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Total Synthesis of (+)-Aspidospermidine

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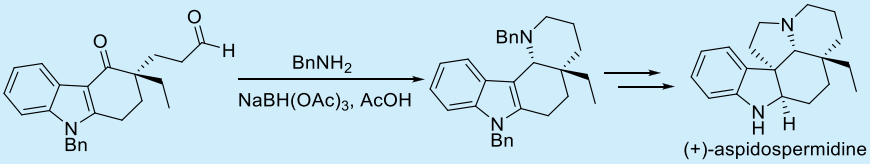
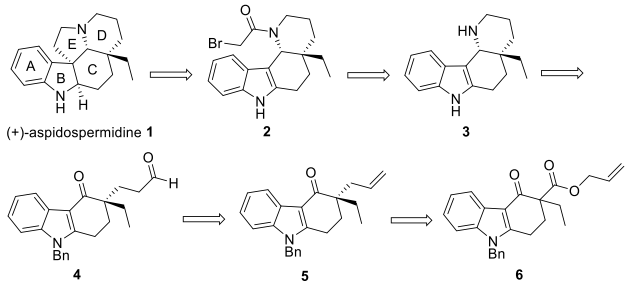
Supporting Information



ABSTRACT: A facile asymmetric total synthesis of (+)-aspidospermidine has been developed, which is accomplished in 11 steps in an overall yield of 9.6%. Key steps involve a palladium-catalyzed enantioselective decarboxylative allylation to install the quaternary carbon stereocenter and a highly efficient reductive amination−carbonyl reduction−dehydration−intramolecular conjugate addition cascade to build the *cis* D-ring.

The *Aspidosperma* alkaloids, originally isolated from the plant species *Aspidosperma* genus which grows wild in South America, constitute the largest family of monoterpene indole alkaloids (>250 members).[1] Because of their unique pharmacological and biological activities, they have long been used in traditional medicine as antimalaria, analgesic, anti-inflammatory, anticancer, and psychotropic drugs.[2] Aspidospermidine **1** (Scheme 1),[3] which possesses the iconic pentacyclic framework of the *Aspidosperma* alkaloid, has stimulated considerable attention among the synthetic community[4−6] and serves as a testing ground for the development of new synthetic strategies toward more complex members of this family.[4b,f,h,j−n,q−s] The most proven approaches for the synthesis of aspidospermidine include final B-ring closure via Fisher indole synthesis using a CDE tricyclic ring system and phenylhydrazine[4d,f,h,o−q,5f−k] and CE-ring formation from a ABD-ring derivative.[4a,b,k,n,5b,e,m−o] Despite all of these achievements, the development of an efficient and enantioselective approach to the synthesis of *Aspidosperma* alkaloids is still desirable. In 1994, Desmaële and d'Angelo developed a novel ring-closing sequence toward the synthesis of (+)-aspidospermidine, in which the crucial *cis* D-ring was assembled into an ABC carbazolone derivative based on an intramolecular capture of an intermediary iminium ion by a carbamate.[4c] Later, a similar ring-closing strategy was applied by She[5q,7] and Shao[4m] for the synthesis of (±)-aspidospermidine and (−)-aspidospermidine, respectively. However, multistep functional group transformations under controlled reaction conditions were required. As part of our continued interest in natural product synthesis,[8] we herein report a concise total synthesis of (+)-aspidospermidine featuring a one-pot reductive amination−carbonyl reduction−dehydration−intramolecular conjugate addition cascade to build the *cis* D-ring under mild reaction conditions. Such a strategy has never been applied previously in the synthesis of *Aspidosperma* alkaloids.

Scheme 1. Retrosynthetic Analysis of (+)-Aspidospermidine



As outlined retrosynthetically in Scheme 1, (+)-aspidospermidine **1** could be obtained from amide **2** via intramolecular alkylation. Amide **2** could be generated by selective N-acylation of **3**. Tetracyclic intermediate **3** was expected to arise from keto-aldehyde **4** via a one-pot sequence involving selective reductive amination of the aldehyde functionality, reduction of the carbazolone keto group, indolic nitrogen-assisted dehydration, and intramolecular capture of the intermediary iminium ion with the amino group introduced during the reductive amination step. This key transformation was challenging in two aspects. First, the amino group from the initial reductive amination reaction could likely attack the carbazolone keto functionality to generate a tetracyclic imine intermediate,[9] the reduction of which would provide the unwanted *trans* D-ring.[4c] Second, conjugation of the indolic nitrogen made the carbazolone keto group less electrophilic, and its reduction normally required the use of strong reducing agents such as $LiAlH_4$. If this is necessarily the case, a tetrahydropyran rather than the piperidine D-ring would be formed.[4m,5q,7] Keto-aldehyde **4** could be derived from

