A Short Path to Erythrina Alkaloid Derivatives

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Erythrina alkaloids which display a variety of biological activity including hypnotic and CNS activity\textsuperscript{1} have drawn attraction for the synthesis over the years. Some of the recent strategies on the construction of the core spirocyclic structure include intramolecular cyclization reactions such as radical cyclizations,\textsuperscript{2} electrophilic substitution cyclizations on N-acyliminium intermediates or Pummerer-induced cyclizations,\textsuperscript{3} Heck reactions,\textsuperscript{4} and anionic substitution reactions.\textsuperscript{5}

A few years ago, we developed a new route to the spirocyclic skeleton by palladium-catalyzed arylation of α,β-unsaturated γ-lactam.\textsuperscript{6} In the route, the precursors for cyclization have been prepared by condensation of arylamine and keto-ester intermediates\textsuperscript{6} under reflux in toluene in the presence of TsOH (Scheme 1).\textsuperscript{6,7}

For the synthetic application of this method toward erythrina alkaloids, we wanted to reinvestigate the palladium catalyzed cyclization of the requisite precursor which would be formed from the condensation of ketoester 1 and bromo-arylamine 2. In the reaction, two main products were formed as shown in the Scheme 2, and the separated yields were 34\% of compound 3 and 18\% of compound 4. For the selective formation of each isomer, we have tried the cyclization reaction under different conditions by changing solvent, catalyst, and temperature. However, the ratio did not shift favorably for the purpose, so we considered that we had better find ways to transform each isomer to proper natural products or derivatives. It was envisioned that major intermediate 3 would be a proper precursor for erysotramidine and the minor intermediate 4 for iso-13-demethoxyerythratidinone (Scheme 2).

When the intermediate 3 was treated with Pd(OAc)\textsubscript{2} in DBU, enol intermediate was formed in 30\% yield through γ-lactam enolate formation followed by cyclization. Some amount of the corresponding ketal compound, the precursor of the enol intermediate, could be obtained if the reaction process was quenched earlier. However, the ketal intermediate was found to be reluctant to hydrolyse to ketone. Treatment of 5 with

![Figure 1](image-url)

**Figure 1**

![Scheme 1](image-url)

**Scheme 1**

![Scheme 2](image-url)

**Scheme 2**

![Scheme 3](image-url)

**Scheme 3**. Reagents and conditions (a) Pd(OAc)\textsubscript{2}, DBU, 140 °C, 15 h, 30\%; (b) TsOH, acetone, reflux, 6 h, 71\%; (c) NaBH\textsubscript{4}, CeCl\textsubscript{3}·7H\textsubscript{2}O, MeOH, 3 h, dr 2.6:1; (d) POCl\textsubscript{3}, DBU, CH\textsubscript{3}Cl, 3 h, 64\% (2 steps)

![Scheme 4](image-url)

**Scheme 4**. Reagents and conditions (a) Pd(OAc)\textsubscript{2}, PPh\textsubscript{3}, DBU, 140 °C, 15 h, 87\%; (b) LiAlH\textsubscript{4}·AlCl\textsubscript{3}, THF; (c) TsOH, acetone, 80 °C, 2 h, 80\% (2 steps)
TsOH in acetic anhydride afforded compound 6 in 71% yield. Reduction of the carbonyl compound 6 under Luche condition, affording a mixture of diastereomers in 2.6 : 1 ratio, was followed by elimination to afford the known intermediate 7 for eryosotramine in 64% yield (Scheme 3).

Meanwhile, intermediate 4 was subjected to the conventional Heck reaction, yielding the 6-membered quaternary structure 8 in 87% yield rather than 7-membered ring compound. Reduction of the amide group of 8 by LAH/AlCl₃ to amine was followed by deprotection of ketal under acid to iso-13-demethoxyerythradiatidine in 80% in two steps.

In conclusion, we have prepared two intermediates from condensation of compound 1 and 2, and suggested concise routes to the synthesis of eryosotramidine and iso-13-demethoxyerythradiatidine through Pd-mediated cyclization of the intermediates.

Experimental Section

1'-[(2-Bromo-4,5-dimethoxyphenethyl)-1',6',7',7a'-tetrahydro-9-spiro[1,3]dioxolane-2,5'-indol-2'-4(4'H)-one (3) and 1'-[(2-bromo-4,5-dimethoxyphenethyl)-3',4',4,6'-tetrahydro-9-spiro[1,3]dioxolane-2,5'-indol-2'-4(1'H)-one (4). To a solution of 1 (2 g, 8.25 mmol) in anhydrous toluene (30 mL) were added TsOH (314 mg, 1.65 mmol) and 2-(2-bromo-4,5-dimethoxyphenethyl)ethanamine (2.36 g, 9.08 mmol). The reaction mixture was refluxed for 15 h using Dean-Stark trap. The solvent was evaporated under reduced pressure and the resultant crude material was purified by silica gel column chromatography with n-hexane/EtOAc (1:1 to 1:3), EtOAc 100% and the resultant crude acetate was observed by silica gel column chromatography (EtOAc/MeOH 20:1) to give 3 (2.23 g, 34%) and 4 (651 mg, 18%).

