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Total Synthesis of (±)-1-Acetylaspidoalbidine and (±)-1-Methylaspidospermidine

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Abstract: (±)-1-Acetylaspidoalbidine and (±)-1-methylaspidospermidine were synthesized from protected tryptamine through the combination of an organocatalytic Diels–Alder reaction, a tandem stereoselective ring-opening reduction, and a double Michael addition.

Keywords: Diels–Alder reaction; double Michael addition; organocatalysis; stereoselectivity; tryptamine

The *Aspidosperma* alkaloid family contains more than 250 compounds, many of which have important biological activities.[1] These compounds share a common pentacyclic structure embedded in an indoline substructure. In addition to these structural complexities, 1-acetylaspidoalbidine (**1**) possesses a unique C_{19} *N,O*-acetal, as is shown in Figure 1.[2] 1-Acetylaspidoalbidine (**1**) and 1-methylaspidospermidine (**2**) were first disclosed in 1963 by Djerassi[3] to have been isolated from *Vallesia dichotoma* Ruiz et Pav in Peru, and **1** was referred to as dehydroxyhaplocidine in a more recent isolation.[4] More highly oxidized *Aspidosperma* alkaloids share further hydroxylation of the aromatic ring, a five-membered lactone *versus* a tetrahydrofuran ring, or further unsaturation in the six-membered rings.

Owing to the structural complexity and potential medicinal applications, the synthesis of the aspidospermine family of the indole alkaloids has elicited substantial interest from the synthetic community. For example, there are six total syntheses so far that have been documented towards the construction of 1-acetylaspidoalbidine and/or 1-methylaspidospermidine. To briefly summarize the previous synthetic efforts, Ban[5] used a relatively complex intermediate that was developed in his previous investigations to furnish 1-acetylaspidoalbidine; Overman[6] applied the aza-Cope rearrangement–Mannich cyclization reactions to achieve a general entry to *Melodinus* and *Aspidosperma* alkaloids; Boger[7] relied on a powerful

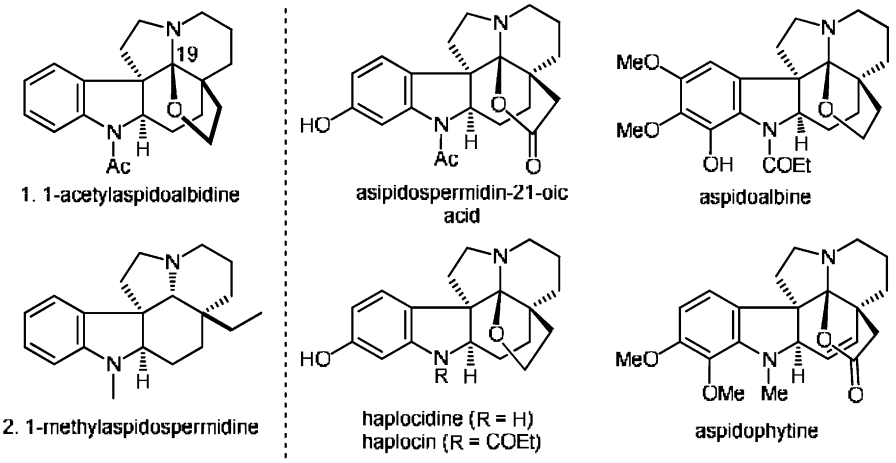
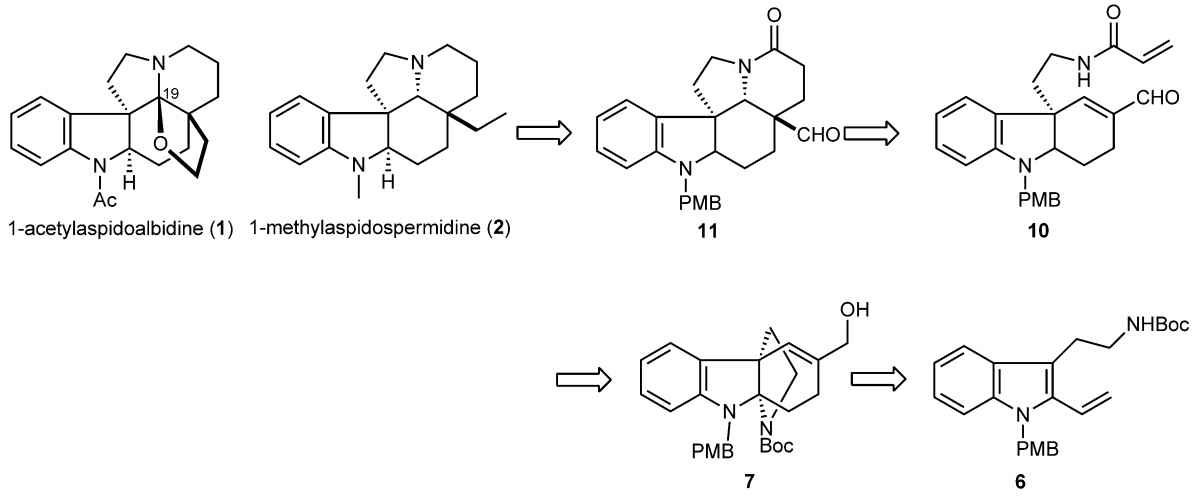


Figure 1. Structures of (±)-1-acetylaspidoalbidine and (±)-1-methylaspidospermidine.

