Divergent Total Syntheses of Aspidospermidine, *N*-Methylaspidospermidine, *N*-Acetylaspidospermidine and Aspidospermine via a Tandem Cyclization of Tryptamine-Ynamide

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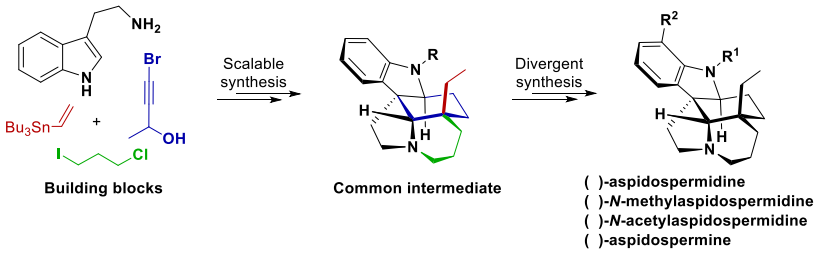
Supporting Information Placeholder



ABSTRACT: The divergent total syntheses of aspidospermidine, *N*-methylaspidospermidine, *N*-acetylaspidospermidine and aspidospermine were achieved from a common pentacyclic indoline intermediate. The common pentacyclic indoline intermediate was synthesized on a gram scale through a Stork-type alkylation of 1*H*-pyrrolo[2,3-*d*]carbazole derivatives, which was prepared based on a Brønsted acid-catalyzed tandem cyclization of tryptamine-ynamide. Scalable synthesis of 1*H*-pyrrolo[2,3-*d*]carbazole afforded a facile access and practical approach to the *Aspidosperma* indole alkaloid family.

The *Aspidosperma* alkaloids are the largest family of monoterpenoid indole alkaloids. With more than 250 members, they have been isolated from a variety of biological sources.[1] Many of them bear a common [6.5.6.6.5] pentacyclic indoline scaffold in structure, only differentiating in substitutions, such as aspidospermidine, *N*-methylaspidospermidine, *N*-acetylaspidospermidine and aspidospermine (Figure 1). The complex [6.5.6.6.5] ring system possesses four contiguous stereocenters, including two all-carbon quaternary chiral centers, posing a great challenge in their syntheses.[2] Since the first pioneering total synthesis achieved by Stork in 1963, many elegant synthetic strategies on the total syntheses of these indole alkaloids have been reported up to date.[3,4] For example, the representative strategies included Fischer indolization of Stork tricyclic ketone intermediate,[3a] intramolecular [4 + 2] cycloaddition,[3c] rearrangement of an indoloquinolizidine,[3b] installation of the E ring after establishment of ABCD core[3d] and so on. Recently, strategies aiming for scalable and practical syntheses of these alkaloids have drawn much attention from synthetic community and have become a significant goal for many synthetic designs,[4c,4g,4p] which might provide a synthetic toolbox to access large collections of these indole alkaloids families and their analogues for use as biological probes or in medicinal chemistry.

