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Synthesis of Boxazomycin B and Related Analogs

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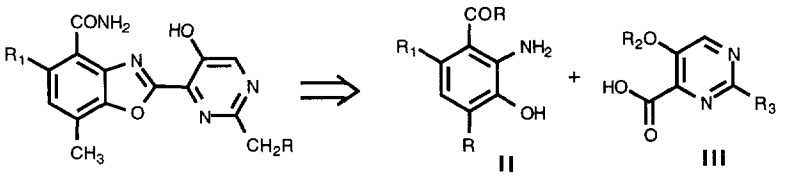
Abstract. The total synthesis of the novel antibacterial agent Boxazomycin B is reported. The synthesis proceeds through a highly functionalized benzene ring in which the key functionalities are introduced early in the synthesis and serve as protecting groups for additional transformations.

Introduction. As part of a program aimed toward identifying novel gram-positive antibacterial agents by mechanism-based screening, we identified several benzoxazole/benzimidazole "hits". These compounds were related to a recently reported new class of benzoxazole-containing compounds, the Boxazomycins[2]. Three members of this class, Boxazomycin A, B, and C (Figure 1) were shown to have good activity against gram-positive and anaerobic

Boxazomycins



1, R_1 = OH, R = OH, A
2, R_1 = OH, R = H, B
3, R_1 = H, R = OH C
4, R_1 = H, R = H

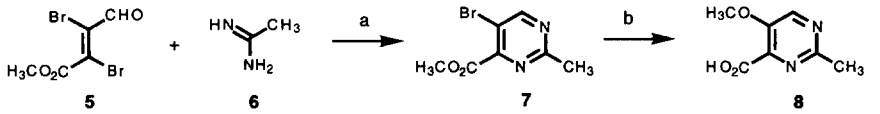
FIGURE 1

bacteria[2]. Thus, the Boxazomycins represented an interesting lead structure for the identification of novel antibacterial agents. Herein, we report the first synthesis of Boxazomycin B (compound **2**) and provide a route for analog preparation.

The synthesis of the Boxazomycin class of compounds was envisioned to proceed by condensing a protected aminophenol (**II**), with the appropriate pyrimidine (**III**, Figure 1). Such a dissection was not only logical, but also provided a route in which one of the fragments, the pyrimidine **III** (R = CH_3) was known[3]. Therefore, when we decided to focus on the synthesis of Boxazomycin B, the key element became the synthesis of the pentasubstituted benzene derivative containing the hydroxy groups para to each other (**II**, when R_1= OH).

Chemistry. The preparation of the pyrimidine **8** proceeded as described in the literature starting from mucobromic acid (**5**) and methylamidine (**6**) (Scheme 1)[3]. The pyrimidine **7**, was obtained in poor and unreliable yields and attempts to improve them failed (alternative routes have been explored[4]).

Scheme 1



5 **6** **7** **8**

Reagents: a) $NaOCH_3$/MeOH b) $NaOCH_3$/MeOH, $CuOAc_2$

The synthesis of the left hand aromatic portion was more difficult and was the key to the successful synthesis of these compounds. We envisioned starting with the commercially available[5] 3-hydroxy-4-methyl-2-nitrobenzoic acid **9**, which contained the necessary atoms in the proper orientation. The key step would be the introduction of an additional oxygen atom adjacent to the carbonyl group to provide a pentasubstituted benzene derivative as depicted in Figure 1. We investigated a number of oxidative methods for introducing this oxygen directly into the starting material or close derivatives, but none was successful. A review of the literature indicated that one of the most promising methods for effecting the required transformation was oxidation of the hydroxy compound to the quinone followed by reduction. However, to do this, the carboxylic acid and the nitro group of compound **9** would have to be protected or modified.

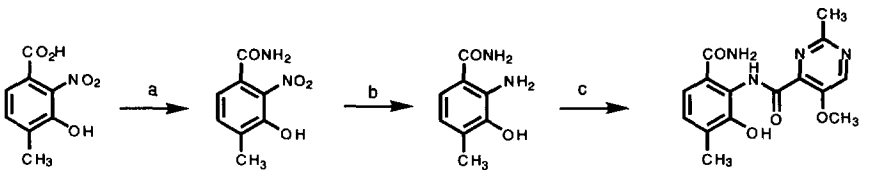
We chose to approach the synthesis in this way and examined the use of the later required amide moiety as a means of protection. We would convert the carboxyl group to a primary amide and the nitro group to an amine, which could also be protected as an amide. We envisioned that the pyrimidine amide of **8** could be used as the protecting group for the amine in **12** and then be cyclized to the benzoxazole later in the synthesis. Synthesizing the compound in this way would avoid the use of several of protection/deprotection steps and introduce the required functionality early in the synthesis.

