Alkaloid Synthesis

DOI: 10.1002/anie.201405609

Concise and Enantioselective Total Synthesis of (−)-Mehranine, (−)-Methylenebismehranine, and Related *Aspidosperma* Alkaloids**

*Marius Mewald, Jonathan William Medley, and Mohammad Movassaghi**

Abstract: *We report an efficient and highly stereoselective strategy for the synthesis of Aspidosperma alkaloids based on the transannular cyclization of a chiral lactam precursor. Three new stereocenters are formed in this key step with excellent diastereoselectivity due to the conformational bias of the cyclization precursor, leading to a versatile pentacyclic intermediate. A subsequent stereoselective epoxidation followed by a mild formamide reduction enabled the first total synthesis of the Aspidosperma alkaloids (−)-mehranine and (+)-(6S,7S)-dihydroxy-N-methylaspidospermidine. A late-stage dimerization of (−)-mehranine mediated by scandium trifluoromethanesulfonate completed the first total synthesis of (−)-methylenebismehranine.*

The *Aspidosperma* alkaloids are a subset of the monoterpene indole alkaloids with great structural diversity in their characteristic pentacyclic skeleton which contains at least four consecutive stereogenic centers.[1] In addition to (−)-aspidospermidine (**1**),[2] the archetype of this family of natural products with only the unfunctionalized pentacyclic core structure, several members with oxidation at C6 and C7 positions are known (Figure 1). (−)-Mehranine (**2**) was first isolated from *Tabernaemontana divaricata* in 1995, but it was also found in *Tabernaemontana bovina* together with its hydrated congener (+)-(6*S*,7*S*)-dihydroxy-*N*-methylaspidospermidine (**3**) in 1998.[3] Moreover, the intriguing (−)-mehranine-derived dimers (−)-methylenebismehranine (**4**) and (+)-tabernaebovine (**5**) were also isolated from *Tabernaemontana bovina*; they possess connectivities through a methylene bridge at both C15 atoms and a direct C2–C15′ bond between two (−)-mehranine monomers, respectively.[4] While aspidospermidine (**1**) has served as a classic target for the application of new synthetic methodologies,[2] no total syntheses of the oxidized monomers (−)-**2** and (+)-**3** or the dimers (−)-**4** and (+)-**5** have been reported to date.[5] Herein, we present the first total synthesis of (−)-mehranine (**2**) and (−)-methylenebismehranine (**4**) as well as access to (+)-(6*S*,7*S*)-dihydroxy-*N*-methylaspidospermidine (**3**) and (−)-aspidospermidine (**1**) based on a highly diastereoselective transannular cyclization.

Recently, we reported a unique method to access *Aspidosperma* alkaloids based on a double-cyclization cascade induced by the electrophilic activation of lactam (−)-**6** (Scheme 1, left).[6] This approach allowed for the rapid assembly of the *Aspidosperma* skeleton and the addition of nucleophiles to the in situ formed diiminium ion **10** in a single step from precursor (−)-**6**. Reduction of **10** with sodium cyanoborohydride resulted in the formation of pentacycle (−)-**15** in 50% overall yield. However, a limitation of the double-cyclization cascade was the low diastereoselectivity of the initial cyclization event [(−)-**6**→**8**] resulting from the small steric difference between the vinyl and ethyl groups at C5. The undesired C12 epimer of spirocyclization intermediate **8** did not follow a productive pathway to a pentacyclic structure, thus resulting in modest yield for the overall process. In addition, the introduction of a double bond at the C6 and C7 positions (Scheme 1, **7**), which would allow for late-stage oxidation to (−)-mehranine-type structures, resulted in the formation of undesired monocyclized products derived from intermediate **9**, and the desired pentacyclic structure **16** was not obtained.[7] Therefore, we sought the development of a milder and highly stereoselective cycliza-

