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Communication

Total Synthesis of Bouchardatine

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Two new, efficient and simple routes using Heck-type reaction and intramolecular cyclization were developed for the synthesis of the naturally occurring cytotoxic alkaloid 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-1*H*-indole-3-carbaldehyde (bouchardatine).

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Bouchardatine (**1**) (Fig. 1) is a naturally occurring alkaloid from the rutaecarpine family. It is a quinazoline type of alkaloid which was isolated[1] from the aerial parts of *Bouchardatia neurococca* (Rutaecae). It structurally resembles rutaecarpine (**2**) which was isolated from *Evodia rutaecarpa* and shows numerous biological activities.[2] Bouchardatine is known[3] to possess cytotoxic activity against HeLa cells.

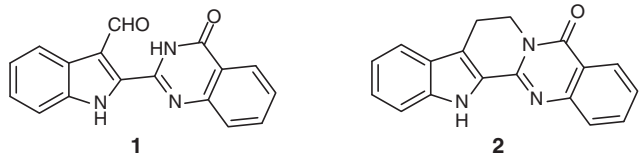
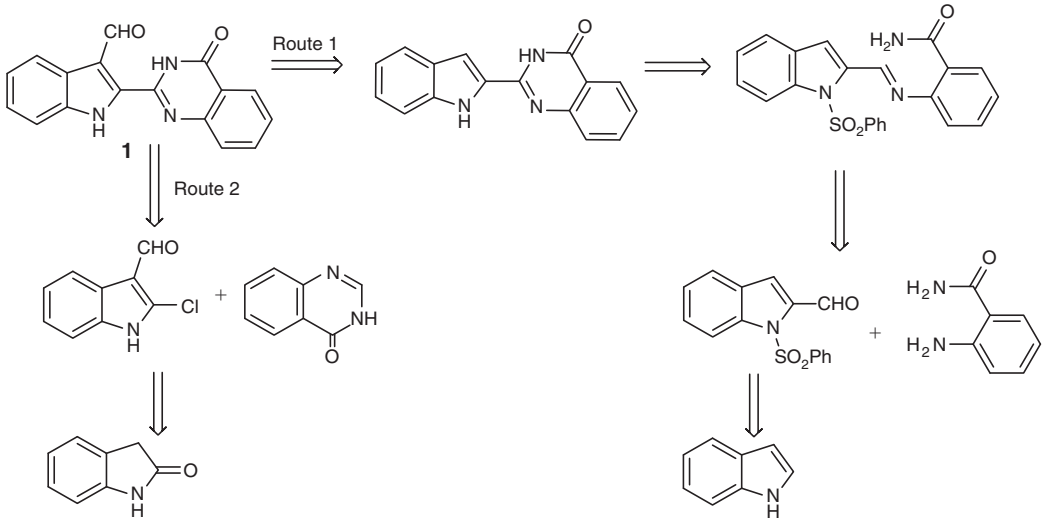


Fig. 1. Structure of bouchardatine **1** and rutaecarpine **2**.

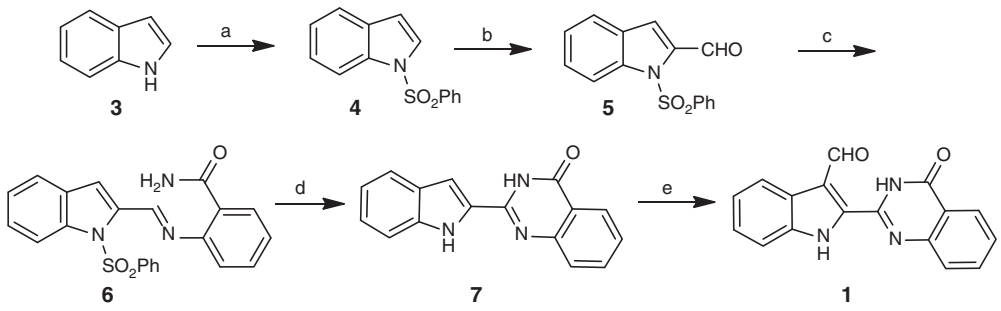
Many methods have been reported so far for the synthesis of rutaecarpine and its analogues.[4] However, to the best of our knowledge, to date only one report[3] is available for the synthesis of bouchardatine. Herein, we report two new efficient and simple strategies for the synthesis of bouchardatine involving a Heck-type reaction and an intramolecular cyclization reaction.

