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Total Synthesis of Benzofuran-Based Aspergillusene B via Halogenative Aromatization of Enones

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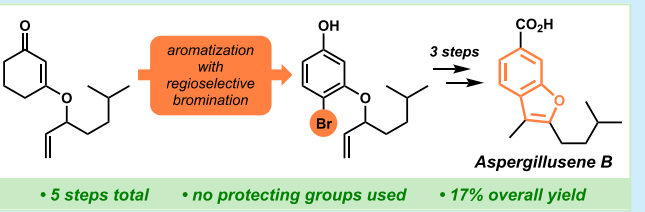
ABSTRACT: A novel "non-aromatic pool" synthetic strategy for the synthesis of benzofuran-based natural products via oxidative haloaromatization of enones is reported. This approach is successfully applied in the first total synthesis of the natural product aspergillusene B. In comparison with a separately executed "aromatic pool" synthesis, the "non-aromatic pool" protocol demonstrates equivalent efficiency but offers a much higher degree of modularity.



Polysubstituted benzofurans represent a common structural motif in naturally occurring medicines.[1a] Members of this family express a diverse range of biological activities, including antioxidant (**1**, **2**),[1b,c] anti-inflammatory (**3**, **4**),[1d] anticancer (**5**),[1e−i] antidiabetic (**6**),[1j] antifungal,[1k] antimalarial,[1l] and antibacterial[1m,n] profiles (Figure 1). As a result, many synthetic

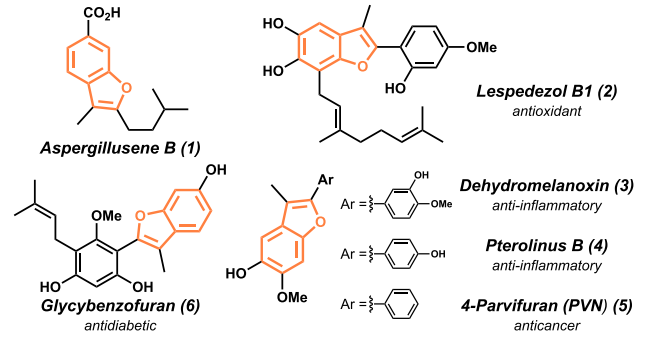


Figure 1. Benzofuran-based natural products.

strategies have been developed to access the substituted benzofuran rings in such natural products. The majority of these reported solutions are based on modification of existing aromatic cores toward fully elaborated benzofurans.[2] Only a few alternative approaches have been realized in which the arene is obtained efficiently from a non-aromatic precursor.[3] However, this synthetic approach provides additional synthetic flexibility since it allows a greater array of functionalization techniques than classical methods of arene decoration, such S_EAr and S_NAr, which have well-established limitations.

Among the aromatization methods for non-aromatic pool-based synthesis, the most common is oxidation of electron-rich systems with quinones (e.g., DDQ), as exemplified in total syntheses of furoventalene,[3a] lanceolatin B,[3b] pongamol,[3b] and corsifuran C[3c] (Scheme 1a). An elegant synthesis of egonol was developed by Herndon in 2003 using a modified Wulff–Dötz reaction between a chromium carbenoid and a protected dienylalkyne (Scheme 1b).[3d]

Recently, Tang reported a highly convergent approach to a series of benzofuran-containing natural products via Rh-catalyzed carbonylative benzannulation (Scheme 1c).[3e] In a creative alternative strategy combining oxidative and acid-mediated transformations en route to propolisbenzofuran B, Thomson employed an oxiditave enol coupling to generate a 1,4-diketone poised for a Paal–Knorr-type furan synthesis (Scheme 1d).[3f] Collectively, these "non-aromatic" approaches toward benzofurans add great value as complementary alternatives to "aromatic pool" methods and offer a greater degree of strategic freedom.

