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Improved asymmetric synthesis of dopamine D1 full agonist, dihydrexidine, employing chiral ligand-controlled asymmetric conjugate addition of aryllithium to a nitroalkene

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Abstract—Asymmetric conjugate addition of 2-trityloxymethylpheyllithium to a nitroalkene was mediated by a chiral ligand to give the key intermediate for dopamine D1 full agonist dihydrexidine **1**. The shortcut of both Curtius rearrangement and Pictet–Spengler type cyclization, which were the drawback of the previously reported synthesis involving asymmetric conjugate addition of phenyllithium to an enoate, was realized by the newly developed asymmetric reaction. Short and efficient synthetic way gave optically pure dihydrexidine in 45% overall yield via eight steps. Improved synthesis of the best chiral ligand **13** was realized under the Buchwald conditions.

1. Introduction

Nitrogen-containing heterocyclic compounds are abundant in nature. Among them chiral arene-fused-piperidine is one of the representative structural motifs often observed in biologically active phenanthridine and isoquinoline alkaloids[1,2] as well as artificial pharmaceuticals.[3] We have previously reported the asymmetric synthesis of a phenanthridine class of compounds, dihydrexidine **1**[4] being characterized by dopamine D1 full agonist activity.[5] The synthesis is featured by a chiral ligand-mediated asymmetric conjugate addition of phenyllithium to a BHA enoate **4** as a key step (Fig. 1). However, the drawbacks of this synthesis are the Curtius rearrangement of a carboxylic acid moiety of **3** to an amine functionality of **2** and the following Pictet–Spengler type cyclization of inactivated phenyl group for the construction of a requisite arene-fused-piperidine motif. The shortcut of the Curtius reaction relies on the conjugate addition of phenyllithium to a nitroalkene **6** instead of an enoate **4** (Fig. 2). Further shortcut is possible by the conjugate addition of ortho-substituted phenyllithium to **6** giving **8** and reduction of a nitro group to an amine **7** that avoids tedious procedure for the Pictet–Spengler type cyclization (Fig. 2). We have already succeeded in the development of the chiral ligand-controlled asymmetric *ortho*-substituted aryllithium addition to **6** and further

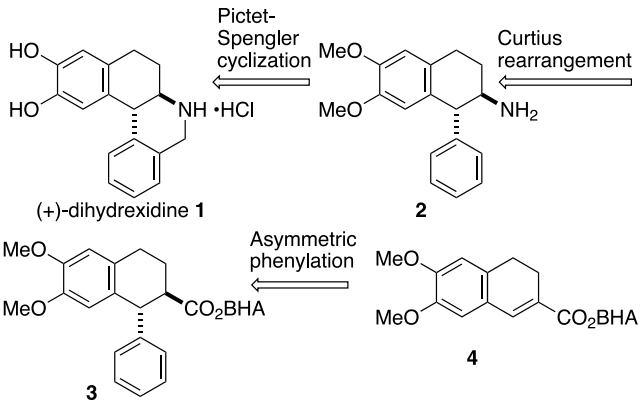

Figure 1. Asymmetric phenylation of **4**, Curtius rearrangement, and Pictet–Spengler cyclization for the synthesis of (+)-dihydrexidine **1**.

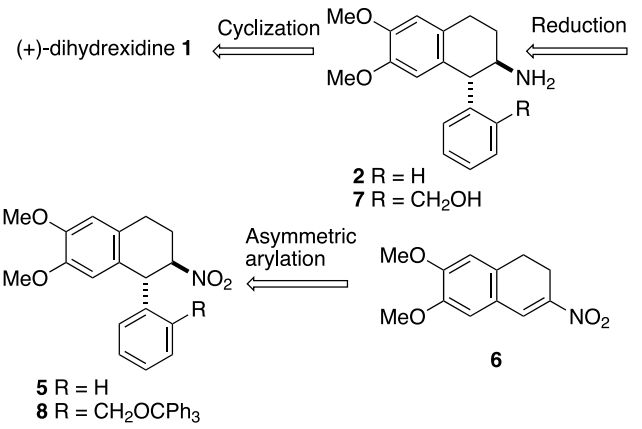

Figure 2. Asymmetric arylation of **6**, reduction to an amine, and Pictet–Spengler reaction or alkylation for the short synthesis of **1**.

