Synthetic Study towards (±)-Vertine and (±)-Lythrine

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Abstract. A synthetic design of (±)vertine and (±)-lythrine was described, and the intermediate, N-protected 2-methoxypiperidine, was synthesized, which contains a protection, reduction and etherification.

Introduction

In 1962, Ferris and co-workers had isolated phenylquinolizidinine alkaloids from a flowering plant in the Lythraceae family, Decodon verticillatus, which was commonly existed in United States. Later, Schwarting and co-workers examined Heimia salicifolia and other Heimia species. Vertine and Lythrine (**Figure 1.**) are two of the most studied alkaloids of this family. They had a wide range of biological activities such as sedative, antispasmodic and anti-inflammatory activities. They also played an important role in regulation of glucose level in blood and lower blood pressure. It has a strained 12-membered ring with three stereogenic centers, two of which are part of the macrocycle and an induced chiral biaryl axis. All of these synthetical challenges attracted scientists' interest. In the 2012, Laetitia Chausset-Boissarie and co-workers described the synthesis of (+)-vertine and the first total synthesis of (+)-lythrine[1,2].

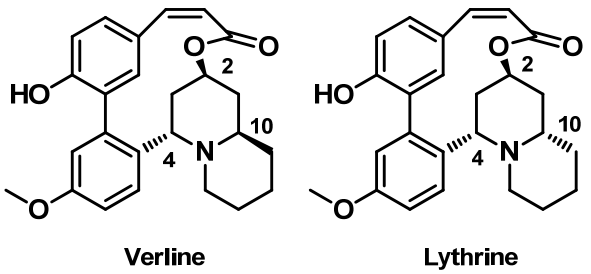
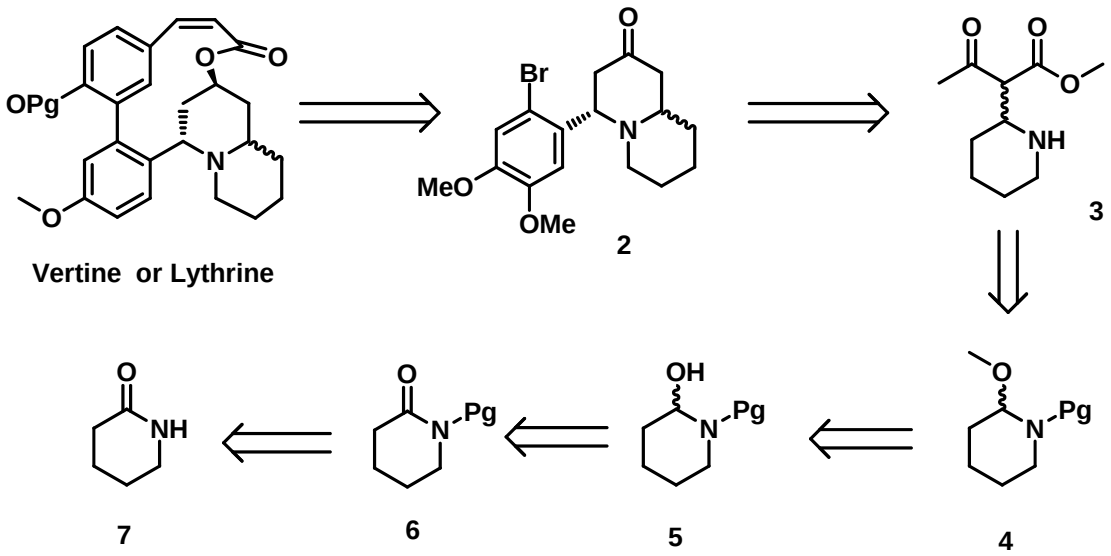


Figure 1. Structure of Vertine and Lythrine

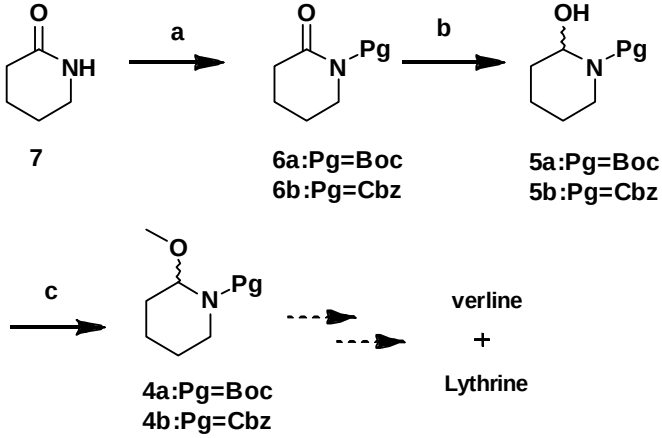
Our retrosynthetic analysis of Vertine and Lythrine is displayed in **Scheme 1.**



Scheme 1. Our retrosynthetic analysis of Vertine and Lythrine

In our retroynthetic analysis, we hypothesized that Vertine and Lythrine could be achieved from intermediate **2** via few steps. Compound **2** was designed to be prepared from β-keto ester **3**, and **3** could be obtained from compound **4** which was designed to be converted from commercial amide **7** through few steps. In this paper we just report our present synthetic work about the intermediate of 2-methoxypiperidine **4**.

