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Total Synthesis of (±)-Mycothiazole and Formal Enantioselective Approach

Alexandre Le Flohic, Christophe Meyer,* and Janine Cossy*

Laboratoire de Chimie Organique, associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

christophe.meyer@espci.fr; janine.cossy@espci.fr

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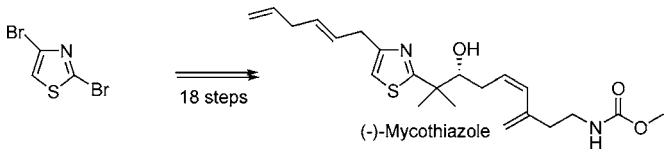
ABSTRACT



A total synthesis of (±)-mycothiazole and a formal enantioselective approach have been achieved from 2,4-dibromothiazole. A chain extension of a homoallylic alcohol proceeding through an unsaturated sultone intermediate, generated by ring-closing metathesis, was used as a key step for the elaboration of the conjugated (*Z*)-dienol moiety.

Over the past few years, natural products of marine origin have continued to be of interest due to their wide spectrum of biological and pharmacological properties. Mycothiazole was first isolated in 1988 from the marine sponge *Spongia mycofijiensis* collected from the Vanuatu islands.[1] Its presence was also detected recently in the extracts of another marine sponge of the genus *Dactylospongia*.[2] Mycothiazole was found to exhibit an antihelminthic activity in vitro. Moreover, screening assays by the National Cancer Institute (NCI) in the United States indicated that mycothiazole exhibits a rather selective toxicity against a small cell lung cancer line.[3] The structure of mycothiazole was established after extensive NMR analysis and confirmed by exhaustive interpretation of a HREIMS spectrum (Figure 1).[4]

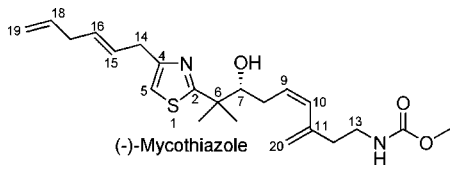


Figure 1. Structure of (−)-mycothiazole.

The most unique structural feature of this natural product is a 2,4-disubstituted thiazole ring, which is imbedded between two acyclic polyunsaturated side chains. The C2 side chain includes a nitrogen substituent at C13 (methyl carbamate), a conjugated diene moiety consisting of a (*Z*)-disubstituted double bond (C9−C10) and a methylene group (C11−C20), a quaternary carbon at C6, adjacent to the thiazole, substituted by a *gem*-dimethyl group and a secondary alcohol at C7 that consitutes the unique stereocenter of mycothiazole. The C4 substituent is a hexadienyl chain containing a (*E*)-disubstituted double bond (C15−C16) and a terminal olefin (C18−C19). To date, a single total synthesis of mycothiazole has been achieved, which enabled the assignment of the (*R*) absolute configuration of the natural product,[5] although some discreapancies were observed between the optical rotation of the synthetic sample and the natural product due to the lability of the latter upon storage. Synthetic approaches toward two subunits containing the 2,4-disubstituted thiazole[6] or the conjugated (*Z*)-diene[7] have also been reported.

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

(2) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem.* **2001**, 775−778.

(3) The results of the National Cancer Institute Human Tumor Cell Line Screen mean graph can be consulted on the Internet at http://dtp.nci.nih.gov (NCS number 647640).

(4) The atom numbering has been chosen so that the positions of the thiazole ring (C2/C4/C5) may be designated in the classical fashion.

(5) (a) Sugiyama, H.; Yokokawa, F.; Shioiri, T. *Org. Lett.* **2000**, *2*, 2149−2152. (b) Sugiyama, H.; Yokokawa, F.; Shioiri, T. *Tetrahedron* **2003**, *59*, 6579−6593.

