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New Cyclization Route to the Skeletons of Lennoxamine and Chilenine

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Abstract: A new cyclization route, triggered by epoxide opening, has been performed to provide the key intermediates for isoindolobenzapine alkaloids, lennoxamine and chilenine. The epoxide was prepared by the Stille reaction using vinyltributylstannane and the following dioxirane treatment. Cyclization under the treatment of $BF_3{\cdot}OEt_2$ provided an azepine moiety, and the oxidative cyclization toward the known precursor for the alkaloids has been achieved by reaction with a stoichiometric amount of $Pd(OAc)_2$. This formal synthesis suggests a new route to the alkaloids.

Keywords: Chilenine, epoxide, lennoxamine, oxidative cyclization, palladium acetate

INTRODUCTION

Isoindolobenzapine alkaloids, lennoxamine **1** and chilenine **2**, have been isolated from Chilean *Berberis darwinii* Hook and *Berberis empetrifolia* Lam, respectively (Fig. 1).[1–3] Because of their unique tetracylic ring feature, many groups have shown interest in their syntheses and suggested several attractive ways to the total synthesis as well as the ring system synthesis.[4–14]

For a new approach to the ring skeleton, we wanted to arrange an expedient formation of acyliminium intermediate **A** and figure out the feature of the following transformation to the ring system (Scheme 1).

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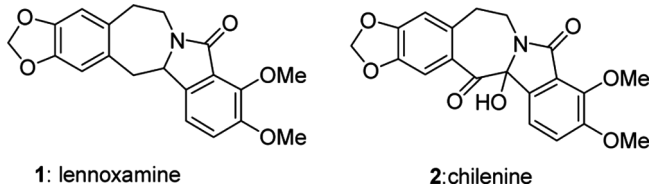


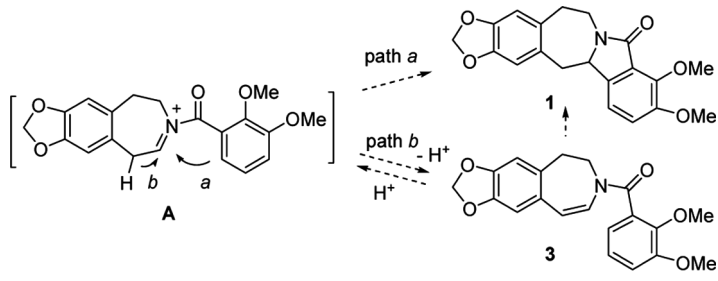
Figure 1. Structure of lennoxamine and chilenine.

As shown in the Scheme 1, the Friedel–Crafts reaction of **A** (path a) would afford lennoxamine **1**; on the other hand the elimination reaction (path b) would provide compound **3**.

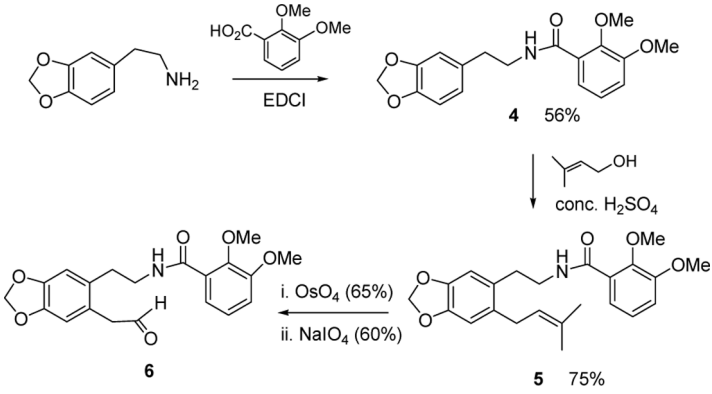
RESULTS AND DISCUSSION

The requisite precursor for **A**, aldehyde **6**, was prepared preliminarily through a three-step sequence. Condensation of 3,4-methyenedioxyphenethyl amine and 2,3-dimethoxybenzoic acid provided **4** (56%), Friedel–Crafts alkylation of **4** with 2-methyl-3-buten-2-ol yielded **5** (75%), and osmylation (65%) followed by oxidative cleavage using $NaIO_4$ (62%) afforded the aldehyde **6**. For the transformation to **A** and the following cyclization, **6** was treated with various acids in different solvents; however, only a negligible amount of **3** has been detected in ^{1}H NMR (Scheme 2).