Scheme 2 depicts the synthesis of the protected pentasubsituted benzene derivative, **12**. The acid **9**, was treated with oxalyl chloride followed by NH_4OH to give the amide **10** (94%), which was reduced (H_2/Pd/C) to provide the amino phenol **11** (85%). The amino phenol was then added to a solution of the pyrimidine imidazolide generated from **8** and CDI in THF. The reaction was heated at reflux to ensure that the only product obtained was the N-acyl derivative (vs. O-acyl). Upon cooling, the amide **12** crystallized, and was filtered (85%).

Before focusing on introduction of the second oxygen atom, we set out to determine if this pathway was indeed viable, and therefore elected to synthesize the des-hydroxy compound **4** (Scheme 3). Treatment of **12** with polyphosphoric acid (neat 110-120°) gave compound **13** in a yield of 51% (after recrystallization). This compound was then demethylated using LiI/pyridine to provide compound **4** (79%). A wide variety of other reagents were investigated (BBr_3, TMSI, HBr), but they did not provide sufficient quantities of the desired compound.

Having successfully completed the synthesis of the benzoxazole portion, we next focused on introduction of the hydroxyl group. As stated earlier, one of the best methods for introducing a hydroxyl group para to an existing phenol is through oxidation of the hydroxy compound. In this particular synthesis, the question remained as to whether the pyrimidine ring as well as the other functional groups would be compatible with the required conditions. It was found that treatment of **12** with Fremy's salt (potassium nitrosodisulfonate[6]) in DMF/H_2O provided cleanly the desired quinone **14**. A small amount of another product was detected by NMR therefore, the quinone was

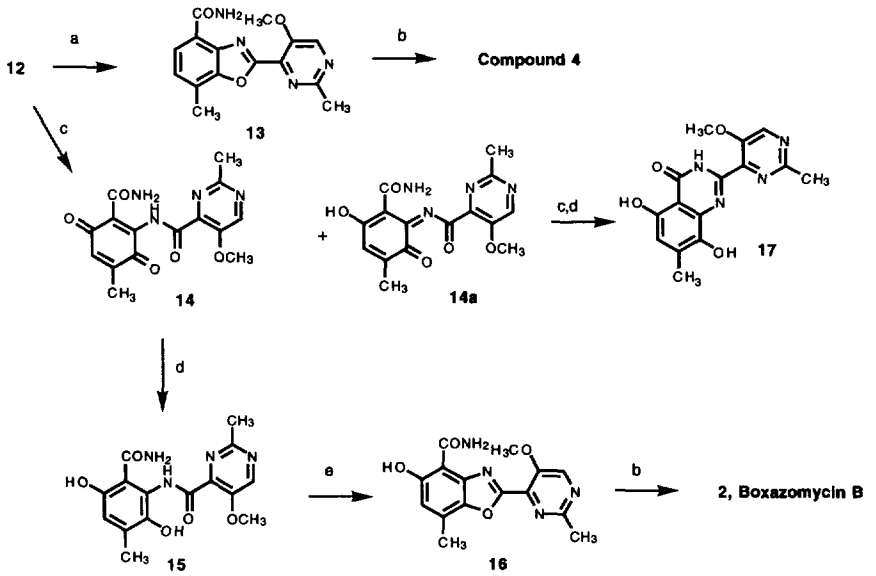
Scheme 2



9 **10** **11** **12**

Reagents: a) 1) $(COCl)_2$ 2) NH_4OH, b) H_2/Pd/EtOH, c) **8**, CDI/THF

Scheme 3



Reagents: a) PPA, 110-120°C, 3 h b) LiI/pyridine/100°C c) $(KSO_3)_2NO/KH_2PO_4$/DMF d) $Na_2S_2O_4$/EtOH e) pyridinium p-toluene sulfonic acid/$ClCH_2CH_2Cl$/4A sieves.

