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Total Synthesis of Bengazole A

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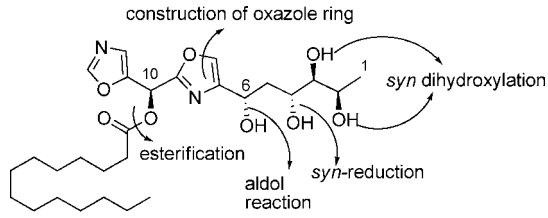
ABSTRACT



BENGAZOLE A (1)

The divergent and enantioselective total synthesis of the powerful antifungal marine natural product bengazole A has been achieved.

Bengazole A (**1**) is a (bis)oxazole sugar hybrid isolated by Crews et al. from the marine sponge *Jaspidae fijisponge*.[1] It exhibited antihelminthic activity against *Nippostrongylus braziliensis*[1] and also showed powerful antifungal properties against *Candida albicans* (MIC 7 μg/mL) comparable to those of amphotericin B.[2] This intriguing biological profile coupled with our own interest in synthesizing natural products of marine origin[3] provoked us to devise an approach amenable for both its synthetic simplicity and its easy access to analogues. The key steps that we hoped to use were a Sharpless asymmetric dihydroxylation,[4] a catalyst-controlled *syn*-reduction,[5] and intramolecular oxazole assembly.

Although bengazole A (**1**) was isolated in 1988, the first synthesis was reported in 1999 by Molinski and co-workers.[6] However, they ended up with an inseparable mixture (1:1) of bengazole A and its C10-epimer. Later, in 2006 Ley and co-workers[7] achieved a stereocontrolled total synthesis of **1** in 3.4% overall yield. Apart from these two total syntheses there are a few reports directed toward the synthesis of bengazole A.[8] Herein, we report a new enantioselective total synthesis of bengazole A.

Bengazole A (**1**), on logical disconnection, provided two fragments: the bisoxazole unit **2** and myristoyl chloride **3**. The bisoxazole unit **2** was further disengaged to the oxazole acid **4** and the amino polyol **5** (Scheme 1).

The oxazole acid **4** was synthesized from the known triisopropyl silyl formyl oxazole **8**[9] following the path shown in Scheme 2. Compound **8** underwent a smooth Wittig olefination ($PPh_3{}^+CH_3I^-$) to provide vinyl oxazole **9**, and this was followed by a Sharpless asymmetric dihydroxylation to yield **10** in 60% ee;[10] the unwanted isomer was separated at a later stage by column chromatography (Scheme 5). Compound **10** was treated with *p*-TsOH followed by selec-

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(10) HPLC method: Chiral pak IC 250 mm × 4.6 mm, 5 μ (column), 10% IPA in hexanes (mobile phase), flow rate 1 mL/min. t_R: 8.12 and 12.65 min.

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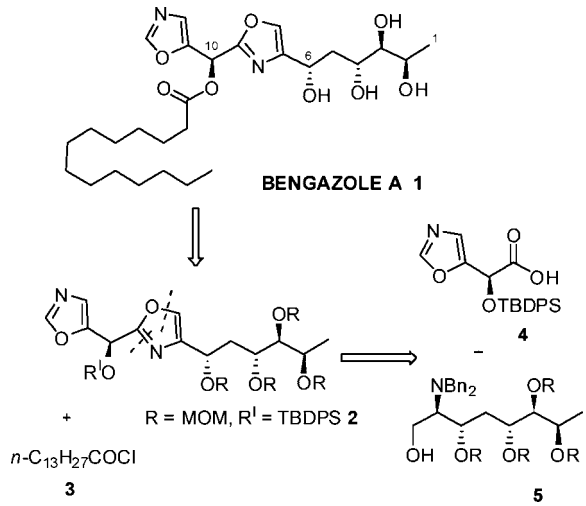
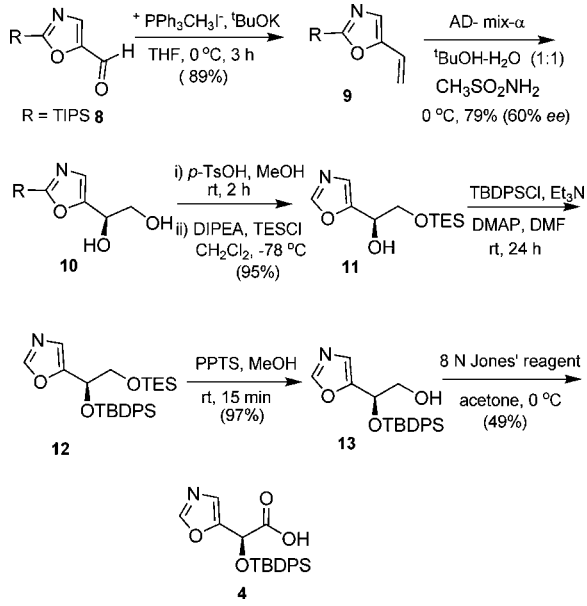
Scheme 1. Retrosynthetic Analysis of Bengazole A (**1**)