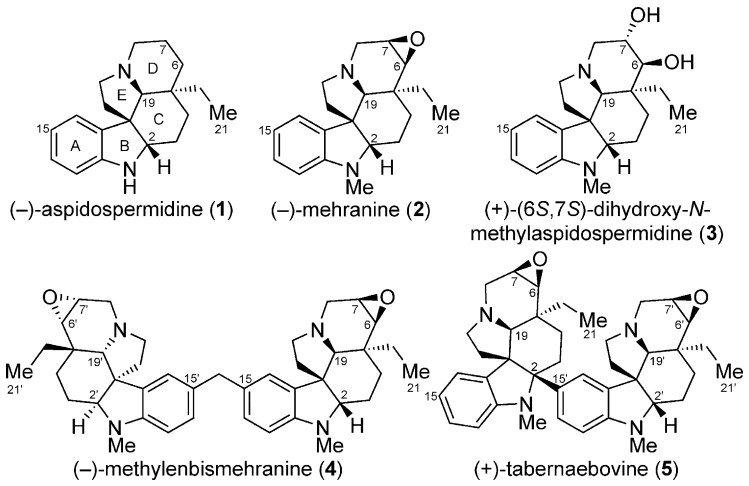
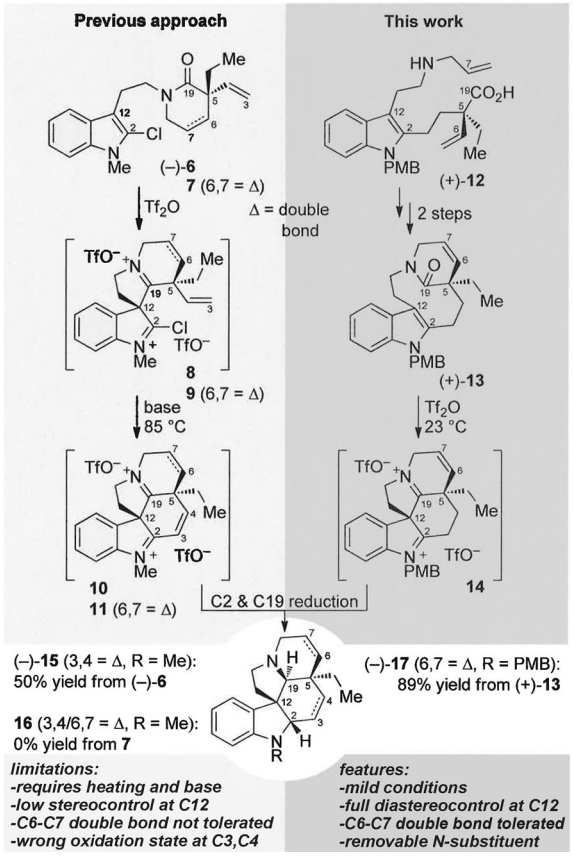


Figure 1. Representative monomeric and dimeric *Aspidosperma* alkaloids.

[*] Dr. M. Mewald, Dr. J. W. Medley, Prof. Dr. M. Movassaghi
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
E-mail: movassag@mit.edu
Homepage: http://web.mit.edu/movassag/www/index.htm

[**] We are grateful for financial support from NIH-NIGMS (GM074825). M. Mewald thanks the German Academic Exchange Service (DAAD) for a postdoctoral fellowship. We thank Dr. Peter Müller (MIT) for X-ray crystal structure analysis of (+)-**13**, Dr. Wen-Tau T. Chang (MIT) for help with the DFT calculations, and Dr. Timothy A. Cernak (Merck, Boston) for providing us with a parallel synthesis reactor.

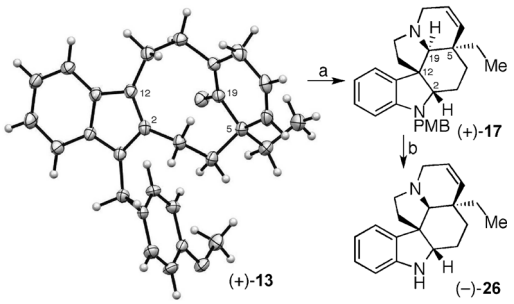
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201405609.



Scheme 1. Comparison of the previous double-cyclization approach with the new transannular cyclization strategy. Tf_2O = trifluoromethanesulfonic anhydride.

tion strategy that would allow for late-stage functionalization to access more complex members of the family.

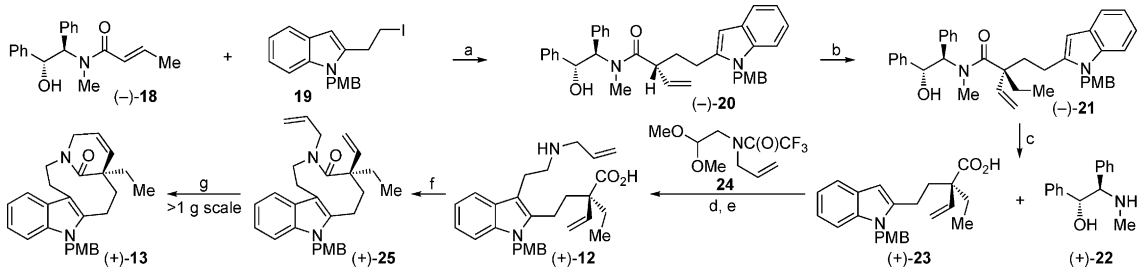
Motivated by our previous studies of related lactams[6a] we hoped to access the pentacyclic skeleton of the *Aspidosperma* alkaloids bearing a double bond at the C6 and C7 positions by a transannular spirocyclization of C12 onto C19 (Scheme 1, right).[2d,g,i,8] We envisioned nine-membered lactam (+)-**13**, accessible from acyclic amino acid (+)-**12** in two steps (Scheme 2), as a suitable cyclization precursor. The rigid conformation of lactam (+)-**13** ensures a high level of



Scheme 3. Transannular cyclization promoted by Tf_2O followed by hydride reduction and cleavage of the *para*-methoxybenzyl group: a) nBu$_3$SnH, Tf_2O, MeCN, −40→23 °C; NaHB(OMe)$_3$, THF, 0→23 °C, 89%, d.r. > 20:1; b) thiophenol, TFA, 55 °C, 79%. ORTEP representation of the crystal structure of lactam (+)-**13**: thermal ellipsoids drawn at 50% probability.

diastereoselection and a more efficient spirocyclization step to pentacycle (−)-**17** via the diiminium intermediate **14** (Schemes 3 and 4). Furthermore, a removable *para*-methoxybenzyl group at the indole nitrogen of lactam (+)-**13** provides access to highly versatile pentacyclic compounds with secondary indoline nitrogen atoms.

