

Cite this: *Chem. Commun.*, 2012, **48**, 10508–10510

www.rsc.org/chemcomm

COMMUNICATION

Catalysis-based enantioselective total synthesis of myxothiazole Z, (14S)-melithiazole G and (14S)-cystothiazole F†

Aude Colon,^a Thomas J. Hoffman,^{ab} Julian Gebauer,^a Jyotirmayee Dash,^a James H. Rigby,^b Stellios Arseniyadis^{*a} and Janine Cossy^{*a}

Received 7th August 2012, Accepted 5th September 2012

DOI: 10.1039/c2cc35721f

A common strategy for the stereoselective and protecting group-free total synthesis of the myxobacterial antibiotics myxothiazole Z, (14S)-melithiazole G and (14S)-cystothiazole F is described featuring an asymmetric organocatalytic transfer hydrogenation, a palladium-catalyzed Stille coupling and a cross-metathesis as the key steps.

Myxobacteria belong to the δ -subgroup of gram-negative proteobacteria that predominantly inhabit the soil. Apart from their distinct cooperative social behaviour and unusually complex life-cycle, these unique microorganisms have gained attention as proficient producers of biologically active secondary metabolites with diverse chemical structures and unusual modes of action.¹

In 1980, Reichenbach *et al.* and Höfle *et al.* reported the isolation of a novel myxobacterial antibiotic named myxothiazole A, **1**,² whose structure is characterized by a central bis-thiazole unit linked to a highly pharmacophoric chiral β -methoxy acrylate (MOA) moiety and a heptadienyl side-chain bearing a stereogenic center at the α -position of the thiazole ring (Fig. 1). Acting as potent inhibitors of mitochondrial respiration,³ both **1** and its corresponding methyl ester, myxothiazole Z, **2**,⁴ exhibit broad antifungal activity as well as significant cytotoxicity against different human tumor cell lines with IC₅₀ values reaching as low as 0.01 ng mL⁻¹.^{4a}

During the following three decades, more than 20 structurally related fungicides have been isolated from various strains of myxobacteria including the congeneric cysto- and melithiazole

families⁵ and several other myxothiazole derivatives.⁶ Although synthetic studies within this intriguing class of natural products have been vigorous, only one total synthesis of **2**^{7a} and its side-chain analogues **3**^{7b} and **4**^{7c} have been reported, respectively, relying on a moderately *E*-selective Wittig reaction between a homochiral bis-thiazolyl phosphonium salt and the appropriate aldehyde. The synthesis of the polypropionate fragment, on the other hand, was achieved by an asymmetric aldol reaction, while the stereogenic center α to the bis-thiazole unit was either introduced starting from the chiral pool^{7a} or through enzymatic kinetic resolution.^{7b}

As an extension to our recently reported cross-metathesis-based synthesis of melithiazole C⁸ and cystothiazole A,⁹ we herein describe a highly convergent and catalysis-based total synthesis of cystothiazole F, **4**, its deshydroxy derivative melithiazole G, **3**, and the cytotoxic myxothiazole Z, **2**, via a common synthetic strategy featuring a key enantioselective organocatalytic transfer hydrogenation to control the absolute configuration of the stereogenic center α to the bis-thiazole unit.¹⁰

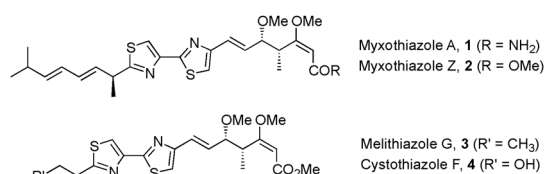


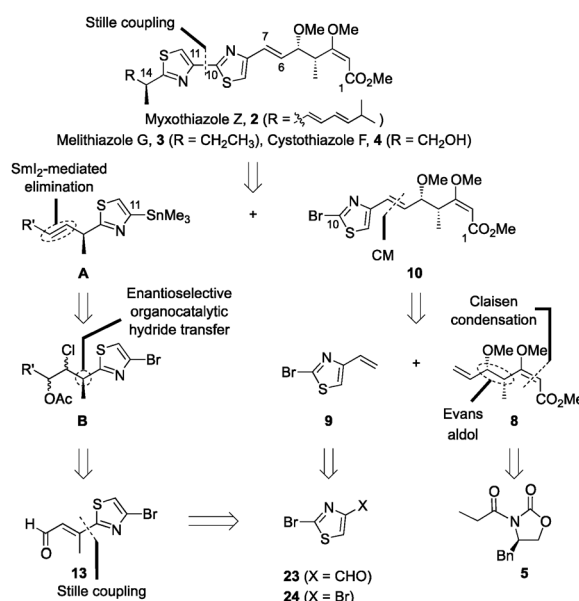
Fig. 1 Selected myxobacterial antibiotics.