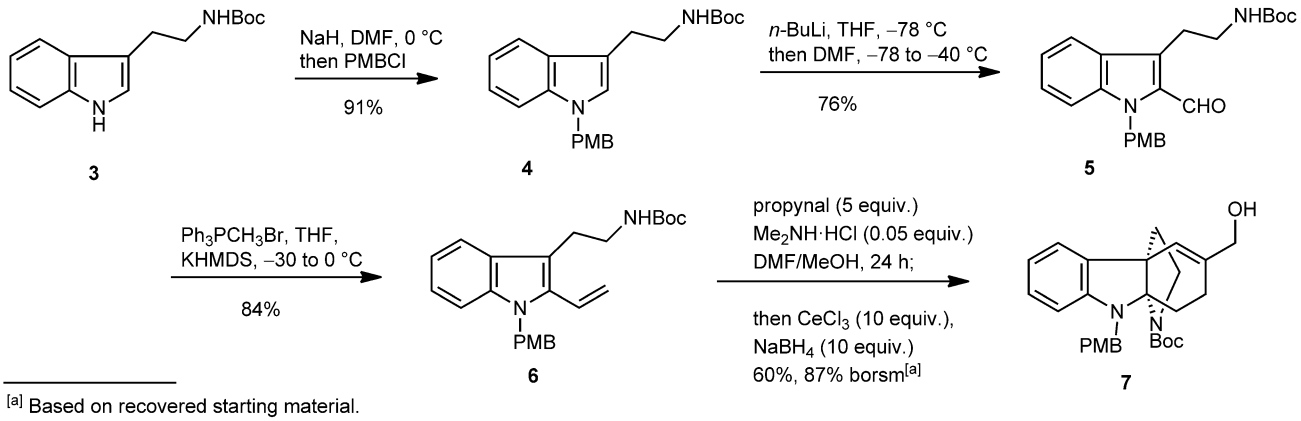
intramolecular [4+2]/[3+2]cycloaddition cascade of a 1,3,4-oxadiazole in which the pentacyclic skeleton and all the stereochemical centers of the natural products are assembled in a single synthetic operation; and Canesi[8] developed an oxidative 1,2- and 1,3-alkyl shift process in a substituted phenol system as a key element for the synthesis of 1-acetylaspidoalbidine. Recently, Banwell reported a concise total synthesis[9] of acetylaspidoalbidine that is strategically more convergent than the previous ones.

The studies described herein were not only formulated to develop a general route to construct the *Aspidosperma* alkaloids, but were seen to have the potential for applications toward other members of this significant family of alkaloids. In this communication, we detail a concise route to 1-acetylaspidoalbidine and 1-methylaspidospermidine, featuring a pivotal organo-catalytic Diels–Alder reaction, which is similar to what has been developed by MacMillan,[10] an effective intramolecular double Michael addition and an iodine-induced formation of the tetrahydrofuran ring. The retrosynthetic analysis is outlined in Scheme 1.

Since the aminal is the most sensitive functionality of **1**, the construction of which should be arranged as the last step *via* the oxidation of either the tertiary amine or the primary hydroxy group of the intermediate precursor. Construction of the latter may be achieved from the pentacyclic aldehyde precursor **11** after a chain elongation and reduction of the lactam to the tertiary amine with concomitant reduction of the aldehyde to the primary alcohol. The pentacyclic intermediate **11** may be synthesized through a tandem Michael addition from the tricyclic enal **10**, which may be obtained *via* a stereoselective ring-opening reduction of indoline **7**. Similar to what has been reported by MacMillan,[10] indoline **7** is the result of a pivotal intermolecular Diels–Alder reaction of an indolyldiene and propynal. The synthesis of the indolyldiene **6** may be realized from the protected tryptamine through a series of transformations (Scheme 2).

