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Note

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Asymmetric Total Synthesis of (+)-Winchinine B

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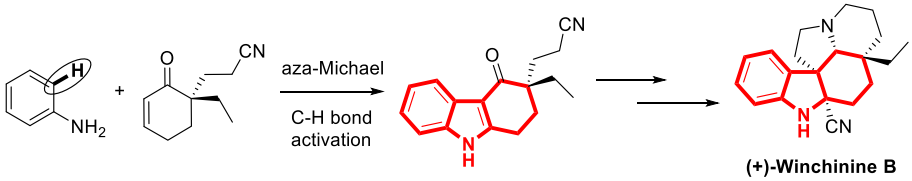
Supporting Information Placeholder



ABSTRACT: The first asymmetric total synthesis of aspidosperma alkaloid (+)-winchinine B was achieved in 12 steps from commercially available materials. A new synthetic strategy which features an efficient aza-Michael addition, a ruthenium-catalyzed transfer dehydrogenation and an intramolecular palladium-catalyzed oxidative coupling was adopted to install the ABC tricycle system. And a one-pot process involving carbonyl reduction/iminium formation/intramolecular conjugate addition developed by our group was utilized to construct the D ring moiety.

The aspidosperma alkaloids are a class of structurally complex compounds isolated from various biological natural sources. Currently, more than 250 members in the aspidosperma family have been discovered, and many of them exhibit significant biological activities.[1] Remarkably, bisindole alkaloids vinblastine (**1f**) and vincristine (**1g**) have already been used for chemotherapy medication to treat various types of cancers.[2] Other members including vincadifformine (**1c**, cytotoxic effect against KB and jurkat cells),[3] jerantinine E (**1d**, cytotoxicity against KB (VJ300) cells, IC_{50} = 0.78 ug/mL and A549 lung cancer cell line, IC_{50} = 0.4 ug/mL) [4, 5] and tabersonine (**1e**, cytotoxicity against SK-BR-3 human cancer cell lines stronger than cisplatin)[6] were known to be pharmacologically important alkaloids. The typical structure of aspidosperma alkaloids is the ABCDE pentacyclic framework embeded with two nitrogen atoms like aspidospermidine (**1a**), vincadifformine (**1c**), jerantinine E (**1d**)

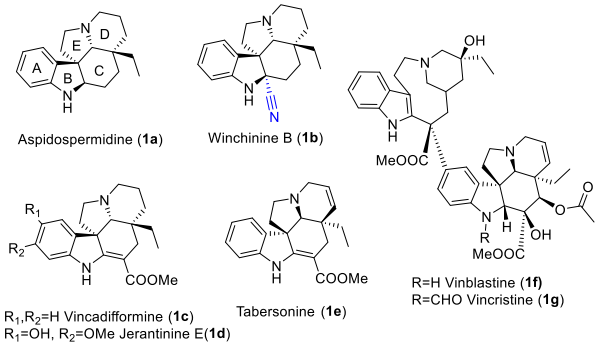
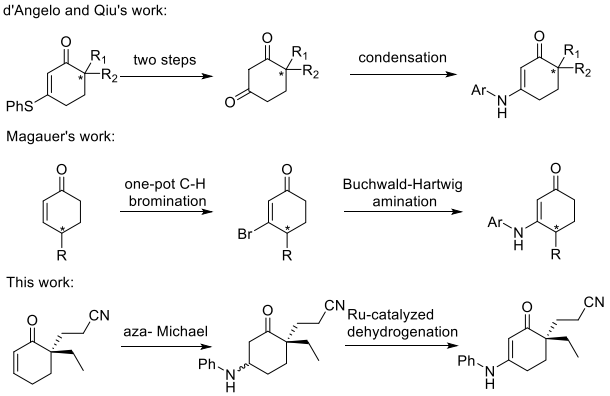


Figure 1. Structures of the representative aspidosperma alkaloids

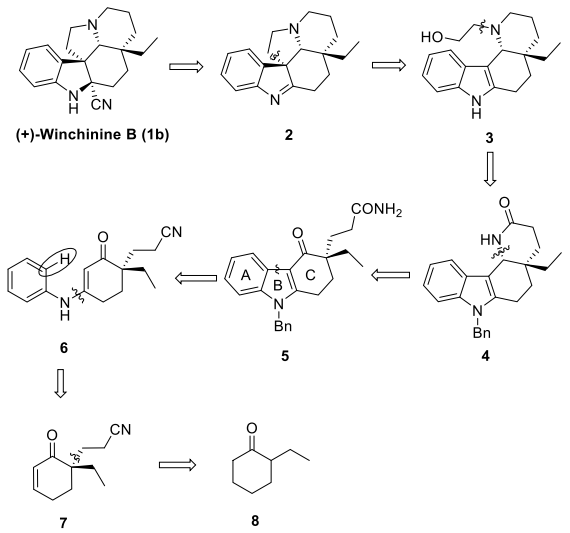
and tabersonine (**1e**) (Figure 1). Recently, a new member of this family, (+)-winchinine B (**1b**) containing a rare cyano group was isolated from the twigs and leaves of *Winchia calophylla* by Ye and co-workers.[7]

Due to their intriguing structures and biological profiles, aspidosperma alkaloids have long been attractive targets for synthetic chemists. Early in 1963, Stork and Dolfini have acomplished the syntheses of aspidospermidine (**1a**) and quebrachamine.[8] Following that, a variety of other members including aspidospermidine (**1a**)[9], vincadifformine (**1d**)[10] and tabersonine (**1e**)[11] have been finished. Among the established syntheses, the main strategies to access the key structure are Fischer indolization of a tricyclic ketone with phenyl-

