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Total synthesis of calothrixins and their analogues via formal [3+2] cycloaddition of arynes and 2-aminophenanthridinedione

Jian Guo [†], I. N. Chaithanya Kiran [†], Jiangsheng Gao, R. Santhosh Reddy, Yun He [*]

School of Pharmaceutical Sciences and Innovative Drug Research Centre, Chongqing University, 55 Daxuecheng South Rd., Shapingba, Chongqing City 401331, PR China

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ABSTRACT

Bioactive indolo[3,2-*j*]phenanthridine alkaloids, calothrixin A, B, and their analogues have been synthesized via formal cycloaddition of arynes and 2-aminophenanthridinedione as the key step, which proceeds through successive C–C/C–N bond formation and subsequent oxidation under transition-metal-free and mild conditions in the final stage of the synthesis.

Calothrixin A (**1a**) and B (**2a**) are quinone-based natural products isolated from cell extracts of *Calothrix* cyanobacterium in 1999.[1] They contain indolo[3,2-*j*]phenanthridine framework with a unique assembly of highly important pharmacophores including indole, quinoline, and quinone (Fig. 1). These compounds act as human DNA topoisomerase I poisons, inhibiting in vitro growth of chloroquine-resistant strain of the human parasite *Plasmodium falciparum* and also exhibiting lethal effects on human cancer cell lines at low nano-molar concentrations.[2]

Owing to their unique indolo[3,2-*j*]phenanthridine scaffold and promise as lead compounds for drug discovery, great efforts have been made for the total synthesis of calothrixins. Several approaches have been reported for their synthesis,[3] utilizing strategies such as *ortho*-lithiation,[4] Pd, or Cu-catalyzed coupling,[5] electrocyclization,[6] Friedel–Crafts acylation/alkylation,[7] and radical reactions.[8] These strategies rely upon functionalized indole, quinoline, or carbazole as synthetic precursors, but a greater challenge lies in developing a practical and flexible synthetic strategy for generating a library of calothrixin analogues, which would be invaluable for structure–activity relationship (SAR) studies. Cascade reactions based on arynes is a powerful tool for organic synthesis and have been used in many total synthesises of natural products.[9] Especially, the introduction of 2-(trimethylsilyl)-aryl triflates as aryne precursors allows the reaction to proceed at transition-metal-free and mild condition.[10] Herein, we report a simple and practical approach for the synthesis of calothrixins based on cascade reaction of arynes, which has the flexibility to modulate the functional groups on ring A at the final stage of their synthesis.

As a part of our research program on the synthesis of bioactive heterocycles and their analogues employing aryne chemistry,[11] calothrixins were identified as important synthetic targets. Based on the knowledge of reaction between aryne and 2-aminoquinone,[11] their retrosynthetic analysis is outlined in Scheme 1. It was hypothesized that ring A of calothrixin B (**2a**) could be prepared via a formal [3+2] cycloaddition reaction of aryne **3a′** with 2-aminophenanthridinedione **4**, and variable aryne precursors could also be used in the final stage to provide diverse analogues of calothrixin B. Intermediate amine **4** could be obtained by oxidation of compound **5**, which in turn could be achieved by the reductive amination of aldehyde **7** with *o*-iodoaniline (**6**) followed by palladium-catalyzed intramolecular coupling.

Our investigation commenced with the synthesis of key intermediate **4** as shown in Scheme 2. Regioselective bromination of commercially available 2,5-dimethoxyaniline (**8**) followed by the protection of primary amine with $(Boc)_2O$ provided compound **10** in good yields. Bromide **10** readily underwent lithium halogen exchange, and quenching of the resulting anion with DMF gave the corresponding aldehyde **7**. Reductive amination of aldehyde **7** with *o*-iodoaniline (**6**) using $NaCNBH_3$ and acetic acid provided amine **11** in 82% yield.[8b] Acetylation of compound **11** with Ac_2O in the presence of catalytic amount of DMAP, followed by intramolecular palladium-catalyzed cyclization afforded compound **5** in 85% yield.[8b] Compound **5** on treatment with CAN in CH_3CN/H_2O (2:1) furnished phenanthridinedione **13** in 64%

* Corresponding author.
E-mail address: yun.he@cqu.edu.cn (Y. He).
† Contributed equally.

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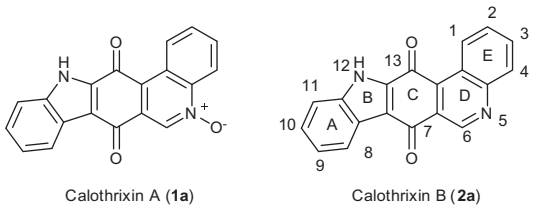
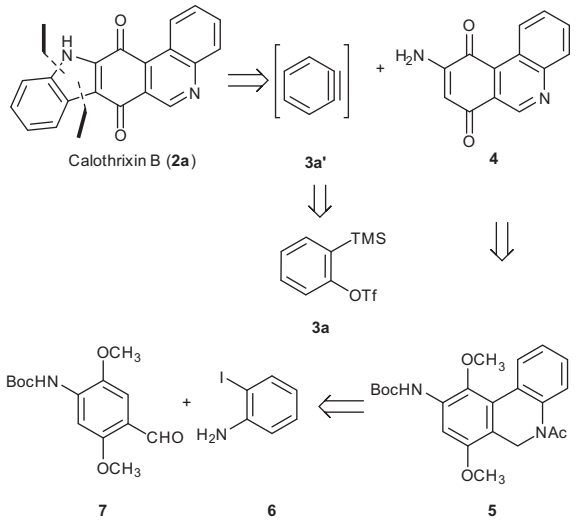


Figure 1. Structures of calothrixins.