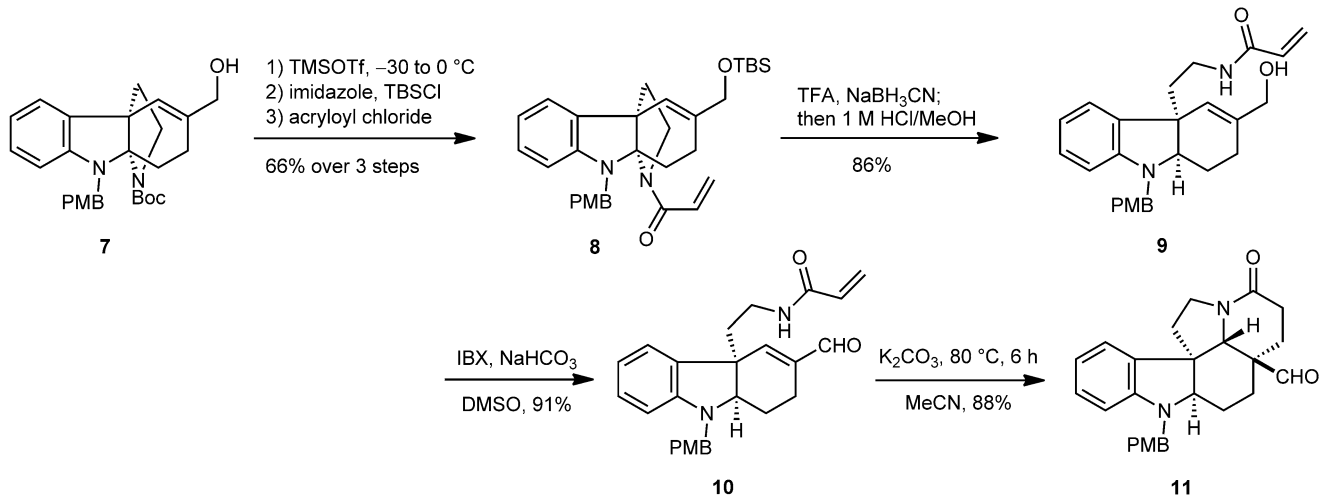


Scheme 1. Retrosynthetic analysis.



[a] Based on recovered starting material.

Scheme 2. Synthesis of indoline **7**.

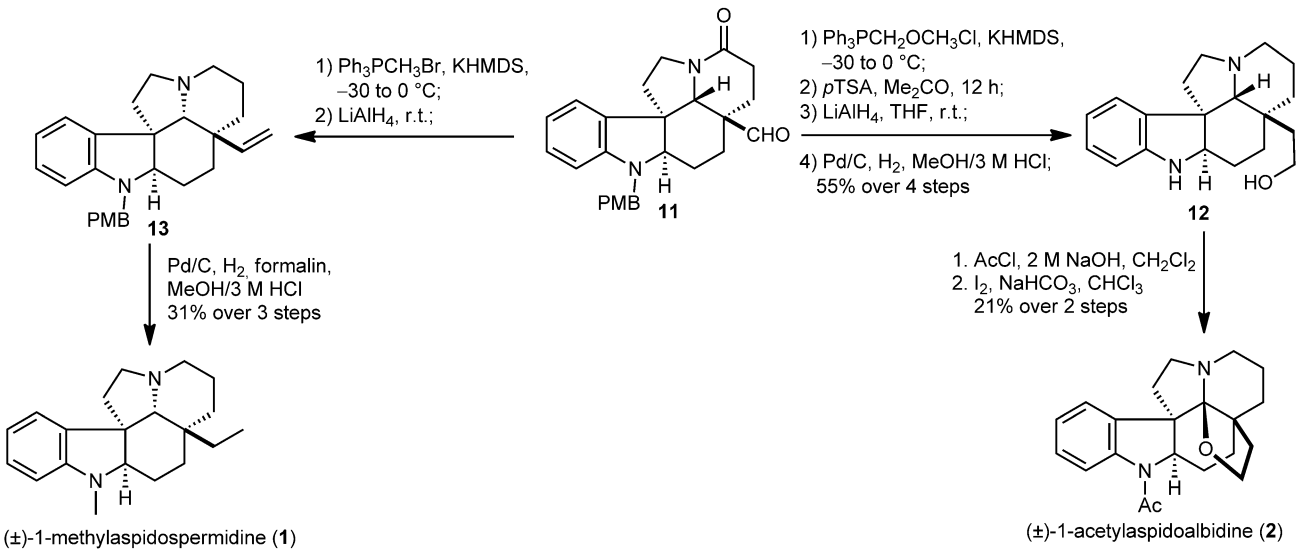


Scheme 3. Synthesis of lactam **11**.

Based on the above analysis, the total synthesis of **1** and **2** was designed to start from the *tert*-butoxycarbonyltryptamine intermediate **3**. The indole ring nitrogen was protected with PMBCl and sodium hydride in DMF (→**4**) in 91% yield. The α-indolyl carbanion generated through the low temperature deprotonation in THF with five equivalents of *n*-butyllithium, when quenched with DMF, afforded in 76% yield the desired indolecarboxaldehyde **5**, which was then olefinated *via* a conventional Wittig reaction to provide the desired diene **6** in 84% yield.

