

Total Syntheses of Dihydroindole *Aspidosperma* Alkaloids: Reductive Interrupted Fischer Indolization Followed by Redox Diversification

Gábor Martin, Péter Angyal, Orsolya Egyed, Szilárd Varga,* and Tibor Soós*



Cite This: <https://dx.doi.org/10.1021/acs.orglett.0c01472>



Read Online

ACCESS |



Metrics & More

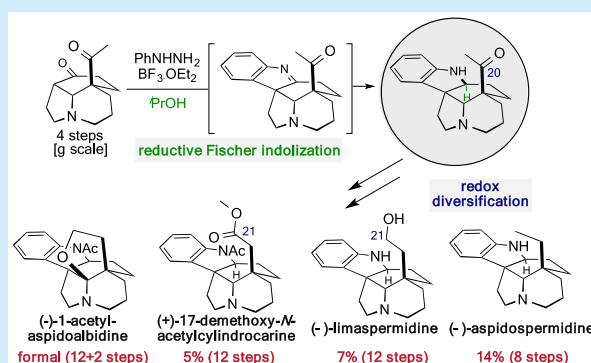


Article Recommendations



Supporting Information

ABSTRACT: We report a novel reductive interrupted Fischer indolization process for the concise assembly of the 20-oxoaspidospermidine framework. This rapid complexity generating route paves the way toward various dihydroindole *Aspidosperma* alkaloids with different C-5 side chain redox patterns. The end-game redox modulations were accomplished by modified Wolff–Kishner reaction and photo-Wolff rearrangement, enabling the total synthesis of (–)-aspidospermidine, (–)-limaspermidine, and (+)-17-demethoxy-*N*-acetylcylindrocarine and the formal total synthesis of (–)-1-acetylaspidoalbidine.



Without rival in the field of total synthesis has been the sustained interest to devise synthetic routes to *Aspidosperma* alkaloids (e.g., the archetypal **1** in Figure 1).¹

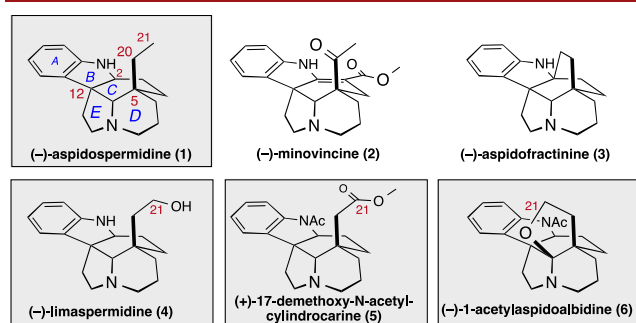


Figure 1. Structure of (–)-aspidospermidine (**1**) and its related C-20 and C-21 oxidized alkaloids **2–6**.

