5-16-2018

The first synthesis of biatriosporin D

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Abstract
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Keywords
Biatriosporin D, Friedel-Crafts cyclization, Ortho-quinone

Disciplines
Organic Chemistry

Comments
This is a manuscript of an article published as Wang, Shuai, and George A. Kraus. "The first synthesis of biatriosporin D." *Tetrahedron Letters* 59, no. 20 (2018): 1968-1969. DOI: 10.1016/j.tetlet.2018.04.027. Posted with permission.

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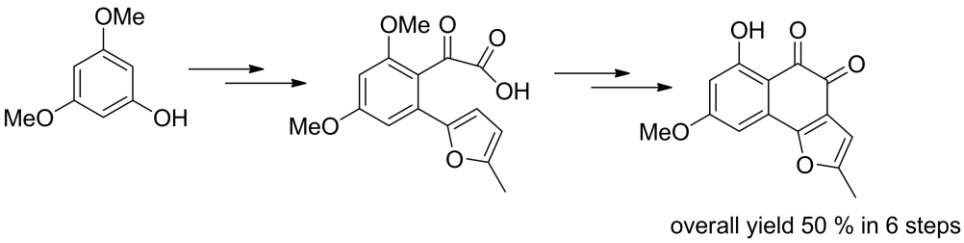

overall yield 50 % in 6 steps

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

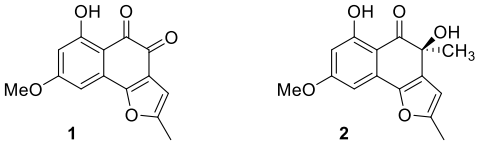
Keywords:
Biatriosporin D
Friedel-Crafts cyclization
Ortho-quinone

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.

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**.

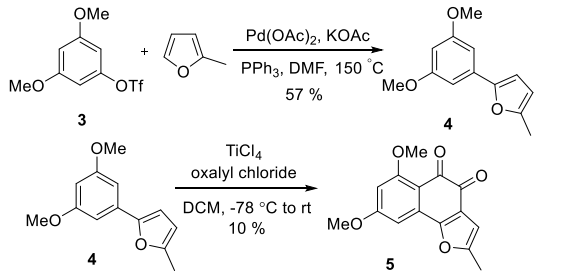
Figure 1. Biatriosporins

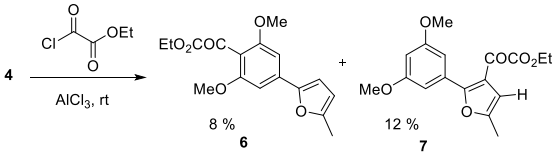


Our initial approach focused on creating the ortho-quinone subunit in **1** via a Friedel-Crafts reaction with oxalyl chloride in Scheme 1. We obtained the requisite aryl furan from the palladium mediated coupling of the triflate of 3,5-dimethoxyphenol (**3**) with 5-methylfuran. Unfortunately, the key acylation with oxalyl chloride was not selective, providing several decomposition products. Various Lewis acids (BF_3, $AlCl_3$, $TiCl_4$, $SnCl_4$) were tried but none of them afforded the desired product in good yield. Despite changes in reaction parameters such as solvent (CH_2Cl_2, 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.

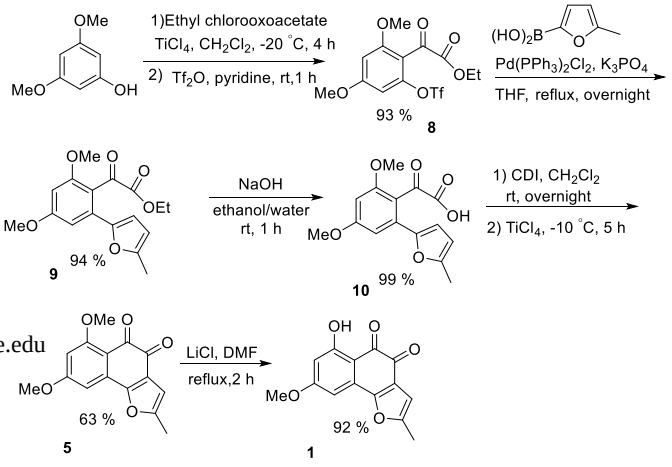
Scheme 1. Friedel-Crafts reaction with oxalyl chloride.

Next, we explored the reaction between **4** and ethyl chlorooxoacetate catalyzed by $AlCl_3$ in Scheme 2.[4] 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 chlorooxoacetate.



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

Our second route began with the reaction of 3,5-dimethyoxyphenol with ethyl chlorooxalate and titanium tetrachloride to produce the phenol,[5] which could be readily converted into triflate **8** in 93 % yield. Coupling of **8** with 5-methylfuranyl 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 Yoshikawa[6] 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.[7]

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

Acknowledgments

We thank the Department of Chemistry for partial support of Shuai Wang.

A. Supplementary data

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

References and notes

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8. **General Experimental Procedure for the cyclization and the demethylation**. To a solution of acid **10 (**145 mg, 1.0 equiv) in CH_2Cl_2 (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 $TiCl_4$ (380 mg, 4.0 equiv) in CH_2Cl_2 (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 CH_2Cl_2. The combined organic solution was washed with sat $NaHCO_3$, water and brine. The organic solution was dried by Na_2SO_4. 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 Na_2SO_4. 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 %). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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.