

Total Synthesis of (+)-Cystothiazole A

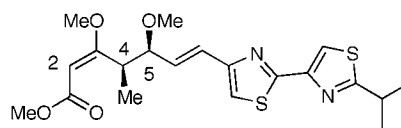
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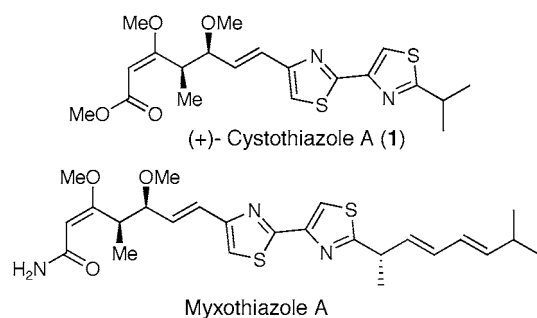
ABSTRACT



(+)-Cystothiazole A (1)

The total synthesis of cystothiazole A is described. Key steps of the synthesis include an Evans asymmetric catalytic aldol reaction, which established the required C₄–C₅ stereochemistry. The [2,4']-bis(thiazole) was obtained applying our methodology of electrophilic activation of amide. Semistabilized Wittig reaction between the phosphonium salt 3 and the aldehyde 2 afforded 1 in nine linear steps and 38% overall yield.

In 1998, Sakagami¹ and co-workers isolated from the myxobacterium *Cystobacter fuscus* a bis(thiazole)-type antibiotic called cystothiazole A.



This natural product was highly active against a wide range of fungi, including *Candida albicans* (AJ-5682, MIC 0.4 μg/mL), with no effect on bacterial growth. Although this compound was structurally similar to the known antibiotic myxothiazol,² cystothiazole A was more active against fungi and less cytotoxic. Its antifungal activity appeared to result from the inhibition of submitochondrial NADH oxidation.^{1,3} It was

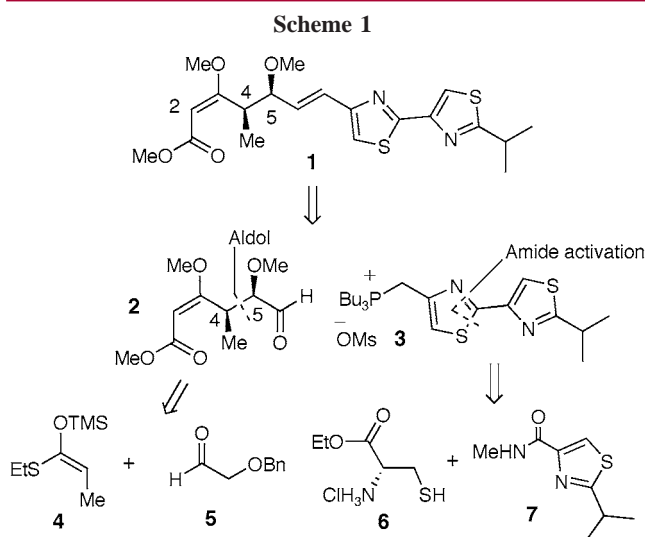
also discovered to possess an in vitro cytotoxicity against human tumor cells: colon carcinoma HCT-116 and Leukaemia K 562 with an IC₅₀ value of, respectively, 130 and 110 ng/mL. The structure of (+)-cystothiazole A (1) was determined by NMR methods (¹H, ¹³C, HETCOR, HMBC), with the *E* geometry of the trisubstituted double bond at C₂ being determined by difference NOE data (H-2/3-OMe). Its absolute chemistry was confirmed by the total syntheses of Williams in 2001^{4a} and Akita and co-workers in 2002.⁵

Our interest in the total synthesis of (+)-cystothiazole A originated not only because of its interesting biological activity but also because of its [2,4']-bis(thiazole) unit. In 1998, we reported an efficient method to synthesize thiazoline moieties,⁶ and since then we have applied this methodology to the total synthesis of curacin A and B.⁷ Herein, we report the total synthesis of (+)-cystothiazole A, extending our methodology to obtain the [2,4']-bis(thiazole) unit.

