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First Total Synthesis of Bauerine C

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Abstract: The first total synthesis of Bauerine C, a unique indoloquinazoline alkoloid, has been achieved from readily available 2,3-dichloroaniline. The key step is the Japp–Klingmann condensation between 2,3-dichloroaniline and ethyl-2-acetyl-5-phthalimido pentanoate to get 3-[(2,3-dichlorophenyl)-hydrozono]-pipiridin-2-one, which cyclizes to 7,8-dichloro-2,3,4,9-tetrahydro-β-carbolin-1-one, which can be methylated by dimethyl sulphate to give 7,8-dichloro-9-methyl 2,3,4,9-tetrahydro-β-carbolin-1-one. This N-methyl derivative is then subjected to dehydrogenation with 2,3-dichloro-5,6-dicayano-1,4-benzoquinone (DDQ) to give the target compound Bauerine C.

Keywords: Bauerine C, cyclization, indoloquinazoline alkaloid, Japp–Klingmann condensation, methylation

INTRODUCTION

Three new chloro-containing β-carbolines, Bauerines A–C,[1] have been isolated from the terrestrial blue-green alga *Dichothrix baueriana*. These

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alkaloids show activity against herpes simplex virus type 2. The biological activity of Bauerine C has attracted considerable interest in its total synthesis. Bauerine C is an attractive target, exhibiting antiviral activity and cytotoxic activity. In connection with our ongoing interest in the total synthesis of β-carboline natural products, here we report the total synthesis of Bauerine C. To the best of our knowledge, this is the first report on total synthesis of Bauerine C. We report here a potentially significant route to Bauerine C, which is not only short but also experimentally simple, involving Japp–klingmann condensation as the key step.

During the course of our process research on Zolmitriptan,[2] we encounter 2,3,4,9-tetrahydro-1H-β-carboline-1-one as an impurity. The β-carboline derivatives that have various biological activities motivated us to explore this work further to synthesis different β-carboline derivatives. The β-carboline moiety is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities. β-Carbolines, conformationally constrained tryptamine analogs, are a fascinating and under-investigated class of compounds. It is worth mentioning that the basic skeleton present in our isolated compounds is interesting, as some biologically active compounds such as incasan,[3] canthin,[4a] manzamine,[4b] and rutecarpine[5] possess this skeleton. These can be prepared by this methodology, and we envisioned a short synthesis of β-carbolines (Figs 1 and 2).

RESULTS AND DISCUSSION

In the first instance, the readily available intermediate ethyl-2-acetyl-5-phthalimido pentanoate[6] on Japp–Klingmann reaction with a diazonium salt of dichloro aniline and hydrazine hydrate treatment gives **1** in moderate yield. We have followed the known and reported literature procedure for the

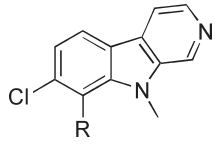


Figure 1. Bauerine A (R = H), Bauerine B (R = Cl).

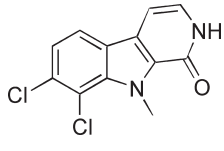


Figure 2. Bauerine C.

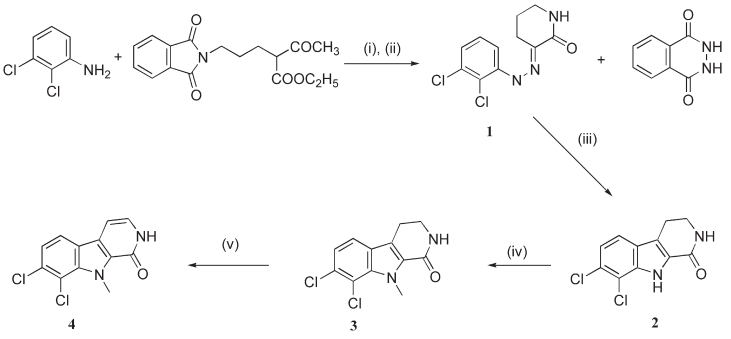
preparation of ethyl-2-acetyl-5-phthalimido pentanoate.[6] The cyclization using hydrazine hydrate in ethanol furnished the intermediate **1**, which was purified by column chromatography. Phthalyl hydrazide was the major by-product in this reaction. Compound **1**, on treatment with formic acid in toluene under reflux condition for 12 h, gives compound **2** in good yield. Alkylation has been tried with methyl iodide in presence of sodium hydride as a base but resulted in a dimethylated product. The reaction conditions were changed, and 7,8-dichloro-2,3,4,9-tetrahydro-1H-β-carbolin-1-one **2** was treated with dimethyl sulphate in the presence of sodium methoxide to give 7,8-dichloro-9-methyl-2,3,4,9-tetrahydro-1H-β-carbolin-1-one **3** in good yield. This was further dehydrogenated by DDQ in 1,4-dioxane at room temperature to give the crude Bauerine C, which was purified by column chromatography using a mixture of ethyl acetate and petroleum ether as eluent to give pure Bauerine C **4** in moderate yield. The spectroscopic data of Bauerine C are in agreement with those described in the literature.[1] The key reactions leading to total synthesis of Bauerine C are schematically shown in Scheme 1.

