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Shuai Wang, George A. Kraus

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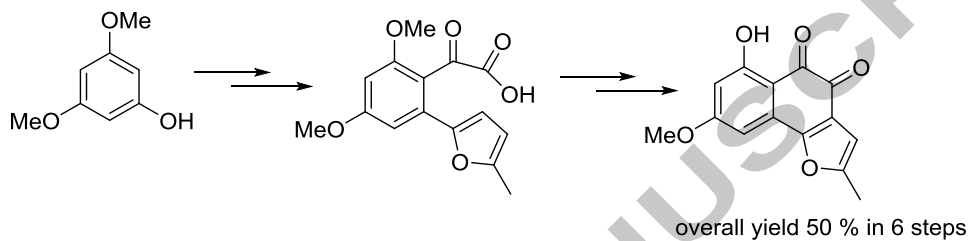
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The First Synthesis of Biatriosporin D

Shuai Wang^a, George A. Kraus^{a,*}

^a Department of Chemistry, Iowa State University, Ames, IA 50010, U.S.A.

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ABSTRACT

Biatriosporin D was synthesized in six steps from 3,5-dimethoxyphenol. The key step was an intramolecular Friedel-Crafts cyclization of an acyl imidazolide to form an ortho-quinone.

Keywords:

Biatriosporin D

Friedel-Crafts cyclization

Ortho-quinone

The biatriosporins are a group of heptaketide metabolites isolated from the endolichenic fungus *Biatrospora* sp.¹ They have been reported to exhibit antifungal activity. Recently, Lou and coworkers reported that biatriosporin D (**1**) shows anti-virulence activity by a mechanism leading to the reduction of intracellular cAMP levels.² In the context of our program in antimicrobials,³ we needed a sample of biatriosporin D and herein report a direct synthetic route to **1**.

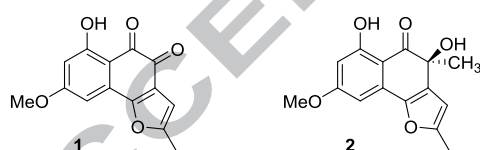
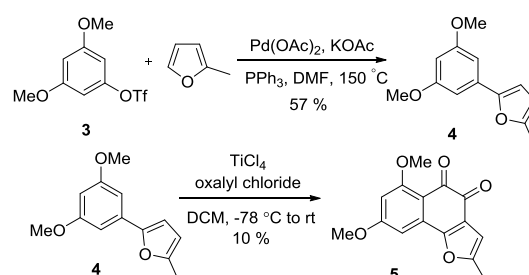


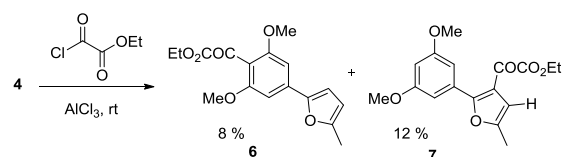
Figure 1. Biatriosporins

Our initial approach focused on creating the ortho-quinone subunit in **1** via a Friedel-Crafts reaction with oxalyl chloride (Scheme 1). We obtained the requisite aryl furan from the palladium mediated coupling of the triflate of 3,5-dimethoxyphenol (**3**) with 5-methylfuran. While Lewis acid mediated acylations with oxalyl chloride had been reported to give low yields, more recent papers reported good yields.⁴ Our key acylation with oxalyl chloride was not selective, providing several decomposition products. Various Lewis acids (BF₃, AlCl₃, TiCl₄, SnCl₄) were tried but none of them afforded the desired product in good yield. Despite changes in reaction parameters such as solvent (CH₂Cl₂, THF, 1,4-dioxane), temperature and the addition of reagents to capture HCl (propylene oxide) the best yield was only 10% with titanium tetrachloride in methylene chloride at -78 °C.



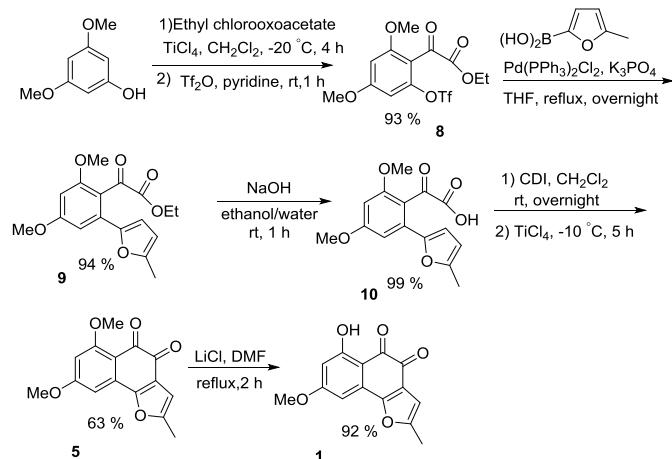
Scheme 1. Friedel-Crafts reaction with oxalyl chloride.

