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Total synthesis of phenanthroindolizidine alkaloids *via* asymmetric deprotonation of *N*-Boc-pyrrolidine†

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A concise and efficient enantioselective strategy to synthesize two typical phenanthroindolizidine alkaloids, 14-hydroxyantofine and antofine, was developed, featuring an asymmetric deprotonation/diastereoselective carbonyl addition sequence during which the formation of a chiral C-13a center and connection of pyrrolidine and phenanthrene moieties were achieved efficiently in one step. The absolute configuration of the C-13a stereocenter can be delicately controlled by using different enantiomers of sparteine, both of which are commercially available.

Introduction

Phenanthroindolizidine alkaloids, isolated mainly from *Tylophora*, *Cynanchun*, *Pergularia*, and some genera of the *Asclepiadaceas* family, have attracted continuous attention from both the synthetic and pharmaceutical communities owing to their unique structural features and low natural abundance, as well as their noteworthy biological activities since the first isolation of (*R*)-tylophorine [(−)-**1b**] (Fig. 1) in 1935.[1]

In the past few decades, a number of impressive enantioselective synthetic routes for phenanthroindolizidine alkaloids have been reported.[1c,2] As these alkaloids possess a stereogenic center at the α position of the nitrogen atom, the chiron approach starting with optical α-amino acids or their derivatives has been widely used.[1c,2b,d,e,h,i,k] In addition, a few other remarkable strategies have also been employed in recent years, including the chiral auxiliary procedure,[2j,3] asymmetric transition-metal-catalyzed intramolecular carboamination,[2c,f] enantioselective phase-transfer alkylation,[2a] and proline-catalyzed asymmetric α-aminoxylation of an aldehyde,[2g] *etc.* Although a sustainable source of these alkaloids for bioactivity studies can be provided by the approaches mentioned above, a more efficient synthetic strategy is still desirable.

Asymmetric deprotonation of *N*-Boc-pyrrolidine using *s*-BuLi/(+)-sparteine, which gives a configurationally preferred carbanion, followed by nucleophilic substitution/addition was an attractive approach developed by Beak *et al.* for the direct functionalization of pyrrolidine (Scheme 1).[4] Although detailed mechanistic studies have been done for this elegant and creative methodology,[5] only a few successful applications in the total synthesis of natural products and chiral drug molecules have been reported, most of which used sinuous approaches to realize the asymmetric functionalization.[4d,e,6] To showcase the efficiency and convenience of this methodology, we wish herein to report a concise synthesis of (+)-14-hydroxyantofine (**2**) and (+)-antofine (**1a**), both of which are enantiomers of these alkaloids in nature (Fig. 1).

Results and discussion

Retrosynthetically, (+)-antofine (**1a**) and (+)-14-hydroxyantofine (**2**) were envisioned to be accessible *via* Pictet–Spengler

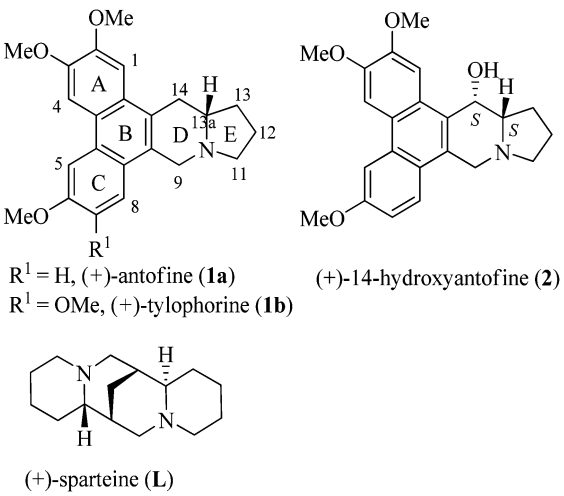

Fig. 1 Representative phenanthroindolizidine alkaloids and (+)-sparteine (L).