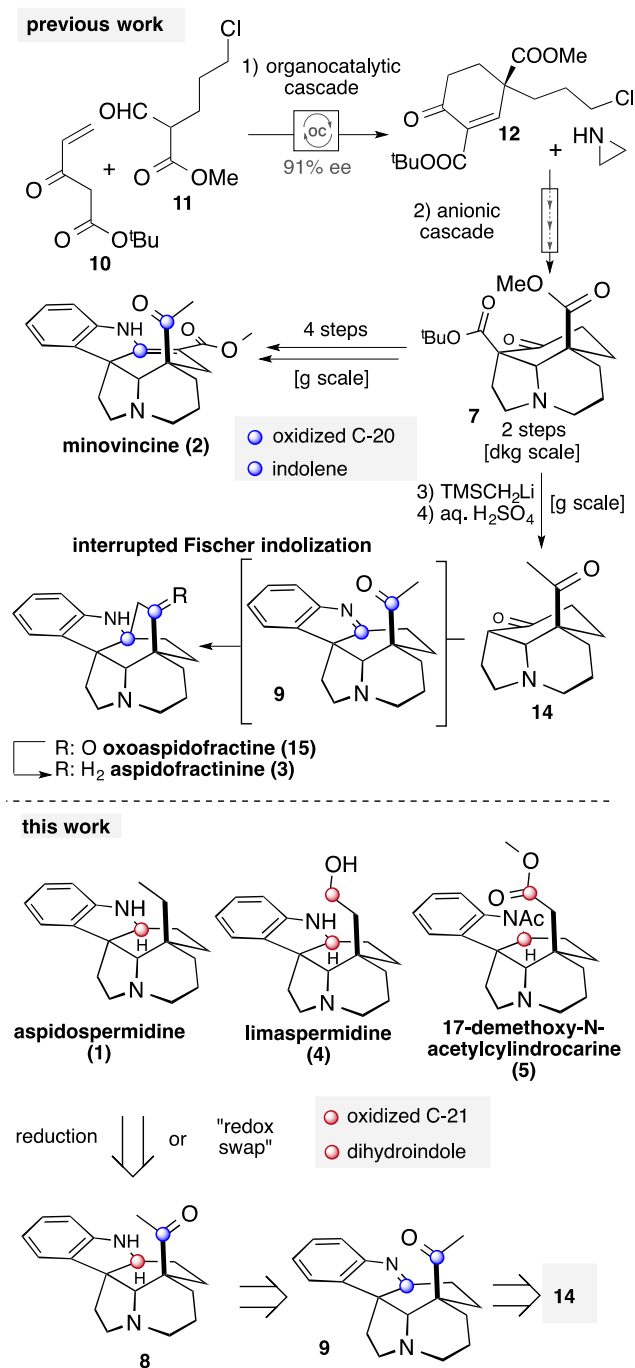
Their important biological activities and stereochemically rich pentacyclic scaffolds have rendered these compounds attractive targets for synthetic programs.² Over the last few decades, various elegant and innovative synthetic approaches have been reported and many of these strategies have made profound contributions to modern organic synthesis.³ Recently, trends such as divergent syntheses⁴ and “ideal synthesis”⁵ have come to the front, forcing practitioners to advance methodologies and strategies in an integrative manner.

A subset of the *Aspidosperma* alkaloids is featuring an oxidized side chain at the C-5 position (Figure 1, alkaloids **2–6**). This subtle but momentous modification in C-20 or C-21

positions not only broadens the list of natural products (e.g., (–)-minovincine (**2**) and (–)-limaspermidine (**4**)) but also serves as a biogenetic link toward structurally more complex, even cage-like derivatives of *Aspidofractinine* and *Aspidospermidine* alkaloids (e.g., **3** and **6** in Figure 1). Despite their (bio)synthetic and biological potential, this subset of natural products has received relatively less attention in stereoselective synthetic programs.⁶

Recently, our laboratory developed a short and scalable (60g) synthetic route for the stereoselective synthesis of *Aspidosperma* tricyclic ketone core **7** with C-5 methoxycarbonyl group and employed this advanced intermediate for the concise syntheses of (–)-minovincine (**2**) and (–)-aspidofractinine (**3**) (Scheme 1).⁷ A key element of these syntheses was the rapid buildup of much of the complexities of the targets through the sequence of organocascade and anionic cascade reactions. These routes are strategically aligned with the Stork–Dolfini synthesis^{3a} of aspidospermidine but delivering C-20 oxidized intermediates and natural products. As an outgrowth of our synthetic studies, we sought the development of the syntheses of C-21 oxygenated and C-20 reduced subclasses of *Aspidosperma* alkaloids. We surmised

Received: April 28, 2020

Scheme 1. Previous Work and Retrosynthetic Plan toward Various Subclasses of *Aspidosperma* Alkaloids

