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Electroreductive Intramolecular Coupling of Phthalimides with Aromatic Aldehydes: Application to the Synthesis of Lennoxamine

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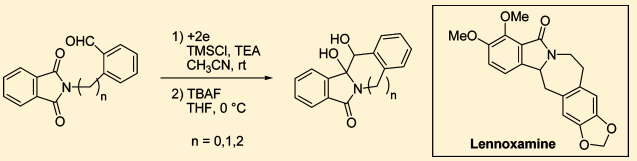
Supporting Information

ABSTRACT: The electroreductive intramolecular coupling of phthalimides with aromatic aldehydes in the presence of chlorotrimethylsilane and triethylamine led to five-, six-, and seven-membered cyclized products (58−84%). The electroreductive cyclization was applied to the total synthesis of lennoxamine.



Recently, we have reported the electroreductive intramolecular coupling of phthalimides with ketones and aldehydes[1] and α,β-unsaturated esters[2] in the presence of chlorotrimethylsilane (TMSCl) and triethylamine (TEA). In this context, we report herein that the electroreductive intramolecular coupling of phthalimides with aromatic aldehydes in the presence of TMSCl and TEA produced tetracyclic compounds **4**−**6** incorporating an isoindolinone ring (Scheme 1). It is worth noting that the seven-membered cyclized product **6** was also obtained in high yield (82%), whereas the intramolecular coupling with aliphatic aldehydes gave the corresponding seven-membered cyclized product in low yield (34%).[1] Because of these results, we planned the synthesis of lennoxamine **7** utilizing this electroreductive intramolecular coupling. Lennoxamine **7** and chilenine **8**, naturally occurring isoindolobenzazepine alkaloids,[3] have attracted much attention from synthetic chemists because of their unique structures.[4] Although the reductive cyclization of **9** to **10** with the expensive SmI_2 reagent has been reported for the formal synthesis of chilenine **8** (Scheme 2),[5] we were able to achieve the reaction by electroreduction, which is an inexpensive process, without using rare-earth reagents. In addition, we improved more conveniently the preparation of the precursor **9** for the cyclized product **10**. Consequently, the present method provides a practical method for the construction of the isoindolobenzazepine skeleton of **7** compared to the other synthetic strategies employing late-stage formation of the C12b−C13 bond of the benzoazepine ring.[4j,l,m,5,6]

The electroreduction of **1**−**3** in the presence of TMSCl and TEA was carried out using Et_4NOTs/acetonitrile as a catholyte according to our reported method.[1] The electrogenerated products were obtained as disilyl ethers of cyclized diols **4**−**6**. Desilylation of the disilyl ethers with TBAF in THF gave **4**−**6** as diastereomeric mixtures (Scheme 1). The major isomer of **5** could be separated by recrystallization, and its stereostructure was confirmed to be cis by X-ray crystallographic analysis.

In order to apply the electroreductive cyclization to the synthesis of lennoxamine **7**, we explored the dehydroxylation of diols **5** and **6** (Scheme 3). Reduction of **5** and **6** with $Et_3SiH/BF_3{\cdot}Et_2O$ in CH_2Cl_2 gave **11** and **12**, respectively. Alcohol **11** was formed as a single stereoisomer (76% yield), and the relative stereochemistry was assigned to be trans by its ^1H NMR coupling constant (J = 9.2 Hz). On the other hand, alcohol **12** was obtained as a 50:50 diastereomeric mixture (70% yield). Both isomers of **12** could be separated by column chromatography, and the structure of each stereoisomer was determined by X-ray crystallographic analysis. Dehydration of alcohols **11** and **12** with $KHSO_4$ in refluxing xylene and subsequent hydrogenation of the resulting alkenes **13** and **14** afforded the saturated products **15** and **16** in high yields.

The synthesis of lennoxamine **7** was then performed as depicted in Scheme 4. The preparation of substrate **9** for the electroreductive cyclization was achieved from known compounds, aldehyde **17**[7] and acid anhydride **20**.[8] Aldehyde **17** was transformed to β-nitrostyrene **18** by addition with nitromethane and subsequent dehydration in 64% yield. $LiAlH_4$ reduction of **18** led to β-arylethylamine **19** quantitatively. On the other hand, acid anhydride **20** was converted to *N*-ethoxycarbonylimide **21** by heating with aq NH_3 and following *N*-ethoxycarbonylation of the resulting imide in 78% yield. Reaction of **19** and **21** with TEA in DMF gave the substrate **9** (60% yield) after subsequent deacetalization with 3 M HCl. Electroreduction of **9** in the presence of TMSCl and TEA followed by desilylation with TBAF led to diol **10** as a 50:50 diastereomeric mixture (68% yield). The diastereomeric mixture of **10** was reduced by $Et_3SiH/BF_3{\cdot}Et_2O$ to give alcohol **22** in 66% yield with a 50:50 diastereomeric ratio. Dehydration of the mixture of **22** with $KHSO_4$ in refluxing toluene afforded dehydrolennoxamine **23** (82% yield), which was subjected to hydrogenation[4j,l] to produce lennoxamine **7** in 97% yield.

