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Total Synthesis of Spirobacillene A

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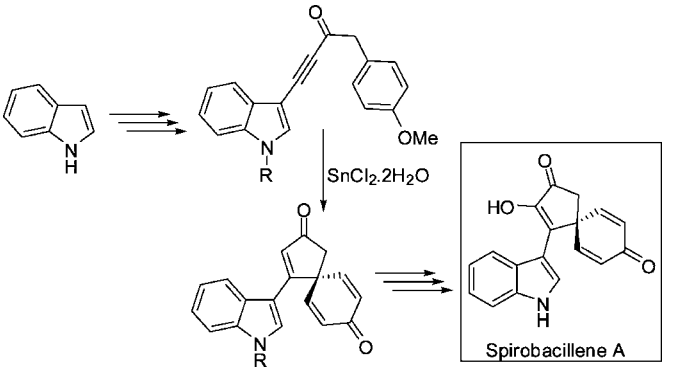
ABSTRACT



The first total synthesis of spirobacillene A, an indole alkaloid isolated from *Lysinibacillus fusiformis*, is reported. A Lewis acid mediated spirocyclization of an anisole derivative onto a tethered ynone was used as a key step, drawing inspiration from a potential biosynthesis of the natural product.

Microorganisms that exist in extreme environments are an abundant source of novel heterocyclic scaffolds.[1] Unique secondary metabolites with useful biological properties are commonly isolated from such organisms (known as extremeophiles), and it is thought that the production of these compounds is often done in response to the harsh ecological conditions in which they live. Kwon et al. recently reported the discovery of a number of natural products derived from a bacterial strain found in such extreme conditions.[2] Four new compounds (**1**–**4**, Figure 1) were isolated from a 24 h broth culture of *Lysinibacillus fusiformis* obtained from coal-mine drainage, contaminated with sulfuric acid (pH 3.0) and iron-rich heavy metals. In addition, two known indole alkaloids soraphinol A (**5**) and kurasoin B (**6**) were also isolated, which are closely related to the diolmycins (for example, **7**).[3]

Of these products, spirobacillenes A and B (**1** and **2**) possess by far the most interesting structures. Both possess completely novel carbon frameworks within the field of natural products, and to date, neither of their total syntheses have been reported. Furthermore, spirobacillene A

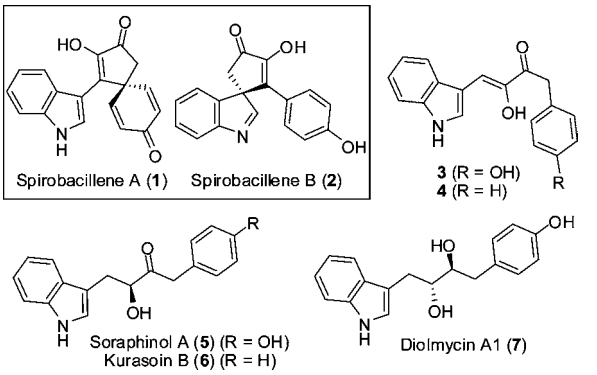


Figure 1. Spirobacillenes and related natural products.

was found to display inhibitory activity against the production of nitric oxide and reactive oxygen species.[2] In view of all this, and of a longstanding interest in the synthesis of quinone[4] and spirocyclic-based[5] natural products in our research group, we decided to investigate their total synthesis.