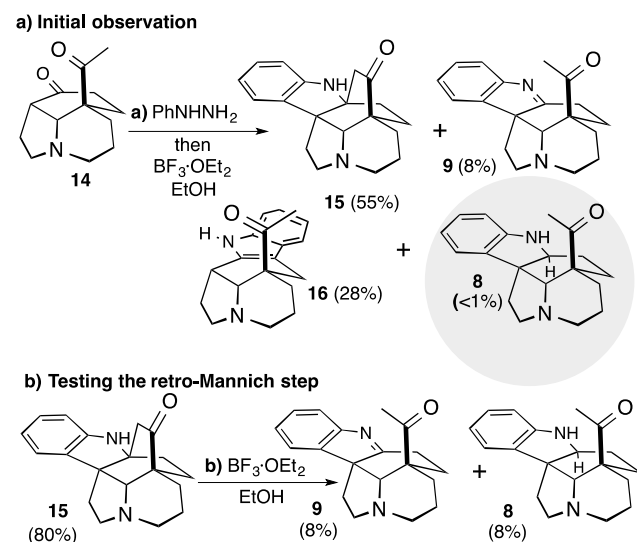
that advanced intermediate **14** might be used for a unified approach that has a late stage redox diversification. Herein, we describe our successful forays that led to total syntheses of (–)-limaspermidine (**4**)^{8,9} and (+)-17-demethoxy-*N*-acetylcyllindrocarine (**5**)^{10,11} and the formal total synthesis of (–)-1-acetylaspidoalbidine (**6**)¹² and the parent member of *Aspidosperma* alkaloids, the (–)-aspidospermidine (**1**).¹³

Our retrosynthetic analysis of the targeted indole alkaloids is illustrated in Scheme 1. The pentacycle **8** was expected to serve as a common intermediate for redox diversification. We envisaged to employ Wolff–Kishner reduction to afford (–)-aspidospermidine (**1**) and Wolff rearrangement to accomplish a C-20 to C-21 redox swap for C-21 oxidized

natural products **4–6**. Accordingly, the heart of our plan was the rapid construction of dihydroindole **8**¹⁴ from diketone **14**. We envisioned that the Fischer indolization of **14** can be halted at the stage **9**; thus, the previously reported Mannich cyclization to cage-like **15** can be avoided. Thus, imino **9** will be accessible which can be selectively reduced into **8**.

We have recently disclosed the concise asymmetric synthesis of tricyclic diketone **14** via organocatalytic and anionic cascade reactions (Scheme 1) followed by chemo- and regioselective acetyl group formation at C-5.^{7b} Thus, using easily available compounds **10** and **11**, the stereochemically complex intermediate **14** can be assembled in only four steps. In order to access the dihydroindole intermediate **8** for the planned diversification, we required optimal conditions to secure the pentacyclic indolenine **9** formation (Scheme 2). First, various reaction temperatures were employed in attempts to divert the course of the original Mannich–Fischer indolization of **14** to **15**. However, we could not reverse or halt the cascade reaction to afford indolenine **9**.¹⁵ Neither higher nor lower reaction temperature gave a synthetically relevant yield of **9**, indicating that the final Mannich reaction step of the interrupted Fischer indolization¹⁶ to oxoaspidofractinine **15** is both kinetically and thermodynamically preferred. Nevertheless, a fortunate observation guided our further development. After carefully analyzing the products of the Mannich–Fischer indolization process at 80 °C, we found that besides the three major components (oxoaspidofractinine **15**, indolenine **9**, and 3*H*-indole **16**) the selectively reduced dihydroindole **8** could be detected. Importantly, prolonged reaction times resulted in an increased yield of this product, which suggested the reversibility of the Mannich step. Additionally, we probed this reductive retro-Mannich step by heating oxoaspidofractinine **15** at 100 °C with BF₃·OEt₂ in ethanol for 2 days. Delightfully, we isolated indolenine **9** and dihydroindole **8** along with unreacted starting material **15**, which unambiguously proved the existence of the reductive retro-Mannich step (Scheme 2).