The asymmetric synthesis of the natural products depicted in Figure 1 required a highly enantioselective synthesis of cyclization precursor (+)-**13** with the C5 stereogenic center. An efficient amplification of stereochemical complexity was envisioned to introduce all other stereocenters of the targeted natural products from the C5 stereocenter. The synthesis of cyclization precursor (+)-**13** commenced with two sequential alkylations of (+)-pseudoephenamine-derived crotonamide (−)-**18** (Scheme 2).[6a,9] Selective γ-deprotonation of (−)-**18** with lithium 2,2,6,6-tetramethylpiperidide in the presence of lithium chloride generated the corresponding enolate, which was trapped with the alkyl iodide **19**.[10] The resulting tertiary amide (−)-**20** was deprotonated with lithium diisopropylamide in the presence of lithium chloride followed by the addition of *N*,*N*′-dimethylpropylene urea and iodoethane at −40 °C. This resulted in the highly diastereoselective formation of α-quaternary amide (−)-**21** (d.r. > 30:1) in 69% yield. The free carboxylic acid (+)-**23** was obtained in 99% yield after cleavage of the chiral auxiliary under basic condi-

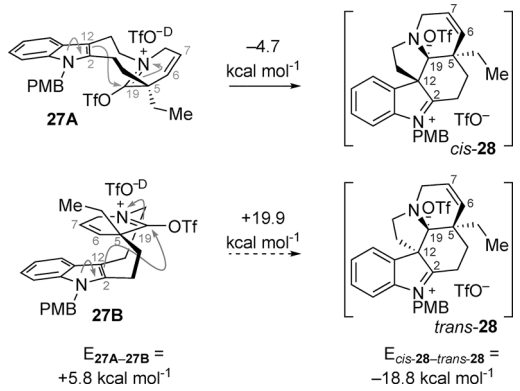


Scheme 2. Enantioselective synthesis of lactam (+)-**13**: a) lithium 2,2,6,6-tetramethylpiperidide, LiCl, THF, 0 °C; **19**, THF, −40→23 °C, 54%; b) lithium diisopropylamide, LiCl, THF, −78→0 °C; *N*,*N*′-dimethylpropylene urea, −40 °C; EtI, −40 °C, 69%, d.r. > 30:1; c) nBu$_4$NOH, H_2O, tBuOH, 100 °C, 99%, > 99% *ee*, 94% recovery of (+)-**22**; d) **24**, Et$_3$SiH, TFA, CH_2Cl_2, 23 °C, 75%; e) NaOH, H_2O, MeOH, 100 °C, 99%; f) Ph_3P, I_2, diisopropylethylamine, CH_2Cl_2, −5→23 °C, 78%; g) 2nd generation Hoveyda–Grubbs catalyst (5 mol%), 1,2-DCE, 80 °C, 87%. TFA = trifluoroacetic acid, PMB = *para*-methoxybenzyl.

tions,[9,11] and the enantiomeric excess of (+)-**23** was determined by HPLC analysis of the corresponding methyl ester to exceed 99%. The substituent at C12 was introduced using a reductive alkylation protocol[12] with acetal **24** in the presence of trifluoroacetic acid and triethylsilane in 75% yield. Hydrolysis of the trifluoroacetamide gave amino acid (+)-**12** in nearly quantitative yield. The penultimate step to the cyclization precursor (+)-**13** consisted of the formation of the lactam derivative of amino acid (+)-**12** induced by triphenylphosphine–iodine.[13] An inverse addition under infinite dilution conditions increased the yield (by ca. 25%) by minimizing intermolecular condensation and allowed for the isolation of lactam (+)-**25** in 78% yield. Finally, a ring-closing metathesis of lactam (+)-**25** promoted by the 2nd generation Hoveyda–Grubbs catalyst[14] at 80°C afforded lactam (+)-**13** in 87% yield on a gram scale.

