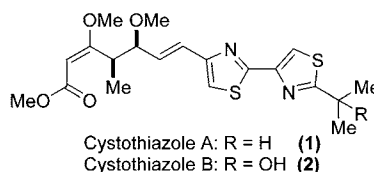
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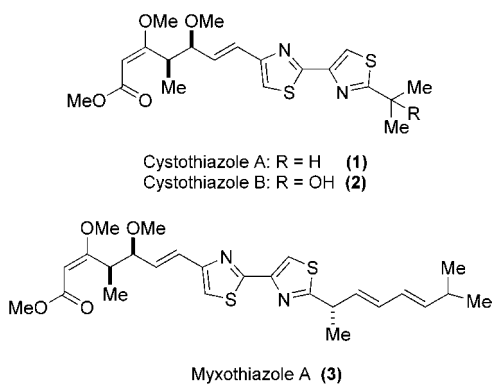
## ABSTRACT



Convergent enantioselective syntheses of the antifungal agents cystothiazoles A and B are described. The routes feature an asymmetric crotylation using a propargylic dicobalt hexacarbonyl complex, which provided enhanced diastereoselectivity over the uncomplexed propargylic acetal. The bisthiazole fragment was united with the side chain through a Stille cross-coupling of a terminal (*E*)-vinylstannane with a 4-triflyl-substituted thiazole.

In 1998, Sakagami and co-workers reported the isolation of cystothiazoles A and B from a culture broth of the myxobacterium, *Cystobacter fuscus*.<sup>1</sup> Cystothiazoles A and B have demonstrated potent antifungal activity against a wide range of fungi. These agents, however, show little or no effect on inhibition of bacterial growth. Although these compounds are structurally related to the known antibiotic myxothiazole,<sup>2</sup> cystothiazole A is more active against fungi and less cytotoxic.

Earlier reports have documented the independent total synthesis of cystothiazoles A, B, C, E and G.<sup>3</sup> In this paper, we describe convergent enantioselective syntheses of cystothiazoles A and B.



Our retrosynthetic strategy is illustrated in Scheme 1. The target molecules could be divided into two subunits, C<sub>1</sub>–C<sub>7</sub> fragment **4** and bisthiazole fragment **5**, which will be coupled at a late stage via a Stille cross-coupling reaction. The C<sub>1</sub>–C<sub>7</sub> fragment could be obtained from the  $\beta$ -ketoester **6**, which was ultimately derived from a crotylsilane addition to the dicobalt hexacarbonyl complex **10**. The bisthiazole fragment **5** was synthesized by a regioselective Stille cross-coupling reaction with the 2,4-bistriflyl thiazole **7** and 4-bromothiazole **8**.<sup>4</sup>

In our preliminary studies, it was found that the direct crotylation between silane (*S*)-**9** and the 3-(trimethylsilyl)

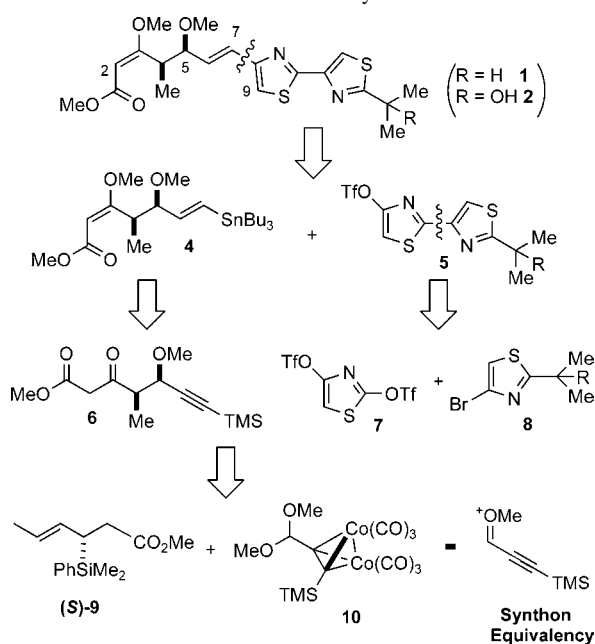
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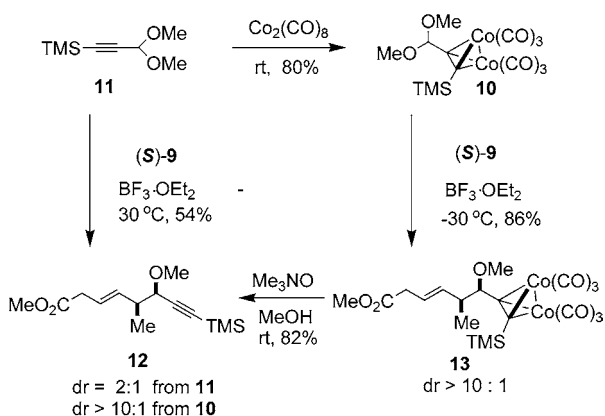
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### Scheme 1. Retrosynthesis