Because of the scarcity of general examples for constructing benzofuran moieties from non-aromatic precursors, we sought to develop an aromatization/annulation sequence as an efficient entry into the benzofuran class. This strategy was based on enone aromatization methodology developed in our group using readily available non-aromatic vinylogous esters.[4] Reasoning that the structural homology within the array of benzofuran-containing targets would facilitate a unified strategic approach, we selected aspergillusene B (**1**)[1b] as a model case for our synthetic development. The deceptively simple structural appearance of this target belies the embedded synthetic challenges of regiocontrol necessary to construct the core and the difficulty of introducing two different aliphatic groups at the 2- and 3-positions of the parent heterocycle.

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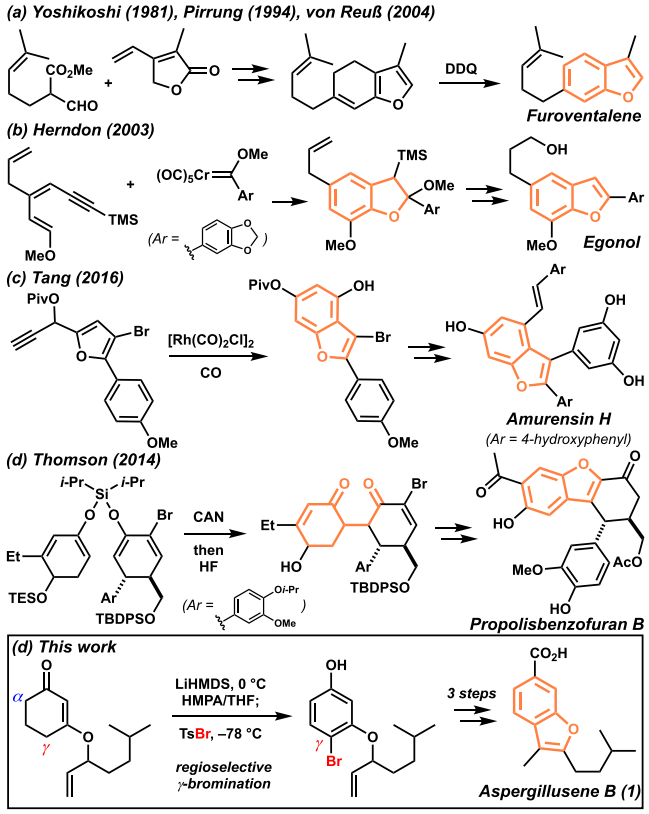
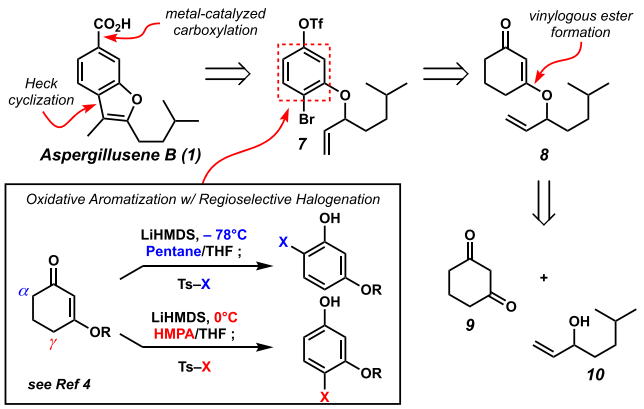
Scheme 1. "Non-aromatic" Approaches to Benzofurans



With these potential pitfalls in mind, we sought a modular strategy that would confront these problems directly.