Gratifyingly, activation of lactam (+)-**13** with Tf_2O led to the efficient formation of diiminium ion **14** (cf. Scheme 1), which was reduced with sodium trimethoxyborohydride to provide pentacycle (+)-**17** with excellent diastereoselectivity (d.r. > 20:1). The introduction of tri-*n*-butyltin hydride prior to lactam activation resulted in an increase in the yield by roughly 10% (Scheme 3), likely due to the immediate and selective reduction of the C2 iminium ion of diiminium ion **14**,[6] thus providing a more stable C19 monoiminium intermediate. With this optimization, pentacycle (+)-**17** was efficiently obtained from (+)-**13** in 89% yield and with full stereocontrol over three newly formed stereogenic centers. Subsequent cleavage of the *para*-methoxybenzyl group under acidic conditions with thiophenol as the nucleophile[15] afforded the key intermediate (−)-**26** in 79% yield.

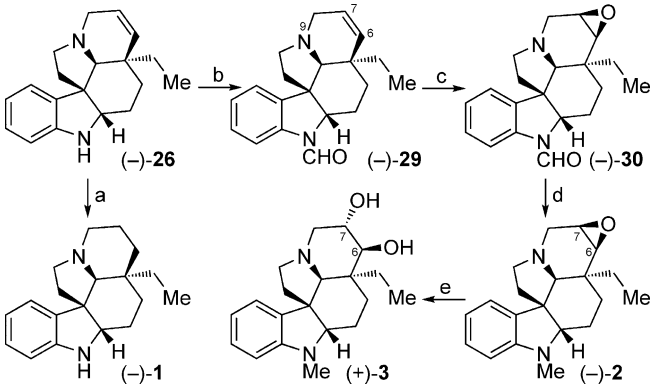
The superb selectivity in the transannular cyclization prompted us to investigate the origin of the stereoselectivity in more detail. An X-ray structure analysis of lactam (+)-**13** confirmed the absolute configuration at C5 (Scheme 3).[16] The conformation of the lactam with the amide on the *si* face of the indole and a C12–C19 distance of 3.22 Å support the observed rapid and highly stereoselective cyclization after amide activation.[17,18] The ^{1}H NMR spectrum of lactam (+)-**13** showed line broadening of several signals at 25°C indicating atropisomerism, which we investigated by a variable-temperature NMR study. We observed only one predominant conformer (> 95%) between −40°C and 55°C and that is likely a conformer similar to the one in the solid state. To further investigate the conformation of lactam (+)-**13**, we conducted DFT calculations on the ground-state conformation of lactam (+)-**13** and other relevant intermediates of the cyclization.[19] The calculations are in agreement with the conformation of lactam (+)-**13** in the solid state being the most stable one; however, we found a similarly stable conformation with the amide on the *re* face of the indole (**27B**).[18] As shown in Scheme 4, this would lead to the C12 epimer *trans*-**28**. The calculations indicate that the respective activated lactam **27B** is more stable than **27A**, probably due to minimization of steric interactions. However, even if conformer **27B** was present after amide activation, the subsequent cyclization would be highly endothermic for **27B** as a strained *trans*-6/5-ring system is formed, whereas the cyclization is exothermic for **27A**. Furthermore, the



Scheme 4. DFT-calculated relative energies of geometry-optimized ground-state conformations of activated lactam conformers **27A** and **27B** as well as putative cyclization intermediates *cis*-**28** and *trans*-**28** (gas phase, B3LYP/6-31G(d); see the Supporting Information for details).

kinetic barrier for the formation of *trans*-**28** must be significantly higher, as amide activation at +30°C (as compared to −40°C) did not decrease the level of stereoselectivity in this transformation.

To further confirm the absolute and relative configuration of the pentacyclic key intermediate (−)-**26**, it was subjected to hydrogenation conditions to access (−)-aspidospermidine (**1**, Scheme 5; $[\alpha]_D^{24} = -16$ ($c = 0.27$, MeOH); Ref. [2af]: $[\alpha]_D^{24} = -17.4$ ($c = 0.32$, MeOH)). The reaction proceeded in 84% yield in the presence of Adam's catalyst, and the



Scheme 5. Synthesis of (−)-aspidospermidine (**1**), (−)-mehranine (**2**), and (+)-(6*S*,7*S*)-dihydroxy-*N*-methylaspidospermidine (**3**): a) PtO_2, H_2 (balloon), EtOH, 23°C, 84%; b) Ac_2O, HCO_2H, 23°C, 91%; c) *m*-CPBA, TFA, CH_2Cl_2, 23°C, 77%; d) nBu_3SnH, Tf_2O, CH_2Cl_2, −20→23°C, 86%; e) TFA, H_2O, 75°C, 67%. *m*-CPBA = *meta*-chloroperbenzoic acid.

