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Note

A short alternative preparation of the bengazoles polyol side-chain segment

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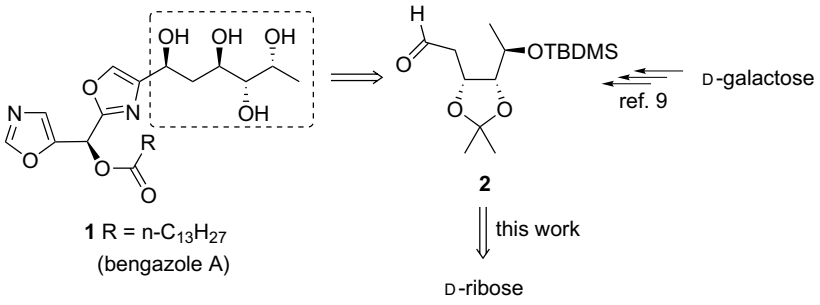
Abstract—A new short and efficient synthesis of the bengazoles side chain is reported using a sequential Grignard addition–hydroboration approach on a readily available D-ribose derivative.

Keywords: Bengazoles; Antihelminthic; D-Ribose; Grignard addition; Hydroboration

Whereas oxazole containing natural products were rare until the late 1980s, a number of naturally occurring oxazoles were isolated from marine organisms during the last 15 years.[1] Among them, Bengazole A (**1**, Scheme 1) and related homologues, are marine natural products isolated from sponges of the genus *Jaspis*.[2–5] Initially, bengazoles were found to have antihelminthic activity against *Nippostrongylus braziliensis*.[2] Later, Molinski and co-workers[6] discovered that they also exhibit a potent in vitro antifungal activity against *Candida albicans* and *Saccharomyces cerevisiae*.[6] This action is comparable to that of amphotericin B but more likely does not follow the same mode.[7] Bengazoles are in general fatty acid esters of a biogenically rare bis(oxazolyl)methanol heterocyclic core, which is further substituted with a polyol side chain, reminiscent of a sugar analogue. Their structure was elucidated by Molinski and co-workers[8] combining NMR, chiroptical methods and synthesis of model compounds. The first total synthesis of bengazole A was accomplished by Molinski's group,[9–11] as well. Their synthetic scheme follows a stepwise construction of the bis-oxazolyl core on the D-galactose derived



Scheme 1.

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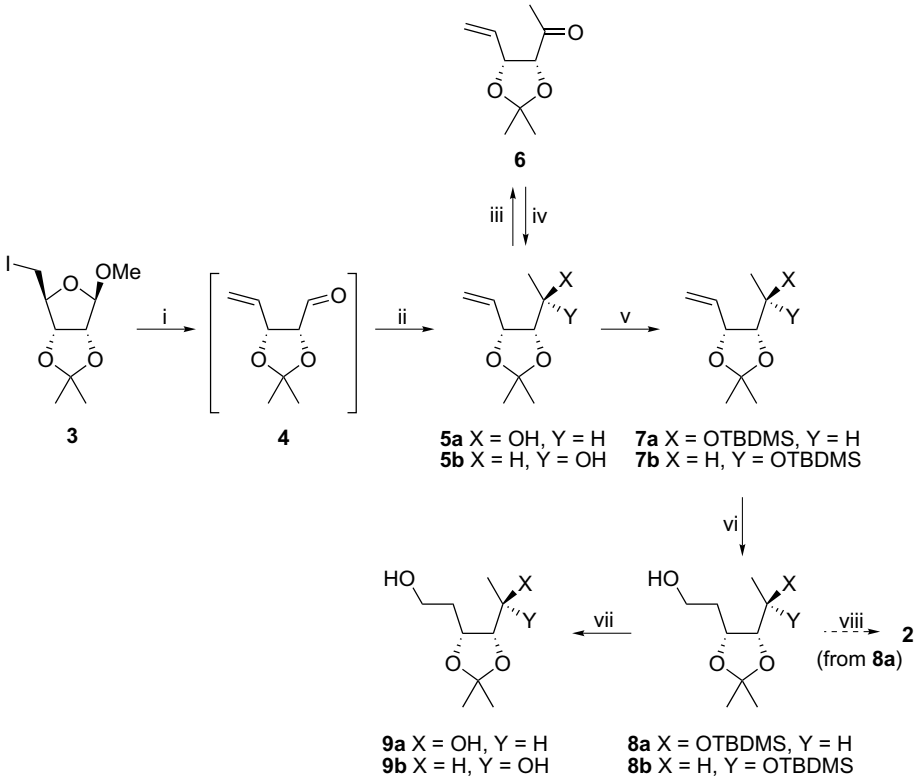
polyol chain segment **2**. According to a second approach by Shioiri and co-workers[12,13] deacylbengazole was prepared by $SnCl_4$ assisted coupling of a preformed bis-oxazolyl aldehyde subunit with a δ-alkoxystannane partner. The obtained intermediate was then further functionalized by Sharpless asymmetric dihydroxylation. Additionally, preliminary studies on the synthesis of bengazoles were lately communicated by Ley.[14] In continuation of our previous work,[15] regarding the synthesis of molecules with intriguing characteristics and properties from carbohydrates, we wish to report here an alternative preparation of aldehyde **2** using a readily available D-ribose derivative as the starting material.