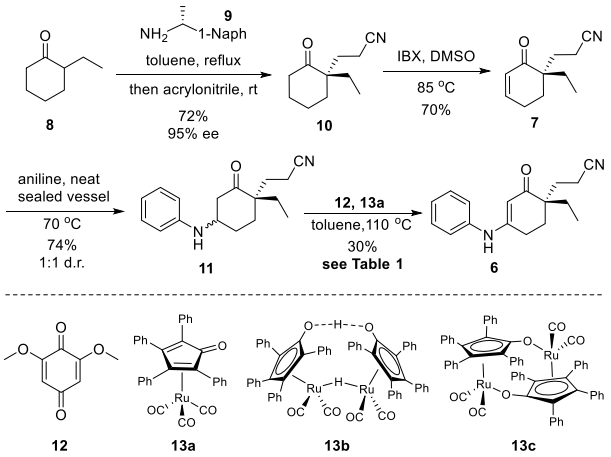
Scheme 1. Methods for the Preparation of the Key *β*-Enaminone Precursor



Scheme 2. Retrosynthetic Analysis of (+)-Winchinine B



Scheme 3. Synthesis of the Key *β*-enaminone Intermediate 6



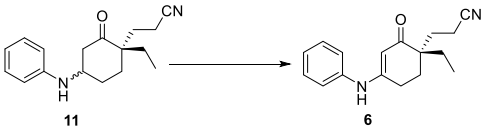
hydrazine[8], rearrangement of an indoloquinolizidine[12], intramolecular Diels−Alder reaction of indole derivatives[13] and dearomatization of indoles to construct the E ring[14].

Owing to their common structural features, constructing of the common ABC tricycle framework via a Heck-type coupling might be a powerful synthetic strategy. Thus, development of an efficient strategy to approach the key *β*-enaminone precursor still invites great interest, and some elegant syntheses had been reported (Scheme 1). In 1994, Desmaële and d'Angelo had reported the synthesis of (+)-aspidospermidine using condensation of 1,3-diketone with aniline.[15] In 2013, Qiu had accomplished the synthesis of (-)-aspidophytine through the same condensation method.[16] Recently, Magauer had developed a one-pot *β*-C−H bromination of enones and a Buchwald-Hartwig amination approaching ABC ring system of jerantinine E.[17] Herein, we report the first asymmetric total synthesis of (+)-winchinine B utilizing a highly efficient aza- Michael addition, a ruthenium-catalyzed dehydrogenation and an intramolecular palladium-catalyzed oxidative coupling.

As shown in Scheme 2, we envisioned that (+)-winchinine B (**1b**) can be obtained from its precursor (+)-1,2-dehydroaspidospermidine (**2**). Then, (+)-1,2-dehydroaspidospermidine (**2**) could be derived from alcohol **3** via an intramolecular alkylation, which could arise from lactam **4** through a N-alkylation reaction. In turn, the lactam **4** might be obtained from ketoamide **5** through our strategic one-pot process involving carbonyl reduction/ iminium formation/intramolecular conjugate addition. As for preparation of the ABC tricycle skeleton **5**, it could be synthesized from *β*-enaminone **6** via an intramolecular palladium-catalyzed oxidative coupling, while **6** could be synthesized through an efficient aza-Michael addition and an oxidation. The chiral enone **7** would arise from an asymmetric Michael addition of 2-ethylcyclohexanone **8** with acrylonitrile.

Our synthesis commenced with preparation of ketone **10** and installing the quaternary carbon stereocenter using asymmetric Michael addition (Scheme 3). According to the literature, Pfau and d'Angelo had developed an asymmetric

Table 1. Conditions Screened for the Oxidation of 11



Entry[a]	Oxidative	Solvent	T(°C)	Time(h)	Yield(%)[b]
1	DMSO /$(COCl)_2$/Et_3N	DCM	-78 to rt	4	N.R.
2	DMP	DCM	rt	12	N.R.
3	PCC	DCM	rt	12	N.R.
4	DDQ	PhMe	reflux	12	N.R.
5	PhIO	DCM	reflux	12	N.R.
6	PhIO	PhMe	reflux	12	N.R.
7	I_2	DMSO	120	12	N.R.
8	IBX	DMSO	80	2	Decomposed
9	$Pd(TFA)_2$/ DMSO/O_2	AcOH	rt	5	Decomposed
10	**12**, **13a**	PhMe	110	36	30, (26[c])
11	**12**, **13b**	PhMe	110	36	20
12	**12**, **13c**	PhMe	110	36	22

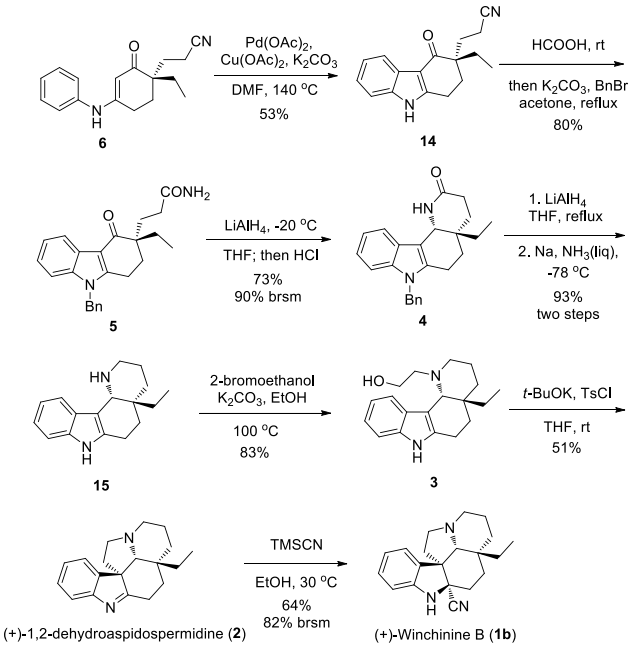
[a] All reactions were performed in freshly distilled solvent. [b] Isolated yields. [c] Carried on 500 mg scale.