^a Laboratoire de Chimie Organique, ESPCI ParisTech, CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France.

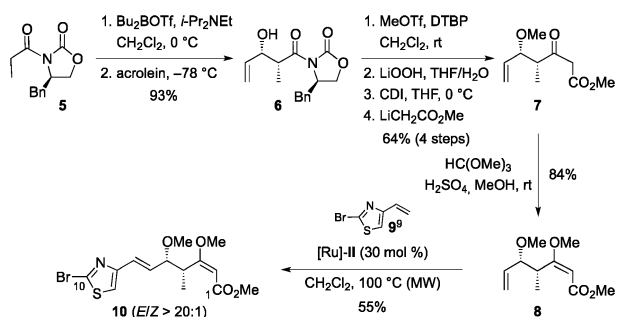
E-mail: stellios.arseniyadis@espci.fr, janine.cossy@espci.fr;
Fax: +33 (0)1 40 79 46 60; Tel: +33 (0)1 40 79 46 62

^b Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489, USA

† Electronic supplementary information (ESI) available: Details of experimental procedures and ¹H NMR, ¹³C NMR spectra for all new compounds. See DOI: 10.1039/c2cc35721f



Scheme 1 Common strategy for the synthesis of myxothiazole Z, **2**, melithiazole G, **3**, and cystothiazole F, **4**.

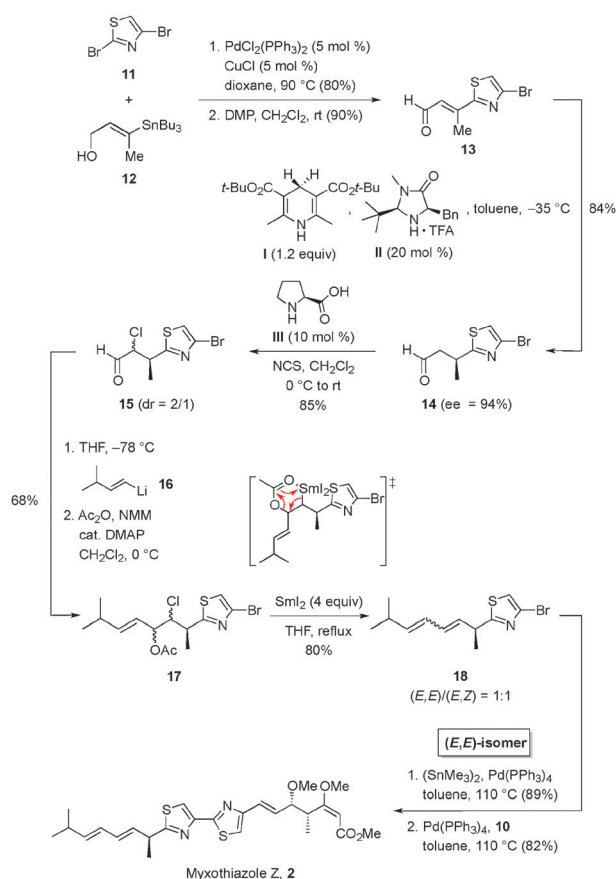


Scheme 2 Synthesis of the common bromothiazole intermediate **10**.

Retrosynthetically, all three natural products were fragmented into the advanced bromothiazole intermediate **10**⁸ and the corresponding thiazolyl stannanes **A** (Schemes 1 and 2). The latter were in turn envisioned to be derived from the same α,β -unsaturated aldehyde intermediate **13** applying the asymmetric organocatalytic conjugate reduction method previously developed in our laboratory¹⁰ followed by side-chain elaboration and palladium-catalyzed stannylation.

