A Concise and Protecting-Group-Free Formal Synthesis of Aspidospermidine: Ring-Opening Cyclization of Spirocyclopropane with Amine Followed by Regioselective Alkylations

Hisanori Nambu,* Takafumi Tamura, and Takayuki Yakura

Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan.

Supporting Information Placeholder

ABSTRACT: A concise formal synthesis of (±)-aspidospermidine via Stork's intermediate, which could be used as a divergent synthesis of *Aspidosperma* alkaloids, was achieved by employing a ring-opening cyclization of spirocyclopropane with amine followed by a regioselective intramolecular/intermolecular alkylation sequence. Stork's intermediate was synthesized in only six steps from a simple starting material, 1,3-cyclohexanedione, and was converted into (±)-aspidospermidine. To the best of our knowledge, this synthesis of Stork's intermediate involves the least number of steps to date. Furthermore, no protecting groups were used during this synthesis.

INTRODUCTION

Over the past half-century, *Aspidosperma* alkaloids **1** (Figure 1) have elicited considerable attention from synthetic chemists due to their structural diversity and interesting biological activities.¹ Aspidospermidine (**1a**) and aspidospermine (**1b**), the prototypical members of the group, contain a pentacyclic [6.5.6.6.5]-ABCDE ring system and have been attractive targets for demonstrating new synthetic approaches to *Aspidosperma* alkaloids.²

Figure 1. Representative structures of *Aspidosperma* alkaloids **1**.

As a pioneering *Aspidosperma* alkaloid synthesis, Stork and Dolfini reported total synthesis of aspidospermine (**1b**) and quebrachamine (**1d**) in 1963, in which tricyclic [6.6.5]-CDE ring compound **2** was used as a key synthetic intermediate (Scheme 1A).³ CDE ring **2** was constructed from a starting material possessing the C ring by forming the D ring followed by the E ring.⁴ Conversion of **2** into natural products was achieved by using a Fischer indolization and reduction sequence, although the stereochemistry of **2** was not determined at this point.⁵ In 2000, Aubé and co-workers reported the total synthesis of (+)-aspidospermidine (**1a**) via intermediate **2** and established the stereochemistry of **2**.⁶ Recently, Jiang and co-workers demonstrated a divergent asymmetric synthesis of *Aspidosperma* alkaloids including (-)-pyrifolidine (**1c**) and (+)-vincadifformine (**1e**) from **2**.⁷ Therefore, intermediate **2** has become an attractive and well-known target as a Stork's intermediate, and various synthetic approaches to **2** have been reported to date.^{8,9}

We previously reported a regioselective ring-opening cyclization of spirocyclopropanes **3** with primary amines **4** to generate 2-substituted tetrahydroindol-4-ones **5** (Scheme 1B).^{10,11} Furthermore, regioselective alkylation of **5** at the C-7 position to form alkylated product **6** was achieved by using lithium hexamethyldisilazide (LiHMDS) as a base.¹² Based on these results, we envisioned that these reactions could be ap-

plied to synthesize tricyclic CDE ring compound **2**. Herein, we report a concise route to *Aspidosperma* alkaloid ($\pm$)-aspidospermidine (**1a**) via Stork's intermediate **2**, employing a ring-opening cyclization of spirocyclopropane **3a** with amine **4** to construct CE ring system **5** followed by a regioselective intramolecular/intermolecular alkylation sequence to form the D ring (Scheme 1C).

Scheme 1. Stork's-Intermediate-based Approaches to *Aspidosperma* Alkaloids **1**

A. Pioneer work: Stork's synthesis of *Aspidosperma* alkaloids **1**

B. Our previous work: Ring-opening cyclization of spirocyclopropane **3** with amine **4** followed by regioselective alkylation

C. This work: A concise synthesis of Stork's intermediate **2** from spirocyclopropane **3a**

RESULTS AND DISCUSSION

Our synthetic strategy for Stork's intermediate **2** is illustrated in Scheme 2. We planned to use 1,3-cyclohexanedione (**7**) as the C ring. After conversion of **7** into spirocyclopropane **3a** by our synthetic method,¹³ construction of the E ring could be achieved through a ring-opening cyclization of spirocyclopropane **3a** with propylamine **4** to produce bicyclic product **5** possessing a C3 unit at the nitrogen atom for constructing the D ring.¹⁰ We then devised two synthetic routes as follows. One was an intermolecular alkylation of **5** for introducing the ethyl group followed by intramolecular alkylation of resulting product **6** to construct the D ring (route A). The other was to use the two alkylations in reverse order, such as an intramolecular/intermolecular alkylation sequence via tricyclic intermediate **8** (route B). Finally, reduction of the obtained tricyclic CDE ring system **9** would produce key intermediate **2**. We predicted that the second alkylation step at the tertiary carbon could be more difficult due to the steric hindrance. Generally, an intramolecular reaction proceeds more easily than an intermolecular one. Therefore, we initially investigated an intermolecular/intramolecular alkylation sequence (route A).

Scheme 2. Synthetic Strategy for Stork's Intermediate **2**

At the outset of this work, synthetic approach by route A starting from 1,3-cyclohexanedione (**7**) is shown in Scheme 3. The reaction of **7** with sulfonium salt **10** and powdered K_2CO_3 in EtOAc provided spirocyclopropane **3a** in 93% yield.¹³ Ring-opening cyclization of **3a** with *tert*-butyldimethylsilyl (TBS)-protected 3-amino-1-propanol **4a** proceeded smoothly in THF at 50 °C to produce tetrahydroindol-4-one **5a** in 96% yield. An intermolecular regioselective alkylation of **5a** with ethyl iodide using LiHMDS as a base afforded ethylated product **6a** in 90% yield. After deprotection of TBS ether **6a** with tetrabutylammonium fluoride (TBAF), halogenation of resulting alcohol **6b** using *N*-halosuccinimide (NXS, X = I, Br) and triphenylphosphine gave the corresponding iodide **6c** and bromide **6d** in 84% and 55% yields, respectively. We then examined an intramolecular alkylation using halogenated alkanes **6c** and **6d**. When these were treated with LiHMDS as a base, cyclization did not proceed. A small amount of corresponding alkene **11** (16%–31% yields) rather than tricyclic compound **9** was obtained by E2 elimination.