We rationalized that this chemoselective reduction of the imine moiety is analogous with a Meerwein–Ponndorf–Verley

Scheme 2. Study of the Retro-Mannich Step and Lewis Acid Mediated Solvent Assisted Reduction

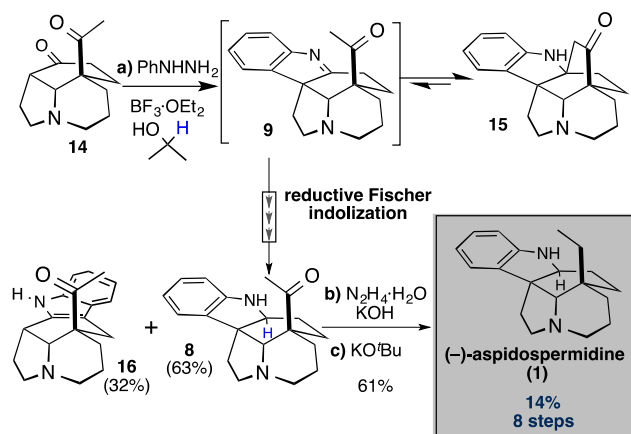
^aReaction conditions: (a) EtOH, 85 °C; (b) EtOH, 100 °C, 2 days.

type reduction,¹⁷ in which the hydride source was the sacrificial alcohol solvent. In light of this, we employed isopropanol as a solvent to amplify the effectiveness of the reductive transformation and raised the reaction temperature from 85 to 115 °C. Gratifyingly, these modifications gave the desired compound **8** as the major product (63% yield) besides the **16** 3*H*-indole (32% yield), the byproduct of Fischer indolization (Scheme 3).

With the key intermediate 20-oxoaspidospermidine (**8**) in our hand, we proceeded to perform the requisite redox modifications (Schemes 3 and 4). First, the (–)-aspidospermidine (**1**) was synthesized using a modified Wolff–Kishner reduction process (Scheme 3).¹⁸ Presumably owing to the steric hindrance of the carbonyl group, optimization of reaction conditions was required. Finally, we found that the telescopic application of Huang–Minlon and Cram modification resulted in the highest yield. The spectroscopic data and optical rotation of **1** were fully consistent with reported values. To sum up, using our tactical modification of the original Stork–Dolfini synthesis,^{3a} (–)-aspidospermidine (**1**) could be accessed in a stereoselective manner in eight steps and 14% overall yield.

Scheme 3. Reductive Interrupted Fisher Indolization and Completion of the Total Synthesis of (–)-Aspidospermidine (**1**)^a

Mechanistic rationale



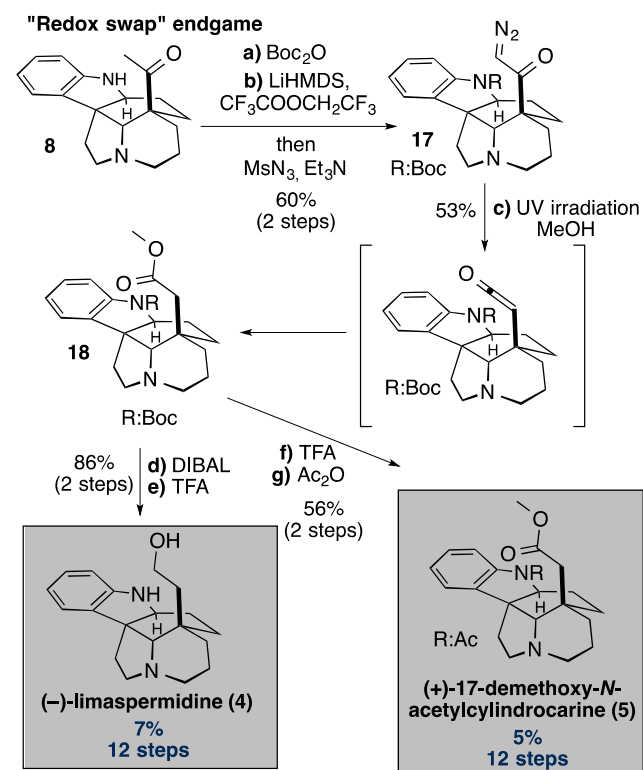
^aReagents and conditions: (a) PhNHNH₂, ⁱPrOH, 85 °C, then BF₃·OEt₂, 115 °C; (b) DEG, 130–210 °C; (c) DMSO, 130 °C; DEG = diethylene glycol, DMSO = dimethyl sulfoxide.