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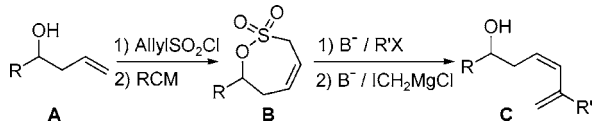
We have previously described that secondary homoallylic alcohols of type **A** could be converted to sultones of type **B** by reaction with allylsulfonyl chloride and subsequent ring-closing metathesis of the intermediate sulfonates.[8,9] Sultones of type **B** could be sequentially deprotonated at the α-position of the sulfonyl group and first alkylated with halides (R′X) and then with the carbenoid ICH_2MgCl,[10] which led after *β*-elimination and loss of sulfur dioxide to the conjugated (*Z*)-dienols of type **C** (Scheme 1).

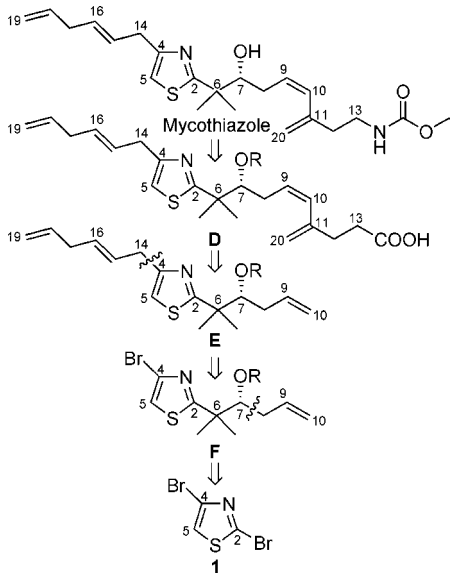
Scheme 1. Synthesis of Conjugated (*Z*)-Dienols from Homoallylic Alcohols



Herein, we would like to report the use of this strategy in the synthesis of (±)-mycothiazole, which contains a conjugated (*Z*)-dienol subunit of type **C**.

In our retrosynthetic analysis, the introduction of the methyl carbamate at C13 was envisaged by a Schmidt reaction applied to the carboxylic acid of type **D**. The key stage will be the elaboration of the conjugated (*Z*)-dienol moiety in compound **D** from the corresponding homoallylic alcohol derivative of type **E** by using the chain extension methodology outlined above. The introduction of the side chain at C4 in compound **E** should be achieved from the substituted 4-bromothiazole of type **F**. In this latter compound, the secondary homoallylic alcohol functionality at C7 would be generated by allylation of an intermediate aldehyde whose preparation was envisaged from the readily available 2,4-dibromothiazole **1**[11] (Scheme 2).

Scheme 2. Retrosynthetic Analysis of Mycothiazole



Our synthesis of mycothiazole began with the chemoselective substitution of the bromine at C2 in 2,4-dibromothiazole **1** by treatment with prenylmagnesium chloride in THF, which reacted with complete allylic transposition[12] and afforded the 2,4-disubstituted thiazole **2** (87%). The terminal olefin in compound **3** was subjected to a dihydroxylation (cat. OsO_4, NMO, *t*-BuOH/H_2O), and the resulting intermediate 1,2-diol underwent an oxidative cleavage with $NaIO_4$ in THF/H_2O to afford the aldehyde **3** (88%). This compound was treated with allylmagnesium bromide, and the resulting secondary alcohol **4** (87%) was protected as a *tert*-butyldimethylsilyl ether (TBSOTf, 2,6-lutidine, 0 °C) to produce compound **5** (95%). As various attempts to introduce the side chain at C4 by direct formation of the C4−C14 bond turned out to be unsuccessful,[13] it was envisaged at first to homologate the substituted 4-bromothiazole **5** at C4 and then create the C14−C15 bond. Thus, the substituted 4-bromothiazole **5** underwent lithium−bromine exchange with *tert*-butyllithium in ether at −78 °C, and subsequent formylation with DMF provided the aldehyde **6** (85%). After reduction (DIBAL-H, Et_2O, −78 °C), the resulting alcohol **7** (95%) was converted to the bromide **8** (97%) by treatment with PPh_3 and CBr_4 in the presence of 2,6-lutidine in acetonitrile. With the aim of elaborating the unsaturated side chain of mycothiazole at C4 in a single operation, the bromide **8** was subjected to a Stille coupling with (*E*)-1-tributylstannylpenta-1,4-diene[14] catalyzed by $PdCl_2(MeCN)_2$ in NMP,[5] and the 1,4-diene **9** was obtained in 95% yield. Subsequent deprotection of the hydroxyl group at C7 with TBAF in THF at 50 °C finally afforded the homoallylic alcohol **10** (94%) (Scheme 3).

