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Biomimetic total syntheses of spirobacillenes A and B†

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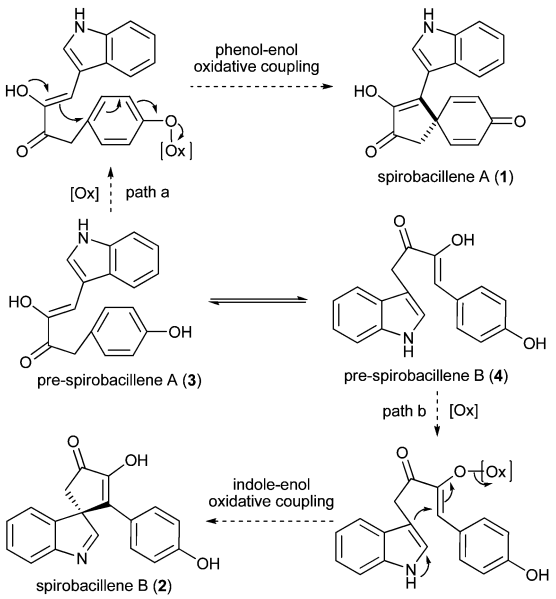
The first total syntheses of spirobacillenes A and B were achieved concisely. The key transformation leading to spirobacillene A features a biomimetic intramolecular phenol–enol oxidative coupling reaction, and that leading to spirobacillene B highlights a bio-inspired intramolecular indole–ketone enolate oxidative coupling reaction.

Microorganisms derived from extreme environments have been recognized as one of the rich resources for the discovery of bioactive secondary metabolites.[1] Recently, a pair of indole alkaloids, named spirobacillenes A (**1**) and B (**2**) (Scheme 1), were isolated by Kwon and co-workers from the broth culture of *L. fusiformis* KMC003, a bacterial strain collected from an acidic coal mine drainage that was highly contaminated with iron-rich heavy-metal ions and sulfuric acid.[2] Structurally, the cores of **1** and **2** feature two highly functionalized spiro-cyclopentenone motifs that are respectively incorporated into a cyclohexadienone and indolenine scaffold, both of which are rarely found in the realm of natural products. Moreover, preliminary biological evaluation showed that **1** exhibited an inhibitory effect against the production of NO and ROS in LPS-induced RAW264.7 macrophages,[2] rendering it an attractive target for further biomedical studies.

In addition to their unusual molecular architectures and potentially important biological profiles, the intriguing biosynthetic pathways of **1** and **2** also attracted our attention. The isolation team[2] suggested that **1** and **2** could be biogenetically derived from pre-spirobacillene A (**3**) and pre-spirobacillene B (**4**), respectively.[3] As further rationalization of this hypothesis, we proposed that **1** could be generated from **3** *via* an intramolecular phenol–enol oxidative coupling reaction (path a, Scheme 1), while **2** might be derived from **4** *via* an intramolecular indole–enol oxidative coupling reaction (path b, Scheme 1).



Scheme 1 Structures and proposed biosynthetic pathways of spirobacillenes A (**1**) and B (**2**).

This assumption, to some extent, is substantiated by the following facts: (1) **3** was isolated as a coexisting substance with **1** and **2** from the same natural source; (2) *L. fusiformis* KMC003, the bacterial strain that produced **1** and **2**, survived in an iron-rich environment,[2] which might provide the requisite oxidative conditions for the aforementioned transformations to occur.

Keeping the hypothesis in mind, we set out to synthesize the precursors **3** and **4**. As depicted in Scheme 2, protection of **5**[4] with the TES group under the standard conditions[5] followed by treatment with Grignard reagent **6**[6] afforded **7** in 76% yield in two steps. Selective removal of the TES group of **7** with PPTS in MeOH–THF[7] followed by oxidation of the resulting alcohol with DMP afforded the diketone **8** as a major product, which was found to gradually tautomerize into the enol–ketone **9**. Without isolation, a mixture of **8** and **9** was treated with TBAF–AcOH to yield pre-spirobacillene A (**3**) as the dominant product. Careful analysis of the ^{1}H NMR of **3** indicated that it was contaminated