The synthesis of bouchardatine was envisaged as shown by the retrosynthetic analysis (Scheme 1).

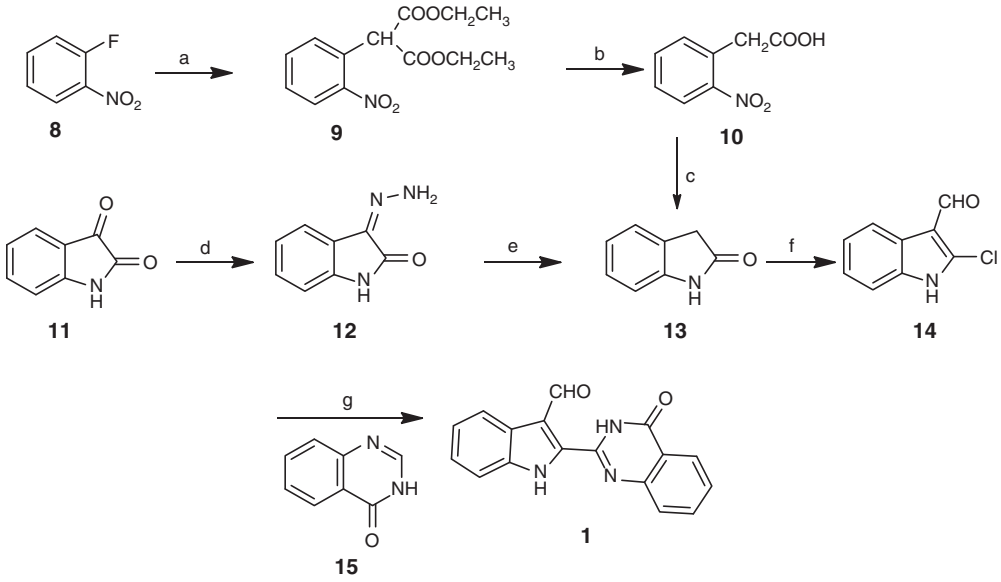
In the first approach, bouchardatine was synthesised from the simple starting material, indole (Scheme 1, route 1). Indole was initially protected using benzenesulfonyl chloride and further formylated at the 2-position in presence of lithium diisopropylamide (LDA) and DMF to get 1-(phenylsulfonyl)-*1H*-indole-2-carbaldehyde **5**.[5] Subsequent Schiff base formation using anthranilamide furnished imine **6**. Intramolecular cyclization



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: a) KOH, DMSO, $PhSO_2Cl$, rt, 5 h, 97 %; b) LDA, DMF, THF, −78°C to rt, 4 h, 85 %; c) anthranilamide, CH_3COOH, 80°C, 30 min, 95 %; d) *t*-BuOK, *t*-BuOH, 85°C, 6 h, 82 %; e) DMF, $POCl_3$, 0°C, 24 h, 87 %.



Scheme 3. Reagents and conditions: a) diethyl malonate, K_2CO_3, DMF, 100°C, 3h, 98 %; b) 6 N HCl, rt, 12 h, 90 %; c) H_2, Pd/C, AcOH, rt, 4 h, 88 %; d) $NH_2NH_2.H_2O$, ethanol, 80°C, 1 h, 97 %; e) 10 % NaOH, ethanol, 80°C, 3 h, 85 %; f) DMF, $POCl_3$, CH_2Cl_2, 0°C to rt, 38 h, 70 %; g) K_2CO_3, $Pd(OAc)_2$, PPh_3, DMF, 120°C, 12 h, 68 %.

along with dehydrogenation and deprotection of the benzenesulfonyl group was achieved using sodium methoxide to furnish compound **7** in 40 % yield over 12 h as shown in Scheme 2. The reaction was optimized using potassium *tert*-butoxide in *t*-butanol which resulted in better yield as well as reduced reaction time (82 %, 6 h). In the final step, Vilsmeier-Haack formylation of product **7** furnished target molecule bouchardatine **1** in 56 % overall yield. The spectral data of **1** were consistent with the reported[3] values.

