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Letter

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Radical Cyclizations for the Synthesis of Pyrroloindoles: Progress toward the Flinderoles

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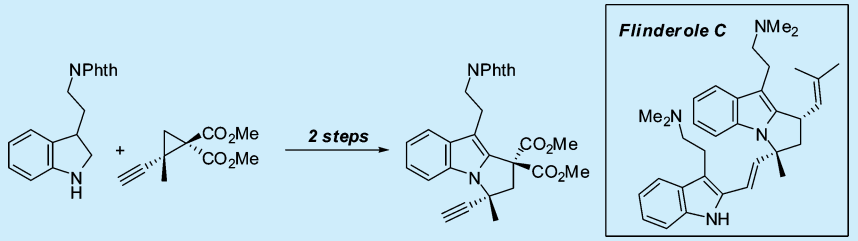
Supporting Information



ABSTRACT: Under the influence of Lewis acid catalysis, donor/acceptor cyclopropanes underwent nucleophilic ring opening by indolines. The resulting *N*-alkyl indolines bearing a pendant malonyl moiety oxidatively cyclized to 1,2-pyrroloindoles. This method was showcased by the preparation of the skeletal structure of the flinderoles.

The pyrroloindole moiety is a substructure common to a number of naturally occurring molecules of biological and medicinal importance. Perhaps the most notable of these is Mitomycin C, a potent and clinically used chemotherapeutic agent.[1] The Flinderoles A−C are recently isolated antimalarial bis-indoles,[2] which have as a key structural feature a 1,2-pyrroloindole (Figure 1). Several elegant syntheses of these natural products have been reported.[3]

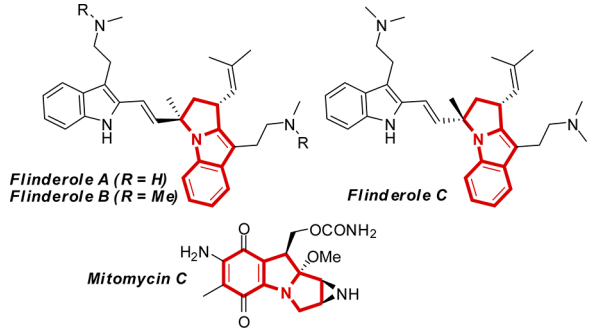
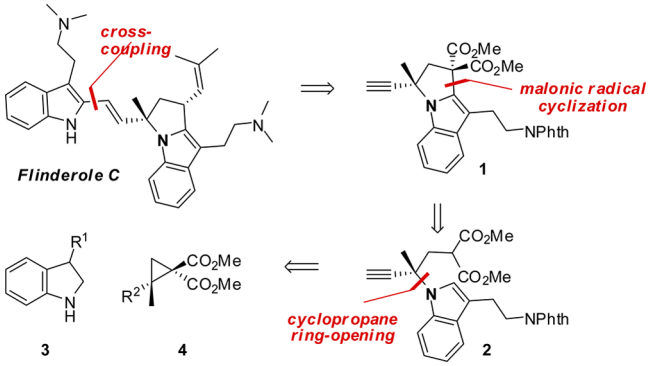


Figure 1. Representative 1,2-pyrrolindole derived compounds.

In this letter, we marry two research themes from our lab and direct them to the development of an efficient pyrroloindole synthesis: namely nucleophilic ring opening of donor−acceptor cyclopropanes[4] and the radical functionalization of indoles.[5] Several years ago we reported that indolines bearing a malonic ester moiety tethered to the nitrogen underwent dehydrogenation to an indole, oxidation to a malonic radical, and subsequent cyclization onto the indole 2-position in a single operation.[6] This was showcased in that report by preparing a series of 1,2-annulated indoles and later by application to the total synthesis of mersicarpine.[7] While most examples were piperidine-fused products, two examples were included in which a three carbon unit was installed on the nitrogen via a cyclopropane ring opening.

In the context of a total synthesis of members of the flinderoles, we sought to develop this chemistry further. Scheme 1 shows a brief retrosynthesis of Flinderole C showing

Scheme 1. Retrosynthesis of Flinderole C



as a key sequence the ring opening of a cyclopropane **4** at a 4° carbon by indoline nucleophile **3** and subsequent radical cyclization of the adduct **2** to the pyrroloindole **1**. In this letter we report the success of this general strategy in the synthesis of highly substituted 1,2-pyrroloindoles and the synthesis of the complete heterocyclic framework of Flinderole C.

