VIP Alkaloid Synthesis

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A Concise and Versatile Double-Cyclization Strategy for the Highly Stereoselective Synthesis and Arylative Dimerization of Aspidosperma Alkaloids**

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The monoterpene indole alkaloids represent the largest family of alkaloid natural products, the more than 2000 members of which show a broad range of chemical diversity and potent biological activity.[1] The structural challenges presented by this family have long been a source of interest, resulting in the development of a variety of inventive synthetic strategies to access various family members. The biogenetically related natural alkaloids *N*-methylaspidospermidine (**1**), *N*-methylquebrachamine (**2**), and tabernaebovine (**3**) represent the aspidosperma subfamily of monoterpene indole alkaloids (Figure 1).[2–5] The dimeric alkaloid **3**, isolated from *Tabernaemontana bovina* in 1998,[2e] has a fascinating molecular constitution that exhibits a unique C2–C15′ linkage between two pentacyclic aspidosperma skeletons. While elegant strategies for the synthesis of other dimeric monoterpene indole alkaloids have been reported,[5] no synthetic solution to the distinctive C2–C15′ bond that is present in **3** exists. As a outgrowth of our studies concerning electrophilic amide activation,[6] we report a concise and convergent strategy for the enantioselective synthesis of alkaloids (−)-**1**, (+)-**2**, and dimeric (+)-dideepoxytabernaebovine (**4**).

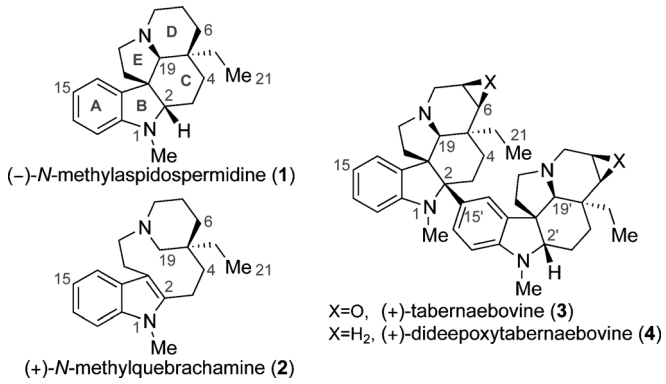
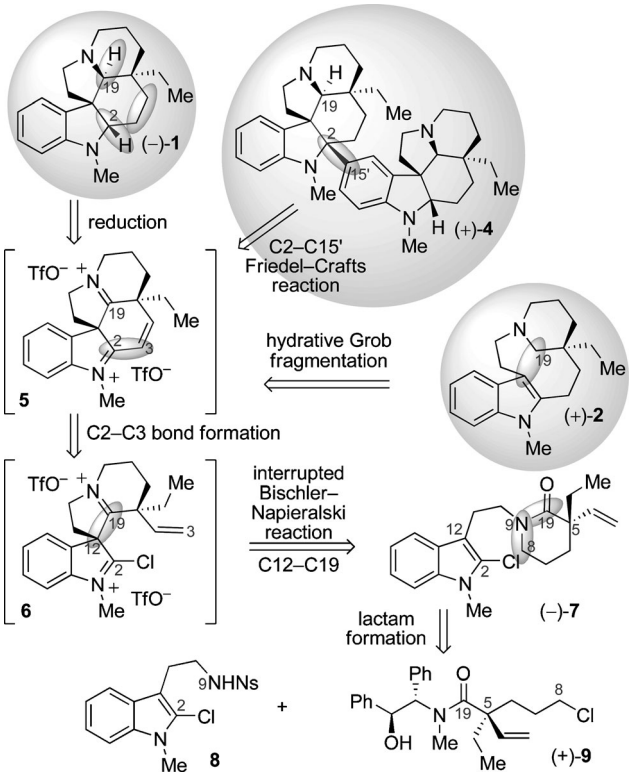


Figure 1. Representative aspidosperma alkaloids.