Michael addition, using a chiral enamine intermediate derivative obtain the corresponding ketoester in 86% ee.[15] Zu had reported the similar asymmetric Michael addition using 2-ethylcyclopentanone to afford the desired addition product in 90% ee.[18] Accordingly, treatment of 2-ethylcyclohexanone **8** with (R)-1-(1-naphthyl)ethylamine **9** in toluene in the presence of *p*-TSA·H_2O at reflux temperature generated thermodynamically more stable enamine, followed by reaction with acrylonitrile at rt to furnish ketone **10** in 72% yield and 95% ee. Subsequently, **10** was oxidized to enone **7** by IBX in DMSO at 85 °C in 70% yield.[19]

With enone **7** in hand, we set our sights on accessing the key *β*-enaminone intermediate. Unfortunately, our initial attempts to use various bases, such as K_2CO_3, Cs_2CO_3, Et_3N, DBU, NaH and *t*-BuOK to promote the aza-Michael addition failed to give desired products under typical conditions. In addition, several Bronsted and Lewis acid such as HOAc, TsOH·H_2O and $BF_3{\cdot}Et_2O$, was also proved to be ineffective. To our delight, when heated with aniline at 70 °C in a sealed vessel, enone **7** was smoothly converted into amine **11** in excellent yield as an 1:1 diastereoisomeric mixture.[20] Subsequent oxidation of the aromatic amine **11** was proved to be extremely difficult (Table 1). Commonly employed reagents such as DMSO/$(COCl)_2$/Et_3N, DMP, PCC, DDQ, PhIO and I_2 were ineffective with only starting material recovered (entries 1-7), while IBX oxidation and Pd$(TFA)_2$/DMSO/O_2[21] resulted in decomposition of **11** (entries 8-9). Finally, inspired by Bäckvall's work, a ruthenium-catalyzed transfer dehydrogenation was carried out.[22] **11** was subjected to the Ru catalysis **13a** and benzoquinone **12** in toluene at 110 °C, giving the desired *β*-enaminone **6** successfully (entry 10). The Ru catalysis **13b** and **13c** were also screened, but they didn't provide better results than **13a** did (entries 11-12).

With a reliable supply of **6** being secured, formation of the ABC tricycle framework was executed. At this stage, C-H bond activation has been considered as an efficient pathway for the construction of the indole moiety (Scheme 4).[23] Thus,

Scheme 4. Completion of the Total Synthesis of (+)-Winchinine B (1b)



through the method developed by Glorius,[23d] treatment of **6**with a mixture of Pd$(OAc)_2$/Cu$(OAc)_2$/K_2CO_3 in DMF at 140 °C afforded the desired indole intermediate **14** in 53% yield. Exposure of nitrile **14** to anhydrous formic acid smoothly generated corresponding amide, which was easily transformed into its N-benzyl derivative **5** with BnBr in 80% yield. Then our previously developed method was performed[24]: when amide **5** was treated with $LiAlH_4$ at -20 °C, the carbonyl group could be selectively reduced to alcohol. Then in presence of aqueous hydrochloric acid, iminium ions could be formed *in situ*, which was trapped intramolecularly by the amide, affording the desired lactam **4** as a single diastereoisomer in 73% yield (90% brsm).

Having achieved **4** efficiently, we next focused on accomplishing the total synthesis of (+)-winchinine B. Reduction of lactam **4** with $LiAlH_4$ afforded the corresponding amine. Then, removement of Bn protection group with Na/NH_3(liq) at -78 °C successfully gave **15** in 93% yield over two steps.[25] Alkylation with excess amount of 2-bromoethanol in the presence of K_2CO_3 afforded the desired amino alcohol **3** in 83% yield. Subsequently, treatment of the amino alcohol with *t*-BuOK and TsCl in THF resulted in (+)-1,2-dehydroaspidospermidine (**2**) in 51% yield.[9a, 9b] In the end, a cyanation reaction was taken by treating the imine **2** with a cyanide reagent.[26] We found that solvent effect was critical to the reaction outcome. Initially, when aprotic solvent like THF or DCM was used, no desired product was detected. When it was changed into protic solvent MeOH, the desired cyanation product (+)-winchinine B (**1b)** was gratifyingly obtained albeit the yield was only 46% yield. The hydrogen bond might activate the imine moiety of **2**, which can further accelerate addition of cyano group. Then, we screened other protic solvents including EtOH, *i*-PrOH and *t*-BuOH to realize a better result. Finally, EtOH was found to be the optimal solvent with 64% yield (82% brsm). Up to this stage, we have successfully achieved the first asymmetric total synthesis of (+)-winchinine B. All the physical data of the synthetic samples are identical with those reported in literature.

In summary, the first asymmetric total synthesis of aspidosperma alkaloids (+)-winchinine B was achieved in 12 steps from commercially available 2-ethylcyclohexanone. The synthetic route features several key transformations, including a highly efficient aza-Michael addition, a ruthenium-catalyzed dehydrogenation, an intramolecular palladium-catalyzed oxidative coupling to approach the ABC tricycle framework and a one-pot process involving carbonyl reduction/iminium formation/intramolecular conjugate addition to construct the D ring system. Study on syntheses of other indole alkaloids using our developed strategy is in progress and will be reported in due course.