Next, we explored the reaction between **4** and ethyl chlorooxacetate catalyzed by AlCl₃ as shown in Scheme 2.⁵ The reaction resulted in two products in approximately equal yields. The structure of compound **7** was supported by the strong NOE between the furan hydrogen and the methyl group on the furan ring. The structure of compound **6** was supported by the symmetry observed in both the proton NMR spectra. Although compound **7** could have been converted into **1**, the yield of **7** was low. Therefore, this strategy was abandoned in favor of the plan described in Scheme 3.



Scheme 2. Friedel-Crafts reaction with ethyl chlorooxacetate.

* Corresponding author. Tel.: +1-515-294-7794; e-mail: gakraus@iastate.edu



Scheme 3. Synthesis of **1** in six steps.

Our second route began with the reaction of 3,5-dimethoxyphenol with ethyl chlorooxalate and titanium tetrachloride to produce the phenol,⁶ which could be readily converted into triflate **8** in 93% yield. Coupling of **8** with 5-methylfuran-2-yl boronic acid afforded furan **9** in 94% isolated yield. Hydrolysis with NaOH in ethanol-water provided the keto acid **10** in 99% yield. Conversion of the keto acid **10** into ortho-quinone **5** proved to be difficult. Reaction with trifluoroacetic anhydride and tin tetrachloride produced 12-20% yields of **5**. Fortunately, a procedure recently reported by Yoshikawa⁷ using carbonyl diimidazole (CDI) followed by titanium tetrachloride at -10 °C afforded a 63% isolated yield of **5** as a sparingly soluble red solid. Attempted deprotection using boron trichloride, boron tribromide or aluminum chloride returned recovered starting material. Finally, lithium chloride in boiling DMF for two hours produced the demethylation product **1** in 92% yield.⁸

Ortho-quinone **1** was synthesized in six steps from 3,5-dimethoxyphenol. This route is scalable, providing 300 milligrams of **1**. This three-component synthetic approach will allow for considerable flexibility in the design of synthetic analogs of **1**.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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9. **General Experimental Procedure for the cyclization and the demethylation.** To a solution of acid **10** (145 mg, 1.0 equiv) in CH₂Cl₂ (3.0 mL) was added carbonyldiimidazole (162 mg, 2.0 equiv). The reaction mixture was stirred at room temperature overnight. The resulting solution was added into a solution of TiCl₄ (380 mg, 4.0 equiv) in CH₂Cl₂ (2.0 mL) at -10 °C. The reaction mixture was stirred at -10 °C for 5 hours and quenched by addition of HCl (2.0 M) and then was extracted twice with CH₂Cl₂. The combined organic solution was washed with sat NaHCO₃, water and brine. The organic solution was dried by Na₂SO₄. The solvent was evaporated in vacuo and red solid **5** was obtained (87 mg, 63%). To a solution of solid **5** (54.4 mg, 1.0 equiv) in DMF (6.0 mL) was added LiCl (50.4 mg, 6.0 equiv). The reaction mixture was heated under reflux for 2 hours and was cooled down. DMF was removed by distillation under reduced pressure. And the residue was acidified by HCl (2.0 M) and then was extracted three times by EtOAc. The combined organic solution was washed with water, brine. The organic solution was dried by Na₂SO₄. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel and product **1** was obtained as red solid (47.4 mg, 92%). ¹H NMR (400 MHz, CDCl₃) δ = 12.43 (s, 1H), 6.74 (d, J=2.3, 1H), 6.41 (s, 1H), 6.31 (d, J=2.3, 1H), 3.90 (s, 3H), 2.40 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ = 182.12, 175.37, 169.22, 168.20, 158.14, 156.31, 129.59, 122.78, 106.82, 105.39, 104.44, 101.26, 56.31, 13.78. HRMS (ESI-QTOF) calcd for [M + H]⁺: 259.0601, found: 259.0597.

Highlights

1. An efficient synthesis of Biatriosporin D
2. Cyclization of an acyl imidazolide to produce an ortho-quinone
3. Selective demethylation using LiCl in DMF