Inspired by precedence in biogenetically relevant dimerizations of other monoterpene indole alkaloids,[1,5] we postulated the biogenesis of (+)-tabernaebovine (**3**) to involve the late-stage union of two aspidosperma fragments at the C2–C15′ linkage. This retrobiosynthetic analysis[7] prompted the development of a regio- and diastereoselective arylation at C2 of pentacycle **5** (Scheme 1) en route to decacycle (+)-**4**. We envisioned that a highly electrophilic diiminium ion **5** would allow stereo- and regioselective transformations that provide divergent access to dimeric decacycle (+)-**4** as well as monomeric aspidosperma alkaloids, such as (−)-**1** and (+)-**2** (Scheme 1). We expected that reduction of the diiminium ion **5** would afford (−)-**1**, whereas hydrative Grob fragmentation followed by reduction would afford (+)-**2**. We hypothesized that the diiminium ion **5** could be generated from lactam (−)-**7** through a novel, stereoselective double-cyclization cascade. We envisioned a transformation that involves spirocyclization of an electrophilically activated lactam inter-



Scheme 1. Retrosynthetic analysis of the aspidosperma alkaloids.

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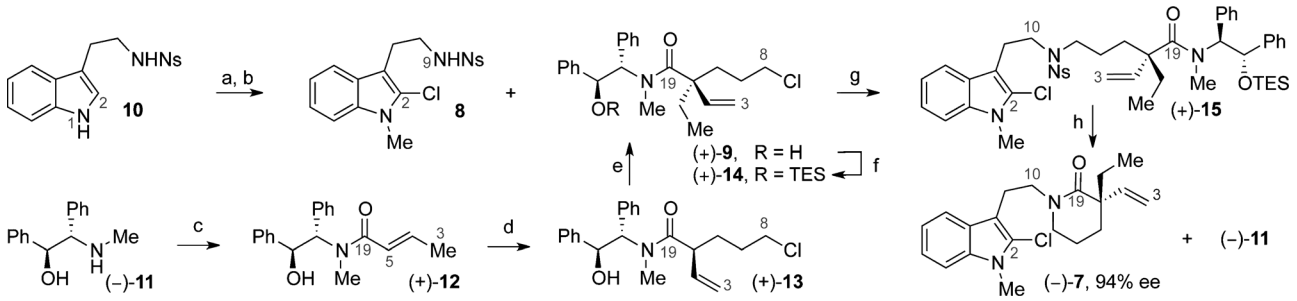
mediate onto the 2-chloroindole, and subsequent interruption of the Bischler–Napieralski reaction by cyclization of an unactivated C3–C4 vinyl group onto the C2 position of the putative 2-chlorospiroindoleninium intermediate **6**. The overall stereochemical outcome of the process would be secured from the resident stereochemistry of the quaternary center at C5. The requisite lactam (−)-**7** could be simplified by N acylation and N alkylation transforms to 2-chlorotryptamine sulfonamide **8** and α-quaternary amide (+)-**9**, the latter of which could be synthesized diastereoselectively by alkylative quaternization of an amide enolate.

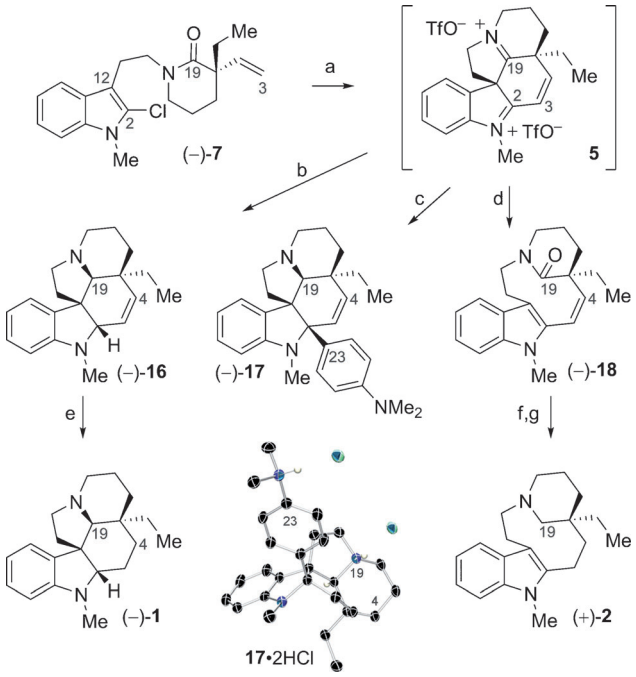
The concise enantioselective synthesis of the key tryptamine lactam (−)-**7** is shown in Scheme 2. Regioselective methylation of sulfonamide **10**[8] via its disodium dianion provided the requisite N1-methylated derivative in 91% yield.[9] Subsequent treatment with *N*-chlorosuccinimide afforded C2-chlorinated tryptamine **8** in 76% yield. The quaternary stereogenic center at C5 that we envisioned would enable stereocontrolled introduction of all stereocenters found in alkaloids (−)-**1**, (+)-**2**, and (+)-**4** was secured by successive diastereoselective α alkylations of crotonamide (+)-**12**. Acylation of (−)-pseudoephenamine (**11**)[10] with *E*-crotonyl chloride gave the enamide (+)-**12** in 97% yield. Chemoselective γ deprotonation of enamide (+)-**12** with lithium 2,2,6,6-tetramethylpiperidide in the presence of lithium chloride,[11] followed by electrophilic trapping of the resulting enolate with 3-chloro-1-iodopropane afforded α-vinyl amide (+)-**13** as a single diastereomer in 83% yield. Inspired by Myers' alkylative quaternizations[12] of pseudoephedrine amides and precedent for α alkylation of α-methyl crotonimides,[13] we reasoned that deprotonation of α-vinyl amide (+)-**13** would afford the corresponding enolate with the sterically less-demanding vinyl group *cis* to the amide nitrogen. Alkylation from the less-sterically shielded face of the enolate[10,11] would secure the desired quaternary stereocenter at C5. Gratifyingly, deprotonation of amide (+)-**13** with lithium diisopropylamide in the presence of lithium chloride, followed by electrophilic trapping with iodoethane at −50 °C in the presence of *N*,*N*′-dimethylpropylene urea provided the α-quaternary amide (+)-**9** in 72% yield with an excellent level of stereoselection (d.r. > 29:1).[9,14,15]