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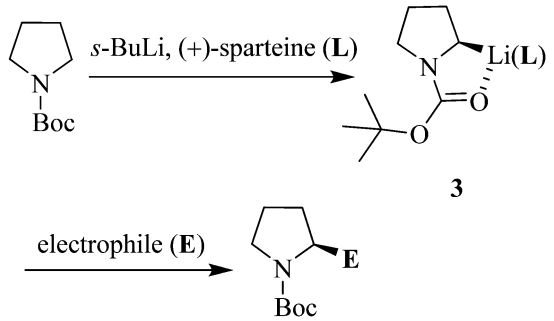
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectroscopic data for **5**, **5a**, **4c**, **7a**, **7b**, **1a**, and **2**. HRMS (ESI) data for **5a**, **4c**, **7a**, **7b**, and **2**. Chiral-HPLC chromatogram for **5**, **2**, **1a**. See DOI: 10.1039/c3ra47465h



Scheme 1 Asymmetric deprotonation of *N*-Boc-pyrrolidine using *s*-BuLi/(+)-sparteine (**L**).

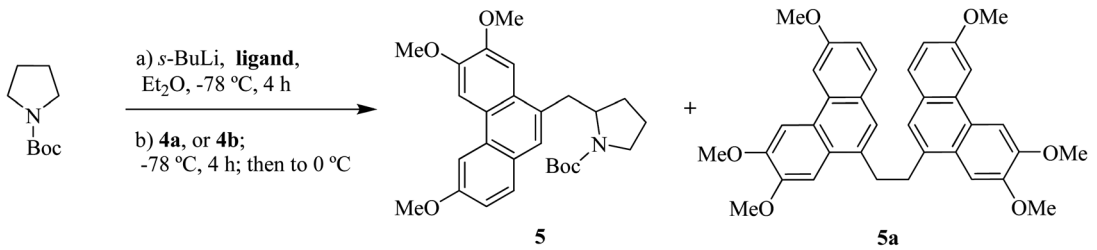
cyclization of compounds **5** (Table 1) and **7a**/**7b** (Scheme 3), respectively. Key intermediate **5** could be obtained by S_N2 substitution of chiral 2-lithio-*N*-Boc-pyrrolidine (**3**) to **4a** or **4b** (Table 1), and **7a**/**7b** by a nucleophilic carbonyl addition of **3** to phenanthryl aldehyde **6** (Table 1). The starting materials **4a**,[7a] **4b** (ref. 2i) and **6** (ref. 7b) were readily available by using an efficient and practical $FeCl_3$-mediated oxidative coupling method for constructing a polymethoxy-phenanthrene moiety developed by our group.[8]

Initially, alkylation of *N*-Boc-pyrrolidine with bromide **4b** was put into practice, as shown in Table 1. To explore the reactivity, tetramethylethylenediamine (TMEDA) was first employed as a ligand. Deprotonation of *N*-Boc-pyrrolidine with *s*-BuLi/TMEDA gave (±)-2-lithio-*N*-Boc-pyrrolidine, then bromide **4b** was added. Gratifyingly, the desired coupled product (±)-**5** was obtained in a moderate yield. It is worth noting that a main by-product **5a** was isolated in a 22% yield, which was believed to be produced from lithium–bromide exchange[9] of **4b** with 2-lithio-*N*-Boc-pyrrolidine and subsequent dimerization. To decrease the lithium–halogen exchange, **4b** was replaced by chloride **4a**, which showed that **4a** could give better results (Table 1, entry 1).

After investigating the reactivity of *N*-Boc-pyrrolidine, it was found that the asymmetric version was affected by the use of chiral ligand (+)-sparteine (Table 1, entries 3 and 4). Although great effort was made to optimize the reaction conditions, unfortunately, the desired product **5** could only be obtained in moderate enantiomeric excess and low yields. The reason for the lower yield was proposed to be the steric effect when the relatively bulky ligand was introduced. The subsequent Pictet–Spengler cyclization proved to be effective, giving antofine (**1a**) in a high yield (91%) and moderate ee (60%).