Keywords: Asymmetric synthesis; Alkaloid; Piperidine; Agonist; Dopamine.
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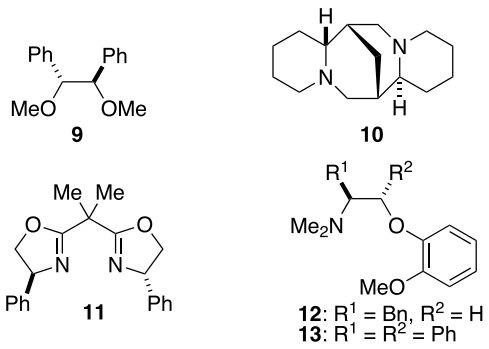


Figure 3. The bidentate and tridentate chiral ligands **9**-**13**.

construction of an arene-fused piperidine motif.[6] We describe herein full detail for the approach toward the improved synthesis of dihydrexidine **1**.

2. Results and discussion

2.1. Chiral ligand-mediated asymmetric conjugate addition of phenyllithium to a nitroalkene

The first chiral ligand-mediated asymmetric alkyllithium addition to nitroalkenes was developed by Seebach, giving the corresponding substituted nitroalkanes in moderate enantioselectivity.[7] The impressive recent successes were the catalytic asymmetric addition of dialkylzinc[8] and arylboronic acid.[9] The sparteine-mediated conjugate addition of the lithiated *N*-Boc allylic and benzylic amines to nitroalkenes was also a great success, which provided an efficient way to the synthesis of simple piperidines in high enantioselectivities.[10] As a challenge to this end,[11,12] we began our study with examination of a chiral ligand-mediated asymmetric conjugate addition of phenyllithium to a cyclic nitroalkene **6**.[13]

The reaction of phenyllithium with **6**[14] in toluene was examined in the presence of a chiral diether ligand **9** that gave a nice stereoselection in the reaction of an enoate **4** (Fig. 3). However, the reaction was not smooth at −20 °C for 0.5 h to give *ent*-**5** as a *trans*/*cis* mixture in 33% yield (Table 1, entry 1). The enantioselectivity was determined to be 22% ee by a chiral stationary phase HPLC. *ortho*-TMS-Substituted phenyllithium, prepared from (2-bromophenyl)-trimethylsilane,[15] was not a good nucleophile, giving the product **5a** (R=TMS) in low chemical yield (entry 2). The bidentate Box ligand **11** mediated the reaction at −78 °C for 0.5 h to give **5** in 68% yield. However, enantioselectivity was only 14% ee (entry 4). A tridentate aminodiether ligand **12** was also not a good mediator, giving **5** in 19% ee and 58% yield (entry 5). Fortunately, (−)-sparteine **10** was found to be the best ligand, at −78 °C for 1 h affording *ent*-**5** in 88% yield and 44% ee (entry 3).

Epimerization of the *cis*-**5** to the requisite *trans*-**5** was easily carried out by treating a *trans*:*cis* 62:38-mixture of *ent*-**5** (entry 3) with triethylamine in acetonitrile at room temperature for 18 h, giving the *trans*:*cis* 86:14-mixture in 98% yield (Fig. 4). Recrystallization of the mixture three times from methanol gave optically and diastereomerically pure nitro compound *ent*-**5** in 27% recovery yield. The following treatment with zinc in 6 N HCl and ethanol at room temperature for 2.5 h gave the amine *ent*-**2** in 86% yield. The spectroscopic and analytical data excepting the sign of specific rotation were identical with those of **2** prepared previously. Thus, the asymmetric synthesis of (−)-dihydrexidine **1** is possible in 11% overall yield from **6**.

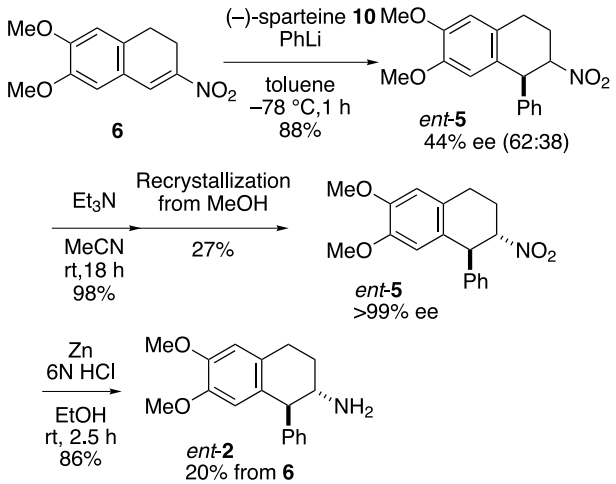
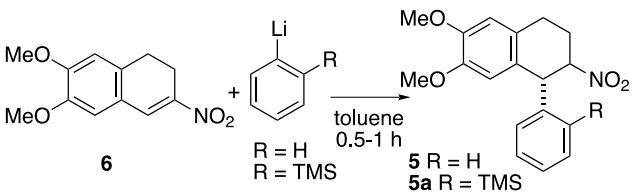


Figure 4. Synthesis of the key intermediate *ent*-**2**.