To facilitate the cyclization and study the aspect of this reaction under milder conditions, we designed an in situ process of cyclization. We considered that epoxide **10** would rearrange to aldehyde **6** with $BF_3{\cdot}OEt_2$ on the carbonyl group, which should expedite the subsequent cyclization.[15] For the preparation of **10**, we first coupled **7** with 2,3-dimethoxybenzoic acid to provide **8** in 57% yield. Stille reaction of **8** with vinyltributylstannane afforded the vinyl compound **9** in 82% yield,[16]

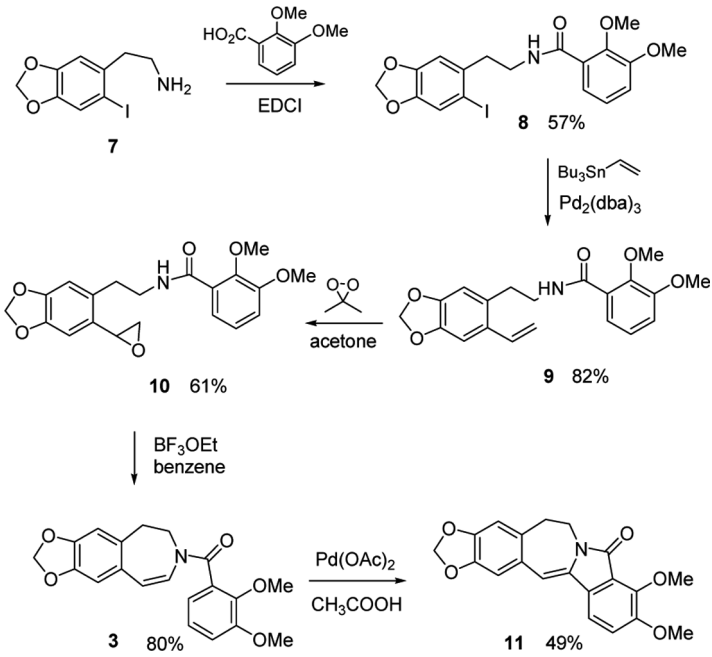


Scheme 1. Suggested cyclization pathways.



Scheme 2. Initial pathway to aldehyde **6**.

and its epoxidation with dimethyldioxirane provided the desired epoxide **10** in 61% yield.[17] Treatment of **10** with $BF_3{\cdot}OEt_2$ in benzene afforded compound **3** as a mixture of ca. 2:1 conformers detected by NMR in 77%



Scheme 3. Synthesis of compound **11**.

yield. The reaction proceeded via only path b. We questioned which vigorous conditions would enforce the equilibrium between **A** and **3** and enable conversion to **1** (Scheme 1). Treatment of **3** with various acids under high temperature in different solvents, however, resulted in only decomposition. As the direct transformation to lennoxamine was not successful, we decided to search for an alternative for the synthesis. We tried oxidative ways to the known tetracyclic precursor **11** for the alkaloids from **3**[18] and found that heating **3** in acetic acid[19] in the presence of a stoichiometric amount of $Pd(OAc)_2$ was best, providing **11** in 49% yield (Scheme 3).

CONCLUSION

In conclusion, we have suggested a new way to isoindolobenzapine alkaloids by making the azepine moiety through epoxide transformation and the following oxidative cyclization, achieving a formal synthesis of lennoxamine and chilenine, in a concise manner.

EXPERIMENTAL

All reactions were performed in oven-dried glassware with magnetic stirring. Commercial-grade reagents and anhydrous solvents were used without further purification. 3,4-Methylenedioxyphenethylamine hydrochloride, 2,3-dimethoxybenzoic acid, N-ethyl-N′-(3-dimethyldiaminopropyl)-carbodiimide HCl (EDCI), 2-methyl-3-buten-2-ol, tributyl(vinyl)tin, $Pd_2(dba)_3$, and $AsPh_3$ were purchased from Aldrich Chemical Co. Silica gel was purchased from Merck.