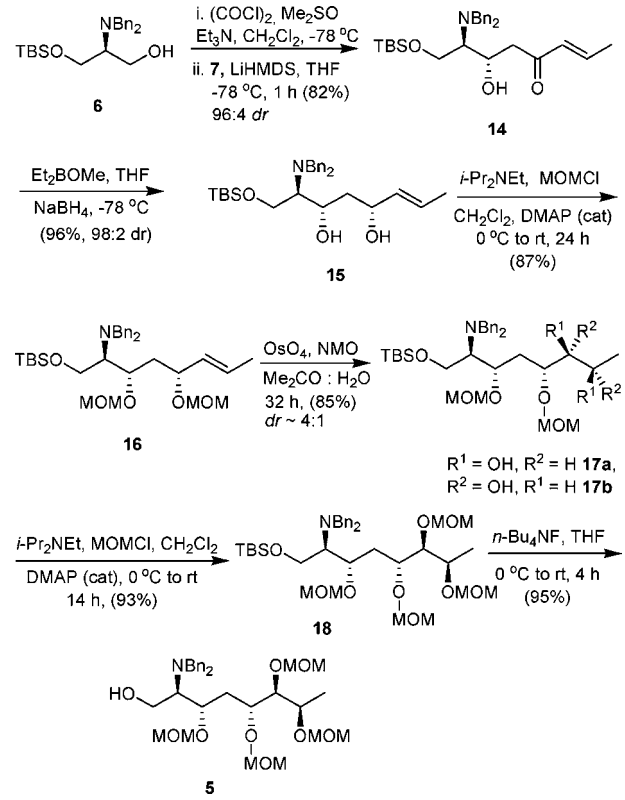
tive protection of the primary hydroxyl group as a TES ether **11**, which was further transformed to desired oxazole acid **4** via intermediates **12** and **13**.[7]

Scheme 2. Synthesis of Oxazole Acid **4**



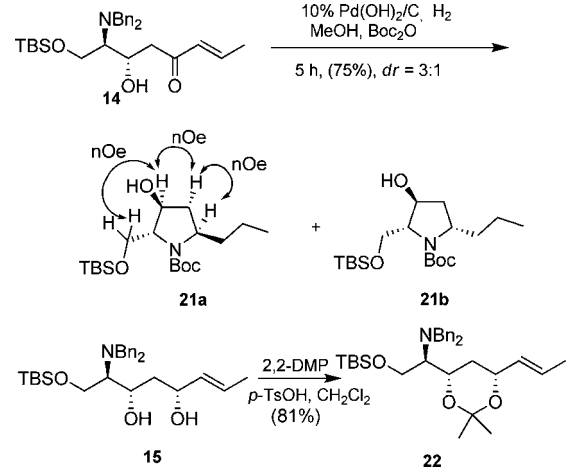
The amino polyol **5** was prepared starting from serinol **6**[11] through aldolization and dihydroxylation (Scheme 3). Thus **6** on Swern oxidation[11,12] followed by aldolization with 3-pentene-2-one **7** in the presence of LiHMDS at −78 °C furnished the aminol **14** (96:4 de).[13] To investigate the stereochemical integrity of the major product, **14** was subjected to $Pd(OH)_2$ catalyzed hydrogenation[14] in the presence of Boc_2O to furnish Boc-protected pyrrolidines **21a** and **21b** (Scheme 4). By 300 MHz NOE analysis in $CDCl_3$ it was found that the *O*-protected silyl group and the

Scheme 3. Synthesis of Aminopolyol **5**



3-hydroxy group were *trans* to each other in **21a**, which implied that the configuration of the newly generated stereocenter in **14** (major) was indeed the required one. Chelation-controlled reduction of the keto group in **14** with Et_2BOMe and $NaBH_4$ at low temperature afforded the *syn*-diol **15** (98:2 de).[5,15] To confirm stereochemistry of the required product, **15** was protected as acetonide, and the stereochemistry of major product was confirmed by Rychnovsky's acetonide method[16] (Scheme 4). Diol **15** was