Attempts to hydrolyze amide (+)-**9** to the corresponding carboxylic acid were unsatisfactory because of competitive lactone formation under either basic or acidic conditions. Initial efforts to couple α-quaternary amide (+)-**9** with sulfonamide **8** through nucleophilic displacement of the chloride atom at C8 proved inefficient; fast N→O acyl transfer of amide (+)-**9** led to intramolecular N alkylation. This propensity of amide (+)-**9**, however, could be used to our advantage for the synthesis of lactam (−)-**7** and recovery of the chiral auxiliary. Sequential treatment of sulfonamide **8** with potassium hydride and O-silyl-protected derivative (+)-**14** in DMF followed by heating to 100 °C afforded *N*-alkylated sulfonamide (+)-**15** in 86% yield. Desulfonylation[16] of (+)-**15** to the corresponding secondary amine and in situ desilylation and heating in ethanol afforded the key lactam (−)-**7** in 95% yield and 94% *ee*.[9] This single-step transformation, which occurs through a desilylation/N→O acyl transfer/lactam cyclization cascade, also leads to efficient recovery of the chiral auxiliary (−)-**11** in 99% yield (Scheme 2).[17]

We next focused on the development of a unified strategy to access a versatile intermediate en route to alkaloids (−)-**1**, (+)-**2**, and (+)-**4**. Electrophilic activation of lactam (−)-**7** with trifluoromethanesulfonic anhydride[6,18] initiated a double-cyclization cascade leading to the versatile diiminium ion **5** (Scheme 3). Guided by our prior studies on the synthesis of azaheterocycles by employing electrophilic amide activation,[6] we recognized that the optimal conditions for conversion of lactam (−)-**7** into diiminium ion **5** involve the use of mildly basic additive 3-cyanopyridine in acetonitrile followed by warming. This transformation relies on electrophilic activation at C19 of lactam (−)-**7** and rapid nucleophilic spirocyclization at C12 affording the putative 2-chlorospiroindoleninium intermediate **6** (Scheme 1) that undergoes addition at C2 by the vinyl group and loss of hydrogen chloride. The ability to employ an unactivated C3–C4 olefin as the nucleophile in the second cyclization is likely a result of the enhanced electrophilicity at C2 of intermediate **6** imparted by the chlorine atom,[19] together with a high resilience of **6** toward an undesired Pictet–Spengler rearrangement.[20,21] Consistent with the sensitivity of this double-cyclization step, the use of less-basic 2-chloropyridine or