propargyl dimethyl acetal **11** produced the homoallylic ether in high yield (> 80%); however, it did so without useful selectivity (syn/anti = 2:1). To get around this problem, a propargylic dicobalt complex<sup>5</sup> was used to add steric bulk to the acetal, which we hoped would create a sufficient energy difference between the competing diastereotopic transition states during the crotylation. Gratifyingly, reaction of silane (*S*)-**9** with the cobalt complexed acetal **10** resulted in a significant enhancement of diastereoselectivity (syn/anti > 10:1), affording the homoallylic ether in 86% yield (Scheme 2).<sup>6</sup> The removal of the dicobalt complex of **13**

### Scheme 2

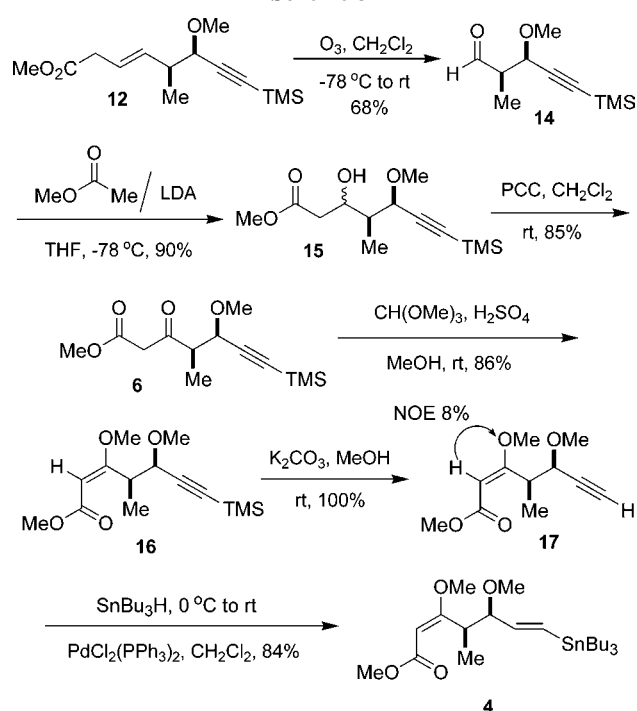


was achieved using trimethylamine *N*-oxide in MeOH. The cleavage of the olefin by ozonolysis gave the aldehyde **14** in 68% yield, which is volatile and prone to decomposition at room temperature. This material was submitted to low-temperature condensation with the lithium enolate derived

from methyl acetate. The resulting mixture of diastereomeric alcohols **15** was subjected to an oxidation using PCC to form the  $\beta$ -ketoester **6** in 85% yield (6:1 ketone/enol form determined by  $^1\text{H}$  NMR).  $\beta$ -Ketoester **6** was treated with trimethyl orthoformate in the presence of catalytic sulfuric acid to form the desired (*E*)- $\beta$ -methoxyacrylate **16** in 86% yield (*E*:*Z* = 7:1 as determined by  $^1\text{H}$  NMR).<sup>7</sup> The *E* geometry was assigned by measurement of NOE for the olefin proton and the methoxy group. After deprotection by  $\text{K}_2\text{CO}_3$  in methanol, the alkyne **17** was subjected to the Pd-catalyzed hydrostannylation.  $\beta$ -(*E*) regioselective product **4** was achieved in 84% yield ( $\alpha$ : $\beta$ -(*E*): $\beta$ -(*Z*) = 1:7:0 as determined by  $^1\text{H}$  NMR relative to the MeO group).<sup>8</sup>

The bisthiazole fragments **5a** and **5b** were derived from three different thiazoles as illustrated in Schemes 4 and 5.