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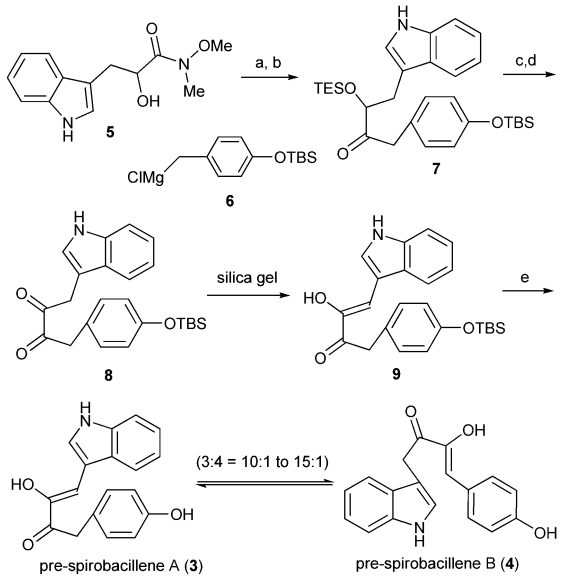
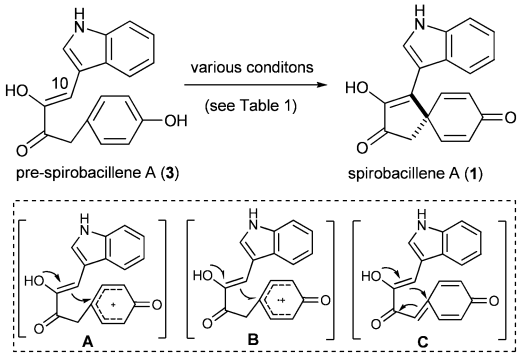


Scheme 2 Synthesis of pre-spirobacillene A. (a) TESCl, imid., CH_2Cl_2, RT, 0.5 h, 80%; (b) **6**, THF, 0 °C to RT, 5 h, 95%; (c) PPTS, MeOH–THF, (3 : 1), 0 °C to RT, 2 h, 82%; (d) DMP, CH_2Cl_2, RT, 0.5 h, 60%; (e) TBAF–AcOH, THF, RT, 2 h, 65%.

with a minor product, whose structure was assigned to be pre-spirobacillene B (**4**) based on the characteristic signals (for details, see ESI†).[8]

With pre-spirobacillene A in hand, the stage was set to explore the bio-inspired intramolecular phenol–enol oxidative coupling reaction. At the outset, the hypervalent iodine(III) reagents,[9] such as $PhI(OAc)_2$ (PIDA) and $PhI(CF_3CO_2)_2$ (PIFA), were attempted, since we assumed that dearomatization of the phenol **3** would generate a carbocation intermediate **A** which could be trapped by the internal enolic carbon (C-10) to furnish the target **1**.[10] To validate this assumption, we performed a systematic screening of the choice of hypervalent iodine(III) reagents, solvents and bases (entries 1–5, Table 1). To our disappointment, all of the reactions failed to afford satisfactory results. In most of the cases, indole-3-carbaldehyde was generated as a major by-product, presumably through a competitive oxidative cleavage of the enolic double bond of **3**.[11] We then turned to evaluate Fe(III)-derived oxidants (*e.g.* $FeCl_3$, $K_3Fe(CN)_6$ and $[Fe(DMF)_3C1_2][FeC1_4]$), given that they have been successfully applied to various oxidative coupling reactions with the phenol type of substrates.[12] However, none of them gave promising outcomes, only leading to decomposition of the starting material (entries 6–8). Encouragingly, after extensive trials we found that DDQ[13] displayed unique reactivity to promote the desired transformation by affording **1** in 25% yield (entry 9). More pleasingly, when Ag_2O was employed, **1** was obtained in 30% yield together with the recovery of substantial amounts of **3** (40%). The recovered material could be further converted into **1** with comparable efficiency, thus increasing the overall yield to 42% (entry 10). To the best of our knowledge, this work represents the first example of phenol–enol oxidative coupling reaction. Mechanistically, a cation-radical intermediate **B** was most likely involved in the transformation from **3** to **1**, given that both DDQ and Ag_2O are

Table 1 Conditional screening of phenol–enol oxidative coupling reaction leading to spirobacillene A (**1**)



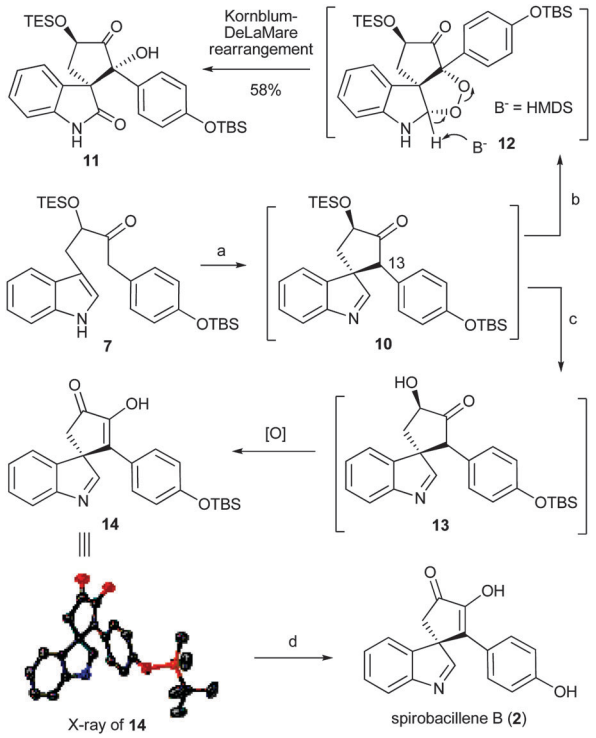
Entry	Conditions	Yield of **1** [a] (%)
1	PIDA (1.2 equiv.), CF_3CH_2OH, RT, 0.5 h	None
2	PIFA (1.2 equiv.), CF_3CH_2OH, RT, 0.5 h	None
3	PIDA (1.2 equiv.), $(CF_3)_2CHOH$, RT, 0.5 h	None
4	PIDA (1.2 equiv.), CH_3CN, RT, 0.5 h	None
5	PIDA (1.2 equiv.), K_2CO_3, CH_3CN, 0 °C, 0.5 h	None
6	$FeCl_3$ (excess), DCM, 0 °C, 0.5 h	None
7	$K_3Fe(CN)_6$ (excess), H_2O–Et_2O, RT, 0.5 h	None
8	$[Fe(DMF)_3C1_2][FeC1_4]$ (excess), Et_2O, RT, 1 h	None
9	DDQ (2.0 equiv.), dioxane, RT, 15 min	25
10	Ag_2O (excess), DCM, RT, 24 h	42[b]