Next, the formation of the C-21 oxidized side chain was probed via a formal “redox swap”, the Wolff rearrangement (Scheme 4).¹⁹ Our preliminary studies indicated that the protection of the dihydroindole NH moiety was essential to avoid undesired alkylation or polymerization reactions during the photo, thermal, or metal salt (e.g., Ag, Rh) activated Wolff rearrangement. Thus, the desired diazo compound **17** was generated by protection of **8** with Boc₂O followed by diazo transfer utilizing Danheiser’s method.²⁰ To our delight, the subsequent redox swap proceeded smoothly through photochemical Wolff rearrangement that afforded ester **18**. This ester was then reduced with DIBAL, followed by the removal of the Boc group to afford (–)-limaspermidine (**4**). This route also constitutes a formal asymmetric total synthesis of the *Aspidosperma* alkaloid (–)-1-acetylaspidoalbidine (**6**), as this target can be accessed in two steps from limaspermidine.¹²

Finally, (+)-17-demethoxy-*N*-acetylcylindrocaryne (**9**) was then achieved through a two-step deprotection/acylation sequence to finish our synthetic endeavor. All spectroscopic data as well as the optical rotation data for our synthetic (–)-limaspermidine (**4**) and (+)-17-demethoxy-*N*-acetylcylindrocaryne (**5**) were consistent with the previously reported values.

In summary, we expanded our previous cascade-sequence-based methodology toward the syntheses of dihydroindole *Aspidosperma* alkaloids with different C-5 side chain redox patterns. Most importantly, a highly efficient reductive interrupted Fischer indole synthesis was developed that delivers an advanced pentacyclic intermediate **8** in a simple, one-pot manner with excellent regio- and chemoselectivity. This key intermediate **8** was then transformed into (–)-aspidospermidine (**1**) in a straightforward manner. Furthermore, using pentacyclic **8**, we completed the total synthesis of two C-21 oxygenated alkaloids (–)-limaspermidine (**4**) and (+)-17-demethoxy-*N*-acetylcylindrocaryne (**5**) via an oxidation state swap approach using photo-Wolff rearrangement. These concise total syntheses provide further demonstration of the power of the sequential organo- and anionic cascade reactions for rapid assembling of stereochemically complex indole alkaloid skeletons, while also directly providing the desired oxidation state at the challenging C-20 or C-21 positions.

Scheme 4. Completion of the Total Synthesis of (–)-Limaspermidine (**4**) and (+)-17-Demethoxy-*N*-acetylcylindrocaryne (**5**) via a Wolff Rearrangement^a



^aReaction conditions: (a) THF, 50 °C; (b) THF, –78 °C then MeCN, rt; (c) UV irradiation (312 nm), MeOH, THF, rt; (d) THF, –78 to 0 °C; (e) CH₂Cl₂, 0 °C; (f) CH₂Cl₂, 0 °C; (g) CH₂Cl₂, rt; TFA = trifluoroacetic acid, THF = tetrahydrofuran, LiHMDS = lithium bis(trimethylsilyl)amide, DIBAL = diisobutylaluminum hydride.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c01472>.

Experimental procedures, characterization data, and NMR spectral data of new compounds (PDF)

FAIR data file, including the primary NMR FID files, for compounds 1, 4, 5, 8, 8', 9, 14, 15, 16, 17, and 18 (ZIP)

■ AUTHOR INFORMATION

Corresponding Authors

Szilárd Varga – Institute of Organic Chemistry, Research Centre for Natural Sciences, Budapest H-1117, Hungary;

orcid.org/0000-0001-9611-5168; Email: varga.szilard@ttk.hu

Tibor Soós – Institute of Organic Chemistry, Research Centre for Natural Sciences, Budapest H-1117, Hungary; orcid.org/0000-0002-2872-4313; Email: soos.tibor@ttk.hu

Authors

Gábor Martin – Institute of Organic Chemistry, Research Centre for Natural Sciences, Budapest H-1117, Hungary

Péter Angyal – Institute of Organic Chemistry, Research Centre for Natural Sciences, Budapest H-1117, Hungary;

orcid.org/0000-0003-4514-2187

Orsolya Egyed – Instrumentation Center, Research Centre for Natural Sciences, Budapest H-1117, Hungary

Complete contact information is available at:

<https://pubs.acs.org/doi/10.1021/acs.orglett.0c01472>

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is dedicated to the memory of Prof. Dr. György Hajós. We are grateful for financial support provided by the National Research, Development and Innovation Office (FK 124863, K 125385). We also thank Dr. Dániel Fegyverneki (Institute of Organic Chemistry, Research Centre for Natural Sciences) for helpful discussions.

