A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

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Accepted Article

Title: 10-Step Total Synthesis of Speradine C

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201902004
Angew. Chem. 10.1002/ange.201902004

Link to VoR: http://dx.doi.org/10.1002/anie.201902004
http://dx.doi.org/10.1002/ange.201902004

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10-Step Total Synthesis of Speradine C

Haichao Liu, Lijun Chen, Kuo Yuan, and Yanxing Jia*

Abstract: The first total synthesis of speradine C has been achieved in only 10 steps from a commercially available 4-bromoindole. Salient features of the work are the formation of four rings via three cyclizations including a bioinspired [3+2] annulation to form the C/D rings, a NCS-mediated oxidation to construct the E ring, and a Ru-catalyzed ketohydroxylation to assemble the F ring. This work highlights how strategic ring constructions can streamline the synthesis.

α-Cyclopiazonic acid (α-CPA, **1**), an ergot-like alkaloid, is a distinguished 3,4-fused indole alkaloid containing a 6/5/6/5/5 pentacyclic ring and a highly substituted tetramic acid moiety (Figure 1A).[1] It was firstly isolated from the fungus *Penicillium cyclopium* as a mycotoxic metabolite in 1968,[2] and was subsequently isolated from a number of species of *Penicillium* and *Aspergillus* fungus. In addition, α-CPA is a nanomolar inhibitor of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) which is essential for calcium reuptake in muscle contraction and relaxation cycles.[3] Importantly, SERCA is a promising target for the development of new drugs against various diseases and insect pests. Thus, α-CPA is one of the few potent, selective and reversible SERCA inhibitors which could act as a lead in drug development.

Since 2003, a number of highly oxygenated cyclopiazonic acid (CPA)-derived alkaloids, such as speradines A-C (**2**-**4**) and aspergillines A-E, were isolated and identified (Figure 1A).[4-8] Among them, speradine C (**4**) has an extraordinary chemical structure containing an unprecedented 6/5/6/5/5/6 hexacyclic ring system with a 5,6-dihydroxy-4-oxo-1,3-oxazinane unit, and six stereocenters including four oxygen-bearing carbon centers. Thus, the most substantial challenge in the synthesis of **4** is how to construct the sterically congested C/D/E/F ring system and the stereogenically correct installation of the four oxygen-bearing carbon centers. A concise synthesis of **4** requires a carefully choreographed introduction of these rings with correct stereogenic carbons.

Biosynthetic studies have revealed that α-CPA (**1**) is derived from L-tryptophan (Figure 1B).[9] The initial formation of tetramic acid ring followed by prenylation gives β-cyclopiazonic acid (β-CPA, **5**) which is the direct biosynthetic precursor of α-CPA. Oxidation of **5** by the flavin-dependent monoamine oxidase Mao A (CpaO) generates a stabilized benzylic cation **6**, which subsequently undergoes cascade cyclization resulting in formation of the C/D rings and finally α-CPA.

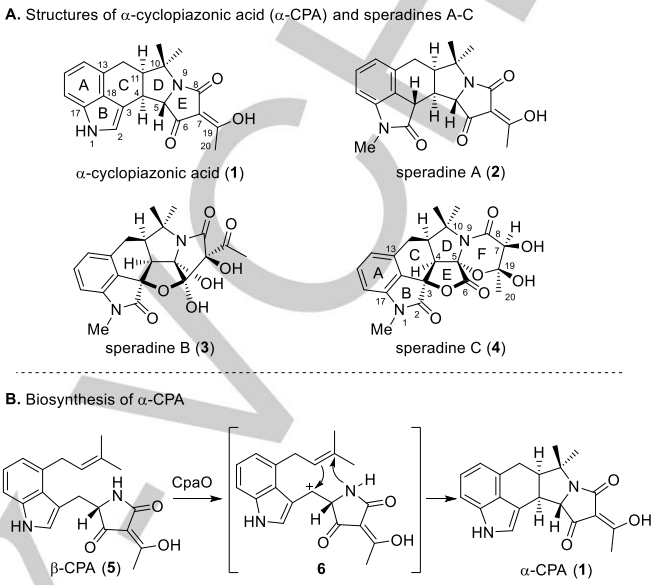

Figure 1. (A) Structures of α-cyclopiazonic acid and speradines A-C. (B) Biosynthesis of α-CPA.

To date, five total syntheses of the related but far less functionalized α-CPA have been reported.[10-14] However, of the highly oxygenated CPA-derived alkaloids, only aspergilline A has succumbed to total synthesis.[15] As part of our ongoing studies towards the concise and efficient synthesis of 3,4-indole alkaloids,[1a,16] we are attracted by the intricate molecular architecture of the highly oxygenated CPA-derived alkaloids. Herein, we report that we have achieved the first total synthesis of speradine C (**4**) in only 10 steps.