Following our synthetic plan, the elaboration of the conjugated (*Z*)-dienol moiety of mycothiazole by chain extension of the homoallylic alcohol **10** required at first the preparation of the key intermediate unsaturated sultone **12**. At first, the sterically hindered secondary alcohol **10** was treated with allylsulfonyl chloride in THF provided that DMAP was used as the base. The intermediate sulfonate **11** was isolated but not purified and underwent ring-closing metathesis by treatment with Grubbs' second generation catalyst (Grubbs II) in benzene at 70 °C. Under these

(6) Serra, G.; Mahler, G.; Manta, E. *Heterocycles* **1998**, *48*, 2035−2048.
(7) Rodriguez-Conesa, S.; Candal, P.; Jiménez, C.; Rodriguez, J. *Tetrahedron Lett.* **2001**, *42*, 6699−6702.
(8) Le Flohic, A.; Meyer, C.; Cossy, J.; Galland, J.-C.; Desmurs, J.-R. *Synlett* **2003**, 667−670.
(9) (a) Karsch, S.; Schwab, P.; Metz, P. *Synlett* **2002**, 2019−2022. (b) Karsch, S.; Freitag, D.; Schwab, P.; Metz, P. *Synthesis* **2004**, 1696−1712.
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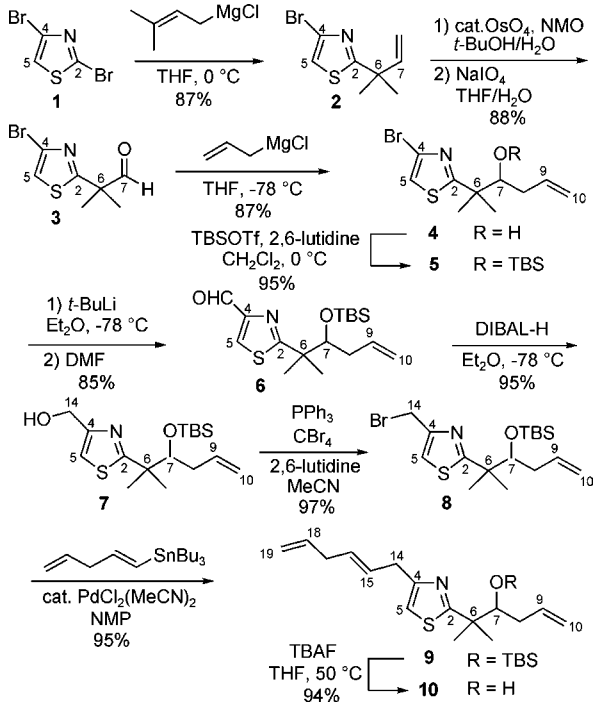
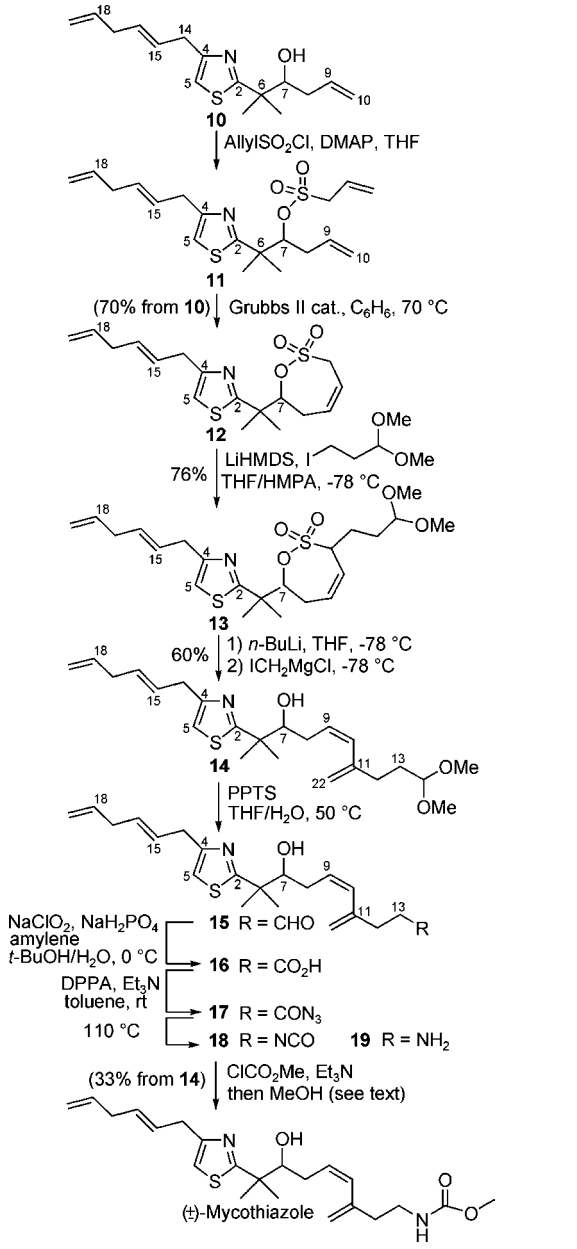
(11) Reynaud, P.; Robba, M.; Moreau, R. C. *Bull. Soc. Chim. Fr.* **1962**, 1735−1738.
(12) Florio, S.; Epifani, E.; Ingrosso, G. *Tetrahedron* **1984**, *40*, 4527−4533.
(13) No satisfactory conditions were found in order to couple an organometallic species generated at C4 from the substituted 4-bromothiazole **5** with allylic electrophiles incorporating the C14−C19 side chain.
(14) (*E*)-1-Tributylstannylpenta-1,4-diene was prepared in four steps (26% overall yield) from trimethylsilylacetylene by allylation (EtMgBr then AllylBr, cat. CuBr·SMe_2, THF) and hydroalumination (Dibal-H, hexanes/Et_2O) and subsequent iodinolysis (I_2, THF), desilylation (MeONa/MeOH), and lithium−iodine exchange (*t*-BuLi, Et_2O, −78 °C) followed by stannylation (Bu_3SnCl, rt).

