

# Directed Oxidative Cyclizations to C2- or C4-Positions of Indole: Efficient Construction of the Bicyclo[4.3.1]Decane Core of Welwitindolinones

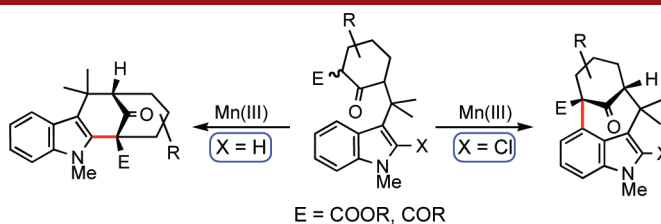
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## ABSTRACT



Regiocontrolled oxidative cyclizations of 3-substituted indoles are described herein. Specifically, it is shown that the installation of a chloride at C2 alters the inherent propensity for cyclization at the 2-position of indole so as to favor the 4-position, enabling the construction of the unique framework found in most welwitindolinone alkaloids. The chloride functions here as more than a blocking group, as it also provides ready access to the corresponding oxindole.

The structural challenges presented by natural products have often stimulated the development of new chemical

methods and the exploration of innovative synthetic strategies. For example, the welwitindolinone family of indole alkaloids,<sup>1</sup> possessing the unique bicyclo[4.3.1]decane skeleton (Figure 1), has inspired the investigation of numerous

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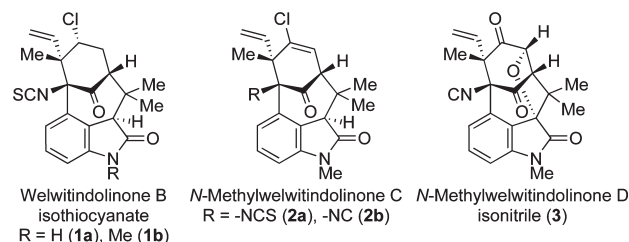
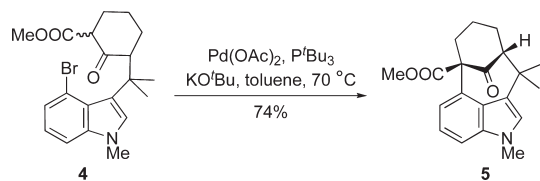


Figure 1. Representative welwitindolinones alkaloids.

creative routes from organic synthesis laboratories around the globe.<sup>2</sup> In our own work on these alkaloids, we employed a palladium-catalyzed enolate arylation reaction to construct the carbon framework of the bridged welwitindolinones (**5**, Scheme 1).<sup>3</sup> This strategy proved successful and culminated in the total synthesis of *N*-methylwelwitindolinone D isonitrile (**3**).<sup>4</sup> The path to the final target

### Scheme 1. Synthesis of Welwitindolinone Skeleton<sup>a</sup>

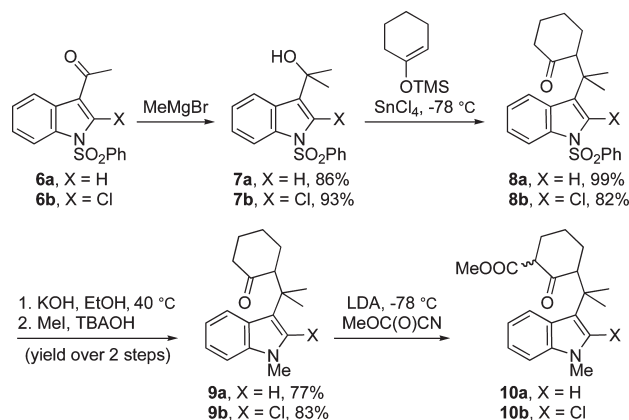


<sup>a</sup> See ref 3.