In conclusion, we report here the first concise total synthesis of Bauerine C. Our present approach is applicable to the synthesis of more β-carbolines targets. Several analogs of β-carbolines derivatives have been prepared and are currently undergoing biological studies. The synthesis and evaluation of the biological activities of Bauerine C analogs will be reported in due course.

EXPERIMENTAL

General Methods

^{1}H NMR spectra were determined in $CDCl_3$, and DMSO-d_6 solution on Varian Gemini 200-MHz spectrometers. Proton chemical shifts (δ) are relative to



Scheme 1. Reagents and conditions: (i) NaOAc/EtOH, $NaNO_2$, con. HCl; (ii) $NH_2NH_2 \cdot H_2O$/EtOH; (iii) HCOOH/toluene; (iv) $(CH_3)_2SO_4$, NaOMe, acetone; (v) DDQ, 1-4 dioxane.

tetramethylsilane (TMS, δ 0.00) as internal standard and expressed in parts per million (ppm). Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet). Coupling constants (J) are given in hertz. Melting points were determined using a scientific capillary melting-point apparatus and are uncorrected. Mass spectra were obtained on a HP-5989A mass spectrometer. Thin-layer chromatography (TLC) was performed on silica-gel plates (SRL 230–400 mesh). All the solvents used were commercially available and was distilled before use.

Preparation of 3-[(2,3-Dichlorophenyl)-hydrozono]-pipiridin-2-one (1)

Part A.

Ethyl 2-acetyl-5-phthalimidopentanoate (10.2 g, 0.0306 mmol) and ethanol (100 ml) were taken into a four-neck, round-bottom flask. To this, 20.6 g (8.3 mmol) of sodium acetate were added while stirring the mixture for 5 min; the resulting solution was then stirred at room temperature for 1 h.

Part B.

2,3-Dichloro aniline (5.0 g, 0.0306 mmol), 12.5 ml of ethanol, and 18.5 ml of water were taken into another four-neck, round-bottom flask, stirred, and cooled to 0°C. To this solution, 16.0 ml of concentrated hydrochloric acid were added during 30 min while stirring. The reaction mixture was allowed to stir at 0°C for 10 min. A freshly prepared solution of sodium nitrite [2.3 g, (1.1 mmol) in 10 ml water] was slowly added to the reaction mixture at 0–5°C and stirred for 30 min.

The part A reaction mass was cooled to 0°C, and part B reaction mass was added to this. The resulting mixture was stirred at room temperature for 3 h. After completion of the reaction (TLC), the mixture was extracted with dichloromethane, the organic layer was evaporated to dryness, and 25 ml of ethanol were added to the residue. The mixture was heated to reflux while ethanolic hydrochloric acid (10%) was added to the mixture at reflex. The reaction mixture was stirred for 2 h at reflux temperature. After completion of the reaction, the mixture was cooled to room temperature. The solid was filtered and washed with precooled ethanol to give 6 g of the intermediate, which was taken in 2.6 ml of ethanol. Hydrazine hydrate (2.6 g) was added. The resulting reaction mixture was stirred at 45°C for 2 h. After completion of the reaction, the mass was cooled to room temperature, and 2 ml of concentrated hydrochloric acid was added. The yellow solid was obtained, which was then purified by column chromatography using a mixture of ethyl acetate and pet. ether as an eluent to yield 2.2 g (26%) of compound **1**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 13.35 (s, 1H), 7.52 (d, 1H), 7.25 (t, 1H), 6.99 (d, 1H), 6.02 (s, 1H), 3.44 (d, 2H), 3.76 (d, 2H), 2.07 (m, 2H), MS (CI method)