Scheme 3. Synthetic Approach Using Regioselective Intermolecular/Intramolecular Alkylations (Route A)

Since the intermolecular/intramolecular alkylation sequence could not be used to synthesize tricyclic compound **9**, we next

investigated an intramolecular/intermolecular alkylation sequence (route B, Scheme 4). To omit the deprotection step, we used 3-amino-1-propanol **4b** for the ring-opening cyclization of **3a**. The reaction proceeded uneventfully to provide tetrahydroindol-4-one **5b** in 91% yield. In this key reaction, amino group, which is more nucleophilic than hydroxy group, in **4b** would attack the cyclopropyl carbon in **3a** to cleave the cyclopropane and the subsequent cyclization would form **5b**.¹⁰ Halogenation of alcohol **5b** using NXS and Ph₃P gave corresponding iodide **5c** and bromide **5d**. We then examined an intramolecular alkylation of **5c** and **5d** using LiHMDS as a base. The use of iodide **5c** afforded tricyclic product **8** in 56% yield, accompanied by a small amount of elimination product. When bromide **5d** was used in this reaction, the yield of **8** increased to 74%. Gratifyingly, the reaction of **5d** in the presence of 0.1 equiv of tetrabutylammonium iodide (TBAI) increased the product yield to 86%. Intermolecular alkylation at the C-7 tertiary carbon of **8** was achieved by using excess amount of alkylating reagent. The reaction of **8** with LiHMDS (1.1 equiv) and ethyl iodide (5 equiv) gave ethylated product **9**^{8a,j} in 88% yield.

Scheme 4. Synthetic Approach Using Regioselective Intramolecular/Intermolecular Alkylations (Route B)

With tricyclic intermediate **9** in hand,^{8a,j} we then investigated the reduction of **9** (Table 1). The use of lithium aluminum hydride (LiAlH₄) as a reductant afforded 9b-*epi*-product **12** in 81% yield (entry 1), as well as the previous reports.¹⁴ Additionally, the reaction under Birch reduction conditions also provided **12** in 54% yield (entry 2). We then examined the hydrogenation of **9**.¹⁵ To our delight, the reaction of **9** with a catalytic amount of Pt/C in acetic acid under hydrogen at 50 °C gave Stork's intermediate **2** in 18% yield (entry 3). Synthetic material **2** showed spectroscopic data (¹H and ¹³C NMR, and IR) consistent with those reported for product **2**.^{8a-c} Because this Pt/C-catalyzed hydrogenation required a long reaction time to reach completion (28 h), the product **2** was partially decomposed under the reaction conditions to cause the low yield of **2**. After considerable screening of the reaction conditions, we found that hydrogenation with a catalytic amount of Pd/C in acetic acid at 50 °C proceeded faster to completion within 12 h, affording **2** in 34% yield along with decomposition products (entry 6).¹⁶ Consequently, Stork's intermediate **2** was synthesized in only six steps from a simple starting material, 1,3-cyclohexanedione (**7**), and no protecting groups were used during this route.

Table 1. Stereoselective Reduction of Enaminone **9**

entry	reductant	solvent	temp.	time (h)	yield (%) ^a	
					2	12
1	LiAlH ₄	THF	reflux	0.5	—	81
2	Na, liq. NH ₃	THF	−78 °C to rt	2	—	54
3	Pt/C, H ₂	AcOH	50 °C	28	18	—
4	PtO ₂ , H ₂	AcOH	50 °C	24	8	—
5	Pd(OH) ₂ , H ₂	EtOAc	50 °C	13	14	—
6	Pd/C, H ₂	AcOH	50 °C	12	34	—
7	cat. Rh(I), ^b H ₂	toluene	50 °C	12	—	NR ^d
8	cat. Ir(I), ^c H ₂	CH ₂ Cl ₂	rt	12	—	NR ^d

^aIsolated yield. ^bWilkinson's catalyst. ^cCrabtree's catalyst. ^dNo reaction.

The synthesis of aspidospermidine (**1a**) from Stork's intermediate **2** by employing Fischer indolization with phenylhydrazine in acetic acid and subsequent reduction with LiAlH₄ or NaBH₄ was achieved by several research groups.¹⁷ We also demonstrated this conversion under the above conditions and obtained natural product **1a** in 32% yield (Scheme 5).¹⁸ With the expectation that isomerization of the stereochemistry at C-9b of **12** could proceed in the indolization step,¹⁹ conversion of **12** into **1a** was also explored. Unfortunately, this approach was unsuccessful, as in previous studies.²⁰

Scheme 5. Synthesis of Aspidospermidine (**1a**)

CONCLUSION

A concise formal synthesis of (±)-aspidospermidine via Stork's intermediate was achieved by employing a ring-opening cyclization of spirocyclopropane followed by a regioselective intramolecular/intermolecular alkylation sequence. Stork's intermediate, which could be converted into various *Aspidosperma* alkaloids, was synthesized in only six steps from a simple starting material, 1,3-cyclohexanedione, and was converted into (±)-aspidospermidine in two steps. To the best of our knowledge, this synthesis of Stork's intermediate involves the least number of steps to date.²¹ Additionally, no protecting groups were used during this synthesis. Further efforts toward the asymmetric synthesis of (+)-aspidospermidine and related alkaloids employing an enantioselective intermolecular alkylation are currently in progress.

EXPERIMENTAL SECTION

General. Melting points are uncorrected. IR spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer and absorbance bands are reported in wavenumber (cm^{-1}). ^1H NMR spectra were recorded on JEOL JNM-ECX400P (400 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane at δ_{H} 0.00 or CDCl_3 at δ_{H} 7.26). Data are presented as follows: chemical shift (δ , ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad), coupling constant and integration. $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were recorded on JEOL JNM-ECX400P (100 MHz) spectrometer. The following internal reference was used (CDCl_3 at δ 77.0). High-resolution mass spectra (HRMS) were recorded on JEOL JMS-GCmate II (EI) and JEOL JMS-AX505HAD (FAB) double-focusing magnetic-sector mass spectrometers. Column chromatography was performed on Silica Gel 60 PF₂₅₄ (Nacalai Tesque) and Kanto silica gel 60 N (63–210 mesh) under pressure. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F₂₅₄ plates. Visualization was accomplished with UV light and phosphomolybdic acid stain solution followed by heating. An oil bath was used for conventional heating.