Figure 2 shows indolines **3a,b** which were used as nucleophiles in reaction with cyclopropanes **4a−h**.[8] The optimum conditions were found to use $Yb(OTf)_3$ (5 mol %)

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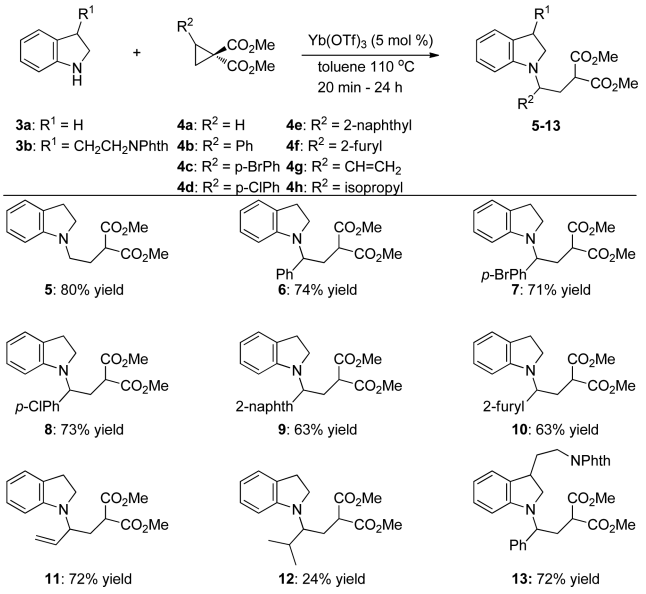

Figure 2. Nucleophilic ring opening of cyclopropanediesters by indolines.

as the Lewis catalyst, in toluene at 110 °C. The reactivity of the cyclopropanes toward nucleophilic ring opening is, to a large degree, influenced by the ability of the group vicinal to the diesters to stabilize a developing positive charge on the attached carbon. This is reflected in the variation of the reaction times as well as the yields in some cases. For example cyclopropane **4h**, in reaction with indoline **3a**, required 24 h to undergo consumption and resulted in a yield of only 24%. The steric effect of the isopropyl moiety seems to override any electronic benefit. Otherwise the yields were consistently good over a range of aryl, heteroaryl, and vinyl substituents.

Using conditions previously found to be effective, attention was turned to the cyclization of substrates **5**−**13** (Figure 3). Treatment with 5 equiv of $Mn(OAc)_3$ in methanol at 70 °C effected the tandem indoline to indole/oxidative malonic radical cyclization to produce pyrroloindoles **14**−**22**.

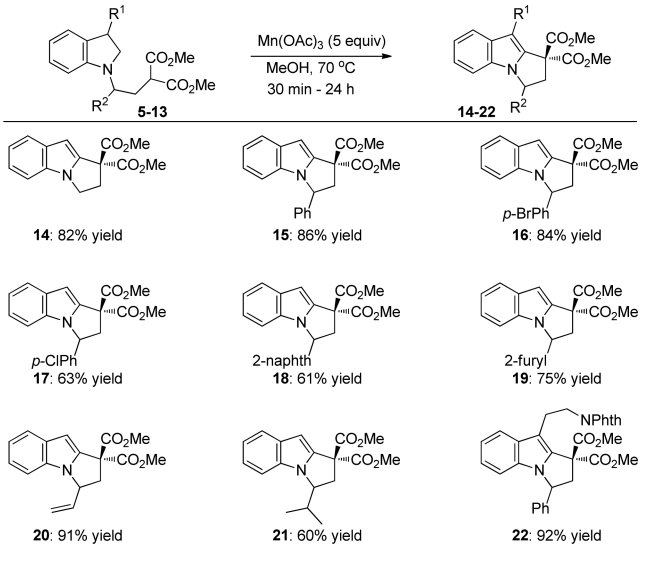

Figure 3. Oxidative radical cyclization of **5**−**13**.

If this method was to be useful in accessing targets such as the flinderoles, cyclopropanes bearing a 4° center vicinal to the diester moiety would be required (see Scheme 1). To this end, we prepared a series of cyclopropanes **4i**−**m** and treated them with several indolines (**3a,c,d**) under Lewis acid catalysis. In addition to $Yb(OTf)_3$ as the catalyst, $Sc(OTf)_3$ also emerged as a viable promoter of this reaction. Figure 4 shows the results.

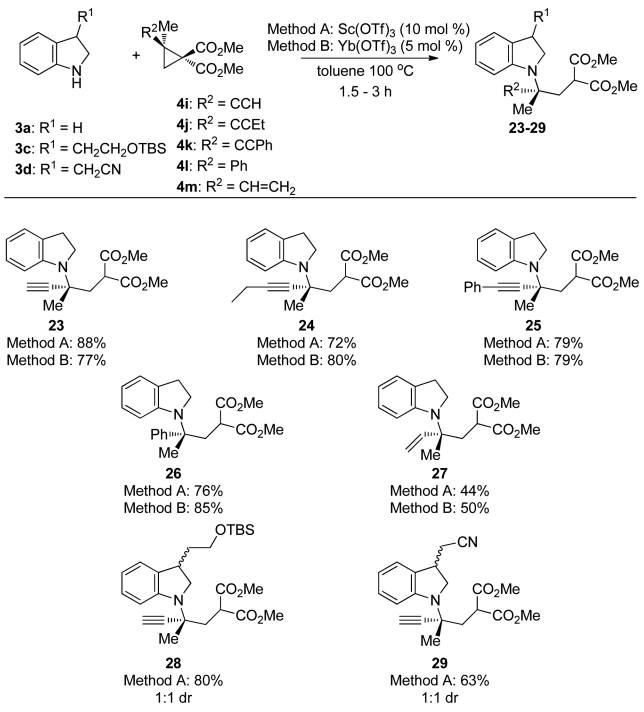

Figure 4. Nucleophilic ring opening of cyclopropanediesters at a 4° center.

