Synthetic study towards (+)-vertine and (+)-lythrine：synthesis of the intermediate of benzyl-2-(1-methoxy-1,3-dioxobutan-2-yl)piperidine-1-carboxylate

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Abstract. Synthetic study of the intermediate of (+) - vertine and (+) - lythrine, benzyl – 2 - (1 – methoxy - 1,3- dioxobutan -2 –yl) piperidine -1- carboxylate was described, which included protection, reduction and addition of silyl enol ether.

Introduction

In 1962, a series of phenylquinolizidinine alkaloids were isolated from a flowering plant in the Lythraceae family by Ferris and co-workers, which was named Decodon verticillatus, commonly known as water willow or swamp loosestrife and endemic to wetlands in the eastern half of the United States. Vertine and lythrine (shown in Figure 1) are two of the most studied alkaloids of this family. Vertine and lythrine was explored to possess a wide range of biological activities such as antiinflammatory, sedative, and antispasmodic actions. Till now, Laetitia Chausset-Boissarie and co-workers reported the synthesis of (±)-vertine and they also described the synthesis of (+)-vertine and the first total synthesis of (+)-lythrine [1, 2]. Herein, we described the intermediate of vertine and lythrine, benzyl-2-(1-methoxy-1,3-dioxobutan-2-yl)piperidine-1-carboxylate.

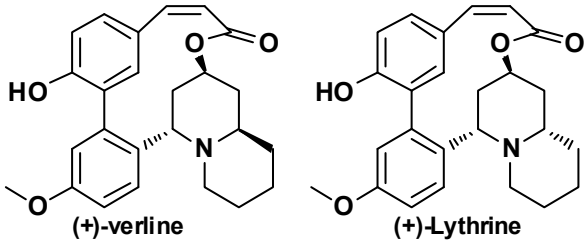
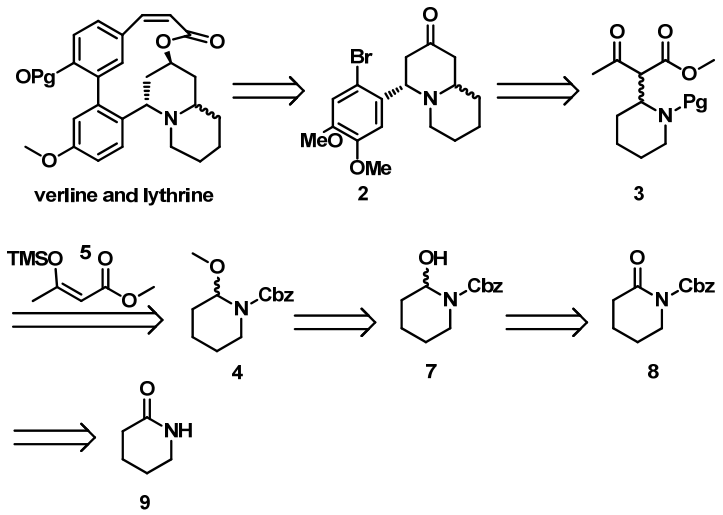


