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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 5263–5264

A new total synthesis of an indolo[3,2-*j*]phenanthridine alkaloid calothrixin B

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Received 23 May 2005; revised 10 June 2005; accepted 13 June 2005

Abstract—A new total synthesis of calothrixin B is described. The key step is an allene-mediated electrocyclic reaction involving the indole 2,3-bond for the construction of a suitable 4-oxygenated 2,3,4-trisubstituted carbazole ring system.

The novel pentacyclic metabolites, calothrixins A (**1**) and B (**2**) having an indolo[3,2-*j*]phenanthridine nucleus were isolated from *Calothrix* cyanobacteria in 1999 (Fig. 1).[1] They display potent inhibitory effects on the in vitro growth of both the human malarial parasite and human cancer cells[1] and inhibition of a bacterial RNA polymerase.[2] Synthetic efforts of these interesting targets have been reported by three groups of Kelly et al.,[3] Chai and co-workers[4] and Guingant and co-workers.[5]

We herein, describe a new total synthesis of calothrixin B (**2**) through a construction of a 4-oxygenated 2,3,4-trisubstituted carbazole ring, derived from a disconnection at the C-5 and C-6 bond, based on an allene-mediated electrocyclic reaction of 6π-electron system involving the indole 2,3-bond.[6] For the synthesis of 4-oxygenated 2,3,4-trisubstituted carbazole **8**, we chose 2-formyl-*N*-phenylsulfonylindole (**3**)[7] as a starting material (Scheme 1).

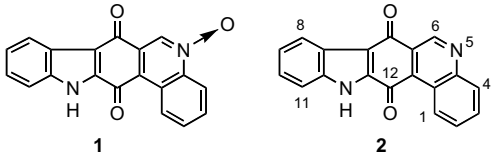

Figure 1.

The Wittig reaction of **3** with 2-nitrobenzyltriphenylphosphorane gave the *trans*-2-(2-styryl)indole **4** (96%).[8] Treatment of **4** with α,α-dichloromethyl methyl ether in the presence of $AlCl_3$[9] at −78 °C afforded the 3-formylindole **5** (96%). The Grignard reaction of **5** with ethynyl magnesium bromide yielded the propargyl alcohol **6** (92%), which was protected with chloromethyl methyl ether in the presence of *i*-Pr_2NEt to produce the methoxymethyl ether **7** (93%). The propargyl ether **7** was subjected to an allene-mediated electrocyclic reaction[6] in the presence of *t*-BuOK in *t*-BuOH and THF at 90 °C to yield the desired 4-oxygenated 2,3,4-trisubstituted carbazole **8** (29%). Subsequent oxidation of **8** with DDQ in the presence of lithium perchlorate in CH_2Cl_2 and H_2O gave the 3-formyl-4-hydroxycarbazole **9** with elimination of methoxymethyl group (70%). Reduction of the nitro group of **9** with 10% Pd–C and H_2, followed by the intramolecular condensation afforded the pentacyclic indolo[3,2-*j*]phenanthridine **10**, which was oxidized to quinone with CAN (cerric ammonium nitrate) to provide calothrixin B (**2**) (67% yield from **9**).[10] The physical and spectroscopic data of synthetic sample **2** were identical with those of natural calothrixin B (**2**).[1]

Thus, a synthetic route to calothrixin B (**2**) was newly completed with a 10.7% overall yield by the construction of an appropriate 4-oxygenated 2,3,4-trisubstituted carbazole ring **8** based on our methodology,[6] followed by the connection between C-5 and C-6 to the pentacyclic

