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A Concise Total Synthesis of Melithiazole C†

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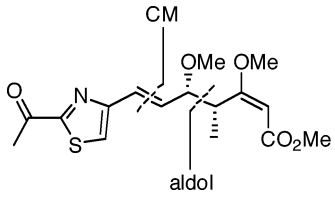
ABSTRACT



Melithiazole C

A short and convergent synthesis of the myxobacterial antibiotic melithiazole C is described featuring a highly *E*-selective cross-metathesis as the key step.

The thiazole subunit is found in many natural and synthetic compounds with a wide range of interesting bioactivities.[1] The melithiazoles A−N represent a group of fungicidal β-methoxy acrylate (MOA) metabolites which have been isolated from different strains of myxobacteria.[2] As a common structural motif they share either a bisthiazole or a thiazole−thiazoline ring system linked via a double bond to a highly pharmacophoric polypropionate moiety that selectively inhibits mitochondrial respiration by binding to the cytochrome bc_1 complex (Figure 1).[3]

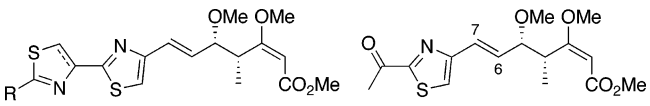


Figure 1. Melithiazoles A−N.

Isolated in only minor quantities from *Melittangium lichenicola*, melithiazole C (**1**) contains a single thiazole ring and additionally occurs as a mixture of *E*/*Z* isomers at C6−C7 (6*E*/6*Z* = 7/2)[2] with only the *trans*-isomer being biologically active.[4] On the other hand, derivatization of the acetyl group in **1** was found to selectively enhance its biological activities.[4] Whereas simple transformation of the carbonyl group into an oxime functionality reduces the antifungal properties and increases the cytotoxicity, an exceptionally high antifungal activity is observed with a methoxime or vinyl derivative. Thus, melithiazole C (**1**) has attracted great attention as a potential lead for the development of agrochemical fungicides.[5]

Despite its very limited natural availability arising from the low efficiency of the fermentation process, only one total synthesis of **1** has been reported proceeding via a moderately stereoselective Wittig reaction (*E*/*Z* ≈ 6/1) to introduce the C6−C7 double bond (14 steps, 15% overall yield).[6] On the basis of our recent work on the cross-metathesis (CM) of vinyl substituted thiazoles,[7] we present herein a short and

† Dedicated to the memory of Charles Mioskowski (1946−2007).

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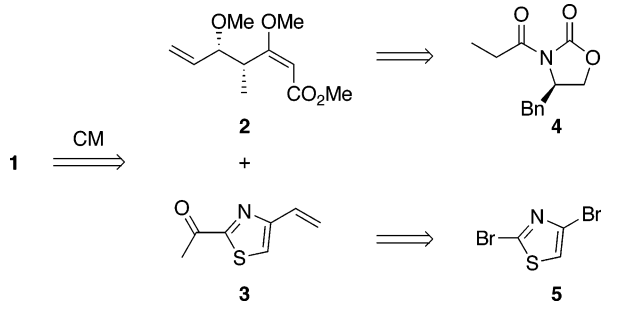
highly stereoselective synthesis of **1** that, at the same time, should allow rapid access to structural derivatives[5c] as well as various heterocyclic analogues.[5b]

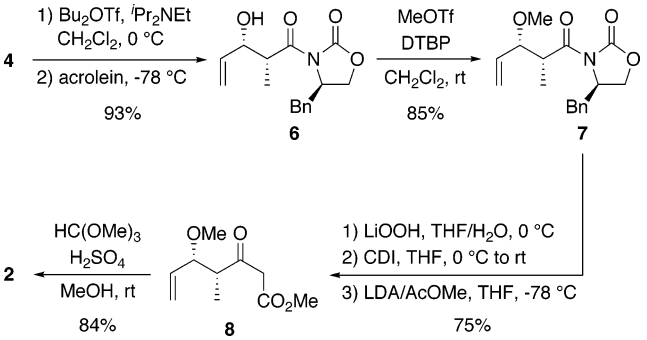
Retrosynthetically, **1** was therefore fragmented into the common β-methoxy acrylate **2** and the vinyl thiazole **3** which would both be readily accessible in a few steps from the commercially available Evans' propionate **4** and the dibromothiazole **5**, respectively (Scheme 1).