EXPERIMENTAL SECTION

General information: All reactions sensitive to air or moisture were carried out under argon atmosphere in dry and freshly distilled solvents under anhydrous conditions, unless otherwise noted. An oil bath was used as the heating source for the reactions that require heating. Column chromatography was performed on silica gel (200–300 mesh). Optical rotations were measured on a precision automated polarimeter. Infrared spectra were recorded on a 670 FT-IR spectrometer. High-resolution mass spectra (HRMS) were measured by the elec-

trospray ionization (ESI) technique on an Orbitrap Elite mass analyzer. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded on 400 MHz and 300 MHz spectrometers. Chemical shifts are reported as δ values relative to internal chloroform (δ 7.26 for ^{1}H NMR and 77.0 for ^{13}C{^{1}H} NMR). Melting points were measured on a melting point apparatus and are uncorrected. Analysis with HPLC was performed using Waters 1100 series chromatograph with JASCO PU-980 pump and Agilent 1100 Series detection system.

Experimental Procedures

(S)-3-(1-ethyl-2-oxocyclohexyl)propanenitrile (10). To a stirred solution of **8** (3.80 g, 30.11 mmol) in toluene (120 mL) were added (R)-(+)-1-(1-Naphthyl)ethylamine **9** (1.1 eq., 5.42 mL, 33.12 mmol) and *p*-TsOH·H_2O (0.01 eq., 57 mg, 0.30 mmol) at rt. After stirring under reflux for overnight with azeotropic removal of water, the reaction mixture was concentrated under reduced pressure to give a crude enamine as yellow oil, which was then treated with acrylonitrile (1.8 eq., 3.60 mL, 54 mmol) in the presence of hydroquinone (10 mg). The mixture was stirred at rt for 7 days. Aqueous acetic acid (20%, 40 mL) and THF (60 mL) were added to the reaction mixture, and the reaction was stirred for 5 h at rt. The solvents were removed under reduced pressure to afford the crude residue, which was treated with 1 N aqueous HCl (40 mL). The mixture was saturated with NaCl and extracted with EtOAc three times, and the combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluted with petroleum/EtOAc = 100:1 to 20:1) to give **10** (3.90 g, 72%, 95% ee[27]) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 – 2.16 (m, 4H), 2.01 – 1.89 (m, 2H), 1.82 – 1.45 (m, 8H), 0.76 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 213.9, 120.1, 51.0, 38.9, 35.2, 29.9, 27.1, 26.9, 20.5, 12.1, 7.5. IR (neat) ν_{max} 3383.7, 2939.6, 2870.1, 2246.4, 1701.8, 1460.8, 1448.5, 1426.3 cm^{-1}. HRMS (ESIMS): calcd for $C_{11}H_{18}NO$ $[M+H]^+$ 180.1388, found 180.1383. $[\alpha]_D^{24.2}$ +67.0 ($CHCl_3$, c=1.0).

(S)-benzyl 3-(1-ethyl-2-oxocyclohexyl)propanoate (S-1). To the solution of **10** (85 mg, 0.474mmol) in EtOH/H_2O (2 mL) was added NaOH (1.0 eq., 19 mg, 0.474 mmol) at room temperature. After stirring at reflux for 17 h, the reaction was cooled to rt. After removal of EtOH under reduce pressure, the aqueous mixture was extracted with Et_2O. Then the aqueous layer was adjusted by 6 N HCl to attain the target of pH (1–2) and the mixture was extracted with DCM three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a crude carboxylic acid as a colorless oil. The crude carboxylic acid was directly subjected to the next reaction without further purification. The solution of the crude carboxylic acid (36 mg) in DMF (1.5 mL) was added K_2CO_3 (126 mg) and BnBr (26 μL) at room temperature. After stirring at the same temperature for 5 h, the reaction was poured into brine and the mixture was extracted with EtOAc three times. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluted with petroleum/EtOAc = 10:1 to 5:1) to give **S-1** (50 mg, 96%, 95% ee) as colorless oil. The enantiomeric excess was determined by HPLC (DAICEL-CHIRALPAK-AY-H, hexane-EtOH = 90/10, flow rate = 1 ml/min, t_1 = 10.7 min, t_2 = 14.0 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 5H), 5.10 (s, 2H), 2.41 – 2.09 (m, 4H), 2.00 – 1.40 (m, 10H), 0.76 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 214.70, 173.53, 135.88, 128.46, 128.13, 128.11, 66.19, 50.91, 39.01, 35.67, 28.84, 28.81, 27.00, 26.95, 20.60, 7.61. IR (neat) ν_{max} 2935.2, 2865.5, 1736.3, 1702.1, 1455.1, 1164.6, 751.8 cm^{-1}. HRMS (ESIMS): calcd for $C_{18}H_{25}O_3$ $[M+H]^+$ 289.1804, found 289.1798. $[\alpha]_D^{22.6}$ +11.3 ($CHCl_3$, c=1.1).