To design another route for bouchardatine, a Heck-type reaction was envisioned as the key step in a convergent synthetic scheme as shown in the retrosynthetic analysis (Scheme 1, route 2). One of the scaffolds, 2-indolinone **13** was synthesized[6] in three steps starting with the reaction of 1-fluoro-2-nitrobenzene with diethylmalonate to produce diethyl 2-(2-nitrophenyl) malonate **9** in 98 % yield. Subsequent hydrolysis and decarboxylation in 6 N HCl furnished carboxylic acid **10** in good yield and further reductive cyclization of carboxylic acid **10** resulted in the formation of 2-indolinone (**13**). Alternatively, Wolff–Kishner reduction[7] of commercially available isatin **11** also furnished compound **13** as shown in Scheme 3. The conversion of 2-indolinone to 2-chloro-1*H*-indole-3-carbaldehyde **14** was achieved[8] using Vilsmeier conditions. The other component required for the convergent synthesis of the target molecule was quinazolinone **15** which was prepared[9] by a reaction between anthranilamide and formamide in acetic acid. In the final step, palladium catalyzed intermolecular Heck type reaction between 2-chloro-1*H*-indole-3-carbaldehyde (**14**) and quinazolin-4(3*H*)-one (**15**) in the presence of triphenyl phosphine and potassium carbonate completed route 2 for the synthesis of bouchardatine **1**.

In summary, two new, simple and efficient routes were developed for the synthesis of the cytotoxic natural product bouchardatine with good overall yield.

Experimental

General

Melting points determined are uncorrected. All solvents used were of reagent grade and, when necessary, were purified and dried by standard methods. Reactions and products were routinely monitored by thin layer chromatography on silica gel (Kieselgel 60 F254, Merck). Column chromatographic purifications were performed using 100–200 mesh silica gel. Fourier transform infrared (FTIR) spectra were recorded on a Nicolet 5700 instrument by attenuated total reflectance (ATR). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Mercury instrument using TMS as an internal standard. ^{1}H NMR peaks expressed as s, br s, d, t, and m correspond to

singlet, broad singlet, doublet, triplet, and multiplet, respectively. Mass spectra (MS) were recorded on a PerkinElmer Clarus500 instrument. High resolution MS were obtained on a Micromass Q-TOF apparatus. Gas chromatography-mass spectrometry (GCMS) electron impact (EI) data were obtained on a PerkinElmer Clarus500 instrument at 70 eV.

Synthesis

*2-(((1-(Phenylsulfonyl)-1*H*-indol-2-yl)methylene)amino) benzamide* ***6***

To a solution of *N*-protected indole-2-carbaldehyde (0.5 g, 1.7 mmol) in acetic acid (5 mL) was added anthranilamide (0.2 g, 1.7 mmol) at room temperature. The mixture was then heated at 80°C for 30 min. Product was filtered and washed with excess water to give imine **6** (0.67 g, 95 %) as a white solid. Mp 258–260°C. ν_{max}(ATR)/cm^{-1} 3371, 3226, 1653, 1607, 1498, 1366. ^{1}H NMR (300 MHz, [D$_6$]DMSO) δ 6.53 (s, 1H, C*H*), 6.67–6.71 (m, 2H, N*H*), 6.89 (d, 1H, *J* 8.1 Hz, Ar*H*), 7.10 (s, 1H, Ar*H*), 7.15–7.32 (m, 3H, Ar*H*), 7.51–7.57 (m, 3H, Ar*H*), 7.64–7.69 (m, 2H, Ar*H*), 7.88–7.96 (m, 3H, Ar*H*), 8.42 (s, 1H, N*H*). ^{13}C NMR (75 MHz, [D$_6$]DMSO) δ 163.2, 145.6, 141.4, 136.6, 136.5, 134.6, 133.4, 129.6, 128.5, 127.1, 126.4, 125.2, 124.1, 121.6, 117.5, 115.3, 114.5, 114.3, 111.6. *m/z* (HR-MS ESI) 404.1075; [M+H]$^+$ requires 404.10689.