All reagents such as 1,3-cyclohexanedione (**7**), powdered potassium carbonate, 3-amino-1-propanol (**4b**), 1,1,1,3,3,3-hexamethyldisilazane (HMDS), ethyl iodide, *N*-iodosuccinimide (NIS), *N*-bromosuccinimide (NBS), triphenylphosphine, tetrabutylammonium iodide (TBAI), phenylhydrazine, acetic acid, and lithium aluminum hydride are commercially available and were purchased from suppliers such as Sigma-Aldrich Co.; Wako Pure Chemical Industries, Ltd.; Tokyo Chemical Industry Co., Ltd.; Nacalai Tesque, INC. Dehydrated CH_2Cl_2 , THF, EtOAc, toluene, and benzene were purchased from Wako Pure Chemical Industries, Ltd. Sulfonium salt **10**¹³ and 3-(*tert*-butyldimethylsilyloxy)propylamine (**4a**)²² were prepared according to literature procedures.

Preparation of LiHMDS (0.83 M in THF/hexane): BuLi (1.64 M in hexane, 6.1 mL, 10.0 mmol) was added to a solution of HMDS (2.3 mL, 11.0 mmol) in THF (3.6 mL) at 0 °C, and then the mixture was stirred at 0 °C for 0.5 h.

Intermolecular/intramolecular alkylation sequence (route A). Spiro[2.5]octane-4,8-dione (**3a**).¹³ Powdered K_2CO_3 (2.51 g, 18.2 mmol) and 1,3-cyclohexanedione (**7**) (0.68 g, 6.06 mmol) were added to a suspension of sulfonium salt **10** (2.95 g, 6.67 mmol) in EtOAc (60 mL). After stirring at rt for 3 h, the reaction mixture was filtered through a pad of Celite. The filter cake was rinsed with EtOAc (30 mL) and the filtrate was quenched with water (20 mL) and the whole mixture was extracted with EtOAc (2×10 mL). The combined organic layer was washed with water (20 mL), brine (20 mL) and dried over anhydrous MgSO_4 . The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 40% EtOAc in hexane) to provide **3a** (778 mg, 93%) as a pale yellow oil: IR (film, cm^{-1}) ν 2956, 1682, 1330, 1162, 1026, 956; ^1H NMR (400 MHz, CDCl_3) δ 2.67 (t, J = 6.4 Hz, 4H), 2.15 (quint, J = 6.4 Hz, 2H), 1.76 (s, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 206.8, 40.6, 39.4, 27.4, 17.9; HRMS (EI) m/z calcd for $\text{C}_8\text{H}_{10}\text{O}_2$ (M^+) 138.0681, found 138.0668.

1-(3-*tert*-Butyldimethylsilyloxy)propyl-2,3,6,7-tetrahydro-1*H*-indol-4(5*H*)-one (**5a**). 3-(*tert*-Butyldimethylsilyloxy)propylamine (**4a**) (232 mg, 1.23 mmol) was added to a solution of spirocyclopropane **3a** (113 mg, 0.82 mmol) in THF (1.6 mL). After stirring at 50 °C for 4.5 h, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide **5a** (243 mg, 96%) as a yellow oil: IR (film, cm^{-1}) ν 2918, 2849, 1509, 1440, 1290, 1254, 1190, 1094; ^1H NMR (400 MHz, CDCl_3) δ 3.59 (t, J = 5.6 Hz, 2H), 3.50 (t, J = 9.8 Hz, 2H), 3.27 (t, J = 7.0 Hz, 2H), 2.73 (t, J = 9.8 Hz, 2H), 2.32 (t, J = 6.2 Hz, 2H), 2.26 (t, J = 6.2 Hz, 2H), 1.94 (t, J = 5.6, 7.0 Hz, 2H), 1.69 (quint, J = 6.2 Hz, 2H), 0.86 (s, 9H), 0.02 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 190.6, 168.8, 108.9, 59.3, 51.3, 42.8, 35.6, 30.7, 25.8, 23.9, 22.5, 22.3, 18.1, -5.5; HRMS (EI) m/z calcd for $\text{C}_{17}\text{H}_{31}\text{NO}_2\text{Si}$ (M^+) 309.2124, found 309.2127.

1-(3-*tert*-Butyldimethylsilyloxy)propyl-7-ethyl-2,3,6,7-tetrahydro-1*H*-indol-4(5*H*)-one (**6a**). A solution of LiHMDS (1.05 mL, 0.83 M

in THF/hexane, 0.88 mmol) was added to a solution of **5a** (246 mg, 0.80 mmol) in THF (8 mL) at -78 °C. After stirring at -78 °C for 1 h, ethyl iodide (0.096 mL, 1.2 mmol) was added to the mixture and the whole was allowed to warm to room temperature over 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), and the whole mixture was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous MgSO_4 . Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide **6a** (268 mg, 90%) as a yellowish brown oil: IR (film, cm^{-1}) ν 2929, 2857, 2360, 2341, 1556, 1504, 1253, 1178, 1092, 836; ^1H NMR (400 MHz, CDCl_3) δ 3.66–3.54 (m, 2H), 3.47 (td, J = 9.8, 2.4 Hz, 2H), 3.33 (dt, J = 15.2, 7.6 Hz, 1H), 3.16 (dt, J = 15.2, 7.6 Hz, 1H), 2.72 (t, J = 9.8 Hz, 2H), 2.41–2.33 (m, 2H), 2.16 (dd, J = 17.6, 2.0 Hz, 1H), 1.98 (dt, J = 13.6, 2.0 Hz, 1H), 1.87 (m, 1H), 1.73–1.71 (m, 2H), 1.59–1.46 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.32 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 190.2, 172.3, 107.8, 59.4, 50.8, 42.9, 33.1, 31.4, 30.7, 25.8, 25.0, 23.9, 23.1, 18.2, 12.5, -5.5; HRMS (FAB) m/z calcd for $\text{C}_{19}\text{H}_{36}\text{NO}_2\text{Si}$ ($\text{M}+\text{H}^+$) 338.2515, found 338.2508.

