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Short and straightforward total synthesis of Ammosamide B

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ABSTRACT

A simple and five steps total synthesis of Ammosamide B has been developed. The tricyclic pyrroloquinoline in Ammosamides was constructed in one step based on Doebner–Miller reaction between 1,3-diamine-4,6-dinitrobenzene **8** and dimethyl-2-oxo glutaconate **9**.

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Ammosamides (Fig. 1) are chlorinated tricyclic pyrroloquinoline alkaloids produced by Streptomyces strain CNR-698, which was isolated from bottom sediments collected at a depth of 1618 m in the Bahamas Islands.[1]Both Ammosamides A and B exhibited significant in vitro cytotoxicity against human colon adenocarcinoma HCT-116 cells with an IC_{50} of 320 nM.[1,2] These compounds showed high selectivity against a diversity of cancer cell lines with values ranging from 20 nM to 1 μM, they target the cellular cytokinetic protein myosin[2], which is a class of important cellular proteins involved in numerous cell processes, including cell cycle regulation, cytokinesis, and cell migration. Fenical[3] recently reported the first total synthesis of Ammosamides A and B over 15 steps from 4-chloroisatin in the total yield of 2.01%. In this Letter, we report a short and straight forward total synthesis of Ammosamide B.

We reasoned (Scheme 1) that the core structure of tricyclic pyrroloquinoline in Ammosamides **4** could be constructed in one step by direct cyclocondensation of dimethyl-2-oxoglutaconate **6** and 1,3-diamin-4,6-dinitrobenzene **5** through Doebner–Miller reaction. Compound **5** could in turn be obtained directly from commercially available 1,3-difluoro-4,6-dinitrobenzene **7**. The required substituents in Ammosamide B could be elaborated via **4** by alkylation, reduction, and chlorination.

The key step in our synthesis was the coupling of 1,3-diamin-4,6-dinitrobenzene **5** with dimethyl-2-oxoglutaconate **6**. As starting material, compound **5**[4] was obtained from compound **7** by treatment with ammonia in THF. Although Doebner–Miller reaction of electron-rich substituted aniline with dimethyl 2-oxoglutaconate has been frequently used for the synthesis of dimethy-2,4-dicarboxylic quinoline[5], electron-poor anilines in this type of reaction were rarely studied. In electron-rich anilines, the synthetic process includes a fast Michael addition, subsequent cyclization, dehydration, and oxidativearomatization. However, when we treated **5** with **6** in several methods according to the Skraup-Doebner–Miller condition, activated in the presence of an acid catalyst, such as HCl (gas), TsOH, AcOH, or H_2SO_4,.[5–9] no expected reaction was observed, resulting in either the recovery of **5** or its decomposition into unidentifiable mixtures of products. Considering the poor solubility of compound **5** we turned to TFA. It was reported[10] that the Skraup-Doebner–Miller reaction could adopt to a reversal fashion in refluxing TFA, the reaction first involves 1,2-addition of anilines to unsaturated α-ketoesters to form Schiff's base followed by cyclization and oxidation to yield the

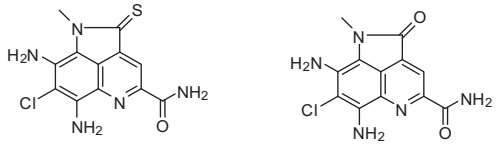
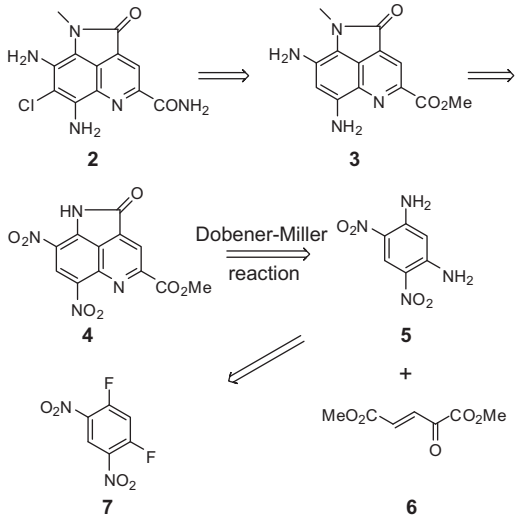


Figure 1. The structure of Ammosamides.



Scheme 1. Retrosynthetic analysis of Ammosamide B.

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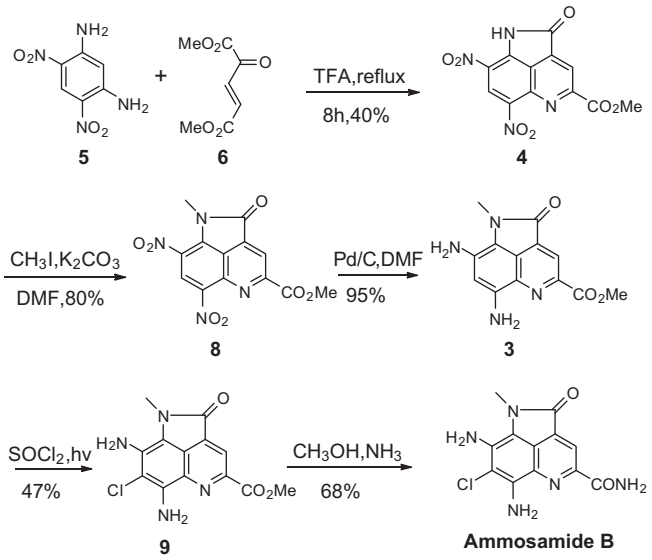

Scheme 2. The synthesis of Ammosamide B.

quinoline. To our delight, when we treated **5** with **6** in TFA under refluxed condition,[10] the expected tricyclic **4**[11]could be formed as a single product despite in moderate yield (40.3%).