Table 1. Chiral ligand-mediated asymmetric reaction of a nitroalkene **6** with aryllithium



Entry	Chiral ligand	R	Temperature (°C)	Product **5**	Yield (%)	*trans*/*cis*	ee (%)
1	**9**	H	−20	*ent*-**5**	33	52:48	22
2	**9**	TMS	−78	**5a**	10	49:51	27
3	**10**	H	−78	*ent*-**5**	88	62:38	44
4	**11**	H	−78	**5**	68	41:59	14
5	**12**	H	−78	**5**	58	71:29	19

The chiral ligand of 1.4–2.0 equiv./ArLi was used. ee of *trans*-**5**. ee of *cis* isomer is nearly same with that of *trans*-**5**.

2.2. 2-Trityloxymethylphenyllithium as the key nucleophile for the efficient asymmetric synthesis of (+) dihydrexidine (1)

A straightforward synthetic way toward **1** is the conjugate addition of 2-hydroxymethylphenyllithium to nitroalkene **6** and subsequent reduction of the nitro group of **8** to an amino group of **7** and cyclization to construct piperidine motif **1** (Fig. 2). The chiral ligand **12** controlled the asymmetric addition of 2-trityloxymethylphenyllithium[16] to **6** at −95 °C for 1 h to afford the adduct **8** as a *trans*/*cis* mixture in 86% ee. Subsequent treatment with sodium bicarbonate in refluxing ethanol for 4 h and following detritylation with conc. HCl in THF-methanol at room temperature for 18 h gave **8a** (R=CH_2OH) of 86% ee in 86% yield (Fig. 5).

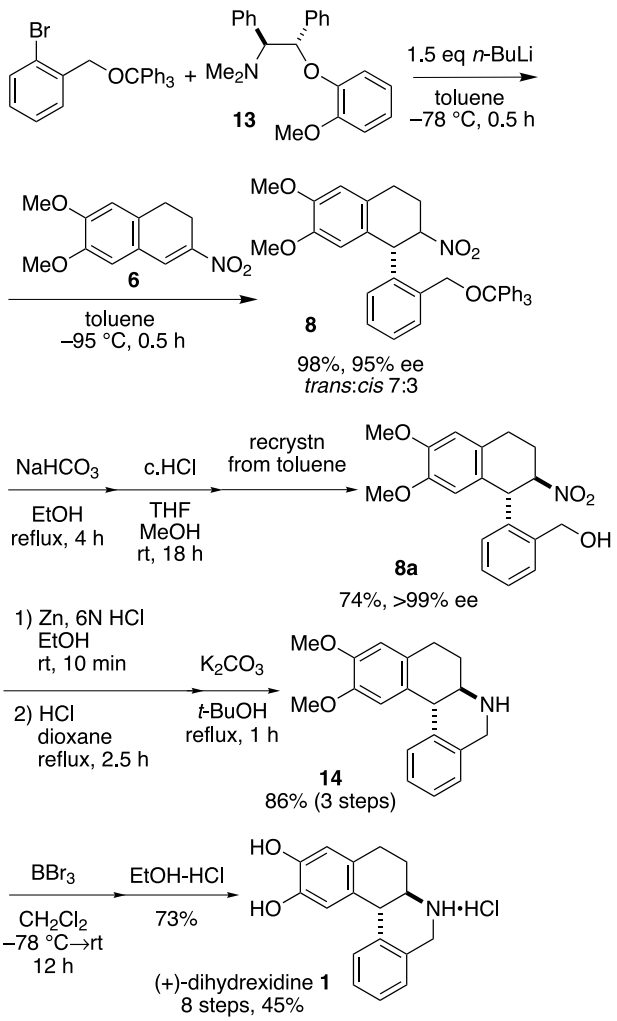


Figure 5. Efficient asymmetric total synthesis of **1**.