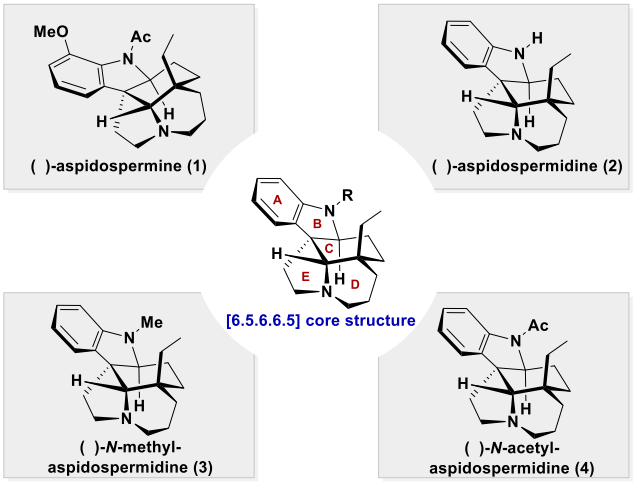


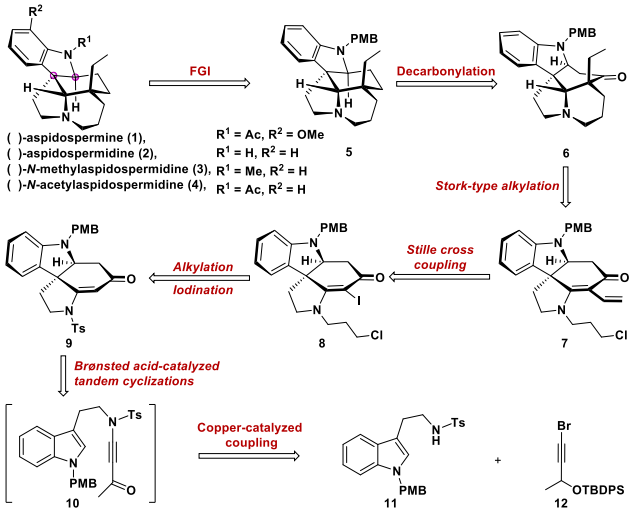
Figure 1. Representative structures of the *Aspidosperma* alkaloids.

In terms of the intrinsic feature of the structures of these indole alkaloids, tryptamine was a key framework contained in *Aspidosperma* alkaloids and an endogenous building block for the biogenetic syntheses of these molecules. In organic synthesis, the cyclization of tryptamine derivatives represented one of

the most straightforward and atom economical strategies to construct the core structure of these indole alkaloids. As our long-term research interest, tandem cyclizations of a series of tryptamine-derived ynamides have yielded a variety of structurally diverse cores of indole alkaloids.[5] Among them, a Brønsted acid-catalyzed tandem cyclization of tryptamine-derived ynamides to 1*H*-pyrrolo[2,3-*d*]carbazole, the tetracyclic framework of *Aspidosperma* alkaloids provided a facile access and practical approach to these indole alkaloids.[5a] Herein, the divergent total syntheses of aspidospermidine, *N*-methylaspidospermidine, *N*-acetylaspidospermidine and aspidospermine were accomplished based on 1*H*-pyrrolo[2,3-*d*]carbazole derivatives, a common tetracyclic intermediate (ABCE core) prepared from the Brønsted acid-catalyzed tandem cyclization of tryptamine-ynamide. This synthetic approach provides a strategy to prepare tetracycle ABCE core of *Aspidosperma* alkaloid followed by the construction of ring D by a Stork-type alkylation in the late-stage of the synthesis.

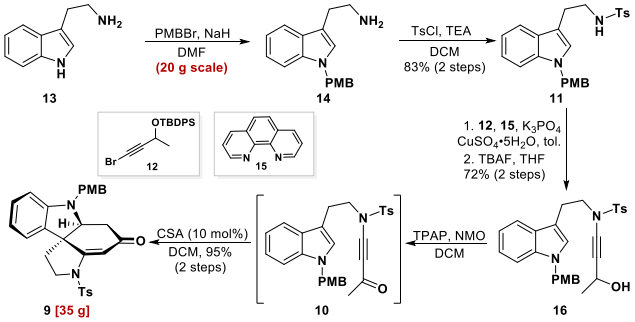
Retrosynthetically, the target molecules could be disconnected into a common pentacyclic intermediate **5**, which was synthesized from intermediate **6** via a decarboxylation. The D ring of intermediate **6** could be readily installed by a Stork-type alkylation starting from intermediate **7**. The vinyl fragment in the intermediate **7** could be introduced by a Stille cross-coupling reaction from intermediate **8**, which could be synthesized from intermediate **9** via several functional group interconversions. The intermediate **9** as the key building block for the synthesis could be derived from **10** via a Brønsted acid-catalyzed tandem cyclization of tryptamine-ynamide, which could be easily prepared from tryptamine derivatives **11** and readily available bromo-alkyne moiety **12** by following our previous procedures (Scheme 1).[5a]