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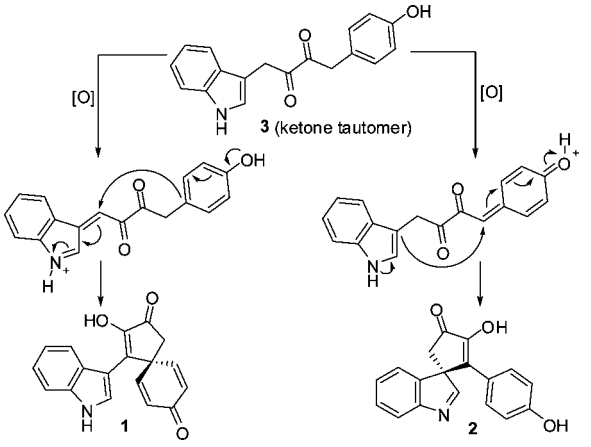
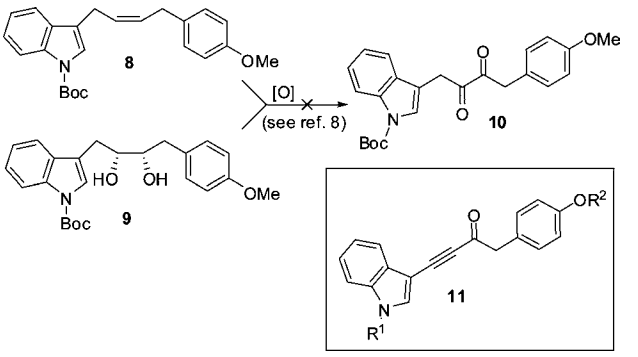
Our original retrosynthetic strategy centered on 1,2-dicarbonyl tautomer **3**, which was isolated along with the spirobacillenes and has been proposed as a potential biosynthetic precursor.[2] We considered that the site-selective oxidation of **3** would allow access to either natural product following spirocyclization (Scheme 1). This approach is appealing, as both targets could be accessed from a single, relatively simple precursor. Similar spirocyclizations are known to take place under acidic conditions,[6] adding support to the idea that this approach may be biomimetic and, furthermore, the high levels of iron-rich heavy metals that contaminate the environment that the *Lysinibacillus fusiformis* was obtained from may help to promote the requisite oxidation.[7]

Scheme 1. Proposed Biomimetic Route to the Spirobacillenes



In order to test this approach, alkene **8** and 1,2-diol **9** were synthesized using a previously reported route, described during the synthesis of the related natural product diolmycin A1 (**7**, Figure 1).[3] It was then hoped to convert one of these compounds into diketone **10**, a protected analogue of diketone tautomer **3**. However, all attempts to generate diketone **10** failed; a number of methods were examined,[8] but all resulted in the formation of complex mixtures of unidentified products (Scheme 2). This result was disappointing, although not entirely unexpected, given that the related compound **3** was reported to be unstable during its isolation.[2] An alternative synthetic strategy was therefore proposed, focusing solely on the synthesis of spirobacillene A. It was hoped that ynone **11**, which is at the same oxidation state as the initially required 1,2-diketone, could be used as a synthetic equivalent. Such ynones are usually stable and are far easier to synthesize than the analogous 1,2-diketones. Furthermore, the ynone moeity should provide a greater degree of regiocontrol in the spirocyclization, compared with the corresponding diketone.

Scheme 2. Attempted Formation of **10** and Ynone **11** as a Synthetic Equivalent



Electrophilic cyclization reactions of alkynes have attracted increasing attention in recent years.[9] One such transformation, the iodonium/bromonium-induced intramolecular *ipso*-cyclization of electron-rich aromatics onto ynone derivatives, first reported by Larock and coworkers[10] and subsequently modified by others,[11] appeared particularly well suited to the synthesis of the spirobacillene A framework. We envisioned that a simple ynone **14** would undergo cyclization (via iodonium ion **15**) to generate spirocycle **16** which, following conversion of the iodide into a hydroxyl, would provide a rapid, high yielding synthesis of the target molecule **1** (Figure 2).

The synthesis began with iodination and Boc-protection of indole to form iodide **18**[12] in excellent yield over the two-step telescoped sequence (Scheme 3). Sonogashira coupling with trimethylsilyl acetylene followed by TMS cleavage then afforded alkyne **19**,[13] again in excellent yield over the two-step sequence. Next, the treatment of **19** with *n*-butyllithium followed by Weinreb amide **20** afforded

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(8) Dess–Martin periodinane and Swern oxidation methods were trialled, in addition to the procedures found in the following: (a) Amon, C. M.; Banwell, M. G.; Gravattpp, G. L. *J. Org. Chem.* **1987**, *52*, 4851. (b) Khurana, J. M.; Kandpal, B. M. *Tetrahedron Lett.* **2003**, *44*, 4909. (c) Plietker, B. *Org. Lett.* **2004**, *6*, 289.

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(10) Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 12230.