As depicted in Scheme 1, the concise route to speradine C was enabled by a unique retrosynthetic design featuring three different cyclizations to forge the C/D/E/F four different ring systems present in **4**. Thus, the F ring of speradine C could be generated from pentacycle **7** by direct ketohydroxylation followed by *in situ* ketalization (Cyclization 3). The E ring could in principle be assembled by an oxidative lactonization of tetracycle **8** (Cyclization 2), which also establish the stereochemistry of the quaternary center at C3. Tetracycle **8** could be readily synthesized from **9** via stereoselective α-hydroxylation. Notably, the C/D ring system could be generated from dehydrotryptophan derivative **10** by an unprecedented acid-catalyzed [3+2] annulation (Cyclization 1), which was serendipitously discovered during attempts to simulate the biosynthesis of α-CPA (Figure 1B). To the best of our knowledge, although the dehydroamino acid derivatives have been widely used in organic synthesis,[17] they have never been used in this kind of [3+2] annulation. In turn, **10** could be readily obtained from commercially available compounds **11**-**13**.

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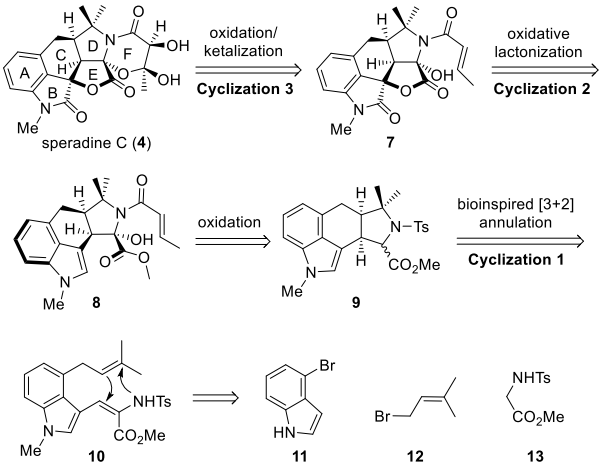
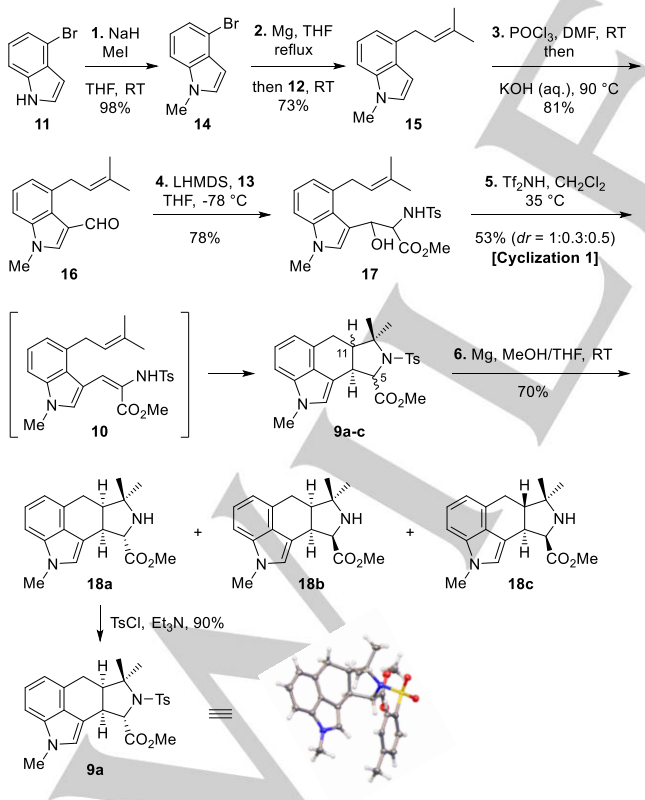


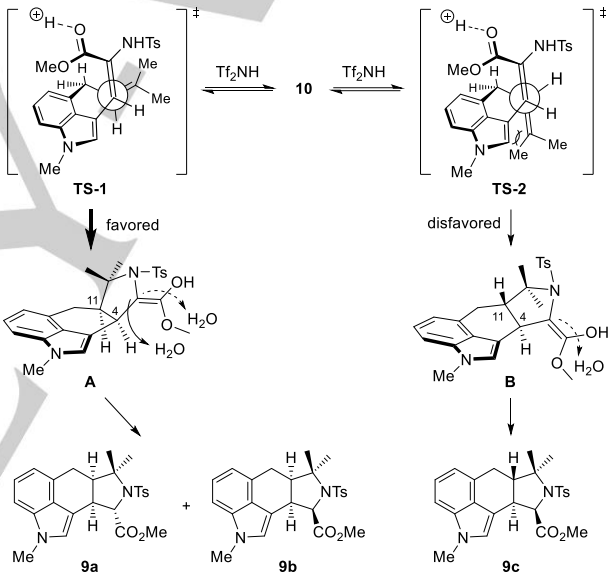
Scheme 1. Retrosynthetic analysis of speradine C.