Scheme 1. Retrosynthetic Analysis of *Aspidosperma* Indole Alkaloids 1-4



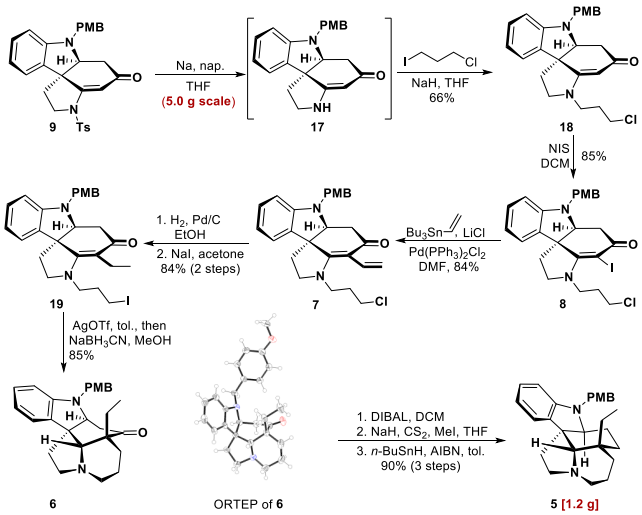
The research commenced with the synthesis of the key intermediate **9**. Protection of the nitrogen on indole (N^{in}) of tryptamine **13** by *para*-methoxybenzyl (PMB) group under a basic condition provided the N^{in}-PMB tryptamine **14**,[5a,6] which was carried out on a 20 g scale. A following introduction of tosyl (Ts) group to the primary amine gave the intermediate **11** in a yield of 83% for 2 steps. The Cu(II)-catalyzed cross-coupling between intermediate **11** and bromo-alkyne moiety[6] formed the tryptamine-ynamide substrate **16** after *O*-desilylation in a yield of 72%. The intermediate **16** was subjected to Ley oxidation condition leading to the formation of the key ynesulfonamide intermediate **10**, which was treated with a catalytic amount of camphorsulfonic acid (CSA) to provide 1*H*-pyrrolo[2,3-*d*]carbazole **9** in a yield of 95%. After this robust tandem cyclization, the tetracyclic intermediate bearing ABCE core was forged and two stereocenters with one quaternary carbon center were established successfully (Scheme 2). It is worth noting that the key intermediate **9** could be synthesized on a decagram scale, which provided enough amounts for the following divergent total syntheses of *Aspidosperma* alkaloids.

Scheme 2. Scalable Synthesis of 1*H*-Pyrrolo[2,3-*d*]carbazole Derivatives 9



Based on the scalable synthesis of tetracyclic intermediate **9**, a concise synthesis of the common intermediate **5** was achieved on a gram scale (Scheme 3). Removal of Ts group on the nitrogen of enamine was performed in the sodium naphthalenide solution followed by a one-pot *N*-alkylation with 1-chloro-3-iodopropane under basic conditions to furnish compound **18** in a yield of 66%. Next, the iodination of compound **18** underwent smoothly by treating with *N*-iodosuccinimide (NIS) to give iodo-substituted compound **8**. Subsequently, an ethyl group needed to be introduced at the α position of enaminone.Various strategies for the installation of the ethyl group have been reported in a plethora of pioneering work,[3l,4k,4l] which often involved tedious multi-step functional group transformations. To develop a straightforward approach to introduce the ethyl group, a Stille coupling/hydrogenation sequential strategy was designed by modifying the readily available enamine moiety derived from the ynamide cyclization.

