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Total Synthesis of (+)-Cystothiazole A

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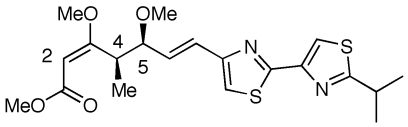
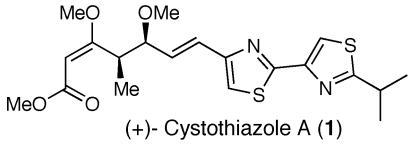
ABSTRACT



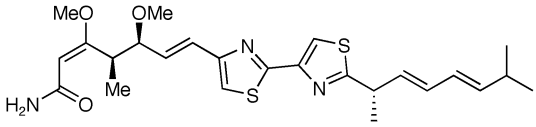
(+)- Cystothiazole A (**1**)

The total synthesis of cystothiazole A is described. Key steps of the synthesis include an Evans asymmetric catalytic aldol reaction, which established the required C_4–C_5 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, Sakagami[1] and co-workers isolated from the myxobacterium *Cystobacter fuscus* a bis(thiazole)-type antibiotic called cystothiazole A.



(+)- Cystothiazole A (**1**)



Myxothiazole 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 IC_{50} value of, respectively, 130 and 110 ng/mL. The structure of (+)-cystothiazole A (**1**) was determined by NMR methods (^{1}H, ^{13}C, HETCOR, HMBC), with the *E* geometry of the trisubstituted double bond at C_2 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.

(1) Ojika, M.; Suzuki, Y.; Tsukamoto, A.; Sakagami, Y.; Fudou, R.; Yoshimura, T.; Yamanaka, S. *J. Antibiot.* **1998**, *51*, 275.

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

(3) Clough, J. M. *Nat. Prod. Rep.* **1993**, 565.

(4) (a) Williams, D. R.; Samarjit, S.; Clark, M. P. *J. Org. Chem.* **2001**, *66*, 8463. For synthtic application see: (b) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331. (c) Freeman, D. J.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 3251. (d) Pattenden, G.; Thompson, T. *Chem. Commun.* **2001**, *8*, 717. (e) Yokokawa, F.; Sameshima, H.; Shioiri, T. *Tetrahedron Lett.* **2001**, *42*, 4171.

(5) Akita, H.; Kato, K.; Nishimura, A.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 643.

(6) Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908.

(7) Charette, A. B.; DeRoy, P. L.; Berthelette, C.; Lacombe, P.; Sametz, G. Manuscript in preparation.

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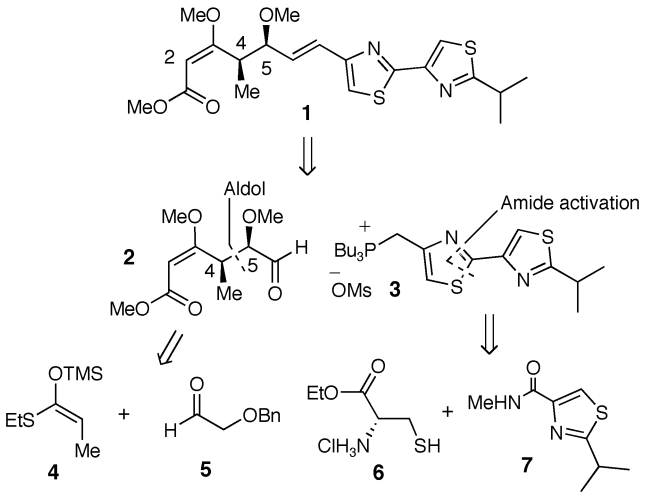
Scheme 1