Scheme 2. Enantioselective synthesis of lactam (−)-**7**: a) NaH, DMF, 23 °C; MeI, 0→23 °C, 91%; b) *N*-chlorosuccinimide, MeCN, 23 °C, 76%; c) *E*-crotonyl chloride, Et_3N, THF, −30→23 °C, 97%; d) lithium 2,2,6,6-tetramethylpiperidide, LiCl, THF, 0→−78 °C; 3-chloro-1-iodopropane, −78→0 °C, 83%; e) lithium diisopropylamide, LiCl, THF, −78→0 °C; *N*,*N*′-dimethylpropylene urea, −40 °C; EtI, −50 °C, 72%, d.r. > 29:1; f) triethylsilyl triflate, 2,6-lutidine, CH_2Cl_2, 23 °C, 100%; g) (+)-**14**, **8**, KH, nBu_4NI, DMF, 100 °C, 86%; h) PhSH, K_2CO_3, DMSO, 23 °C; KOEt, $Et_3N{\cdot}3HF$, EtOH, 85 °C, 95%, 94% *ee*, 99% recovery of (−)-**11**. DMF = *N*,*N*′-dimethylformamide, Ns = 2-nitrobenzenesulfonyl, TES = triethylsilyl.



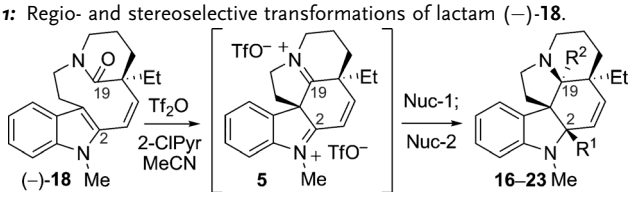
Scheme 3. Synthesis of aspidosperma alkaloids by interception of diiminium ion **5**: a) Tf_2O, 3-cyanopyridine, MeCN, 85 °C; b) $NaBH_3CN$, THF, 50%; c) 4-(Me_2N)-C_6H_4MgBr, −40 °C; Red-Al, 40%; d) trifluoroacetic acid, sodium trifluoroacetate, H_2O, 70 °C, 57%; e) H_2, Pt/C, THF, 100%; f) H_2, Pt/C, THF; g) $LiAlH_4$, THF, 65 °C, 82% (two steps). Thermal ellipsoids in crystal structure of **17**·2 HCl drawn at 50% probability. Tf = trifluoromethanesulfonyl, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride.

more-nucleophilic pyridine as the additive gave the desired diiminium ion **5** with reduced efficiency as evidenced by the presence of singly cyclized side products, recovered starting material, and significant decomposition.[22] The synthetic versatility of diiminium ion **5** is illustrated by its conversion into alkaloids (−)-**1**, (+)-**2**, and (−)-**17** (Scheme 3). In situ reduction of intermediate **5** with sodium cyanoborohydride furnished (−)-*N*-methyldehydroaspidospermidine (**16**) in 50% yield as a single diastereomer. Catalytic hydrogenation of *cis*-alkene (−)-**16** with a carbon-supported platinum catalyst quantitatively afforded (−)-*N*-methylaspidospermidine (**1**; $[\alpha]_D^{24} = -23$ ($c = 0.17$, $CHCl_3$); Ref. [3d]: $[\alpha]_D^{25} = -23$ ($c = 1.1$, $CHCl_3$); Ref. [2c] for (+)-**1**: $[\alpha]_D^{20} = +24$ ($c = 1.25$, $CHCl_3$); Scheme 3). All spectroscopic data for our synthetically obtained (−)-**1** were consistent with those reported in the literature.[3d] The concise enantioselective synthesis of lactam (−)-**7** combined with the double-cyclization strategy described above enables rapid access to useful intermediates with highly reactive iminium functions at C2 and C19.

The unique reactivity of diiminium ion **5** is demonstrated by its utility in an arylation at C2, reminiscent of the C2–C15′ bond adjoining the two halves of the complex natural alkaloid (+)-tabernaebovine (**3**, Figure 1). We reasoned that the vicinal iminium ion at C19 of intermediate **5** would enhance the electrophilicity of the iminium ion at C2 both inductively and by reducing the steric bulk through the flattening of the DE ring system (see Figure 1). Gratifyingly, treatment of in situ generated diiminium ion **5** with 4-(*N*,*N*-dimethylamino)phenyl magnesium bromide at −40 °C for 30 seconds followed by addition of Red-Al afforded hexacyclic C2 aniline adduct (−)-**17** in 40% yield as a single diastereomer (Scheme 3).[9] The steric congestion around C2 in adduct (−)-**17** is evidenced by the rotation barrier of approximately 20 kcal mol^{-1} [9] around the C2–C23 σ bond, as measured by coalescence-temperature experiments in NMR spectroscopy. Also, heating an acidic aqueous solution of diiminium ion **5** to 70 °C effected Grob fragmentation to give the tetracyclic lactam (−)-**18**[23] in 57% yield in a single step from lactam (−)-**7**. Platinum-catalyzed hydrogenation[24] of the C3–C4 olefin and subsequent carbonyl reduction at C19 with lithium aluminium hydride at 60 °C provided (+)-*N*-methylquebrachamine (**2**; $[\alpha]_D^{24} = +102$ ($c = 0.22$, $CHCl_3$); Ref. [2a]: $[\alpha]_D^{24} = +110$ ($CHCl_3$)) in 82% yield over two steps.[9]