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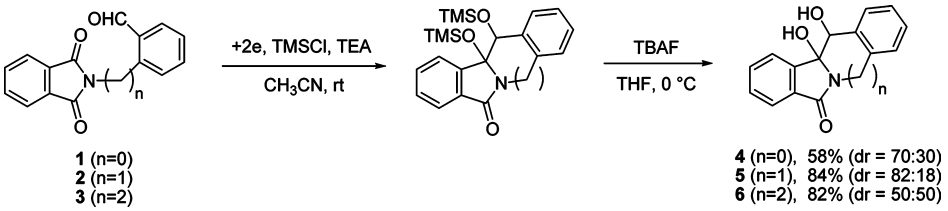
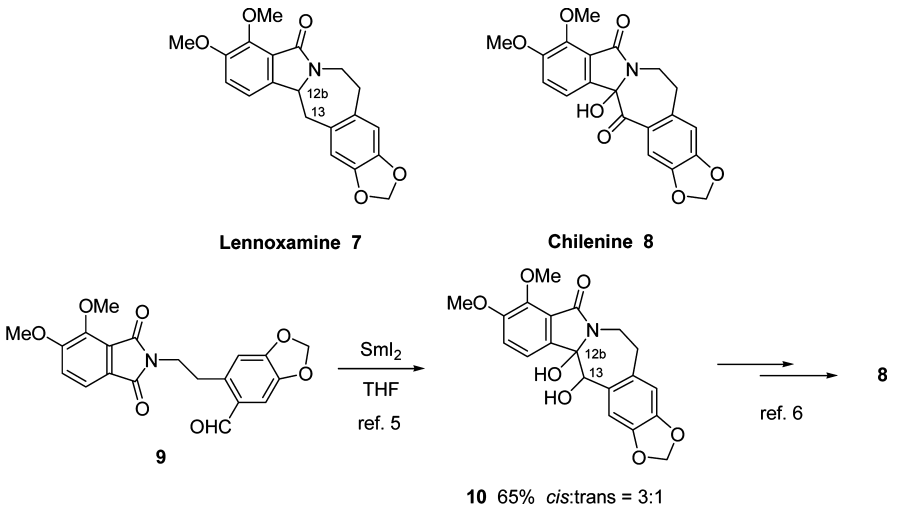
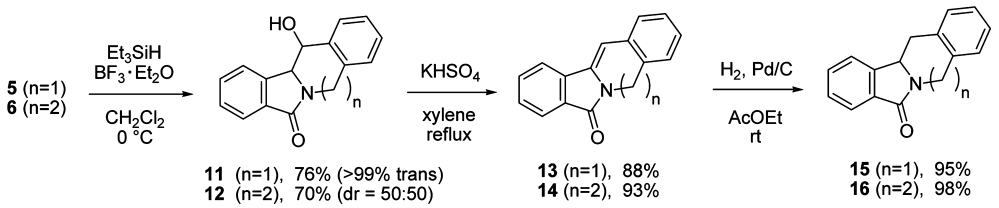
Scheme 1



Scheme 2



Scheme 3



Incidentally, the synthesis of chilenine **8** from **10** and **23** has been reported by Danishefsky et al.[6]

In conclusion, the electroreduction of **1**–**3** in the presence of TMSCl and TEA gave five-, six-, and seven-membered cyclized products **4**–**6** respectively. The diols **5** and **6** were transformed to the dehydroxylated compounds **15** and **16**. Lennoxamine **7**, an isoindolobenzazepine alkaloid, was synthesized utilizing the electroreductive cyclization of **9** as a key step (in five steps with an overall yield of 36% from **9**).

EXPERIMENTAL SECTION

General Methods. Column chromatography was performed on silica gel 60. Solvents, TMSCl, and TEA were distilled from CaH_2.

Starting Materials. 2-(1,3-Dioxoisoindolin-2-yl)benzaldehyde (**1**) was prepared from *o*-aminobenzaldehyde ethylene acetal[9] by usual phthaloylation with phthalic anhydride in refluxing toluene and following deacetalization with 3 M HCl. 2-((1,3-Dioxoisoindolin-2-yl)methyl)benzaldehyde (**2**) and 2-(2-(1,3-dioxoisoindolin-2-yl)-ethyl)benzaldehyde (**3**) were synthesized from *o*-bromomethylbenzaldehyde[10] and *o*-(2-bromoethyl)benzaldehyde,[11] respectively, by treatment with potassium phthalimide in DMF at 50 °C.

1: White solid; R_f 0.5 (hexanes/EtOAc, 2:1); mp 163–164 °C (recryst. from hexanes/EtOAc, 2:1); IR (KBr) 1780, 1709, 1688, 1655, 1599, 1578, 1514, 1487, 1464, 889, 874, 856, 816, 799, 772, 721, 708, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41–7.46 (m, 1 H), 7.64–7.69 (m, 1 H), 7.75–7.85 (m, 3 H), 7.96–8.04 (m, 3 H), 9.96 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 123.9 (d), 129.5 (d), 130.0 (d), 131.6 (s), 131.8 (s), 132.2 (s), 132.6 (d), 134.5 (d), 134.6 (d), 167.2 (s), 189.3 (s). Anal. Calcd for $C_{15}H_9NO_3$: C, 71.71%; H, 3.61%; N, 5.58%. Found: C, 71.66%; H, 3.62%; N, 5.53%.