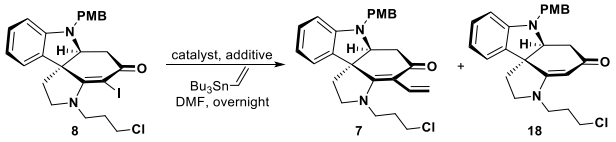
Scheme 3. Concise Syntheses of Common Pentacyclic Intermediate 5



To verify the feasibility of this strategy for installation of the ethyl group, different conditions for Stille cross-coupling

reaction of compound **8** was screened.[7] The reactions using palladium catalysts such as $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$ and $Pd(dppf)_2Cl_2$ in DMF at 120 °C was unsuccessful to afford the desired compound **7**, only leading to the isolation of deiodination byproduct **18** (Table 1, entries 1-3). To suppress the byproduct, some selected additives such as copper iodide (CuI),[7d] zinc chloride ($ZnCl_2$),[7b] zinc bromide ($ZnBr_2$)[7a] and lithium chloride (LiCl)[7c] were added to the reaction. To our delight, when the combination of $Pd(PPh_3)_2Cl_2$ and LiCl was attempted, the vinyl group was introduced effectively resulting in the formation of product **7** in a yield of 63% (Table 1, entries 4-7). Further condition screening revealed that 90 °C was the optimal temperature for this transformation, affording product **7** in a yield of 84% (Table 1, entries 8-9). Other solvents such as 1,4-dioxane, tetrahydrofuran (THF) and toluene were also screened and none of them was better than DMF (Table 1, entries 10-12).

Table 1. Condition Screening of Stille Cross-Coupling



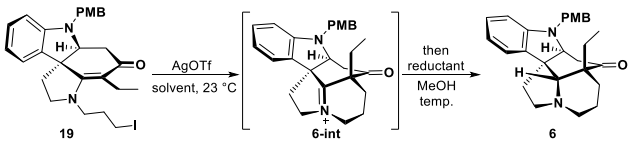
entry	catalyst	additive	temp. (°C)	yield of **7** (%)	yield of **18** (%)
1	$Pd(PPh_3)_2Cl_2$	-	120	0	95
2	$Pd(PPh_3)_4$	-	120	0	98
3	$Pd(dppf)_2Cl_2$	-	120	0	95
4	$Pd(PPh_3)_2Cl_2$	CuI	120	0	93
5	$Pd(PPh_3)_2Cl_2$	$ZnCl_2$	120	48	50
6	$Pd(PPh_3)_2Cl_2$	$ZnBr_2$	120	10	85
7	$Pd(PPh_3)_2Cl_2$	LiCl	120	63	30
8	$Pd(PPh_3)_2Cl_2$	LiCl	90	84	10
9[a]	$Pd(PPh_3)_2Cl_2$	LiCl	60	83	10
10[b]	$Pd(PPh_3)_2Cl_2$	LiCl	90	0	97
11[c]	$Pd(PPh_3)_2Cl_2$	LiCl	90	50	20
12[d]	$Pd(PPh_3)_2Cl_2$	LiCl	90	0	90

[a] The reaction was run for 24 h; [b] 1,4-dioxane was used as the solvent at 60 °C; [c] THF was used as the solvent; [d] toluene was used as the solvent.

A following Pd/C-catalyzed hydrogenation and Finkelstein reaction with sodium iodide (NaI) in acetone[8] gave the corresponding precursor **19** in 84% yield with one purification operation. It was ready for the construction of the D ring via Stork-type alkylation on the basis of precursor **19**. After a thorough examination of reductants including sodium cyanoborohydride ($NaBH_3CN$), sodium borohydride ($NaBH_4$), triethylsilane (Et_3SiH) and Hantzsch esters (HEH) as shown in Table 2, a silver triflate (AgOTf)-initiated alkylation of enamine proved effective to provide the iminium intermediate **6-int** in toluene (Table 2, entries 1-3) and $NaBH_3CN$ acted as a suitable hydride donor[4j,4m] to reduce the iminium intermediate **6-int**, delivering the key pentacyclic intermediate **6** in 85% yield at –20 °C without isolating the iminium intermediate (Table 2, entries 4-8). Two continuous stereocenters were established in this one-pot operation and the relative stereochemistry of the key pentacyclic indoline **6** was confirmed by an X-ray single crystal analysis, which was consistent with the stereochemistry as in the natural products (Scheme 3).

