Synthesis of a goniothalamin derivative for cell-imaging experiments in tumor cells.

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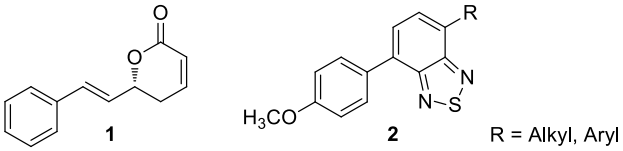
Introduction

(*R*)-goniothalamin (**1**) is a styryl lactone found in plants of the genus *Goniothalamus* displaying *in vitro* antiproliferative effects in different human tumor cell lines.[1]

In order to probe the location of **1** at the cellular level, we decided to prepare 2,1,3-benzothiadiazole (BTD) derivative **9** as the BTD chromophore **2** has shown fluorescent properties with expressive results in cell-imaging.[2]



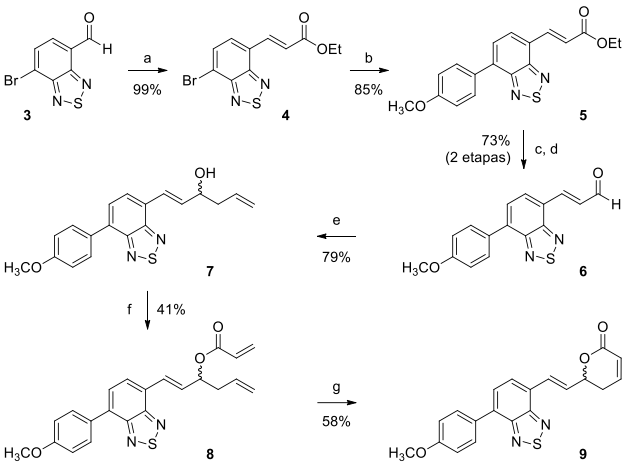
This work presents the synthesis of the goniothalamin analog **9** wherein the aromatic group was replaced by BTD fluorophore, keeping the α,β-insaturated lactone identified as the pharmacophore.[3]

Results and Discussion

Synthesis of **9** was carried out using the methodology developed in our lab[1] and it is depicted in Scheme 1.

Initially, aldehyde **3** was subjected to Horner-Wadsworth-Emmons olefination to obtain *E* isomer in excellent yield (99%). After that, a Suzuki coupling reaction was performed to insert the electron-donor core of the fluorescent portion of the molecule, and compound **5** was prepared in good yield (85%). Aldehyde homologation was accomplished in two steps: ester reduction of **5** with DIBAL-H to form the allylic alcohol (79% yield), followed by oxidation of the hydroxyl group with manganese dioxide to aldehyde **6** (92% yield).

Homoallylic alcohol **7** was obtained after Grignard addition into aldehyde **6** (79% yield). Esterification of **7** was carried out in low yield (41%) perhaps due to the facile elimination of the acrylate group in **8**. Goniothalamin analog **9** was synthetized through the ring close metathesis reaction of the terminal alkenes in **8** employing 20 mol% of the second-generation Grubbs catalyst in refluxing dichloromethane.



Scheme 1. a) triethyl phosphonoacetate, NaH, DMF, THF, 0 ºC to r.t., 1 h; b) $Pd(OAc)_2$ (cat.), PPh_3, Na_2CO_3, toluene, 85 ºC, 24 h; c) DIBAL-H, CH_2Cl_2, -78 ºC, 0,5 h; d) MnO_2, CH_2Cl_2, r.t., 1 h; e) allylmagnesium bromide, THF, -78 ºC, 0,5 h; f) acryloyl chloride, Et_3N, CH_2Cl_2, 0 ºC to r.t., 0,5 h; g) 2nd generation Grubbs catalyst (cat.), CH_2Cl_2, Δ, 5 h.

Compound **9** was characterized (m.p., IR, NMR ^1H and ^{13}C) and its fluorescence spectrum was measured showing maximum excitation peak at 400 nm and emission peak at 535 nm (in dichloromethane), thus qualifying **9** to cell-imaging experiments.

Conclusions

Goniotalamina-BTD derivative **9** was synthetized in seven steps starting from **3** in 11,5 % overall yield, and spectroscopically characterized for the future cell-imaging experiments.

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