■ REFERENCES

- (1) Reviews on synthesis of *Aspidosperma* and related alkaloids: (a) Saxton, J. E. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Eds.; Academic Press: San Diego, CA, 1998; Vol. 50, pp 343–376. (b) Lopchuk, J. M. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Oxford, U.K., 2011; Vol. 23, pp 1–25. (c) Hájíček, J. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1681–1767. (d) Hájíček, J. *Collect. Czech. Chem. Commun.* **2007**, *72*, 821–898. (e) Pritchett, B. P.; Stoltz, B. M. *Nat. Prod. Rep.* **2018**, *35*, 559–574. (f) Wang, Y.; Xie, F.; Lin, B.; Cheng, M.; Liu, Y. *Chem. - Eur. J.* **2018**, *24*, 14302–14315. (g) Saya, J. M.; Ruijter, E.; Orru, R. V. A. *Chem. - Eur. J.* **2019**, *25*, 8916–8935.
- (2) Reviews on *Aspidosperma* and related alkaloids: (a) Saxton, J. E. *Chemistry of Heterocyclic Compounds*; Wiley-Interscience: New York, 1983; Vol. 25, pp 331–437. (b) Saxton, J. E. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Eds.; Academic Press: San Diego, CA, 1998; Vol. 51, pp 1–197.
- (3) Selected papers: (a) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872–2873. (b) Harley-Mason, J.; Kaplan, M. *Chem. Commun.* **1967**, *0*, 915–916. (c) Kutney, J. P.; Abdurahman, N.; Gletsos, C.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1970**, *92*, 1727–1735. (d) Overman, L. E.; Sworin, M.; Bass, L. S.; Clardy, J. *Tetrahedron* **1981**, *37*, 4041–4045. (e) Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1982**, *104*, 1140–1141. (f) Wenkert, E.; Orito, K.; Simmons, D. P.; Kunesch, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, *39*, 3719–3724. (g) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523–13524. (h) Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519–1522. (i) Wilkie, G. D.; Elliott, G. I.; Blagg, B. S. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292–11294. (j) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 6159–6162. (k) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183–188. (l) Zhao, S.; Andrade, R. B. *J. Am. Chem. Soc.* **2013**, *135*, 13334–13337. (m) Wagnières, O.; Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 15102–15108. (n) Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nat. Chem.* **2014**, *6*, 57–64. (o) Tan, P. W.; Seayad, Y.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 13436–13440. (p) Pritchett, B. P.; Kikuchi, J.; Numajiri, Y.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2016**, *55*, 13529–13532. (q) Wang, X.; Xia, D.; Qin, W.; Zhou, R.; Zhou, X.; Zhou, Q.; Liu, W.; Dai, X.; Wang, H.; Wang, S.; Tan, L.; Zhang, D.; Song, H.; Liu, X.-Y.; Qin, Y. *Chem.* **2017**, *2*, 803–816. (r) Kim, R.; Ferreira, A. J.; Beaudry, C. M. *Angew. Chem., Int. Ed.* **2019**, *58*, 12595–12598.
- (4) Reviews on divergent natural product synthesis: (a) Anagnostaki, E. E.; Zografos, A. L. *Chem. Soc. Rev.* **2012**, *41*, 5613–5625. (b) Li, L.; Chen, Z.; Zhang, X.; Jia, Y. *Chem. Rev.* **2018**, *118*, 3752–3832. (c) Xu, Z.; Wang, Q.; Zhu, J. *Chem. Soc. Rev.* **2018**, *47*, 7882–7898.