2: White solid; R_f 0.5 (hexanes/EtOAc, 2:1); mp 183–185 °C (recryst. from hexanes/EtOAc, 1:2, lit.[12] 183–185 °C); IR (KBr) 1771, 16945, 1599, 1574, 1481, 1466, 962, 939, 854, 772, 762, 721, 712, 685, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.37 (s, 2 H), 7.25–7.28 (m, 1 H), 7.45–7.54 (m, 2 H), 7.73–7.78 (m, 2 H), 7.86–7.92 (m, 3 H), 10.35 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 38.7 (t), 123.5 (d), 127.5 (d), 127.9 (d), 131.9 (s), 133.4 (s), 133.7 (d), 133.9 (d), 134.2 (d), 137.8 (s), 168.0 (s), 192.9 (s). Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.45%; H, 4.18%; N, 5.28%. Found: C, 72.40%; H, 4.21%; N, 5.22%.

3: White solid; R_f 0.5 (hexanes/EtOAc, 2:1); mp 156–157 °C (recryst. from hexanes/EtOAc, 1:2); IR (KBr) 1769, 1697, 1676, 1599, 1572, 1491, 1464, 943, 858, 839, 773, 718, 656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.44 (t, 2 H, J = 7.1 Hz), 4.00 (t, 2 H, J = 7.1 Hz), 7.20–7.23 (m, 1 H), 7.39–7.45 (m, 2 H), 7.67–7.72 (m, 2 H), 7.78–7.82 (m, 2 H), 7.82–7.85 (m, 1 H), 10.28 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 31.5 (t), 38.6 (t), 123.1 (d), 127.4 (d), 131.5 (d), 131.8 (s), 133.4 (d), 133.6 (d), 133.8 (d), 134.2 (s), 140.2 (s), 168.0 (s), 192.6 (s). Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11%; H, 4.69%; N, 5.02%. Found: C, 73.00%; H, 4.69%; N, 4.99%.

Synthesis of 18. To a solution of 6-(1,3-dioxolan-2-yl)benzo[d]-[1,3]dioxole-5-carbaldehyde (**17**)[7] (4.44 g, 20 mmol) and CH_3NO_2

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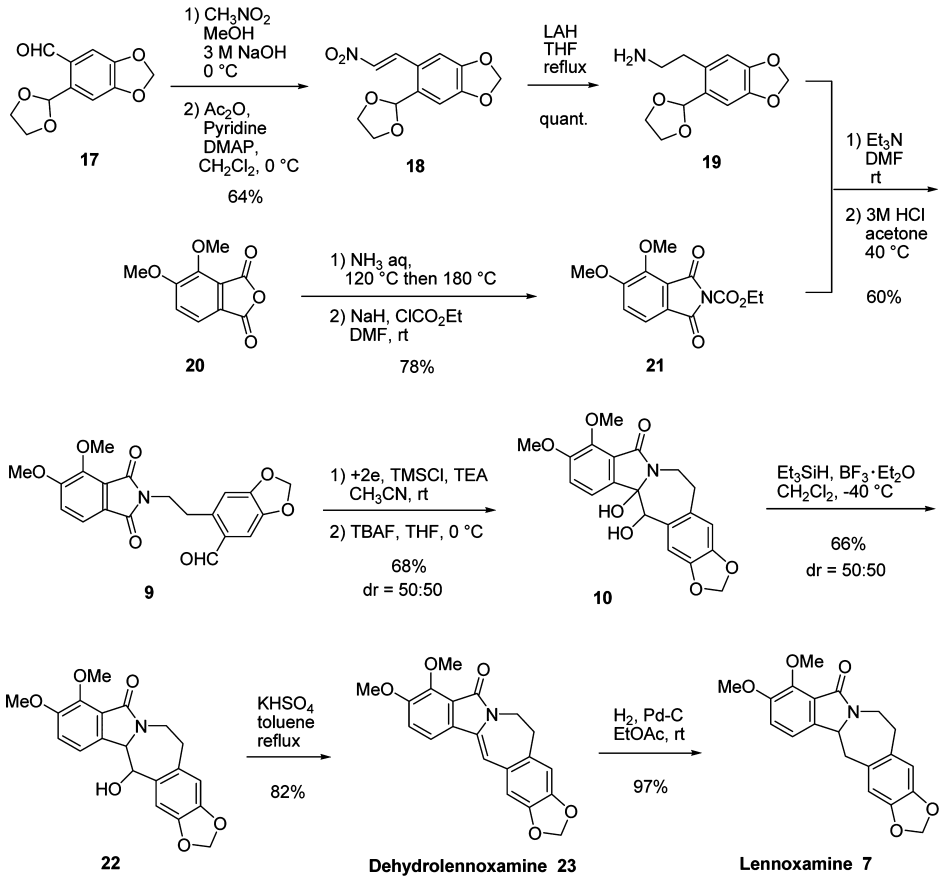
Scheme 4