*2-(1*H*-Indol-2-yl)quinazolin-4(3*H*)-one* ***7***

Potassium *tert*-butoxide (0.4 g, 3.7 mmol) was added to a solution of imine **6** (0.5 g, 1.2 mmol) in 2 mL dry *tert*-butanol and the reaction was heated at reflux for 6 h. The progress of the reaction was monitored by TLC. After completion of reaction, solvent was evaporated and the contents were poured on crushed ice and extracted with ethyl acetate (3 × 20 mL).The organic layer was dried over sodium sulfate and concentrated under vacuum. Subsequently, the product was purified by column chromatography (ethyl acetate : hexane, 3 : 7) to get compound **7** (0.26 g, 82 %) as a white solid. Mp above 300°C, (lit. 319-320°C[10]). ν_{max}(ATR)/cm^{-1} 3417, 3357, 1670, 1592, 1466. ^{1}H NMR (300 MHz, [D$_6$]DMSO) δ 7.06 (t, 1H, *J* 7.6 Hz, Ar*H*), 7.23 (t, 1H, *J* 8.1 Hz, Ar*H*), 7.48–7.54 (m, 2H, Ar*H*), 7.62–7.66 (m, 2H, Ar*H*), 7.73 (d, 1H, *J* 8.1 Hz, Ar*H*), 7.85 (t, 1H, *J* 8.1 Hz, Ar*H*), 8.14 (d, 1H, *J* 7.6 Hz, Ar*H*), 11.80 (s, 1H, N*H*), 12.62 (s, 1H, N*H*). ^{13}C NMR (75 MHz, [D$_6$]DMSO) δ 161.7, 148.6, 146.5, 137.6, 134.6, 129.9, 127.4, 126.8, 126.2, 126.0, 124.0, 121.4, 121.1, 119.9, 112.3, 104.9. *m/z* (EI) 261 [100 %, (M)$^{+\bullet}$], 142 (10), 119 (70), 92 (20).

*2-(4-Oxo-3,4-dihydroquinazolin-2-yl)-1*H*-indole-3-carbaldehyde* ***1***

2-Chloro-1*H*-indole-3-carbaldehyde **14** (0.5 g, 2.7 mmol) and quinazolin-4(3*H*)-one **15** (0.4 g, 2.7 mmol) in dry DMF were placed in a two-necked round bottom flask fitted with a reflux condenser. Palladium acetate (0.06 g, 10 mol-%), triphenyl phosphine (0.21 g, 30 mol-%), and potassium carbonate (0.46 g, 3.3 mmol) were then added to the above reaction mixture. The contents were heated at 120°C for 12 h under nitrogen atmosphere. After completion of reaction, the mixture was filtered over Celite through a sintered funnel. Water was then added to the filtrate and the product was extracted with ethyl acetate (3 × 20 mL). Concentration of solvent under vacuum and purification by column chromatography (1 : 9, ethyl acetate : hexane) provided bouchardatine (**1**) as an off white solid (0.55 g, 68 %). Mp: 255 −257°C (lit. > 260°C[3]). ν_{max}(ATR)/cm^{-1} 3051, 2922, 2852, 1693, 1665, 1607, 1572, 1437, 1188. ^{1}H NMR (300 MHz, [D$_6$]DMSO) δ 7.17 −7.2 (m, 2H, Ar*H*), 7.35 (t, 1H, *J* 7.1 Hz, Ar*H*), 7.60–7.65 (m, 2H, Ar*H*), 7.83 (d, 1H, *J* 7.1 Hz, Ar*H*), 8.01 (m, 2H, Ar*H*), 10.13 (s, 1H, C*H*O), 11.69 (s, 1H, N*H*), 12.35 (s, 1H, N*H*). ^{13}C NMR (75 MHz, [D$_6$]DMSO) δ 184.1, 166.5, 160.4, 142.7, 138.5, 135.8, 133.2, 129.5, 129.0, 124.8, 124.4, 123.8, 123.4, 122.8, 120.2, 118.5, 112.5. *m/z* (EI) 289 [3 %, (M)$^{+\bullet}$], 261 (2), 144 (100), 130 (20), 102 (30), 76 (20).

Supplementary Material

The ^{1}H and ^{13}C NMR spectra of compounds **6**, **7** and **1** are available on the Journal's website.

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