Keywords: Indolo[3,2-*j*]phenanthridine; Calothrixin B; Synthesis; Quinone.
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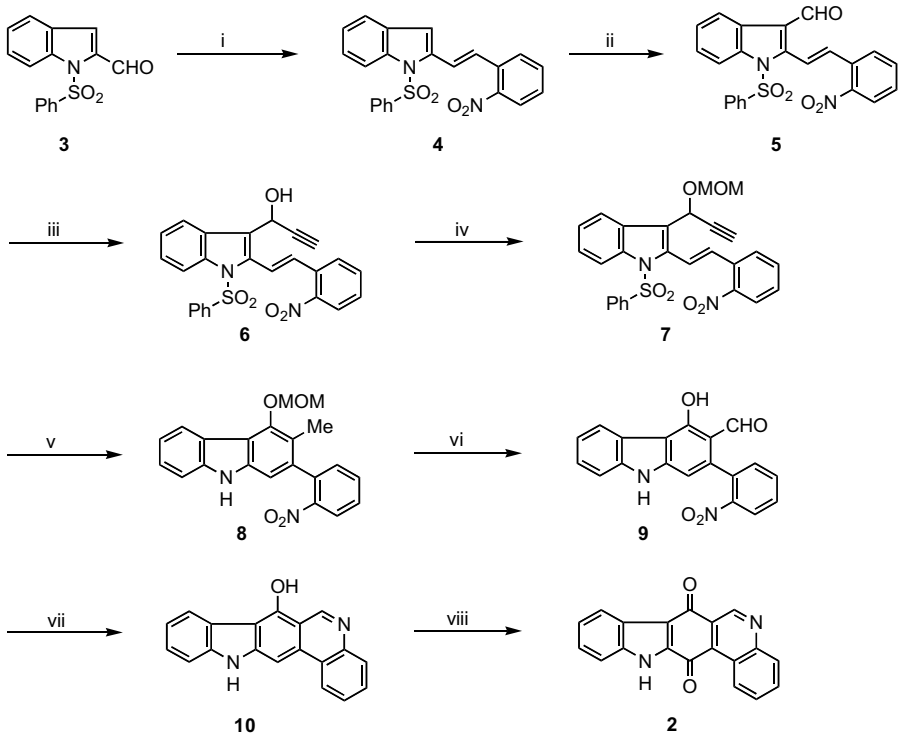
doi:10.1016/j.tetlet.2005.06.042



Scheme 1. Reagents and conditions: (i) 2-nitrobenzyl triphenylphosphonium bromide, *n*-BuLi, THF, 0 °C, 3 h (96%); (ii) Cl_2CHOMe, $AlCl_3$, CH_2Cl_2, −78 °C, 1 h (96%); (iii) ethynylmagnesium bromide, THF, 0.5 h (92%); (iv) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 50 °C, 12 h (93%); (v) *t*-BuOK, *t*-BuOH, THF, 0.5 h (29%); (vi) (1) DDQ, $LiClO_4$, CH_2Cl_2, H_2O, rt, 40 h, (2) 6 N HCl, ethylene glycol, THF, 60 °C, 3 h (70%); (vii) 10% Pd–C, H_2, EtOH, rt, 5 h; (viii) CAN, MeCN, H_2O, 0 °C, 1 h (67% from **9**).

indolo[3,2-*j*]phenanthridine ring **10**. Although our route to **2** had the lower overall yield in the comparison with those of the earlier three groups,[3–5] it would be characterized that our synthetic strategy facilitates a construction of a chemical library, in particular E-ring of calothrixins A (**1**) and B (**2**) for biological evaluations.

Acknowledgements

This work was supported in part by Grants-in Aid for Scientific Research (C) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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10. Calothrixin B: mp >300 °C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 7.39 (1H, t, J = 7.7 Hz), 7.47 (1H, t, J = 7.7 Hz), 7.63 (1H, d, J = 7.7 Hz), 7.89 (1H, t, J = 7.7 Hz), 7.96 (1H, t, J = 7.7 Hz), 8.17 (1H, d, J = 7.7 Hz), 8.19 (1H, d, J = 7.7 Hz), 9.58 (1H, d, J = 7.7 Hz), 9.63 (1H, s), 13.18 (1H, br s).