### Scheme 3



Accordingly, 4-bromo-2-isopropyl-thiazole **8a** was obtained by a regioselective Negishi cross-coupling reaction from the dibromide **18**<sup>9</sup> in 72% yield.<sup>10</sup> As predicted, the reaction occurred at the most electron-deficient position of the heterocycle. The synthesis of the 4-bromo-2-(isopropyl-*tert*-butyldimethylsilyloxy)-thiazole **8b** involved a bromine–lithium exchange, followed by the addition of anhydrous acetone, followed by treatment of the derived secondary

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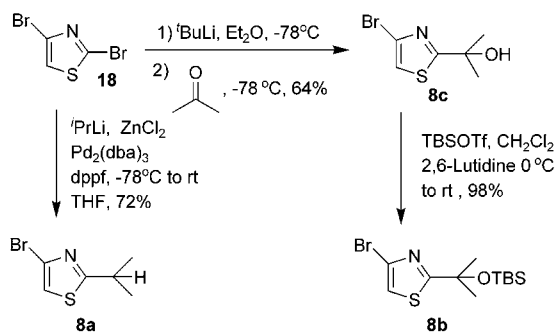
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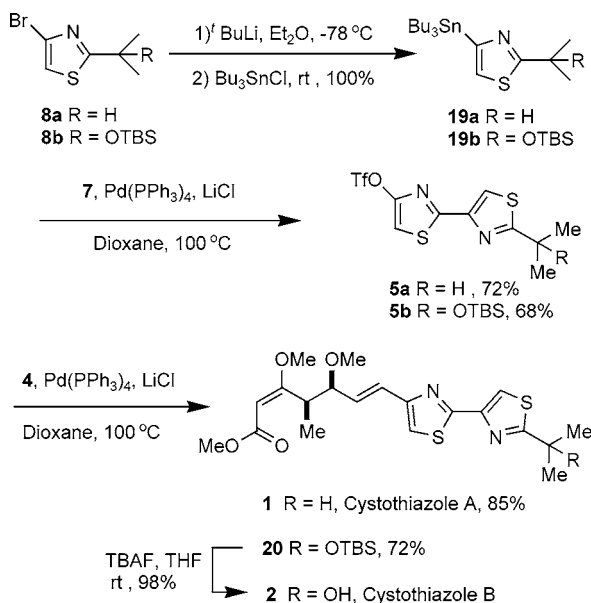
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Scheme 4



Scheme 5



alcohol with TBSOTf and 2,6-lutidine, and gave the silyl-protected bromothiazole **8b** in 98% yield.

The bithiazole fragments of **1** and **2** were formed through Stille cross-coupling reactions. The required 4-tributylstannylthiazoles **19a** and **19b** were prepared from the bromide by bromine–lithium exchange and the subsequent quench

with  $\text{Bu}_3\text{SnCl}$ . The crude stannane was submitted directly to the Stille cross-coupling reaction with the ditriflate **7** using  $\text{Pd}(\text{PPh}_3)_4$  as a catalyst, dioxane as a solvent, and the addition 3 equiv of  $\text{LiCl}$ . The reactions were achieved in 72 and 68% yields when  $\text{R} = \text{H}$  or OTBS, respectively.<sup>4,11</sup> Identical conditions were employed for the construction of the bithiazole fragments in the final Stille cross-coupling reaction. Cystothiazole A (**1**) could be synthesized directly from the coupling of the  $\text{C}_1$ – $\text{C}_7$  fragment **4** and bithiazole fragment **5a** in 85% yield. After the Stille cross-coupling of the  $\text{C}_1$ – $\text{C}_7$  fragment **4** and bithiazole fragment **5b** (72% yield), a final deprotection step using TBAF gave cystothiazole B (**2**) in 98% yield.

In summary, convergent enantioselective syntheses of the antifungal agents cystothiazoles A and B have been achieved. Cystothiazole A was synthesized in 12 linear steps and 15% overall yield, and cystothiazole B was synthesized in 13 linear steps and 13% overall yield. Key features of the synthesis include high levels of selectivity in the crotylation using a propargylic dicobalt hexacarbonyl complex to establish the syn-homoallylic ether of the side chain. The bithiazole fragment was coupled to the left-hand side chain using a Stille cross-coupling. On balance, the asymmetric crotylation methodology, together with transition metal-mediated cross-coupling reaction, offers a promising and efficient approach to these natural products.

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**Supporting Information Available:** General experimental procedures, including spectroscopic and analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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