7-Ethyl-1-(3-hydroxy)propyl-2,3,6,7-tetrahydro-1*H*-indol-4(5*H*)-one (**6b**). TBAF (1.16 mL, 1 M in THF, 1.16 mmol) was added to a solution of **6a** (390 mg, 1.16 mmol) in THF (5.8 mL) at 0 °C. After stirring at room temperature for 0.5 h, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 11% MeOH in CH_2Cl_2) to provide **6b** (258 mg, quant.) as a yellowish brown oil: IR (film, cm^{-1}) ν 3278, 2935, 2871, 1579, 1534, 1507, 1446, 1299, 1198, 1181; ^1H NMR (400 MHz, CDCl_3) δ 3.73–3.63 (m, 2H), 3.57–3.40 (m, 4H), 3.28 (dt, J = 13.2, 6.6 Hz, 1H), 2.73 (t, J = 9.6 Hz, 2H), 2.47 (dd, J = 4.8, 4.0 Hz, 1H), 2.39 (ddd, J = 17.8, 14.0, 4.0 Hz, 2H), 2.16 (dd, J = 17.8, 3.2 Hz, 2H), 2.02 (dt, J = 13.2, 2.4 Hz, 1H), 1.93 (dt, J = 14.0, 4.8 Hz, 1H), 1.84 (td, J = 12.8, 6.6 Hz, 2H), 1.59–1.49 (m, 2H), 1.04 (t, J = 7.2 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 190.0, 173.3, 107.7, 58.9, 50.9, 43.1, 33.2, 31.1, 30.4, 24.9, 23.6, 23.1, 12.5; HRMS (EI) m/z calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_2$ (M^+) 223.1572, found 223.1573.

Typical procedure for halogenation of alcohols. 7-Ethyl-1-(3-iodo)propyl-2,3,6,7-tetrahydro-1*H*-indol-4(5*H*)-one (**6c**). NIS (170 mg, 0.65 mmol) and triphenylphosphine (146 mg, 0.65 mmol) were added to a solution of **6b** (97 mg, 0.43 mmol) in CH_2Cl_2 (2.2 mL). After stirring at room temperature for 0.5 h, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide **6c** (122 mg, 84%) as a yellowish brown oil: IR (film, cm^{-1}) ν 2934, 2870, 1581, 1542, 1503, 1445, 1299, 1248, 1195, 1181; ^1H NMR (400 MHz, CDCl_3) δ 3.48 (td, J = 9.6, 2.0 Hz, 2H), 3.39–3.14 (m, 4H), 2.75 (t, J = 9.6 Hz, 2H), 2.47–2.36 (m, 2H), 2.21 (ddd, J = 17.2, 5.0, 2.0 Hz, 1H), 2.11–2.03 (m, 3H), 1.96 (tt, J = 13.6, 5.0 Hz, 1H), 1.66–1.45 (m, 2H), 1.08 (t, J = 7.6 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 190.8, 171.9, 108.7, 51.1, 46.8, 33.5, 31.5, 31.1, 25.0, 24.0, 23.3, 12.6, 2.1; HRMS (FAB) m/z calcd for $\text{C}_{13}\text{H}_{21}\text{INO}$ ($\text{M}+\text{H}^+$) 334.0668, found 334.0676.

1-(3-Bromo)propyl-7-ethyl-2,3,6,7-tetrahydro-1*H*-indol-4(5*H*)-one (**6d**). According to the typical procedure for halogenation of alcohols, bromide **6d** was prepared from **6b** (138 mg, 0.62 mmol), NBS (100 mg, 0.93 mmol), and triphenylphosphine (243 mg, 0.93 mmol). The crude product was purified by column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide **6d** (98 mg, 55%) as a yellowish brown oil: IR (film, cm^{-1}) ν 2936, 2871, 1581, 1542, 1504, 1446, 1300, 1261, 1197, 1181; ^1H NMR (400 MHz, CDCl_3) δ 3.52–3.29 (m, 6H), 2.74 (t, J = 9.6 Hz, 2H), 2.47–2.36 (m, 2H), 2.23–2.03 (m, 4H), 1.96 (m, 1H), 1.64–1.50 (m, 2H), 1.07 (t, J = 7.6 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 190.7, 172.1, 108.5, 50.9, 44.5, 33.3, 31.3, 30.3, 29.9, 24.9, 23.9, 23.2, 12.5; HRMS (EI) m/z calcd for $\text{C}_{13}\text{H}_{20}\text{BrNO}$ (M^+) 285.0728, found 285.0714.

1-Allyl-7-ethyl-2,3,6,7-tetrahydro-1*H*-indol-4(5*H*)-one (**11**). A solution of LiHMDS (0.21 mL, 0.83 M in THF/hexane, 0.17 mmol) was added to a solution of **6c** (52 mg, 0.16 mmol) in THF (1.6 mL) at -78 °C. After stirring at -78 °C for 1 h, the reaction mixture was allowed to warm to room temperature over 1.5 h. The reaction mixture was

quenched with saturated aqueous NH_4Cl (5 mL), and the whole mixture was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), and dried over anhydrous MgSO_4 . Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide **11** (5.7 mg, 16%) as a brown oil: IR (film, cm^{-1}) ν 2937, 2866, 1601, 1554, 1496, 1444, 1352, 1298, 1244, 1173, 946, 908; ^1H NMR (400 MHz, CDCl_3) δ 5.78 (m, 1H), 5.25 (dd, J = 10.4, 2.4 Hz, 1H), 5.21 (dd, J = 17.2, 2.4 Hz, 1H), 3.80 (d, J = 5.0 Hz, 2H), 3.58–3.43 (m, 2H), 2.78–2.72 (m, 2H), 2.43–2.35 (m, 2H), 2.20 (m, 1H), 2.05 (dt, J = 13.6, 3.2 Hz, 1H), 1.95 (t, J = 13.6, 5.0 Hz, 1H), 1.69–1.49 (m, 2H), 1.05 (t, J = 7.6 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 190.5, 171.7, 132.4, 117.7, 108.4, 51.0, 48.7, 33.3, 31.3, 25.0, 23.8, 23.2, 12.4; HRMS (FAB) m/z calcd for $\text{C}_{13}\text{H}_{20}\text{NO}$ ($\text{M}+\text{H}$) $^+$ 206.1545, found 206.1541.

Intramolecular/intermolecular alkylation sequence (route B). *1-(3-Hydroxy)propyl-2,3,6,7-tetrahydro-1H-indol-4(5H)-one (5b)*. 3-Amino-1-propanol (**4b**) (535 mg, 7.12 mmol) was added to a solution of spirocyclopropane **3a** (492 mg, 3.56 mmol) in THF (7 mL). After stirring at 50 °C for 2.5 h, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 11% MeOH in CH_2Cl_2) to provide **5b** (630 mg, 91%) as a pale yellow solid: mp 80–81 °C; IR (KBr, cm^{-1}) ν 3398, 2939, 2869, 1585, 1535, 1511, 1439, 1290, 1190; ^1H NMR (400 MHz, CDCl_3) δ 3.96 (s, 1H), 3.65 (t, J = 6.4 Hz, 2H), 3.57 (t, J = 9.6 Hz, 2H), 3.37 (t, J = 6.4 Hz, 2H), 2.75 (t, J = 9.6 Hz, 2H), 2.39 (t, J = 6.2 Hz, 2H), 2.27 (t, J = 6.2 Hz, 2H), 1.97 (quint, J = 6.4 Hz, 2H), 1.80 (quint, J = 6.2 Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 190.5, 169.6, 108.6, 58.7, 51.4, 43.1, 35.4, 30.4, 23.8, 22.5, 22.1; HRMS (FAB) m/z calcd for $\text{C}_{11}\text{H}_{18}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$ 196.1338, found 196.1337.