Our synthetic approach toward aspergillusene B (Scheme 2) is founded on our recently developed regioselective enone

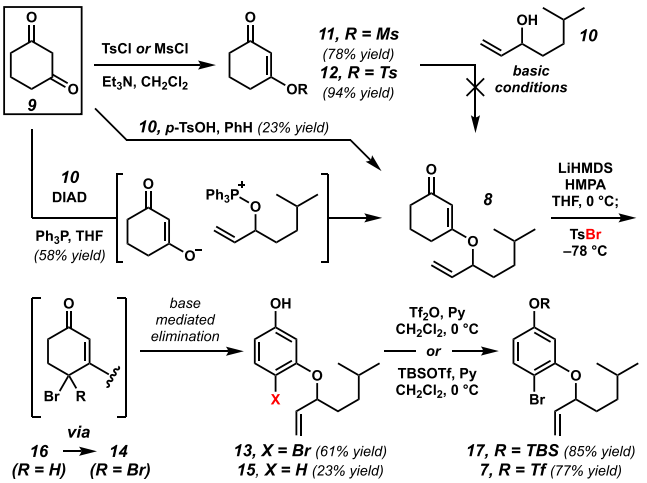
Scheme 2. Retrosynthetic Analysis of the "Non-aromatic Pool" Synthesis of Aspergillusene B via Oxidative Aromatization



aromatization/halogenation methodology[4] that has already proven to be a powerful synthetic tool in the total synthesis of a family of phenolic natural products.[5] In particular, we envisioned the benzoic acid moiety to be available via a metal-catalyzed carboxylation protocol from the corresponding aryl triflate, while the furan ring was predicted to be available via an intramolecular 5-*exo*-trig Heck-type cyclization (with concomitant alkene isomerization) between an aryl halide and a tethered allylic ether. Thus, we targeted the resorcinol derivative **7** as a suitable substrate for the endgame metal catalysis. We expected the specifically functionalized arene to be readily prepared via our oxidative aromatization methodology[4,5] applied to vinylogous ester **8**. This non-aromatic monocycle could be constructed from commercially available cyclohexane-1,3-dione (**9**) and known 2° allylic alcohol **10**.[6] We note that this approach is highly modular since analogues of alcohol **10** could readily vary the 2- and 3-substituents in the target and the established reactivity of vinylogous esters,[7] such as intermediate **8**, could be leveraged to introduce functionality around the benzene ring system embedded in the target molecule.

We commenced our synthesis by attempting esterification of cyclohexane-1,3-dione (**9**) with allylic alcohol **10**,[6] which proved surprisingly challenging (Scheme 3). At first, diketone

Scheme 3. Preparation of Key Aromatic Intermediates



9 was converted into the corresponding known vinylogous mesylate[8] and tosylate[9] (compounds **11** and **12**) under basic conditions on a multigram scale in excellent yield. Unfortunately, treatment of either of these materials with 2° allylic alcohol **10** under various basic conditions did not afford the substitution product. An attempt to overcome this challenge by forming the vinylogous mesylate in situ[10] followed by nucleophilic displacement with alcohol **10** did not result in any detectable ester **8**. Direct acid-catalyzed condensation between cyclohexadione **9** and 2° allylic alcohol **10** yielded the desired intermediate **8**, albeit in only 23% yield on a 1 mmol scale. This yield was reduced to 14% on a larger scale (5 mmol). Seeking further improvements, we examined a Mitsunobu displacement process to reverse the polarity of the coupling. Thus, treatment of a DIAD/Ph_3P mixture with a solution of diketone **9** and alcohol **10** in THF furnished the desired vinylogous ester **8** in a much improved 58% yield. The efficiency of this reaction was not affected by changes in the alcohol/diketone ratio, temperature, or choice of solvent; all of the performed trials afforded **8** in yields of ~60%. Most importantly, the yield was maintained at this level on a larger scale, allowing reasonable throughput of material to further the synthesis.