Scheme 1. Retrosynthesis of Melithiazole C (**1**)



As depicted in Scheme 2, the synthesis of the β-methoxy acrylate **2** began with a previously described asymmetric aldol reaction between **4** and acrolein (dr >95:5)[8] followed by *O*-methylation with methyl triflate in the presence of 2,6-ditertbutylpyridine (DTBP). While initial attempts to directly

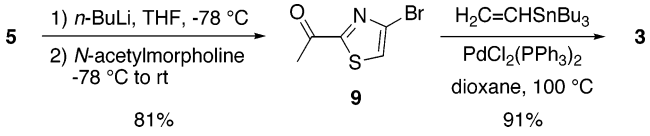
Scheme 2. Synthesis of the β-Methoxy Acrylate **2**



transform the resulting oxazolidinone **7** into the required β-keto ester **8** under Reformatsky conditions failed ($BrCH_2CO_2Me$, Zn, THF, reflux),[9] activation of the corresponding carboxylic acid with use of carbonyl diimidazole (CDI) and direct condensation with the lithium enolate of methyl acetate at −78 °C in THF proceeded smoothly to produce **8** in 75% yield (3 steps). Finally, acid-catalyzed methyl enol ether formation with MeOH in the presence of trimethyl orthoformate gave the desired β-methoxy acrylate **2** as a single stereoisomer in 50% overall yield from **4**.[10]

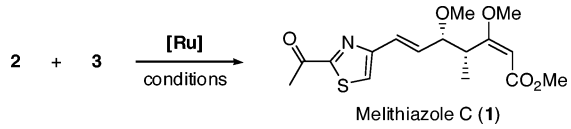
Concerning the preparation of the vinyl thiazole **3**, the thiazolyl bromide **9** was considered a suitable precursor since it is readily available from 2,4-dibromothiazole (**5**) via regioselective metalation (*n*-BuLi, Et_2O, −78 °C) and treatment with *N*-acetylmorpholine.[11] In our approach, a change of solvent from Et_2O to THF furnished the known bromide **9** in a significantly improved yield (81% vs 66%).[11] The latter was then subjected to a Stille cross-coupling reaction with vinyl tributyltin (1.1 equiv) under standard conditions [2 mol % of $PdCl_2(PPh_3)_2$, dioxane, 100 °C][12] to efficiently afford the desired vinyl thiazole **3** (Scheme 3).

Scheme 3. Synthesis of the Vinyl Thiazole **3**



With both fragments in hand, the conditions for the final metathesis reaction were investigated. While Grubbs first generation catalyst (G I)[13] proved completely ineffective (Table 1, entry 1), CM of an equimolar mixture of **2** and **3**

Table 1. Optimization of the CM Reaction



Melithiazole C (**1**)

entry	[Ru]	mol %	equiv of **3**	solvent[a]	temp (°C)	time (h)	conversion[b,c] (%)
1	G I	10	1	CH_2Cl_2	40	48	0
2	G II	10	1	CH_2Cl_2	40	48	27
3	H-G	10	1	CH_2Cl_2	40	48	18
4	G II	20	2	CH_2Cl_2	40	60	50
5	G II	20	2	C_6H_6	60	60	26
6	G II	20	2	CH_2Cl_2	20	72	5
7	G II	30	2	CH_2Cl_2	40	60	68 (56)[d]
8	G II	40	2	CH_2Cl_2	40	60	72

[a] 0.05 M. [b] Ratio of **1**:**2** determined by ^{1}H NMR. [c] *E*/*Z* > 20/1. [d] Isolated yield.

in refluxing CH_2Cl_2 with 10 mol % of Grubbs second generation catalyst (G II)[14] or with Hoveyda−Grubbs catalyst (H-G)[15] resulted mainly in homodimerization of the vinyl

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thiazole **3** while **2** was consumed only slowly (Table 1, entries 2 and 3).

Since protected allylic alcohols such as **2** do not undergo any self-metathesis (Type III olefins),[16] better results were obtained under more forcing conditions by employing 20 mol % of G II and an excess of thiazole **3**, whereas higher or lower temperatures were detrimental (Table 1, entries 4−6). Finally, CM was best effected with 30 mol % of G II in the presence of 2 equiv of **3** at 40 °C in CH_2Cl_2 (Table 1, entry 7) affording melithiazole C (**1**) as a single diastereoisomer (E/Z > 20/1) in 56% isolated yield. The spectroscopic and physical data of **1** were identical with those reported for the natural product {$[\alpha]^{20}_D$ +167 (*c* 0.3, MeOH); lit. $[\alpha]^{22}_D$ +169 (*c* 0.3, MeOH)}.[2,4]

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In conclusion we have described a short and convergent synthesis of melithiazole C (**1**), which was obtained in 6 steps and 28% overall yield starting from the commercially available Evans' propionate **4**. The key feature of this novel approach consists of a highly *E*-selective CM reaction between a vinyl thiazole and a polypropionate fragment. Further applications of this strategy to the synthesis of related natural products are currently under investigation.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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