- (5) (a) Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784–5800. (b) Wender, P. A.; Verma, V. A.; Paxton, T.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40–49. (c) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010–3021. (d) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854–2867. (e) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193–205. (f) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657–4673. (g) Hayashi, Y. *Chem. Sci.* **2016**, *7*, 866–880.
- (6) Selected paper about the total synthesis from C-20 and C-21 oxidized alkaloids: (a) Langlois, N.; Andriamialisoa, R. Z. *J. Org. Chem.* **1979**, *44*, 2468–2471. (b) Kuehne, M. E.; Li, Y.-L. *Org. Lett.* **1999**, *1*, 1749–1750. Selected asymmetric syntheses for C-20 or C-21 oxidized *Aspidosperma* alkaloids: (c) Gagnon, D.; Spino, C. *J. Org. Chem.* **2009**, *74*, 6035–6041. (d) Laforteza, B. N.; Pickworth, M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 11269–11272. (e) Kang, T.; White, K. L.; Mann, T. J.; Hoveyda, A. H.; Movassaghi, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 13857–13860.
- (7) (a) Berkes, B.; Ozsváth, K.; Molnár, L.; Gáti, T.; Holczbauer, T.; Kardos, Gy.; Soós, T. *Chem. - Eur. J.* **2016**, *22*, 18101–18106. (b) Varga, Sz.; Angyal, P.; Martin, G.; Egyed, O.; Holczbauer, T.; Soós, T. *Angew. Chem. Int. Ed.* **2020**, DOI: 10.1002/anie.202004769.
- (8) Isolation of limaspermidine: Medina, J. D.; Di Genova, L. *Planta Med.* **1979**, *37*, 165–167.
- (9) Total syntheses of (±)-limaspermidine: (a) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610. (b) Guérard, K. C.; Guérinot, A.; Bouchard-Aubin, C.; Ménard, M.-A.; Lepage, M.; Beaulieu, M. A.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 2121–2133. (c) Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A. *Org. Lett.* **2012**, *14*, 5621–5623. (d) Jin, J.; Qiu, F. G. *Adv. Synth. Catal.* **2014**, *356*, 340–346. Enantioselective total syntheses of limaspermidine: (e) Zhang, S.-X.; Shen, X.-L.; Li, Z.-Q.; Zou, L.-W.; Wang, F.-Q.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* **2013**, *78*, 11444–11449. (f) Du, J.-Y.; Zeng, C.; Han, X.-J.; Qu, H.; Zhao, X.-H.; An, X.-T.; Fan, C.-A. *J. Am. Chem. Soc.* **2015**, *137*, 4267–4273. (g) White, K. L.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138*, 11383–11389.
- (10) Isolation of 17-demethoxy-N-acetylcylindrocaryne: Milborrow, B. V.; Djerassi, C. *J. Chem. Soc. C* **1969**, 417–424.
- (11) Total synthesis of (±)-12-demethoxy-N-acetylcylindrocaryne: Brennan, J. P.; Saxton, J. E. *Tetrahedron* **1986**, *42*, 6719–6734.
- (12) Isolation of 1-acetylaspidoalbidine: (a) Brown, K. S.; Budzikiewicz, H.; Djerassi, C. *Tetrahedron Lett.* **1963**, *4*, 1731–1736. Total synthesis of (±)-1-acetylaspidoalbidine: (b) Ban, Y.