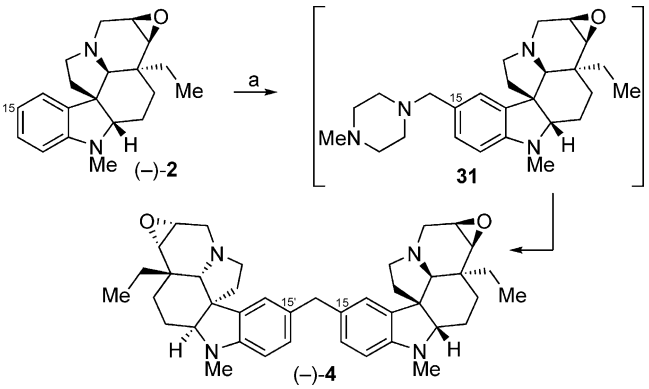
characterization data of alkaloid (−)-**1** matched previously reported data.[2,18]

Having established the key transformation needed to access (−)-6,7-didehydroaspidospermidine (**26**), we wanted to capitalize on its C6–C7 double bond and complete the first total synthesis of (−)-mehranine (**2**). Epoxidation attempts on the N-methylated derivative of pentacycle (−)-**26** failed due

to the low reactivity of the double bond and/or rapid and competitive *N*-oxide formation.[20] We aspired to achieve the desired epoxidation with the N-formylated derivative of pentacycle (−)-**26**, based on important observations by Kalaus, Szántay, and co-workers[5,21] regarding the presence of an electron-withdrawing substituent on the aniline nitrogen. Importantly, we envisioned the direct reduction of the *N*-formyl amide to the *N*-methyl group present in the targeted natural products. Formylation of amine (−)-**26** to amide (−)-**29** with a formic acid/acetic anhydride mixture[22] proceeded smoothly and set the stage for the epoxidation event (Scheme 5). We were glad to see that the epoxidation of amide (−)-**29** was successful using trifluoroacetic acid in dichloromethane with *meta*-chloroperbenzoic acid as the stoichiometric oxidant. The quantitative protonation of N9 was essential to prevent *N*-oxide formation and rapid quenching of the reaction mixture with saturated aqueous sodium thiosulfate solution prevented overoxidation of the product. This optimized protocol allowed for the isolation of epoxide (−)-**30** in 77% yield as a single diastereomer. To accomplish the total synthesis of (−)-mehranine (**2**), a selective reduction of the *N*-formyl group of pentacycle (−)-**30** to an *N*-methyl group was required. As known protocols for amide reduction gave unsatisfactory yields due to incomplete reduction or competitive cleavage of the N−C bond, we sought a new and mild formamide reduction method.[23] Based on our findings in the key transformation (cf. Scheme 3), we intended to use a combination of Tf_2O and tri-*n*-butyltin hydride for the activation and immediate reduction of the formamide. To our delight, this led to mild and efficient reduction of formamide (−)-**30** and provided (−)-mehranine (**2**; $[\alpha]_D^{24}=-52$ ($c=0.61$, $CHCl_3$); Ref. [3a]: $[\alpha]_D^{24}=-49$ ($c=0.831$, $CHCl_3$)) in 86% yield. The characterization data matched previous reports.[3,5,18]

To accomplish the first total synthesis of (+)-(6*S*,7*S*)-dihydroxy-*N*-methylaspidospermidine (**3**), we envisioned the stereoselective opening of the epoxide in (−)-mehranine (**2**) with water as nucleophile. We anticipated the regioselective attack of the nucleophile at the C7 electrophilic center due to its reduced steric crowding compared to the neopentylic C6 position. Under optimal conditions, heating a solution of (−)-mehranine (**2**) in a trifluoracetic acid/water mixture (1:1) to 75 °C provided (+)-(6*S*,7*S*)-dihydroxy-*N*-methylaspidospermidine (**3**, $[\alpha]_D^{24}=+7$ ($c=0.27$, MeOH); Ref. [3b]: $[\alpha]_D^{24}=+15.3$ ($c=0.06$, MeOH)) in 67% yield.[18] The characterization data of (+)-**3** matched the previously reported data.[3b,18,24]

Finally, we intended the dimerization of (−)-mehranine (**2**) to (−)-methylenebismehranine (**4**) utilizing a formaldehyde equivalent. While the use of formaldehyde and closely related acetal reagents was found to be completely ineffective for this advanced-stage dimerization, the most promising results for the direct functionalizion of C15 were obtained with a Mannich reaction using aminal reagents which allowed for a mild aminomethylation under acidic conditions.[25] However, the ionization of the resulting benzylic amines such as **31** proved to be challenging and decomposition of the intermediate was observed in most cases due to the high temperatures required for activation under acidic conditions. Importantly, we discovered that when bis(4-methylpiperazin-1-yl)methane was used as source of the methylene carbon, the resulting intermediate **31** could be ionized by scandium trifluoromethanesulfonate at room temperature. The use of this new reagent combination afforded (−)-methylenebismehranine (**4**, $[[\alpha]_D^{24}=-14$ ($c=0.28$, MeOH); Ref. [4]: $[\alpha]_D^{24}=-5.9$ ($c=0.5$, MeOH)) from (−)-**2** in a single operation in 49% yield (Scheme 6).[18] The appearance of a single set of signals in the ^{1}H NMR spectrum of (−)-**4** for the two mehranine units together with an additional singlet for the new methylene protons confirmed the formation of (−)-**4** and all analytic data were in full accordance with the data in the