Much more improvement was possible by the mediation of a chiral ligand **13** to afford, after epimerization and detritylation, **8a** (R=CH_2OH) of 95% ee in 83% overall yield (Fig. 5).[6] Recrystallization from toluene gave back optically pure **8a** (R=CH_2OH) in 87% yield.

The zinc reduction of a nitro group of **8a** in a mixture of conc. HCl and ethanol at room temperature for 10 min, chlorination of the resulting alcohol with HCl in refluxing dioxane for 2.5 h, and then cyclization with potassium carbonate in refluxing *tert*-butanol for 1 h provided a fused piperidine **14** in 86% three step overall yield. Further demethylation with boron tribromide and hydrochloride formation completed the total synthesis of (+)-dihydrexidine **1** in 45% overall yield via 8 steps from a nitroalkene **6**.

2.3. Improved synthesis of a chiral tridentate aminodiether ligand (13)

The chiral ligand **13** was prepared in much more sophisticated way than the previous synthesis[12e] (Fig. 6). Treatment of a chiral amino alcohol with 2-iodoanisole under the Buchwald's conditions,[17] copper(I) iodide, cesium carbonate in butyronitrile at 125 °C for 1 day, gave **13** in 82% yield. Production of **13** over 10 g was possible under the conditions. It is also important to note that both enantiomers of **13** are available from the corresponding chiral amino alcohols.

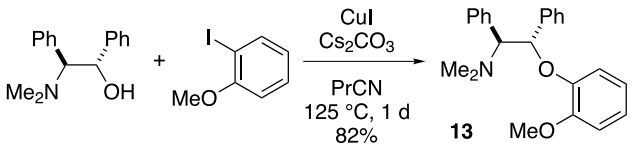


Figure 6. One step synthesis of **13**.

3. Conclusion

Improvement of the previously reported synthetic route to dihydrexidine **1** was realized by employing chiral ligand-mediated asymmetric conjugate addition of aryllithium to a nitroalkene **6**. Shortcut of both Curtius rearrangement and Pictet–Spengler type cyclization enabled an efficient and short step synthesis of optically pure target. The asymmetric reaction to a nitroalkene becomes the fundamental for the synthesis of the related candidates of pharmaceuticals.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were taken in $CDC1_3$ unless otherwise noted. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. IR was expressed in cm^{-1}. The extract was dried over Na_2SO_4 unless otherwise noted. Purification was carried out using silica gel column chromatography. All reactions were carried out under an argon atmosphere unless otherwise stated.

4.1.1. (1*S*,2*S*)-6,7-Dimethoxy-2-nitro-1-phenyl-1,2,3,4-tetrahydronaphthalene (*ent*-5) (Table 1, entry 3). To a solution of (−)-sparteine **10** (984 mg, 4.2 mmol) in toluene (25 mL) was added phenyllithium (1.7 mL, 1.8 M in cyclohexane-ether, 3.0 mmol) at −78 °C over 1 min. After 0.5 h stirring, nitroalkene **6**[14] (235 mg, 1.0 mmol) in toluene (5.0 mL) was added over 2 min, and the mixture was stirred for additional 1 h. The mixture was quenched with MeOH (2.0 mL) and then satd NH_4Cl (30 mL), and extracted with AcOEt. The extract was washed with 10% HCl, satd

$NaHCO_3$, and brine, and then dried. Concentration and chromatography (hexane/AcOEt=10/1) gave a mixture of 62/38 *trans*- and *cis*-*ent*-**5** (277 mg, 88% yield) as pale yellow amorphous of $[\alpha]_D^{25}=+75.3$ (*c* 1.0, $CHCl_3$). The ratio of the stereoisomers was determined to be (1*S*,2*S*)/(1*R*,2*R*)=72:28 and (1*S*,2*R*)/(1*R*,2*S*)=71:29 by a chiral HPLC analysis (Daicel Chiralcel OD-H, hexane/*i*-PrOH=9/1, 1.0 mL/min, 254 nm, 14.5 min for (1*S*,2*S*), 18.6 min for (1*R*,2*R*), 25.2 min for (1*R*,2*S*), and 30.1 min for (1*S*,2*R*)). ^{1}H NMR: 2.17–2.21 (0.38H, m, *cis*), 2.29–2.49 (1.62H, m, *trans* and *cis*), 2.90–3.11 (2H, m, *trans* and *cis*), 3.61 (1.86H, s, *trans*), 3.71 (1.14H, s, *cis*), 3.87 (1.86H, s, *trans*), 3.89 (1.14H, s, *cis*), 4.72 (0.62H, d, *J*=7.9 Hz, *trans*), 4.82 (0.38H, d, *J*=5.8 Hz, *cis*), 4.85–4.88 (0.62H, m, *trans*), 4.98–5.02 (0.38H, m, *cis*), 6.24 (0.62H, s, *trans*), 6.40 (0.38H, s, *cis*), 6.62 (0.62H, s, *trans*), 6.66 (0.38H, s, *cis*), 6.93 (0.76H, dd, *J*=3.7, 7.1 Hz, *cis*), 7.12 (1.24H, d, *J*=7.7 Hz, *trans*), 7.23–7.33 (3H, m, *trans* and *cis*).

