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Total Synthesis of Cystothiazoles A and B

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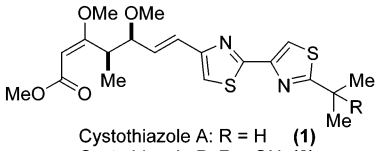
ABSTRACT

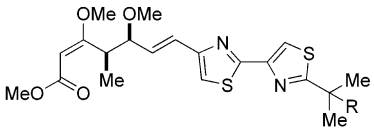


Cystothiazole A: R = H **(1)**
Cystothiazole B: R = OH **(2)**

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-trifloyl-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*.[1] 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,[2] 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.[3] In this paper, we describe convergent enantioselective syntheses of cystothiazoles A and B.



Cystothiazole A: R = H **(1)**
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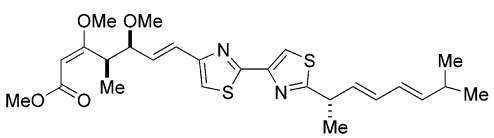

Myxothiazole A **(3)**

Our retrosynthetic strategy is illustrated in Scheme 1. The target molecules could be divided into two subunits, C_1-C_7 fragment **4** and bisthiazole fragment **5**, which will be coupled at a late stage via a Stille cross-coupling reaction. The C_1-C_7 fragment could be obtained from the β-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-bistrifloyl thiazole **7** and 4-bromothiazole **8**.[4]

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

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(2) (a) Gerth, K.; Irschik, H.; Reichenbach, H.; Trowitzsch, W. *J. Antibiot.* **1980**, *33*, 1474−1479. (b) Trowitzsh, W.; Reifenstahl, G.; Wray, W.; Gerth, K. *J. Antibiot.* **1980**, *33*, 1480−1490.

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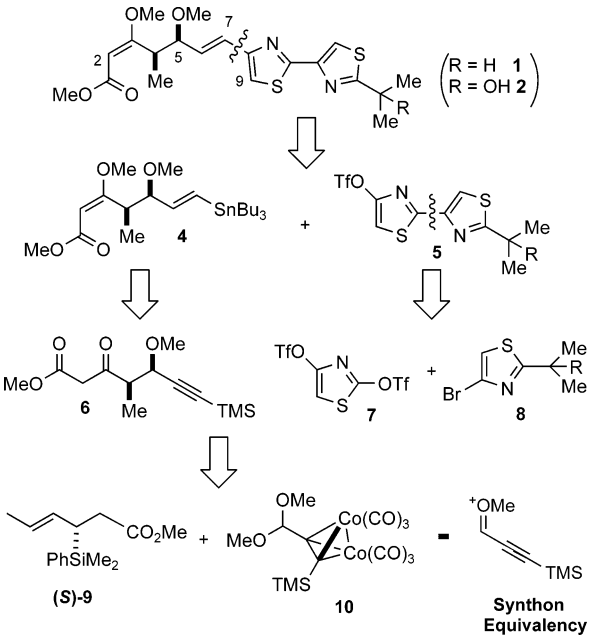
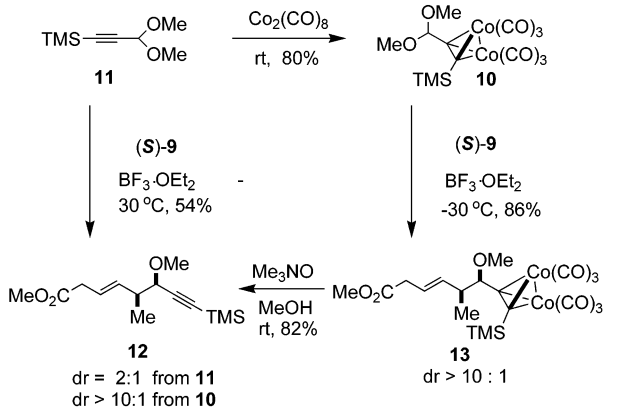
Scheme 1. Retrosynthesis



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[5] 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).[6] The removal of the dicobalt complex of **13**