(S)-3-(1-ethyl-2-oxocyclohex-3-en-1-yl)propanenitrile (7). To a stirred solution of **10** (3.40 g, 18.97 mmol) in DMSO (150 ml) was added IBX (3 eq., 15.9 g, 59.90 mmol). The mixture was stirred at 85 °C and additional IBX (4 eq., 21.2 g, 75.88 mmol) was added in portions. After stirring for 24 h, aqueous saturated sodium bicarbonate (200 ml) and diethyl ether (300 ml) were added to the reaction mixture at room temperature, which was filtered through a Celite pad. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluted with petroleum/EtOAc = 50:1 to 10:1) to give **7** (2.32 g, 70%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (dt, *J* = 9.9, 3.9 Hz, 1H), 5.86 (dt, *J* = 9.9, 1.9 Hz, 1H), 2.46 – 2.18 (m, 4H), 1.99 (ddd, *J* = 13.9, 9.4, 6.7 Hz, 1H), 1.87 (t, *J* = 6.0 Hz, 2H), 1.75 (ddd, *J* = 14.0, 9.7, 6.3 Hz, 1H), 1.62 – 1.43 (m, 2H), 0.80 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 201.9, 148.8, 128.4, 120.0, 46.9, 29.9, 29.5, 26.2, 22.6, 12.1, 7.8. **IR** (neat) ν_{max} 3487.3, 2969.8, 2936.1, 2881.3, 2246.9, 1667.5, 1447.1, 1427.8 cm^{-1}. HRMS (ESIMS): calcd for $C_{11}H_{16}NO$ $[M+H]^+$ 178.1232, found 178.1226. $[\alpha]_D^{24.5}$ +32.0 ($CHCl_3$, c=1.0).

3-((1S)-1-ethyl-2-oxo-4-(phenylamino)cyclohexyl)-propanenitrile (11). A mixture of **7** (590 mg, 3.329 mmol) and aniline (1.5 eq., 0.46 mL, 4.993 mmol) in a sealed vessel was heated at 70 °C for 48 h. After consumption of the starting material, the resulting mixture was cooled to rt. The crude product was purified by silica gel column chromatography (eluted with petroleum/EtOAc = 10:1 to 5:1) to give **11** (665 mg, 74%, d.r. 1:1) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 4H), 6.73 (td, *J* = 7.3, 0.9 Hz, 2H), 6.63 – 6.57 (m, 4H), 3.88 (dd, *J* = 9.1, 4.9 Hz, 1H), 3.60 (ddd, *J* = 10.8, 9.6, 4.1 Hz, 1H), 2.89 – 2.73 (m, 2H), 2.43 – 1.71 (m, 20H), 1.69 – 1.47 (m, 4H), 0.84 – 0.76 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 212.1, 211.1, 146.0, 145.8, 129.4, 129.3, 120.1, 119.9, 118.2, 118.0, 113.4, 113.4, 52.5, 51.7, 50.4, 50.3, 45.5, 44.8, 31.1, 30.2, 29.6, 29.3, 27.4, 27.1, 26.8, 25.3, 12.1, 12.0, 7.8, 7.5. IR (neat) ν_{max} 3379.9, 2967.1, 2939.2, 2878.9, 2246.5, 1701.2, 1665.5, 1602.6, 1509.0, 1449.4, 751.9, 695.2 cm^{-1}. HRMS (ESIMS): calcd for $C_{17}H_{23}N_2O$ $[M+H]^+$ 271.1810, found 271.1805.

(S)-3-(1-ethyl-2-oxo-4-(phenylamino)cyclohex-3-en-1-yl)propanenitrile (6). Ruthenium complex **13a**[28] (5 mol%, 2 mg, 0.004 mmol) and dry quinone **12** (1.2 eq., 15 mg, 0.089 mmol) were dissolved under an argon atmosphere in toluene (2 mL) in a round bottomed flask equipped with a condenser and a stirring bar. Amine **11** (20 mg, 0.074 mmol) was added and the reaction mixture was heated to 110 °C for 36 h. The resulting mixture was cooled to rt, and poured into saturated aqueous $Na_2S_2O_3$. After stiring for 5 h, the mixture was extracted with EtOAc three times. The combined organic ex-

tracts were washed with water and brine then dried over Na_2SO_4. The solution was concentrated to dryness in vacuo and was purified by column chromatography (eluted with petroleum/acetone = 10:1 to 5:1) to give **6** (6 mg, 30 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.7 Hz, 2H), 7.17 – 7.10 (m, 3H), 6.81 (br s, 1H), 5.43 (s, 1H), 2.68 – 2.41 (m, 2H), 2.37 – 2.24 (m, 2H), 2.00 (ddd, *J* = 17.8, 12.0, 7.9 Hz, 1H), 1.94 – 1.84 (m, 2H), 1.84 – 1.73 (m, 1H), 1.70 – 1.47 (m, 2H), 0.85 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.1, 160.5, 137.9, 129.3, 125.6, 123.9, 120.5, 98.7, 45.2, 30.6, 29.1, 27.4, 25.7, 12.4, 8.1. IR (neat) ν_{max} 3268.1, 2964.8, 2931.3, 2264.5, 1604.0, 1580.4, 1534.6, 1496.2, 1447.3, 757.8, 695.4 cm^{-1}. HRMS (ESIMS): calcd for $C_{17}H_{21}N_2O$ $[M+H]^+$ 269.1654, found 269.1648. $[\alpha]_D^{24.4}$ +3.0 ($CHCl_3$, c=1.0); m.p. 137-140 °C.

