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Total synthesis of γ-trifluoromethylated analogs of goniothalamin and their derivatives

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ABSTRACT

An efficient method for the construction of chiral γ-trifluoromethylated α,β-unsaturated δ-lactone, a widely existing pharmacophore, has been developed and successfully applied for synthesis of γ-trifluoromethylated goniothalamins. The key steps included Evans-Aldol reaction of chiral titanium enolate of α-CF_3 imide, Wittig olefination and lactonization. The transformation of γ-trifluoromethylated α,β-unsaturated δ-lactone to a series of trifluoromethylated styryllactones was also investigated.

1. Introduction

Goniothalamin and its analogs having a common α,β-unsaturated δ-lactone moiety have been demonstrated to possess interesting biological activities [1]. The structure–activity relationship studies revealed that the α,β-unsaturated δ-lactone moiety plays a key role in their bioactivities, as it is an excellent potential Michael acceptor for nucleophilic amino acid residues of target enzymes [2]. We hypothesized that the introduction of fluorine or fluorinated group into the γ-position of α,β-unsaturated δ-lactone would make the double bond more electron-deficient and lead to a better Michael acceptor. Accordingly, two kinds of fluorine-containing analogs of goniothalamin **1**, γ-*gem*-difluoromethylenated goniothalamin **2** and γ-monofluorinated goniothalamin **3**, have been designed and successfully synthesized by our group (Fig. 1) [3]. The trifluoromethyl group (–CF_3) is one of the most electronegative groups and has widely been incorporated into medicinal compounds [4]. Thus, we are interested in the introduction of a trifluoromethyl group into the γ-position of goniothalamin. Herein, we report the total synthesis of trifluoromethylated analogs of goniothalamin **4** (Fig. 1).

2. Results and discussion

The retrosynthetic analysis of compound **4** is outlined in Scheme 1. Lactone **4** could be made using the intramolecular ester exchange reaction of linear α,β-unsaturated ester **5**, which could be assembled from aldehyde **6** via Wittig olefination. The aldehyde **6** could be prepared from the key chiral intermediate **7**. The Evans-Aldol reaction of the chiral α-CF_3 imide derived from 3,3,3-trifluoropropanoic acid should provide compound **7** [5].

Our synthesis commenced with the stereocontrolled construction of the chiral vicinal hydroxyl and trifluoromethyl groups. The $TiCl_4$-catalyzed Evans-Aldol reaction of oxazolidinone **8** with cinnamaldehyde went smoothly to deliver α-CF_3-β-OH imide **9** in high diastereoselectivity (11:1 dr; Scheme 2) [5]. However, the removal of the Evans' chiral auxiliary of imide **9** in the presence of $NaBH_4$ gave cinnamyl alcohol instead of the desired trifluoromethylated aldehyde **6**. The proposed mechanism for the formation of cinnamyl alcohol is shown in Scheme 2. As the trifluoromethyl group (CF_3–) is a strong electron-withdrawing group, the C3 hydroxyl group of imide **9** was transformed to alkoxy anion under the base reaction conditions and the subsequent cleavage of the carbon–carbon bond between C2 and C3 resulted in the formation of cinnamaldehyde. Finally, reduction of cinnamaldehyde with $NaBH_4$ gave cinnamyl alcohol. To address this problem, the protection of the free hydroxyl group of compound **9** with *t*-butyldimethylsilyl (TBS) group gave silyl ether **10** (Scheme 2). However, the removal of the Evans' oxazolidinone

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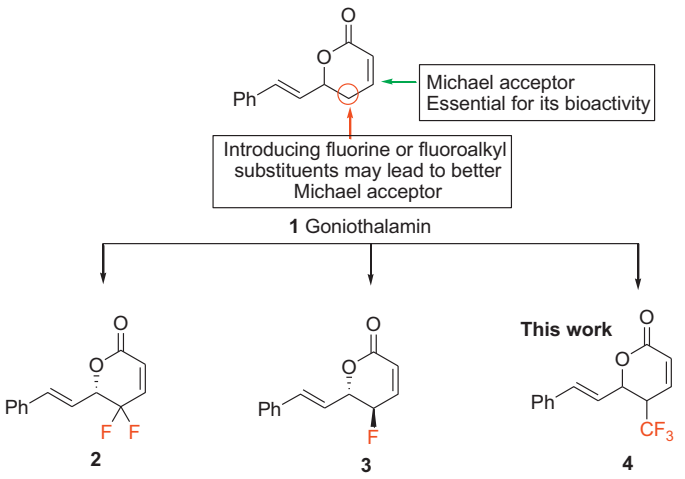
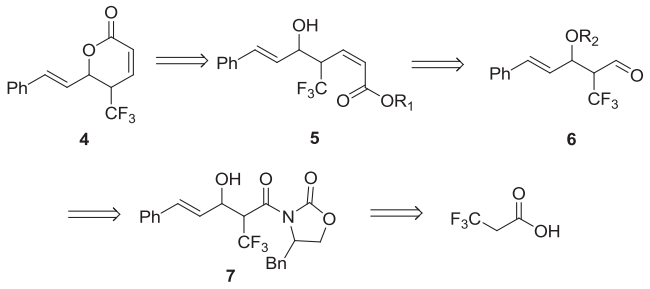


Fig. 1. Design of fluorinated goniothalamin.



