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Catalysis-based enantioselective total synthesis of myxothiazole Z, (14*S*)-melithiazole G and (14*S*)-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]

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A common strategy for the stereoselective and protecting group-free total synthesis of the myxobacterial antibiotics myxothiazole Z, (14*S*)-melithiazole G and (14*S*)-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 IC_{50} 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 families[5] 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 C[8] 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]

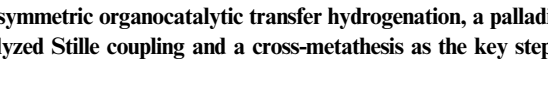
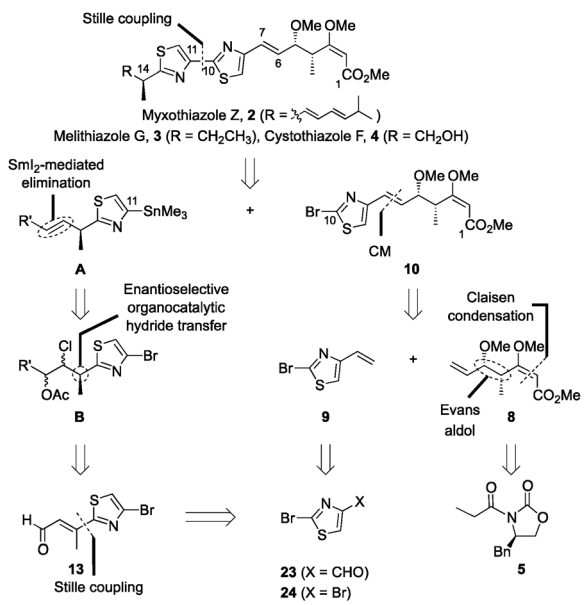


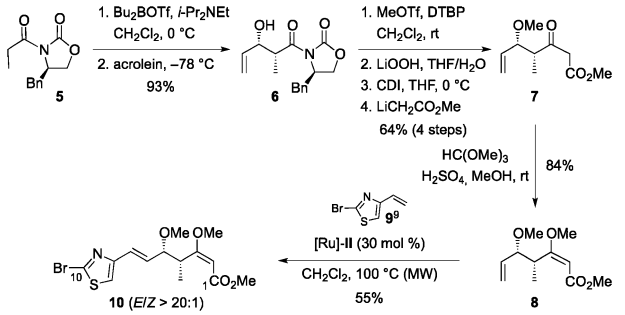
Fig. 1 Selected myxobacterial antibiotics.

[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 ^{1}H NMR, ^{13}C 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**.

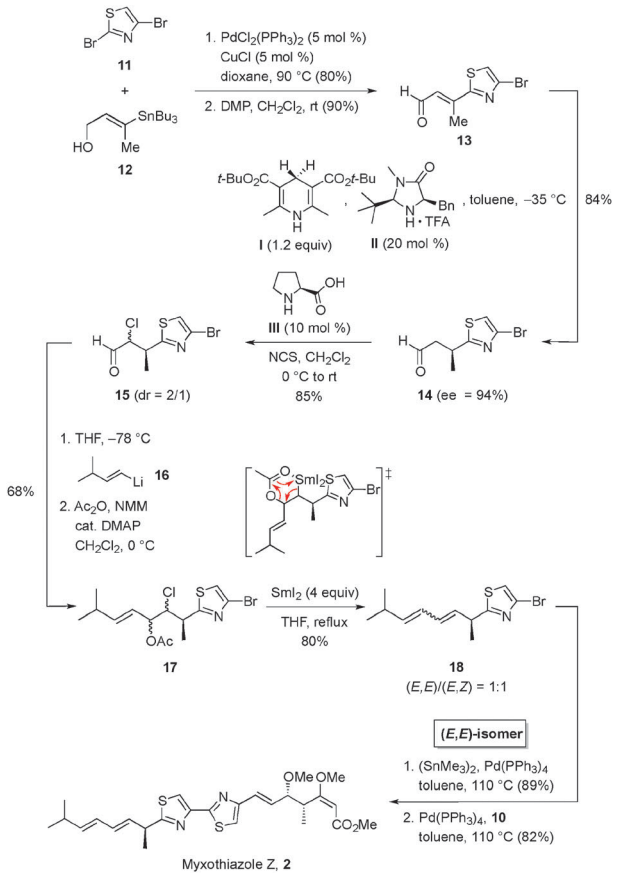


Scheme 2 Synthesis of the common bromothiazole intermediate **10**.

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 laboratory[10] 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 acrolein[11] 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 $LiCH_2CO_2Me$ 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 irradiation[14] (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 coupling[15] between 2,4-dibromothiazole **11** and vinylstannane **12** [$PdCl_2(PPh_3)_4$ (5 mol%), CuCl (5 mol%), dioxane, 90 °C] followed by a Dess–Martin periodinane-mediated oxidation[16] (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 conditions[10] 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

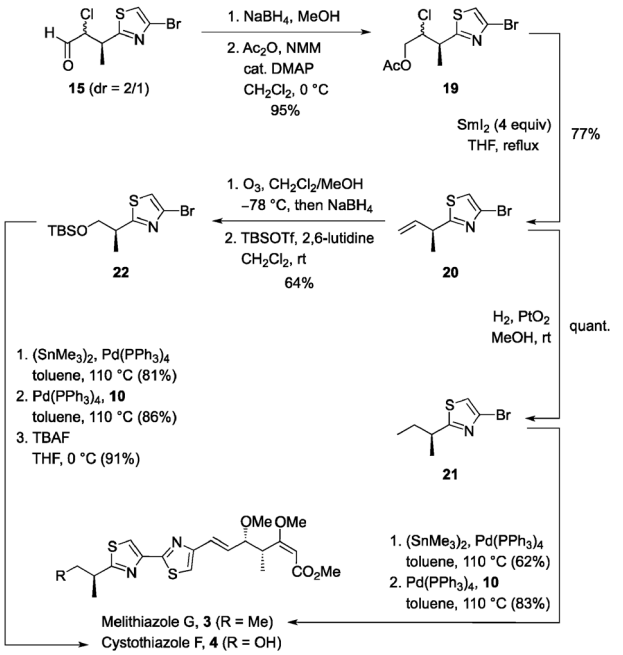


Scheme 3 Protecting-group free total synthesis of myxothiazole Z, **2**.

three-step sequence featuring a proline-catalyzed α-chlorination[17] of the aldehyde (*N*-chlorosuccinimide, CH_2Cl_2, 0 °C) followed by an alkenyl homologation using (*E*)-3-methyl-l-butenyllithium[18] (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 $Pd(PPh_3)_4$ to introduce the stananne 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 $Pd(PPh_3)_4$ (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 [$(SnMe_3)_2$, $Pd(PPh_3)_4$, toluene, 110 °C] and engaged in the key Stille coupling with the bromothiazole intermediate **10** [$Pd(PPh_3)_4$, toluene, 110 °C][19] to afford melithiazole G, **3**, and, after TBAF-mediated deprotection of the primary alcohol, cystothiazole F, **4**, 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**: $[\alpha]_D^{20}$ + 106.6 (*c* 1.3, $CHCl_3$); ref. 7*b* $[\alpha]_D^{25}$ + 100.0 (*c* 0.9, $CHCl_3$), (14*S*)-cystothiazole F, **4**: $[\alpha]_D^{20}$ + 89.8 (*c* 0.85, $CHCl_3$); ref. 7*c* $[\alpha]_D^{25}$ + 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.

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