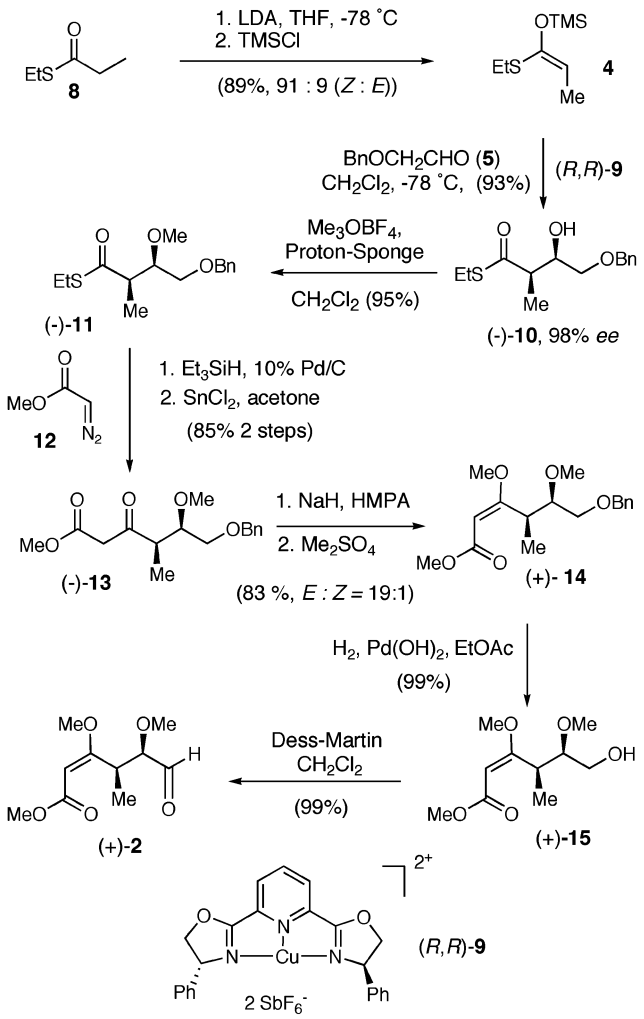


Our retrosynthetic strategy of **1** is illustrated in Scheme 1 and involves a catalytic asymmetric synthesis of the *β*-methoxyacrylate system, and the application of our electrophilic amide activation methodology for constructing the [2,4′]-bis(thiazole) moiety. Thus, **1** would be synthesized by Wittig-type reaction of an aldehyde **2** with a phosphonium salt **3**.[8] The C_4-C_5 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*)-Ph-pybox)]$(SbF_6)_2$ (**9**)-catalyzed aldol reaction between benzyloxyacetaldehyde **5** and (Z)-silylketene acetal **4** smoothly afforded the *syn* aldol adduct (−)-**10** ($[\alpha]^{25}_D$ −42.4° (*c* 0.55, CH_2Cl_2)) in excellent diastereoselectivity (97.5:2.5 *syn*:*anti* ratio determined by ^{1}H NMR) with >98% ee for the *syn* isomer. The hydroxyl functionality was methylated, using the Meerwein[11] 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

Scheme 2



homologated, using methyldiazoacetate[13] **12** in the presence of $SnCl_2$ to obtain the *β*-ketoester (−)-**13** (85%, 2 steps, ratio 10.5:1 (−)-**13**:enol form determined by ^{1}H 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** ($[\alpha]_D^{25}$ +105.0 (*c* 0.46, $CHCl_3$); lit.[5] $[\alpha]_D^{25}$

(8) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Victor, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 10033.

(9) (a) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 687.

(10) For a general procedure of the *Z* or *E* silylketene acetal see: Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Connell, B. T. *J. Am. Chem. Soc.* **1999**, *121*, 669.

(11) (a) Meerwein, H.; Laasch, P.; Mersch, R.; Spille, J. *Chem. Ber.* **1956**, *89*, 203. (b) Pettit, G. R.; Singh, S. B.; Herald, D. L.; Lloyd-Williams, P.; Kantoci, D.; Burkett, D. D.; Barkoczy, J.; Hogan, F.; Wardlaw, T. R. *J. Org. Chem.* **1994**, *59*, 6287.

(12) For synthetic application see: (a) Tokuyama, H.; Yokoshima, S.; Lin, S.-C.; Li, L.; Fukuyama, T. *Synthesis* **2002**, *8*, 1121. (b) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *19*, 7050. (c) Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451.

