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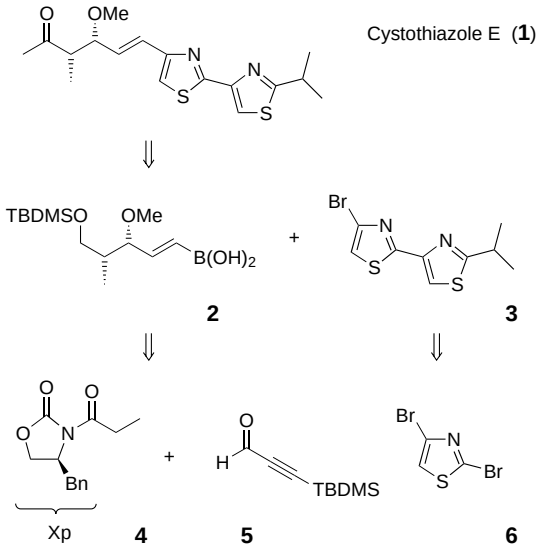
Regioselective Cross-Coupling Reactions as an Entry into Biologically Relevant Bithiazoles: First Total Synthesis of Cystothiazole E**

Thorsten Bach* and Stefan Heuser

Dedicated to Professor Rolf Gleiter on the occasion of his 65th birthday

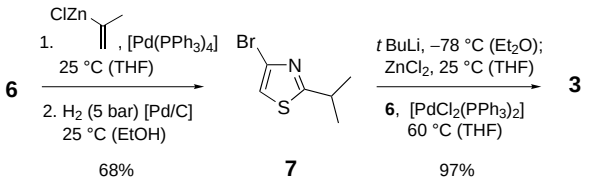
2′,4-Disubstituted 2,4′-bithiazoles are incorporated in several biologically relevant natural products which exhibit antiinfective and cytotoxic properties.[1] In previous syntheses access to the heterocyclic bithiazole core was based exclusively on the classical Hantzsch thiazole methodology.[2] Because of their regioselectivity[3] Pd-catalyzed cross-coupling reactions[4] of 2,4-dibromothiazole[5] appeared to offer an alternative shorter entry into bithiazoles which would allow a great variability in the choice of substituents at the 2′- and 4-positions. Herein we report the application of this strategy to the total synthesis of cystothiazole E (**1**).

The bithiazole **1** and several structurally related products were isolated by Sakagami et al. from a culture broth of the myxobacterium *Cystobacter fuscus* AJ-13278.[1a] The absolute and relative configuration of the stereogenic centers of **1** could not be determined. In analogy to related bithiazoles a *syn*-arrangement of the methyl and the methoxy group was likely. Following the above-mentioned concept we envisioned a Suzuki cross-coupling[6] of the building blocks **2** and **3** as a possible key step for the construction of the carbon skeleton of **1** (Scheme 1). While the vinyl boronic acid **2** was to be derived from the fragements **4** and **5** by a stereoselective aldol reaction,[7] the synthesis of bithiazole **3** was planned starting from 2,4-dibromothiazole (**6**).



Scheme 1. Retrosynthetic disconnection of the target molecule cystothiazole E (**1**); TBDMS = *tert*-butyldimethylsilyl.

Initial attempts aimed at a cross-coupling of isopropyl zinc chloride with 2,4-dibromothiazole (**6**) were not promising and delivered only minor quantities of the desired product **7**. In contrast, isopropenyl zinc chloride reacted smoothly (96% yield, Scheme 2). The subsequent hydrogenation proceeded



Scheme 2. Synthesis of the bithiazole building block **3** by a regioselective cross-coupling.

slowly at atmospheric pressure. At elevated pressure (5 bar) the conversion went to completion, however, the product is prone to hydrodebromination under these conditions and a prolonged hydrogenation should be avoided. The 4-bromothiazole **7** was converted into a carbon nucleophile by a halogen – metal exchange reaction.[8] After transmetalation with zinc chloride the aryl metal compound reacted regioselectively with **6** to afford the desired intermediate **3** (Scheme 2).