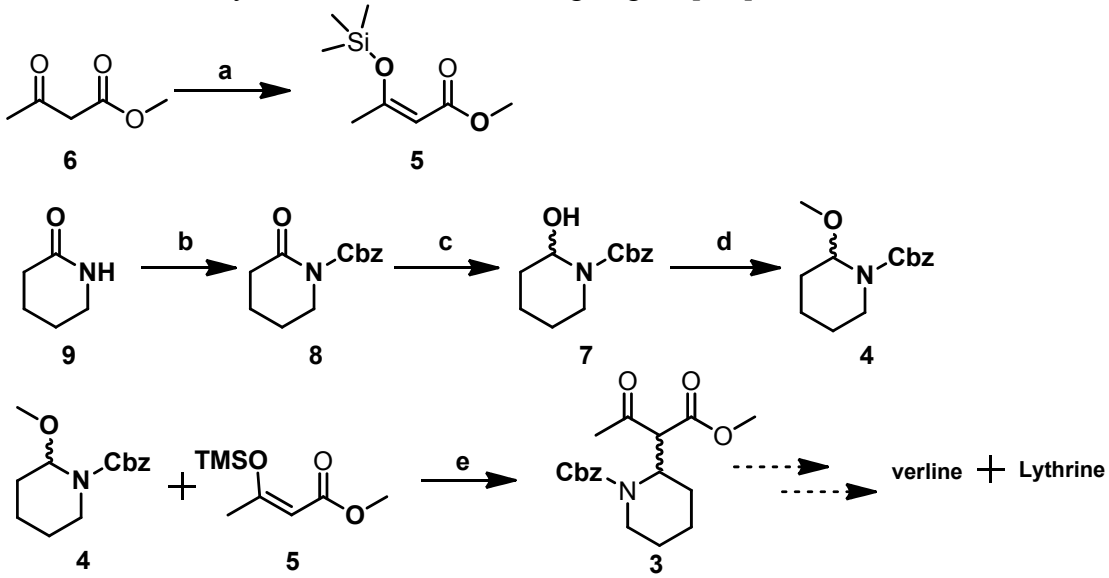
Figure 1 Structure of verline and lythrine.

Our retrosynthetic analysis of verline and lythrine is displayed in Scheme 1. In our retroynthetic analysis, we devised that the target molecule, Vertine and Lythrine, could be achieved from **2** with few steps. Compound 2 was designed to get from β-keto ester **3**. **3** was disconnected to compound **4** and sily enol ether **5**, and the later was devised to be obtained from amide **9**. Herein, we described the synthetic study of the intermediate benzyl-2-(1-methoxy-1,3-dioxobutan-2-yl) piperidine-1-carboxylate **3**.



Scheme 1 Restrosynthetic analysis of 1 (verline and lythrine).

The detailed synthetic route of **3** is show in Scheme 2 [3,4]. The synthesis of compound **3** was commenced from amide **9**. **9** was subjected to protection with CbzCl to give **8** [5,6]. Then **8** underwent DIBAL-H reduction another protection with methyl group to give 4. In parallel, silyl enol ether **5** was obtained from acetacetic ester **6**. With compound **6** in hand, it was subjected to addition with prepared **5** to give the desiredβ-keto ester **3**. The study efforts towards the total synthesis of vertine and lythrine based on **3** is now going on [7-8].



Reagent and condition: (a) Et_3N, TMSCl, THF/hexane, rt; (b) Boc_2O, DMAP, Et_3N, CH_2Cl_2, rt; (c) DIBAL-H, CH_2Cl_2, -78℃; (d) *p*-TsOH, CH_3OH, reflux; (e) TMSOTf, -78℃, CH_2Cl_2

Scheme 2 Synthesis of benzyl-2-(1-methoxy-1,3-dioxobutan-2-yl)piperidine-1-carboxylate.

Experimental

NMR spectra were recorded on Bruker AV-400MHz spectrometers. The solvents and reagents were purified and dried according to standard procedures: CH_2Cl_2 were distilled from CaH_2 prior to use.

Methyl 3-((trimethylsilyl)oxy)but-2-enoate 5

182.21 g (1.4 mol) of ethyl acetoacetate and 169.98 g (1.4 mol) of triethylamine were dissolved in a mixed solvent of 182 mL of tetrahydrofuran and 1.64 L of hexane under nitrogen atmosphere. To this solution, 167.3 g (1.54 mol) of trimethylsilyl chloride was added dropwise at a temperature of 21 to 45°C, and then the solution was stirred at 25°C for 3 hours. The reaction mixture was cooled to 10°C, the reaction was ceased by adding 547 mL of water thereto and an organic layer was separated. The organic layer was washed two times with 273 mL of water, dried over 54.7 g of

anhydrous magnesium sulfate, and then filtered. The solvent was evaporated to obtain 301.3 g (crude yield 106.4percent) of 3-(trimethylsilyloxy) but-2-enoic acid ethyl ester.^{1}H NMR ($CDCl_3$): δ 0.17 (s, 9H), 2.17 (s, 3H), 3.56 (s, 3H), 5.04 (s, 1H).