Nuclear magnetic resonance spectra were recorded on a Jeol-JNM-AL400 instrument with Me_4Si as the internal standard and $CDCl_3$ as solvent. Chemical shifts are reported in parts per million (ppm). Mass spectra were recorded on a Hewlett-Packard 5890A gas chromatograph/Hewlett-Packard 5971A mass selective detector. Analytical thin-layer chromatography (TLC) was performed on silica-gel 60F-254 plates and visualized with UV light (254 nm) and/or anisaldehyde-H_2SO_4-AcOH as detecting agent. Flash-column chromatography was performed on silica gel (Kieselgel 60, EM Regents, 230–400 mesh).

Synthesis of Amide 4

2,3-Dimethoxybenzoic acid (0.580 g, 3.20 mmol), EDCI (0.940 g, 4.95 mmol), and 4-dimethylaminopyridine (DMAP) (15 mg, 0.12 mmol) were added to a solution of 3,4-methylenedioxyphenethyl amine

(0.410 g, 2.48 mmol) in 10 ml of THF. The mixture was stirred for 5 h at rt and diluted with 50 mL of CH_2Cl_2, and the organic layer was washed with water (10 mL × 3) and brine. After drying over $MgSO_4$, filtering, and concentrating, the crude product was purified by silica-gel column chromatography (hexane–EtOAc = 2:1) to afford **4** (0.450 g, 56%). MS $m/z = 329$ (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (br s, 1H), 7.69 (dd, 1H, $J = 6.4$, 8.0 Hz), 7.13 (t, 1H, $J = 8.0$ Hz), 7.01 (d, 1H, $J = 6.4$ Hz), 6.76–6.70 (m, 3H), 5.92 (s, 2H), 3.87 (s, 3H), 3.73–3.64 (m, 5H), 2.86 (t, 2H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 152.4, 147.7, 147.3, 146.0, 132.7, 126.4, 124.2, 122.6, 121.5, 115.1, 108.9, 108.2, 100.7, 60.9, 55.9, 40.8, 35.0.

Synthesis of Amide 5

Concentrated H_2SO_4 (0.17 mL, 3.3 mmol) was added slowly to a solution of **4** (1.0 g, 3.0 mmol) in 10 mL of CH_2Cl_2 containing 2-methyl-3-buten-2-ol (3.1 mL, 30 mmol) at 0 °C. The mixture was stirred for 3 h at rt. Dilution of the mixture with 30 mL of CH_2Cl_2 was followed by washing with water (10 mL) three times. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica-gel column chromatography (hexane–EtOAc = 3:1) to afford **5** (0.91 g, 75%). 2 MS $m/z = 397$ (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.90 (br s, 1H), 7.69 (d, 1H, $J = 8.4$ Hz), 7.14 (t, 1H, $J = 8.4$ Hz), 7.02 (d, 1H, $J = 8.4$ Hz), 6.69 (s, 1H), 6.66 (s, 1H), 5.88 (s, 2H), 5.17 (br, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.65 (q, 2H, $J = 6.4$ Hz), 3.28 (d, 2H, $J = 6.8$ Hz), 2.87 (t, 2H, $J = 4$ Hz), 1.69 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 152.4, 147.4, 146.1, 145.6, 133.3, 132.4, 129.6, 126.6, 124.3, 123.1, 122.7, 115.2, 109.6, 109.5, 100.6, 61.0, 56.0, 40.4, 36.3, 32.2, 25.6, 17.8.

Synthesis of Aldehyde 6

Osmium tetroxide (6.4 mg, 0.025 mmol) and 4-methylmorphorine N-oxide (NMO) (76 mg, 0.64 mmol) were added to a solution of compound **5** in 2 mL of H_2O–acetone–acetonitrile (1:1:1). The mixture was stirred for 1.5 h at rt, and 3 mL of distilled water were added. The mixture was extracted with CH_2Cl_2 three times, and the organic layer was dried over $MgSO_4$. After filtration, concentration, and separation by silica-gel column chromatography, a diol product was obtained in 65% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (br s, 1H), 7.65 (d, 1H, $J = 6.4$ Hz), 7.12 (t, 1H, $J = 8.0$ Hz), 7.02 (d, 1H, $J = 6.4$ Hz), 6.72 (s, 1H), 6.71 (s, 1H), 5.90 (s, 2H), 3.88–3.80 (m, 8H), 2.94–2.65 (m, 7H),

1.31 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 152.4, 147.3, 146.2, 146.1, 131, 130.4, 126.2, 124.4, 122.7, 115.4, 110.4, 109.5, 100.8, 79.5, 72.7, 61.1, 56, 41.1, 34.5, 32.5, 25.6, 24.4.

