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Communication

Seven-step total synthesis of α-cyclopiazonic acid

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ABSTRACT

A seven-step total synthesis of α-cyclopiazonic acid is reported from a commercially available 4-bromoindole. Salient feature of the work is the rapid formation of tetracyclic skeleton *via* a bioinspired [3 + 2] annulation to form the C/D rings.

α-Cyclopiazonic acid (α-CPA, **1**), a mycotoxin, was firstly isolated from the fungus *Penicillium cyclopium* Westling, which is often isolated from stored grain and cereal products (Fig. 1A) [1]. In addition, α-CPA is also a nanomolar inhibitor of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), which are essential for calcium reuptake in muscle contraction and relaxation cycles [2–4]. 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.

Structurally, α-CPA is a distinguished 3,4-fused indole alkaloid containing a 6/5/6/5/5 pentacyclic ring system and a highly substituted tetramic acid moiety (Fig. 1A) [1]. Since 2003, a number of highly oxygenated α-CPA-derived alkaloids, such as speradines A–C and aspergillines A–E, were isolated and identified [5–10].

Biosynthetic studies have revealed that β-cyclopiazonic acid (β-CPA, **4**) is the direct biosynthetic precursor of α-CPA (Fig. 1B) [11,12]. Oxidation of **4** by the flavin-dependent monoamine oxidase Mao A (CpaO) to generate a benzylic cation **5** that subsequently undergoes cascade cyclization to result in formation of the C/D rings of **1**.

To date, five total syntheses of α-CPA have been reported (Scheme 1A) [13–19]. The Kozikowski and Natsume groups constructed the C and D rings in a stepwise manner in which the C ring was formed by an intramolecular Michael addition [13,14]. In 2005, the Knight group assembled the C/D rings with high stereocontrol by an elegant carbocationic cascade [15,16]. In 2011, the Scherkenbeck group accomplished the first asymmetric synthesis of **1** by a modification of the Knight synthesis and found that cyclization of the same substrate **9** produced a 1:1 mixture of diastereomers across the C/D ring junction [17,18]. In 2018, the Aggarwal group reported the enantioselective synthesis of **1** by a formal [3 + 2] cycloaddition to form the C/D rings [19].

As part of our ongoing studies towards the concise and efficient synthesis of 3,4-indole alkaloids [20–25], we are attracted by the structure and biological activity of α-CPA and the related natural products. Inspired by the biosynthesis of α-CPA (Fig. 1B), we have discovered an unprecedented acid-catalyzed [3 + 2] annulation of *N*-Me dehydrotryptophan derivative **11** to produce tetracycle **12** by formation of the C/D rings, which enabled a ten-step total synthesis of speradine C (**2**) (Scheme 1B) [26]. Encouraged by this result, we envisioned that the cascade cyclization of the analogous *N*-Ts dehydrotryptophan derivative could be applied to the total synthesis of α-CPA. Herein, we report a concise total synthesis of α-CPA by using this novel acid-catalyzed [3 + 2] annulation.

Retrosynthetic analysis of α-CPA (**1**) was shown in Scheme 2. We envisioned that the tetramic acid residue of **1** could be generated from tetracycle **13** and diketene **14** by Dieckmann cyclization (Scheme 2) [14]. The C/D rings of the key tetracycle **13** could be constructed by acid-catalyzed [3 + 2] annulation of the indole *N*-Ts dehydrotryptophan derivative **15**. In turn, the cyclization precursor **15** could be readily prepared from compounds **16**-**18**.