A solution of the above mixture of *ent*-**5** (230 mg, 0.74 mmol) and Et_3N (0.10 mL, 0.74 mmol) in MeCN (3.0 mL) was stirred for 18 h at rt. The mixture was concentrated, and the resulting residue was dissolved in AcOEt. The solution was washed with 10% HCl, satd $NaHCO_3$, and brine, and then dried. Concentration gave a 86:14 *trans*/*cis* mixture of *ent*-**5** (226 mg, 98% yield), whose recrystallization 3 times from methanol afforded the enantiomerically and diastereomerically pure *trans*-*ent*-**5** (77 mg, 27% yield) as colorless needles of mp 139.5–140.5 °C and $[\alpha]_D^{25}=+93.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR: 2.37–2.49 (2H, m), 2.92–3.05 (2H, m), 3.61 (3H, s), 3.87 (3H, s), 4.72 (1H, d, *J*=8.3 Hz), 4.84–4.88 (1H, m), 6.24 (1H, s), 6.62 (1H, s), 7.11 (2H, d, *J*=7.7 Hz), 7.26–7.33 (3H, m). ^{13}C NMR: 26.7, 26.9, 48.8, 55.8, 55.9, 89.8, 110.7, 112.4, 126.7, 127.3, 127.6, 128.9, 129.0, 141.4, 147.8, 148.0. IR (KBr): 1554, 1512. EIMS *m*/*z*: 313 (M^+), 280, 265, 235, 176, 165, 91. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.91; H, 6.03; N, 4.21.

4.1.2. (1*S*,2*S*)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-amine (*ent*-2). To a solution of *ent*-**5** (31 mg, 0.10 mmol) in EtOH (1.0 mL) and 6 N HCl (0.3 mL, 1.8 mmol) was added Zn (65 mg, 1.0 mmol). After stirred for 2.5 h at rt the mixture was filtered, and the filtrate was concentrated. The residue was dissolved in $CHCl_3$, and the solution was washed with satd $NaHCO_3$ and brine, and then dried. Concentration and recrystallization from AcOEt gave *ent*-**2** (24 mg, 86% yield) as colorless needles of mp 101.0–102.5 °C and $[\alpha]_D^{25}=-20.6$ (*c* 1.3, $CHCl_3$). ^{1}H NMR: 1.27 (2H, s), 1.73 (1H, m), 2.04 (1H, m), 2.87 (1H, ddd, *J*=4.3, 4.9, 16.5 Hz), 2.97 (1H, ddd, *J*=4.9, 5.5, 6.1 Hz), 3.18 (1H, m), 3.58 (3H, s), 3.68 (1H, d, *J*=7.9 Hz), 3.86 (3H, s), 6.18 (1H, s), 6.62 (1H, s), 7.16–7.33 (5H, m). ^{13}C NMR: 27.7, 30.7, 54.5, 55.5, 55.7, 55.8, 110.9, 113.0, 126.6, 128.4, 129.9, 128.5, 130.3, 144.5, 147.2,147.4. IR (KBr): 3400, 3100, 1610, 1510. EIMS *m*/*z*: 283 (M^+), 266, 251. Anal. Calcd for $C_{18}H_{21}NO_2\cdot 1/10H_2O$: C, 75.81; H, 7.49; N, 4.91. Found: C, 75.79; H, 7.43; N, 4.68.