The diol product (0.210 g, 0.490 mmol) in 5 mL of CH_2Cl_2 was treated with $NaIO_4$ supported on silica gel (1.0 g) for 1.5 h at rt. After addition of water to the solution, the reaction mixture was extracted with CH_2Cl_2 (10 ml $\times$ 3). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified on a silica-gel column to afford aldehyde **6** (0.11 g, 60%). MS $m/z = 371$ (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.72 (t, 1H, $J = 2.0$ Hz), 8.10 (br s, 1H), 7.67 (d, 1H, $J = 6.4$ Hz), 7.68 (d, 1H, $J = 6.4$ Hz), 7.14 (t, 1H, $J = 6.4$ Hz), 7.02 (s, 1H), 7.03 (s, 1H), 6.78 (s, 1H), 6.64 (s, 1H), 5.93 (s, 2H), 3.88 (s, 3H), 3.78 (s, 3H), 3.76 (d, 2H, $J = 1.6$ Hz), 3.57 (dd, 2H, $J = 8.8$, 20.8 Hz), 2.82 (t, 2H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 165.4, 152.4, 147.4, 147.1, 146.5, 131.3, 126.2, 124.3, 123.4, 122.6, 115.3, 110.7, 109.9, 101, 61.1, 55.9, 47.7, 40.6, 32.5.

Synthesis of Iodo-amide 8

2,3-Dimethoxybenzoic acid (0.58 g, 3.2 mmol), EDCI (0.94 g, 4.95 mmol), DMAP (15 mg, 0.12 mmol), and NaH (0.11 g, 4.95 mmol) were added to a solution of 2-iodo-4,5-methylenedioxyphenethyl amine (0.722 g, 2.48 mmol). After the solution was stirred for 5 h at rt, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2 (10 ml $\times$ 3). The organic layer was dried over $MgSO_4$, filtered, concentrated, and separated by silica-gel column chromatography (hexane–EtOAc = 1:1) to afford compound **8** (0.654 g, 57%). MS $m/z = 455$ (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (br s, 1H), 7.71 (d, 1H, $J = 6.4$ Hz), 7.26 (s, 1H), 7.16 (t, 1H, $J = 6.4$ Hz), 7.04 (d, 1H, $J = 6.4$ Hz) 6.81 (s, 1H), 5.94 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 3.69–3.65 (t, 2H, $J = 7.2$ Hz), 3.00 (t, 2H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 153.4, 148.5, 146.5, 145.9, 131.6, 125.3, 123.5, 121.9, 121.2, 114.8, 108.2, 100.1, 89.2, 60.2, 54.9, 41.8, 36.2.

Synthesis of Vinyl Amide 9

To a solution of compound **8** (0.500 g, 0.110 mmol) in 20 mL of DMF, tributyl(vinyl)tin (0.38 mL, 0.140 mmol), $Pd_2(dba)_3$ (100 mg, 0.011 mmol) mmol) and $AsPh_3$ (0.270 g, 0.088 mmol) were added. The solution was stirred for 12 h at 50 °C under an N_2 atmosphere. After cooling to rt, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethylacetate (20 mL $\times$ 3). The organic layer was washed

with water (10 ml × 3), dried over $MgSO_4$, and concentrated after filtration. The crude product was purified by silica-gel column chromatography (hexane–EA = 1:1) to afford compound **9** (0.340 g, 82%). MS $m/z = 355$ (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (br s, 1H), 7.71 (d, 1H, $J = 8.0$ Hz), 7.16 (dd, 1H, $J = 8.0$ Hz, $J = 8.0$ Hz), 7.03–6.94 (m, 2H), 7.01 (s, 1H), 6.69 (s, 1H), 5.92 (s, 2H), 5.54 (d, 1H, $J = 16.8$ Hz), 5.22 (d, 1H, $J = 11.2$ Hz), 3.87 (s, 3H), 3.75 (s, 3H), 3.62 (bt, 2H), 2.96 (t, 2H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 152.3, 147.3, 146.5, 133.4, 130.3, 130.2, 126.4, 124.0, 122.5, 115.1, 114.0, 109.5, 105.3, 100.8, 60.9, 55.8, 40.5, 32.5.