The detailed synthetic route of **4** is show in **Scheme 2** [3,4]. We conducted a protection of the nitrogen with Boc_2O[5,6] and CbzCl[7, 8] to give compound **6a** and **6b**, which underwent a reduction and etherification to give the intermediate **4a** and **4b**. Our future work towards the total synthesis of Vertine and Lythrine would be going on based on **4a** and **4b**.



(a) Boc_2O, DMAP, Et_3N, CH_2Cl_2 , rt; (b) DIBAL-H, CH_2Cl_2, -78℃; (c) *p*-TsOH, CH_3OH, reflux;

Scheme 2. Our retrosynthetic route of Vertine and Lythrine

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.

***tert*-butyl 2-oxopiperidine-1-carboxylate 6a**

To a solution of piperidin-2-one **7** (5g, 50.4 mmol) in CH_2Cl_2 (150 mL) were added DMAP (6.16 g, 50.4 mmol), Et_3N (7 mL, 50.4 mmol), Boc_2O (2.2 g, 100.8 mmol) at 0℃. The reaction was then stirred at room temperature for 12 h. After that, the solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography to afford **6a** as the colorless oil. NMR: ^1H NMR ($CDCl_3$) δ 3.67-3.64(m,2H), 2.52-2.49(m,2H), 1.86-1.78(m ,4H),1.53 (s, 9H).

***tert*-butyl 2-hydroxypiperidine-1-carboxylate 5a**

To a stirred solution of **6a** (1.55g, 7.76 mmol) in CH_2Cl_2 (60 mL) at -78 °C., DIBAL-H (2.87 mL,

16.1 mmol) in 10 mL of CH_2Cl_2 was added dropwise and the mixture was stirred at -78 °C for 2 h. The reaction was then quenched by the addition of 10 mL of MeOH and the mixture was allowed to warm up room temperature. Then, Rochelle's salt solution (15 mL) were added, and the mixture was stirred vigorously for another 3 h. 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 **5a** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9 H), 1.79 (m, 4 H), 2.48 (m, 2 H), 3.63 (m, 2 H).

***tert*-butyl 2-methoxypiperidine-1-carboxylate 4a**

To a solution of *tert*-butyl 2-hydroxypiperidine-1-carboxylate **5a** (1.41 g, 7.0 mmol) in MeOH (35 mL), *p*-toluenesulfonic acid monohydrate (0.13 g, 0.70 mmol) was added in one portion and the mixture was refluxed for 4 hours. After TLC monitored the **5a** was completely consumed, the reaction mixture was cooled to room temperature and removed the solvent under reduced pressure and then extracted with ethyl acetate. After being washed with saturated sodium bicarbonate solution and the saturated sodium chloride solution, the organic layer was dried with anhydrous magnesium sulfate. Subsequently, the organic layer was concentrated under reduced pressure, the residue was purified by silica gel column chromatography to afford *tert*-butyl 2-methoxypiperidine-1-carboxylate **4a**.^{1}H NMR δ 1.47 (s, 9H), 1.59–1.68 (m, 2H), 1.71–1.79 (m, 2H), 1.82–1.84 (m, 2H) , 3.21 (s, 3H), 3.79–3.91 (m, 2H), 5.23 (m,1H).

benzyl 2-oxopiperidine-1-carboxylate 6b

To a solution of 7.36 g (184 mmol) of NaH (60%) in 200 ml of THF was added 18.24 g (184 mmol) of piperidin-2-one **7** with stirring under ice-cooling, and further the mixture was stirred at room temperature for 1 hr. until H2 gas ceased to evolve. The reaction solution was added to a solution of 29.7 g (190 mmol) of phenyl chloroformate in 100 ml of THF cooled at -60° C. and then stirred at room temperature for 4 hr. 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 **6b** as the colorless oil. ^{1}H NMR($CDCl_3$): δ3.65 (t, 2H), 2.50 (t, 2H), 1.82 (m, 4H), 1.52 (s, 9H).

benzyl 2-hydroxypiperidine-1-carboxylate 5b

To a stirred solution of **6b**(1.41g, 6 mmol) in CH_2Cl_2 (60 mL) at -78° C, DIBAL-H (2.01 mL, 12 mmol) was added dropwise and the mixture was stirred at -78° C for 2 h. 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 h. 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 **5b** 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 4b

To a solution of benzyl 2-hydroxypiperidine-1-carboxylate **5b** (1.18 g,5.0 mmol) in MeOH (35 mL), *p*-toluenesulfonic acid monohydrate (0.1g, 0.50 mmol) was added in one portion and the mixture was refluxed for 4 hours. After the reaction finished, 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, the residue was purified by silica gel column chromatography to give *tert*-butyl 2-methoxypiperidine-1-carboxylate **4b**. ; ^{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)

Acknowledgement

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