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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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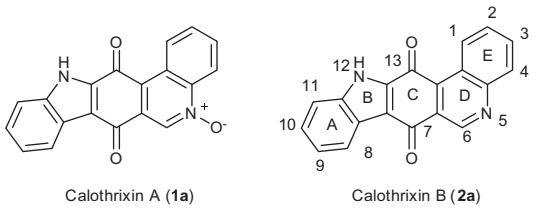
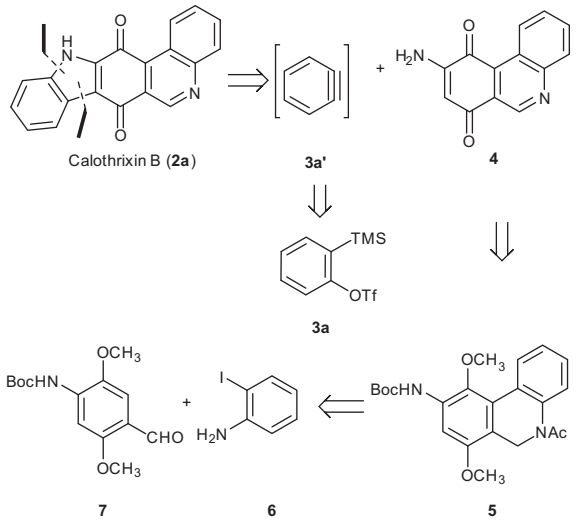


Figure 1. Structures of calothrixins.



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%),

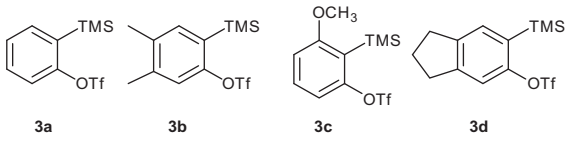
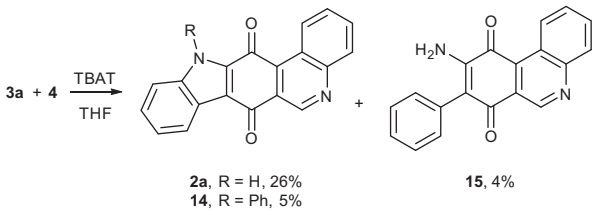


Figure 2. Aryne precursors **3a**–**3d**.

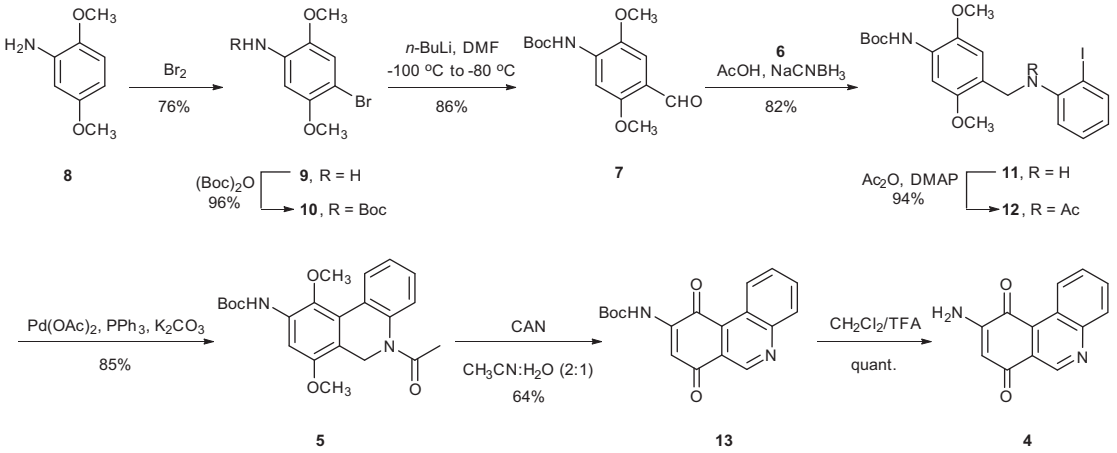


Scheme 3. Preliminary results of formal [3+2] cycloaddition. Conditions: **3a** (0.64 mmol), **4** (0.4 mmol), TBAT (1.28 mmol), THF (8.0 mL), N_2, 25 °C.

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.

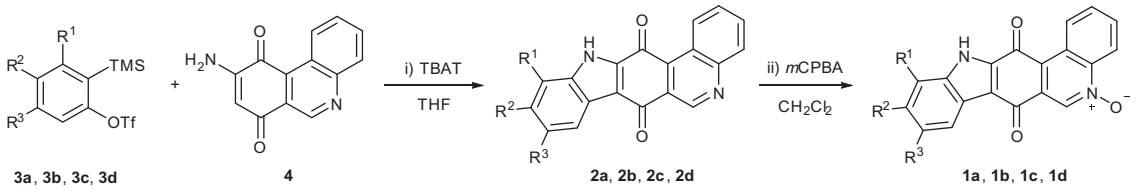
When unsymmetrical aryne precursor **3c** was used as the aryne source, calothrixin analogue **2c** was obtained regioselectively. To establish the regioselectivity of the reaction, compound **1c** was treated with CH_3I/NaH, followed by quenching the reaction mixture with methanol, leading to the formation 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



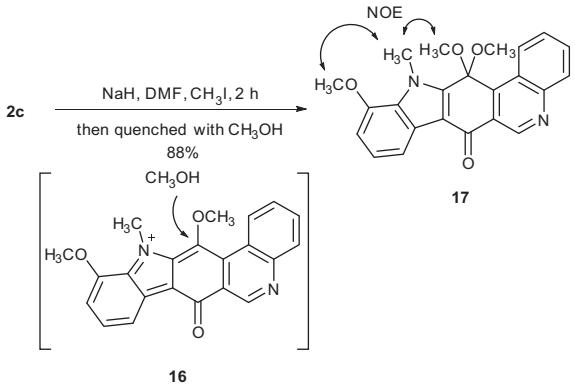
Scheme 2. Synthesis of aminophenanthridinedione **4**.