1-(3-Iodo)propyl-2,3,6,7-tetrahydro-1H-indol-4(5H)-one (5c). According to the typical procedure for halogenation of alcohols, iodide **5c** was prepared from **5b** (100 mg, 0.51 mmol), NIS (201 mg, 0.77 mmol), and triphenylphosphine (173 mg, 0.77 mmol) at 0 °C for 0.5 h. The crude product was purified by column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide **5c** (150 mg, 96%) as a brown oil: IR (film, cm^{-1}) ν 2936, 2862, 1594, 1556, 1506, 1187; ^1H NMR (400 MHz, CDCl_3) δ 3.51 (t, J = 9.6 Hz, 2H), 3.31 (t, J = 6.6 Hz, 2H), 3.19 (t, J = 6.6 Hz, 2H), 2.78 (t, J = 9.6 Hz, 2H), 2.40 (t, J = 6.2 Hz, 2H), 2.32 (t, J = 6.2 Hz, 2H), 2.10–1.99 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 191.2, 168.4, 109.7, 51.5, 46.6, 35.7, 31.0, 24.1, 22.9, 22.2, 2.3; HRMS (EI) m/z calcd for $\text{C}_{11}\text{H}_{16}\text{INO}$ (M^+) 305.0277, found 305.0284.

1-(3-Bromo)propyl-2,3,6,7-tetrahydro-1H-indol-4(5H)-one (5d). According to the typical procedure for halogenation of alcohols, bromide **5d** was prepared from **5b** (1.05 g, 5.35 mmol), NBS (1.43 g, 8.03 mmol), and triphenylphosphine (2.11 g, 8.03 mmol) at 0 °C for 0.5 h. The crude product was purified by column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide **5d** (1.27 g, 93%) as a yellowish brown oil: IR (film, cm^{-1}) ν 2941, 2868, 1581, 1542, 1508, 1438, 1190; ^1H NMR (400 MHz, CDCl_3) δ 3.52 (t, J = 9.6 Hz, 2H), 3.44 (t, J = 6.4 Hz, 2H), 3.38 (t, J = 6.4 Hz, 2H), 2.77 (t, J = 9.6 Hz, 2H), 2.39 (t, J = 6.4 Hz, 2H), 2.30 (t, J = 6.4 Hz, 2H), 2.11 (quint, J = 6.4 Hz, 2H), 2.01 (quint, J = 6.4 Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 191.2, 168.4, 109.6, 51.4, 44.4, 35.7, 30.3, 30.0, 24.0, 22.6, 22.2; HRMS (FAB) m/z calcd for $\text{C}_{11}\text{H}_{17}\text{BrNO}$ ($\text{M}+\text{H}$) $^+$ 258.0494, found 258.0496.

1,2,4,5,6,6a,7,8-Octahydro-9H-pyrrolo[3,2,1-ij]quinolin-9-one (8). A solution of LiHMDS (11.9 mL, 0.83 M in THF/hexane, 9.87 mmol) was added to a solution of **5d** (1.27 g, 4.93 mmol) and TBAI (182 mg, 0.49 mmol) in THF (49 mL) at –78 °C. After stirring at –78 °C for 1 h, the reaction mixture was allowed to warm to room temperature over 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), and the whole mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous MgSO_4 . Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide **8** (753 mg, 86%) as a pale yellow solid: mp 62–63 °C; IR (KBr, cm^{-1}) ν 2936, 2860, 1550, 1524, 1436, 1361, 1294,

1196; ^1H NMR (400 MHz, CDCl_3) δ 3.62 (td, J = 10.8, 4.0 Hz, 1H), 3.32–3.24 (m, 2H), 2.86 (td, J = 12.0, 4.0 Hz, 1H), 2.80 (td, J = 12.0, 4.0 Hz, 1H), 2.68 (dtd, J = 14.8, 11.2, 2.0 Hz, 1H), 2.41–2.34 (m, 3H), 2.01–1.94 (m, 3H), 1.85 (m, 1H), 1.61 (t, J = 12.0, 9.4 Hz, 1H), 1.17 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 190.8, 169.5, 107.8, 53.4, 46.3, 37.0, 33.4, 29.9, 26.7, 24.0, 22.8; HRMS (EI) m/z calcd for $\text{C}_{11}\text{H}_{15}\text{NO}$ (M^+) 177.1154, found 177.1147.

6a-Ethyl-1,2,4,5,6,6a,7,8-octahydro-9H-pyrrolo[3,2,1-ij]quinolin-9-one (9).^{8a,j} A solution of LiHMDS (0.88 mL, 0.83 M in THF/hexane, 0.73 mmol) was added to a solution of **8** (120 mg, 0.67 mmol) in THF (6.7 mL) at –78 °C. After stirring at –78 °C for 1 h, ethyl iodide (0.27 mL, 3.35 mmol) was added to the mixture and the whole was allowed to warm to room temperature over 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), and the whole mixture was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), and dried over anhydrous MgSO_4 . Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide **9** (123 mg, 88%) as a pale yellow solid: mp 63–64 °C; IR (KBr, cm^{-1}) ν 2940, 2860, 1551, 1522, 1463, 1439, 1355, 1302, 1267, 1192; ^1H NMR (400 MHz, CDCl_3) δ 3.60 (ddd, J = 11.2, 10.4, 3.6 Hz, 1H), 3.30 (dd, J = 11.2, 5.2 Hz, 1H), 3.17 (q, J = 10.4 Hz, 1H), 2.85–2.74 (m, 2H), 2.62 (dt, J = 14.8, 11.2 Hz, 1H), 2.44 (ddd, J = 17.6, 13.2, 2.8 Hz, 1H), 2.27 (ddd, J = 17.6, 5.2, 2.4 Hz, 1H), 1.99 (dd, J = 4.4, 2.0 Hz, 1H), 1.96 (dd, J = 5.2, 2.0 Hz, 1H), 1.90 (dt, J = 13.4, 3.2 Hz, 1H), 1.79 (m, 1H), 1.71–1.63 (m, 2H), 1.55 (tdd, J = 13.4, 5.2, 1.2 Hz, 1H), 1.13 (td, J = 13.2, 3.6 Hz, 1H), 0.89 (t, J = 7.6 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 190.1, 174.8, 107.7, 53.9, 47.2, 35.0, 33.6, 32.5, 28.7, 25.2, 24.1, 18.7, 7.8; HRMS (FAB) m/z calcd for $\text{C}_{13}\text{H}_{20}\text{NO}$ ($\text{M}+\text{H}$) $^+$ 206.1545, found 206.1542.