recrystallized, resulting in an intense color change (yellow powder to red crystals). Apparently, the recrystallization caused an isomeric rearrangement, which was not recognized immediately. This rearrangement was discovered by taking the apparently purified quinone on and finding that it did not give Boxazomycin B, but instead gave the quinazoline **17** (Scheme **3**). Closer examination of the ^{1}H NMR's of the crude quinone and the purified compound revealed that the product that was initially the minor product was the only product present after recrystallization. There were only very slight differences in the NMR spectra of the desired quinone (**14**) and the impurity (**14a**), which were more easily discernible after both compounds were purified. The analytical data for both compounds were almost identical. It was found however, that if the crude quinone was not purified (>90% pure directly from the reaction) but immediately reduced with sodium dithionite ($Na_2S_2O_4$), the stable dihydroxy derivative **15** (81%) could be obtained. Dehydration with pyridinium p-toluenesulfonic acid[7] (PPA did not work) gave the benzoxazole derivative **16** (82%), which was converted to **2** (Boxazomycin B) using LiI/pyridine as described above (91%). The spectral and analytical data clearly substantiated that we had synthesized Boxazomycin B. Compounds **2** and **4** were also found to have antibacterial activity against a number of gram-positive organisms[8].

In summary, we have described an efficient synthesis of Boxazomycin B and the corresponding deshydroxy compound (**4**). The synthesis and antibacterial evaluation of several related analogs are in progress and will be reported shortly.

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9. All compounds had elemental analyses and mass spectral data consistent with the proposed structures. **Compound 10**; mp 193-195°C; ^{1}H NMR ($CDCl_3$/d_6DMSO) δ 2.32 (s, 3H), 6.84 (bs,1H,ex), 7.02 (d, 1H, J=8), 7.31 (d,1H, J=8), 7.45 (bs, 1H,ex), 10.02 (s, 1H, ex); **Compound 11**; mp 173-174°C (water); ^{1}H NMR ($CDCl_3$) δ 1.56 (bs, 2H, ex), 2.24 (s, 3H), 6.44 (d, 1H, J=8), 6.54 (m, 3H), 6.92 (d, 1H), 7.13 (bs, 1H, ex); **Compound 12**; mp 222-228°C (dec, THF); ^{1}H NMR (d_6DMSO) δ 2.24 (s, 3H), 2.65 (s, 3H), 4.00 (s, 3H), 7.15 (m, 2H), 7.68 (s, 1H), 8.10 (s, 1H, ex), 8.84 (s, 1H), 9.34 (s, 1H, ex), 12.38 (s, 1H, ex); **Compound 14**; mp >260°C dec (MeOH); ^{1}H NMR (d_6DMSO) δ 2.03 (s, 3H), 2.63 (s, 3H), 3.99 (s, 3H), 6.76 (s, 1H), 7.71 (m, 2H, ex), 8.84 (s,1H), 11.08 (s, 1H, ex); **Compound 15**;mp >285°C (DMF) ; ^{1}H NMR (d_6DMSO) δ 2.18 (s, 3H), 2.64 (s, 3H), 3.99 (s, 3H), 6.71 (s,1H), 7.83 (bs, 1H, ex), 7.93 (bs, 1H, ex), 8.36 (s,1H), 8.81 (s, 1H), 10.84 (bs, 1H, ex),11.61 (bs, 1H ex); **Compound 16**; mp>285 °C (DMF); ^{1}H NMR (d_6DMSO) δ 2.56 (s, 3H), 2.69 (s, 3H), 4.08 (s,3H), 6.96 (s, 1H), 8.47 (s, 1H, ex), 8.65 (bs, 1H, ex), 8.91 (bs, 1H), 13.21 (s, 1H, ex); **Compound 17**; mp >250°C;); ^{1}H NMR (d_6DMSO) δ 2.26 (s, 3H), 2.63 (s, 3H), 3.94 (s, 3H), 6.73 (s, 1H), 8.75 (s, 1H); Compound **2 (Boxazomycin B);** mp >270°C (MeOH/DMF); ^{1}H NMR (d_6DMSO) δ 2.55 (s, 3H), 2.63 (s, 3H), 6.94 (s, 1H), 8.47 (s, 1H, ex), 8.66 (bs, 2H, ex),11.15 (1H, bs, ex), 13.29 (s, 1H, ex); **Compound 13**; mp 255-256 °C; ^{1}H NMR ($CDCl_3$) δ 2.69 (s, 3H), 2.84 (s, 3H). 4.12 (s, 3H), 5.99 (bs, 1H, ex), 7.37 (d, 1H), 8.16 (d, 1H), 8.64 (s, 1H), 8.86 (bs, 1H); **Compound 4**; mp >275 °C; ^{1}H NMR (d_6DMSO/TFA δ 2.65 (s, 3H), 2.69 (s, 3H), 7.46 (d, 1H), 7.94 (m, 3H), 8.76 (s, 1H).

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