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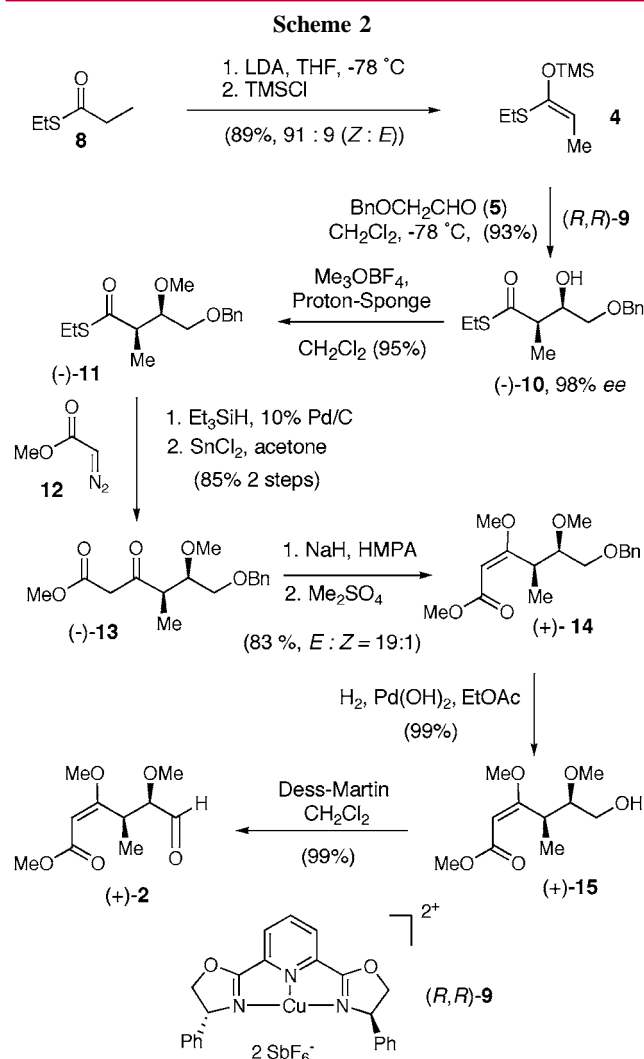
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Our retrosynthetic strategy of **1** is illustrated in Scheme 1 and involves a catalytic asymmetric synthesis of the β -methoxyacrylate system, and the application of our electrophilic amide activation methodology for constructing the [2,4']-bis(thiazole) moiety. Thus, **1** would be synthesized by Wittig-type reaction of an aldehyde **2** with a phosphonium salt **3**.⁸ The C₄–C₅ vicinal stereogenic centers would be introduced by an Evans catalytic asymmetric aldol reaction between silylketene acetal **4** and (benzyloxy)acetaldehyde **5**.⁹ The latter process would then be followed by an activation of amide **7** and treatment with L-cysteine hydrochloride **6**, and an oxidation step would be used to obtain the bis(thiazole) unit.

Synthesis of (+)-**2** began with the formation of the (*Z*)-silylketene thioacetal **4** (Scheme 2).¹⁰ The [Cu(*R,R*-Phpybox)](SbF₆)₂ (**9**)-catalyzed aldol reaction between benzyloxyacetaldehyde **5** and (*Z*)-silylketene acetal **4** smoothly afforded the *syn* aldol adduct (–)-**10** ($[\alpha]_{\text{D}}^{25}$ –42.4° (*c* 0.55, CH₂Cl₂)) in excellent diastereoselectivity (97.5:2.5 *syn:anti* ratio determined by ¹H NMR) with >98% ee for the *syn* isomer. The hydroxyl functionality was methylated, using the Meerwein¹¹ reagent in the presence of a proton sponge as a base, to afford (–)-**11** (95%).

The thioester was reduced in the corresponding aldehyde using triethylsilane as a source of hydride in the presence of 10% palladium on carbon.¹² The crude aldehyde was then



homologated, using methyl diazoacetate¹³ **12** in the presence of SnCl₂ to obtain the β -ketoester (–)-**13** (85%, 2 steps, ratio 10.5:1 (–)-**13**:enol form determined by ¹H NMR).

The (*E*)- β -methoxyacrylate (+)-**14** was prepared via deprotonation of β -ketoester (–)-**13** in hexamethylphosphoric triamide (HMPA) as a solvent, followed by the methylation using dimethyl sulfate.^{4a,14} Cleavage of the benzyl group was then achieved using Pearlman's catalyst to form the primary alcohol (+)-**15** in a good yield. The reaction had to be monitored to prevent hydrogenation of the *E* double bond. This side reaction was observed when the reaction was left more than 30 min under a hydrogen atmosphere. Dess–Martin periodinane oxidation of (+)-**15** afforded the desired aldehyde (+)-**2** ($[\alpha]_{\text{D}}^{25}$ +105.0 (*c* 0.46, CHCl₃); lit.⁵ $[\alpha]_{\text{D}}^{25}$