With the diene in hand,[10a] the pivotal Diels–Alder reaction is in place. Propynal was generated directly before use.[11] At this point, a variety of reaction conditions was examined. Initially, piperidinium acetate was tested but the reaction did not proceed at various temperatures. Our attention was then turned to MacMillan's catalyst, which is known to work well for similar Diels–Alder reactions.[10a,b] Unfortunately, only a low yield was obtained without any enantioselectivity. This reaction was also tried with various Lewis acids, but no reaction was observed. Finally, the reaction was found to work nicely to afford the tetracyclic enal in a solvent system containing DMF and methanol. In this reaction, five equivalents of propynal was used with dimethylamine hydrochloride being the catalyst, although the reaction was incomplete even after 24 h. Since the resulting enal was unstable during the following transformations, the aldehyde functionality was reduced *in situ* with sodium borohydride in the presence of cerium trichloride. The combined overall yield was 87% based on recovered starting diene (Scheme 3).

The seemingly straightforward combination of the removal of the *tert*-butoxycarbonyl group and subsequent amidation of **7** with acryloyl chloride had encountered some difficulties. A complex mixture was obtained under a variety of reaction conditions. For instance, when TMSI or aqueous HCl was used to remove the Boc protecting group, the reaction turned into a complex mixture; when trifluoroacetic acid was used, the reaction led to esterification of the allylic alcohol; When the Schotten–Bauman conditions were applied to the amidation, it was found that the selectivity between the amino group and the hydroxy group was very poor. After a few unsuccessful attempts, we decided to tackle the problem in a stepwise manner. The problem was solved by leaving the amidation process to a later stage. Thus, the *tert*-butoxycarbonyl protection was removed upon treatment with TMSOTf at low temperatures. After protection of the primary alcohol with TBSCl, the free amine was reacted with acryloyl chloride to afford intermediate **8** in 66% combined yield for the three steps. The next step was to reduce the aminal to the indoline intermediate **9**. The stereochemistry was controlled by taking advantage of the difference between the thermodynamic stability of the *cis*- and *trans*-[5,6] fused ring systems. Following the treatment with trifluoroacetic acid in acetonitrile and sodium cyanoborohydride, the TBS protecting group was removed using dilute aqueous hydrochloric acid in methanol to furnish in 87% overall yield the desired tricyclic intermediate **9**, which was oxidized in 91% yield to the corresponding enal with the proper set-up of all the functionalities for the key tandem Michael addition. However, no reaction occurred when the reaction mixture was treated with Na_2CO_3 in refluxing acetonitrile; when it was treated with MeONa in MeOH a complicated reaction mixture was obtained; on treatment with *t*-BuOK in THF the reaction also turned into a complex mixture. When treated with potassium carbonate in acetonitrile, to our delight, the reaction proceeded cleanly to give the desired product in 88% isolated yield. Subsequent olefination of the aldehyde functionality was realized using triphe-



Scheme 4. The total synthesis of (±)-1-actylaspidoalbidine and (±)-1-methylaspidospermidine.

nylmethoxymethylphosphonium chloride at low temperatures and KHMDS as the base. The resulting methoxy vinyl ether was hydrolyzed to afford the elongated aldehyde, which provided the desired intermediate hydroxylamine upon reduction with lithium aluminum hydride at room temperature (Scheme 4). Palladium-catalyzed hydrogenolysis in methanol removed the PMB protective group. The combined overall yield was 55% for the four-step operation. At this point, there was only one known transformation toward the completion of the total synthesis of 1-acetylaspidoalbidine. However, it was this last step that had delayed the completion of the total synthesis for about one year. As pointed out by Banwell,[9] the conversion reported by Ban[5b,12] et al. encountered difficulties in our synthesis. Many other reaction conditions that seemed to work well for the oxidation of other architectures containing a tertiary amine[13] did not work. The major problem was irreproducibilty of the reaction yield since numerous side products were detected under the reaction conditions. Fortunately, iodination of the hydroxy group and subsequent *in situ* cleavage of the iodine-oxygen bond led to the formation of the desired tetrahydrofuran ring.[14] Since this reaction produced more side products at prolonged reaction times, it was quenched before going to completion. Thus, the unreacted starting material was recovered and the net reaction yield was 21%.

At this point, we believed that our protocol may also be good for the synthesis of (±)-1-methylaspidospermidine. Thus, aldehyde **11** was transformed into terminal olefin **13** through a Wittig reaction using methylenetriphenylphosphorane, and reduction of the lactam functional group with $LiAlH_4$. Acid-promoted palladium-catalyzed hydrogenolysis of **13** in methanol led to the removal of the PMB protective group, simultaneous methylation of the indolyl nitrogen atom, and hydrogenation of the terminal olefin, affording (±)-1-methylaspidospermidine (**2**) in 31% yield over 3 steps.

In conclusion, the total syntheses of (±)-1-acetylaspidoalbidine (**1**) and (±)-1-methylaspidospermidine (**2**) were achieved in 16 and 13 linear steps (2.5% and 7.1% overall yield from intermediate **3**). There are several notable features in this synthetic strategy: (i) the organocatalytic regioselective Diels–Alder reaction; (ii) the regio- and stereoselective reductive ring opening of the aminal; (iii) the steroecontrolled double Michael addition; (iv) the iodine-mediated tetrahydrofuran ring formation; and (v) the acid-promoted *in situ* hydrogenolysis–methylation. All these effective elements combined with mild reaction conditions make this synthesis practicable.