**Compound 3:** H-NMR (400 MHz, CDCl₃) δ 6.99 (1H, s), 6.76 (1H, s), 4.91 (1H, m), 4.06-3.92 (4H, m), 3.86 (3H, s, OMe), 3.85 (3H, s, OMe), 3.76 (1H, m), 3.50 (1H, m), 3.15-2.82 (3H, m), 2.58 (1H, dd, J = 6.8, 16.4 Hz), 2.50-2.32 (2H, m), 2.17 (1H, dd, J = 10.4, 16.4 Hz), 2.06 (1H, dd, J = 4.8, 12.4 Hz), 1.64 (1H, t, J = 12.4 Hz). ¹³C-NMR (100 MHz, CDCl₃) δ 174.1, 148.3, 148.1, 141.1, 129.6, 115.2, 113.9, 113.2, 107.8, 94.1, 64.3, 64.1, 55.9, 55.8, 39.4, 36.5, 36.1, 34.6, 32.9, 32.6.

**Compound 4:** H-NMR (400 MHz, CDCl₃) δ 7.00 (1H, s), 6.81 (1H, s), 5.85 (1H, s), 4.05-3.89 (4H, m), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.67 (1H, dd, J = 6.0, 12.0 Hz), 3.40 (1H, m), 2.92 (3H, m), 2.81 (1H, dd, J = 2.4, 14.0 Hz), 2.53 (1H, dd, J = 2.0, 14.0 Hz), 2.35 (1H, m), 1.85 (1H, m), 1.71 (1H, ddd, J = 3.6, 14.0, 17.6 Hz), 1.27 (1H, m). ¹³C-NMR (100 MHz, CDCl₃) δ 171.4, 158.3, 148.5, 148.2, 129.9, 120.7, 115.4, 113.9, 113.5, 109.5, 64.8, 64.6, 61.5, 56.1, 40.1, 38.2, 34.8, 27.7.

(S)-3-(2-Hydroxyethoxy)-1,2,8,9-tetrahydro-11,12-dimethyloxindolo[1,2-a][1-alisoquinolin-6]-4(4'H)-one (8). A mixture of 2 (548 mg, 1.25 mmol) and Pd(OAc)₂ (14 mg, 0.063 mmol) in 5 mL DBU in a sealed tube was heated at 140 °C for 15 h. The reaction mixture was quenched with 40 mL aqueous HCI 2M solution, and then extracted with CH₂Cl₂ (30 mL × 3). The organic layers were dried over anhydrous MgSO₄ and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (EtOAc/MeOH 20:1 to 10:1) to afford 8 (124 mg, 87%) as a colorless liquid. ¹HNMR (400 MHz, CDCl₃) δ 6.78 (1H, s), 6.59 (1H, s), 5.85 (1H, d, J = 10.4 Hz), 5.77 (1H, d, J = 10.4 Hz), 4.35 (1H, m), 4.12-3.97 (4H, m), 3.86 (3H, s, OMe), 3.85 (3H, s, OMe), 3.06-2.83 (3H, m), 2.68-2.60 (2H, m), 2.49-2.39 (2H, m), 2.09 (1H, dd, J = 4.8, 14.8 Hz). ¹³C-NMR (100 MHz, CDCl₃) δ 172.9, 148.2, 147.9, 131.0, 130.3, 126.7, 126.2, 111.9, 109.3, 103.2, 64.9, 64.3, 61.1, 56.0, 55.9, 39.1, 36.1, 35.1, 34.1, 28.6.

Iso-demethoxyerythradiatidine (9). To a solution of anhydrous AlCl₃ (60 mg, 0.45 mmol) in anhydrous THF (2 mL) at 0 °C was added 1.5 mL solution of LiAlH₄ 1M in THF. This solution

was added via cannula to a solution of 8 (100 mg, 0.28 mmol) in THF (3 mL) at 0 °C. The reaction mixture was quenched with ice-water after 1 h, and extracted with CHCl₃ (20 mL × 3), dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product. ¹H-NMR (400 MHz, CDCl₃) δ 6.87 (1H, s), 6.55 (1H, s), 5.83 (1H, d, J = 12.0 Hz), 5.69 (1H, d, J = 12.0 Hz), 4.09-3.95 (4H, m), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.18-3.11 (3H, m), 3.01-2.90 (2H, m), 2.62 (1H, m), 2.48 (1H, m), 2.12 (1H, dd, J = 5.2, 13.6 Hz), 2.04 (1H, dd, J = 8.4, 13.6 Hz), 1.95 (1H, m), 1.81 (1H, m). The crude product was dissolved in acetone (5 mL) followed by addition of 10 mg of TsOH. The reaction solution was heated at 80 °C for 2 h, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (CHCl₃/MeOH 20:1 to 10:1) to yield 9 (67 mg, 80%) as a colorless liquid. ¹H-NMR (400 MHz, CDCl₃) δ 6.69 (1H, s), 6.68 (1H, s), 6.58 (1H, dd, J = 2.0, 10.4 Hz), 6.04 (1H, d, J = 10.4 Hz), 3.88 (3H, s, OMe), 3.80 (3H, s, OMe), 3.17-2.84 (6H, m), 2.66-2.52 (2H, m), 2.07 (1H, m), 1.74-1.63 (2H, m). ¹³C-NMR (100 MHz, CDCl₃) δ 198.6, 151.9, 147.9, 147.6, 129.1, 127.5, 125.

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References and Footnotes