Scheme 6. Dimerization of (−)-mehranine (**2**) to (−)-methylenebismehranine (**4**): a) bis(4-methylpiperazin-1-yl)methane, $Sc(OTf)_3$, MeCN, 23 °C, 49%.

isolation report.[4,18] Interestingly, besides the recovery of (−)-mehranine (**2**) in 7% yield, this dimerization reaction afforded a trimeric structure derived from the reaction of (−)-**4** with **31** in 31% yield.[18]

In summary, we have developed a highly enantio- and diastereoselective route to monomeric and dimeric *Aspidosperma* alkaloids with oxidation at the C6 and C7 positions, which allowed for the synthesis of four natural products. The key step is a transannular spirocyclization induced by the electrophilic activation of a nine-membered lactam, which afforded a 6,7-unsaturated pentacycle in high yield and with excellent level of diastereoselection. The resulting versatile intermediate (−)-6,7-didehydroaspidospermidine (**26**) allowed for the synthesis of (−)-aspidospermidine (**1**) by simple hydrogenation and for the first total synthesis of (−)-mehranine (**2**) through the stereoselective epoxidation of the C6–C7 double bond. Hydrolysis of the epoxide afforded (+)-(6*S*,7*S*)-dihydroxy-*N*-methylaspidospermidine (**3**) and a scandium trifluoromethanesulfonate-mediated dimerization of (−)-mehranine (**2**) resulted in the first total synthesis of (−)-methylenebismehranine (**4**). While further development of the required new synthetic methodologies described here, including the mild reduction of formamide (−)-**30** and advanced-stage dimerization of (−)-mehranine (**2**), for broader application is ongoing, our highly efficient new synthetic strategy outlined above forms the basis of our approach to other members of this family of complex alkaloids.

Received: May 24, 2014
Published online: ■■ ■■, ■■■■

Keywords: alkaloids · dimerization · epoxidation · indole · total synthesis

[1] a) J. E. Saxton, *Alkaloids* **1998**, *51*, 1 – 197; b) P. M. Dewick in *Medicinal Natural Products: A Biosynthetic Approach*, 2ednd edWiley, Chichester, **2001**, pp. 350 – 359; c) S. E. O'Connor, E. McCoy, *Recent Adv. Phytochem.* **2006**, *40*, 1 – 22; d) S. E. O'Connor in *Comprehensive Natural Products II*, *Vol. 1* (Eds.: L. Mander, H.-W. Liu), Elsevier, Amsterdam, **2010**, pp. 977 – 1007.

