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A biomimetic synthesis of the indolo[3,2-*j*]phenanthridine alkaloid, calothrixin B

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Abstract—A biomimetic approach to calothrixin B via a hypothetical metabolite, 6-formylindolo[2,3-*a*]carbazole, is described. The construction of a suitable indolo[2,3-*a*]carbazole ring system was carried out using an allene-mediated electrocyclic reaction involving two [*b*]-bonds of indoles as the key step.

The novel pentacyclic metabolites, calothrixin A (**1a**) and B (**1b**), were isolated from *Calothrix cyanobacteria* in 1999 by Rickards et al. (Fig. 1).[1] They have been shown to inhibit the growth of both the human malarial parasite and human cancer cells.[2] Calothrixins have been an object of synthetic interest of several research groups, in view of their biological activities as well as their rare pentacyclic indolo[3,2-*j*]phenanthridine framework. Synthetic studies of calothrixins have been reported by the four groups of Kelly et al.,[3] Chai et al.,[4] Guingant et al.,[5] and Bennasar et al.[6]

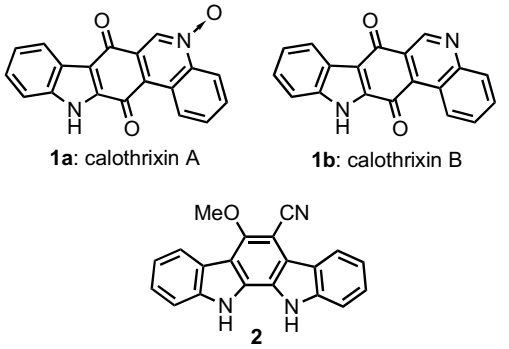
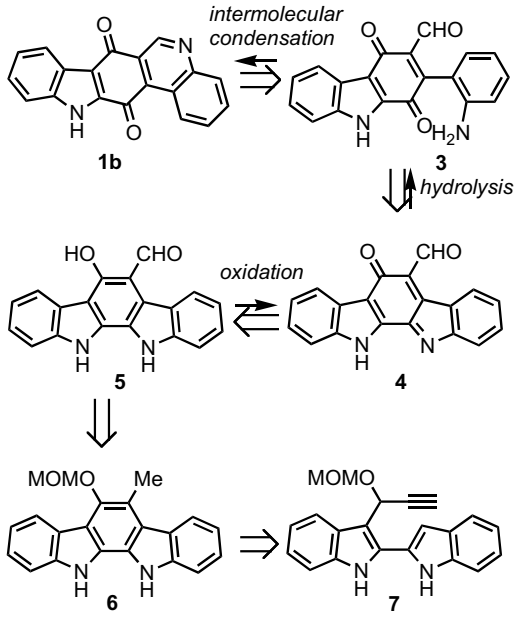


Figure 1.

On the other hand, Rickards et al.[1] have suggested that **1a** and **1b** may be derived from a hypothetical metabolite **5** of the relatively common indolo[2,3-*a*]carbazole type, closely related to the known 6-cyano-5-methoxyindolo[2,3-*a*]carbazole (**2**)[8] isolated from cyanobacterium *Nostoc sphaericum*. As shown in Scheme 1, they reasoned



Scheme 1.

Keywords: Indolo[3,2-*j*]phenanthridine; Calothrixin B; Biomimetic synthesis; Quinone.
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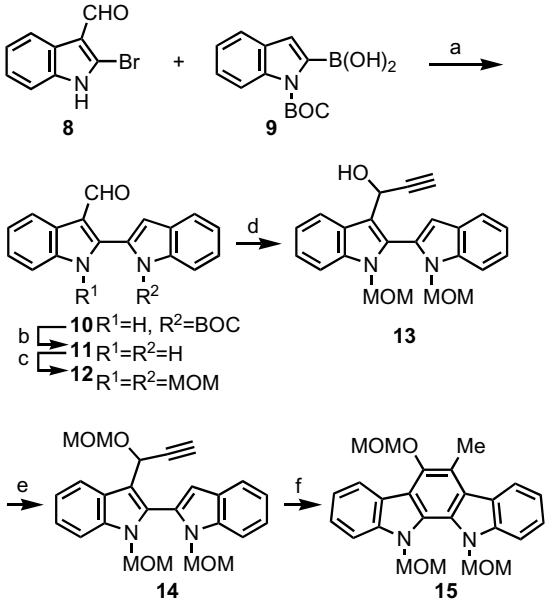
that the oxidation of the 6-formylindolocarbazole **5** to quinone-imine **4** followed by hydrolytic cleavage of the resulting imino group would afford quinone **3**, and then rotation around the biaryl bond and intramolecular condensation of the amine with the formyl group would yield **1b** (Scheme 1).