Synthesis of (±)-aspidospermidine (1a). *rac-(6aR,9aR,9bS)-6a-Ethyldecahydro-4H-pyrrolo[3,2,1-ij]quinolin-9-one (2)*.^{6–8} 10% Pd/C (82 mg, 200 wt% of **9**) was added to a solution of **9** (41 mg, 0.2 mmol) in AcOH (4 mL). The reaction mixture was vigorously stirred under H_2 atmosphere at 50 °C for 12 h. The mixture was filtered through a pad of Celite and the filter cake was rinsed with CH_2Cl_2 (20 mL). The filtrate was concentrated in vacuo, and saturated aqueous NaHCO_3 (20 mL) was added to the residue. The whole mixture was extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic layer was washed with brine (10 mL) and dried over anhydrous MgSO_4 . The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 1% MeOH in CHCl_3) to provide **2** (14 mg, 34%) as a colorless oil: IR (film, cm^{-1}) ν 2929, 1711, 1457; ^1H NMR (400 MHz, CDCl_3) δ 3.03–2.99 (m, 2H), 2.67 (ddd, J = 9.0, 4.8, 1.6 Hz, 1H), 2.45–2.17 (m, 3H), 1.97–1.60 (m, 7H), 1.51–1.47 (m, 2H), 1.37–1.28 (m, 2H), 1.10 (td, J = 13.4, 4.8 Hz, 1H), 0.94 (t, J = 7.6 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 211.5, 73.6, 53.2, 52.9, 48.2, 36.8, 34.8, 32.9, 30.1, 29.7, 26.1, 21.3, 7.1; HRMS (EI) m/z calcd for $\text{C}_{13}\text{H}_{21}\text{NO}$ (M^+) 207.1623, found 207.1616.

(±)-Aspidospermidine (1a).^{6b} According to the procedure of Aubé *et al.*, we demonstrated conversion of **2** into aspidospermidine (**1a**). Phenylhydrazine (3.8 mg, 0.035 mmol) was added to a solution of **2** (6.0 mg, 0.029 mmol) in benzene (0.83 mL). After stirring at reflux for 3 h, the reaction mixture was concentrated in vacuo, and the residue was dissolved in AcOH (0.83 mL). After stirring at reflux for 3.5 h, the reaction mixture was concentrated in vacuo, and the residue was dissolved in THF (0.83 mL). LiAlH_4 (11 mg, 0.29 mmol) was added to a solution of the crude product at 0 °C, and the reaction mixture was stirred at reflux for 11 h. After cooling to 0 °C, the reaction mixture was quenched by addition of one drop of aqueous 10% NaOH. The mixture was filtered through a pad of Celite and the filter cake was rinsed with CH_2Cl_2 (10 mL). The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 11% MeOH in EtOAc) to provide **1a** (2.6 mg, 32%) as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 7.07 (d, J = 8.0 Hz, 1H), 7.02 (t, J = 7.2 Hz, 1H), 6.73 (t, J = 7.2 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 3.52 (m, 1H), 3.12–3.06 (m, 2H), 2.35–2.20 (m, 3H), 1.98–1.91 (m, 2H), 1.79–1.66 (m, 3H), 1.53–1.34 (m, 4H), 1.13 (m, 1H), 1.07 (m, 1H),

0.87 (m, 1H), 0.64 (t, $J = 7.6$ Hz, 3H). ^1H NMR spectroscopic data corresponded to that quoted in ref. 6b.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxx.

^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra for new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

* E-mail: nambu@pha.u-toyama.ac.jp.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This research was supported, in part, by a Grant-in-Aid for Scientific Research (C) (Grant No. 18K05119) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