(13) (a) The methyldiazoacetate was prepared as described in: Womack, E. B.; Nelson, A. B. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p. 392. (b) For synthetic application, see: Yajura, T.; Ueki, A.; Kitamura, T.; Tanaka, K.; Nameki, M.; Ikeda, M. *Tetrahedron* **1999**, *55*, 7461. (c) Yakura, T.; Yuamada, S.; Azuma, M.; Ueki, A.; Ikeda, M. *Synthesis* **1998**, *7*, 973. (d) Yakura, T.; Ueki, A.; Kitamura, T.; Tanaka, K.; Nameki, M.; Ikeda, M. *Tetrahedron* **1999**, *55*, 7461. (e) Phukan, P.; Mohan, J. M.; Sudalai, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, *24*, 3685.

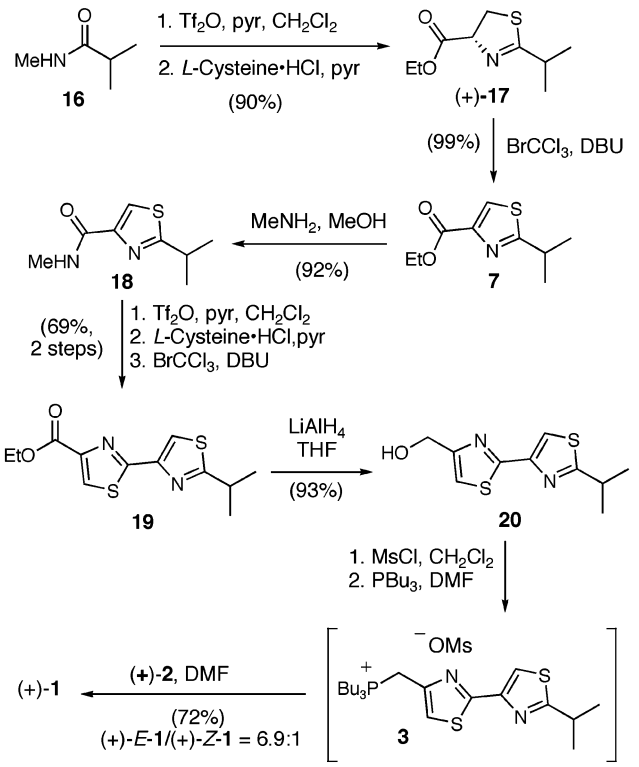
(14) Backhaus, D. *Tetrahedron Lett.* **2000**, *41*, 2087.

+104.7 (*c* 0.55, $CHCl_3$)) 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 (Tf_2O).[6] The isopropylamide **16**[15] was activated with Tf_2O 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 bromotrichloromethane[4] ($BrCCl_3$) 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 Tf_2O and pyridine followed by addition of L-cysteine·HCl.[18] The corresponding crude thiazoline was then oxidized using $BrCCl_3$/DBU to afford the bis(thiazole) **19**[17] in 69% yield over two steps. The ester functionality was reduced with lithium aluminum hydride ($LiAlH_4$) to obtain the corresponding alcohol **20** (93%). This primary alcohol **20** was mesylated, and addition of tributylphosphine (Bu_3P) afforded a solution in DMF of the phosphonium salt **3**. The reaction conditions developed by Evans in the total synthesis of phorboxazole B[19] 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 $[\alpha]_D^{25}$ +104.0 (*c* 0.21, $CHCl_3$); lit. $[\alpha]_D^{25}$ +109 (*c* 0.24, $CHCl_3$)).[1]

Scheme 3



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 aminothiol salt. Finally we have synthesized (+)-cystothiazole A in nine linear steps and 38% overall yield.

Acknowledgment. This work was supported by NSERC and the Université de Montréal.

Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C 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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(15) Alfred, E. L.; Huwitz, M. D. *J. Org. Chem.* **1965**, *30*, 2376.
(16) Charette, A. B.; Grenon, M. *Can. J. Chem.* **2001**, *79*, 1694.
(17) NMR spectra are identical to those reported: see ref 4a.
(18) Thiazoline prepared from **18** was not purified since it partially oxidized on silica gel.
(19) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Victor, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 10033.