4.1.3. (1*S*,2*S*)- and (1*S*,2*R*)-6,7-Dimethoxy-2-nitro-1-(2-trityloxymethylphenyl)-1,2,3,4-tetrahydronaphthalene (*cis*- and *trans*-8). The title compound was prepared in 98% yield as a 70/30 *trans*/*cis* mixture of pale yellow needles of mp 71–74 °C by using a chiral ligand **13**.[6]

4.1.4. {2-[(1*S*,2*R*)-6,7-Dimethoxy-2-nitro-1,2,3,4-tetrahydronaphthalen-1-yl]phenyl}methanol (8a). A mixture of above **8** (289 mg, 0.49 mmol) and $NaHCO_3$ (414 mg, 4.9 mmol) in EtOH (5.0 mL) was heated under reflux for 4 h. The mixture was filtered and the filtrate was concentrated to give a 98:2 *trans*/*cis* mixture. The solution of the residue in MeOH (1.9 mL), THF (1.9 mL), and 12 N HCl (0.6 mL, 7.4 mmol) was stirred at rt for 18 h, and then diluted with AcOEt. The organic layer was washed with satd $NaHCO_3$ and brine, and then dried. Concentration and chromatography (hexane/AcOEt=4:1) gave **8a** (109 mg, 85% yield) as colorless prisms of mp 47–49 °C and $[\alpha]_D^{25}=-147$ (*c* 0.90, $CHCl_3$) for 95% ee (HPLC: Daicel Chiralpak AD; hexane/*i*-PrOH=4:1, 1.0 mL/min; 254 nm, major 12.8 min and minor 16.7 min). ^{1}H NMR: 1.89 (1H, brs), 2.41–2.51 (2H, m), 2.94–3.06 (2H, m), 3.58 (3H, s), 3.86 (3H, s), 4.77 (1H, s), 5.08–5.10 (1H, m), 6.20 (1H, s), 6.62 (1H, s), 6.96 (1H, d, *J*=6.1 Hz), 7.23–7.40 (2H, m), 7.42 (1H, d, *J*=7.4 Hz). ^{13}C NMR: 26.3, 26.5, 44.6, 55.8, 63.3, 88.5, 110.8, 112.3, 126.7, 127.6, 127.7, 128.6, 129.6, 129.9, 138.8, 140.0, 147.9, 148.0. IR (neat): 3487, 1547, 1516, 1462, 1404, 1369, 1254. EIMS *m*/*z*: 343 (M^+), 326, 296, 278, 265. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.16; H, 6.17; N, 3.93.

Recrystallization from toluene afforded the enantiomerically and diastereomerically pure **8a** (77 mg, 87% yield) as colorless prisms of mp 52–53 °C and $[\alpha]_D^{25}=-154$ (*c* 0.81, $CHCl_3$) for >99% ee.

4.1.5. (6a*R*,12b*S*)-10,11-Dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine (14). A suspension of the above **8a** (31 mg, 0.09 mmol) and Zn (59 mg, 0.90 mmol) in EtOH (3.0 mL) and 6 N HCl (0.5 mL, 3.0 mmol) was stirred for 10 min at rt. The mixture was filtered, and the filtrate was concentrated. A solution of the resulting amine in 1,4-dioxane (1.3 mL) and 12 N HCl (0.8 mL) was heated under reflux for 2.5 h. Concentration gave the intermediate chloride, which was immediately dissolved in *t*-BuOH (2.5 mL). To the solution was added K_2CO_3 (500 mg, 3.6 mmol), and the mixture was heated under reflux for 1 h. The mixture was cooled to rt, poured into water, and extracted with $CHCl_3$. The organic layer was washed with brine and dried over K_2CO_3. Concentration and chromatography (AcOEt/MeOH=9:1) gave **14** (23 mg, 86% yield) as colorless prisms of mp 155–156 °C (>99% ee) and $[\alpha]_D^{25}=-222$ (*c* 1.1, $CHCl_3$). ^{1}H NMR: 1.69–1.75 (2H, m), 2.14–2.21 (1H, m), 2.71 (1H, ddd, *J*=6.7, 10.7, 10.7 Hz), 2.78–2.84 (1H, m), 2.90–2.95 (1H, m), 3.77 (3H, s), 3.83 (1H, d, *J*=10.7 Hz), 3.88 (3H, s), 4.03 (1H, d, *J*=15.6 Hz), 4.11 (1H, d, *J*=15.6 Hz), 6.74 (1H, s), 6.91 (1H, s), 7.16 (1H, d, *J*=7.4 Hz), 7.21–7.29 (2H, m), 7.47 (1H, d, *J*=7.4 Hz). ^{13}C NMR: 27.4, 28.9, 44.6, 49.1, 56.0, 56.1, 58.8, 110.0, 111.9, 126.0, 126.1, 126.8, 128.5, 130.7, 130.9, 136.1, 137.7, 146.6, 147.1. IR (KBr): 3294, 1504. EIMS *m*/*z*: 295 (M^+), 278, 263, 165. The hydrochloride: colorless needles of mp >236 °C (dec) (>99% ee). $[\alpha]_D^{25}=+123$ (*c* 0.75, EtOH). Anal. Calcd for $C_{19}H_{22}ClNO_2$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.53; H, 6.69; N, 4.16.