Table 1
Synthesis of calothrixin A (**1a**), calothrixin B (**2a**) and their analogues[a]



Entry	Aryne precursor	R^1	R^2	R^3	Yield of **2** (%)	Yield of **1** (%)
1	**3a**	H	H	H	**2a** (26, 43[b])	**1a** (71)
2	**3b**	H	CH_3	CH_3	**2b** (22, 38[b])	**1b** (70)
3	**3c**	OCH_3	H	H	**2c** (25, 41[b])	**1c** (76)
4	**3d**	H	$-(CH_2)_3-$		**2d** (25, 40[b])	**1d** (74)

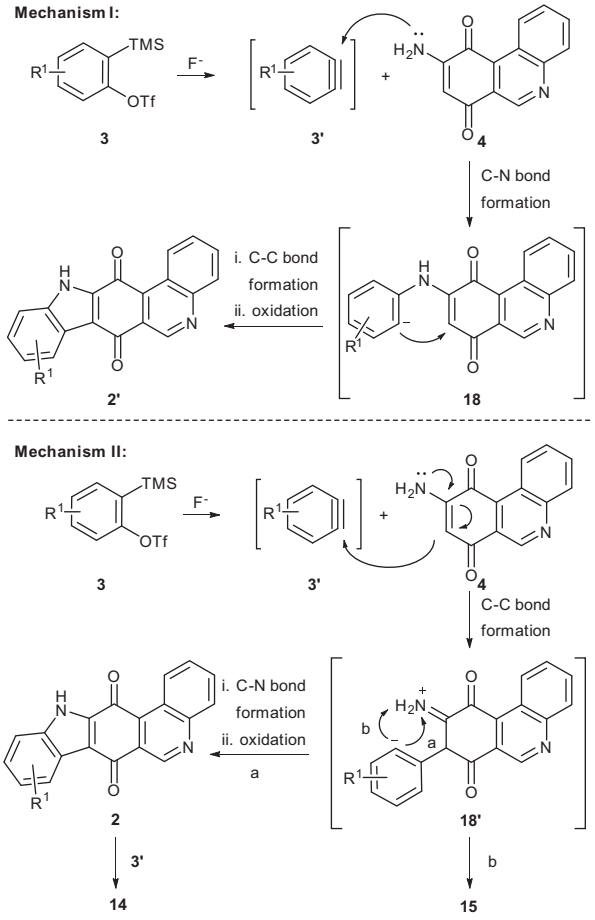
[a] Conditions: (i) **3** (0.64 mmol), **4** (0.4 mmol), TBAT (1.28 mmol), THF (8.0 mL), N_2, 25 °C. (ii) **2** (0.05 mmol), *m*CPBA (0.25 mmol), CH_2Cl_2 (50 mL), reflux.
[b] Yield based on brsm.



Scheme 4. Synthesis of **17** and NOE correlations.

in **4** could serve as a nucleophile to initiate a cascade reaction by attacking the intermediately generated aryne **3′**, leading to *N*-arylated anion intermediate **18**. The newly generated aryl carbanion may undergo subsequent Michael addition onto the quinone moiety followed by in situ oxidation to furnish **2′**. In Mechanism II, the carbon of enamine moiety acts as a nucleophile to attack aryne **3′** to initiate the cascade reaction,[15] leading to the zwitterionic intermediate **18′**.[16] The newly generated aryl carbanion attacks the electron-deficient nitrogen (path a), followed by aromatization to provide **2**. The electron-withdrawing character of naphthalenedione makes the iminium nitrogen of **18′** to behave as an electrophile, resulting in C–N bond formation.[17] Compound **2** could react further with arynes to provide arylated compound **14**, demonstrating potential expandability of this method in forming *N*-arylated analogues. Alternatively, the zwitterionic intermediate **18′** could abstract a proton in an intra-molecular fashion, followed by imine–enamine tautomerization to form **15** (path b). Based on the fact that the nucleophilic attack usually favors *meta* position to the methoxy group of the aryne generated in situ from unsymmetrical aryne precursor **3c**[16,18] and the regioselectivity of obtained product **2c**, it is presumed that the cascade reaction proceeds through mechanism II, in line with our previous studies.[11] The formation of by-product **15** also support Mechanism II, favouring *C*-arylation over *N*-arylation.

In summary, we have developed a novel and flexible strategy for the synthesis of calothrixins A, B, and their analogues. Calothrixins A and B have been achieved in 4.8% (ten steps) and 6.8% (nine steps) overall yield involving transition-metal-free formal [3+2] cycloaddition of arynes and 2-aminophenanthridinedione as the key reaction. Various aryne precursors could be used to quickly prepare ring-A modified calothrixins at the final stage of their synthesis. Application of this methodology in synthesizing a library of complex calothrixins and biological evaluations of the synthetic calothrixins are currently underway in our laboratory and will be reported in due course.



Scheme 5. Plausible mechanisms of the cascade reaction.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and ^{1}H NMR and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.091.

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