Synthesis of Epoxy Amide 10

Oxone (0.270 g, 0.442 mmol) was added to a solution of compound **9** (0.157 g, 0.442 mmol) in acetone/H_2O (4 mL/2 mL) containing $NaHCO_3$ (0.130 g, 1.55 mmol). The mixture was stirred for 10 min, and the same amount of $NaHCO_3$ and Oxone was added. The mixture was stirred for 1.5 h at rt. The reaction mixture was diluted with ethylacetate (30 mL) and washed with water (10 ml × 3). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica-gel column chromatography (hexane–EA = 1:2, and then 1:4) to afford compound **10** (0.101 g, 61%). MS $m/z = 371$ (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (br s, 1H), 7.58 (d, 1H, $J = 8.0$ Hz), 7.12 (dd, 1H, $J = 8.0$ Hz, $J = 8.0$ Hz), 7.02 (s, 1H), 7.01 (d, 1H, $J = 8.0$ Hz), 6.66 (s, 1H), 5.12 (m, 1H), 3.86 (s, 3H), 3.51–3.70 (m, 4H), 2.96 (m, 1H), 2.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 152.3, 147.3, 146.7, 146.4, 132.8, 129.3, 126.1, 124.2, 122.3, 115.3, 109.4, 106.9, 100.8, 77.3, 77.0, 76.6, 70.6, 67.6, 61.0, 55.8, 41.0, 32.1.

Synthesis of Azonin Amide 3

$BF_3{\cdot}OEt_2$ was added to a solution of epoxide **10** (0.748 g, 2.014 mmol) in anhydrous benzene (25 mL). The reaction mixture was stirred at rt for 12 h, and the mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica-gel column chromatography (hexane–EA = 1:2, and then 1:4) to afford compound **3** as a ca. 2:1 mixture of conformers (0.572 g, 77%). MS $m/z = 353$ (M^+); minor conformer, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, 1H, $J = 10.8$ Hz), 7.12 (dd, 1H, $J = 8.0$ Hz, $J = 8.0$ Hz), 6.97 (d, 1H, $J = 8.0$ Hz), 6.85 (d, 1H, $J = 8.0$ Hz), 6.70 (s, 1H), 6.50 (s, 1H), 5.91 (s, 2H), 5.75 (d, 1H, $J = 10.8$ Hz), 3.89 (s, 3H), 3.85 (s, 3H), 3.75–4.25 (m,

2H), 2.94 (m, 2H); major conformer, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10 (dd, 1H, $J = 8.0$ Hz, $J = 8.0$ Hz), 6.97 (d, 1H, $J = 8.0$ Hz), 6.84 (d, 1H, $J = 8.0$ Hz), 6.63 (s, 1H), 6.59 (s, 1H), 6.28 (d, 1H, $J = 10.8$Hz), 5.91 (s, 2H), 5.34 (d, 1H, $J = 10.8$ Hz), 3.89 (s, 3H), 3.85 (s, 3H), 3.75–4.25 (m, 2H), 3.04 (m, 2H).

Synthesis of Dehydrolennoxamine 11

$Pd(OAc)_2$ (0.126 g, 0.56 mmol) was added to a solution of compound **3** (0.100 g, 0.28 mmol) in CH_3COOH (10 mL), and the mixture was heated to reflux for 6 h. After concentration, the crude product was diluted with CH_2Cl_2, and the organic layer was washed with water twice, saturated $NaHCO_3$ solution, and brine. Drying over $MgSO_4$ was followed by filtration, concentration, and purification by silica-gel column chromatography (hexane–EA = 1:2, and then 1:4) to afford compound **11** (0.049 g, 49%). The spectroscopic data of **11** (^{1}H and ^{13}C NMR, mp, and mass) were identical to the reported values in Ref. 7 in the main text.

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