The absolute configuration was determined to be (6a*R*,12b*S*) by comparison of the specific rotation with that reported ($[\alpha]_D^{25}$=+106 (*c* 0.75, EtOH) for >99% ee).[18]

4.1.6. (6a*R*,12b*S*)-10,11-Dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (1). To a solution of **14** (20 mg, 0.06 mmol) in CH_2Cl_2 (3.0 mL) was added BBr_3 (0.3 mL, 1.0 M in hexane, 0.3 mmol) over 10 min at −78 °C, and the mixture was stirred at rt for 12 h. The mixture was quenched with MeOH (3.0 mL), stirred for 0.5 h, and then concentrated. The residue was dissolved in water, and the pH was adjusted to 9–10 with $NaHCO_3$ under Ar atmosphere. The mixture was extracted with $CHCl_3$, and the combined organic layers were dried and concentrated to give 20 mg of a pale yellow powder. A solution of the powder in EtOH (1 mL) and EtOH–HCl (3 mL) was stirrer at rt for 0.5 h and concentrated. The residue was azeotoropically dried with benzene (3 mL) and recrystallized from AcOEt/isopropanol to give **1** (15 mg, 73% yield) as pale yellow powder of mp >122 °C (dec) and $[\alpha]_D^{25}$=+85.5 (*c* 0.24, EtOH). ^{1}H NMR (DMSO): 1.98 (1H, m), 2.23 (1H, m), 2.70–2.85 (2H, m), 3.00 (1H, m), 4.22 (1H, d, *J*=11.0 Hz), 4.41 (1H, d, *J*=15.8 Hz), 4.44 (1H, d, *J*=15.8 Hz), 6.68 (1H, s), 6.78 (1H, s), 7.35–7.50 (4H, m), 8.93 (1H, m), 8.95 (1H, m), 9.67 (1H, s), 9.95 (1H, s). ^{13}C NMR (DMSO): 25.3, 26.3, 40.3, 43.9, 56.6, 114.6, 115.9, 124.3, 126.3, 126.8, 127.5, 127.7, 127.8, 130.5, 143.2, 144.0. IR (nujol): 3000–3700, 1610, 1510. CIMS *m*/*z*: 268 (M^++1). HRMS-CI (*m*/*z*): $[M+H]^+$ Calcd for $[C_{17}H_{19}NO_2]^+$, 268.1337. Found, 268.1135.

4.1.7. (1*S*,2*S*)-1-Dimethylamino-2-(2-methoxyphenoxy)-1,2-diphenylethane (13). A mixture of CuI (7.80 g, 33.3 mmol, 67 mol %), cesium carbonate (41.5 g, 133 mmol), (1*S*,2*S*)-2-(dimethylamino)-1,2-diphenylethanol[19] (12.1 g, 50 mmol), and 2-iodoanisole (23.5 g, 100 mmol) in butyronitrile (60 mL) was stirred at 125 °C for 1 day.[17] The reaction mixture was cooled to rt and filtered, and the filter cake was washed well with AcOEt. The combined filtrate and the washings were extracted with 10% HCl (3×100 mL) and the acid extracts were cooled at 0 °C for 1 h. The resulting precipitates were filtered and washed with AcOEt. The collected precipitates were dissolved in 5 M NaOH (200 mL), and the solution was extracted with Et_2O several times. The extracts were washed with brine and dried over K_2CO_3. Concentration and recrystallization from hexane gave **13** (14.3 g, 82% yield) as colorless needles of mp 72–73 °C.[12e]