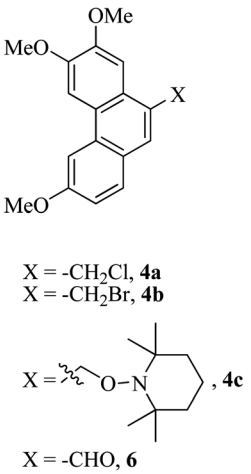
It was thought that the notable lithium–halogen exchange[9] during the alkylation should be responsible for the unsatisfying yield and ee. To explore the mechanism, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was introduced into the reaction system (Table 1, entry 5).[10] Product **5** was gained in a lower yield (23%) but a slightly raised ee (58%). Meanwhile, radical trapping product **4c** (Table 1) was isolated in an 18% yield, which suggested a free radical process, as shown in Scheme 2. Besides being generated by direct S_N2 substitution of chiral **3** with **4b**, **5** could also be produced by free radical

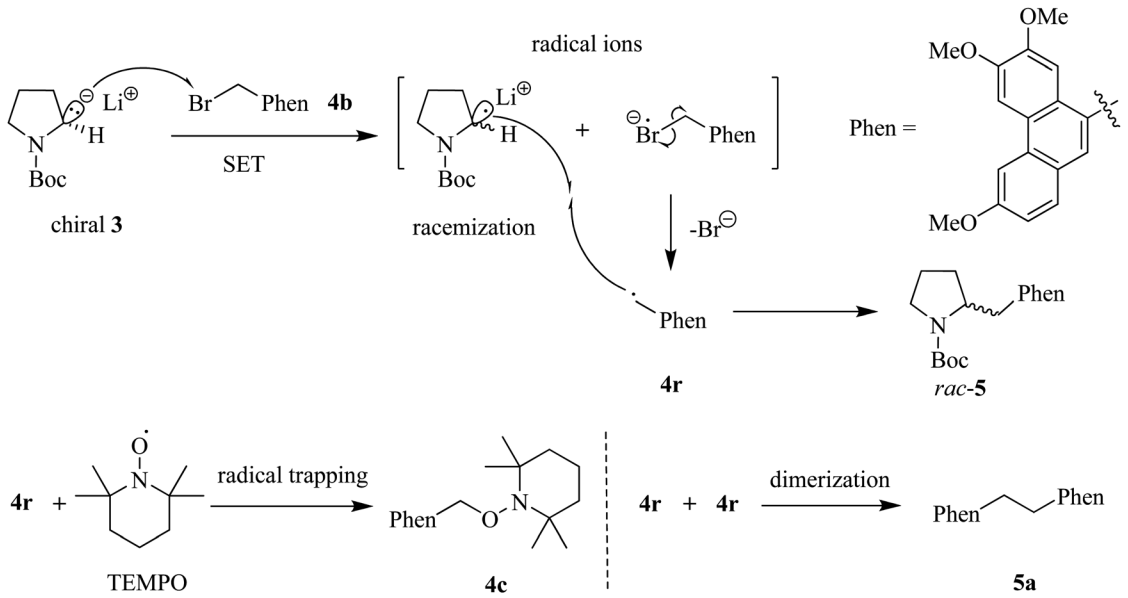
Table 1 Synthesis of (+)-antofine (**1a**) by alkylation of *N*-Boc-pyrrolidine



Entry	Ligand	Electrophiles	Yield (%)[a]		ee%
			5	**5a**	
1	TMEDA	**4a**	62	16	--
2	TMEDA	**4b**	50	22	--
3	(+)-sparteine	**4a**	33	11	62
4	(+)-sparteine	**4b**	37	17	53
5[b]	(+)-sparteine	**4b**	23	12	58

General reaction conditions: see procedure **A** and **B** in experimental section. a) Isolated yield; b) 2.0 equiv. TEMPO was added along with **4b**, and product **4c** was isolated in 18% yield .