Experimental Section

General Methods

Tetrahydrofuran (THF) was dried over Na and diphenyl ketone. Acetonitrile (MeCN) was dried over activated 4 Å molecular sieves, and dimethylformamide (DMF) was dried over calcium hydride. Dichloromethane (DCM), and trimethylsilyl trifluoromethanesulfonate (TMSOTf) were distilled from calcium hydride immediately prior to use. Acetone (Me_2CO) was distilled from calcium chloride before use. 2-Iodoxybenzoic acid (IBX) was synthesized according to literature procedures.[15] All reagents were of reagent grade and used without purification unless otherwise noted. All reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that had been oven-dried. Reaction temperatures referred to the temperature of the cool-

ing/heating bath. Chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on 230–400 mesh silica gel (Silicycle flash F60) according to the method of Still,[16] unless otherwise noted. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at the indicated field strengths as solutions in $CDCl_3$. Chemical shifts were referenced to the deuterated solvent (e.g., for $CDCl_3$, $\delta = 7.26$ ppm and 77.0 ppm for ^{1}H and ^{13}C NMR, respectively) and reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, $\delta = 0.00$ ppm). Coupling constants (J) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Indoline 7

To a solution of **6** (2.22 g, 5.5 mmol) in DMF/MeOH (2 mL/2 mL) was added $Me_2NH{\cdot}HCl$ (2.3 mg, 0.028 mmol) in one portion. The resulting solution was stirred for 10 min before the addition of propynal[11] (1.48 g, 27.5 mmol). The reaction mixture was stirred at room temperature for 24 h and then cooled to 0 °C. $CeCl_3{\cdot}7H_2O$ (20.49 g, 55 mmol) in MeOH (20 mL) was added in one portion, followed by $NaBH_4$ (2.08 g, 55 mmol). After being stirred for 10 min, the reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (50 mL). The aqueous layer was extracted with ethyl acetate (50 mL × 2), and the combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by using column chromatography (ethyl acetate/hexane 1/10 to 1/5) to give **7** as a white powder; yield: 1.54 g (60%; 87% based on recovered starting material). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.14$–7.06 (m, 3H, Ar*H*), 6.96 (t, J = 7.5 Hz, 1H, indoline Ar*H*), 6.84–6.79 (m, 2H, Ar*H*), 6.64 (t, $J = 7.1$ Hz, 1H), 6.13 (d, $J = 7.6$ Hz, 1H, indoline Ar*H*), 6.06* (d, $J = 7.6$, indoline Ar*H*), 5.81 (s, 1H, C*H*=C), 4.86 (d, J = 16.4 Hz, 1H, PMB ArC*H*H), 4.78* (d, $J = 16.5$ Hz, PMB ArC*H*H), 4.65 (d, $J = 16.5$ Hz, 1H, PMB ArCH*H*), 4.49* (d, $J = 16.2$ Hz, PMB ArCH*H*), 4.04 (d, $J = 5.6$ Hz, 2H, CH_2OH), 3.77 (s, 3H, OCH_3), 3.72–3.25 (m, 2H), 2.67–2.21 (m, 3H), 2.03–1.79 (m, 3H), 1.45 [s, 9H, C$(CH_3)_3$]; HR-MS (ESI): $m/z = 463.2583$, exact mass calculated for $[M+H]^+$ ($C_{28}H_{34}N_2O_4$): 463.2591.