With a reliable protocol established for the synthesis of functionalized tricyclic **4**, the synthesis was set into motion as outlined in Scheme 2. Treating **4** with iodomethane in the presence of K_2CO_3 furnished compound **8**[12] in high yield. Owing to the poor solubility, reduction of the nitro groups to diamine **3**[13] was carried out in the presence of Pd–C in DMF. The remainder test was to install chlorine substituent onto 1,3-dianiline. When we attempted to treat **3** with NCS, only decomposed products were found. The problem was finally solved by following Fenical's method.[3] Treating **3** in neat thionyl chloride under UV light (254 nm) afforded compound **9**[14] in 47% yield. Finally, Ammosamide B[15] was obtained after ammoniation of **9**.

In summary, we have developed a short and straightforward total synthesis of Ammosamide B, which features an efficient Doebner–Miller reaction. Although the yield of tricyclic pyrroloquinoline was moderate, the simplicity of the procedure as well as the ready availability of the starting materials makes it attractive. We are currently exploring the use of this methodology for other pyrroloquinoline alkaloids' synthesis.

Acknowledgment

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Supplementary data

Supplementary data (experimental details for the synthesis and characteristic data for key intermediates are provided. ^{1}H NMR and ^{13}C NMR spectra of compound **4**,**8**,**3**,**9** and synthetic Ammosamide B) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.022.

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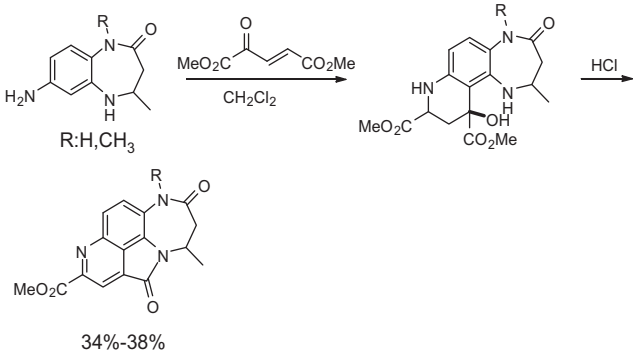

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11. *Experimental procedure*: A mixture of 1,3-diamin-6-dinitrobe nzene **5** (100 mg,0.51 mmol) and dimethyl 2-oxoglutaconate **6** (43.7 mg,0.25 mmol) in 20 ml TFA was refluxed for 8 h, after which TFA was chilled out for reuse.The residue was dissolved in methylene chloride (40 mL). The methylene chloride solution was washed with saturated aqueous $NaHCO_3$ and with brine, dried over anhydrous sodium sulfate, and evaporated to dryness. Compound **4** was isolated by flash chromatography on silica gel (160–200 mesh) with methylene chloride/ethyl acetate mixture (200:1, v/v) to yield a yellow solid (32 mg, 40.3%): mp >250 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.67 (s, 1H), 9.04 (s, 1H), 8.58 (s, 1H), 4.01 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 168.2, 163.9, 155.5, 142.2, 138.4, 138.0, 136.1, 126.1, 125.3, 124.7, 119.8, 53.5; MS (ESI) *m*/*z* 319 (M+H$^+$) HRMS calcd for $C_{12}H_7N_4O_7$ (M+H$^+$): 319.0309; fund: *m*/*z* 319.0308.
12. *Compound* **8**: ^{1}H NMR (300 MHz, DMSO) δ 9.02 (s, 1H), 8.63 (s, 1H), 4.01 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 167.0, 163.8, 155.0, 140.3, 138.6, 136.9, 134.8, 128.2, 127.6, 123.9, 119.8, 53.4, 30.2; MS (ESI) *m*/*z* 333 (M+H$^+$) HRMS calcd for $C_{13}H_9N_4O_7$ (M+H$^+$): 333.0466; found: *m*/*z* 333.0458.
13. *Compound* **3**: ^{1}H NMR (300 MHz, DMSO) δ 8.31 (s, 1H), 6.35 (br s, 2H), 6.23 (s, 1H), 6.02 (br s, 2H), 3.91 (s, 3H), 3.53 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 165.6, 163.4, 144.6, 139.9, 137.9, 133.9, 129.2, 120.8, 118.3, 105.7, 101.7, 52.3, 28.4; MS (ESI) *m*/*z* 273 (M+H$^+$) HRMS calcd for $C_{13}H_{13}N_4O_3$ (M+H$^+$): 273.0982; found: *m*/*z* 273.0984.
14. *Compound* **9**: ^{1}H NMR (300 MHz, DMSO) δ 8.37 (s, 1H), 6.33 (br s, 2H), 6.16 (br s, 2H), 3.93 (s, 3H), 3.59 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 165.2, 163.6, 141.6, 140.3, 133.1, 131.9, 130.2, 119.1, 118.5, 106.5, 105.4, 52.5, 28.6; MS (ESI) *m*/*z* 307 (M+H$^+$) HRMS calcd for $C_{13}H_{12}ClN_4O_3$ (M+H$^+$): 307.0592; found: *m*/*z* 307.0589.
15. *Synthetic ammosamide B* (**2**): ^{1}H NMR (300 MHz, DMSO) δ 8.89 (br s, 1H), 8.33 (s, 1H), 7.61 (br s, 1H), 6.69 (br s, 2H), 6.14 (br s, 2H), 3.58 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 166.2, 163.9, 144.7, 140.5, 132.4, 130.8, 130.6, 119.1, 115.3, 106.3, 104.6, 28.6; MS (ESI) *m*/*z* 292 (M+H$^+$) HRMS calcd for $C_{12}H_{11}ClN_5O_2$ (M+H$^+$): 292.0596; found: *m*/*z* 292.0603.