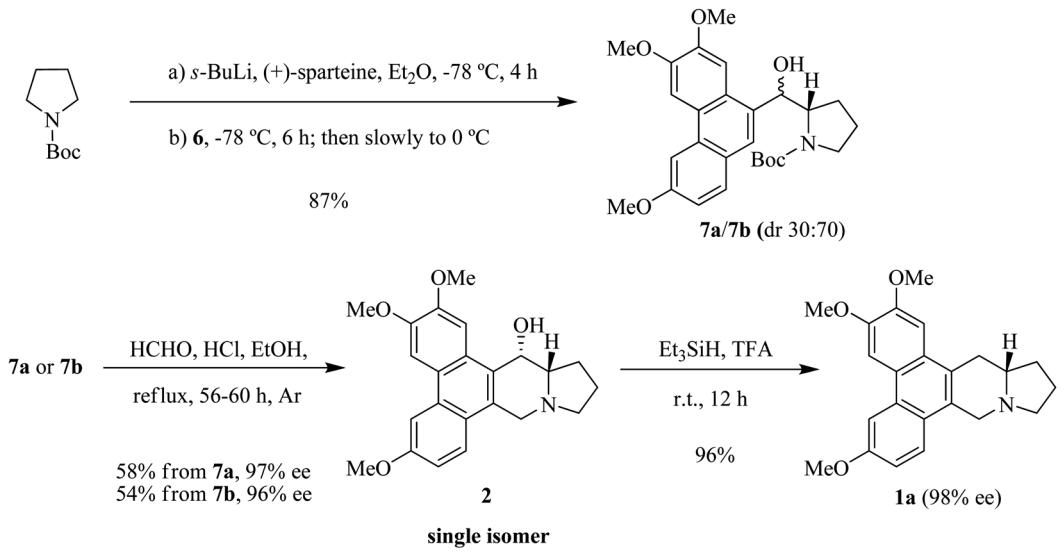




Scheme 2 Proposed mechanism of lithium–halogen exchange between 3 and 4b.

coupling after the single electron transfer (SET) process between 3 and **4b**, during which the racemization of chiral 3 and dimerization of free radical intermediate **4r** were unavoidable. We declare that this SET mechanism is at least a minor pathway but there must exist a lithium–halogen exchange pathway not involving SET.[9,11]

To avoid lithium–halogen exchange, a second strategy—carbonyl addition of 3 to **6**—was explored (Scheme 3). To our delight, treatment of *N*-Boc-pyrrolidine with *s*-BuLi/(+)-sparteine in diethyl ether gave chiral 3, which underwent reaction with phenanthryl aldehyde **6** to give the enantiomerically enriched, diastereomeric intermediates **7a** and **7b** in 26% and 61% yields, respectively. Then diastereoisomers **7a** and **7b** were subjected to Pictet–Spengler cyclization conditions separately. Interestingly, both isomers gave the same cyclization product **2** in moderate yields (58%, 54%) and high ee (97%, 96%), and the other diastereomeric product was not detected. It is believed that racemization at the C-14 stereocenter occurred under the harsh acidic Pictet–Spengler cyclization conditions, so only one configurationally preferred product was obtained. The NMR data of synthesized product **2** were identical to those reported in literature.[12] However, the specific rotation of compound **2** was opposite to the natural product, thus we confirmed that the absolute configuration of **2** was (13a*S*, 14*S*). After dehydroxylation, **1a** was obtained in a 96% yield and 98% ee.



Scheme 3 Synthesis of (+)-14-hydroxyantofine (**2**) and (+)-antofine (**1a**) by carbonyl addition of *N*-Boc-pyrrolidine.

Conclusions

In conclusion, a concise strategy to synthesize two typical phenanthroindolizidine alkaloids, antofine (**1a**) and 14-hydroxyantofine (**2**), has been explored, featuring asymmetric deprotonation of the *N*-Boc-pyrrolidine followed by reaction with carbon electrophiles. For the alkylation of compound **3** with **4**, a notable lithium–halogen exchange was observed, which should account for the unsatisfying yield and ee. For the carbonyl addition of **3** to **6**, a gratifying result was obtained. Product **2** was gained in a 47% total yield and 96–97% ee from **6** in two steps, then after undergoing one more step **1a** could be obtained in a 96% yield and 98% ee.

Experimental section

General information

The melting points were determined using an X-4 binocular microscope melting-point apparatus and were uncorrected. ^{1}H NMR spectra were obtained using a Bruker AV 400 spectrometer. Chemical shifts (δ) were given in parts per million (ppm) and were measured downfield from internal tetramethylsilane. ^{13}C NMR spectra were recorded using a Bruker AV 400 instrument (100 MHz) and $CDCl_3$ as the solvent. Chemical shifts (δ) were reported in parts per million. High-resolution mass spectra were obtained using an FT-ICR MS spectrometer (Ionspec, 7.0 T). Optical rotations were measured using an Autopol IV auto digital polarimeter (Rudolph Research Analytical). All anhydrous solvents were dried and purified by standard techniques just before use. All reagents were purchased from commercial suppliers without further purification. Reactions were monitored by thin layer chromatography on plates (GF254) using UV light as a visualizing agent. (+)-Sparteine was purchased from Aladdin Industrial Corporation. If not noted otherwise, flash column chromatography used silica gel (200–300 mesh).