With particular interest in evaluating this chemistry as a general entry to the synthesis of complex aspidosperma alkaloids, we investigated a series of addition reactions at C2, which are of relevance in synthetic planning. Importantly, lactam (−)-**18**, which required mild activation conditions, proved to be an excellent precursor to diiminium ion **5**. Treatment of lactam (−)-**18** with the reagent combination Tf_2O/2-chloropyridine[6] in acetonitrile (23 °C, 10 min) resulted in rapid stereo- and regioselective electrophilic transannular spirocyclization to **5** en route to various

Table 1: Regio- and stereoselective transformations of lactam (−)-**18**.

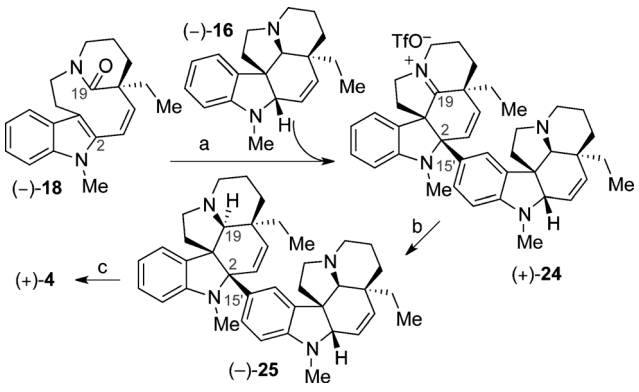


No.	Nuc-1[a]	Nuc-2	R^1	R^2	Product	Yield [%][b]
1	$NaBH_3CN$	–	H	H	(−)-**16**	95
2	nBu_3SnH	$NaBD_4$	H	D[c]	(−)-**19**	94
3	BrMg, NMe_2	Red-Al	H	H	(−)-**17**	76
4		–	23, NMe_2	–[d]	(−)-**20**	76
5	BrMg, Me, Me	Red-Al	Me, Me	H	(−)-**21**	59
6	Me, $SiMe_3$	$NaHB(OMe_3)$	Me	H	(−)-**22**	92
7	OMe, $OSiMe_2tBu$	$NaHB(OMe_3)$	OMe, O	H	(−)-**23**	79
8		$NaHB(OMe_3)$		H	(−)-**17**	74
9	NMe_2	–	NMe_2	–[d]	(−)-**20**	73

[a] Grignard reagents used at −40 °C. Other nucleophiles used at 23 °C. [b] Yield of isolated single diastereomer. [c] 93% Deuterium incorporation at C19. [d] Isolated as C19 iminium triflate. 2-ClPyr = 2-chloropyridine.