(3.2 mL) in MeOH (30 mL) was added 3 M aq NaOH (15 mL) at 0 °C. After being stirred for 3 h at this temperature, the mixture was neutralized with 3 M HCl (15 mL), extracted with CH_2Cl_2, and dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 (20 mL). To the solution were successively added DMAP (100 mg), pyridine (8 mL), and Ac_2O (4 mL) at 0 °C. After being stirred for 6 h at this temperature, the mixture was diluted with saturated aq $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2. The extract was successively washed with 1 M HCl and saturated aq NaCl and then dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was recrystallized from hexanes/EtOAc (1:2) to give 3.39 g of (*E*)-5-(1,3-dioxolan-2-yl)-6-(2-nitrovinyl)benzo[d][1,3]dioxole (**18**) in 64% yield.

18: Yellow solid; R_f 0.6 (hexanes/EtOAc, 2:1); mp 179−180 °C (recryst. from hexanes/EtOAc, 1:2); IR (KBr) 1632, 1603, 1501, 1483, 972, 945, 924, 903, 883, 833, 804, 737, 716, 669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.05−4.21 (m, 4 H), 5.95 (s, 1 H), 6.06 (s, 2 H), 7.00 (s, 1 H), 7.16 (s, 1 H), 7.43 (d, 1 H, J = 13.7 Hz), 8.43 (d, 1 H, J = 13.7 Hz); ^{13}C NMR ($CDCl_3$) δ 65.4 (t), 101.2 (t), 102.2 (d), 106.6 (d), 107.8 (d), 122.9 (s), 134.0 (s), 135.9 (d), 136.6 (d), 148.7 (s), 150.8 (s). Anal. Calcd for $C_{12}H_{11}NO_6$: C, 54.34%; H, 4.18%; N, 5.28%. Found: C, 54.45%; H, 4.24%; N, 5.03%.

Synthesis of 19. To a suspension of LAH (0.57 g, 15 mmol) in THF (20 mL) was added dropwise a solution of **18** (1.33 g, 5 mmol) in THF (20 mL) at room temperature, and the mixture was refluxed for 12 h. After the mixture was cooled to 0 °C, to the mixture were added H_2O (1.0 mL) and 3 M aq NaOH (1.0 mL). The mixture was filtered and evaporated in vacuo to give 1.25 g (quantitative yield) of crude **19**, which was employed in the next step without further purification.

Crude **19**: Yellow paste; ^1H NMR ($CDCl_3$) δ 2.80 (t, 2 H, J = 7.2 Hz), 2.94 (t, 2 H, J = 7.2 Hz), 3.99−4.06 (m, 2 H), 4.11−4.18 (m, 2 H), 5.94 (s, 3 H), 6.68 (s, 1 H), 7.08 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 35.8 (t), 43.5 (t), 65.0 (t), 100.8 (d), 100.9 (t), 106.4 (d), 109.6 (d), 128.8 (s), 132.3 (s), 146.0 (s), 147.9 (s).

Synthesis of 21. A solution of 4,5-dimethoxyisobenzofuran-1,3-dione (**20**)[8] (2.08 g, 10 mmol) in aq NH_3 (40 mL) was stirred at 120 °C until almost all of the water evaporated and then heated at 180 °C for 1.5 h. The residue was dissolved in DMF (20 mL), and the solution was added dropwise to a suspension of NaH (12 mmol) in DMF (20 mL) at 0 °C. After the mixture was stirred for 1 h at room temperature, $ClCO_2Et$ (1.2 mL, 12.5 mmol) was added to the mixture at 0 °C. After being stirred for 12 h at room temperature, the mixture was diluted with water (80 mL) and extracted with EtOAc. The extract was washed with saturated aq NaCl and then dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was recrystallized from hexanes/EtOAc (1:1) to give 2.18 g of ethyl 1-hydroxy-4,5-dimethoxy-3-oxoisoindoline-2-carboxylate (**21**) in 78% yield.

21: White solid; R_f 0.45 (hexanes/EtOAc, 1:1); mp 150−151 °C (recryst. from hexanes/EtOAc, 1:1); IR (KBr) 1759, 1709, 1599, 1492, 928, 889, 833, 775, 662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (t, 3 H, J = 7.2 Hz), 3.98 (s, 3 H), 4.14 (s, 3 H), 4.48 (q, 2 H, J = 7.2 Hz), 7.22 (d, 1 H, J = 8.0 Hz), 7.67 (d, 1 H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 56.7 (q), 62.6 (q), 64.0 (t), 117.4 (d), 120.7 (d), 121.3 (s), 123.4 (s), 148.0 (s), 148.5 (s), 158.6 (s), 161.7 (s), 163.1 (s). Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91%; H, 4.69%; N, 5.02%. Found: C, 55.96%; H, 4.70%; N, 4.91%.