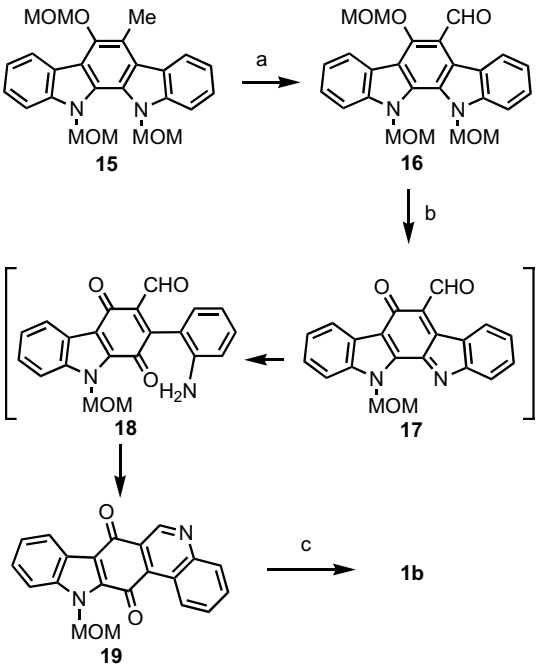
We began our investigation by attempting to mimic the biomimetic hypothesis outlined in Scheme 1. The synthesis of indolo[2,3-*a*]carbazole **6** was based on an allene-mediated electrocyclic reaction of the 6π-electron system involving two [*b*]-bonds of indoles, because we have also achieved a total synthesis of calothrixin B (**1b**) by the construction of an appropriate 4-oxygenated 2,3,4-trisubstituted carbazole ring based on an allene-mediated electrocyclic reaction as a key step.[7] We chose 2-bromoindole-3-carbaldehyde **8** as the starting material.

The Suzuki–Miyaura coupling reaction of **8** with indole-2-boronic acid **9** gave the bisindole **10**. Cleavage of the *N*-BOC group in **10** with TFA, followed by protection of the nitrogen atom of bisindole **11** with chloromethyl methyl ether (MOMCl) and NaH afforded *N*,*N*′-bis(methoxymethyl)bisindole **12**. The Grignard reaction of **12** with ethynylmagnesium bromide yielded propargyl alcohol **13**, which was protected with MOMCl to produce MOM ether **14**. Propargyl ether **14** was subjected to an allene-mediated electrocyclic reaction to yield the desired indolocarbazole **15** (Scheme 2).

Next, oxidation of 6-methylindolocarbazole **15** to 6-formylindolocarbazole **16** was attempted by DDQ to produce aldehyde **16**.



Scheme 2. Reagents and conditions: (a) 2 M Na_2CO_3, $PdCl_2$(dppf), 80 °C (96%); (b) TFA, 0 °C→rt (82%); (c) MOMCl, NaH, DMF, 0 °C→rt (71%); (d) ethynylmagnesium bromide, THF, 0 °C→rt (86%); (e) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 45 °C (78%); (f) *t*-BuOK, *t*-BuOH–THF, 90 °C (93%).



Scheme 3. Reagents and conditions: (a) DDQ, DMF, rt (55%); (b) CAN, MeOH–H_2O, 0 °C (40%); (c) concd HCl, THF, 55 °C (65%).

Further oxidation of **16** in order to convert to a quinone-imine like compound was examined with CAN (cerium ammonium nitrate) to give the *N*-MOM-calothrixin B **19** directly. This result shows that quinone-imine **17** was formed, and then immediate hydrolysis of an imino group in **17** followed by an intramolecular condensation occurred to give the indolo[3,2-*j*]phenanthridine framework. Finally, cleavage of the *N*-MOM group using Kelly's method[3] was carried out to yield calothrixin B (**1b**). The physical and spectroscopic data of *N*-MOM-calothrixin B **19**[9] and synthetic sample **1b** were identical with those of Kelly's synthetic compound **19** and natural calothrixin B (**1b**), respectively (Scheme 3).

In conclusion, we have achieved construction of the indolo[2,3-*a*]carbazole framework using the allene-mediated electrocyclic reaction as a key step, and demonstrated a biomimetic synthesis of calothrixine B (**1b**) via the hypothetical material, 6-formylindolo[2,3-*a*]-carbazole. We are sure that this proved that calothrixine B (**1b**) has been formed naturally in the route of Rickard's protocol.

Acknowledgement

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9. *N*-MOM-calothrixin B **19**: mp: 246–247 °C. IR (neat) *v*: 2919, 2850, 1650 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.45 (3H, s), 6.18 (2H, s), 7.48 (1H, t, $J = 8.1$ Hz), 7.56 (1H, t, $J = 7.0$ Hz), 7.68 (1H, d, $J = 8.1$ Hz), 7.82 (1H, t, $J = 7.4$ Hz), 7.91 (1H, t, $J = 6.6$ Hz), 8.34 (1H, d, $J = 9.5$ Hz), 8.47 (1H, d, $J = 8.4$ Hz), 9.65 (1H, d, $J = 8.1$ Hz), 9.82 (1H, s). MS *m*/*z*: 342 (M^+).