Ohnuma, T.; Seki, K.; Oisgi, T. *Tetrahedron Lett.* **1975**, *16*, 727–730. (c) Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A. *Org. Lett.* **2012**, *14*, 5621–5623. Enantioselective total synthesis of 1-acetylaspidoalbidine: (d) Campbell, E. L.; Zuhl, A. M.; Liu, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3009–3012. (e) Reference 9g. (f) Ghosh, A. K.; Born, J. R.; Kassekert, L. A. *J. Org. Chem.* **2019**, *84*, 5167–5175.

(13) Selected total syntheses of (±)-aspidospermidine: (a) Harley-Mason, J.; Kaplan, M. *Chem. Commun.* **1967**, *0*, 915–916. (b) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750–4757. (c) Wenkert, E.; Liu, S. *J. Org. Chem.* **1994**, *59*, 7677–7682. (d) Sharp, L. A.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 831–834. (e) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 6159–6163. (f) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941–2943. (g) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563–14572. (h) McMurray, L.; Beck, E. M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9288–9291. (i) Kawano, M.; Kiuchi, T.; Negishi, S.; Tanaka, H.; Hoshikawa, T.; Matsuo, J.-I.; Ishibashi, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 906–910. Selected enantioselective total syntheses of aspidospermidine: (j) Iyengar, R.; Schildknecht, K.; Aubé, J. *Org. Lett.* **2000**, *2*, 1625–1627. (k) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628–4641. (l) Marino, P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398–13399. (m) Suzuki, M.; Kawamoto, Y.; Sakai, T.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2009**, *11*, 653–655. (n) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 4117–4121. (o) Zhao, S.; Andrade, R. B. *J. Am. Chem. Soc.* **2013**, *135*, 13334–13337. (p) Pandey, G.; Burugu, S. K.; Singh, P. *Org. Lett.* **2016**, *18*, 1558–1561. (q) Du, K.; Yang, H.; Guo, P.; Feng, L.; Xu, G.; Zhou, Q.; Chung, L. W.; Tang, W. *Chem. Sci.* **2017**, *8*, 6247–6256. (r) Shemet, A.; Carreira, E. M. *Org. Lett.* **2017**, *19*, 5529–5532. (s) Kim, J.-Y.; Suhl, C.-H.; Lee, J.-H.; Cho, C.-G. *Org. Lett.* **2017**, *19*, 6168–6171. (t) Antropow, A. H.; Garcia, N. R.; White, K. L.; Movassaghi, M. *Org. Lett.* **2018**, *20*, 3647–3650. (u) Xu, H.; Huang, H.; Zhao, C.; Song, C.; Chang, J. *Org. Lett.* **2019**, *21*, 6457–6460.

(14) Racemic synthesis of **8**: (a) Dufour, M.; Gramain, J.-C.; Husson, H.-P.; Sinibaldi, M.-E.; Troin, Y. *J. Org. Chem.* **1990**, *55*, 5483–5490. (b) Saya, J. M.; Roose, T. R.; Peek, J. J.; Weijers, B.; de Waal, T. J. S.; Vande Velde, C. M. L.; Orru, R. V. A.; Ruijter, E. *Angew. Chem., Int. Ed.* **2018**, *57*, 15232–15236.

(15) For the details, see the [Supporting Information](#).

(16) Recent review on the Fischer indole reaction: (a) Heravi, M. M.; Rohani, S.; Zadsirjan, V.; Zahedi, N. *RSC Adv.* **2017**, *7*, 52852–52887. Review on interrupted Fischer indolization: (b) James, J. M.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Chem. - Eur. J.* **2016**, *22*, 2856–2881. Recent applications: (c) Boal, B. W.; Schammel, A. W.; Garg, N. K. *Org. Lett.* **2009**, *11*, 3458–3461. (d) Schammel, A. W.; Chiou, G.; Garg, N. K. *Org. Lett.* **2012**, *14*, 4556–4559. (e) Moreno, J.; Picazo, E.; Morrill, L. A.; Smith, J. M.; Garg, N. K. *J. Am. Chem. Soc.* **2016**, *138*, 1162–1165. (f) Picazo, E.; Morrill, L. A.; Susick, R. B.; Moreno, J.; Smith, J. M.; Garg, N. K. *J. Am. Chem. Soc.* **2018**, *140*, 6483–6492.

(17) (a) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1994, 1007–1017. (b) Cha, J. S. *Org. Process Res. Dev.* **2006**, *10*, 1032–1053.

(18) (a) Huang-Minlon, N. A. *J. Am. Chem. Soc.* **1946**, *68*, 2487–2488. (b) Cram, D. J.; Sahyun, M. R. V. *J. Am. Chem. Soc.* **1962**, *84*, 1734–1735.

(19) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2002, 2193–2256.

(20) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–1964.