C2 adducts **16**–**23** (Table 1). Use of sodium cyanoborohydride afforded (−)-*N*-methyldehydroaspidospermidine (**16**) in 95% yield (Table 1, entry 1), consistent with efficient generation of the same electrophilic intermediate **5** accessed from lactam (−)-**7** (Scheme 3). The greater reactivity at C2 compared to C19 of diiminium ion **5** can be used for regioselective addition of the first nucleophile at C2.[25] For example, treatment of **5** with tributylstannane followed by introduction of sodium borodeuteride afforded pentacycle (−)-**19**, which is deuterated at C19, in 94% yield with no deuterium enrichment at C2 and 93% deuterium incorporation at C19 (Table 1, entry 2). Notably, the C2-arylated product (−)-**17** could be prepared efficiently from lactam (−)-**18** by using 4-(*N*,*N*-dimethylamino)phenyl magnesium bromide as the first nucleophile followed by in situ reduction at C19 (Table 1, entry 3, 76% yield). Alternatively, hexacyclic iminium triflate (−)-**20** could be isolated and reduced with sodium cyanoborohydride to (−)-**17** in a subsequent step (Table 1, entries 4 and 9). That this reduction at C19 of pentacycle (−)-**20** occurs in the absence of an acidic additive is consistent with the spectroscopic data of (−)-**20**, thus revealing its iminium ion structure.[9] It is notable that the rotation barrier of approximately 12 kcal mol^{-1} [9] around the C2–C23 σ bond in iminium ion (−)-**20** is significantly lower than in the reduced product (−)-**17** (see above), consistent with the aforementioned structural flattening effect of the iminium ion at C19. The high electrophilicity of diiminium ion **5** allows C–C bond formation at C2 with highly hindered and mildly nucleophilic species. Treatment of intermediate **5** with 2,6-dimethylphenyl magnesium bromide followed by hydride reduction afforded the highly congested xylene adduct (−)-**21** in 59% yield (Table 1, entry 5). The high degree of steric congestion around C2 in (−)-**21** is evidenced by the complete lack of observable C2–C23 σ-bond rotation on the ^{1}H NMR timescale, even at 140 °C. Reaction of **5** with 2-methallyltrimethylsilane or 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene and subsequent hydride reduction afforded methallyl adduct (−)-**22** (Table 1, entry 6, 92% yield) and methyl acetate adduct (−)-**23** (Table 1, entry 7, 79% yield), respectively. The utility of this strategy to access C2-arylated derivatives is highlighted by a Friedel–Crafts reaction of **5** with *N*,*N*-dimethylaniline (23 °C, 90 min) and either in situ reduction at C19 to provide C2-arylated amine (−)-**17** or isolation of the pentacyclic C19 iminium salt (−)-**20** (Table 1, entries 8 and 9, 74% and 73% yield, respectively).

With insight gained from these studies, in particular entries 8 and 9 of Table 1, we sought to implement this chemistry in effecting the dimerization of two pentacyclic aspidosperma-type molecular frameworks at the challenging C2–C15′ linkage (Scheme 4). In the event, electrophilic activation of tetracyclic lactam (−)-**18** followed by treatment with equimolar (−)-*N*-methyldehydroaspidospermidine (**16**) and heating to 85 °C afforded the decacyclic iminium triflate (+)-**24** in 80% yield. Subsequent reduction at C19 of (+)-**24** gave (−)-didehydrodideepoxytabernaebovine (**25**), which upon hydrogenation provided (+)-dideepoxytabernaebovine (**4**) in 64% yield over two steps (Scheme 4). Alternatively, in situ reduction at C19 of dimeric iminium ion (+)-**24**, which was formed through the union of lactam (−)-**18** with (−)-*N*-methyldehydroaspidospermidine (**16**) as described above, with sodium trimethoxyborohydride directly afforded product (−)-**25** from (−)-**18** in 73% yield.[9] Apart from increasing the electrophilicity of the vicinal C2 iminium ion, the C19 iminium ion may be responsible for reducing the nucleophilicity of the dimeric intermediate (+)-**24**, as no oligomerized products could be observed, even when only one equivalent of (−)-**16** was employed as nucleophile.



Scheme 4. Synthesis of (+)-dideepoxytabernaebovine (**4**): a) Tf_2O, 2-ClPyr, MeCN, 23 °C; (−)-**16** (1.0 equiv), 85 °C, 80%; b) Red-Al, 0 °C, 76%; c) H_2, Pt/C, THF, 84%.

We have developed a concise synthetic strategy to access the aspidosperma-type molecular framework by employing a double-cyclization cascade that results in up to three contiguous stereogenic centers and forms up to three carbon–carbon bonds with complete regio- and stereochemical control in a single step. The use of the chiral auxiliary (−)-**11**[10] was critical in enabling our concise and enantioselective synthesis of the key intermediate (−)-**7**. The ability to use an unactivated olefin as a pendant nucleophile minimizes the need for functional group removal and allows for concise and convergent access to complex aspidosperma alkaloids. We have shown putative diiminium ion **5** to be a highly reactive and versatile intermediate, allowing the rapid enantioselective total syntheses of (−)-*N*-methylaspidospermidine (**1**) and (+)-*N*-methylquebrachamine (**2**) in eight and nine steps, respectively, from *E*-crotonyl chloride and (−)-pseudoephenamine (**11**), as well as the unprecedented C–C bond formations onto the highly congested C2 position of the aspidosperma skeleton. The power of this synthetic strategy has been demonstrated in the first example of a C2–C15′ dimerization of two aspidosperma-type systems, a complex assembly drawing on biogenetic considerations of (+)-**3**, in the synthesis of (+)-dideepoxytabernaebovine (**4**).

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