Synthesis of 9. To a solution of crude **19** (5 mmol) and **21** (1.4 g, 5 mmol) in DMF (20 mL) was added triethylamine (1.4 mL, 10 mmol), and the mixture was stirred for 6 h at room temperature. To the mixture was added 3 M HCl (40 mL) and acetone (40 mL), and the mixture was stirred for 12 h at 40 °C. After acetone was removed in vacuo, the mixture was diluted with saturated aq NaCl (60 mL) and extracted with EtOAc. The extract was washed successively with 1 M NaOH and saturated aq NaCl and then dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was recrystallized from hexanes/EtOAc (1:5) to give 1.15 g of 6-(2-(4,5-dimethoxy-1,3-

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dioxoisoindolin-2- yl)ethyl)benzo[d][1,3]dioxole-5-carbaldehyde (**9**) in 60% yield.

9: White solid; R_f 0.5 (hexanes/EtOAc, 1:1); mp 182−184 °C (recryst. from hexanes/EtOAc, 1:5); IR (KBr) 1755, 1701, 1665, 1609, 1497, 1477, 997, 986, 924, 878, 849, 797, 770, 750, 669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.31 (t, 2 H, J = 7.2 Hz), 3.89 (t, 2 H, J = 7.2 Hz), 3.95 (s, 3 H), 4.13 (s, 3 H), 6.02 (s, 2 H), 6.74 (s, 1 H), 7.08−7.11 (m, 1 H), 7.31 (s, 1 H), 7.51−7.53 (m, 1 H), 10.20 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 30.9 (t), 39.3 (t), 56.6 (q), 62.5 (q), 102.0 (t), 109.4 (d), 110.9 (d), 115.8 (d), 119.4 (d), 121.6 (s), 124.3 (s), 128.9 (s), 138.0 (s), 147.20 (s), 147.23 (s), 152.3 (s), 157.7 (s), 166.0 (s), 167.3 (s), 189.3 (d). Anal. Calcd for $C_{20}H_{17}NO_7$: C, 62.66%; H, 4.47%; N, 3.65%. Found: C, 62.62%; H, 4.52%; N, 3.58%.

Typical Procedures for Electroreduction and Subsequent Desilylation. A 0.3 M solution of Et_4NOTs in CH_3CN (15 mL) was placed in the cathodic chamber of a divided cell (40 mL beaker, 3 cm diameter, 6 cm height) equipped with a lead cathode (5 × 5 cm^2), a platinum anode (2 × 1 cm^2), and a ceramic cylindrical diaphragm (1.5 cm diameter). A 0.3 M solution of Et_4NOTs in DMF (4 mL) was placed in the anodic chamber (inside the diaphragm). Substrate **2** (265 mg, 1 mmol), TMSCl (0.64 mL, 5 mmol), and TEA (0.70 mL, 5 mmol) were added to the cathodic chamber. After 300 C of electricity was passed at a constant current of 100 mA at room temperature, the catholyte was evaporated in vacuo. The residue was dissolved in ethyl acetate (20 mL), and insoluble Et_4NOTs was filtered off. After removal of the solvent, the residue was dissolved in THF (10 mL). To the solution was added 1 M TBAF in THF (1 mL) at 0 °C, and the mixture was stirred for 15 min. After removal of the solvent, the crude product was purified by column chromatography on silica gel (hexanes/EtOAc) to give **5** in 84% yield with a 82:18 dr. The major isomer of **5** (***cis*-5**) was isolated as a single crystal by recrystallization from EtOAc.

4 (70:30 diastereomeric mixture): Colorless paste; R_f 0.55 (hexanes/EtOAc, 1:2); ^1H NMR ($CDCl_3$, DMSO-d_6) δ 3.65 (d, 0.3 H, J = 7.2 Hz), 4.71 (d, 0.7 H, J = 9.8 Hz), 5.09 (d, 0.3 H, J = 7.2 Hz), 5.27 (d, 0.7 H, J = 9.8 Hz), 5.69 (brs, 0.3 H), 6.47 (brs, 0.7 H), 7.15−7.86 (m, 8 H); ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 73.7 (d), 73.8 (d), 95.5 (s), 97.9 (s), 114.9 (d), 115.0 (d), 121.5 (d), 121.8 (d), 122.0 (d), 122.5 (d), 122.9 (d), 123.0 (d), 123.3 (d), 125.1 (d), 126.8 (d), 127.5 (d), 127.8 (d), 128.1 (d), 130.3 (s), 131.1 (d), 131.3 (s), 131.5 (d), 136.1 (s), 136.2 (s), 137.8 (s), 137.9 (s), 143.8 (s), 145.4 (s), 164.5 (s), 165.8 (s); HRMS (ESI) m/z calcd. for $C_{15}H_{12}NO_3$ $(M + H)^+$ 254.0817, found 254.0820.