271.8 (M + 1). Anal. calcd. for $C_{11}H_{11}Cl_2N_3O$ (271.03); C, 48.55; H, 40.72; N, 15.44. Found: C, 48.72; H, 40.82; N, 15.56. MS (CI method) 271.8 (M + 1).

Preparation of 7,8-Dichloro-2,3,4,9-dihydro-1H-β-carbolin-1-one (2)

3-[(2,3-Dichlorophenyl)-hydrozono]-pipiridin-2-one (1.0 g, 0.0036 mmol) and toluene (10 ml) were taken in a round-bottom flask, and formic acid (0.33 g, 0.0072 mmol) was added slowly to the reaction mixture. The reaction was heated to reflux and stirred for 12 h. The solvent was evaporated, the residue was neutralized with ammonia solution, and the resulting mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulphate and evaporated to give 0.48 g (52%) of compound **2**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.1 (s, 1H), 7.44 (d, 2H), 5.64 (s, 1H), 3.74 (t, 2H), 3.04 (t, 2H). Anal. calcd. for $C_{11}H_8Cl_2N_2O$ (254); C, 51.79; H, 3.16; N, 10.98. Found: C, 51.82; H, 3.26; N, 10.99. MS (CI method) 255 (M + 1).

Preparation of 7,8-Dichloro-9-methyl-2,3,4,9-tetrahydro-1H-β-carbolin-1-one (3)

Compound **2** (0.45 g, 0.0017 mmol), 50% solution of sodium hydroxide (2.0 ml), and 5.0 ml of methanol were taken in a round-bottom flask and stirred for 30 min at 60°C. The solvent was evaporated, 10 ml of acetone were added to the residue, and 120 mg (0.0019 mmol) of methyl sulfide were added slowly to this. The reaction mixture was heated to reflux and stirred at this temperature for 12 h. The reaction mass was evaporated and extracted with 20 ml of chloroform. The organic layer was washed with water, dried over sodium sulphate, and concentrated to dryness. The crude residue was then purified by column chromatography using a mixture of ethyl acetate and pet. ether as an eluent to yield 120 mg (37%) of compound **3**. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6) δ 7.45 (d, 1H), 7.23 (d, 1H), 7.12 (s, 1H), 4.50 (s, 3H), 3.61 (m, 2H), 2.98 (t, 2H). Anal. calcd. for $C_{11}H_8Cl_2N_2O$ (268): C, 53.55; H, 3.75; N, 10.41. Found: C, 53.62; H, 3.83; N, 10.63. MS (CI method) 269 (M + 1).

Preparation of 7,8-Dichloro-9-methyl-2,9-dihydro-1H-β-carbolin-1-one (4)

Compound **3** (0.100 g, 0.00037 mmol), 10 ml of 1,4-dioxane, and 0.253 g (0.0011 mmol) of DDQ were taken in a round-bottom flask and stirred at room temperature for 2 h. Ten ml of 10% sodium hydroxide solution were added to the reaction mass, stirred for 30 min, and extracted with 20 ml of

chloroform. The organic layer was washed with water, dried over sodium sulphate, and concentrated. The residue was purified by column chromatography using a mixture of ethyl acetate–pet. ether as an eluent to yield 0.060 g (61%) of compound **4**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (s, 1H), 7.82 (d, 1H), 7.80 (s, 1H), 7.31 (d, 1H), 7.04 (s, 1H), 6.84 (d, 1H), 4.72 (s, 3H). Anal. calcd. for $C_{12}H_8Cl_2N_2O$ (266.11); C, 53.96; H, 3.02; N, 10.49. Found: C, 53.98; H, 3.10; N, 10.52. MS (CI method) 267 (M + 1).

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