Our synthesis commenced with 4-bromoindole **16**, which underwent a Suzuki cross-coupling with *tert*-prenylboronate **17** to give indole **19** as the sole regioisomer (Scheme 3) [27]. Vilsmeier-Haack formylation of **19** followed by *N*-tosylation provided the desired aldehyde **21**. Aldol reactions of *N*-Ts amino acid esters **18** with aldehyde **21** yielded the corresponding α-amino β-hydroxy

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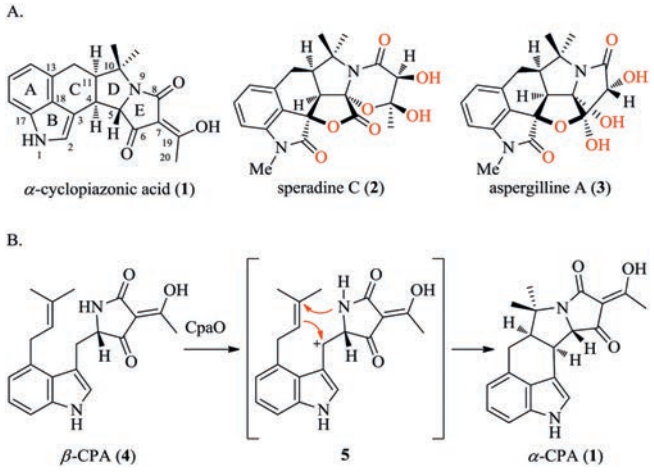
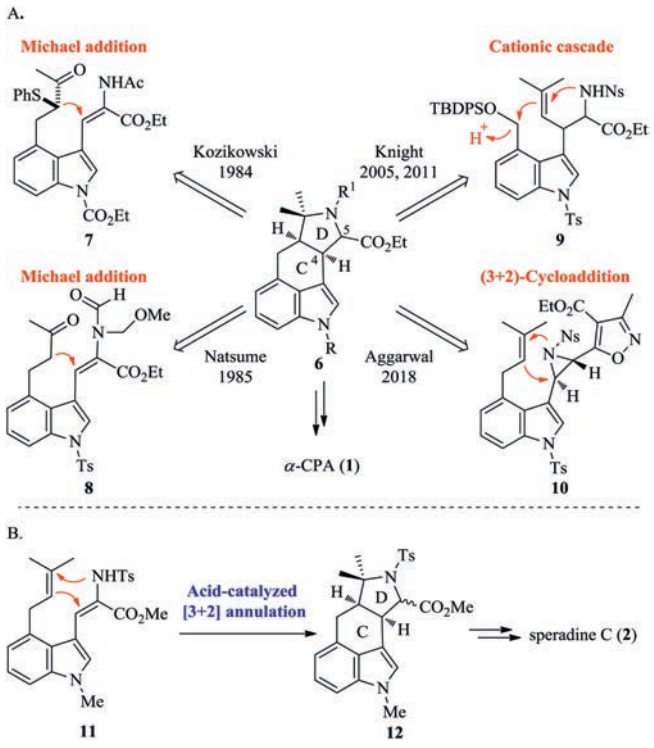
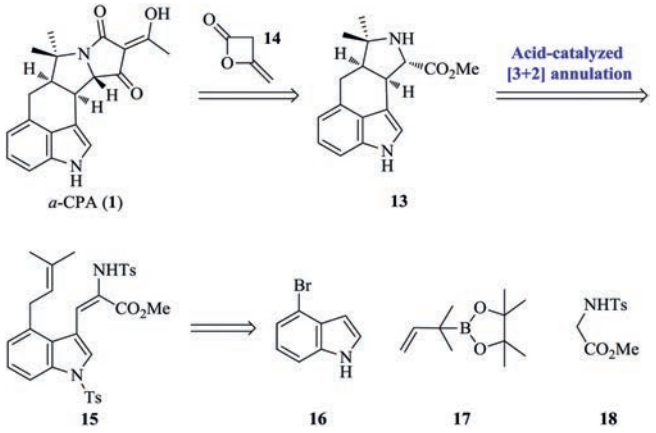