Based on our retrosynthesis of the flinderoles, acetylenic cyclopropanes were studied; however, vinyl and phenyl substituents were also tolerated. The vinyl cyclopropane **4m** underwent competitive polymerization and resulted in lower yields. Indolines bearing a side chain capable of elaboration in the context of flinderole synthesis also performed well in this reaction yielding a 1:1 mixture of diastereomers. Since the indolines were to be oxidized to indoles in the next step, this was inconsequential.

As expected, indolines **23**−**29** performed well in the oxidative radical cyclization event yielding 1,2-pyrroloindoles **30**−**36**. Figure 5 shows the results. It was worrisome to us at the outset that the malonic radical may react in some way with the pendant alkynyl moiety;[9] however, this was unfounded. For the most part the yields paralleled their less substituted counterparts.

In order to showcase this method in the milieu of total synthesis, we targeted the heterocyclic substructure of the flinderoles. To this end, the alkynyl moiety of **35** was hydrostannylated[10] to yield vinylstannane **37** in 85% yield (Scheme 2). This compound was subjected to Stille coupling conditions with N-tosylated 2-bromoindole to yield the bisindolyl compound **38**. With the skeletal structure of the flinderoles secured in four steps, a series of functional group manipulations (admittedly nontrivial) are necessary to convert **38** to the target molecule.

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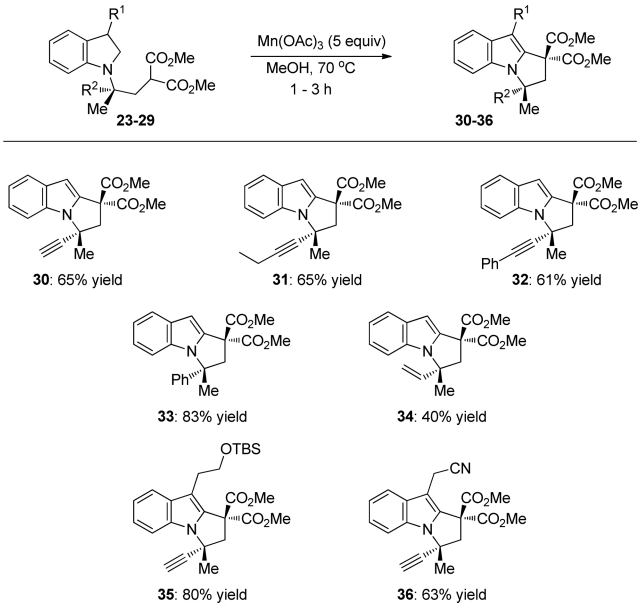
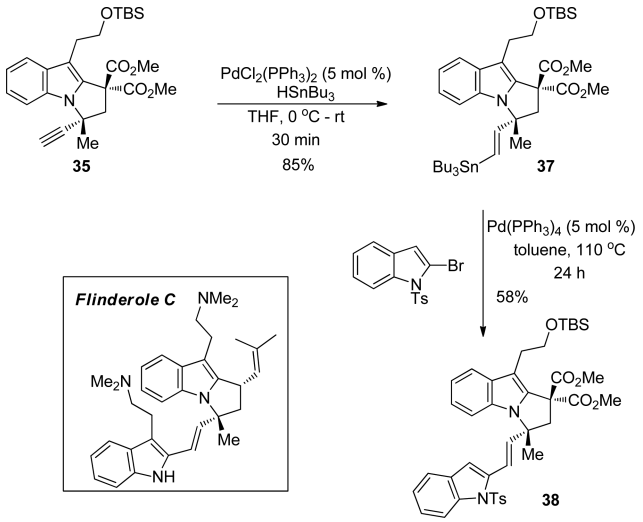


Figure 5. Oxidative radical cyclization of **23**−**29**.

Scheme 2. Synthesis of the Heterocyclic Framework of the Flinderoles



In summary we have demonstrated herein a method for the formation of 1,2-pyrroloindoles in an expeditious fashion. Key elements include the nucleophilic ring opening of donor−acceptor cyclopropanes by indoline nucleophiles and the oxidative radical cyclization of the resulting compounds. Efforts to use this chemistry for the total synthesis of the flinderoles are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00768.

Full experimental details and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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