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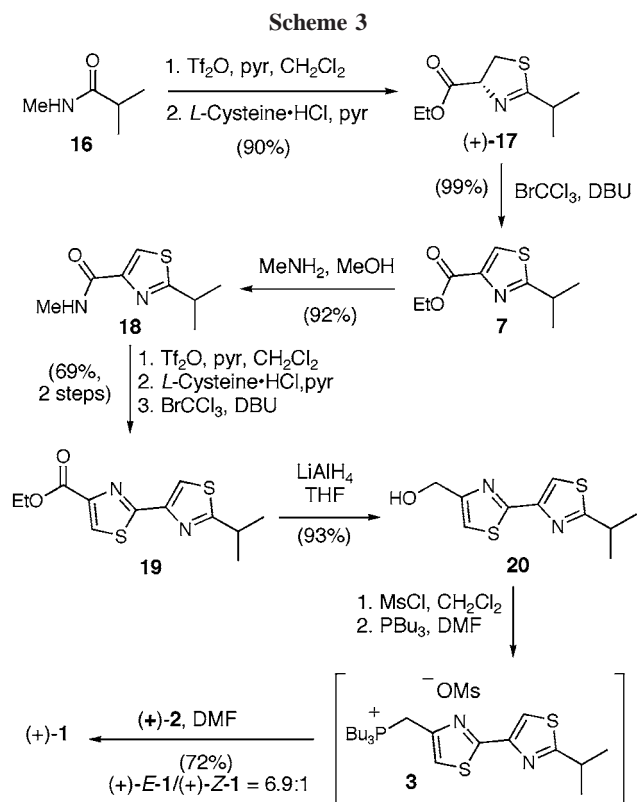
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+104.7 (*c* 0.55, CHCl₃) in 99% yield. The spectral properties were identical to those reported.¹⁴

The right-hand side of the cystothiazole containing the [2,4']-bis(thiazole) moiety was prepared using methodology that we developed for the preparation of thiazoline via an electrophilic activation of amide using triflic anhydride (Tf₂O).⁶ The isopropylamide **16**¹⁵ was activated with Tf₂O in the presence of pyridine to afford a pyridinium salt intermediate.¹⁶ Addition of *L*-cysteine·HCl afforded the thiazoline (+)-**17** in 90% yield. Oxidation of the thiazoline ring using bromotrichloromethane⁴ (BrCCl₃) in the presence of 2 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the first thiazole ring **7**¹⁷ (99%). The ester functionality was then transformed into the corresponding *N*-methylamide **18** (92%), using a solution of 2.5 M methylamine in methanol. Amide **18** was treated with Tf₂O and pyridine followed by addition of *L*-cysteine·HCl.¹⁸ The corresponding crude thiazoline was then oxidized using BrCCl₃/DBU to afford the bis(thiazole) **19**¹⁷ in 69% yield over two steps. The ester functionality was reduced with lithium aluminum hydride (LiAlH₄) to obtain the corresponding alcohol **20** (93%). This primary alcohol **20** was mesylated, and addition of tributylphosphine (Bu₃P) afforded a solution in DMF of the phosphonium salt **3**. The reaction conditions developed by Evans in the total synthesis of phorboxazole B¹⁹ were used to obtain a *E* double bond using a similar semistabilized Wittig reagent. This methodology uses a tributylphosphonium salt and an aldehyde in the presence of DBU at room temperature and gave a good mixture of (*E*/*Z*) isomers (21:1 to 27:1). When we mixed the phosphonium salt **3** with the aldehyde **2** followed by the addition of DBU, we obtained a mixture of (+)-(*E*)-**1**/(+)-(*Z*)-**1** = 1.8:1 in 66% yield.

When the Wittig was run at 0 °C, we obtained a mixture of *E*/*Z* isomers in a ratio of 6.9:1. Both isomers were separated by HPLC to afford pure (+)-**1**. The physical data of synthetic (+)-**1** were identical with those reported for the natural product (+)-**1** (exptl [α]_D²⁵ +104.0 (*c* 0.21, CHCl₃); lit. [α]_D²⁵ +109 (*c* 0.24, CHCl₃).¹



In summary, a convergent total synthesis of **1** was accomplished employing a Wittig-type olefination between **2** and **3** as the final step. The [2,4']-bis(thiazole) moiety was successfully synthesized using electrophilic activation of an amide followed by condensation with an aminothiolsalt. Finally we have synthesized (+)-cystothiazole A in nine linear steps and 38% overall yield.

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Supporting Information Available: Spectral data for all new compounds (¹H NMR, ¹³C NMR, IR, HRMS) and HPLC traces for isomers or enantioselectivity. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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