Performed on 500 mg scale: Ruthenium complex **13a** (8 mol%, 93 mg, 0.187 mmol) and dry quinone **12** (1.5 eq., 588 mg, 3.500 mmol) were dissolved under an argon atmosphere in toluene (20 mL) in a round bottomed flask equipped with a condenser and a stirring bar. Amine **11** (630 mg, 2.333 mmol) was added and the reaction mixture was heated to 110 °C for 40 h. The resulting mixture was cooled to rt, and poured into saturated aqueous $Na_2S_2O_3$. After stiring for 5 h, the mixture was extracted with EtOAc three times. The combined organic extracts were washed with water and brine then dried over Na_2SO_4. The solution was concentrated to dryness in vacuo and was purified by column chromatography (eluted with petroleum/acetone = 10:1 to 5:1) to give **6** (160 mg, 26 %) as a yellow solid.

(S)-3-(3-ethyl-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-3-yl)propanenitrile (14). A mixture of compound **6** (1.33 g, 4.978 mmol), $Pd(OAc)_2$ (10 mol%, 112 mg, 0.498 mmol), $Cu(OAc)_2{\cdot}H_2O$ (3 eq., 2.98 g, 14.934 mmol), and K_2CO_3 (3 eq., 2.06 g, 14.934 mmol) in DMF (30mL) was stirred for 2 h at 140 °C under an atmosphere of argon. After cooling to room temperature, the solution was filtered through a pad of Celite, and the residue was washed with ethyl acetate. The solution was washed with aqueous ammonia (10%), brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluted with DCM/EtOAc = 200:1) to give 14 (698 mg, 53%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (br s, 1H), 8.22 – 8.15 (m, 1H), 7.38 – 7.32 (m, 1H), 7.26 – 7.21 (m, 2H), 3.10 – 2.95 (m, 2H), 2.53 – 2.34 (m, 2H), 2.27 – 2.11 (m, 3H), 1.92 – 1.86 (m, 1H), 1.81 – 1.60 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.8, 149.5, 136.1, 125.1, 123.5, 122.6, 121.3, 120.4, 112.1, 111.1, 47.5, 31.2, 30.3, 27.3, 20.0, 12.6, 8.4. IR (neat) ν_{max} 3265.9, 2966.4, 2935.8, 2247.9, 1627.1, 1614.0, 1470.4, 753.8, 737.4 cm^{-1}. HRMS (ESIMS): calcd for $C_{17}H_{19}N_2O$ $[M+H]^+$ 267.1497, found 267.1492. $[\alpha]_D^{22.9}$ +34.4 ($CHCl_3$, c=1.0); m.p. 154-157 °C.

(S)-3-(9-benzyl-3-ethyl-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-3-yl)propanamide (5). The nitrile **14** (588 mg, 2.211 mmol) was dissolved in anhydrous formic acid (20 mL) and the resulting solution was stirred at room temperature for 20 h. After removal of the solvent in vacuo, the resultant residue and excess amount of K_2CO_3 (5 eq., 1.52 g, 11.0 mmol) was dissolved in acetone (20 mL) and added dropwise BnBr (1.1 eq., 0.30 mL, 2.42 mmol) at 0 °C. After refluxing for 8 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. The crude product was purified by silica gel column chromatography (eluted with DCM/MeOH = 100:1) to give **5** (659 mg, 80 % two steps) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.4 Hz, 1H), 7.33 – 7.19 (m, 6H), 7.02 (d, *J* = 6.5 Hz, 2H), 6.02 (br s, 1H), 5.60 (br s, 1H), 5.27 (s, 2H), 2.98 – 2.81 (m, 2H), 2.37 – 2.18 (m, 2H), 2.16 – 2.07 (m, 3H), 1.88 (ddd, *J* = 13.7, 11.0, 5.7 Hz, 1H), 1.68 (dtd, *J* = 21.5, 14.1, 7.3 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.9, 176.1, 150.3, 137.4, 135.8, 129.0, 127.9, 126.0, 125.3, 123.2, 122.6, 121.6, 112.0, 109.7, 47.6, 46.9, 31.2, 31.0, 29.8, 27.6, 19.1, 8.5. IR (neat) ν_{max} 3445.7, 3202.2, 3054.9, 2967.2, 2933.9, 1664.3, 1656.2, 1637.0, 1457.7, 736.0, 700.8 cm^{-1}. HRMS (ESIMS): calcd for $C_{24}H_{27}N_2O_2$ $[M+H]^+$ 375.2067, found 375.2062. $[\alpha]_D^{24.0}$ -10.0 ($CHCl_3$, c=1.0); m.p. 66-68 °C.

(4aS,11cR)-7-benzyl-4a-ethyl-1,3,4,4a,5,6,7,11c-octahydro-2H-pyrido[3,2-c]carbazol-2-one (4). To a solution of the amide **5** (653 mg, 1.746 mmol) in anhydrous THF (20 mL) at -20 °C was added $LiAlH_4$ (265 mg, 6.984 mmol, 4.0 equiv) slowly over 3 min and the resulting mixture was stirred at -20°C for 4 h. The reaction was quenched by water and then adjusted by 2 N HCl to attain the target of pH (1–2). After removal of THF under reduced pressure, the aqueous layer was extracted with DCM three times. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine then dried over Na_2SO_4. The solution was concentrated to dryness in vacuo and was purified by column chromatography on silica gel (eluted with petroleum/acetone = 2:1) to give pure lactam **4** (456 mg, 73% yield) as a white solid, along with 119 mg recovered amide **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 5.6, 3.0 Hz, 1H), 7.31 – 7.21 (m, 4H), 7.17 – 7.10 (m, 2H), 6.95 (d, *J* = 7.0 Hz, 2H), 5.90 (s, 1H), 5.27 (s, 2H), 4.49 (s, 1H), 2.69 (ddd, *J* = 16.7, 6.0, 2.0 Hz, 1H), 2.59 (ddd, *J* = 16.8, 11.0, 5.6 Hz, 1H), 2.52 – 2.34 (m, 2H), 2.13 – 2.02 (m, 1H), 1.94 – 1.81 (m, 2H), 1.62 (dt, *J* = 13.4, 6.8 Hz, 1H), 1.54 (dt, *J* = 14.9, 7.5 Hz, 1H), 1.35 – 1.24 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.0, 137.3, 137.0, 135.7, 128.8, 127.4, 126.0, 125.9, 121.6, 119.8, 116.9, 109.6, 108.8, 53.6, 46.4, 34.1, 29.6, 27.9, 27.8, 24.8, 18.8, 8.0. IR (neat) ν_{max} 3391.3, 3216.3, 3052.1, 2962.6, 2933.8, 2862.6, 1658.2, 1614.0, 1465.0, 1454.3, 737.6 cm^{-1}. HRMS (ESIMS): calcd for $C_{24}H_{27}N_2O$ $[M+H]^+$ 359.2118, found 359.2114. $[\alpha]_D^{24.0}$ -77.0 ($CHCl_3$, c=1.0); m.p. 119-121 °C.