With good quantities of vinylogous ester **8** in hand, we continued the synthesis of **1** with exploration of the key oxidative aromatization/bromination reaction (Scheme 3). To our delight, the established reaction protocol (LiHMDS, HMPA, *p*-TsBr) secured a 61% yield of the desired γ-

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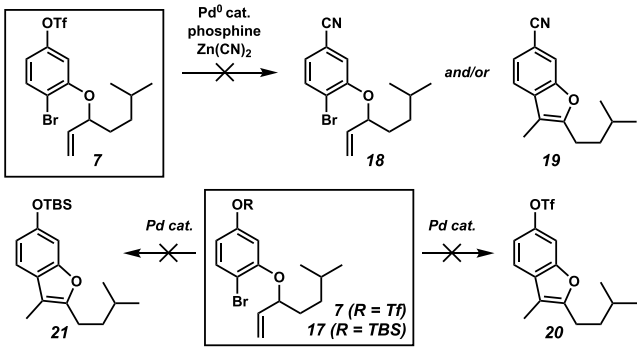
brominated arene product **13** via putative γ,γ-dibromoenone **14**. We also obtained a 23% yield of the desbromo congener **15**, presumably as a result of premature elimination from γ-monobromoenone **16**. Screening of various Br^+ sources (including NBS, DBDMH, Me_3PhNBr_3, Br_2, and DABCO·$2Br_2$) and other reaction parameters did not improve efficiency or selectivity in this case. Predicting that the free phenol functionality might be problematic, two derivatives were prepared: aryl triflate **7** and silyl ether **17**.

With both resorcylic intermediates **7** and **17** in hand, we began exploring the intramolecular Heck-type cyclization (Scheme 4). We first attempted cyanation of the aryl triflate,

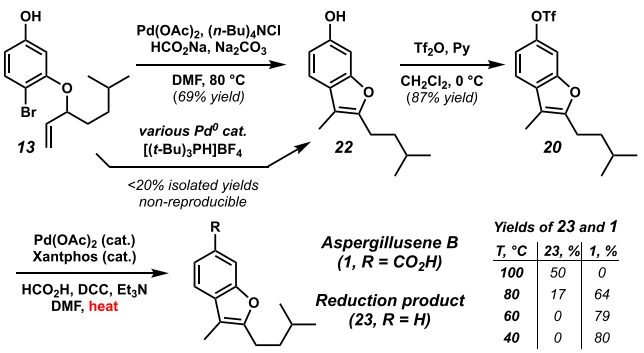
Scheme 4. Intramolecular Heck Cyclization with Resorcinols



a fragment that would later be converted into the requisite carboxylic acid in the target molecule. Unfortunately, Pd-catalyzed conditions[11] with $Zn(CN)_2$ did not deliver the desired benzonitrile **18** or the benzofuran **19** that might result from cascade cyclization with or without cyanation of aryl triflate **7**. Disappointingly, neither aryl silyl ether **17** nor aryl triflate **7** participated in Heck cyclization under several metal-catalyzed reaction conditions,[12,13] and no benzofuran products (**20** or **21**) were isolated in any explored case. Attempts involving triflate **7** returned unchanged starting material, and those utilizing silyl ether **17** led to a complex mixture with no detectable cyclization.

Confronted with the difficulty of benzofuran construction, we took one step back and started exploring the feasibility of Pd-catalyzed reactions with free phenol **13** (Scheme 5). Although we anticipated that this electron-rich arene would resist oxidative addition, we were delighted to discover that benzofuran **22** was observed under conditions with a Pd(P(*t*-Bu)$_3$)$_2$ catalyst reported for related aromatic systems.[4] Unfortunately, we were not able to improve this set of conditions and therefore continued testing of other parameters. We were pleased to find that Larock's intramolecular cyclization protocol[14] employing Jeffrey's Pd catalyst system and sodium formate as a reducing agent resulted in very clean conversion of aryl bromide **13** into the desired benzofuran **22**.