[2] For a review of the synthesis of aspidospermidine (**1**) and related alkaloids, see: a) J. M. Lopchuk, *Prog. Heterocycl. Chem.* **2011**, *23*, 1 – 25; for selected syntheses of **1** in racemic form, see: b) A. Camerman, N. Camerman, J. P. Kutney, E. Piers, *Tetrahedron Lett.* **1965**, *6*, 637 – 642; c) J. Harley-Mason, M. Kaplan, *J. Chem. Soc. Chem. Commun.* **1967**, 915 – 916; d) J. P. Kutney, E. Piers, R. T. Brown, *J. Am. Chem. Soc.* **1970**, *92*, 1700 – 1704; e) J. P. Kutney, N. Abdurahman, C. Gletsos, P. Le Quesne, E. Piers, I. Vlattas, *J. Am. Chem. Soc.* **1970**, *92*, 1727 – 1735; f) J. Y. Laronze, J. Laronze-Fontaine, J. Levy, J. Le Men, *Tetrahedron Lett.* **1974**, *15*, 491 – 494; g) Y. Ban, K. Yoshida, J. Goto, T. Oishi, *J. Am. Chem. Soc.* **1981**, *103*, 6990 – 6992; h) T. Gallagher, P. Magnus, J. Huffman, *J. Am. Chem. Soc.* **1982**, *104*, 1140 – 1141; i) Y. Ban, K. Yoshida, J. Goto, T. Oishi, E. Takeda, *Tetrahedron* **1983**, *39*, 3657 – 3668; j) T. Gallagher, P. Magnus, J. C. Huffman, *J. Am. Chem. Soc.* **1983**, *105*, 4750 – 4757; k) P. Le Menez, N. Kunesch, S. Liu, E. Wenkert, *J. Org. Chem.* **1991**, *56*, 2915 – 2918; l) P. Forns, A. Diez, M. Rubiralta, *J. Org. Chem.* **1996**, *61*, 7882 – 7888; m) M. G. Banwell, D. W. Lupton, A. C. Willis, *Aust. J. Chem.* **2005**, *58*, 722 – 737; n) L. A. Sharp, S. Z. Zard, *Org. Lett.* **2006**, *8*, 831 – 834; o) I. Coldham, A. J. M. Burrell, L. E. White, H. Adams, N. Oram, *Angew. Chem. Int. Ed.* **2007**, *46*, 6159 – 6162; *Angew. Chem.* **2007**, *119*, 6271 – 6274; p) A. J. M. Burrell, I. Coldham, L. Watson, N. Oram, C. D. Pilgram, N. G. Martin, *J. Org. Chem.* **2009**, *74*, 2290 – 2300; q) C. Sabot, K. C. Guerard, S. Canesi, *Chem. Commun.* **2009**, 2941 – 2943; r) F. De Simone, J. Gertsch, J. Waser, *Angew. Chem. Int. Ed.* **2010**, *49*, 5767 – 5770; *Angew. Chem.* **2010**, *122*, 5903 – 5906; s) L. Jiao, E. Herdtweck, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 14563 – 14572; t) L. McMurray, E. M. Beck, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2012**, *51*, 9288 – 9291; *Angew. Chem.* **2012**, *124*, 9422 – 9425; u) M. Kawano, T. Kiuchi, S. Negishi, H. Tanaka, T. Hoshikawa, J. Matsuo, H. Ishibashi, *Angew. Chem. Int. Ed.* **2013**, *52*, 906 – 910; *Angew. Chem.* **2013**, *125*, 940 – 944; for syntheses of **1** in enantiomerically enriched form, see: v) M. Node, H. Nagasawa, K. Fuji, *J. Am. Chem. Soc.* **1987**, *109*, 7901 – 7903; w) M. Node, H. Nagasawa, K. Fuji, *J. Org. Chem.* **1990**, *55*, 517 – 521; x) D. Desmaeele, J. d'Angelo, *J. Org. Chem.* **1994**, *59*, 2292 – 2303; y) A. G. Schultz, L. Pettus, *J. Org. Chem.* **1997**, *62*, 6855 – 6861; z) R. Iyengar, K. Schildknegt, J. Aubé, *Org. Lett.* **2000**, *2*, 1625 – 1627; aa) S. A. Kozmin, T. Iwama, Y. Huang, V. H. Rawal, *J. Am. Chem. Soc.* **2002**, *124*, 4628 – 4641; ab) J. P. Marino, M. B. Rubio, G. Cao, A. de Dios, *J. Am. Chem. Soc.* **2002**, *124*, 13398 – 13399; ac) D. Gnecco, E. Vazquez, A. Galindo, J. L. Teran, L. Orea, S. Bernes, R. G. Enríquez, *ARKIVOC* **2003**, 185 – 192; ad) R. Iyengar, K. Schildknegt, M. Morton, J. Aubé, *J. Org. Chem.* **2005**, *70*, 10645 – 10652; ae) T. Ishikawa, K. Kudo, K. Kuroyabu, S. Uchida, T. Kudoh, S. Saito, *J. Org. Chem.* **2008**, *73*, 7498 – 7508; af) M. Suzuki, Y. Kawamoto, T. Sakai, Y. Yamamoto, K. Tomioka, *Org. Lett.* **2009**, *11*, 653 – 655; ag) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183 – 188; ah) Z. Li, S. Zhang, S. Wu, X. Shen, L. Zou, F. Wang, X. Li, F. Peng, H. Zhang, Z. Shao, *Angew. Chem. Int. Ed.* **2013**, *52*, 4117 – 4121; *Angew. Chem.* **2013**, *125*, 4211 – 4215; ai) J. E. Nidhiry, K. R. Prasad, *Tetrahedron* **2013**, *69*, 5525 – 5536; aj) S. Zhao, R. B. Andrade, *J. Am. Chem. Soc.* **2013**, *135*, 13334 – 13337.

[3] a) T.-S. Kam, S. Anuradha, *Phytochemistry* **1995**, *40*, 313 – 316; b) T. P. Lien, H. Ripperger, A. Porzel, K. Merzweiler, T. V. Sung, G. Adam, *Phytochemistry* **1998**, *49*, 1457 – 1461; c) K. Merzweiler, T. P. Lien, T. V. Sung, H. Ripperger, G. Adam, *J. Prakt. Chem.* **1999**, *341*, 69 – 71.

[4] T. P. Lien, C. Kamperdick, T. V. Sung, G. Adam, H. Ripperger, *Phytochemistry* **1998**, *49*, 1797 – 1799.

[5] A semisynthesis of (−)-mehranine (**2**) has been reported: J. Éles, G. Kalaus, I. Greiner, M. Katjár-Peredy, P. Szabó, G. M. Keserû, L. Szabó, C. Szántay, *J. Org. Chem.* **2002**, *67*, 7255 – 7260.

[6] a) J. W. Medley, M. Movassaghi, *Angew. Chem. Int. Ed.* **2012**, *51*, 4572 – 4576; *Angew. Chem.* **2012**, *124*, 4650 – 4654; b) J. W. Medley, M. Movassaghi, *Org. Lett.* **2013**, *15*, 3614 – 3617.

[7] The dihydropyridinium fragment in intermediate **9** makes it more sensitive than diiminium intermediate **8** and the forcing conditions required for the second cyclization led to decomposition.