***cis*-5**: White solid; R_f 0.4 (hexanes/EtOAc, 1:2); mp 187−189 °C (recryst. from EtOAc); IR (KBr) 3439, 3215, 1672, 1612, 1580, 1466, 758, 737, 712, 694 cm^{-1}; ^1H NMR ($CDCl_3$, DMSO-d_6) δ 4.51 (d, 1 H, J = 17.0 Hz), 4.52 (brs, 1 H), 5.18 (d, 1 H, J = 17.0 Hz), 8.31 (brs, 1 H), 7.21−7.36 (m, 3 H), 7.52−7.57 (m, 1 H), 7.60−7.66 (m, 1 H), 7.44−7.66 (m, 1 H), 7.74−7.79 (m, 1 H), 7.81−7.85 (m, 1 H), 7.95−8.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 38.4 (t), 71.3 (d), 84.5 (s), 121.8 (d), 123.0 (d), 124.4 (d), 125.7 (d), 125.9 (d), 126.2 (d), 128.3 (d), 130.3 (s), 130.5 (s), 130.9 (d), 135.3 (s), 146.5 (s), 164.6 (s). Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90%; H, 4.90%; N, 5.24%. Found: C, 71.98%; H, 4.88%; N, 5.07%.

6 (50:50 diastereomeric mixture): Colorless paste; R_f 0.35 and 0.25 (hexanes/EtOAc, 1:2); ^1H NMR ($CDCl_3$, DMSO-d_6) δ 2.71−2.82 (m, 0.5 H), 2.88−2.98 (m, 0.5 H), 3.05−3.25 (m, 1 H), 3.26−3.36 (m, 0.5 H), 3.34−3.58 (m, 0.5 H), 4.16 (brs, 0.5 H), 4.46−4.59 (m, 1 H), 4.81 (d, 0.5 H, J = 6.0 Hz), 5.08−5.13 (m, 1 H), 5.50 (brs, 0.5 H), 5.73 (brs, 1 H), 7.12−7.28 (m, 3 H), 7.31−7.36 (m, 0.5 H), 7.45−7.51 (m, 1 H), 7.56−7.63 (m, 1.5 H), 7.72−7.80 (m, 1.5 H), 7.94−7.99 (m, 0.5 H); ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 32.7 (t), 34.7 (t), 35.0 (t), 35.3 (t), 74.5 (d), 76.8 (d), 88.47 (s), 88.54 (s), 120.4 (d), 120.7 (d), 120.8 (d), 124.6 (d), 124.8 (d), 125.2 (d), 125.6 (d), 126.0 (d), 126.3 (d), 127.3 (d), 127.4 (d), 127.5 (d), 128.6 (d), 129.69 (d), 129.74 (s), 130.2 (d), 131.0 (s), 136.5 (s), 138.0 (s), 138.5 (s), 145.8 (s), 146.4 (s), 164.2 (s), 164.8 (s); HRMS (ESI) m/z calcd. for $C_{17}H_{16}NO_3$ $(M + H)^+$ 282.1130, found 282.1135.

10 (50:50 diastereomeric mixture): Colorless paste; R_f 0.4 (hexanes/EtOAc, 1:5); ^1H NMR ($CDCl_3$) δ 2.55−3.35 (m, 5 H), 3.84 (s, 3 H), 3.91 (s, 3 H), 4.26−4.40 (m, 1 H), 4.77 (s, 0.5 H), 4.94 (s, 0.5 H), 5.87−5.98 (m, 2 H), 6.64 (s, 0.5 H), 6.66 (s, 0.5 H), 6.79 (brs, 0.5 H), 6.83 (brs, 0.5 H), 6.99−7.04 (m, 1 H), 7.31−7.35 (m, 0.5), 7.45−7.50 (m, 0.5 H); ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 32.1 (t), 32.6 (t), 34.2 (t), 35.0 (t), 54.8 (q), 60.29 (q), 60.31 (q), 74.3 (d), 75.0 (d), 87.1 (s), 87.4 (s), 99.2 (t), 99.3 (t), 106.8 (d), 107.9 (d), 109.1 (d), 113.9 (d), 114.1 (d), 116.0 (d), 120.6 (d), 121.8 (s), 122.7 (s), 130.0 (s), 131.4 (s), 131.5 (s), 132.4 (s), 138.6 (s), 139.2 (s), 143.7 (s), 144.0 (s), 144.2 (s), 144.3 (s), 144.4 (s), 144.8 (s), 151.3 (s), 151.5 (s), 162.2 (s), 162.9 (s); HRMS (ESI) m/z calcd. for $C_{20}H_{19}NO_7$ $(M + H)^+$ 385.1162, found 385.1166.

Typical Procedure for Reduction with Et_3SiH. To a solution of **5** (134 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) were added Et_3SiH (0.32 mL, 2 mmol) and $BF_3{\cdot}Et_2O$ (0.26 mL, 20 mmol) at 0 °C, and the mixture was stirred for 1.5 h at this temperature. After addition of triethylamine (0.3 mL), the solvent was removed in vacuo. From the residue, ***trans*-11** was isolated in 76% yield by column chromatography on silica gel (hexanes/EtOAc).