Procedure A: racemic deprotonation of *N*-Boc-pyrrolidine and subsequent functionalization (Table 1, entries 1 and 2)

To a solution of TMEDA (278 mg, 2.4 mmol, 1.2 equiv.) and *N*-Boc-pyrrolidine (344 mg, 2.0 mmol, 1.0 equiv.) in Et_2O (60 mL) at −78 °C was added *s*-BuLi (2.2 mL, 1.0 M in hexane, 1.1 equiv.). The reaction mixture was stirred for 4 h at −78 °C, and then a suspension of electrophile **4** or **6** (1.0 mmol, 0.5 equiv.) in Et_2O (10 mL) was added. The mixture was stirred for 4–6 h at −78 °C, then allowed to warm slowly to 0 °C in 3 h. Workup consisted of the addition of water (20 mL), extraction of the aqueous layer with Et_2O (2 × 10 mL), extraction of the combined Et_2O extracts with 5% phosphoric acid (2 × 10 mL) and brine (2 × 10 mL), drying over anhydrous magnesium sulfate, filtration, and concentration *in vacuo*.

Procedure B: asymmetric deprotonation of *N*-Boc-pyrrolidine and subsequent functionalization (Table 1, entries 3–5)

To a solution of (+)-sparteine (563 mg, 2.4 mmol, 1.2 equiv.) and *N*-Boc-pyrrolidine (344 mg, 2.0 mmol, 1.0 equiv.) in Et_2O (60 mL) at −78 °C was added *s*-BuLi (2.2 mL, 1.0 M in hexane, 1.1 equiv.). The following operation was in accordance with procedure A.

Preparation of racemic 5 and 5a from 4a or 4b (Table 1, entries 1 and 2)

Taking **4a** as an example (Table 1, entry 1), lithiation of *N*-Boc-pyrrolidine was carried out according to procedure A, then a suspension of **4a** (317 mg, 1.0 mmol) in Et_2O (10 mL) was added. Purification by flash chromatography with 1/6 (v/v) EtOAc–hexane, followed by recrystallization from 1.0 mL methanol gave racemic **5** (280 mg, 62%) as a white solid; m.p. 150–152 °C (ref. 2b: 99–101 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (s, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 7.85 (d, J = 2.0 Hz, 1H, Ar-H), 7.73 (d, J = 8.8 Hz, 1H, Ar-H), 7.39 (s, 1H, Ar-H), 7.17 (dd, J = 8.8, 2.0 Hz, 1H, Ar-H), 4.26 (m, 1H, N-CH, 2-H), 4.22 (s, 3H, OMe), 4.12 (s, 3H, OMe), 4.02 (s, 3H, OMe), 3.92 (m, 1H, Ar-CH_2), 3.49 (m, 1H, Ar-CH_2), 3.32 (m, 1H, N-CH_2, 5-H), 2.59 (m, 1H, N-CH_2, 5-H), 2.02 (m, 1H, 3-H), 1.84 (m, 2H, 3-H, 4-H), 1.67 (m, 1H, 4-H), 1.51 (s, 9H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.8, 154.7, 149.8, 148.7, 131.1, 130.6, 129.5, 127.3, 126.0, 125.7, 124.5, 115.2, 106.8, 103.9, 103.4, 78.9, 57.2, 56.7, 56.0, 55.6, 46.8, 38.6, 29.0, 28.6, 23.5 ppm. Filtering the insoluble solid out of the organic/aqueous phase during the workup procedure gave **5a** (45 mg, 16%) as an off-white solid; m.p. 265–270 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (s, 2H, Ar-H), 7.87 (d, J = 2.4 Hz, 2H, Ar-H), 7.74 (d, J = 8.8 Hz, 2H, Ar-H), 7.58 (s, 2H, Ar-H), 7.37 (s, 2H, Ar-H), 7.20 (dd, J = 8.7, 2.4 Hz, 2H, Ar-H), 4.12 (s, 6H, OMe), 4.04 (s, 6H, OMe), 3.87 (s, 6H, OMe), 3.57 (s, 4H, Ar-CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.9, 149.3, 148.7, 133.1, 130.3, 129.6, 126.8, 126.2, 124.8, 124.1, 115.5, 104.7, 104.7, 103.9, 56.0, 55.8, 55.6, 33.8 ppm. HRMS (ESI): calcd for $C_{36}H_{35}O_6$ $[M + H]^+$ 563.2428, found 563.2423.