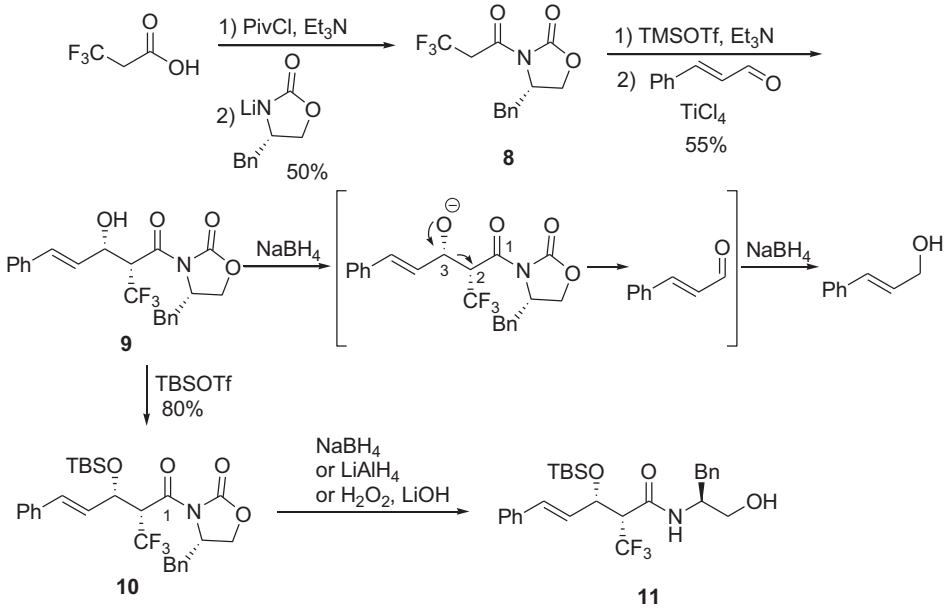
Scheme 1. Retrosynthetic analysis of γ-trifluoromethylated goniothalamin **4**.

chiral auxiliary of **10** under a number of reaction conditions ($NaBH_4$, $LiAlH_4$, and H_2O_2/LiOH/H_2O) failed to give the desired product, and compound **11** was formed.

At this stage, we thought that the more stable auxiliary would make the C1 carbonyl group of imide to be easily attacked by reduction agents. Accordingly, an alternative synthetic route using oxazolidinethione instead of oxazolidinone as the chiral auxiliary was investigated. The coupling reaction of 3,3,3-trifluoropropanoic acid and oxazolidinethione **12** gave α-CF_3 imide **13** in high yield (Scheme 3) [6,7]. Treatment of **13** with $TiCl_4$ (1.1 equiv.) and TMEDA (2.5 equiv.) and followed by cinnamaldehyde (1.5 equiv.) provided compound **14** in 81% yield and excellent diastereoselectivity (>97:2 dr) [7]. Protection of the free hydroxyl of imide **14** with TBS group afforded silyl ether **15** in 93% yield. As we expected, the removal of the oxazolidinethione of **15** in the presence of $LiAlH_4$ at −78 °C gave the desired alcohol **16** in 83% yield with a nearly quantitative recovery of chiral auxiliary **12**. However, the oxidization of primary alcohol **16** led to a complex reaction, probably due to the instability of the resulting α-CF_3 aldehyde **17** (Scheme 3). Thus, an alternative route based on the Wittig olefination between phosphonium salt derived from **16** and the corresponding aldehyde was investigated. Treatment of alcohol **16** with I_2, PPh_3 and imidazole yielded iodide **18** in 95% yield. Finally, the reaction of **18** with PPh_3 gave the desired phosphonium salt **19** in high yield.

The Wittig reaction of **19** with ethyl glyoxalate in the presence of *n*-BuLi at −78 °C proceeded smoothly to afford the linear α,β-unsaturated ester **20** in 57% with a Z/E selectivity of C2=C3 double bond up to 6.9/1. Treatment of **20** with $Et_3N{\cdot}3HF$ provided alcohol **21** in 96% yield (Scheme 4).

The lactonization of linear ester **21** was initially carried out in toluene in the presence of *p*-toluenesulfonic acid (0.2 equiv.) at 80 °C for 3 h. No target molecular **4** was detected, while compound **21** was totally consumed (Table 1, entry 1). When the reaction temperature was decreased to 30 °C, the expected γ-trifluoromethylated goniothalamin **4a** was formed in 74% yield along with the epimer **4b** in 11% yield (entry 2). Interestingly, the higher concentration of TsOH was, the more epimer **4b** was formed (entries 2–4). When the dosage of TsOH was increased to 1.0 equiv., the epimer **4b** was formed as the major product (entry 5). When CF_3CO_2H was used instead of TsOH, the epimerization was significantly suppressed and thus **4a** was formed as the single product (entry 6). Overall, a practical way was developed to control the epimerization during lactonization of linear ester **21**, enabling efficient synthesis of two diastereoisomers of target γ-trifluoromethylated goniothalamins **4a** and **4b**. The absolute configuration of product **4b** was assigned to be 5*R*, 6*S* by X-ray crystal analysis of compound **22** (Fig. 2) [8]. The Michael addition of 4-methylbenzenethiol with **4b** in the presence of 1,



Scheme 2. Synthesis of chiral α-CF_3-β-OH imide **9** and attempts to remove its auxiliary.