Scheme 3. Preparation of Homoallylic Alcohol **10**



Scheme 4. Total Synthesis of (±)-Mycothiazole



conditions, the unsaturated sultone **12** was obtained in 70% yield (2 steps from the alcohol **10**). Addition of LiHMDS to a mixture of sultone **12** and 1,1-dimethoxy-3-iodopropane[15] in the presence of HMPA in THF at −78 °C cleanly afforded the monoalkylated sultone **13** (76%) as a 1/1 mixture of diastereomers. The crucial step of our synthetic plan could be investigated next. Thus, sultone **13** was efficiently deprotonated with *n*-butyllithium in THF at −78 °C, and subsequent addition of the carbenoid ICH_2MgCl (generated from CH_2I_2 and *i*-PrMgCl, THF, −80 °C) led to the conjugated (*Z*)-dienol **14** in 60% yield (Scheme 4).[8]

Having successfully accomplished the key transformation of our synthesis, only functional groups manipulations were required in order to complete the total synthesis of mycothiazole. Hydrolysis of the dimethyl acetal in compound **14** (PPTS, THF/H_2O, 50 °C) quantitatively afforded aldehyde **15**, which was not purified but directly oxidized chemoselectively by $NaClO_2$ in the presence of amylene and excess NaH_2PO_4 in *t*-BuOH/H_2O.[16] The resulting carboxylic acid **16**, which turned out to be an extremely sensitive compound, was directly extracted from the reaction mixture and immediately treated with diphenylphosphoryl azide (DPPA) and Et_3N in toluene. After formation of the acyl azide **17**, the reaction mixture was heated at reflux in order to induce the Curtius rearrangement to the corresponding isocyanate **18**. As the latter was not readily converted to mycothiazole when MeOH was added to the reaction mixture at reflux, we initially thought that it had probably accidentally hydrolyzed to the amine **19**. However, the compound obtained after purification by preparative TLC on silica gel did not react with $ClCO_2Me$ in the presence of Et_3N. This result suggested that we had isolated the rather robust isocyanate **18**, and therefore the reaction mixture was treated with an excess of MeOH. Under these conditions, a smooth methanolysis took place,[17] which produced mycothiazole **1** in 33% overall yield from the dimethyl acetal **14** (4 steps) (Scheme 4). The NMR data of this compound were in agreement with those described in the literature.[5]