Preparation of (+)-5 and 5a from 4a or 4b (Table 1, entries 3 and 4)

Taking **4a** as an example (Table 1, entry 4), lithiation of *N*-Boc-pyrrolidine was carried out according to procedure B and then a suspension of **4a** (317 mg, 1.0 mmol) in Et_2O (10 mL) was added. Purification by flash chromatography with 1/6 (v/v) EtOAc–hexane, followed by recrystallization from 1.0 mL methanol gave (+)-**5** (150 mg, 33%) as a white solid. Chiral HPLC analysis (Chiralcel AD-H column, i-PrOH : hexane = 10 : 90, 1.0 mL min^{-1}) showed that the product had an enantiomeric excess of 62%. Filtering the insoluble solid out of the organic/aqueous phase during the workup procedure gave **5a** (31 mg, 11%) as an off-white solid. Other data were identical to those of racemic **5** and **5a** in procedure A.

Preparation of (+)-5, 4c, and 5a from 4b (Table 1, entry 5)

Lithiation of *N*-Boc-pyrrolidine according to procedure B was carried out, then a suspension of **4b** (361 mg, 1.0 mmol, 0.5 equiv.) and TEMPO (624 mg, 4.0 mmol, 2.0 equiv) in Et_2O (10 mL) was added. Purification by flash chromatography with 1/10 (v/v) EtOAc–hexane gave (+)-**5** (106 mg, 23%) as a white solid [chiral HPLC analysis (Chiralcel AD-H column,

i-PrOH : hexane = 10 : 90, 1.0 mL min^{-1}) showed that the product had an enantiomeric excess of 58%]; and **4c** (80 mg, 18%) as a white solid; m.p. 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (s, 1H, Ar-H), 7.86 (d, J = 2.4 Hz, 1H, Ar-H), 7.81 (d, J = 8.8 Hz, 1H, Ar-H), 7.66 (s, 1H, Ar-H), 7.50 (s, 1H, Ar-H), 7.20 (dd, J = 8.8, 2.4 Hz, 1H, Ar-H), 5.24 (s, 2H, Ar-CH_2), 4.12 (s, 3H, OMe), 4.07 (s, 3H, OMe), 4.03 (s, 3H, OMe), 1.59–1.52 (m, 6H, CH_2), 1.37 (s, 6H, CH_3), 1.18 (s, 6H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.3, 149.3, 148.7, 131.0, 130.3, 129.2, 126.4, 125.8, 125.0, 124.6, 115.4, 105.4, 103.9, 103.6, 78.4, 56.1, 56.0, 55.6, 39.4, 32.9, 20.5, 17.0 ppm. HRMS (ESI): calcd for $C_{27}H_{36}NO_4$ $[M + H]^+$ 438.2639, found 438.2635. Filtering the insoluble solid out of the organic/aqueous phase during the workup procedure gave **5a** (34 mg, 12%) as an off-white solid. Other data were identical to those of racemic **5** and **5a** in procedure A.