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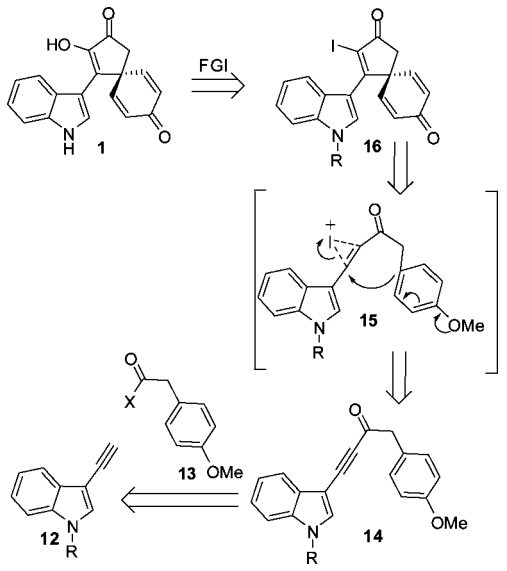
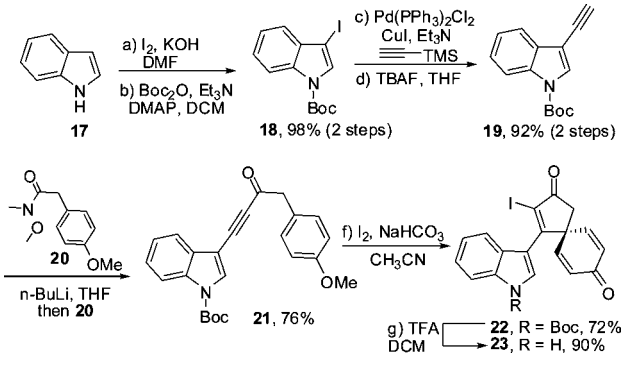


Figure 2. Retrosynthesis of spirobacillene A (**1**).

ynone **21**. We were then pleased to find that the treatment of **21** with iodine and $NaHCO_3$ afforded spirocycle **22** in good yield after stirring at room temperature for 10 min. Protecting group cleavage was also achieved smoothly, following treatment with TFA, affording indole **23**, the structure of which was confirmed by X-ray crystallography[14] (Figure 3). Unfortunately, all attempts to convert either vinyl iodide **22** or **23** into the requisite enol were unsuccessful; a range of copper- and palladium-catalyzed C−O bond forming methods were screened, but all led to substrate decomposition.[15]

Scheme 3. Synthesis of Spirocycle **23**



(14) CCDC 934317 (**23**) and CCDC 934316 (**25**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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This forced us to consider an alternative strategy. It was hoped that ynone **21** would undergo spirocyclization promoted by a Lewis or Brønsted acid, rather than iodine, to afford an unsubstituted cyclopentenone which, following oxidation,[16] would allow access to the enolized 1,2-diketone moiety of spirobacillene A. While there is no direct precedent for this type of cyclization, Haack introduced a conceptually similar reaction. In this work, terminal alkynes were reacted with acid chlorides and aluminum trichloride to form spirocyclic cyclohexadienones, via ynones, in one pot,[17] but this reaction has received remarkably little attention. This may be because the majority of the reported examples are low-yielding,[17,18] possibly due to the formation of naphthalene-based side products (related spirocyclic compounds are known to rearrange under similarly harsh acidic reaction conditions).[17,19] Previous work in our group has demonstrated the efficacy of $SnCl_2 \cdot 2H_2O$ as a promoter of a diverse array of cyclization reactions, and it was hoped that this reagent would be sufficiently mild to promote spirocyclization without subsequent rearrangement and degradation.[20] $SnCl_2 \cdot 2H_2O$ is a versatile, cheap, nontoxic reagent that can be used without any special care or precautions, and it was anticipated that the water present in the reagent would be beneficial, as it could facilitate the loss of methanol via hydrolysis following cyclization.

Thus, ynone **21** was stirred with 5 equiv of $SnCl_2 \cdot 2H_2O$ in DCM for 18 h at room temperature, and we were pleased to observe remarkably clean conversion into the desired spirocyclic cyclohexadienone **24**, which was isolated in 89% yield after chromatography (Scheme 4). Furthermore, the treatment of the same ynone with TFA also led to spirocyclization, but with concomitant Boc-cleavage, affording spirocycle **25** in 92% isolated yield. To the best of our knowledge, these reactions are the first reported examples in which an acid has been used to promote the direct conversion of an ynone into a spirocyclic cyclohexadienone. An X-ray crystal structure of spirocycle **25** was obtained, supporting its assigned structure (Figure 3).[14]

Unfortunately all attempts to oxidize either enone **24** (to obtain **28**) or **25** (to obtain **1**) failed; a range of oxidants and conditions were trialled but resulted in either no reaction[21] or substrate decomposition.[22] It appears that the enone is

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(21) *m*-CPBA, with and without $NaHCO_3$, DCM, 0 °C and rt; PIFA, CF_3CH_3OH, 0 °C and rt; PIDA, DCM, rt; Davies oxaziridine, $NaHCO_3$, CH_3CN, rt and 70 °C.