As reported previously,⁸ β -methoxy acrylate **8** was prepared in six steps and 32% overall yield *via* an asymmetric Evans aldol reaction between Evans' propionate **5** and acrolein¹¹ followed by *O*-methylation of the resulting allylic alcohol using methyl triflate in the presence of 2,6-di-*tert*-butylpyridine, cleavage of the chiral auxiliary using basic peroxide, activation of the resulting carboxylic acid using carbonyl diimidazole, condensation with $\text{LiCH}_2\text{CO}_2\text{Me}$ to generate the corresponding β -keto ester and H_2SO_4 -mediated methyl enol ether formation.¹² The required 4-vinyl thiazole **9**, on the other hand, was prepared in one step and 53% yield starting from commercially available 2-bromo-4-formylthiazole **23**¹³ *via* a Wittig olefination using methylenetriphenylphosphorane. In order to complete the synthesis of the common C1–C10 fragment, olefins **8** and **9** were eventually cross-coupled using Grubbs' second generation catalyst (30 mol%) under microwave irradiation¹⁴ (400 W, 100 °C, CH_2Cl_2). Under these conditions, the bromothiazole intermediate **10** was obtained in 55% yield (17% yield over seven steps) as a single stereoisomer ($E/Z > 20:1$).

The preparation of the thiazolyl stannane fragment of myxothiazole **Z** is based on two key transformations: an enantioselective organocatalytic transfer hydrogenation of a β -thiazole-containing α,β -unsaturated aldehyde to control the configuration of the C14 stereogenic center and a SmI_2 -mediated *O*-acetyl chlorohydrin elimination to afford the required (*E,E*)-diene moiety (Scheme 3). Accordingly, the synthesis began with the preparation of α,β -unsaturated aldehyde **13** *via* a palladium-catalyzed Stille coupling¹⁵ between 2,4-dibromothiazole **11** and vinylstannane **12** [$\text{PdCl}_2(\text{PPh}_3)_4$ (5 mol%), CuCl (5 mol%), dioxane, 90 °C] followed by a Dess–Martin periodinane-mediated oxidation¹⁶ (CH_2Cl_2 , rt) of the resulting allylic alcohol (72% yield over two steps). The corresponding enal **13** was then reduced under our optimized organocatalytic transfer hydrogenation conditions¹⁰ using Hantzsch ester **I** as the hydride donor and imidazolidinone **II** as the chiral organocatalyst (toluene, –35 °C) thus affording the saturated aldehyde **14** in 84% yield and 94% ee. The latter was then converted to the corresponding *O*-acetyl chlorohydrin **17** *via* a

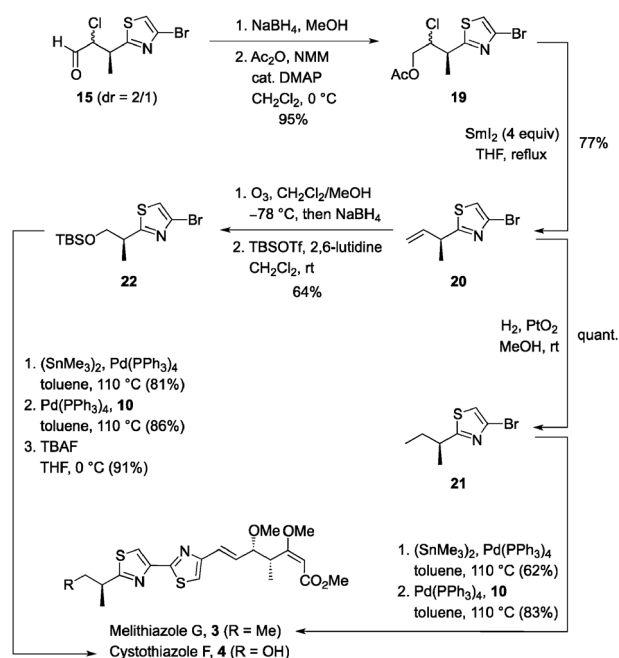


Scheme 3 Protecting-group free total synthesis of myxothiazole **Z**, **2**.

three-step sequence featuring a proline-catalyzed α -chlorination¹⁷ of the aldehyde (*N*-chlorosuccinimide, CH_2Cl_2 , 0 °C) followed by an alkenyl homologation using (*E*)-3-methyl-1-butenyllithium¹⁸ (THF, –78 °C) and a final acetylation in the presence of acetic anhydride, *N*-methylmorpholine and a catalytic amount of DMAP (CH_2Cl_2 , 0 °C). Elimination of the *O*-acetyl chlorohydrin moiety through two consecutive single electron transfers mediated by SmI_2 eventually afforded diene **18** in 80% yield as a 1 : 1 mixture of stereoisomers.¹⁸ Fortunately, the separation of the two isomers was possible by flash column chromatography over silica gel thus allowing us to isolate the required (*E,E*)-diene, which was subsequently taken up in toluene and heated in a sealed tube in the presence of hexamethylditin and $\text{Pd}(\text{PPh}_3)_4$ to introduce the stannane moiety. After purifying the crude residue over a short plug of silica, the resulting 4-stannyl thiazole was finally coupled with the bromothiazole intermediate **10** in the presence of $\text{Pd}(\text{PPh}_3)_4$ (5 mol%) in refluxing toluene to afford the desired natural product, myxothiazole **Z**, **2**, in 73% yield.