(4aR,11cR)-4a-ethyl-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazole (15). To a solution of the lactam **4** (440 mg, 1.229 mmol) in THF (15 mL) was added $LiAlH_4$ (280 mg, 7.374 mmol, 6.0 equiv) at 0 °C. After stirring at reflux temperature for 10 h, water (0.28 mL), 10% aqueous sodium hydroxide (0.56 mL) and water (0.84 mL) were sequentially added. Then, the mixture was filtrated through a pad of Celite, and the filtrate was evaporated under reduced pressure. The resulting crude amine (419 mg) was immediately used for the following step without further purification. Freshly cut Na (280 mg) was added to liquid ammonia at -78 °C. Then a solution of crude **4** (419 mg) in THF (10 mL) was added to the blue ammonia solution. After 30 min, the reaction was quenched with solid NH_4Cl and ammonia was allowed to evaporate at 0 °C. After removal of the solvent in vacuo, the resultant residue was taken up in water and the mixture was extracted with $CHCl_3$. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated to dryness in vacuo and was purified by flash column chromatography on silica gel (eluted with

DCM/MeOH = 5:1) to give the product **15** (290 mg, 93% yield over two steps) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.58 (dd, *J* = 5.6, 2.7 Hz, 1H), 7.19 (dd, *J* = 6.0, 2.6 Hz, 1H), 7.14 – 7.02 (m, 2H), 3.71 (s, 1H), 3.02 (d, *J* = 12.0 Hz, 1H), 2.75 (td, *J* = 11.9, 2.8 Hz, 1H), 2.52 (dd, *J* = 8.6, 3.8 Hz, 2H), 2.27 (dt, *J* = 17.8, 8.9 Hz, 1H), 1.81 (d, *J* = 13.3 Hz, 1H), 1.72 – 1.51 (m, 2H), 1.49 – 1.34 (m, 4H), 1.15 – 0.98 (m, 1H), 0.83 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 136.1, 134.6, 127.1, 120.7, 119.0, 117.4, 111.1, 110.6, 56.5, 46.0, 34.4, 34.0, 29.3, 23.9, 22.3, 19.8, 7.5. IR (neat) ν_{max} 3398, 3290, 3150, 3105, 3055, 2930, 2876, 2859, 2744, 1623, 1590, 1465, 1452, 1434, 1379, 1305, 1230, 1167, 1114, 1012, 738 cm^{-1}. HRMS (ESIMS): calcd for $C_{17}H_{23}N_2$ $[M+H]^+$ 255.1856, found 255.1857. $[\alpha]_D^{24.1}$ -30.0 ($CHCl_3$, c=1.0); m.p. 171-173 °C.

2-((4aR,11cR)-4a-ethyl-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazol-1-yl)ethan-1-ol (3). To a solution of **15** (280 mg, 1.102 mmol) in absolute ethanol (10 mL) were sequentially added anhydrous potassium carbonate(8 eq., 1.22 g, 8.819 mmol) and 2-bromoethanol (8 eq., 0.64 mL, 8.819 mmol) in a sealed-vessel. The resulting suspension was heated to 100 °C for 6 h. The reaction mixture was cooled to room temperature. After removal of EtOH, the residue was purified by flash chromatography on silica gel (eluted with EtOAc with 2% Et_3N) to afford the alkylated product **3** (270 mg, 83% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (br s, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 10.5 Hz, 1H), 7.21 – 7.06 (m, 2H), 4.50 (s, 1H), 3.73 (ddd, *J* = 14.3, 7.1, 3.0 Hz, 1H), 3.63 (ddd, *J* = 14.4, 5.8, 2.9 Hz, 1H), 3.57 – 3.49 (m, 1H), 3.47 (s, 1H), 3.31 – 3.23 (m, 1H), 2.84 – 2.63 (m, 3H), 2.56 – 2.48 (m, 2H), 2.07 (ddd, *J* = 13.7, 10.4, 6.9 Hz, 1H), 1.99 – 1.88 (m, 1H), 1.65 (dt, *J* = 13.5, 6.7 Hz, 2H), 1.39 – 1.20 (m, 3H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.6, 136.2, 136.1, 128.1, 121.7, 120.1, 117.5, 111.0, 106.8, 63.6, 59.1, 48.1, 37.0, 29.7, 29.5, 28.0, 26.3, 20.0, 8.1. IR (neat) ν_{max} 3397, 3217, 3185, 3109, 3058, 2937, 2877, 2794, 1620, 1585, 1461, 1377, 1331, 1308, 1265, 1233, 1169, 1141, 1120, 1041, 739 cm^{-1}. HRMS (ESIMS): calcd for $C_{19}H_{27}N_2O$ $[M+H]^+$ 299.2118, found 299.2117. $[\alpha]_D^{24.3}$ -3.0 ($CHCl_3$, c=1.0); m.p. 86-88 °C.