Acrylamide 8

To a solution of **7** (1.536 g, 3.3 mol) in dry MeCN (10 mL) at −30 °C was added TMSOTf (2.938 g, 13.3 mmol) dropwise. After the reaction mixture had been slowly warmed up to room temperature, saturated $NaHCO_3$ (30 mL) was added, and then the mixture was diluted with ethyl acetate (50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in dry DCM (10 mL), imidazole (221 mg, 3.3 mmol) and TBSCl (497 mg, 3.3 mmol) were added. After being stirred for 1 hour, the reaction mixture was diluted with ethyl acetate (20 mL), washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in dry DCM (10 mL), pyridine (391 mg, 4.95 mmol) and acryloyl chloride (448 mg, 4.95 mmol) were added. The reaction mixture was stirred for 1 hour and then washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by using column chromatography (EA/hexane 1/20) to give **8** as a white foam; yield: 1.159 g (66% over 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.10$ (t, J = 8.5 Hz, 3H, indoline Ar*H*, PMB Ar*H*), 6.95 (tt, $J = 13.6$, 6.8 Hz, 1H, indoline Ar*H*), 6.78 (d, $J = 8.7$ Hz, 2H, PMB Ar*H*), 6.67 (t, $J = 7.1$ Hz, 1H, indoline Ar*H*), 6.40 (dd, J = 16.7, 10.1 Hz, 1H, C*H*=CHH), 6.30 (dd, $J = 16.7$, 2.2 Hz, 1H, CH=CH*H*), 6.13 (d, $J = 7.8$ Hz, 1H, indoline Ar*H*), 5.75 (s, 1H, C*H*=C), 5.63 (dd, $J = 10.0$, 2.2 Hz, 1H, CH=C*H*H), 5.04 (d, $J = 16.8$ Hz, 1H, PMB ArC*H*H), 4.80 (d, $J = 16.5$ Hz, 1H, PMB ArCH*H*), 4.01 (s, 2H, CH_2OTBS), 3.76 (s, 3H, OCH_3), 3.66 (m, 1H), 3.54–3.41 (m, 1H), 3.02 (dt, $J = 14.1$, 5.1 Hz, 1H), 2.51–2.29 (m, 2H), 2.18–1.80 (m, 3H), 0.89 [s, 9H, OSiC$(CH_3)_3(CH_3)_2$], 0.04 [d, $J = 2.9$ Hz, 6H, OSiC$(CH_3)_3(CH_3)_2$]; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 165.72$, 158.03, 148.45, 137.23, 131.88, 131.56, 130.29, 128.08, 127.47, 127.41, 121.81, 121.67, 117.54, 113.67, 108.06, 92.20, 66.21, 56.00, 55.17, 47.78, 47.38, 35.09, 25.88, 25.16, 22.69, 18.36, −5.29, −5.35; HR-MS (ESI): $m/z = 531.3031$, exact mass calculated for $[M+H]^+$ ($C_{32}H_{42}N_2O_3Si$): 531.3037.

Allyl alcohol 9

To a solution of **8** (1.159 g, 2.2 mmol) in MeCN (10 mL) was added trifluoroacetic acid (423 mg, 4.3 mmol) in one portion. After the mixture had been stirred for 10 min, $NaBH_3CN$ (148 mg, 2.2 mmol) was added in one portion, and the mixture was stirred for 10 min before MeOH (5 mL) and aqueous solution of HCl (3 M, 1 mL) were added. The solution was stirred for 5 min and then neutralized with saturated $NaHCO_3$, diluted with ethyl acetate (10 mL), and washed with water. The aqueous layer was extracted with ethyl acteate (10 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (MeOH/CH_2Cl_2 1/40) to give **9** as a white foam; yield: 787 mg (86%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.22$ (d, $J = 8.6$ Hz, 2H, PMB Ar*H*), 7.07–6.98 (m, 2H, indoline Ar*H*), 6.85 (d, $J = 8.6$ Hz, 2H, PMB Ar*H*), 6.66 (t, $J = 7.3$ Hz, 1H, indoline Ar*H*), 6.42 (d, $J = 8.1$ Hz, 1H, indoline Ar*H*), 6.21 (dd, $J = 16.8$, 1.2 Hz, 1H, HC=CH*H*), 5.96 (dd, $J = 16.8$, 10.3 Hz, 1H, *H*C=CHH), 5.60 (dd, $J = 10.3$, 1.2 Hz, 1H, HC=C*H*H), 5.52 (s, 2H, C*H*=C, N*H*CO), 4.39 (d, $J = 15.6$ Hz, 1H, PMB ArC*H*), 4.14 (d, J = 15.6 Hz, 1H, PMB ArC*H*), 3.97 (s, 2H, CH=CCH_2OH), 3.80 (s, 3H, OCH_3), 3.68–3.64 (m, 1H), 3.45–3.29 (m, 2H), 2.12–1.70 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 165.49$, 158.64, 150.80, 137.89, 134.66, 130.79, 130.45, 128.51, 127.97, 126.26, 125.87, 122.59, 117.68, 113.95, 107.62, 66.68, 66.38, 55.24, 49.55, 46.63, 38.77, 36.09, 22.41, 20.94; HR-MS (ESI): $m/z = 419.2324$, exact mass calculated for $[M+H]^+$ ($C_{26}H_{30}N_2O_3$): 419.2329.

Aldehyde 10

To a dimethyl sulfoxide (5 mL) solution of **9** (787 mg, 1.9 mmol) was added IBX (644 mg, 2.3 mmol) and $NaHCO_3$ (193 mg, 2.3 mmol) in one portion. The reaction mixture was stirred at room temperature for 3 h before it was diluted with ethyl acetate (20 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with water and brine,

dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by using column chromatography (ethyl acetate/hexane, 1/4) to give **10** as a gray foam; yield: 748 mg (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (s, 1H, C*H*O), 7.20 (d, J = 8.6 Hz, 2H, PMB Ar*H*), 7.08 (m, 2H, Ar*H*), 6.85 (d, J = 8.6 Hz, 2H, PMB Ar*H*), 6.71 (t, J = 7.2 Hz, 1H, indoline Ar*H*), 6.50 (s, 1H, C*H*=CCHO), 6.47 (d, J = 7.8 Hz, 1H, indoline ArH), 6.22 (dd, J = 17.0, 1.3 Hz, 1H, CH=CH*H*), 5.96 (dd, J = 17.0, 10.3 Hz, 1H, C*H*=CHH), 5.62 (dd, J = 10.3, 1.2 Hz, 1H, CH=C*H*H), 5.51 (s, 1H, N*H*), 4.40 (d, J = 15.8 Hz, 1H, PMB Ar C*H*H), 4.14 (d, J = 15.8 Hz, 1H, PMB Ar CH*H*), 3.87–3.77 (m, 4H), 3.35 (dd, J = 14.0, 7.6 Hz, 2H), 2.28–2.01 (m, 5H), 1.72–1.64 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.68, 165.45, 158.75, 152.43, 151.27, 139.94, 131.08, 130.55, 129.84, 128.92, 128.47, 126.47, 123.04, 118.07, 114.02, 108.19, 66.12, 55.21, 49.64, 48.04, 37.34, 35.92, 21.47, 16.49; HR-MS (ESI): m/z = 439.2171, exact mass calculated for $[M+H]^+$ ($C_{26}H_{28}N_2O_3$): 417.2173.

Lactam 11

To a solution of **10** (748 mg, 1.8 mmol) in dry MeCN (50 mL) was added anhydrous sodium carbonate (2.48 g, 18 mmol) in one portion. The mixture was stirred at 80 °C under nitrogen for 6 h and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (DCM/MeOH, 60/1 to 20/1) to give **11** as a white solid; yield: 661 mg (88%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.43 (s, 1H, C*H*O), 7.25 (d, J = 8.2 Hz, 2H, PMB, Ar*H*), 7.18–6.96 (m, 2H, indoline Ar*H*), 6.88 (d, J = 8.4 Hz, 2H, PMB Ar*H*), 6.70 (t, J = 7.3 Hz, 1H, indoline Ar*H*), 6.41 (d, J = 7.8 Hz, 1H, indoline Ar*H*), 4.39 (d, J = 14.4 Hz, 2H, PMB Ar*H*H, C*H*NCO), 4.00 (d, J = 14.6 Hz, 1H, PMB ArC*H*), 3.82 (s, 3H, OC***H*****$_3$**), 3.75–3.60 (m, 1H), 3.45–3.50 (m, 1H), 3.12 (dd, J = 9.1, 5.0 Hz, 1H), 2.66–2.51 (m, 1H), 2.28–2.45 (m, 2H), 2.01–1.93 (m, 1H), 1.84–1.63 (m, 3H), 1.57–1.45 (m, 1H), 1.40–1.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.30, 167.85, 158.94, 150.34, 129.54, 129.00, 128.85, 128.78, 122.49, 118.12, 114.09, 107.70, 63.62, 60.84, 55.28, 53.63, 48.00, 47.77, 43.53, 34.76, 27.65, 27.07, 21.56, 20.26; HR-MS (ESI): m/z = 417.2166, exact mass calculated for $[M+H]^+$ ($C_{26}H_{28}N_2O_3$): 417.2173.

Alcohol 12

To a mixture of $Ph_3PCH_2OCH_3Cl$ (548 mg, 1.6 mmol) in dry THF (10 mL) at −30 °C under nitrogen was added KHMDS (1.6 mL, 1 M in THF) dropwise. After the mixture had ben stirred for 30 min at the same temperature, **11** (661 mg, 1.6 mmol) in dry THF (10 mL) was added slowly. The reaction mixture was gradually warmed up to 0 °C, and saturate NH_4Cl (5 mL) was added. The resulting mixture was diluted with ethyl acetate (20 mL), washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in Me_2CO (10 mL) and *p*-TsOH (10 mg) was added in one portion. The reaction mixture was stirred at room temperature for 12 h and then neutralized with saturated $NaHCO_3$ (5 mL), diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in dry ether (20 mL), and $LiALH_4$ (61 mg, 1.6 mmol) was added in one portion. The mixture was stirred at room temperature for 4 h and then quenched with saturated aqueous Na_2SO_4, diluted with ethyl acetate, washed with water, brine, and concentrated under reduced pressure. The residue was dissolved in MeOH/3 M HCl (5 mL/0.5 mL) and Pd/C (10 mg) was added. The mixture was stirred under H_2 for 10 min, and filtered. The filtrate was diluted with DCM (10 mL), washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by using column chromatography (DCM/MeOH, 100/1 to 20/1) to give **12** as a white solid; yield: 262 mg (55% over 4 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, J = 7.3 Hz, 1H), 7.01 (td, J = 7.6, 1.2 Hz, 1H), 6.73 (td, J = 7.4, 0.8 Hz, 1H), 6.64 (d, J = 7.7 Hz, 1H), 3.71–3.42 (m, 4H), 3.22–2.97 (m, 2H), 2.40–2.18 (m, 3H), 2.13–1.91 (m, 2H), 1.82–1.60(m, 4H), 1.54–1.40 (m, 3H), 1.33–1.14 (m, 2H), 1.03 (d, J = 13.8 Hz, 1H), 0.89 (dd, J = 12.6, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.48, 135.23, 127.35, 122.74, 119.17, 110.49, 70.69, 65.33, 58.64, 53.74, 73.47, 52.84, 40.50, 38.55, 35.48, 35.41, 28.22, 24.32, 21.70; HR-MS (ESI): m/z = 299.2118, exact mass calculated for $[M+H]^+$ ($C_{19}H_{26}N_2O$): 299.2118.