It has been reported in the literature[15] that D-ribose is easily converted to iodide **3** following a simple two-step procedure and with an overall yield higher than 60%. Since pentenal **4** is also accessible in a straightforward manner from **3** we envisioned a synthetic scheme, which could lead from **4** to **2** using a Grignard addition-*anti*-Markovnikov oxidation sequence approach.

Indeed, treatment of iodide **3** with Zn in refluxing methanol for 2 h, afforded aldehyde **4**, which, being volatile, was roughly purified by removal of the solids and careful evaporation of the solvent at temperature not exceeding 35 °C (Scheme 2). Without any further purification a reasonable excess of MeMgI was added to **4**, to produce in excellent yield (91% overall from **3**) secondary alcohols **5a** and **5b** as an inseparable mixture of two diastereoisomers, lacking any appreciable selectivity (~3:2). The absolute configuration of the newly formed stereocentre in **5** was undoubtfully assigned after the conversion of **5** to diols **9** (vide infra).

Obviously, intermediate alcohol **5a** could be used to prepare the targeted aldehyde **2** but an improved pathway to it, regarding diastereoselectivity, had to be investigated. As it was not possible to separate the undesirable isomer **5b** from **5a**, in order to invert its C-2 stereocentre, we initially explored the possibility of altering the diastereoselection of the Grignard addition step. After several attempts, we realized that we could not achieve any significant change in the ratio of **5a** and **5b** and an indirect approach was adopted. According to this the mixture of alcohols **5** was oxidized to ketone **6** and the latter, without isolation was diastereoselectively reduced back to **5**. The best results we achieved hitherto were obtained when DIBAL-H (Table 1) was employed at a low temperature, favouring alcohol **5a**, with the desired C-2 configuration (dr ~8:1). Then, silylation of secondary alcohols **5** gave a mixture of alkenes **7**, which were chromatographically inseparable as well. Hydroboration of **7** followed by oxidation yielded alcohols **8**. At this stage it was practically feasible to separate **8a** and **8b** using



Scheme 2. Reagents and conditions: (i) Zn, MeOH, reflux, 2 h; (ii) MeMgI, Et_2O, 0–20 °C, 4 h, 91% from **3**; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60–20 °C; (iv) DIBAL-H, THF, −130 °C, 90 min, 85% overall for two steps; (v) TBDMSCl, imidazole, CH_2Cl_2, 20 °C, 20 h, 81%; (vi) $BH_3{\cdot}SMe_2$, THF, 0–20 °C, 1 h, then NaOH, H_2O_2, 0–20 °C, 1 h, 65% of **8a** and 8% of **8b**; (vii) TBAF, THF, 0–20 °C, 30 min, 96% for **9a** and 97% for **9b**; (viii) Ref. 9.