(+)-1,2-dehydroaspidospermidine (2). To a solution of primary alcohol **3** (74 mg, 0.248 mmol) in THF (12 mL) was added dropwise a 1 M solution of *t*-BuOK in THF (3.34 eq., 0.83 mL, 0.829 mmol) at 0 °C. After stirring for 10 min, TsCl (1.48 eq., 70 mg, 0.367 mmol) was added and the reaction mixture was allowed to warm to room temperature. After stirring for 1 h, the reaction was diluted with Et_2O and quenched with water at 0 °C. Then the mixture was saturated with NaCl and extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography on silica gel (eluted with petroleum/EtOAc = 4:1 with 2% Et_3N) to afford (+)-1,2-dehydroaspidospermidine (**2**) as a pale yellow oil (35 mg, 51% yield), which matched the previously reported analytical data.[9a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.6 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.17 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.21 – 3.15 (m, 2H), 3.14 – 3.07 (m, 1H), 2.76 (ddd, *J* = 14.0, 10.4, 3.4 Hz, 1H), 2.59 (ddd, *J* = 11.5, 8.5, 5.7 Hz, 1H), 2.45 (td, *J* = 12.7, 3.2 Hz, 1H), 2.40 (s, 1H), 2.23 – 2.12 (m, 2H), 1.91 – 1.78 (m, 1H), 1.64 (dd, *J* = 12.4, 5.6 Hz, 1H), 1.61 – 1.52 (m, 2H), 1.51 – 1.44 (m, 1H), 1.00 (td, *J* = 13.5, 4.9 Hz, 1H), 0.71 – 0.56 (m, 2H), 0.49 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.3, 154.4, 147.1, 127.4, 125.0, 120.9, 120.0, 79.0, 61.2, 54.5, 52.0, 36.4, 35.1, 33.1, 29.7, 27.1, 23.7, 22.0, 7.2. IR (neat) ν_{max} 2936, 2776, 1577, 1454, 1323, 1249, 1193, 1123, 1013, 750 cm^{-1}. HRMS (ESIMS): calcd for $C_{19}H_{25}N_2$ $[M+H]^+$ 281.2012, found 281.2018. $[\alpha]_D^{24.3}$ +146.0 ($CHCl_3$, c=1.0).

(+)-Winchinine B (1b). To a solution of imine (+)-1,2-dehydroaspidospermidine **2** (23 mg, 0.082 mmol) in EtOH (1 mL) was added TMSCN (5.0 eq., 0.05 mL, 0.411 mmol). The mixture was allowed to stir 1.5 h at 30 °C before the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with petroleum/EtOAc 20:1 to 10:1) afforded (+)-winchinine B (**1b**) (16 mg, 64% yield) as a white solid, along with 5 mg recovered imine **2**. The synthetic (+)-winchinine B (**1b**) matched the analytical data of natural sample.[7] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (m, 2H), 6.80 (dd, *J* = 7.4 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 3.93 (s, 1H), 3.26 (td, *J* = 9.0, 4.3 Hz, 1H), 3.04 (br d, *J* = 10.7 Hz, 1H), 2.67 (m, 1H), 2.36 (s, 1H), 2.29 (m, 1H), 2.24(m,1H), 1.97 (m, 2H), 1.77 (m, 2H), 1.62 (d, *J* = 13.6 Hz, 1H), 1.49 (m, 2H), 1.39 (dd, *J* = 14.4, 7.4 Hz, 1H), 1.13 (m, 1H), 1.08 (m, 1H), 0.92 (m, 1H), 0.64 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 146.5, 133.2, 128.2, 123.3, 122.2, 120.8, 111.0, 69.7, 64.8, 57.9, 53.4, 51.8, 36.7, 36.0, 34.3, 32.7, 29.9, 22.1, 21.6, 7.0. IR (neat) ν_{max} 3332, 2935, 2788, 2374, 1687, 1545, 1510, 1466, 1377, 1330, 1181, 1141, 734 cm^{-1}. HRMS (ESIMS): calcd for $C_{20}H_{26}N_3$ $[M+H]^+$ 308.2121, found 308.2123. $[\alpha]_D^{24.5}$ +35.0 (MeOH, c=1.0); m.p. 154-156 °C.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Full spectroscopic data for all new compounds (PDF).

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Notes

The authors declare no competing financial interest.

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(27) The ee% was measured through converting **10** into (S)-benzyl 3-(1-ethyl-2-oxocyclohexyl)propanoate (**S-1**). And the absolute

configuration of **10** was determined by comparing the optical rotation value of **S-1** with that of the known compound benzyl (R)-benzyl 3-(1-ethyl-2-oxocyclohexyl)propanoate. For the optical rotation value of benzyl (R)-3-(1-ethyl-2-oxocyclohexyl)propanoate see: Sugimoto, K.; Toyoshima, K.; Nonaka, S.; Kotaki, K.; Ueda, H.; Tokuyama, H. Protecting-Group-Free Total Synthesis of (-)-Rhazinilam and (-)-Rhazinicine using a Gold-Catalyzed Cascade Cyclization. *Angew. Chem. Int. Ed.*, **2013**, 52, 7168−7171.

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