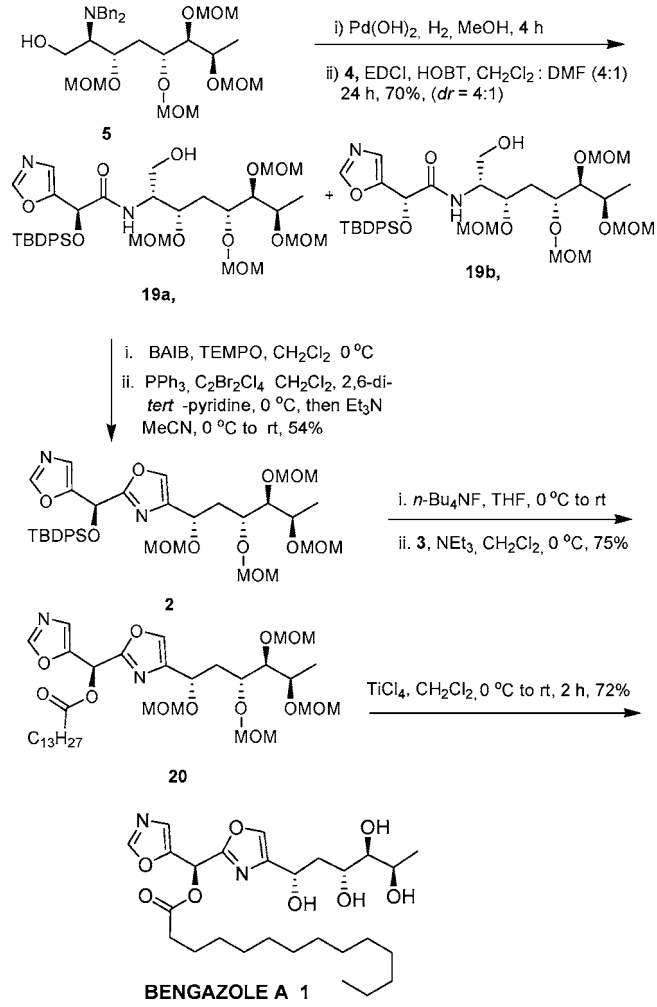
Scheme 4. Confirmation of Stereocenters



protected as di-MOM ether **16** in 87% yield (MOMCl, *i*-Pr_2NEt). Oxidative osmylation of **16** provided the *syn*-diol **17a** as a major diastereomer (4:1); the latter was separated from the unwanted diastereomer by column chromatography. The stereochemical outcome of the dihydroxylation was confirmed by NMR studies in addition to reports from the literature that Sharpless asymmetric dihydroxylation of **16** using AD mix-β[4] provided exclusively the required diol **17** (matched pair).[17] The protection of the two hydroxyl groups as MOM ethers was a rather trivial one (*i*-Pr_2NEt, MOMCl, CH_2Cl_2, 87% yield) to obtain **18**. Selective desilylation of **18** (*n*-Bu_4NF, 0 °C) provided the desired fragment **5** in 95% yield (Scheme 3).

With substantial quantities of the key synthons **4** and **5** in hand, we completed the total synthesis of bengazole A. Thus, compound **5** was subjected to hydrogenolysis to liberate the free amine, which was immediately reacted with **4** under EDCI-HOBT conditions to produce **19a**.[18] A smooth oxidative intramolecular cyclization[19] of **19a** was accomplished in two steps to give bisoxazolyl methanol derivative **2** in moderate yield. Desilylation liberated the free C-10 hydroxy group, and esterification with myristoyl chloride **3** generated the fully protected bengazole A, **20**, which on exposure to $TiCl_4$[20] in CH_2Cl_2 yielded the final compound bengazole A (Scheme 5). This compound is identical in all respects to the reported natural product including NMR, optical rotation, and HRMS. The synthesis, thus constitutes the shortest reported to date for this powerful antifungal agent.

Scheme 5. Total Synthesis of Bengazole A



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Supporting Information Available: Spectroscopic, analytical data, and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17)

$$\mathbf{16} \xrightarrow[{}^{t}\mathrm{BuOH-H_2O\ (1:1);\ CH_2SO_2NH_2}]{\text{AD mix-}\beta} \mathbf{17a}\ \text{(exclusive product)}$$

(18) The unwanted isomer **19b** was separated by column chromatography.
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