Gratifyingly, the spectroscopic and physical data of **2** were consistent with the ones reported in the literature for the natural product, with an optical rotation $\{[\alpha]_D^{20} + 111.5$ (*c* 0.75, MeOH) $\}$ which was in the range of those reported by Ahn *et al.* $\{[\alpha]_D^{25} + 152.0$ (*c* 0.67, MeOH) $\}$ ^{4a} and by Höfle *et al.* $\{[\alpha]_D^{25} + 79.2$ (*c* 1.40, MeOH) $\}$.^{4b}

As depicted in Scheme 1, our strategy for the synthesis of melithiazole **G**, **3**, and cystothiazole **F**, **4**, is based on the same key disconnections as for myxothiazole **Z**, thus requiring the synthesis of the corresponding thiazolyl stannanes. The latter



Scheme 4 Total synthesis of melithiazole G, **3**, and cystothiazole F, **4**.

were prepared starting from α -chloro aldehyde **15**, which was first reduced to the corresponding α -chlorohydrin (NaBH_4 , MeOH) and acetylated under the exact same conditions as previously described (Scheme 3). The resulting α -chloro acetate **19** was then treated with SmI_2 to afford olefin **20**, which was used as a common intermediate in the synthesis of both natural products (Scheme 4). Hence, the double bond was either reduced under a hydrogen atmosphere (PtO_2 , MeOH, rt) to afford the saturated product **21** quantitatively or converted to the corresponding silyl ether **22** via ozonolysis, reduction and subsequent protection of the resulting primary alcohol (64% overall yield). Both 4-bromo thiazole derivatives **21** and **22** were then stannylated [$(\text{SnMe}_3)_2$, $\text{Pd}(\text{PPh}_3)_4$, toluene, 110 °C] and engaged in the key Stille coupling with the bromothiazole intermediate **10** [$\text{Pd}(\text{PPh}_3)_4$, toluene, 110 °C]¹⁹ to afford melithiazole G, **3**, and, after TBAF-mediated deprotection of the primary alcohol, cystothiazole F, **4** (R = OH), in 51% and 63% yield respectively. Once again, the spectroscopic and physical data of **3** and **4** were consistent with those reported in the literature {(14*S*)-melithiazole G, **3**: $[\alpha]_{\text{D}}^{20} + 106.6$ (c 1.3, CHCl_3); ref. 7b $[\alpha]_{\text{D}}^{25} + 100.0$ (c 0.9, CHCl_3), (14*S*)-cystothiazole F, **4**: $[\alpha]_{\text{D}}^{20} + 89.8$ (c 0.85, CHCl_3); ref. 7c $[\alpha]_{\text{D}}^{25} + 86.2$ (c 1.05, CHCl_3)}.

In summary, we have described a stereoselective and protecting group-free total synthesis of the myxobacterial antibiotic myxothiazole Z, **2**, and two of its side-chain analogues (14*S*)-melithiazole G, **3**, and (14*S*)-cystothiazole F, **4**, using a common strategy which features an asymmetric organocatalytic transfer hydrogenation to control the configuration of the C14 stereogenic center, a Stille coupling to link the two thiazole units

together and a cross-metathesis to introduce the highly pharmacophoric chiral β -methoxy acrylate fragment. This straightforward and particularly flexible approach provides expedient access to the cysto- and melithiazole families as well as a variety of synthetic analogues thereof.

This work was supported by the Ministère de l'Éducation Nationale, de l'Enseignement Supérieur et de la Recherche and by the Centre National de la Recherche Scientifique (CNRS).