(22) H_2O_2, NaOH, MeOH at 0 °C; *m*-CPBA, with and without $NaHCO_3$, 50 °C; DMDO, acetone, rt.

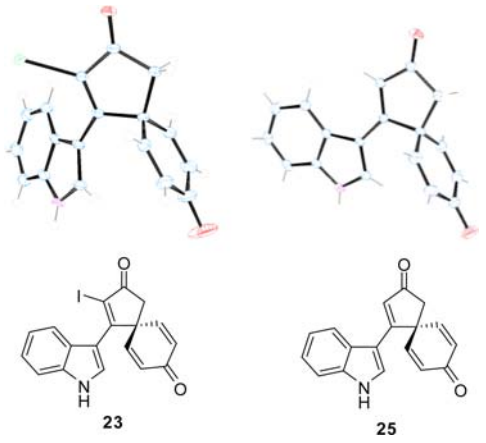


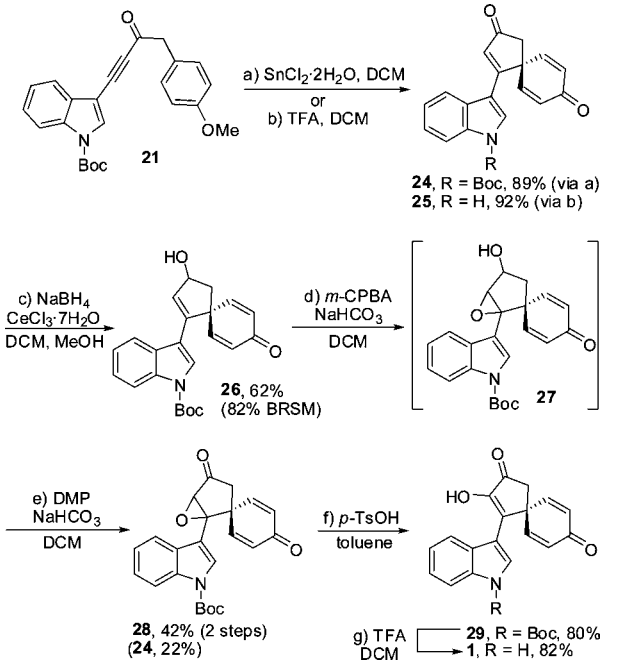
Figure 3. X-ray structures of cyclohexadienones **23** and **25**.

not reactive enough to be oxidized in the presence of the sensitive cyclohexadienone moiety. In order to negate this problem, the carbonyl of enone **24** was reduced under Luche conditions, thus rendering the alkene more electron rich and generating allylic alcohol **26** in 62% yield, or 82% based on recovered starting material.[23] Epoxidation of allylic alcohol **26** with *m*-CPBA gave an unstable epoxy-alcohol (**27**), which was directly oxidized with buffered Dess–Martin periodinane (DMP), affording epoxy ketone **28** in 42% yield over the two steps, as well as 20% of enone **24**, which presumably is formed by a known rearrangement[16] of **27**. The reaction of **28** with *p*-TsOH effected epoxide opening, completing the hydroxyl installation, affording enol **29**. Finally, treatment with TFA in DCM resulted in Boc-cleavage to give spirobacillene A (**1**).[24] The spectroscopic data accrued closely matched those reported for the natural product, but it should be noted that in our hands compound **1** is only sparingly soluble in CD_3CN, the NMR solvent used during the natural product isolation.[2] This meant that some of its ^{13}C NMR signals were not observed, and therefore additional NMR data were recorded in DMSO-d_6 (see Supporting Information for a fuller discussion and comparison of these data).

(23) A small amount of unreacted starting material **24** and over-reduced side products were isolated as a mixture, which was reoxidized with buffered DMP regenerating **24** (see Supporting Information).

(24) The treatment of epoxide **28** with TFA to produce **1** directly was unsuccessful.

Scheme 4. Total Synthesis of Spirobacillene A (**1**)



In summary, we have completed the first total synthesis of the recently isolated natural product spirobacillene A (**1**) in 11 steps and 14% overall yield from indole. The most pleasing aspects of this work were the extremely efficient six-step syntheses of spirobacillene A analogues **24** and **25** (61% and 63% overall yields, respectively). These routes, which were inspired by a potential biosynthesis of the natural products, were performed on a large scale and culminated in high yielding acid-mediated spirocyclic cyclohexadienone formations. Future work will focus on the synthesis of spirobacillene B and will be reported in due course.

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Supporting Information Available. Synthetic procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.