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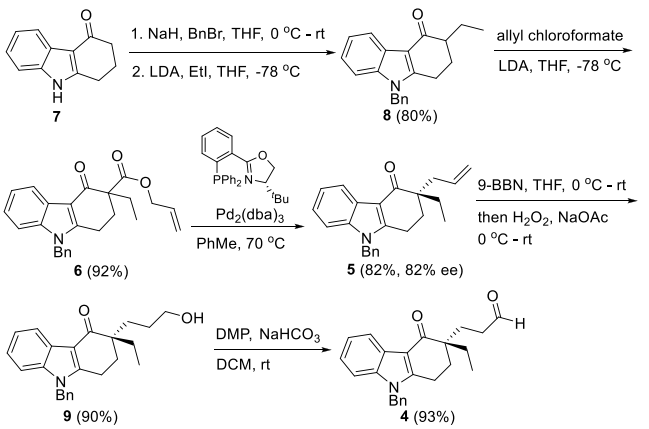
carbazolone **5**, which in turn was generated from β-ketoester **6** through palladium-catalyzed enantioselective decarboxylative allylation.[10,4m]

Our synthesis commenced with the commercially available carbazolone **7**, which was transformed into **8** following a two-step literature procedure (Scheme 2).[5q] Treatment of

Scheme 2. Synthesis of Keto-Aldehyde Intermediate 4 for the Key Cascade Reaction



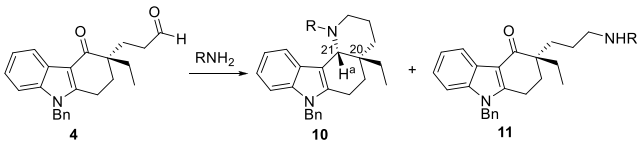
compound **8** with allyl chloroformate in the presence of LDA provided keto-ester **6** in 92% yield. The palladium-catalyzed decarboxylative allylation was then explored, and allyl carbazolone **5** could be obtained in an optimized 82% yield and 82% ee by treatment of **6** with the complex derived from $Pd_2(dba)_3$ and (*S*)-*t*Bu-PHOX.[4m,10] Hydroboration−oxidation of the double bond in compound **5** provided alcohol **9**, which was oxidized to keto-aldehyde **4** with Dess−Martin periodinane in an excellent yield.

With keto-aldehyde **4** in hand, the key cascade reaction for the construction of the D-ring was investigated, and the results are listed in Table 1. Under conventional conditions with either $NaBH(OAc)_3$ or $NaBH_3CN$ as the reductant, both benzyloxy ethylamine and benzylamine reacted with **4** to give exclusively the mono-reductive amination products **11a** and **11b**, respectively, in good isolated yields (entries 1−4). Treatment of **11a** or **11b** with $LiAlH_4$ resulted in complete decomposition, while no reaction occurred when $NaBH_4$ was applied. Delightfully, desired tetracyclic compound **10b** could be isolated in 8% yield (apart from **11b** in 70% yield) when 0.5 equiv of TFA was added to the reaction system of **4**, benzylamine, $NaBH_3CN$, and THF (entry 6).[11] A slightly better result was obtained when $NaBH(OAc)_3$ was applied (entry 7). The *cis* configuration of the D-ring in compound **10b** was assigned on the basis of NOE correlations of H^a with the protons of the ethyl group at C-20. Because no trace of corresponding tetracyclic **10a** was observed with benzyloxy ethylamine (entry 5), benzylamine was used as reactant for the optimization of reaction conditions. While **10b** could be isolated in 30% yield in the presence of AcOH (entry 8), **11b** was generated exclusively when a stronger acid TsOH was applied (entry 9). Further optimization indicated that the best result was obtained when 1.0 equiv of AcOH was applied (entry 10 vs entries 8 and 11). Surprisingly, formation of **10b** was completely hampered when MeOH was used as a solvent (entry 12). Finally, the amount of $NaBH(OAc)_3$ and reaction temperatures were briefly explored, yet a better result could not be obtained (entries 13−15 vs entry 10).

A plausible mechanism for the formation of **10b** is depicted in Scheme 3. Reductive amination of the aldehyde functionality in **4** provided **11b**. Interaction of boron tetraacetate and water would regenerate acetic acid, which preferentially protonated the amino group in **11b** to provide intermediate **B**. Intramolecular proton transfer of **B** generated **C** with a more electrophilic carbonyl group, which was reduced by $NaBH(OAc)_3$ to give intermediate **D**. The indolic nitrogen atom-assisted elimination yielded **E**, which spontaneously cyclized via intramolecular conjugate addition to generate **10b**.