Notes and references

- (a) K. J. Weissman and R. Müller, *Bioorg. Med. Chem.*, 2009, **17**, 2121; (b) K. J. Weissman and R. Müller, *Nat. Prod. Rep.*, 2010, **27**, 1276.
- (a) K. Gerth, H. Irschick, W. Trowitzsch and H. Reichenbach, *J. Antibiot.*, 1980, **33**, 1474; (b) W. Trowitzsch, G. Höfle and W. S. Sheldrick, *Tetrahedron Lett.*, 1981, **22**, 3829.
- P. L. Toogood, *Curr. Opin. Chem. Biol.*, 2008, **12**, 457.
- (a) J.-W. Ahn, S.-H. Woo, C.-O. Lee, K.-Y. Cho and B.-S. Kim, *J. Nat. Prod.*, 1999, **62**, 495; (b) H. Steinmetz, E. Forche, H. Reichenbach and G. Höfle, *Tetrahedron*, 2000, **56**, 1681.
- (a) M. Ojika, Y. Suzuki, A. Tsukamoto, Y. Sakagami, R. Fudou, T. Yoshimura and S. Yamanaka, *J. Nat. Prod.*, 1998, **51**, 275; (b) Y. Suzuki, M. Ojika, Y. Sakagami, R. Fudou and S. Yamanaka, *Tetrahedron*, 1998, **54**, 11399; (c) F. Sasse, B. Böhlendorf, M. Hermann, B. Kunze, E. Forche, H. Steinmetz, G. Höfle and H. Reichenbach, *J. Nat. Prod.*, 1999, **52**, 721; (d) H. Akita, T. Sasaki, K. Kato, Y. Suzuki, K. Kondo, Y. Sakagami, M. Ojika, R. Fudou and S. Yamanaka, *Tetrahedron*, 2004, **60**, 4735; (e) B. Böhlendorf, M. Hermann, H.-J. Hecht, F. Sasse, E. Forche, B. Kunze, H. Reichenbach and G. Höfle, *Eur. J. Org. Chem.*, 1999, 2601.
- J.-W. Ahn, K. H. Jang, H.-C. Yang, K.-B. Oh, H.-S. Lee and J. Shin, *Chem. Pharm. Bull.*, 2007, **55**, 477.
- (a) J. M. Clough, H. Dube, B. J. Martin, G. Pattenden, K. S. Reddy and I. R. Waldron, *Org. Biomol. Chem.*, 2006, **4**, 2906; (b) H. Takayama, K. Kato, M. Kimura and H. Akita, *Heterocycles*, 2007, **71**, 1203; (c) H. Akita, Y. Iwaki, K. Kato, J. Qi and M. Ojika, *Tetrahedron: Asymmetry*, 2007, **18**, 513.
- J. Gebauer, S. Arseniyadis and J. Cossy, *Org. Lett.*, 2007, **9**, 3425.
- J. Gebauer, S. Arseniyadis and J. Cossy, *Eur. J. Org. Chem.*, 2008, 2701.
- T. J. Hoffman, J. Dash, J. H. Rigby, S. Arseniyadis and J. Cossy, *Org. Lett.*, 2009, **11**, 2756.
- K. C. Nicolaou, W. E. Brenzovich, P. G. Bulger and T. M. Francis, *Org. Biomol. Chem.*, 2006, **4**, 2119.
- J. Shao and J. S. Panek, *Org. Lett.*, 2004, **6**, 3083.
- Purchased from the Synthorix Corporation.
- (a) T. J. Hoffman, J. H. Rigby, S. Arseniyadis and J. Cossy, *J. Org. Chem.*, 2008, **73**, 2400; (b) J. Dash, S. Arseniyadis and J. Cossy, *Adv. Synth. Catal.*, 2007, **349**, 152; (c) J. Dash, B. Melillo, S. Arseniyadis and J. Cossy, *Tetrahedron Lett.*, 2011, **52**, 2246. For recent reviews on microwave-assisted CM, see: (d) J. Rodriguez and Y. Coquerel, *Eur. J. Org. Chem.*, 2008, 1125.
- T. Bach and S. Heuser, *J. Org. Chem.*, 2002, **67**, 5789.
- (a) D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4122; (b) R. K. Boeckman, Jr., P. Shao and J. J. Mullins, *Org. Synth.*, 2004, **10**, 696.
- (a) N. Halland, A. Branton, S. Bachmann, M. Marigo and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2004, **126**, 4790; (b) M. P. Brochu, S. Brown and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2004, **126**, 4108.
- J. M. Chong and S. B. Park, *J. Org. Chem.*, 1993, **58**, 523.
- For related cross-coupling reactions employed in previous cystothiazole syntheses, see: T. Bach and S. Heuser, *Chem.-Eur. J.*, 2002, **8**, 5585.