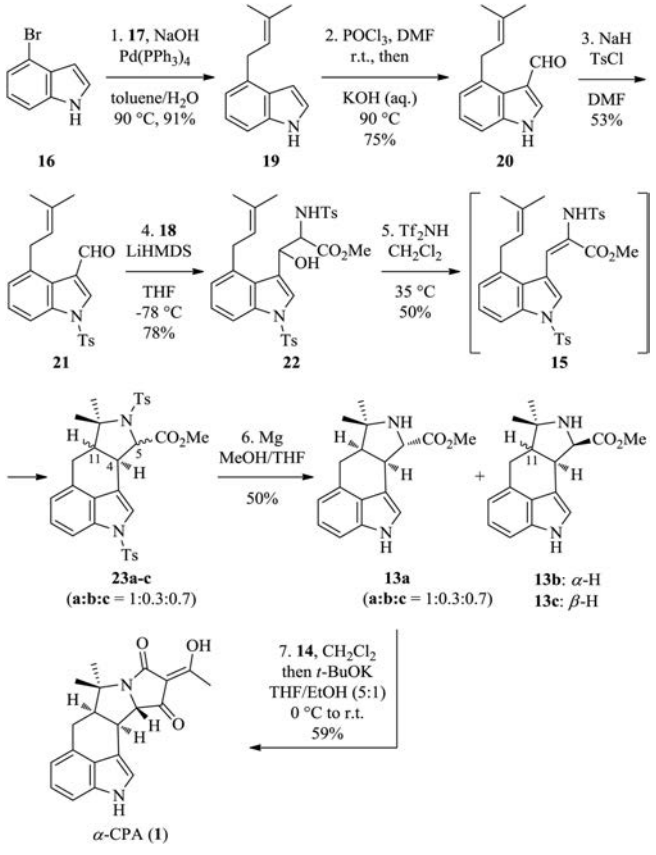
Fig. 1. (A) Structures of α-cyclopiazonic acid, speradines C, and aspergilline A. (B) Biosynthesis of α-CPA.



Scheme 1. (A) Previous syntheses of α-CPA. (B) Our strategy for the synthesis of speradine C (**2**).



Scheme 2. Retrosynthetic analysis of α-CPA.



Scheme 3. Total synthesis of α-CPA.

ester **22** as a mixture of *syn/anti* diastereoisomers (*dr* = 1:1), which could be separated and identified by careful column chromatography. Considering that compound **22** would then be converted to dehydrotryptophan derivative **15** that has no chiral center, compound **22** could be directly used for next step without separation.

With the α-amino β-hydroxy ester **22** in hand, we then investigated the critical [3 + 2] annulation. To our delight, compound **22** could be readily converted to the desired tetracycle **23a–c** (*dr* = 1:0.3:0.7 at C-5 and C-11) through dehydrotryptophan derivative **15** under the optimal reaction conditions (0.2 equiv. of Tf_2NH in CH_2Cl_2 at 35 °C) [26]. Tetracycles **23a–c** were very hard to be separated by column chromatography, and only small amount of pure **23a** was obtained.

Having successfully constructed the C/D ring system, we turned our attention to the synthesis of α-CPA (**1**). At this stage, we needed to remove the two Ts groups in **23**, however, it proved exceptionally difficult, especially for the pyrrolidine N-Ts group. After several trials, removal of the two Ts groups in **23a–c** with a large excess of amount of Mg in MeOH/THF gave amines **13a–c**, and **13a** could be readily separated from **13b** and **13c** by chromatography. The relative configurations of **13a–c** were determined by extensive NMR spectra analysis (the Supporting information) and comparison with the known N-Me-**13a–c** (*dr* = 1:0.3:0.7 at C-5 and C-11) [26]. Finally, treatment of tetracycle **13a** with diketene **14** in CH_2Cl_2 followed by stirring with *t*-BuOK in THF/EtOH (5:1) led smoothly to give α-CPA

(**1**). The physical data of our synthesized α-CPA (**1**) were identical to those reported in the literature.

In summary, we have achieved the total synthesis of α-CPA in only seven steps from commercially available 4-bromoindole (**16**). The synthesis features an acid-catalyzed [3 + 2] annulation to form the tetracyclic skeleton. This synthesis represents the shortest pathway for the total synthesis of α-CPA to date.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.06.048.

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