was, however, less than straightforward. Indeed, while facing seemingly insurmountable hurdles, we also explored alternate methods for the arylative cyclization to yield the bicyclo[4.3.1]decane ring system. Particularly attractive among these was the possibility of intramolecular oxidative arylation to close the seven-membered ring. An examination of the literature identified the formative work of Muchowski<sup>5</sup> and Chuang<sup>6</sup> on the intramolecular oxidative cyclizations of pyrroles and indoles bearing a pendant malonyl group. Significant further advances to this area have come from the laboratories of Kerr<sup>7</sup> and Li.<sup>8</sup> What is noteworthy in all these examples is that the tether through which the new ring is formed is attached at either the nitrogen or the C3-position of the indole, such that the newly formed 5-, 6-, or 7-membered rings are fused to the 1,2- or 2,3-positions of the heterocycles.<sup>9</sup> In other words, the cyclization takes place on the pyrrolo part of the indole, not the benzo unit. To our knowledge, there appear to be no reports describing intramolecular oxidative cyclizations at the 4-position of indole. The development of such a cyclization pathway would not only extend the scope of these oxidative cyclizations but also generate the sought-after welwitindolinone skeleton (Figure 2).

With the welwitindolinones in mind, we examined the oxidative cyclization of several 3-substituted indole

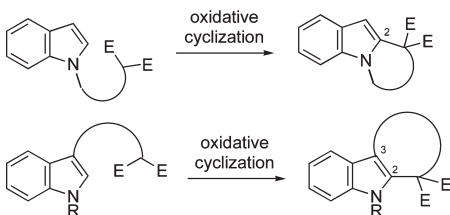
### Scheme 2. Synthesis of Cyclization Precursors



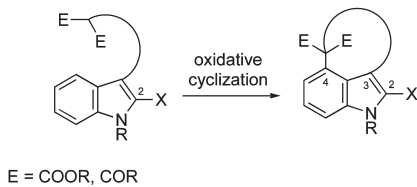
derivatives, synthesized by the general route shown in Scheme 2. Thus, ketone **8a** was prepared by alkylative coupling of alcohol **7a** with the silyl enol ether of cyclohexanone.<sup>3,10</sup> Substitution of the sulfonyl group with a methyl group and carbomethoxylation<sup>11</sup> gave the required substrate, **10a**. Subjecting ketoester **10a** to standard oxidative cyclization conditions<sup>12</sup>—heating in acetic acid in the presence of Mn(OAc)<sub>3</sub>—afforded tetracycle **11** cleanly and in high yield (entry 1, Table 1).<sup>13</sup> Given the precedents of Kerr and others, we were not surprised to find that the product was tetracycle **11**, arising from cyclization at the 2-position of indole. The connectivity present in **11** was established unambiguously through X-ray crystallography (Figure 3).

In an effort to overcome the inherent propensity for cyclization at C2, we sought to install a blocking group at

#### Previous work



#### This work



**Figure 2.** Complementary approach to current methods.

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**Table 1.** Mn(III)-Promoted Oxidative Cyclizations

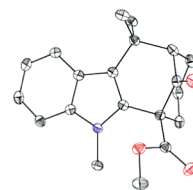
entry	substrate	product	time (h)	% yield	entry	substrate	product	time (h)	% yield
1.			2	82	5.			3	66
2.			5	43	6.			3	67
3.			0.75	87	7.			5.5	<b>21a</b> , 51 <b>21b</b> , 52
4.			4	64	8.			0.5	0 <sup>a</sup>

<sup>a</sup> Compound **15** was isolated in 34% yield.

this position. The requirements for the blocking group were that it must not only impart steric and electronic deactivation of the 2-position, but it must also withstand the oxidative cyclization conditions and allow future conversion to an oxindole, the functionality found in the welwitindolinones. These requirements appeared to be met by chloride. The necessary 2-chloro-substituted keto-ester **10b** was prepared through the route outlined in Scheme 2, starting from ketone **6b**.<sup>14</sup>

The key oxidative cyclization was carried out using the previously employed conditions, with Mn(OAc)<sub>3</sub> as the oxidant. Gratifyingly, the primary product of the reaction was tetracycle **17**, obtained in 66% yield, wherein the cyclization had taken place on the benzene ring (entry 5,