Scheme 1. Retrosynthetic analysis of calothrixin B.

yield.[12] Deprotection of Boc with TFA provided 2-aminophenanthridinedione **4** in quantitative yield.

With the required key intermediate **4** and aryne precursors **3a**–**3d** (Fig. 2) (synthesized following the reported procedures)[13] in hand, the formal [3+2] cycloaddition for constructing ring A of calothrixin B was explored. We systematically examined the effect of solvent (THF, Et_2O, CH_3CN, CH_2Cl_2, and TolH), fluoride source (KF, CsF, TBAF, and TBAT), temperature (0 °C, 25 °C, and 60 °C) and additive (18-crown-6) (see Supporting Information, Table S1). When TBAT was used as fluoride source and THF as reaction solvent at room temperature,[11] calothrixin B (**2a**) was obtained in 26% yield (43% brsm), along with *N*-arylated **14** (5%),

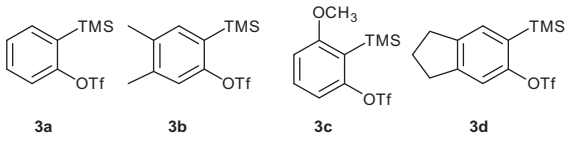
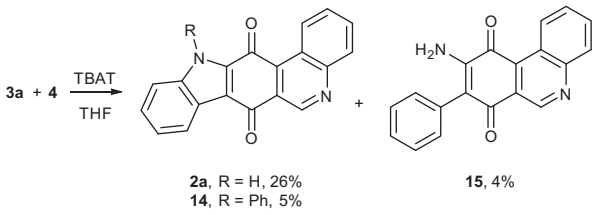


Figure 2. Aryne precursors **3a**–**3d**.

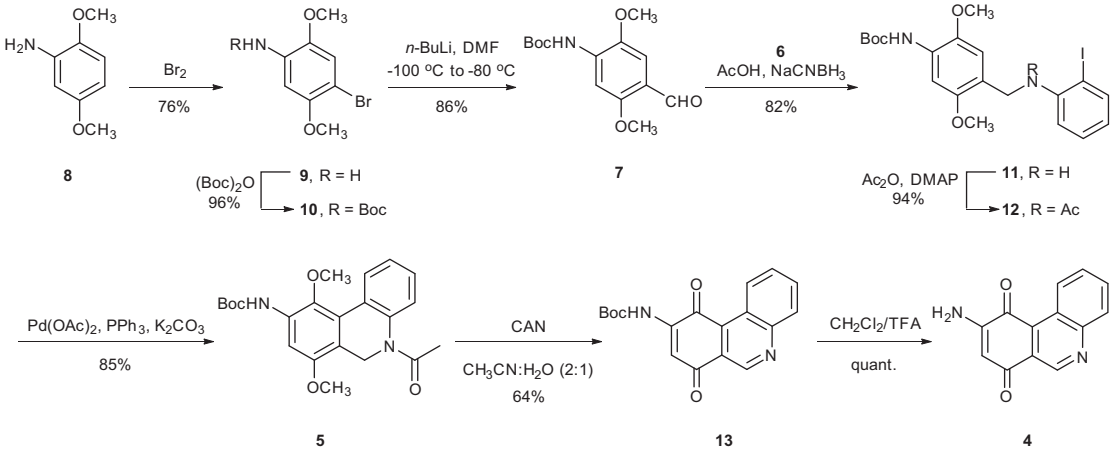


Scheme 3. Preliminary results of formal [3+2] cycloaddition. Conditions: **3a** (0.64 mmol), **4** (0.4 mmol), TBAT (1.28 mmol), THF (8.0 mL), N_2, 25 °C.

uncyclized *C*-arylated **15** (4%), and other several unidentifiable by-products (Scheme 3). Based on the literature precedents, the nitrogen atom in quinoline moiety could induce side reaction by reacting with aryne,[14] which might account for the low yield of the desired product. It is noteworthy that other fluoride sources (KF and CsF) led to decrease in desired product **2a** and significant increase of side products such as **14** and **15**. Oxidation of calothrixin B with *m*CPBA in CH_2Cl_2 afforded calothrixin A in 71% yield (Table 1). Utilizing the same strategy, the synthesis of calothrixin analogues was conducted. Under the optimized reaction condition, key intermediate **4** was subjected to transition-metal-free cascade reaction with symmetric and unsymmetrical aryne precursors (**3b**–**3d**) to provide calothrixin B analogues (**2b**–**2d**) in moderate yields. Calothrixin A analogues (**1b**–**1d**) were obtained in good yield using the same oxidizing procedure with **1a**, and the results are summarized in Table 1.

When unsymmetrical aryne precursor **3c** was used as the aryne source, calothrixin analogue **2c** was obtained regioselectively. To establish the regioselectivity of the reaction, compound **1c** was treated with CH_3I/NaH, followed by quenching the reaction mixture with methanol, leading to the formation of derivative **17** in 88% yield, presumably through intermediate **16**. Structure of compound **17** was confirmed by NOE correlations (Scheme 4).

Two plausible mechanisms for this cascade reaction are depicted in Scheme 5. In Mechanism I, quinone amine nitrogen



Scheme 2. Synthesis of aminophenanthridinedione **4**.