***trans*-11**: White solid; R_f 0.45 (hexanes/EtOAc, 1:2); mp 214−215 °C (recryst. from EtOAc); IR (KBr) 3246, 1663, 1616, 1580, 1493, 1470, 758, 743, 709, 689 cm^{-1}; ^1H NMR ($CDCl_3$, DMSO-d_6) δ 4.27 (t, 1 H, J = 9.2 Hz), 4.43 (d, 1 H, J = 9.2 Hz), 4.55 (d, 1 H, J = 17.2 Hz), 5.22 (d, 1 H J = 17.2 Hz), 6.22 (d, 1 H, J = 9.2 Hz), 7.25−7.36 (m, 3 H), 7.51−7.56 (m, 1 H), 7.60−7.64 (m, 1 H), 7.72−7.76 (m, 1 H), 7.81−7.85 (m, 1 H), 7.93−7.97 (m, 1 H); ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 39.8 (t), 58.4 (d), 68.5 (d), 121.0 (d), 122.5 (d), 124.2 (d), 124.3 (d), 125.1 (d), 125.5 (d), 126.6 (d), 129.4 (s), 129.5 (d), 130.4 (s), 136.6 (s), 143.3 (s), 164.9 (s). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48%; H, 5.21%; N, 5.57%. Found: C, 76.28%; H, 5.24%; N, 5.38%.

***trans*-12**: White solid; R_f 0.5 (hexanes/EtOAc, 1:2); mp 215−216 °C (recryst. from EtOAc); IR (KBr) 3258, 1659, 1591, 1470, 937, 908, 800, 773, 760, 735, 692, 669 cm^{-1}; ^1H NMR ($CDCl_3$, DMSO-d_6) δ 2.92−3.10 (m, 3 H), 4.39 (d, 1 H, J = 8.2 Hz), 4.61 (dd, 1 H, J = 5.4, 8.2 Hz), 4.75−4.82 (m, 1 H), 5.06 (d, 1 H J = 5.4 Hz), 7.19−7.23 (m, 1 H), 7.24−7.29 (m, 1 H), 7.31−7.37 (m, 1 H), 7.47−7.52 (m, 1 H), 7.55−7.60 (m, 1 H), 7.78−7.88 (m, 2 H), 7.92−7.96 (m, 1 H); ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 33.4 (t), 33.8 (t), 63.3 (d), 71.8 (d), 120.8 (d), 124.1 (d), 124.8 (d), 125.6 (d), 126.4 (d), 127.5 (d), 129.0 (d), 130.1 (s), 136.5 (s), 140.6 (s), 141.9 (s), 165.2 (s). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96%; H, 5.70%; N, 5.28%. Found: C, 76.87%; H, 5.78%; N, 5.15%.

***cis*-12**: White solid; R_f 0.3 (hexanes/EtOAc, 1:2); mp 199−200 °C (recryst. from EtOAc); IR (KBr) 3316, 1651, 1616, 1597, 1491, 1470, 914, 808, 750, 737, 721, 712, 686, 667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77 (d, 1 H, J = 3.7 Hz), 2.83 (dd, 1 H, J = 5.1, 14.8 Hz), 3.10 (t, 1 H, J = 14.8 Hz), 3.49−3.57 (m, 1 H), 4.71 (s, 1 H), 4.81−4.88 (m, 1 H), 5.18 (d, 1 H, J = 3.7 Hz), 7.21−7.25 (m, 1 H), 7.27−7.34 (m, 2 H), 7.36−7.41 (m, 1 H), 7.50−7.55 (m, 1 H), 7.59−7.66 (m, 2 H), 7.88−7.92 (m, 1 H); ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 33.6 (t), 40.5 (t), 63.9 (d), 75.1 (d), 121.2 (d), 122.3 (d), 125.8 (d), 127.3 (d), 127.6 (d), 128.7 (d), 129.8 (d), 130.6 (d), 132.2 (s), 139.6 (s), 140.1 (s), 142.8 (s), 167.2 (s). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96%; H, 5.70%; N, 5.28%. Found: C, 76.90%; H, 5.68%; N, 5.21%.

22a (upper isomer): White solid; R_f 0.55 (hexanes/EtOAc, 1:5); mp 258−260 °C (recryst. from EtOAc); IR (KBr) 3416, 1668, 1591, 1495, 1479, 1470, 995, 961, 941, 920, 878, 854, 845, 827, 806, 791, 754, 729, 664 cm^{-1}; ^1H NMR ($CDCl_3$, DMSO-d_6) δ 2.80−2.98 (m, 3 H), 3.91 (s, 3 H), 4.04 (s, 3 H), 4.21 (d, 1 H, J = 7.9 Hz), 4.48 (dd, 1 H, J = 5.3, 7.9 Hz), 4.66−4.72 (m, 1 H), 5.04 (d, 1 H, J = 5.3 Hz), 5.96 (s, 2 H), 6.69 (s, 1 H), 7.12 (d, 1 H, J = 8.2 Hz), 7.30 (brs, 1 H), 7.55 (d, 1 H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 33.4 (t), 39.1 (t), 54.8 (q), 60.3 (q), 62.6 (d), 72.1 (d), 99.3 (t), 105.3 (d), 108.2 (d), 114.1 (d), 120.4 (d), 122.6 (s), 130.2 (s), 134.7 (s), 135.0 (s), 144.3 (s), 144.5 (s), 144.6 (s), 150.7 (s), 163.8 (s). Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03%; H, 5.18%; N, 3.79%. Found: C, 64.95%; H, 5.22%; N, 3.58%.