Table 1). To the best of our knowledge this result represents the first example of an oxidative cyclization onto the 4-position of indole. Up to 10% of the C2-cyclized product (**11**) was also obtained. The structure assigned to the

**Figure 3.** ORTEP image of tetracycle **11**.

(14) See the Supporting Information for details.

cyclized product was confirmed through its independent synthesis, by chlorination of tetracyclic ketoester **5**, which was prepared by the Pd-catalyzed arylation route.<sup>3</sup>

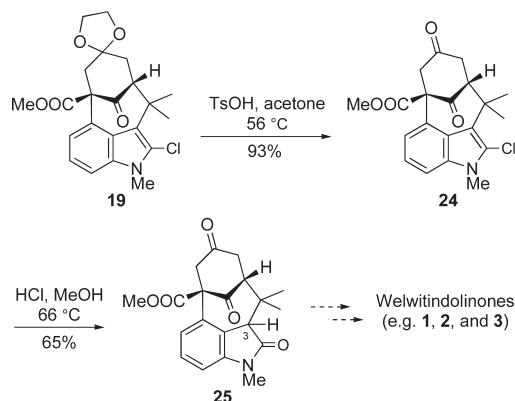
The strategy of modulating regioselectivity by positioning a blocking group at C2 proved to be general and provided good yields of the bicyclo[4.3.1]decane welwitindolinone skeletons with chloride at the 2-position (entries 5–8) and bicyclo[3.3.1]nonanes (entries 1–4) in the absence of chloride at C2. The reaction conditions are tolerant of a variety of functional groups including alkyl chlorides (entries 2 and 7), acetals (entries 6 and 7), and aryl bromides (entry 4). Of particular interest to us was the arylative cyclization of vinylogous acids (i.e.,  $\alpha$ -formyl ketones), for which there are few precedents in the literature.<sup>4,15</sup> To that end, treatment of acid **14** (entry 3) under the standard conditions cleanly furnished the expected cyclization product, **15**. Interestingly, the corresponding 2-chlorosubstituted compound (**22**, entry 8) did not undergo the desired cyclization but, instead, produced the C2-cyclized tetracyclic aldehyde **15** in 34% yield.

A brief solvent study identified acetic acid as the optimum solvent for these reactions, with methanol delivering slightly lower yields. The use of NaOAc as an additive was beneficial for the C2-cyclization reactions (entries 1–4), yet had no advantageous effect on the C4-cyclization substrates (entries 5–8). Other oxidants such as CAN, Mn(pic)<sub>3</sub>, and Fe(ClO<sub>4</sub>)<sub>3</sub>·9H<sub>2</sub>O gave essentially none of the desired products.

Entries 6 and 7 are of special interest as they represent highly advanced intermediates toward welwitindolinones B–D (**1**–**3**). Deprotection of the acetal group in **19** readily yielded the diketone **24** (Scheme 3). The oxindole functionality was then revealed through acidic hydrolysis of 2-chloroindole **24** affording oxindole **25** which is suitably adorned for further elaboration to the aforementioned targets.<sup>16</sup>

The results presented above illustrate the possibility of divergent oxidative cyclization reactivity of 3-substituted indoles. Consistent with literature precedent, simple

**Scheme 3.** Synthesis of Oxindole **25**



indoles, unsubstituted at the 2-position, undergo selective cyclizations at the 2-position. On the other hand, 2-chloro-substituted indoles display altered reactivity, favoring cyclization at the 4-position, on the benzene ring. This simple modification enables the efficient synthesis of the complex bicyclo[4.3.1]decane core of the welwitindolinones. The chloride group at the 2-position is more than just a blocking group, diverting the cyclization to the 4-position; it also provides a handle for further manipulations. The broad functional group tolerance makes this an attractive route toward welwitindolinones and conceivably other intricate indole alkaloids.

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**Supporting Information Available.** Full experimental procedures, characterization data, NMR spectra, complete ref 2r, and X-ray crystal data (CIF) for **11**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) Oxindole **25** was obtained as a single diastereomer; however, the absolute configuration at the C3-position was not determined.