As mycothiazole contains a single stereocenter at C7, a formal enantioselective approach of this natural product has

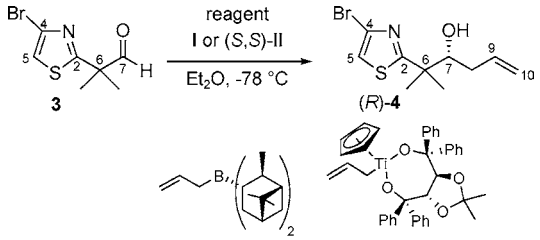
(15) Clive, D. L. J.; Chua Paul, C.; Wang, Z. *J. Org. Chem.* **1997**, *62*, 7028−7032.

(16) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175−1176.

(17) The reaction between $ClCO_2Me$ and MeOH may have generated traces of HCl, which can catalyze the methanolysis of isocyanates, see: Khoukhi, M.; Vaultier, M.; Banalil, A.; Carboni, B. *Synthesis* **1996**, 483−487.

also been investigated with the preparation of the optically active alcohol (*R*)-**4**. Thus, addition of the chiral allylic borane **I** [generated from allylmagnesium bromide and (+)-chlorodiisopinocampheyl borane ((+)-DIPCl)][18] to aldehyde **3** in Et_2O at −78 °C led to the corresponding secondary homoallylic alcohol (*R*)-**4** (70%) with low optical purity (ee = 54%).[19] Although this result probably could have been optimized by modifying the reaction conditions, an enantioselective allyltitanation of aldehyde **3** with the allyltitanium complex (*S*,*S*)-**II** [generated from allylmagnesium chloride and the corresponding ((*S*,*S*)-TADDOL)-CpTiCl complex][20] in THF/Et_2O at −78 °C afforded (*R*)-**4** in much better yield and enantiomeric excess[19] (82% yield, ee = 99%) (Scheme 5).

Scheme 5. Preparation of Homoallylic Alcohol (*R*)-**4**



reagent	I	(*S*,*S*)-II
yield of (*R*)-**4**	70%	82%
ee of (*R*)-**4**	54%	99%

The (*R*) configuration of the homoallylic alcohol **4** obtained from these reactions was attributed on the basis of the known face-selectivities of the chiral allylating reagents and particularly the allyltitanium complex **II**, which displays an extremely high face-selectivity regardless of the nature of the aldehydes.[20]

In summary, we have achieved a total synthesis of (±)-mycothiazole in 18 steps from 2,4-dibromothiazole with an overall yield of 5%. The side chain at C2 was created in a stepwise fashion by using a chemoselective prenylation, an aldehyde allylation, a chain extension of a homoallylic alcohol to a conjugated (*Z*)-dienol, proceeding through an intermediate unsaturated sultone, and a Curtius rearrangement. The installation of the side chain at C4 was based on a one-carbon homologation followed by a Stille coupling. A formal enantioselective approach has also been demonstrated with the preparation of the secondary homoallylic alcohol **4** in high enantiomeric purity (ee = 99%).

Acknowledgment. A.L.F. thanks the CNRS and Rhodia for a grant, and financial support from Rhodia is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for key intermediate compounds **4**, (*R*)-**4**, **9**, **12**, **13**, **14**, and mycothiazole and copies of their ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432−439.

(19) Determined by chiral HPLC analysis: chiral OD-H column; eluent, hexane; elution rate, 1 mL/min; detection, 230−260 nm; retention times, (*S*)-enantiomer 48.4 min, (*R*)-enantiomer 55.5 min.

(20) (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321−2336. (b) Cossy, J.; BouzBouz, S.; Pradaux, F.; Willis, C.; Bellosta, V. *Synlett* **2002**, 1595−1606.