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References and notes

1. Reviews: (a) Martin, S. F. *The alkaloids*; Brossi, A., Ed.; Academic: New York, 1987; Vol. 30, pp 251–376. (b) Grundon, M. F. *Nat. Prod. Rep.* **1989**, *6*, 79–84. (c) Lewis, J. R. *Nat. Prod. Rep.* **1995**, *12*, 339–345. (d) Hoshino, O. *The alkaloids*; Cordell, G. A., Ed.; Academic: San Diego, 1998; Vol. 51, pp 323–424.
2. Pancratistatin: (a) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693–1694. (b) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 1018–1020. Lycorine: (c) Yui, S.; Mikami, M.; Kitahara, M.; Yamazaki, M. *Immunopharmacology* **1998**, *40*, 151–162. Galantamine: (d) *WHO Drug Information*, **1998**, *12*, 205.
3. Benzothienoquinoline, A-86929 (DAS-431): (a) Giardina, W. J.; Williams, M. *CNS Drug Rev.* **2001**, *7*, 305–316. (b) Ehrlich, P. P.; Ralston, J. W.; Michaelides, M. R. *J. Org. Chem.* **1997**, *62*, 2782–2785.
4. Brewster, W. K.; Nichols, D. E.; Riggs, R. M.; Mottola, D. M.; Lovenberg, T. W.; Lewis, M. H.; Mailman, R. B. *J. Med. Chem.* **1990**, *33*, 1756–1764.
5. Asano, Y.; Yamashita, M.; Nagai, K.; Kuriyama, M.; Yamada, K.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 8493–8495.
6. Yamashita, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1954–1955.
7. Seebach, D.; Crass, G.; Wilka, E.-M.; Hilvert, D.; Brunner, E. *Helv. Chim. Acta* **1979**, *62*, 2695–2698.
8. (a) Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305–2324. (b) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263. (c) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192–8193. (d) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *5*, 79–80. (e) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700–3701.
9. (a) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716–10717. (b) Hayashi, T. *Synlett* **2001**, 879–887. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844.
10. Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2002**, *124*, 11689–11698.
11. (a) Tomioka, K. *Synthesis* **1990**, 541–549. (b) Tomioka, K.; Nagaoka, Y. *Comprehensive asymmetric catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, Chapter 31. (c) Tomioka, K. In *Modern carbonyl chemistry*; Otera, J., Ed.; Wiley: Weinheim, 2000; Chapter 12. (d) Iguchi, M.; Yamada, K.; Tomioka, K. In *Organolithiums in enantioselective synthesis*; Hodgson, D. M., Ed.; Springer: Berlin, 2003; pp 37–59.
12. (a) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266–8268. (b) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351–9357. (c) Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron Lett.* **2000**, *41*, 5533–5536. (d) Tomioka, K.; Shioya, Y.; Nagaoka, Y.; Yamada, K. *J. Org. Chem.* **2001**, *66*, 7051–7054. (e) Nishimura, K.; Tomioka, K. *J. Org. Chem.* **2002**, *67*, 431–434. (f) Kuriyama, M.; Nagai, K.; Yamada, K.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc.* **2002**, *124*, 8932–8939. (g) Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2886–2887.
13. Unfortunately, rhodium-catalyzed phenylation with phenylboronic acid was unsuccessful under Hayashi (Ref. 9) and our conditions: Kuriyama, M.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 921–923, and Ref. 12f.
14. Michaelides, M. R.; Hong, Y.; DiDomenico, S., Jr.; Bayburt,

E. K.; Asin, K. E.; Britton, D. R.; Lin, C. W.; Shiosaki, K. *J. Med. Chem.* **1997**, *40*, 1585–1599.
15. Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Organomet. Chem.* **1980**, *193*, 283–289.
16. Full details on the effect of a trityl group on efficiency were presented in the Supporting Information of Ref. 6.
17. Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3703–3706.
18. Knoerzer, T. A.; Nichols, D. E.; Brewster, W. K.; Watts, V. J.; Mottola, D.; Mailman, R. B. *J. Med. Chem.* **1994**, *37*, 2453–2460.
19. (a) Weijlard, J.; Pfister, K., III; Swanezy, E. F.; Robinson, C. A.; Tishler, M. *J. Am. Chem. Soc.* **1951**, *73*, 1216–1218. (b) Saigo, K.; Ogawa, S.; Kikuchi, S.; Kasahara, A.; Nohira, H. *Bull. Chem. Soc. Jpn* **1982**, *55*, 1568–1573.