22b (lower isomer): White solid; R_f 0.35 (hexanes/EtOAc, 1:5); mp 253−256 °C (recryst. from EtOAc); IR (KBr) 3372, 3291, 1647, 1618, 1599, 1489, 980, 962, 930, 897, 854, 824, 810, 797, 768, 745,

694, 685, 656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.98−3.08 (m, 1 H), 3.42−3.53 (m, 1 H), 3.79 (brs, 1 H), 3.92 (s, 3 H), 4.08 (s, 3 H), 4.55 (brs, 1 H), 4.67−4.76 (m, 1 H), 4.98 (d, 1 H, J = 3.1 Hz), 5.96 (s, 2 H), 6.69 (s, 1 H), 6.86 (s, 1 H), 7.14 (d, 1 H, J = 8.1 Hz); 7.25 (d, 1 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 32.4 (t), 39.6 (t), 55.1 (q), 60.6 (q), 62.2 (d), 74.0 (d), 99.6 (t), 108.7 (d), 109.6 (d), 114.5 (d), 116.2 (d), 123.7 (s), 132.7 (s), 133.0 (s), 135.5 (s), 144.1 (s), 144.9 (s), 145.3 (s), 150.8 (s), 164.6 (s). Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03%; H, 5.18%; N, 3.79%. Found: C, 65.05%; H, 5.19%; N, 3.65%.

Typical Procedure of Dehydration. A mixture of ***trans*-11** (126 mg, 0.5 mmol) and $KHSO_4$ (50 mg) in xylene (10 mL) was refluxed using a Dean−Stark apparatus for 6 h. After the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to give **13** in 88% yield.

13: Yellow solid; mp 157−158 °C (lit.[13] 157−158 °C).

14: Yellow solid; mp 128−129 °C (lit.[14] 128−130 °C).

Dehydrolennoxamine **23**: Yellow solid; mp 208−209 °C (lit.[15] 208−209 °C).

Typical Procedure for Hydrogenation. A suspension of **13** (93 mg, 4 mmol) and 10% Pd−C (40 mg) in EtOAc (10 mL) was stirred for 6 h under an atmospheric pressure of hydrogen. After the catalyst was filtered off, the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel to give **15** in 95% yield.

15: White solid; mp 134−136 °C (lit.[14] 126−128 °C).

16: White solid; mp 197−198 °C (lit.[14] 193−195 °C).

Lennoxamine **7**: White solid; mp 234−235 °C (lit.[41] 235−235.5 °C).

X-ray Crystallographic Analysis of *cis*-5, *trans*-12, and *cis*-12. All measurements of X-ray crystallographic analysis were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo Kα radiation. The structure was solved by direct methods with SIR-97 and refined with SHELXL-97. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. All calculations were performed using the YADOKARI-XG software package.

***cis*-5** (CCDC 838890): $C_{16}H_{13}NO_3$, FW = 267.27, mp 187−189 °C, monoclinic, $P2_{1/c}$ (No. 14), colorless block, a = 17.296(3) Å, b = 9.0264(16) Å, c = 17.030(3) Å, β = 28.664(4), V = 1275.3(4) $Å^3$, T = 298 K, Z = 4, D_{calcd} = 1.392 g/cm^3, μ = 0.97 cm^{-1}, GOF = 1.062.

***trans*-12** (CCDC 838891): $C_{17}H_{15}NO_2$, FW = 265.30, mp 215−216 °C, monoclinic, $P2_{1/c}$ (No. 14), colorless block, a = 14.500(2) Å, b = 7.1527(12) Å, c = 25.930(4) Å, β = 99.797(9), V = 2650.1(7) $Å^3$, T = 298 K, Z = 8, D_{calcd} = 1.330 g/cm^3, μ = 0.87 cm^{-1}, GOF = 0.942.

***cis*-12** (CCDC 838889): $C_{17}H_{15}NO_2$, FW = 265.30, mp 199−200 °C, monoclinic, $P2_{1/c}$ (No. 14), colorless block, a = 10.8606(16) Å, b = 8.0593(8) Å, c = 15.861(2) Å, β = 105.485(6), V = 1337.9(3) $Å^3$, T = 298 K, Z = 4, D_{calcd} = 1.317 g/cm^3, μ = 0.87 cm^{-1}, GOF = 1.026.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of **1**−**7**, **9**−**16**, **18**, **19**, and **21**−**23** and X-ray crystallographic structures (Ortep) of ***cis*-5**, ***trans*-12**, and ***cis*-12** (PDF), as well as crystallographic CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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