(±)-1-Acetylaspidoalbidine (1)

To a solution of **12** (18 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) was added 2 M NaOH in water (2 mL). The mixture was cooled to 0 °C and AcCl (0.1 mL) was added. The reaction mixture was stirred for one hour and then separated. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (1 mL). To this solution was added I_2 (19 mg, 0.06 mmol) and saturated $NaHCO_3$ (1 mL). The mixture was stirred at room temperature for 4 h and diluted with DCM (10 mL), washed with saturated $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by using column chromatography (ethyl acetate/hexane, 0.5/1 to 2/1) to give (±)-1-Acetylaspidoalbidine (**1**) as a colorless solid; yield: 4.2 mg (21% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.19 (td, J = 7.6, 1.1 Hz, 1H), 7.05 (td, J = 7.6, 1.0 Hz, 1H), 4.16 (t, J = 8.5 Hz, 1H), 4.13–4.02 (m, 1H), 3.86 (dd, J = 10.7, 5.1 Hz, 1H), 3.02 (td, J = 8.8, 4.4 Hz, 1H), 2.96–2.88 (m, 1H), 2.79 (dd, J = 15.5, 6.9 Hz, 1H), 2.65 (d, J = 11.0 Hz, 1H), 2.25 (s, 3H), 2.0–2.25 (m, 1H), 1.99–1.64 (m, 6H), 1.50–1.58 (m, 1H), 1.47–1.31 (m, 2H), 1.26 (dd, J = 12.5, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.05, 141.12, 137.76, 127.35, 124.77, 124.66, 117.77, 102.01, 68.82, 64.97, 58.21, 48.90, 43.92, 39.63, 37.11, 34.73, 33.09, 26.45, 25.37, 23.35, 21.06; HR-MS (ESI): m/z = 339.2064, exact mass calculated for $[M+H]^+$ ($C_{21}H_{26}N_2O_2$): 339.2067.

(±)-1-Methylaspidospermidine (2)

To a mixture of Ph_3PCH_3Br (47 mg, 0.13 mmol) in dry THF (2 mL) at −30 °C was added KHMDS (0.26 mL, 1 M in THF) dropwise. After this mixture had been stirred for 30 min at the same temperature, **11** dissolved in dry THF (2 mL) was added dropwise. The reaction mixture was gradually warmed up to 0 °C, and saturated NH_4Cl (5 mL) was added. The resulting mixture was diluted with ethyl acetate (20 mL), washed with water, brine, dried over Na_2SO_4, and

concentrated under reduced pressure. The residue was dissolved in dry ether (20 mL), and $LiALH_4$ (3.4 mg, 0.09 mmol) was added in one portion. The mixture was stirred at room temperature for 4 h and then quenched with saturated aqueous Na_2SO_4, diluted with ethyl acetate, washed with water, brine, and concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL) before Pd/C (10 mg), formaldehyde (0.01 mL, 37% in water) were added. The mixture was stirred under H_2 for 30 min. HCl (3 M, 0.2 mL) was then added to the mixture, which was stirred for another 1 hour and filtered. The filtrate was diluted with DCM (10 mL), washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by using column chromatography (ethyl acetate/hexane, 1/10 to 1/5) to give **2** as a white solid; yield: 5.6 mg (31% over 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.06$ (t, $J = 7.6$ Hz, 1H), 7.01 (d, $J = 7.4$ Hz, 1H), 6.63 (t, $J = 7.4$ Hz, 1H), 6.37 (d, $J = 7.7$ Hz, 1H), 3.41 (d, $J = 4.5$ Hz, 1H), 3.23–2.96 (m, 2H), 2.74 (s, 3H), 2.39–2.13 (m, 3H), 2.01–1.81 (m, 2H), 1.80–1.36 (m, 7H), 1.35–1.03 (m, 3H), 0.94–0.78 (m, 1H), 0.60 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 150.55$, 136.87, 127.21, 122.14, 117.09, 106.38, 71.75, 71.23, 53.83, 53.02, 52.59, 39.12, 35.50, 34.50, 31.46, 30.07, 22.95, 21.99, 21.80, 6.79. The ^{1}H and ^{13}C data for synthetic (±)-1-methylaspidospermidine (**2**) were consistent with those reported.[7a] HR-MS (ESI): $m/z = 297.2323$, exact mass calculated for $[M+H]^+$ ($C_{20}H_{29}N_2$): 297.2325.

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