[a] The results of entries 1–8 were judged by crude ^1H NMR, while those of entries 9 and 10 refer to isolated yields. [b] The combined yield for two runs of reaction (see the text). PIDA = phenyliodonium diacetate. PIFA = phenyliodonium bis(trifluoroacetate). DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone.

well-known single-electron transfer reagents. However, the possibility of generation of a *p*-quinone methide intermediate **C** cannot be ruled out,[14] since it can also account for the formation of **1** from **3** *via* a Nazarov reaction (Table 1).

Having achieved the target **1**, we then moved towards the synthesis of **2**. Since the equilibrium between **3** and **4** favoured **3** as the dominant isomer, we were precluded from exploring the originally proposed indole–enol oxidative coupling reaction (path b, Scheme 1). Alternatively, a bio-inspired strategy featured by an intramolecular indole–ketone enolate oxidative coupling reaction was adopted. Indeed, both inter- and intramolecular indole–ketone enolate oxidative coupling reactions have been well established recently, mainly attributed to the seminal contributions from Baran's group[15] and Ma's group.[16] Thus, following the protocol developed by Ma and co-workers, **7** was first treated with LiHMDS at −40 °C, and then with I_2 at −78 °C, leading to the formation of a major product. However, the product appeared to be unstable and quickly transferred into another compound during the routine work-up process, whose structure was determined to be **11** on the basis of extensive spectroscopic studies (for details, see ESI†). Mechanistically, **11** might be generated from **7** through a tandem indole–ketone enolate oxidative coupling, cyclic peroxide formation[17] and Kornblum–DeLaMare rearrangement[18] (Scheme 3).

Albeit the desired product was not obtained, the above results suggested that the indole–ketone enolate oxidative coupling reaction did work. Encouraged by this clue, we sought to explore the effective work-up procedures that could allow for obtaining the oxidative coupling product **10**. After several trials



Scheme 3 Total synthesis of spirobacillene B. (a) LiHMDS, −40 °C, THF, 0.5 h; then I_2, −78 °C, 0.5 h; (b) quenched with sat. $Na_2S_2O_3$ sol., 58% from **7**; (c) PPTS–MeOH, RT, 12 h, 27% of **14** and 10% of **2** from **7**; (d) TBAF–AcOH, THF, RT, 2 h, 65%.

we were delighted to find that direct treatment of the reaction mixture with PPTS–MeOH, followed by stirring at room temperature for 12 h, led to the formation of two products. One of them, isolated in 27% yield, was unambiguously confirmed as **14** by the X-ray crystallographic study.[19] The other, isolated in 10% yield, turned out to be spirobacillene B (**2**). Thus, an unexpected one-pot reaction involving sequential indole–ketone enolate oxidative coupling, deprotection of the TES group, autoxidation of the resulting alcohol and deprotection of the TBS group was serendipitously achieved. Moreover, removal of the TBS group of **14** could be effected with TBAF–AcOH to afford **2** in 65% yield, thus increasing the overall yield of **2** to 28% in four steps.

In summary, the total syntheses of spirobacillenes A (**1**) and B (**2**),[20] two newly isolated indole alkaloids, were achieved in a biomimetic manner. The key transformation leading to **1** featured an unprecedented Ag_2O-promoted intramolecular phenol–enol oxidative coupling reaction and that leading to **2** highlighted an I_2-promoted intramolecular indole–ketone enolate oxidative coupling reaction. Our work provides decisive evidence for the proposed biogenetic pathways toward **1** and **2**. Meanwhile, it affords rapid access to the titled natural products as well as their analogs for further biomedical studies.

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19 CCDC 933153 (**14**)†.
20 Notably, both **1** and **2** were reported as optically active substances in ref. 2, however, we think it is questionable. Actually, **1** is obviously an achiral compound, and the naturally occurring **2** maybe a racemic substance. For detailed analysis, see ESI†.