With key tetracyclic intermediate **10b** in hand, we directed our attention to the construction of the E-ring to complete the total synthesis of (+)-aspidospermidine (Scheme 4). Consec-

Table 1. Optimization of Reaction Conditions for the Construction of the D-Ring



entry	R	reductant (equiv)	additive (equiv)	solvent	*T* (°C)	**10** (% yield)	**11** (% yield)
1	$BnO(CH_2)_2$	$NaBH(OAc)_3$ (3)	–	THF	30	**10a** (0)	**11a** (91)
2	$BnO(CH_2)_2$	$NaBH_3CN$ (3)	–	THF	30	**10a** (0)	**11a** (81)
3	Bn	$NaBH(OAc)_3$ (3)	–	THF	30	**10b** (0)	**11b** (88)
4	Bn	$NaBH_3CN$ (3)	–	THF	30	**10b** (0)	**11b** (85)
5	$BnO(CH_2)_2$	$NaBH_3CN$ (3)	TFA (0.5)	THF	30	**10a** (0)	**11a** (83)
6	Bn	$NaBH_3CN$ (3)	TFA (0.5)	THF	30	**10b** (8)	**11b** (70)
7	Bn	$NaBH(OAc)_3$ (3)	TFA (0.5)	THF	30	**10b** (13)	**11b** (67)
8	Bn	$NaBH(OAc)_3$ (3)	AcOH (0.5)	THF	30	**10b** (30)	**11b** (52)
9	Bn	$NaBH(OAc)_3$ (3)	TsOH (0.5)	THF	30	**10b** (0)	**11b** (85)
10	Bn	$NaBH(OAc)_3$ (3)	AcOH (1.0)	THF	30	**10b** (61)	**11b** (23)
11	Bn	$NaBH(OAc)_3$ (3)	AcOH (1.5)	THF	30	**10b** (40)	**11b** (36)
12	Bn	$NaBH(OAc)_3$ (3)	AcOH (1.0)	MeOH	30	**10b** (0)	**11b** (80)
13	Bn	$NaBH(OAc)_3$ (4)	AcOH (1.0)	THF	30	**10b** (11)	**11b** (61)
14	Bn	$NaBH(OAc)_3$ (3)	AcOH (1.0)	THF	20	**10b** (38)	**11b** (44)
15	Bn	$NaBH(OAc)_3$ (3)	AcOH (1.0)	THF	40	**10b** (46)	**11b** (32)

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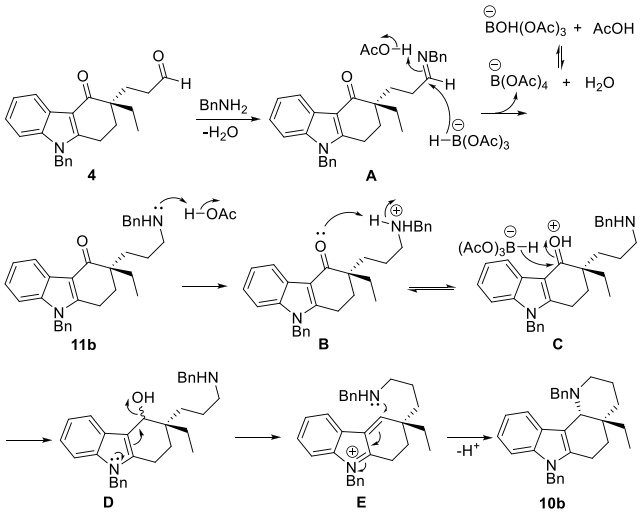
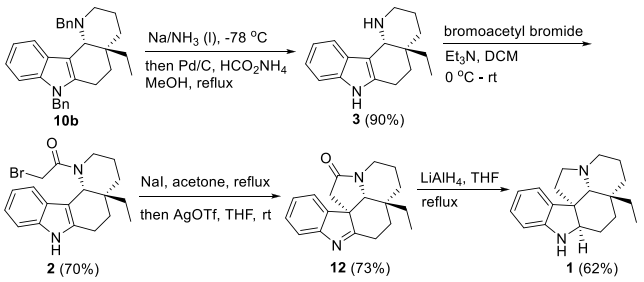
Scheme 3. Proposed Mechanism for the Formation of 10b



Scheme 4. Synthesis of (+)-Aspidospermidine from 10b



utive removal of the indolic and piperidinic benzyl protecting group with Na/NH_3 and $Pd/C/HCO_2NH_4$, respectively, produced **3** in excellent yield. Selective acylation of the piperidine nitrogen in **3** with bromoacetyl bromide proceeded smoothly to give compound **2** in 70% isolated yield. Subsequent application of the protocol developed by Heathcock closed the final E-ring to provide compound **12** in 73% isolated yield.[5e] Further studies indicated that **12** could be obtained in 56% yield from **3** without isolation of intermediate **2**. Finally, reduction of compound **12** with $LiAlH_4$ in refluxing THF furnished (+)-aspidospermidine **1**, the spectroscopic and optical data of which were in accordance with those reported in the literature.[4m,s]

In summary, we have developed a novel approach for the asymmetric total synthesis of (+)-aspidospermidine. Starting from the commercially available carbazolone **7**, the target natural product is obtained in an overall yield of 9.6% following an 11-step procedure. The strategy developed herein is well adapted to the total synthesis of other *Aspidosperma* alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02346.

General procedure, analytical and spectroscopic data, copies of ^1H and ^{13}C NMR spectra of compounds **1**–**6**, **8**, **9**, **10b**, **11a**, **11b**, and **12**, and HPLC spectra of compound **5** (PDF)

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Notes

The authors declare no competing financial interest.

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