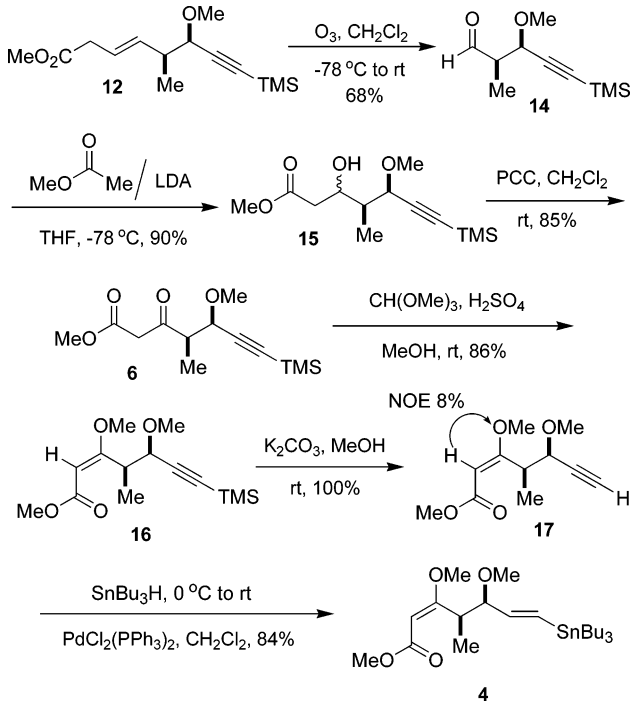
Scheme 2



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 *β*-ketoester **6** in 85% yield (6:1 ketone/enol form determined by ^{1}H NMR). *β*-Ketoester **6** was treated with trimethyl orthoformate in the presence of catalytic sulfuric acid to form the desired (*E*)-*β*-methoxyacrylate **16** in 86% yield (*E*:*Z* = 7:1 as determined by ^{1}H NMR).[7] The *E* geometry was assigned by measurement of NOE for the olefin proton and the methoxy group. After deprotection by K_2CO_3 in methanol, the alkyne **17** was subjected to the Pd-catalyzed hydrostannylation. *β*-(*E*) regioselective product **4** was achieved in 84% yield (α:*β*-(*E*):*β*-(*Z*) = 1:7:0 as determined by ^{1}H NMR relative to the MeO group).[8]

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**[9] in 72% yield.[10] 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

(5) (a) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749−5759. (b) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353−4363.
(6) Sui, M.; Panek, J. S. *Org. Lett.* **2001**, *3*, 2439−2442.
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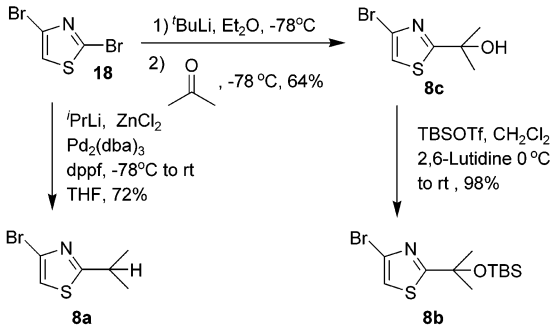
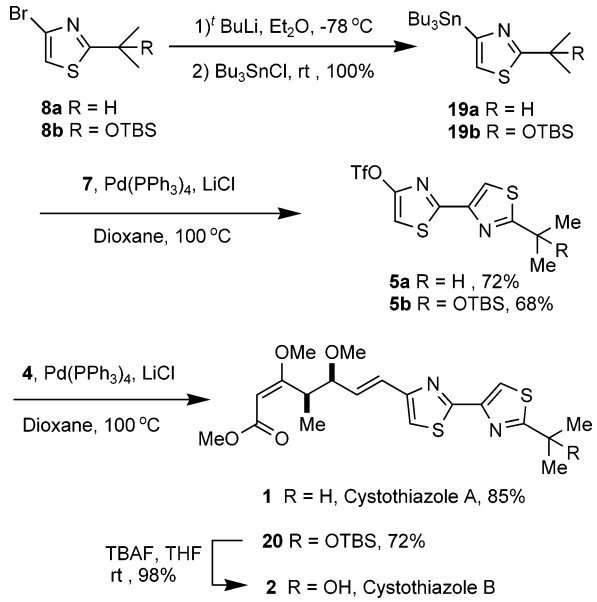
(10) Bach, T.; Heuser, S. *J. Org. Chem.* **2002**, *67*, 5789−5795.

Scheme 4



Scheme 5



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

The bisthiazole 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 Bu_3SnCl. The crude stannane was submitted directly to the Stille cross-coupling reaction with the ditriflate **7** using $Pd(PPh_3)_4$ as a catalyst, dioxane as a solvent, and the addition 3 equiv of LiCl. The reactions were achieved in 72 and 68% yields when R = H or OTBS, respectively.[4,11] Identical conditions were employed for the construction of the bisthiazole fragments in the final Stille cross-coupling reaction. Cystothiazole A (**1**) could be synthesized directly from the coupling of the C_1-C_7 fragment **4** and bisthiazole fragment **5a** in 85% yield. After the Stille cross-coupling of the C_1-C_7 fragment **4** and bisthiazole 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 bisthiazole 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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