REFERENCES

- (1) (a) Saxton, J. E. *Alkaloids of the Aspidospermine Group*. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, Chapter 1, pp 1–197. (b) Aquino, P. G. V.; de Aquino, T. M.; Alexandre-Moreira, M. S.; de Oliveira Santos, B. V.; Santana, A. E. G.; de Araújo-Júnior, J. X. *Aspidosperma Terpenoid Alkaloids – Biosynthetic Origin, Chemical Synthesis and Importance*; InTech, 2015. (c) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. Simple indole alkaloids and those with a nonrearranged monoterpenoid unit. *Nat. Prod. Rep.* **2015**, *32*, 1389–1471. (d) Saya, J. M.; Ruijter, E.; Orru, R. V. A. Total Synthesis of *Aspidosperma* and *Strychnos* Alkaloids through Indole Dearomatization. *Chem. Eur. J.* **2019**, *25*, 8916–8935.
- (2) For selected examples of *Aspidosperma* alkaloid syntheses, see: (a) Büchi, G.; Matsumoto, K. E.; Nishimura, H. The Total Synthesis of ($\pm$)-Vindorosine. *J. Am. Chem. Soc.* **1971**, *93*, 3299–3301. (b) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. Collective synthesis of natural products by means of organocascade catalysis. *Nature* **2011**, *475*, 183–188. (c) Bin, H.-Y.; Wang, K.; Yang, D.; Yang, X.-H.; Xie, J.-H.; Zhou, Q.-L. Scalable Enantioselective Total Synthesis of ($\pm$)-Goniomitine. *Angew. Chem. Int. Ed.* **2019**, *58*, 1174–1177. (d) Matsuoka, J.; Kumagai, H.; Inuki, S.; Oishi, S.; Ohno, H. Construction of the Pyrrolo[2,3-*d*]carbazole Core of Spiroindoline Alkaloids by Gold-Catalyzed Cascade Cyclization of Ynamide. *J. Org. Chem.* **2019**, *84*, 9358–9363 and references cited therein. One of the authors has reported the synthetic approach to *Aspidosperma* alkaloid. (e) Nambu, H.; Hikime, M.; Krishnamurthi, J.; Kamiya, M.; Shimada, N.; Hashimoto, S. Asymmetric approach to the pentacyclic skeleton of *Aspidosperma* alkaloids via enantioselective intramolecular 1,3-dipolar cycloaddition of carbonyl ylides catalyzed by chiral dirhodium(II) carboxylates. *Tetrahedron Lett.* **2009**, *50*, 3675–3678.
- (3) Stork, G.; Dolfini, J. E. The Total Synthesis of *dl*-Aspidospermine and of *dl*-Quebrachamine. *J. Am. Chem. Soc.* **1963**, *85*, 2872–2873.
- (4) Meyers and Berney reported asymmetric formal synthesis of (+)-aspidospermidine from optically active starting material along the Stork's synthetic route. Meyers, A. I.; Berney, D. Asymmetric Synthesis of the (4a*S*,8a*R*,8*S*)-Hydroxylololone System. A Formal Total Synthesis of Unnatural (+)-Aspidospermine. *J. Org. Chem.* **1989**, *54*, 4673–4676.
- (5) The Ban and Kuehne groups synthesized Stork's intermediate **2**, in which the stereochemistry of **2** was discussed. (a) Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. Total Synthesis of Aspidospermine. *Tetrahedron Lett.* **1965**, 2261–2268. (b) Kuehne, M. E.; Bayha, C. A Synthetic Route to Aspidospermine and Quebrachamine. *Tetrahedron Lett.* **1966**, 1311–1315.
- (6) (a) Iyengar, R.; Schildknecht, K.; Aubé, J. Regiocontrol in an Intramolecular Schmidt Reaction: Total Synthesis of (+)-Aspidospermidine. *Org. Lett.* **2000**, *2*, 1625–1627. (b) Iyengar, R.; Schildknecht, K.; Morton, M.; Aubé, J. Revisiting a Classic Approach to the *Aspidosperma* Alkaloids: An Intramolecular Schmidt Reaction Mediated Synthesis of (+)-Aspidospermidine. *J. Org. Chem.* **2005**, *70*, 10645–10652.
- (7) Wang, N.; Du, S.; Li, D.; Jiang, X. Divergent Asymmetric Total Synthesis of (+)-Vincadifformine, (–)-Quebrachamine, (+)-Aspidospermidine, (–)-Aspidospermine, (–)-Pyrifolidine, and Related Natural Products. *Org. Lett.* **2017**, *19*, 3167–3170.
- (8) Racemic syntheses of Stork's intermediate **2**: (a) Banwell, M. G.; Smith, J. A. Exploiting multiple nucleophilic sites on pyrrole for the assembly of polyheterocyclic frameworks: application to a formal synthesis of ($\pm$)-aspidospermidine. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2613–2618. (b) Sharp, L. A.; Zard, S. Z. A Short Total Synthesis of ($\pm$)-Aspidospermidine. *Org. Lett.* **2006**, *8*, 831–834. (c) Callier-Dublanche, A.-C.; Cassayre, J.; Gagosz, F.; Quiclet-Sire, B.; Sharp, L. A.; Zard, S. Z. Amidyls in radical cascades. The total synthesis of ($\pm$)-aspidospermidine and ($\pm$)-13-deoxyserrattine. *Tetrahedron* **2008**, *64*, 4803–4816. (d) Pearson, W. H.; Aponick, A. Formal Synthesis of *Aspidosperma* alkaloids via the Intramolecular [3 + 2] Cycloaddition of 2-Azapentadienyllithiums. *Org. Lett.* **2006**, *8*, 1661–1664. (e) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. Highly Efficient Synthesis of Tricyclic Amines by a Cyclization/Cycloaddition Cascade: Total Syntheses of Aspidospermine, Aspidospermidine, and Quebrachamine. *Angew. Chem. Int. Ed.* **2007**, *46*, 6159–6162. (f) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. Stereoselective Formation of Fused Tricyclic Amines from Acyclic Aldehydes by a Cascade Process Involving Condensation, Cyclization, and Dipolar Cycloaddition. *J. Org. Chem.* **2009**, *74*, 2290–2300. (g) Sabot, C.; Guérard, K. C.; Canesi, S. Concise total synthesis of ($\pm$)-aspidospermidine via an oxidative Hosomi–Sakurai process. *Chem. Commun.* **2009**, 2941–2943. (h) Guérard, K. C.; Sabot, C.; Beaulieu, M.-A.; Giroux, M.-A.; Canesi, S. 'Aromatic ring umpolung', a rapid access to the main core of several natural products. *Tetrahedron* **2010**, *66*, 5893–5901. (i) Cho, H.-K.; Tam, N. T.; Cho, C.-G. Total Synthesis of ($\pm$)-Aspidospermidine Starting from 3-Ethyl-5-bromo-2-pyrone. *Bull. Korean Chem. Soc.* **2010**, *31*, 3382–3384. (j) Huang, J.-Z.; Jie, X.-K.; Wei, K.; Zhang, H.; Wang, M.-C.; Yang, Y.-R. Formal Synthesis of Aspidospermidine via the Intramolecular Cascade Transannular Cyclization. *Synlett* **2013**, *24*, 1303–1306.
- (9) Asymmetric syntheses of Stork's intermediate **2**: (a) Fukuda, Y.; Shindo, M.; Shishido, K. Total Synthesis of (–)-Aspidospermine via Diastereoselective Ring-Closing Olefin Metathesis. *Org. Lett.* **2003**, *5*, 749–751. (b) Gnecco, D.; Vázquez, E.; Galindo, A.; Terán, J. L.; Orea, L.; Bernès, S.; Enríquez, R. G. Synthesis of an *aspidosperma* alkaloid precursor: synthesis of (+)-aspidospermidine. *ARKIVOC* **2003**, *xi*, 185–192. (c) Ishikawa, T.; Kudo, K.; Kuroyabu, K.; Uchida, S.; Kudoh, T.; Saito, S. Domino Double Michael–Claisen Cyclizations: A Powerful General Tool for Introducing Quaternary Stereocenters at C(4) of Cyclohexane-1,3-diones and Total Synthesis of Diverse Families of Sterically Congested Alkaloids. *J. Org. Chem.* **2008**, *73*, 7498–7508. (d) Pandey, G.; Burugu, S. K.; Singh, P. Efficient Strategy for the Construction of Both Enantiomers of the Octahydropyrroloquinoline Ring System: Total Synthesis of (+)-Aspidospermidine. *Org. Lett.* **2016**, *18*, 1558–1561. (e) Shemet, A.; Carreira, E. M. Total Synthesis of (–)-Rhazinilam and Formal Synthesis of (+)-Eburenine and (+)-Aspidospermidine: Asymmetric Cu-Catalyzed Propargylic Substitution. *Org. Lett.* **2017**, *19*, 5529–5532.
- (10) Nambu, H.; Fukumoto, M.; Hirota, W.; Yakura, T. Ring-Opening Cyclization of Cyclohexane-1,3-dione-2-spirocyclopropanes with Amines: Rapid Access to 2-Substituted 4-Hydroxyindole. *Org. Lett.* **2014**, *16*, 4012–4015.
- (11) We have also reported ring-opening cyclizations of spirocyclopropanes. (a) Nambu, H.; Ono, N.; Yakura, T. Acid-Catalyzed Ring-Opening Cyclization of Spirocyclopropanes for the Construction of a 2-Arylbenzofuran Skeleton: Total Synthesis of Cuspidan B. *Syn-*