Our synthesis commenced with 4-bromoindole **11**, which underwent *N*-methylation to provide **14** (Scheme 2). The C4-indole Grignard reagent was prepared by reacting **14** with Mg in THF which *in situ* reacted with prenyl bromide **12** to successfully afford **15** in 73% yield.[18] Vilsmeier-Haack formylation of **15** provided the desired aldehyde **16**. Treatment of **13** with LHMDS yielded the corresponding *C,N*-dianion which was treated with aldehyde **16** to furnish α-amino β-hydroxy ester **17** as a mixture of two inseparable diastereoisomers (*dr* = 3:1).[19]



Scheme 2. Synthesis of tetracycle **9**.

Considering the feasibility of *in situ* formation of dehydrotryptophan derivative via acid-mediated elimination of β-hydroxy in **17**, we turned our attention to the critical bioinspired cascade cyclization for the construction of C/D ring system. A variety of Lewis and Brønsted acids, solvent, reaction temperature, and concentration were screened (see SI for detailed information). We were delighted to find that the desired tetracycle **9** could be obtained as three inseparable diastereomers (**9a-c**, *dr* = 1:0.3:0.5) at C-4 and C-5 under the optimal reaction conditions (0.2 equiv of Tf_2NH in CH_2Cl_2 at 35 °C).[20] It is noteworthy that upon the addition of Tf_2NH to the solution of **17**, the starting material **17** was immediately consumed to yield the *E*-dehydrotryptophan derivative **10** as the major product and **9** as the minor product; as prolonging the reaction time, **10** was further converted to **9**. Attempts to catalyze this transformation with the strong chiral Brønsted acids were examined, however, the desired **9** was obtained in moderate yield without any enantioselectivity (for detailed information see SI).[21]



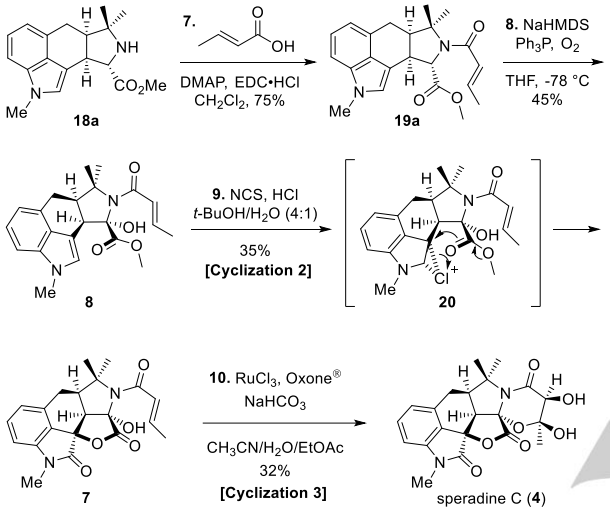
Scheme 3. Proposed mechanism for the formation of **9a**-**c**.

In fact, the ratio of **9a-c** was almost the same under different reaction conditions (see SI). Based on the literature and the aforementioned results, a possible mechanism for the stereochemical outcome of the cascade cyclization is proposed in Scheme 3. Tf_2NH binds to the lone pair of ester to produce two possible transition states (TS), **TS-1** and **TS-2**, which underwent cascade cyclization to form the C4-C11 *cis* enol **A** and the C4-C11 *trans* enol **B**, respectively. Since the disfavoured steric repulsion between the methyl group in the prenyl group and the indole core would be enhanced in **TS-2**, the sterically less hindered **TS-1** should be favoured, allowing the formation of **A** predominantly. Intermediates **A** and **B** can be transformed into **9** through protonation. For enol **A**, since the concave face is less sterically hindered than the convex face due to the C4-H and Ts groups located on the convex face, the formation of **9a** is preferred comparing with the formation of **9b**. For enol **B**, due to

10.1002/anie.201902004

the steric hinderance of C11-H and Ts groups, water can only attack from the β face to give **9c**.