Preparation of 1a from (+)-5

(+)-**5** (45 mg, 0.1 mmol, 62% ee) provided by the above procedure (Table 1, entry 4) was dissolved in ethanol (2 mL). Conc. HCl (0.5 mL, 36–38%) and formaldehyde solution (0.5 mL, 37%) were then added and the reaction mixture was heated under reflux for 12 h under an Ar atmosphere. After removing most of the ethanol, aqueous NaOH (1.0 M, 10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography with 20/1 (v/v) CH_2Cl_2–CH_3OH gave **1a** (33 mg, 91%) as a white solid; m.p. 215–217 °C (ref. 2h: 209–211 °C). Chiral HPLC analysis (Chiralcel AD-H column, i-PrOH : hexane = 50 : 50, 1.0 mL min^{-1}) showed that the product had an enantiomeric excess of 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (s, 1H, Ar-H), 7.91 (d, J = 2.4 Hz, 1H, Ar-H), 7.83 (d, J = 9.2 Hz, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 7.21 (dd, J = 9.2, 2.4 Hz, 1H, Ar-H), 4.71 (d, J = 14.8 Hz, 1H, 9-H), 4.11 (s, 3H, OMe), 4.07 (s, 3H, OMe), 4.02 (s, 3H, OMe), 3.71 (d, J = 14.8 Hz, 1H, 9-H), 3.44–3.50 (m, 1H, 13a-H), 3.40–3.33 (m, 1H, 14-H), 2.85–2.96 (m, 1H, 14-H), 2.42–2.50 (m, 2H, 11-H), 2.19–2.26 (m, 1H, 13-H), 2.00–2.06 (m, 1H, 13-H), 1.89–1.94 (m, 1H, 12-H), 1.75–1.79 (m, 1H, 12-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.4, 149.4, 148.3, 130.2, 127.1, 126.8, 125.6, 124.3, 124.2, 123.5, 114.9, 104.7, 104.0, 103.8, 60.2, 56.0, 55.9, 55.5, 55.1, 53.9, 33.8, 31.3, 21.6 ppm.

Preparation of 7a/7b from 6

Lithiation of *N*-Boc-pyrrolidine was carried out according to procedure B, then a suspension of **6** (296 mg, 1.0 mmol) in Et_2O (10 mL) was added. Purification by flash chromatography with 1/4 (v/v) EtOAc–hexane gave the minor diastereomer **7a** (122 mg, 26%) as a white solid; m.p.195–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (s, 1H, Ar-H), 7.88–7.75 (m, 4H, Ar-H), 7.18 (dd, J = 8.8, 2.0 Hz, 1H, Ar-H), 6.11 (s, 1H, Ar-CH), 4.28–4.35 (m, 1H, N-CH, 2-H), 4.18 (s, 3H, OMe), 4.08 (s, 3H, OMe), 4.01 (s, 3H, OMe), 3.40–3.48 (m, 2H, N-CH_2, 5-H), 2.43–2.47 (m, 1H, 3-H), 2.07–2.15 (m, 1H, 3-H), 1.93–2.02 (m, 1H, 4-H), 1.64–1.72 (m, 1H, 3-H), 1.53 (s, 9H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.0, 155.5, 149.6, 148.5, 133.0, 130.6, 130.3, 125.7, 125.3, 124.3, 121.5, 115.2, 105.6, 103.8, 103.3, 79.4, 70.2, 61.6, 56.7, 55.9, 55.6, 48.1, 28.6, 25.0, 24.1 ppm; HRMS (ESI): calcd for $C_{27}H_{33}NNaO_6$ $[M + Na]^+$ 490.2200, found 490.2197; and the major diastereomer **7b** (286 mg, 61%) as a white foamy solid; m.p. 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (brs, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 7.82 (s, 1H, Ar-H), 7.75 (d, J = 8.8 Hz, 1H, Ar-H), 7.63 (brs, 1H, Ar-H), 7.17 (dd, J = 8.8, 2.0 Hz, 1H, Ar-H), 6.21 (brs, 1H, OH), 5.09 (brs, 1H, Ar-CH), 4.63 (brs, 1H, N-CH, 2-H), 4.10 (s, 3H, OMe), 4.08 (s, 3H, OMe), 3.99 (s, 3H, OMe), 3.42–3.50 (m, 2H, N-CH_2, 5-H), 1.79–1.91 (m, 1H, 3-H), 1.66–1.76 (m, 1H, 3-H), 1.54 (s, 9H, CH_3), 1.37–1.47 (m, 2H, 4-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.6, 158.3, 149.0, 148.6, 133.0, 131.0, 130.3, 126.0, 125.6, 125.2, 115.5, 106.0, 103.7, 103.7, 80.9, 63.6, 56.0, 55.9, 55.5, 47.8, 29.0, 28.5, 24.1 ppm; HRMS (ESI): calcd for $C_{27}H_{33}NNaO_6$ $[M + Na]^+$ 490.2200, found 490.2196.