thesis **2016**, *48*, 1892–1901. (b) Nambu, H.; Onuki, Y.; Ono, N.; Yakura, T. Iodide-Catalyzed Ring-Opening Cyclization of Cyclohexane-1,3-dione-2-spirocyclopropanes. *Adv. Synth. Catal.* **2018**, *360*, 2938–2944. (c) Nambu, H.; Onuki, Y.; Ono, N.; Tsuge, K.; Yakura, T. Ring-opening cyclization of spirocyclopropanes with stabilized sulfonium ylides for the construction of a chromane skeleton. *Chem. Commun.* **2019**, *55*, 6539–6542.

(12) Nambu, H.; Hirota, W.; Fukumoto, M.; Tamura, T.; Yakura, T. An Efficient Route to Highly Substituted Indoles via Tetrahydroindol-4(5*H*)-one Intermediates Produced by Ring-Opening Cyclization of Spirocyclopropanes with Amines. *Chem. Eur. J.* **2017**, *23*, 16799–16805.

(13) Nambu, H.; Ono, N.; Hirota, W.; Fukumoto, M.; Yakura, T. An Efficient Method for the Synthesis of 2',3'-Nonsubstituted Cycloalkane-1,3-dione-2-spirocyclopropanes Using (2-Bromoethyl)diphenylsulfonium Trifluoromethanesulfonate. *Chem. Pharm. Bull.* **2016**, *64*, 1763–1768.

(14) The Banwell^{8a} and Yang^{8j} groups have independently reported reduction of **9** with LiAlH₄ afforded 9*b*-*epi*-product **12** in 65% and 82% yields, respectively.

(15) Several groups have reported reduction of enaminones under hydrogenation conditions. (a) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.-L.; Gerasuto, A. I.; Brennessel, W. B. Stereoselective Formal [3+3] Cycloaddition Approach to *cis*-1-Azadecalins and Synthesis of (–)-4*a*,8*a*-*diepi*-Pumiliotoxin C. Evidence for the First Highly Stereoselective 6*π*-Electron Electrocyclic Ring Closures of 1-Azatrienenes. *J. Am. Chem. Soc.* **2002**, *124*, 10435–10442. (b) Pu, X.; Ma, D. Total Synthesis of Lepadins B, D, E, and H; Determination of the Configuration of the Latter Three Alkaloids. *Angew. Chem. Int. Ed.* **2004**, *43*, 4222–4225. (c) Zi, W.; Yu, S.; Ma, D. A Convergent Route to the *Galbulimima* Alkaloids (–)-GB 13 and (+)-GB 16. *Angew. Chem. Int. Ed.* **2010**, *49*, 5887–5890. (d) Maiti, S.; Menéndez, J. C. Brief, efficient and highly diastereoselective synthesis of (±)-pumiliotoxin C based on the generation of an octahydroquinoline precursor *via* a four-component reaction. *Chem. Commun.* **2011**, *47*, 10554–10556.

(16) The Banwell^{8a} and Carreira^{9c} groups independently reported that a stereoselective hydrogenation of pyrrole derivative **13** in the presence of PtO₂ under hydrogen in acetic acid followed by Dess-Martin oxidation provided **2** in 28% and 25% yields, respectively.

(17) The synthesis of **1a** from **2** has been reported by the research groups of Aubé (51% yield),⁶ Gnecco (55% yield),^{9b} Zard (55% yield),^{8b,c} Coldham (42% yield),^{8e,f} Ishikawa and Saito (51% yield),^{9c} Canesi (43% yield),^{8g,h} Cho (45% yield),⁸ⁱ Pandey (50% yield),^{9d} Jiang (53% yield),⁷ and Carreira (42% yield).^{9c}

(18) Regioisomer during Fischer indolization was also obtained in 11% yield. See the Supporting Information for details.

(19) Stork mentioned that the stereochemistries at C-9*a* and C-9*b* of tricyclic intermediates such as **2** and **12** were not operationally significant in the indolization step for synthesizing aspidopermine. See ref. 3.

(20) The Banwell^{8a} and Yang^{8j} groups examined the conversion of **12** into aspidospermidine (**1a**) using Fischer indolization and subsequent reduction but were unsuccessful.

(21) As the shortest-step synthesis of Stork's intermediate **2** to date, Coldham and co-workers reported the synthesis of racemic **2** in six steps from the known 1,5-dibromopentan-3-one, which was prepared in two steps from ethyl 3-bromopropionate. See ref. 8e,f and Denmark, S. E.; Marcin, L. R. Asymmetric Construction of a Quaternary Carbon Center by Tandem [4 + 2]/[3 + 2] Cycloaddition of a Nitroalkene. The Total Synthesis of (–)-Mesembrine. *J. Org. Chem.* **1997**, *62*, 1675–1686.

(22) (a) Prabhakaran, P. C.; Gould, S. J.; Orr, G. R.; Coward, J. K. Synthesis of Chirally Deuteriated Phthalimidopropanols and Evaluation of Their Absolute Stereochemistry. *J. Am. Chem. Soc.* **1988**, *110*, 5779–5784. (b) Ravnsbæk, J. B.; Jacobsen, M. F.; Rosen, C. B.; Voigt, R. N. V.; Gothelf, K. V. DNA-Programmed Glaser–Eglinton Reactions for the Synthesis of Conjugated Molecular Wires. *Angew. Chem. Int. Ed.* **2011**, *50*, 10851–10854.