Benzyl 2-oxopiperidine-1-carboxylate 8

To a solution of 4 g (100 mmol) of NaH (60%) in 200 ml of THF was added 9.91 g (100 mmol) of piperidin-2-one **9** with stirring under 0ºC, and the mixture was further stirred at room temperature for 1 hour until H_2 gas ceased to evolve. The reaction solution was added to a solution of 1.61 g (103 mmol) of phenyl chloroformate in 100 ml of THF cooled at -60°C. and then stirred at room temperature for 4 hour. The reaction solution was poured into ice water, and then extracted with ethyl acetate. After drying, the solvent was removed by evaporation and the residue was purified by silica gel chromatography to afford **8** as the colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.65 (t, 2H), 2.50 (t, 2H), 1.82 (m, 4H), 1.52 (s, 9H).

Benzyl 2-hydroxypiperidine-1-carboxylate 7

To a stirred solution of **8** (2.82g, 12 mmol) in CH_2Cl_2 (60 mL) at -78°C, DIBAL-H (4.02 mL, 24 mmol) was added dropwise and the mixture was stirred at -78°C for 2 hour. The reaction was then quenched by the addition of 10 mL of MeOH and the mixture was allowed to warm up to room temperature. Then Rochelle's salt solution (15 mL) was added and the mixture was stirred vigorously for another 3 hour. The aqueous phase was then separated and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography to give **7** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4 H), 2.50 (m, 2 H), 3.70 (m, 2 H,), 5.26 (s, 2 H), 7.24–7.50 (m, 5 H);

Benzyl 2-methoxypiperidine-1-carboxylate 4

To a solution of benzyl 2-hydroxypiperidine-1-carboxylate **7** (2.36 g,10 mmol) in MeOH (35 mL), *p*-toluenesulfonic acid monohydrate (0.2g, 1 mmol) was added in one portion and the mixture was refluxed for 4 hours. After the reaction completed, the mixture was concentrated under reduced pressure and then extracted with ethyl acetate. Then it was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution. Subsequently, the organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give *tert*-butyl 2-methoxypiperidine-1-carboxylate **4**. ^{1}H NMR ($CDCl_3$) δ 1.25-2.03 (m, 6H), 2.98 (q, 1H), 3.18(s, 1.5 H), 3.25 (s, 1.5 H), 3.98 (t, 1H), 5.16 (m,2H), 5.34 (s, 0.5H), 5.43 (s, 0.5H), 7.26-7.60 (m, 5H).

Benzyl 2-(1-methoxy-1,3-dioxobutan-2-yl)piperidine-1-carboxylate 3

To a solution of **4** (49.0 mg, 0.208mmol) in 1.0 mL of CH_2C1_2 were added at -78°C methyl-3-trimethylsiloxy-2-butenoate **5** (50 μL, 0.26 mmol) and TMSOTf (42 μL, 0.23 mmol), and the mixture was stirred at -78 ^{o}C for 1 hour. After warming to room temperature, the mixture was stirred for an additional 45 min, poured out into a saturated aqueous solution of $NaHCO_3$ (4 mL) and extracted with CH_2C1_2 (4 times 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:1) afforded 9 (66.6mg,0.208 mmol, 100%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 1.25-1.75 (m, 4H), 2.05-2.5 (d, 3H), 2.75-3.10 (m, 1H), 3.75 (s, 3H), 3.85-4.20 (m, 2H), 5.0-5.5 (m, 3H), 7.28-7.45 (m, 5H).

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