Indeed, both **9a** and **9b** could be used for the synthesis of speradine C (**4**) (vide infra). Deprotection of Ts in **9a-c** with Mg in MeOH/THF gave amines **18a-c**, and **18a** could be readily separated from **18b** and **18c** by chromatography. The relative configurations of **18a-c** were determined by extensive NMR spectra analysis. Finally, protection of **18a** with TsCl provided pure **9a**, and its structure was further confirmed by X-ray crystallographic analysis.[22]



Scheme 4. Total synthesis of speradine C.

Having successfully constructed the C/D ring system, the completion of the synthesis of **4** is shown in Scheme 4. Coupling **18a** with crotonic acid smoothly afforded **19a**. The next step was the α-hydroxylation of **19a**. After several trials, we found that the oxidation of enolates with O_2 in the presence of Ph_3P produced the desired α-hydroxyl ester **8** in 45% yield.[23] Of note, this reaction proceeded with complete diastereoselectivity, presumably due to the caged ring system of **19a**, with molecular oxygen attacking the enloates from the less sterically hindered convex face. It is worth noting that the base also played a pivotal role in this reaction and NaHMDS gave the best result. In addition, coupling the mixture of **18b** and **18c** with crotonic acid provided the corresponding **19b** and **19c**, which could be readily separated by chromatography. α-Hydroxylation of **19b** also yielded **8** (see SI).

With the key cyclization precursor **8** in hand, we proceeded to strategically construct the E-ring to form spirocyclic butyrolactone oxindole **7**. Since the ester moiety of **8** is located on the *endo*-face of this concave skeleton, we thought if the ester could participate in this reaction, the intramolecular nucleophilic attack of the carbonyl oxygen of ester moiety on the position C3 of the intermediate **20** would give the desired spirolactone product. However, established protocols such as NBS,[24a-c] *t*-BuBr/DMSO,[24d] NaI/H_2O_2,[24e] Ms_2O/DMSO,[24f] $(COCl)_2$/DMSO,[24g] TTN[24h,i] suffered from no reaction or low yield. Pleasingly, after extensive experimentation, we found that treatment of **8** with NCS in *t*-BuOH/H_2O provided lactone **7** as a single diastereoisomer. The one-step formation of the desired **7** obviously streamlined the synthesis. It is noteworthy that the use of ester gave the same result as that of acid and amide. Importantly, it was also the first time that NCS was used as oxidant in this kind of oxidative cyclization.

At this stage, all that remained to complete the synthesis of **4** was the formation of F ring via ketohydroxylation/ketalization with the requisite configuration of the hydroxyl groups. After several trials, direct ketohydroxylation of **7** with $RuCl_3$ and Oxone in the presence of $NaHCO_3$ stereoselectively afforded the natural product **4**, which not only generated the F ring, but also established the C7 and C19 stereochemistry.[25,26] The physical data of our synthesized speradine C (**4**) were identical to those reported in the literature.[4a]

In summary, we have achieved the first total synthesis of speradine C in only 10 steps from commercially available 4-bromoindole (**11**). Significantly, of the 10 discrete steps of this synthesis, only one was not used for the formation of the C-C, C-O, and C-N bonds (step 6). The critical C/D/E/F ring system in **4** was strategically generated by employing three key cyclizations. Two of them are oxidative cyclizations, NCS-mediated spriolactonization (step 9) and Ru-catalyzed ketohydroxylation/ketalization (step 10), that constructed two sterically congested E and F rings and installed three oxygen-bearing carbon centers with correct configuration. The other one is the newly developed intramolecular [3+2] annulation using dehydrotryptophan derivative (step 5) for assembling the C/D ring system in tryptophan-derived tetracyclic building block, which could be applied to the syntheses of α-CPA and the related natural products as well as their analogues. These studies are ongoing and will be reported in due course.

Acknowledgements

We thank Prof. Benjamin List for providing the strong chiral Brønsted acids and Prof. Dehai Li for providing the authentic ^1H and ^{13}C NMR spectra. This research was supported by the National Natural Science Foundation of China (Nos. 21871013 and 21572008) and the Drug Innovation Major Project (Grant No. 2018ZX09711-001-005-005).

Keywords: indole alkaloids • total synthesis • oxidative cyclization • cascade cyclization • natural products

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Layout 2:

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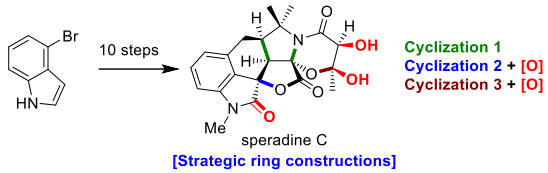

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Page No. – Page No.

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