Next, removal of the carbonyl group in compound **6** was tried with Wolff-Kishner-Huang and various modified conditions.[9] However, our substrate did not work well under these conditions. Alternatively, the carbonyl group was reduced to secondary alcohol with diisobutylaluminum hydride (DIBAL) followed by reacting with sodium hydride (NaH), carbon disulfide (CS_2) and methyl iodide (MeI) to form the monoxanthate intermediate. By treating the monoxanthate with tributyltin hydride (*n*-Bu_3SnH) and 2,2′-azobis(2-methylpropionitrile) (AIBN) in toluene at 90 °C,[10] the desired deoxygenation common intermediate **5** was generated in 90% yield for 3 steps on 1.2 g scale with only one purification operation (Scheme 3).

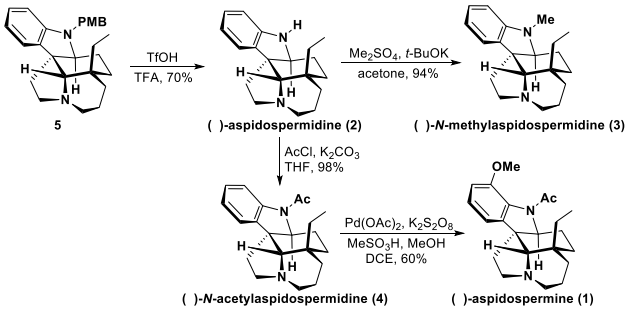
Table 2. Optimization of Stork-Type Alkylation/Reduction Condition



entry	solvent	reductant	temp. (°C)	yield (%)
1	THF	$NaBH_3CN$	23	0
2	DCM	$NaBH_3CN$	23	0
3	toluene	$NaBH_3CN$	23	70
4	toluene	$NaBH_4$	23	45
5	toluene	Et_3SiH	23	0
6	toluene	HEH	23	0
7	toluene	$NaBH_3CN$	0	80
8	toluene	$NaBH_3CN$	-20	85

With the common pentacyclic intermediate **5** in hand, the divergent syntheses of several *Aspidosperma* indole alkaloids were fulfilled as shown in Scheme 4. Unraveling of the PMB group on indole nitrogen afforded (±)-aspidospermidine **2** in a yield of 70%.[4o] A subsequent *N*-methylation provided (±)-*N*-methylaspidospermidine **3**[4e] and *N*-acetylation provided (±)-*N*-acetylaspidospermidine **4**,[4p] in 94% and 98% yields, respectively. It is noteworthy that a Pd-catalyzed *ortho*-alkoxylation[11] of indoline using acetamide moiety as the directing group yielded (±)-aspidospermine **1**[4h] from (±)-*N*-acetylaspidospermidine **4** in a single step and acceptable yield under mild conditions.

Scheme 4. Divergent Total Syntheses of (±)-Aspidospermidine (2), (±)-*N*-Methylaspidospermidine (3), (±)-*N*-Acetylaspidospermidine (4) and (±)-Aspidospermine (1)



In summary, we have developed a concise and divergent strategy for the total syntheses of (±)-aspidospermidine (10 steps from **9**, 21.2% over yield), (±)-*N*-methylaspidospermidine (11 steps from **9**, 19.9% over yield), (±)-*N*-acetylaspidospermidine (11 steps from **9**, 20.7% over yield) and (±)-aspidospermine (12 steps from **9**, 12.5% over yield) based on a tandem cyclization of tryptamine-ynamide. The synthetic approach to 1*H*-pyrrolo[2,3-*d*]carbazole could be performed on a large scale, which allowed the gram scale synthesis of the key pentacyclic common intermediate. The late-stage C−H functionalization allowed a facile entry to *ortho*-methoxy substituted indole alkaloids from advanced intermediates in a divergent way. The enantioselective syntheses of these indole alkaloids and related chemical biology study are undergoing in our lab and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures and compound characterization data, NMR spectra and X-ray analysis of the intermediates and target molecules (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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