Preparation of 2 from 7a

To a solution of **7a** (94 mg, 0.2 mmol) in ethanol (5 mL) was added conc. HCl (0.5 mL, 36–38%), the reaction mixture was heated under reflux for 1 h, then formaldehyde solution (2.0 mL, 37%) was added, and the reaction mixture was heated under reflux for 56 h under an Ar atmosphere. After removing most of the ethanol, aqueous NaOH (1.0 M, 10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography with 20/1 (v/v) CH_2Cl_2–CH_3OH gave **2** (44 mg, 58%) as a light-yellow solid; m.p. 221–223 °C. $[\alpha]_D^{26}$ = +197.4 (c 0.23, $CHCl_3$); {ref. 12: m.p. 237–239 °C, $[\alpha]_D^{11}$ = −217.1 (c 0.23, $CHCl_3$)}; chiral HPLC analysis (Phenomenex Lux Cellulose-1 column, i-PrOH : CH_3CN (0.1% Et_3N) = 5 : 95, 1.0 mL min^{-1}) showed that the product had an enantiomeric excess of 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (s, 1H, Ar-H), 7.84 (s, 1H, Ar-H), 7.72 (d, J = 2.0 Hz, 1H, Ar-H), 7.03 (d, J = 9.2 Hz, 1H, Ar-H), 6.85 (dd, J = 9.2, 2.0 Hz, 1H, Ar-H), 4.94 (s, 1H, 14-H), 4.79 (brs, 1H, OH), 4.15 (s, 3H, OMe), 4.11 (s, 3H, OMe), 4.02 (s, 3H, OMe), 3.55 (d, J = 15.6 Hz, 1H, 9-H), 3.16–3.20 (d, J = 15.6 Hz, 1H, 9-H), 3.13–3.16 (m, 1H, 11-H), 2.35–2.42 (m, 2H, 13a-H, 12-H), 2.17–2.25 (m, 1H, 11-H), 2.07–1.95 (m, 1H, 12-H), 1.95–1.85 (m, 2H, 13-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.7, 149.4, 148.3, 130.5, 127.7, 127.2, 126.8, 124.2, 123.7, 122.8, 114.6, 105.2, 104.0, 103.3, 65.4, 64.8, 56.1, 55.9, 55.4, 55.3, 53.4, 24.0, 21.6 ppm.

Preparation of 2 from 7b

To a solution of compound **7b** (219 mg, 0.47 mmol) in ethanol (12 mL) was added conc. HCl (1.0 mL, 36–38%), the reaction mixture was heated under reflux for 1 h, then formaldehyde solution (4.0 mL, 37%) was added and the reaction mixture was heated under reflux for 60 h under an Ar atmosphere. Workup was similar to the above procedure and purification by flash chromatography gave **2** (95 mg, 54%) as a light-yellow solid. $[\alpha]_D^{26}$ = +191.6 (c 0.23, $CHCl_3$); chiral HPLC analysis (Phenomenex Lux Cellulose-1 column, i-PrOH : CH_3CN (0.1% Et_3N) = 5 : 95, 1.0 mL min^{-1}) showed that the product had an enantiomeric excess of 96%. Other data were identical to those above.

Preparation of 1a from 2

Two parts of **2** (44 + 95 mg, 0.367 mmol) prepared from **7a** and **7b** were gathered and dissolved in trifluoroacetic acid (4 mL), then triethylsilane (0.36 g, 3.1 mmol) was added, and the resulting mixture was stirred at room temperature for 12 h in the dark. The solvent was made basic with aqueous NaOH (2.0 M, 40 mL) and extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography using basic alumina (200–300 mesh) with 40/1 (v/v) CH_2Cl_2–CH_3OH gave **1a** (127 mg, 96%) as a white solid. Chiral HPLC analysis (Chiralcel AD-H column, i-PrOH : hexane = 50 : 50, 1.0 mL min^{-1}) showed that the product had an enantiomeric excess of 98%. $[\alpha]_D^{25}$ = +80.9 (*c* 0.45, $CHCl_3$); {ref. 2h: $[\alpha]_D^{20}$ = +85 (*c* 2.0, $CHCl_3$); 99% ee}; other data were identical to those of **1a** prepared from **5**.

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