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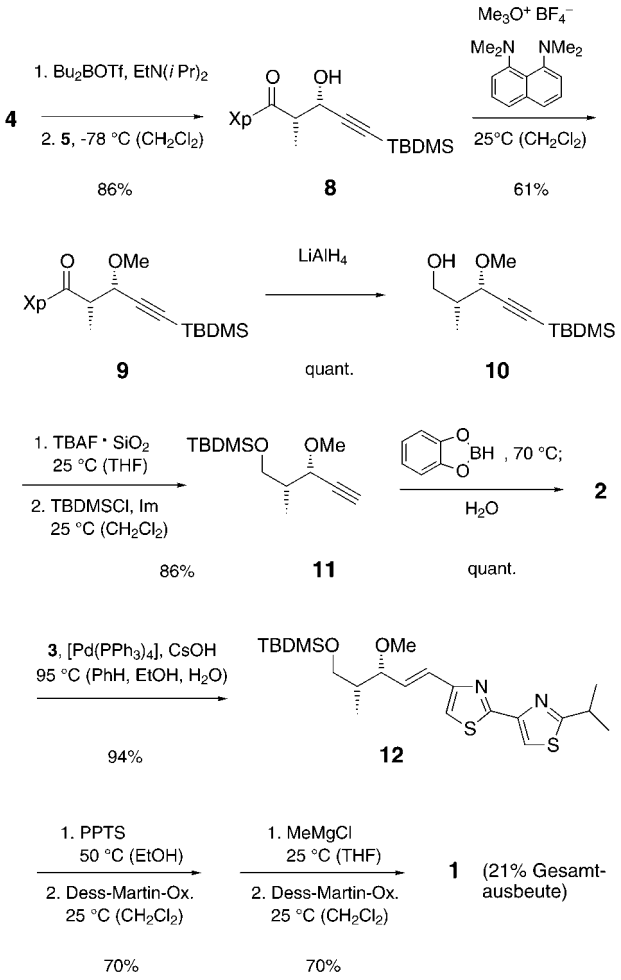
For the construction of the anticipated *syn*-aldol functional group we employed the L-phenylalanine derived *N*-propionyl oxazolidinone **4** (Scheme 3).[9] The reaction of **4** and the TBDMS-protected aldehyde **5** afforded **8** with excellent



Scheme 3. Overview of the individual steps in the total synthesis of (−)-cystothiazole E (**1**); Tf = trifluoromethanesulfonate, TBAF = tetrabutylammonium fluoride, im = imidazole, PPTS = pyridinium *p*-toluenesulfonate.

control of the facial and simple diastereoselectivity.[10] After alkylation to methyl ether **9**[11] and subsequent reduction the alkyne part of alkynol **10** was deprotected and the hydroxy group was TBDMS-protected (Scheme 3). The hydroboration of the alkyne with catecholborane proceeded quantitatively.[12] The choice of base in the Suzuki cross-coupling of boronic acid **2** with the bithiazole building block **3** required some optimization; the best result was with CsOH (94% yield). As in other coupling reactions[13] 5 mol% of the Pd-catalyst was employed. A variation of the catalyst ratio and further mechanistic studies have not yet been performed. In successive steps the TBDMS-protected primary alcohol **12** was converted into a methyl ketone.[14] The product **1** so obtained proved to be identical to the natural product in all scalar spectroscopic properties which supported the presumed relative configuration.[15] The direction of the specific rotation, however, was opposite to the one reported for the natural product ($[\alpha]_D^{20} = -17.5$ ($c = 0.12$, $CHCl_3$); natural product:[1a] $[\alpha]_D^{24} = +17.8$ ($c = 0.2$, $CHCl_3$)). Consequently, we assign the (3*R*,4*S*)-configuration to the naturally occurring (+)-cystothiazole E (*ent*-**1**), whereas (−)-cystothiazole E (**1**) as prepared by us has the (3*S*,4*R*)-configuration.

In summary, we have achieved the synthesis of (−)-cystothiazole E in a convergent route, which includes 10 synthetic operations, with an overall yield of 21%. Further applications of the reported bithiazole synthesis are being studied in our laboratories.

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