[8] a) G. Stork, J. E. Dolfini, *J. Am. Chem. Soc.* **1963**, *85*, 2872 – 2873; b) K. Yoshida, Y. Sakuma, Y. Ban, *Heterocycles* **1987**, *25*, 47 – 50.

[9] M. R. Morales, K. T. Mellem, A. G. Myers, *Angew. Chem. Int. Ed.* **2012**, *51*, 4568 – 4571; *Angew. Chem.* **2012**, *124*, 4646 – 4649.

[10] Iodide **19** was prepared in four steps from commercially available 2-iodoaniline in an overall yield of 72%. See the Supporting Information for further details.

[11] The chiral auxiliary (+)-pseudoephenamine (**22**) was recovered in 94% yield in the same step.

[12] M. Righi, F. Topi, S. Bartolucci, A. Bedini, G. Piersanti, G. Spadoni, *J. Org. Chem.* **2012**, *77*, 6351 – 6357.

[13] A. Kumar, H. K. Akula, M. K. Lakshman, *Eur. J. Org. Chem.* **2010**, 2709 – 2715.

[14] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168 – 8179.

[15] S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 13606 – 13607.

[16] CCDC 997229 [(+)-**13**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] Two similar conformations are present in the unit cell with C12–C19 distances of 3.22 and 3.24 Å.

[18] See the Supporting Information for further details.

[19] The geometries in the gas phase were optimized with molecular modeling (MMFF) followed by density functional calculations at the B3LYP level with 6-31G(d) as the basis set (Spartan '14, Version 1.1.1, by Wavefunction, INC.).

[20] For example, *m*-CPBA/$HClO_4$ led to full *N*-oxide formation at N9.

[21] The epoxidation conditions described in Ref. [5] were utilized in the total synthesis of (−)-conophylline: Y. Han-ya, H. Tokuyama, T. Fukuyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 4884 – 4887; *Angew. Chem.* **2011**, *123*, 4986 – 4989.

[22] B. V. Milborrow, C. Djerassi, *J. Chem. Soc. C* **1969**, 417 – 424.

[23] For related amide reductions involving electrophilic amide activation, see: a) F. Borch, *Tetrahedron Lett.* **1968**, *9*, 61 – 65; b) Atta-ur-Rahman, A. Basha, N. Waheed, S. Ahmed, *Tetrahedron Lett.* **1976**, *17*, 219 – 222; c) M. E. Kuehne, P. J. Shannon, *J. Org. Chem.* **1977**, *42*, 2082 – 2087; d) G. Barbe, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 18 – 19; e) S.-H. Xiang, J. Hu, H.-Q. Yuan, P.-Q. Huang, *Synlett* **2010**, 1829 – 1832; for a formamide reduction in the total synthesis of aspidophytine, see: f) J. P. Marino, G. Cao, *Tetrahedron Lett.* **2006**, *47*, 7711 – 7713.

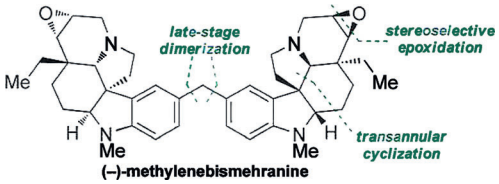
[24] The opening of the epoxide is evident by the coupling constant of the C6 and C7 methine protons ($^3J_{6,7}$) which is 4.0 Hz in *cis*-configured (−)-**2** and 9.3 Hz in *trans*-configured (+)-**3**.
[25] For a general procedure for the preparation of bis(dialkylamino)methanes and their use in Mannich and Morita–Baylis–Hillman reactions, see: a) A. Porzelle, C. M. Williams, *Synthesis* **2006**, 3025 – 3030; for the synthesis and characterization of bis(4-piperazin-1-yl)methane, see: b) G. P. Mrug, S. P. Bondarenko, V. P. Khilya, M. S. Frasinyuk, *Chem. Nat. Compd.* **2013**, *49*, 235 – 241; for a related dimerization of *N*-methylpyrrole, see: c) S. C. Eyley, H. Heaney, G. Papageorgiou, R. F. Wilkins, *Tetrahedron Lett.* **1988**, *29*, 2997 – 3000.

Communications

Alkaloid Synthesis

M. Mewald, J. W. Medley,
M. Movassaghi* ———— ▮▮▮▮–▮▮▮▮

Concise and Enantioselective Total Synthesis of (−)-Mehranine, (−)-Methylenebismehranine, and Related *Aspidosperma* Alkaloids



Cyclize, oxidize, dimerize! A highly stereoselective transannular cyclization induced by the electrophilic activation of a chiral nine-membered lactam precursor allowed for the rapid and efficient access to the *Aspidosperma* skeleton. A late-stage stereoselective epoxidation afforded (−)-mehranine, which was dimerized using a formaldehyde equivalent to provide (−)-methylenebismehranine.