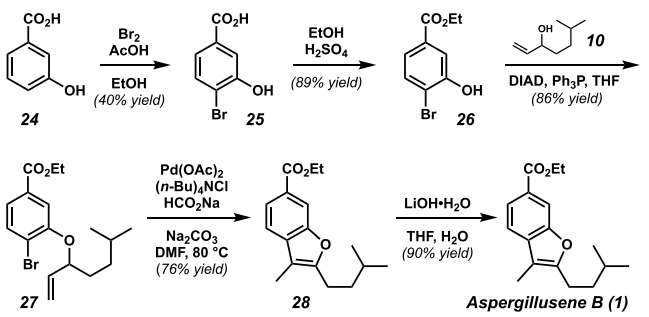
Scheme 5. Completion of the "Non-aromatic Pool" Synthesis of Aspergillusene B



Triflation of phenol **22** supplied benzofuran **20** in high yield. Unfortunately, subsequent cyanation attempts with $Zn(CN)_2$ and Pd catalyst[11] again failed, with complete recovery of unchanged starting material. Fortunately, aryl triflate **20** proved to be reactive under recently developed carboxylation conditions reported by Peng and Wu.[15] Interestingly, in the initial disclosure only the parent aryl triflate (PhOTf) was reported, and our success in a more complex case suggests that the scope of this transformation may be significantly broader. However, we were surprised to discover that the desired carboxylation of aryl triflate **20** is highly sensitive to temperature. Moderate heating is required since at higher temperature competing hydrodetriflation prevails, delivering benzofuran **23** exclusively. This optimization led to an efficient end to the first total synthesis of aspergillusene B (**1**) via a "non-aromatic pool" approach.

To benchmark the success of our aromatization strategy, we proposed an alternative "aromatic pool" route to assemble this molecule. To this end, 3-hydroxybenzoic acid (**24**) was converted to known bromoarene **25**[16] in moderate yield, which was then esterified to furnish known benzoate derivative **26**[17] (Scheme 6). The aryl bromide was then coupled with 2°

Scheme 6. "Aromatic Pool" Total Synthesis of Aspergillusene B



allylic alcohol **10** under the Mitsunobu protocol that we developed for vinylogous ester formation (see Scheme 3), efficiently yielding aryl ether **27**. With full knowledge of suitable Heck cyclization conditions from our already completed synthesis, brominated arene **27** was readily transformed to benzofuran **28** with the Jeffrey-type Pd-based system[14] in good yield. The "aromatic pool" total synthesis of **1** was then completed through saponification with aqueous LiOH in THF.

Having developed two different approaches to the benzofuran-based natural product aspergillusene B (**1**), we conclude that the syntheses offer comparable efficiency in terms of yield and step count (Scheme 7). The non-aromatic strategy has significant potential for diversification since standard transformations of intermediate vinylogous ester **8** are readily incorporated, whereas the alternative "aromatic" route relies on aromatic substitution reactions with well-established limitations. Notably, the "non-aromatic" route does not require protective groups. We therefore anticipate that the

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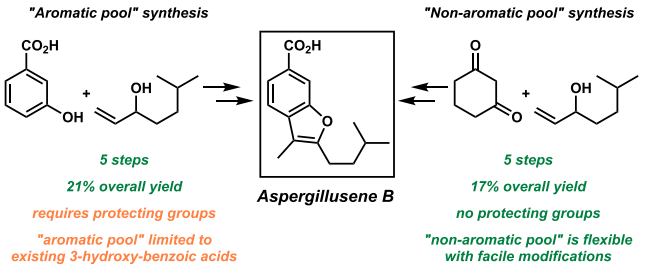
Scheme 7. Comparison of Aspergillusene B Total Syntheses



non-aromatic route will be better suited to analogue synthesis.[18]

In conclusion, we have developed the first two total syntheses of the natural product aspergillusene B (**1**). The "non-aromatic" route utilizes a novel oxidative haloaromatization of enones, is efficient and free from protecting groups, and offers equivalent efficiency as the conventional "aromatic pool" synthesis. The non-aromatic pool approach is poised for analogue synthesis, which is a current pursuit in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01259.

Experimental procedures, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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